N-H/*N*-Me Aziridination Using *O*-(Sulfonyl)hydroxylamines as Aminating Agents and Their Computational Studies

Thesis

Submitted to

Babasaheb Bhimrao Ambedkar University
(A Central University)
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For The Degree

Of

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In

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Submitted By

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(M. Phil, CSIR-UGC NET)
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December, 2021

"Dedicated

To

My Beloved Parents

and Family"

BABASAHEB BHIMRAO AMBEDKAR UNIVERSITY
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प्रज्ञा शील करुणा
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This is to certify that **Ajay Kumar Yadav**, Enrollment No. 952/17 Ph.D. Research Scholar, Department of Applied Chemistry of the University has successfully completed his Ph.D. Course work in the examination held during December, 2018.

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CERTIFICATE

This is to certify that the thesis titled **"*N*-H/*N*-Me Aziridination Using *O*-(Sulfonyl)hydroxylamines as Aminating Agents and Their Computational Studies"** submitted by Mr. Ajay Kumar Yadav is an original research work and has not been previously submitted in part or full for the award of any other degree or diploma to this or any other university.

The thesis submitted to Babasaheb Bhimrao Ambedkar University Lucknow satisfies all the requirements as stipulated in the *Doctor of Philosophy (Ph.D.) regulations -1999 as amended in 2008/2010/2013* and it is fit for submission and evaluation for the award of the degree of Doctor of Philosophy of the University.

Date: 30.12.2021

Supervisor

30.12.21

Head of the Department

DECLARATION

I, Ajay Kumar Yadav declare that the thesis titled "***N*-H/*N*-Me Aziridination Using *O*-(Sulfonyl)hydroxylamines as Aminating Agents and Their Computational Studies**" submitted by me for the degree of Doctor of Philosophy is the record of work carried out by me under the supervision of **Dr. Jawahar Lal Jat**, Assistant Professor, Department of Applied Chemistry, School for Physical Sciences, Babasaheb Bhimrao Ambedkar University (A Central University), Lucknow, U.P., India. I further confirm that said work has not been submitted anywhere else for the award of any degree, diploma, fellowship, etc. either in this or any other University or other institution of higher learning. I, further declare that the material obtained from other sources has been duly acknowledged in the thesis. I, also declare that the thesis is essentially free from all kinds of plagiarism.

Date: Lucknow
Place: 30-12-2021

Ajay Kumar Yadav

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Last, but not least, I would like to thank the authors of various research articles and books whose work has been consulted, utilized, and cited in my thesis.

(***Ajay Kumar Yadav***)

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Table of Contents

Annexures

List of Abbreviation

Ac	acetyl
ADMET	adsorption, distribution, metabolism, excretion and toxicity
aq.	aqueous
Ar	aromatic
b.p.	boiling point
BAS	Bioactivity score
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	t-butyloxycarbonyl
br	broad (NMR and IR spectroscopy)
Bu	butyl
CADD	computer-aided drug design
Cbz	carbobenzyloxy
d	doublet (NMR Spectroscopy)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBVS	docking-based virtual screening
DCM	dichloromethane
DDD	drug design and development
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPH	2,4-dinitrophenylhydroxylamine
Dpp	diphenylphosphinyl
DPPHA	*O*-(diphenylphosphinyl)hydroxylamine
dr	diastereomeric ratio
ee	enantiomeric excess
equiv.	equivalent
esp	α,α,α’,α’-tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
EtOAc	ethylacetate
EWG	electron withdrawing group
h	hour(s)
HFIP	Hexafluro-2-propanol

HOSA	Hydroxylamine-*O*-sulfonic acid
HRMS	High resolution mass spectra
Hz	Hertz
i	iso
IPA	isopropyl alcohol
J	coupling constants
L	ligand
LARMD	Ligand and receptor molecular dynamics
m	multiplet (NMR spectroscopy)
m.p.	melting point
MD	molecular dynamics
MDs	molecular descriptors
Me	methyl
min.	minute(s)
MSH	*O*-mesitylenesulfonyl hydroxylamine
n	primary
NMM	*N*-methylmorpholine
NMP	*N*-methylpyrrolidine
NMR	nuclear magnetic resonance
NR	no reaction
p	para
PARP1	Poly [ADP-Ribose] polymerase 1
PASS	prediction of activity spectra for substances
Ph	phenyl
ppm	part(s) per million
Pr	propyl
Py	pyridine
Q-TOF	quadrupole time of flight
R	alkyl group
Rf	retention factor
Rg	radius of gyration
rt	room temperature
s	singlet (NMR spectroscopy)

sec	secondary
t	triplet
t	tertiary
TBDPS	t-butyldiphenylsilyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl (4-methylphenylsulfonyl)
TsONHMe	*N*-methyl-*O*-tosyl-hydroxylamine

Abstract

The thesis entitled "***N*-H/*N*-Me Aziridination Using *O*-(Sulfonyl)hydroxylamines as Aminating Agents and Their Computational Studies**" consists of five chapters. Aziridines are highly interesting molecules, present in numerous bio-active natural, semi-synthetic and synthetic products. They exhibit various important transformation reactions *via* ring-opening, rearrangement and ring-expansion and they also display several biological activities such as anticancer, antimicrobial, antifungal, antimalarial and antiviral etc. Consequently, the synthesis of aziridines has been the focus of intense research over the last two decades. However, the majority of the developed protocols were devoted to the synthesis of protected aziridines (*N*-Ts, acyl, Ns etc.) only, as the removal of the protective groups from nitrogen is difficult because of the unwanted opening of the strain aziridine ring. Indeed, synthesis of unprotected (*N*-H/N-Me) aziridines would alleviate the aforesaid issue. However, practical and direct syntheses of unprotected aziridines from olefins are very limited. The development of powerful nitrogen transfer reagents such as *O*-(Sulfonyl)hydroxylamine derivatives have played an important role in the placement of nitrogen into a variety of useful molecules. Recently, they have been used in C-H amination, Beckmann and aziridination reaction etc. Some special features of *O*-(Sulfonyl)hydroxylamine reagent, such as benign nature to generate water-soluble by-product, lower cost, operative under mild reaction conditions, commercially available, ease of synthesis and non-toxicity etc., made them very popular among the scientific community for further exploration. In this context, we have developed the highly efficient, one-pot, atom-economical, environmentally benign, mild and operationally simple methods for the synthesis of *N*-H and *N*-Me aziridines from olefins using *O*-(sulfonyl)hydroxylamines as the aminating agents. In addition, we have also developed the first *N*-Me aziridination of Enones.

Chapter 1: **A General Overview on Aziridines and *O*-(Sulfonyl)hydroxylamines: Introduction and Motivation of Present Work**

This chapter starts with a brief introduction to the origin, structure, properties, reactivity and general reactions of aziridine synthesis. The synthetic and biological application of aziridines is summarized in Figure A. The importance and reactivity of *O*-(sulfonyl)hydroxylamines reagents have been briefly described in this chapter. The

experimental investigations and findings are described in the subsequent chapters (Chapters 2 to 5). Each chapter is individually discussed, and distributed in introduction, literature review, results and discussions, experimental section, and references.

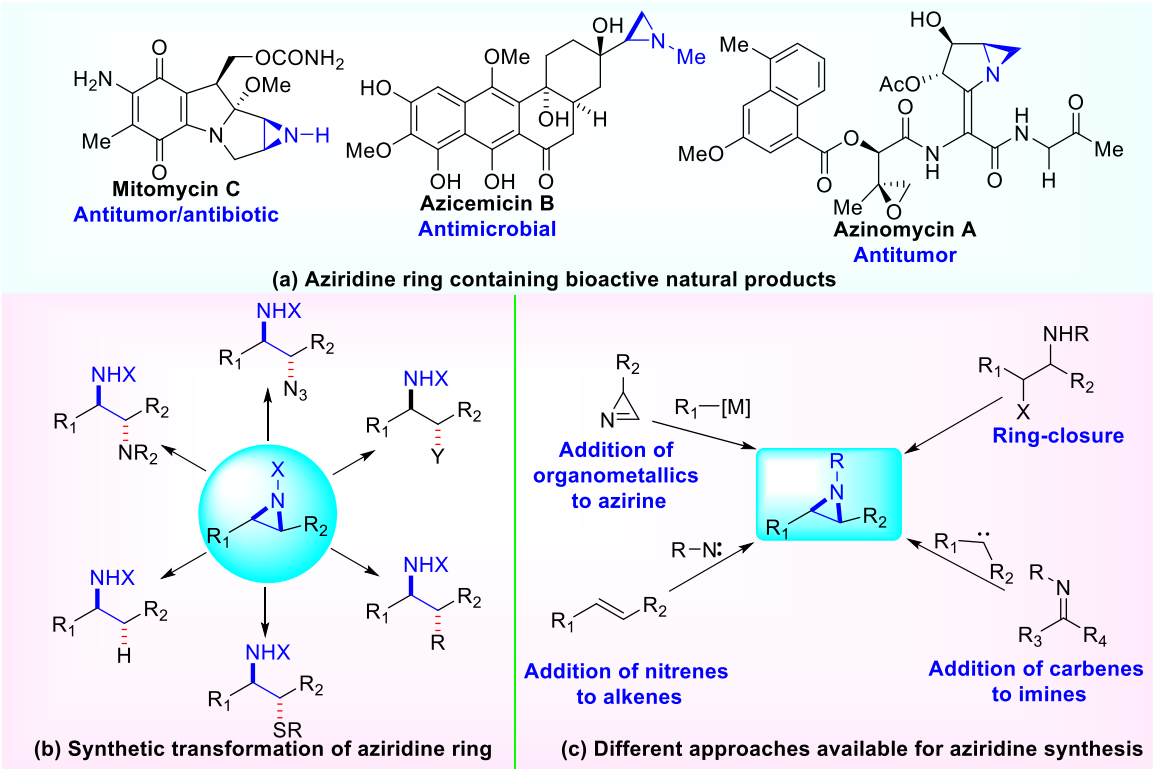
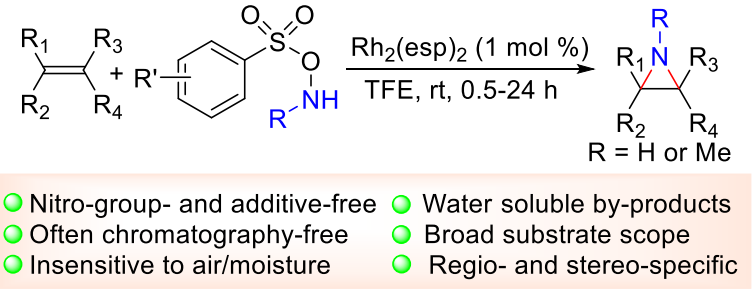


Figure A. General applications and synthesis of aziridines

Chapter 2: Rh(II)-Catalyzed Direct *N*-H/*N*-Me Aziridination of Unactivated Olefins Using *O*-(Sulfonyl)hydroxylamines

This chapter describes the development of Rh(II)-catalyzed synthesis of *N*-H/*N*-Me aziridines from olefins using *O*-(sulfonyl)hydroxylamines as the aminating agent (Scheme A).

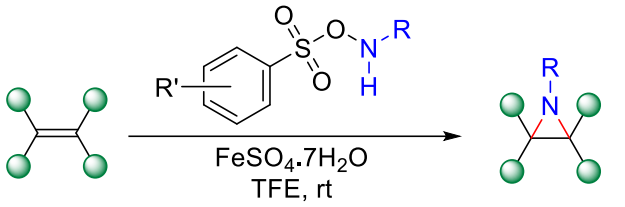


Scheme A. Rh(II)-catalyzed synthesis of *N*-H/*N*-Me aziridines from olefins

This one-pot, mild, simple, practical and stereospecific method afforded varieties of aziridines in good to excellent yields. Most of the products could be isolated in high purity without column chromatography, just after aqueous workup.

Chapter 3: **Fe(II)-Catalyzed Unactivated (*N*-H/*N*-Me) Aziridination of Olefins using O-Arylsulfonyl Hydroxylamines as Nitrogen Source**

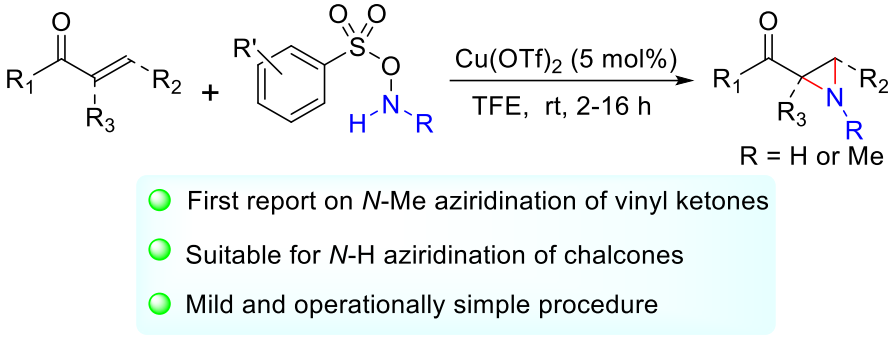
This chapter describes the information about Fe(II)-catalyzed synthesis of *N*-H and *N*-Me aziridines from alkenes using *O*-arylsulfonyl hydroxylamines (Scheme B). This stereospecific, one-pot, economical aziridination could be conducted under the mild and operationally simple condition to provide the unprotected aziridines in excellent yields within a short period of time.



Scheme B. Fe(II)-catalyzed synthesis of unactivated aziridines from olefins

Chapter 4: **Cu(II)-Catalyzed Direct and Stereospecific *N*-H and *N*-Me Aziridination of Enones**

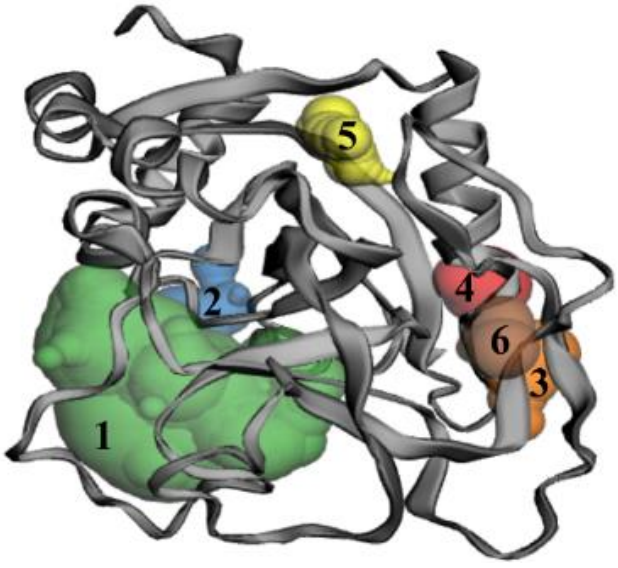
This chapter describes the $Cu(OTf)_2$ catalyzed first and direct *N*-Me aziridination of vinyl ketones employing *N*-methyl-*O*-tosylhydroxylamine as the aminating agent. Under this reaction condition, *N*-H aziridination of chalcones could also be achieved by using *O*-(mesitylenesulfonyl)hydroxylamine (Scheme C). This one-pot, open-flask, stereospecific, and practical method afforded a broad range of *N*-H/*N*-Me aziridines in good to excellent yields.



Scheme C. Cu(II)-catalyzed synthesis of *N*-H/*N*-Me aziridines from enones

Chapter 5: **Evaluation of anticancer activity of *N*-H/*N*-Me Aziridine derivatives as a potential poly (ADP-ribose) polymerase 1 inhibitor**

Poly [ADP-Ribose] polymerase 1 (PARP1) has recently been thought to be one of the potentially successful targets against cancer, specifically for ovarian and BRCA mutated breast cancers. Here, unprotected (*N*-H/*N*-Me) aziridine derivatives were recognized as potential anticancer compounds targeting the apoptotic pathway using a combined molecular descriptors (MDs) computation, prediction of activity spectra for substances (PASS), adsorption, distribution, metabolism, excretion and toxicity (ADMET) evaluation, Brain Or Intestinal Estimated (BOILED-Egg), Bioactivity score (BAS), docking-based virtual screening (DBVS), integral docking and molecular dynamics (MD) simulation. Twenty one *N*-H/*N*-Me aziridine derivatives were screened to identify molecular binding to the PARP1 binding pocket followed by docking and MD simulation. Compound 3a has a good binding profile along with all the targets but potentially can interact better with the PARP1 as observed by the molecular docking evaluations (Figure B).



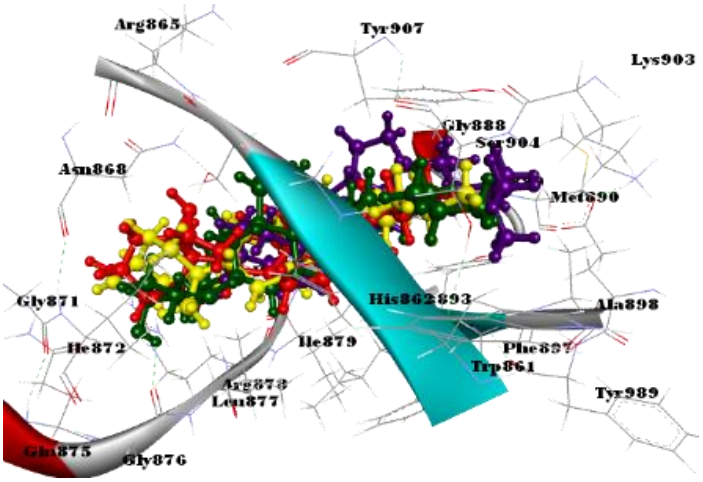


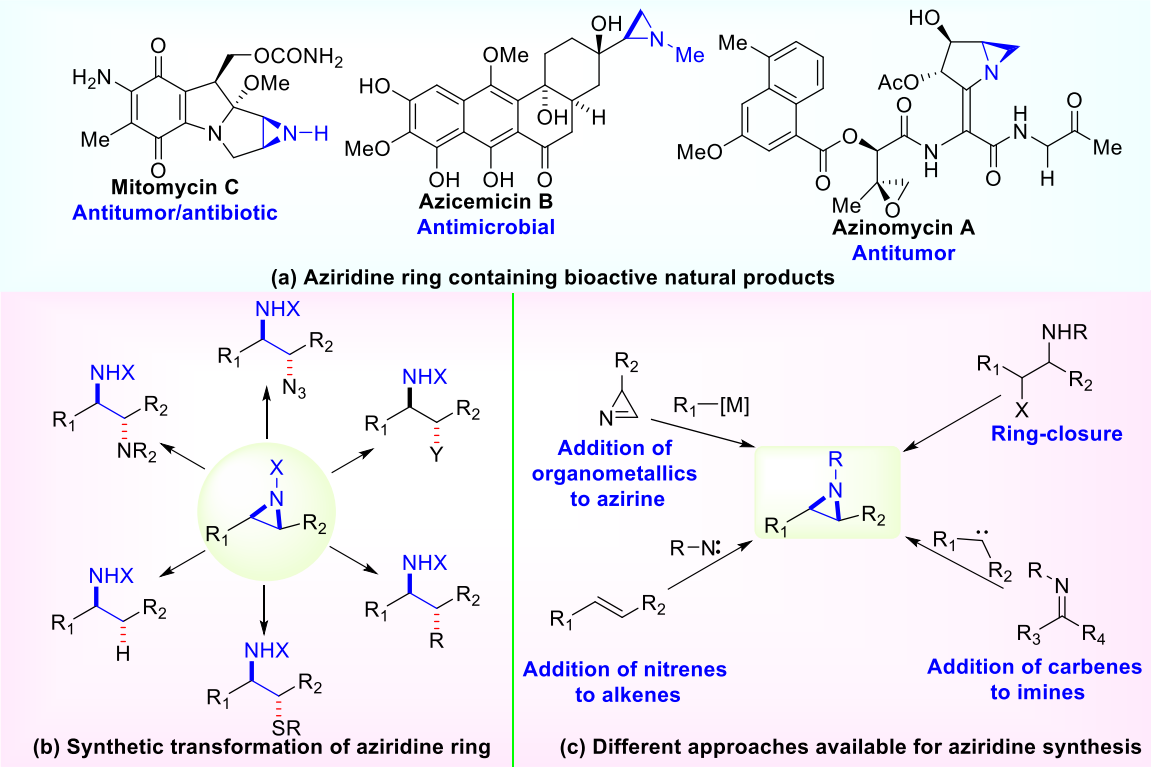
Figure B. Computational study of aziridine derivatives against anticancer activity

The docking complexes of the lead compound 3a with the target PARP1 were found stable during molecular dynamics simulations as represented by the obtained parameters including radius of gyration (Rg) and root mean square deviation (RMSD). Compound 3a yielded good binding free energy using the analysis of molecular mechanics generalized born surface area (MM-GBSA) and molecular mechanics Poisson–Boltzmann surface area (MMPBSA). Therefore, the finding of the studies unravels the possible compounds 3a as lead anticancer candidate against selected PARP1.

Chapter 1

A General Overview on Aziridines and *O*-(Sulfonyl)hydroxylamines: Introduction and Motivation of Present Work

Aziridines are an attractive class of heterocyclic molecules present in various naturally occurring bioactive compounds. They are also used as a versatile synthetic intermediate in organic chemistry. *O*-(sulfonyl)hydroxylamines serve as a useful aminating reagent. Recently, these reagents have been used in C-H amination, aziridination, amide bond formation etc. In this chapter, we have described the structure, general properties, synthesis and synthetic importance of aziridines followed by emerging synthetic applications of *O*-(sulfonyl)hydroxylamine reagents.



1.1 Introduction

Aziridine is the most valuable class of the three-membered nitrogen-containing saturated heterocycles, it is also known as azacyclo-propane or ethyleneimine.[1] Gabriel reported the first synthesis of aziridine in 1888.[2] Aziridines also exist in type I and II fused ring derivatives, nitrogen atom present at the bridgehead position in type II aziridine (Figure 1.1a).[3]

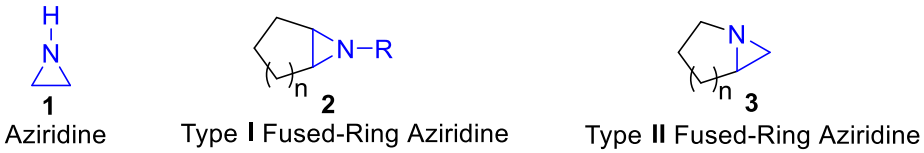


Figure 1.1a. Aziridine and their fused-ring derivatives

Aziridines are further divided into two types: activated and non-activated (Figure 1.1b). The nitrogen atom of the activated aziridine has electron-withdrawing groups (*N*-Ts, Ns, COR, etc.) while non-activated aziridine has electron-donating groups (*N*-alkyl, aryl, or hydrogen atom).[4]

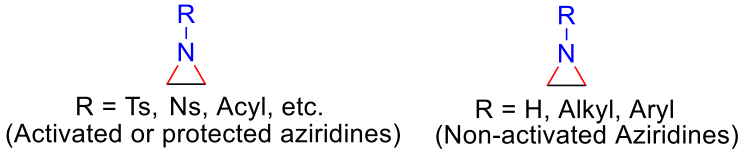


Figure 1.1b. Activated and non-activated aziridines

Aziridines have the smallest strained-ring system, and the alleviation of this strain determines their chemistry. They afford either functionalized ring-opening or ring expanded products with various carbon and heteroatom nucleophiles. The associated ring strain is also considered to be essential for the pharmacological activities of natural products comprising aziridine.

1.2 General properties of aziridines

1.2.1 Basic characteristics of aziridines

The high reactivity of aziridine is due to the presence of electronegative nitrogen atom, small ring size, and high Baeyer or Pitzer ring strains similar as present in other three-

membered cyclic ring systems like cyclopropane and epoxide. The bond angle of aziridine is around 60°, highly distorted to the normal sp^3 hybridized hydrocarbons (bond angle 109.5°) (Figure 1.2).[5]

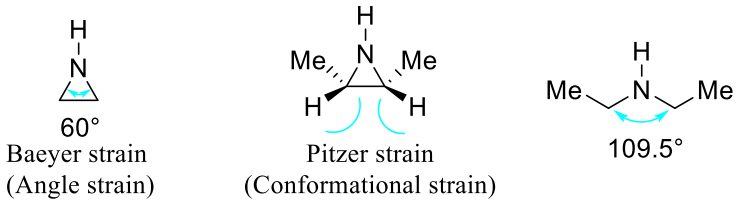


Figure 1.2. Ring-strain in aziridines

Aziridine has a calculated ring strain energy of 26.7 kcal/mol, which is equivalent to the epoxide and cyclopropane (26.3 kcal/mol and 27.5 kcal/mol respectively) (Figure 1.3).[6]

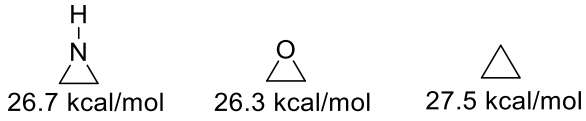


Figure 1.3. Comparison of ring-strain energy in aziridine

Three-membered cyclic compounds consist of a bent or banana bond model (Figure 1.4a). As a consequence, azacyclopropane acquires a bond angle of 59.7°, comparably smaller than a tetrahedral bond angle of 109.5° which results in ring-strain in these compounds. In aziridine, the C-N bond must have increased *p*-character and lower C-N-C bond angle, which subsequently enhances the s-character in the *N*-H bond (Figure 1.4b).[1,7]

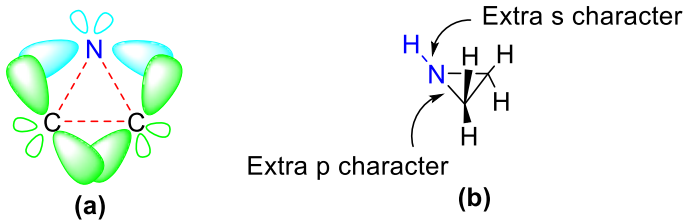


Figure 1.4. Bent or banana bond model in aziridine

This phenomenon suppresses the pyramidalization of the substituent of *N*-atom (Thorpe-Ingold-effect, Figure 1.5) and promotes the basicity from 3- to 6-membered cyclic amines.[8]

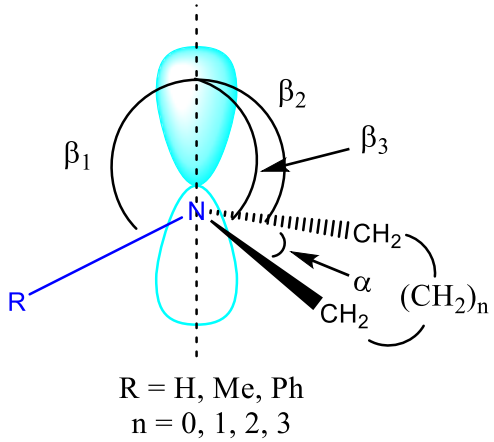


Figure 1.5. C-N-C bond angles in cyclic amines

Owing to the apparent greater s-character of the nitrogen lone pair in *N*-H aziridine (2° amine) exhibits weaker basicity (pKa = 8.04) than homologs such as pyrrolidine and piperidine. Likewise, *N*-Me aziridine (3° amine) also exhibits weaker basicity (pKa = 7.86) than *N*-Me substituted homologs of pyrrolidine and piperidine (Figure 1.6).[9]

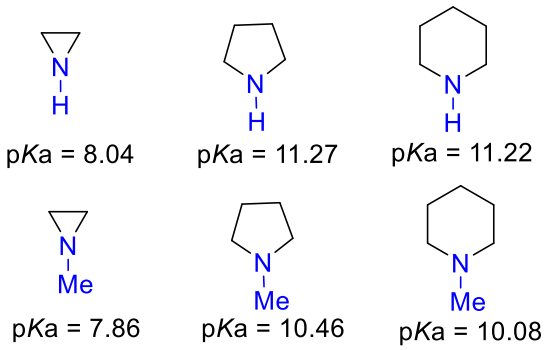


Figure 1.6. Basic strength in cyclic amines

Aziridines have a significantly higher barrier to nitrogen inversion than acyclic counterparts because they are restricted within a small ring. The inversion process at nitrogen involves a transition from pyramidal sp^3 to transition state **4**, planar sp^2 hybridization, and as a result, the *p*-character of the C-N ring bonds is reduced (Figure 1.7).[10]

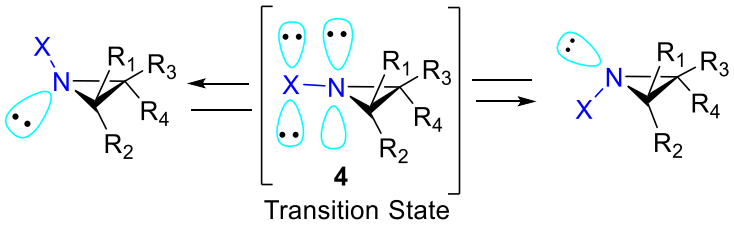


Figure 1.7. Nitrogen-inversion in aziridines

Because endocyclic bonds necessitate an excess p-character, the barrier to *N*-inversion is higher in aziridines, which avoids this hybridization modification. Increased strain in accommodating the C-N-C ring bond-angle may explain the larger barrier in the transition state where nitrogen hybridization is effectively sp^2. The pyramidal inversion barrier is influenced by the type of nitrogen substituent. As a result, The *N*-inversion activation enthalpy of 2-methylaziridine is nearly 70 KJ mol^{-1}, which is higher than that of a normal secondary amine but insufficient to suppress racemization. In the case of electronegative substitution of *N*-atom, the inversion barrier is much increased, and 1-chloro-2-methylaziridine (with an inversion barrier of ΔG = 112 KJ mol^{-1}) splitted into stable diastereomers as shown in Figure 1.8.[11]

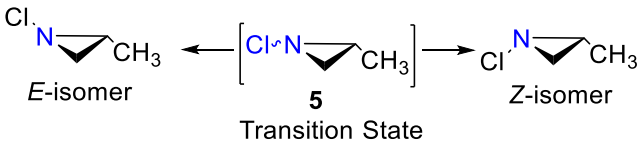


Figure 1.8. Diastereomers of 1-chloro-2-methylaziridine

1.2.2 Biological properties of aziridines

A large number of bioactive natural products contain aziridine moiety in their structure, used as potential therapeutic agents (Figure 1.9).[1,11-12] They are interesting synthetic targets with a wealth of biological activity associated with the reactivity of the strain aziridine ring. The common aziridine (azacyclopropane) is intensely hazardous as it shows the potential carcinogenic effect on humans.[13] Selected examples of aziridine rings containing natural products like mitomycin C,[14] azinomycin B,[15] and miraziridine are present in figure 1.9. Mitomycins A-C were discovered to exhibit significant anticancer and antibiotic action after being obtained from *Streptomyces caespitus*.[1] Porfiromycin was isolated from

Streptomyces ardus. Mitomycin C possesses significant antitumor potency and has been utilized therapeutically since the early 1960s.

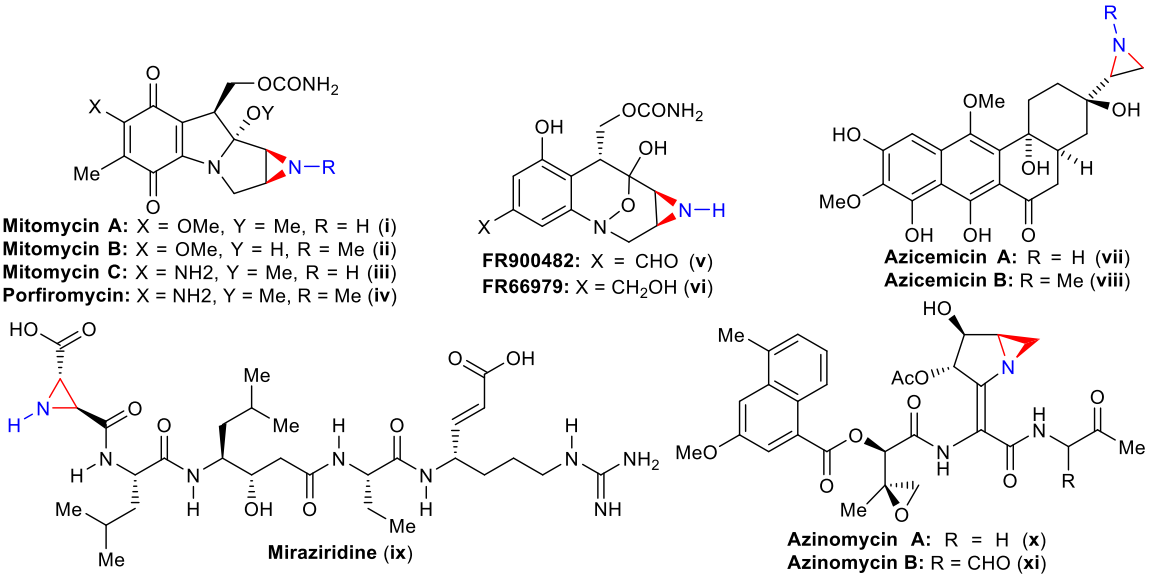


Figure 1.9. Selected examples of the natural product containing aziridine moiety

They exhibit potent anticancer properties because of their propensity to cross-link DNA *via* quinone-reduction followed by ring-opening of aziridine (Figure 1.10).[16-17]

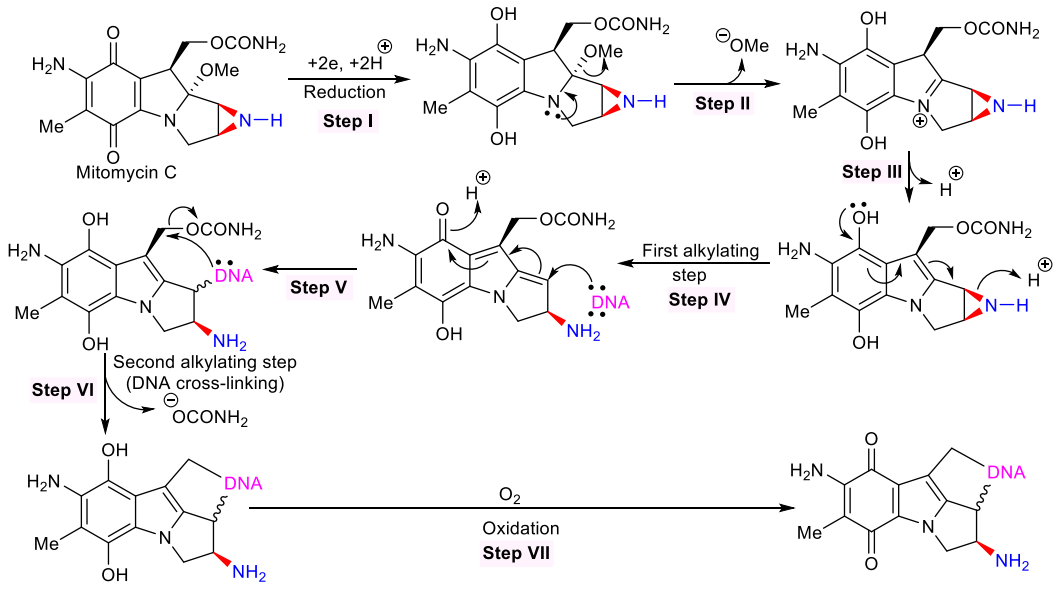


Figure 1.10. Mitomycin C: mechanism of action

Both FR900482 (**v)** and FR66979 (**vi)** natural products are structurally related to the mitosane family, were isolated from *Streptomyces sandaensis*, and have antitumor and antibiotic activity. They also have significant cytotoxic activity *in vitro* against a variety of cancerous cells. The formation of free radicals by breaking the weak *N*-O bond has also been linked to the biological activity of aziridines.[18,19]

Azicemicins A and B, which were isolated from *Amycolatopsis sulphurea*, were studied for their physicochemical features as well as antimicrobial efficacy. They showed modest inhibition of growth of Gram-positive bacteria and pathogens.[12]

Miraziridine was discovered in a marine sponge called *Theonella mirabilis*. It is made up of three primary components: aziridine carboxylic acid, statine, and vinylogous arginine.[20] They show cysteine protease inhibitor properties.[21]

Azinomycins A and B, (**x**, **xi**) which contain both electrophilic epoxide and aziridine moieties, were first isolated from the *Streptomyces qriseofucus*. They exhibit considerable *in vitro* cytotoxicities and notable anticancer activity (*in vivo*) against various tumor cells.[22]

Natural products containing aziridine moiety have shown considerable pharmacological activities, hence, straightforward, inexpensive, practical methodologies for the unprotected (*N*-H/*N*-Me) aziridine synthesis is essentially desired.

1.3 Synthetic transformations of aziridines

Several reviews, books and chapters on aziridines reactivity and synthetic implications are available.[4,23] In the following section, we have summarized some of the important synthetic transformation reactions of aziridine.

1.3.1 Ring-opening of aziridines

Aziridines undergo the most common and important nucleophilic ring-opening reactions under relatively milder circumstances. A wide range of nucleophiles can act as both inter- and intra-molecular ring-opening of aziridines, resulting in high-value of 1,2-difunctionalized amine products such as amino alcohols, diamines, amino ethers, and amino acid derivatives (Figure 1.11).[4,23]

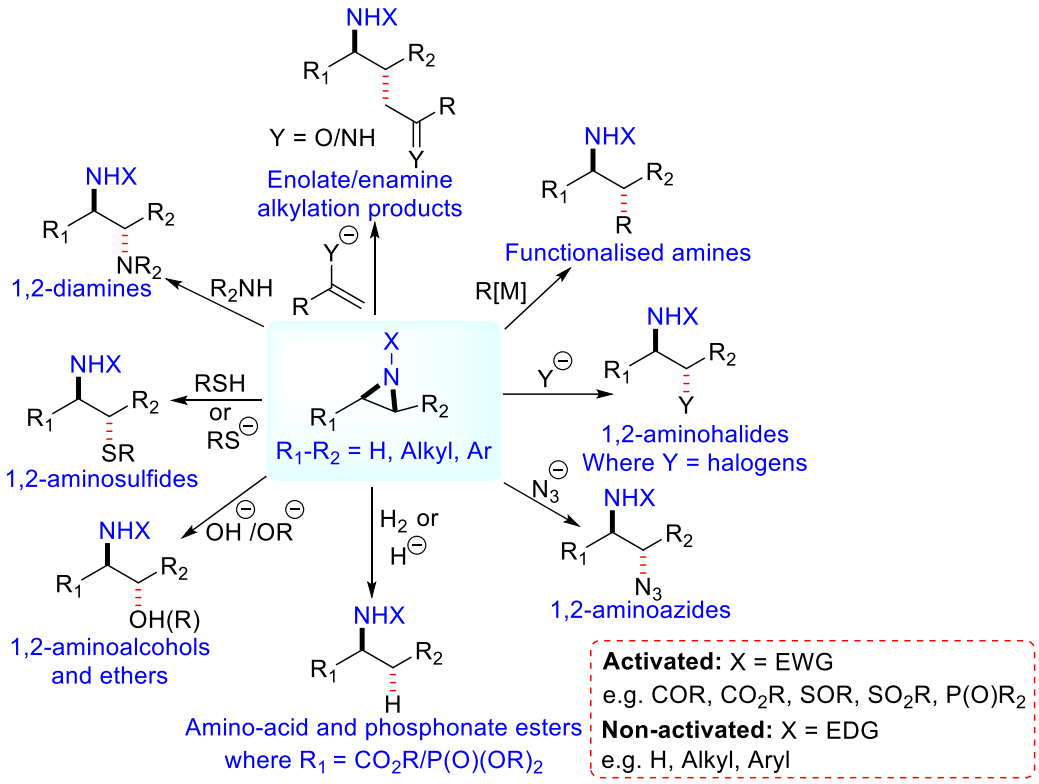


Figure 1.11. Nucleophilic ring-opening reactions of aziridines

Furthermore, aziridine ring-opening might be used in the production of several important natural and synthetic pharmaceuticals (Figure 1.12).[4,23]

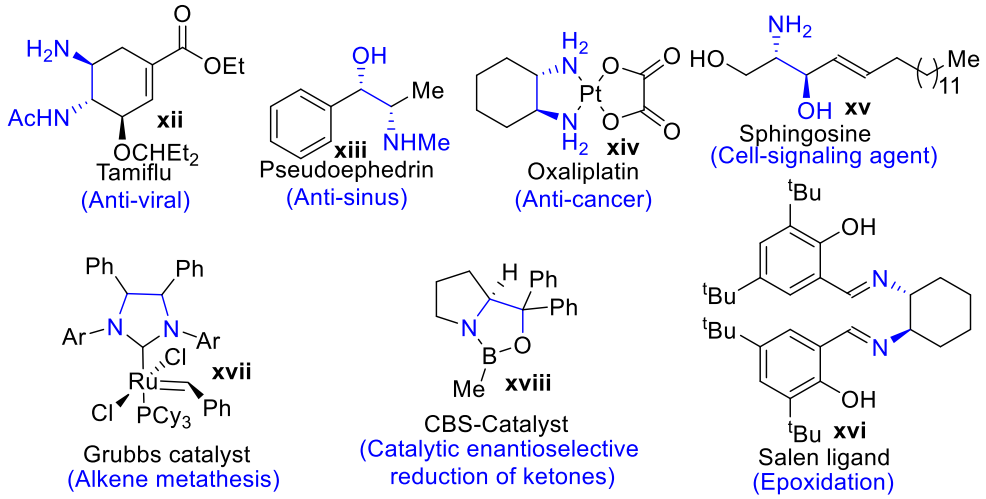
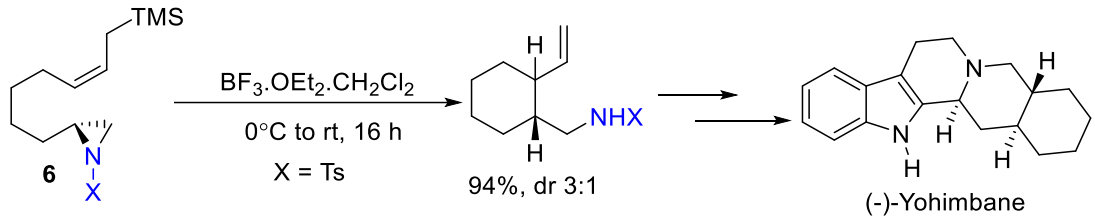


Figure 1.12. Synthetically useful compounds prepared *via* aziridine ring-opening

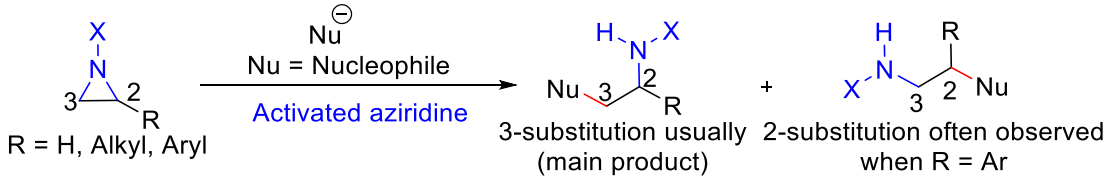
The nucleophilic ring-opening of aziridines is driven by the nucleophilic substitution bimolecular (S_N2) mechanism, which entails a configuration inversion at the carbon atom. If the aziridine is substituted unsymmetrically, ring-opening can result in two regioisomers. The preferential attack occurs at the lesser substitution site as predicted, however, the electronic effect of the substituent may cause this to change. The neighboring group participation can also be affected the regiochemistry. The size of the produced ring, which is often different from what is predicted by an intermolecular interaction, influences the intramolecular ring opening of aziridine.[24] Bergmeier, for instance, demonstrated that targeting for the highly substituted site of aziridine intramolecularly only resulted in the creation of a six-membered ring (Scheme 1.1).[25]



Scheme 1.1. Intramolecular allylation of aziridine **6**

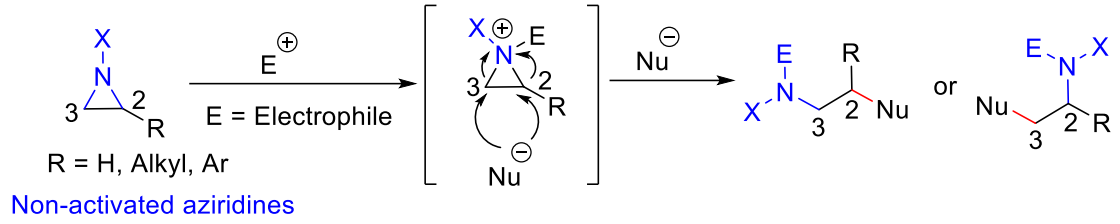
1.3.2 Effect of the *N*-substituent towards ring-opening in aziridines

Aziridines were traditionally classified as "Activated" (*N*-substituted with electron-withdrawing groups, EWG) and "non-activated" (*N*-substituted with electron-donating groups, EDG) (Figure 1.12).[4,26] Both activated and non-activated aziridines show different reactivity and regioselectivity in nucleophilic ring-opening reactions.[23,27] Nucleophilic attack on activated aziridines occurs most frequently at the C-3 position of the aziridine, which is less hindered. When the R substituent at the C-2 position is an aromatic group, nucleophilic assault on the C-2 position of an activated aziridine is generally favoured (Scheme 1.2).[28-29]



Scheme 1.2. Ring-opening reaction of activated aziridines

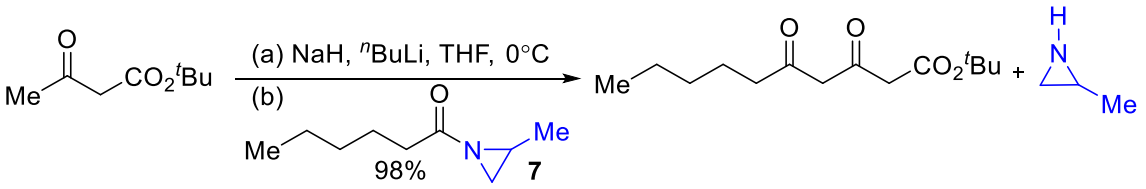
However, depending on the type of acidic catalyst used as well as the electrophiles, nucleophiles, and substituents present, non-activated aziridines can experience nucleophilic assault at the C-2 or C-3 position (Scheme 1.3).[27]



Scheme 1.3. Ring-opening reaction of non-activated aziridines

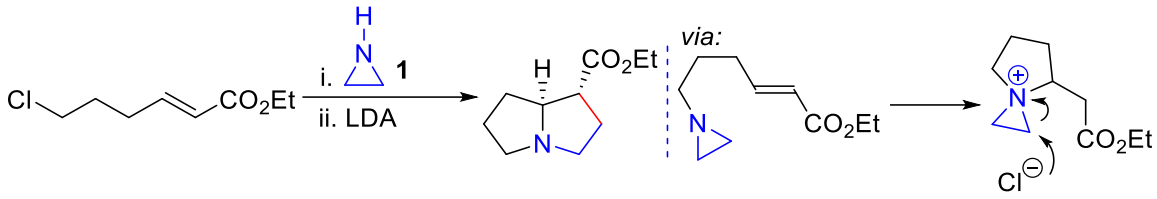
Ring-opening is more complicated in non-activated *N*-H and *N*-alkyl aziridines, and it generally requires protonation, quaternization, or the production of a Lewis acid adduct. Non-activated aziridines have suffered a scarcity of effective research work on their ring-opening methods than their activated counterparts.[23]

Another issue with activated aziridines is that, because of the highly electrophilic carbonyl group (activating group) on the aziridine nitrogen, ring-opening reactions with carbon-centered nucleophiles are commonly absent. Since it appears that a nucleophilic attack on the electrophilic activation group is possible. This is demonstrated by the dearth of resonance interaction between the nitrogen lone pair and the activating carbonyl group. Which allows the carbonyl group to behave more like a ketone than an amide. The *N*-acyl aziridine, **7** have therefore been discovered to be excellent *C*-acylation agents for enolates of 1,3-dicarbonyl compounds (Scheme 1.4).[30]



Scheme 1.4. C-Acylation of β-ketoesters by *N*-acylaziridine (**7**)

In situ production of aziridinium cations can also be done with non-activated *N*-H aziridine; these cations are highly activated due to quaternization at the nitrogen atom, which further polarises the C-N bonds and accelerates inter and intramolecularly ring-opening reactions in mild conditions (Scheme 1.5).[11]



Scheme 1.5. Activation *via* aziridinium ion intermediate

1.3.3 Aziridines in the synthesis of biological relevance heterocyclic motifs

The associated ring-strain in aziridines has a high reactivity that makes it a useful building block for the synthesis of the diverse variety of 4- to 7-membered heterocyclic motifs (Figure 1.13).[31]

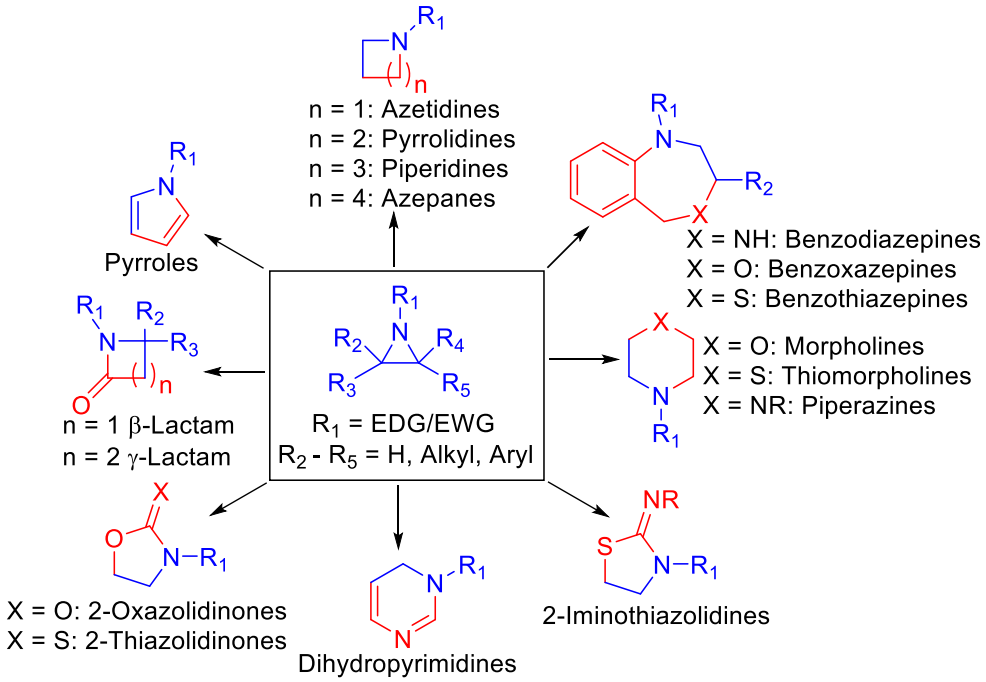
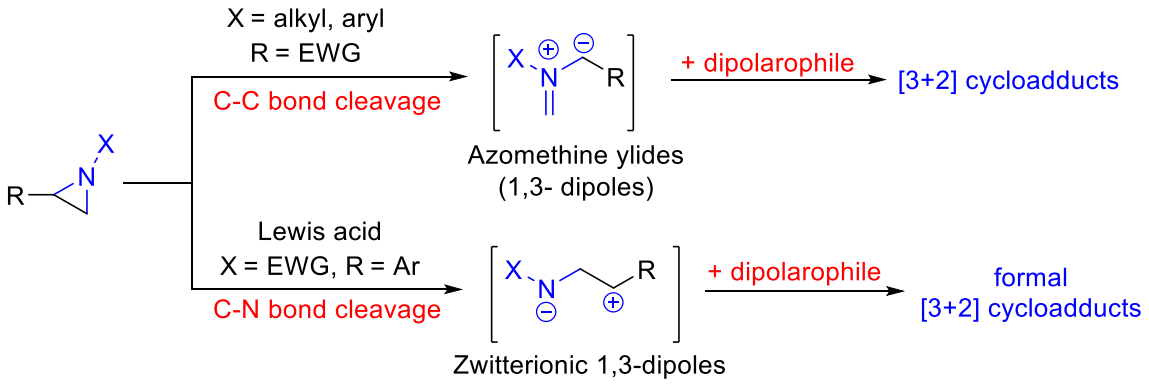


Figure 1.13. Biological relevant heterocyclic compounds from aziridines

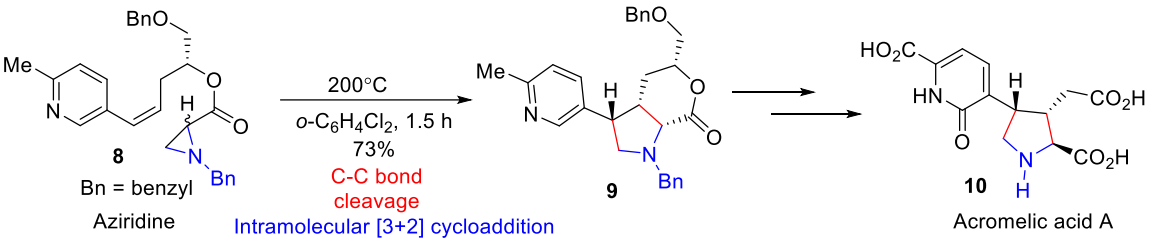
1.3.4 Electrocyclic ring-opening of aziridines in cycloaddition reactions

Aziridines can be utilized as an azomethine ylide and undergo cycloaddition reactions by stereospecific production of zwitterionic 1,3-dipoles, which are usually produced by breakage of the C-N or C-C bond under Lewis acid, thermolysis, or transition-metal catalysed reaction conditions (Scheme 1.6).[32] These can participate in a [3+2] or [3+3] cycloaddition reaction to give five or six-membered nitrogen heterocycles.[32-33]



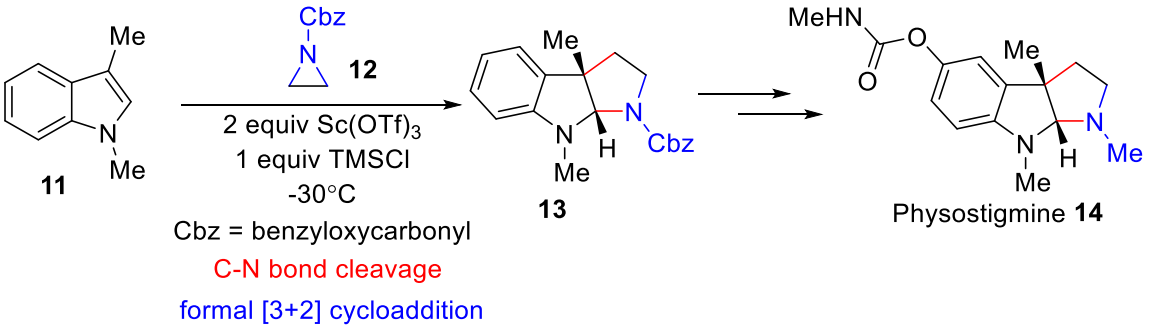
Scheme 1.6. C-N or C-C Electrocyclic bond cleavage in aziridines

Aziridines are commonly utilized in the total synthesis of several natural compounds.[34] Takano has used the aziridine derivative **8** for the enantioselective synthesis of acromelic acid A (Scheme 1.7).[35]



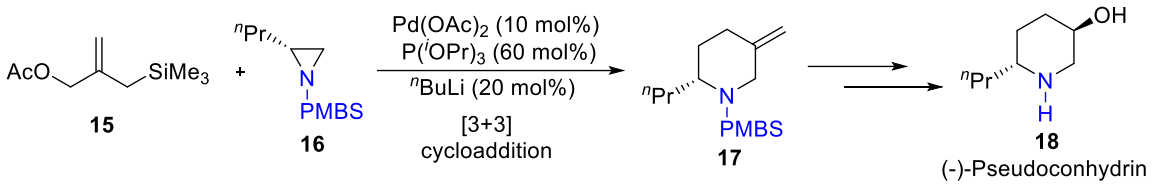
Scheme 1.7. Total synthesis of acromelic acid A

The utilization of aziridines in the total synthesis of physostigmine **14** demonstrates that aziridines have additional synthetic potential in this strategy (Scheme 1.8).[36]



Scheme 1.8. Synthesis of physostigmine *via* [3+2] cycloaddition reaction

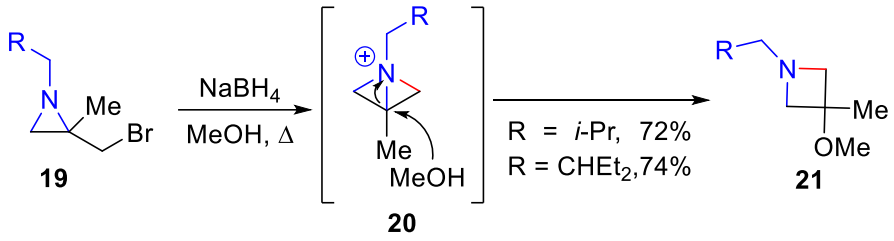
This approach was also applied for the diastereoselective total synthesis of the poison hemlock alkaloid (-)-pseudoconhydrin **18** *via* [3+3] cycloaddition process of *n*-propyl substituted aziridine **16** (Scheme 1.9).[37]



Scheme 1.9. Synthesis of (-)-pseudoconhydrin *via* [3+3] cycloaddition reaction

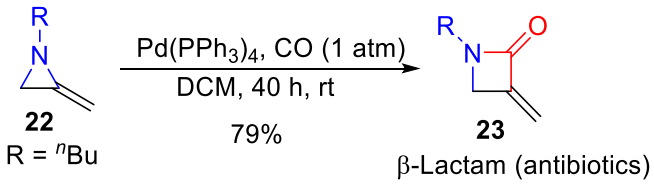
1.3.5 Rearrangement and ring-expansion reactions of aziridines

The conversion of 2-bromomethyl-2-methylaziridines **19** has been utilized to develop the rearrangement of aziridine to azetidine (Scheme 1.10).[38] When aziridine is reacted with sodium borohydride, a bicyclic intermediate **20** is formed which is subsequently transformed to azetidines **21** by reacting with methanol.



Scheme 1.10. Rearrangement of aziridine **19** into azetidine **21**

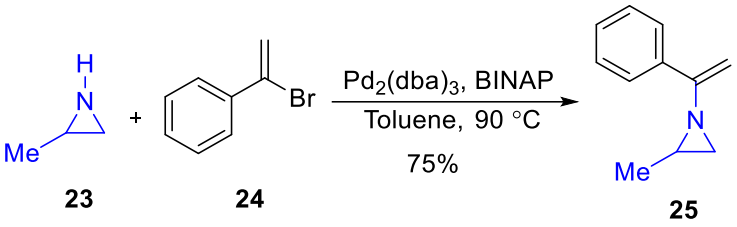
Alper *et al.* established that aziridines can function as a precursor to β-lactams *via* transition metal-assisted processes. One example is the transformation of α-methylene aziridines **22** to β-lactams **23** *via* carbonylative ring expansion catalyzed by palladium catalyst (Scheme 1.11).[39]



Scheme 1.11. Carbonylative ring-expansion of aziridine **22** into β-lactam **23**

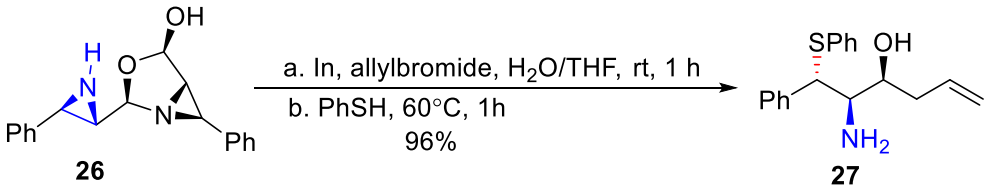
1.3.6 Transformations without aziridine ring-opening

Non-activated aziridines can undergo a wide range of side-chain reactions as well as targeted changes at the ring atom (including C and N atom) while preserving the ring structure. Non-activated *N*-H aziridines can be used in various *N*-functionalization reactions involving the basic nitrogen atom, however, reactions such as alkylation, halogenation, reductive aminations are difficult owing to the existence of easily opened intermediate *i.e.* activated aziridinium ion. Yudin revealed that *N*-H aziridines can be involved in a wide range of transition metal-catalyzed reactions, including cross-coupling reactions. (Scheme 1.12).[40]



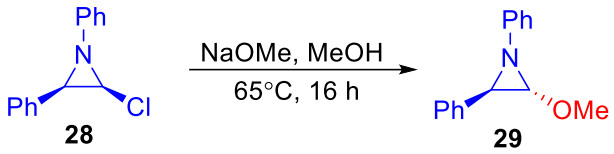
Scheme 1.12. Pd-catalyzed *N*-alkenylation of aziridines

Yudin discovered in 2006 that *N*-H aziridine-2-aldehydes behave like unprotected amino aldehydes which could be used in a diverse array of synthetic organic transformations like homologation to form alkynyl aziridines, as well as repeated carbonyl allylation and *N*-H aziridine ring opening to make *syn β*-amino-alcohols **27** (Scheme 1.13).[41]



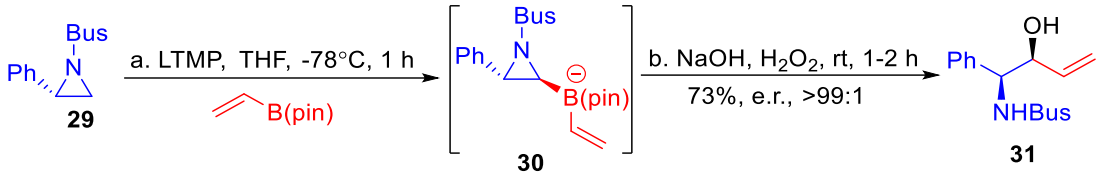
Scheme 1.13. *Syn β*-amino alcohol **27** from dimeric *N*-H aziridine **26**

Aziridines can also undergo selective transformations at the ring carbon attained *via* nucleophilic displacement. In 1965, Deyrup successfully demonstrated the first example of nucleophilic displacement at the carbon atom of a non-activated aziridine **28** with clean inversion (Scheme 1.14).[42]



Scheme 1.14. Nucleophilic displacement at C-centre of aziridine

α-Aziridinyl anions emphasize the chemistry of aziridine even more, and Florio and Luisi released comprehensive research on this issue in 2010.[43] Several groups have recently demonstrated that certain *N*-protected aziridines while maintaining the ring structure, can undergo *α*-deprotonation and electrophilic trapping processes.[44-46] In 2009, the Aggarwal group reported that *N*-Boc and *N*-Bus aziridines, including aziridine **29**, might be *α*-lithiated and trapped with boronic esters to get access to *syn* amino-alcohols **31** (Scheme 1.15).[47]



Scheme 1.15. *Syn* amino-alcohols **31** alcohol from *N*-Bus aziridines **29**

1.4 General approaches for the synthesis of aziridines

As discussed previously, aziridines are a large family of amines that present in both therapeutically useful molecules and synthetic motifs. As a result, aziridine synthesis is appraised as a subject of considerable research. The general methods for the synthesis of aziridines are: (a) electrophilic nitrene addition to alkenes and addition to azirines (b) carbenoid, carbanion, and ylide addition to imines, (c) conjugate addition to α-bromoacrylates (the Gabriel-Cromwell reaction) and conjugate addition of a nucleophilic nitrogen source (d) cyclization of 1,2-amino alcohols, halides. The reader is urged to study numerous reviews on the generic synthesis of aziridines for a more thorough overview.[4,48] The illustration of general methods for the synthesis of aziridines is shown in Figure 1.14.

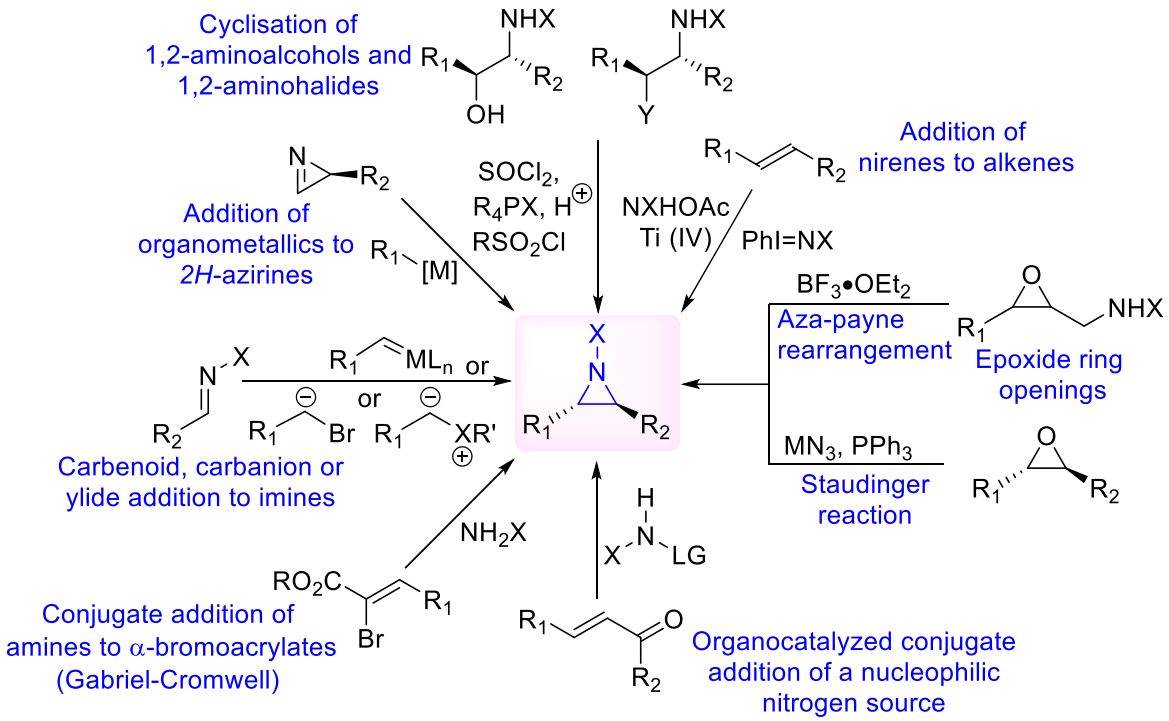


Figure 1.14. General methods for the aziridines synthesis

Most of the developed methods are devoted to the synthesis of protected aziridines, the removal of protecting group requires harsh reaction conditions, hence recently, research on unprotected aziridinations has attracted the attention of scientific communities.[49] The literature review of unprotected aziridination methods has been discussed in chapter 2 of this thesis.

1.5 General overview of *O*-(sulfonyl)hydroxylamine reagents

Many important transformation reactions in organic synthesis entail the use of *O*-(sulfonyl)hydroxylamine reagents including hydroxylamine-*O*-sulfonic acid, *O*-(mesitylsulfonyl)hydroxylamine, and *N*-methyl-*O*-tosyl-hydroxylamine (Figure 1.15). These reagents act as electrophilic aminating agents and are used as a source of nitrogen for C-N, S-N, N-N, etc. bond formation.[50]

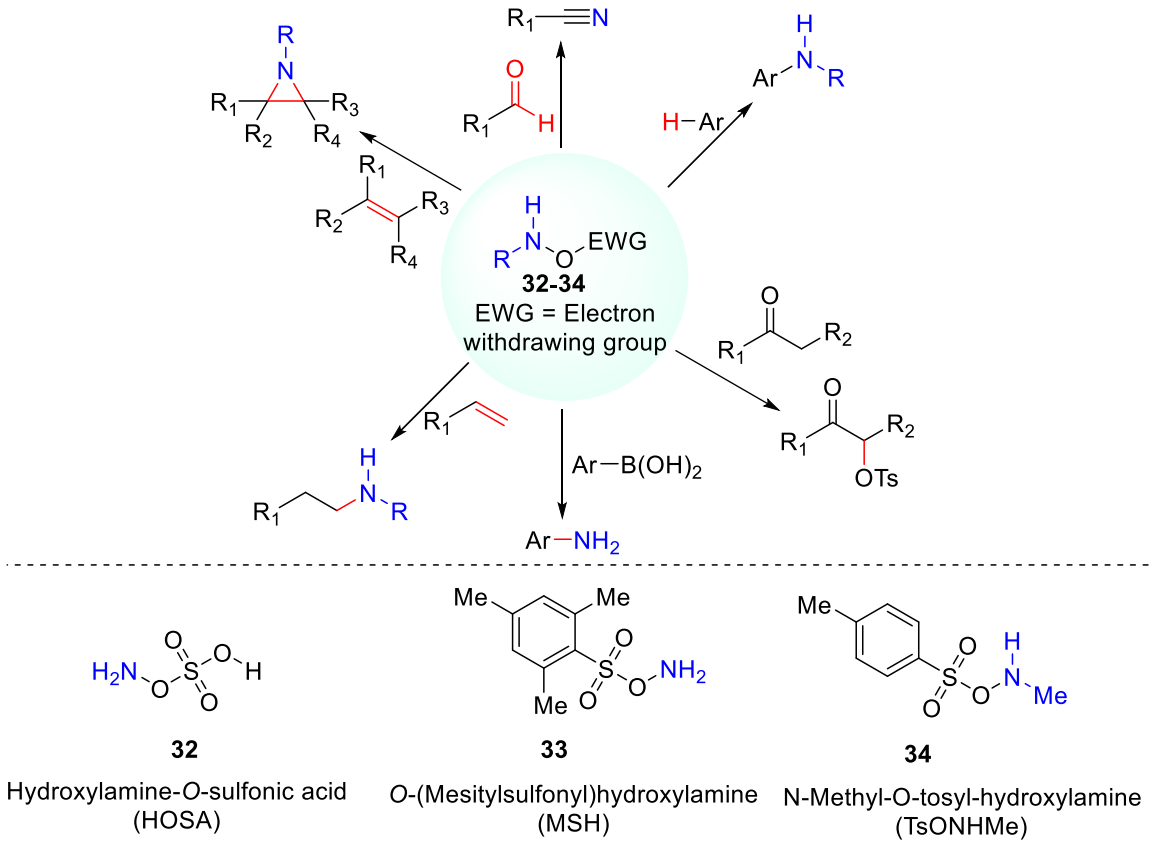
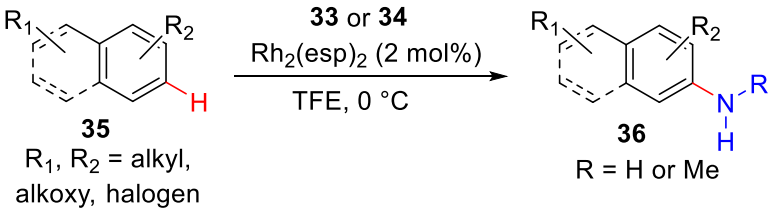


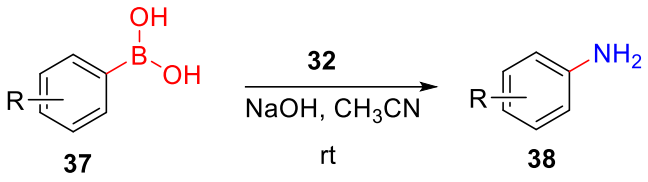
Figure 1.15. Synthetic applications of *O*-(Sulfonyl)hydroxylamines reagents

Recently, Falck and co-workers demonstrated that both *O*-(mesitylsulfonyl)hydroxylamine **33** (MSH) and *N*-methyl-*O*-sulfonyl-hydroxylamine **34** (TsONHMe) reagents were used for direct C-H arene amination in the presence of $Rh_2(esp)_2$ (Du-Bois) catalyst in TFE solvent at 0 °C (Scheme 1.16).[51]



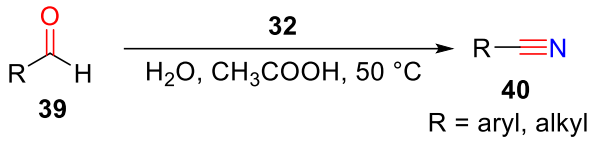
Scheme 1.16. C-H arene amination using MSH and TsONHMe reagents

McCubbin *et al.* used the hydroxylamine-*O*-sulfonic acid **32** (HOSA) reagent for the preparation of primary anilines **38** from aryl boronic acid **37** in aqueous basic condition at room temperature (Scheme 1.17).[52]



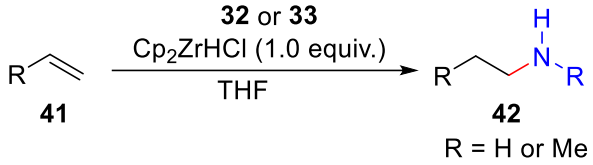
Scheme 1.17. Conversion of arylboronic acid into primary anilines using HOSA

Moura-Letts *et al.* used HOSA **32** for the synthesis of nitriles **40** from aldehydes **39** (aliphatic and aromatic) in mild aqueous acidic reaction condition (Scheme 1.18).[53]



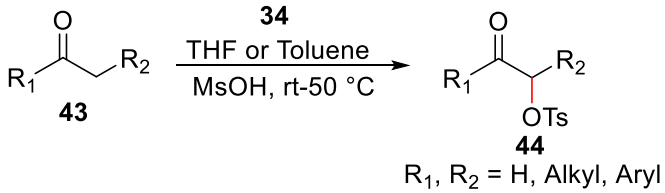
Scheme 1.18. Synthesis of nitriles from aldehydes

Hartwig and Strom[54] developed an efficient approach for the synthesis of diverse primary and secondary amines **42** from nonactivated olefins **41**, utilizing Schwartz reagent and HOSA **32** and its *N*-alkyl derivative as aminating reagents. Similarly, Morris Srebnik *et al.*[55] reported the same reaction using MSH **33** to synthesize the primary amines at 0 °C (Scheme 1.19).



Scheme 1.19. Preparation of primary/secondary amines from olefins

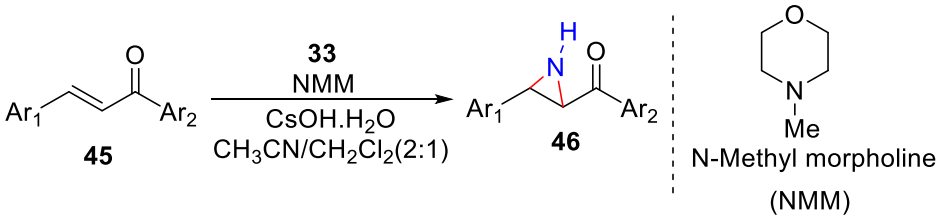
Nicholas C. O. Tomkinson *et al*. used *N*-methyl-*O*-tosyl-hydroxylamine **34** reagent for the direct α-oxytosylation of carbonyl compounds (Scheme 1.20).[56]



Scheme 1.20. α-Oxytosylation of carbonyl compounds using TsONHMe

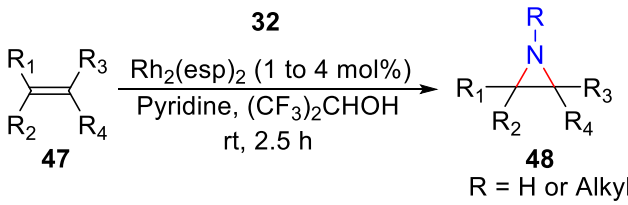
MSH has been considered as one of the greatest ubiquitously used reagents in the last decade for N, S amination of heterocyclic compounds,[57] secondary and tertiary amines,[58] anionic nitrogen of heterocycles,[59] sulfides,[60] sulfoxides,[61] thioether crown systems,[62] and carbanions, as well as reactions with electrophiles for Beckmann[63] and Neber[64] rearrangements.

One of the most interesting applications of these reagents is the aziridination of electron-deficient alkenes.[5] Shi *et al*. reported an organocatalytic *N*-H Aziridination of α,β-unsaturated ketones using MSH **33** as a nitrogen source (Scheme 1.21).[65]



Scheme 1.21. Amine-promoted *N*-H aziridination of enones using MSH

Kürti and co-workers first time reported the use of HOSA **32** with pyridine for the direct *N*-H/*N*-alkyl aziridination of alkenes in the presence of Rh(II)-catalyst (Scheme 1.22).[66]



Scheme 1.22. Direct *N*-H/*N*-Alkyl Aziridination of Alkenes using HOSA

Overall all these reagents have wide applications in synthetic chemistry but aziridination methods using these reagents are limited. These reagents can be easily prepared from widely accessible low-cost starting ingredients utilizing simple synthetic procedures as well as they generate water soluble by-products. In that direction, we were interested to develop a highly efficient method for aziridination using *O*-(substituted)hydroxylamines as a nitrogen source.

1.6 Conclusion

N-H/*N*-Me aziridines play an important role in pharmacological activity because of their core-substructures present in numerous bioactive natural, synthetic and semi-synthetic products. Due to the small ring size, they are highly reactive thus they are also used to synthesize various valuable compounds. In the literature survey, the methods for activated aziridination are well developed while the methods for unactivated aziridination are limited and few of these have the multi-step route. Aminating agents, like *O*-(Sulfonyl)hydroxylamines, have very interesting properties to deliver nitrogen in various synthetic reactions (such as C-H amination, Beckmann rearrangement, etc.) and also can transfer the nitrogen in aziridination reactions. However, only a few reactions are available for aziridination using these reagents. Some of the special features of *O*-(Sulfonyl)hydroxylamine reagent like benign nature to generate water-soluble by-products, lower cost, commercially available, ease of synthesis and non-toxicity makes them popular among the scientific community. It can easily react with transition metals to generate a highly reactive nitrene intermediate which could easily convert the diverse class of olefins into aziridines. In this context, the development of any direct method for unactivated aziridines using *O*-(sulfonyl)hydroxylamines reagent will be highly novel and desirable.

1.7 Motivation of present work

Diverse applications of unprotected (*N*-H/*N*-Me) aziridines discussed above have confidently motivated us to further develop aziridination methods to superior heights with a broad range of applications and understandings in synthetic organic chemistry. We were interested to develop a one-pot, mild, simple, economical and practical method for the synthesis of *N*-H/*N*-Me aziridines from a diverse variety of olefins using *O*-(sulfonyl)hydroxylamines as the aminating agents. The synthesized aziridine products will be highly novel and potent biologically active as well as they could also be used in various important transformation reactions. Hence, the main aim of this thesis is to develop a highly efficient and novel direct method for *N*-H and *N*-Me aziridines from alkene precursors using *O*-(sulfonyl)hydroxylamines as the aminating agents and their computational studies.

In chapter 2, the development of Rh(II)-catalyzed direct method for the synthesis of unactivated (*N*-H/*N*-Me) aziridines from unactivated olefins using *O*-(sulfonyl)hydroxylamines as aminating agents is discussed. In chapter 3, described the Fe(II)-catalyzed direct method for the synthesis of *N*-H/*N*-Me (unactivated) aziridines from olefins using *O*-arylsulfonyl hydroxylamines. In chapter 4, we have described the Cu(II)-catalyed first direct method for the synthesis of *N*-Me aziridines from vinyl ketones using TsONHMe as an aminating agent and *N*-H aziridines from chalcones using MSH as the aminating agent. In chapter 5, we have mentioned the outcomes of the computational studies for anticancer activity of aziridines synthesized in chapter 2.

1.8 References

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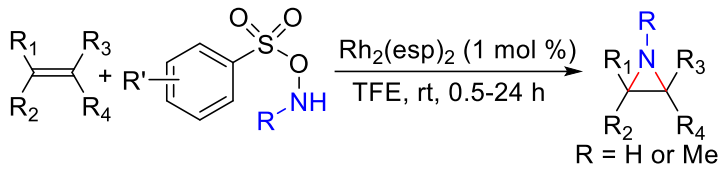
Chapter 2

Rh(II)-Catalyzed Direct *N*-H/*N*-Me Aziridination of Unactivated Olefins Using *O*-(Sulfonyl)hydroxylamines

N-H/*N*-Me aziridines are present in myriad bioactive natural products and they are also used as an important building block in synthetic organic chemistry. Despite several developments, only few protocols are available to achieve them directly from olefins and the majority of them are for their activated counterparts (*N*-EWG) only. Herein, we have developed a highly effective method for the direct synthesis of *N*-H/*N*-Me aziridines from olefins using *O*-(sulfonyl)hydroxylamines as the aminating agent in the presence of Rh(II)-catalyst. This one-pot, mild, simple, practical and stereospecific method afforded varieties of aziridines in very good yield.

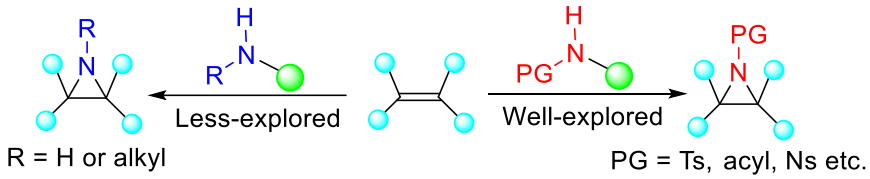


- Nitro-group- and additive-free
- Often chromatography-free
- Insensitive to air/moisture
- Water soluble by-products
- Broad substrate scope
- Regio- and stereo-specific

(*J. Org. Chem.* **2018**, *83*, 12255-12260)

2.1 Introduction

Aziridine moieties are present in many natural, semi-synthetic and synthetic bioactive products which have made them an intensely valuable precursor in organic synthesis.[1] They are indeed important intermediates in synthetic organic chemistry due to their high reactivity involving several transformation reactions *via* strain ring manipulations.[2] Varieties of unprotected value-added compounds such as amino alcohols, di-amines, thio-amines, halo-amines etc. are generated from the aziridine ring-opening.[3] Synthesis of activated aziridines (such as *N*-Ts, acyl, Ns) from olefins are well-explored,[4] whereas, the direct synthesis of non-activated aziridines from the same target are less-explored (Scheme 2.1)[5]. Herein, an up-to-date progress on unprotected aziridination of alkenes are being summarized in section 2.2.

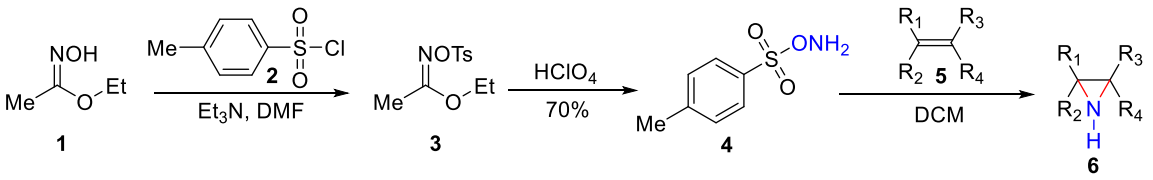


Scheme 2.1. General scheme for activated and non-activated alkene aziridination

2.2 Literature review of unprotected aziridines

2.2.1 Aziridination of olefins using *O*-tosylhydroxylamine

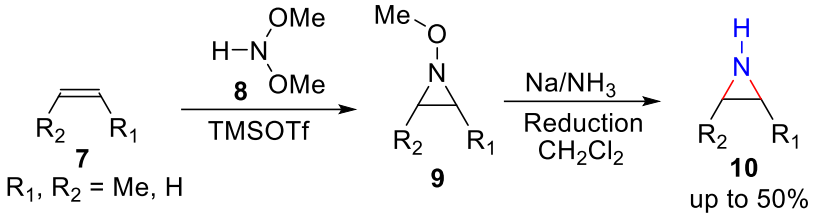
Jeffrey C Bottaro reported the aziridination of olefins using *O*-tosylhydroxylamine **4** as a nitrogen source (Scheme 2.2).[6] The main disadvantage of this method is the instability of the hydroxylamine reagent, most of the alkenes were either failed to generate aziridine or yields were extremely poor.



Scheme 2.2. Aziridination of olefins using *O*-tosylhydroxylamine reagent

2.2.2 Aziridination of olefins using *N*-methoxy-*O*-methylhydroxylamine

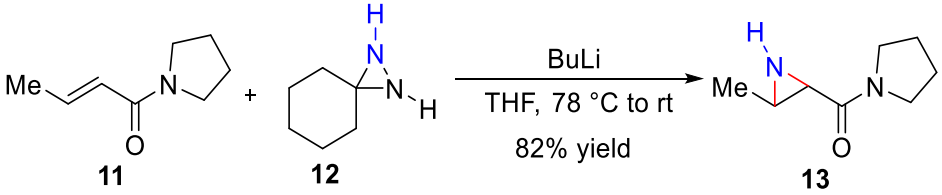
Vedejs and Sam demonstrated a two-step method for the synthesis of *N*-H aziridines **10** from electron-rich olefins **7** using $HN(OMe)_2$ **8** with moderate yields (Scheme 2.3).[7]



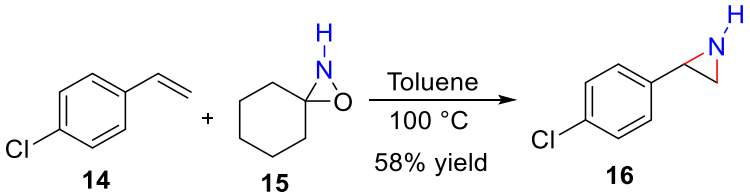
Scheme 2.3. *N*-H aziridination of olefins

2.2.3 Alkene aziridination using oxaziridines and diaziridines

Houk and Armstrong developed the method for the synthesis of *N*-H aziridines from alkenes by using diaziridine and oxaziridine as nitrogen donors (Schemes 2.4 and 2.5). They found *N*-silyl, *N*-trifluoroacetyl, and *N*-alkyl oxaziridines and diaziridiniums as potentially viable alkene aziridinators, but the field is still in its infancy.[8]



Scheme 2.4. Alkene *N*-H aziridination using diaziridine

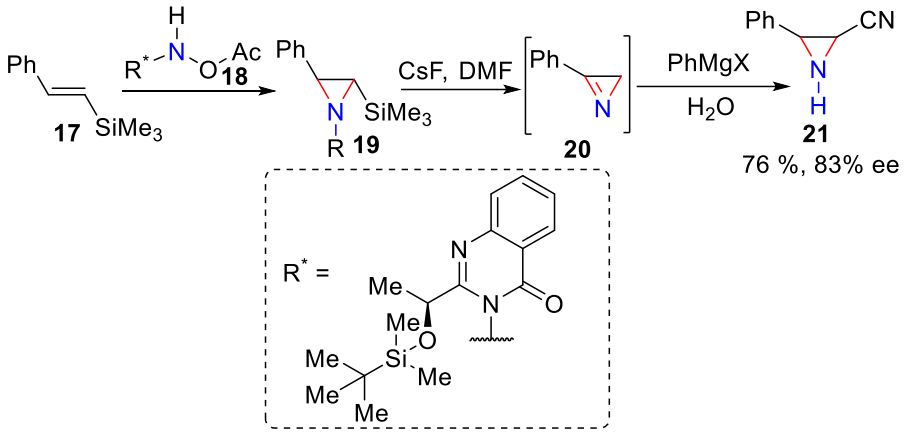


Scheme 2.5. Alkene *N*-H aziridination using oxaziridine

2.2.4 Aziridination of vinylsilane using acetoxyamino quinazoline

Lochrie *et al.* reported the three-step method for diastereoselective *N*-H aziridination of vinylsilane **17** using enantiopure 3-acetoxyamino quinazoline (R*NHOAc) **18** (Scheme

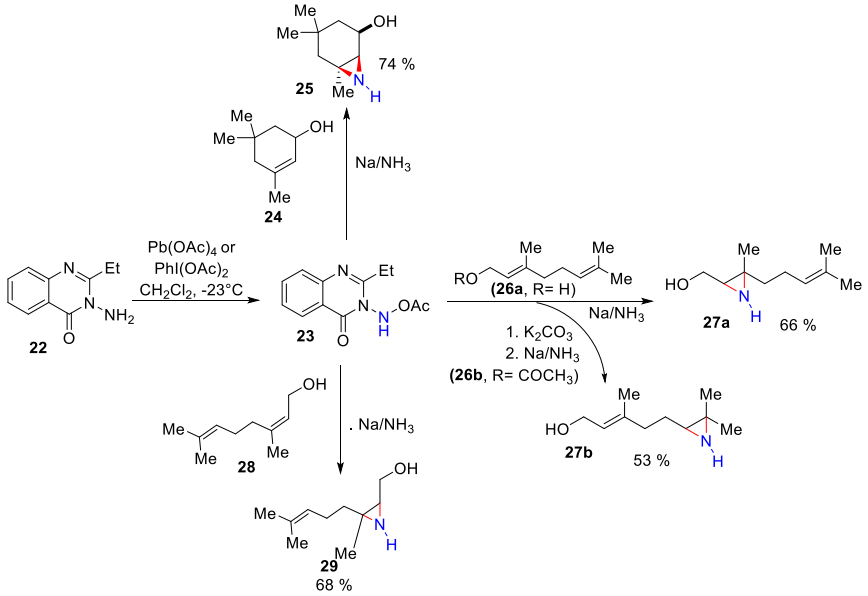
2.6).[9] They prepared *N*-H aziridines **21** with good yield and enantiomeric excess. The reaction was progressed *via* aziridine-azirine-aziridine pathway by *in situ* formation of azirine intermediate **20**.



Scheme 2.6. *N*-H Aziridination of vinylsilane

2.2.5 Aziridination using atkinson's *N*-acetoxyamino quinazolone reagent

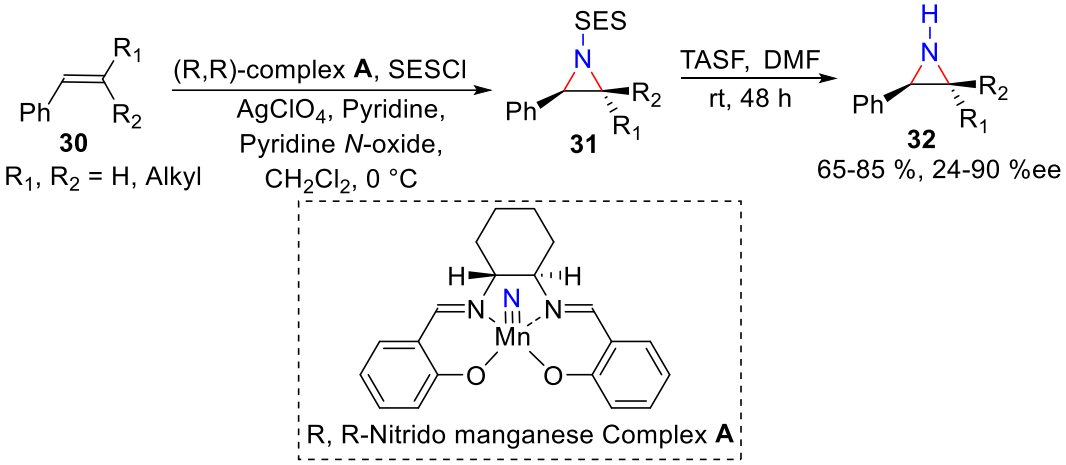
Coates *et al*. reported a two-step synthesis of hydroxyl group directed *N*-H aziridines from isoprenoid alcohols such as geraniol, nerol, and isophorol employing Atkinson's *N*-acetoxyamino quinazolone reagent **23**, followed by the reduction with Na/NH_3 (Scheme 2.7).[10]



Scheme 2.7. Hydroxyl group directed *N*-H aziridination of isoprenoid alcohols

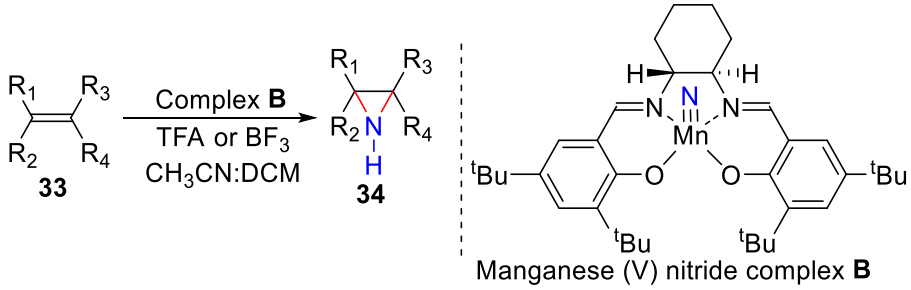
2.2.6 Chiral nitridomanganese complex for aziridination of olefins

Komatsu *et al*. described a two-step approach for the synthesis of different chiral *N*-H aziridines **32** from olefins **30**. They utilized a chiral nitridomanganese complex **A** as a potential *N*-donor and 2-trimethylsilylethanesulfonyl chloride (SES-Cl) as an activator in presence of pyridine, pyridine-*N*-oxide, and $AgClO_4$. SES-group was easily de-protected with *tris*-(dimethylamino) sulfonium diflurotrimethyl silicate (TASF) yielding *N*-H aziridines **32** with good yields and moderate to good enantiomeric excess (Scheme 2.8).[11]



Scheme 2.8. Chiral *N*-H aziridination of olefins using R, R-nitridomanganese complex **A**

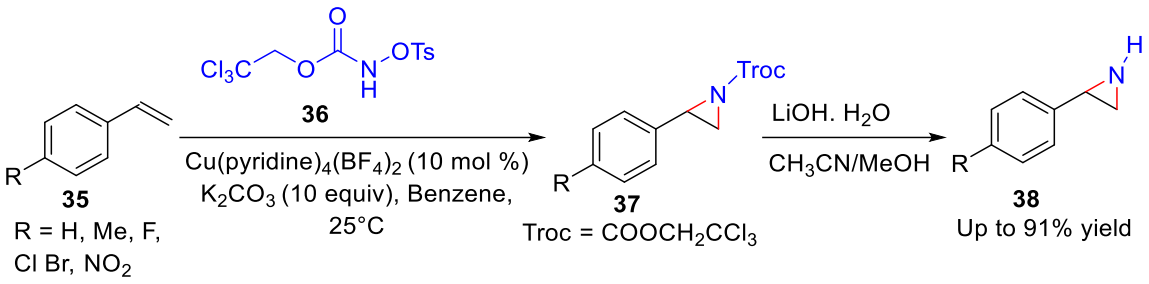
Lau and co-workers demonstrated the asymmetric *N*-H aziridination from a variety of olefins **33** using manganese (V) nitride complex **B** as a nitrogen transfer agent (Scheme 2.9).[12] In this method, aliphatic alkenes delivered poor yields of the desired product **34**.



Scheme 2.9. Olefin aziridination using manganese (V) nitride complex **B**

2.2.7 Aziridination of olefins using *N*-tosyloxycarbamate

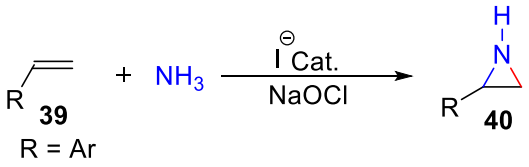
Lebel *et al.* reported the inter and intramolecular olefin aziridination using Cu(pyridine)$_4$(BF$_4$)$_2$ complex and *N*-tosyloxycarbamate reagent **36** (Scheme 2.10).[13] This two-step method produced *N*-H aziridines with good to excellent yields.



Scheme 2.10. *N*-H aziridination of styrenes using *N*-tosyloxycarbamate

2.2.8 Aziridination of olefins using ammonia

Dirk E. De Vos *et al.* developed the first iodide catalyzed one-pot synthesis of *N*-H aziridines **40** from olefins **39** in a micellar system using aqueous NaOCl (bleach) as an oxidant (Scheme 2.11).[14]



Scheme 2.11. *N*-H aziridination of olefins using ammonia in a micellar system

This method was shown to be the most efficient for aromatic olefins only. The plausible catalytic cycle shows the initial electrophilic attack of iodonium ion accelerate the reaction

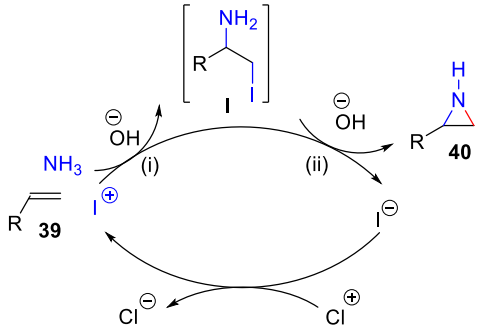
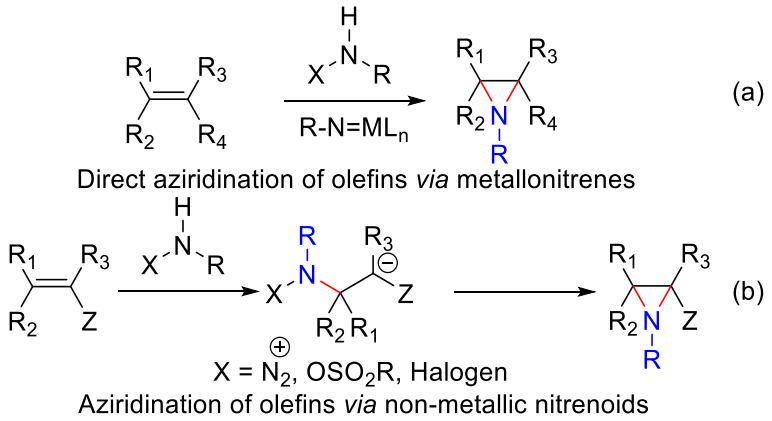


Figure 2.1. Plausible catalytic cycle

and then ammonia insertion and ring closure occur in alkaline condition (Figure 2.1). Before this method, NH_3 was used as a sole nitrogen source for aziridination reaction with a limited substrate scope (Gabriel-Cromwell reaction).[15]

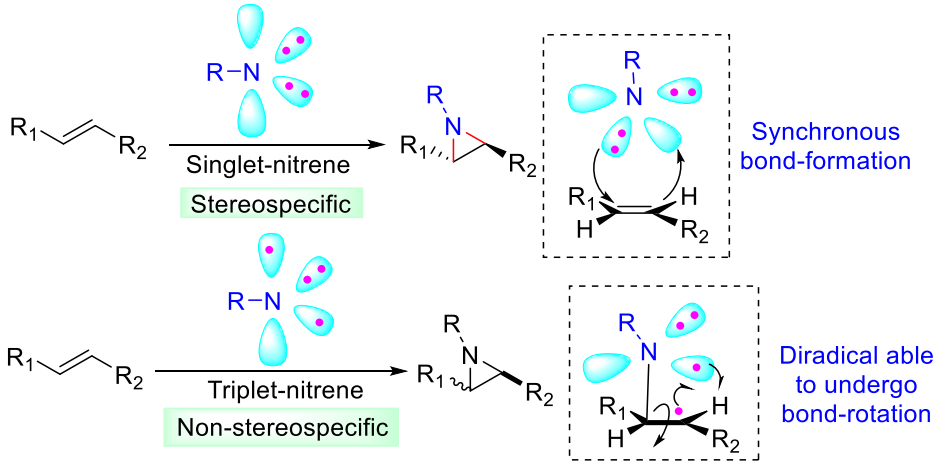
2.2.9 Aziridination *via* addition of nitrenes or nitrenoids to olefins

Direct aziridination of olefins could be achieved by the metallonitrenes or non-metallic nitrenoids pathways (Scheme 2.12a-b)[16]



Scheme 2.12. Aziridination of olefins by addition of nitrenes or nitrenoids

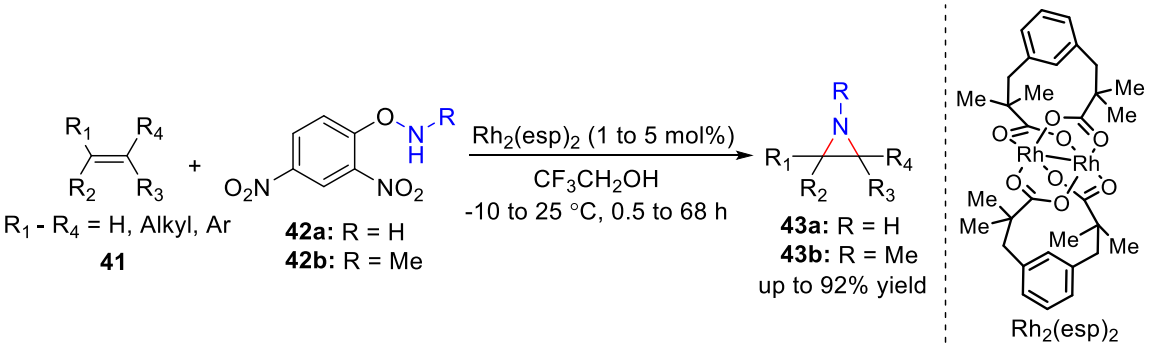
A mixture of singlet and triplet nitrenes was formed in these methods, only singlet nitrenes reacted stereospecifically with alkenes and triplet nitrene shows non-specific addition to alkenes and gives a mixture of *cis* and *trans* isomers of aziridines (Scheme 2.13).



Scheme 2.13. Aziridination by singlet and triplet nitrene intermediate

2.2.10 Aziridination of olefins using DPH

Falck, Kürti & Ess (2014) developed the first direct and stereospecific method for the synthesis of *N*-H and *N*-Me aziridines from olefins using *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) **42a** and its *N*-Me derivative **42b** as the electrophilic aminating agent with Rh(II)-catalyst (Scheme 2.14).[17] This excellent methodology allows for the direct stereospecific conversion of structurally diverse *mono*-, *di*-, *tri*-, and *tetra*-substituted alkenes to *N*-H and *N*-Me aziridines in good to excellent yields. The author also mentioned a possible mechanism for this aziridination method, which proceeds *via* Rh-nitrene pathway (Figure 2.2). This elegant method has some limitations like generation of toxic waste (DNP) and co-elution of DNP along with aziridines, etc.



Scheme 2.14. Direct stereospecific *N*-H/*N*-Me olefin aziridination using DPH

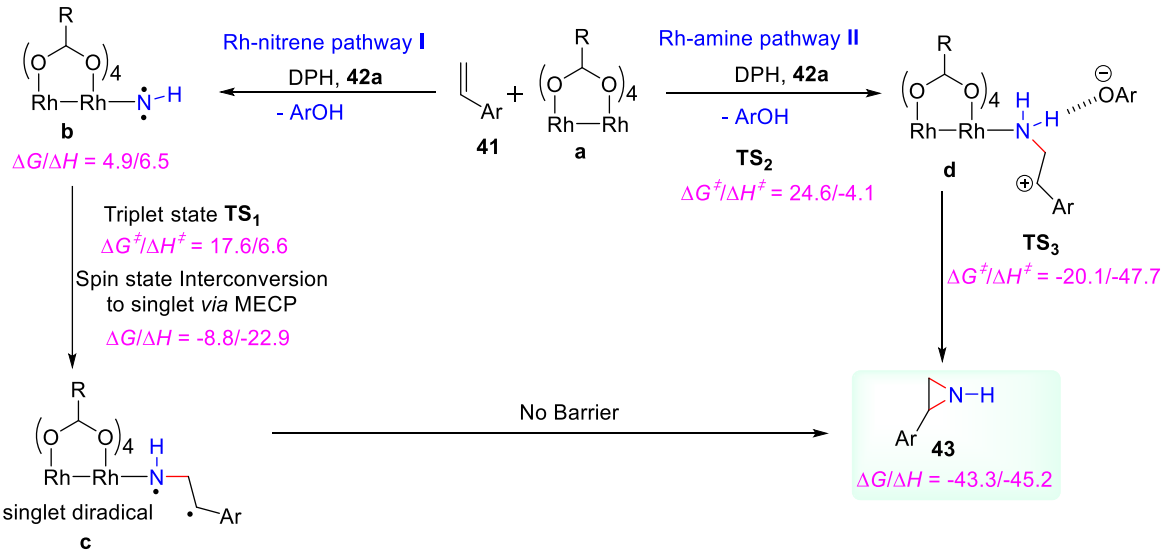
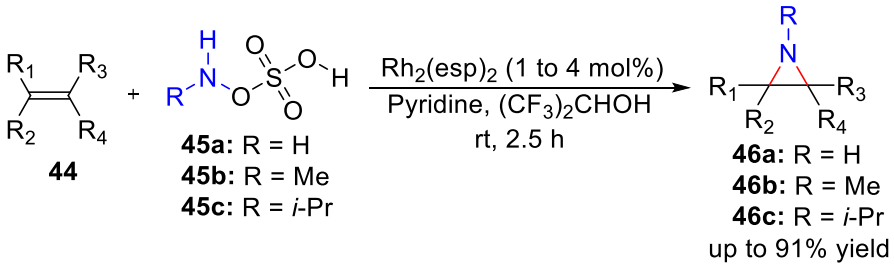


Figure 2.2. Proposed aziridination reaction pathways

2.2.11 Aziridination of olefins using HOSA

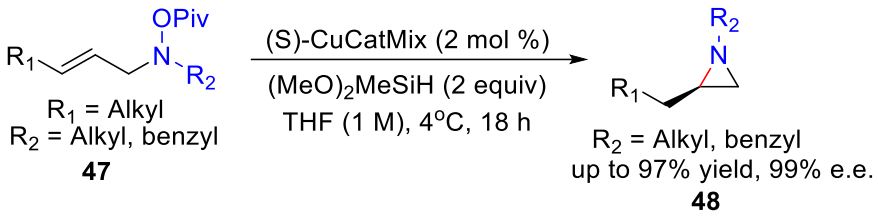
Kürti *et al.* improved their previous method by utilizing hydroxylamine-*O*-sulfonic acid (HOSA) as the nitrogen source in HFIP solvent with good yields (Scheme 2.15).[18] This reaction proceeds *via* a similar rhodium-nitrene pathway as earlier reported by Falck, Kürti & Ess aziridination (Figure 2.2).[17] This method overcome several drawbacks associated with DPH reagent.



Scheme 2.15. *N*-H and *N*-Alkyl aziridination with HOSA

2.2.12 Intramolecular olefin aziridination

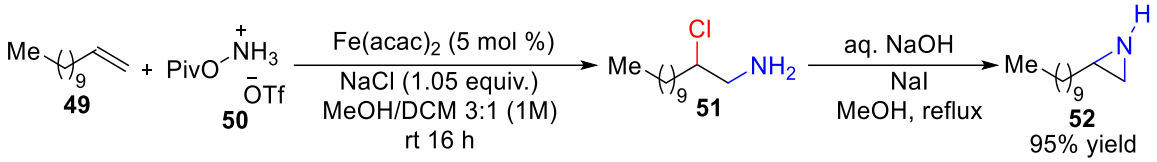
Buchwald *et al.* developed the intramolecular method for the direct preparation of chiral aziridines from allylic hydroxylamine esters (achiral) using a chiral copper catalyst. This method provides aziridines with good to high yields and enantiomeric excess (Scheme 2.16).[19]



Scheme 2.16. Enantioselective intramolecular aziridination of allylic hydroxylamine esters

2.2.13 Olefin *N*-H aziridination using Fe(II)-catalyst

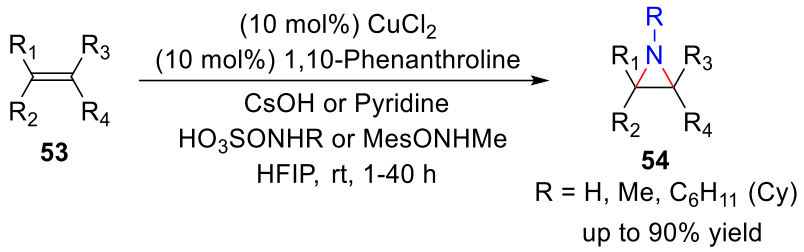
Morandi *et al.* reported the Fe(II)-catalyzed two-step method for the synthesis of *N*-H aziridine **52** from alkene **49** with excellent yield (Scheme 2.17).[20]



Scheme 2.17. Fe(II)-Catalyzed two step synthesis of *N*-H aziridine from alkene

2.2.14 Cu(II)-Catalyzed *N*-H/*N*-alkyl aziridination of unactivated olefins

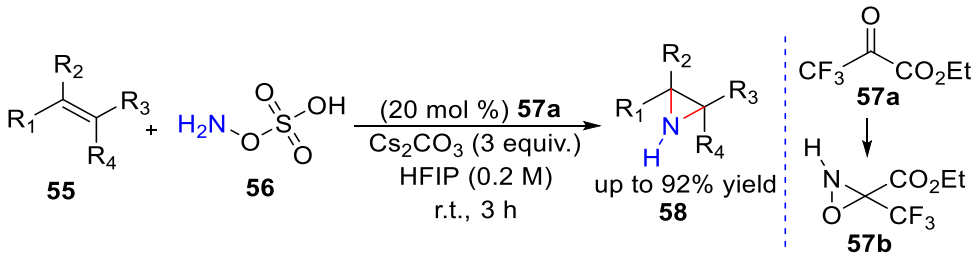
Falck *et al*. reported the Cu(II)-catalyzed synthesis of *N*-H and *N*-alkyl aziridines from olefins using $HO_3SONHR/MesSO_2ONHMe$ as the aminating reagents, in presence of ligand (1,10-phenanthroline) and base (CsOH or pyridine) in HFIP solvent at room temperature (Scheme 2.18).[21] This methodology produced the *N*-H/*N*-alkyl aziridines in good to excellent yields.



Scheme 2.18. *N*-H/*N*-Alkyl aziridination of olefins

2.2.15 Organocatalytic *N*-H aziridination of unactivated olefins

In 2020, Kürti *et al*. first reported the organocatalytic synthesis of *N*-H aziridines from unactivated olefins *via* transient oxaziridines with good to high yields. (Scheme 2.19).[22] The proposed reaction proceeds *via* an *in situ* generated oxaziridine intermediate **57b** from electron-deficient ketone **57a** and HOSA (Figure 2.3).[22]



Scheme 2.19. Organocatalytic synthesis of *N*-H aziridines from unactivated olefins

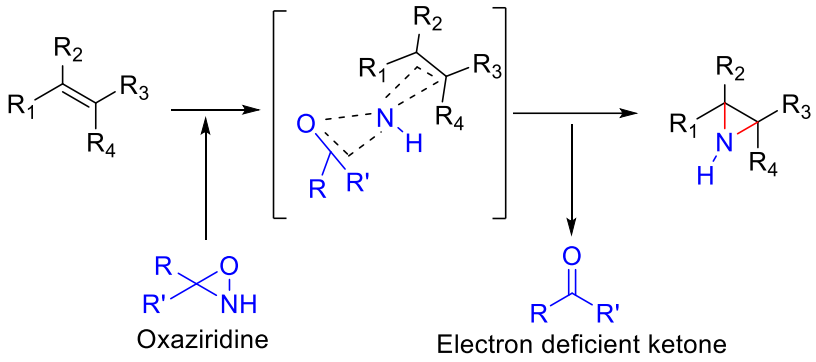
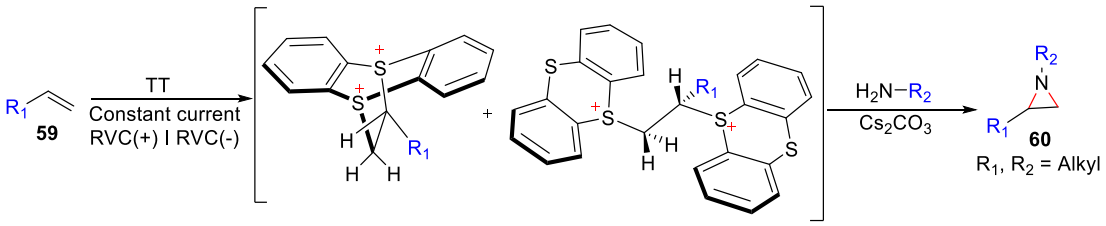


Figure 2.3. Proposed reaction mechanism

2.2.16 Aziridination by coupling amines and alkenes *via* electrogenerated dication

Very recently, Wickens *et al.* developed an efficient method for the preparation of *N*-alkyl aziridines by coupling a variety of amines as a base and alkenes using electrogenerated dication (Scheme 2.20).[23] This methodology produced aziridines in good to excellent yields.



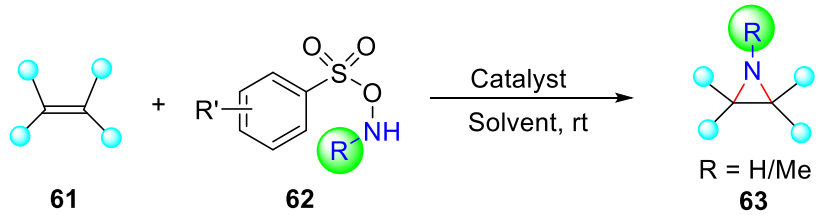
Scheme 2.20. Synthesis of *N*-alkyl aziridines by coupling of amines and olefins using electrogenerated dication

In conclusion, the literature reports show that the direct methods of *N*-H/*N*-alkyl aziridines from alkenes are less explored and most of the developed methods have several limitations like, limited substrate scope, poor functional group tolerance, multi-step, non-economical, generated toxic and interfering by-products, longer reaction time, lower yield, requirement of additives and column purification etc. In this context, the development of a highly efficient method for unactivated aziridines which will overcome the above limitations is in demand. The method would be atom-economical, additive/base free, column chromatography free because strained aziridine rings generally open up during silica gel column chromatography.

2.3 Objective of the work

So, the objective of this part of the thesis were the development of a new methodology for *N*-H/*N*-Me aziridination of alkenes under mild and additive free condition utilizing O-(sulfonyl)hydroxylamines as a new aminating agent. The method should have broad substrate scope along with good yields, high functional group tolerance and insensitive to air/moisture, column chromatography free, etc.

To accomplish these tasks, we chose *O*-(Sulfonyl)hydroxylamines as an aminating reagent for the following reasons: (a) Its existence in non-zwitterionic form (b) Stable and readily available and (c) Generated a non-interfering and non-nucleophilic by-products that can be easily removed by using an aqueous work-up (Scheme 2.21).

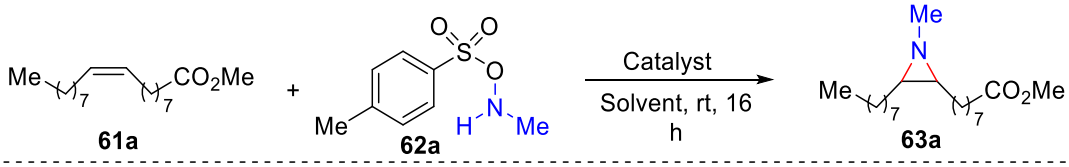


Scheme 2.21. Synthesis of *N*-H and *N*-Me aziridines from alkenes

2.4 Results and discussion

2.4.1 Optimization of the reaction condition

Table 2.1 Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	Yield (%)[b]
1	(5 mol%) $FeCl_2$	TFE	-
2	(5 mol%) $FeCl_3$	TFE	-
3	(5 mol%) CuBr	TFE	trace
4	(5 mol%) $Cu(OAc)_2$	TFE	20

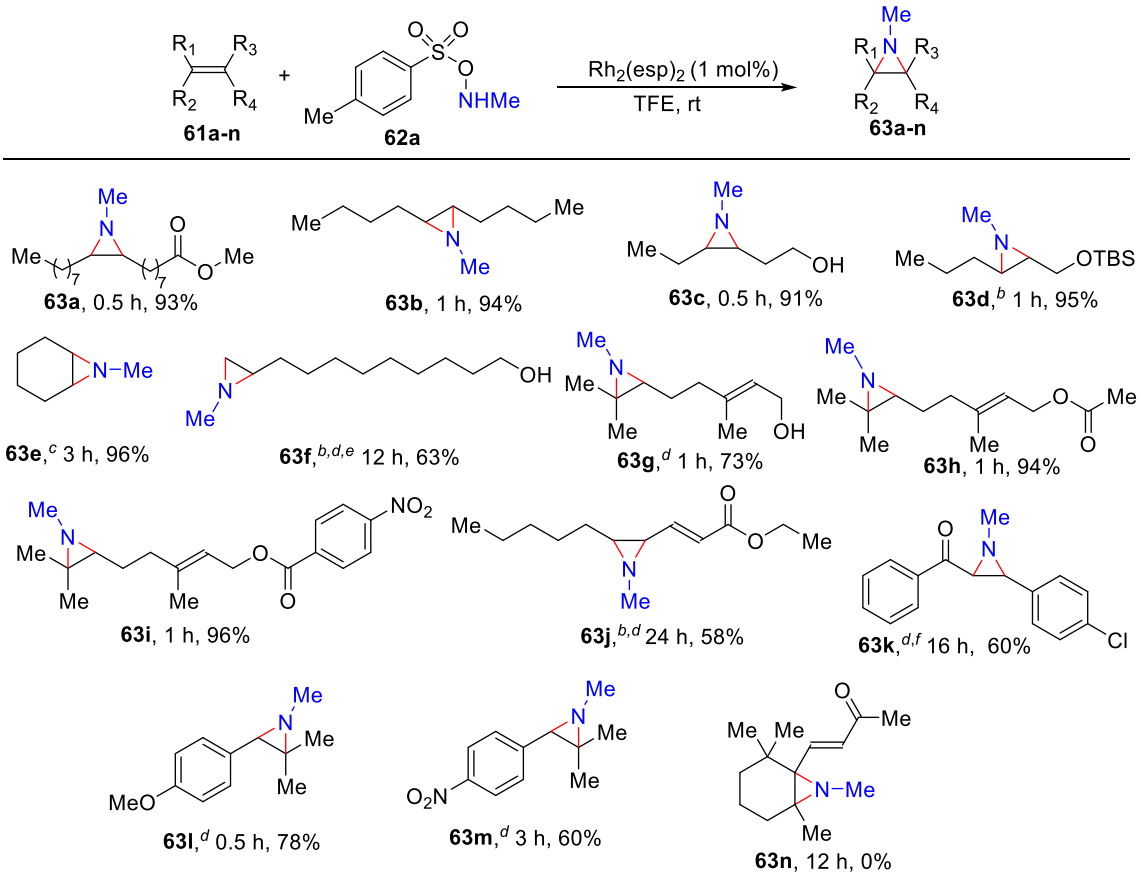
5	(5 mol%) $Cu(acac)_2$	TFE	35
6	(5 mol%) $FeSO_4.7H_2O$	TFE	52
7	(5 mol%) $Rh_2(OAc)_2$	TFE	65
8	(5 mol%) $Rh_2(TFA)_2$	TFE	-
9	(5 mol%) $Rh_2(esp)_2$	TFE	96[c]
10	**(1 mol%) $Rh_2(esp)_2$**	**TFE**	**93[c]**
11	(1 mol %) $Rh_2(esp)_2$	EtOH	trace
12	(1 mol %)$Rh_2(esp)_2$	THF	-
13	(1 mol %) $Rh_2(esp)_2$	CH_3CN	trace
14	(1 mol %) $Rh_2(esp)_2$	DMF	-
15	(1 mol %) $Rh_2(esp)_2$	CH_2Cl_2	-
16	-	TFE	-

[a]Unless otherwise noted, the reaction conditions are: olefin **61a** (0.25 mmol), aminating agent **62a** (1.2 equiv.), $Rh_2(esp)_2$ catalyst (1-5 mol%), 16 h, at room temperature. [b]Isolated yield after purification. [c]Isolated yield after work-up, TFE = 2,2,2-trifluroethanol solvent, esp = α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid.

Our investigation for *N*-Me aziridination began using methyl oleate **61a** as the model substrate and *N*-methyl-*O*-tosylhydroxylamine **62a** as the aminating reagent in TFE solvent (Table 2.1). At first, we screened different metal catalysts, under this condition, both $FeCl_2$ and $FeCl_3$ failed to produce the desired product (entries 1 and 2). CuBr was proven to be inactive, however, $Cu(OAc)_2$ and $Cu(acac)_2$ catalyzed the reaction, providing **63a** with 20-35% yield (entries 3-5). While in the case of $FeSO_4.7H_2O$, the yield increased dramatically to 52% (entry 6). Moving to many Rh(II)-based catalysts increased the reaction yield even further, finally $Rh_2(esp)_2$ catalyst yielding the required product in high yield (96%), the reaction was completed in 30 minutes (entry 9). Reduced catalyst loading from 5 to 1 mol% did not affect yield (93%, entry 10). Screening several alternative solvents under comparable conditions showed an adverse effect on the reaction yields (entries 11-15). A simple workup with saturated aqueous $NaHCO_3$ solution effectively removed the by-product *i.e. p*-toluenesulfonic acid (*p*-TsOH) and yielded the desired product with high NMR purity.

2.4.2 Scope of alkenes for *N*-Me aziridination

To determine the scope of this method, a variety of olefins were tested under standard condition (entry 10, Table 2.1).



[a]Reaction condition unless otherwise mentioned: Olefins **61a-n** (0.5 mmol), aminating agent **62a** (1.2 equiv.), $Rh_2(esp)_2$ (1 mol%) catalyst, TFE (2.0 mL) solvent , rt. The yields are isolated yield after an aqueous work-up. [b]Reaction was performed at -10 °C. [c]The purity of this compound was checked by HPLC. [d]Column purification was required. [e]Rh-catalyst (5 mol%) was used. [f]A mixture of TFE:$CHCl_3$ (1:1) was used as the solvent.

Scheme 2.22. Preparation of *N*-Me aziridines from alkenes

The results are given in Scheme 2.22. *Cis* and *trans* alkenes were stereospecifically aziridinated in good yields (**63a-b**). Olefins containing an unprotected hydroxyl group aziridinated with excellent yield (91%, **63c**) and its tertiarybutylsilyl-protected analogue yielded **63d** in 95% yield at a lower temperature. The TBS-protected alkene/aziridine was partially deprotected when the reaction was stirred at rt. The reaction also works very well

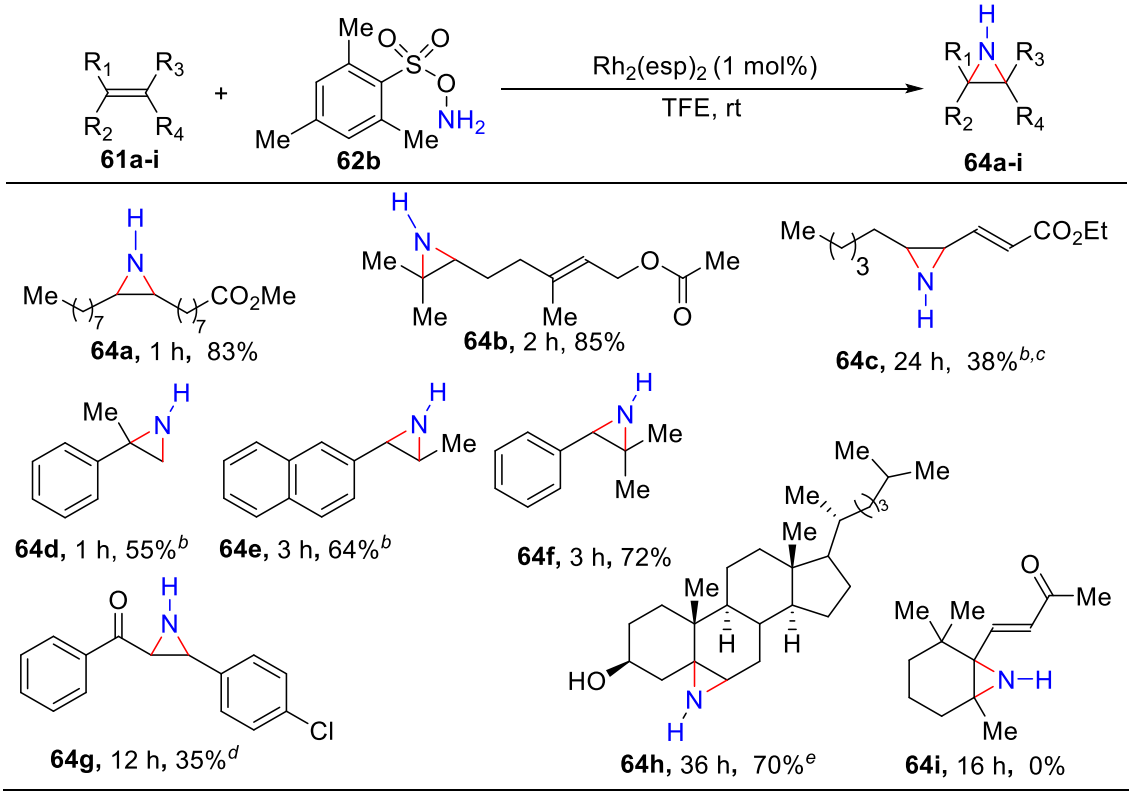
with a cyclic alkene, yielding desired aziridine **63e** with a high yield (96%). Switching to a terminal alkene, a minor change is required in the reaction condition because the reaction was sluggish at room temperature. This reaction required a slightly higher loading of Rh-catalyst (5 mol%) and lower temperature (-10 ^{o}C) to produce desired aziridine **63f** in a good yield.

Geraniol was used to investigate the regioselectivity under this reaction condition, it gives **63g** in 73% yield by selectively aziridinated at the 6,7-olefinic position. Other geraniol derivatives also reacted efficiently to generate **63h** and **63i** as a single regiomer with 94% and 96% yields respectively. This regioselectivity is due to the inductive deactivation of the proximal double bond (2,3-position) by the acetoxy or benzoyloxy group. The electron deficient chalcones had a significantly slower reactivity, which took 16 hours to complete the reaction in a mixture of solvents TFE:$CHCl_3$ (1:1) (**63k**). Conjugated diene esters, aziridinated exclusively at the distal double bond (**63j**, 58%). The electron-rich and electron-deficient trisubstituted styrenes successfully reacted and produced the required products in good yields (**63l-m**), albeit the electron-deficient styrene reacts slower. Tetra-substituted olefins, such as *β*-ionone, did not react under the optimized reaction condition (**63n**). All of the reactions were highly stereospecific, with no allylic C-H amination side products were observed.

2.4.3 Scope of alkenes for *N*-H aziridination

After demonstrating the method for *N*-Me aziridination, we moved on to direct *N*-H aziridination of alkenes. Because the unprotected analogue of **62a** ($TsONH_2$) was unstable in this condition, the literature survey, as well as our own efforts using it to achieve N-H aziridination, were unsuccessful. Under similar conditions as in Scheme 2.22, *O*-(mesitylenesulfonyl)hydroxylamine **62b** was proved to be an effective aminating agent (Scheme 2.23). Different alkenes reacted successfully in this condition, affording good to excellent yield of the desired products. Methyl oleate, for example, produced an 83% yield of *N*-H aziridine **64a**. Geranyl acetate and (2*E*,4*Z*)-ethyl deca-2,4-dienoate delivered **64b** and **64c** in 85% and 38% yield respectively as a single regiomer. At lower temperature simple and substituted styrenes were good substrates for this methodology, providing good

yields of the corresponding *N*-H aziridines (**64d** and **64f**). *β*-Naphthyl styrene produced **64e** in a 64% yield.



[a]Unless otherwise indicated, reaction conditions are as follows: alkenes **61a-i** (0.5 mmol), aminating agent **62b** (1.2 equiv.) $Rh_2(esp)_2$ (1 mol%) catalyst, TFE (2.0 mL) solvent, rt. Yields are isolated after silica gel column chromatography. [b]The reaction was stirred at -10°C. [c]The reaction was clean, although the conversion was poor, and the olefin could be recovered. [d]The mixture of TFE:$CHCl_3$ (1:1) solvent was used. [e]Rh-catalyst (2.5 mol%) and **62b** (2.5 equiv.) were used.

Scheme 2.23. Synthesis of *N*-H aziridines from olefins

Chalcone was less reactive and generated 35% of aziridine (**64g**). On the next move, we tried our reaction condition for more complex substrates like cholesterol. Only a minor conversion was observed in TFE solvent and the yield increased significantly (**64h**, 70% yield) when a mixture of TFE:$CHCl_3$ (1:1) solvent was used. Tetra substituted olefin (β-ionone) did not react under our optimization reaction condition (**64i**). We anticipate that these reactions will follow the same mechanistic pathway as proposed by the Falck group (Figure 2.2).[17]

2.5 Conclusion

In conclusion, we have established Rh(II)-catalyzed efficient approach for the direct synthesis of *N*-H and *N*-Me aziridines from olefins using *O*-(sulfonyl)hydroxylamines as aminating agents in TFE. The success of this protocol does not depend upon the presence of additives like bases or ligands etc. Aminating agents used in this methodology do not generate explosive or interfering by-products. This methodology produces various unactivated aziridines with good to excellent yields and in most of the cases, *N*-Me aziridines could be isolated with high purity just after an aqueous work-up. Even extremely reactive and labile functional groups including keto, ester, alcohol, and silyl were well-tolerated. The reactions proceeded with good chemoselectivity as no undesired C-H amination product was observed.

Highlights

The main highlights of our developed methodology are as follows:

- Nitro-group and additive free method
- Generates water soluble by-products
- Often chromatography free
- Broad substrate scope
- Regio- and stereospecific
- Insensitive to air/moisture

This work has been published in *J. Org. Chem*, **2018**, *83*, 12255-12260.

This work was also has been highlighted in Organic Chemistry Portal:

(i) C-N Ring Construction: The Mori Synthesis of Lycopodine: https://www.organic-chemistry.org/Highlights/2019/22April.shtm

(ii) Synthesis of aziridines: https://www.organic-chemistry.org/abstracts/lit6/530.shtm

2.6 Experimental section

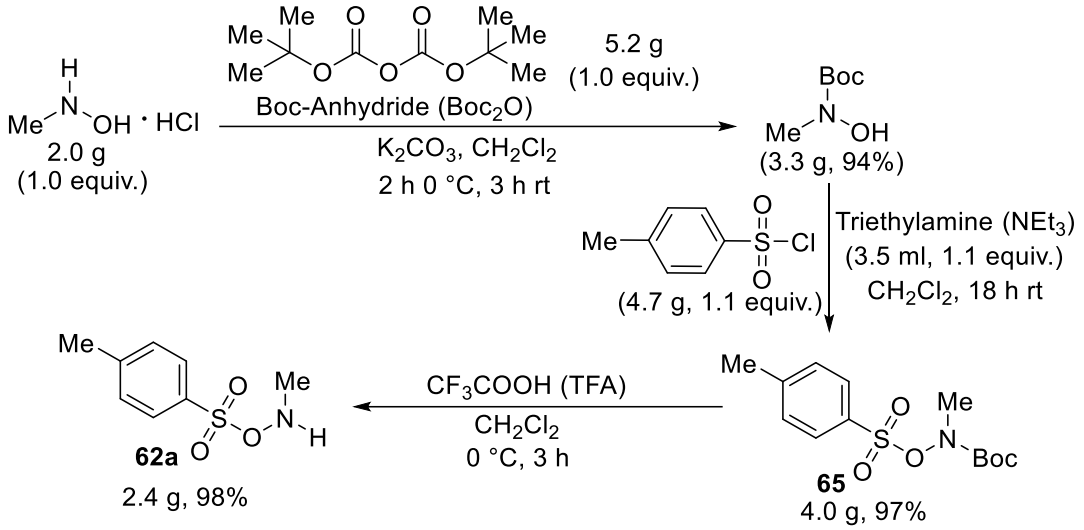
2.6.1 General information

Unless otherwise indicated, all aldehydes and alkenes were purchased from a commercial source and used without further purification. Following standard methods, the solvents were dried and distilled. In a single-neck round bottom flask, all reactions were carried out in an open atmosphere. Reactions were monitored by thin layer chromatography (TLC) using plates pre-coated (silica gel 60, F-254) purchased from Merck. The spot of compounds were visualized by UV light and stains PMA or $KMNO_4$ followed by heating. For purification of compounds, column chromatography was performed with silica gel (230-400 mesh) in distilled solvents. ^1H NMR spectra were obtained at 400 MHz instrument and ^{13}C NMR spectra were obtained at 100 MHz instrument in $CDCl_3$ solvent. Chemical shifts (δ) and coupling constants (J) are measured in ppm and Hz, respectively. Chemical shifts (δ) were recorded in reference to the internal standard tetramethylsilane (TMS, 0.00 ppm) or residual protiated solvent signals ($CDCl_3$, ^1H NMR: = 7.26 ppm; ^{13}C NMR: = 77.00 ppm). Multiplicities were known as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), td (triplet of doublets), or m (multiplet). High resolution mass spectra (HRMS) were obtained on an Agilent 6530 series quadrupole time of flight (Q-TOF) *mass spectrometer* equipped with electron spin ionization (ESI).

2.6.2 Preparation of reagents

N-Methyl-O-tosyl-hydroxylamine (*62a*)

N-Methyl-*O*-tosyl hydroxylamine **62a** (TsONHMe) was prepared in three steps by the following known literature procedure (Scheme 2.24).[24] In the first step *N*-Boc-*N*-methyl hydroxylamine was prepared from *N*-methyl hydroxylamine hydrochloride and di-tert-butyl dicarbonate (Boc-anhydride). In the second step, the tosyl protection of *N*-Boc-*N*-Me hydroxylamine was performed using TsCl in presence of TEA in DCM solvent. In the final step of the reaction, *N*-Methyl-*O*-tosyl hydroxylamine **62a** was obtained by selective deprotecting of the Boc-group from *N*-Boc-*N*-methyl-*O*-tosyl hydroxylamine **65**.



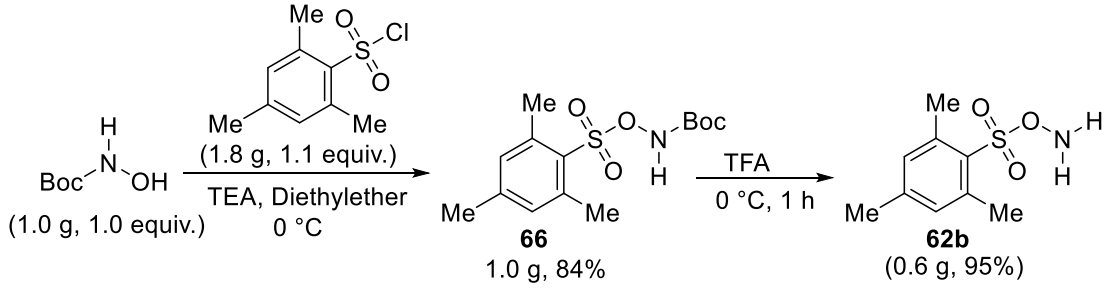
Scheme 2.24. Synthesis of *N*-methyl-*O*-tosyl hydroxylamine **62a**

N-Boc-N-methyl-O-tosyl hydroxylamine **(65):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 3.21 (s, 3H), 2.43 (s, 3H), 1.18 (s, 9H). ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 156.04, 145.77, 131.11, 129.68, 129.56, 83.30, 40.14, 27.55, 21.68.

N-Methyl-O-tosyl hydroxylamine **(62a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.74 (s, 3H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.98, 132.29, 129.54, 128.99, 40.15, 21.70.

O-(mesitylsulfonyl)hydroxylamine (62b)

O-(mesitylsulfonyl)hydroxylamine **62b** (MSH) was prepared in two steps by following a known literature procedure.[25] *N*-Boc-*O*-(mesitylsulfonyl)hydroxylamine **66** was prepared from *N*-Boc-hydroxylamine at 0 °C. In the last step, de-protection of the Boc-group was carried out in the presence of TFA (Scheme 2.25).



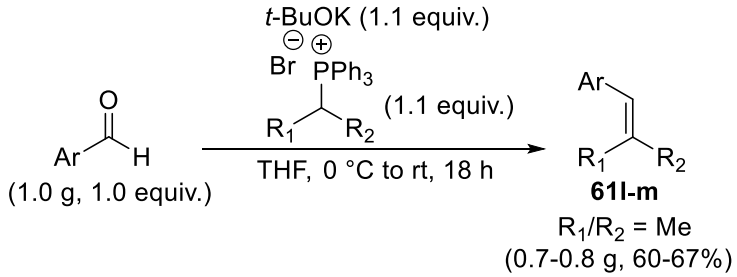
Scheme 2.25. Synthesis of *O*-(mesitylsulfonyl)hydroxylamine (**62b**)

***N-Boc-O-(mesitylsulfonyl)hydroxylamine* (66):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 6.98 (s, 2H), 2.66 (s, 6H), 2.31 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.35, 144.42, 141.94, 131.65, 128.51, 83.79, 27.72, 23.12, 21.11.

***O-(mesitylsulfonyl)hydroxylamine* (62b):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 2H), 5.27 (br, 2H), 2.62 (s, 6H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.82, 140.95, 131.73, 129.10, 22.72, 21.09.

2.6.3 Synthesis of starting materials (alkenes)[26]

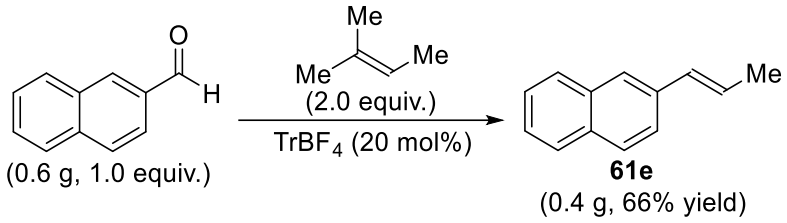
Alkenes (**61l-m**) were prepared according to the reported Wittig olefination procedure (Scheme 2.26).



Scheme 2.26. Preparation of *tri*-substituted alkenes **61l** and **61m**

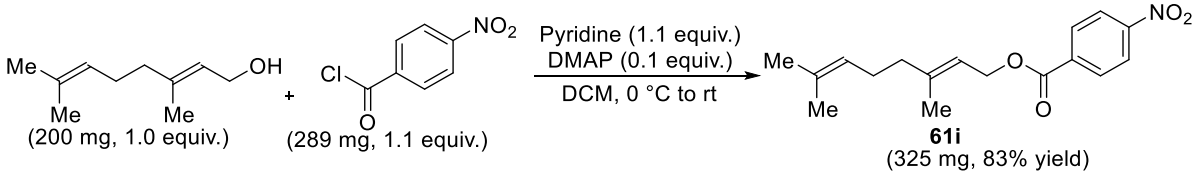
Potassium *tert*-butoxide was added to a suspension of the wittig salt in THF solvent at 0 °C and the resulting reaction mixture was stirred for 30 min at room temperature. Then, the appropriate aldehyde was added and stirred for 18 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to provide the crude residue which was purified by silica gel column chromatography (1% EtOAc/hexane) affording the corresponding alkenes **61** in good yields (**61l-m**).

Substrate, (*E*)-2-(prop-1-en-1-yl)naphthalene (β-Naphthyl Styrene, **61e**) was prepared by following the reported literature procedure (Scheme 2.27). 2-napthaldehyde (0.940 g, 6.0 mmol) and 2-methyl-2-butene (0.127 mL, 1.2 mmol) were combined with 20.0 mol% $TrBF_4$ (0.079 g, 0.24 mmol) to synthesize title compound **61e**.



Scheme 2.27. Preparation of substrate **61e**

Substrate (*E*)-3,7-Dimethylocta-2,6-dienyl 4-nitrobenzoate (**61i**) prepared according to the common acylation procedure (Scheme 2.28).



Scheme 2.28. Preparation of Substrate **61i**

To a stirred solution of geraniol (200 mg, 1.29 mmol) and *p*-nitrobenzoyl chloride (289 mg, 1.54 mmol) in CH_2Cl_2 (15 mL) at 0 ^oC, pyridine (136 μL, 1.54 mmol) and DMAP (18 mg, 0.15 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. After completion of the reaction, CH_2Cl_2 (10 mL) was added and the organic layer was washed with water (2 x 5 mL) and brine solution (5 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated in *vacuo* and the crude product was purified by silica gel column chromatography (2% EtOAc in hexane) to give the title compound **61i** as a thick oil. (325 mg, 83%). TLC: R_f = 0.5 (5% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 8.28-8.23 (m, 2H), 8.22-8.17 (m, 2H), 5.49-5.42 (m, 1H), 5.10-5.04 (m, 1H), 4.87 (d, *J* = 7.1 Hz, 2H), 2.14-2.03 (m, 4H), 1.76 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 150.4, 143.3, 135.8, 131.8, 130.6, 123.5, 123.4, 117.6, 62.7, 39.4, 26.2, 25.6, 17.6, 16.5. HRMS (ESI) $[M+H]^+$ calcd. for $C_{17}H_{22}NO_4$: 304.1543, found: 304.1525.

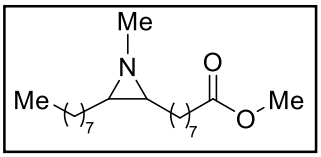
2.6.4 General procedure for the preparation of *N*-H and *N*-Me aziridines

To a single-neck round bottom flask equipped with a magnetic stirring bar, was added alkene **61** (0.5 mmol) and aminating agent **62a** or **62b** (1.2 equiv.) in TFE (2 mL) solvent

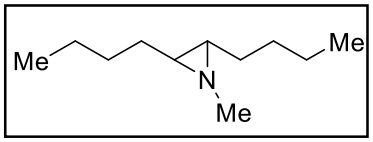
at room temperature. To this stirred solution, $Rh_2(esp)_2$ (1 mol %) catalyst was added. The reaction mixture was stirred at the specified temperature and monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with a saturated aqueous $NaHCO_3$ solution (2 x 5 mL). The aqueous layer was extracted twice with CH_2Cl_2 (5 mL) and washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in *vaccuo* to provide the title product.

2.7 Characterization of the products

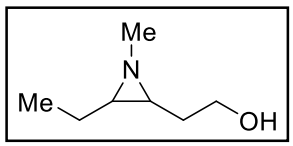
***Methyl 8-(1-methyl-3-octylaziridin-2-yl)octanoate (63a)*:**[17] Following the general aziridination procedure, the title aziridine was obtained as a colorless oil (151 mg, 93% yield) whose spectral data were in accord with the literature values.



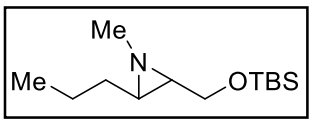
***2,3-Dibutyl-1-methylaziridine (63b)*:** Following the general aziridination procedure, the title product was obtained as a colorless oil (80 mg, 94% yield). TLC: R_f = 0.3 (50% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 1.64-1.56 (m, 2H), 1.46-1.28 (m, 11H), 0.93-0.86 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 47.2, 42.9, 38.6, 32.8, 30.6, 29.6, 25.3, 22.6, 22.5, 14.0, 13.9. HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{11}H_{24}N$:170.1903, found: 170.1903.



2-(3-Ethyl-1-methylaziridin-2-yl)ethanol (63c): Following the general aziridination procedure, the title product was obtained as a pale-yellow oil (58 mg, 91% yield). TLC: R_f = 0.3 (5% MeOH in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84-3.71 (m, 2H), 2.34 (s, 3H), 1.76-1.68 (m, 1H), 1.56-1.29 (m, 4H), 1.25-1.19 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 61.9, 47.8, 46.2, 43.1, 29.5, 21.2, 11.8. HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_7H_{16}NO$: 130.1226, found: 130.1225.

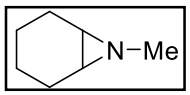


***2-(2-(tert-Butyldimethylsilyloxy)ethyl)-3-ethyl-1-methyl aziridine (63d)*:** The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using ^{t}Bu$_3$N:EtOAc:hexane (1:29:70) as an eluent to give the title

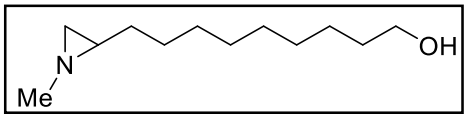


product as a colorless oil (115 mg, 95% yield). TLC: R_f = 0.2 (50% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$; a mixture of invertomers) δ 3.77-3.65 (m, 2H), 2.39 (s, 1.5H), 2.38 (s, 1.5H), 1.90-1.78 (m, 0.5H), 1.71-1.53 (m, 3H), 1.52-1.43 (m, 0.5H), 1.42.1.33 (m, 1H), 1.29-1.11 (m, 2H), 1.07-1.01 (m, 2H), 0.95 (t, *J* = 7.4Hz, 1H), 0.91-0.85 (m, 8H), 0.07-0.03 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 62.2, 61.3, 48.3, 44.4, 44.0, 39.8, 39.1, 38.5, 36.4, 29.6, 29.1, 26.1, 25.9, 19.0, 18.3, 12.7, 11.4, 1.0, -5.3. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{13}H_{30}NOSi$, 244.2091; found, 244.2090.

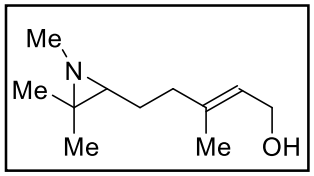
***7-Methyl-7-azabicyclo[4.1.0]heptanes (63e)*:**[27] Following the general aziridination procedure, the title aziridine was obtained as a light yellow oil (53 mg, 96% yield). TLC: R_f = 0.4 (50% EtOAc in hexane), whose spectral data were in accord with the literature values.



***9-(1-Methylaziridin-2-yl)nonan-1-ol (63f)*:** The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using Bu_3N:MeOH:CH_2Cl_2 (1:2:97) as an eluent to give the title compound as an oil (63 mg, 63% yield). TLC: R_f = 0.25 (5% MeOH in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (t, *J* = 6.6 Hz, 2H), 2.30 (s, 3H), 1.70 (brs, 1H), 1.58-1.53 (m, 2H), 1.48 (d, *J* = 3.5 Hz, 1H), 1.40-1.17 (m, 17H), 1.11 (d, *J* = 3.1, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 62.8, 53.4, 47.8, 40.8, 34.8, 32.9, 32.7, 29.6, 29.4, 29.3, 29.3, 27.5, 25.7. HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{12}H_{26}NO$: 200.2009, found: 200.2017.

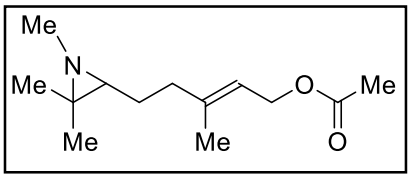


***(E)-3-Methyl-5-(1,3,3-trimethylaziridin-2-yl)pent-2-en-1-ol (63g)*:** The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using Bu_3N:MeOH:CH_2Cl_2 (1:4:95) as an eluent to give the title product as an oil (66 mg, 73% yield). TLC: R_f = 0.3 (10% MeOH in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47-5.40 (m, 1H), 4.15 (d, *J* = 6.9 Hz, 2H), 2.36 (s, 3H), 2.20-2.04 (m, 2H), 1.68 (s, 3H), 1.58-1.42 (m, 2H), 1.24 (s, 1H), 1.17 (s, 3H), 1.09 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.2, 123.7, 59.3, 52.0, 39.5, 39.3, 37.7,



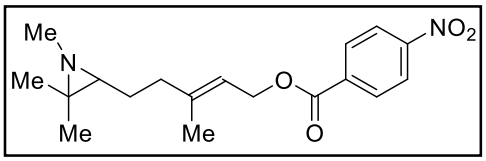
27.5, 21.6, 17.9, 16.2. HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{11}H_{22}NO$: 184.1623, found: 184.1642.

(E)-3-Methyl-5-(1,3,3-trimethylaziridin-2-yl)pent-2-en-1-yl acetate (63h):[17] Following



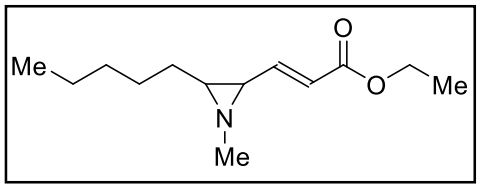
the general aziridination procedure, the title aziridine was obtained as an oil (106 mg, 94% yield). ^1H NMR and ^{13}C NMR data were in accord with the literature value.

(E)-3-Methyl-5-(1,3,3-trimethylaziridin-2-yl)pent-2-enyl 4-nitrobenzoate (63i): Following the general aziridination procedure, the title product was obtained as a thick



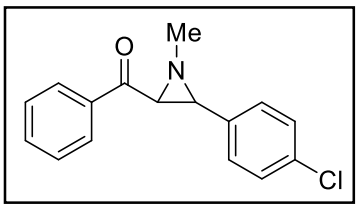
yellow liquid. (158 mg, 96% yield). TLC: $R_f = 0.3$ (40% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 8.28-8.23 (m, 2H), 8.21-8.16 (m, 2H), 5.52-5.44 (m, 1H), 4.87 (d, $J = 7.1$ Hz, 2H), 2.34 (s, 3H), 2.25-2.09 (m, 2H), 1.77 (s, 3H), 1.62-1.43 (m, 2H), 1.15 (s, 3H), 1.07 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.6, 150.4, 143.1, 135.8, 130.6, 123.4, 117.9, 62.6, 51.8, 39.5, 39.3, 37.7, 27.5, 21.7, 17.9, 16.4. HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{18}H_{25}N_2O_4$: 333.1809, found: 333.1815.

(E)-Ethyl-3-(1-methyl-3-pentylaziridin-2-yl)acrylate (63j): The product was prepared



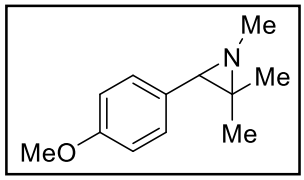
following the general aziridination procedure and the crude product was purified by silica gel column chromatography using Bu_3N:EtOAc:hexane (1:29:70) as an eluent to give the title product as a colorless oil (64 mg, 58% yield). TLC: $R_f = 0.6$ (20% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, $J = 15.6$, 7.8 Hz, 1H), 6.00 (dd, $J = 15.6$, 0.7 Hz, 1H), 4.22-4.09 (m, 2H), 2.38 (s, 3H), 1.91 (t, $J = 7.1$ Hz, 1H), 1.59 (q, $J = 5.8$ Hz, 1H), 1.31-1.19 (m, 10H), 0.88 (t, $J = 7.0$ Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 145.9, 123.0, 60.1, 49.3, 47.4, 45.0, 31.4, 28.4, 27.2, 22.5, 14.2, 13.9. HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{13}H_{24}NO_2$: 226.1802, found: 226.1800.

***(3-(4-Chlorophenyl)-1-methylaziridin-2-yl) (phenyl) methanone (63k)*:** The product was



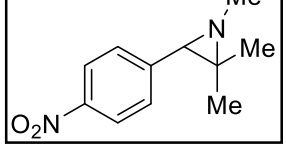
prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (1:5:94) as an eluent to give the title compound as a light yellow sticky semi-solid (81 mg, 60% yield). TLC: R_f = 0.5 (10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7, 2H), 7.32 - 7.23 (m, 4H), 3.53 (d, *J* = 2.4 Hz, 1H), 3.33 (d, *J* = 2.2 Hz, 1H), 2.67 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.1, 137.9, 137.2, 133.5, 133.2, 128.7, 128.5, 128.4, 127.5, 48.7, 48.5, 38.6. HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{16}H_{15}ClNO$: 272.0837, found: 272.0843.

***3-(4-Methoxyphenyl)-1,2,2-trimethylaziridine (63l)*:** The product was prepared following



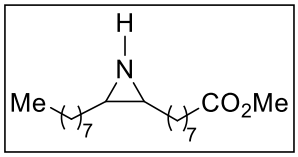
the general aziridination procedure and the crude product was purified by silica gel column chromatography using Bu_3N:EtOAc:hexane (1:5:94) as an eluent to give the title compound as a light yellow sticky semi-solid (74 mg, 78% yield). TLC: R_f = 0.5 (10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.17 (m, 2H), 6.87-6.81 (m, 2H), 3.79 (s, 3H), 2.54 (s, 3H), 2.28 (s, 1H), 1.33 (s, 3H), 0.88 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.3, 130.8, 128.4, 113.4, 55.2, 53.9, 42.3, 39.5, 21.4, 17.6. HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{12}H_{17}NO$: 192.1344, found: 192.1389.

***1,2,2-Trimethyl-3-(4-nitrophenyl)aziridine (63m)*:** The product was prepared following

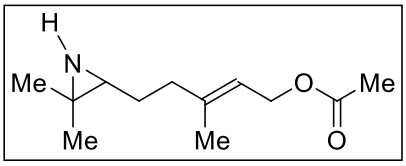


the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (1:5:94) as an eluent to give the title compound as a light yellow sticky semi-solid (62 mg, 60% yield). TLC: R_f = 0.5 (10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.12 (m, 2H), 7.47-7.42 (d, 2H), 2.57 (s, 3H), 2.39(s, 1H), 1.38 (s, 3H), 0.87 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 146.9, 146.7, 128.18, 123.2, 53.6, 44.2, 39.3, 21.3, 17.6. HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{11}H_{14}N_2O_2$: 207.1139, found: 207.1089.

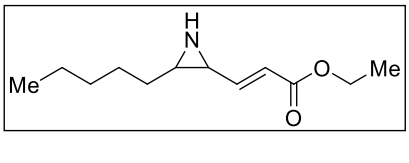
***Methyl 8-(3-octylaziridin-2-yl)octanoate 64a*:**[17] The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:MeOH:CH_2Cl_2 (1:2:97) as an eluent to give the title compound as an oil (129 mg, 83% yield), whose spectral data were in accord with the literature values.



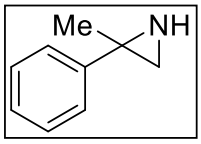
***(E)-5-(3,3-Dimethylaziridin-2-yl)-3-methylpent-2-enyl acetate (64b)*:**[17] The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:MeOH:CH_2Cl_2 (1:2:97) as an eluent to give the title compound as oil (89 mg, 85% yield), whose spectral data were in accord with the litera-ture values.



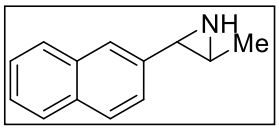
***(E)-Ethyl 3-(3-pentylaziridin-2-yl)acrylate (64c)*:** The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (1:49:50) as an eluent to give the title compound as a light yellow oil (40 mg, 38% yield). TLC: Rf = 0.4 (40% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, J = 15.6, 8.3 Hz, 1H), 6.07 (d, J = 15.6 Hz, 1H), 4.23-4.14 (m, 2H), 2.89 (brs, 1H), 2.70 (brs, 1H), 2.33 (d, J = 5.3 Hz, 1H), 1.54-1.36 (m, 2H), 1.34 -1.19 (m, 7H), 0.87 (t, J = 7.0 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 145.6, 123.7, 60.3, 38.9, 35.4, 31.4, 29.1, 27.3, 22.5, 14.2, 13.9. HRMS (ESI) [M+H]+ calcd. for $C_{12}H_{22}NO_2$: 212.1645, found: 212.1633.



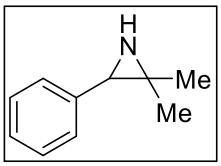
***2-Methyl-2-phenylaziridine (64d)*:**[17] The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (1:19:80) as an eluent to give the title compound as a colorless oil (37 mg, 55% yield). TLC: Rf = 0.3 (50% EtOAc in hexane), whose spectral data were in accord with the literature values.



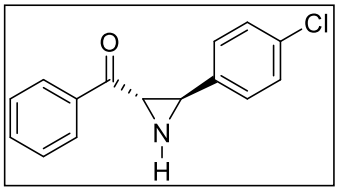
***(E)-2-Methyl-3-(naphthalene-2-yl)aziridine (64e)*:** The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chro-matography using $^{t}Bu_3N$:EtOAc:hexane (1:19:80) as an eluent to give the title compound as a colorless oil (59 mg, 64% yield) TLC: Rf = 0.4 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.75 (m, 3H), 7.68 (s, 1H), 7.49-7.39 (m, 2H), 7.31-7.24 (m, 1H), 2.83 (d, J = 2.9 Hz, 1H), 2.27-2.19 (m, 1H), 1.42 (d, J = 5.4Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 137.8, 133.3, 132.6, 128.1, 127.6, 127.5, 126.1, 125.5, 124.3, 123.5, 40.6, 37.2, 19.6. HRMS (ESI) m/z [M+H]+ calcd. for $C_{13}H_{14}N$, 184.1048; found, 184.1118.



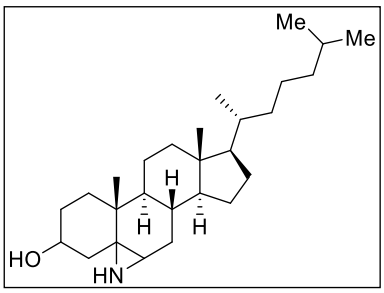
***2,2-Dimethyl-3-phenylaziridine (64f)*:**[17] The product was pre-pared following the general aziridination procedure and the crude product was purified by silica gel column chromatog-raphy using $^{t}Bu_3N$:EtOAc:hexane (1:19:80) as an eluent to give the title compound as a colorless oil (53 mg, 72% yield). TLC: Rf = 0.5 (50% EtOAc in hexane), whose spectral data were in accord with the literature values.



***(3-(4-Chlorophenyl)aziridin-2-yl)(phenyl)methanone (64g)*:**[28] The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (1:9:90) as an eluent to give the title compound as a light yellow sticky solid (45 mg, 35% yield), whose spectral data were in accord with the literature values.

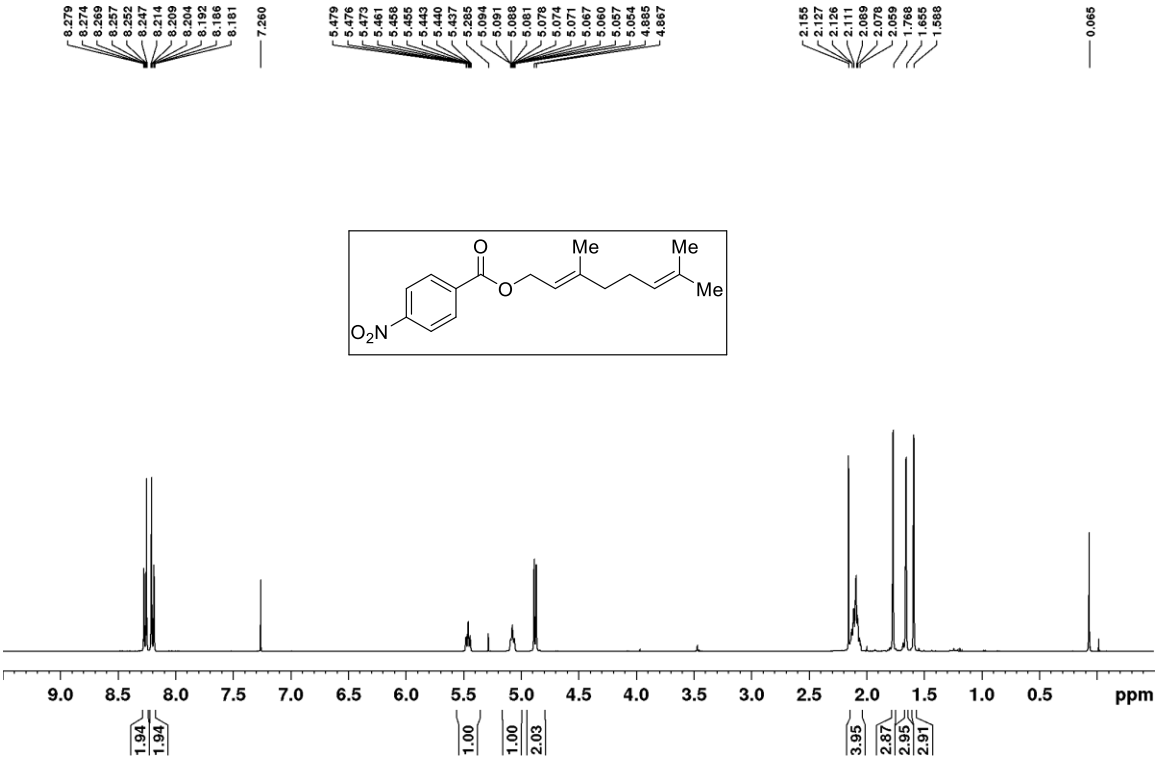


***Aziridinylcholestan-3-β-ol (64h)*:**[17] The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using EtOAc:hexane (60:40) as an eluent to give the title compound as an off white solid (73 mg, 70% yield). ^{1}H and ^{13}C NMR data were in accord with the literature values.

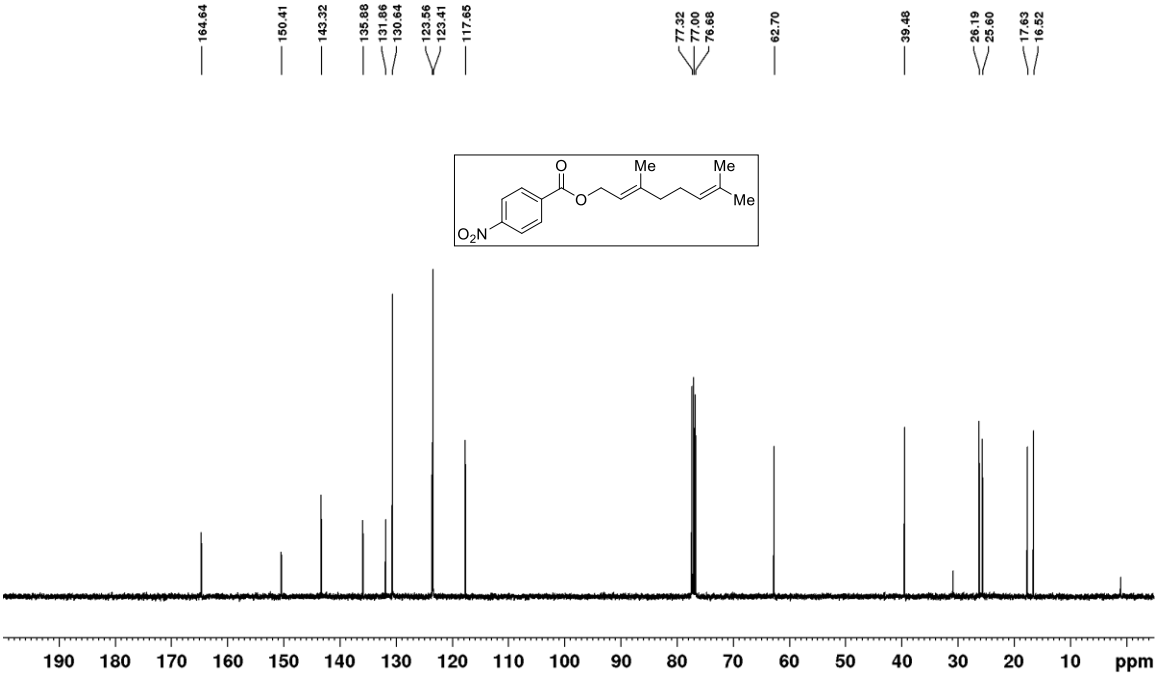


2.8 ^{1}H, $^{13}C\{^{1}H\}$ NMR Spectra of the starting materials

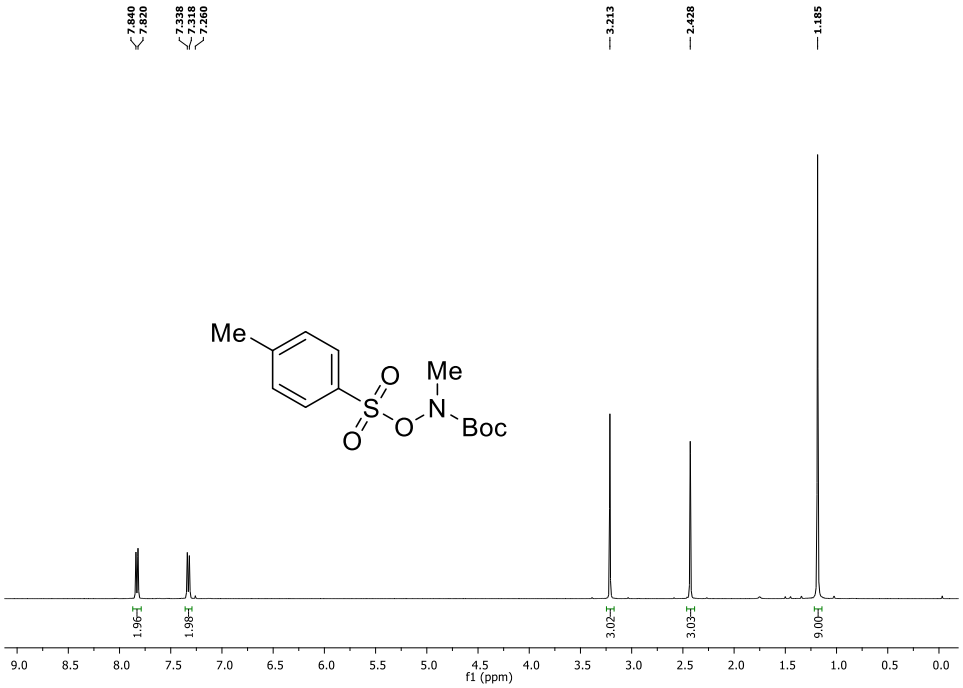
^{1}H NMR spectrum of compound **61i** (400 MHz/$CDCl_3$)



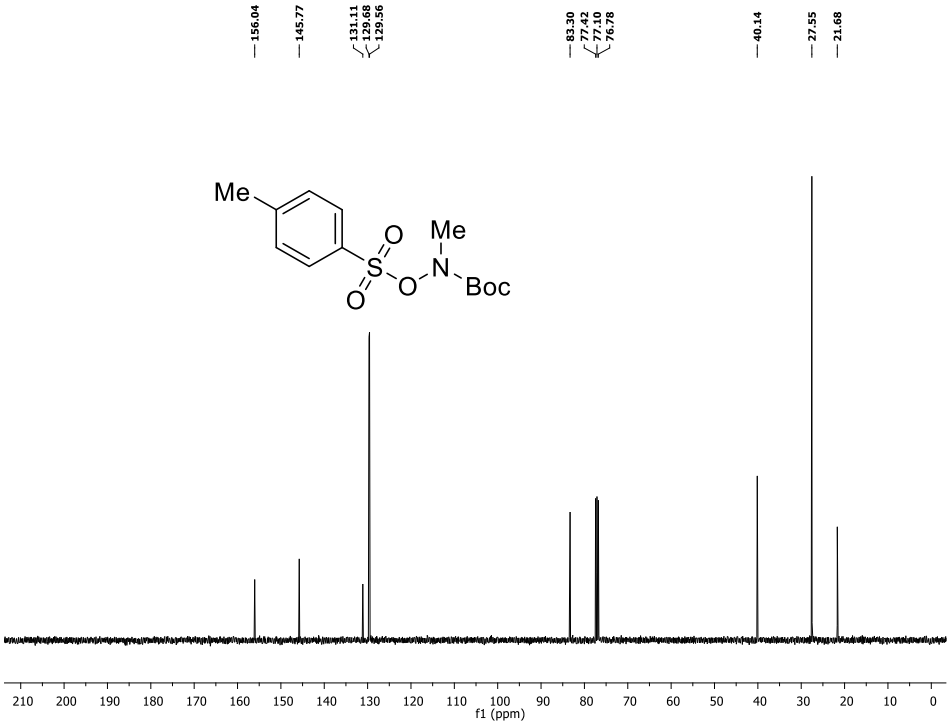
$^{13}C\{^{1}H\}$ NMR spectrum of compound **61i** (100 MHz/$CDCl_3$)



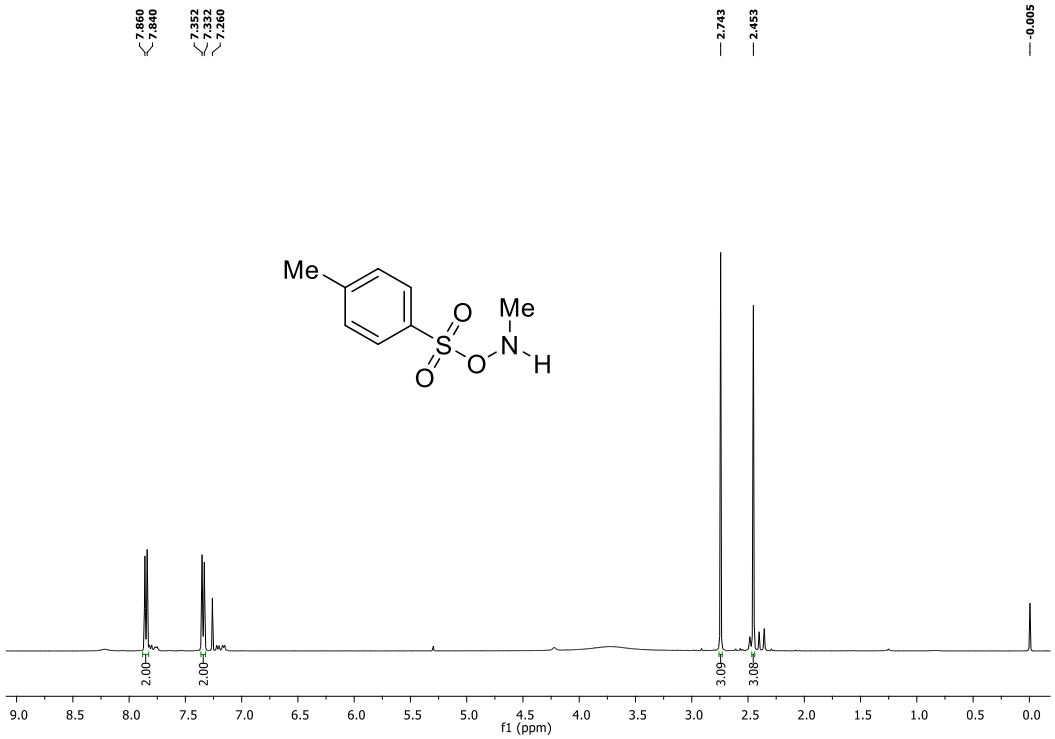
^{1}H NMR spectrum of compound **65** (400 MHz/$CDCl_3$)



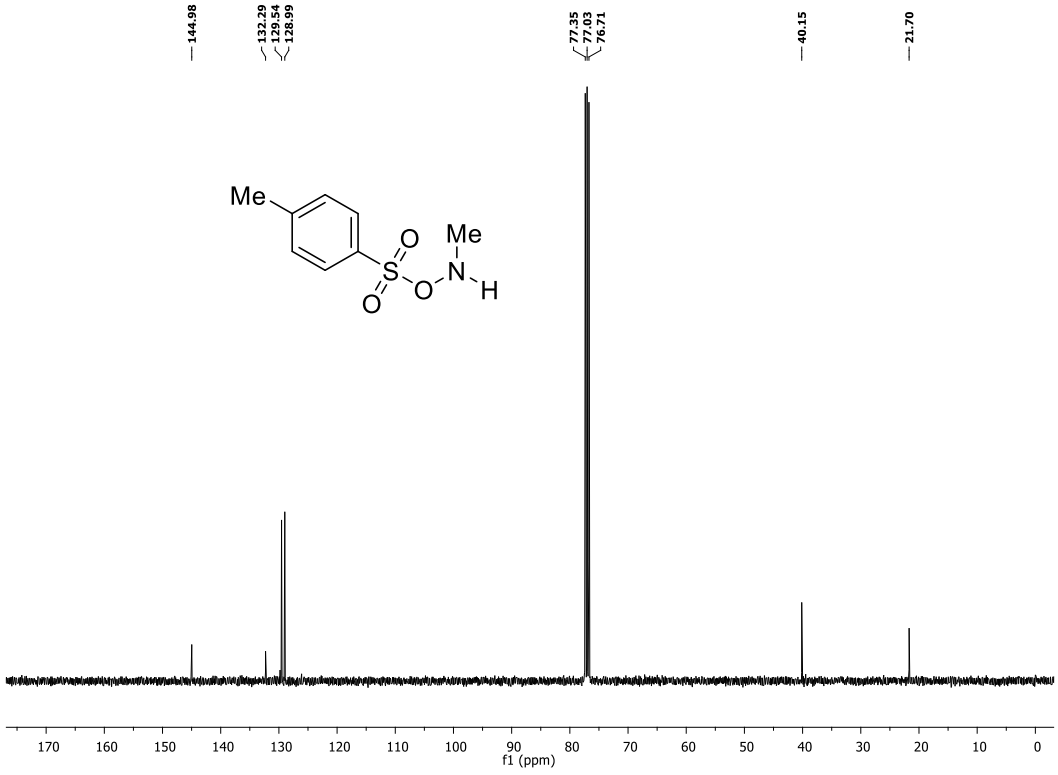
^{13}C{^{1}H} NMR spectrum of compound **65** (100 MHz/$CDCl_3$)



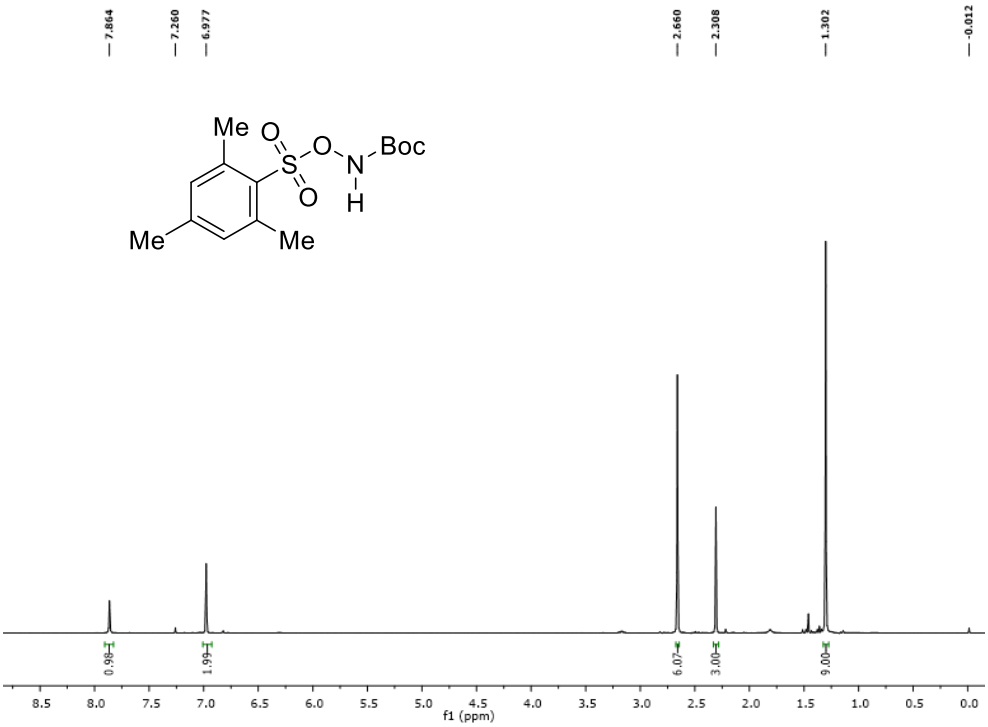
^{1}H NMR spectrum of compound **62a** (400 MHz/$CDCl_3$)



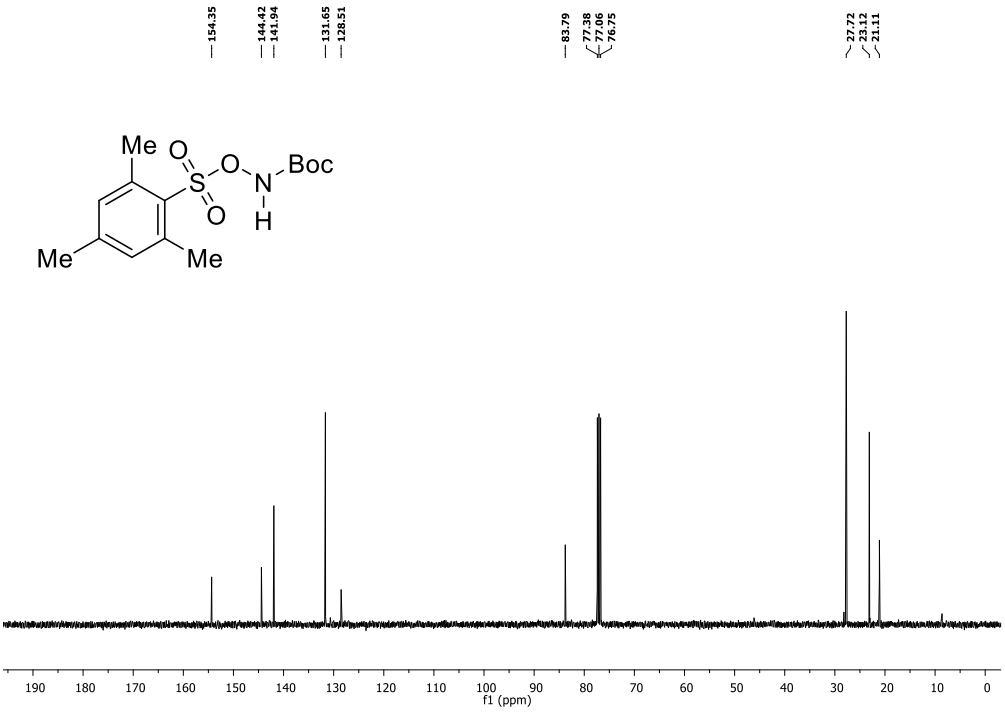
^{13}C{^{1}H} NMR spectrum of compound **62a** (100 MHz/$CDCl_3$)



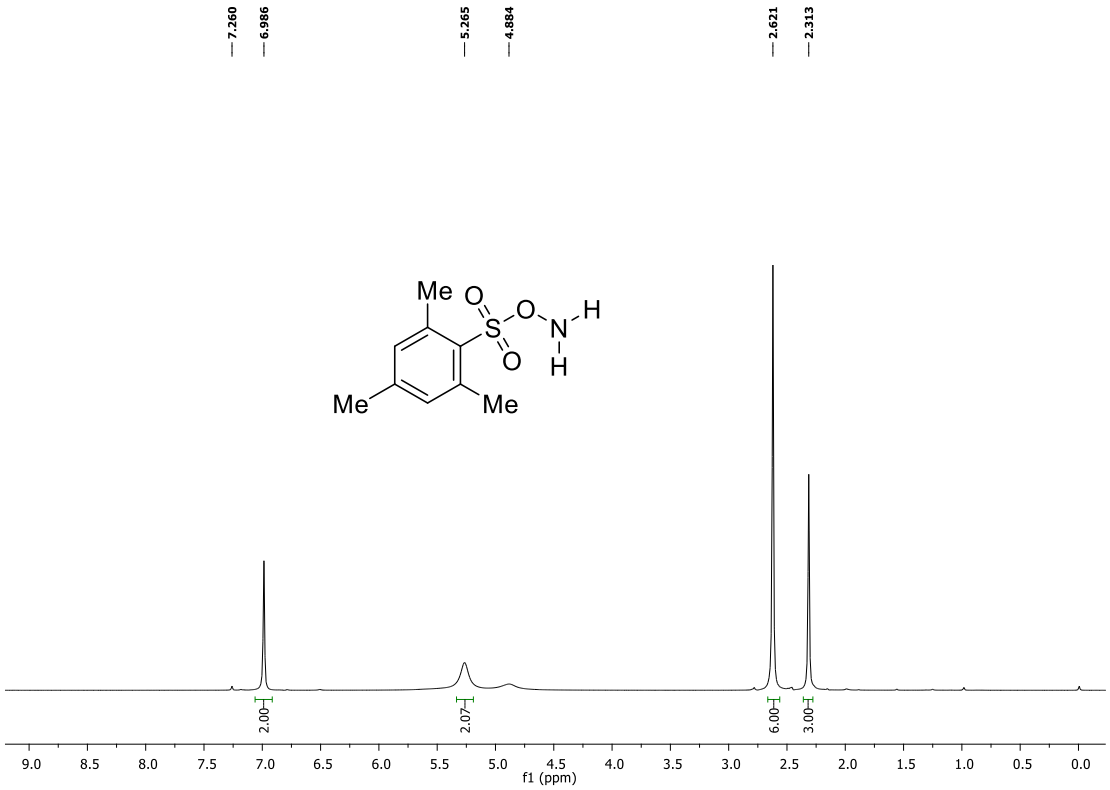
^{1}H NMR spectrum of compound **66** (400 MHz/$CDCl_3$)



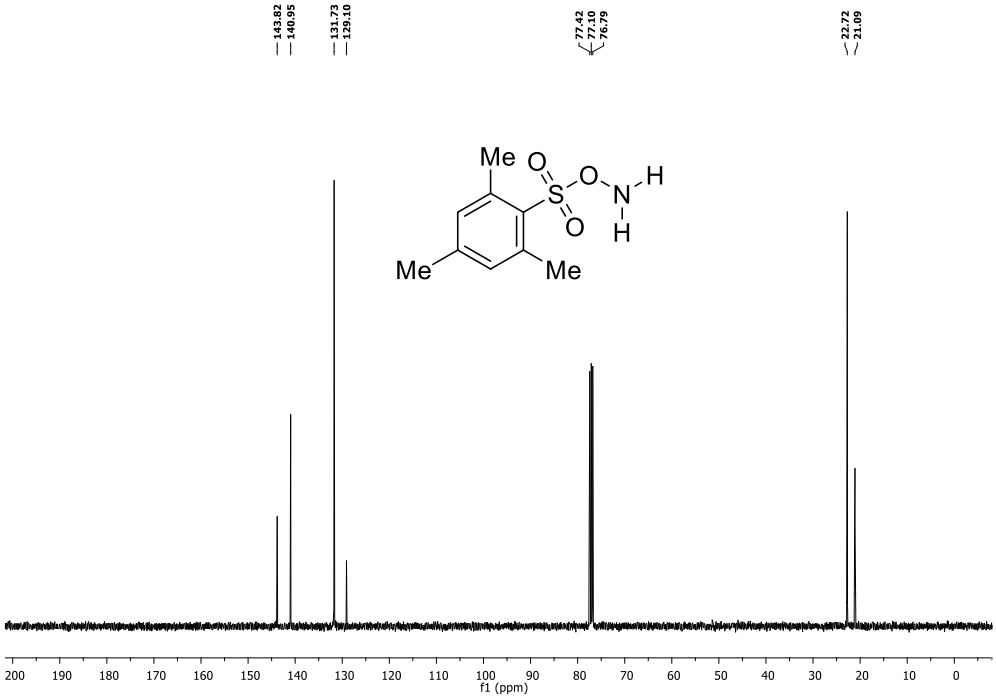
^{13}C{^{1}H}NMR spectrum of compound **66** (100 MHz/$CDCl_3$)



^{1}H NMR spectrum of co mpound **62b** (400 MHz/$CDCl_3$)

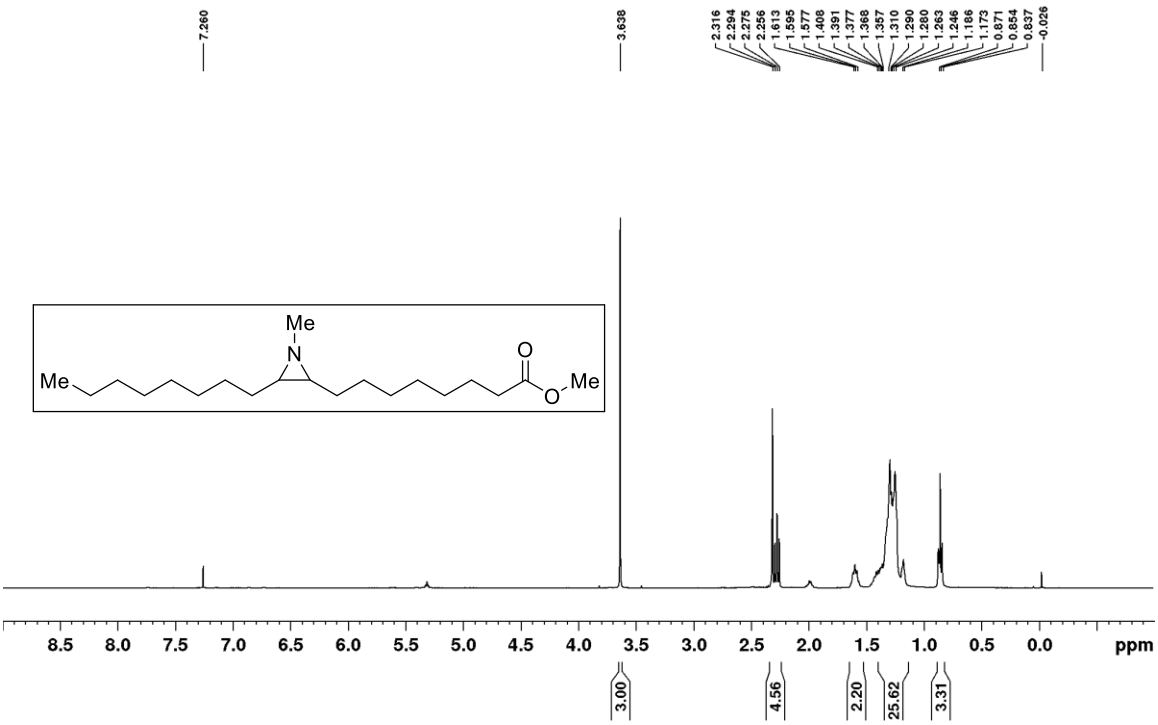


13C{1H} NMR spectrum of co mpound **62b** (100 MHz/$CDCl_3$)

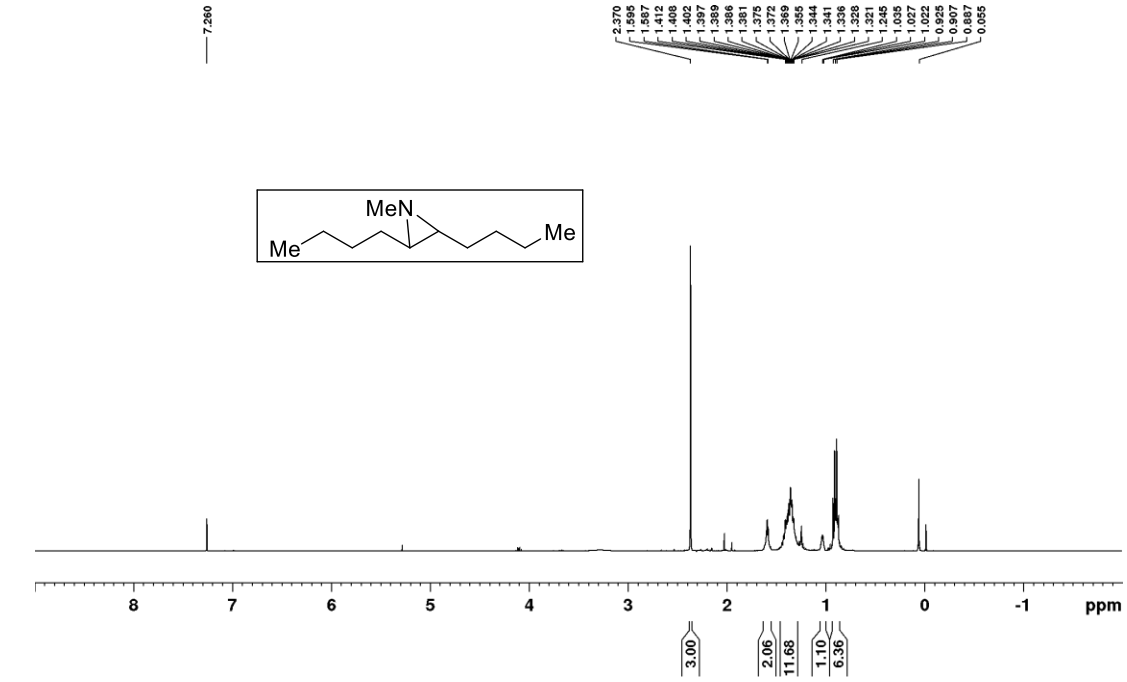


2.9 ^{1}H, $^{13}C\{^{1}H\}$ NMR and HPLC Spectra of the products

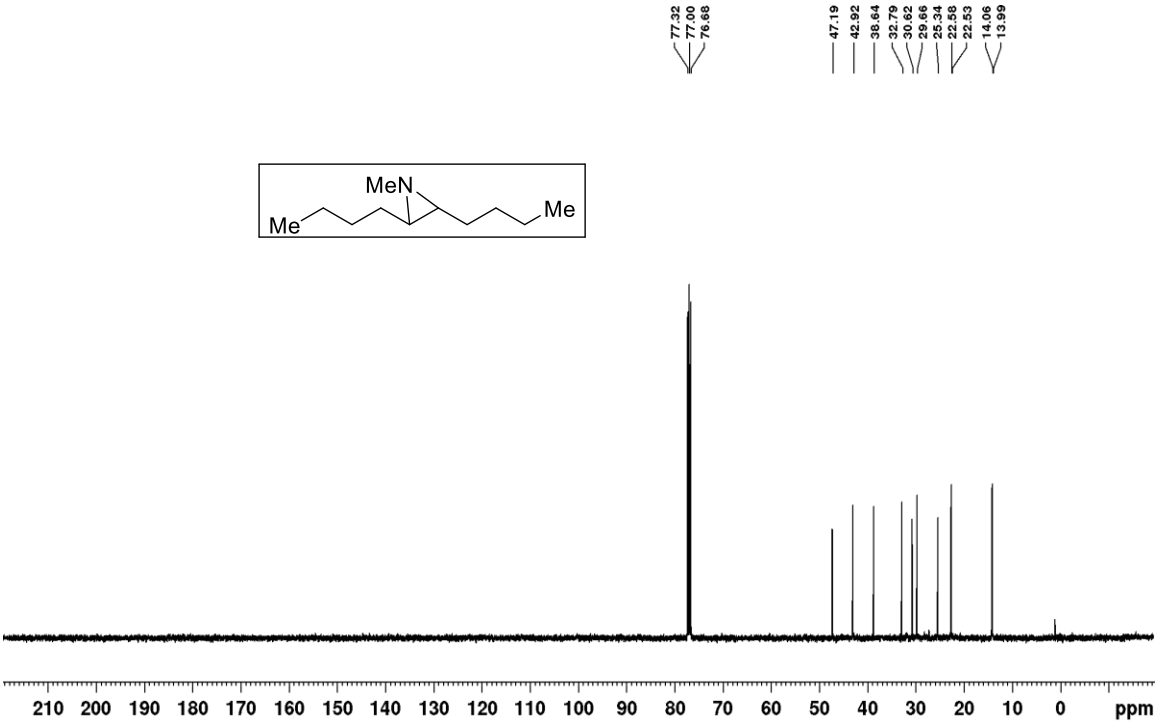
^{1}H NMR spectrum of compound **63a** (400 MHz/$CDCl_3$)



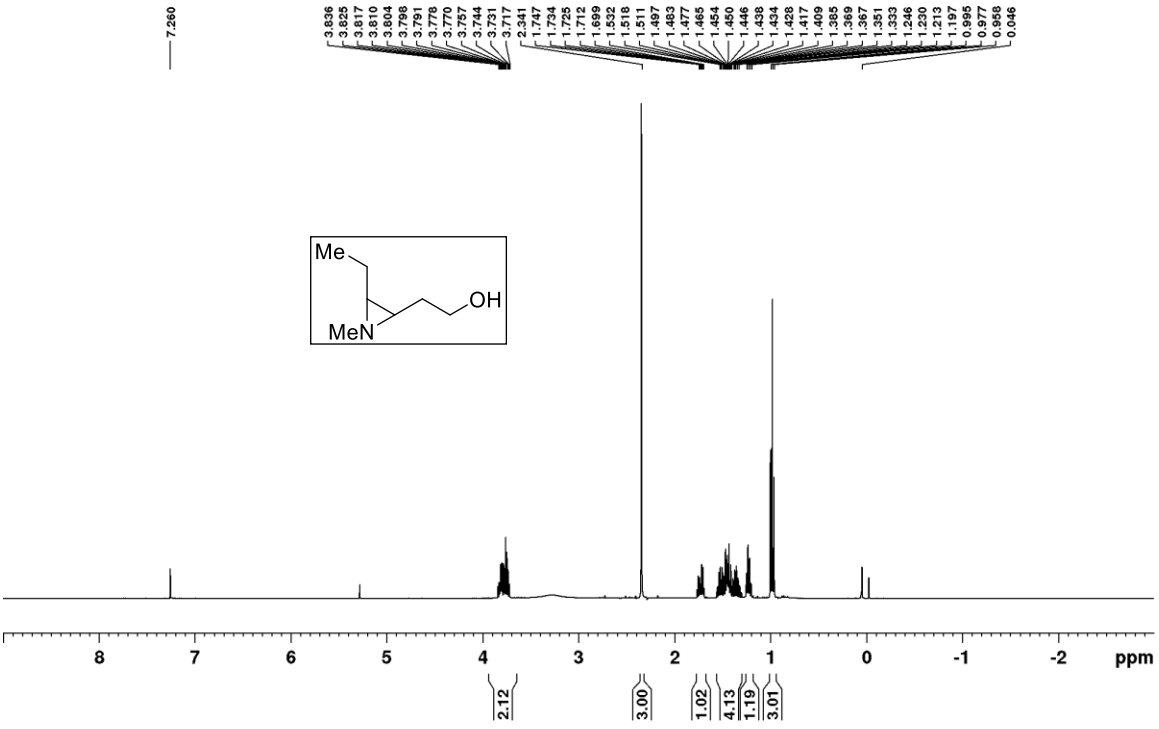
^{1}H NMR spectrum of compound **63b** (400 MHz/$CDCl_3$)



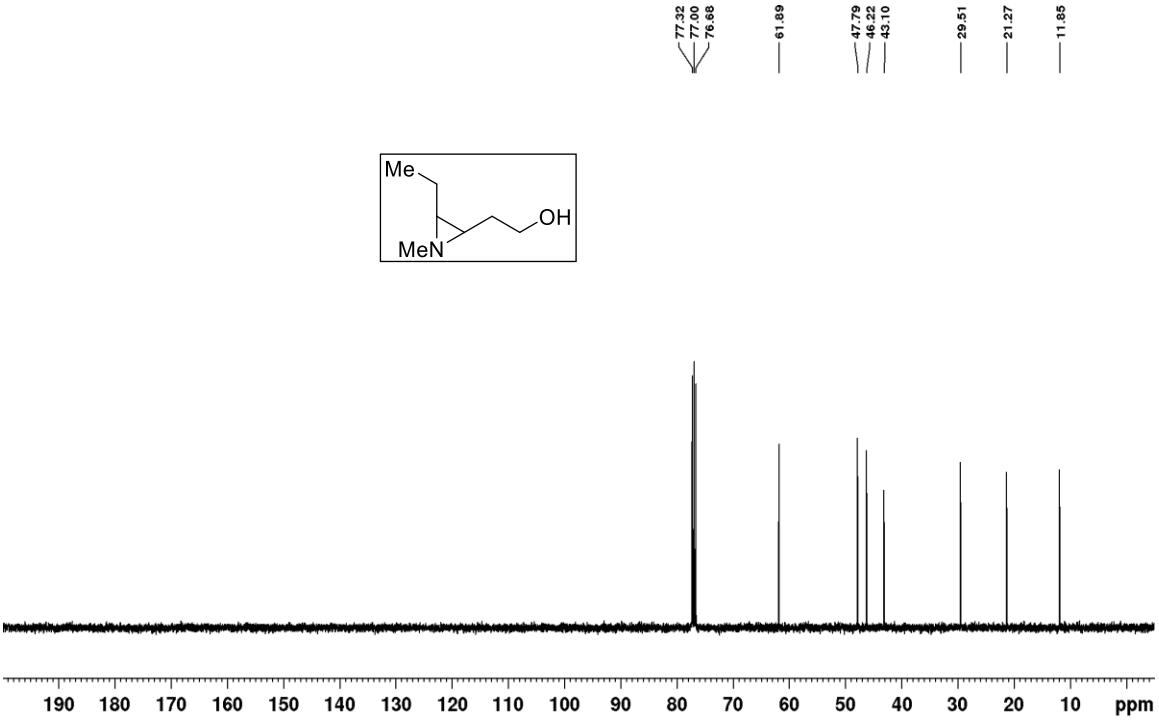
$^{13}C\{^{1}H\}$ NMR spectrum of compound **63b** (100 MHz/$CDCl_3$)



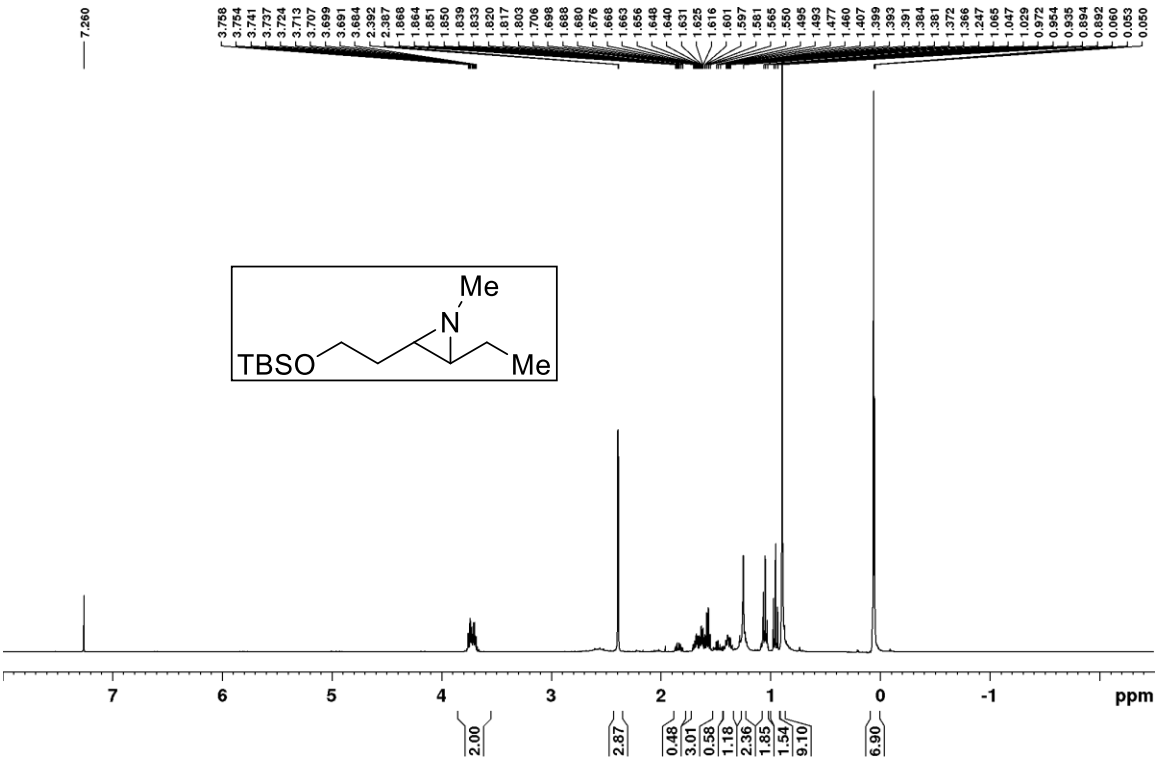
^{1}H NMR spectrum of compound **63c** (400 MHz/$CDCl_3$)



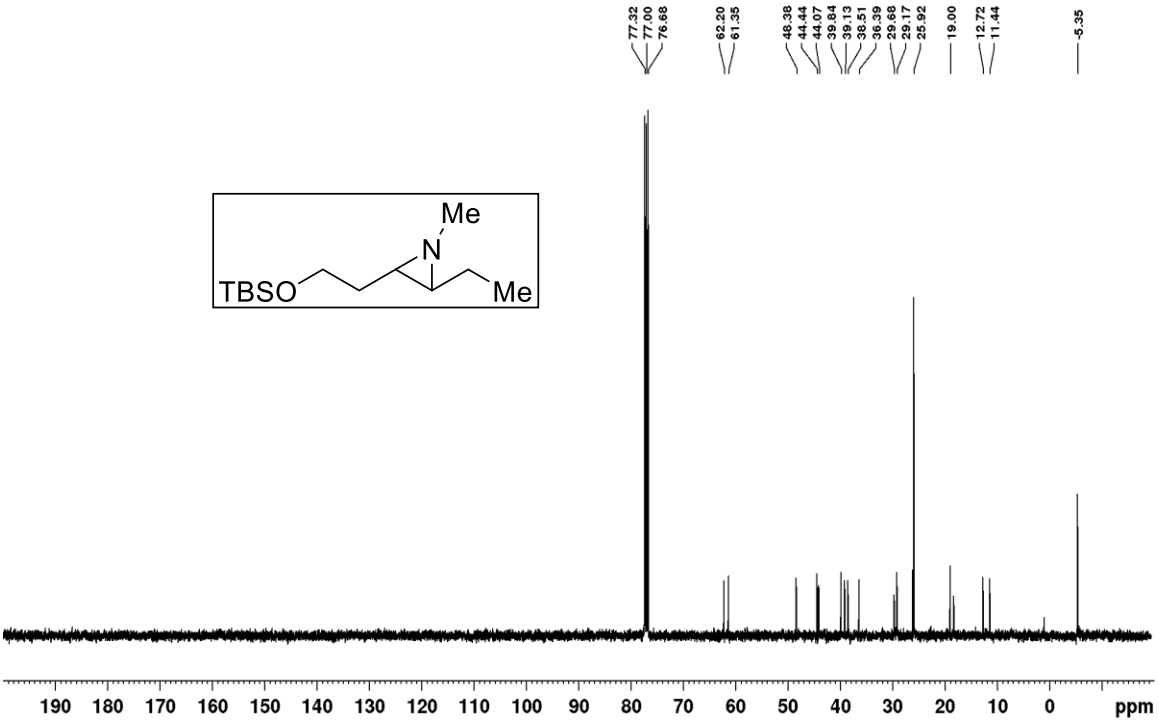
$^{13}C\{^{1}H\}$ NMR spectrum of compound **63c** (100 MHz/$CDCl_3$)



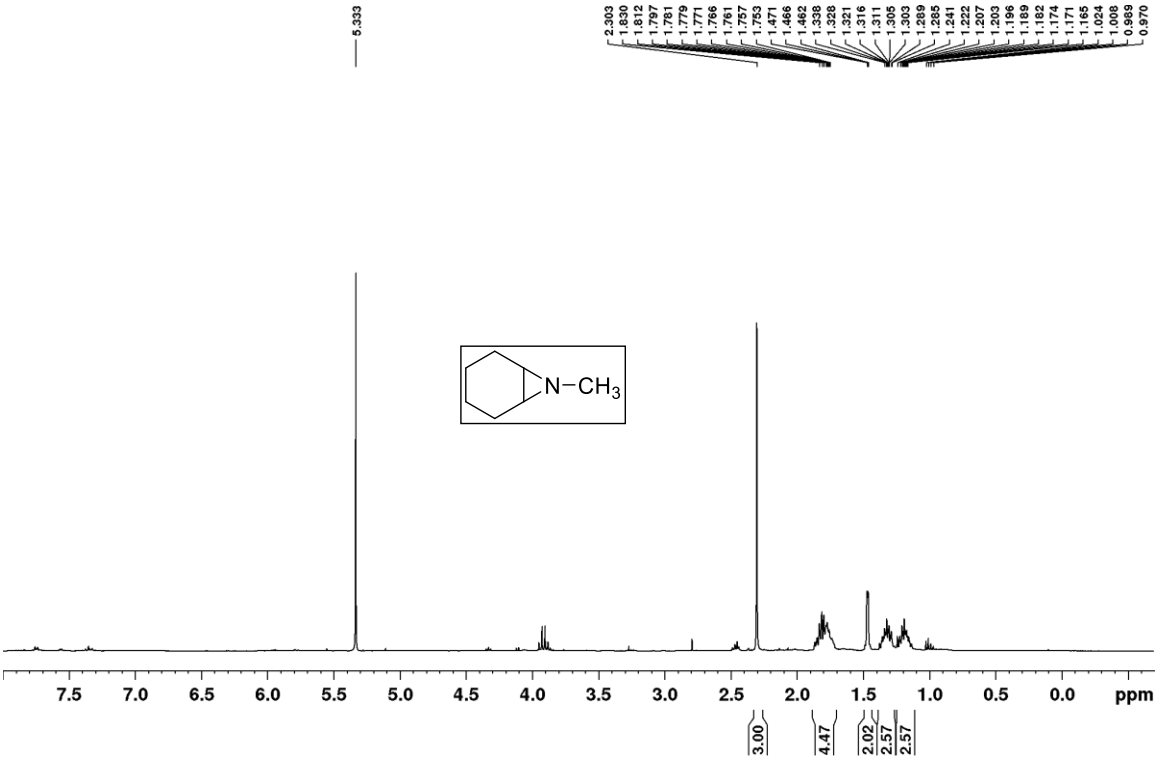
^{1}H NMR spectrum of compound **63d** (400 MHz/$CDCl_3$)



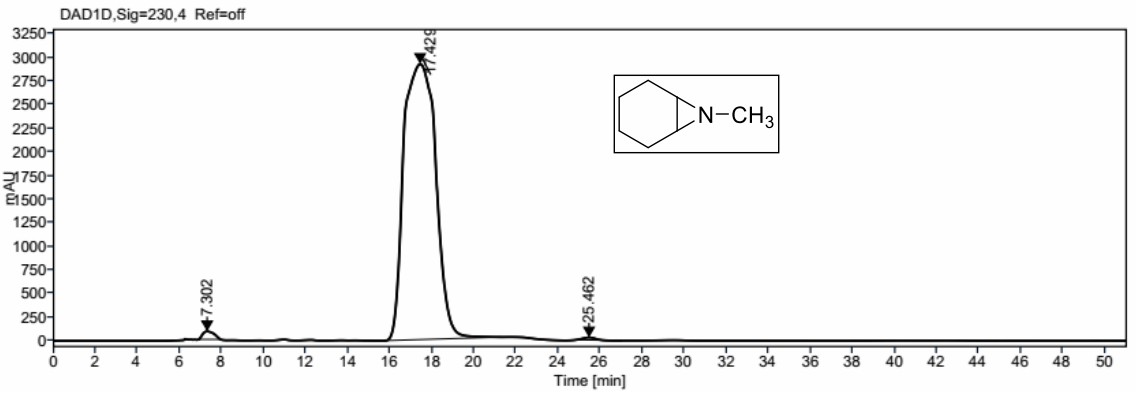
$^{13}C\{^{1}H\}$ NMR spectrum of compound **63d** (100 MHz/$CDCl_3$)



^{1}H NMR spectrum of compound **63e** (400 MHz/$CDCl_3$)



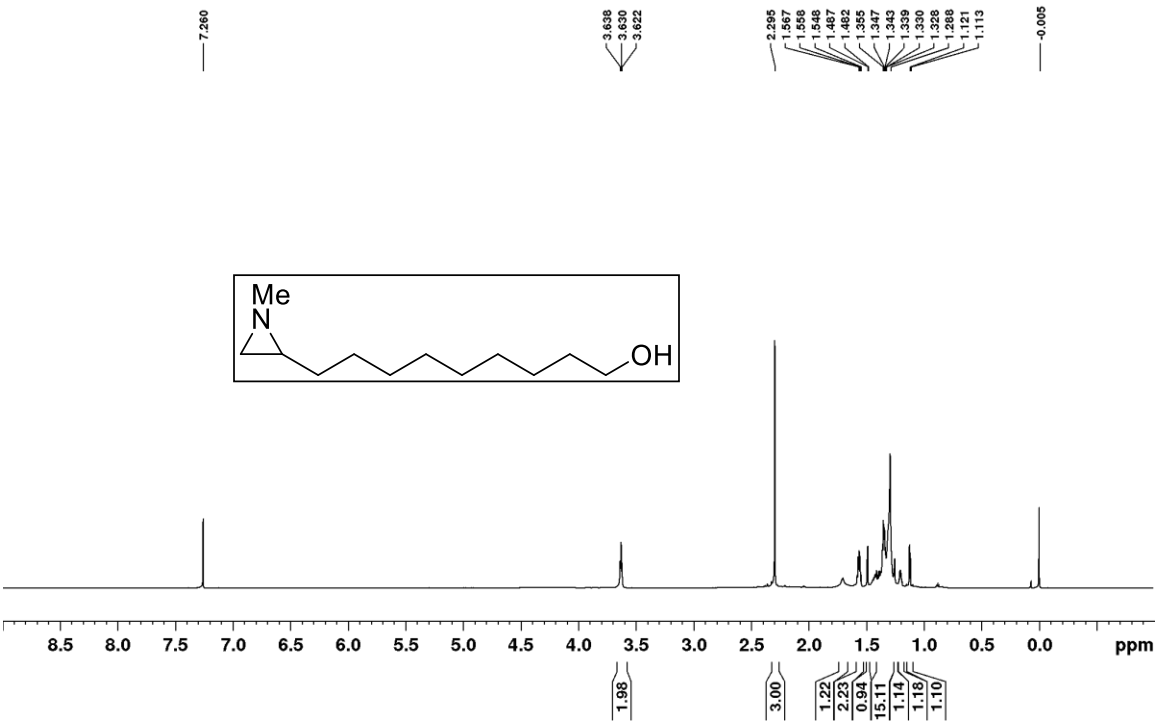
HPLC spectrum of compound **63e** (crude product) (Chiralcel IA, IPA/hexane:2/98, 0.5 ml/min)



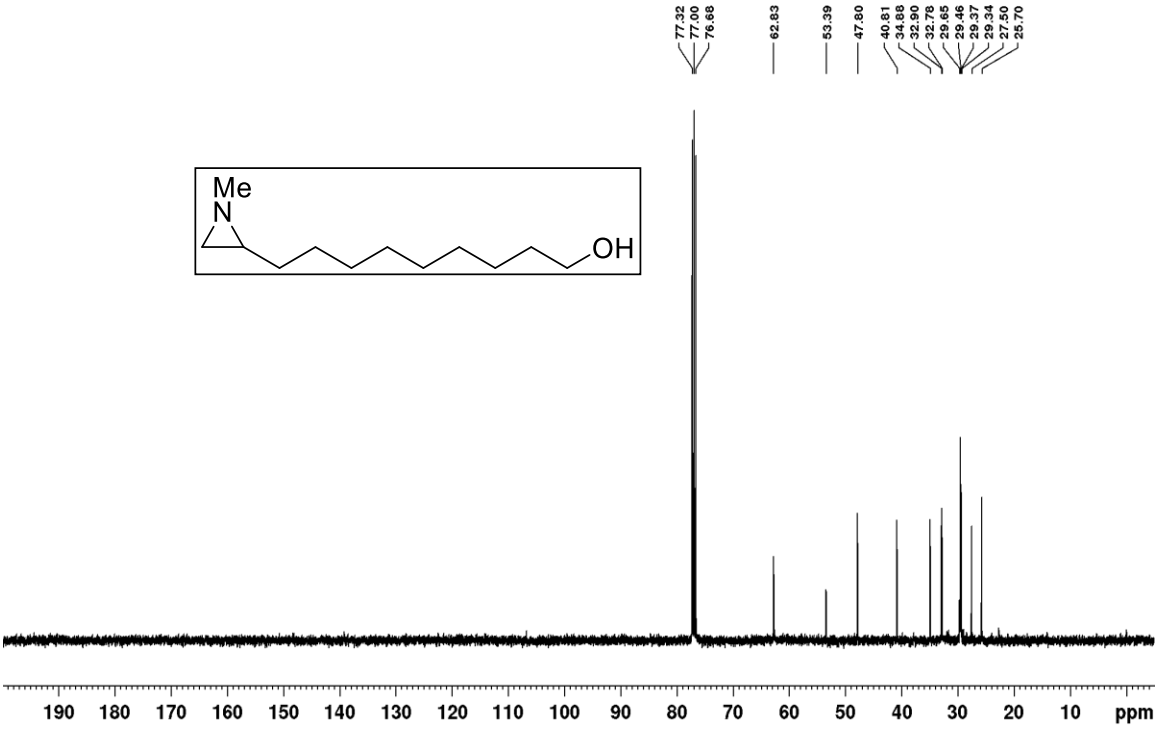
Signal: DAD1D,Sig=230,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
7.302	MM m	0.67	3238.23	84.73	1.03	
17.429	BB	5.59	309518.33	2920.69	98.64	
25.462	MM m	0.64	1029.37	26.42	0.33	
		Sum	313785.93			

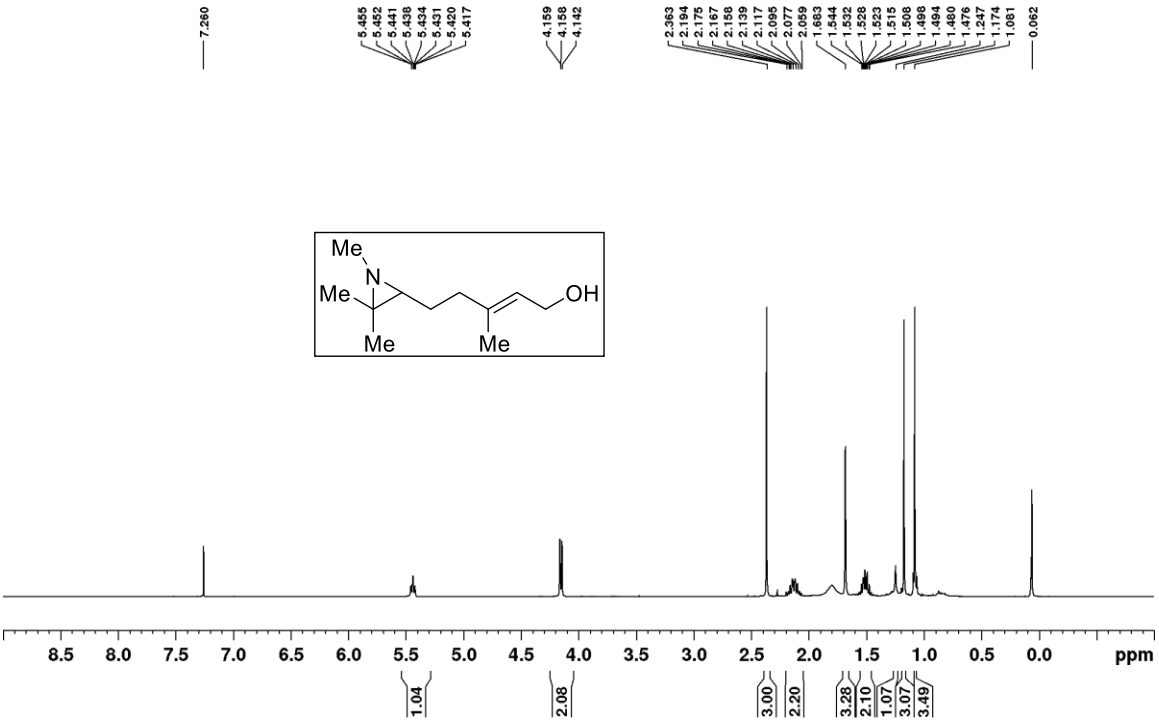
^{1}H NMR spectrum of compound **63f** (400 MHz/$CDCl_3$)



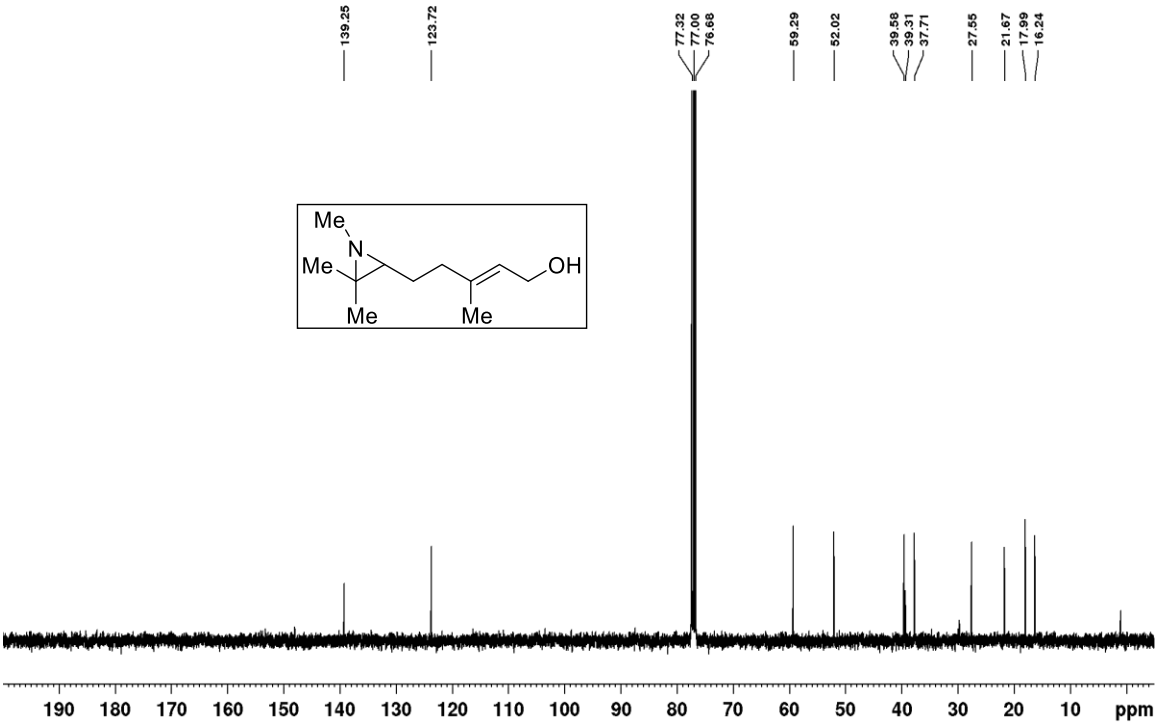
$^{13}C\{^{1}H\}$ NMR spectrum of compound **63f** (100 MHz/$CDCl_3$)



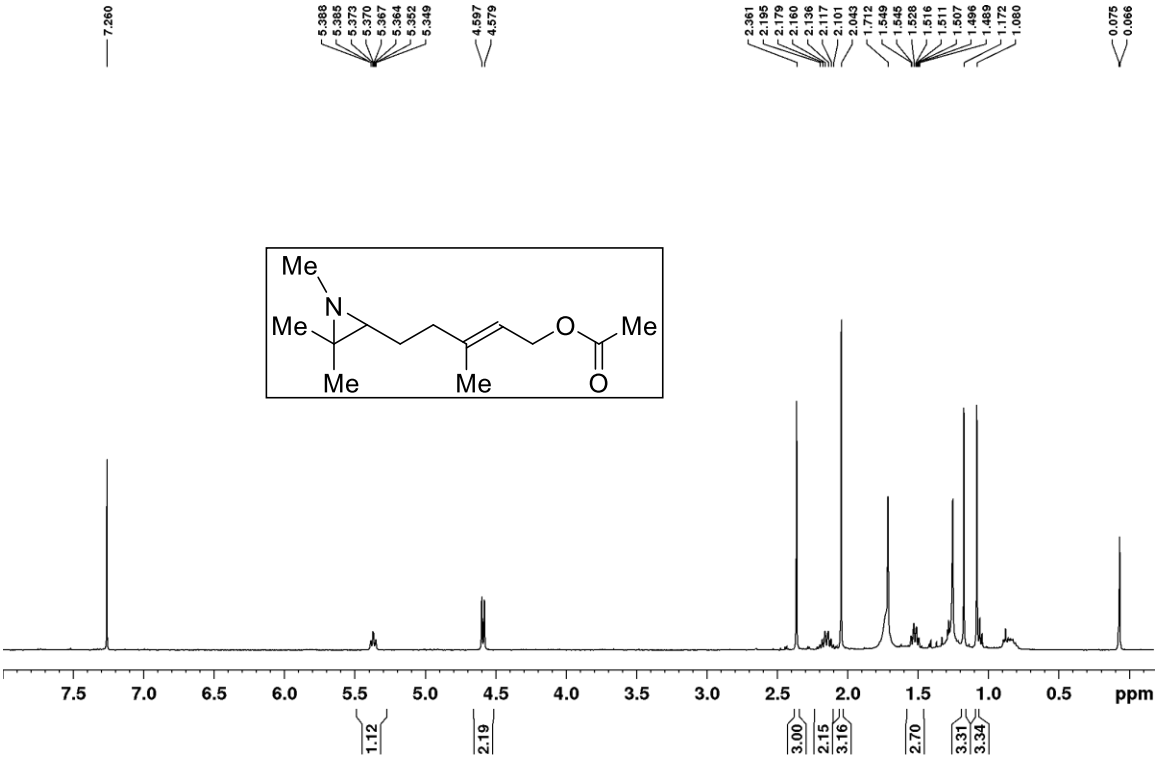
^{1}H NMR spectrum of compound **63g** (400 MHz/$CDCl_3$)



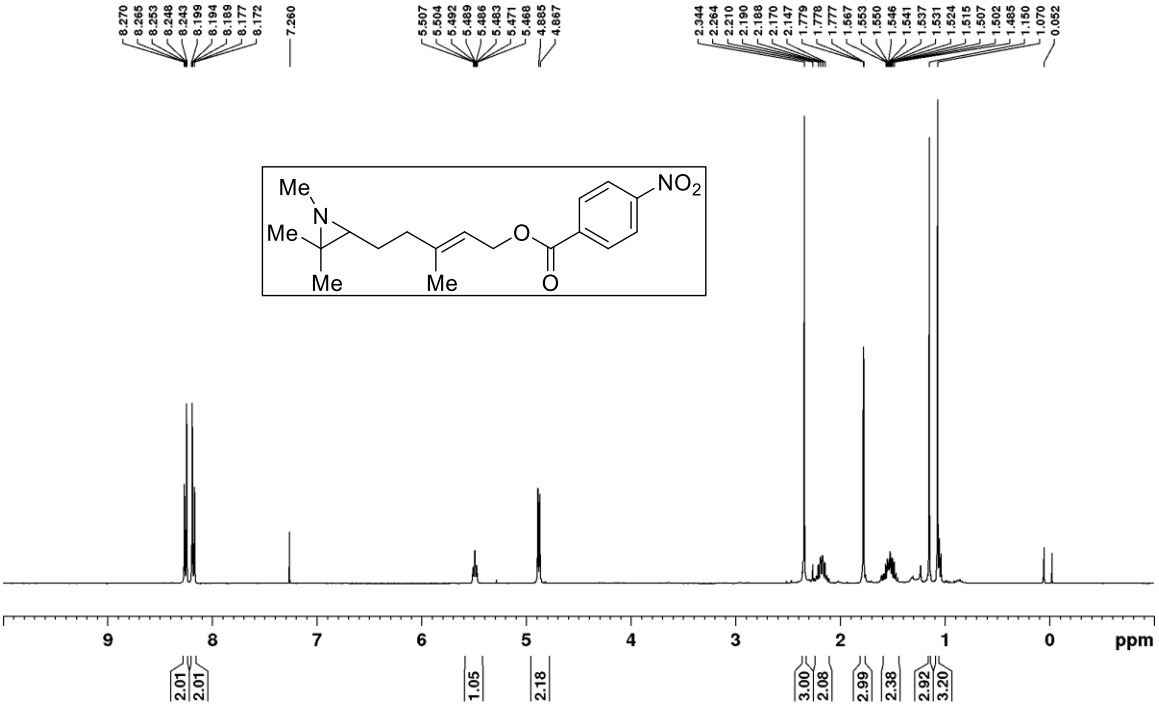
$^{13}C\{^{1}H\}$ NMR spectrum of compound **63g** (100 MHz/$CDCl_3$)



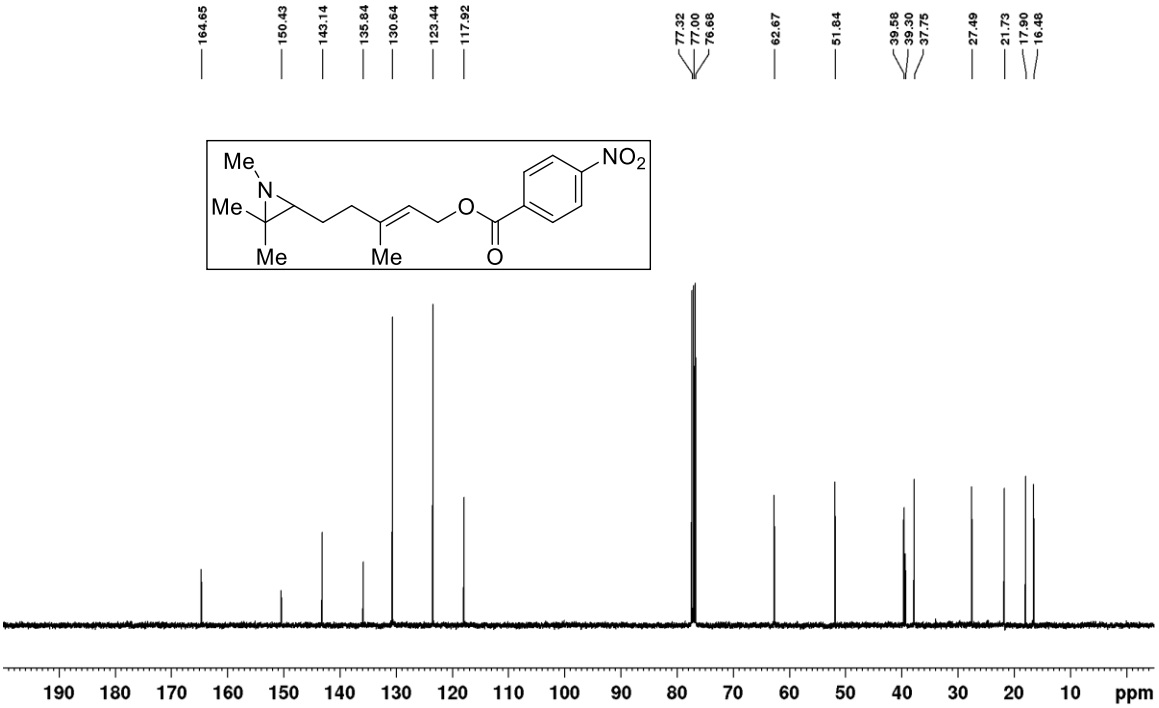
^{1}H NMR spectrum of compound **63h** (crude product) (400 MHz/$CDCl_3$)



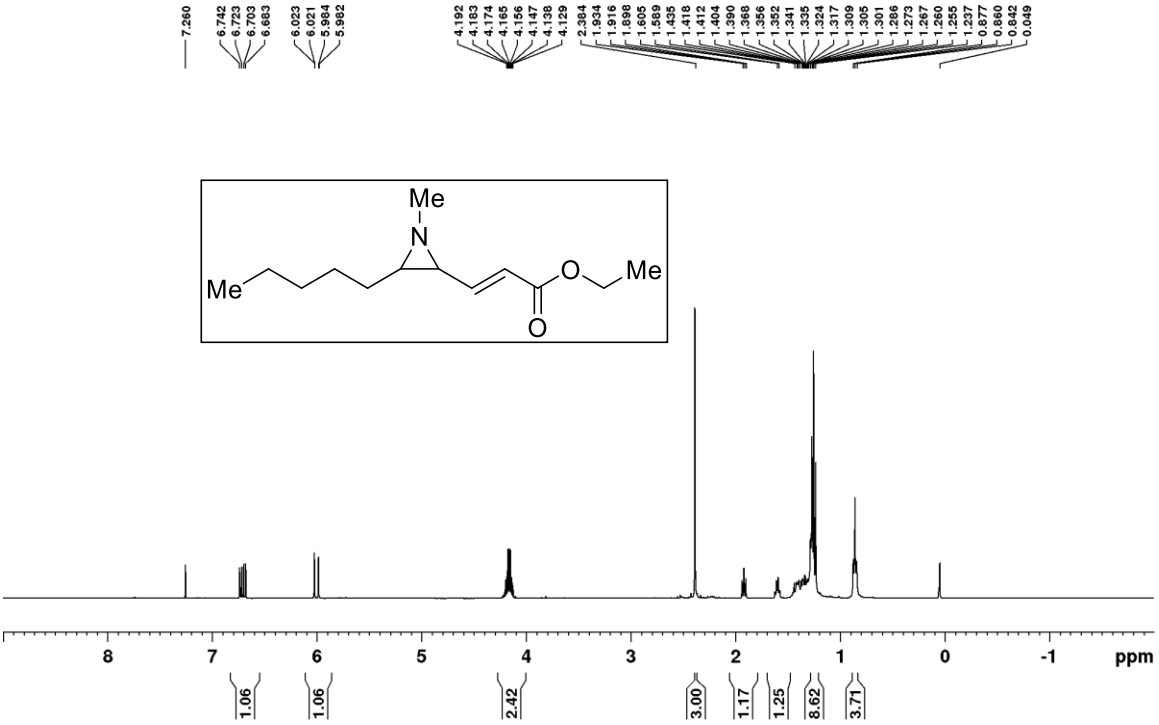
^{1}H NMR spectrum of compound **63i** (crude product) (400 MHz/$CDCl_3$)



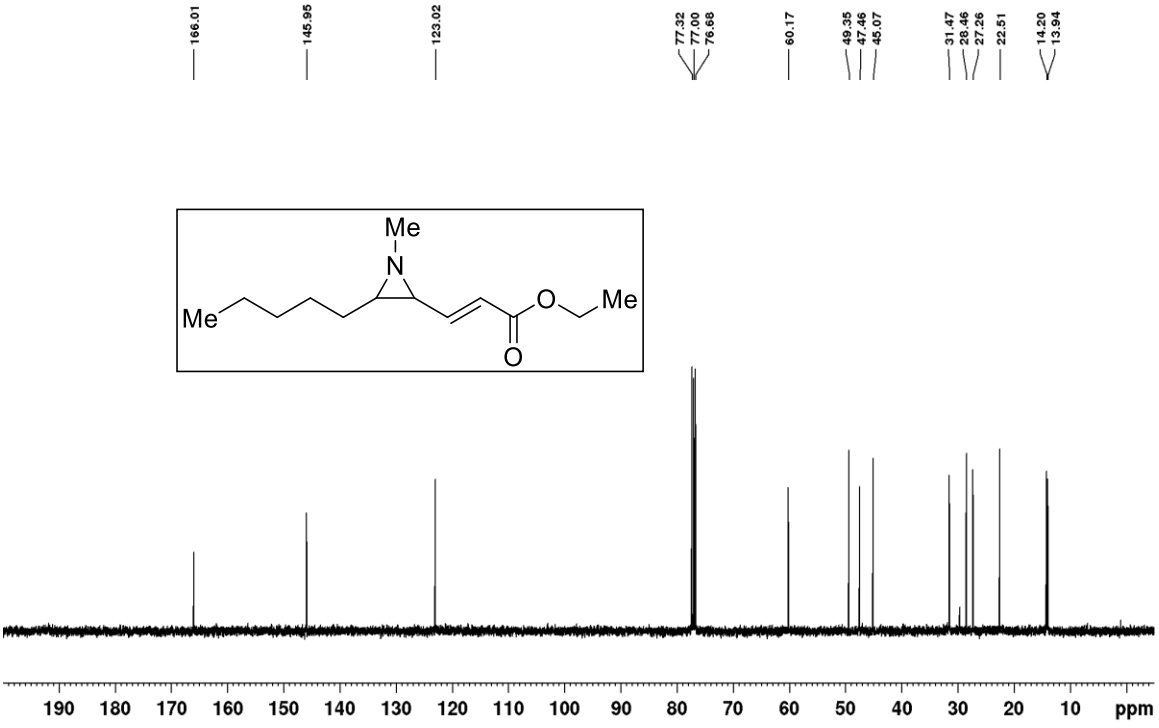
^{13}C{^{1}H} NMR spectrum of compound **63i** (crude product) (100 MHz/$CDCl_3$)



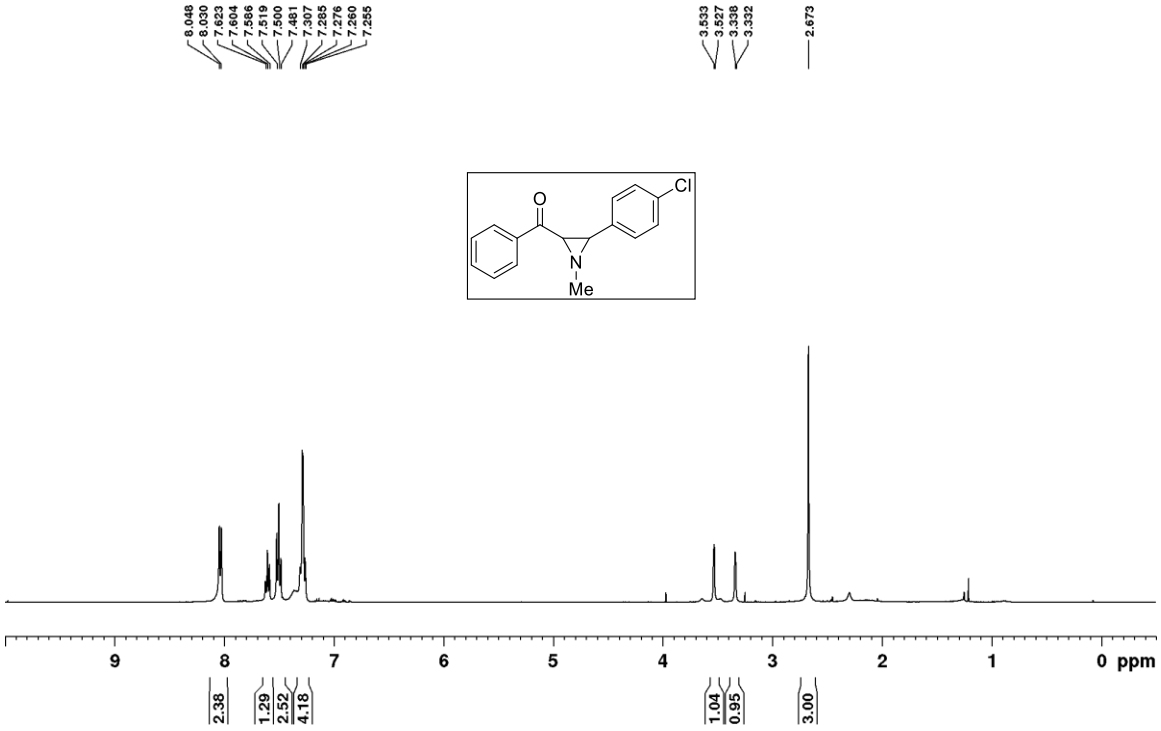
^{1}H NMR spectrum of compound **63j** (400 MHz/$CDCl_3$)



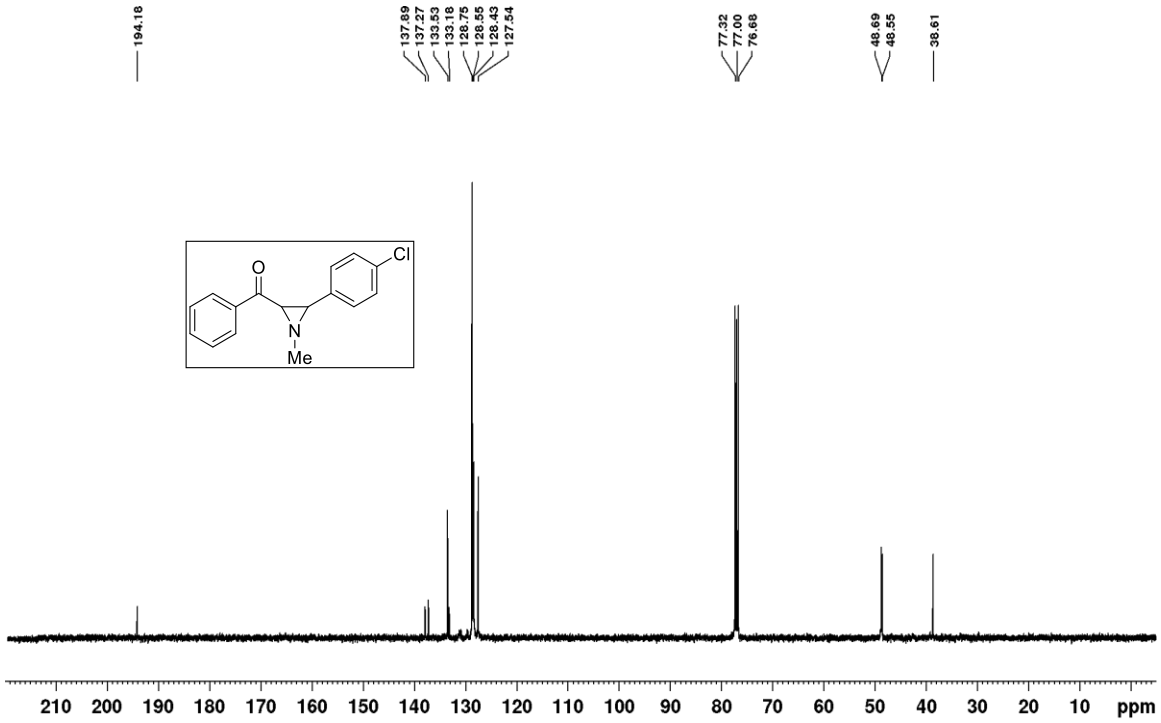
^{13}C{^{1}H} NMR spectrum of compound **63j** (100 MHz/$CDCl_3$)



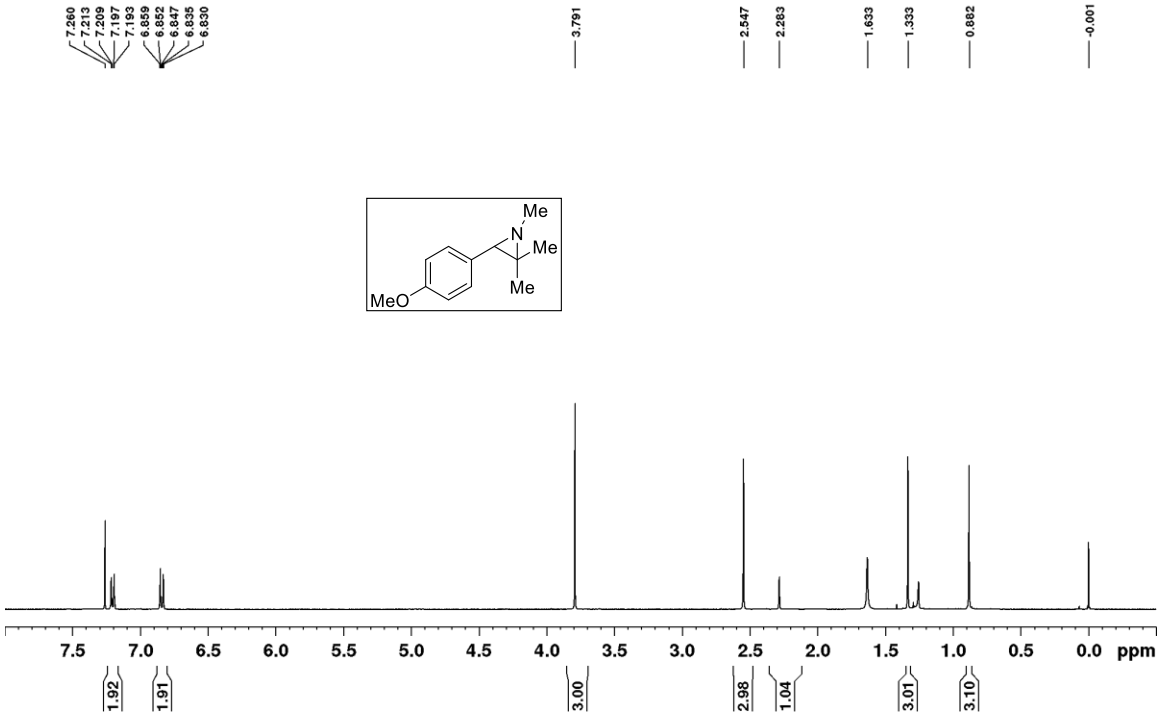
^{1}H NMR spectrum of compound **63k** (400 MHz/$CDCl_3$)



^{13}C{^{1}H} NMR spectrum of compound **63k** (100 MHz/$CDCl_3$)



^{1}H NMR spectrum of compound **63l** (400 MHz/$CDCl_3$)



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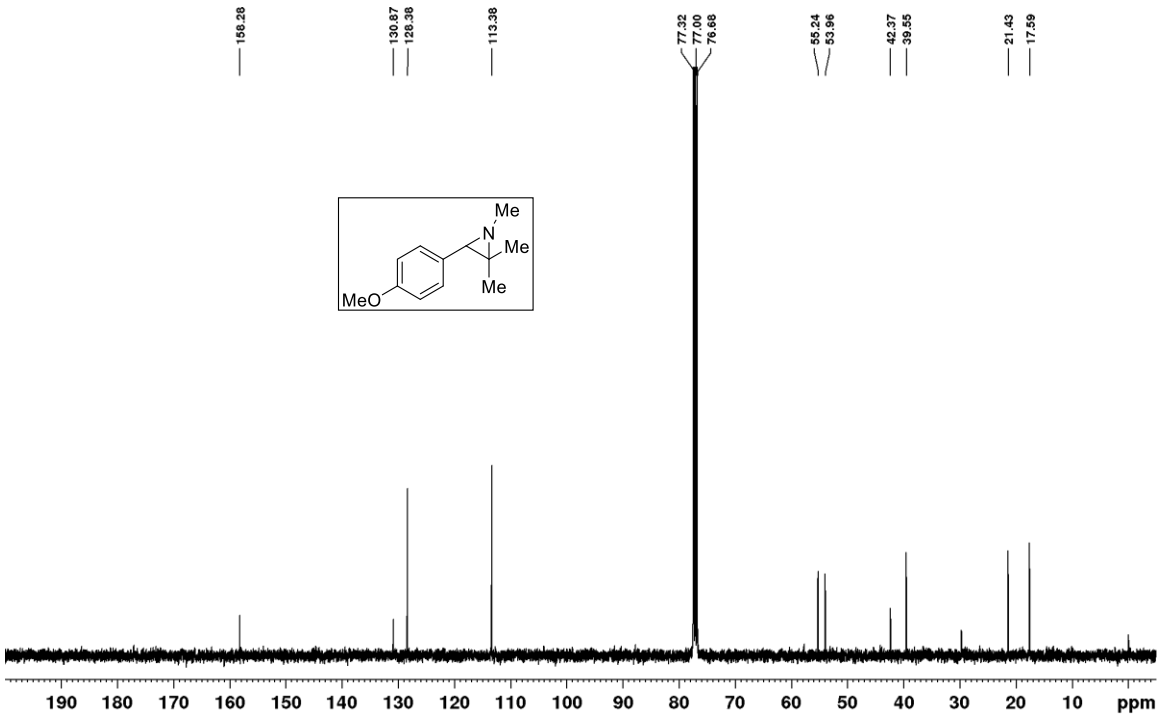

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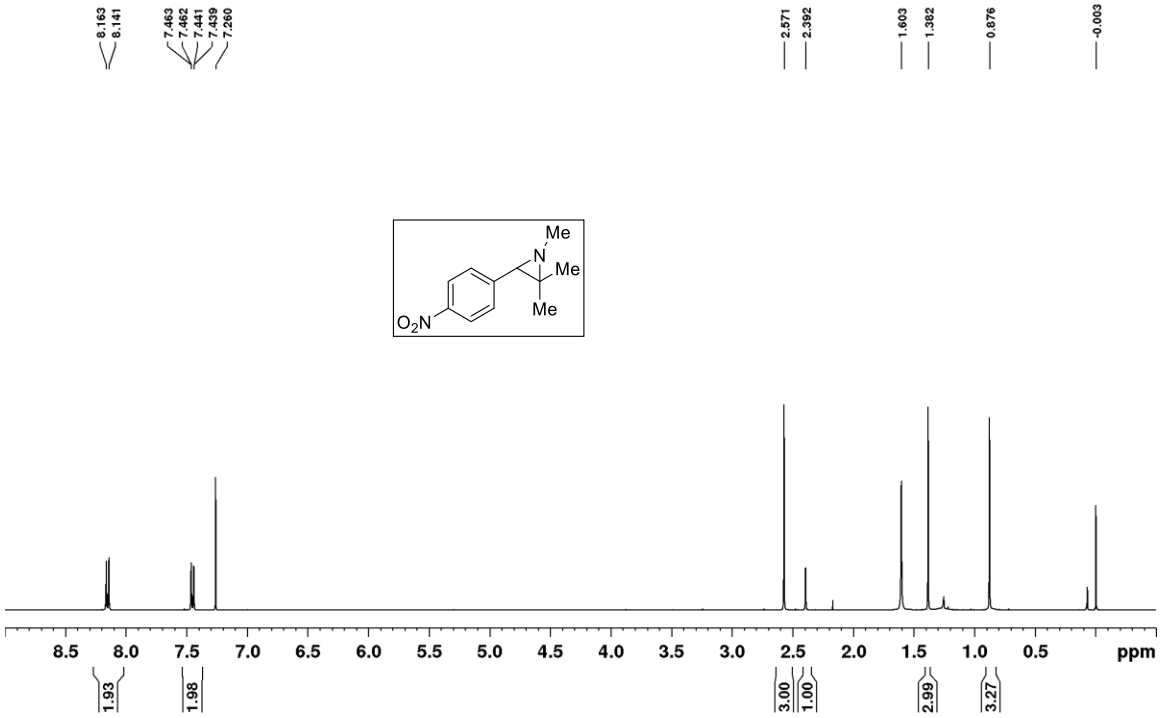

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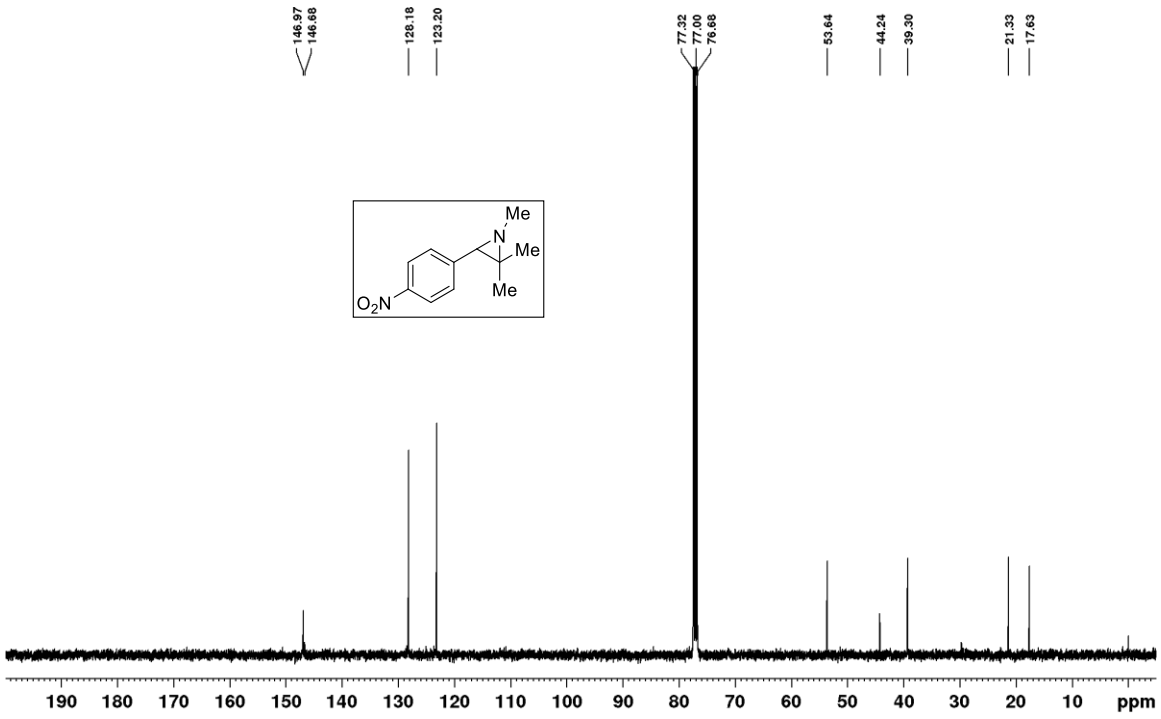

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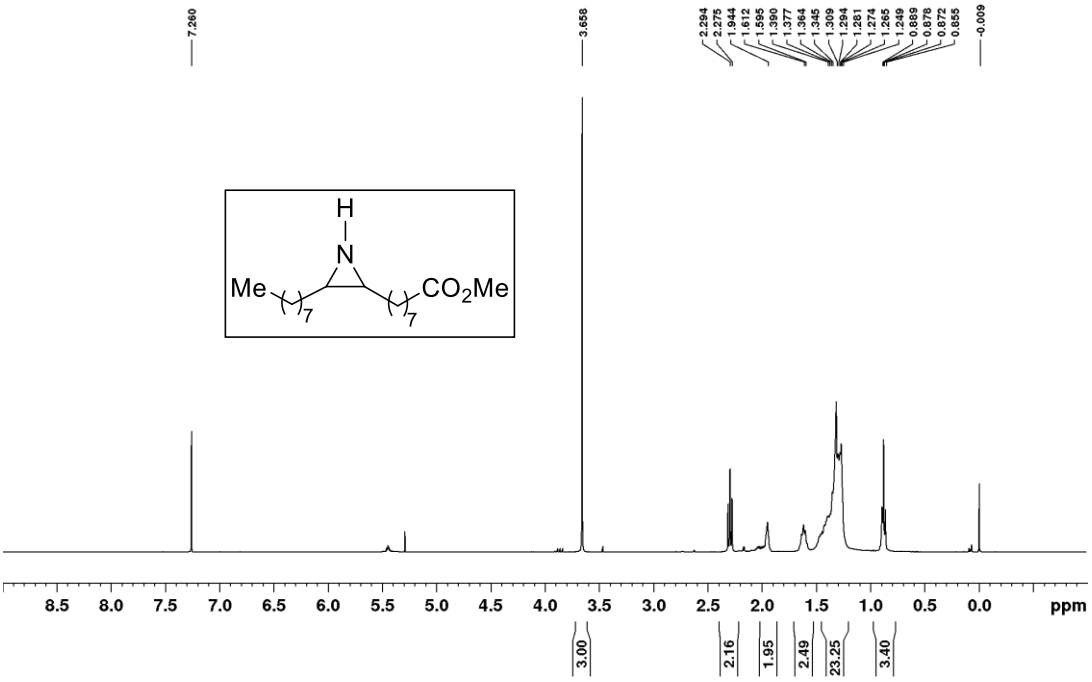

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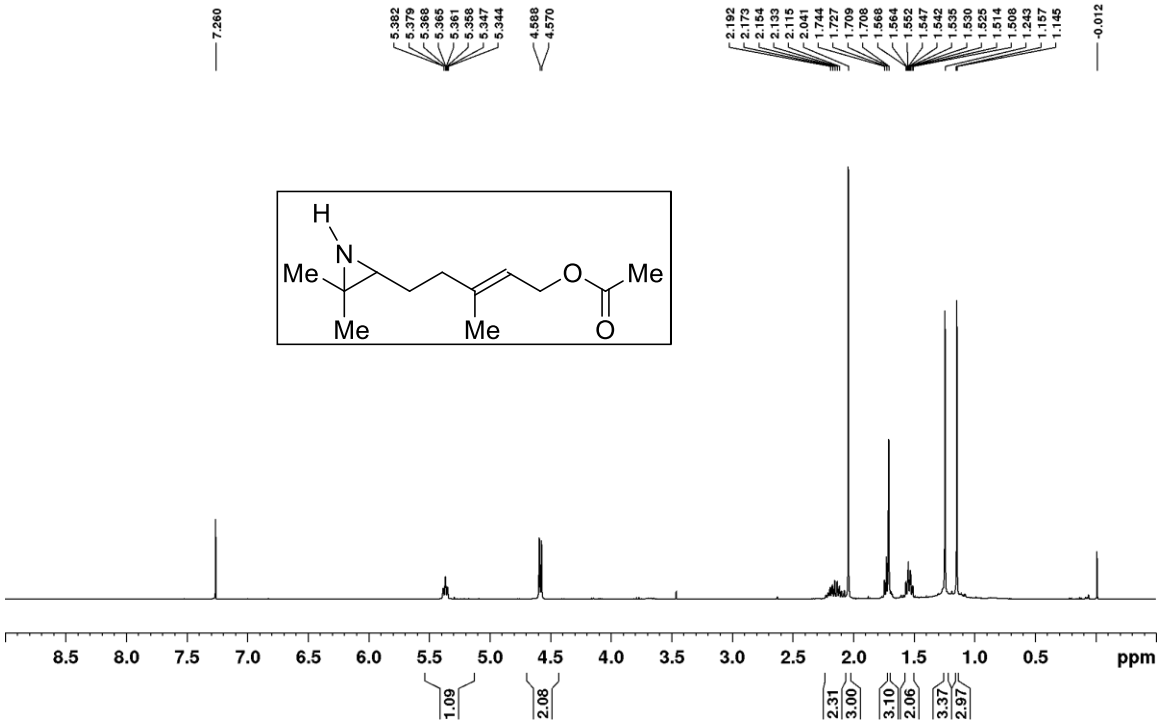
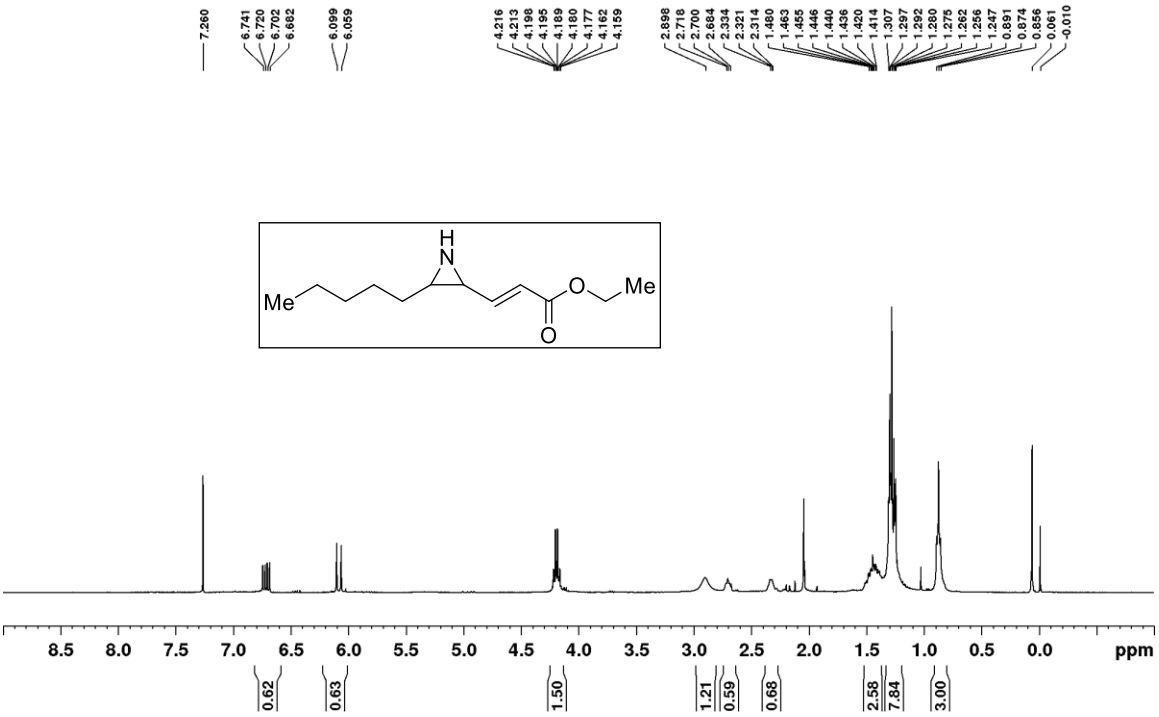


^{1}H NMR spectrum of compound **64c** (400 MHz/$CDCl_3$)



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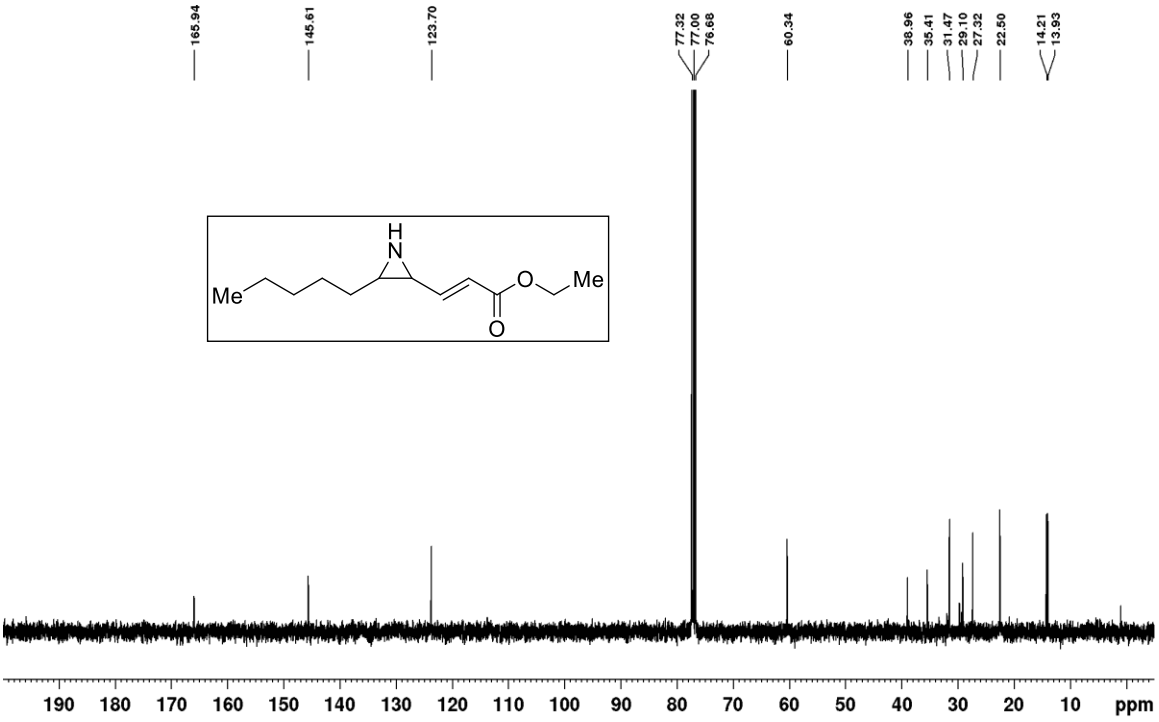
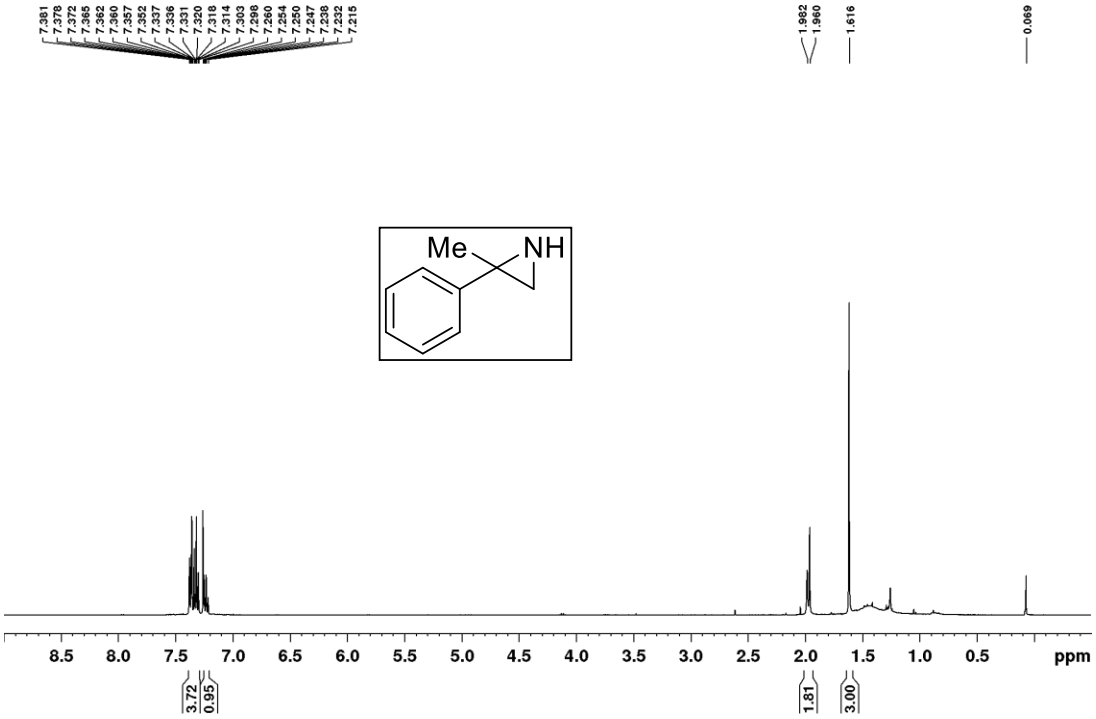


^{1}H NMR spectrum of compound **64d** (400 MHz/$CDCl_3$)



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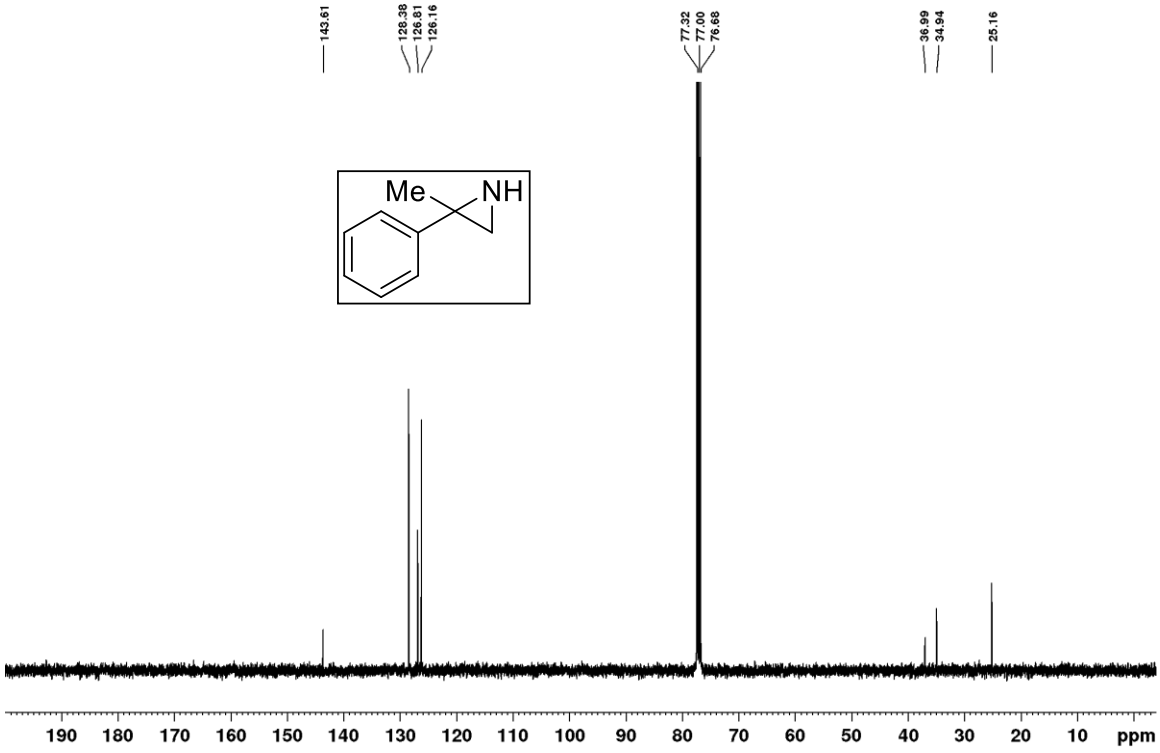
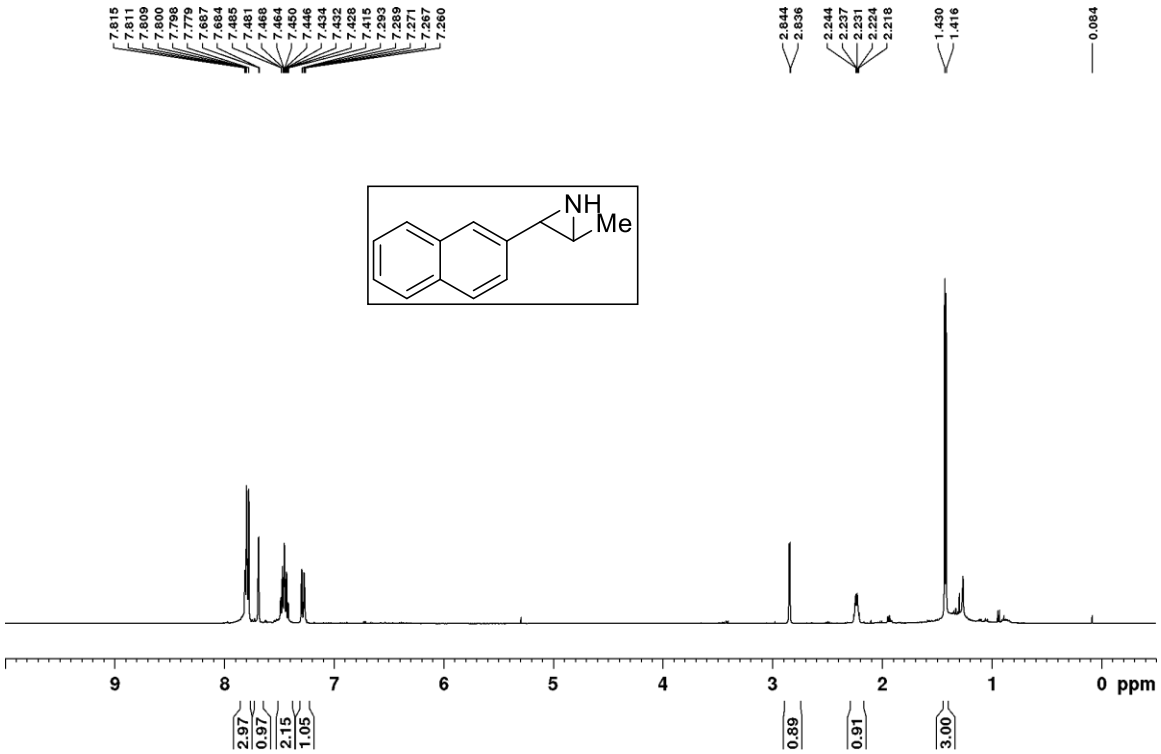
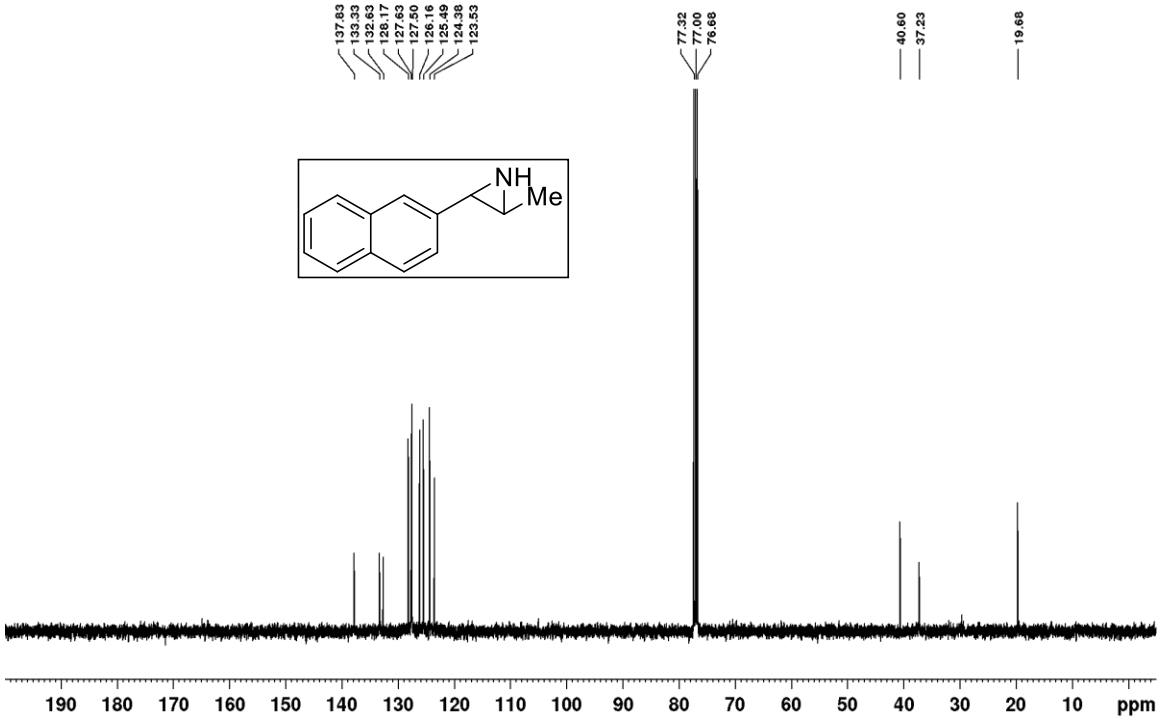


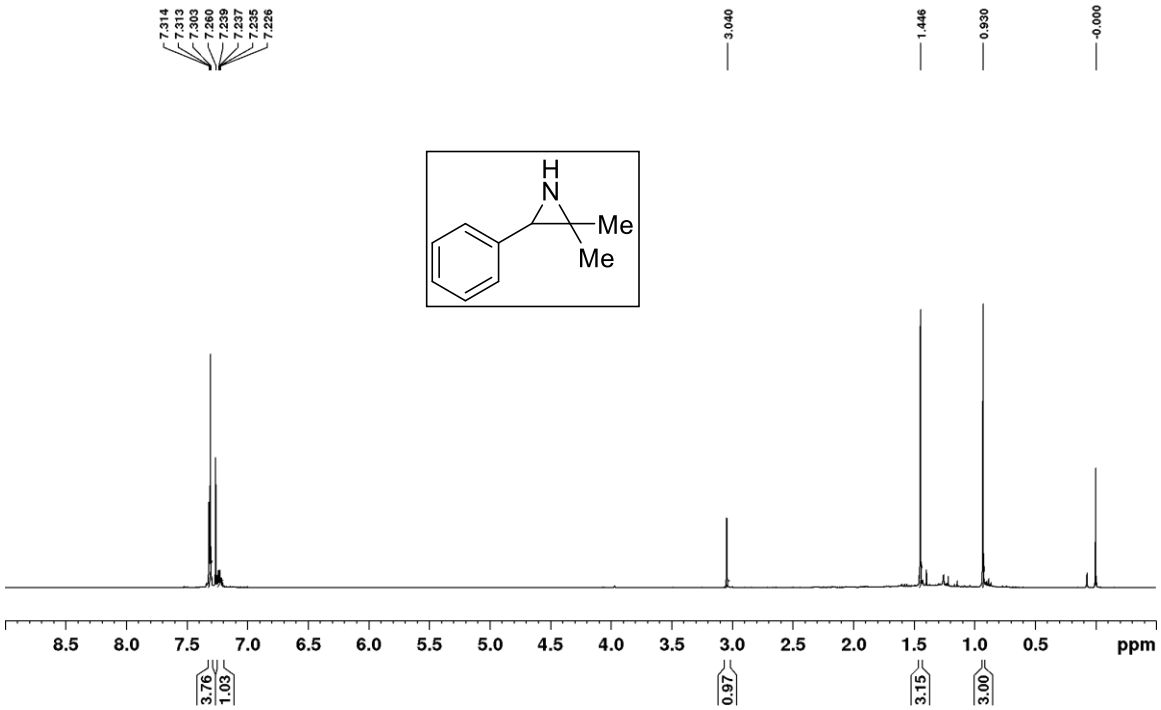
^{1}H NMR spectrum of compound **64e** (400 MHz/$CDCl_3$)



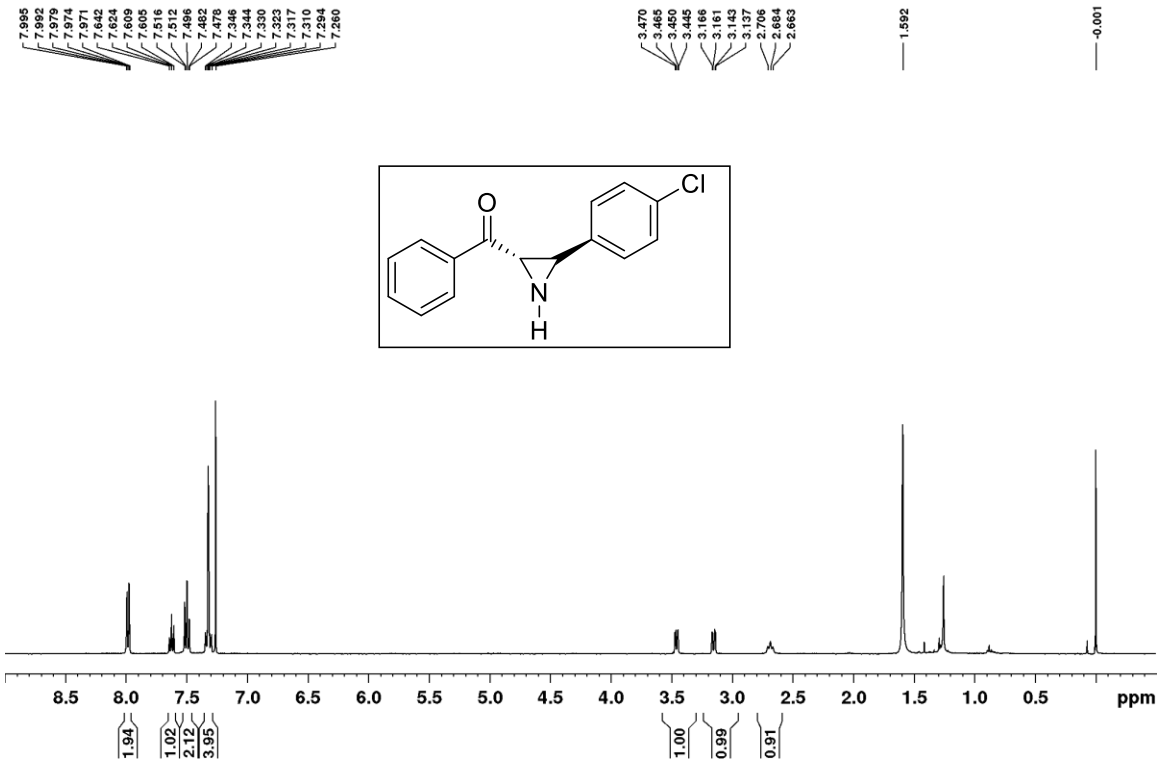
^{13}C{^{1}H} NMR spectrum of compound **64e** (100 MHz/$CDCl_3$)



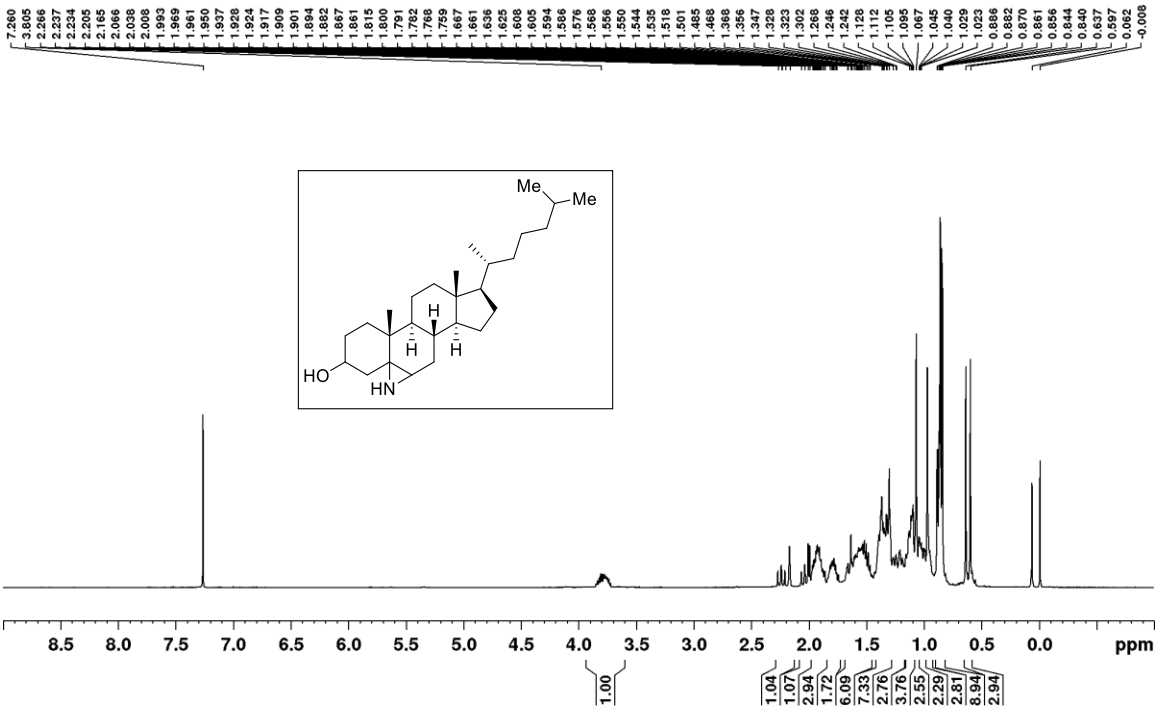
^{1}H NMR spectrum of compound **64f** (400 MHz/$CDCl_3$)



^{1}H NMR spectrum of compound **64g** (400 MHz/$CDCl_3$)



^{1}H NMR spectrum of compound **64h** (400 MHz/$CDCl_3$)



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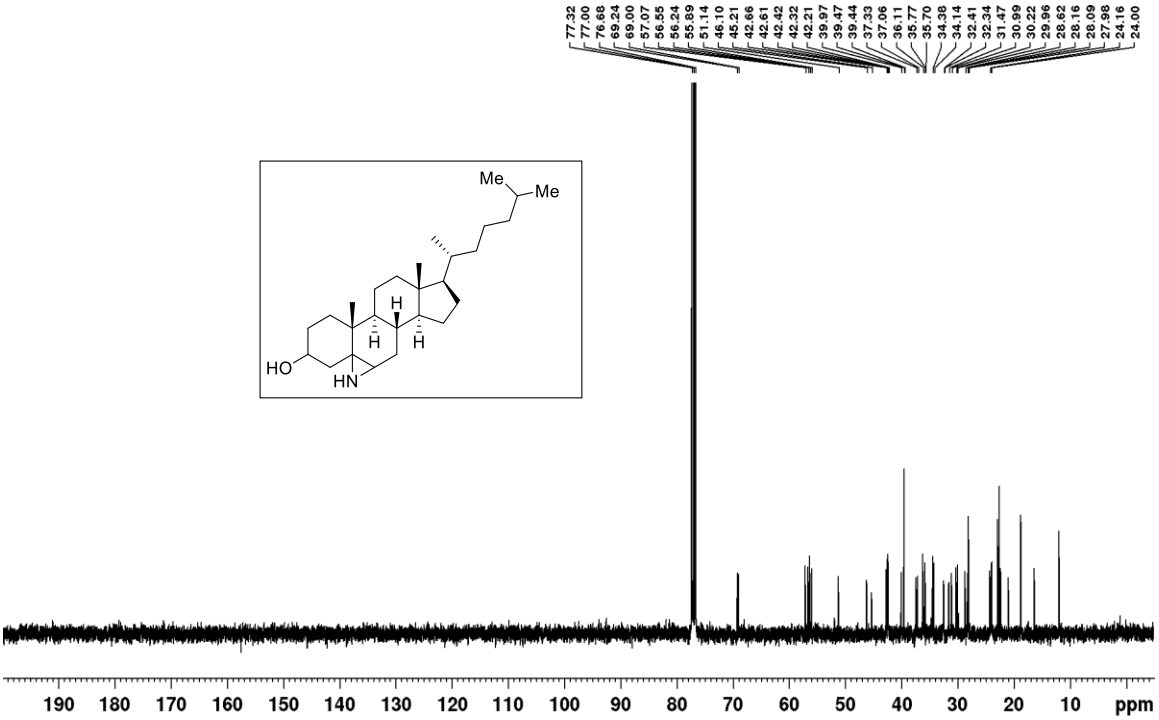

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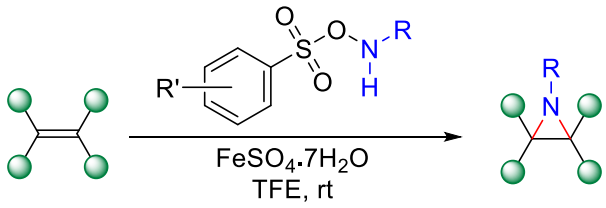
Chapter 3

Fe(II)-Catalyzed Unactivated (*N*-H/*N*-Me) Aziridination of Olefins using *O*-Arylsulfonyl Hydroxylamines as Nitrogen Source

Fe(II)-catalyzed synthesis of *N*-H and *N*-Me aziridines from alkenes using *O*-arylsulfonyl hydroxylamines has been described. This stereospecific protocol is one-pot, economical, mild and operationally simple and provided the unprotected aziridines in excellent yield within a short period of time.



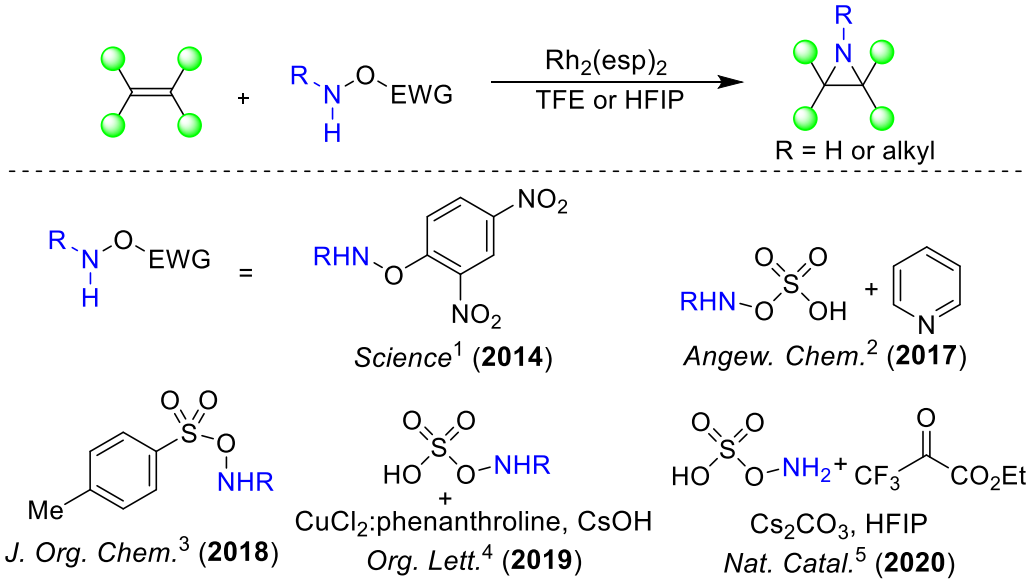
R = H or Me; R' = 2,4,6-trimethyl or *p*-Methyl

- Iron metal catalyzed
- Shorter reaction time
- Easily removable by-product
- Regio, stereo and chemoselective
- Insensitive to air/moisture

(*ChemistrySelect* **2021**, *6*, 10524-10526)

3.1 Introduction

As already described in chapter 2, *N*-H and *N*-Me aziridines are significant compounds. Therefore, several methodologies have been recently developed out of which a few important protocols are summarized in Scheme 3.1[1-5]



Scheme 3.1. The recent development of *N*-H/*N*-Me aziridination

Although there are significant advancements in this field, nevertheless existing aziridination methods have the following drawbacks.

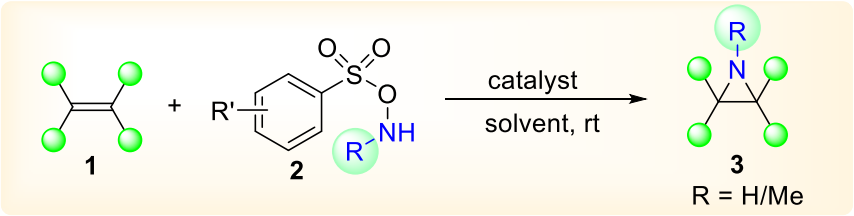
- Requirement of an expensive metal catalyst $Rh_2(esp)_2$, [US $ 267/500 mg, and HFIP solvent (~$247/100g)].
- Necessity of additives (pyridine, cesium carbonate, ligands, etc.).
- Reactivity of conjugated and terminal olefins is very low and requires high catalyst loading along with a longer reaction time. In most cases, poor yields of the products are reported.

So, there is a high demand for a novel protocol that can overcome the above limitations. In this context, iron metal has attracted our attention as it is inexpensive, readily available, non-toxic and environment friendly catalyst, and so far, Iron salts have mostly been

investigated for the preparation of protected or activated (*N*-Ts) aziridines from styrenes only.[6]

3.2 Objective of the work

So, the objective of this part of the thesis was to develop a novel protocol on Fe(II)-catalyzed aziridination of olefins for the direct synthesis of unactivated (*N*-H/*N*-Me) aziridines using *O*-(arylsulfonyl)hydroxylamines as aminating reagents (Scheme 3.2).



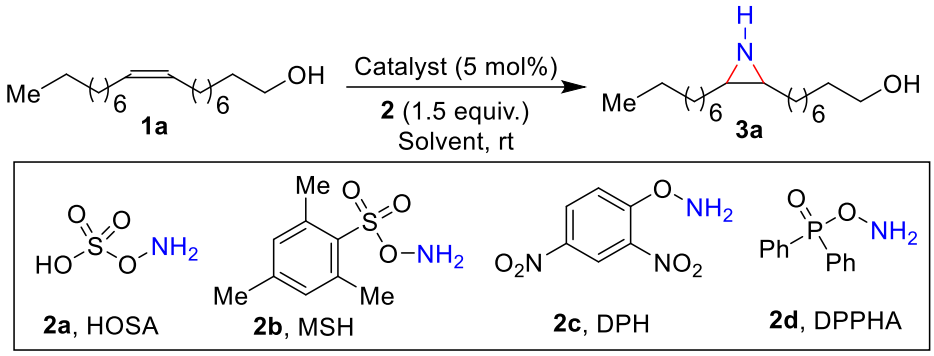
Scheme 3.2. Synthesis of *N*-H/*N*-Me aziridines from olefins

3.3 Results and discussion

3.3.1 Optimization of the reaction conditions

We initiated our study using oleyl alcohol **1a** as the model substrate (Table 3.1). At first, we screened different Iron salts (such as $FeCl_2$, $FeCl_3$, and $FeSO_4.7H_2O$) with HOSA **2a** in a 2,2,2-trifluoroethanol solvent at rt. In all the cases no product was observed on TLC (entries 1-4). When switching to MSH **2b** in the presence of $FeCl_2$ and $FeCl_3$ catalyst, desired product **3a** was obtained in moderate yields (entries 5-6). Whereas, $FeSO_4.7H_2O$ was proved to be the best catalyst, produced the desired product **3a** with 72% yield (entry 7). By increasing the catalyst loading from 5 to 10 mol% the aziridine **3a** was obtained with 86% yield in a shorter reaction time (entry 8). Other aziridinating agents like DPH (**2c)** or DPPHA (**2d)** could not produce the desired product under this reaction condition (entries 9-10). Next, we screened the effect of solvents which resulted in the extremely poor conversion of starting materials (entries 11-17).

Table 3.1. Optimization of Reaction Conditions[a]

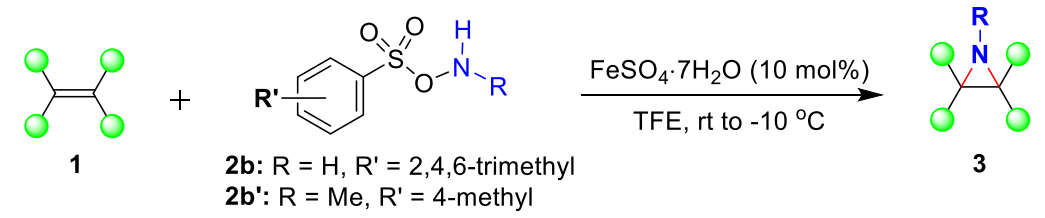


S. No.	Catalyst	Aminating agent	Solvent	Time [h]	Yield [%][b]
1	$FeCl_2$	2a	TFE	12	-
2[c]	$FeCl_2$	2a	TFE	12	
3	$FeCl_3$	2a	TFE	12	-
4	$FeSO_4{\cdot}7H_2O$	2a	TFE	12	-
5	$FeCl_2$	2b	TFE	12	40
6	$FeCl_3$	2b	TFE	12	51
7	$FeSO_4{\cdot}7H_2O$	2b	TFE	8	72
8[d]	**$FeSO_4{\cdot}7H_2O$**	**2b**	**TFE**	**4**	**86**
9	$FeSO_4{\cdot}7H_2O$	2c	TFE	12	-
10	$FeSO_4{\cdot}7H_2O$	2d	TFE	12	-
11	$FeSO_4{\cdot}7H_2O$	2b	DCM	12	trace
12	$FeSO_4{\cdot}7H_2O$	2b	MeOH	12	trace
13	$FeSO_4{\cdot}7H_2O$	2b	THF	12	trace
14	$FeSO_4{\cdot}7H_2O$	2b	CH_3CN	12	trace
15	$FeSO_4{\cdot}7H_2O$	2b	Toluene	12	trace
16	$FeSO_4{\cdot}7H_2O$	2b	EtOH	12	-
17	$FeSO_4{\cdot}7H_2O$	2b	EtOH/H_2O (1:1)	12	-
18[e]	$FeSO_4{\cdot}7H_2O$	2b	TFE	4	85

[a]Reaction conditions: Oleyl alcohol **1a** (0.5 mmol), Aminating reagents **2a-d** (0.75 mmol), catalyst (5 mol %), solvents, rt. [b]Isolated yields, [c]Pyridine (2.0 equiv.) was used. [d]10 mol% of Fe(II) catalyst was used. [e]Reaction was performed under anhydrous condition. TFE = 2,2,2-Trifluroethanol. HOSA = Hydroxylamine-*O*-sulfonic acid. MSH = *O*-(mesitylsulfonyl)hydroxylamine; DPH = 2,4-dinitrophenylhydroxylamine. DPPHA = *O*-(diphenylphosphinyl)hydroxylamine.

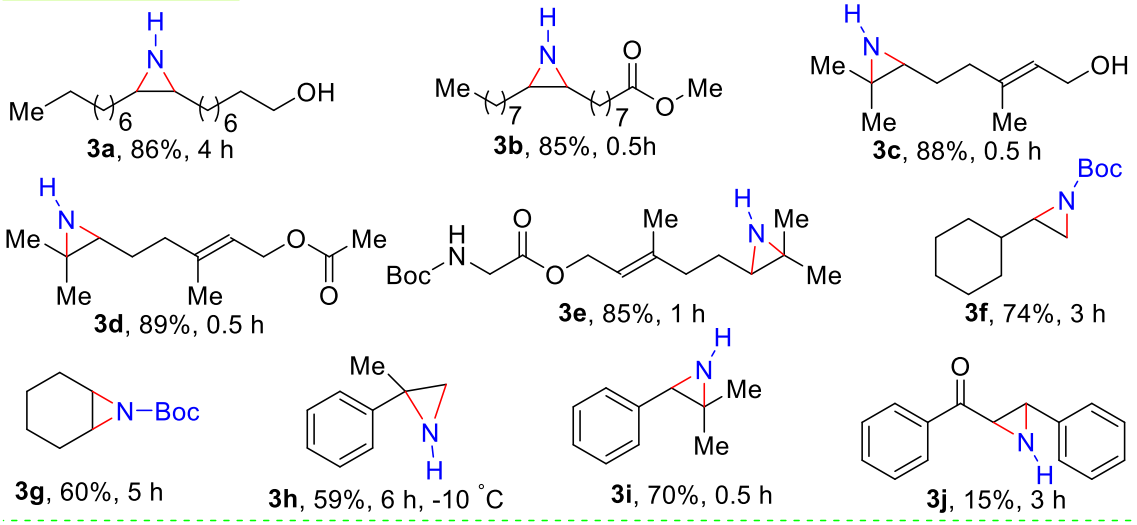
3.3.2 Substrate scope for *N*-H/*N*-Me aziridination

With the optimized reaction condition in hand, we next investigated a variety of alkenes to check the generality of this method (Scheme 3.3). Di-substituted *cis*-olefins reacted smoothly in a stereospecific manner to produce the desired products with high yields (**3a-b**). Geraniol and its derivatives **1c-e** (*tri*-substituted olefins) were reacted very well exclusively at 6,7-olefinic position in a regioselective manner (>95%) to afford the aziridines with excellent yields (**3c-e**). The terminal and cyclic olefins such as vinyl cyclohexane and cyclohexene produced the aziridines with good yields, for the ease of purification they were isolated as Boc-protected aziridines (**3f-g**). *Di*- and *tri*-substituted styrenes successfully reacted to form the desired product with moderate to good yields (**3h-i**). In all of the above examples, no side products such as C-H amination and ring-opening of aziridines were observed.[7] The electron-deficient conjugated olefin such as chalcone **1j** reacted very slow to furnish the desired product **3j** with a lower yield (15%). An alkene bearing an electron-withdrawing group such as *n*-butyl acrylate did not produce the desired product. We next moved to investigate this method for the direct synthesis of *N*-Me aziridines from a variety of olefins using *N*-methyl-*O*-tosylhydroxylamine (TsONHMe, **2b'**) as the aminating reagent under similar reaction conditions. Methyl oleate transformed to *N*-Me aziridine **3k** with 79% yield. Geraniol and its derivatives were smoothly reacted exclusively at 6,7-olefinc position (>95%) to afford the desired product with good to high yields (**3l-n)**. The terminal olefin **1o** is efficiently aziridinated to give the corresponding aziridine **3o** with good yield and the *trans*-alkene **1p** afford the **3p** with good yield. Some of the alkenes **3q-t** generated a mixture of inseparable products under the optimal reaction condition. These reactions were expected to occur *via* an Iron-nitrene intermediate followed a similar mechanistic pathway as postulated by Falck, Kürti, and Ess (Figure 2.2, Chapter 2).[1]

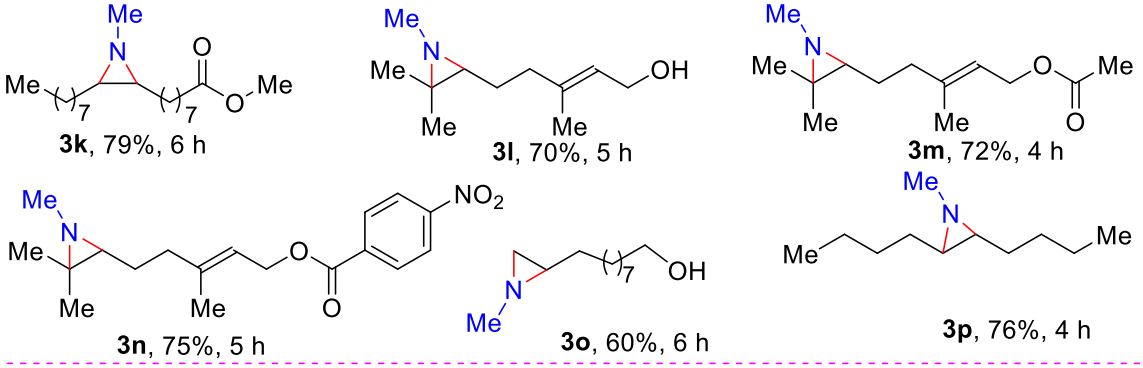


1 **2b:** R = H, R' = 2,4,6-trimethyl **2b':** R = Me, R' = 4-methyl **3**

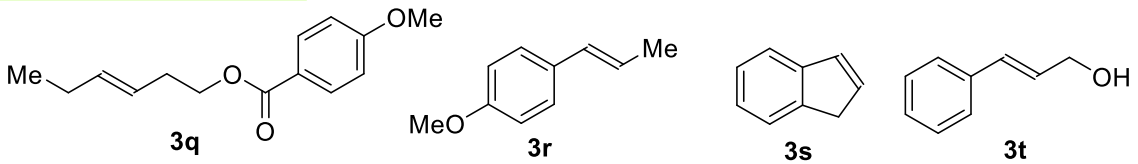
N-H Aziridination



N-Me Aziridination



Unsuccessful subtrates



[a]Reaction condition: Alkenes **1** (0.5 mmol), aminating reagent **2b** (for **3a**-**3j**) or **2b'** (for **3k**-**3p**) (0.75 mmol), catalyst (10 mol%), TFE, rt. The yields mentioned are isolated yields after silica gel column chromatography.

Scheme 3.3. Direct and stereospecific *N*-H/*N*-Me aziridination of alkenes

3.4 Conclusion

In conclusion, we have successfully developed a highly efficient protocol for the preparation of direct *N*-H/*N*-Me aziridines from a broad range of alkenes using *O*-arylsulfonyl hydroxylamines as aminating agents and $FeSO_4.7H_2O$ catalyst in TFE solvent at rt. This regio- and stereospecific method produced a variety of unactivated aziridines in good to excellent yields with a tolerance of a variety of labile and reactive functional groups (such as alcohol, ester, and Boc). This method did not work well on conjugated substrates like styrenes, chalcones etc.

Highlights

The main highlights of this methodology are (a) Iron metal-catalyzed (b) Insensitive to air/moisture (c) Shorter reaction time (d) Regio, stereo and chemoselective (f) Economical and environmentally benign etc.

This work has been published in *ChemistrySelect*, **2021**, 6, 10524-10526.

3.5 Experimental Section

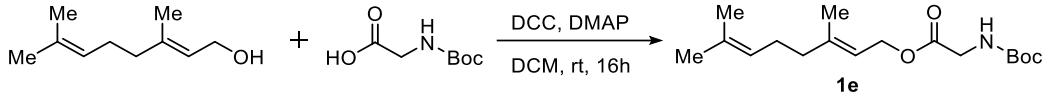
3.5.1 General Information

Unless otherwise indicated, all alkenes were purchased from a commercial source and used without further purification. The solvents were dried and distilled following the standard methods. All the reactions were carried out under an open atmosphere in a single-neck round bottom flask. Reactions were monitored by thin layer chromatography (TLC) using pre-coated plates (silica gel 60, F-254) purchased from Merck. The spot of compounds were visualized by UV light and stained PMA or $KMNO_4$ or Ninhydrin followed by heating. For purification of compounds, column chromatography was performed with silica gel (230-400 mesh, neutralized with $^tBu_3N$) in distilled solvents. NMR spectra were recorded on Bruker 400 MHz (^1H NMR spectra were obtained at 400 MHz instrument and ^{13}C NMR spectra were obtained at 100 MHz instrument) in $CDCl_3$ solvent. Chemical shifts (δ) and coupling constants (J) are measured in ppm and Hz respectively. Chemical shifts (δ) were recorded in reference to the internal standard tetramethylsilane (TMS, 0.00 ppm) or the residual solvent signals were used as references ($CDCl_3$, ^1H NMR: = 7.26 ppm;

$^{13}C\{^{1}H\}$ NMR: = 77.00 ppm). Multiplicities were known as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), td (triplet of doublets), or m (multiplet). High resolution mass spectra (HRMS) were obtained on an Agilent 6530 series quadrupole time of flight (Q-TOF) mass spectrometer equipped with electron spin ionization (ESI). IR spectra were recorded on an FT-IR spectrometer (Perkin Elmer FT-IR C101907) and only major peaks are reported in cm^{-1}.

3.5.2 Synthesis of Starting Materials

Preparation of (E)-3,7-dimethylocta-2,6-dien-1-yl (tert-butoxycarbonyl)glycinate (**1e**)



1e

To a stirred solution of *Boc*-Glycine (200 mg, 1.142 mmol), DMAP (14 mg, 0.114 mmol), Geraniol (176 mg, 1.142 mmol) in DCM (10 mL) was added DCC (282 mg, 1.371 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 16 h. Progress of the reaction was monitored by TLC. After completion of the reaction, water (20 mL) was added to the reaction mixture and extracted with DCM (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified using silica gel column chromatography using 10-15% EtOAc/hexanes to give (*E*)-3,7-dimethylocta-2,6-dien-1-yl(tert-butoxycarbonyl)glycinate as a viscous oil (302 mg, 85%). TLC: R_f = 0.5 (20% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (t, *J* = 7.2 Hz, 1H), 5.07 (t, *J* = 6.4 Hz, 1H), 5.00 (brs, 1H), 4.67 (d, *J* = 7.2 Hz, 2H), 3.91 (d, *J* = 5.3 Hz, 2H), 2.16 – 2.00 (m, 4H), 1.71 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.45 (s, 9H).

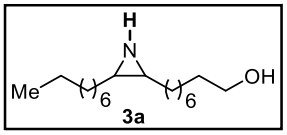
3.6.3 General Procedure for *N*-H and *N*-Me Aziridination

In a single-neck round bottom flask equipped with a magnetic stirring bar were added olefin **1** (0.5 mmol) and TFE (0.5 – 1.0 mL). To this stirred solution aminating agent *O*-(mesitylsulfonyl)hydroxylamine (MSH) **2b** or *N*-methyl-*O*-tosylhydroxylamine (TsONHMe) **2b'** and $FeSO_4$•$7H_2O$ (10 mol%) was added at the specified temperature. The reaction mixture was stirred at the specified time and temperature. The progress of the

reaction was monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3 × 5 mL). The aqueous layer was extracted three times with CH_2Cl_2 (5 mL), and the combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4. The organic layer was evaporated in *vacuo* and crude obtained was purified through silica gel column chromatography (silica gel was neutralized by 2% *t*-butylamine) using EtOAc/hexane or MeOH/DCM as an eluent to furnish the title products **3** with high purity.

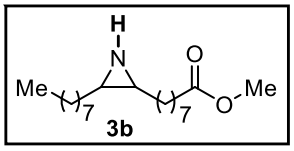
3.6 Characterization of the products

8-(3-octylaziridin-2-yl)octan-1-ol (**3a**): Following the general aziridination procedure, oleyl alcohol (135 mg, 0.502 mmol), MSH (162 mg, 0.754 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (1 mL) at RT for 4 h. Chromatographic purification of crude product afforded **3a** as colorless syrupy liquid (123 mg, 86% yield). TLC R_f = 0.5 in 10% MeOH/DCM.



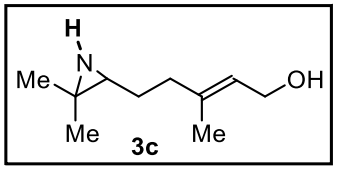
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (t, *J* = 6.7 Hz, 2H), 1.92 (s, 1H), 1.70 (brs, 1H), 1.61 – 1.46 (m, 3H), 1.45 – 1.17 (m, 27H), 0.84 (t, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 62.55, 37.88, 35.11, 34.20, 32.82, 31.87, 29.60, 29.58, 29.52, 29.38, 29.27, 28.72, 28.69, 28.03, 27.64, 25.79, 22.66, 14.09. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $[C_{18}H_{38}NO]^+$ 284.2948, found 284.2934

Methyl (Z)-8-(3-octylaziridin-2-yl)octanoate (**3b**): Following the general aziridination procedure, methyl oleate (148 mg, 0.50 mmol), MSH (161.25 mg, 0.75 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (1 mL) at RT for 0.5 h. Chromatographic purification of crude product afforded **3b** as colourless oil (132 mg, 85% yield) whose spectral data were in accord with the literature values.[3] TLC R_f = 0.3 in 50% EtOAc/Hexane.



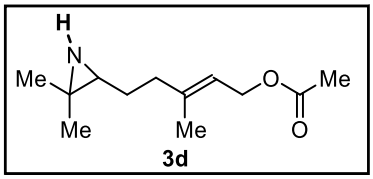
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 2.26 (t, *J* = 7.5 Hz, 2H), 1.91 (brs, 1H), 1.66-1.50 (m, 2H), 1.49 – 1.12 (m, 25H), 0.84 (t, *J* = 6.6 Hz, 3H).

(E)-5-(3,3-dimethylaziridin-2-yl)-3-methylpent-2-en-1-ol (**3c**): Following the general aziridination procedure, geraniol (77 mg, 0.50 mmol), MSH (161.25 mg, 0.75 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (0.5 mL) at RT for 0.5 h. Chromatographic purification of crude product afforded **3c** as yellowish liquid (75 mg, 88% yield) whose spectral data were in accord with the literature values.[1] TLC R_f = 0.4 in 10% MeOH/DCM.



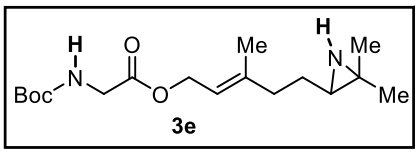
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (t, *J* = 6.8 Hz, 1H), 4.10 (d, *J* = 6.8 Hz, 2H), 2.52 (brs, 2H), 2.23 – 2.03 (m, 2H), 1.81 (t, *J* = 6.5 Hz, 1H), 1.65 (s, 3H), 1.61-1.48 (m, 2H), 1.24 (s, 3H), 1.16 (s, 3H).

(E)-5-(3,3-dimethylaziridin-2-yl)-3-methylpent-2-en-1-yl acetate (**3d**): Following the general aziridination procedure, geranyl acetate (98 mg, 0.50 mmol), MSH (161.25 mg, 0.75 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (0.5 mL) at RT for 0.5 h. Chromatographic purification of crude product afforded **3d** as yellowish liquid (94 mg, 89% yield) whose spectral data were in accord with the literature values.[3] TLC R_f = 0.45 in 50% EtOAc/Hexane.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (t, *J* = 7.0 Hz, 1H), 4.53 (d, *J* = 7.1 Hz, 2H), 2.21 – 2.02 (m, 2H), 2.02 – 1.94 (m, 3H), 1.74 – 1.68 (m, 1H), 1.66 (s, 3H), 1.53 – 1.45 (m, 2H), 1.20 (s, 3H), 1.10 (s, 3H).

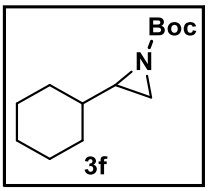
(E)-5-(3,3-dimethylaziridin-2-yl)-3-methylpent-2-en-1-yl(tert-butoxycarbonyl)glycinate (**3e**): Following the general aziridination procedure, (*E*)-3,7-dimethylocta-2,6-dien-1-yl (tert-butoxycarbonyl)glycinate (156 mg, 0.50 mmol), MSH (161.25 mg, 0.75 mol%) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (1 mL) at RT for 1 h. Chromatographic purification of crude product afforded **3e** as yellowish liquid (139 mg, 85% yield). TLC R_f = 0.45 in 50% EtOAc/Hexane.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (t, *J* = 7.0 Hz, 1H), 5.21 (brs, 1H), 4.58 (d, *J* = 7.1 Hz, 2H), 3.81 (d, *J* = 5.2 Hz, 2H), 2.18 – 1.98 (m, 2H), 1.70 – 1.66 (m, 1H), 1.64 (s, 3H), 1.47

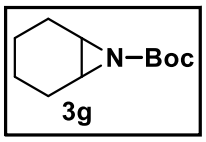
(dd, *J* = 14.6, 7.3 Hz, 2H), 1.36 (s, 9H), 1.17 (s, 3H), 1.08 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.35, 155.71, 142.49, 118.08, 79.83, 62.00, 42.93, 42.41, 37.68, 35.70, 28.28, 27.93, 27.42, 19.63, 16.47. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $[C_{17}H_{31}N_2O_4]^+$ 327.2278, found 327.2269. IR (CH_2Cl_2, cm^{-1}): 2928, 1712, 1513, 1366, 1264, 1164, 1054, 961, 732.

Tert-butyl 2-cyclohexylaziridine-1-carboxylate (**3f**): Following the general aziridination procedure, vinyl cyclohexane (55mg, 0.5 mmol) MSH (161mg, 0.75mmol) and $FeSO_4 \cdot 7H_2O$ (14mg, 10 mol %) were stirred in TFE (0.5 mL) at RT for 0.5 h. The progress of reaction was monitored by TLC. After complete consumption of olefin, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3 × 5 mL). The aqueous layer was extracted thrice with CH_2Cl_2 (5 mL), and the combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4. The organic layer was evaporated in *vacuo* and crude obtained was dissolved in DCM (5mL) and Boc_2O (218mg, 1mmol) and TEA (178 µL, 1.25mmol) were added at 0 °C. The reaction mixture was stirred room temperature for 4-5hrs. The progress of reaction was monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (3 × 5 mL). The aqueous layer was extracted twice with CH_2Cl_2 (5 mL), and the combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4. The organic layer was evaporated in *vacuo* and crude obtained was purified by column chromatography (silica gel neutralized by *tert*-butylamine) using 10-20% EtOAc in hexane. Aziridine **3f** was obtained as colourless liquid (84 mg, 74% yield over two steps). TLC R_f = 0.4 in 30% EtOAc/Hexane.



^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (d, *J* = 6.2 Hz, 1H), 2.13 (ddd, *J* = 10.2, 7.1, 3.2 Hz, 1H), 1.95 – 1.86 (m, 2H), 1.79 – 1.56 (m, 4H), 1.43 (s, 9H), 1.29 – 0.98 (m, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.91, 80.70, 43.19, 40.29, 30.41, 29.72, 27.90, 27.40, 26.26, 25.72, 25.57. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $[C_{13}H_{23}NO_2Na]^+$ 248.1621, found 248.1612. IR (CH_2Cl_2, cm^{-1}): 2983, 2935, 1807, 1757, 1718, 1478, 1460, 1396, 1371, 1308, 1261, 1211, 1162, 1114, 1064, 950, 844, 775.

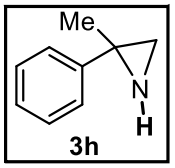
Tert-butyl 7-azabicyclo[4.1.0]heptane-7-carboxylate (**3g**): Following the general



aziridination procedure, cyclohexene (41mg, 0.5mmol) MSH (161mg, 0.75mmol) and $FeSO_4 \cdot 7H_2O$ (14mg, 10 mol %) were stirred in TFE (0.5 mL) at room temperature for 30 minutes. The progress of reaction was monitored by TLC. After complete consumption of olefin, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3 × 5 mL). The aqueous layer was extracted thrice with CH_2Cl_2 (5 mL), and the combined organic layer was washed with brine solution then dried over anhydrous Na_2SO_4. The organic layer was evaporated in *vacuo* and crude obtained was dissolved in DCM (5mL) and Boc_2O (218mg, 1.0mmol) and TEA (178 µL, 1.25mmol) were added at 0 °C. The reaction mixture was stirred room temperature for 4-5hrs. The progress of reaction was monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (3 × 5 mL). The aqueous layer was extracted twice with CH_2Cl_2 (5 mL), and the combined organic layer was washed with brine solution then dried over anhydrous Na_2SO_4. The organic layer was evaporated in *vacuo* and crude obtained was purified by column chromatography (silica gel neutralized by *tert*-butylamine) using 10-20% EtOAc in hexane. Aziridine **3g** was obtained as colourless liquid (59 mg, 60% yield) whose spectral data were in accord with the literature values.[8] TLC R_f = 0.4 in 30% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 – 2.47 (m, 2H), 1.94 – 1.82 (m, 2H), 1.80 – 1.68 (m, 2H), 1.41 (s, 9H), 1.39 – 1.32 (m, 2H), 1.27 – 1.10 (m, 2H). HRMS (ESI) *m/z* $[M + H]^+$ calcd for $[C_{11}H_{20}NO_2]^+$ 198.1479, found 198.1393

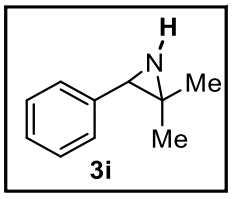
2-methyl-2-phenylaziridine (**3h**): Following the general aziridination procedure, α-methyl



styrene (59 mg, 0.50 mmol), MSH (161.25 mg, 0.75 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (0.5 mL) at -10 °C for 6 h. Chromatographic purification of crude product afforded **3h** as colorless oil (39 mg, 59% yield) whose spectral data were in accord with the literature values.[3] TLC R_f = 0.4 in 50% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 4H), 7.26 – 7.21 (m, 1H), 1.98 (s, 1H), 1.96 (s, 1H), 1.61 (s, 3H)

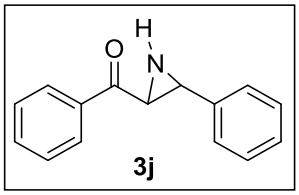
2,2-dimethyl-3-phenylaziridine (**3i**): Following the general aziridination procedure, (2-methylprop-1-en-1-yl)benzene (66 mg, 0.50 mmol), MSH (161.25 mg, 0.75 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (0.5 mL) at RT for 0.5 h. Chromatographic purification of crude product afforded **3i** as colourless liquid (51 mg, 70% yield) whose spectral data were in accord with the literature values.[3] TLC R_f = 0.5 in 50% EtOAc/Hexane.



3i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 5H), 3.04 (s, 1H), 1.44 (s, 3H), 0.93 (s, 3H).

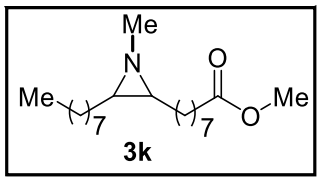
Phenyl(3-phenylaziridin-2-yl)methanone **(3j)**: Following the general aziridination procedure, (*E*)-chalcone (104 mg, 0.50 mmol), MSH (161.25 mg, 0.75 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (0.5 mL) at RT for 3 h. Chromatographic purification of crude product afforded **3j** as yellowish liquid (17 mg, 15% yield) whose spectral data were in accord with the literature values.[9] TLC R_f = 0.5 in 50% EtOAc/Hexane.



3j

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.40 – 7.28 (m, 5H), 3.51 (dd, *J* = 7.1, 0.8 Hz, 1H), 3.18 (dd, *J* = 9.9, 0.6 Hz, 1H), 2.76 – 2.59 (m, 1H).

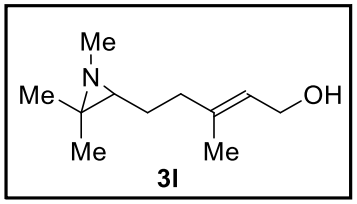
Methyl (Z)-8-(1-methyl-3-octylaziridin-2-yl)octanoate (**3k**): Following the general aziridination procedure, methyl oleate (148 mg, 0.50 mmol), TsONHMe (150.75 mg, 0.75 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (1 mL) at RT for 6 h. Chromatographic purification of crude product afforded **3k** as colorless liquid (128 mg, 79% yield) whose spectral data were in accord with the literature values.[1] TLC R_f = 0.5 in 50% EtOAc/Hexane.



3k

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.32 – 2.26 (m, 5H), 1.64 – 1.54 (m, 2H), 1.44 – 1.15 (m, 26H), 0.85 (t, *J* = 6.8 Hz, 3H).

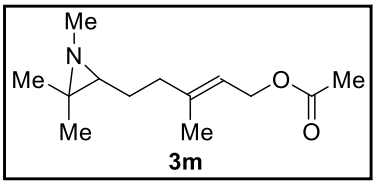
(E)-3-methyl-5-(1,3,3-trimethylaziridin-2-yl)pent-2-en-1-ol (**3l**): Following the general aziridination procedure, geraniol (77 mg, 0.50 mmol), TsONHMe (150.75 mg, 0.75 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (0.5 mL) at RT for 5 h. Chromatographic purification of crude product afforded **3l** as colorless liquid (64 mg, 70% yield) whose spectral data were in accord with the literature values.[3] TLC R_f = 0.2 in 10% MeOH/DCM.



3l

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 – 5.40 (m, 1H), 4.15 (d, *J* = 7.0 Hz, 2H), 2.36 (s, 3H), 2.20 – 2.04 (m, 2H), 1.68 (s, 3H), 1.57 – 1.45 (m, 2H), 1.25 (s, 1H), 1.17 (s, 3H), 1.08 (s, 3H).

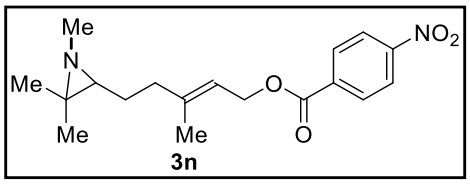
(E)-3-methyl-5-(1,3,3-trimethylaziridin-2-yl)pent-2-en-1-yl acetate (**3m**): Following the general aziridination procedure, geranyl acetate (98 mg, 0.50 mmol), TsONHMe (150.75 mg, 0.75 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (0.5 mL) at RT for 4 h. Chromatographic purification of crude product afforded **3m** as colorless oil (81 mg, 72% yield) whose spectral data were in accord with the literature values.[1] TLC R_f = 0.3 in 10% MeOH/DCM.



3m

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (t, *J* = 7.1 Hz, 1H), 4.56 (d, *J* = 7.1 Hz, 2H), 2.37 (s, 3H), 2.23 – 2.06 (m, 2H), 2.03 (s, 3H), 1.69 (s, 3H), 1.59 – 1.43 (m, 2H), 1.18 (s, 3H), 1.09 (s, 3H) 1.07 – 1.02 (m, 1H).

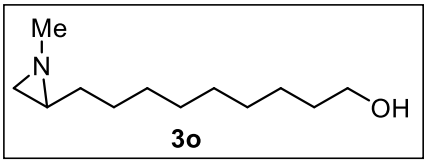
(E)-3-methyl-5-(1,3,3-trimethylaziridin-2-yl)pent-2-en-1-yl 4-nitrobenzoate (**3n**): Following the general aziridination procedure, (*E*)-3,7-dimethylocta-2,6-dien-1-yl 4-nitrobenzoate (150 mg, 0.495 mmol), TsONHMe (149.25 mg, 0.742 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (1 mL) at RT for 5 h. Chromatographic purification of crude product afforded **3n** as colourless oil (124 mg, 75% yield), whose spectral data were in accord with the literature values.[3] TLC R_f = 0.3 in 10% MeOH/DCM.



3n

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.23 (m, 2H), 8.22 – 8.15 (m, 2H), 5.53 – 5.44 (m, 1H), 4.88 (d, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 2.25 – 2.10 (m, 2H), 1.78 (s, 3H), 1.63 – 1.44 (m, 2H), 1.15 (s, 3H), 1.07 (s, 3H), 1.05 – 1.03 (m, 1H).

9-(1-methylaziridin-2-yl)nonan-1-ol (**3o**): Following the general aziridination procedure,

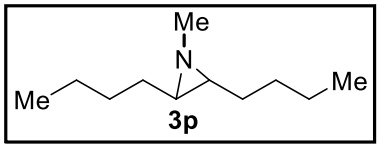


3o

undec-10-en-1-ol (85 mg, 0.50 mmol), TsONHMe (150.75 mg, 0.75 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (0.5 mL) at RT for 6 h. Chromatographic purification of crude product afforded **3o** as colorless oil (60 mg, 60% yield) whose spectral data were in accord with the literature values.[3] TLC R_f = 0.3 in 10% MeOH/DCM.

^{1}H NMR (800 MHz, $CDCl_3$) δ 3.63 (t, *J* = 6.6 Hz, 2H), 2.29 (s, 3H), 1.70 (brs, 1H), 1.60 – 1.52 (m, 2H), 1.48 (d, *J* = 3.5 Hz, 1H), 1.40 – 1.26 (m, 15H), 1.22 – 1.18 (m, 1H).

2,3-dibutyl-1-methylaziridine (**3p**): Following the general aziridination procedure, (*E*)-



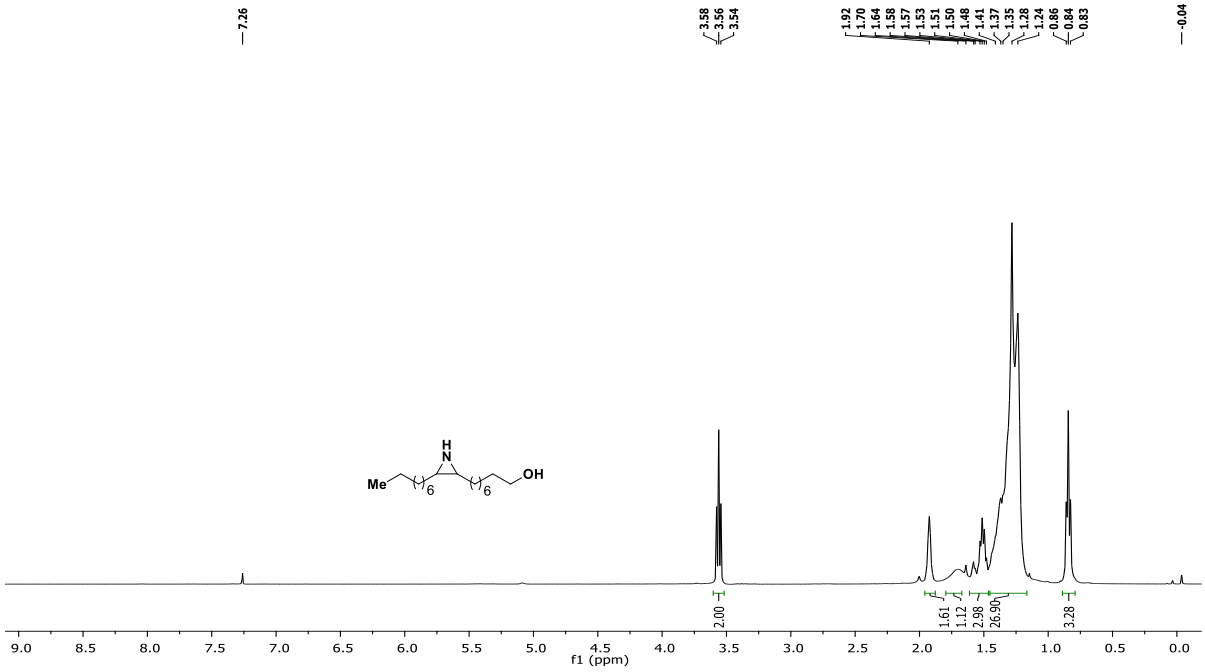
3p

dec-5-ene (70 mg, 0.50 mmol), TsONHMe (150.75 mg, 0.75 mmol) and $FeSO_4.7H_2O$ (14 mg, 10 mol%) were stirred in TFE (0.5 mL) at RT for 4 h. Chromatographic purification of crude product afforded **3p** as oil (64 mg, 76% yield) whose spectral data were in accord with the literature values.[3] TLC R_f = 0.5 in 50% EtOAc/Hexane.

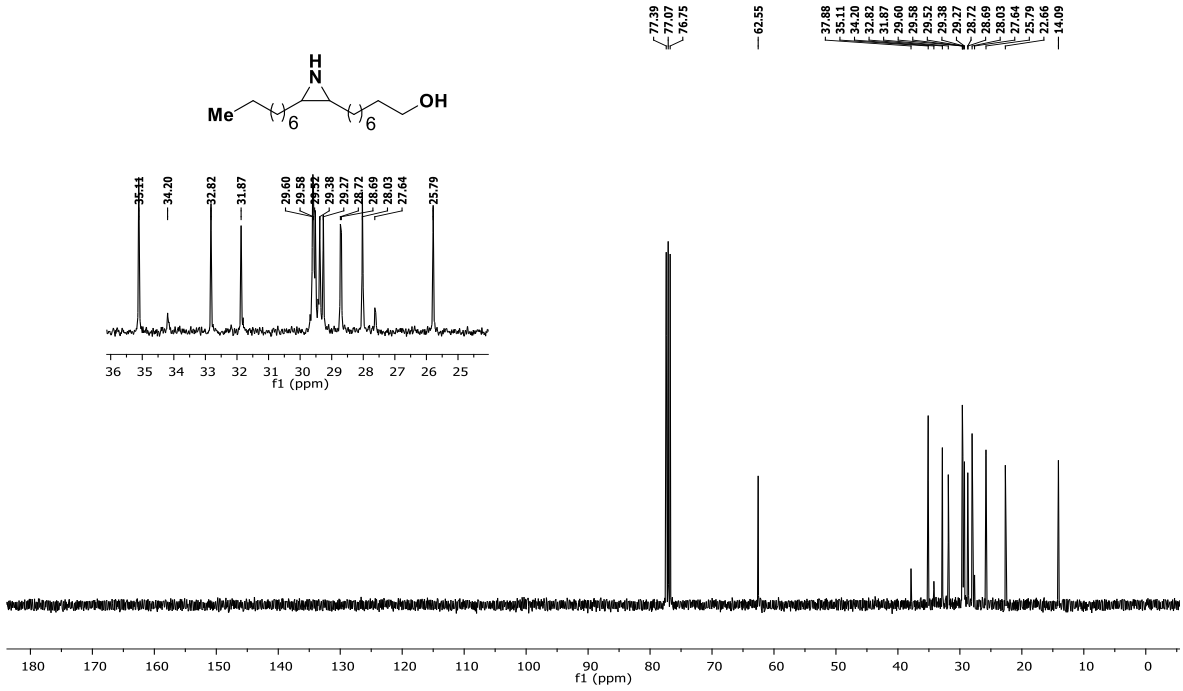
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 1.65 – 1.54 (m, 2H), 1.46 – 1.28 (m, 11H), 1.07 – 0.99 (m, 1H), 0.94 – 0.85 (m, 6H).

3.7 ^{1}H, $^{13}C\{^{1}H\}$ NMR and FT-IR Spectra of the Products

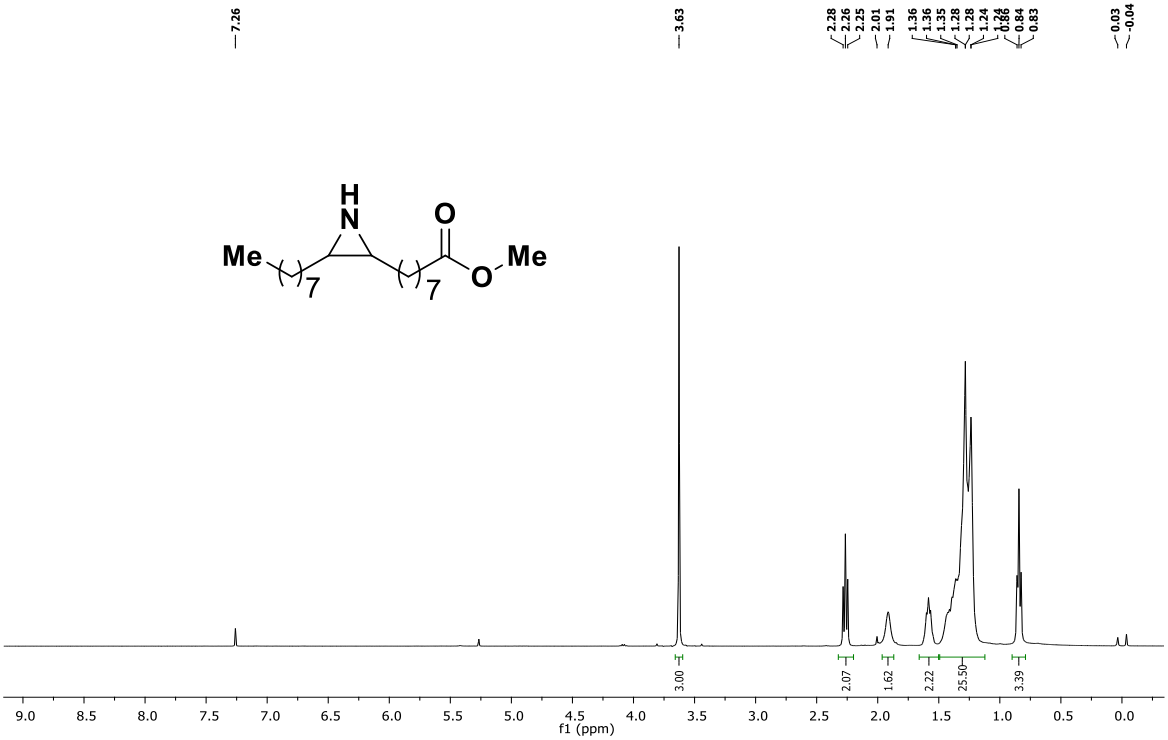
^{1}H NMR spectrum of compound **3a** (400 MHz/$CDCl_3$)



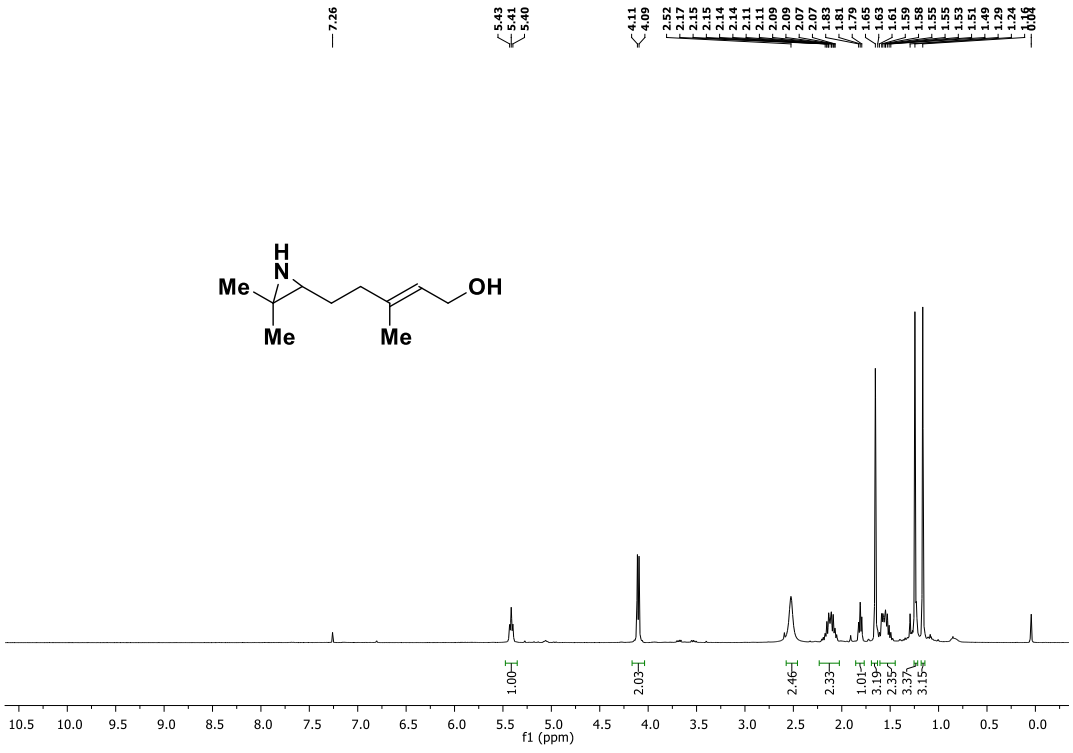
^{13}C NMR spectrum of compound **3a** (101 MHz/$CDCl_3$)



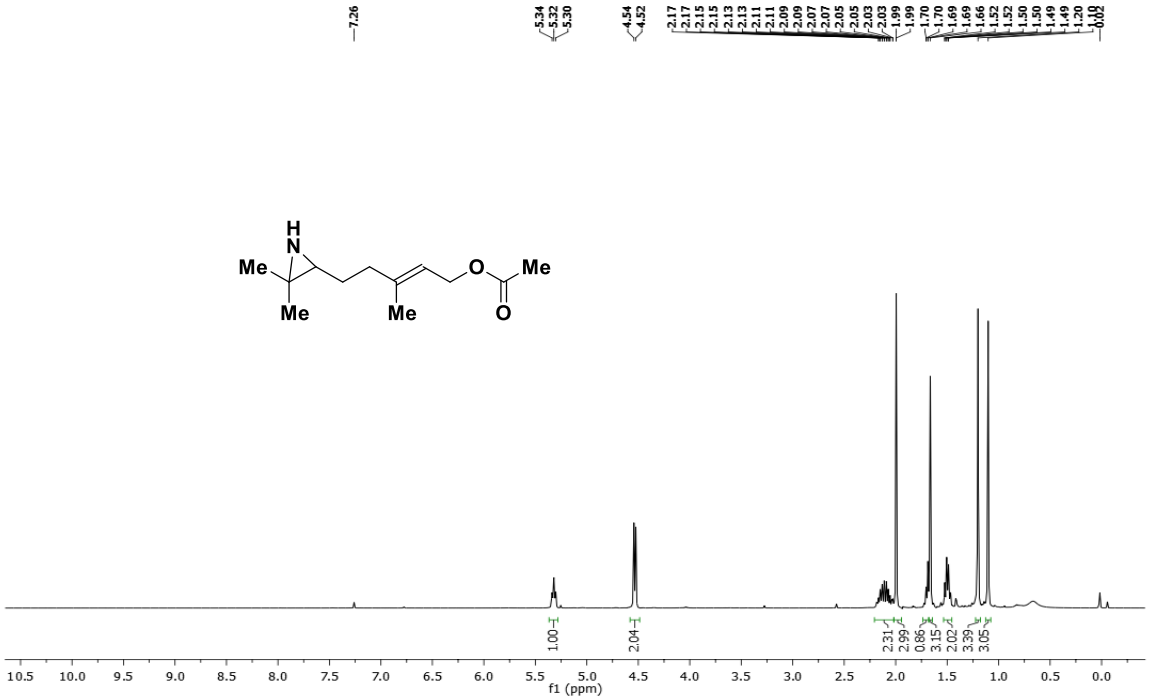
^{1}H NMR spectrum of compound **3b** (400 MHz/$CDCl_3$)



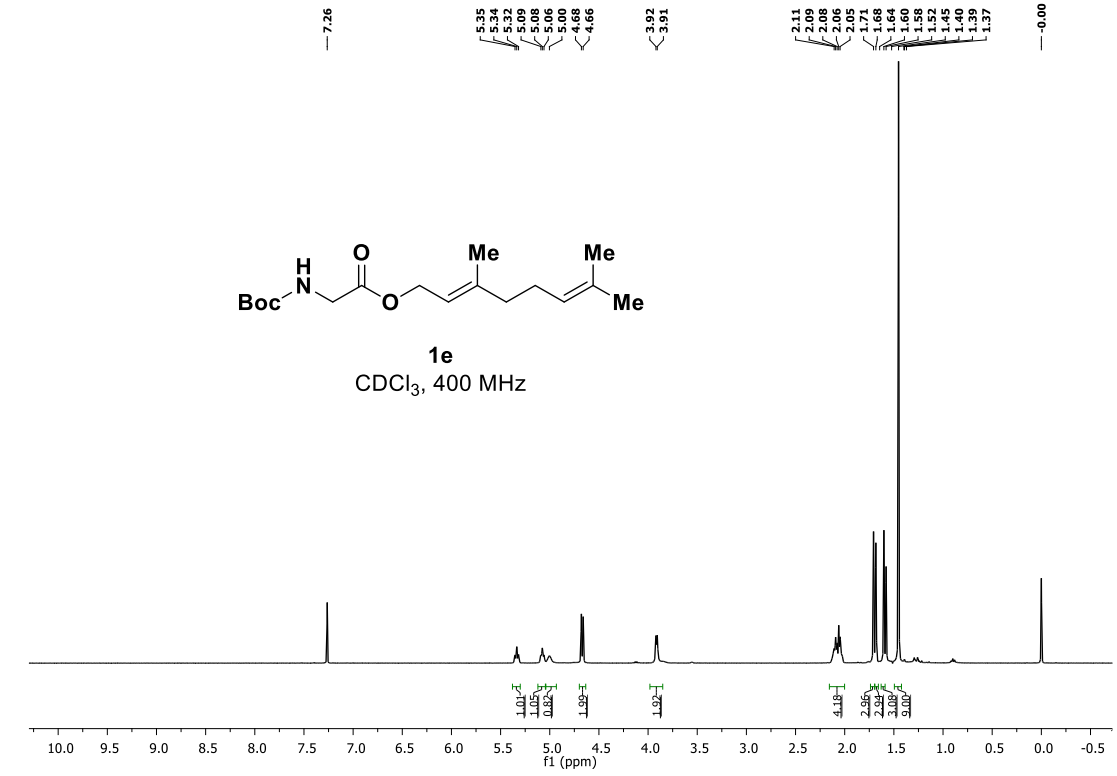
^{1}H NMR spectrum of compound **3c** (400 MHz/$CDCl_3$)



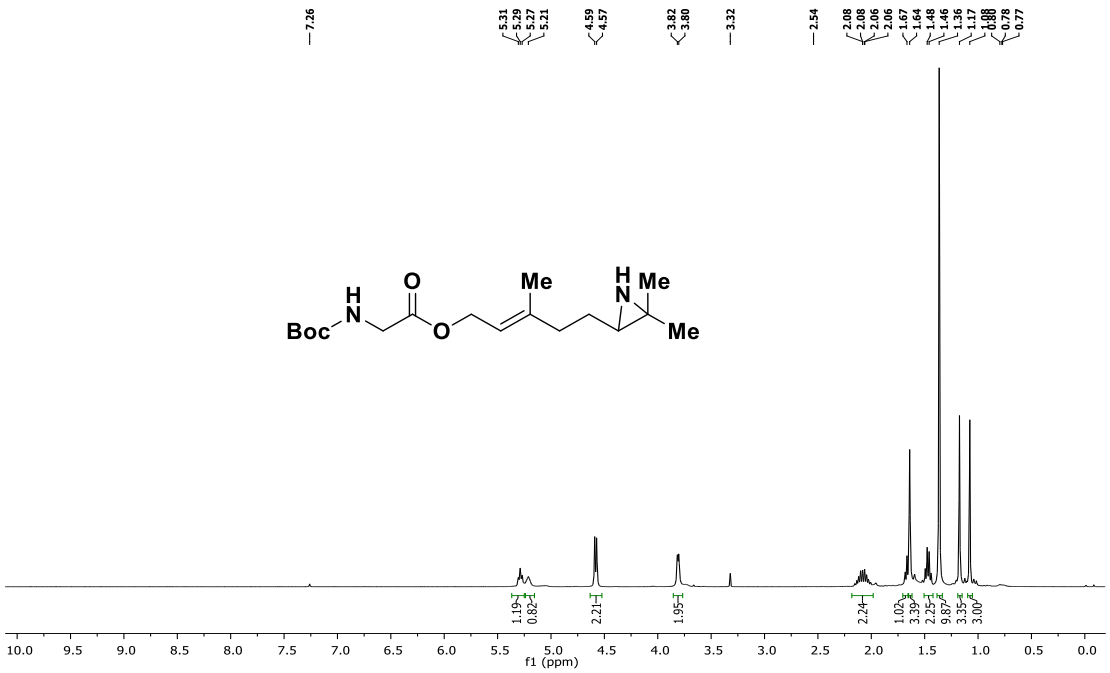
^{1}H NMR spectrum of compound **3d** (400 MHz/$CDCl_3$)



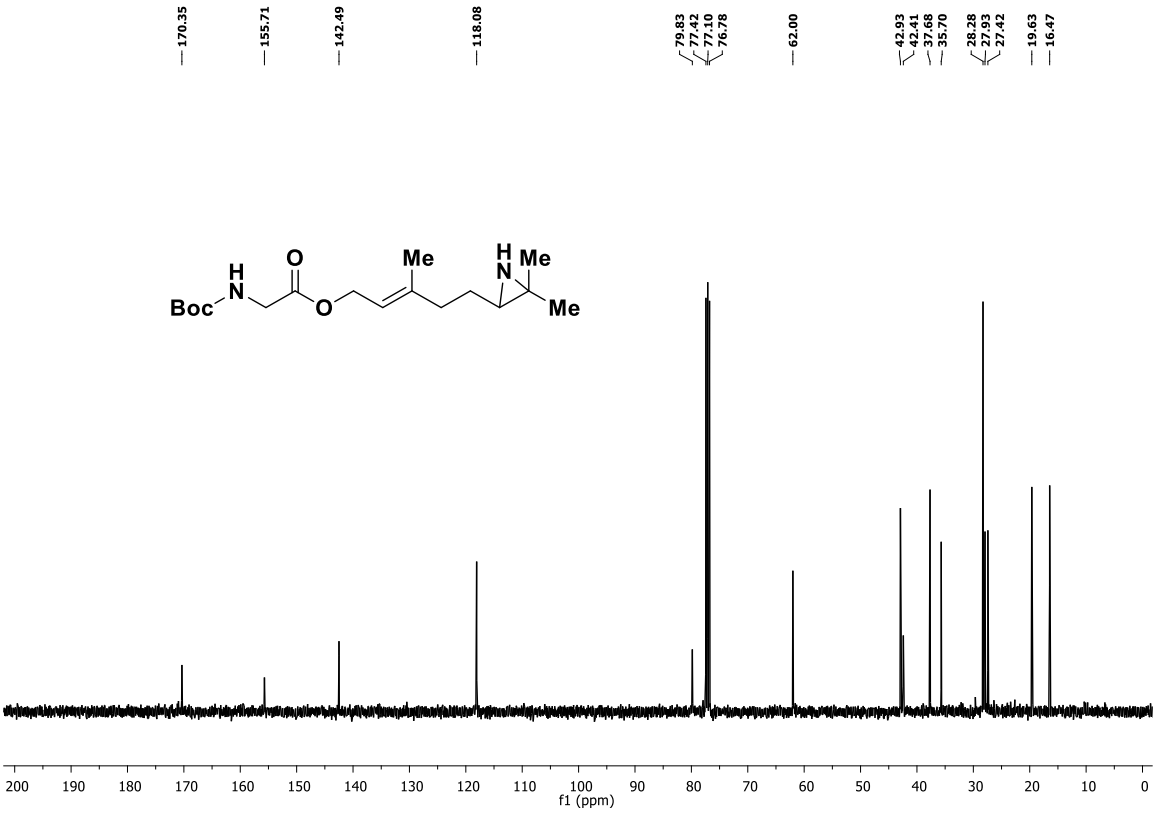
^{1}H NMR spectrum of compound **1e** (400 MHz/$CDCl_3$)



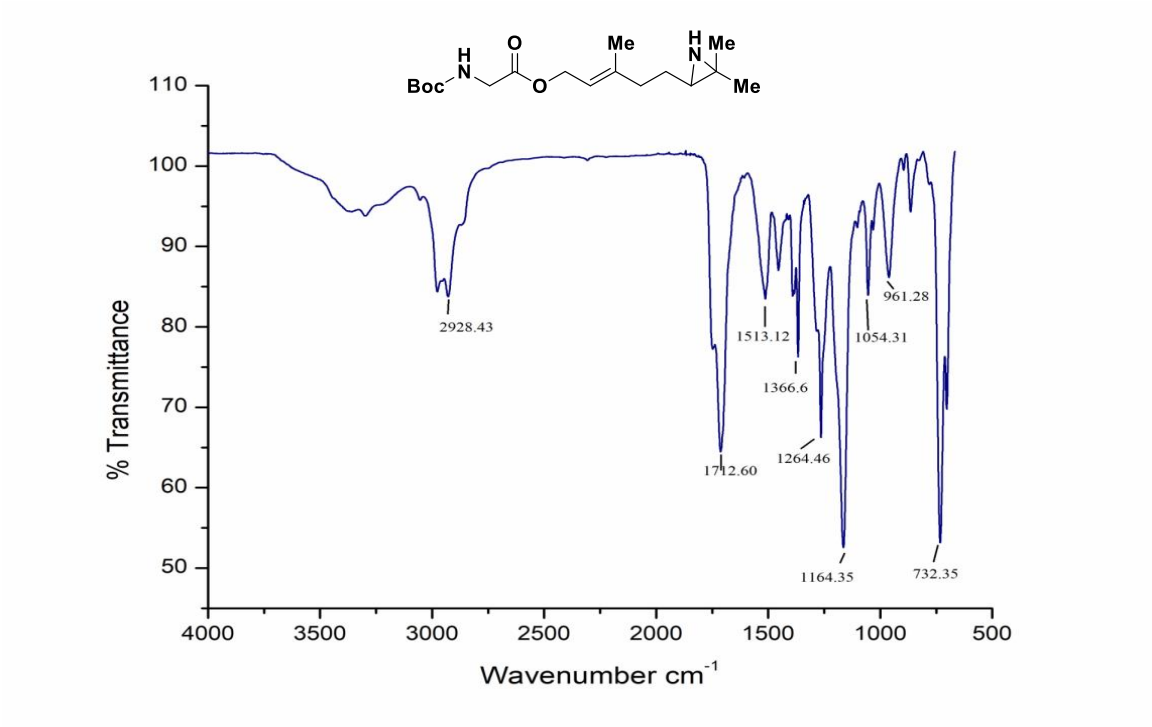
^{1}H NMR spectrum of compound **3e** (400 MHz/$CDCl_3$)



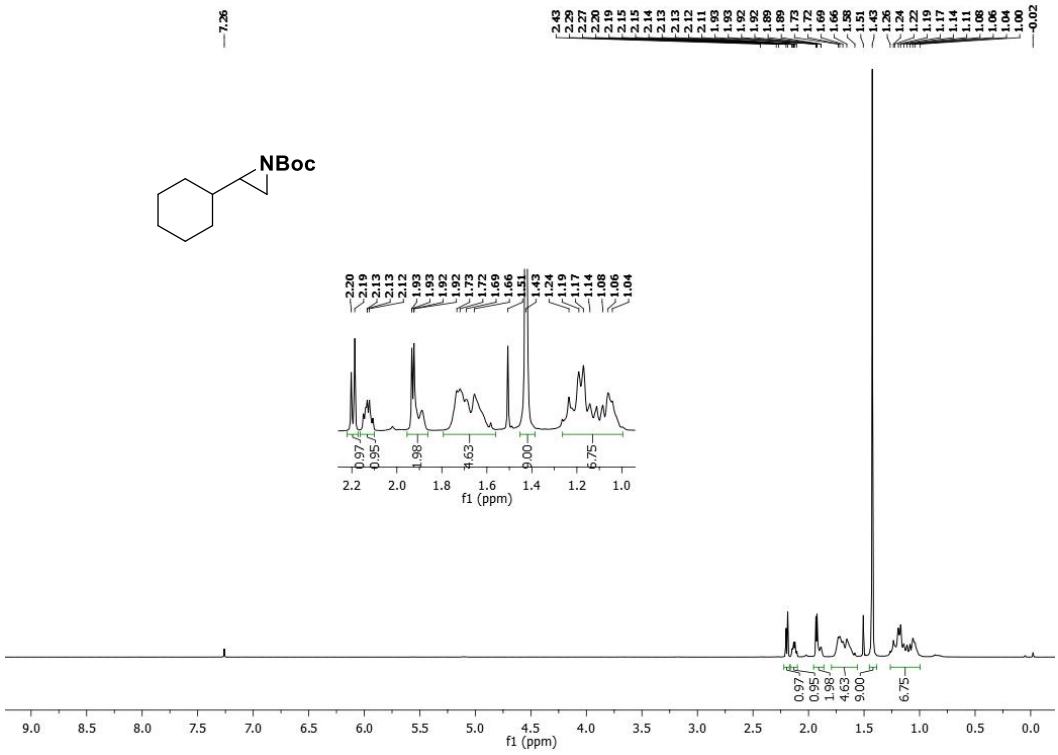
^{13}C NMR spectrum of compound **3e** (101 MHz/$CDCl_3$)



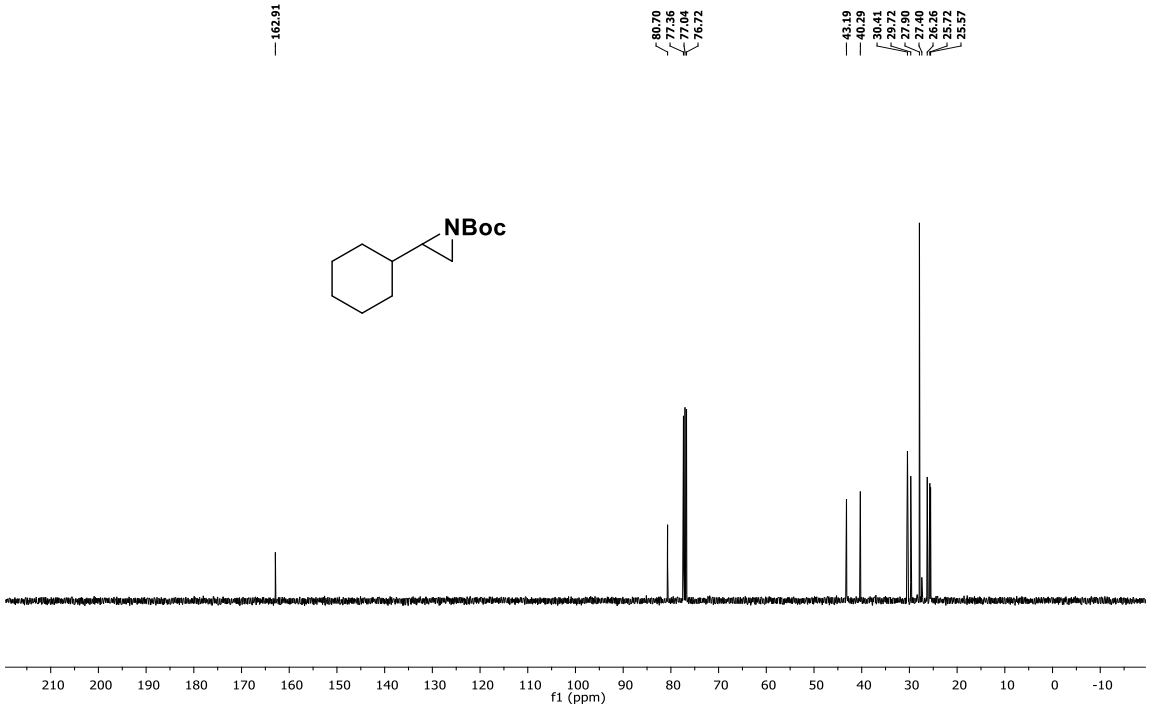
IR spectrum of compound **3e** (CH_2Cl_2)



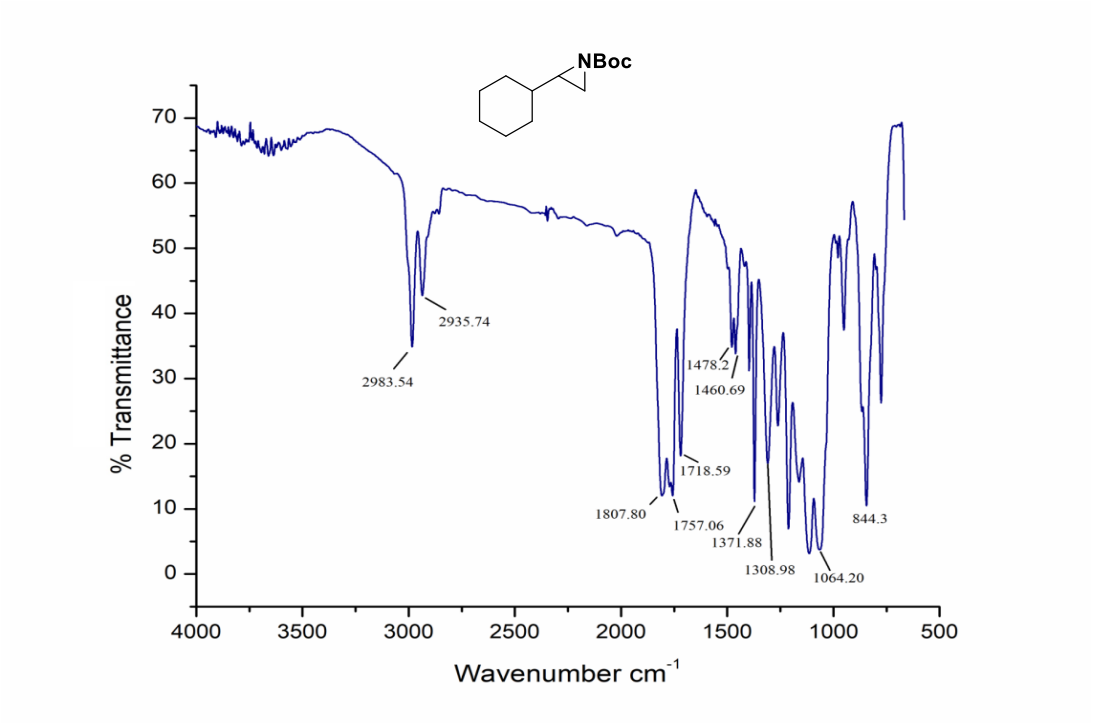
^{1}H NMR spectrum of compound **3f** (400 MHz/$CDCl_3$)



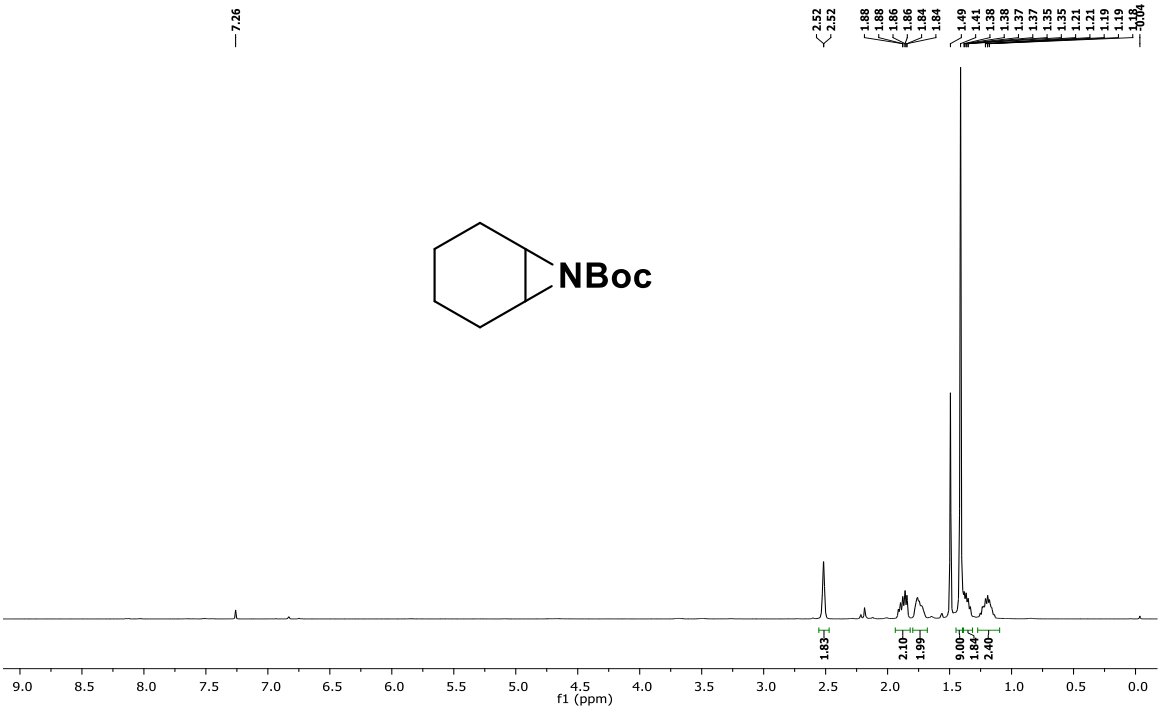
^{13}C NMR spectrum of compound **3f** (101 MHz/$CDCl_3$)



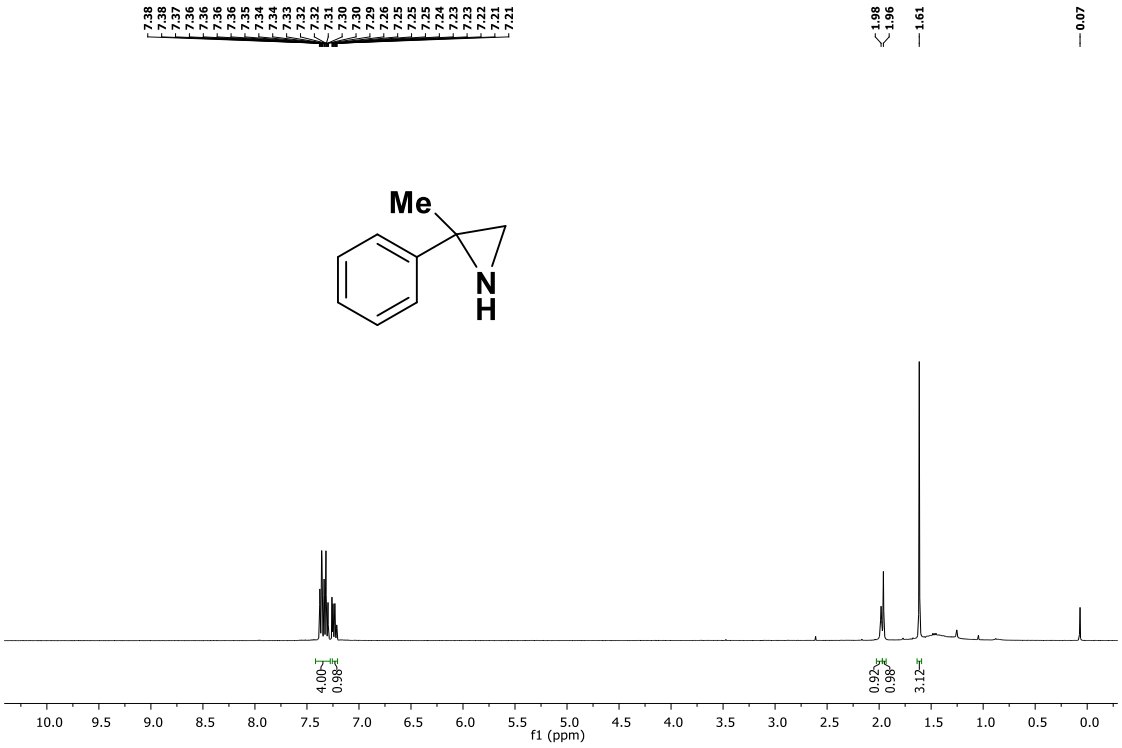
IR spectrum of compound **3f** (CH_2Cl_2)



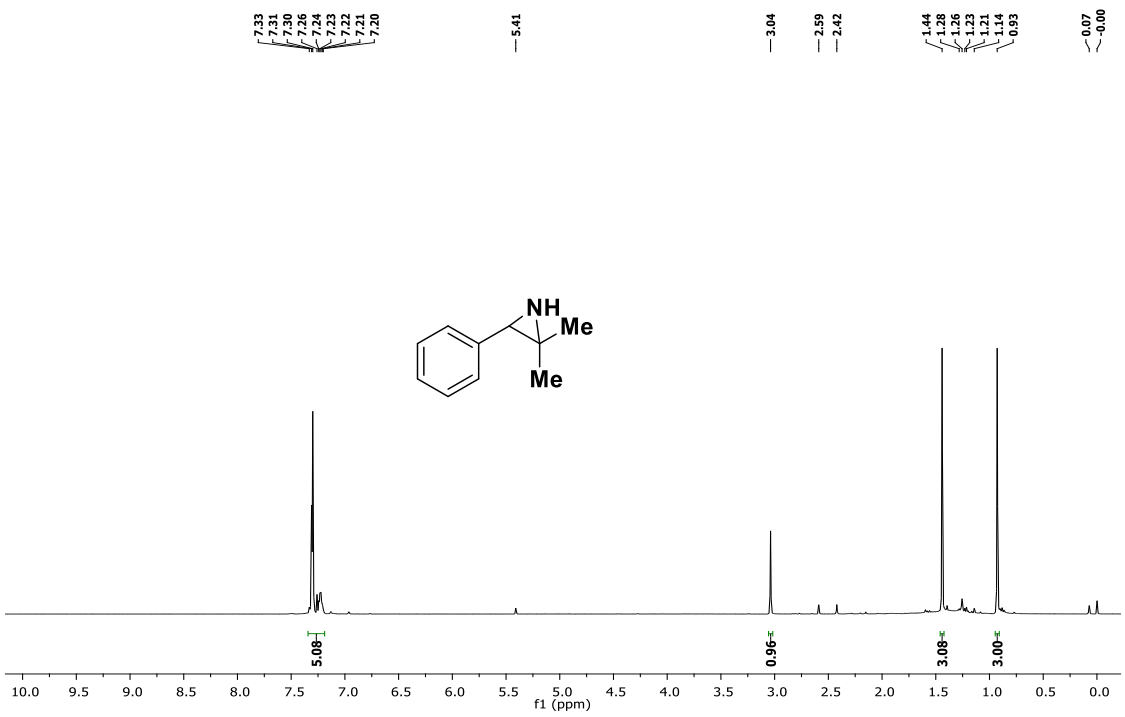
^{1}H NMR spectrum of compound **3g** (400 MHz/$CDCl_3$)



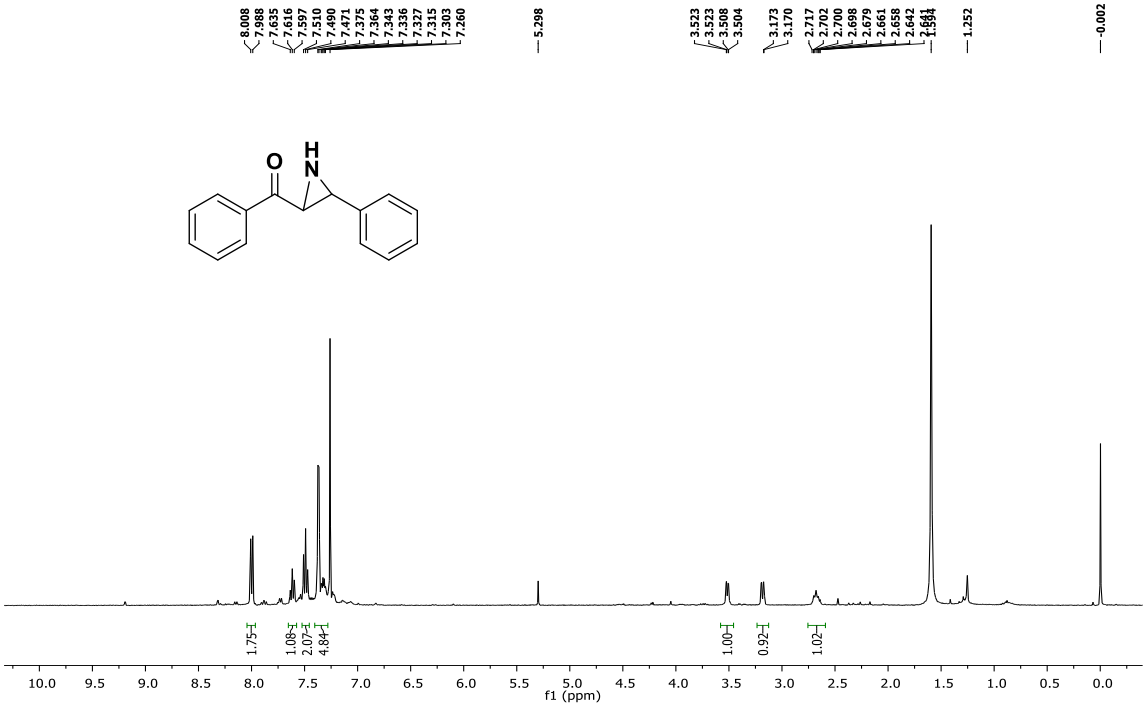
^{1}H NMR spectrum of compound **3h** (400 MHz/$CDCl_3$)



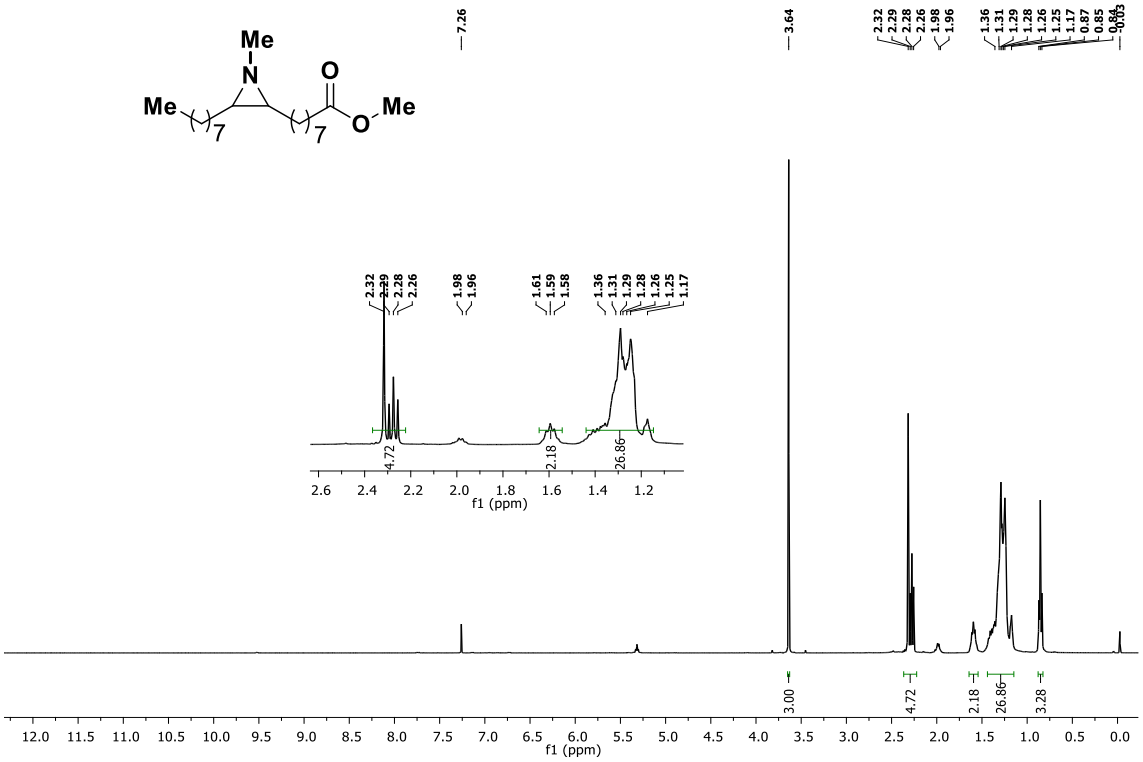
^{1}H NMR spectrum of compound **3i** (400 MHz/$CDCl_3$)



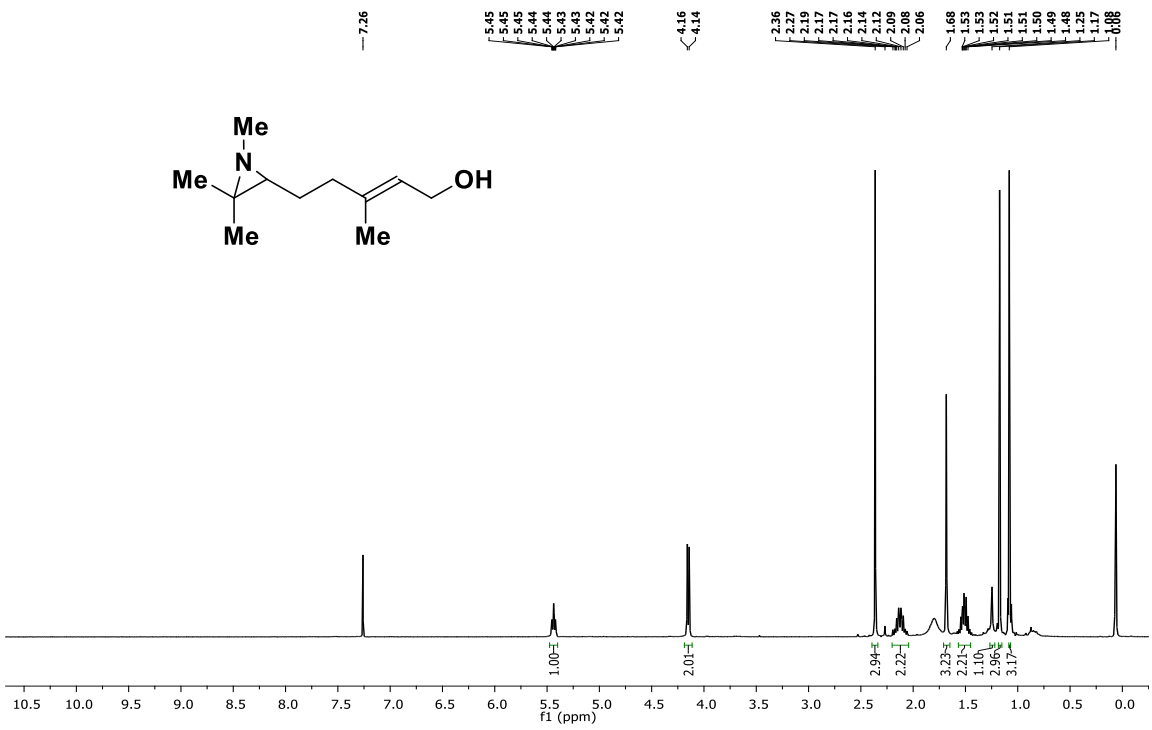
^{1}H NMR spectrum of compound **3j** (400 MHz/$CDCl_3$)



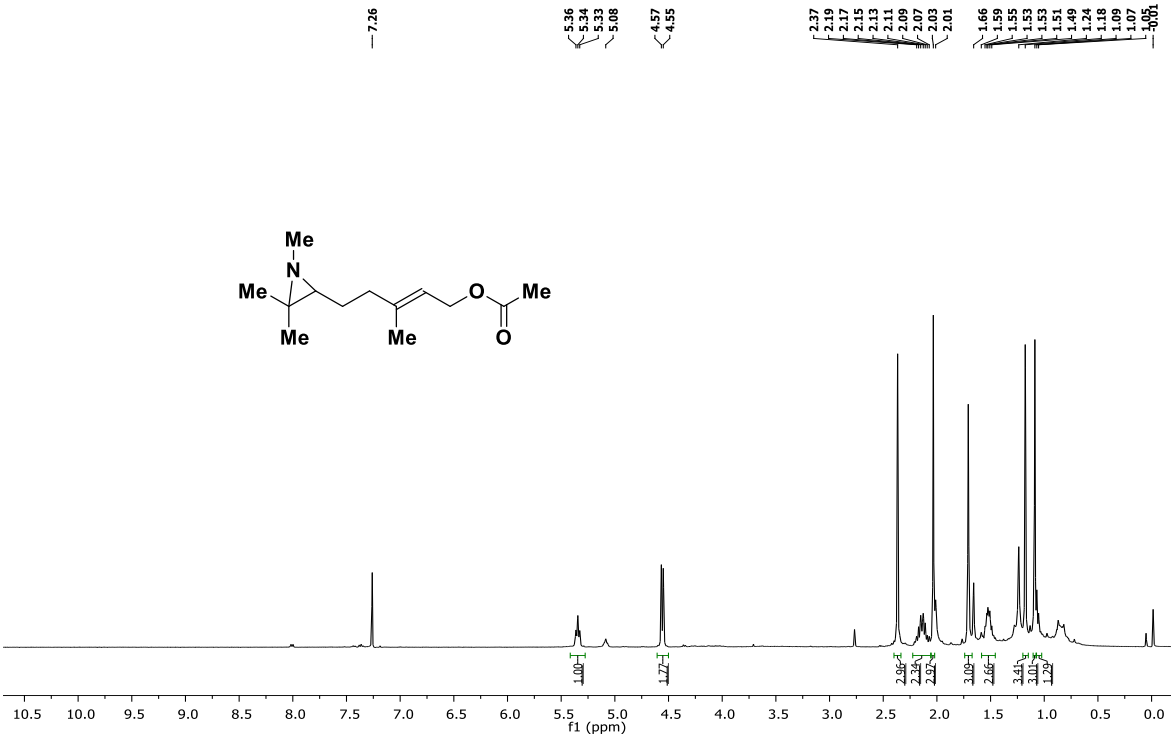
^{1}H NMR spectrum of compound **3k** (400 MHz/$CDCl_3$)



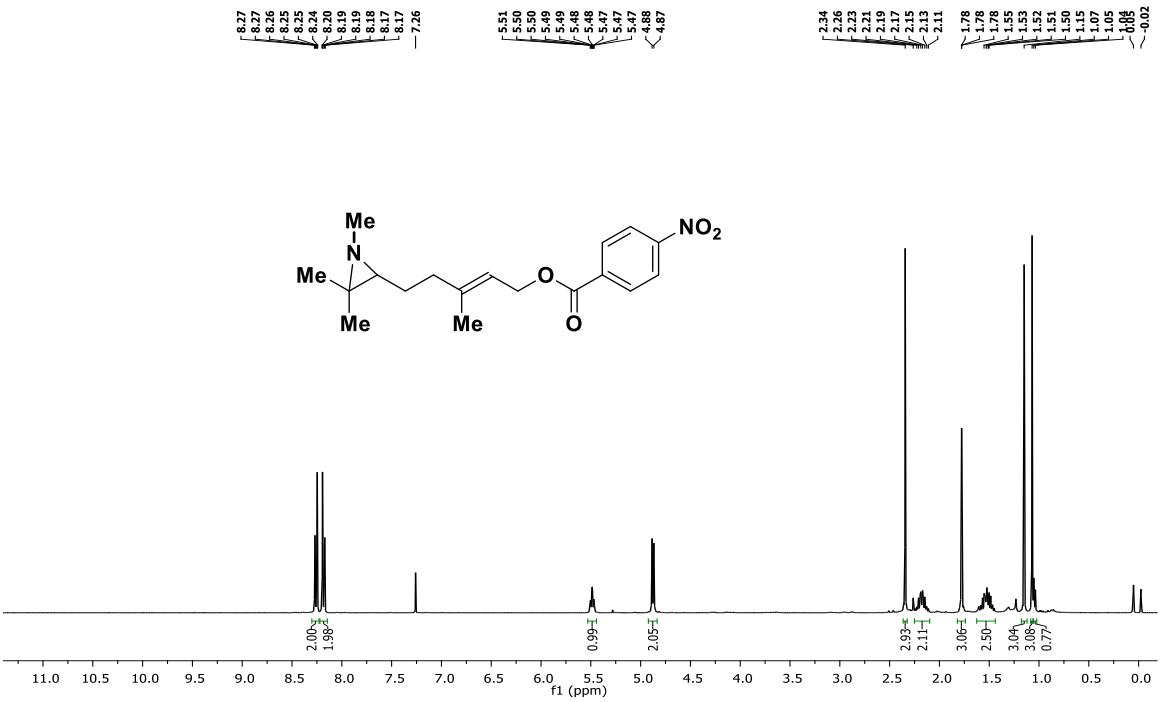
^{1}H NMR spectrum of compound **3l** (400 MHz/$CDCl_3$)



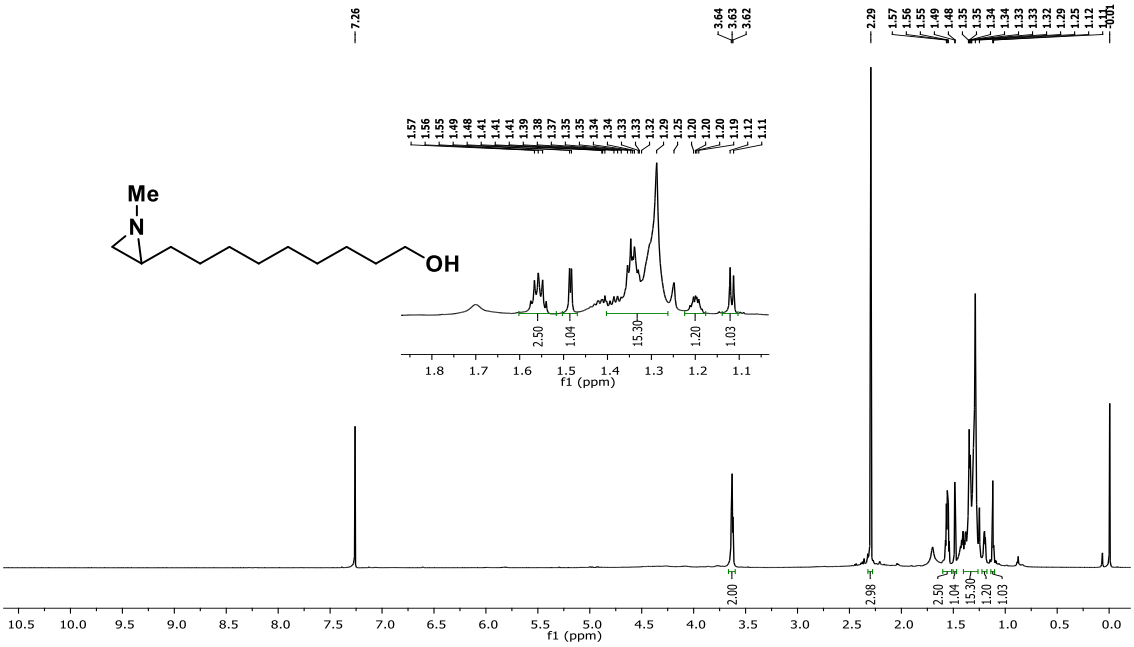
^{1}H NMR spectrum of compound **3m** (400 MHz/$CDCl_3$)



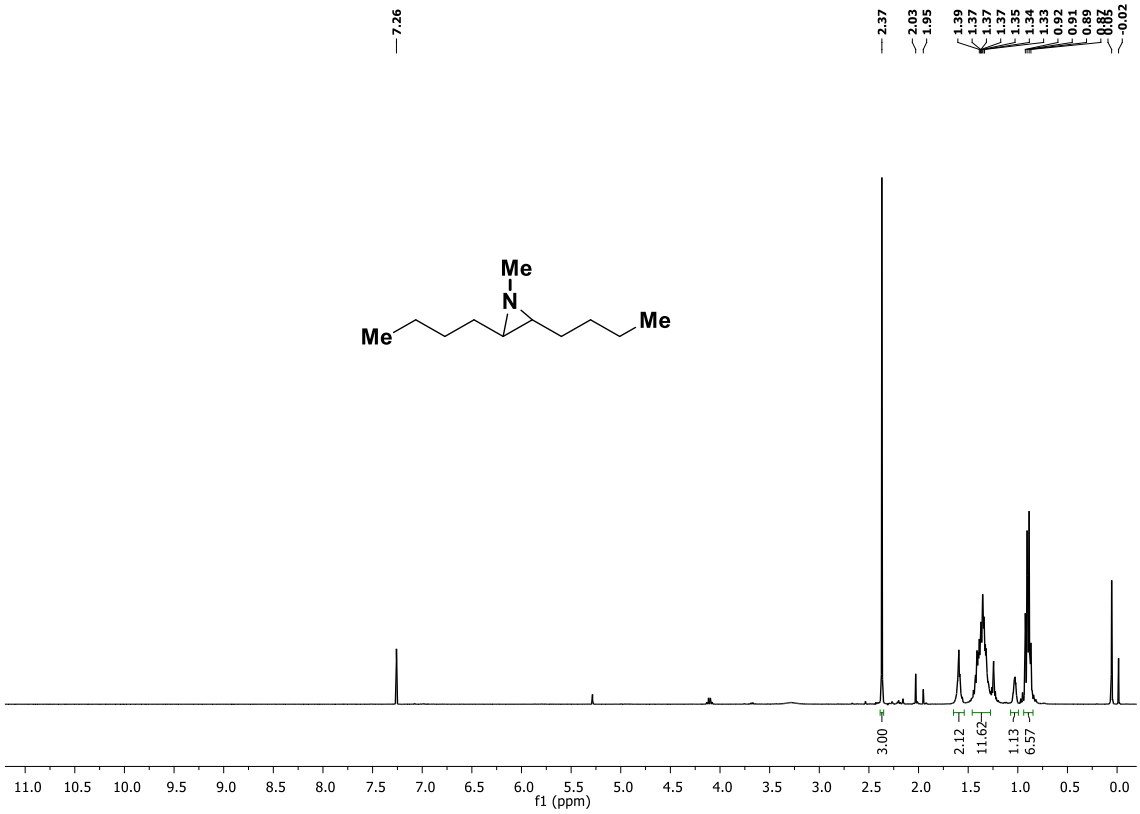
^{1}H NMR spectrum of compound **3n** (400 MHz/$CDCl_3$)



^{1}H NMR spectrum of compound **3o** (400 MHz/$CDCl_3$)



^{1}H NMR spectrum of compound **3p** (400 MHz/$CDCl_3$)



3.8 References

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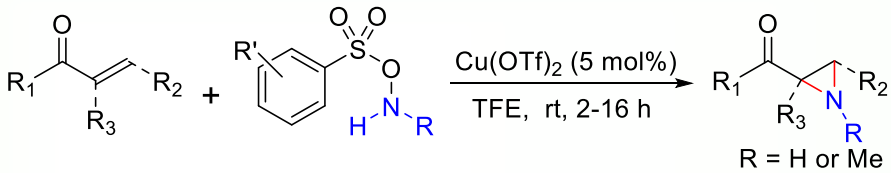
Chapter 4

Cu(II)-Catalyzed Direct and Stereospecific *N*-H and *N*-Me Aziridination of Enones

$Cu(OTf)_2$ catalyzed first and direct *N*-Me aziridination of vinyl ketones is disclosed employing *N*-methyl-*O*-tosylhydroxylamine as the aminating agent. Under this reaction condition, *N*-H aziridination of chalcones were also developed by using *O*-(mesitylenesulfonyl)hydroxylamine. This one-pot, open-flask, stereospecific, and practical method afforded a broad range of *N*-H/*N*-Me aziridines in good to excellent yields.



- First report on *N*-Me aziridination of vinyl ketones
- Suitable for *N*-H aziridination of chalcones
- Mild and operationally simple procedure

(*J. Org. Chem.* **2021**, under revision)

4.1 Introduction

The *α,β*-unsaturated ketones (enones) are widely available and useful compounds in medicinal as well as in synthetic chemistry. Chalcones (*i.e.* 1,3-diaryl-2-propene-1-one) are widely present in naturally occurring bioactive compounds.[1] They can be transformed into various value-added compounds *via* either 1,2- or 1,4-addition reactions (Michael addition). Significantly they are used in the synthesis of various important heterocyclic compounds such as pyrazoles, pyrazoline, isoxazoles, pyrimidines, triazoles, imidazoles, etc.[2] They possess promising pharmacological activities including anti-cancer, anti-bacterial, anti-inflammatory, anti-diabetic, anti-oxidant, anti-microbial and anti-viral, etc.[1,3] Like chalcones, vinyl ketones are also useful synthetic intermediates and they also display various important michael type addition reactions.[4] Recently, great interest has been shown in the field of enone aziridination and epoxidation as they are extremely important motifs present in various natural and unnatural bioactive products.[5] Bioactive natural products containing aziridine moiety into their structural skeleton at α,β-position of ketones, acids, and amides have been widely used in cathepsin B inhibition, antibacterial agents and treatment of multiple sclerosis (Figure 4.1).[6]

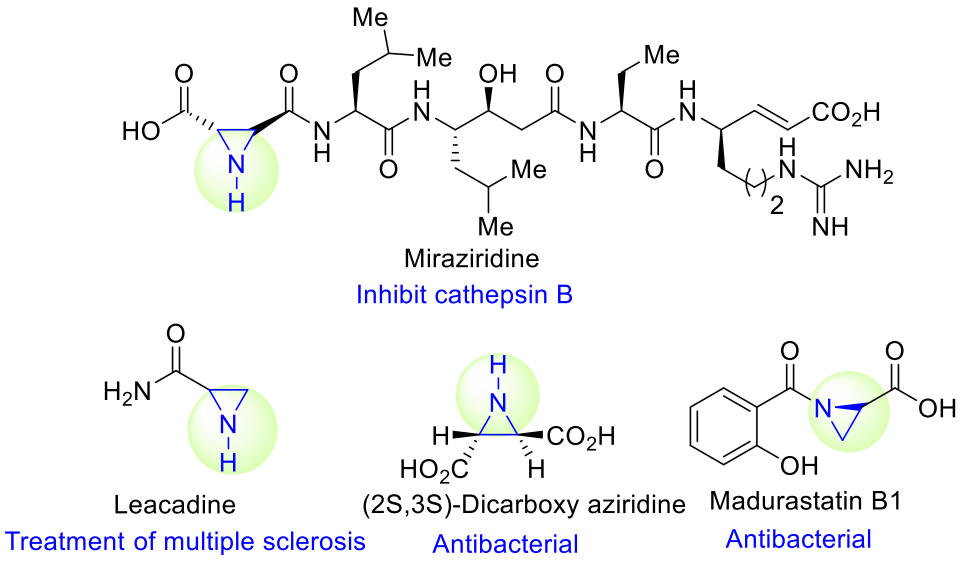
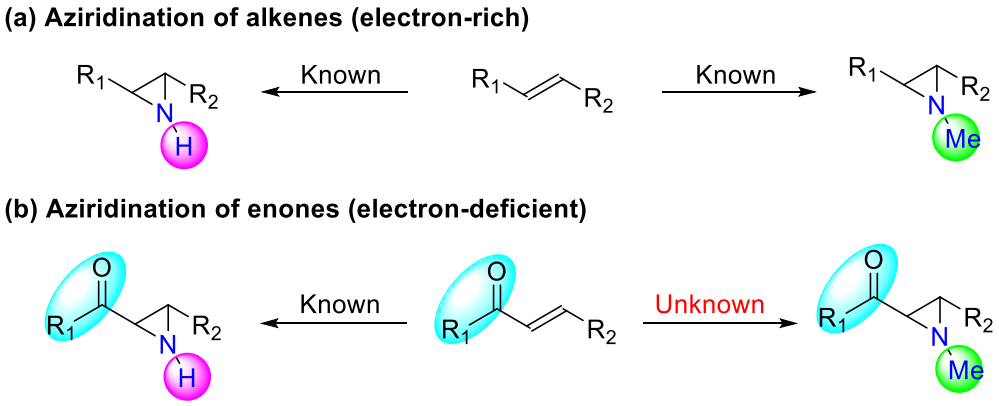


Figure 4.1. Aziridine moiety present in natural and synthetic products

The methods for the direct synthesis of *N*-H and *N*-Me aziridines from alkenes are known (Scheme 4.1a),[7-8] whereas, in the case of chalcones, direct methods for the synthesis of *N*-H aziridines are known but, the method for the direct synthesis of *N*-Me aziridines is unknown (Scheme 4.1b).[9] Hence, the development of the methods for the synthesis of *N*-H and *N*-Me aziridines from enones is highly essential.



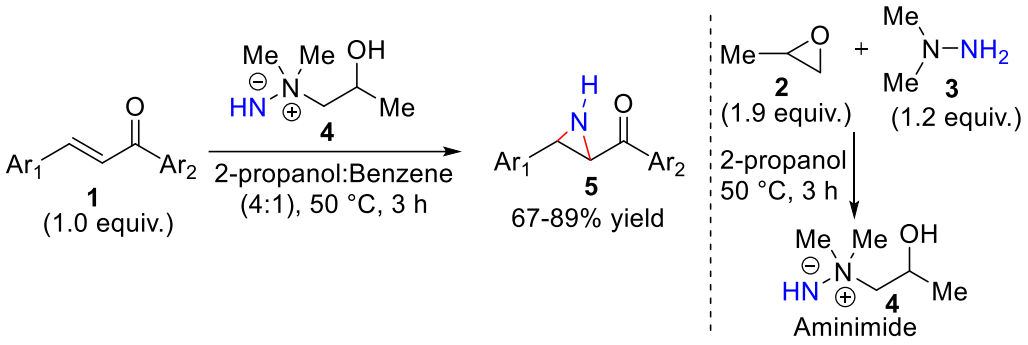
Scheme 4.1. *N*-H and *N*-Me Aziridination of alkenes or enones

A synthetic overview of enone aziridination are summarized below:

4.2 Literature review of *N*-H/*N*-alkyl aziridination of enones

4.2.1 Enone aziridination using aminimides

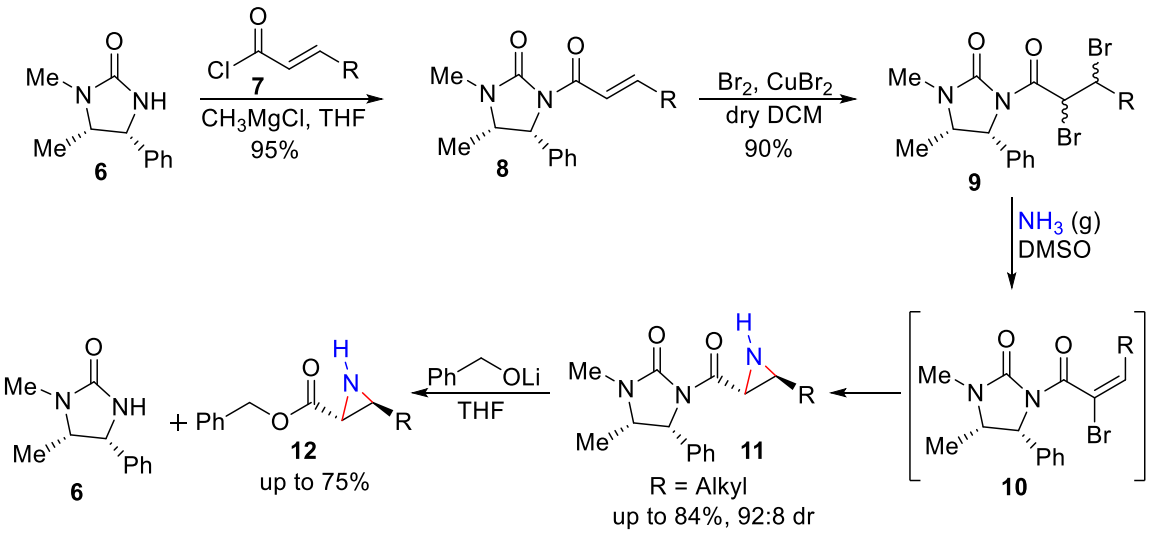
In 1980, Ikeda and coworkers reported a one-pot *N*-H aziridination of chalcones **1** using aminimide or aminimine **4** (N-N ylide) (Scheme 4.2).[10] The *trans N*-H aziridine **5** is produced from conjugate addition of chalcones by the aminimide **4** (produced *in situ* by the reaction of propene oxide **2** and 1,1-dimethylhydrazine **3**). The substrate scope was limited in this methodology, as only four substrates reported with 67-89% yields.



Scheme 4.2. *N*-H Aziridination of chalcones by aminimide

4.2.2 Diastereoselective aziridination of *α,β*-unsaturated *α*-bromoimides

Giuliana Cardillo *et al.* established a multi-step methodology for the synthesis of *trans N*-H aziridine-2-carboxylates **12** using *α,β*-unsaturated α-bromoimides **10** *via* Gabriel-Cromwell reaction. (Scheme 4.3).[11]

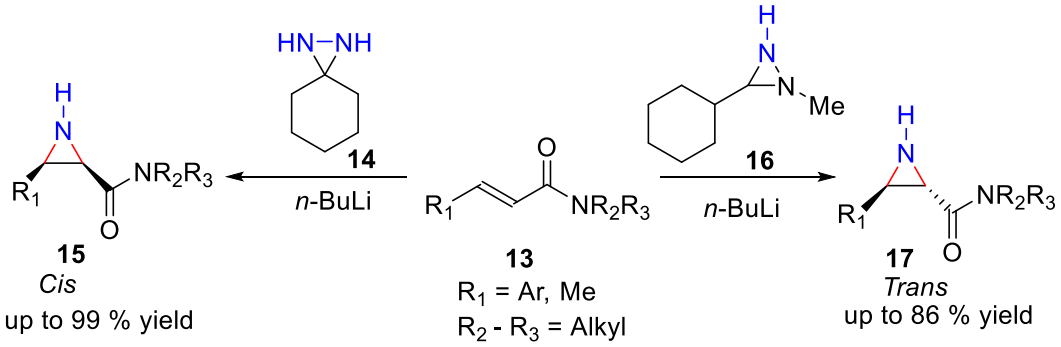


Scheme 4.3. Diastereoselective *N*-H aziridination of *α,β*-unsaturated-*α*-bromoimides

4.2.3 Diaziridine mediated aziridination of *α,β*-unsaturated amides

Katsuki *et al.* developed a method to produce *cis N*-H aziridines **15** from *α,β*-unsaturated amides **13** using diaziridine **14** as a nitrogen source.[12] They also disclosed that the use of 3,3-disubstituted diaziridine was suitable for *cis*-selective *N*-H aziridination whereas for *trans*-selective *N*-H aziridination 3-monosubstituted diaziridine was suitable (Scheme

4.4).[13] The reaction proceeded *via* sterically less hindered configuration of the enolate intermediate **I** to produce the *cis N*-H aziridines (Figure 4.2).



Scheme 4 .4. *Cis*- and *trans*- *N*-H aziridination of α,β-unsaturated amides

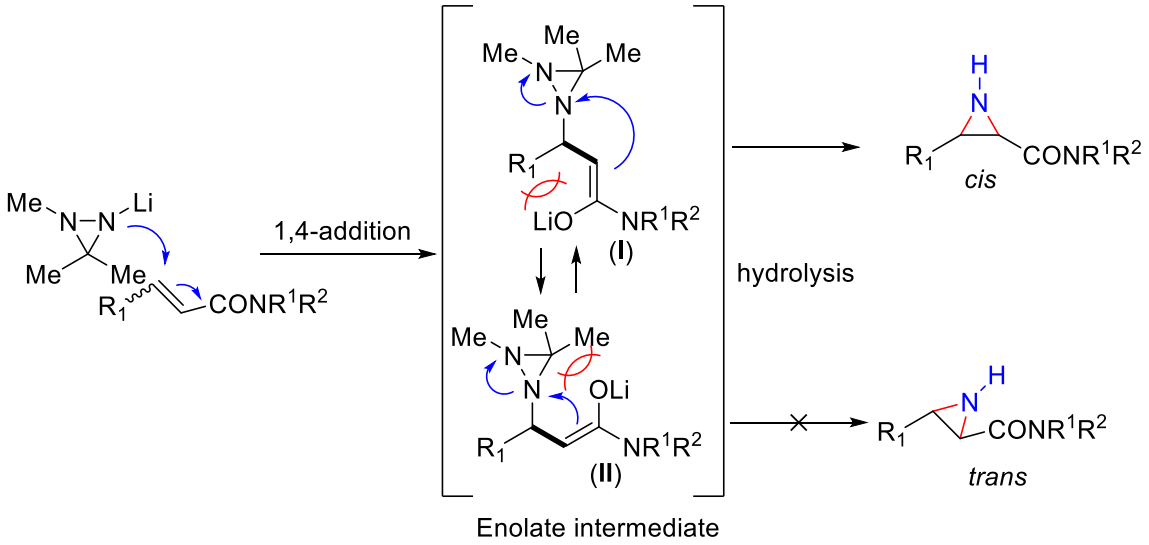
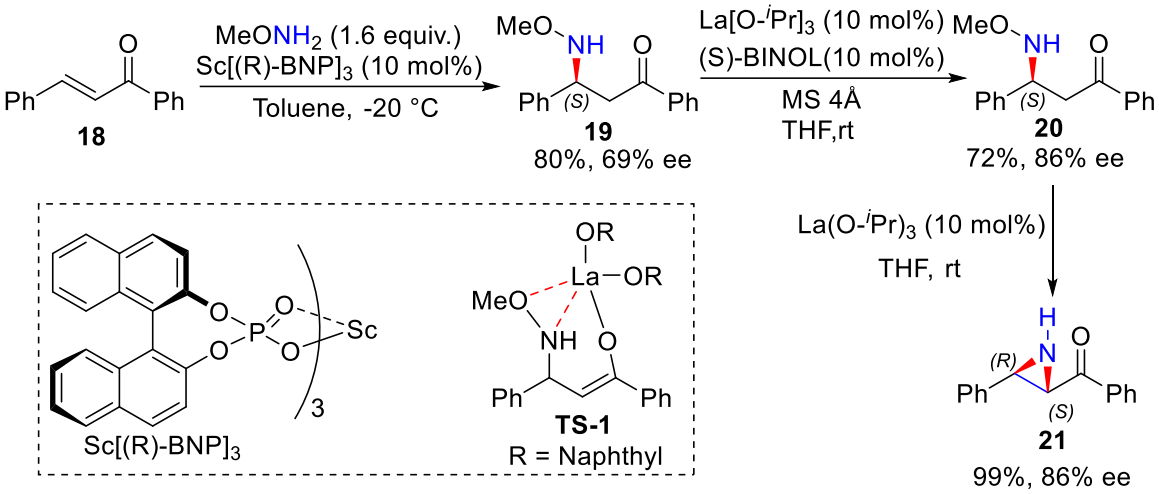


Figure 4.2. Proposed reaction mechanism

4.2.4 Enantioselective aziridination of enones using *O*-methylhydroxylamine

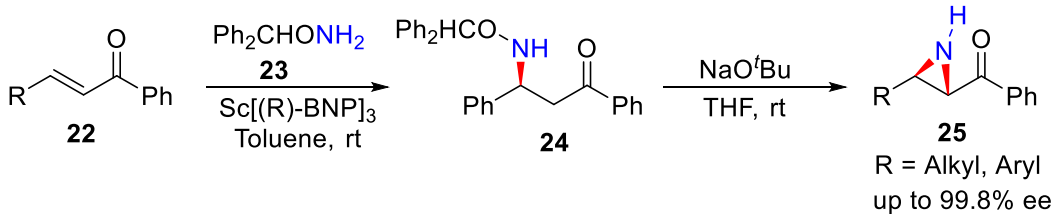
Junji Inanaga *et al.* established a three-step method for the synthesis of asymmetric *N*-H aziridines **21** from the α,β-unsaturated ketones **18** using chiral Sc[(R)-BNP]$_3$ catalyst. This method provides a moderate to a good yield of aziridines with high *ee*. (Scheme 4.5).[14] This methodology failed to produce aziridines from aliphatic enones.



Scheme 4.5. Unprotected *N*-H aziridination of enones

4.2.5 Enone aziridination using *O*-benz-hydryl-hydroxylamine

The above described process was further improved by the same group. They developed a two-step procedure for preparing unprotected *N*-H aziridines **25** from α,β-unsaturated ketones **22** using Ph_2CHONH_2 (*O*-Benz-hydryl-hydroxylamine) as a nitrogen source and Sc[(R)-BNP]$_3$ chiral (scandium complex) as Lewis acid catalyst (Scheme 4.6).[15]

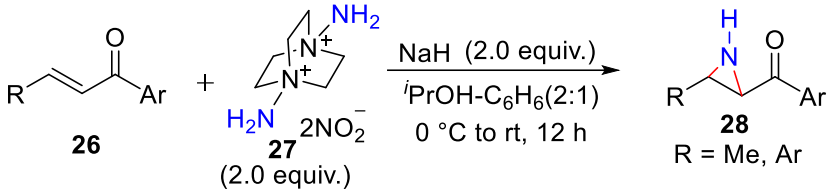


Scheme 4.6. *N*-H Aziridination of enones using *O*-benz-hydryl-hydroxylamine

4.2.6 Aziridination of enones using hydrazinium salt

Jiaxi Xu and Peng Jiao demonstrated the method for the synthesis of *trans N*-H aziridines from a variety of α,β-unsaturated ketones **26** using *N*,*N*-diamino-1,4-diazoniabicyclo-[2.2.2]octane dinitrate (hydrazinium salt) as a nitrogen source (Scheme 4.7).[16] Electron-donating groups bearing, α,β-unsaturated ketones (both -alkyl and -aryl substrates) afforded the high to excellent yields of *trans N*-H aziridines while electron-withdrawing groups bearing substrates like nitro (NO_2) produced lower yields. In this reaction,

hydrazinium nitrate was converted into diamine imide **III** using NaH as a base which further reacted with *α,β*-unsaturated ketones *via* Michael addition followed by the cyclization to provide *trans N*-H aziridines **28** (Figure 4.3). Aliphatic enones, enoates, or enamides were not explored under this reaction condition.



Scheme 4.7. Aziridination of enones using hydrazinium salt

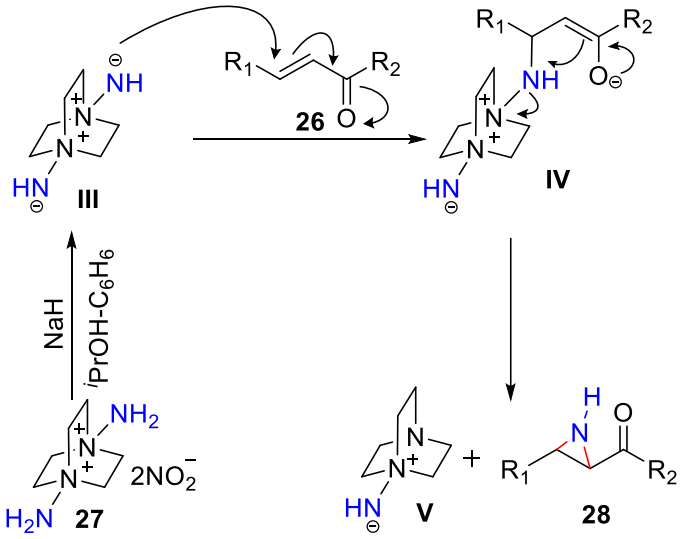
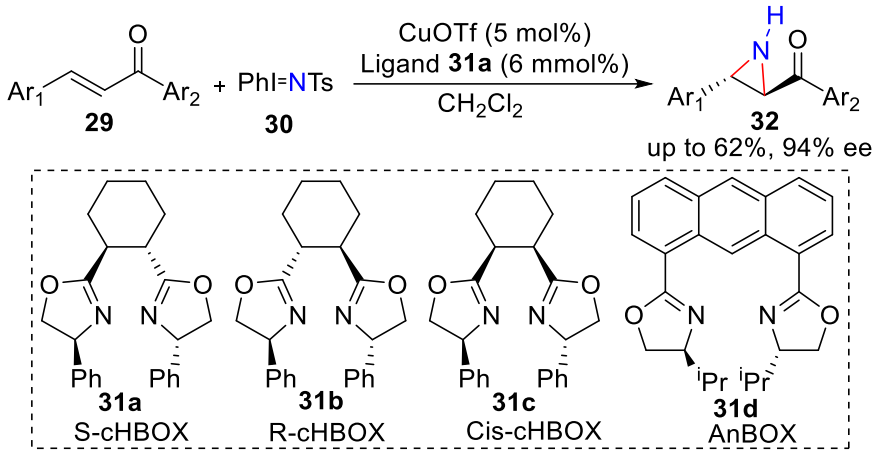


Figure 4.3. Proposed mechanism for *N*-H aziridination by hydrazinium salt

4.2.7 Aziridination of chalcones using [*N*-(*p*-toluenesulfonyl)imino]-phenyliodinane]

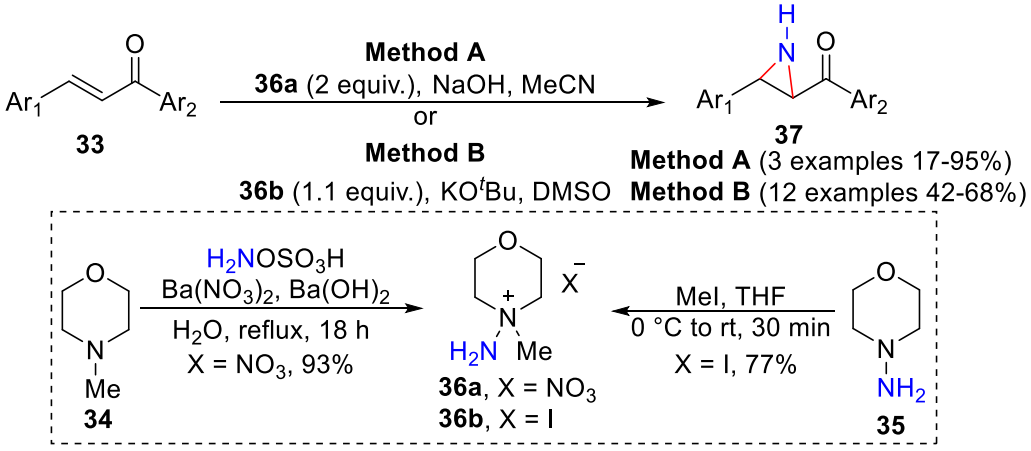
Enantioselective aziridination of chalcones was achieved using [*N*-(*p*-toluenesulfonyl)imino]-phenyliodinane] **30** as a nitrogen source, CuOTf as a catalyst, and cHBOXes as chiral ligands (**31a-c**). The CHBOXes ligands did not display substituent-dependent enantioselectivity, unlike AnBOXes **31d**. Chalcones bearing electron-donating groups had better enantioselectivity than those with electron-withdrawing groups (Scheme 4.7).[17]



Scheme 4.7. Enantioselective aziridination of chalcones

4.2.8 Aziridination of enones using *N*-amino-*N*-methylmorpholinium salts

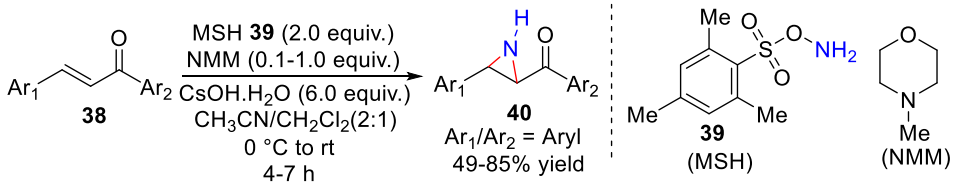
Armstrong *et al.* utilized the *N*-amino-*N*-methylmorpholinium salts for the synthesis of *N*-H aziridines **37** from enones **33** (Scheme 4.8).[18] They established two sets of aziridination reaction conditions (Method A and B). In Method A, Chalcones bearing electron-withdrawing groups exhibited greater reactivity using salt **36a** and base (NaOH) in MeCN solvent, whereas in Method B, chalcones bearing electron-donating groups exhibited greater reactivity using salt **36b** and base (KO^{t}Bu) in DMSO solvent. In all the cases, *trans* *N*-H aziridines were predominantly formed (>90:10). However, these conditions did not work with alkyl-substituted chalcones (aliphatic enones).



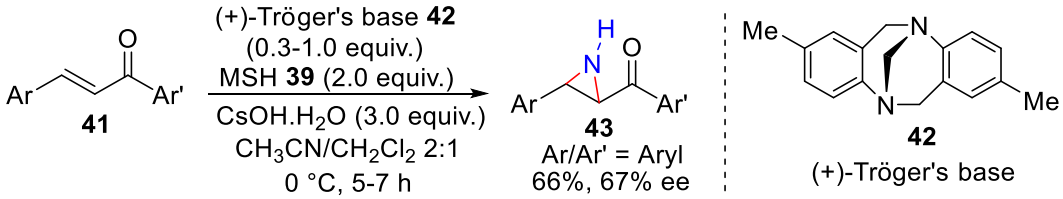
Scheme 4.8. Aziridination of chalcones with hydrazinium salts **36a** and **36b**

4.2.9 Amine-promoted organocatalytic aziridination of enones using MSH

Shi *et al.* published a report in 2006 that involve a tertiary amine-promoted organocatalytic *N*-H aziridination of enones **38** in the presence of $CsOH.H_2O$ as a base (Scheme 4.9).[9b] They used catalytic amount of tertiary amine such as *N*-methyl morpholine (NMM) and *O*-mesitylenesulfonylhydroxylamine **39** (MSH) as a nitrogen source and $CsOH.H_2O$ as a base to get the *N*-H aziridines **40** in good to excellent yields. Shi also reported enantioselective aziridination of enones using (+)-Tröger's base **42**, where moderate amounts of asymmetric induction up to 67% *ee* were observed (Scheme 4.10).



Scheme 4.9. *N*-H Aziridination of enones using MSH as an aminating agent



Scheme 4.10. Asymmetric *N*-H aziridination of enones using (+)-Tröger's base

A catalytic mechanistic cycle was reported, according to which the reaction proceeded *via* Aza-michael addition of *in situ* generated aminimide **VII** followed by an intramolecular nucleophilic displacement furnishes the aziridines (Figure 4.4).

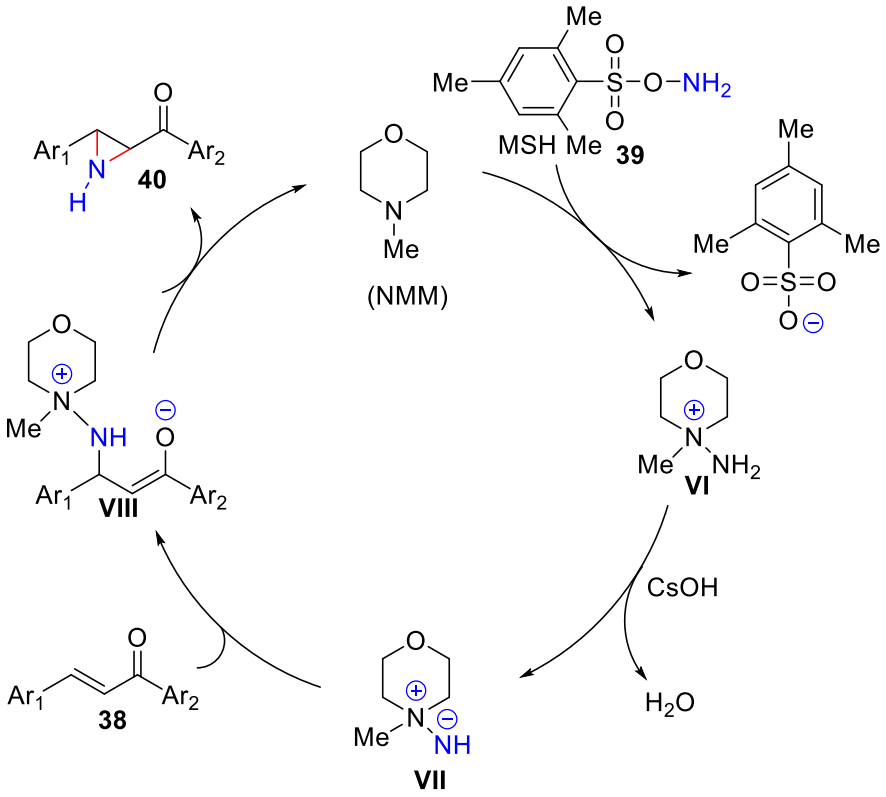
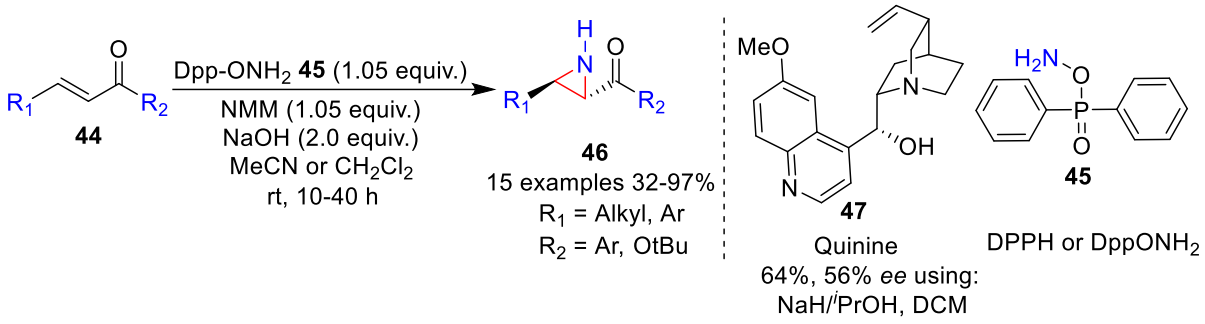


Figure 4.4. A catalytic mechanistic cycle for *N*-H aziridination of chalcone

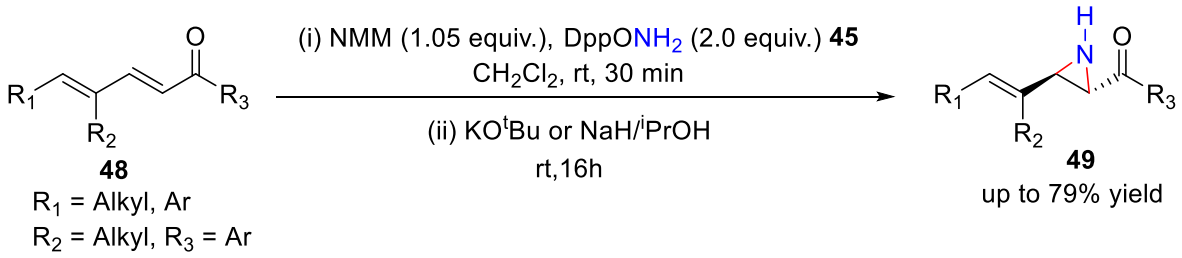
4.2.10 Enone aziridination using DPPH

Alan Armstrong and co-workers demonstrated the tertiary amine facilitated aziridination of enones by using *O*-(diphenylphosphinyl)hydroxylamine **45** ($DppONH_2$) as the nitrogen source (Scheme 4.11).[9a] The *N-N* ylide (aminimine) was formed *in situ* in the presence of a base. This method effectively aziridinated with a variety of enones and produced the good to excellent yields of *trans N*-H aziridines. The aziridination of *α,β*-unsaturated esters might likewise be done using this methodology. The initial research also found that utilizing the cinchona alkaloid (quinine) as the tertiary amine resulted in modest asymmetric induction (56% *ee*). For the aziridination reaction, the author described a mechanistic cycle similar to one reported in an earlier study (Figure 4.4).[8]



Scheme 4.11. Aziridination of enones/enoates using *in situ* generated aminimines

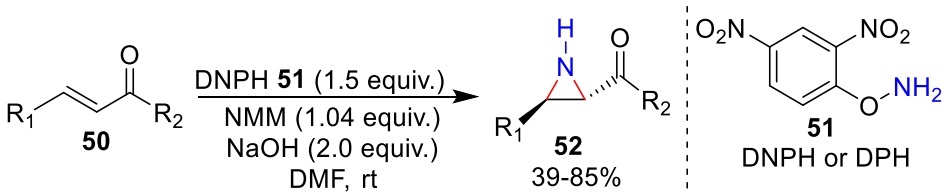
Similarly, they also demonstrated the regio and diastereoselective preparation of *trans N*-H vinyl aziridines **49** from *α,β,γ,δ*-unsaturated carbonyl compounds **48** in the presence of base using *N*-methyl morpholine (NMM) and $DppONH_2$ **45** as nitrogen sources (Scheme 4.12).[19] Electron-rich substrates provided vinyl aziridine with good yields, whereas yields were moderate in the case of electron-deficient substrates. Dienes with heteroaromatic ring and acyclic as well as cyclic substituted dienes also underwent aziridination reaction to afford corresponding vinyl aziridines with good yields.



Scheme 4.12. Regio and diastereoselective synthesis of *trans N*-H vinyl aziridines from *α,β,γ,δ*-unsaturated carbonyl compounds

4.2.11 Enone aziridination using DPH or DNPH

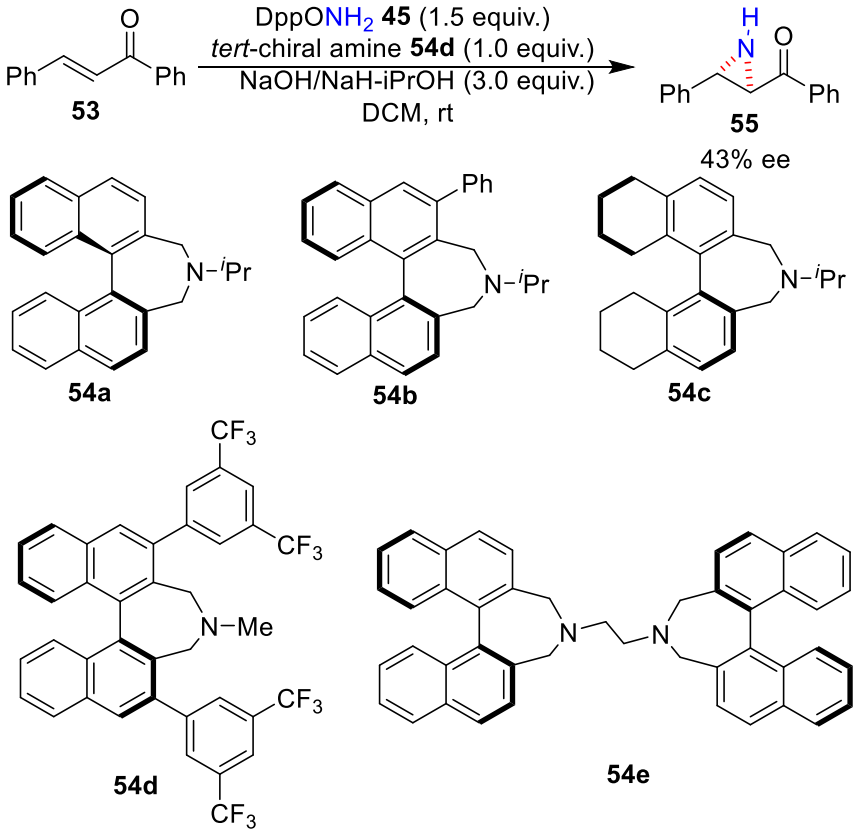
Ming Yan *et al*. reported aminimide-mediated aziridination of *α,β*-unsaturated ketones **50** using *O*-(2,4-dinitrophenyl)hydroxylamine **51** (DPH or DNPH) as an aminating reagent, tertiary amines such as *N*-methylpyrrolidine (NMP) or *N*-methylmorpholine (NMM), and NaOH as the base (Scheme 4.13).[20] Under these reaction conditions, several substituted, *α,β*-unsaturated ketones converted to their corresponding aziridines with moderate to excellent yields.



Scheme 4.13. *Trans N*-H aziridination of enones by using DPH

4.2.12 Enantioselective aziridination of enones using DPPH

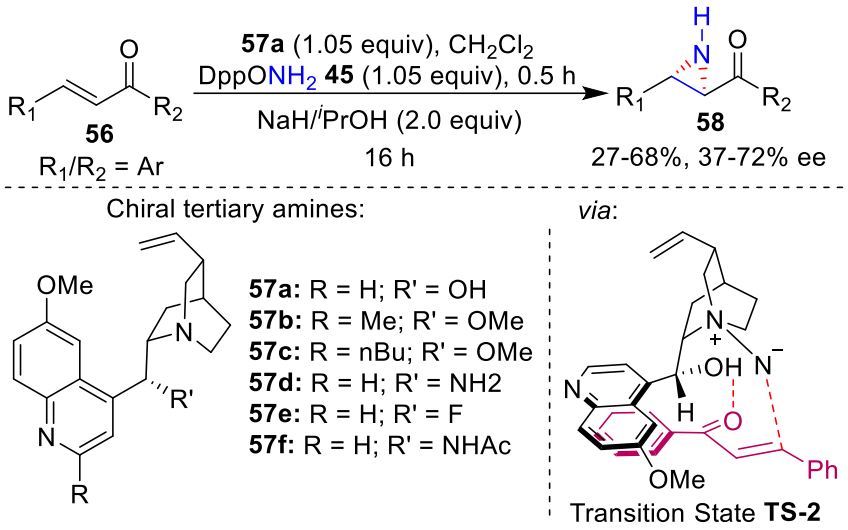
Philip C. Bulman and co-workers reported the enantioselective aziridination of *E*-chalcones using $DppONH_2$ and chiral tertiary amines containing binaphthyl group as ammonium amide ylides. Under this reaction condition, moderate enantiomeric excess was observed. Chiral amine **54d** provided the best results with 43% *ee* among all the screened chiral *tert*-amines **54a-e** (Scheme 4.14).[21]



Scheme 4.14. Asymmetric *N*-H aziridination of *E*-chalcones

4.2.13 Enantioselective aziridination of enones using DPPH

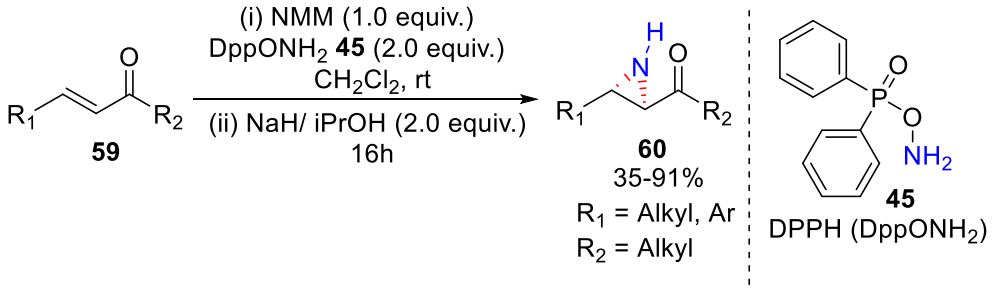
The group of Alan Armstrong also investigated the asymmetric aziridination of chalcones using chiral tertiary amine **57a** and DPPH as the electrophilic aminating agent (Scheme 4.15).[22] They screened several chiral tertiary amines, among them quinine **57a** provided **58** in a moderate to good enantioselectivity (27-68%, 37-72% *ee*). Different derivatives of quinine such as quinidine, cinchonine, cinchonidine, hydroquinine, quincorine, *etc.* were also screened but either aziridination yields or enantioselectivity were reduced. The substrates containing electron-donating groups at the ketone-bearing aromatic ring had a higher enantiomeric excess than the substrates containing electron-withdrawing groups. The enantioselective aziridination was achieved *via* transition state **TS-2**.



Scheme 4.15. Asymmetric *N*-H aziridination of chalcones using quinine derivative

4.2.14 Aziridination of aliphatic enones using DPPH

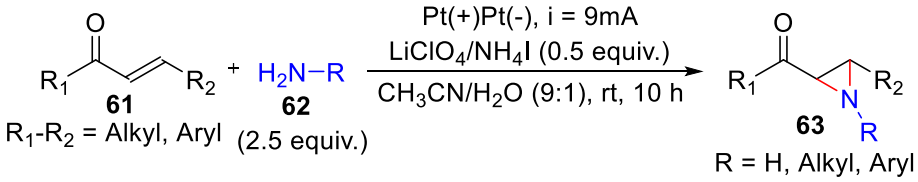
Armstrong group also reported the tertiary amine promoted synthesis of *N*-H aziridines **60** from aliphatic α,β-unsaturated ketones **59** using $DppONH_2$ **45** as the aminating reagent and NaH as the base (Scheme 4.16).[23] The reaction proceeds *via in situ* generated N,N-ylides. The yield was good with the tertiary butyl group containing substrates while cyclic alkenes like cyclohexenone produced a moderate yield of the equivalent *N*-H aziridine.



Scheme 4.16. *N*-H aziridination of enones using DPPH

4.2.15 Aziridination *via* electrochemical oxidative annulation of chalcones using primary amines as nitrogen source

Yonghui He and coworkers recently revealed an efficient method for producing *N*-H/alkyl/aryl aziridines **63** in moderate to good yields by electrochemical oxidative annulation of chalcones **61** with primary amines **62** (Scheme 4.17).[24] A mechanism based on cyclic voltammetry was also proposed by the author. Iodine (I_2) is released in this reaction by electrochemical oxidation of I^-, and subsequently the amine combines with iodine to form *N*-iodoamine species **IX**. The Aza-Michael addition of another amine molecule, resulting in the intermediate **XI**, is facilitated by the coordination of *N*-iodoamine with the carbonyl group of **61**. The final product **63** is obtained through an intramolecular cyclization of **XI** (Figure 4.5). Under this reaction condition methyl substituted enones were failed to react.



Scheme 4.17. Electrochemical aziridination of chalcones using primary amines

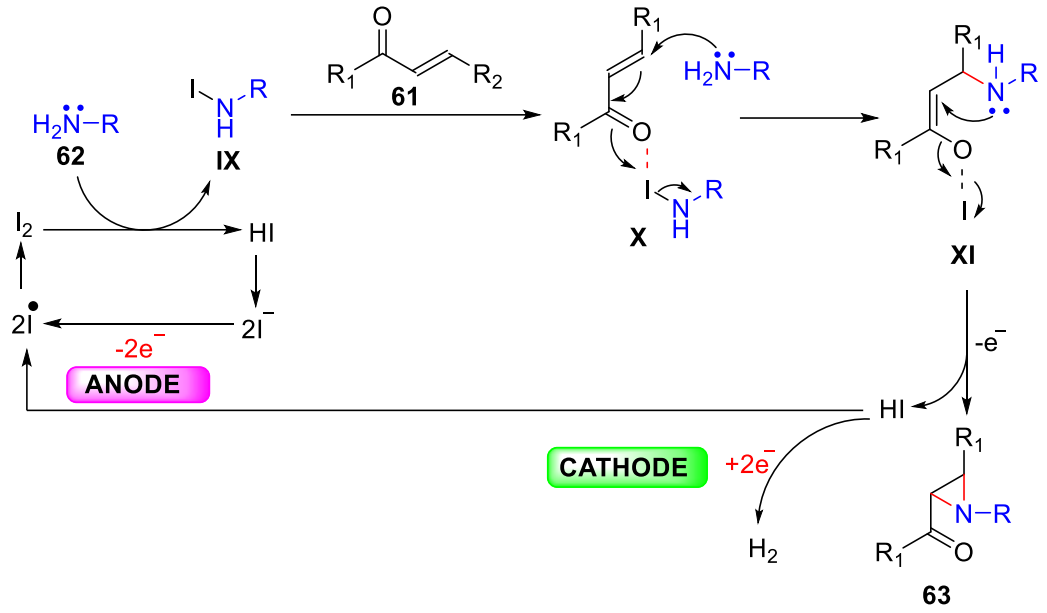


Figure 4.5. Plausible reaction mechanism

The literature study shows that the methods for the synthesis of *N*-H aziridines from enones are well-explored whereas only very few reports are available for the synthesis of *N*-alkyl aziridines, while no report was found on the aziridination of vinyl ketones. These methods have some limitations, such as: (a) multi-step and limited to *N*-H aziridines only (b) limited substrate scope with lower yield and low functional group tolerance (c) low reactivity and longer reaction time (d) requirement of base and additive which could cause ring-opening of the aziridine (e) some of the aziridinating reagents generated toxic/explosive and interfering by-products. In that context, the development of an effective method for the direct synthesis of unactivated (*N*-H/*N*-alkyl) aziridines from enones is in high demand.

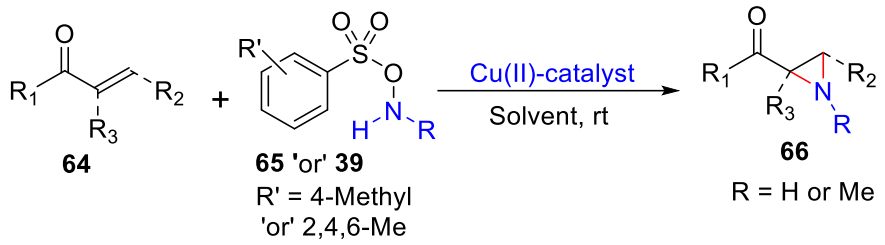
4.3 Objective of the work

So, the objective of this part of the thesis were:

(i) To develop a new methodology for direct *N*-Me/*N*-H aziridination of enones under mild and additive free condition.

(ii) This method should have one pot, stereospecific, direct, practical, high yielding, faster, etc.

Herein, we reported the Cu(II)-catalyzed first direct method for the synthesis of *N*-Me aziridines from vinyl ketones using *N*-methyl-*O*-tosyl-hydroxylamine as the aminating reagent. Next, we have also disclosed the method for the synthesis of *N*-H aziridines from chalcones using *O*-(mesitylenesulfonyl)hydroxylamine as the nitrogen source while *N*-Me aziridination of chalcones are currently under progress in our laboratory (Scheme 4.17).



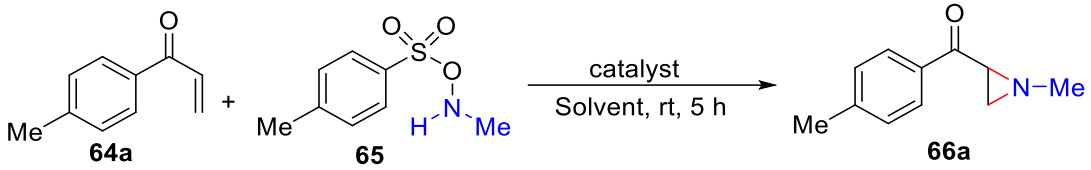
Scheme 4.17. *N*-H/*N*-Me aziridination of enones/vinyl ketones

4.4 Results and discussion

4.4.1 Optimization of the reaction condition

We began our study by using 1-(*p*-tolyl)prop-2-en-1-one **64a** as the model substrate and **65** as the aminating agent (Table 4.1). Initially, we screened different iron salts such as $FeSO_4$, $FeCl_2$, $FeCl_3$ and $Fe(acac)_3$ for aziridination of **64a** in TFE solvent but the poor conversion was observed (entries 1-4). Comparatively better yields were obtained when we move to investigate the different copper catalysts (entries 5-9). Among the screened copper catalysts, $Cu(OTf)_2$ was found to be the best catalyst producing **66a** with 70% yield (entry 9). Much to our delight, when $Cu(OTf)_2$ was used with lower loading (10 to 5 mol%) generated the desired product **66a** with high yield (entry 10). A further decrease in the catalyst or aminating agent **65** resulted in a lower yield (entries 11-12). A different category of solvents was investigated, among them TFE was found to be the most suitable solvent (entries 13-17).

Table 4.1. Optimization of the reaction conditions[a]



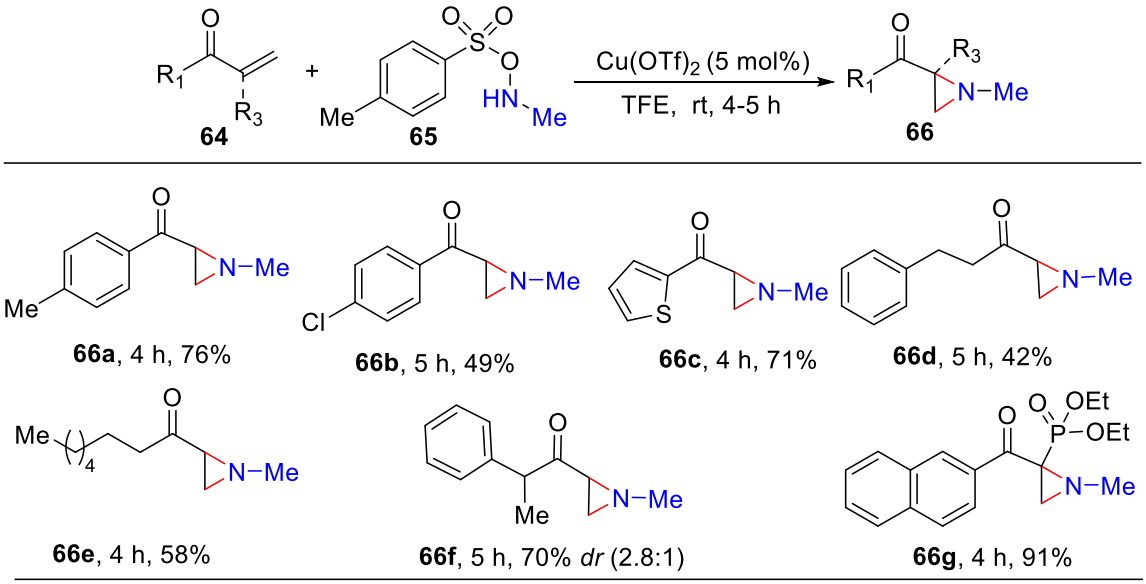
Entry	Catalyst (mol %)	Solvent	Yield (%)[b]
1	$FeSO_4.7H_2O$ (10 mol %)	TFE	25
2	$FeCl_2$ (10 mol %)	TFE	30
3	$FeCl_3$ (10 mol %)	TFE	38
4	$Fe(acac)_3$ (10 mol %)	TFE	35
5	CuBr (10 mol %)	TFE	30
6	$CuBr_2$ (10 mol %)	TFE	46
7	$Cu(OAc)_2$ (10 mol %)	TFE	60
8	$Cu(acac)_2$ (10 mol %)	TFE	53
9	$Cu(OTf)_2$ (10 mol %)	TFE	70
10	**$Cu(OTf)_2$ (5 mol %)**	**TFE**	**76**
11	$Cu(OTf)_2$ (2 mol %)	TFE	65
12[c]	$Cu(OTf)_2$ (5 mol %)	TFE	60
13	$Cu(OTf)_2$ (5 mol %)	MeOH	trace
14	$Cu(OTf)_2$ (5 mol %)	THF	20
15	$Cu(OTf)_2$ (5 mol %)	CH_3CN	35
16	$Cu(OTf)_2$ (5 mol %)	DMF/DMSO	Trace
17	$Cu(OTf)_2$ (5 mol %)	CH_2Cl_2	40
18	Nil	TFE	20

[a]Reaction condition unless otherwise mentioned: **64a** (0.25 mmol), **65** (1.5 equiv.), catalyst (5-10 mol %), solvent, rt, 5 h. [b]Isolated yield after silica gel column chromatography. [c]1.0 equiv. of **65** was used.

4.4.2 Substrate scope for *N*-Me aziridination of vinyl ketones

With the optimized reaction condition in hand, we next evaluate the generality of this method with a diverse variety of vinyl ketones (Scheme 4.18). The aryl vinyl ketones

substituted with an EDG like Me on the aryl ring led to the corresponding aziridine in higher yield compared to that substituted with an electron-deficient arene (**66a** and **66b**). Heteroaryl-derived vinyl ketone smoothly converted into desired aziridine **66c** in 71% yield. Alkyl chain derived substrates easily reacted to produce the desired products with moderate yield (**66d** and **66e**). The use of a substrate with α-branched did not affect the reaction and produced the **66f** in 70% yield. We next examined sterically hindered α-phosphorylated vinyl ketones that generated the corresponding aziridine **66g** in excellent yield (91%).



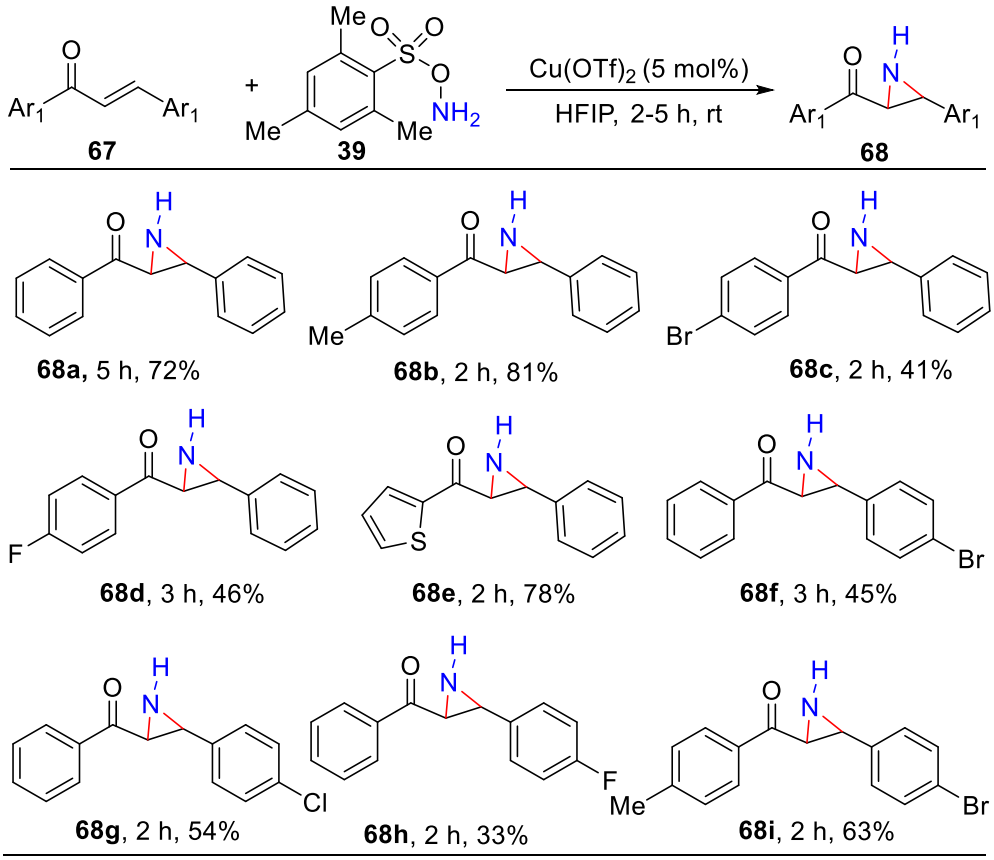
[a]Reaction condition unless otherwise mentioned: **64** (0.5 mmol), **65** (1.5 equiv.), $Cu(OTf)_2$ (5 mol %), TFE (2.0 mL), rt. Yields are the isolated yield after column chromatography.

Scheme 4.18. Preparation of *N*-Me aziridines from vinyl ketones

4.4.3 Substrates scope for *N*-H aziridination of chalcones

We next move to investigate the *N*-H aziridination of chalcones using *O*-(Mesitylenesulfonyl)hydroxylamine (MSH) **39** (Scheme 4.19) under similar reaction conditions as described in Scheme 4.18. *E*-Chalcone smoothly reacted to produce the **68a** with a good yield (72%). First, different substituents on the Ar_1 ring were evaluated. It seems that substrate substituted with an electron-donating group (Me) results in a

somewhat higher yield of the desired product **68b** (81%). Whereas, substrates substituted with electron-withdrawing groups (Br, F) furnished the moderate yield of desired products (**68c-d**). Heterocyclic substrate **67e** smoothly reacted to produce a good yield of the product (**68e**). Substrates substituted on the Ar_2 ring resulted in a moderate yield of desired aziridines (**68f-h**). The substrate containing substituents at both rings (Ar_1 & Ar_2) also reacted very well to afford the **68i** with a 63% yield. All the reactions proceeded in a highly stereospecific manner, generating the trans *N*-H aziridines exclusively (>95%).

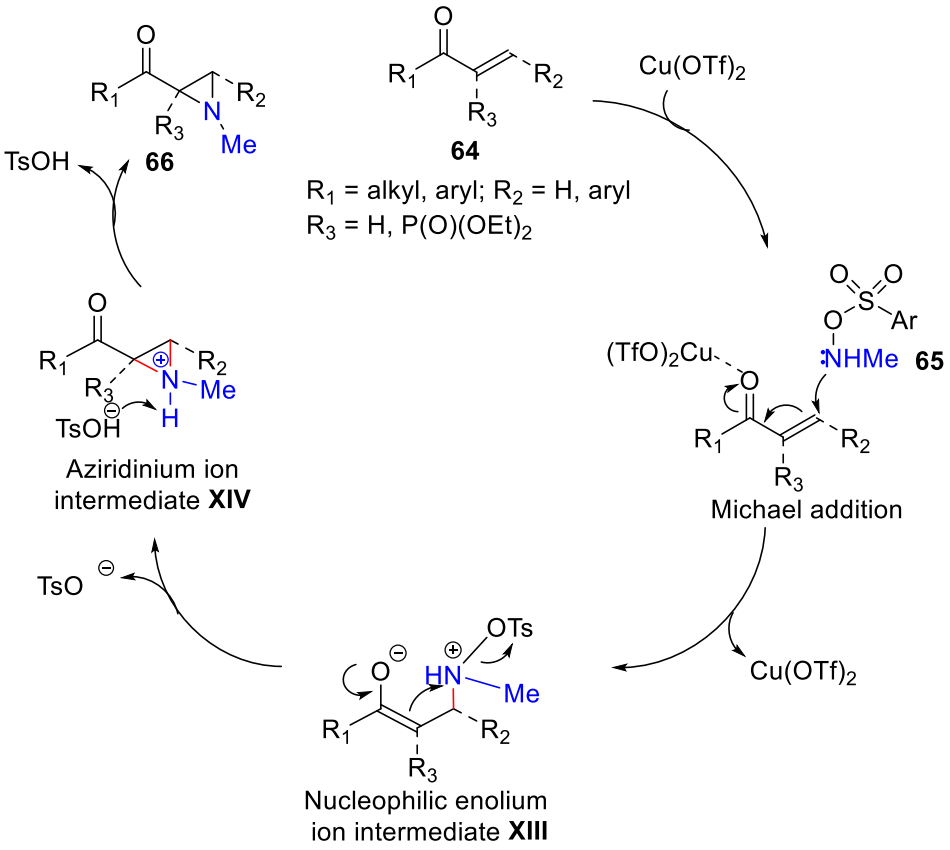


[a]Reaction condition unless otherwise mentioned: **67** (0.5 mmol), **39** (2.0 equiv.), $Cu(OTf)_2$ (5 mol %), HFIP (1.0 mL), rt. Yields are the isolated yield after an column chromatography.

Scheme 4.19. Synthesis of *N*-H aziridines from chalcones

4.5 Proposed reaction mechanism

We assume that the reaction proceeded *via* Michael addition of aminating agent **65** with vinyl ketones **64** in the presence of $Cu(OTf)_2$ to form the nucleophilic enolium ion intermediate **XIII** which is converted into aziridinium ion intermediate **XIV** *via* intramolecular cyclization that eventually produces the desired aziridine **66** (Scheme 4.20).[25]



Scheme 4.20. Plausible catalytic reaction mechanism

4.6 Conclusion

In conclusion, we have established the first highly efficient catalytic method for the synthesis of *N*-Me aziridines directly from vinyl ketones using *N*-methyl-*O*-tosyl-hydroxylamine as an aminating agent. It is the first method for the preparation of *N*-Me aziridines directly from vinyl ketones and their bulkier derivatives. This method

also efficiently produces *N*-H aziridines from chalcones using *O*-(Mesitylenesulfonyl)hydroxylamine as an aminating reagent. Further *N*-Me aziridination of chalcones are currently under progress in our laboratory. All the reactions in this method proceeded in a highly stereospecific fashion.

Highlights

(i) First *N*-Me aziridination of vinyl ketones
(ii) Suitable for *N*-H aziridination of chalcones
(iii) One-pot and open flask, mild and simple procedure
(iv) Stereospecific and broad substrate scope
(v) Good to excellent yields

This work is under revision, in *J. Org. Chem.*

4.7 Experimental section

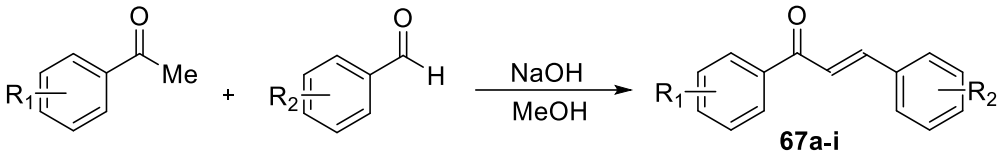
4.7.1 General information

Unless otherwise indicated, all aldehydes and acetophenones were purchased from commercially available sources and used without further purification. Solvents were dried and distilled following the standard procedures. In a single-neck round bottom flask, all reactions were carried out in an open atmosphere. Reactions were monitored by thin layer chromatography (TLC) using precoated plates (silica gel 60, F-254) purchased from Merck. The spot of compounds was visualized by UV light, PMA or $KMNO_4$ stains followed by heating. The melting points were recorded on a Buchi M-560 melting point apparatus and are uncorrected. For purification of compounds, column chromatography was performed with silica gel (230-400 mesh) in distilled solvents. Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra for compounds were recorded on 400 MHz and 100 MHZ spectrometer using $CDCl_3$ solvent. Chemical shifts (δ) and coupling constants (J) are reported in ppm and Hz, respectively. Chemical shifts (δ) were recorded in reference to the internal standard tetramethylsilane (TMS, 0.00 ppm) or residual solvent signals ($CDCl_3$, ^1H NMR: = 7.26 ppm; ^{13}C NMR: = 77.00 ppm). Multiplicities were known as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), td (triplet of doublets), or m (multiplet). High resolution mass spectra (HRMS) were obtained on an

Agilent 6530 series quadrupole time of flight (Q-TOF) *mass spectrometer* equipped with electron spin ionization (ESI).

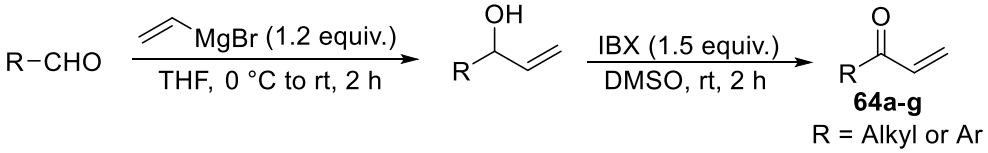
4.7.2 Synthesis of enones

The aldehydes and ketones were used from commercially available sources without further purification. We have prepared all the chalcone derivatives by the following literature procedure (Scheme 4.21).[26] Aqueous NaOH was added to a stirred solution of substituted acetophenone in methanol at 0 °C, followed by drop-wise addition of substituted benzaldehyde solution in methanol. The reaction mixture was stirred for 2-4 hours at room temperature. Progress of the reaction was monitored by TLC. After completion of the reaction, the obtained precipitate was filtered, dried, and recrystallized by EtOH (**67a-i**).



Scheme 4.21. General procedure for preparation of chalcones.

We have also prepared the vinyl ketone derivatives in two steps by following the known literature procedure (Scheme 4.22).[27] In the first step allyl alcohol was formed by the reaction of an aldehyde with Grignard reagent, in the next step, vinyl ketones were formed by oxidation of allyl alcohol in the presence of IBX in DMSO solvent.



Scheme 4.22. General preparation procedure of vinyl ketones

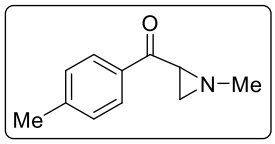
4.7.3 General protocol for *N*-Me and *N*-H aziridination

In a single-neck round bottom flask equipped with a magnetic stirring bar, were added enone **64** or **67** (0.5 mmol), aminating agent **65** or **39** (1.5 equiv.) in TFE or HFIP solvent (2 mL) respectively at room temperature. $Cu(OTf)_2$ (5 mol%) catalyst was added to this

stirring solution. The reaction mixture was further stirred at this temperature and the progress of the reaction was monitored by TLC. After completion, the reaction mixture was neutralized with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (5 ml) and brine (10 ml) and dried over anhydrous Na_2SO_4. The crude product obtained after removal of all the volatiles was purified by a silica gel column chromatography to afford the pure desired product **66** or **68** using 0.5% of $^{t}Bu_3N$ in EtOAc/hexane as eluent.

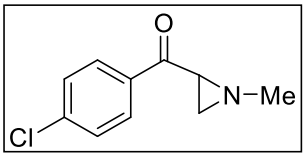
4.8 Characterization of the compounds

***(1-Methylaziridin-2-yl)(p-tolyl)methanone (66a)*:** The product was prepared following



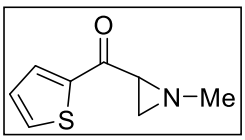
the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (0.5:1:5) as an eluent to give the title compound as a yellow oil (66 mg, 76% yield). TLC: Rf = 0.5 (30% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 7.8 Hz, 2H), 2.85 (dd, J = 6.3 Hz, J = 2.9 Hz, 1H), 2.50 (s, 3H), 2.41 (s, 3H), 2.26 (s, 1H), 1.69 (d, J = 6.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 195.6, 143.9, 134.1, 129.1, 128.1, 47.3, 41.6, 37.7, 21.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{11}H_{13}NO^+$ 176.1070, found: 176.1068.

***(4-Chlorophenyl)(1-methylaziridin-2-yl)methanone (66b)*:** The product was prepared

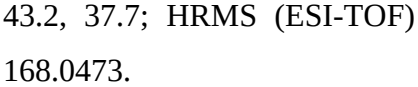


following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (0.5:1:5) as an eluent to give the title compound as a yellow liquid (48 mg, 49% yield). TLC: Rf = 0.5 (30% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 2.78 (dd, J = 6.4 Hz, J = 2.9 Hz, 1H), 2.49 (s, 3H), 2.26 (s, 1H), 1.71 (d, J = 6.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 195.1, 139.6, 134.9, 129.6, 128.8, 47.5, 42.1, 38.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{10}H_{10}ClNO^+$ 196.0524, found: 196.0528.

***(1-Methylaziridin-2-yl)(thiophen-2-yl)methanone (66c)*:** The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (0.5:1:5) as an eluent to give the title compound as a yellow thick liquid (59 mg, 71% yield). TLC: Rf = 0.4 (30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 3.7 Hz, 1H), 7.62 (d, J = 4.8 Hz, 1H), 7.10 (t, J = 4.4 Hz, 1H), 2.62 (dd, J = 6.4 Hz, J = 2.8 Hz, 1H), 2.45 (s, 3H), 2.25 (s, 1H), 1.66 (d, J = 6.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 189.2, 142.4, 134.0, 132.6, 127.9, 47.2, 43.2, 37.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_8H_9NOS^+$ 168.0478, found: 168.0473.



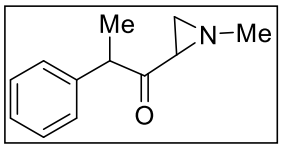
***1-(1-Methylaziridin-2-yl)-3-phenylpropan-1-one (66d)*:** The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (0.5:1:5) as an eluent to give the title compound as a yellow oil (40 mg, 42% yield). TLC: Rf = 0.5 (30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J = 8.5 Hz, 2H), 7.18 (t, J = 5.8 Hz, 3H), 2.85 (q, J = 7.5 Hz, 2H), 2.76 (q, J = 9.7 Hz, 1H), 2.62-2.52 (m, 1H), 2.36 (s, 3H), 2.02 (s, 2H), 1.52 (d, J = 7.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 208.0, 141.0, 128.4, 128.3, 126.0, 47.2, 45.2, 39.3, 36.2, 29.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{15}NO^+$ 190.1226, found: 190.1226.



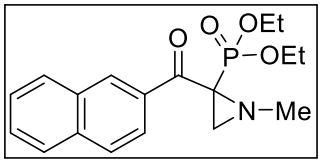
***1-(1-Methylaziridin-2-yl)octan-1-one (66e)*:** The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (0.5:1:5) as an eluent to give the title compound as a colourless oil (53 mg, 58% yield). TLC: Rf = 0.4 (40% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 2.47-2.39 (m, 1H), 2.38 (s, 3H), 2.30-2.20 (m, 1H), 2.08 (s, 1H), 2.04 (dd, J = 6.6 Hz, J = 2.9 Hz, 1H), 1.55 (d, J = 6.6 Hz, 1H), 1.24 (s, 10H), 0.86 (t, J = 6.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 209.0, 47.2, 45.8, 38.0,

36.3, 31.8, 29.4, 29.3, 29.2, 29.1, 23.4, 22.6, 14.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{11}H_{21}NO^+$ 184.1696, found: 184.1695.

***1-(1-Methylaziridin-2-yl)-2-phenylpropan-1-one (66f)*:** The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using ^{t}Bu$_3$N:EtOAc:hexane (0.5:1:5) as an eluent to give the title compound as a yellow oil (66 mg, 70% yield). TLC: Rf = 0.5 (40% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 8.2 Hz, 3H), 3.99-3.90 (m, 1H), 2.24 (d, *J* = 13.8 Hz, 3H), 2.01 (s, 2H), 1.43 (d, *J* = 6.8 Hz, 1H), 1.38 (d, *J* = 6.9 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 207.7, 140.1, 140.0, 128.8, 128.7, 128.1, 128.0, 127.0, 127.0, 50.2, 49.5, 47.1, 46.9, 44.5, 44.1, 37.2, 36.9, 18.0, 17.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{15}NO^+$ 190.1226, found: 190.1225.



***Diethyl (2-(2-naphthoyl)-1-methylaziridin-2-yl)phosphonate (66g)*:** The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using ^{t}Bu$_3$N:EtOAc:hexane (0.5:1:4) as an eluent to give the title compound as a yellow gummy liquid (158 mg, 91% yield). TLC: Rf = 0.4 (50% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 13.5 Hz, 1H), 8.07 (t, *J* = 8.0 Hz, 1H), 7.98 (dd, *J* = 15.3 Hz, *J* = 8.0 Hz, 1H), 7.87 (q, J = 7.6 Hz, 2H), 7.65-7.51 (m, 2H), 4.32-3.96 (m, 4H), 3.01 (s, 1H), 2.86 (d, *J* = 8.2 Hz, 1H), 2.47 (s, 2H), 2.11 (d, *J* = 6.4 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 9.8 Hz, 3H), 1.14 (t, *J* = 7.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.8, 193.7, 193.0, 192.9, 135.7, 135.7, 133.8, 132.8, 132.6, 132.2, 132.1, 132.1, 129.8, 129.7, 129.0, 128.6, 128.1, 127.8, 127.7, 127.6, 126.8, 126.5, 124.9, 124.4, 63.6, 63.6, 63.4, 63.3, 63.0, 62.9, 62.5, 62.4, 45.9, 45.6, 43.9, 43.9, 43.6, 43.5, 40.8, 40.7, 39.7, 39.6, 39.4, 16.2, 16.2, 16.1, 16.0, 16.0; ^{135}DEPT (100 MHz, $CDCl_3$) δ 132.9, 132.7, 129.9, 129.8, 129.0, 128.7, 128.2, 127.9, 127.8, 127.7, 126.9, 126.6, 125.0, 124.5, 63.7, 63.7, 63.5, 63.4, 63.1, 63.0, 62.6, 62.5, 43.6, 43.6, 40.9, 40.8, 16.3, 16.3, 16.2, 16.1, 16.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{22}NO_4P^+$ 348.1359, found: 348.1360.



Phenyl(3-phenylaziridin-2-yl)methanone (68a):[9] The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (0.5:1:8) as an eluent to give the title compound as a light yellow solid (80 mg, 72% yield). TLC: Rf = 0.5 (10% EtOAc in hexane); mp 98-101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.9 Hz, 2H), 7.61 (t, J = 6.9 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.38-7.30 (m, 5H), 3.51 (s, 1H), 3.18 (s, 1H); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}NO^+$ 224.1070, found: 224.1068.

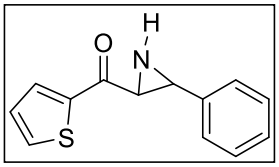
(3-Phenylaziridin-2-yl)(p-tolyl)methanone (68b):[9] The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (0.5:1:4) as an eluent to give the title compound as a pale yellow solid (96 mg, 81% yield). TLC: Rf = 0.5 (10% EtOAc in hexane); mp 89-92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.9 Hz, 2H), 7.27-7.18 (m, 5H), 7.16 (d, J = 4.2 Hz, 2H), 3.40 (s, 1H), 3.07 (s, 1H), 2.32 (s, 3H); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{15}NO^+$ 238.1226, found: 238.1225.

(4-Bromophenyl)(3-phenylaziridin-2-yl)methanone (68c):[28] The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (0.5:1:4) as an eluent to give the title compound as a pale orange solid (62 mg, 41% yield). TLC: Rf = 0.5 (10% EtOAc in hexane); mp 99-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.36-7.30 (m, 5H), 3.45 (s, 1H), 3.18 (s, 1H); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{12}BrNO^+$ 302.0175, found: 302.0171.

(4-Fluorophenyl)(3-phenylaziridin-2-yl)methanone (68d):[28] The product was prepared following the general aziridination procedure and the crude product was purified by silica gel column chromatography using $^{t}Bu_3N$:EtOAc:hexane (0.5:1:4) as an eluent to give the title compound as a yellow solid (55 mg, 46% yield). TLC: Rf = 0.5 (10% EtOAc in

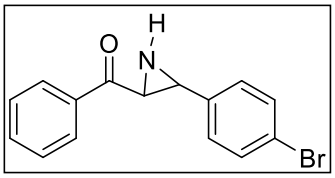
hexane); mp 69-72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (q, J = 5.5 Hz, 2H), 7.38-7.30 (m, 5H), 7.16 (t, J = 8.4 Hz, 2H), 3.46 (s, 1H), 3.18 (s, 1H); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{12}FNO^+$ 242.0976, found: 242.0977.

(3-Phenylaziridin-2-yl)(thiophen-2-yl)methanone (68e):[22] The product was prepared



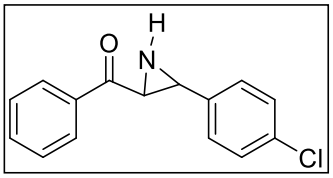
following the general aziridination procedure and the crude product was purified by silica gel column chromatography using ^{t}Bu$_3$N:EtOAc:hexane (0.5:1:5) as an eluent to give the title compound as a yellow solid (89 mg, 78% yield). TLC: Rf = 0.4 (10% EtOAc in hexane); mp 115-116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 3.0 Hz, 1H), 7.72 (d, J = 4.6 Hz, 1H), 7.36-7.29 (m, 5H), 7.16 (t, J = 3.8 Hz, 1H), 3.39 (s, 1H), 3.26 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.2, 142.7, 138.2, 134.7, 132.8, 128.5, 128.4, 127.8, 126.2, 44.3, 43.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{11}NOS^+$ 230.0634, found: 230.0634.

(3-(4-Bromophenyl)aziridin-2-yl)(phenyl)methanone (68f):[28] The product was prepared



following the general aziridination procedure and the crude product was purified by silica gel column chromatography using ^{t}Bu$_3$N:EtOAc:hexane (0.5:1:4) as an eluent to give the title compound as a yellow solid (68 mg, 45% yield). TLC: Rf = 0.5 (10% EtOAc in hexane); mp 109-112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.8 Hz, 4H), 7.24 (s, 2H), 3.45 (s, 1H), 3.13 (s, 1H); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{12}BrNO^+$ 302.0175, found: 302.0175.

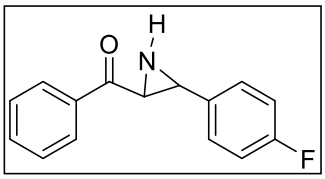
(3-(4-Chlorophenyl)aziridin-2-yl)(phenyl)methanone (68g):[8] The product was prepared



following the general aziridination procedure and the crude product was purified by silica gel column chromatography using ^{t}Bu$_3$N:EtOAc:hexane (0.5:1:5) as an eluent to give the title compound as a orange solid (69 mg, 54% yield). TLC: Rf = 0.5 (10% EtOAc in hexane); mp 89-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.8 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.33-7.27 (m, 4H), 3.45 (d, J = 2.7 Hz, 1H), 3.15

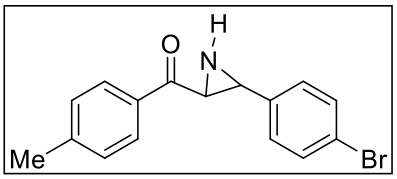
(d, *J* = 5.4 Hz, 1H); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{12}ClNO^+$ 258.0680, found: 258.0678.

(3-(4-Fluorophenyl)aziridin-2-yl)(phenyl)methanone (68h):[15] The product was prepared



following the general aziridination procedure and the crude product was purified by silica gel column chromatography using ^{t}Bu$_3$N:EtOAc:hexane (0.5:1:5) as an eluent to give the title compound as a yellow solid (40 mg, 33% yield). TLC: Rf = 0.4 (10% EtOAc in hexane); mp 79-72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.8 Hz, 2H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.33 (q, *J* = 5.6 Hz, 2H), 7.04 (t, *J* = 8.5 Hz, 2H), 3.46 (s, 1H), 3.16 (s, 1H); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{12}FNO^+$ 242.0976, found: 242.0977.

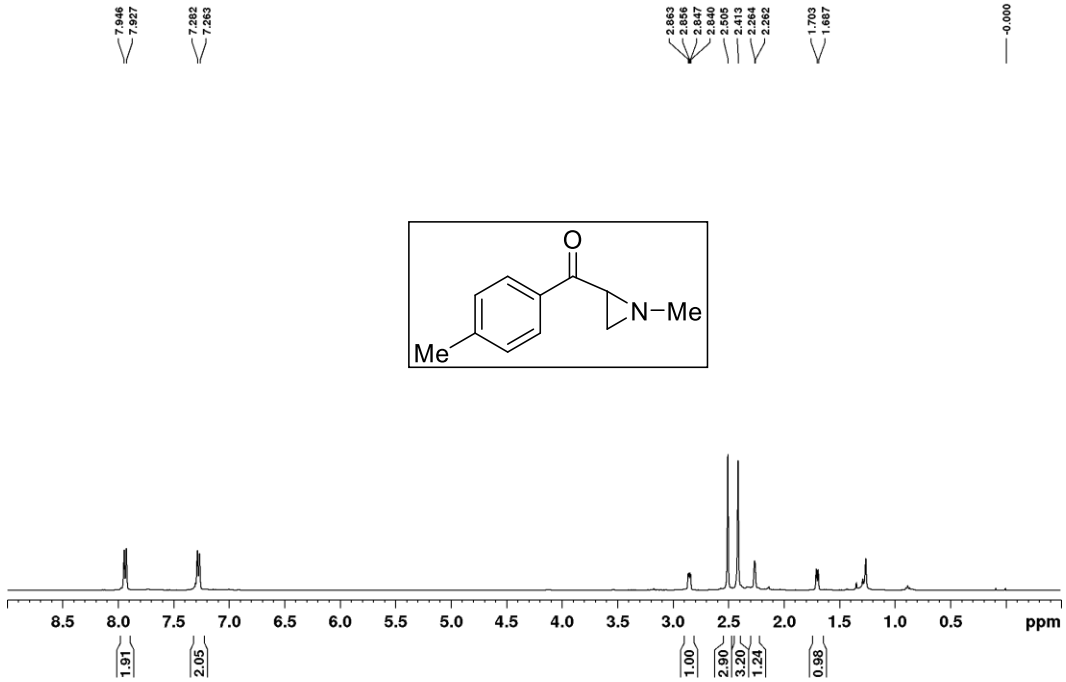
(3-(4-Bromophenyl)aziridin-2-yl)(p-tolyl)methanone (68i): The product was prepared



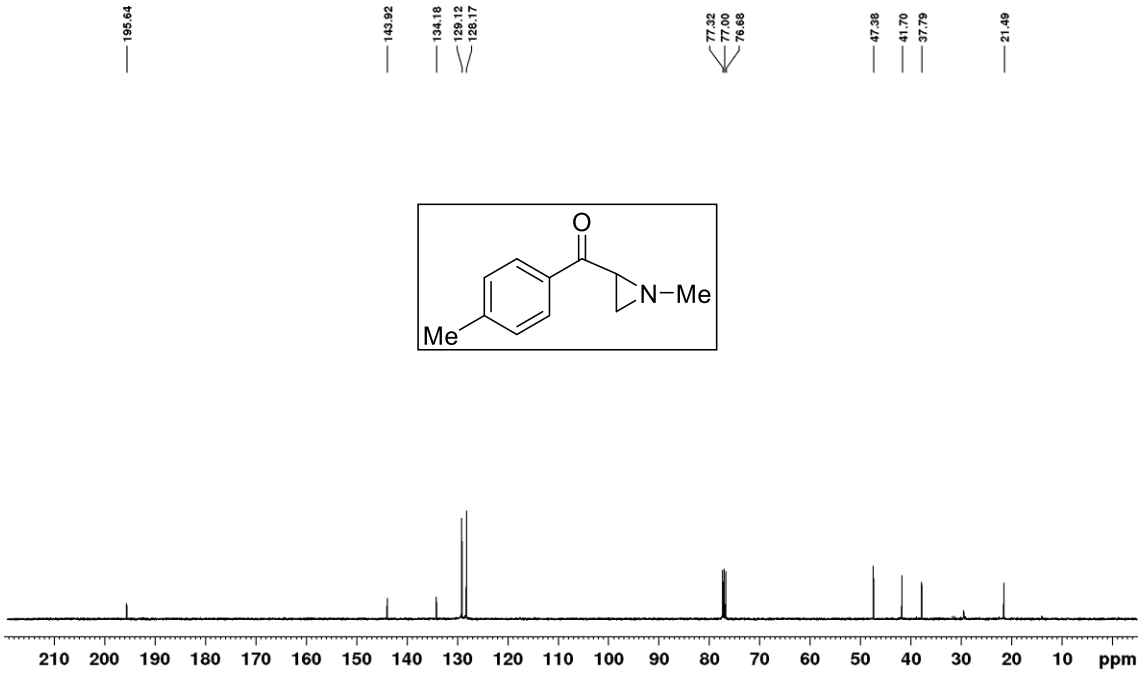
following the general aziridination procedure and the crude product was purified by silica gel column chromatography using ^{t}Bu$_3$N:EtOAc:hexane (0.5:1:5) as an eluent to give the title compound as a yellow semi-solid (99 mg, 63% yield). TLC: Rf = 0.5 (10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.9 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 3.42 (s, 1H), 3.11 (s, 1H), 2.42 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.8, 145.0, 137.5, 133.3, 131.6, 129.5, 128.4, 127.9, 121.7, 43.9, 42.6, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{12}BrNO^+$ 316.0332, found: 316.0335.

4.9 ^{1}H, $^{13}C\{^{1}H\}$ and ^{135}DEPT NMR spectra of the compounds

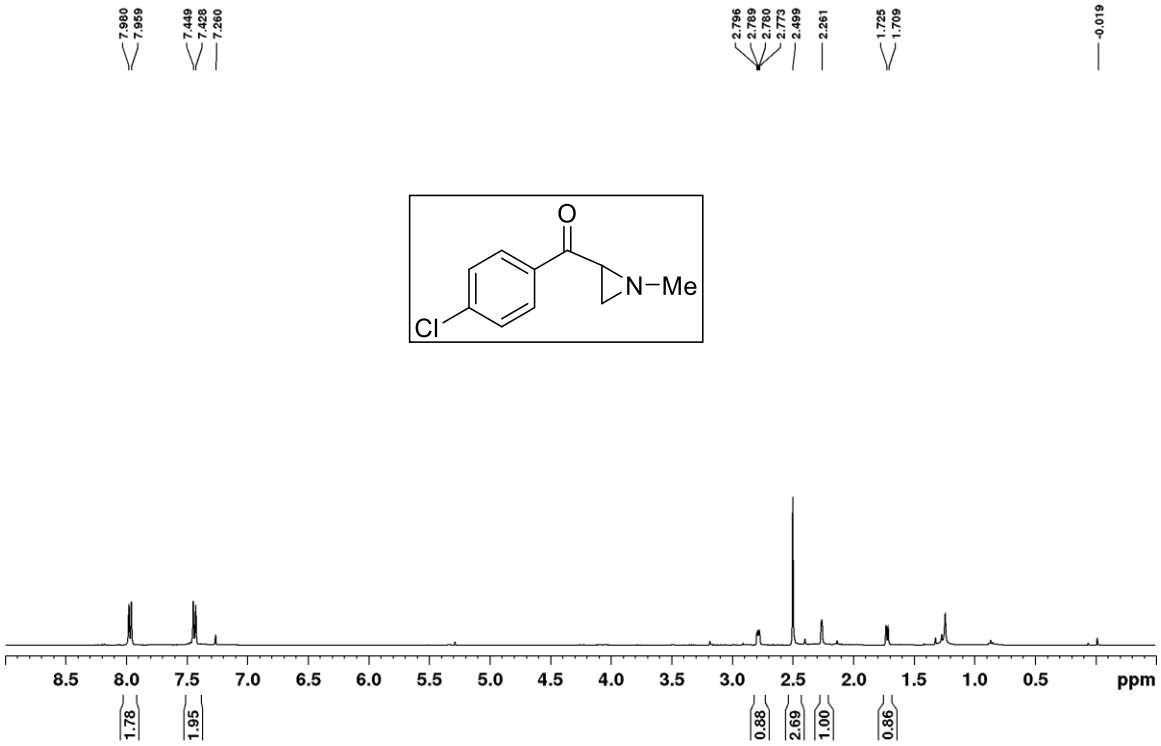
^{1}H NMR spectrum of compound **66a** (400 MHz/$CDCl_3$)



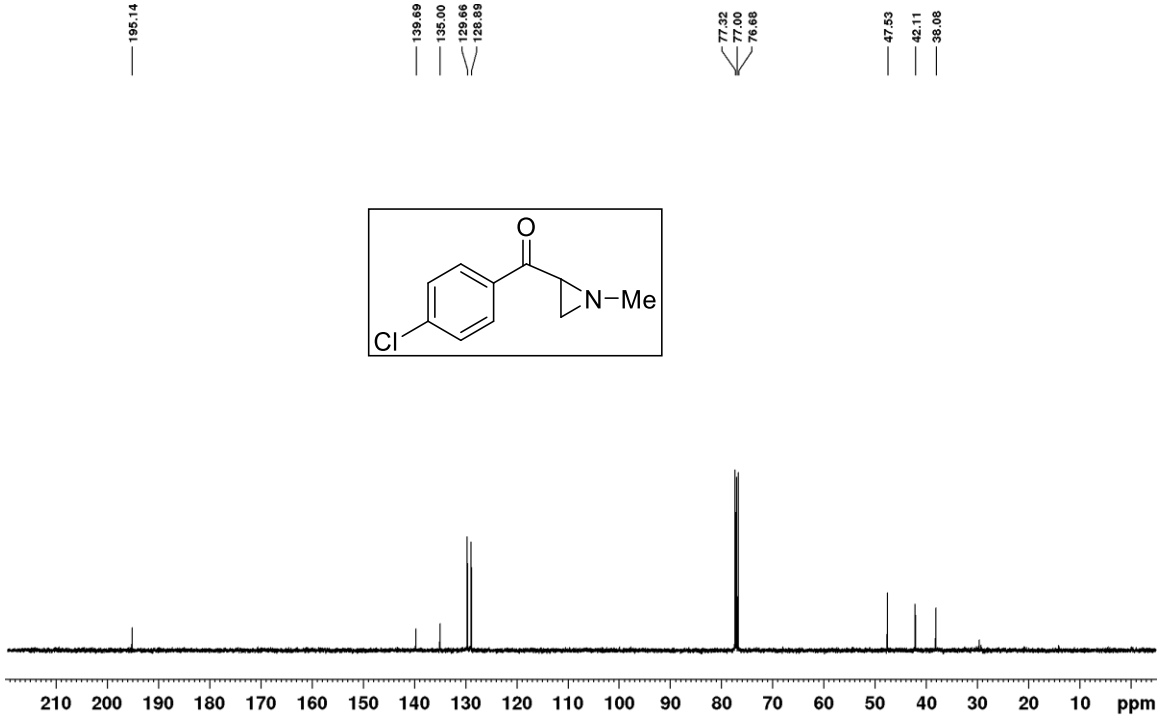
^{13}C NMR spectrum of compound **66a** (100 MHz/$CDCl_3$)



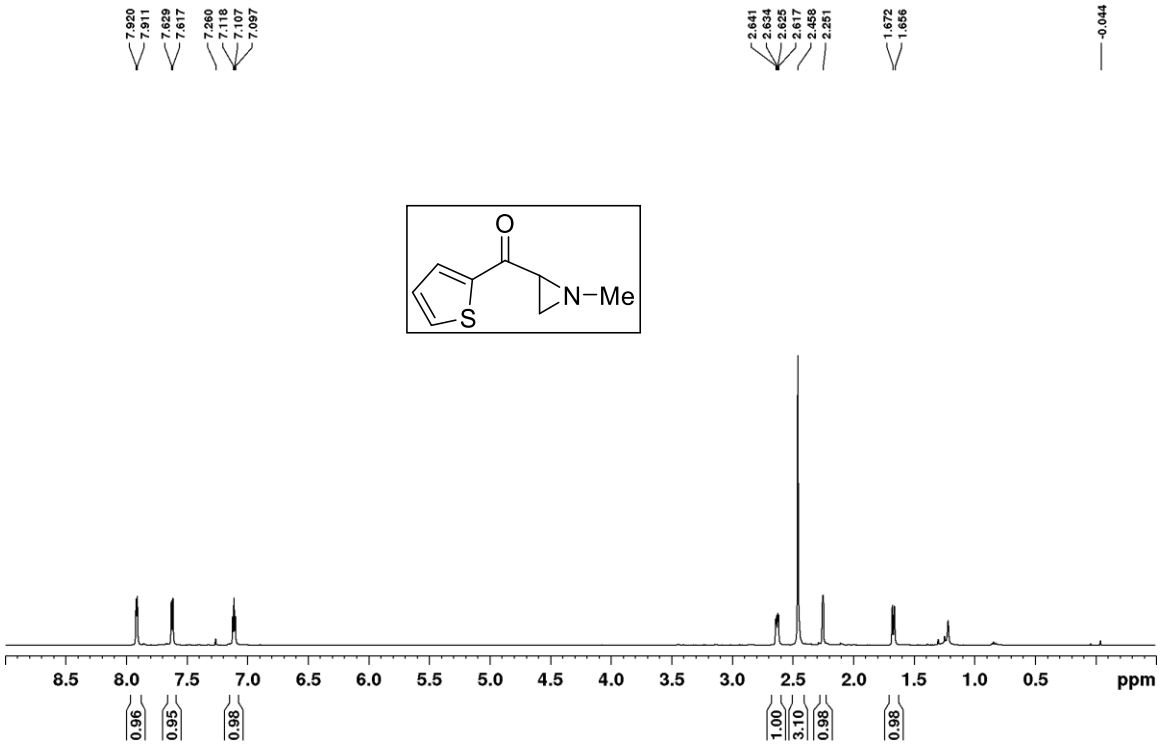
^{1}H NMR spectrum of compound **66b** (400 MHz/$CDCl_3$)



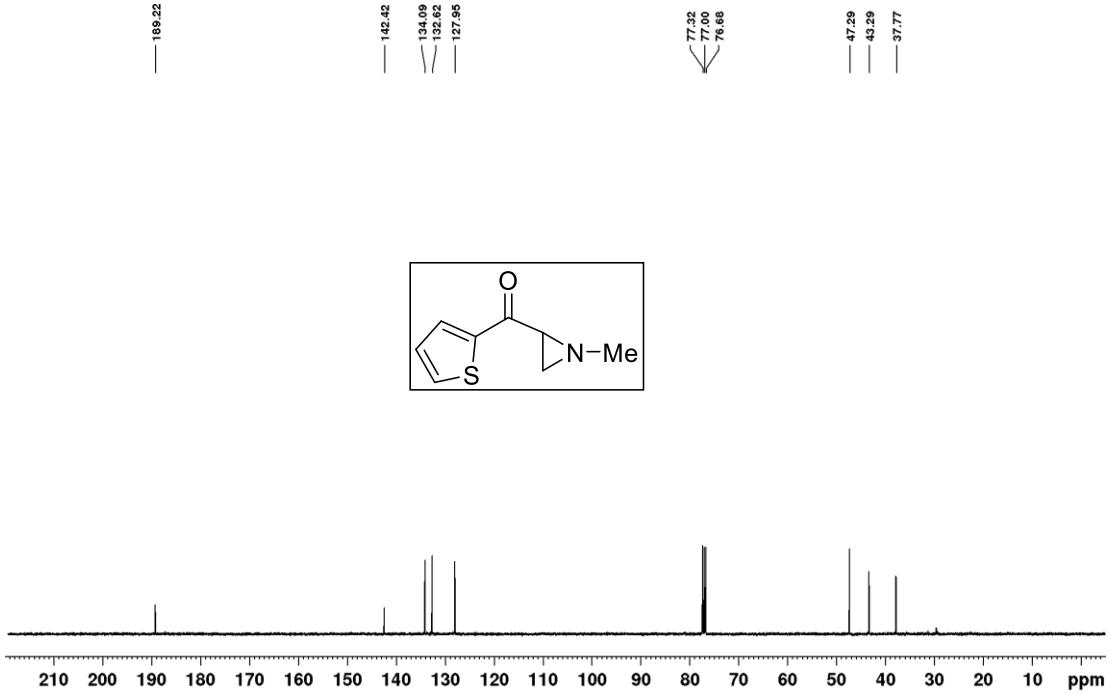
^{13}C NMR spectrum of compound **66b** (100 MHz/$CDCl_3$)



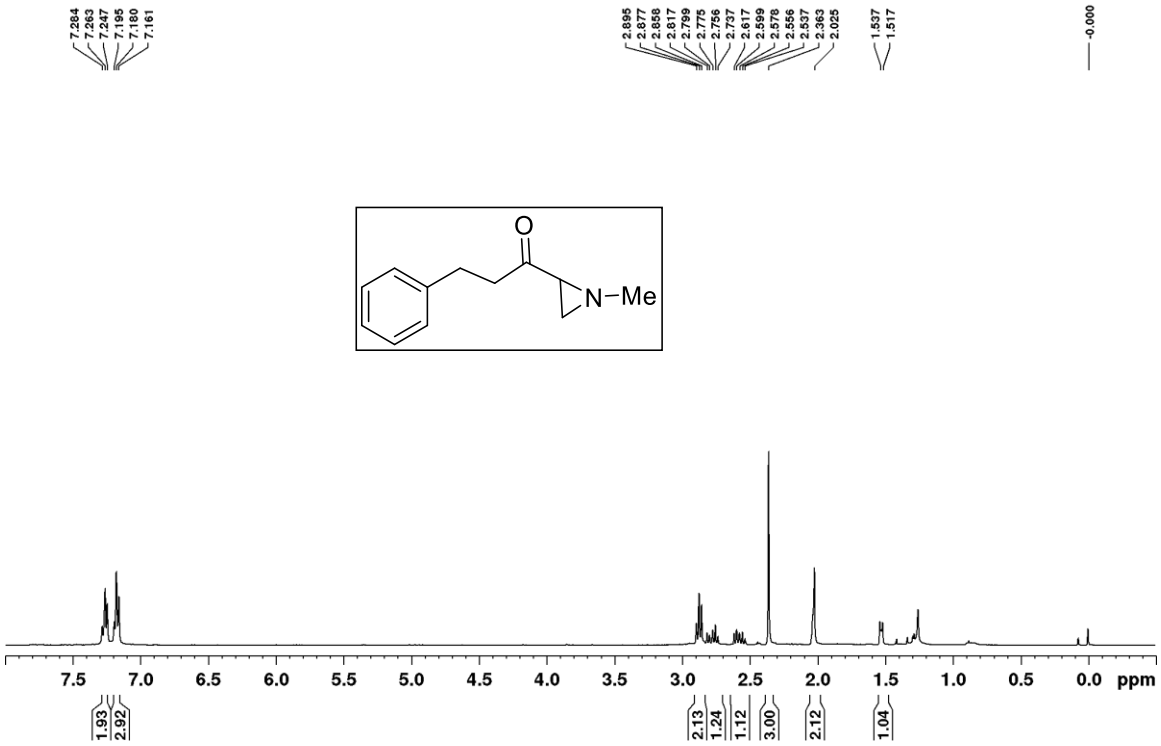
^{1}H NMR spectrum of compound **66c** (400 MHz/$CDCl_3$)



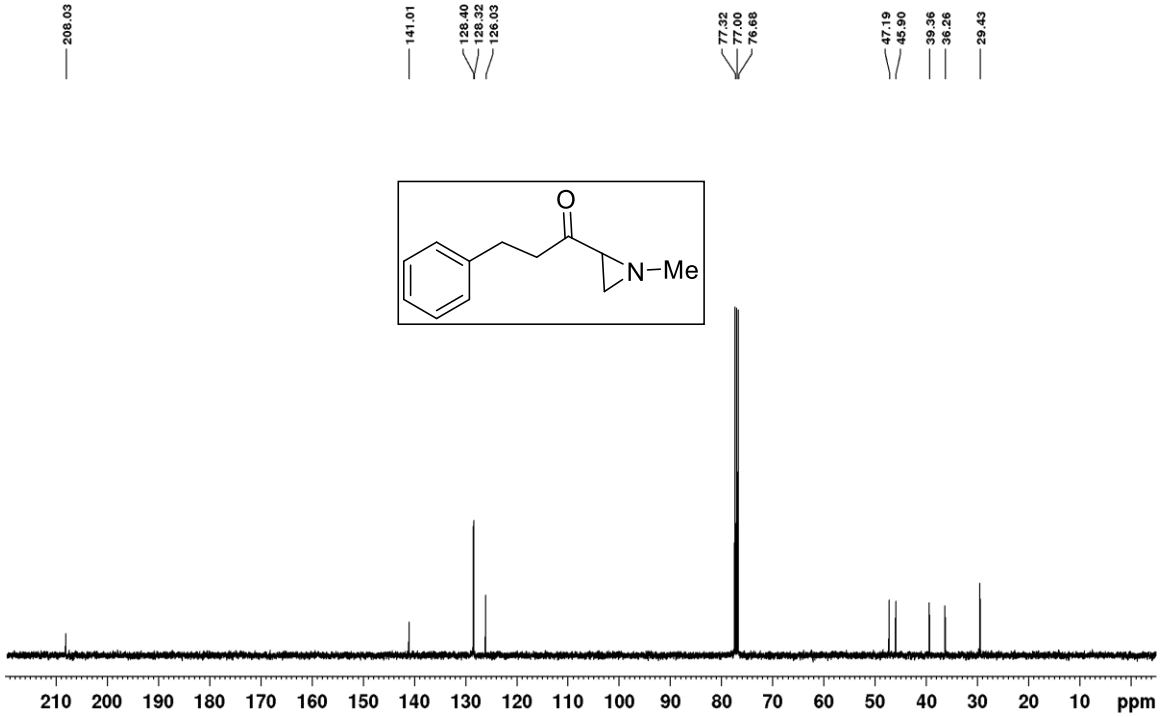
^{13}C NMR spectrum of compound **66c** (100 MHz/$CDCl_3$)



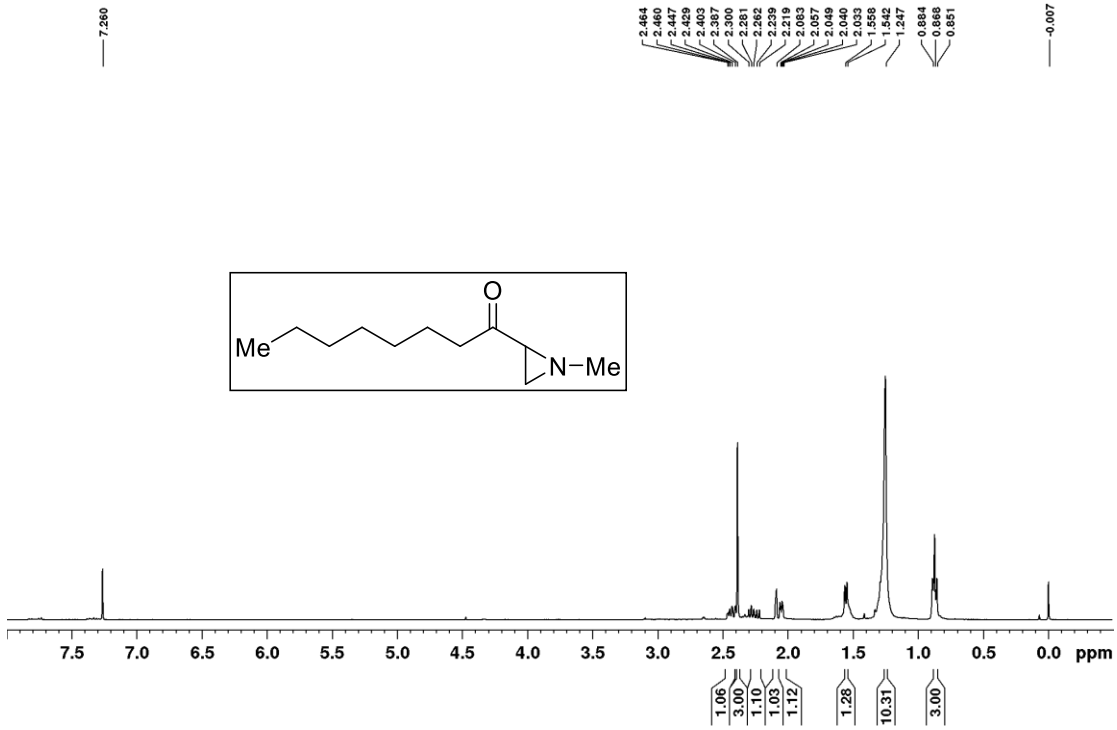
^{1}H NMR spectrum of compound **66d** (400 MHz/$CDCl_3$)



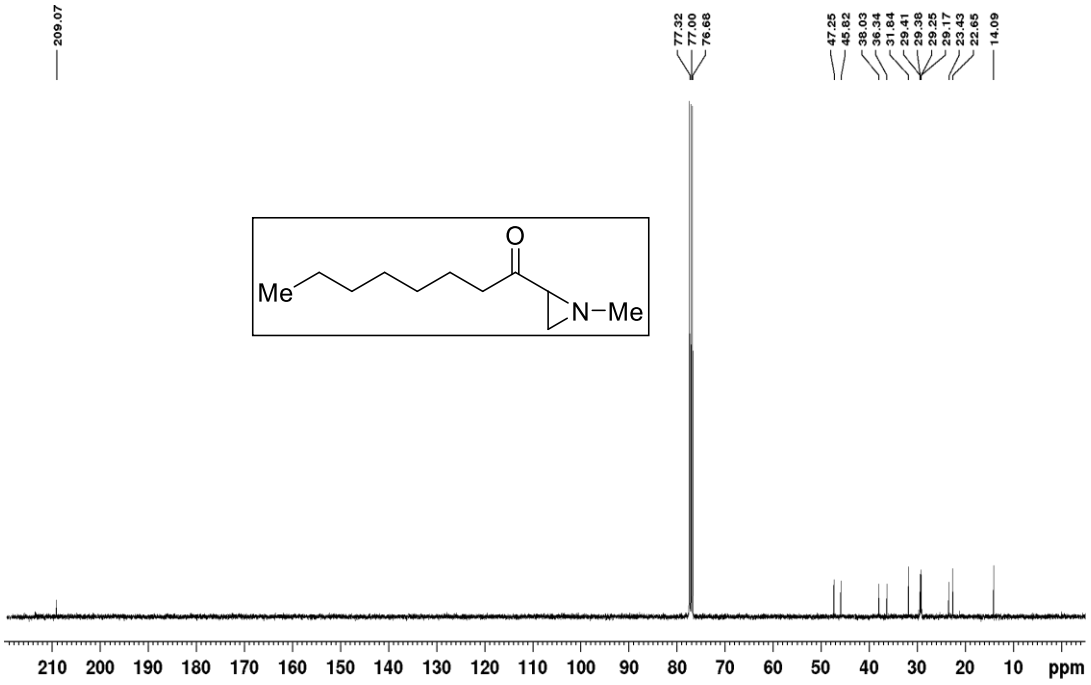
^{13}C NMR spectrum of compound **66d** (100 MHz/$CDCl_3$)



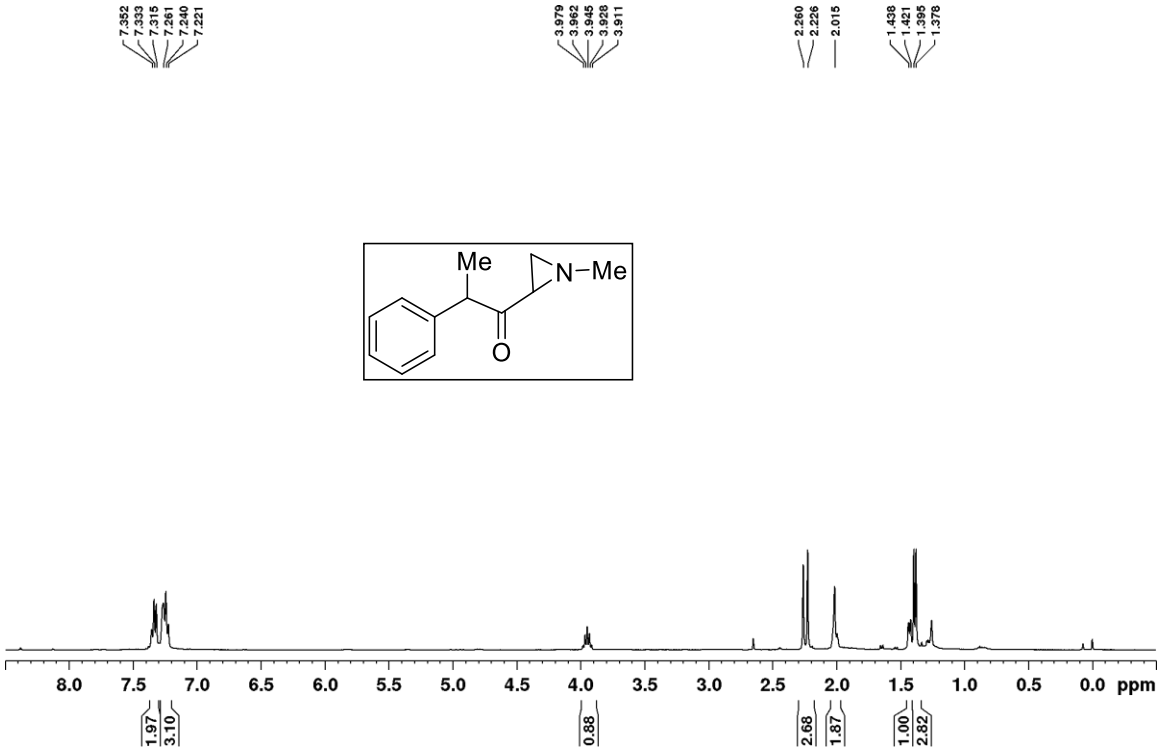
^{1}H NMR spectrum of compound **66e** (400 MHz/$CDCl_3$)



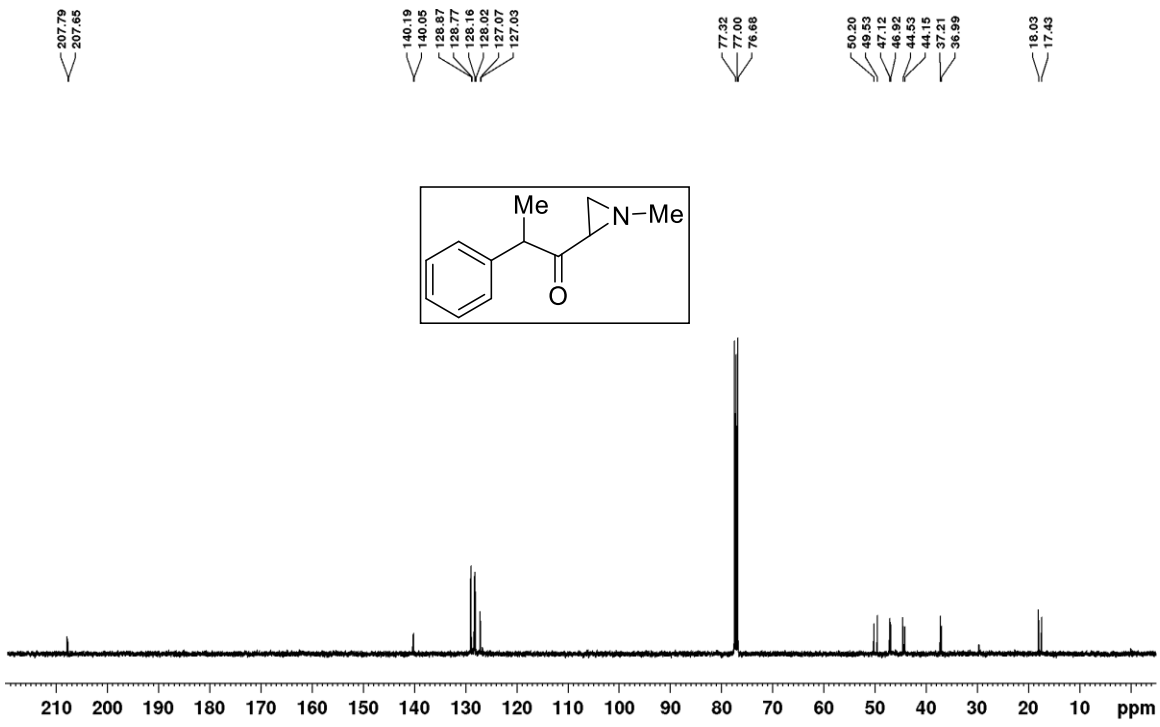
^{13}C NMR spectrum of compound **66e** (100 MHz/$CDCl_3$)



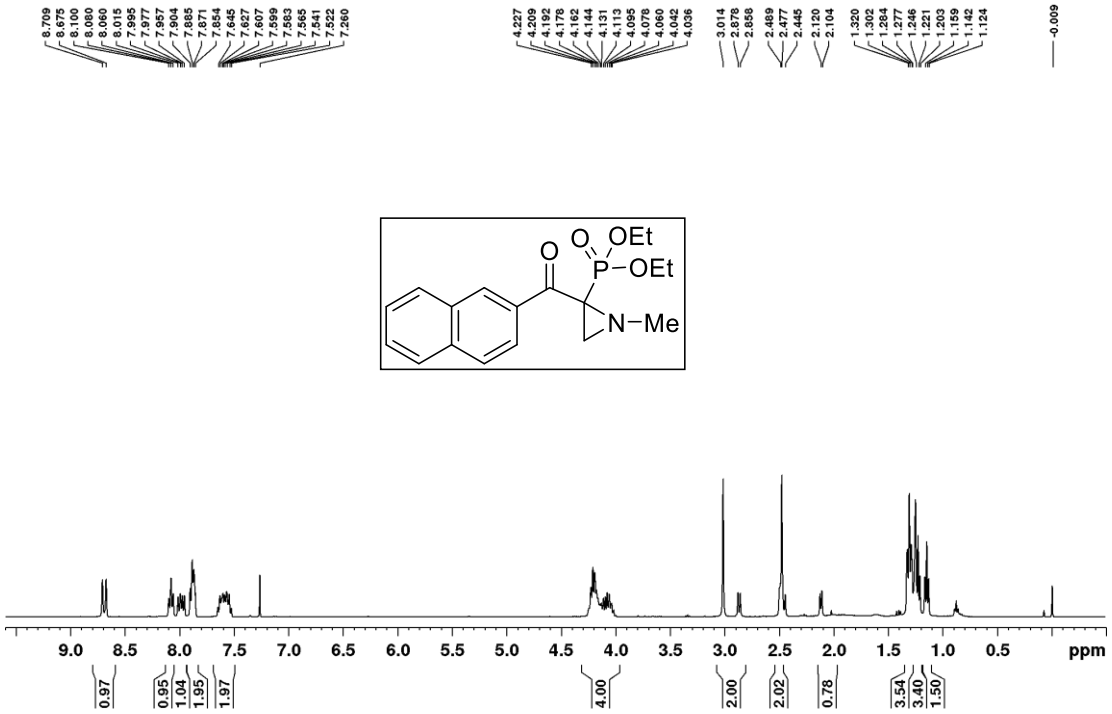
^{1}H NMR spectrum of compound **66f** (400 MHz/$CDCl_3$)



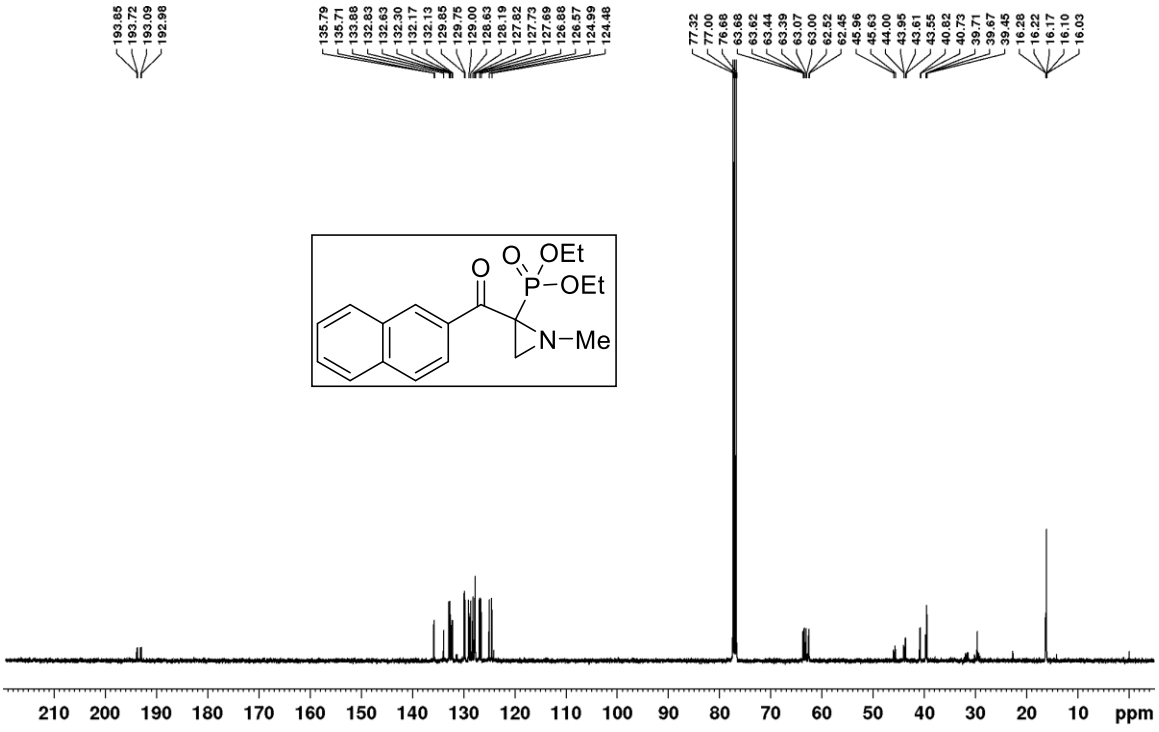
^{13}C NMR spectrum of compound **66f** (100 MHz/$CDCl_3$)



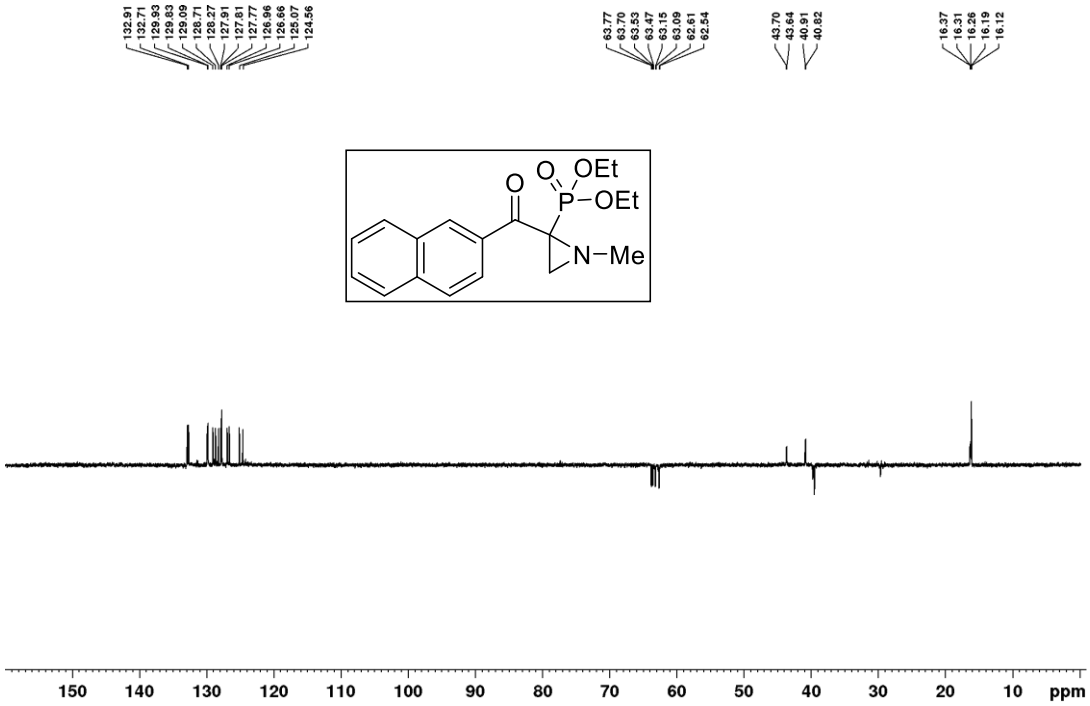
^{1}H NMR spectrum of compound **66g** (400 MHz/$CDCl_3$)



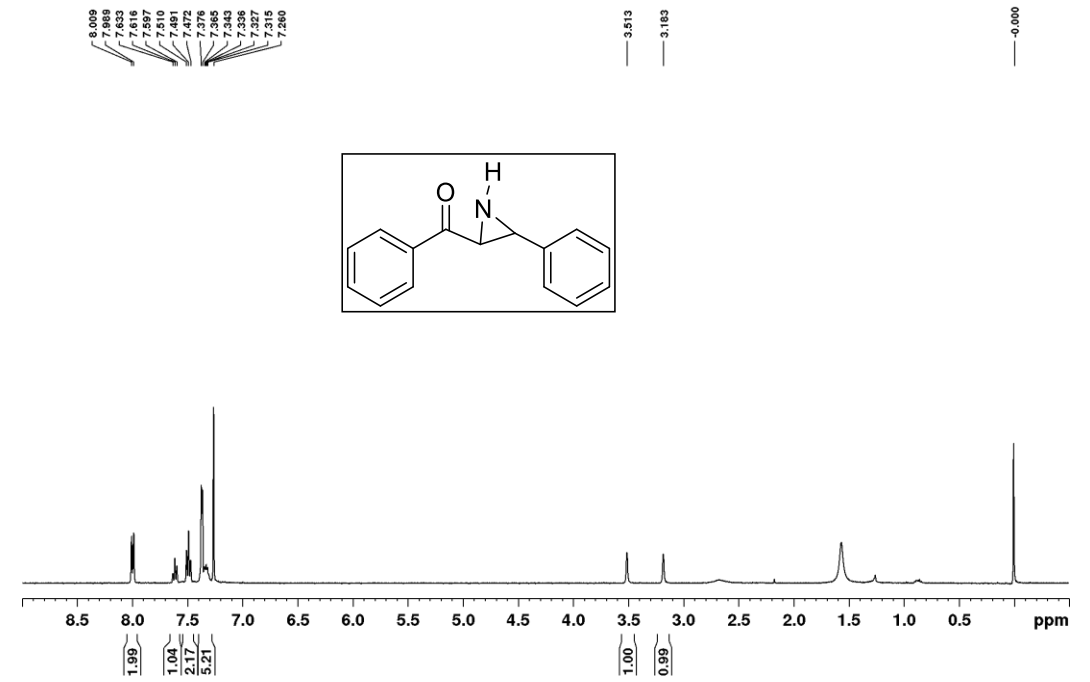
^{13}C NMR spectrum of compound **66g** (100 MHz/$CDCl_3$)



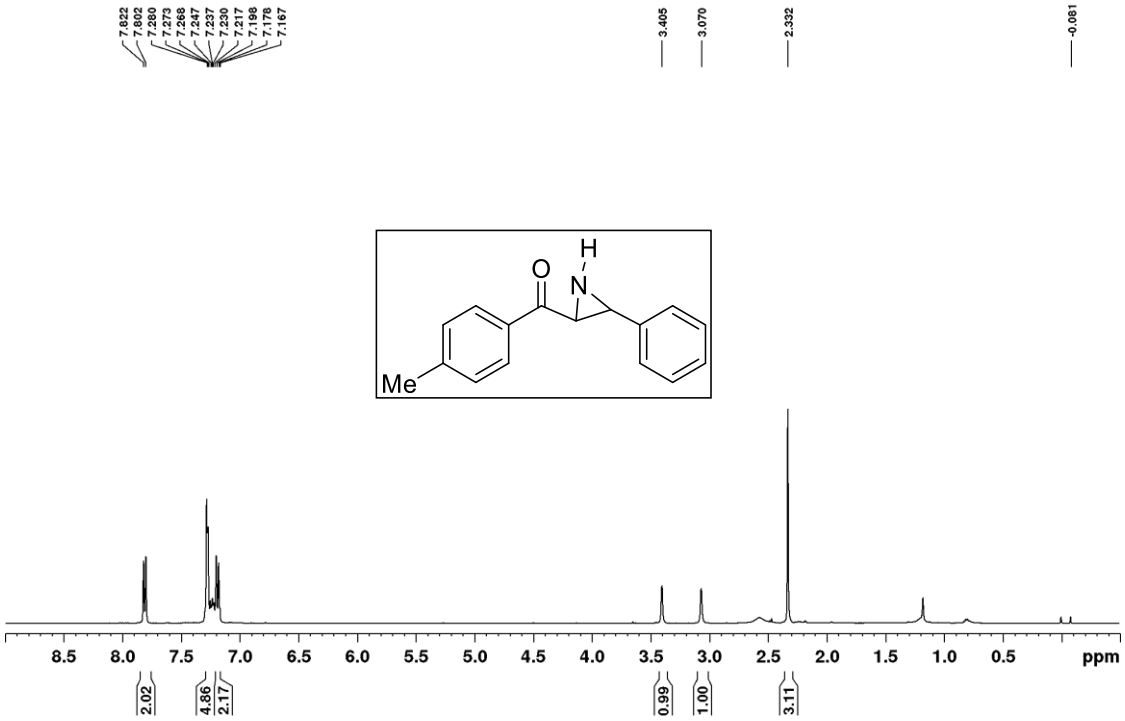
^{135}DEPT NMR spectrum of compound **66g** (100 MHz/$CDCl_3$)



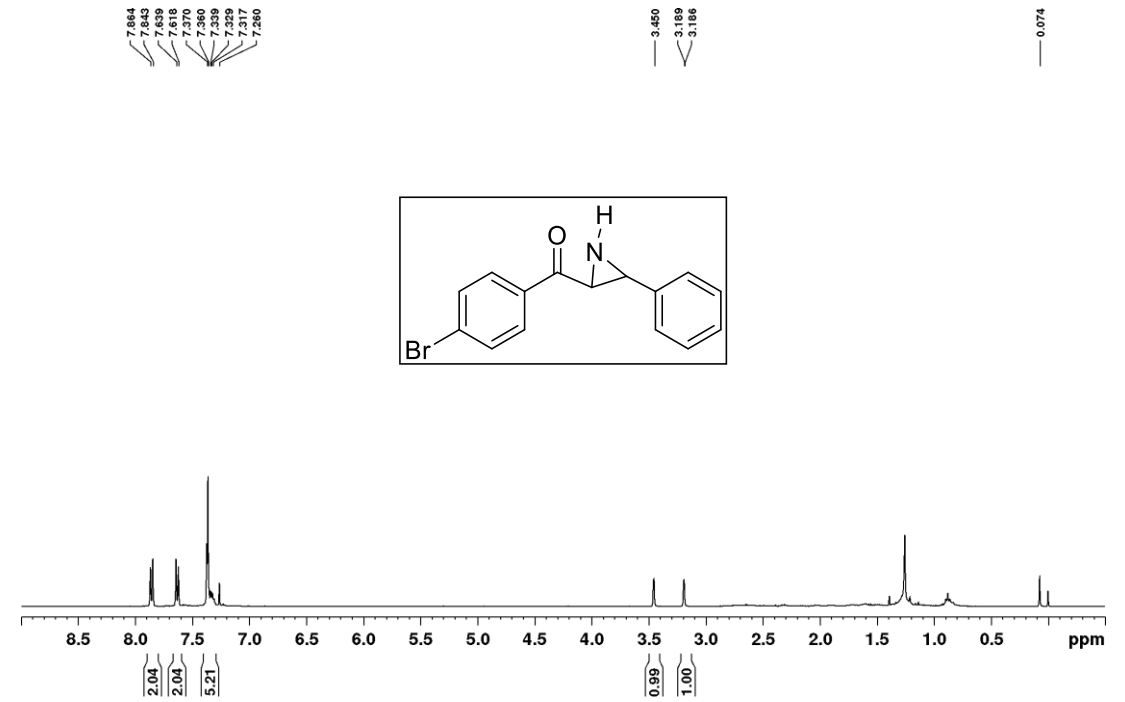
^{1}H NMR spectrum of compound **68a** (400 MHz/$CDCl_3$)



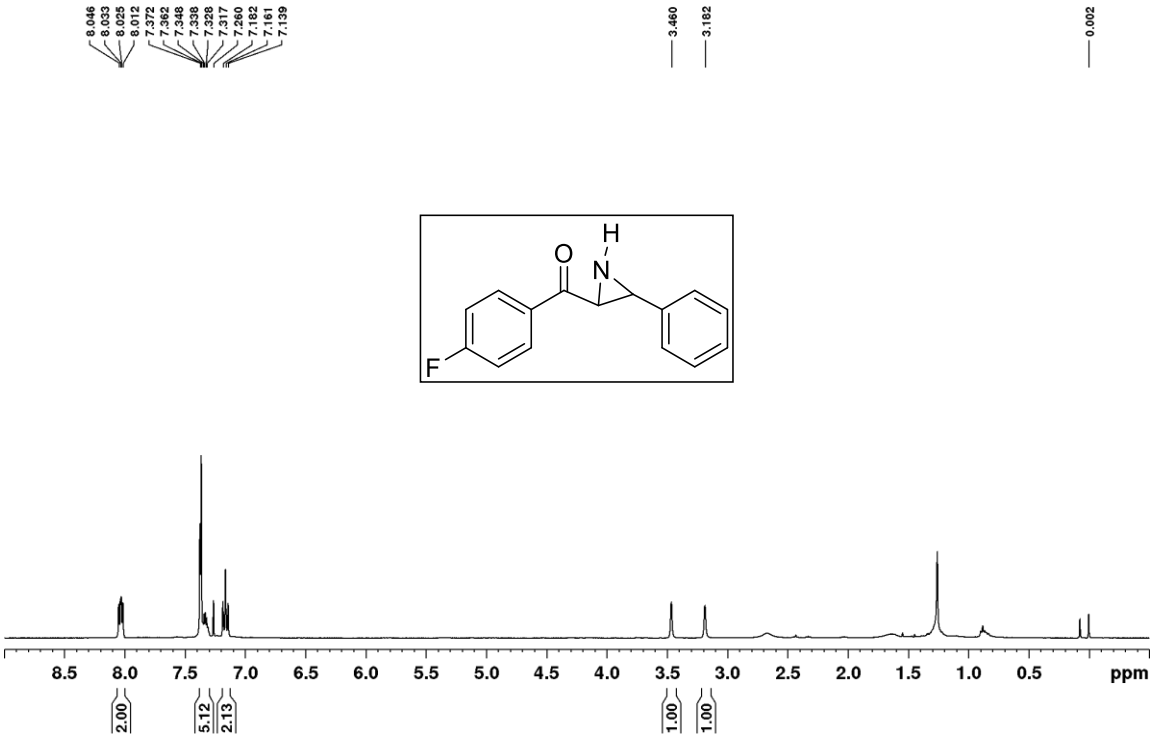
^{1}H NMR spectrum of compound **68b** (400 MHz/$CDCl_3$)



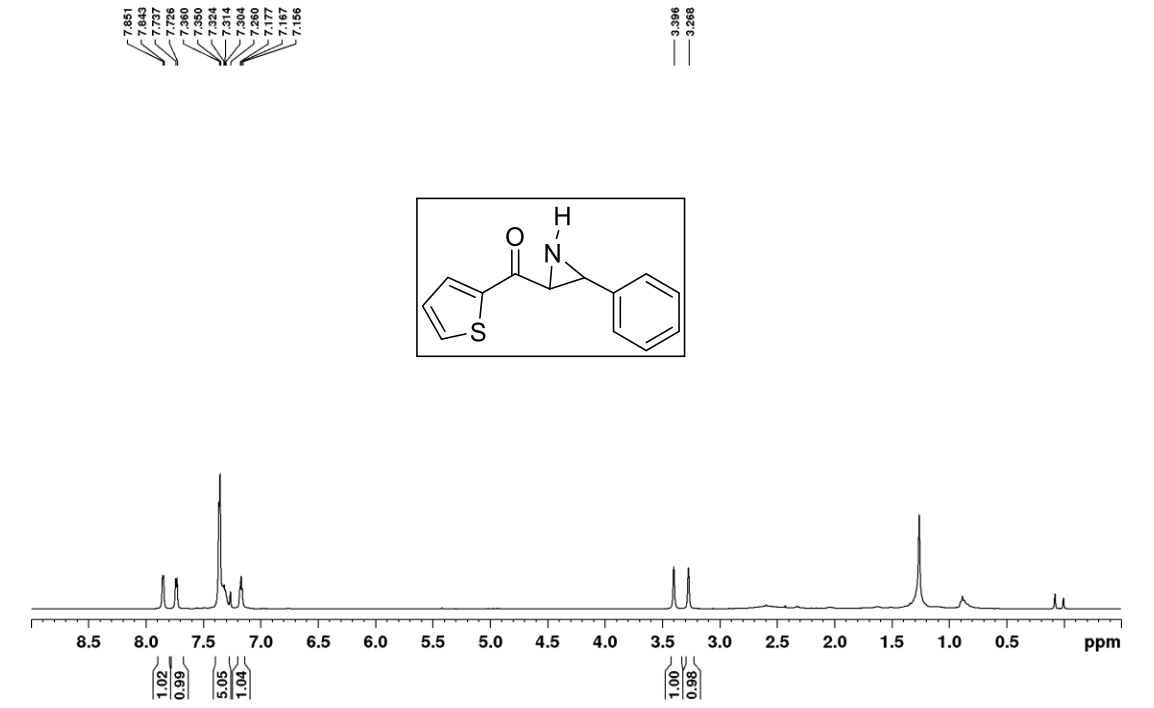
^{1}H NMR spectrum of compound **68c** (400 MHz/$CDCl_3$)



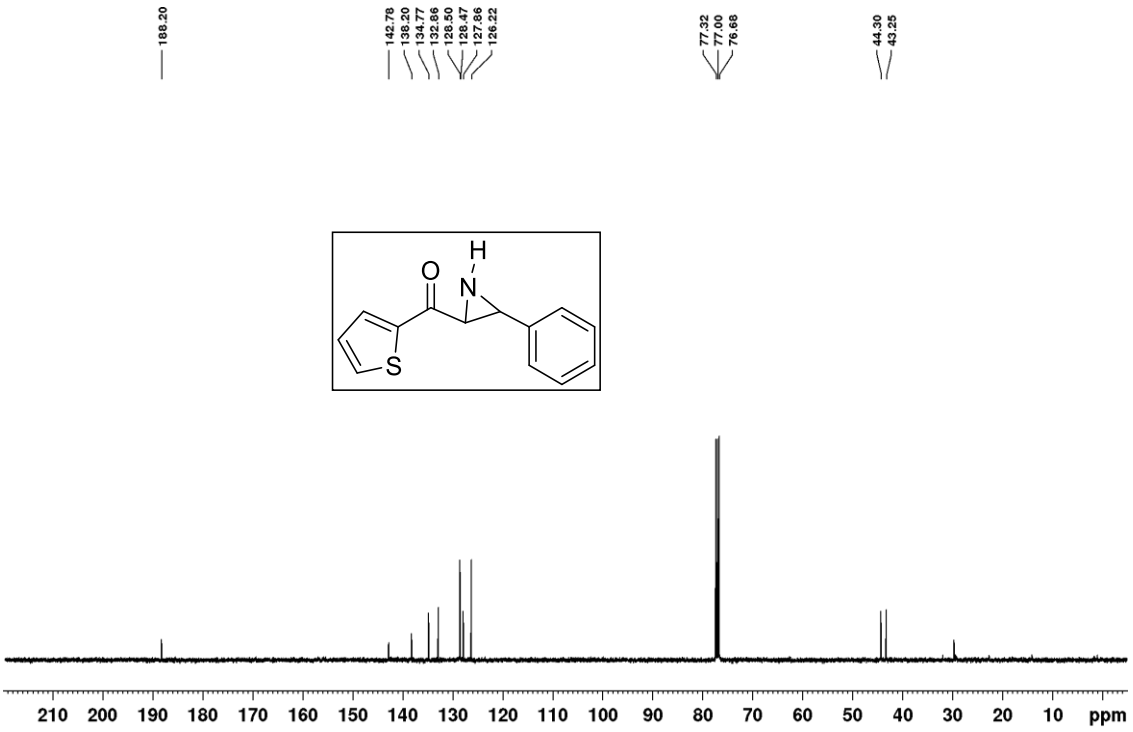
^{1}H NMR spectrum of compound **68d** (400 MHz/$CDCl_3$)



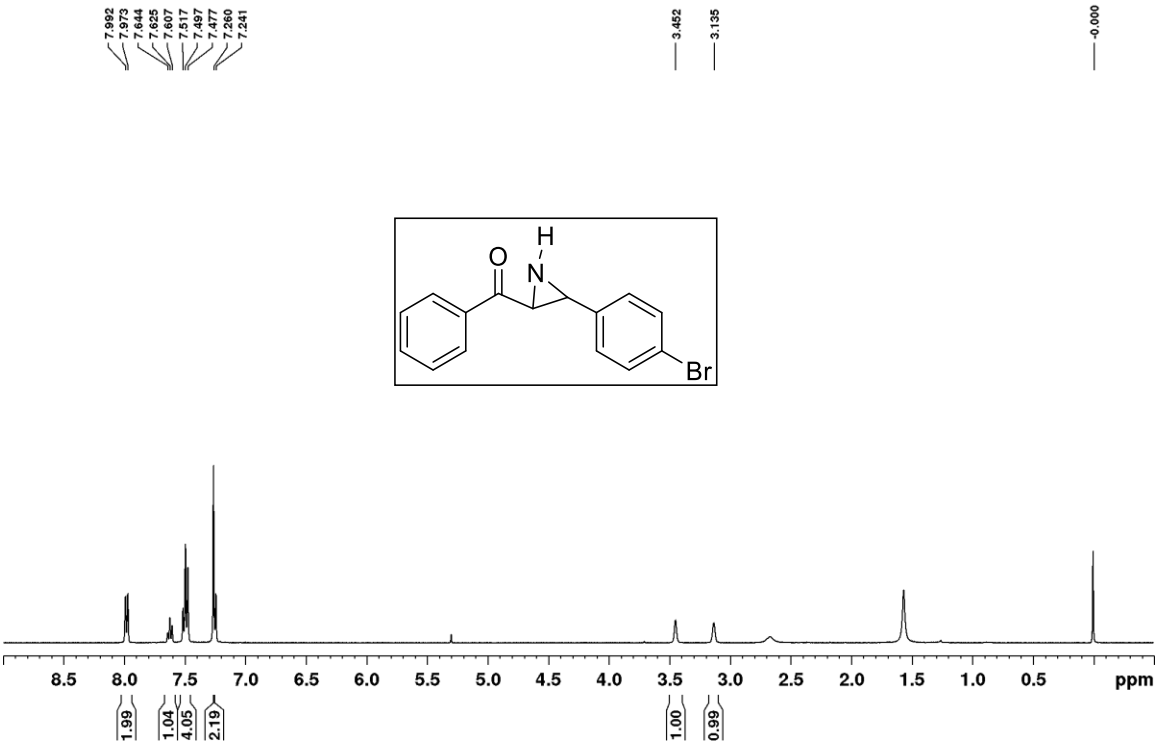
^{1}H NMR spectrum of compound **68e** (400 MHz/$CDCl_3$)



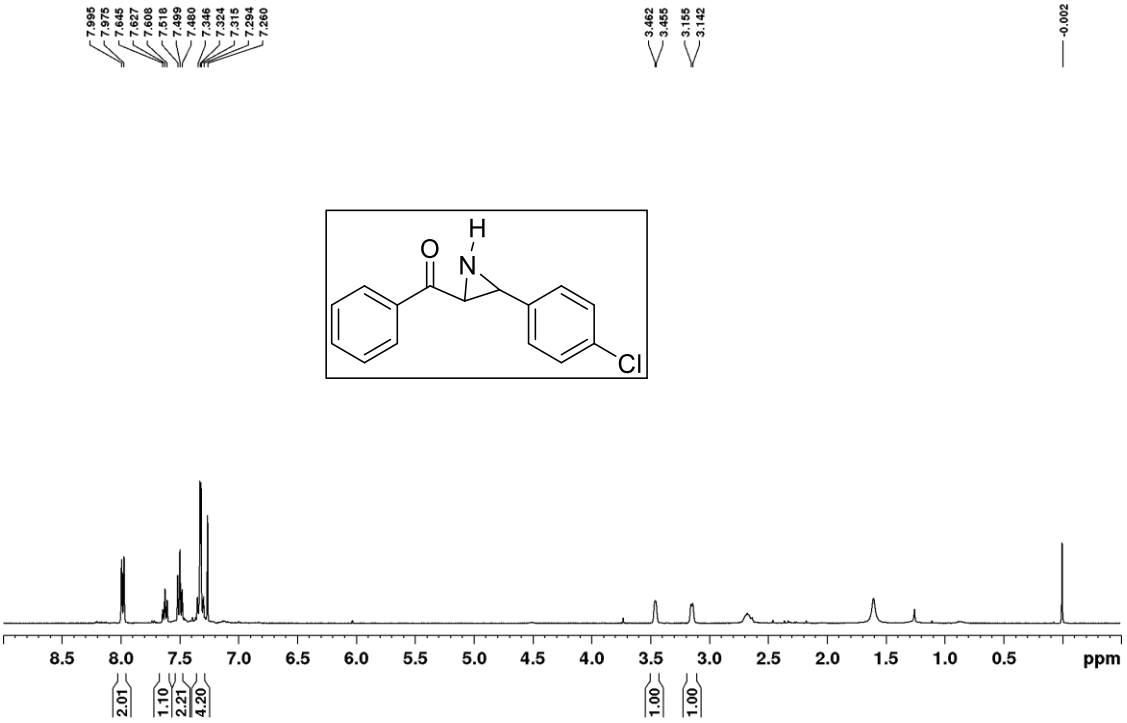
^{13}C NMR spectrum of compound **68e** (100 MHz/$CDCl_3$)



^{1}H NMR spectrum of compound **68f** (400 MHz/$CDCl_3$)

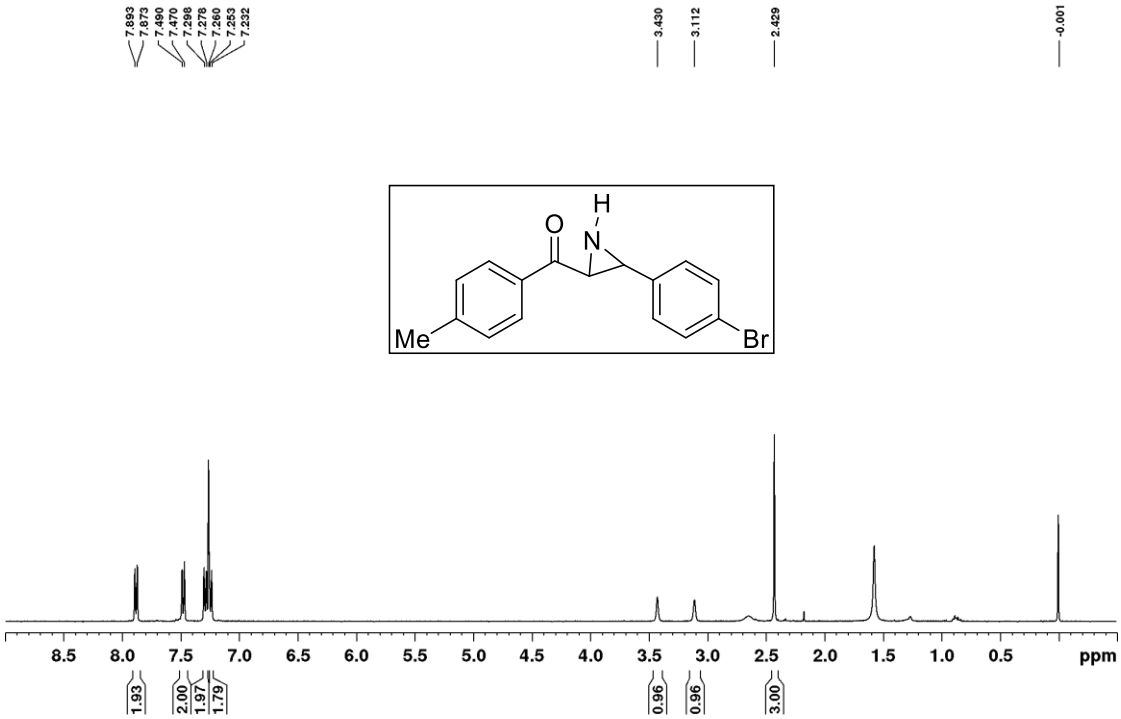


^{1}H NMR spectrum of compound **68g** (400 MHz/$CDCl_3$)

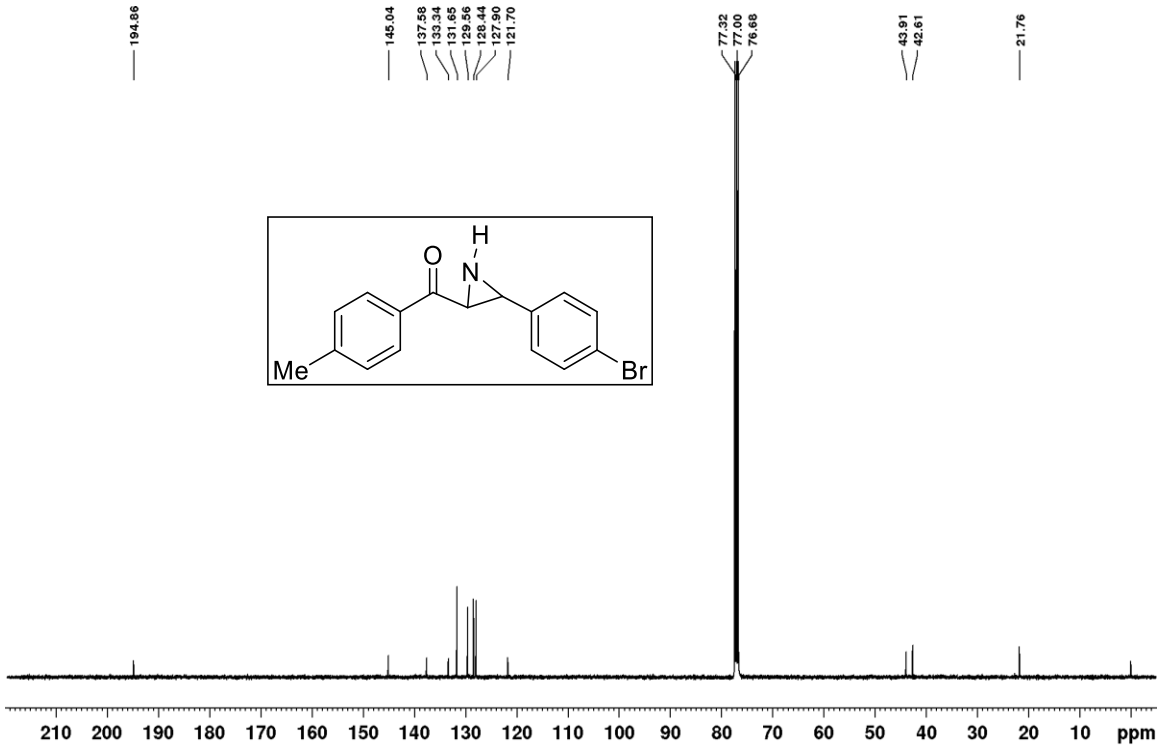


^{1}H NMR spectrum of compound **68h** (400 MHz/$CDCl_3$)

^{1}H NMR spectrum of compound **68i** (400 MHz/$CDCl_3$)



^{13}C NMR spectrum of compound **68i** (100 MHz/$CDCl_3$)



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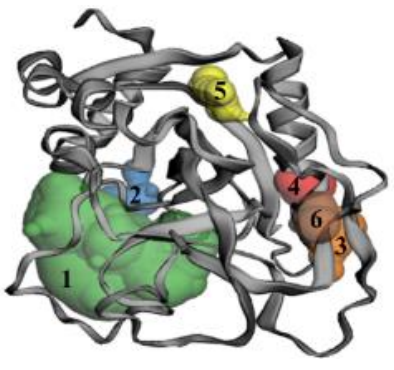
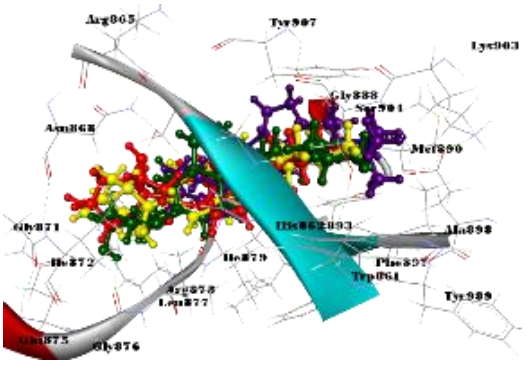
Chapter 5

Evaluation of Anticancer Activity of *N*-H/*N*-Me Aziridine Derivatives as a Potential Poly (ADP-Ribose) Polymerase 1 Inhibitor

The Poly [ADP-Ribose] polymerase 1 (PARP1) has recently been thought to be one of the potentially successful targets against cancer, specifically for ovarian and BRCA mutated breast cancers. Here, unprotected (N-H/N-Me) aziridine derivatives were recognized as potential anticancer compounds targeting the apoptotic pathway using a combined molecular descriptors (MDs) computation, prediction of activity spectra for substances (PASS), adsorption, distribution, metabolism, excretion and toxicity (ADMET) evaluation, Brain or Intestinal Estimated (BOILED-Egg), Bioactivity score (BAS), docking-based virtual screening (DBVS), integral docking and molecular dynamics (MD) simulation. Twenty one N-H/N-Me aziridine derivatives were screened to identify molecules binding to the PARP1 binding pocket followed by docking and MD simulation. Compound 3a has a good binding profile along with all the targets, but potentially better interact with the PARP1 as observed by the molecular docking evaluations. The docking complexes of the lead compound 3a with the target PARP1 were found stable during molecular dynamics simulations as represented by the obtained parameters including radius of gyration (Rg) and root mean square deviation (RMSD). The compound 3a yielded good binding free energy using the analysis of molecular mechanics generalized born surface area (MM-GBSA) and molecular mechanics Poisson–Boltzmann surface area (MMPBSA). Therefore, the finding of the studies unravels the possible compounds 3a as lead anticancer candidate against selected PARP1.





5.1 Introduction

Cancer is a lethal disease that affects people all over the world. It is classified as a disease that causes broad cellular/tissue multiplication, putting an unnecessary metabolic load on the body of the patient. Cancer is broadly responsible for ~9.6 million fatalities in developing and underdeveloped countries.[1] In India alone, more than 17 hundred thousand new cancer cases will be registered by 2020. According to Pfizer, cancer accounts for 40% of overall health-care spending in the European Union, and this figure is expected to climb by 50% in the future.[2,3] The wide-range of biological impact of compounds that contain nitrogen in their skeleton are well-known. The huge majority of compounds incorporating aziridine functionality in their structure because they have various potent biological activity (Figure 5.1).[4]

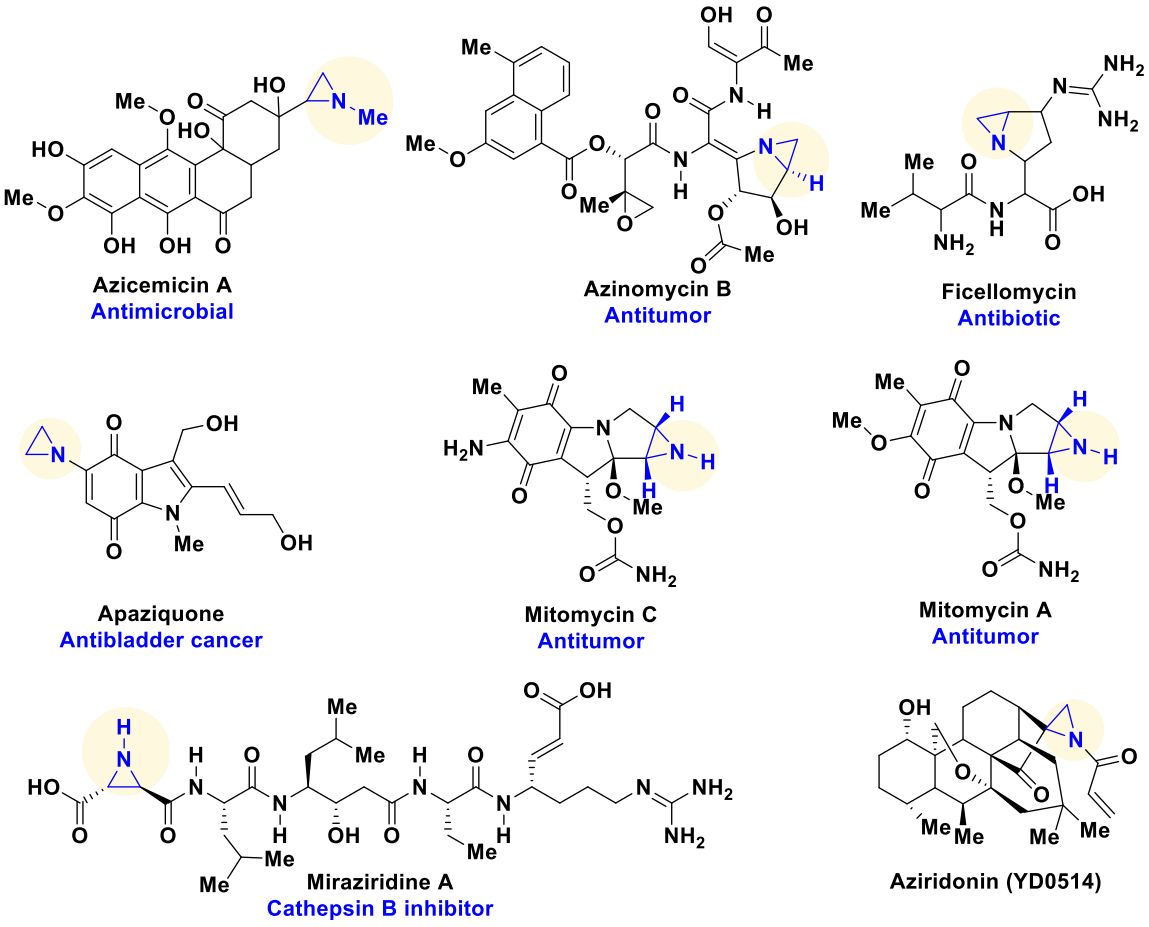
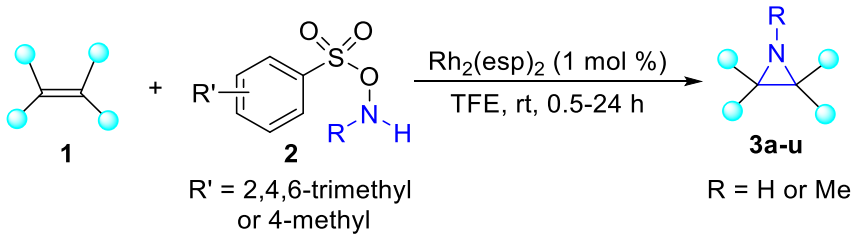


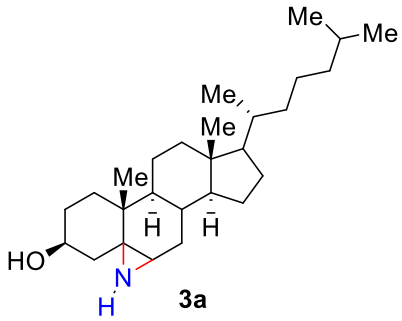
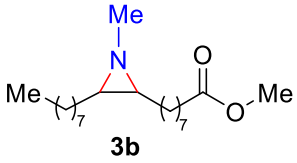
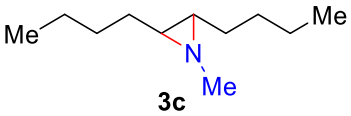
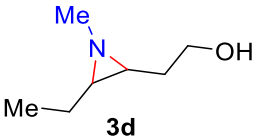
Figure 5.1. Some examples of available marketed drugs possess aziridine moiety

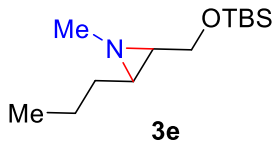
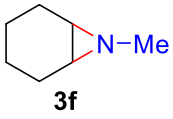
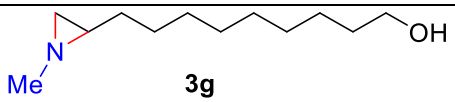
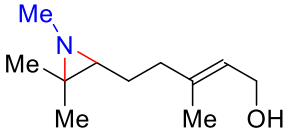
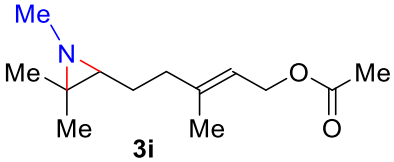
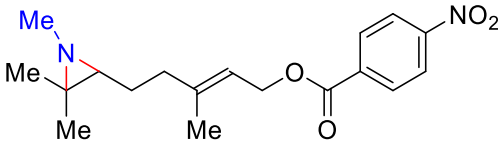
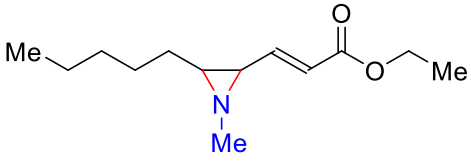
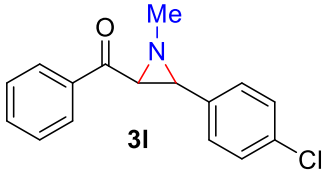
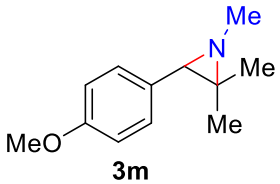
In that direction few methods are reported for direct unactivated (*N*-H/*N*-Me) aziridination of alkenes.[5a-e] In context, of development any study in this field would be highly efficient and desirable. We have reported highly efficient method for direct *N*-H/*N*-Me aziridination of unactivated olefins using *O*-(sulfonyl)hydroxylamines as aminating agents as explained in previous chapter 2 (Scheme 5.1, Table 5.1).[5c]

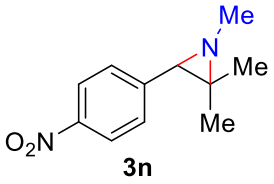
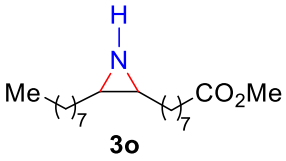
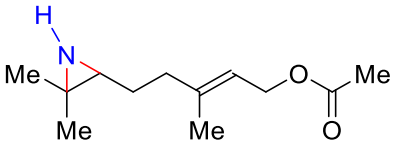
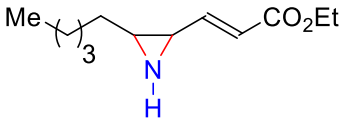
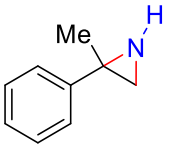
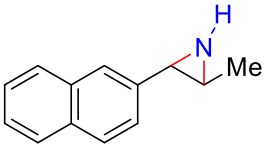
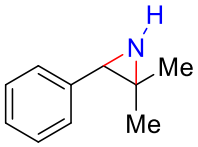
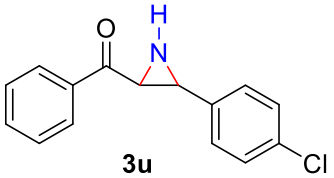


Scheme 5.1. Direct *N*-H/*N*-Me Aziridination of Unactivated Olefins

Table 5.1. Two-dimensional structure of *N*-H/*N*-Me Aziridine derivatives along with the general formula and energy

S. No.	2D structure	Formula	Energy (Kj/mol)	Gibbs Energy (kJ/mol)
1.	 3a	$C_{27}H_{47}NO$	558.888	342.61
2.	 3b	$C_8H_{14}NO_2$	227.112	-117.97
3.	 3c	$C_{11}H_{23}N$	93.5748	217.66
4.	 3d	$C_7H_{15}NO$	135.284	47.16

5.	 **3e**	$C_{13}H_{29}NOSi$	159.235	-
6	 **3f**	$C_7H_{13}N$	143.936	240.34
7	 **3g**	$C_{12}H_{25}NO$	95.5648	96.97
8	 **3h**	$C_{11}H_{21}NO$	152.919	147.02
9	 **3i**	$C_{13}H_{23}NO_2$	124.373	-9.69
10	 **3j**	$C_{18}H_{24}N_2O_4$	449.113	-
11	 **3k**	$C_{13}H_{23}NO_2$	13.8279	4.35
12	 **3l**	$C_{16}H_{14}ClNO$	347.431	334.1
13	 **3m**	$C_{12}H_{17}NO$	193.795	218.37

14	 **3n**	$C_{11}H_{14}N_2O_2$	335.739	-
15	 **3o**	$C_7H_{13}NO_2$	50.155	-161.56
16	 **3p**	$C_{12}H_{21}NO_2$	110.481	-53.28
17	 **3q**	$C_{10}H_{17}NO_2$	23.362	-56.08
18	 **3r**	$C_9H_{11}N$	145.806	280.28
19	 **3s**	$C_{13}H_{13}N$	189.049	408.76
20	 **3t**	$C_{10}H_{13}N$	150.946	280.99
21	 **3u**	$C_{15}H_{12}ClNO$	348.144	290.51

5.2 Background of the cancer treatment approaches

Different therapeutic approaches are available for the treatment of cancer, and chemotherapeutics offers several advantages over other therapies in terms of flexibility and worldwide benefits.[6–8] Small covalent molecules (SCM) now provide a crucial skeleton for the drug design and development (DDD) of a novel chemical entity with progressive therapies. Anticancer therapeutics based on SCM have their unique leading fragments, which account for 90% of the worldwide pharmaceutical marketplace. An effective anti-cancer drug discovery will have improved cellular penetration, target selectivity, and reduced toxicity in the future.[9] Furthermore, in the presence of reaction economy, high product yield, ancillary reagents, the minimum requirement of principle, fewer synthetic steps, defined synthetic protocol, optimum reaction time, predictive reaction/manufacturing path, and low molecular weight, SM analogue has several synthetic as well as characteristic advantages over a traditional macromolecular skeleton.[10,11] Prior to experimental evaluations, computer-aided drug design (CADD) techniques were extremely useful in the discovery and characterization of the druglikeness and toxicity of SCM. A good candidate drug molecule favours a number of factors such as absorption, distribution, metabolism, excretion, and toxicity (ADMET), bioactivity score, bioavailability radar, druglikeness, toxicity evaluations, and etc.[12] A good oral bioavailability is required for a prospective therapeutic molecule to be successful. The primary goal of DADD is to identify a leading SCM with exceptional pharmacokinetics and pharmacodynamics characteristics.[13] OSIRIS Data Warrior, Molinspiration, Bioclipse, admet SAR, Swiss ADME, PASS, and other computational tools are currently available (both online and offline) in support of CADD. The OSIRIS Data Warrior software was shown to be suitable for toxicity and druglikeness evaluations. The pharmacokinetics, pharmacodynamics, and bioactivity scores were monitored using Molinspiration and Bioclipse.[14–16] Other useful tools for determining ADMET parameters including Swiss ADME and admet SAR. The Lipinski rule of five (Ro5) and the Ghose filter are two extensively used criteria for describing molecular descriptors (MDs) for medical purposes.[17–19] Molecular docking and molecular dynamics (MD) simulations are also effective methods for determining the binding interaction profile between a prospective therapeutic molecule and the target protein. Open-source

docking programmes such as AutoDockVina, AutoDock4, iGEMDOCK, and PLANTS are well-known.[20] The major findings of molecular docking study are the best ligand conformation, values of free binding energies, and dissociation constant (Kd). MD simulations have been shown to be effective at the atomic level for considering the association between target protein structure and binding kinetics with potential inhibitors. Ligand and Receptor Molecular Dynamics (LARMD) was created recently to investigate ligand-protein dynamics. LARMD provides a straightforward interface for investigating the dynamic properties of the ligand-protein complex.[21] As a result, sophisticated molecular modelling and chemoinformatics justify the multi-parametric evaluation of SCM to determine its therapeutic potentials before completing expensive synthetic and biological laboratory research, given the availability of a significant number of web-based tools. Similarly, SCM is exceedingly helpful when it comes to identifying the best candidate medication molecule. SCM has reached a specific site of action, can easily cross biological membranes, and may bind with an appropriate target protein and/or handle a certain metabolic/biological procedure/path without triggering the immune system. Covalent therapeutics can have incredibly high ligand proficiency, effectiveness, and long-term effects, demonstrating their direct interactions with targets to form covalent bonds and generate bioactivities.[22] Throughout modern medicine, covalent medicines have been found to be highly effective drugs for a huge array of human diseases. From 1982 to 2009, the FDA approved thirty-nine covalent medications.[23,24] In the presence of their safety risks and potential toxicities, electrophiles, on the other hand, have been described as undruglike.

In addition, covalent natural products (like sesquiterpenoid artemisinin) and other synthetic drugs (like aspirin) have remained to be extremely successful, providing encouragement for the development of a number of therapeutic agents. The functional groups aziridine, ethylene oxide, and enone are important features of covalent natural compounds and their derivatives. These functional groups establish covalent interactions with the nucleophilic sites of receptor proteins such as cysteine.[25]

Our approach, which is based on recent developments in unprotected aziridination[5], demonstrates how anticancer pre-evaluation of aziridine derivatives can be accomplished.

As a consequence, in the current investigation, a number of natural leads were selected for aziridination and their pharmacological potential was assessed.[26] Molecular docking analysis was used to investigate the anticancer potential of several apoptotic pathway target proteins. To determine the stability of the drug-target complex, molecular dynamics simulations were also used.[27, 28] The occurrence of the *N*-H/*N*-alkyl aziridine functional group in natural compounds probably introduces certain beneficial properties to enhance druglikeness, anticancer potential optimization, and biological safety aspects.

5.3 Objective of the work

- First design the 2-D structure of synthesized *N*-H/*N*-Me aziridine derivatives
- Molecular docking of the compounds
- Evaluation of anticancer activity

5.4 Methods

5.4.1 Molecular descriptors (MDs)

The physiochemical activities of a chemical entity are influenced by the MDs. Different MDs such as hydrogen bond acceptor site (ON), hydrogen bond donors (OHNH), partition coefficient (log P), rotatable bonds (RB), topological polar surface area (TPSA), and molecular weight (MW), etc. are played a significant role in oral bioavailability of the chemical compound. Similarly, MW, TPSA, and RB are well-known descriptors to explain the drug-likeness of an applicant molecule. Higher values of MW, TPSA, and RB have defined the lowering in their cell penetration power. Today, a large number of MDs rules are available, to elucidate the medicinal application of a chemical compound like Lipinski's rule of five (Ro5), Veber rule, Muegge rule, Egan rule, Ghose filter, and Leadlikeness. There all rules are very effective in the reduction of miss leading, in drug discovery and development (DDD).[29] In the current study, several MDs were calculated by ChemDraw Professional v15.1 and Molinspiration (http://www.molinspiration.com/).

Lipinski's (Ro5)

In 2002, Lipinski prepare a filtering rule based on certain MDs to define the oral bioavailability of a chemical entity. Lipinski's rule of oral bioavailability is also known

as the rule of five (Ro5), in the presence of their five molecular parameters including OHNH, ON, RB, MW TPSA, and logP. This rule is broadly utilized all over the world to find the most suitable candidate drug molecule. The decided molecular parameters of Ro5 are OHNH ≤5, ON ≤10, RB ≤10, MW ≤500, TPSA ≤140 Å2, and logP ≤5.[30]

Veber rule

In 2002, Veber et al. also define some MDs such as TPSA, OHNH, ON, and RB for membrane permeability as well as oral bioavailability of a candidate drug molecule. Cell permeation increases with a decrease in TPSA and RB values. This rule specifies TPSA ≤140 Å2 (or 12 or below OHNH, ON) and 10 ≤RB.[31]

Muegge rule

For an effective candidate drug molecule, in 2001 Muegge et al. also prepare a set of filters which is states that a good drug molecule must have TPSA <150, no. of carbon atoms >4, no. of rings < 7, no. of heteroatoms >1, no. of RB < 15, no. of ON < 10, no. of OHNH < 5, XLogP between -2 and 5 and MW between 200 and 600 Da (Muegge et al., 2001).[32]

Egan rule

This rule also classifies the drug-likeness of a chemical entity. According to this rule logP,>5.88 or TPSA > 131.6 $Å^2$ is essential for a candidate drug molecule (Egan et al., 2000).[33]

Ghose filter

Molar refractivity and molecular lipophilicity both MDs strongly influenced the bioavailability, cellular uptake, and receptor binding potentials of a chemical entity. These descriptors are denoted various interactions such as van der Waals and hydrophobic within a drug candidate and also use in 3D-QSAR analysis to calculate the drug-likeness of a molecular system. According to the Ghose filter, a drug applicant must be qualify following parameters including clogS: -0.4- 5.6 (2.52); MW: 160-480 (357); MR: 40-130 (97) and the total number of atoms 20-70 (48).[34]

Leadlikeness

For lead likeness, according to Teague et al. (1999), a drug candidate molecule must possess RB <7, XLOGP3 <3.5, and MW 250–350 Da.[35]

5.4.2 Prediction of activity spectra for substances (PASS) analysis

The biological activity of a molecular system is evaluated with the help of the structure-activity relationship (SAR) along with the already known drug skeletons. PASS online (http://195.178.207.233/PASS/index.html) server is openly available for the prediction of the biological activity spectrum of a chemical entity.[36]

5.4.3 ADMET evaluation

The open-source tool admetSAR v2.0 was developed to predict the ADMET characteristics of molecular systems. It is commonly utilized in structural-based search of ADMET properties in pharmaceutical as well as chemical synthesis fields. The database update regularly their ADMET information based on published kinds of literature.[37] It obtained the ADMET associated information from the peer-reviewed scientific articles from PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Google Scholar (http://scholar.google.com/) etc. The updated model of admetSAR mainly targeted the modification of quantity and quality of the training dataset. In which 47 models are presented for the analysis of drug discovery as well as environmental risk assessment.[38] Almost 50 ADMET-related properties such as human intestinal absorption (HIA), blood-brain barrier penetration (BBB), oral bioavailability (OB), solubility in water, plasma protein binding (PPB), AMES mutagenicity, carcinogenicity, etc., are deposited in the admetSAR database (http://lmmd.ecust.edu.cn/admetsar2/).

5.4.4 Brain or intestinal estimated (boiled-egg)

BOILED-Egg model is recently proposed to estimate the blood-brain barrier penetrability and gastrointestinal absorption of a chemical entity.[38] This model is very beneficial during the evaluation of the drug-likeness of a candidate molecule. WLOGP (Lipophilicity) and TPSA (topological polar surface area) are two significant parameters for the bioavailability of a molecular system. SwissADME server is allowed to plot BOILED-Egg by using WLOGP and TPSA.[39,40] Here a single BOILED-Egg model was

prepared to recognize the penetrability of aziridine derivatives along with the reference compounds and standard drug molecule.

5.4.5 Bioactivity score (BAS) prediction

Molinspiration v2018.10 is also offered to calculate BAS, which is another parameter to estimate the overall druglikeness of a chemical entity. Based on the general BAS rule, there higher value is support or represent the greater is the possibility of the molecular system under study for being biologically active.[37]

5.4.6 Principal component analysis (PCA)

In DDD for a particular chemical entity, a large number of MDs parameters are calculated, their values are multidimensional, and a huge numeric. PCA recalculates this multidimensional data and is confined in a compact graphic presentation to highlight and identify the most prominent configurations of the candidate drug molecule.

5.5 Molecular docking

Molecular docking evaluations help in analyzing the interaction between the small-molecule system and biological target macromolecules.[41] The investigation includes binding of the small molecule (Ligand) with the desired pocket (active site) of the target protein which is mentioned as a receptor. The interaction involves a covalent mode prominent to probable specificity.[42]

5.5.1 Target protein identification

In the search for a suitable drug target of a molecule system, in-silico tools are very effective. In-silico tools are the main players in shorting the dataset of available targets and signifying alternate targets for a particular molecular system.[43] To understand the molecular behaviors of a chemical entity, evaluation of their mode of actions are very helpful. Swiss Target Prediction (STP) is an openly available online tool, which is helpful in the find the most suitable target for a biologically active molecule based on SAR and its fragments.[44] Here, all the synthesized compounds were also subjected to SAT server to find out their percentage of biological activity against the known intracellular targets.

Enzyme, hydrolase, membrane receptor, and G-protein coupled receptors are the most common targets of all the aziridine derivatives (Figure 5.2).

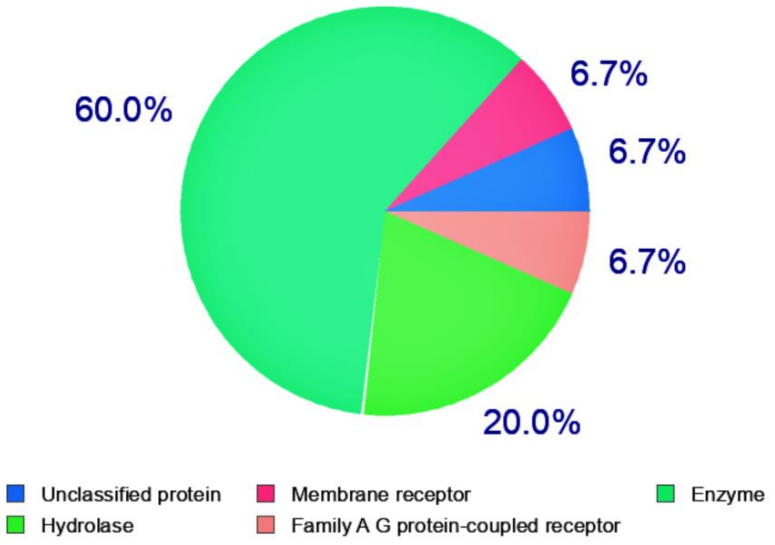


Figure 5.2. Rate of recurrence of target prediction of aziridine derivative as exposed in the pie chart produced by SwissTarget Prediction

5.5.2 Target protein procurement and pocket analysis

All aziridine derivatives have successfully targeted enzymes were represented in the SAT results. The apoptotic pathway is well known for its carcinogenic activity. Some common factors such as caspase 3, caspase 8, Bcl-xl, Bcl-2, BAX, and BAD proteins of the apoptosis pathway play the most significant role in the development of cancer. Therefore, apoptotic pathway factors were chosen for the evaluation of the anticancer potential of aziridine derivatives.[45] The crystal structures of apoptosis pathway factors were obtained from protein data bank (PDB, http://www.rcsb.org/pdb/home/home.do) with the PDB IDs: 1GJH, 4PRZ, 5H31, 5W60, 6BFK, 6BHV, and 6DCN. Packet analysis was performed with the help of Computed Atlas of Surface Topography of Protein (CASTp, http://sts.bioe.uic.edu/castp/). The 3D structure of target proteins was subjected for energy minimization by using the default RMSD further AMBER force field 14SB through Chimera v1.12. Before molecular docking, the analysis adds Kollman charge, polar hydrogen bonds, and marge non-polar hydrogen bond with the help of AutoDock v4.2.6 (Table 5.2 and Figure 5.3).

Table 5.2. Poly [ADP-Ribose] polymerase 1 (PDB ID: 6BHV) pocket amino acid residues with sequance ID (Atom)

Pockets	Area (SA)	Volume (SA)	Pocket Color	Pocket amino acid with Sequance ID (Atom)
1	469.70	572.40	Green	HIS862 (CA, ND1, CE1, NE2); GLY863 (N, O); SER864 (CA, CB, OG); ARG865 (N, CG, CD, NE), NH2); ASN868 (CA, O, CB, CG, OD1, ND2); GLY871 (CA, C, O); ILE872 (N, CA, CG1, CD1); GLN875 (CB, OE1, O); LEU877 (CA, CD2, N); ARG878 (O, CB, CG, NE, CZ, NH1, NH2); ILE879 (CA, C, O); ALA880 (N, CA, CB); PRO881 (CA, CB, CD); ALA884 (CB); PRO(O), CG, CD); GLY888 (CA, C, O); TYR889 (CA, CD2, CE1, CE2, CZ, OH); MET890 (N, CB, CE); LYS893 (CA); GLY894 (O), ILE895 (CA, CG2); TYR896 (N, C, O, CB, CG, CD1, CD2, CE1, CE2, CZ); PHE897 (N, CA, C, O); ALA898 (N, CB); LYS903 (CG, CE); SER904 (CA, CB, OG); TYR907 (O, CB, CG, CD1, CD2, CE1, CE2, CZ, OH); HIS909 (CD2, NE2); GLU988 (CB, CD, OE1, OE2).
2	64.43	27.99	Blue	MET777 (CG); SER864 (O); ARG865 (CA, CB, CG, CD, NH1); THR866 (N, CB, OG1, CG2); THR867 (N, OG1, CG2); CYS908 (O, CB); HIS909 (O, CB); THR910 (CA, CG2); ASP914 (OD1, OD2); ILE916 (O); GLY917 (CA); LEU918 9N).
3	48.19	20.21	Orange	ASN820 (O); THR821 (CA, C); HIS822 (C, O); ALA823 (CA, CB); THR824 (N, OG1, CG2); MET900 (SD, CE); THR 954 (CB, OG1, CG2, OG1); GLY974 (N, A); TYR986 (CE1, OH).
4	30.32	17.55	Red	VAL818 (O, CG1); LYS819 (CA, O, CG); HIS822 (CB, CG, ND1, CD2); ASP 830 (CA, CB, OD2); LEU831 (N, O, CB, CG, NZ, CE, NZ).
5	56.05	10.70	Yellow	ARG857 (NH2); LEU859 (CD1, CD2); GLU923 (CB, OE1, OE2); LEU964 (O, CB, CD2); ASP965 (CB, OD2); GLY966 (N); VAL967 (CB, CG2): LYS1000 (CB, CG, CD, CE, NZ); TYR1001 (CE2, CZ, OH).
6	32.58	10.70	Brawn	ARG858 (NH1, NH2); ASP899 (OD2); LYS949 (NZ); THR955 (OG1); PRO956 (O, CB, CG, CD); PRO958 (CA, CB, CD); ASN961 (OD1, ND2, CB); ASN987 (ND2); TYR989 (OH).

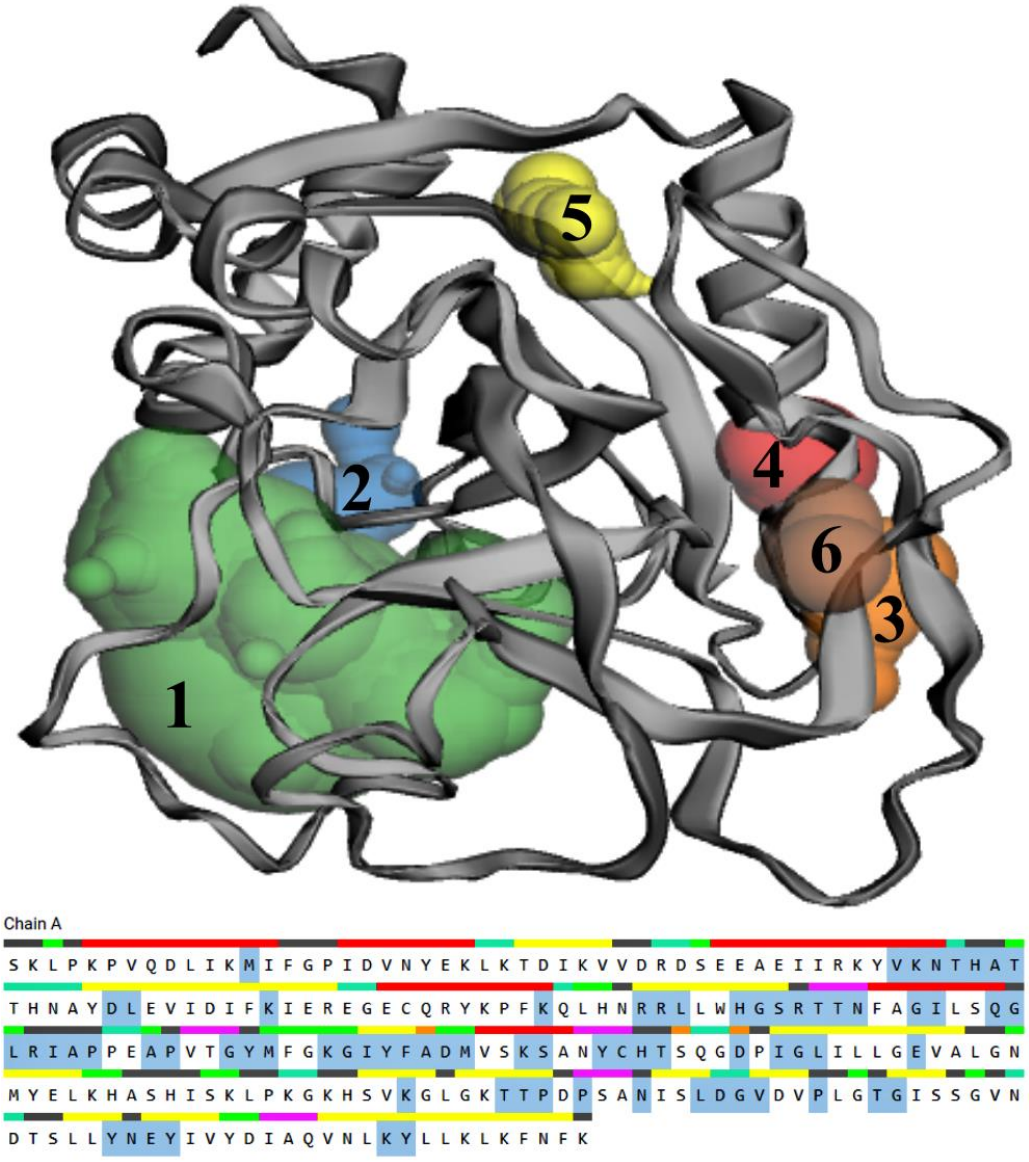


Figure 5.3. Cartoon structure of PARP1 with variable pockets highlighted with certain colures, the priority order of pockets are as green>blue>orange>red>yellow>brawn.

5.5.3. Ligand Selection by Natural Product Likeness Score (NaPLeS) analysis

NaPLeS calculator is provided a new dimension for the evaluation of the natural product likeness (NPL) of a chemical entity.[46] This tool is effective in the find of NPL of a molecular system and very helpful for designing a natural product like chemical species.[47] Here, most of the synthesized aziridine derivatives are found as a natural lead molecule (Figure 5.4).

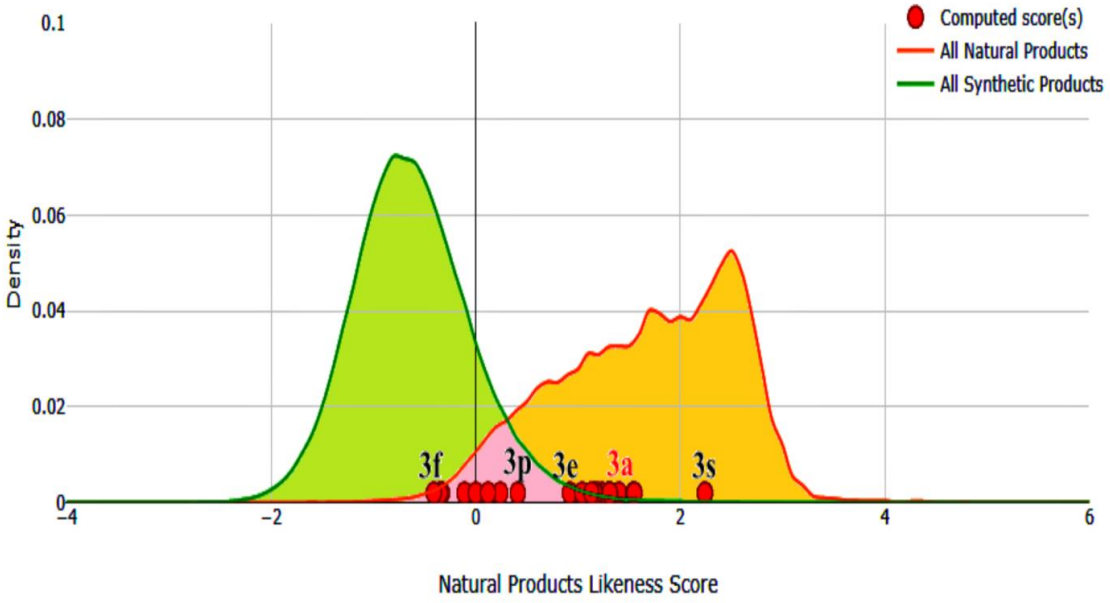


Figure 5.4. NPL scores of aziridine derivatives and reference compounds (synthetic and natural) presents in the NaPLeS database

5.5.4. Ligand preparation

2D structure of Aziridine derivatives was prepared with the help of ChemDraw Professional v15.1 and then convert into the 3D structure by using Chem3D v15.1. Mark method of the force field (MMFF94) was used to optimize the structure of ligands with the help of Avogadro v1.2.0. Biovia DSV v2017R was utilized to obtain .SMILES and .pdb files of the ligands. Furthermore, add Gasteiger charge and rotatable bonds by using AutoDock.[45] Doxorubicin HCl was selected as a standard drug and downloading from PubChem (https://pubchem.ncbi.nlm.nih.gov) (Table 5.1).

5.5.5. AutoDockVina

AutoDockVina v1.1.2 is automated software utilized for the estimation of interactions between ligands andreceptors.[48] The software offers the minimum energy complex formed due to interaction between the ligand and the receptor protein by exploring all accessible degrees of freedom (DOF) for the system.[49] Vinaprocedures the Lamarckian Genetic algorithm and empirical scoring function. It delivers reproducible docking consequences for ligands with around 10 flexible bonds.[50] Before the docking analysis

grid parameter file is also prepare and the size of grid x, y, z directions for all the receptor proteins were set to 30×30×30 Å and variable grid centers x, y, z directions were set such as -6.10, -2.10, 1. 10 Åfor 1gjh, 66.10, 79.10, 141.10Å for 4prz, 10.10, -10.10, 8.10Å for 5h31, -13.10, -1.10, 7.10 Å for 5w60, 69.10, 16.10, 89.10 Å for 6bfk, -12.10, 25.10, 47.10Å for 6bhv and 13.10, -6.10, 30.10Å for 6dcn.

5.5.6 iGEMDOCK

In the study, iGEMDOCK v2.1 was applied for the validation of virtual screening. It is an automated-graphical tool for combinational docking, screening, and post-analysis. It required the .pdb file for the docking analysis and gives results in the form of a fitness score.[51] Fitness is the total energy of a predicted confirmation in the pocket site of the receptor.[50] The empirical scoring function of iGEMDOCK is estimated as:

$$\boldsymbol{Fitness = vdW + Hbond + Elec} \qquad \mathbf{1}$$

Here, the vdW term represents van der Waal energy whereas H bond and Elect terms are hydrogen bonding and electro statistic energies, respectively. In the current analysis, the set parameters were as follows: screening: population size = 800, generations = 80, number of solutions = 10. The ligand was docked with the binding site using an accurate docking function.

5.5.7. AutoDock4 (AD4)

AD4 tool is broadly used to explore the best conformation of ligand bindings along with the target protein.[52] Here, molecular docking was performed with the help of AutoDock 4.0 and ADT v4.2.6 package, which is basically based on the Lamarckian genetic algorithm (LGA)[53,54]. AD4 tool is delivering results in the form of binding energies and disso

5.5.8. PLANTS docking

Ant colony optimization (ACO) algorithm is used to develop PLANTS (Protein-Ligand ANT System) for molecular docking analysis.[55] This algorithm is established with the

help of the general activity of ants when they are struggling to discover the shortest route between their nest (= initial site of the ligand) and food (= receptor location). Therefore, this algorithm is a type of agent-based swarm model, in which the interaction of ligand (ants) in a complex system is observed directly.[56]

5.6 LARMD (Ligand and receptor molecular dynamics) analysis

The MD simulation of the lead molecule and most favorable receptor docking complex was performed with the help of the AMBER16 program offered by ligand and receptor molecular dynamics (LARMD).[20] It is also encompassed three modules as an interactional, structural, and normal binding mode to explore the ligand-driven protein dynamics. Here, the interactional binding mode (Int_mod) was used for MD simulation with 4ns in an explicit water model. The Gibbs free energy of binding (ΔGbind) was calculated with the help of Eq.:

$$\Delta G_{bind} = \Delta E_{bind} - T\Delta S_{sol} - T\Delta S_{conf} \quad \textbf{2}$$

5.7 Results and discussion

5.7.1 Molecular Descriptors (MDs)

Oral bioavailability and drug-like characteristics of any molecular system are to be evaluated with the help of MDs. Similarly, large sets of molecules can be short out through MDs. Several rotatable bonds are directly correlated with molecular flexibility and deliver significant information on the oral bioavailability of the molecular system.[29] Molecular weight (MW) is also another important parameter for the assessment of transportability and bioavailability of a molecular system, 350 and 400 dalton (<500) range are most favorable for the development of a drug candidate. Ertl et al were developed a methodology to evaluate the topological polar surface area (TPSA) of a molecular system. It is also used to predict the adsorption of molecules in the intestine. LogP (octanol/water partition coefficient) is anticipated as a calculation of fragmentbased support and correction factor. The molar refractivity (MR) is another parameter to estimate the interaction profile among the target-receptor complex. Therefore, based on MDs certain filtering rules were also be developed like Ro5, Veber, Muegge, Egan,

Ghose filter, and Leadlikeness. These all filters were used to short and evaluated the molecular profile of ligands and their oral bioavailability. All the synthesized compounds follow filtering rules with certain limitations and show moderate to good oral bioavailability.[18] Likewise, this is serving as all the compounds **3a-u** clear first step and allow us to evaluate other properties (Table 5.3).

Table 5.3. Physiochemical parameters of the aziridine compounds **3a-u**

Comp.	SA[a]	Abs %[b]	MW[c]	nAtom[d]	nArom. Atom[e]	Csp3[f]	RB[g]	nON[h]	nOHNH[i]	MR[j]	TPSA[k]	iLOGP[l]	Lead.[m]	Lip.[n]	Muegge[o]
3a	5.64	94.45	401.67	29	0	1	5	2	2	128.73	42.17	4.64	2	1	1
3b	1.68	99.93	158.24	11	0	0.89	7	2	0	46.66	26.3	2.56	2	0	1
3c	2.27	107.96	169.31	12	0	1	6	1	0	59.69	3.01	3.31	2	0	2
3d	2.17	100.98	129.2	9	0	1	3	2	1	41.62	23.24	2.01	1	0	1
3e	4.58	104.78	243.46	16	0	1	6	2	0	78.25	12.24	3.73	2	0	0
3f	1.95	107.96	111.18	8	0	1	0	1	0	38.35	3.01	2.11	1	0	2
3g	2.17	100.98	199.33	14	0	1	9	2	1	65.66	23.24	3.22	2	0	1
3h	2.67	100.98	183.29	13	0	0.82	4	2	1	60.41	23.24	2.69	1	0	1
3i	2.97	98.89	225.33	16	0	0.77	6	3	0	70.15	29.31	3.02	1	0	0
3j	3.29	83.08	332.39	24	6	0.50	8	5	0	98.87	75.13	3.03	2	0	0
3k	3.66	98.89	225.33	16	0	0.77	8	3	0	70.11	29.31	3.52	2	0	0
3l	2.47	102.07	271.74	19	12	0.19	3	2	0	80.44	20.08	2.71	1	0	0
3m	1.79	104.78	191.27	14	6	0.5	2	2	0	61.86	12.24	2.78	1	0	1
3n	2.12	92.15	206.24	15	6	0.45	2	3	0	64.19	48.83	2.15	1	0	0
3o	2.12	92.36	311.51	22	0	0.49	16	3	1	98.87	48.24	3.01	2	1	0
3p	2.86	92.36	211.3	15	0	0.75	6	3	1	65.25	48.24	2.64	1	0	0
3q	3.55	98.89	211.3	15	0	0.75	7	3	0	65.31	29.31	3.22	1	0	0
3r	1.18	101.43	133.19	10	6	0.33	1	1	1	45.51	21.94	2.04	1	0	2
3s	1.78	101.43	183.25	14	10	0.23	1	1	1	63.13	21.94	2.49	1	0	2
3t	1.37	101.43	147.22	11	6	0.4	1	1	1	50.47	21.94	2.28	1	0	2
3u	2.37	95.54	257.71	18	12	0.13	3	2	1	75.54	39.01	2.43	0	0	0

[a]SA=Synthetic accessibility.

[d]Abs % = Percentage absorption (% absorption) was calculated by % absorption = 109–[0.345 x topological polar surface area].

[c]MW = Molecular weight.

[d]nAtom = Number of atoms.

[e]nArom.Atomd = Number of aromatic atoms.

[f]Csp3 = Fraction Csp3

[g]nRB = Rotatable bonds.

[h]nON = Hydrogen bond acceptor.

[i]nOHNH = Hydrogen bond donor.

[j]MR = Molar refractivity.

[k]TPSA = Topological polar surface area.

[l]iLogP= Logarithm of compound partition coefficient between n-octanol and water.

[m]Lead. = Leadlikeness violation.

[n]Lip. = Lipinski's violation.

[o]Mug. = Mueggeviolation.

5.7.2 ADMET properties

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) parameter play a vital role the drug discovery. Thousands of drugs were withdrawn from the market due to failure in clinical trials that is way evaluation of in silico ADMET properties before the experimental performance is more beneficial.[57] Through ADMET properties evaluate the oral bioavailability of drug candidates by calculating the certain properties, viz., blood-brain barrier (BBB) penetration, caco-2 permeability, human intestinal absorption (HIA), human oral bioavailability (HOB), carcinogenicity, eye irritation (EI), AMES mutagenesis, hepatotoxicity and acute oral toxicity (AOT).[58] Doxorubicin hydrochloride (doxorubicin) was used as a standard drug to correlate with synthesized compounds. During the initial investigation, AOT of doxorubicin was found to be highest 4.199 kg/mol while synthesized twenty-one compounds display an average of 2.464 kg/mol AOT but compounds 21, 4, and 5 showing better or more than average AOT 3.257, 3.237, and 3.21 kg/mol individual. BBB penetration is another significant parameter, it representing the absorption of the molecular system to the central nervous system (CNS).[50] Caco-2 cell permeability and HIA, both also play an important role in the transportation and absorption of drug candidates and also provide information about HOB. Here all the synthesized compounds represent good BBB penetration, Caco-2, HIA, and HOB except compound 21 do not cross Caco-2 cell; compounds 1, 6, 7, 10, 11, 12, 14, and 16 also do not show HOB but standard drug (doxorubicin) also do not cross Caco-2 cell, not absorbed in HI and not showing HOB, that is way our synthesized compounds are more significant. For the evaluation of toxicity, compounds were also subjected to predict their carcinogenicity (binary), eye irritation, AMES mutagenesis, and hepatotoxicity. All the synthesized compounds do not show carcinogenicity (binary); eye irritation except compounds 1-6, 8, 13, 14, and 17; AMES mutagenesis except compounds 9-13, 18, and 21; hepatotoxicity except compounds 11 and 20, all obtained results were compared with the standard doxorubicin and found that it is also do not showing any toxicity except AMES mutagenesis. Therefore, it is observed that

compound 21 is most appropriate for further modification and drug analysis, compounds 15 and 19 also good but display AOT with low concentration (Table 5.4).

Table 5.4. Shows the relative ADMET profiles of the synthesized molecules (as obtained from admetSAR server)

	ADMET Prediction																
Comp.	**BBB[a]**		**Caco2[b]**		**HIA[c]**		**HOB[d]**		**Carcino.[e]**		**EI[f]**		**AMES[g]**		**Hepato.[h]**		**AOT[i]**
	Val.	**Prob.**	**Val.**	**Prob.**	**Val.**	**Prob.**	**Val.**	**Prob.**	**Val.**	**Prob.**	**Val.**	**Prob.**	**Val.**	**Prob.**	**Val.**	**Prob.**	
3a	+	0.9751	-	0.5233	+	0.9608	+	0.7429	-	1.0000	-	0.9277	+	0.5600	-	0.5750	3.257
3b	+	0.9810	+	0.7704	+	0.9262	-	0.5571	-	0.6714	+	0.8111	-	0.9100	-	0.6750	2.376
3c	+	0.9936	+	0.9572	+	0.9634	+	0.6571	-	0.8143	+	0.8938	-	0.8600	-	0.8000	2.407
3d	+	0.9846	+	0.8440	+	0.9560	+	0.5857	-	0.9000	+	0.8949	-	0.8200	-	0.8000	2.194
3e	+	0.9759	+	0.8790	+	0.9498	+	0.6286	-	0.8143	+	0.5253	-	0.6883	-	0.7750	3.237
3f	+	0.9636	+	0.7603	+	0.9948	+	0.8571	-	0.9571	+	0.9616	-	0.8900	-	0.7750	3.21
3g	+	0.9316	+	0.7578	+	0.9861	-	0.6143	-	0.9571	+	0.7336	-	0.8200	-	0.8750	2.535
3h	+	0.9827	+	0.8947	+	0.9626	-	0.5143	-	0.8857	-	0.5383	-	0.7200	-	0.8250	2.383
3i	+	0.9813	+	0.7699	+	0.9594	+	0.5429	-	0.6857	+	0.5319	-	0.5400	-	0.7750	2.424
3j	+	0.9683	+	0.6625	+	0.9729	+	0.7286	-	0.7286	-	0.9197	+	0.8400	-	0.5750	2.304
3k	+	0.9850	+	0.9122	+	0.9878	-	0.6571	-	0.7000	-	0.9095	-	0.7800	-	0.8250	2.666
3l	+	0.9833	+	0.8061	+	0.9967	-	0.5143	-	0.8143	-	0.9800	-	0.8500	+	0.7000	1.811
3m	+	0.9872	+	0.8797	+	0.9966	-	0.5429	-	0.9429	-	0.6188	-	0.8400	-	0.7750	2.336
3n	+	0.9793	+	0.9522	+	0.9785	+	0.6857	-	0.8286	+	0.7159	+	0.7000	-	0.6250	2.507
3o	+	0.9851	+	0.6146	+	0.9211	-	0.5857	-	0.7000	+	0.7800	-	0.9400	-	0.6250	2.454
3p	+	0.9787	+	0.6719	+	0.9354	+	0.5857	-	0.7000	-	0.5000	-	0.6000	-	0.7000	1.849
3q	+	0.9866	+	0.9412	+	0.9878	-	0.6286	-	0.7000	-	0.7861	-	0.9100	-	0.8250	2.331
3r	+	0.9962	+	0.9585	+	0.9881	+	0.7714	-	0.7857	+	0.9119	-	0.8200	-	0.9250	2.505
3s	+	0.9969	+	0.9291	+	0.9896	+	0.5857	-	0.8571	-	0.4915	+	0.6600	-	0.6500	1.996
3t	+	0.9948	+	0.8684	+	0.9881	+	0.5429	-	0.7857	-	0.5620	-	0.8300	-	0.8500	2.091
3u	+	0.9836	+	0.7685	+	0.9916	+	0.6000	-	0.7316	-	0.8581	-	0.8400	+	0.6500	2.867
Doxo	**+**	**0.8720**	**-**	**0.8650**	**-**	**0.8447**	**-**	**0.9143**	**-**	**0.9000**	**-**	**0.9540**	**+**	**0.9900**	**+**	**0.8000**	**4.199**

[a]BBB: blood brain barrier penetration, [b]Caco-2: Caco-2 cell permeability, [c]HIA: human intestinal absorption, [d]HOB: Human oral bioavailability, [e]Carcino: Carcinogenicity (binary), [f]EI: Eye irritation, [g]AMES: AMES Mutagenesis, [h]Hepato: Hepatotoxicity, [i]AOT: Acute Oral Toxicity (kg/mol); Val: value; Prob: Probability; +: Yes; -: No.

5.7.3. Brain or intestinal estimated (boiled-egg)

To estimate the gastrointestinal (GI) absorption and blood-brain barrier (BBB) permeability, recently the BOILED-Egg model was developed. It is a simple graphical presentation and was successfully plotted by using SwissADME.[38] In the available BOILED-Egg model, the white area signifies the favorable space for absorption of the compound by the GI tract. Similarly, the yellow area (yolk) of the Model illustrates their

greater suitability to cross BBB. In this study, the model represents our candidate molecule 3a positively absorbed through the GI tract and cross BBB (Figure 5.5).

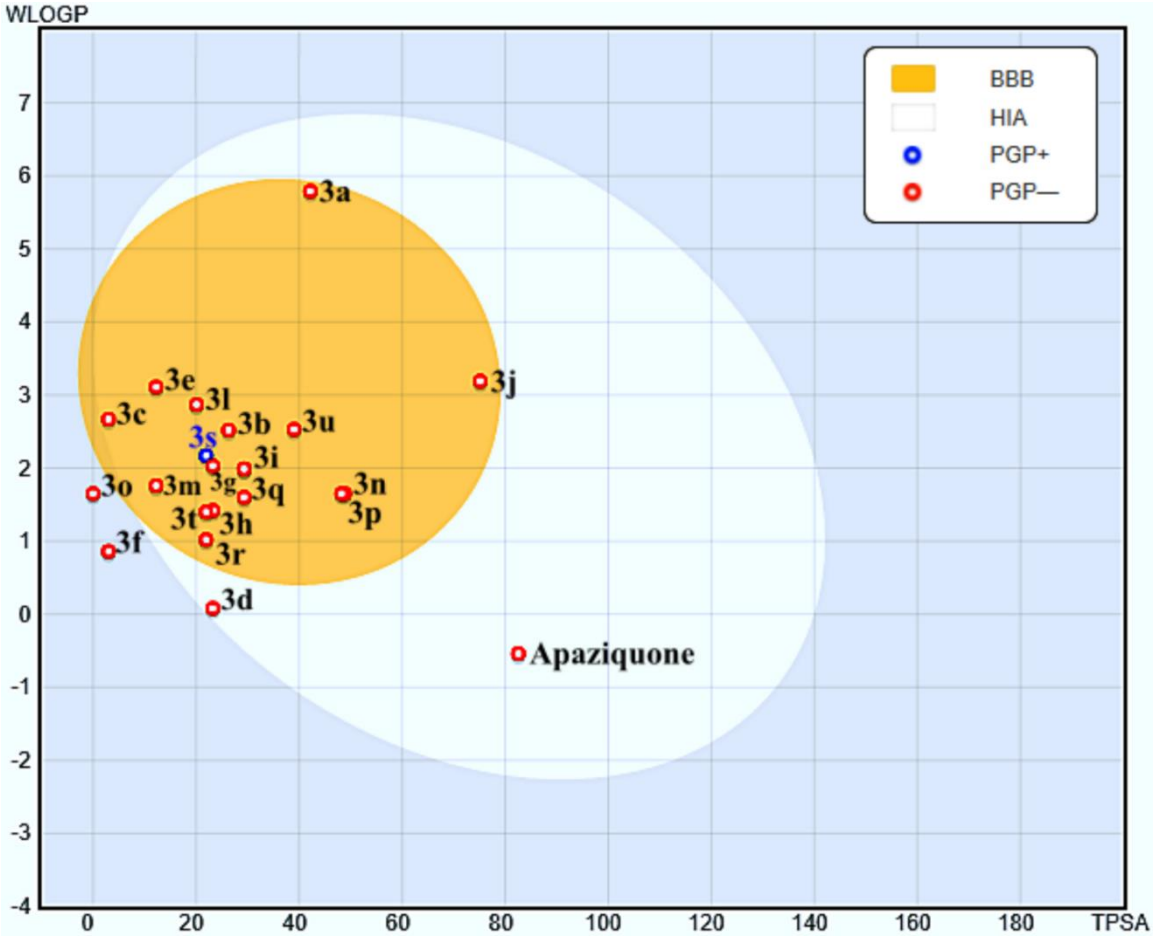


Figure 5.5. Boiled-egg's presentation of all aziridine derivatives (**3a-u**) and physiological ligands (Apaziquone)

Bioactivity score (BAS) calculation

All the synthesized compounds showing moderate BAS, but lead molecule **3a** display positive values of BAS in all the aspects expect kinase inhibitor probably.[37] The decreasing order of reactivity of **3a** is Nuclear receptor ligand>Enzyme inhibitor>Protease inhibitor>Ion channel modulator>GPCR ligand>Kinase inhibitor along with the values 0.50, 0.48, 0.21, 0.18, 0.10 and -0.31, respectively. Likewise, compound **3a** was showing a very promising biological activity spectrum (Table 5.5).

Table 5.5. Parameters of Bioactivity Score Prediction for different aziridine compounds (**3a-u**)

Comp.	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
3a	**0.10**	**0.18**	**-0.33**	**0.50**	**0.21**	**0.48**
3b	0.05	-0.03	-0.17	0.06	0.04	0.07
3c	-0.63	-0.26	-0.95	-0.72	-0.71	-0.42
3d	-1.98	-1.44	-2.25	-1.98	-1.97	-1.62
3e	0.49	0.27	-0.29	-0.27	0.66	1.41
3f	-2.96	-2.62	-3.26	-3.04	-2.94	-2.87
3g	-0.54	0.01	-0.45	-0.15	-0.36	-0.17
3h	-0.56	-0.04	-1.13	-0.17	-0.81	-0.02
3i	-0.45	-0.06	-0.95	-0.08	-0.60	-0.02
3j	-0.32	-0.17	-0.58	0.06	-0.43	-0.17
3k	-0.40	-0.22	-0.76	-0.22	-0.28	-0.21
3l	-0.47	-0.39	-0.62	-0.46	-0.51	-0.42
3m	-0.89	-0.58	-0.99	-0.91	-1.01	-0.72
3n	-0.96	-0.48	-1.03	-0.92	-1.04	-0.73
3o	-0.05	-0.08	-0.23	0.03	0.14	0.15
3p	-0.63	-0.13	-1.12	-0.25	-0.71	0.07
3q	-0.41	-0.24	-0.82	-0.28	-0.32	-0.21
3r	-1.17	-0.44	-1.20	-1.18	-1.11	-0.46
3s	-0.79	-0.28	-0.73	-0.60	-0.72	-0.33
3t	-1.35	-0.78	-1.46	-1.51	-1.35	-0.80
3u	-0.57	-0.40	-0.67	-0.58	-0.55	-0.30

5.7.4 Virtual screening (VS)

VS analysis of synthesized aziridine derivatives (**3a-u**) were performed against the human apoptosis pathway factors (caspase 3, caspase 8, Bcl-xl, Bcl-2, BAX, and BAD proteins) using AutoDockVina and iGEMDOCK, to find and identify the most suitable binding mode, intermolecular interactions, favorable confirmation of synthesized compounds with the receptor proteins.[56] From our VS, it was clear that all the synthesized compounds (**3a-u**) display good interaction. But along with the apoptosis pathway factors mainly poly [ADP-ribose] polymerase 1 (PARP1) with minimum binding energies. Out

of all twenty-one compounds, compound **3a** is dispatched the minimum binding energy -9.1 kcal/mol, concerning Vina as well as -95.54 kcal/mol concerning iGEMDOCK, showing in Table 5.6. Obtained docking results also correlate with the standard drug (Doxorubicin HCl), it also favorably interacts with the apoptosis pathway factors and showing minimum binding energy against PARP1. Therefore, it is clear that compound **3a** displays their anticancer activity due to their inhibitory action against PARP1 along with the standard drug. The binding energies of all the synthesized compounds (**3a-u**) and standard drug found very vast differences but compound **3a** displays near about the same binding interaction. All the compounds showing closer contact (< 5.0 Å) within the deep active site of the receptor protein. (Table 5.6).

Table 5.6. Binding energies of synthesized compounds withapoptosis pathway factors (PDB IDs: 1gjh, 4prz, 5h31, 5w60, 5bfk, 6bhv and 6dcn)obtained by using AutoDockVina and iGEMDOCK

Comp.	AutoDockVina (kcal/mol)							iGEMDOCK (kcal/mol)						
	1gjh	**4prz**	**5h31**	**5w60**	**5bfk**	**6bhv**	**6dcn**	**1gjh**	**4prz**	**5h31**	**5w60**	**5bfk**	**6bhv**	**6dcn**
3a	-6.1	-7.7	-8.0	-6.4	-5.8	-9.1	-7.4	-79.77	-65.24	-80.67	-71.32	-84.41	-95.54	-83.42
3b	-4.3	-5.0	-5.3	-4.2	-4.3	-6.1	-4.9	-74.41	-63.49	-85.28	-67.68	-76.14	-82.82	-76.33
3c	-4.1	-4.0	-5.1	-4.2	-3.9	-5.3	-4.8	-58.66	-53.33	-60.86	-54.30	-54.34	-59.95	-54.81
3d	-3.9	-4.1	-4.3	-4.0	-3.6	-4.5	-4.2	-52.92	-47.83	-50.64	-53.45	-50.31	-64.21	-46.03
3e	-4.1	-4.8	-5.0	-4.8	-4.4	-5.5	-5.0	-59.91	-51.64	-54.94	-62.76	-57.39	-62.07	-56.75
3f	-4.0	-3.5	-4.3	-4.0	-3.4	-4.6	-4.0	-46.34	-43.92	-44.48	-42.81	-42.15	-53.83	-38.67
3g	-4.3	-4.1	-4.9	-3.9	-3.7	-5.1	-4.5	-60.67	-62.33	-69.80	-60.84	-56.20	-66.49	-64.19
3h	-5.0	-4.8	-5.7	-4.4	-4.2	-6.1	-5.2	-62.94	-56.60	-71.72	-57.45	-54.96	-69.37	-58.55
3i	-5.6	-5.5	-5.8	-4.8	-4.5	-6.6	-5.3	-63.10	-70.48	-60.85	-60.85	-57.23	-69.25	-66.71
3j	-5.7	-6.8	-6.6	-5.5	-5.0	-8.3	-6.6	-83.64	-74.62	-82.23	-74.77	-79.61	-87.37	-78.73
3k	-4.7	-4.8	-5.5	-4.7	-4.2	-6.1	-5.0	-69.30	-64.20	-70.09	-65.39	-66.85	-68.05	-71.39
3l	-6.1	-6.0	-6.4	-5.3	-5.5	-7.7	-6.9	-67.99	-61.94	-77.88	-65.63	-72.33	80.97	-65.26
3m	-5.5	-4.9	-6.4	-4.4	-4.2	-6.4	-5.2	-67.00	-50.32	-70.02	-59.27	-64.41	-72.97	-64.83
3n	-5.6	-6.2	-6.2	-4.7	-4.5	-7.2	-5.6	-79.06	-64.89	-71.24	-70.68	-68.03	-80.57	-70.66
3o	-4.8	-5.0	-5.3	-4.3	-3.9	-6.5	-5.4	-86.98	-70.86	-71.91	-70.23	-74.17	-85.71	-68.55
3p	-5.9	-5.3	-6.1	-4.5	-4.2	-6.2	-5.0	-71.49	-67.50	-59.77	-62.33	-65.28	-67.60	-64.73
3q	-4.8	-4.8	-5.3	-4.5	-4.0	-5.8	-4.9	-67.46	-61.86	-69.33	-60.98	-61.12	-64.43	-68.66
3r	-4.8	-4.3	-5.5	-5.2	-4.1	-6.6	-4.7	-53.67	-44.77	-60.34	-55.49	-54.93	-68.69	-47.79

3s	-6.2	-5.6	-7.1	-5.8	-4.9	-8.2	-6.4	-64.60	-55.14	-73.53	-63.73	-62.59	-86.54	-60.91
3t	-4.9	-4.7	-5.7	-4.7	-4.1	-6.5	-4.9	-52.79	-46.86	-59.48	-55.94	-52.11	-64.21	-49.68
3u	-5.7	-6.0	-6.7	-5.5	-5.4	-7.5	-6.7	-71.45	-63.28	-78.35	-73.96	-72.41	-81.74	-64.56

5.7.5 Multi-grids Docking (MGD)

From VS it very clears, anticancer potential of all the aziridine derivatives (**3a-u**) were due to interaction with the PARP1 target protein. With keeping this in mind here MGD also performed to find out the most prominent grid, where aziridine derivatives (**3a-u**) displayed their highest binding potentials or interactions along with the PARP1 target (Table 5.1). In this study, MGD was performed through the world wildly used docking tool AD4. This tool provides multiple routes and setting for docking. To perform MGD all the default parameters were set along with the population size 200, the maximum number of evals 25000000, and generations 270000. Various grids were set with different sizes and coordination to cover all the amino acid residues found in the active pocket.[59] The obtained result is delivered Grid VII is most prominent for the binding interaction and dissociation constant (Kd) analysis. Compound 3a potentially -7.32 kcal/mol interacts with the amino acid residues of PARP1 in Grid VII as compared to other Grids. The physiological ligand also interacts with the same amino acid residues cover by Grid VII (Table 5.7).

Table 5.7. Multiple grids of PARP1, which are selected for further binding interaction analysis along with the aziridine derivative **3a** performed with the help of AD4

	Grid size (Å)			**Grid coordinate (Å)**			**BE**	**Kd (µM)**
	x	**y**	**z**	**x**	**y**	**z**		
Grid I	30	30	30	-12.1	25.1	47.1	-5.97	42.41
Grid II	40	40	40	-11.5	32.5	40.0	-6.72	11.91
Grid III	20	20	20	-22.7	23.0	40.5	-6.22	27.71
Grid IV	26	26	26	-20.0	24.2	40.5	-6.06	36.31
Grid V	18	18	18	-9.7	25.6	28.1	-4.83	286.35
Grid VI	20	20	20	-14.4	35.8	24.2	-4.16	896.39
Grid VII	**24**	**24**	**24**	**-22.4**	**29.0**	**39.7**	**-7.14**	**5.88**

5.7.6 Integral Docking

All the aziridine derivatives (**3a-u**) were also subjected for integral docking study against PARP1 target protein based on data obtained from VS and MGD. Here, AD4, Vina, iGEMDOCK, and PLANTS docking tools were selected to precede docking investigation. Today, many approaches are offered to evaluate the ligand-receptor interaction. For that reason, the reliability and accuracy of docking methods become more critical and challenging. Therefore, in this study integral score (I-Score) was also intended to relate the binding free energies attained by some revealed docking tools. This score is based on the Z-Score,[60] which is very prominent to increase the accuracy in the binging free energy calculation.[61,62]

I-Score was calculated by Eq.:

$$\boldsymbol{I - Score = \frac{(Docking\ Scores) - \mu}{\sigma}} \qquad \mathbf{3}$$

Where, μ = mean and σ = standard deviation

$$\boldsymbol{Docking\ Scores = \frac{PLANTS\ Score + iGEMDOCK\ Score}{10} + (AD4\ Score + Vina\ Score)} \qquad \mathbf{4}$$

The most prominent active pocket, accurate docking parameters as well as grid-VII were selected to perform integral docking analyses.[63] All the synthesized compounds deliver moderate binding potential out of which compound 3a displays the highest binging potential against the PARP1 target protein. I-Score also preferred compound **3a** as a potential inhibitor. Integral docking score and their respective binding energies are represented in the Table. In this study, validation of the docking protocol and algorithm are also performed by re-docking. A root mean square deviation (RMSD) between the docked and innate co-crystal sites is less than 2 Å. This serves that the docking protocols and constraints used here could favorably calculate the innate conformations of the molecule.

I-Score of compound **3a** of integral docking analysis is -14.62kcal/mol and dissociation constant (Kd) value is 4.98 μM. While other compounds showing I-Score between -6.23 to -11.98kcal/mol as well as the value of Kd is 45,850.00 to 49.42 μM. Here, obtained results were also associated with the standard drug and spuriously observed that

compound **3a** delivers batter potentials. Consequently, compound **3a** is showing a potential interaction profile with the PARP1 target protein to show their anti-cancer potential. Evaluation of docking poses represents compound **3a** potentially interact along with the 21 amino acid residues (ARG878, TRP861, GLY863, SER864, ASN868, GLN875, GLY876, LEU877, ILE879, ALA880, PRO881, PHE897, LYS903, SER904, HIS862, ILE872, ALA880, TYR889, ILE895, TYR896, and TYR907). Out of which ARG878 amino acid is potentially involved in hydrogen bonding (Table 5.8 and Figure 5.6-5.7). In the presence of the Aziridine motif, the probability of hydrogen bonding interactions increase, H bonding is directly involved in the biological activity of any motif. Therefore, the modification of the Aziridine motif is in favor of the enhancement of biological activity (Table 5.8 and Figure 5.6-5.7).

Table 5.8. Integral docking analysis along with the I-Score and Kd

Ligands	AD4	VINA	PLANTS	IGEMDOCK	I-Score	K_d (µM)
3a	-7.23	-9.5	-103.29	-102.92	-14.62	4.98
3b	-1.83	-6.0	-85.24	-99.61	-9.36	45,850.00
3c	-3.47	-4.7	-73.89	-69.16	-7.52	2,850.00
3d	-2.62	-4.3	-64.11	-64.27	-6.23	12,070.00
3e	-3.09	-4.7	-76.49	-69.60	-7.49	5,470.00
3f	-3.07	-5.2	-58.54	-53.80	-6.11	5,580.00
3g	-1.92	-5.9	-86.09	-76.88	-8.31	39,120.00
3h	-3.83	-6.4	-79.22	-77.16	-9.14	1,560.00
3i	-3.57	-7.7	-81.10	-79.76	-9.85	2,410.00
3j	-5.87	-5.9	-94.98	-99.14	-11.68	49.42
3k	-3.52	-7.4	-85.05	-81.06	-9.94	2,630.00
3l	-5.77	-6.4	-85.72	-93.30	-11.15	59.01
3m	-4.22	-7.2	-78.97	-75.31	-9.61	801.14
3n	-4.47	-6.5	-81.11	-86.82	-10.05	531.39
3o	-4.76	-6.0	-98.97	-96.37	-11.25	324.85
3p	-3.10	-5.4	-88.56	-75.68	-8.69	5,340.00
3q	-3.87	-6.6	-82.30	-76.68	-9.38	1,460.00
3r	-4.07	-8.2	-69.42	-72.85	-9.44	1,160.00
3s	-5.60	-6.1	-88.05	-88.66	-10.81	78.40
3t	-4.17	-7.2	-68.97	-64.13	-8.58	872.52

3u	-5.18	-9.5	-78.54	-92.92	-11.98	160.55

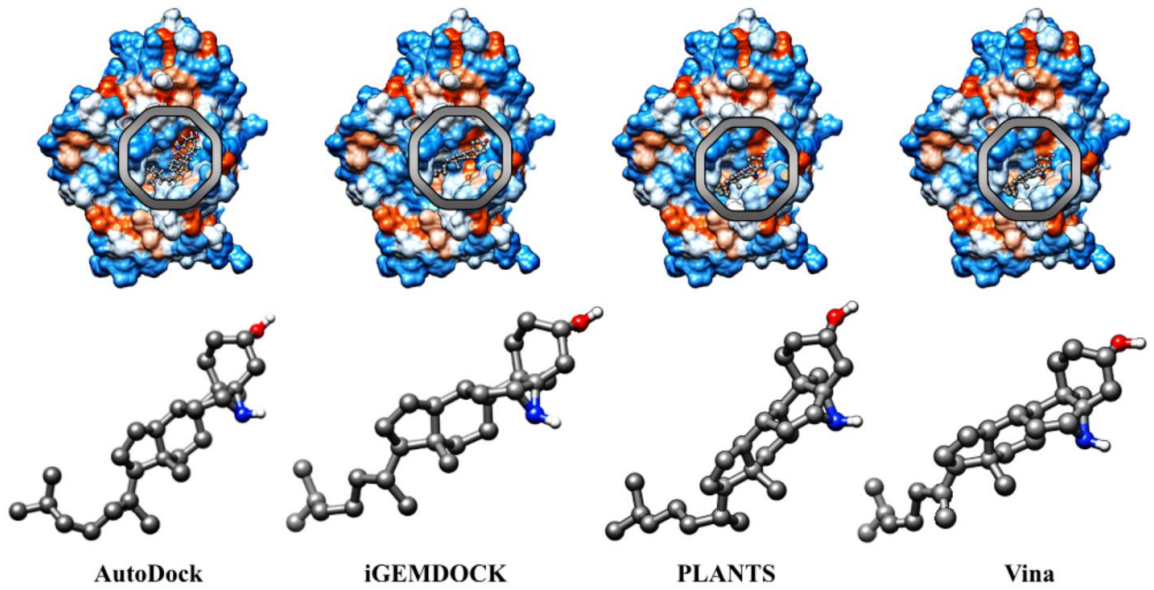


Figure 5.6. (PyMol image) showing the 3D interaction profile of standard drug (I, Doxorubicin HCl) and synthesized compound 21 (II) with the target protein (PDB ID: 6bhv), yellow dash lines indicate display H-bond interactions.

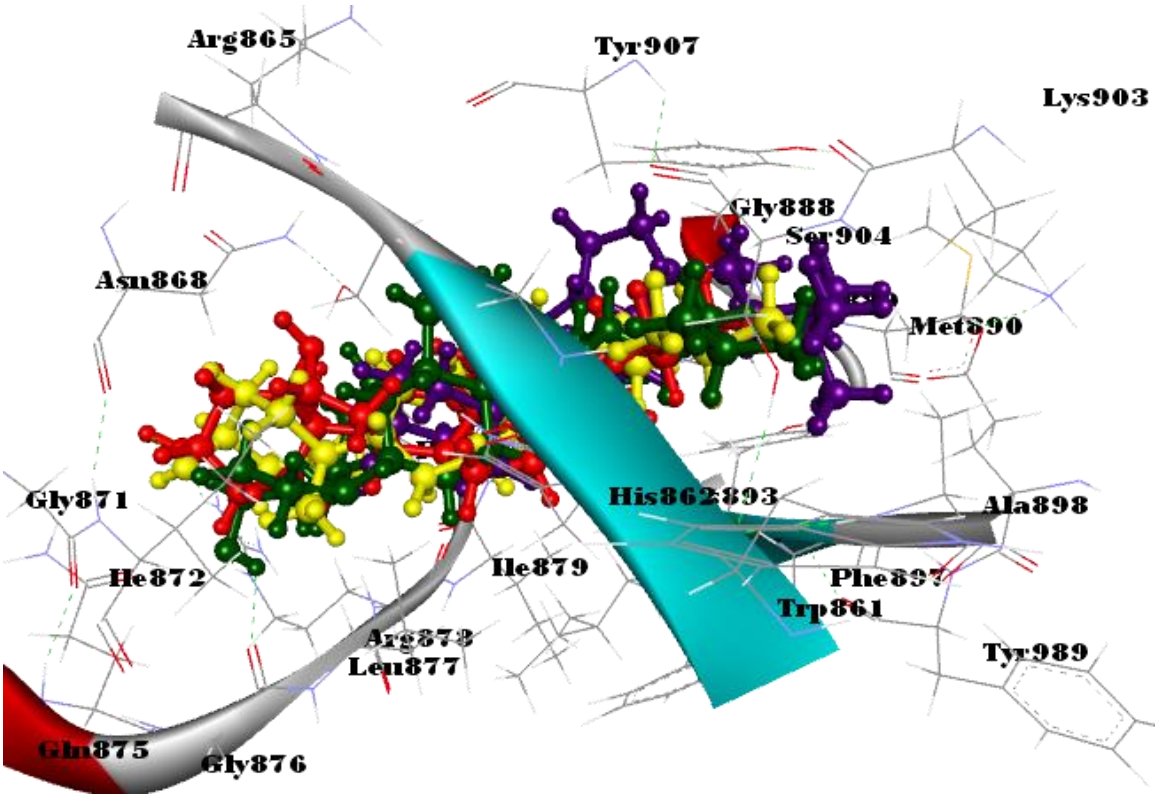


Figure 5.7. (DSV image) showing the 3D interaction profile of compound 3alead confirmation generated through AutoDock (Red), iGEMDOCK (Green), PLANTS (Yellow) and Vina (Violate) along with the target poly [ADP-ribose] polymerase 1 (PDB ID: 6bhv)

5.7.7. Molecular dynamics (MD) simulation of docking complexes

Thermodynamics behaviors analyses including structural, conformation, and fluctuation deviations along with other diverse properties of bioactive molecules were furnished with the help of MD simulation. The most favorable interaction mode of the lead docking molecule (**3a**) along with their best appropriate receptor molecule (PARP1) were additionally evaluated through MD simulation analysis with simulation time 1000ps and an aqueous system. Here, certain geometrical parameters of the docking complex like a fraction of native contacts (Qx), the radius of gyration (Rg), and root mean square deviation (RMSD) were considered to inspect the stability of the complex. Int_mod, Str_mod, and Nor_mod were used to perform MD simulation display in Figures. Atomic positions are measured through the RMSD, which is also delivered the average distance among the atoms of ligand and receptor over some time.[64] The usual RMSD of the ligand and the receptor in the docking complex was observed to be 1.4173 ±0.0826 Å and 1.4378 ±0.0844 Å, respectively. Obtained RMSD values specify that the difference in the RMSD values was very low, which is characterized by stability of the docking complexes (Figure 5.7). The Rg of a frame is associated with the space of a time mainly related to molecular rotation, which mostly evaluates the reactivity and folding of the target molecule. The value of Rg is generally affected by any change in the folding condition of the target molecule.[65] The Rg values for docking complexes display stable fluctuations among 17.3020 to 17.3633 Å, respectively (Figure 5.7). The movement of folding is directly associated with some non-innate interactions conditions, There are variable folding (simulations) models are offered which deliver only innate interactions. The Qx value is a sign of the conformational dynamics and the transition states of a target molecule with a folding free energy barrier.[66] The Q value for ligand was observed to be 0.977526±0.999999, respectively, which is demonstrating the better stability of complexes of 3a during the simulation process (Figure 5.7). The temperature factors such

as RMSF and B-factor state that the flagging of x-ray scattering is a significant attribute to thermal motion. Therefore, the RMSF value confirmed the atomic distinction of amino acids. The value RMSF and B-factor of docking complex, amino acid residues observed among 3 to 17 Å and 100-7000 (Figure 5.7). Principal component (PC) analysis is measured as a strong process for clustering the conformations of a target receptor and sorting out the large rigorous modes of oscillations from paths of MD simulations.[59] The contribution of PC1, PC2, and PC3 to the total mean square oscillations was observed to be 23.36%, 10.56%, and 7.14%, respectively. In the figure blue color signifies the associated residues while the red color is offered in non-associated residues. Likewise, the light pink and blue color lines, denote prominent correlated coefficient (>0.8) and prominent non-correlated coefficient (< -0.4) (Figure 5.8-5.10). Furthermore, molecular mechanics Poisson–Boltzmann surface (MM-PBSA) and molecular mechanics generalized Born surface area (MM-GBSA) analysis were also implemented to assess the interaction profile of the docking complexes. The binding free energies of lead docking complex is ΔPB = -9.04 kcal/mol and ΔGB = -15.56 kcal/mol) (Table 5.9 and Figure 5.8-5.11).

Table 5.9. Binding free energy calculation of lead docking complexes (kcal/mol)

ELE	VDW	GAS	PBSOL	PBTOT	GBSOL	GBTOT	TS	ΔPB	ΔGB
36.89	-42.45	-5.56	-15.27	-20.83	-21.79	-27.35	11.79	-9.04	-15.56

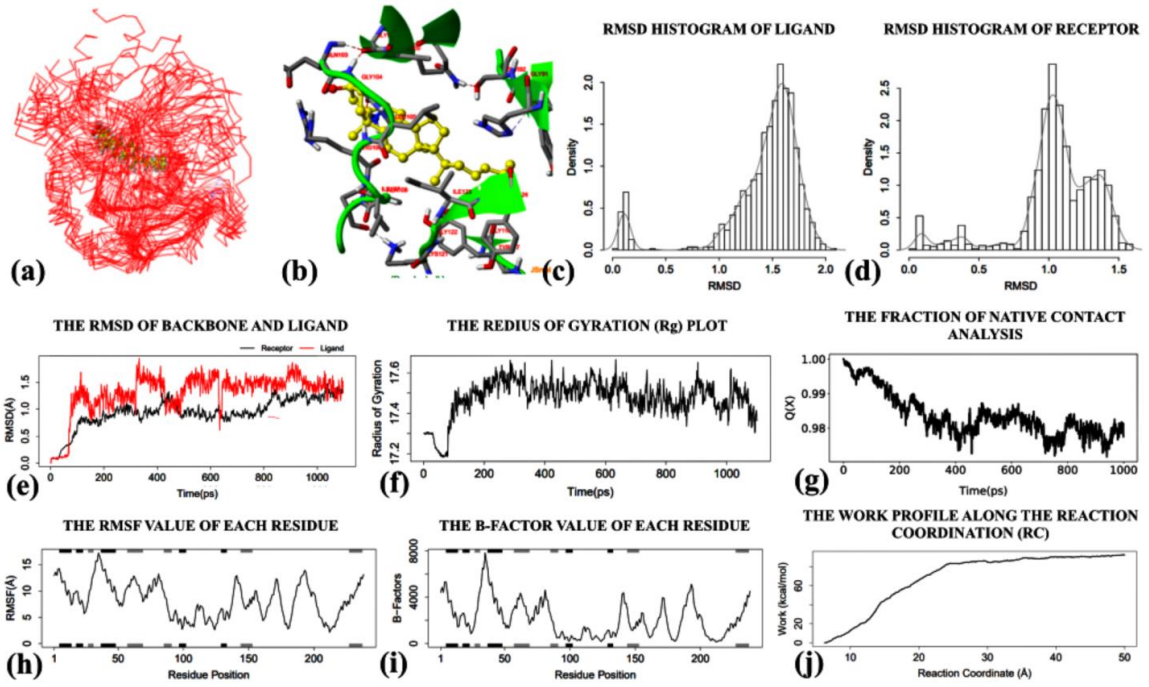


Figure 5.8. MD Simulation of lead aziridine compound **3a** with PARP1. (a) Ligand-receptor conformation, (b) B-factor value (changing from blue to red with increase in value),(c) RMSD histogram of ligand (3a), (d) RMSD histogram of receptor (PARP1), (e) RMSD of receptor and ligand (3a), (f) Radius of gyration value, (g) Fraction of native contacts analysis of PARP1with 3a over a time frame of 1000ps. (h) RMSF value of each residue (Int_mod), (i) B-factor analysis of defined complex and (j) The work profile along with the reaction coordination.

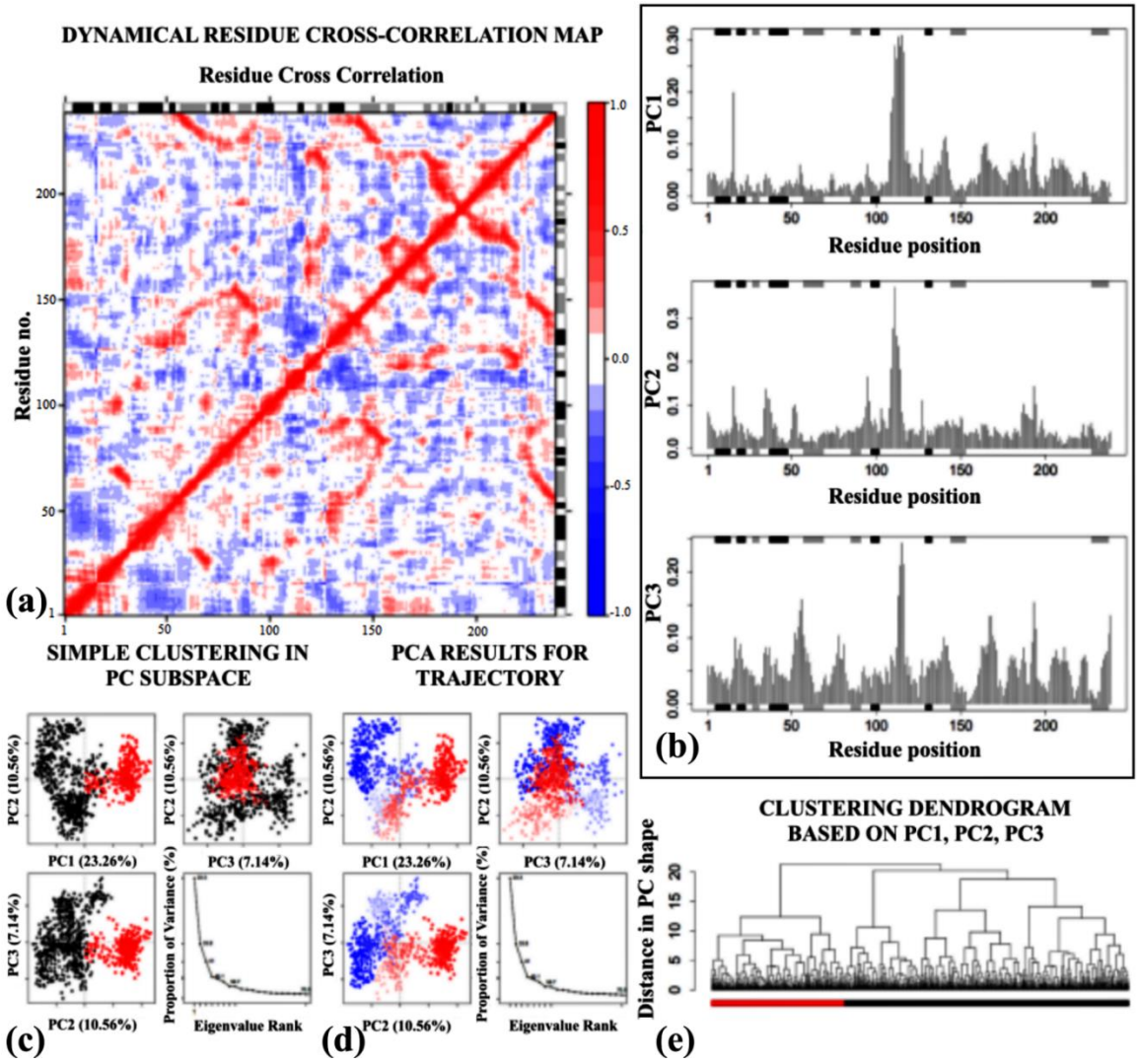


Figure 5.9. PCA of docking complex of lead aziridine compound 3a with PARP1. (a) Dynamical residue cross-correlation Map (The correlated residues denoted by blue color, anti-correlated residues denoted by red color; the pairwise residues with higher correlated coefficient (>0.8) and with higher anti-correlated coefficient (< -0.4) are linked with light pink and light blue), (b) Residue-wise loadings for PC1, PC2 and PC3, (c) Simple clustering in PC subspace,(d) PCA results for trajectory and (e) Clustering dendrogram based on PC1, PC2 and PC3

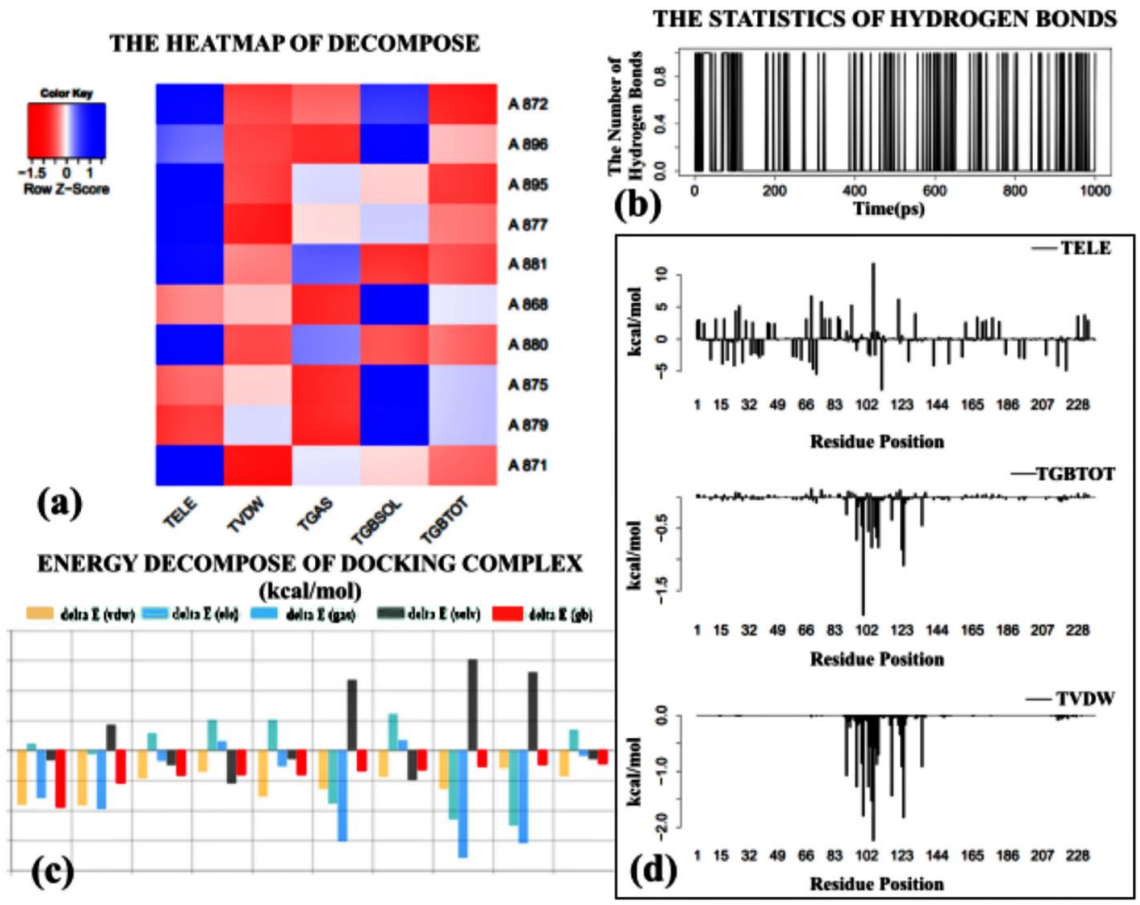


Figure 5.10. Energy, hydrogen bond analysis and decomposition analysis of docking complex lead aziridine compound **3a** with PARP1. (a) Heatmap of decompose, (b) Statistics of hydrogen bonds, (c) Energy decompose of protein-ligand complex (kcal/mol), (d) Graphical representation of decompose result

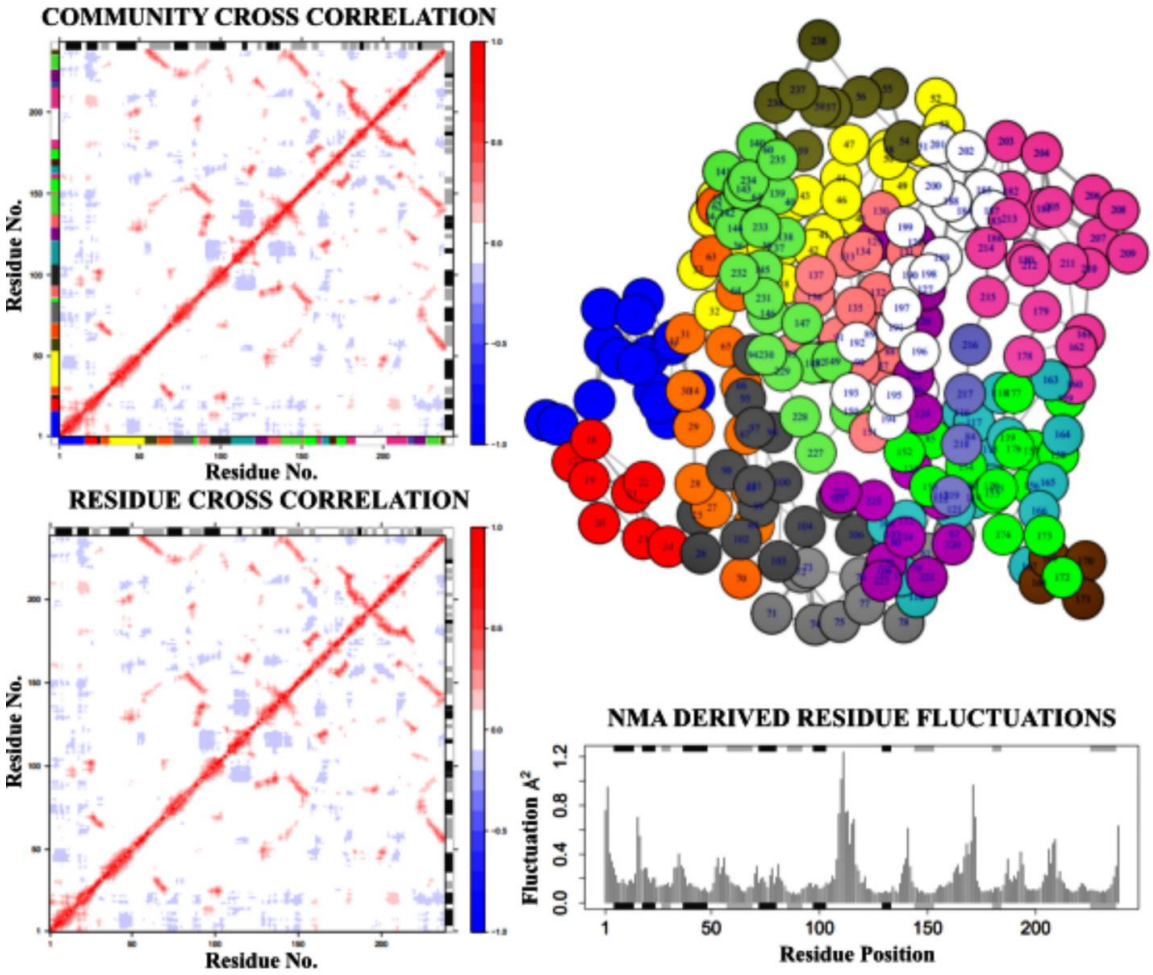


Figure 5.11. Cross correlation analysis of docking complex lead aziridine compound **3a** with PARP1 along with the NMA derived residue fluctuation

5.8 Conclusion

With the help of a combined approach of evaluating molecular descriptors, docking-based virtual screening, molecular docking, and molecular dynamics simulation, this study obtained structural signatures into conceivable binding modes of drug-like aziridine derivatives against PARP1. Compound 3a was observed to be the lead docking molecule against all the selected apoptotic pathway targets. In our analysis, their promising activity was recorded against PARP1. Therefore, compound 3a may be established into a potential multi-target molecule that can prevent the activity of PARP1 in cancer cells.

5.9 References

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List of Publications

1. **Direct *N*-H/*N*-Me Aziridination of Unactivated Olefins Using O-(Sulfonyl)hydroxylamines as Aminating Agents.**
   Shekh Sabir, Chandra Bhan Pandey, **Ajay K. Yadav**, Bhoopendra Tiwari, Jawahar L. Jat *J. Org. Chem.* **2018**, *83*, 12255-12260. DOI:10.1021/acs.joc.8b01673.
2. **Direct Synthesis of Secondary Amides from Ketones through Beckmann Rearrangement using *O*-(mesitylsulfonyl)hydroxylamine.**
   Dinesh Chandra, Saumya Verma, Chandra Bhan Pandey, **Ajay K. Yadav**, Puneet Kumar, Bhoopendra Tiwari, Jawahar L. Jat *Tetrahedron Lett.* **2020**, *61*, 151822. DOI: 10.1016/j.tetlet.2020.151822.
3. **Zinc(II)-Catalyzed Synthesis of Secondary Amides from Ketones *via* Beckmann Rearrangement Using Hydroxylamine-*O*-sulfonic Acid in Aqueous Media.**
   Saumya Verma, Puneet Kumar, Anil K. Khatana, Dinesh Chandra, **Ajay K. Yadav**, Bhoopendra Tiwari, Jawahar L. Jat *Synthesis* **2020**, *52*, 3272-3276. DOI: 10.1055/s-0040-1707809.
4. **Fe(II)-Catalyzed Synthesis of Unactivated Aziridines (*N*-H/*N*-Me) from Olefins Using *O*-Arylsulfonyl Hydroxylamines.**
   Dinesh Chandra, **Ajay K. Yadav**, Vikram Singh, Bhoopendra Tiwari, Jawahar L. Jat *ChemistrySelect* **2021**, *6*, 10524-10526. DOI: 10.1002/slct.202102884.
5. **Direct *N*-Me Aziridination of Enones**.
   Jawahar L. Jat, **Ajay K. Yadav**, Chandra Bhan Pandey, Dinesh Chandra, Bhoopendra Tiwari **2021,** *J. Org. Chem.* (Manuscript under revision).
6. **Evaluation of Anticancer Activity of *N*-H/*N*-Me Aziridine Derivatives as a Potential Poly (ADP-Ribose) Polymerase 1 Inhibitor**
   Iqbal Azad, Jawahar L. Jat, **Ajay K. Yadav**, Sudipta Saha, Yusuf Akhter **2021**, *J. Mol. Struct.* (Manuscript under review).
7. **A Synthetic Overview of Enones Aziridination**
   Dinesh Chandra, **Ajay K. Yadav**, Ganesh Kumar, Jawahar L. Jat (Manuscript under preparation).

List of Conferences, Seminars, Webinars and Workshop

A. International conferences

1. ***Oral Presentation*:** Global Conference on the Control of Green House Gases at the Source by Physical and Chemical Technology (GCCGHGSPCT2k19), organized by Department of Chemistry, Babasaheb Bhimrao Ambedkar University (A Central University) Lucknow, Uttar Pradesh (India), 22-24 April 2019.
2. ***Poster Presentation***: 25th ISCB International Conference (ISCBC-2019) Trends in Chemical and Biological Sciences: Impact on Health and Environment, Organized by Indian Society of Chemists & Biologists (ISCB), Hotel Golden Tulip, Lucknow, Uttar Pradesh (India), 12-14 January 2019.
3. ***Oral Presentation:*** Virtual International Conference on Chemical Sciences in Sustainable Technology and Development (IC^2S^2TD-2020), organized by Applied Chemistry Department, S. V. National Institute of Technology, Surat, Gujarat, India, In Association with Department of Chemistry, Chung-Ang University, Seoul, South Korea, (1-3 December 2020).
4. ***Oral Presentation:*** 57^{th} Annual Convention of Chemists, International Conference on Recent Trends in Chemical Sciences (RTCS-2020), Organized by Indian Chemical Society, Kolkata, West Bengal, (26-29 December, 2020).
5. Participated in Virtual International Conference on "Multifunctional Advanced Materials (VICMAM-2021)", Organized by Department of Chemistry, Jnan Vikas Mandal's Degree College in Collaboration with Association of Chemistry Teachers (ACT), Plot No.9, Sector-19, Airoli, Navi Mumbai, Maharastra-400708, India on (9-10 August 2021).

B. National conferences

1. ***Poster Presentation:*** National Conference "Dr Ambedkar: Interdisciplinary Ideology on Aspirations for Nation's Better Future", Organized by Babasaheb Bhimrao Ambedkar University (A Central University) Lucknow, Uttar Pradesh (India), 14 April 2018.
2. ***Oral Presentation:*** National Seminar on Application of elements of Periodic table in Natural Sciences, organized by Department of Chemistry and Department of

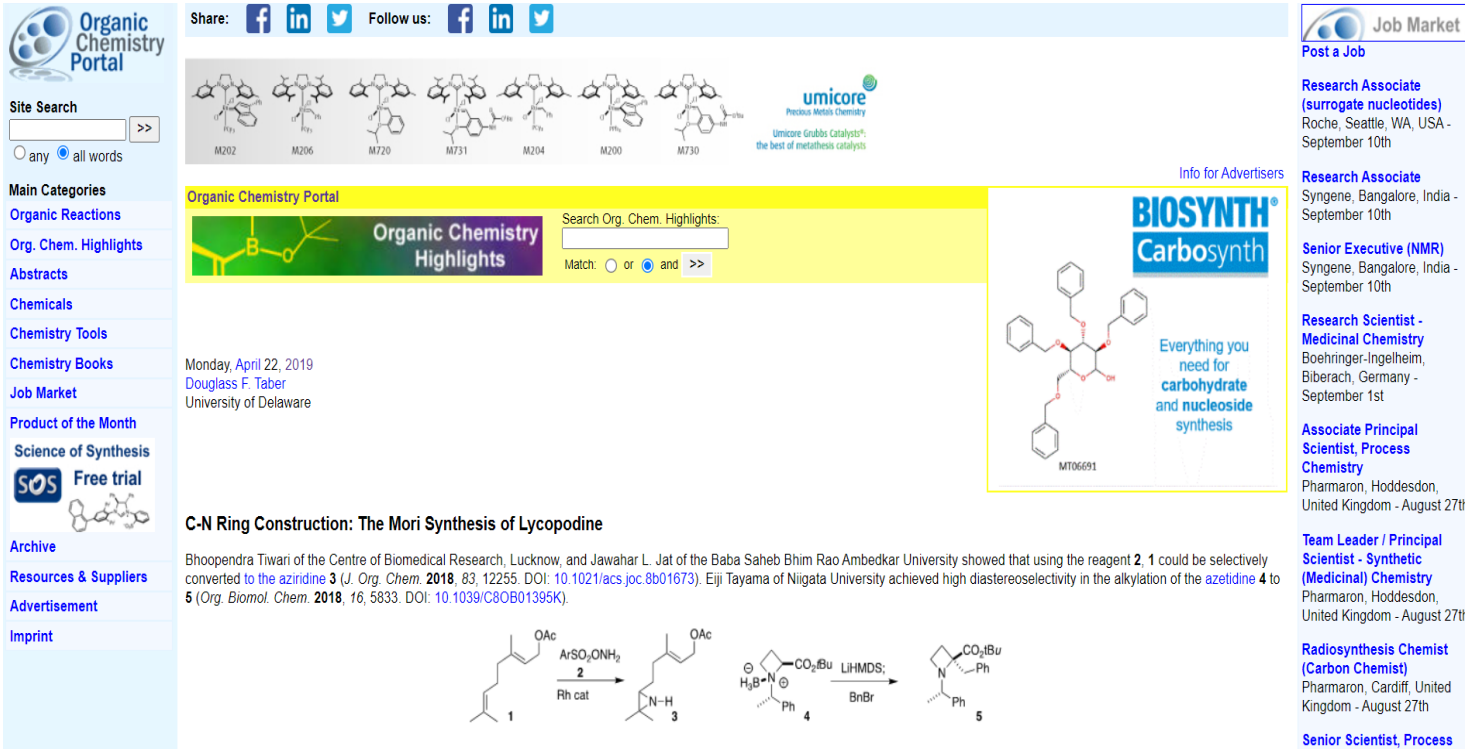
Physics, Christ Church College Kanpur, Uttar Pradesh, India, (14-15 November 2019).

3. ***Oral Presentation:*** National Conference on, "Trends and Innovation in Chemistry" (NCTIC-2019), Sponsored by Science and Engineering Research Board (Govt. of India), RNT P.G. College, Kapasan, District Chittorgarh, Rajasthan, India, (6-7 December 2019).

C. Workshop

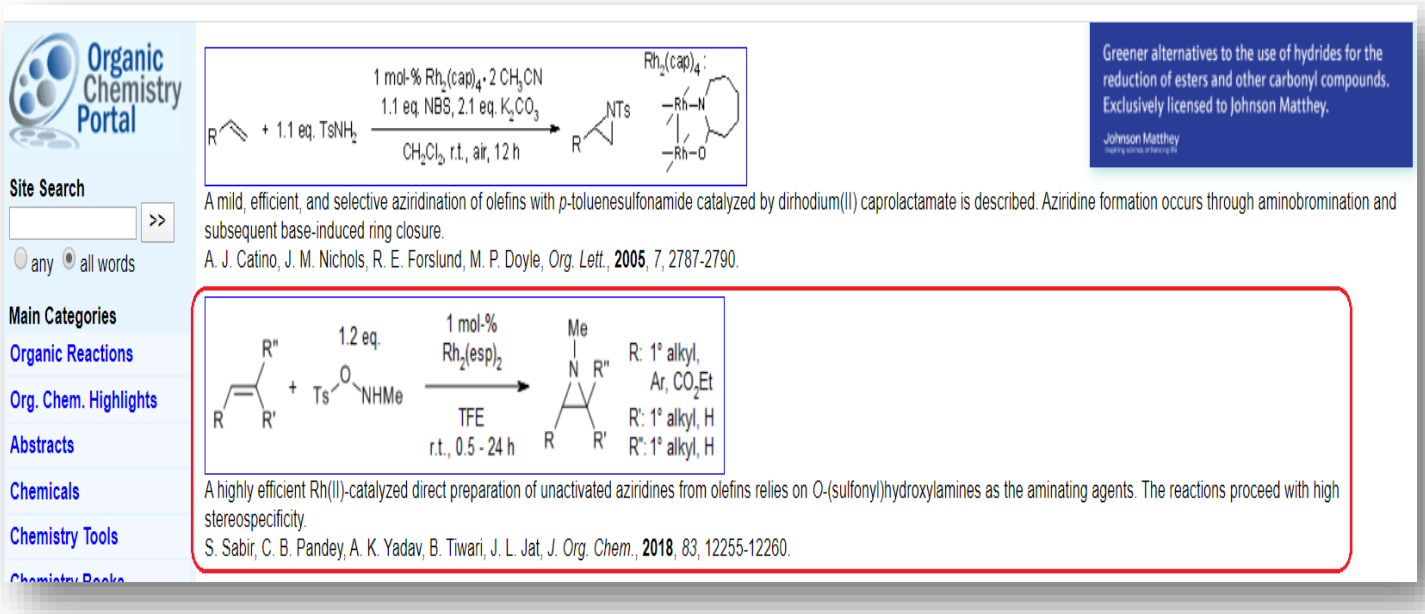
1. Participated in one week workshop on "Important Techniques for Characterization of Molecules" held at Faculty of Chemical Sciences, Institute of National Sciences and Humanities, Shri Ramswaroop Memorial University, Lucknow from 25th March 2019.
2. Participated in online workshop on "Writing Literature Review Article: Weekened" Presented by Mr. Daniel C., Director, Manuscriptpedia and organized by Manuscriptpedia Kanyakumari, India through online Pedagogy, (27 May 2020).
3. Attended One Week Online Short Term Training Programme (STTP) on Micro-& Macro-Chemistry Meets Technological Developments (M^2CMTD–2021) under Center for Continuing Education (CCE), Organized by Department of Chemistry, Sardar Vallabhbhai National Institute of Technology, Surat, (5-9 July **2021**).

Highlights of Our Work



https://www.organic-chemistry.org/Highlights/2019/22April.shtm

Our work has been highlighted in abstract section of Organic Chemistry Portal



https://www.organic-chemistry.org/abstracts/lit6/530.shtm

Published Research Papers

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Direct *N*-H/*N*-Me Aziridination of Unactivated Olefins Using *O*-(Sulfonyl)hydroxylamines as Aminating Agents

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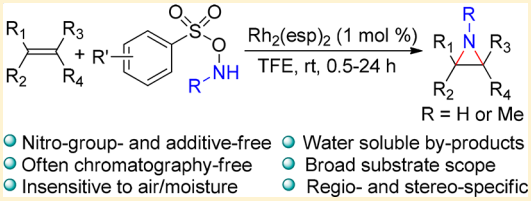
Supporting Information

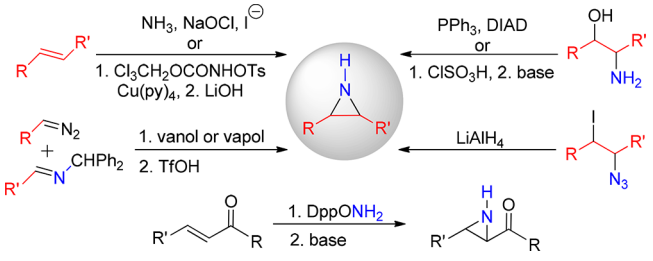
ABSTRACT: Unactivated aziridines are the core substructures in a plethora of bioactive natural products and serve as building blocks in organic synthesis. Despite this, very limited methods are available to access them directly from olefins, as most of the known methods are devoted to their activated counterparts. Herein, we have developed a highly efficient Rh(II)-catalyzed method for the direct preparation of unactivated aziridines from olefins using *O*-(sulfonyl)hydroxylamines as the aminating agent. The reactions proceed with a high stereospecificity.



Unactivated aziridines (*N*-H/*N*-Me) are in high demand because of their presence in many natural, semisynthetic, and synthetic bioactive molecules.[1] They also serve as important building blocks in organic synthesis because of their remarkable reactivity via ring opening, ring expansion, and rearrangements.[2] The regio- and stereospecific ring opening of unprotected (unactivated) aziridines with different nucleophiles (N, O, S, C) offers various functionalized unprotected scaffolds such as amino alcohols, diamines, thioamines, haloamines, etc.[3] Whereas the methods for activated aziridine (e.g., *N*-Ts, *N*-Ns, *N*-acyl) preparation from alkenes are well-established, the direct method for accessing nonactivated aziridines is less explored, and most of these methods are multistep (Scheme 1).[4,5] In 2014, Falck, Kürti, Ess, and co-workers (including the corresponding author of this paper) reported the first direct method for the preparation of *N*-H and *N*-Me aziridines from alkenes using 2,4-dinitrophenyl hydroxylamine (DPH) as the aminating agent in the presence of a rhodium catalyst (Du Bois catalyst) (**A**, Figure 1).[6] This elegant method requires DPH in a stoichiometric amount that has several intrinsic drawbacks. For instance, the byproduct, 2,4-dinitrophenol (DNP), interferes via an undesired ring opening reaction. Both DPH and DNP are relatively unstable/explosive in nature due to a high NO_2/C ratio, and DNP occasionally coelutes along with the product during column chromatography. Improving their previous method, Kürti et al. demonstrated another protocol using hydroxylamine-*O*-sulfonic acid (HOSA), instead of DPH, as the aminating reagent in the presence of 1.2 equiv of pyridine and the same rhodium catalyst (**B**, Figure 1).[7] This modification could overcome the drawbacks of their previous method to a great extent; however, (i) it necessitated the use of 1.2 equiv of pyridine; (ii) column chromatography was still necessary, and (iii) it required the use of a relatively costly hexafluoroisopropanol (HFIP) as the solvent.

We were interested to develop an atom-economical, additive/base-free and possibly a column-chromatography-free method, as the strained aziridine rings frequently open during silica gel purification. To achieve these objectives, the aminating reagent desirably should (i) exist in a non-

Scheme 1. General Methods To Access Unprotected Aziridines[a]



[a]Vanol = 3,3′-diphenyl-2,2′-bi-1-naphthalol; vapol = 2,2′-diphenyl-(4-biphenanthrol); $DppONH_2$ = *O*-(diphenylphosphinyl)hydroxylamine.

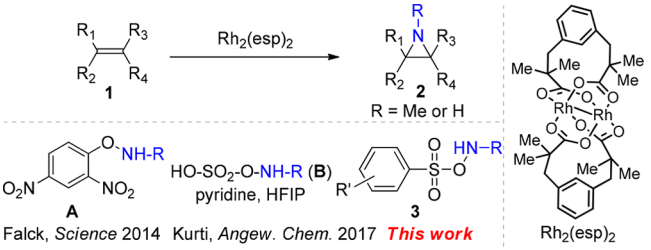


Figure 1. Aminating agents used for *N*-H and *N*-Me aziridination of alkenes.

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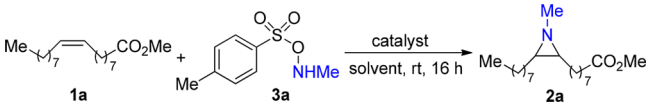
zwitterionic form, (ii) be stable and readily available, and (iii) essentially generate a noninterfering byproduct that can be easily removed just by an aqueous workup. In this regard, *O*-sulfonylhydroxylamines (**3**, Figure 1) attracted our attention. This class of reagents has been mainly explored for α-oxytosylation of carbonyl compounds as well as C(sp^2)−H and C(sp^3)−H amination.[8] We herein report a rhodium-catalyzed synthesis of *N*-Me and *N*-H aziridines from alkenes using *N*-methyl-*O*-tosylhydroxylamine[8] (**3a**) and 2,4,6-$Me_3C_6H_2S(O)_2ONH_2$ (**3b**) as the aminating reagents,[9] respectively.

Our study for *N*-Me aziridination began using methyl oleate **1a** as the model substrate in the presence of **3a** as the aminating reagent in 2,2,2-trifluoroethanol (TFE) (Table 1).

Table 1. Reaction Condition Optimization[a]



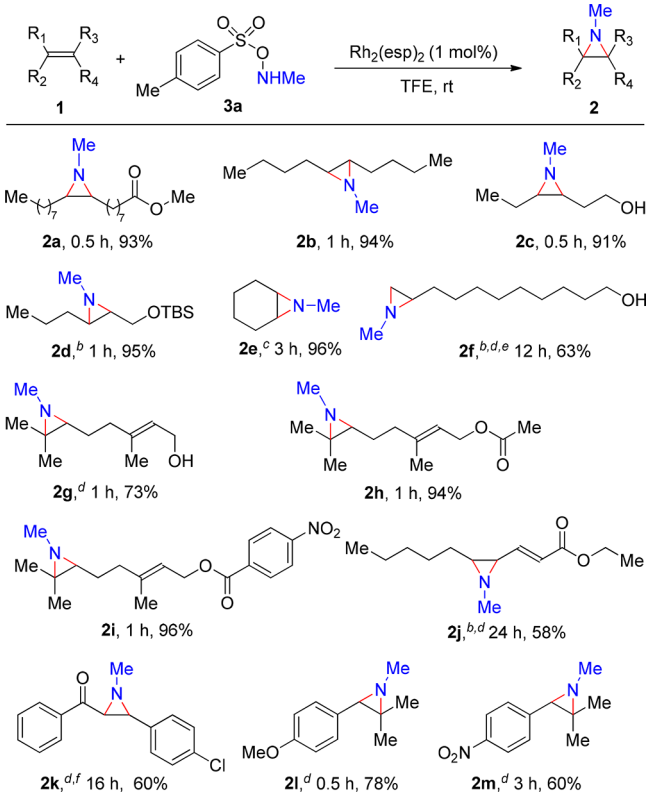
entry	catalyst	solvent	yield (%)[b]
1	$FeCl_2$ (5 mol %)	TFE	
2	$FeCl_3$ (5 mol %)	TFE	
3	CuBr (5 mol %)	TFE	trace
4	$Cu(OAc)_2$ (5 mol %)	TFE	20
5	$Cu(acac)_2$ (5 mol %)	TFE	35
6	$FeSO_4{\cdot}7H_2O$ (5 mol %)	TFE	52
7	$Rh_2(OAc)_2$ (5 mol %)	TFE	65
8	$Rh_2(TFA)_2$ (5 mol %)	TFE	
9	$Rh_2(esp)_2$ (5 mol %)	TFE	96[c]
10	**$Rh_2(esp)_2$ (1 mol %)**	**TFE**	**93**[c]
11	$Rh_2(esp)_2$(1 mol %)	EtOH	trace
12	$Rh_2(esp)_2$(1 mol %)	THF	
13	$Rh_2(esp)_2$ (1 mol %)	CH_3CN	trace
14	$Rh_2(esp)_2$ (1 mol %)	DMF	
15	$Rh_2(esp)_2$ (1 mol %)	CH_2Cl_2	
16		TFE	

[a]Reaction conditions unless otherwise mentioned: **1a** (0.25 mmol), **3a** (1.2 equiv), catalyst (1.0−5.0 mol %), solvent, rt, 16 h. [b]Isolated yield after silica gel column chromatography. [c]Isolated yield after workup using saturated $NaHCO_3$ aqueous solution; silica gel chromatography was not needed. TFE = 2,2,2-trifluoroethanol; esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid.

Under this condition, both Fe(II)- and Fe(III)-based catalysts did not produce the desired product (entries 1 and 2). Whereas CuBr was found to be ineffective, $Cu(OAc)_2$ and $Cu(acac)_2$ could catalyze the reaction to produce **2a** in 20−35% yield (entries 3−5). The yield improved significantly to 52% with $FeSO_4{\cdot}7H_2O$ (entry 6). Switching to various Rh-based catalysts further improved the yield of the reaction, eventually giving the desired product in excellent yield (96%) with $Rh_2(esp)_2$ in 30 min (entry 9). Decreasing the catalyst loading from 5 to 1 mol % did not affect the yield significantly (93%, entry 10). The screening of various other solvents under a condition similar to that of entry 10 had a detrimental effect on the reaction outcome (entries 11−15). To our delight, a simple workup using saturated $NaHCO_3$ aqueous solution completely removed the byproduct (TsOH), giving the desired product with good purity (by NMR).

To explore the scope of this method, a variety of alkenes were evaluated under the standard condition (as in entry 10, Table 1). Both *cis*- and *trans*-alkenes reacted well within an hour to give the corresponding aziridines in excellent yields (**2a** and **2b**, Scheme 2). Olefins bearing even unprotected hydroxy group smoothly aziridinated with 91% (**2c**) isolated

Scheme 2. Preparation of *N*-Me Aziridines[a]



[a]Reaction conditions unless otherwise mentioned: **1** (0.5 mmol), **3a** (1.2 equiv), $Rh_2(esp)_2$ (1 mol %), TFE (2.0 mL), rt. Yields are the isolated yield after an aqueous workup. [b]Reaction was performed at −10 °C. [c]The purity of this compound was checked by HPLC. [d]Column purification was required. [e]5 mol % of Rh catalyst was used. [f]A mixture of TFE/$CHCl_3$ (1:1) was used as the solvent.

yield, whereas its TBS-protected derivative produced **2d** in 95% yield at a lower reaction temperature. This TBS-protected alkene/aziridine was partially deprotected by stirring the reaction at room temperature. Cyclic alkene also participated in the reaction, affording **2e** with 96% yield. Switching to a terminal alkene required a minor variation in the reaction condition as it was sluggish under the above optimized condition, and a prolongation of the reaction time under this condition led to the decomposition of the product. This reaction proceeded well with a slightly higher Rh catalyst loading of 5 mol % and at a lower reaction temperature (−10 °C), giving **2f** in 63% isolated yield.

We next investigated the regioselectivity of the reaction using geraniol, which exclusively aziridinated at $\Delta^{6,7}$-olefinic position to furnish **2g** in 73% yield. Different derivatives of geraniol also reacted smoothly to give **2h** and **2i** in 94 and 96% yields, respectively, as a single regiomer. This regioselectivity can be attributed to the inductive deactivation of the proximal double bond ($\Delta^{2,3}$) by an acetoxy or a benzoyloxy group toward aziridination. This observation was further supported by a much slower reactivity of the electron-deficient chalcone requiring 16 h for completion of the reaction (**2k**). A mixture of TFE and $CHCl_3$ (1:1) was used as the solvent as the chalcone was not soluble in TFE alone. For conjugated diene

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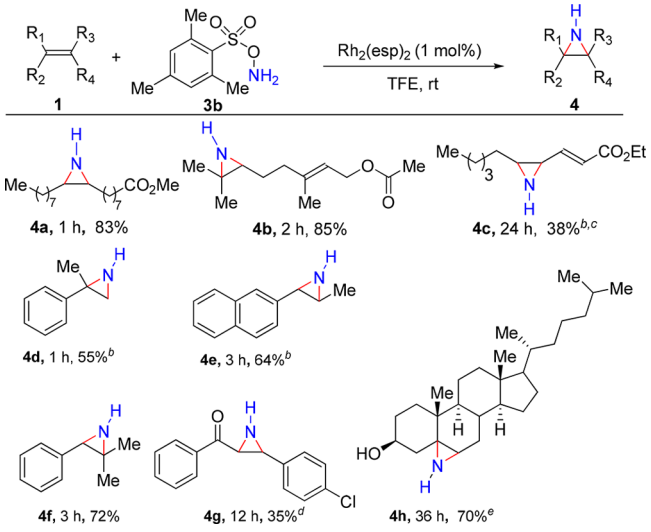
ester also, the aziridination occurred at the distal ($\Delta^{3,4}$) double bond selectively (**2j**, 58% yield). Both electron-rich as well as electron-deficient trisubstituted styrenes smoothly reacted to give the desired products (**2l** and **2m**) in good yield, albeit the reaction was slower in the case of electron-deficient styrene. Tetra-substituted olefin, like β-ionone, failed to react under this optimized condition for *N*-Me (as well as for *N*-H) aziridination. It is worth noting that all the reactions proceeded with high stereospecificity and without formation of any allylic aminated side product.

After demonstrating the method for *N*-Me aziridination, we turned our attention to the direct *N*-H aziridination of alkenes. The literature survey and our own studies using the unprotected analogue of **3a** ($TsONH_2$) to achieve *N*-H aziridination was not successful as this reagent was unstable under this condition. A 2,4,6-trimethyl derivative of tosyl hydroxylamine (**3b**, Scheme 3) was found to be a good

Scheme 3. Preparation of *N*-H Aziridines[a]



[a]Reaction conditions unless otherwise stated: **1** (0.5 mmol), **3b** (1.2 equiv), $Rh_2(esp)_2$ (1 mol %), TFE (2.0 mL), rt. Yields are isolated yield after silica gel column chromatography. [b]Reaction stirred at −10 °C. [c]Reaction was clean but with low conversion, and the olefin could be recovered. [d]A mixture of TFE/$CHCl_3$ (1:1) was used as the solvent. [e]2.5 equiv of **3b** and 2.5 mol % of Rh catalyst were used.

aminating agent under a condition similar to those in Scheme 2. Under this condition, different alkenes reacted well to give the desired products in good to excellent yield. For example, methyl oleate furnished the *N*-H aziridine **4a** in 83% yield. Geranyl acetate and (2*E*,4*Z*)-ethyl deca-2,4-dienoate (a conjugated diene ester) afforded **4b** (85% yield) and **4c** (38% yield), respectively, as a single regiomer. Simple as well as substituted styrenes were good substrates for this reaction at lower temperature to give the corresponding *N*-H aziridines in good yield (**4d** and **4f**). β-Naphthylstyrene was also examined to obtain **4e** in 64% yield. Chalcone reacted slowly to give the corresponding aziridine in 35% yield (**4g**). We also examined our reaction on a complex substrate like cholesterol. Under the optimized condition with TFE as the solvent, only a minor conversion was observed; the yield improved dramatically when a mixture of TFE/$CHCl_3$ (1:1) was used as the solvent (**4h**, 70% yield), although the reaction took a longer time to complete (36 h). We expect these reactions to follow the same mechanistic pathway as previously proposed by Falck, Kürti, and Ess.[6]

In conclusion, we have developed a direct, stereospecific Rh(II)-catalyzed *N*-H/*N*-Me aziridination method for alkenes using *O*-(sulfonyl)hydroxylamines as the aminating agents. These reagents do not generate explosive/interfering by-products and do not require base (pyridine) as an additive. This method provides various unactivated aziridines in good to excellent yield, and *N*-Me aziridines, in many cases, could be isolated with high purity just after an aqueous workup. Even highly reactive and labile functional groups like keto, ester, alcohol, and silyl were well-tolerated. The reactions proceeded with a good chemoselectivity as neither the undesired amination nor the nitrene insertion on the aromatic ring was observed.

EXPERIMENTAL SECTION

General Information. Unless otherwise specified, all reactions were carried out under an open atmosphere in a round-bottom flask. All aldehydes were of commercial quality and used without further purification. Olefins **1b**, **1i**, **1l**, **1m**, and β-naphthylstyrene were prepared following a known literature procedure.[10] Solvents were dried and distilled following the standard procedures. TLC was carried out on precoated plates (Merck silica gel 60, f254), and the spots were visualized with UV light or by charring the plates dipped in PMA or $KMNO_4$ solution. The compounds were purified by flash column chromatography using silica gel (230−400 mesh) with distilled solvents. ^1H and ^{13}C NMR spectra were recorded with 400 and 100 MHz instruments, respectively, in $CDCl_3$ as the solvent. Chemical shifts (δ) are given in parts per million. The residual solvent signals were used as references ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.0 ppm). High-resolution mass spectrometry (HRMS) was performed on an agilent 6530 Q-TOF using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode.

General Procedure for *N*-H and *N*-Me Aziridination. To a round-bottom flask equipped with a magnetic stirring bar were added alkene **1** (0.5 mmol), aminating agent **3a** or **3b** (1.2 equiv), and TFE (2 mL) at room temperature. To this stirred solution was added $Rh_2(esp)_2$ (1 mol %). The reaction mixture was stirred at the specified temperature and monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with a saturated aqueous $NaHCO_3$ solution (2 × 5 mL). The aqueous layer was extracted twice with CH_2Cl_2 (5 mL), and the combined organic layer was dried over anhydrous Na_2SO_4.

Purification Method for Scheme 2. The organic layer was concentrated in vacuo to afford the pure desired product **2**, unless reported otherwise.

Purification Method for Scheme 3. The crude product obtained after concentration of the organic layer in vacuo was purified by silica gel column chromatography to give the pure desired product **4** using 1% Bu_3N in EtOAc/hexane or MeOH/CH_2Cl_2 as an eluent.

(*E*)-3,7-Dimethylocta-2,6-dienyl 4-Nitrobenzoate (1j). To a solution of geraniol (200 mg, 1.29 mmol) and *p*-nitrobenzoyl chloride (289 mg, 1.54 mmol) in CH_2Cl_2 (15 mL) at 0 °C were added pyridine (136 μL, 1.54 mmol) and DMAP (18 mg, 0.15 mmol), and the reaction was stirred at room temperature for 18 h. After completion of the reaction, CH_2Cl_2 (10 mL) was added and the organic layer was washed with water (2 × 5 mL) and brine solution (5 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo, and the crude product was purified by silica gel column chromatography (2% EtOAc in hexane) to give the title compound as a thick oil (325 mg, 83%): TLC R_f = 0.5 (5% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.28−8.23 (m, 2H), 8.22−8.17 (m, 2H), 5.49−5.42 (m, 1H), 5.10−5.04 (m, 1H), 4.87 (d, J = 7.1 Hz, 2H), 2.14−2.03 (m, 4H), 1.76 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 150.4, 143.3, 135.8, 131.8, 130.6, 123.5, 123.4, 117.6, 62.7, 39.4, 26.2, 25.6, 17.6, 16.5;

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HRMS (ESI) $[M + H]^+$ calcd for $C_{17}H_{22}NO_4$ 304.1543, found 304.1525.

Methyl 8-(1-Methyl-3-octylaziridin-2-yl)octanoate (2a).[6] Following the general aziridination procedure, the title aziridine was obtained as a colorless oil (151 mg, 93% yield) whose spectral data were in accord with the literature values.

2,3-Dibutyl-1-methylaziridine (2b). Following the general aziridination procedure, the title product was obtained as a colorless oil (80 mg, 94% yield): TLC R_f = 0.3 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 1.64−1.56 (m, 2H), 1.46−1.28 (m, 11H), 0.93−0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.2, 42.9, 38.6, 32.8, 30.6, 29.6, 25.3, 22.6, 22.5, 14.0, 13.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_{24}N$ 170.1903, found 170.1903.

2-(3-Ethyl-1-methylaziridin-2-yl)ethanol (2c). Following the general aziridination procedure, the title product was obtained as a pale yellow oil (58 mg, 91% yield): TLC R_f = 0.3 (5% MeOH in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84−3.71 (m, 2H), 2.34 (s, 3H), 1.76−1.68 (m, 1H), 1.56−1.29 (m, 4H), 1.25−1.19 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.9, 47.8, 46.2, 43.1, 29.5, 21.2, 11.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_7H_{16}NO$ 130.1226, found 130.1225.

2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-3-ethyl-1-methyl Aziridine (2d). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/EtOAc/hexane (1:29:70) as an eluent to give the title product as a colorless oil (115 mg, 95% yield): TLC R_f = 0.2 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$; a mixture of invertomers) δ 3.77−3.65 (m, 2H), 2.39 (s, 1.5H), 2.38 (s, 1.5H), 1.90−1.78 (m, 0.5H), 1.71−1.53 (m, 3H), 1.52−1.43 (m, 0.5H), 1.42.1.33 (m, 1H), 1.29−1.11 (m, 2H), 1.07−1.01 (m, 2H), 0.95 (t, J = 7.4 Hz, 1H), 0.91−0.85 (m, 8H), 0.07−0.03 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.2, 61.3, 48.3, 44.4, 44.0, 39.8, 39.1, 38.5, 36.4, 29.6, 29.1, 26.1, 25.9, 19.0, 18.3, 12.7, 11.4, 1.0, −5.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{30}NOSi$ 244.2091, found 244.2090.

7-Methyl-7-azabicyclo[4.1.0]heptanes (2e).[11] Following the general aziridination procedure, the title aziridine was obtained as a light yellow oil (53 mg, 96% yield): TLC R_f = 0.4 (50% EtOAc in hexane), whose spectral data were in accord with the literature values.

9-(1-Methylaziridin-2-yl)nonan-1-ol (2f). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/MeOH/CH_2Cl_2 (1:2:97) as an eluent to give the title compound as an oil (63 mg, 63% yield): TLC R_f = 0.25 (5% MeOH in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (t, J = 6.6 Hz, 2H), 2.30 (s, 3H), 1.70 (brs, 1H), 1.58−1.53 (m, 2H), 1.48 (d, J = 3.5 Hz, 1H), 1.40−1.17 (m, 17H), 1.11 (d, J = 3.1, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.8, 53.4, 47.8, 40.8, 34.8, 32.9, 32.7, 29.6, 29.4, 29.3, 29.3, 27.5, 25.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{26}NO$ 200.2009, found 200.2017.

(*E*)-3-Methyl-5-(1,3,3-trimethylaziridin-2-yl)pent-2-en-1-ol (2g). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/MeOH/CH_2Cl_2 (1:4:95) as an eluent to give the title product as an oil (66 mg, 73% yield): TLC R_f = 0.3 (10% MeOH in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47−5.40 (m, 1H), 4.15 (d, J = 6.9 Hz, 2H), 2.36 (s, 3H), 2.20−2.04 (m, 2H), 1.68 (s, 3H), 1.58−1.42 (m, 2H), 1.24 (s, 1H), 1.17 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 123.7, 59.3, 52.0, 39.5, 39.3, 37.7, 27.5, 21.6, 17.9, 16.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_{22}NO$ 184.1623, found 184.1642.

(*E*)-3-Methyl-5-(1,3,3-trimethylaziridin-2-yl)pent-2-en-1-yl Acetate (2h).[6] Following the general aziridination procedure, the title aziridine was obtained as an oil (106 mg, 94% yield). ^{1}H NMR and ^{13}C NMR data were in accord with the literature value.

(*E*)-3-Methyl-5-(1,3,3-trimethylaziridin-2-yl)pent-2-enyl 4-Nitrobenzoate (2i). Following the general aziridination procedure, the title product was obtained as a thick yellow liquid (158 mg, 96% yield): TLC R_f = 0.3 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.23 (m, 2H), 8.21−8.16 (m, 2H), 5.52−5.44 (m, 1H), 4.87 (d, J = 7.1 Hz, 2H), 2.34 (s, 3H), 2.25−2.09 (m, 2H), 1.77 (s, 3H), 1.62−1.43 (m, 2H), 1.15 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 150.4, 143.1, 135.8, 130.6, 123.4, 117.9, 62.6, 51.8, 39.5, 39.3, 37.7, 27.5, 21.7, 17.9, 16.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{25}N_2O_4$ 333.1809, found 333.1815.

(*E*)-Ethyl-3-(1-methyl-3-pentylaziridin-2-yl)acrylate (2j). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/EtOAc/hexane (1:29:70) as an eluent to give the title product as a colorless oil (64 mg, 58% yield): TLC R_f = 0.6 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, J = 15.6, 7.8 Hz, 1H), 6.00 (dd, J = 15.6, 0.7 Hz, 1H), 4.22−4.09 (m, 2H), 2.38 (s, 3H), 1.91 (t, J = 7.1 Hz, 1H), 1.59 (q, J = 5.8 Hz, 1H), 1.31−1.19 (m, 10H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 145.9, 123.0, 60.1, 49.3, 47.4, 45.0, 31.4, 28.4, 27.2, 22.5, 14.2, 13.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{24}NO_2$ 226.1802, found 226.1800.

(3-(4-Chlorophenyl)-1-methylaziridin-2-yl)(phenyl)-methanone (2k). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/EtOAc/hexane (1:5:94) as an eluent to give the title compound as a light yellow sticky semisolid (81 mg, 60% yield): TLC R_f = 0.5 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.4 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.7, 2H), 7.32−7.23 (m, 4H), 3.53 (d, J = 2.4 Hz, 1H), 3.33 (d, J = 2.2 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 137.9, 137.2, 133.5, 133.2, 128.7, 128.5, 128.4, 127.5, 48.7, 48.5, 38.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{15}ClNO$ 272.0837, found 272.0843.

3-(4-Methoxyphenyl)-1,2,2-trimethylaziridine (2l). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/EtOAc/hexane (1:5:94) as an eluent to give the title compound as a light yellow sticky semisolid (74 mg, 78% yield): TLC R_f = 0.5 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.17 (m, 2H), 6.87−6.81 (m, 2H), 3.79 (s, 3H), 2.54 (s, 3H), 2.28 (s, 1H), 1.33 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 130.8, 128.4, 113.4, 55.2, 53.9, 42.3, 39.5, 21.4, 17.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{17}NO$ 192.1344, found 192.1389.

1,2,2-Trimethyl-3-(4-nitrophenyl)aziridine (2m). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/EtOAc/hexane (1:5:94) as an eluent to give the title compound as a light yellow sticky semisolid (62 mg, 60% yield): TLC R_f = 0.5 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18−8.12 (m, 2H), 7.47−7.42 (d, 2H), 2.57 (s, 3H), 2.39(s, 1H), 1.38 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 146.7, 128.18, 123.2, 53.6, 44.2, 39.3, 21.3, 17.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_{14}N_2O_2$ 207.1139, found 207.1089.

Methyl 8-(3-Octylaziridin-2-yl)octanoate (4a).[6] The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/MeOH/CH_2Cl_2 (1:2:97) as an eluent to give the title compound as an oil (129 mg, 83% yield), whose spectral data were in accord with the literature values.

(*E*)-5-(3,3-Dimethylaziridin-2-yl)-3-methylpent-2-enyl Acetate (4b).[6] The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/MeOH/CH_2Cl_2 (1:2:97) as an eluent to give the title compound as oil (89 mg, 85% yield), whose spectral data were in accord with the literature values.

(*E*)-Ethyl 3-(3-Pentylaziridin-2-yl)acrylate (4c). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/EtOAc/hexane (1:49:50) as an eluent to give the title compound as a light yellow oil (40 mg, 38% yield): TLC R_f = 0.4 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, J = 15.6, 8.3 Hz, 1H), 6.07 (d, J = 15.6 Hz, 1H), 4.23−4.14 (m, 2H), 2.89 (brs, 1H), 2.70 (brs, 1H), 2.33 (d, J = 5.3 Hz, 1H), 1.54−1.36 (m,

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2H), 1.34−1.19 (m, 7H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 145.6, 123.7, 60.3, 38.9, 35.4, 31.4, 29.1, 27.3, 22.5, 14.2, 13.9; HRMS (ESI) $[M + H]^+$ calcd for $C_{12}H_{22}NO_2$ 212.1645, found 212.1633.

2-Methyl-2-phenylaziridine (4d).[6] The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/EtOAc/hexane (1:19:80) as an eluent to give the title compound as a colorless oil (37 mg, 55% yield): TLC R_f = 0.3 (50% EtOAc in hexane), whose spectral data were in accord with the literature values.

(*E*)-2-Methyl-3-(naphthalene-2-yl)aziridine (4e). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/EtOAc/hexane (1:19:80) as an eluent to give the title compound as a colorless oil (59 mg, 64% yield): TLC R_f = 0.4 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.75 (m, 3H), 7.68 (s, 1H), 7.49−7.39 (m, 2H), 7.31−7.24 (m, 1H), 2.83 (d, J = 2.9 Hz, 1H), 2.27−2.19 (m, 1H), 1.42 (d, J = 5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 133.3, 132.6, 128.1, 127.6, 127.5, 126.1, 125.5, 124.3, 123.5, 40.6, 37.2, 19.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{14}N$ 184.1048, found 184.1118.

2,2-Dimethyl-3-phenylaziridine (4f).[6] The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/EtOAc/hexane (1:19:80) as an eluent to give the title compound as a colorless oil (53 mg, 72% yield): TLC R_f = 0.5 (50% EtOAc in hexane), whose spectral data were in accord with the literature values.

(3-(4-Chlorophenyl)aziridin-2-yl)(phenyl)methanone (4g).[12] The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu_3N/EtOAc/hexane (1:9:90) as an eluent to give the title compound as a light yellow sticky solid (45 mg, 35% yield), whose spectral data were in accord with the literature values.

Aziridinylcholestan-3-β-ol (4h).[6] The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using EtOAc/hexane (60:40) as an eluent to give the title compound as an off white solid (73 mg, 70% yield). ^{1}H and ^{13}C NMR data were in accord with the literature values.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01673.

^{1}H, ^{13}C, and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Organic & Supramolecular Chemistry

Fe(II)-Catalyzed Synthesis of Unactivated Aziridines (N-H/N-Me) from Olefins Using *O*-Arylsulfonyl Hydroxylamines

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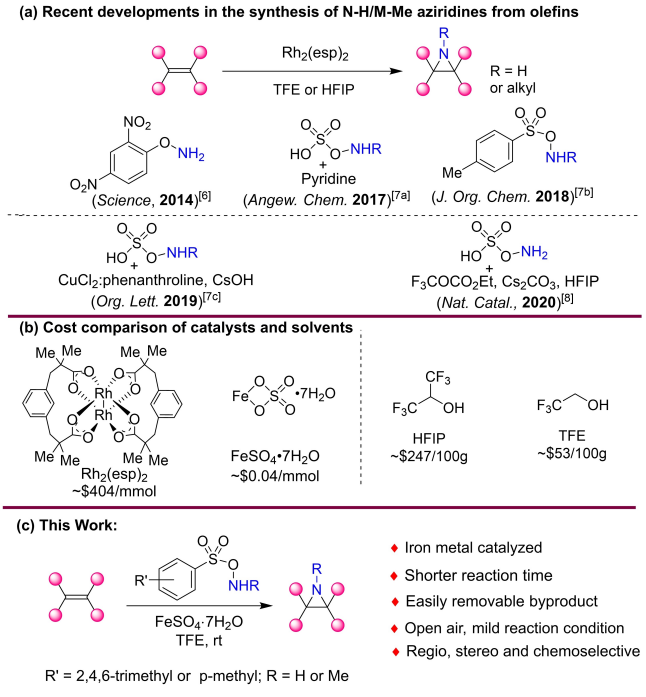
Iron(II) catalyzed direct N–H/N–Me aziridination of olefins using *O*-arylsulfonyl hydroxylamines is described. This stereospecific, mild, economical, open-air, operationally simple, and environmentally benign procedure afforded the high yields of aziridines in a shorter reaction time.

Aziridines are the common motifs in many biologically active natural and synthetic products,[1] and serve as unique synthetic intermediates for accessing a variety of useful compounds through ring manipulations.[2] As a result, impressive efforts have been made to synthesize aziridines *via* transfer of nitrenes to C=C and ylides, the addition of carbenes to imines, cyclization of amino and azido-alcohols, *etc.*[3] However, the majority of these methods produce activated aziridines (such as *N*-Ts or *N*-Ns) and the deprotection of these groups necessitates harsh reaction conditions and an extra step to get the useful *N*-H aziridines.[4] To address the aforementioned issues, numerous synthetic methodologies for the direct preparation of non-activated aziridines (*N*-H, *N*-alkyl, *N*-aryl) have been reported. Nevertheless, wide applications of these methods are restricted due to a limited substrate scope, multi-step routes, vigorous reaction conditions, requirement of pre-functionalized starting materials, etc.[5]

Falck, Kurti and Ess developed the direct approach for the preparation of *N*–H/N–Me aziridines from alkenes using a di-rhodium catalyst, [$Rh_2(esp)_2$], and 2,4-dinitrophenyl hydroxylamine (DPH) as an aminating agent.[6] This method produced a broad array of aziridines, but the toxic byproduct (2,4-dinitrophenol) led to several challenges such as co-elution with the product during purification and participation in an undesired aziridine ring-opening reaction, among others. These limitations could be largely addressed later through the methods developed by Kurti,[7a] Falck,[7c] and our lab[7b] utilizing hydroxylamine-O-sulfonic acid (HOSA) and *O*-(mesitylsulfonyl) hydroxylamine (MSH) as the aminating agents (Scheme 1a). Recently, the group of Kurti reported an effective organo-catalytic aziridination of unactivated olefins *via* transient oxaziridines generated from ethyltrifluoropyruvate in the presence of HOSA:Cs_2CO_3 in hexafluoroisopropanol (HFIP).[8] Despite this progress, these methods have one or the other limitations like the requirement of expensive metal catalyst [$Rh_2(esp)_2$, US$ 267/500 mg], additives (pyridine, cesium carbonate, ligands), relatively costly HFIP as the solvent, longer reaction time, and low reactivity for terminal and conjugated alkenes, etc. Therefore, any method that replaces the expensive catalyst and solvent with an economical, non-toxic and readily available catalyst and solvent is highly desired. We herein



Scheme 1. Recent Methods for the Direct Synthesis of N–H/N–Me Aziridines from Olefins.

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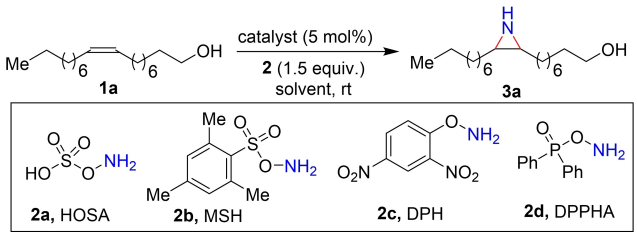
report a Fe(II)-catalyzed synthesis of *N*–H/*N*–Me aziridines from alkenes using *O*-arylsulfonyl hydroxylamines as a nitrogen source. It is noteworthy that iron salts/catalysts have been mainly explored for the preparation of protected/activated aziridines (*N*–Ts) from styrenes.[9]

Our study commenced using oleyl alcohol **1a** as a model substrate. At first, we tested several iron salts as a catalyst in the presence of commercially available HOSA **2a** as an aminating agent in TFE solvent at room temperature. No reaction was observed, as detailed in Table 1, entries 1–4. Switching to MSH **2b** in the presence of $FeCl_2$ and $FeCl_3$ catalyst gave a modest yield of aziridine, whereas $FeSO_4.7H_2O$ was found to be the most effective catalyst producing the desired aziridine **3a** in 72% yield (entries 5–7). Enhancing the catalyst loading from 5 mol% to 10 mol% led to **3a** in 86% yield over a shorter reaction time (entry 8). Other aminating reagents such as DPH **2c** or DPPHA **2d** did not work under a similar reaction condition (entries 9–10) and the evaluation of different solvents resulted in an extremely low conversion (entries 11–17).

Following the optimization of the reaction condition, we next evaluated the robustness of this method using a diverse spectrum of olefins (Scheme 2). *Cis*-alkenes aziridinated stereospecifically to afford *cis*-aziridines **3a** and **3b** in high yields. The trisubstituted alkenes, geraniol and its derivatives **1c–e** reacted in a regioselective fashion, exclusively at 6,7-olefinic position (> 95%), to produce the desired aziridines **3c–3e** in excellent yields. Terminal alkene such as vinyl cyclohexane **1f** and cyclic alkene such as cyclohexene **1g** provided good yields of the N–H aziridines. For the ease of purification, they were isolated as Boc protected aziridines **3f–g**. Di- and tri-substituted styrenes smoothly converted into the desired aziridines **3h** and **3i**, albeit the former required a lower temperature. In both cases, no C–H amination side-product was observed.[10] The electron-deficient conjugated olefin **1j** furnished **3j** with a 15% yield. Alkene directly bonded with electron withdrawing group such as *n*Butyl acrylate didn't produce the corresponding aziridine under this condition.

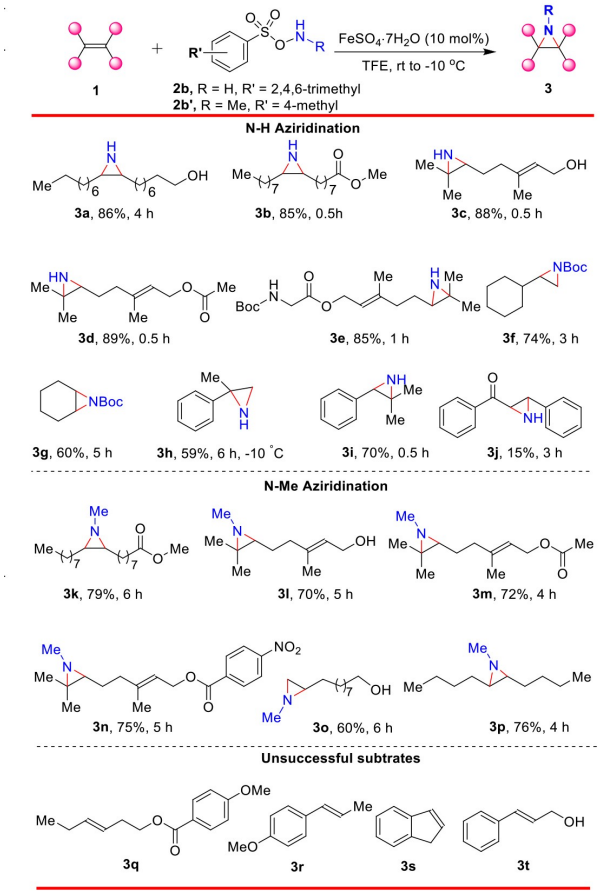
We were next interested to extend this protocol for the direct *N*-Me aziridination of alkenes using *N*-methyl-*O*-tosylhydroxylamine (TsONHMe, **2b′**) as the aminating reagent under a similar reaction condition. Various olefins were treated under this condition to obtain the corresponding *N*-Me aziridines in good to excellent yields. For example, methyl oleate produced

Table 1. Optimization of Aziridination Reaction Condition.[a]



S. No.	Catalyst	Aminating reagent	Solvent	Time [h]	Yield [%][b]
1	$FeCl_2$	2a	TFE	12	–
2[c]	$FeCl_2$	2a	TFE	12	
3	$FeCl_3$	2a	TFE	12	–
4	$FeSO_4 \cdot 7H_2O$	2a	TFE	12	–
5	$FeCl_2$	2b	TFE	12	40
6	$FeCl_3$	2b	TFE	12	51
7	$FeSO_4 \cdot 7H_2O$	2b	TFE	8	72
8[d]	$FeSO_4 \cdot 7H_2O$	2b	TFE	4	86
9	$FeSO_4 \cdot 7H_2O$	2c	TFE	12	–
10	$FeSO_4 \cdot 7H_2O$	2d	TFE	12	–
11	$FeSO_4 \cdot 7H_2O$	2b	DCM	12	trace
12	$FeSO_4 \cdot 7H_2O$	2b	MeOH	12	trace
13	$FeSO_4 \cdot 7H_2O$	2b	THF	12	trace
14	$FeSO_4 \cdot 7H_2O$	2b	CH_3CN	12	trace
15	$FeSO_4 \cdot 7H_2O$	2b	Toluene	12	trace
16	$FeSO_4 \cdot 7H_2O$	2b	EtOH	12	–
17	$FeSO_4 \cdot 7H_2O$	2b	EtOH/H_2O (1:1)	12	–
18[e]	$FeSO_4$	2b	TFE	4	85

[a] Reaction condition: **1a** (0.5 mmol), Aminating reagents (0.75 mmol) catalyst (5 mol%), solvent, rt. [b] Isolated yields. [c] Pyridine (2.0 equiv.) was used. [d] 10 mol% of Fe(II) catalyst was used. [e] Reaction was performed under anhydrous condition. TFE = 2,2,2-Trifluroethanol. HOSA = Hydroxylamine-*O*-sulfonic acid. MSH = *O*-(mesitylsulfonyl)hydroxylamine; DPH = 2,4-dinitrophenylhydroxylamine. DPPHA = *O*(diphenylphosphinyl)hydroxylamine.



[a] Reaction condition: **1a** (0.5 mmol), aminating reagent **2b** (for 3a-3j) or **2b'** (for **3k-3p**) (0.75 mmol), catalyst (10 mol%), TFE, rt. The yields mentioned are isolated yields after silica gel column chromatography.

Scheme 2. N–H and N–Me Aziridination of Olefins.[a]

aziridine **3k** in a 79% yield. Geraniol and its derivatives regioselectively (>95%) aziridinated with good to excellent yields **3l**–**n**. Terminal olefin **1o** provided the corresponding *N*-Me aziridine **3o** with 60% yield while the *trans*-alkene **1p** aziridinated to give **3p** with 76% yield. While this methodology has been suitable for a wide range of functionalized olefins, some of the olefins **3q**–**t** produced a complex mixture of inseparable products under the optimized reaction conditions. These reactions are presumed to proceed *via* an Iron-nitrene intermediate following a similar mechanistic pathway as proposed by Falck, Kürti, and Ess.[6]

In conclusion, we developed an efficient one-pot, stereo- and regio-selective Fe(II)-catalyzed method for the direct *N*–H and *N*–Me aziridination of alkenes. This method yields a wide range of unactivated aziridines in good to excellent yields and tolerates a wide range of labile and reactive functional groups such as ester, alcoholsand Boc.

Supplementary Information Summary

General information, detailed experimental procedures, characterization data and copies of IR, ^{1}H and $^{13}C\{^{1}H\}$ NMR can be found.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Aziridination · *O*-(mesitylsulfonyl)hydroxylamine · iron(II) · Olefins · Regioselective

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