Lewis and Brønsted Acid Mediated Synthesis of Nitrogen and Oxygen Heterocycles

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Submitted by

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Dedicated
To
My Family

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "**Lewis and Brønsted Acid Mediated Synthesis of Nitrogen and Oxygen Heterocycles**" is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Professor Anil K. Saikia.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

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CERTIFICATE

This is to certify that Miss **Priya Ghosh** has been working under my supervision since July 2011 as a regular registered Ph. D. student. I am forwarding her thesis entitled "**Lewis and Brønsted Acid Mediated Synthesis of Nitrogen and Oxygen Heterocycles**" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that she has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in her thesis and this work has not been submitted elsewhere for a degree.

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Priya Ghosh

LIST OF ABBREVIATIONS

Ac	acetyl	*m*-CPBA	meta-chloroperbenzoic acid
Bn	benzyl	mp	melting point
Bu	butyl	MS	molecular sieves
CCDC	cambridge crystallographic data centre	m/z	mass to charge ratio
CSA	camphorsulfonic acid	NMO	*N*-methylmorpholine *N*-oxide
Cy	cyclohexyl	NMR	nuclear magnetic resonance
DCE	1,2-dichloroethane	NOESY	nuclear overhauser enhancement spectroscopy
DCM	dichloromethane	ORTEP	oak ridge thermal ellipsoid plot
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	Ph	phenyl
DIAD	diisopropylazodicarboxylate	ppm	parts per million
DFT	Density Function Theory	Pr	propyl
DMF	*N*, *N*-dimethylformamide	*p*-TSA	*p*-toluenesulfonic acid
DMSO	dimethylsulfoxide	rt	room temperature
de	diastereomeric excess	THF	tetrahydrofuran
dr	diastereomeric ratio	Tf	trifluoromethanesulfonyl
ee	enantiomeric excess	TFA	trifluoroacetic acid
HRMS	high resolution mass spectrometry	TIPS	triisopropylsilyl
IR	infrared	TLC	thin layer chromatography
LA	Lewis acid	TMS	trimethylsilyl
LAH	lithiumaluminium hydride	TMEDA	N,N,N',N'-tetramethylenediamine
LDA	lithiumdiisopropyl amine	Ts	*p*-toluenesulfonyl

Abbreviations for intensities of ^{1}H-NMR signals

s	singlet	t	triplet
d	doublet	q	quartet
dd	doublet of doublet	m	multiplet
ddd	doublet of doublet of doublet	brs	broad signal
dddd	doublet of doublet of doublet of doublet	Hz	Hertz
dt	doublet of triplet	MHz	Mega-Hertz

Abstract

The contents of this thesis have been divided into five chapters based on the results of experimental work performed during the complete course of the research period. The chapter 1 of the thesis presents introduction to nitrogen and oxygen containing heterocyclic compounds, their biological significance and literature methods for their synthesis. Chapter 2 gives a description about Lewis acid mediated intramolecular C−C bond formation of alkyne-epoxide leading to six-membered nitrogen and oxygen heterocycles. Chapter 3 illustrates Lewis acid mediated intramolecular C-O bond formation of alkanol-epoxide leading to substituted morpholine and 1,4-oxazepane and its application towards the total synthesis of (±)-viloxazine. In chapter 4, synthesis of dihydroindeno[1,2-*c*]isochromene *via* cascade cyclization and Friedel-Crafts reaction has been described. Chapter 5 presents Brønsted acid mediated synthesis of 4-trifluoromethanesulfonate substituted 3,6-dihydropyrans and their application in various C-C coupling reactions.

Chapter 1: Introduction to Nitrogen and Oxygen containing Heterocyclic Compounds

Oxygen and nitrogenated heterocyclic compounds are essential to life since they are encountered in almost all the drugs, most vitamins and many other naturally occurring molecules. They are key components of pharmaceutical chemistry and therefore, they have been a fruitful source of inspiration for the design of structural analogues to be used as pharmacological tools as well as new drugs.

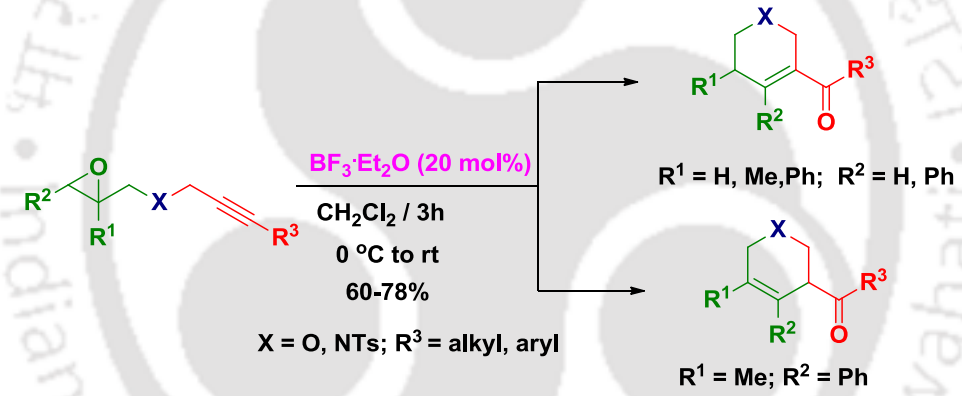
The search for the development of synthetic methodology to make these heterocycles is a major objective for many synthetic chemists. The most widely used methods are the Prins cyclization, hetero-Diels–Alder cyclization, intramolecular oxonium-ene cyclization, the intramolecular Michael additions, ring-closing metathesis electrophile-induced cyclizations of non-activated alkenes, Lewis acid promoted cyclizations of epoxy alcohols/amines and cascade reaction. These methods have their own advantages and disadvantages. Among various available methods stated, this thesis mainly discusses about Prins cyclization, cascade reaction and Lewis acid promoted cyclizations from *O*- and *N*-tethered starting materials in details for the construction of *O*- and *N*-containing heterocycles**.**

Chapter 2: Lewis acid mediated synthesis of six-membered nitrogen and oxygen heterocycles *via* intramolecular C-C Bond Formation of Alkyne-Epoxide

Transition-metal-free reactions are often practical, as they are generally less sensitive to air and moisture. Furthermore, transition metals are associated with drawbacks such as cost, toxicity, need for non-commercial ligands and threshold values in pharmaceutical products. Therefore, the search to develop metal-free reactions as efficient alternatives to reactions normally performed by transition-metal catalysis has undoubtedly attracted the interest of

synthetic chemists. In this chapter we describe mild and an efficient method for the synthesis of six-membered oxygen and nitrogen heterocyclic compounds by intramolecular C−C bond formation of alkyne-epoxide mediated by boron trifluoride etherate. The method is highly substrate-specific and works well for alkyl- and aryl-substituted alkyne-epoxide substrates.

The reaction is generalized as shown in *Scheme 1*.

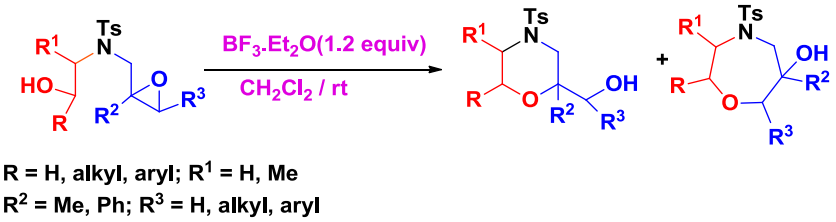


Scheme 1: *Synthesis of pyran and piperidine derivatives*

Chapter 3: Lewis acid mediated intramolecular C-O bond formation of alkanol-epoxide leading to substituted morpholine and 1,4-oxazepane derivatives: Total synthesis of (±) – viloxazine

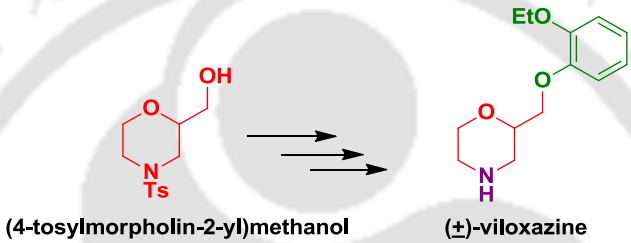
Morpholines or 1,4-oxazepane derivatives have attracted considerable attention owing to the biological activity associated with this motif. Therefore, in this chapter we have established a strategy for the synthesis of morpholines and 1,4-oxazepanes, using intramolecular C-O bond formation of alkanol-epoxide. The reaction is mediated by boron trifluoride etherate at ambient temperature.

The reaction can be generalized as shown in *Scheme 2*.



Scheme 2: *Synthesis of morpholines and 1,4-oxazepanes*

The strategy was successfully applied for the synthesis of (±)-viloxazine, an anti-depressant agent, starting from (4-tosylmorpholin-2-yl)methanol in 3 steps with an overall yield of 49%. **(***Scheme 3***)**.

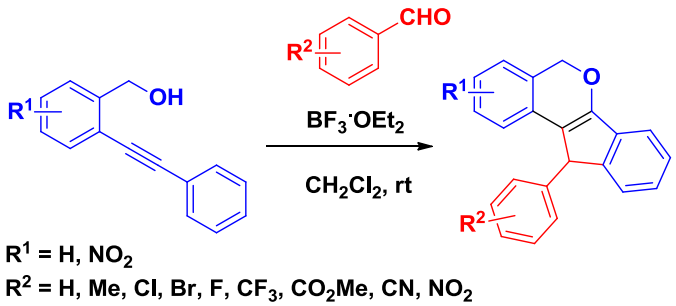


Scheme 3: *Total synthesis of (±)-viloxazine*

Chapter 4: Synthesis of dihydroindeno[1,2-*c*]isochromene *via* cascade cyclization and Friedel-Crafts reaction

Functionalized 1*H*-isochromene frameworks are found in a variety of natural products, bioactive molecules and pharmaceuticals. They have important biological effects including antitumor properties and their efficient and versatile synthesis has been a great source of inspiration to chemists. Of the various available methods to prepare the isochromene skeleton, one particularly straightforward and atom economical process has been the use of transition-metal-catalyzed cyclization of ortho-alkynylarylaldehydes or ortho-alkynylbenzylalcohols. However, methodology for the synthesis of isochromene skeleton under metal-free conditions are very limited in the literature. Therefore, in this chapter we have developed a novel route for the synthesis of dihydroindeno[1,2-*c*]isochromene *via* cascade cyclization and Friedel-Crafts reaction of internal alkynols and aldehydes mediated by borontrifluoride etherate. This protocol provides a straightforward entry to construct the complex polycyclic skeleton.

The reaction is generalized as *scheme 4*.

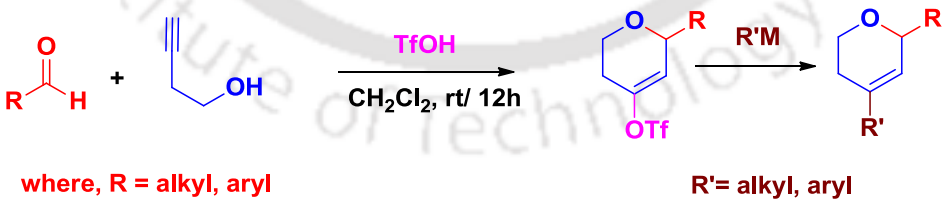


Scheme 4: *Synthesis of isochromene*

Chapter 5: Synthesis of 4-trifluoromethanesulfonate substituted 3,6-dihydropyrans and their application in various C-C coupling reactions

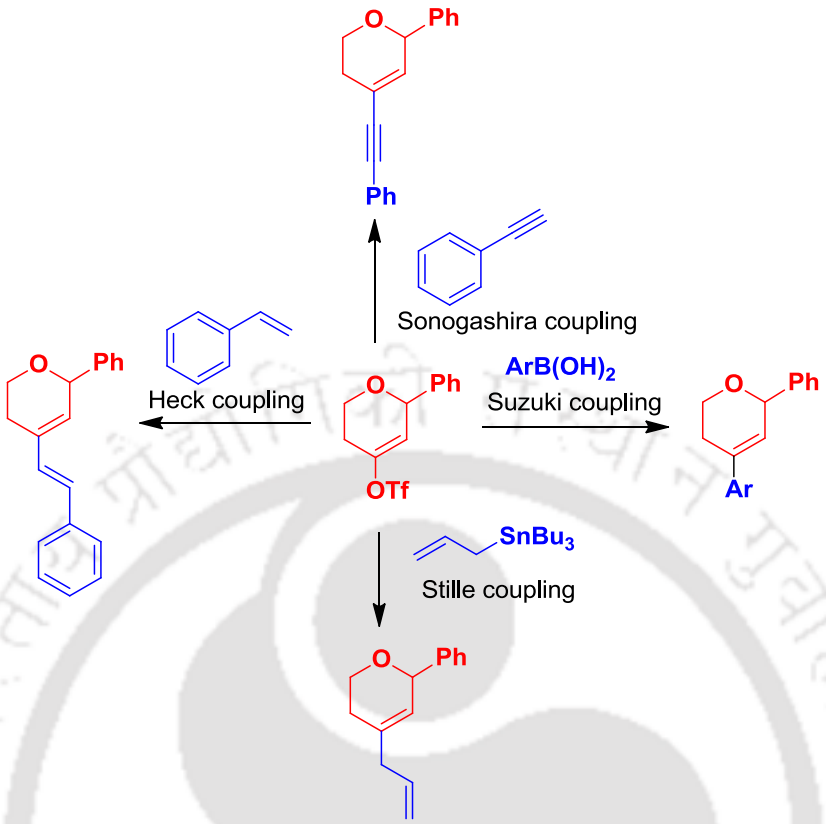
Unsaturated triflates, considered as pseudohalogens, are important intermediate in organic synthesis for numerous organic transformations. Although there are several reports which illustrate the preparation of 4-halotetrahydropyran derivatives, there are only a couple of reports which demonstrates the preparation of 4-halo-5,6-dihydro-2*H*-pyrans mediated by Lewis acids. Besides triflates, present at vinylic position, in general, are valuable substrates owing to its importance for further functionalization. Metal catalyzed bond forming reactions and C-C bond forming reactions *via* coupling reactions have been well explored starting from the triflate derivatives. Therefore, in this chapter we have develped a one pot, three component and highly selective Prins cyclization reaction for efficient synthesis of 3,6-dihydro-2*H*-pyran-4-yl trifluoromethane-sulfonates from homopropargylic alcohols and aldehydes mediated by triflic acid and also demonstrates C-C cross coupling reaction.

The reaction can be generalized as shown in Scheme 5.



Scheme 5

The reaction is further utilized for the synthesis of 4-arylated dihydropyrans *via* Suzuki coupling reaction (*Scheme 6*). Similarly, the methodology was used for Heck, Stille and Sonogashira coupling to produce the corresponding coupling products, in excellent yields (*Scheme 6*).



Scheme 6

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CHAPTER 1

Introduction to Heterocyclic Compounds

1.1. Background

Cyclic compound containing all carbon atoms in ring formation is referred to as carbocyclic compound and the carbocyclic compound can be classified as heterocyclic compound by replacing one or more carbon atoms of the ring with a different element. The most common hetero atoms are oxygen, nitrogen and sulphur but other hetero atoms such as B, P, Si, and Se containing heterocyclic analogs are also well known. The chemistry of heterocyclic compounds occupies the largest branch in the organic chemistry for the reason that more than half of the existed compounds belong to this category. Heterocyclic compounds are valuable subject of interest as it constitutes the core structural unit in many naturally occurring molecules, for e.g. from the amino acids - tryptophan, from the alkaloids - morphine, from the vitamins – vitamin B_1, from the coenzymes - coenzyme A, nucleic acids, from the antibiotics - penicillin, etc.[1]

Heterocyclic compounds can be divided into aliphatic and aromatic heterocycles. The aliphatic heterocycles are the cyclic analogues of amines, ethers and thioethers and their properties are influenced by the ring strain. The three and four membered aliphatic heterocyclic rings are more reactive compared to five and six membered analogues due to ring strain. The common aliphatic heterocyclic compounds are oxirane **1**, aziridine **2**, thiirane **3**, oxetane **4**, azetidine **5**, thietane **6**, tetrahydrofuran **7**, pyrrolidine **8**, tetrahydrothiophene **9**, tetrahydropyran **10**, piperidine **11** and tetraydothiopyran **12**.

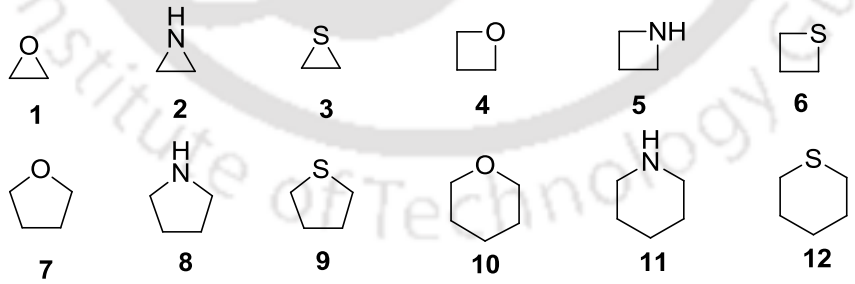


***Figure 1.1.1*:** Some common three to six membered saturated heterocycles

The most widely used systematic method for naming three to ten membered monocyclic heterocycles of various degree of unsaturation containing one or more heteroatoms is Hantzsh-Widman system.[2] This nomenclature specifies the ring size, position of the heteroatom and the degree of unsaturation in the ring. In this method, the ring atoms are normally numbered such that the heteroatom carries the least number. Yet, difficulty arises with the names of unsaturated heterocycles containing a sp^3 hybridized atom in the ring for instance, pyran, a heterocycle

formally the product of the addition of a single hydride ion to the pyrylium cation **13**. However, as this addition could occur either at C-2 or C-4, two isomers of pyran are possible, which are called as 2*H*-pyran **14** and 4*H*-pyran **15**, respectively (*Figure 1.1.2*).

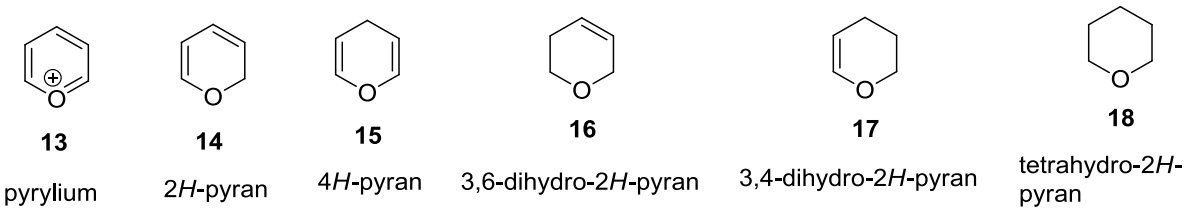


***Figure 1.1.2*:** Systematic names of the heterocycles having sp^3 carbon in the ring

It is also common to use the prefixes dihydro and tetrahydro while referring to compounds that are partly or fully reduced. For illustration 3,6-dihydro-2*H*-pyran **16** in which "dihydro" refers to the two added hydrogen atoms, which are required to reduce one double bond from the parent compound 2*H*-pyran. It is also important to note that the lowest possible number is always selected for the heteroatom. For example, the fully reduced pyrylium cation is referred to as 3,4,5,6-tetrahydro-2*H*-pyran **18** (*Figure 1.1.2*).

Numbering of the heterocyclic rings becomes essential when substituents are placed on the ring. Conventionally, the hetero atom is assigned position 1 and the substituents are then counted around the ring in a manner so as to give them the lowest possible numbers. While writing the name of the compound, the substituents are placed in an alphabetical order. In case the heterocyclic ring contains more than one hetero atom, the order of preference for numbering is O, S and N. The ring is numbered from the atom of preference in such a way so as to give the smallest possible number to the other hetero atoms in the ring. As a result the position of the substituent plays no part in determining how the ring is numbered in such compounds. The following examples illustrate this rule:

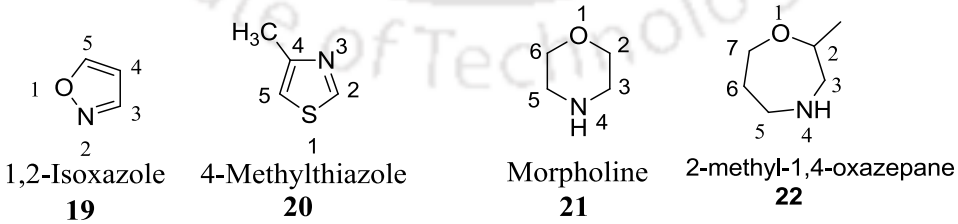


***Figure 1.1.3*:** Numbering of heterocycles having substituents on the ring

This introductory chapter is intended to provide an insight into the evolution of some oxygen and nitrogen containing biologically active compounds and their biological significance. This chapter also demonstrates on important routes for the construction of oxygen and nitrogen containing

heterocycles *viz.*, dihydropyran, piperidine, morpholine and isochromenes and their application in natural product synthesis.

1.2. Importance of Dihydropyrans, Piperidines, Morpholines, Oxazepanes and Isochromenes in Nature

Cyclic ethers such as 2*H*-pyrans and 4*H*-pyrans are widespread in the core of many naturally occurring biomolecules.[3] These molecules display a range of biological properties and have got diverse applications in cosmetics and agro chemicals as well. Dihydropyrans are important precursors for the synthesis of biologically active natural products. For example, ambruticin S **23**, a structurally novel antifungal antibiotic, was isolated from fermentation extracts of PolyangiumcellulosumVarfulVumin.[4] (-)-Kendomycin **24**, isolated from *Streptomyces* bacteria, exhibiting potent antagonism of the endothelin receptor agonism has pyran unit.[5] Neopeltolide **25** is a new type of biofunctional oceanic natural product, sequestered from the Caribbean sponge of Neopeltidae family, found in the deep waters of north Jamaican coast and collected by Wright *et al.* It has been found to possess considerable in-vitro cytotoxicity towards a number of different cancer cell lines, like, A-549 human lung adenocarcinoma, NCI-ADR-RES human ovarian sarcoma and P388 murine leukemia cell lines, with IC_{50} of 1.2, 5.1, and 0.56 nM, respectively. It also repressed the growth of the fungal pathogen Candida albicans with a minimum inhibitory concentration of 0.62 & 956 micro gram/ mL.[6] Diospongins A, **26** and B, **27,** the intriguing C-aryl glycoside natural products which were isolated from the rhizomes of Diocorea spongiosa through a bioassay-guided fractionation show promising antiosteoporotic activity (45Ca release at 200 μM (30.5%) and 20 μM (18.2%),3 hence, can be considered to be a lead for the discovery of potent and novel antiosteoporotic agents. Besides, Diospongin B displays potent inhibitory activity on bone resorption induced by parathyroid hormone, which is comparable to that of elcitionin, a drug used clinically for osteoporosis while diospongin A did not show any activity.[7] The 4-methyl substituted dihydropyran unit is present in the macrolide natural products laulimalide and okadaic acid.[8] Laulimalide **28** is a macrolide, obtained from a marine sponge. It exhibits potent cytotoxicity toward numerous cancer cell lines and microtubule stabilizing activity similar to that of paclitaxel and the epothilones. Okadaic acid **29** is a naturally occurring polyether toxin that was originally derived from marine dinoflagellates, *Prorocentrium spp*. It is a reversible, potent and selective inhibitor of two serine threonine protein phosphatases. The hydrophobic backbone of okadaic acid enables it to enter cells where it stimulates intracellular protein phosphorylation. It mimics the effects of insulin, enhances transmitter release at neuromuscular junctions, causes vasodilation and is a very potent tumor promoter. Okadaic acid

is an extremely useful tool for studying cellular processes that are regulated by phosphorylation. Okadaic Acid is an activator of protein kinase C (PKC).

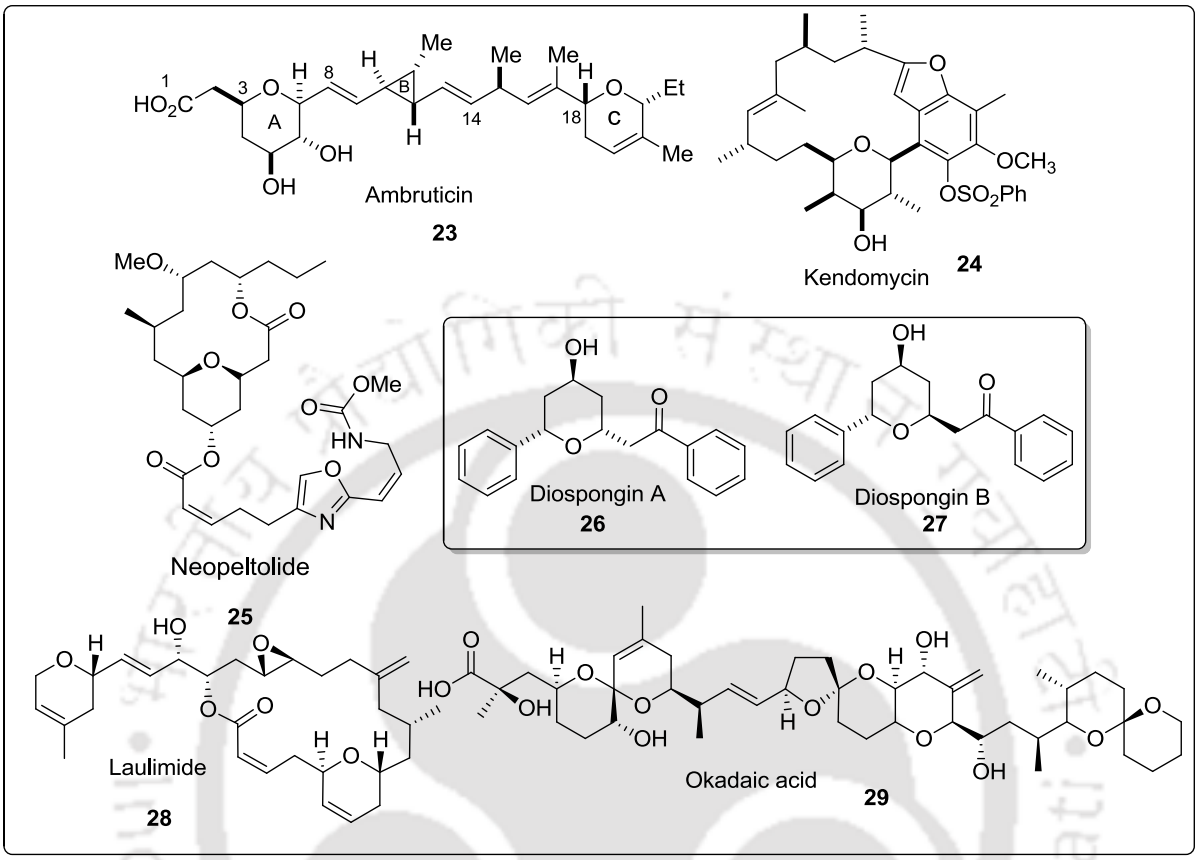


***Figure 1.2.1*:** Some biologically active oxygen heterocycles

Similarly, nitrogen heterocyclic compounds are important in synthetic chemistry because of their presence in many biologically active natural products and pharmaceuticals.[9] Substituted piperidines are important heterocycles, which appear in many drugs and drug candidates, as out of the 200 brand-name drugs by US retail sales in 2009, top 32 contain the piperidine fragments and thousands of piperidine compounds are submitted to clinical and preclinical studies in last ten years.[10] For example, the compound selfotel (CGS-19755) **30**, having a simple piperidine unit acts as a competitive NMDA antagonist and argatrobane **31** shows thrombin inhibiting properties.[11] α-Conine **32**, having a simple piperidine unit is a powerful poison, isolated from hemlock Conium maculatum.[12] Likewise, naturally occurring piperidine alkaloid (-)-pelletierine **33**, which was isolated from pomegranate (Punica granatum) root bark, has been found to have anthelmintic properties.[13] Prosophylline **34**, a hydroxyl piperidine derivative, was isolated from various Prosopis species and found to exhibit antibiotic and anaesthetic properties.[14]

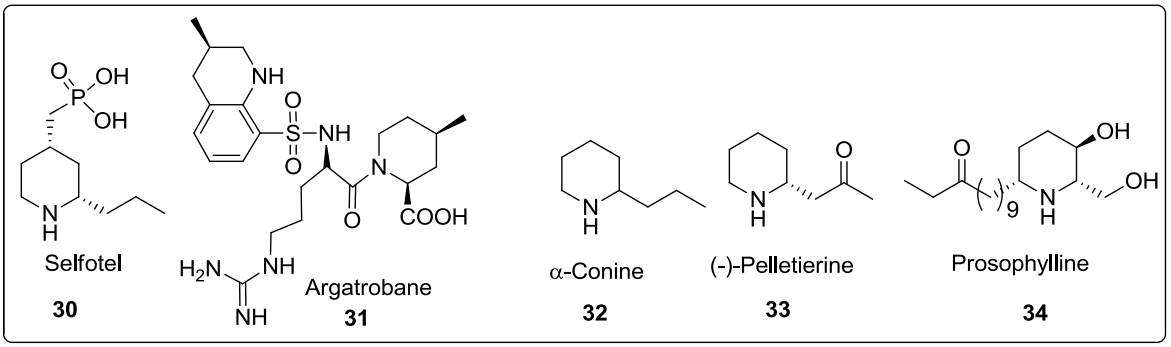


Figure 1.2.2: Some piperidine containing biological active compounds

Of the various heterocyles known, morpholine derivatives are of particular importance. Substituted morpholine derivatives are also widely distributed in many naturally occurring and biologically active molecules.[15] Morpholines are some of the most important pharmacophores in medicinal chemistry as well.[15a, 16] Various morpholine derivatives were extracted from natural sources. For example, alkaloid polygonapholine **35**, isolated from the methanol extract of the rhizome of Polygonatum altelobatum is used as a tonic drug by Taiwanese, the alkaloids chelonin **36** and Chelonin **37** were the first natural products incorporated 2,6-disubstituted morpholine fragment isolated from the marine sponge Chelonaplysilla sp. from a lake in Palau, chelonin exhibited antimicrobial activity against Bacillus subtilis and also anti-inflammatory effect. Again, nitrogen-substituted morpholines are important as drug candidates with a broad spectrum of biological activities. For example, linezolid **38** is commercially available antimicrobial agent that contains a morpholine cycle. Morpholine containing aprepitant **39** is neurokinin 1 (NK1) receptor antagonist and also, the first drug approved by Food and Drug Administration to be used against chemotherapy-induced nausea and vomiting.[17]

Again, among 1,4-heterocycles, 1,4-oxazepane, which is a seven-membered analogue of morpholine, also shows significant biological activity[18] and is present in very essential natural products such as neurotoxin batrachotoxin **40** (*Figure 1.2.3*).[19] In the preparation of peptide nucleic acids (PNAs), amino acid derived oxazepanes are being used to regulate biological functions.[20] The importance of 1,4-oxazepanes is also reflected in their capability to inhibit a wide range of glycosidase enzymes[21] and nitric oxide synthases.[22]

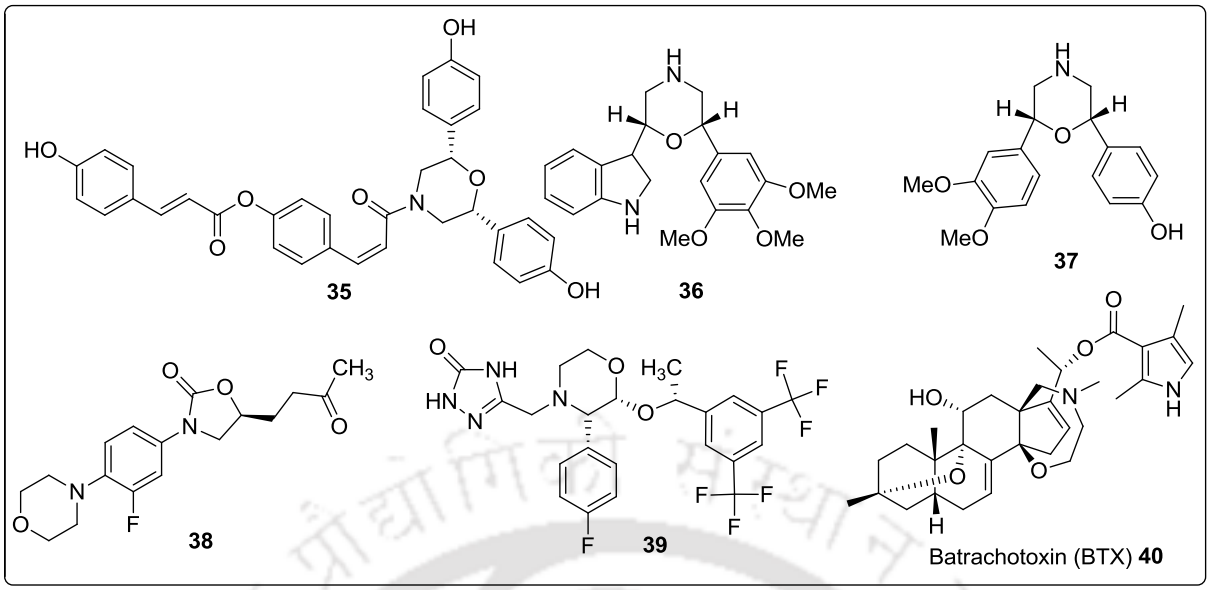


Figure 1.2.3: Some morpholine containing bioactive molecules

Interestingly, isochromene and its derivatives have become popular building blocks in a vast array of natural products and biologically active compounds.[23] For example, pyranonapthoquinone exhibits pharmaceutical activity: the carboxamides analog, BCH-2051 **41**, acts as an anticancer agent in its ability to fight cancer cell line SKOV3 and methyl 1,5,8-trimethoxy-1*H*-isochromene-3-carboxylate **42** displays a moderate antitumor function.[24] Some natural products containing 1*H*-isochromene can be found in bacteria, fungi and higher plants. Recently reported natural products include banchromene,[25] indigotide A,[26] and kalafungin[27] and some of their derivatives were found to show good antitumor activities.[28]

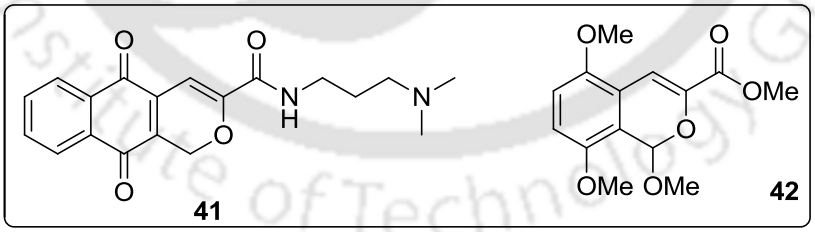


***Figure 1.2.4*:** Bioactive isochromene derivatives

1.3. An Overview for the Synthesis of Dihydropyran, Piperidine, Morpholine, Oxazepane and Isochromene Derivatives

Construction of these rings from simple and readily available acyclic building blocks remains a challenge, due to the constraints associated with enthalpic and entropic factors and the reaction is disfavoured in most of the cases. Despite of these problems, cyclic ethers of these ring sizes were prepared in high yield by either C-C[29] and C-O[30] bond formation. For the synthesis of these

heterocycles, many strategies have been proposed over the years. However, the most widely used methods are

1) Prins cyclization

2) Oxonium-ene cyclization,

3) 1,*n*-Enyne rearrangement

4) Lewis acid promoted cyclization of epoxy alcohols/amines

5) Cascade reaction

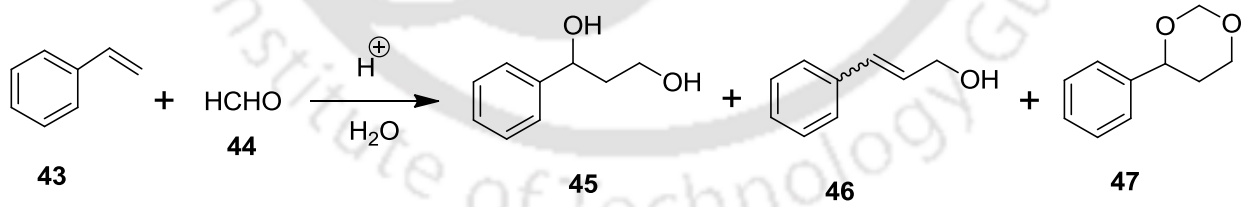
6) Hetero-Diels–Alder (HDA) reaction and

7) Ring-closing metathesis.

Among these methods stated, this thesis mainly discusses about Prins cyclization, cascade reaction and Lewis acid promoted cyclizations from *O*- and *N*-tethered starting materials in details for the construction of *O*- and *N*- containing heterocycles**.**

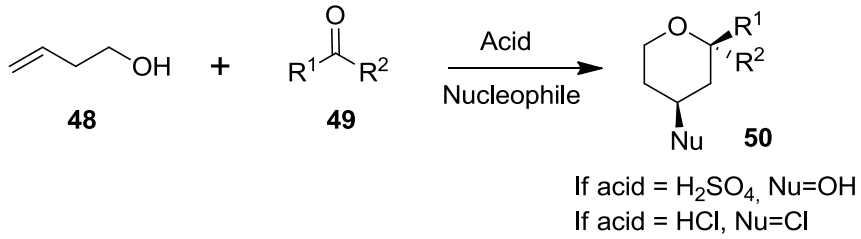
1.3.1. Prins cyclization reaction

The reaction is named after H. J. Prins in the year 1919. In his study, he performed a reaction between simple styrene **43** and formaldehyde **44** in aqueous acidic medium, and a mixture of diol **45**, unsaturated alcohol **46** and 1,3-dioxane **47** were obtained as products (*Scheme 1.3.1.1)*.[31]



Scheme 1.3.1.1

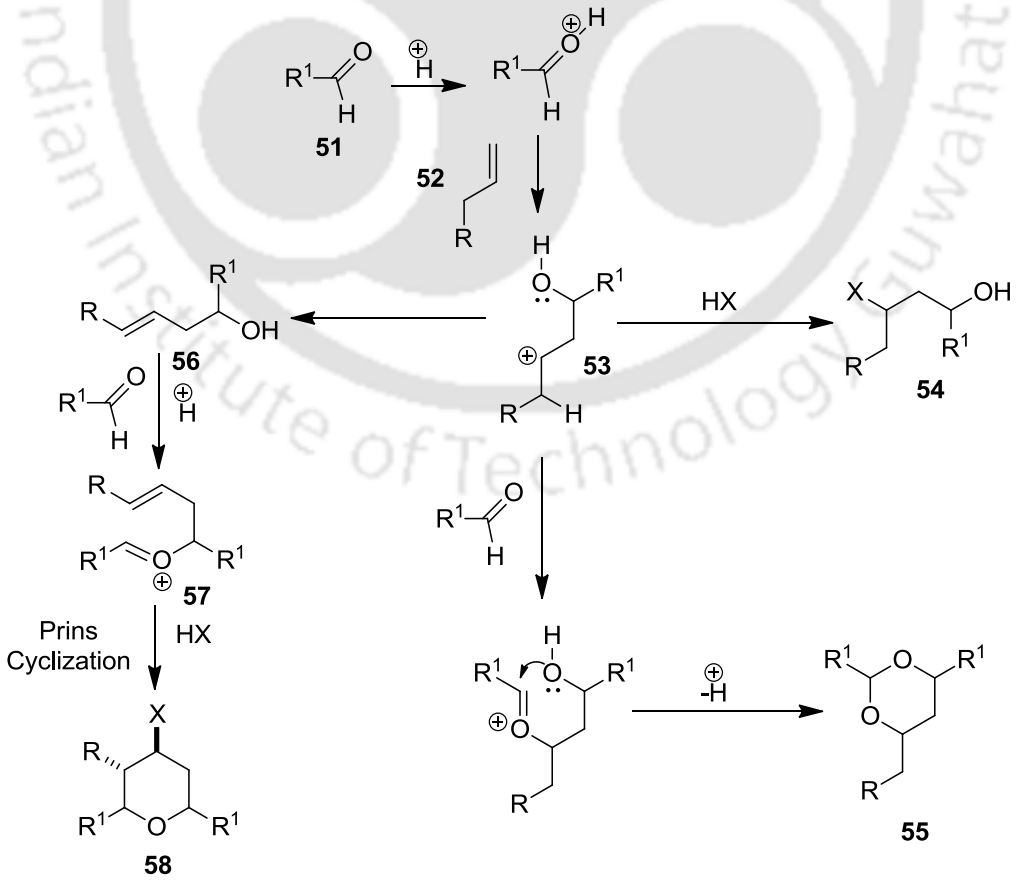
In 1955, Hanschke has further developed Prins reaction for the selective synthesis of tetrahydropyran (THP) rings **50** by combining 3-buten-1-ol **48** with a variety of aldehydes or ketones **49** in the presence of acid, called Prins cyclization reaction *(Scheme 1.3.1.2)*.[32]



Scheme 1.3.1.2

1.3.2. Mechanism of the Prins Reaction

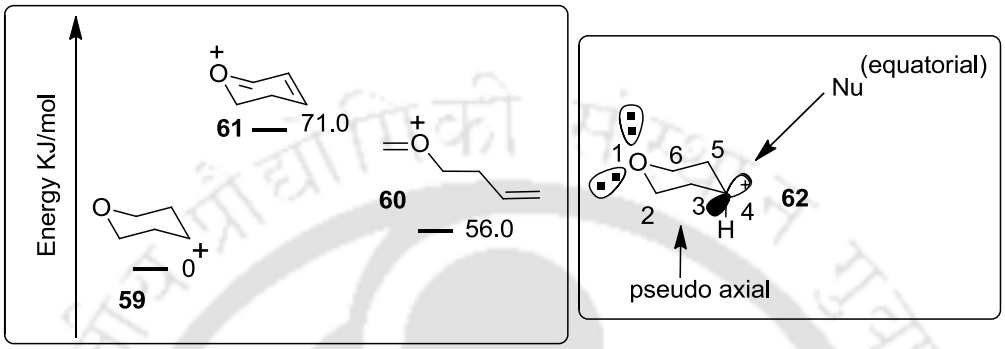
The general mechanism is shown in (*Scheme 1.3.2.1*). The alkene **52** reacts with carbonyl compounds **51** in the presence of Lewis or Brønsted acid and generates *β*-hydroxy carbocation as a key intermediate **53**, which either can react with a nucleophile such as chloride, water or acetate to give **54**, or adds to a second molecule of aldehyde to give **55** or loses a proton to give homoallylic alcohol **56**. Thus, the in- situ generated homo allylicalcohol **56** reacts with another molecule of aldehyde in the presence of acidic medium to afford oxocarbenium ion **57**, which after Prins cyclization and subsequent addition of nucleophile gives the 2,4,6-trisubstitutedtetrahydropyran **58**.[33]



***Scheme 1.3.2.1*:** Mechanism of the Prins reaction

1.3.3. Stereoselectivity in Prins Cyclization

There have been numerous reports in the literature on the Prins cyclization, which demonstrate excellent diastereoselectivity in favor of equatorial trapping of the cyclic carbocation by the nucleophiles. Alder has performed the DFT calculations on different possible reaction intermediates.[34]

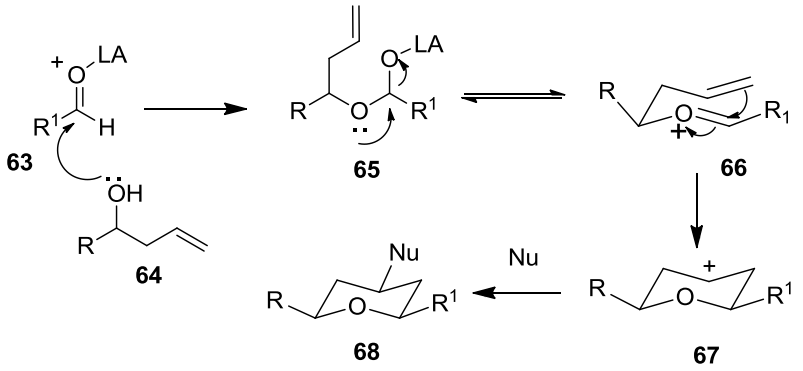


Scheme 1.3.3.1.

Carbocation **59** in its chair conformation is more stable by 56.0 kJ/mol than cation **60** in its most stable staggered conformation, which reveals that the reaction proceeds through a chair like transition state very close to **61** (*Scheme 1.3.3.1*). According to DFT calculations, carbocation in its chair conformation **62** is stabilized by stereoelectronic effects. The C2- C3 and C5-C6 σ* and σ orbital overlap both the equatorial lone pair of the oxygen atom and the vacant p orbital at C4. Optimal overlap is reached when the hydrogen atom at C4 is pseudo-axial. This stabilization favors equatorial attack by the nucleophile.

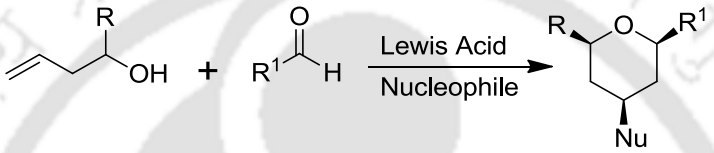
1.3.4. Scope of the Prins Reaction

In the simplest case, oxa-prins cyclization involves a homoallylic alcohol, an aldehyde and a Lewis acid. A general mechanism is shown in (*Scheme 1.3.4.1*). Aldehyde **63** reacts with homoallylic alcohol **64** in the presence of lewis acid to generate an oxocarbenium ion **66** as a key intermediate, which undergoes 6-endo cyclization to give selectively a secondary tetrahydropyranyl cation **67**, which is trapped by the nucleophile to produce tetrahydropyran **68**. Thus, the carbocation that is generated at 4th position in Prins cyclization can be trapped with a wide range of nucleophiles (*Table 1.3.4.1*). This tendency enables it to have many variations in the Prins cyclization.[35]



***Scheme 1.3.4.1*:** Mechanism of the Prins cyclization reaction

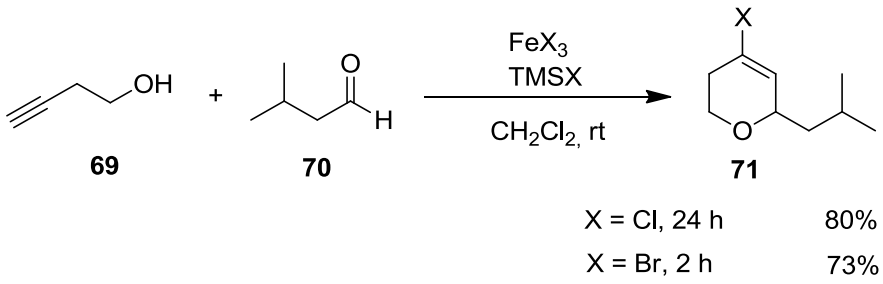
***Table 1.3.4.1*:** Scope of the prins cyclization with a large array of nucleophiles



	Lewis acid (Nucleophile)[a]/Nucleophile[b]	Nu
1	TiF_4, $NEt_4.5HF$, $BF_3.OEt_2$	F
2	HCl, $TiCl_4$, $SnCl_4$, $AlCl_3$, $InCl_3$, $ZnCl_2$, $SbCl_5$, $ZrCl_4$, $NbCl_5$, $In(OTf)_3$/TMSCl	Cl
3	$SnBr_4$, $TiBr_4$, $InBr_3$, $FeBr_3$	Br
4	I_2, TMSCl/NaI, $CeCl_3.7H_2O$/LiI, TMSCl/NaI	I
5	CF_3COOH, Montmorillonite KSF, $O_3ReOSiPh_3$, $Sc(OTf)_3$, Amberlyst 15, Amberlite® IR-120, $Ce(OTf)_3.H_2O$/IL/Ph_2CO	OH
6	$BF_3.OEt_2$/AcOH, TsOH/AcOH, TESOTf/TMSOAc/AcOH	OAc
7	TFA/NaN_3	N_3
8	$In(OTf)_3/NH_4SCN$	SCN
9	$BF_3.OEt_2/CH_3CN$, PMA/CH_3CN, $CeCl_3.7H_2O$-AcCl/ CH_3CN	$NHCOCH_3$
10	$BF_3.OEt_2$/Arene	Ar
11	$BF_3.OEt_2$/CuI/ Ph—≡—H	$PhCOCH_2$

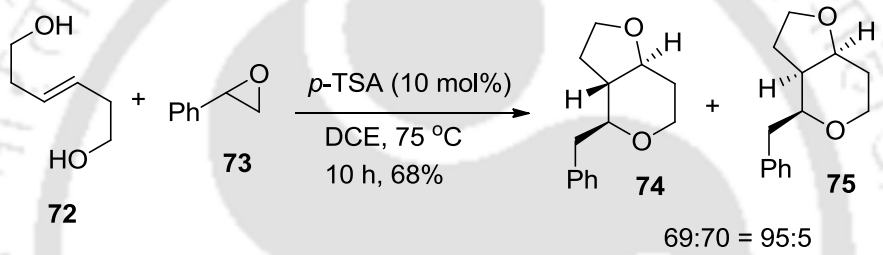
[a]Nucleophile comes from lewis acid, [b]separate nucleohile source has to be added

Martín had explored the synthetic potential of cyclization involving homopropargylic alcohols.[36] Reactions of homopropargylic alcohol **69** and aldehyde **70** mediated by anhydrous $FeCl_3$ or $FeBr_3$ led to 4-halo-2-alkyl-5,6-dihydro-2*H*-pyrans **71** in yields ranging from 30 to 98%. Optimization of the experimental conditions established that the best source of halide anion was TMSX in the presence of 7 mol% of the iron catalyst FeX_3 (*Scheme 1.3.4.2*). The cyclization could also be mediated with $InCl_3$ and $InBr_3$, but the times of reaction were much longer and the yields were slightly lower.



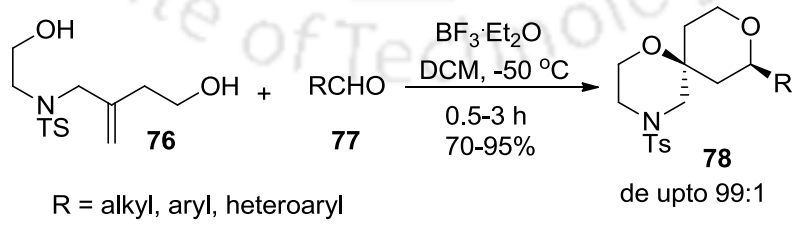
Scheme 1.3.4.2

Yadav *et al*. reported a novel route to access stereoselective bicyclic oxygen heterocycles *via* epoxy-Prins cyclization reaction. The Prins cyclization reaction between styrene oxide **73** and (*E*)-hex-3-ene-1,6-diol **72**, followed by trapping of carbocation with alcohol in intramolecular fashion produced fused bicyclic compounds **74** and **75** (*Scheme 1.3.4.3*).[37]



Scheme 1.3.4.3

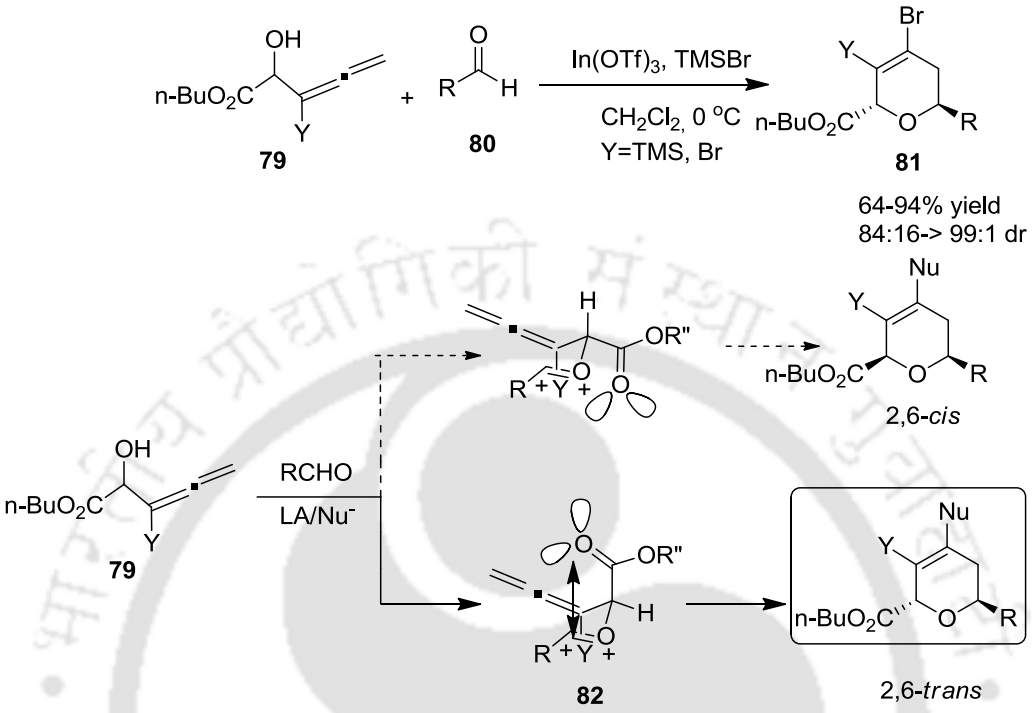
Reddy and his group showed a novel route for the synthesis of spiromorpholinotetrahydropyran derivatives *via* cascade Prins cyclization and intra molecular C-O bond formation. The coupling of aldehydes **77** with *N*-(4-hydroxy-2-methylenebutyl)-*N*-(2-hydroxyethyl)-4-methylbenzene-sulfonamide **76** mediated by boron trifluoride etherate at low temperature produced 1,9-dioxa-4-azaspiro[5.5]undecane derivatives **78** in good yields and high selectivity (*Scheme 1.3.4.4*).[38]



Scheme 1.3.4.4

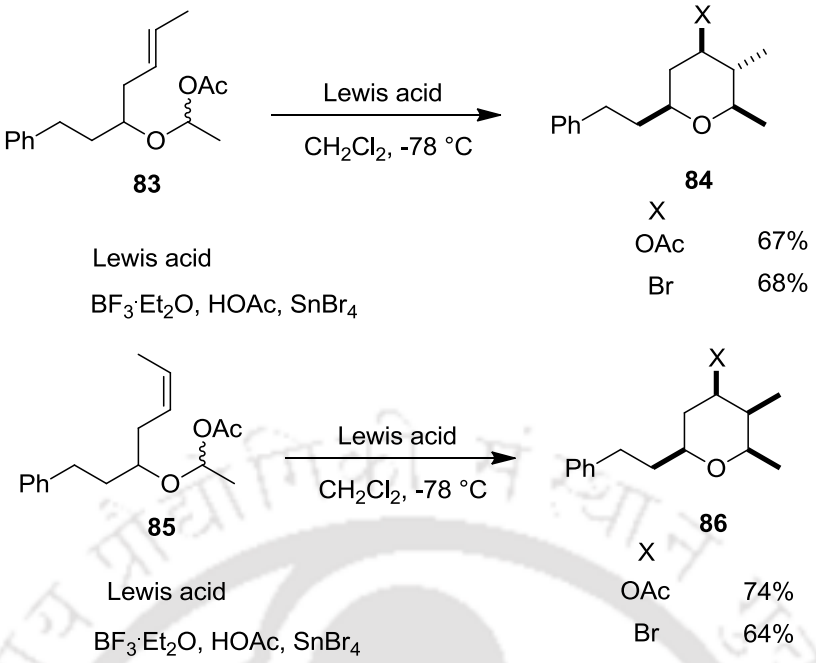
Loh and his group had developed a method that allowed easy access to 2,6-*trans* pyranyl motifs in good yields. Indium triflate catalysed Prins cyclization of carboalkoxyl allenic alcohol **79** and aldehydes **80** in dichloromethane at 0 °C, followed by trapping of the carbocation with Br^- ion of TMSBr produced highly diastereoselective 2,6-*trans* dihydropyrans **81** (*Scheme 1.3.4.5*).[39] The

reason of high trans diastereoselectivity of the reaction can be explained as the formation of a Distorted Chair Transition State **82** where the lone pair electron of the ester group stabilizes oxo-carbenium ion and there is no 1,3- axial interaction.



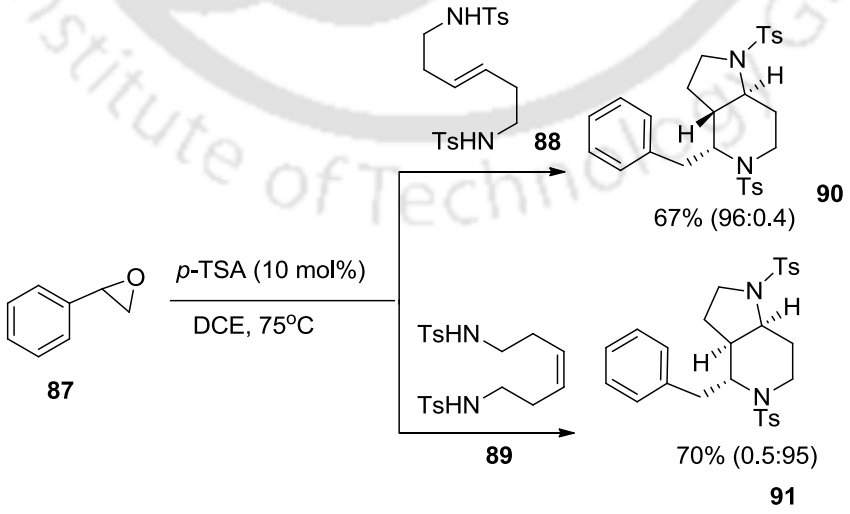
Scheme 1.3.4.5

Rychnovsky and co-workers had reported the synthesis of highly substituted tetrahydropyrans by treatment of α-acetoxy ether with Lewis acid. Here, alkene geometries dictate the product configurations, with *E*-alkenes **83** leading to equatorial substituents **84** and *Z*-alkenes **85** leading to axial substituents **86** (*Scheme 1.3.4.6*).[40]



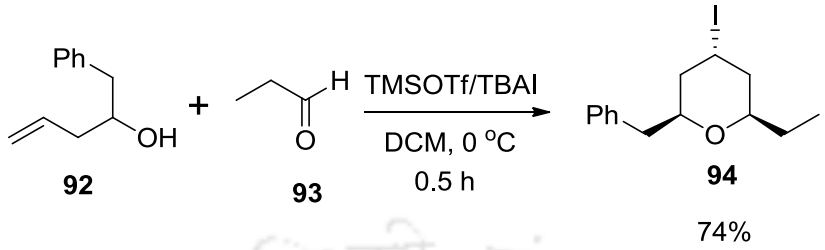
Scheme 1.3.4.6

Yadav and co-workers developed Brønsted acid catalyzed intramolecular aza-Prins cyclization for the synthesis of fused aza-bicyclic systems. Thus, reaction of (*E*)-hex-3-ene-1,6-ditosylamide **88** and styrene oxide **87** in the presence of 10 mol % *p*-TSA in 1,2-dichloroethane at 75 °C afforded the corresponding 1,5-ditosyl-octahydro-1*H*-pyrrolidino[3,2-*c*]pyridines **90** in good yields with high *trans*-selectivity, whereas the reaction of (*Z*)-hex-3-ene-1,6-ditosylamide **89** afforded *cis*-fused octahydro-1*H*-pyrrolidino[3,2-*c*]pyridines **91** predominantly (*Scheme 1.3.4.7*).[41]



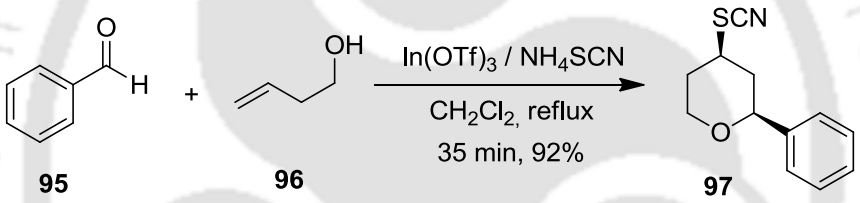
Scheme 1.3.4.7

Saikia and coworkers reported an axial selective Prins cyclization reaction for the synthesis of axial-4-iodotetrahydropyran **94** from simple homoallylic alcohol **92** and aldehyde **93** promoted by TMSOTf and tetrabutylammonium iodide (TBAI) (*Scheme 1.3.4.8*).[42]



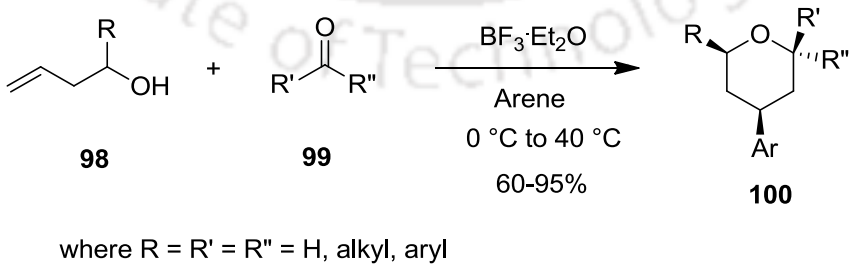
Scheme 1.3.4.8

Jadav *et al.* had reported the synthesis of 4-thiocyanotetrahydropyrans **97** in good yields from the reaction of aldehydes **95**, homoallylic alcohols **96** and ammonium thiocyanate in the presence of 10 mol% $In(OTf)_3$ in refluxing dichloromethane (*Scheme 1.3.4.9*).[43]



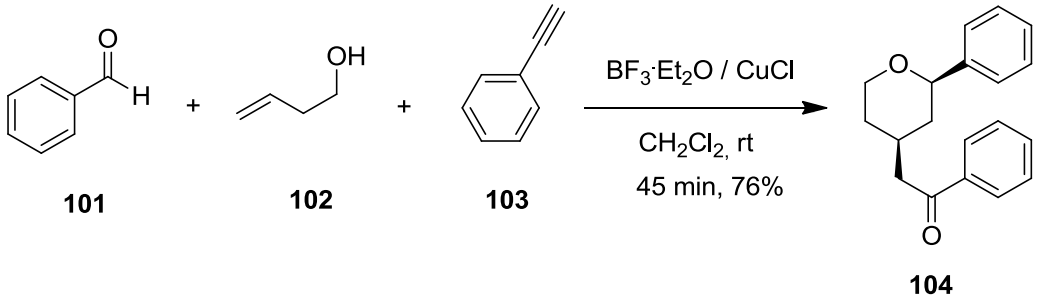
Scheme 1.3.4.9

Saikia and co-workers reported a diastereoselective one-pot, three-component Prins-Friedel-Crafts reaction for the synthesis of 4-aryltetrahydropyran derivatives **100** from the reaction of carbonyl compounds **99** with homoallylic alcohols **98** in the presence of arene promoted by boron trifluoride etherate(*Scheme 1.3.4.10*).[44]



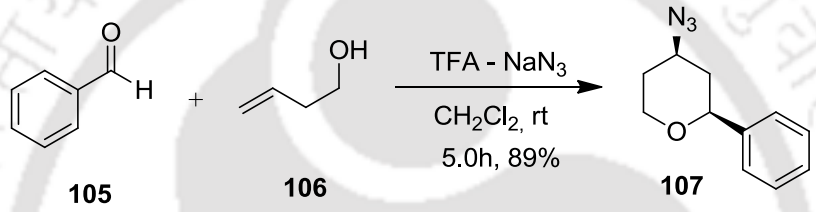
Scheme 1.3.4.10

Aldehyde **101**, homoallylic alcohol 100 and alkyne **103** underwent smooth Prins-type cyclization in the presence of $BF_3{\cdot}Et_2O$ / CuCl (10 mol% each) in dichloromethane under mild reaction conditions to afford 4-phenacyl tetrahydropyran derivatives **104** in good yields (*Scheme 1.3.4.11*).[45]



Scheme 1.3.4.11

A three component coupling of aldehydes **105**, homoallylic alcohols **106** and sodium azide in the presence of trifluoroacetic acid in dichloromethane had been developed to produce 4-azidotetrahydropyran **107** derivatives in high yields with all *cis*-selectivity (*Scheme 1.3.4.12*).[46]



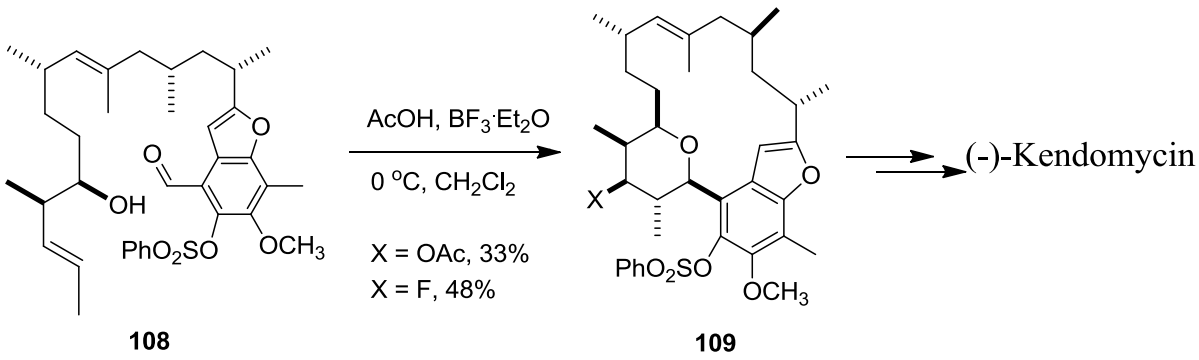
Scheme 1.3.4.12

1.3.5. Applications of Prins cyclization towards natural product synthesis

The Prins cyclization is a potentially powerful method for preparing oxygen heterocycles. A number of research groups have been investigating Prins cyclization reactions towards the synthesis of natural products.

Synthesis of Kendomycin

(–)-Kendomycin is an antitumor macrolide antibiotic isolated from the bacteria *Streptomyces violaceoruber*. It exhibits potent antagonism of the endothelin receptor agonism.[5]

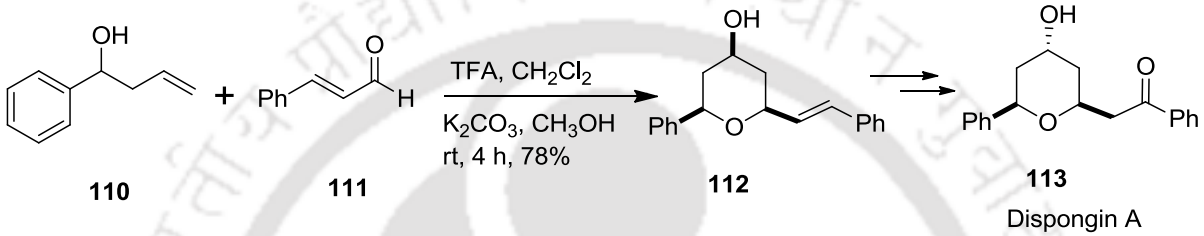


Scheme 1.3.5.1

In an approach towards the formal synthesis of this macrolide **109**, Rychnovsky *et al.* utilized a $BF_3{\cdot}Et_2O$ mediated intramolecular Prins cyclization of **108** containing an electron-rich benzaldehyde and a homoallylic alcohol moiety within the framework (*Scheme 1.3.5.1*).[47] For the electron rich benzaldehyde, the use of acetic acid is necessary to suppress the side reactions.

Synthesis of diospongin A

Dispongin A **113** exhibits antiosteoporotic acitivity. Piva and coworkers developed a concise and efficient method for total synthesis of dispongin A using Prins cyclization and kinetic resolution.[48] It enabled control of the relative configuration of the three stereogenic centres contained in the natural product.



Scheme 1.3.5.2

1.3.6. Intramolecular cyclization from *O*- and *N*- containing tethered molecule

Intramolecular reactions offer distinct advantages over their intermolecular counterparts providing the tethering unit, which connects the reacting functionalities, is neither too long such that the reaction resembles an intermolecular process, nor too short, in which case geometrical constraints can physically prevent the reaction. When these conditions on the tether are satisfied, however, the proximity of the reacting partners, combined with a reduction in the degrees of freedom in the system, render the intramolecular reaction more entropically and kinetically favourable. This can result in a more stereo-, regio- and chemoselective process, which is often reflected in an increased yield of the desired product.

1.3.7. Baldwin's rules

The presence of cyclic structures in the basic framework of many complex and biologically active molecules has attracted the attention of many chemists for their formation in organic synthesis. A series of guidelines that describe the propensity of various systems to participate in ring forming reactions was put forth by J. E. Baldwin in 1976. This set of guidelines, which describe the relative ease of ring formations, has become known as Baldwin's rules of ring closure and has proved a useful tool in evaluating the feasibility of ring forming reactions. He suggested that the rules are applicable to reactive intermediates.

Baldwin described his rules in terms of three features of the reaction: (1) the ring size being formed (indicated through a numerical prefix), (2) the hybridized state of the carbon atom

undergoing the ring closing reaction (sp= digonal, sp^2= trigonal, and sp^3 = tetrahedral), and (3) the nature of the breaking bond (exo- the breaking bond it is external to the newly formed ring, and endo - the breaking bond is within newly formed ring.).[49] Examples of these formalizations are shown in *Figure 1.3.7.1*. The attacking species could be a carbanion, a carbonium ion or a free radical.

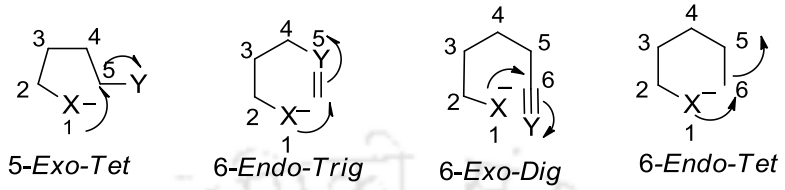
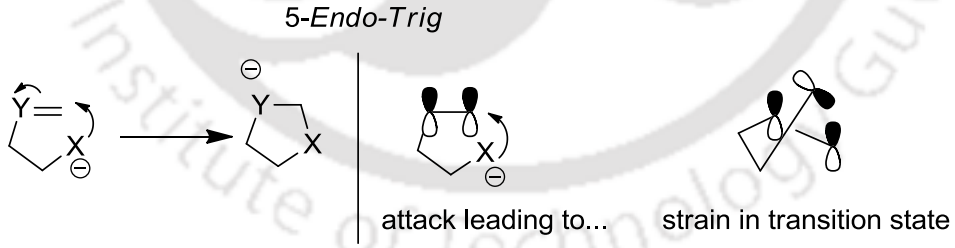


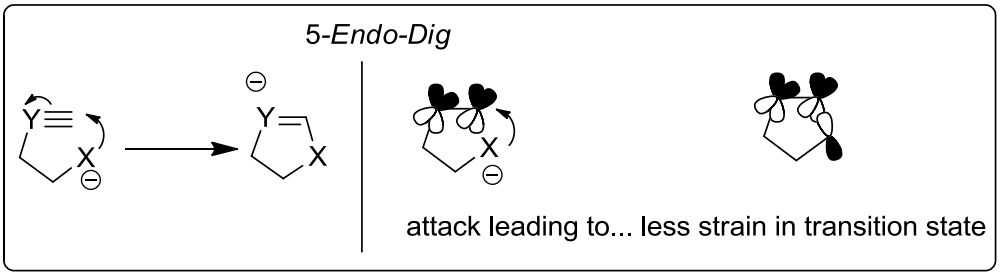
Figure 1.3.7.1

Baldwin's rules describe the relative rates of ring formation involving 3-7 membered rings as either favorable or unfavourable. These terms are used in a relative sense. A reaction forms a favoured product faster than a disfavoured one. However, a disfavoured product may be observed if there is no any alternate pathway. Since these rules are for rates, they reflect the free energy of activation at the transition state, $\Delta G^{\acute{a}}$, which depends on the number of atoms in the forming ring, and on the geometry where the electrophile and nucleophile must interact to achieve maximum orbital overlap and subsequent bonding. The reaction is favourable if the two nuclei of the tethered chain are aligned with the required orientation i.e. minimum energy transition state.

For example, 5-*endo-trig* is unfavorable whereas 5-*endo-dig* is favorable.[50]



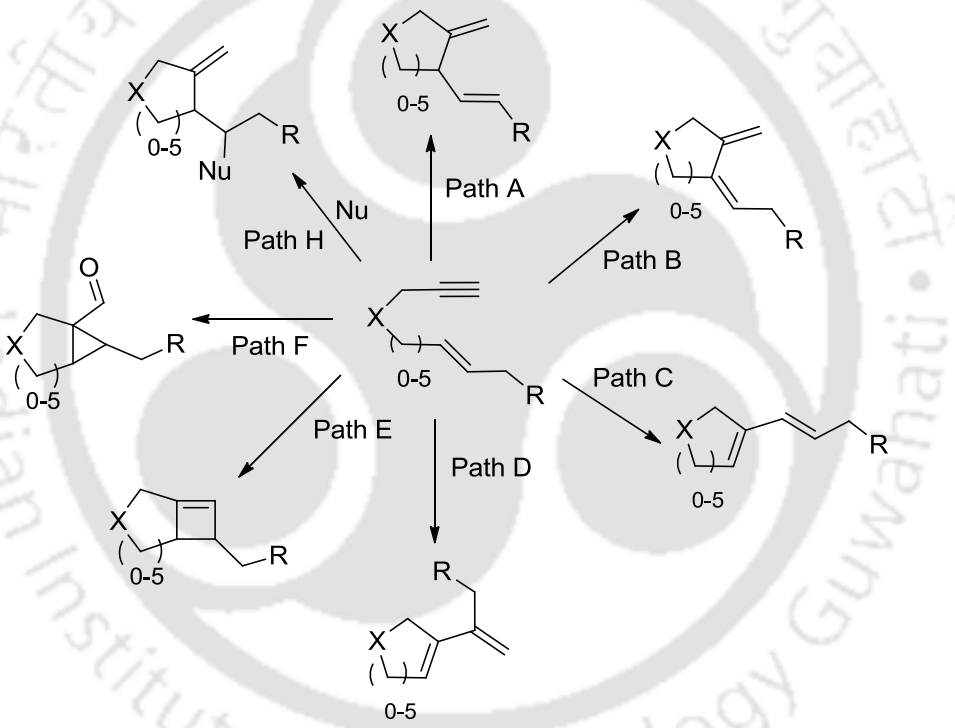
Scheme 1.3.7.1*:* Extreme transition state bond-angle distortion leads to disfavoured 5-endo-trig



Scheme 1.3.7.2: Favored transition-state geometry for effective orbital overlap. Nucleophile can approach the acetylenic orbitals in a nearly planar fashion

The carbon-carbon triple bond of alkynes is one of the basic groups in organic synthesis because of their rigidity, electronic properties, and versatile reactivity.[51] In the past decades, acetylene chemistry has experienced a renaissance, due to not only its occurrence in molecules in the frontiers of organic chemistry such as biochemistry or material sciences, but also as building blocks or versatile intermediates for the synthesis of a vast array of chemicals.[52]

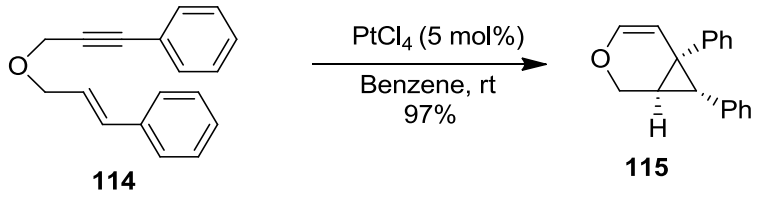
Metal-catalyzed reactions contribute to the major part of research in this domain of research. This has led to the development of numerous transition metal catalysts which can perform the cyclization reaction easily by undergoing a cascade of events with the change in oxidation state of metal. Metal-catalyzed cycloisomerizations have been employed for the preparation of oxygen and nitrogen heterocycles of varying ring sizes.



Scheme 1.3.7.3: Metal catalyzed cycloisomerizations and related reactions

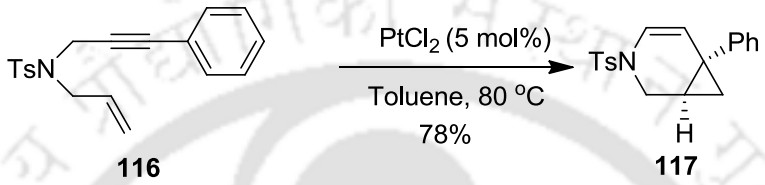
Among variety of transformations involved in the preparation of pyrans, piperidines and their derivatives, metal-catalyzed 1,*n*-enyne rearrangements have been studied extensively. Metal-catalyzed 1,*n*-enyne rearrangements are atom economical, simple, and safe and can be performed even on large scale. Transition metal catalysts like Cu,[53] Pd,[54] Pt[55] and Au[56] are the prominent among them.

In 1995, Blum *et al.* reported the synthesis of cyclo-propane annulated dihydropyrans from allyl propargyl ethers in the presence of $PtCl_4$ (*Scheme 1.3.7.4*).[57]



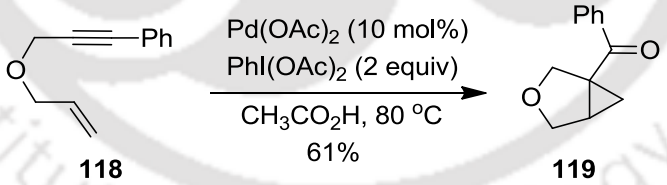
***Scheme 1.3.7.4*:** Synthesis of cyclo-propane annulated dihydropyrans

Further expanding the scope of this methodology, Furstner *et al.* reported the synthesis of nitrogen analogues using $PtCl_2$ (*Scheme 1.3.7.5*).[58]



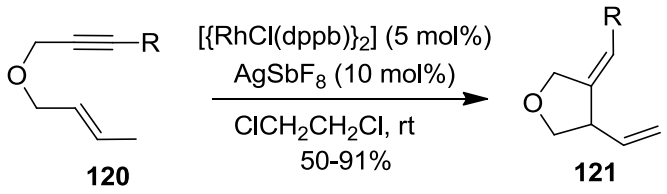
***Scheme 1.3.7.5*:** Synthesis of piperidine derivative using $PtCl_2$

The research groups of Tse[59] and Sanford[60] independently reported the first examples of oxidative cyclization of 1,6-enynes, which allowed the formation of cyclopropylketones of type **119**. Enyne **118** is treated with the oxidating agent (diacetoxyiodo)benzene in the presence of $Pd(OAc)_2$ in acetic acid at 80 ^oC to give **119** in modest yields. The reaction scope of the transformation is large, as a wide range of alkyl and aryl substituents as well as ynone and ynamide functionnalities are tolerated.



Scheme 1.3.7.6

The research group of Zhang described a rhodium-catalyzed Alder–ene-type reaction. The use of [{Rh(dppb)Cl}$_2$](dppb : 1,4-*bis*-(diphenylphosphanyl)-butane) in combination with a silver salt in dichloroethane promoted the cycloisomerization of several ether-linked 1,6- enynes **120.**[61]

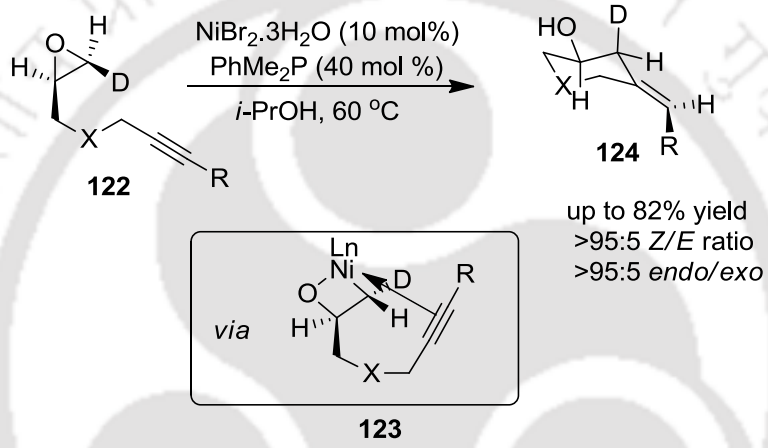


R = Ph, *p*-Me-C_6H_4, *p*-Cl-C_6H_4, *p*-CF_3-C_6H_4, CH_2Ph, CO_2Me, Me

Scheme 1.3.7.7

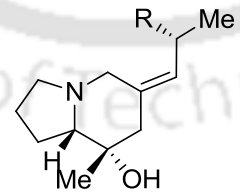
Reductive coupling of alkyne and epoxide using metal-catalyst has been well explored for the construction of cyclic ethers and its nitrogen analogues starting from an *O*- or *N*-tethered compounds containing epoxide and alkyne group (π-system). Some reports are given below:

1) Jamison *et al.* had developed a methodology for the synthesis of homoallylic alcohol *via* Ni-catalysed reductive coupling of alkynes and epoxides. In this report, air-stable and inexpensive Ni(II)salts are used as precatalysts (eg. $NiBr_2.3H_2O$) and *i*-PrOH as reducing agents in the presence of 40 mol % Ph_2Me. Deuterium labeling experiments showed that oxidative addition of an epoxide C-O bond occurred with an inversion of configuration and then stereospecific cis-addition to the alkyne provided the desired tetrahydropran product as a single regioisomer.[62]



Scheme 1.3.7.8

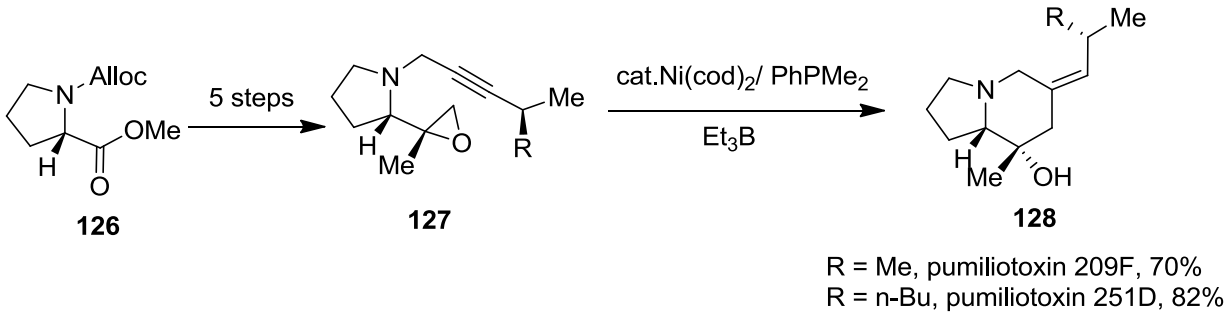
2) The pumiliotoxins were first isolated in 1967 from the *Dendrobates pumilio* frogs in South America.[63] These are a subclass of indolizidine alkaloids isolated from the skin secretion of neotropical frogs.[64] It shows many biological activities.



R = Me, pumiliotoxin 209F, 70%
R = n-Bu, pumiliotoxin 251D, 82%

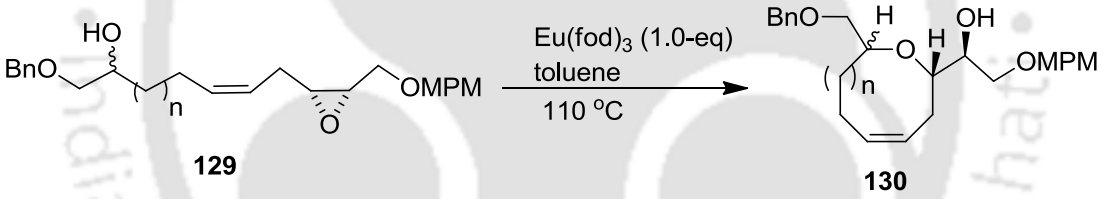
125

In an approach towards the toal synthesis of Pumiliotoxins **125** (**209F** and **251D)**, Jamison *et al.* utilized Ni-catalysed reductive coupling reaction of alkyne-epoxide.[65] Thus, intramolecular cyclization containing alkyne-epoxide tethered molecule plays a vital role in natural product synthesis.



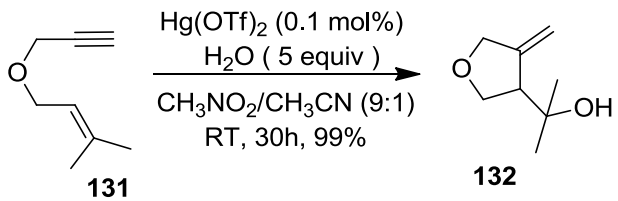
Scheme 1.3.7.9

Suzuki *et al.* developed a highly efficient and versatile methodology for the stereospecific synthesis of α,ω-*cis*- and α,ω-*trans*-disubstituted eight- and nine-membered cyclic ethers through Lewis acid mediated cyclization of hydroxy epoxides. For example, the model compound **129** having a *cis*-epoxide group when refluxed with a stoichiometric amount of $Eu(fod)_3$ at 110 ^oC in toluene, the corresponding eight membered cyclic ether **130** possessing alkyl substituents at the *α*-and *ω*-positions with *cis*-orientation was obtained in 97% yield, arising from cyclization *via* the selective S_N2 process and *exo* mode. Similarly, cyclization of the trans isomer of **129** gave the α,ω-*trans*-derivative in 76% yield.[66]



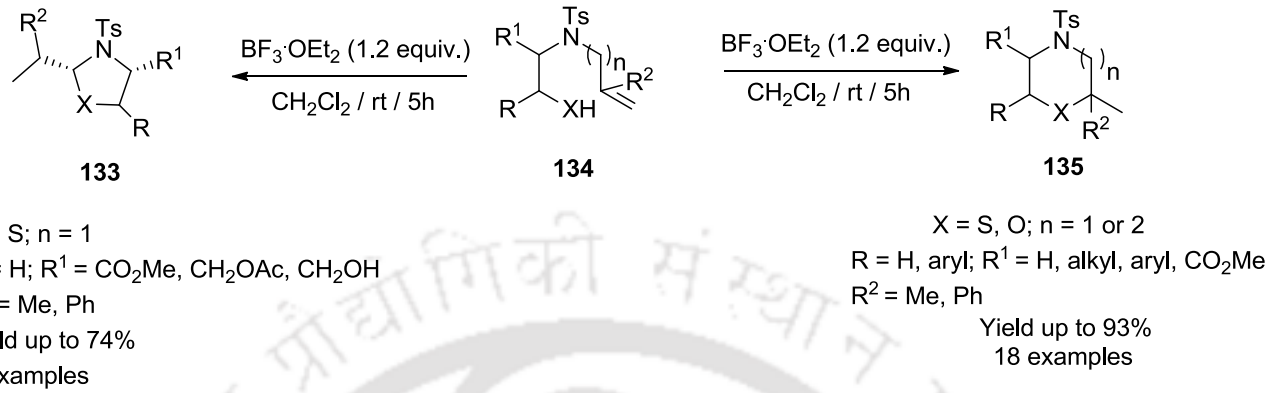
Scheme 1.3.7.10

Nishizawa *et al.* developed a highly active strategy for mercuric triflate catalyzed hydroxylative carbocyclization of 1,6-enynes **131** to construct five-membered ring products **132** in good to excellent yields. Enyne was converted into alcohol at room temperature through mercuration of a terminal alkyne, carbocyclization, hydration, and protodemercuration that reproduced the catalyst, $Hg(OTf)_2$. The catalyst was used in quantities as low as 0.1 mol %.[67]



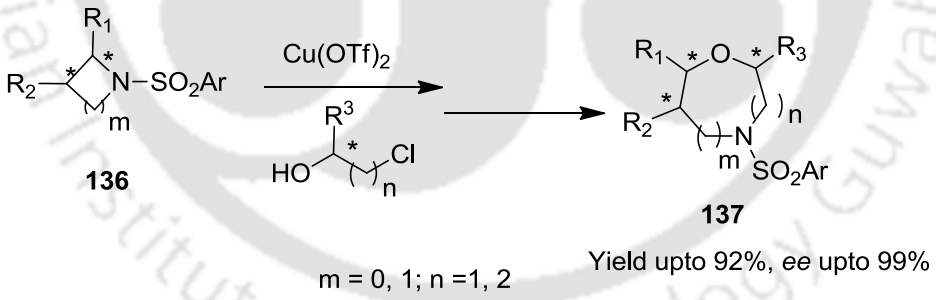
Scheme 1.3.7.11

Saikia and coworkers reported intramolecular hydroalkoxylation/hydrothioalkoxylation of nitrogen-tethered alkenes and alcohols/thiols mediated by boron trifluoride etherate for the preparation of five-,six-, and seven-Membered 1,3- and 1,4- heterocyclic Compounds.[68]



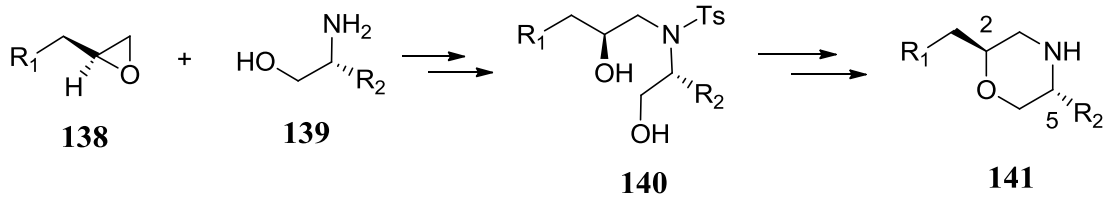
Scheme 1.3.7.12

Ghorai and his coworkers had developed a simple and practical protocol for the synthesis of nonracemic 2-substituted morpholines, 2,3-disubstituted morpholines, enantiopure 2,6-disubstituted morpholines, homomorpholines, and higher homologues using $Cu(OTf)_2$ as a catalyst. The reaction proceeds *via* a S_N2-type ring opening of activated aziridines and azetidines by suitable halogenated alcohols in the presence of Lewis acid followed by base-mediated intramolecular ring closure of the resulting haloalkoxy amine (*Scheme 1.3.7.13*).[69]



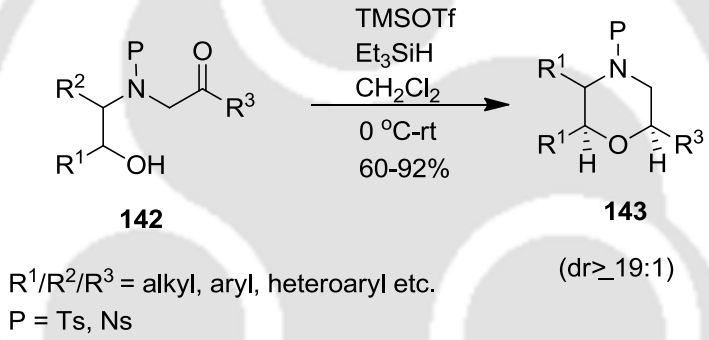
Scheme 1.3.7.13

Myers and co-workers reported the synthesis of enantio- and diastereoselective *trans*-2,5-disubstituted morpholine derivatives **141** from enantiopure epoxides **138** with amino alcohols **139** *via* the regioselective hydroxyl activation-ring closure of the resulting amino diol adducts **140** (*Scheme 1.3.7.14*).[70]



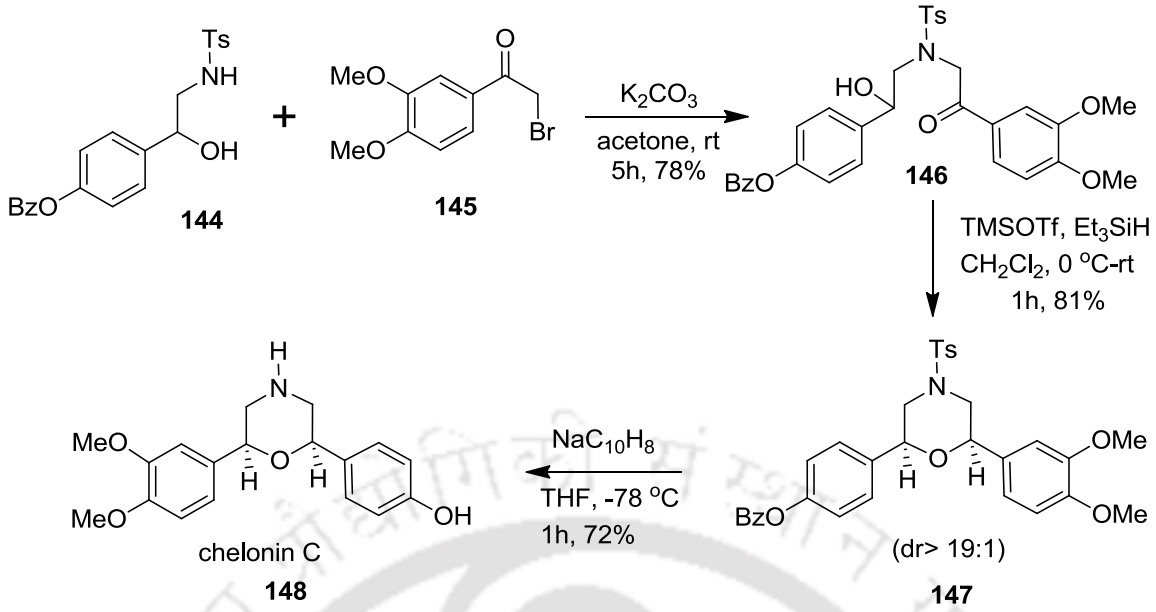
Scheme 1.3.7.14

A versatile approach for the stereoselective synthesis of C-substituted morpholine derivatives using intramolecular reductive etherification reaction of keto alcohol **142** with a Lewis acid has been reported by Gharpure (*Scheme 1.3.7.15*). The reaction of enantiomerically enriched amino alcohols with α-bromo ketones using potassium carbonate as a base in acetone generates the keto alcohol, which, in presence of TMSOTf and Et_3SiH was reduced in a highly stereoselective fashion to furnish diversely substituted morpholines **143** in good yields and excellent diastereoselectivities.[71]



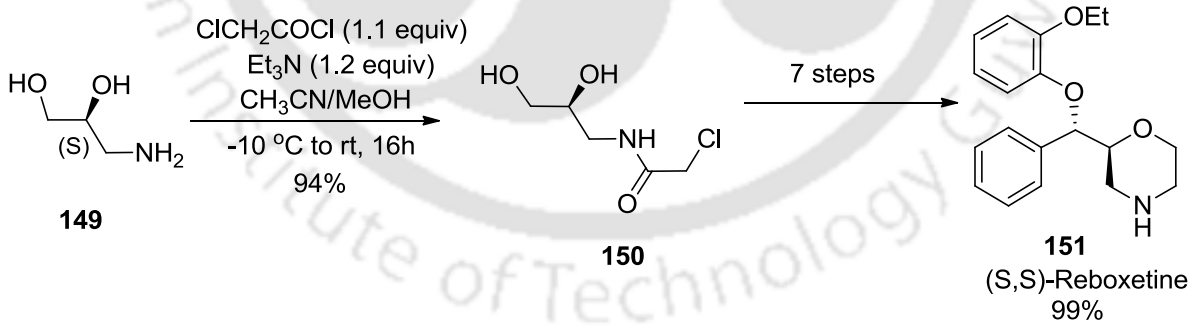
Scheme 1.3.7.15

The protocol was further extended to the first stereoselective total synthesis of (±)-chelonin C. Chelonin C is a marine natural product. It was isolated from the marine sponge *Chelonaplysilla* sp.[72] and belongs to the family of 2,6-disubstituted morpholines. This family of alkaloids exhibits antimicrobial activity against *Bacillus subtilis* and in vivo anti-inflammatory activity.



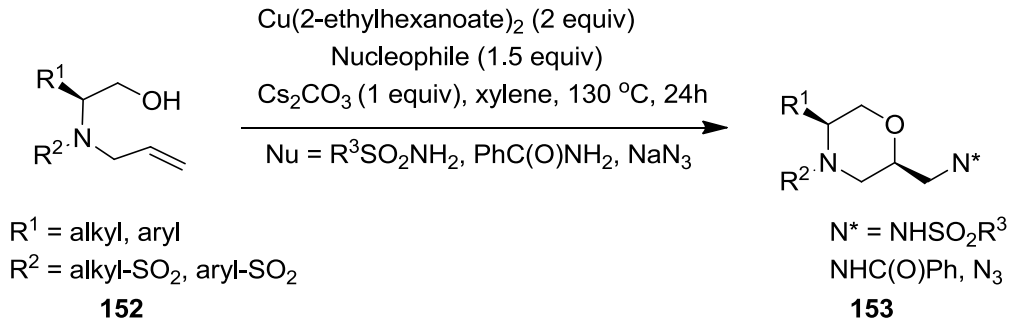
Scheme 1.3.7.16

Reboxetine is a potent selective norepinephrine reuptake inhibitor (NRI) and widely studied for its pharmacological properties.[73] Commercially sold as an antidepressant, reboxetine has comparable efficacy to that of imipramine, desipramine, and fluoxetine and has an improved side-effect profile.[74] Tamagnan and his coworkers developed a methodology which describes the stereospecific synthesis of (S,S)-reboxetine **151** *via* a new and particularly effective preparation of (*S*)-2-(hydroxymethyl)morpholine. The synthesis proceeded in 30% overall yield and 99% ee in eight linear steps starting from commercially available (*S*)-3-amino-1,2-propanediol **149**.[75]



Scheme 1.3.7.17

Chemler *et al.* reported the formation of 2-amino methyl functionalized morpholines mediated by copper(II) 2-ethylhexanoate promoted alkene oxyamination reaction.[76]



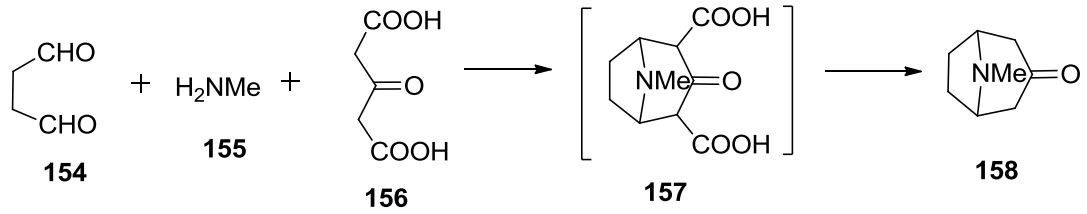
Scheme 1.3.7.18

1.3.8. Cascade reaction

A cascade reaction, also known as a domino reaction or tandem reaction, is a consecutive series of intramolecular organic reactions which often proceed *via* highly reactive intermediates. In cascade reactions, isolation of intermediates is not required, as each reaction composing the sequence occurs spontaneously. These reactions involve careful design of a multistep reaction in a one-pot sequence in which the first step creates the functionality to trigger the second reaction and so on, making this approach economical and environmentally friendly.

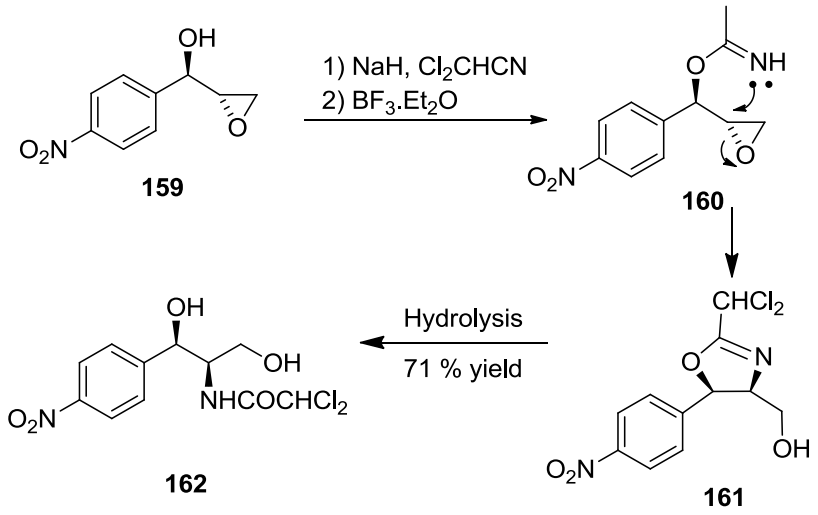
Based on the mechanism of the steps involved, K. C. Nicolaou labels the cascades as nucleophilic/electrophilic, radical, pericyclic or transition-metal-catalyzed.[77]

The history of cascade reaction began with the first report by Robert Robinson in 1917 for the synthesis of tropinone **158**. The reaction proceeds through intramolecular double Mannich reaction and the reactants used in its preparation are succinaldehyde **154** , methylamine **155** and acetonedicarboxylic acid **156** (or even acetone).[78]



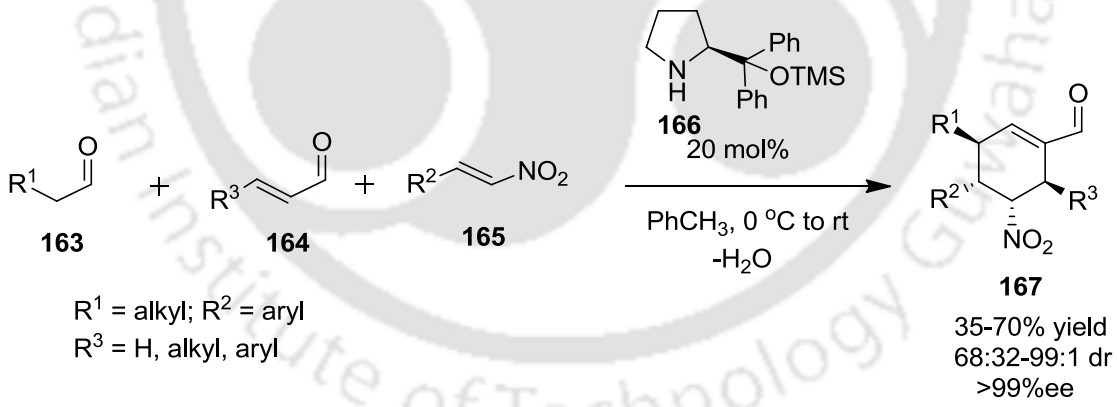
Scheme 1.3.8.1

In 2004, Rao *et al.* reported a short enantioselective synthesis of the broad-spectrum antibiotic (–)-chloramphenicol. Herein, the chiral epoxy-alcohol **159** was first treated with dichloroacetonitrile in the presence of NaH. The resulting intermediate **160** then underwent a $BF_3{\cdot}Et_2O$-mediated cascade reaction. Intramolecular opening of the epoxide ring yielded intermediate **161**, which, after an *in situ* hydrolysis facilitated by excess $BF_3{\cdot}Et_2O$, afforded (–)-chloramphenicol **162** in 71% overall yield.[79]



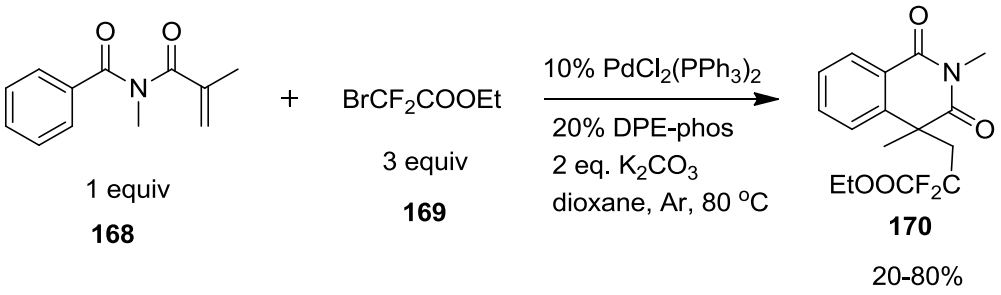
Scheme 1.3.8.2: Synthesis of (–)-chloramphenicol via a nucleophilic cascade

Raabe *et al.* in 2006 reported organocatalytic cascade in which linear aldehydes **163**, nitroalkenes **165** and *α,β*-unsaturated aldehydes **164** were condensed together organocatalytically to afford *tetra*-substituted cyclohexane carbaldehydes **167** with moderate to excellent diastereoselectivity and complete enantiocontrol (*Scheme 1.3.8.3*). The transformation is mediated by the readily available proline-derived organocatalyst **166.**[80]



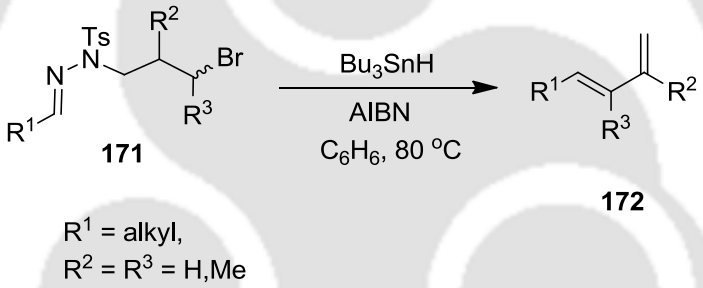
***Scheme 1.3.8.3*:** Asymmetric synthesis of *tetra*-substituted cyclohexane carbaldehydes *via* a triple organocatalytic cascade reaction

Xia and his group had developed an efficient and mild reaction conditions for the synthesis of difluoromethylated isoquinoline-1,3-dione **170** *via* Pd(0)-catalyzed radical cascade difluoroalkylation/cyclization of acrylamide **168** with ethyl difluorobromoacetate **169**. In this protocol Pd-catalyzed single electron transfer processes was introduced into radical addition/cyclization of N-alkyl-*N*-methacryloyl benzamides, leading to fluoroalkylated isoquinoline-1,3-diones in a good to moderate yields.[81]



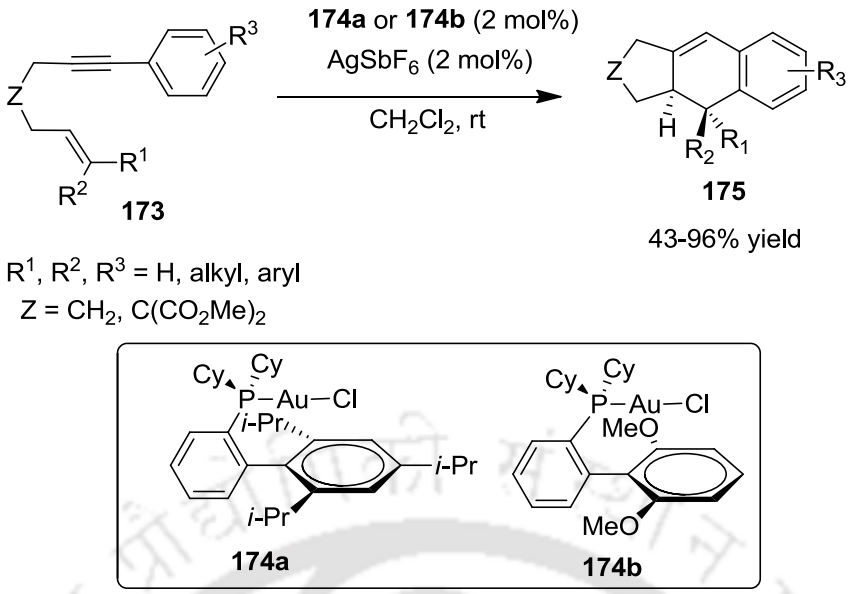
***Scheme 1.3.8.4*:** Pd(0)-catalyzed radical reactions.

Sammis and his group had developed a highly efficient and diastereoselective synthesis of *E*-dienes through radical cyclization of bromoallyl hydrazones. This reaction proceeded *via* one-pot condensation/radical cyclization/cycloreversion cascade starting from aldehydes in high yields (>75%) and high diastereoselectivities (>95:5). This methodology is a new and direct method for the conversion of hydrazines into dienes and also the first example of forming dienes from alkyl hydrazones.[82]



Scheme 1.3.8.5: Formation of diene from bromoallyl hydrazones

Echavarren and his coworkers had established a methodology of a transition-metal-catalyzed cascade for the formal intramolecular [4+2] cycloaddition of 1,6-enynes **171** mediated by gold catalyst. 1,6-enynes underwent intramolecular cyclization under mild conditions in the presence of Au(I) complexes **172a**–**b** to yield the tricyclic products **173** in moderate to excellent yields.[83]



Scheme 1.3.8.6

1.4. References

1. Eicher, T.; Hauptmann, S. In *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications, 2nd edn*, 2003; Wiley-VCH Verlag GmbH, Weinheim.
2. Joule, J. A. and Mills, K. *Heterocyclic Chemistry*, 4th edn., Blackwell Science, Oxford, 2000. (b) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*, Pergamon Press, Oxford, 1985.
3. (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996. (b) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (c) Class, Y. J.; DeShong, P. *Chem. Rev.* **1995**, *95*, 1843. (d) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. (e) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670. (f) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485. (g) Bahnck, K. B.; Rychnovsky, S. D. *Chem. Commun.* **2006**, 2388. (h) Wickel, S. M.; Citron, C. A.; Dickschat, J. S. *Eur. J. Org. Chem.* **2013**, *14*, 2906.
4. (a) Connor, D. T.; Greenough, R. C.; von Strandtmann, M. *J. Org.Chem.* **1977**, *42*, 3664. (b) Connor, D. T.; von Strandtmann, M. *J. Org.Chem.* **1978**, *43*, 4606.
5. (a) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529. (b) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2008**, *10*, 3813.
6. Raghavan, S.; Samanta, P. K. *Org. Lett.* **2012**, *14*, 2346.
7. (a) Kumaraswamy, G.; Ramakrishna, G.; Naresh, P.; Jagadeesh B.; Sridhar, B. *J. Org. Chem.* **2009**, *74*, 8468. (b) Reddy, C. R.; Reddy G. B.; and Srikanth, B. *Tetrahedron Asymm.* **2011**, *22*, 1725.

8. (a) Paterson, I.; Menche, D.; Håkansson, A. E.; Longstaff, A.; Wong, D.; Barasoain, I.; Buey, R. M. and Díaz, J. F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2243. (b) Gollner, A.; Altmann, K.-H.; Gertsch, J. and Mulzer, J. *Tetrahedron Lett.* **2009**, *50*, 5790. (c) Trost, B. M.; Amans, D.; Seganish, W. M. and Chung, C. K. *J. Am. Chem. Soc.* **2009**, *131*, 17087.
9. (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166. Previous reports in this series. (b) Uchida, R.; Imasato, R.; Shiomi, K.; Tomoda, H.; Omura, S. *Org. Lett.* **2005**, *7*, 5701. (c) Barluenga, S.; Simonsen, S.; Zhao, Q.; Han, Q.; Hermann, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 713. (d) Neelamkavil, S. F.; Boyle, C. D.; Chackalamannil, S.; Greenlee, W. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4563.
10. For details see http://www.drugs.com/top200_2009.html
11. (a) Howard, N.; Abell, C.; Blakemore, W.; Chessari, G.; Congreve, M.; Howard, S.; Jhoti, H.; Murray, C. W.; Seavers, L. C. A.; van Montfort, R. L. M. *J. Med. Chem.* **2006**, *49*, 1346. (b) Wright, J. L.; Gregory, T. F.; Kesten, S. R.; Boxer, P. A.; Serpa, K. A.; Meltzer, L. T.; Wise, L. D. *J. Med. Chem.* **2000**, *43*, 3408.
12. Vetter, J. *Food Chem. Toxicol.* **2004**, *42*, 1373.
13. (a) Tanret, C. *Compt. Rend.* **1878**, *86*, 1270. (b) Tanret, C. *Compt. Rend.* **1880**, *90*, 695.
14. (a) Bourrinet, P.; Quevauviller, A. *Compt. Rend. Soc. Biol.* **1968**, *162*, 1138. (b) Ratle, G.; Monseur, X.; Das, B. C.; Yassi, J.; Khuong-Huu, Q.; Goutarel, R. *Bull. Soc. Chim. Fr.* **1966**, 2945. (c) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 425. (d) Khuong-**Huu**, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 443.
15. For a review see: (a) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641. (b) Audouze, K.; Nielson, E. Ø.; Peters, D. *J. Med. Chem.* **2004**, *47*, 3089. (c) Sharma, G.; Park, J. Y.; Park, M. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3188. (d) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 8333. (e) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 8337.
16. For recent examples see: (a) Breuning, M.; Winnacker, M.; Steiner, M. *Eur. J. Org. Chem.* **2007**, 2100. (b) D'hooghe, M.; Vanlangendonck, T.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 4678. (c) Pedrosa, R.; Andrés, C.; Mendiguchía, P.; Nieto, J. *J. Org. Chem.* **2006**, *71*, 8854. (d) Wilkinson, M. C. *Tetrahedron Lett.* **2005**, 46, 4773. (e) Lanman, B. A.; Myers, A. G. *Org. Lett.* **2004**, *6*, 1045.
17. Al-Ghorbani, M.; Begum, B.; Zabiulla, A.; Mamatha, S.V.; Khanum, S. A. *J. Chem. Pharm. Res.* **2015**, *7*, 281.
18. a) Audouze, K.; Nielsen, E. Ø.; Peters, D. *J. Med. Chem.* **2004**, *47*, 3089. b) Sharma, G.; Park, J. Y.; Park, M. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3188.

19. a) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 8333. b) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 8337.
20. a) Wittung, P.; Nielsen, P. E.; Buchardt, O. Egholm, M.; Nordén B. *Nature* **1994**, *368*, 561. b) Nelson, K. E., Levy, M.; Miller, S. L. *Proc. Natl. Acad. Sci.* USA **2000**, *97*, 3868.
21. Burland, P. A.; Osborn, H. M. I.; Turkson, A.; *Bioorg. Med. Chem.* **2011**, *19*, 5679.
22. Shankaran, K.; Donnelly, K. L.; Shah, S. K.; Caldwell, C. G.; Chen, P.; Hagmann, W. K.; MacCoss, M.; Humes, J. L.; Pacholok, S. G.; Kelly, T. M.; Grant, S. K.; Wong, K. K.; *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5907.
23. (a) Moloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597. (b) Lin, Y. L.; Shen, C.-C.; Huang, Y.-J.; Chang, Y.-Y. *J. Nat. Prod.* **2005**, *68*, 381. (c) Wang, Y.; Shang, X.; Wang, S.; Mo, S.; Li, S.; Yang, Y.; Ye, F.; Shi, J.; He, L. *J. Nat. Prod.* **2007**, *70*, 296. (d) Trisuwan, K.; Khamyhong, N.; Rukachaisirikul, V.; Phongpaichit, S.; Preedanon, S.; Sakayaroj, J. *J. Nat. Prod.* **2010**, *73*, 1507. (e) Gao, J.-M.; Yang, S.-X.; Qin, J. C. *Chem. Rev.* **2013**, *113*, 4755. (e) Brown, C. W.; Liu, S.; Klucik, j.; Berlin, K. D.; Brennan, P. J.; Kaur, D.; Benbrook, D. M. *J. Med. Chem.* **2004**, *47*, 1008.
24. (a) Sperry, J.; Bachu, P.; Brimble, M. A. *Nat. Prod. Rep.* **2008**, *25*, 376. (b) Claessens, S.; Verniest, G.; Jacobs, J.; Van Hende, E.; Habonimana, P.; Van Nguyen, T.; Van Puyvelde, L.; De Kimpe, N. *Synlett* **2007**, 829. (c) Jacobs, J.; Claessens, S.; De Kimpe, N. *Tetrahedron* **2008**, *64*, 412. (d) Lee, H.; Hong, S.-S.; Kim, Y.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 933; (e) Brimble, M. A.; Duncalf, L. J.; Nairn, M. R. *Nat. Prod. Rep.* **1999**, *16*, 267. (f) Larghi, E. L.; Kaufman, T. S. Eur. *J. Org. Chem.* **2011**, 5195.
25. Tatong, M. D. K.; Talontsi, F. M.; Rahim, H. M. D. A.; Islam, M. T.; Oswald, R. B.; Laatsch, H. *Tetrahedron Lett.* **2014**, *55*, 4057.
26. Asai, T.; Yamamoto, T.; Chung, Y.-M.; Chang, F.-R.; Wu, Y.-C.; Yamashita, K.; Oshima, Y. *Tetrahedron Lett.* **2012**, *53*, 277.
27. Heapy, A. M.; Patterson, A. V.; Smaill, J. B.; Jamieson, S. M. F.; Guise, C. P.; Sperry, J.; Hume, P. A.; Rathwell, K.; Brimble, M. A. *Bioorg. Med. Chem.* **2013**, *21*, 7971.
28. Thi, T. A. D.; Thi, T. H. V.; Phuong, H. T.; Nguyen, T. H.; The, C. P.; Duc, C. V.; Depetter, Y.; Nguyen, T. V.; D'hooghe, M. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3355.
29. (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. (b) Nicolaou, K. C.; Hwang, C. K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136.
30. (a) Nicolaou, K. C.; Hwang, C. K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136. (b) Nicolaou, K. C. ; Hwang, C. K.; Duggan, M. E. ; Nugiel, D. A.; Abe, Y; Bal Reddy, K; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T.; Theodorakis, E. A. *J. Am. Chem. Soc*. **1995**, *117*, 10227.

31. (a) Prins, H. J. *Proc. Acad. Sci. Amsterdam*, **1919**, *22*, 51. (b) Prins, H. J. *Chem. Weekbl*. **1919**, *16*, 1510.
32. Hanschke, E. *Chem. Ber.* **1955**, *88*, 1053.
33. (a) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661. (b) Arundale, E.; Mikesa, L. A. *Chem. Rev.*, **1952**, *51*, 505.
34. Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960.
35. Olier, C.; Gastaldi, S.; Gil, G.; Bertrand, M. P. *Tetrahedron Lett.* **2007**, *48*, 7801.
36. Miranda, P. O.; Carballo, R. M.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2009**, *11*, 357.
37. Yadav, J. S.; Borkar, P.; Chakravarthy, P. P.; Reddy, B. V. S.; Sarma, A. V. S.; Basha, S. J.; Sridhar, B.; Grée, B. *J. Org. Chem.* **2010**, *75*, 2081.
38. Reddy, B. V. S.; Medaboina, D.; Sridhar, B.; Singarapu, K. K. *J. Org. Chem.* **2014**, *79*, 2289.
39. Hu, X. H.; Liu, F.; Loh, T. P. *Org. Lett.* **2009**, *11*, 1741.
40. Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679.
41. (a) Yadav, J. S.; Borkar, P.; Chakravarthy, P. P.; Reddy, B. V. S.; Sarma, A. V. S.; Basha, S. J.; Sridhar, B.; Gree, R. *J. Org. Chem.* **2010**, *75*, 2081. (b) Reddy, B. V. S.; Borkar, P.; Chakravarthy, P. P.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 3412.
42. Saikia, A. K.; Bondalapati, S.; Indukuri, K.; Gogoi, P. *Chem. Lett*. **2011**, 1176.
43. Yadav, J. S.; Reddy, B. V. S.; Maity, T.; Kumar, G. G. K. S. N. *Tetrahedron Lett.* **2007**, *48*, 8874.
44. Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *J. Org. Chem.* **2009**, *74*, 2605.
45. Yadav, J. S.; Reddy, B. V. S.; Reddy, Y. J.; Reddy, Bh. P.; Reddy, P. A. *Tetrahedron Lett.* **2010**, *51*, 1236.
46. Yadav, J. S.; Reddy, B. V. S.; Maity, T.; Kumar, G. G. K. S. N. *Tetrahedron Lett.* **2007**, *48*, 7155.
47. Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **2008,** *130***,** 13177.
48. Hiebel, M. A.; Pelotiera, B.; Piva, O. *Tetrahedron* **2007**, *63*, 7874.
49. (a) Baldwin, J. E.; *J. Chem. Soc., Chem. Commun.* **1976**, 18, 734-736. (b) Baldwin, J. E.; *J. Org. Chem.* **1977**, *42*, 3846.
50. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry* Part A: Structures and Mechanisms, 3rd ed.; Plenum Press: New York, **1990**; pp. 165.
51. Brand, J.P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165.
52. Chinchilla, R.; Nájera, C. *Chem. Rev.* **2013**, *114*, 1783.
53. Gao, P.; Yan, X.-B.; Tao, T.; Yang, F.; He, T.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. *Chem.-Eur. J.* **2013**, *19*, 14420.

54. (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc*. **1988**, *110*, 1636. (b) Mikami, K.; Hatano, M. *Proc. Natl. Acad. Sci. U. S. A.*, **2004**, *101*, 5767. (c) Jiang, M.; Jiang, T. Bäckvall, J.-E. *Org. Lett*. **2012**, *14*, 3538.
55. (a) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901. (b) Nevado, C.; Ferrer, C.; Echavarren, A. M. *Org. Lett*. **2004**, *6*, 3191.
56. (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev*. **2008**, *108*, 3326. (b) Michelet, V; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268. (c) Lee, S. L.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K. *J. Org. Chem*. **2006**, *71*, 9366.
57. Blum, J.; Beer-Krafts, H.; Badrieh, Y. *J. Org. Chem*. **1995**, *60*, 5567.
58. Furstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc*. **2000**, *122*, 6785.
59. Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4926.
60. Weibes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836.
61. Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000**, *122*, 6490.
62. Beaver, M. G.; Jamison, T. F. *Org. Lett*. **2011**, *13*, 4140.
63. (a) Daly, J. W.; Myers, C. W. *Science* **1967**, *156*, 970-973. (b) For a recent review of pumiliotoxins, see: Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556.
64. Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556.
65. Woodin, K. S.; Jamison, T. F. *J. Org. Chem.* **2007**, *72*, 7451.
66. Saitoh, T.; Suzuki, T.; Onodera, N.; Sekiguchi, H.; Hagiwara, H.; Hoshi, T. *Tetrahedrom Lett.* **2003,** *44*, 2709.
67. a) Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609. (b) for a recent review, see M. Nishizawa, H. Imagawa, J. *Synth. Org. Chem. Jpn.* **2006**, *64*, 744.
68. Deka, M. J.; Indukuri, K.; Sultana, S.; Borah, M.; Saikia, A. K. *J. Org. Chem*. **2015**, *80*, 4349.
69. Ghorai, M. K.; Shukla, D.; Das, K. *J. Org. Chem.* **2009,** *74***,** 7013.
70. Lanman, B. A.; Myers, A. G. *Org. Lett*. **2004**, *6*, 1045.
71. Gharpure, S. J.; Prasad, J. V. K. *J. Org. Chem.* **2011**, *76*, 10325.
72. Bobzin, S. C.; Faulkner, D. J. *J. Org. Chem.* **1991**, *56*, 4403.
73. (a) Hajos, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. *CNS Drug Rev*. **2004**, *10*, 23. (b) Versiani, M.; Cassano, G.; Perugi, G.; Benedetti, A.; Mastalli, L.; Nardi, A.; Savino, M. *J. Clin. Psychiatry* **2002**, *63*, 31. (c) Wong, E. H. F. et al. *Biol. Psychiatry* **2000**, *47*, 818.

74. Berzewski, H.; Van Moffaert, M.; Gagiano, C. A. *Eur. Neuropsychopharmacol.* **1997**, *7*, S37.
75. Brenner, E.; Balwin, R. M.; Tamagnan, G. *Org. Lett.* **2005**, *7*, 937.
76. Sequeira, F. C.; Chemler, S. R. *Org. Lett.* **2012**, *14*, 4482.
77. Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chemie Int. Ed.* **2006**, *45*, 7134.
78. Robinson, R. *J. Chem. Soc. Trans.* **1917**, *111*, 762.
79. Bhaskar, G.; Satish Kumar, V.; Venkateswara Rao, B. *Tetrahedron: Asymmetry* **2004**, *15*, 1279.
80. Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861.
81. Xia, X.-F.; Zhu, S.-L.; Li, Y.; Wang, H. *RSC Adv.* **2016**, *6*, 51703.
82. Campbell, N. E.; Sammis, G. M. *Angew. Chem. Int. Ed.* **2014**, 53, 6228.
83. Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.

CHAPTER 2

Lewis Acid Mediated Intramolecular C−C Bond Formation of Alkyne- Epoxide Leading to Six-Membered Oxygen and Nitrogen Heterocycles

2.1. Importance of Pyrans and Piperidines

Cyclic ethers are widely present in many natural products exhibiting several important biological activities and have diverse applications in cosmetics and agro chemicals as well.[1] The dihydro- and tetrahydropyrans are core units of many biologically active natural products, such as aspergillide A-C[2] **1** and pyranicin[3] **2** (*Figure 2.1.1*). Aspergillides A-C, were isolated by Kusumi and co-workers from a marine-derived fungus, Aspergillus ostianus strain 01F313, collected off the coast of Pohnpei. Importantly, aspergillides A-C displayed cytotoxicity against mouse lymphocytic leukemia cells (L1210) with LD50 values of 2.1, 71.0, and 2.0 µg/mL, respectively. Pyranicin, a tetrahydropyran containing natural product from annonaceous acetogenin family, isolated from the stem bark of the *Goniothalamus giganteus* tree, native to Thailand by McLaughlin *et al.* in 1997, acts as antimalarial, antiparasitic, and antitumor drug and it has recently exhibited promising results against Parkinsonism.

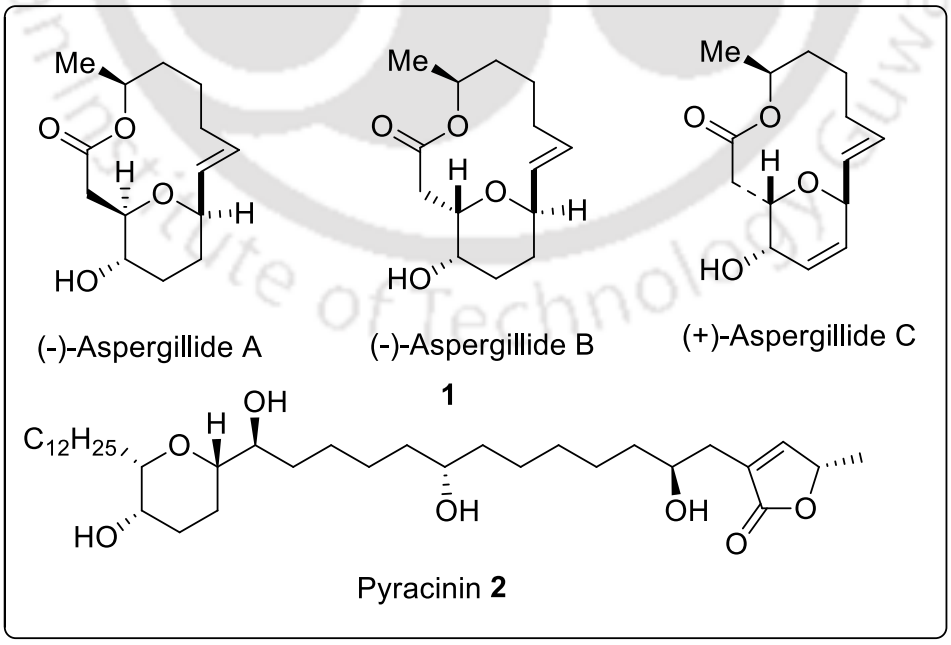


Figure 2.1.1

Similarly, nitrogen containing cyclic structures such as piperidine and its derivatives are also present in several biologically active natural products and pharmaceuticals.[4] Compounds with the piperidine sub-structure exhibit anti-hypertensive,[5] and antibacterial activity.[6] Many natural products having a piperidine moiety have been isolated and thus this moiety is an important building block for various biologically significant compounds. For example, Yaequinolone J1 and J2 (*Figure 2.1.2*) with *p*-methoxyphenylquinoline skeleton fused with pyran ring have been isolated from penicillium sp. FKI 2140 and exhibit insecticidal antibiotic property.[7]

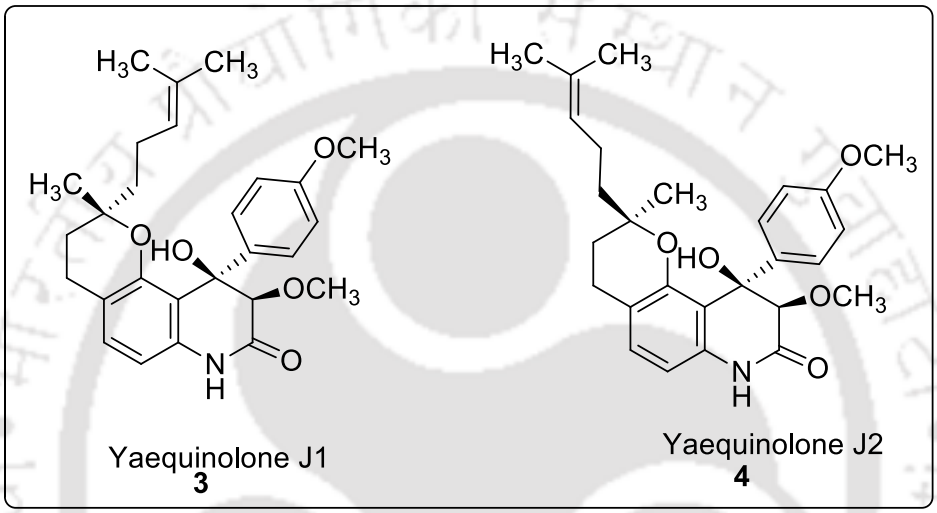


Figure 2.1.2

4-Amido piperidine derivative indoramine **5** is used as an alpha-1 selective adrenoceptor antagonist.[8] The compounds with 4-arylpiperidine backbone such as (-)-paroxetine **6**, (+)-femoxetine **7** and their analogues are significantly important class of serotonin (5-hydroxytryptamine) reuptake inhibitors[9] (*Figure 2.1.3).*

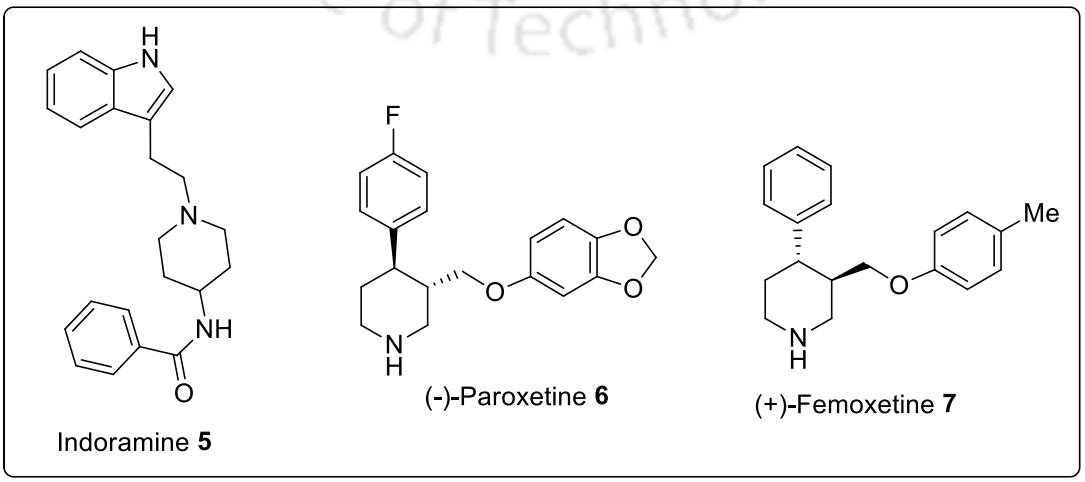
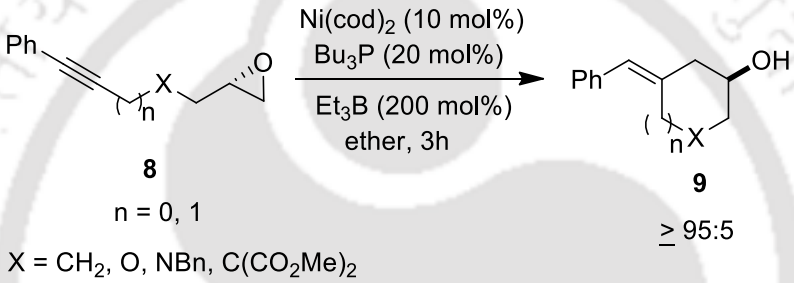


Figure 2.1.3

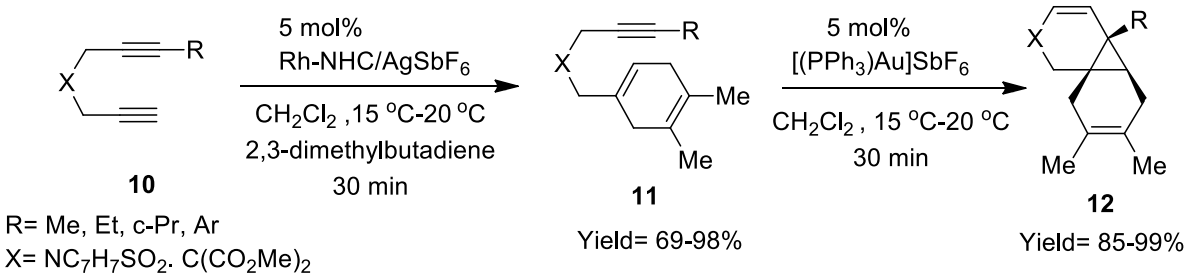
2.2. Literature Methods

Metal catalyzed reductive coupling between alkyne and epoxide for C-C bond formation was developed with complete (>95:5) regioselectivity. This methodology unlike 1,*n*-enyne cyclization requires π-system of one molecule (alkyne) and functional group that has no multiple bonds (epoxide). Jamison and his group described a novel methodology for nickel catalyzed multicomponent coupling reactions. This method demonstrated intermolecular and intramolecular reductive coupling of alkynes and epoxides using Bu_3P and Et_3B as reducing agents. Here, the usually disfavoured *endo* epoxide-opening product in alkyne-epoxide reductive cyclizations was shown, thus, the compound **8** in presence of Ni-catalyst underwent cyclization to give the compound **9** (*Scheme 2.2.1*).[10]



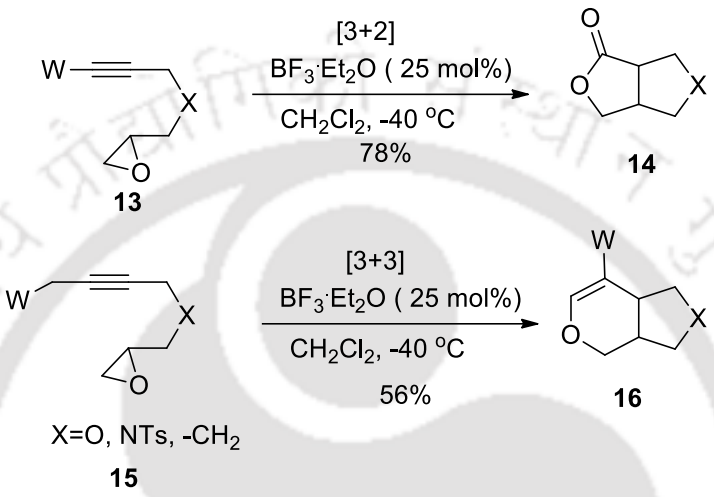
Scheme 2.2.1

Chung *et al.* reported a methodology which describes Gold(I)-catalyzed cyclization of enynes containing an olefinic cycle. Enynes bearing a cyclic olefin **11** were prepared by a rhodium-catalyzed intermolecular [4 + 2] cycloaddition of diynes **10** with 2,3-dimethylbutadiene in 30 min with high yields in the presence of dichloromethane at room temparature. These compounds then subjected to Diels alder reaction, using gold-catalyst to afford the expected polycyclic diene compound **12** in 85-99% yields. Consecutive rhodium-catalyzed Diels-Alder/gold(I)-catalyzed cycloisomerization reactions were integrated in one-pot. First, Diels-Alder reaction was carried out in the presence of [Rh(NHC)(cod)Cl]/$AgSbF_6$, after completion of the reaction, $Au(PPh_3)Cl$ and $AgSbF_6$ were added, and the whole mixture was stirred at the same temperature for 1 h (*Scheme 2.2.2*).[11]



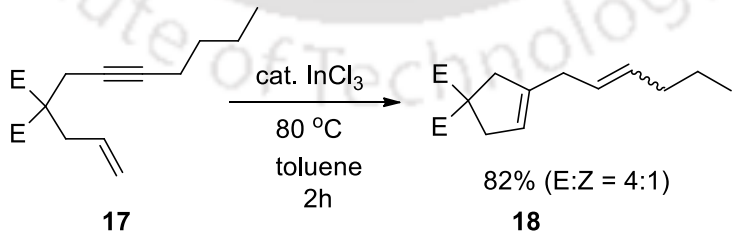
Scheme 2.2.2

Liu and co-workers reported a one-pot operation for the highly diastereo and enantiospecific synthesis of bicyclic heterocycles with multiple stereogenic centers. Tungsten-promoted two new cycloadditions for common epoxides and functionalized alkynes in the presence of Lewis acid catalyst was shown. Alkynyltungsten complex **13** and propargyltungsten complex **15** in the presence of $BF_3{\cdot}Et_2O$ underwent [3+2] and [3+3] cycloaddition in dichloromethane at -40 ^oC to give enantiospecific bicyclic lactones **14** and **16**. (*Scheme 2.2.3*).[12]



Scheme 2.2.3

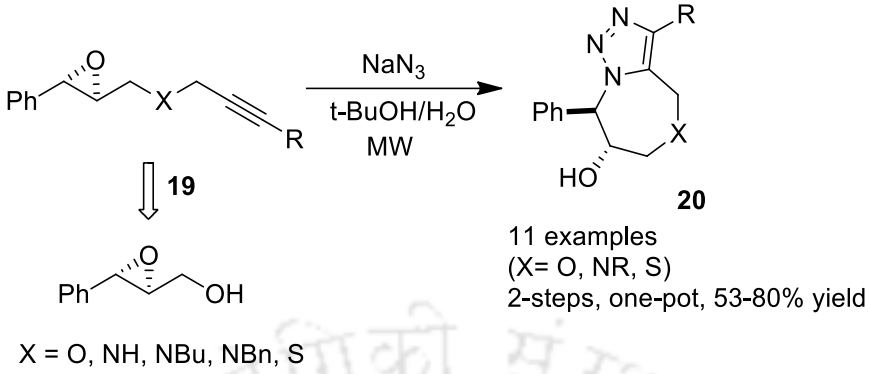
Chatani and his group proposed a methodology for the skeletal reorganization of enynes in the presence of Lewis acid as a catalyst. The reaction of 1,6-enynes with an alkyl group at the acetylenic carbon **17** in the presence of 10 mol % of $InCl_3$ in toluene at 80 ^oC, resulted in a new type of skeletal reorganization to give 1-allyl-1-cyclopentenes **18** in good yields, in which a terminal olefinic carbon migrates between the acetylenic carbons (*Scheme 2.2.4*).[13]



Scheme 2.2.4

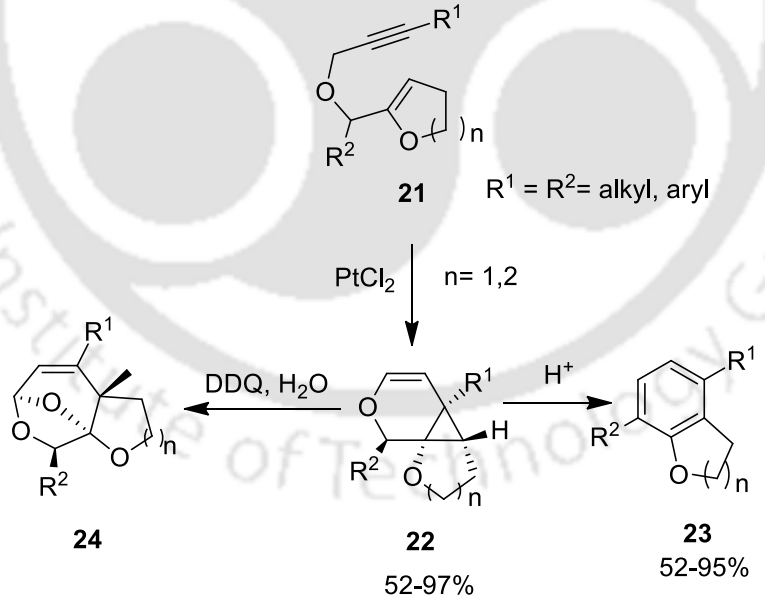
Pericas and co-workers developed a one-pot procedure for the synthesis of triazolooxazepinols, triazolodiazepinols and triazolothiazepinols *via* stereospecific and regioselective epoxide ring opening followed by intramolecular azide-alkyne cycloaddition under metal-free conditions. Treatment of phenyl glycidyl propargylethers or amines or thioethers **19** with 3 equivalents of NaN_3 in *t*-BuOH/H_2O under micro-wave (MW) irradiation condition gave a bicyclic systems

featuring a triazole ring fused to a seven membered hetrocycles **20**. The reaction gave single diastereomer having the trans configuration in a good to moderate yields (*Scheme 2.2.5*).[14]



Scheme 2.2.5

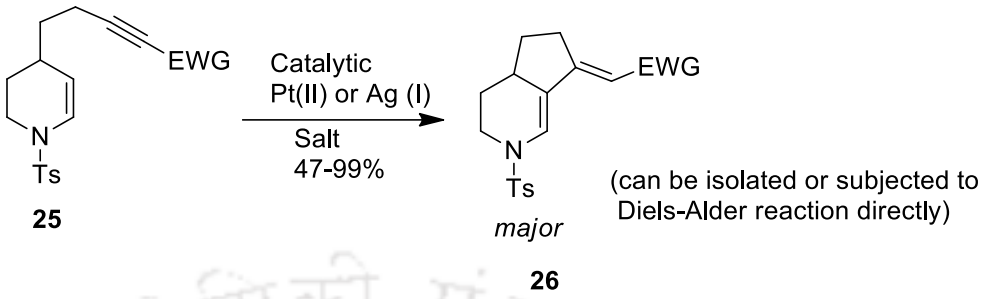
Echavarren *et al.* reported a strategy which describes the formation of oxepane derivatives via oxidative ring opening of 3-oxabicyclo[4.1.0]hept-4-enes **22**, formed by the intramolecular Pt(II) catalyzed cyclopropanation of enol ethers by alkynes. The facile oxidative cleavage was performed with DDQ or CAN to give seven-membered ring double acetals **24**. In addition, a novel benzannulation had been found to take place by simply heating the cyclopropane derivatives in the presence of a protic acid to provide the compound **23** (*Scheme 2.2.6*).[15]



Scheme 2.2.6

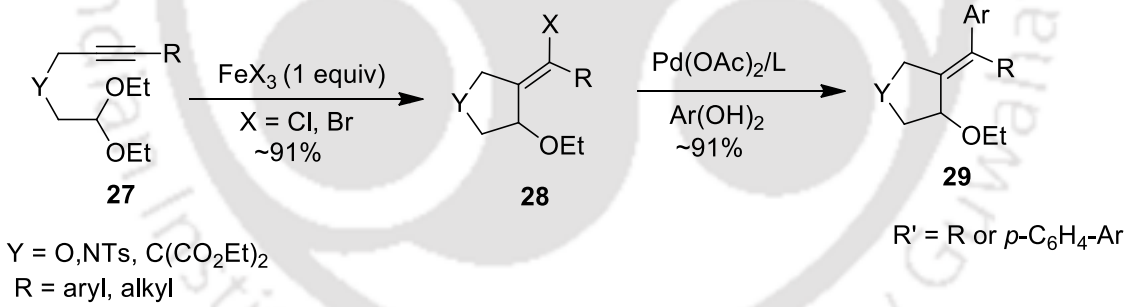
Dake and co-workers demonstrated an alternative route for the synthesis of azahydrindan. Cyclic ene-*N*-*p*-toluenesulfonamides tethered to an electron-deficient alkyne **25** under the influence of catalytic Pt(II) salts ($PtCl_2$ or $[dppbPt\mu\text{-}OH]_2(BF_4)_2$) or AgOTf cyclised to produce **26** in a good to moderate yields, ranging from 47% to 99%. The resulting functionalized 2-azahydrindans can be further manipulated using the Diels−Alder reaction. Thus, the synthetic concept is based on

tandem cycloisomerization−cycloaddition reactions in one-pot, two-step process which generate highly functionalized 1-azadecalin ring systems in a highly stereocontrolled manner (*Scheme 2.2.7*).[16]



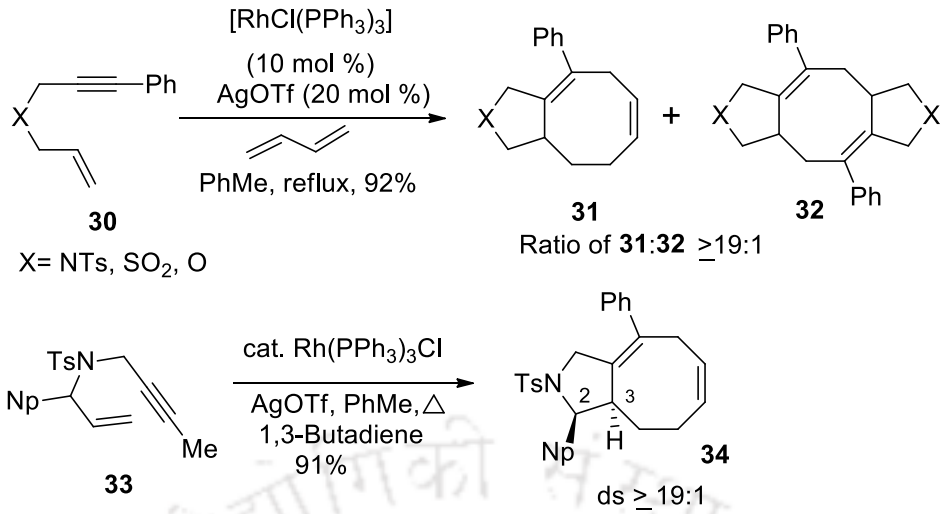
Scheme 2.2.7

Yu and co-workers developed a new alternative route for the synthesis of vinylic C-Cl and C-Br bond. Here, $FeCl_3$- and $FeBr_3$-promoted cyclization/halogenation of alkynyl diethyl acetals **27** gave (*E*)-2-(1-halobenzylidene or alkylidene)-substituted five-membered carbo- and heterocycles **28** selectively.The compound then subjected to Suzuki coupling with aryl boronic acid to afford the coupling product **29**. The present protocol has provided a new alternative route to vinylic C-Cl and C-Br bond formation (*Scheme 2.2.8*).[17]



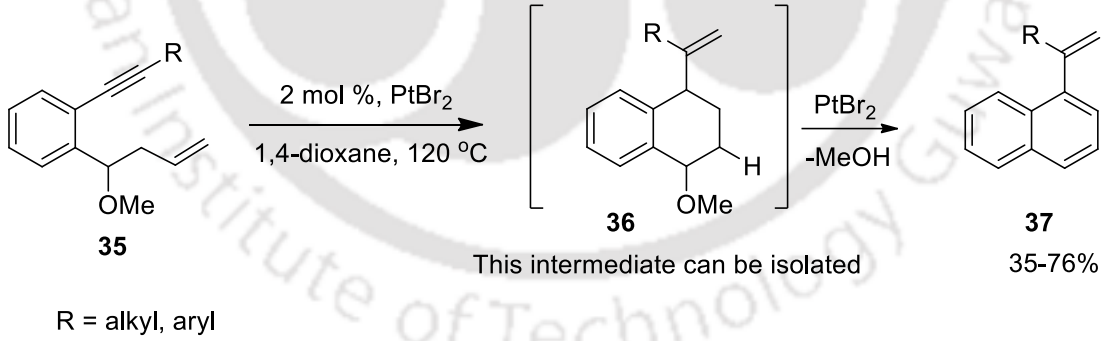
Scheme 2.2.8

Evans and his coworkers developed a new method that demonstrates intermolecular metal catalyzed [4 + 2 + 2] cycloaddition. The reaction of heteroatom-tethered enyne **30** and 1,3-butadiene in the presence of the Wilkinson catalyast and a silver salt led to a fused five and eight-membered ring product **31** as well as **32**. Depending on the metal counterion, excellent selectivity can be obtained for either the homo- or heterocycloaddition adducts. The stereochemistry of the reaction was also studied by introducing a stereogenic center at C-2 of **33**, which leads to a diastereoselective product **34**. (*Scheme 2.2.9*).[18]



Scheme 2.2.9

Yamamoto and his group developed a one pot procedure for the synthesis of vinylnaphthalene derivatives **37** *via* $PtBr_2$-catalyzed consecutive enyne metathesis-aromatization in good to moderate yields. In this reaction Pt-catalyst plays a dual role. 1,7-enynes **35**, fused with an aromatic ring and bearing a leaving methoxy group at the 4-position, in the presence of $PtBr_2$ underwent enyne metathesis to produce an intermediate **36** which was isolated. The presence of a methoxy substituent in the tether further extends the scope of this reaction to generate an aromatic ring **37** where $PtBr_2$ acts as a lewis acid to facilitate elimination of MeOH from the isolated intermediate to give the aromatized product (*Scheme 2.2.10*).[19]



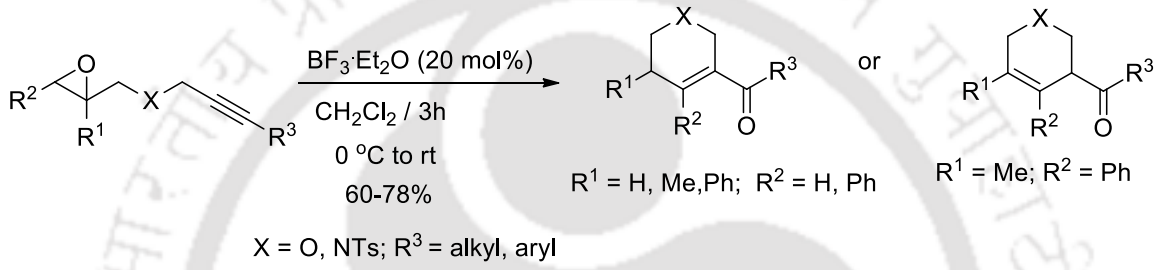
Scheme 2.2.10

2.3. Present Work

Considering the importance of oxygen and nitrogen heterocycles,[20] we were in search of methods for synthesizing multifunctional oxygen and nitrogen heterocyclic frameworks. Cyclic ethers are prepared in high yield by either C–C[21] or C–O[22] bond formation. Literature reports revealed that cyclization of enyne is one of the best method for achieving such goals. Di- and tetrahydropyrans can also be synthesized using epoxides and homoallylic alcohols under Prins cyclization

conditions.[23] Taking clues from these we envisioned that functionalized oxygen and nitrogen heterocyclic compounds could be prepared from *O*- and *N*-tethered alkyne-epoxide substrates mediated by Lewis acid. Although there are reports for the synthesis of *O*- and *N*-heterocyclic compounds from alkyne-epoxide coupling *via* intramolecular alkyne–azide cycloadditions[14] and nickel-catalyzed reductive coupling of alkyne epoxide,[10] to our knowledge the synthetic potential of the use of a Lewis acid for the synthesis of such rings using substrates with an epoxide and an alkyne has not been examined so far.

In this chapter we have developed a strategy that describes intramolecular C-C bond formation of oxygen- and nitrogen-tethered alkynes and epoxides mediated by Lewis acid under ambient conditions. The reaction can be generalized as shown in *Scheme 2.3.1*.



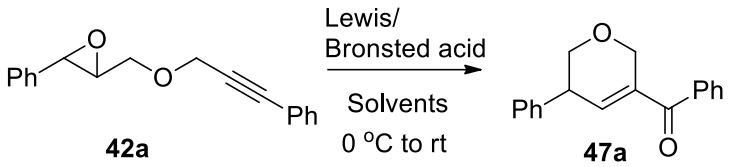
Scheme 2.3.1

Accordingly, 2-((3-phenylprop-2-ynyloxy)methyl)-3-phenyloxirane **42a** was treated with 0.2 equivalents of boron trifluoride etherate in dichloromethane at room temperature and the reaction proceeded smoothly to afford phenyl(4-phenyl-3,6-dihydro-2*H*-pyran-3-yl)methanone **47a** in 68% yield, the structure of which was determined by NMR and X-ray analysis.[24]

In order to optimize the reaction conditions, alkyne-epoxide **42a** was subjected to react with several Lewis and Bronsted acids (*Table 2.3.1*). It was observed that apart from $BF_3{\cdot}Et_2O$, $InCl_3$ and $Bi(OTf)_3$ also resulted in the desired product in good yields. $Zn(OTf)_2$ and $In(OTf)_3$ gave 28% and 20% yield, respectively. Brønsted acids CSA gave low yield but TfOH gave moderate yield. $FeCl_3$ yielded only 25% of the desired product. However, reaction using TMSOTf was unsuccessful in which decomposed product was observed. $BF_3{\cdot}Et_2O$ with 0.2 equivalents was found to be the best reagent for the reaction.

Survey of the various solvents revealed that THF and dioxane gave relatively lower yields, and no progress in the reaction was noticed in toluene and acetonitrile. Dichloromethane (DCM) proved to be the best than all other solvents. The reaction was also performed at -20 °C in CH_2Cl_2 for 10 h but gave only 50% yield.

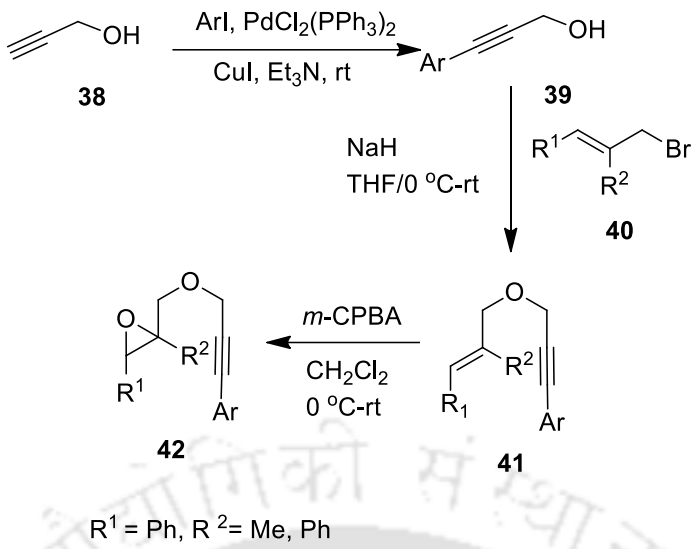
Table 2.3.1. Optimization of the reaction



S.No.	Lewis/Brønsted acid (equiv.)	Time (h)	Solvent	%Yield[a]
1.	$BF_3 \cdot Et_2O$ (1)	3	CH_2Cl_2	68
2.	$InCl_3$ (1)	3	CH_2Cl_2	65
3.	$Bi(OTf)_3$ (0.5)	3	CH_2Cl_2	63
4.	TMSOTf (0.5)	8	CH_2Cl_2	trace
5.	$BF_3 \cdot Et_2O$ (0.5)	3	CH_2Cl_2	68
6.	**$BF_3 \cdot Et_2O$ (0.2)**	**3**	**CH_2Cl_2**	**68**
7.	$BF_3 \cdot Et_2O$ (0.2)	3	THF	d
8.	$BF_3 \cdot Et_2O$ (0.2)	3	Toluene	d
9.	$BF_3 \cdot Et_2O$ (0.2)	8	CH_3CN	d
10	$Zn(OTf)_2$ (1)	10	CH_2Cl_2	28
11	CSA (1)	8	CH_2Cl_2	32
12	TfOH (1)	5	CH_2Cl_2	50
13	$FeCl_3$ (1)	10	CH_2Cl_2	25
14	$In(OTf)_3$ (1)	8	CH_2Cl_2	20

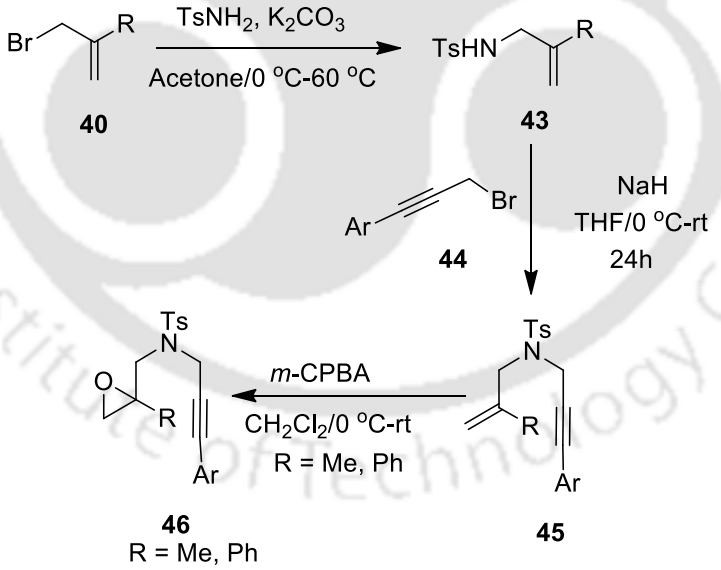
[a]Yields refer to isolated yield. The compounds were characterized by IR, NMR and Mass spectrometry.
d = decomposed product.

Having obtained the optimized conditions, the scope of the reaction was investigated with a variety of substrates **42a-j** and **46a-g** (*Table 2.3.2* and *2.3.3*). Oxygen-[25] and Nitrogen–tethered[26] alkyne-epoxide substrates were prepared using a previously described method by Balamurugan *et al*.. Substrates were prepared in the manner shown in the *Scheme 2.3.2* and *Scheme 2.3.3*. Commercially available propargyl alcohol **38** was treated with iodo benzene derivatives under Sonogashira coupling conditions to afford corresponding terminal alkyne substituted propargylic alcohols **39**. Allyl bromide **40** was coupled with aryl substituted propargylic alcohols using reported procedure to accomplish *O*-tethered alkene-alkynes **41**. *O*-tethered alkene and alkyne compounds were treated with *meta*-chloroperbenzoic acid in dichloromethane at 0 °C to achieve *O*-tethered alkyne-epoxide derivatives **42** as starting materials (*Scheme 2.3.2*).



Scheme 2.3.2. Starting material preparation of *O*-tethered ether

On the other hand, *N*-tethered alkyne-epoxide substrates were prepared from allyl bromide **40** and sulphonamide to produce corresponding *N*-tosyl amines **43**. The compound **43** was



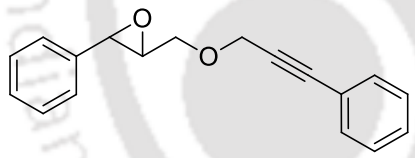
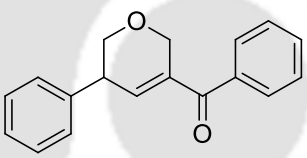
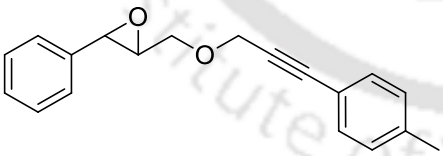
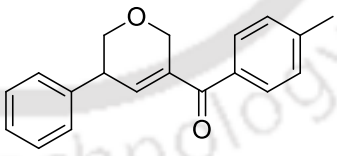
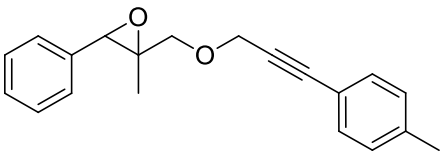
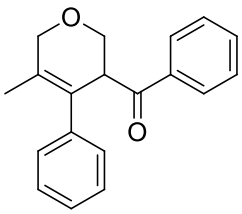
Scheme 2.3.3. Starting material preparation of *N*-tethered ether

coupled with aryl substituted propargyl bromide **44** using reported procedure to accomplish *N*-tethered alkene-alkynes **45.** *N*-tethered alkene and alkyne compounds were treated with *m*-CPBA in dichloromethane at 0 °C to achieve *N*-tethered alkyne-epoxide derivatives **46** as starting materials (*Scheme 2.3.3*).

During the course of this study, we noticed that varying the substitution of methyl and phenyl group on the epoxide ring resulted in the products with different dihydropyrans and 3,4-

dehydropiperidines along with some decomposed products. It was observed from the *Table 2.3.2.* that 1,2-disubstituted (entries 1-3, 6-7, 10) and terminal epoxides (entries 4,5) gave dihydropyrans in good yields. Substrates **42a-b**, **42d-g, 41j** (entries 1-2,4-7,10, in *Table 2.3.2.*) gave 5,6-dihydropyrans while substrate 4**2c** (entry 3) gave 3,6-dihydropyran **47c**. The formation of **47c** might be due to higher stability of the conjugated enone 3,6-dihydropyran compared to 5,6-dihydropyran. Unsubstituted alkyne **42h** (entry 8) was found to be unreactive under the same reaction conditions. Similarly, terminal methyl substituted alkyl-epoxide **42i** (entry 9) did not give any product. This is attributed to the lower stability of the carbocation **A** (*Scheme 2.3.4*), formed from methyl substituted epoxide compared to the aryl substituted epoxide.[23] Alkyl substituted alkyne-epoxide **42f-g** (entries 6,7) gave 74 and 76% yields, respectively. Thiophene substituted alkyne-epoxide **42j** (entry 10) also worked well giving 60% yield. Similarly, *N*-tethered epoxides **46a-g** (entries 1-7, in *Table 2.3.3.*) having alkyl and aryl substituents gave 3,4-dehydropiperidines **48a-g** in good yields.

Table 2.3.2. $BF_3{\cdot}Et_2O$ mediated intramolecular C-C- bond formation of *O*-tethered alkyne and epoxide

Entry	Alkyne-Epoxide **42**	Product **47**	% Yield[a]
1	 **42a**	 **47a**	68
2	 **42b**	 **47b**	71
3	 **42c**	 **47c**	62

Continue….

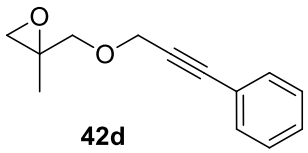
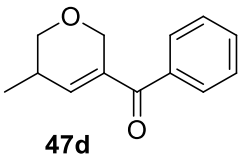
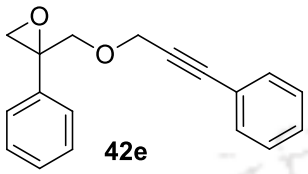
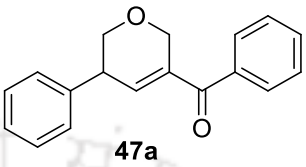
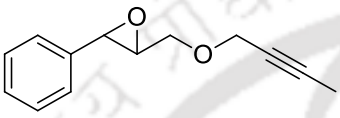
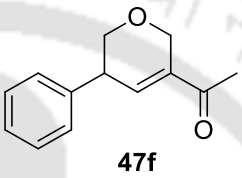
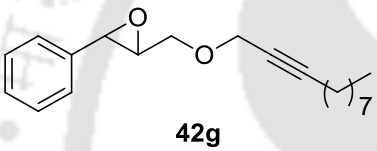
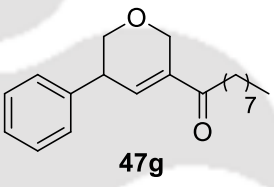
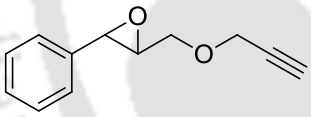
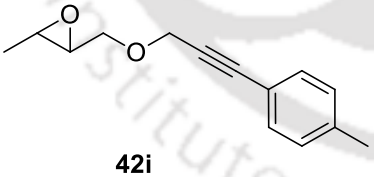
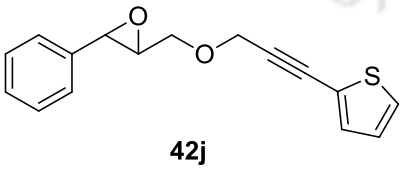
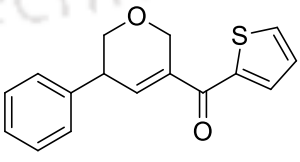
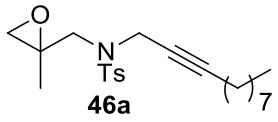
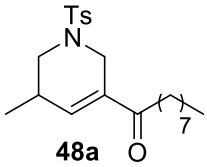
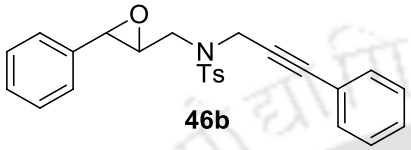
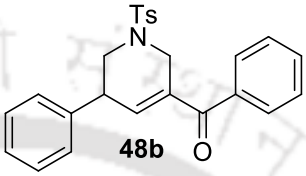
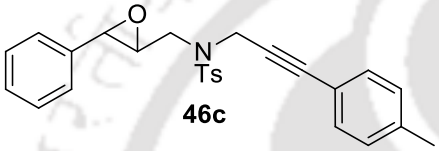
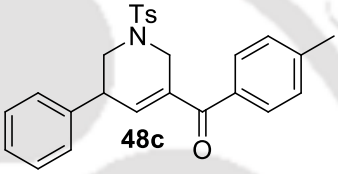
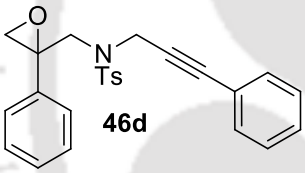
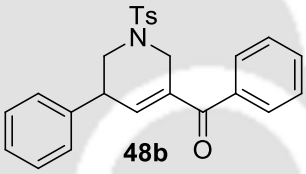
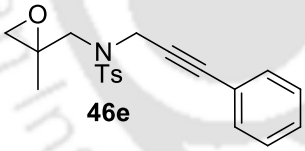
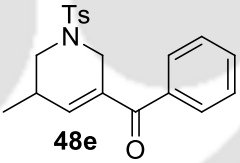
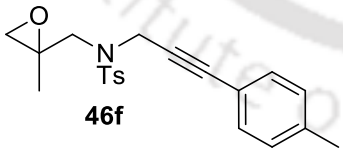
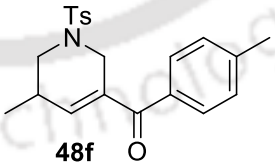
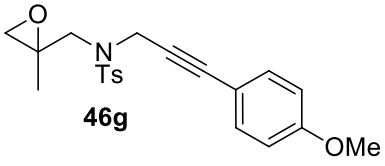
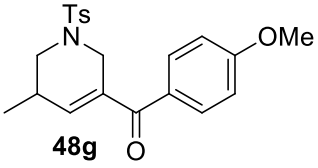
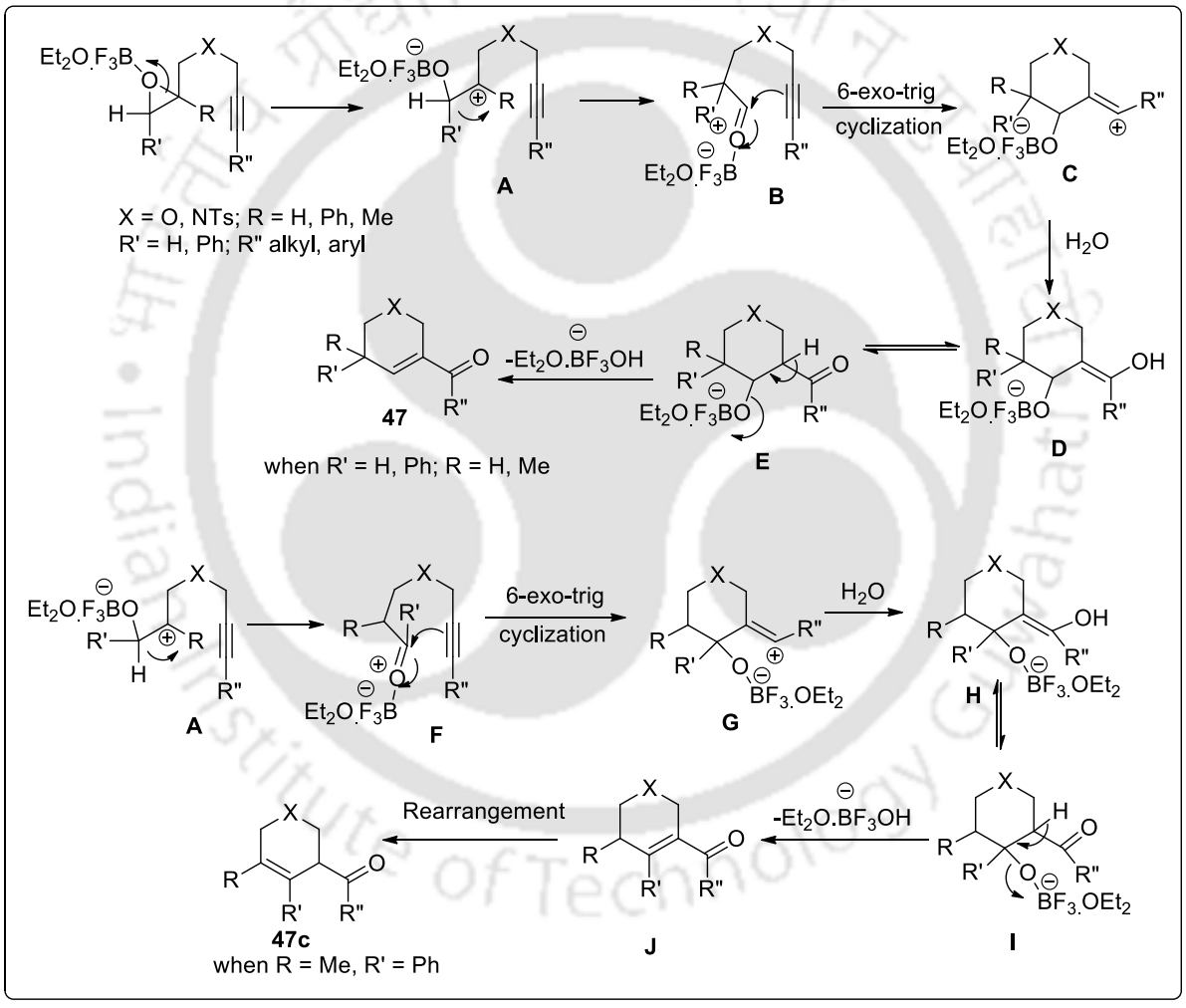
Entry	Alkyne-Epoxide **42**	Product **47**	% Yield[a]
4	 **42d**	 **47d**	65
5	 **42e**	 **47a**	67
6	 **42f**	 **47f**	74
7	 **42g**	 **47g**	76
8	 **42h**	---	d
9	 **42i**	---	d
10	 **42j**	 **47j**	60

Table 2.3.3. $BF_3{\cdot}Et_2O$ mediated intramolecular C-C- bond formation of *N*-tethered alkyne and epoxide

Entry	Alkyne-Epoxide **46**	Product **48**	% Yield[a]
1	 **46a**	 **48a**	77
2	 **46b**	 **48b**	60
3	 **46c**	 **48c**	61
4	 **46d**	 **48b**	69
5	 **46e**	 **48e**	78
6	 **46f**	 **48f**	75
7	 **46g**	 **48g**	73

[a]Yield refers to isolated yield. The compounds are characterized by IR, ^1H, ^{13}C NMR and mass spectrometry. d = Decomposed product.

The mechanism of the reaction can be explained as follows. The epoxide **42 or 46** in the presence of $BF_3{\cdot}Et_2O$ opens up to generate carbocation **A**, which after rearrangement gives most stable oxocarbenium ions **B** and **F** *via* phenyl and hydrogen migration, respectively.[27] The oxocarbenium ions **B** and **F** are then attacked by alkyne group, *via* a 6-*exo-trig* cyclization to give carbocations C and **G,** respectively. The intermediates **C** and **G** are then trapped by water to give enols **D** and **H**, which after rearrangement gives ketones **E** and **I**. The ketone **E** after elimination gives final compound **47 or 48**. On the other hand, ketone **I** initially forms compound **J**, then rearranges to give more stable compound **47c**.



Scheme 2.3.4. Mechanism of the reaction

The structure of the compound **47a** was confirmed by the ^{1}H, ^{13}C, COSY, DEPT and X-ray analysis.

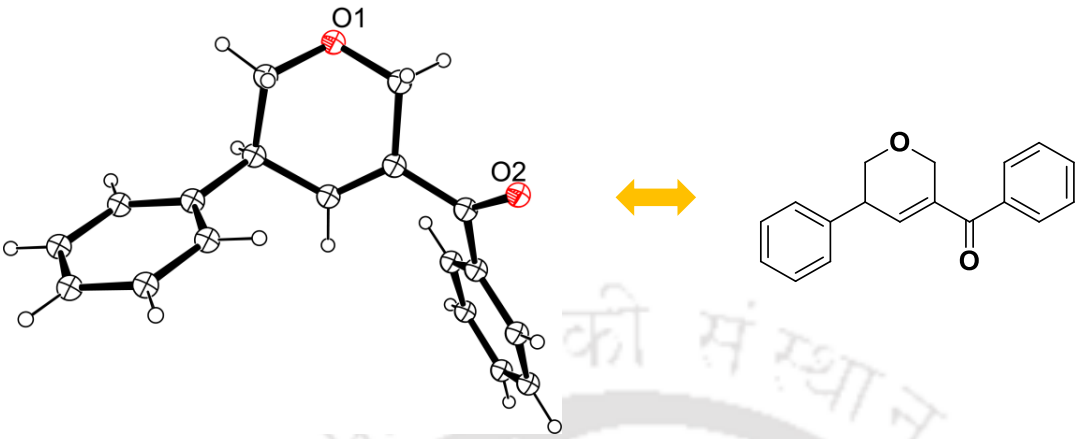


Figure 2.3.1 **:** ORTEP diagram is drawn with 30% probability elipsoid.

Conclusions

In conclusion, we have developed a mild and an efficient method for the synthesis of six membered oxygen and nitrogen heterocyclic compounds by intramolecular C-C bond formation of alkyne-epoxide mediated by boron trifluoride etherate. The method is highly substrate specific and works well for alkyl and aryl substituted alkyne-epoxide substrates.

2.4. Experimental section

2.4.1. Instrumentation and Characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded in open capillary tubes and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on 600, 400, 300 and 150, 100, 75 MHz NMR spectrometers, respectively, using TMS as internal standard. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

2.4.2. Synthesis of starting materials

Compounds **42a** and **42h** are known that were prepared according to the literature procedure.[10,14,25] Their IR, NMR and HRMS data agreed well with the reported data. The same

procedure was used to prepare compounds **42b-g**, **42i** and **42j**.[10,14,25] *N*-tethered compounds **46a-46g** were prepared as per the literature procedures.[10,14,26]

2.4.3. General Procedure for preparation of *O*-tethered compounds 42a-j:

In an oven dried round bottom flask NaH (1.5 equiv.) was taken and dry tetrahydrofuran (THF) (20 mL) was added to it. To this a solution of propargyl alcohol (1 equiv.) or its derivatives were added slowly. The reaction mixture was stirred for 0.5 h at 0 °C. Allyl bromide (1 equiv.) was added to the reaction mixture drop wise. The reaction was monitored by thin layer chromatography and after completion of the reaction, THF was removed by evaporation. The residue was extracted with ethyl acetate (30 ml), washed with water and brine solution (20 ml x 2). Organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated using rotary evaporator to give crude product. The crude product was purified on silica gel column chromatography using ethyl acetate and hexane as eluents. The ether (1.0 equiv.) thus obtained was treated with *meta*-chloroperbenzoic acid (*m*-CPBA) (1.5 equiv.) in dichloromethane (15 mL) at 0 ^oC. The reaction mixture was brought to room temperature and stirred for specific time. After completion of the reaction which was found by TLC, a saturated aqueous solution of Na_2SO_3 was added to quench excess *m*-CPBA. Dichloromethane was added to the reaction mixture, washed with saturated sodium bicarbonate and brine solution, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product which was purified by neutral alumina using ethyl acetate and hexane as eluents.

Synthesis of 2-Phenyl-3-(((3-(p-tolyl)prop-2-yn-1-yl)oxy)methyl)oxirane (42b):

In an oven dried round bottom flask NaH (36 mg, 1.5 mmol) was taken and dry THF (3 mL/mmol) was added to it. To this a solution 3-*p*-tolylprop-2-yn-1-ol (146 mg, 1mmol) were added slowly. After stirring for 0.5 h at 0 °C, 3-Bromo-1-phenyl-1-propene (148 mg, 1 mmol) was added to the reaction mixture drop wise. The reaction was monitored by TLC and after completion of the reaction THF was removed by evaporation. The residue was extracted with ethyl acetate (10 ml), washed with water and brine solution (5 ml x 2). Organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated using rotary evaporator to give crude product. The crude product was purified on silica gel column chromatography using ethyl acetate and hexane as eluents. The 1-((E)-3-(3-*p*-tolylprop-2-ynyloxy)prop-1-enyl)benzene (262 mg, 1mmol) thus obtained was treated with meta-chloroperbenzoic acid (258 mg, 1.5 mmol) in dichloromethane (5 mL) at 0 ^oC. The reaction mixture was brought to room temperature and stirred for specific time. After completion of the reaction which was found by TLC, a saturated

aqueous solution of Na_2SO_3 was added to quench excess *m*-CPBA. Dichloromethane was added to the reaction mixture, washed with saturated sodium bicarbonate and brine solution, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product which was purified by neutral alumina using ethyl acetate and hexane as eluents over silica gel to give 2-Phenyl-3-(((3-(*p*-tolyl)prop-2-yn-1-yl)oxy)methyl)oxirane **42b** (242 mg, 87%) as a colourless oil.

2.4.4. General Procedure for the Synthesis of *N*-tethered compounds 46a-g:

To an oven dried round bottom flask with magnetic stir bar was added allyl bromide (1.1 equiv.), 4-methylbenzenesulfonamide (1 equiv.), K_2CO_3 (2 equiv.) and acetone (5 mL/mmol). The round bottom flask was heated at 60 ^oC. Upon completion of the reaction (16 h), the solution was cooled to room temperature, filtered through a short plug of celite and washed with EtOAc, and solvent was removed in vacuo to afford a crude product. Purification of the resulting crude residue via silica gel flash column chromatography afforded the desired *N*-toysl allylic amine. In an oven dried round bottom flask NaH (1.5 equiv.) was taken and dry THF (20 mL) was added to it. To this a solution of *N*-tosyl allylic amine (1 equiv.) or its derivatives were added slowly. The reaction mixture was stirred for 0.5 h at 0 °C. Propargyl bromide (1 equiv.) was added to the reaction mixture drop wise. The reaction was monitored by thin layer chromatography and after completion of the reaction THF was removed by evaporation. The residue was extracted with ethyl acetate (30 ml) and washed with water and brine solution (20 ml x 2). Organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated using rotary evaporator to obtain crude product. The crude product was purified on silica gel column chromatography using ethyl acetate and hexane as eluents to give the *N*-tethered product. The product (1.0 equiv.) thus obtained was treated with *meta* chloroperbenzoic acid (1.5 equiv.) in dichloromethane at 0 ^oC. The reaction mixture was brought to room temperature and stirred for specific time. After completion of the reaction which was found by TLC, a saturated aqueous solution of Na_2SO_3 was added to quench excess *m*-CPBA. Dichloromethane (30 mL) was added to the reaction mixture, washed with saturated sodium bicarbonate and brine solution, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product which was purified by neutral alumina using ethyl acetate and hexane as eluents.

Synthesis of 4-Methyl-*N*-((2-methyloxiran-2-yl)methyl)-*N*-(undec-2-yn-1-yl)benzenesulfonamide (46a):

To an oven dried round bottom flask with magnetic stir bar was added 3-Bromo-2-methylpropene (0.11 ml, 1.1 mmol), 4-Toluenesulfonamide (171mg, 1 mmol), K_2CO_3 (276 mg, 2mmol) and acetone (10 mL). The round bottom flask was heated at 60 ^0C. Upon completion of

the reaction (6 h), the solution was cooled to room temperature, filtered through a short plug of celite and washed with EtOAc, and solvent was removed in vacuo to afford a crude product. Purification of the resulting crude residue via silica gel flash column chromatography afforded 2-methyl-N-tosylprop-2-en-1-amine. In an oven dried round bottom flask NaH (36 mg, 1.5 mmol) was taken and dry THF (10 mL) was added to it. To this a solution of 2-methyl-*N*-tosylprop-2-en-1-amine (225 mg, 1 mmol) was added slowly. After stirring for 0.5 h at 0 °C, 1-bromopent-2-yne (230 mg,1 mmol) was added to the reaction mixture drop wise. The reaction was monitored by TLC and after completion of the reaction THF was removed by evaporation. The residue was extracted with ethyl acetate (20 ml) and washed with water and brine solution (10 ml x 2). Organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated using rotary evaporator to obtain crude product. The crude product was purified on silica gel column chromatography using ethyl acetate and hexane as eluents to give *N*-(2-methylallyl)-*N*-tosylundec-2-yn-1-amine. The product (375 mg, 1.0 mmol) thus obtained was treated with meta-chloroperbenzoic acid (258 mg, 1.5 mmol) in dichloromethane at 0 ^oC. The reaction mixture was brought to room temperature and stirred for specific time. After completion of the reaction which was found by TLC, a saturated aqueous solution of Na_2SO_3 was added to quench excess *m*CPBA. Dichloromethane (30 mL) was added to the reaction mixture, washed with saturated sodium bicarbonate and brine solution, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product which was purified by neutral alumina using ethyl acetate and hexane as eluents to afford 4-Methyl-*N*-((2-methyloxiran-2-yl)methyl)-*N*-(undec-2-yn-1-yl)benzenesulfonamide **46a (**352 mg, 90%) as a colourless oil.

2.4.5. General Procedure for Lewis Acid Catalyzed Intramolecular C−C Bond Formation of Alkyne-Epoxide 47a-j and 48a-g:

To a corresponding alkyne-epoxide substrates (1.0 equiv) in dichloromethane (5 ml) at 0 ^oC, $BF_3{\cdot}Et_2O$ (0.2 equiv.) was added drop wise and the reaction mixture was brought to room temperature. The reaction was continued for specified time and monitored by TLC. After completion of the reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (5 ml). The product was extracted with CH_2Cl_2 (2 x 10 ml) and washed with brine. Organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using rotary evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluents to afford the cyclic compounds 2.

Synthesis of Phenyl(4-phenyl-3,6-dihydro-2*H*-pyran-3-yl)methanone (47a):

To 1-((Z)-3-(3-phenylprop-2-ynyloxy)prop-1-enyl)benzene **41a** (248 mg, 1.0 mmol) in CH_2Cl_2 (5 mL/mmol) at 0 ^oC, $BF_3{\cdot}Et_2O$ (0.025 ml, 0.2 mmol) was added drop wise and the reaction mixture was brought to room temperature. The reaction was continued for specified time and monitored by TLC. After completion of the reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (5 ml). The product was extracted with CH_2Cl_2 (2 x 10 ml) and washed with brine. Organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using rotary evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluents to afford Phenyl(4-phenyl-3,6-dihydro-2H-pyran-3-yl)methanone **47a,** (179 mg, 68%) as a colourless solid.

2.5. References

1. (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (b) Faulkner, D. J. *Nat. Prod. Rep*. **1984**, *1*, 251 and 551. (c) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 1, pp 43-121.
2. Nagasawa, T.; Kuwahara, S. *Org. Lett*. **2009**, *11*, 761.
3. (a) McLaughlin, J. L. *J. Nat. Prod*. **2008**, *71*, 1311. (b) Alali, F. Q.; Rogers, L.; Zhang, Y.; McLaughlin, J. L. *Tetrahedron* **1998**, *54*, 5833.
4. (a) Michael, J. P. *Nat. Prod. Rep*. **2008**, *25*, 166 and previous reports in this series. (b) Kim, W.-G.; Kim, J.-P.; Kim, C-J.; Lee, K.-H.; Yoo, I.-D. *J. Antibiot*. **1996**, *49*, 20. (c) Barluenga, S.; Simonsen, K. B.; Littlefield, E. S.; Ayida, B. K.; Vourloumis, D.; Winters, G. C.; Takahashi, M.; Shadrick, S.; Zhao, Q.; Han, Q.; Hermann, T. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 713. (d) Neelamkavil, S. F.; Boyle, C. D.; Chackalamannil, S.; Greenlee, W. J. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 4563.
5. Petit, S.; Nallet, J. P.; Guillard, M.; Dreux, J.; Chermat, R.; Poncelet, M.; Bulach, C.; Simon, P.; Fontaine, C.; Barthelmebs, M.; Imbs, J. L. *Eur. J. Med. Chem*. **1991**, *26*, 19.
6. Zhou, Y.; Gregor, V. E.; Ayida, B. K.; Winters, G. C.; Sun, Z.; Murphy, D.; Haley, G.; Bailey, D.; Froelich, J. M.; Fish, S.; Webber, S. E.; Hermann, T.; Wall, D. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 1206.
7. Uchida, R.; Imasato, R.; Shiomi, K.; Tomoda, H.; Omura, S. *Org. Lett*. **2005**, *7*, 5701.

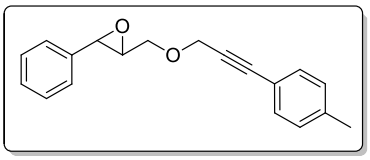
8. (a) Collins, P.; Sheridan, D. *Br. Heart. J.* **1985**, *53*, 488. (b) Julius, B. K.; Vassalli, G.; Mandinov, L.; Hess, O. M. *J. Am. Coll. Cardiol.* **1999**, *33*, 1499.
9. Yamada, S.; Jahan, I. *Tetrahedron Lett.* **2005**, *46*, 8673.
10. Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc*. **2003**, *125*, 8076.
11. Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K. *J. Org. Chem.* **2006**, *71*, 9366.
12. Madhushaw, R. J.; Li, C. L.; Shen, K. H.; Hu, C. C.; Liu, R. S. *J. Am. Chem. Soc.* **2001,** *123*, 7427.
13. Miyanohana, Y.; Chatani, N. *Org. Lett*. **2006,** *8*, 2155.
14. Sau, M.; Escrich, C. R.; Pericas, M. A. *Org. Lett*. **2011,** *13*, 5044.
15. Nevado, C.; Ferrer, C.; Echavarren, A. M. *Org. Lett*. **2004,** *6*, 3191.
16. Harrison, T. J.; Dake, G. R. *Org. Lett*. **2004,** *6*, 5023.
17. Xu, T.; Yu, Z.; Wang, L. *Org. Lett*. **2009,** *11*, 2113.
18. Evans, P. A.; Yu, Z.; Wang, L. *J. Am. Chem. Soc.* **2002**, *124*, 8782.
19. Bajracharya, G. B.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 892.
20. (a) Reddy, U. C.; Raju, B. R.; Kumar, E. K.; Saikia, A. K. *J. Org. Chem.* **2008**, *73*, 1628. (b) Saha, P.; Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *Org. Lett*. **2010**, *12*, 1824. (c) Bondalapati, S.; Indukuri, K.; Ghosh, P.; Saikia, A.K. *Eur. J. Org. Chem*. **2013**, 952. (d) Indukuri, K.; Unnava, R.; Deka, M. J.; Saikia, A. K. *J. Org. Chem.* **2013**, *78*, 10629.
21. (a) Illuminati, G; Mandolini, L *Acc. Chem. Res.* **1981**, *14*, 95. (b) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev*. **1986**, *86*, 857. (c) Castañeda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695.
22. (a) Nicolaou, K. C.; Hwang, C. K. ; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136. (b) Nicolaou, K. C. ; Hwang, C. K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y; Bal Reddy, K; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 10227.
23. (a) Indukuri, K.; Bondalapati, S.; Kotipalli, T.; Gogoi, P.; Saikia, A. K. *Synlett* **2012**, *23*, 233. (b) Indukuri, K.; Bondalapati, S.; Sultana, S.; Saikia, A. K. *RSC Advances* **2012**, *2*, 9398. (c) Chio, F. K.; Warne, J.; Gough, D.; Penny, M.; Green, S.; Coles, S. J.; Hursthouse, M. B.; Jones, P.; Hassall, L.; McGuire, T. M.; Dobbs, A. P. *Tetrahedron* **2011**, *67*, 5107. (d) Li, J.; Li, C.-J. *Tetrahedron Lett*. **2001**, *42*, 793. (e) Dobbs, A. P.; Martinović, S. *Tetrahedron Lett*. **2002**, *43*, 7055. (f) Yadav, J. S.; Rajasekhar, K.; Murty, M. S. R. *Tetrahedron Lett*. **2005**, *46*, 2311. (g) Dobbs, A. P.; Guesné, S. J. J. Martinović, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem*. **2003**, *68*, 7880. (h) Yadav, J. S.;

Borker, P.; Chakravarthy, P. P.; Reddy, B. V. S.; Sarma, A. V. S.; Basha, S. J.; Sridhar, Greé, B. R. *J Org. Chem.* **2010**, *75*, 2081. (i) Reddy, B. V. S.; Chaya, D. N.; Yadav, J. S.; Chatterjee, D.; Kunwar, A. C. *Tetrahedron Lett*. **2011**, *52*, 2961.

24. Crystallographic data for compound **47a** has been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication number **CCDC 979057**.
25. Gudla, V.; Balamurugan, R. *J. Org. Chem*. **2011**, *76*, 9919.
26. Wang, K-B.; Ran, R.-Q.; Xiu, S.-D.; Li, C.-Y. *Org. Lett*. **2013**, *15*, 2374.
27. (a) House, H. O. *J. Am. Chem. Soc*. **1955**, *77*, 3070. (b) Nokami, J.; Maruoka, K.; Souda, T.; Tanaka, N. *Tetrahedron* **2007**, *63*, 9016.

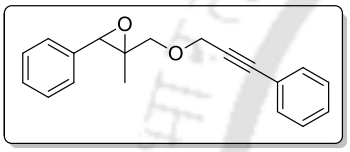
2.6. Characterization Data:

2-Phenyl-3-(((3-(*p*-tolyl)prop-2-yn-1-yl)oxy)methyl)oxirane (42b):



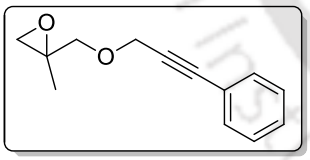
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.60; yield 242 mg, 87%; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.34-7.26 (m , 7 H), 7.11 (d, *J* = 8 Hz, 2 H), 4.47 (s, 2 H), 3.97 (dd, *J* = 11.6 and 3.6 Hz, 1 H), 3.84 (d, *J* = 1.6 Hz, 1 H), 3.76 (dd, *J* = 11.6 and 4.8 Hz, 1 H), 3.29-3.26 (m, 1 H), 2.34 (s, 3 H); **^{13}C NMR** (75 MHz, $CDCl_3$) □ 138.6, 136.6, 131.6, 128.5, 128.4, 128.2, 125.5, 119.2, 86.8, 83.7, 69.3, 60.9, 59.3, 55.9, 21.4. **IR** (KBr, neat) 2922, 2851, 1256, 1098, 1073, 749, 697 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{19}O_2$ $(M + H)^+$ 279.1385, found 279.1387.

2-Methyl-3-phenyl-2-(((3-phenylprop-2-yn-1-yl)oxy)methyl)oxirane (42c):



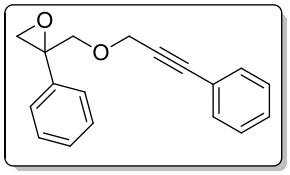
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.50; yield 242 mg, 87%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47- 7.26 (m, 10 H), 4.49 (s, 2 H), 4.23 (s, 1 H), 3.79 (d, *J* = 10.8 Hz, 1 H), 3.75 (d, *J* = 10.8 Hz, 1 H), 1.15 (s, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 135.8, 132.0, 128.6, 128.5, 128.3, 127.9, 126.6, 122.7, 86.9, 85.0, 73.9, 62.1, 61.5, 59.2, 20.3; **IR** (KBr, neat) 2926, 2853, 1490, 1255, 1092, 1027, 700 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{19}O_2$ $(M + H)^+$ 279.1385, found 279.1386.

2-Methyl-2-(((3-phenylprop-2-yn-1-yl)oxy)methyl)oxirane (42d):



Colorless oil; Rf (hexane/EtOAc 9:1) 0.60; Yield 186 mg, 92%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45- 7.31 (m, 5 H), 4.43 (d, J = 2.4 Hz, 2H), 3.69 (d, J = 11.2 Hz, 1 H), 3.58 (d, J = 11.2 Hz, 1 H), 2.81 (d, J =4.8 Hz, 1 H), 2.64 (d, J = 4.8 Hz, 1 H), 1.42 (s, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 131.9, 128.7, 128.5, 122.7, 86.7, 84.9, 73.2, 59.4, 56.0, 51.8, 18.7; **IR** (KBr, neat) 2916, 2848, 1255, 1095, 757 cm−1; **HRMS** (ESI) m/z calcd for $C_{13}H_{15}O_2$ $(M + H)^+$ 203.1072, found 203.1069.

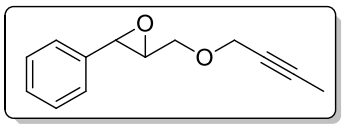
2-Phenyl-2-(((3-phenylprop-2-yn-1-yl)oxy)methyl)oxirane (42e):



Colourless oil; R_f (hexane/ EtOAc 9:1): 0.50; Yield 248 mg, 94%; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58-7.15 (m, 10 H), 4.47 (s, 2 H), 4.20 (d, *J* = 11.4 Hz, 1 H), 3.95 (d, *J* = 11.4 Hz, 1 H), 3.20 (d, *J* = 5.4 Hz, 1 H), 2.83 (d, *J* = 5.4 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.6, 131.7, 128.5, 128.4, 128.3, 127.4, 126.2, 122.4, 86.6, 84.6, 71.4, 59.3, 58.8, 53.3; **IR** (KBr, neat): 2925,

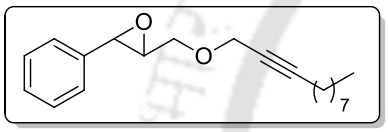
2854, 1490, 1256, 1098, 1027, 698 cm^{-1}; **HRMS** (ESI) calcd. for $C_{18}H_{17}O_2$ $(M + H)^+$ 265.1229, found 265.1228.

2-((But-2-yn-1-yloxy)methyl)-3-phenyloxirane (42f):



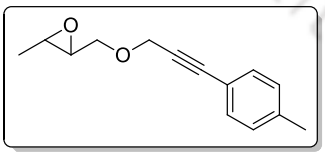
Colourless oil; R_f (hexane/ EtOAc 9:1): 0.50; Yield 213 mg, 95%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5 H), 4.21 (s, 2 H), 3.87 (dd, *J* = 11.6 and 3.2 Hz, 1 H), 3.82 (brs, 1 H), 3.67 (dd, *J* = 11.6 and 4.8 Hz, 1 H), 3.24 (t, *J* = 2.4 Hz, 1 H), 1.85 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.8, 128.5, 128.3, 125.7, 83.0, 74.8, 69.2, 60.8, 59.1, 55.9, 3.6; **IR** (KBr, neat): 2920, 1497, 1461, 1357, 1139, 1095, 1023, 698 cm^{-1}; **HRMS** (ESI^+) calcd. for $C_{13}H_{14}O_2$ $(M + Na)^+$ 225.0886, found 225.0885.

2-Phenyl-3-((undec-2-yn-1-yloxy)methyl)oxirane (42g):



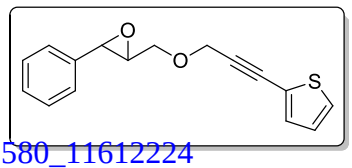
Colourless oil; R_f (hexane/ EtOAc 9:1): 0.60; Yield 276 mg, 92%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5 H), 4.23 (s, 2 H), 3.87 (d, *J* = 11.2 Hz, 1 H), 3.81 (s, 1 H), 3.68 (dd, *J* = 11.2 and 5.2Hz, 1 H), 3.23 (d, *J* = 1.6 Hz, 1 H), 2.21 (t, *J* = 5.6 Hz, 2 H), 1.54-1.47 (m, 2 H), 1.41-1.20 (m, 10 H), 0.87 (t, *J* = 6.4 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.9, 128.6, 128.3, 125.8, 87.8, 75.5, 69.2, 60.9, 59.2, 56.1, 31.9, 29.5, 29.2, 29.0, 28.7, 22.8, 18.9, 14. 2; **IR** (KBr, neat): 2927, 2855, 1461, 1357,1137, 1095, 750, 698 cm^{-1}; **HRMS** (ESI) calcd. for $C_{20}H_{29}O_2$ $(M + H)^+$ 301.2162, found 301.2158.

2-Methyl-3-(((3-(*p*-tolyl)prop-2-yn-1-yl)oxy)methyl)oxirane (42i):



Colourless oil; R_f (hexane/ EtOAc 9:1) 0.50; yield 194 mg, 90%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 2 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 4.41 (d, *J* = 9.6 Hz, 2 H), 3.80 (dd, *J* = 10.8 and 3.0 Hz, 1 H), 3.60 (dd, *J* = 11.4 and 5.4 Hz, 1 H), 2.93-2.97 (m, 2 H), 2.34 (s, 3 H), 1.33 (d, *J* = 7.0 Hz, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 138.7, 131.7, 129.1, 119.4, 86.8, 83.9, 69.9, 59.3, 57.6, 52.3, 21.5, 17.3; **IR** (KBr, neat) 2924, 2855, 1510, 1356, 1258, 1120, 1091, 817, 753 cm^{-1}; **HRMS** (ESI): m/z calcd. for $C_{14}H_{17}O_2$ $(M + H)^+$ 217.1229, found 217.1227.

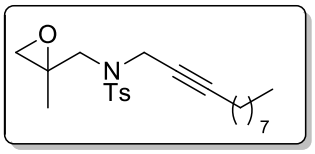
2-Phenyl-3-(((3-(thiophen-2-yl)prop-2-yn-1-yl)oxy)methyl)oxirane (42j):



Colourless oil; R_f (hexane/ EtOAc 9:1) 0.50; yield 238 mg, 88%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 7 H), 6.99-6.96 (dd, *J*

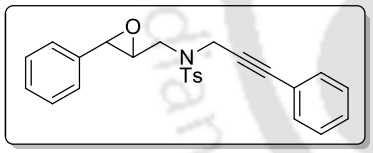
= 4.8 and 3.6 Hz, 1 H), 4.50 (s, 2 H), 3.97 (dd, *J* = 11.2 and 3.2 Hz, 1 H), 3.85 (d, *J* = 1.6 Hz, 1 H), 3.75 (dd, *J* = 11.2 and 4.8 Hz, 1 H), 3.29-3.26 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.8, 132.7, 128.6, 128.4, 127.6, 127.1, 125.8, 122.4, 88.8, 80.1, 69.5, 60.9, 59.5, 56.0; **IR** (KBr, neat) 2923, 2854, 1674, 1463, 1359, 1190, 1098, 848, 697 cm^{-1}; **HRMS** (ESI): m/z calcd. for $C_{16}H_{15}O_2S$ $(M + H)^+$ 271.0787, found 271.0789.

4-Methyl-*N*-((2-methyloxiran-2-yl)methyl)-*N*-(undec-2-yn-1-yl)benzenesulfonamide (46a):



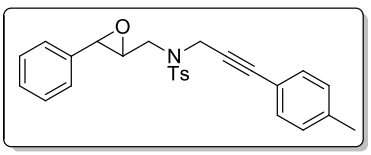
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.45; yield 352 mg, 90%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.2 Hz, 2 H), 7.26 (d, *J* = 7.2 Hz, 2 H), 4.23 (d, *J* = 18.4 Hz, 1 H), 4.12 (d, *J* = 18.4 Hz, 1 H), 3.28 (s, 2 H), 2.75 (d, *J* = 4.4 Hz, 1 H), 2.62 (d, *J* = 3.6 Hz, 1 H), 2.39 (s, 3 H), 1.82 (t, *J* = 6.0 Hz, 2 H), 1.39 (s, 3 H), 1.28-1.14 (m, 12 H), 0.87 (t, *J* = 6.8 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.5, 136.2, 129.5, 128.0, 86.7, 72.3, 55.7, 51.9, 50.9, 38.4, 32.0, 29.3, 29.2, 28.9, 28.4, 22.8, 21.6, 19.0, 18.6, 14.3; **IR** (KBr, neat) 2927, 2856, 1442, 1351, 1164, 1090, 1047, 658 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{34}NO_3S$ $(M + H)^+$ 392.2254, found 392.2261.

4-Methyl-*N*-((3-phenyloxiran-2-yl)methyl-*N*-(3-phenylprop-2-yn-1-yl)benzene-sulfonamide (46b):



Colourless oil; R_f (hexane/ EtOAc 4:1) 0.40; yield 342 mg, 82%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2 H), 7.35-7.21 (m, 10 H), 7.06 (d, *J* = 7.2 Hz, 2 H), 4.52 (d, *J* = 18.6 Hz, 1 H), 4.44 (d, *J* = 18.6 Hz, 1 H), 3.74 (d, *J* = 2.4 Hz, 1 H), 3.58 (d, *J* = 3.6 Hz, 2 H), 3.26 (dt, *J* = 4.8 and 4.2 Hz, 1 H), 2.34 (s, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.8, 136.3, 135.8, 131.5, 129.6, 128.6, 128.5, 128.4, 128.2, 127.8, 125.7, 122.0, 86.0, 81.7, 60.5, 57.0, 48.0, 39.0, 21.4; **IR** (KBr, neat) 2922, 2851, 1643, 1447, 1383, 1265 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{24}NO_3S$ $(M + H)^+$ 418.1477, found 418.1474.

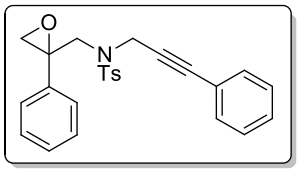
4-Methyl-*N*-((3-phenyloxiran-2-yl)methyl)-*N*-(3-(*p*-tolyl)prop-2-yn-1-yl)benzene sulfonamide (46c):



Colourless oil; R_f (hexane/ EtOAc 4:1) 0.45; yield 357 mg, 83%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2 H), 7.27-7.11 (m, 7 H), 6.96 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 4.44 (d, *J* = 18.0 Hz, 1 H), 4.34 (d, *J* = 18.0 Hz, 1 H), 3.74 (d, *J* = 1.2 Hz, 1 H), 3.50 (dd, *J* = 12.0 and 4.8 Hz, 2 H), 3.17 (dt, *J* = 5.4 and 4.2 Hz, 1 H), 2.27 (s, 3 H), 2.26 (s, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.9, 138.9, 136.5, 131.6, 129.8, 129.1, 128.7, 128.6, 127.6, 127.5, 125.8, 119.2, 86.3,

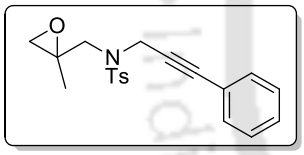
81.2, 60.6, 57.3, 48.2, 39.2, 21.7 (2C); **IR** (KBr, neat) 2922, 2851, 1462, 1349, 1163, 1090, 843, 744 cm^{-1}; **HRMS** (ESI) calcd. for $C_{26}H_{26}NO_3S$ $(M + H)^+$ 432.1633, found 432.1639.

4-Methyl-*N*-((2-phenyloxiran-2-yl)methyl)-*N*-(3-(*p*-tolyl)prop-2-yn-1-yl)benzene sulfonamide (46d):



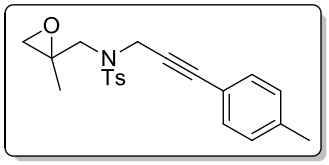
Colourless oil; R_f (hexane/ EtOAc 4:1) 0.50; yield 371 mg, 89%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2 H), 7.48 (d, *J* = 8.4 Hz, 2 H), 7.38 (t, *J* = 8.4 Hz, 3 H), 7.25- 7.19 (m, 5 H), 7.00 (d, *J* = 8.4 Hz, 2 H), 4.38 (brs, 2 H), 3.97 (d, *J* = 15 Hz, 1 H), 3.74 (d, *J* = 15.0 Hz, 1 H), 3.27 (d, *J* = 5.4 Hz, 1 H), 2.83 (d, *J* = 5.4 Hz, 1 H), 2.32 (s, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.9, 137.6, 136.2, 131.7, 129.8, 128.7, 128.6, 128.4, 128.3, 128.1, 126.5, 122.4, 86.0, 82.0, 59.4, 53.3, 49.5, 39.2, 21.6; **IR** (KBr, neat) 2923, 2853, 1447, 1350, 1161, 1027, 757, 696 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{24}NO_3S$ $(M + H)^+$ 418.1477, found 418.1476.

4-Methyl-*N*-((2-methyloxiran-2-yl)methyl-*N*-(3-phenylprop-2-yn-1-yl)benzene-sulfonamide (46e):



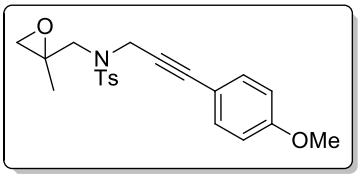
Colourless oil; R_f (hexane/ EtOAc 4:1) 0.50; yield 298 mg, 84%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 2 H), 7.34- 7.20 (m, 5 H), 7.00 (d, *J* = 8.1 Hz, 2 H), 4.48 (d, *J* = 18.6 Hz, 1 H), 4.40 (d, *J* = 18.6 Hz, 1 H), 3.39 (d, , *J* = 13.2 Hz, 2 H), 2.82 (d, *J* = 4.8 Hz, 1 H), 2.67 (d, *J* = 4.8 Hz, 1 H), 2.33 (s, 3 H), 1.45 (s, 3 H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.6, 135.8, 131.4, 129.5, 128.4, 128.0, 127.7, 122.0, 85.8, 81.5, 55.7, 51.6, 50.9, 38.6, 21.4, 18.9. **IR** (KBr, neat): 2923, 2853, 1491, 1349, 1162, 1090, 1027, 757 cm^{-1}; **HRMS** (ESI) calcd. for $C_{20}H_{22}NO_3S$ $(M + H)^+$ 356.1320, found 356.1315.

4-Methyl-*N*-((2-methyloxiran-2-yl)methyl-*N*-(3-(*p*-tolyl)prop-2-yn-1-yl)benzene-sulfonamide (46f):



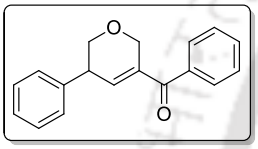
Colourless oil; R_f (hexane/ EtOAc 4:1) 0.50; yield 306 mg, 83%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8.0 Hz, 2 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 4.47 (d, *J* = 18.6 Hz, 1 H), 4.39 (d, *J* = 18.6 Hz, 1 H), 3.39 (s, 2 H), 2.81 (d, *J* = 4.2 Hz, 1 H), 2.66 (d, *J* = 4.8 Hz, 1 H), 2.33 (s, 3 H), 2.32 (s, 3 H), 1.43 (s, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.6, 138.6, 136.0, 131.4, 129.6, 128.8, 127.8, 119.0, 86.0, 80.9, 55.7, 51.7, 51.0, 38.7, 21.4 (2C), 19.0; **IR** (KBr, neat) 2921, 2851, 1348, 1162, 1090, 1039, 844, 743 cm^{-1}; **HRMS** (ESI) calcd. for $C_{21}H_{24}NO_3S$ $(M + H)^+$ 370.1477, found 370.1476.

_N_-(3-(4-methoxyphenyl)prop-2-yn-1-yl)-4-methyl-_N_-((2-methyloxiran-2-yl)methyl)-benzenesulfonamide (46g):



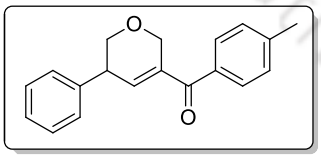
Colourless oil; R_f (hexane/ EtOAc 4:1) 0.50; yield 315 mg, 82%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 2 H), 7.25 (d, *J* = 7.8 Hz, 2 H), 6.96 (d, *J* = 8.4 Hz, 2 H), 6.75 (d, *J* = 8.4 Hz, 2 H), 4.46 (d, *J* = 18.6 Hz, 1 H), 4.37 (d, *J* = 18.6 Hz, 1 H), 3.78 (s, 3 H), 3.38 (s, 2 H), 2.82 (d, *J* = 4.8 Hz, 1 H), 2.66 (d, *J* = 4.8 Hz, 1 H), 2.34 (s, 3 H), 1.44 (s, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.8, 143.8, 136.2, 133.1, 130.1, 129.7, 114.4, 113.9, 85.9, 80.4, 55.9, 55.5, 51.9, 51.2, 38.9, 21.6, 19.1; **IR** (KBr, neat) 2923, 2850, 1606, 1509, 1348, 1248, 1162, 1031, 750 cm^{-1}; **HRMS** (ESI) calcd. for $C_{21}H_{24}NO_4S$ $(M + H)^+$ 386.1426, found 386.1422.

Phenyl(4-phenyl-3,6-dihydro-2*H*-pyran-3-yl)methanone (47a):



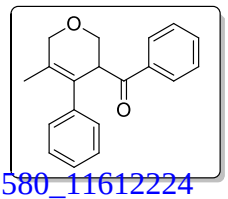
Colourless solid; mp 111-112 ^{o}C; R_f (hexane/ EtOAc 9:1) 0.50; Yield 179 mg, 68%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 1 H), 7.43-7.40 (m, 2 H), 7.34-7.31 (m, 2 H), 7.27 (t, *J* = 7.8 Hz, 1 H), 7.22 (d, *J* = 7.8 Hz, 2 H), 6.73 (dd, *J* = 1.8 and 1.2 Hz, 1 H), 4.63 (dd, *J* = 2.4 and 1.8 Hz, 2 H), 4.12 (dd, *J* = 11.4 and 5.4 Hz, 1 H), 3.78-3.74 (m, 1 H), 3.63 (dd, *J* = 11.4 and 7.2 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.0, 143.0, 140.1, 137.7, 137.5, 132.2, 129.3, 129.0, 128.5, 128.3, 127.5, 70.6, 65.4, 42.1; **IR** (KBr, neat) 2923, 2852, 1640, 1447, 1265, 1105, 1047, 742, 700 cm^{-1}; **HRMS** (ESI) calcd. for $C_{18}H_{17}O_2$ $(M + H)^+$ 265.1229 found 265.1229.

(4-Phenyl-3,6-dihydro-2H-pyran-3-yl)(*p*-tolyl)methanone (47b):



Yellow oil; R_f (hexane/ EtOAc 9:1) 0.50; yield 197 mg, 71%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 1 H), 7.35- 7.21 (m, 8 H), 6.71 (dd, *J* = 2.8 and 1.6 Hz,1 H), 4.62 (dd, *J* = 2.8 and 2.0 Hz, 2 H), 4.12 (dd, *J* = 11.2 and 5.6 Hz, 1 H), 3.78-3.74 (m, 1 H), 3.63 (dd, *J* = 11.2 and 7.2 Hz, 1 H), 2.38 (s, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 195.8, 142.1, 140.3, 137.9, 134.8, 130.6, 129.6, 129.4, 129.2, 128.4, 127.5, 70.7, 65.5, 42.1, 21.7; **IR** (KBr, neat) 2924, 2852, 1641, 1454, 1264, 1106, 759, 7001 cm^{-1}; **HRMS** (ESI) calcd. For $C_{19}H_{19}O_2$ $(M + H)^+$ 279.1385, found 279.1384.

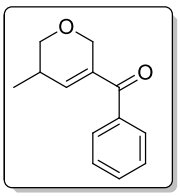
(5-Methyl-4-phenyl-3,6-dihydro-2*H*-pyran-3-yl)(phenyl)methanone (47c):



Yellow oil; R_f (hexane/EtOAc 9:1) 0.50; yield 172 mg, 62%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.4 Hz, 1 H), 7.59-7.26 (m, 9 H), 4.48-4.38 (m, 2 H), 4.07 (dd, *J* = 11.2 and 4.4 Hz, 1 H), 3.87 (dd, *J* = 11.2 and 4.0 Hz, 1 H),

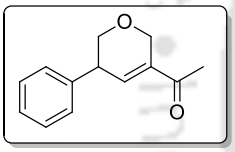
3.33 (brs, 1 H), 1.45 (s, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 198.4, 141.4, 137.3, 135.5, 133.8, 133.7, 129.4, 129.1, 128.9, 128.8, 127.3, 71.4, 66.9, 46.5, 19.7; **IR** (KBr, neat) 2923, 2852, 1641, 1447, 1265, 1105, 1047, 742, 701 cm^{-1}; **HRMS** (ESI) calcd. For $C_{19}H_{19}O_2$ $(M + H)^+$ 279.1385, found 279.1383.

(5-Methyl-5,6-dihydro-2*H*-pyran-3-yl)(phenyl)methanone (47d):



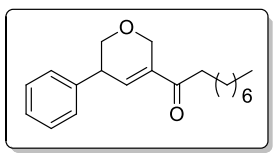
Yellow oil; R_f (hexane/EtOAc 9:1) 0.50; yield 131 mg, 65%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67-7.65 (m, 2 H), 7.56-7.52 (m, 1 H), 7.47-7.43 (m, 2 H), 6.54 (brs, 1 H), 4.49 (dd, *J* = 12.0 and 2.0 Hz, 2 H), 3.95 (dd, *J* = 10.8 and 5.6 Hz, 1 H), 3.34 (dd, *J* = 10.8 and 7.2 Hz, 1 H), 2.63-2.58 (m, 1 H), 1.06 (d, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.0, 146.0, 137.8, 136.9, 132.0, 129.3, 128.4, 70.1, 65.3, 30.3, 16.7; **IR** (KBr, neat) 2924, 2852, 1641, 1447, 1264, 1111, 1024, 820, 711 cm^{-1}; **HRMS** (ESI) calcd. For $C_{13}H_{15}O_2$ $(M + H)^+$ 203.1072, found 203.1074.

1-(5-Phenyl-5,6-dihydro-2*H*-pyran-3-yl)ethanone (47f):



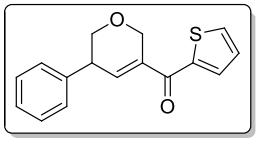
Yellow oil*;* R_f (hexane/EtOAc 9:1) 0.40; yield 166 mg, 74%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 2 H), 7.32-7.29 (m, 1 H), 7.26-7.22 (m, 2 H), 6.98 (brs, 1 H), 4.48 (d, *J* = 16.8 Hz, 1 H), 4.42 (d, *J* = 16.8 Hz, 1 H), 4.06 (dd, *J* = 11.6 and 5.2 Hz, 1 H), 3.74-3.69 (m, 1 H), 3.56 (dd, *J* = 10.8 and 7.6 Hz, 1 H), 2.33 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.8, 140.5, 140.1, 138.6, 129.0, 128.3, 127.5, 70.2, 64.6, 41.9, 25.2; **IR** (KBr, neat) 2922, 2850, 1667, 1389, 1239, 1107, 701 cm^{-1}; **HRMS** (ESI) calcd. For $C_{13}H_{14}O_2$ $(M + Na)^+$ 225.0886, found 225.0871.

1-(5-Phenyl-5,6-dihydro-2*H*-pyran-3-yl)nonan-1-one (47g):



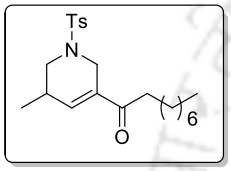
Yellow oil*;* R_f (hexane/EtOAc 9:1) 0.50; yield 228 mg, 76%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.33 (m, 2 H), 7.30-7.27 (m, 1 H), 7.23-7.20 (m, 2 H), 6.97 (brs, 1 H), 4.47 (d, *J* = 16.4 Hz, 1 H), 4.39 (d, *J* = 16.4 Hz, 1 H), 4.04 (dd, *J* = 13.6 and 5.6 Hz, 1 H), 3.74-3.66 (m, 1 H), 3.53 (dd, *J* = 10.8 and 7.2 Hz, 1 H), 2.65 (t, *J* = 16.4 Hz, 2 H), 1.65-1.58 (m, 2 H), 1.32-1.20 (m, 10 H), 0.87 (t, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.3, 140.2, 139.2, 138.2, 129.0, 128.3, 127.5, 70.4, 64.8, 41.9, 37.2, 32.0, 29.5, 29.4, 29.3, 24.7, 22.8, 14.3; **IR** (KBr, neat) 2925, 2854, 1667, 1454, 1108, 1024, 700 cm^{-1}; **HRMS** (ESI) calcd. For $C_{20}H_{29}O_2$ $(M + H)^+$ 301.2162, found 301.2168.

(5-Phenyl-5,6-dihydro-2*H*-pyran-3-yl)(thiophen-2-yl)methanone (47j):



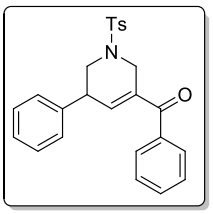
Pale yellow oil; R_f (hexane/EtOAc 9:1) 0.40; yield 163 mg, 60%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 1 H), 7.41-7.34 (m, 2 H), 7.31-7.27 (m, 4 H), 7.11 (t, *J* = 3.6 Hz, 1 H), 6.95 (brs, 1 H), 4.60 (brs, 2 H), 4.13 (dd, *J* = 11.2 and 4.0 Hz, 1 H), 3.82-3.75 (m, 1 H), 3.64 (dd, *J* = 11.2 and 7.2 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.9, 142.7, 140.3, 139.8, 138.2, 133.9, 133.6, 129.1, 128.4, 128.1, 127.6, 70.7, 65.4, 42.0; **IR** (KBr, neat) 2957, 2824, 1621, 1414, 1121, 1052, 700 cm^{-1}; **HRMS** (ESI) calcd. For $C_{16}H_{15}O_2S$ $(M + H)^+$ 271.0787, found 271.0790.

1-(5-Methyl-1-tosyl-3,4-dehydropiperidin-3-yl)nonan-1-one (48a):



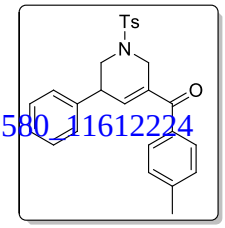
Yellow oil*;* R_f (hexane/EtOAc 9:1) 0.40; yield 301 mg, 77%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 2 H), 7.31 (d, *J* = 7.6 Hz, 2 H), 6.70 (brs, 1 H), 3.90 (d, *J* = 16.8 Hz, 1 H), 3.48 (d, *J* = 18.0 Hz, 1 H), 3.43 (dd, *J* = 11.6 and 4.4 Hz, 1 H), 2.72-2.64 (m, 1 H), 2.58 (t, *J* = 6.8 Hz, 2 H), 2.49 (dd, *J* = 11.2 and 7.6 Hz, 1 H), 2.41 (s, 3 H), 1.58-1.50 (m, 2 H), 1.30-1.18 (m, 10 H), 1.11 (d, *J* = 7.2 Hz, 3 H), 0.86 (t, *J* = 6.8 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$)δ 199.6, 143.8, 142.3, 134.8, 133.1, 129.9, 127.8, 48.7, 43.8, 36.9, 31.8, 31.2, 29.4, 29.3, 29.2, 24.5, 22.7, 21.6, 17.7, 14.1; **IR** (KBr, neat) 2925, 2854, 1667, 1459, 1348, 1166, 1025, 657 cm^{-1}; **HRMS** (ESI) calcd. For $C_{22}H_{34}NO_3S$ $(M + H)^+$ 392.2254, found 392.2258.

Phenyl(4-phenyl-1-tosyl-3,4- dehydropiperidin-3-yl)methanone (48b):



Yellow oil; (hexane/EtOAc 4:1) 0.30; yield 250 mg, 60%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 7.8 Hz, 2 H), 7.42-7.27 (m, 8 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 6.63 (s, 1 H), 4.35 (dd, *J* = 18.0 and 1.8 Hz, 1 H), 3.95-3.89 (m, 2 H), 3.75 (d, *J* = 16.8 Hz, 1 H), 2.67 (dd, *J* = 10.8 and 7.2 Hz, 1 H), 2.43 (s, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 195.4, 143.9, 139.3, 137.1, 135.3, 132.2, 130.9, 129.9, 129.4, 128.5, 127.9, 127.7, 127.3, 124.4, 114.1, 49.6, 44.5, 42.8, 21.5; **IR** (KBr, neat) 2922, 2852, 1643, 1163, 1090, 1039, 1026, 761, 670 cm^{-1}; **HRMS** (ESI) calcd. for $C_{25}H_{24}NO_3S$ $(M + H)^+$ 418.1477 found 418.1477.

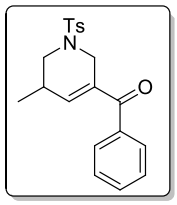
(4-Phenyl-1-tosyl-3,4-dehydropiperidin-3-yl)(*p*-tolyl)methanone (48c):



Yellow oil; R_f (hexane/EtOAc 4:1) 0.35; yield 263 mg, 61%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 7.36-7.27

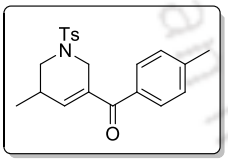
(m, 5 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 6.60 (brs, 1 H), 4.34 (dd, *J* = 16.8 and 1.8 Hz, 1 H), 3.95-3.88 (m, 2 H), 3.74(d, *J* = 16.8 Hz, 1 H), 2.64 (dd, *J* = 12.0 and 7.2 Hz, 1 H), 2.43 (s, 3 H), 2.37 (s, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 195.3, 144.1, 143.3, 142.7, 139.5, 135.6, 134.6, 130.1, 129.6, 129.5, 129.3, 129.2, 128.2, 128.0, 114.3, 49.9, 44.8, 42.9, 22.8 (2C); **IR** (KBr, neat) 2923, 2853, 1642, 1454, 1348, 1166, 1091, 701 cm^{-1}; **HRMS** (ESI) calcd. For $C_{26}H_{26}NO_3S$ $(M + H)^+$ 432.1633, found 432.1632.

(5-Methyl-1-tosyl-3,4-dehydropiperidin-3-yl)(phenyl)methanone (48e):



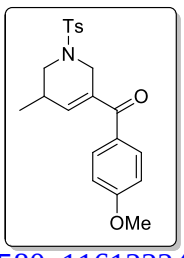
Yellow oil; R_f (hexane/EtOAc 4:1) 0.50; yield 277 mg, 78%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 7.8 Hz, 2 H), 7.53 (t, *J* = 7.2 Hz, 1 H), 7.43 (t, *J* = 7.8 Hz, 2 H), 7.35 (d, *J* = 7.8 Hz, 2 H), 6.45 (d, *J* = 4.2 Hz, 1 H), 4.09 (d, *J* = 16.2 Hz, 1 H), 3.74 (dt, *J* = 16.8 and 2.4 Hz, 1 H), 3.53 (dd, *J* = 11.4 and 5.4 Hz, 1 H), 2.71-2.76 (m,1 H), 2.58 (dd, *J* = 11.4 and 7.8 Hz, 1 H), 2.44 (s, 3 H), 1.10 (d, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.4, 146.3, 143.7, 137.2, 132.8, 131.4, 129.9, 129.6, 128.7, 128.0, 127.5, 48.7, 44.3, 31.1, 21.5, 17.5; **IR** (KBr, neat) 2964, 2926, 1644, 1346, 1167, 1091, 713 cm^{-1}; **HRMS** (ESI) calcd. For $C_{20}H_{22}NO_3S$ $(M + H)^+$ 356.1320 found 356.1314.

(5-Methyl-1-tosyl-3,4-dehydropiperidin-3-yl)(*p*-tolyl)methanone (48f):



Yellow oil; R_f (hexane/EtOAc 4:1) 0.4; yield 278 mg, 75%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 6.42 (d, *J* = 3.0 Hz, 1 H), 4.08 (d, *J* = 16.8 Hz, 1 H), 3.74 (dt, *J* = 16.8 and 2.4 Hz, 1 H), 3.53 (dd, *J* = 11.4 and 5.4 Hz, 1 H), 2.70-2.78 (m, 1 H), 2.57 (dd, *J* = 11.4 and 7.2 Hz, 1 H), 2.43 (s, 3 H), 2.41 (s, 3 H), 1.09 (d, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 195.4, 145.6, 144.0, 143.1, 134.8, 134.2, 133.4, 130.0, 129.6, 129.2, 128.0, 49.0, 44.7, 31.4, 21.8, 21.7, 17.9; **IR** (KBr, neat) 2925, 2854, 1727, 1643, 1605, 1347, 1167, 1091, 745 cm^{-1}; **HRMS** (ESI) calcd. For $C_{21}H_{24}NO_3S$ $(M + H)^+$ 370.1477 found 370.1477.

(4-Methoxyphenyl)(5-methyl-1-tosyl-3,4-dehydropiperidin-3-yl)methanone (48g):

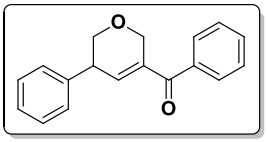


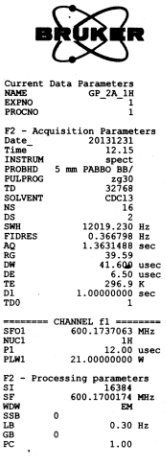
Yellow oil; R_f (hexane/EtOAc 4:1) 0.35; yield 281 mg, 73%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2 H), 7.64 (d, *J* = 8.1 Hz, 2 H), 7.34 (d, *J* = 7.8 Hz, 2 H), 6.91 (d, *J* = 7.8 Hz, 2 H), 6.38 (d, *J* = 3.6 Hz, 1 H), 4.07 (d, *J* = 16.2 Hz, 1 H), 3.87 (s, 3 H), 3.67 (dt, *J* = 16.8 and 2.4 Hz, 1 H), 3.54 (dd, *J* =

11.4 and 5.4 Hz, 1 H), 2.70-76 (m, 1 H), 2.56 (dd, *J* = 11.4 and 7.2 Hz, 1 H), 2.43 (s, 3 H), 1.10 (d, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 194.4, 163.3, 144.3, 144.0, 134.2, 133.4, 131.8, 130.0, 129.9, 128.0, 113.8, 55.7, 49.1, 44.9, 31.3, 21 .7, 17.9; **IR** (KBr, neat) 2918, 2849, 1640, 1598, 1256, 1165, 1091, 1028, 842, 746 cm^{-1}; **HRMS** (ESI) calcd. for $C_{21}H_{24}NO_4S$ $(M + H)^+$ 386.1426 found 386.1421.

2.7. Selected Spectra

^{1}H and ^{13}C NMR Spectra of Phenyl(4-phenyl-3,6-dihydro-2*H*-pyran-3-yl)methanone 47a:





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PROCNO                       1

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TD                      32768
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RG                       39.59
DW                      41.600 usec
DE                       6.50 usec
TE                      296.9 K
D1                    1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
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NUC1                        1H
P1                       12.00 usec
PLW1                21.00000000 W

F2 - Processing parameters
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SF                  600.1700174 MHz
WDW                         EM
SSB                  0
LB                       0.30 Hz
GB                   0
PC                       1.00
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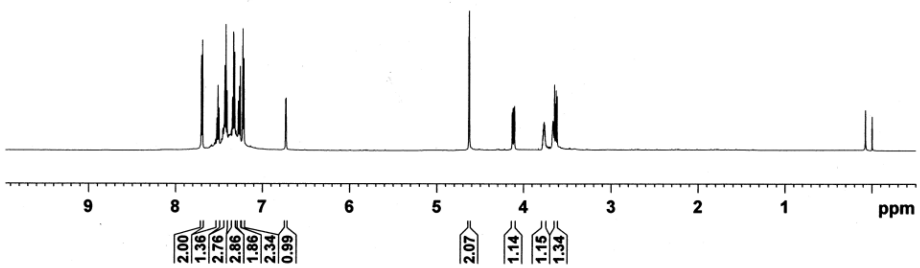


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expl  s2pul

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file             exp    spin      not used
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at            1.199     alfa          20.000
np             60270            FLAGS
fb             13000    il                n
bs                16    in                n
d1             1.000    dp                y
nt              5000    hs               nn
ct              1988          PROCESSING
  TRANSMITTER           lb             2.00
tn               C13    fn            65536
sfrq        188.554           DISPLAY
tof          1536.3     sp          -356.2
tpwr             61     wp         21658.2
pw            4.700     rf1         9276.7
  DECOUPLER             rfp         7764.9
dn               H1     rp            -0.5
dof               0     lp          -366.1
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                        nm  no  ph
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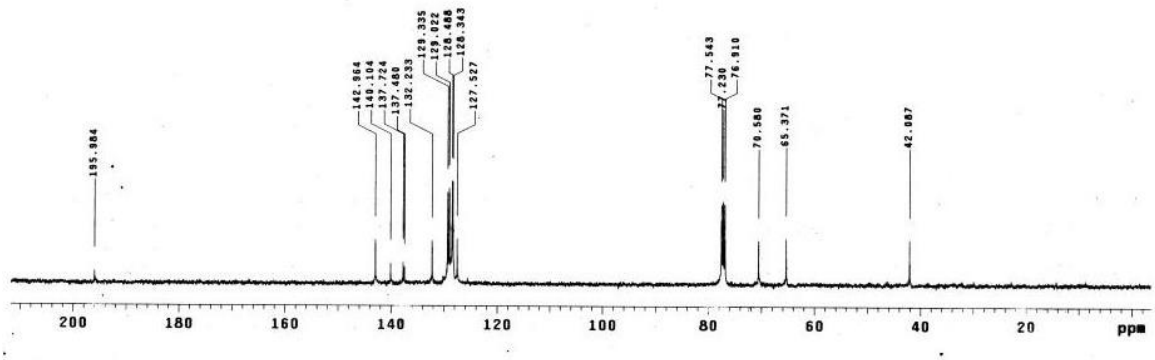
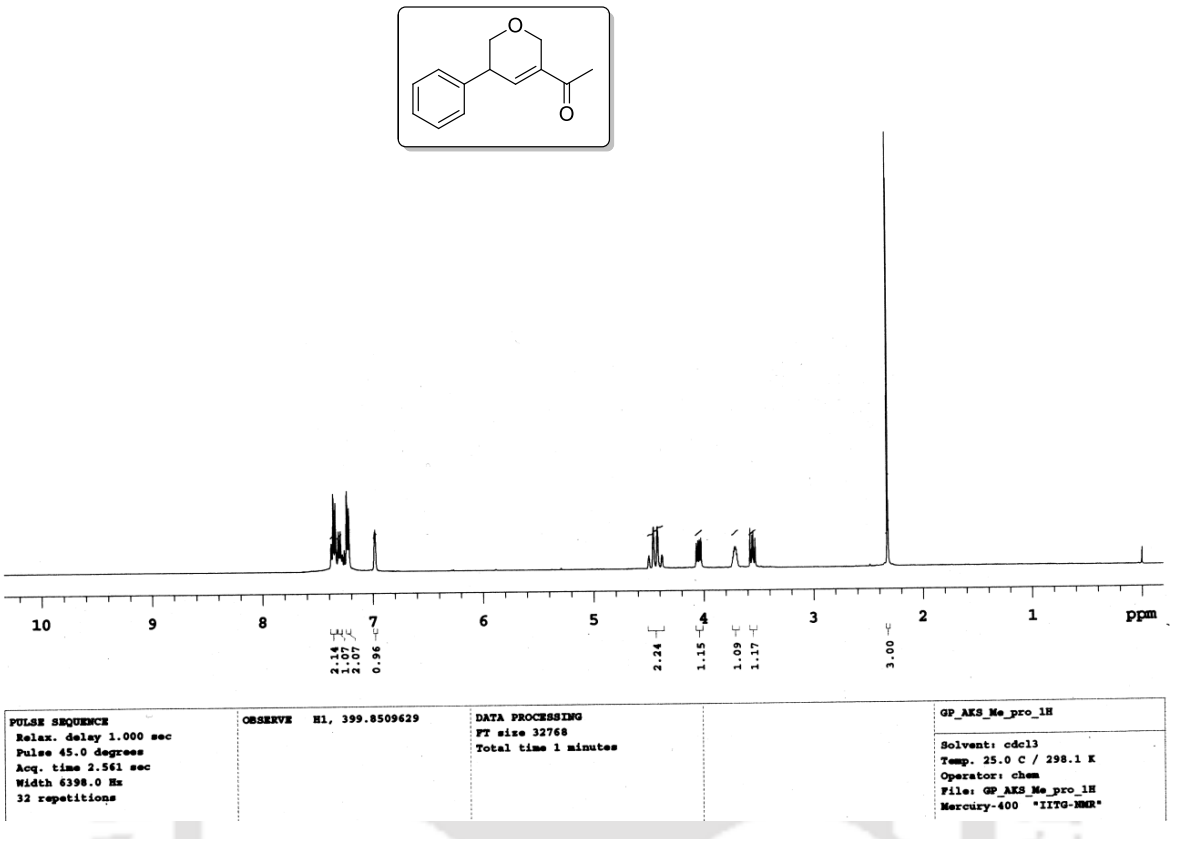
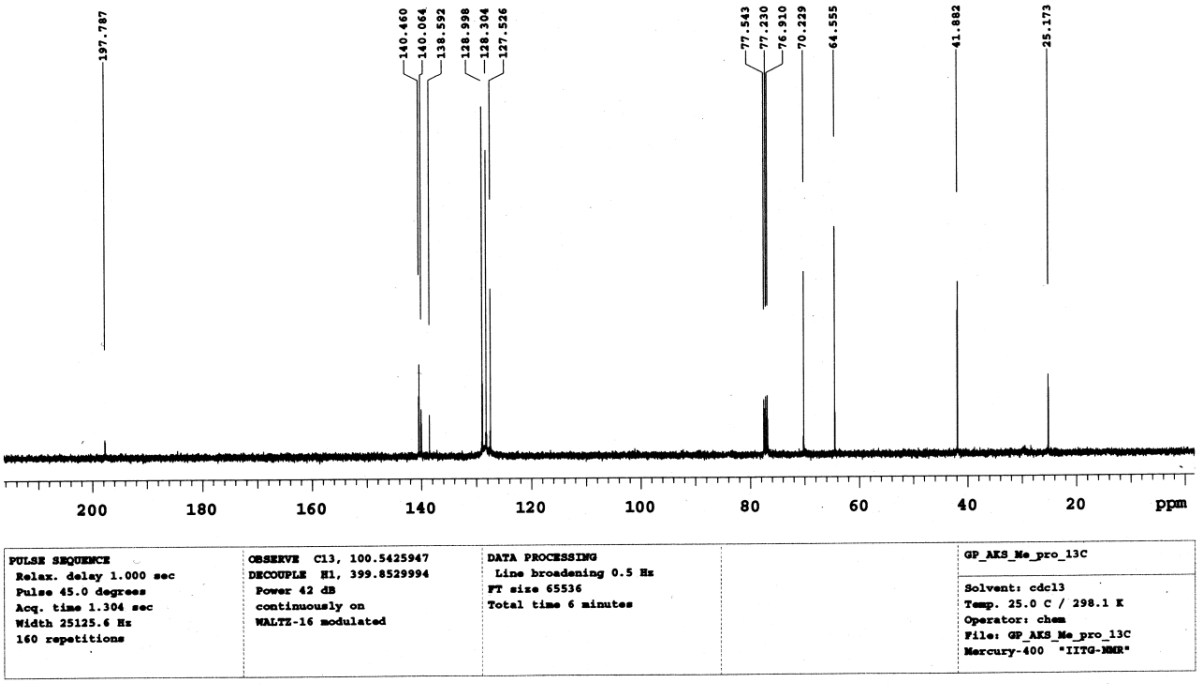
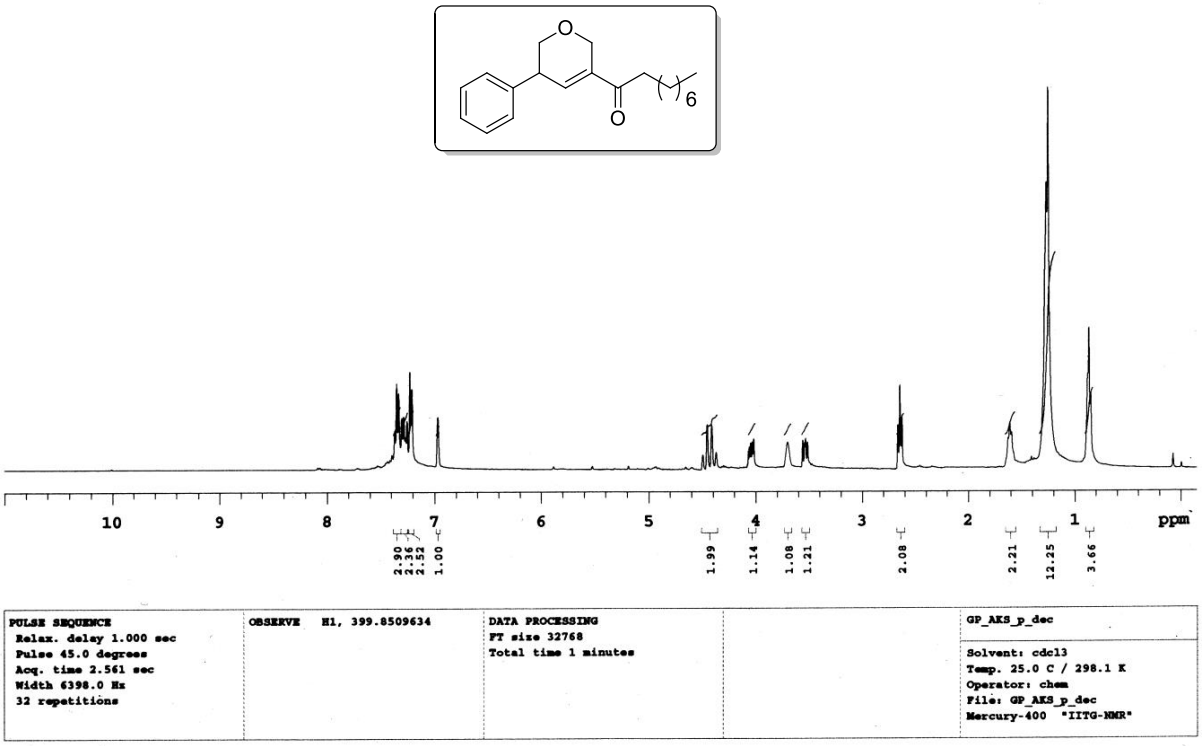


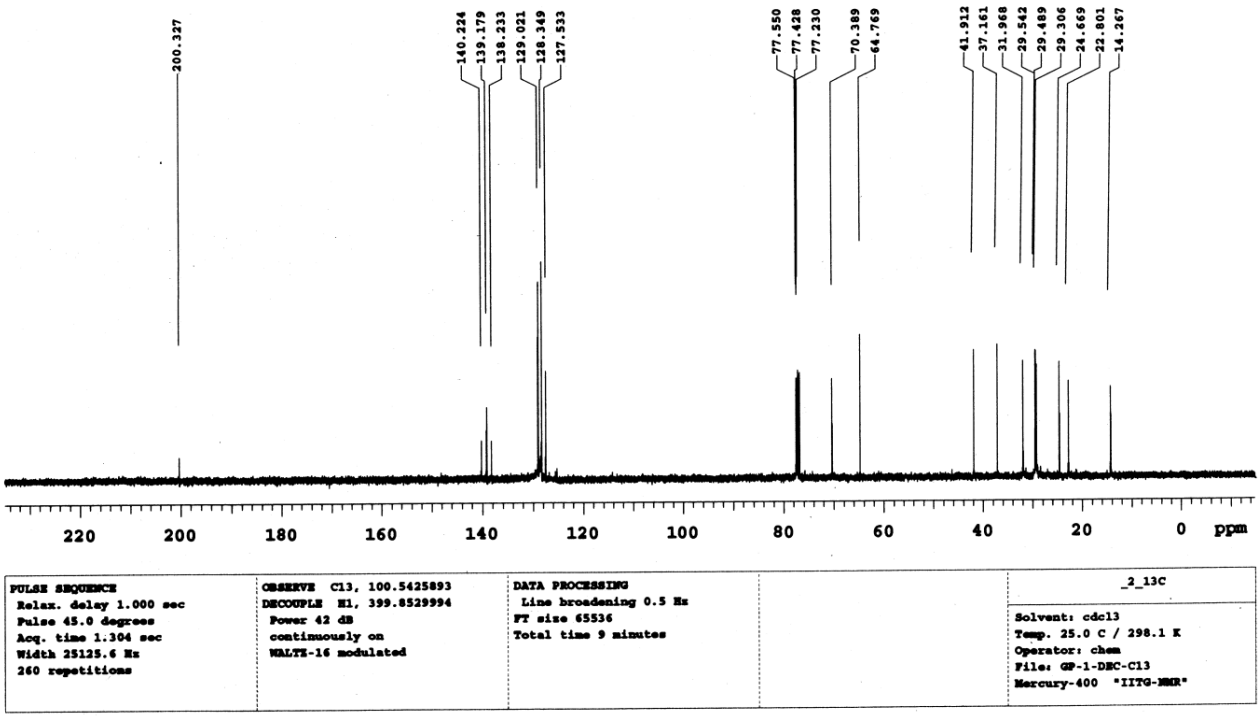
^{1}H and ^{13}C NMR Spectra of 1-(5-Phenyl-5,6-dihydro-2*H*-pyran-3-yl)ethanone 47f:



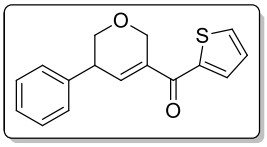


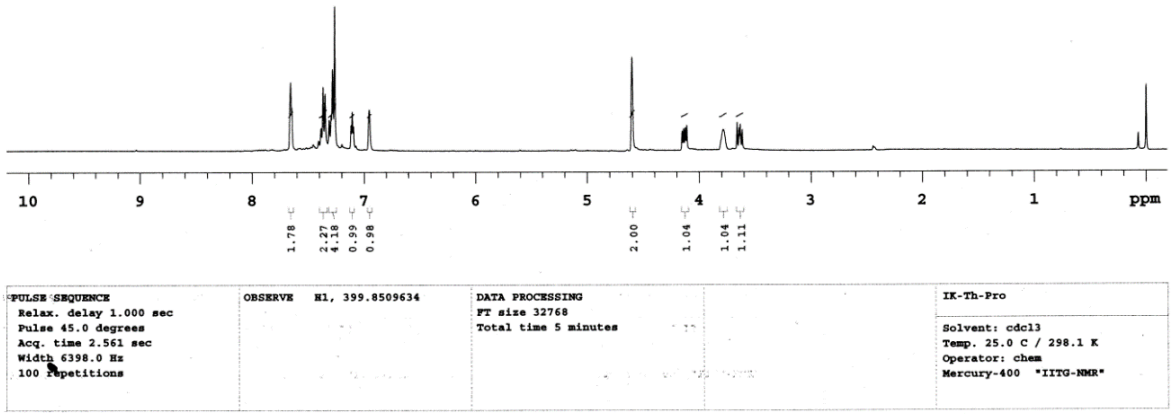
^{1}H and ^{13}C NMR Spectra of 1-(5-Phenyl-5,6-dihydro-2*H*-pyran-3-yl)nonan-1-one 47g:

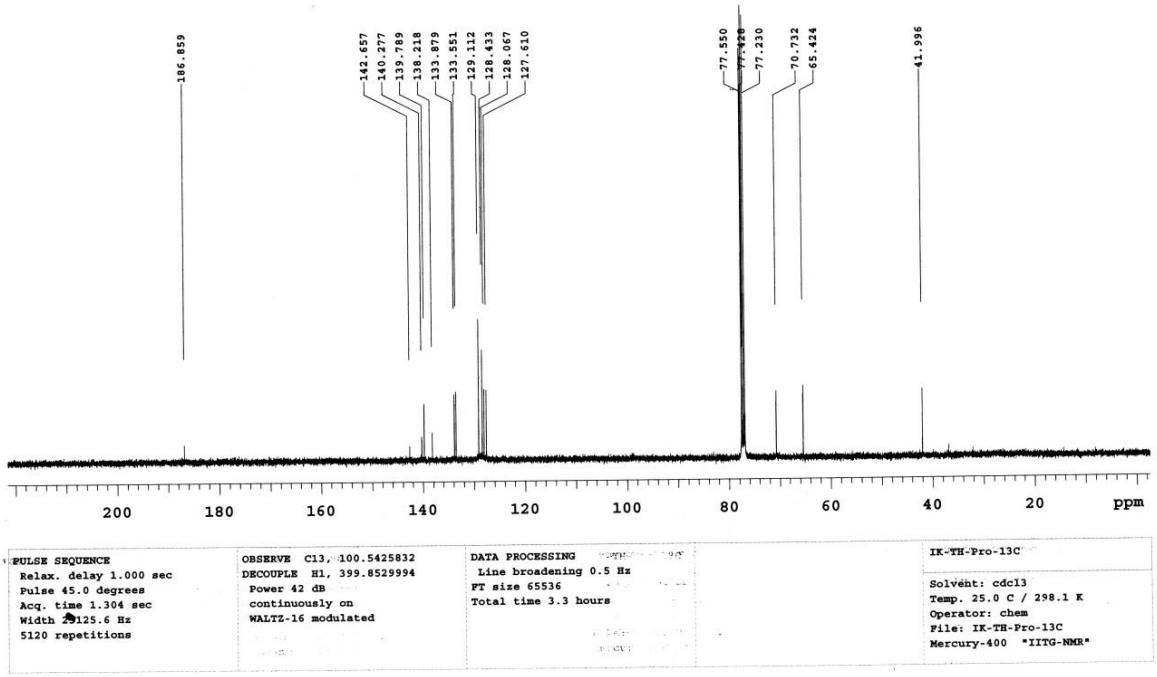




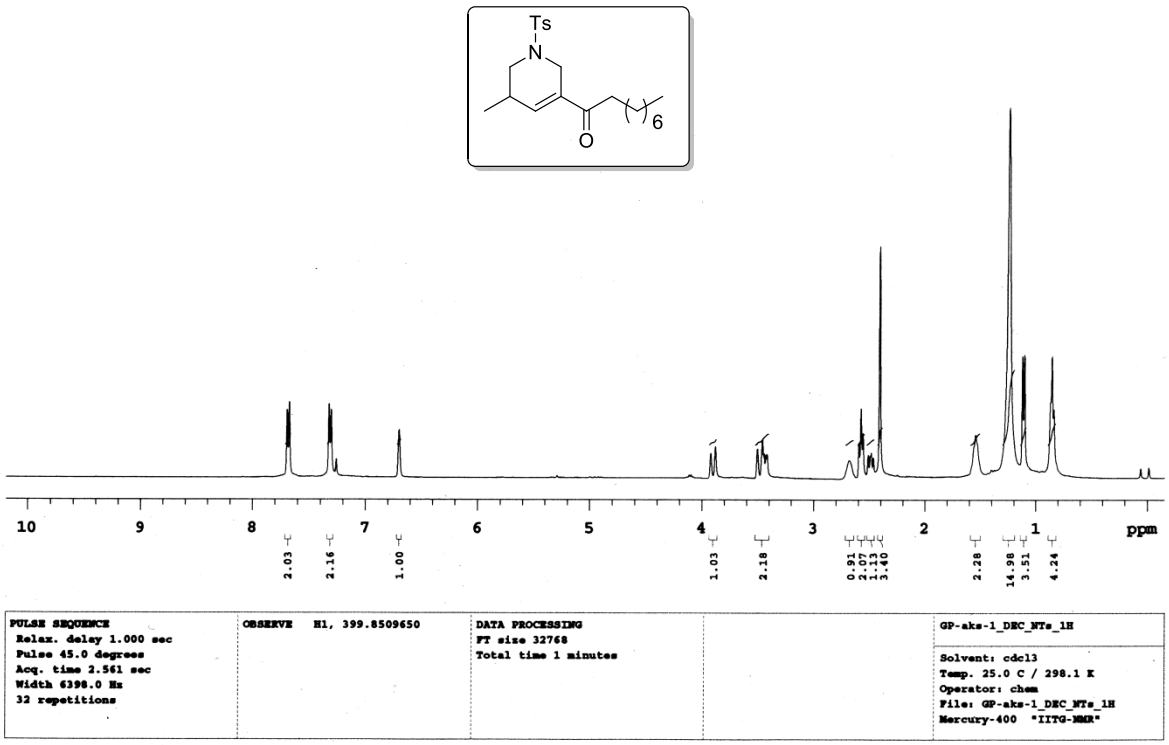
^{1}H and ^{13}C NMR Spectra of (5-Phenyl-5,6-dihydro-2*H*-pyran-3-yl)(thiophen-2-yl)methanone 47j:

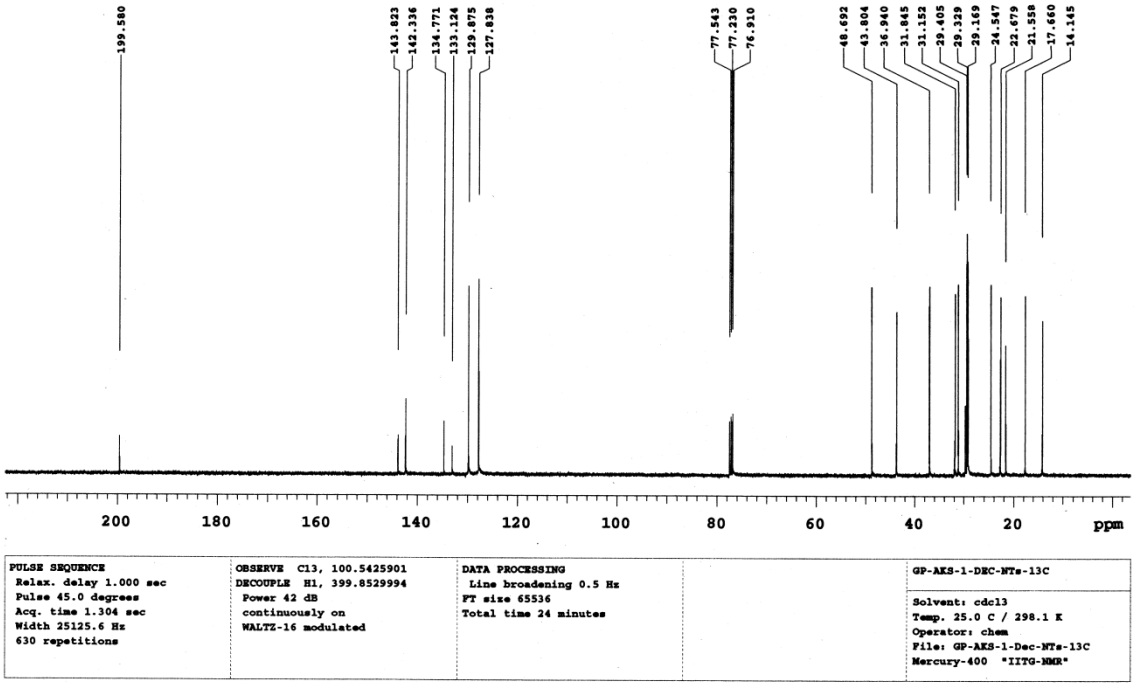




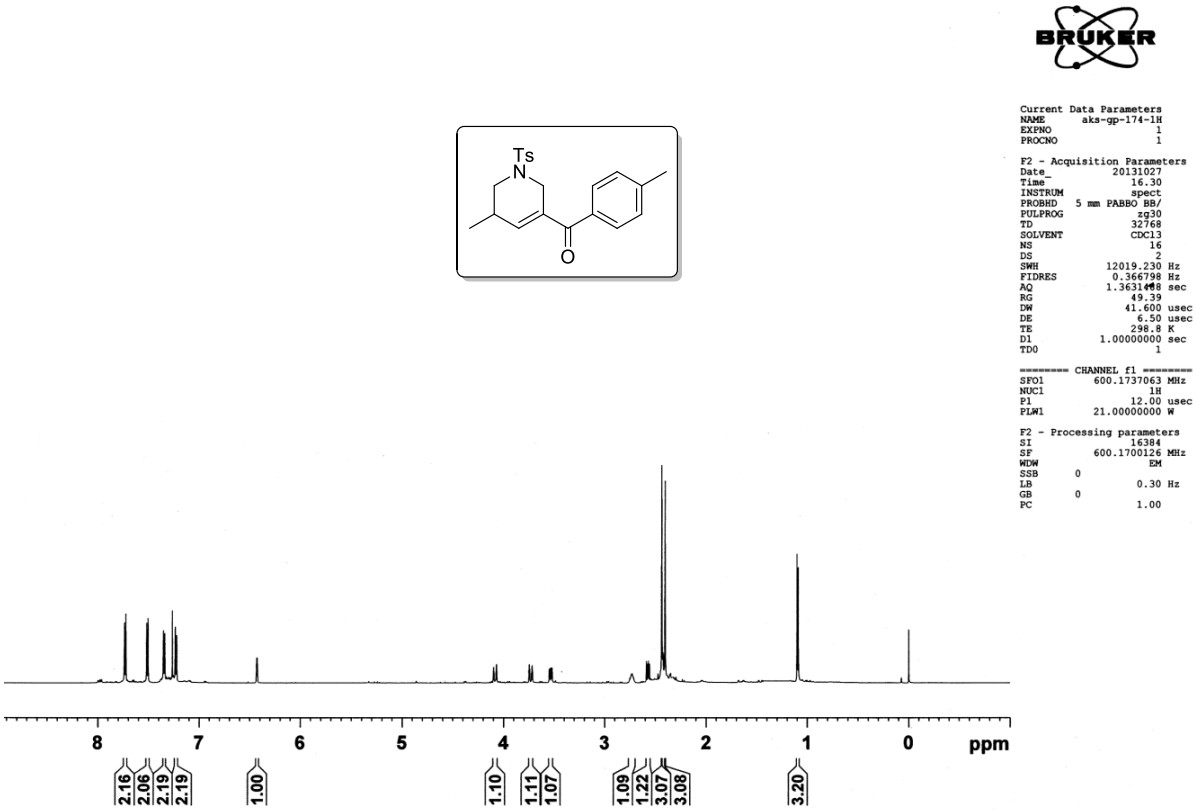


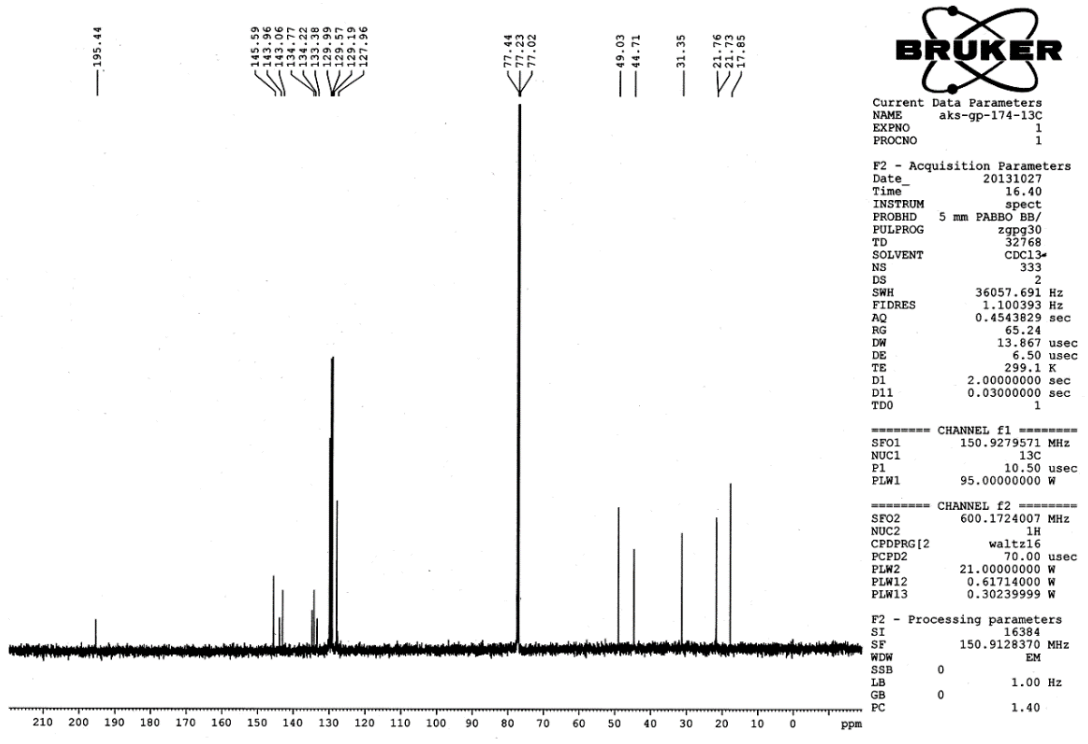
^{1}H and ^{13}C NMR Spectra of 1-(5-Methyl-1-tosyl-3,4-dehydropiperidin-3-yl)nonan-1-one 48a:



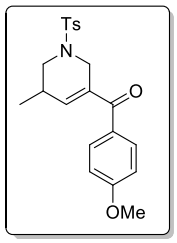


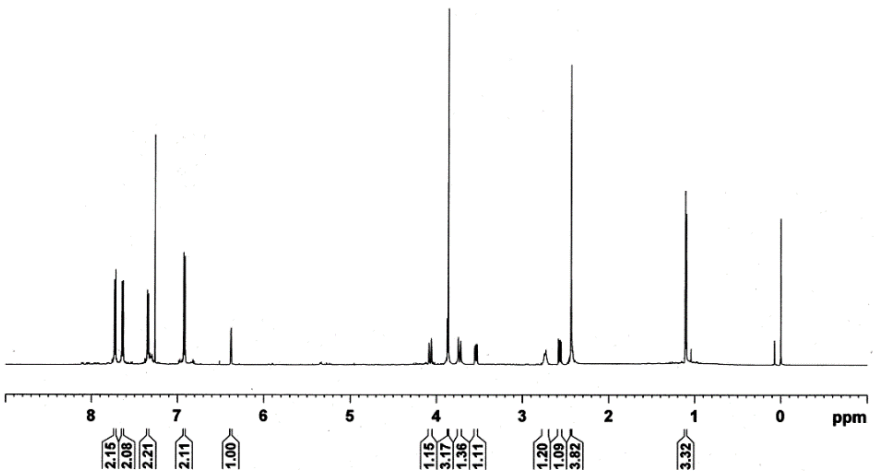
^{1}H and ^{13}C NMR Spectra of (5-Methyl-1-tosyl-3,4-dehydropiperidin-3-yl)(*p*-tolyl) methanone48f:





^{1}H and ^{13}C NMR Spectra of (4-Methoxyphenyl)(5-methyl-1-tosyl-3,4-dehydropiperidin-3-yl)methanone 48g:





BRUKER

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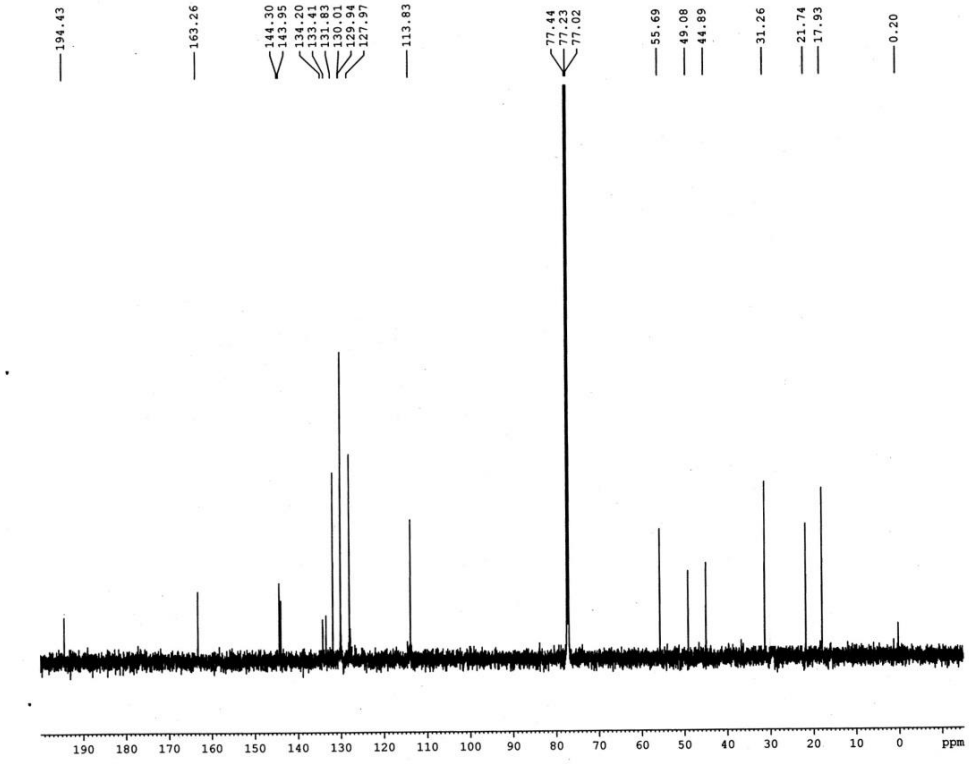

BRUKER

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PROCNO                 1

F2 - Acquisition Parameters
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TD              32768
SOLVENT          CDCl3
NS                479
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SWH          36057.691 Hz
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RG                65.24
DW              13.867 usec
DE               6.50 usec
TE              299.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                 1

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NUC1               13C
P1               10.50 usec
PLW1        95.00000000 W

======== CHANNEL f2 ========
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NUC2               1H
CPDPRG[2         waltz16
PCPD2            70.00 usec
PLW2        21.00000000 W
PLW12        0.61714000 W
PLW13        0.30239999 W

F2 - Processing parameters
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WDW               EM
SSB       0
LB              1.00 Hz
GB        0
PC              1.40
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2.8. Crystal Parameters

The crystal parameters of compound **47a**

	47a- CCDC 979057
Formula	C_{18} H_{16} O_2
Formula weight	264.31
T/K	296(2)
Crystal system	Monoclinic
Space group	P 21/c
a/Å	12.3796(15)
b/Å	10.5493(15)
c/Å	11.3168(13)
α/º	90.00
β/º	106.991(8)
γ/º	90.00
V/Å^3	1413.4(3)
Z	4
Abs. Coeff./mm^{-1}	0.080
Abs. Correction	Multi-scan
GOF on F^2	1.008
Final *R* indices [*I* > 2σ(I)]	*R1* = 0.0448 *wR2* = 0.1138
R indices [all data]	*R1* = 0.0752 *wR2* = 0.1295

CHAPTER 3

Lewis Acid Mediated Intramolecular C-O Bond Formation of Alkanol-Epoxide Leading to Substituted Morpholine and 1,4-Oxazepane Derivatives: Total Synthesis of (±)- Viloxazine

3.1. Importace of Morpholines and Oxazepane Derivatives

Morpholines are some of the most important biologically active compounds.[1] High popularity of the morpholine moiety is caused by several factors. First, the oxygen atom in the morpholine core can participate in the donor-acceptor type interactions with the corresponding receptor, increasing binding affinity. Second, the electronegative effect of the oxygen atom reduces the basicity of the nitrogen atom. Morpholine and their derivatives have attracted the attention of researchers over the years due to their immense significance as synthetic intermediates for a number of medicinally active molecules. For instance, isoflav- 3-enes **1** is a vital group of chromene intermediates, applicable in the production of a number of natural products and medicinal agents such as potassium channel activating drugs. Moreover, morpholine's basic structural framework is the common feature of several tannins and polyphenols found in fruits, vegetables, teas, and red wines, which are known for their health-promoting effects.[2] Many compounds of this class have shown notable biological properties, for example, viloxazine **2**, reboxetine **3** and edivoxetine **4** show antidepressant properties.[3] Similarly, the compounds **5** and **6** containing morpholine unit have anti-inflammatory and $GABA_B$ receptor-antagonist properties (*Figure 3.1.1.*).[4] Morpholines are not only used in organic synthesis as bases or *N*-alkylating agents[5] but also used as versatile synthetic units in organic synthesis, particularly for the construction of agrochemicals, fungicides and bactericides.[6] They are also used as chiral auxiliary in some chemical transformations.[7] Furthermore, 2,6-disubstituted morpholines are used as antitumor agents,[8a] mild diuretics, and anorectics.[8b] Likewise, seven-membered analogues of morpholine are very important as we have already discussed in chapter 1.

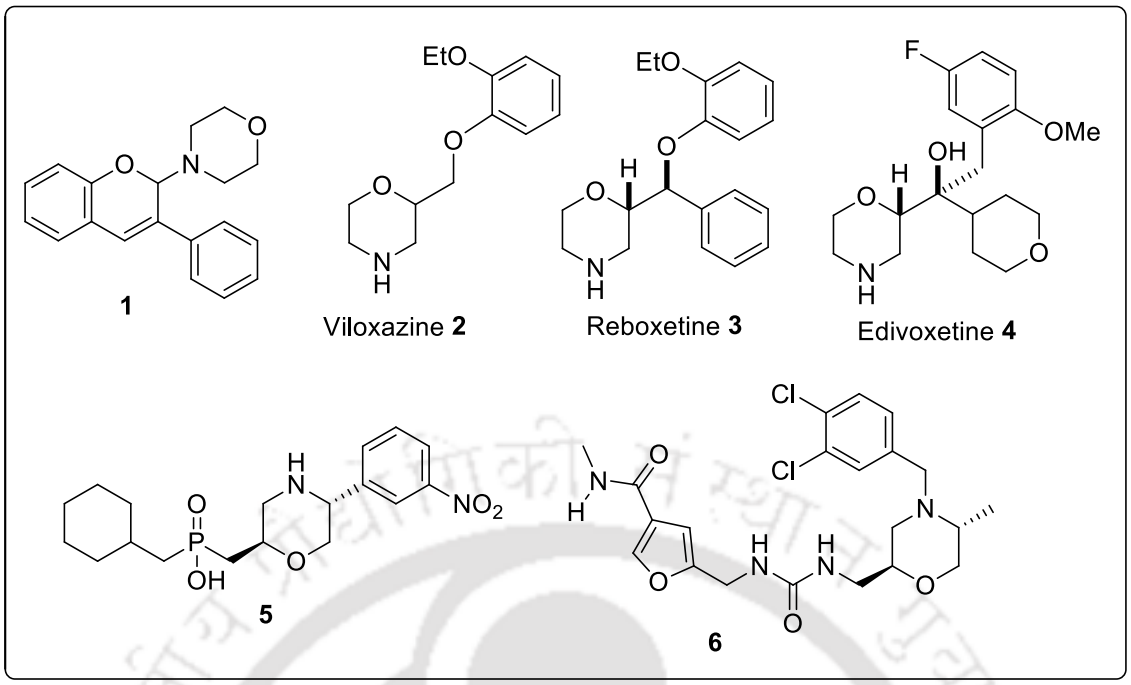
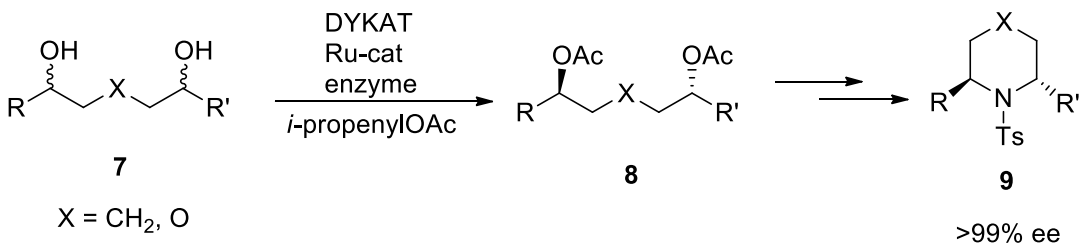


Figure 3.1.1. Some biologically active Morpholines

3.2. Literature Methods

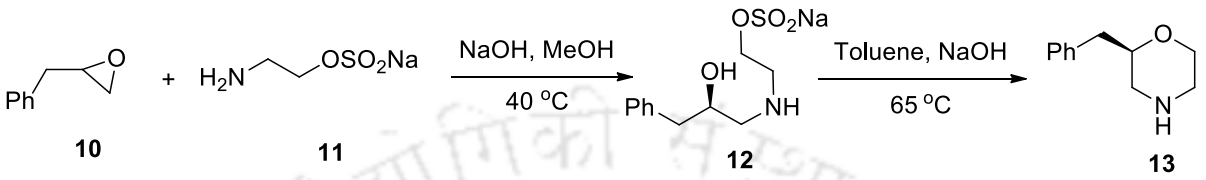
Over the years, several synthetic approaches have been developed for the preparation of 1,4-heterocycles. Some reports are given below-

The use of enantiopure 1,5-diacetates for the preparation of chiral heterocycles was explored by Bäckvall and co-workers. They first performed a reaction for an efficient enantio- and diastereoselective synthesis of 1,5-diol diacetates **8** *via* dynamic kinetic asymmetric transformation (DYKAT) in the presence of Candida antarctica lipase B (CALB), Pseudomonas cepacia lipase II (PS-C II), and ruthenium catalyst. The enantiopure diacetates were then used for the enantioselective synthesis of 2,6-disubstituted piperidine and 3,5-disubstituted morpholine **9** (*Scheme 3.2.1*).[9]



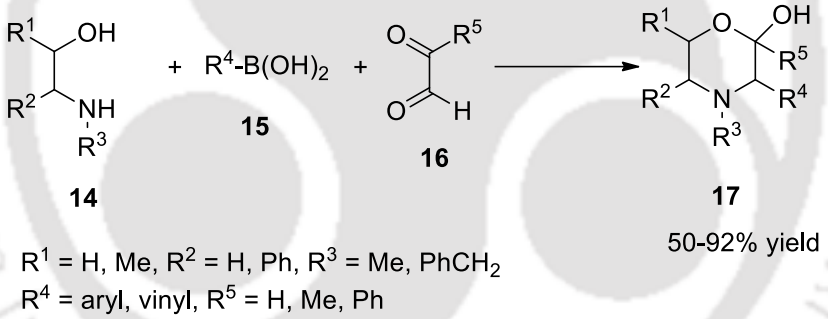
Scheme 3.2.1

Also, epoxide was used as a starting material to form the morpholine ring. In this example, (*R*)-2-benzylmorpholine was achieved by reacting epoxide with ethanolamine sulfonate. Ethanolamine sulfonate **11** was used for the ring opening of epoxide **10** under basic condition, followed by ring closure of sulfate ester **12** upon treatment with base resulted (*R*)-2-benzylmorpholine **13** in 66% isolated yield (*Scheme 3.2.2*).[10]



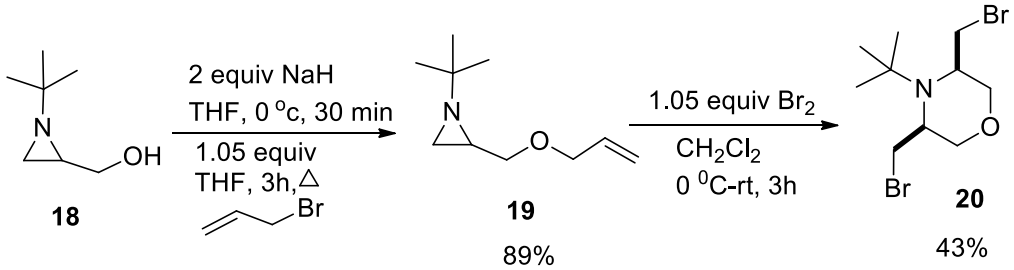
Scheme 3.2.2

Carboni and his group had successfully synthesized morpholine derivatives by applying three-component Petasis coupling reaction. 1,2-Aminoalcohols **14** was directly engaged in a one-pot cyclisation procedure with boronic acid **15** and glyoxal to produce 2-hydroxymorpholines **17** (*Scheme 3.2.3*).[11]



Scheme 3.2.3

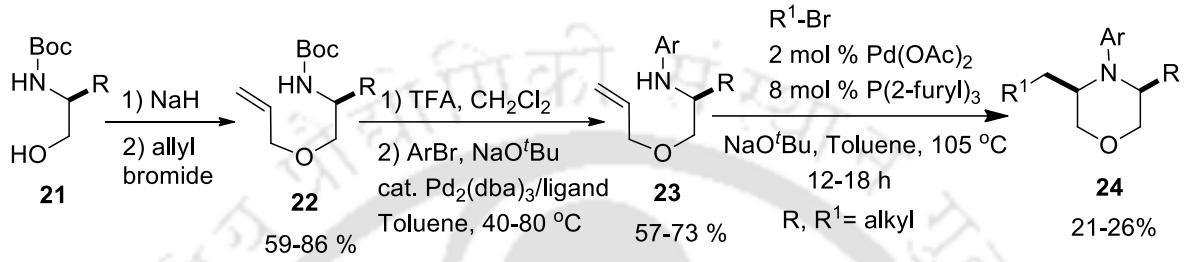
Kimpe *et al*. reported the synthesis of *cis*-3,5- disubstituted morpholine derivatives **20** based on expansion of 2-(allyloxymethyl)aziridine ring **19** *via* an electrophile induced ring closure using bromine in dichloromethane (*Scheme 3.2.4*). [12]



Scheme 3.2.4

Wolfe *et al.* reported the synthesis of 3,5-disubstituted morpholines from enantiomerically pure amino alcohols. Treatment of the *N*-protected amino alcohols **21** with NaH and allyl bromide afforded allyl ethers **22**. Cleavage of the Boc-group followed by Pd-catalyzed *N*-arylation of the resulting amine trifluoroacetate salts provided **23** in moderate to good yield.

Then, Pd-catalyzed carboamination reaction between a substituted ethanolamine derivative **23** and an aryl or alkenyl bromide afforded enantiopure *cis*-3,5-disubstituted morpholines **24** (*Scheme 3.2.5)* .[13]

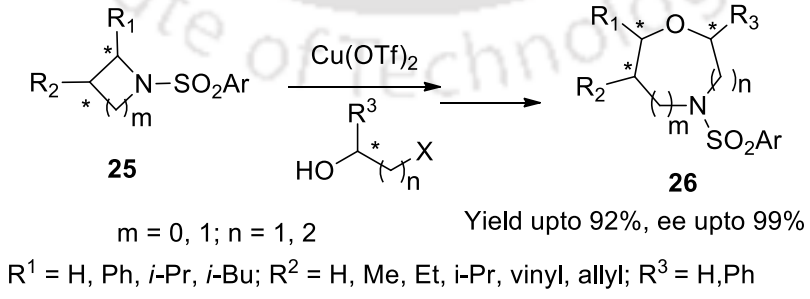


Scheme 3.2.5

Ghorai and his group proposed an alternative route for the enantioselective synthesis of morpholines and their homologues in good yields. The reaction proceeds via an S_N2-type ring opening of activated aziridines and azetidines by suitable halogenated alcohols in the presence of Lewis acid followed by base-mediated intramolecular ring closure of the resulting haloalkoxy amine.

The ring opening of chiral (*R*)-2-phenyl-*N*-tosylaziridine **25** (ee>99%) with haloethanol in the presence of Cu-$(OTf)_2$-catalyst at 0 °C, followed by KOH-promoted cyclization to afford the nonracemic morpholine **26** (*Scheme 3.2.6*).[14]

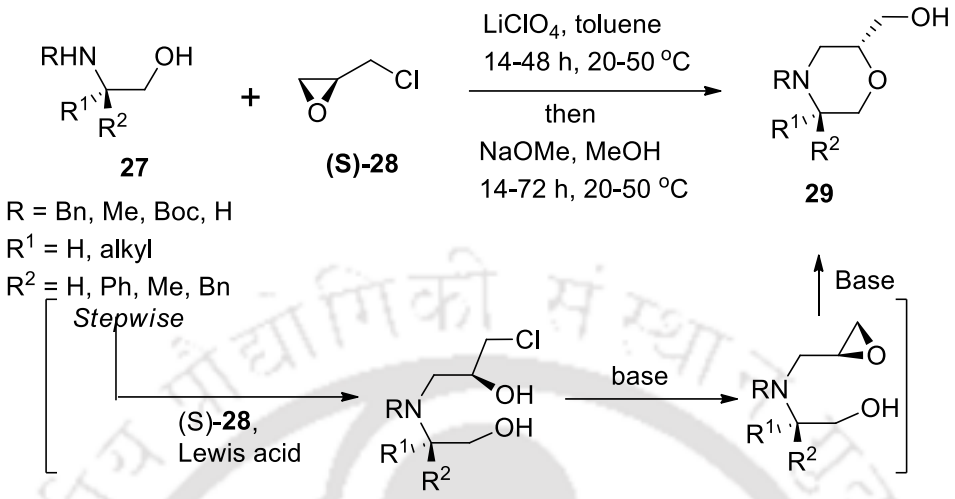
The strategy was extended further for the syntheses of morpholine homologue 1,4-oxazepanes in good yields.



Scheme 3.2.6

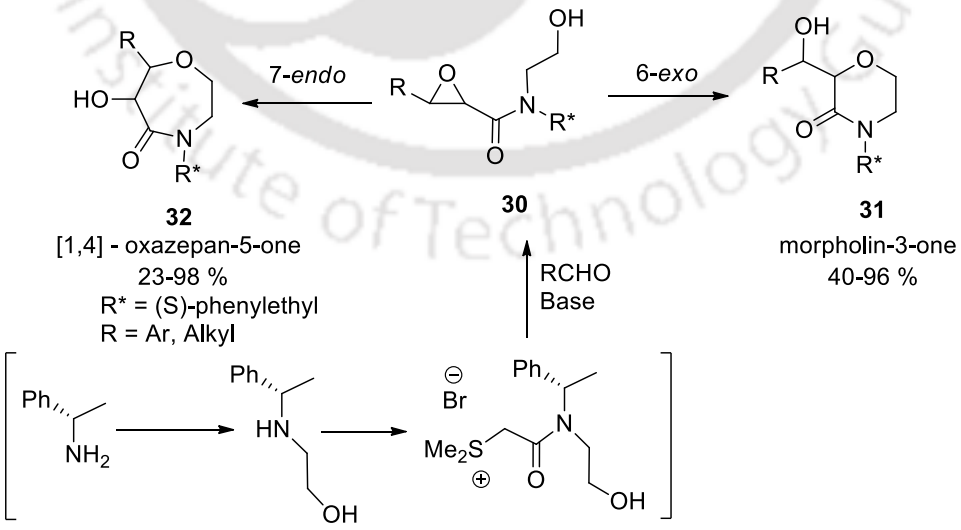
Breuning *et al.* proposed a straightforward one-pot procedure for the preparation of enantiomerically pure 2-(hydroxymethyl)-morpholines with a widely variable substitution pattern. Addition of chiral β-amino alcohols **27** to (S) or (R)-epichlorohydrin **28** in the presence

of $LiClO_4$ afforded the corresponding chloro alcohols, which were treated with NaOMe to give the epoxides and, by subsequent intramolecular cyclization gave the morpholines **29** in good yields 57-77% (*Scheme 3.2.7*).[15]



Scheme 3.2.7

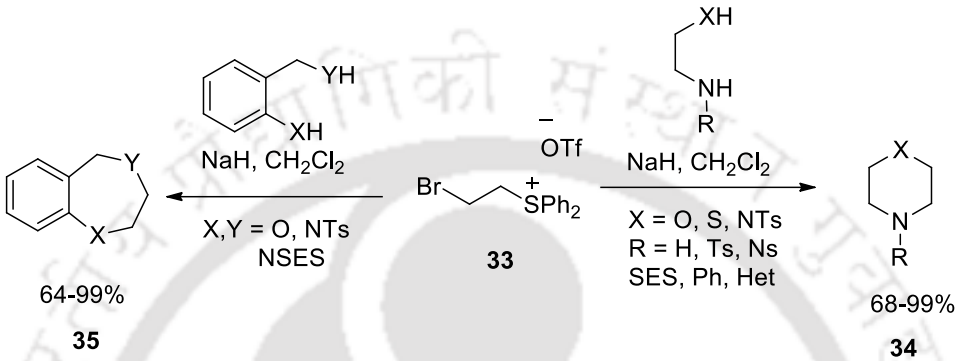
Teràn and his co-workers reported a regiospecific synthesis of 7-alkyl- or 7-aryl-6-hydroxy-1,4-oxazepan-5-ones and 2-[aryl(hydroxyl)methyl]- or 2-[1-hydroxyalkyl)morpholine-3-ones from a diastereomeric mixture of *trans*-3-alkyl- or 3-aryl-*N*-(2-hydroxyethyl)-N-(1-phenylethyl)oxirane-2-carboxamides. Chiral sulphonium salt was first synthesized from (*S*)-phenylethylamine, then asymmetric epoxidation was carried out with aldehydes in presence of a base. Finally, the chiral trans-epoxyamides **30** in presence of Lewis acid underwent 6-*exo* and 7-*endo* cyclization to give 1,4-oxazepan-5-ones **32** and morpholin-3-ones **31** (*Scheme 3.2.8*).[16]



Scheme 3.2.8

Aggarwal and his group demonstrated an alternative route for the synthesis of 6- and 7-membered

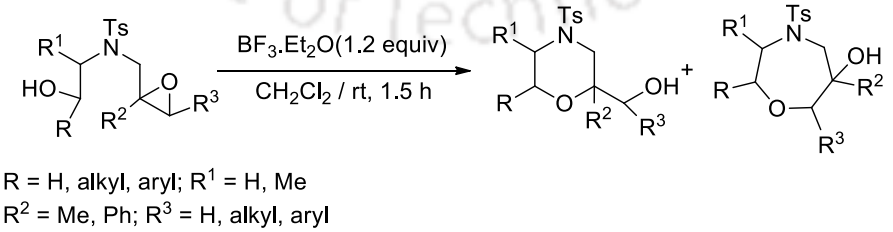
1,4-heterocyclic compounds in good-to-excellent yields. In this, 1,2-/1,3-aminoalcohols was reacted with bromoethylsulfonium salt **33** in presence of NaH or DBU to afford the 1,4-heterocyclic compounds such as morpholines **34** and benzoxazepines **35**. The reactions proceed through generation of a vinyl sulfonium salt from bromoethylsulphonium salt in presence of a base followed by annulation to give the desired products. The method accommodates a range of nitrogen substituents and the amino alcohol can be substituted by amino thiols and diamines to give thiomorpholines, piperazines and benzodiazepines (*Scheme 3.2.9*).[17]



Scheme 3.2.9

3.3. Present Work

In the previous chapter we have developed a methodology for the synthesis of oxygen and nitrogen heterocyclic compounds *via* intramolecular C-C bond formation of alkyne-epoxide mediated by boron trifluoride etherate. This chapter presents a methodology for the synthesis of morpholines and 1,4-Oxazepanes, using intramolecular C-O bond formation of alkanol-epoxide mediated by boron trifluoride etherate at ambient temperature in moderate to good yields. Furthermore, the synthesis of (±)-viloxazine, which has been found to show anti-depression property, is presented as a demonstration of the synthetic utility of this method. The reaction can be generalized as shown in *Scheme 3.3.1*.

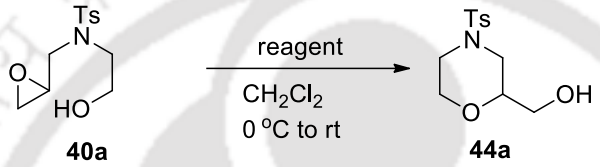


Scheme 3.3.1

To start with, alkanol epoxide **40a** was treated with 1.2 equivalents of boron trifluoride etherate in dichloromethane at room temperature for 1.5 h and (4-tosylmorpholin-2-yl) methanol **44a** was obtained in 78% yield. The reaction was also performed using different Lewis acids and

Brønsted acids and the results are shown in *Table 3.3.1*. The reaction with metal triflates such as $Zn(OTf)_2$, $Cu(OTf)_2$ and $In(OTf)_3$ (entries 3-5) gave 30, 15 and 19% yields, respectively. $Bi(OTf)_3$ produced 40% of the product, $Sc(OTf)_3$ was found to be poor for the reaction resulting only trace amount of the desired product (entry 10). On the other hand, metal salts $InCl_3$ (entry 2) gave 46%, whereas $FeCl_3$ produced only trace amount (entry 11). Brønsted acids such as camphor sulfonic acid (CSA) and triflic acid (TfOH) gave 33% and 52% yields, respectively. Strong Lewis acid Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (entry 8) failed to produce the desired product, instead starting material was found to be decomposed.

Table 3.3.1 Optimization of the reaction condition



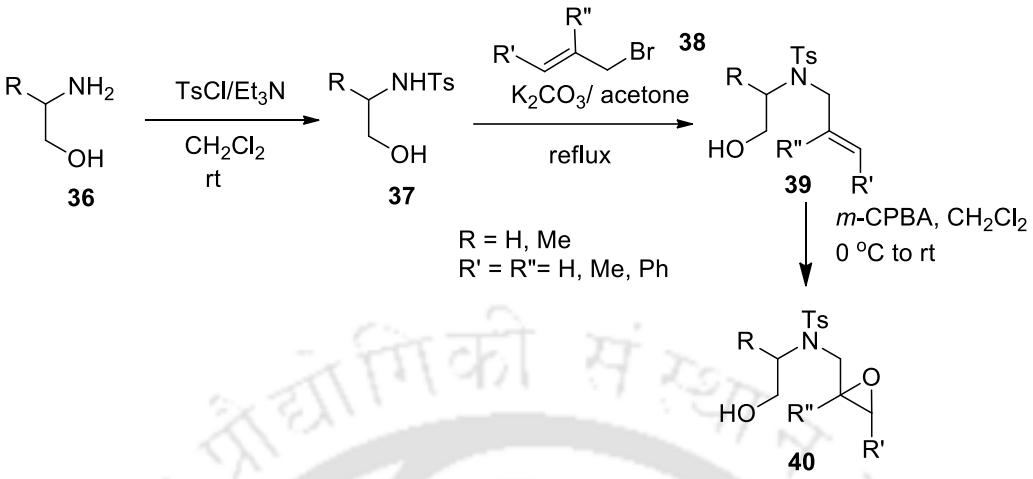
40a **44a**

entry	reagent (mmol)	yield (%)[a]
1	**$BF_3{\cdot}OEt_2$ (1.2)**	**78**
2	$InCl_3$ (1.0)	46
3	$Zn(OTf)_2$ (1.0)	30
4	$Cu(OTf)_2$ (1.0)	15
5	$In(OTf)_3$ (1.0)	19
6	CSA (1.2)	33
7	TfOH (1.2)	52
8	TMSOTf (1.0)	--[b]
9	$Bi(OTf)_3$ (1.0)	40
10	$Sc(OTf)_3$ (1.0)	trace
11	$FeCl_3$ (1.0)	trace

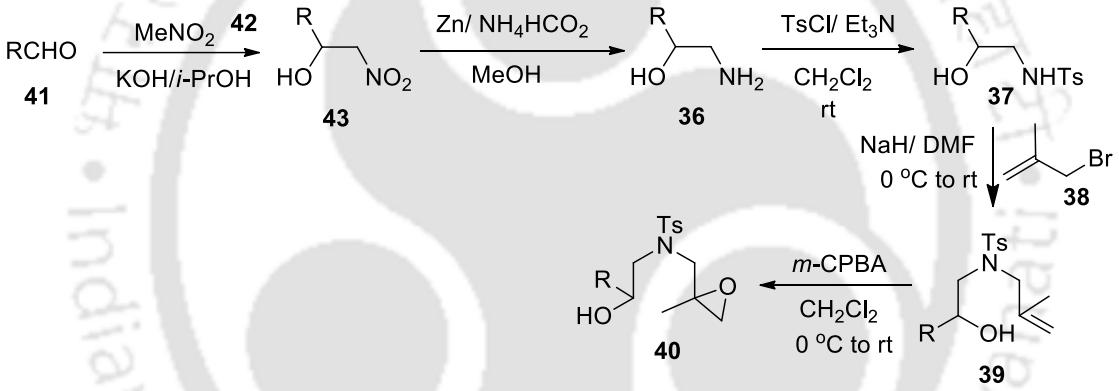
[a]Yield refers to isolated yield. [b]Decomposed.

Once optimized conditions were obtained, we further examined the scope of the reaction with variety of substrates **40a**-**40m**, which were prepared as per literature methods (*Scheme 3.3.2* and *3.3.3*). For the synthesis of *N*-tethered primary alkenol, commercially available ethanol amine **36** was treated with tosyl chloride in dichloromethane to afford corresponding *N*-tosylated ethanol amine **37**, which was coupled with allyl bromide **38** using potassium carbonate as base.[18] On the other hand, the secondary alcohol was synthesized using Henry reaction and subsequent reduction of nitro group to amine, which was then coupled with allyl bromide using sodium

hydride as base. The *N*-tethered alkenol **39** was then treated with *m*-chloroperbenzoic acid to give corresponding epoxide **40**.[19]



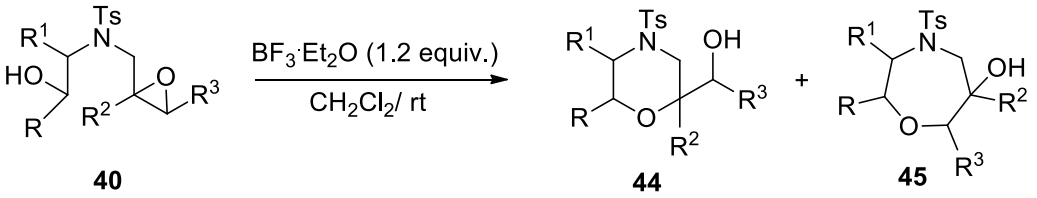
Scheme 3.3.2

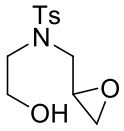
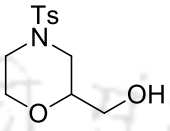
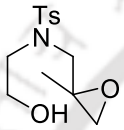
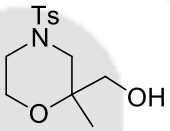
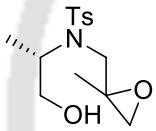
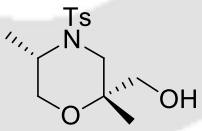
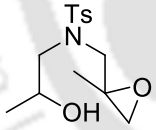
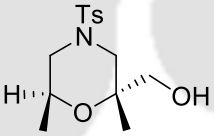
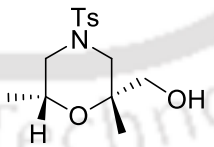
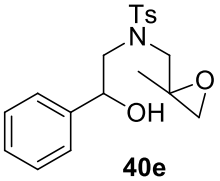
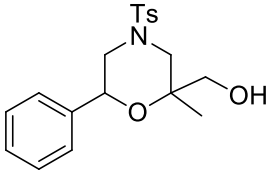


Scheme 3.3.3

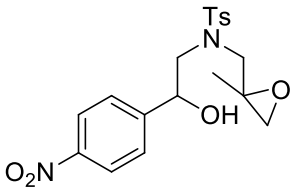
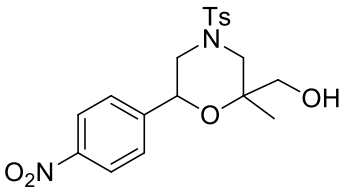
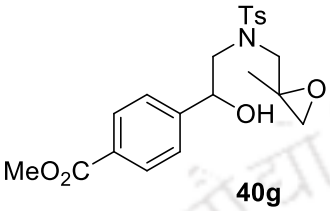
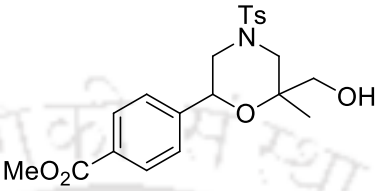
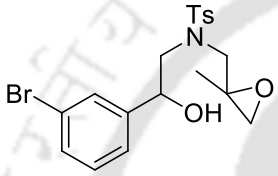
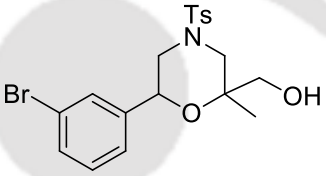
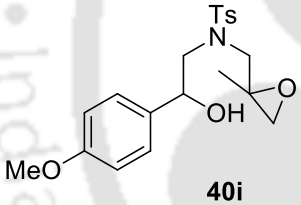
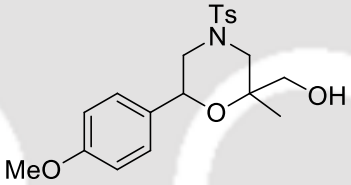
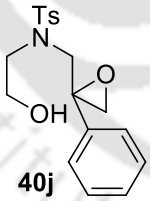
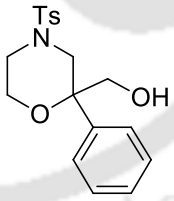
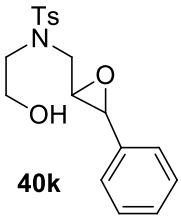
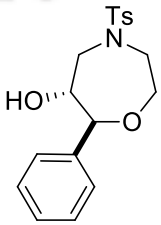
It was observed from the *Table 3.3.2* that terminal epoxides (entries 1-10) gave the desired morpholines whereas 1,2-disubstituted epoxides (entries 11-13) produced 1,4-oxazepanes in good yields. It has been observed that yield is determined by the nature of the substituent present in the substrates. Alkanol epoxides **40a-c** gave single isomer **44a-c** in 78, 80 and 72% yields, respectively. The relative stereochemistry of compound **44c** was determined from the NOE experiment (*Figure 3.3.1*). The compound **44c** showed a clear characteristic NOE correlation between the hydrogen C-5H and hydrogens of methyl substituent at C-2 position. There is another NOE correlation between the hydrogens of C-5Me and two hydrogens of -CH_2OH at C-2 position of **44c**. Substrate **40d** gave two separable diastereomers **44d** and **44d'** in 40 and 42% yields, respectively. The stereochemistry of the two diastereomers was determined by NOE experiment. There is a NOE correlation between hydrogen C-6H and hydrogens of methyl (-$\underline{CH_3}$) substituent at C-2 position of compound **44d´** (*Figure 3.3.1*).

Table 3.3.2 Synthesis of morpholines and 1,4-oxazepanes

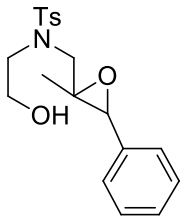
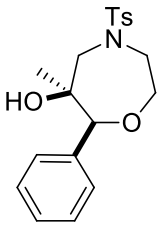
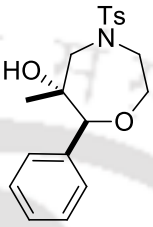
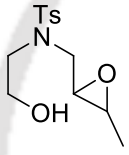
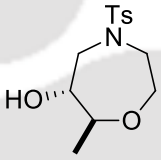
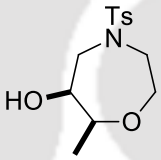
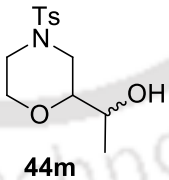


Sl.No.	Substrate **40**	Product **44/45**	Yield(%)[a]	dr
1	 **40a**	 **44a**	78	
2	 **40b**	 **44b**	80	
3	 **40c**	 **44c**	72	
4	 **40d**	 **44d**	40	–
		 **44d'**	42	–
5	 **40e**	 **44e**	75	1:1

Continue…

Sl.No.	Substrate **40**	Product **44/45**	Yield(%)[a]	dr
6	 **40f**	 **44f**	70	3:2
7	 **40g**	 **44g**	68	1:1
8	 **40h**	 **44h**	61	1:1
9	 **40i**	 **44i**	65	3:2
10	 **40j**	 **44j**	95	
11	 **40k**	 **45k**	48	–

Continue…..

Sl.No.	Substrate **40**	Product **44/45**	Yield(%)[a]	dr
12	 **40l**	 **45l**	48	–
		 **45l'**	35	–
13	 **40m**	 **45m**	15	–
		 **45m'**	51	–
		 **44m**	25	9:1

[a]Yield refers to isolated yield. All the products were characterized by ^{1}H, ^{13}C NMR and Mass spectrometry. [b]Inseperable mixture of diastereomers. Ratio was determined by 1H NMR.

Again there is a NOE correlation between two hydrogens of C-2$\underline{CH_2}$OH and hydrogens of C-6Me of **44d´**.

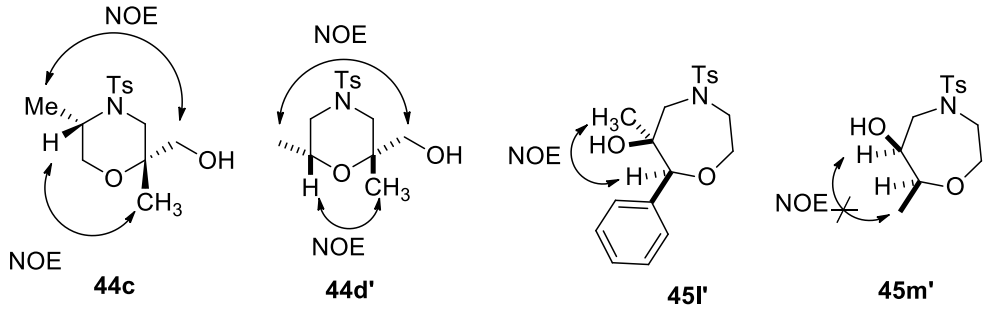


Figure 3.3.1 NOE of compounds **44c**, **44d´, 45l'** and **45m'**

The formation of compounds **44c**, **44d** and **44d'** may be due to the stability imparted by hydrogen bonding between the hydroxyl group and the tertiary amine group (*Figure 3.3.2).* The starting material for the synthesis of **44c** is a chiral compound **40c** and therefore, it produces only single diastereomer **44c**, whereas diastereomeric mixture **40d** produces both the diastereomers **44d** and **44d'.**

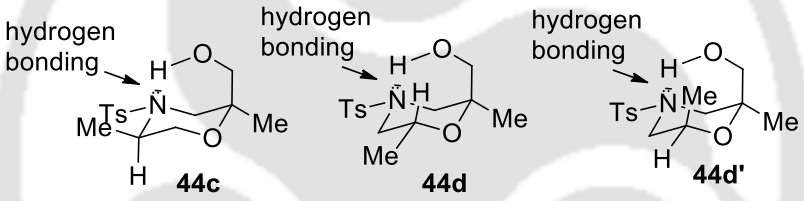


Figure 3.3.2.

On the other hand, substrates **40e-i** furnished two inseparable diastereomers each with varied ratios. Substrate **40j** gave single isomer **44j** with very good yield (95%). Epoxide **40k-m** having terminal groups produced seven membered 1,4- oxazepanes. Epoxide **40k** furnished only *anti* diasteromer **45k** with 48% yield and **40l** gave separable diastereomers **45l** and **45l'** with 48% and 35% yields, respectively. The relative stereochemistry of **45k** was determined from coupling constant (C-7H, 4.43 ppm, J = 7.8 Hz) and X-ray crystallographic analysis (*Figure 3.3.3*).[20] The relative stereochemistry of compounds **45l** and **45l'** was determined from NOE experiment of **45l**. There is a NOE correlation between hydrogen C-7H and hydrogens of methyl (-CH_3) substituent at C-6 position of compound **45l** (*Figure 3.3.1*). The compound **40m** having terminal methyl group gave three isolable compounds, two of which are diastereomeric oxazepanes **45m** and **45m'** with 15% and 51% yields, respectively, and six membered diastereomeric mixture **44m** with a ratio of 9:1 and 25% overall yield. The relative stereochemistry of these two compounds is determined from NOE experiment of **45m´** (*Figure 3.3.1*). There was no NOE between C-6H proton and protons of methyl group at C-7Me, which indicates that OH group at C-6 and Me at C-7 are *cis* to each other.

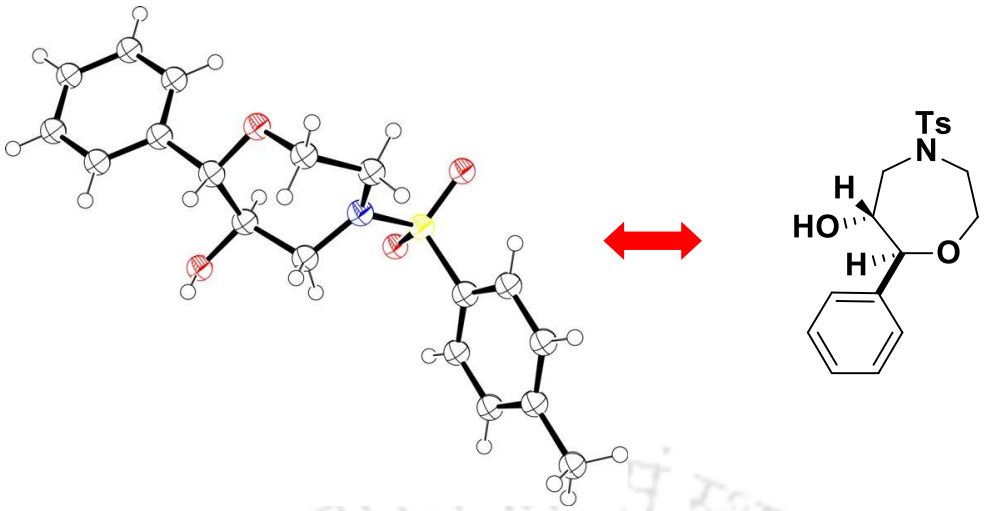
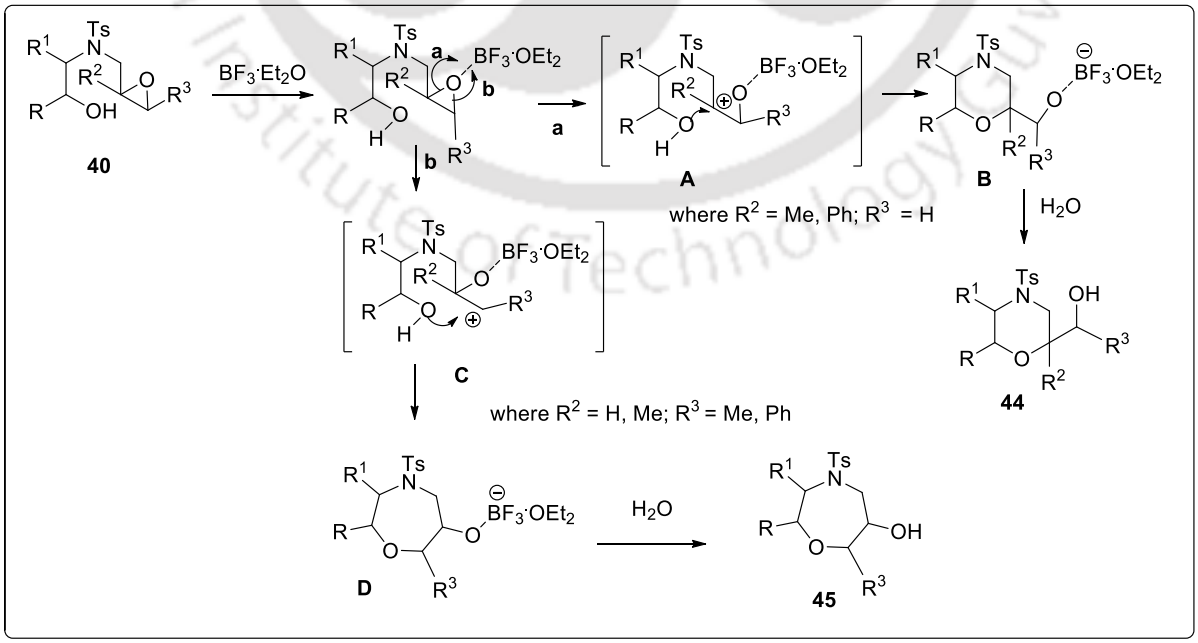


Figure 3.3.3. ORTEP diagram of compound **45k** with 45% probability ellipsoid

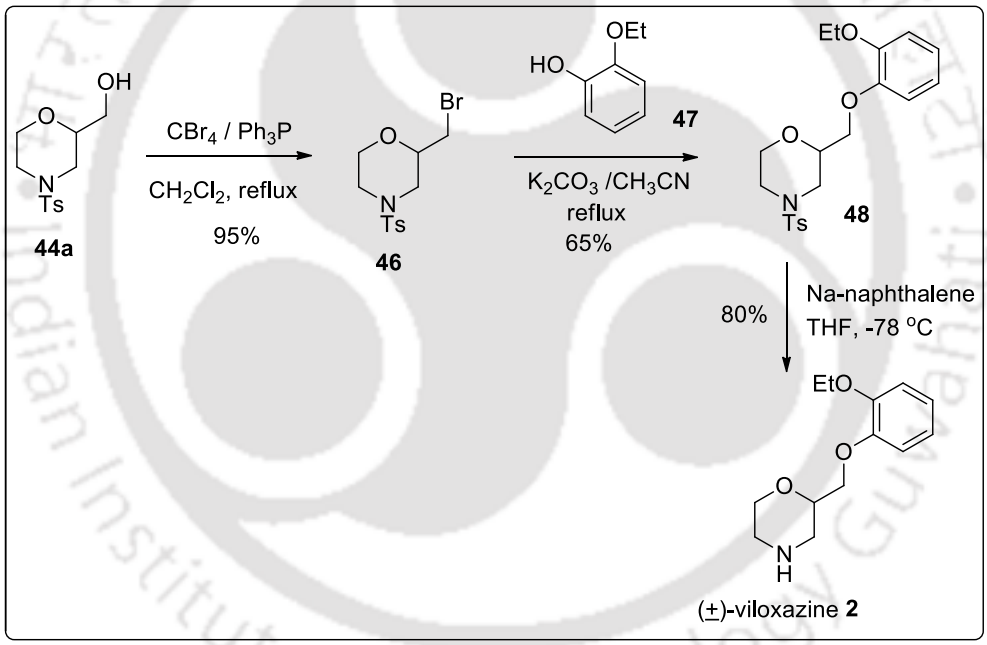
The mechanism of formation of morpholines and oxazepanes can be rationalized by considering the formation of different stable carbocations. The boron trifluoride etherate opens the monosubstituted terminal epoxide ring of **40** to give more stable either secondary or tertiary carbocation **A**, where R^2 = Me, Ph; R^3 = H (entries 1-10, path a), which is attacked by alkanol to give six membered intermediate **B**. The intermediate **B** is then hydrolyzed to form morpholine **44**. On the other hand, disubstituted epoxide **40k,l** opens under the same reaction conditions to give more stable benzylic carbocation **C**, where R^2 = H, Me; R^3 = Ph (entries 11,12, path b), or



Scheme 3.3.4. Plausible mechanism of the reaction

secondary carbocation **A** or **C**, R^2 = H; R^3 = Me (entry 13, in this case both carbocations **A** and **C** are secondary). The carbocation **C** is subsequently attacked by alkanol to give seven membered intermaediate **D** (entries 11, 12). Similarly, secondary carbocations **A** and **C** are attacked by alkanol to produce **B** and **D** (entry 13), respectively. The intermediates **B** and **D** are then hydrolysed to give morpholine **44** and oxazepane **45**, respectively (*Scheme 3.3.4*).

The strategy is successfully applied for the synthesis of (±)-viloxazine **2**. The compound is considered as an anti-depression agent. Only a few protocols have been introduced for total synthesis of viloxazine till date.[1b,21] The synthesis started with the bromination of alcohol **44a** with carbon tetrabromide and triphenyl phosphine in dichloromethane at room temperature to give bromide **46**, which was then treated with 2-ethoxyphenol **47** to provide *N*-tosyl protected (±)-viloxazine **48**. Deprotection of **48** with sodium naphthalide gave the final product (±)-viloxazine **2** in 80% yield (*Scheme 3.3.5*)**.**



Scheme 3.3.5. Total synthesis of (±)-viloxazine **2**

Conclusions

In conclusion, we have developed a mild and efficient method for the synthesis of substituted morpholines *via* intramolecular cyclization reaction of *N*-tethered alkanols-epoxides in good yields. The reaction is compatible with a wide range of functional groups such as ester, ether, -NO_2, and bromo. The major advantage of this reaction is that it generates alcohols in side chain of the morpholine ring, which is used for the synthesis of biologically active molecule (±)-viloxazine **2**.

3.4. Experimental section

3.4.1. Instrumentation and Characterization

As described in chapter 2 section 2.4.1

3.4.2. General Procedure for the Synthesis of *N*-Tethered Alkanol-Epoxide:

The alkenols **40a-m** (1equiv) was treated with *meta*-chloroperbenzoic acid (*m*-CPBA) (1.5 equiv) in dicholomethane (15 ml) at 0 ^{o}C. The reaction mixture was brought to room temperature and stirred for a specific time. After completion of the reaction, as determined by TLC, a saturated aqueous solution of Na_2SO_3 was added to quench excess *m*-CPBA. Dichloromethane was added to the reaction mixture, washed with saturated sodium bicarbonate and brine solutions, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by neutral alumina using ethyl acetate and hexane as eluents.

Synthesis of *N*-(2-hydroxyethyl)-4-methyl-*N*-(oxiran-2ylmethyl)benzene-sulfonamide (40a):

To a stirred solution of *N*-allyl-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (254 mg, 1.0 mmol) in dichlorormethane (6.0 mL/mmol), was added *m*-chloroperbenzoic acid (258.0 mg, 1.49 mmol) at 0 ^{0}C. The reaction mixture was brought to room temperature and stirred for 12 h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, a saturated aqueous solution of Na_2SO_3 was added to quench excess *m*CPBA. Dichloromethane was added to the reaction mixture, washed with saturated sodium bicarbonate and brine solution. The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over neutral alumina using ethyl acetate and hexane as eluents to give *N*-(2-hydroxyethyl)-4-methyl-*N*-(oxiran-2-ylmethyl)benzenesulfonamide **40a** as a colourless oil.

3.4.3. General Procedure for Lewis Acid Catalyzed Intramolecular C−O Bond Formation of Alkanol-Epoxide:

To a corresponding hydroxyl-epoxide substrates (1.0 equiv) in dichloromethane (5.0 mL) at 0 °C was added boron triflouride etherate (1 equiv) dropwise, and the reaction mixture was brought to room temperature. The reaction was continued for a specified time and monitored by TLC. After completion of the reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (5.0 mL). The product was extracted with CH_2Cl_2 (2 × 10.0 mL) and washed with brine. Organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using rotary

evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluents to afford the cyclic compounds.

Synthesis of (4-Tosylmorpholin-2-yl)methanol (44a):

To a stirred solution of *N*-(2-hydroxyethyl)-4-methyl-*N*-(oxiran-2-ylmethyl)benzenesulfonamide (270 mg, 1.0 mmol) in dichloromethane (5.0 mL/mmol), was added boron triflouride etherate (0.15 mL, 1.2 mmol) dropwise at 0 ^{o}C. The reaction mixture was brought to room temperature and stirred for 1.5 h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was washed with saturated sodium bicarbonate solution and brine solution. The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product which was purified by column chromatography over silica gel using ethyl acetate and hexane as eluents to give (4-tosylmorpholin-2-yl)methanol **44a** as a white solid.

3.4.4. Synthesis of 2-(Bromomethyl)- 4-tosylmorpholine (46):

Carbon tetrabromide (671 mg, 2.0 mmol) was added in one portion to a solution of **44a** (500 mg, 1.84 mmol) in dry CH_2Cl_2 (3.5 mL/mmol) at 0 °C, and the reaction was stirred at 0 °C. After 10 minutes, a solution of Ph_3P (530 mg, 2.0 mmol) in CH_2Cl_2 (1.5 mL/mmol) was added *via* cannula and stirred at 0 °C for 10 min. Then the reaction mixture was allowed to warm to room temperature and further stirred for 2 h. After reaction completed, the mixture was evaporated in vacuo. The residue was purified by silica gel column chromatography to give the bromide **46** as white solid.

3.4.5. Synthesis of 2-((2-Ethoxyphenoxy)methyl)-4-tosylmorpholine (48):

To a solution 2-ethoxyphenol **47** (414 mg, 3 mmol) in acetonitrile (3 mL/mmol) was added K_2CO_3 (620 mg, 4.5 mmol) at room temperature, followed by a solution of **46** (1200 mg, 4.5 mmol) in CH_3CN (1 mL). The reaction mixture was heated to reflux overnight. After cooling to rt, silica gel was added to the reaction mixture and the solvent was removed on the vacuum. The residue was purified by column chromatography to give **48** as a white solid.

3.4.6. Synthesis of 2-((2-Ethoxyphenoxy)methyl)morpholine, (±)-viloxazine (2):

To a cooled (-78 °C) green suspension of sodium metal (33 mg, 1.44 mmol) and naphthalene (208 mg, 1.62 mmol) in dry tetrahydrofuran (3 mL/mmol) was added the corresponding *N*-tosyl protected (±)-viloxazine **48** (140 mg, 0.36 mmol) under argon, and the mixture was stirred for 45

min at the same temperature. Then, the reaction was hydrolyzed with brine (10.0 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. The resulting residue was purified by flash chromatography (deactivated silica gel, ether/acetone) to yield the corresponding pure product as a colourless solid.

3.5. References

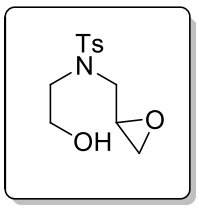
1. (a) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641. (b) Audouze, K.; Nielson, E. Ø.; Peters, D. *J. Med. Chem*. **2004**, *47*, 3089. (c) Sharma, G.; Park, J. Y.; Park, M. S. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 3188. (d) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett*. **1994**, *35*, 8333. (e) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett*. **1994**, *35*, 8337.
2. Polshettiwar, V., Varma, R.S. *Pure Appl. Chem.* **2008**, *80*, 777.
3. (a) Hajos, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. *CNS Drug Rev*. **2004**, *10*, 23. (b) Versiani, M.; Cassano, G.; Perugi, G.; Benedetti, A.; Mastalli, L.; Nardi, A.; Savino M. J. *Clin. Psychiatry* **2002**, *63*, 31. (c) Wong, E. H. F.; Sonders, M. S.; Amara, S. G.; Tinholt, P. M.; Piercey, M. F. P.; Hoffmann, W. P.; Hyslop, D. K.; Franklin, S.; Porsolt, R. D.; Bonsignori, A.; Carfagna, N.; McArthur, R. A. *Biol. Psychiatry* **2000**, *47*, 818. (d) Audouze, K.; Nielsen, O.; Peters, D. *J. Med. Chem*. **2004**, *47*, 3089.
4. (a) Ancliff, R. A.; Cook, C. M.; Eldred, C. D.; Gore, P. M.; Harrison, L. A.; Hayes, M. A.; Hodgson, S. T.; Judd, D. B.; Keeling, S. E.; Lewell, X. Q.; Mills, G.; Robertson, G. M.; Swanson, S.; Walker, A. J.; Wilkinson, M. 2003, PCT Int. Appl. WO 03082861. (b) Ong, J.; Kerr, D. I. B.; Bittiger, H.; Waldmeier, P. C.; Baumann, P. A.; Cooke, Mickel, N. G.; S. J.; Froestl, W. *Eur. J. Pharmacol.* **1998**, *362*, 27. (c) Kuo, S.-C.; Blythin, D. J.; Kreutner, W. 1999, U.S.Patent 5929236.
5. (a) Eisenhut, M.; Brandau, Missfeldt, W.; M. *Nuclear Medicine and Biology* **1989**, *16*, 805. (b) Kenneth, B.; Sloan, K. G. S. *Tetrahedron* **1984**, *40*, 3997. (c) Han, Y.; Tang, W.-Q.; Yan, C.-G. *Tetrahedron Lett.* **2014**, *55*, 1441. (d) Liang, S.; Jasinski, J.; Hammond, G. B.; Xu, B. *Org. Lett.* **2015**, *17*, 162.
6. (a) Bowers, W. S.; Ebing, W.; Fukuto, T. R.; Martin, D. *In Chemistry of Plant Protection*; Springer: Berlin, 1986; Vol. 1, pp 55. (b) Worthing, C. R.; The Pesticide Manual, 7th ed.; British Crop Protection Council: 1983; pp 265, 550.
7. (a) Licandro, E.; Maiorana, S.; Papagni, A.; Pryce, M.; Zanotti-Gerosa, A.; Rivaa, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1891. (b) Baldoli, C.; Del Buttero, P.; Licandro, E.;

Maiorana, S.; Papagni, S.; Zanotti-Gerosa, A. *J. Organomet. Chem.* **1995**, *486*, 279. (c) Enders, D.; Meyer, O.; Raabe, G.; Runsink, J. *Synthesis* **1994**, 66.

8. (a) Hikichi, M.; Yokokura, T.; Furuta, T.; Yaegashi, T. JP 62135472; *Chem. Abstr.* **1987**, *107*, 198358 (b) GB 831933; *Chem. Abstr.* **1961**, *55*, 2697.
9. Leijondahl, K.; Borén, L.; Braun, R.; Bäckvall, J. *Org. Lett.* **2008**, 10, 2027.
10. D'Arrigo, P.; Lattanzio, M.; Pedrocchi, G.; Servi, S. *Tetrahedron Asymm,* **1998**, *9*, 4021.
11. Berrée, F.; Debache, A.; Marsac, Y.; Carboni, B. *Tetrahedron Lett.* **2001**, *42*, 3591.
12. D'hooghe, M.; Vanlangendonck, T.; Törnroos, K. W.; Kimpe, N. D. *J. Org. Chem.* **2006**, *71*, 4678.
13. Leathen, M. L.; Rosen, B. R.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 5107.
14. Ghorai, M. K.; Shukla, D.; Das, K. *J. Org. Chem.* **2009**, *74*, 7013.
15. Breuning, M.; Winnacker, M.; Steiner, M. *Eur. J. Org. Chem.* **2007**, 2100.
16. Aparicio, D. M.; Teràn, J. L.; Roa, L. F.; Gnecco, D.; Juàrez, J. R.; Orea, M. L.; Mendoza, A.; Flores-Alamo, M.; Micouin, L. *Synthesis* **2011**, 2310.
17. Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2009,** *11*, 257.
18. Liu, H.; Qiao, Z.; Jiang, X. *Org. Biomol. Chem.* **2012**, *10*, 7274.
19. Gudla, V.; Balamurugan, R. *J. Org. Chem.* **2011**, *76*, 9919.
20. The crystallographic data for compounds **45k** has been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication numbers CCDC 1419078.
21. (a) Balsamo, A.; Giorgi, I.; Lapucci, A.; Lucacchini, A.; Macchia, B.; Macchia, F.; Martini, C.; Rossi, A. J. Med. Chem. **1987**, *30*, 222. (b) Liang, L.; Bhatt, P. P.; Dain, D.; Taquet, J.-P.; Pechenov, A.; Tchesnokov, A.; Mariaux, R. U.S. Pat. Appl. Publ. 2011, US 20110251198 A1.

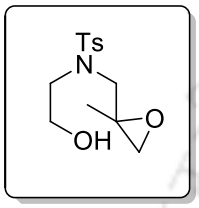
3.6. Characterization Data

***N*-(2-hydroxyethyl)-4-methyl-*N*-(oxiran-2ylmethyl)benzene-sulfonamide (40a):**



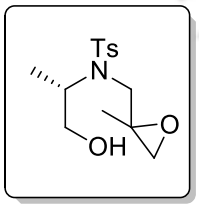
Colourless oil. R_f (hexane/ EtOAc 3:2) 0.50; yield 203 mg, 75%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.18 (t, *J* = 10.2 Hz, 1 H), 2.33 (t, *J* = 11.4 Hz, 1 H), 2.37 (s, 3 H), 3.44-3.48 (m, 2 H), 3.50-3.64 (m, 4 H), 3.86 (d, *J* = 11.4 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 2 H), 7.56 (d, *J* = 7.2 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.5, 45.5, 47.1, 63.2, 65.8, 75.5, 127.8, 129.9, 131.9, 144.1; **IR** (KBr, neat) 3508, 2923, 2866, 1453, 1339, 1166, 1048, 754 cm^{-1}; **HRMS** (ESI) calcd. for $C_{12}H_{18}NO_4S$ $(M + H)^+$ 272.0951, found 272.0950.

***N*-(2-Hydroxyethyl)-4-methyl-*N*-((2-methyloxiran-2-yl)methyl)benzenesulfonamide (40b):**



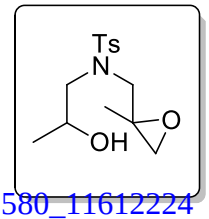
Colourless oil; R_f (hexane/ EtOAc 3:2) 0.47; yield 271 mg, 95%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.37 (s, 3 H), 2.41 (s, 3 H), 2.69 (d, *J* = 4.2 Hz, 1 H), 2.94 (d, *J* = 4.2 Hz, 1 H), 3.01-3.07 (m, 1 H), 3.24 (d, *J* = 15.0 Hz, 1 H), 3.32 (t, *J* = 6.0 Hz, 1 H), 3.34-3.38 (m, 1 H), 3.40 (d, *J* = 15.0 Hz, 1 H), 3.69-3.72 (m, 1 H), 3.73-3.78 (m, 1 H), 7.31 (d, *J* = 7.8 Hz, 2 H), 7.67 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 19.3, 21.7, 52.0, 53.5, 54.5, 57.2, 61.4, 127.5, 130.1, 135.7, 144.0; **IR** (KBr, neat) 3454, 2927, 1598, 1338, 1162, 1090, 1029, 816, 706 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{20}NO_4S$ $(M + H)^+$ 286.1108, found 286.1108.

***N*-(1-Hydroxypropan-2-yl)-4-methyl-*N*-((2-methyloxiran-2- -yl)methyl)benzenesulfonamide (diastereomeric mixture, 7:3: 40c):**



Colourless oil; Rf (hexane/ EtOAc 3:2) 0.40; yield 230 mg, 77%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.69 (d, J = 6.4 Hz, 3 H, major), 0.83 (d, J = 6.8 Hz, 3 H, minor), 1.41 (s, 3 H, major), 1.49 (s, 3 H, minor), 2.43 (s, 3 H), 2.71-2.84 (m, 2 H), 3.24-3.28 (m, 1 H), 3.36-3.41 (m, 1 H), 3.48-3.61 (m, 2 H), 3.72-3.94 (m, 2 H), 7.30-7.33 (m, 2 H), 7.68-7.72 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.0, 13.3, 18.9, 20.0, 21.7, 45.9, 49.9, 52.9, 53.2, 55.8, 56.8, 58.4, 64.9, 65.1, 127.2, 127.5, 129.9, 130.0, 137.2, 137.4, 143.8, 144.0; **IR** (KBr, neat) 3522, 2928, 2876, 1598, 1453, 1337, 1216, 1153, 1091, 1025, 756 cm-1; **HRMS** (ESI) calcd. for $C_{14}H_{22}NO_4S$ $(M + H)^+$ 300.1264, found 300.1263.

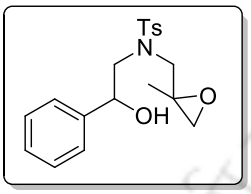
***N*-(2-hydroxypropyl)-4-methyl-*N*-((2-methyloxiran-2-yl)methyl)benzenesulfonamide (diastereomeric mixture, 3:2, 40d):**



Colourless oil; R_f (hexane/ EtOAc 3:2) 0.45; yield 278 mg, 93%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.12 (d, *J* = 6.4 Hz, 3 H, major), 1.16 (d, *J* = 6.8 Hz, 3 H, minor), 1.37 (s, 3 H, minor), 1.42 (s, 3 H, major), 2.44 (s, 3 H), 2.71-2.74 (m,

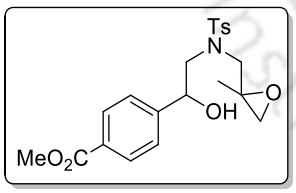
1 H, major), 2.77-2.87 (m, 1 H, minor), 3.14-3.18 (m, 1 H), 3.20-3.23 (m, 1 H), 3.45 (d, *J* = 15.2 Hz, 1 H), 3.57 (d, *J* = 15.2 Hz, 1 H), 3.90-3.98 (m, 1 H), 4.04-4.12 (m, 1 H), 7.34 (d, *J* = 7.6 Hz, 2 H), 7.69 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 19.2, 19.3, 19.5, 20.5, 20.7, 21.7, 52.0, 52.2, 53.6, 55.9, 57.0, 57.3, 58.4, 59.4, 65.2, 67.2, 127.4, 127.5, 129.9, 130.0, 135.4, 135.5, 144.0, 144.1; **IR** (KBr, neat) 3450, 2925, 1598, 1494, 1339, 1161, 1020, 908, 729 cm^{-1}; **HRMS** (ESI) calcd. for $C_{14}H_{22}NO_4S$ $(M + H)^+$ 300.1264, found 300.1267**.**

***N*-(2-Hydroxy-2-phenylethyl)-4-methyl-*N*-((2-methyloxiran-2-yl)methyl) benzenesulfonamide (diastereomeric mixture, 5:4, 40e):**



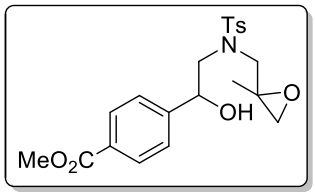
Colourless oil; R_f (hexane/ EtOAc 3:2) 0.45; yield 339 mg, 94%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.35 (s, 3 H, minor), 1.45 (s, 3 H, major), 2.40 (s, 3 H), 2.70 (d, *J* = 4.0 Hz, 1 H, minor), 2.76 (d, *J* = 4.0 Hz, 1 H, major), 2.97-3.04 (m, 3 H, major), 3.06-3.15 (m, 3 H, minor), 3.28-3.35 (m, 1 H), 3.44-3.48 (m, 1 H, major), 3.68 (d, *J* = 15.6 Hz, 1 H, minor), 4.89 (d, *J* = 9.2 Hz, 1 H, major), 5.08 (d, *J* = 9.2 Hz, 1 H, minor), 7.26-7.43 (m, 6 H), 7.42 (d, *J* = 7.2 Hz, 1 H), 7.67 (d, *J* = 7.6 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 19.1, 19.3, 21.6, 52.0, 52.1, 52.5, 56.2, 56.7, 57.3, 58.4, 60.3, 71.4, 73.6, 126.0, 126.1, 127.4, 127.5, 127.7, 128.0, 128.5, 128.6, 129.9, 130.0, 135.4, 135.6, 141.4, 141.7, 144.0, 144.2; **IR** (KBr, neat) 3485, 2924, 1495, 1334, 1161, 1091, 1024, 754 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421, found 362.1423.

***N*-(2-hydroxy-2-(4-nitrophenyl)ethyl)-4-methyl-*N*-((2-methyl-oxiran-2-yl)methyl) benzene-sulfonamide (diasteromeric mixture 4:3, 40f):**



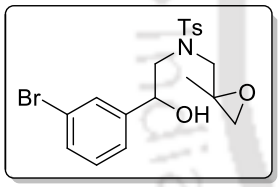
Colourless oil; R_f (hexane/ EtOAc 3:2) 0.50; yield 292 mg, 72%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.35 (s, 3 H, minor), 1.49 (s, 3 H, major), 2.42 (s, 3 H, major), 2.43 (s, 3 H, minor), 2.75 (d, *J* = 4.2 Hz, 1 H, minor), 2.81 (d, *J* = 4.2 Hz, 1 H, major), 3.00-3.09 (m, 3 H), 3.29 (dd, *J* = 15.0 and 1.2 Hz, 1 H, minor), 3.41 (dd, *J* = 15.0 and 5.4 Hz, 1 H, major), 3.48 (d, *J* = 15.0 Hz, 1 H, minor), 3.76 (d, *J* = 15.0 Hz, 1 H, major), 5.06 (d, *J* = 8.4 Hz, 1 H, minor), 5.23 (d, *J* = 8.4 Hz, 1 H, major), 7.30-7.34 (m, 2 H), 7.51-7.60 (m, 2 H), 7.64-7.71 (m, 2 H), 8.19 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 36.0, 49.5, 62.2, 62.4, 116.3, 126.8, 126.9, 127.8, 128.5, 128.8, 128.83, 129.2, 130.0, 137.5, 138.0, 138.6, 143.9, 145.4; **IR** (KBr, neat) 3499, 2923, 2852, 1521, 1453, 1347, 1161, 1090, 853, 698 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{23}N_2O_6S$ $(M + H)^+$ 407.1271, found 407.1275.

Methyl 4-(1-hydroxy-2-(4-methyl-*N*-((2-methyloxiran-2-yl)methyl)phenylsulfonamido) ethyl)-benzoate (diastereomeric mixture, 1:1, 40g):



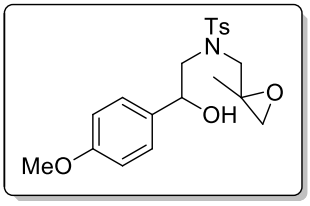
Colourless oil; R_f (hexane/ EtOAc 3:2) 0.50; yield 306 mg, 73%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.24 (s, 3 H), 2.39 (s, 1.5 H), 2.41 (s, 1.5 H), 2.70 (s, 0.5 H), 2.77 (s, 0.5 H), 2.97 (s, 1 H), 3.01-3.10 (m, 2 H), 3.28 (d, *J* = 15.0 Hz, 0.5 H), 3.26-3.42 (m, 1 H), 3.69 (d, *J* = 15.0 Hz, 0.5 H), 3.89 (s, 3 H), 4.96 (d, *J* = 10.2 Hz, 0.5 H), 5.14 (d, *J* = 12.0 Hz, 0.5 H), 7.29 (d, *J* = 7.2 Hz, 2 H), 7.43-7.50 (m, 2 H), 7.65 (d, *J* = 7.8 Hz, 2 H), 7.98 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 19.1, 19.3, 21.7, 22.8, 51.9, 52.0, 52.2, 53.6, 56.4, 56.8, 57.4, 58.3, 60.3, 71.2, 73.5, 126.0, 126.1, 127.4, 127.5, 129.9, 129.93, 130.1, 130.2, 135.3, 135.7, 144.2, 144.3, 146.6, 146.9, 167.0, 167.1; **IR** (KBr, neat) 3498, 2925, 2854, 1722, 1612, 1437, 1339, 1282, 1159, 1089, 1019, 987, 816, 758 cm^{-1}; **HRMS** (ESI) calcd. for $C_{21}H_{26}NO_6S$ $(M + H)^+$ 420.1481, found 420.1478.

***N*-(2-(3-Bromophenyl)-2-hydroxyethyl)-4-methyl-*N*-((2-methyloxiran-2-yl)methyl) benzene-sulfonamide (diastereomeric mixture, 1:1, 40h):**



Colourless oil; R_f (hexane/ EtOAc 3:2) 0.39; yield 312mg, 71%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.34 (s, 1.5 H), 1.46 (s, 1.5 H), 2.40 (s, 3 H), 2.71 (d, *J* = 3.0 Hz, 0.5 H), 2.77 (d, *J* = 3.6 Hz, 0.5 H), 2.96-3.02 (m, 1.5 H), 3.06-3.10 (m, 1 H), 3.26 (d, *J* = 15.0 Hz, 0.5 H), 3.35-3.44 (m, 1.5 H), 3.70 (d, *J* = 15.0 Hz, 0.5 H), 4.87 (d, *J* = 9.6 Hz, 0.5 H), 5.05 (d, *J* = 9.6 Hz, 0.5 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 7.28-7.39 (m, 4 H), 7.52 (s, 0.5 H), 7.59 (s, 0.5 H), 7.65-7.68 (m, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 19.1, 19.3, 21.6, 51.9, 52.0, 53.5, 56.4, 56.7, 57.3, 58.3, 60.2, 70.8, 73.1, 122.7, 124.7, 124.8, 127.4, 127.5, 129.1, 129.2, 130.0, 130.1, 130.16, 130.2, 130.8, 130.9, 135.3, 135.5, 143.8, 144.1, 144.2, 144.3; **IR** (KBr, neat) 3492, 2925, 2855, 1597, 1428, 1338, 1159, 1090, 804, 762 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{23}BrNO_4S$ $(M + H)^+$ 440.0526, found 440.0526 for ^{79}Br.

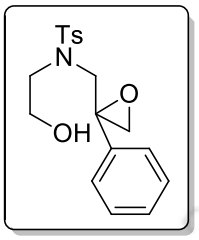
***N*-(2-Hydroxy-2-(4-methoxyphenyl)ethyl)-4-methyl-*N*-((2-methyloxiran-2-yl)methyl) benzene-sulfonamide (diastereomeric mixture, 1:1, 40i):**



Colourless oil; R_f (hexane/ EtOAc 3:2) 0.50; yield 301 mg, 77%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.33 (s, 1.5 H), 1.43 (s, 1.5 H), 2.39 (s, 3 H), 2.68 (d, *J* = 3.0 Hz, 0.5 H), 2.74 (d, *J* = 3.0 Hz, 0.5 H), 2.93-3.01 (m, 1.5 H), 3.06-3.13 (m, 1 H), 3.26 (d, *J* = 15.0 Hz, 0.5 H), 3.33 (d, *J* = 15.6 Hz, 0.5 H), 3.41-3.47 (m, 1 H), 3.66 (d, *J* = 15.0 Hz, 0.5 H), 3.77 (s, 3 H), 4.84 (d, *J* = 9.6

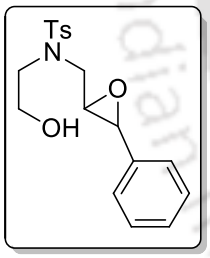
Hz, 0.5 H), 5.02 (d, *J* = 9.0 Hz, 0.5 H), 6.85 (d, *J* = 7.8 Hz, 2 H), 7.21-7.67 (m, 4 H), 7.65-7.70 (m, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 19.0, 19.2, 21.6, 51.9, 52.0, 53.4, 53.6, 55.3, 56.1, 56.6, 57.2, 58.2, 60.0, 70.9, 72.1, 73.1, 113.8, 114.0, 127.1, 127.2, 127.3, 127.4, 129.9, 130.0, 133.5, 133.9, 135.5, 135.7, 143.9, 144.1, 159.2, 159.3; **IR** (KBr, neat) 3508, 2978, 1598, 1455, 1341, 1162, 1092, 815, 770 cm^{-1}; **HRMS** (ESI) calcd. for $C_{20}H_{26}NO_5S$ $(M + H)^+$ 392.1526, found 392.1527.

***N*-(2-Hydroxyethyl)-4-methyl-*N*-((2-phenyloxiran-2-yl)methyl)benzenesulfonamide (40j):**



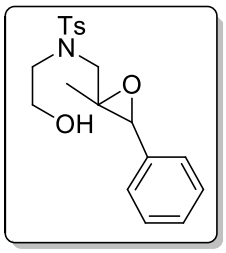
Colourless oil; Rf (hexane/ EtOAc 3:2) 0.40; yield 336 mg, 97%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 2.87 (d, J = 6.6 Hz, 1 H), 2.93 (dt, J = 9.6 and 4.4 Hz, 1 H), 3.41 (d, J = 6.6 Hz, 1 H), 3.46 (dt, J = 9.6 and 4.8 Hz, 1 H), 3.69-3.81 (m, 4 H), 7.29-7.39 (m, 5 H), 7.43 (d, J = 7.6 Hz, 2 H), 7.65 (d, J = 7.2 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.7, 53.1, 53.5, 53.6, 60.7, 61.3, 126.3, 127.6, 128.5, 128.8, 130.1, 135.1, 137.3, 144.2; **IR** (KBr, neat) 3508, 2977, 2876, 1598, 1452, 1336, 1153, 1091, 1024, 815, 679 cm-1; **HRMS** (ESI) calcd. for $C_{18}H_{22}NO_4S$ $(M + H)^+$ 348.1264, found 348.1262.

***N*-(2-hydroxyethyl)-4-methyl-*N*-((3-phenyloxiran-2-yl)methyl)benzenesulfonamide (40k):**



Colourles oil, Rf (hexane/ EtOAc 3:2) 0.50; yield 330 mg, 95%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.25-3.30 (m, 2 H), 3.32-3.34 (m, 2 H), (dd, J = 16.8 and 4.8 Hz, 1 H), 3.82 (t, J = 4.8 Hz, 2 H), 3.86 (d, J = 1.8 Hz, 1 H), 7.25 (d, J = 8.4 Hz, 2 H), 7.29-7.35 (m, 5 H), 7.71 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 51.2, 52.6, 57.6, 61.6, 61.7, 125.9, 127.4, 128.6, 128.7, 130.1, 135.7, 136.0, 144.1; **IR** (KBr, neat) 3499, 2923, 2873, 1598, 1451, 1337, 1160, 1089, 978, 815, 756 cm-1; **HRMS** (ESI) calcd. for $C_{18}H_{22}NO_4S$ $(M + H)^+$ 348.1264, found 414.1359.

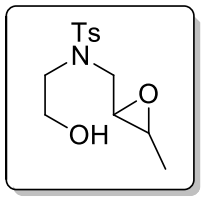
***N*-(2-Hydroxyethyl)-4-methyl-*N*-((2-methyl-3-phenyloxiran-2-yl)methyl)benzene sulfonamide (diastereomeric mixture, 4:1, 40l):**



Colourless oil, R_f (hexane/ EtOAc 3:2) 0.48 yield; 332 mg, 92%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.13 (s, 3 H, major), 1.58 (s, 3 H, minor), 2.38 (s, 3 H, minor), 2.44 (s, 3 H, major), 3.03-3.08 (m, 1 H), 3.46 (d, *J* = 6.0 Hz, 2 H), 3.49-3.54 (m, 1 H), 3.66 (t, *J* = 4.8 Hz, 1 H), 3.77-3.81 (m, 1 H), 3.83-3.87 (m, 1 H), 3.99 (s, 1 H, minor), 4.32 (s, 1 H, major), 7.23-7.37 (m, 7 H), 7.53 (d, *J* = 7.8 Hz, 2 H, minor), 7.72 (d, *J* = 7.8 Hz, 2 H, major); **^{13}C NMR** (150 MHz, $CDCl_3$) δ

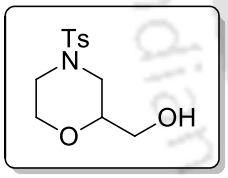
20.5, 21.6, 21.7, 51.4, 51.7, 53.4, 55.4, 61.1, 61.6, 61.7, 62.3, 63.7, 63.9, 126.5, 126.6, 127.4, 127.6, 127.9, 128.2, 128.3, 128.6, 130.0, 130.1, 135.0, 135.1, 135.5, 136.0, 143.8, 144.1; **IR** (KBr, neat) 3520, 2928, 1598, 1450, 1339, 1161, 1089, 751, 656 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421, found 380.1323.

***N*-(2-Hydroxyethyl)-4-methyl-*N*-((3-methyloxiran-2-yl)methyl)benzenesulfonamide (diastereomeric mixture, 1:2, 40m):**



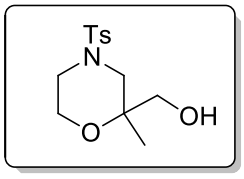
Colourless oil; Rf (hexane/ EtOAc 3:2) 0.46; yield 257 mg, 90%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.25 (d, J = 5.2 Hz, 3 H, minor), 1.29 (d, J = 5.2 Hz, 3 H, major), 2.39 (s, 3 H), 2.93-3.00 (m, 2 H, major) 3.01-3.09 (m, 2 H, minor), 3.10-3.15 (m, 1 H, major), 3.16-3.19 (m, 1 H, minor), 3.20-3.30 (m, 2 H), 3.45-3.51 (m, 1 H, minor), 3.57-3.63 (m, 1 H, major), 3.74 (t, J = 5.2 Hz, 2 H, major), 3.77-3.80 (m, 2 H, minor), 7.29 (d, J = 7.6 Hz, 2 H), 7.69 (d, J = 7.6 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.0, 18.7, 20.0, 21.5, 51.1, 51.6, 52.4, 52.7, 53.7, 55.7, 58.6, 61.4, 65.9, 68.0, 127.2, 129.8, 129.9, 135.5, 143.8; **IR** (KBr, neat) 3518, 2926, 2854, 1625, 1598, 1452, 1337, 1161, 1090, 1020, 802, 752 cm-1; **HRMS** (ESI) calcd. for $C_{13}H_{20}NO_4S$ $(M + H)^+$ 286.1108, found 328.1219.

(4-Tosylmorpholin-2-yl)methanol (44a):



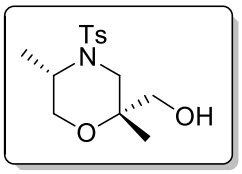
White solid; mp 120-121 ^oC; Rf (hexane/ EtOAc 3:2) 0.47; yield 211 mg, 78%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.27 (dd, J = 11.6 and 10.4 Hz, 1 H), 2.39 (dt, J = 11.6 and 3.6 Hz, 1 H), 2.45 (s, 3 H), 3.52-3.59 (m, 3 H), 3.64-3.70 (m, 2 H), 3.74 (dd, J = 11.2 and 2.8 Hz, 1 H), 3.92-3.97 (m, 1 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.63 (t, J = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) 21.6, 45.6, 47.1, 63.3, 65.9, 75.5, 128.0, 129.9, 132.1, 144.2; **IR** (KBr, neat) 3498, 2921, 2863, 1597, 1344, 1168, 1097, 974, 756 cm-1; **HRMS** (ESI) calcd. for $C_{12}H_{18}NO_4S$ $(M + H)^+$ 272.0951 found 272.0951.

(2-Methyl-4-tosylmorpholin-2-yl)methanol (44b):



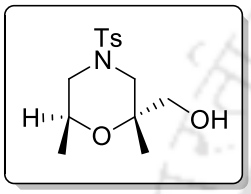
Pale yellow oil; Rf (hexane/ EtOAc 3:2) 0.47; yield 228 mg, 80%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.25 (s, 3 H), 2.42 (s, 3 H), 2.64-2.68 (m, 1 H), 2.77 (d, J = 12.0 Hz, 1 H), 2.95 (d, J = 12.0 Hz, 1 H), 3.19 (dt, J = 11.4 and 2.4 Hz, 1 H), 3.50 (dd, J = 11.4 and 5.4 Hz, 1 H), 3.55 (d, J = 10.8 Hz, 1 H), 3.75 (dt, J = 12.0 and 4.2 Hz, 1 H), 3.84-3.88 (m, 1 H), 7.32 (d, J = 7.8 Hz, 2 H), 7.60 (d, J = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) 19.2, 21.7, 45.8, 50.6, 60.5, 66.8, 73.5, 127.9, 130.0, 132.4, 144.1; **IR** (KBr, neat) 3509, 2925, 2879, 1598, 1455, 1350, 1166, 1090, 1057, 760 cm-1; **HRMS** (ESI) calcd. for $C_{13}H_{20}NO_4S$ $(M + H)^+$ 286.1108 found 286.1111.

((2R*,5S*)-2,5-dimethyl-4-tosylmorpholin-2-yl)methanol (44c):



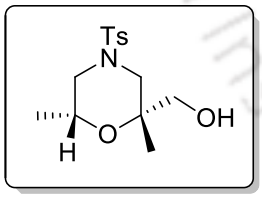
Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.40; yield 215 mg, 72%; **[α]$_D^{25}$** +13.6 (c 0.25, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.09 (d, *J* = 5.2 Hz, 3 H), 1.22 (s, 3 H), 2.43 (s, 3 H), 2.96 (d, *J* = 13.6 Hz, 1 H), 3.37 (m, 2 H), 3.60 (d, *J* = 10. 8 Hz, 1 H), 3.73 (d, *J* = 11. 6 Hz, 1 H), 3.86-3.94 (m, 2 H), 7.26 (d, *J* = 6.8 Hz, 2 H), 7.67 (d, *J* = 7.2 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) 13.8 21.7, 22.4 22.9 (minor), 45.2, 48.6, 62.3, 66.0, 73.2, 127.2, 130.0, 137.1, 143.8; **IR** (KBr, neat) 3434, 29 24, 2854, 1454, 1337, 1161, 1037, 953, 815, 680 cm^{-1}; **HRMS** (ESI) calcd. for $C_{14}H_{22}NO_4S$ (M + H)$^+$ 300.1264 found 300.1278.

((2R*,6S*)-2,6-Dimethyl-4-tosylmorpholin-2-yl)methanol (44d):



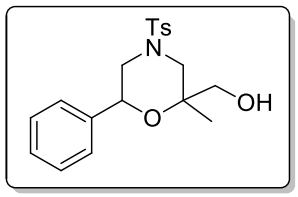
White solid, mp 127-128 ^{o}C; Rf (hexane/ EtOAc 3:2) 0.45; yield 120 mg, 40%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.11 (d, J = 6.0 Hz, 3 H), 1.16 (s, 3 H), 1.92 (t, J = 10.8 Hz, 1 H), 2.05 (d, J = 11.6 Hz, 1 H), 2.45 (s, 3 H), 3.52-3.60 (m, 2 H), 3.69 (d, J = 11.2 Hz, 1 H), 3.91 (d, J = 11.2 Hz, 1 H), 3.94-3.98 (m, 1 H), 7.36 (d, J = 8.0 Hz, 2 H), 7.62 (d, J = 8.0 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) 19.2, 21.7, 23.3, 50.4, 51.3, 62.5, 65.6, 73.7, 127.9, 130.0, 132.5, 144.2; **IR** (KBr, neat) 3463, 2925, 2852, 1598, 1493, 1342, 1166, 1094, 1030, 814, 662 cm-1; **HRMS** (ESI) calcd. for $C_{14}H_{22}NO_4S$ (M + H)$^+$ 300.1264 found 300.1271.

((2S*,6S*)-2,6-Dimethyl-4-tosylmorpholin-2-yl)methanol (44d'):



White solid, mp 125-126 ^{o}C; Rf (hexane/ EtOAc 3:2) 0.48; yield 126 mg, 42%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.07 (d, J = 6.4 Hz, 3 H), 1.29 (s, 3 H), 1.82 (t, J = 10.4 Hz, 1 H), 2.38 (d, J = 11.2 Hz, 1 H), 2.42 (s, 3 H), 3.27-3.33 (m, 2 H), 3.50 (d, J = 7.2 Hz, 1 H), 3.55 (dt, J = 11.2 and 3.0 Hz, 1 H), 3.96-4.05 (m, 1 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.59 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) 18.3, 19.0, 21.7, 49.8, 51.6, 65.4, 68.8, 74.0, 127.9, 130.0, 132.6, 144.0; **IR** (KBr, neat) 3461, 2920, 2857, 1592, 1490, 1348, 1169, 1098, 1032, 817, 665 cm-1; **HRMS** (ESI) calcd. for $C_{14}H_{22}NO_4S$ (M + H)+ 300.1260 found 300.1271.

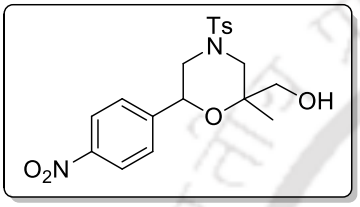
(2-Methyl-6-phenyl-4-tosylmorpholin-2-yl)methanol (diastereomeric mixture, 1:1, 44e):



White solid, M. P. 133-136 ^{o}C; Rf (hexane/ EtOAc 3:2) 0.40; yield 271 mg, 75%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.26 (s, 1.5 H), 1.43 (s, 1.5 H), 2.07-2.17 (m, 1.5 H), 2.40 (s, 1.5 H), 2.42 (s, 1.5 H), 2.53 (d, 11.2 Hz, 0.5 H), 3.44 (dd, J = 10.8 and 3.2 Hz, 1 H), 3.60 (d, J = 11.6 Hz, 0.5

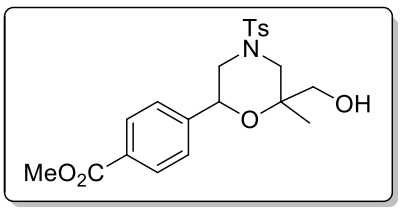
H), 3.67 (d, J = 11.6 Hz, 0.5 H), 3.76 (dd, J = 11.6 and 1.6 Hz, 1 H), 3.81 (d, J = 11.6 Hz, 0.5 H), 3.94 (d, J = 11.2 Hz, 0.5 H), 4.88 (dd, J = 10.8 and 2.8 Hz, 0.5 H,), 4.94 (d, J = 10.4 Hz, 0.5 H), 7.28-7.32 (m, 7 H), 7.58 (d, J = 6.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) 18.0, 21.6, 23.2, 50.0, 50.4, 51.8, 51.9, 62.2, 68.8, 71.5, 71.6, 74.1, 74.5, 126.3, 126.4, 127.7, 127.8, 128.4, 128.5, 128.57, 128.6, 129.9, 130.0, 132.2, 132.4, 138.7, 138.8, 144.0, 144.1; **IR** (KBr, neat) 3531, 2925, 1598, 1454, 1342, 1160, 1092, 1021, 816, 755 cm-1; **HRMS** (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421 found 362.1418.

(2-Methyl-6-(4-nitrophenyl)-4-tosylmorpholin-2-yl)methanol (diastereomeric mixture, 3:2, 44f):



White solid, mp 142-144 ^oC; Rf (hexane/ EtOAc 3:2) 0.45; yield 284 mg, 70%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.30 (s, 3 H, major), 1.46 (s, 3 H, minor), 2.05-2.10 (m 1 H), 2.19 (d, J = 12.0 Hz, 1 H, major), 2.42 (s, 3 H, minor), 2.43 (s, 3 H, major), 2.55 (d, J = 11.5 Hz, 1 H, minor), 3.50 (t, J = 12.0 Hz, 1 H), 3.67 (d, J = 11.4 Hz, 1 H, minor), 3.71 (dd, J = 11.4 and 1.2 Hz, 1 H, major), 3.82 (d, J = 12.0 Hz, 1 H), 3.86 (d, J = 11.4 Hz, 1 H, major), 3.99 (d, J = 11.4 Hz, 1 H, minor), 5.05 (dd, J = 10.8 and 2.4 Hz, 1 H, major), 5.08 (dd, J = 10.8 and 2.4 Hz, 1 H, minor), 7.32 (t, J = 8.4 Hz, 2 H), 7.49-7.53 (m, 2 H), 7.59 (d, J = 8.4 Hz, 2 H), 8.18 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.0, 21.7, 22.9, 23.2, 50.1, 50.5, 51.5, 51.7, 62.4, 68.9, 70.8, 71.0, 74.7, 75.2, 123.8, 123.9, 126.5, 127.2, 127.8, 127.9, 128.1, 128.5, 130.1, 130.2, 132.3, 144.4, 144.5, 146.0, 148.0; **IR** (KBr, neat) 3528, 2925, 1600, 1522, 1454, 1349, 1166, 1092, 1022, 759, 698 cm-1; **HRMS** (ESI) calcd. for $C_{19}H_{23}N_2O_6S$ $(M + H)^+$ 407.1271 found 407.1277.

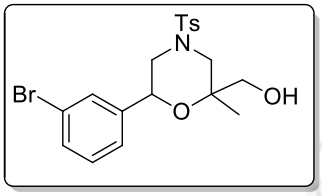
Methyl 4-(6-(hydroxymethyl)-6-methyl-4-tosylmorpholin-2-yl)benzoate (diastereomeric mixture, 1:1, 44g):



White solid, mp 150-152 oC; Rf (hexane/ EtOAc 3:2) 0.40; yield 285 mg, 68%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.27 (s, 1.5 H), 1.44 (s, 1.5 H), 2.05-2.10 (m, 1 H), 2.18 (d, J = 12.0 Hz, 0.5 H), 2.40 (s, 1.5 H), 2.41 (s, 1.5 H), 2.54 (d, J = 11.4 Hz, 0.5 H), 3.46 (t, J = 12.0 Hz, 1 H), 3.64 (d, J = 11.4 Hz, 0.5 H), 3.67 (d, J = 11.4 Hz, 0.5 H), 3.78 (dd, J = 12.0 and 1.2 Hz, 1 H), 3.81 (d, J = 11.4 Hz, 0.5 H), 3.89 (s, 1.5 H), 3.90 (s, 1.5 H), 4.00 (d, J = 11.4 Hz, 0.5 H), 4.95 (d, J = 10.2 Hz, 0.5 H), 4.98 (d, J = 10.8 Hz, 0.5 H), 7.30 (t, J = 8.4 Hz, 2 H), 7.36-7.40 (m, 2 H), 7.57 (d, J = 7.8 Hz, 2 H), 8.98 (dd, J = 8.4 and 3.6 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 18.1, 21.7, 22.9, 23.3, 50.0, 50.5, 51.7, 51.8, 52.4, 62.4, 68.9, 71.3, 71.4,

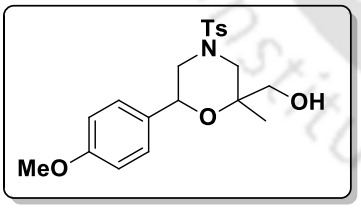
74.4, 74.8, 126.3, 126.32, 127.8, 127.9, 129.9, 130.0, 130.1, 130.2, 130.3, 132.4, 143.7, 143.8, 144.2, 144.3, 166.8, 166.9; **IR** (KBr, neat) 3492, 2925, 2854, 1721, 1455, 1342, 1282, 1166, 1091, 1020, 779, 705 cm-1; **HRMS** (ESI) calcd. for $C_{21}H_{26}NO_6S$ $(M + H)^+$ 420.1475, found 420.1480.

(6-(3-Bromophenyl)-2-methyl-4-tosylmorpholin-2-yl)methanol (diastereomeric mixture, 1:1, 44h):



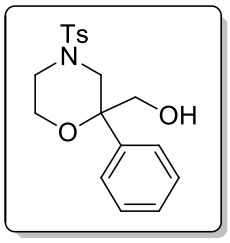
Pale yellow oil; Rf (hexane/ EtOAc 3:2) 0.48; yield 268 mg, 61%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.26 (s, 1.5 H), 1.42 (s, 1.5 H), 2.02-2.07 (m, 1 H), 2.14 (d, J = 12.0 Hz, 0.5 H), 2.40 (s, 1.5 H), 2.42 (s, 1.5 H), 2.50 (d, J = 11.4 Hz, 0.5 H), 3.45 (dd, J = 11.4 and 6.0 Hz, 1 H), 3.61 (d, J = 11.4 Hz, 0.5 H), 3.66 (d, J = 12.0 Hz, 0.5 H), 3.74 (d, J = 11.4Hz, 1 H), 3.81 (d, J = 11.4 Hz, 0.5 H), 3.92 (d, J = 11.4 Hz, 0.5 H), 4.87 (dd, J = 10.2 and 3.0 Hz, 0.5 H), 4.90 (d, J = 10.8 Hz, 0.5 H), 7.16-7.23 (m, 2 H), 7.30 (t, J = 9.0 Hz, 2 H), 7.40 (t, J = 6.0 Hz, 1 H), 7.45 (s, 0.5 H), 7.47 (s, 0.5 H), 7.57 (d, J = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 18.0, 21.2, 23.2, 50.4, 51.7, 51.8, 62.3, 68.8, 70.9, 71.0, 72.1, 74.4, 74.8, 122.8, 125.0, 125.1, 127.8, 129.3, 129.9, 130.1, 130.2, 130.3, 131.5, 131.6, 132.1, 132.3, 141.1, 141.2, 144.2, 144.3; **IR** (KBr, neat) 3509, 2925, 2853, 1597, 1341, 1165, 1071, 808, 774, 682 cm-1; **HRMS** (ESI) calcd. for $C_{19}H_{23}BrNO_4S$ $(M + H)^+$ 440.0526, found 440.0527 for ^{79}Br.

(6-(4-Methoxyphenyl)-2-methyl-4-tosylmorpholin-2-yl)methanol (diastereomeric mixture, 3:2, 44i):



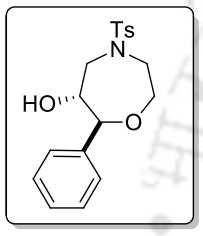
Colourless oil; Rf (hexane/ EtOAc 3:2) 0.38; yield 254 mg, 65%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.25 (s, 3 H, major), 1.43 (s, 3 H, minor), 2.04-2.14 (m, 1 H), 2.18 (d, J = 12.0 Hz, 1 H, minor), 2.42 (s, 3 H, major), 2.43 (s, 3 H, minor), 2.55 (d, J = 11.4 Hz, 1 H, major), 3.41-3.44 (m, 1 H), 3.61 (d, J = 11.4 Hz, 1 H, major), 3.65 (dd, J = 11.4 and 1.2 Hz, 1 H, minor), 3.72 (d, J = 11.4 Hz, 1 H), 3.76 (d, J = 11.4 Hz, 1 H, major), 3.78 (s, 3 H), 4.02 (dd, J = 11.4 and 2.4 Hz, 1 H, minor), 4.83 (dd, J = 10.2 and 2.4 Hz, 1 H, minor), 4.90 (d, J = 10.2 and 2.4 Hz, 1 H, major), 6.83-6.87 (m, 2 H), 7.20-7.26 (m, 2 H), 7.32 (t, J = 8.4 Hz, 2 H), 7.58 (d, J = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 18.2, 21.7, 23.4, 49.9, 50.5, 52.0, 55.5, 62.5, 68.9, 71.3, 71.5, 74.2, 74.4, 114.1, 114.2, 127.7, 127.8, 127.86, 127.9, 128.4, 128.7, 130.0, 131.0, 132.5, 144.1, 144.2, 159.8, 159.9; **IR** (KBr, neat) 3527, 2925, 2853, 1613, 1456, 1341, 1249, 1165, 1092, 1033, 815, 755 cm-1; **HRMS** (ESI) calcd. for $C_{20}H_{26}NO_5S$ $(M + H)^+$ 392.1526, found 392.1525.

(2-Phenyl-4-tosylmorpholin-2-yl)methanol (44j):



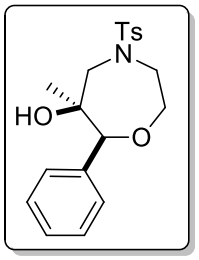
Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.45; yield 330 mg, 95%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.45 (s, 3 H), 2.50-2.57 (m, 1 H), 2.88 (d, *J* = 12.4 Hz, 1 H), 3.33 (d, *J* = 11.6 Hz, 1 H), 3.50 (d, *J* = 11.6 Hz, 1 H), 3.67 (d, *J* = 12.4 Hz, 1 H), 3.72 (d, *J* = 7.6 Hz, 2 H), 4.17 (d, *J* = 12.4 Hz, 1 H), 7.32-7.37 (m, 3 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.51 (d, *J* = 7.6 Hz, 2 H), 7.66 ((d, *J* = 7.6 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.6, 45.7, 47.9, 60.8, 69.3, 78.2, 127.3, 127.9, 128.1, 128.8, 129.9, 131.9, 138.3, 144.1; **IR** (KBr, neat) 3509, 2925, 2854, 1598, 1450, 1350, 1166, 1092, 1017, 816, 759 cm^{-1}; **HRMS** (ESI) calcd. for $C_{18}H_{22}NO_4S$ $(M + H)^+$ 348.1264, found 348.1267.

(6S*,7R*)-7-Phenyl-4-tosyl-1,4-oxazepan-6-ol (45k).



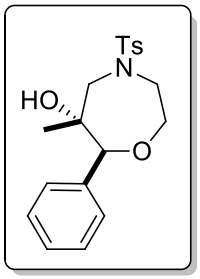
White solid, mp 132-134 ^{o}C; R_f (hexane/ EtOAc 3:2) 0.37; yield 167 mg, 48%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.45 (s, 3 H), 3.05-3.10 (m, 1 H), 3.40 (dd, J = 15.0 and 3.6 Hz, 1 H), 3.73 (dd, J = 15.0 and 1.2 Hz, 1 H), 3.88 (d, 3.0 Hz, 1 H), 3.89 (d, 3.0 Hz, 1 H), 3.91-3.95 (m, 1 H), 4.19 (dd, J = 12.6 and 3.0 Hz, 1 H), 4.43 (d, J = 7.8 Hz, 1 H), 7.28 (t, J = 7.2 Hz, 1 H), 7.33-7.36 (m, 4 H), 7.40 (d, J = 7.8 Hz, 2 H), 7.72 (d, J = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 52.6, 54.5, 73.5, 76.2, 88.3, 126.6, 127.2, 128.0, 128.6, 130.1, 136.0, 141.2, 144.0; **IR** (KBr, neat) 3508, 2923, 1597, 1494, 1336, 1161, 1089, 1029, 816, 757 cm^{-1}; **HRMS** (ESI) calcd. for $C_{18}H_{22}NO_4S$ $(M + H)^+$ 348.1264 found 348.1268.

(6R*,7S*)-6-Methyl-7-phenyl-4-tosyl-1,4-oxazepan-6-ol (45l).



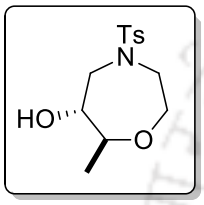
Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.40; yield 173 mg, 48%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 0.75 (s, 3 H), 2.44 (s, 3 H), 3.00 (dt, *J* = 12.6 and 4.2 Hz, 1 H), 3.10 (d, *J* = 15.6 Hz, 1 H), 3.64 (d, *J* = 15.0 Hz, 1 H), 3.88 (dt, *J* = 12.0 and 3.6 Hz, 1 H), 3.98 (dd, *J* = 13.8 and 3.6 Hz, 1 H), 4.17 (dd, *J* = 12.6 and 4.2 Hz, 1 H), 4.68 (s, 1 H), 7.23-7.26 (m, 1 H), 7.31 (t, *J* = 7.8 Hz, 2 H), 7.34 (d, *J* = 7.8 Hz, 2 H), 7.41 (d, *J* = 7.2 Hz, 2 H), 7.72 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.2, 21.7, 53.3, 61.6, 74.0, 76.4, 89.2, 126.9, 127.0, 127.2, 127.7, 130.1, 136.0, 139.3, 144.0; **IR** (KBr, neat) 3507, 2929, 2872, 1595, 1451, 1335, 1157, 1024, 815, 750 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421 found 362.1431.

(6R*,7R*)-6-Methyl-7-phenyl-4-tosyl-1,4-oxazepan-6-ol (45l').



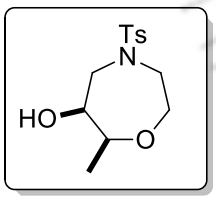
Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.45; yield 126 mg, 35%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.13 (s, 3 H), 2.44 (s, 3 H), 3.24 (d, *J* = 13.8 Hz, 1 H), 3.27-3.31 (m, 1 H), 3.45 (d, *J* = 14.4 Hz, 1 H), 3.53 (dt, *J* = 13.8 and 3.6 Hz, 1 H), 3.77-3.82 (m, 1 H), 4.10-4.15 (m, 1 H), 4.41 (s, 1 H), 7.29-7.35 (m, 7 H), 7.70 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 24.4, 51.9, 60.8, 71.4, 74.8, 88.0, 127.4, 128.1, 128.2, 128.3, 130.1, 135.5, 138.1, 143.9; **IR** (KBr, neat) 3507, 2929, 2872, 1595, 1451, 1335, 1157, 1024, 815, 750 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421 found 362.1431.

(6R*,7S*)-7-Methyl-4-tosyl-1,4-oxazepan-6-ol (45m).



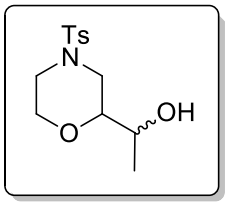
Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.45; yield 43 mg, 15%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.6 Hz, 3 H), 2.43 (s, 3 H), 3.28 (d, *J* = 13.8 and 4.2 Hz, 1 H), 3.31-3.34 (m, 1 H), 3.44 (dt, *J* = 13.8 and 4.2 Hz, 1 H), 3.49 (dd, *J* = 14.4 and 4.2 Hz, 1 H), 3.64 (dt, *J* = 12.6 and 3.0 Hz, 1 H), 3.78-3.83 (m, 2 H), 3.97 (dt, *J* = 12.0 and 4.2 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.67 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) 18.5, 21.7, 51.2, 54.1, 70.0, 72.2, 79.2, 127.0, 130.0, 135.9, 143.8; **IR** (KBr, neat) 3508, 2973, 2925, 1598, 1495, 1337, 1163, 1089, 1039, 763, 701 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{20}NO_4S$ $(M + H)^+$ 286.1108 found 332.1318.

(6S*,7S*)-7-Methyl-4-tosyl-1,4-oxazepan-6-ol (45m').



Pale yellow oil; R_f (hexane/ EtOAc 4:1) 0.38; yield 145 mg, 51%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.30 (d, *J* = 6.0 Hz, 3 H), 2.42 (s, 3 H), 2.87-2.92 (m, 1 H), 3.02 (d, *J* = 8.4 Hz, 1 H), 3.22 (d, *J* = 15.0 Hz, 1 H), 3.53-3.56 (m, 2 H), 3.64 (d, *J* = 15.0 Hz, 1 H), 3.74 (ddd, *J* = 12.0, 9.0 and 3.0 Hz, 1 H), 4.04 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) 20.1, 21.7, 52.8, 54.5, 73.1 76.6, 83.1, 127.0, 130.0, 136.0, 143.9; **IR** (KBr, neat) 3508, 2973, 2925, 1598, 1495, 1337, 1163, 1089, 1039, 763, 701 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{20}NO_4S$ $(M + H)^+$ 286.1108 found 332.1318.

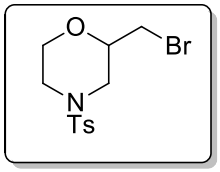
1-(4-Tosylmorpholin-2-yl)ethanol (diastereomeric mixture, 9:1, 44m).



Pale yellow oil; R_f (hexane/ EtOAc 3:2) 0.40; yield 75 mg, 25%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.0 Hz, 3 H), 2.21 (t, *J* = 10.8 Hz, 1 H), 2.30 (brs, 1 H), 2.38 (dd, *J* = 10.8 and 1.8 Hz, 1 H), 2.45 (s, 3 H), 3.35 (dd, *J* = 7.8 and 7.2 Hz, 1 H), 3.53-3.62 (m, 3 H), 3.69 (t, *J* = 12.0 Hz, 1 H), 3.96

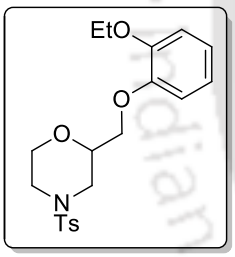
(d, *J* = 11.4 Hz, 1 H), 7.32 (d, *J* = 8.4 Hz, 2 H, minor), 7.35 (d, *J* = 8.4 Hz, 2 H, major), 7.63 (d, *J* = 7.8 Hz, 2 H, major), 7.67 (d, *J* = 8.4 Hz, 2 H, minor); **^{13}C NMR** (100 MHz, $CDCl_3$) 18.9, 20.2, 21.7, 22.8, 45.6, 47.2, 52.8, 54.6, 66.0, 68.2, 73.2, 76.7, 79.2, 83.2, 127.0, 128.0, 130.0, 130.1, 132.3, 143.9, 144.2; **IR** (KBr, neat) 3508, 2973, 2925, 1598, 1495, 1337, 1163, 1089, 1039, 763, 701 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{20}NO_4S$ $(M + H)^+$ 286.1108 found 332.1318.

2-(Bromomethyl)- 4-tosylmorpholine (46):



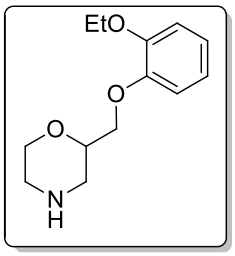
White solid M.P. 81-82 ^oC; R_f (hexane) 0.80; yield 583 mg, 95%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.24 (t, *J* = 10.2 Hz, 1 H), 2.42-2.47 (m, 1 H), 2.45 (s, 3 H), 3.31 (dd, *J* = 10.8 and 5.4 Hz, 1 H), 3.35 (dd, *J* = 10.2 and 5.4 Hz, 1 H), 3.51 (d, *J* = 11.4 Hz, 1 H), 3.69-3.77 (m, 3 H), 3.95 (d, *J* = 10.2 Hz, 1 H), 7.36 (d, *J* = 7.8 Hz, 2 H), 7.64 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 31.5, 45.4, 49.0, 66.2, 74.3, 128.0, 130.0, 132.2, 144.3; **IR** (KBr, neat) 2920, 2862, 1597, 1452, 1344, 1167, 1097, 974, 756 cm^{-1}; **HRMS** (ESI) calcd. for $C_{12}H_{17}BrNO_3S$ $(M + H)^+$ 334.0107, found 334.0115 for ^{79}Br.

2-((2-Ethoxyphenoxy)methyl)-4-tosylmorpholine (48):



White solid, M.P. 90-92 ^oC; R_f (hexane/ EtOAc 4:2) 0.40; yield 381 mg, 65%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.2 Hz, 3 H), 2.36 (t, *J* = 5.4 Hz, 1 H), 2.43 (s, 3 H), 2.45 (dt, *J* = 11.4 and 3.6 Hz, 1 H), 3.55 (d, *J* = 11.4 Hz, 1 H), 3.72 (dt, *J* = 11.4 and 2.4 Hz, 1 H), 3.80 (d, *J* = 11.4 Hz, 1 H), 3.93-3.97 (m, 3 H), 4.02-4.05 (m, 3 H), 6.84-6.89 (m, 3 H), 6.92-6.96 (m, 1 H), 7.33 (d, *J* = 7.8 Hz, 2 H), 7.64 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 15.0. 21.7, 45.7, 48.0, 64.6, 66.1, 70.5, 73.8, 114.0, 116.1, 121.1, 122.7, 128.0, 129.9, 132.3, 144.1, 148.4, 149.6; **IR** (KBr, neat) 2924, 2854, 1596, 1504, 1453, 1346, 1256, 1167, 1122, 1041, 961, 754 cm^{-1}; **HRMS** (ESI) calcd. for $C_{20}H_{26}NO_5S$ $(M + H)^+$ 392.1526, found 392.1536.

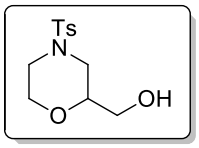
2-((2-Ethoxyphenoxy)methyl)morpholine, (±)-viloxazine (2).

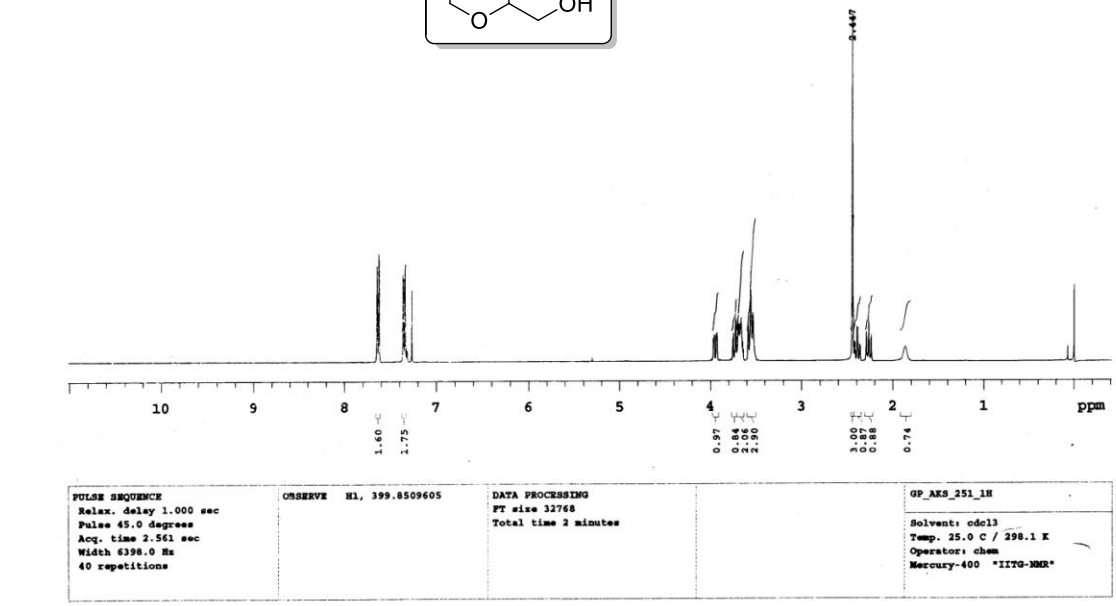


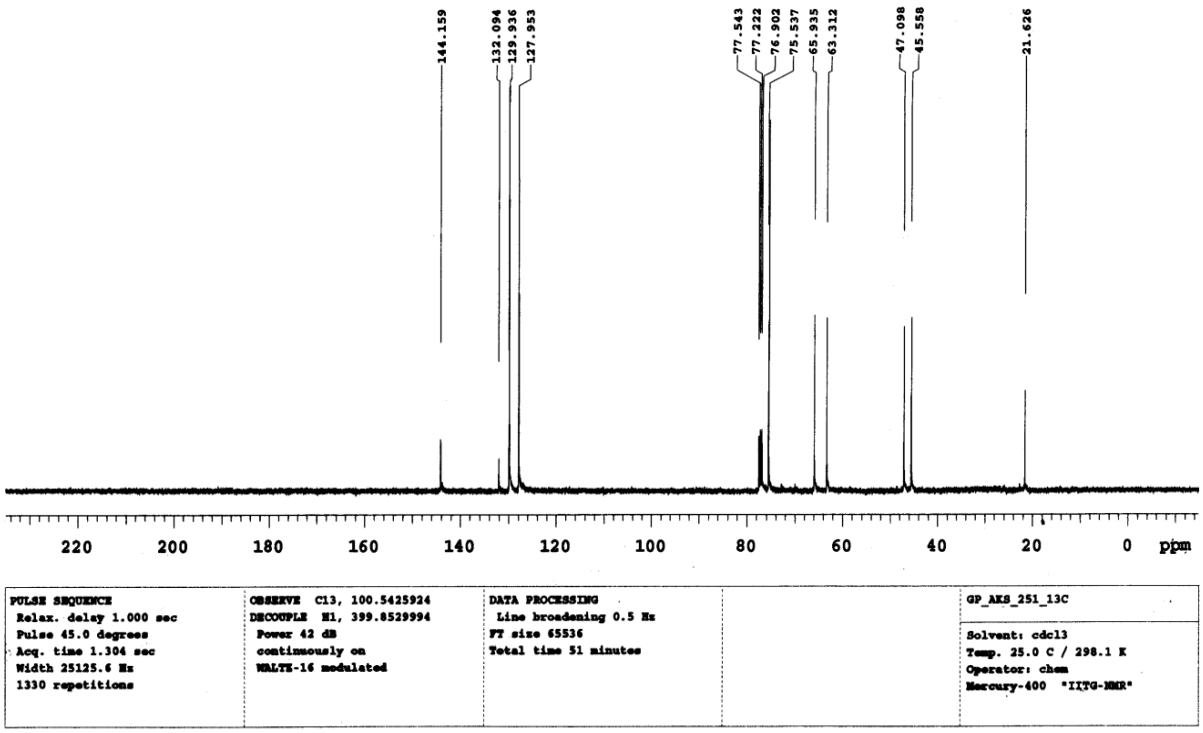
Colourless solid, M.P. 177-179 ^oC; R_f (MeOH/ $CHCl_3$, 9:1) 0.40; yield 145 mg, 80%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.2 Hz, 3 H), 2.81 (t, *J* = 11.4 Hz, 1 H), 2.89 (d, *J* = 9.0 Hz, 1 H), 2.95 (dd, *J* = 12.6 and 6.6 Hz, 1 H), 3.15 (d, *J* = 12.0 Hz, 1 H), 3.70 (t, *J* = 11.4 Hz, 1 H), 3.75 (t, *J* = 6.0 Hz, 1 H), 3.91-3.97 (m, 3 H), 4.04-4.08 (m, 3 H), 6.87-6.89 (m, 2 H), 6.91-6.93 (m, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 15.1, 45.7, 48.3, 64.7, 67.8, 71.0, 74.9, 114.1, 115.4, 121.2, 122.2, 148.8, 149.5; **IR** (KBr, neat) 3440, 2924, 1503, 1453, 1255, 1125, 1039, 1002, 745 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{20}NO_3$ $(M + H)^+$ 238.1438, found 238.1437.

3.7. Selected Spectra

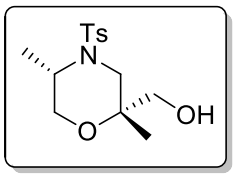
^{1}H NMR and ^{13}C NMR spectra of (4-Tosylmorpholin-2-yl)methanol (44a):

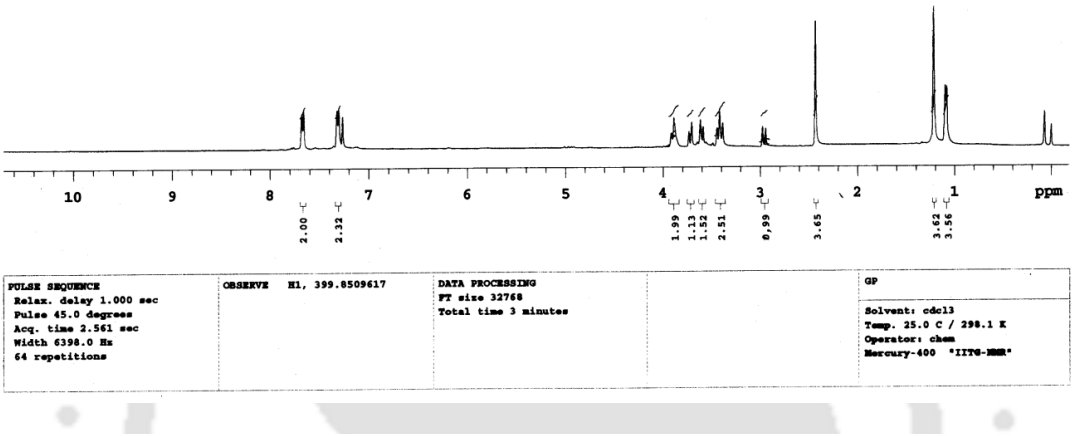


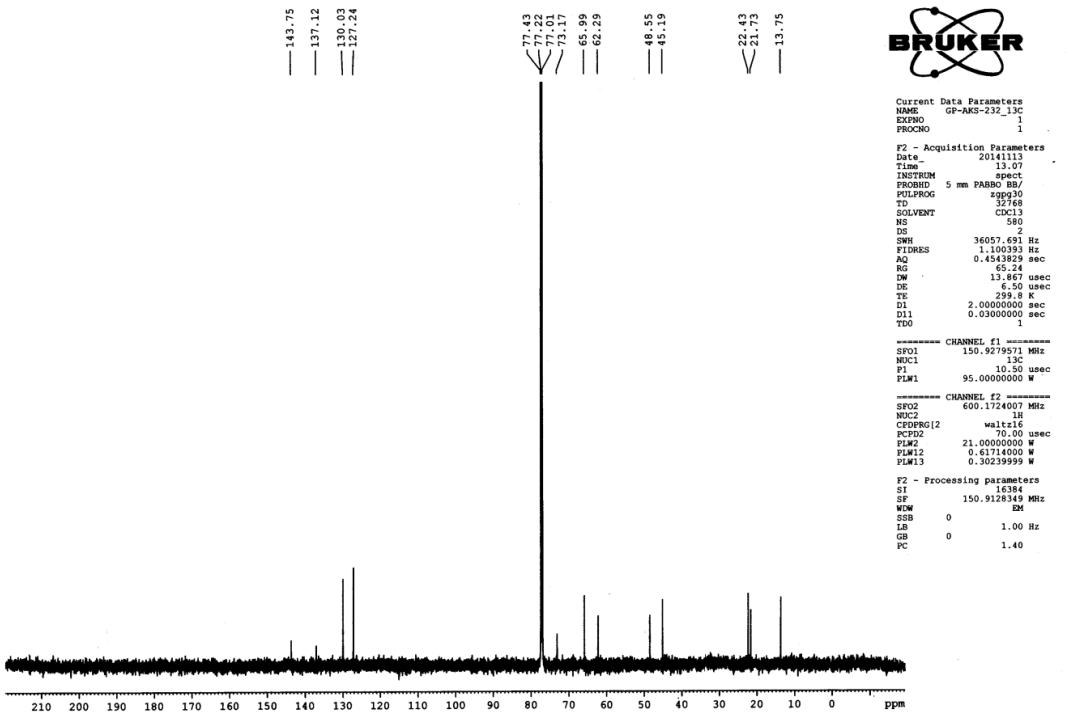




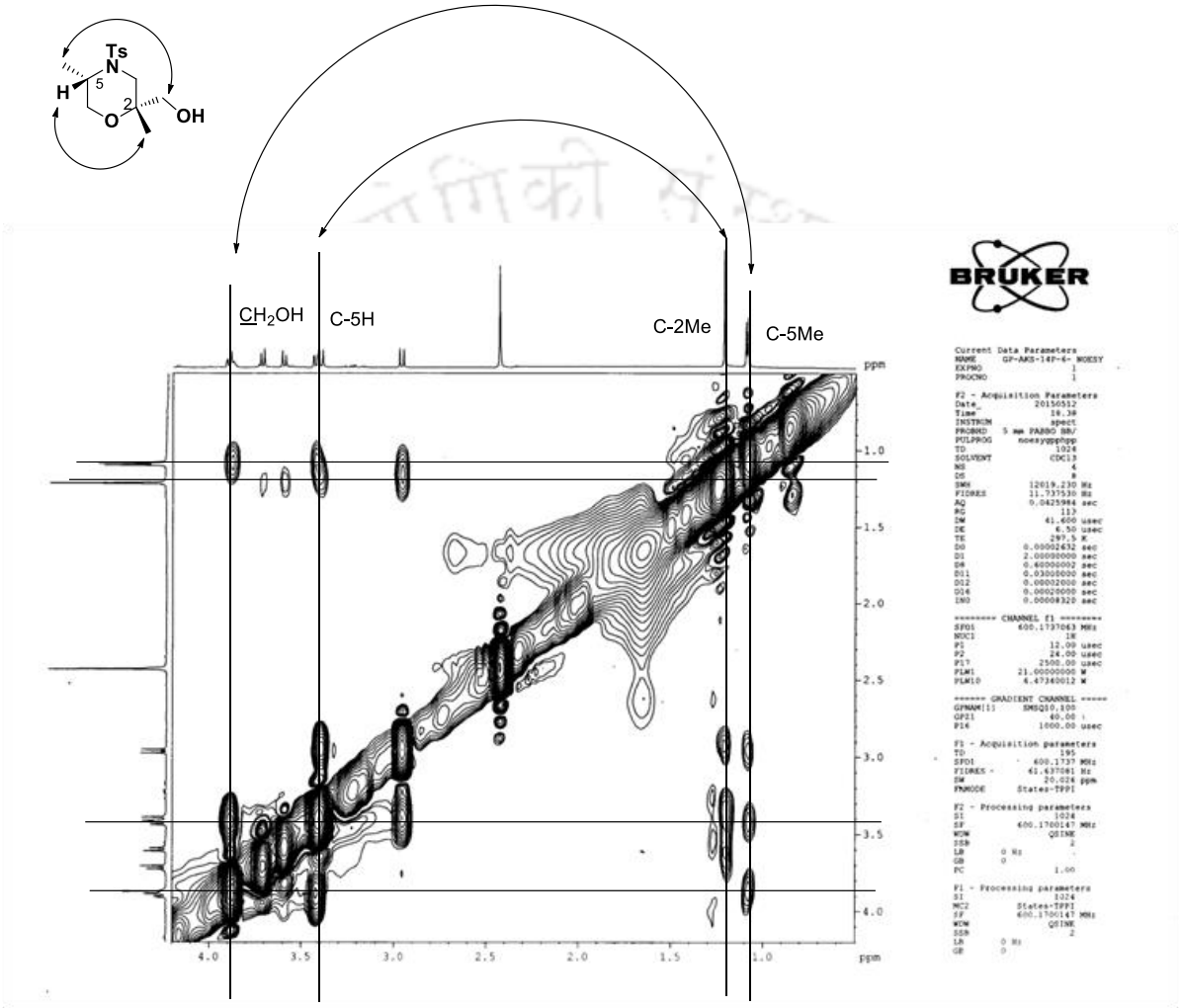
^{1}H NMR and ^{13}C NMR spectra of ((2R*,5S*)-2,5-dimethyl-4-tosylmorpholin-2-yl)methanol (44c):



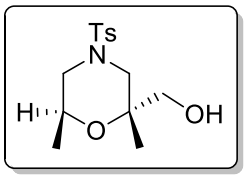


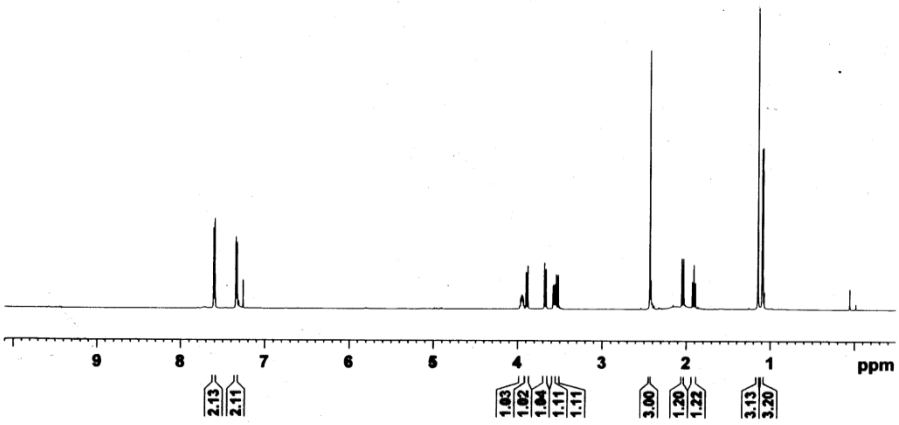


NOESY of ((2R*,5S*)-2,5-dimethyl-4-tosylmorpholin-2-yl)methanol (44c):



^{1}H NMR and ^{13}C NMR spectra of ((2R*,6S*)-2,6-Dimethyl-4-tosylmorpholin-2-yl)methanol (44d):



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PROCNO                         1

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PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                   12019.230 Hz
FIDRES                0.183399 Hz
AQ                    2.7262976 sec
RG                         31.5
DW                       41.600 usec
DE                        6.50 usec
TE                       298.2 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
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NUC1                        1H
P1                       12.00 usec
PLW1                21.00000000 W

F2 - Processing parameters
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SF                  600.1700139 MHz
WDW                          EM
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GB                            0
PC                         1.00
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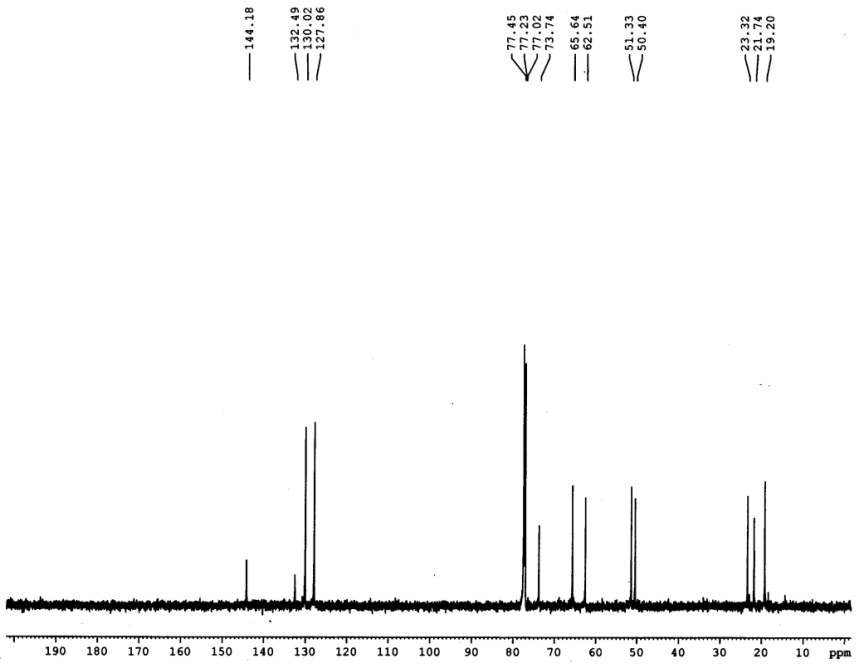


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Current Data Parameters
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EXPNO                         1
PROCNO                        1

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PULPROG                  zgpg30
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TE                       297.6 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                            1

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NUC1                        13C
P1                       10.50 usec
PLW1                95.00000000 W

======== CHANNEL f2 ========
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NUC2                        1H
CPDPRG[2                waltz16
PCPD2                    70.00 usec
PLW2                21.00000000 W
PLW12                0.61714000 W
PLW13                0.30239999 W

F2 - Processing parameters
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WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
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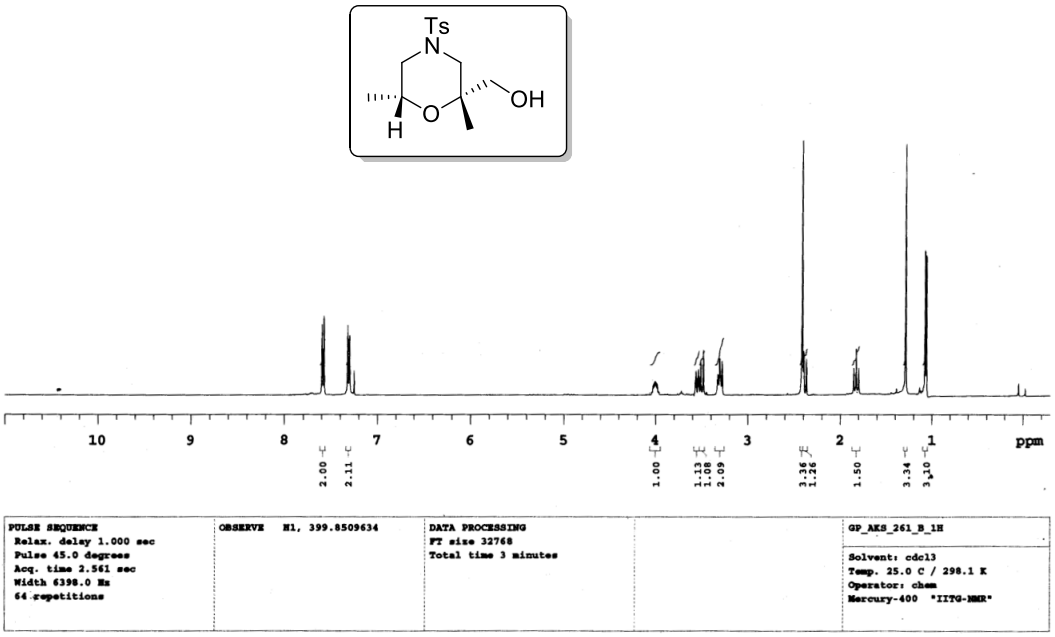
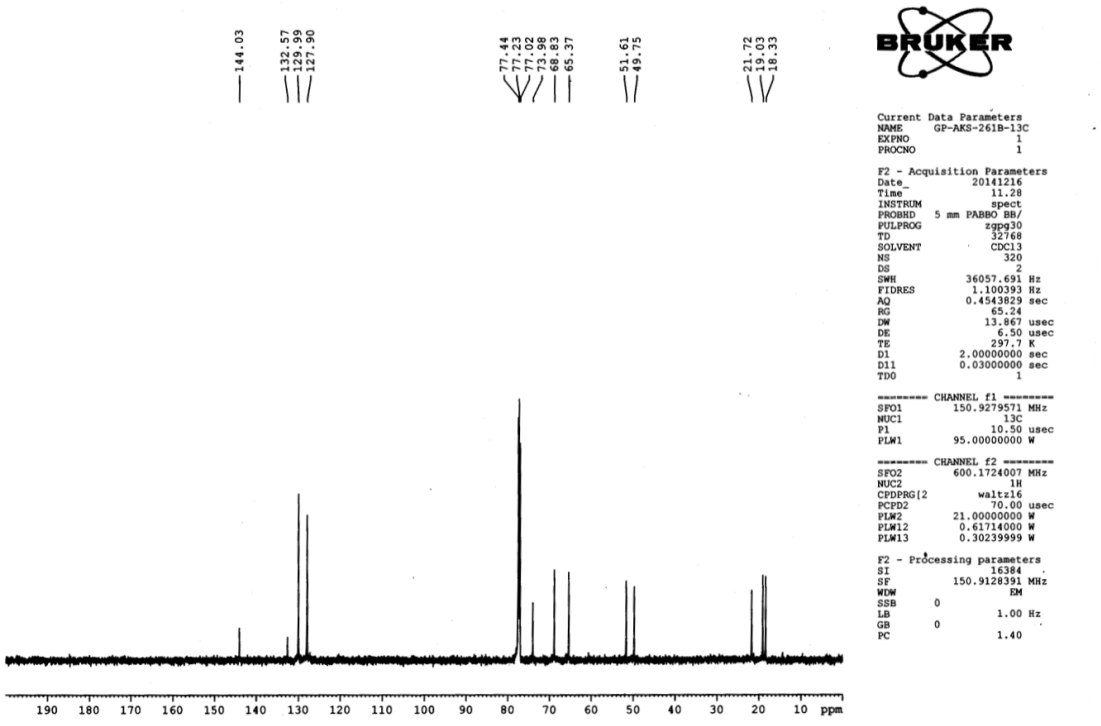
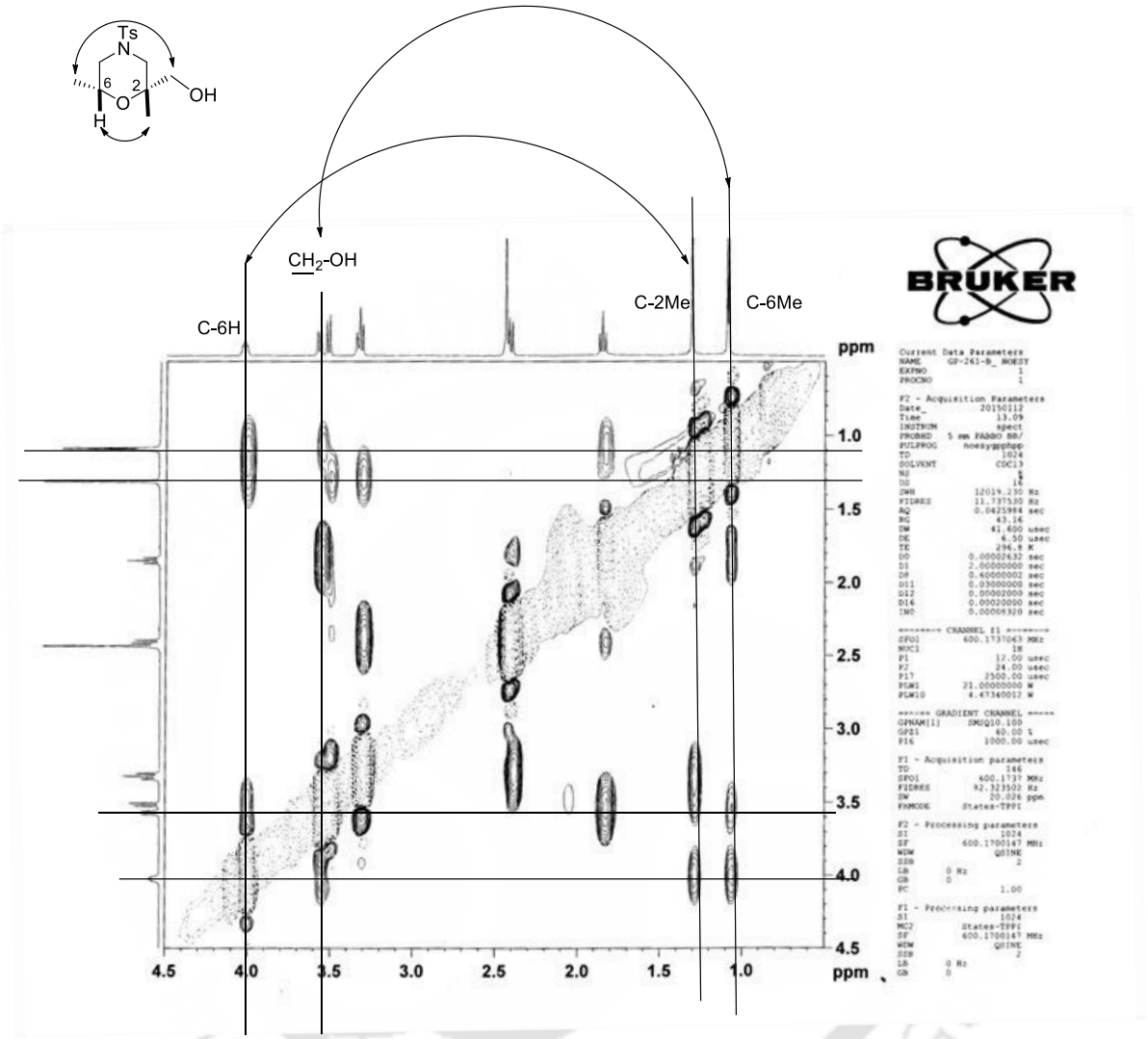
^{1}H NMR and ^{13}C NMR spectra of ((2S*,6S*)-2,6-Dimethyl-4-tosylmorpholin-2-yl)methanol (44d'):

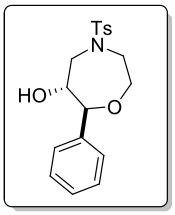


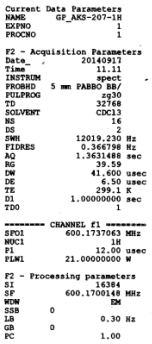


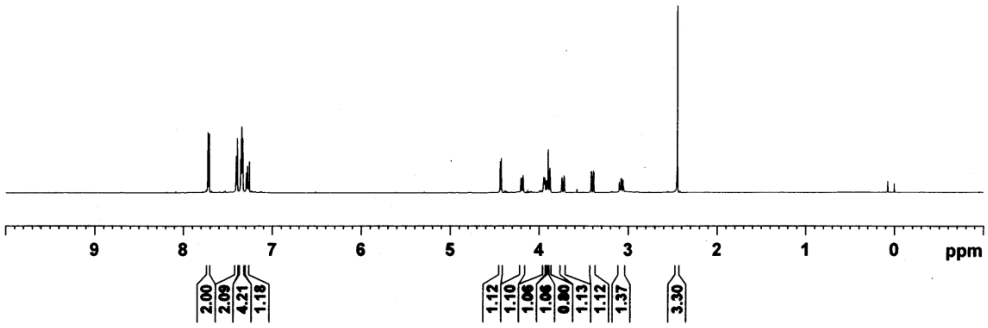
NOESY of ((2S*,6S*)-2,6-Dimethyl-4-tosylmorpholin-2-yl)methanol (44d'):

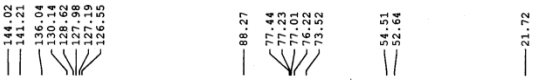


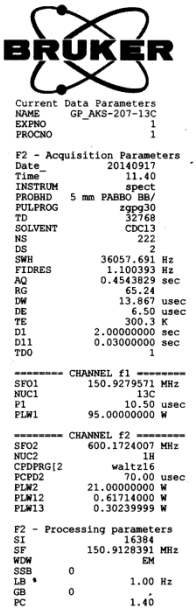
^{1}H NMR and ^{13}C NMR spectra of (6S*,7R*)-7-Phenyl-4-tosyl-1,4-oxazepan-6-ol (45k):

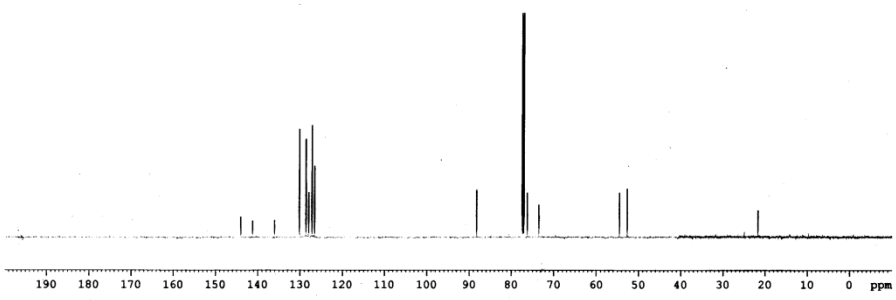




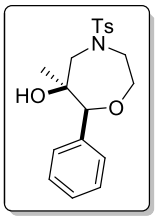


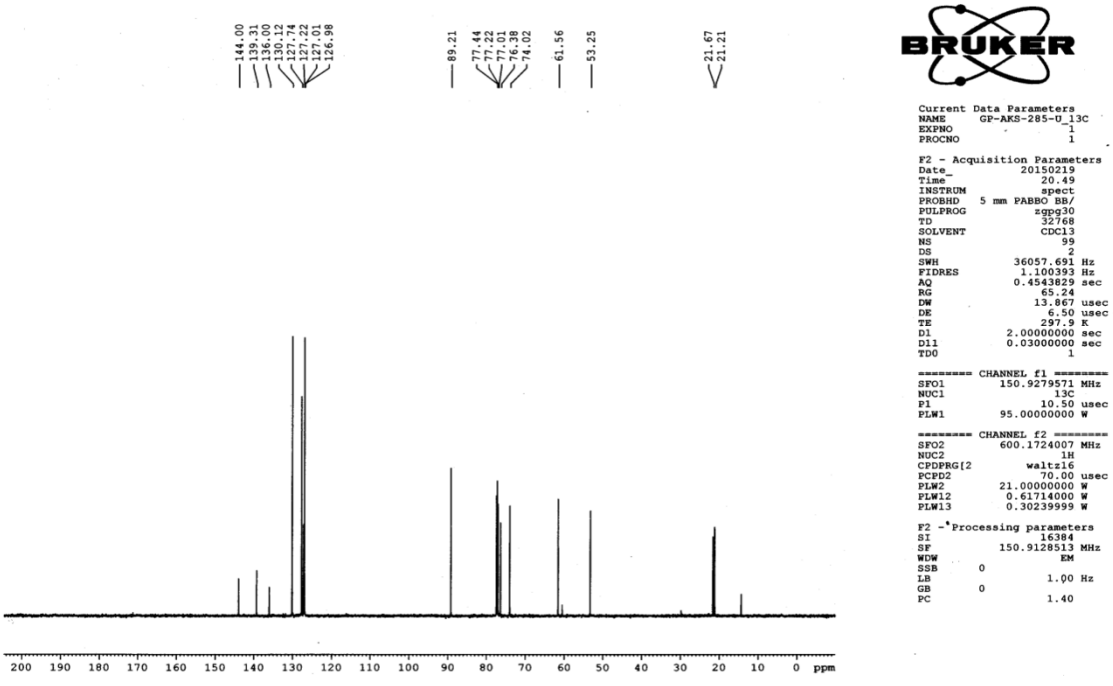






^{1}H NMR, ^{13}C NMR and NOESY spectra of (6R*,7S*)-6-Methyl-7-phenyl-4-tosyl-1,4-oxazepan-6-ol (45l):





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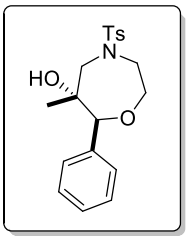

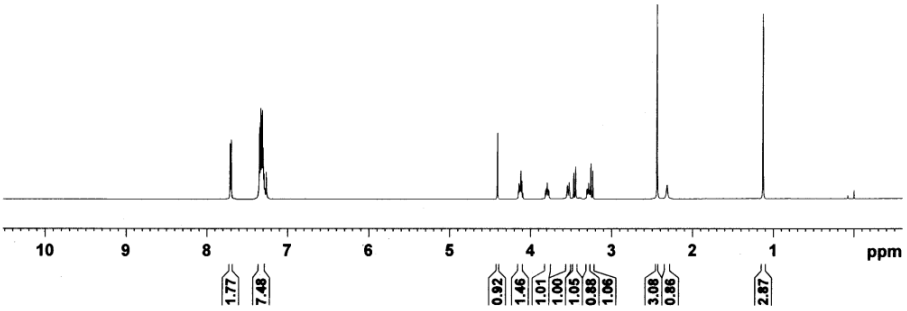


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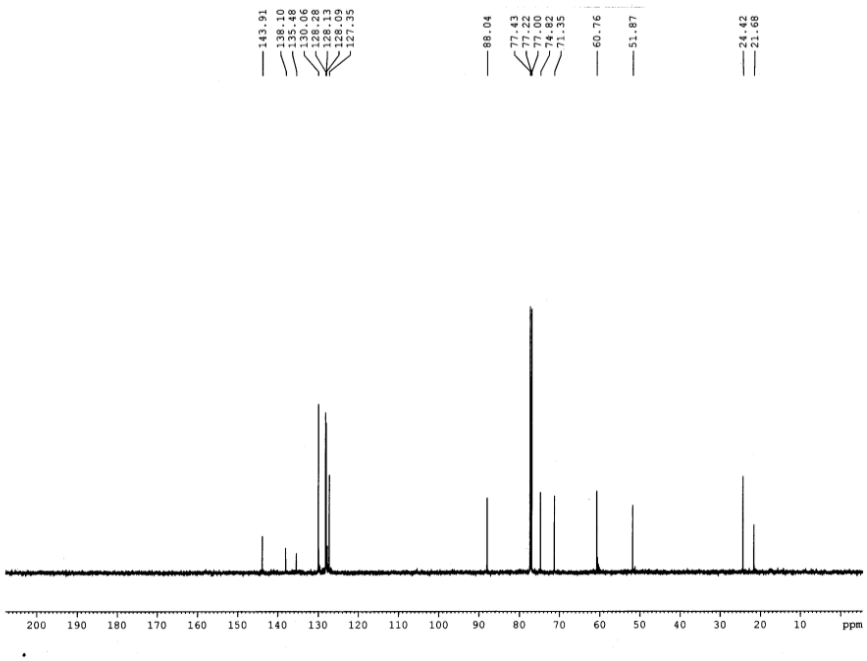

BRUKER

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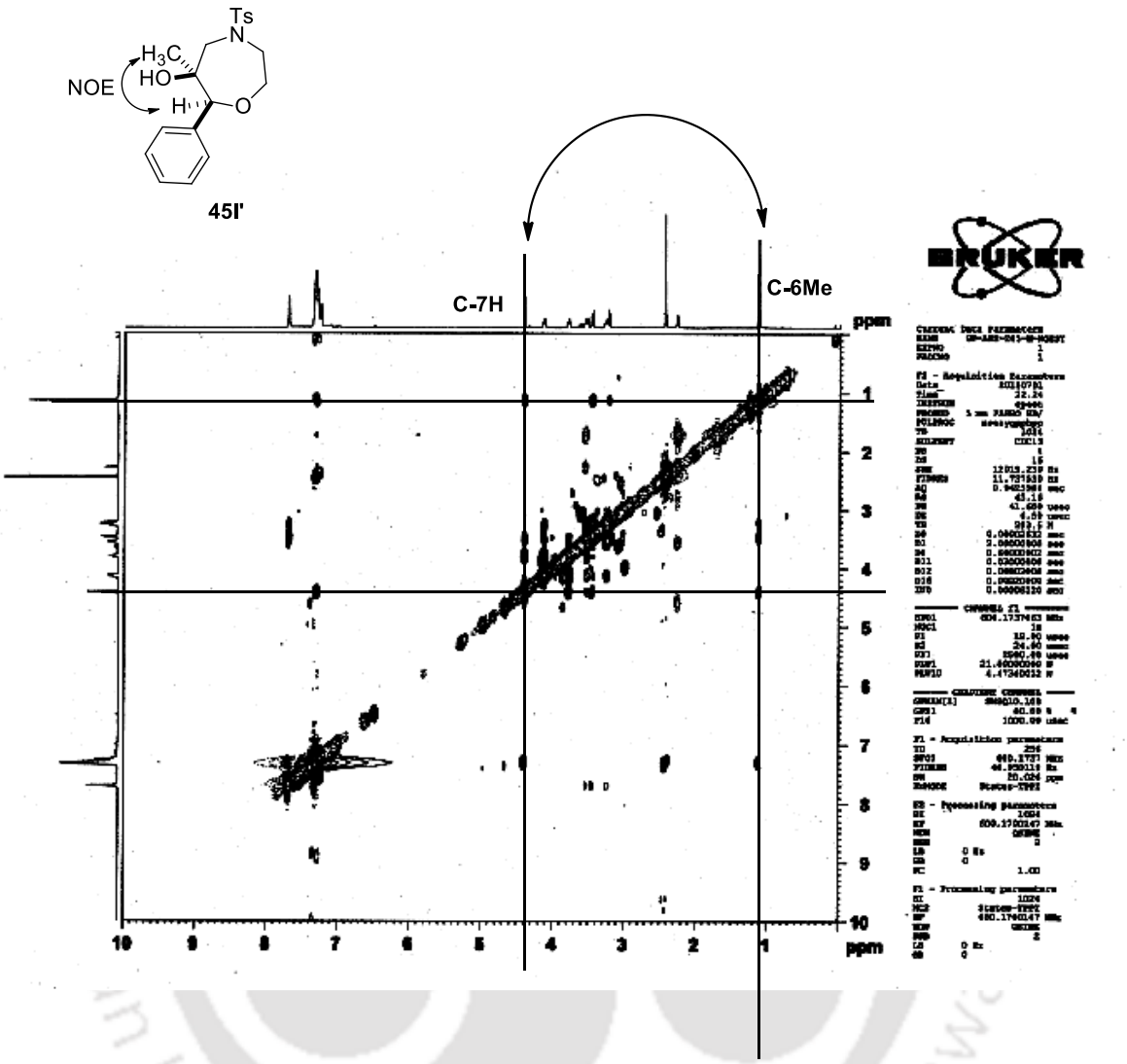

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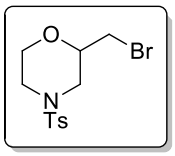

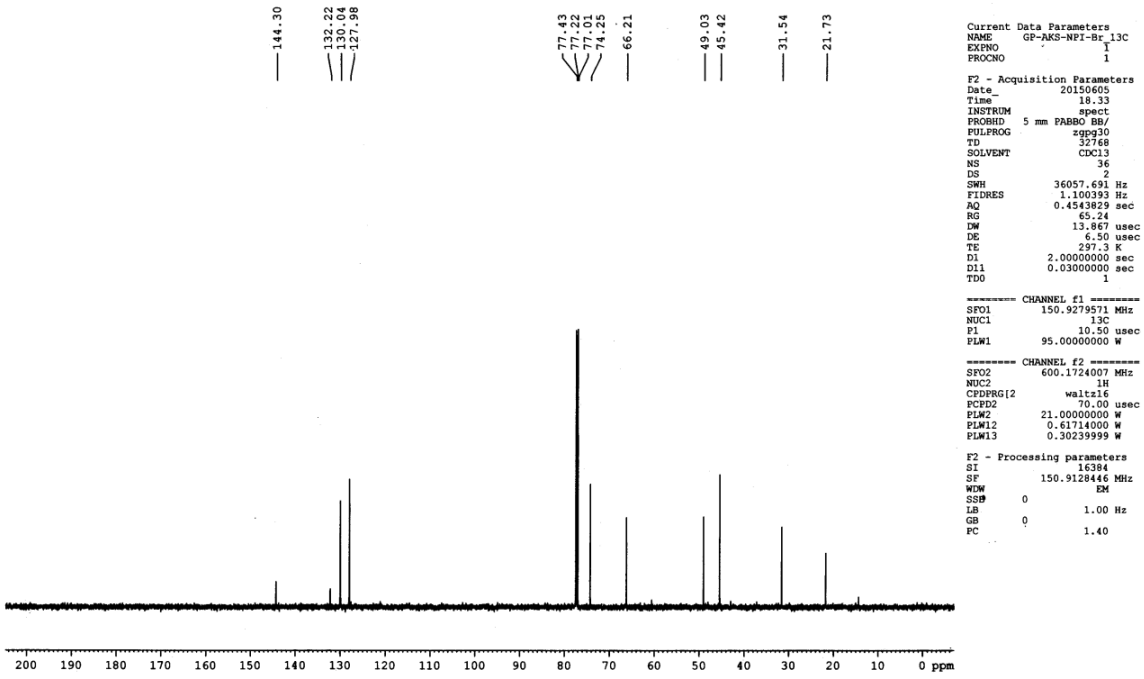

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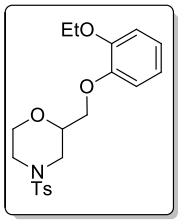
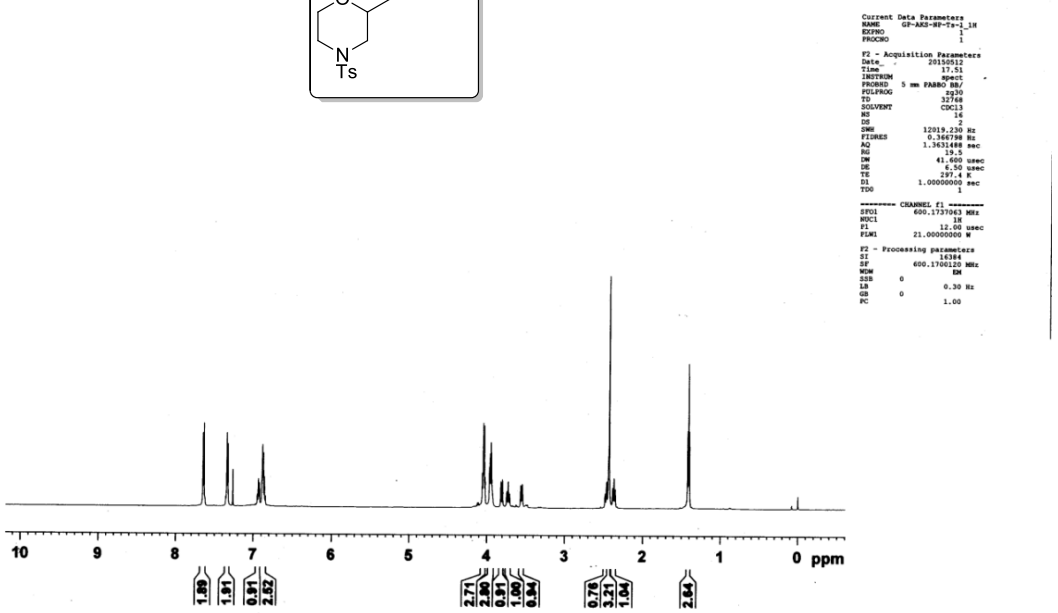
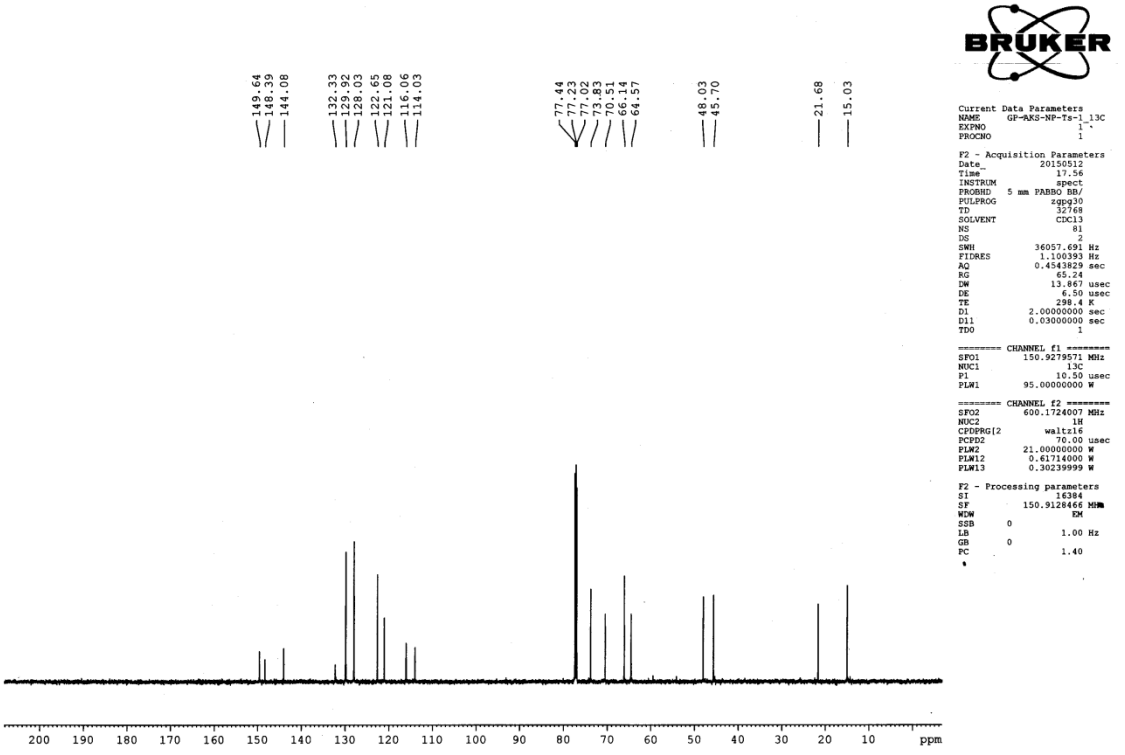
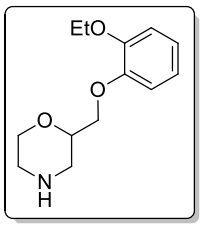
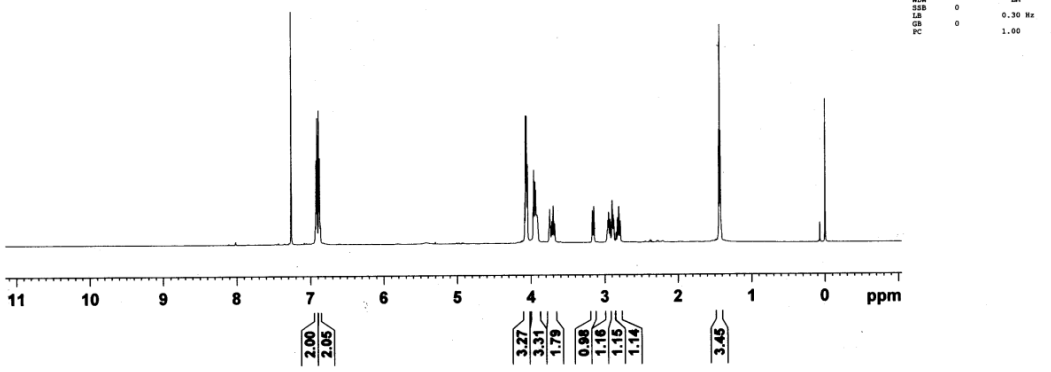






^{1}H NMR and ^{13}C NMR spectra of 2-((2-Ethoxyphenoxy)methyl)morpholine, (±)-viloxazine (2):



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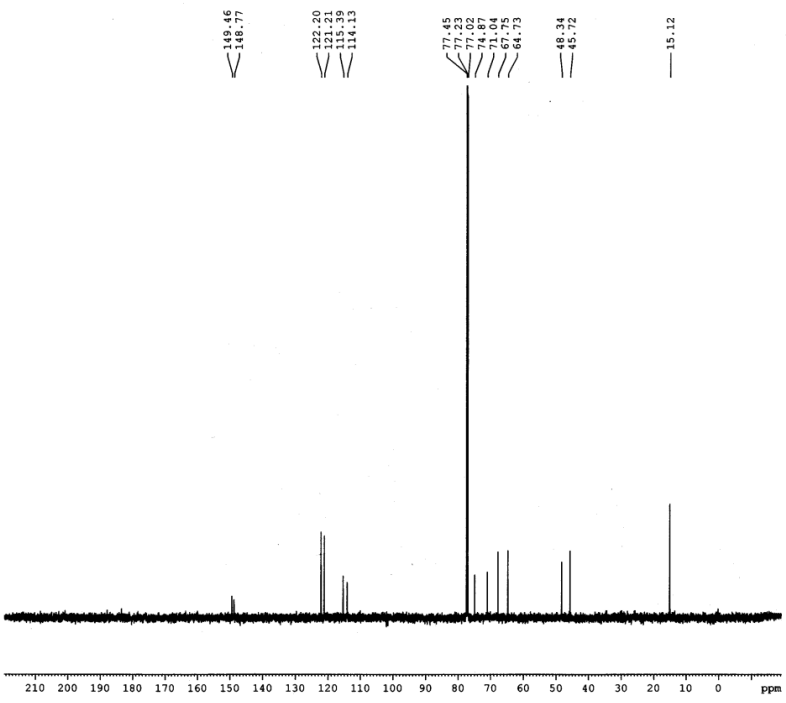


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3.8. The crystal parameters of compound 45k

	CCDC 1419078
Formula	$C_{18}H_{21}NO_4S$
Formula weight	347.42
T/K	296(2)
Crystal system	Monoclinic
Space group	P21
a/Å	11.6233(9)
b/Å	5.2394(4)
c/Å	14.2882(9)
α/°	90.00
β/°	100.456(8)
γ/°	90.00
V/Å^3	855.70(11)
Z	2
Abs. Coeff./mm^{-1}	0.211
Abs. Correction	None
GOF on F^2	1.131
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0655
	wR2 = 0.1350
R indices [all data]	*R1* = 0.0764
	wR2 = 0.1416

CHAPTER 4

Synthesis of Dihydroindeno[1,2-*c*]Isochromene *via* Cascade Cyclization And Friedel-Crafts Reaction

4.1. Importance of Isochromenes

Isochromene frameworks are prevalent in a wide variety of natural products, bioactive molecules, and pharmaceuticals.[1] Pentalongin **1,** for example, which was isolated from Pentas longiflora Oliv. (Rubiaceae), shows antifungal and antiparasital activity, and the powder from the roots of P. longiflora is used by the traditional healers of the Dispensary of Traditional Medicine of Curphametra (Butare, Rwanda) to treat the skin disease pityriasis versicolor.[2] The quinone dehydroherbarin **2** has been isolated from the dematiaceous fungus *Torula herbarum*[3] that is often found on the dry leaves and twigs of *Felia microphylla*. It has also been found in the endolichenic fungal strain, *Corynesspora* sp. BA-10763, which occurs in the cavern beard lichen *Usnea cavernosa,*[4] and exhibits antimicrobial and antiamoebic activity, as well as cause significant inhibition of both metastatic prostate and breast cancers (PC-3M and MDA-MB-231 respectively).[3,4] On the other hand, 1,3-disubstituted-3,4-dehydropyranonaphthoquinones **3a-c** have been found as very effective antitumor chemotherapeutics.[5]

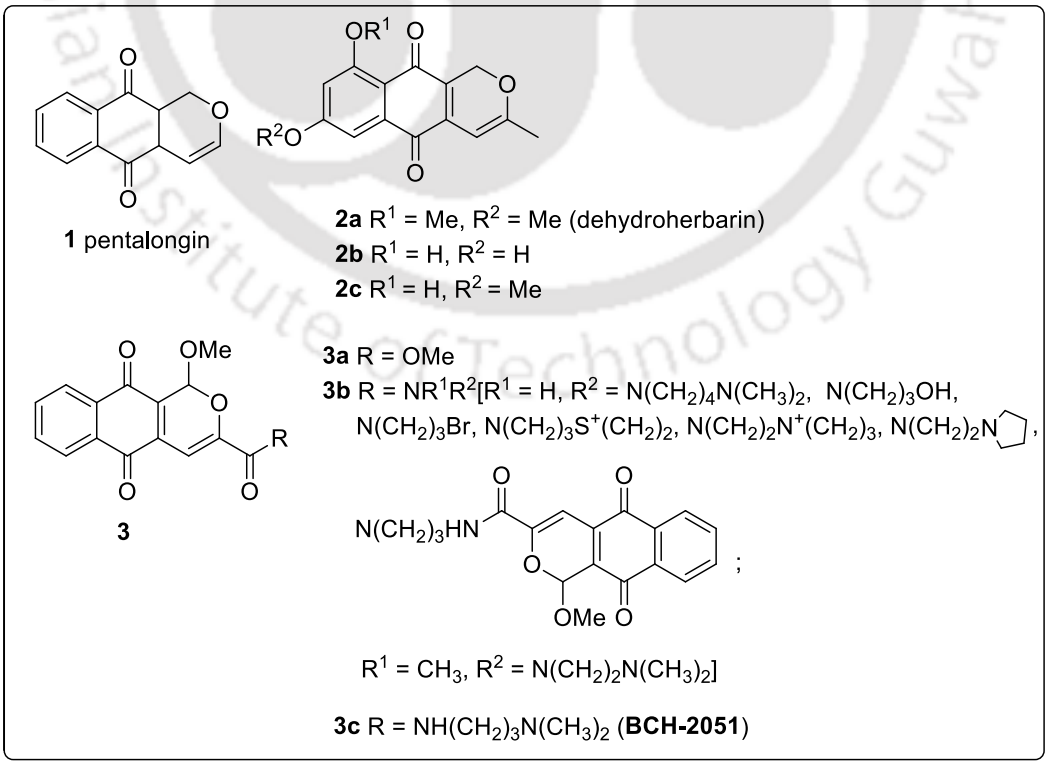


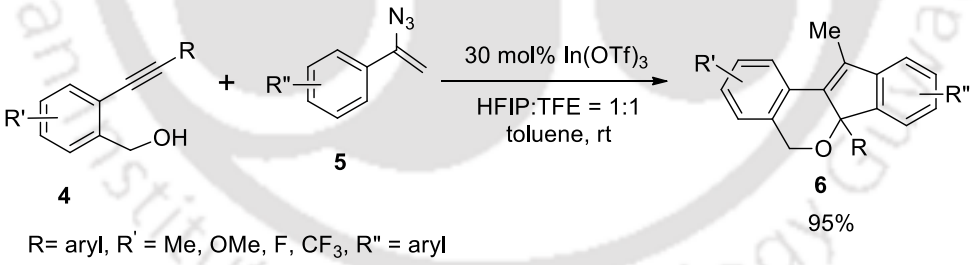
Figure 5.1.1. Bioactive molecules containing isochromene unit

4.2. Literature Methods

Innumerable synthetic approaches have been proposed and utilized for the preparation of isochromene and its derivatives. Review of literature reveals that transition metal-catalyzed cyclization such as the representative Pd(II) Heck reaction,[6] cycloisomerization of Au(I),[7] or Pd(II)[8] catalyzed, Os-catalyzed,[9] Ru(II)-catalyzed,[10] complex with a tetradentate N-P mixed ligand,[11] Ir pincer complexes-catalyzed,[12] or Rh(III)-catalyzed oxidative coupling,[13] have been generally used for the synthesis of these units.

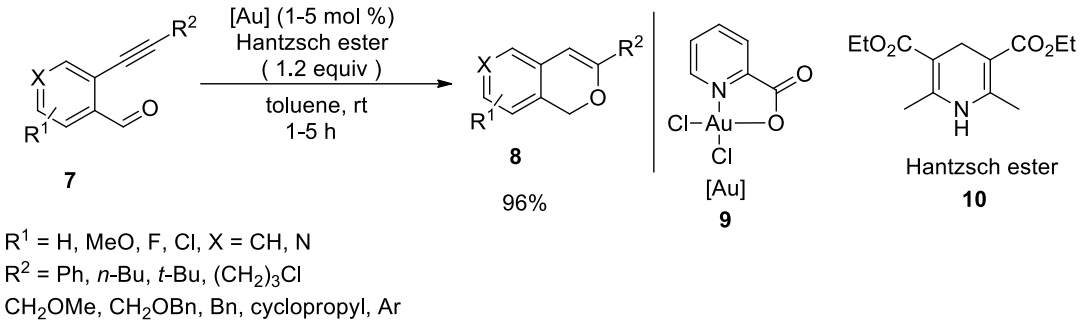
However, cascade reactions have become increasingly important for achieving such goals.[14] These reactions involve careful design of a multistep reaction in a one-pot sequence, making this approach economical and environmentally friendly.

Liu and co-workers have reported the synthesis of four membered complex indeno[1,2-*c*]isochromene *via* Lewis acid catalyzed tandem polycyclization of *ortho*-arylethylnylphenylmethanol and vinyl azides (*Scheme 4.2.1*).[15] The recation of internal alkynols **4** and vinyl azides **5** in presence of $In(OTf)_3$ using a mixed additive of 2,2,2-trifluoroethanol (TFE) (3 equiv) and hexafluoroisopropanol (HFIP) (3 equiv) afforded pyran-based indeno[1,2-*c*]isochromene **6** scaffold in moderate to high yields. This tandem polycyclization protocol proceeded through cycloisomerization, formal [4+2] cycloaddition, and an elimination process.



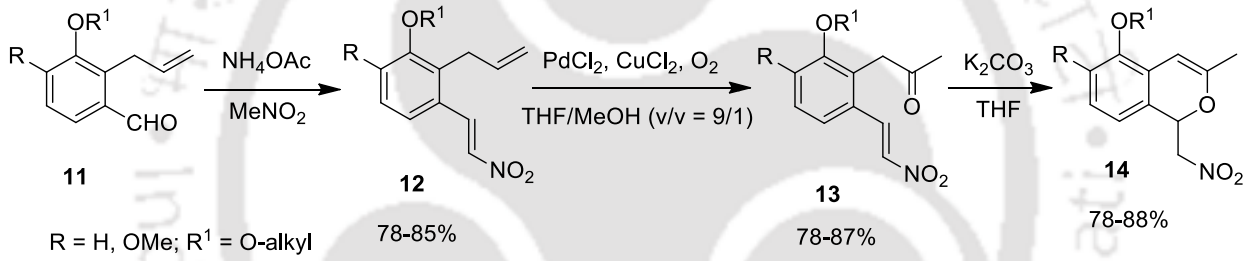
Scheme 4.2.1.

Michelet and co-workers have reported a methodology for the synthesis of 1*H*-isochromene derivatives *via* gold catalyzed domino cycloisomerization/reduction approach. Functionalized ortho-alkynylbenzaldehydes **7**, in presence of 1 mol % of $[AuCl_2(Pic)]$ **9** and 1.2 equiv of Hantzsch ester (HEH) **10** at room temperature in toluene gave the desired 1*H*-isochromenes **8** in a very good yields up to 96% (*Scheme 4.2.2*). The reaction was highly chemo- and regioselective and proceeds through 6-*endo* cyclization mode as well as *in situ* reduction and the reaction conditions were compatible with both aryl- and alkyl-substituted alkynyl derivatives.[16]



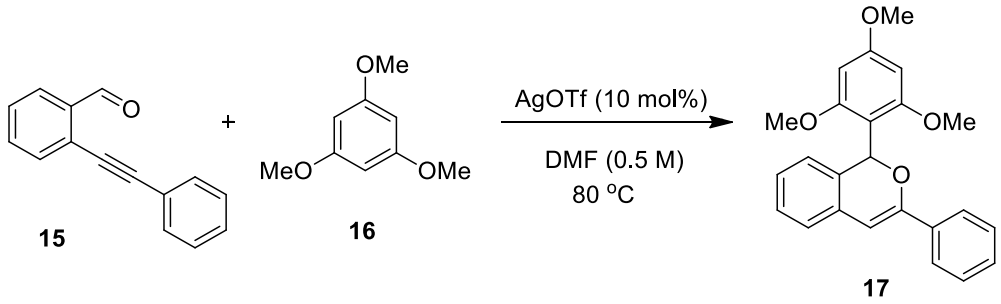
Scheme 4.2.2.

Chang and his group have developed a three-step synthetic route for the synthesis of isochromenes in a good to excellent yields. This novel approach was carried out by the Henry reaction of aldehydes **11** with NH_4OAc and nitroalkanes ($MeNO_2$ or $EtNO_2$), aerobicWacker-type oxidation of the resulting nitroalkenes **12**, followed by K_2CO_3-promoted intramolecular Michael cyclization leading to isochromene derivatives **14** (*Scheme 4.2.3*).[17]



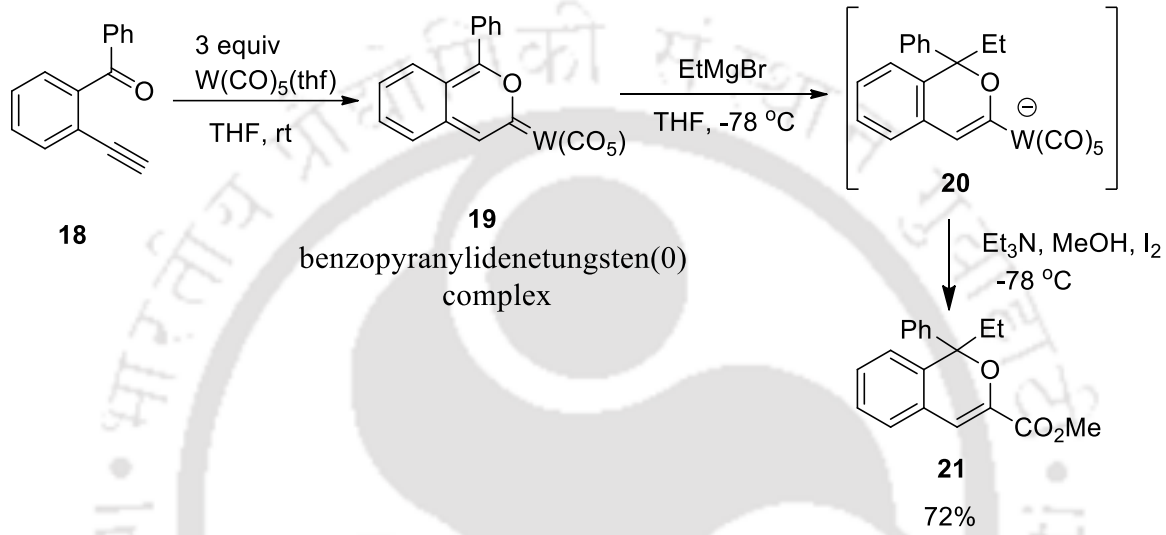
Scheme 4.2.3.

Belmont and co-workers have described a method for the synthesis of isochromenes using silver catalysed hydroarylation/cycloisomerization domino reaction starting from *ortho*-alkynylbenzaldehydes. The reaction of *ortho*-phenylacetylenyl benzaldehyde **15** with silver triflate (10 mol %) in dimethylformamide in presence of an external nucleophile trimethoxybenzene **16** (3 equiv.) at 80 ^oC led to arylisochromenes **17** in 3h with 91% isolated yield (*Scheme 4.2.4*).[18]



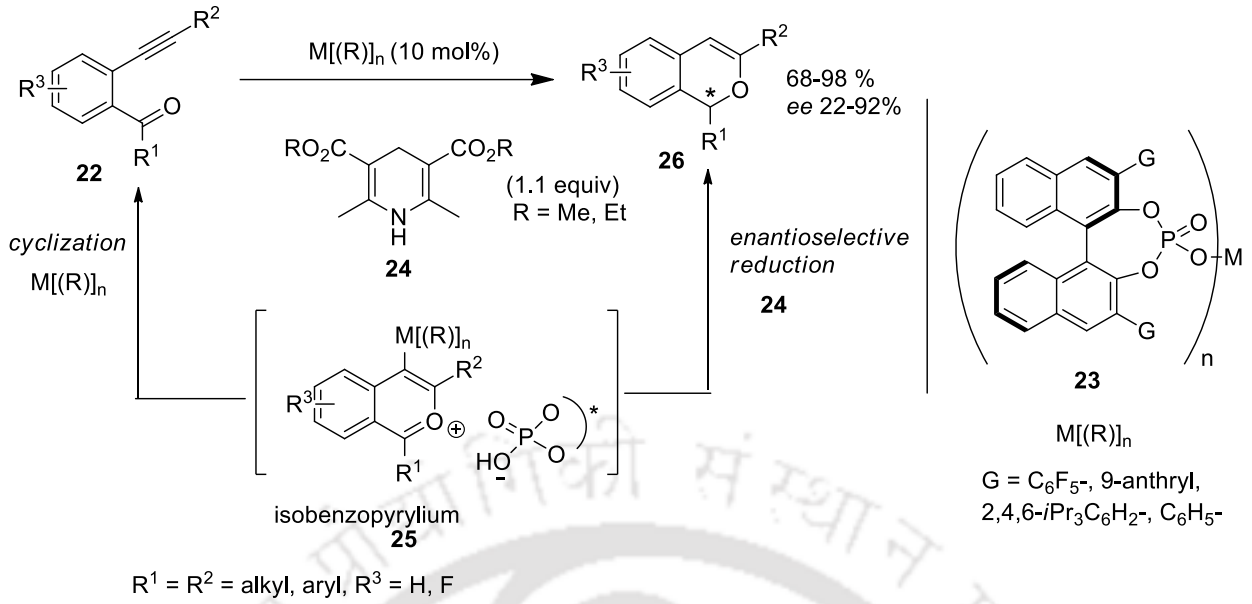
Scheme 4.2.4.

Iwasawa and co-workers have reported the synthesis of isochromene esters utilizing 1,6-addition of nucleophiles to benzopyranylidenetungsten(0) complexes. The reaction of phenyl-substituted benzopyranylidene complex **19** with ethylmagnesium bromide proceeded smoothly in tetrahydrofuran (THF) at -78 °C to give alkenyltungsten species **20** utilizing a facile 1,6-addition reaction of various nucleophile such as Grignard reagents, alkoxide, and cyanide onto the tungsten complex and iodine oxidation of the addition intermediates gave isochromene ester derivatives **21** in good yield (*Scheme 4.2.5*).[19]



Scheme 4.2.5.

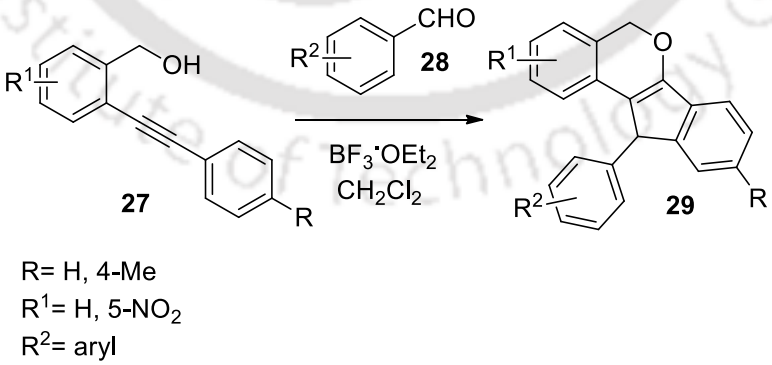
Terada and his group have reported the enantioselective transformation of *ortho*-alkynylaryl ketones into optically active 1*H*-isochromene derivatives through a cyclization/enantioselective reduction sequence with a chiral silver phosphate catalyst and Hantzsch ester as the reducing agent. The proposed sequence involves a two-step transformation, intramolecular cyclization of **22** catalyzed by a π-Lewis acidic metal complex with a binolderived phosphate **23** (binol=1,1′-binaphthalene-2,2′-diol) as the chiral counteranion to generate isobenzopyrylium ion **25** as a key intermediate, and then enantioselective reduction of **25** with a Hantzsch ester **24** to afford the final product **26** in an enantioselective manner (*Scheme 4.2.6*).[20]



Scheme 4.2.6.

4.3. Present Work

Cascade[14] and Friedel-Crafts[21] reactions play a major role in organic synthesis due to their stereoselectivity and C-C bond forming ability in a single step. Bearing the significance of these reactions in mind herein, we report a novel Lewis acid mediated intermolecular cascade reaction, starting from alkynol and commercially available aromatic aldehydes leading to tetracyclic dihydroindeno[1,2-*c*]isochromene in good to excellent yields. The reaction can be generalized as shown in *Scheme 4.3.1*.

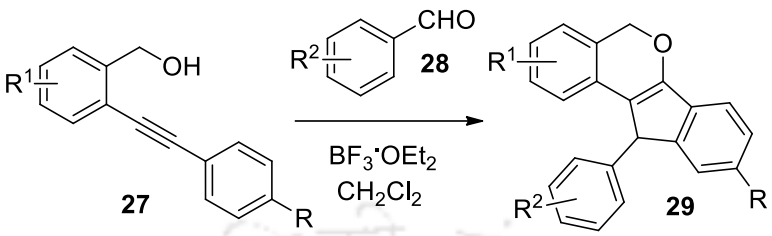


Scheme 4.3.1.

Initially, (2-(phenylethynyl)phenyl)methanol **27a** (1.0 equiv) was treated with benzaldehyde **28a** in presence of borontrifluoride etherate (1.0 equiv) in dichloromethane at room temperature for 12 h and 11-phenyl-5,11-dihydroindeno[1,2-*c*]isochromene **29a** was obtained in 65% isolated yield. Increasing the Lewis acid loading upto 1.5 equivalents resulted in 87% yield of the desired

product under the same reaction conditions. In order to optimize the reaction conditions, other parameters such as Lewis and Brønsted acids, solvents, reaction time were studied.

Table 4.3.1. Optimization of the reaction



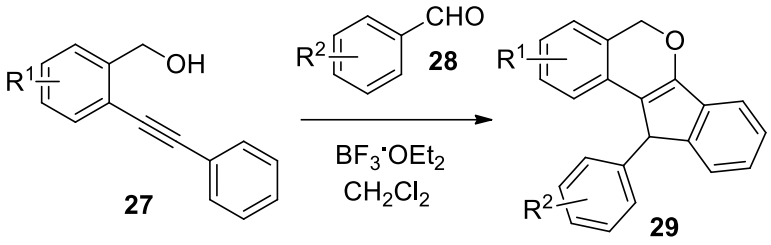
Entry	Lewis/Brønsted acid (equiv)	Time (h)	solvent	(%)yield[a]
1	$BF_3 \cdot Et_2O$ (1)	12	CH_2Cl_2	65
2	**$BF_3 \cdot Et_2O$ (1.5)**	**12**	**CH_2Cl_2**	**87**
3	$BF_3 \cdot Et_2O$ (1.5)	12	DCE	80
4	$BF_3 \cdot Et_2O$ (1.5)	12	Toluene	35
5	$InCl_3$ (1)	24	CH_2Cl_2	20
6	$In(OTf)_2$ (1)	24	CH_2Cl_2	15
7	$Cu(OTf)_2$ (1)	24	CH_2Cl_2	22
8	$Zn(OTf)_2$ (1)	24	CH_2Cl_2	20
9	$FeCl_3$ (1)	24	CH_2Cl_2	25
10.	TfOH (1)	24	CH_2Cl_2	30
11.	CSA (1)	24	CH_2Cl_2	--

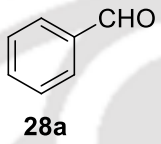
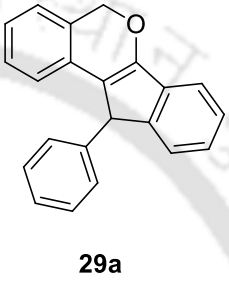
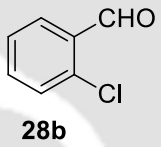
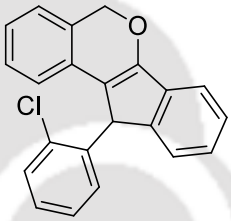
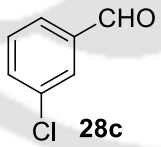
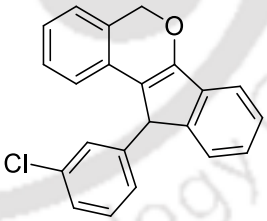
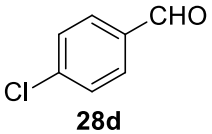
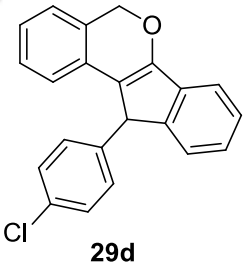
[a]Yields refer to isolated yield. Compound is characterized by ^1H, ^{13}C NMR, IR and mass spectrometry.

Survey of the various solvents revealed that dichloromethane is the best solvent over 1,2-dichloroethane and toluene. Therefore, dichloromethane (DCM) was chosen as a solvent for further investigations (*Table 4.3.1*). From the *Table 4.3.1*, it was observed that other Lewis and Brønsted acids were found to be inefficient. $InCl_3$ gave 20% yield while $In(OTf)_3$ gave only 15% yield. Likewise, $Cu(OTf)_2$, $Zn(OTf)_2$ and $FeCl_3$ produced 22, 20, and 25% yield respectively. However, among the Brønsted acids, TfOH yielded 30% whereas, camphor sulfonic acid (CSA) failed to give the desired product.

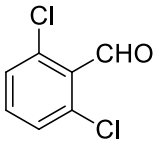
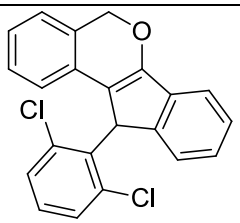
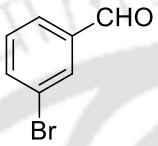
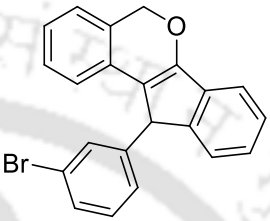
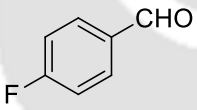
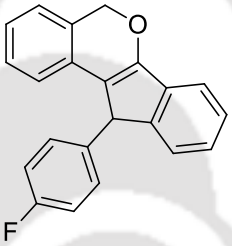
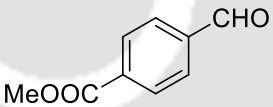
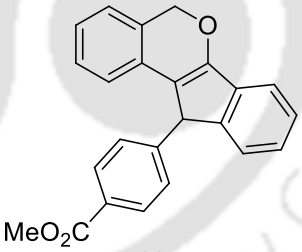
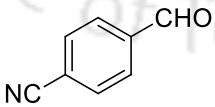
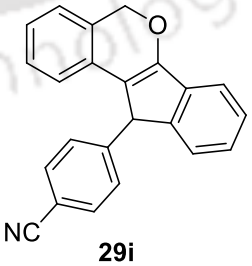
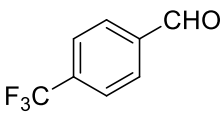
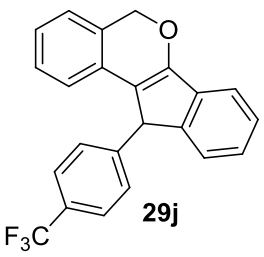
With this optimized conditions in hand, a variety of alkyne alcohols and aldehydes were evaluated as substrates and the results are summarized in *Table 4.3.2.*

Table 4.3.2. Synthesis of tetrahydro-1*H*-indeno[1,2-*b*]pyridine and hexahydrobenzo[*g*]quinolone

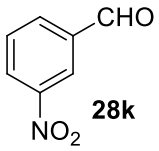
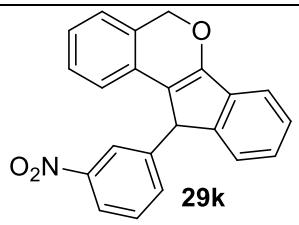
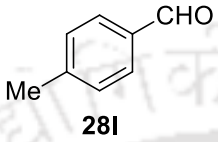
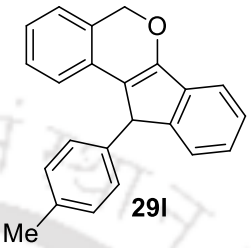
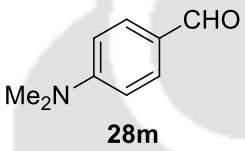
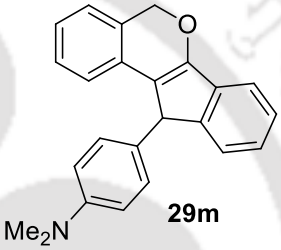
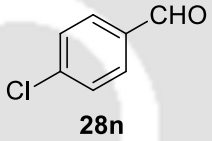
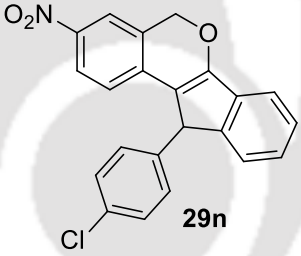
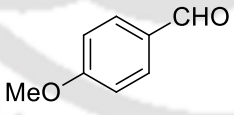
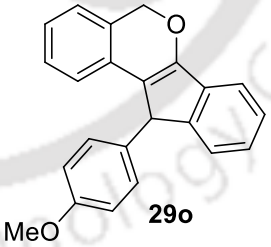
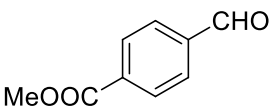
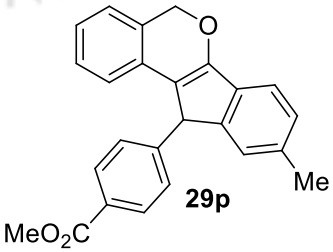
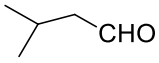
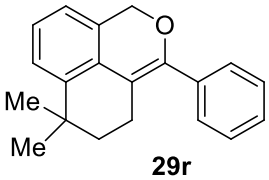


Entry	Alcohol **27,** R= R^1=	Aldehyde **28**	Product **29**	Yield[a] (%)
1	R, R^1=H	 **28a**	 **29a**	87
2	R, R^1=H	 **28b**	 **29b**	89
3	R, R^1=H	 **28c**	 **29c**	88
4	R, R^1=H	 **28d**	 **29d**	85

Continue….

Entry	Alcohol **27,** R^1=	Aldehyde **28**	Product **29**	Yield[a] (%)
5	R, R^1=H	 **28e**	 **29e**	65
6	R, R^1=H	 **28f**	 **29f**	83
7	R, R^1=H	 **28g**	 **29g**	80
8	R, R^1=H	 **28h**	 **29h**	86
9	R, R^1=H	 **28i**	 **29i**	70
10	R, R^1=H	 **28o**	 **29j**	75

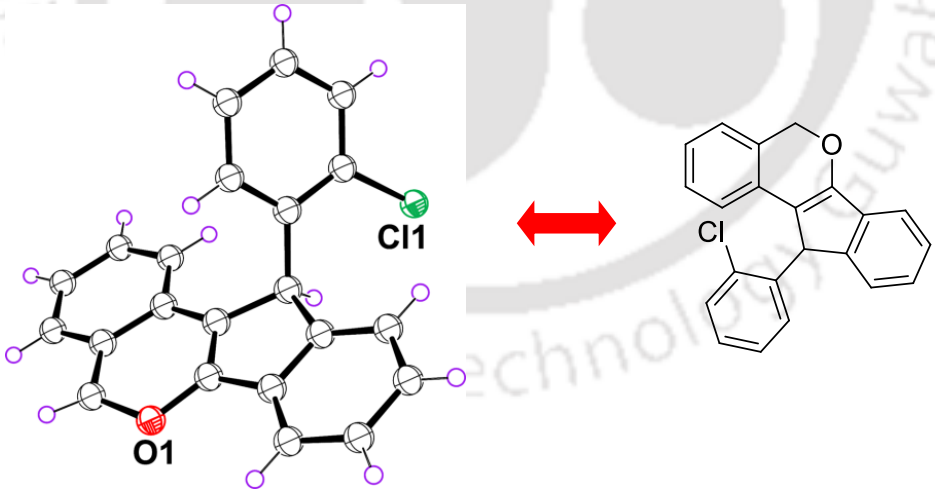
Continue…

Entry	Alcohol **27,** R, R^1	Aldehyde **28**	Product **29**	Yield[a](%)
11	R, R^1=H	 **28k**	 **29k**	84
12	R, R^1=H	 **28l**	 **29l**	78
13	R, R^1=H	 **28m**	 **29m**	71
14	R=H, R_1=5-NO_2	 **28n**	 **29n**	73
15	R, R^1=H	 **28o**	 **29o**	72
16	R=Me, R^1=H	 **28h**	 **29p**	90
17	R, R^1=H		 **29r**	85

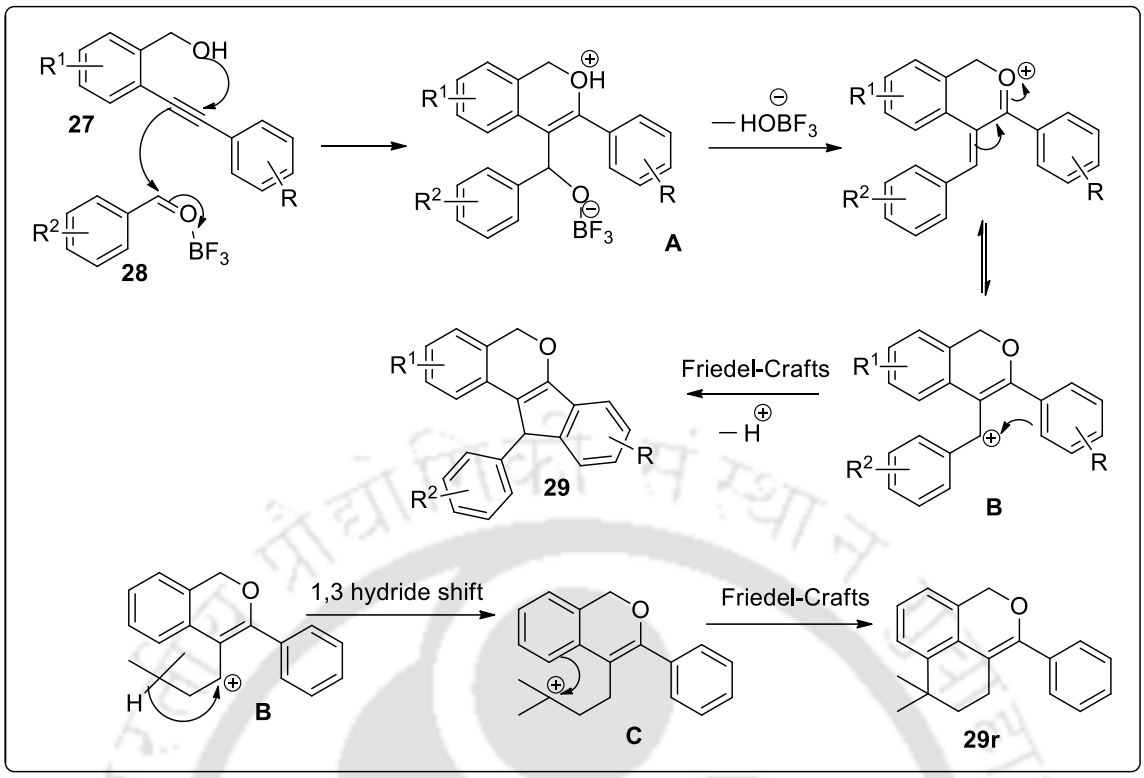
[a]Yields refer to isolated yield. Compound is characterized by ^{1}H, ^{13}C NMR, IR and mass spectrometry.

It was observed from *Table 4.3.2* that there is no role of electron-withdrawing and electron-donating groups on the aromatic ring of the aldehydes. Both electron withdrawing and electron donating groups on the aromatic ring of the aldehydes gave in good to high yields. This is due to the resonance stabilization of carbocation **B** both by aryl group as well as isochromene oxygen (*Scheme 4.3.2*). The low yield for the 2,6-dichlorobenzaldehyde may be attributed to steric hindrance. The electronic effect of substituents on the aromatic side chain of the substrates was also studied considering electron donating methyl and electron withdrawing nitro groups. It was observed that as usual the aromatic group with methyl substituent facilitates the Friedel-Crafts reaction and gave product **29p** with 90% yield, whereas substrate with electron-withdrawing nitro group failed to give desired product (**29q** 0%,). Aliphatic aldehyde such as isovalaraldehyde gave tricyclic compound 6,6-dimethyl-3-phenyl-1,4,5,6-tetrahydrobenzo[de]isochromene **29r** in 85% yield. The structure of the compounds was determined by ^{1}H, ^{13}NMR, IR and HRMS analysis. Finally it was confirmed by the X-ray crystallographic analysis of **3b**.[22]

Figure 4.3.1. X-ray crystallographic structure of **29b**



The mechanism of the reaction can be explained as follows. Lewis acid activates the aldehydes **28** for the nucleophilic attack by the alkyne group of **27** and subsequent cascade type attack by benzylic alcohol to form intermediate **A**, which after elimination of BF_3OH^- gives carbocation **B**. The carbocation **B**, after Fridel-Crafts reaction produces final compound **3** (*Scheme 4.3.2.*). The mechanism for the formation of **29r** can be depicted as follows.



Scheme 4.3.2. Mechanism of the reaction

The intermediate **B** rearranges to more stable carbocation **C**, which after Friedel-Crafts cyclization gives **3r** (*Scheme 4.3.2.*).

Conclusions

In conclusion, we have developed a mild and efficient method for the synthesis of dihydroindeno[1,2-*c*]isochromene from alkynol and aldehydes *via* cascade cyclization and Fridel-Crafts reaction mediated by boron trifluoride etherate in good yields. The reaction is compatible with a wide range of functional groups such as halo, ether, ester, nitro, amine and nitrile. The important aspect of this reaction is that it produces dihydroindeno[1,2-*c*]isochromene regioselectively.

4.4. Experimental

4.4.1. Instrumentation and Characterization

As described in chapter 2 section 2.4.1

4.4.2. Synthesis of Starting Material: The alkynol was synthesized by the literature procedure.[23]

4.4.3. General Procedure for the formation of isochromene 29a-r:

To a stirred solution of aldehyde (1.0 equiv) and alkynol (1.5 equiv) in dry dichloromethane (5.0 mL) was added $BF_3{\cdot}OEt_2$ (1.5 equiv) dropwise at 0 ^oC. The reaction mixture was brought to room temperature and stirred for a specific time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (5.0 mL). The product was extracted with CH_2Cl_2 (2 x 10.0 mL) and washed with brine. Organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using rotary evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (49:1) as eluents to afford the cyclic compounds.

Synthesis of 5,11-dihydro-11-phenylindeno[1,2-*c*]isochromene 29a:

To a stirred solution of benzaldehyde **28a** (0.1 mL, 1 mmol) and (2-(2-phenylethynyl)phenyl)methanol **27a** (312 mg, 1.5 mmol) in CH_2Cl_2 (5 mL/mmol) was added $BF_3{\cdot}OEt_2$ (0.18 mL, 1.5 mmol) dropwise at 0 ^oC. The reaction mixture was brought to room temperature and stirred for 12 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, CH_2Cl_2 (10 mL) was added and the reaction mixture was washed with saturated sodium bicarbonate solution and brine solution. The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using rotary evaporator to leave the crude product which was purified by column chromatography over silica gel using ethyl acetate and hexane as eluents to give 5,11-dihydro-11-phenylindeno[1,2-*c*]isochromene **29a** as a yellow solid.

4.5. References

(1) For examples of the importance of isochromenes and some derivatives, see: (a) Moloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597. (b) Singh, I. P.; Bodiwala, H. S. *Nat. Prod. Rep.* **2010**, *27*, 1781. (c) Gao, J.-M.; Yang, S.-X.; Qin, J.-C. *Chem. Rev.* **2013**, *113*, 4755. (d) De Angelis, M.; Stossi, F.; Waibel, M.; Katzenellenbogen, B. S.; Katzenellenbogen, *J. A. Bioorg. Med. Chem.* **2005**, *13*, 6529. (e) Brown, C. W.; Liu, S.; Klucik, J.; Berlin, K. D.; Brennan, P. J.; Kaur, D.; Benbrook, D. M. *J. Med. Chem.* **2004**, *47*, 1008. (h) Trisuwan, K.; Khamthong, N.;\ Rukachaisirikul, V.; Phongpaichit, S.; Preedanon, S.; Sakayaroj, J. *J. Nat. Prod.* **2010**, *73*, 1507.

(2) Hari, L.; De Buyck, L. F.; De Pooter, H. L. *Phytochemistry* **1991**, *30*, 1726. (b) De Kimpe, N.; Van Puyvelde, L.; Schripsema, J.; Erkelens, C.; Verpoorte, R. *Magn. Reson. Chem.* **1993**, *31*, 329.

(3) Kadkol, M. V.; Gopalkrishnan, K. S.; Narasimhachari, N. *J. Antibiot.* **1971**, *24*, 245.

(4) Paranagama, P. A.; Wijeratne, E. M. K.; Burns, A. M.; Marron, M. T.; Gunatilaka, M. K.; Arnold, A. E.; Gunatilaka, A. A. L. *J. Nat. Prod.* **2007**, *70*, 1700.

(5) Wang, W.; Li, T.; Milburn, R.; Yates, J.; Hinnant, E.; Luzzio, M. J.; Noble, S. A.; Attardo, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1579.

(6) Gharpure, S. J.; Shelke, Y. G.; Reddy, S. R. B. *RSC Adv.* **2014**, *4*, 46962.

(7) (a) Feng, Y.; Jiang, X.; Brabander, J. K. D. *J. Am. Chem. Soc.* **2012**, *134*, 17083. (b) Lu, D.; Zhou, Y.; Li, Y.; Yan, S.; Gong, Y. *J. Org. Chem.* **2011**, *76*, 8869. (c) De Brabander, J. K.; Liu, B.; Qian, M. *Org. Lett.* **2008**, *10*, 2533.

(8) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251.

(9) Varela-Fernandez, A.; Garcia-Yebra, C.; Varela, J. A.; Ester, M. A.; Saa, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 4278.

(10) Varela-Fernandez, A.; Gonzalez-Rodriguez, C.; Varela, J. A.; Castedo, L.; Saa, C. *Org. Lett.* **2009**, *11*, 5350.

(11) Liu, P. N.; Su, F. H.;Wen, T. B.; Sung, H. H.-Y.;Williams, I. D.; Jia, G. *Chem.-Eur. J.* **2010**, *16*, 7889.

(12) Yao, W.; Zhang, Y.; Jia, X.; Huang, Z. *Angew. Chem. Int. Ed.* **2014**, *53*, 1390.

(13) Zhang, M.; Zhang, H.-J.; Han, T.; Ruan, W.;Wen, T.-B. *J. Org. Chem.* **2015**, *80*, 620.

(14) (a) For review see Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; (b) Poulsen, P. H.; Vergura, S.; Monleón, A.; Danny Kaare Bech Jørgensen, D. K. B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2016**, *138*, 6412. (b) Senadi, G. C.; Gore, B. S.; Hu, W.-P.; Wang, J.-J. *Org. Lett.* **2016**, *18*, 2890. (c) Wang, H.; Wang, C.; Huang, K.; Liu, L.; Chang, W.; Li, J. *Org. Lett.* **2016**, *18*, 2367.

(15) Siyang, H. X.; Ji, X. Y.; Wu, X. R.; Wu, X. Y.; Liu, P. N. *Org. Lett.* **2015**, *17*, 5220.

(16) Tomás-Mendivil, E,; Starck, J.; Ortuno, J.-C.; Michelet, V. *Org. Lett.* **2015**, *17*, 6126.

(17) Chan, C.-K.; Chan, Y.-L.; Chang, M.-Y. *Tetrahedron* **2016**, *72*, 547.

(18) Mariaule, G.; Newsome, G.; Toullec, P. Y.; Belmont, P.; Michelet, V. *Org. Lett.* **2014**, *16*, 4570.

(19)Kusama, H.; Sawada, T.; Okita, A.; Shiozawa, F.; Iwasawa, N. *Org. Lett.* **2006**, *8*, 1077.

(20) Terada, M.; Li, F. Toda, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 235.

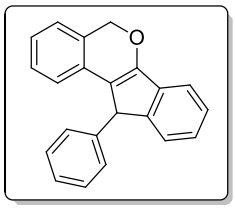
(21) (a) Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2010**, 6, No. 6 (b) Gabriele, B.; Mancuso, R.; Veltri, L. *Chem. Eur. J.* **2016**, *22*, 5056. (c) Smith, N. D.; Hayashida, J.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 4309. (d) Saikia, A. K.; Sultana, S.; Devi, N. R.; Deka, M. J.; Tiwari, K.; Dubey, V. K. *Org. Biomol. Chem.* **2016**, *14*, 970 and references cited therein.

(22)The crystallographic data for compounds **29b** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC- 1483531.

(23)Ackermann, M.; Bucher, J.; Rappold, M.; Graf, K.; Rominger, F.; Hashmi, A. S. K. *Asian J. Org. Chem.* **2013**, *8*, 1786.

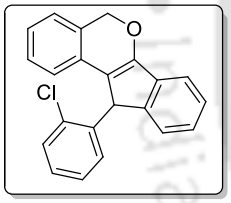
4.6. Characterization Data:

11-Phenyl-5,11-dihydroindeno[1,2-*c*]isochromene (29a):



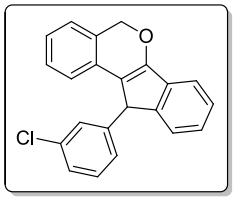
White solid, mp 118-120 ºC; R_f (hexane/ EtOAc 49:1) 0.20; yield 257 mg, 87%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.79 (s, 1 H), 5.40 (d, *J* = 4.5 Hz, 2 H), 6.75 (d, *J* = 7.2 Hz, 1 H), 7.05 (s, 3 H), 7.17 (d, *J* = 7.2 Hz, 2 H), 7.21-7.30 (m, 6 H), 7.41 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 50.7, 70.7, 118.4, 118.9, 120.9, 124.2, 124.4, 126.1, 127.1, 127.2, 127.21, 128.1, 128.5, 129.0, 130.0, 130.8, 136.9, 140.0, 148.2, 156.1; IR (KBr, neat) 3060, 2849, 1605, 1492, 1451, 1142, 1086, 1029, 972, 753 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{17}O$ $(M + H)^+$ 297.1274, found 297.1279.

11-(2-Chlorophenyl)-5,11-dihydroindeno[1,2-*c*]isochromene (29b):



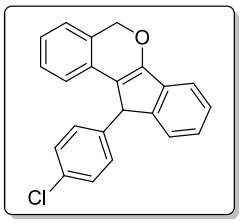
Pale yellow solid, mp 130-132 ºC; R_f (hexane/ EtOAc 49:1) 0.20; yield 294 mg, 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40-5.49 (m, 3 H), 6.70 (d, *J* = 7.6 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.99 (t, *J* = 7.2 Hz, 1 H), 7.06-7.20 (m, 5 H), 7.30 (t, *J* = 7.6 Hz, 2 H), 7.42 (d, *J* = 7.6 Hz, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 46.2, 70.7, 118.5, 120.9, 124.2, 124.4, 126.2, 127.2, 127.4, 127.6, 127.8, 128.4, 128.6, 129.9, 134.4, 136.9, 137.6, 147.7, 156.4; IR (KBr, neat) 2925, 2851, 1615, 1491, 1261, 1145, 1086, 1034, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{16}{}^{35}ClO$ $(M + H)^+$ 331.0884, found 331.0879.

11-(3-Chlorophenyl)-5,11-dihydroindeno[1,2-*c*]isochromene (29c):



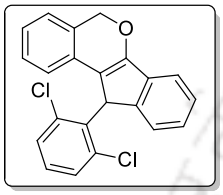
Colourless oil; R_f (hexane/ EtOAc 49:1) 0.20; yield 290 mg, 88%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.72 (s, 1 H), 5.41 (d, *J* = 4.4 Hz, 2 H), 6.73 (d, *J* = 7.2 Hz, 1 H), 7.05-7.10 (m, 3 H), 7.12-7.16-7.21 (m, 5 H), 7.23 (s, 1 H), 7.29 (t, *J* = 7.2 Hz, 1 H), 7.41 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 50.1, 70.7, 118.3, 118.5, 120.7, 124.2, 124.5, 126.3, 126.4, 127.2, 127.7, 128.0, 128.5, 130.3, 130.5, 134.7, 136.8, 142.2, 147.5, 156.3; IR (KBr, neat) 2924, 2852, 1604, 1491, 1406, 1281, 1117, 1034, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{16}{}^{35}ClO$ $(M + H)^+$ 331.0884, found 331.0888.

11-(4-Chlorophenyl)-5,11-dihydroindeno[1,2-*c*]isochromene (29d):



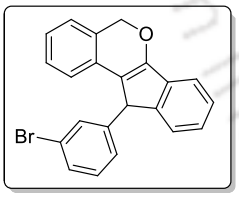
Colourless oil; R_f (hexane/ EtOAc 49:1) 0.20; yield 280 mg, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (s, 1 H), 5.41 (d, *J* = 4.4 Hz, 2 H), 6.72-6.74 (m, 1 H), 7.07-7.11 (m, 3 H), 7.15-7.22 (m, 4 H), 7.24 (t, , *J* = 7.2 Hz, 1 H), 7.26 (d, *J* = 7.2 Hz, 1 H), 7.30 (t, *J* = 7.2 Hz, 1 H), 7.42 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.9, 70.8, 118.4, 118.5, 120.7, 124.2, 124.5, 126.3, 127.2, 127.4, 127.8, 128.5, 129.2, 129.5, 130.5, 132.8, 136.8, 138.6, 147.7, 156.2; IR (KBr, neat) 2924, 2852, 1604, 1440, 1407, 1261, 1117, 1034, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{16}{}^{35}ClO$ $(M + H)^+$ 331.0884, found 331.0853.

11-(2,6-Dichlorophenyl)-5,11-dihydroindeno[1,2-*c*]isochromene (29e):



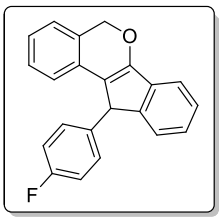
Colourless oil; R_f (hexane/ EtOAc 49:1) 0.20; yield 236 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.39 (d, *J* = 4.4 Hz, 2 H), 5.73 (s, 1 H), 6.72 (d, *J* = 7.2 Hz, 1 H), 7.07-7.12 (m, 4 H), 7.15 (d, *J* = 7.2 Hz, 2 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 7.34 (t, *J* = 7.2 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.51 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 46.8, 70.7, 117.4, 118.6, 120.1, 123.2, 124.5, 126.1, 127.0, 127.4, 127.9, 128.0, 128.4, 128.6, 128.7, 128.9, 130.3, 140.0, 144.5, 156.3; IR (KBr, neat) 2925, 2853, 1615, 1471, 1218, 1117, 1087, 973, 772 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{15}{}^{35}Cl_2O$ $(M + H)^+$ 365.0494, found 365.0424.

11-(3-Bromophenyl)-5,11-dihydroindeno[1,2-*c*]isochromene (29f):



Yellow solid, mp 146-148 °C; R_f (hexane/ EtOAc 49:1) 0.19; yield 310 mg, 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (s, 1 H), 5.44 (d, *J* = 4.4 Hz, 2 H), 6.71 (d, *J* = 7.2 Hz, 1 H), 7.08-7.12 (m, 3 H), 7.15-7.22 (m, 2 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.54 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.2, 70.7, 118.3, 118.6, 120.6, 124.2, 124.5, 125.9, 125.99, 126.0, 126.3, 127.3, 127.6, 127.7, 128.4, 128.5, 128.53, 130.3, 136.9, 144.4, 147.3, 156.4; IR (KBr, neat) 2925, 2853, 1619, 1466, 1324, 1121, 1066, 755 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{16}{}^{79}BrO$ $(M + H)^+$ 377.0359, found 377.0319.

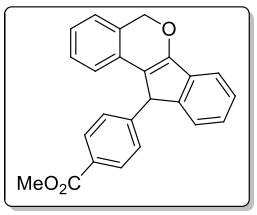
11-(4-Fluorophenyl)-5,11-dihydroindeno[1,2-*c*]isochromene (29g):



Yellow solid, mp 125-127 °C; R_f (hexane/ EtOAc 50:1) 0.18; yield 251mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (s, 1 H), 5.42 (d, *J* = 4.4 Hz, 2 H), 6.74 (t, *J* = 7.2 Hz, 1 H), 6.97 (t, *J* = 8.0 Hz, 2 H), 7.06-7.11 (m, 3 H), 7.15-7.24 (m, 4 H), 7.30 (t, *J* = 8.0 Hz, 1 H), 7.42 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.8, 70.7, 115.9 (d, *J* = 21.3 Hz), 118.4, 118.6, 120.7,

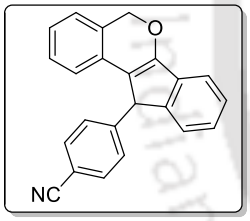
124.1, 124.4, 126.2, 127.1, 127.3, 127.8, 128.5, 129.5 (d, *J* = 8.0 Hz), 130.6, 135.5, 135.6 (d, *J* = 3.5 Hz), 136.8, 148.0, 156.1, 162.1 (d, *J* = 243.2 Hz); ^{19}F NMR (376 MHz, C_6F_6/$CDCl_3$) δ 45.92 (s, -F); IR (KBr, neat) 2924, 2853, 1600, 1489, 1220, 1150, 1066, 1016, 772 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{16}FO$ $(M + H)^+$ 315.1180, found 315.1189.

Methyl 4-(5,11-dihydroindeno[1,2-*c*]isochromen-11-yl)benzoate (29h):



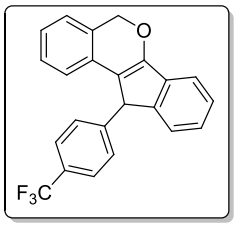
White solid, mp 121-123 °C; R_f (hexane/ EtOAc 49:1) 0.25; yield 304 mg, 86%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.86 (s, 3 H), 4.80 (s, 1 H), 5.41 (d, *J* = 4.4 Hz, 2 H), 6.68-6.70 (m, 1 H), 7.04-7.08 (m, 3 H), 7.13-7.18 (m, 2 H), 7.29 (t, *J* = 7.2 Hz, 1 H), 7.31-7.33 (m, 2 H), 7.42 (d, *J* = 7.6 Hz, 1 H), 7.95 (d, *J* = 7.6 Hz, 2 H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 50.4, 52.2, 70.7, 118.4, 118.6, 120.6, 124.2, 124.4, 126.3, 127.2, 127.5, 127.7, 128.1, 128.5, 129.2, 130.0, 130.4, 136.9, 145.7, 147.3, 156.3, 167.1; IR (KBr, neat) 2950, 2847, 1721, 1610, 1435, 1281, 1112, 1019, 970, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{19}O_3$ $(M + H)^+$ 335.1329, found 335.1293.

4-(5,11-Dihydroindeno[1,2-*c*]isochromen-11-yl)benzonitrile (29i):



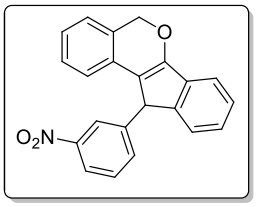
Colourless oil; R_f (hexane/ EtOAc 49:1) 0.28; yield 225mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (s, 1 H), 5.42 (d, *J* = 2.0 Hz, 2 H), 6.74-6.76 (m, 1 H), 7.07-7.11 (m, 3 H), 7.13 (d, *J* = 7.2 Hz, 1 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.36 (d, *J* = 7.2 Hz, 2 H), 7.44 (d, *J* = 7.2 Hz, 1 H), 7.56 (d, *J* = 2.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.3, 70.7, 111.0, 118.7, 120.4, 124.1, 124.6, 126.5, 127.4, 127.7, 128.4, 128.6, 128.8, 128.9, 129.2, 132.9, 136.8, 146.1, 146.7, 156.6; IR (KBr, neat) 2924, 2853, 2227, 1606, 1489, 1408, 1260, 1142, 1085, 970, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{16}NO$ $(M + H)^+$ 322.1226, found 322.1190.

11-(4-(Trifluoromethyl)phenyl)-5,11-dihydroindeno[1,2-*c*]isochromene (29j):



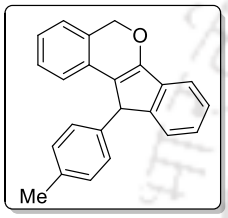
Yellow oil; R_f (hexane/ EtOAc 49:1) 0.20; yield 273 mg, 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.76 (s, 1 H), 5.38 (d, *J* = 3.0 Hz, 2 H), 6.67-6.69 (m, 1 H), 7.00-7.10 (m, 3 H), 7.12 (d, *J* = 7.2 Hz, 1 H), 7.14-7.17 (m, 1 H), 7.28 (t, *J* = 7.2 Hz, 1 H), 7.34 (d, *J* = 7.8 Hz, 2 H), 7.42 (d, *J* = 7.2 Hz, 1 H), 7.51 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 50.2, 70.7, 118.3, 118.6, 120.6, 122.3, 123.5, 124.2 (q, *J* = 270.0 Hz), 124.5, 126.0 (q, *J* = 3.0 Hz), 126.4, 127.3, 127.6, 127.8, 128.4, 128.6, 130.4, 136.9, 144.5, 147.3, 156.5; ^{19}F NMR (376 MHz, C_6F_6/$CDCl_3$) δ 99.33 (s, -F); IR (KBr, neat) 3068, 2845, 1617, 1491, 1325, 1123, 1066, 857, 752 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{16}F_3O$ $(M + H)^+$ 365.1148, found 365.1136.

11-(3-Nitrophenyl)-5,11-dihydroindeno[1,2-*c*]isochromene (29k):



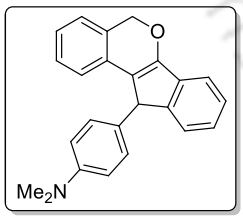
Yellow oil; R_f (hexane/ EtOAc 49:1) 0.30; yield 286 mg, 84%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.87 (s, 1 H), 5.45 (d, *J* = 2.0 Hz, 2 H), 6.69-6.70 (m, 1 H), 7.08-7.10 (m, 3 H), 7.15 (d, *J* = 7.2 Hz, 1 H), 7.21 (t, *J* = 7.2 Hz, 1 H), 7.33 (t, *J* = 7.2 Hz, 1 H), 7.43-7.47 (m, 2 H), 7.56 (d, *J* = 7.2 Hz, 1 H), 8.10 (d, *J* = 7.2 Hz, 1 H), 8.17 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.8, 70.7, 117.9, 118.7, 120.3, 122.4, 123.0, 124.1, 124.6, 126.4, 127.4, 127.6, 127.8, 128.5, 129.2, 130.0, 134.2, 136.8, 142.5, 146.8, 148.7, 156.6; IR (KBr, neat) 2926, 2853, 1604, 1529, 1490, 1351, 1281, 1145, 1087, 972, 753 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{16}NO_3$ $(M + H)^+$ 342.1125, found 342.1097.

11-(*p*-Tolyl)-5,11-dihydroindeno[1,2-*c*]isochromene (29l):



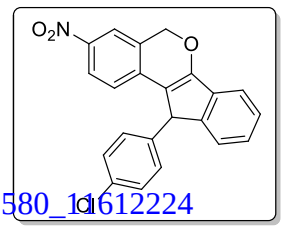
Yellow oil; R_f (hexane/ EtOAc 49:1) 0.23; yield 242 mg, 78%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.29 (s, 3 H), 4.74 (s, 1 H), 5.40 (d, *J* = 4.0 Hz, 2 H), 6.78 (d, *J* = 7.2 Hz, 1 H), 7.04-7.09 (m, 5 H), 7.13-7.18 (m, 4 H), 7.27 (t, *J* = 7.2 Hz, 1 H), 7.40 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 50.3, 70.7, 118.3, 118.9, 120.9, 124.2, 124.3, 126.0, 127.0, 127.1, 127.8, 127.9, 128.5, 129.7, 130.8, 136.6, 136.7, 136.8, 148.4, 155.9; IR (KBr, neat) 2922, 2853, 1604, 1490, 1405, 1259, 1142, 1085, 973, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{19}O$ $(M + H)^+$ 311.1430, found 311.1391.

4-(5,11-Dihydroindeno[1,2-*c*]isochromen-11-yl)-N,N-dimethylaniline (29m):



Colourless oil; R_f (hexane/ EtOAc 49:1) 0.27; yield 241mg, 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (s, 6 H), 4.72 (s, 1 H), 5.40 (d, *J* = 2.4 Hz, 2 H), 6.66 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 7.2 Hz, 1 H), 7.06-7.11 (m, 2 H), 6.12 (d, *J* = 7.2 Hz, 2 H), 7.16-7.22 (m, 2 H), 7.25-7.29 (m, 2 H), 7.40 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.9, 40.9, 49.9, 70.7, 113.3, 118.2, 119.2, 121.0, 124.2, 124.3, 125.9, 127.0, 127.3, 127.9, 128.5, 128.8 (2C), 131.1, 136.8, 149.0, 149.8, 155.7; IR (KBr, neat) 2923, 2852, 1604, 1460, 1349, 1219, 1198, 1085, 974, 773 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{22}NO$ $(M + H)^+$ 340.1696, found 340.1710.

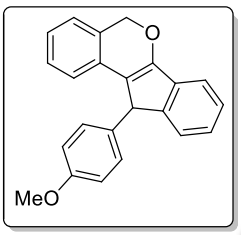
11-(4-Chlorophenyl)-3-nitro-5,11-dihydroindeno[1,2-*c*]isochromene (29n):



Yellow oil; R_f (hexane/ EtOAc 49:1) 0.29; yield 274mg, 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (s, 1 H), 5.50 (d, *J* = 12.4 Hz, 2 H), 6.77 (d, *J* = 8.4 Hz, 1 H), 7.16-7.21 (m, 3 H), 7.27-7.31 (m, 3 H), 7.36 (t, *J* = 7.2

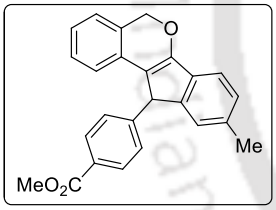
Hz, 1 H), 7.49-7.53 (m, 1 H), 7.97-8.0 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 49.9, 70.3, 117.1, 119.7, 120.1, 120.2, 124.5, 124.8, 127.8, 127.9, 129.0, 129.3, 129.3, 129.7, 131.1, 133.4, 135.5, 137.1, 137.5, 145.4, 148.4, 160.5; IR (KBr, neat) 2925, 2854, 1603, 1583, 1507, 1489, 1329, 1219, 1126, 1087, 894, 772 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{15}ClNO_3$ $(M + H)^+$ 376.0735, found 376.0753.

11-(4-Methoxyphenyl)-5,11-dihydroindeno[1,2-*c*]isochromene (29o):



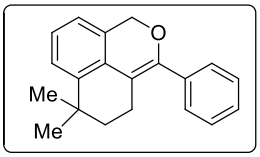
Colourless oil; R_f (hexane/EtOAc 49:1) 0.21; yield 235 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3 H), 5.11 (s, 1 H), 5.14 (d, *J* = 14.8 Hz, 2 H), 7.00-7.06 (m, 4 H), 7.10 (d, *J* = 7.6 Hz, 1 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 7.24-7.31 (m, 3 H), 7.37 (d *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.5, 69.9, 82.0, 114.6, 120.7, 123.8, 124.7, 125.8, 126.0, 126.8, 127.3, 127.8, 129.1, 129.8, 130.4, 134.6, 136.8, 136.81, 141.2, 146.6, 159.5; IR (KBr, neat) 2926, 2835, 1605, 1569, 1461, 1247, 1195, 1033, 852, 759 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{19}O_2$ $(M + H)^+$ 327.1380, found 327.1382.

Methyl 4-(9-methyl-5,11-dihydroindeno[1,2-c]isochromen-11-yl)benzoate (29p):



Colourless solid, mp 140-142 ^{o}C; R_f (hexane/EtOAc 49:1) 0.21; yield 331 mg, 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 3.87 (s, 3 H), 4.78 (s, 1 H), 5.40 (dd, *J* = 16.2 and 13.2 Hz, 2 H), 6.65-6.67 (m, 1 H), 6.96 (s, 1 H), 7.04-7.05 (m, 3 H), 7.11 (d, *J* = 7.8 Hz, 1 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 7.30-7.36 (m, 3 H), 7.96 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 50.3, 52.2, 53.6, 70.7, 117.5, 118.3, 120.4, 124.4, 125.1, 126.0, 127.6, 128.1, 128.2, 128.5, 129.1, 130.4, 130.6, 134.2, 137.3, 146.0, 147.7, 156.5, 167.1; IR (KBr, neat) 2951, 2853, 1722, 1610, 1492, 1435, 1280, 1111, 1048, 813, 779 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{21}O_3$ $(M + H)^+$ 369.1485, found 369.1509.

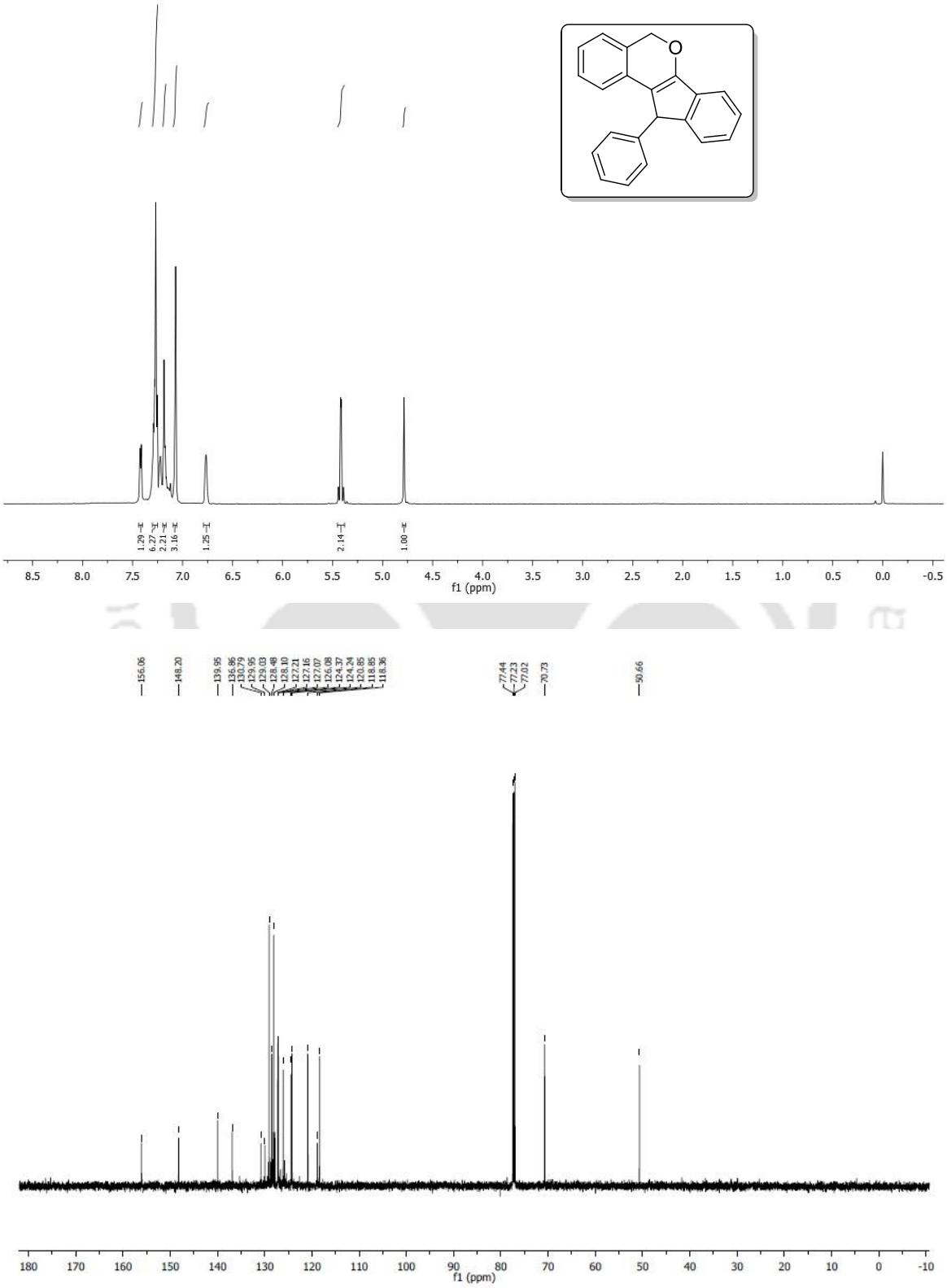
6,6-Dimethyl-3-phenyl-1,4,5,6-tetrahydrobenzo[*de*]iso-chromene (29r):



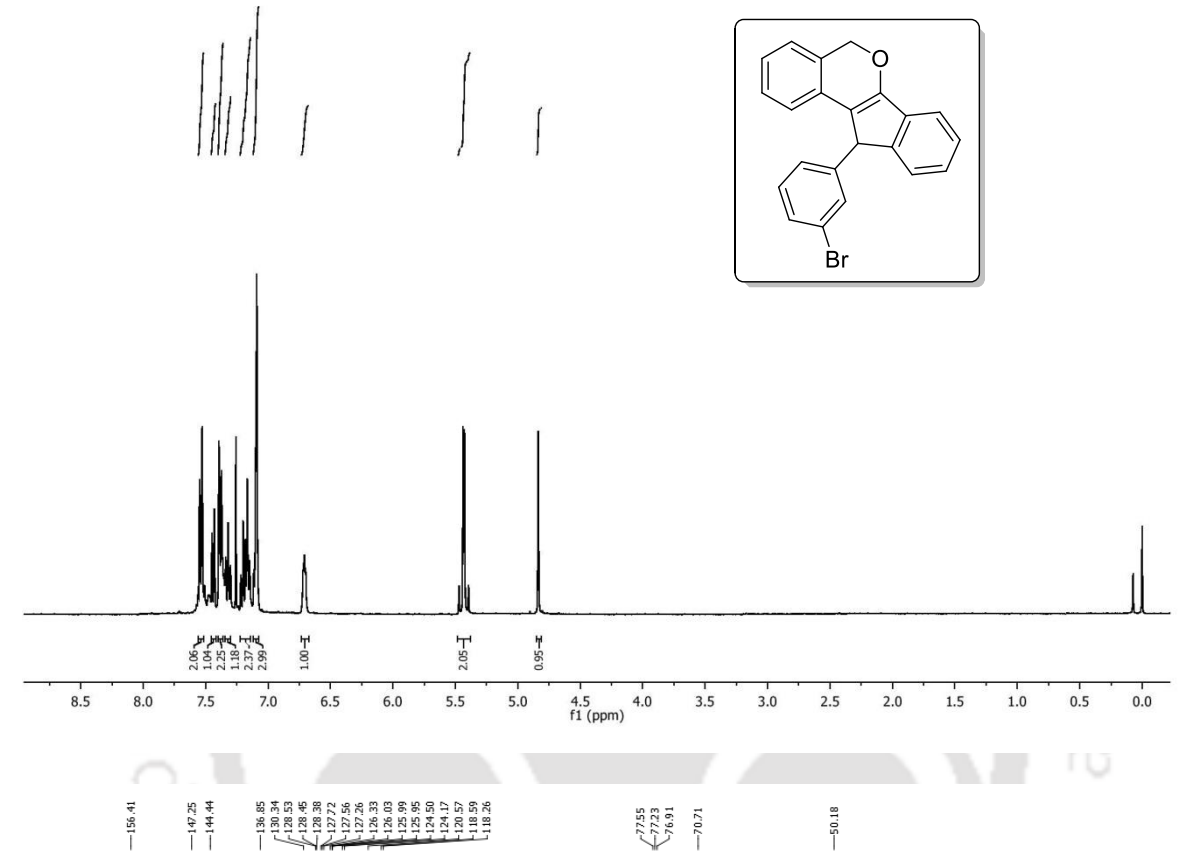
Colourless oil; R_f (hexane/EtOAc 49:1) 0.21; yield 234 mg, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (s, 3 H), 1.25 (d, *J* = 10.6 Hz, 1 H, shielded), 1.31 (s, 3 H), 2.31 (d, *J* = 16.0 Hz, 1 H), 2.48 (d, *J* = 16.0 Hz, 1 H), 3.75 (s, 1 H, deshielded), 5.22 (s, 2 H), 6.42-6.45 (m, 1 H), 6.97-6.99 (m, 2 H), 7.16-7.23 (m, 3 H), 7.25-7.32 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.5, 31.5, 40.7, 45.6, 57.9, 70.1, 112.4, 120.4, 123.8, 125.3, 126.5, 127.3, 127.4, 128.0, 128.1, 128.3, 128.4, 128.6, 128.7, 131.4, 141.2, 157.0; IR (KBr, neat) 2955, 2837, 1649, 1492, 1452, 1365, 1170, 1080, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}O$ $(M + H)^+$ 277.1587, found 277.1591.

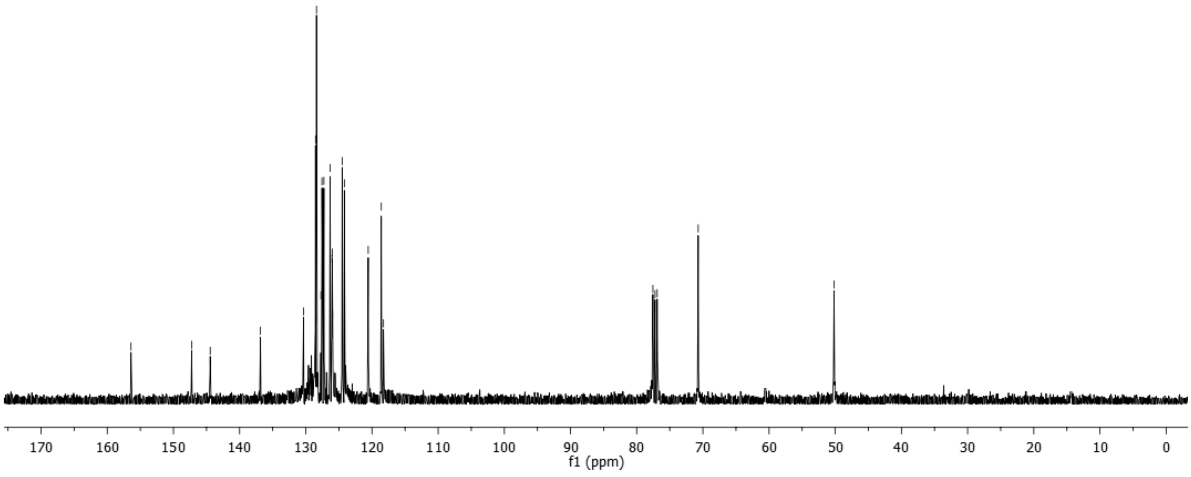
4.7. Selected Spectra

^{1}H NMR and ^{13}C NMR spectra of 11-Phenyl-5,11-dihydroindeno[1,2-*c*]isochromene (29a)

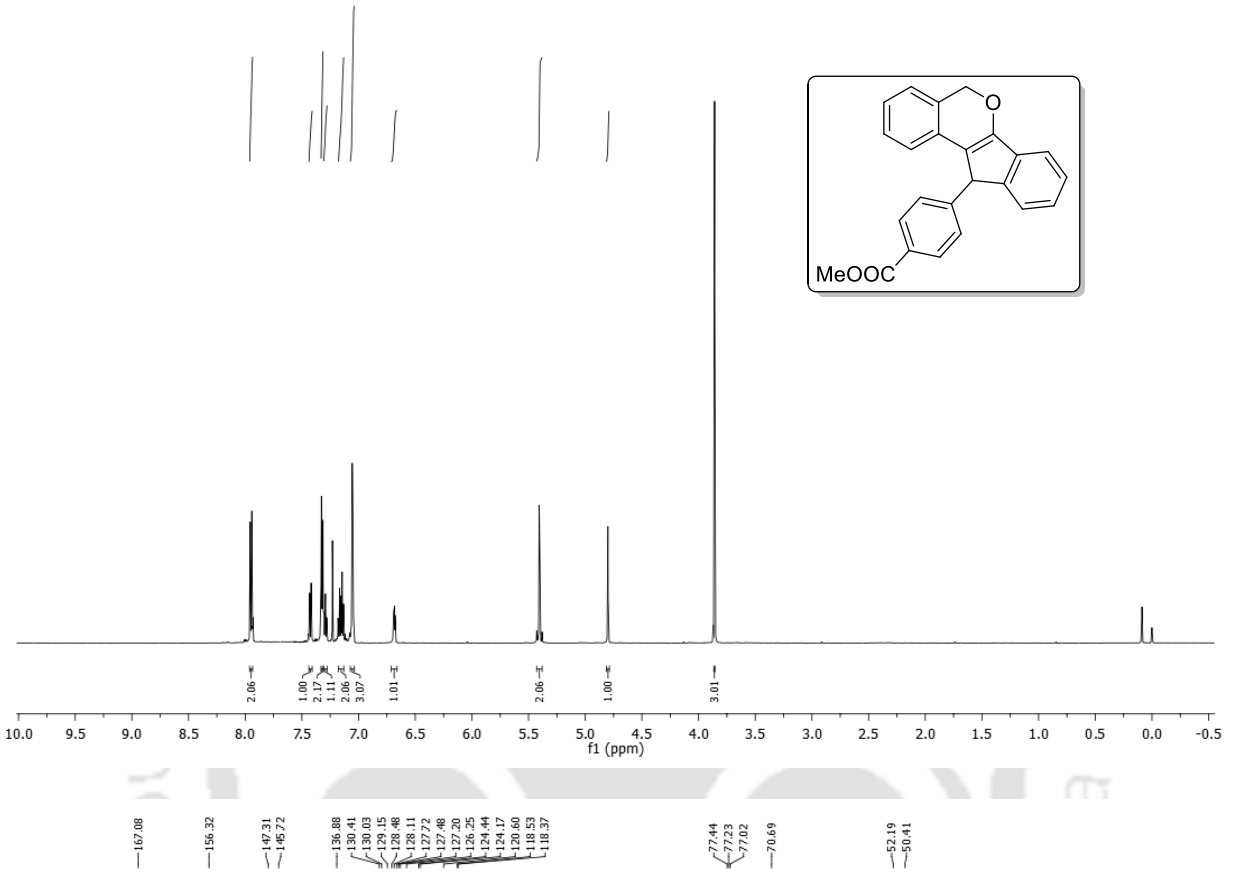


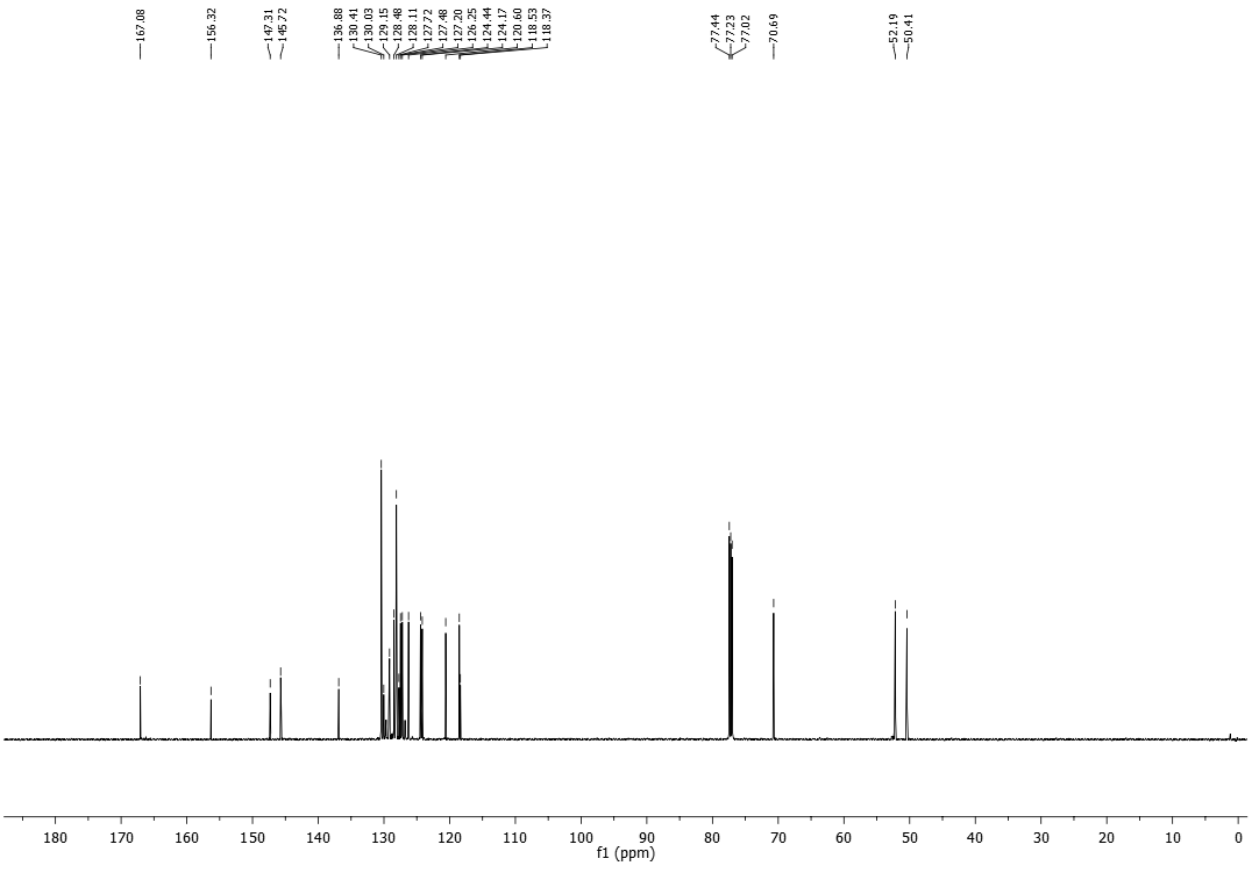
^{1}H NMR and ^{13}C NMR spectra of compound 11-(3-Bromophenyl)-5,11-dihydroindeno[1,2-*c*]isochromene
(29f):



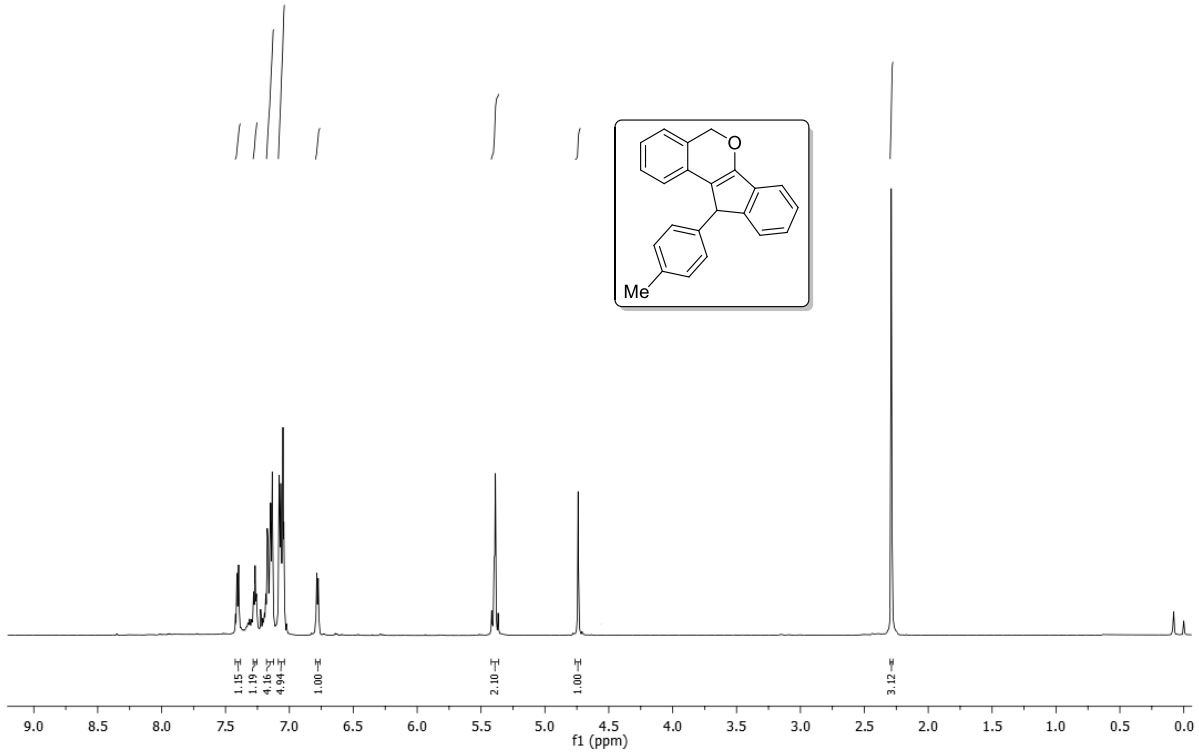


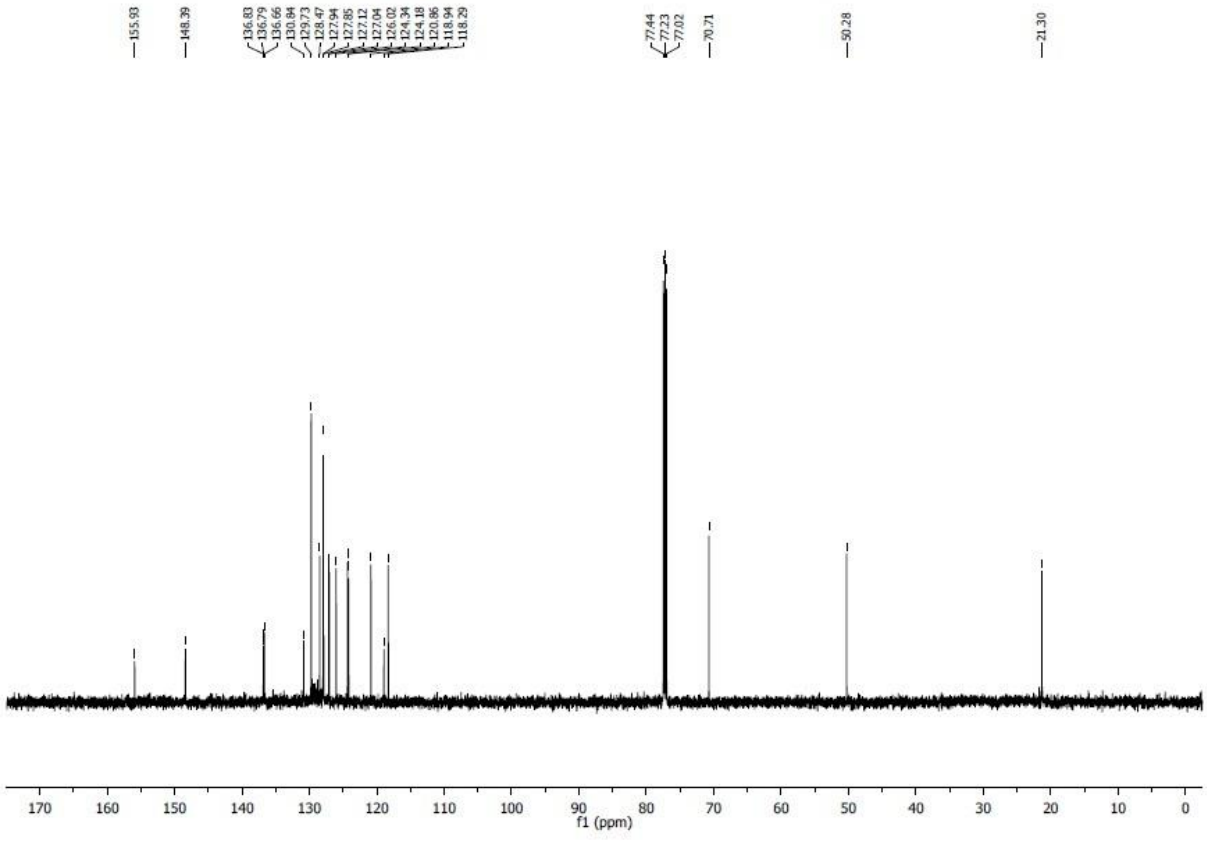
^{1}H NMR and ^{13}C NMR spectra of Methyl 4-(5,11-dihydroindeno[1,2-*c*]isochromen-11-yl)benzoate (29h):



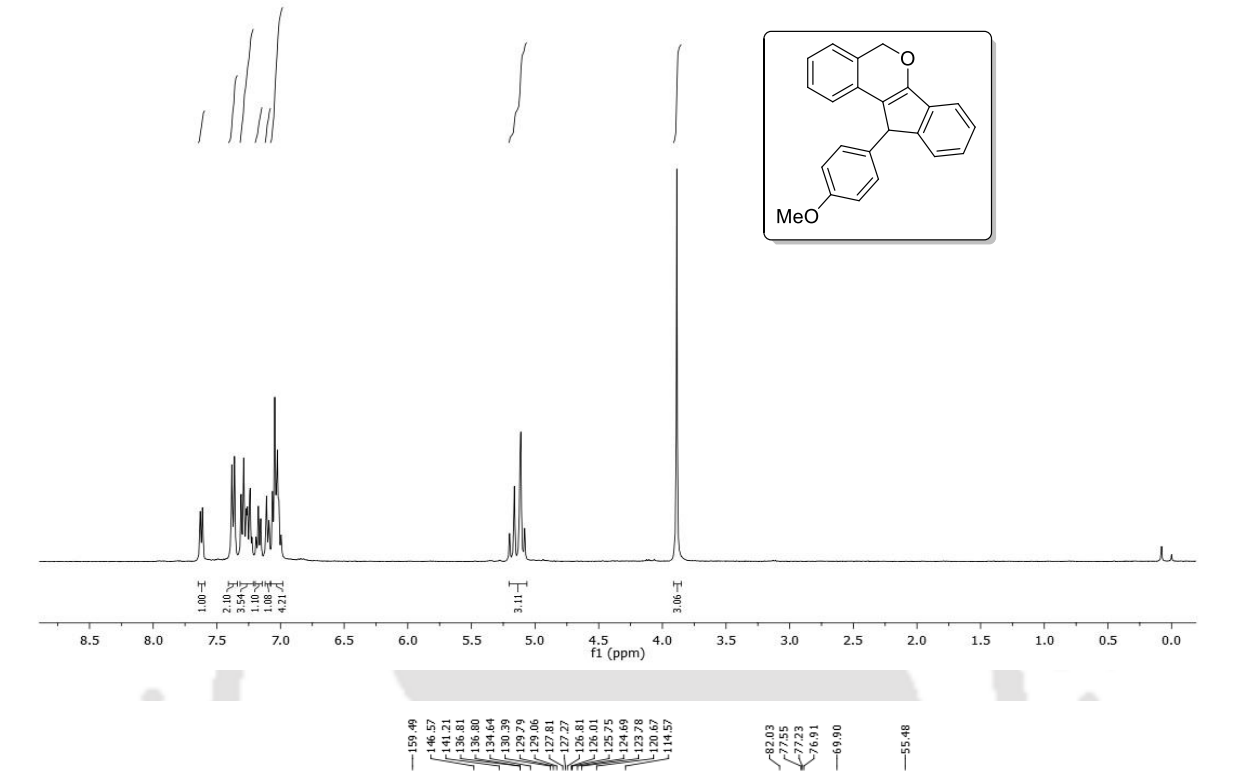


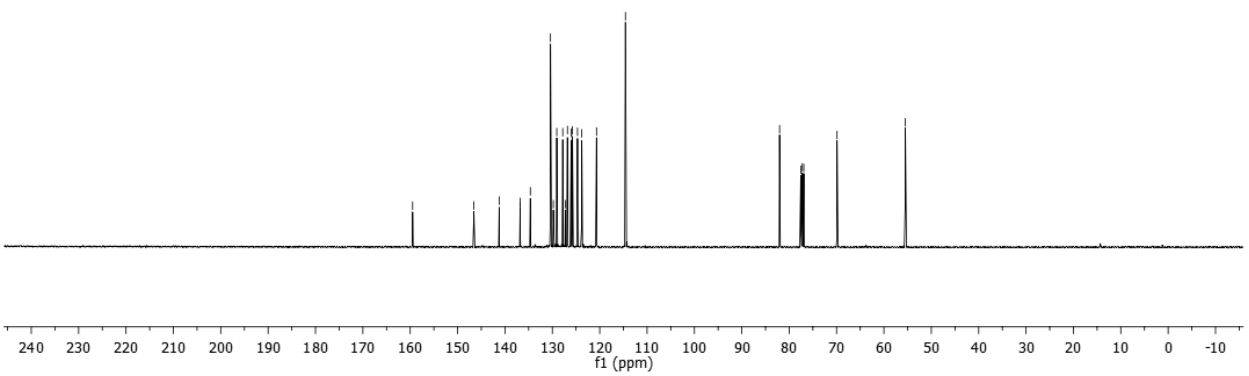
^{1}H NMR and ^{13}C NMR spectra of 11-(*p*-Tolyl)-5,11-dihydroindeno[1,2-*c*]isochromene (29l):





^{1}H NMR and ^{13}C NMR spectra of 11-(4-Methoxyphenyl)-5,11-dihydroindeno[1,2 *c*]isochromene (29o):





4.8. Crystal Parameters

The crystal parameters of compound 29b

	CCDC 1483531
Formula	$C_{22}H_{14}ClO$
Formula weight	329.78
T/K	296(2)
Crystal system	Monoclinic
Space group	P21/c
a/Å	17.382(19)
b/Å	6.286(7)
c/Å	17.040(18)
α/°	90.00
β/°	117.003(18)
γ/°	90.00
V/Å^3	1659(3)
Z	4
Abs. Coeff./mm^{-1}	0.234
Abs. Correction	multi-scan
GOF on F^2	1.016
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0683
	wR2 = 0.1508
R indices [all data]	*R1* = 0.0915
	wR2 = 0.1664

CHAPTER 5

Brønsted Acid Mediated Synthesis of 4-Trifluoromethanesulfonate Substituted 3,6-Dihydropyrans And Their Application In Various C-C Coupling Reactions

5.1. Importance of Dihydropyrans

Multicomponent reactions have attracted the considerable attention in synthetic organic chemistry due to their ability to form a series of bonds in a single step.[1] In particular, multicomponent reactions can provide functionalized heterocyclic compounds with high stereoselectivity.[2] Dihydropyran units are valuable compounds of interest for the reason that these units constitute important structural unit in many natural products of biological importance. Compounds such as martiriol and salinomycin carry dihydropyran unit in which double bond in cyclic system is responsible for the biological activity. Martiriol **1**, for that matter, is a biologically active molecule, isolated from the red algae of the genus *Laurencia*, shows potent activity against various tumour cell lines.[3] Similarly, salinomycin **2**, isolated from a culture broth of *Streptomyces albus* is known to possess interesting antibacterial and anticoccidial properties.[4] The presence of double bond in cyclic system is not only responsible for their biological properties but also serve as a functional group for further manipulations in organic synthesis.[5] They can also be used as building blocks in organic synthesis.[6]

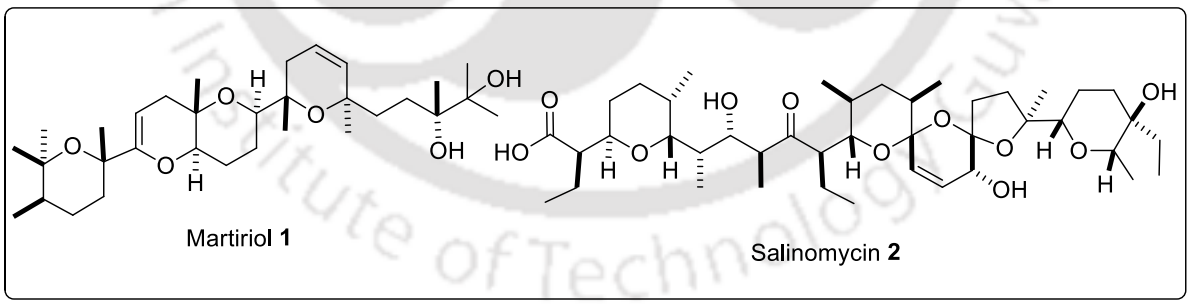


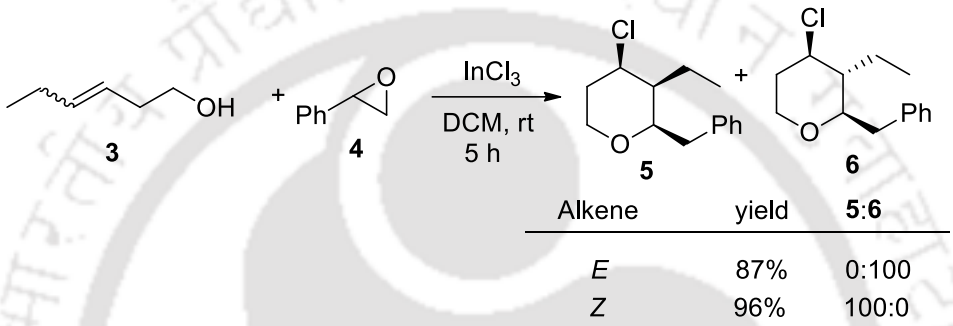
Figure 5.1.1. Bioactive molecules containing dihydropyran ring

5.2. Literature Methods

Over the years, many strategies have been developed for the synthesis of dihydropyrans, which include hetero-Diels-Alder reactions,[7] olefin metathesis,[8] base promoted cyclizations of sulfenyl dienols,[9] oxonium-ene reactions,[10] [4+2] annulations,[11] intramolecular C-C bond formation of alkyne-epoxide,[12] and Prins cyclization reactions.[13] Among existing methodologies, the Prins

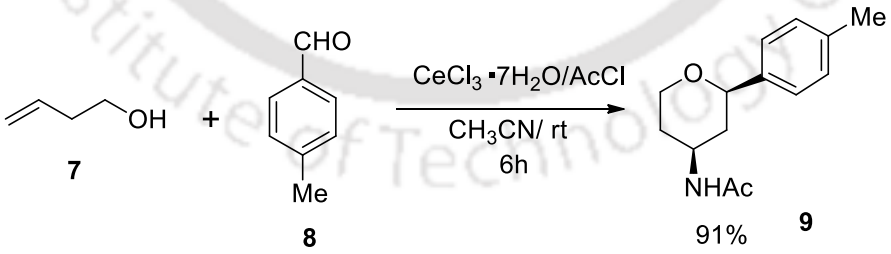
cyclization has emerged as a powerful tool as it provides the desired product in a single step with high diastereoselectivity.

Li and coworkers reported a methodology for the synthesis of 4-chlorotetrahydropyrans **5** and **6** from homoallylic alcohols **3** and epoxides **4** as aldehyde alternates in the presence of $InCl_3$ (*Scheme 5.2.1*). The stereochemistry depends upon the geometry of olefin, when *cis* unsaturated alcohol was used, 2,3,4-trisubstituted tetrahydropyran **5** with *cis* conformation was obtained as the major product. However, when *trans* unsaturated alcohol, such as *trans*-3-hexene-1-ol was used, 2,3,4-trisubstituted tetrahydropyran **6** with a *trans–trans* conformation was obtained as the dominant product.[14]



Scheme 5.2.1.

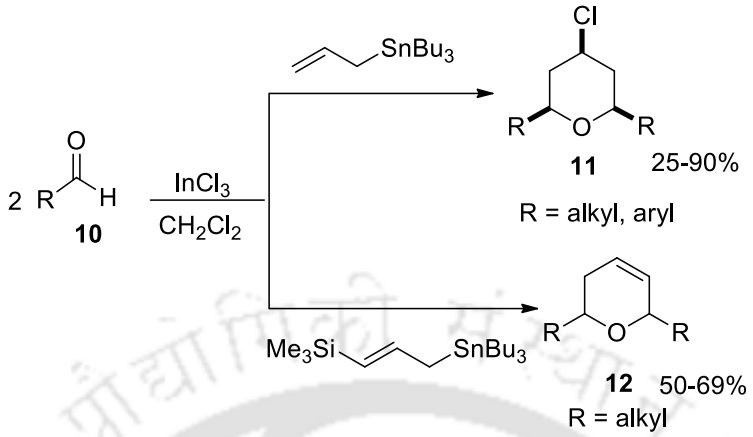
The construction of C-N bond at 4th position of THPs was successfully demonstrated by Yadav and co-workers *via* Prins-Ritter sequence. The reaction of homoallyl alcohol **7** with aldehyde **8** in the presence of $CeCl_3{\cdot}7H_2O$/AcCl underwent Prins cyclization to give the 4-tetrahydropyranyl cation, which was trapped by acetonitrile through Ritter reaction to produce the corresponding 4-amidotetrahydropyran **9** with high *cis*-selectivity (*Scheme 5.2.2*).[15]



Scheme 5.2.2.

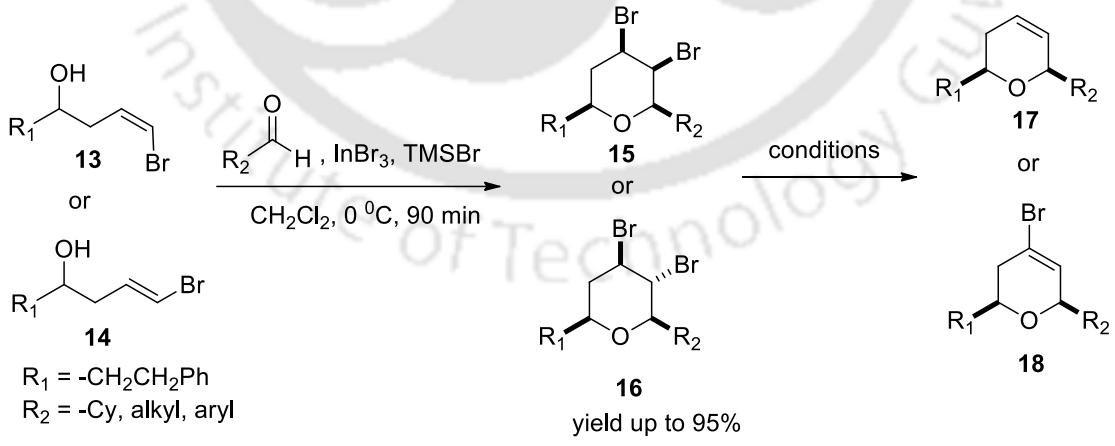
Li *et al.* reported a novel route to access diastereoselective 4-halotetrahydropyrans in high yields *via* carbonyl allylation-Prins cyclization. The Prins cyclization reaction between two equivalents of aldehydes **10** with 1 equiv of allyltributylstannane in presence of indium chloride and methylene chloride at room temperature produced 4-chlorotetrahydropyrans **11** with high diastereoselectivity. But, the reaction with 3-trimethylsilylallyltributylstannane under the same

reaction conditions led to a diastereoselective formation of 3,4-dihydropyrans **12** *(Scheme 5.2.3).*[16]



Scheme 5.2.3.

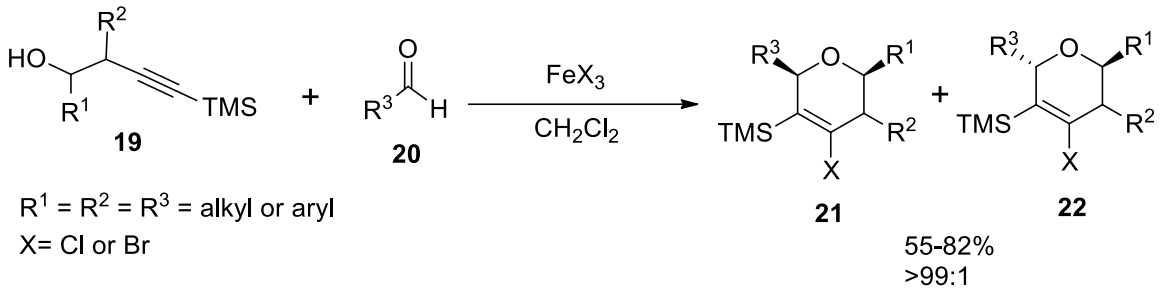
Loh and his group developed an efficient Prins cyclization reaction to construct 2,6-*cis*-4,5-dibromo-tetrasubstituted THP rings with high stereoselectivity and in good yields. The reaction between *γ*-brominated homoallylic alcohol **13** or **14** and aldehydes promoted by 1.0 equivalents of $InBr_3$ with 1.2 equivalents of TMSBr in CH_2Cl_2 at 0 °C to afford 2,4,5,6-tetrasubstituted tetrahydropyrans **15** or **16** as a single isomer. The stereochemistry of the bromine substituent at the 5-position was controlled by the geometric configuration of the *γ*-brominated homoallylic alcohols. Dibromo-THP products were further functionalized to various substituted pyran-containing compounds (*Scheme 5.2.4.*).[17]



Scheme 5.2.4.

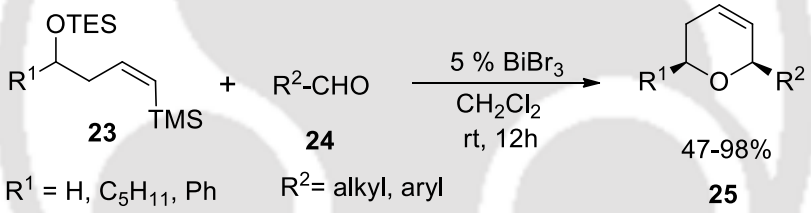
Martín and his group showed a novel route for the synthesis of tetra- and penta-substituted dihydropyrans *via* silylalkyne-Prins cyclization. The coupling between chiral secondary homopropargylic alcohols **19** bearing a trimethylsilyl group at the triple bond and aldehydes **20** in the presence of iron(III) halides, provided (2,5,6-trialkyl-4-halo-5,6-dihydro-*2H*-pyran-3-

yl)trimethylsilane **21** in good yields. The protocol is highly stereoselective, affording cis-dihydropyran as a major isomer (*Scheme 5.2.5.*).[18]



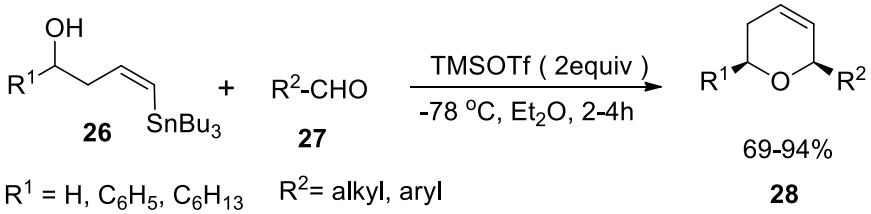
Scheme 5.2.5.

Hinkle and co-workers reported a tandem silyl-Prins reaction between *δ*-triethyl-silyloxyvinyltrimethylsilanes **23** and a variety of aldehydes **24** to afford *cis*-2,6-disubstituted dihydropyrans (DHPs) **25** using 5 mol % of $BiBr_3$ in CH_2Cl_2 (*Scheme 5.2.6.*).[19] The diastereoselectivities in the crude products are significantly affected by aldehyde substitution, with electron-rich aldehydes, providing 2-3:1 (*cis:trans*) and neutral (or electron-poor) aldehydes affording dr ≥ 19:1 (*cis:trans*).

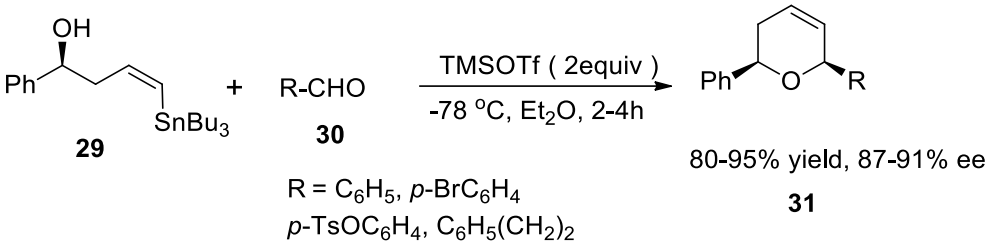


Scheme 5.2.6.

Furman and co-workers reported a stereoselective synthesis of *cis*-2,6-disubstituted dihydropyrans (DHPs) *via* stannyl-Prins cyclization. The reaction of vinylstannes **26** with aldehydes **27** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) afforded *cis*-2,6-disubstituted dihydropyrans **28** in good yields with excellent stereoselectivity (*Scheme 5.2.7.*).[20] Although the dihydropyrans are obtained in the racemic form but the use of optically pure vinylstanne afforded optically pure 2,6-disubstituted dihydropyrans (*Scheme 5.2.8.*). Finally, they applied this methodology for the synthesis of natural product (-)-centrolobine.

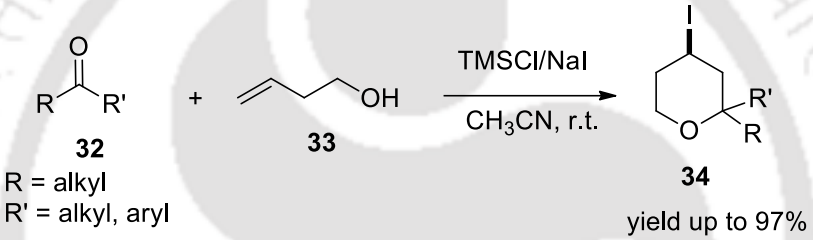


Scheme 5.2.7.



Scheme 5.2.8.

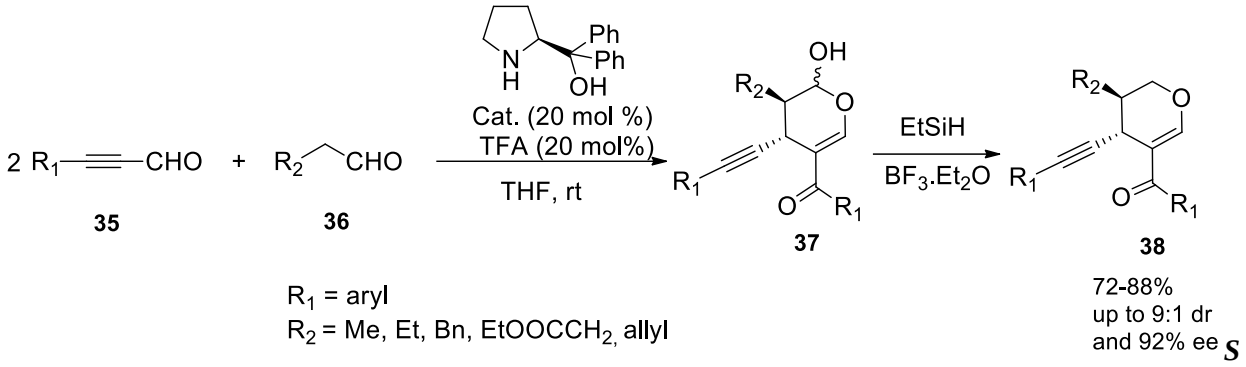
Sabitha *et al.* reported a protocol for Prins cyclization reaction from various ketones and homoallylic or homopropargylic alcohols in the presence of TMSI, generated in situ from TMSCl and NaI. The reaction was performed at room temperature to afford the corresponding 2,2-disubstituted-, spirocyclic-4-iodotetrahydropyrans and spirocyclic- 4-iodo-5,6-dihydro-2*H*-pyrans in good yields (*Scheme 5.2.9*).[21]



Scheme 5.2.9.

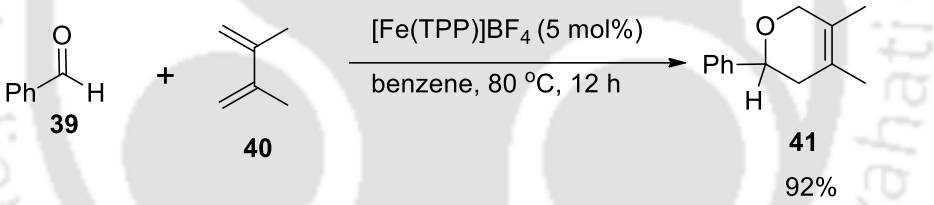
Apart from Prins cyclization, there are several other synthetic routes reported in the literature for the synthesis of dihydropyrans.

Sun and his group developed a novel strategy for one-pot formation of chiral polyfunctionalized 3,4-dihydropyrans through organocatalytic hydration/aldol/oxa-Diels Alder domino reaction method. Alkynl aldehyde **35** was reacted with aldehyde **36** in the presence of (*S*)-diphenylprolinol catalyst using TFA as an additive in THF at room temperature to furnish the 3,4-dihydropyran hemiacetal **37** and its diastereomer *syn*-**37**. The products **37** and *syn*-**37** were then reduced with $Et_3SiH/BF_3{\cdot}Et_2O$ to furnish chiral 3,4-dihydropyrans products **38** and *syn*-**38** with good to high yields, moderate to good diastereoselectivities, and high enantioselectivities. In this protocol, the self-condensation of alkynals was first time implemented under organocatalytic conditions (*Scheme 5.2.10*).[22]



cheme 5.2.10.

Kurahashi and co-workers reported an unprecedented hetero-Diels−Alder-type [4+2] cycloaddition for the synthesis of dihydropyrans from unactivated aldehydes and simple dienes. The reaction of aldehyde **39** with diene **40** in the presence of the cationic iron(III) porphyrin catalyst (5 mol %) in benzene at 80 °C for 12 h afforded the pyran motif **41** in excellent yield. In this protocol, the high functional group tolerance and robustness of the catalyst were shown. Further, the reaction was performed in water using unactivated ketone such as cyclohexanone with a diene to show the potential applicability of the catalyst (*Scheme 5.2.11*).[23]



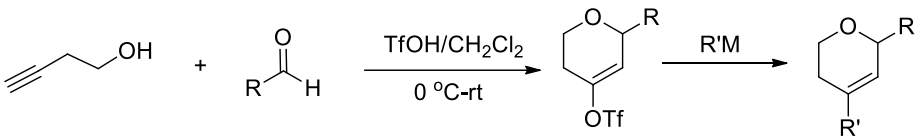
Scheme 5.2.11.

5.3. Present work

One-pot, multi component and selective reactions are considered as green synthetic routes.[24] Again, Prins cyclization[25] reactions are known for C-C and C-O bond forming reaction in a single step. Considering the importance of these reactions, herein, we report a one-pot, three component and highly selective Prins cyclization reaction for efficient synthesis of 3,6-dihydro-2*H*-pyran-4-yl trifluoromethane-sulfonates from homopropargylic alcohols and aldehydes mediated by triflic acid in which triflic acid acts as Brønsted acid as well as a nucleophile. In this work, we have developed an unprecedented Prins cyclization for the synthesis of dihydropyran that contains triflate group at the vinylic position of the ring. Triflates, present at vinylic position, in general, are valuable substrates owing to its importance for further functionalization. Metal catalyzed bond forming reactions and C-C bond forming reactions, such as Suzuki,[26] Heck,[27] Stille,[28] and Sonogashira[29] coupling reactions have been well explored starting from the triflate

derivatives. The dihydropyran thus formed is transformed into different 4-alkyl and aryl substituted products using Suzuki, Heck, Stille and Sonogashira coupling reactions.

The reaction can be generalized as shown in *Scheme 5.3.1*.

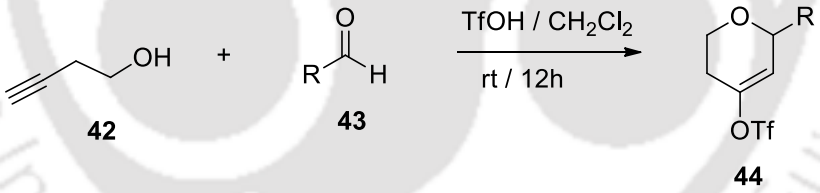


R = alkyl, aryl
R' = alkyl,aryl, alkene, alkyne

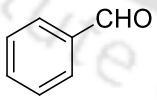
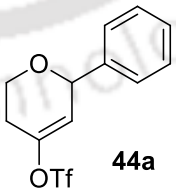
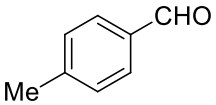
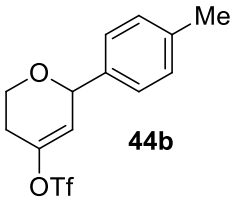
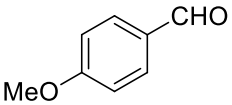
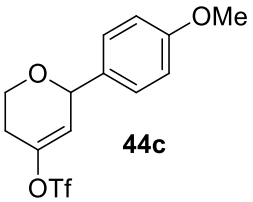
Scheme 5.3.1.

For this investigation, homopropargyl alcohol **42** (1.5 equiv) and benzaldehyde **43a** (1.0 equiv) were treated with 1.2 equivalents of triflic acid in dry dichloromethane at room temperature for 12 h and 3,6-dihydro-2-phenyl-2*H*-pyran-4-yl trifluoromethane-sulfonate **44a** was obtained in 92% yield. The reaction is regioselective and only 3,6-dihydropyran was formed in the reaction. The stereochemistry of the compound was determined by ^{1}H, ^{13}C, DEPT and HMQC analysis. Finally, the structure was confirmed by X-ray crystallographic analysis (*Figure 5.3.1*).[30] The scope of the reaction was examined with variety of aliphatic and aromatic aldehydes (*Table 5.3.1*).

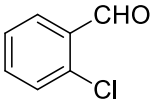
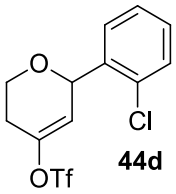
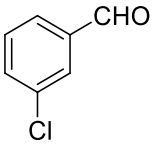
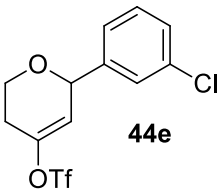
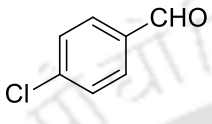
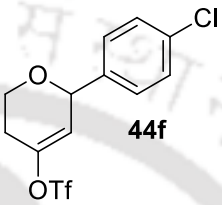
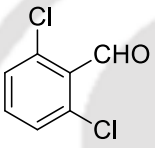
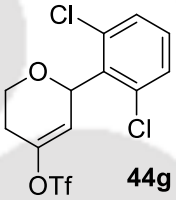
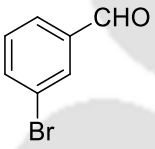
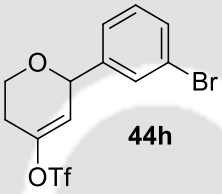
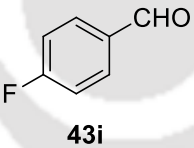
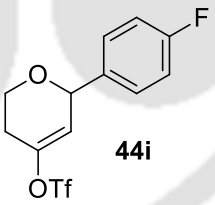
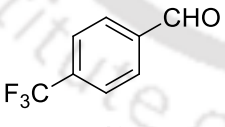
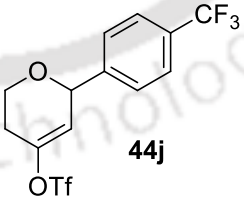
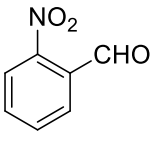
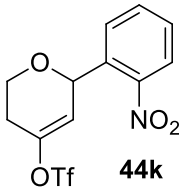
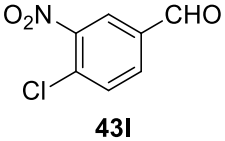
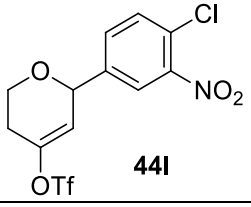
Table 5.3.1. Synthesis of dihydropyrans[a]



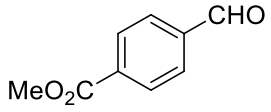
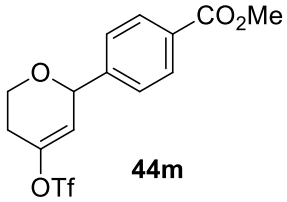
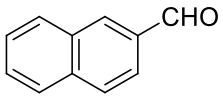
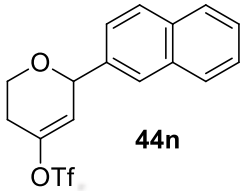
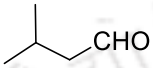
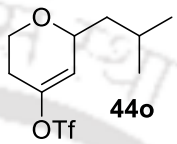
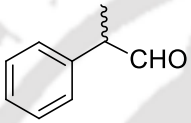
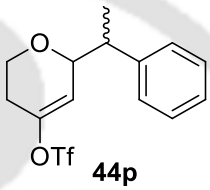
42 **43** **44**

Entry	Aldehyde **43**	Product **44**	Yield (%)[b]
1	 **43a**	 **44a**	92
2	 **43b**	 **44b**	80
3	 **43c**	 **44c**	d

Continue…

Entry	Aldehyde **43**	Product **44**	Yield (%)[b]
4	 **43d**	 **44d**	72
5	 **43e**	 **44e**	74
6	 **43f**	 **44f**	75
7	 **43g**	 **44g**	60
8	 **43h**	 **44h**	78
9	 **43i**	 **44i**	70
10	 **43j**	 **44j**	65
11	 **43k**	 **44k**	70
12	 **43l**	 **44l**	61

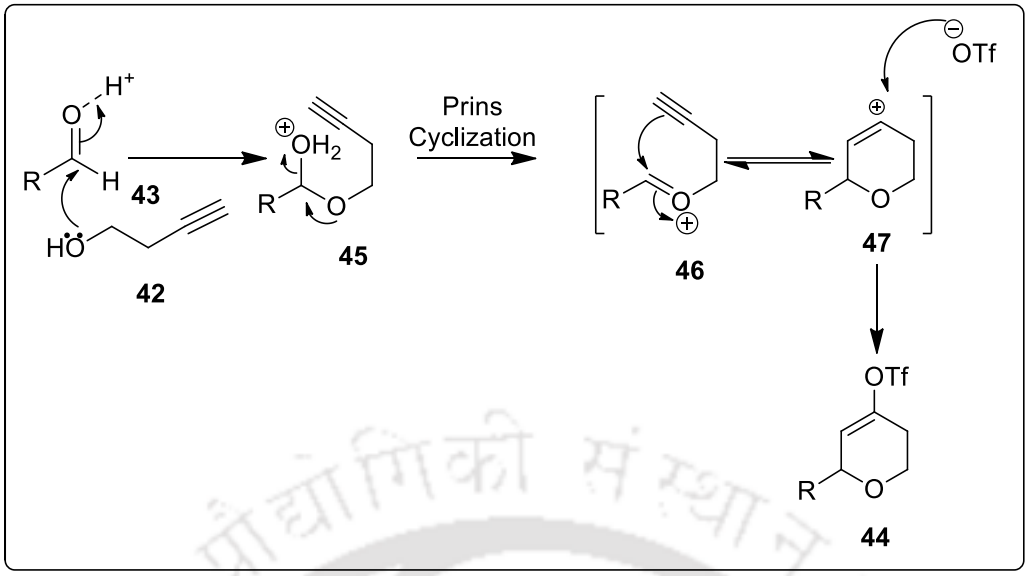
Continue….

Entry	Aldehyde **43**	Product **44**	Yield (%)[b]
13	 **43m**	 **44m**	72
14	 **43n**	 **44n**	73
15	 **43o**	 **44o**	67
16	 **43p**	 **44p**	64[b]

[a]Yields refer to isolated yield. Compounds are characterized by IR, NMR and mass spectrometry. d = decomposed. [b]Two inseparable diastereomeric mixture with a ratio of 2:1 determined by ^{1}H NMR.

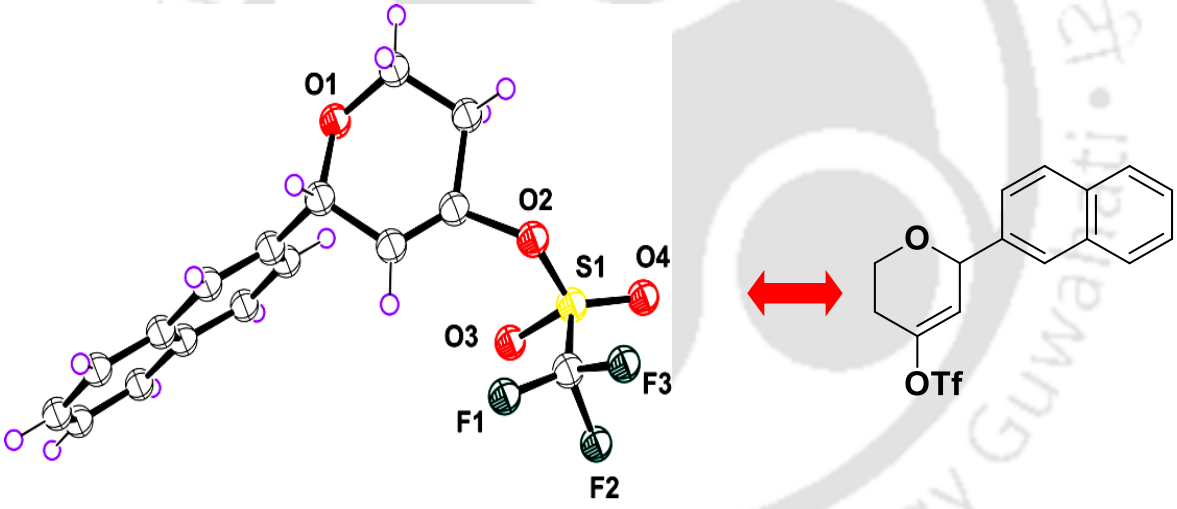
It was observed from the *Table 5.3.1.* that both aromatic and aliphatic aldehydes gave good yields. Aromatic aldehydes are better substrates than the aliphatic substrates. There is no major role of electron withdrawing and donating groups on the aromatic rings, both groups are providing comparable yields. To study the steric effect, *ortho*-, *meta*- and *para*-chlorobenazaldehydes (entries 4-6) were reacted with alcohol **42**, but the effect is not noticeable. On the other hand, highly sterically hindered 2,6-dichlorobenzaldehyde (entry 7) and 4-chloro-3-nitrobenzaldehyde (entry 12) gave low yields. 4-Methoxybenzaldehyde was found to be decomposed under these reaction conditions. Reaction of **43p** gave two inseparable diastereomers with a ratio of 2:1, which was determined by ^{1}H NMR.

The mechanism of the reaction can be explained as follows. The acidic proton activates the aldehyde for nucleophilic attack by homopropargylic alcohols to form oxocarbenium ion **46**, which after Prins cyclization generates carbocation **47**. The carbocation **47** is then attacked by triflate ion to give dihydropyran **44** (*Scheme 5.3.2*).



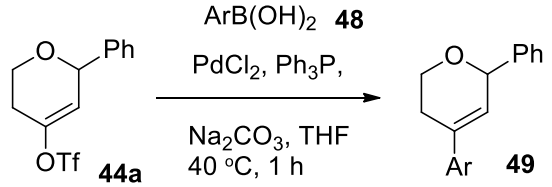
Scheme 5.3.2. Mechanism of the reaction

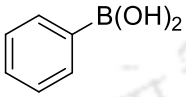
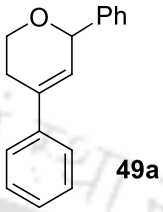
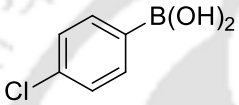
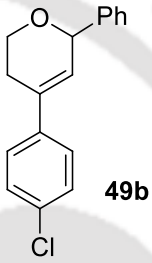
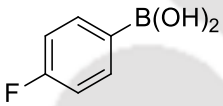
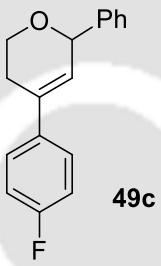
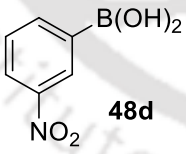
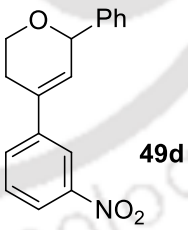
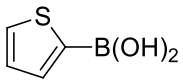
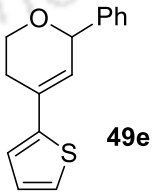
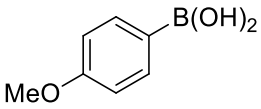
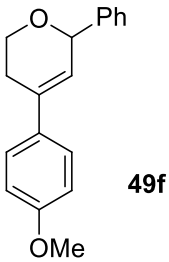
Figure 5.3.1. ORTEP diagram of compound **44n** with 50% ellipsoid probability



To explore this methodology, the reaction is further utilized for the synthesis of 4-arylated dihydropyrans. It may be noted that 4-arylated tetrahydropyrans are found in many biologically active natural products.[31] Generally, 4-aryl tetrahydropyrans are prepared by Prins-Friedel-Crafts reactions.[25b,c, 32] The major drawback of the existing methods is that the electron deficient aromatic rings cannot participate in this reaction. Therefore, use of triflates **44** as an arylating unit *via* Suzuki coupling would be a better alternative for introduction of various aryl groups including both electron donating and electron withdrawing groups. Thus, the reaction of **44a** with different aryl and heteroaryl boronic acids **48a-f** under Suzuki coupling conditions afforded 4-aryl- dihydropyrans **49a-f** in good yields (*Table 5.3.2*). Similarly, Heck, Stille and Sonogashira coupling of **44a** produce corresponding coupling products **50**, **51** and **52**, respectively, in excellent yields (*Scheme 5.3.3.-5.3.5*).

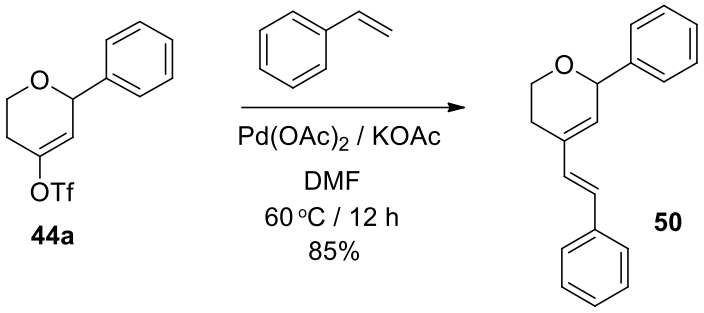
Table 5.3.2. Suzuki coupling reaction



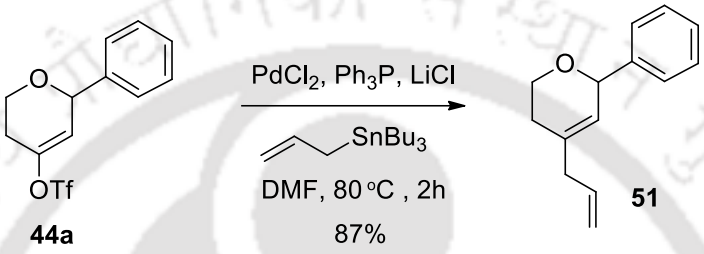
Entry	Boronic acid **48**	Product **49**	Yield (%)[a]
1	 **48a**	 **49a**	95
2	 **48b**	 **49b**	93
3	 **48c**	 **49c**	94
4	 **48d**	 **49d**	91
5	 **48e**	 **49e**	92
6	 **48f**	 **49f**	90

[a]Yields refer to isolated yield. Compounds are characterized by IR, NMR and mass spectrometry.

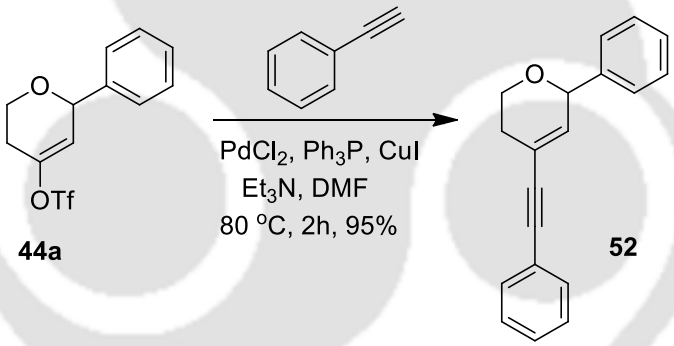
Scheme 5.3.3. Heck coupling reaction



Scheme 5.3.4. Stille coupling reaction



Scheme 5.3.5. Sonogashira coupling reaction



Conclusions

In conclusion, we have developed one-pot, three component, mild and efficient method for the synthesis of 4-trifluoromethanesulfonate substituted dihydropyrans *via* Prins cyclization reaction in good yields. The reaction is compatible with a wide range of functional groups such as ester, ether, nitro, and bromo. The important aspect of this reaction is that it introduces trifluoromethanesulfonate group at 4-position of the dihydropyrans, which can be used for subsequent coupling reactions such as Suzuki, Heck, Stille and Sonogashira coupling reactions.

5.4. Experimental Section

5.4.1. Instrumentation and Characterization

As described in chapter 2 section 2.4.1

5.4.2. General Procedure for the formation of 4-trifluoromethanesulfonate 3,6-dihydropyan 44:

To a stirring solution of aldehyde (1.0 equiv) and 3-butyn-1-ol (1.5 equiv) in dry dichloromethane (5.0 mL/mmol) was added triflic acid (1.2 equiv) dropwise at 0 ^{o}C. The reaction mixture was brought to room temperature and stirred for a specific time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (5.0 mL). The product was extracted with CH_2Cl_2 (2 x 10.0 mL) and washed with brine. Organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using rotary evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluents to afford the cyclic compounds.

Synthesis of 6-phenyl-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate (44a).

To a stirring solution of benzaldehyde **43a** (0.1 mL, 1 mmol) and 3-butyn-1-ol **42** (0.11 mL, 1.5 mmol) in CH_2Cl_2 (5 mL/mmol) was added TfOH (0.1 mL, 1.2 mmol) dropwise at 0 ^{o}C. The reaction mixture was brought to room temperature and stirred for 12 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, CH_2Cl_2 (10 mL) was added and the reaction mixture was washed with saturated sodium bicarbonatesolution and brine solution. The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using rotary evaporator to leave the crude product which was purified by column chromatography over silica gel using ethyl acetate and hexane as eluents to give 6-phenyl-3,6-dihydro-2*H*-pyran-4-yl trifluoromethanesulfonate **44a** as a colourless oil; R_f (hexane/ EtOAc 50:1) 0.20; yield 292 mg, 92%.

5.4.3. General procedure of Suzuki coupling reaction 49a-e:

To a solution of **44** (1.0 mmol) in THF (4.0 mL/mmol) were added PPh_3 (5 mol %), $PdCl_2$ (5 mol %), boronic acid **48** (1.56 mmol) and 2M aqueous solution of Na_2CO_3 (2.0 mL) under inert atmosphere. The reaction mixture was stirred at 40 ^{0}C for 1hr. Then water was added to reaction mixture and extracted with EtOAc (3×10 mL). Combined organic layer was dried and concentrated under reduced pressure. Residue obtained was purified by silica gel column chromatography using EtOAc/hexane as eluent to furnish the compound **49**.

Synthesis of 4,6-Diphenyl-3,6-dihydro-2*H*-pyran (49a):

To a solution of 3,6-dihydro-2-phenyl-2H-pyran-4-yl trifluoromethanesulfonate **44a** (308 mg, 1 mmol) in THF (4.0 mL/mmol) were added PPh_3(14 mg, 5 mol %), $PdCl_2$ (9 mg, 5 mol%), phenyl boronic acid **48a** (183 mg, 1.56 mmol) and 2M aqueous solution of Na_2CO_3 (2.0 mL) under inert atmosphere. The reaction mixture was stirred at 40 ^oC for 1h. Then water was added to reaction mixture and extracted with EtOAc (3×10 mL). Combined organic layer was dried and concentrated under reduced pressure. Residue obtained was purified by silica gel column chromatography using EtOAc/hexane as eluent to furnish the 2,4-diphenyl-3,6-dihydro-2*H*-pyran **49a** as a yellow oil; R_f (hexane/ EtOAc 50:1) 0.3; yield 224 mg, 95%.

5.4.4. Synthesis of 4-(4-methoxyphenyl)-6-phenyl-3,6-dihydro-2*H*-pyran (49f):

A mixture of **44a** (308 mg, 1.0 mmol), aqueous sodium carbonate (1.4 mL, 2.80 mmol), lithium chloride (125 mg, 2.98 mmol), $Pd(Ph_3P)_4$ (23 mg, 0.02 mmol), 4-methoxyphenylboronic acid **48f** (166 mg, 1.09 mmol), and THF (5 mL/mmol) was refluxed for 3 h. After completion of the reaction the solvent was removed by evaporation; water was added and the mixture was extracted with ethyl acetate (2x10 mL). Combined organic layer was dried and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (ethyl acetate/hexane, 1/4) to give **49f** as a pale yellow oil; R_f (hexane/ EtOAc 50:1) 0.40; yield 239 mg, 90%.

5.4.5. Synthesis of (*E*)-6-Phenyl-4-styryl-3,6-dihydro-2*H*-pyran (50):

To a solution of **44** (308 mg, 1.0 mmol) in DMF (10 mL/mmol) were added $Pd(OAc)_2$ (11 mg, 5 mol%) and AcOK (196 mg, 2 mmol) under inert atmosphere. The reaction mixture was stirred at 60 ^oC for overnight. Then water was added to reaction mixture and extracted with EtOAc (3×10 mL). Combined organic layer was dried and concentrated under reduced pressure. Residue obtained was purified by silica gel column chromatography using EtOAc/Pet. ether as eluent to furnish the compound **50** as a yellow oil; R_f (hexane/ EtOAc 50:1) 0.35; yield 222 mg, 85%.

5.4.6. Synthesis of 4-allyl-6-phenyl-3,6-dihydro-2*H*-pyran (51):

A dried reaction tube was charged with triflate **44** (308 mg, 1mmol). To this PPh_3 (14 mg, 5 mol%), $PdCl_2$ (9 mg, 5 mol %) was added and reaction tube was evacuated. Then LiCl (126 mg, 3 mmol), dry DMF (10 mL/mmol) and allyltributylstannane (397 mg, 1.21mmol) were added under nitrogen atmosphere. Reaction mixture was heated at 80 ^oC for 2 h. Reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (4×5 mL). Combined organic layer was dried and concentrated under reduced pressure. Residue obtained was purified by silica

gel column chromatography using EtOAc/hexane as eluent to furnish 4-allyl-3,6-dihydro-2-phenyl-2*H*-pyran **51** (174 mg, 87%) as yellow oil; R_f (hexane/ EtOAc 50:1) 0.35; yield 174 mg, 87%.

5.4.7. Synthesis of 6-phenyl-4-(phenylethynyl)-3,6-dihydro-2*H*-pyran (52):

A dried reaction flask was charged with triflate **44** (308 mg, 1.0 mmol). To this PPh_3 (14 mg, 5 mol %), $PdCl_2$ (9 mg, 5 mol %), CuI (19 mg, 1 mol %) were added and the reaction flask was evacuated. Then Et_3N (2.5 mL, 18 mmol), dry DMF (10 mL/mmol) and phenyl acetylene (0.17 ml, 1.58 mmol) were added under nitrogen atmosphere. Reaction mixture was heated at 80 ^oC for 2 h. Reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (4×5 mL). Combined organic layer was dried and concentrated under reduced pressure. Residue obtained was purified by silica gel column chromatography using EtOAc/hexane as eluent to furnish the 6-phenyl-4-(phenylethynyl)-3,6-dihydro-2H-pyran **52** (247 mg, 95 %) as a yellow oil; R_f (hexane/ EtOAc 50:1) 0.35; yield 247mg, 95%.

5.5. References

1. (a) Tieze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Yus, D. J.; Ramon, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602. (c) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (d) *Multicomponent Reaction*; Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005.
2. (a) Strubing, D.; Neumann, H.; Hubner, S.; Klaus, S.; Beller, M. *Tetrahedron* **2005**, *61*, 11345. (b) Nair, V.; Sreekumar, V.; Bindu, S.; Suresh, E. *Org. Lett.* **2005**, *7*, 2297.
3. (a) Souto, M. L.; Gavin, J. A.; Manriquez, C. P.; Norte, M.; Fernandez, J. J. *Tetrahedron* **2001**, *57*, 3117. (b) Soriente, A.; De Rosa, M. M.; Scettri, A.; Sodano, G.; Terencio, M. C.; Paya, M.; Alcarez, M. *Curro Med. Chem.* **1999**, *6*, 415.
4. (a) Kinashi, H.; Otake, N.; Yonehara, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1973**, *49*, 4955. (b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000,** *100*, 2407.
5. (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (c) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911. (d) Li, C.-J.; Zhang, W.-C. *Tetrahedron* **2000**, *56*, 2403. (e) Schmidt, B.; Westhus, M. *Tetrahedron* **2000**, *56*, 2421. (f) Pham, M.; Allatabakhsh, A.; Minehan, T. G. *J. Org. Chem.* **2008**, *73*, 741. (g) Miranda, P. O.; Diaz, D. V. ; Padrón, J. I. ; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003**, *5*, 1979.
6. (a) Donslund, B. S.; Monleón, A.; Ibsen, L. Jørgensen, K. A. *Chem. Commun.* **2015**, *51*, 13666. (b) Mack, D. J.; Guo, B.; Njardarson, J. T. *Chem. Commun.* **2012**, *48*, 7844. (c) Chouthaiwale, P. V.; Tanaka, F. *Chem. Commun.* **2014**, *50*, 14881. (d) Mori-Quiroz, L.

M.; Maleczka, R. E. Jr. *J. Org. Chem.* **2015**, *80*, 1163. (e) Sun, S.; Cheng, C.; Yang, J.; Tahery, A.; Jiang, D.; Zhang B.; Gu, Y. *Org. Lett.* **2014**, *16*, 4520. (f) Peh, G. R.; Floreancig, P. E. *Org. Lett.* **2015**, *17*, 3750. (g) Isobe, M.; Chang, W.C.; Tsou, P.-K.; Ploysuk, C.; Yu, C.-H. J. *Org. Lett.* **2015**, *80*, 6222. (h) Weise, C. F.; Lauridsen, V. H.; Rambo, R. S.; Iversen, E. H.; Olsen, M.-L.; Jørgensen, K. A. *J. Org. Chem.* **2014**, *79*, 3537.

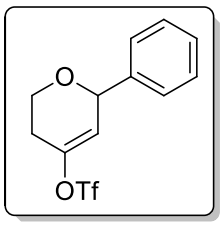
7. (a) Sako, S.; Kurahashi, T.; Matsubara, S. *Chem. Commun*. **2011**, *47*, 6150. (b) Li, Z.; Jung, H.; Park, M.; Lah, M. S.; Koo, S. *Adv. Synth. Catal*. **2011**, *353*, 1913. (c) Fujiwara, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc*. **2012**, *134*, 5512. (d) Chaladaj, W.; Kowalczyk, R.; Jurczak, J. *J. Org. Chem*. **2010**, *75*, 1740. (e) Mal, K.; Das, S.; Maiti, N. C.; Natarajan, R.; Das, I. *J. Org. Chem*. **2015**, *80*, 2972.
8. (a) Schmidt, B.; Wildemann, H. *J. Org. Chem.* **2000**, *65*, 5817. (b) Wildemann, H.; Dünkelmann, P.; Müller, M.; Schmidt, B. *J. Org. Chem.* **2003**, *68*, 799. (c) Donnard, M.; Tschamber, T.; Nouën, D. L.; Desrat, S.; Hinsinger, K.; Eustache, J. *Tetrahedron* **2011**, *67*, 339.
9. (a) de la Pradilla, R. F.; Tortosa, M. *Org. Lett*. **2004**, *6*, 2157. (b) de la Pradilla, R. F.; Tortosa, M.; Lwoff, N.; del Águila, M. A.; Viso, A. *J. Org. Chem*. **2008**, *73*, 6716.
10. (a) Bonbdalapati, S.; Reddy, U. C.; Saha, P.; Saikia, A. K. *Org. Biomol. Chem*. **2011**, *9*, 3428. (b) Saha, P.; Ghosh, P.; Sultana, S.; Saikia, A. K. *Org. Biomol. Chem*. **2012**, *10*, 8730.
11. (a) Huang, H.; Panek, J. S. *J. Am. Chem. Soc*. **2000**, *122*, 9836. (b) Yao, W.; Dou, X.; Lu, Y. *J. Am. Chem. Soc*. **2015**, *137*, 54.
12. Ghosh, P.; Saha, P.; Bondalapati, S.; Indukuri, K.; Saikia, A. K. *J. Org. Chem*. **2014**, *79*, 4119.
13. (a) Arundale, E.; Mikeska, L. A. *Chem. Rev*. **1952**, *52*, 505. (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661. (c) Snider, B. B. In *The Prins Reaction and Carbonyl Ene Reactions*; Trost, B. M.; Fleming, I.; Heathcock, C. H.; Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527. (d) Overman, L. E.; Pennington, L. D. *J. Org. Chem*. 2003, 68, 7143. (e) Yadav, V. K.; Kumar, N. V. *J. Am. Chem. Soc*. **2004**, *126*, 8652. (f) Yadav, J. S.; Thrimurtulu, N.; Lakshmi, K. A.; Prasad, A. R.; Reddy, B. V. S. *Tetrahedron Lett.* **2010**, *51*, 661. (g) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett*. **2002**, *4*, 577.
14. Li, J.; Li, C. J. *Tetrahedron Lett.* **2001**, *42*, 793.
15. Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N.; Reddy, G. M. *Tetrahedron Lett.* **2007**, *48*, 4903.

16. Viswanathan, G. S.; Yang, J.; Li, C. J. *Org. Lett.* **1999**, *1*, 993.
17. Liu, F.; Loh, T. P. *Org. Lett.* **2007**, *9*, 2063.
18. Miranda, P. O.; Ramírez, M. A.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2006**, *8*, 1633.
19. Lian, Y.; Hinkle, R. J. *J. Org. Chem.* **2006**, *71*, 7071.
20. Dziedzic, M.; Furman, B. *Tetrahedron Lett.* **2008**, *49*, 678.
21. Sabitha, G.; Reddy, K. B.; Bhikshapathi, M.; Yadav, J. S. *Tetrahedron Lett*. **2006**, *47*, 2807.
22. Dong, L. J.; Fan, T. T.; Wang, C.; Sun, J. *Org. Lett.* **2013**, *15*, 204.
23. Fujiwara, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2012**, *134*, 5512.
24. (a) Warner, J. C.; Cannon, A. S.; Dye, K. M. *Environment Impact Assesment Review* **2004**, *24*, 775; (b) Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438.
25. Reddy, U. C.; Raju, B. R.; Kumar, E. K. P.; Saikia, A. K. *J. Org. Chem*. **2008**, *73*, 1628. (b) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *Eur. J. Org. Chem*. **2009**, 1625. (c) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *J. Org. Chem*. **2009**, *74*, 2605. (d) Reddy, Borah, M.; Gogoi, P.; Indukuri, K.; Saikia, A. K. *J. Org. Chem*. **2015**, 80, 2641. (e) Saikia, A. K.; Indukuri, K.; Das, J. *Org. Biomol. Chem*. **2014**, *12*, 7026. (f) Indukuri, K.; Unnava, R.; Deka, M. J.; Saikia, A. K. *J. Org. Chem*. **2013**, *78*, 10629. (g) Gogoi, P.; Das, V. K.; Saikia, A. K. *J. Org. Chem*. **2014**, *79*, 8592. (h) Van Orden, L. J.; Patterson, B. D.; Rychnovsky, S. D. *J. Org. Chem.* **2007**, *72*, 5784. (i) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (j) Tadpetch, K.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 4839. (k) Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499.
26. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101. (c) Umei, K.; Nishigaya, Y.; Kamiya, M.; Kohno, Y.; Seto, S. *Synthesis* **2015**, *47*, 3221.
27. Crisp, G. T.; Glink, P. T. *Tetrahedron* **1992**, *48*, 3541.
28. Mee, S. P. H; V. V.; Baldwin, J. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 1132.
29. Wu, X.-F.; Sundararaju, B.; Neumann, H.; Dixneuf, P. H.; Beller, M. *Chem. Eur. J.* **2011**, *17*, 106.
30. The crystallographic data for compound **44n** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. **CCDC 1433323**.
31. Tian, X.; Rychnovsky, S. D. *Org. Lett*. **2007**, *9*, 4955. (b) Washio, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2007**, *18*, 2606.
32. Tian , X.; James J. Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176. (b) Dintzner, M. R.; Maresh, J. J.; Kinzie, C. R.; Arena, A. F.; Speltz, T. *J. Chem. Educ.* **2012**, *89*, 265. (c) Indukuri, K.; Bondalapati, S.; Kotipalli, T.; Gogoi, P.; Saikia, A. K.

Synlett **2012**, *23*, 233. (d) Reddy, U. C.; Saikia, A. K. *Synlett* **2010**, 1027-1032. (e) Dintzner, M. R. *Synlett* **2013**, *24*, 1091.

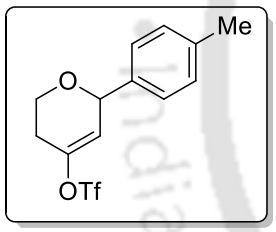
5.6. Characterization Data:

6-phenyl-3,6-dihydro-2*H*-pyran-4-yl trifluoromethanesulfonate (44a):



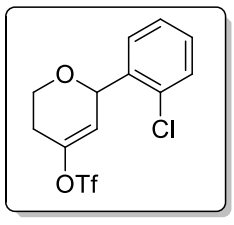
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.20; yield 292 mg, 92%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.05 (dd, *J* = 12.0 and 6.0 Hz, 1 H), 2.68-2.73 (m, 1 H), 3.86 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.11 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.26 (d, *J* = 4.0 Hz, 1 H), 5.93 (s, 1 H), 7.34-7.38 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.5, 63.1, 75.8, 118.7 (q, *J* = 318.0 Hz), 120.2, 127.8, 128.9, 128.9, 139.0, 146.9; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 2.03 (s, -F); **IR** (KBr, neat) 2929, 2869, 1690, 1455, 1422, 1351, 1246, 1141, 1029, 894, 762 cm^{-1}; **HRMS** (ESI) calcd. for $C_{12}H_{12}F_3O_4S$ $(M + H)^+$ 309.0403, found 309.0408.

6-(*p*-Tolyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoromethane-sulfonate (44b):



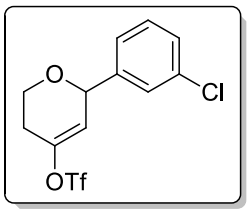
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.21; yield 257mg, 80%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 2.40 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 2.65-2.70 (m, 1 H), 3.83 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.11 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.22 (d, *J* = 4.0 Hz, 1 H), 5.91 (s, 1 H), 7.18 (d, *J* = 7.2 Hz, 2 H), 7.23 (d, *J* = 7.2 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.3, 28.5, 62.9, 75.5, 118.7 (q, *J* = 318.0 Hz), 120.3, 127.7, 129.6, 136.0, 138.8, 146.8; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 1.99 (s, -F); **IR** (KBr, neat) 2926, 2866, 1689, 1420, 1349, 1212, 1142, 1071, 899, 816 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{14}F_3O_4S$ $(M + H)^+$ 323.0559, found 323.0565.

6-(2-Chlorophenyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoro-methanesulfonate (44d):



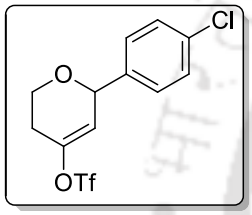
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.2; yield 246 mg, 72%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.38 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 2.70-2.76 (m, 1 H), 3.88 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.16 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.70 (d, *J* = 4.0 Hz, 1 H), 5.90 (s, 1 H), 7.24-7.29 (m, 2 H), 7.39 (dd, *J* = 7.2 and 4.0 Hz, 1 H), 7.45 (d, *J* = 7.2 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 28.4, 63.4, 72.4, 117.4 (q, *J* = 319.5 Hz), 119.7, 127.3, 128.9, 129.9, 130.0, 133.1, 136.4, 147.1; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 2.01 (s, -F); **IR** (KBr, neat) 2928, 2872, 1690, 1420, 1219, 1142, 1065, 764 cm^{-1}; **HRMS** (ESI) calcd. for $C_{12}H_{11}ClF_3O_4S$ (M + H)+ 343.0013, found 343.0010.

6-(3-Chlorophenyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoro-methanesulfonate (44e):



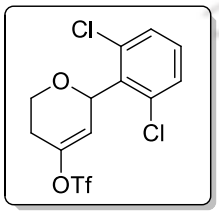
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.2; yield 253 mg, 74%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.41 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 2.66-2.73 (m, 1 H), 3.86 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.11 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.24 (d, *J* = 4.0 Hz, 1 H), 5.90 (s, 1 H), 7.21-7.23 (m, 1 H), 7.31-7.32 (m, 2 H), 7.35 (d, *J* = 7.2 Hz, 1 H); **^{13}C NMR** (150 MHz, CDCl3) δ 28.4, 63.1, 75.0, 118.7 (q, *J* = 318.0 Hz), 119.7, 125.7, 127.9, 129.0, 130.2, 134.8, 141.1, 147.2; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 2.08 (s, -F); **IR** (KBr, neat) 2928, 2870, 1689, 1421, 1214, 1142, 1073, 875 cm^{-1}; **HRMS** (ESI) calcd. for $C_{12}H_{11}ClF_3O_4S$ (M + H)+ 343.0013, found 343.0035.

6-(4-Chlorophenyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoro-methanesulfonate (44f):



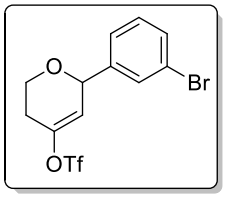
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.2; yield 256 mg, 75%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.42 (dd, *J* = 12.0 and 6.0 Hz, 1 H), 2.67-2.74 (m, 1 H), 3.86 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.16 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.25 (d, *J* = 6.0 Hz, 1 H), 5.89 (s, 1 H), 7.28 (d, *J* = 7.2 Hz, 2 H), 7.36 (d, *J* = 7.2 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.3, 63.0, 74.9, 115.4 (q, *J* = 318.0 Hz), 120.2, 129.0 (2C), 134.6, 137.6, 147.1; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 1.97 (s, -F); **IR** (KBr, neat) 2929, 2869, 1692, 1421, 1213, 1148, 1091, 1066, 900, 765, 613 cm^{-1}; **HRMS** (ESI) calcd. for $C_{12}H_{11}ClF_3O_4S$ $(M + H)^+$ 343.0013, found 343.0017.

6-(2,6-Dichlorophenyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoro-methanesulfonate (44g):



Colourless oil; R_f (hexane/ EtOAc 50:1) 0.19; yield 225mg, 60%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.38 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 2.81-2.91 (m, 1 H), 3.88 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.24 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 5.78 (s, 1 H), 5.97 (s, 1 H), 7.17 (t, *J* = 7.2 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 28.1, 65.2, 72.7, 118.6 (q, *J* = 318.0 Hz), 119.7, 129.6, 130.5, 133.1, 136.1, 146.9; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 1.91 (s, -F); **IR** (KBr, neat) 2923, 2857, 1659, 1437, 1219, 1119, 1052, 775 cm^{-1}; **HRMS** (ESI) calcd. for $C_{12}H_{10}Cl_2F_3O_4S$ $(M + H)^+$ 376.9623, found 376.9627.

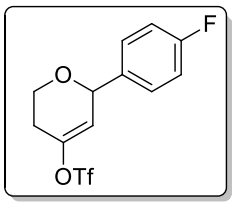
6-(3-Bromophenyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoro-methanesulfonate (44h):



Colourless oil; R_f (hexane/ EtOAc 50:1) 0.18; yield 301mg, 78%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.42 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 2.66-2.74 (m, 1 H), 3.87 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.11 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.24 (d, *J* = 4.0 Hz, 1 H), 5.90 (s, 1 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.46-7.51 (m, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 28.4, 63.1, 74.9, 118.6 (q, *J* = 319.5 Hz),

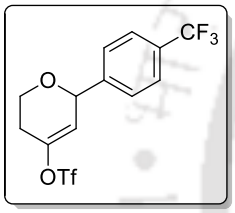
119.7, 122.9, 126.2, 130.5, 130.8, 131.9, 141.4, 147.2; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 2.04 (s, -F); **IR** (KBr, neat) 2871, 1690, 1420, 1213, 1141, 1072, 784 cm^{-1}; **HRMS** (ESI) calcd. for $C_{12}H_{11}{}^{79}BrF_3O_4S$ $(M + H)^+$ 386.9508, found 386.9520.

6-(4-Fluorophenyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoro-methanesulfonate (44i):



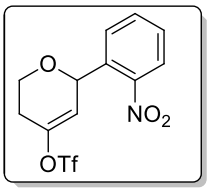
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.19; yield 228mg, 70%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.41 (dd, *J* = 12.0 and 6.0 Hz, 1 H), 2.67-2.74 (m, 1 H), 3.86 (ddd, *J* = 12.0, 6.0 and 6.0 Hz, 1 H), 4.11 (ddd, *J* = 12.0, 6.0 and 6.0 Hz, 1 H), 5.25 (d, *J* = 6.0 Hz, 1 H), 5.90 (s, 1 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 28.4, 63.0, 75.0, 115.7, 118.7 (q, *J* = 318.0 Hz), 119.9, 129.4, 134.9, 147.0, 163.0 (q, *J* = 246.0 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 2.06 (s, -F); **IR** (KBr, neat) 2925, 2869, 1690, 1421, 1219, 1141, 1071, 897, 775 cm^{-1}; **HRMS** (ESI) calcd. for $C_{12}H_{11}F_4O_4S$ $(M + H)^+$ 327.0309, found 327.0313.

6-(4-(Trifluoromethyl)phenyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoromethanesulfonate (44j):



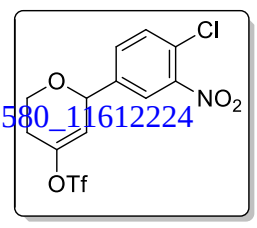
Pale yellow oil; R_f (hexane/ EtOAc 50:1) 0.20; yield 244mg, 65%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.42 (dd, *J* = 18.0 and 6.0 Hz, 1 H), 2.69-2.76 (m, 1 H), 3.90 (ddd, *J* = 12.0, 6.0 and 6.0 Hz, 1 H), 4.14 (ddd, *J* = 12.0, 6.0 and 6.0 Hz, 1 H), 5.33 (d, *J* = 6.0 Hz, 1 H), 5.92 (s, 1 H), 7.48 (d, *J* = 8.0 Hz, 2 H), 7.66 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 28.4, 63.3, 75.1, 118.7 (q, *J* = 319.5 Hz), 119.5, 121.9, 124.1 (q, *J* = 270.0 Hz), 126.0, 128.0, 130.3, 143.0, 147.3; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 2.20 (s, -F), 13.27 (s, -F); **IR** (KBr, neat) 2928, 2872, 1622, 1421, 1327, 1216, 1130, 1069, 858, 792 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{11}F_6O_4S$ $(M + H)^+$ 377.0277, found 377.0249.

6-(2-Nitrophenyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoro-methanesulfonate (44k):



Yellow oil; R_f (hexane/ EtOAc 50:1) 0.25; yield 247mg, 70%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.39 (dd, *J* = 18.0 and 6.0 Hz, 1 H), 2.79-2.85 (m, 1 H), 3.91 (ddd, *J* = 12.0, 6.0 and 6.0 Hz, 1 H), 4.22 (ddd, *J* = 12.0, 6.0 and 6.0 Hz, 1 H), 5.86 (d, *J* = 6.0 Hz, 1 H), 6.02 (s, 1 H), 7.50 (t, *J* = 7.2 Hz, 1 H), 7.66 (d, *J* = 7.2 Hz, 1 H), 7.73 (d, *J* = 7.2 Hz, 1 H), 7.98 (d, *J* = 7.2 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 28.3, 63.9, 71.4, 118.6 (q, *J* = 318.0 Hz), 119.9, 124.8, 129.3, 129.4, 133.9, 134.6, 147.1, 148.2; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 1.97 (s, -F); **IR** (KBr, neat) 2929, 2873, 1689, 1531, 1419, 1353, 1211, 1141, 1073, 901, 789, 751 cm^{-1}; **HRMS** (ESI) calcd. for $C_{12}H_{11}F_3NO_6S$ $(M + H)^+$ 354.0259, found 354.0259.

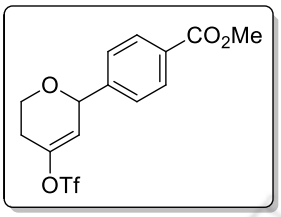
6-(4-Chloro-3-nitrophenyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoromethanesulfonate (44l):



Yellow oil; R_f (hexane/ EtOAc 50:1) 0.25; yield 236mg, 61%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.44 (dd, *J* = 18.0 and 6.0 Hz, 1 H), 2.70-2.76 (m, 1

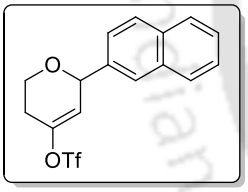
H), 3.90 (ddd, *J* = 12.0, 6.0 and 6.0 Hz, 1 H), 4.13 (ddd, *J* = 12.0, 6.0 and 6.0 Hz, 1 H), 5.33 (d, *J* = 4.0 Hz, 1 H), 5.90 (s, 1 H), 7.51 (d, *J* = 7.2 Hz, 1 H), 7.57 (d, *J* = 7.2 Hz, 1 H), 7.89 (d, *J* = 7.2 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 28.3, 63.3, 74.0, 118.6, 118.7 (q, *J* = 318.0 Hz), 124.6, 127.3, 131.9, 132.5, 139.8, 147.8, 148.2; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 2.1 (s, -F); **IR** (KBr, neat) 2927, 2873, 1690, 1539, 1421, 1353, 1214, 1141, 1073, 888, 792 cm^{-1}; **HRMS** (ESI) calcd. for $C_{12}H_9F_3NO_6SNa$ $(M + Na)^+$ 409.9689, found 409.9691.

Methyl 4-(4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydro-2*H*-pyran-2-yl)benzoate (44m):



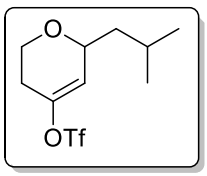
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.23; yield 263 mg, 72%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.41 (dd, *J* = 16.0 and 6.0 Hz, 1 H), 2.68-2.74 (m, 1 H), 3.88 (ddd, *J* = 12.0, 6.0 and 6.0 Hz, 1 H), 3.91 (s, 3 H), 4.12 (ddd, *J* = 12.0, 6.0 and 6.0 Hz, 1 H), 5.31 (s, 1 H), 5.91 (s, 1 H), 7.42 (d, *J* = 7.2 Hz, 2 H), 8.04 (d, *J* = 7.2 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 28.4, 52.4, 63.2, 75.2, 118.6 (q, *J* = 319.5 Hz), 119.7, 127.5, 130.2, 130.6, 144.0, 147.1, 166.8; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 2.07 (s, -F); **IR** (KBr, neat) 2925, 2850, 1725, 1690, 1418, 1282, 1213, 1142, 1113, 1072, 860, 771 cm^{-1}; **HRMS** (ESI) calcd. for $C_{14}H_{14}F_3O_6S$ $(M + H)^+$ 367.0458, found 367.0465.

6-(Naphthalen-2-yl)-3,6-dihydro-2*H*-pyran-4-yl trifluoro-methanesulfonate (44n):



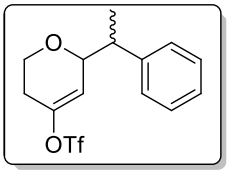
Colourless solid; mp 71-73 ºC R_f (hexane/ EtOAc 50:1) 0.20; yield 261mg, 73%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.42 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 2.67-2.83 (m, 1 H), 3.86 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.10 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.39 (d, *J* = 4.0 Hz, 1 H), 5.99 (s, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.47-7.50 (m, 2 H), 7.77 (s, 1 H), 7.81-7.85 (m, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 28.5, 62.9, 75.7, 118.7 (q, *J* = 318.0 Hz), 120.1, 125.2, 126.5, 126.6, 127.0, 127.9, 128.3, 128.9, 133.3, 133.5, 136.4, 147.0; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 2.04 (s, -F); **IR** (KBr, neat) 2976, 2868, 1689, 1464, 1422, 1244, 1114, 1058, 886, 757 cm^{-1}; **HRMS** (ESI) calcd. for $C_{16}H_{14}F_3O_4S$ $(M + H)^+$ 359.0559, found 359.0564.

6-Isobutyl-3,6-dihydro-2*H*-pyran-4-yl trifluoromethane-sulfonate (44o):



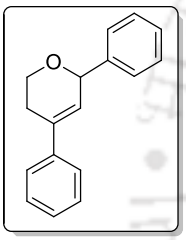
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.20; yield 193mg, 67%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 0.94 (s, 3 H), 1.27-1.32 (m, 1 H), 1.55-1.60 (m, 1 H), 1.79-1.87 (m, 1 H), 2.26 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 2.58-2.64 (m, 1 H), 3.71 (ddd, *J* = 12.0, 6.0 and 6.0 Hz, 1 H), 4.09 (ddd, *J* = 12.0, 6.0 and 6.0 Hz, 1 H), 4.27 (d, *J* = 6.0 Hz, 1 H), 5.72 (s, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 22.1, 23.3, 24.5, 28.6, 43.8, 63.2, 71.9, 117.6 (q, *J* = 318.0 Hz), 121.2, 146.4; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 2.05 (s, -F); **IR** (KBr, neat) 2960, 2872, 1690, 1442, 1211, 1143, 1072, 884, 614 cm^{-1}; **HRMS** (ESI) calcd. for $C_{10}H_{16}F_3O_4S$ $(M + H)^+$ 289.0721, found 289.0715.

6-(1-Phenylethyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoro-methanesulfonate (diastereomeric mixture, 2:1, 44p):



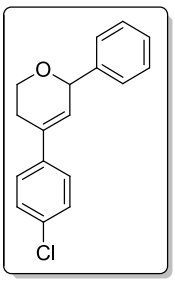
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.20; yield 215mg, 64%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.30 (d, *J* = 4.0 Hz, 3 H, minor), 1.35 (d, *J* = 8.0 Hz, 3 H, major), 2.07-2.12 (m, 1 H, minor), 2.16-2.24 (m, 1 H, major), 2.56-2.64 (m, 1 H), 2.82-2.89 (m, 1 H, major), 3.08-3.15 (m, 1 H, minor), 3.62-3.71 (m, 1 H), 4.09-4.13 (m, 1 H), 4.24-4.26 (m, 1 H, major), 4.36-4.37 (m, 1 H, minor), 5.54 (s, 1 H, major), 5.68 (s, 1 H, minor), 7.20-7.26 (m, 3 H), 7.29-7.35 (m, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 15.0, 17.0, 28.4, 43.6, 44.7, 63.4, 63.8, 78.1, 78.2, 118.6 (q, *J* = 319.5 Hz), 119.7, 126.9, 127.0, 128.0, 128.1, 128.6, 128.7, 142.1, 142.9, 147.0, 147.3; **^{19}F NMR** (376 MHz, $CDCl_3$/TFA) δ 1.9 (s, -F); **IR** (KBr, neat) 2972, 2873, 1690, 1420, 1213, 1143, 1073, 891, 763 cm^{-1}; **HRMS** (ESI) calcd. for $C_{14}H_{16}F_3O_4S$ $(M + H)^+$ 337.0716, found 337.0722.

4,6-diphenyl-3,6-dihydro-2*H*-pyran (49a):



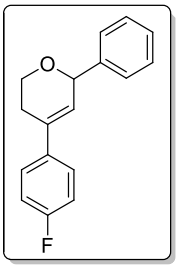
Yellow oil; R_f (hexane/ EtOAc 50:1) 0.3; yield 224 mg, 95%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.49 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 2.71-2.80 (m, 1 H), 2.92 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.19 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.31 (d, *J* = 4.0 Hz, 1 H), 6.22 (s, 1 H), 7.27-7.39 (m, 6 H), 7.41-7.45 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 27.2, 63.6, 76.9, 125.1, 125.5, 127.7, 127.8, 128.2, 128.6, 128.7, 135.0. 140.2, 141.5; **IR** (KBr, neat) 2924, 2853, 1600, 1493, 1263, 1120, 1029, 771 cm^{-1}; **HRMS** (ESI) calcd. for $C_{17}H_{17}O$ $(M + H)^+$ 237.1274, found 237.1277.

4-(4-Chlorophenyl)-6-phenyl-3,6-dihydro-2*H*-pyran (49b):



Pale yellow oil; R_f (hexane/ EtOAc 50:1) 0.28; yield 251 mg, 93%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.44 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 2.67-2.76 (m, 1 H), 3.91 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.19 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.29 (d, *J* = 4.0 Hz, 1 H), 6.20 (s, 1 H), 7.29-7.42 (m, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 27.2, 63.5, 76.8, 126.1, 126.4, 127.7, 128.2, 128.8 (2C), 133.5, 134.0, 138.6. 141.2; **IR** (KBr, neat) 2924, 2853, 1598, 1493, 1368, 1177, 1074, 762 cm^{-1}; **HRMS** (ESI) calcd. for $C_{17}H_{16}ClO$ $(M + H)^+$ 271.0884, found 271.0886.

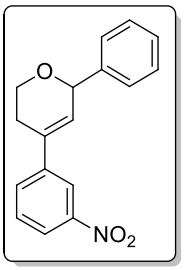
4-(4-Fluorophenyl)-6-phenyl-3,6-dihydro-2*H*-pyran (49c):



Pale yellow oil; R_f (hexane/ EtOAc 50:1) 0.25; yield 238 mg, 94%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.45 (dd, *J* = 16.0 and 4.0 Hz, 1 H), 2.68-2.77 (m, 1 H), 3.92 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.19 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.30 (d, *J* = 4.0 Hz, 1 H), 6.16 (s, 1 H), 7.03 (t, *J* = 8.0 Hz, 2 H), 7.29-7.43 (m, 7 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 27.3, 63.6, 76.9, 115.5 (d, *J* = 21.0 Hz), 125.4, 126.3 (d, *J* = 8.0 Hz), 127.8, 128.2, 128.7, 134.1, 136.3 (d, *J* = 3.3 Hz), 141.3, 162.5

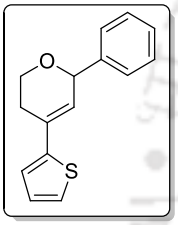
(d, *J* = 245.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$/TFA) δ -39.2 (s, -F); **IR** (KBr, neat) 2925, 2854, 1601, 1451, 1275, 1231, 1160, 1071, 836, 700 cm^{-1}; **HRMS** (ESI) calcd. for $C_{17}H_{16}FO$ $(M + H)^+$ 255.1180, found 255.1185.

4-(3-Nitrophenyl)-6-phenyl-3,6-dihydro-2*H*-pyran (49d):



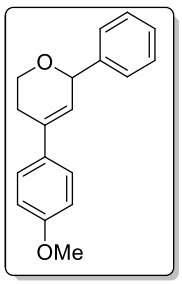
Yellow oil; R_f (hexane/ EtOAc 50:1) 0.30; yield 255 mg, 91%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.51 (dd, *J* = 16.0 and 4.0 Hz, 1 H), 2.76-2.85 (m, 1 H), 3.96 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.25 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.34 (d, *J* = 4.0 Hz, 1 H), 6.38 (s, 1 H), 7.31-7.43 (m, 5 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.76 (t, *J* = 8.0 Hz, 1 H), 8.13 (d, *J* = 8.0 Hz, 1 H), 8.28 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 27.0, 63.4, 76.8, 119.9, 122.4, 127.6, 128.4, 128.8, 129.6, 130.9, 133.1, 140.8, 141.8, 148.7; **IR** (KBr, neat) 2924, 2855, 1528, 1453, 1349, 1269, 1121, 1063, 892, 737 cm^{-1}; **HRMS** (ESI) calcd. for $C_{17}H_{16}NO_3$ $(M + H)^+$ 282.1125, found 282.1130.

6-Phenyl-4-(thiophen-2-yl)-3,6-dihydro-2*H*-pyran (49e):



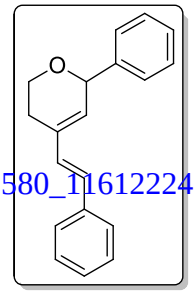
Yellow oil; R_f (hexane/ EtOAc 50:1) 0.30; yield 222 mg, 92%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.49 (dd, *J* = 16.0 and 4.0 Hz, 1 H), 2.71-2.78 (m, 1 H), 3.90 (ddd, *J* = 16.0, 8.0 and 4.0 Hz, 1 H), 4.15 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.28 (d, *J* = 4.0 Hz, 1 H), 6.20 (s, 1 H), 6.99 (t, *J* = 8.0 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 7.17 (d, *J* = 8.0 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.32-7.42 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 27.6, 63.3, 76.6, 122.5, 124.1, 127.5, 127.8, 128.2, 128.7, 129.7, 141.1, 144.8; **IR** (KBr, neat) 2924, 2854, 1639, 1453, 1361, 1263, 1116, 1062, 879, 698 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{15}OS$ $(M + H)^+$ 243.0844, found 243.0851.

4-(4-methoxyphenyl)-6-phenyl-3,6-dihydro-2*H*-pyran (49f):



Pale yellow oil; R_f (hexane/ EtOAc 50:1) 0.40; yield 239 mg, 90%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.51 (dd, *J* = 16.0 and 6.0 Hz, 1 H), 2.68-2.74 (m, 1 H), 3.80 (s, 3 H), 3.91 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.17 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.29 (d, *J* = 4.0 Hz, 1 H), 6.12 (s, 1 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 7.30 (t, *J* = 8.0 Hz, 1 H), 7.34-7.38 (m, 4 H), 7.42 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 27.3, 55.5, 63.7, 76.9, 114.0, 123.8, 126.2, 127.8, 128.1, 128.7, 132.8, 134.4, 141.7, 159.4; **IR** (KBr, neat) 2957, 2836, 1607, 1456, 1309, 1248, 1180, 1062, 1034, 832, 761, 700 cm^{-1}; **HRMS** (ESI) calcd. for $C_{18}H_{19}O_2$ $(M + H)^+$ 267.1385, found 267.1385.

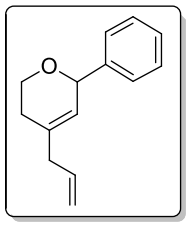
(*E*)-6-Phenyl-4-styryl-3,6-dihydro-2*H*-pyran (50):



Yellow oil; R_f (hexane/ EtOAc 50:1) 0.35; yield 222 mg, 85%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.38 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 2.53-2.62 (m, 1 H), 3.87 (ddd, *J* = 16.0, 8.0 and 4.0 Hz, 1 H), 4.15 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H),

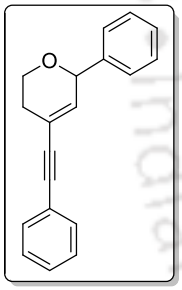
5.27 (d, *J* = 4.0 Hz, 1 H), 5.92 (s, 1 H), 6.57 (d, *J* = 16.0 Hz, 1 H), 6.81 (d, *J* = 16.0 Hz, 1 H), 7.20-7.25 (m, 1 H), 7.30-7.43 (m, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 25.0, 63.4, 76.9, 126.5, 127.3, 127.6, 127.7, 128.2, 128.7, 128.8, 130.2, 130.5, 134.2, 137.4, 141.3; **IR** (KBr, neat) 2924, 2853, 1593, 1492, 1274, 1118, 1092, 1012, 830, 699 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{19}O$ $(M + H)^+$ 263.1430, found 263.1436.

4-allyl-6-phenyl-3,6-dihydro-2*H*-pyran (51):



Yellow oil; R_f (hexane/ EtOAc 50:1) 0.35; yield 174 mg, 87%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.98 (dd, *J* = 16.0 and 4.0 Hz, 1 H), 2.25-2.33 (m, 1 H), 2.80 (d, *J* = 8.0 Hz, 2 H), 3.78 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.02 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.05-5.12 (m, 3 H), 5.56 (s, 1 H), 5.76-5.87 (m, 1 H), 7.27-7.37 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.4, 41.7, 63.5, 76.4, 116.8, 124.0, 127.6, 127.9, 128.6, 135.3, 135.7, 141.9; **IR** (KBr, neat) 2924, 2854, 1689, 1450, 1364, 1220, 1075, 771 cm^{-1}; **HRMS** (ESI) calcd. for $C_{14}H_{17}O$ $(M + H)^+$ 201.1274, found 201.1277.

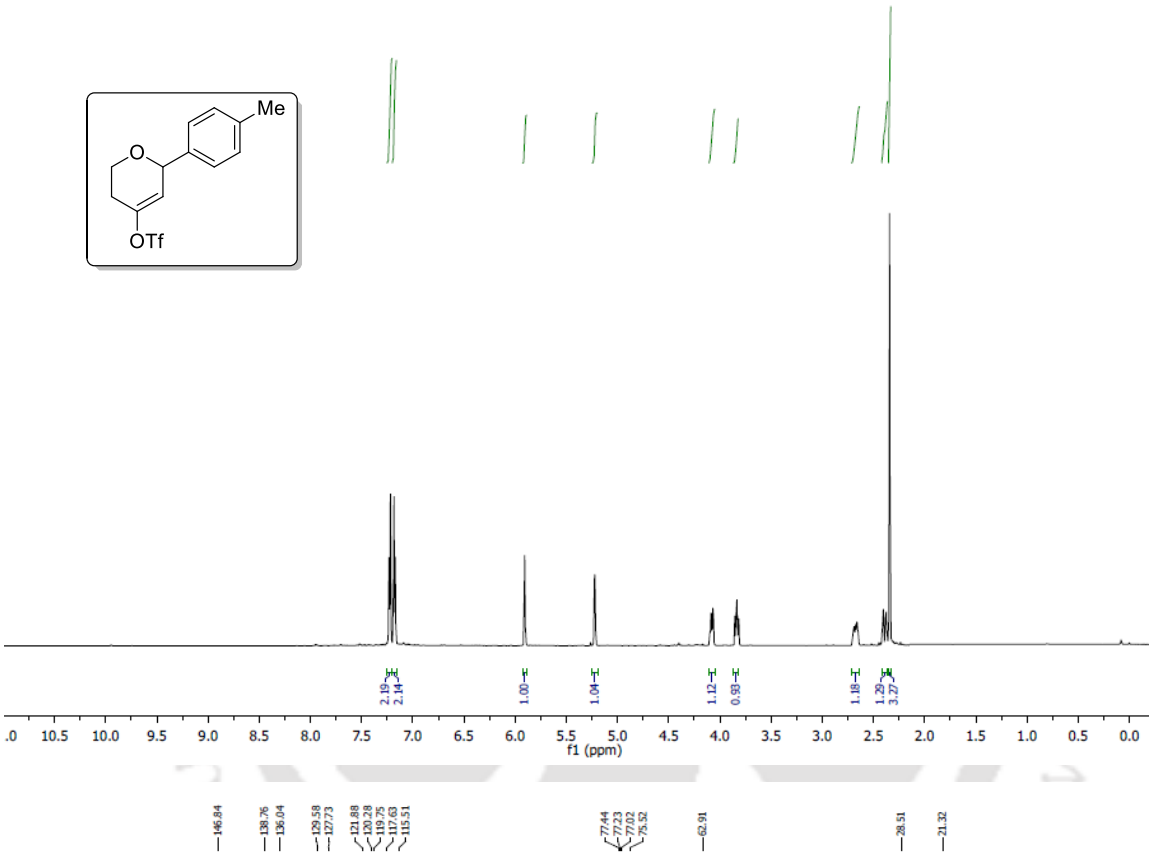
6-phenyl-4-(phenylethynyl)-3,6-dihydro-2*H*-pyran (52):

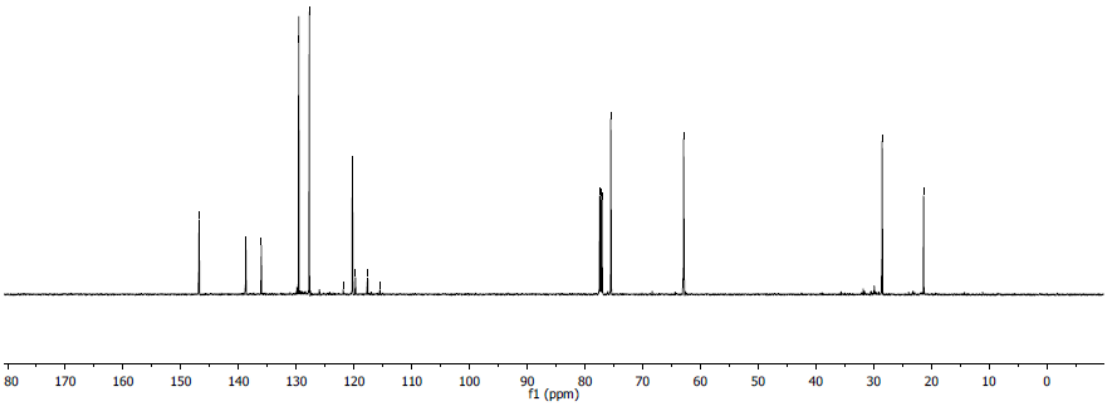


Yellow oil; R_f (hexane/ EtOAc 50:1) 0.35; yield 247mg, 95%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.28 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 2.53-2.62 (m, 1 H), 3.83 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 4.06 (ddd, *J* = 12.0, 8.0 and 4.0 Hz, 1 H), 5.23 (d, *J* = 4.0 Hz, 1 H), 6.25 (s, 1 H), 7.28-7.32 (m, 4 H), 7.33-7.40 (m, 4 H), 7.42-7.45 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 29.2, 63.2, 76.6, 89.1, 89.2, 119.6, 123.3, 127.7, 128.3, 128.4, 128.5, 128.8, 131.7, 135.2, 140.6; **IR** (KBr, neat) 2919, 2850, 1597, 1490, 1450, 1253, 1120, 1062, 756, 699 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{17}O$ $(M + H)^+$ 261.1274, found 261.1279.

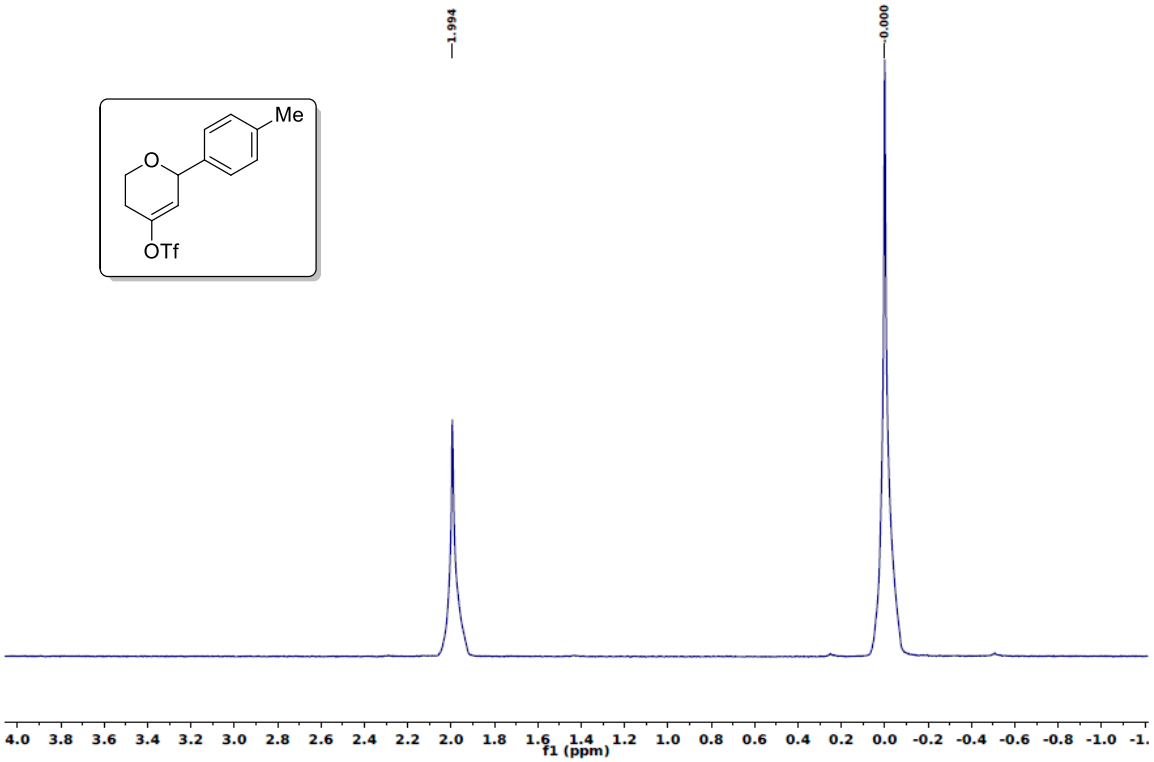
5.7. Selected Spectra

^{1}H and ^{13}C NMR Spectra of 6-(*p*-Tolyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoromethane-sulfonate (44b):

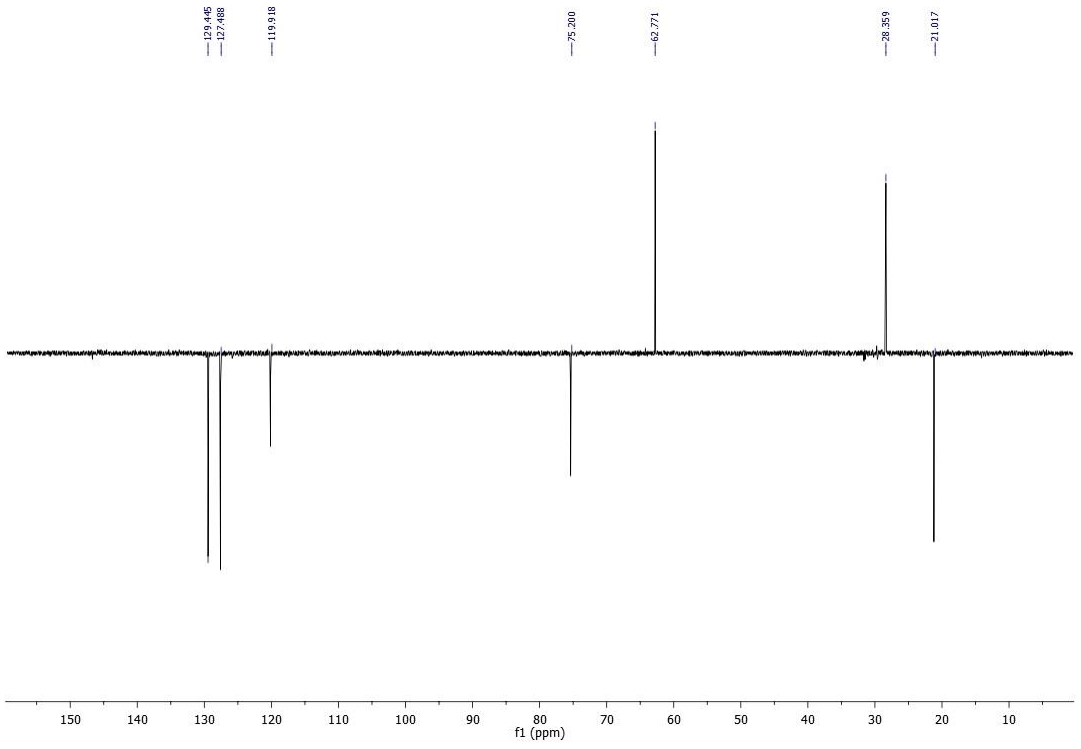




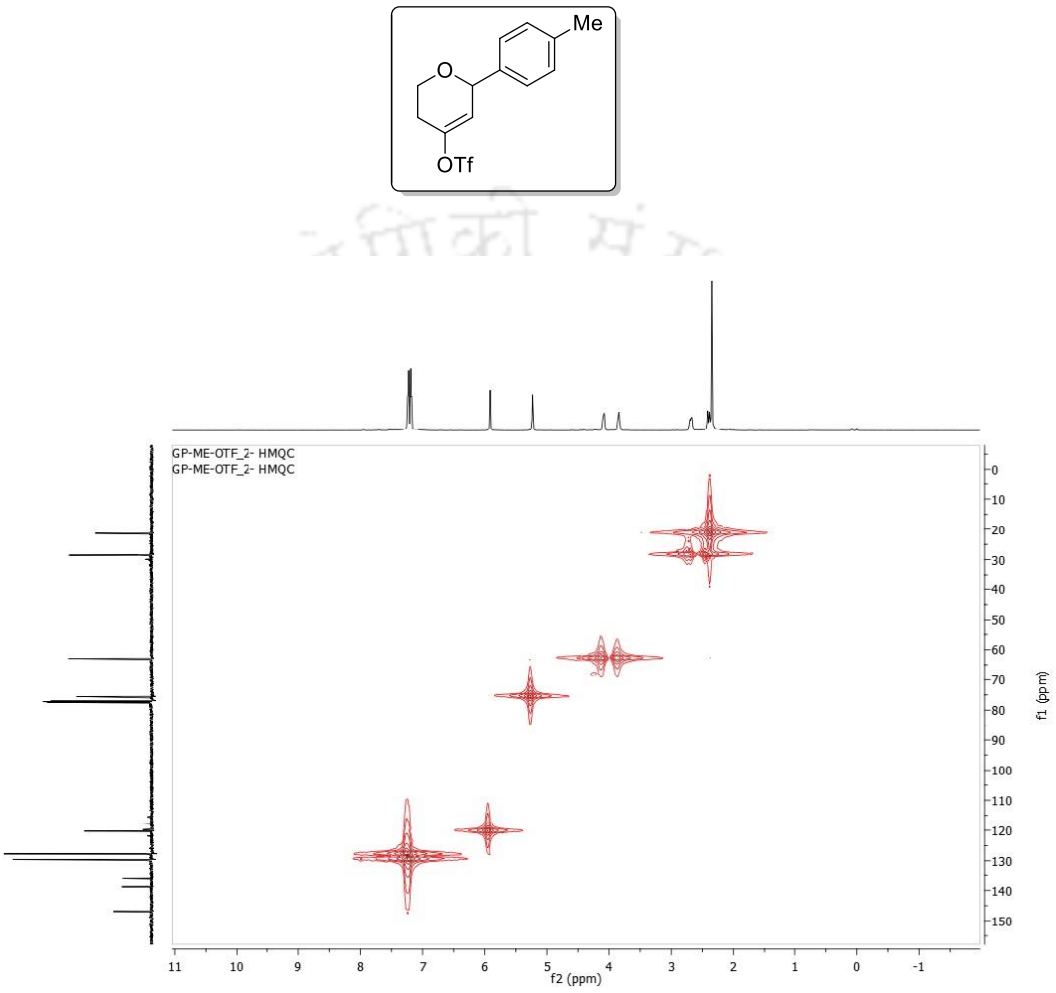
^{19}F NMR spectrum of 44b



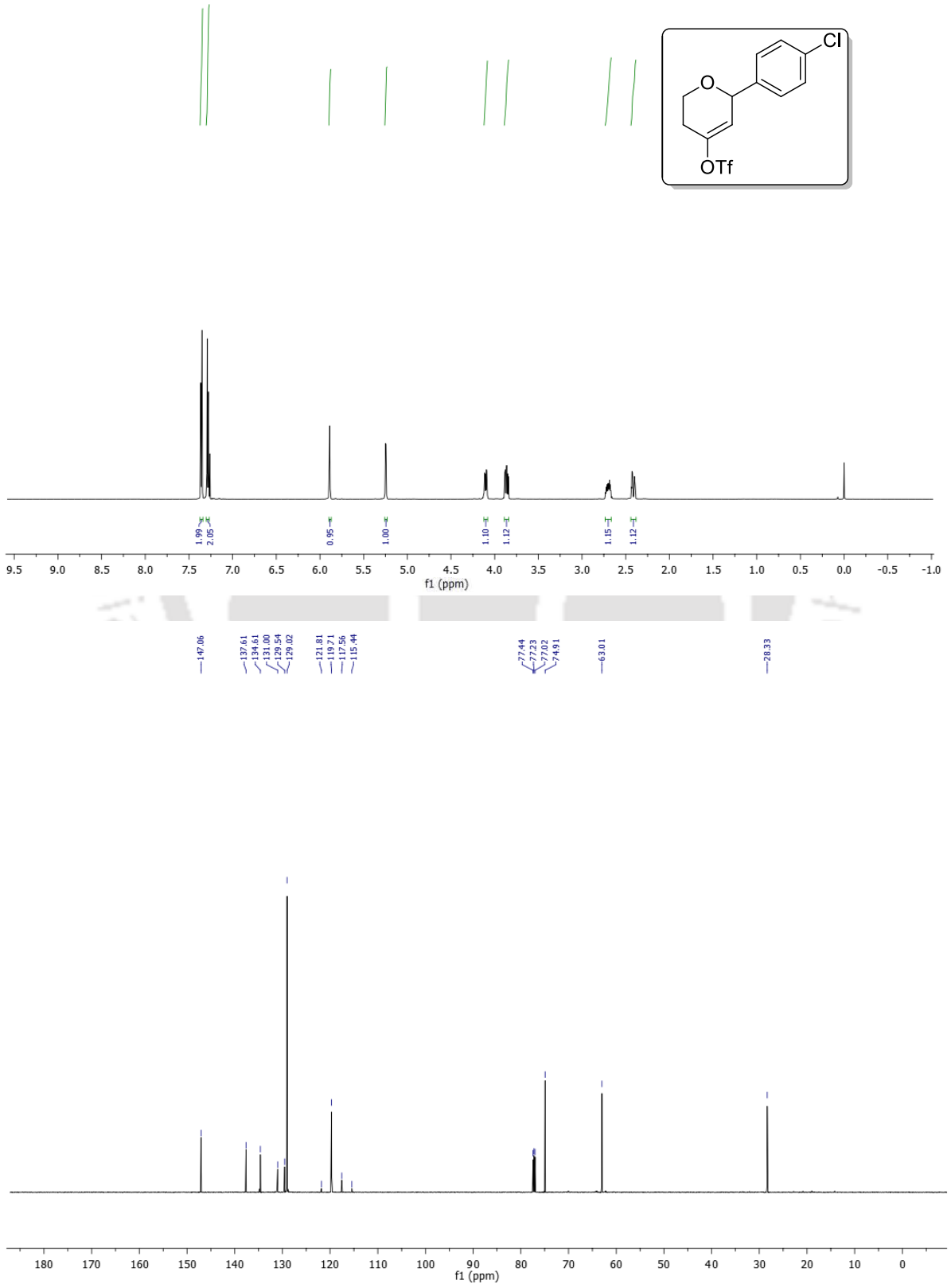
DEPT Spectra of 44b



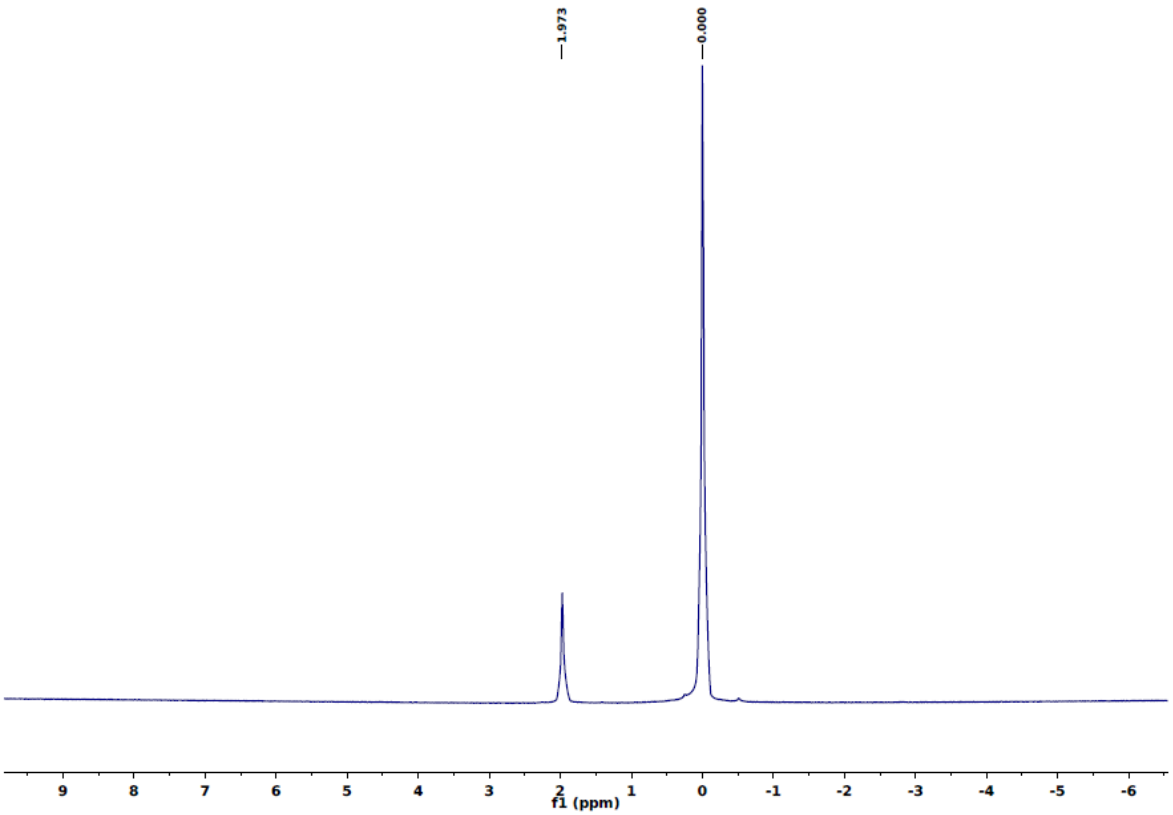
HMQC spectra of 44b



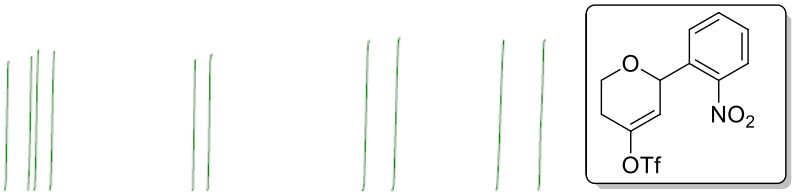
^{1}H NMR and ^{13}C NMR spectra of compound 6-(4-Chlorophenyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoro-methanesulfonate (44f):

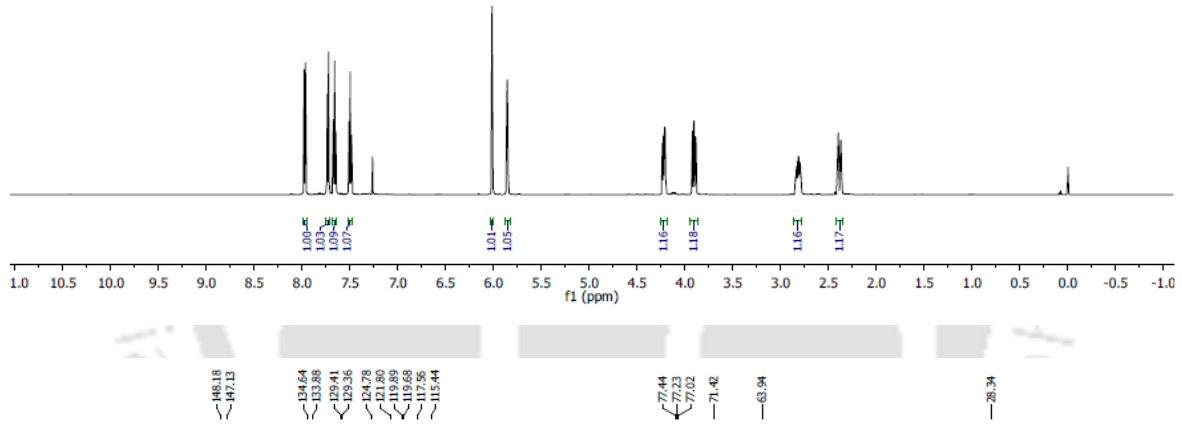


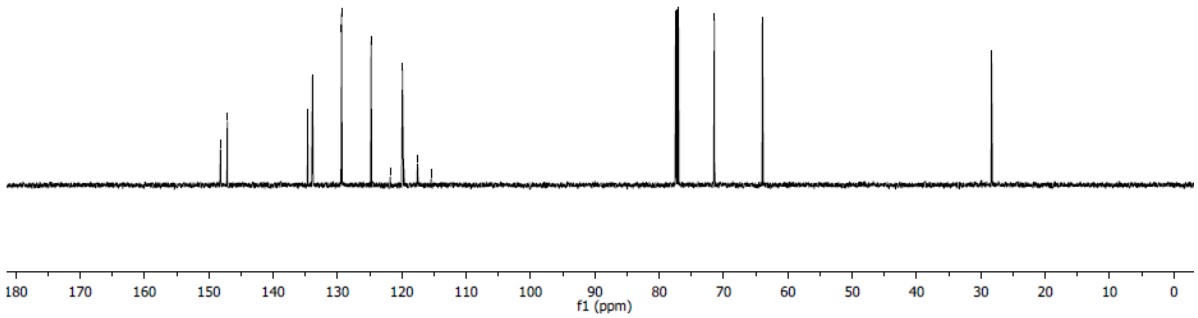
^{19}F NMR spectrum of 44f



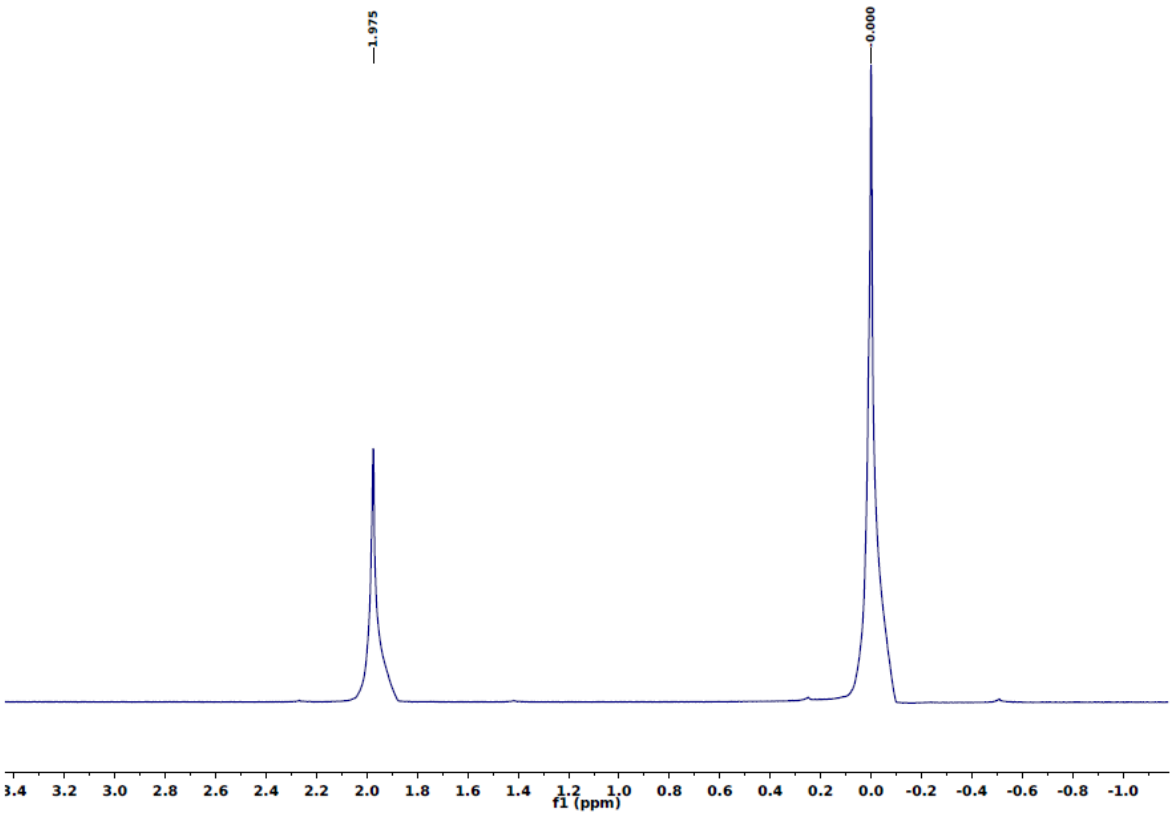
^{1}H NMR and ^{13}C NMR spectra of 6-(2-Nitrophenyl)-3,6-dihydro-2*H*-pyran-4-yl trifluoromethanesulfonate (44k)



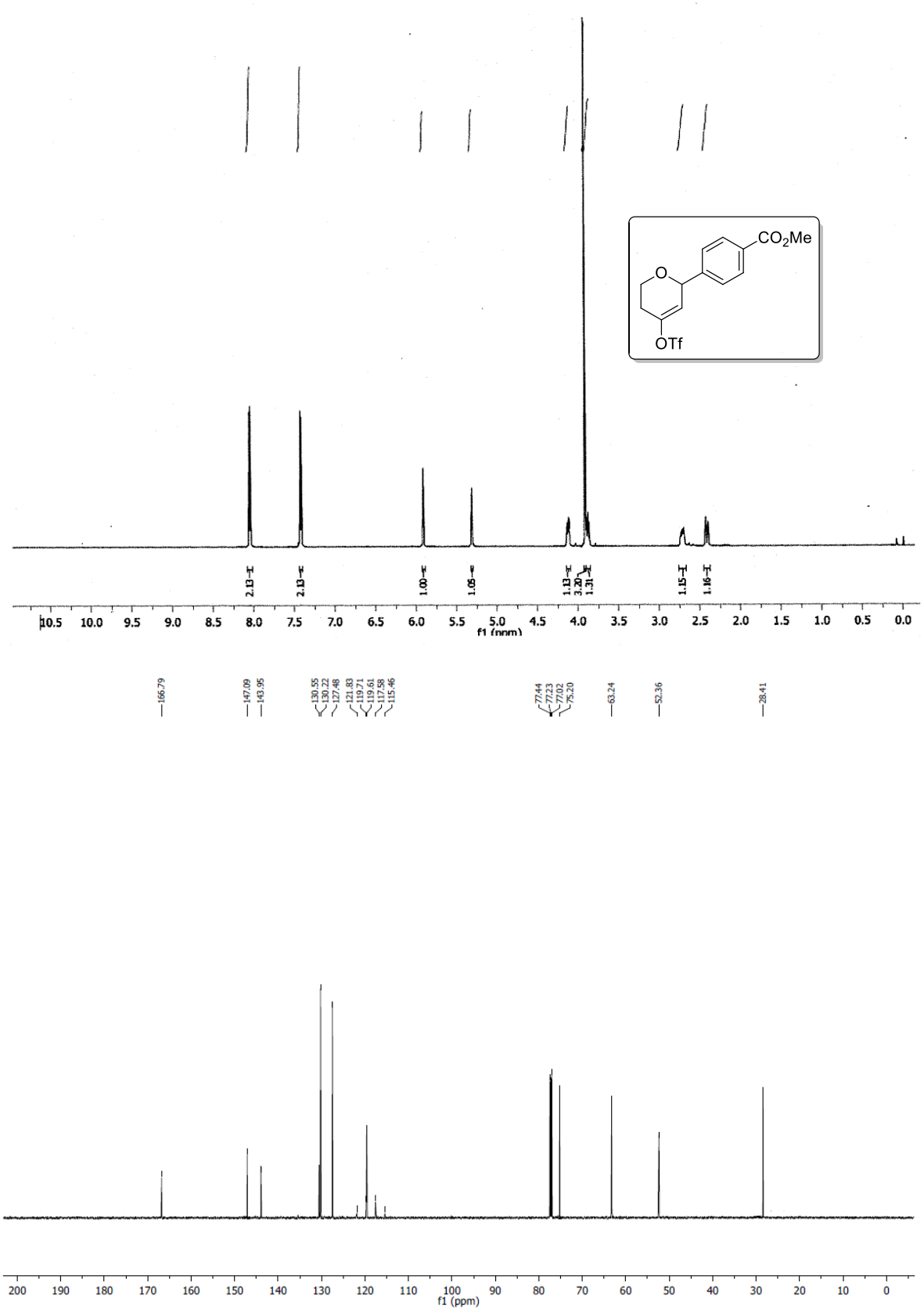




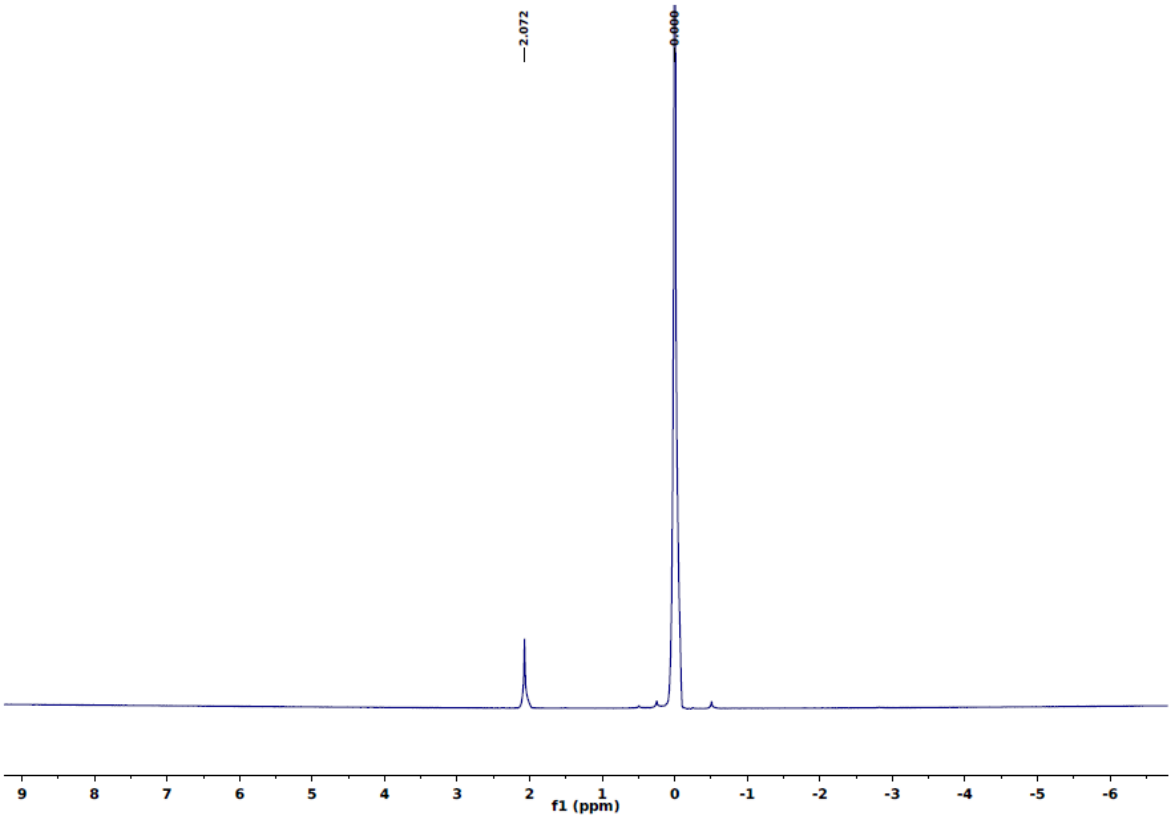
^{19}F NMR spectrum of 44k



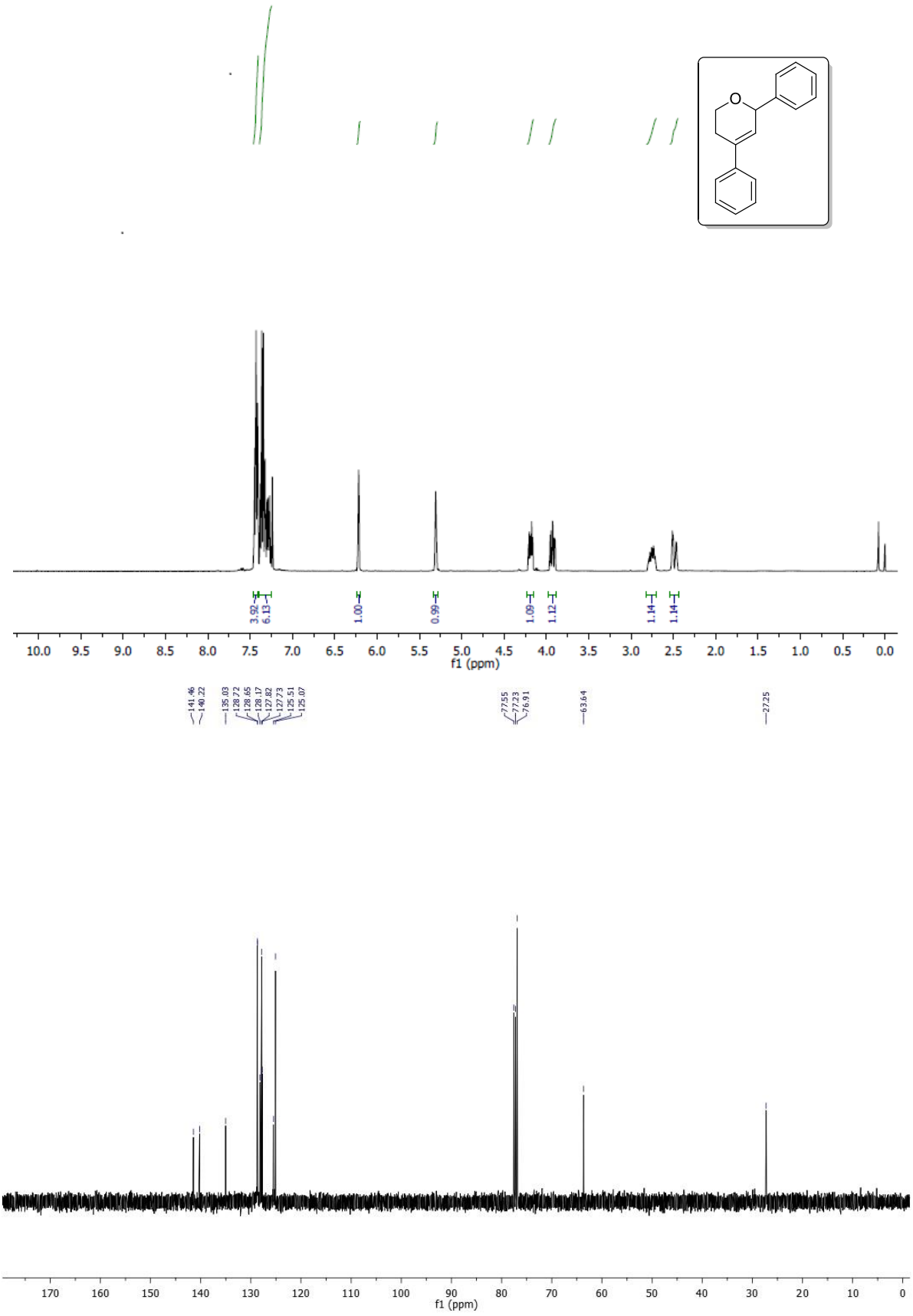
^{1}H NMR and ^{13}C NMR spectra of Methyl 4-(4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydro-2*H*-pyran-2-yl)benzoate (44m):



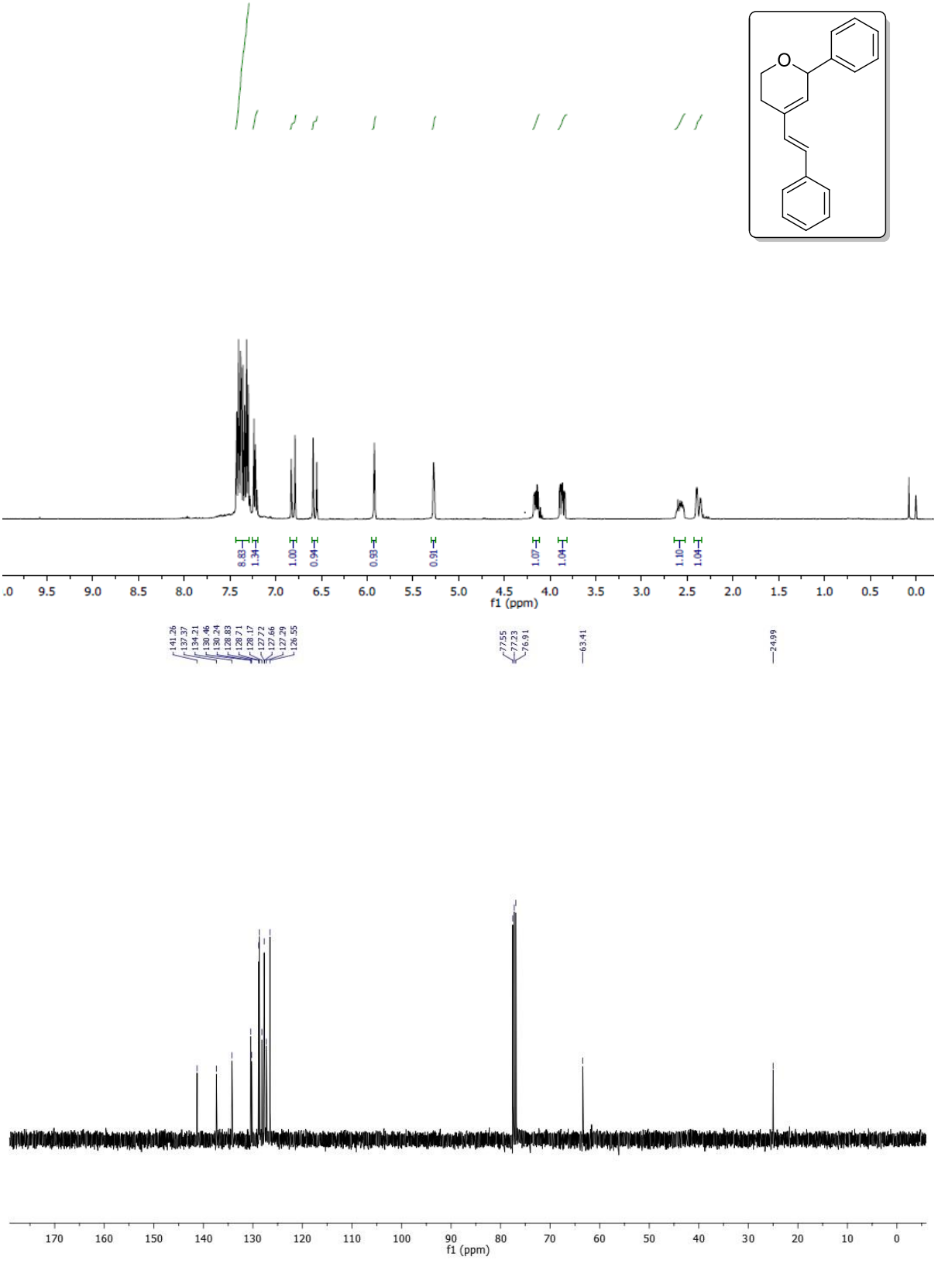
^{19}F NMR spectrum of 44m



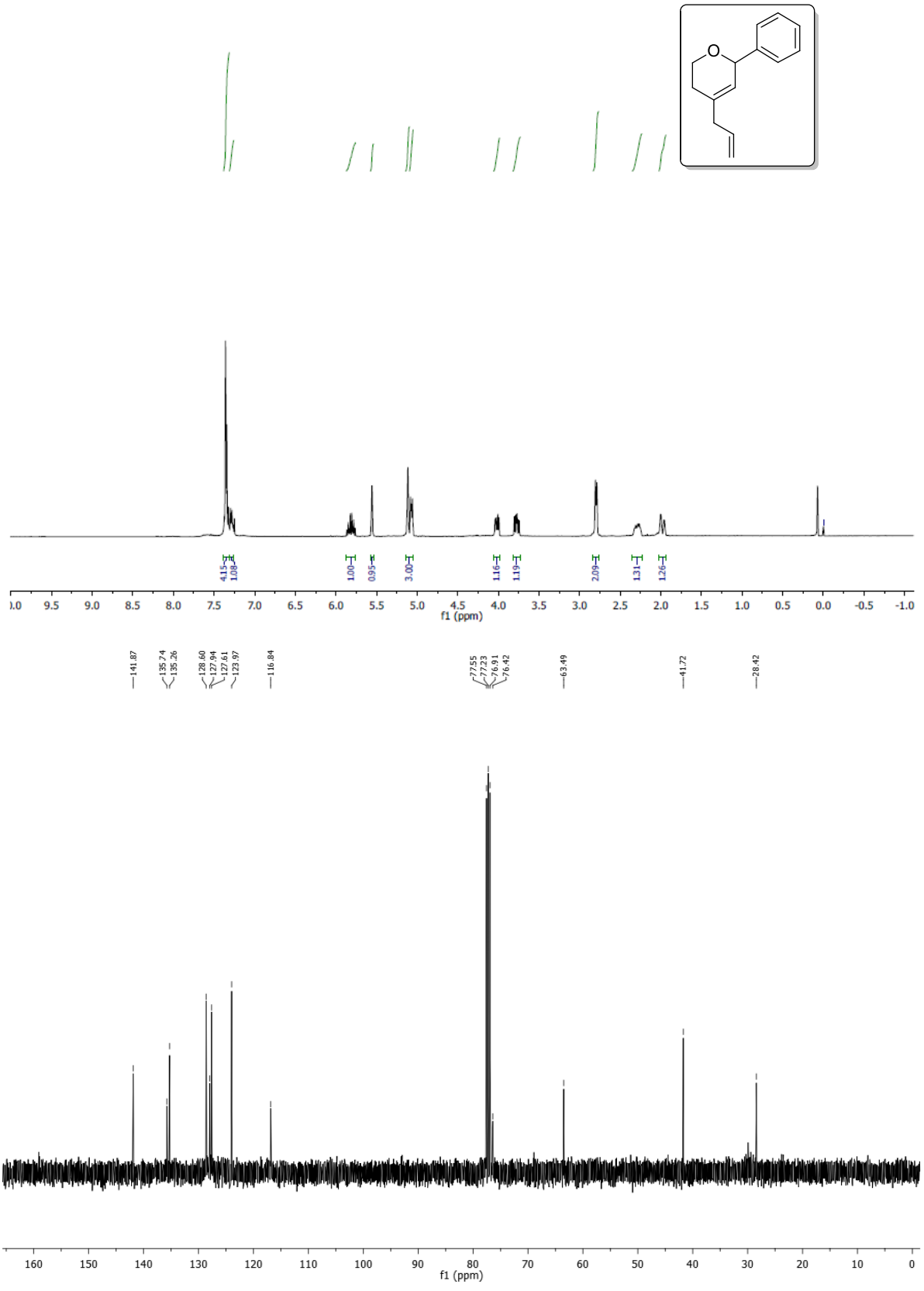
^{1}H NMR and ^{13}C NMR spectra of 4,6-diphenyl-3,6-dihydro-2*H*-pyran (49a):



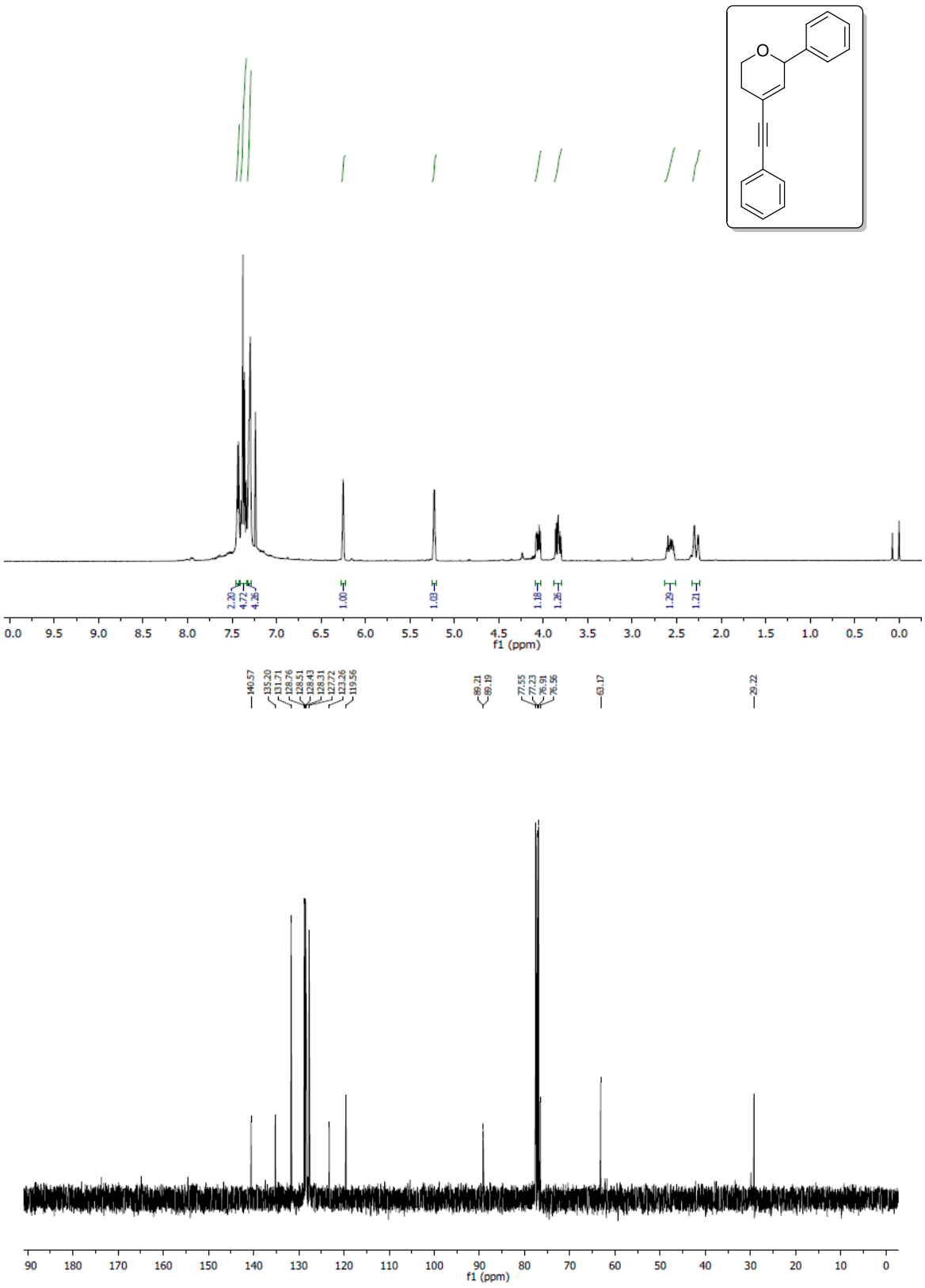
^{1}H NMR and ^{13}C NMR spectra of (*E*)-6-Phenyl-4-styryl-3,6-dihydro-2*H*-pyran (50):



^{1}H NMR and ^{13}C NMR spectra of 4-allyl-6-phenyl-3,6-dihydro-2*H*-pyran (51):



^{1}H NMR and ^{13}C NMR spectra of 6-phenyl-4-(phenylethynyl)-3,6-dihydro-2*H*-pyran (52):



2.8. Crystal Parameters

The crystal parameters of compound 44n

	CCDC 1433323
Formula	$C_{16}H_{13}F_3O_4S$
Formula weight	358.32
T/K	296(2)
Crystal system	Monoclinic
Space group	P21
a/Å	5.8732(3)
b/Å	8.2240(4)
c/Å	33.7553(17)
α/°	90.00
β/°	94.151(3)
γ/°	90.00
V/Å^3	1626.14(14)
Z	4
Abs. Coeff./mm^{-1}	0.248
Abs. Correction	multi-scan
GOF on F^2	1.041
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.1452
	wR2 = 0.2197
R indices [all data]	*R1* = 0.2008
	wR2 = 0.2402

List of Publications

1. "Brønsted acid mediated synthesis of 4-trifluoromethanesulfonate substituted 3,6-dihydropyrans and their application in various C-C coupling reactions" Saikia, A. K.; **Ghosh, P.**; Kautarya, A. K. *RSC Adv.* **2016**, *6*, 44774.
2. "Lewis Acid Mediated Intramolecular C−C Bond Formation of Alkyne- Epoxide Leading to Six-Membered Oxygen and Nitrogen Heterocycles" **Ghosh, P.**; Deka, M. J.; Saikia, A. K. *Tetrahedron* **2016**, *72*, 690-698.
3. "Lewis Acid Mediated Intramolecular C-C bond formation of Alkyne-Epoxide Leading to Six Membered Nitrogen and Oxygen Heterocycles" **Ghosh, P.**; Saha, P.; Bondalapati, S.; Indukuri, K.; Saikia A. K. *J. Org. Chem.* **2014**, *79*, 4119.
4. "Stereoselective Synthesis of 2,3-Disubstituted Tetrahydroquinolines" Bondalapati, S.; Indukuri, K.; **Ghosh, P.**; Saikia A. K. *Eur. J. Org. Chem.* **2013**, 952.
5. "Diastereoselective Synthesis of Substituted Dihydropyrans *via* Oxonium-Ene Cyclization Reaction" Saha, P.; **Ghosh, P.**; Sultana, S.; Saikia, A. K. *Org. Biomol. Chem.*, **2012**,*10*, 8730.
6. "Synthesis of dihydroindeno[1,2-*c*]isochromene *via* cascade cyclization and Friedel-Crafts reaction" **Ghosh, P.**; Borah, M.; Saikia, A. K. 2016, (Communicated).