Total Synthesis of Thia-Calanolide A and Analogues, Asymmetric Aziridination of Alkenes and Development of Environmentally Benign Green Methodologies

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)
TO THE
UNIVERSITY OF PUNE

BY

ANIL UMAJI CHOPADE

UNDER THE GUIDANCE OF

DR. (MRS) BHANU M. CHANDA

DIVISION OF ORGANIC CHEMISTRY
NATIONAL CHEMICAL LABORATORY
PUNE-411 008, INDIA

MARCH 2009

DEDICATED TO MY PARENTS

AND

MY WIFE JYOTI

D E C L A R A T I O N

The research work presented in this thesis entitled *"**Total Synthesis of Thia-Calanolide A and Analogues, Asymmetric Aziridination of Alkenes and Development of Environmentally Benign Green Methodologies**"* and being submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune, India has been carried out under the supervision of **Dr. (Mrs) Bhanu M. Chanda** at Division of Organic Chemistry, National Chemical Laboratory, Pune-411008. The work presented here is original and has not been submitted in part or in full by me for any other degree or diploma of this or any other university.

Date: March 2009

Anil Umaji Chopade

Division of Organic Chemistry
National Chemical Laboratory
Pune-411 008, Maharashtra
India

राष्ट्रीय रासायनिक प्रयोगशाला
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद)
डॉ. होमी भाभा मार्ग पुणे - 411 008. भारत
NATIONAL CHEMICAL LABORATORY
(Council of Scientific & Industrial Research)
Dr. Homi Bhabha Road, Pune - 411 008. India.

Dr. (Mrs) Bhanu M. Chanda
Ex-Scientist G
E-mail: bhanuchanda@gmail.com
Telephone (Res): +91-20-25898567

CERTIFICATE

This is to certify that the work presented in the thesis entitled *"**Total Synthesis of Thia-Calanolide A and Analogues, Asymmetric Aziridination of Alkenes and Development of Environmentally Benign Green Methodologies**"* and being submitted to the University of Pune by **Mr. Anil Umaji Chopade** has been carried out by the candidate at National Chemical Laboratory, Pune, under my supervision. The work presented is original and has not been submitted for any other degree or diploma of this or any other University. Whenever references have been made to previous works of others it has been clearly indicated as such and included in the bibliography.

Pune-411 008
Date:

Dr. (Mrs) B. M. Chanda
(Research Guide)

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Anil Umaji Chopade

Abbreviations

Aq.	:	Aqueous
AcOH	:	Acetic acid
Cat.	:	Catalytic/catalyst
Conc.	:	Concentrated
Bn	:	Benzyl
BnBr	:	Benzyl bromide
d	:	Doublet
dd	:	Doublet of doublet
DCC	:	1,3-Dicyclohexylcarbodiimide
DCM	:	Dichloromethane
DEPT	:	Distortionless Enhancement by Polarization Transfer
DIAD	:	Diisopropyl azodicarboxylate
DMAP	:	4-(Dimethylamino)pyridine
DMF	:	Dimethylformamide
DMSO	:	Dimethyl sulphoxide
EDCI	:	1-Ethyl-3-(dimethylaminopropyl)carbodiimide
Et	:	Ethyl
ee	:	Enantiomeric excess
equiv.	:	Equivalent(s)
g	:	gram
GC	:	Gas Chromatography
h	:	Hour(s)
HIV	:	Human Immunodeficiency Virus
HPLC	:	High Performance Liquid Chromatography

Hz	:	Hertz
IC	:	Inhibitory concentration
ILs	:	Ionic liquids
IR	:	Infra Red
LAH	:	Lithium aluminum hydride
mg	:	Milligram
Me	:	Methyl
MEK	:	Methyl ethyl ketone
min.	:	Minute(s)
mL	:	Millilitre(s)
mmol	:	Millimole(s)
Mp	:	Melting point
MS	:	Mass Spectrum
NNRTI	:	Non-Nucleoside Reverse Transcriptase Inhibitors
NMR	:	Nuclear Magnetic Resonance
Ph	:	Phenyl
PhINTs	:	[N-(p-tosylsulfonyl)imino]phenyliodinane
PILs	:	Phosphonium Ionic Liquids
PLE	:	Porcine Liver Esterase
PMB	:	*p*-Methoxybenzyl
ppm	:	Parts per million
rt	:	Room temperature
s	:	singlet
Satd.	:	Saturated
p-TSA	:	*p*-Toluenesulfonic acid
p-TsCl	:	*p*-Toluenesulfonyl chloride
TBAB	:	Tetrabutylammonium iodide

TBAF	:	Tetrabutylammonium fluoride
TEA	:	Triethylamine
THF	:	Tetrahydrofuran
TMSCl	:	Trimethylchlorosilane
Ts	:	Tosyl
TPP	:	Triphenylphosphine

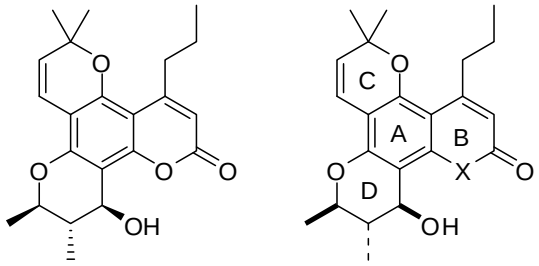
General Remarks

- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- ^{1}H Nuclear Magnetic Resonance spectra were recorded on Varian FT-200 MHz (Gemini), AC-200 MHz, MSL-300 MHz, AV-400 MHz and Bruker-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C Nuclear Magnetic Resonance spectra were recorded on AC-50 MHz, MSL-75 MHz, AV-100 MHz and Bruker-125 MHz spectrometer.
- Mass spectra were recorded on a CEC-21-110B, AP-1 QSTAR PULSAR, Finnigan Mat 1210 or MICRO MASS 7070 spectrometer at 70 eV using a direct inlet system.
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV, I_2 and anisaldehyde reagent in ethanol as development reagents.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50 °C.
- All solvents and reagents were purified and dried according to procedures given in Vogel's Text Book of Practical Organic Chemistry.
- Silica gel (60-120 & 230-400 mesh) used for column chromatography was purchased from Spectrochem Company, Mumbai, India.
- Molecular weights of the compounds and *m/z* values in the mass spectra are corrected to nearest integers.
- Starting materials were obtained from commercial sources or prepared using known procedures.

Abstract

The thesis entitled "**Total Synthesis of Thia-Calanolide A and Analogues, Asymmetric Aziridination of Alkenes and Development of Environmentally Benign Green Methodologies**" is divided into three chapters and each chapter is further sub-divided into the following sections: Introduction, Present work, Experimental, Spectroscopic data and References. The first chapter consists of the total synthesis of (±)-thia-calanolide A and related analogues. The second chapter deals with aziridination of alkenes and asymmetric aziridination of alkenes using chiral ligands (homogeneous and heterogeneous). The third chapter comprises application of phosphorus based ionic liquids in the synthesis of the β-enaminones and benzodiazepine derivatives.

Chapter 1: First synthesis of (±)-thia-calanolide A and related analogues



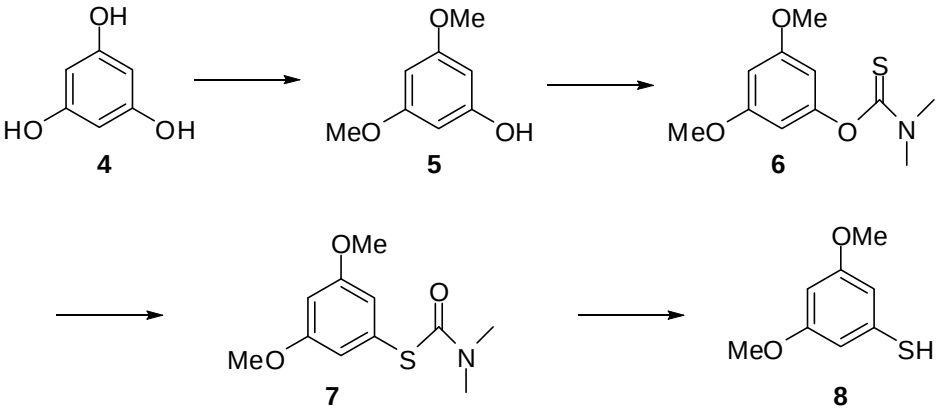
(+)-Calanolide A [(+)-**1**] X = NH : (±)-Aza-calanolide A [(±)-**2**]
X = S : (±)-Thia-calanolide A [(±)-**3**]

Figure 1

Calanolide A (**1**), a dipyranocoumarin isolated from the leaves and twigs of the tropical rain forest tree *Calophyllum lanigerum* var *austrocoriaceum,* has been recently identified as a potent representative of a pharmacologically distinct subclass of non-nucleosidal human immunodeficiency virus-1 (HIV-1) specific reverse transcriptase inhibitors. In addition, calanolide was reported to have activity against the azidothymidine-resistant HIV-1 strain and the pyridinone-resistant HIV-1 strain. The aza analogue of calanolide (**2**) was synthesised to study the structure activity relationship and it exhibited enhanced anti-HIV activity compared to the natural product calanolide A. Interesting anti-HIV activity of calanolide A and its aza analogue as well as longstanding interest in the field of total synthesis of

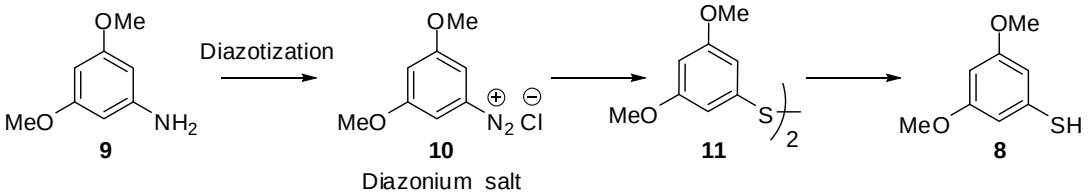
biologically active natural products and their analogues prompted execution of the synthesis of thia-calanolide A (**3**).

An important part of the synthesis of thia-calanolide is the synthesis of substituted thiocoumarin ring system. For this purpose, 3,5-dimethoxy thiophenol **8** was found to be suitable starting material. The same was synthesized from phloroglucinol **4** following the literature procedure. The key reaction involved intramolecular Newmann-Kwart rearrangement from O-3,5-dimethoxyphenyl dimethylcarbamothioate **6** to S-3,5-dimethoxyphenyl dimethylcarbamothioate **7** (Scheme 1).



Scheme 1

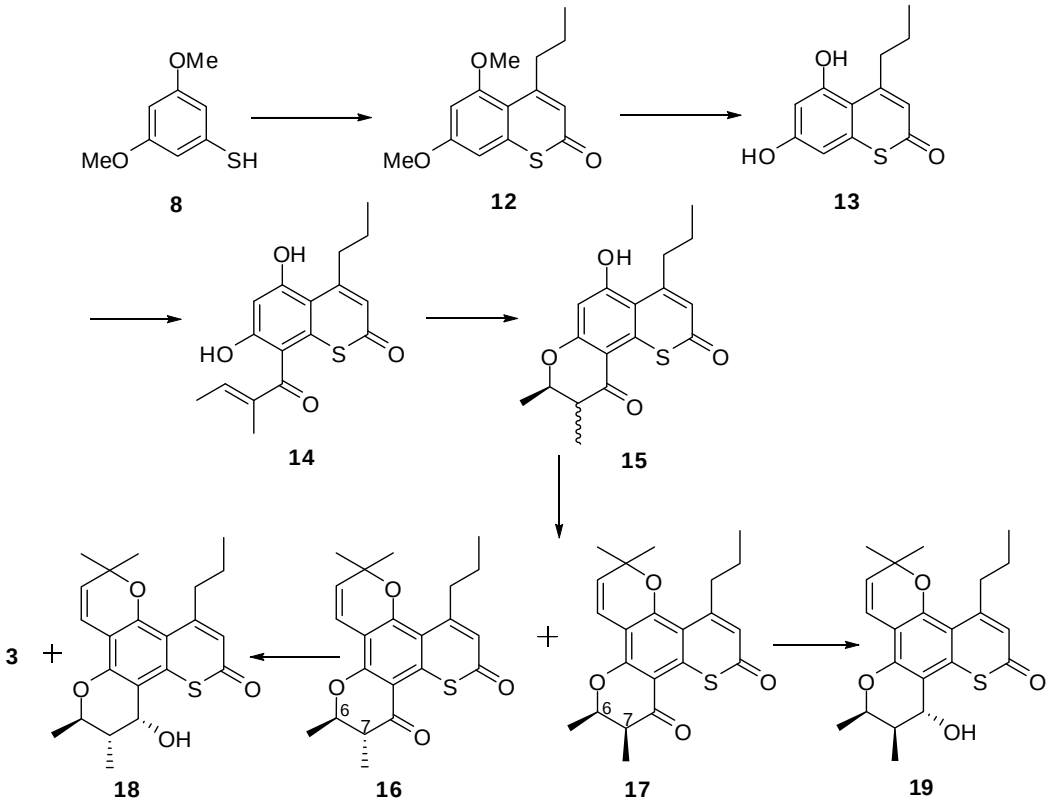
Alternate route for the synthesis of **8** from 3,5-dimethoxyaniline **9** by diazotization followed by reaction with Na_2S and S or NaSH gave **8** in poor yield and thus this route was not amenable to large scale preparation (Scheme 2).



Scheme 2

With the substituted thiophenol **8** in hand, the next task was to synthesise dimethoxy thiocoumarin ring system **12**. This was effected by condensation of 3,5-dimethoxythiophenol **8** with ethyl butyrylacetate in the presence of triflic acid. Demethylation of both the methoxy groups was conveniently carried out with aluminium chloride in chlorobenzene at 100 ºC to give 3,5-dihydroxy thiocoumarin **13**. The next step was to build the dimethylchromanone ring (ring D). Thus the compound **13** was subjected to the Friedel-Crafts acylation conditions, with tigloyl

chloride and aluminium chloride. Unfortunately, C-tigloylation did not proceed under standard conditions and the major product obtained was the unwanted O-tigloyl derivative as confirmed by analytical methods. After altering reaction conditions and using different ratio of solvent system, we were successful in synthesis compound **14** in 65% yield with carbon disulphide-nitrobenzene in 7:3 ratio and the scheme was carried out further according to Dreyer's route (Scheme 3) to yield (±)-thia-calanolide A.

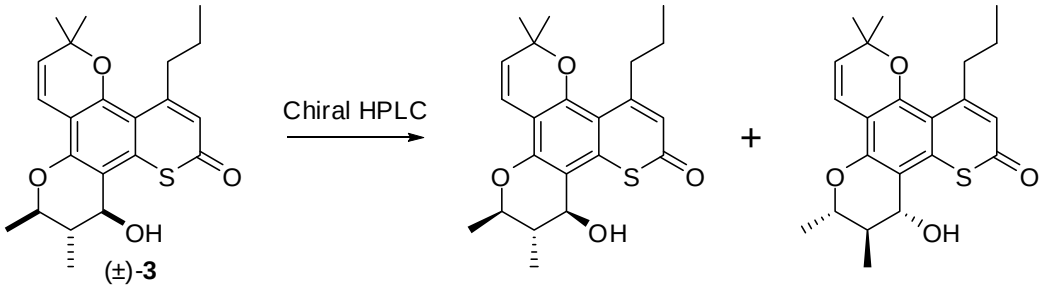


Scheme 3

The chromene segment (ring C) was constructed on **15** with 3-chloro-3-methyl-1-butyne in 2-butanone–DMF in the presence of K_2CO_3, *n*-Bu_4NI and $ZnCl_2$ at 70 °C by which a mixture of *trans* and *cis* ketones **16** and **17** in a combined yield of 42% was obtained. The *trans-cis* mixture was separated by silica gel column chromatography. In ^1H NMR spectroscopy, compound **16** exhibited a coupling constant of 6.8 Hz and 11.5 Hz respectively whereas in **17**, the same was observed to be 3.6 Hz and 7.3 Hz for H-6 and H-7 of ring D. Both the ketones **16** and **17** were reduced separately with sodium borohydride in ethanol to give (±)-**3** (44%) and (±)-**19** (78%) respectively.

(±)-Thia-calanolide A (**3)** was conveniently resolved by chiral HPLC (Chiralcel OD, 9:1 hexane-isopropanol, 1 mL/min) to afford two isomers having optical rotation $[\alpha]_D$ +54.3° (*c* 0.5, $CHCl_3$) and $[\alpha]_D$ –49.8° (*c* 0.3, $CHCl_3$) (Scheme 4).

Compound (±)-**3** was evaluated for anti-HIV reverse transcriptase activity but it was found to be a relatively weaker inhibitor (28%) compared to the synthetic (±)-**1** (99.7%).



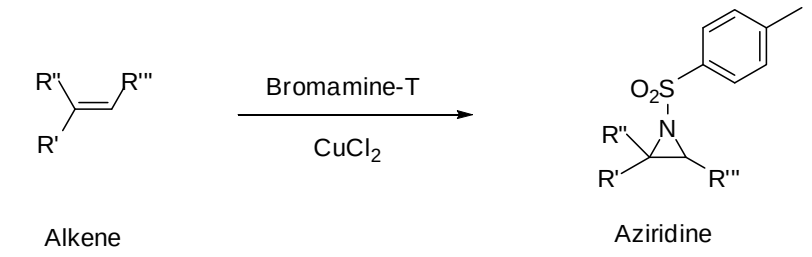
Scheme 4

Thus the first synthesis of (±)-thia-calanolide A **3** has been successfully accomplished. During its biological evaluation it was found to be relatively less active as compared to natural product calanolide A **1** and synthetic aza-calanolide A **2**. Perhaps, the bulkier sulfur atom and amphoteric nature of sulphur in (±)-thia-calanolide A **3** could have contributed to the retarded activity. For a complete study of the structure activity relationship (SAR), several thia analogues need to be synthesized and evaluated. Work in this direction is currently in progress.

Chapter 2: Studies towards aziridination of alkenes and asymmetric aziridination of alkenes with known and new chiral ligands

Aziridines belong to an important class of organic compounds with three membered nitrogen containing heterocycles, which are important subunits in several natural products. The aziridine moiety is successfully used in the synthesis of various alkaloids, amino acids, amino sugars, polymers, pyrrolidines and *β*-lactum antibiotics.

Almost all the types of chiral aziridinations reported so far have utilised N-tosyliminophenyliodinane (PhI=NTs) or N-nosyliminophenyliodinane (PhI=NNs) as the nitrene source. Also a few reports describe the use of *p*-toluene sulfonyl azide as well as chloramine-T for this purpose. For the first time, bromamine-T as a superior source of nitrene in aziridination was reported in 1998 (Scheme 5).

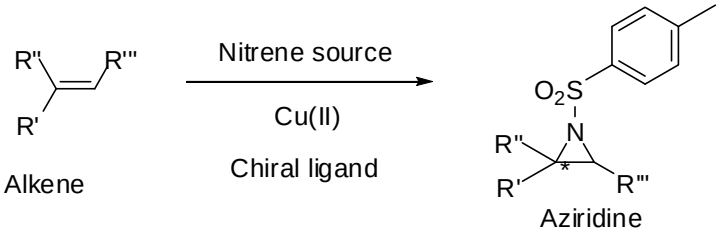


Alkene Aziridine

Alkene = Styrene, α-methylstyrene, β-methylstyrene, cyclohexene, cyclooctene

Scheme 5

Recent developments in aziridine chemistry follow two main paths: the development of reliable synthesis and control over subsequent ring opening transformations of aziridines. Functionalized aziridines are considered highly valuable three-membered ring systems in modern synthetic chemistry, due to their widely recognized versatility as synthetic building blocks and their application in functional group transformations. In synthetic transformations, their utility is mostly associated with stereo- and regio-controlled ring-opening reactions of the highly strained three membered rings. Chiral aziridines (Scheme 6) can serve as a source of chirality in stereocontrolled reactions and have been employed as both ligands and chiral auxiliaries in asymmetric synthesis.



Alkene Aziridine

Alkene = Styrene, α-methylstyrene, β-methylstyrene

Scheme 6

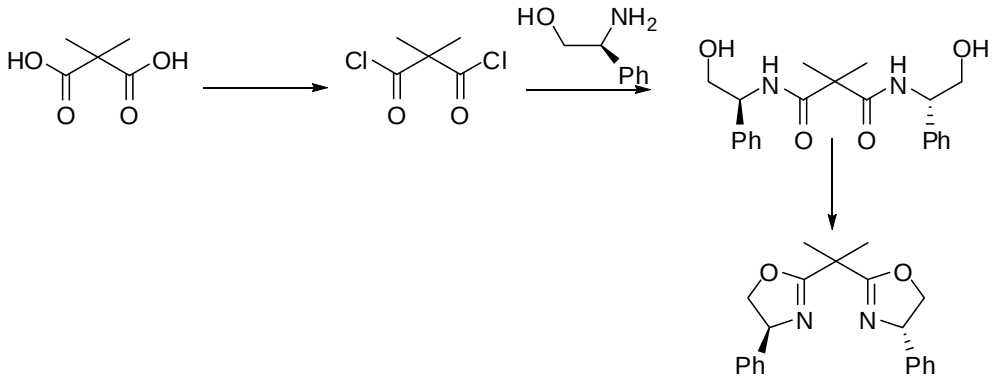
Section I: Synthesis of chiral ligands and catalysts and asymmetric aziridination of alkenes

A few new chiral ligands and catalysts have been synthesized and characterized. Their application in asymmetric aziridination have been studied and the results obtained are reported here.

Part I. Homogeneous Ligands

A. Synthesis of (4S,4'S)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole), chiral bis-(oxazoline) ligand

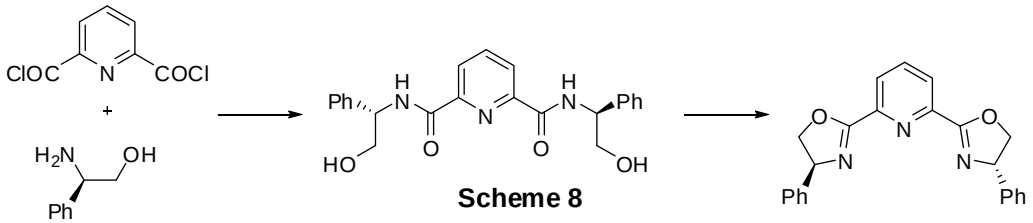
Synthesis of bis-(oxazoline) involves sodium borohydride-calcium chloride reduction of commercially available (*S*)-phenyl glycine to the corresponding (*S*)-phenyl glycinol, followed by acylation with dimethylmalonate dichloride. The dihydroxy malonodiamide was cyclized to the bis-(oxazoline) with tosyl chloride and catalytic amount of DMAP (Scheme7).



Scheme 7

B. Synthesis of (*S*,*S*)-2,6-Bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine

The pybox ligand was synthesized from the commercially available amino alcohol in three steps. 2,6-Pyridine dicarboxylic acid was refluxed with thionyl chloride and the diacid chloride isolated by distillation of excess thionyl chloride. The residue was treated with the amino alcohol in DCM at 0 °C, followed by addition of thionyl chloride to yield the pybox ligand hydrochloride. Neutralization of the salt was achieved by stirring a methanolic solution of the salt with aqueous sodium hydroxide at room temperature for 3 days. Recrystallization from ethyl acetate and petroleum ether yielded the pybox (Scheme 8).

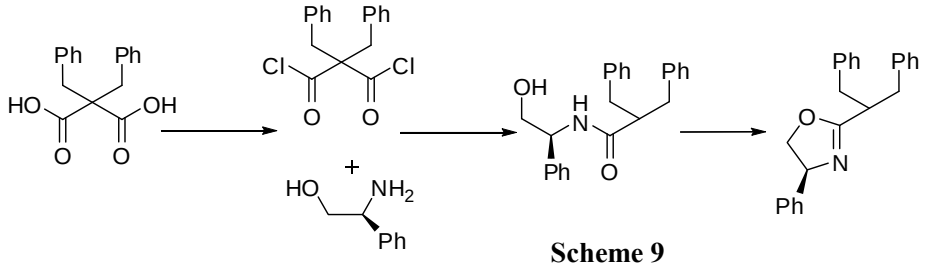


Scheme 8

C. Synthesis of dibenzyl bis-oxazoline ligand

A new chiral dibenzyl bis-oxazolines were synthesised starting from diethyl malonate. Diethyl malonate was reacted with benzyl bromide in presence of potassium carbonate in acetonitrile to furnish dibenzyl derivatives of diethyl malonate. In the second step of hydrolysis there was formation of dibenzyl derivatie of malonic acid. The acid was converted into acid chloride with thionyl chloride and

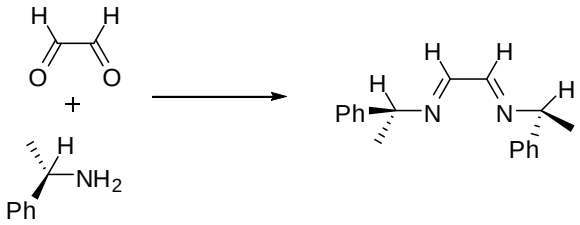
further reacted with phenyl glycinol and triethyl amine in dichloromethane at room temperature to yield the amide. The latter was cyclised *via* reaction with tosyl chloride in presence of catalytic amount of DMAP in dichloromethane to yield the undesired dibenzyl mono-oxazoline ligand (Scheme 9).



Scheme 9

D. Synthesis of N,N'-(ethane-1,2-diylidene) bis (1-phenylethanamine) and (*S*)-1-phenylethanamine a new chiral diimine ligand

Glyoxal and (*S*)-PhCH(CH_3)NH_2 were mixed in MeOH at room temperature. The mixture was then stirred for 3h at 70 °C and the ligand formed was extracted with hexane (Scheme 10).

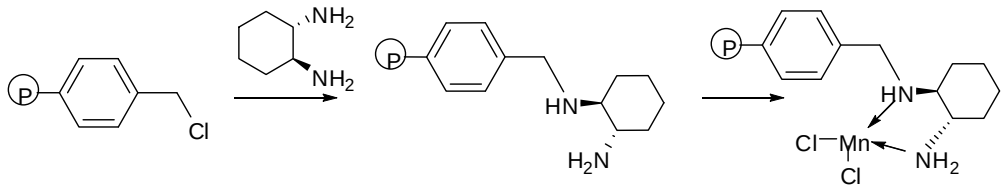


Scheme 10

Part II. Heterogeneous metal catalyst

Synthesis of novel manganese based heterogeneous metal catalyst

A novel manganese based chiral metal catalyst with 8% cross-linked of chloromethylated polydivinylbenzene (Ps-DVB) was synthesized starting from *trans* 1,2-diaminocyclohexane (Scheme 11).



Scheme 11

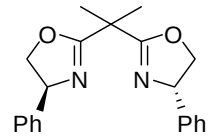
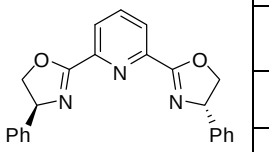
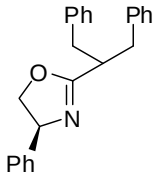
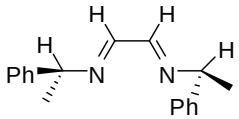
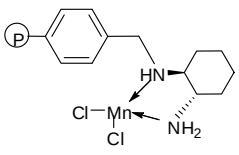
The first step in the synthesis of the catalyst was to bind 1,2-diaminocyclohexane to the polymer. The Ps-DVB (8% cross linked) polymer resin was chosen as the support. In this step 1,2-diaminocyclohexane was loaded on activated polymer beads. The loading of 1,2-diaminocyclohexane was confirmed by the estimation of nitrogen.

The second step in the catalyst synthesis included coordination of the metal ion with the polymer anchored ligand. Thus an ethanolic solution of $MnCl_2.4H_2O$ with polymer anchored 1,2-diaminocyclohexane was stirred to obtain manganese catalyst.

Part III: Asymmetric aziridination of alkene using chiral ligands and catalyst

Asymmetric aziridination of alkene using known and new chiral ligand was summarized in table 1.

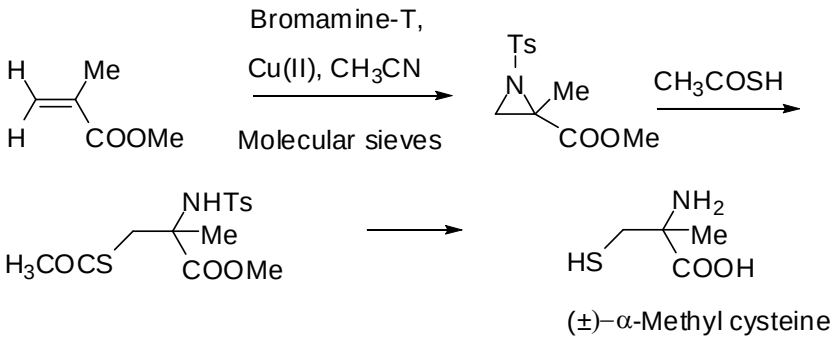
Table 1

Ligand/Catalyst	Substrate	Nitrene Source	Cu(II)	Yield (%)	ee (%)
	Styrene	PhINTs	$Cu(OTf)_2$	78	53
	α-Methyl styrene	Bromamine-T	$CuCl_2$	56	10
	β-Methyl styrene	Bromamine-T	$CuCl_2$	52	7
	Methyl methacrylate	Bromamine-T	$Cu(OTf)_2$	73	18
	Styrene	Bromamine-T	$CuCl_2$	75	0
	α-Methyl styrene	Bromamine-T	$CuCl_2$	64	0
	β-Methyl styrene	PhINTs	$CuCl_2$	59	0
	Methyl methacrylate	PhINTs	$Cu(OTf)_2$	72	9
	Styrene	Bromamine-T	$CuCl_2$	72	0
	α-Methyl styrene	Bromamine-T	$CuCl_2$	60	0
	β-Methyl styrene	Bromamine-T	$CuCl_2$	55	0
	Methyl methacrylate	Bromamine-T	$Cu(OTf)_2$	71	0
	Styrene	Bromamine-T	$CuCl_2$	79	10
	α-Methyl styrene	Bromamine-T	$CuCl_2$	68	0
	β-Methyl styrene	Bromamine-T	$CuCl_2$	54	0
	Methyl methacrylate	Bromamine-T	$Cu(OTf)_2$	56	5
	Styrene	Bromamine-T	-	49	0
	α-Methyl styrene	Bromamine-T	-	34	0
	β-Methyl styrene	Bromamine-T	-	47	0
	Methyl methacrylate	Bromamine-T	-	15	0

Reaction condition: Acetonitrile, molecular sieves (4Å), rt, 1-4h.

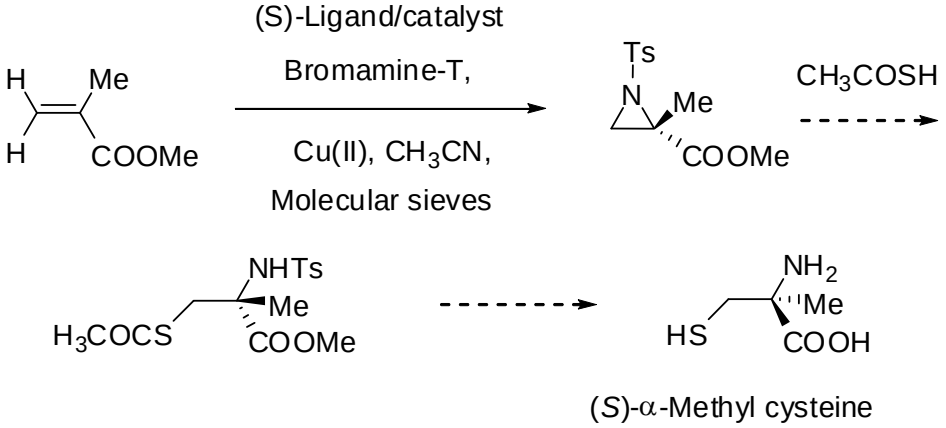
Section II: A new route to synthesis of α-methyl cysteine *via* aziridination and asymmetric aziridination of methylmethacrylate catalysed by natural cinchona alkaloids

Synthesis of α-methyl cysteine was carried out with methyl methacrylate as the alkene. Initially, anhydrous Cu(II)) in dry acetonitrile was stirred under nitrogen atmosphere at room temperature, then methyl methacrylate was added to this solution followed by addition of bromamine-T and activated 4Å molecular sieves which afforded aziridine. The aziridine was then opened with thioacetic acid and subsequently hydrolysed with hydrogen bromide in acetic acid to furnish α-methyl cysteine (Scheme 12).



Scheme 12: Synthesis of (±)-α-methyl cysteine

In the synthesis of chiral α-methyl cysteine, asymmetric aziridination of methyl methacrylate with different chiral ligands was carried out (Scheme 13).



Scheme 13: Chiral synthesis of α-methyl cysteine

A maximum enantioselectivity (40%) was observed when the cinchona alkaloids especially when preformed copper-cinchonidine complex was used as a ligand.

Application of known and new chiral ligands in asymmetric aziridination has been demonstrated and asymmetric aziridination of alkenes with bromamine-T as source of nitrogen has been evaluated. Synthesis of α-methyl cysteine was achieved by a new route *via* aziridination of methyl methacrylate followed by regioselective opening of the aziridine formed with thioacetic acid. Hydrolysis of the N-protected thio ester furnished α-methyl cysteine. In the synthesis of chiral α-methyl cysteine, the feasibility of asymmetric aziridination with several chiral ligands yielded only up to 40% ee of the aziridine. Further work is in progress to improve the enantioselectivity in the asymmetric aziridination step.

Asymmetric aziridination of methyl methacrylate with cinchona alkaloids

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, dihydroquinine, cinchonidine**,** N-benzyl ephedrine and sparteine (Figure 2) were chosen as ligands for asymmetric aziridination of olefins. Initially the metal ligand complex was formed by stirring a suspension of anhydrous copper (II) chloride and ligand in dry acetonitrile. Then bromamine-T or PhI=NTs and finally the alkene was added and reaction mixture was stirred at room temperature for six hours (Scheme 14).

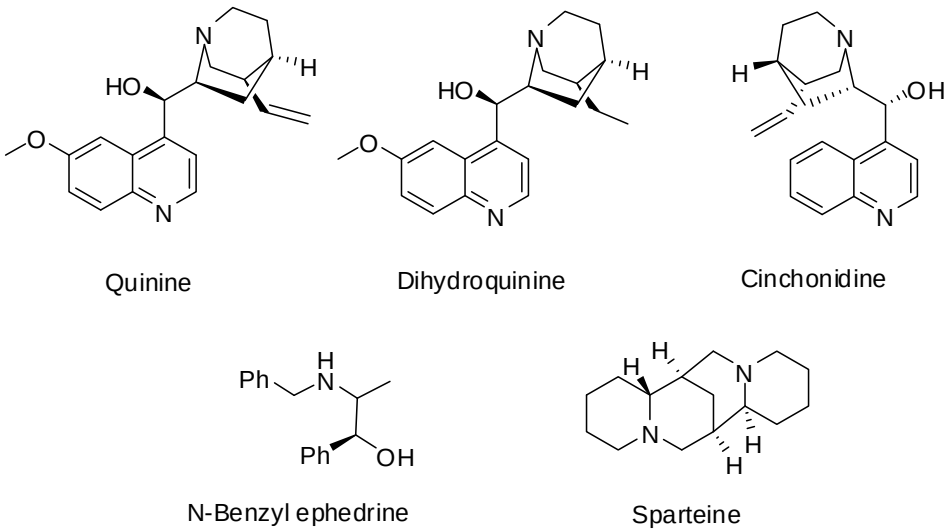
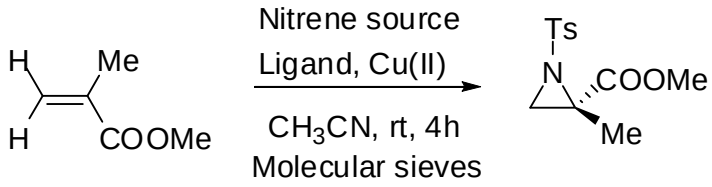


Figure 2

Heterogeneous catalysts containing alkaloids like cinchonidine, quinine, dihydroquinine, spartine and N-benzyl ephedrine were prepared by sol–gel technique The required alkaloid was dissolved in isopropyl alcohol and ethyl silicate-40 was added with stirring followed by dropwise addition of ammonia solution (25%) to effect the gel formation. The transparent white gel thus obtained was air dried for 3 h. The silica complex thus obtained was treated with Cu(II) and the copper silica complex obtained was directly used in asymmetric aziridination of alkene (Scheme 14).



Scheme 14

Chapter 3: Application of phosphorus based ionic liquids (ILs) in the synthesis of biologically active intermediates

Generally IL refers to molten salts, which contain ions. Only those liquids, which are non-corrosive and have low viscosity, are chosen to be called as ionic liquids. The phosphonium ionic liquids have the generic formula [PR_3R'] X, where both R and R′ are alkyl groups and X is halide, borate or tosylate. There are many potential applications of phosphonium ionic liquids for palladium catalyzed Suzuki and Heck coupling reactions. Ionic liquids were used as a reaction medium as well as promoter in the absence of any added catalyst for both the methodologies.

Ionic liquids used in the present work are as follows:

Triisobutyl (methyl) phosphonium chloride

Triisobutyl (methyl) phosphonium tosylate

Trihexyl (tetradecyl) phosphonim tetrafluoroborate

Trihexyl (tetradecyl) phosphoniumhexafluoro phosphate

Trihexyl (tertadecyl) phosphonium dicyanamide

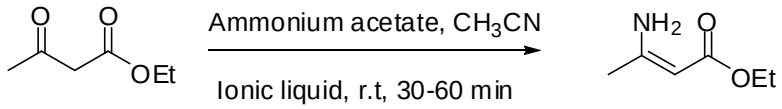
Trihexyl (tertadecyl) phosphonium bis(2,4,4-trimethylpentyl) phosphinate

Section I: Synthesis of β-enaminonester

Enaminones are an important class of organic synthetic intermediates. They have a very high impact as synthons for the synthesis of various heterocycles and

biologically active analogues. Due to their wide range of activity and importance it was decided to synthesize β-enaminonester by simple method using ionic liquids.

β-Enaminonester was synthesized in excellent isolated yields using ILs, at room temperature in the absence of any added catalyst. A mixture of ethyl acetoacetate, ammonium acetate and ionic liquid was stirred at room temperature for 6 h, then reaction mixture was diluted with hexane and washed with water. Hexane layer was dried over sodium sulfate and concentrated under reduced pressure and purified by flash column chromatography to afford β-enaminonester in good yields (Scheme 15).

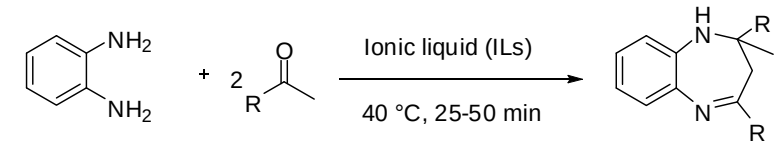


Scheme 15

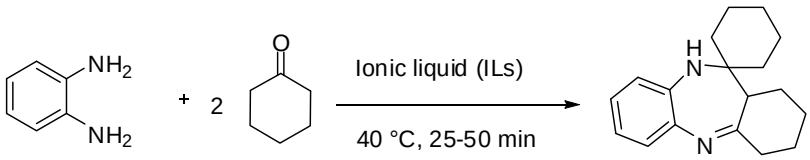
A recyclable ionic liquid was used as a reaction medium as well as a promoter in the absence of any added catalyst. The reaction rates were found to be significantly higher than those reported so far for the synthesis of β-enaminones at room temperature.

Section II: Synthesis of benzodiazepine derivatives

Benzodiazepines are an important class of pharmacologically active compounds finding application as anticonvulsant, anti-anxiety and hypnotic agents. Benzodiazepine derivatives also find commercial use as dyes for acrylic fibers and as anti-inflammatory agents. Moreover, they are key intermediates for the preparation of other fused ring compounds such as triazolo-, oxazino-oxadiazolo or furano-benzodiazepines. Many of the literature methods for the synthesis of 1,5-benzodiazepines suffer from one or other limitations such as requiring harsh conditions, expensive reagents and low to moderate yields, relatively long reaction times and occurrence of several side reactions.



R = CH_3, CH_2CH_3, Ph, *m*-tolyl, 4-nitrophenyl



Scheme 16

Syntheses of 1,5-benzodiazepine derivatives in excellent isolated yields and in relatively short reaction times using the ILs and at ambient temperature in the absence of any added catalyst are reported here. *o*-Phenylenediamine (OPD) was reacted with both acyclic and cyclic ketones at 40 °C in ILs (both as catalyst and as solvent) to afford the desired benzodiazepine derivative in high yields (Scheme 16).

The reactions in ILs gave excellent yields of the 1,5-benzodiazepines in a relatively short reaction time (30 min). No reaction was observed when OPD was reacted with acetone under similar conditions in the absence of the ILs, thus highlighting the role of the ILs as a promoter. Similarly, ILs as catalysts in solvent like acetone, MIBK, 2-butanone for the reaction are being studied to assess the efficiency of ILs as catalyst.

Note: *Compound numbers in the abstract are different from those in the thesis.*

Chapter 1

First Synthesis of (±)-Thia-Calanolide A and Related Analogues

1.1. Introduction

Synthesis of (±)-thia-calanolide A deals with anti-HIV compound. It is considered necessary to discuss history and background of anti-HIV compounds. Human immunodeficiency virus (HIV) is the cause of acquired immunodeficiency syndrome (AIDS). Since its first report in 1981,[1] the virus has spread rapidly through the human population worldwide and was recently reported as third on the World Health Organization's list of global cause of death. HIV leads to the destruction and functional impairment of the immune system, subsequently destroying the body's ability to fight against infections.[2] The search for biologically active compounds and/or chemotherapeutic strategies to treat HIV/AIDS and related opportunistic infections remains among the highest priorities of present day research.[3]

Symptoms of AIDS:

AIDS patients usually exhibit one or more of the symptoms[4] such as, reduced appetite and malabsorption, increased excretion of nutrients, endocrine and neurological abnormalities, metabolic and immune derangement, severe malnutrition as evidenced by progressive weight loss, lymphadenopathy, opportunistic infections, neoplasms e.g. Kaposi's sarcoma (KS), malignant lymphoma, etc.

HIV Life Cycle - How HIV Harms:

Human immunodeficiency virus (HIV) attacks two sorts of white blood cells: macrophages, which play an early role in immune defense by phagocytosing and then digesting the invader, and certain lymphocytes (CD4+ T lymphocytes). HIV accumulates in the infected macrophages, which are veritable viral reservoirs and very much inaccessible to antiviral treatments. Multiplication of HIV destroys the CD4+ T lymphocytes.

Initially virus gains access to the interior of these cells (and certain other cell types) by binding to the CD4 itself and to molecule, a co-receptor on the cell surface. Such binding enables HIV to fuse with the cell membrane and to release its contents in to the cytoplasm.[5] These contents include various enzymes and two strands of RNA each of which carries the entire HIV genome: the genetic blueprint for making new HIV particles.[6]

One of the enzymes, reverse transcriptase (RT), copies HIV RNA into double strand DNA. Then a second enzyme, integrase (IN), helps to splice the HIV and/or DNA permanently in to a chromosome in the host cell. When a T cell, that harbors this integrated DNA, becomes activated against HIV or other microbes, the cell replicates and also unwittingly begins to produce new copies of both the viral genome and viral proteins. Now another HIV enzyme, protease (PR) cuts the new protein molecules into forms that are packed with the virus's RNA genome in new viral particles. These particles bud from the cell and infect other cells. If enough particles form, they can overwhelm and kill the cell that produced them.

At the start of the infection, hefty viral replication and the killing of CD4+ T cells are manifested by high levels of HIV in the blood and by a dramatic drop in CD4+ T concentrations from the normal level. About three weeks in to this acute phase, many people display symptoms reminiscent of mononucleosis, such as fever, enlarged lymph nodes, rash, muscle aches and headaches. These maladies resolve within another one to three weeks, as the immune system starts to gain some control over the virus. i.e., the CD4+ T cell population responds in ways that spur other immune cells CD8 or cytotoxic T lymphocytes to increase their killing of infected, virus producing cells. The body also produces antibody molecules in an effort to contain the virus; they bind to free HIV particles and assist in their removal.

Despite all these activities, the immune system rarely, if ever, fully eliminates the virus by about six months, the rate of viral replication reaches a lower, but relatively steady state that is reflected in the maintenance of viral levels at a kind of set point. The apparent good health continuous because CD4+ T cell levels remain high enough to preserve defensive response to other pathogens. But over time, CD4+ T cell concentration gradually falls and people are said to have AIDS.

Anti AIDS therapies:

At present, a vaccine comprising a single antigen has not been found out which will act against both infected cells B-cell and T-cell. While some B-cell and T-cell epitopes lie within the more conserved regions of HIV-1 proteins, many are localized to variable regions and differ from one virus to the next. Neutralizing B-cell responses may vary toward viruses with different antibody contact residues and/or protein conformations, while T-cell responses may vary toward viruses with different T-cell receptor contact residues and/or amino acid sequences pertinent to antigen

processing. Hurwitz *et al.*[7] have shown that multi-vectored, multi-envelope vaccine elicit HIV-1-specific B- and T-cell functions with a diversity and durability that may be required to prevent HIV-1 infections in humans. Xin Ma *et al.*[8] have discussed the neutralizing antibody problem, elusive immune protection, immunogen design, pre-existing anti-vector immunity and design of phase 3 vaccine trials and the challenges and opportunities in development of HIV/AIDS vaccine.

Chemotherapy

Since HIV was identified as the etiological cause of AIDS, chemotherapy of AIDS has been one of the most challenging scientific projects. The United States Food and Drug Administration (FDA) have approved several anti-HIV drugs, including seven nucleoside reverse transcriptase inhibitors (NRTIs). It has been the most widely studied class of anti HIV agents and majority of these nucleoside inhibitors belong to the family of 2',3'-dideoxynucleosides. Clinically approved anti-AIDS drugs belonging to this class include Zidovudine (AZT **1**), Didanosine (DDI **2**), Zalcitabine (DDC **3**), Stavudine (D4T **4**), Lamividine (3TC **5**), Abacavir (ABC **6**), Emtricitabine (FTC **7**) (Figure 1).

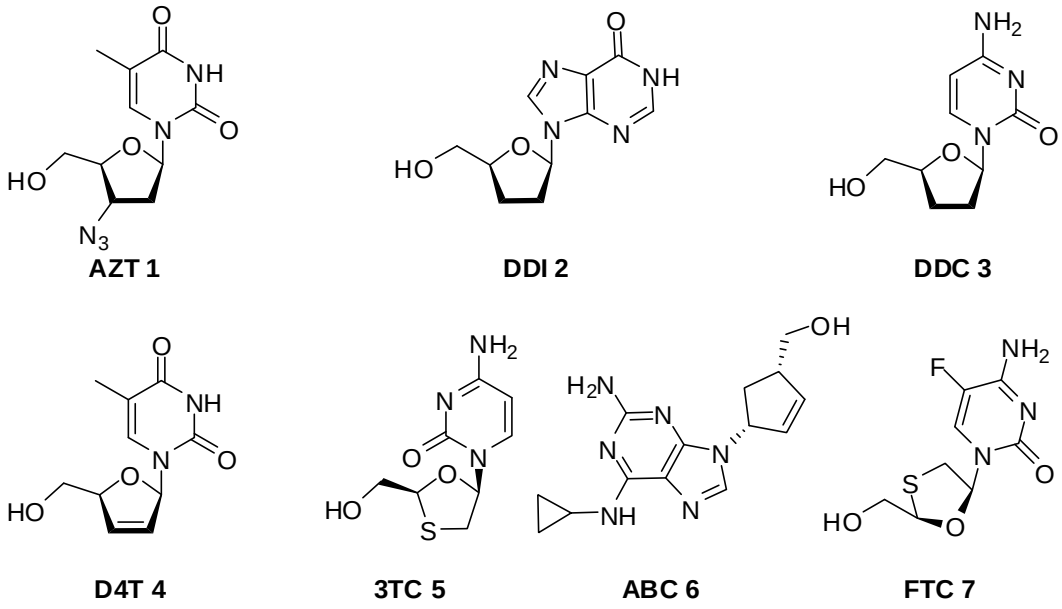
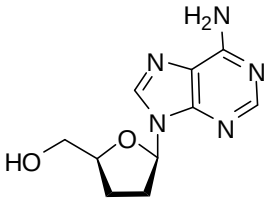


Figure 1

Zidovudine or AZT[9] **1** was the first approved antiviral drug for HIV infection. Although AZT is efficacious, the most serious side effect associated with it is bone marrow suppression resulting in anemia and neutropenia, probably resulting from the toxic effect of AZT on bone marrow progentier cells. A particular advantage of AZT is its ability to penetrate the blood-brain barrier, since HIV

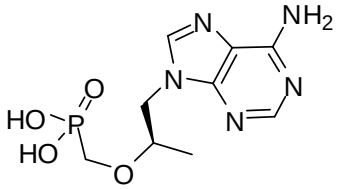
infects cells in CNS causing dementia. It has been shown that D4T[10] **4** is less toxic than AZT in mice and human bone marrow cells. Following the discovery of the anti-HIV activity of AZT search for superior analogues resulted in the discovery of DDA **8** (Figure 2) and DDI **2**.[11]



DDA 8

Figure 2

The only one nucleotide reverse transcriptase inhibitor approved by FDA is tenofovir **9** (Figure 3). Normally, nucleoside analogs are converted into nucleotide analogs by the body. Taking nucleotide analog reverse transcriptase inhibitors (NtARTIs or NtRTIs) directly allows conversion steps to be skipped, causing less toxicity.



Tenofovir 9

Figure 3

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) represent a group of highly potent and specific inhibitors of HIV-1 replication that interact non competitively with the enzyme at an allosteric nonsubstrate binding site that is distinct from, but functionally and also spatially associated with the substrate binding site. This particular site corresponds to a flexible highly hydrophobic pocket that is exclusively found in the RT of HIV-1 and hence, NNRTI are only inhibitory to HIV-1 and not HIV-2 or other retroviruses.

Well known NNRTI[12] (Figure 4) include 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine (HEPT, **10**),[13a] 4,5,6,7-tetrahydro-5-methylimazo[4,5,1-*jk*][14]benzodiepin-2-(1H)-ones (TIBO) derivatives[13b] **11** pyridinone derivatives **12**,[13c] TSAO derivatives **13**,[13d] delaviridine 1**4**,[13e] nevirapine[14] **15**. Among NNRTIs, TSAO derivatives represent a particular and peculiar group of specific RT inhibitors

that are able to interfere at the interface between the p51 and p66 RT subunits. TSAO was the first sugar derivative found to be specifically inhibit HIV-1 RT. Delaviridine and nevirapine were the first two drugs to be approved under this class. The investigational NNRTI efavirenz **16**[15] holds promise because of potency and possibility for once daily dosing.

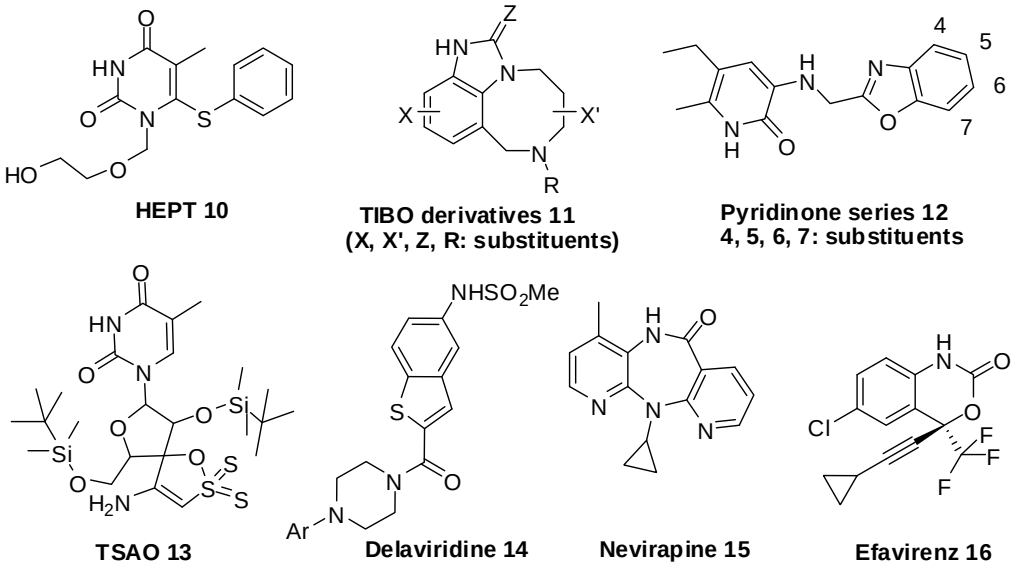
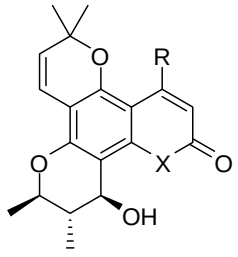


Figure 4

Certain coumarin derivatives isolated form several tropical plants of *Calophyllum species* were recently identified as HIV-1 specific NNRTIs, amongst which (+)-calanolide A **17**, inophyllum B **18** and (+)-cordatolide A **19** are the most potent.[16] Recently, the synthetic analogue aza-calanolide A **20** is also found to be equally active against HIV-1.[17] Since these compounds are active not only against AZT-resistant strains of HIV-1 but also against the pyridinone-resistant strain A-17 they belong to a second generation of HIV-1 specific NNRTIs (Figure 5).



X = O: (+)-Calanolide A (R = n-Propyl) 17

X = O: (+)-Inophyluum B (R = phenyl) 18

X = O: (+)-Cardatolide A (R = methyl) 19

X = NH: (±)-Aza-calanolide A (R = n-propyl) 20

Figure 5

In designing HIV protease inhibitors (PI) which is another class of inhibitors, the transcription state peptidomimetic principle was followed, which means that in the inhibitors the hydrolysable peptide linkage was replaced by non-hydrolysable transition state isostere. Well known examples are saquinavir **21**, norstatine **22**, retonavir **23** (Figure 6).

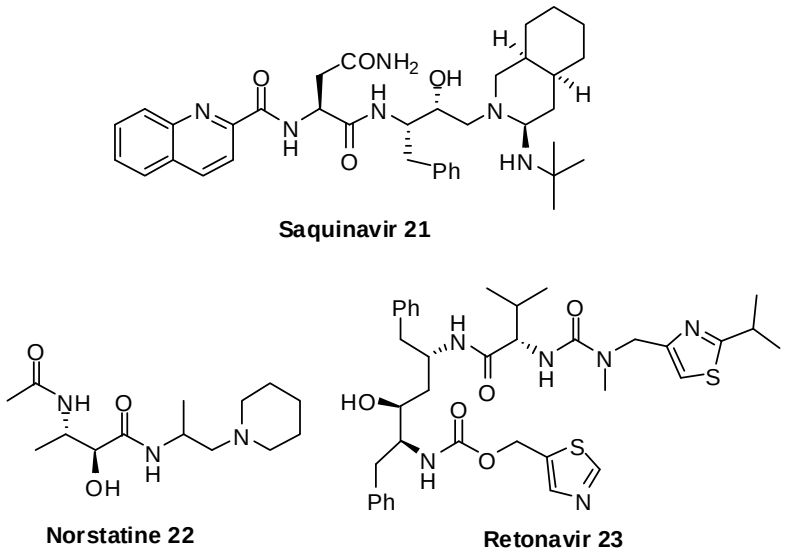


Figure 6

Although highly active antiretroviral therapy (HAART) using a combination of anti-HIV drugs has been very effective in suppressing the HIV load and decreasing mortality in AIDS patients, the emergence of drug resistance among HIV carriers, the unavoidable viral recurrency after drug treatments, and the toxicity of the therapies have made the continued search for novel anti-HIV drugs necessary.[18,19]

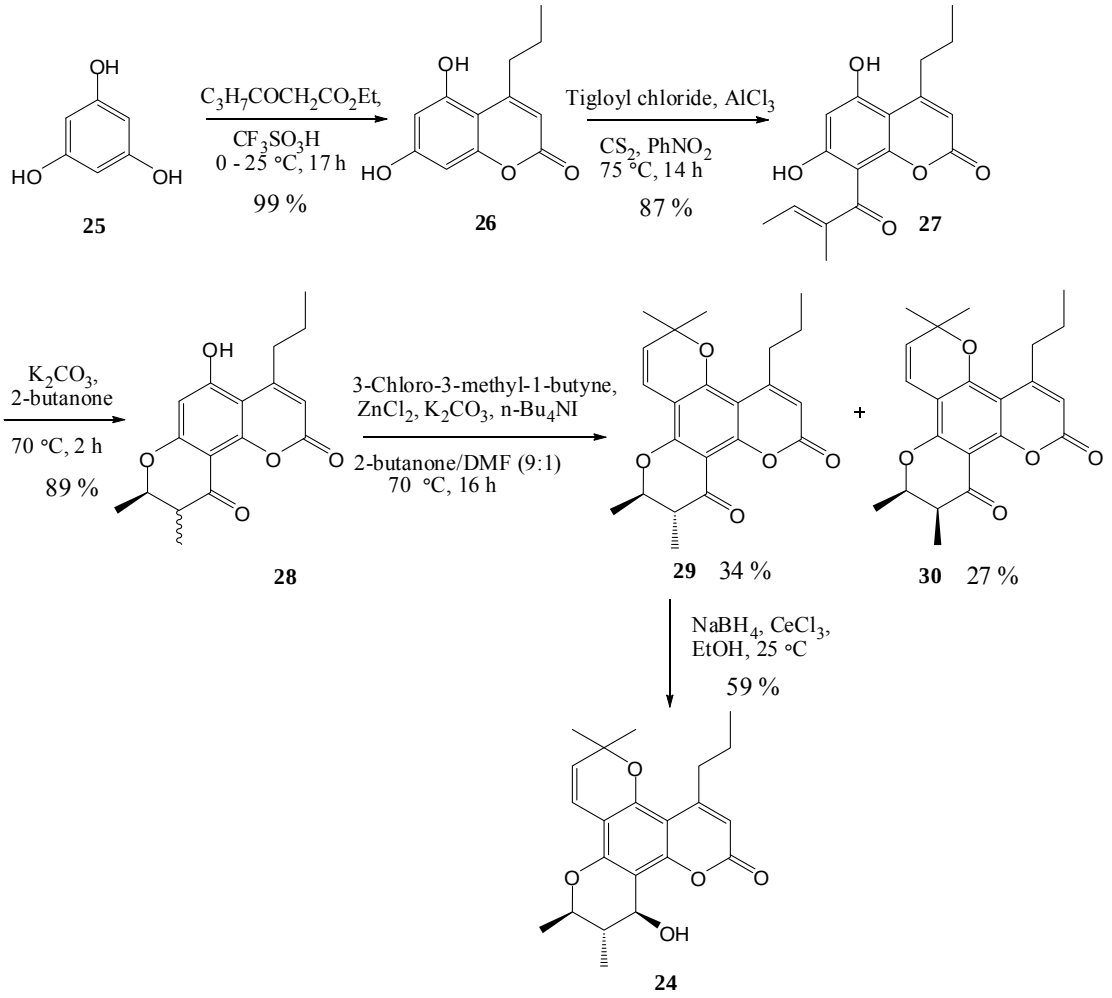
Boyd and co-workers isolated (+)-calanolide A **17**, a non-nucleoside reverse transcriptase inhibitor (NNRTI) along with a few new coumarin derivatives, from *Calophyllum langerum* which showed promising activity against HIV-1 replication and cytopathicity.[16,20] It is also active against many strains of *M. tuberculosis* including those resistant to the standard antitubercular drugs[21] and is demonstrated to be a potent SARS-CoV proteinase inhibitor.[22] Calanolide A has been in clinical testing phase II as anti HIV drug;[23] hence unprecedented interest arose particularly in developing its analogues. So far, most of the analogues were either less potent or devoid of any anti-HIV activity.[17]

1.2. Review of Literature: Synthesis of calanolides

Being an important non-nucleoside reverse transcriptase inhibitor (NNRTI), calanolide A has been synthesized by different groups either in racemic form or as the required (+)-isomer.

Dreyer's approach (1993)[24]

The first synthesis of (±)-calanolide A **24** and the related (±)-calanolide C and D have been achieved by Dreyer and co-workers, starting from phloroglucinol **25**. Pechmann reaction on **25** with ethyl butyrylacetate in the presence of triflic acid afforded coumarin **26**. Acylation of **26** with tigloyl chloride in the presence of $AlCl_3$ led to afford 8-tigloyl coumarin **27**. Cylization of **27** afforded the pyranocoumarin **28**. Chromene ring formation was achieved by treatment with 3-chloro-3-methyl-1-butyne in presence of $ZnCl_2$. The *trans* ketone **29** after reduction afforded (±)-calanolide A **24** (Scheme 1).

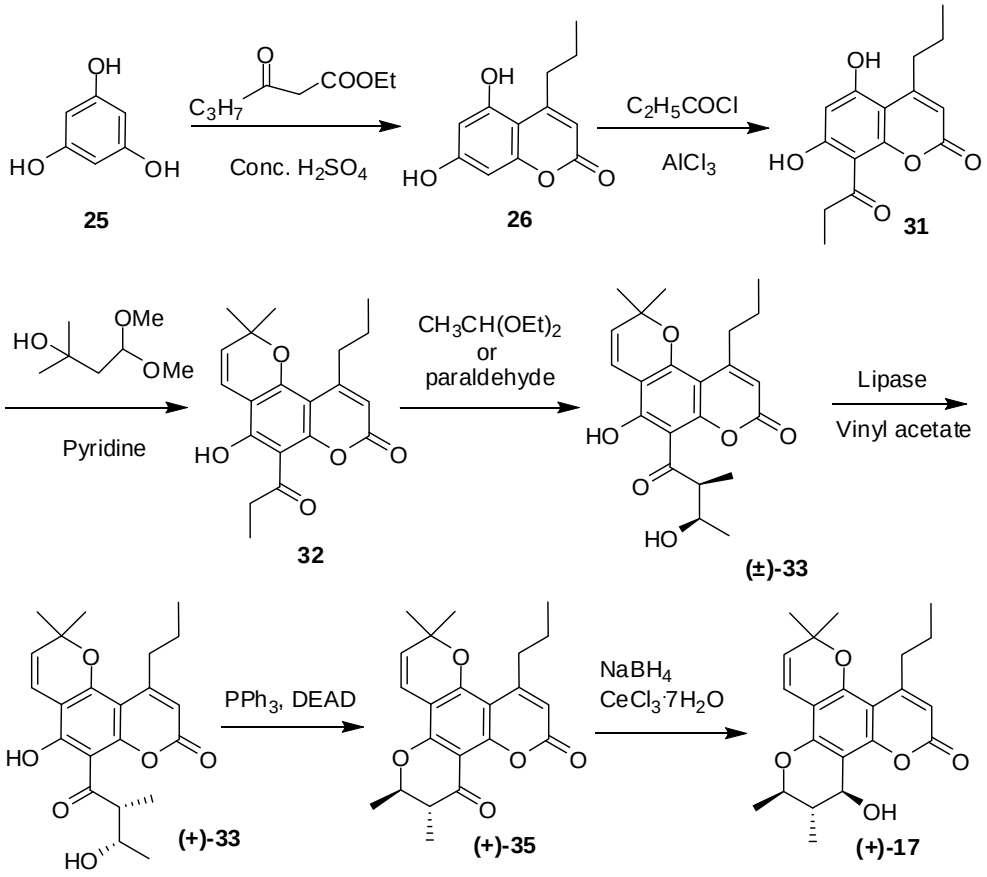


Scheme 1

Khilevich's approach (1995 & 1996)[25]

A. Khilevich and co-workers have synthesized key intermediate **31** in the total synthesis of (+)-calanolide A, starting with phloroglucinol (Scheme 2). Pechmann reaction on phloroglucinol with ethyl butyrylacetate in the presence of concentrated sulfuric acid afforded coumarin **26**. Acylation of coumarin **26** with propionyl chloride in the presence of $AlCl_3$ afforded 8-acylated coumarin **31**. The chromene ring was then introduced upon treatment of the acylated coumarin **31** with 4,4-dimethoxy-2-methylbutan-2-ol in presence of pyridine to provide chromene **32**.

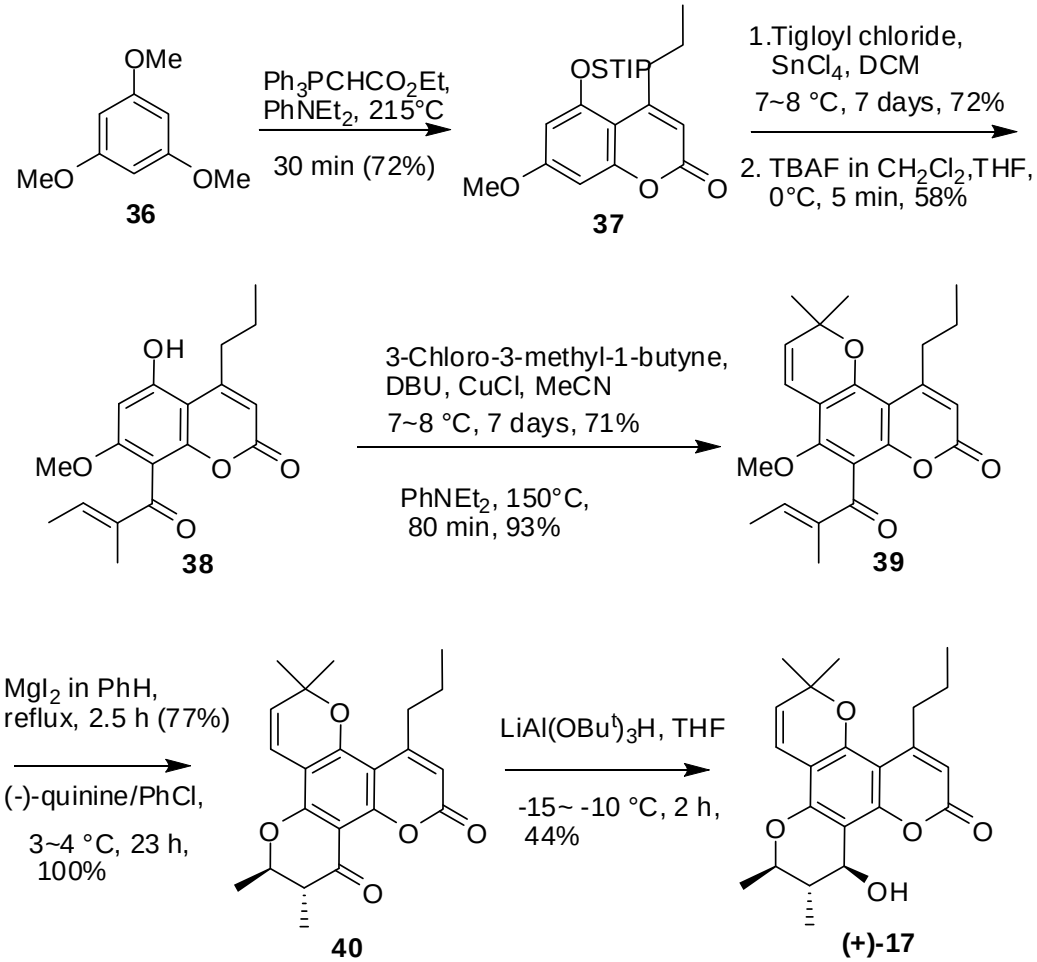
Chromene **32** was further subjected for Aldol reaction with acetaldehyde diethyl acetal or paraldehyde in the presence of trifluoroacetic acid and pyridine or PPTS, affording both *syn* and *anti* β-hydroxy ketones **33** and **34**. Further, they synthesized stereoselectively *syn* (±)-**35** by $TiCl_4$-mediated Aldol reaction of compound **32**. S*yn* (±)-**33** was resolved by a lipase-catalyzed acylation reaction into its enantiomer (+)-**33**. It was then cyclized by Mitsunobu reaction, selectively leading to the formation of the racemic *trans*-chromanone (+)-**35**, which yielded (+)-calanolide A (**17**) after Luche reduction.



Scheme 2

Tanaka's approach (2000)[26]

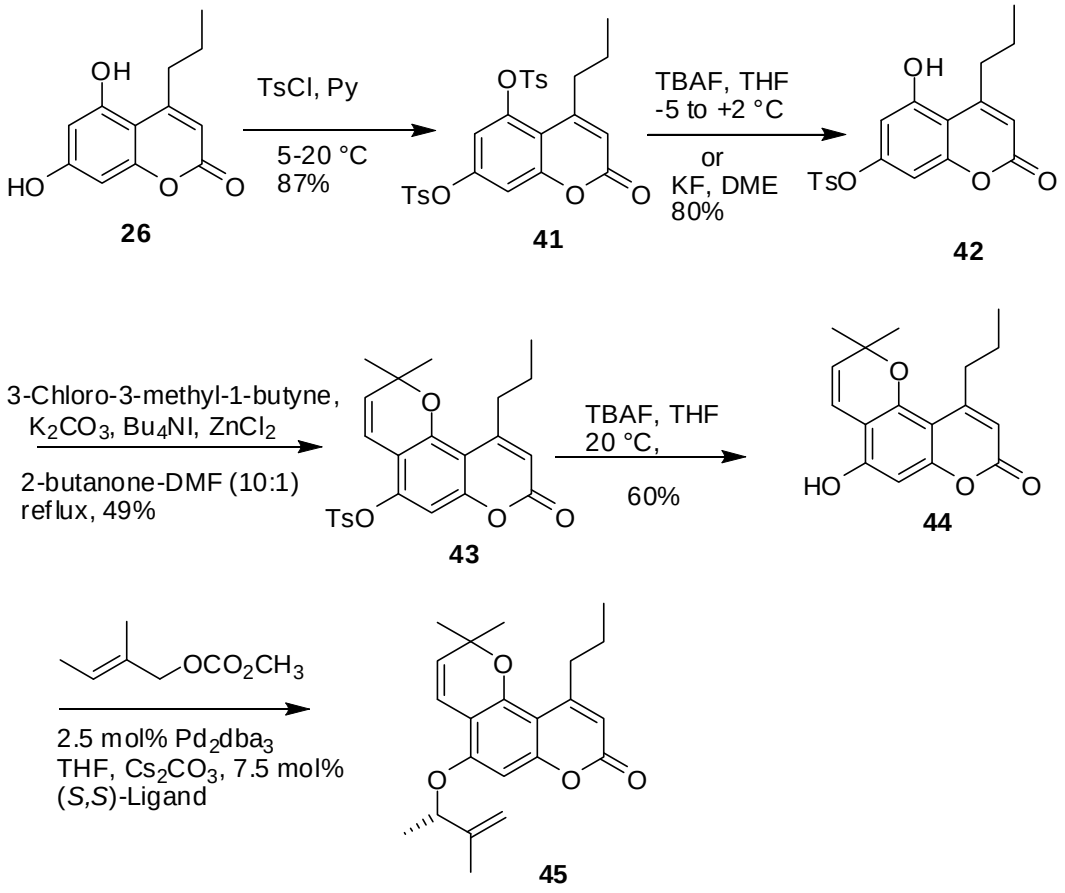
Tanaka *et al.* synthesized (+)-calanolide A using quinine-catalysed asymmetric intramolecular oxo-Michael addition (IMA) reaction. Treatment of butyryl chloride with 1,3,5-trimethoxybenzene **36** and selective demethylation and treatment with carbomethoxymethylenetriphenylphosphorane offered 5,7-dimethoxycoumarin **37**. Regioselective introduction of a tigloyl function into **37** followed by deprotection at C-5 group yielded the 8-tigloyl coumarin derivative **38**. Compound **38** was treated with 3-chloro-3-methyl-1-butyne to obtain chromene ring **39** which on demethylation was subjected to (-)-quinine-catalyzed IMA in chlorobenzene afforded *trans*-(+)-5-methoxychromanone coumarin **40**. Reduction of the enantiomerically rich *trans* **40** with lithium tri(tert-butoxy)aluminum hydride afforded (+)-calanolide A **17** (Scheme 3).



Scheme 3

Fox's approach (2002)[27]

Fox and co-workers readily synthesized ditosylate **41** by the reaction of **26** with tosyl chloride (Scheme 4). Treatment of the ditosylate **41** with tetra-*n* -butylammonium fluoride (TBAF) in THF below room temperature gave selectively the 7-monotosylate **42** (8:1 ratio of regioisomers). The monophenol **42** was converted to the chromene **43** by annulation with 3-chloro-3-methyl-1-butyne. The remaining sulfonyl group was removed with TBAF to give the desired chromene phenol **44.** Asymmetric allylic alkylation of the phenol **44** with tigloyl methyl carbonate gave the intermediate **45** which could be used in the asymmetric synthesis of calanolide A.

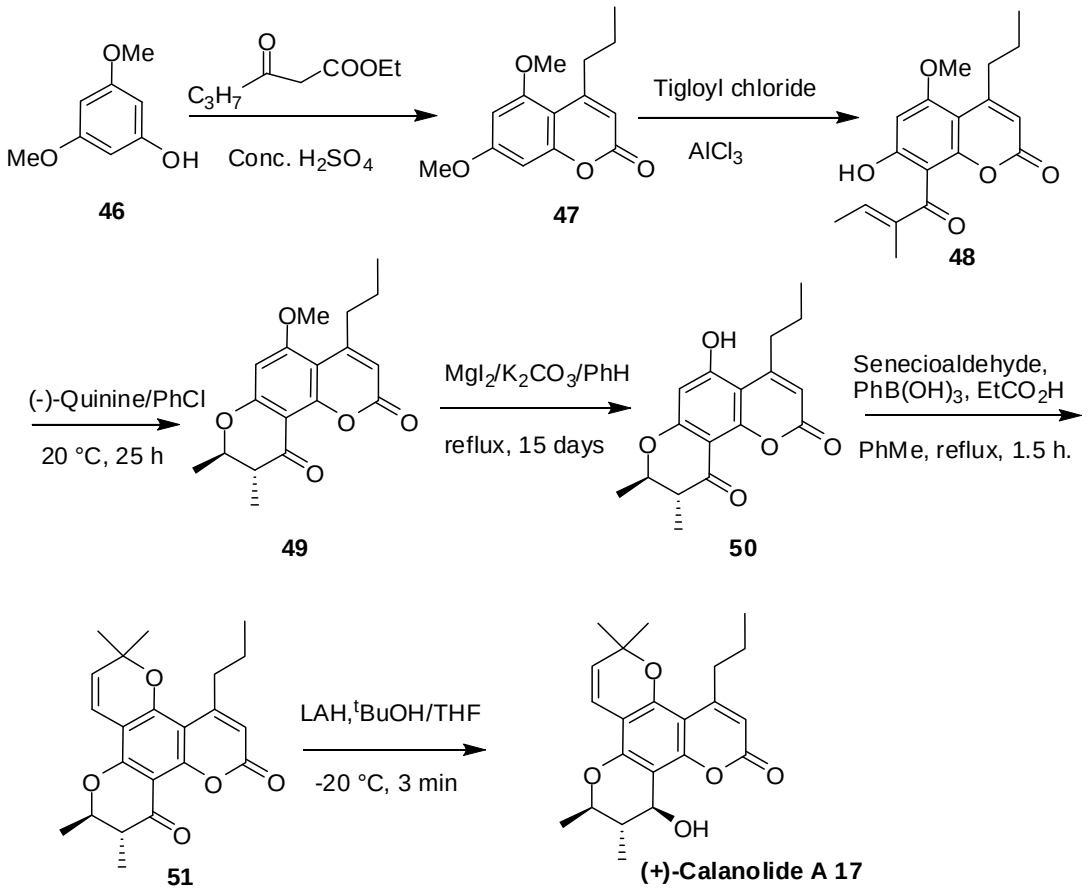


Scheme 4

Sekino's approach (2004)[28]

Etsuko Sekino *et al*. synthesized (+)-calanolide A from dimethoxy phenol **46** (Scheme 5) by (-)-quinine-catalyzed intramolecular oxo-Michael addition (IMA) of 7-hydroxy-5-methoxy-8-tigloylcoumarin **48** to afford enantioselective pyranocoumarin **49** which on demethylation gave **50**. Construction of chromene ring was achieved by

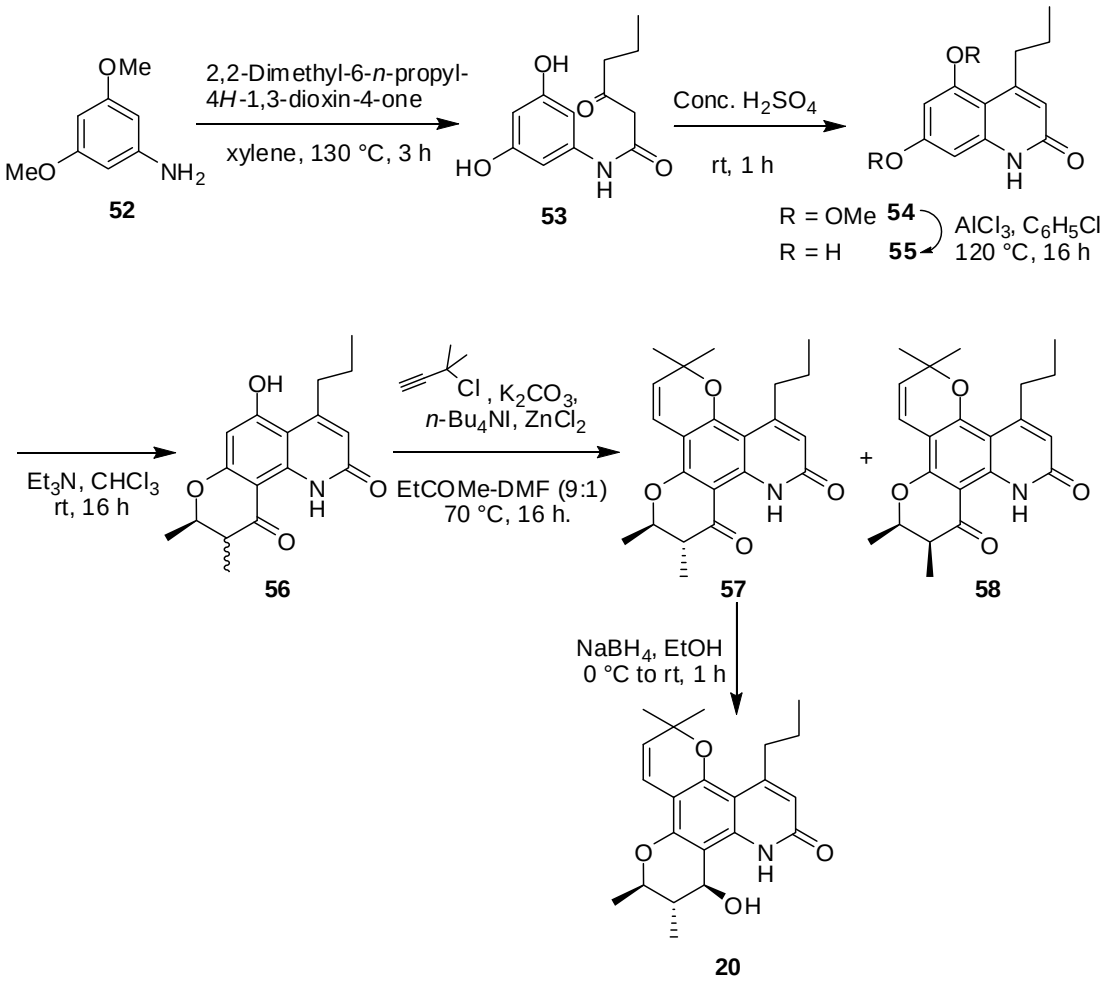
treatment of **50** with senecioaldehyde in presence of borane complex. (+)-Calanolide A **17** was obtained on LAH reduction of ketone **51**.



Scheme 5

Sharma's approach for synthesis of (±)-aza-calanolide A (2003)[17]

Sharma and co-workers synthesized **(**±)-aza-calanolide A **15** by constructing the quinolinone system first and then reacting 3,5-dimethoxyaniline **52** with 2,2-dimethyl-6-*n*-propyl-4*H*-1,3-dioxin-4-one to give the acetanilide intermediate **53** which on subsequent cyclisation afforded **54** (Scheme 6). The didemethylated intermediate **55** was subjected to Friedel-Crafts acylation with tigloyl chloride and further cyclization in Et_3N gave compound **56**. Chromanone **56** was then treated with 3-chloro-3-methyl-1-butyne in 2-butanone–DMF in the presence of K_2CO_3, *n*-Bu_4NI and $ZnCl_2$ to afford a mixture of *trans* and *cis* ketones (**57** and **58**). Reduction of **57** afforded (±)-aza-calanolide A **20**.



Scheme 6

1.3. Present work

The finding as described earlier together with the importance of calanolide A and its analogue aza-calanolide A prompted us to undertake the total synthesis of thia analogue of calanolide A (thia-calanolide A, **59**) by replacing oxygen in ring B with a sulphur atom, which might exhibit better activity. Structure-activity studies could assist in generation of several similar analogues.

The target molecule **59** was visualized as a hexa-substituted aromatic system (ring A) fused on either side with thiocoumarin (ring B), chromene (ring C) and dimethylchromanol (ring D) rings by successive introduction of these three rings on 3,5-dimethoxythiophenol **60** (Figure 7).

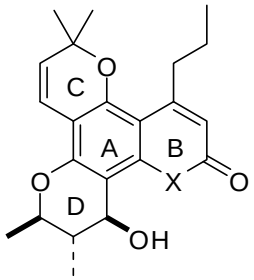
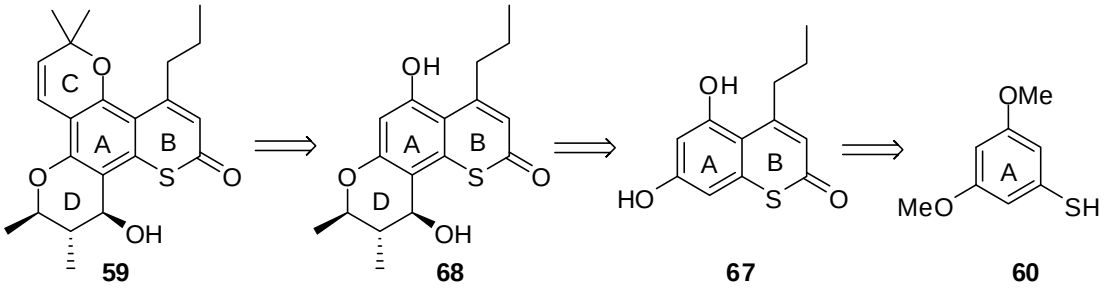


Figure 7: (±)-Thia-calanolide A **59**

Thus an efficient synthetic strategy was designed based on the retro synthetic analysis (Scheme 7). From the retrosynthetic reasoning it was envisaged that the dipyranothiocoumarin **59** could be conveniently made by regiospecific chromene ring (ring C) formation on pyranothiocoumarin **68** which in turn could be made by regioselecive Friedel-Crafts acylation and ring D formation on thiocoumarin **67** with tigloyl chloride and the thiocoumarin derivative **67** itself could be obtained from 3,5-dimethoxy thiophenol **60**.

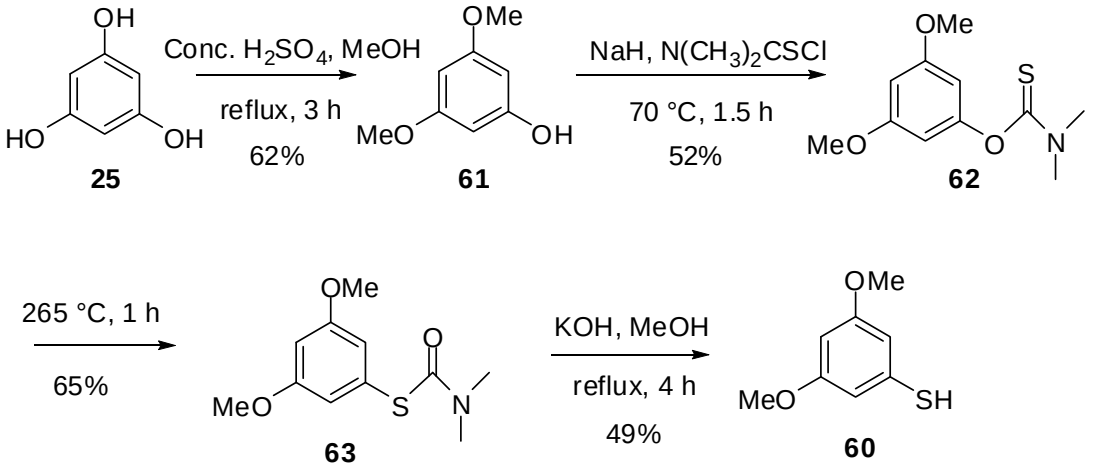


Scheme 7: Retrosynthetic analysis of (±)-thia-calanolide A

1.4. Results and Discussion

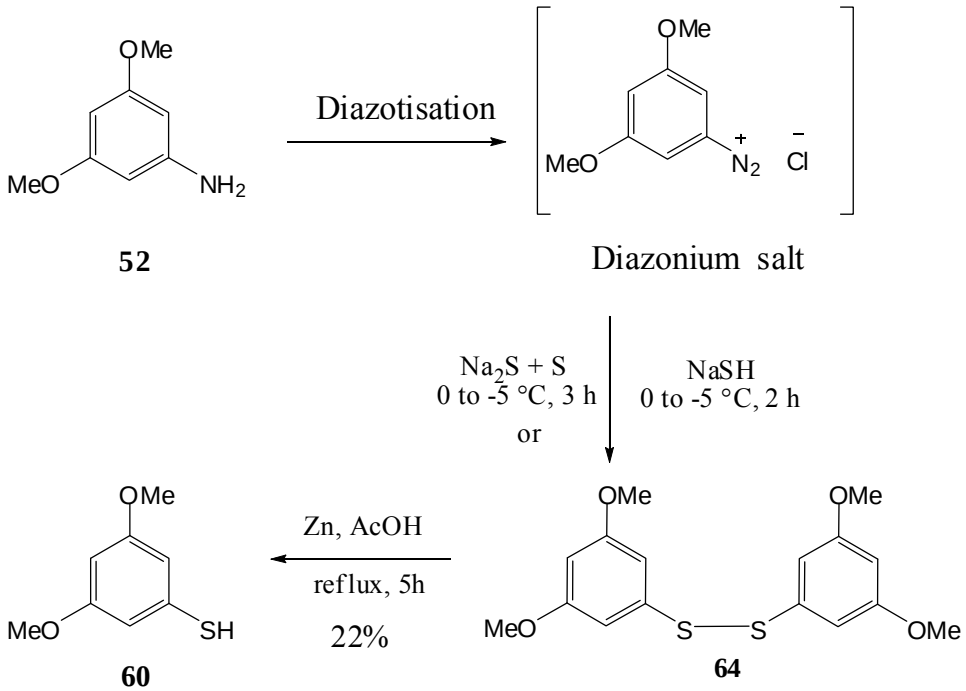
Based on the above synthetic strategy our initial task was to construct thiocoumarin ring on the core of 3,5-dimethoxythiophenol **60**. Thus the required starting material **60** was synthesized from phloroglucinol **25** following literature procedure (Scheme 8).[29a]

Commercially available phloroglucinol **25** was converted to 3,5-dimethoxy phenol **61** which on reaction with N,N-dimethylthiocarbamoylchloride with sodium hydride in DMF gave *O*-3,5-dimethoxyphenyl dimethylcarbamothioate **62**. It was subjected to intramolecular Newmann-Kwart rearrangement on heating at 265 °C to give *S*-3,5-dimethoxyphenyl dimethylcarbamothioate **63** which on hydrolysis with aq. KOH in methanol gave 3,5-dimethoxythiophenol **60**.



Scheme 8

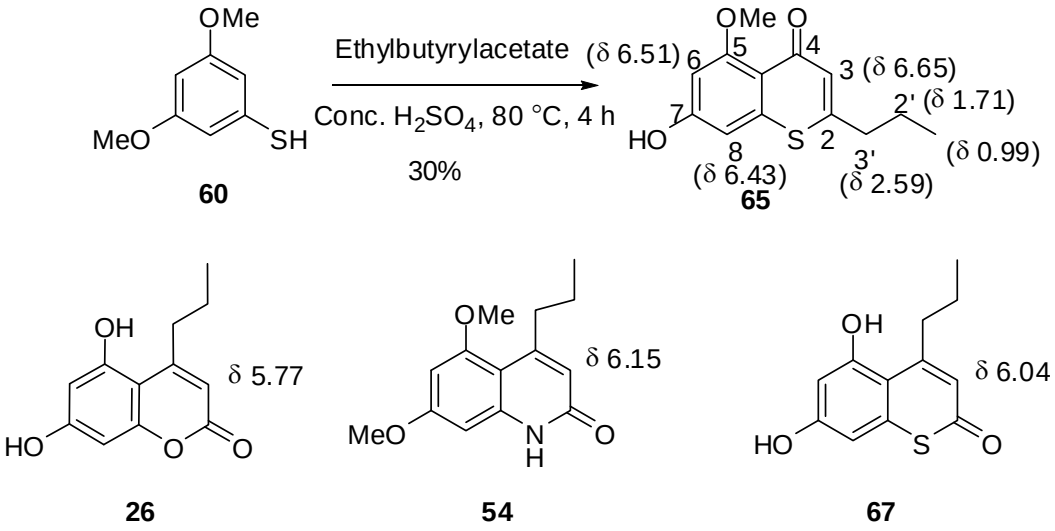
3,5-dimethoxythiophenol **60** was synthesized by an alternate route from 3,5-dimethoxyaniline **52** by diazotisation followed by reaction with Na_2S + S or NaSH.[29b] However, the yield obtained were poor (Scheme 9).



Scheme 9

Thiophenol **60**, thus synthesized, was reacted with ethylbutyrylacetate in presence of conc. sulphuric acid using Pechmann reaction[30] (Scheme 10). However, the product obtained was 7-hydroxy-5-methoxy-2-*n*-propyl-4*H*-thiochromen-4-one **65** instead of required 5,7-dimethoxy-4-*n*-propyl-2*H*-thiochromen-2-one **66**. In ^{1}H NMR spectrum of **65**, the *n*-propyl methyl group appeared at δ 0.99 ppm as it appeared in 5,7-dihydroxy-4-*n*-propyl-2*H*-thiochromene-2-one **67** and 5,7-dimethoxy-4-*n*-propyl-2*H*-azachromene-2-one **54**. But the signals of 2'-CH_2 and 3'-

CH_2 of *n*-propyl group appeared at δ 1.71 (m) and 2.59 (q) ppm whereas in 5,7-dihydroxy-4-*n*-propyl-2*H*-chromene-2-one **26** and **54** they appeared at δ 1.54-1.64 and 2.90 ppm respectively. The olefinic proton in both O-coumarin and N-coumarin appeared at δ 5.77 and 6.15 ppm respectively, but in ^{1}H NMR spectrum of **65** it appeared at lower field at δ 6.65 ppm. The spectrum also showed a methoxy signal at δ 3.84 ppm accounting for 3 protons only. Its mass spectrum showed the expected molecular ion peak at 251 [M+H].



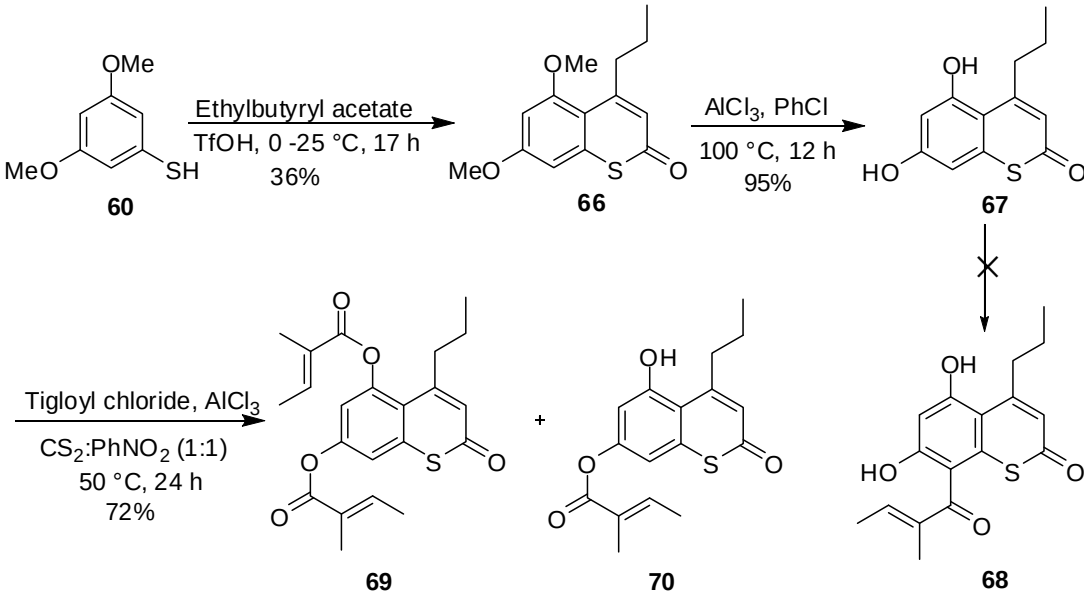
Scheme 10

5,7-Dimethoxythiocoumarin **66** was obtained by a modified Pechmann method[31] using triflic acid instead of conc. H_2SO_4 (Scheme 11). Its ^{1}H NMR spectrum, 2'-CH_2 and 3'-CH_2 of *n*-propyl group appeared at δ 1.58 (m) and 2.90 (q) ppm as expected. Further it showed signal due to C-3 olefinic proton at δ 6.20 ppm and two aromatic protons at δ 6.37 and 6.49 ppm as doublet along with two methoxy singlets at δ 3.82 and 3.86 ppm. The IR spectrum showed absorption at 1670 cm^{-1} for enone carbonyl group and the mass spectrum showed the expected molecular ion peak at 265 [M+H]. 5,7-Dimethoxythiocoumarin **66** was further demethylated by using anhydrous aluminium chloride in chlorobenzene to yield 5,7-dihydroxythiocoumarin **67**. The ^{1}H NMR spectrum of the latter revealed that characteristic signal of dimethoxy group disappeared and two hydroxyl protons appeared at δ 9.70 and 10.02 ppm. Additionally in the IR spectrum characteristic absorption of hydroxyl group at 3159 cm^{-1} was observed.

Having successfully constructed thiocoumarin ring on 3,5-dimethoxy thiophenol **60**, the next task was to introduce dimethyl chomanone ring, which in turn

would lead to dimethyl chromanol ring at later stage of synthesis. Synthesis of the 10,11-dimethyl-chroman-12-one ring has drawn much attention because the *trans-trans*-10,11-dimethyl chroman-12-ol ring in *Calophyllum* coumarins has been suggested to be important for their activity against HIV-RT. The most practical construction of chromanone ring would be through intramolecular Michael addition of 8-tigloyl thiocoumarin. Based on literature procedure[24] it is clearly evident that the 8-tigloyl thiocoumarin could be synthesized in a regioselective manner.

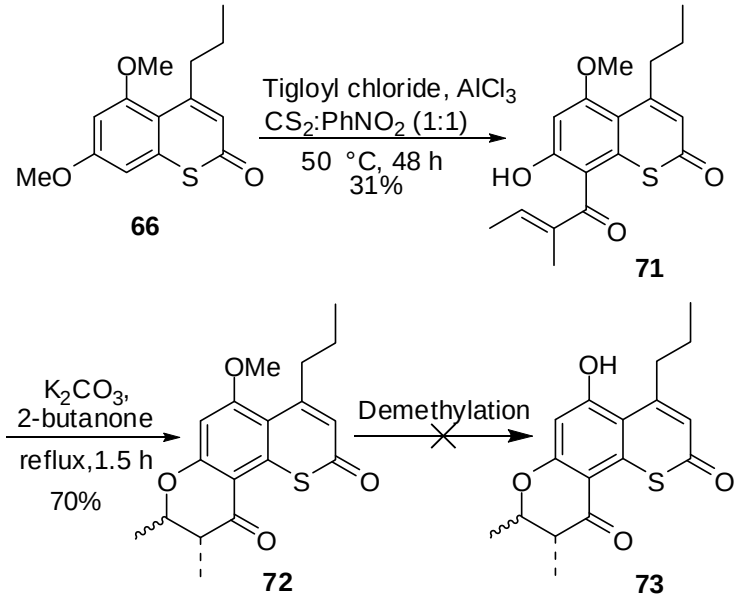
However, Friedel-Crafts acylation[32] of **67** with tigloyl chloride did not proceed under standard condition to yield C-8 tigloyl thiocoumarin **68**. Instead it yielded a 3:1 mixture of 5,7-ditigloyloxy thiacoumarin **69** and 5-hydroxy-7-tigloyloxy thiacoumarin **70** (Scheme 11). In ^{1}H NMR spectrum of **69**, both the aromatic protons resonated at δ 6.89 and 7.22 ppm and phenolic protons were missing, while the newly introduced tigloyl group was confirmed by signals observed in olefin and aliphatic region. Mass spectral analysis confirmed the ditigloyloxy group present in the compound. The compound **70** was confirmed by observing the free phenolic group signal at 3135 cm^{-1} in its IR spectrum. The ^{1}H NMR spectrum revealed all the proton signals at the expected chemical shift values.



Scheme 11

Failure of C-tigloylation necessitated an alternate route (Scheme 12) similar to that reported[27] for calanolide A **17** by constructing ring 'D' on 4-*n*-propyl-5,7-dimethoxythiocoumarin **67**. Thus Friedel-Crafts acylation of **66** with tigloyl chloride yielded the C-tigloyl compound 5-methoxy-7-hydroxy-8-tigloylthiacoumarin **71**. In

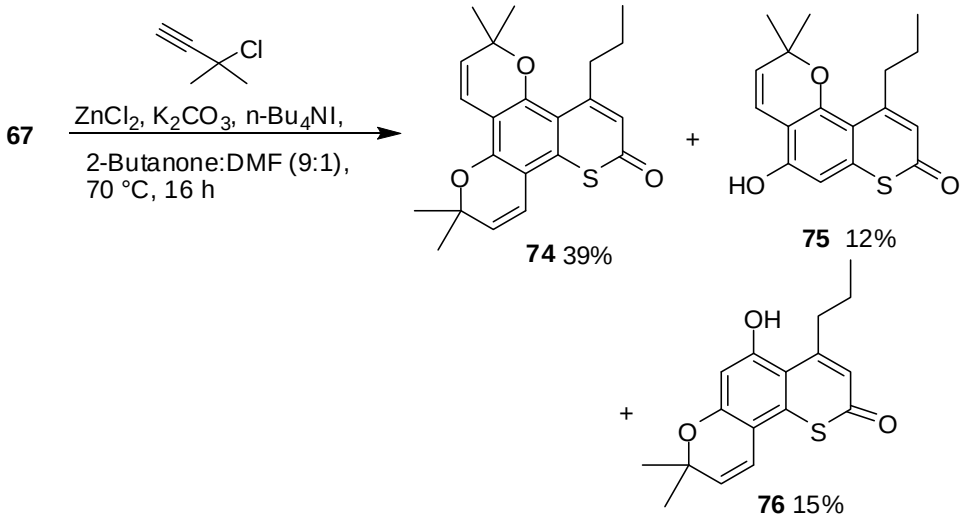
the ^{1}H NMR spectrum of **71** the tigloyl olefinic proton was observed at δ 6.38 ppm as quartet with coupling constant 5.5 Hz and the two methyl group signals, one at δ 1.83 ppm as doublet with coupling constant 5.5 Hz and another at δ 1.96 ppm as singlet were observed. Only one methoxy signal was observed at δ 3.92 ppm. The IR spectrum revealed an absorption at 3058 cm^{-1} due to phenolic group. Further confirmation for the proposed structure was obtained from the molecular ion peak observed in its mass spectrum. Cyclisation of this compound could be effected by treatment of **71** with K_2CO_3 in 2-butanone to yield the dimethyl chromanone **72** as an inseparable *cis-trans* diastereomeric mixture in 1:1 ratio. However, demethylation of **72** did not yield the expected 5-hydroxythiacoumarin **73**. Attempts to demethylate in BBr_3/CH_2Cl_2 at -70 °C,[33] yielded compound **71.** While treatment with BBr_3-SMe_2/CH_2Cl_2 at 0-10 °C,[34] BF_3-Et_2O/CH_2Cl_2,[35] $AlCl_3$/PhCl at 120 °C,[36] HBr/CH_3COOH[37] at room temperature resulted in recovery of the unchanged starting thiocoumarin **72**. Though Tanaka *et al*.[26] could demethylate 5-methoxy group with MgI_2/K_2CO_3/PhH, over 12 days, demethylation of **72** could not occur using same reagents even after 15 days.



Scheme 12

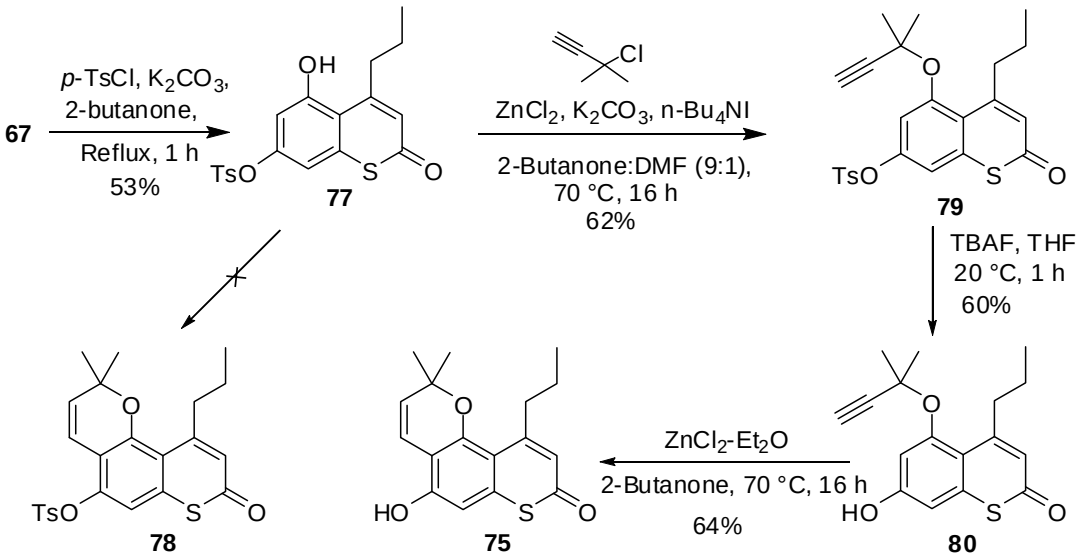
Alternately, attempt to construct the 'C' ring on **67** was resorted to. Thus, treatment of **67** with 3-chloro-3-methyl-1-butyne in presence of zinc chloride, potassium carbonate and tetrabutylammonium iodide in a mixture of 2-butanone, dimethylformamide and diethyl ether at 70 °C gave a complex mixture of not only expected 2,2-dimethylchromenethiacoumarin **75** but also other monochromene **76** and

a dichromenecoumarin **74** (Scheme 13). Hence, this route was not elaborated further.



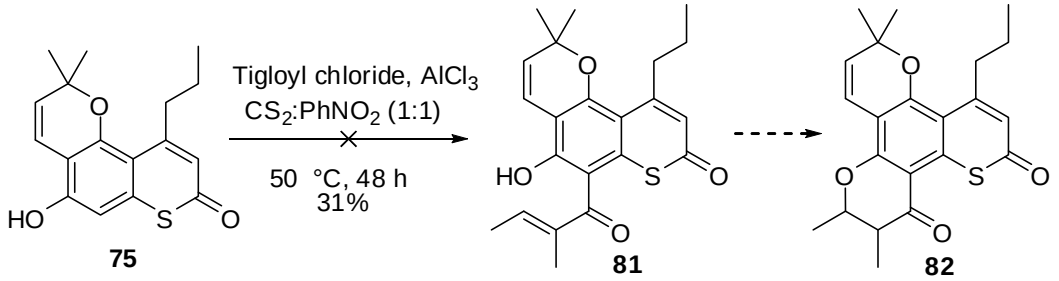
Scheme 13

Complexity of the mixture and poor yield of **75** prompted us first to protect 7-hydroxy group and then construct ring C as reported by Fox *et al.*[27] Thus, 7-tosyl-5-hydroxy thiacoumarin **77** was synthesized by treatment of **67** with *p*-toluenesulfonyl chloride in 2-butanone in presence of K_2CO_3 as per literature.[38] Further treatment of **77** with 3-chloro-3-methyl-1-butyne did not give the expected Claisen rearrangement product **78** but resulted in 1,1-dimethylpropargyl ether **79** at C-5 hydroxy group even after prolonged treatment at 70 °C. In ^{1}H NMR spectrum of **79,** the gem dimethyl protons resonated at δ 1.72 ppm as singlet, acetylenic proton appeared at δ 3.69 ppm and both C-6 and C-8 protons were seen intact at their expected chemical shift. In IR spectrum characteristic acetylenic group signal was observed at 3310 and 2136 cm^{-1}. Probably, presence of bulky tosyl group at C-7 hindered Claisen rearrangement, hence detosylation of **79** was carried out by treating it with tetrabutylammonium fluoride at 20 °C to yield 5-(1,1-dimethylproparlgyloxy)-7-hydroxy thiacoumarin **80**. The latter was cyclised using $ZnCl_2$ in ether to obtain the required 2,2-dimethylchromene compound **75** (Scheme 14).



Scheme 14

Friedel-Crafts acylation of **75** at C-8 with tigloyl chloride to yield tigloyl derivative **81** was the next logical step, which then could be cyclized to the required dihydrobenzothiopyranone **82**. However, tigloylation could not be achieved under standard reaction conditions (Scheme 15).



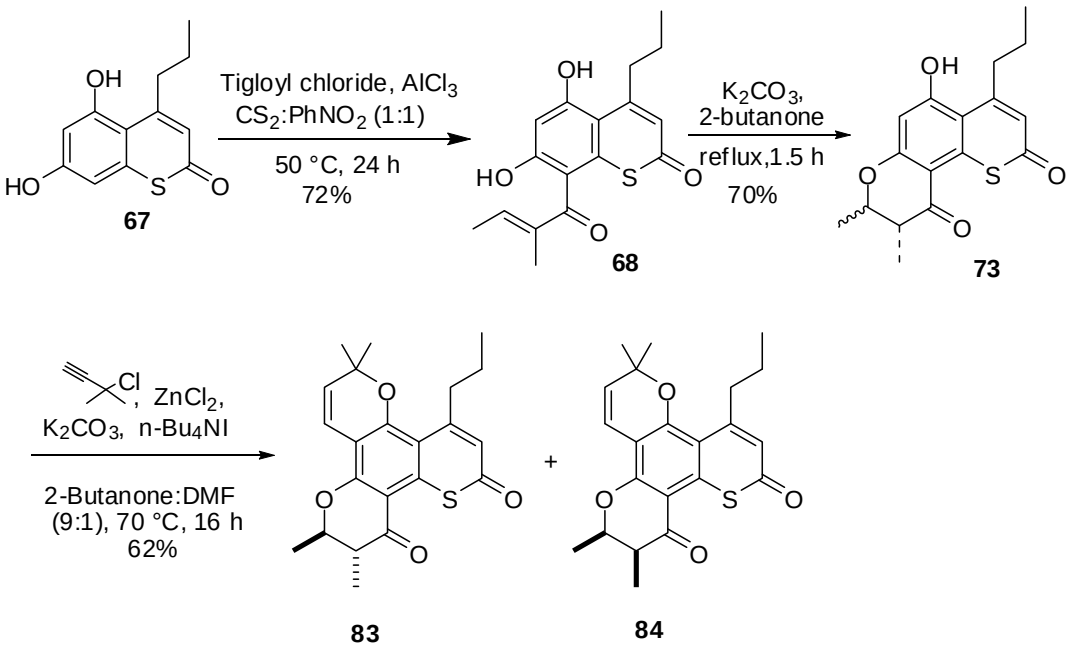
Scheme 15

Failure to achieve the target compound **59** with all the attempted routes as described above, prompted us to study the key Friedel-Crafts reaction under several other solvent ratios. Successful tigloylation of **67** was effected with CS_2-$PhNO_2$ (7:3) as the solvent, resulting in the formation of **68.** The regioselectivity of acylation was indicated from the ^{1}H NMR spectrum of **68**, where the resonance due to H-8 in compound **67** at δ 6.15-6.30 ppm disappeared. The two methyl signals due to tigloyl group appeared as a doublet and a singlet at δ 1.84 and 1.87 ppm respectively. The latter on cyclization with K_2CO_3 yielded the desired 2,3-dimethyldihydrobenzopyranones **73** as an unseparable 1:1 epimeric mixture. Further it was observed from ^{1}H NMR spectrum of **73** that H-8 proton resonated at δ 4.20-4.35

ppm and as well as δ 4.60-4.70 ppm. The signal which appeared at δ 4.20-4.40 ppm was a multiplet having coupling constants 6.6 Hz and 11.4 Hz for *trans* relationship. Similarly signal at δ 4.60-4.70 ppm was a multiplet having coupling constants 3.5 Hz and 6.5 Hz indicative of *cis* relationship of H-8 with adjacent H-9. H-9 was observed at δ 2.52-2.7 ppm as a multiplet, which confirmed the formation of chromonone ring system. Mass spectrum further confirmed its molecular weight.

Having successfully incorporated chromanone ring regioselectively, next part of the synthetic strategy was to introduce chromene ring on **73**. There has long been an interest in the chemistry of 2*H*-chromene as consequences of their widespread natural occurrences. These compounds can be obtained through a multistep sequence from chromanones, involving Kabbe's synthesis or thermal cyclisation of propargyl ethers. Alternatively, chromene ring was also constructed using reagents like trifluoroacetyl ester of 2-methyl-3-butyn-2-ol, 4,4-dimethoxy-2-methyl butan-2-ol, 3-chloro-3-methyhl-1-butyne.

In the present study chromene ring was constructed on **73** essentially by adopting procedure developed by Dreyer *et al*.[24] Thus, reaction of compound **73** with 3-chloro-3-methyhl-1-butyne in 9:1 mixture of 2-butanone-DMF in presence of K_2CO_3, *n*-Bu_4NI and $ZnCl_2$ at 70 °C afforded a diastereomeric mixture of *trans* and *cis* ketones **83** and **84** in a 1.8:1 ratio, which were conveniently separated by column chromatography (Silica gel, 200 mesh, pet-ether-EtOAc, 9:1) to afford **83** and **84** in 42 % combined yield (Scheme 16). In the ^{1}H NMR spectrum of *trans* ketone **83**, the chromene ring methyls resonated at δ 1.58 ppm as singlet and the newly introduced olefinic protons H-7 and H-8 resonated at δ 5.64 and 6.67 ppm respectively as doublets, whereas the chromanone ring methyl groups at C-10 and C-11 appeared as doublets at δ 1.53 ppm (J = 6.5 Hz) and δ 1.22 ppm (J = 6.9 Hz) respectively. H-10 proton resonated at δ 4.20-4.35 ppm as a multiplet with coupling constant 6.3 and 11.5 Hz indicating a *trans* relationship with H-11 proton. *Cis* ketone **84** in its ^{1}H NMR spectrum showed gem dimethyl protons as singlets at δ 1.56 and 1.58 ppm, H-7 and H-8 olefinic protons at δ 5.65 and 6.69 ppm respectively while H-10 resonated at δ 4.68-4.73 ppm as a multiplet with coupling constant 2.9 and 6.6 Hz indicative of a *cis* relationship with H-11.



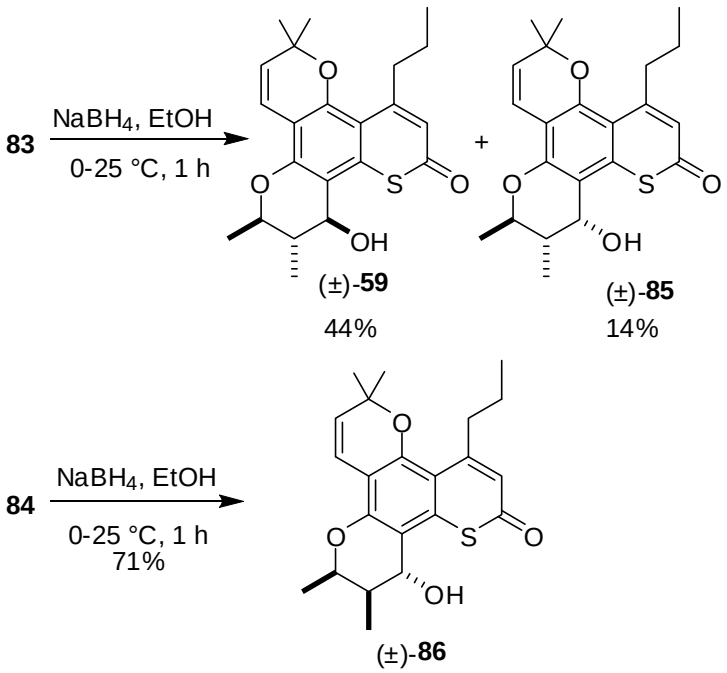
Scheme 16

Both the ketones **83** and **84** were separately reduced with $NaBH_4$ (Scheme 17). Reduction of ketone **83** with sodium borohydride gave stereoisomers (±)-thia-calanolide A **59** and (±)-thia-calanolide B **85**. In the ^{1}H NMR of **59**, H-12 proton resonated at δ 4.56 ppm as a doublet with J = 8.3 Hz indicating the *trans* relationship with the adjacent H-11 proton. H-10 proton resonated at δ 3.95-4.09 ppm as a quintet with J = 6.6 and 13.1 Hz indicating a *trans* relationship with H-11 proton, showing that the two methyl groups and hydroxyl group are *trans* to each other. Rest of the protons resonated at the expected chemical shifts.

In ^{1}H NMR of **85**, H-12 proton resonated at δ 4.56 ppm as a doublet with J = 3.1 Hz indicating the *cis* relationship with the adjacent H-11 proton. H-10 proton resonated at δ 3.85-4.04 ppm as a multiplet with J = 6.2 and 10.5 Hz indicating a *trans* relationship with H-11 proton; it means the C-11 methyl group and hydroxy group at C-12 are *cis* to each other and both methyl groups are *trans* to each other. Rest of the protons resonated at the expected chemical shifts.

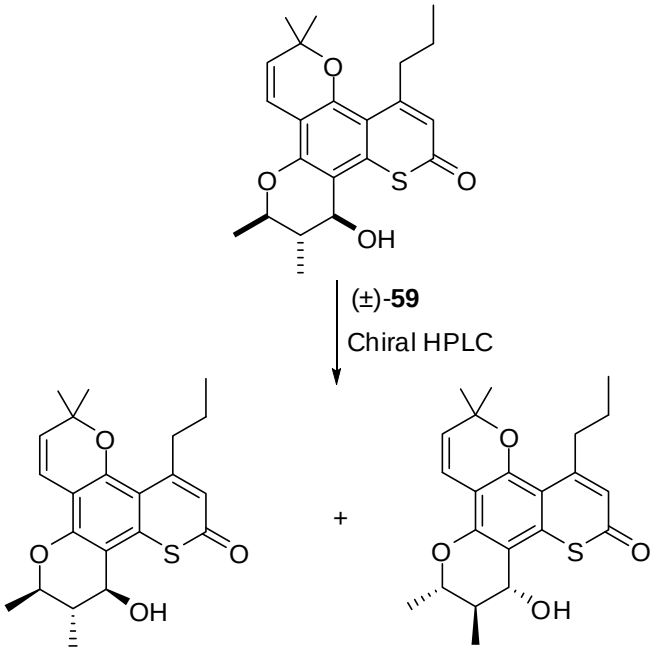
Similarly, *cis* ketone **84** was subjected to $NaBH_4$ reduction to afford only one product (±)-thia-calanolide C **86**. The structure of compound **86** was established by spectroscopic data. In ^{1}H NMR of **86**, H-12 proton resonated at δ 5.64 ppm as a doublet with J = 9.5 Hz indicating the *trans* relationship with the adjacent H-11 proton. H-10 resonated at δ 4.23-4.32 ppm as a multiplet with coupling constant of J = 2.2 and 6.6 Hz indicative of a *cis* relationship with H-11 proton indicating both

methyl groups are placed *cis* to each other and hydroxyl group are placed *trans* to H-11 methyl group. Rest of the protons resonated at the expected chemical shifts.



Scheme 17

(±)-Thia-calanolide A **59** was resolved by preparative chiral HPLC (Chiralcel (OD), 9:1 hexane-isopropanol, 1 mL/min) to afford both isomers having optical rotation $[\alpha]_D$ +54.3° (*c* 0.5, $CHCl_3$) and $[\alpha]_D$ -49.8° (*c* 0.3, $CHCl_3$) (Scheme 18).



Scheme 18

Anti-HIV activity assays:

Compound (±)-**59** was evaluated for anti-HIV reverse transcriptase activity by following HIV-1 p24 antigen capture ELISA (Perkin Elmer NEN) as per manufacturer's protocol. Briefly, CEM cells were infected with HIV-1 NL4.3 isolate for 4 hours in presence of Poltbrene in complete medium. The infected cells were kept for 7-10 days in culture before the supernatant was used for HIV-1 p24 antigen capture. The percentage inhibition of virus production was calculated based on p24 values of untreated control. The inhibition data obtained from p24 values (350) revealed that (±)-**59** is a weak inhibitor (28%) compared to synthetic (±)-**24** (99.7%).

1.5. Conclusion

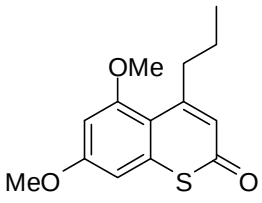
The first total synthesis of (±)-thia-calanolide **59**, has been successfully accomplished. During its biological evaluation it was found to be less active as compared to natural product calanolide A **17** and synthetic aza-calanolide A **20**. Perhaps, the bulkier molecule could have contributed to the retarded activity. Further work on synthesis of related analogues of thia-calanolide with simplified structures are in progress.

Attempts to modify thia-calanolide to synthesise several analogues with modified groups are underway for example, *n*-propyl at the C-4 could be substituted with methyl, phenyl, isobutyl groups etc and the double bond in the dimethyl chromene ring could be selectively reduced. All these compounds when synthesised will be evaluated for their activity.

In this manner, structurally modified diverse compounds can be synthesised with possibility of generating a chemical library in the thia-calanolide series. This work could also compliment results of a recent publication[39] wherein it was found that modifications in C-ring may lead to promising drug candidates against HIV-1.

1.6. Experimental

5,7-Dimethoxy-4-*n*-propyl-2*H*-thiochromen-2-one (66):



A mixture containing 3,5-dimethoxythiophenol (**60**, 0.540 g, 3.17 mmol) and ethylbutyrylacetate (0.527 g, 3.3 mmol) was added dropwise to cold (5 °C) trifluoromethanesulfonic acid (0.55 mL, 6.34 mmol) over a 10 min period and the reaction mixture was warmed to 25 °C and stirred for 17 h. After quenching with ice water (10 mL) the mixture was extracted with EtOAc (3 X 10 mL). The combined organic layer was washed with brine (2 X 10 mL), dried (Na_2SO_4) and concentrated. The crude semi-solid product was subjected to chromatographic purification to give **66** as lemon yellow crystals (0.301 g, 36%), m.p. 110-112 °C.

Mol. Formula : $C_{14}H_{16}O_3S$

Mol. Weight : 264

FT IR ($CHCl_3$) : 3016, 2965, 1630, 1593 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) : δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.58 (m, 2H), 2.90 (t, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 6.20 (s, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 6.49 (d, *J* = 2.5 Hz, 1H)

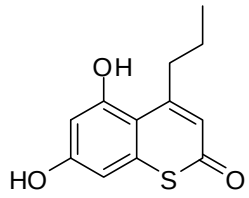
^{13}C NMR (75 MHz, $CDCl_3$) : δ 14.1, 24.0, 41.8, 55.5, 55.6, 98.2, 101.8, 111.5, 122.7, 142.4, 156.9, 160.7, 160.8, 184.1

ESI-MS *m/z* : 265.17 $[M+H]^+$

Elemental Analysis : Calcd: C, 63.61; H, 6.10; S, 12.13 %

Found: C, 63.61; H, 6.21; S, 11.97 %

5,7-Dihydroxy-4-*n*-propyl-2*H*-thiochromen-2-one (67):



To a stirred solution containing (**66,** 1 g, 3.78 mmol) in chlorobenzene (10 mL), anhydrous $AlCl_3$ (2.5 g, 1.89 mmol) was added in portions over a period of 15 min. The stirred reaction mixture was heated at 100 ^oC for 12 h. It was then cooled to room temperature and poured over crushed ice (20 g) and stirred for 30 min. The precipitated solid was filtered, washed with water (50 mL) till the washing are neutral and then washed with hexane (5 mL), vacuum drying gave **67 (**0.849 g, 95%) a**s** a dark brown solid m.p. 230-235 ^oC (decomp.). This product **67** was used as such for the next step.

Mol. Formula **:** $C_{12}H_{12}O_3S$

Mol. Weight **:** 236

FT IR ($CHCl_3$) **:** 3159, 1600 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) **:** δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.60 (m, 2H), 2.97 (t, *J* = 7.3 Hz, 2H), 6.04 (s, 1H), 6.39 (s, 2H), 9.70 (s, 1H), 10.02 (s, 1H)

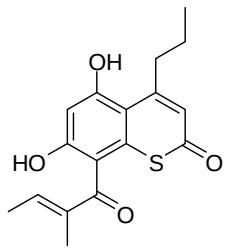
^{13}C NMR (75 MHz, DMSO-d_6) **:** δ 14.0, 24.0, 40.7, 102.6, 104.4, 108.2 ,120.3, 140.9, 158.1, 159.7, 159.9, 182.6

ESI-MS *m/z* **:** 237.32 $[M+H]^+$

Elemental Analysis **:** Calcd: C, 61.00; H, 5.12; S, 13.57 %

Found: C, 60.75; H, 4.98; S, 13.38 %

5,7-Dihydroxy-8-(2-methyl but-2-enoyl)-4-*n*-propyl-2*H*-thiochromen-2-one (68):



A mixture containing (**67**, 0.5 g, 2.11 mmol), anhydrous $AlCl_3$ (1.4 g, 10.59 mmol) and CS_2 (7 mL) was heated at 50 °C with stirring for 30 min. Nitrobenzene (2 mL) was added dropwise and stirred for additional 30 min. to get a homogeneous mixture. Tigloyl chloride (0.262 g, 2.21 mmol) in nitrobenzene (1 mL) was added dropwise to the reaction mixture and stirred at 50 °C for 24 h. The reaction

mixture was cooled to room temperature and quenched with crushed ice and dil. HCl before extracting with EtOAc (3 X 30 mL). The combined organic layer was washed with brine (3 X 20 mL), dried (Na_2SO_4) and evaporated. The residue obtained was purified by column chromatography on silica gel to furnish **68** (0.437 g, 65%) as a brown solid m.p. 162-164 °C.

Mol. Formula : $C_{17}H_{18}O_4S$

Mol. Weight : 318

FT IR ($CHCl_3$) : 3263, 3019, 1720, 1610 cm^{-1}

^{1}H NMR (200 MHz, DMSO-d_6) : δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.62 (m, 2H), 1.84 (d, *J* = 7.0 Hz, 3H), 1.87 (s, 3H), 3.04 (t, *J* = 7.5 Hz, 2H), 6.17 (s, 1H), 6.49 (q, J = 7.0 Hz, 1H), 6.64 (s, 1H), 10.69 (s, 1H), 11.03 (s, 1H)

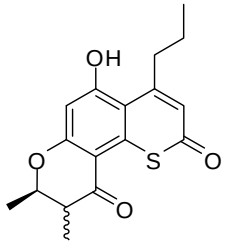
^{13}C NMR (50 MHz, DMSO-d_6) : δ 10.5, 14.0, 14.9, 24.1, 41.1, 102.1, 107.9, 117.4, 120.1, 137.9, 138.1, 142.4, 156.7, 158.4, 159.9, 181.6, 196.2

ESI-MS *m/z* : 319.31$[M+H]^+$

Elemental Analysis : Calcd: C, 64.13; H, 5.70; S, 10.07 %

Found: C, 63.41; H, 5.58; S, 9.83 %

5-Hydroxy-8,9-dimethyl-4-*n*-propyl-8,9-dihydrothiopyrano[2,3-*f*]chromene-2,10-dione (73):



Anhydrous K_2CO_3 (0.520 g, 3.77 mmol) was added to a solution containing (**68**, 0.4 g, 1.25 mmol) in 2-butanone (5 mL), and the mixture was refluxed for 1.5 h. It was then cooled to room temperature, acidified (2 pH) with dil. HCl and extracted with EtOAc (3 X 20 mL). The combined organic layer was washed with brine (3 X 10 mL), dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel column to give a 1:1 mixture of isomeric chromanones 7**3** (0.360 g, 90%) as white solid, m.p. 243-245 °C. This product **73** was used as such for the next step.

Mol. Formula : $C_{17}H_{18}O_4S$

Mol. Weight : 318

FT IR (Nujol) : 3130, 3020, 1621 cm^{-1}

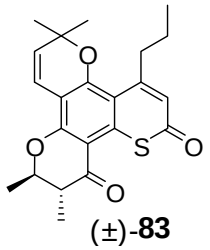
ESI-MS *m/z* : 319.24 $[M+H]^+$

Elemental Analysis : Calcd: C, 64.13; H, 5.70; S, 10.07 %

Found: C, 63.86; H, 5.72; S, 9.85 %

6,7-Dihydro-2*H*-1,5-dioxa-12-*n*-propyl-2,2,6,7-tetramethyl-9-thia-triphenylene-8,10-dione (83 *trans* and 84 *cis*):

Anhydrous K_2CO_3 (0.65 g, 4.71 mmol), 3-chloro-3-methyl-1-butyne (0.8 g, 7.85 mmol) and *n*-Bu_4NI (0.49 g, 1.22 mmol) were added successively to a stirred solution of **73** (0.5 g, 1.57 mmol) in 2-butanone:DMF (10 mL, 9:1 mixture) at room temperature. The reaction mixture was heated at 60 °C for 1 h and $ZnCl_2$ (0.278 g, 2.04 mmol) was added. The reaction mixture was further heated to 70 °C for 20 h. It was cooled to room temperature and quenched with saturated aq. solution of NH_4Cl (3 mL) and extracted with EtOAc (2 X 30 mL). The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4) and evaporated. The residue obtained was purified by column chromatography on silica gel (230-400 mesh). The initial fractions afforded (±)-**83** (0.132 g, 22%) as a white solid m.p.143-144 °C.



(±)-**83**

Mol. Formula : $C_{22}H_{24}O_4S$

Mol. Weight : 384

FT IR ($CHCl_3$) : 1670, 1627, 1201 cm^{-1}

^{1}H NMR : δ 1.01 (t, *J* = 7.2 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.53

(200 MHz, $CDCl_3$) (d, *J* = 6.5 Hz, 3H), 1.58 (s, 6H), 1.67 (m, 2H), 2.54-2.63 (m, *J* = 6.8, 11.5 Hz, 1H), 2.98 (t, *J* = 7.2 Hz, 2H), 4.20-4.35 (dq, *J* = 6.3, 11.5 Hz, 1H), 5.64 (d, *J* = 10.1 Hz, 1H), 6.37 (s, 1H), 6.67 (d, *J* = 10.1 Hz, 1H)

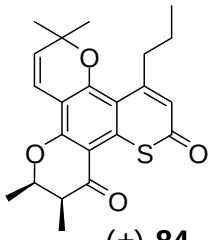
^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 10.2, 13.9, 19.5, 24.2, 27.7, 28.1, 42.0, 46.5, 78.8, 79.4, 107.5, 109.0, 112.9, 115.8, 123.9, 128.0, 143.9, 156.0, 158.3, 158.8, 186.3, 192.5

ESI-MS *m/z* **:** 385,09 $[M+H]^+$

Elemental Analysis **:** Calcd: C, 68.72; H, 6.29; S, 8.34 %

Found: C, 68.36; H, 6.32; S, 8.19 %

Further elution afforded (±)-thia-calanolide D (±)-**84** (0.072 g, 12%) as a syrup.



(±)-**84**

Mol. Formula **:** $C_{22}H_{24}O_4S$

Mol. Weight **:** 384

FT IR ($CHCl_3$) **:** 1670, 1627, 1201 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) **:** δ 1.02 (t, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 7.3 Hz, 3H), 1.43 (d, *J* = 5.8 Hz, 3H), 1.56 (s, 6H), 1.64 (m, 2H), 2.70-2.75 (m, *J* = 3.6, 7.3 Hz, 1H), 2.96 (t, *J* = 7.2 Hz, 2H), 4.70 (m, *J* = 2.9, 6.6 Hz, 1H), 5.65 (d, *J* = 9.5 Hz, 1H), 6.39 (d, 1H), 6.69 (d, *J* = 9.5 Hz, 1H)

^{13}C NMR **:** δ 10.4, 13.9, 19.5, 24.3, 27.9, 28.2, 42.0, 46.7, 77.7, 78.9, 79.4, 96.1, 107.5, 116.0, 124.1, 127.9, 144.4, 155.7,

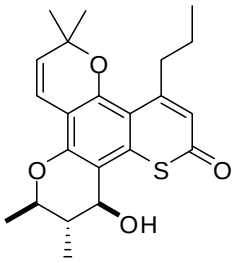
(75 MHz, $CDCl_3$) 158.1, 158.8, 186.0, 192.1

ESI-MS *m/z* **:** 385.09 $[M+H]^+$

Elemental Analysis **:** Calcd: C, 68.72; H, 6.29; S, 8.34 %

Found: C, 68.88; H, 6.33; S, 8.29 %

(±)-6,7-Dihydro-*2H*-1,5-dioxa-8-hydroxy-12-*n*-propyl-2,2,6,7-tetramethyl-9-thia-triphenylene-10-one (59, 85):



To a solution of (±)-**83** (20 mg, 0.052 mmol) in EtOH (2 mL) at 0 °C, $NaBH_4$ (3 mg, 0.083 mmol) was added and the reaction temperature was allowed to rise to room temperature over a period of 1 h. After completion of reaction 2-3 drops of water were added and the reaction mixture was extracted with EtOAc (3 X 3 mL), combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated. The residue obtained was purified through flash column chromatography to give (±)-thia-calanolide A (±)-**59** (0.009 g, 44%) as a white solid m.p. 158-160 °C..

Mol. Formula **:** $C_{22}H_{26}O_4S$

Mol. Weight **:** 386

FT IR ($CHCl_3$) **:** 3400, 1619, 1215 cm^{-1}

^{1}H NMR **:** δ 1.01 (t, *J* = 7.3 Hz, 3H), 1.12 (d, *J* = 7 Hz, 3H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.52 (s, 6H), 1.57-1.71 (m, 2H), 1.99-2.09 (sextet, *J* = 6,13.4 Hz, 1H), 2.86-3.16 (dq, 2H), 3.95-4.09 (quintet, *J* = 6.6, 13.1 Hz, 1H), 4.54-4.57 (d, *J* = 8.3 Hz, 1H), 5.58-5.63 (d, *J* = 9.9 Hz, 1H,), 6.3 (s, 1H), 6.64-6.69 (d, *J* = 9.9 Hz, 1H)

(200 MHz, $CDCl_3$)

^{13}C NMR **:** δ 14.0, 15.9, 19.2, 24.5, 27.5, 27.9, 41.7, 42.1, 68.2, 77.8, 108.9, 112.0, 112.7, 116.8, 122.5, 128.0, 140.9, 151.5, 153.3, 157.9, 183.6

(75 MHz, $CDCl_3$)

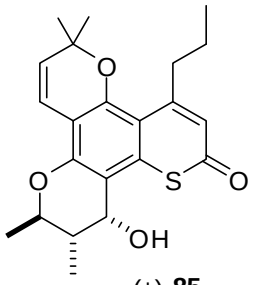
^{13}C NMR (75 MHz, Acetone-d_6) **:** δ 14.1, 15.5, 19.3, 25.2, 27.3, 27.8, 42.4, 43.2, 68.6, 77.3, 78.4, 109.2, 112.1, 114.6, 117.2, 122.9, 128.9, 142.1, 153.2, 153.6, 157.5, 183.8

ESI-MS *m/z* **:** 387.09 $[M+H]^+$

Elemental Analysis **:** Calcd: C, 68.37; H, 6.78; S, 8.30 %

Found: C, 68.51; H, 6.82; S, 8.03 %

The column chromatography was continued further to afford (±)-thiacalanolide B (±)-**85** (0.003 g, 14%) as a white solid m.p. 156-158 °C.



(±)-**85**

Mol. Formula **:** $C_{22}H_{26}O_4S$

Mol. Weight **:** 386

FT IR ($CHCl_3$) **:** 3400, 1621, 1533, 1122 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 1.03 (t, *J* = 7.2 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.41 (d, *J* = 6.3 Hz, 3H), 1.49 (s, 6H), 1.6-1.7 (m, 2H), 2.27-2.35 (m, *J* = 5.8,12.7 Hz, 1H), 2.89-3.13 (m, 2H), 4-45-4.53 (m, *J* = 6.8, 13.7 Hz, 1H), 4.81-4.83 (d, *J* = 6 Hz, 1H), 5.60-5.64 (d, *J* = 9.8 Hz, 1H), 6.31 (s, 1H), 6.68-6.71 (d, *J* = 9.8 Hz, 1H).

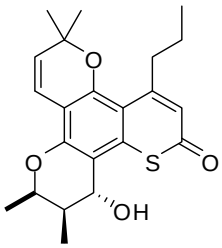
^{13}C NMR (75 MHz, $CDCl_3$) **:** δ 14.0, 15.9, 19.2, 24.5, 27.5, 27.9, 41.7, 42.1, 68.2, 77.8, 108.9, 112.0, 112.7, 116.8, 122.5, 128.0, 140.9, 151.5, 153.3, 157.9, 183.6

ESI-MS *m/z* **:** 387.09 $[M+H]^+$

Elemental Analysis **:** Calcd: C, 68.37; H, 6.78; S, 8.30 %

Found: C, 68.62; H, 6.87; S, 8.03 %

(±)-6,7-Dihydro-2*H*-1,5-dioxa-8-hydroxy-12-*n*-propyl-2,2,6,7-tetramethyl-9-thia-triphenylene-10-one (86):



$NaBH_4$ (9 mg, 0.26 mmol) was added to a solution of **84** (50 mg, 0.13 mmol) in EtOH (5 mL) at 0 °C under stirring and the temperature was allowed to rise to 30 °C and stirred further for 1 h. After completion of reaction ice water (1 mL) was added and the reaction mixture was extracted with EtOAc (3 X 5 mL). The combined organic layer was washed with brine (5 mL), dried (Na_2SO_4) and evaporated to dryness. The residue obtained was purified through flash column chromatography on silica gel (230-400 mesh) to give (±)-**86** (0.036 g, 71%) as a white solidm.p. 167-168 °C.

Mol. Formula **:** $C_{22}H_{26}O_4S$

Mol. Weight **:** 386

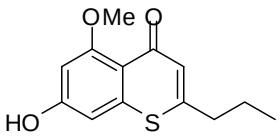
FT IR ($CHCl_3$) **:** 3400, 1619, 1201cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) **:** δ 1.01 (t, *J* = 7.3 Hz, 3H), 1.21 (d, *J* = 7.3 Hz, 3H), 1.53 (d, *J* = 6.5 Hz, 3H), 1.55 (s, 3H), 1.58 (s, 6H), 1.63-1.71 (m, 2H), 2.57-2.66 (m, 1H), 2.94-3.98 (m, 2H), 4.23-4.32 (m, *J* = 2.2, 6.6 Hz, 1H), 4.78-4.80 (d, *J* = 3.6 Hz, 1H), 5.64-5.69 (d, *J* = 9.5 Hz, 1H), 6.37 (d, 1H), 6.67-6.72 (d, *J* = 9.5 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$) **:** δ 14.0, 15.9, 19.2, 24.5, 27.5, 27.9, 41.7, 42.1, 68.2, 77.8, 108.9, 112.0, 112.7, 116.8, 122.5, 128.0, 140.9, 151.5, 153.3, 157.9, 183.6

ESI-MS *m/z* **:** 387.14 $[M+H]^+$

7-Hydroxy-5-methoxy-2-propyl-4*H*-thiochromen-4-one (65):



To a cold (10 °C) mixture of **60** (510 mg, 3 mmol) and ethylbutyrylacetate (519 mg, 3.3 mmol), cold (10 °C) conc. sulphuric acid (2 mL) was added and the mixture was heated at 80 °C with stirring for 4 h. The reaction mixture was diluted with ice water and extracted with ethylacetate (3 X 5 mL). Combined organic layers were washed with brine (2 X 10 mL), dried (Na_2SO_4) and concentrated. The residue was subjected to chromatographic purification to give 4-coumarin derivative **65** (0.225 g, 30%).

Mol. Formula : $C_{13}H_{14}O_3S$

Mol. Weight : 250

ESI-MS *m/z* : 273 $[M+Na]^+$

FT IR ($CHCl_3$) : 3018, 1626, 1581 cm^{-1}

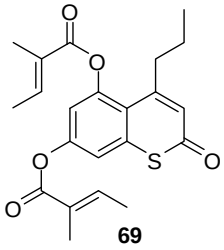
Elemental Analysis : Calcd: C, 62.38; H, 5.64; S, 12.81 %

Found: C, 62.25; H, 5.92; S, 13.01 %

^{1}H NMR (300 MHz, $CDCl_3$) : δ 0.99 (t, *J* = 7.3 Hz, 3H), 1.71 (m, 2H), 2.59 (t, *J* = 7.3 Hz, 2H), 3.84 (s, 3H), 6.43 (d, *J* = 2.5 Hz, 1H), 6.51 (d, *J* = 2.5 Hz, 1H), 6.65 (s, 1H)

MP : 128-130 °C

Compound 69 & 70:



69

A mixture containing (**67**, 0.5 g, 2.11 mmol), $AlCl_3$ (1.4 g, 10.59 mmol) and CS_2 (7 mL) was heated at 50 °C while stirring for 30 min. $PhNO_2$ (5 mL) was added dropwise and stirred for additional 30 min. to get a homogeneous mixture. Tigloyl chloride (0.262 g, 2.21 mmol) in $PhNO_2$ (2 mL) was added dropwise to the reaction mixture and stirred at 50 °C for 24 h. The reaction mixture was cooled to room temperature and quenched with crushed ice and dil. HCl before extracting with EtOAc (3 X 30 mL). The combined organic layer was washed with

brine (3 X 20 mL), dried (Na_2SO_4) and evaporated. The residue obtained was illution with hexane:EtOAc (19:1) column chromatography on silica gel to furnished 2-oxo-4-propyl-2H-thiochromene-5,7-diyl bis(2-methylbut-2-enoate) **69** as a solid m.p. 254-257 °C.

Mol. Formula : $C_{22}H_{24}O_5S$

Mol. Weight : 400

FT IR ($CHCl_3$) : 3018, 1626, 1581 cm^{-1}

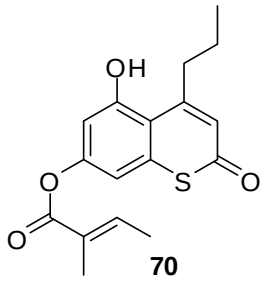
^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.62 (sextet, 2H), 1.93 (d, *J* = 5.5 Hz, 3H), 1.97 (d, *J* = 5.5 Hz, 3H), 2.83 (t, *J* = 7.3 Hz, 2H), 6.44 (s, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 7.15 (q, *J* = 5.5 Hz, 2H), 7.22 (d, *J* = 2.4 Hz, 1H)

ESI-MS *m/z* : 401.08 $[M+H]^+$

Elemental Analysis : Calcd: C, 65.98; H, 6.04; S, 8.01 %

Found: C, 65.71; H, 6.24; S, 7.94 %

Further elution afforded 5-hydroxy-2-oxo-4-propyl-2H-thiochromen-7-yl 2-methylbut-2-enoate **70** as a solid m.p. 224-227 °C.



70

Mol. Formula : $C_{17}H_{18}O_4S$

Mol. Weight : 318

FT IR ($CHCl_3$) : 3018, 1626, 1581 cm^{-1}

^{1}H NMR : δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.52 (sextet, 2H), 1.96 (d, *J* =

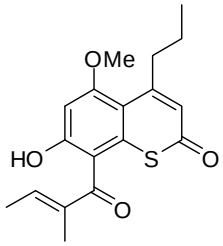
(200 MHz, $CDCl_3$) 5.5 Hz, 3H), 2.92 (t, *J* = 7.3 Hz, 2H), 6.34 (s, 1H), 6.61(s, 1H), 6.79 (s, 1H), 7.18 (q, *J* = 5.5 Hz, 1H), 8.67 (s, 1H)

ESI-MS *m/z* **:** 318.16 $[M+H]^+$

Elemental Analysis **:** Calcd: C, 64.13; H, 5.70; S, 10.07 %

Found: C, 64.02; H, 5.95; S, 10.19 %

7-Hydroxy-5-methoxy-8-(2-methylbut-2-enoyl)-4-*n*-propyl-2*H*-thiochromen-2-one (71):



A mixture of **66** (0.5 g, 1.89 mmol), $AlCl_3$ (1.26 g, 9.45 mmol) and CS_2 (7 mL) was heated at 50 °C while stirring for 30 min. Nitrobenzene (5 mL) was added dropwise and stirred for additional 30 min. to get a homogeneous mixture. Tigloyl chloride (0.268 g, 2.27 mmol) in nitrobenzene (2 mL) was added dropwise to the reaction mixture and stirred at 50 °C for 24 h. The reaction mixture was cooled to room temperature and quenched with crushed ice, dil. HCl before extracting with EtOAc (3 X 30 mL). The combined organic layers were washed with brine (3 X 20 mL), dried (Na_2SO_4) and evaporated. The residue obtained was purified by column chromatography on silica gel to furnish **71** (0.332 g, 53%) as a brown solid m.p. 210-212 °C.

Mol. Formula **:** $C_{18}H_{20}O_4S$

Mol. Weight **:** 332

FT IR ($CHCl_3$) **:** 3058, 1626, 1581 cm^{-1}

^{1}H NMR **:** δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.60 (sextet, *J* =7.2 Hz, 2H), 1.83 (d, *J* = 5.5 Hz, 3H), 1.96 (s, 3H), 2.93 (t, *J* =7.2 Hz, 2H), 3.92 (s, 3H), 6.24 (s, 1H), 6.38 (q, *J* = 5.5 Hz, 1H), 6.47 (s, 1H)

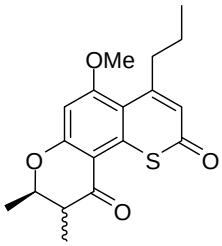
($CDCl_3$, 300 MHz)

ESI-MS *m/z* **:** 333.17 $[M+H]^+$

Elemental Analysis **:** Calcd: C, 65.04; H, 6.06; S, 9.65 %

Found: C, 64.89; H, 6.17; S, 9.84 %

5-Methoxy-8,9-dimethyl-4-*n*-propyl-8,9-dihydrothiopyrano[2,3-*f*]chromene-2,10-dione (72)



To a solution containing (**71**, 0.4 g, 1.20 mmol) in 2-butanone (5 mL), K_2CO_3 (0.498 g, 3.60 mmol) was added and the reaction mixture was refluxed for 1.5 h. It was cooled to room temperature, acidified (2 pH) with dil. HCl and extracted with EtOAc (3 X 20 mL). Combined organic layers were washed with brine (3 X 10 mL), dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel column to give a 1:1 mixture of isomeric chromanones **72** (0.280 g, 70%) as white solid m.p. 310-315 °C (decomp.).

Mol. Formula : $C_{18}H_{20}O_4S$

Mol. Weight : 332

FT IR ($CHCl_3$) : 3018, 1626, 1581 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.52 (d, *J* = 6.4 Hz, 3H), 1.50 (sextet, *J* =7.3, 2H), 2.58 (q, *J* = 6.8 Hz, 1H), 2.93 (t, *J* = 7.3 Hz, 2H), 3.96 (s, 3H), 4.24 (q, *J* = 6.4 Hz, 1H), 6.36 (s, 1H), 6.42 (s, 1H)

ESI-MS *m/z* : 333.19 $[M+H]^+$

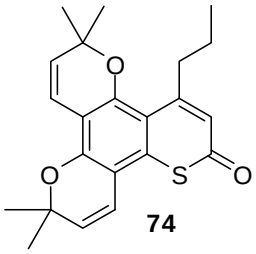
Elemental Analysis : Calcd: C, 65.04; H, 6.06; S, 9.65 %

Found: C, 64.92; H, 6.23; S, 9.51 %

Compound 74, 75 & 76:

To a stirred solution of **67** (0.275 g, 1.16 mmol) in mixture of 2-butanone-DMF (10 mL, 9:1) at room temperature, K_2CO_3 (0.317 g, 2.29 mmol), 3-chloro-3-methyl-1-butyne (0.239 g, 2.33 mmol), *n*-Bu_4NI (0.420 g, 1.16 mmol) were added successively. The reaction mixture was heated at 60 °C for 1 h, and $ZnCl_2$ (0.205 g, 1.50 mmol) was added .The reaction mixture was further heated to 70 °C for 20 h. It was cooled to room temperature and quenched with saturated aq. solution of NH_4Cl (3 mL), extracted with EtOAc (2 X 30 mL). The combined organic layers were

washed with brine (20 mL), dried (Na_2SO_4) and evaporated. The residue obtained was purified through column chromatography on silica gel (230-400 mesh) first to afforded Compound **74**.



74

Mol. Formula : $C_{22}H_{24}O_3S$

Mol. Weight : : 368

FT IR ($CHCl_3$) : 1619, 1581, 1260 cm^{-1}

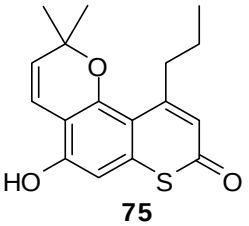
^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.02 (t, *J* = 7.3 Hz, 3H), 1.46 (s, 6H), 1.51 (s, 6H), 1.69 (m, 2H), 2.96 (t, *J* = 7.3 Hz, 3H), 5.68 (d, *J* = 9.9 Hz, 2H), 6.25 (s, 1H), 6.70 (d, *J* = 9.9 Hz, 2H)

ESI-MS *m/z* : 369.08 $[M+H]^+$

Elemental Analysis : Calcd: C, 71.71; H, 6.56; S, 8.70 %

Found: C, 71.58; H, 6.74; S, 8.66 %

Further elution afforded 5-Hydroxy-2,2-dimethyl-10-propylthiopyrano[2,3-*h*]chromen-8(2*H*)-one **75,**



75

Mol. Formula : $C_{17}H_{18}O_3S$

Mol. Weight : 302

FT IR ($CHCl_3$) **:** 3145, 3027, 1626, 1581, 1201 cm^{-1}

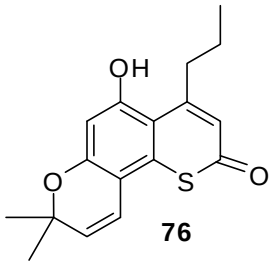
^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 0.77 (t, *J* = 7.3 Hz, 3H), 1.21 (s, 6H), 1.42 (m, 2H), 2.82 (t, *J* = 7.3 Hz, 3H), 5.38 (d, *J* = 10.1, Hz, 1H), 5.97 (s, 1H), 6.21 (s, 1H), 6.31 (d, *J* = 10.1 Hz, 1H)

ESI-MS *m/z* **:** 303.05 $[M+H]^+$

Elemental Analysis **:** Calcd: C, 67.52; H, 6.00; S, 10.60 %

Found: C, 67.32; H, 6.24; S, 10.46 %

and 5-Hydroxy-8,8-dimethyl-4-propylthiopyrano[2,3-*f*]chromen-2(8*H*)-one **(76)**



76

Mol. Formula **:** $C_{17}H_{18}O_3S$

Mol. Weight **:** 302

FT IR ($CHCl_3$) **:** 3130, 3024, 1621, 1579, 1201 cm^{-1}

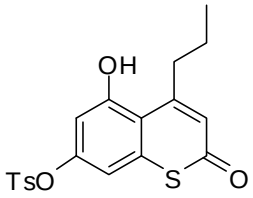
^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 0.87 (t, *J* = 7.3 Hz, 3H), 1.36 (s, 6H), 1.50 (m, 2H), 2.84 (t, *J* = 7.3 Hz, 3H), 5.43 (d, *J* = 10.1 Hz, 1H), 6.03 (s, 1H), 6.39 (s, 1H), 6.51 (d, *J* = 10.1 Hz, 1H)

ESI-MS *m/z* **:** 303.16 $[M+H]^+$

Elemental Analysis **:** Calcd: C, 67.52; H, 6.00; S, 10.60 %

Found: C, 67.39; H, 6.18; S, 10.39 %

5-Hydroxy-2-oxo-4-propyl-2*H*-thiochromen-7-yl-4-methylbenzenesulfonate (77):

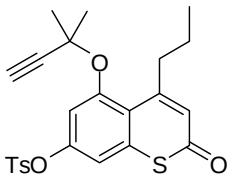


A mixture containing coumarin (**67**, 2 g, 0.01 mmol), *p*-toluensulphonyl chloride (2 g, 0.0104 mmol), acetone (50 mL) and K_2CO_3 (6 g) was refluxed for 12 hours. After removal of acetone, the solid was treated with 5% NaOH solution. The insoluble ditosyl derivative was filtered. The filtrate containing monotosyl derivative on acidification with dil. HCl was extracted with EtOAc (3 X 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and evaporated to afford **77** (2.24 g, 68%).

Mol. Formula	**:**	$C_{19}H_{18}O_5S_2$
Mol. Weight	**:**	390
FT IR ($CHCl_3$)	**:**	3018, 1626, 1581 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.52 (sextet, *J* = 7.3, 2H), 2.37 (s, 3H), 2.92 (t, *J* = 7.3 Hz, 2H), 6.20 (s, 1H), 6.31 (d, *J* =2.3 Hz, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H)
ESI-MS *m/z*	**:**	391.15 $[M+H]^+$
Elemental Analysis	**:**	Calcd: C, 58.44; H, 4.65; S, 16.42 % Found: C, 58.32; H, 4.79; S, 16.30 %

5-(2-Methylbut-3-yn-2-yloxy)-2-oxo-4-propyl-2*H*-thiochromen-7-yl-4-methylbenzenesulfonate (79):

This compound was prepared using similar to the preparation of (±)-**86** by using coumarin **67** as starting material; yield: 60%.



Mol. Formula : $C_{24}H_{24}O_5S_2$

Mol. Weight : 456

FT IR ($CHCl_3$) : 3310, 2136, 1645, 1578 cm^{-1}

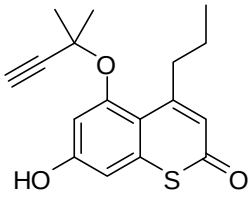
^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.61 (m, 2H), 1.72 (s, 6H), 2.46 (s, 3H), 2.68 (s, 1H), 2.99 (t, *J* = 7.3 Hz, 2H), 3.69 (s,1H), 6.37 (s, 1H), 6.66 (d, *J* = 2.3, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 2H)

ESI-MS *m/z* : 457.12 $[M+H]^+$

Elemental Analysis : Calcd: C, 63.13; H, 5.30; S, 14.05 %

Found: C, 63.02; H, 5.46; S, 13.92 %

7-Hydroxy-5-(2-methylbut-3-yn-2-yloxy)-4-propyl-2*H*-thiochromen-2-one (80):



The monotosylate **79** (11.6 g, 24.75 mmol) was suspended in THF (40 ml). The reaction flask was purged with nitrogen, and the suspension was stirred. The suspension was cooled to 20 °C and tetra-*n*-butylammonium fluoride (1 M in THF, 22 ml) is added, keeping the temperature 20 °C. During the addition, the suspension gives a dark solution. The solution was stirred for 30 min then ethyl acetate (40 ml), saturated ammonium chloride solution (5 ml) and water (10 ml) are added. The organic layer was washed with brine, dried and concentrated.

Mol. Formula : $C_{17}H_{18}O_3S$

Mol. Weight : 302

FT IR ($CHCl_3$) **:** 3018, 2418, 1634, 1581 cm^{-1}

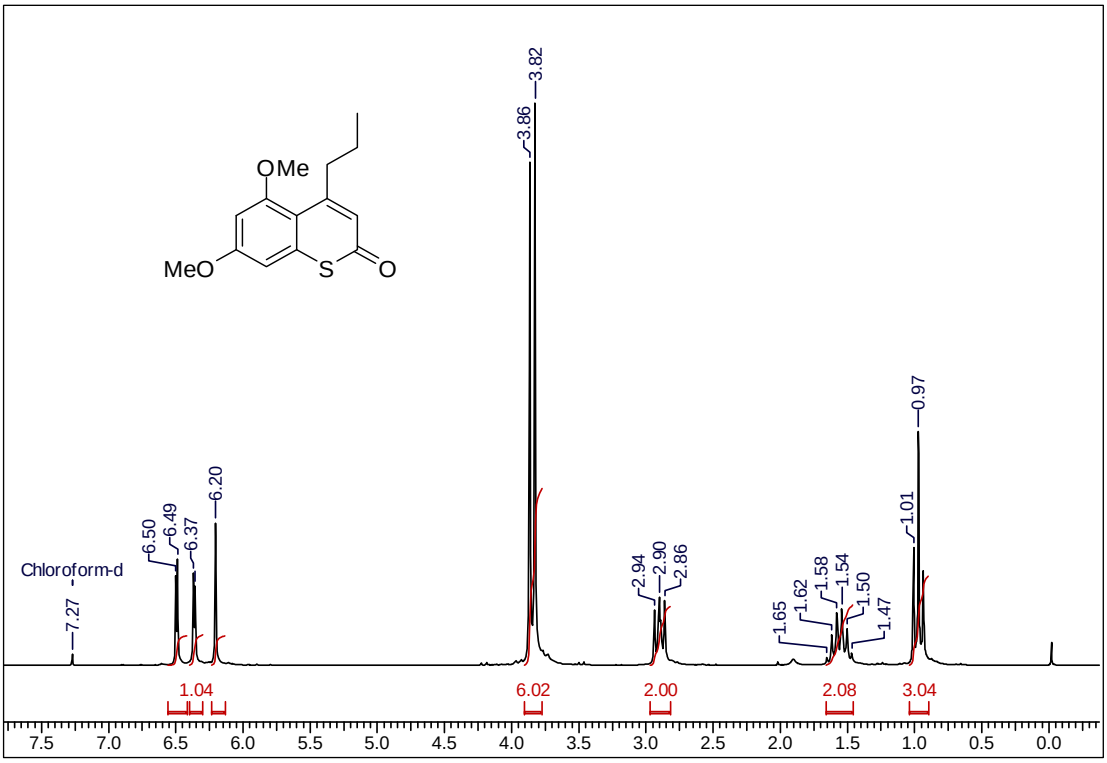
^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.58 (m, 2H), 1.78 (s, 6H) 2.68 (s, 1H), 3.00 (t, *J* = 7.3 Hz, 2H), 6.31 (s, 1H), 6.65 (d, *J* =2.3,1H), 7.28 (d, *J* = 2.3 Hz, 1H)

ESI-MS *m/z* **:** 303.14 $[M+H]^+$

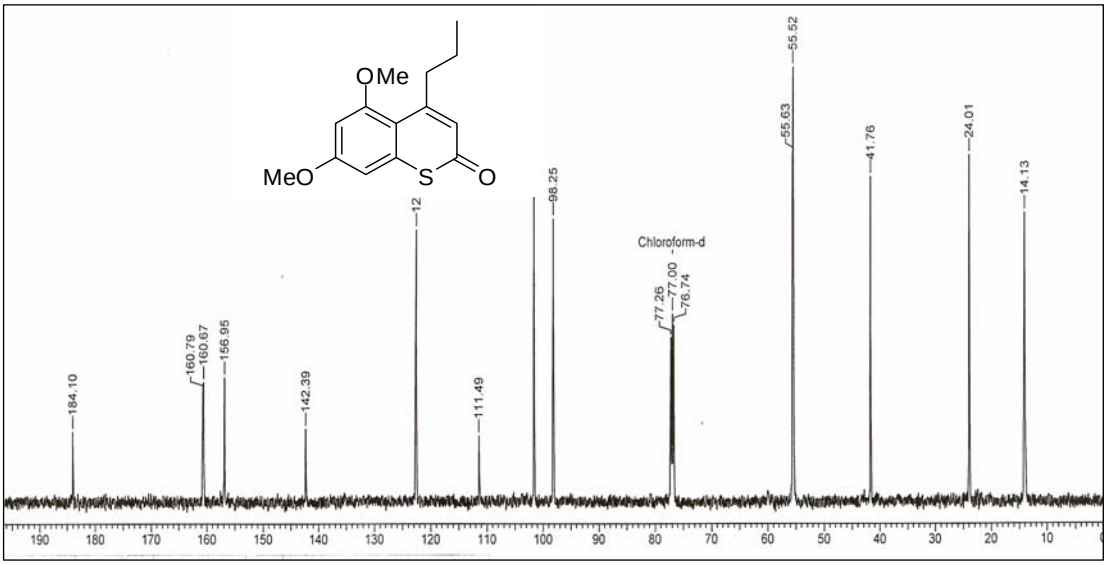
Elemental Analysis **:** Calcd: C, 67.52; H, 6.00; S, 10.60 %

Found: C, 67.40; H, 6.18; S, 10.45 %

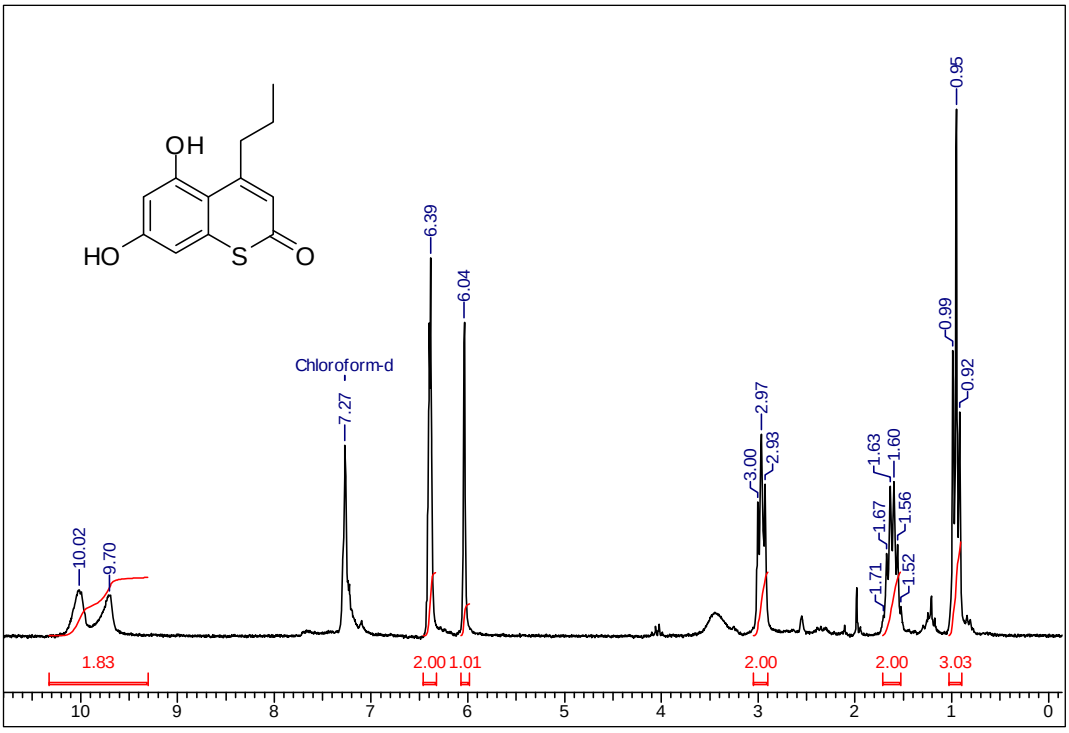
1.7. Spectra



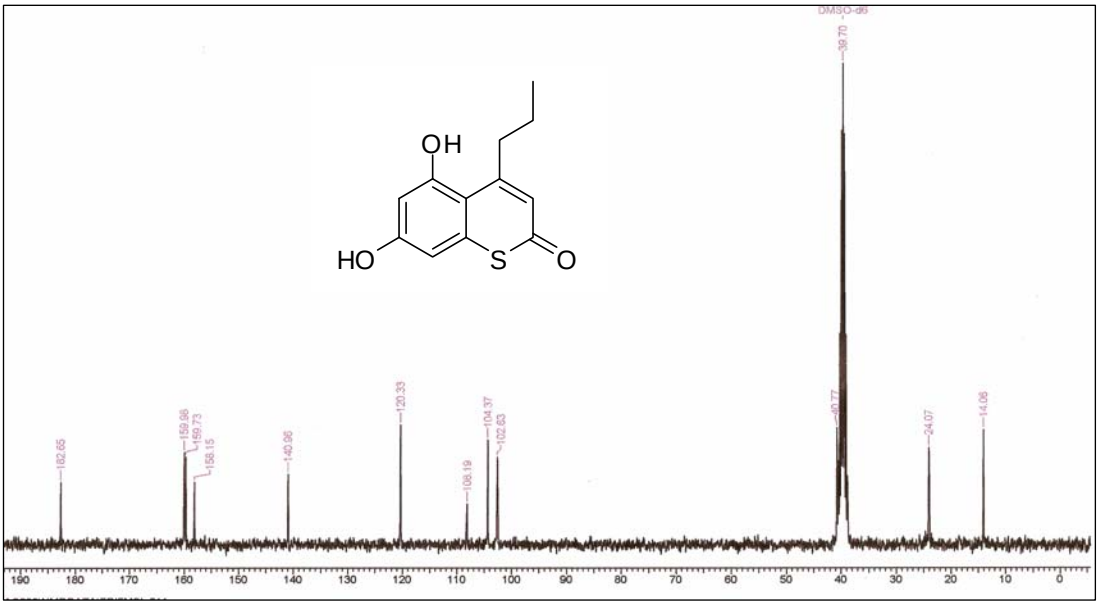
^{1}H NMR spectrum of **66** (200 MHz, $CDCl_3$)



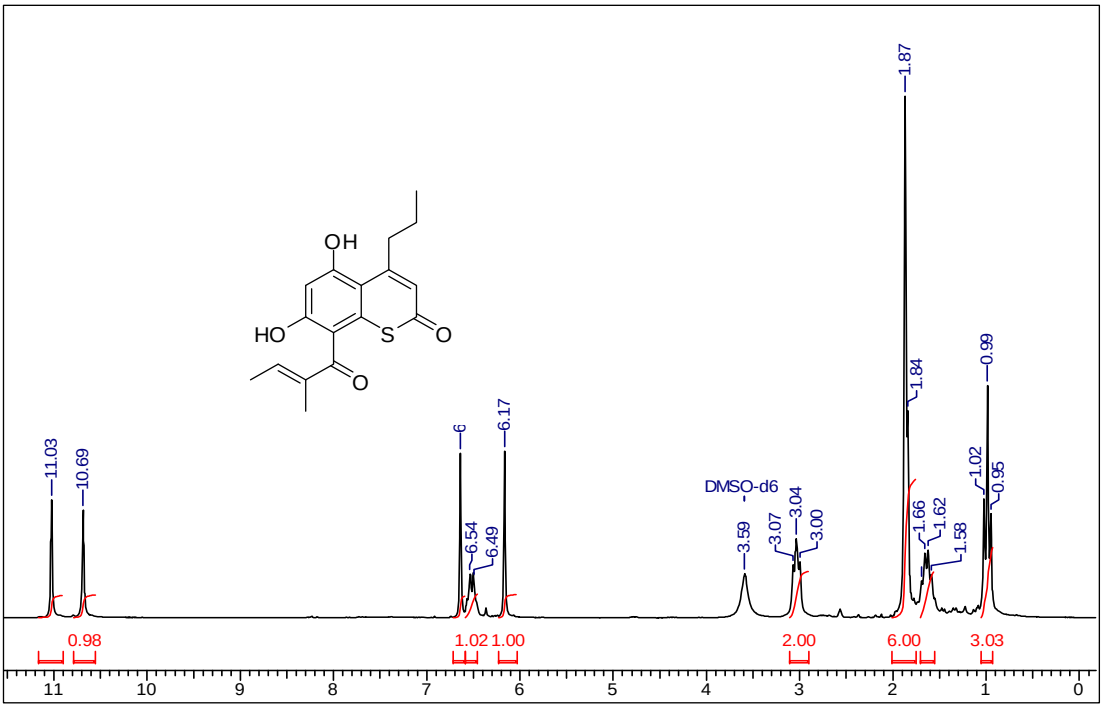
^{13}C NMR spectrum of **66** (50 MHz, $CDCl_3$)



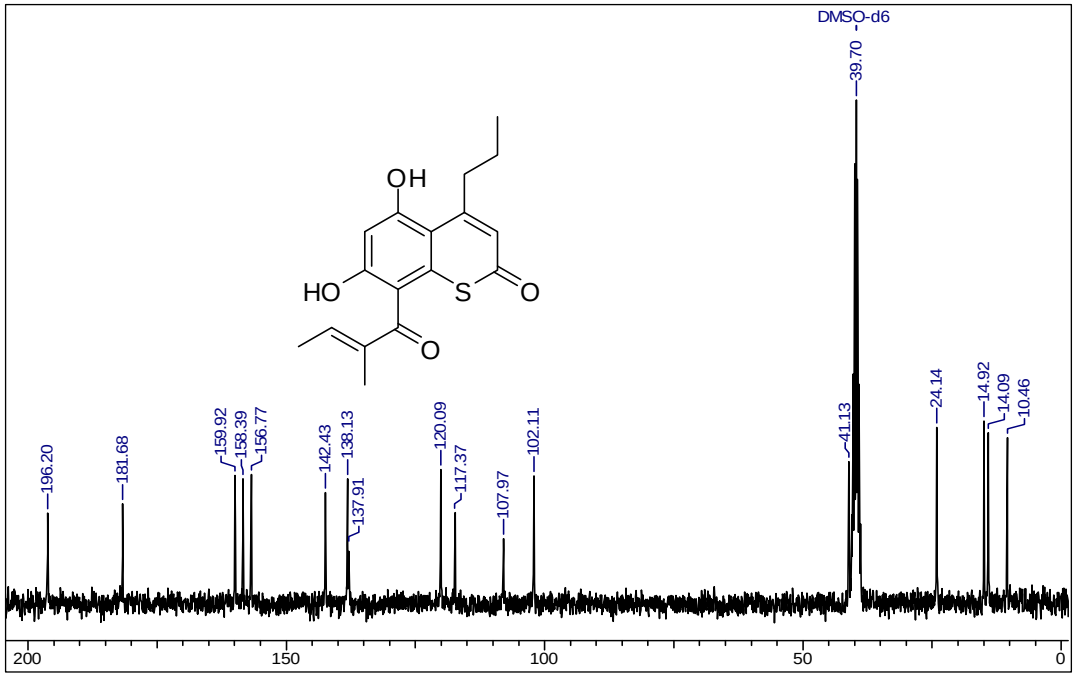
^{1}H NMR spectrum of **67** [300 MHz, $CDCl_3$: DMSO-d_6 (8:2)]



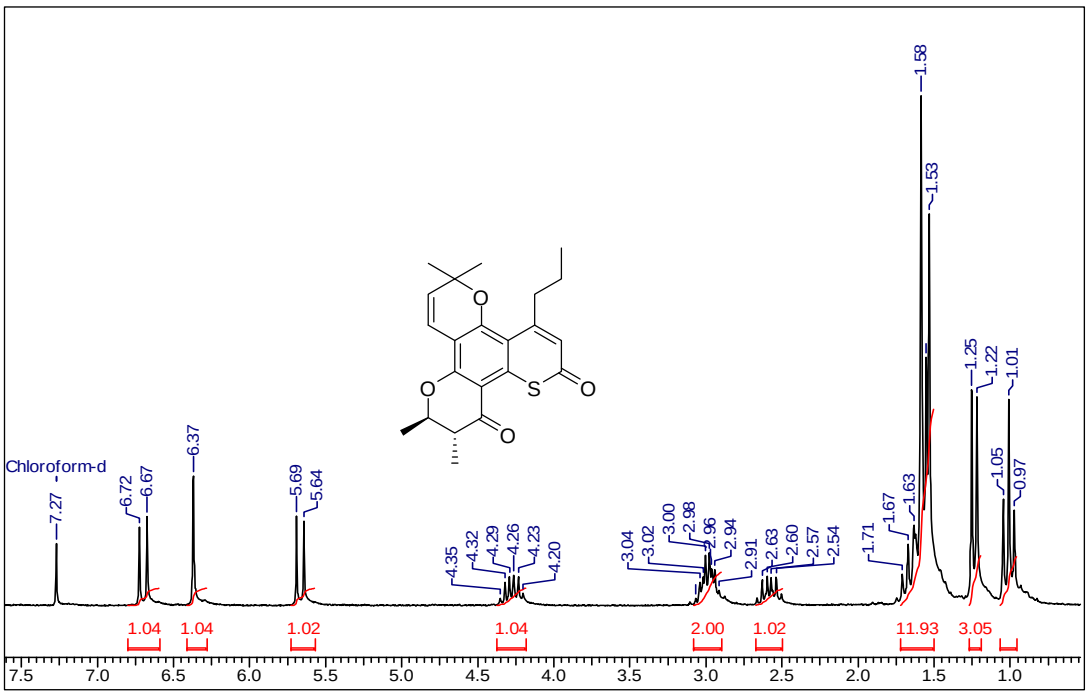
^{13}C NMR spectrum of **67** (75 MHz, DMSO-d_6)



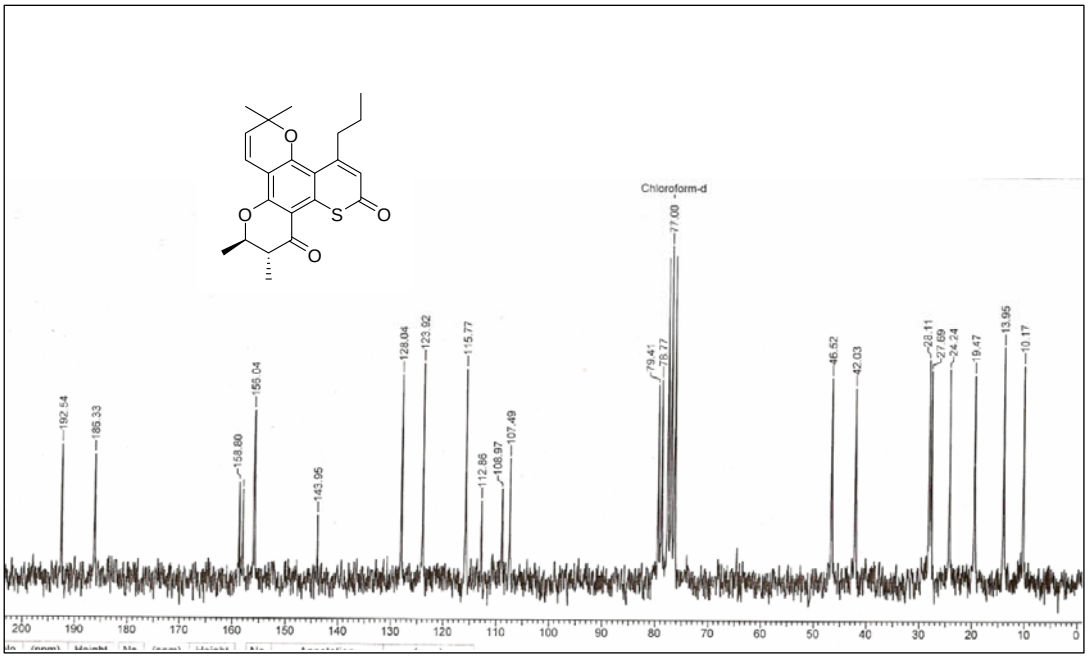
^{1}H NMR spectrum of **68** (200 MHz, DMSO-d_6)



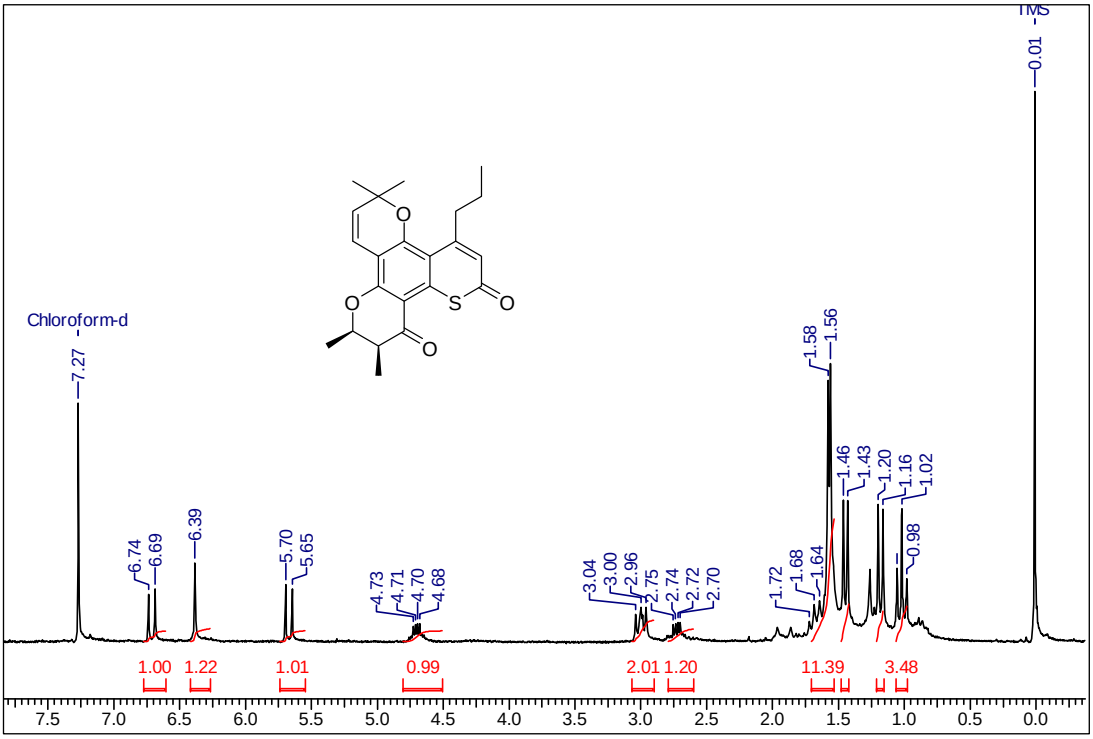
^{13}C NMR spectrum of **68** (50 MHz, DMSO-d_6)



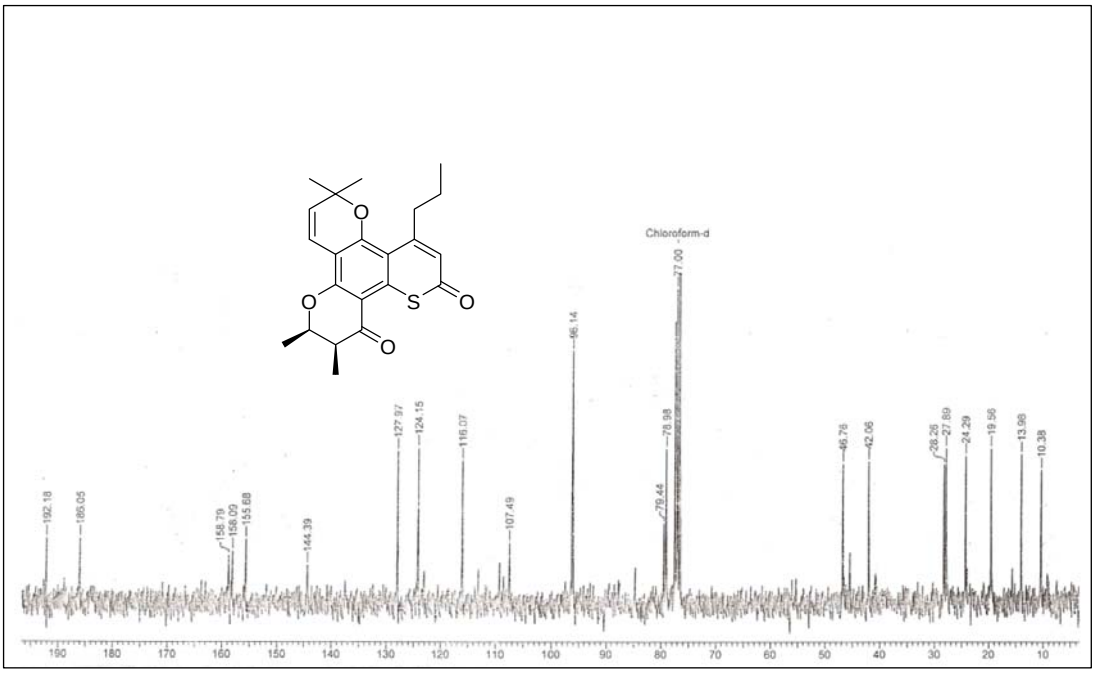
^{1}H NMR spectrum of **83** (200 MHz, $CDCl_3$)



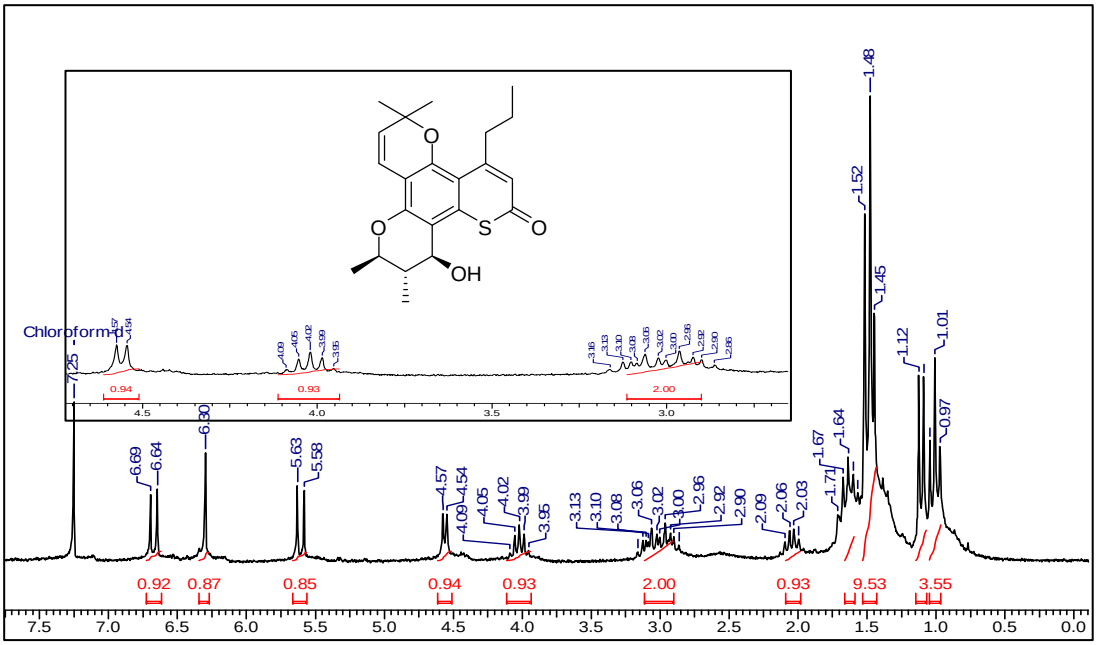
^{13}C NMR spectrum of **83** (50 MHz, $CDCl_3$-d_6)



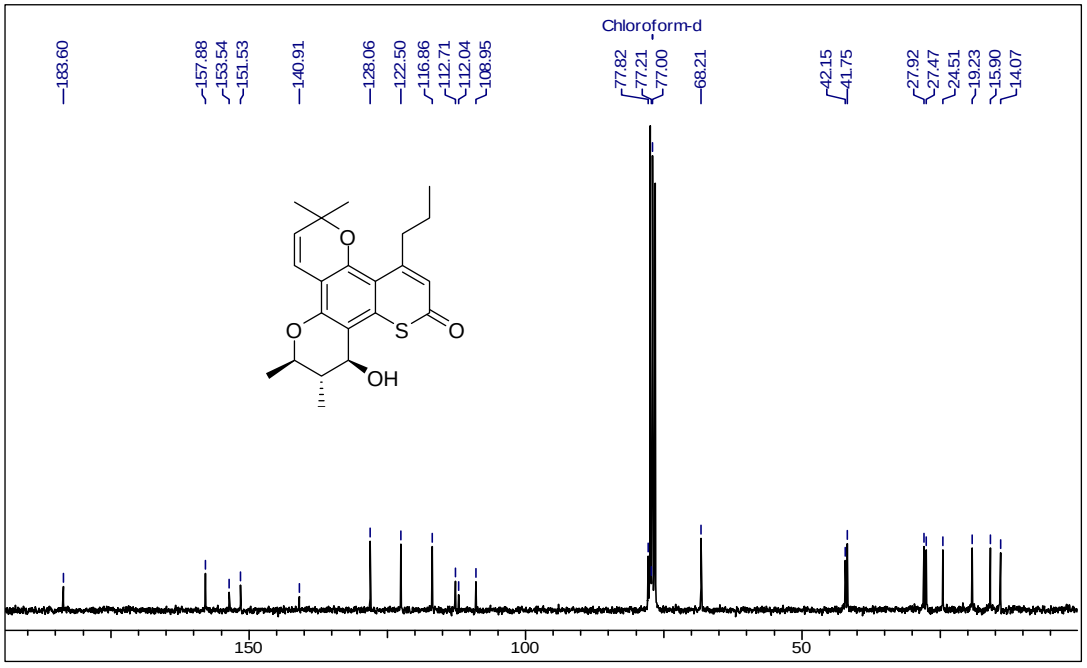
^{1}H NMR spectrum of **84** (200 MHz, $CDCl_3$)



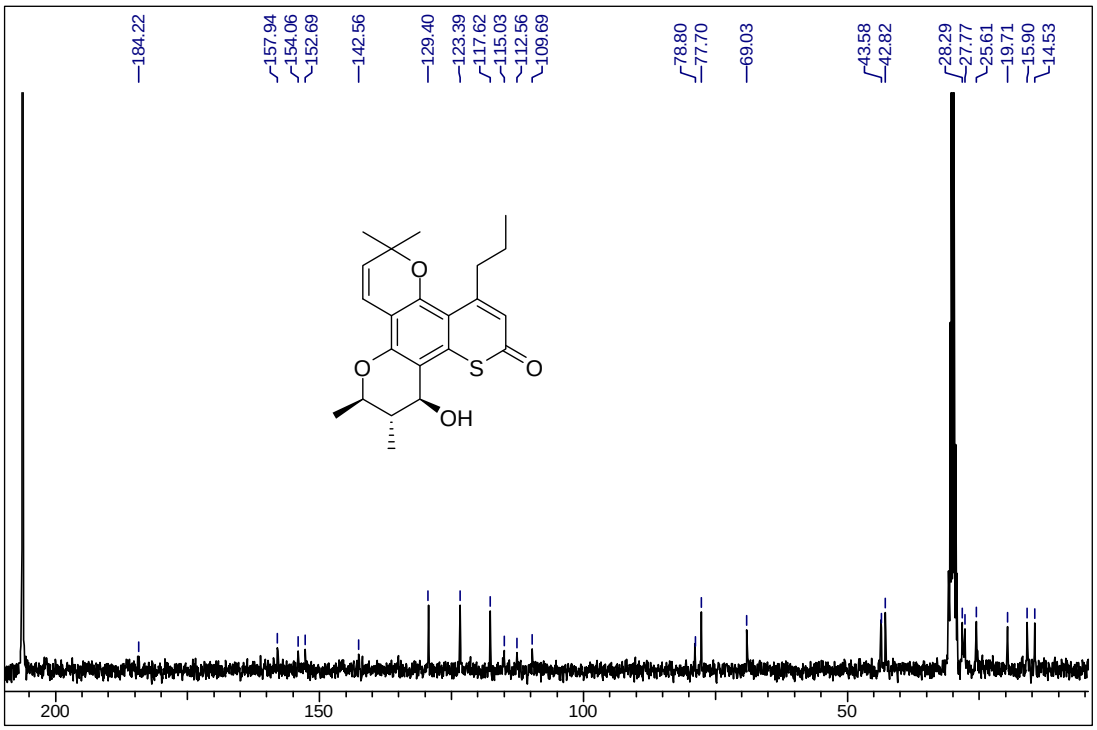
^{13}C NMR spectrum of **84** (50 MHz, $CDCl_3$)



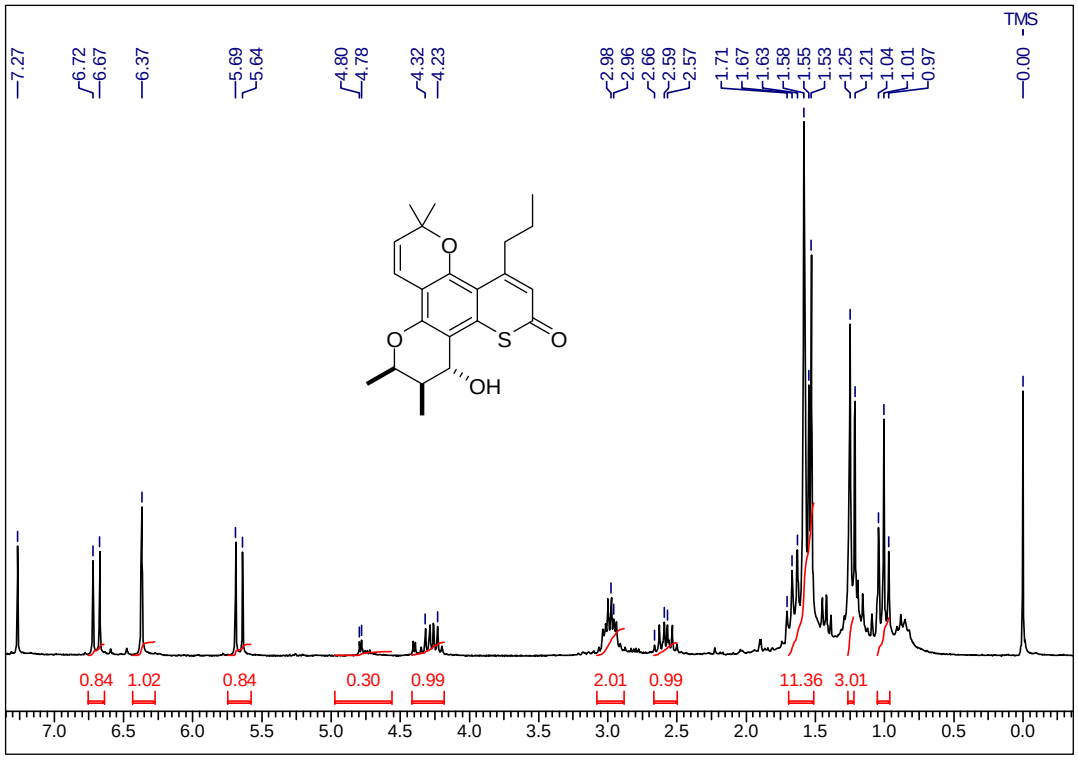
^{1}H NMR spectrum of **59** (200 MHz, $CDCl_3$)



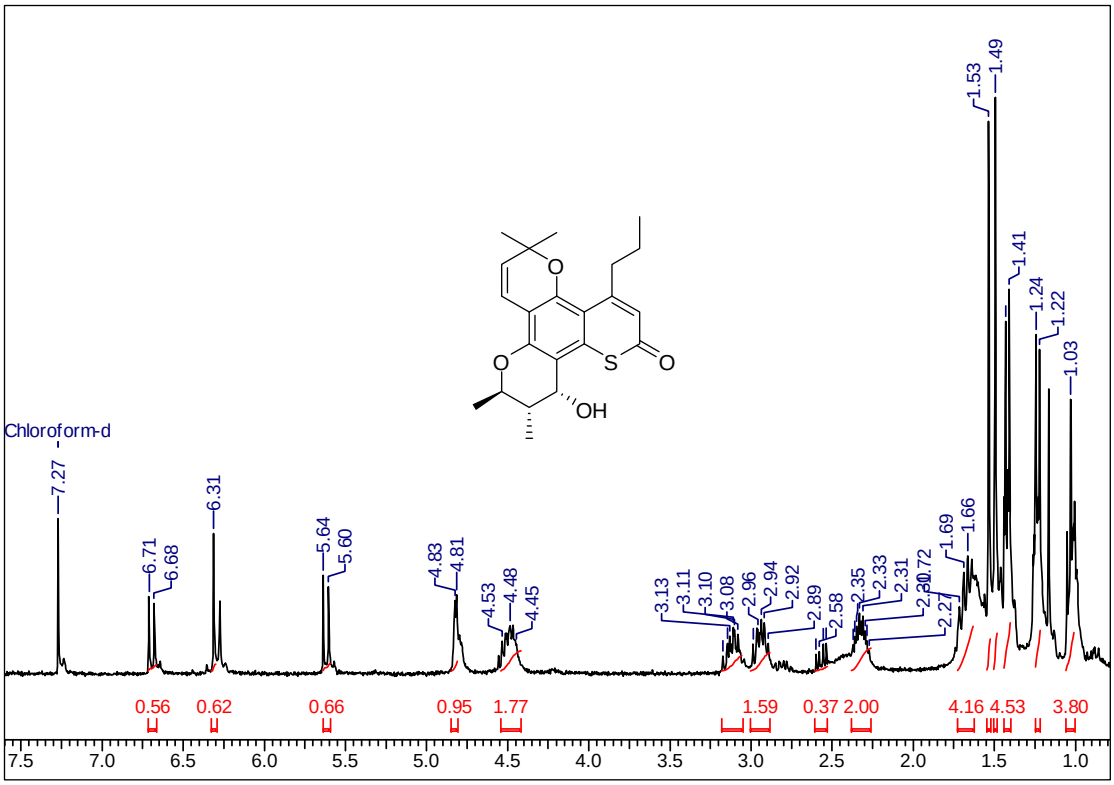
^{13}C NMR spectrum of **59** (50 MHz, $CDCl_3$)



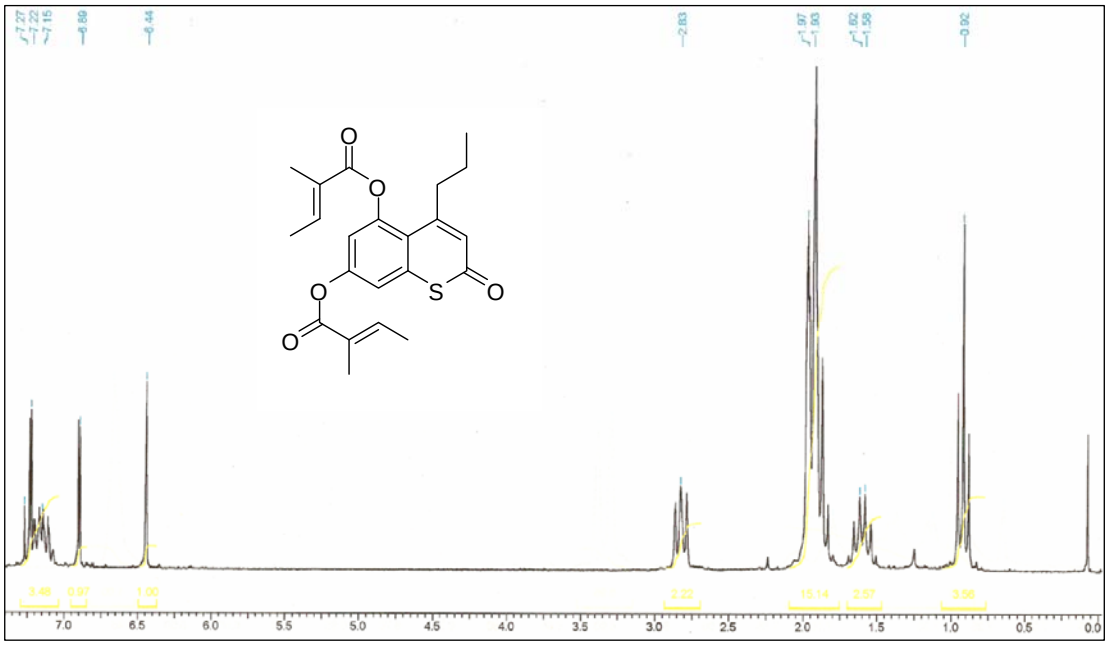
^{13}C NMR spectrum of **59** (50 MHz, Acetone-d_6)



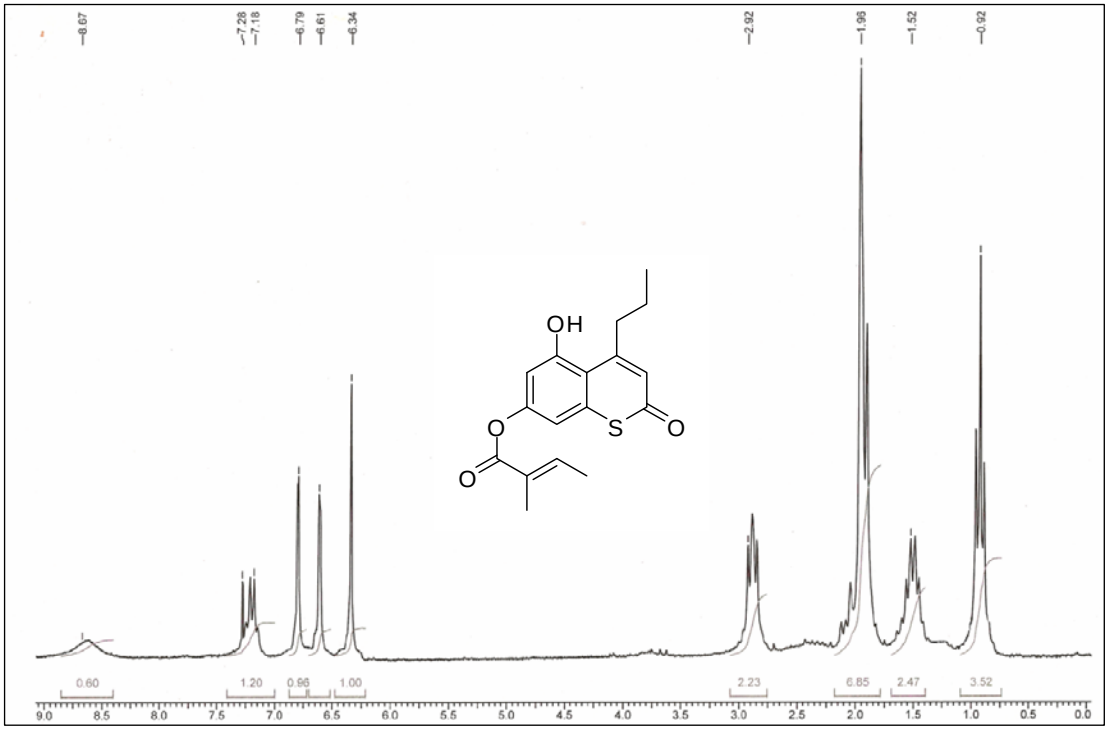
^{1}H NMR spectrum of **86** (200 MHz, $CDCl_3$)



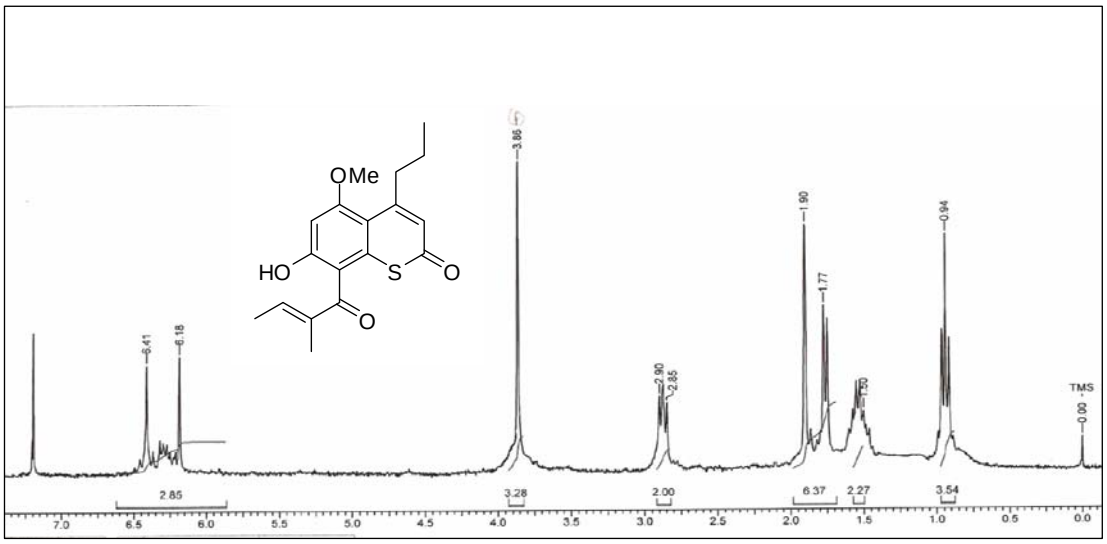
^{1}H NMR spectrum of **85** (200 MHz, $CDCl_3$)



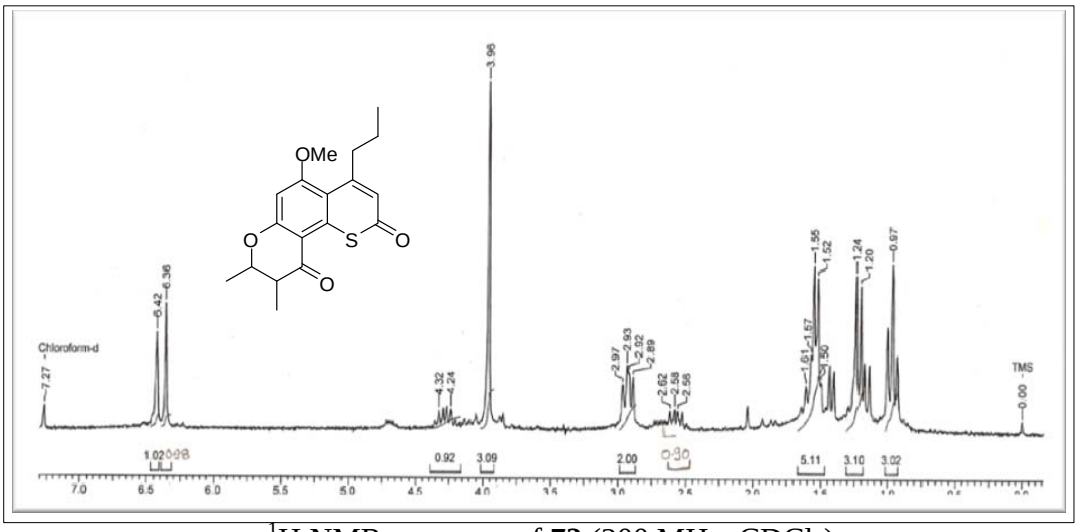
^{1}H NMR spectrum of **69** (200 MHz, $CDCl_3$)



^{1}H NMR spectrum of **70** (200 MHz, $CDCl_3$)

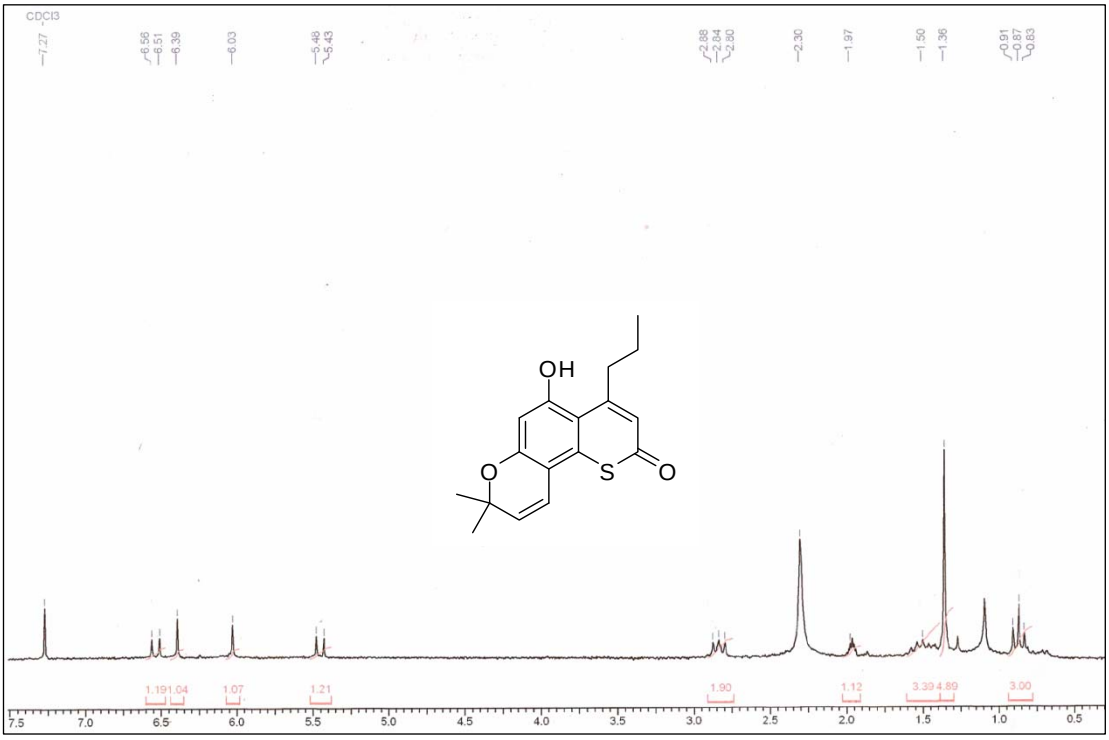


^{1}H NMR spectrum of **71** (200 MHz, $CDCl_3$)

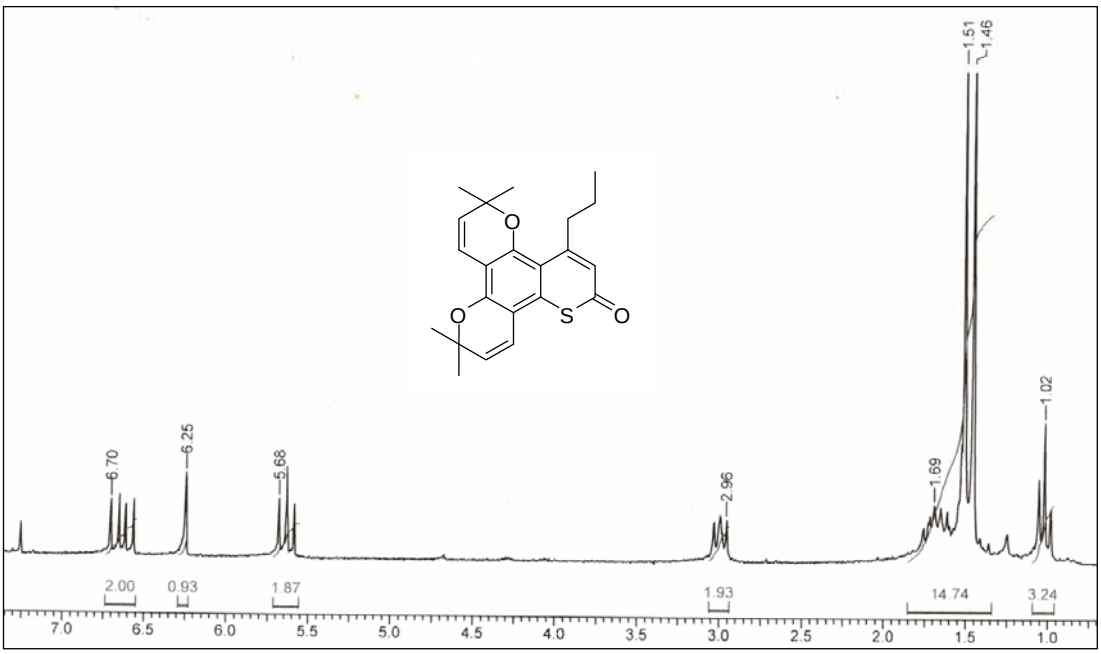


^{1}H NMR spectrum of **72** (200 MHz, $CDCl_3$)

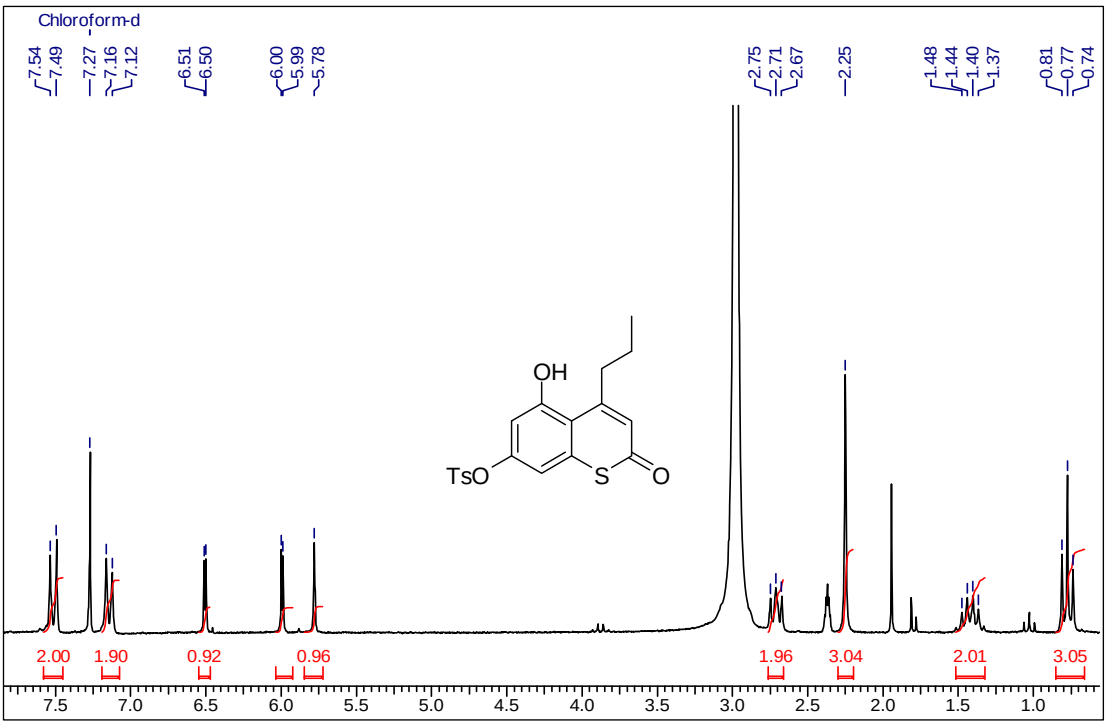
^{1}H NMR spectrum of **75 [**200 MHz, $CDCl_3$: DMSO-d_6 (8:2)]



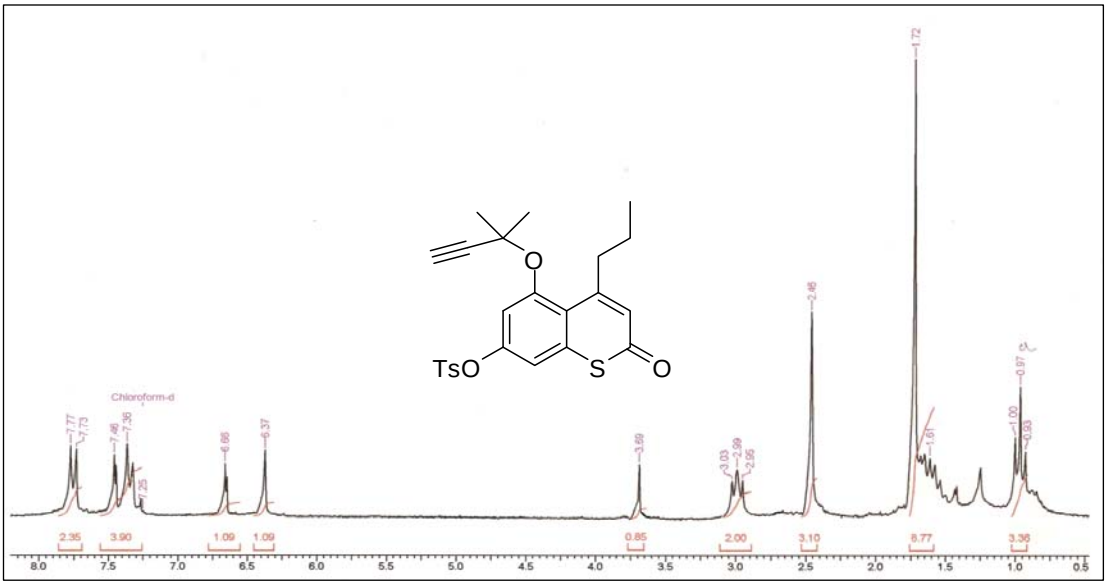
^{1}H NMR spectrum of **76** [200 MHz, $CDCl_3$: DMSO-d_6 (8:2)]



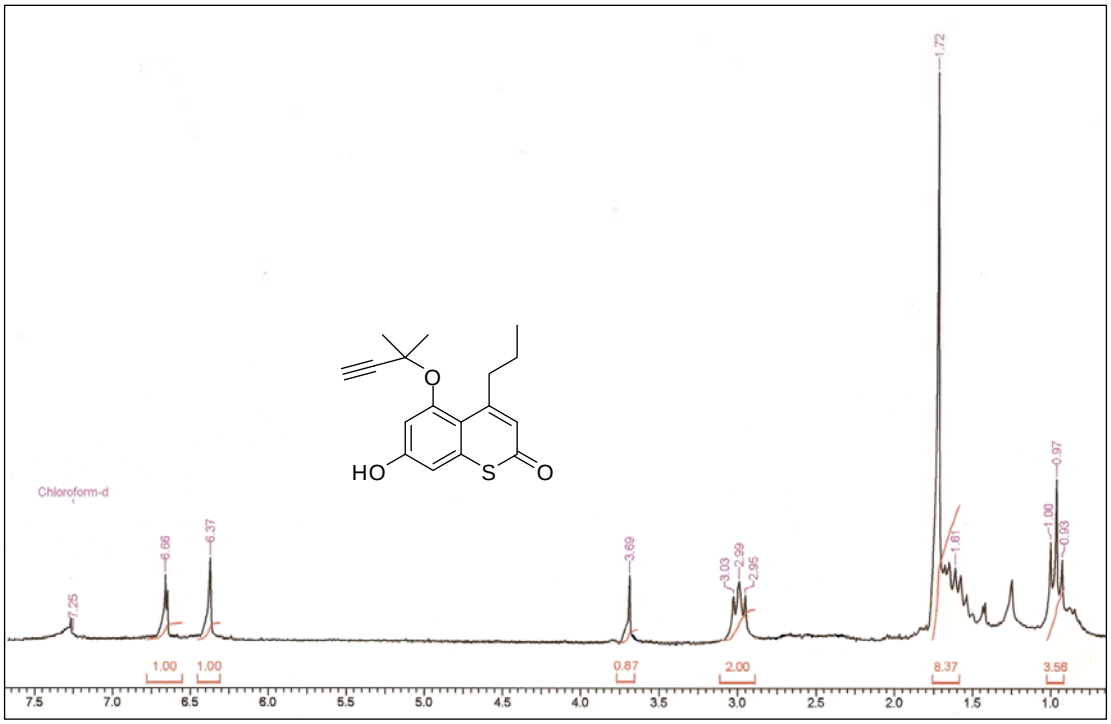
^{1}H NMR spectrum of **74** (200 MHz, $CDCl_3$)



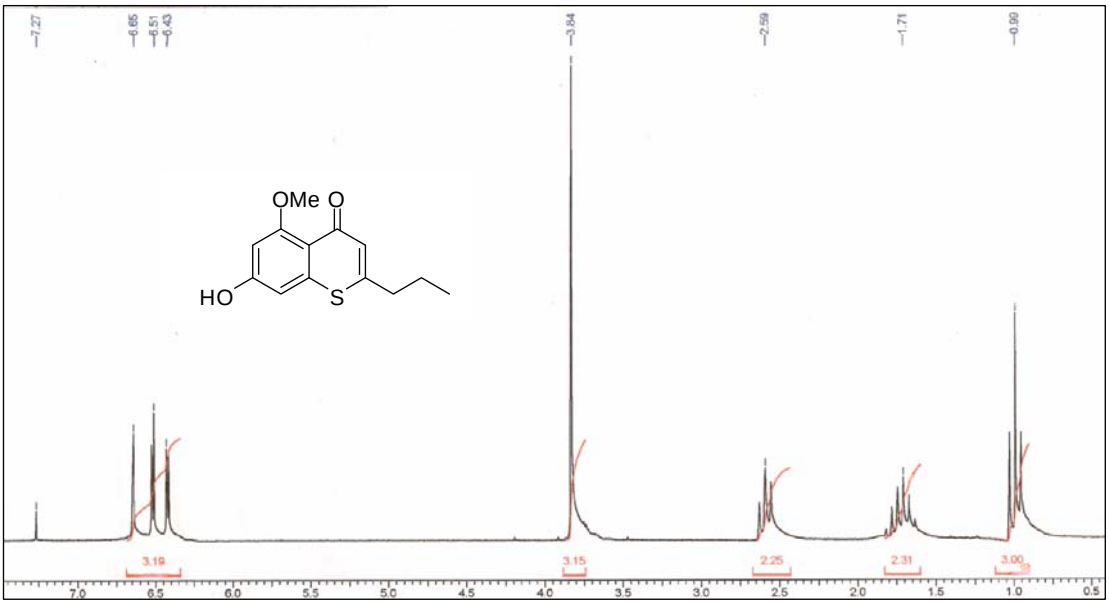
^{1}H NMR spectrum of **77 (**200 MHz, $CDCl_3$)



^{1}H NMR spectrum of **79 (**200 MHz, $CDCl_3$)



^{1}H NMR spectrum of **80 (**200 MHz, $CDCl_3$)



^{1}H NMR spectrum of **65 (**200 MHz, $CDCl_3$)

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Chapter 2

Study Towards Aziridination of Alkenes and Asymmetric Aziridination of Alkenes by Using Chiral Ligands

2.0.1. Aziridination: A Brief Review

Aziridines belong to an important class of organic compounds with three membered nitrogen containing heterocycles, which are important subunits in several natural products. The aziridine moiety is successfully used in the synthesis of various alkaloids, amino acids, amino sugars, polymers, pyrrolidines and *β*-lactum antibiotics.[1] There are a number of methods reported for the synthesis of aziridines.[2-6]

Synthesis of aziridine:

From 1,2-aminoalcohols and 1,2-aminohalides [2a-d]

This particular class of aziridine-forming reaction is the oldest class of reaction leading to these heterocycles. In 1888 Gabriel demonstrated that aziridines could be prepared in a two-step process, by chlorination of ethanolamines with thionyl chloride followed by alkali-mediated cyclization. In 1935, Wenker showed that heating of ethanolamine in the presence of sulfuric acid to high temperature formed a *β*-aminoethyl sulfuric acid which was distilled from aqueous base to furnish aziridine.

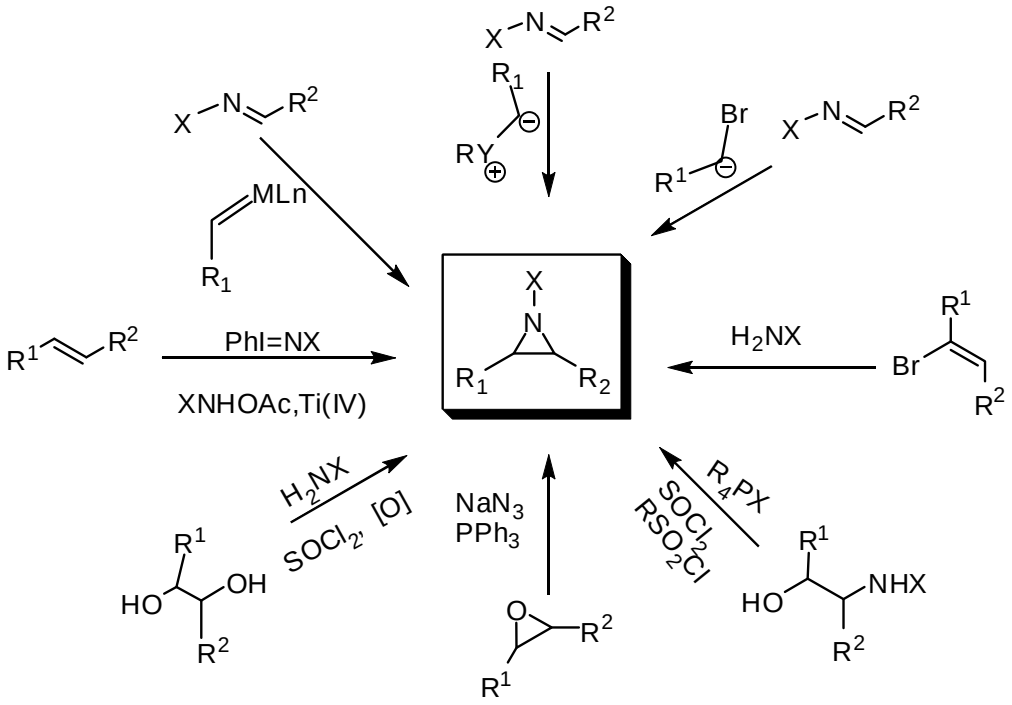
These conditions were not generally applicable to a wide range of aminoalcohols, leading to mixtures of cyclized and elimination product when any substitution *α*- to the hydroxy moiety was present. From this relatively primitive reaction a wide range of conditions for activation of the hydroxy group has evolved. In particular, Mitsunobu-like oxyphosphonium activation has been used extensively to execute the transformation.

From 1,2-azidoalcohols or epoxide[2c-e]

Epoxides react with sodium azide to give α-azido alcohols, which are readily converted to aziridines in the presence of triphenyl phosphine. α-Iodo azides can be reduced to aziridines with lithium aluminium hydride (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 which on subsequent ring closure affords the aziridine.

From *α*-bromoacrylates: Gabriel-Cromwell reaction[2e]

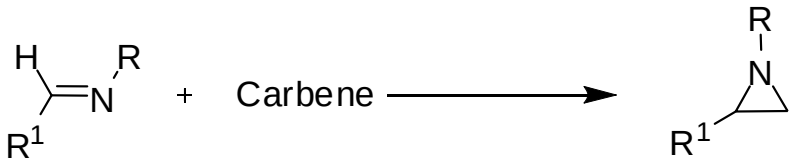
A range of chiral derivatives of α-bromoacrylates undergo reaction with amines to yield chiral aziridines (the Gabriel-Cromwell reaction). Ammonia itself may be used as the nitrogen source, providing a useful entry to chiral aziridines.



Scheme 1: Synthesis of aziridine

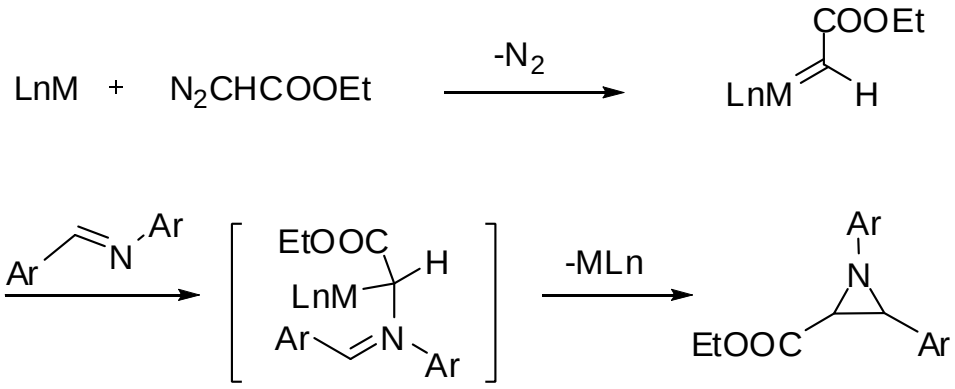
Aziridine synthesis *via* carbene addition

The reaction of imines with a carbene donor in the presence of a metal complex as a catalyst is a new entry for the synthesis of aziridines (Scheme 2).



Scheme 2

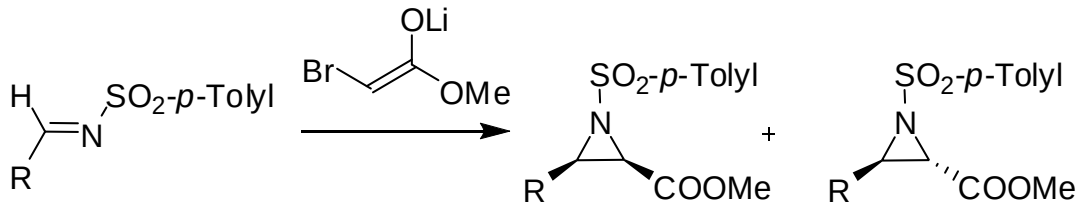
Aziridine formation by the reaction of imines with diazo compounds, such as ethyldiazoacetate (EDA), as the carbene donor fragment in the presence of a metal complex can take place by two different reaction paths. The metal complex first reacts with EDA followed by elimination of N_2 resulting in metal carbene complex, which in turn transfers the carbene fragment to the imine to form the corresponding aziridine (Scheme 3).



Scheme 3

Aza- Darzens approach

Darzen reaction type synthesis of racemic aziridines is known in the literature[7a] and has been reviewed earlier. However asymmetric synthesis of aziridines *via* Darzens reaction has been recently reported by Davis *et al.*[7b] 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 sulfinimies (Scheme 4).

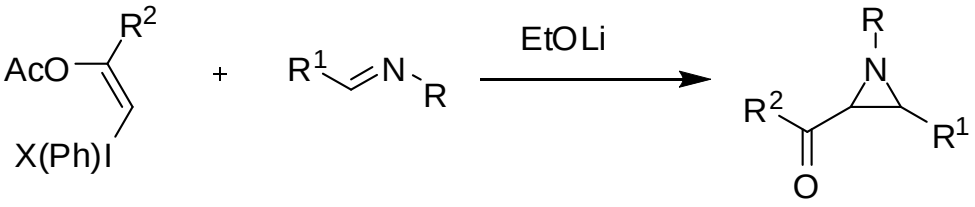


Scheme 4

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, Aggarwal[8] developed a process for aziridination of imines utilizing diazo compounds and mediated by catalytic quantities of transition metals and sulfides.

The process could be rendered asymmetric by the use of chiral sulfides in the catalytic process. Ochiai and Kitagawa[9] generated monocarbonyl iodonium ylides *in situ* 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 5).

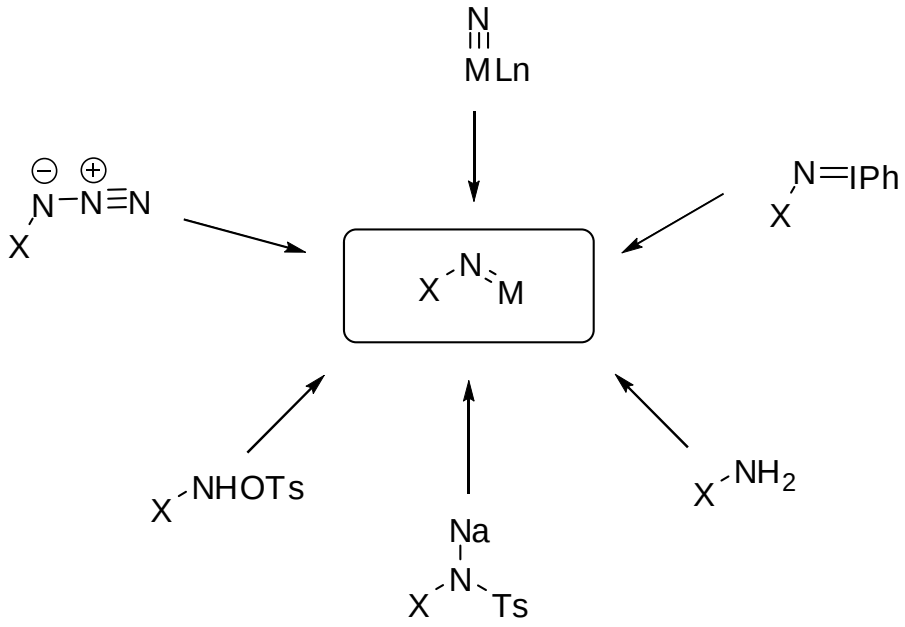


Scheme 5

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.

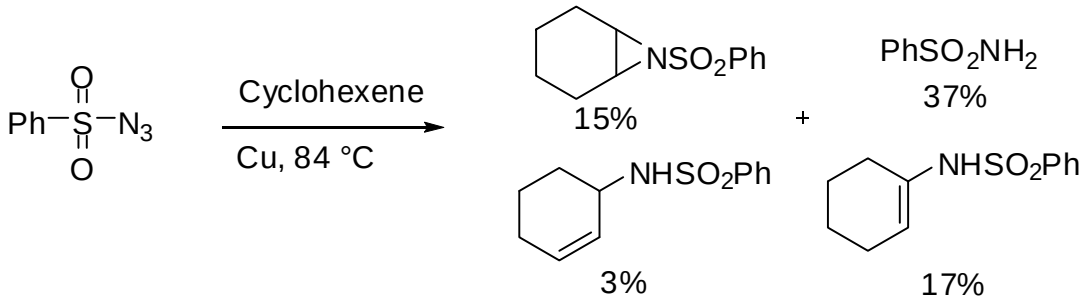
Aziridine synthesis *via* transition metal-catalyzed nitrene transfer to olefin

Transition metal-catalyzed nitrene addition to olefins provides an extremely important transformation to this class of compounds and remarkable advances have been made in this area during the past decade. Several pathways for generation of metal nitrene intermediates have been described in the literature (Scheme 6).[1b,i,j,m,o]



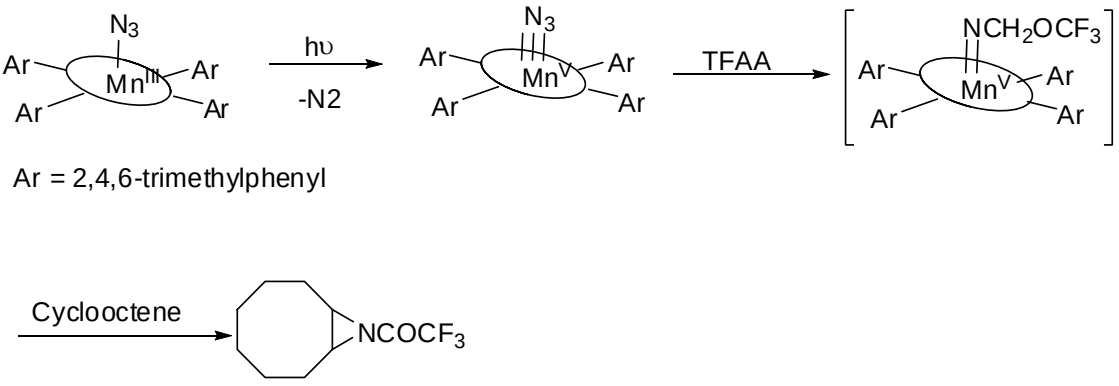
Scheme 6: Pathways for generation of metal nitrene intermediates

The first metal-catalyzed nitrogen atom-transfer process reported by Kwart and Kahn[6] in 1967 demonstrated the decomposition of bezenesulfonyl azide when heated in cyclohexene in the presence of copper powder. The resulting products arising from C-H insertion and alkene aziridination were considered to be formed *via* a nitrene (or metal nitrenoid) intermediate (Scheme 7).



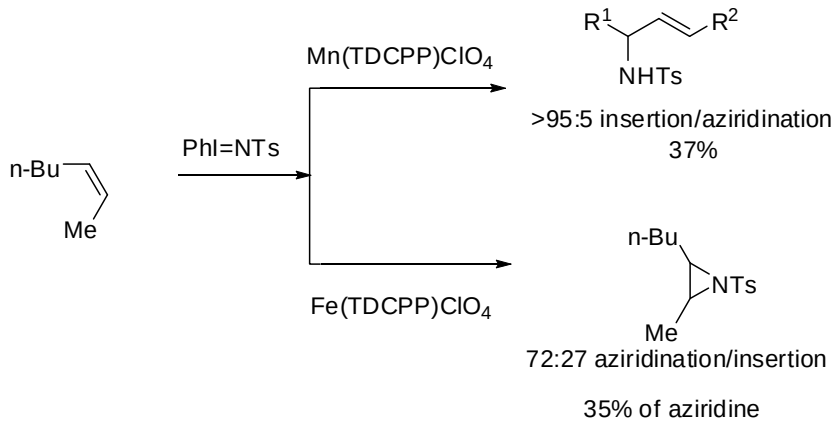
Scheme 7

In 1983, Groves *et al.*[10] reported aziridination of alkenes wherein the reaction of nitride (5,10,15,20-tetramesitylporphyrinato)manganese(V) (TMPMn≡N), 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 (Scheme 8).



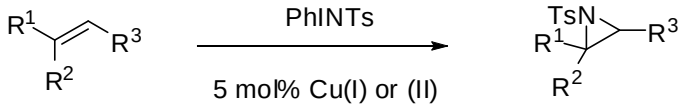
Scheme 8

The real breakthrough came in the early 80's when Breslow and Mansuy[11] reported their seminal findings which revealed the utility of the *N*-arenesulfonyl iminoiodinanes ($ArSO_2N{=}IPh$) as nitrene precursors *via* a C-H insertion process in the aziridination of alkenes. Both reactions were catalyzed by Mn(III)- or Fe(III)-porphyrin complexes (Scheme 9). However, these reactions were of limited application in organic synthesis due to their low efficiency and selectivity.



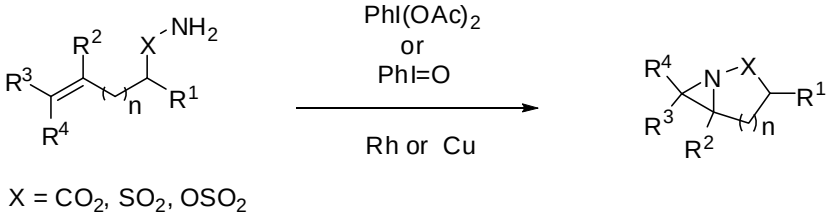
Scheme 9: Iminoiodinane as nitrene precursor for amination and aziridination

The situation was changed when Evans *et al*.[12a] investigated nitrene transfer to alkene with PhINTs as nitrogen source. Cu(I) and Cu(II) salts in acetonitrile were found to be efficient catalyst/solvent combinations for the nitrene transfer reaction. The yields of aziridines were in the range of 23-95% when the alkene was used in 5-fold excess over PhINTs in the presence of 5-10 mol% of copper catalyst (Scheme 10). The enantioselective variants of this reaction reported by both Evan's and Jacobsen's groups further improved its utility.[12b-f] In addition to copper compounds, other metal complexes such as rhodium,[12g,h] silver[12i] and more recently gold complexes[12j] were also reported to be able to efficiently catalyze this reaction.



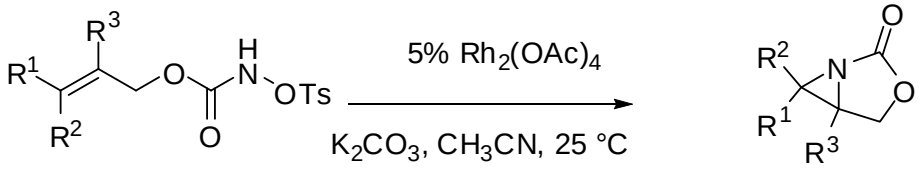
Scheme 10

However, there existed one major drawback caused by the difficulty to prepare the iminoiodinanes. This consideration promoted the recent developments involving their *in situ* generation allowing more convenient one-pot processes. These improvements led to more choices of nitrene sources such as carbamates esters,[13a,b] sulfamate esters[13c,d] and sulfonamides[13e,f] and more choices of hypervalent iodine reagents (Scheme 11). Both rhodium and copper complexes are efficient for these reactions.



Scheme 11

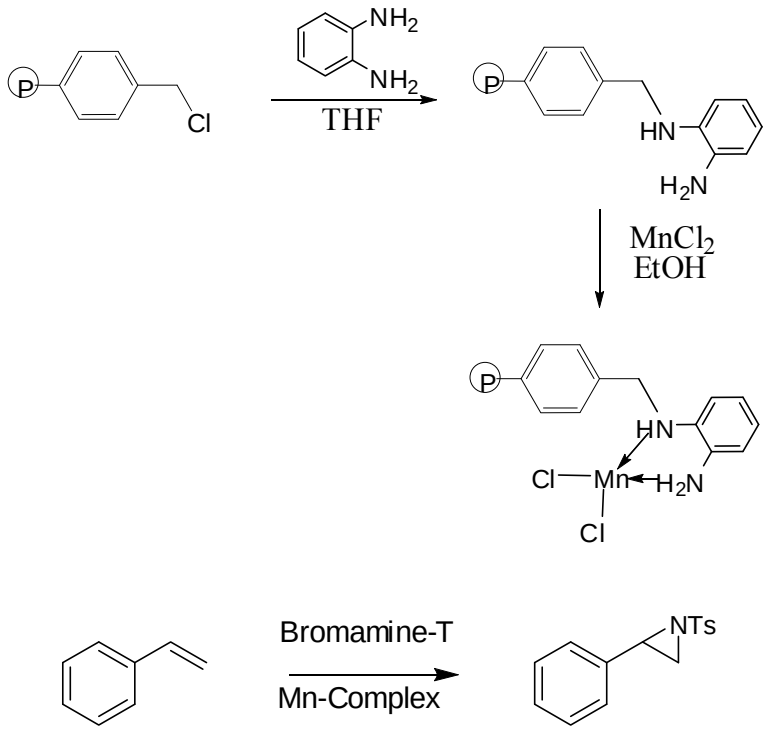
In spite of these advancements made for this area, another drawback is the formation of a stoichiometric amount of iodobenzene. Recently, Lebel *et al.*[14] have reported a highly efficient method using rhodium-catalysis for nitrenes which undergo C-H insertion to give amines or alkene addition to give aziridines (Scheme 12). They used *N*-tosyl derivatives of carbamates as nitrene sources, thus avoiding addition of hypervalent iodine reagents which generate iodobenzene.



Scheme 12

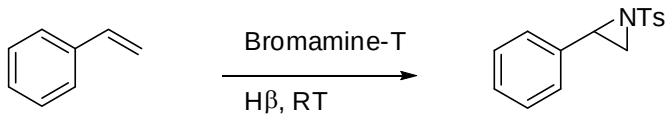
More recently, progress on the application of new type of nitrene source has been reported. Bromamine-T as nitrene source for copper catalyzed aziridination of olefins under homogeneous conditions was demonstrated and in comparison with chloramine-T as nitrene source, bromamine-T was found to be superior nitrene source.

Chanda *et al.*[15] demonstrated the aziridination using two new catalysts. The first catalyst contained manganese chelated metal complex on a polymer support and was used as catalyst in the aziridination of olefins using bromamine-T as a source of nitrene. Chloromethylated styrene-divinyl benzene (Ps-DVB) of 8% cross-link was functionalized using *o*-phenylene diamine and finally it was treated with Mn(II) for the formation of metal complex on the surface. Good to moderate yields of aziridines were obtained using acetonitrile as solvent (Scheme 13). The other catalyst was iron derived and gave similar results.



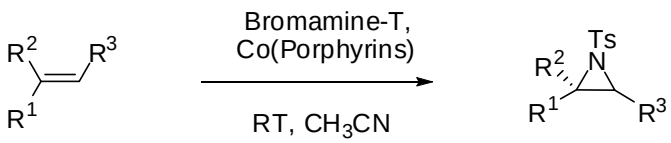
Scheme 13

This group also reported for the first time the aziridination using Hβ-zeolite and in the absence of metal catalyst with bromamine-T as nitrene source wherein moderate to good yields of aziridines were observed. *Trans* selectivity to aziridination was also one of the key feature of using Hβ-zeolite as catalyst (Scheme 14).



Scheme 14

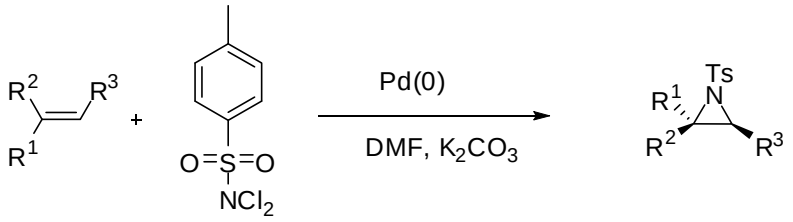
Zhang *et al*.[16] introduced cobalt porphyrins as the new entry for aziridination of various alkyl and halogen substituted styrene derivatives using bromamine-T as source of nitrene. Among different porphyrins used Co(TDCIPP)[17] is found to be an effective catalyst that can take part in aziridination of different alkenes[18] (Scheme 15).



Scheme 15

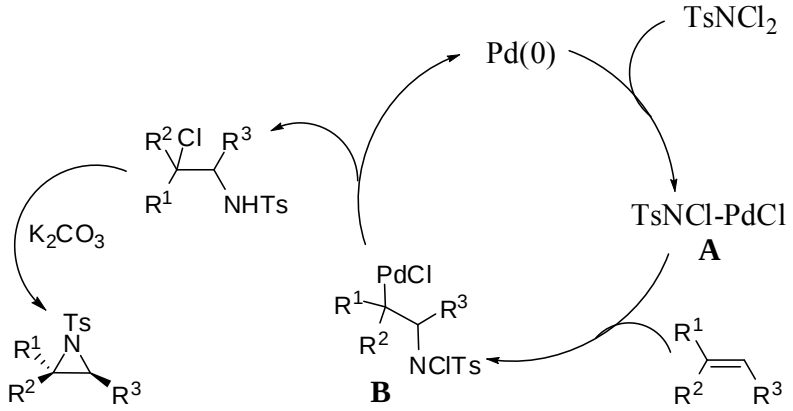
Guigen Li *et al*.[19] reported palladium-catalyzed aziridination of alkenes using *N*,*N*-dichloro-*p*-toluene sulfonamide as nitrogen source. Substrate scope was studied for different substituted styrene derivatives, cyclooctene and diphenyl substituted alkenes. Good to moderate yields of aziridines were observed. Methyl cinnamate

failed to react under these conditions (Scheme 16).



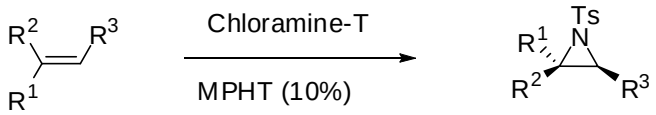
Scheme 16

Palladium (0) is assumed to be the catalytic species produced by reduction of Pd (II) with olefin. The first step of catalytic cycle involves the formation of Pd-nitrogen intermediate **A**, which reacts with olefin to form intermediate **B**. It decomposes further to give the aminochlorination product and to regenerate Pd(0) species (Scheme 17).



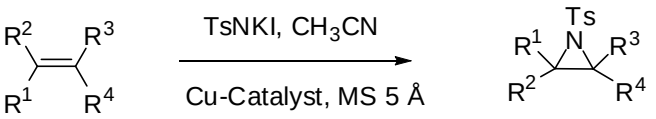
Scheme 17

Sain *et al*.[20a] published *N*-methyl pyrrolidine-2-one hydrotribromide catalyst for aziridination of alkenes using chloramine-T as nitrene source (Scheme18).



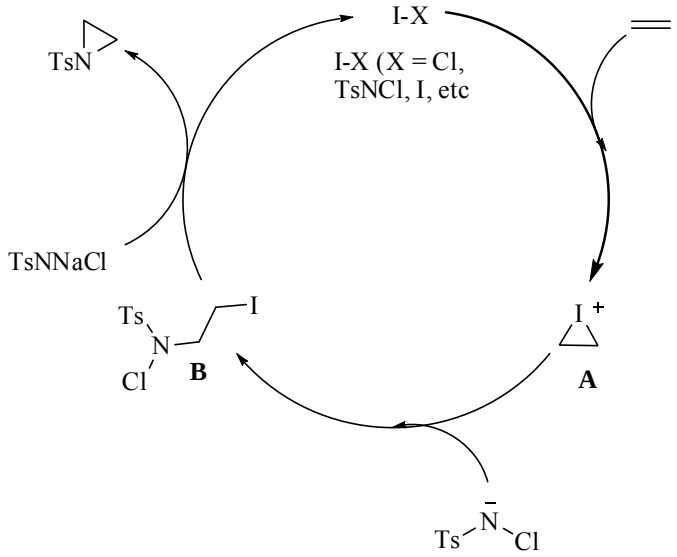
Scheme 18

Among the various alkenes studied, *trans* methyl cinnamate was found to be least reactive. This group also demonstrated *N*-iodo-*N*-potassio-*p*-toluenesulfonamide[20b] as a source of nitrene for aziridination of olefins using CuCl as catalyst (Scheme 19).



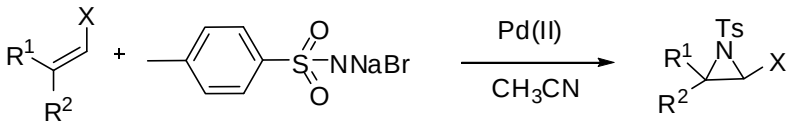
Scheme 19

Xia *et al.*[21] reported aziridination of olefins using hydrated chloramine-T as nitrene donor and copper iodide as catalyst in water as solvent. Tetrabutylammonium bromide is used as phase transfer catalyst. Various metal halides of Mn and Cu were studied for aziridination wherein copper iodide was found to be the best. The combination of chloramine-T and iodide is an efficient iodination reagent. The reaction probably involves the formation of I^+ species by the reaction of chloramine-T with copper iodide. The proposed pathway for aziridination of olefin in water involves reaction of iodine with I^+ source (I-X) to give iodonium ion **A**. The iodoaminated intermediate **B** leads to the aziridine and the generated I-X species is available to initiate another turn of catalytic cycle (Scheme 20).



Scheme 20

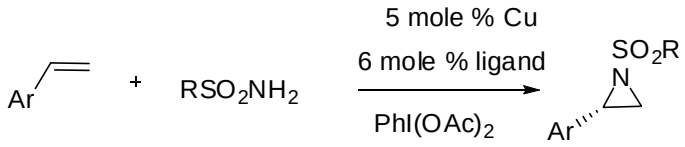
Branco *et al.*[22] reported Pd (II) promoted reaction of a variety of olefins and bromamine-T under mild conditions. Synthetically useful *N*-tosyl-2-substituted aziridine can be obtained in good to moderate yield. It is suggested that an oxidative addition of bromamine-T to $PdCl_2$ results in the formation of aziridine (Scheme 21).



Scheme 21

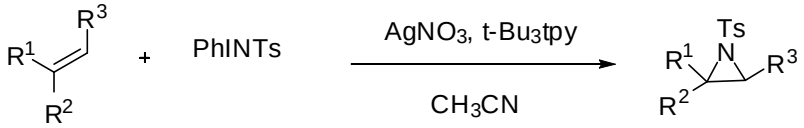
Kwong *et al.*[23]demonstrated one pot synthesis of aziridine, using $PhI(OAc)_2$ and copper as catalyst. Benzene sulfonamide and various 4-substituted benzene sulfonamides are used as source of nitrenes. Among all the copper catalysts studied,

$Cu(CH_3CN)_4\ ClO_4$ gave best results (Scheme 22).



Scheme 22

He *et al*.[24] studied aziridination of various substituted styrene derivatives and terminal alkenes using $[Ag_2(t\text{-}Bu_3tpy)_3(NO_3)](NO_3)$ and PhINTs as nitrene donor in acetonitrile solvent (Scheme 23).



Scheme 23

Conclusion

The above illustrations distinctly carry out the importance of aziridination strategy in synthetic organic chemistry. It is clear from this review that future strategies should be chosen effectively for achieving catalytic asymmetric aziridination reactions. The significance of aziridine chemistry and our contribution in asymmetric synthesis of aziridine are presented in both sections.

Chapter 2

Section I

Synthesis of Chiral Ligands, Catalysts and Asymmetric Aziridination of Alkenes

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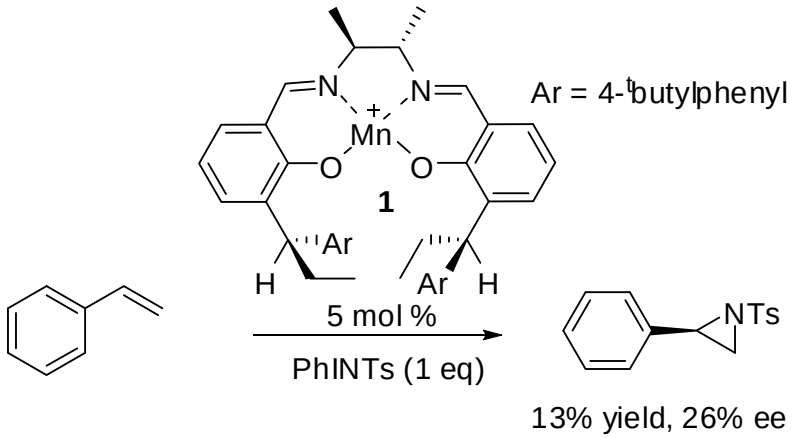
2.1.1. Introduction

Chiral aziridines are used widely in organic synthesis. The readily available methods for stereo- and regioselective ring opening or expansion of the strained aziridine rings allow quick access to a variety of chiral amines, which would be useful building blocks for natural product synthesis. Due to the versatile utilities of chiral aziridines in organic synthesis, the development of efficient enantioselective synthetic methods for chiral aziridines has received considerable interest.

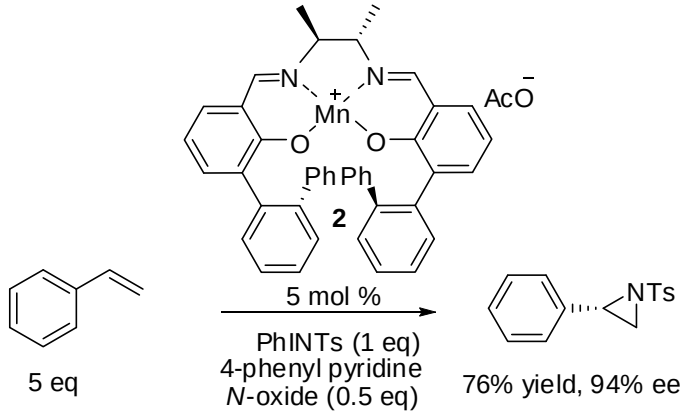
2.1.2. Review of Literature: Asymmetric aziridination of alkenes

Katsuki *et al*.[25] reported for the first time asymmetric aziridination of alkene catalysed by chiral salen-manganese(III) complexes **1**. Optically active salen complex was found to show moderate level of asymmetric induction in the aziridination of styrene, though chemical yield was poor (Scheme 24).



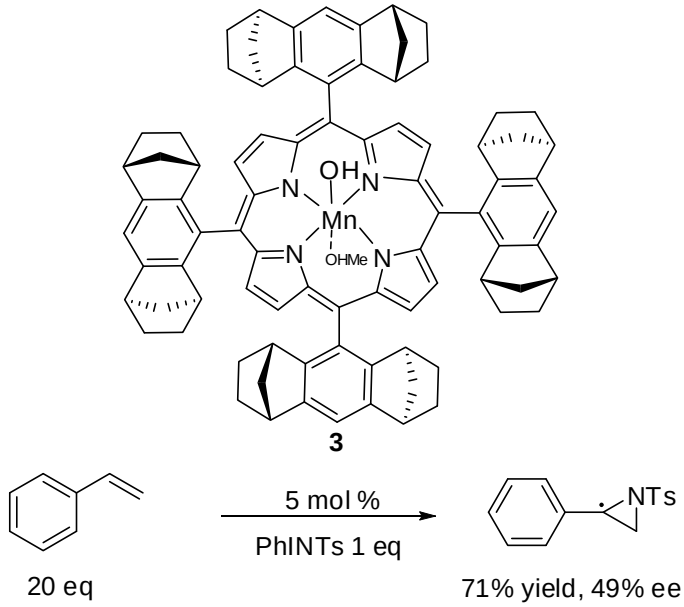
Scheme 24: First asymmetric Mn^{III} catalytic aziridination

High enantioselectivity was obtained with newly designed salen-manganese(III) complex **2** as a catalyst in combination with 4-phenylpyridine *N*-oxide (Scheme 25). Thus styrene is converted to its *N*-tosyl aziridine compound in 76% yield and in 94% ee.



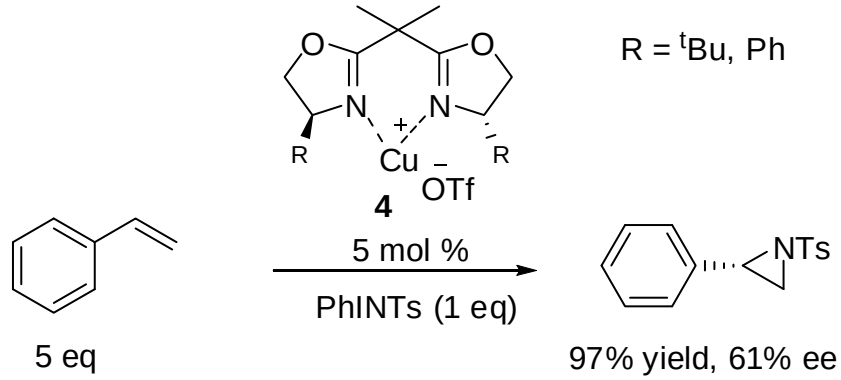
Scheme 25: Asymmetric Mn^{III} catalytic aziridination

Che *et al.*[26] reported that D_4-manganese(III) porphyrin complex **3** catalyzed aziridination of alkenes in which the complex **3** enables asymmetric aziridination of styrene derivatives with moderate enantioselectivities (Scheme 26).



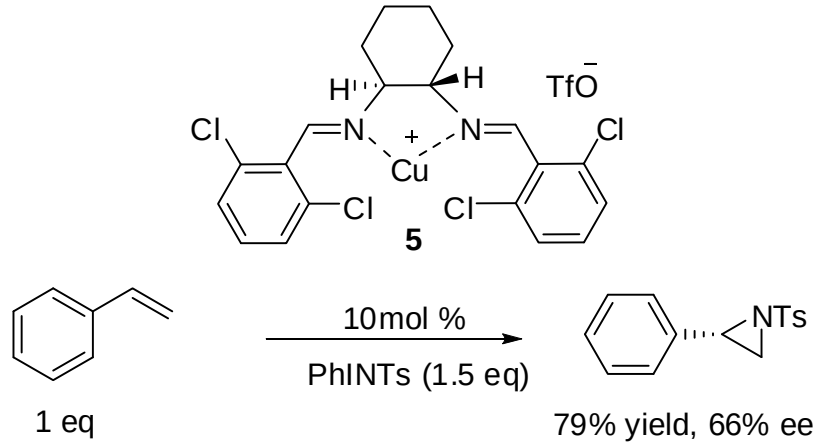
Scheme 26: D_4-Mn^{III} Porphyrin catalyst for asymmetric aziridination

Among all the reported methods, transition metal-catalyzed asymmetric alkene aziridination has drawn a lot of attention. Evans *et al.*[27] introduced a series of bis(oxazoline)-Cu-complexes **4** as chiral catalysts for the enantioselective aziridination of olefins[12]. Upto 67% ee was achieved with aryl substituted olefins with PhINTs as the nitrene source and CuOTf as the metal salt (Scheme 27).



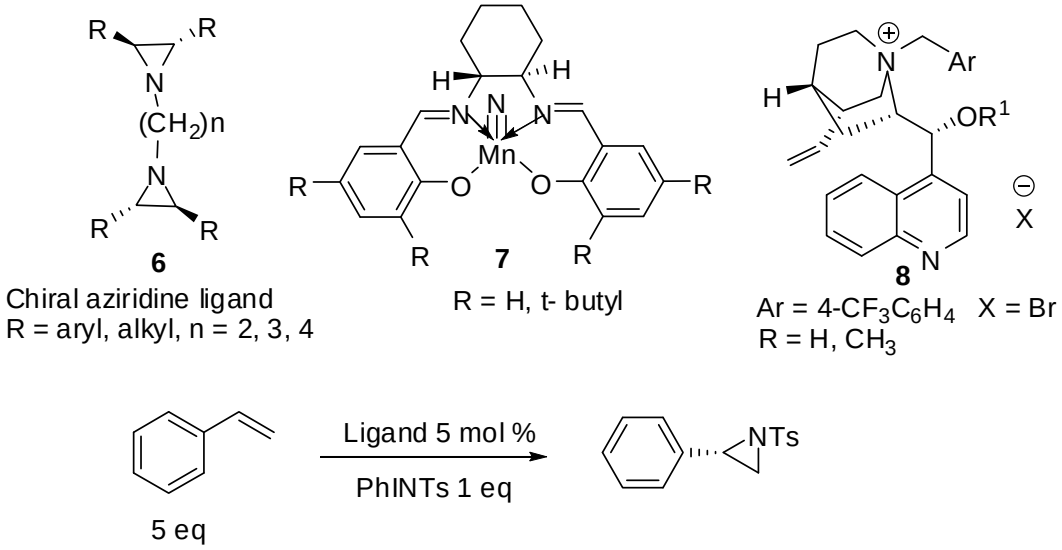
Scheme 27: Evans bis(oxazoline)-Cu catalyzed asymmetric aziridination

In the same year, Jacobsen *et al.*[28] published a paper on asymmetric aziridination of styrene with readily available chiral diamine-based catalyst **5**. Three such ligands/catalysts are reported and upto 98% ee was achieved with some of the substrates (Scheme 28).



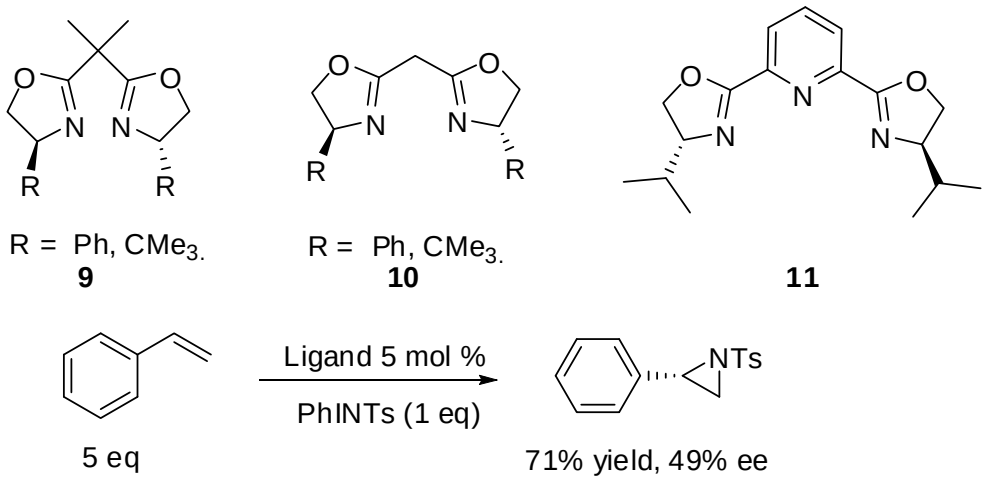
Scheme 28: Jacobsen's Cu-catalyzed asymmetric aziridination

C_2-Symmetric bis(aziridines) **6** as a new class of chiral ligands for transition metal-mediated asymmetric synthesis was developed by Tanner *et al.*[29] who reported upto 33% ee with styrene in the aziridination reaction. Komatsu[30] reported a novel asymmetric and stereospecific aziridination of alkenes with a chiral nitridomanganese complex **7** where use of additives like pyridine N-oxide to enhance performance and selectivity was also mentioned. Moderate to good enantioselectivity of aziridination could be achieved[31] with chiral quaternary salts based on cinchona alkaloid **8**, especially with that of cinchonine (Scheme 29).



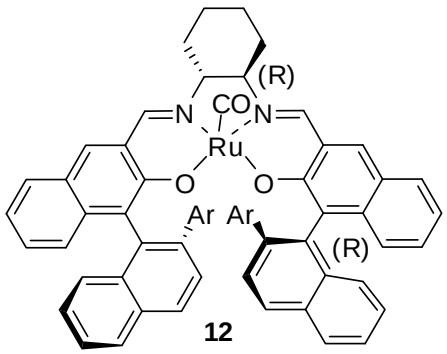
Scheme 29: Jacobsen's Cu-catalyzed asymmetric aziridination

The first catalytic asymmetric heterogeneous aziridination of styrene with CuHY (copper exchanged zeolite H-Y) and modified by chiral bisoxazolines (**9, 10, 11**) with moderate ees was reported by Hutchings *et al.*[32] who used PhINTs as the source of nitrene (Scheme 30).

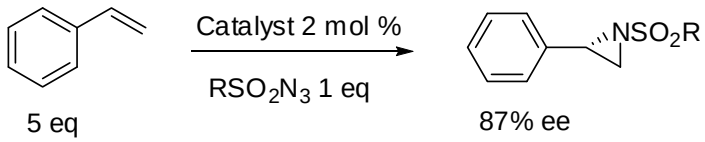


Scheme 30: Bis-oxazolines Cu-catalyzed asymmetric aziridination

Recently Katsuki *et al.*[33] reported design of a robust Ru(salen) complex **12** in aziridination of alkenes with an improved turnover number (TON). Enantioselectivities up to 87% have been reported with styrene and other alkenes (Scheme 31).



12

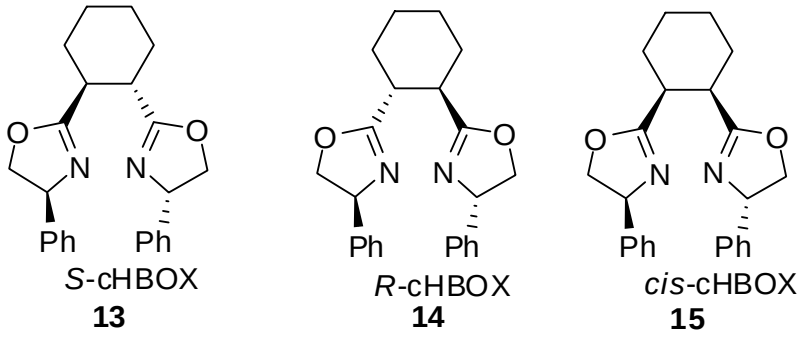


5 eq 87% ee

Scheme 31: Ru(salen)(CO)-catalyzed asymmetric aziridination using azide compound

Other ligands used are S-Vapol and S-Vanol[34] in the catalytic asymmetric aziridination from benzhydryl imines and ethyldiazoacetate.

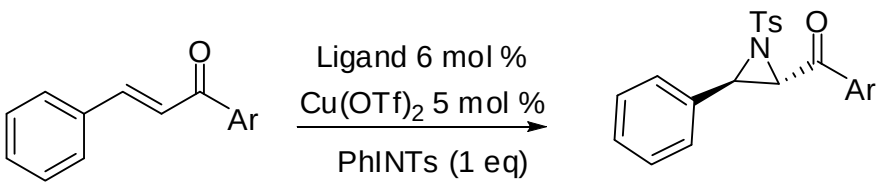
Jiaxi *et al*.[35] developed a new class of cyclohexane-linked bis-oxazolines (**13**, **14**, **15**). They found that highly enantioselective aziridination of chalcones with >99% ee could be achieved using these ligands (Scheme 32).



S-cHBOX **13**

R-cHBOX **14**

cis-cHBOX **15**

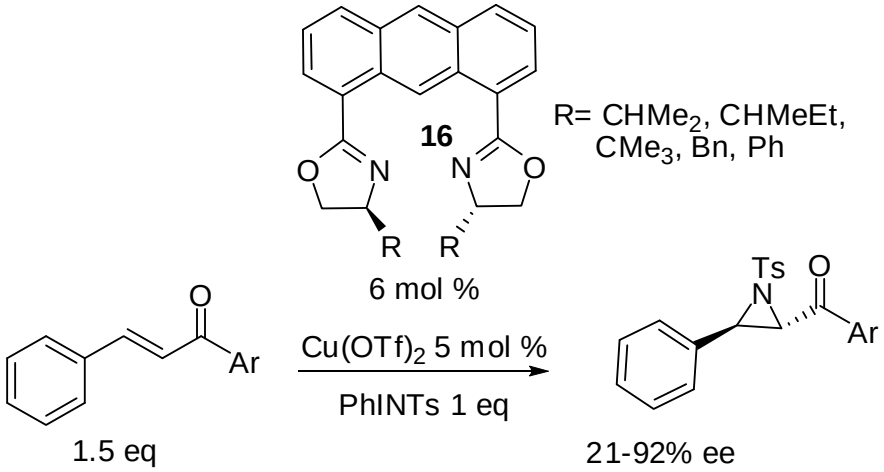


1.5 eq 80-99% ee

Scheme 32: cHBOX- Cu-catalyzed asymmetric aziridination of chalcones

In the same year Jiaxi *et al*.[36] reported a rigid backbone 1,8-anthracene-linked bis-oxazolines (AnBOXs) **16** and evaluated them for the catalytic asymmetric

aziridination with PhINTs as a nitrene source. The results indicated that highly enantioselective aziridination of chalcones catalyzed by AnBOX and CuOTf complex could be achieved with excellent ees and the opposite enantioselectivity, compared with the Evans bis(oxazoline) ligands (Scheme 33).



Scheme 33: Cu-catalyzed asymmetric aziridination of chalcones

2.1.3. Present Work:

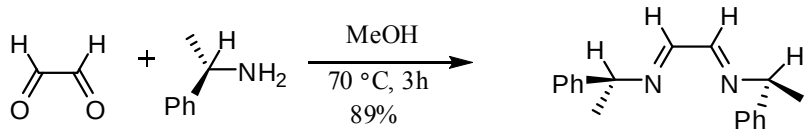
Aziridination reactions using bromamine-T and other nitrene precursors with olefins have been carried out in the presence of various transition metal catalysts. Almost all reactions involving chiral aziridination reported so far have used PhINTs or PhINNs as the nitrene source. A few have reported use of *p*-toluene sulfonylazide for this purpose. Chanda *et al*.[15] reported for the first time, use of bromamine-T as a superior source of nitrene in aziridination. Use of PhINTs as nitrene source has some limitation as it generates iodobenzene which is difficult to separate from the product and there are also reports on PhINTs leading to faster reactions and explosions. We have developed some new chiral ligands and catalysts with a view to apply them in asymmetric aziridination.

2.1.4. Results and Discussion:

Part I. Homogeneous Ligands

A. Synthesis of *N,N'*-(ethane-1,2-diylidene) bis ((*S*)-1-phenylethanamine) a new chiral diimine ligand (19)

Glyoxal **17** and (*S*)-α-methyl benzyl amine **18** were mixed in MeOH at room temperature. The mixture was then stirred for 3h at 70 °C and the ligand **19** formed was extracted with hexane (Scheme 34).

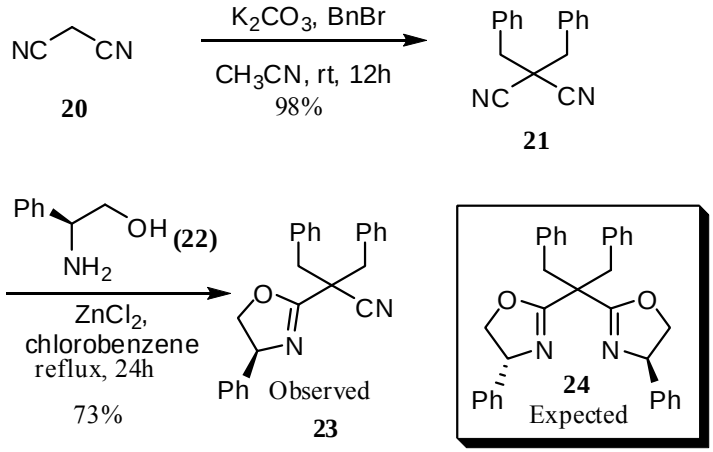


17 **18** **19**

Scheme 34

B. Attempted synthesis of 2-benzyl-3-phenyl-2-(*S*)-(4-phenyl-4,5-dihydro-oxazol-2-yl) propanenitrile (24)

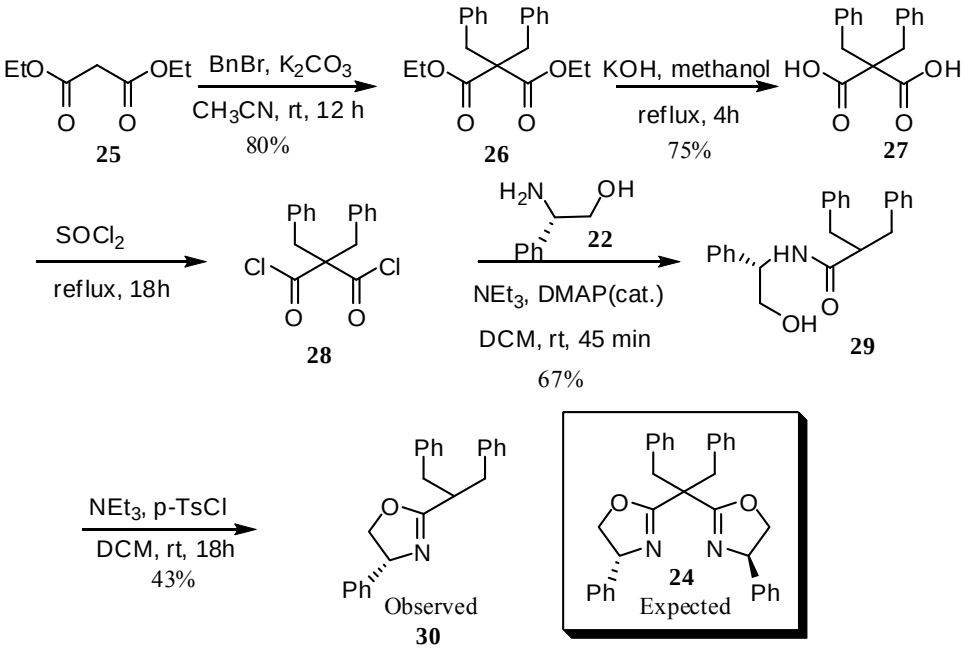
Commercially available malononitrile **20** was converted into dibenzylmalononitrile **21** which was further reacted with (*S*)-(+)-2-amino-3-methyl-1-butanol **22** (3 eq) in anhydrous chlorobenzene under reflux for 2 days in the presence of a catalytic amount of anhydrous zinc dichloride (10 mol%). However the product obtained was 2-benzyl-3-phenyl-2-(*S*)-(4-phenyl-4,5-dihydrooxazol-2-yl) propanenitrile **23** in 73% yield instead of the required dibenzyl bis(oxazoline) **24** (Scheme 35).



Scheme 35

C. Attempted synthesis of dibenzyl bis-oxazoline ligand (24)

Diethyl malonate **25** was reacted with benzyl bromide in presence of anhydrous potassium carbonate in acetonitrile to furnish dibenzyl derivative of diethyl malonate **26** which on hydrolysis afforded dibenzyl derivative of malonic acid **27**. The acid **27** was converted to acid chloride **28** with thionyl chloride and further reacted with phenyl glycinol **22** and triethyl amine in dichloromethane at room temperature to yield the amide **29**. Amide **29** was cyclised *via* reaction with tosyl chloride in presence of catalytic amount of DMAP in dichloromethane. However, the undesired dibenzyl mono-oxazoline ligand **30** was obtained instead of the expected ligand **24** (Scheme 36).

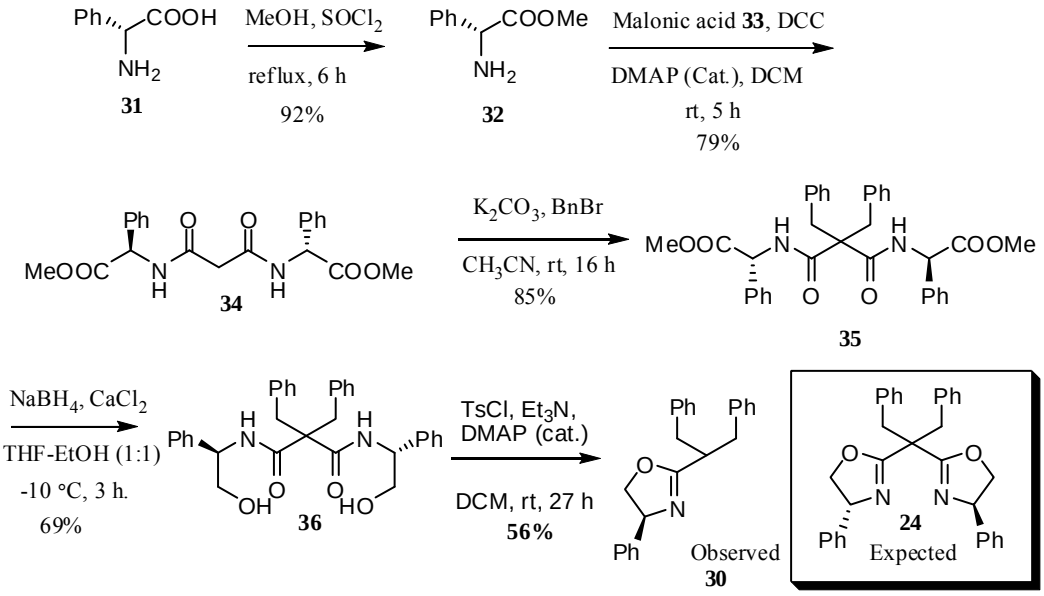


Scheme 36

D. Attempted synthesis of dibenzyl bis-oxazoline ligand (24)

Failure in the synthesis of dibenzyl bis(oxazoline) **24** necessitated development of an alternate route (Scheme 38) where phenyl glycine **31** was converted to phenyl glycine methylester **32** with thionyl chloride in methanol. Ester **32** was coupled with malonic acid **33** using DCC in the presence of catalytic amount of DMAP to furnish diamide **34** in 79% yield. Dibenzylation of **34** using benzyl bromide in acetonitrile afforded dibenzyl derivate **35**. Compound **35** was subjected to sodium borohydride/calcium chloride reduction to afford dihydroxy diamide **36**.

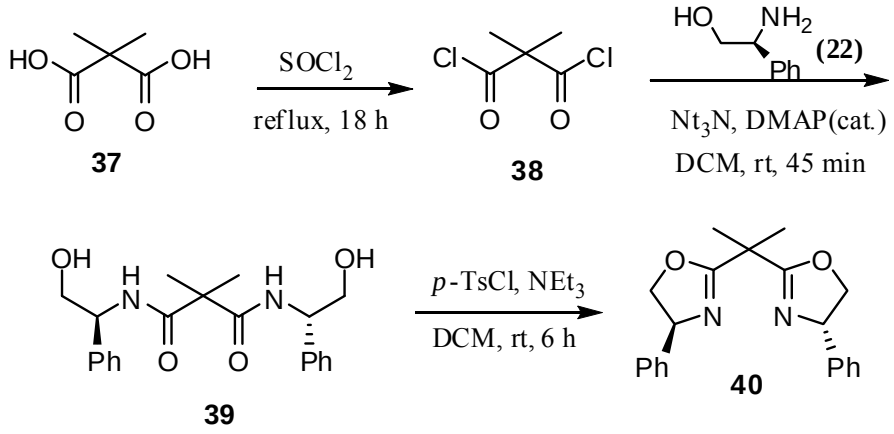
Further it was cyclised by treatment of its tosylate in the presence of catalytic amount of DMAP in dichloromethane. The undesired dibenzyl mono-oxazoline ligand **30** was obtained as the sole product and the required bis-oxazoline **24** was not formed at all (Scheme 37).



Scheme 37

E. Synthesis of 2,2'-isopropylidenebis(*S*)-(-)-(4-phenyl)-2-oxazoline, chiral bis-(oxazoline) ligand[27]

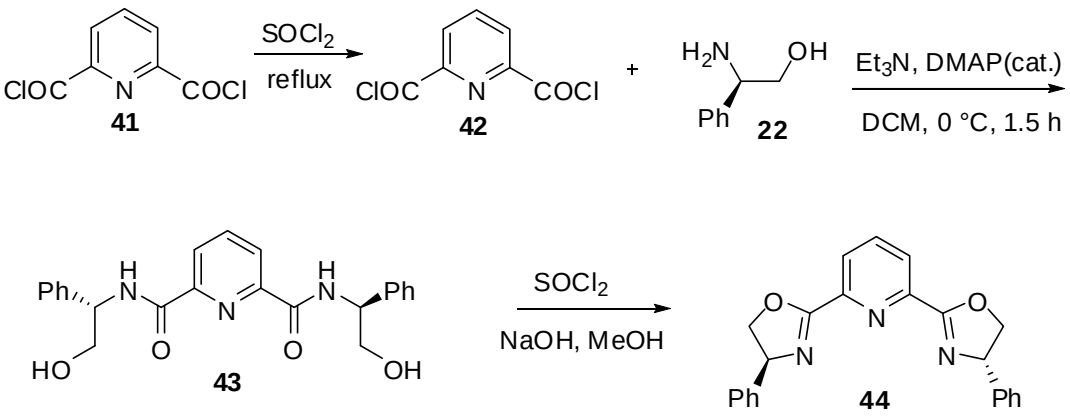
Synthesis of bis-(oxazoline) involves lithium aluminium hydride (LAH) reduction of commercially available (*S*)-phenyl glycine to the corresponding (*S*)-phenyl glycinol **22**, followed by acylation with dimethylmalonate dichloride **38**. The dihydroxy malonodiamide **39** was cyclized to the bis-(oxazoline) **40** with tosyl chloride and catalytic amount of DMAP (Scheme 38).



Scheme 38

F. Synthesis of (*S*,*S*)-2,6-bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine (44)[37]

The pybox ligand **44** was synthesized from the commercially available phenyl glycinol **22** in three steps. 2,6-Pyridine dicarboxylic acid **41** was refluxed with thionyl chloride and the diacid chloride **42** was isolated by distillation of excess thionyl chloride. The residue was treated with the amino alcohol **22** in DCM at 0 °C, followed by addition of thionyl chloride to yield the pybox ligand hydrochloride. Neutralization of the salt was achieved by stirring a methanolic solution of the salt with aqueous sodium hydroxide at room temperature for 3 days. Recrystallization from ethyl acetate and petroleum ether yielded the pybox **44** (Scheme 39).



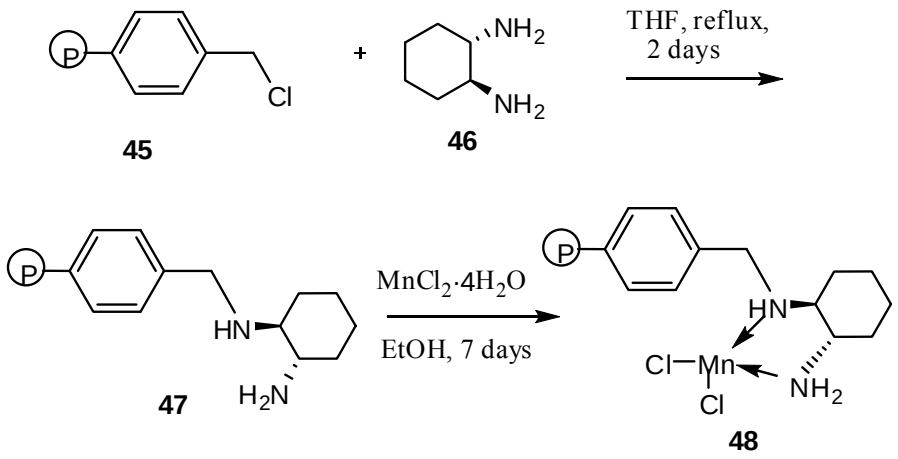
Scheme 39

Part II. Heterogeneous metal catalyst

Synthesis of novel manganese based heterogeneous metal catalyst

A manganese based chiral metal catalyst with 8% cross-linked chloromethylated polydivinylbenzene (Ps-DVB) **48** was synthesized starting from *trans* 1,2-diaminocyclohexane **46** (scheme 40).

The first step in the synthesis of the catalyst was to bind 1,2-diaminocyclohexane to the polymer **45**. The Ps-DVB **45** (8% cross linked) polymer resin was chosen as the support. In this reaction 1,2-diaminocyclohexane **46** was loaded on activated polymer beads. The loading of 1,2-diaminocyclohexane **46** was confirmed by the estimation of nitrogen



Scheme 40

The second step in the catalyst synthesis included coordination of the metal ion with the polymer anchored ligand **47**. Thus an ethanolic solution of $MnCl_2 \cdot 4H_2O$ with polymer anchored 1,2-diaminocyclohexane **47** was stirred to obtain manganese catalyst **48**.

Characterization of the Catalyst

Elemental analyses at different stages of preparation of catalyst are given in Table 1. 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.

Table 1: Elemental analysis at different stages of polymer catalyst preparation

Polym. **45**			Polym. **47**				Polym. **48**		
72.95	5.93	17.50	54.27	9.35	3.45	11.18	61.76	10.59	10.47
% C	% H	% Cl	% C	% H	% N	% Cl	% C	% H	% 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 3326, 526 and 1699 cm^{-1} respectively (Figure 1).

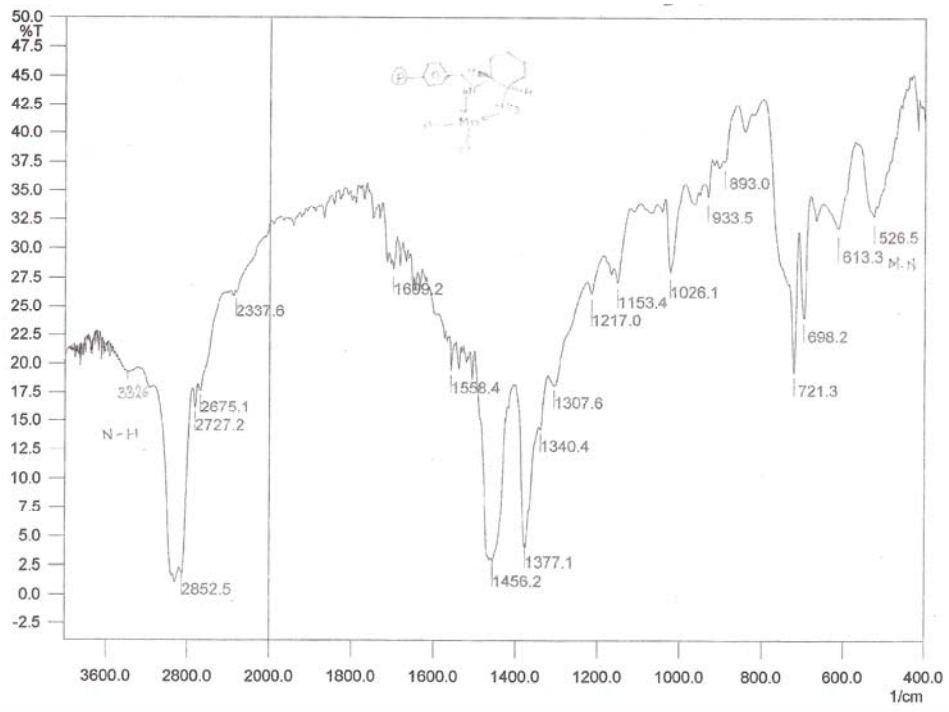


Figure 1: FT-IR spectrum of **48**

ESR was recorded in the granular form on ESR, Bruker EMX instrument. The main peak at 3124 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 (Figure 2).

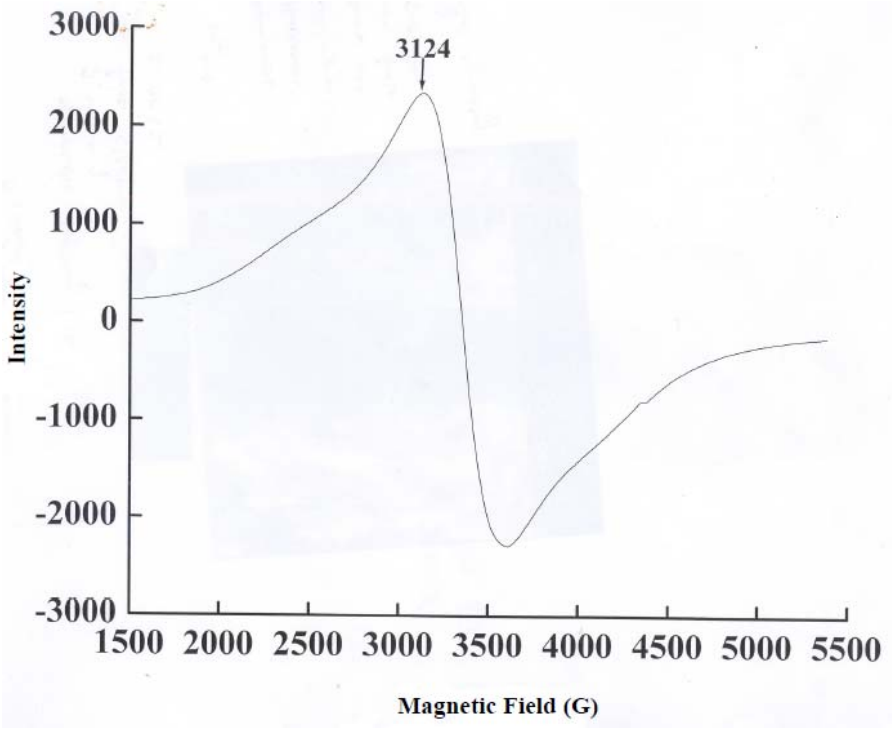


Figure 2: ESR spectrum of **48**

In DTA-TG analysis, it was found that polymer degradation starts above 225 °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 225 °C (Figure 3).

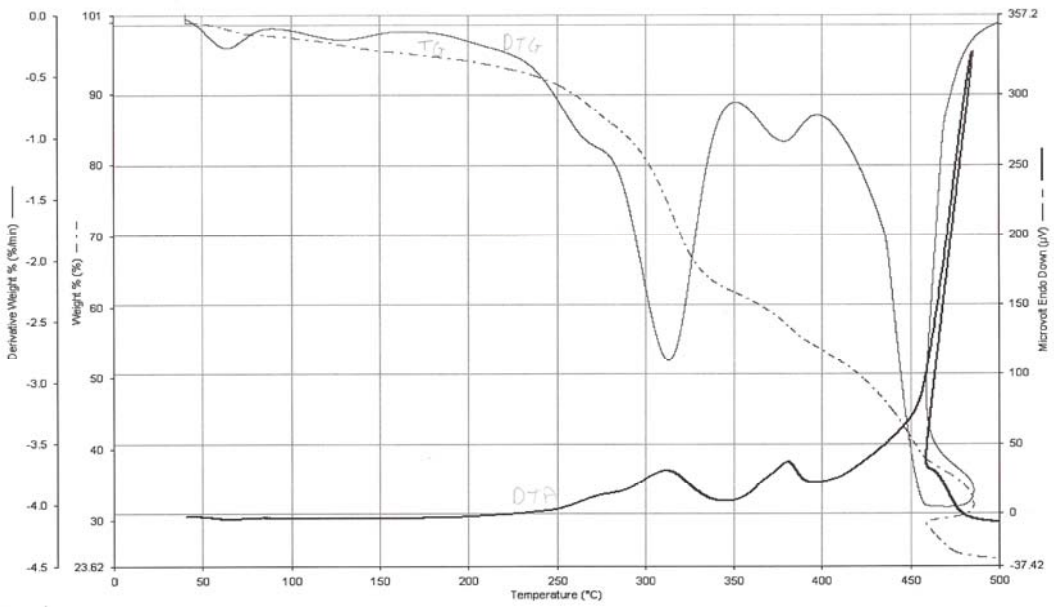
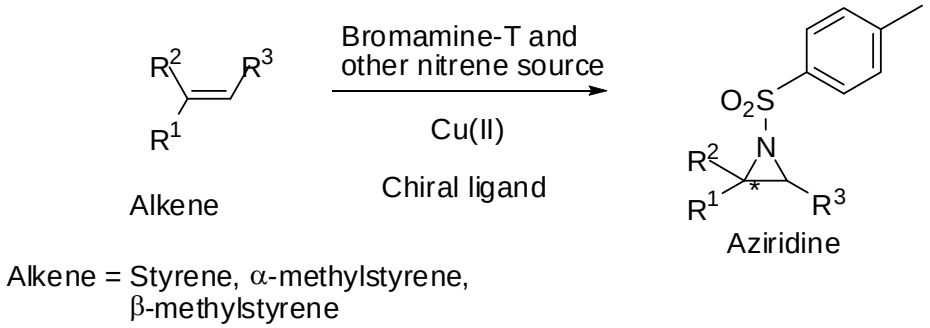


Figure 3: DTA-TG spectrum of **48**

The surface area of the support **45** was found to be 37.37 m^2/g while that of the catalyst **48** 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.

Part III: Asymmetric aziridination of alkenes using chiral ligands and catalyst

Asymmetric aziridination reaction of olefins using of bromamine-T and other nitrene precursors was carried out in the presence of various transition metal catalysts using chiral ligands (Scheme-41).

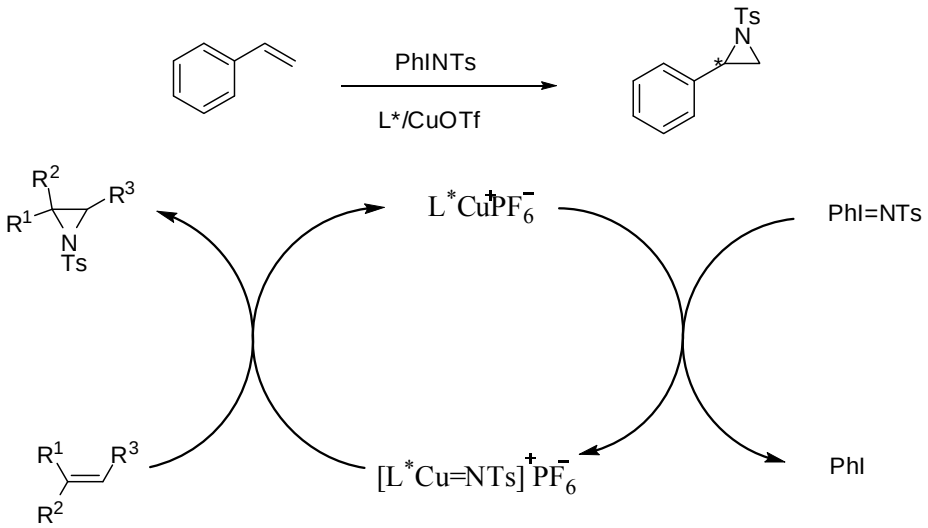


Scheme 41

Mechanistic studies of copper-catalyzed alkene aziridination

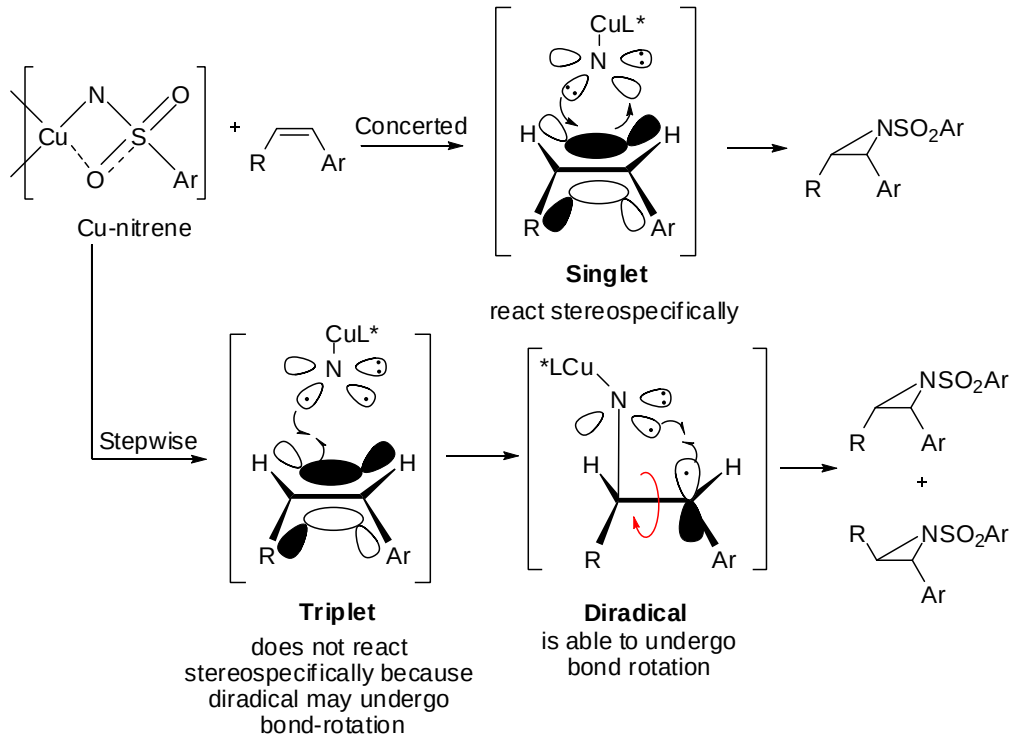
According to Jacobsen *et al.*[12d] copper-catalysed asymmetric aziridination reaction mechanism involves transfer of nitrene generated from PhINTs in presence of Cu catalyst *via* Cu nitrenoid intermediate (Scheme 42).

Evans[12a] has suggested that the active catalyst in their system is in the +II oxidation state [Cu(II)] and most successful for *trans* alkenes. Jacobsen has concluded that the reaction is strictly first order in alkene as a result of kinetic studies and suggested a Cu(III)-nitrene species to be the reactive intermediate in a Cu(I)/Cu(II) catalytic cycle. It is quite clear that the mechanism is system-dependent.



Scheme 42: Mechanism of asymmetric aziridination

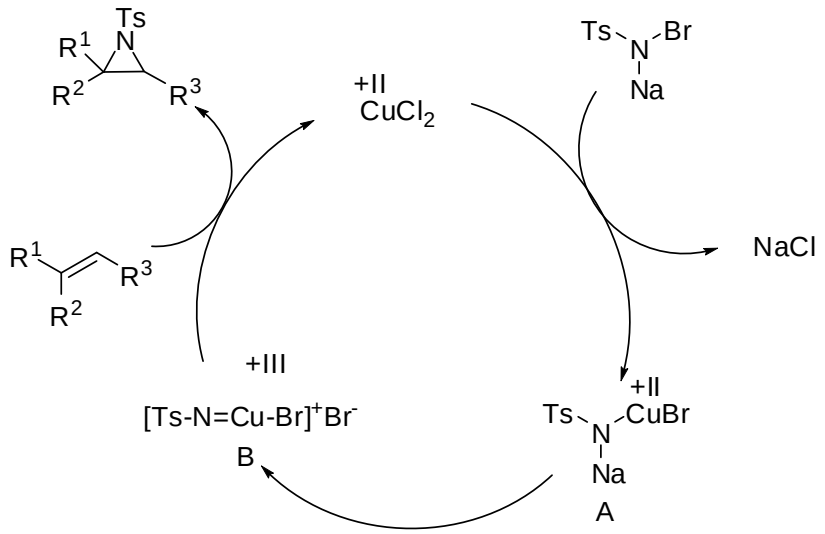
Nitrenes usually were generated by thermal or photochemical decomposition of the corresponding nitrene source and these methods basically lead to mixtures of more reactive singlet and more stable triplet nitrenes; only singlet nitrenes in which nitrogen may be imagined to retain its non-bonded electrons in two orbitals, each containing an anti-parallel electron pair may be relied upon to react stereospecifically with alkenes (Scheme 43).



Scheme 43: Nitrene transfer in the Cu-catalyzed asymmetric aziridination

Triplet nitrenes bearing non-bonded electrons in three orbitals, one filled with an anti-parallel electron-pair and two other orbitals being semi-filled with one electron each, of parallel spin react in a two-step process with alkenes, in which an N–C bond is formed in each step, whereas singlet nitrenes are able to form two new bonds in a concerted process.

A probable mechanistic pathway for aziridination using bromamine-T was proposed by Chanda *et al.*[15] Initially, bromamine-T reacts with copper chloride giving intermediate **A** with elimination of sodium chloride. The intermediate **A** provides **B**, which is similar to the one suggested by Jacobsen in the redox mechanism, having a discrete Cu(III) nitrene reactive active species capable of transferring the nitrogen center to alkene affording an aziridine (Scheme 44).



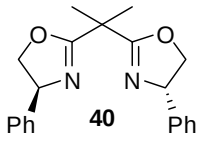
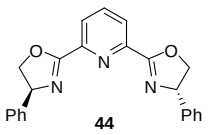
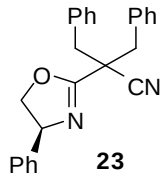
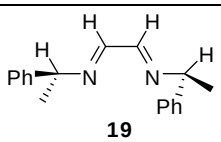
Scheme 44: Plausible mechanism of aziridination of alkenes

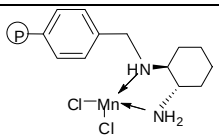
A few new chiral ligands and catalysts have been synthesized and characterized. Their application in asymmetric aziridination has been studied and the results obtained are summarized in Table 1.

Various chiral ligands and their metal complexes, for example Evans bis(oxazoline) **40**, Py-BOX **44**, dibenzyl oxazoline **23**, bis(imine) **19** and a manganese based heterogeneous metal complex **48** in acetonitrile were tried for the asymmetric aziridination reaction. In these cases unfortunately there were not promising enantioselectivities observed in aziridination reactions.

Our initial studies were focused on examining the effects of various copper complexes on aziridination of alkenes using bromamine-T in acetonitrile at ambient temperature. Among all the copper catalysts used, $Cu(OTf)_2$ gave the best yield of the aziridine product (79%), while $CuCl_2$ gave only 45-62% yields (Table 1). When Evan's chiral bis(oxazoline) **40** ligand was introduced to the system, we could fetch the enantioselectivity up to its highest (18% ee). In this case, addition of 12 mol% of the chiral ligand in acetonitrile gave 73% of aziridine with the use of $Cu(OTf)_2$ as catalyst (Table 2).

Table 2. Asymmetric aziridination of alkene using Known and new chiral ligand

Ligand/Catalyst	Substrate	Nitrene Source	Cu(II)	Yield (%)	ee (%)
 **40**	Styrene	PhINTs	$Cu(OTf)_2$	78	53
	α-Methyl styrene	Bromamine-T	$CuCl_2$	56	10
	β-Methyl styrene	Bromamine-T	$CuCl_2$	52	7
	Methyl methacrylate	Bromamine-T	$Cu(OTf)_2$	73	18
 **44**	Styrene	Bromamine-T	$CuCl_2$	75	0
	α-Methyl styrene	Bromamine-T	$CuCl_2$	64	0
	β-Methyl styrene	PhINTs	$CuCl_2$	59	0
	Methyl methacrylate	PhINTs	$Cu(OTf)_2$	72	9
 **23**	Styrene	Bromamine-T	$CuCl_2$	72	0
	α-Methyl styrene	Bromamine-T	$CuCl_2$	60	0
	β-Methyl styrene	Bromamine-T	$CuCl_2$	55	0
	Methyl methacrylate	Bromamine-T	$Cu(OTf)_2$	71	0
 **19**	Styrene	Bromamine-T	$CuCl_2$	79	10
	α-Methyl styrene	Bromamine-T	$CuCl_2$	68	0
	β-Methyl styrene	Bromamine-T	$CuCl_2$	54	0
	Methyl methacrylate	Bromamine-T	$Cu(OTf)_2$	56	5

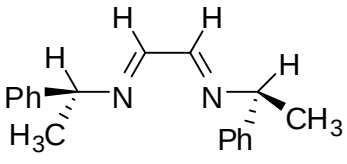
 **48**	Styrene	Bromamine-T	-	49	0
	α-Methyl styrene	Bromamine-T	-	34	0
	β-Methyl styrene	Bromamine-T	-	47	0
	Methyl methacrylate	Bromamine-T	-	15	0

2.1.5. Conclusion

Application of known and new chiral ligands in asymmetric aziridination with bromamine-T as source of nitrene has been evaluated. Moderate enantiomeric excess (upto 50%) with different alkenes have been achieved with bis-oxazoline ligand **40**. However, with better modified ligands of different types, both homogeneous and heterogeneous, improvement in enantiomeric excess upto 80-85% is possible. With these ideas in mind, further work is planned and the same is being executed in our group.

2.1.6. Experimental

N,N'-(Ethane-1,2-diylidene) bis(1-phenylethanamine) (19)



Glyoxal (40% aq. Solution, 0.4 g, 15.5 mmol) and (*S*)-$PhCH(CH_3)NH_2$ (1.7 ml, 13.7 mmol) were mixed in 10 ml of MeOH at room temperature. The mixture was then stirred for 3 h at 70 °C. The product was extracted with 30 mL of hexane and the hexane layer was washed with water, brine and dried (Na_2SO_4). Concenctration and removal of hexane yielded the required ligand as a semi solid, yield 1.7 g (93%).

Mol. Formula : $C_{18}H_{20}N_2$

Mol. Weight : 264

FT IR ($CHCl_3$) : 2123, 1615, 1521 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.56 (d, *J* = 1.9 Hz, 6H), 4.48 (q, *J* = 1.9 Hz, 2H), 7.22 (m, 10H), 8.05 (s, 2H).

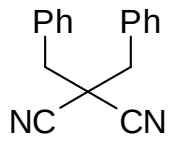
^{13}C NMR (75 MHz, $CDCl_3$) : 23.8, 69.5, 125.4, 127.0, 128.4, 143.4, 160.4

ESI-MS *m/z* : 265.12 $[M+H]^+$

Elemental Analysis : Calcd: C, 81.78; H, 7.63; N, 10.60 %
Found: C, 81.88; H, 7.71; N, 10.48 %

Rotation : $[\alpha]_D^{25}$ = +70.3°, c = 2 in $CHCl_3$

2,2-Dibenzylmalononitrile (21)



To a stirred mixture of malononitrile (500 mg, 7.57 mmol) and benzyl bromide (2.59 g, 1.8 mL, 15.14 mmol) in dry acetonitrile, dried and activated powdered potassium carbonate (2.3 g, 37.84 mmol) was added in one portion. The reaction mixture was further stirred at room temperature for 14 h. The inorganic material was removed by filtration and the reaction mixture was extracted with ether (2 X 20 mL). The combined washing after drying (Na_2SO_4) was

concentrated in vacuum to give a crude product which was purified *via* column chromatography to give the desired dibenzylmalononitrile, yield = 1.79 g (96%).

Mol. Formula : $C_{17}H_{14}N_2$

Mol. Weight : 246

FT IR ($CHCl_3$) : 3389, 2135, 1497, 1216 cm^{-1}

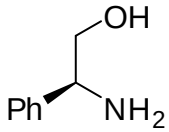
^{1}H NMR (300 MHz, $CDCl_3$) : δ 3.26 (s, 4H), 7.42 (m, 10 H)

^{13}C NMR (75 MHz, $CDCl_3$) : δ 41.0, 43.1, 114.8, 128.6, 128.8, 130.1, 131.9.

ESI-MS *m/z* : 247.36 $[M+H]^+$

Elemental Analysis : Calcd: C, 82.90; H, 5.73; N, 11.37 %
Found: C, 82.82; H, 5.85; N, 11.21 %

(*S*)-2-Amino-2-phenylethanol (Phenyl glycinol) (22)



To a stirred solution of sodium borohydride (3.13 g, 82.69 mmol) in anhydrous THF (50 mL) was added (*S*)-phenyl glycine (5 g, 33 mmol) in one portion. The reaction mixture was cooled to 0 °C and fitted with a reflux condenser and an addition funnel on top of the condenser. The addition funnel was charged with a solution of I_2 (8.4 g, 33 mmol) in 50 mL of THF, which was added dropwise to the contents in the flask over a 1.5 h period with considerable gas evolution. The solution was allowed to warm to room temperature. When the brown color had dissipated to give a cloudy white solution, the reaction was brought to reflux for 19 h. The cloudy white suspension was allowed to cool to room temperature. The addition funnel was charged with 50 mL of MeOH, which was added dropwise with rapid stirring. Vigorous gas evolution was observed. Small aliquots of MeOH were then added until all of the solid white material had dissolved. The reaction mixture gave a white pasty oil that was dissolved in 60 mL of 20% (w/w) aqueous KOH and mechanically stirred for 6 h at room temperature. The light green solution was extracted with CH_2Cl_2 (3 X 25 mL). The combined organic extracts were dried over Na_2SO_4, the organic layer was then filtered through glass wool and concentrated in *vacuo* to give phenyl glycinol as a white solid, mp. 73-77 °C

(lit. mp. 74-77 °C), yield 3.52 g (77%).

Mol. Formula : $C_8H_{11}NO$

Mol. Weight : 137

FT IR ($CHCl_3$) : 3420, 2970, 2880, 1615, 1480 cm^{-1}

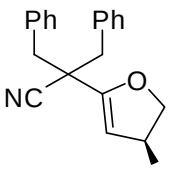
^{1}H NMR (300 MHz, $CDCl_3$) : δ 2.41 (br s, 3H), 3.45 (t, *J* = 10.3, 1H), 3.66 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.02 (dd, *J* = 10.3, 3.8 Hz, 1H), 7.21-7.29 (m, 5H).

ESI-MS *m/z* : 138.12 $[M+H]^+$

Elemental Analysis : Calcd: C, 85.45; H, 6.34; N, 3.83 %
Found: C, 85.62; H, 6.47; N, 3.72 %

Rotation : $[\alpha]_D^{25}$ = - 31.5° c = 0.76 in 1N HCl

(*R*)-2-Benzyl-3-phenyl-2-(4-phenyl-4,5-dihydrofuran-2-yl)propanenitrile (23)



A solution of anhydrous $ZnCl_2$ (27 mg, 0.203 mmol, melted under high vacuum and cooled under nitrogen), in dry chlorobenzene (3 mL) was reacted with dibenzylmalonitrile (500 mg, 2.03 mmol) and (*S*)-phenyl glycinol (696 mg, 5.07 mmol) at room temperature. The resulting mixture was heated under reflux for 24 h. The residue obtained by evaporation of the solvent under reduced pressure was dissolved in dichloromethane, washed with water. The aqueous phase was extracted further with dichloromethane. The combined organic phase was dried with Na_2SO_4, evaporated to dryness and purified by column chromatography to give (*R*)-2-benzyl-3-phenyl-2-(4-phenyl-4,5-dihydrofuran-2-yl)propanenitrile as a pale yellow solid, mp. 156 °C, yield 634 mg (85%).

Mol. Formula : $C_{26}H_{23}NO$

Mol. Weight : 365

FT IR ($CHCl_3$) : 3020, 2948, 2212, 1649, 1598 cm^{-1}

^{1}H NMR : δ 3.21-3.43 (m, 4H), 4.02 (t, 1H), 4.54 (dd, 1H), 5.07 (t,

(300 MHz, $CDCl_3$) 1H), 6.75-6.79 (m, 2H), 7.21-7.25 (m, 3 H), 7.32-7.36 (m, 12 H)

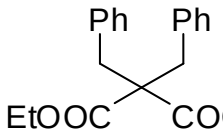
^{13}C NMR : δ 43.1, 43.3, 47.4, 69.5, 75.5, 118.9, 126.5, 127.4, 127.6, 128.3, 128.4, 128.5, 130.0, 134.1, 134.3, 140.8, 163.6
(75 MHz, $CDCl_3$)

Elemental Analysis : Calcd: C, 85.45; H, 6.34; N, 3.83 %
Found: C, 85.62; H, 6.47; N, 3.72 %

ESI-MS *m/z* : 366. 47 $[M+H]^+$

Rotation : $[\alpha]_D^{25} = +53.42°$, c = 0.8 in $CHCl_3$

Diethyl 2,2-dibenzylmalonate (26)



To a stirred mixture of diethylmalonate (1 g, 6.24 mmol) and benzyl bromide (2.46 g, 1.7 mL, 14.36 mmol) in dry acetonitrile, dried and activated powdered potassium carbonate (4.31 g, 31.22 mmol) was added in one portion. The reaction mixture was further stirred at room temperature for 14 h. The inorganic material was removed by filtration and the reaction mixture was extracted with ether (2 X 20 mL). The combined washing after drying (Na_2SO_4) was concentrated in vacuum to give a crude product which was purified *via* column chromatography to give the desired dibenzylmalononitrile, yield = 1.79 g (84%).

Mol. Formula : $C_{21}H_{24}O_4$

Mol. Weight : 340

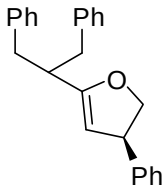
FT IR ($CHCl_3$) : 1736, 1614, 1518 cm^{-1}

^{1}H NMR : δ 1.15 (t, *J* = 7.08, 6H), 3.23 (s, 4H), 4.12 (q, *J* = 7.08, 4H), 7.15-7.28 (m, 10H)
(300 MHz, $CDCl_3$)

ESI-MS *m/z* : 341.13 $[M+H]^+$

Elemental Analysis : Calcd: C, 74.09; H, 7.11 %
Found: C, 74.15; H, 7.24 %

(*R*)-5-(1,3-diphenylpropan-2-yl)-3-phenyl-2,3-dihydrofuran (30)



This compound was synthesis using a procedure similar to the synthesis of bis-oxazoline (**40**) by using diol as starting material.

Mol. Formula : $C_{25}H_{24}O$

Mol. Weight : 340

FT IR ($CHCl_3$) : 3020, 1649, 1598 cm^{-1}

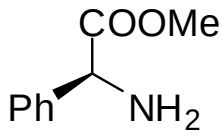
^{1}H NMR (300 MHz, $CDCl_3$) : δ 2.76 (m, 1H), 3.21-3.43 (m, 4H), 4.02 (t, 1H), 4.54 (dd, 1H), 5.07 (t, 1H), 6.75-6.79 (m, 2H), 7.21-7.25 (m, 3 H), 7.32-7.36 (m, 12 H)

^{13}C NMR (75 MHz, $CDCl_3$) : δ 43.1, 43.3, 47.4, 69.5, 75.5, 126.5, 127.4, 127.6, 128.3, 128.4, 128.5, 130.0, 134.1, 134.3, 140.8, 163.6

Elemental Analysis : Calcd: C, 88.20; H, 7.11 %
Found: C, 89.20; H, 7.23 %

Rotation : $[\alpha]_D^{25} = +36°$, c = 0.8 in $CHCl_3$

(*S*)-Methyl 2-amino-2-phenylacetate (32)



Phenyl glycine (6 g, 0.0397 mol) was dissolved in MeOH (50 mL) and freshly distilled thionyl chloride (7 g, 4.3 mL, 0.059 mol) was added cautiously to this solution. The mixture was refluxed for 6 h. Solvent was distilled off and ice-cold water was added to the residue. It was then extracted with EtOAc, washed with $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to furnish white solid, mp. 188-192 °C (lit. 189-191 °C), yield 6 g (92%).

Mol. Formula : $C_9H_{11}NO_2$

Mol. Weight : 165

FT IR ($CHCl_3$) : 3524, 2870, 2880, 1665, 1465 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) : δ 2.00 (s, 2H), 3.70 (s, 3H), 4.62 (s, 1H), 7.34-7.36 (m, 5H)

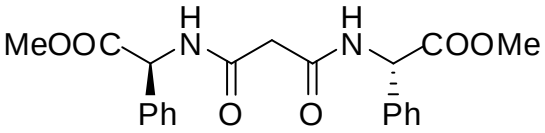
^{13}C NMR (75 MHz, $CDCl_3$) : δ 52.2, 58.5, 126.6, 128.6, 140.0, 174.2

Elemental Analysis : Calcd: C, 65.44; H, 6.71; N, 8.48 %

Found: C, 65.29; H, 6.83; N, 8.36 %

Rotation : $[\alpha]_D^{25}$ = -144°, c = 1 in 1N HCl

***N,N'*-Bis((*S*)-2-acetamido-2-phenylacetate)malonoamide (34)**



To a solution of malonic acid (1.5 g, 0.014 mol), phenyl glycinemethyl ester (5.2 g, 0.031 mol) and DMAP (cat.) in dry CH_2Cl_2, was added a solution of DCC (6.3 g, 0.031 mol) in dry CH_2Cl_2 at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. The urea formed was filtered off and the organic layer was concentrated *in vacuo*. Silica gel column chromatographic purification of the residue using ethyl acetate and petroleum ether mixture (1:9) gave the amide in quantitative yield, mp.88-90 °C.

Mol. Formula : $C_{21}H_{22}N_2O_6$

Mol. Weight : 398

FT IR ($CHCl_3$) : 3289, 2870, 2880, 1751, 1666, 1498 cm^{-1}

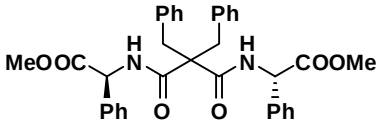
^{1}H NMR (300 MHz, $CDCl_3$) : δ 3.29 (s, 2H), 3.72 (s, 6H), 5.57 (d, 2H), 7.36 (m, 5H), 7.80 (d, 2H)

Elemental Analysis : Calcd: C, 63.31; H, 5.57; N, 7.03%

Found: C, 63.43; H, 5.61; N, 7.15 %

Rotation : $[\alpha]_D^{25} = +14°$, c = 1 in $CHCl_3$

***N,N'*-Bis((*S*)-2-acetamido-2-phenylacetate)-2,2-dibenzylmalonoamide (35)**



To a stirred mixture of diamide (500 mg, 1.25 mmol) and benzyl bromide (493 mg, 0.34 mL, 2.89 mmol) in dry acetonitrile, dried and activated powdered potassium carbonate (867 mg, 6.27 mmol) was added in one portion. The reaction mixture was further stirred at room temperature for 14 h. The inorganic material was removed by filtration and the reaction mixture was extracted with ether (2 X 20 mL). The combined washing after drying (Na_2SO_4) was concentrated in vacuum to give a crude product which was purified *via* column chromatography to give the desired dibenzylmalononitrile, yield 701 mg (96%).

Mol. Formula : $C_{35}H_{34}N_2O_6$

Mol. Weight : 578

FT IR ($CHCl_3$) : 3429, 2870, 2480, 1745, 1654, 1497 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) : δ 3.34 (t, 4H), 3.66 (d, 6H), 5.44 (d, 2H), 7.12 (m, 20H), 8.08 (m, 2H)

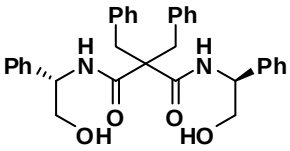
^{13}C NMR (75 MHz, $CDCl_3$) : δ 43.3, 52.4, 56.7, 58.9, 126.5, 127.2, 128.1, 128.6, 129.2, 135.6, 135.8, 170.5, 171.2

Elemental Analysis : Calcd: C, 72.65; H, 5.92; N, 4.84 %

Found: C, 72.53; H, 6.14; N, 4.95 %

Rotation : $[\alpha]_D^{25} = +26°$, *c* = 1 in $CHCl_3$

_N,N'_-Bis((S,S)-2-hydroxy-1-phenylethyl)-2,2-dibenzylmalonamide (36)



To a suspension of $NaBH_4$ (196 mg, 5.18 mmol) in 20 mL THF was added powdered anhydrous $CaCl_2$ (383 mg, 3.46 mmol). After one hour of stirring, methylester (500 mg, 0.86 mmol) in 30 mL of THF was added dropwise and the mixture was stirred overnight at room temperature. After diluting in ethyl acetate (30 mL) for 1 h, the upper layer was separated, and again 20 mL of ethyl acetate was added and the separation repeated. The combined washing after drying (Na_2SO_4) was concentrated in vacuum to give a crude product which was purified *via* column chromatography to give the desired diol as a semi solid, yield 412 mg (91%).

Mol. Formula : $C_{33}H_{34}N_2O_4$

Mol. Weight : 522

FT IR ($CHCl_3$) : 3429, 2870, 2480,1654, 1497 cm^{-1}

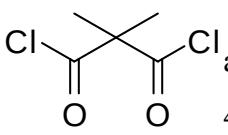
^{1}H NMR (300 MHz, $CDCl_3$) : δ 3.38 (t, 4H), 3.71 (d, 4H), 4.98-5.03 (m, 2H), 7.09-7.26 (m, 20H), 7.91-7.96 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 45.2, 57.2, 60.3, 65.8, 127.7, 128.6, 130.0, 137.8, 140.9, 175.5.

Elemental Analysis : Calcd: C, 75.84; H, 6.56; N, 5.36 %
Found: C, 75.73; H, 6.61; N, 5.38 %

Rotation : $[\alpha]_D^{25} = +38°$, c = 1 in $CHCl_3$

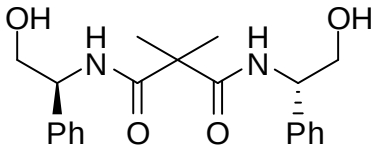
Dimethylmalonyl dichloride (37)



A dry round-bottom flask equipped with an addition funnel and magnetic stir bar was charged with dimethylmalonic acid (5.7 g, 43.14 mmol), dimethylformamide (630 mg, 0.61 mL, 8.6 mmol) and 50 mL of CH_2Cl_2. The solution was cooled to 0 °C and the addition funnel was charged with oxalyl chloride (16.43 g, 130 mmol, 11.3 mL), which was added

dropwise with gas evolution over 1.5 h. The cloudy yellow solution was stirred for 18 h at 25 °C. The solution cleared and turned to a deep yellow color as the reaction progressed. The solution was concentrated *in vacuo* to give a yellow liquid with denser orange oil droplets. The mixture was distilled immediately (150-152 °C, 760 mm of Hg) under N_2 to afford 6.7 g (90%) as a clear, colorless liquid.

***N,N'*-Bis((S,S)-2-hydroxy-1-phenylethyl)-2,2-dimethylmalonamide (39)**

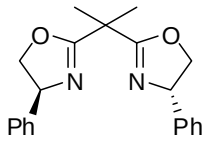


A 500 mL flask was charged with a solution of phenyl glycinol (2.68 g, 19.53 mmol) (based on a 100% yield of the previous reaction), in 50 mL of CH_2Cl_2. The solution was cooled in an ice bath and triethylamine (4.49 g, 44.38 mmol, 6.4 mL) was added *via* syringe. To this, a solution of dimethylmalonyl dichloride (1.5 g, 8.8 mmol) in 50 mL of CH_2Cl_2 was slowly added to the vigorously stirred reaction over 20 min. The ice bath was removed and the thick white suspension was stirred at room temperature for 35 min. CH_2Cl_2 (50 mL) was added, dissolving most of the white solid. The reaction mixture was washed with 100 mL of 1N HCl and the aqueous layer was back-extracted with CH_2Cl_2. The combined organic extract was washed with 100 mL of saturated aqueous $NaHCO_3$ and the aqueous layer was back-extracted with CH_2Cl_2. The combined organic extracts were washed with 100 mL of brine. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give *N,N'*-bis((S,S)-2-hydroxy-1-phenylethyl)-2,2-dimethylmalonamide as a pale yellow solid, mp. 109-112 °C (lit. mp. 110-111 °C), yield 3.1 g, (81%).

Mol. Formula	**:**	$C_{21}H_{26}N_2O_4$
Mol. Weight	**:**	370
FT IR ($CHCl_3$)	**:**	3340, 2970, 2910, 2880, 1645, 1545 cm^{-1}
^{1}H NMR (300 MHz, $CDCl_3$)	**:**	δ 1.49 (s, 6H), 3.69-3.71 (m, 4H), 4.63 (br s, 2H), 5.01-5.07 (m, 2H), 7.22-7.39 (m, 10H), 7.56 (d, 2H)
Elemental Analysis	**:**	Calcd: C, 68.09; H, 7.07; N, 7.56 % Found: C, 68.17; H, 7.21; N, 7.69 %

Rotation : $[\alpha]_D^{25} = +28°$, c = 1, in $CHCl_3$

Bis(oxazoline): (4S,4'S)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole) (40)



A 100 mL round-bottom flask with a magnetic stir bar was charged with dihydroxymalonodiamide **7** (2.6 g, 7 mmol), 4-(dimethylamino)pyridine (0.085 g, 0.7 mmol) and 40 mL of CH_2Cl_2. Triethylamine (2.8 g, 28 mmol, 4 mL) was added *via* syringe. The flask was placed in a room temperature water bath, and a solution of *p*-toluenesulfonyl chloride (2.68 g, 14 mmol) in 25 mL of CH_2Cl_2 was added. The bright yellow solution was stirred at room temperature for 27 h. The reaction mixture containing crystalline solid was diluted with 50 mL of CH_2Cl_2 and upon washing with 50 mL of saturated aqueous NH_4Cl, a white solid formed in the aqueous layer. Water (50 mL) was added, the layers were separated and the aqueous layer was back extracted with CH_2Cl_2. The combined organic extracts were washed with 50 mL of saturated aqueous $NaHCO_3$. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give bis-oxazoline as a semi solid, yield 1.17 g (50%).

Mol. Formula : $C_{21}H_{22}N_2O_2$

Mol. Weight : 334

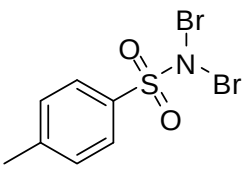
FT IR ($CHCl_3$) : 2960, 2870, 2880, 1665, 1465 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.69 (s, 6H), 4.17 (t, *J* = 10.3, 2H), 4.68 (dd, *J* = 10.3, 3.8 Hz, 2H), 5.23 (dd, *J* = 10.3, 3.8 Hz, 2H), 7.30 (m, 10H).

Elemental Analysis : Calcd: C, 75.42; H, 6.63; N, 8.38 %
Found: C, 75.37; H, 6.81; N, 8.27 %

Rotation : $[\alpha]_D^{25} = +159°$, c = 1 in EtOH

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 addition funnel 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 h.

Mol. Formula : $C_7H_7O_2Br_2NS$

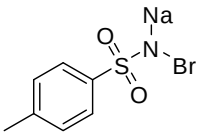
Mol. Weight : 329

M.P. : 92 °C (lit M.P. 92-93 °C)

Analysis : Calcd: N, 4.20; S, 9.70; Br, 48.6 %

: Found: N, 4.26; S, 9.73; Br, 48.56 %

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 bromamine-T separated out. The solid was filtered under suction, washed quickly with minimum quantity of water and dried over P_2O_5 in a desiccator, yield 2.8 g (86%), mp. 112 °C.

Mol. Formula : $C_7H_7BrNNaO_2S$

Mol. Weight : 272

FT IR ($CHCl_3$) : 3020,1741, 1331, 1215, 1163, 882, 759 cm^{-1}

^{1}H NMR (300 MHz, D_2O) : δ 2.41 (s, 3H), 7.43 (d , *J* = 1.9 Hz, 2H), 7.71 (d, *J* = 1.9 Hz, 2H)

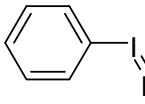
^{13}C NMR (75 MHz, D_2O) : δ 143.38, 134.30, 131.26, 129.31

ESI-MS *m/z* : 273.09 $[M+H]^+$

Elemental Analysis : Calcd: C, 30.90; H, 2.59; Br, 29.37; N, 5.15; S, 11.78 %

Found: C, 30.87; H, 2.63; Br, 29.05; N, 5.28; S, 11.61 %

[N- (p-tosylsulfonyl) imino]phenyliodinane (PhINTs)



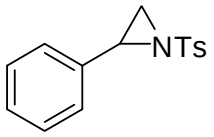
Iodobenzene diacetate (3.22 g, 1.0 mmol) was added to a stirred mixture of potassium hydroxide (1.4 g, 0.025 mmol) and *p*-toluenesulfonamide (1.71 g, 1.0 mmol) in methanol (40 mL) keeping the temperature below 10 °C during the addition. The resulting clear yellow solution was stirred for 3 h at room temperature, poured into a large excess of ice cold water and stirred for 1 h. Yellow colored solid precipited on standing overnight which was isolated by filtration and dried at room temperature in vacuum desiccators; yield 2.56 g, 68%.

Mol. Formula	**:**	$C_{13}H_{12}INO_2S$
Mol. Weight	**:**	373
^{1}H NMR (300 MHz, DMSO-d_6)	**:**	δ 2.37 (s, 3H), 7.73-7.14 (m , 9H)
^{13}C NMR (75 MHz, DMSO-d_6)	**:**	δ 95.2, 125.9, 126.1, 128.1, 129.6, 129.7, 131.0, 137.5, 141.6, 142.2, 142.5
Elemental Analysis	**:**	Calcd: C, 41.84; H, 3.24; N, 3.75 % Found: C, 41.79; H, 3.27; N, 3.62 %

Typical experimental procedure for aziridination

Alkene (0.101 g, 1.0 mmol), nitrene donor (1.5 mmol) and copper (II) triflate (0.15 mmol) were stirred in acetonitrile (2.5 mL) at 25 °C. If a chiral ligand (0.07 mmol) was added, this was added together with the copper(II) triflate in dry acetonitrile prior to the addition of the alkene and nitrene donor. Reaction time varied according to the nitrene precursor used. The reaction mixture was then filtered through a plug of silica gel with ethyl acetate (50 mL) as eluent. The filtrate was evaporated under vacuum to afford crude product, which was further purified by column chromatography over silica gel using hexane: ethyl acetate as eluent.

N-(p-Tolylsulfonyl)-2-phenylaziridine:



Mol. Formula : $C_{15}H_{15}NO_2S$

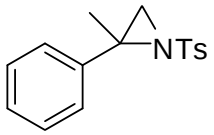
Mol. Weight : 273

FT IR ($CHCl_3$) : 3017, 1600, 1327, 1217, 1161 cm^{-1}

1H NMR (300 MHz, $CDCl_3$) : δ 2.72 (d, *J* = 6.3 Hz, 1H), 2.82 (s, 3H), 3.39 (d, *J* = 9.8 Hz, 1H), 4.18 (1H, dd, *J* = 9.7, 6.5 Hz,), 7.7-7.5 (7H, m), 8.20 (d, *J* = 10.8 Hz, 2H)

MP : 86-87 °C (lit. mp. 87-88 °C)

N-(p-Tolylsulfonyl)-2-methyl-2-phenylaziridine:



Mol. Formula : $C_{16}H_{17}NO_2S$

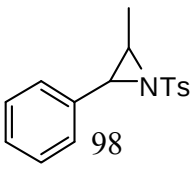
Mol. Weight : 287

FT IR ($CHCl_3$) : 3060, 2992, 1600, 1160 cm^{-1}

1H NMR (300 MHz, $CDCl_3$) : δ 2.16 (3H, s), 2.81 (3H, s), 7.55 – 7.15 (7H, m), 7.80 (d, *J* = 8 Hz, 2H)

MP : 80-81 °C (lit mp 82-83 °C)

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



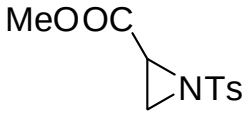
Mol. Formula : $C_{16}H_{17}NO_2S$

Mol. Weight : 287

FT IR ($CHCl_3$) : 3060, 3028, 2992, 1440, 930 cm^{-1}

1H NMR (300 MHz, $CDCl_3$) : δ 1.86 (d, *J* = 7 Hz, 3H), 2.47 (s, 3H), 2.97 (m, 1H), 3.82 (d, *J* = 7 Hz, 1H), 7.18 – 7.29 (m, 7H), .84 (d, *J* = 8 Hz, 2H)

Methyl 1-tosylaziridine-2-carboxylate:



Mol. Formula : $C_{11}H_{13}NO_4S$

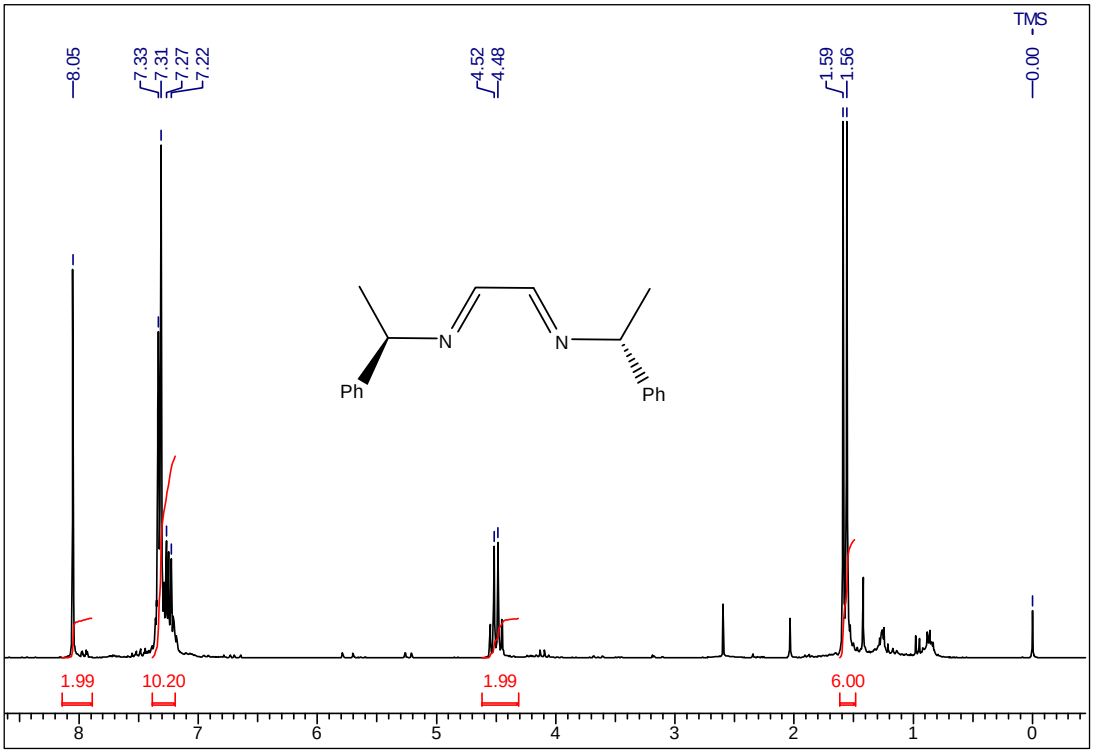
Mol. Weight : 255

FT IR ($CHCl_3$) : 3010, 17381, 1331, 1215, 1163 cm^{-1}

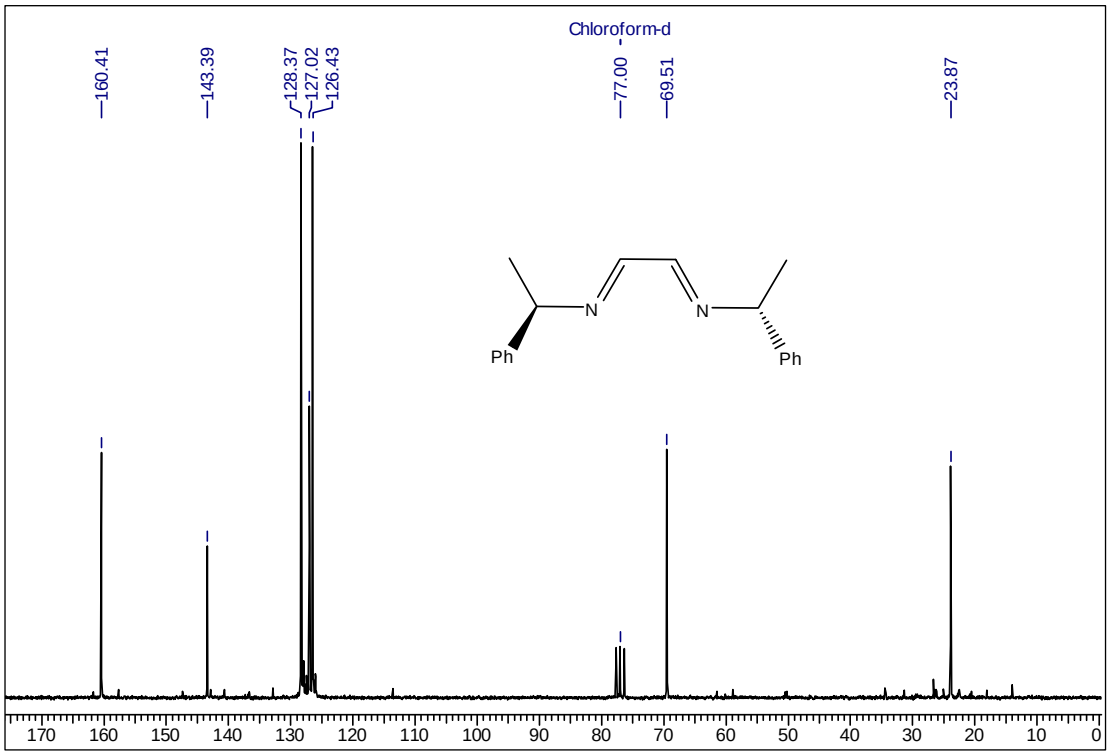
1H NMR (300 MHz, $CDCl_3$) : δ 2.45 (s, 3H); 2.57 (d, *J* = 15 Hz, 1H); 2.78 (d, *J* = 15 Hz, 1H); 3.35 (dd, 1H); 3.74 (s, 3H), 7.34 (d, *J* = 8 Hz, 2H); 7.82 (d, *J* = 8 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) : δ 21.60, 31.94, 35.57, 52.81, 128.11, 129.81, 133.78, 145.23, 167.15

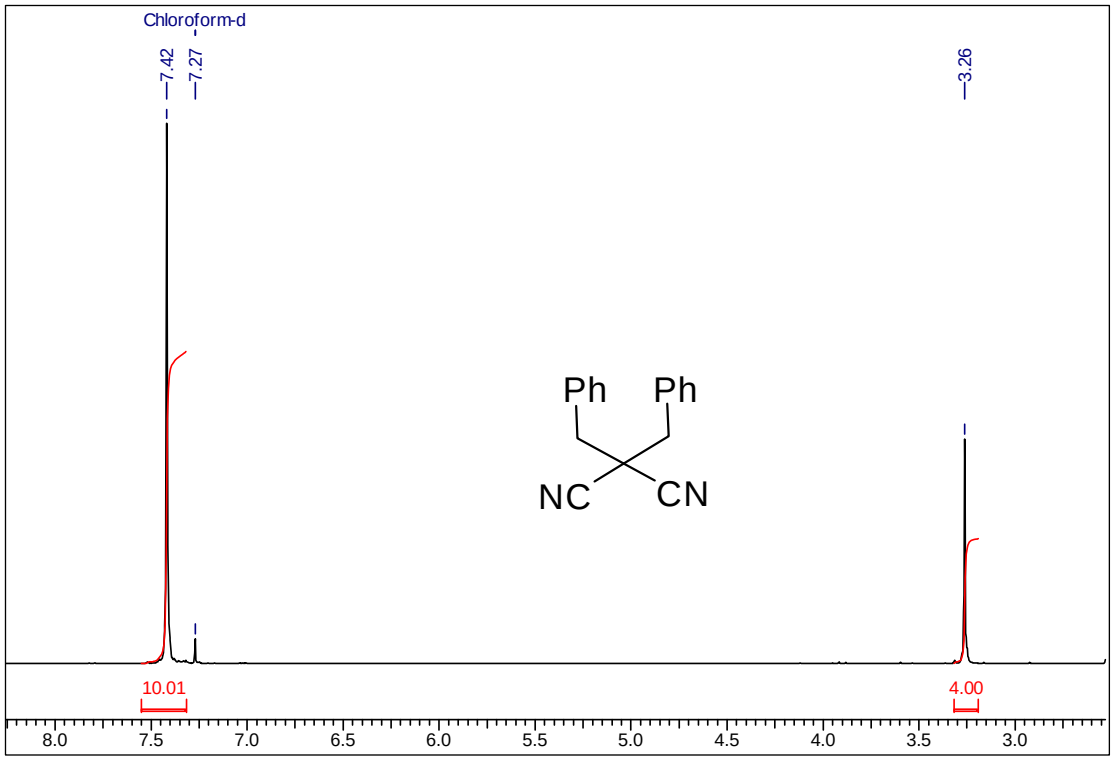
2.1.7. Spectra



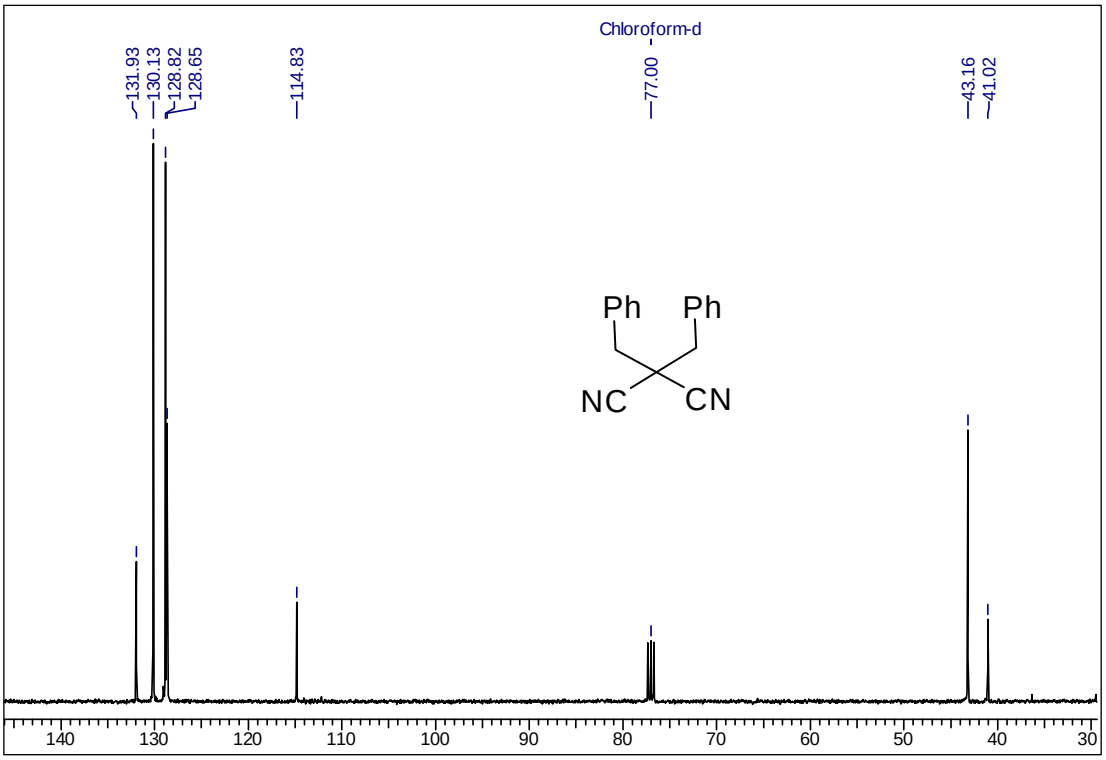
^{1}H NMR spectrum of **19** (200 MHz, $CDCl_3$)



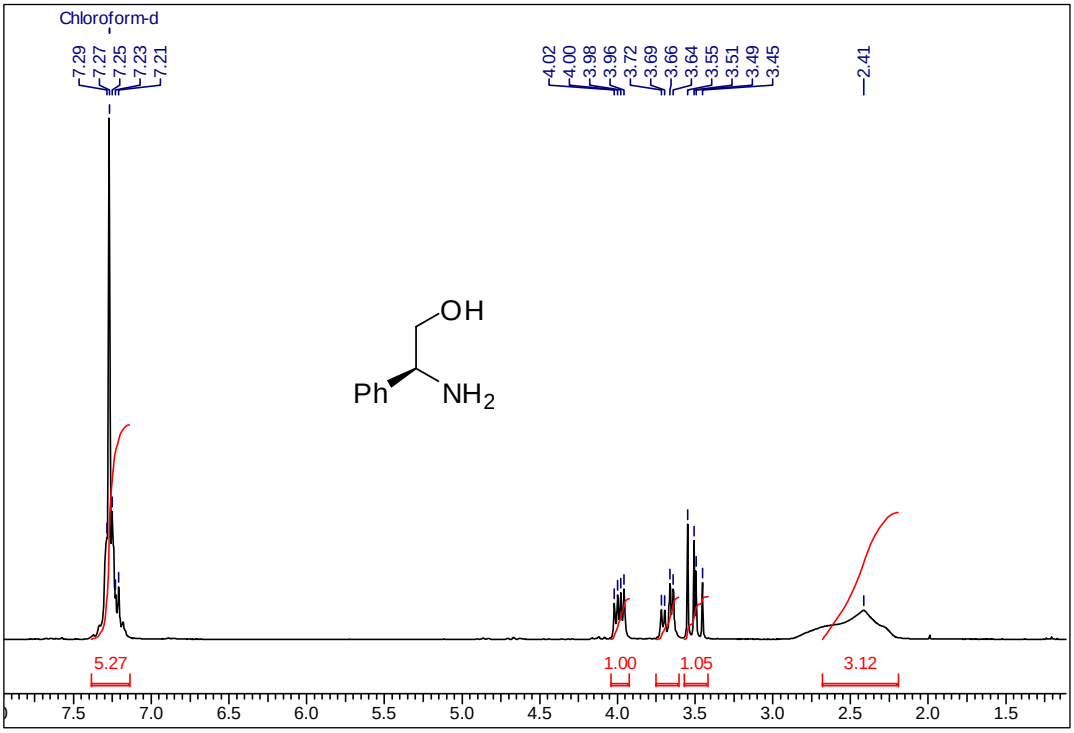
^{13}C NMR spectrum of **19** (50 MHz, $CDCl_3$)



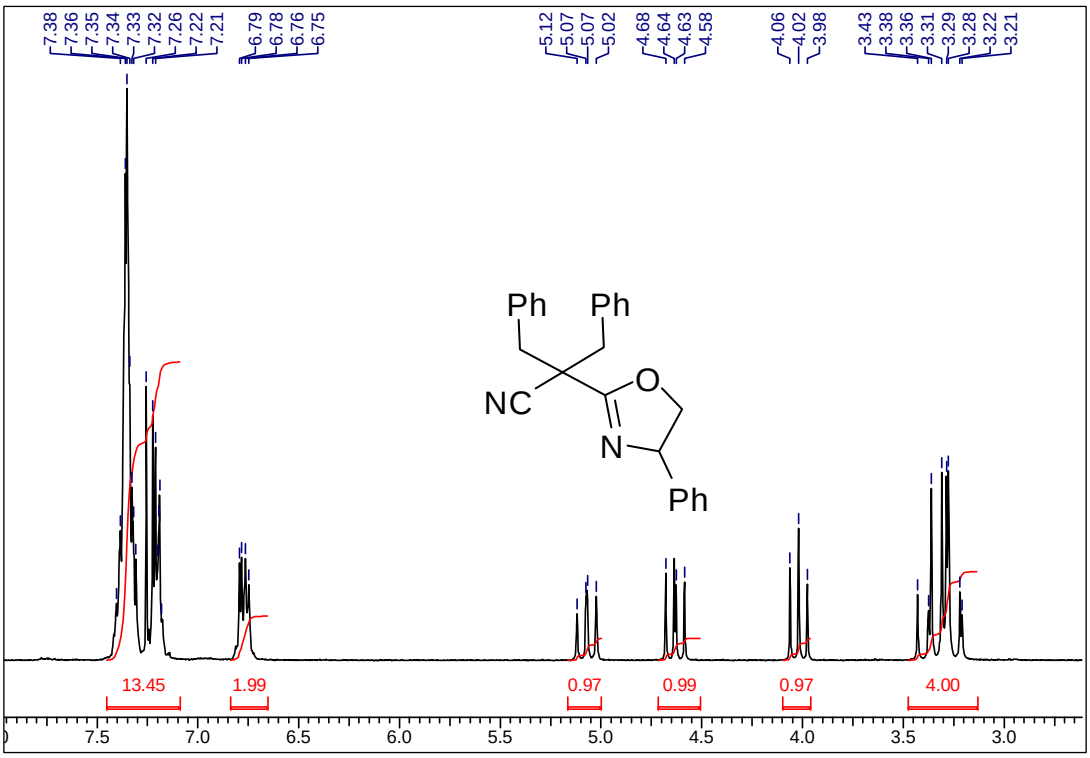
^{1}H NMR spectrum of **21** (200 MHz, $CDCl_3$)



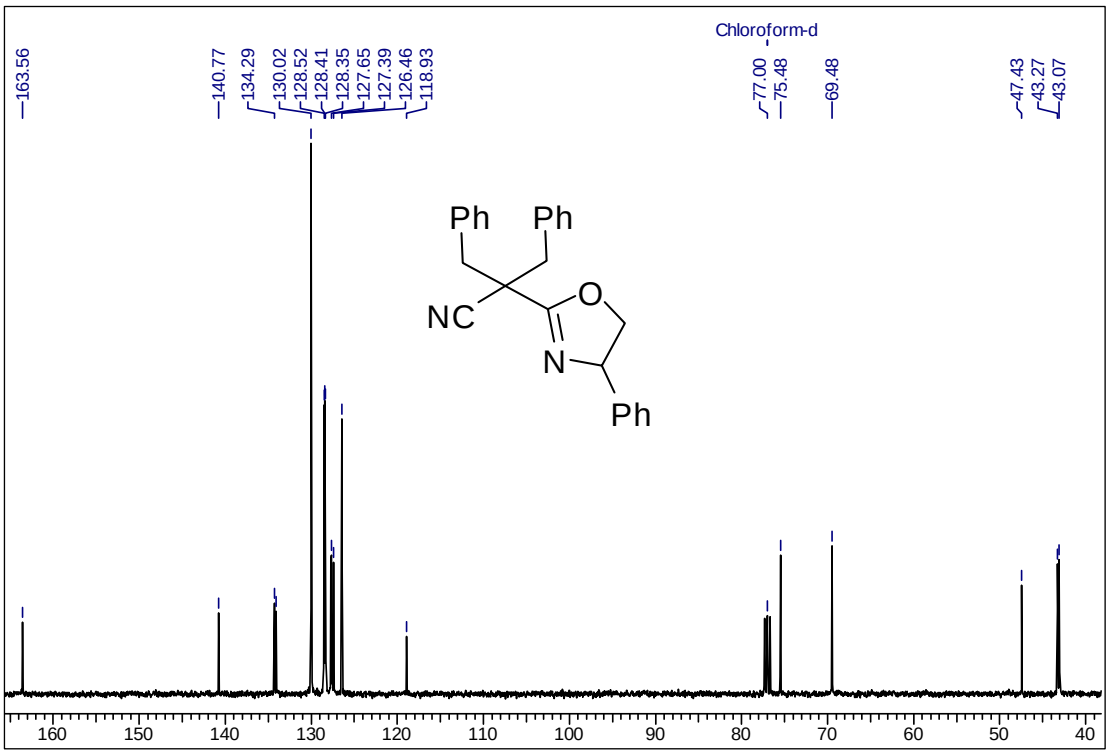
^{13}C NMR spectrum of **21** (50 MHz, $CDCl_3$)



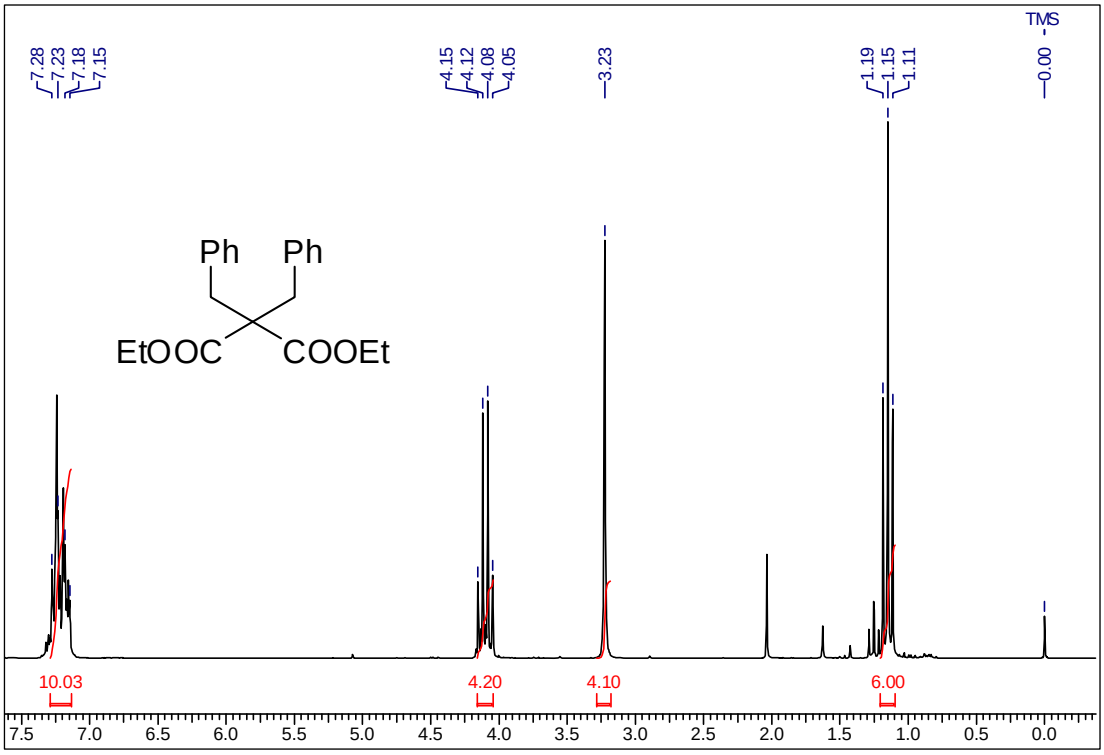
^{1}H NMR spectrum of **22** (200 MHz, $CDCl_3$)



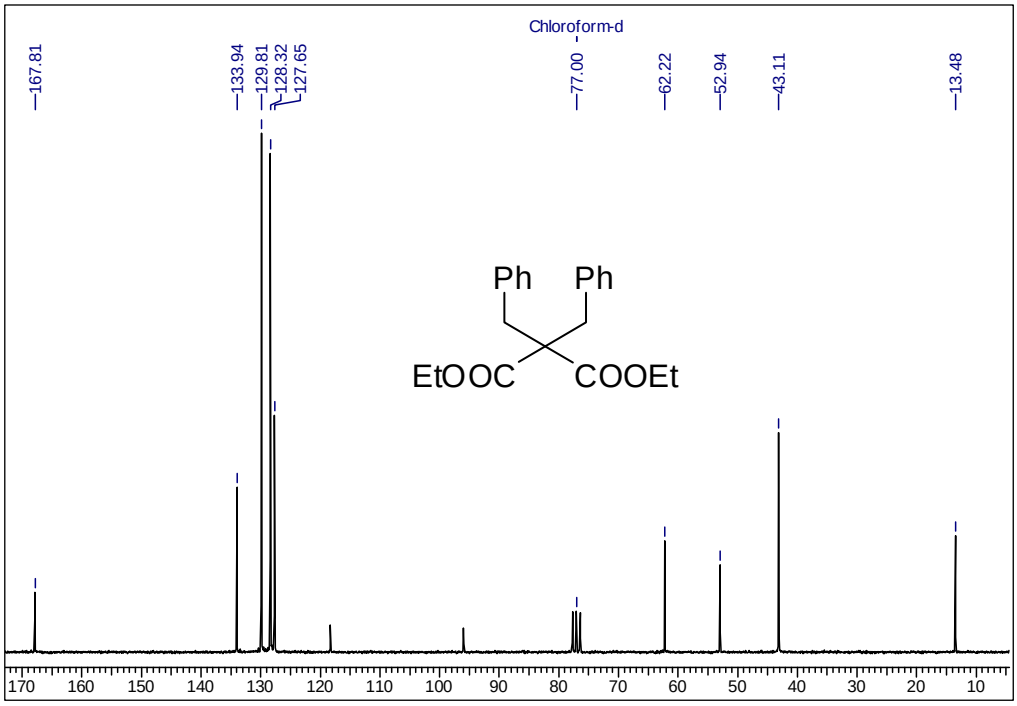
^{1}H NMR spectrum of **23** (200 MHz, $CDCl_3$)



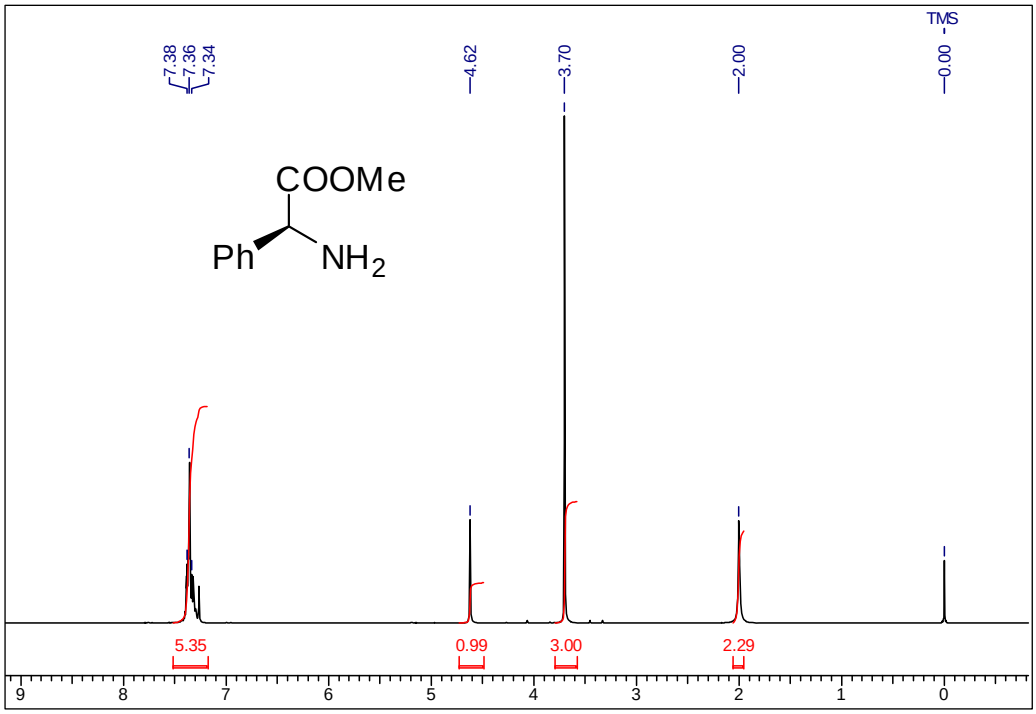
^{13}C NMR spectrum of **23** (50 MHz, $CDCl_3$)



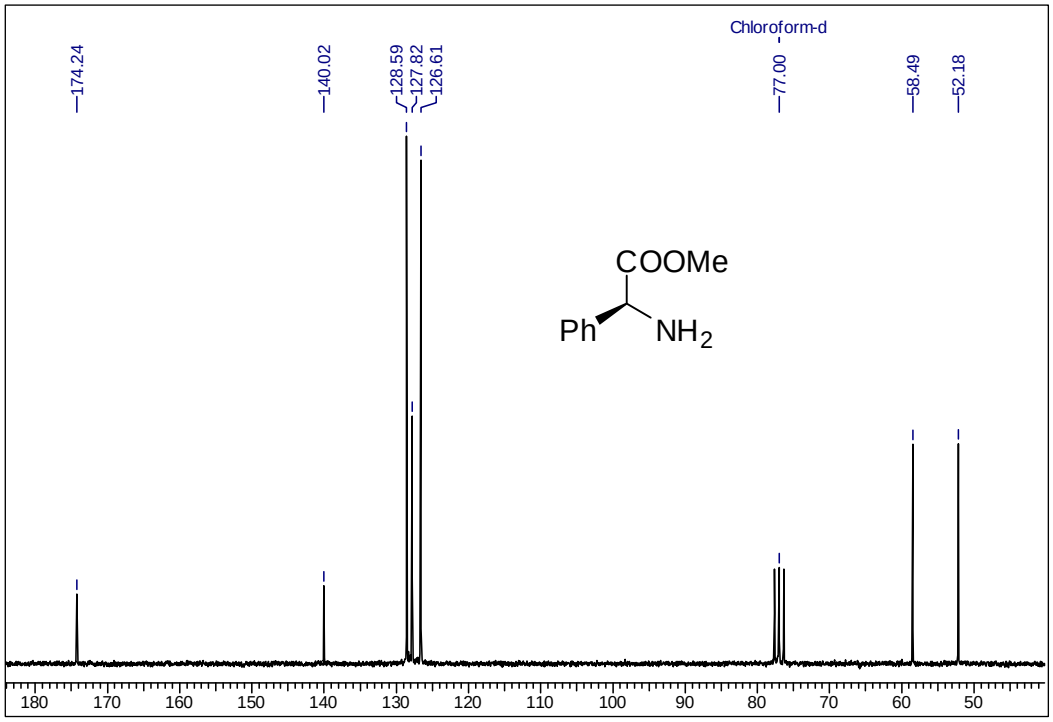
^{1}H NMR spectrum of **26** (200 MHz, $CDCl_3$)



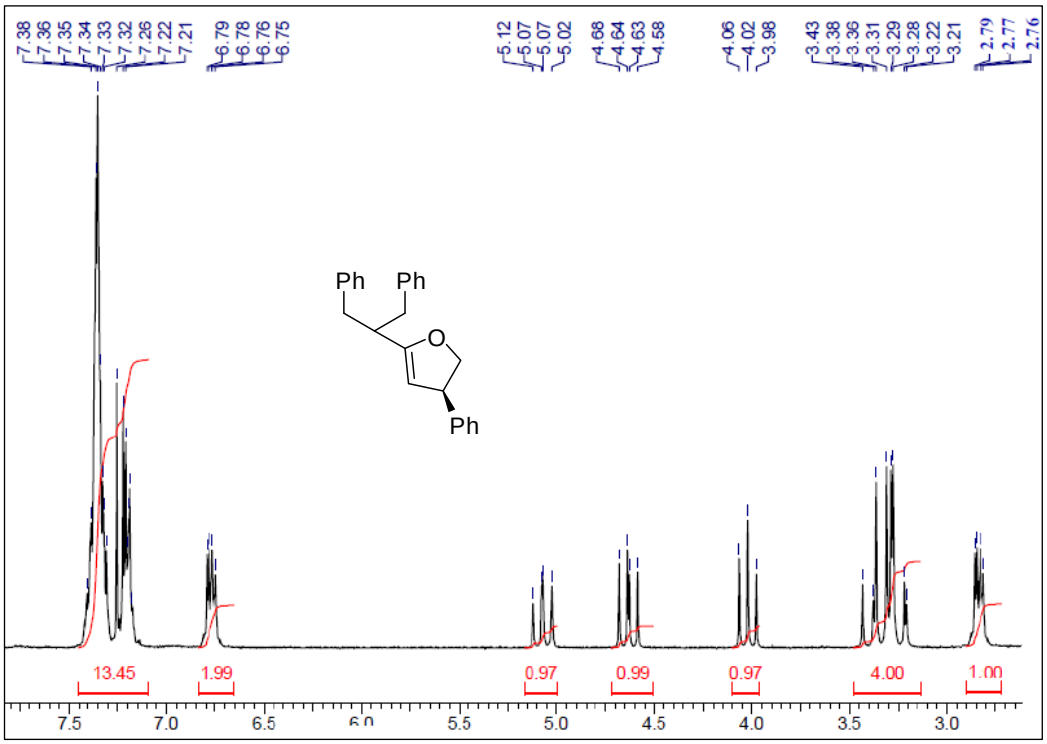
^{13}C NMR spectrum of **26** (50 MHz, $CDCl_3$)



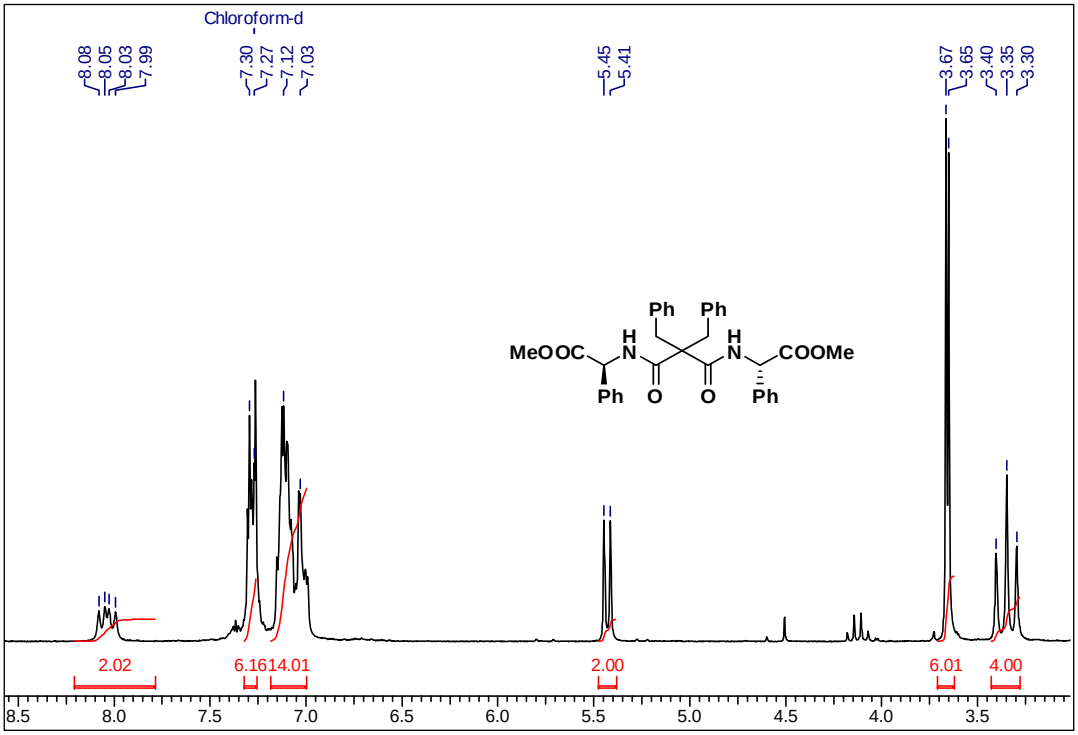
^{1}H NMR spectrum of **32** (200 MHz, $CDCl_3$)



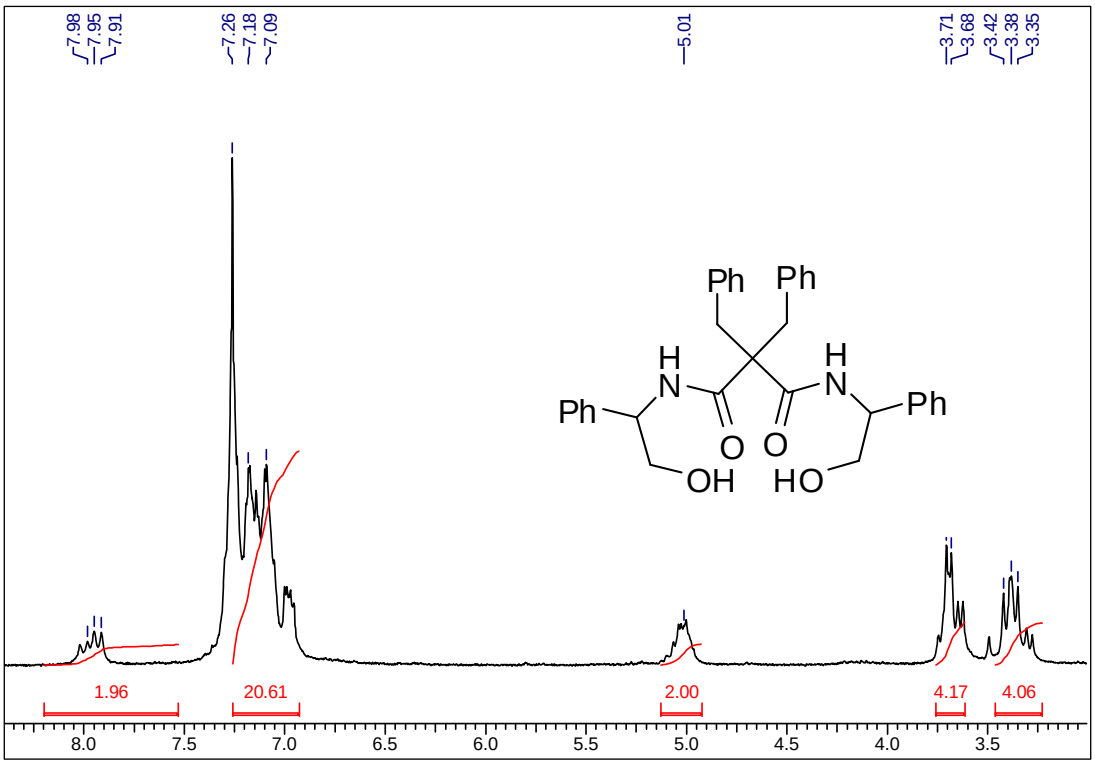
^{1}H NMR spectrum of **32** (200 MHz, $CDCl_3$)



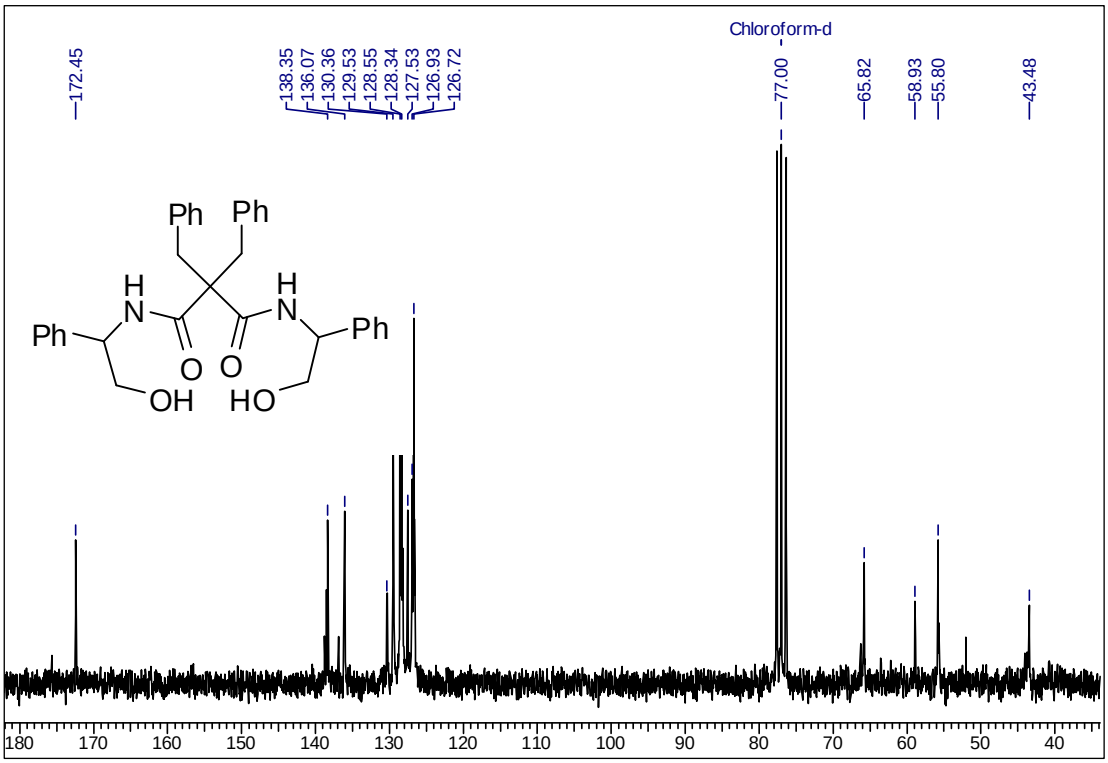
^{1}H NMR spectrum of **34** (200 MHz, $CDCl_3$)



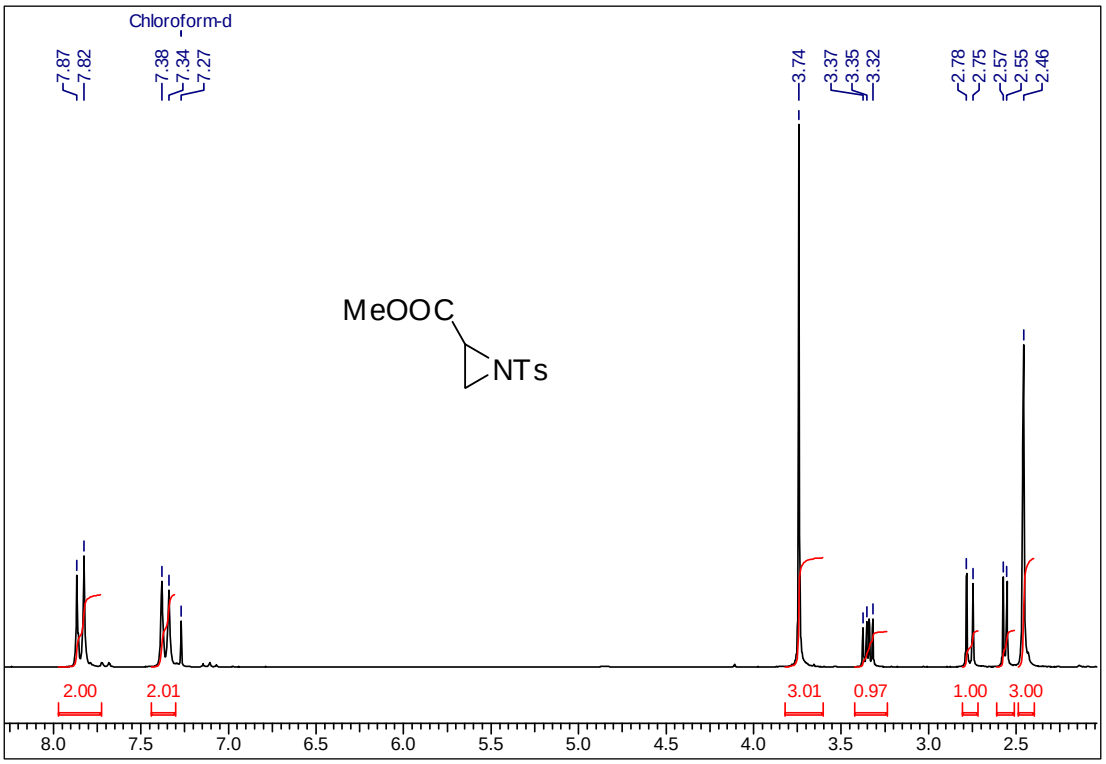
^{1}H NMR spectrum of **35** (200 MHz, $CDCl_3$)



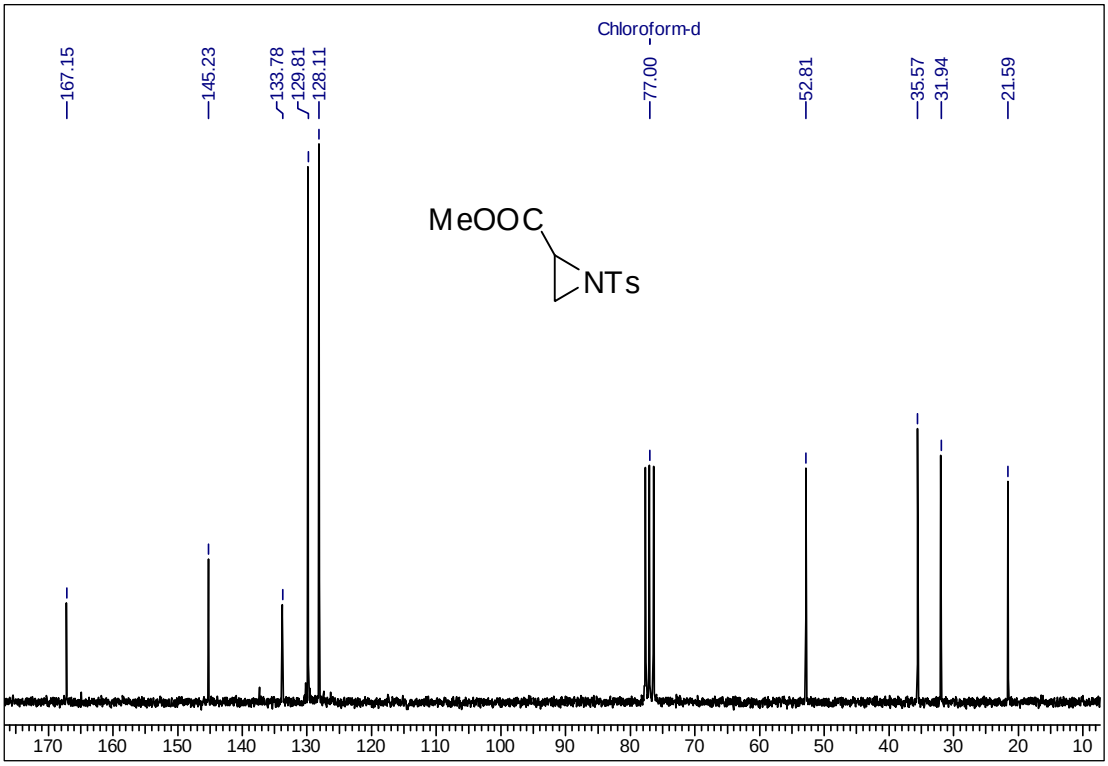
^{1}H NMR spectrum of **36** (200 MHz, $CDCl_3$)



^{13}C NMR spectrum of **36** (50 MHz, $CDCl_3$)



^{1}H NMR spectrum of **Methyl 1-tosylaziridine-2-carboxylate** (200 MHz, $CDCl_3$)



^{13}C NMR spectrum of **Methyl 1-tosylaziridine-2-carboxylate** (50 MHz, $CDCl_3$)

2.1.8. References

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Chapter 2

Section II

A New Route to Synthesis of α-Methylcysteine via. Aziridination and Asymmetric Aziridination of Methylmethacrylate Catalysed by Natural Cinchona Alkaloids

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2.2.1. Introduction

Modified amino acids are valuable building blocks for the preparation of peptides and peptide analogues[1]. α-Methylcysteine is an unusual amino acid and an important building block for a new family of natural products, thiangazoles **1**[2], tantazoles **2**[3] and mirabazoles **3**[4] which exhibit antitumor and anti HIV activities.[5] α-Methylcysteine and derivatives are attractive target molecules as they can form further constrained cyclic peptide structure *via* disulphide bridge formation[6]. Due to the labile nature of the sulfhydryl group, very few routes have been successfully applied to the asymmetric synthesis of α-methylcysteines. (*S*)-Desferrithiocin (**4**)[7] is an unique and unusual naturally occurring ferric iron chelator (siderophore) which also has α-methylcysteine moiety (Figure 1).

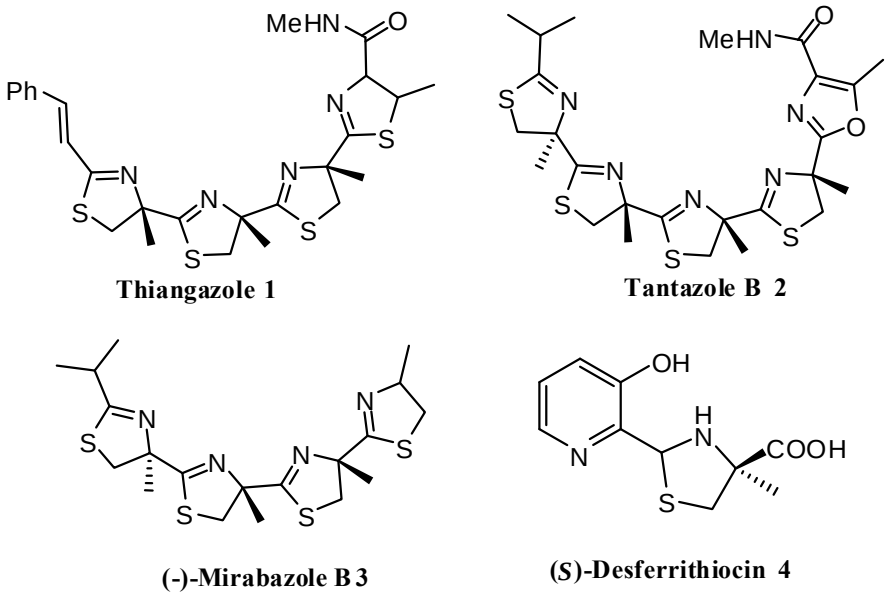
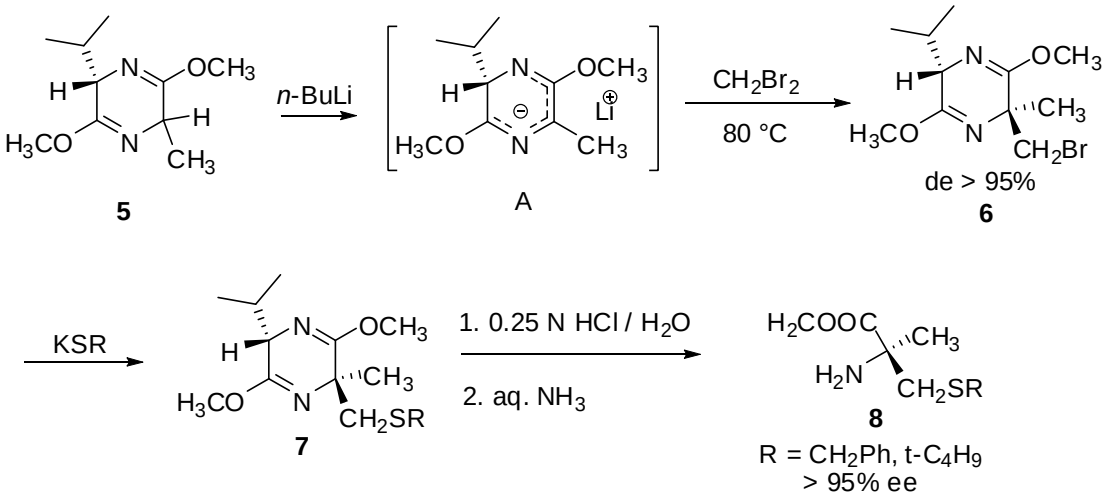


Figure 1

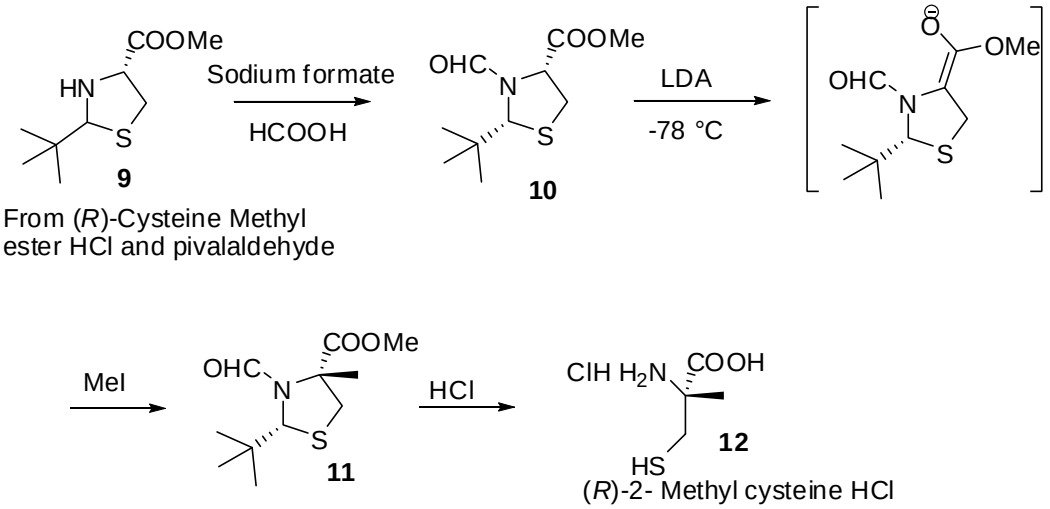
2.2.2. Review of Literature: Synthesis of chiral α-methylcysteines

Schöllkopf and Groth[8] reported an enantioselective synthesis of (*R*)-*α*-methyl-*S*-benzylcysteine methyl ester and (*R*)-*α*-methyl-*S*-*t*-butylcysteine methyl ester using L-valine as chiral auxiliary agent. (Scheme 1). The lithio intermediate **A** of the bis-lactim ether **5** obtained from cyclo(L-Val-Ala) reacts with dibromomethane to give the bromomethyl compound **6**. Compound **6** reacted with potassium *t*-butylmercaptide to furnish the *S*-alkyl compound **7** which on hydrolysis with 0.25 N hydrochloric acid afforded (*R*)-*α*-methyl-*S*-alkylcysteine methyl ester **8** with >95% ee (Sheme 1).



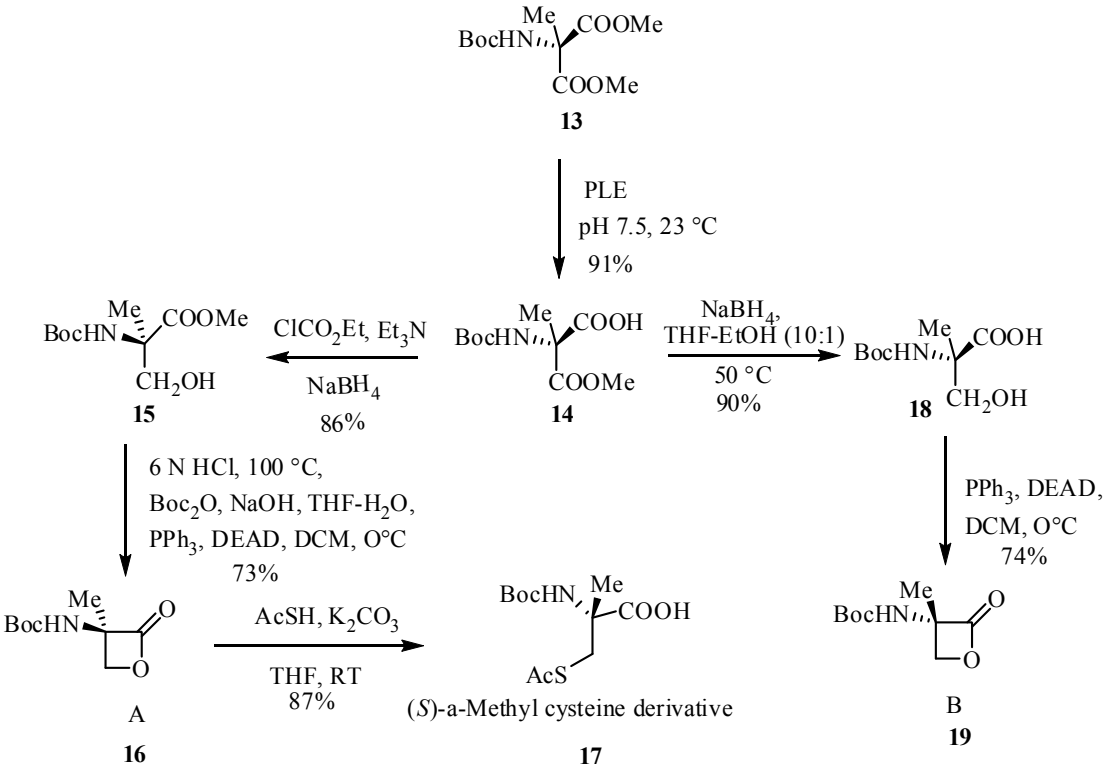
Scheme 1

A concise synthesis of enantiomerically pure (*R*) and (*S*)-α-methylcysteine has been developed by Pattenden *et al.*[9] using a modification of Seebach's "self-regeneration of chirality product". This method offers the chiral α-methylcysteine in large quantities (Scheme 2). (*S*)-*α*–Methylcysteine HCl prepared similarly was applied in the synthesis of thiazoline based siderophore (*S*)-Desferrthiocin (**1**)[7]. *N*-Formylation of the thiazolidine **9** using sodium formate in the presence of formic acid gave the intermediate **10**. Treatment of formyl intermediate **10** at -78 °C with lithiumdiisopropyl amide followed by quenching the resulting enolate within iodomethane produced the corresponding methylated thiazoline **11.** Hydrolysis of **11** in the presence of hydrochloric acid then afforded (*R*)-*α*-methylcysteine hydrochloride **12.**



Scheme 2

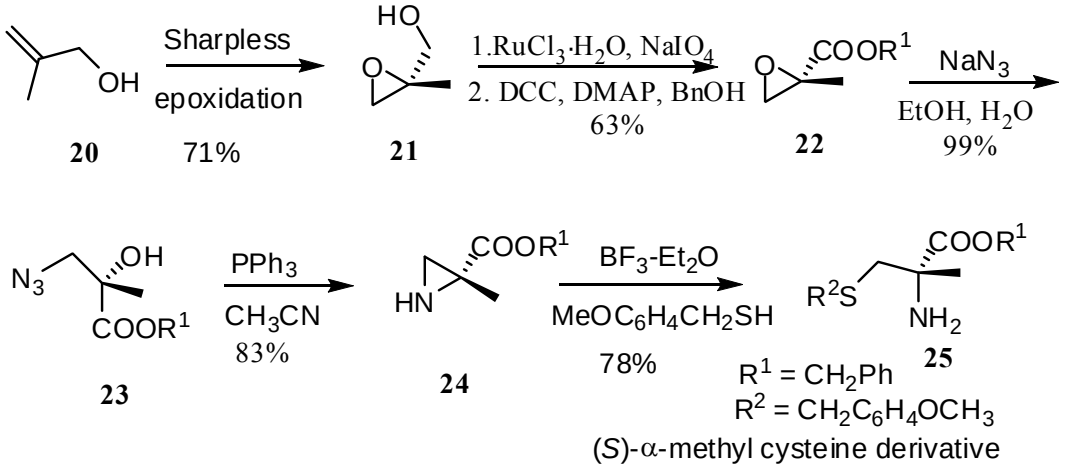
In connection with the total synthesis of (-)-tantazole B which shows selective toxicity against marine solid tumours, the lactone A was prepared from the readily available malonate derivative.[10] Enzymatic hydrolysis of malonate **13** by pig liver esterase (PLE) gave the acid **14**. Selective reduction of the acid group of **14** *via* mixed anhydride gave **15**, which was converted to the β-lactone A **16**. Upon treatment with thioisobutyric acid and potassium carbonate at room temperature, β-lactone A **16** underwent smooth cleavage to give the α-methylcysteine derivative **17.** Similarly, selective reduction of the ester **14** with $NaBH_4$ provided (*S*)-*N*-(*t*-Boc)-α-methylserine **18**, which was subjected to the Mitsunobu reaction condition to give the β-lactone B **19** (Scheme 3).



Scheme 3

Goodman *et al*[11]. developed a new asymmetric synthesis of α-methylcysteine *via* chiral aziridines. Starting with the allylic alcohol, the (*R*)-2-methylglycidol **21** was readily obtained in high enantimeric purity by Sharpless asymmetric epoxidation. Oxidation of **21** with ruthenium(VIII) oxide provided the corresponding carboxylic acid (R^1= H). The carboxylic acid was converted to the benzyl ester (R^1= CH_2Ph) **22** Treatment of ester **22** with sodium azide resulted in regioselective ring oening to from the azido alcohol **23.** Refluxing the azido alcohol **23** with triphenylphosphine in

acetonitrile generated the benzyl aziridinecarboxylate **24.** Regioselective ring opening of the chiral aziridine **24** with 4-methoxy-α-toluenethiol and boron trifluoride etherate resulted in the desired (*S*)-α-methylcysteine **25** (Scheme 4).



Scheme 4

Later the same group reported[12] an enantioselective synthesis of α-methyl-D-cysteine and lanthionine building blocks *via* α-methyl-D-serine-β-lactone and starting from methacrylic acid **26**. The latter was transformed into the Weinreb amide **27** *via* displacement of the acid chloride with *N,O*-dimethylhydroxylamine hydrochloride. Amide **27** was subjected to the Sharpless asymmetric dihydroxylation using modified β-AD mix to obtain diol **28**. The diol **28** was then saponified with lithium hydroxide and esterified with acidic methanol to form methyl ester which was converted into cyclic sulfite **29** by refluxing with thionyl chloride. The selectively opening of the cyclic sulfite with sodium azide gave the azido alcohol **30**. The ester group of **30** was saponified with potassium hydroxide, the azide was then reduced with palladium on carbon and protected with Boc-anhydride to give Boc-α-methyl-D-serine **31**. Boc-α-methyl-D-serine-β-lactone **32** was formed from **31** through a Mitsunobu reaction employing diisopropyl azodicarboxylate (DIAD) and triphenylphosphine. The lactone ring in **32** was opened in the presence of cesium carbonate to give Boc-α-methyl-D-cysteine (PMB)-OH **33** (Scheme 5)

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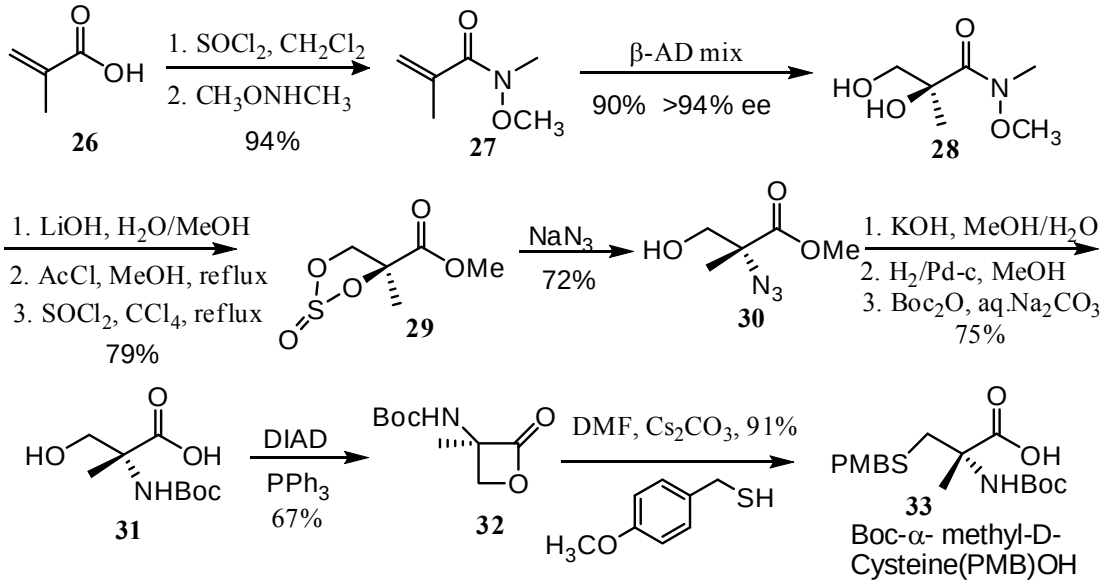
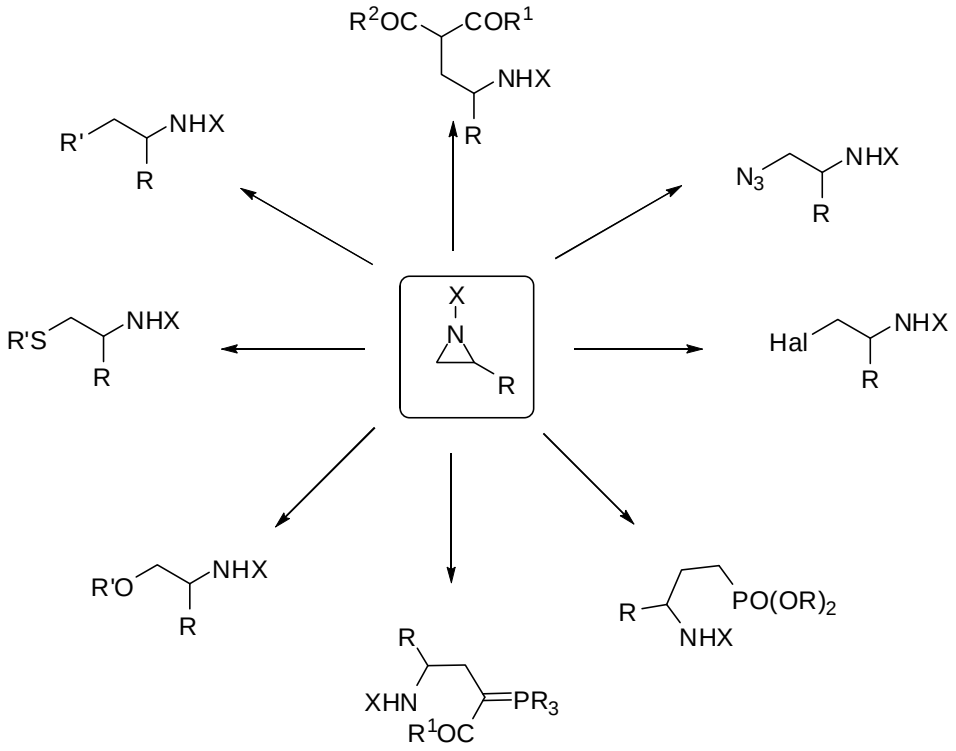


26 **27** **28** **29** **30** **31** **32** **33**

Scheme 5

Ring opening reactions of aziridine [11]

The three-membered heterocycle and the electronegativity of the heteroatom mean that aziridines readily undergo ring-cleavage reactions under relatively mild conditions (Scheme 6). As might be expected, due to the diminished electronegativity of nitrogen compared to oxygen, ring-opening reactions of these heterocycles are less facile than the corresponding reactions of epoxides. Ring-cleavage reactions of aziridines proceed by nucleophilic attack at carbon. When an aziridine is unsymmetrically-substituted reaction with a nucleophile can lead to two products of ring-opening. As would be expected, most nucleophiles preferentially direct their attack to the site of lesser substitution, though electronic considerations for instance in the ring-opening of 2-arylaziridines may not favour this preference. An anomalous reactivity profile is occasionally observed where the nucleophile concerned is either hindered or is a relatively weak Lewis base. The aziridine *N*-substituent is a relatively weak activator; hence, under this situation, attack at a quaternary carbon atom is preferred over the alternative, less substituted atom.



Scheme 6: Aziridine ring opening

2.2.3. Present Work

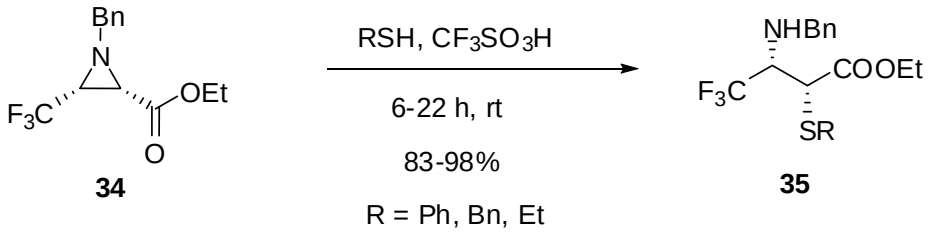
A new route to the synthesis of α-methylcysteine **37** starting from methylmethacrylate **34** has been developed. The reaction sequence involves aziridination of methylmethacrylate, regioselective opening of the aziridine ring with thioacetic acid and subsequent hydrolysis with hydrogen bromide in acetic acid.

Nucleophilc ring opening of aziridines with anion derived from thiols:

The ring opening reaction of aziridines by thiols can readily proceed in either an activated or a non-activated form. The aziridine ring nitrogen in the non-activated form can served as a base to abstract a proton from the thiophinols or alkyl thiols to form an aziridinium intermediate, which is a very labile species. The nucleophiles of the deprotonated thiol anion then attack the aziridine ring carbon. The orientation of the attack generally occurs at a less hindered site to provide 2-amino sulfide products. On the other hand, activated aziridines, lacking basic nitrogen, often require a Lewis acid for further activation; thiol nucleophiles approach the less hindered site to open the ring. Consistently high chemical yields and high regio-selectivity have been observed in many reports.

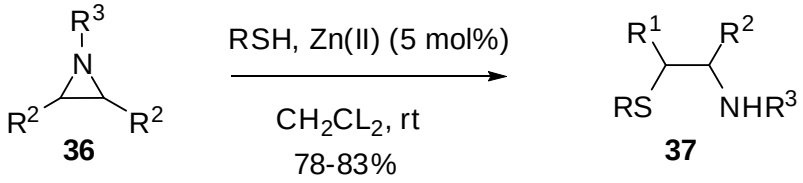
Thiophenols and aliphatic mercaptans are nucleophiles sufficient to induce ring opening of aziridines without assistance of catalysts or bases. Alternatively, the

ring opening reaction proceeded more readily with thiols in the presence of a strong acid (CF_3SO_3H).[13a] In this case, the reaction was carried out at room temperature and completed in less than 16 h with alkyl thiols, but 22 h with thiophenol (Scheme 7).



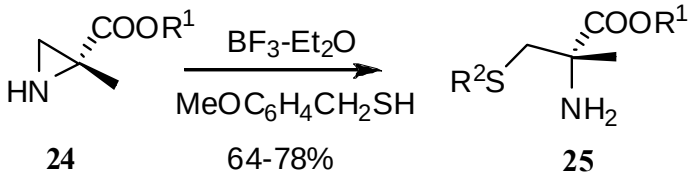
Scheme 7

The Lewis acid could catalyze the ring opening of the activated and non-activated aziridines in good to excellent yields.[13b] The addition occurred at the less hindered ring carbon with high regio-selectivity. Lewis acid catalysts were found to effectively promoted the ring opening of aziridines in $ZnCl_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Yb(OTf)_3$ (Scheme 8).



Scheme 8

Boron trifluoride-diethyl etherate has been widely used in catalytic ring opening of aziridines under nucleophilic conditions using thiols. However, at least a stoichiometric amount of $BF_3{\cdot}OEt_2$[11] and excess thiol were needed to achieve practical chemical results (Scheme 9).



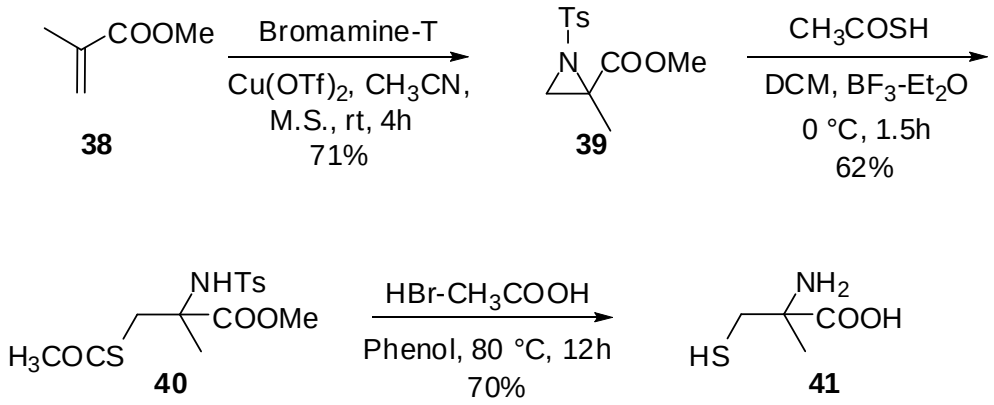
Scheme 9

Only limited reports were found in the literature describing addition of thioacyl acids to aziridines in recent years. It was believed that the proton transfer from thio acids to aziridines to form aziridinium cation was the rate determining step. Therefore, in a study of the acidity influence of thio acids to aziridines was carried out and found that the aziridine ring opening was significantly fast with thioacetic acid,

whereas thiophenols and other thiols took longer time at room temperature to complete the reaction as discussed earlier.

2.2.4. Results and Discussion

A new synthetic method for α-methylcysteine **38** hinges on regioselective aziridine opening strategy. Synthesis of α-methylcysteine **41** started using methyl methacrylate **38** as the alkene source and bromamine-T as a nitrene source.[13] Initially, anhydrous Cu(II) in dry acetonitrile was stirred under nitrogen atmosphere at room temperature. Then methyl methacrylate **38** was added to this solution followed by addition of bromamine-T and activated 4Å molecular sieves which afforded aziridine **39**. Aziridination of methyl methacrylate gave 40% and 71 % yield with $CuCl_2$ and $Cu(OTf)_2$ respectively. Regioselective ring opening of **39** with thioacetic acid in presence of boron trifluoride etherate in dichloromethane[11] furnished the protected α-methylcysteine **40**. Compound **40** on hydrolysis using hydrogen bromide in acetic acid and phenol as an activator yielded α-methylcysteine **41** (Scheme 10). Here, in one step, the *N*-tosyl, the ester and the thio ester groups are hydrolysed with the reagent mentioned and the final product was obtained in 70% yield.



Scheme 10: Synthesis of 2-methylcysteine

Asymmetric aziridination of methyl methacrylate with cinchona alkaloids

Cinchona 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 **42**, dihydroquinine **43**, cinchonidine **44,** *N*-benzyl ephedrine **45** and sparteine **46** were chosen as ligands for asymmetric aziridination of methylmethacrylate (Figure 2).

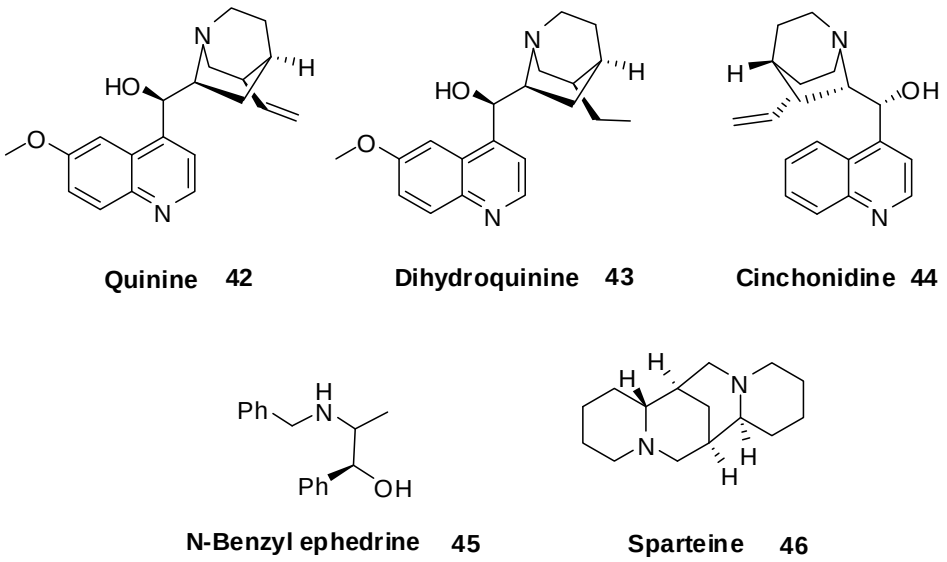


Figure 2

In the synthesis of chiral 2-methylcysteine the key reaction involved was asymmetric aziridination of methyl methacrylate.

Initially the metal ligand complex was formed by stirring a suspension of anhydrous copper (II) chloride and ligand in dry acetonitrile. Then bromamine-T and alkene were added and reaction mixture was stirred at room temperature for four hours (Scheme 11).

Sol-gel technique:

The sol-gel process is a wet-chemical technique widely used recently in the fields of materials science. Such methods are used primarily for the fabrication of materials (typically a metal oxide) starting from a chemical solution (sol, short for solution) which acts as the precursor for an integrated network (or gel) of either discrete particles or network polymers. Typical precursors are metal alkoxides and metal chlorides, which undergo hydrolysis and polycondensation reactions to form a network "elastic solid". Formation of a metal oxide involves connecting the metal centers with oxo (M-O-M) or hydroxo (M-OH-M) bridges, therefore generating metal-oxo or metal-hydroxo polymers in solution. Thus, the sol evolves towards the formation of a gel-like diphasic system containing both a liquid phase and solid phase.

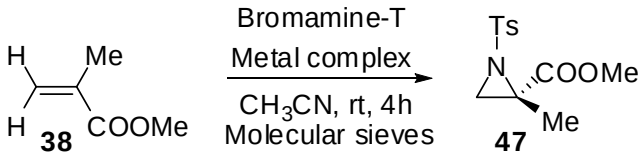
In order to utilize the unique properties of the mesoporous material for specific applications in catalysis. Introduction of reactive organic functional groups, by the incorporation of organic components as part of the silicate walls to form organic-inorganic hybrid materials is quite important. The advantages of organic-inorganic hybrid materials arise from the fact that inorganic components can provide

mechanical, thermal or structural stability, while the organic features can be readily modified for various specific applications.

Through the development of organic-inorganic hybrid mesoporous solids, much progress has been made in the last few years towards their application in a variety of fields. Such mesoporous solids have been functionalized at precise sites and were demonstrated to exhibit improved activity and selectivity in a large number of catalytic reactions and adsorption processes. The synthesis procedures of organic-inorganic hybrid materials, developed so far, effectively utilize the large amount of silanol groups resting on the surface of organic materials. Another advantage of these materials is that the hydrophilic-hydrophobic properties can be tailored by the judicious choice of the organo alkoxy silanes. The pore walls of mesoporous materials are easily modified with either purely inorganic or with hybrid, semiorganic functional groups and can be successfully used as catalysts for green chemistry. Grafting method has been widely used in the field of catalysis for functionalization of surface hydroxyl groups as anchor points by organosilanes in silica network.

Important applications of these modified and functionalized systems include selective heterogeneous ligands. In this method, the organic functional groups are introduced to the surface of mesoporous silica as the terminal groups of an organic monolayer by post synthesis modification of pre-synthesized mesoporous materials. This can be done usually after removal of surfactant from the inorganic matrix. Mesoporous silicas possess high concentration of silanol groups (Si-OH) at the surface. These silanol groups are well-situated anchoring points for functionalization of organic group to the silica network. In this work chiral ligands used to immobilize coordination compounds on silica surfaces using sol-gel technique.

Heterogeneous catalysts containing alkaloids like cinchonidine, quinine, dihydroquinine, spartine and *N*-benzyl ephedrine were prepared by sol–gel technique.[14] The required alkaloid was dissolved in isopropyl alcohol and ethyl silicate-40 was added with stirring followed by dropwise addition of ammonia solution (25%) to effect the gel formation. The transparent white gel thus obtained was air dried for 3 h. The silica complex thus obtained was treated with copper (II) chloride and the copper silica complex obtained was directly used in asymmetric aziridination of alkene (Scheme 11).



Scheme 11

Table 1: Asymmetric aziridination of methyl methacrylate with natural alkaloids

Sr. No.	Nitrene Source	Complex	Yield (%)	ee (%)
1.	Bromamine-T	QUI-$CuCl_2$	67	18
2.	Bromamine-T	DHQ-$CuCl_2$	45	10
3.	Bromamine-T	CIN-$CuCl_2$	62	40
4.	Bromamine-T	*N*-Benzyl ephedrine	48	0
5.	Bromamine-T	Sparteine	53	8
6.	Bromamine-T	DHQ-$CuCl_2$-SiO_2	12	0
7.	Bromamine-T	CIN-$CuCl_2$-SiO_2	No. reaction	-
8.	Bromamine-T	QUI-$CuCl_2$-SiO_2	No. reaction	-

In the synthesis of chiral α-methyl cysteine, asymmetric aziridination of methyl methacrylate with different chiral ligands was carried out. A maximum enantioselectivity (40%) was observed when the cinchona alkaloids especially when preformed copper-cinchonidine complex was used as a ligand (Table 1, entry 3).

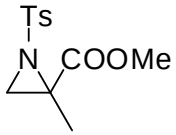
2.2.5. Conclusion

An efficient and versatile route for synthesis of α-methylcysteine *via* aziridination of methyl methacrylate followed by regioselective opening of the aziridine with thioacetic acid and hydrolysis of the *N*-protected thio-ester in three steps in an overall yield of 30%.

Modified and new chiral ligands as well as ligands from cinchona alkaloids group could be employed in asymmetric aziridination of methylmethacrylate to achieve enantiomerically pure α-methylcysteine. Additionally, opening of aziridine thus formed to furnish α-methylcysteine could be carried out with different thiol nucleophiles like thiobenzoic acid, thiopropionic acid as well as substituted thiobenzoic acids. Thus a better enantioselective synthesis of chiral α-methylcysteine could be achieved. Work is in progress in our group.

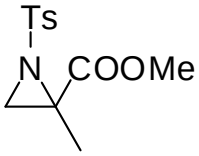
2.2.6. Experimental

N-p-Toluenesulphonyl-2-carbomethoxy-2-methylaziridine (39)



Anhydrous $CuCl_2$ (265 mg, 1.97 mmol) in dry. acetonitrile (70 ml) was stirred under nitrogen at room temperature. Methyl methacrylate **38** (4.35 g, 3.51 ml, 43 mmol) was then added to this solution followed by addition of bromamine-T (5.37 g, 19 mmol) and 4Å molecular sieves (5 g). The reaction mixture was stirred at room temperature for 4 hours. Then it was diluted with ethyl acetate (150 ml) and filtered through a pad of silica gel. The clear solution was dried over sodium sulphate and solvent concentrated under vacuum. A thick colorless oil was obtained which was purified by silica gel column chromatography using ethyl acetate and petroleum-ether (1:4) affording the aziridine derivative **39** (2.15 g, 40 %) as a colorless solid.

N-p-Toluenesulphonyl-2-carbomethoxy-2-methylaziridine (39)



Anhydrous $Cu(OTf)_2$ (713 mg, 1.97 mmol) in dry. acetonitrile (70 ml) was stirred under nitrogen at room temperature. Methyl methacrylate **38** (4.35 g, 3.51 ml, 43 mmol) was then added to this solution followed by addition of bromamine-T (5.37 g, 19 mmol) and 4Å molecular sieves (5 g). The reaction mixture was stirred at room temperature for 4 hours. Then it was diluted with ethyl acetate (150 ml) and filtered through a pad of silica gel. The clear solution was dried over sodium sulphate and solvent concentrated under vacuum. A thick colorless oil was obtained which was purified by silica gel column chromatography using ethyl acetate and petroleum-ether (1:4) affording the aziridine derivative **39** as a colorless solid (3.8 g, 71 %), m.p. 112 °C.

Mol. Formula **:** $C_{12}H_{15}NO_4S$

Mol. Weight **:** 269

FT IR ($CHCl_3$) **:** 3020, 1741, 1331, 1215, 1163, 882, 759 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) **:** δ 1.90 (s, 3H); 2.44 (s, 3H); 2.71 (d, *J* = 15 Hz, 1H); 2.79 (m, *J* = 15 Hz, 1H); 3.75 (s, 3H); 7.31 (d, *J* = 8 Hz, 2H); 7.82 (d, *J* = 8 Hz, 2H)

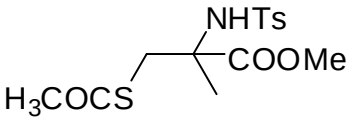
^{13}C NMR (75 MHz, $CDCl_3$) **:** δ 15.04, 21.41, 38.77, 46.28, 52.79, 127.42, 129.45, 136.78, 144.28, 168.71

ESI-MS *m/z* **:** 270.24 $[M+H]^+$

Elemental Analysis **:** Calcd: C, 53.53; H, 5.51; N, 5.20; S, 11.89 %

Found: C, 53.41; H, 5.68; N, 4.93; S, 12.09 %

Methyl (2-N-tosylamino-3-acetomercapto) propionate (40)



N-p-Toluenesulphonyl-2-carbomethoxy-2-methyl aziridine **39** (200 mg, 74 mmol) was taken 25 ml two necked round bottom flask under nitrogen and then DCM (5 mL) and thioacetic acid (0.79 ml, 1.11 mmol) was added. Reaction mixture was cooled at 0 °C, followed by addition of BF_3-OEt_2 (1.8 ml, 1.11 mmol) and reaction mixture was stirred for 1.5 hours at 0 °C. It was then diluted with DCM (10 ml), the combined layer was washed with saturated sodium bicarbonate solution and dried. Removal of the solvent under vacuum yielded on oily residue, which was purified by column chromatography yield **40** (160 mg, 62%).

Mol. Formula **:** $C_{14}H_{19}NO_5S_2$

Mol. Weight **:** 345

FT IR ($CHCl_3$) **:** 3280, 1740, 1694, 1597, 1331, 1159 cm^{-1}

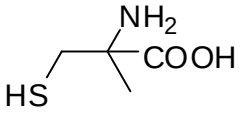
^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.46 (s, 3H), 2.32 (s, 3H), 2.42 (s, 3H), 3.37 (q, 2H), 3.65 (s, 3H), 7.31 (d, *J* = 8 Hz, 2H), 7.72 (d, *J* = 8 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) : δ 21.46, 21.89, 30.32, 37.52, 53.07, 61.67, 126.97, 129.49, 138.93, 143.40, 172.15, 194.50

ESI-MS *m/z* : 346.13 $[M+H]^+$

Elemental Analysis : Calcd: C, 48.91; H, 5.51; N, 4.06; S, 18.55 %
Found: C, 48.65; H, 5.27; N, 3.93; S, 18.62 %

2-Amino-3-mercapto-2-methylpropanoic acid (2-methylcysteine) (41):



Methyl (2-N-tosylamino-3-acetomercapto) propionate **40** (100 mg, 0.28 mmol), phenol (81.73 mg, 0.86 mmol), 10 ml of 32% hydrogen bromide in acetic acid was charged in a thick walled glass tube. It was sealed and heated in a metallic bomb for 12 hours at 80 °C. The reaction mixture was allowed to cool to room temperature and then was poured into 150 ml of ether and stirred for 5 min. The ether solution was decanted and the residue was dissolved in 6 ml of water. This aqueous solution was stirred with charcoal and filtered. The filtrate was passed through Dowex 50-X8 (Na) bed and washed with 10 ml water. Total aqueous solution was concentrated under vacuum at room temperature to obtain 2-methylcysteine 4**1** (27 mg, 70 %) as sticky mass.

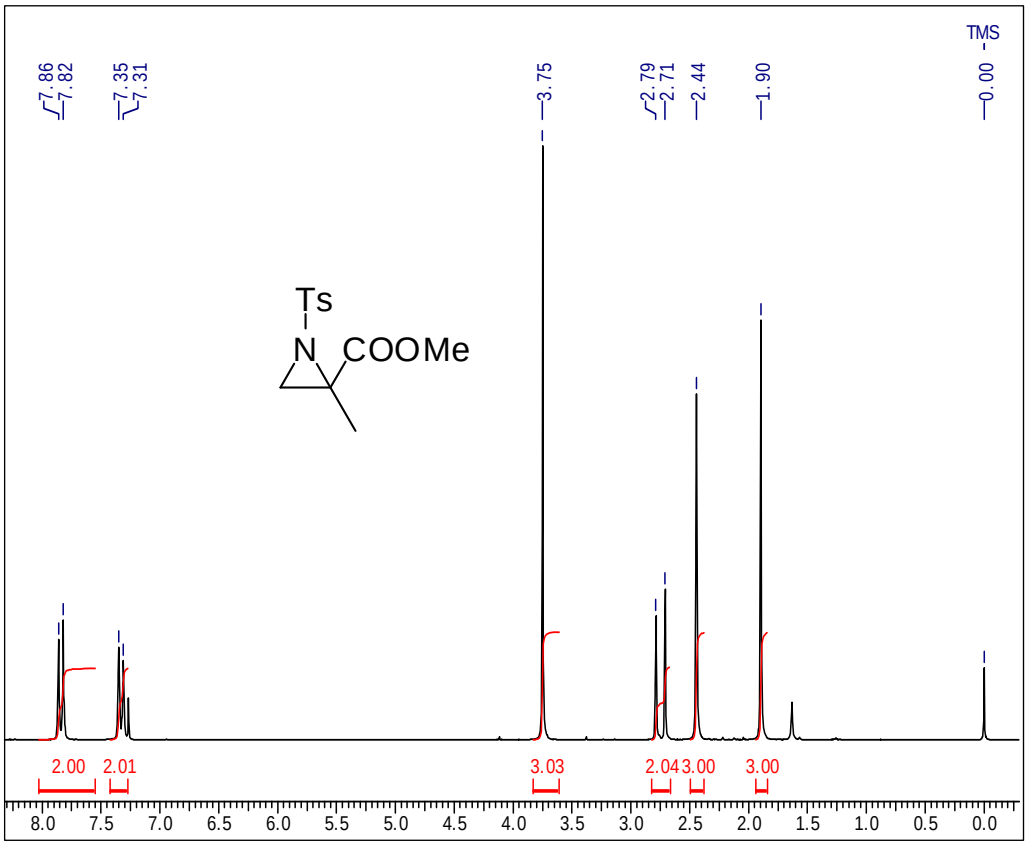
Mol. Formula : $C_4H_9NO_2S$

Mol. Weight : 135

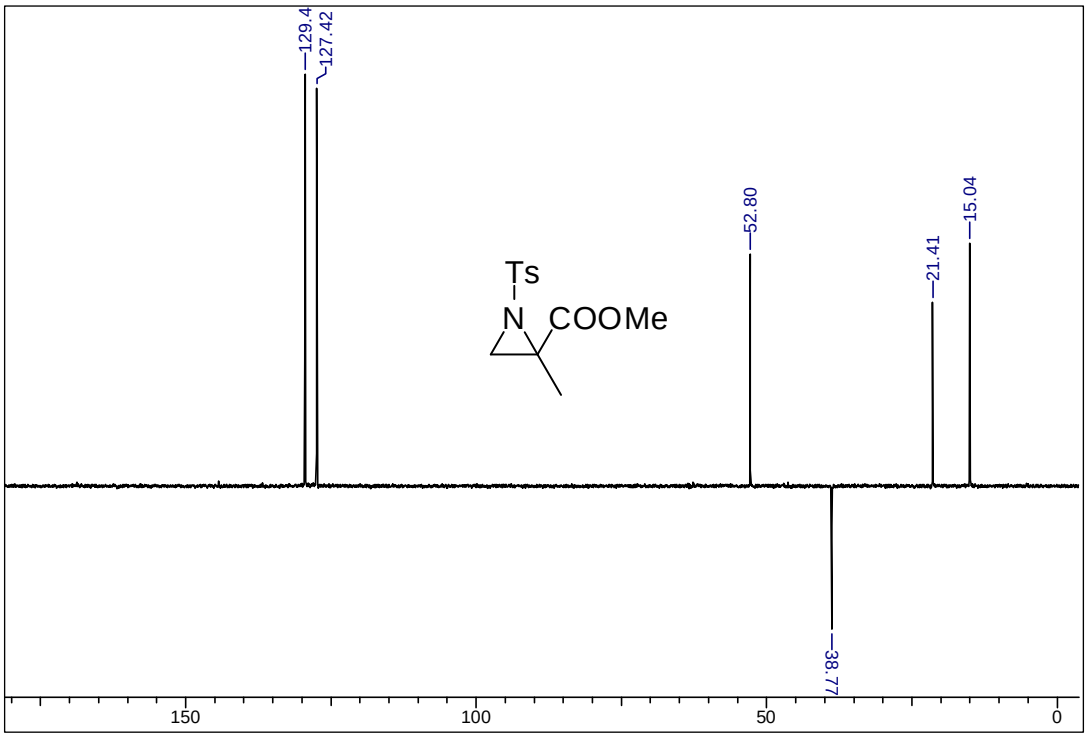
FT IR (Nujol) : 3615, 2542, 1611, 1511 cm^{-1}

^{1}H NMR (300 MHz, D_2O) : δ 1.74 (s, 1H), 1.72 (s, 3H), 3.25 (m, 1H), 3.62 (m, 1H)

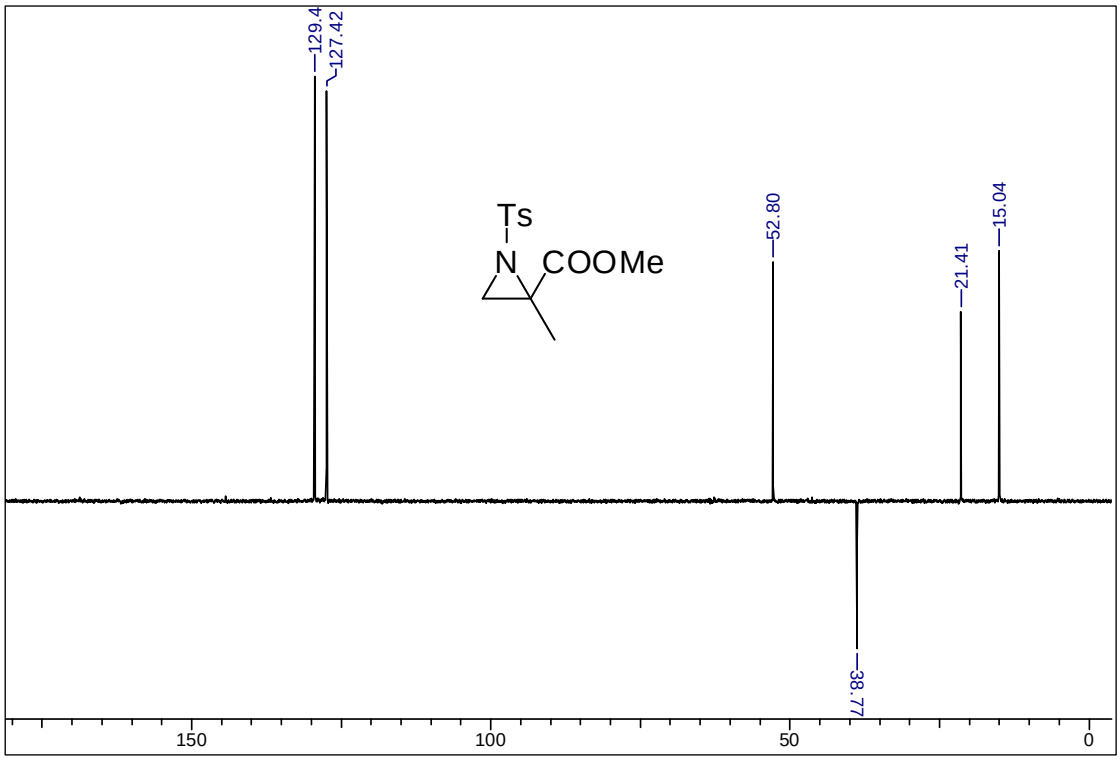
2.2.7. Spectra



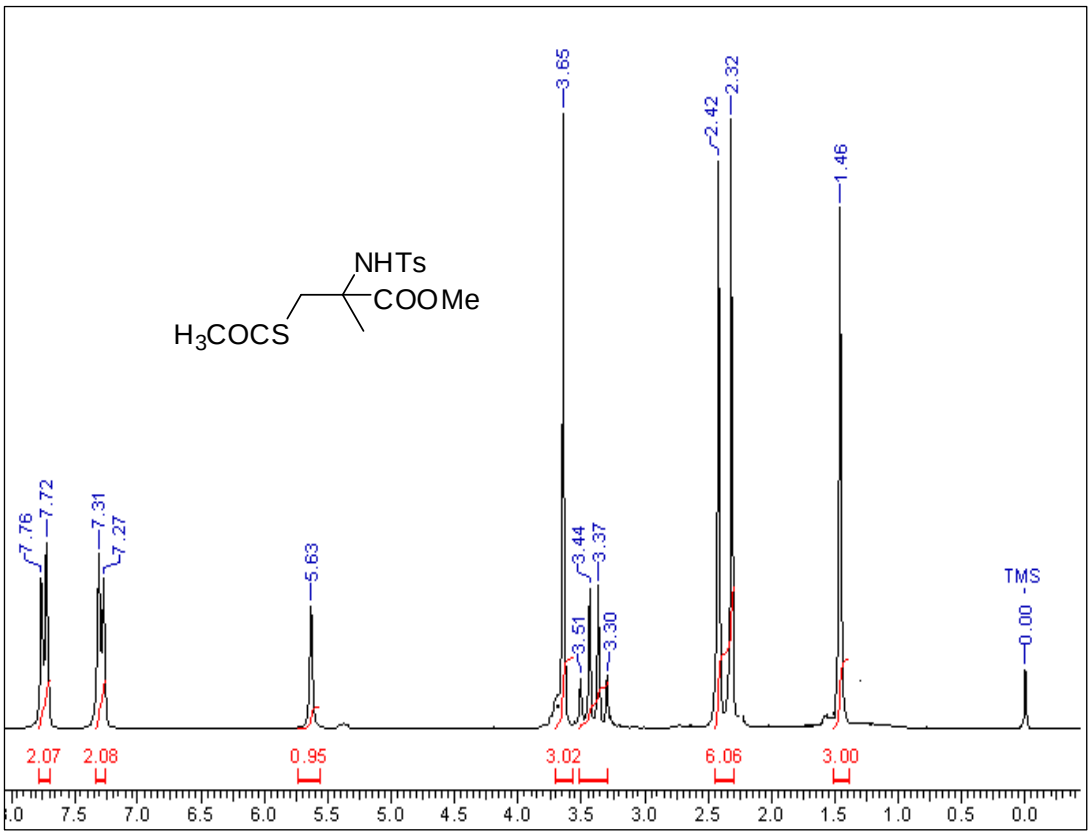
^{1}H NMR spectrum of **39** (200 MHz, $CDCl_3$)



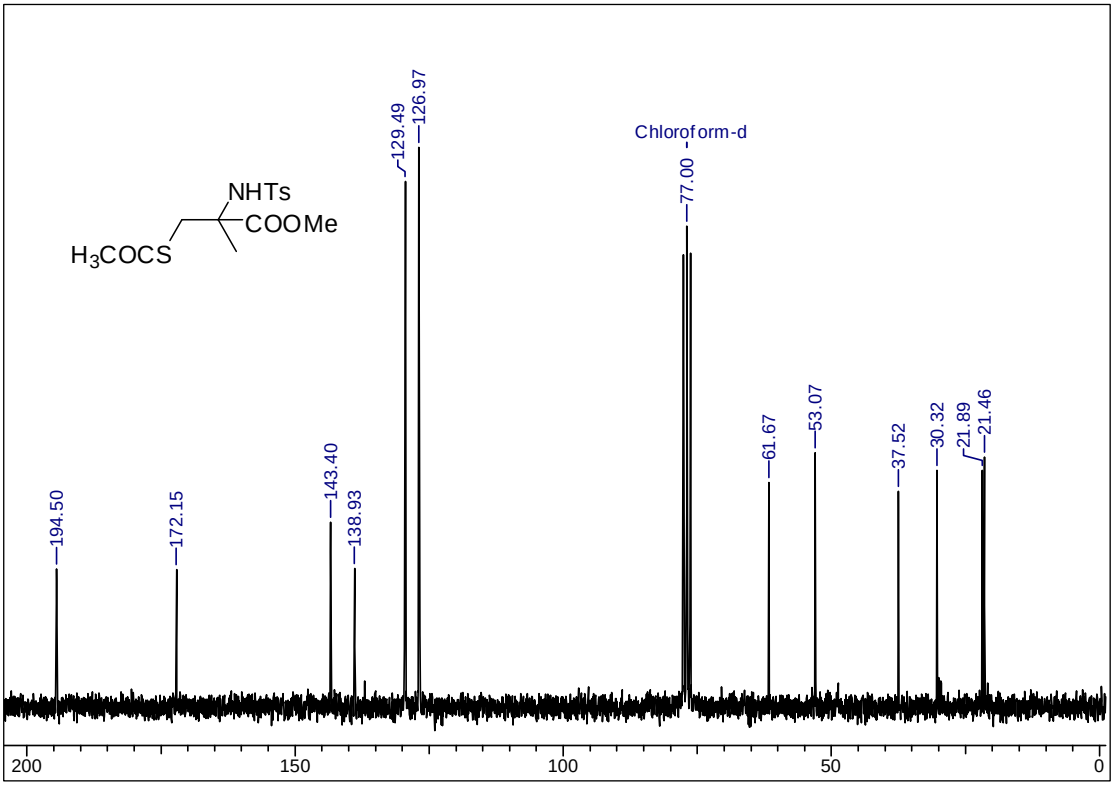
^{13}C NMR spectrum of **39** (50 MHz, $CDCl_3$)



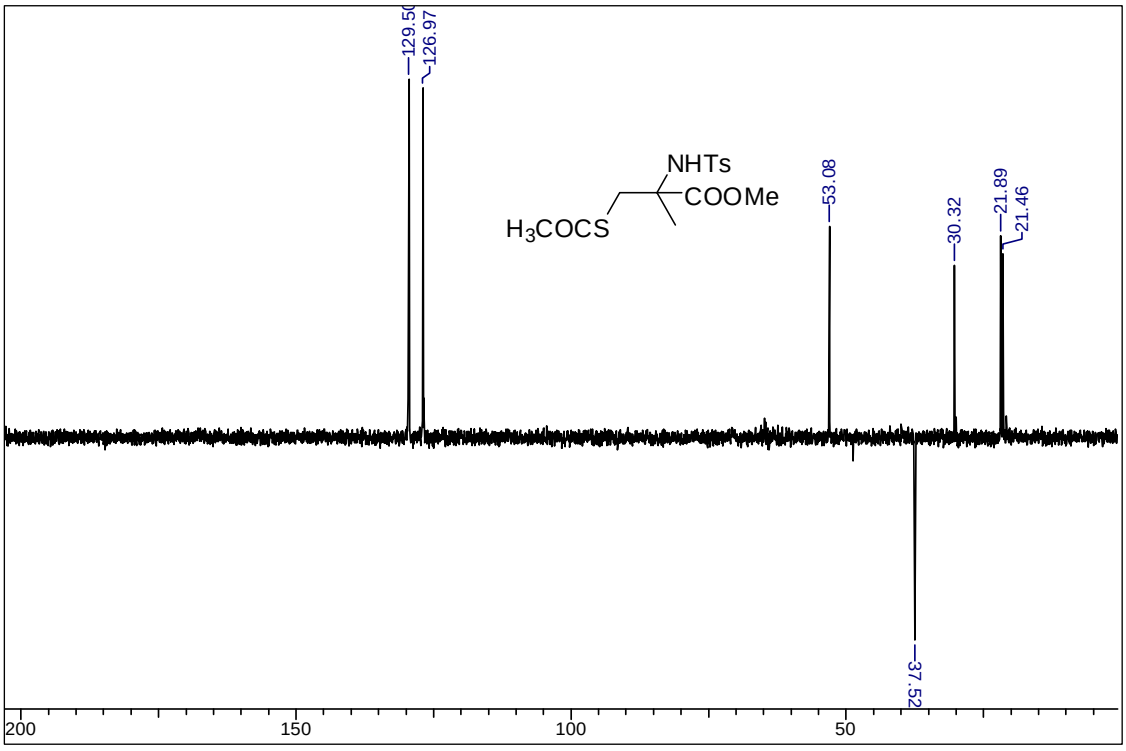
DEPT spectrum of **39** (50 MHz, $CDCl_3$)



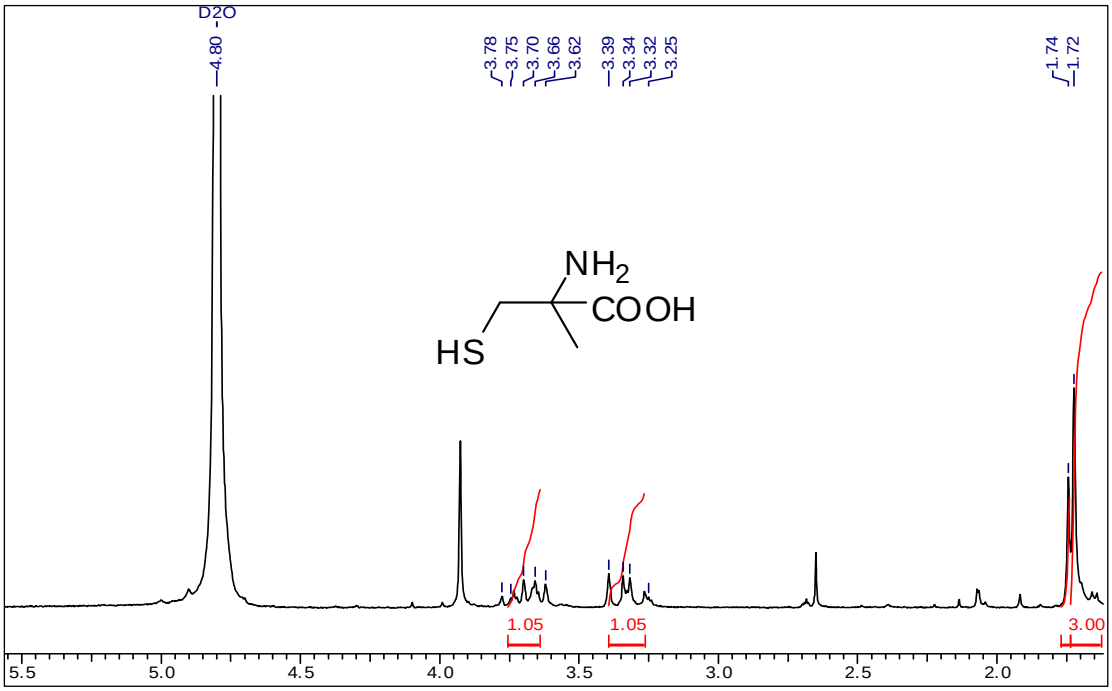
^{1}H NMR spectrum of **40** (200 MHz, $CDCl_3$)



^{13}C NMR spectrum of **40** (50 MHz, $CDCl_3$)



DEPT spectrum of **40** (50 MHz, $CDCl_3$)



^{1}H NMR spectrum of **41** (200 MHz, D_2O)

2.2.8. References

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Chapter 3

Application of Phosphorus Based Ionic Liquids in the Synthesis of Biologically Active Intermediates

3.0.1 Brief history of ionic liquids:

In past 15 years, ionic liquids (ILs) used in organic reactions have become alternative reaction media for organic transformations. An ionic liquid is a liquid containing only ions, but it is different from the classic definition of a molten salt.[1] More recently melting point criteria has been proposed to distinguish between molten salts and ionic liquids. Molten salts are usually defined as a high-melting, highly viscous and highly corrosive liquid medium, while ionic liquids are defined as pure compounds, consisting only of cations and anions (Figure 1), which melt at or below 100 °C and have lower viscocity.[2] Some ionic liquids are free-flowing liquids at room temperature and are called room temperature ionic liquids (RTILs).

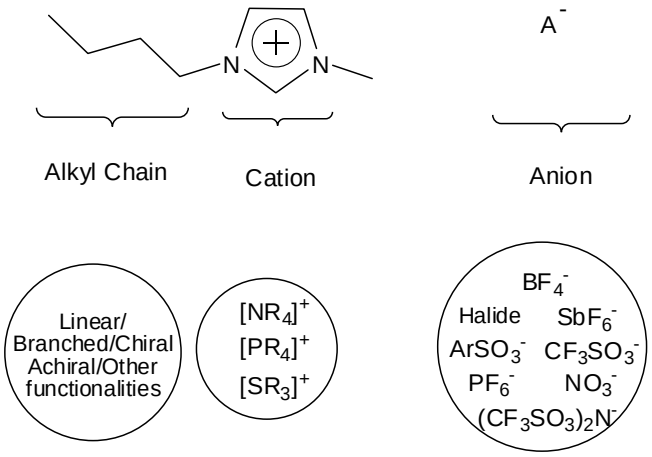


Figure 1: Diagrammatic representation of various components of ionic liquids

The great interest for ionic liquids relies on the fact that they possess several attractive properties such as negligible vapor pressure, chemical and thermal stability, non-flammability, high ionic conductivity, wide electrochemical potential window and moreover the ability to act as catalysts. In addition, many of their physicochemical properties are changed substantially by variation of the cation and the anion; thus, they are "tunable" to the desired reaction. For this reason ILs have been referred to as "designer solvents'' in many publications.

In 1914, Walden[3] reported the synthesis of ethyl ammonium nitrate salt ($[EtNH_3]NO_3$). He reported the physical properties, including melting point of this compound, which melts at 12 °C and is liquid at room temperature and formed by the reaction of ethylamine with concentrated nitric acid. This interesting property did not attract a lot of interest until it was observed that mixture of $AlCl_3$ and N-alkyl pyridium halide salt could be liquid at room temperature. The first research into

chloroaluminate ionic liquids was oriented toward their use in electrochemistry, for example the first ionic liquid with chloroaluminate ion such as ethyl pyridinium chloride with $AlCl_3$ ionic liquid was developed in 1948 by Hurley and Wier. at the Rice Institute as bath solution for electroplating aluminium.[4] However, these systems were not studied further until the late 1970s when groups of Osteryoung and Wilkes rediscovered them. They synthesized and studied the all-chloride system butyl pyridinium chloride/$AlCl_3$, which was not stable toward reduction, limiting its use as an electrolyte.[5] Efforts were made to develop alternative low-melting chloroaluminate ionic liquids that would be less subject to reduction and this led to the discovery by Wilkes *et al*. in 1982 who synthesized ionic liquids from dialkyl imidazolium chloride salts and $AlCl_3$.[6]

Though in 1980 decade chloroaluminate ionic liquids were studied especially by the groups of Hussey *et al*.[7] and Seddon *et al*.[8] as solvents for transition metal complexes, mainly through electrochemical and spectroscopic investigations, the first report on the use of this type of low melting ionic liquids as reaction media for organic synthesis was reported in 1986, as combined solvents and catalysts for Friedel–Crafts reactions.[9] Their first applications as solvents for biphasic catalysis came in 1990 by Chauvin *et al.,* who reported the dimerisation of propene by nickel complexes dissolved in acidic chloroaluminate melts[10] and Osteryoung who reported the polymerisation of ethylene by Ziegler-Natta catalysts.[11] The ionic liquids based on $AlCl_3$ can be regarded as the first generation of ionic liquids.

The hygroscopic nature of $AlCl_3$ based ionic liquids delayed the progress in their use in many applications since they must be synthesized and handled under inert atmosphere. Thus, the synthesis of air and water stable ionic liquids, which are considered as the second generation of ionic liquids, attracted further interest in the use of ionic liquids in various fields. The real breakthrough occurred in 1992; when Wilkes and Zaworotko[12] reported the first air and moisture stable ionic liquids based on 1-ethyl-3-methylimidazolium cation with either tetrafluoroborate or hexafluorophosphate as anions. This is due to the formation of HF as a result of decomposition of the ionic liquid in the presence of water. Therefore, ionic liquids based on more hydrophobic anions such as trifluoromethanesulfonate ($CF_3SO_3^-$), bis-(trifluoromethanesulfonyl)imide [$(CF_3SO_2)_2N^-$] and tris-(trifluoromethanesulfonyl)methide [$(CF_3SO_2)_3C^-$] were developed.[13-15]

Rogers[16] is one of the highly cited authors in the field of ionic liquids. He

focuses on the synthesis and characterization of environmentally friendly ionic liquids as green solvents. Welton[17] has published many papers dealing with the applications of ionic liquids as solvents for synthesis and catalysis. He focuses on how the ionic liquids interact with solute species to affect their reactivity and on replacing environmentally damaging solvents with more benign alternatives.

Wasserscheid[18] is an active member of the ionic liquid community and focuses on the synthesis and characterization of ionic liquids for use in the biphasic catalysis. MacFarlane *et al.*[15] have synthesized new air and water stable ionic liquids with the purpose of employing such ionic liquids as indicators for sensing and displaying an environmental parameter such as humidity.

Recent developments in cations and anions

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

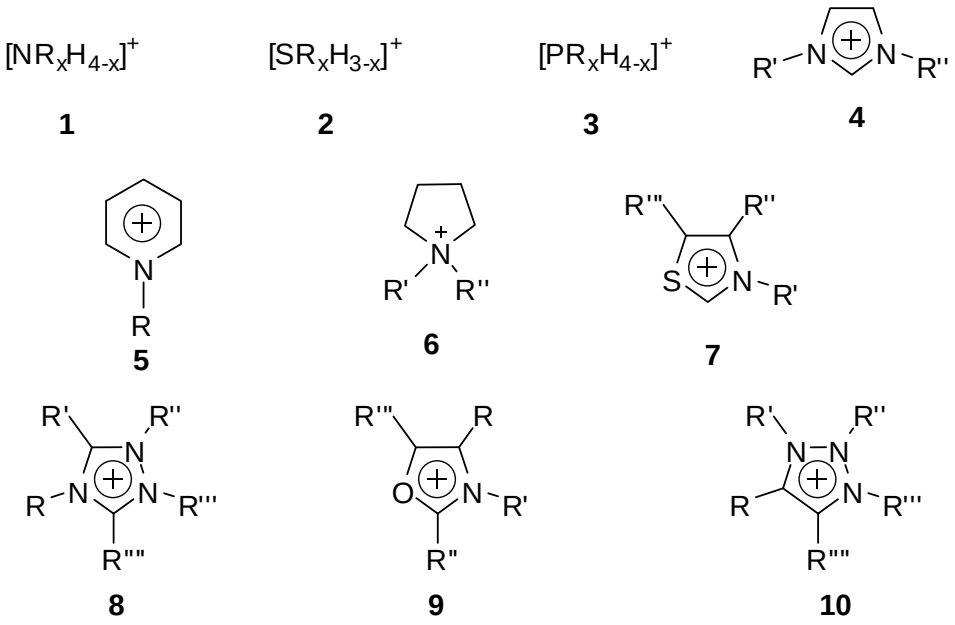


Figure 2: Examples of cations described in ionic liquids

Concerning the anions, they can be classified in two categories, those which give polynuclear anions, e.g. Al_2Cl_7, Al_3Cl_{10}, Fe_2Cl_7, Sb_2F_{11} and mononuclear anions which gives neutral stoichiometric ionic liquids like Cl, Br, ClO_4, CF_3SO_3, CH_3SO_3, CF_3CO_2, etc. The series of zwitterionic type ionic liquids (Figure 3) consisting of imidazolium cations containing covalently bound counter anionic sites, such as sulfonate or a sulfonamide group have been synthesized.

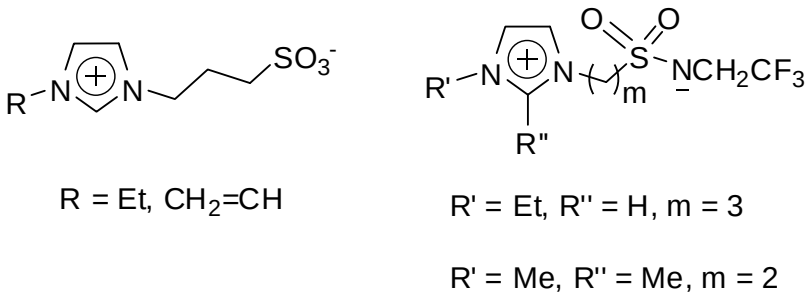


Figure 3: Examples of zwitterionic salts

Chiral ionic liquids

Even though a limited number of chiral ILs have been designed and synthesized in an attempt to influence the outcome of asymmetric organic reactions,[19] there are only a few chiral ionic liquids that can effectively influence the outcome of asymmetric reactions.[20] These new chiral solvents should play a central role in enantioselective organic synthesis and hopefully expand the scope of chiral solvents. Chiral ILs can be particularly attractive if one considers their potential applications to chiral discrimination, including asymmetric syntheses and optical resolution of racemates.

A thorough literature review reveals that the design of existing chiral ILs is based on modifications of the ammonium,[21] pyridinium,[22] oxazolinium,[22] or thiazolium cations.[23] There are several chiral ILs in which the chiral moiety is contained in the anion **11** and **12** (Figure 4), but the modification of imidazolium cation-derived ILs **13-16** offers extreme promise in the design of chiral ILs due to their facile synthesis, low melting points, and relatively favorable viscosity.

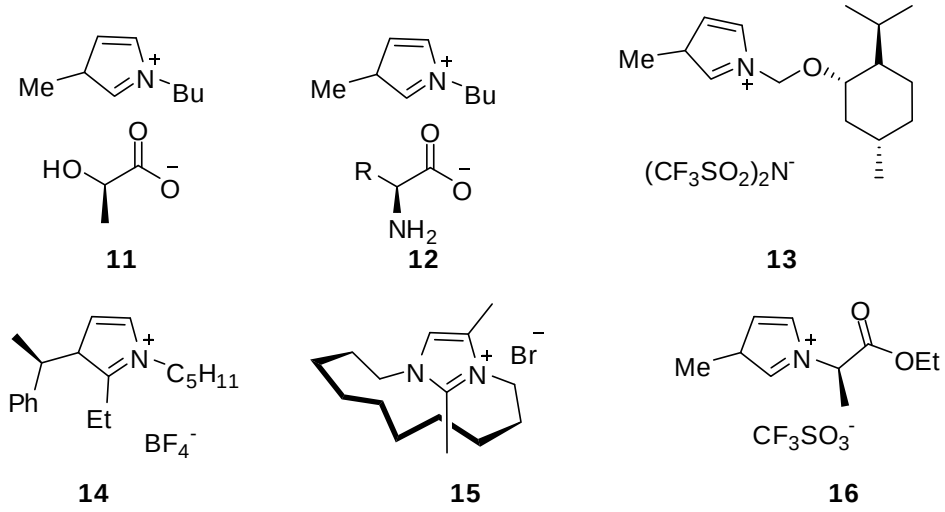


Figure 4: Chiral ionic liquids

Imidazolium ionic liquids:

The most extensively studied class of ILs are based upon the imidazolium cation and the most common examples are the ethylmethylimidazolium ions with anions such as $[BF_4]^-$ and $[AlCl_4]^-$. However, imidazolium-based solvent systems are unsuitable for reactions involving either active metals (e. g. Na or K) or in reactions those involve strong bases (e.g. Grignard, organolithium and amide) since these reagents react with the imidazolium-based solvents. For instance, imidazolium ions react with potassium metal to produce imidazol-2-ylidenes (N-heterocyclic carbenes, NHCs), or reaction with lithium di-iso-propylamide or potassium t*ert*-butoxide to generate NHCs. Aggarwal *et al*.[24] have shown that imidazolium-based ionic liquid in Baylis-Hillman reaction resulted in the addition of deprotonated imidazolium cation to an aldehyde in presence of weak bases. Handy *et al.*[25] studied the deuterium exchange on substituted imidazolium and investigated that under more basic conditions the exchange is possible.

Phosphorus containing ionic liquids

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

The first group of ionic liquids (phosphorus containing imidazolium based ionic liquids) was introduced[26] and thoroughly studied and lot of literature is available regarding properties, synthesis and applications. A review article by Keglevich[27] explains various green chemistry aspects of both phosphorus based ionic liquids along with their applications. Various applications of 1-alkyl-3-methylimidazolium hexafluorophosphates as alternative reaction media are found in the literature.[28] Dzyuba *et al*.[29] reported the synthesis and properties of 1,3-dialkylimidazolium hexafluorophosphates (Figure 5). All these 1,3-dialkylimidazolium hexafluorophosphates with dibutyl, dioctyl, dinonyl, and didecyl substitutents have melting points less than 100 °C.

Imidazolium phosphine type ionic liquids (Figure 5) were introduced for reactions involving metal complexes as catalyst.[30]

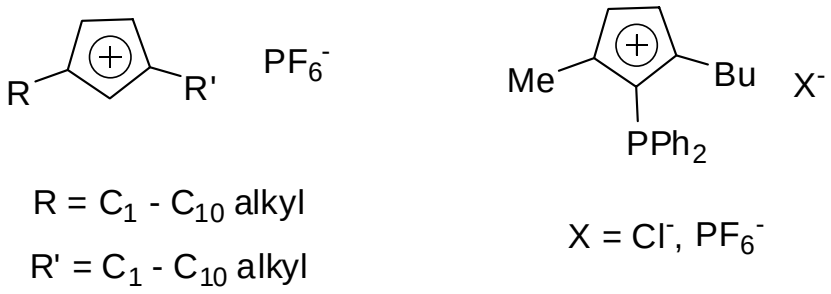


Figure 5

Phosphonium based ionic liquid (PILs):

Very recently, a new class of ionic liquids has been introduced in organic reactions. These are popularly known as phosphonium ionic liquids (PILs). They are phosphonium based ionic liquids, which differ from the well known imidazolium ILs in which phosphorus acts as a cation (quaternary phosphonium salts). Following are some anions that can be paired with phosphorus cation (Figure 6).

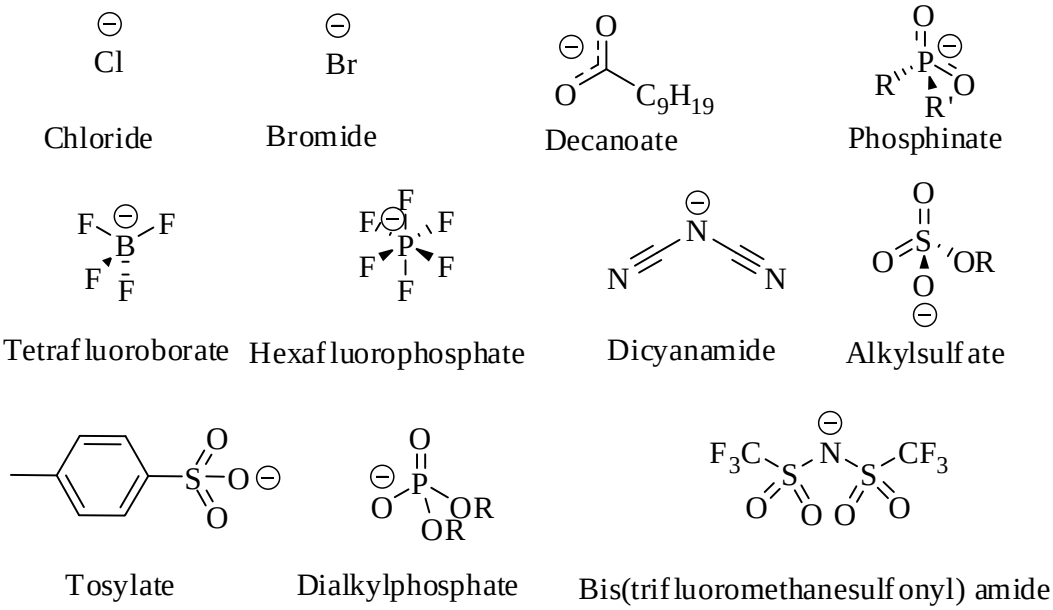


Figure 6

Advantages of phosphonium ionic liquids:

Phosphonium ionic liquids are much more thermally stable than the corresponding ammonium salts and even have an edge on imidazolium salts. This is very important for processes which operate at temperatures greater than 100 °C. In addition to being slightly less thermally stable, the imidazolium cation contains protons which are not entirely inert. They are little acidic which can result in carbene formation. Phosphonium salts, on the other hand, have no such acidic protons.

Table 1

Sr. No	Phosphonium ionic liquid	PIL
1	Tetradecyl(trihexyl) phosphonium tetrafluoroborate	PIL-1
2	Tetradecyl(trihexyl) phosphonium chloride	PIL-2
3	Tetradecyl(trihexyl) phosphonium dicyanamide	PIL-3
4	Tetradecyl(trihexyl) phosphoniumdecanoate	PIL-4
5	Tetradecyl(trihexyl) phosphonium hexafluorophosphate	PIL-5
6	Tetradecyl(trihexyl) phosphonium bistriflamide	PIL-6
7	Triisobutyl(methyl)phosphonium tosylate	PIL-7
8	Tetradecyl(trihexyl) phosphonium dodecylsulfonate	PIL-8
9	Tetradecyl(trihexyl) phosphonium bromide	PIL-9

The fact that, alkylphosphonium salts are in general, less dense than water can be beneficial in product work-up steps while decanting aqueous streams which contain inorganic salt byproducts. Imidazolium salts, on the other hand are denser than water. Some unsymmetrical alkyl substituted phosphonium ionic liquids are depicted in Table 1.

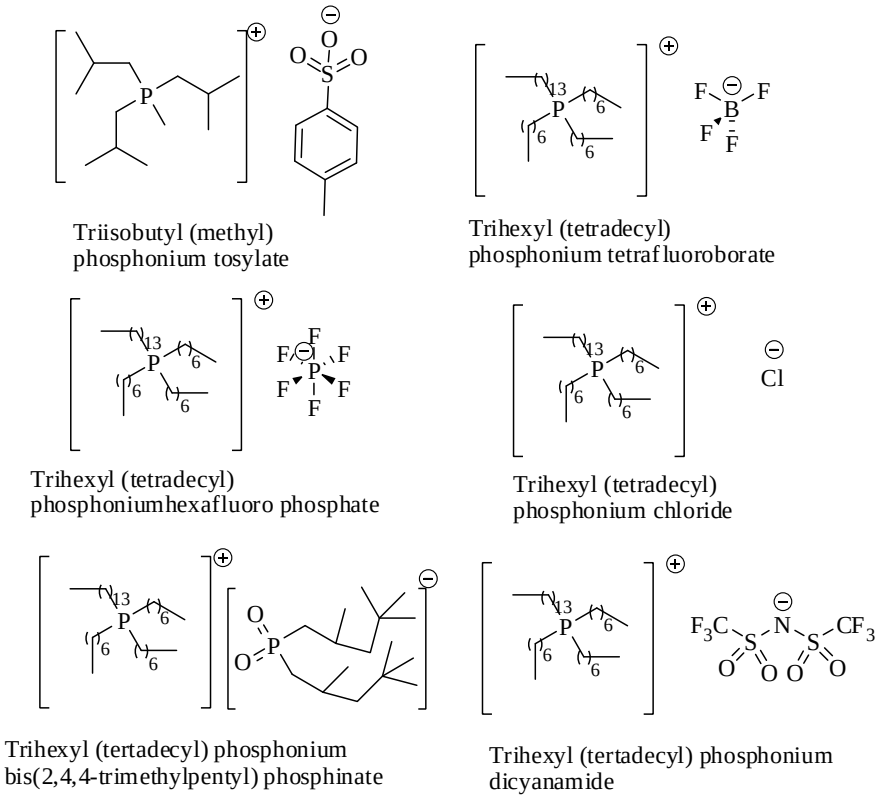


Figure 7: Structures of various phosphonium ionic liquids

Applications of phosphonium ionic liquids:

Phosphonium ionic liquids have been used as reaction medium for various chemical transformations. Trihexyl(tetradecyl)phosphonium chloride has been used for the enhancement of the enantioselectivity and the stability of Ru-BINAP during hydrogenation of dimethyl itaconate to (*S*)-dimethyl methylsuccinate. Palladium catalyzed Suzuki cross-coupling of aryl boronic acids with aryl halides under mild conditions was demonstrated in same ionic liquid with 76-100% yields.[31] It was also demonstrated by Wong *et al*.[32] for 4-bromo acetophenone in three different PILs.

Buchwald-Hartwig amination[33]of aryl halides using palladium as catalyst was studied in phosphonium ionic liquids containing trihexyl(tetradecyl)phosphonium cation with a range of anions. Trihexyl(tetradecyl)phosphonium bis(trifluoromethylsulfonyl)imide was found to be better among used ionic liquids.

The Heck cross-coupling[34] of aryl iodides and bromides with methyl acrylate was reported in trihexyl(tetradecyl)phosphonium chloride and trihexyl(tetradecyl) phosphonium decanoate with high yields. Trihexyl(tetradecyl)phosphonium chloride was easier to separate during the purification stage. Tetrabutylphosphonium bromide was used for thiolyzation of epoxides with aryl disulfides catalyzed by cerium(III) chloride heptahydrate.[35]

Comyns *et al.*[36] demonstrated hydrogen transfer to acetophenone using ethyltrioctylphosphonium tosylate and Ru as catalyst. Similarly, selective hydrogenation of 1,3-butadiene to 1-butene[37] and the hydroformylation of 1-hexene to C-7- aldehyde[38] are described in phosphonium ionic liquids.

The conversion of methanol to acetic acid was reported in presence of phosphonium ionic liquids with tetrafluoroborate as anion and Ru and Co as catalyst.[39] Highly regioselective O-alkylation of β-naphthol with benzyl bromide was demonstrated in tetraalkylphosphonium halides.[40]

Design of novel PILs that are compatible with Grignard reagents have been investigated.[41] It has been established that even basic aliphatic Grignard reagent-mediated reactions are possible when methoxyethyl(tri-n-butyl)phosphonium bis(trifluoromethanesulfonyl)imide is used as the solvent.

Ramnial *et al*.[42] reported in 2005 that Grignard reagents are persistent in tetradecyl(trihexyl)phosphonium chloride and may be more suitable for reactions involving strong bases. They further suggested[43] that Grignard reagents in

phosphonium ionic liquids possessing O-donor anions are excellent reaction media for electron transfer processes and transmetallation reactions.

Itoh *et al*.[41] in 2007 further verified that Grignard reagent-mediated reactions are possible when methoxyethyl (tri-*n*-butyl) phosphonium bis (trifluoromethanesulfonyl) imide is used as the solvent. Reactions of saturated chlorides with hydrogen fluoride in PIL were also reported.[44] This method may be suitable for the synthesis of industrially useful fluorine derivatives such as freons.

Phosphonium tosylates were used in Diels-Alder reactions of isoprene with methyl acrylate, but-2-en-2-one and acrylonitrile; demonstrating a high regioselectivity (>99%) of 1,4-isomer with oxygen-containing dienophiles even without Lewis acids as catalysts.[45]

Forbes *et al*.[46] demonstrated esterification of acetic acid using ethanol and phosphonium ionic liquid bearing sulfopropyl moiety which act as an acid catalyst for esterification reaction. Friedel-Crafts acylation of substituted benzene with benzoyl chloride was also reported by Earle *et al*, [47-50] in presence of phosphonium ionic liquid.

Chanda *et al*.[51] demonstrated kinetic resolution of racemic 1-phenylethanol by transesterification with vinyl acetate in phosphonium ionic liquids. Phosphonium ionic liquids are also found to be suitable solvents for electrophilic reactions such as nitration and sulfonation. [52-54]

Accordingly, on top of literature specifies effectiveness of phosphonium-based ionic liquids for various catalytic reactions along with nucleophilic and electrophilic reactions. It is with this view in mind; synthesis of some biologically active intermediates in phosphorus based ionic liquids was undertaken. . As all reactions dealing with ionic liquids are classified as green reactions, it is considered necessary to discuss green chemistry and its principles here.

Green chemistry:

It is extensively acknowledged that there is a rising need for more environmentally satisfactory processes in the chemical industry. This trend towards what has become known as ‘Green Chemistry’ or ‘Sustainable Technology’ necessitates a paradigm shift from traditional concepts of process efficiency, that focus largely on chemical yield, to one that assigns economic value to eliminating waste at source and avoiding the use of toxic and/or hazardous substances.

A reasonable working definition of green chemistry can be formulated as follows: *green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.*

Twelve principles of green chemistry:

Since its inception in 1991, green chemistry has grown into a significant, internationally engaged focus area within chemistry. The following twelve principles of green chemistry are viewed as the guidelines or directions that have been set by some pioneering scientists who have laid the groundwork for future.

1. Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.
2. Design chemical products to be fully effective, yet have little or no toxicity.
3. Design syntheses to use and generate substances with little or no toxicity to humans and the environment.
4. Use raw materials and feedstocks that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.
5. Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.
6. Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.
7. Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.
8. Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.
9. Run chemical reactions at ambient temperature and pressure whenever possible.
10. Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.

11. Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.
12. Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment.

A green solvent must ideally have negligible vapour pressure, high boiling point and nontoxic, have capacity to dissolve wide range of organic, inorganic and organometallic compounds, it should be chemically and physically stable, recyclable, reusable, inexpensive and eventually easy to handle. In addition to these, solvents that allow more selective and rapid transformations will have a significant impact. Therefore, many attempts have been made to substitute conventional organic solvents with novel alternative reaction media which include:

- Supercritical fluids
- Poly (ethylene glycol)-PEG
- Perfluorinated (fluorous) solvents
- Water
- Ionic liquid

Chapter 3

Section I

Synthesis of β-Enamino ester

3.1.1. Introduction:

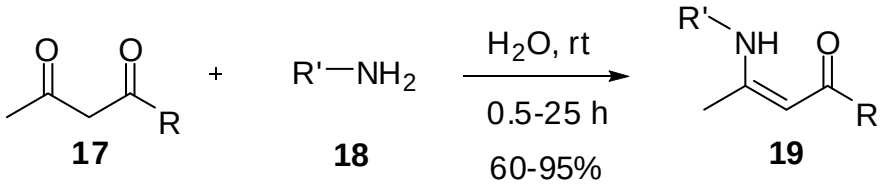
β-Enaminones are versatile synthetic intermediates, extensively employed in organic synthesis.[55] They have attracted much attention due to the fact that they are important synthons for the synthesis of many biologically active compounds such as dopamine auto-receptor agonists,[56] acetylcholinesterase inhibitors[57] and anticonvulsants.[58] They are also useful intermediates for the synthesis of several aminoacids,[549] aminols,[60] peptides and alkaloids.[61] In particular, such compounds are important precursors for the synthesis of a wide variety of heterocycles.[62] Also they have been employed as synthons of pharmaceutical compounds having anti-epileptic,[63] anti-molluscicidal and larvicidal activities.[64] Thus it is very important to search for a convenient and efficient method for the synthesis of this type of compounds. As a result several methods have been developed for the synthesis of enaminones.

3.1.2. Review of Literature

The most well known and explored route to β-enaminones involves the direct condensation of β-dicarbonyl compounds with amines in refluxing aromatic hydrocarbons with azeotropic removal of water.[65] In recent years, several important improved environmentally benign procedures have been reported, some of the representative methods are discussed below.

Stefani's approach (2000)[66]

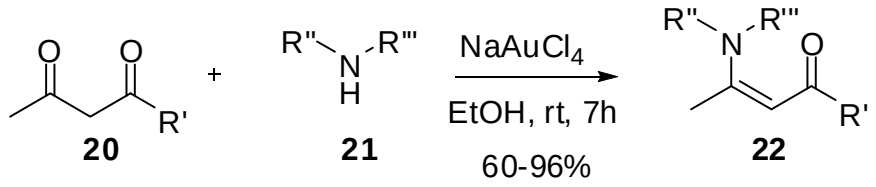
Stefani, H. A. *et al.* reported a simple procedure for the synthesis of β-enamino esters and β-enaminoketones **19** starting from β-ketoesters /1,3-diketones **17** and primary amines **18** using water as solvent (Scheme 1).



Scheme 1

Marinelli's approach (2003)[67]

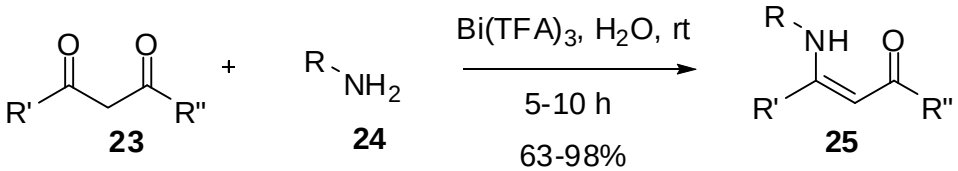
Marinelli, F. *et al.* reported an efficient gold (III) catalyzed environmental friendly method for the synthesis of β-enaminones **22** in ethanol at room temperature (Scheme 2).



Scheme 2

Khosropour's approach (2004)[68]

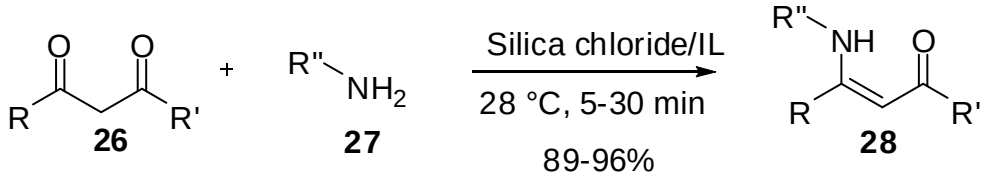
Khosropour, A. R. *et al.* reported bismuth (III)trifluoroacetate as an extremely efficient catalyst for the synthesis of β-enaminones **25** in water at room temperature (Scheme 3).



Scheme 3

Srinivasan's approach (2006)[69]

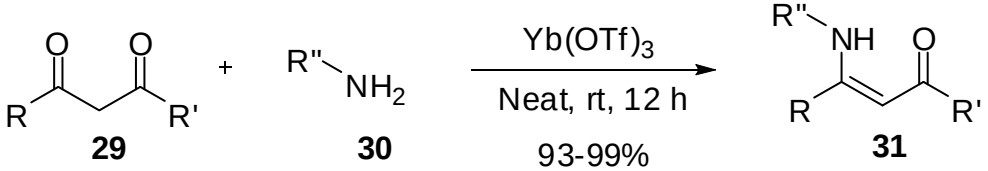
Srinivasan, K. V. *et al.* reported a remarkably rapid regioselective synthesis of β-enaminones **28** using imidazolium ionic liquid in homogeneous medium as well as silica chloride in a heterogeneous medium (Scheme 4).



Scheme 4

Epifano's approach (2007)[70]

Epifano, F. *et al.* have reported the synthesis of β-enaminones **31** by using ytterbium triflate as a catalyst under solvent-free conditions (Scheme 5).

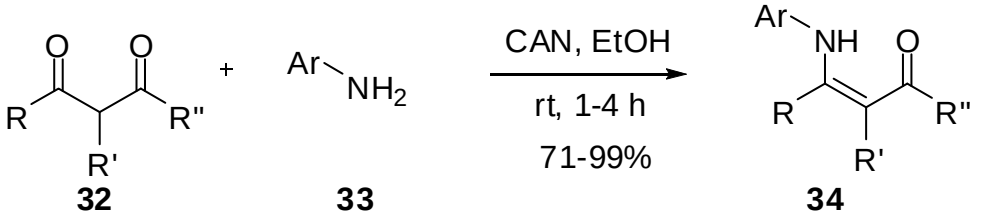


Scheme 5

Menendez's approach (2007)[71]

Menendez, J. C. *et al.* reported general, mild and efficient synthesis of β-enaminones **34** catalyzed by ceric ammonium nitrate in ethanol at room temperature

(Scheme 6).

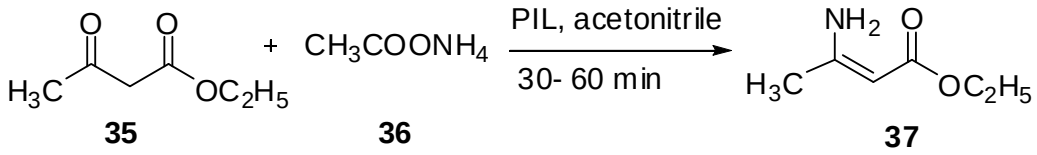


Scheme 6

3.1.3. Present work

Due to their wide range of activity and importance, a simple and high yielding one-pot approach for the synthesis of β-enaminones is highly desirable. The conventional method for the synthesis of enaminones is the azeotropic removal of water by refluxing an amine with 1,3-diketone in an aromatic solvent. A simple, efficient and environment friendly, one-pot synthesis of β-enamino ester by direct reaction of ammonium acetate as source of amine with ethyl acetoacetate was undertaken using catalytic amount of some phosphonium ionic liquids.

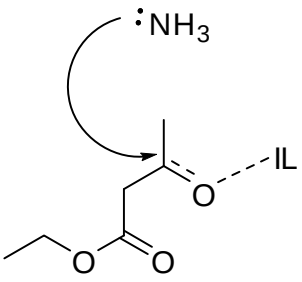
β-Enamino ester **37** was synthesized by stirring 1.0 equivalent of ethyl acetoacetate **35**, 1.6 equivalent of ammonium acetate **36** and 20% w/w of ionic liquid in acetonitrile at 30 °C (Scheme 7). The crude mixture was purified by column chromatography. The compound was characterized by ^{1}H NMR and ^{13}C NMR spectroscopy.



Scheme 7

3.1.4. Results and Discussion

The reaction was studied in the presence of six different ionic liquids (Table 2) as catalysts at room temperature and at 50 °C. These ionic liquids were obtained as gifts from CYTEC Canada. Ammonium acetate was used as source of ammonia.



Scheme 8

It was observed that the nature of the anion governs the electrophilicity of the phosphonium cataion, which in turn influences the acidity of the phosphorus. This phosphorus is capable of partial bonding with acetyl oxygen generating the cationic center as shown in scheme 8 which is easily attacked by the nucleophilic amines. Consequently, it can be observed from table 2, the PIL-2 (chloride) with most electrophilic phorphorus afforded the best results in terms of time of complete conversion although all the ILs afforded more or less similar isolated yields.

Table 2: Synthesis of 3-amino-but-2-enoic acid ethyl ester using phosphonium ionic liquids as catalyst (20% w/w) in acetonitrile as solvent

Sr. No.	Ionic Liquid	Temperature 25 °C		Temperature 50 °C	
		Time (min)	Yield (%)	Time (min)	Yield (%)
1	PIL-1	60	69	45	65
2	PIL-2	30	89	30	92
3	PIL-3	40	56	40	59
4	PIL-4	55	48	35	52
5	PIL-5	35	73	35	79
6	PIL-6	60	64	40	62

Various ionic liquids were screened in the model reaction of ethyl acetoacetate **35** and ammonium acetate **36** at room temperature and at 50 °C (Table 2) for β-

enamino ester **37** formation reaction. The efficacy of the ILs to promote this reaction was correlated to the basicity of the anions. It was assumed that the nature of the anion would govern the electrophilicity of the phosphinum cation, which in turn has a bearing on the acidity of the PILs. It was observed that with increasing basicity of the anion, there was a progressive increase in yield (Table 2, entry 2, 5). The yield of desired product was increased progressively with increasing acidity of the PILs.

Thus among the PILs tested in enamino ester formation reaction, it was found that the PIL-2 (chloride) efficiently promoted this reaction by virtue of its inherent acidity. This makes the PIL capable of bonding with the carbonyl oxygen increasing the reactivates of the parent carbonyl compounds without any added acid catalyst.

All the PILs catalyzed the reaction providing the desired products. The catalytic activities of the ionic-liquid in product formation varied slightly with different anions in the PIL catalysts. For example, in PILs from chloride anion (PIL-2) improved activity as well as higher yield (Table 2, entry 2) of the desired product was observed. In phosphinate gating higher yield comparatively borate, triflamide, tosylate, decanoate, and dicynamide in both condition. In overall, chloride gave the best outcome in terms of the yield. A rate enhancement with higher yield was observed when temperature was increased.

The recyclability and reusability of PIL were examined for the enamino ester reactions. It was found that PIL could be easily recycled by triphasic separation method. The PILs were recycled and reused at least six times with a slightly decreased activity. The scope and generality of this method could be validated by observing that catalyatic property was well tolerated giving excellent isolated yields of the β-enamino ester. Moreover, the various ionic liquids such as chloride, borate, dicyanamide and triflate were used for the reaction resulting in the formation of β-enamino ester in excellent isolated yields.

3.1.5. Conclusion

A simple, clean, atom-efficient, environment friendly synthesis of β-enamino ester **37** using ionic liquids as catalysts. A simple experimental procedure, relatively fast reaction rates and excellent yields are the key advantages of our protocol. Most significantly, efficiency, cost-effectiveness and green methodology will make this procedure useful to academia as well as industry.

3.1.6 Experimental

Procedure for synthesis of 3-amino-but-2-enoic acid ethyl ester in ionic liquid:

A mixture containing ethyl acetoacetate (300 mg, 2.30 mmol), ammonium acetate (210 mg, 2.76 mmol) and ionic liquid (60 mg, 20 % w\w) in acetonitrile was stirred at 25 and 50 °C for 30-60 min. depending upon the ionic liquid used (See Table 2, page 146 for details). The completion of reaction was followed by TLC using 10% EtOAc in petroleum ether as eluent. After completion of reaction, the product was extracted with *n*-hexane (2 × 10 ml) and the hexane layer was carefully separated leaving behind the ionic liquid and aqueous layer. The separated hexane layer was then, dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure to afford the crude product. The crude product was purified by column chromatography to give 3-amino-but-2-enoic acid ethyl ester as yellow oil.

Yields: PIL -1(208 mg, 69%), PIL-2(265 mg, 89%), PIL-3(167 mg, 56%), PIL-4 (143 mg, 48%), PIL-5(218 mg, 73%), PIL-6 (192 mg, 64%).

Mol. Formula : $C_6H_{11}NO_2$

Mol. Weight : 129

FT IR ($CHCl_3$) : 3450, 3336, 2981, 1716, 1621, 788, 565 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.25 (t, 3H, J = 7.2 Hz), 1.90 (s, 3H), 4.12 (q, 2H, J = 7.2Hz), 4.50 (s, 1H), 7.95 (br s, 2H)

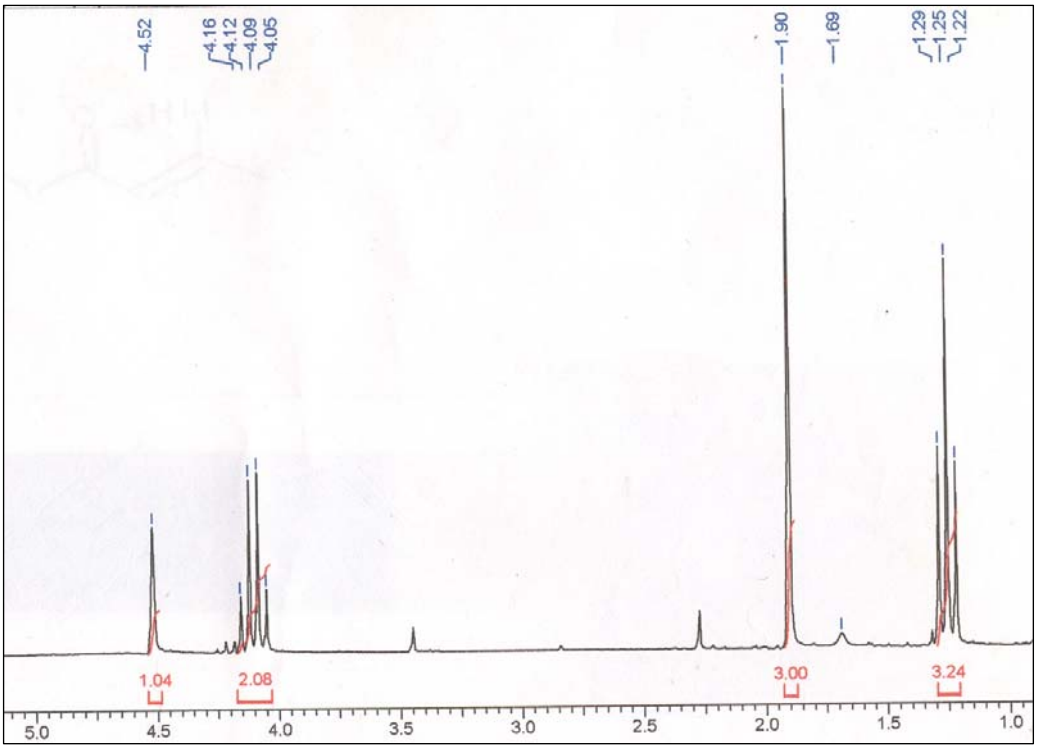
^{13}C NMR (75 MHz, $CDCl_3$) : δ 14.0, 21.5, 57.9, 83.0, 159.9, 169.8

ESI-MS *m/z* : 130.24 $[M+H]^+$

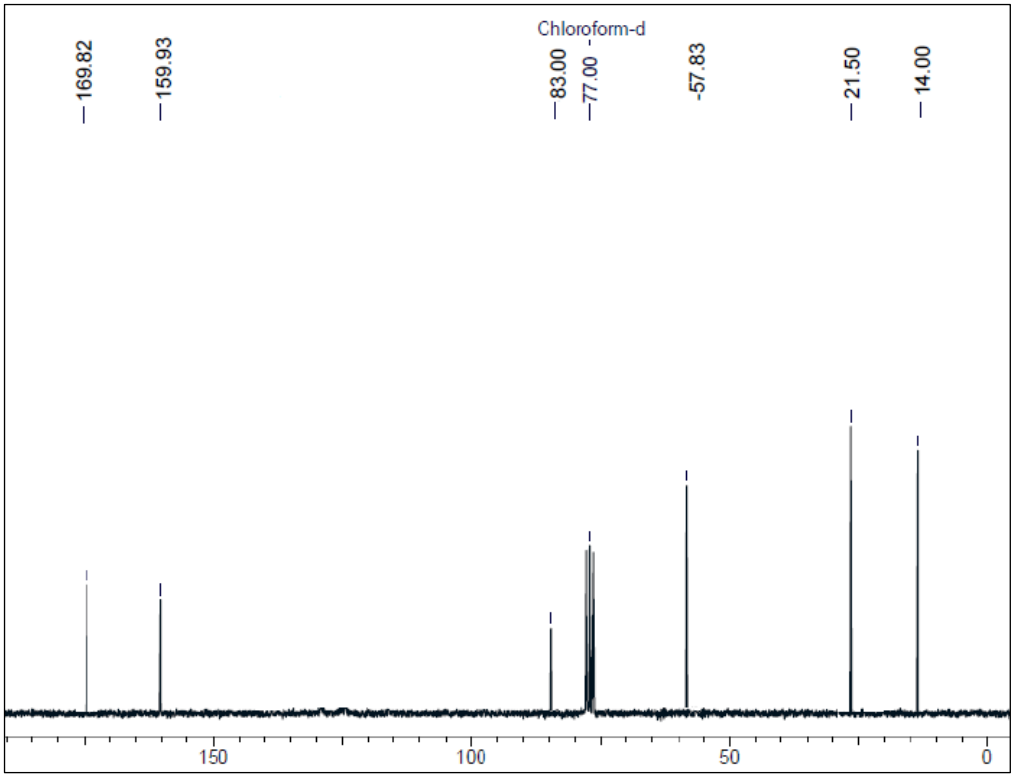
Elemental Analysis : Calcd: C, 55.80; H, 8.58; N, 10.84 %

Found: C, 55.72; H, 8.51; N, 10.86 %

3.1.7 Spectra



^{1}H NMR spectrum of **3-amino-but-2-enoic acid ethyl ester** (200 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3-amino-but-2-enoic acid ethyl ester** (50 MHz, $CDCl_3$)

3.1.8. References

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Chapter 3

Section II

Synthesis of Benzodiazepine Derivatives

3.2.1. Introduction

Benzodiazepines are bicyclic heterocyclic compounds having a benzene nucleus fused to a seven-membered ring containing two nitrogen atoms. The following six formulae represent the basic ring structures of benzodiazepines. The term benzodiazepine implies a maximum degree of instauration, i.e. a total of three double bonds in the seven-membered ring. The position of the odd hydrogen atom (even if occupied by another mono- or divalent substituent) is indicated by the term *1H*, *2H*, *3H*, etc (Figure 1).

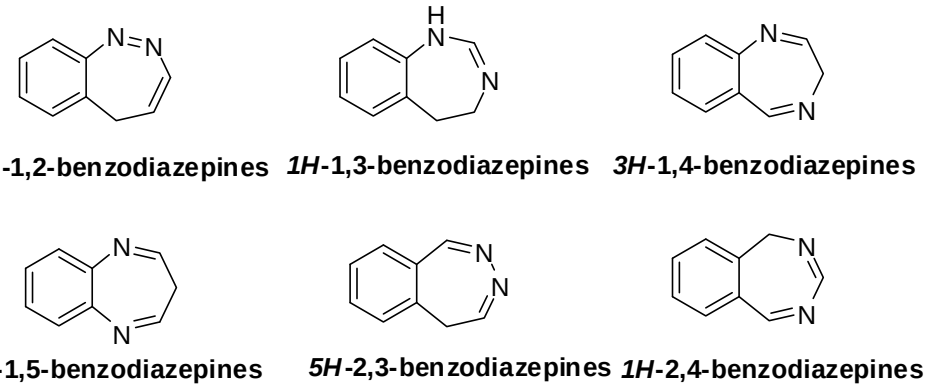


Figure 1

The 1,4 benzodiazepines form the most extensively explored group in this series, mostly outstanding to the discovery of their interesting biological activity, which has led to the introduction of four drugs. The l,5-benzodiazepines have been thoroughly studied during a period of several decades, largely because of their relatively easy synthesis from common starting materials. The other four groups of benzodiazepines have so far failed to attract very much interest.

1,5-Benzodiazepines may exit in either of the tautomeric forms A or B (Figure 2). While the *3H* tautomer is in general, thermodynamically preferred, mono protonation renders the *1H* tautomer energetically more favorable, and most of the salts of 1,5-benzodiazepines occur in this form.

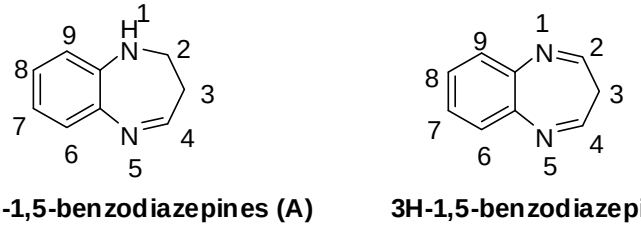


Figure 2

The benzodiazepine nucleus is a well-studied traditional pharmacophoric

scaffold that has emerged as a core structural unit of various sedative hypnotic, muscle relaxant, anxiolytic, antistaminic, and anticonvulsant agents. Although the first benzodiazepine was introduced as a drug nearly 35 years ago the research in this area is still very active and is directed toward the synthesis of compounds with enhanced pharmacological activity.

The discovery of diazepam followed by many other psychotropic agents sharing a 1,4-benzodiazepines skeleton has also promoted the studies on the isomeric 1,5-benzodiazepine ring system[1] along with the synthetic approaches to mono and diannelated 1,5-benzodiazepines[2] due to their accessibility, easy functionalization and potential pharmacological properties, mainly 1,5-benzodiazepines and 1,5-benzodiazepinone derivatives have received significant attention. Peripheral choleecystokinin receptor agonists,[3] CCK-B/gastrin receptor agonists,[4] arginine vasopressin antagonists,[5] CNS depressants,[6,7] antiamoebics[8] and antiproliferative agents[9] derived from 1,5-benzodiazepinones have been reported. Heterofused 1,5-benzodiazepinones have also been evaluated towards benzodiazepine receptor binding[10] or HIV reverse transcriptase inhibition[11] and found to possess anticonvulsant,[12] analgesic or anti-inflammatory,[13] anti psychotic (clozapine)[14] or PAF-induced aggregation inhibitory activities (Figure 3).[15,16]

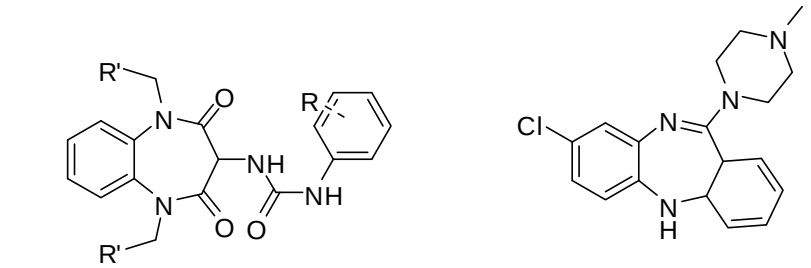


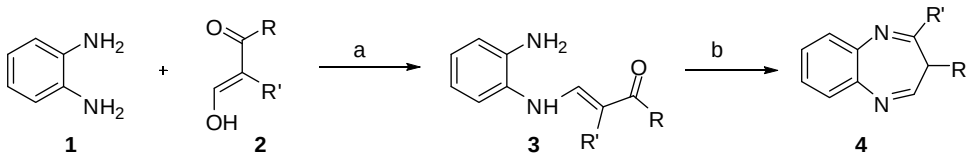
Figure 3: CCK-B/gastrin Receptor Antagonists

3.2.2. Review of Literature

Due to the wide range of application of 1,5-benzodiazepines from drugs to fibers to dyes, there are several synthetic methods reported in the literature for the synthesis of 1,5-benzodiazepines. In this section we have covered some of more significant and useful synthetic methods for the synthesis of 1,5-benzodiazpeines.

Weissnfels approach (1967)[17]

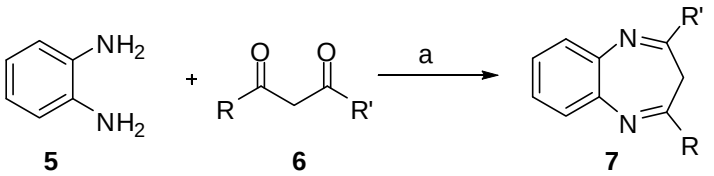
Weissnfels and coworkers studied the condensation of *o*-phenylenediamine with various a-hydroxymethyl ketones to give the intermediate which was further cyclized to 1,5-benzodiazepine in good yield in the presence of perchloric acid (Scheme 1).



Scheme 1: Reaction conditions: a) 100 °C, 12 h; b) $HClO_4$, EtOH, reflux, 70-80%.

Neumann's approach (1976)[18]

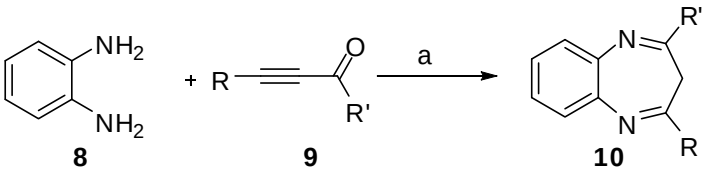
Neumann and workers synthesized 1,5-benzodiazepines in good yield by condensation of *o*-pheneylenediamine with pentane-2,4-dione under acidic condition to give an unstable intermediate which spontaneously tautomerizes benzodiazpine (Scheme 2).



Scheme 2: Reaction conditions: a) heat, HX.

Amey's approach (1976)[19]

Amey *et al.* reported synthesis of 1,5-benzodiazepines from *o*-phenylenediamine**,** which on condensation with different acetylene ketones in a hot mixture of acetic acid and ethanol gave benzodiazepines in excellent isolated yield (Scheme 3).

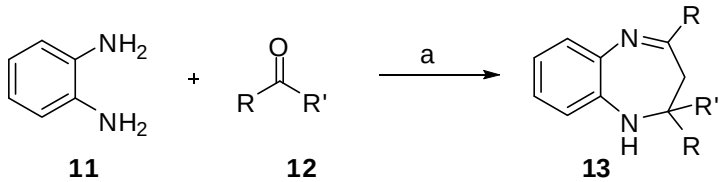


Scheme 3: Reaction conditions: a) acetic acid, ethanol, reflux, 80-95%.

Jung's approach (1999)[20]

Jung *et al.* reported the synthesis of 1,5-benzodiazepines by the condensation of *o*-phenylenediamine with different ketones in the presence of polypohoshporic

acid or SiO_2, which afforded the corresponding 1,5-benzodiazepines in moderate yield (Scheme 4).

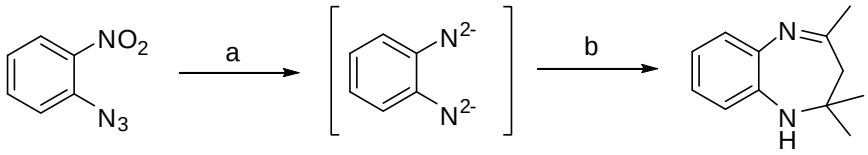


11 **12** **13**

Scheme 4: Reaction conditions: a) PPA or SiO_2, solvent, reflux, 75-93%.

Zhong's approach (2001)[21]

Zhong *et al.* synthesized 1,5-benzodiazepines from o-nitro phenyl azide which was treated with the low-valent titanium reagent (derived from the TiCl:Sm system) to give rise to the intermediate in situ, which reacted with ketones to afford the 1,5-benzodiazepine in high yields (Scheme 5).

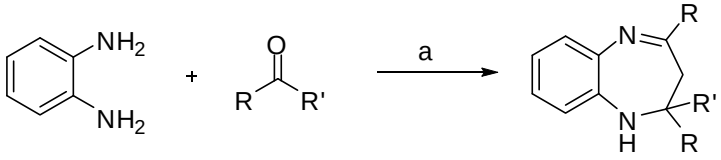


14 **15** **16**

Scheme 5: Reaction conditions: a) $TiCl_1$:Sm; b) ketones 85-93%.

Curini's approach (2001)[22]

Curini *et al.* synthesized 1,5-benzodiazepines in good yield by the condensation *o*-phenylenediamines with different ketones in the presence of a catalytic amount of Ytterbium triflate [$Yb(OTf)_3$] under solvent free conditions (Scheme 6).

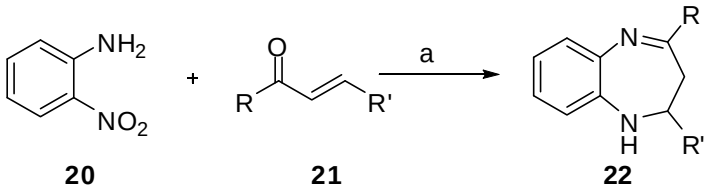


17 **18** **19**

Scheme 6: Reaction conditions: a) $Yb(OTf)_3$, solvent free, rt, 80-95%.

Ma's approach (2002)[23]

Ma *et al.* synthesized 1,5-benzodiazepine from *o*-nitro anilines and chalcones**,** insitu reduction of nitro group followed by cyclization using low-valent titanium afforded target compound in excellent isolated yield (Scheme 7).

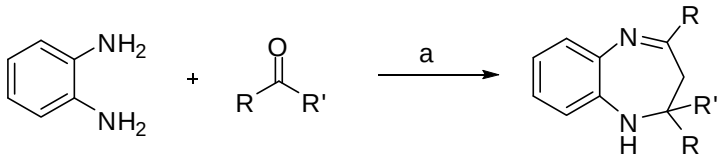


20 **21** **22**

Scheme 7: Reaction conditions: a) Sm, THF, rt, 60-75%.

Pozarentzi's approach (2002)[24]

Pozarentzi *et al.* synthesized library of 1,5-benzodiazepines by condensing *o*-phenylenediamine and different ketones in the presence of a catalytic amount of acetic acid under microwave irradiation which offers better results compare to conventional heating with respect to reaction time and yield (Scheme 8).

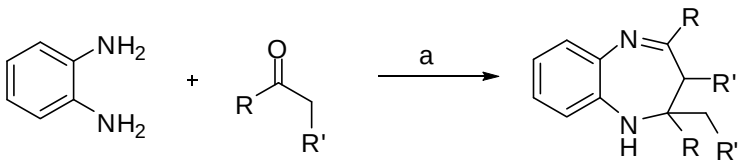


23 **24** **25**

Scheme 8: Reaction condition: a) AcOH, MW. 80-95%

Yadav's approach (2003)[25]

Yadav *et al.* reported the synthesis of 1,5-benzodiazepines by the condensation of *o*-phenylenediamine with ketones in the presence of catalyst Amberlyst-15® in ionic liquid as a reaction media, which gave benzodiazepines in good yield at room temperature (Scheme 9)

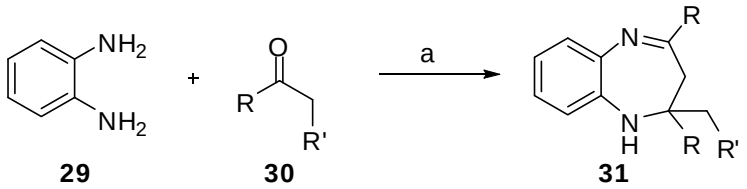


26 **27** **28**

Scheme 9: Reaction conditions: a. Ionic Liquid ([bmim]PF_6), Amberlyst-15®, 5 h, 85-95%.

Heravi's approach (2007)[26]

Very recently Heravi *et al.* reported synthesis of 1,5-benzodiazepines by the condensation of *o*-phenylenediamine and various ketones in the presence of Preyssler heteropolyacid ($Ti_{14}[NaP_5W_{30}O_{110}]$), as a heterogeneous catalyst in refluxing ethanol gave benzodiazepines in good yield (Scheme 10).



29 **30** **31**

Scheme 10: Reaction conditions: i) $Ti_{14}[NaP_5W_{30}O_{110}]$, ethanol, reflux.

Due to its wide range of applications in pharmacology, dyes, fibers and other areas numerous papers can be found in the literature for the synthesis of 1,5-benzodiazepines Some other general synthetic methods for the synthesis of 1,5-benzodiazepines are also reported in the literature.[27-32]

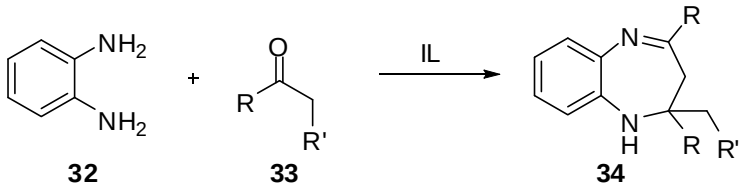
3.2.3. Present Work

1,5-benzodiazepines are useful precursors for the synthesis of some fused ring benzodiazepine derivatives, such as triazolo, oxadiazolo, oxazino, or furano benzodiazepines. Due to their wide range of applications these compounds have received a great deal of attention in connection with their synthesis. Although many reagents and preparatory method have been reported in the literature many of these methodologies are associated with several shortcomings such as long reaction times, expensive reagents, harsh reaction conditions, low-product yields, occurrence of several side products etc.

In recent years, ionic liquids have attracted intensive interest as possible alternatives to traditional solvents for organic reactions, particularly in the area of green chemistry. They have also been referred to as 'designer solvents' as their physical and chemical properties can be adjusted by the careful choice of cation and anion. These compounds also exhibit acidic properties. The use of ionic liquids as reaction media may offer a convenient solution to both the solvent-emission and catalytic-recycling problem.

3.2.4. Results and Discussion

Initially we performed reaction of *o*-phenylenediamine (OPD) with acetone in the ionic liquid at room temperature for 1h, after that TLC was checked, which shows complete disappearance of starting material and formation of the compound (Scheme 11), where its spectral data and physical constant were comparable to that reported in the literature for the known compound.



32 **33** **34**

Scheme 11

The IR spectra of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine **35** shows absorption at 1638 and 3350 cm^1 corresponding to the C=N and -NH functional group respectively. The ^{1}H NMR spectra showed singlet of six protons at δ 2.09 ppm for two methyl groups, singlet of two protons at δ 2.09 ppm for methylene group and broad singlet at δ 2.94 ppm corresponding to -NH. The ^{13}C NMR-DEPT shows peak at δ 44.7 ppm corresponding to methylene group which confirmed the compound formation. Elemental analysis and physical constants match with the literature data**.**

Table 1

Sr. No.	Ionic Liquid	Ketone	Temperature (°C)	Time (min)	Yield[a] (%)
1	Borate	Acetone	40	40	58
		2-Butanone	40	40	76
		Acetophenone	40	40	73
		4-Methyl acetophenone	40	40	75
		3-Nitro acetophenone	40	40	43
		Cyclohexane	40	40	74
2	Chloride	Acetone	40	25	79
		2-Butanone	40	25	92
		Acetophenone	40	25	88
		4-Methyl acetophenone	40	25	94
		3-Nitro acetophenone	40	25	56
		Cyclohexane	40	25	78
3	Phosphinate	Acetone	40	50	54
		2-Butanone	40	50	63
		Acetophenone	40	50	76
		4-Methyl acetophenone	40	50	71

		3-Nitro acetophenone	40	50	49
		Cyclohexane	40	50	50
4	Tosylate	Acetone	40	45	59
		2-Butanone	40	45	66
		Acetophenone	40	45	69
		4-Methyl acetophenone	40	45	76
		3-Nitro acetophenone	40	45	44
		Cyclohexane	40		56

[a] Isolated yield after colunm chromatography

The reaction of OPD with acetone was performed under similar conditions in the several ILs. It was found that chloride and phosphonat afforded the best results. Consequently, all further studies were conducted using the IL chloride as the reaction medium cum promoter to synthesize a variety of 1,5-benzodiazepines.

The results are summarized in Table 1. As is evident, the reactions in IL gave rise to excellent isolated yields of the 1,5-benzodiazepines in a relatively short reaction time (50 mm) under ambient temperature. The isolated benzodiazepines were completely characterized by IR, ^{1}H and ^{13}C NMR analysis, and their melting points were also recorded. The elemental analysis was in agreement with their structures. The IL could be recovered and recycled at least four times for the reaction of the OPD with acetone without incurring any loss in yield of the benzodiazepine**.**

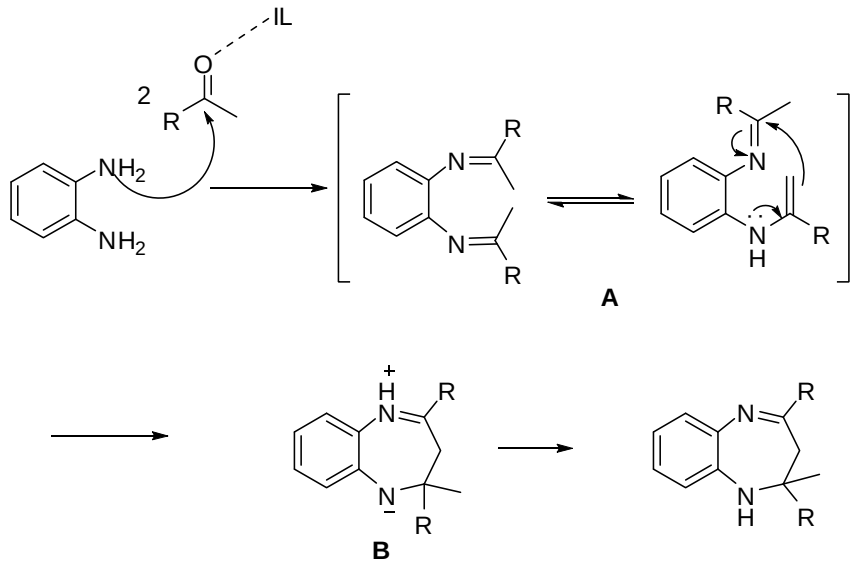
Interestingly, cyclic ketones such as cyclohexanone also reacted well and equally efficiently with similar success to afford fused ring 1,5-benzodiazepines in high yields.

Table 2: Catalytic study of PIL-2 in the synthesis of benzodiazepine **35** in acetonitrile.

Entry	Mol % of IL	Time (h)	Yield (%)
1	0	18	Nil
2	10	10	32
3	20	8	45
4	100	1	97

After that we performed the same reaction again to optimize the reaction condition and time for complete conversion. We found that starting material completely disappeared after 50 mm. at room temperature (progress of reaction was monitored by TLC). No reaction was observed when OPD was reacted with acetone under similar conditions in the absence of the IL for 18 h (Table 2, entry 1), thus highlighting the role of the IL as a promoter. It was also ascertained that a minimum of an equimolar proportion of the IL with respect to the OPD is needed to achieve optimum conversion. Any excess of IL beyond this proportion did not show any further increase in conversion and yield (Table 2, entry 4).

The enhanced reactivity for the synthesis of the benzodiazepines in the IL even in the absence of a catalyst may be attributed to the inherent Brønsted and Lewis acidities of the ILs.



Scheme 12: Plausible mechanism for the formation of 1,5-benzodiazepines

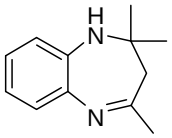
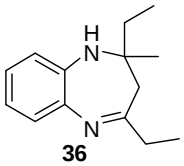
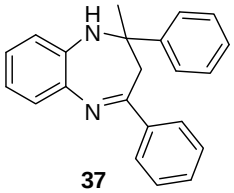
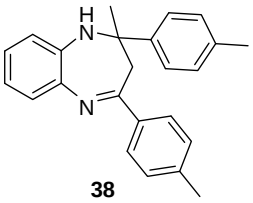
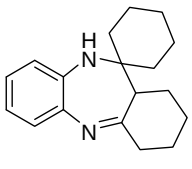
The mechanism of the reaction probably involves an intramolecular imines-enamine cyclization promoted by IL as shown in Fig. 4. Amino goup of *o*-phenylenediamine attacks carbonyl group of ketone giving the intermediate diimine **A**. 1,3-shift of the hydrogen attached methyl group then occurs to form an isomeric enamine **B**, which cyclizes to afford seven-membered ring (1,5-benzodiazepines).

Microwave mediated synthesis of benzodiazepines:

The application of microwave energy for conducting organic reactions at highly accelerated rates is an emerging technique. In recent years, microwaves

have become popular among synthetic organic chemists both to improve classical organic reactions, shortening reaction times and/or improving yields, as well as to promote new reactions.[33]

Table 3

Reactant	Product	Yield (%)	Irrad. Time(Min)	Power (W)
OPD + Acetone	 **35**	92	4	180
OPD + 2-butanone	 **36**	95	4	180
OPD + Acetophenone	 **37**	89	4	180
OPD + 4-Methyl acetophenone	 **38**	87	4	180
OPD + Cyclohexane	 **39**	81	4	180

Moreover, often when carrying out a reaction in a microwave oven, the use of a solvent can be avoided, which is important in order to make the synthesis more environmentally friendly (green chemistry). These observations led us to investigate the possibility of improving the methods used for the synthesis of the 1,5-

benzodiazepine.

Synthesis of benzodiazepines by condensation of ketones with *o*-phenylenediamines **32** (Scheme 11) by application of microwave irradiation without solvent. The syntheses were carried out simply by mixing the *o*-phenylenediamine (1 mmol) with the ketone (2.1 mmol) in the presence of ionic liquid (PIL-2, 30% w\w) and irradiating in a domestic microwave oven, whereupon the benzodiazepine derivatives were obtained in almost quantitative yield.

The desired parameters (microwave power, time) were set as reported in Table 3. The crude products were purified by column chromatography through silica-gel using 20% EtOAc in petroleum ether as eluent and fully characterized.

3.2.5. Conclusion

A novel and efficient method for the synthesis of 1,5-benzodiazepines which not only afforded the product in excellent yields but also avoid the problems associated with catalyst cost, handling, safety and pollution. Ionic liquid can have acted as eco-friendly, non-volatile, recyclable, non-explosive and thermally robust solvent. Importantly, the IL not only acts as a solvating medium but also as a promoter for the reaction giving rise to twin advantages of ambient temperature conditions and the non-requirement of a catalyst. We have described a rapid and efficient synthesis of benzodiazepines using a microwave irradiation in environmentally friendly.

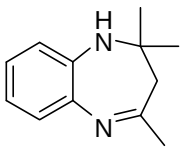
3.2.6. Experimental

Typical procedure of benzodiazepine synthesis: *o*-Phenylenediamine (499 mg, 4.62 mmol) and the various ketones (9.72 mmol) in ionic liquids were stirred at ambient temperature (See Table 1, page 161 for details). After completion of reaction the reaction mixture was diluted with water and wash with hexane-EtOAc (90:10). The organic layer was separated, dried and concentrated under reduced pressure. It was further purification by column chromatography through silica-gel using 20% EtOAc in petroleum ether as eluent and fully characterized.

Typical procedure of benzodiazepine synthesis under microwave: A mixture containing *o*-Phenylenediamine (499 mg, 4.62 mmol) and the various ketones (9.72 mmol) in ionic liquids (PIL-2, 30% w\w) were kept in domestic microwave oven and irradiated for 4 min (see Table 3, page 164, for details). After completion of reaction the reaction mixture was diluted with water and wash with hexane-EtOAc (90:10). The organic layer was separated, dried and concentrated under reduced pressure. It was further purification by column chromatography through silica-gel using 20% EtOAc in petroleum ether as eluent and fully characterized.

Characterization data for 1,5-benzodiazepines

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (35):



Mol. Formula **:** $C_{12}H_{16}N_2$

Mol. Weight **:** 188

FT IR ($CHCl_3$) **:** 3350, 1638, cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) **:** δ 7.12–7.14 (m, 1H), 6.96–7.01 (m, 2H), 6.72–6.74 (m, 1H), 2.97 (s, 1H), 2.37 (s, 3H), 2.22 (s, 2H), 1.34 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$) **:** δ 173.1, 141.1, 138.3, 127.1, 125.9, 122.5, 122.2, 68.9, 45.4, 30.8, 30.2

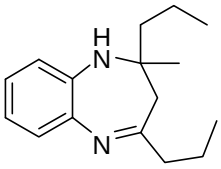
ESI-MS *m/z* **:** 189.27 $[M+H]^+$

Elemental Analysis **:** Calcd: C, 76.55; H, 8.57; N, 14.88%

Found: C, 76.33; H, 8.68; N, 14.69%

MP **:** 136–138 °C (lit. 137–138 °C).

2,4-Diethyl-2-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (36):



Mol. Formula **:** $C_{16}H_{24}N_2$

Mol. Weight **:** 244

FT IR ($CHCl_3$) **:** 3329 , 1637 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) **:** δ 0.99 (t, *J* = 6.9 Hz, 3H), 1.25 (t, *J* = 6.9 Hz, 3H), 1.70 (q, *J* = 6.9 Hz, 2H) 2.15 (m, 2H), 2.35 (s, 3H), 2.69 (q, *J* = 6.9 Hz, 2H), 3.25 (br s, 1H), 6.78–7.35 (m, 4H)

^{13}C NMR (75 MHz, $CDCl_3$) **:** δ 8.7, 10.6, 26.9, 35.5, 35.7, 42.0, 70.7, 121.7, 125.2, 126.2, 127.1, 138.0, 140.9, 175.5.

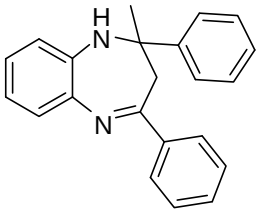
ESI-MS *m/z* **:** 245. 29 $[M+H]^+$

Elemental Analysis **:** Calcd: C, 78.64; H, 9.90; N, 11.46 %

Found: C, 78.53; H, 10.12; N, 11.32 %

MP **:** 137–139 °C (lit. 138-139 °C)

2-Methyl-2,4-(phenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (37):



Mol. Formula : $C_{22}H_{20}N_2$

Mol. Weight : 312

FT IR ($CHCl_3$) : 3346, 1630, 1593 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 6.83–7.60 (m, 14H), 3.52 (s, 1H), 2.96–3.15 (d, *J* = 13.2 Hz, 2H), 1.76 (s, 3H)

^{13}C NMR ($CDCl_3$) : δ 168.2, 148.0, 140.5, 139.9, 130.2, 128.8, 128.5, 127.5, 126.7, 125.9, 122.1, 121.9, 74.2, 43.5, 30.3

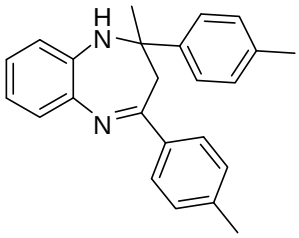
ESI-MS *m/z* : 313.41 $[M+H]^+$

Elemental Analysis : Calcd: C, 84.58; H, 6.45; N, 8.97 %

Found: C, 84.27; H, 6.62; N, 8.74 %

MP : 150– 152 °C (lit. 150–152 °C).

2-Methyl-2,4-(*p*-tolyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (38):



Mol. Formula : $C_{24}H_{24}N_2$

Mol. Weight : 340

FT IR ($CHCl_3$) : 3357, 1625 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) **:** δ 6.81–7.59 (m, 12H), 3.52 (s, 1H), 2.96–3.11 (m, 2H), 2.34 (s, 3H), 2.31 (s, 3H), 1.74 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) **:** δ 168.1, 145.5, 140.8, 140.5, 138.7, 137.4, 137.2, 129.5, 129.3, 129.0, 127.6, 126.6, 125.7, 122.1, 122.0, 73.9, 43.3, 30.3, 21.8, 21.4.

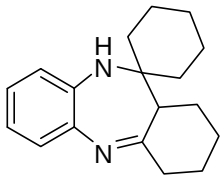
ESI-MS *m/z* **:** 341. 33 $[M+H]^+$

Elemental Analysis : Calcd: C, 84.67; H, 7.11; N, 8.23 %

Found: C, 84.37; H, 7.41; N, 8.02 %

MP : 99– 101 °C (lit. 98–99 °C).

10-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine (39):



Mol. Formula : $C_{18}H_{24}N_2$

Mol. Weight : 268

FT IR ($CHCl_3$) **:** 3356, 1642 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) **:** δ 6.99–7.33 (m, 4H), 3.80 (br, 1H), 2.87–3.24 (m, 3H), 1.55–2.75 (m, 16H).

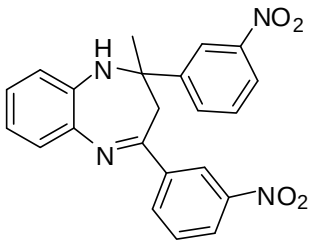
ESI-MS *m/z* **:** 267. 29 $[M+H]^+$

Elemental Analysis : Calcd: C, 80.55; H, 9.01; N, 10.44 %

Found: C, 80.24; H, 9.27; N, 10.31 %

MP : 134–136 °C. (lit. 137–139 °C).

2-Methyl-2,4-(3-nitrophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (40):



Mol. Formula : $C_{22}H_{18}N_4O_4$

Mol. Weight : 402

FT IR ($CHCl_3$) : 3327, 1649 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) : δ 6.92–8.48 (m, 12H), 3.56 (s, 1H), 2.99–3.28 (m, 2H), 1.87 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) : δ 164.6, 149.6, 148.7, 141.0, 139.8, 137.6, 133.0, 132.4, 130.0, 129.7, 129.4, 127.9, 124.9, 122.9, 122.7, 122.0, 121.3, 104.0, 74.6, 43.3, 37.6, 30.4

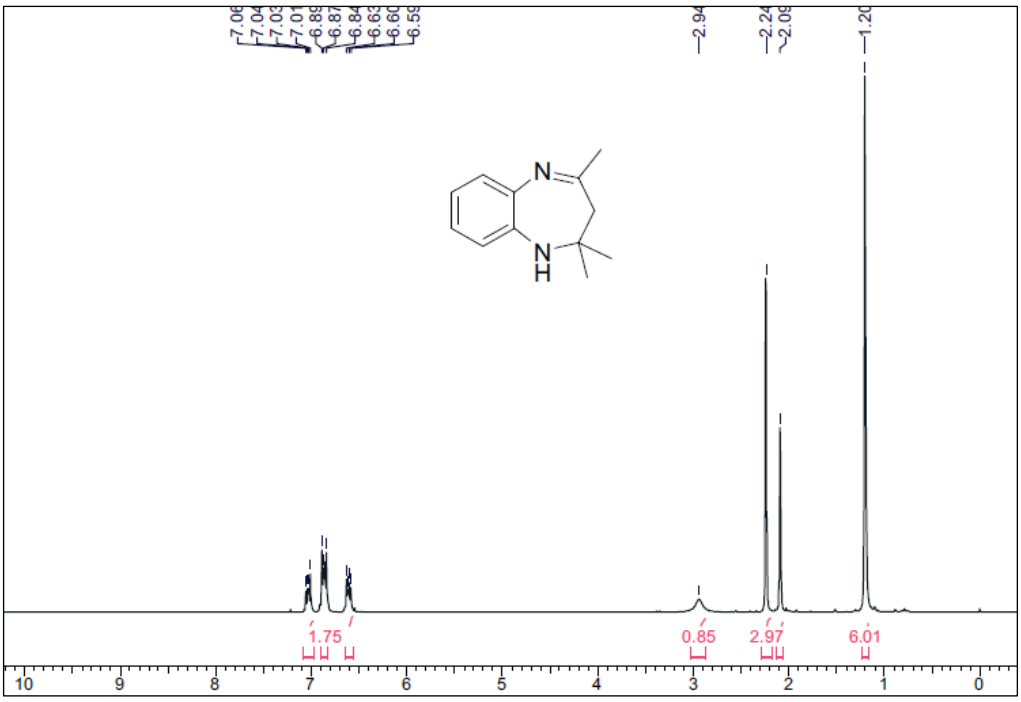
ESI-MS *m/z* : 403.39 $[M+H]^+$

Elemental Analysis : Calcd: C, 65.66; H, 4.51; N, 13.92 %

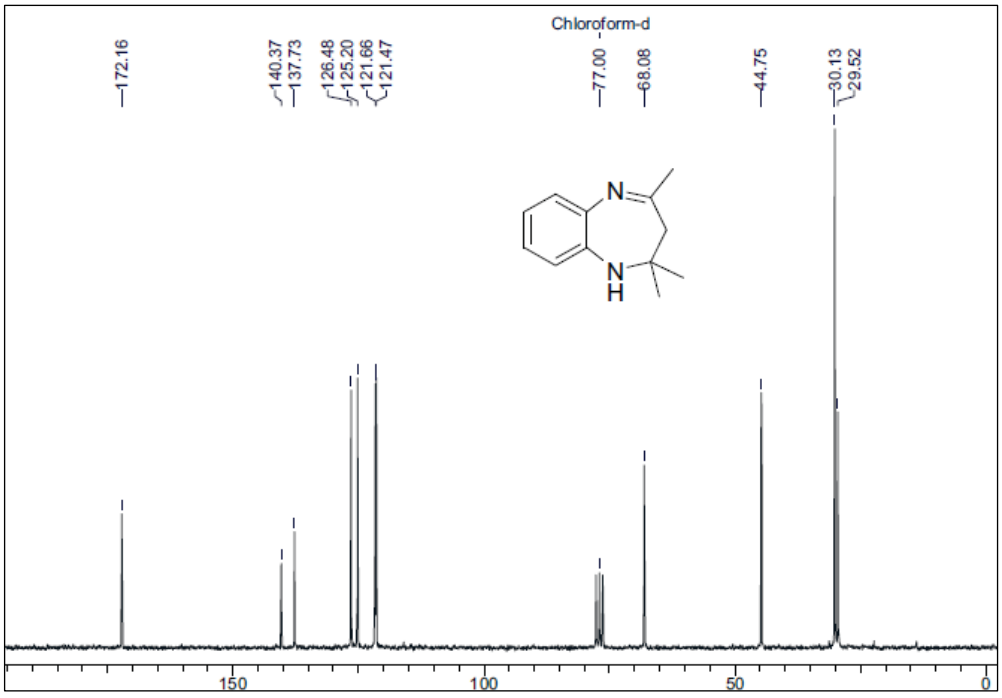
Found C, 65.47; H, 4.72; N, 13.75 %

MP : 150–154 °C (lit. 151–153 °C).

3.2.7. Spectra



Copy of ^{1}H NMR spectrum of **35** (200 MHz, $CDCl_3$)



Copy of ^{13}C NMR spectrum of **35** (50 MHz, $CDCl_3$)

3.2.8. References

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LIST OF PUBLICATIONS:

1. A synthesis of (±)-thia-calanolide A and its in vitro biological evaluation
   Bhanu M. Chanda, **Anil U. Chopade**, Dilip D. Sawaikar, Kiran B. Sonawane and Mukund K. Gurjar (to be submitted: *Tetrahedron*).

2. A new approach to the synthesis of 2-methylcysteine via aziridination of methyl methacrylate
   Bhanu M. Chanda, **Anil U. Chopade**, Sudhir S. Landge, Mukund K. Gurjar and Mukund S. Chorghade (manuscript under preparation).

3. Asymmetric aziridination of methylmethacrylate catalysed by natural cinchona alkaloids.
   Bhanu M. Chanda, **Anil U. Chopade** (targetted for *J. Mol. Catal***.** A)

4. Asymmetric aziridination of alkenes using chiral liqands with bromamine-T as the nitrene source.
   Bhanu M. Chanda, **Anil U. Chopade** (To be submitted: *Bio-organic chem. lett.*)

5. Development of a cost-efficient synthesis for a novel, orally available iron chelator
   Mukund S. Chorghade, Mukund K. Gurjar, Joseph Cherian, Bhanu Chanda, **Anil Chopade** and co-workers (to be submitted: *Tetrahedron*).

6. Phosphonium Ionic Liquids promoted synthesis of 1,5-benzodiazepine derivatives under ambient comditions.
   Bhanu M. Chanda, **Anil U. Chopade** (Targeted for *Chem. Commun*).

7. Synthesis of β-Enaminonester using New Phosphonium Ionic Liquids. Bhanu M. Chanda, **Anil U. Chopade** (Targeted for *Chem. Commun).*

SYMPOSIA ATTENDED/POSTER/ORAL PRESENTATIONS

1. Oral presentation at the International Conference on Chemistry Biology Interface: Synergistic New Frontiers (CBISNF-**2004**) New Delhi November 21-26.
   (Synthetic Approaches Towards ***(±)-Thia-calanolide A*** *and Some Novel Bromotyrosine Alkaloids).* Bhanu M. Chanda, **Anil U. Chopade** and Rohidas S. Sulake.

2. Participant at Joint International Conference on Building Bridges, Forging Bonds for 21st Century Organic Chemistry and Chemical Biology (ACS-CSIR-OCCB) NCL Pune January 7-9, **2006**. **Anil U. Chopade**.

3. Oral presentation at the Indo-Italian Seminar On Green Chemistry and Natural products New Delhi 5-6 December **2008**.
   (Total Synthesis of Mutisianthol, ***2-Methylcysteine*** *and a Green Synthesis of Quinolinones).* Bhanu M. Chanda, Rohidas S. Sulake, Dharap Y. V. and **Anil U. Chopade**.

4. Oral presentation at the International Conference on Interplay of Chemical and Biological Sciences: Impact on Health and Environment (ISCBC-**2009**) Delhi 26 Feb.-1 March **2009**.
   (Synthesis and Biological Evaluation of Analogues of Calanolide A and Design and Synthesis of Mycothiol-S-Conjugate Amidase Inhibitors via 'Click Chemistry'). Bhanu M. Chanda, **Anil U. Chopade** and Rohidas S. Sulake.

Erratum