Synthesis of Nitrogen, Oxygen and Sulfur Containing Heterocyclic Compounds

A Dissertation Submitted to the
Indian Institute of Technology Guwahati
As Partial Fulfillment for the Degree of

Doctor of Philosophy in Chemistry

Submitted by

Manashjyoti Deka

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati-781039, Assam, India
February 2018

Dedicated

To

My Parents

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "**Synthesis of Nitrogen, Oxygen and Sulfur containing Heterocyclic Compounds**" 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.

Date: Manashjyoti Deka
IIT Guwahati

Indian Institute of Technology Guwahati
Department of Chemistry
North Guwahati, Guwahati-781039, India
Phone: +91 (361) 2582316; Fax: +91 (361) 2690762
e-mail: asaikia@iitg.ernet.in

Dr. Anil K. Saikia
Professor

CERTIFICATE

This is to certify that Mr. **Manashjyoti Deka** has been working under my supervision since July 2012 as a regular registered Ph. D. student. I am forwarding his thesis entitled "**Synthesis of Nitrogen, Oxygen and Sulfur containing Heterocyclic Compounds**" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Date:
IIT Guwahati

Prof. Anil K. Saikia
Supervisor

Acknowledgement

First and foremost I want to thank my supervisor Prof. Anil Kumar Saikia for the continuous support in my Ph.D study and related research, for his patience, motivation, and immense knowledge. It has been an honor to work under his guidance. The joy and enthusiasm that he has for research together with his hardworking ethics has been a great learning experience and lesson for me. I could not have imagined having a better advisor and mentor for my Ph.D study.

Besides my supervisor, I would like to thank the rest of my thesis committee members: Prof. G. Krishnamoorthy, Prof. Pranab Goswami and Dr. Chandan kr Jana, for their insightful comments and encouragement, but also for the hard question which incented me to widen my research from various perspectives. I would also like to thank all faculty members of Department of Chemistry of IIT Guwahati for their timely help whenever and wherever required. A special mention to Prof. G. Bez of NEHU, who guided me during my MSc days and suggested me to join IIT Guwahati for my Ph.D study.

I am very grateful to the Council of Scientific and Industrial Research (CSIR), India for providing financial assistance and IIT Guwahati for all the facilities that were made available to me. I thank Central Instrument Facility (CIF), IIT Guwahati for providing the instrument facilities with special references to Dr. Babulal Das (for Single Crystal XRD) of Department of Chemistry and Mr. Chandan Borogohain of Central Instruments Facility (for NMR). I thank all the non-teaching staff of Department of Chemistry for their help during the tenure.

The members of our group have contributed immensely to my personal and professional time at IIT Guwahati. The group has been a source of friendships as well as good advice and collaboration. I am especially grateful for my seniors Dr. Paramartha Gogoi under whom I initially learned all the techniques of organic synthesis, Dr. Kiran Indukuri for willingness to share his in-depth knowledge in chemistry. It was an enriching experience to have shared the same laboratory with Dr. Sabera Sultana, Dr. Priya Ghosh, Dr. R. Unnava, Madhurjya Borah, Sujit Sarkar, Upasana Borthakur, Renubala Devi, Malay Das, Archana Sahu , Subhamoy Biswas, Sudip Shit and Bipin Behera.

A life of a research scholar is filled with joyous, nervous as well as stressful moments and to share these moments we need people who can understand our thoughts. I have been lucky to have been surrounded by such positive people, namely Dr. Pranjal Protim, Prakash Hazam, Sayan RC, Rahul Nhan, Chiranjib Das, Mrinal Kanti Borah. The quality time that we spent together will always remain as a good memory for me.

A special thanks to my wife Dr. Ananya Barman. Without her encouragement and support the journey would have been very tiresome. You have been a motivation for me. You have supported me throughout and I will forever remain grateful to you.

Finally I would like to thank my parents. My mother late Madhuri Deka, who left for her heavenly abode in 2003, your teachings and upbringing is the sole reason for whatever small or big I have achieved so far. Your desire and sacrifices to see me achieve heights will forever be my motivation to work harder. My father, who have always supported and backed me in all my decision. Special thanks to my father in law, Dr. Atul Kr Barman and my mother in law Mrs. Bharati Barman, your faith in my capabilities has always pushed me to go and achieve higher goals.

LIST OF ABBREVIATIONS

Boc	*tert*-butoxycarbonyl	MS	molecular sieves
CCDC	cambridge crystallographic data centre	m/z	mass to charge ratio
CSA	camphorsulfonic acid	NaH	sodium hydride
CMATB	Hexadecyltrimethylammonium bromide	NMM	*N*-methylmorpholine
DCE	1,2-dichloroethane	NMR	nuclear magnetic resonance
DCM	dichloromethane	NOESY	nuclear overhauser enhancement spectroscopy
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	NBS	*N*-Bromosuccinimide
DIAD	diisopropyl azodicarboxylate	ORTEP	oak ridge thermal ellipsoid plot
DFT	density function theory	Ph	phenyl
DMAP	4-dimethylaminopyridine	ppm	parts per million
DMF	*N*, *N*-dimethylformamide	*p*-TSA	*p*-toluenesulfonic acid
de	diastereomeric excess	rt	room temperature
dr	diastereomeric ratio	SES	2-(trimethylsilyl)ethanesulfonyl
ee	enantiomeric excess	THF	tetrahydrofuran
HPLC	high-performance liquid chromatography	TBATB	tetrabutylammoniumtribromide
HRMS	high resolution mass spectrometry	TEA	triethyl amine
IR	infrared	TFA	trifluoroacetic acid
LA	Lewis acid	Tf	trifluoromethanesulfonyl
LAH	lithium aluminium hydride	TLC	thin layer chromatography
LDA	lithium diisopropyl amide	TMS	trimethylsilyl
KBr	potassium bromide	Ts	*p*-toluenesulfonyl

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

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

ABSTRACT

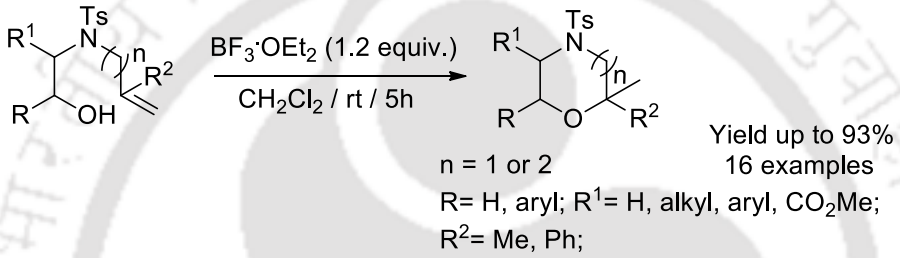
The contents of this thesis have been presented under four chapters based on the results gathered by various experimental work undertaken during the entire tenure of the research period. Chapter 1- gives an overview of some selected nitrogen, oxygen and sulfur containing heterocyclic moieties, their biological importance and different reported literature methods for their synthesis. Chapter 2 - describes a methodology for the synthesis of five, six-, and seven-membered 1,3- and 1,4-heterocyclic compounds *via* Intramolecular hydroalkoxylation/hydrothioalkoxylation of alkenols/thioalkenols. Chapter 3 is about a highly regioselective synthesis of 4-tosylthiomorpholine *via* intramolecular cyclization of *N*-tethered thioalkenols. Chapter 4 - presents a diastereoselective synthesis of substituted tetrahydrothiopyrans *via* thia-Prins cyclization of thioenol ethers.

Chapter 1: Introduction to Nitrogen, Oxygen and Sulfur Containing Heterocyclic Compounds

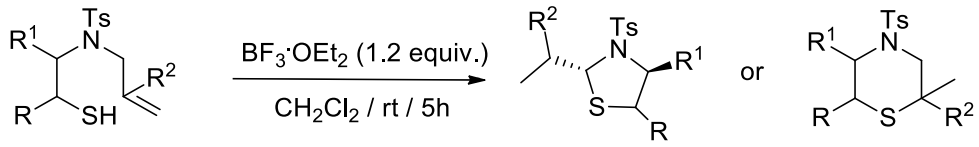
The six membered ring heterocycles of oxygen, nitrogen and sulfur are structural motifs of many bioactive molecules. 1,4-oxazines and 1,4-oxazepanes are widely distributed in many naturally occurring and biologically active molecules. These are also versatile synthetic building blocks in organic synthesis particularly for the construction of agrochemical fungicides and bactericides. Morpholine such as reboxetine is an antidepressant drug, and *cis*-2, 3-disubstituted morpholine such as aprepitant (hNK1 antagonist) is used for chemotherapy-induced nausea and vomiting (CINV) and commercially available under the name of Emend. Many sulphur and nitrogen containing heterocycles such as benzothiomorpholines possess antibacterial, antiarrhythmic, antidiabatic, antihypertensive, and antitumor activities. Some of the reported methologies for the synthesis of the morpholine moieties include ring closure of amino diols, amino alcohols, and bromosulfonium salts, double allylic substitution by amino alcohols, cyclization of *N*-tethered halo alcohols, reductive amination of diketones, reductive etherification of *N*-tethered keto alcohols, cyclization of *O*-protected amino alcohols, oxirane ring opening by tosylamide and subsequent cyclization, and ring opening of aziridines. Due to the remarkably rich array of functionalities and chiral centers, the stereoselective synthesis of these motifs has become a continuous challenge for organic synthesis practitioners. They can be synthesized by means of hetero-Diels Alder reactions or intra molecular cyclizations, or oxonium-ene reactions, or Prins cyclization reactions.

Chapter 2: Synthesis of Five-, Six-, and Seven-Membered 1,3- and 1,4-Heterocyclic Compounds *via* Intramolecular Hydroalkoxylation/Hydrothioalkoxylation of Alkenols/ Thioalkenols:

Numerous synthetic approaches have been developed for the preparation of 1,4-oxazines and 1,4-oxazepanes. These methods have their own merits and demerits, but some of them suffer from serious problems such as lack of selectivity, low yields, and harsh reaction conditions. This chapter describes a general methodology for the synthesis of 1,4-oxazines, 1,4-oxazepanes and thiazolidines using intramolecular hydroalkoxylation/hydrothioalkoxylation of alkenols/thioalkenols mediated by boron trifluoride etherate at ambient temperature to give moderate to good yields.



Various alkenols were treated with 1.2 equivalents of boron trifluoride etherate in dichloromethane at room temperature, to yield substituted 1,4-oxazines and 1,4-oxazepanes in 60-90% yields. To determine the optimum reaction conditions, a series of experiments were carried out by varying the lewis and Brønsted acidic conditions in different solvents. Metal salts and metal triflates were also explored. The optimum condition for the reaction was found out to be of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temperature for 5 h. The optimized reaction was explored with a variety of substrates, which were synthesized according to the literature methods. Substrate having a terminal alkene, was unreactive under the same reaction conditions, for which the starting material was recovered in 98%. After successful study of this methodology for the synthesis of 1,4-oxazines and oxazepanes, its application to the synthesis of 1,4-thiazines and thiazepanes was explored. The stereochemistry of the thiazolidine was determined by ^1H NMR and NOE experiments.



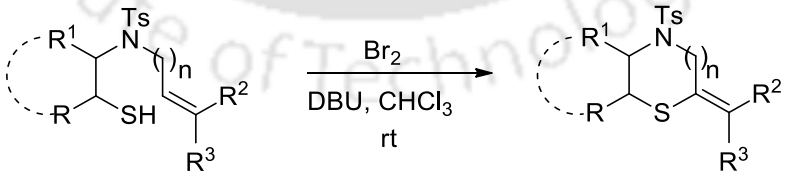
To conclude, a mild and efficient general method for the synthesis of substituted 1,4-oxazines, 1,4- oxazepanes, 1,4-thiazines and thiazolidines *via* intramolecular cyclization

reaction of alkenols/thioalkenols is developed. The method gives the desired products in good yields with excellent diastereoselectivity.

Chapter 3: Highly Regioselective Synthesis of 4-Tosylthiomorpholine via Intramolecular Cyclization of *N*-Tethered Thioalkenols.

Saturated heterocyclic compounds containing nitrogen and sulphur atoms, such as thiomorpholines, thiazines, thiazolidines and thiazepines and their oxidized derivatives are considered as important structural motifs in organic synthesis. Further the presence of double bonds in a cyclic system is not only responsible for their biological properties but also serves as a functional group for further manipulations in organic synthesis. They can also be used as building blocks in organic synthesis. This chapter describes a one-pot, metal-free procedure for the synthesis of 4-tosylthiomorpholine from *N*-tethered thioalkenols via bromination, cyclization and subsequent elimination reaction in good yields.

To start with thioalkenols (1.0 equiv.) were treated with molecular bromine in $CHCl_3$ at 0 ^oC. After 15 minutes, DBU (0.5 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 4 h and substituted 2-methylene-4-tosylthiomorpholine was obtained in 80% yield. Other bases like K_2CO_3, Et_3N and KOH were found to be inefficient. With this optimized conditions in hand, a variety of *N*-tethered thioalkenols were evaluated as substrates. It was observed that the reaction provides only exo-olefinic 4-tosylthio-morpholine in good to high yields. The reaction proceeds with differently substituted thioalkenols such as alkyl, benzylic and aryl to give substituted thiomorpholines in good yields.



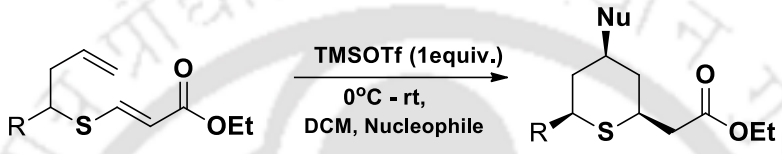
63-80%

R = H, aryl; R^1 = H, alkyl;
R^2 = R^3 = H, alkyl, aryl
n = 1,2

In conclusion, a one-pot, metal free, mild and efficient method for the synthesis of 4-tosylthiomorpholine from *N*-tethered thioalkenols via bromination, cyclization and subsequent elimination reaction in good yields has been developed.

Chapter 4: Diastereoselective Synthesis of Substituted Tetrahydrothiopyrans via thia-Prins cyclization of Thioenol Ethers.

This chapter describes an efficient methodology for the diastereoselective synthesis of dihydropyrans using Prins enol-ether cyclization reaction from enol ethers mediated by trimethylsilyl trifluoromethanesulfonate (TMSOTf) in good yields under mild reaction conditions.



Initially a reaction of thioenol-ether with TMSOTf in dry dichloromethane at room temperature was performed with an aim to synthesize dihydrothiopyran ring system. The reaction gave the desired 5, 6-dihydrothiopyran product in 25% yield, however the product was found to be unstable with its disintegration with time. The reaction was then performed in Benzene: CH_2Cl_2 (1:1) solvent system where benzene acted as a nucleophile to give 2,4,6-trisubstitutedtetrahydrothiopyran. The reaction was then carried out with different Lewis acids, solvents and nucleophiles. TMSOTf was found to be a good reagent for the cyclization reaction, with 75% yield. The reaction was generalized with different substituents and gave good yields with aromatic substituents. The reaction with an aromatic group having a methoxy group on the aromatic ring gave decomposed products. The various nucleophiles used gave satisfactory yields except for anisole where the yield was 20%.

To conclude, a methodology has been developed for the synthesis of substituted tetrahydrothiopyran from thio-enol ethers using the thia-Prins cyclization reaction. The reaction is highly diastereoselective with *dr* upto 93:7.

Index

CHAPTER 1

Introduction to Nitrogen, Oxygen and Sulfur Containing Heterocyclic Compounds

1.1 Heterocyclic compounds

Organic molecules can be broadly classified into two categories namely, acyclic and cyclic. The cyclic systems called the carbocyclic contains only carbon atoms (e.g. cyclohexane, benzene) and the cyclic systems containing carbons and at least one other element are called heterocyclic. Though many heteroatoms are known to be part of the heterocyclic system the most prevalent are nitrogen, oxygen and sulfur. Various heterocycles occur naturally and play pivotal role in many biological systems e.g. nucleic acids, vitamins, heme, chlorophyll, etc. The chemistry of heterocyclic compounds deals with the synthesis, properties and applications of heterocyclic compounds. They form an integral components of many pharmaceutical and therapeutic drugs. Due to their widespread presence, heterocyclic chemistry has been fascinating many scientist and has become a vast, expanding area of chemistry.

Heterocyclic compounds can be further classified as aliphatic and aromatic heterocycles. The aliphatic heterocycles are the cyclic analogues of amines, ethers and thioethers. These compounds generally consist of small (3- and 4-membered) and common (5 to 7 membered) ring systems. Ring strain influences the intrinsic properties of these heterocyles. Heterocycles with three heteroatoms in the ring are more reactive because of ring strain. Those containing one heteroatom are in general, stable. Those with two heteroatoms are more likely to occur as reactive intermediates. Some of the common aliphatic heterocyclic compounds are aziridine **1**, azetidine **2**, pyrrolidine **3**, piperidine **4**, oxirane **5**, oxetane **6**, tetrahydrofuran **7**, tetrahydropyran **8**, thiirane **9**, thietane **10**, tetrahydrothiophene **11**, tetrahydrothiopyran **12.** The aromatic heterocyclic compounds, in contrast, are those which have a heteroatom in the ring and fulfil the Huckel's rule for aromaticity, which states that cyclic, conjugated and planar systems having (4n+2) π electrons are aromatic. Furthermore, some of their properties are found to have resemblance with those of benzene.

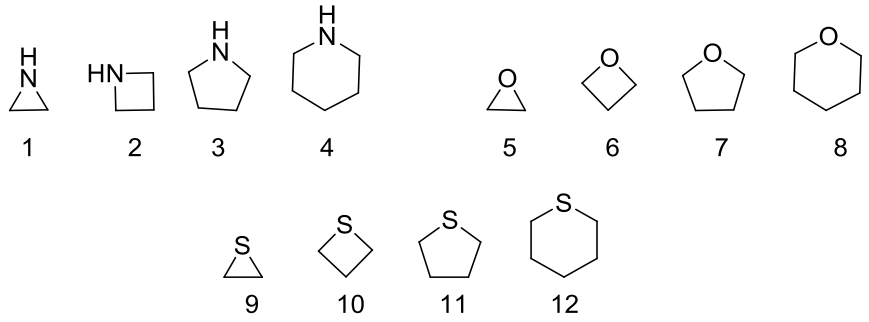


Figure 1.1.1. *Some examples of three to six membered saturated heterocycles.*

The best known simple aromatic heterocyclic compounds are pyridine **13**, pyrrole **14**, furan **15** and thiophene **16**. Another large class of heterocycles are fused to benzene rings, which for pyridine, thiophene, pyrrole, and furan are quinolone **17**, benzothiophene **18**, indole **19** and benzofuran **20** respectively. The unsaturated rings can be classified according to the participation of the heteroatom in the conjugated system, π system. Heterocyclic compounds containing two heteroatoms such as pyrazole **21**, pyrazine **22**, morpholine **23**, thiomorpholine **24**, dithiane **25**, oxazepane **26**, gives a complete new dimension to the diverse chemical application of the heterocyclic compounds.

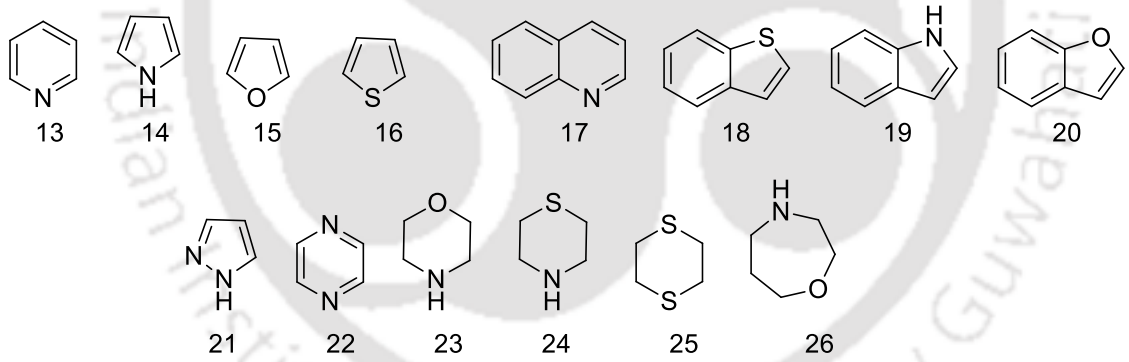


Figure 1.1.2. *Common heterocyclic compounds.*

Hantzsh-Widman system is the most widely used systematic method for naming three to ten membered monocylic heterocyles of various degree of unsaturation containing one or more heteroatom.[1] The method determines the ring size, position of the heteroatom and the degree of unsaturation in the ring. In this method, the ring atoms are numbered such that the heteroatom carries the least number. This thesis focuses on important synthetic routes for the synthesis of five, six and seven membered nitrogen, oxygen and sulfur containing heterocycles such as morpholines, thiomorpholines, thaizines, oxazepanes and tetrahydrothiopyrans.

1.2 Importance and Applications

The six membered ring heterocycles of oxygen, nitrogen and sulfur are structural motifs of many bioactive molecules.[2] Tetrahydropyrans are structural features of many biologically active natural products such as polyether antibiotics, marine toxins and pheromones. They are an important moiety in pharmaceuticals. For example, over the last ten years thousands of tetrahydropyran-containing compounds are under preclinical and clinical trials.[3] Consequently, a huge amount of effort has been directed towards developing ever more efficient methods to synthesize them. The macrocycle, (-)-Kendomycin **27** has a diverse and fascinating pharmacological profile. It was isolated in 1996 from *Streptomyces* bacteria and exhibits potent

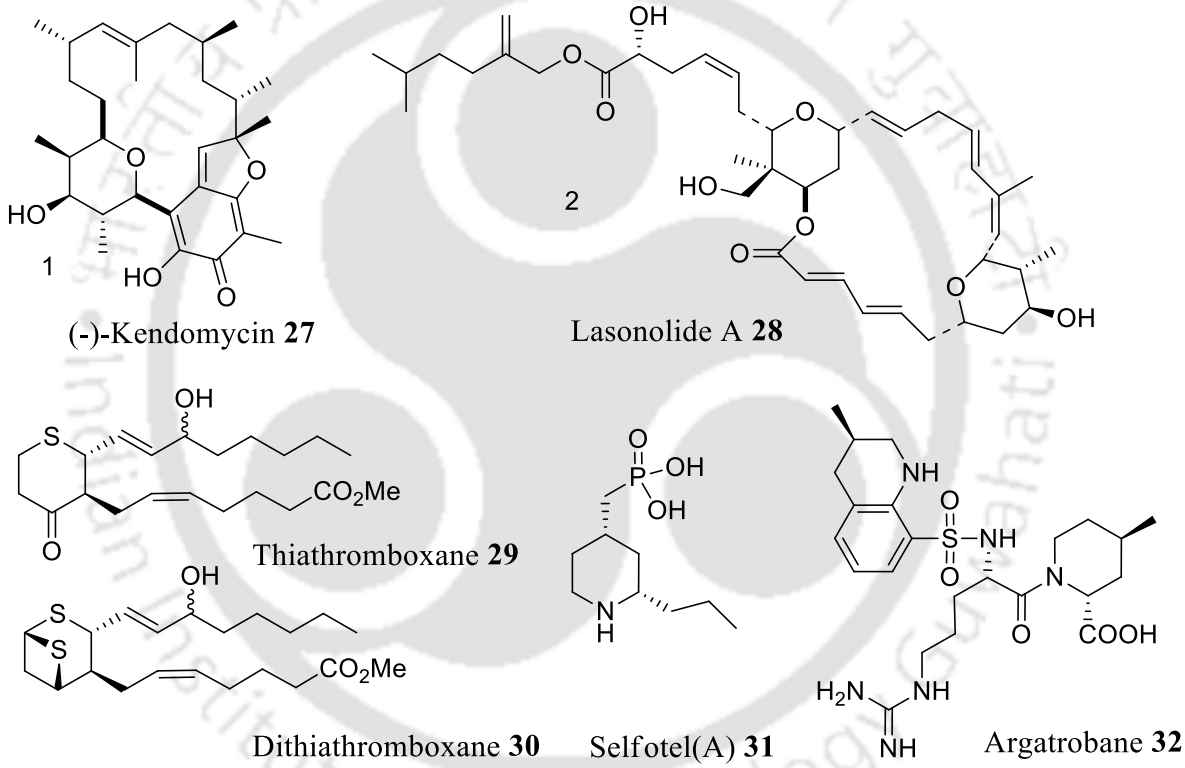


Figure 1.2.1. *Important natural products.*

antagonism of the endothelin receptor agonism.[4] Lasonolide A **28**, isolated from a shallow water Caribbean sponge, species *Forcepia* shows potent activity against A-549 human lung carcinoma.[5] Compared to the tetrahydropyrans their sulfur analogues tetrahydrothiopyrans are less frequently encountered in nature. A reasonable number of thiacyclohexane derivatives are found in petroleum oil.[6] The thiacyclohexane ring plays a key role in the biological activities of a number of pharmaceutical agents such as cephalosporins,[7] thiathromboxane **29** and dithiathromboxane A_2 **30**.[8] Similarly substituted piperidines are

also an important class of heterocycles, which appear in many drugs and drug candidates, the compounds selfotel **31** acts as a competitive NMDA agonist and argatroban **32** shows thrombin inhibiting properties.[9] Compounds with the piperidine sub-structure exhibit anti-hypertensive,[10a] antibacterial,[10b] anticonvulsant,[10c] anti-inflammatory and antiproliferative activities. Many natural products having a piperidine moiety have been isolated,[10d] which acts as an important building block for various biologically significant compounds. Similarly, a wide variety of functionalized morpholines occur in nature and due to their vivid presence they attract the interest of synthetic chemist worldwide to develop newer methodologies towards their synthesis. Some of the examples include alkaloid polygonapholine (**33**, R = 4-HOC_6H_4) which was isolated from *Polygonatum altelobatum* and is used as tonic by the people living in Taiwan.[11] The spiroalkaloids acortatarins A **34** and B **35** is reported to have been isolated from the rhizome of *Acorus tatarinowii*,[12] they have antioxidant properties. Many attempts have been made towards the total stereoselective syntheses of compounds **34** and **35**.[13] They are considered to be valuable starting materials for the design of new antidiabetic and anticancer drugs. The naturally occurring alkaloids chelonin A [**36**, R^1 = indol-3-yl, R^2 = 3, 4, 5- $(MeO)_3C_6H_2$] and chelonin C [**37**, R^1 = 3,4-$(MeO)_2$- C_6H_3, R^2 = 4-HOC_6H_4] contains 2,6-disubstituted morpholine fragment. The total synthesis of compound **36** was reported in 1995 which showed antimicrobial activity against *Bacillus subtilis.* The total synthesis of alkaloid **37** was described only recently by Gharpure *et al.*[14] Apart from these naturally occurring products many synthetic biologically active compounds containing morpholine ring are used in

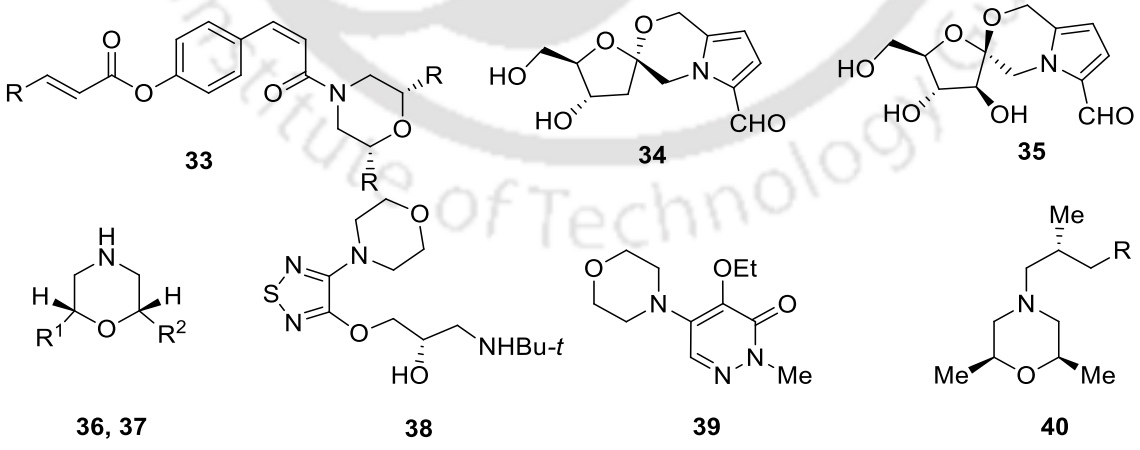
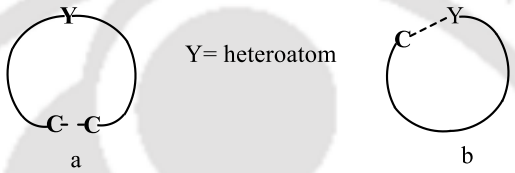


Figure 1.2.2. *Compounds containing morpholine moiety.*

medical practice such as timolol (**38**, non-selective beta-adrenergic receptor antagonist indicated for treating glaucoma),[15] emorfazone (**39**, analgesic and anti-inflammatory drug),[16] fenpropimorph (**40**, R = 4-*t*-Bu- C_6H_4; fungicide).[17]

1.3 Literature Review

The stereoselective synthesis of nitrogen, oxygen and sulfur heterocycles has been a subject of great interest for organic researchers because of their ubiquity in natural products and bioactive compounds. The catalytic construction of heterocyclic skeletons is classified into two major processes, as shown in *Scheme 1.3.1*: (a) C-C bond formation from the corresponding acyclic precursors and (b) C-Y bond formation from the corresponding acyclic precursors.



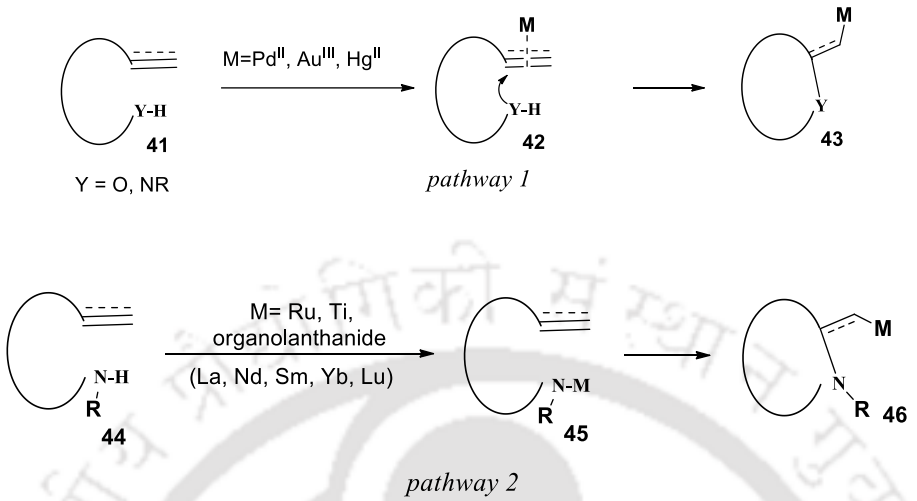
Scheme 1.3.1

The two processes, C-C and C-Y bond formation, take place together in the intra- and intermolecular hetero-cycloaddition of alkenes and alkynes bearing a hetero-unsaturated bond at an appropriate position of the carbon chain to synthesize four-, five- or six-membered heterocycles, depending on the partner of the intra and intermolecular reaction. To build this heterocycles, many strategies have been developed over the years. The most widely used methods are the ring-closing metathesis, cascade reactions, Prins cyclization reaction, transition metal salts catalyzed cyclization reactions, nucleophilic substitution reaction of activated alcohols/thiols etc. Among these methods stated, this thesis mainly discusses Prins, thia-Prins cyclization and heterocyclization reactions in detail for the construction of these heterocycles.

1.3.1 Heterocyclization Reactions

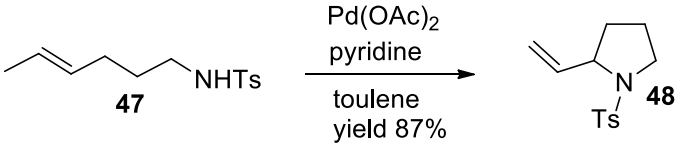
Intramolecular reactions of carbon-carbon unsaturated compounds such as alkenes, allenes, methylenecyclopanes, and alkynes, tethered with N-H, O-H, CO, CN functional groups have been performed with various transition metals and other reagents. It is considered to be an important methodology for the synthesis of various heterocycles. A wide range of transition –metal complexes of palladium, platinum, gold, copper, titanium, tungsten, and

organolanthanides, have been used as a catalyst. The addition of the Y-H group to the C-C unsaturated bonds can be broadly classified into two major groups. (*Scheme 1.3.1.1*).

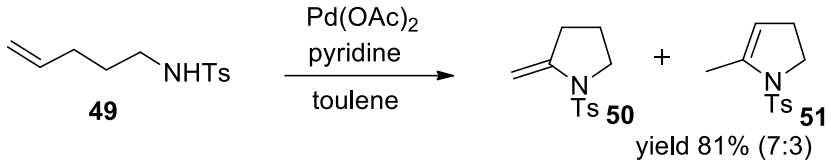


Scheme 1.3.1.1

Metal catalysts like Pd^{II}, Au^{III} and Hg^{II} go through pathway 1 where the reaction is initiated *via* the formation of a metal-olefin complex **42** followed by intramolecular nucleophilic attack of the heteroatom to the electron deficient metal-olefin complex to form the heterocyclic organometallic compound **43**. Other metals such as ruthenium, titanium and organolanthanides react with amine derivatives with a formation of metal-amido complex **45** followed by intramolecular aminometallation of the unsaturated bond to produce heterocyclic organometallics **46**. Subsequent metal elimination of the organometallic intermediate gives the desired heterocycles. An insight into some of the reported literature methods will further enhance the understanding of these type of heterocyclization reactions.[18] Fix *et al.* reported that the reaction of aminoalkenes **47** having a methyl group on the olefin moiety undergo palladium-catalyzed oxidative cyclization to give the 2-vinylpyrrolidines **48**, while the reaction of the aminoalkene **49** having a terminal olefin give a mixture of the cyclic enamines **50** and **51** (*Schemes 1.3.1.2 and Scheme 1.3.1.3*).

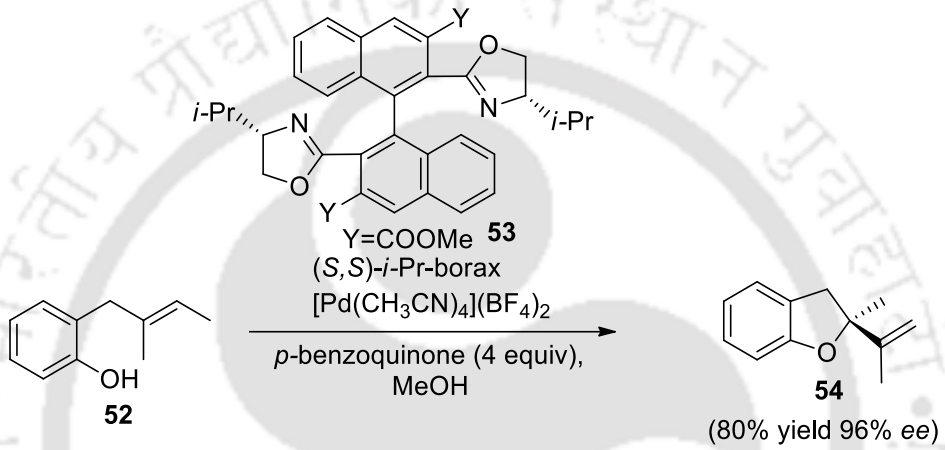


Schemes 1.3.1.2



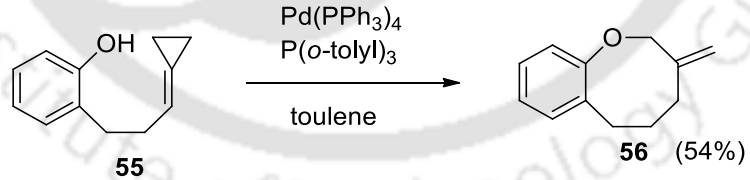
Schemes 1.3.1.3

Uozumi *et al.* studied the palladium-catalyzed asymmetric heterocyclization of the *o*-allylphenol **52** in the presence of $[Pd(CH_3CN)_4](BF_4)_2$ and (*S,S*)-*i*-Pr-boxax. The reaction gave the dihydrobenzofuran **54** in 80% yield with 96% *ee* (*Schemes 1.3.1.4*).[19]



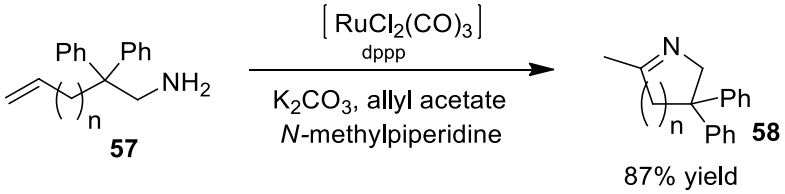
Scheme 1.3.1.4

Yamamoto *et al.* reported the intramolecular hydroalkoxylation of the methylenecyclopropanephenol **55** in the presence of a palladium catalyst. An eight-membered cyclic ether **56** was obtained in good yield (*Scheme 1.3.1.5*).[20]



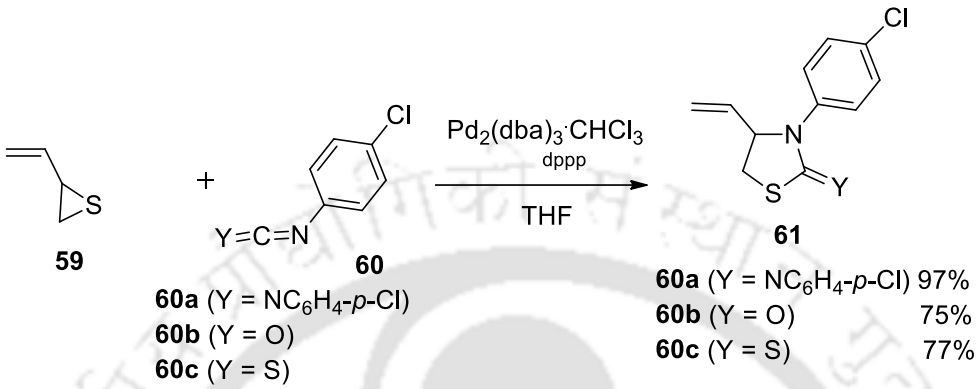
Scheme 1.3.1.5

A ruthenium catalyzed intramolecular oxidative amination of the aminoalkenes **57** was reported by Mitsudo *et al.*, cyclic imines **58** were obtained in high yields (*Scheme 1.3.1.6*).[21]

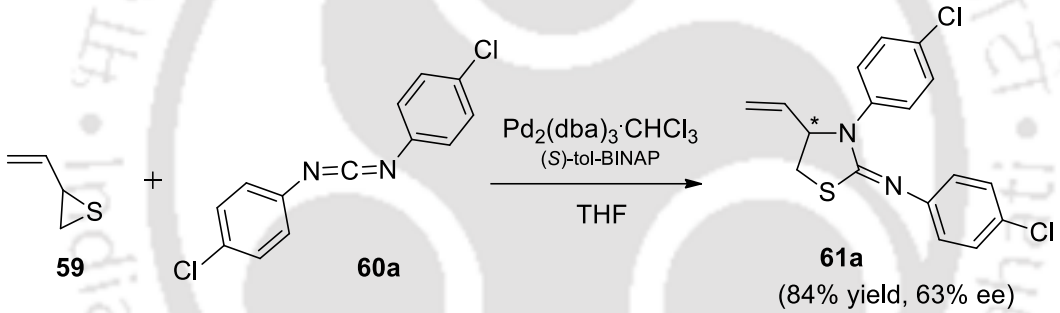


Scheme 1.3.1.6

A regio- and enatioselective formation of the thiaolidine, oxathiolane, and dithiolane derivatives **61** by the palladium catalyzed cyclization reaction of 2-vinylthiirane **59** with heterocumulenes **60** was reported by Larksarp *et al.* (*Scheme 1.3.1.7.1*).[22] The asymmetric reaction was performed using (*S*)-tol-BINAP as a chiral phosphine ligand (*Scheme 1.3.1.7.2*).



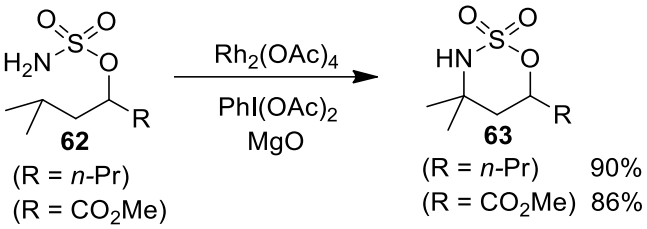
Scheme 1.3.1.7.1



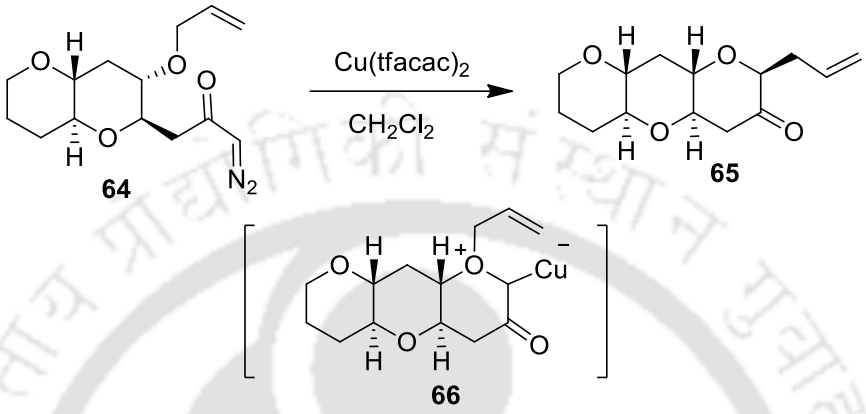
Scheme 1.3.1.7.2

Espino *et al.* reported that sulfamate esters **62** on oxidative cyclization with $PhI(OAc)_2$, in the presence of $Rh_2(OAc)_4$, give the heterocycles **63**, which have both S-O and S-N bonds in the ring, in high yields (*Scheme 1.3.1.8*).[23]

Marmsater and West reported that the copper-catalyzed [2,3]-shift of oxonium ylides gave polycyclic ethers with high diastereoselectivity.[24] The reaction of the diazocarbonyl compound **64** bearing an allyl ether in the presence of copper(II) trifluoroacetylacetate ($Cu(tfacac)_2$) produced the polycyclic ether **65** in 80% yield as a single diastereomer (*Scheme 1.3.1.9*). The reaction proceeds through the oxonium ylide **66**, and subsequent [2,3]-shift of an allyl group gives **65**.

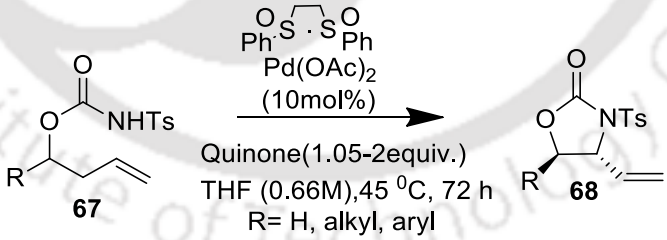


Scheme 1.3.1.8



Scheme 1.3.1.9

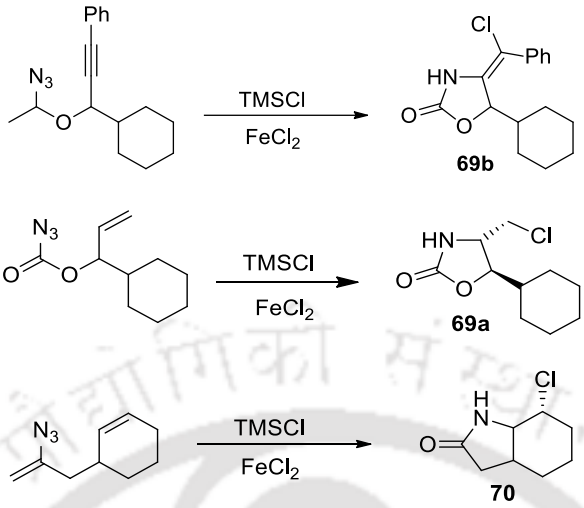
Kenneth J. Fraunhoffer and M. Christina White reported the successful development of allylic C-H amination reaction and the exploration of its scope and synthetic utility. Furthermore, they provided evidence in support of a mechanism that proceeds *via* a Pd(II)/sulfoxide-promoted allylic C-H cleavage to furnish a ð-allylPd intermediate followed by acetate counter ion promoted functionalization with the tethered *N*-tosyl carbamate nucleophile.[25](*Scheme 1.3.1.10*)



Scheme 1.3.1.10

Organic azides have also been used extensively for the synthesis of the heterocyclic cores. One of the first example of a metal catalyzed intramolecular amination of an olefin by an azido group was the reaction of 2-alkenyloxycarbonyl azides, in the presence of TMSCl and $FeCl_2$ as catalyst, towards the formation of 4-(chloromethyl)oxazolidinone in (60-80% yield) *via* a stepwise single electron transfer pathway. A dominance of the *trans*-diastereoisomer was observed over the *cis* analogue.[26] The procedure, summarized in

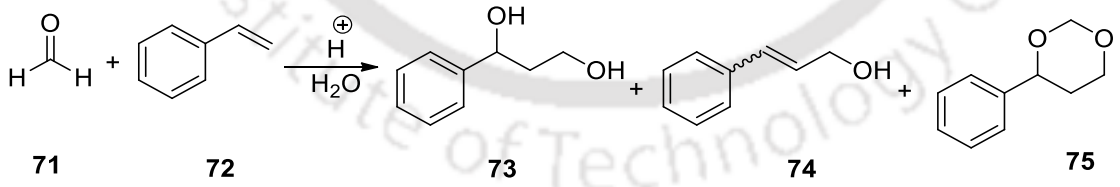
(*Scheme 1.3.1.11*), led to the iron(II) chloride catalyzed intramolecular chloroamination yielding to oxazolidinones **69** and lactams **70** in moderate to good yields.[27]



Scheme 1.3.1.11

1.3.2 Prins Cyclization Reaction

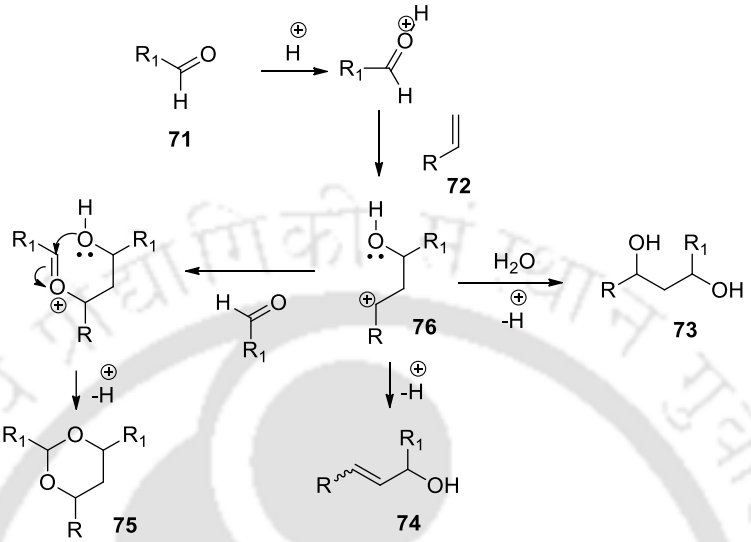
The Prins reaction is one of the fundamental carbon-carbon bond formation reaction, developed by H. J. Prins in the year 1919. It involves the electrophilic addition of aldehydes or ketones to alkenes in the presence of acid. Initially, H. J. Prins carried out the reaction of formaldehyde **71** and styrene **72** in aqueous acidic medium, resulting in a mixture of products such as 1,3-butanediol **73**, unsaturated alcohol **74** and 1,3-dioxane **75** (*Scheme 1.3.2.1*).[28] Usually, the outcome of the reaction depends on the nature of reaction conditions.



Scheme 1.3.2.1

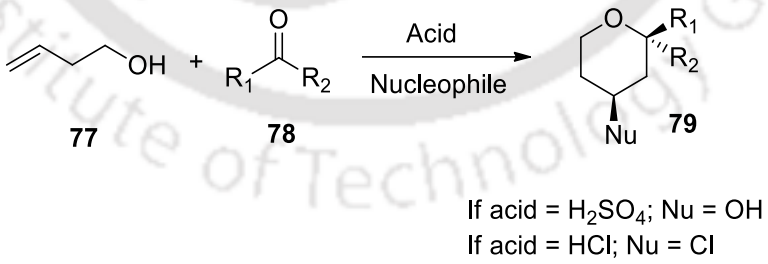
The general mechanism of the reaction is shown in (*Scheme 1.3.2.2)*. The alkene **72** reacts with carbonyl compounds **71** in the presence of acid to generate the key intermediate *β*-hydroxy carbocation **76**. This intermediate **76** may lose a proton to give homoallylic alcohol **74** or reacts with a number of species present in the reaction medium. Reaction of carbocation **76** with a second molecule of aldehyde **71** forms 1,3-dioxane **75** after ring

closure. Similarly, intermediate **76** can react with solvent (H_2O) to give the 1,3-diol adduct **73**.



Scheme 1.3.2.2

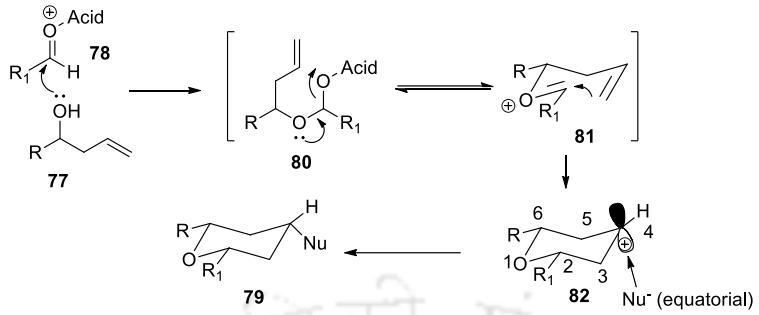
In 1955, Hanschke has further modified Prins reaction for the stereoselective synthesis of tetrahydropyran (THP) derivatives **79** by reaction of 3-buten-1-ol **77** with a variety of aldehydes or ketones **78** in the presence of acid, called Prins cyclization reaction (*Scheme 1.3.2.3).*[29] In most of the cases, the Prins cyclization reaction is highly diastereoselective and give 2,4,6-substituted tetrahydropyrans with all equatorial substitutions.



Scheme 1.3.2.3

The general mechanism is shown in (*Scheme 1.3.2.4)*. The reaction of aldehyde **78** and homoallylic alcohol **77** in the presence of acid generates an oxocarbenium ion **81** as a key intermediate. The six-membered oxocarbenium intermediate adopts chair-like conformation and undergoes 6-endo cyclization to give selectively a secondary

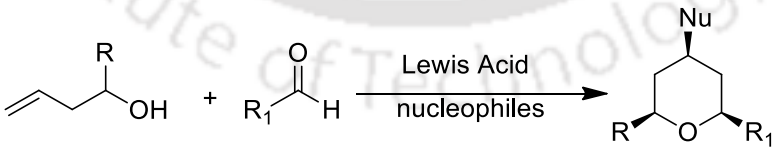
tetrahydropyrynyl cation **82**, which is trapped by the nucleophile present in the reaction mixture to produce tetrahydropyran **79**.



Scheme 1.3.2.4

Alder has performed the DFT calculations on different possible reaction intermediates and rationalized the diastereoselectivity through a chair-like transition state.[30] According to Alder's DFT calculations; stereoelectronic effects stabilize the tetrahydropyrynyl cation **82** in its chair conformation. 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 to give tetrahydropyran **79**. Over the last six decades, many research groups including the work from our group have broadened the scope of Prins cyclization reaction. Several protocols have been developed to introduce different functionalities at the C-4 position of tetrahydropyran ring by trapping the secondary tetrahydropyranyl carbocation **82** with a broad spectrum of nucleophiles (*Table 1.3.2.1*).

Table 1.3.2.1 *Scope of the Prins cyclization with various nucleophiles*



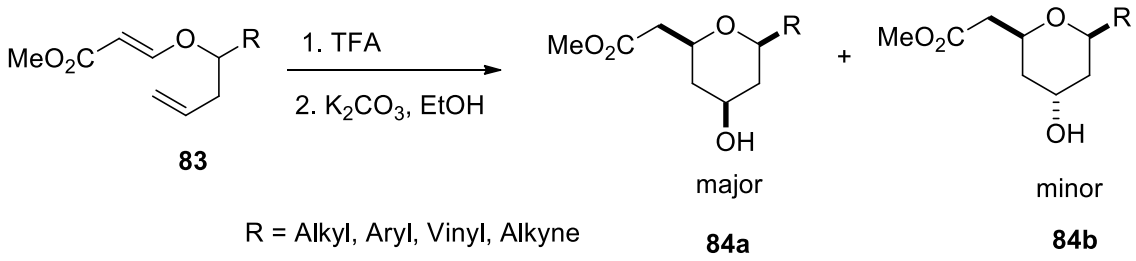
Lewis Acid/ Nucleophile	Nu
TiF_4, $NEt_4{\cdot}5HF$, $BF_3{\cdot}OEt_2$	F
HCl, $TiCl_4$, $SnCl_4$, $AlCl_3$, $InCl_3$, $ZnCl_2$, $SbCl_5$, $ZrCl_4$, $NbCl_5$, $In(OTf)_3$/TMSCl	Cl
$SnBr_4$, $TiBr_4$, $InBr_3$, $FeBr_3$	Br
I_2, TMSCl/NaI, $CeCl_3{\cdot}7H_2O$/LiI, TMSCl/NaI	I

$BF_3{\cdot}OEt_2$/Arene	Ar
$BF_3{\cdot}OEt_2/CH_3CN$, PMA/CH_3CN, $CeCl_3{\cdot}7H_2O$-AcCl/CH_3CN	$NHCOCH_3$
CF_3COOH, Montmorillonite KSF, $O_3ReOSiPh_3$, $Sc(OTf)_3$, Amberlyst 15, Amberlite® IR-120, $Ce(OTf)_3.H_2O$/IL/PhCOOH	OH
$BF_3{\cdot}OEt_2$/AcOH, TsOH/AcOH, TESOTf/TMSOAc/AcOH	OAc
TFA/NaN_3	N_3
$In(OTf)_3/NH_4SCN$	SCN
$BF_3{\cdot}OEt_2$/CuI/ Ph—≡—H	$PhCOCH_2$

Different investigators have used several halogenated Lewis acids as well as combination of Lewis acids and halide ion source to trap the tetrahydropyranyl cation by halide nucleophiles. Combination of Lewis acids and arenes has been utilized in tandem Prins/Friedel-Crafts reaction sequences to trap the tetrahydropyranyl cation by aryl nucleophile. Similarly, nitrile nucleophile has been used in tandem Prins/Ritter sequences to trap the tetrahydropyranyl cation. Trapping of the cation with oxygenated, nitrogenated, sulfur nucleophiles such as hydroxide, acetate, azide, thiocyanate etc. have also been reported.

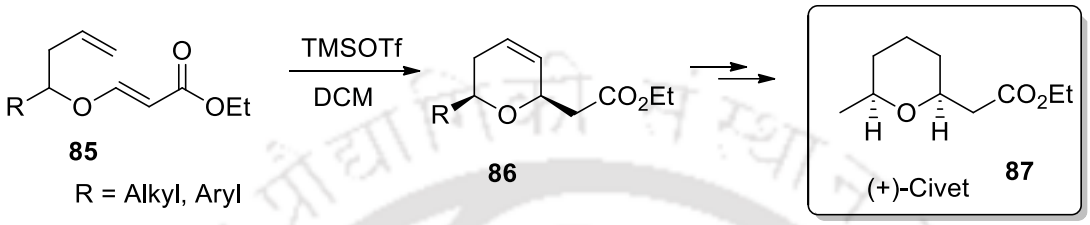
1.3.3 Enol Ethers in Prins Cyclization

One of the important variation of the Prins cyclization is the *in-situ* generation of oxocarbenium ion from enol ethers derived from homoallylic alcohols. This protocol was first demonstrated by Fráter and Nussbaumer for the synthesis of the natural product (±)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid.[31] Later in 2003, Bennett and Hart extended the scope of this route towards the synthesis of trisubstituted tetrahydropyrans **84** *via* TFA catalysed cyclization of enol ether **83** *(Scheme 1.3.3.1).*[32] In most cases, these tetrahydropyrans are isolated with moderate to good yields in excellent diastereoselectivity at C4 ranging from 95:5 to 50:50 depending on the nature of the substituent R.



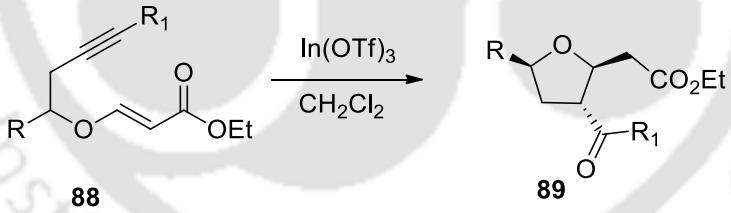
Scheme 1.3.3.1

Another example of using enol ether as the source of the oxocarbenium ion intermediate was demonstrated by our group in 2013.[33] Trimethylsilyl trifluoromethanesulfonate (TMSOTf) mediated Prins cyclization of acrylyl enol ethers **85** afforded 5,6-dihydro-2*H*-pyran-2-acetates **86** in good yields and in stereo- and regio-selective fashion (*Scheme 1.3.3.2)*. The methodology was further used for the total synthesis of natural product (+)-civet cat compound (**87**), which is used as an additive in the perfumery industry.



Scheme 1.3.3.2

Recently, our group developed a mild and efficient method for the synthesis of di- and tri-substituted tetrahydrofurans **89** from acrylyl enol ethers **88** *via* $In(OTf)_3$-mediated Prins cyclization reaction in good yields (*Scheme 1.3.3.3)*.[34] The method is highly diastereoselective and produced exclusively single diastereomers having a *cis* relationship between the C2-H and C5-H of the tetrahydrofuran ring.

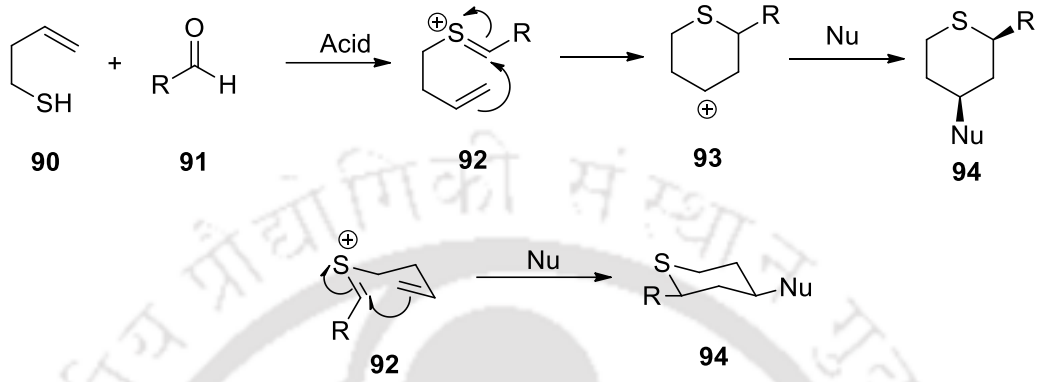


Scheme 1.3.3.3

1.3.4 Thia-Prins Cyclization Reaction

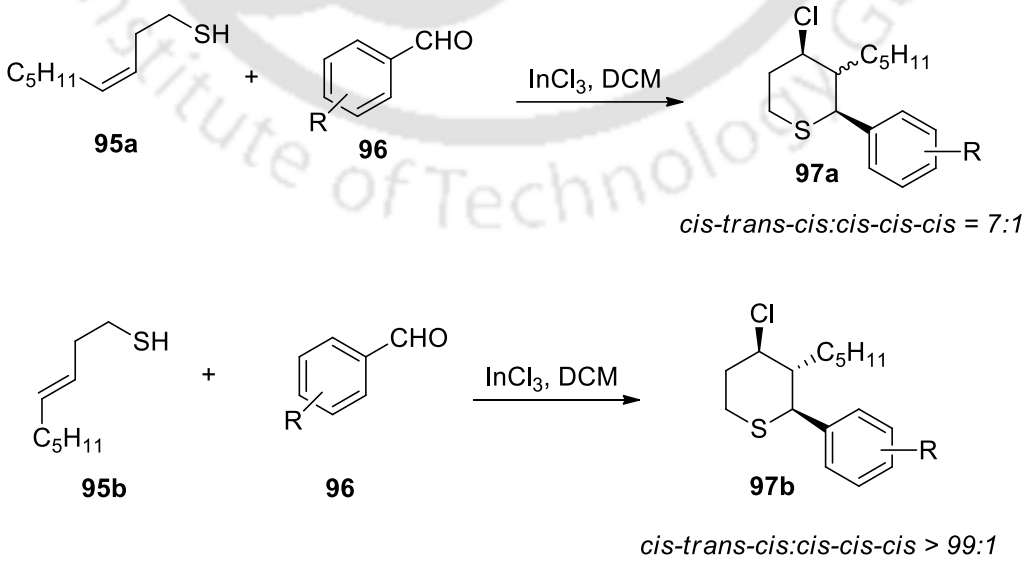
Thia-Prins reaction is the acid promoted/catalysed electrophilic addition reaction of aldehydes or ketones with homoallylic thiols. Analogues to oxa-Prins cyclization, thia-Prins cyclization gives direct access to the tetrahydrothiopyran skeleton, with the introduction of the nucleophile in C-4 position. Compared to Prins and aza-Prins reactions, its thia version has limited application in organic synthesis.The mechanism of thia-Prins cyclization reaction is similar to that of Prins cyclization, comprising the formation of

thiocarbenium ion **92** by the reaction of homoallylic thiol **90** and aldehyde **91**, in presence of acid. This thiocarbenium ion **92** undergoes 6-endo cyclization with an internal olefin resulting in the formation of secondary carbocation **93** that can be trapped by various nucleophiles from equatorial position to form the 2, 4-*cis*-tetrahydrothiopyran derivatives **94** as shown in *(Scheme 1.3.4.1.*)



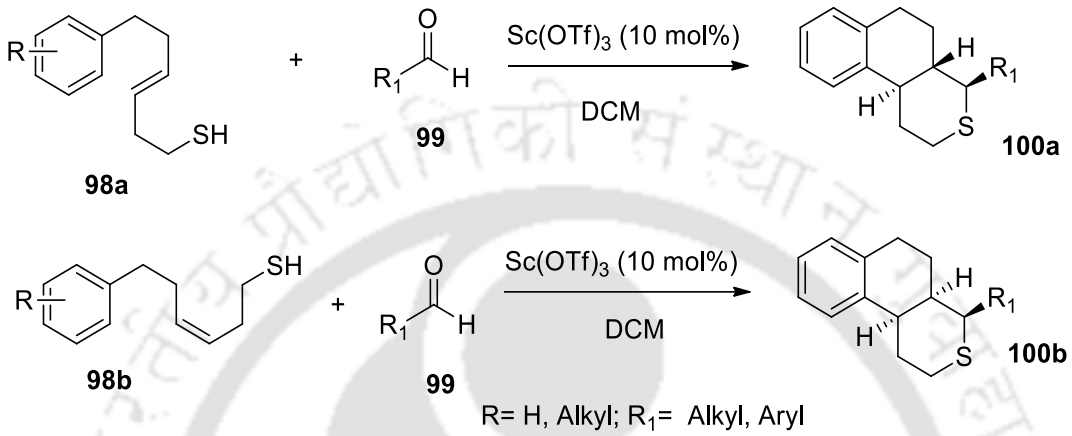
Scheme 1.3.4.1

In 2000, Li and co-workers have reported a strategy for the synthesis of 4-chloro-tetrahydrothiopyrans *via* thia-Prins cyclization of nonene-1-thiol **95** and aldehydes **96** in presence of indium trichloride ($InCl_3$) under mild condition.[35] The coupling of *cis*-mercaptan **95a** with aldehydes **96** gave rise to a mixture of *cis-cis-cis* and *cis-trans-cis* tetrahydrothiopyran derivatives **97a** with the latter as a predominant product, whereas the reaction of the *trans*-mercaptan **95b** produced the *cis-trans-cis* tetrahydrothiopyran derivative **97b** exclusively (*Scheme 1.3.4.2*).



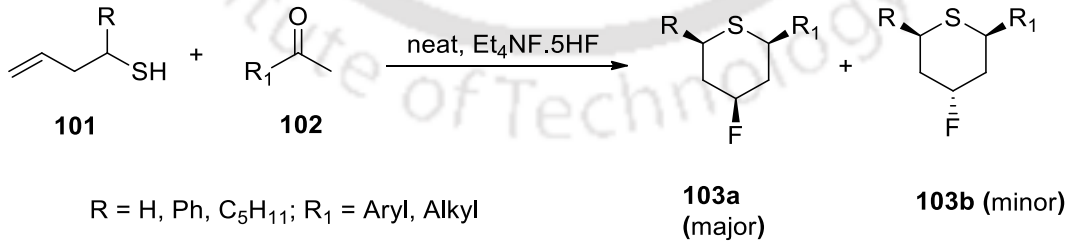
Scheme 1.3.4.2

Yadav *et al.* have developed an intramolecular tandem thia-Prins/Friedel-Crafts process, using (*E/Z*)-6-arylhex-3-enyl thiols **98**, aldehydes **99** in the presence of 10 mol % $Sc(OTf)_3$ to afford the *trans*/*cis* fused-hexahydro-1*H*-benzo[*f*]isothiochromenes **100** with excellent diastereoselectivity (*Scheme 1.3.4.3*).[36] Coupling of (*E*)-6-arylhex-3-enyl thiols **98a** produced the *trans* fused isothiochromenes **100a**, whereas (*Z*)-6-arylhex-3-enyl thiols **98b** afforded the *cis* fused products **100b**.



Scheme 1.3.4.3

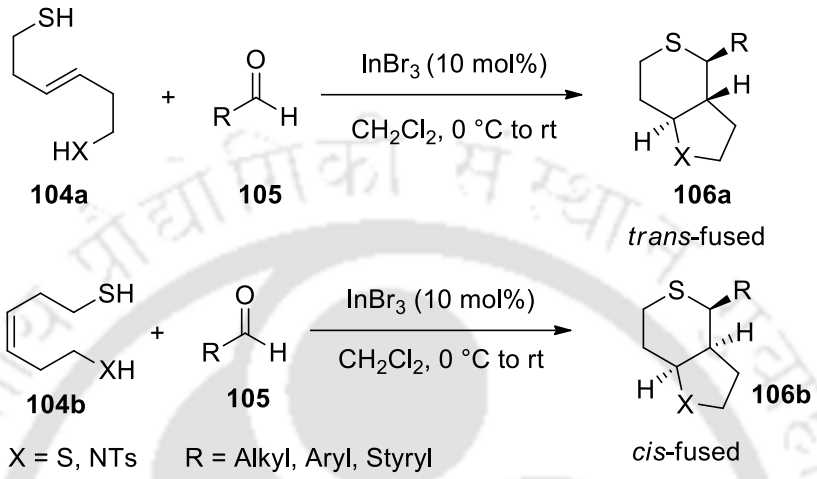
Kishi *et al*. have investigated the thia-Prins cyclization of homoallylic thiols **101** with various aldehydes **102** in ionic liquid hydrogen fluoride salts *i.e.* $Et_4NF.5HF$ to synthesize 4-fluoro-tetrahydrothiopyrans **103** with excellent yields.[37] In the reaction, ionic liquid hydrogen fluoride salts act as a reaction medium, a promoter, and a fluorine source. The reaction is highly diastereoselective with *cis* products **103a** as the major product (*Scheme 1.3.4.4*).



Scheme 1.3.4.4

In 2013, Yadav and co-workers have reported a tandem thia-Prins bicyclization approach for the stereoselective synthesis of dithia- and azathia-bicycles.[38] Coupling of homoallylic mercaptans such as hex-3-ene-1,6-dithiol and *N*-(6-mercaptohex-3-enyl)-4-methylbenzenesulfonamide **104** with various aldehydes **105** using 10 mol % $InBr_3$ in

dichloromethane gave hexahydro-*2H*-thieno[3,2-*c*]thiopyran derivatives and octahydrothiopyrano[4,3-*b*]pyrrole **106** derivatives, respectively, with excellent diastereoselectivity. *Trans*-fused products **106a** were obtained from *E*-homoallylic mercaptans **104a** whereas *Z*-homoallylic mercaptans **104b** afforded *cis*-fused products **106b** (*Scheme 1.3.4.5*).



Scheme 1.3.4.5

1.4. Reference

1. (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th edn., Blackwell Science, Oxford, **2000**. (b) Katritz ky, A. R. *Handbook of Heterocyclic Chemistry*, Pergamon Press, Oxford, **1985.**
2. (a) Kishi, Y. *Pure Appl. Chem.* **1998**, *70*, 339. (b) Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379. (c) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1. (d) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.
3. (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, VCH, Weinhein, **1996**. (b) Bahnck, K. B.; Rychnovsky, S. D. *Chem. Commun.* **2006**, 2388.
4. (a) Funahashi, Y.; Kawamura, N.; Ishimaru, T. Japan Patent 08231551 [A2960910], **1996**. (b) Bode, H. B.; Zeeck, A. *J. Chem. Soc., Perkin Trans. 1*. **2000**, 2665.
5. Horton, P. A.; Koehn, F. E.; Longley, R. E.; McConnell, O. J. *J. Am. Chem. Soc*. **1994**, *116*, 6015.
6. (a) Galpern, G. D. Int. J. Sulfur Chem. B. **1971**, *6*, 115**.** (b) Payzant, J.D.; Cyr, T. D.; Montgomery, D. S.; Strausz, O. P. *Tetrahedron Lett*. **1985**, *26*, 4175.
7. (a)Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbruggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852.
8. (a) Casy, G.; Lane, S.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1*. **1986**, 1397. (b)-Ohuchida, S.; Hamanaka, N.; Hagashi, M. *Tetrahedron* **1983**, *39*, 4273.
9. 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.
10. (a) 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. (b) 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. (c) Bin, H.; Crider, A. M.; Stables, J. P. Eur. *J. Med. Chem*. **2001**, *36*, 265. (d) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun*. **1998**, *6*, 633.
11. Lin, C.-N.; Huang, P.-L.; Lu, C.-M.; Wu, R.-R.; Hu, W.-P.; Wang, J.-J. *Tetrahedron* **1997**, *53*, 2025.
12. (a) Tong, X.-G.; Zhou, L.-L.; Wang, Y.-H.; Xia, C.; Wang, Y.; Liang, M.; Hou, F.-F.; Cheng, Y.-X. *Org. Lett.* **2010**, *12*, 1844. (b) Tong, X.-G.; Zhou, L.-L.; Wang,

Y.-H.; Xia, C.; Wang, Y.; Liang, M.; Hou, F.-F.; Cheng, Y.-X.; *Org. Lett.* **2011**, *13*, 4478.

13. (a) Sudhakar, G.; Kadam, V.D.; Bayya, S.; Pranitha, G.; Jagadeesh, B. *Org. Lett.* **2011**, *13*, 5452. (b) Wurst, J.M.; Verano, A.L.; Tan, D.S. *Org. Lett*. **2012**, *14*, 4442. (c) Borrero, N.V.; Aponick, A. *J. Org. Chem.* **2012**, *77*, 8410.
14. (a) Gharpure, S.J.; Prasad, J.V.K. *J. Org. Chem.* **2011,** *76*, 10325. (b) Blunt, J.W.; Copp, B.R.; Keyzers, R.A.; Munro, M.H.G.; Prinsep, M.R. *Nat. Prod. Rep*. **2013**, *30*, 237.
15. Tosi, G.; Zironi, F.; Caselli, E.; Forni, A.; Prati, F. *Synthesis* **2004**, 1625.
16. Shvaika, Ol. Osnovi sintezu likars'kikh rechovin *(Principles of Synthesis of Medicines)*, Donets'k: Skhidnii Vidavn. Dim, **2002.**
17. Forsyth, S.A.; Gunaratne, H.Q.N.; Hardacre, C.; McKeown, A.; Rooney, D.W. *Org. Process Res. Dev*., **2006**, *10*, 94; Tatsumi, Y.; Yokoo, M.; Senda, H.; Kakehi, K. *Antimicrob. Agents Chemother*. **2002**, *46*, 3797.
18. Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164.
19. Uozumi, Y.; Kyota, H.; Kato, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 1620.
20. Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 270.
21. (a) Kondo, T.; Okada, T.; Mitsudo, T. *J. Am. Chem. Soc.* **2002**, *124*, 186. (b) Kondo, T.; Tsunawaki, F.; Sato, R.; Ura, Y.; Wada,K.; Mitsudo, T. *Chem. Lett.* **2003**, *32*, 24.
22. Larksarp, C.; Sellier, O.; Alper, H. *J. Org. Chem.* **2001**, *66*, 3502.
23. Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935.
24. Marmsa¨ter, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144.
25. Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274.
26. (a) Bach, T.; Schlummer, B.; Harms, K. *Chem. Eur. J.* **2001,** *7*, 2581. (b) Bach, T.; Schlummer, B.; Harms, K. *Chem. Commun.* **2000**, 287.
27. Danielec, H.; Kluegge, J.; Schlummer, B.; *Synthesis* **2006**, 551.
28. (a) Prins, H. J. *Proc. Acad. Amsterdam*. **1919**, *22*, 51. (b) Prins, H. J. *Chem Weekbl.* **1919**, *16*, 1510.
29. Hanschke, E. *Chem. Ber.* **1955**, *88*, 1053.

30. Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc*. **2002**, *124*, 4960.
31. Nussbaumer, C.; Frater, G. *HelV. Chim. Acta.* **1987**, *70*, 396.
32. Hart, D. J.; Bennett, C. E. *Org. Lett*. **2003**, *5*, 1499.
33. Sultana, S.; Indukuri, K.; Deka, M. J.; Saikia. A. K. *J. Org. Chem*. **2013**, *78*, 12182.
34. Gogoi, P.; Das, V. K.; Saikia, A. K. *J. Org. Chem*. **2014**, *79*, 8592.
35. (a) Yang, X.-F.; Mague, J. T.; Li, C.-J. *J. Org. Chem.* **2001**, *66*, 739. (b) Yang, X.-F.; Li, C.-J. *Tetrahedron Lett*. **2000**, *41*, 1321.
36. Reddy, B. V. S.; Borkar, P.; Yadav, J. S.; Sridhar, B.; Gree, R. *J. Org. Chem*. **2011**, *76*, 7677.
37. (a) Kishi, Y.; Inagi, S.; Fuchigami, T. *Eur. J. Org. Chem*. **2003**, 103. (b) Kishi, Y.; Nagura, H.; Inagi, S.; Fuchigami, T. *Chem. Commun*. **2008**, 3876.
38. Reddy, B. V. S.; Venkateswarlu, A.; Borkar, P.; Yadav, J. S.; Kanakaraju, M.; Kunwar, A. C.; Sridhar B. *J. Org. Chem.* **2013**, *78*, 6303.

CHAPTER 2

Synthesis of Five-, Six-, and Seven-Membered 1,3- and 1,4-Heterocyclic Compounds *via* Intramolecular Hydroalkoxylation/Hydrothioalkoxylation of Alkenols/Thioalkenols

2.1 Importance and Applications

The high biological and chemical reactivity of oxaza heterocycles have led to continuous efforts in developing newer methodologies towards their synthesis. The tetrahydro derivatives of monocyclic 1,4-oxazines are found to be most prevalent ones.[1] The parent compound, morpholine or 1-oxa-4-azacyclohexane, has become commercially available in USA in 1935; since that time, it is one of the most widely used heterocyclic secondary amines. Morpholine being a fairly strong base (pKa 8.7, which is lower than that of piperidine) and potent solvent (morpholine > dioxane > pyridine > benzene) is widely used in industry and organic synthesis.[2] Substituted 1,4-oxazines, tetrahydro-2*H*-1,4-thiazines, and 1,4- oxazepanes are noted examples of widely distributed naturally occurring and biologically active molecules.[3] These are also considered to be diverse synthetic building blocks in organic synthesis particularly for the construction of agrochemicals, fungicides and bactericides.[4] *Figure 2.1.1* represents some examples of naturally occurring molecules containing oxaza moieties like reboxetine **1**, an antidepressant drug,[5] *cis*-2,3-disubstituted morpholine such as aprepitant (hNK1 antagonist) **2** is used for chemotherapy-induced nausea and vomiting (CINV) and commercially available under the name of Emend,[6] compounds **3** and **4** possess anti-inflammatory and $GABA_B$ receptor-antagonist properties.[7] The naturally occurring alkaloid batrachotoxin **5**, features the 1,4-oxazepane unit which acts as a ligand for CC chemokine receptors, such as CCRl.[8] Furthermore, 2,6-disubstituted morpholines are used as antitumor agents,[9a] mild diuretics, and anorectics.[9b] 1,4-Oxazines are also used as chiral auxiliaries[10] and have also found applications as catalysts and ligands in asymmetric addition of organozinc compounds to aldehydes,[11] cyclization of enals with ketones and amides for the synthesis of γ-lactones and γ-lactams,[12] δ- lactones,[13] aldolization,[14] alkylation of indoles with unsaturated aldehydes,[15]

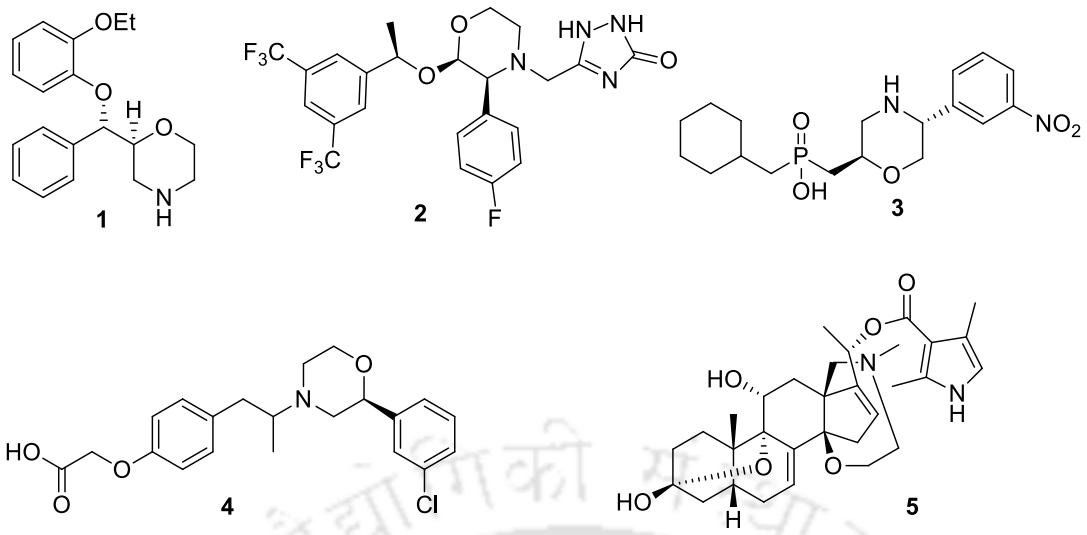


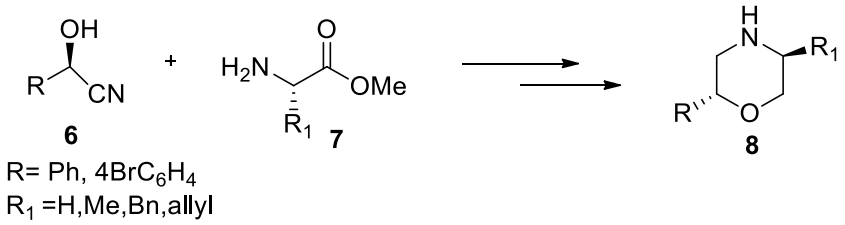
Figure 2.1.1. *Some natural moleules containing morpholine and oxazepane moiety.*

intramolecular Stetter reaction,[16] Heck cross-coupling of aryl halides with alkenes,[17] Michael addition of *α,β*-unsaturated aldehydes to 1,3-diketones,[18] Buchwald–Hartwig amination of (hetero)aryl chlorides,[19] and synthesis of pyrano[2,3-*b*]indoles *via* hetero-Diels-Alder reaction.[20] On the other hand, thiazolines are known as flavouring agents and are found in fruits and vegetables.[21] They are also known to possess biological activities such as antihypertensive,[22] antimicrobial,[23] and anticancer,[24] activity and are used as building blocks in peptide synthesis.[25]

2.2 Literature Methods

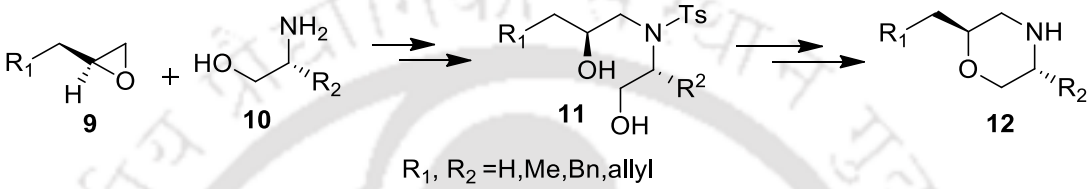
Several synthetic methodologies have been developed for the preparation of morpholines such as ring closure of amino diols,[26] ring closure of amino alcohols with bromosulphonium salts,[27] double allylic substitution by amino alcohols,[28] cyclization of *N*-tethered halo-alcohols,[29] reductive amination of diketones,[30] reductive etherification of *N*-tethered ketoalcohols,[31] cyclization of *O*-protected amino alcohols,[32] oxirane ring opening by tosylamide and subsequent cyclization,[33] ring opening of aziridines[34] and others. These methods have their own advantages and disadvantages. Therefore, development of new and efficient methods is imperative especially to address the issue of stereoselectivity.

Ritzen *et al*. reported a versatile method for the synthesis of enantiomerically pure *cis*- and *trans*-2, 5-disubstituted morpholines.[26a] *(Scheme 2.2.1)*



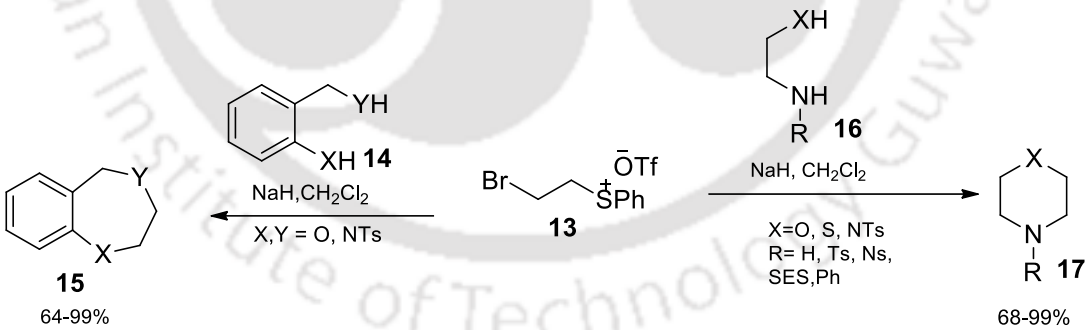
Scheme 2.2.1

Myers *et al*. developed a method for enantio- and diastereoselective syntheses of *trans*-2, 5-disubstituted morpholine derivatives initiated by the reaction of enantiopure epoxides with amino alcohols.[26b] *(Scheme 2.2.2)*



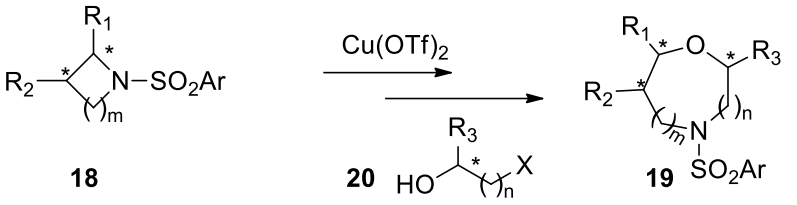
Scheme 2.2.2

Aggarwal and his group have demonstrated the reaction of bromoethylsulfonium salt with 1,2-/1,3-aminoalcohols giving six- and seven-membered rings in good to excellent yields. The reactions proceed through generation of a vinyl sulfonium salt followed by annulation to give 1,4-heterocyclic compounds such as morpholines and benzoxazepines.[27] *(Scheme 2.2.3)*



Scheme 2.2.3

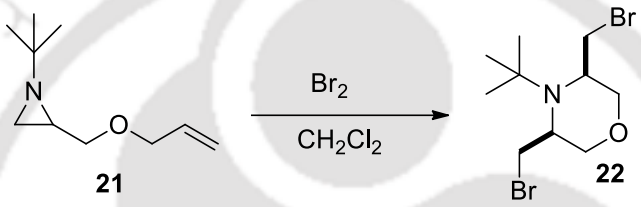
Ghorai *et al.* reported a highly regio- and stereoselective strategy for the syntheses of substituted nonracemic morpholines and their homologues in high yield and enantioselectivity. The reaction proceeds *via* an S_N2-type ring opening of activated aziridines and azetidines by suitable halogenated alcohols in the presence of Lewis acid followed by base-mediated intramolecular ring closure of the resulting haloalkoxy amine.[34a] *(Scheme 2.2.4)*



m = 0,1; n = 1,2 yield upto 92%, *ee* upto 99%
R_1 = H, Ph, *i*-Pr, *i*-Bu; R_2 = H, Me, Et, *i*-Pr, vinyl, Allyl ; R_3 = H, Ph

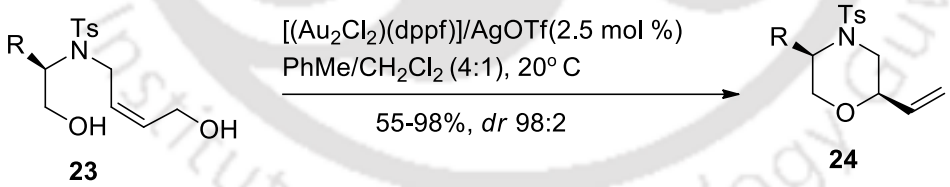
Scheme 2.2.4

Kimpe *et al.* reported the diastereoselective transformation of 1-*tert*-Butyl-2-(allyloxymethyl)aziridine into *cis*-3,5-di(bromomethyl)-4-*tert*-butylmorpholine *via* an electrophile induced ring closure using bromine in dichloromethane.[34b] *(Scheme 2.2.5)*



Scheme 2.2.5

Bandini *et al.* reported a highly stereo controlled synthesis of substituted morpholines *via* gold-catalyzed dehydrative allylic cyclization of diols. The reported methodology represents one of the few examples of enantioselective gold-catalyzed transformations of unactivated alkenes.[35] *(Scheme 2.2.6)*

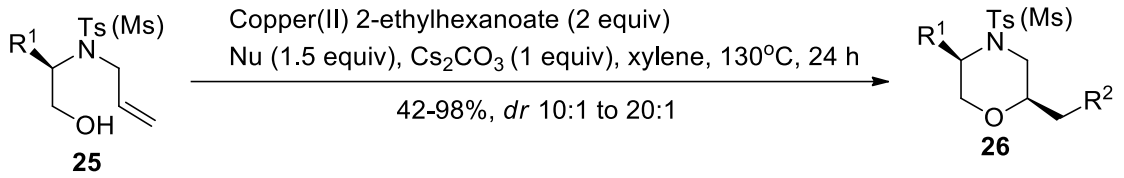


Scheme 2.2.6

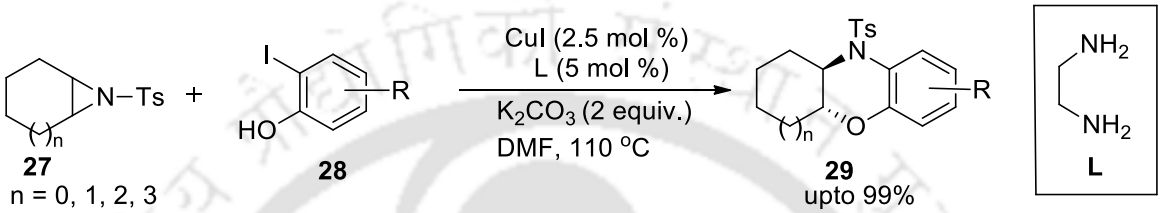
A new copper(II) 2-ethylhexanoate-promoted addition of an alcohol and an amine across an alkene (oxyamination) was reported by Chemler *et al.* The addition of alcohol is intramolecular, while coupling with the amine occurs intermolecularly. Several 2-aminomethyl morpholines were synthesized in good to excellent yields with high diastereoselectivities.[36] *(Scheme 2.2.7)*

Sekar *et al* reported the synthesis of *trans*-3,4-Dihydro-2*H*-1,4-benzoxazine moieties by domino aziridine ring opening with *o*-iodophenols followed by the copper-catalyzed

Goldberg coupling cyclization (intramolecular C(aryl)−*N*(amide) bond formation) with good to excellent yields.[37] *(Scheme 2.2.8)*

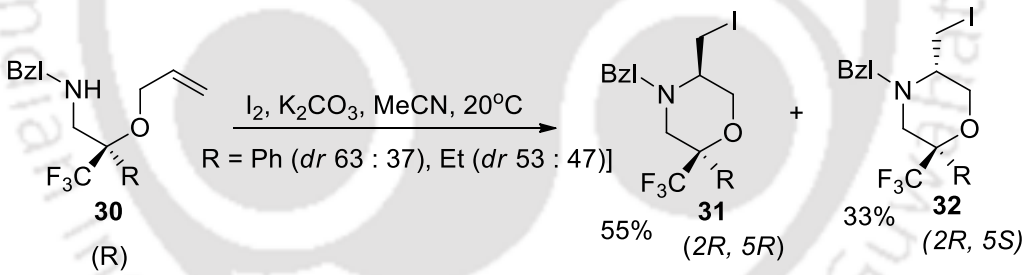


Scheme 2.2.7



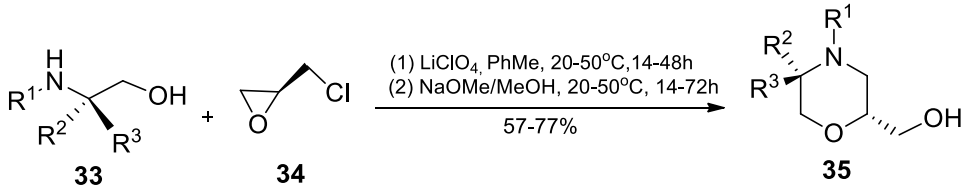
Scheme 2.2.8

Portella *et al.* demonstrated the synthesis of morpholines and oxazepanes derivatives containing a trifluoromethyl group on a quaternary carbon from a common enantiopure *O*-allyl amino ether precursor. Classic 6-exo iodoamination provided the iodomorpholines, whereas a a 7-endo cyclization sequence allowed the synthesis of oxazepanes.[38]



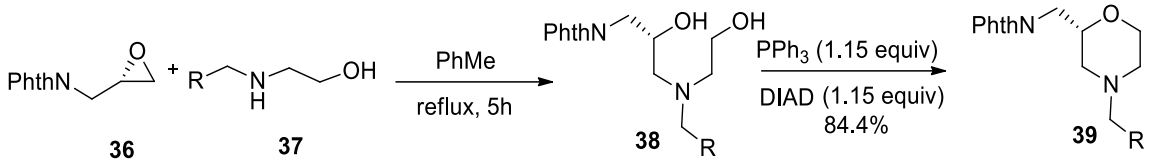
Scheme 2.2.9

Breuning *et al.* proposed a one-pot procedure for the synthesis of enantiomerically pure 2-(hydroxymethyl) morpholines from *(S)*-epichlorohydrin and amino alcohols **35** (R^1 = Me, Bzl; R^2 = H, Me, *i*-Pr, *t*-Bu; R^3 = H, Me, Ph).[39] *(Scheme 2.2.10)*



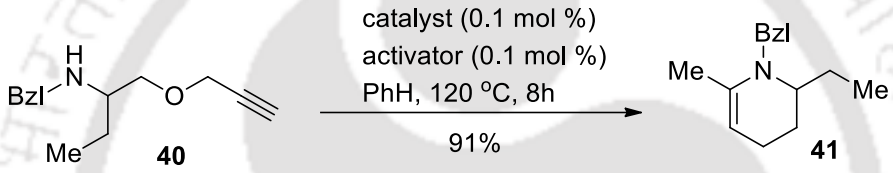
Scheme 2.2.10

Morpholine **39** (R = 3,4-$Cl_2C_6H_3$) was prepared according to Mitsunobu using triphenylphosphine (TPP, PPh_3) and diisopropyl azodicarboxylate (DIAD) as dehydrating agents by walker and group.[40] *(Scheme 2.2.11)*



Scheme 2.2.11

Zulys *et al*. reported an intramolecular hydroamination of various functionalized propargyl ethers, **40** using [*N*-isopropyl-2 (isopropylamino)troponiminato]- methylzinc as catalyst and [$PhNMe_2H$][$B(C_6F_5)_4$] as activator. A broad series of dehydromorpholines **41** were obtained in high yields.[41] (*Scheme 2.2.12)*



Scheme 2.2.12

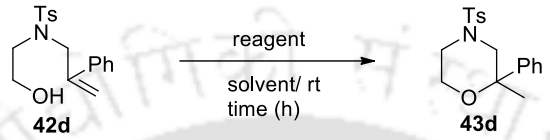
2.3 Present Work

Intramolecular hydroalkoxylation/ hydrothioalkoxylation reactions are currently of great interest for the synthesis of five- and six-membered cyclic ethers and thioethers using γ- and δ-hydroxy/thio olefins in the presence of transition-metal and lanthanide catalysts such as [$PtCl_2(H_2C{=}CH_2)]_2$, AgOTf, $Ph_3PAuOTf$, Au nanocluster (Au/PVP), $CeCl_3{\cdot}7H_2O$-NaI, $Ln(OTf)_3$, $In(OTf)_3$, and $Yb(OTf)_3$.[42] Similarly, $BF_3{\cdot}OEt_2$ has been used for the synthesis of tetrahydrocannabinols and cannabinoid derivatives and in the total synthesis of quinone and hydroquinone sesquiterpenes *via* intermolecular addition of phenol to alkene.[43] However, the use of $BF_3{\cdot}OEt_2$ in intramolecular hydroalkoxylation/hydrothioalkoxylation reaction for the synthesis of five-, six-, and seven membered 1,3- and 1,4-heterocyclic compounds has not been reported so far. This chapter presents a general and transition-metal free methodology for the synthesis of 1,4-oxazines, 1,4-oxazepanes, and thiazolidines using intramolecular hydroalkoxylation/hydrothioalkoxylation of alkenols/thioalkenols using $BF_3{\cdot}OEt_2$.

2.3.1 Results and Discussion

To start with, alkenol **42d** was treated with 1.2 equiv. of boron trifluoride etherate in dichloromethane at room temperature for 5 h, and 2-methyl-2-phenyl-4-tosylmorpholine **43d** was obtained in 90% yield. The reaction was also performed in different Lewis and Brønsted acidic conditions, and the results are shown in *Table 2.3.1.1*. The reaction with 0.5 equiv. of $BF_3{\cdot}OEt_2$ furnished only 38% yield over 12 h. Metal triflates such as zinc, copper, indium, and silver triflates were also screened for the reaction. Out of these, only

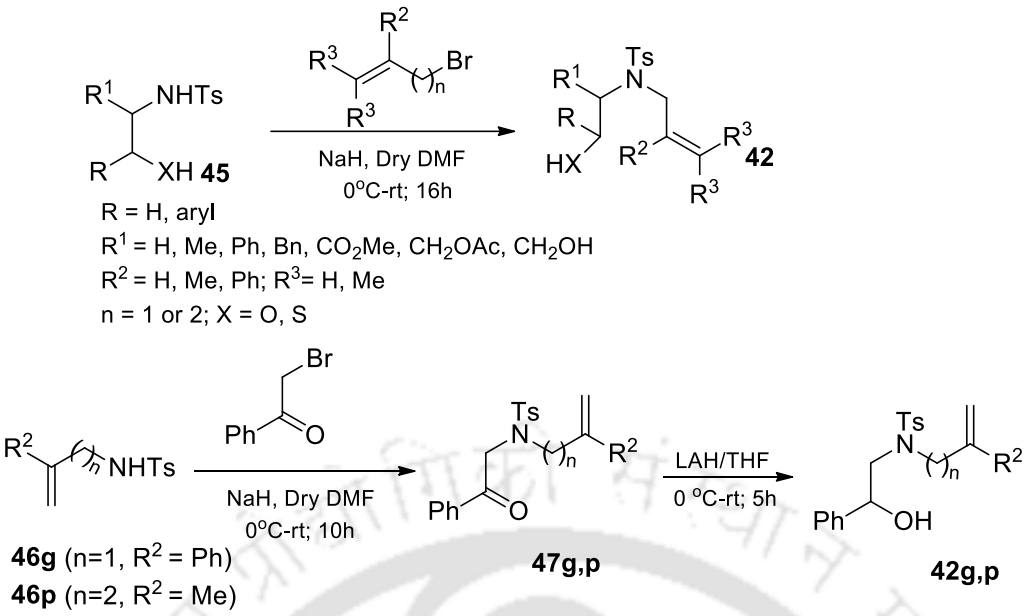
Table 2.3.1.1 Optimization of the reaction



entry	reagent amt, mmol	solvent	time (h)	conversion[b] (%)	yield[c] (%)
1	$BF_3{\cdot}OEt_2$ (1.2)	CH_2Cl_2	5	100	90
2	$BF_3{\cdot}OEt_2$ (0.5)	CH_2Cl_2	12	44	38
3	$Zn(OTf)_2$ (0.2)	CH_2Cl_2	24	g	5
4	$Cu(OTf)_2$ (0.2)	CH_2Cl_2	24	0	*d*
5	$In(OTf)_3$ (0.2)	CH_2Cl_2	24	36	30
6	$Ag(OTf)_2$ (0.2)	CH_2Cl_2	24	0	d
7	$InCl_3$ (0.2)	CH_2Cl_2	24	0	d
8	$CeCl_3.7H_2O$ (1.2)	CH_2Cl_2	24	0	d
9	$FeCl_3$	CH_2Cl_2	24	0	d
10	TsOH (1.2)	CH_2Cl_2	24	22	19
11	CSA (1.2)	CH_2Cl_2	24	34	26
12	TfOH (1.2)	CH_2Cl_2	24	63	52
13	HF (1.2)	CH_2Cl_2	24	0	*d*
14	$BF_3{\cdot}OEt_2$ (1.2)	toulene	12	70	72
15	$BF_3{\cdot}OEt_2$ (1.2)	CH_3CN	12	35	26
16	$BF_3{\cdot}OEt_2$ (1.2)	THF	12	61	53

Reaction Conditions: alkenol (1.0 mmol)/, solvent (5 ml). [b]Determined by ^1H NMR. [c]yield refers to isolated yield. [d]No reaction; starting material was recovered

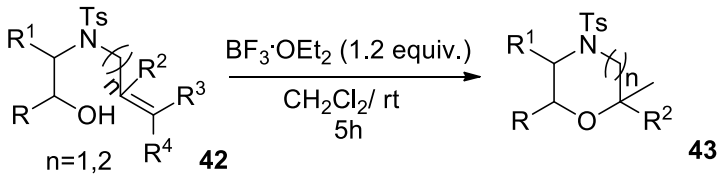
zinc and indium triflates gave 5% and 30% yields, respectively. Similarly, metal salts $InCl_3$, $CeCl_3{\cdot}7H_2O$, and $FeCl_3$ failed to give the desired product, but starting material was recovered in 98% yield. Brønsted acids such as toluenesulfonic acid (TsOH), camphorsulfonic acid (CSA), and triflic acid (TfOH) gave 19%, 26%, and 52% yields, respectively, whereas HF did not work. The reaction was also screened in other solvents such as toluene (entry 14), acetonitrile (entry 15), and THF (entry 16), and gave 72%, 26%, and 53% yields, respectively. Therefore, $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temperature was found to be the best conditions for this reaction.

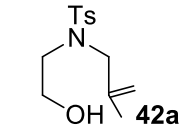
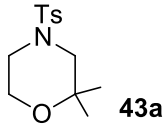
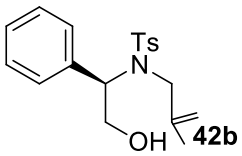
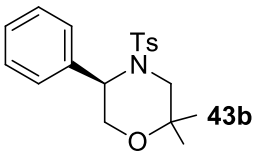
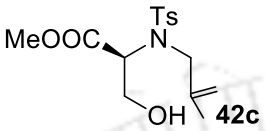
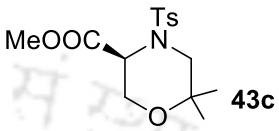
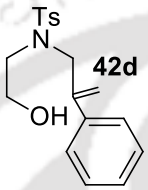
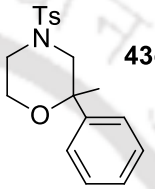
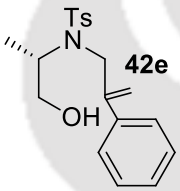
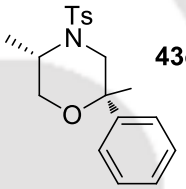
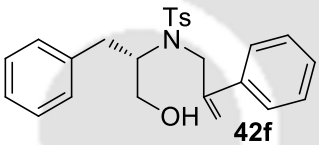
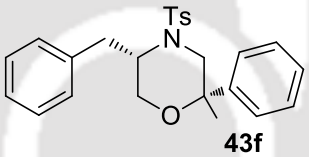
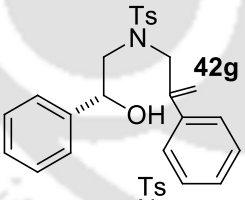
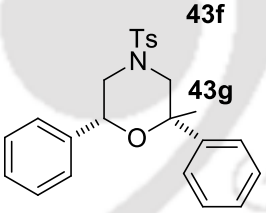
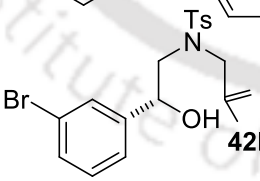
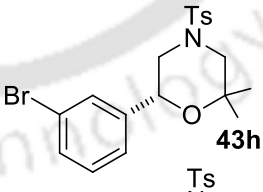
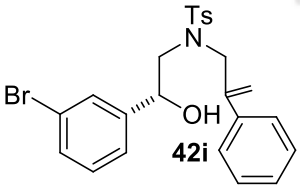
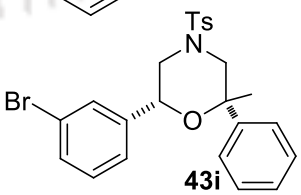


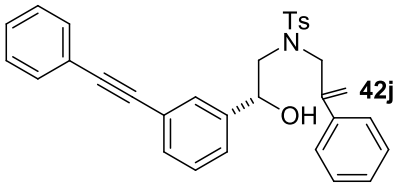
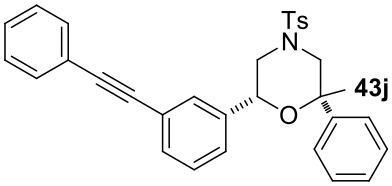
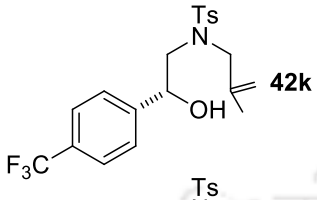
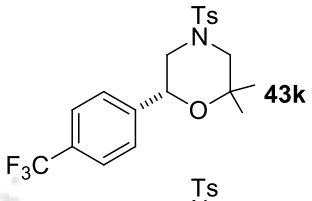
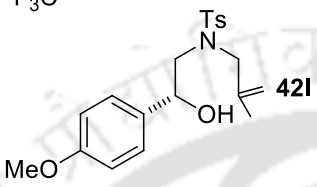
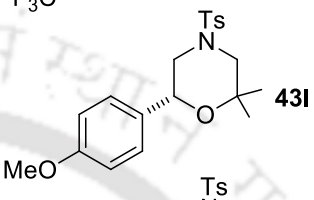
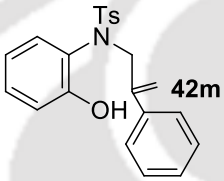
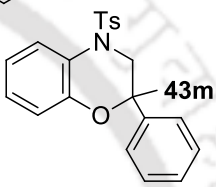
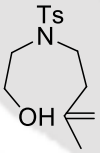
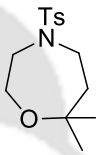
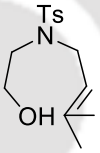
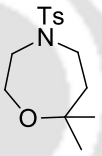
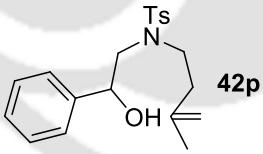
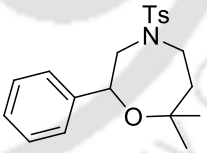
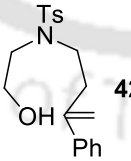
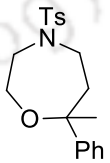
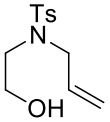
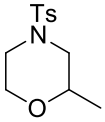
Scheme 2.3.1.1 *Synthesis of starting materials.*

Having obtained the optimized conditions, the scope of the reaction was further examined with a variety of substrates, which were synthesized according to the literature methods either by allylation of *N*-tosylamino alcohols/thiols or by substitution reaction between phenylacetyl bromide and *N*-allyl/ homoallyltosylamide followed by the reduction of the ketone.[44] (*Scheme 2.3.1.*) It was observed from (*Table 2.3.1.2)* that primary and secondary alkenols **42a-42l** (entries 1-12) having alkyl- and aryl substituted olefinic groups gave the desired 1,4-oxazines in good yields. In the case of secondary alkenols, the substrates having electron-withdrawing aromatic substituents (entries 7-11) gave good yields, whereas electron-donating aromatic substituted alkenol **42l** decomposed under these reaction conditions (entry 12). The chiral substrates **42e** and **42f** (entries 5 and 6) gave single diastereomers with 2-alkyl and 5-phenyl groups *cis* to each other. Similarly, the secondary alkenols **42g, 42i, and 42j** also produced exclusively single diastereomers

Table 2.3.1.2 Synthesis of morpholines



entry	substrate	product	yield(%)[a]
1	 **42a**	 **43a**	83
2	 **42b**	 **43b**	71
3	 **42c**	 **43c**	86
4	 **42d**	 **43d**	90
5	 **42e**	 **43e**	74
6	 **42f**	 **43f**	63
7	 **42g**	 **43g**	79
8	 **42h**	 **43h**	81
9	 **42i**	 **43i**	73

entry	substrate	product	yield (%)[a]
10			73
11			92
12			0
13			68
14			93
15			88
16			72
17			75
18			0

having a *cis* relationship between the phenyl groups at the 2- and 6- positions. The *cis* stereochemistry was confirmed by the X-ray crystallographic structures of **42f,g** *(Figure 2.3.1.1).*[45] This method also worked well for the phenolic compound **42m** (entry 13) and

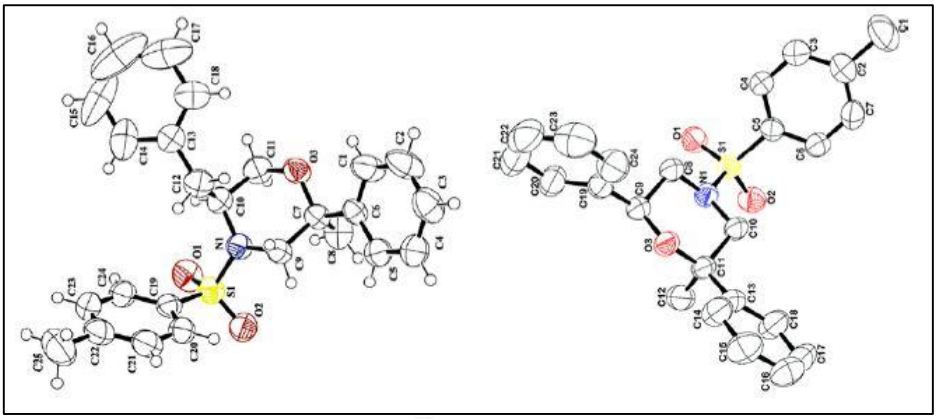
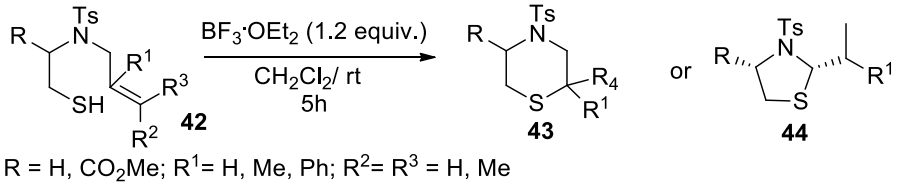


Figure 2.3.1.1 Ortep diagram of 43f and 43g.

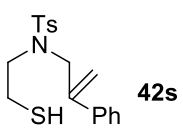
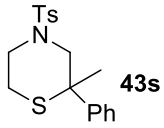
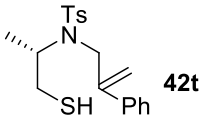
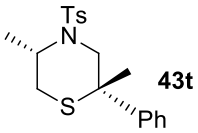
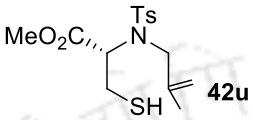
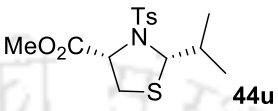
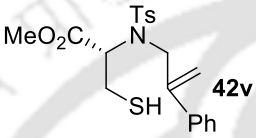
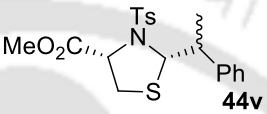
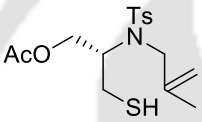
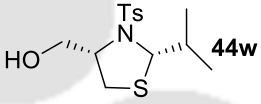
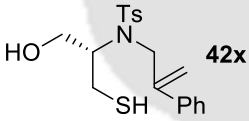
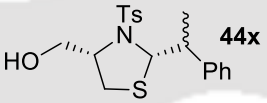
gave 2-methyl-2-phenyl-4-tosyl-3,4-dihydro-2*H*-benz[b][1,4]oxazine **43m** in 68% yield. Similarly, alkenols **42n-42q** (entries 14−17) gave the corresponding 1,4-oxazepanes **43n-43q** in good yields. The isomeric alkenols **42n and 42o** gave the same product, **43n**. On the other hand, a substrate having a terminal alkene, **42r** (entry 18), was unreactive under the same reaction conditions, and starting material was recovered in 98%.

After successful study of this methodology for the synthesis of 1,4 oxazines and oxazepanes, its application to the synthesis of 1,4-thiazines and thiazepanes was explored. The starting material thioalkenes **42s,t** (*Table 2.3.3*, entries 1 and 2) when treated with boron trifluoride etherate under the same reaction conditions gave 2-methyl-2-phenyl-4-tosylthiomorpholine **43s** and 2,5-dimethyl-2-phenyl-4-tosylthiomorpholine **43t** in 70% and 73% yields, respectively. On the other hand, substrates **42u-x** (*Table 2.3.3*, entries 3−6**)** having substitution at the *α*-position to the *N*-tosyl group gave thiazolidines **44u-x** (*Table 2.3.3*), in 66%, 71%, 59%, and 74% yields, respectively. Substrates **42v and 42x** (entries 4 and 6) gave two inseparable diastereomers, **44v and 44x,** in 71% and 74% overall yield, respectively. The substrate **42w** gave hydrolyzed product **44w** under these reaction conditions. On the other hand, **42x** having hydroxyl and thiol groups gave thiazolidine **44x** selectively, without formation of any morpholine products.

TABLE 2.3.1.3 Synthesis of tetrahydro-2H-1, 4-thiazine and thiazolidine.



R = H, CO_2Me; R^1= H, Me, Ph; R^2= R^3 = H, Me

Sl. No.	Substrate **42**	Product **43 / 44**	Yield (%) [a]
1	 **42s**	 **43s**	70[b]
2	 **42t**	 **43t**	86
3	 **42u**	 **44u**	66
4	 **42v**	 **44v**	71[c]
5	 **42w**	 **44w**	59
6	 **42x**	 **44x**	74[d]

[a]Yield refers to isolated yield. All the products were characterized by ^{1}H,^{13}C NMR and Mass spectrometry. [b]Reaction took 12 h. [c]Inseperable mixture of diastereomers with a ratio 7:3. Ratio is determined by ^{1}H NMR.

The stereochemistry of the thiazolidine was determined by ^{1}H NMR and NOE experiments of **44u** (*Figure 2.3.2*). There is a strong NOE between protons at C-2 and C-4 of **44u**, which confirms that they are *cis* to each other.

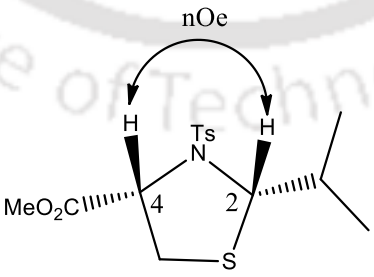
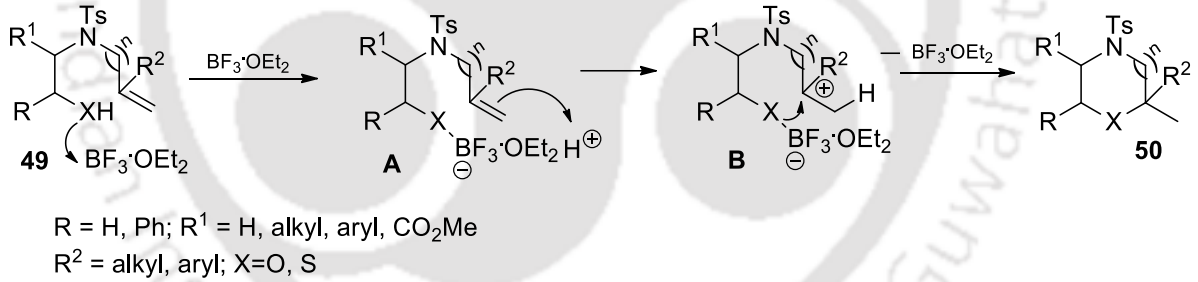


Figure 2.3.2. NOE diagram of compound 44u.

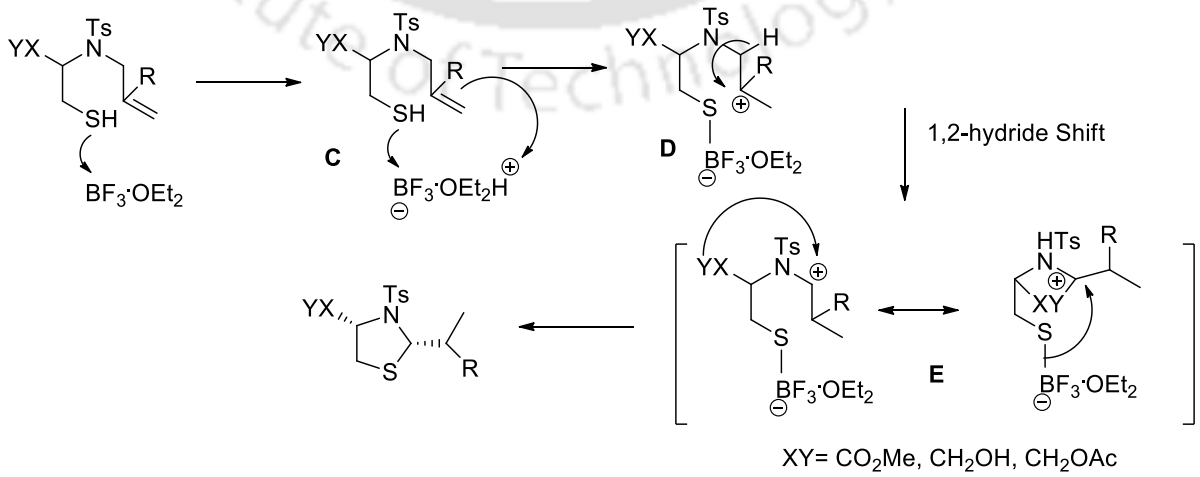
2.3.2 Plausible Mechanism

The exact mechanism of formation of 1,4-oxazines and 1,4-oxazepanes or their sulfur analogues *via* intramolecular hydroalkoxylation/hydrothioalkoxylation of

alkenols/thioalkenols mediated by boron trifluoride etherate is not known, but mechanisms for the hydroalkoxylation of alkenols promoted by transition metal or lanthanide reagents are proposed by different groups, where the metal forms a coordinated complex with alcohols and olefinic groups.[46] The same mechanism cannot be applied in this case as boron cannot form such type of complex. An alternative mechanism proposed, can be explained as follows. The alkenols/thioalkenols **42** react with boron trifluoride etherate to form intermediate **A**, an ion pair, the proton of which adds to the double bond to give more stable carbocation **B**. The carbocation **B** is then attacked by alkoxide/ion to form 1,4-oxazines, 1,4-oxazepanes, and thiazines (*Scheme 2.4.2, mechanism I*). This explains the incapability of formation of product by the substrate **42r**, where the carbocation B is not stable. On the other hand, the mechanism for the formation of thiazolidine products **44u-x** can be explained as follows. First thiol reacts with boron trifluoride etherate to form intermediate **C**, an ion pair, the proton of which adds to the double bond to give carbocation **D**, which is similar to intermediate **B**. This intermediate **D** undergoes a 1,2-hydride shift to give rearranged carbocation **E**, which is stabilized by ester or hydroxyl groups present at position 2. Finally, the thiol group attacks the carbocation **E** to give more stable five-membered compounds **44u-x** (*Scheme 2.3.3, mechanism II*). The presence of



Scheme 2.3.2.1 mechanism I.



Scheme 2.3.2.2 mechanism II.

ester and hydroxyl groups at the 2- position is crucial for the formation of the five-membered ring, which can be exemplified by the fact that compound **42t** having a methyl group at the 2-position gave six-membered ring **43t**.

2.4. Conclusion

In conclusion, this chapter describes a mild, metal-free and efficient general method for the synthesis of substituted 1,4-oxazenes, 1,4-oxazepanes and thiazolidines *via* intramolecular cyclization reaction of alkenols/thioalkenols with good yields. The reaction is highly diastereoselective and highly atom economic and compatible with a wide range of functional groups, such as ester, hydroxy, -CF_3, bromo, and alkyne. Furthermore, N-tethered alkenthiol having substituents at the α-position to nitrogen provides excellent access to a diverse array of thiazolidine derivatives with a 2,4-*cis* relationship.

2.5 Experimental section

2.5.1 Instrumentation and characterization

All the reagents were of analytical reagent (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 an open capillary tube and are uncorrected. Fourier transform infrared (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (600 MHz, 400 MHz) and ^{13}C (150 MHz, 100 MHz) NMR. Chemical shifts *(δ)* are reported in parts per million, and spin−spin coupling constants (*J*) are given in hertz. HRMS spectra were recorded using a Q-TOF mass spectrometer.

2.5.2 Synthesis of Starting Materials

2.5.2.1 General Procedure for the Synthesis of Starting Materials 42a−f, 42h−o, and 42q−x.

Amino alcohols and thiols **45a−f**, **45h−o**, and **45q−x** (1.0 equiv) in anhydrous DMF were added to a stirred solution of sodium hydride (1.2 equiv) in dry DMF under an inert atmosphere at 0 °C. After complete evolution of hydrogen gas, substituted allyl bromide (1.0 equiv) in DMF was added dropwise for 10 min, and the reaction was stirred at room temperature for 16 h. After completion of the reaction, brine solution was added to the reaction mixture, and the reaction mixture was extracted with ethyl acetate. The organic

layer was further washed with brine solution 2−3 times. The combined organic layers were dried over Na_2SO_4 and concentrated in a rotary evoparator. The obtained crude was subjected to column chromatography over silica gel, giving corresponding products **42a−f, 42h−o,** and **42q−x**.

2.5.2.2 General Procedure for the Synthesis of Starting Materials 42g, p.

Tosyl amides **46g, p** (1.0 equiv.) in anhydrous DMF were added to a stirred solution of sodium hydride (1.2 equiv.) in dry DMF under an inert atmosphere at 0 °C. After complete evolution of hydrogen gas, bromoacetophenone (1.0 equiv.) in DMF was added dropwise for 10 min, and the reaction was stirred at room temperature for 10 h. After completion of the reaction, brine solution was added to the reaction mixture, and the reaction mixture was extracted with ethyl acetate. The organic layer was further washed with brine solution (2 × 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude was subjected to column chromatography over silica gel, giving corresponding products **47g, p**. (1.0 equiv.) of **47g, p** in dry THF was added to a stirred suspension of LAH (1.0 equiv.) in THF at 0 °C. The reaction mixture was stirred at room temperature for 5 h, after which the reaction mixture was quenched with 2 N NaOH, passed through a Celite pad, and washed with ethyl acetate. The mixture was treated with brine and extracted with EtOAc, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified using column chromatography to give compounds **42g, p.**

2.5.2.3 General Procedure for the Synthesis of 43a−t and 44u−x. To a stirred solution of compounds 5a−x (1 mmol) in dichloromethane (5 mL) was added 1.2 equiv of borontrifluoride etherate under a nitrogen atmosphere at room temperature. The resulting solution continuously stirred for 5 h. After completion of the reaction, the reaction mixture was quenched by addition of saturated sodium bicarbonate solution (5 mL). The aqueous layer was extracted with dichloromethane (3 × 10 mL), and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was purified using column chromatography on silica gel with ethyl acetate and hexane as eluents.

2.6 References

1. Landquist, J.K., Comprehensive Organic Chemistry, Barton, D. and Ollis, W.D., Eds., Oxford: Pergamon, **1979**, vol. 4. Kas'yan, L.I., Pal'chikov, V.A., and Tokar', A.V., Oksazageterotsikly na osnove aminospirtov, epoksidovi aziridinov (Oxaza Heterocycles Based on Amino Alcohols, Epoxides, and Aziridines), Dnepropetrovsk: Dnepropetr. Univ., **2012**.
2. (a) Sawargave, S.P.; Kudale, A.S.; Deore, J.V.; Bhosale, D.S.; Divse, J.M.; Chavan, S.P.; Borate, H.B. *Tetrahedron Lett*. **2011**, *52*, 5491. (b) Balamurugan, K.; Jeyachandran, V.; Perumal, S.; Menéndez, J.C. *Tetrahedron* **2011**, *67*, 1432. (c) Heravi, M.M.; Zakeri, M.; Mohammadi, N.; *Chin. J. Chem*. **2011**, *29*, 1163. (d) Gomes, M.N.; De Oliveira, C.M.A.; Garrote, C.F.D.; De Oliveira, V.; Menegatti, R. *Synth. Commun*. **2011**, *41*, 52. (e) Heravi, M.M.; Zekeri, M.; Pooremamy, S.; Oskooie, H.A. *Synth. Commun.* **2011**, *41*, 113. (f) Song, W.; Liu, P.; Lei, M.; You, H.; Chen, X.; Chen, H.; Ma, L.; Hu, L. *Synth. Commun.* **2012**, *42*, 236. (g) Guo, M., Zhu, Z., Huang, H., and Zhang, Q., *Catal. Commun.* **2009**, *10*, 865.
3. (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.
4. (a) Bowers, W. S.; Ebing, W.; Fukuto, T. R.; Martin, D. *Chemistry of Plant Protection*; *Springer: Berlin*, **1986**; *1*, 55. (b) Worthing, C. R. The Pesticide Manual, 7th ed.; British Crop Protection Council: Alton, Hampshire, U.K., **1983**, p 265.
5. Hajos, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. *CNS Drug Rev.* **2004**, *10*, 23.
6. Pendergrass, K.; Hargreaves, R.; Petty, K. J.; Carides, A. D.; Evans, J. K.; Horgan, K. *J. Drugs Today* **2004**, *40*, 853.
7. (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. PCT Int. Appl. WO 03082861, **2003**. (b) Ong, J.; Kerr, D. I. B.; Bittiger, H.; Waldmeier, P. C.;

Baumann, P. A.; Cooke, N. G.; Mickel, S. J.; Froestl, W. *Eur. J. Pharmacol*. **1998**, *362*, 27. (c) Kuo, S.-C.; Blythin, D. J.; Kreutner, W. U.S. Patent 5929236, **1999**.

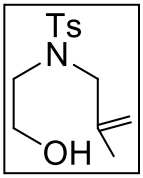
8. (a) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994**, *45*, 8333. (b) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 8337. (c) Khamrai, U.; Karak, S. K.; Ronsheim, M.; Saha, A. K. U.S. Patent 068191, **2010**.
9. (a) Hikichi, M.; Yokokura, T.; Furuta, T.; Yaegashi, T. JP 62135472; *Chem. Abstr.* **1987**, *107*, 198358. (b) GB 831933; *Chem. Abstr*. **1961**, *55*, 2697.
10. (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.
11. (a) Sánchez-Carnerero, E.M.; de las Casas Engel, T.; Maroto, B.L.; de la Moya Cerero, S. *Arkivoc*, **2011**, 359. (b) Binder, C.M., Bautista, A., Zaidlewicz, M., Krzemiski, M.P., Oliver, A., and Singaram, B., *J. Org. Chem*. **2009**, *74*, 2337. (c) Dave, R. and Sasaki, N.A. *Tetrahedron: Asymmetry* **2006**, *17*, 388. (d) Scarpi, D.; Lo Galbo, F.; Guarna, A. *Tetrahedron: Asymmetry* **2006**, *17*, 1409.
12. (a) Lv, H.; Tiwari, B.; Mo, J.; Xing, C.; Chi, Y.R. *Org. Lett.* **2012**, *14*, 5412. (b) Matsuoka, Y.; Ishida, Y.; Saigo, K. *Tetrahedron Lett.* **2008**, *49*, 2985. (c) Raup, D.E.A.; Cardinal-David, B.; Holte, D.; Scheidt, K.A. *Nat. Chem*. **2010**, *2*, 766.
13. Dai, Y.; Feng, X.; Wang, B.; He, R.; Bao, M. *J. Organomet. Chem*. **2012**, *696*, 4309.
14. (a) Emer, E.; Galletti, P.; Giacomini, D. *Tetrahedron* **2008**, *64*, 11205.(b) Xiang, S.-K.; Zhang, B.; Zhang, L.-H.; Cuia, Y.; Jiao, N. *Chem. Commun*. **2011**, *47*, 8097.
15. Xiang, S. K.; Zhang, B.; Zhang, L. H. Cuia, Y.; Jiao, N. *Chem. Commun.* **2011**, *47*, 8097.
16. (a) Jia, M. Q.; Liu, C.; You, S. L. *J. Org. Chem.* **2012**, *77*, 10996. (b) Rong, Z. Q.; Li, Y.; Yang, G. Q.; You, S.-L. *Synlett* **2011**, 1033.
17. (a) Kucukbay, H.; Sireci, N.; Yilmaz, U.; Akkurt, M.; Yalcin, S.P.; Tahir, M.N.; Ott, H. *Appl. Organomet. Chem.* **2011**, *25*, 255. (b) Singh, P.; Das, D.; Prakash, O.; Singh, A.K. *Inorg. Chim. Acta* **2013**, *394*, 77. (c) Niknam, K.; Gharavi, A.; Nezhad, M.R.H.; Panahi, F.; Sharbati, M.T. *Synthesis* **2011**, 1609.

18. (a) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 4080. (b) Biswas, A.; Sarkar, S.D.; Fröhlich, R.; Studer, A. *Org. Lett.* **2011**, *13*, 4966. (c) Reddi, Y.; Sunoj, R.B. *Org. Lett.* **2012**, *14*, 2810.
19. Tardiff, B.J.; McDonald, R.; Ferguson, M.J.; Stradiotto, M. *J. Org. Chem.* **2012**, *77*, 1056.
20. Yang, L.; Wang, F.; Chua, P.J.; Lv, Y.; Zhong, L.-J.; Zhong, G. *Org. Lett*. **2012**, *14*, 2894.
21. (a) MacLeod, G.; Ames, J. *Flavour Fragrance J*. **1986**, *1*, 91. (b) MacLeod, G.; Ames, *J. J. Food Sci.* **1987**, *52*, 42. (c) Ong, P.; Acree, T. *J. Agric. Food Chem.* **1998**, *46*, 2282.
22. (a) Wipf, P.; Fritch, P. *Tetrahedron Lett.* **1994**, *35*, 5377. (b) Pattenden, G.; Boden, C.; Ye, T. *Synlett* **1995**, 417. (c) Paul, B.; Korytnyk, W. *J. Med. Chem*. **1976**, *19*, 1002.
23. Cook, A. H.; Heilborn, I. M. The Chemistry of Penicilin; PrincetonUniversity Press: Princeton, NJ, **1949**; p 921.
24. Oya, M.; Kato, E.; Iwao, J.; Yasuoka, N. *Chem. Pharm. Bull*. **1982**, *30*, 484.
25. Haack, T.; Mutter, M. *Tetrahedron Lett.* **1992**, *33*, 1589.
26. (a) Ritzen, B.; Hoekman, S.; Verdasco, E. D.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem*. **2010**, *75*, 3461. (b) Lanman, B. A.; Myers, A. G. *Org. Lett*. **2004**, *6*, 1045.
27. Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett*. **2009**, *11*, 257.
28. Wilkinson, M. C. *Tetrahedron Lett*. **2005**, *46*, 4773.
29. (a) Brenner, E.; Baldwin, R. M.; Tamagnan, G. *Org. Lett*. **2005**, *7*, 937. (b) Jagtap, R. S.; Joshi, N. N. *Tetrahedron: Asymmetry* **2011**, *22*, 1861. (c) O'Reilly, M. C. Lindsley, C. W. *Tetrahedron Lett*. **2012**, *53*, 1539.
30. Burland, P. A.; Osborn, H. M.; Turkson, A. *Biorg. Med. Chem*. **2011**, *19*, 5679.
31. (a) Gharpure, S. J.; Prasad, J. V. K. *J. Org. Chem*. **2011**, *76*, 10325. (b) Gharpure, S. J.; Prasad, J. V. K. *Eur. J. Org. Chem*. **2013**, 2076.
32. Dave, R.; Sasaki, N. A. *Org. Lett*. **2004**, *6*, 15.
33. Lupi, V.; Albanese, D.; Landini, D.; Scaletti, D.; Penso, M. *Tetrahedron* **2004**, *60*, 11709.

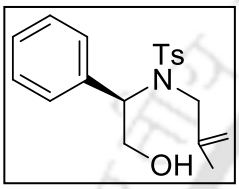
34. (a) Ghorai, M. K.; Shukla, D.; Das, K. *J. Org. Chem*. **2009**, *74*, 7013. (b) D'hooghe, M.; Anlangendonck, T.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem*. **2006**, *71*, 4678. (c) Bornholdt, J.; Felding, J.; Kristensen, J. L. *J. Org. Chem*. **2010**, *75*, 7454.
35. Bandini, M.; Monari, M.; Romaniello, A.; Tragni, M. *Chem. Eur. J.* **2010**, *16*, 14272.
36. Sequeira, F.C.; Chemler, S.R. *Org. Lett*. **2012**, *14*, 4482.
37. Rao, R.K.; Naidu, A.B.; Sekar, G. *Org. Lett.* **2009**, *11*, 1923.
38. (a) Nonnenmacher, J.; Grellepois, F.; Portella, C. *Eur. J. Org. Chem.* **2009**, 3726. (b) Taylor, A.M.; Schreiber, S.L. *Tetrahedron Lett.* **2009**, *50*, 3230.
39. Breuning, M.; Winnacker, M.; Steiner, M. *Eur. J. Org. Chem.* **2007**, *2007*, 2100.
40. Wilkinson, M.C.; Bell, R.; Landon, R.; Nikiforov, P.O.; Walker, A.J. *Synlett* **2006**, *13*, 2151.
41. Zulys, A.; Dochnahl, M.; Hollmann, D.; Löhnwitz, K. Steffen, *J. Angew. Chem. Int. Ed*. **2005**, *44*, 7794.
42. (a) Dzudza, A.; Marks, T. J. *Org. Lett*. **2009**, *11*, 1523. (b) Marotta, E.; Foresti, E.; Marcelli, T.; Peri, F.; Righi, P.; Scardovi, N.; Rosini, G. *Org. Lett*. **2002**, *4*, 4451. (c) Yang, C.-G.; He, C. *J. Am. Chem. Soc*. **2005**, *127*, 6966. (d) Sakurai, H.; Kamiya, I.; Kitahara, *H. Pure Appl. Chem.* **2010**, *82*, 2005. (e) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc.* **2001**, *123*, 2450. (f) Guérinot, A.; Serra-Muns, A.; Bensouussan, C.; Reymond, S.; Cossy, J. *Tetrahedron* **2011**, *67*, 5024. (g) Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536. (h) Yang, C.-G.; Reich, N. W.; Shi, Z.; He, C. *Org. Lett*. **2005**, *7*, 4553. (i) Dzudza, A.; Marks, T. J. C*hem. Eur. J*. **2010**, *16*, 3403. (j) Weiss, C. J.; Marks, T. *J. Dalton Trans*. **2010**, *39*, 6576. (k) Weïwer, M.; Coulombel, L.; Duňach, E. *Chem. Commun*. **2006,** 332.
43. (a) Kuan, K. K. W.; Pepper, H. P.; Bloch, W. M.; George, J. H. *Org. Lett*. **2012**, *14*, 4710. (b) Marcos, L. S.; Conde, A.; Moro, R. F.; Basabe, P.; Diez, D.; Urones, J. G. *Tetrahedron* **2010**, *66*, 8280. (c) Papahatjis, D. P.; Nahmias, V. R.; Nikas, S. P.; Andreou, T.; Alapafuja, S. O.; Tsotinis, A.; Guo, J.; Fan, P.; Makriyannis, A. *J. Med. Chem.* **2007**, *50*, 4048. (d) Papahatjis, D. P.; Nahmias, V. R.; Andreou, T.; Fanb, P.; Makriyannis, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1616.

44. a) Poornachandran, M.; Raghunathan, R. *Tetrahedron* **2008**, *64*, 6461. (b) Bera, S.; Panda, G. *ACS Comb. Sci.* **2012**, *14*, 1. (c) Tarantino, K. T.; Liu, P.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 10022.
45. The crystallographic data for compounds **43f,g** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1051766 and 1041712, respectively.
46. Sequeira, F. C.; Chemler, S. R. *Org. Lett*. **2012**, *14*, 4482.

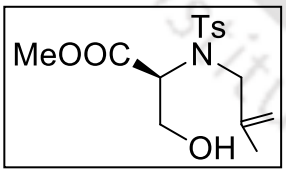
2.7 Spectral Data



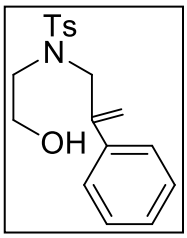
***Data for N-(2-hydroxyethyl)-4-methyl-N-(2-methylallyl)-benzenesulfonamide (42a)*:** white solid; mp 74−76 °C; R_f (hexane/EtOAc, 7:3) 0.47; yield 393 mg, 73%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.70 (s, 3 H), 2.40 (s, 3 H), 3.15 (t, *J* = 5.6 Hz, 2 H), 3.65 (t, *J* = 5.6 Hz, 2 H), 3.68 (s, 2 H), 4.84 (s, 1 H), 4.88 (s, 1 H), 7.28 (d, *J* = 7.6 Hz, 2 H), 7.68 (d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.0, 21.7, 50.6, 56.4, 61.2, 115.0, 127.5, 129.9, 136.0, 141.0, 143.8; **IR** (KBr, neat) 3440, 2924, 1334, 1159, 1020, 708 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{13}H_{20}NO_3S$ $(M + H)^+$ 270.1158, found 270.1157.



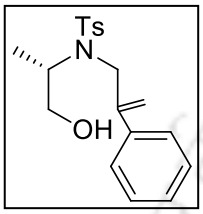
Data for (R)-N-(2-hydroxy-1-phenylethyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (42b): colorless gum; R_f (hexane/EtOAc, 7:3) 0.54; yield 566 mg, 82%; $[\alpha]_{25}^{D}$ = −81.0 (c = 0.15, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.68 (s, 3 H), 2.45 (s, 3 H), 3.32 (d, *J* = 16.0 Hz, 1 H), 3.93 (d, *J* = 16.0 Hz, 1 H), 4.02 (dd, *J* = 11.2 and 6.0 Hz, 1 H), 4.16 (dd, *J* = 11.2 and 8.8 Hz, 1 H), 4.82 (s, 1 H), 4.87 (s, 1 H), 4.95 (dd, *J* = 8.8 and 6.4 Hz, 1 H), 6.83 (d, *J* = 7.6 Hz, 2 H), 7.16−7.27 (m, 3 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.0, 21.7, 51.3, 62.8, 62.9, 114.0, 127.5, 128.5, 128.6, 128.8, 129.9, 135.2, 138.0, 142.6, 143.7; **IR** (KBr, neat) 3532, 2953, 2925, 1742, 1658, 1439, 1339, 1159, 1093, 816, 709 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{19}H_{24}NO_3S$ $(M + H)^+$ 346.1471, found 346.1477.



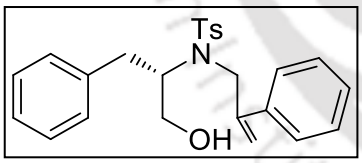
Data for (S)-methyl 3-hydroxy-2-(4-methyl-N-(2-methylallyl)-benzenesulfonamido)propanoate (42c): pale yellow oil; R_f (hexane/ EtOAc, 7:3) 0.46; yield 432 mg, 66%; $[\alpha]_{25}^{D}$ = −29.0 (c = 0.1, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 1.67 (s, 3 H), 2.43 (s, 3 H), 3.59 (s, 3 H), 3.75 (d, *J* = 16.2 Hz, 1 H), 3.82 (dd, *J* = 11.4 and 6.0 Hz, 1 H), 3.92 (d, *J* = 15.6 Hz, 1 H), 4.10−4.14 (m, 1 H), 4.41 (t, *J* = 6.6 Hz, 1 H), 4.94 (s, 1 H), 5.00 (s, 1 H), 7.30 (d, *J* = 7.8 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) *δ* 20.0, 21.7, 52.3, 53.5, 61.0, 61.7, 114.9, 127.8, 129.7, 136.8, 141.6, 143.9, 170.4; **IR** (KBr, neat) 3528, 2924, 2855, 1598, 1496, 1330, 1159, 1020, 898, 701 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{15}H_{22}NO_5S$ $(M + H)^+$ 328.1213, found 328.1219.



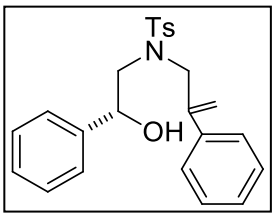
***Data for N-(2-hydroxyethyl)-4-methyl-N-(2-phenylallyl)-benzenesulfonamide (42d)*:** colorless solid; mp 83−85 °C; R_f (hexane/EtOAc, 7:3) 0.48; yield 596 mg, 90%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 3.16 (t, J = 5.4 Hz, 2 H), 3.56 (t, J = 5.4 Hz, 2 H), 4.24 (s, 2 H), 5.23 (s, 1 H), 5.50 (s, 1 H), 7.26−7.36 (m, 5 H), 7.46 (d, J = 7.8 Hz, 2 H), 7.67 (d, J = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 50.3, 53.9, 61.2, 117.0, 126.7, 127.7, 128.5, 128.8, 130.0, 135.4, 138.0, 143.2, 143.9; **IR** (KBr, neat) 3527, 2925, 1598, 1495, 1334, 1185, 1016, 916, 709 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{18}H_{22}NO_3S$ $(M + H)^+$ 332.1315, found 332.1318.



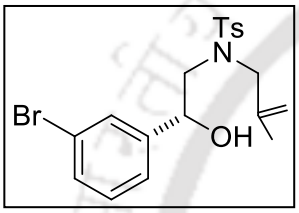
Data for (S)-N-(1-hydroxypropan-2-yl)-4-methyl-N-(2-phenylallyl)benzenesulfonamide (42e): pale yellow gum; R_f (hexane/ EtOAc, 7:3) 0.53; yield 449 mg, 65%; $[\alpha]_{25}^{D}$ = +26.0 (c = 0.14, (CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 0.86 (d, J = 6.6 Hz, 3 H), 2.43 (s, 3 H), 3.35 (dd, J = 11.4 and 4.8 Hz,1 H), 3.48 (dd, J = 12.0 and 9.0 Hz, 1 H), 3.91−3.97 (m, 1 H), 4.04 (d, J = 15.6 Hz, 1 H), 4.62 (d, J = 16.2 Hz, 1 H), 5.39 (s, 1 H), 5.45 (s, 1 H), 7.25−7.40 (m, 5 H), 7.46 (t, J = 7.2 Hz, 2 H), 7.69 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 13.6, 21.7, 48.3, 56.2, 65.0, 115.9, 126.9, 127.5, 128.5, 128.8, 130.0, 137.5, 138.6, 143.7, 145.5; **IR** (KBr, neat) 3538, 2925, 1598, 1495, 1334, 1155, 1026, 912, 738 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{19}H_{24}NO_3S$ $(M + H)^+$ 346.1471, found 346.1469.



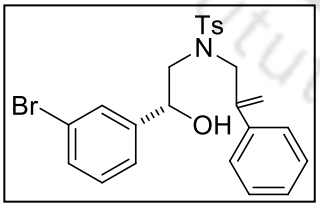
Data for (S)-N-(1-hydroxy-3-phenylpropan-2-yl)-4-methyl-N-(2-phenylallyl)benzene sulfonamide (42f): pale yellow oil; R_f(hexane/ EtOAc, 4:1) 0.55; yield 598 mg, 71%; $[\alpha]_{25}^{D}$ = −26.0 (c = 0.1, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 2.54 (dd, J = 13.8 and 4.2 Hz, 1 H), 2.73 (dd, J = 13.2 and 10.8 Hz, 1 H), 3.44 (dd, J = 11.4 and 3.0 Hz, 1 H), 3.57 (dd, J = 12.0 and 9.0 Hz, 1 H), 3.88− 3.94 (m, 1 H), 4.31 (d, J = 16.2 Hz, 1 H), 4.57 (d, J = 16.2 Hz, 1 H), 5.44 (s, 1 H), 5.49 (s, 1 H), 6.93 (d, J = 6.6 Hz, 2 H), 7.16−7.21 (m, 2 H), 7.29 (d, J = 7.8 Hz, 2 H), 7.32−7.36 (m, 4 H), 7.43 (d, J = 8.4 Hz, 2 H), 7.71 (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) 3479, 2926, 1494, 1331, 1157, 1041, 814, 701 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{25}H_{28}NO_3S$ $(M + H)^+$ 422.1784, found 422.1781.



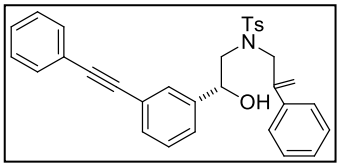
Data for N-(2-hydroxy-2-phenylethyl)-4-methyl-N-(2-phenylallyl)benzenesulfonamide (42g): colorless gum; R_f (hexane/ EtOAc, 4:1) 0.50; yield 459 mg, 56%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 3.05 (dd, J = 15.2 and 2.4 Hz, 1 H), 3.25 (dd, J = 15.2 and 9.6 Hz, 1 H), 4.16 (d, J = 14.8 Hz, 1 H), 4.46 (d, J = 14.8 Hz, 1 H), 4.79 (dd, J = 10.0 and 2.4 Hz, 1 H), 5.23 (s, 1 H), 5.54 (s, 1 H), 7.22−7.37 (m, 10 H), 7.45−7.49 (m, 2 H), 7.65 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.4, 53.8, 56.1, 72.1, 117.1, 125.7, 126.0, 126.4, 127.2, 127.4, 127.7, 128.3, 128.6, 129.6, 129.7, 137.8, 142.9, 143.7; **IR** (KBr, neat) 3538, 2925, 1598, 1495, 1334, 1155, 1026, 912, 738 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{24}H_{25}NNaO_3S$ $(M + Na)^+$ 430.1447, found 430.1456.



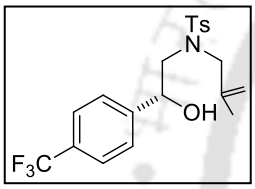
Data for N-(2-(3-bromophenyl)-2-hydroxyethyl)-4-methyl-N-(2- methylallyl) benzenesulfonamide (42h): white solid; mp 89−91 °C; R_f (hexane/EtOAc, 9:1) 0.39; yield 711 mg, 84%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.70 (s, 3 H), 2.42 (s, 3 H), 3.04 (dd, J = 15.0 and 3.0 Hz, 1 H), 3.31 (dd, J = 15.0 and 9.6 Hz, 1 H), 3.43 (br s, 1 H), 3.58 (d, J = 14.4 Hz, 1 H), 3.92 (d, J = 15.0 Hz, 1 H), 4.86 (d, J = 9.0 Hz, 1 H), 4.89 (s, 1 H), 4.97 (s, 1 H), 7.18 (t, J = 7.8 Hz, 1 H), 7.23 (d, J = 7.8 Hz, 1 H), 7.30 (d, J = 7.8 Hz, 2 H), 7.38 (d, J = 7.8 Hz, 1 H), 7.47 (s, 1 H), 7.70 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.0, 21.7, 56.4, 56.9, 72.0, 115.7, 122.8, 124.8, 127.5, 129.2, 130.0, 130.2, 131.0, 135.9, 140.8, 144.0, 144.1; **IR** (KBr, neat) 3482, 2923, 1597, 1427, 1333, 1155, 1091, 922, 655 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{19}H_{23}BrNO_3S$ $(M + H)^+$ 424.0577, found 424.0574.



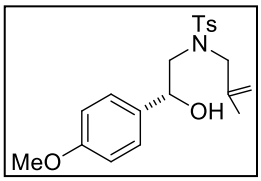
Data for N-(2-(3-bromophenyl)-2-hydroxyethyl)-4-methyl-N-(2- phenylallyl) benzenesulfonamide (42i): pale yellow gum; R_f (hexane/ EtOAc, 4:1) 0.50; yield 757 mg, 78%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.01−3.07 (m, 2 H), 3.21 (dd, J = 15.0 and 9.0 Hz, 1 H), 4.12 (d, J = 14.4 Hz, 1 H), 4.46 (d, J = 14.4 Hz, 1 H), 4.73 (d, J = 9.6 Hz, 1 H), 5.23 (s, 1 H), 5.56 (s, 1 H), 7.16 (t, J = 7.2 Hz, 2 H), 7.29 (d, J = 7.8 Hz, 2 H), 7.32−7.38 (m, 4 H), 7.40 (s 1 H), 7.48 (d, J = 7.8 Hz, 2 H), 7.65 (d, J = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 54.4, 56.3, 71.8, 117.6, 122.8, 124.7, 126.7, 127.7, 128.7, 128.9, 129.1, 130.1, 130.2, 131.0, 135.2, 137.8, 143.1, 143.9, 144.2; **IR** (KBr, neat) 3501, 2923, 1597, 1449, 1334, 1157, 1093, 911, 696 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{24}H_{25}BrNO_3S$ $(M + H)^+$ 486.0733, found 486.0730.



Data for N-(2-hydroxy-2-(3-(phenylethynyl)phenyl)ethyl)-4-methyl-N-(2 phenylallyl) benzenesulfonamide (42j): pale yellow gum; R_f (hexane/EtOAc, 4:1) 0.40; yield 720 mg, 71%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 3.02−3.08 (m, 2 H), 3.26 (dd, J = 15.0 and 9.6 Hz, 1 H), 4.15 (d, J = 14.4 Hz, 1 H), 4.47 (d, J = 14.4 Hz, 1 H), 4.79 (d, J = 9.0 Hz, 1 H), 5.25 (s, 1 H), 5.56 (s, 1 H), 7.23 (d, J = 7.8 Hz, 1 H), 7.26−7.36 (m, 9 H), 7.43 (d, J = 7.8 Hz, 2 H), 7.50 (d, J = 7.8 Hz, 2 H), 7.53 (d, J = 7.8 Hz, 2 H), 7.66 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 54.3, 56.3, 72.0, 89.4, 89.8, 117.5, 123.4, 123.6, 126.0, 126.7, 127.7, 128.5, 128.57, 128.6, 128.7, 128.9, 129.2, 130.0, 131.1, 131.8, 135.4, 138.0, 141.9, 143.1, 144.1; **IR** (KBr, neat) 3497, 2923, 1599, 1493, 1444, 1334, 1157, 1093, 912, 812, 696 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{32}H_{30}NO_3S$ $(M + H)^+$ 508.1941, found 508.1939.

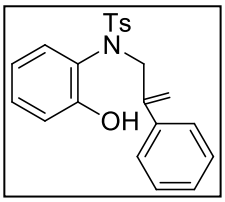


Data for N-(2-hydroxy-2-(4-(trifluoromethyl)phenyl)ethyl)-4-methyl-N-(2 methylallyl)benzenesulfonamide (42k): colorless gum; R_f (hexane/EtOAc, 9:1) 0.50; yield 653 mg, 79%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.72 (s, 3 H), 2.42 (s, 3 H), 3.05 (d, J = 15.2, 1 H), 3.31 (dd, J = 15.2 and 9.6 Hz, 1 H), 3.58 (d, J = 15.2 Hz, 2 H), 3.95 (d, J = 14.4 Hz, 1 H), 4.90 (s, 1 H), 4.95−4.99 (m, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.46 (d, J = 8.0 Hz, 2 H), 7.58 (d, J = 8.0 Hz, 2 H), 7.70 (d, J = 8.0 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 20.0, 21.7, 56.5, 57.0, 72.3, 115.8, 124.3 (q, J = 270.0 Hz), 125.6, 126.5, 127.5, 130.1, 130.2 (q, J = 31.5 Hz), 135.9, 140.9, 144.1, 145.8; **19F NMR** (376 MHz, C_6F_6/$CDCl_3$): 99.22; **IR** (KBr, neat) 3502, 2925, 1598, 1417, 1326, 1158, 1123, 1067, 921, 815, 777 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{20}H_{23}F_3NO_3S$ $(M + H)^+$ 414.1345, found 414.1359.

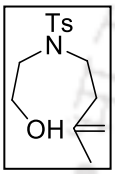


Data for N-(2-hydroxy-2-(4-methoxyphenyl)ethyl)-4-methyl-N- (2 methylallyl) benzenesulfonamide (42l): pale yellow gum; R_f (hexane/EtOAc, 4:1) 0.48; yield 503 mg, 67%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.71 (s, 3 H), 2.41 (s, 3 H), 3.03 (dd, J = 15.6 and 3.0 Hz, 1 H), 3.16 (br s, 1 H), 3.35 (dd, J = 15.6 and 9.6 Hz, 1 H), 3.61 (d, J = 14.4 Hz, 1 H), 3.79 (s, 3 H), 3.90 (d, J = 15.0 Hz, 1 H), 4.85 (d, J = 9.0 Hz, 1 H), 4.88 (s, 1 H), 4.96 (s, 1 H), 6.86 (d, J = 9.0 Hz, 2 H), 7.24 (d, J = 9.0 Hz, 2 H), 7.29 (d, J = 7.8 Hz, 2 H), 7.71 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 20.1, 21.7, 55.5, 56.6, 56.7, 72.2, 114.1, 115.5, 127.3, 127.5, 130.0, 133.9, 136.3, 141.0, 143.9, 159.5; **IR** (KBr, neat) 3508, 2924,

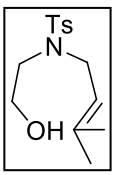
1612, 1514, 1444, 1334, 1156, 1033, 919, 656 cm^{-1}; **Anal.** Calcd for $C_{20}H_{26}NO_4S$: C 63.97, H 6.71, N 3.73, found C 64.05, H 6.76, N 3.64.



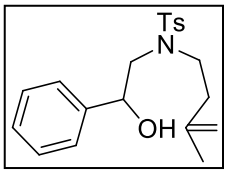
Data for N-(2-hydroxyphenyl)-4-methyl-N-(2-phenylallyl)-benzenesulfonamide (42m): pale yellow gum; R_f (hexane/EtOAc, 7:3) 0.57; yield 570 mg, 75%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.45 (s, 3 H), 4.94 (s, 1 H), 5.26 (s, 1 H), 5.68 (s, 1 H), 6.32 (d, J = 8.4 Hz, 1 H), 6.50 (t, J = 8.6 Hz, 1 H), 6.87 (d, J = 8.4 Hz, 1 H), 7.13 (t, J = 7.6 Hz, 1 H), 7.26−7.45 (m, 8 H), 7.52 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.9, 55.6, 117.4, 117.8, 120.1, 124.9, 126.8, 127.5, 128.5, 128.6, 128.9, 129.8, 130.1, 133.7, 137.7, 142.2, 144.6, 155.3; **IR** (KBr, neat) 3508, 2852, 1597, 1493, 1344, 1161, 1091, 814, 704 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{22}H_{22}NO_3S$ $(M + H)^+$ 380.1315, found 380.1323.



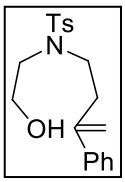
Data for N-(2-hydroxyethyl)-4-methyl-N-(3-methylbut-3-en-1-yl)-benzenesulfonamide (42n): colorless oil; R_f (hexane/EtOAc, 7:3) 0.40; yield 490 mg, 90%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.70 (s, 3 H), 2.24 (t, J = 7.8 Hz, 2 H), 2.41 (s, 3 H), 2.57 (br s, 1 H), 3.23 (t, J = 5.4 Hz, 2 H), 3.26 (t, J = 7.8 Hz, 2 H), 3.74 (t, J = 4.8 Hz, 2 H), 4.67 (s, 1 H), 4.76 (s, 1 H), 7.30 (d, J = 7.8 Hz, 2 H), 7.69 (d, J = 7.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.6, 22.6, 37.0, 48.6, 51.0, 61.4, 112.4, 127.4, 129.9, 136.1, 142.3, 143.7; **IR** (KBr, neat) 3517, 2931, 1598, 1454, 1378, 1158, 1088, 815, 734 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{14}H_{21}NNaO_3S$ $(M + Na)^+$ 306.1134, found 306.1133.



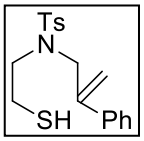
Data for N-(2-hydroxyethyl)-4-methyl-N-(3-methylbut-2-en-1-yl)-benzenesulfonamide (42o): pale yellow oil; R_f (hexane/EtOAc, 7:3) 0.40; yield 496 mg, 81%; **1H NMR** (400 MHz, $CDCl_3$) δ 1.62 (s, 3 H), 1.67 (s, 3 H), 2.43 (s, 3 H), 3.20 (t, J = 5.6 Hz, 2 H), 3.72 (t, J = 4.8 Hz, 2 H), 3.84 (d, J = 7.2 Hz, 2 H), 5.02 (dt, J = 6.8 and 1.6 Hz, 1 H), 7.31 (d, J = 8.4 Hz, 2 H), 7.70 (d, J = 7.6 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.0, 21.7, 25.9, 47.1, 49.9, 61.4, 119.0, 127.5, 129.9, 136.6, 137.7, 143.6; **IR** (KBr, neat) 3524, 2926, 1598, 1448, 1336, 1158, 1090, 816, 702 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{14}H_{21}NaNO_3S$ $(M + Na)^+$ 306.1134, found 306.1136.



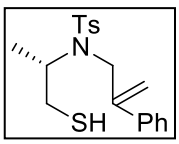
Data for N-(2-hydroxy-2-phenylethyl)-4-methyl-N-(3-methylbut- 3-en-1-yl)benzenesulfonamide (42p): pale yellow gum; R_f (hexane/ EtOAc, 7:3) 0.60; yield 470 mg, 66%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.71 (s, 3 H), 2.14 (t, J = 7.2 Hz, 2 H), 2.41 (s, 3 H), 3.05 (dd, J = 13.2 and 6.6 Hz, 2 H), 3.26−3.35 (m, 2 H), 4.68 (s, 1 H), 4.78 (s, 1 H), 4.95 (dd, J = 9.0 and 3.6 Hz, 1 H), 7.28−7.39 (m, 7 H), 7.71 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 22.7, 37.4, 49.1, 57.1, 73.0, 112.5, 126.1, 127.3, 127.5, 128.8, 129.9, 130.0, 141.6, 142.4, 143.8; **IR** (KBr, neat) 3504, 2924, 1494, 1454, 1329, 1157, 1092, 814, 700 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{20}H_{26}NO_3S$ $(M + H)^+$ 360.1628, found 360.1635.



Data for N-(2-hydroxyethyl)-4-methyl-N-(3-phenylbut-3-en-1-yl)-benzenesulfonamide (42q): pale yellow gum; R_f (hexane/EtOAc, 7:3) 0.45; yield 492 mg, 67%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 2.82 (t, J = 7.2 Hz, 2 H), 3.23−3.27 (m, 4 H), 3.73 (t, J = 5.4 Hz, 2 H), 5.01 (s, 1 H), 5.36 (s, 1 H), 7.28 (d, J = 8.4 Hz, 2 H), 7.33 (t, J = 7.2 Hz, 3 H), 7.38 (d, J = 7.8 Hz, 2 H), 7.68 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 35.4, 49.5, 51.6, 61.5, 114.6, 126.1, 127.5, 128.0, 128.7, 130.0, 136.3, 140.1, 143.7, 145.0; **IR** (KBr, neat) 3427, 2923, 2853, 1494, 1463, 1261, 1154, 1089, 1020, 801, 705 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{19}H_{23}NNaO_3S$ $(M + Na)^+$ 368.1291, found 368.1300.

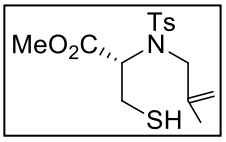


Data for N-(2-mercaptoethyl)-4-methyl-N-(2-phenylallyl)-benzenesulfonamide (42s): pale yellow gum; R_f (hexane/EtOAc, 7.3) 0.60; yield 638 mg, 92%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 2.49 (dd, J = 8.8 and 5.6 Hz, 2 H), 3.21 (dd, J = 10.8 and 8.0 Hz, 2 H), 4.18 (s, 2 H), 5.18 (s, 1 H), 5.46 (s, 1 H), 7.26−7.33 (m, 5 H), 7.41−7.46 (m, 2 H), 7.66 (d, J = 8.0 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 35.9, 47.4, 53.2, 117.3, 126.6, 127.5, 128.4, 128.7, 130.0, 135.7, 137.8, 142.7, 143.8; **IR** (KBr, neat) 3058, 2924, 1597, 1445, 1339, 1159, 1090, 914, 818, 658 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{18}H_{22}NO_2S_2$ $(M + H)^+$ 348.1086, found 348.1078.

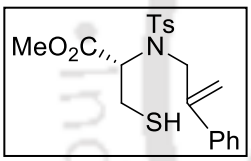


Data for N-(1-mercaptopropan-2-yl)-4-methyl-N-(2-phenylallyl)-benzenesulfonamide (42t): pale yellow gum; R_f (hexane/EtOAc, 19:1) 0.30; yield 267 mg, 74%; $[\alpha]_{25}^{D}$ = +8.0 (c = 0.1, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.07 (d, J = 6.6 Hz, 3 H), 2.36−2.41 (m, 1 H), 2.43 (s, 3 H), 2.54−2.59 (m, 1 H), 3.81−3.87 (m, 1 H), 4.07 (d, J = 16.2 Hz, 1 H), 4.49 (d, J = 16.2 Hz, 1 H), 5.36 (s, 1

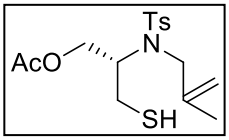
H), 5.46 (s, 1 H), 7.28−7.32 (m, 3 H), 7.34 (t, *J* = 7.8 Hz, 2 H), 7.42 (d, *J* = 7.2 Hz, 2 H), 7.69 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 16.3, 21.7, 30.0, 48.5, 57.8, 116.3, 126.8, 127.5, 128.3, 128.7, 129.9, 137.6, 138.7, 143.6, 145.1; **IR** (KBr, neat) 3464, 2925, 2855, 1598, 1495, 1448, 1334, 1154, 1090, 998, 701 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{19}H_{24}NO_2S_2$ $(M + H)^+$ 362.1243, found 362.1245.



Data for (S)-methyl 3-mercapto-2-(4-methyl-N-(2-methylallyl)-benzenesulfonamido)propanoate (42u): pale yellow gum; R_f (hexane/EtOAc, 7:3) 0.58; yield 453 mg, 66%; $[\alpha]_{25}^{D}$ = +33.0 (c = 0.1, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.76 (s, 3 H), 2.42 (s, 3 H), 2.78 (d, *J* = 5.4 Hz, 2 H), 3.05 (d, *J* = 10.2 Hz, 2 H), 3.57 (s, 3 H), 4.10−4.14 (m, 1 H), 4.81 (s, 1 H), 4.86 (s, 1 H), 5.40 (d, *J* = 8.4 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 20.6, 21.7, 33.9, 39.9, 52.8, 55.5, 114.7, 127.4, 129.8, 136.9, 140.6, 143.9, 170.8; **IR** (KBr, neat) 3277, 2923, 2854, 1744, 1598, 1436, 1341, 1160, 1090, 815, 662 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{15}H_{22}NO_4S_2$ $(M + H)^+$ 344.0985, found 344.0989.

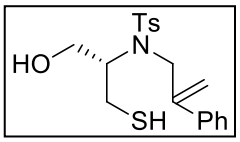


Data for (S)-methyl 3-mercapto-2-(4-methyl-N-(2-phenylallyl)-benzenesulfonamido)propanoate (42v): pale yellow gum; R_f (hexane/ EtOAc, 7:3) 0.60; yield 494 mg, 61%; $[\alpha]_{25}^{D}$ = +10.0 (c = 0.05, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 2.83 (d, *J* = 5.4 Hz, 2 H), 3.53 (s, 3 H), 3.57 (s, 2 H), 4.11−4.16 (m, 1 H), 5.21 (s, 1 H), 5.46 (s, 1 H), 7.26−7.30 (m, 3 H), 7.34 (t, *J* = 7.2 Hz, 2 H), 7.41 (d, *J* = 7.2 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 34.3, 37.1, 52.9, 55.6, 116.2, 126.5, 127.4, 128.1, 128.6, 129.9, 136.9, 139.0, 143.1, 144.0, 170.7; **IR** (KBr, neat) 3447, 2924, 1742, 1626, 1494, 1444, 1341, 1161, 1092, 908, 779 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{20}H_{24}NO_4S_2$ $(M + H)^+$ 406.1141, found 406.1141.

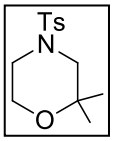


Data for (S)-3-mercapto-2-(4-methyl-N-(2-methylallyl)-benzenesulfonamido)propyl acetate (42w): pale yellow oil; R_f (hexane/EtOAc, 7:3) 0.42; yield 607 mg, 85%; $[\alpha]_{25}^{D}$ = +15.0 (c = 0.1, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.75 (s, 3 H), 1.94 (s, 3 H), 2.43 (s, 3 H), 2.54 (d, *J* = 10.8 Hz, 1 H), 2.56 (d, *J* = 9.2 Hz, 1 H), 2.93 (d, *J* = 7.2 Hz, 2 H), 3.58 (dt, *J* = 12.8 and 5.6 Hz, 1 H), 3.99 (dd, *J* = 12.0 and 4.4 Hz, 1 H), 4.18 (dd, *J* = 11.2 and 5.6 Hz, 1 H), 4.73 (s, 1 H), 4.82 (s, 1 H), 5.01 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.77 (d, *J*

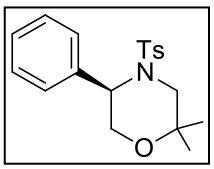
= 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.6, 20.8, 21.7, 33.0, 39.8, 51.9, 64.7, 114.5, 127.3, 129.9, 137.7, 140.7, 143.8, 170.9; **IR** (KBr, neat) 3450, 2932, 1728, 1616, 1503, 1449, 1350, 1149, 1093, 909, 777 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{16}H_{24}NO_4S_2$ $(M + H)^+$ 358.1141, found 358.1140.



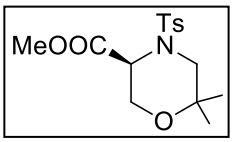
Data for N-(1-hydroxy-3-mercaptopropan-2-yl)-4-methyl-N-(2-phenylallyl)benzenesulfonamide (42x): pale yellow oil; R_f (hexane/ EtOAc, 3:2) 0.49; yield 566 mg, 75%; $[\alpha]_{25}^{D}$ = −9.0 (c = 0.4, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 2.55 (dd, J = 6.6 and 2.4 Hz, 2 H), 3.29−3.34 (m, 2 H), 3.40 (d, J = 13.8 Hz, 1 H), 3.60 (s, 2 H), 5.07 (s, 1 H), 5.32 (br s, 1 H), 5.37 (s, 1 H), 7.26−7.37 (m, 7 H), 7.75(d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 33.0, 36.8, 54.1, 63.6, 115.8, 126.4, 127.4, 128.2, 128.6, 130.0, 137.2, 139.0, 143.2, 143.9; **IR** (KBr, neat) 3504, 3279, 2924, 1598, 1494, 1444, 1327, 1157, 1092, 1036, 814, 702 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{19}H_{24}NO_3S_2$ $(M + H)^+$ 378.1192, found 378.1193.



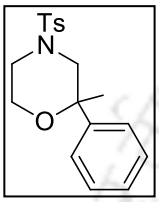
Data for 2,2-dimethyl-4-tosylmorpholine (43a): white solid; mp 92−94 °C; R_f (hexane/EtOAc, 4:1) 0.47; yield 223 mg, 83%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.26 (s, 6 H), 2.44 (s, 3 H), 2.72 (s, 2 H), 2.91 (t, J = 4.8 Hz, 2 H), 3.77 (t, J = 4.8 Hz, 2 H), 7.33 (d, J = 7.8 Hz, 2 H), 7.61 (t, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7 (2C), 24.6, 45.9, 54.9, 60.4, 71.2, 128.0, 129.9, 132.6, 144.0; **IR** (KBr, neat) 2978, 2877, 1598, 1351, 1166, 1099, 759 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{13}H_{20}NO_3S$ $(M + H)^+$ 270.1158 found 270.1157.



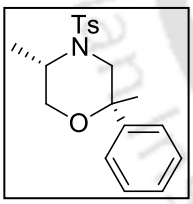
Data for (R)-2,2-dimethyl-5-phenyl-4-tosylmorpholine (43b): pale yellow solid; mp 77−79 °C; R_f (hexane/EtOAc, 4:1) 0.47; yield 245 mg, 71%; $[\alpha]_{25}^{D}$ = −68.5 (c = 0.33, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.24 (s, 3 H), 1.25 (s, 3 H), 2.37 (s, 3 H), 3.11 (d, J = 13.2Hz, 1 H), 3.23 (d, J = 12.6 Hz, 1 H), 3.99 (dd, J = 12.0 and 2.4 Hz, 1 H), 4.10 (dd, J = 12.0 and 4.2 Hz, 1 H), 4.71 (t, J = 3.0 Hz, 1 H), 7.16 (d, J = 8.4 Hz, 2 H), 7.21−7.23 (m, 3 H), 7.36−7.38 (m, 2 H), 7.47 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.6, 22.4, 26.7, 50.6, 55.8, 64.7, 71.4, 127.5, 127.9, 128.4, 128.7, 129.5, 137.1, 137.8, 143.3; **IR** (KBr, neat) 2975, 2872, 1599, 1495, 1340, 1164, 1026, 705 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{19}H_{24}NO_3S$ $(M + H)^+$ 346.1471 found 346.1471.



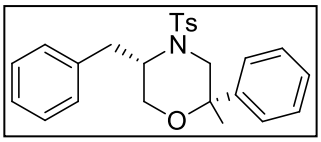
Data for (S)-methyl 6,6-dimethyl-4-tosylmorpholine-3-carboxylate (43c): pale yellow gum; R_f (hexane/EtOAc, 4:1) 0.50; yield 281 mg, 86%; $[\alpha]_{25}^{D}$ = −70.0 (c = 0.1, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.14 (s, 3 H), 1.26 (s, 3 H), 2.40 (s, 3 H), 3.12 (d, *J* = 12.4 Hz, 1 H), 3.32 (d, *J* = 12.8 Hz, 1 H), 3.52 (s, 3 H), 4.00−4.10 (m, 2 H), 4.44 (d, *J* = 3.6 Hz, 1 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.8, 21.7, 27.5, 50.6, 52.5, 54.5, 62.5, 71.2, 127.5, 129.6, 136.6, 143.6, 169.7; **IR** (KBr, neat) 2981, 1339, 1154, 1091, 1049, 905, 815, 741 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{15}H_{22}NO_5S$ $(M + H)^+$ 328.1213 found 328.1225.



Data for 2-methyl-2-phenyl-4-tosylmorpholine (43d): pale yellow solid; mp 126−128 °C; R_f (hexane/EtOAc, 4:1) 0.50; yield 298 mg, 90%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.44 (s, 3 H), 2.45 (s, 3 H), 2.71−2.78 (m, 2 H), 3.13 (d, *J* = 11.4 Hz, 1 H), 3.62−3.68 (m, 1 H), 3.72−3.79 (m, 2 H), 7.28 (d, *J* = 7.8 Hz, 1 H), 7.34−7.39 (m, 4 H), 7.47 (d, *J* = 7.8 Hz, 2 H), 7.65 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.6, 28.1, 45.7, 52.7, 60.7, 75.1, 126.1, 127.3, 127.9, 128.6, 129.9, 132.1, 142.7, 144.0; **IR** (KBr, neat) 2977, 2853, 1599, 1458, 1351, 1168, 1093, 802, 701 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{18}H_{22}NO_3S$ $(M + H)^+$ 332.1315 found 332.1318.

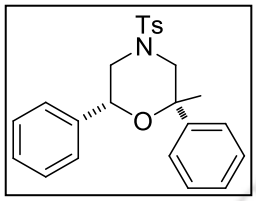


Data for (2S,5S)-2,5-dimethyl-2-phenyl-4-tosylmorpholine (43e): pale yellow oil; R_f (hexane/EtOAc, 4:1) 0.60; yield 255 mg, 74%; $[\alpha]_{25}^{D}$ = +48.0 (c = 0.1, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.6 Hz, 3 H), 1.58 (s, 3 H), 2.41 (s, 3 H), 3.26 (d, *J* = 12.6 Hz, 1 H), 3.52 (d, *J* = 11.4 and 2.4 Hz, 2 H), 3.84−3.88 (m, 1 H), 4.07−4.10 (m, 1 H), 7.26−7.30 (m, 3 H), 7.37 (t, *J* = 7.2 Hz, 2 H), 7.47 (d, *J* = 7.2 Hz, 2 H), 7.68 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.5, 21.7, 22.6, 49.0, 49.5, 65.9, 74.7, 124.9, 127.3, 127.5, 128.6, 129.9, 137.1, 143.6, 144.9; **IR** (KBr, neat) 2978, 2874, 1590, 1447, 1338, 1152, 1021, 800, 701 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{19}H_{24}NO_3S$ $(M + H)^+$ 346.1471 found 346.1471.

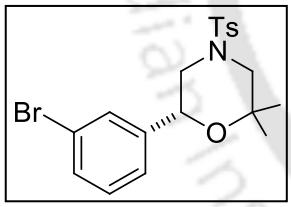


Data for (2S,5S)-5-benzyl-2-methyl-2-phenyl-4-tosylmorpholine (43f): pale yellow solid; mp 95−97 °C; R_f (hexane/EtOAc, 4:1) 0.65; yield 265 mg, 63%; $[\alpha]_{25}^{D}$ = +26.0 (c = 0.1, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.60 (s, 3 H), 2.41 (s, 3 H), 2.44 (dd, *J* =

13.2 and 3.0 Hz, 1 H), 3.03 (dd, *J* = 13.2 and 10.8 Hz, 1 H), 3.19 (d, *J* = 12.6 Hz, 1 H), 3.64 (d, *J* = 12.0 Hz, 1 H), 3.77 (d, *J* = 12.6 Hz, 1 H), 3.93−3.99 (m, 2 H), 7.14 (d, *J* = 7.2 Hz, 2 H), 7.21 (t, *J* = 7.2 Hz, 1 H), 7.27− 7.33 (m, 5 H), 7.40 (t, *J* = 7.8 Hz, 2 H), 7.53 (d, *J* = 7.8 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.5, 21.7, 32.3, 49.7, 54.4, 61.1, 74.2, 124.7, 126.8, 127.2, 127.6, 128.7, 128.9, 129.7, 130.1, 137.8, 138.0, 143.7, 145.4; **IR** (KBr, neat) 2924, 2872, 1599, 1448, 1339, 1165, 1052, 814, 702 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{25}H_{28}NO_3S$ $(M + H)^+$ 422.1784 found 422.1782.

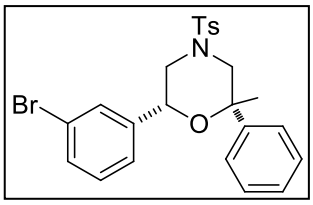


Data for (2S*,6R*)-2-methyl-2,6-diphenyl-4-tosylmorpholine (43g): pale yellow solid; mp 191−193 °C; R_f (hexane/EtOAc, 4:1) 0.70; yield 180 mg, 79%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.83 (s, 3 H), 2.14 (t, *J* = 10.8 Hz, 1 H), 2.29 (d, *J* = 11.4 Hz, 1 H), 2.37 (s, 3 H), 3.87 (dd, *J* = 10.8 and 2.4 Hz, 1 H), 5.18 (dd, *J* = 10.2 and 3.0 Hz, 1 H), 7.24 (d, *J* = 7.2 Hz, 2 H), 7.27−7.45 (m, 8 H), 7.52 (d, *J* = 7.8 Hz, 1 H), 7.55 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.7, 22.3, 52.5, 54.8, 71.4, 75.4, 124.7, 126.5, 127.6, 127.9, 128.4, 128.6, 128.8, 130.0, 132.6, 139.5, 144.1, 145.3; **IR** (KBr, neat) 2928, 1558, 1447, 1351, 1168, 1091, 999, 699 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{24}H_{26}NO_3S$ $(M + H)^+$ 408.1628 found 408.1644.

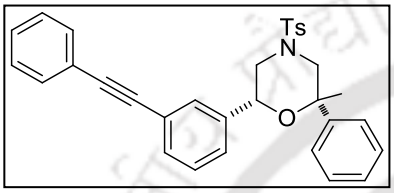


Data for (2S*,6R*)-6-(3-bromophenyl)-2,2-dimethyl-4-tosylmorpholine (43h): white solid; mp 150−152 °C; R_f (hexane/EtOAc, 9:1) 0.65; yield 343 mg, 81%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.27 (s, 3 H), 1.47 (s, 3 H), 1.99 (t, *J* = 10.8 Hz, 1 H), 2.14 (d, *J* = 11.4 Hz, 1 H), 2.42 (s, 3 H), 3.47 (dd, *J* = 10.8 and 1.2 Hz, 1 H), 3.73 (dd, *J* = 9.6 and 1.8 Hz, 1 H), 4.87 (dd, *J* = 10.8 and 3.0 Hz, 1 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 7.31 (d, *J* = 7.8 Hz, 2 H), 7.40 (d, *J* = 7.8 Hz, 1 H), 7.48 (s, 1 H), 7.58 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 21.8, 28.0, 52.0, 54.4, 70.8, 72.3, 122.8, 125.1, 127.9, 129.4, 130.0, 130.2, 131.4, 132.6, 141.7, 144.1; **IR** (KBr, neat) 2978, 1597, 1453, 1352, 1165, 1093, 998, 694 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{19}H_{23}BrNO_3S$ $(M + H)^+$ 424.0577, found 424.0576.

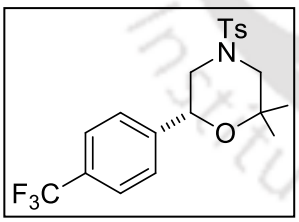
Data for (2S*,6R*)-6-(3-bromophenyl)-2-methyl-2-phenyl-4-tosylmorpholine (43i): white solid; mp 134−136 °C; R_f (hexane/EtOAc, 9:1) 0.48; yield 417 mg, 86%; **^{1}H NMR**



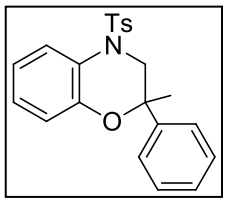
(600 MHz, $CDCl_3$) δ 1.82 (s,3 H), 2.10 (t, J = 11.4 Hz, 1 H), 2.29 (d, J = 11.4 Hz, 1 H), 2.38 (s, 3 H), 3.85 (d, J = 11.4 Hz, 2 H), 5.14 (dd, J = 10.2 and 2.4 Hz, 1 H), 7.23−7.28 (m, 3 H), 7.30 (t, J = 7.8 Hz, 1 H), 7.34−7.40 (m, 4 H), 7.50 (d, J = 7.8 Hz, 2 H), 7.57 (d, J = 8.4 Hz, 2 H), 7.60 (s, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 22.3, 52.3, 54.7, 70.9, 75.7, 122.9, 124.6, 125.1, 127.7, 127.9, 128.7, 129.5, 130.1, 130.3, 131.6, 132.6, 141.8, 144.2, 145.0; **IR** (KBr, neat) 2984, 1597, 1449, 1344, 1164, 1091, 999, 756, 694 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{24}H_{25}BrNO_3S$ $(M + H)^+$ 486.0733, found 486.0731.



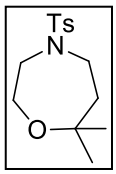
Data for (2S*,6R*)-2-methyl-2-phenyl-6-(3-(phenylethynyl)- phenyl)-4-tosylmorpholine (43j): colorless gum; R_f (hexane/EtOAc, 9:1) 0.38; yield 370 mg, 73%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.84 (s, 3 H), 2.14 (t, J = 11.4 Hz, 1 H), 2.31 (d, J = 11.4 Hz, 1 H), 2.38 (s, 3 H), 3.87 (d, J = 9.6 Hz, 2 H), 5.18 (dd, J = 10.8 and 3.0 Hz, 1 H), 7.31 (d, J = 7.2 Hz, 2 H), 7.35−7.41 (m, 7 H), 7.50 (d, J = 7.8 Hz, 2 H), 7.52−7.55 (m, 4 H), 7.57 (d, J = 8.4 Hz, 2 H), 7.61 (s, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 22.4, 52.4, 54.8, 71.2, 75.6, 89.2, 90.0, 123.3, 123.8, 124.7, 125.1, 126.4, 127.7, 127.9, 128.6, 128.63, 128.8, 129.6, 130.1, 131.6, 131.9, 132.6, 139.8, 144.1, 145.2; **IR** (KBr, neat) 2924, 1600, 1493, 1450, 1348, 1165, 1094, 1002, 909, 697 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{32}H_{30}NO_3S$ $(M + H)^+$ 508.1941, found 508.1947.



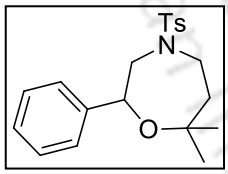
Data for (2S*,6R*)-2,2-dimethyl-4-tosyl-6-(4-(trifluoromethyl)-phenyl)morpholine (43k): colorless solid; mp 141−143 °C; R_f (hexane/EtOAc, 9:1) 0.65; yield 380 mg, 92%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.29 (s, 3 H), 1.49 (s, 3 H), 2.00 (t, J = 10.8 Hz, 1 H), 2.16 (d, J = 11.4 Hz, 1 H), 2.43 (s, 3 H), 3.49 (dd, J = 11.4 and 1.2 Hz, 1 H), 3.78 (dt, J = 10.8 and 1.2 Hz, 1 H), 4.96 (dd, J = 10.8 and 3.0 Hz, 1 H), 7.31 (d, J = 8.4 Hz, 2 H), 7.44 (d, J = 8.4 Hz, 2 H), 7.57− 7.60 (m, 4 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 21.8, 28.0, 52.0, 54.5, 71.0, 72.4, 124.2 (q, J = 270.0 Hz), 125.6, 126.8, 127.9, 130.1, 130.5 (q, J = 33.0 Hz), 132.6, 143.4, 144.2; 19F NMR (376 MHz, C_6F_6/$CDCl_3$): 99.12; **IR** (KBr, neat) 2926, 1599, 1454, 1325, 1165, 1093, 1029, 941, 667 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{20}H_{23}F_3NO_3S$ $(M + H)^+$ 414.1345, found 414.1343.



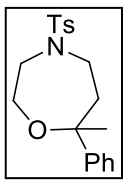
Data for 2-methyl-2-phenyl-4-tosyl-3,4-dihydro-2H-benz[b][1,4]-oxazine (43m): colorless solid; mp 119−121 °C; R_f (hexane/EtOAc, 4:1) 0.73; yield 258 mg, 68%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.67 (s, 3 H), 2.34 (s, 3 H), 3.97 (d, J = 12.6 Hz, 1 H), 4.14 (d, J = 12.6 Hz, 1 H), 6.77−6.80 (m, 1 H), 6.95−6.98 (m, 1 H), 7.02 (dd, J = 7.8 and 1.2 Hz, 1 H), 7.15 (d, J = 7.8 Hz, 1 H), 7.32 (t, J = 7.2 Hz, 1 H), 7.36 (t, J = 7.2 Hz, 2 H), 7.44−7.50 (m, 6 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 26.0, 53.0, 77.5, 118.2, 119.0, 120.9, 124.5, 124.6, 125.3, 127.4, 127.9, 128.9, 129.9, 136.7, 142.6, 144.1, 144.7; **IR** (KBr, neat) 2927, 2869, 1598, 1493, 1352, 1165, 1090, 813, 700 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{22}H_{22}NO_3S$ $(M + H)^+$ 380.1315 found 380.1316.



Data for 7,7-dimethyl-4-tosyl-1,4-oxazepane (43n): colorless solid; mp 62−64 °C; R_f (hexane/EtOAc, 4:1) 0.50; yield 263 mg, 93%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.13 (s, 6 H), 1.91 (t, J = 4.8 Hz, 2 H), 2.42 (s, 3 H), 3.20−3.23 (m, 4 H), 3.70 (t, J = 4.2 Hz, 2 H), 7.31 (d, J = 7.8 Hz, 2 H), 7.64 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.5, 27.7 (2C), 41.3, 43.8, 51.3, 62.6, 76.9, 127.3, 129.7, 134.8, 143.4; **IR** (KBr, neat) 2973, 2870, 1598, 1452, 1385, 1163, 1034, 862, 718 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{14}H_{22}NO_3S$ $(M + H)^+$ 284.1315 found 284.1316.

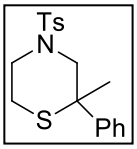


Data for 7,7-dimethyl-2-phenyl-4-tosyl-1,4-oxazepane (43p): yellow solid; mp 137−139 °C; R_f (hexane/EtOAc, 4:1) 0.68; yield 258 mg, 72%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.20 (s, 3 H), 1.21 (s, 3 H), 1.96 (dd, J = 15.6 and 7.2 Hz, 1 H), 2.13 (dd, J = 15.6 and 9.6 Hz,1 H), 2.42 (s, 3 H), 2.66 (dd, J = 12.6 and 9.6 Hz, 1 H), 2.83 (dd, J = 13.8 and 10.2 Hz, 1 H), 3.88 (dd, J = 13.2 and 7.8 Hz, 1 H), 3.98 (d, J = 12.6 Hz, 1 H), 4.84 (d, J = 9.6 Hz, 1 H), 7.26−7.35 (m, 7 H), 7.63 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 26.5, 29.5, 42.3, 44.0, 57.0, 73.9, 75.2, 126.1, 127.4, 127.7, 128.5, 129.9, 135.5, 141.0, 143.5; **IR** (KBr, neat) 2972, 2927, 1598, 1449, 1339, 1162, 1026, 890, 724 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{20}H_{26}NO_3S$ $(M + H)^+$ 360.1628 found 360.1631.

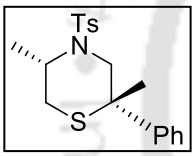


Data for 7-methyl-7-phenyl-4-tosyl-1,4-oxazepane (43q): colorless gum; R_f (hexane/EtOAc, 7:3) 0.58; yield 275 mg, 75%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.44 (s, 3 H), 2.45 (s, 3 H), 2.72 (d, J = 12.0 Hz, 1 H), 2.76 (d, J = 8.4 Hz,1 H), 3.12 (d, J = 11.4 Hz, 1 H), 3.62−3.67 (m, 2 H), 3.73 − 3.79 (m, 3 H), 7.28 (t, J

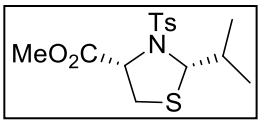
= 7.2 Hz, 1 H), 7.35 (d, *J* = 7.8 Hz, 2 H), 7.38 (t, *J* = 7.8 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.64 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.8, 28.3, 29.9, 45.9, 52.8, 60.9, 75.3, 126.3, 127.5, 128.1, 128.9, 130.0, 132.4, 142.8, 144.1; **IR** (KBr, neat) 2923, 2853, 1530, 1453, 1349, 1165, 1092, 761, 660 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{19}H_{23}NNaO_3S$ $(M + Na)^+$ 368.1291 found 368.1288.



Data for 2-methyl-2-phenyl-4-tosylthiomorpholine (43s): pale yellow solid; mp 121−123 °C; R_f (hexane/EtOAc, 4:1) 0.70; yield 243 mg, 70%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.65 (s, 3 H), 2.44 (s, 3 H), 2.56−2.64 (m, 1 H), 2.75−2.82 (m, 1 H), 3.18−3.30 (m, 2 H), 3.32−3.39 (m, 1 H), 3.87 (d, *J* = 11.6 Hz, 1 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 7.31−7.38 (m, 4 H), 7.62 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.7, 26.2, 46.5, 47.5 (2C), 57.6, 127.0, 127.4, 127.7, 128.7, 130.0, 133.8, 143.3, 144.0; **IR** (KBr, neat) 2922, 2853, 1597, 1494, 1454, 1338, 1285, 1164, 1089, 899, 762 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{18}H_{22}NO_2S_2$ $(M + H)^+$ 348.1086, found 348.1080.

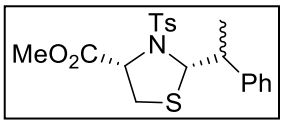


Data for 2,5-dimethyl-2-phenyl-4-tosylthiomorpholine (43t): pale yellow gum; R_f (hexane/EtOAc, 19:1) 0.30; yield 311 mg, 86%; $[\alpha]_{25}^{D}$ = +42.83 (c = 0.6, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.12 (d, *J* = 6.6 Hz, 3 H), 1.85 (s, 3 H), 2.35 (d, *J* = 13.2 Hz, 1 H), 2.42 (s, 3 H), 3.44−3.50 (m, 1 H), 3.85 (d, *J* = 13.2 Hz, 1 H), 4.48 (br s, 1 H), 7.27−7.31 (m, 3 H), 7.38 (t, *J* = 7.8 Hz, 2 H), 7.60 (d, *J* = 7.8 Hz, 2 H), 7.66 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 13.5, 21.7, 24.0, 32.2, 45.4, 46.8, 51.2, 126.4, 127.1, 127.8,, 129.9, 137.9, 143.4, 143.7; **IR** (KBr, neat) 2924, 2855, 1598, 1495, 1446, 1337, 1167, 1029, 995, 697 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{19}H_{24}NO_2S_2$ $(M + H)^+$ 362.1243, found 362.1248.

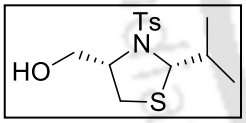


Data for (2S,4S)-methyl 2-isopropyl-3-tosylthiazolidine-4-carboxylate (44u): yellow gum; R_f (hexane/EtOAc, 4:1) 0.56; yield 226 mg, 66%; $[\alpha]_{25}^{D}$ = −2.0 (c = 0.06, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 0.98 (d, *J* = 6.6 Hz, 3 H), 1.11 (d, *J* = 6.6 Hz, 3 H),1.88− 1.95 (m, 1 H), 2.44 (s, 3 H), 2.82 (dd, *J* = 11.4 and 7.8 Hz, 1 H), 3.23 (dd, *J* = 11.4 and 6.0 Hz, 1 H), 3.78 (s, 3 H), 4.61 (t, *J* = 6.6 Hz, 1 H), 4.71 (d, *J* = 8.4 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 19.3, 20.5, 21.8, 33.9, 36.1, 53.1, 65.3, 74.9, 128.1, 130.1, 134.5, 144.6, 170.8; **IR** (KBr, neat) 2959, 2924, 1742, 1438, 1350,

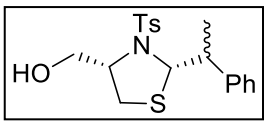
1164, 1090, 1009, 815, 661 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{15}H_{22}NO_4S_2$ $(M + H)^+$ 344.0985 found 344.0984.



Data for (2S,4S)-methyl 2-(1-phenylethyl)-3-tosylthiazolidine-4-carboxylate (44v, two diastereomers with a ratio of 7:3): pale yellow gum; R_f (hexane/EtOAc, 4:1) 0.50; yield 288 mg, 71%; $[\alpha]_{25}^{D}$ = −5.0 (c = 0.08, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.43 (d, *J* = 7.2 Hz, 3 H, minor), 1.54 (d, *J* = 7.2 Hz, 3 H, major), 2.41 (s, 3 H, minor), 2.43 (s, 3 H, major), 2.72 (dd, *J* = 11.4 and 7.8 Hz, 1 H, major), 2.92 (dd, *J* = 11.4 and 7.8 Hz, 1 H, minor), 3.00−3.06 (m, 2 H, major), 3.30 (dd, *J* = 11.4 and 6.6 Hz, 1 H, minor), 3.49 (dd, *J* = 11.4 and 6.0 Hz, 1 H, minor), 3.78 (s, 3 H, minor), 3.80 (s, 3 H, major), 4.57−4.62 (m, 2 H, H, minor), 7.22−7.34 (m, 14 H, major, minor), 7.59 (d, *J* = 7.8 Hz, 2 H, minor), 7.77 (d, *J* = 8.4 Hz, 2 H, major); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 20.3, 21.7, 21.8, 22.9, 33.9, 34.0, 46.2, 48.0, 53.0, 53.1, 65.6, 66.2, 74.0, 74.1, 127.1, 127.2, 128.1, 128.2, 128.3, 128.5, 128.6, 130.0, 130.2, 134.1, 134.4, 142.8, 142.9, 144.6, 144.8, 170.5, 170.7; **IR** (KBr, neat) 2924, 2853, 1747, 1597, 1494, 1453, 1352, 1165, 1091, 815, 701 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{20}H_{24}NO_4S_2$ $(M + H)^+$ 406.1141 found 406.1143.



Data for ((2S,4S)-2-isopropyl-3-tosylthiazolidin-4-yl)methanol (44w): yellow oil; R_f (hexane/EtOAc, 7:3) 0.30; yield 186 mg, 59%; $[\alpha]_{25}^{D}$ = −40.0 (c = 0.1, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.6 Hz, 3 H), 1.13 (d, *J* = 6.6 Hz, 3 H), 1.93−1.99 (m, 1 H), 2.45 (s, 3 H), 2.66 (dd, *J* = 12.0 and 7.2 Hz, 1 H), 2.80 (dd, *J* = 12.0 and 6.0 Hz, 1 H), 3.74 (d, *J* = 6.0 Hz, 2 H), 4.01−4.06 (m, 1 H), 4.72 (d, *J* = 9.0 Hz, 1 H), 7.34 (d, *J* = 7.8 Hz, 2 H), 7.73 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 19.6, 20.8, 21.8, 33.2, 36.1, 65.2, 66.3, 75.3, 128.3, 130.1, 134.3, 144.6; **IR** (KBr, neat) 3412, 2924, 2854, 1712, 1637, 1462, 1344, 1161, 1090, 1037, 812, 661, 584, 550 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{14}H_{22}NO_3S_2$ $(M + H)^+$ 316.1036 found 316.1035.

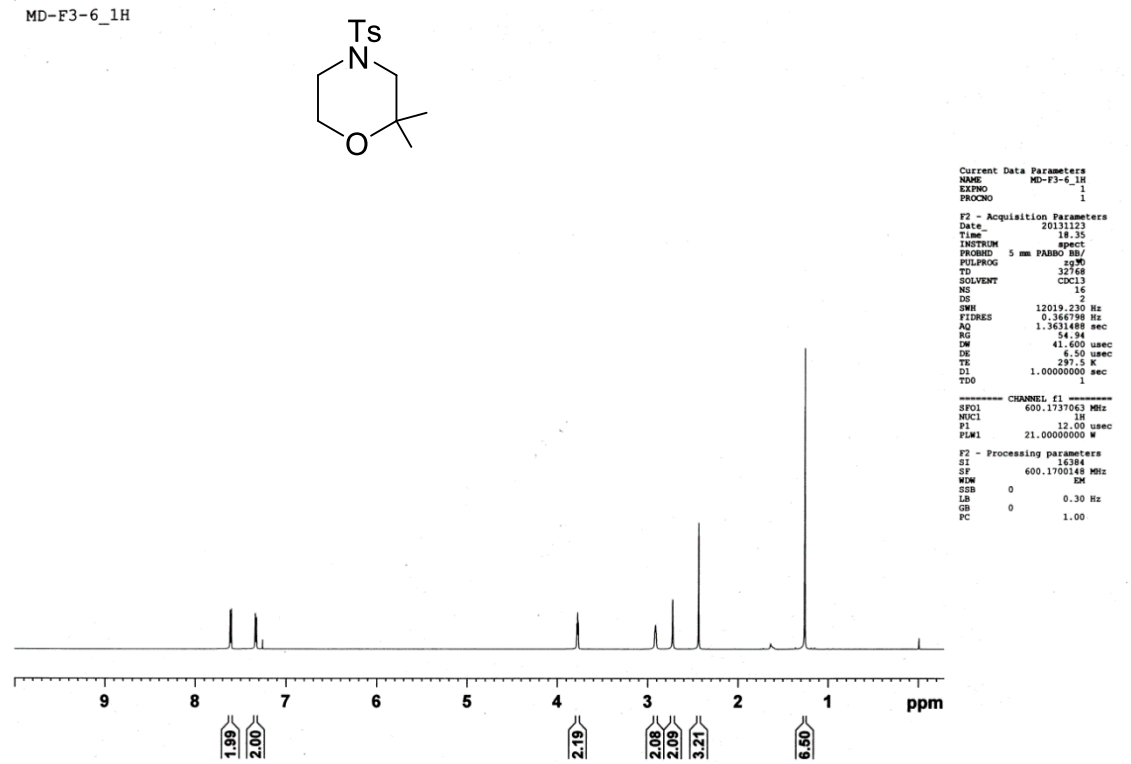


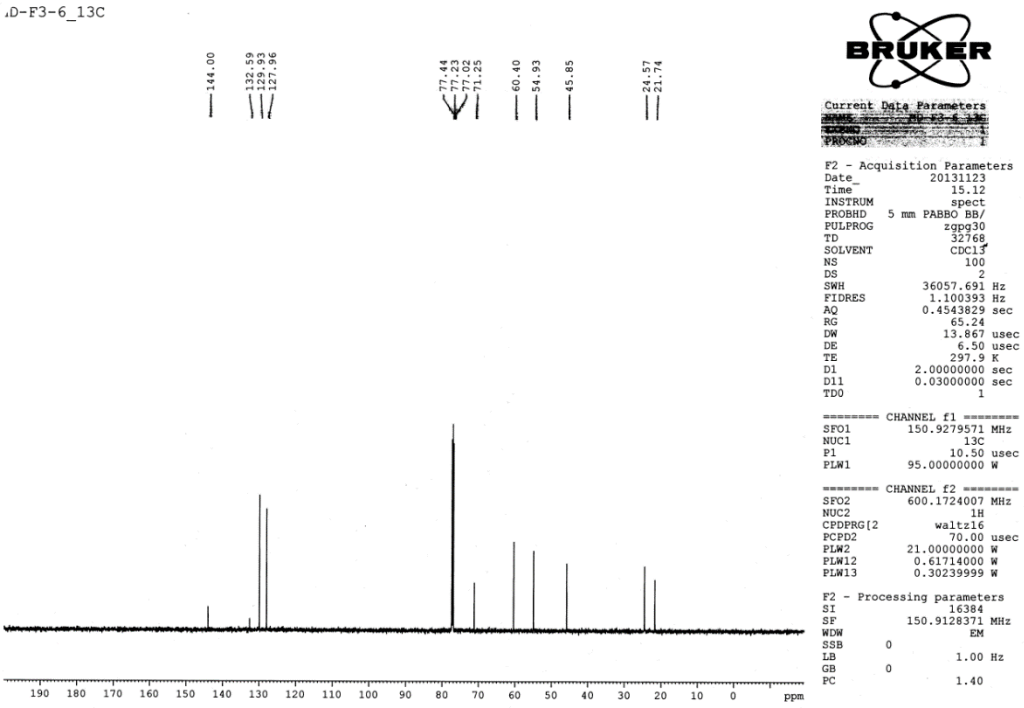
Data for ((2S,4S)-2-(1-phenylethyl)-3-tosylthiazolidin-4-yl)-methanol (44x, diastereomeric mixture with a ratio of 3:2): pale yellow gum; R_f (hexane/EtOAc, 3:2) 0.75; yield 279 mg, 74%; $[\alpha]_{25}^{D}$ = +32.0 (c = 0.3, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.42 (d, *J* = 6.6 Hz, 3 H, minor), 1.46 (d, *J* = 7.2 Hz, 3 H, major), 2.33 (br s, 1 H), 2.42 (s, 3 H, minor), 2.44 (s, 3 H, major),

2.49 (d, *J* = 6.0 Hz, 2 H, major), 2.60 (dd, *J* = 12.0 and 7.2 Hz, 1 H, minor), 2.80 (dd, *J* = 12.0 and 4.8 Hz, 1 H, minor), 3.28 (pentet, *J* = 7.2 Hz, 1 H, major), 3.35 (dd, *J* = 10.8 and 5.4 Hz, 1 H, major), 3.40 (dd, *J* = 11.4 and 6.6 Hz, 1 H, major), 3.48 (pentet, *J* = 6.6 Hz, 1 H, minor), 3.74 (dd, *J* = 10.8 and 6.0 Hz, 1 H, minor), 3.80 (dd, *J* = 11.4 and 6.6 Hz, 1 H, minor), 3.96 (pentet, *J* = 6.6 Hz, 1 H, major), 4.06 (pentet, *J* = 6.6 Hz, 1 H, minor), 5.15 (d, *J* = 7.8 Hz, 1 H, major), 5.21 (d, *J* = 6.6 Hz, 1 H, minor), 7.25−7.36 (m, 7 H), 7.62 (d, *J* = 8.4 Hz, 2 H, minor), 7.76 (d, *J* = 8.4 Hz, 2 H, major); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.3, 14.4, 19.9, 21.3, 21.8, 22.9, 32.1, 33.1, 46.6, 47.2, 64.5, 64.7, 74.2, 74.3, 127.3, 127.5, 128.2, 128.3, 128.5, 128.7, 129.2, 130.1, 130.2, 134.1, 142.0, 142.7, 144.6, 144.7; **IR** (KBr, neat) 3421, 2926, 1598, 1454, 1346, 1162, 1091, 1035, 813, 661 cm^{-1}; **HRMS** (ESI) m/z calcd for $C_{19}H_{24}NO_3S_2$ $(M + H)^+$ 378.1192 found 378.1191.

2.8 Selected Spectra

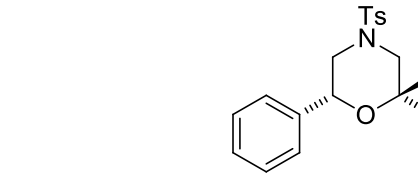
^{1}H and ^{13}C NMR spectra of **2,2-dimethyl-4-tosylmorpholine**



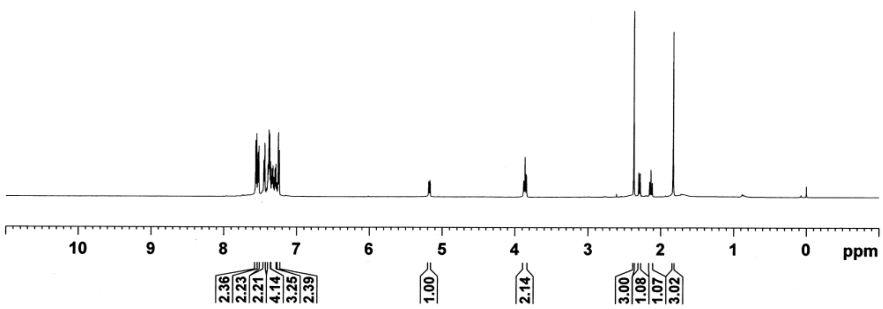


^{1}H and ^{13}C NMR spectra of **(2S*,6R*)-2-methyl-2,6-diphenyl-4-tosylmorpholine**

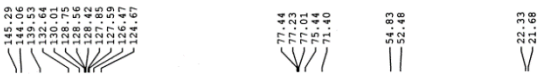
MD-F6_10_1H



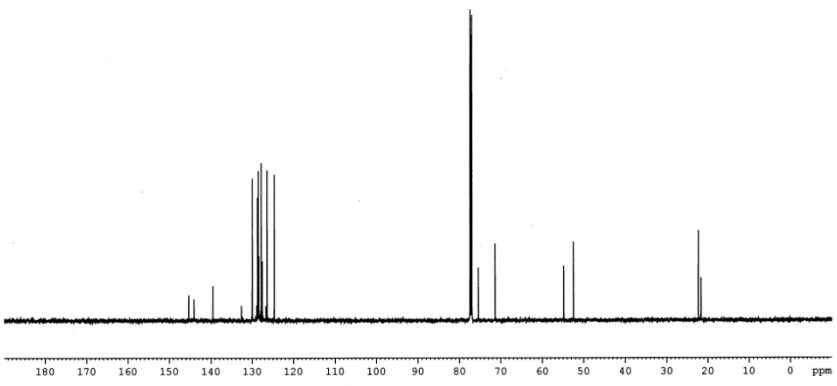

```
Current Data Parameters
NAME                  MD-F6_10_1H
EXPNO                           1
PROCNO                          1

F2 - Acquisition Parameters
Date_                    20140404
Time                        12.20
INSTRUM                     spect
PROBHD    5 mm PABBO BB/
PULPROG                     zg30
TD                         32768
SOLVENT                    CDCl3
NS                             16
DS                              2
SWH                  12019.230 Hz
FIDRES                0.366798 Hz
AQ                    1.3631488 sec
RG                        80.22
DW                       41.600 usec
DE                        6.50 usec
TE                       299.0 K
D1                    1.00000000 sec
TD0                             1

======== CHANNEL f1 ========
SFO1                600.1737063 MHz
NUC1                        1H
P1                       12.00 usec
PLW1                21.00000000 W

F2 - Processing parameters
SI                         16384
SF                  600.1700205 MHz
WDW                           EM
SSB                0
LB                           0.30 Hz
GB                 0
PC                           1.00
```



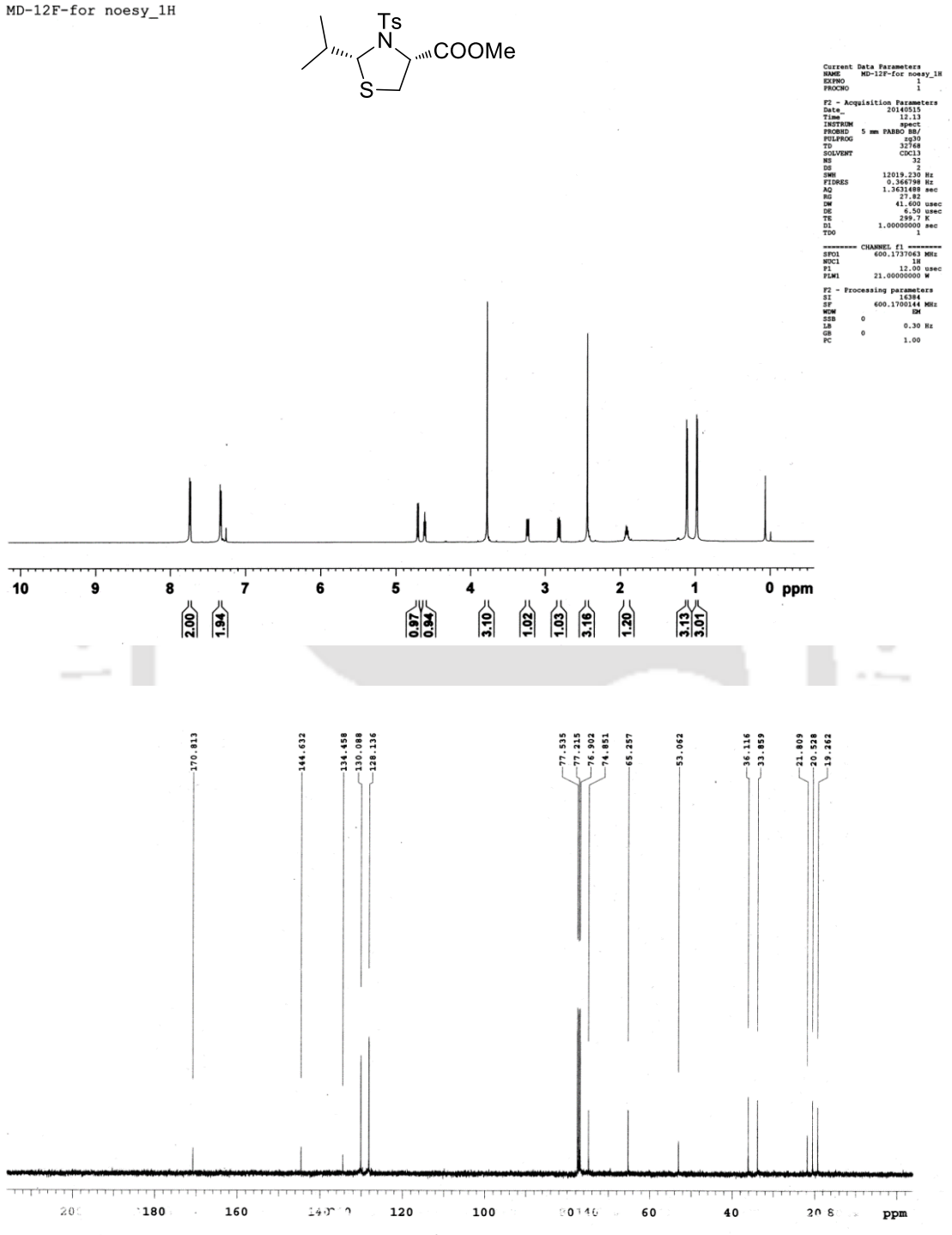
MD-F6_10_13C



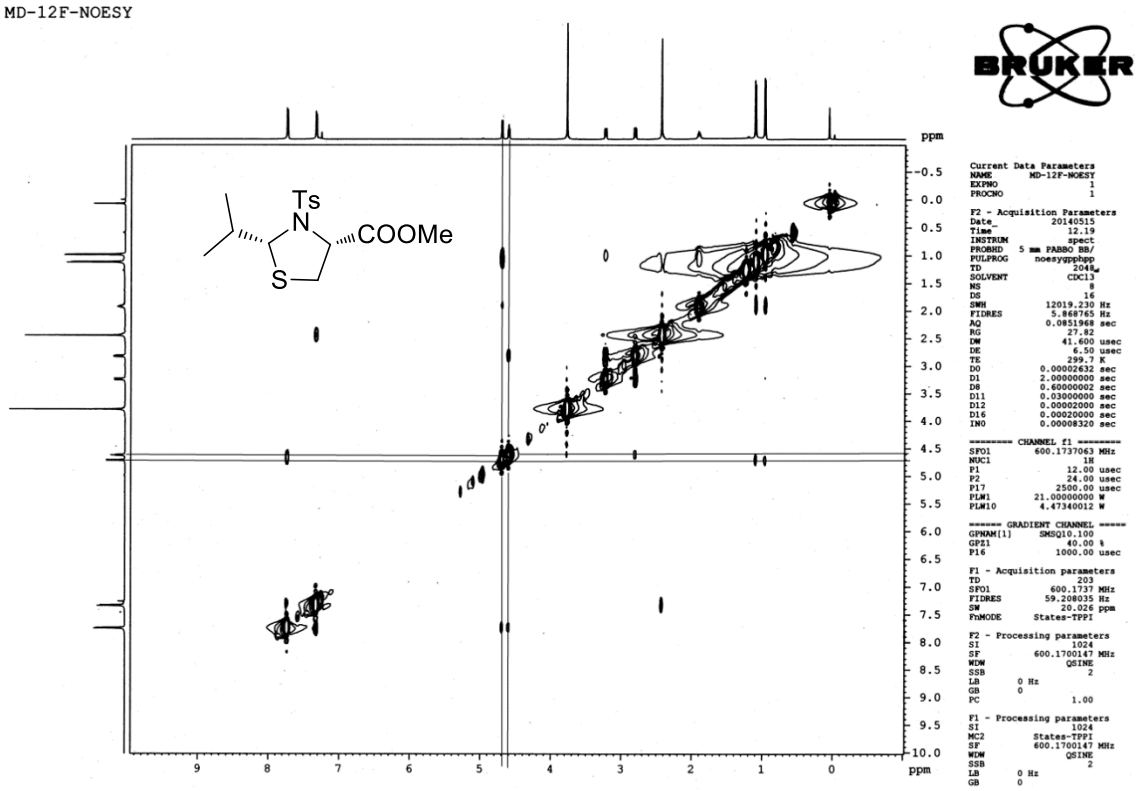

```
Current Data Parameters
NAME                  MD-F6_10_13C
EXPNO                           1
PROCNO                          1

F2 - Acquisition Parameters
Date_                    20140404
Time                        12.34
INSTRUM                     spect
PROBHD    5 mm PABBO BB/
PULPROG                  zgpg30
TD                         32768
SOLVENT                     CDCl3
NS                            291
DS                              2
SWH                  36057.691 Hz
FIDRES                1.100393 Hz
AQ                    0.4543829 sec
RG                       200.18
DW                       13.867 usec
DE                        6.50 usec
TE                       300.1 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                             1

======== CHANNEL f1 ========
SFO1                150.9279571 MHz
NUC1                        13C
P1                       10.50 usec
PLW1                95.00000000 W

======== CHANNEL f2 ========
SFO2                600.1724007 MHz
NUC2                        1H
CPDPRG[2                waltz16
PCPD2                    70.00 usec
PLW2                21.00000000 W
PLW12                0.61714000 W
PLW13                0.30239999 W

F2 - Processing parameters
SI                         16384
SF                  150.9128389 MHz
WDW                           EM
SSB                0
LB                           1.00 Hz
GB                 0
PC                           1.40
```

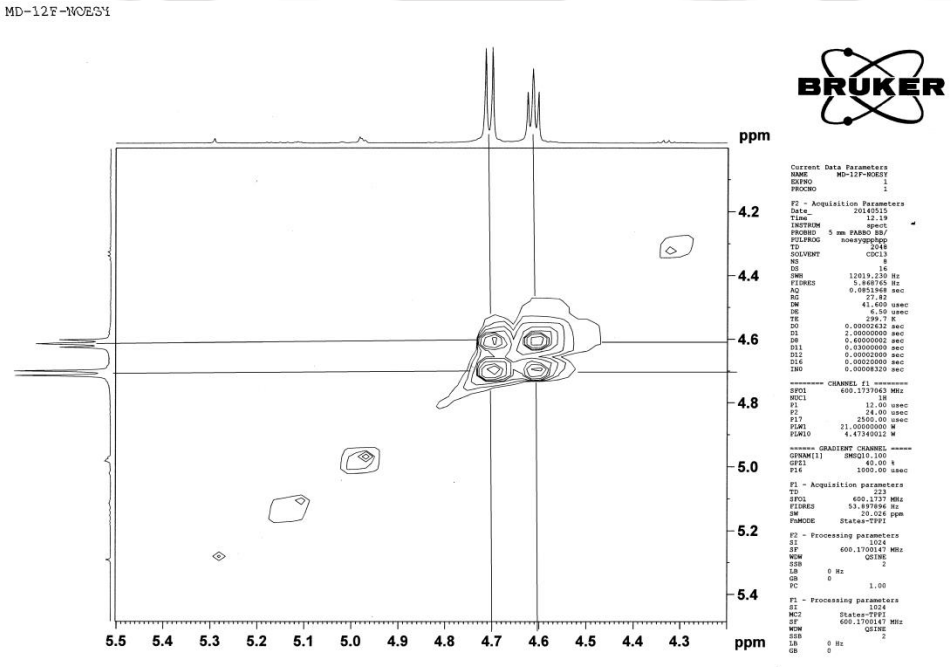


^{1}H and ^{13}C NMR spectra of **(2S,4S)-methyl 2-isopropyl-3-tosylthiazolidine-4-carboxylate**



NOE Spectra of **(2S,4S)-methyl 2-isopropyl-3-tosylthiazolidine-4-carboxylate**



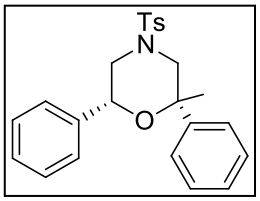


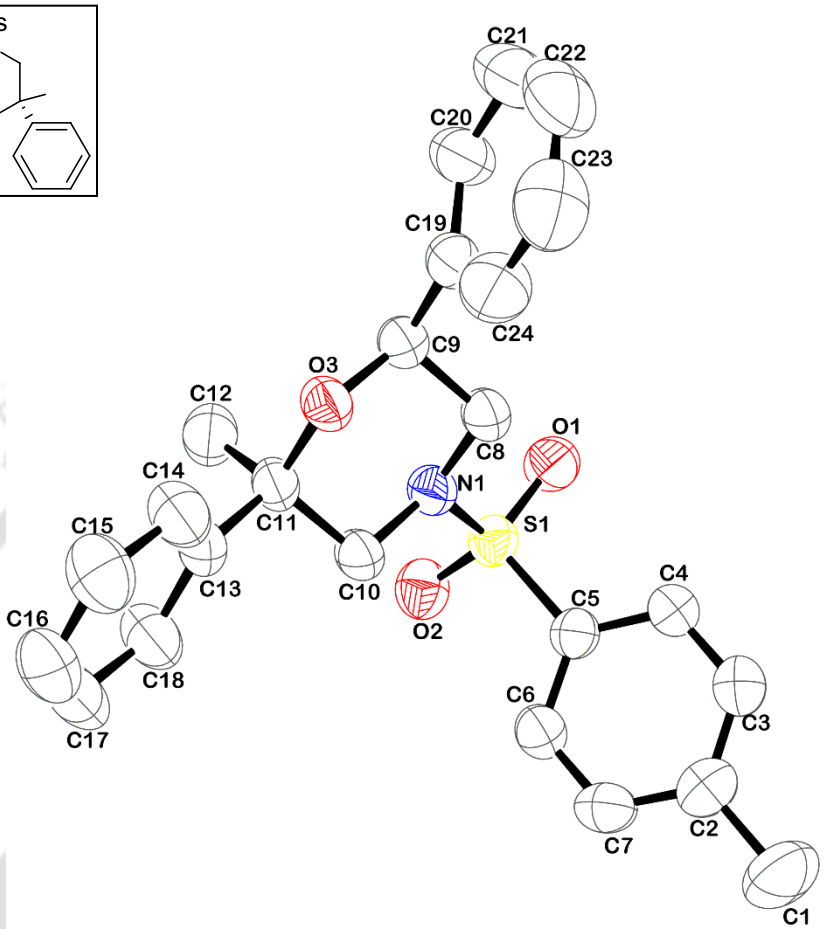
2.9 Crystal Parameters

The crystal parameters of compound ***(2S*,6R*)-2-methyl-2,6-diphenyl-4-tosylmorpholine (43g)***

	CCDC 1041712
Formula	$C_{24}H_{25}NO_3S$
Formula weight	407.51
T/K	296(2)
Crystal system	Monoclinic
Space group	P2(1)/c
a/Å	10.8180(5)
b/Å	10.4424(4)
c/Å	19.4723(9)
α/°	90.00
β/°	19.4723(9)
γ/°	90.00
V/Å^3	2158.93(16)
Z	4
Abs. Coeff./mm^{-1}	0.174
Abs. Correction	None
GOF on F^2	1.072
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0476
	wR2 = 0.1432
R indices [all data]	*R1* = 0.0697
	wR2 = 0.1600

ORTEP Diagram of ***(43g)***





CHAPTER 3

Highly Regioselective Synthesis of 4-Tosylthiomorpholine *via* Intramolecular Cyclization of N-tethered Thioalkenols

3.1 Importance and Applications

Thiazines are organic compounds with molecular formula C_4H_5NS. They are a six member heterocyclic ring system, which contains two heteroatoms (N & S) placed in the heterocyclic ring.Thiazine derivatives may be 1, 2-thiazine, 1, 3-thiazine or 1, 4-thiazines.[1] The tetrahydro derivatives of 1,4 thiazines (C_4H_9NS) are known as thiomorpholines. These heterocyclic compounds, such as thiomorpholines, thiazines, thiazolidines and thiazepines and their oxidized derivatives are considered as important structural motifs in organic synthesis. Examples include Phenothiazines **1**, used as vermifuge for liver stock and also as an insecticide.[2] Anti-hypertensive drug[3] semotiadil **2**, thiomorpholine or its disulfoxide ring containing molecules such as sutezolid[4] **3** and artemisone[5] **4** are undergoing human clinical trials for the treatment of malaria and tuberculosis, respectively (*Fig. 3.1.1*). Many sulphur and nitrogen containing heterocycles such as benzothiomorpholines possess antibacterial, antiarrhythmic, antidiabetic, antihypertensive, and antitumor properties.[6] Similarly, thiomorpholines display local anesthetic,[7] anticonvulsant,[8] antimycobacterial,[9] anti-inflammatory,[10] and antidiabetic activities.[11] Due to their potent activity in various biological activities, the synthesis of these molecules is an important topic for the academia and industrial chemistry.

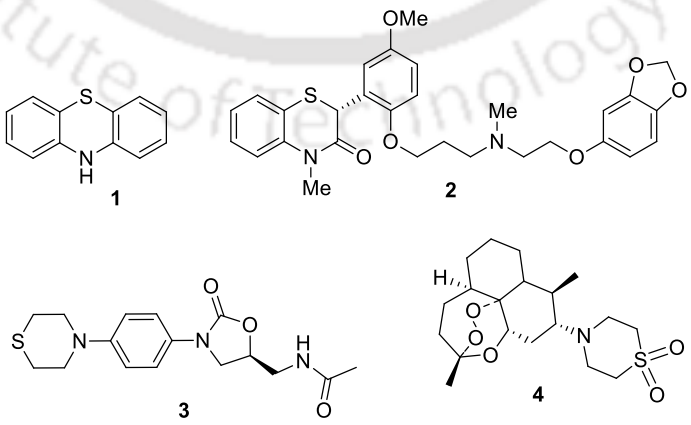
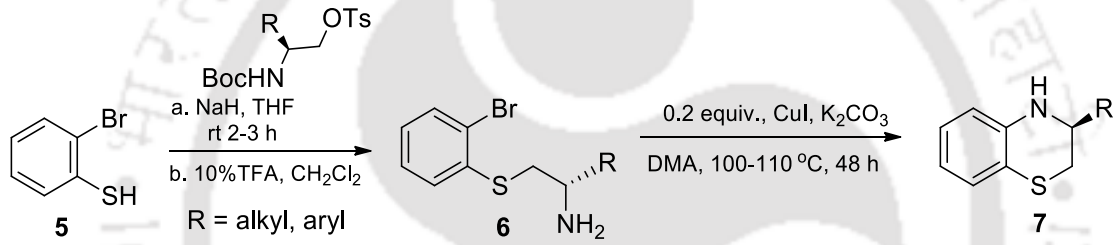


Figure 3.1.1. *Some examples of biologically important molecules.*

3.2 Literature Methods

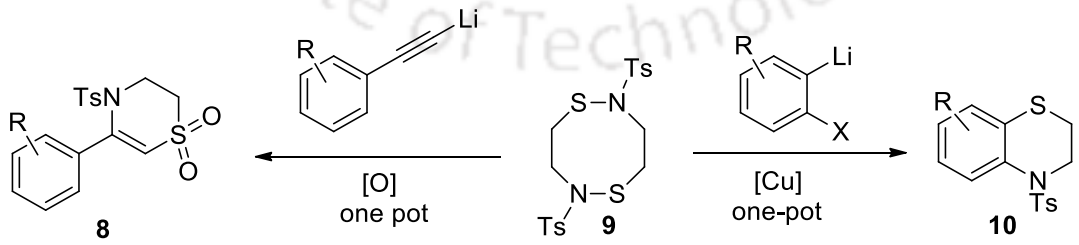
Over the years many strategies have been developed for the synthesis of thiomorpholines. These procedures should have economic advantages. In such an approach, the reduction in the number of steps, metal free nature and increase in selectivity are valuable standards for green synthesis.

Panda *et al.* synthesized a series of 3,4-dihydro-2*H*-benzo[b][1,4]thiazine **7** derivatives *via* a copper-catalyzed intramolecular *N*-aryl amination reaction on substituted 2-(2-bromophenylthio)-ethanamines **6**. The enamines were synthesized by the nucleophilic substitution reaction of 2-bromobenzenethiol **5** with Boc-protected amino alcohol derivatives.[12] (*Scheme 3.2.1*)



Scheme 3.2.1

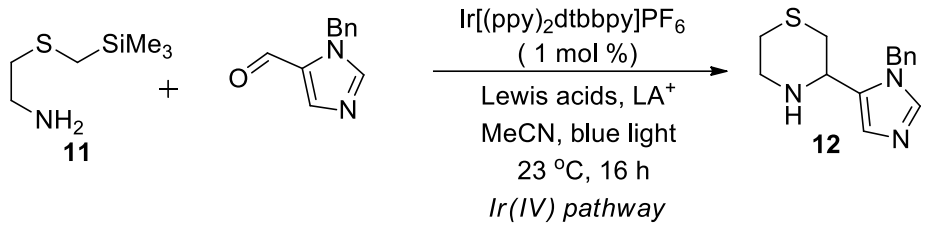
Orentas *et al.* developed an eight-membered C_2-symmetric sulfenamide **9** derivative from simple chromatography free, multi gram scale, three step synthesis from known sulfides **8**. The sulfenamide was further used as a new convenient and highly reactive electrophilic sulfur–nucleophilic nitrogen synthon for the synthesis of medium-ring *S*, *N*-heterocyclic systems **10**.[13] (*Scheme 3.2.2*)



Scheme 3.2.2

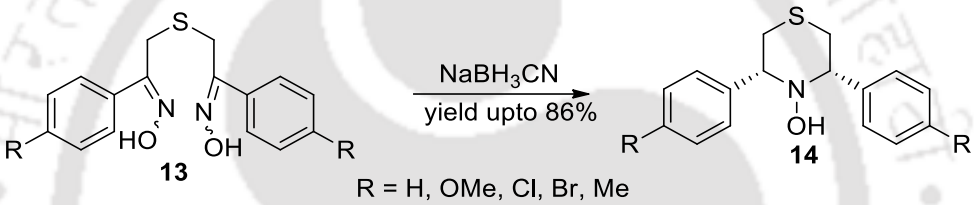
Bode and his coworkers have worked on the silicon amine protocol (SLAP) reagents for the photocatalytic synthesis of *N*-heterocycles. They reported that the inclusion of Lewis

acids in photocatalytic reactions of organosilanes **11** allows access to a distinct reaction pathway featuring an Ir(III)*/Ir(IV) couple enabling the transformation of aromatic and aliphatic aldehydes to thiomorpholines and thiazepanes **12**.[14] (*Scheme 3.2.3*)



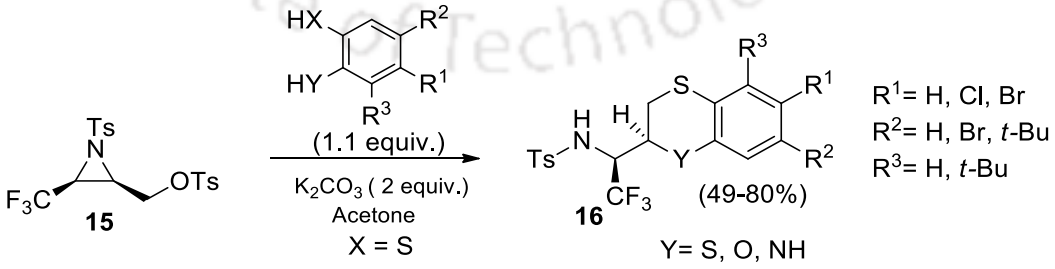
Scheme 3.2.3

Muthusubramanian *et al.* reported a simple and efficient protocol for the construction of substituted thiomorpholines, bearing *N*-hydroxy substituents **14** through intramolecular reductive cyclization of diketoximes **13** using sodium cyanoborohydride.[15] (*Scheme 3.2.4*)



Scheme 3.2.4

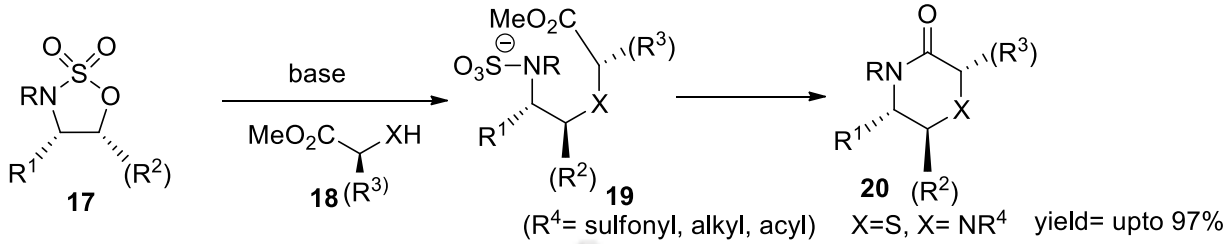
Kimpe and his group, reported a five-step procedure for the synthesis of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine **15**, starting from 1-ethoxy-2,2,2-trifluoroethanol, involving imination, aziridination, ester reduction, hydrogenation, and *N*-,*O*-ditosylation steps. The substituted aziridine moiety showed remarkable difference in their reactivity with respect to aromatic sulfur and oxygen nucleophiles, which enabled the syntheses of functionalized thiomorpholines **16**.[16] (*Scheme 3.2.5*)



Scheme 3.2.5

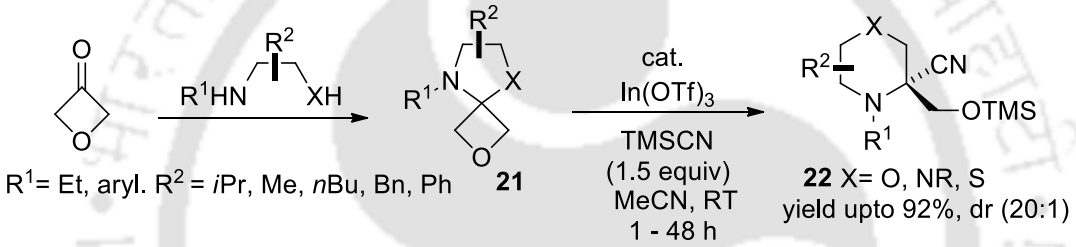
Gallagher *et al*. reported a methodology for the synthesis of thiomorpholin-3-ones **19** and piperazin-2-ones by using 1,2-cyclic sulfamidates. The procedure utilizes 1,2-cyclic

sulfamidates (*scheme 3.2.5*), and **18** (a heteroatom nucleophile adjacent to an acetate moiety). Under the presence of a base a regioselective nucleophilic displacement occur on **17,** followed by lactamization to give a six-ring *N*-heterocycle **20**.[17] (*Scheme 3.2.6*)



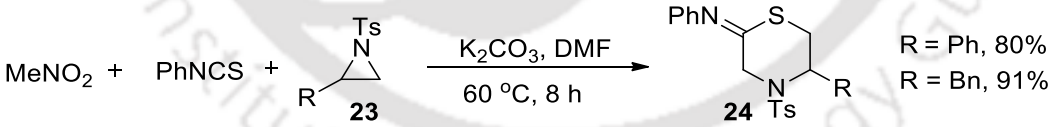
Scheme 3.2.6

Carreira *et al.* reported a Lewis acid mediated cascade reaction of 4,5-Spirocycles **21** (derived from 3-oxetanone) and *β*-heteroatom-substituted amino compounds to form saturated nitrogen heterocycles **22**.[18] (*Scheme 3.2.7*)



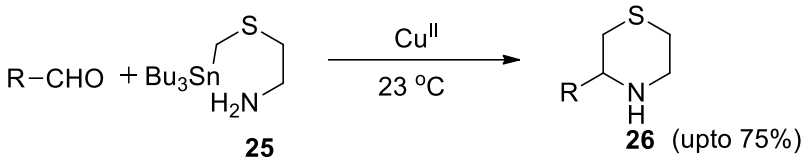
Scheme 3.2.7

Kermani *et al*. reported an efficient one-pot reaction of nitromethane, isothiocyanates, and aziridines **23** for the synthesis of 1,4-thiomorpholine derivatives **24**. The reaction is carried out in the presence of K_2CO_3 in DMF at 60 °C.[19] (*Scheme 3.2.8*)



Scheme 3.2.8

Bode *et al.* conveniently demonstrated the use of SnAP reagents **25** for the transformation of aldehydes into *N*-unprotected piperazines and morpholines **26**. The method provides a simple and mild conditions compatible with aromatic, heteroaromatic, aliphatic, and glyoxylic aldehydes and facilitates the synthesis of mono- and disubstituted *N*-heterocycles in a single step.[20] (*Scheme 3.2.9*)

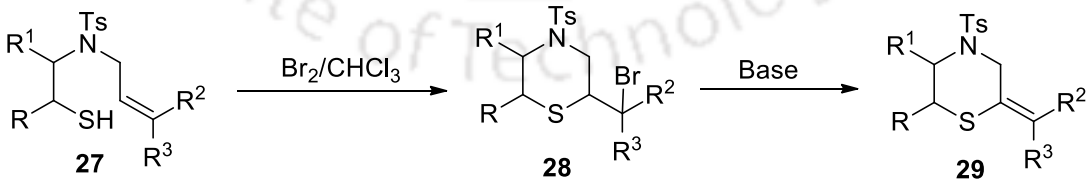


Scheme 3.2.9

A general approach to improve synthetic efficiency is the design of chemical transformations in one-pot with high regioselectivity. As control in selectivity is the primary challenging aspect in elimination reaction, the development of new methodologies with a high degree of selectivity is highly desirable. On the other hand, the presence of double bonds in a cyclic system is not only responsible for their biological properties but also serves as a functional group for further manipulations in organic synthesis.[21] They can also be used as building blocks in organic synthesis.[22] This chapter describes an one-pot, metal free methodology for the regioselective synthesis of 4-tosylthiomorpholines from *N*-tethered thioalkenols in good yields.

3.3 Present work

Although investigators have prepared benzothiomorpholines,[23] less attention has been given to the synthesis of thiomorpholines.[24] The use of thioalkenols has already been discussed in chapter 2 for the synthesis of thiazolidine and thiomorpholine *via* intramolecular hydrothioalkoxylation of *N*-tethered thioalkenols.[25] To further validate the synthetic applicability of *N*-tethered thioalkenols, in accordance to similar works in sulfur heterocyclic compounds,[26] it was envisioned that bromination of double bonds followed by nucleophilic attack by a thiol would generate a bromide intermediate, which after dehydrodebromination by a suitable base would give thiomorpholines (*Scheme 3.3.1*).



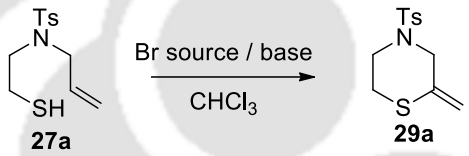
Scheme 3.3.1

3.3.1 Results and Discussion

Thioalkenol **27a** (1.0 equiv.) was treated with molecular bromine in chloroform at 0 °C. After 15 minutes, DBU (2.0 equiv.) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 4 h and 2-methylene-4-tosylthiomorpholine

29a was obtained in 80% yield. Other bases such as K_2CO_3, Et_3N and KOH were found to be inefficient (*Table 3.3.1.1*). On the other hand, reaction with tetrabutylammonium tribromide (TBATB), which is known for its brominating ability of different functionalities,[27] and DBU in $CHCl_3$ afforded 70% yield (*Table 3.3.1.1*, entry 5). Similarly, cetyltrimethylammonium tribromide (CTMATB), another brominating agent, under basic (DBU) conditions yielded only 68% yield.[28] The reaction with *N*-bromosuccinimide (NBS) failed to give the product. The reaction was also carried out in different solvents such as DMSO, CH_2Cl_2, DMF and THF. But $CHCl_3$ was found to be the best amongst the solvents studied. It was evident that 1.1 equiv. of molecular bromine and 2 equiv. of DBU in $CHCl_3$ are the optimal conditions for the reaction.

Table 3.3.1.1 Optimization of reaction condition



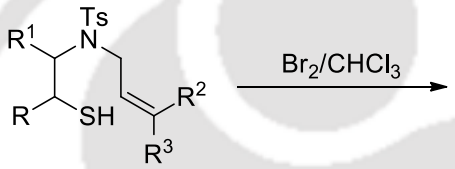
Sl No.	Bromine source (equiv.)	Base (equiv.)	Solvent	Yield (%)[a]
1	Br_2 (1.1)	DBU(2.0)	$CHCl_3$	80
2	Br_2 (1.1)	K_2CO_3 (2.0)	$CHCl_3$	50
3	Br_2 (1.1)	Et_3N (2.0)	$CHCl_3$	42
4	Br_2 (1.1)	KOH (2.0)	$CHCl_3$	30
5	TBATB (1.1)	DBU(2.0)	$CHCl_3$	70
6	CMATB (1.1)	DBU(2.0)	$CHCl_3$	68
7	NBS (1.1)	DBU(2.0)	$CHCl_3$	0
8	Br_2 (1.1)	DBU(2.0)	DMSO	0
9	Br_2 (1.1)	DBU(2.0)	CH_2Cl_2	68
10	Br_2 (1.1)	DBU(2.0)	DMF	40
11	Br_2 (1.1)	DBU(2.0)	THF	55

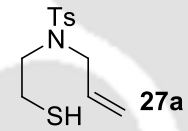
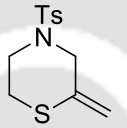
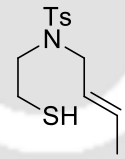
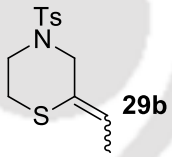
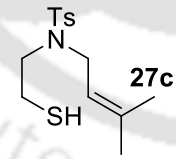
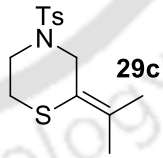
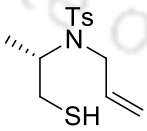
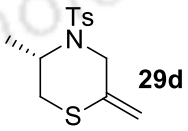
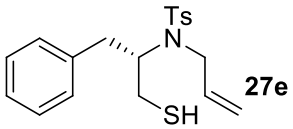
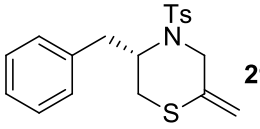
[a]yield refers to isolated yield.

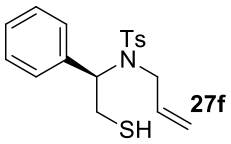
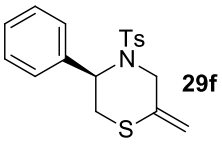
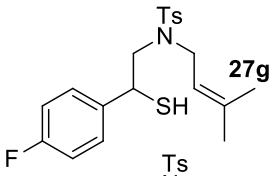
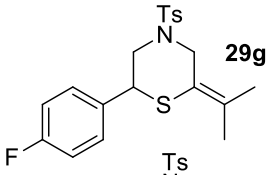
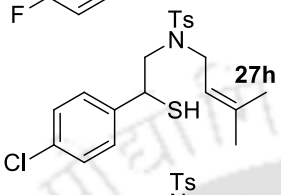
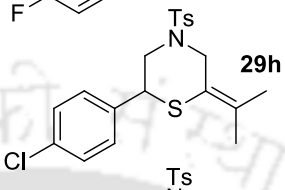
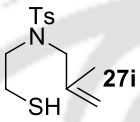
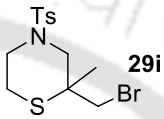
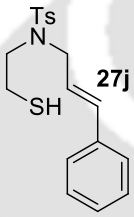
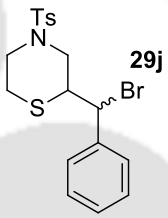
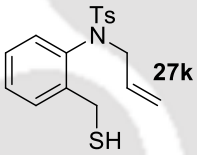
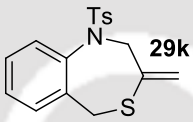
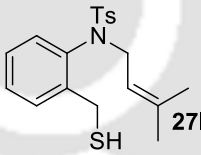
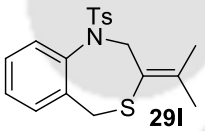
With these optimized conditions in hand, a variety of *N*-tethered thioalkenols were evaluated as substrates and the results are summarized in (*Table 3.3.1.2)*. It was observed from (*Table 3.3.1.2)* that the reaction provides only *exo*-olefinic 4-tosylthiomorpholine **29a–l** in good to high yields, regioselectively. The reaction proceeds with differently substituted thioalkenols such as alkyl (entry 4), benzyl (entry 5) and aryl (entries 6-8) to give substituted thiomorpholines in good yields. Terminal and 1,1-disubstituted alkenes gave single product, whereas 1,2-disubstituted alkene **27b** produced an inseparable *cis*–

trans isomeric mixture with a ratio of 1:3 which was determined by ^{1}H NMR. Substrate **27i** having a 2,2-disubstituted alkene gave an intermediate bromo compound, 2-(bromomethyl)-2-methyl-4-tosylthiomorpholine **29i** (*Scheme 3.3.2.1*). However, the substrate having a terminal phenyl group on the alkene side chain yielded brominated thiomorpholine **29j** as an inseparable diastereomeric mixture with a ratio of 4:1 in 65% yield (entry 10). This might be due to the steric hindrance imparted by the phenyl group to the incoming bulky DBU. On the other hand, aromatic thioalkenols **27k** and **27l** gave thiazepines **29k** and **29l** in 78 and 75% yields, respectively. Chiral starting materials **27d–27f** produced the corresponding chiral thiomorpholines **29d-29f**, in 65, 67 and 65% yields, respectively.

Table 3.3.1.2 Synthesis of Thiomorpholines

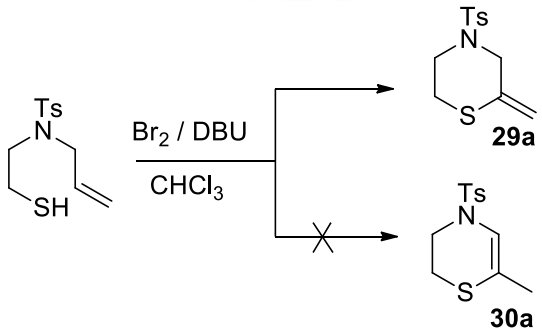


entry	Thiol	product	yield[a]
1			80
2			72[b]
3			78
4			65
5			67

entry	Thiol	product	yield[a]
6			65
7			63
8			65
9			77
10			65[c]
11			78
12			75

[a]yields refer to isolated yields. compounds are characterized by ^{1}H ,^{13}C NMR, IR and mass spectrometric analysis. [b] Mixture of the *E/Z* iomer with a ratio of 3:1 (2b). [c] Mixture of diastereomers with a ratio of 6:1 (2j) determined by ^{1}H NMR.

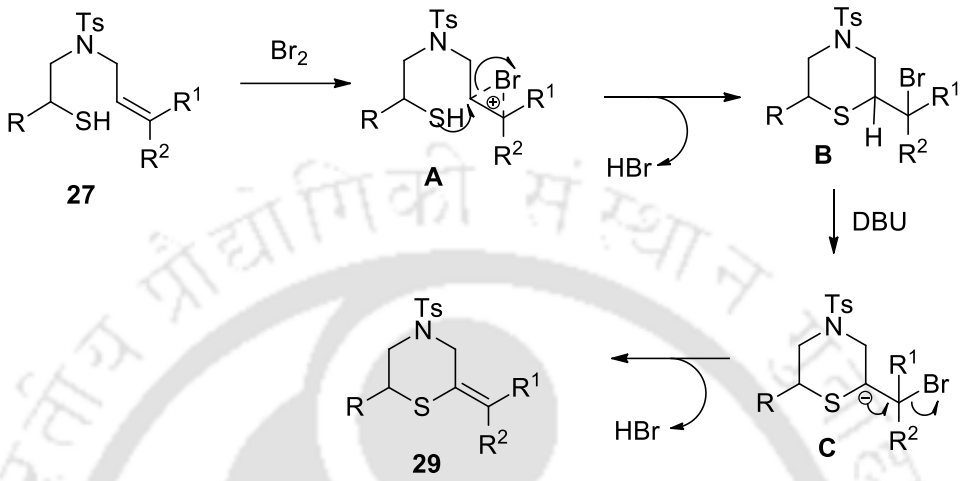
.



Scheme 3.3.1.1 *Selective formation of exocyclic thiomorpholine.*

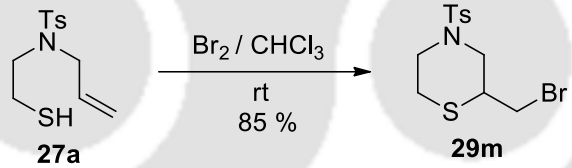
3.3.2 Plausible Mechanism

The mechanism of the reaction can be explained as follows. The reaction proceeds in two steps. In the first step molecular bromine adds to the double bond to form bromonium ion **A**, which after nucleophilic attack by thiol gives bromide **B**. The bromide **B** after dehydrobromination under basic conditions gives the desired product **29.** (*Scheme 3.3.2.1*)



Scheme 3.3.2.1. *Plausible mechanism for the reaction.*

To prove the formation of intermediate **B**, amino thiol **27a** was treated with bromine in the absence of DBU (*Scheme 3.3.2.2*). It was observed that the intermediate monobrominated compound **29m** was obtained in 85% yield.



Scheme 3.3.2.2 *Formation of brominated thiomorpholine.*

3.4 Conclusion

In conclusion, a one-pot, metal free, mild and efficient method for the synthesis of 4-tosylthiomorpholine from *N*-tethered thioalkenols *via* bromination, cyclization and subsequent elimination reaction in good yields has been developed. An important aspect of this reaction is that it produces exocyclic tosylthiomorpholine regioselectively. The method can also be extended for the synthesis of benzo[1,4]thiazepine.

3.5 Experimental section

3.5.1 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 an open capillary tube and are uncorrected. Fourier transform-infrared (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H (600 MHz, 400 MHz) or ^{13}C (150 MHz, 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin–spin coupling constants (J) are given in Hz. HRMS spectra were recorded using a Q-TOF mass spectrometer. Elemental analysis was performed on a Perkin Elmer 2400 series II CHNS analyzer. Starting compounds **27a, 27c, 27e** and **27i** are known and their analytical data are in agreement with the reported compounds.[26/29]

3.5.2 Synthesis of Starting Materials

3.5.2.1 General procedure for the synthesis of thiols

To a stirred solution of triphenylphosphine (1.5 equiv.) in anhydrous THF (10 mL), DIAD (1.5 equiv.) was added at 0 °C and stirred for 30 min. Then a solution of amino alcohol (2.5 mmol) (1 equiv.) and thioacetic acid (1 equiv.) in THF (5 mL) was added into the reaction mixture at 0 °C. It was allowed to warm to 25 °C and stirred for an additional 5 h. It was stirred with a 1:1 mixture of hexane:diethylether; triphenylphosphine oxide was filtered off. The filtrate was concentrated. The crude mixture (1 equiv.) was added portion wise at 0 °C to a stirred solution of $LiAlH_4$ (1 equiv.) in anhydrous THF (10 mL). The reaction mixture was stirred for 30 min at room temperature. The reaction was quenched by addition of ethyl acetate (30 mL) followed by water (30 mL) at 0 °C. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel (eluent = hexane/ethyl acetate, 9:1) to furnish the thiol compounds.

3.5.3 Synthesis of 4-tosylthiomorpholine

3.5.3.1 General procedure for the synthesis of 4-tosylthiomorpholine.

To a stirred solution of thioalkenols (0.5 mmol) (**27a–27k**) in $CHCl_3$ (2 mL) at 0 °C was added molecular bromine (0.5 mmol) dropwise. After 15 minutes, DBU (1.0 mmol) was

added to the reaction mixture. The reaction mixture was stirred at room temperature for 4 h. 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 ethyl acetate (2 × 10.0 mL) and washed with brine. The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using a rotary evaporator to give 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 in 60–80% yield.

3.5.3.2 Typical procedure for the synthesis of 2-methylene-4-tosylthiomorpholine 29a.

To a stirred solution of thioalkenols (269 mg, 1 mmol) in $CHCl_3$ (5 mL) at 0 °C was added molecular bromine (0.1 mL, 1 mmol) dropwise. After 15 minutes, DBU (0.4 mL, 2.0 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 4 h. 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 ethyl acetate (2 × 10.0 mL) and washed with brine. The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using a 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 methylene-4-tosylthiomorpholine **29a**.

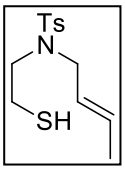
3.6 References

1. (a) Raj k Bansal. Heterocyclic Chemistry, Fourth edition; New Age International Publishers; 501. (b) Alan RK. The principles of Heterocyclic Chemistry; Pharma Med press publishers; 503.
2. Didwagh S and Pravina BP. Green synthesis of thiazine and oxazine derivatives-A Short Review, *International Journal of Pharmaceutical Sciences and Research* **2013**, *4*, 2045.
3. Morino, T.; Yamamoto, T. *J. Chem. Eng. Jpn*. **1997**, *30*, 1005.
4. (a) Barbachyn, M. R.; Hutchinson, D. K.; Brickner, S. J.; Cynamon, M. H.; Kilburn, J. O.; Klemens, S. P.; Glickman, S. E.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C.W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 680.(b) Villemagne, B.; Crauste, C.; Flipo, M.; Baulard, A. R.;Déprez, B.; Willand, N. *Eur. J. Med. Chem.* **2012**, *51*, 1.
5. (a) Haynes, R. K.; Fugmann, B.; Stetter, J.; Rieckmann, K.; Heilmann, H.-D.; Chan, H.-W.; Croft, S. L.; Vivas, L.; Rattray, L.; Stewart, L.; Peters, W.; Robinson, B. L.; Edstein, M. D.; Kotecka, B.; Kyle, D. E.; Beckermann, B.; Gerisch, M.; Radtke, M.; Schmuck, G.; Steinke, W.; Wollborn, U.; Schmeer, K.; Römer, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 2082. (b) Nagelschmitz, J.; Voith, B.; Wensing, G.; Römer, A.; Fugmann, B.; Haynes, R. K.; Kotecka, B. M.; Rieckmann, K. H.; Edstein, M. D. *Antimicrob. Agents Chemother.* **2008**, *52*, 3085.
6. (a) R. Fringuelli, L. Milanese and F. Schiaffella, Mini-Rev. *Med. Chem*. **2005**, *5*, 1061. (b) R. R. Gupta and K. G. Ojha, in Phenothiazines and benzothiazenes: chemical and biochemical aspects, ed. R. R. Gupta, Elsevier, Amsterdam, **1988**, vol. *4*, p. 163. (c) S. Mitra, S. Mukherjee and A. Hajra, *RSC Adv*. **2016**, *6*, 201.
7. Burrows, L. A; Reid, E. E. *J. Am. Chem. Soc*. **1934**, *56*, 1720.
8. Edayadulla, N; Ramesh, P. *Eur. J. Med. Chem*. **2015**, *106*, 44.
9. Indumathi, S.; Perumal, S.; Banerjee, D.; Yogeeswari, P. *Eur. J. Med. Chem.* **2009**, *44*, 4978.
10. Nobelos, P. T.; Kourti, M.; Gavalas, A.; Rekka, E. A. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 910.
11. Han, B.; Liu, J. L.; Huan, Y.; Li, P.; Wu, Q.; Lin, Z. Y.; Shen, Z. F.; Yin, D. L.; Huang, H. H. *Chin. Chem. Lett*. **2012**, *23*, 297.
12. Parai, M. K.; Panda, G. *Tetrahedron Lett*. **2009**, *50*, 4703.

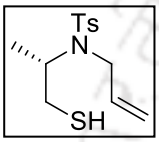
13. Javorskis, T; Bagdziunas, G.; Orentas,E. *Chem. Commun*. **2016**, *52*, 4325.
14. Hsieh, S. Y.; Bode, J. W. *ACS Cent. Sci.* **2017**, *3*, 66.
15. Nagaraj, M.; Boominathan, M.; Bhuvanesh, N.; Muthusubramanian, S. *Org. Biomol. Chem.* **2011**, *9*, 4642.
16. Kenis, S.; D'hooghe, M.; Verniest, G.; Reybroeck, M.; Thi,T. A. D.; The, P. C.; Pham, T. T.; Tçrnroos, K. W.; Tuyen, N. V.; Kimpe, N. D. *Chem. Eur. J.* **2013**, *19*, 5966.
17. Williams, A. J; Chakthong, S.; Gray, D.; Lawrence, R. M.; Gallagher, T. *Org. Lett.* **2003**, *5*, 811.
18. Ruider, S. A.; Muller, S.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 11908.
19. Samzadeh, A. S. *Synlett*. **2014**, *25*, 1839.
20. T. Vo, C. T.; Mikutis, G.; Bode, J. W. *Angew. Chem. Int. Ed*. **2013**, *52*, 1705.
21. (a) Johannesson, P.; Lindeberg, G.; Johansson, A.; Gregory, A.; Nikiforovich, V.; Gogoll, A.; Synnergren, B.; Grèves, M. L.; Nyberg, F.; Karlén, A.; Hallberg, A.; *J. Med. Chem.* **2002**, *45*, 1767. (b) Sader, H. S.; Johnson, D. M.; Jones, R. N. *Antimicrob. Agents Chemother*. **2004**, *48*, 53. (c) Pham, M.; Allatabakhsh, A.; Minehan, T. G.; *J. Org. Chem*. **2008**, *73*, 741. (d) Miranda, P. O.; Diaz, D. V.; Padrón, J. I.; Bermejo, J.; Martin, V. S.; *Org. Lett*. **2003**, *5*, 1979.
22. (a) Trost, B. M.; Lavoie, A. C.; *J. Am. Chem. Soc.* **1983**, *105*, 5075. (b) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958. (c) Isobe, M.; Chang, W. C.; Tsou, P. K.; Ploysuk, C.; Yu, C.H. J. *J. Org. Chem*., **2015**, *80*, 6222. (d) Weise, C. F.; Lauridsen, V. H.; Rambo, R. S.; Iversen, E. H.; Olsen, M.L.; Jørgensen, K. A. *J. Org. Chem*. **2014**, *79*, 3537.
23. (a) Javorskis, T.; Bagdziunas, G.; Orentas, E. *Chem. Commun.* **2016**, *52*, 4325. (b) Parai, M. K.; Panda, G. *Tetrahedron Lett*. **2009**, *50*, 4703.
24. (a) Bieniek, M.; Koloda, D.; Grela, K. *Org. Lett*. **2006,** *8*, 5689. (b) Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc., Perkin Trans*. **1998**, *1*, 3127.
25. Deka, M. J.; Indukuri, K.; Sultana, S.; Borah, M. Saikia, A. K. *J. Org. Chem.* **2015**, *80*, 4349.
26. (a) Borah, M.; Gogoi, P.; Indukuri, K.; Saikia, A. K. *J. Org. Chem.* **2015**, *80*, 2641. (b) Bondalapati, S.; Gogoi, P.; Indukuri, K.; Saikia, A. K. *J. Org. Chem*. **2012**, 77, 2508. (c) Raju, B. R.; Sarkar, S.; Reddy, U. C.; Saikia, A. K. *J. Mol. Catal. A: Chem.* **2009**, *308*, 169.

27. (a) Fournier, M.; Fournier, F.; Berthelot, J. *Bull. Soc. Chim. Belg*. **1984**, *93*, 157. (b) Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Fujisaki, S.; *Bull. Chem. Soc. Jpn*. **1987**, *60*, 1159.
28. Kar, G.; Saikia, A. K.; Bora, U.; Dehury, S. K.; Chaudhuri, M. K.; *Tetrahedron Lett*. **2003**, *44*, 4503.
29. Bera, S.; Panda, G. *ACS Comb. Sci*. **2012**, *14*, 1.

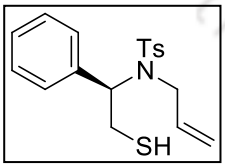
3.7 Spectral data



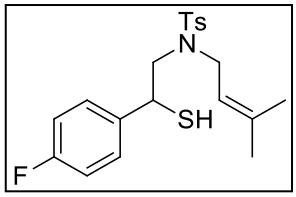
Data for (E,Z)-N-(But-2-en-1-yl)-N-(2-mercaptoethyl)-4-methyl-benzenesulfonamide **(27b)** (E:Z::3:1). White solid; mp 86–88 °C; R_f (hexane/EtOAc 9 : 1) 0.55; yield 399 mg, 55%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.65 (d, J = 6.6 Hz, 3 H), 2.43 (s, 3 H), 2.78–2.84 (m, 2 H), 3.30–3.37 (m, 2 H), 3.73 (d, J = 6.6 Hz, 2 H, major), 3.85 (d, J = 7.2 Hz, 2 H, minor), 5.27–5.32 (m, 1 H), 5.59–5.64 (m, 1 H), 7.33 (d, J = 8.4 Hz, 2 H), 7.71 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 17.8, 21.6, 49.5, 51.6, 61.2, 125.7, 127.4, 129.8, 129.9, 131.1, 143.6; **IR** (KBr, neat) 2921, 2826, 1598, 1447, 1338, 1160, 1090, 932, 715 cm−1, **HRMS** (ESI) calcd for $C_{13}H_{20}NO_2S_2$ $(M + H)^+$ 286.0930, found 286.0912.



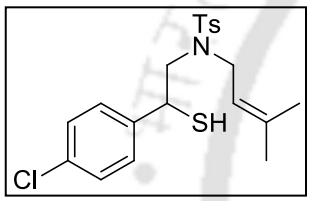
Data for N-Allyl-N-(1-mercaptopropan-2-yl)-4-methylbenzenesulfonamide **(27d).** Gum; R_f (hexane/EtOAc 9:1) 0.55; yield 428 mg, 60%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.11 (d, J = 7.2 Hz, 3 H), 1.41 (t, J = 8.4 Hz, 1 H), 2.40 (s, 3 H), 2.45–2.50 (m, 1 H), 2.67–2.71 (m, 1 H), 3.67 (dd, J = 16.2 and 7.2 Hz, 1 H), 3.88 (dd, J = 16.2 and 5.4 Hz, 1 H), 3.94 (t, J = 6.6 Hz, 1 H), 5.10 (d, J = 10.2 Hz, 1 H), 5.18 (d, J = 16.8 Hz, 1 H), 5.80–5.87 (m, 1 H), 7.27 (d, J = 7.8 Hz, 2 H), 7.69 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.4, 21.6, 30.0, 46.8, 57.3, 117.7, 127.3, 129.8, 136.1, 138.0, 143.4; **IR** (KBr, neat) 2925, 2855, 1598, 1452, 1336, 1158, 1090, 815, 661 cm^{-1}; **HRMS** (ESI) calcd for C13H20NO2S2 $(M + H)^+$ 286.0930, found 286.0905.



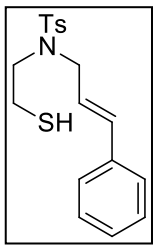
Data for N-Allyl-N-(2-mercapto-1-phenylethyl)-4-methylbenzene-sulfonamide **(27f).** Gum; R_f (hexane/EtOAc 9:1) 0.55; yield 520 mg, 58%; **^{1}H NMR** (600 MHz, $CDCl_3$) 1.38 (t, J = 8.4 Hz, 1 H), 2.43 (s, 3 H), 2.97–3.03 (m, 1 H), 3.22–3.28 (m, 1 H), 3.43 (dd, J = 15.6 and 3.0 Hz, 1 H), 3.88 (dd, J = 16.2 and 5.4 Hz, 1 H), 5.02–5.08 (m, 3 H), 5.59–5.65 (m, 1 H), 7.09 (s, 2 H), 7.27–5.28 (m, 5 H), 7.69 (d, J = 7.2 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 26.7, 47.5, 64.2, 117.8, 127.5, 128.8, 128.9, 129.8, 135.8, 138.1, 143.6; **IR** (KBr, neat) 2924, 2855, 1598, 1449, 1336, 1156, 1091, 814, 736 cm^{-1}; **HRMS** (ESI) calcd for $C_{18}H_{22}NO_2S_2$ $(M + H)^+$ 348.1086, found 348.1085.



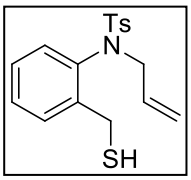
Data for N-(2-(4-Fluorophenyl)-2-mercaptoethyl)-4-methyl-N-(3-methylbut-2-en-1-yl)benzene-sulfonamide **(27g).** Gum; R_f (hexane/EtOAc 9:1) 0.55; yield 510 mg, 50%; **^{1}H NMR** (400 MHz, $CDCl_3$) 1.53 (s, 3 H), 1.60 (s, 3 H), 2.12 (d, J = 5.2 Hz, 1 H), 2.42 (s, 3 H), 3.33 (dd, J = 14.4 and 8.0 Hz, 1 H), 3.46 (dd, J = 14.4 and 7.2 Hz, 1 H), 3.52 (dd, J = 15.6 and 6.8 Hz, 1 H), 3.72 (dd, J = 15.6 and 7.2 Hz, 1 H), 4.35–4.41 (m, 1 H), 4.70 (dt, J = 6.8 and 1.6 Hz, 1 H), 7.00 (t, J = 8.4 Hz, 2 H), 7.26–7.31 (m, 4 H), 7.64 (d, J = 8.0 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 17.9, 25.9 (2C), 42.9, 47.1, 55.7, 115.7 (d, J = 21.5 Hz), 118.7 (d, J = 7.7 Hz), 127.5, 129.5, 129.6, 129.8, 136.6, 136.7, 136.8, 137.4, 143.6, 162.3 (d, 245.3 Hz); **IR** (KBr, neat) 2924, 2840, 1600, 1447, 1342, 1159, 1091, 837, 655 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{25}FNO_2S_2$ $(M + H)^+$ 394.1305, found 394.1307.



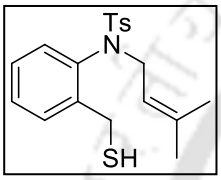
Data for N-(2-(4-Chlorophenyl)-2-mercaptoethyl)-4-methyl-N-(3-methylbut-2-en-1-yl)benzene-sulfonamide **(27h).** Gum; R_f (hexane/ EtOAc 9:1) 0.55; yield 532 mg, 52%; **^{1}H NMR** (400 MHz, $CDCl_3$) 1.53 (s, 3 H), 1.60 (s, 3 H), 2.10 (d, J = 5.2 Hz, 1 H), 2.43 (s, 3 H), 3.32 (dd, J = 14.4 and 8.4 Hz, 1 H), 3.45 (dd, J = 14.4 and 6.8 Hz, 1 H), 3.53 (dd, J = 15.6 and 6.8 Hz, 1 H), 3.70 (dd, J = 15.6 and 7.2 Hz, 1 H), 4.33–4.38 (m, 1 H), 4.69 (t, J = 6.4 Hz, 1 H), 7.26–7.31 (m, 6 H), 7.63 (d, J = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.0, 21.7, 26.0, 42.9, 47.2, 55.5, 118.6, 127.5, 129.0, 129.3, 129.8, 133.7, 136.5, 137.5, 139.6, 143.7; **IR** (KBr, neat) 2964, 2825, 1597, 1492, 1342, 1163, 1092, 914, 736 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{25}ClNO_2S_2$ $(M + H)^+$ 410.1010, found 410.0940.



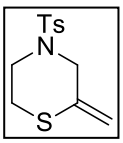
Data for N-Cinnamyl-N-(2-mercaptoethyl)-4-methylbenzenesulfonamide **(27j).** Gum; R_f (hexane/EtOAc 9:1) 0.55; yield 477 mg, 55%; **^{1}H NMR** (600 MHz, $CDCl_3$) 1.39 (t, J = 8.4 Hz, 1 H), 2.43 (s, 3 H), 2.72 (q, J = 8.4 Hz, 2 H), 3.30 (t, J = 7.8 Hz, 2 H), 3.97 (d, J = 6.6 Hz, 1 H), 5.95–6.01 (m, 1 H), 6.45 (d, J = 16.2 Hz, 1 H), 7.26–7.27 (m, 3 H), 7.29–7.32 (m, 4 H), 7.73 (d, J = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 24.0, 51.1, 51.4, 124.2, 126.7, 127.4, 128.3, 128.8, 130.0, 134.3, 136.1, 136.9, 143.8; **IR** (KBr, neat) 3495, 2923, 2868, 1597, 1450, 1339, 1162, 1092, 913, 815, 740, 668 cm^{-1}; **HRMS** (ESI) calcd for $C_{18}H_{22}NO_2S_2$ $(M + H)^+$ 348.1086, found 348.1086.



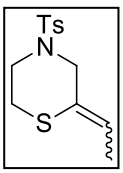
***Data for N-Allyl-N-(2-(mercaptomethyl)phenyl)-4-methylbenzene-sulfonamide* (27k).** Light yellow solid; mp 128–130 °C; Rf (hexane/ EtOAc 9:1) 0.55; yield 466 mg, 55%; **^{1}H NMR** (400 MHz, $CDCl_3$) 1.98 (t, J = 8.0 Hz, 1 H), 2.44 (s, 3 H), 3.80 (dd, J = 13.6 and 7.6 Hz, 1 H), 3.87–4.00 (m, 2 H), 4.44 (dd, J = 13.6 and 8.4 Hz, 1 H), 4.98 (d, J = 17.2 Hz, 1 H), 5.03 (d, J = 10.4 Hz, 1 H), 5.75–5.82 (m, 1 H), 6.49 (d, J = 7.6 Hz, 1 H), 7.07 (t, J = 7.6 Hz, 1 H), 7.27–7.31 (m, 3 H), 7.53–7.57 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.7, 24.4, 55.0, 119.9, 127.4, 128.0, 128.2, 129.0, 129.7, 130.7, 132.5, 135.2, 136.8, 143.0, 143.9; **IR** (KBr, neat) 2923, 2868, 1597, 1454, 1344, 1160, 1092, 922, 814, 657 cm^{-1}; **HRMS** (ESI) calcd for $C_{17}H_{20}NO_2S_2$ $(M + H)^+$ 334.0930, found 334.0933.



***Data for N-(2-(Mercaptomethyl)phenyl)-4-methyl-N-(3-methylbut-2-en-1-yl)benzenesulfonamide* (27l).** Gum; R_f (hexane/EtOAc 9:1) 0.55; yield 542 mg, 58%; **^{1}H NMR** (400 MHz, $CDCl_3$) 1.41 (s, 3 H), 1.59 (s, 3 H), 1.96 (t, J = 8.0 Hz, 1 H), 2.44 (s, 3 H), 3.80–3.88 (m, 2 H), 3.98 (dd, J = 14.0 and 5.2 Hz, 1 H), 4.39 (dd, J = 14.0 and 6.4 Hz, 1 H), 5.12 (t, J = 7.2 Hz, 1 H), 6.52 (d, J = 8.0 Hz, 1 H), 7.06 (t, J = 7.6 Hz, 1 H), 7.25–7.30 (m, 3 H), 7.55–7.57 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.8, 21.7, 24.4, 25.8, 49.7, 118.3, 127.3, 127.9, 128.1, 128.9, 129.6, 130.7, 135.7, 137.1, 138.3, 143.3, 143.7; **IR** (KBr, neat) 2963, 2827, 1598, 1451, 1345, 1159, 1091, 809, 711, 654 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{24}NO_2S_2$ $(M + H)^+$ 362.1243, found 362.1253.

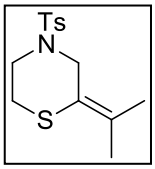


***Data for 2-Methylene-4-tosylthiomorpholine* (29a).** White solid; mp 105–107 °C; R_f (hexane/EtOAc 9:1) 0.5.8; yield 215 mg, 80%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 2.73 (t, J = 5.4 Hz, 2 H), 2.43–2.45 (m, 2 H), 3.82 (s, 2 H), 5.27 (s, 1 H), 5.29 (s, 1 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.65 (d, J = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) $_{\delta}$ 21.7, 28.1, 46.8, 53.1, 116.9, 127.8, 130.0, 134.1, 134.6, 144.1; **IR** (KBr, neat) 2923, 2850, 1615, 1597, 1449, 1348, 1163, 1092, 902, 753 cm−1; **HRMS** (ESI) calcd for $C_{12}H_{16}NO_2S_2$ $(M + H)^+$ 270.0617, found 270.0620.

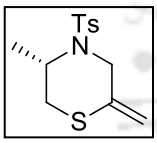


***Data for (E/Z)-2-Ethylidene-4-tosylthiomorpholine* (3:1) (29b).** White solid; mp 110–112 °C; *Rf* (hexane/EtOAc 9:1) 0.5.8; yield 204 mg, 72%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.72 (d, J = 6.6 Hz, 3 H, minor), 1.75 (d, J = 7.2 Hz, 3 H, major), 2.43 (s, 3 H), 2.67–2.71 (m, 2 H), 3.45 (t, J = 4.8 Hz, 2 H, minor), 3.48 (t, J = 4.8

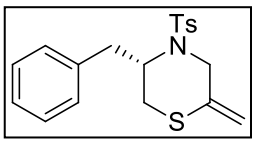
Hz, 2 H, major), 3.77 (s, 2 H, minor), 3.91 (s, 2 H, major), 5.80 (q, *J* = 6.6 Hz, 1 H, minor), 5.84 (q, *J* = 6.6 Hz, 1 H, major), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.65 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) *δ* 14.0, 14.6, 21.7, 27.4, 28.9, 47.3, 47.7, 54.0, 125.0, 127.5, 127.7, 127.8, 128.0, 129.9, 130.0, 134.5, 143.9; **IR** (KBr, neat) 2924, 2852, 1639, 1597, 1450, 1355, 1166, 1092, 1060, 920, 742 cm^{-1}; **HRMS** (ESI) calcd for $C_{13}H_{18}NO_2S_2$ $(M + H)^+$ 284.0773, found 284.0775.



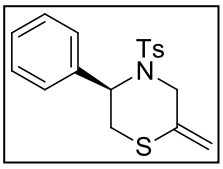
***Data for 2-(Propan-2-ylidene)-4-tosylthiomorpholine* (29c).** Colourless oil; R_f (hexane/EtOAc 9:1) 5.8; yield 232 mg, 78%; **^{1}H NMR** (600 MHz, CDCl3) δ 1.85 (s, 6 H), 2.43 (s, 3 H), 2.68 (t, *J* = 5.4 Hz, 2 H), 3.46 (t, *J* = 5.4 Hz, 2 H), 3.97 (s, 2 H), 7.31 (d, *J* = 7.8 Hz, 2 H), 7.64 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) *δ* 20.6, 21.7, 22.5, 28.4, 47.4, 48.9, 118.4, 127.7, 129.9, 130.0, 134.8, 143.8; **IR** (KBr, neat) 2963, 2925, 1637, 1458, 1422, 1356, 1297, 1164, 1091, 927, 739 cm^{-1}; **HRMS** (ESI) calcd for $C_{14}H_{20}NO_2S_2$ $(M + H)^+$ 298.0930, found 298.0934.



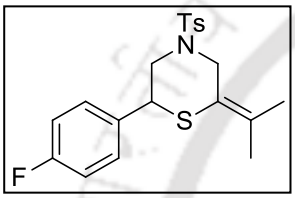
***Data for 5-Methyl-2-methylene-4-tosylthiomorpholine* (29d).** Colourless oil; R_f (hexane/EtOAc 9:1) 5.8; yield 184 mg, 65%; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 1.37 (d, *J* = 6.4 Hz, 3 H), 2.42 (s, 3 H), 2.46 (d, *J* = 6.4 Hz, 1 H), 2.80 (dd, *J* = 13.6 and 4.4 Hz, 1 H), 3.89 (d, *J* = 15.6 Hz, 1 H), 4.18–4.24 (m, 1 H), 4.39 (d, *J* = 15.6 Hz, 1 H), 5.01 (s, 1 H), 5.15 (s, 1 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7.70 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.3, 21.7, 32.6, 46.0, 49.4, 112.5, 127.6, 129.6, 136.7, 137.0, 143.5; **IR** (KBr, neat) 2924, 2848, 1653, 1457, 1351, 1272, 1152, 1089, 860, 669 cm^{-1}; **HRMS** (ESI) calcd for $C_{13}H_{18}NO_2S_2$ $(M + H)^+$ 284.0773, found 284.0775.



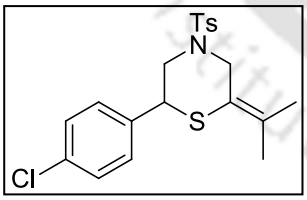
***Data for 5-Benzyl-2-methylene-4-tosylthiomorpholine* (29e).** Colourless oil; R_f (hexane/EtOAc 9:1) 5.8; yield 241 mg, 67%; **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 2.40 (s, 3 H), 2.46 (dd, *J* = 13.8 and 6.6 Hz, 1 H), 2.63 (d, *J* = 13.8 Hz, 1 H), 3.03 (dd, *J* = 13.2 Hz, 1 H), 3.27 (t, *J* = 11.4 Hz, 1 H), 3.85 (d, *J* = 15.6 Hz, 1 H), 4.20–4.25 (m, 1 H), 3.38 (d, *J* = 15.6 Hz, 1 H), 5.01 (s, 1 H), 5.15 (s, 1 H), 7.23–7.31 (m, 7 H) 7.68 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) *δ* 21.7, 31.8, 38.7, 47.0, 55.1, 112.5, 127.0, 127.7, 128.9, 129.6, 129.7, 136.6, 136.8, 137.4, 143.7; **IR** (KBr, neat) 2924, 2856, 1611, 1495, 1345, 1157, 1091, 1032, 750 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{22}NO_2S_2$ $(M + H)^+$ 360.1086, found 360.1184.



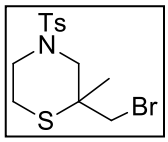
***Data for 2-Methylene-5-phenyl-4-tosylthiomorpholine* (29f).** Colourless oil; R_f (hexane/EtOAc 9:1) 5.8; yield 224 mg, 65%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 2.91 (dd, J = 14.4 and 5.4 Hz, 1 H), 3.00 (dd, J = 14.4 and 8.4 Hz, 1 H), 4.02 (dd, J = 16.2 and 3.0 Hz, 1 H), 4.59 (d, J = 16.2 Hz, 1 H), 4.92 (s, 1 H), 5.11 (s, 1 H), 5.12 (t, J = 6.0 Hz, 1 H), 7.25 (d, J = 8.4 Hz, 2 H), 7.28 (t, J = 7.2 Hz, 1 H), 7.35 (t, J = 7.2 Hz, 2 H), 7.39 (d, J = 7.2 Hz, 2 H), 7.71 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.8, 31.0, 47.5, 58.0, 110.7, 126.5, 127.9, 128.0, 128.9, 129.6, 136.8, 137.5, 140.2, 143.7; **IR** (KBr, neat) 2924, 2853, 1611, 1494, 1345, 1156, 1044, 945, 732 cm^{-1}; **HRMS** (ESI) calcd for $C_{18}H_{20}NO_2S_2$ $(M + H)^+$ 346.0930, found 346.0899.



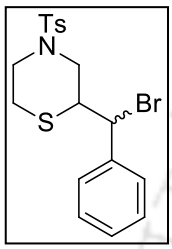
***Data for 2-(4-Fluorophenyl)-6-(propan-2-ylidene)-4-tosylthiomorpholine* (29g).** Colourless oil; R_f (hexane/EtOAc 9:1) 5.8; yield 246 mg, 63%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.89 (s, 3 H), 1.91 (s, 3 H), 2.45 (s, 3 H), 2.93 (dd, J = 19.8 and 16.8 Hz, 1 H), 3.24 (d, J = 19.8 Hz, 1 H), 4.05–4.10 (m, 2 H), 4.83 (d, J = 19.8 Hz, 1 H), 7.00 (t, J = 7.2 Hz, 2 H), 7.27–7.31 (m, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 7.65 (d, J = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.8, 21.7, 22.6, 45.6, 48.5, 53.6, 115.7, 115.8 (d, J = 32.1 Hz), 119.2, 127.6, 129.7, 129.9, 130.0, 144.0, 162.6 (d, J = 245.8 Hz); **IR** (KBr, neat) 2924, 2865, 1599, 1340, 1228, 1161, 1093, 837, 760, 657 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{23}FNO_2S_2$ $(M + H)^+$ 392.1149, found 392.1148.



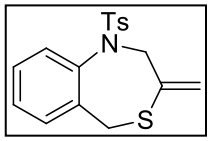
***Data for 2-(4-Chlorophenyl)-6-(propan-2-ylidene)-4-tosylthiomorpholine* (29h).** Colourless oil; R_f (hexane/EtOAc 9:1) 5.8; yield 267 mg, 65%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.88 (s, 3 H), 1.91 (s, 3 H), 2.44 (s, 3 H), 2.94 (dd, J = 12.4 and 11.2 Hz, 1 H), 3.26 (d, J = 12.4 Hz, 1 H), 4.03–4.07 (m, 2 H), 4.80 (d, J = 12.4 Hz, 1 H), 7.24–7.30 (m, 4 H), 7.32 (d, J = 8.0 Hz, 2 H), 7.65 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.8, 21.7, 22.6, 45.6, 48.5, 53.4, 119.0, 127.6, 129.1, 129.3, 130.0, 134.1, 134.6, 135.8, 136.9, 144.0; **IR** (KBr, neat) 2922, 2853, 1597, 1491, 1351, 1163, 1092, 1014, 928, 708 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{23}ClNO_2S_2$ $(M + H)^+$ 408.0853, found 408.0834.



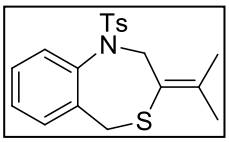
***Data for 2-(Bromomethyl)-2-methyl-4-tosylthiomorpholine* (29i).** Colourless oil; R_f (hexane/EtOAc 9:1) 5.8; yield 280 mg, 77%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.28 (s, 3 H), 2.43 (s, 3 H), 2.49 (d, J = 12.6 Hz, 1 H), 2.51 (d, J = 13.8 Hz, 1 H), 2.64 (t, J = 12.0 Hz, 1 H), 2.99 (dt, J = 13.8 and 2.4 Hz, 1 H), 3.61 (d, J = 10.8 Hz, 1 H), 3.88 (d, J = 12.0 Hz, 1 H), 3.95 (d, J = 12.0 Hz, 1 H), 3.99 (d, J = 11.4 Hz, 1 H), 7.33 (d, J = 7.8 Hz, 2 H), 7.63 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 23.2, 25.4, 42.8, 47.4, 49.5, 54.2, 127.7, 130.1, 133.8, 144.1; **IR** (KBr, neat) 2926, 2851, 1597, 1452, 1339, 1164, 1096, 916, 741 cm^{-1}; **HRMS** (ESI) calcd for $C_{13}H_{19}BrNO_2S_2$ $(M + H)^+$ 364.0035, found 364.0040.



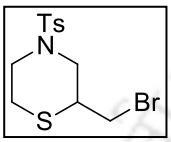
***Data for* 2-(Bromo(phenyl)methyl)-4-tosylthiomorpholine (diastereomeric mixture, 6:1, 29j)**. Colourless oil; R_f (hexane/EtOAc 9:1) 5.8; yield 276 mg, 65%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H, minor), 2.44 (s, 3 H, major), 2.60–2.63 (m, 1 H, major), 2.68–2.71 (m, 1 H, major), 2.80–2.83 (m, 1 H, minor), 3.01 (dt, J = 10.8 and 2.4 Hz, 1 H), 3.10 (t, J = 9.0 Hz, 1 H), 3.25 (t, J = 10.8 Hz, 1 H), 3.48–3.51 (m, 1 H, major), 3.56–3.58 (m, 1 H, minor), 3.81 (d, J = 10.8 Hz, 1 H), 4.16 (brs, 1 H, minor), 4.26 (d, J = 8.4 Hz, 1 H), 7.28 (d, J = 8.4 Hz, 2 H), 7.32–7.37 (m, 5 H), 7.64 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 22.9, 26.6, 28.8, 45.5, 47.3, 47.7, 48.3, 50.1, 127.5, 127.6, 127.7, 127.8, 128.5, 128.8, 128.9, 130.0, 131.8, 134.3, 139.7, 143.8; **IR** (KBr, neat) 2924, 2853, 1597, 1452, 1354, 1164, 1093, 916, 718 cm−1; **Anal. calcd** for $C_{18}H_{20}BrNO_2S_2$: C, 50.70; H, 4.73; N, 3.28. Found: C, 50.66; H, 4.64; N, 3.34.



***Data for 3-Methylene-1-tosyl-1,2,3,5-tetrahydrobenzo[e][1,4]thiazepine* (29k).** Colourless oil; R_f (hexane/EtOAc 9:1) 5.8; yield 258 mg, 78%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.29 (s, 2 H), 4.45 (s, 2 H), 5.43 (s, 1 H), 5.49 (s, 1 H), 7.16 (t, J = 8.4 Hz, 1 H), 7.25–7.28 (m, 4 H), 7.32–7.36 (m, 1 H), 7.58 (d, J = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.8, 34.2, 57.6, 122.2, 127.5 (2C), 128.5, 129.1 (2C), 129.8, 137.7, 138.5, 138.8, 140.3, 143.8; **IR** (KBr, neat) 2923, 2847, 1698, 1489, 1349, 1162, 1091, 814, 735, 659 cm^{-1}; **HRMS** (ESI) calcd for $C_{17}H_{18}NO_2S_2$ $(M + H)^+$ 332.0773, found 332.0774.



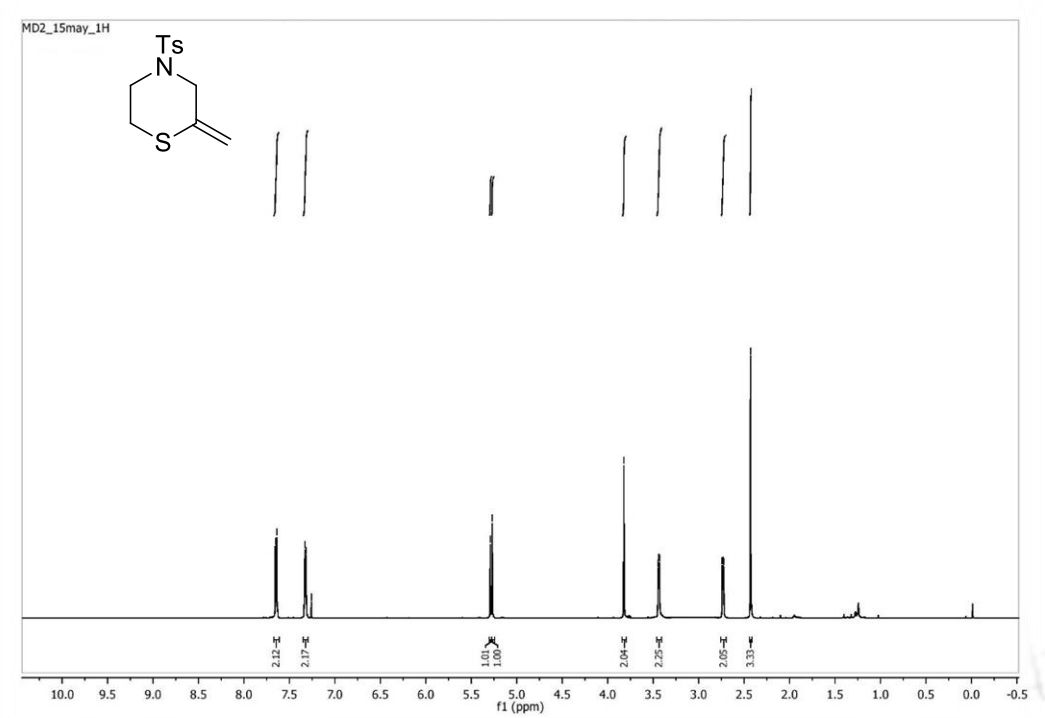
***Data for 3-(Propan-2-ylidene)-1-tosyl-1,2,3,5 tetrahydrobenzo[e][1,4]thiazepine* (29l).** Colourless oil; R_f (hexane/EtOAc 9:1) 5.8; yield 269 mg, 75%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.81 (s, 3 H), 1.95 (s, 3 H), 2.41 (s, 3 H), 3.08 (s, 2 H), 4.54 (s, 2 H), 7.05–7.08 (m, 1 H), 7.21–7.25 (m, 4 H), 7.41–7.44 (m, 1 H), 7.47 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.2, 21.8, 23.2, 34.3, 53.7, 121.2, 127.4, 128.1, 128.7, 128.8, 129.7, 131.1, 137.2, 138.5,139.3, 141.5, 143.7; **IR** (KBr, neat) 2924, 2854, 1598, 1490, 1348, 1163, 1093, 1034, 807, 683 cm^{-1}; **HRMS** (ESI) calcd for $C_{19}H_{22}NO_2S_2$ $(M + H)^+$ 360.1086, found 360.1085.

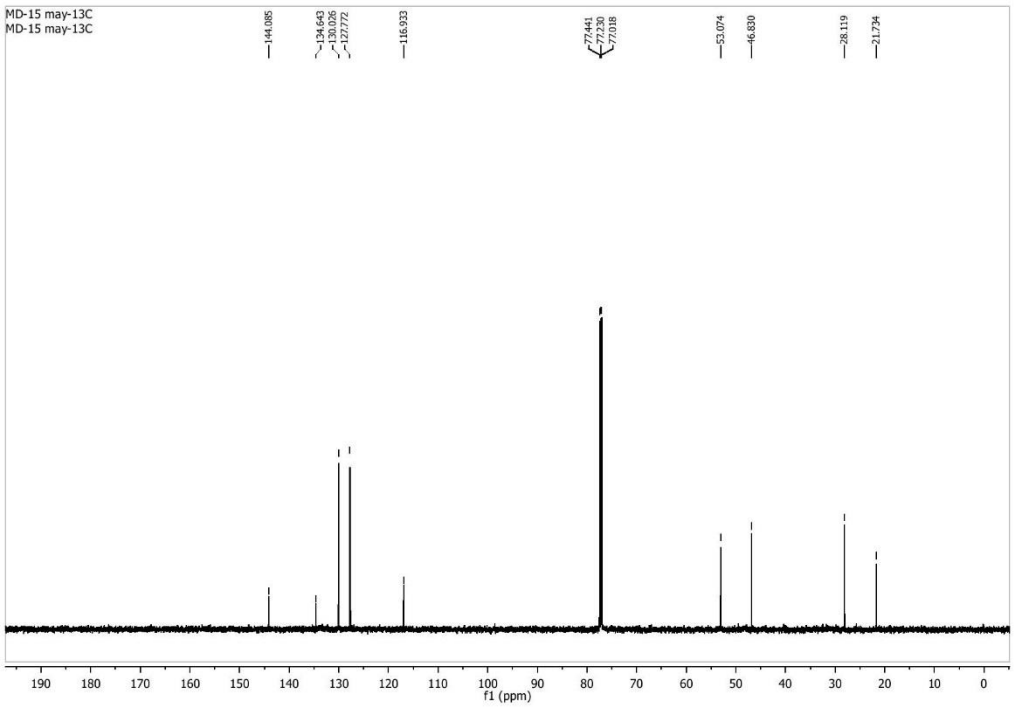


***Data for 2-(Bromomethyl)-4-tosylthiomorpholine* (29m).** Colourless oil; R_f (hexane/EtOAc 9:1) 5.8; yield 280 mg, 85%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.01–2.06 (m, 2 H), 2.43 (s, 3 H), 2.75–2.77 (m, 2 H), 2.84 (t, J = 12.0 Hz, 2 H), 3.46–3.51 (m, 3 H), 7.30 (d, J = 8.4 Hz, 2 H), 7.68 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 31.3, 31.9, 36.2, 49.0, 54.0, 127.0, 130.0, 137.1, 143.5; **IR** (KBr, neat) 2922, 2853, 1598, 1452, 1330, 1157, 1092, 923, 715, 548 cm^{-1}; **Anal. calcd** for $C_{12}H_{16}BrNO_2S_2$: C, 41.14; H, 4.60; N, 4.00. Found: C, 41.20; H, 4.52; N, 4.05.

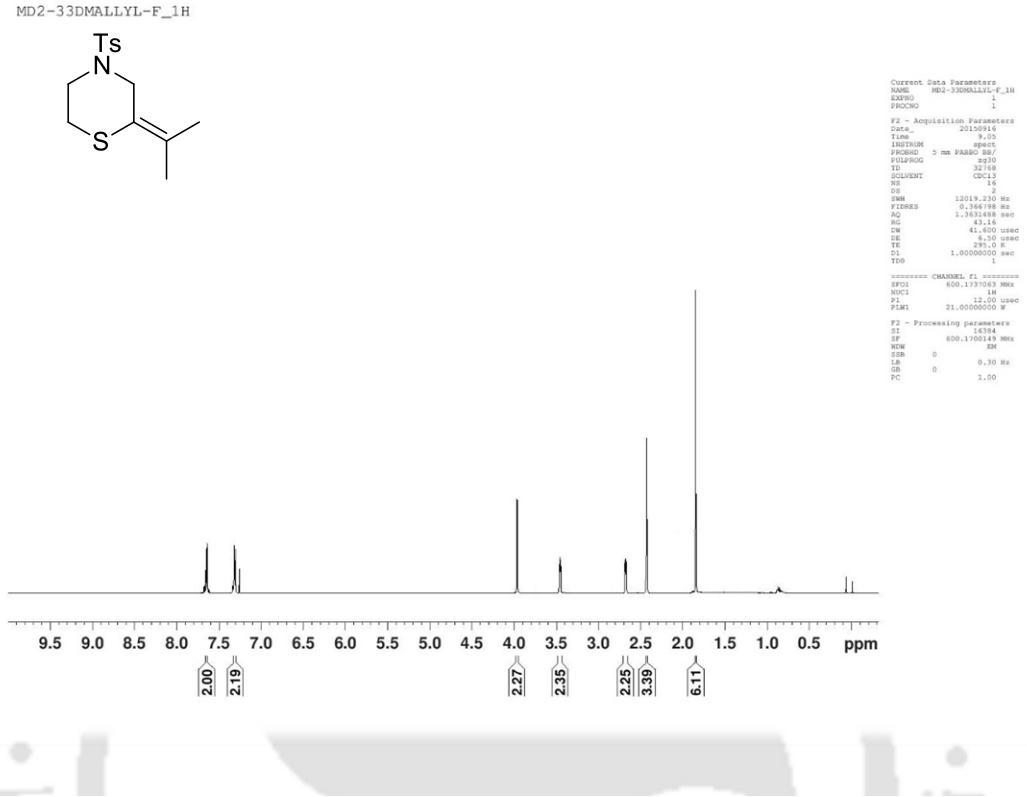
3.8 Selected spectra

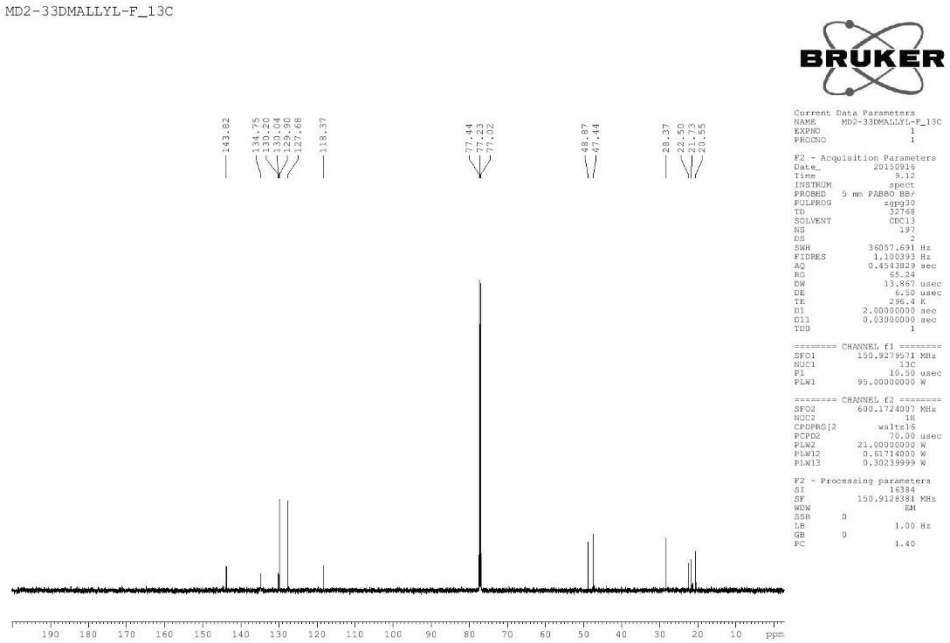
^{1}H and ^{13}C NMR Spectra of compound of ***2-Methylene-4-tosylthiomorpholine (29a)***



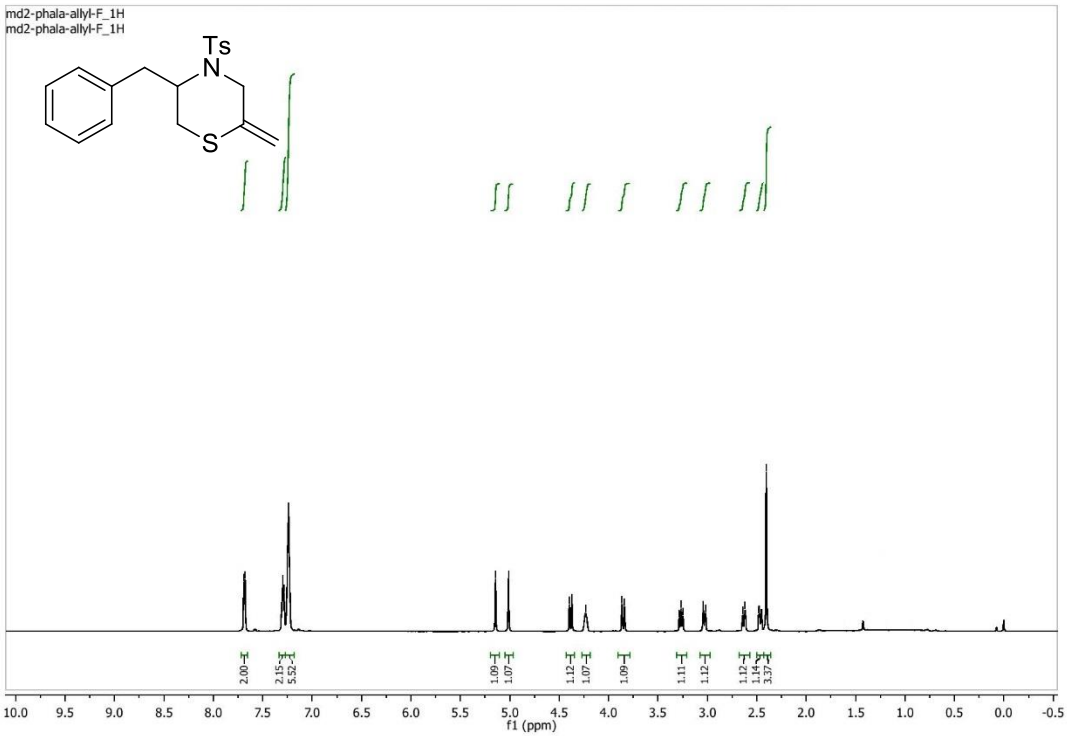


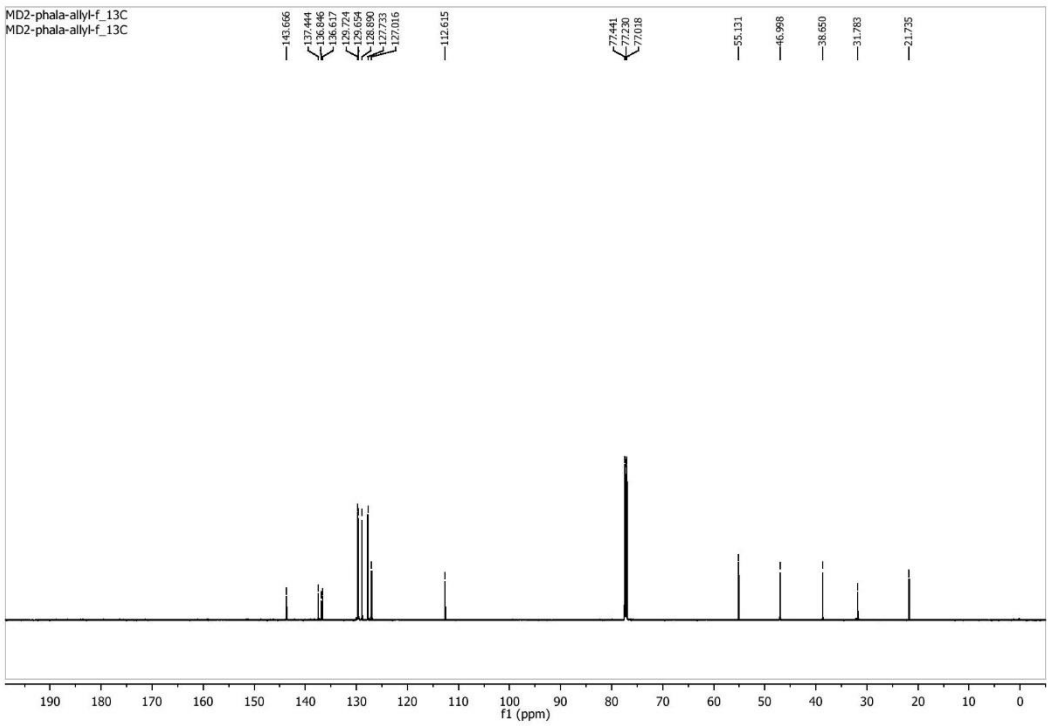
^{1}H and ^{13}C NMR Spectra of ***2-(Propan-2-ylidene)-4-tosylthiomorpholine*** **(29c)**





^{1}H and ^{13}C of Spectra of ***5-Benzyl-2-methylene-4-tosylthiomorpholine (29e)***





CHAPTER 4

Diastereoselective Synthesis of Substituted Tetrahydrothiopyrans

4.1 Importance and Applications

Tetrahydropyrans and its derivatives are important structural moiety of many bioactive naturally occurring molecules.[1] They are found in many petroleum products.[2]. The sulfur analogues of mono- and oligosaccharides **1, 2** are found to be potential glycosidase enzyme inhibitors.[3] The tetrahydrothiopyrans also play a key role in the biological activities of a number of pharmaceutical agents showing antihypersensitive **3**,[4] antidiabetic **4**,[5] antimicrobial[6] **5** and antimitotic **6,**[7] properties (*Figure 4.1.1*). Synthetically the tetrahydrothiopyrans can be transformed into a variety of structures through simple reactions, such as hydrogenolysis, oxidation and olefination.[8]

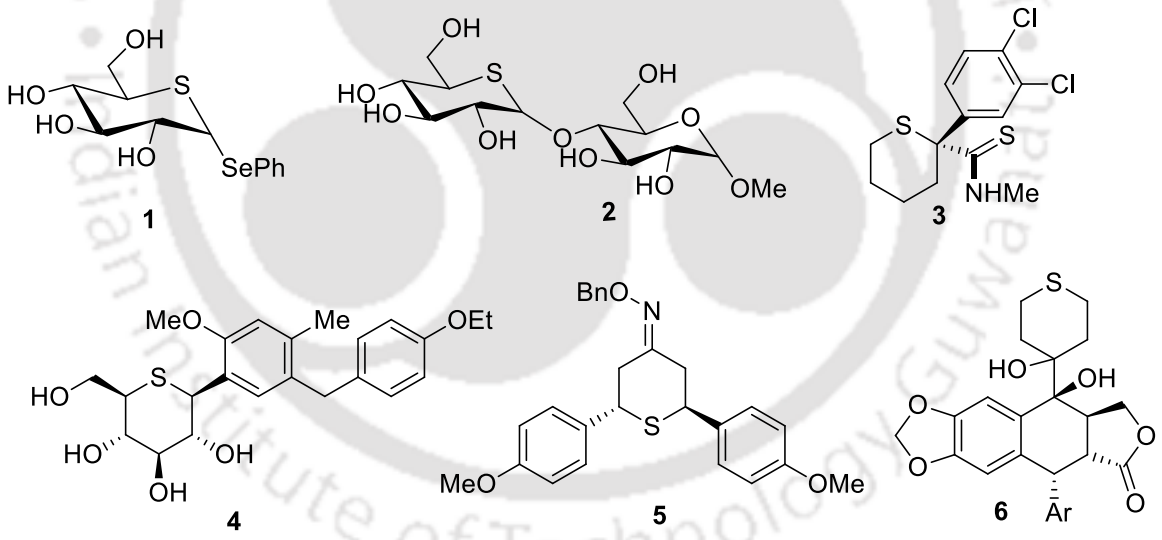


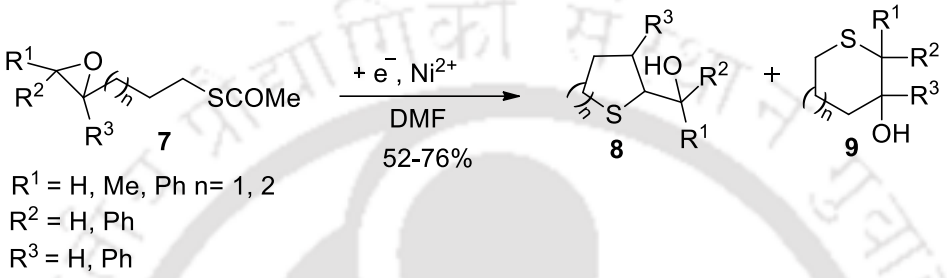
Figure 4.1.1. *Some biologically active molecules containing tetrahydrothiopyran moiety.*

4.2 Literature Methods

The tetrahydrothiopyran moiety is less encountered in nature. A very few methods have been developed for their synthesis such as double-conjugate addition of sulfide to divinyl ketone, hydrothiolation of nonactivated olefins, ring-opening of epoxides by molecular thiolates and thia-Prins cyclization reactions are some of the reported literature methods for

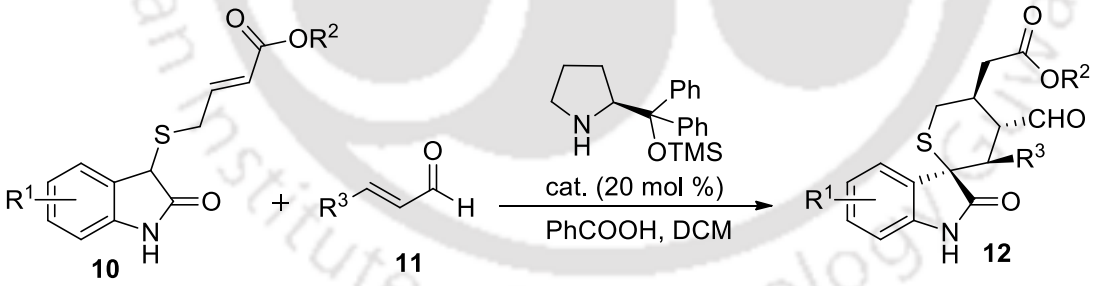
the synthesis of tetrahydrothiopyrans. Amongst these, thia-prins cylisation has received considerable attention and showed significant progress in the synthesis of tetrahydropyrans over the years as discussed already in chapter 1, (*Section 1.3.4*).

Ozaki *et al.* described the regioselective synthesis of the five-, six- and seven membered cyclic sulfides **8**, **9** through an intramolecular ring opening reaction of epoxide **7** by *in situ* generated thiolate ion. The thiolate ion were prepared *via* selective catalytic electroreduction of the thioacetate group by a nickel(II) complex on substrate **7** (*Scheme 4.2.1*).[9]



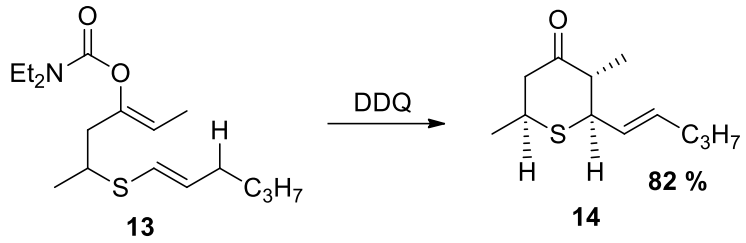
Scheme 4.2.1

Sheng *et al.* described an organocatalytic Michael–aldol cascade reaction for the synthesis of spiro-tetrahydrothiopyran oxindoles. Proline was used as catalyst to derive highly functionalized scaffold in moderate to good yields (51–78%) and excellent diastereoselectivities (>20 : 1 *dr*, *Scheme 4.2.2*).[10]



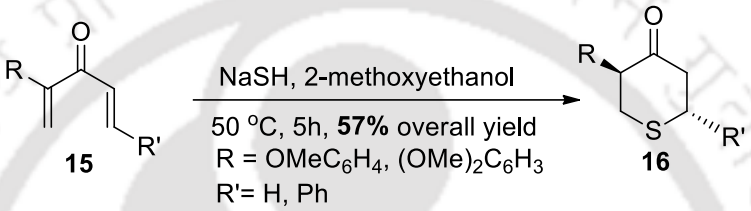
Scheme 4.2.2

Floreancig *et al.* reported a methodology for the synthesis of sulfur-containing heterocycles **14** through carbon-carbon bond formation. Vinyl sulfides **13** react rapidly with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give an α,β-unsaturated thiocarbenium ions through oxidative carbon-hydrogen bond cleavage. The electrophiles generated further couple with appended π-nucleophiles to yield heterocycles. [11] (*Scheme 4.2.3*)



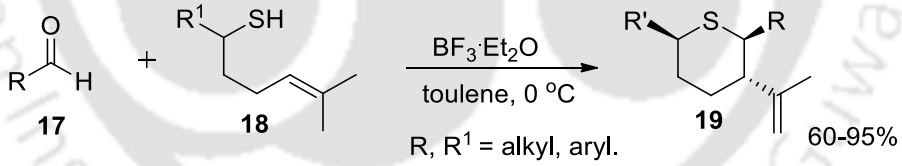
Scheme 4.2.3

Christoffers *et al.* reported the synthesis of tetrahydrothiopyran-4-one derivatives **16** with a 3-aryl substituent by double-conjugate addition of H_2S to divinyl ketones **15**. The methodology is highly diastereoselective with *trans* isomer as the major product.[12] (scheme 4.2.4)



Scheme 4.2.4

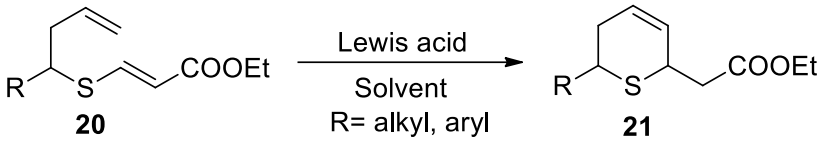
Saikia *et al.* have efficiently synthesized tetrahydrothiopyrans **19** in good yields with excellent diastereoselectivity from aldehydes **17** and substituted 5-methylhex-4-ene-1-thiol **18** *via* (3,5)-thionium–ene cyclization reaction mediated by boron trifluoride etherate.[13] (*Scheme 4.2.5*)



Scheme 4.2.5

4.3 Present Work

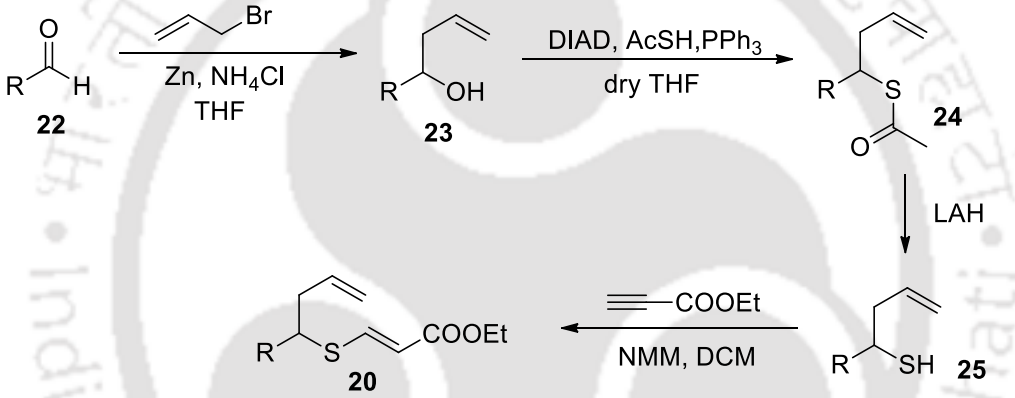
Prins cyclization as already been described in Chapter 1, (Section *1.3.2.*) has been an important methodology for the organic chemist for the synthesis of cyclic five[14] and six[15] membered oxygen heterocycles. Recently, Saikia and co-workers have developed a methodology for the synthesis of dihydrothiopyran derivatives by employing intramolecular Prins cyclization of enol ethers, in which alkene acts as a nucleophile.[14d] In continuation of the work done previously on the synthesis of dihydropyrans *via* Prins cyclization,[16] it was visualised to develop a methodology for the synthesis of dihydrothiopyran moiety from thioenol ethers. (*Scheme 4.3.1*).



Scheme 4.3.1

4.3.1 Results and Discussion

The thioenol ethers **20** were synthesized from thiols **25** and ethyl propiolate *via* Michael reaction in presence of *N*-methyl morpholine (NMM) in dichloromethane. The yields were up to 95%. The thiols **25** were synthesized from alcohols **23** *via* Mitsunobu reaction with thioacetic acid in presence of triphenyl phosphine and diisopropyl azodicarboxylate (DIAD), followed by reduction of resulted thioester **24** with lithium aluminium hydride. The alcohols **23** were prepared from commercially available aldehydes **22** and allylbromide under Barbier reaction condition. (*Scheme 4.3.1.1*).

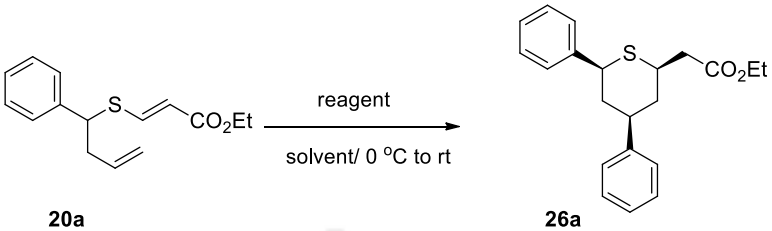


Scheme 4.3.1.1. *Synthesis of thioenol ether.*

In an initial experiment, the thioenol-ether **20a** was treated with TMSOTf in dry dichloromethane at 0 ^{o}C for 2 hours. The reaction gave the desired 5,6-dihydrothiopyran product in 20% yield, however the product was found to be unstable undergoing disintegration with time. In a similar manner, treatment of **20a** with $BF_3.OEt_2$ also produced decomposed product. Further, the reaction was performed with TMSOTf in Benzene/CH_2Cl_2 (1:1) solvent system in order to trap the carbocation **B** (*Scheme 4.3.2.1*) with an external aryl nucleophile. The reaction produced 2,4,6-trisubstituted tetrahydrothiopyran **26a** in 75% yield in *dr* 88:12. The structure of the compound was confirmed by ^{1}H, ^{13}C NMR, IR and mass spectrometry. The diastereomeric ratio was determined from the ^{1}H NMR of crude reaction mixture. The reaction was also screened with various Lewis and Brϕnsted acids such as $BF_3{\cdot}OEt_2$, $In(OTf)_3$, $Zn(OTf)_2$, $Sc(OTf)_3$,$FeCl_3$ and Triflic acid as shown in *Table 4.3.1.1*. It was observed that reaction

with 1 equivalent of TMSOTf in DCM/Benzene (1:1) solvent was found to be the optimum condition for the desired transformation.

Table 4.3.1.1 Optimization of the reaction



20a **26a**

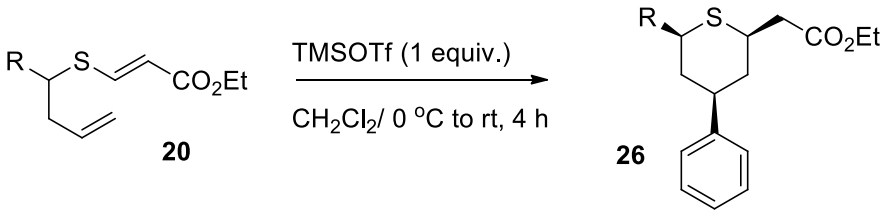
Entry	Lewis acid (Equiv.)	Solvent/Nucleophile, Time	dr ratio[a]	% yield[b]
1	TMSOTf (1 equiv.)	CH_2Cl_2, 2 h	--	d
2	$BF_3 \cdot Et_2O$ (1 equiv.)	CH_2Cl_2, 2 h	--	d
3	TMSOTf (1 equiv.)	CH_2Cl_2/Benzene (1:1), 4 h	88:12	75
4	$Sc(OTf)_3$ (1 equiv.)	CH_2Cl_2/Benzene (1:1), 12 h	86:14	15
5	$FeCl_3$ (1 equiv.)	CH_2Cl_2/Benzene (1:1), 12 h	80:20	52
6	$BF_3 \cdot Et_2O$ (1 equiv.)	CH_2Cl_2/Benzene (1:1), 12 h	75:25	58
7	$In(OTf)_3$ (1 equiv.)	CH_2Cl_2/Benzene (1:1), 24 h	--	trace
8	$Zn(OTf)_2$ (1 equiv.)	CH_2Cl_2/Benzene (1:1), 24 h	--	trace
9	Triflic acid (1 equiv.)	CH_2Cl_2/Benzene (1:1), 12 h	82:18	30

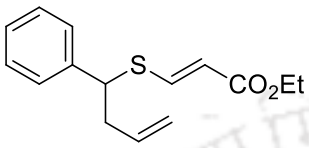
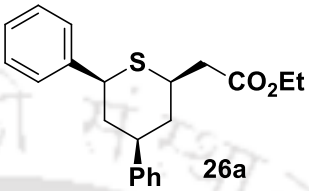
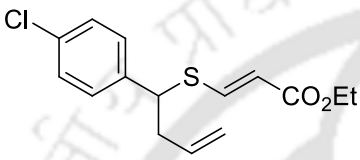
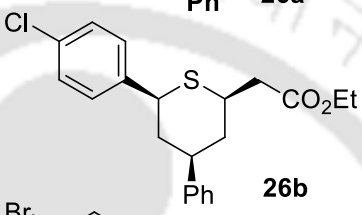
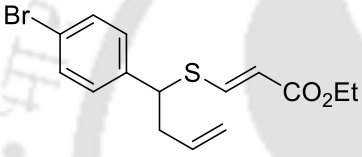
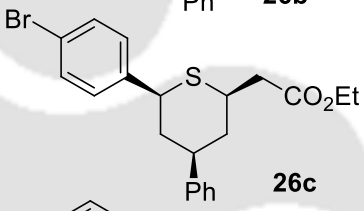
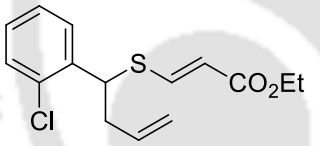
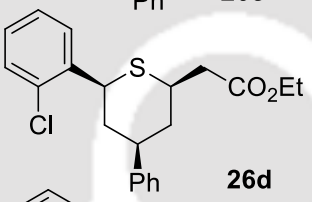
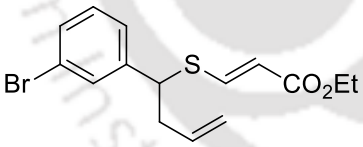
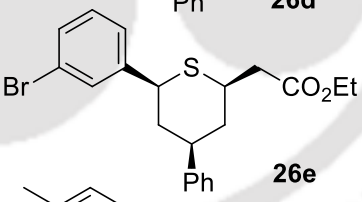
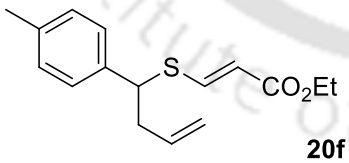
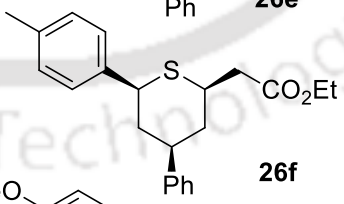
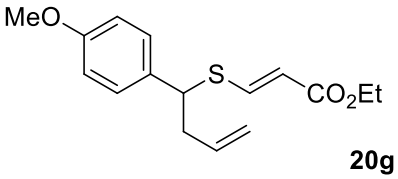
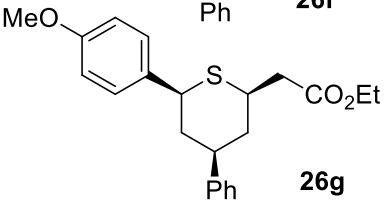
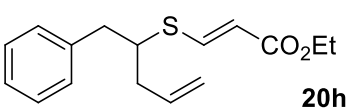
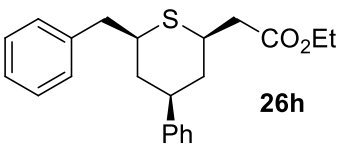
[a]the ratio was determined by the ^1H NMR of crude reaction mixture. [b]refers to isolated yields. d = decomposed

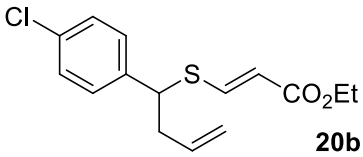
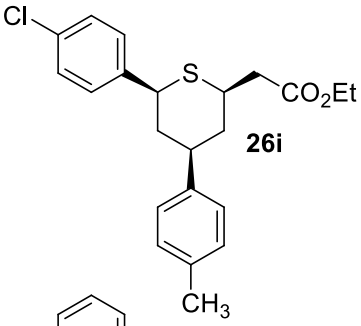
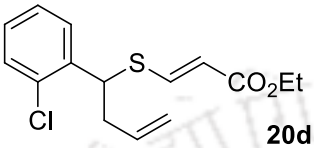
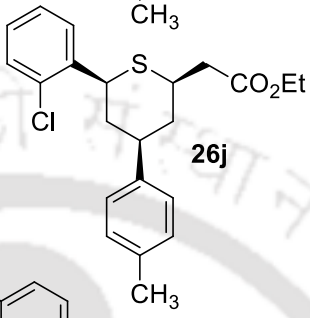
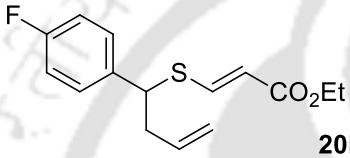
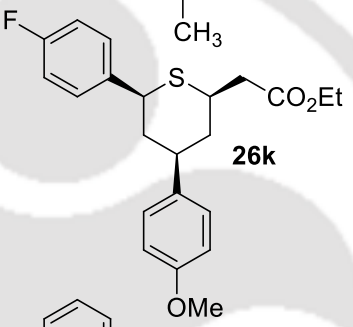
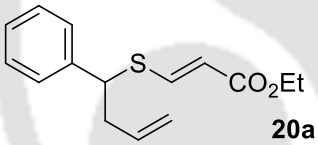
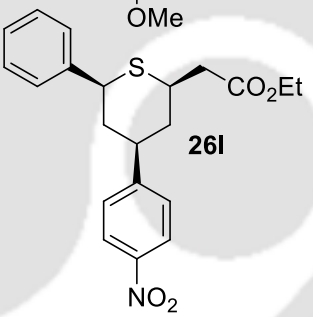
After optimizing the reaction conditions the scope of the reaction was explored with various substrates and different aryl nucleophiles (*Table 4.3.1.2*). It was observed that the reaction was compatible with various substituents on the aromatic ring such as fluoro, chloro, bromo and alkyl group. The thioenol ether with *α*-alkyl substituent also produced the desired product in good yields (*Table 4.3.1.2, entry 8*). On the contrary, presence of a strong electron donating group (-OMe) on the aromatic ring decomposed under the optimized reaction condition. (*entry 7*).

Further the scope of the reaction was explored with different external aryl nucleophiles such as toluene, anisole, nitrobenzene etc. The reaction with toluene and anisole gave the product in good yield (*entries 9-12*). Whereas with nitrobenzene the reaction failed to produce any product (*entry 12*).

Table 4.3.1.2 Synthesis of tetrahydrothiopyrans

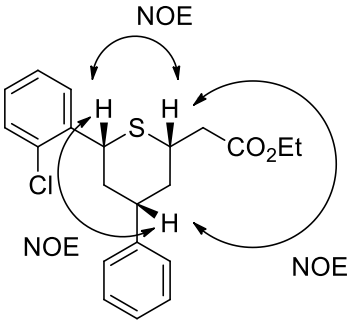


entry	substrate	product	*dr* ratio[a]	yield(%)[b]
1	 **20a**	 **26a**	88:12	75
2	 **20b**	 **26b**	80:20	71
3	 **20c**	 **26c**	77:23	74
4	 **20d**	 **26d**	93:7	67
5	 **20e**	 **26e**	93:7	69
6	 **20f**	 **26f**	90:10	74
7	 **20g**	 **26g**	--	d
8	 **20h**	 **26h**	89:11	69

entry	substrate	product	dr ratio[a]	yield (%)[b]
9	 **20b**	 **26i**	82:18	77
10	 **20d**	 **26j**	88:12	62
11	 **20i**	 **26k**	90:10	56
12	 **20a**	 **26l**	---	d

[a]The ratio was determined by ^{1}H NMR spectroscopy of products. [b]Yield refers to isolated yield. d = Decomposed

The reaction was highly diastereoselective with all the substituents at 2,4,6 positions being *cis* to each other. The diastereoselectivity was confirmed by the NOESY analysis of **26d,** which clearly indicates that substituents at 2,4,6 positions are *cis* to each other (*Scheme 4.3.1.2*).

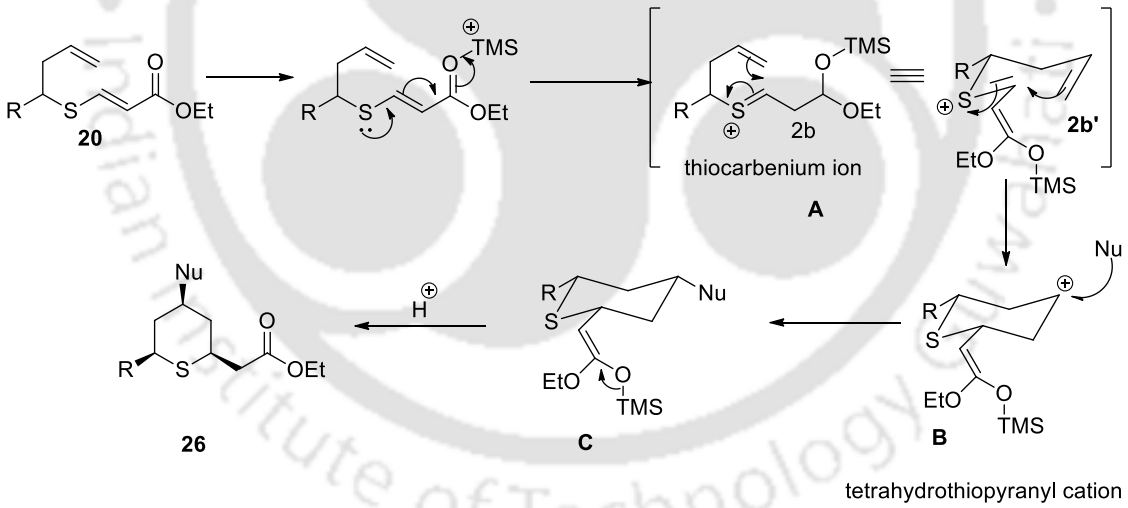


26d

Scheme 4.3.1.2

4.3.2 Plausible Mechanism

The mechanism of the reaction can be explained as follows (*Scheme 4.3.2.1*). The ester group of thioenol ether **20** is activated by TMSOTf to form thiocarbenium ion **A**, which is then attacked by the alkene *via* 6-endo-trig cyclization to give the tetrahydrothiopyranyl cation **B**. The six-membered thiopyranyl cation **B** is then trapped by external aryl nucleophile to give intermediate **C**, which after aqueous workup produced the tetrahydrothiopyran derivatives **26**.



Scheme 4.3.2.1

4.4 Conclusion

In conclusion, a methodology for the synthesis of 2,4,6-trisubstituted tetrahydrothiopyran derivatives *via* TMSOTf mediated thia-Prins cyclization of thioenol ethers has been developed. The reaction is highly diastereoselective with *dr* upto 93:7.

4.5 Experimental section

4.5.1 Instrumentation and Characterization

As described in chapter 2 *section* ***2.5.1.***

4.5.2 General procedure for preparation of thioacrylates (20a-20i):

To a solution of thiol **25** (1 mmol) in dichloromethane (5 mL), *N*-methyl morpholine (1 mmol) and ethyl propiolate (1.1 mmol) were added. The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed on a rotary evaporator and extracted with ethyl acetate (3 × 20 mL), washed with brine (10 mL), and the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was concentrated in a rotary evaporator, and the crude product was purified on silica gel column chromatography using ethyl acetate and hexane as eluents.

4.5.3 Synthesis of (*E*)-ethyl 3-((1-phenylbut-3-en-1-yl)thio)acrylate (20a):

To a solution of 1-phenylbut-3-ene-1-thiol (0.164 mg, 1.0 mmol) in dichloromethane (5 mL), *N*-methyl morpholine (0.11 mL, 1 mmol) and ethyl propiolate (0.11 mL, 1.1 mmol) were added. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed on a rotary evaporator and diluted with water (5 mL). The product was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were washed with brine (10 mL) and finally dried over anhydrous Na_2SO_4. The solvent was concentrated in a rotary evaporator and the crude product was purified on silica gel column chromatography using hexane and ethyl acetate (hexane:EtOAc, 95:5) as eluents to give **25a** (236 mg, 90%) as a colourless oil.

4.5.4 General procedure for the synthesis of substituted tetrahydrothiopyrans (26a-26k):

To a solution of thioenol ether **20** (0.5 mmol) in a mixture of dry dichloromethane (2 mL) and dry benzene (2 mL) at 0 °C was added trimethylsilyl trifluoromethanesulphonate (TMSOTf) (0.5 mmol) dropwise under a nitrogen atmosphere. The reaction mixture was brought to room temperature, and the reaction was stirred for 4 h. 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 × 10 mL), and the combined organic layer was washed with brine. The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated in a 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 title compounds.

4.5.5 Synthesis of ethyl 2-(4,6-diphenyltetrahydro-2*H*-thiopyran-2-yl)acetate (26a):

To a solution of (*E*)-ethyl 3-((1-phenylbut-3-en-1-yl)thio)acrylate **20a** (131 mg, 0.5 mmol) in a mixture of dry dichloromethane (2 mL) and dry benzene (2 mL) at 0 °C was added trimethylsilyl trifluoromethanesulphonate (TMSOTf) (0.09 mL, 0.5 mmol) dropwise under a nitrogen atmosphere. The reaction mixture was brought to room temperature, and the reaction was stirred for 4 h. After completion of reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (5 mL). The product was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layer was washed with brine. The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using a rotary evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography over silica gel using hexane and ethyl acetate (hexane:EtOAc, 95:5) as eluents to give **26a** (128 mg, 75%) as a colourless oil.

4.6 References

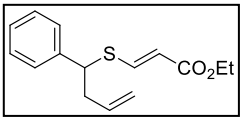
1. (a) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbruggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852. (b) Ohuchida, S.; Hamanaka, N.; Hayashi, M. *Tetrahedron* **1983**, *39*, 4273.
2. (a) Galpern, G. D. *Int. J. Sulfur Chem. B.* **1971**, *6*, 115. (b) Payzant, J. D.; Cyr, T. D.; Montgomery, D. S.; Strausz, O. P. *Tetrahedron Lett*. **1985**, *26*, 4175. (c) Mehta, S.; Andrews, J. S.; Johnston, B. D.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 9783.
3. (a) Block, E. Reactions of organosulfur Compounds; Academic Press: New York, **1978**. (b) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Wartd, D. E.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981,** *103***,** 3210.
4. Cook, D. C.; Hart, T. W.; Mclay, I. M.; Palfreyman, M. N.; Walsh, R. J. A.; Aloup, J. C. EP 0326297, **1989**.
5. Kakinuma, H.; Oi, T.; Hashimoto-Tsuchiya, Y.; Arai, M.; Kawakita, Y.; Fukasawa, Y.; Iida, I.; Hagima, N.; Takeuchi, H.; Chino, Y.; Asami, J.; Okumura-Kitajima, L.; Io, F.; Yamamoto, D.; Miyata, N.; Takahashi, T.; Uchida, S.; Yamamoto, K. *J. Med. Chem*. **2010**, *53*, 3247.
6. Parthiban, P.; Aridoss, G.; Rathika, P.; Ramkumar, V.; Kabilan, S. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 2981.
7. Abad, A.; López-Pérez, J. L.; del Olmo, E.; García-Fernández, L. F.; Francesch, A.; Trigili, C.; Barasoain, I.; Andreu, J. M.; Díaz, J. F.; San Feliciano, A. *J. Med. Chem.* **2012**, *55*, 6724.
8. Boullasa, S.; Gandara, Z.; Perez, M.; Gomez, G.; Fall, Y. *Tetrahedron Lett*. **2008**, *49*, 4040.
9. Ozaki, S.; Matsui, E.; Yoshinaga, H.; Kitagawa, S. *Tetrahedron Lett*. **2000**, *41*, 2621.
10. Wang, S.; Chen, S.; Guo, Z.; He, S.; Zhang, F.; Liu, X.; Chen, W.; Zhanga, S.; Sheng, C. *Org. Biomol. Chem.* **2018**, *16*, 625.
11. Yubo Cui, Y.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 1721.
12. Rosiak, A.; Frey, W.; Christoffers, J. *Eur. J. Org. Chem.* **2006**, 4044.
13. Bondalapati, S.; Gogoi, P.; Indukuri, K.; Saikia, A. K. *J. Org. Chem*. **2012**, *77*, 2508.

14. (a) Arundale, E.; Mikeska, L. A. *Chem. Rev*. **1952**, *51*, 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 . (d) Gogoi, P.; Das, V. K.; Saikia, A. K. *J. Org. Chem.* **2014**, *79*, 8592.

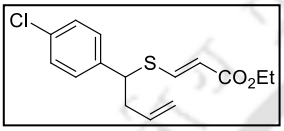
15. (a) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413. (b) Overman, L. E.; Pennington, L. D. *J. Org. Chem*. **2003**, *68*, 7143. (c) Yadav, V. K.; Kumar, N. V. *J. Am. Chem. Soc*. **2004**, *126*, 8652. (d) Yadav, J. S.; Thrimurtulu, N.; Lakshmi, K. A.; Prasad, A. R.; Reddy, B. V. S. *Tetrahedron Lett.* **2010**, *51*, 661.

16. Sultana, S.; Indukuri, K.; **Deka, M. J.**; Saikia, A. K. *J. Org. Chem.* **2013**, *78*, 12182.

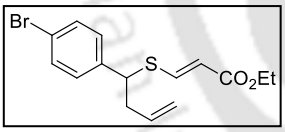
4.7 Spectral Data



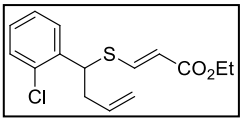
***Data for (E)-ethyl 3-((1-phenylbut-3-en-1-yl)thio)acrylate* (20a).** Colourless oil; R_f (hexane/EtOAc 95:5) 0.55; yield 236 mg, 90%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3 H), 2.57-2.64 (m, 2 H), 4.04-4.09 (m, 3 H), 4.99-5.04 (m, 2 H), 5.56-5.63 (m, 1 H), 5.68 (d, J = 15.6 Hz, 1 H), 7.12-7.20 (m, 3 H), 7.33-7.39 (m, 2 H), 7.44 (d, J = 15.2 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.4, 40.9, 50.5, 60.5, 115.8, 118.8, 130.5, 130.8, 131.2, 133.7, 142.9, 144.9, 165.3; **IR** (KBr, neat) : 2981, 2922, 1712, 1635, 1482, 1367, 1135, 1040, 831, 744 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{19}O_2S$ $(M + H)^+$ 263.1100, found 263.1100.



***Data for (E)-ethyl 3-((1-(4-chlorophenyl)but-3-en-1-yl)thio)acrylate* (20b).** Colourless oil; R_f (hexane/EtOAc 95: 5) 0.55; yield 281 mg, 95%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 2.62-2.73 (m, 2 H), 4.10-4.19 (m, 3 H), 5.61-5.68 (m, 2 H), 5.62-5.69 (m, 1 H), 5.75 (d, J = 15.6 Hz, 1 H), 7.27 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 15.6 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.4, 40.8, 50.2, 60.4, 115.6, 118.6, 129.13, 129.19, 133.6, 133.7, 138.9, 145.0, 165.3; **IR** (KBr, neat) : 2982, 2927, 1705, 1584, 1484, 1254, 1164, 1039, 828, 702 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{18}ClO_2S$ $(M + H)^+$ 297.0711, found 296.0717.

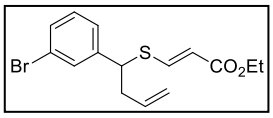


***Data for (E)-ethyl 3-((1-(4-bromophenyl)but-3-en-1-yl)thio)acrylate* (20c).** Colourless oil; R_f (hexane/EtOAc 95: 5) 0.55; yield 306 mg, 90%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 2.60-2.73 (m, 2 H), 4.01-4.20 (m, 3 H), 5.03-5.10 (m, 2 H), 5.60-5.69 (m, 1 H), 5.75 (d, J = 15.2 Hz, 1 H), 7.21 (d, J = 8.4 Hz, 2 H), 7.47 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 15.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.5, 40.8, 50.4, 60.5, 115.8, 118.7, 121.8, 129.6, 132.2, 133.8, 139.6, 145.0, 165.3; **IR** (KBr, neat) : 2981, 2925, 1706, 1579, 1485, 1249, 1149, 1031, 827, 703 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{18}BrO_2S$ $(M + H)^+$ 341.0205, found 341.0214.

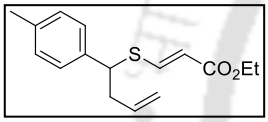


***Data for (E)-ethyl 3-((1-(2-chlorophenyl)but-3-en-1-yl)thio)acrylate* (20d).** Colourless oil; R_f (hexane/EtOAc 95:5) 0.55; yield 263 mg, 89%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3 H), 2.63 (t, J = 6.8 Hz, 2 H), 4.63 (q, J = 6.8 Hz, 2 H), 4.74 (t, J = 7.2 Hz, 1 H), 4.99-5.04 (m, 2 H), 5.60-5.71 (m, 2 H), 7.15 (t, J = 7.6 Hz, 1 H), 7.21 (d, J = 7.2 Hz, 1 H), 7.32 (d, J = 8.0 Hz,

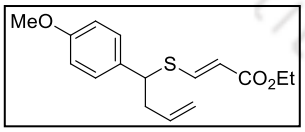
1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.51 (d, *J* = 15.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.4, 40.9, 50.6, 60.7, 115.2, 118.3, 126.8, 127.8, 127.9, 128.6, 129.2, 134.1, 140.3, 145.5, 165.4; **IR** (KBr, neat) : 2983, 2924, 1708, 1576, 1479, 1250, 1144, 1033, 831, 701 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{18}ClO_2S$ $(M + H)^+$ 297.0711, found 297.0711.



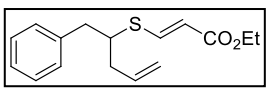
***Data for (E)-ethyl 3-((1-(3-bromophenyl)but-3-en-1-yl)thio)acrylate* (20e).** Colourless oil; R_f (hexane/EtOAc 95:5) 0.55; yield 309 mg, 91%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 6.6 Hz, 3 H), 2.69-2.71 (m, 2 H), 4.12 (dq, *J* = 7.2 and 2.4 Hz, 2 H), 4.18 (q, *J* = 7.2 Hz, 1 H), 5.04-5.09 (m, 2 H), 5.64-5.75 (m, 1 H), 5.77 (d, *J* = 15.6 Hz, 1 H), 7.26-7.28 (m, 1 H), 7.32-7.37 (m, 3 H), 7.56 (d, *J* = 15.6 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.4, 40.9, 51.0, 60.4, 115.2, 118.3, 126.0, 127.8, 128.0, 128.5, 129.0, 134.2, 140.4, 145.7, 165.4; **IR** (KBr, neat) : 2983, 2924, 1708, 1576, 1479, 1250, 1144, 1033, 831, 701 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{18}BrO_2S$ $(M + H)^+$ 341.0205, found 341.0218.



***Data for (E)-ethyl 3-((1-(p-tolyl)but-3-en-1-yl)thio)acrylate* (20f).** Colourless oil; R_f (hexane/EtOAc 95:5) 0.55; yield 243 mg, 88%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3 H), 2.33 (s, 3 H), 2.67-2.71 (m, 2 H), 4.09-4.19 (m, 3 H), 5.03-5.10 (m, 2 H), 5.63-5.73 (m, 1 H), 5.73 (d, *J* = 15.2 Hz, 1 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 7.56 (d, *J* = 15.6 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.5, 21.3, 40.9, 50.8, 60.4, 115.2, 118.2, 127.8, 129.7, 134.4, 137.3, 137.7, 145.9, 165.5; **IR** (KBr, neat) : 2983, 2924, 1708, 1576, 1479, 1250, 1144, 1033, 831, 701 cm^{-1}; **HRMS** (ESI) calcd. for $C_{16}H_{21}O_2S$ $(M + H)^+$ 277.1257, found 277.1257.

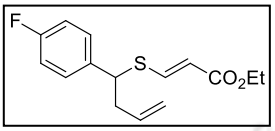


***Data for (E)-ethyl 3-((1-(4-methoxyphenyl)but-3-en-1-yl)thio)acrylate* (20g).** Colourless oil; R_f (hexane/EtOAc 9: 1) 0.55; yield 257 mg, 88%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.2 Hz, 3 H), 2.66-2.70 (m, 2 H), 3.78 (s, 3 H), 4.09-4.18 (m, 3 H), 5.01-5.08 (m, 2 H), 5.63-5.74 (m, 1 H), 5.78 (d, *J* = 15.0 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.56 (d, *J* = 15.0 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.3, 40.9, 50.3, 55.2, 60.8, 114.1, 115.0, 118.0, 128.8, 132.1, 134.2, 145.7, 159.0, 165.3; **IR** (KBr, neat) : 2985, 2926, 1708, 1576, 1481, 1250, 1147, 1033, 831, 701 cm^{-1}; **HRMS** (ESI) calcd. for $C_{16}H_{21}O_3S$ $(M + H)^+$ 293.1206, found 293.1206.

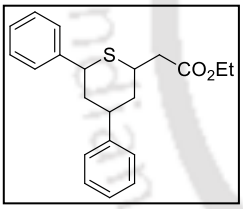


***Data for (E)-ethyl 3-((1-phenylpent-4-en-2-yl)thio)acrylate* (20h).** Colourless oil; R_f (hexane/EtOAc 95:5) 0.55; yield 254 mg, 92%;

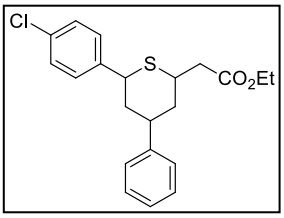
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3 H), 2.31-2.50 (m, 2 H), 2.94 (q, J = 14 Hz and 2.4 Hz, 2 H), 3.32 (p, J = 7.2 Hz, 1 H), 4.16 (q, J = 7.2 Hz, 2 H), 5.10-5.16 (m, 2 H), 5.73-5.89 (m, 2 H), 7.18-7.25 (m, 3 H), 7.30 (t, J = 7.2 Hz, 2 H), 7.60 (d, J = 15.2 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.5, 38.3, 40.7, 48.5, 60.4, 114.9, 118.6, 127.0, 128.7, 129.5, 134.3, 138.3, 146.1, 165.5; **IR** (KBr, neat) : 2982, 2921, 1709, 1577, 1480, 1252, 1143, 1030, 837, 706 cm^{-1}; **HRMS** (ESI) calcd. for $C_{16}H_{21}O_2S$ $(M + H)^+$ 277.1257, found 277.1262.



***Data for (E)-ethyl 3-((1-(4-fluorophenyl)but-3-en-1-yl)thio)acrylate* (20i).** Colourless oil; R_f (hexane/EtOAc 95:5) 0.55; yield 238 mg, 85%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 2.61-2.74 (m, 2 H), 4.10-4.20 (m, 3 H), 5.04-5.10 (m, 2 H), 5.61-5.70 (m, 1 H), 5.75 (d, J = 16.0 Hz, 1 H), 7.01-7.06 (m, 2 H), 7.29-7.32 (m, 2 H), 7.52 (d, J = 16.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.5, 41.1, 50.3, 60.5, 115.6, 115.9 (d, J = 22.5 Hz), 118.5, 121.8, 129.6, 134.0, 136.2 (d, J = 3.3 Hz), 145.2, 162.3 (d, J = 245.3 Hz), 165.4; **IR** (KBr, neat) : 2981, 2925, 1706, 1579, 1485, 1249, 1149, 1031, 827, 703 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{18}FO_2S$ $(M + H)^+$ 281.1006, found 281.0998.

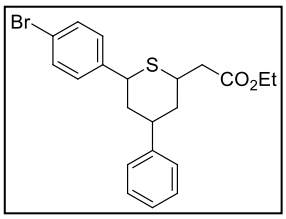


***Data for ethyl 2-(4,6-diphenyltetrahydro-2H-thiopyran-2-yl)acetate* (26a).** Pale yellow liquid; R_f (hexane/EtOAc 95: 5) 0.6; yield 128 mg, 75%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 1.61-1.71 (m, 1 H), 1.95-2.05 (m, 1 H), 2.26-2.30 (m, 2 H), 2.51-2.53 (m, 2 H), 2.73-2.79 (m, 1 H), 3.50-3.57 (m, 1 H), 4.06-4.17 (m, 3 H), 7.13-7.23 (m, 5 H), 7.28-7.38 (m, 4 H), 7.51-7.53 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.4, 40.5, 40.8, 41.0, 42.1, 45.0, 47.8, 61.0, 122.7, 127.0, 128.8, 130.3, 130.7, 130.8, 144.0, 145.7, 171.1; **IR** (KBr, neat) : 2983, 2919, 1715, 1639, 1477, 1370, 1140, 1041, 832, 743 cm^{-1}; **HRMS** (ESI) calcd. for $C_{21}H_{25}O_2S$ $(M + H)^+$ 341.1570, found 341.1570.

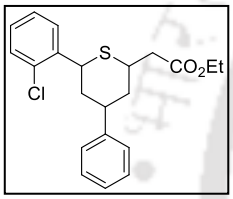


***Data for ethyl 2-(6-(4-chlorophenyl)-4-phenyltetrahydro-2H-thiopyran-2-yl)acetate* (26b).** Pale yellow liquid; R_f (hexane/EtOAc 95:1) 0.6; yield 133 mg, 71%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3 H), 1.58 (q, J = 12.6 Hz, 1 H), 1.93 (q, J = 12.6 Hz, 1 H), 2.20 (dd, J = 13.2 and 2.4 Hz, 2 H), 2.45 (dd, J = 7.2 and 1.8 Hz, 2 H), 2.67-2.72 (m, 1 H), 3.44-3.49 (m, 1 H), 4.10-4.12 (m, 3 H), 7.15 (d, J = 7.2 Hz, 2 H), 7.19-7.25 (m, 7 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.4, 40.5, 40.8, 41.1, 42.2, 45.1, 47.7, 61.0, 126.8, 127.0, 128.9, 129.0, 129.1, 133.4, 140.2, 145.8, 171.2; **IR** (KBr, neat) : 2981,

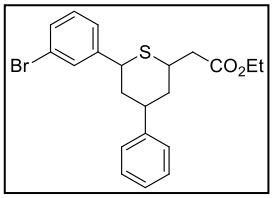
2923, 1714, 1630, 1480, 1364, 1133, 1041, 833, 744 cm^{-1}; **HRMS** (ESI) calcd. for $C_{21}H_{24}ClO_2S$ $(M + H)^+$ 375.1180, found 375.1179.



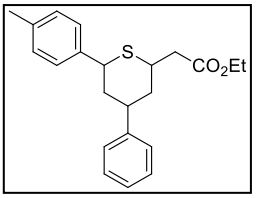
***Data for ethyl 2-(6-(4-bromophenyl)-4-phenyltetrahydro-2H-thiopyran-2-yl)acetate* (26c).** Pale yellow liquid; R_f (hexane/EtOAc 95:5) 0.6; yield 155 mg, 74%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3 H), 1.58 (q, J = 12.6 Hz, 1 H), 1.93 (q, J = 12.6 Hz, 1 H), 2.20 (d, J = 13.2, 2 H), 2.45 (dd, J = 7.8 and 3.6 Hz, 2 H), 2.67-2.72 (m, 1 H), 3.45-3.49 (m, 1 H), 3.99-4.10 (m, 3 H), 7.13-7.19 (m, 5 H), 7.24 (d, J = 7.8 Hz, 2 H), 7.35 (d, J = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.4, 40.5, 40.8, 41.1, 42.1, 45.1, 47.8, 61.0, 121.5, 126.8, 127.0, 128.9, 129.4, 132.0, 140.7, 145.8, 171.1; **IR** (KBr, neat) : 2982, 2920, 1711, 1633, 1480, 1365, 1132, 1041, 832, 743 cm^{-1}; **HRMS** (ESI) calcd. for $C_{21}H_{24}BrO_2S$ $(M + H)^+$ 419.0675, found 419.0675.



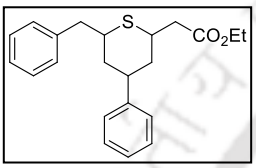
***Data for ethyl 2-(6-(2-chlorophenyl)-4-phenyltetrahydro-2H-thiopyran-2-yl)acetate* (26d).** Pale yellow liquid; R_f (hexane/EtOAc 95:5) 0.6; yield 125 mg, 67%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 1.67 (q, J = 12.4 Hz, 1 H), 1.96 (q, J = 12.0 Hz, 1 H), 2.26-2.31 (m, 2 H), 2.47-2.60 (m, 2 H), 2.81-2.86 (m, 1 H), 3.56-3.62 (m, 1 H), 4.14 (q, J = 7.2 Hz, 2 H), 4.63 (dd, J = 8.0 and 2.4 Hz, 1 H), 7.13-7.24 (m, 5 H), 7.28-7.37 (m, 3 H), 7.50 (d, J = 7.8 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.3, 40.5, 40.7, 41.2, 41.6, 44.2, 45.0, 61.0, 126.7, 127.0, 127.4, 128.5, 128.6, 128.8, 129.8, 133.3, 139.0, 145.8, 171.1; **IR** (KBr, neat) : 2980, 2921, 1716, 1634, 1488, 1369, 1133, 1041, 831, 744 cm^{-1}; **HRMS** (ESI) calcd. for $C_{21}H_{24}ClO_2S$ $(M + H)^+$ 375.1180, found 375.1185.



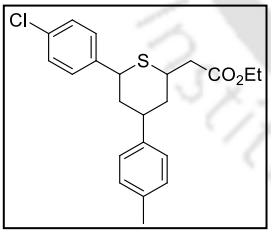
***Data for ethyl 2-(6-(3-bromophenyl)-4-phenyltetrahydro-2H-thiopyran-2-yl)acetate* (26e).** Pale yellow liquid; R_f (hexane/EtOAc 95:5) 0.6; yield 144 mg, 69%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.2 Hz, 3 H), 1.66 (q, J = 12.4 Hz, 1 H), 1.93 (q, J = 12.0 Hz, 1 H), 2.27-2.33 (m, 2 H), 2.46-2.60 (m, 2 H), 2.80-2.86 (m, 1 H), 3.56-3.62 (m, 1 H), 4.13 (q, J = 7.2 Hz, 2 H), 4.39-4.41 (m, 1 H), 7.13-7.24 (m, 5 H), 7.32-7.37 (m, 3 H), 7.56 (d, J = 15.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.3, 40.5, 40.7, 41.2, 41.6, 44.4, 45.1, 61.1, 126.7, 127.1, 127.4, 128.5, 128.6, 128.9, 129.8, 133.5, 139.0, 145.8, 171.1; **IR** (KBr, neat) : 2980, 2921, 1715, 1636, 1480, 1365, 1137, 1041, 831, 744 cm^{-1}; **HRMS** (ESI) calcd. for $C_{21}H_{24}BrO_2S$ $(M + H)^+$ 419.0675, found 419.0673.



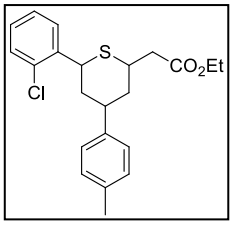
***Data for ethyl 2-(4-phenyl-6-(p-tolyl)tetrahydro-2H-thiopyran-2-yl)acetate* (26f).** Pale yellow liquid; R_f (hexane/EtOAc 95:5) 0.62; yield 131 mg, 74%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 1.64 (q, J = 12.6 Hz, 1 H), 2.04 (q, J = 12.6 Hz, 1 H), 2.26-2.32 (m, 5 H), 2.52 (dd, J = 8.4 and 3.6 Hz, 2 H), 2.77 (q, J = 12.0 Hz, 1 H), 3.51-3.56 (m, 1 H), 4.08-4.18 (m, 3 H), 7.10 (d, J = 7.8 Hz, 2 H), 7.19-7.26 (m, 5 H), 7.30 (t, J = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.4, 21.3, 40.6, 40.8, 41.3, 42.3, 45.2, 48.2, 61.0, 126.7, 127.0, 127.5, 128.8, 129.5, 137.3, 138.7, 146.1, 171.2; **IR** (KBr, neat) : 2984, 2921, 1718, 1633, 1489, 1366, 1135, 1040, 836, 741 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{27}O_2S$ $(M + H)^+$ 355.1726, found 355.1738.



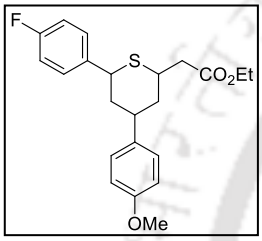
***Data for ethyl 2-(6-benzyl-4-phenyltetrahydro-2H-thiopyran-2-yl)acetate* (26h).** Pale yellow liquid; R_f (hexane/EtOAc 95:5) 0.64; yield 122 mg, 69%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 1.53 (dq, J = 12.6 and 3.6 Hz, 2 H), 2.10 (dt, J = 12.6 and 2.4 Hz, 1 H), 2.18 (dt, J = 12.6 and 2.4 Hz, 1 H), 2.42-2.58 (m, 3 H), 2.74 (dd, J = 12.6 and 7.8 Hz, 1 H), 2.88 (dd, J = 12.6 and 6.0 Hz, 1 H), 3.20-3.42 (m, 1 H), 3.34-3.38 (m, 1 H), 4.13 (q, J = 7.2 Hz, 2 H), 7.15 (d, J = 7.8 Hz, 2 H), 7.18-7.21 (m, 4 H), 7.26-7.29 (m, 4 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.4, 39.7, 40.7, 40.9, 41.7, 42.4, 44.7, 45.4, 60.9, 126.6, 126.7, 127.0, 128.5, 128.7, 129.4, 138.6, 146.2, 171.3; **IR** (KBr, neat) : 2981, 2922, 1712, 1635, 1482, 1367, 1135, 1040, 831, 744 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{27}O_2S$ $(M + H)^+$ 355.1726, found 355.1721.



***Data for ethyl 2-(6-(4-chlorophenyl)-4-(p-tolyl)tetrahydro-2H-thiopyran-2-yl)acetate* (26i).** Pale yellow liquid; R_f (hexane/EtOAc 95:5) 0.65; yield 149 mg, 77%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 1.64 (q, J = 12.6 Hz, 1 H), 2.01 (q, J = 12.6 Hz, 1 H), 2.20-2.2 (m, 2 H), 2.34 (s, 3 H), 2.50-2.55 (m, 2 H), 2.97-2.99 (m, 1 H), 3.51-3.59 (m, 1 H), 4.07-4.10 (m, 3 H), 7.10-7.18 (m, 2 H), 7.25-7.31 (m, 6 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.4, 21.2, 40.5, 40.8, 41.0, 42.2, 45.0, 47.9, 61.0, 126.6, 126.8, 128.9, 129.0, 129.5, 133.3, 140.2, 145.7, 171.2; **IR** (KBr, neat) : 2980, 2919, 1714, 1639, 1479, 1367, 1132, 1047, 833, 741 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{26}ClO_2S$ $(M + H)^+$ 389.1337, found 389.1330.



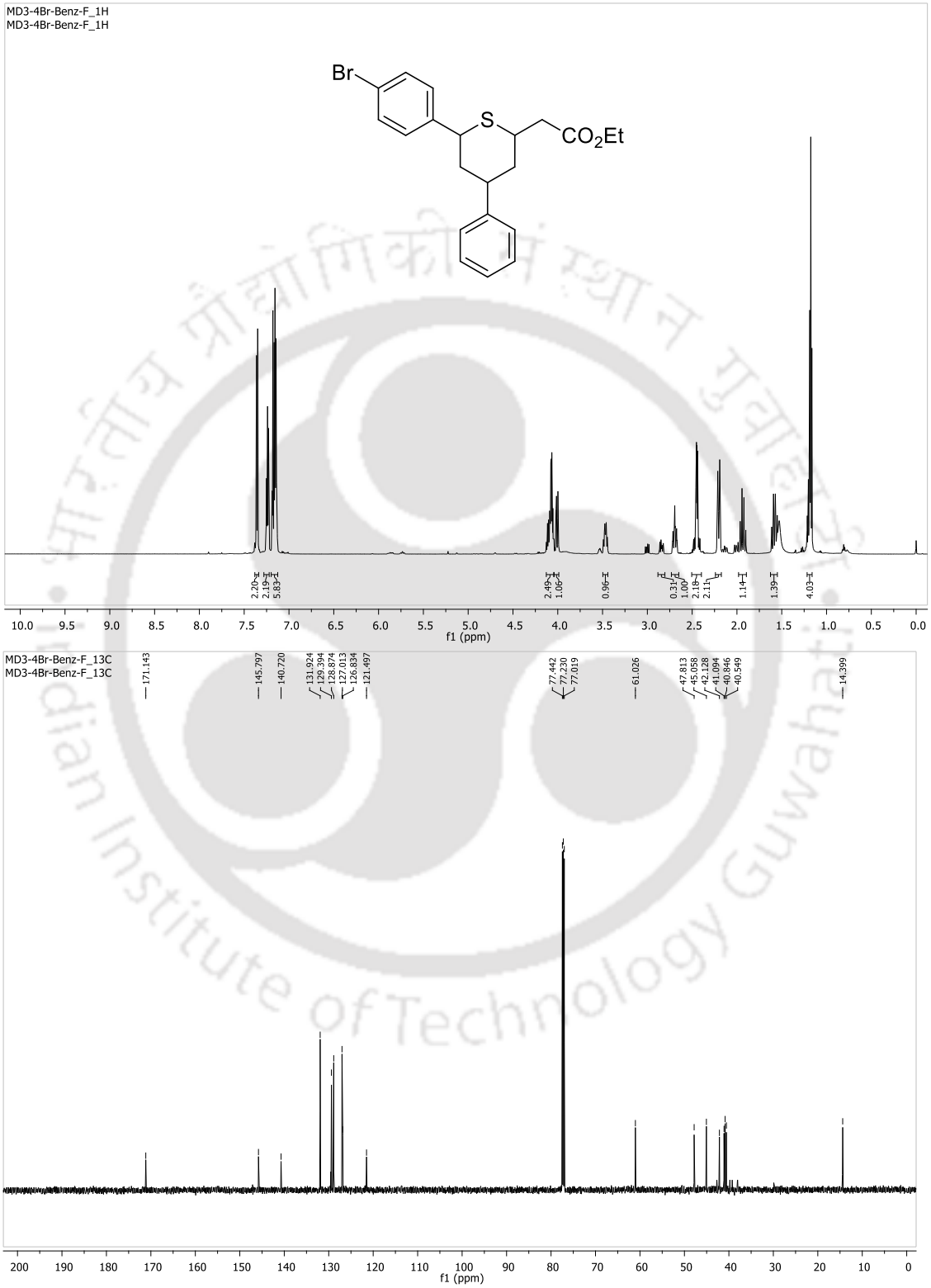
***Data for ethyl 2-(6-(2-chlorophenyl)-4-(p-tolyl)tetrahydro-2H-thiopyran-2-yl)acetate* (26j).** Pale yellow liquid; R_f (hexane/EtOAc 95:5) 0.62; yield 120 mg, 62%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3 H), 1.67 (q, J = 12.4 Hz, 1 H), 1.95 (q, J = 12.0 Hz, 1 H), 2.25-2.30 (m, 2 H), 2.37 (s, 3 H), 2.49-2.60 (m, 2 H), 2.81-2.85(m, 1 H), 3.56-3.64 (m, 1 H), 4.16 (q, J = 7.2 Hz, 2 H), 4.63 (dd, J = 8.0 and 2.4 Hz, 1 H), 7.03 (t, J = 7.2 Hz, 1 H), 7.10-7.24 (m, 5 H), 7.34 (d, J = 7.8 Hz, 1 H), 7.50 (t, J = 7.2 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.3, 21.3, 40.5, 40.7, 41.2, 41.6, 44.2, 45.0, 61.0, 126.7, 127.0, 127.4, 128.5, 128.6, 128.8, 129.6, 133.5, 139.2, 145.8, 171.2; **IR** (KBr, neat) : 2981, 2921, 1711, 1641, 1479, 1361, 1131, 1045, 833, 741 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{26}ClO_2S$ $(M + H)^+$ 389.1337, found 389.1336.



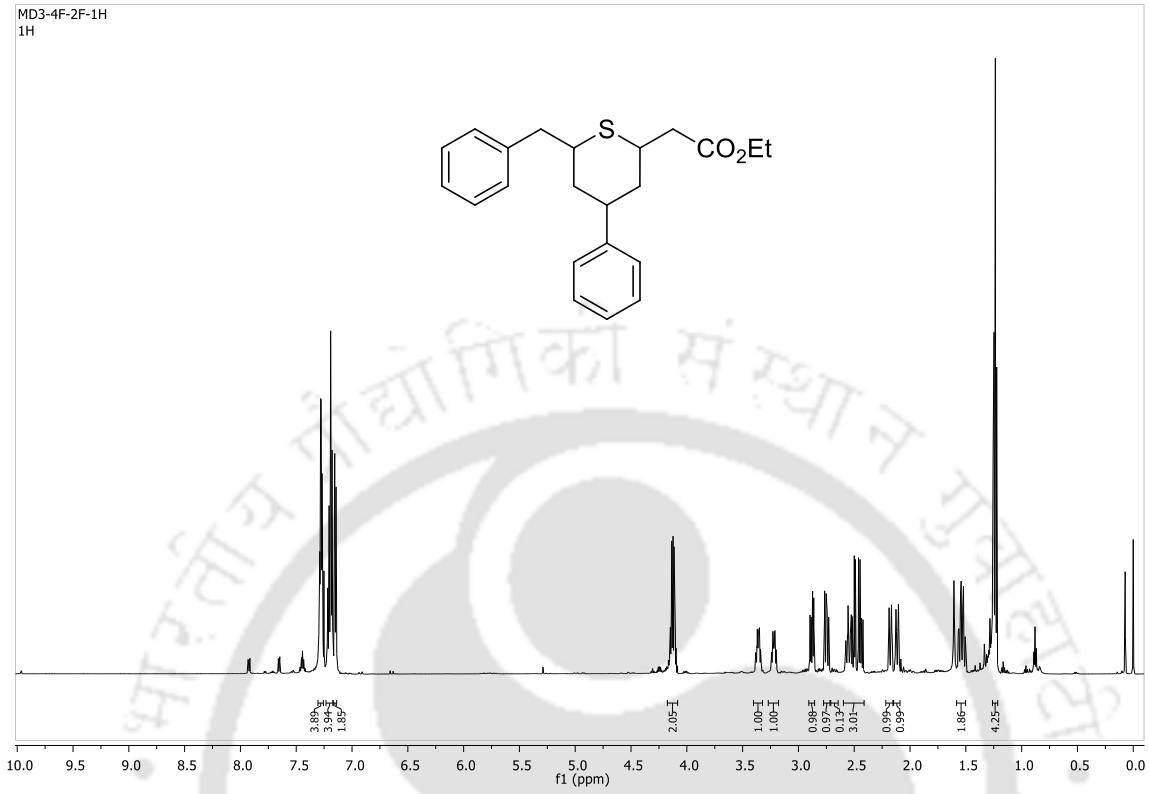
***Data for ethyl 2-(6-(4-fluorophenyl)-4-(4-methoxyphenyl)tetrahydro-2H-thiopyran-2-yl)acetate* (26k).** Pale yellow liquid; R_f (hexane/EtOAc 95:5) 0.40 yield 109 mg, 56%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3 H), 1.64-1.68 (m, 1 H), 1.99 (q, J = 12.6 Hz, 1 H), 2.19-2.26 (m, 2 H), 2.50-2.53 (m, 2 H), 2.97-2.99 (m, 1 H), 3.72-3.82 (m, 4 H), 4.12-4.19 (m, 3 H), 6.81 (d, J = 7.2 Hz, 2 H), 6.97-7.01 (m, 2 H), 7.12 (d, J = 7.2 Hz, 2 H), 7.29-7.32 (m, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.4, 40.5, 40.8, 41.0, 42.2, 45.7, 47.9, 55.4, 61.0, 114.0, 115.9 (d, J = 22.5 Hz), 128.7, 129.6, 134.0, 136.2, 158.2, 162.3 (d, J = 245.3 Hz), 171.2; **IR** (KBr, neat) : 2983, 2921, 1710, 1641, 1477, 1371, 1131, 1043, 830, 744 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{26}FO_3S$ $(M + H)^+$ 389.1581, found 389.1572.

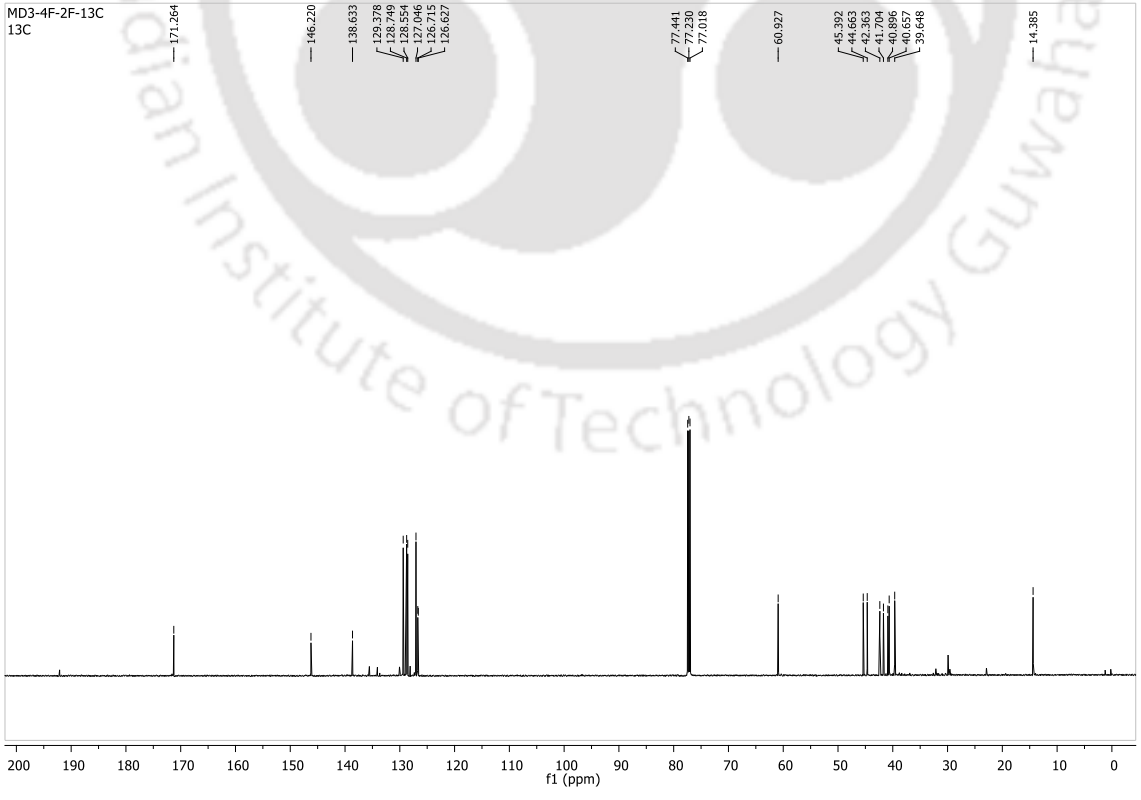
4.8 Selected Spectra

ethyl 2-(6-(4-bromophenyl)-4-phenyltetrahydro-2H-thiopyran-2-yl)acetate (26c):

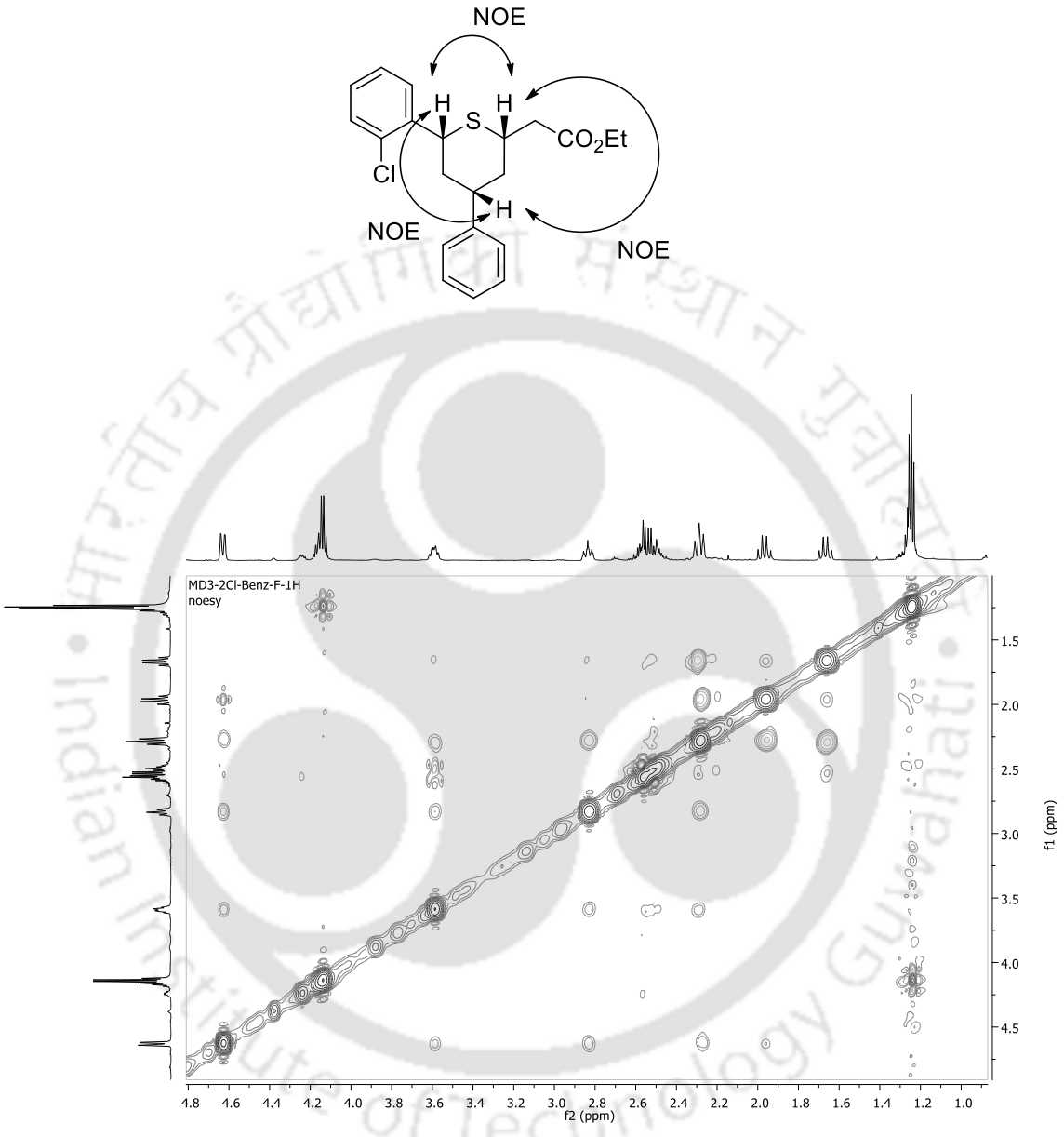


ethyl 2-(6-benzyl-4-phenyltetrahydro-2H-thiopyran-2-yl)acetate (26h):





2D NOESY spectra of ethyl 2-(6-benzyl-4-phenyltetrahydro-2H-thiopyran-2-yl)acetate (26d).



List of Publications

1. "Synthesis of Five-, Six-, and Seven-Membered 1,3- and 1,4- Heterocyclic Compounds *via* Intramolecular Hydroalkoxylation/Hydrothioalkoxylation of Alkenols/Thioalkenols" **Deka, M. J**.; Indukuri, K.; Sultana, S.; Borah, M.; Saikia, A. K. *J. Org. Chem.* **2015**, *80*, 4349-4359.
2. "Highly regioselective synthesis of 4-tosylthiomorpholine *via* intramolecular cyclization of N-tethered thioalkenols" **Deka, M. J.**; Borthakur, U.; Saikia, A. K. *Org. Biomol. Chem*. **2016**, *14*, 10489-10495.
3. "Synthesis of Tetrahydro-1*H*-indeno[1,2-*b*]pyridine *via* Cascade Cyclization and Friedel-Crafts Reaction" Borthakur, U.; Borah, M.; **Deka, M. J**.; Saikia, A. K. *J. Org. Chem.* **2016**, 81, 8736-8743.
4. "Synthesis of dihydroindeno[1,2-*c*]isochromene *via* cascade cyclization and Friedel-Crafts reaction " Saikia, A. K.; Ghosh, P.; **Deka, M. J**.; Borah, M.; *RSC Adv.*, **2016**, *6*, 106656-106661.
5. "Lewis acid mediated intramolecular C-O bond formation of alkanol-epoxide leading to substituted morpholine and 1,4-oxazepane derivatives: total synthesis of (±)Viloxazine" Ghosh, P.; **Deka, M. J.**; Saikia, A. K. *Tetrahedron.* **2016**, *72*, 690-698.
6. "Diastereoselective Synthesis of Dihydropyrans *via* Prins Cyclization of Enol Ethers: Total Asymmetric Synthesis of (+)-Civet Cat Compound" Sultana, S.; Indukuri, K.; **Deka, M. J.**; Saikia, A. K. *J. Org. Chem.* **2013**, *78*, 12182-12188.
7. "Stereoselective Synthesis of Amido and Phenyl Azabicyclic Derivatives *via* a Tandem Aza Prins-Ritter/Friedel−Crafts Type Reaction of Endocyclic N-Acyliminium Ions" Indukuri, K.; Unnava. R; **Deka, M. J.**; Saikia, A. K. *J. Org. Chem*. **2013**, *78*, 10629-10641.
8. "Diastereoselective synthesis of substituted hexahydrobenzo[*de*]isochromanes and evaluation of their antileishmanial activity" Saikia, A. K.; Sultana, S.; Devi. N. R.; **Deka, M. J.**; Tiwari, K; Dubey, V. K. *Org. Biomol. Chem*. **2016**, *14*, 970-979.
9. "Synthesis of Highly Substituted 4-Iodopyrazole N-oxides and Pyrazoles from Propargylamines" Unnava, R.; **Deka, M. J.**; Saikia, A. K. *Asian J. Org. Chem*. **2016**, *5*, 528-536.

10. “Diastereoselective synthesis of substituted tetrahydrothiopyrans *via* thia-Prins cyclization reaction” **Deka**, **M**. **J**.; Saikia, A. K. *manuscript under preparation*.