Synthesis of Five- and Six-membered Nitrogen and Sulfur Heterocyclic Compounds

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Doctor of Philosophy in Chemistry

Submitted by

Madhurjya Borah

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati-781039, Assam, India
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Dedicated
To
My Parents, Brother and Sisters

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INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "**Synthesis of Five- and Six-membered Nitrogen and Sulfur 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: Madhurjya Borah
IIT Guwahati

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

CERTIFICATE

This is to certify that Mr. **Madhurjya Borah** has been working under my supervision since July 2013 as a regular registered Ph. D. student. I am forwarding his thesis entitled "**Synthesis of Five- and Six-membered Nitrogen and Sulfur 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: Prof. Anil K. Saikia
IIT Guwahati Supervisor

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Madhurjya Borah

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LIST OF ABBREVIATIONS

Boc	*tert*-butoxycarbonyl	mp	melting point
CCDC	cambridge crystallographic data centre	MS	molecular sieves
CSA	camphorsulfonic acid	m/z	mass to charge ratio
DABCO	1,4-diazabicyclo[2.2.2]octane	NaH	sodium hydride
DCE	1,2-dichloroethane	NMM	*N*-methylmorpholine
DCM	dichloromethane	NMR	nuclear magnetic resonance
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	NOESY	nuclear overhauser enhancement spectroscopy
DIAD	diisopropyl azodicarboxylate	Ns	nitrobenzenesulfonyl
DFT	density function theory	ORTEP	oak ridge thermal ellipsoid plot
DMAP	4-dimethylaminopyridine	Ph	phenyl
DMF	*N*, *N*-dimethylformamide	ppm	parts per million
de	diastereomeric excess	*p*-TSA	*p*-toluenesulfonic acid
dr	diastereomeric ratio	rt	room temperature
ee	enantiomeric excess	SES	2-(trimethylsilyl)ethanesulfonyl
HPLC	high-performance liquid chromatography	THF	tetrahydrofuran
HRMS	high resolution mass spectrometry	THIQ	tetrahydroisoquinoline
IR	infrared	TEA	triethyl amine
LA	Lewis acid	TFA	trifluoroacetic acid
LAH	lithium aluminium hydride	Tf	trifluoromethanesulfonyl
LDA	lithium diisopropyl amide	TLC	thin layer chromatography
KBr	potassium bromide	TMS	trimethylsilyl
m-CPBA	*meta*-chloroperoxybenzoic acid	Ts	*p*-toluenesulfonyl

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

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

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Abstract

The content of this thesis has been divided into five chapters based on the results of experiment work performed during the complete course of the research period. The chapter **1** of the thesis presents an introduction to nitrogen and sulfur heterocyclic compounds, their biological significance and the literature method for their synthesis. Chapter **2** describes a method for the diastereoselective synthesis of substituted tetrahydro-thiophenes and -thiopyrans *via* thia-Prins cyclization reaction. Chapter **3** deals with the diastereoselective synthesis of substituted morpholines from *N*-tethered alkenols and its application in total synthesis of (±)-chelonin A. In chapter **4**, $FeCl_3$-mediated carbenium-ion induced intramolecular cyclization of *N*-tethered alkyne-benzyl alkanols is described. Chapter **5** presents the synthesis of tetrahydroisoquinolines from *N*-tethered aryl-benzyl alkanols mediated by $BF_3{\cdot}OEt_2$.

Chapter 1: Introduction to Nitrogen and Sulfur Heterocyclic Compounds

Saturated five- and six-membered nitrogen and sulfur heterocyclic compounds are the core structural component found in a broad array of natural products, bioactive compounds and important synthetic intermediates. The wide range of biological activities and the synthetic usefulness give nitrogen and sulfur heterocyclic compounds a privileged role in organic chemistry.

To build these classes of heterocycles, many strategies have been developed over the years. The most widely used methods are the 1,*n*-enyne rearrangement, ring-closing metathesis, cascade reactions, Prins cyclization reactions, transition metal salts catalyzed cyclization reactions and nucleophilic substitution reactions of activated alcohols etc. Among these methods stated, introductory chapter mainly discusses Prins cyclization, aza-Prins cyclization, thia-Prins cyclization and nucleophilic substitution reactions of activated alcohols in detail for the construction of these heterocycles.

Chapter 2: Diastereoselective Synthesis of Substituted Tetrahydro-thiophenes and -thiopyrans *via* Thia-Prins Cyclization Reaction

Prins cyclization is a powerful strategy for the synthesis of five- and six-membered oxygen heterocycles. Although the Prins cyclization is familiar in organic synthesis, its

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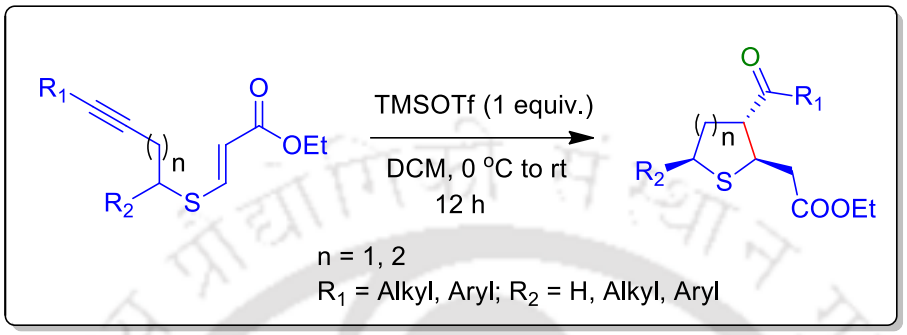
analogue thia-Prins cyclization is less familiar. Analogous to Prins cyclization reaction, thia-Prins cyclization leads to five- and six-membered tetrahydrothiophenes and tetrahydrothiopyrans. In this chapter, we described an efficient method for the synthesis of tetrahydro-thiophenes and -thiopyrans from thioacrylates *via* intramolecular thia-Prins cyclization (*Scheme 1*).



Scheme 1

The reaction is highly diastereoselective and the stereochemistry of the trisubstituted tetrahydrothiophenes was characterized by 2-D nuclear Overhauser effect spectroscopy (NOESY). It showed a clear characteristic nOe correlations between the hydrogens C-2H and C-5H and the absence of nOe between C-3H and C-5H, which clearly indicates that the substituents at 2,5 positions are *cis* to each other and the benzoyl substituent at C-3 is *trans* to other two substituents. It was further confirmed by X-ray crystallographic analysis (Figure 1).

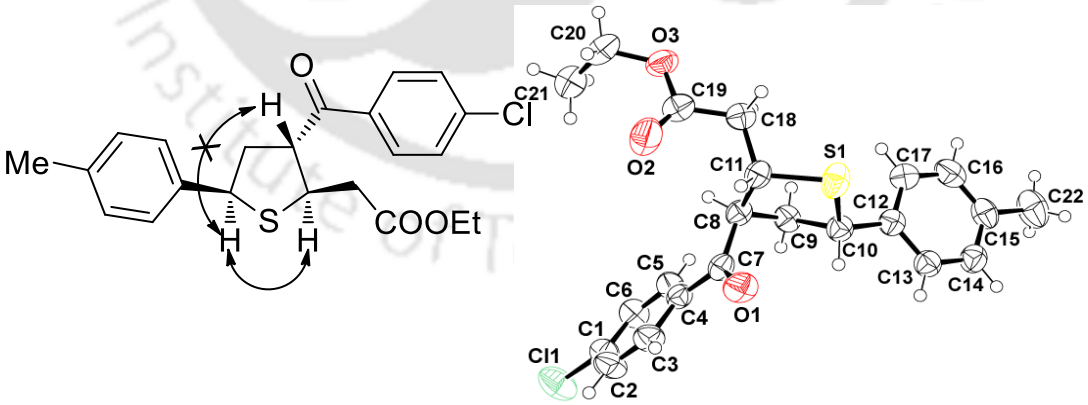


Figure 1. *nOe and ORTEP diagram of ethyl 2-((2R*,3R*,5R*)-3-(4-chlorobenzoyl)-5-(p-tolyl)tetrahydrothiophen-2-yl)acetate*

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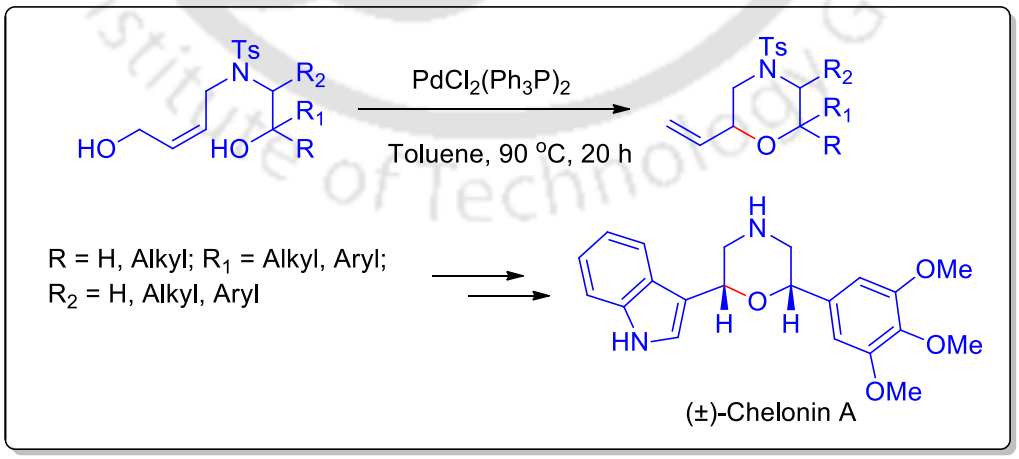
Similarly, the stereochemistry of 2,3,6-trisubstituted tetrahydrothiopyrans was confirmed by NOE spectroscopy of ethyl 2-((2*R**,3*R**,6*R**)-3-benzoyl-6-phenyltetrahydro-2*H*-thiopyran-2-yl)acetate, which indicates that the substituents at 2,6 positions are *cis* to each other and the benzoyl substituent at C-3 is *trans* to the other two substituents.

In conclusion, an efficient and highly diastereoselective method for the synthesis of di- and tri-substituted tetrahydro-thiophenes and -thiopyrans in good yields has been developed from thioacrylates *via* intramolecular thia-Prins cyclization reaction.

Chapter 3: Diastereoselective Synthesis of Substituted Morpholines from *N*-Tethered Alkenols: Total Synthesis of (±)-Chelonin A

Morpholine derivatives are widely distributed in many naturally occurring and biologically active molecules. In particular, 2,6-disubstituted and 2,5-disubstituted morpholine derivatives are important pharmacophores in medicinal chemistry. For example, the natural product chelonin A, which was isolated from the marine sponge *Chelonaplysilla* sp. have been reported to exhibit antimicrobial activity against *Bacillus subtilis* and *in-vivo* antiinflammatory activity in the mouse. In this chapter, we discuss an efficient method for the diastereoselective synthesis of 2,6-disubstituted and 2,5-disubstituted morpholines using intramolecular C-O bond formation of *N*-tethered diols consisting of alkanol and alkenol catalyzed by palladium(II) chloride. This methodology was further utilized for the total synthesis of (±)-chelonin A, starting from *N*-tethered diol in 5 steps with an overall 26% yields (*Scheme 2*).



Scheme 2

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The reaction is highly diastereoselective with predominant formation of *cis* isomers for both 2,6-disubstituted and 2,5-disubstituted morpholines. The relative stereochemistry of 2,6-disubstituted morpholines was determined by 2-D nuclear Overhauser enhancement spectroscopy (NOESY) and X-ray crystallographic analysis of (2*R**,6*S**)-2-(4-Nitrophenyl)-4-tosyl-6-vinylmorpholine (Figure 2). Similarly, the relative stereochemistry of the 2,5-disubstituted morpholines was determined by X-ray crystallographic analysis of compound (*2S**,*5S**)-5-Benzyl-4-tosyl-2-vinylmorpholine (Figure 2).

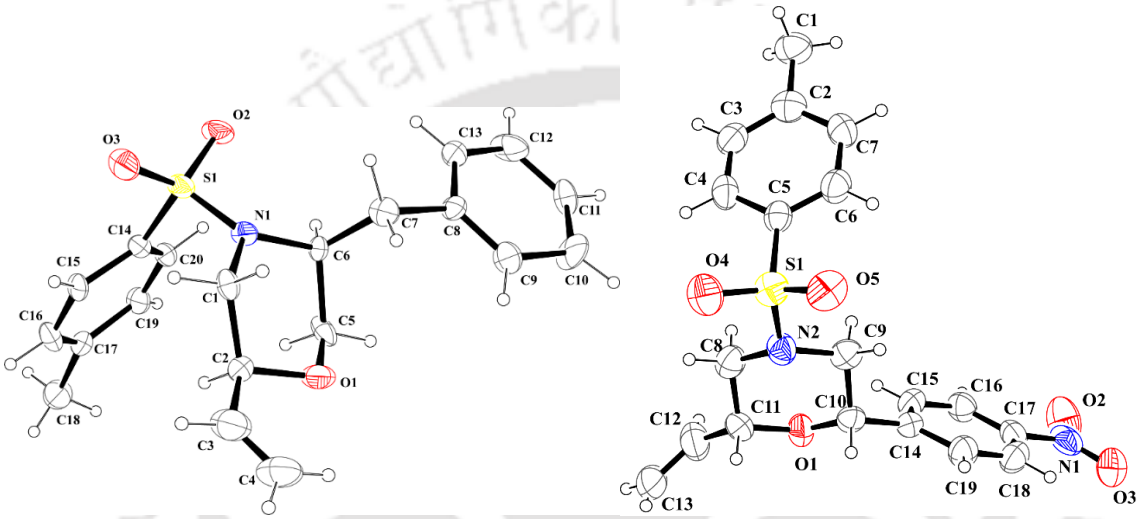

Figure 2. *ORTEP diagram of (2S*,5S*)-5-Benzyl-4-tosyl-2-vinylmorpholine and (2R*,6S*)-2-(4-Nitrophenyl)-4-tosyl-6-vinylmorpholine*

In conclusion, we developed an efficient method for the synthesis of substituted morpholines *via* palladium(II) catalysed intramolecular cyclization reaction of *N*-tethered diols in good yields. The major advantage of this reaction is that it regioselectively generates a vinyl group at position 2 of the morpholine ring, which can be used for the synthesis of natural product (±)-chelonin A.

Chapter 4: $FeCl_3$-Mediated Carbenium Ion Induced Intramolecular Cyclization of *N*-Tethered Alkyne-Benzyl Alkanols

Nucleophilic substitution of alcohols *via* a formal dehydration process is an important strategy for the organic chemists to access wide variety of functionalised derivatives. Direct nucleophilic substitution of an alcohol is not possible as hydroxide is a poor leaving group and therefore activation is usually required. However, π-activated

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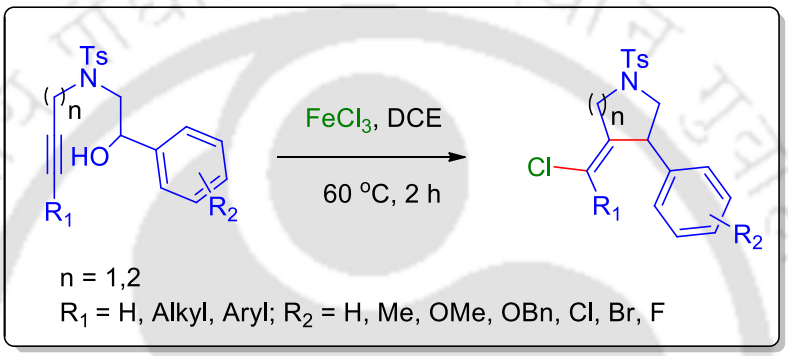
alcohols, such as allylic, benzylic and propargylic alcohols can be activated towards nucleophilic attack by the use of Lewis and Brønsted acids. In this chapter, we present a methodology for the synthesis of pyrrolidines and piperidines derivatives from *N*-tethered alkyne-benzyl alkanols *via* ferric chloride ($FeCl_3$) mediated intramolecular carbenium-ion induced cyclization reaction (*Scheme 3*). In this reaction, ferric chloride acts as a Lewis acid to remove hydroxyl group of benzyl alkanol to afford benzyl carbenium ion followed by nucleophilic attack by alkyne and simultaneous *anti*-addition of chloride ion across the alkyne to form pyrrolidine and piperidine derivatives with exocyclic chloro-alkylidene and -arylidene moiety.



Scheme 3

The reaction is highly *Z* selective for pyrrolidines and *E* selective for piperidines. The addition reaction to the triple bond proceeds with *anti*-mode in preference to *syn*-mode in both the cases. Therefore, the *E*/*Z* selectivity is just a consequence of the IUPAC nomenclature. The stereochemistry of the pyrrolidine products was confirmed by X-ray crystallographic analysis of (*Z*)-3-(Chloro(phenyl)methylene)-4-(2-chlorophenyl)-1-tosylpyrrolidine (Figure 3).

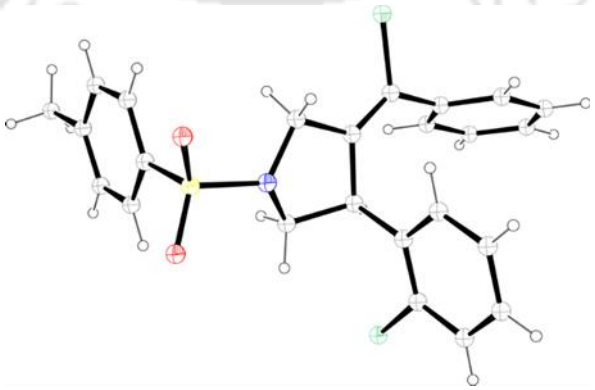


Figure 3. *ORTEP diagram of (Z)-3-(Chloro(phenyl)methylene)-4-(2-chlorophenyl)-1-tosylpyrrolidine*

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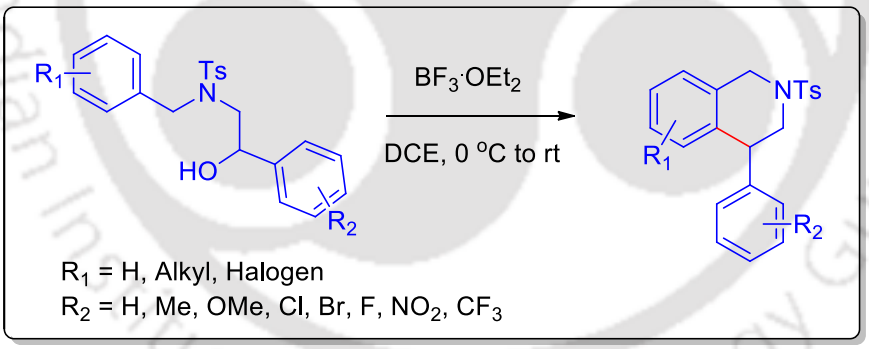
In conclusion, we have developed an efficient method for the synthesis of substituted pyrrolidine and piperidine derivatives with exocyclic chloro-alkylidene and -arylidene moiety in good yields. The reaction is *Z* selective for pyrrolidines and *E* selective for piperidines. One of the important aspects of the reaction is the dual role exhibited by ferric chloride as Lewis acid as well as chloride nucleophile.

Chapter 5: Synthesis of Tetrahydroisoquinolines from *N*-Tethered Aryl-Benzyl Alkanols mediated by $BF_3{\cdot}OEt_2$

The Friedel-Crafts reaction is one of the most powerful methods to synthesize aromatic compounds and has been widely used in various industrial processes. Carbocation generated from the treatment of π-activated alcohols with Lewis and Brønsted acids may be used as electrophilic alkyl equivalents in Friedel-Crafts alkylation reactions. In this chapter, we discuss a general methodology for the synthesis of 4-aryl-tetrahydroisoquinolines from *N*-tethered aryl-benzyl alkanols mediated by boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) in good to excellent yields (*Scheme 4*). In the process, benzylic alcohol is used as an electrophilic alkyl equivalent in presence of Lewis acid $BF_3{\cdot}OEt_2$ for the intramolecular Friedel-Crafts alkylation reactions.



Scheme 4

In conclusion, we have developed an alternate, efficient methodology for the synthesis of 4-aryl-tetrahydroisoquinoline derivatives in good to excellent yields. The reaction is very mild and can be carried out by inexpensive and commercially available $BF_3{\cdot}Et_2O$ as Lewis acid.

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CHAPTER 1

Introduction to Nitrogen and Sulfur Heterocyclic Compounds

1.1. Heterocyclic compounds

Heterocyclic compounds are characterized as cyclic organic compounds having at least one atom other than carbon as ring members. Generally, nitrogen, oxygen and sulfur are the most common heteroatoms but heterocyclic rings containing other heteroatoms, such as boron, silicon, phosphorus and selenium, are also widely known. An enormous number of heterocyclic compounds are known and this number is increasing rapidly. The chemistry of heterocyclic compounds deals with the synthesis, properties and applications of heterocyclic compounds. It constitutes the most varied family of the organic compounds with nearly half of the known compounds coming under this category. Heterocyclic compounds may be classified into aliphatic and aromatic heterocyclic compounds. 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. The most common aliphatic heterocyclic compounds are aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, tetrahydrofuran, tetrahydrothiophene and piperidine. The aromatic heterocyclic compounds, in contrast, are those which have a heteroatom in the ring and fulfil the Huckel rule for aromaticity, which states that cyclic, conjugated and planar systems having (4n+2) π electrons are aromatic. Furthermore, some of their properties resemble with those of the benzene. The best known simple aromatic heterocyclic compounds are pyridine, pyrrole, furan, and thiophene. Heterocyclic compounds are widely distributed in nature and essential to sustaining life. For example, nucleic acids (purine and pyrimidine bases), vitamins (thiamine B_1, riboflavin B_2, nicotinamide B_3, pyridoxol B_6 and ascorbic acid C), chlorophyll, haemoglobin, antibiotics and much more contain the heterocyclic ring in the major skeleton. A large number of heterocyclic compounds, both synthetic and natural, are pharmacologically active and are in clinical use.

This introductory chapter is designed to highlight the importance of some five- and six-membered nitrogen and sulfur containing biologically active compounds and their

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significance. This chapter also focuses on important synthetic routes for the synthesis of five- and six-membered nitrogen and sulfur containing heterocycles such as tetrahydrothiophenes, tetrahydrothiopyrans, pyrrolidines, piperidines, and tetrahydroisoquinolines.

1.2. Importance of tetrahydrothiophenes and tetrahydrothiopyans

Five- and six-membered sulphur containing heterocyclic compounds possess significant biological properties. The tetrahydrothiophene moiety is the core structural unit of many natural products, bioactive compounds, and pharmaceutical agents. For example, coenzyme Biotin (**1**), which is required by all living organisms for normal cellular functions and growth, contains tetrahydrothiophene moiety.[1] Tetronothiodin (**2**), which was isolated from the fermentation broth of *Streptomyces sp*. NR0489 is the cholecystokinin type-B receptor antagonist.[2] Similarly, the nucleoside **3** shows a potent activity against human cytomegalovirus.[3] Some other examples of bioactive compounds containing tetrahydrothiophene moiety are the anti-HIV nucleoside **4**,[4] and the analogues of penicillins **5**[5] (*Figure 1.2.1*). Tetrahydrothiophenes also act as anti-oxidative agents,[6] hypercholesterolemic agents,[7] and plant growth regulators.[8]

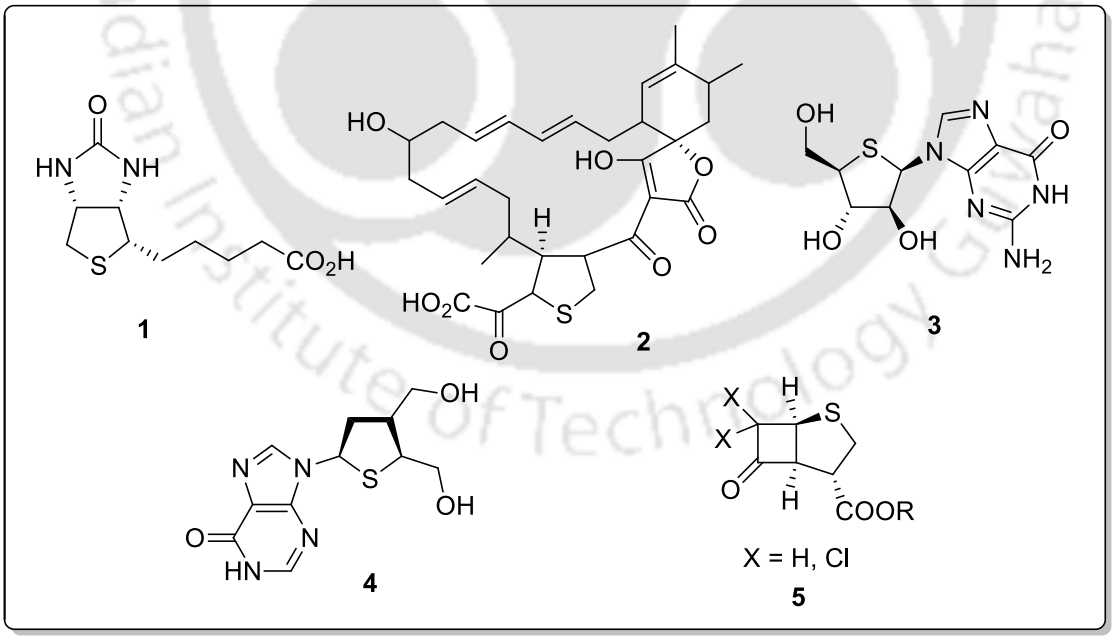

Figure 1.2.1. *Bioactive molecules containing tetrahydrothiophenes*

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Similarly, tetrahydrothiopyrans, analogues of tetrahydropyrans, are also an important structural unit in various biologically active molecules.[9] In addition to these, the sulfur analogues of oligosaccharides are known to be potential enzyme inhibitors.[10]

1.3. Importance of pyrrolidines, piperidines and tetrahydroisoquinolines

Nitrogen heterocycles belong to a highly privileged class of heterocyclic compounds that are found in numerous natural products, biologically active compounds and medicinally relevant compounds. In particular, pyrrolidines, piperidines, and tetrahydroisoquinolines have gained considerable attention in medicinal chemistry and pharmaceutical science. Pyrrolidines, a five-membered saturated *N*-heterocycle are found in a wide variety of natural products and pharmaceuticals.[11] Some examples of biologically active compounds containing pyrrolidine moieties are shown in *Figure 1.3.1*. (-)- Kianic acid (**6**), is a natural marine acid originally isolated from the red marine alga *Digenea. Simplex*, used as antiworming agent. It is also a powerful neurotoxin, which kills neurons by means of overexcitation and therefore used in the study of serious neuronal disorders such as Alzheimer's disease and epilepsy in animal models.[12] The pyrrolidine derivative **7** (BIRZ-227) acts as LTB_4 inhibitor and can be useful for the treatment of inflammatory disorders such as asthma, arthritis, inflammatory bowel disease, and psoriasis.[13]

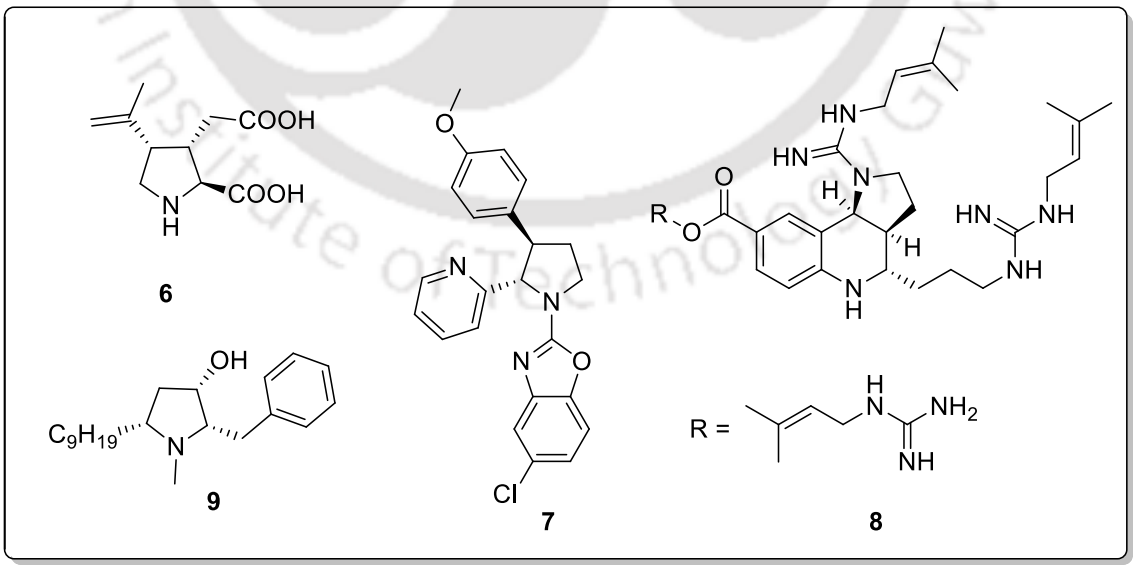

Figure 1.3.1. *Bioactive molecules containing pyrrolidines*

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Similarly, the pyrroloquinoline alkaloid martinelline (**8**), which was isolated from an organic extract of *Martinella iquitosensis* roots, were found to possess antibacterial activity as well as affinity for adrenergic, muscarinic, and bradykinin receptors.[14] (+)-Preussin (**9**), which was isolated from a liquid fermentation broth of *Aspergillus ochraceus* displays significantly broader spectrum of antifungal activity.[15]

On the other hand, piperidine derivatives are widely found within nature as part of several alkaloid skeletons. In fact, piperidine moiety is present in more than half of the alkaloids known today.[16] In addition to these, piperidine derivatives, both natural and synthetic are found to possess interesting biological and therapeutic properties. Indeed, thousands of piperidine derivatives have undergone clinical and preclinical studies over the last two decades.

Another important class of six-membered benzo-fused *N*-heterocyclic compound is 1,2,3,4-tetrahydroisoquinolines. The tetrahydroisoquinoline unit forms the basic skeleton of many naturally occurring alkaloids of pharmaceutical importance. For example, naturally occurring alkaloids such as cryptostylines **10**-I, **10**-II, and **10**-III (*Figure 1.3.2*) belong to this family of alkaloids and show interesting pharmacological properties such as probes for dopamine receptor D_1.[17a] Cryptostylines **10**-I, **10**-II and **10**-III, were isolated from plant *Cryptostylis fulva* and *Cryptostylis erythroglosa*.[17b,c] Dioncophylline E (**11**), which is a naphthylisoquinoline alkaloid isolated from the roots of the rare West African liana *Dioncophyllum thollonii* by Bringmann and co-workers, exhibits good antimalarial activity against both chloroquine-sensitive and -resistant strains of *Plasmodium falciparum*.[18]

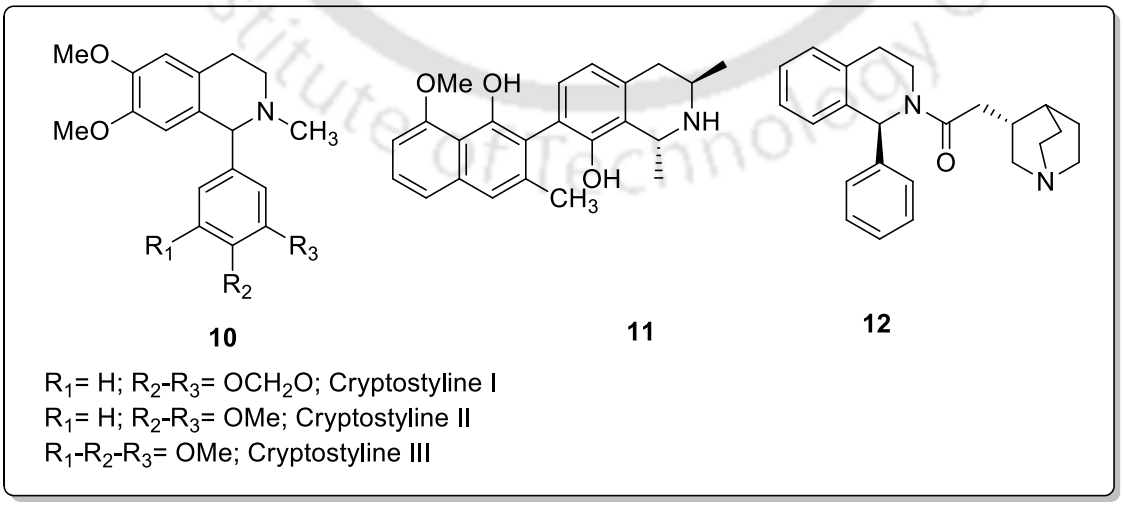

Figure 1.3.2. *Bioactive molecules containing tetrahydroisoquinolines*

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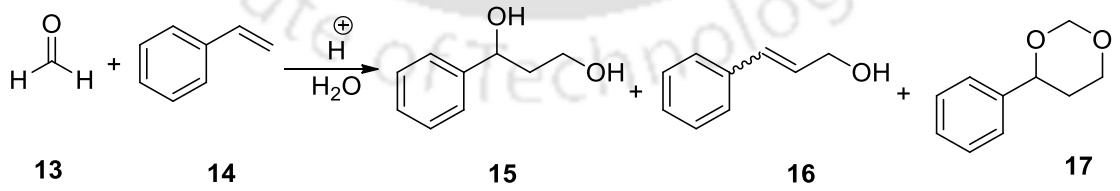
Similarly, solifenacin (**12**), a urinary antispasmodic prescription drug used for the treatment of an overactive bladder also contain tetrahydroisoquinoline moiety.[19]

1.4. An overview for the synthesis of five- and six-membered nitrogen and sulfur heterocycles

The stereoselective synthesis of five- and six-membered nitrogen and sulfur heterocycles has been a subject of great interest for organic researchers because of their ubiquity in natural products and bioactive compounds. To build this nitrogen and sulfur heterocycles, many strategies have been developed over the years. The most widely used methods are the 1,*n*-enyne rearrangement, ring-closing metathesis, cascade reaction, Prins cyclization reaction, transition metal salts catalyzed cyclization reactions, nucleophilic substitution reaction of activated alcohols etc. Among these methods stated, this thesis mainly discusses Prins, aza-Prins cyclization, thia-Prins cyclization and nucleophilic substitution reactions of activated alcohols in detail for the construction of these heterocycles.

1.4.1. 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 **13** and styrene **14** in aqueous acidic medium, resulting in a mixture of products such as 1,3-butanediol **15**, unsaturated alcohol **16** and 1,3-dioxane **17** (*Scheme 1.4.1.1*).[20] Usually, the outcome of the reaction depends on the nature of reaction conditions.



13 **14** **15** **16** **17**

Scheme 1.4.1.1

The general mechanism of the reaction is shown in *Scheme 1.4.1.2*. The alkene **14** reacts with carbonyl compounds **13** in the presence of acid to generate the key intermediate *β*-hydroxy carbocation **18**. This intermediate **18** may lose a proton to give homoallylic alcohol **16** or reacts with a number of species present in the reaction medium. Reaction

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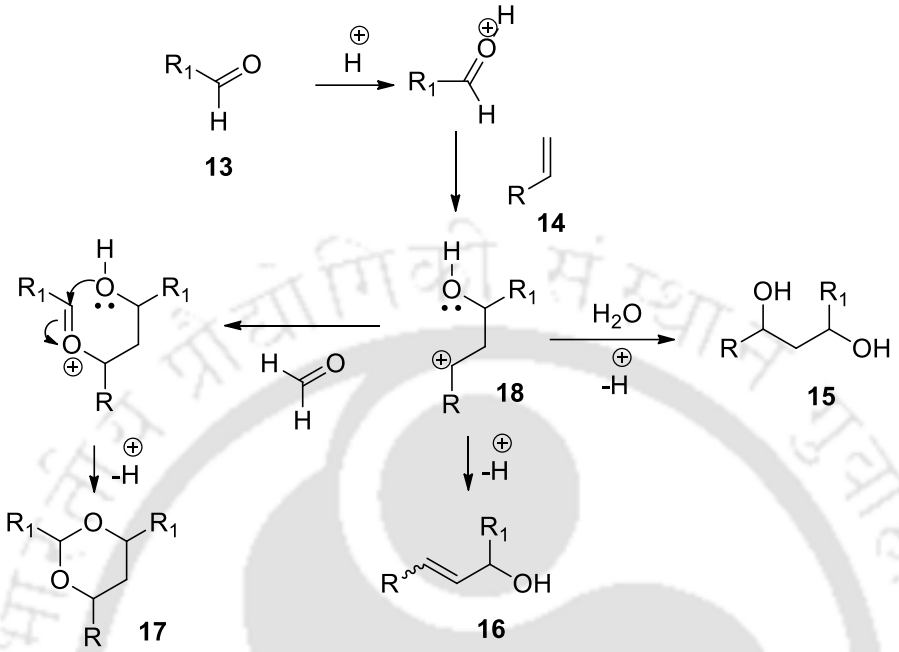
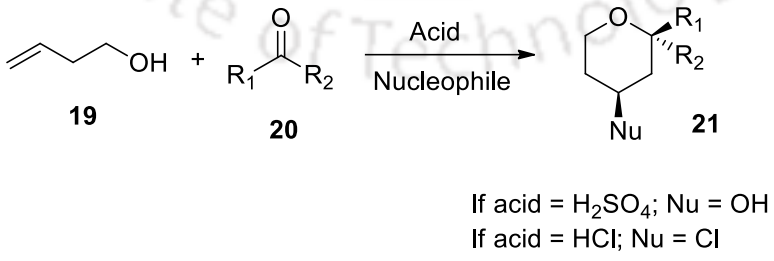
of carbocation **18** with a second molecule of aldehyde **13** forms 1,3-dioxane **17** after ring closure. Similarly, intermediate **18** can react with solvent (H_2O) to give the 1,3-diol adduct **15**.



Scheme 1.4.1.2

In 1955, Hanschke has further modified Prins reaction for the stereoselective synthesis of tetrahydropyran (THP) derivatives **21** by reaction of 3-buten-1-ol **19** with a variety of aldehydes or ketones **20** in the presence of acid, called Prins cyclization reaction (*Scheme 1.4.1.3*).[21] In most of the cases, the Prins cyclization reaction is highly diastereoselective and give 2,4,6-substituted tetrahydropyrans with all equatorial substitutions.



Scheme 1.4.1.3

The general mechanism is shown in *Scheme 1.4.1.4*. The reaction of aldehyde **20** and homoallylic alcohol **19** in the presence of acid generates an oxocarbenium ion **23** as a

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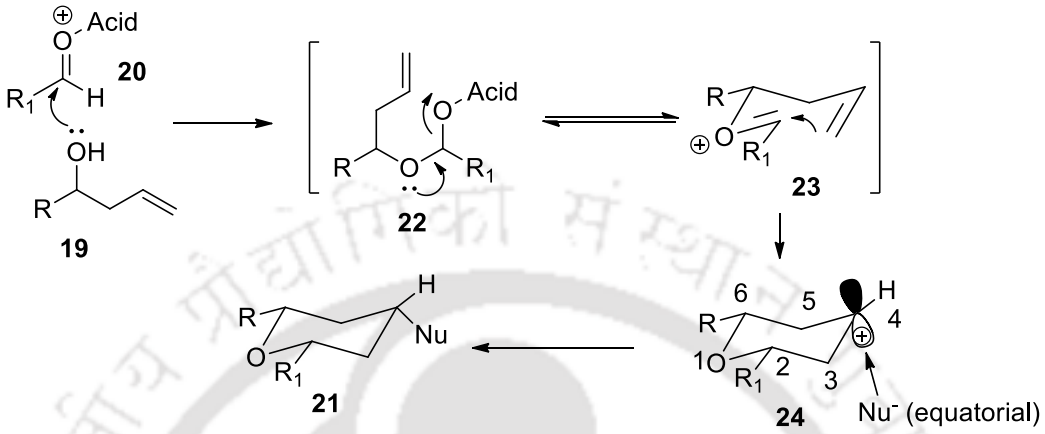
key intermediate. The six-membered oxocarbenium intermediate adopts chair-like conformation and undergoes 6-endo cyclization to give selectively a secondary tetrahydropyrynyl cation **24**, which is trapped by the nucleophile present in the reaction mixture to produce tetrahydropyran **21**.



Scheme 1.4.1.4

Alder has performed the DFT calculations on different possible reaction intermediates and rationalized the diastereoselectivity through a chair-like transition state.[22] According to Alder's DFT calculations; stereoelectronic effects stabilize the tetrahydropyrynyl cation **24** 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 **21**.

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 **24** with a broad spectrum of nucleophiles (*Table 1.4.1.1*). 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

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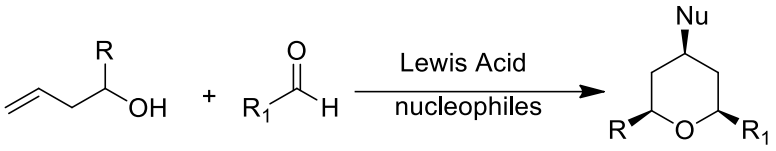
cation with oxygenated, nitrogenated, sulfur nucleophiles such as hydroxide, acetate, azide, thiocyanate etc. have also been reported.

Table 1.4.1.1. *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	$PhCOCH_2$

1.4.2. 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.[23] Later in 2003, Bennett and Hart extended the scope of this route towards the synthesis of trisubstituted tetrahydropyrans **26** *via* TFA catalysed cyclization of enol ether **25** *(Scheme 1.4.2.1)*.[24] In most cases, these tetrahydropyrans are isolated with in moderate to good yields with excellent diastereoselectivity at C4 ranging from 95:5 to 50:50 depending on the nature of the substituent R.

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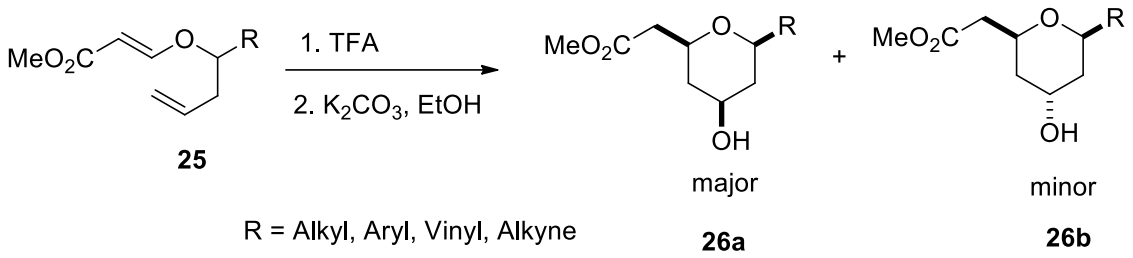
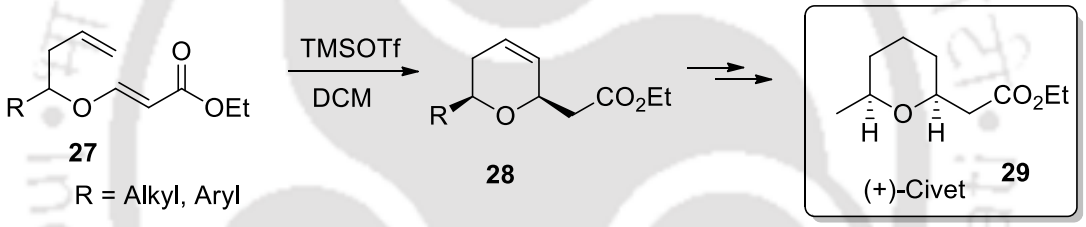


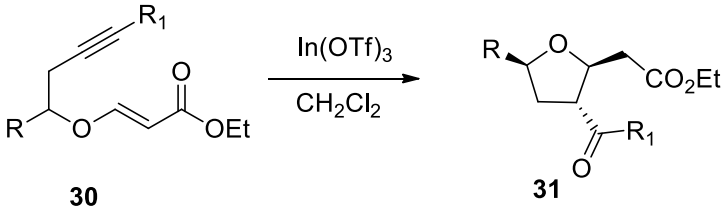
Scheme 1.4.2.1

Another example of using enol ether as the source of the oxocarbenium ion intermediate was demonstrated by our group in 2013.[25] Trimethylsilyl trifluoromethanesulfonate (TMSOTf) mediated Prins cyclization of acrylyl enol ethers **27** afforded 5,6-dihydro-2*H*-pyran-2-acetates **28** in good yields and in stereo- and regio-selective fashion (*Scheme 1.4.2.2).* The methodology was further used for the total synthesis of natural product (+)-civet cat compound (**29**), which is used as an additive in the perfumery industry.



Scheme 1.4.2.2

Recently, our group developed a mild and efficient method for the synthesis of di- and tri- substituted tetrahydrofurans **31** from acrylyl enol ethers **30** *via* $In(OTf)_3$-mediated Prins cyclization reaction in good yields (*Scheme 1.4.2.3).*[26] 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 1.4.2.3

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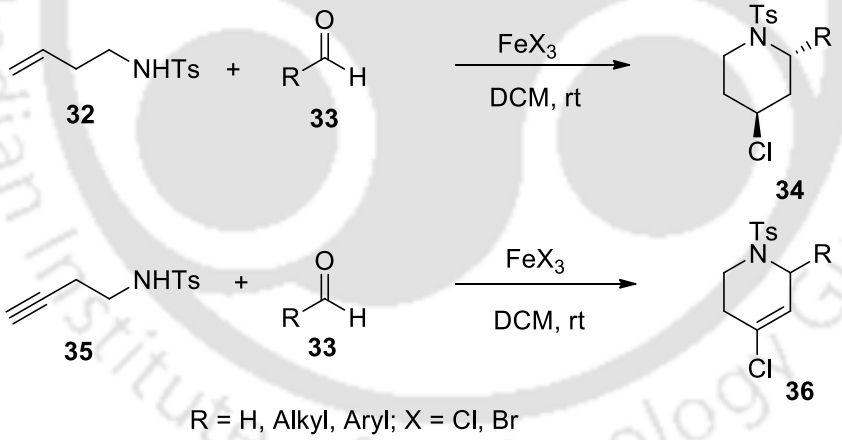
1.4.3. Aza-Prins cyclization reaction

Basically, aza-Prins cyclization is the nitrogen version of Prins cyclization reaction. In aza-Prins cyclization, homoallyl amines are used as the counterpart of homoallyl alcohol in oxa-Prins cyclization, in order to synthesize piperidine rings. The mechanism of aza-Prins cyclization is similar to that of Prins cyclization, whereby the nonbonding electrons on the nitrogen attacks the electrophilic site of the aldehyde in presence of acid to form an iminium ion, in analogy to the oxonium ion. Compared to oxa-Prins cyclization, examples of aza-Prins cyclization using iminium ions leading to nitrogen-containing heterocycles have been less developed due to less electrophilic nature of iminium ions compared to oxocarbenium ions.

In 2006, Padrón and co-workers have reported the synthesis of halogenated six-membered azacycles *via* an iron(III) halide-promoted aza-Prins cyclization between *γ,δ*-unsaturated tosylamides and aldehydes **33**. The reaction of homoallyl tosylamides **32** and homopropargyl tosylamides **35** provides *trans*-2-alkyl-4-halo-1-tosylpiperidine **34** and 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines **36**, respectively in good yields (*Scheme 1.4.3.1).* [27]



Scheme 1.4.3.1

Dobbs *et al*. have developed a methodology for the synthesis of disubstituted tetrahydropyridines **39** *via* indium trichloride ($InCl_3$) mediated silyl-aza-Prins cyclization between 4-trimethylsilyl-3-butenyl-1-amines **37** with aldehydes **38** in good yields (*Scheme 1.4.3.2).*[28] The reaction demonstrates exclusive *trans*-selectivity between the two substituents at the C-2 and C-6 positions.

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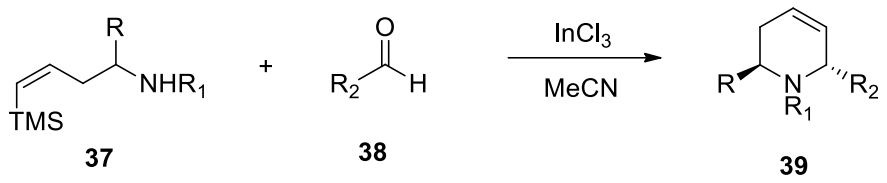
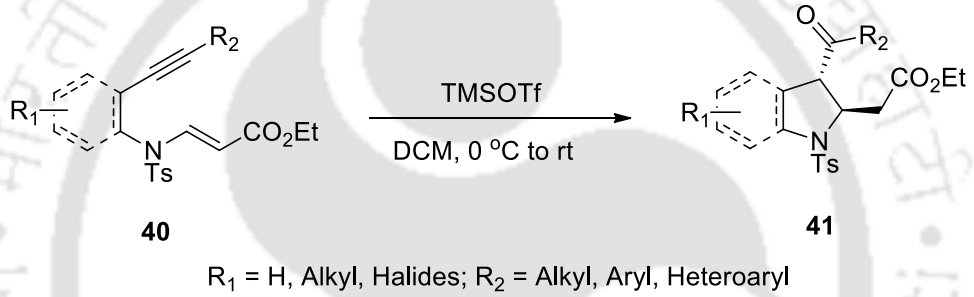


R = H, Me; R_1 = Alkyl, Aryl, CBz; R_2 = Alkyl, Aryl

Scheme 1.4.3.2

Gharpure and co-workers have devised a general strategy for the stereoselective synthesis of *trans*-2,3-disubstituted indolines and pyrrolidine derivatives **41** *via* trimethylsilyl trifluoromethanesulfonate (TMSOTf) mediated intramolecular, alkyne iminium ion cyclization of vinylogous carbamates **40** (*Scheme 1.4.3.3).*[29] The method is highly diastereoselective with dr ≥ 19:1.



R_1 = H, Alkyl, Halides; R_2 = Alkyl, Aryl, Heteroaryl

Scheme 1.4.3.3

Yadav and co-workers demonstrated a Brønsted acid catalyzed intramolecular aza-Prins cyclization for the synthesis of fused aza-bicyclic systems.[30] Reaction of styrene oxide **42** with (*E*)-hex-3-ene-1,6-ditosylamide **43a** in the presence of *p*-TSA catalyst (10 mol %) in 1,2-dichloroethane at 75 °C afforded the corresponding 1,5-ditosyl-octahydro-1*H*-pyrrolidino[3,2-*c*]pyridines **44a** in good yields with high *trans*-selectivity at ring junction, whereas the reaction of (*Z*)-hex-3-ene-1,6-ditosylamide **43b** afforded *cis*-fused octahydro-1*H*-pyrrolidino[3,2-*c*]pyridines **44b** predominantly (*Scheme 1.4.3.4).*

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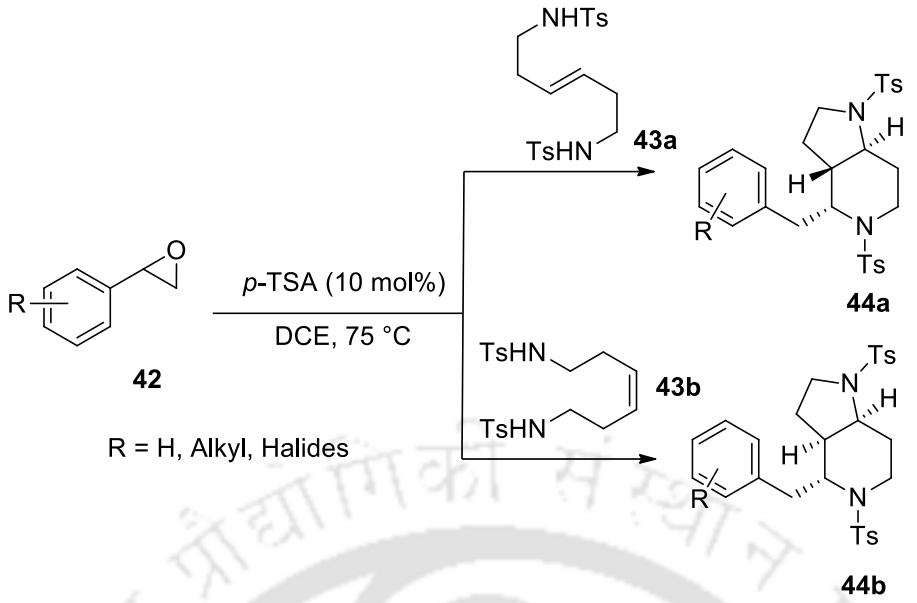
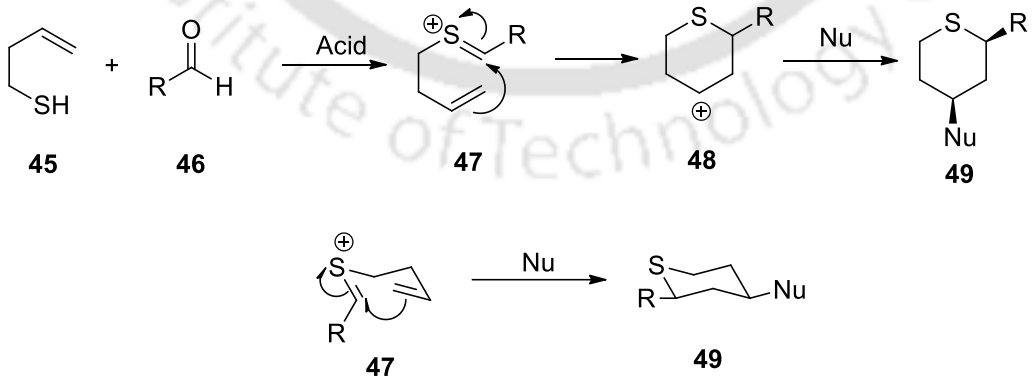


Scheme 1.4.3.4

1.4.4. 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 **47** by the reaction of homoallylic thiol **45** and aldehyde **46**, in presence of acid.



Scheme 1.4.4.1

This thiocarbenium ion **47** undergoes 6-endo cyclization with an internal olefin resulting in the formation of secondary carbocation **48** that can be trapped by various nucleophiles

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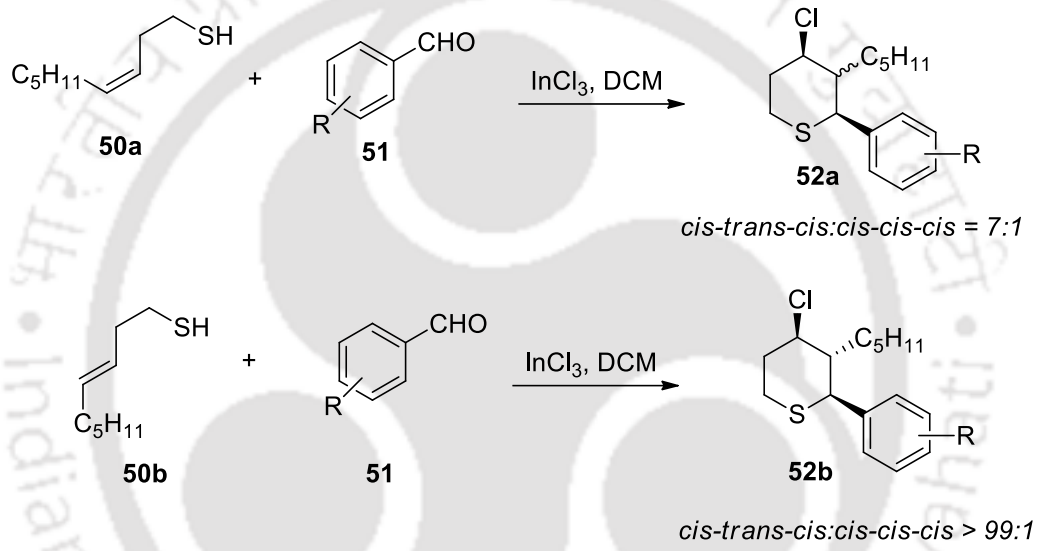
from equatorial position to form the 2,4-*cis*-tetrahydrothiopyran derivatives **49** as shown in *Scheme 1.4.4.1*.

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 **50** and aldehydes **51** in presence of indium trichloride ($InCl_3$) under mild condition.[31] The coupling of *cis*-mercaptan **50a** with aldehydes **51** gave rise to a mixture of *cis-cis-cis* and *cis-trans-cis* tetrahydrothiopyran derivatives **52a** with the latter as a predominant product, whereas the reaction of the *trans*-mercaptan **50b** produced the *cis-trans-cis* tetrahydrothiopyran derivative **52b** exclusively (*Scheme 1.4.4.2*).



Scheme 1.4.4.2

Yadav *et al.* have developed an intramolecular tandem thia-Prins/Friedel-Crafts process, using (*E/Z*)-6-arylhex-3-enyl thiols **53**, aldehydes **54** in the presence of 10 mol % $Sc(OTf)_3$ to afford the *trans*/*cis* fused-hexahydro-1*H*-benzo[*f*]isothiochromenes **55** with excellent diastereoselectivity (*Scheme 1.4.4.3*).[32] Coupling of (*E*)-6-arylhex-3-enyl thiols **53a** produced the *trans* fused isothiochromenes **55a**, whereas (*Z*)-6-arylhex-3-enyl thiols **53b** afforded the *cis* fused products **55b**.

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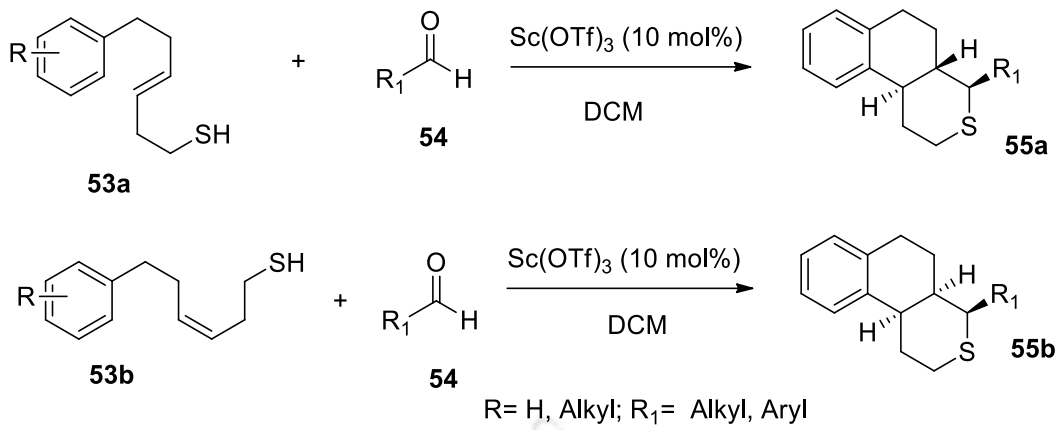
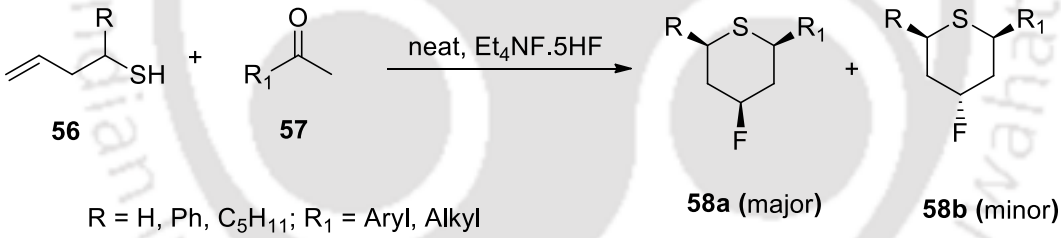


Scheme 1.4.4.3

Kishi *et al*. have investigated the thia-Prins cyclization of homoallylic thiols **56** with various aldehydes **57** in ionic liquid hydrogen fluoride salts *i.e.* $Et_4NF.5HF$ to synthesize 4-fluoro-tetrahydrothiopyrans **58** with excellent yields.[33] 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 **58a** as the major product (*Scheme 1.4.4.4*).



Scheme 1.4.4.4

In 2013, Yadav and co-workers have reported a tandem thia-Prins bicyclization approach for the stereoselective synthesis of dithia- and azathia-bicycles.[34] Coupling of homoallylic mercaptans such as hex-3-ene-1,6-dithiol and *N*-(6-mercaptohex-3-enyl)-4-methylbenzenesulfonamide **59** with various aldehydes **60** using 10 mol % $InBr_3$ in dichloromethane gave hexahydro-*2H*-thieno[3,2-*c*]thiopyran derivatives and octahydrothiopyrano[4,3-*b*]pyrrole **61** derivatives, respectively, with excellent diastereoselectivity. *Trans*-fused products **61a** were obtained from *E*-homoallylic mercaptans **59a** whereas *Z*-homoallylic mercaptans **59b** afforded *cis*-fused products **61b** (*Scheme 1.4.4.5*).

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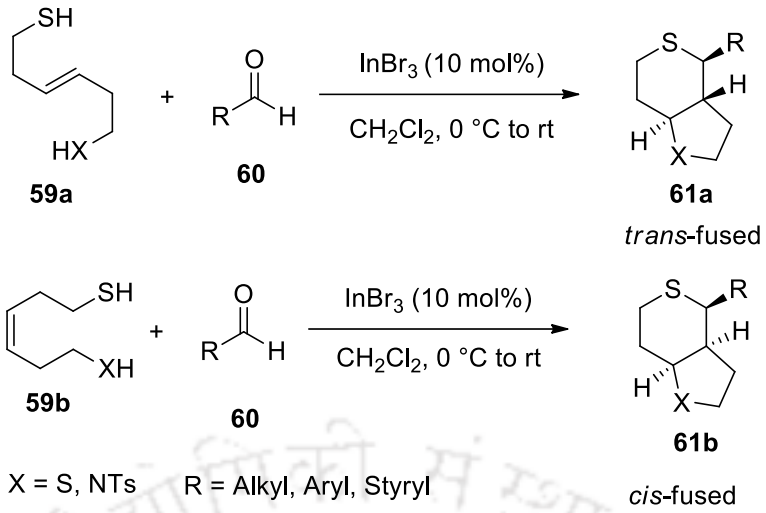

Scheme 1.4.4.5

1.4.5. Nucleophilic substitution of alcohols

Nucleophilic substitution of alcohols is a very important process in organic chemistry, used widely to convert readily accessible alcohols into a variety of functionalized derivatives. Direct nucleophilic substitutions of alcohols are an atom-efficient and environmentally greener transformation, as water would be the solely generated by-product in the reaction. However, alcohols are the poor substrate for substitution reactions, as the hydroxyl group is a poor nucleofuge. In order to increase the leaving group ability of the OH group, a pre-activation of alcohols is usually required. Traditionally, the hydroxyl group is converted into better leaving groups such as halides, tosylates etc. prior to the nucleophilic substitution. Another alternate method involves an *in-situ* conversion of the OH group into a better leaving group, *e.g.* as in the Mitsunobu reaction by using triphenylphosphine (PPh_3) and dialkyl azodicarboxylate such as diethyl azodicarboxylate (DEAD). The nucleophile then attacks the activated alcohol to generate the product. However, these methods have various demerits including; the use of stoichiometric and harmful reagents, multistep processes and purification of intermediates, thus increasing the cost and environmental impact of the transformation.

In 2007, the *ACS Green Chemistry Institute Pharmaceutical Roundtable* developed a list of key research areas where it encouraged the integration of green chemistry and green engineering into the pharmaceutical industry. The direct nucleophilic substitution of the hydroxyl groups was considered as the one of the most desired reactions along with other eleven desired research topics for pharmaceutical industries.[35]

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Recently, direct nucleophilic substitution of π-activated alcohols has been achieved by the use of Lewis or Brønsted acids *(Figure 1.4.5.1)*. Typically, π-activated alcohols are organic compounds where the carbon attached to the hydroxyl group is adjacent to a carbon-carbon double/triple bond or aromatic ring (i.e., allylic, benzylic and propargylic alcohols). This unique structural arrangement may activate the hydroxyl group for nucleophilic substitution reactions. The Lewis and Brønsted acid catalyzed/mediated nucleophilic substitution reactions of π-activated alcohols have emerged as one of the most efficient and convenient synthetic strategies for C-C and C-X (X=N, O, S) bond formation.

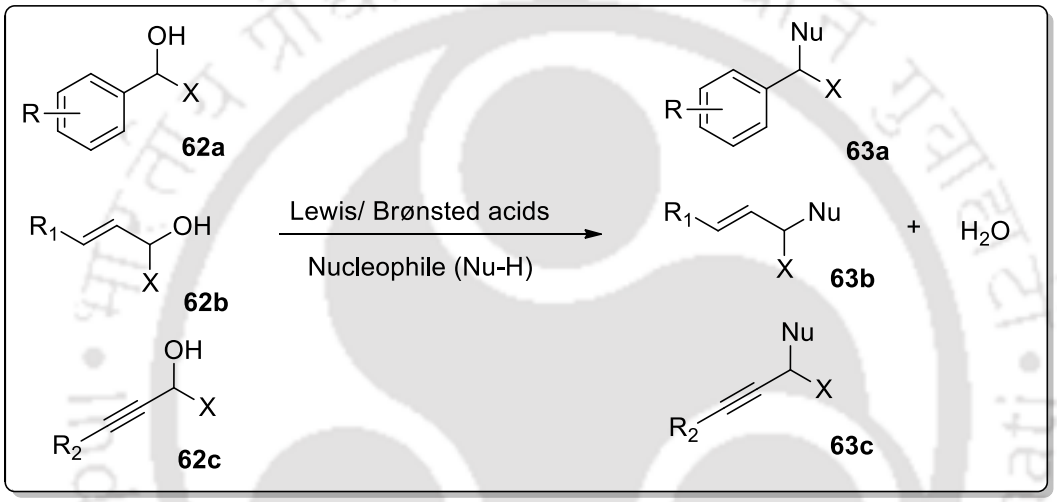
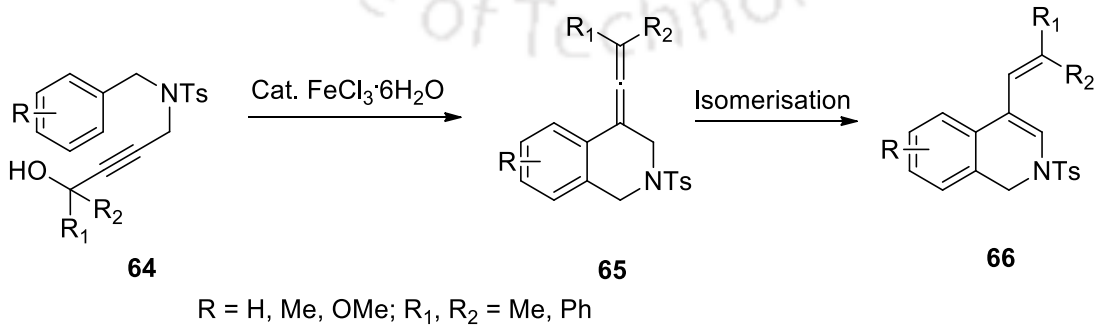


Figure 1.4.5.1. *Graphical representation of nucleophilic substitution of π-alcohols*

Zhou and co-workers reported an efficient $FeCl_3 \cdot 6H_2O$-catalyzed methodology for the synthesis of substituted dihydro- and tetrahydro-isoquinolines **65**, **66** from benzylamino-substituted propargylic alcohols **64** (*Scheme 1.4.5.1*).[36]



Scheme 1.4.5.1

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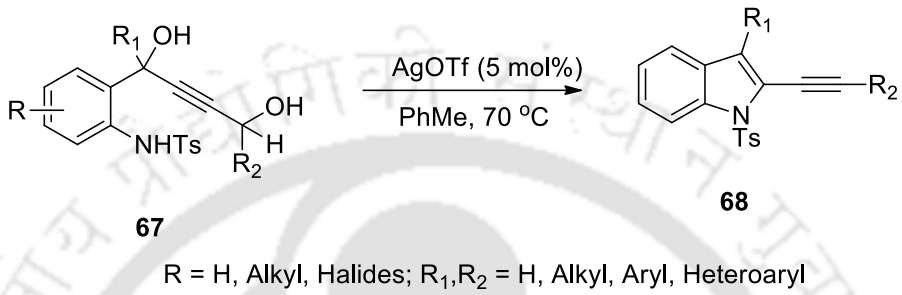
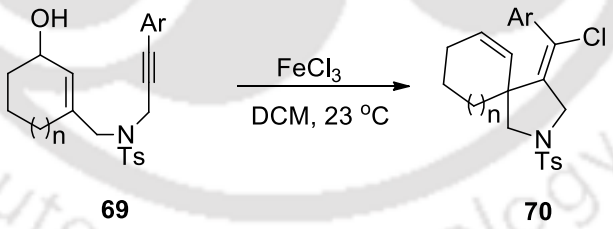
In the process, propargylic alcohols act as an electrophilic alkyl equivalent for the intramolecular Friedel-Crafts reaction.

Very recently, an Ag(I)-catalysed C-OH bond activation of 1,4-propargylic diols was demonstrated by Chan *et al*.[37] Intramolecular tandem heterocyclization/alkynylation of 1,4-propargylic diols **67** in presence of 5 mol % AgOTf afforded 2-alkynyl indoles **68** in good yields and in chemoselective fashion (*Scheme 1.4.5.2*).



Scheme 1.4.5.2

In 2012, Yeh *et al*. have described a mild and efficient $FeCl_3$-mediated synthesis of aza-spiro[4.5] bicycles **70** from cyclic *N*-tethered enynols **69** (*Scheme 1.4.5.3*).[38] In this reaction, $FeCl_3$ reacts as both the Lewis acid and the chloride nucleophile for cyclization/chlorination reaction. The method is highly diastereoselective and gives only (*Z*)-4-(arylchloromethylene)-substituted azaspirocycles in good to excellent yields.



Scheme 1.4.5.3

Chan and co-workers developed an efficient synthetic route towards the synthesis of 1,2-dihydroquinolines **72** *via* $AuCl_3/AgSbF_6$-catalyzed intramolecular allylic amination of 2-tosylaminophenylprop-1-en-3-ols **71** under mild conditions (*Scheme 1.4.5.4*).[39] The synthetic utility of the strategy was further extended towards the synthesis of natural product (±)-angustureine (**73**). Angustureine is a tetrahydroquinoline alkaloid isolated from the bark of the Venezuelan shrubby tree *Galipea officinalis* Hancock, which is

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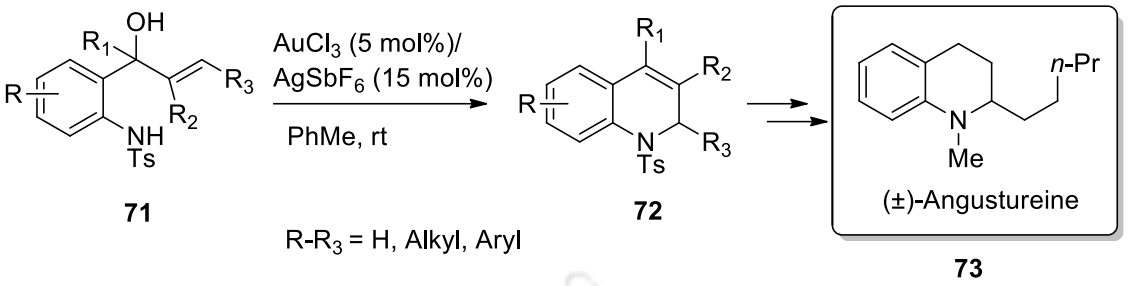
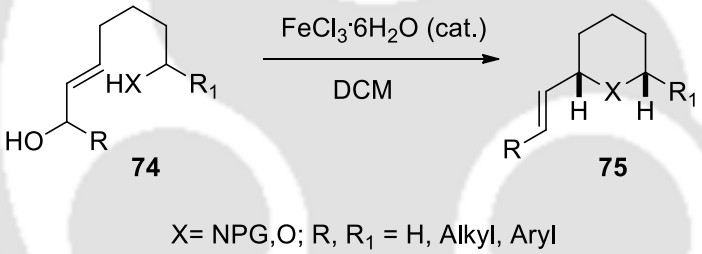
reported to exhibit antimalarial activity on *Plasmodium falciparum* and cytotoxic properties on the human cell lines.[40]



Scheme 1.4.5.4

Guérinot *et al*. have described a highly stereoselective method for the synthesis of substituted 2,6- piperidines and 2,6-tetrahydropyrans **75** *via* $FeCl_3{\cdot}6H_2O$-catalysed cyclization of *ζ*-amino and *ζ*-hydroxy allylic alcohol derivatives **74** (*Scheme 1.4.5.5*).[41] The method is highly diastereoselective with the exclusive formation of *cis*-isomers.



Scheme 1.4.5.5

1.4.6. Pd(II)-catalysed nucleophilic substitution of allylic alcohols

Palladium-catalyzed nucleophilic allylic substitution, also known as the "Tsuji-Trost reaction" is a most versatile and powerful tool in organic synthesis for carbon-carbon and carbon-heteroatom bond formation, with high chemo-, regio-, and stereo-selectivities (*Scheme 1.4.6.1*). This work was first demonstrated by Jiro Tsuji in 1965[42] and subsequently modified by Trost and co-workers in 1973,[43] hence the name "Tsuji-Trost reaction". Traditionally, Tsuji-Trost reactions utilize a pre-activated allylic substrate by transforming the alcohol moiety into a better leaving group such as halide, acetate, carbonate etc. However, all these approaches lead to the formation of substantial amounts of waste by-products, and thus lower the atom economy and increase the environmental factor, which can be avoided by the direct catalytic activation of the

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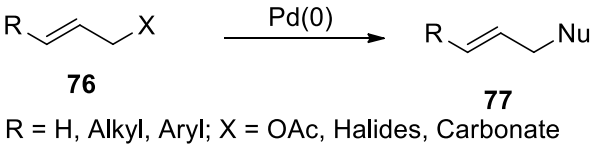
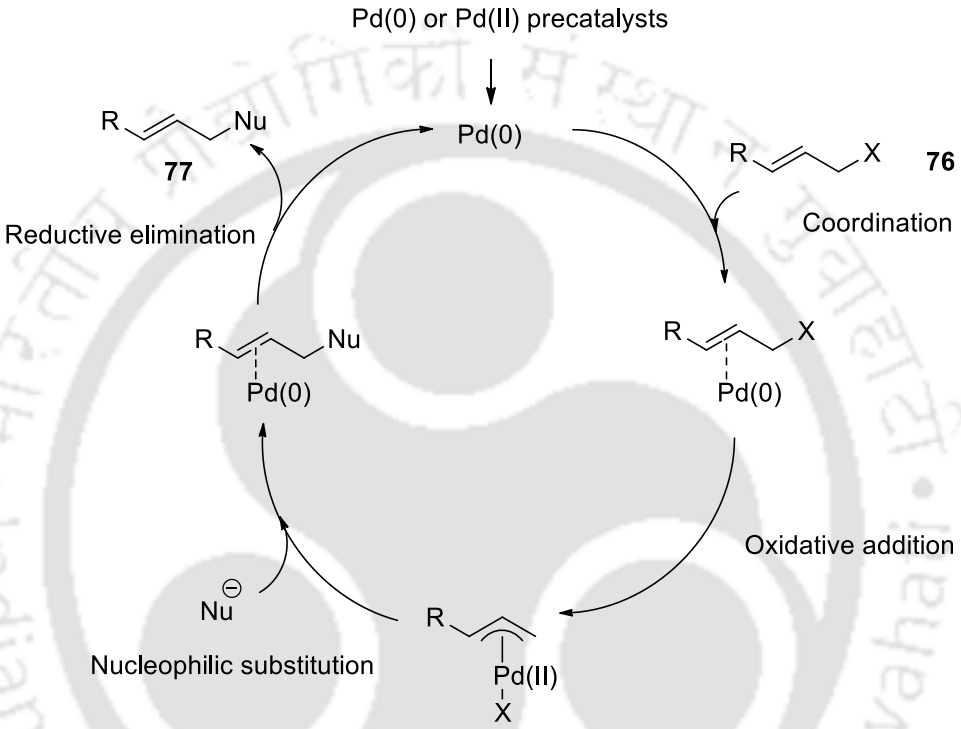
allylic alcohol. Over the last two decades, different investigators have extensively studied the Pd(II) catalysed direct nucleophilic substitution reactions of allylic alcohols and successfully utilized this route for the synthesis of natural products.





Scheme 1.4.6.1

Uenishi *et al*. have described a stereospecific synthesis of 2,6-disubstituted tetrahydropyran **79** and 3,6-dihydro[2*H*]pyran **81** *via* Pd(II)-catalyzed cyclization of the *ζ*-hydroxy-*δ*,*ε*-unsaturated **78** and *β*-hydroxy-*γ*,*δ*-unsaturated alcohols **80** (*Scheme 1.4.6.2*).[44] The important aspect of the method is the stereospecific transfer of chirality of the carbon center of the chiral allylic alcohol to a newly generated stereogenic center on pyran ring *via syn*-S_N2' type process.

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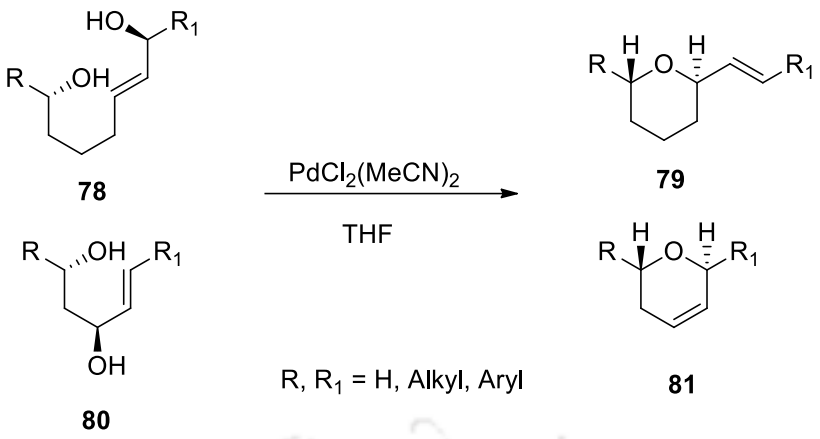
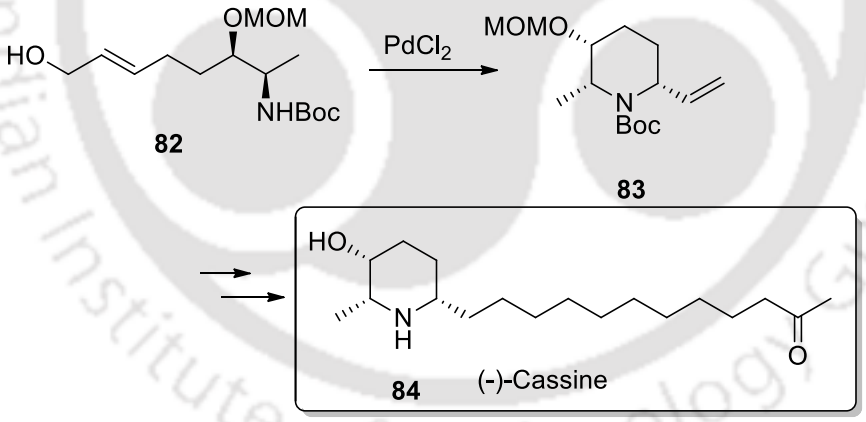


Scheme 1.4.6.2

An instructive example of the intramolecular Tsuji-Trost reaction of allylic alcohols can be found in the total synthesis of (-)-cassine (**84**) by Hirota and co-workers.[45] (-)-Cassine is a piperidine alkaloid isolated from the leaves and twigs of *Cassia excels*, which exhibits antimicrobial activity against *Staphylococcus aureus*.[46] The key step of the synthesis is the diastereoselective Pd(II)-catalyzed cyclization of allyl alcohol **82** to give the *cis*-2,6-piperidine derivative **83** (*Scheme 1.4.6.3*).



Scheme 1.4.6.3

1.5. References:

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CHAPTER 2

Diastereoselective Synthesis of Substituted Tetrahydro-thiophenes and -thiopyrans *via* Thia-Prins Cyclization Reaction

2.1. Importance and applications

Tetrahydro-thiophenes and -thiopyrans are important structural motifs that are frequently encountered in many natural products and biologically active molecules. For example, breynin A (**1**), which contains a tetrahydrothiophene moiety shows remarkable hypocholesterolemic activity in rats.[1] It was isolated by Kawaguchi in 1976 from the plant *Breynia officinalis* Hemsl growing in Taiwan. Salacinol (**2**), a natural product isolated from the herb *Salacia reticulate* WIGHT used in Indian traditional medicine for diabetes, is a potent natural α-glucosidase inhibitor (*Figure 2.1.1*).[2] Apart from these, tetrahydrothiophenes also act as antioxidative agents,[3] hypercholesterolemic agents,[4] and plant growth regulators.[5] Moreover, they are also used as ligands in catalysis[6] and substrates for carbon-carbon bond forming reactions.[7]

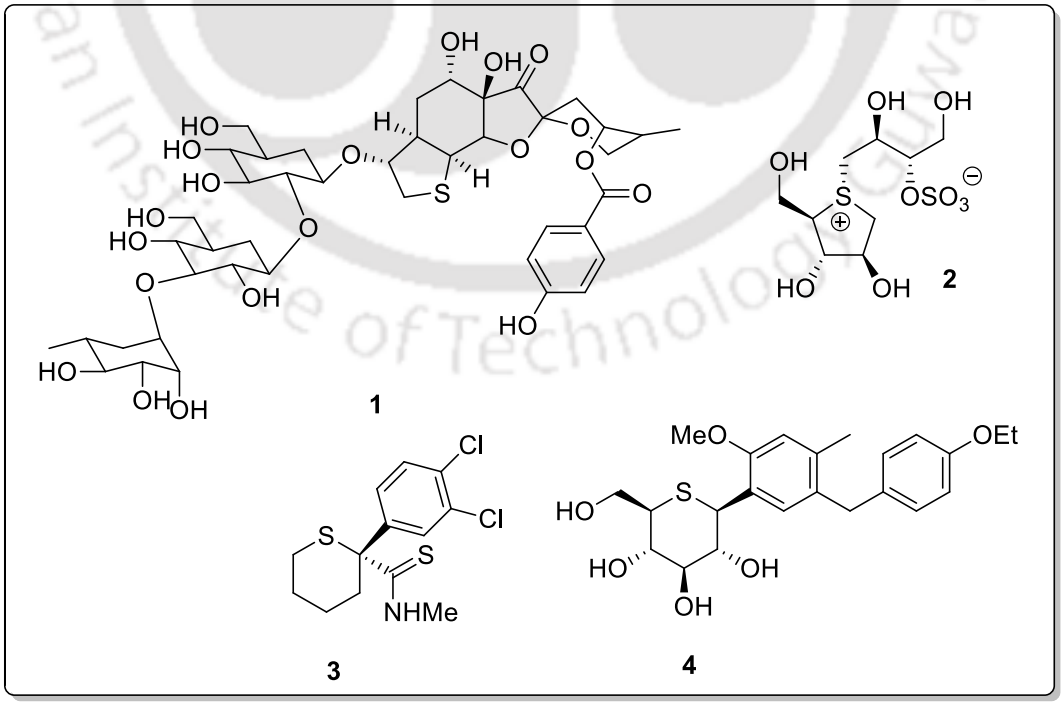

Figure 2.1.1. *Bioactive molecules containing tetrahydro- thiophenes and - thiopyrans*

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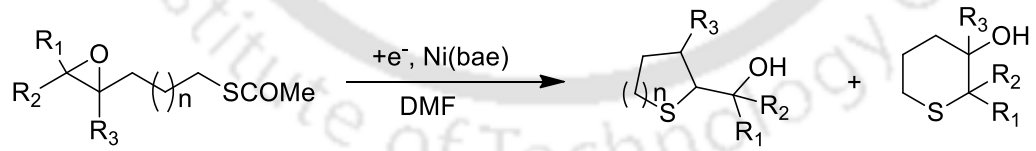
Similarly, tetrahydrothiopyrans are abundant in promising pharmaceuticals such as antihypertensive **3** and antidiabetes **4** agents (*Figure 2.1.1*).[8] Some tetrahydrothiopyran derivatives are found in petroleum oil.[9] In addition to these, the tetrahydrothiopyrans can be transformed into a variety of structures through simple reactions such as hydrogenolysis, oxidation, and olefination.[10]

2.2. An overview of relevant synthetic methods

There are numerous methods for the synthesis of five- and six-membered sulfur heterocycles namely intramolecular ring opening of epoxides by thiolates,[11] double conjugate addition of sulphide into divinyl ketone,[12] hydrothiolation of nonactivated olefins,[13] Pummerer rearrangement,[14] *via* (3,5)-thionium-ene cyclization reaction,[15] Michael/Aldol reaction,[16] trapping of thiocarbonyl ylides with suitable dipolarophiles,[17] photolysis of diazo compounds,[18] sulfonium ylides,[19] *via* oxidative carbon-hydrogen bond functionalization[20] and Baylis-Hillman reaction.[21] Some of the recent methodologies for synthesizing tetrahydro-thiophene and -thiopyrans derivatives are discussed below.

Kitagawa and co-workers reported the synthesis of tetrahydro-thiophene and -thiopyrans by intramolecular ring opening reactions of epoxides by the thiolate which was generated by the selective catalytic electro-reduction of the thioacetate groups by use of the nickel complex (*Scheme 2.2.1*). The formation of *exo*-cyclized product **6** and *endo*-cyclized product **7** depends on the substituents on the epoxide group **5**.[11]



5 **6** **7**

R_1 = H, Me, Ph; R_2 = H, Ph; R_3 = H, Ph; n = 1,2

Scheme 2.2.1

In 2012, Floreancig and his group demonstrated the formation of stabilized *α,β*-unsaturated thiocarbenium ion through the oxidation of unsaturated sulfides **8** with DDQ. The oxidatively generated electrophiles react with *π*-nucleophiles to form

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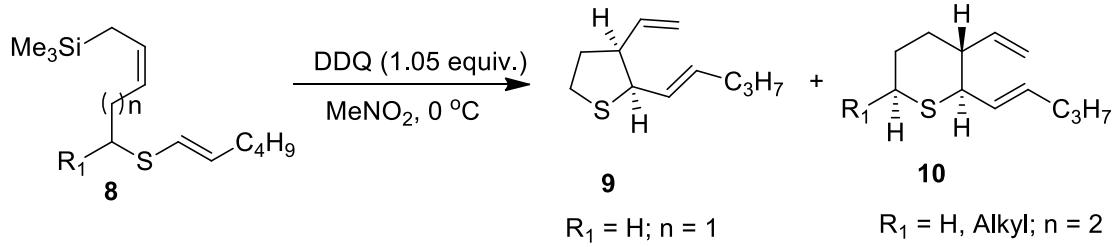
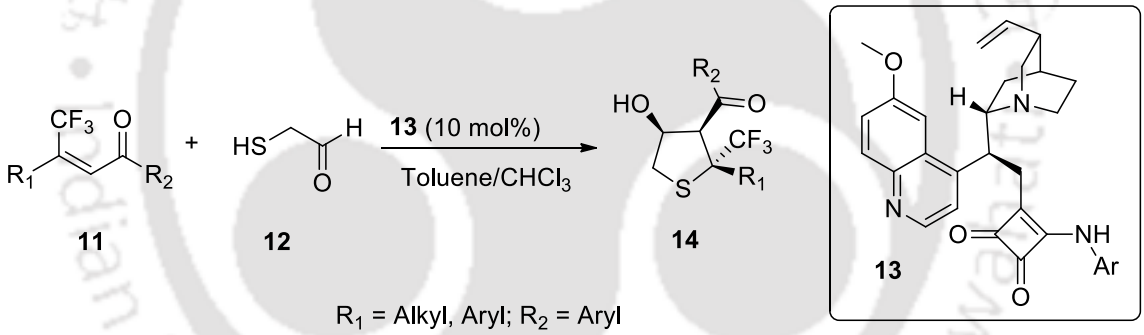
tetrahydrothiophenes **9** and tetrahydrothiopyrans **10** (*Scheme 2.2.2*). Several nucleophiles are compatible with the procedure such as enol acetate, enol carbamate and enol silane.[20]



Scheme 2.2.2

Xu and co-workers demonstrated a method for enantioselective synthesis of tetrahydrothiophenes with a trifluoromethylated quaternary center **14** from *β*-aryl-*β*-trifluoromethylated enones **11** and mercaptoacetaldehyde **12** *via* organocatalyzed (bifunctional squaramides **13**) tandem sulfa-Michael/aldol reaction in good yields with excellent enantioselectivities (*Scheme 2.2.3*).[16e]



Scheme 2.2.3

Recently, Wang and co-workers devised an intermolecular DABCO catalyzed domino Michael/aldol reaction of 1,4-dithiane-2,5-diol **15** with maleimides **16** to afford highly functionalized bicyclic compounds **17** containing tetrahydrothiophene and pyrrolidine backbones in excellent yields and diastereoselectivity (*Scheme 2.2.4).* The reaction involves intermolecular sulfa-Michael addition of mercaptoacetaldehyde to maleimide, followed by intramolecular aldol reaction of in situ formed enolate to the aldehyde moiety.[16f]

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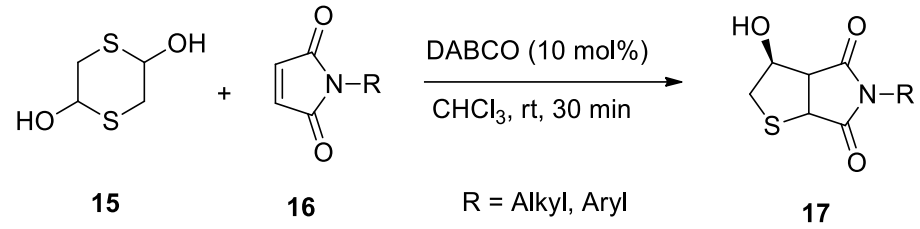
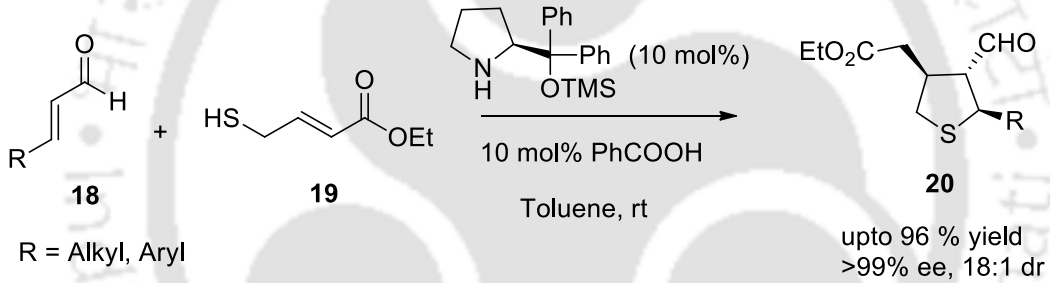


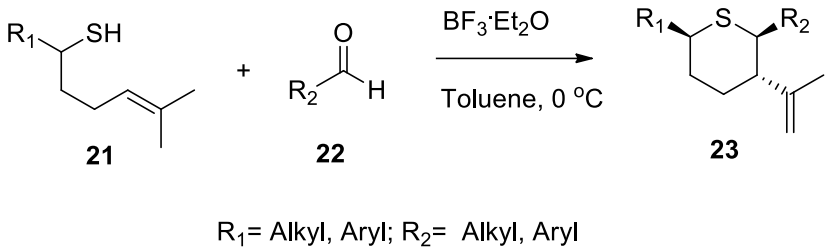
Scheme 2.2.4

Wang *et al*. have developed an organocatalytic method for the synthesis of tetrahydrothiophenes **20** *via* domino thia-Michael/Michael addition reaction between *α,β*-unsaturated aldehydes **18** and *trans*-ethyl 4-mercapto-2-butenoate **19** (*Scheme 2.2.5*). The process, efficiently catalyzed by readily available (*S*)-diphenylprolinol TMS ether, furnishes highly functionalized tetrahydrothiophenes with excellent enantioselectivity (94-99% ee) and good dr (6:1 to 18:1).[22]



Scheme 2.2.5

Saikia *et al.* has reported a stereoselective synthesis of substituted tetrahydrothiopyrans **23** from substituted 5-methylhex-4-ene-1-thiol **21** and aldehydes **22** *via* (3,5)-thionium-ene cyclization reaction mediated by boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) in good yields and with excellent diastereoselectivity (*Scheme 2.2.6*).[15]



Scheme 2.2.6

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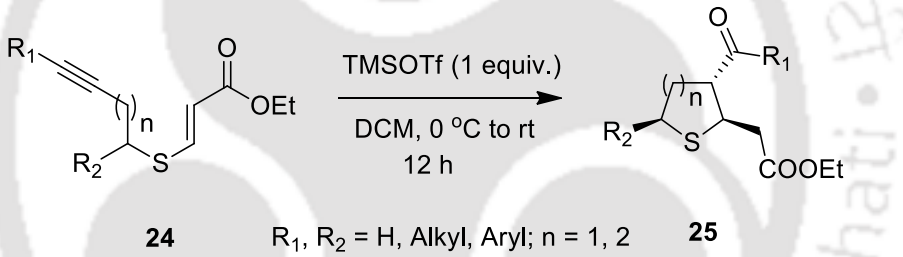
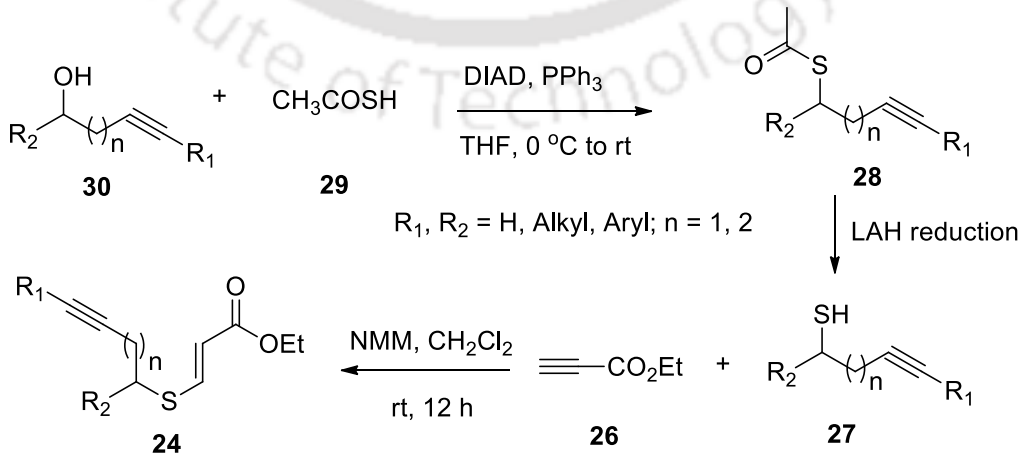
2.3. Present strategy and objective

Prins cyclization is an important reaction in organic synthesis particularly for the synthesis of cyclic five[23] and six[24] membered oxygen heterocycles. Although the Prins cyclization is familiar in organic synthesis, its analogue thia-Prins cyclization is less familiar. Analogues to Prins cyclization reaction thia-Prins cyclization leads to five- and six-membered tetrahydrothiophenes and tetrahydrothiopyrans.[25] Recently, Saikia and co-workers developed a methodology for the synthesis of tetrahydrofuran derivatives by employing intramolecular Prins cyclization of acrylyl enol ethers, in which alkyne acts as a nucleophile.[23d] In line with the previous work from our research group, we now present an efficient method for the synthesis of tetrahydro-thiophenes and -thiopyrans from thioacrylates *via* intramolecular thia-Prins cyclization. Thus, the reaction of thioacrylate **24** in dichloromethane mediated by trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave tetrahydro-thiophenes and -thiopyrans **25** in good yields (*Scheme 2.3.1*).



Scheme 2.3.1

The thioacrylates **24** were synthesized from thiols **27** and ethyl propiolate **26** *via* michael reaction in presence of *N*-methyl morpholine (NMM) in dichloromethane.



Scheme 2.3.2

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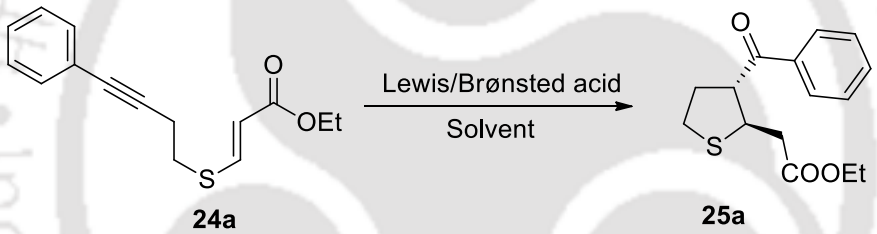
The yields were up to 95%. The thiols **27** were synthesized from alcohols **30** *via* mitsunobu reaction with thioacetic acid **29** in presence of triphenyl phosphine and diisopropyl azodicarboxylate (DIAD), followed by reduction of resulted thioester **28** with lithium aluminium hydride (*Scheme 2.3.2*).

2.4. Results and discussion

2.4.1. Optimization studies

To start with, the (*E*)-ethyl 3-((4-phenylbut-3-yn-1-yl)thio)acrylate **24a** was treated with one equivalent of indium(III) triflate in dichloromethane initially at 0 °C and then at room temperature for 24 h, but the reaction gave tetrahydrothiophene **25a** in 25% yield (Table 2.4.1.1, entry 1).

Table 2.4.1.1. Optimization of the reaction



24a **25a**

Entry	Lewis/Brønsted acid (equiv.)	Time (h)	Solvent	Temp. (°C)	%Yield[a]
1	$In(OTf)_3$ (1.0)	24	CH_2Cl_2	0 °C to rt	25
2	$In(OTf)_3$ (1.0)	24	CH_2Cl_2	rt	27
3	**TMSOTf (1.0)**	**12**	**CH_2Cl_2**	**0 °C to rt**	**77**
4	TMSOTf (1.0)	12	CH_2Cl_2	rt	42
5	TMSOTf (1.0)	12	CH_3CN	0 °C to rt	52
6	$BF_3{\cdot}Et_2O$ (1.0)	12	CH_2Cl_2	0 °C to rt	32
7	$FeCl_3$ (1.0)	24	CH_2Cl_2	0 °C to rt	trace
8	$Zn(OTf)_2$ (1.0)	24	CH_2Cl_2	0 °C to rt	trace
9	$Cu(OTf)_2$ (1.0)	24	CH_2Cl_2	0 °C to rt	22
10	TfOH (1.0)	12	CH_2Cl_2	0 °C to rt	--[d]
11	CSA (1.0)	24	CH_2Cl_2	0 °C to rt	10

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

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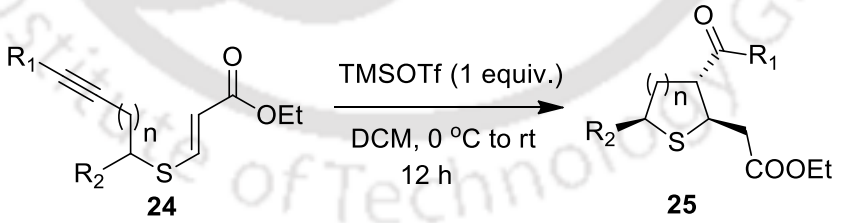
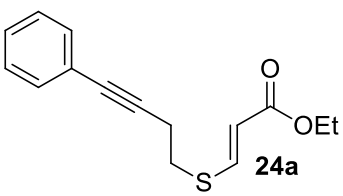
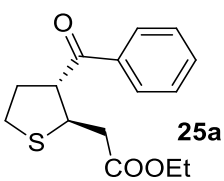
The structure of the compound was determined by NMR analysis and and mass spectrometry. The same reaction at room temperature also resulted in the same yield (entry 2). In order to optimize the reaction conditions, the thioacrylate **24a** was treated with various Lewis and Brønsted acids as summarized in Table 2.4.1.1. It was observed that reaction with trimethylsilyl trifluoromethanesulphonate (TMSOTf) in dichloromethane proceeded well to furnish the tetrahydrothiophene derivative **25a** in 77% yield (entry 3). Reaction with $BF_3{\cdot}Et_2O$ (entry 6) gave only 32% yield. On the other hand, metal salt $FeCl_3$ (entry 7) gave only trace amount of the product. Other triflates such as $Cu(OTf)_2$ gave low yields (entry 9) whereas, $Zn(OTf)_2$ yielded only trace amount of the desired product. Brønsted acids TfOH (entry 10) produced decomposed products whereas CSA (entry 11) yielded only 10% of the desired product. When the reaction with TMSOTf (entry 4) was carried out at room temperature it gave only moderate yield, while changing solvent from dichloromethane to acetonitrile (entry 5) yielded only 52% yield. Therefore, strong Lewis acid TMSOTf in dichloromethane at 0 ^oC to room temperature was stands out to be the optimum condition for the reaction.

2.4.2. Substrate scope of the reaction

Having obtained the optimized conditions in hand, we further examined the scope of the reaction with variety of substrates (**24a-24v**), which were synthesized from alkanols as shown in *Scheme 2.3.2*. The results are outlined in the Table 2.4.2.1.

Table 2.4.2.1. TMSOTf mediated intramolecular thia-Prins cyclization reaction



Entry	Thioacrylates **24**	Product **25**	dr[a]	Yield (%)[b]
1	 **24a**	 **25a**	100:0	77

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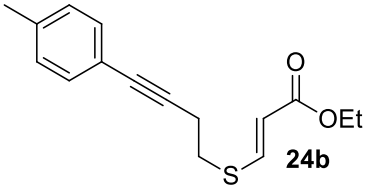
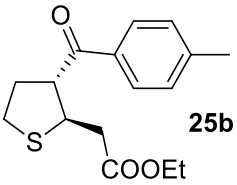
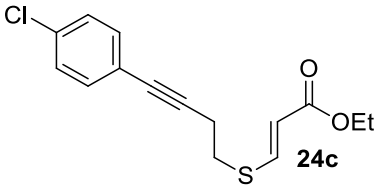
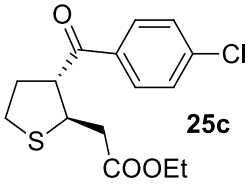
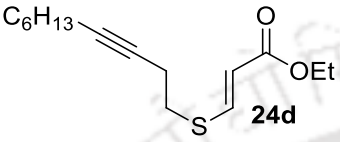
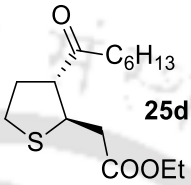
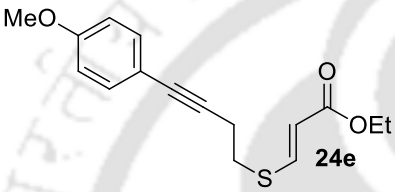
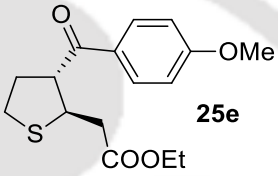
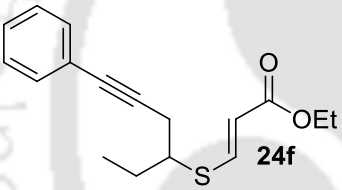
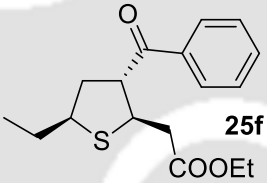
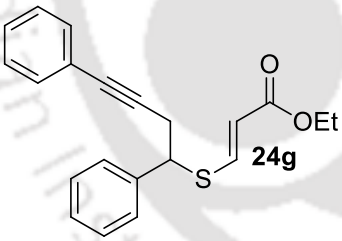
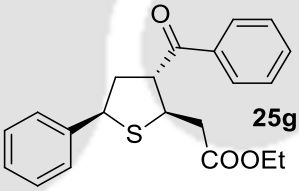
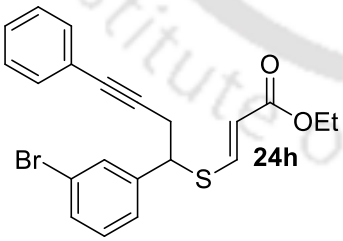
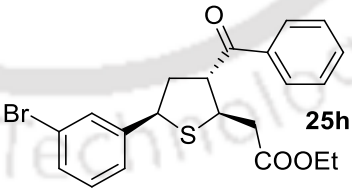
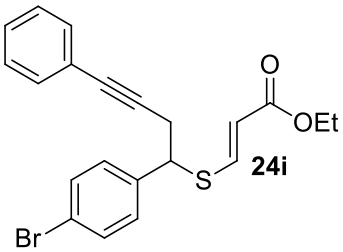
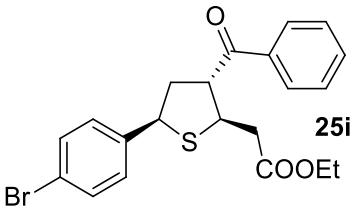
2	 **24b**	 **25b**	100:0	65
3	 **24c**	 **25c**	100:0	72
4	 **24d**	 **25d**	100:0	61
5	 **24e**	 **25e**	----	d[c]
6	 **24f**	 **25f**	100:0	67
7	 **24g**	 **25g**	100:0	76
8	 **24h**	 **25h**	100:0	82
9	 **24i**	 **25i**	100:0	83

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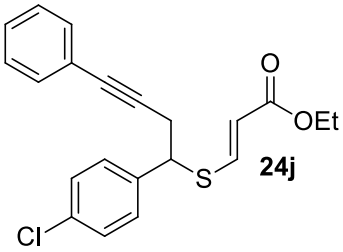
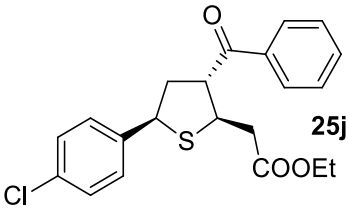
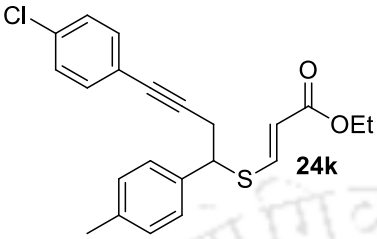
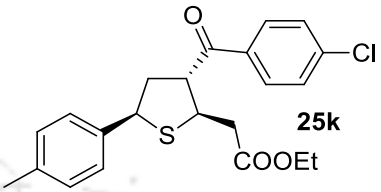
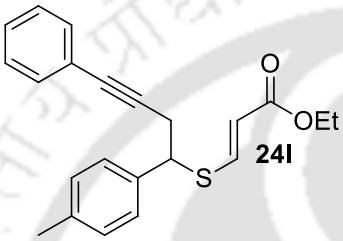
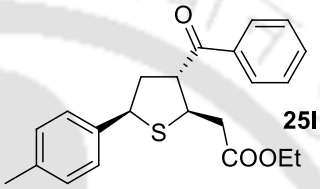
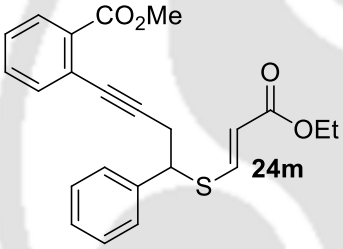
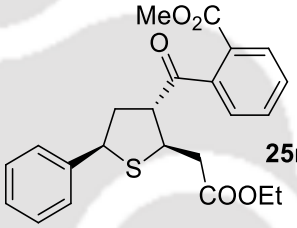
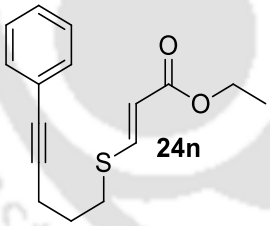
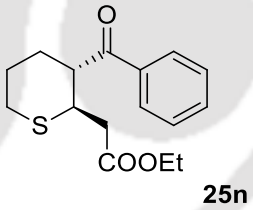
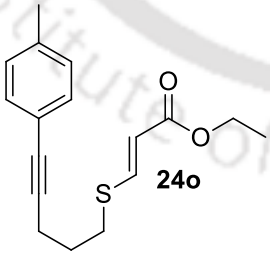
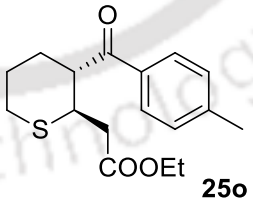
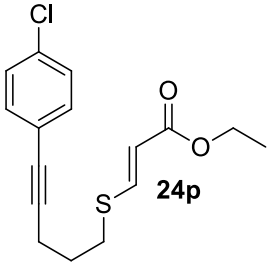
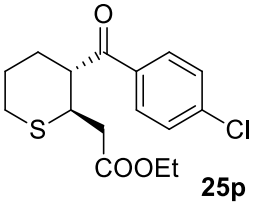
10	 **24j**	 **25j**	100:0	78
11	 **24k**	 **25k**	100:0	65
12	 **24l**	 **25l**	100:0	68
13	 **24m**	 **25m**	----	d
14	 **24n**	 **25n**	91:9	69
15	 **24o**	 **25o**	90:10	68
16	 **24p**	 **25p**	96:4	62

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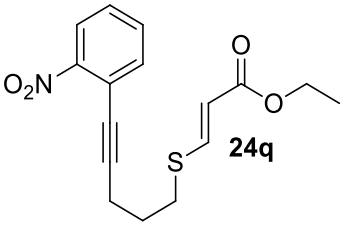
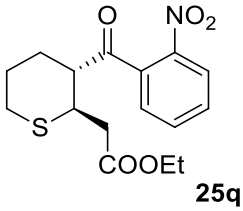
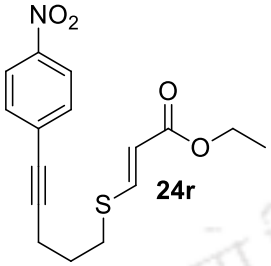
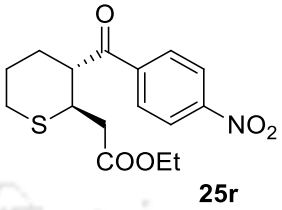
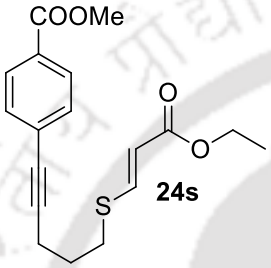
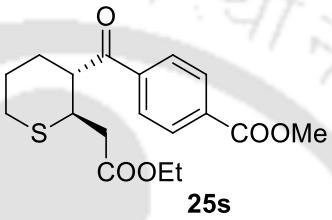
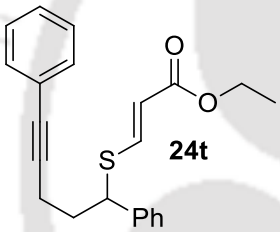
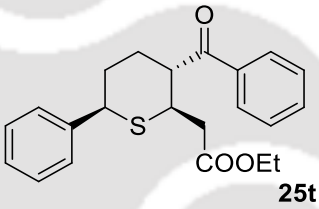
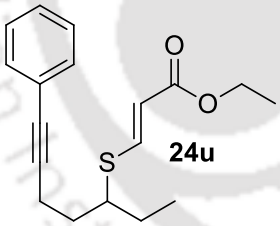
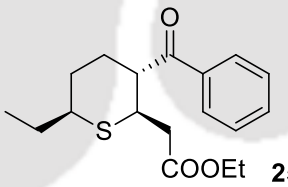
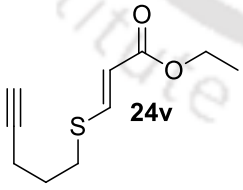
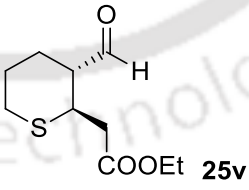
17	 **24q**	 **25q**	----	d
18	 **24r**	 **25r**	100:0	81
19	 **24s**	 **25s**	100:0	86
20	 **24t**	 **25t**	100:0	70
21	 **24u**	 **25u**	100:0	65
22	 **24v**	 **25v**	----	0

[a]The ratio was determined by ^{1}H NMR spectroscopy of crude compounds. [b]Yield refers to isolated yield. The compounds were characterized by IR, NMR and Mass spectrometry. [c]The reaction was also performed at -78 ^{o}C and recovered starting material in 96% yield. d = Decomposed product.

It was observed from the Table 2.4.2.1 that the thioacrylates **24a-d** & **24f-l** (entries 1-4 & 6-13) derived from homopropargyl thiols gave tetrahydrothiophenes as single diastereomers in good yields. On the other hand, homologous thioacrylates derived from

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primary thiols such as **24n-p** yielded a mixture of diastereomers **25n-p** with a ratio ranging from 90:10 to 96:4. The reactions with substrates having electron-withdrawing groups at the *ortho* position of the aromatic ring present in alkyne side chain (entries 13, 17) decompose under these reaction conditions. However, aromatic ring with *para*-substituted electron-withdrawing groups in the alkyne side chain (entries 18, 19) gave the desired 2,3-substituted tetrahydrothiopyrans **25r** and **25s** in 81% and 86% yields, respectively, as single diastereomer. The decomposition of **24m** and **24q** might be due to the steric factor of the *ortho*-substituted aryl ring of the alkyne side chain. Thioacrylates having alkyl and aryl substitutions at α-position **24t-u** produced exclusively single diastereomers **25t-u** in good yields. The presence of strong electron donating group (-OMe) in the aromatic ring of the alkyne side chain (entry 5) resulted in decomposed products under optimized conditions. The reaction at -78 ^{o}C produced neither the desired product nor decomposed product, but starting material was recovered in 96% yield. It was also observed that thioacrylates having alkyl substituted alkyne side chain (entry 4) gave the corresponding tetrahydrothiophene in 61% yield. On the contrary, unsubstituted alkyne **24v** (entry 22) was found to be unreactive under these reaction conditions. This is attributed to the lower stability of the carbocation **B** formed from **24v** (*Scheme 2.4.4.1*).

2.4.3. Stereochemistry of the tetrahydro-thiophenes and -thiopyrans

The reaction is highly diastereoselective and the stereochemistry of the trisubstituted tetrahydrothiophenes was determined by 2-D nuclear Overhauser effect spectroscopy (NOESY) of **25k**.

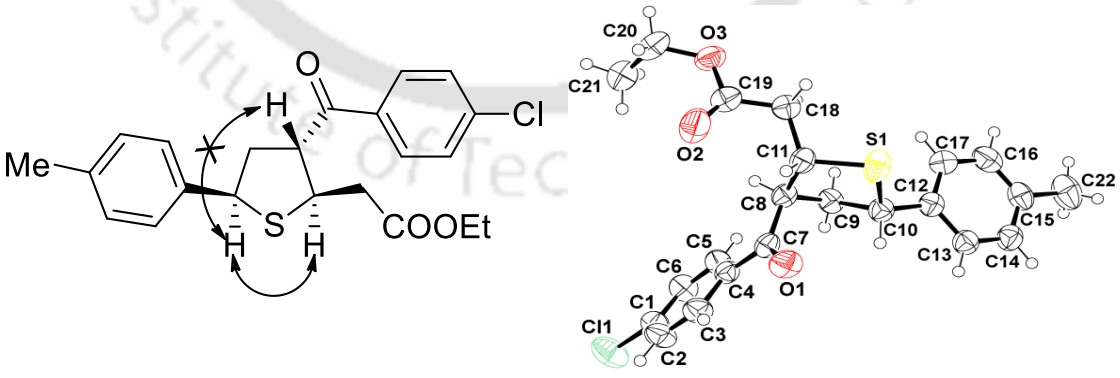

Figure 2.4.3.1. *nOe and ORTEP diagram of* ***25k***

It showed a clear characteristic nOe correlations between the hydrogens C-2H and C-5H and the absence of nOe between C-3H and C-5H, which clearly indicates that the

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substituents at 2,5 positions are *cis* to each other and the benzoyl substituent at C-3 is *trans* to other two substituents. The stereochemistry of the five-membered tetrahydrothiophene products was further confirmed by X-ray crystallographic analysis of **25k** (*Figure 2.4.3.1*).[26] The stereochemistry of 2,3-disubstituted tetrahydrothiopyrans is determined from the vicinal coupling constants of C-2H (J = 13.6, 11.6, and 2.8 Hz) and C-3H (J = 13.6, 9.6, and 4.0 Hz) of compound **25s**. Similarly, the stereochemistry of 2,3,6-trisubstituted tetrahydrothiopyrans was confirmed by NOE spectroscopy of **25t**, which indicates that the substituents at 2,6 positions are *cis* to each other and the benzoyl substituent at C-3 is *trans* to the other two substituents (*Figure 2.4.3.2*).

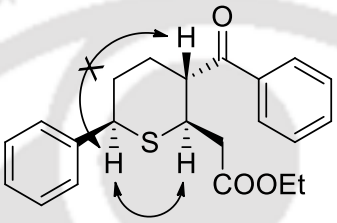
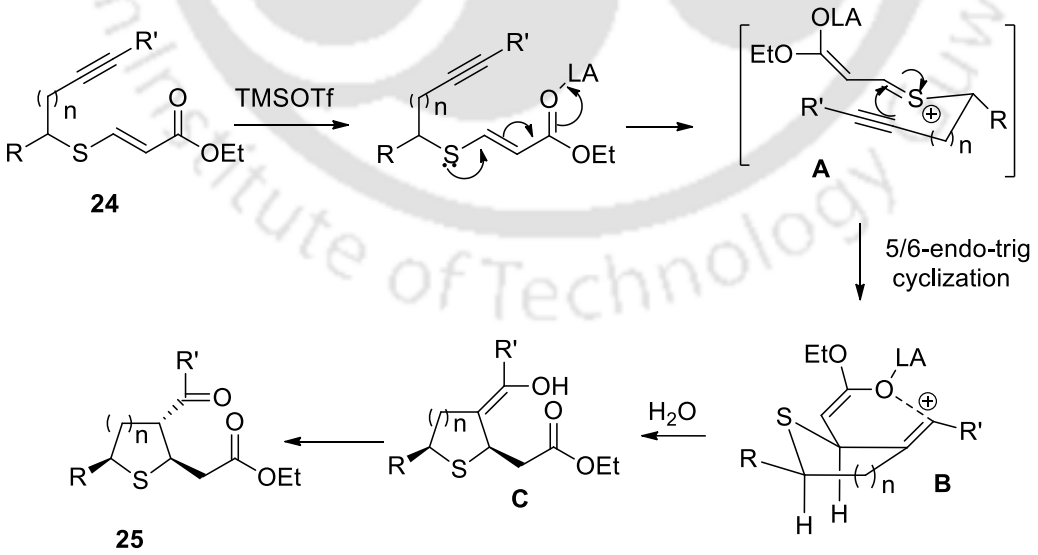


Figure 2.4.3.2. *nOe of* ***25t***

2.4.4. Plausible mechanism for the synthesis of tetrahydro-thiophenes and -thiopyrans

The mechanism of the reaction can be explained as portrayed in *Scheme 2.4.4.1*.



Scheme 2.4.4.1 *Proposed mechanism of the reaction*

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The ester group of thioacrylate **24** is activated by TMSOTf to form thiocarbenium ion **A**, which is then attacked by the alkyne group *via* 5-endo-trig cyclization and 6-endo-trig cyclization to give vinyl carbocation **B**, with a five and six-membered rings (n = 1 and 2), respectively. The formation of five membered rings is against the Baldwin's rule,[27] but in the present situation, the formation of five-membered rings is possible because of proper alignment of the molecular orbitals of the alkyne group with the sp^2-hybridized thiocarbenium ion as described by Baldwin.[28] The intermediate **B** is stabilized by enolate,[23d] which is then trapped by water during the work up of the reaction to give enol **C**, which after tautomerization gives ketone **25**.

2.5. Conclusion:

In conclusion, we have developed a mild, efficient, and general method for the synthesis of di- and tri-substituted tetrahydro-thiophenes and -thiopyrans *via* intramolecular thia-Prins cyclization reaction from thioacrylates in good yields. The method is highly diastereoselective with predominate formation of *cis*-2,5 substituted tetrahydrothiophenes and *cis*-2,6 substituted tetrahydrothiopyrans respectively.

2.6. Experimental section

2.6.1. Instrumentation and characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. The solvents were of commercial grade and purified according to established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm).

Melting points were recorded in open capillary tubes and are uncorrected. Fourier transform-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) 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.

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2.6.2. General procedure for preparation of thioacrylates (24a-24v):

To a solution of thiol **27** (2 mmol) in dichloromethane (5 mL), *N*-methyl morpholine (2 mmol) and ethyl propiolate **26** (2.2 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.

2.6.3. Synthesis of (*E*)-ethyl 3-((4-phenylbut-3-yn-1-yl)thio)acrylate (24a):

To a solution of 4-phenylbut-3-yne-1-thiol (0.324 mg, 2.0 mmol) in dichloromethane (5 mL), *N*-methyl morpholine (0.22 mL, 2 mmol) and ethyl propiolate (0.22 mL, 2.2 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, 9:1) as eluents to give **24a** (484 mg, 93%) as a colourless oil.

2.6.4. General procedure for the synthesis of substituted tetrahydro-thiophenes and -thiopyrans (25a-25v):

To a solution of thioenol ether **24** (1 mmol) in dry dichloromethane (5 mL) at 0 °C was added trimethylsilyl trifluoromethanesulphonate (TMSOTf) (1 mmol) dropwise under a nitrogen atmosphere. The reaction mixture was brought to room temperature, and the reaction was stirred for 12 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

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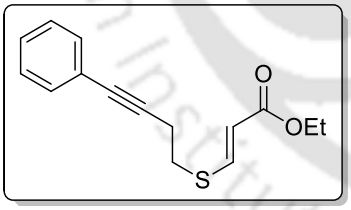
column chromatography using ethyl acetate and hexane as eluents to afford the title compounds.

2.6.5. Synthesis of ethyl 2-((2*R**,3*R**)-3-benzoyltetrahydrothiophen-2-yl)acetate (25a):

To a solution of (*E*)-ethyl 3-((4-phenylbut-3-yn-1-yl)thio)acrylate **24a** (260 mg, 1 mmol) in dry dichloromethane (5 mL) at 0 °C was added trimethylsilyl trifluoromethanesulphonate (TMSOTf) (0.18 ml, 1 mmol) dropwise under a nitrogen atmosphere. The reaction mixture was brought to room temperature, and the reaction was stirred for 12 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 ethyl acetate and hexane as eluents (hexane: EtOAc, 9:1) to give **25a** (214 mg, 77%) as a colourless oil.

2.7. Spectral data

(*E*)-Ethyl 3-((4-phenylbut-3-yn-1-yl)thio)acrylate (24a):



Colourless oil; R_f (hexane/EtOAc 9:1) 0.55; yield 484 mg, 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.2 Hz, 3 H), 2.72 (t, *J* = 7.2 Hz, 2 H), 2.97 (t, *J* = 7.2 Hz, 2 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 5.75 (d, *J* = 15.2 Hz, 1 H), 7.20-7.22 (m, 3 H), 7.32-7.44 (m, 2 H), 7.63 (d, *J* = 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 20.2, 31.3, 60.4, 82.7, 86.9, 114.6, 123.3, 128.2, 128.4, 131.8, 146.1, 165.3. IR (KBr, neat) 2982, 2932, 1712, 1578, 1367, 1170, 1035, 947, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{17}O_2S$ $(M + H)^+$ 261.0944, found 261.0945.

(*E*)-Ethyl 3-((4-(*p*-tolyl)but-3-yn-1-yl)thio)acrylate (24b):

Colourless oil; R_f (hexane/EtOAc 9:1) 0.55; yield 449 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3 H), 2.32 (s, 3 H), 2.77 (t, *J* = 7.2 Hz, 2 H), 3.03 (t, *J* = 7.2 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.81 (d, *J* = 15.2 Hz, 1 H), 7.08 (d, *J* = 7.6 Hz, 2 H),

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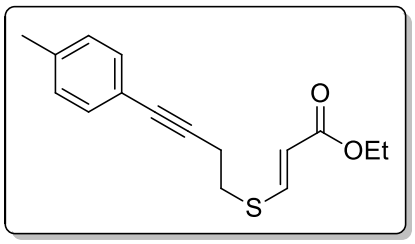
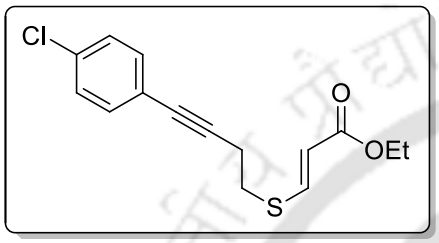


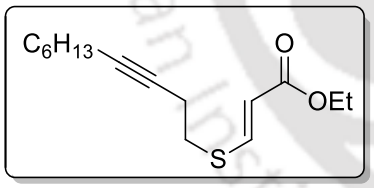
7.29 (d, *J* = 8.0 Hz, 2 H), 7.71 (d, *J* = 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 20.3, 21.6, 31.4, 60.4, 82.7, 86.1, 114.5, 120.2, 129.2, 131.6, 138.2, 146.2, 165.4. IR (KBr, neat) 2980, 2926, 1706, 1581, 1159, 1037, 946, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{19}O_2S$ $(M + H)^+$ 275.1100, found 275.1102.

(*E*)-Ethyl 3-((4-(4-Chlorophenyl)but-3-yn-1-yl)thio)acrylate (24c):



Colourless oil; Rf (hexane/EtOAc 9:1) 0.56; yield 506 mg, 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3 H), 2.79 (t, *J* = 7.2 Hz, 2 H), 3.05 (t, *J* = 7.2 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.82 (d, *J* = 15.2 Hz, 1 H), 7.26 (d, *J* = 8.8 Hz, 2 H), 7.32 (d, *J* = 8.8 Hz, 2 H), 7.71 (d, *J* = 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 20.3, 31.2, 60.5, 81.6, 88.0, 114.6, 121.8, 128.7, 133.0, 134.2, 146.1, 165.3; IR (KBr, neat) 2982, 2927, 1705, 1584, 1484, 1254, 1164, 1039, 828, 702 cm-1; HRMS (ESI) calcd. for $C_{15}H_{16}ClO_2S$ $(M + H)^+$ 295.0554, found 295.0553.

(*E*)-Ethyl 3-((1-phenylnon-3-yn-1-yl)thio)acrylate (24d):



Colourless oil; R_f (hexane/EtOAc 9:1) 0.71; yield 594 mg, 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.29-1.39 (m, 6 H), 1.43-1.51 (m, 2 H), 2.12-2.17 (m, 2 H), 2.50-2.55 (m, 2 H), 2.94 (t, *J* = 7.2 Hz, 2 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 5.78 (d, *J* = 15.2 Hz, 1 H), 7.69 (d, *J* = 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.5, 18.8, 19.5, 22.7, 28.7, 28.9, 31.5, 31.8, 60.3, 76.9, 82.9, 114.3, 146.4, 165.4; IR (KBr, neat) 2928, 2860, 1709, 1583, 1254, 1164, 1040, 831 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{25}O_2S$ $(M + H)^+$ 269.1570, found 269.1566.

(*E*)-Ethyl 3-((4-(4-Methoxyphenyl)but-3-yn-1-yl)thio)acrylate (24e):

Colourless oil; Rf (hexane/EtOAc 9:1) 0.52; yield 412 mg, 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.6 Hz, 3 H), 2.69 (t, *J* = 7.2 Hz, 2 H), 2.96 (t, *J* = 7.2 Hz, 2 H), 3.71 (s, 3 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 5.74 (d, *J* = 15.2 Hz, 1 H), 6.73 (d, *J* = 8.4 Hz, 2

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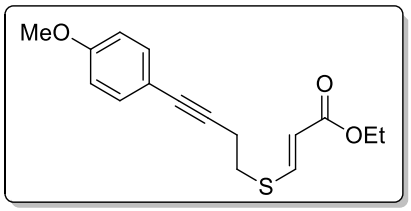
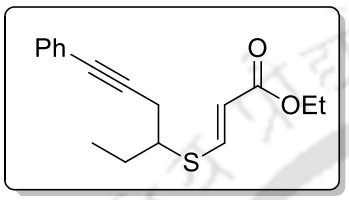


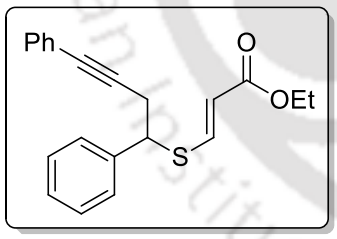
H), 7.26 (d, *J* = 8.8 Hz, 2 H), 7.64 (d, *J* = 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 20.2, 31.4, 55.4, 60.4, 82.4, 85.3, 114.0, 114.4, 115.3, 133.1, 146.2, 159.5, 165.3; IR (KBr, neat) 2931, 2837, 1706, 1582, 1509, 1300, 1247, 1169, 1035, 832 cm^{-1}; HRMS (ESI) calcd. For $C_{16}H_{19}O_3S$ $(M + H)^+$ 291.1049, found 291.1050.

(*E*)-Ethyl 3-((6-phenylhex-5-yn-3-yl)thio)acrylate (24f):



Colourless oil; R_f (hexane/EtOAc 9:1) 0.58; yield 484 mg, 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.72-1.82 (m 1 H), 1.91-2.01 (m, 1 H), 2.80 (dd, *J* = 12.0 and 5.6 Hz, 2 H), 3.19 (p, *J* = 6.0 Hz, 1 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 5.86 (d, *J* = 15.2 Hz, 1 H), 7.27-7.29 (m, 3 H), 7.39-7.42 (m, 2 H), 7.76 (d, *J* = 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 14.5, 26.1, 26.9, 48.2, 60.4, 83.2, 86.2, 114.9, 123.4, 128.1, 128.4, 131.8, 146.4, 165.5; IR (KBr, neat) 2978, 2930, 1715, 1576, 1490, 1301, 1157, 1036, 948, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{21}O_2S$ $(M + H)^+$ 289.1257, found 289.1257

(*E*)-Ethyl 3-((1,4-diphenylbut-3-yn-1-yl)thio)acrylate (24g):



Colourless oil; R_f (hexane/EtOAc 9:1) 0.57; yield 638 mg, 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3 H), 3.07 (dd, *J* = 6.4 and 1.6 Hz, 2 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.44 (t, *J* = 6.8 Hz, 1 H), 5.83 (d, *J* = 15.6 Hz, 1 H), 7.25-7.27 (m, 3 H), 7.29-7.33 (m, 3 H), 7.38 (t, *J* = 7.2 Hz, 2 H), 7.42-7.44 (m, 2 H), 7.64 (d, *J* = 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 28.2, 50.4, 60.5, 83.9, 85.9, 115.6, 123.3, 127.9, 128.2, 128.3, 128.4, 129.1, 131.8, 139.7, 145.5, 165.4; IR (KBr, neat) 2978, 2923, 1705, 1582, 1449, 1256, 1163, 1035, 754 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{21}O_2S$ $(M + H)^+$ 337.1257, found 337.1255.

(*E*)-Ethyl 3-((1-(3-bromophenyl)-4-phenylbut-3-yn-1-yl)thio)acrylate (24h):

Colourless oil; R_f (hexane/EtOAc 9:1) 0.58; yield 662 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3 H), 3.04 (dd, *J* = 6.4 and 5.6 Hz, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 4.38 (t, *J* = 6.8 Hz, 1 H), 5.81 (d, *J* = 15.2 Hz, 1 H), 7.15-7.28 (m, 4 H), 7.33-

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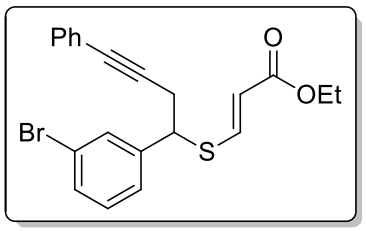
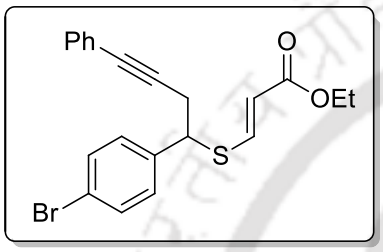


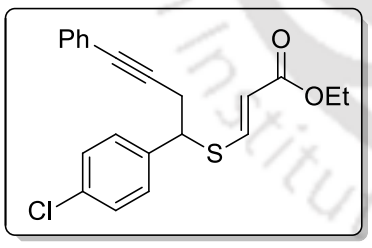
7.38 (m, 3 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.60 (d, *J* = 15.2 Hz, 1 H), 7.62 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 28.1, 49.7, 60.5, 84.3, 85.3, 116.1, 123.0, 123.1, 126.6, 128.3, 128.4, 130.5, 131.0, 131.5, 131.8, 141.9, 144.6, 165.2; IR (KBr, neat) 2983, 2922, 1705, 1581, 1478, 1256, 1164, 1036, 949, 759 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{20}BrO_2S$ $(M + H)^+$ 415.0362, found 415.0341.

(*E*)-Ethyl 3-((1-(4-bromophenyl)-4-phenylbut-3-yn-1-yl)thio)acrylate (24i):



Colourless oil; R_f (hexane/EtOAc 9:1) 0.58; yield 729 mg, 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3 H), 3.03 (dd, *J* = 6.0 and 5.2 Hz, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.39 (t, *J* = 7.2 Hz, 1 H), 5.80 (d, *J* = 15.6 Hz, 1 H), 7.25-7.28 (m, 3 H), 7.31-7.33 (m, 4 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 7.59 (d, *J* = 15.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 27.9, 49.6, 60.5, 84.1, 85.4, 116.0, 122.3, 123.1, 128.3, 128.4, 129.6, 131.8, 132.1, 138.7, 144.7, 165.2; IR (KBr, neat) 2982, 1712, 1582, 1484, 1254, 1164, 1038, 830, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{20}BrO_2S$ $(M + H)^+$ 415.0362, found 415.0360.

(*E*)-Ethyl 3-((1-(4-chlorophenyl)-4-phenylbut-3-yn-1-yl)thio)acrylate (24j):



Colourless oil; R_f (hexane/EtOAc 9:1) 0.59; yield 607 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3 H), 3.04 (dd, *J* = 6.4 and 5.6 Hz, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.40 (t, *J* = 7.2 Hz, 1 H), 5.80 (d, *J* = 15.2 Hz, 1 H), 7.25-7.28 (m, 3 H), 7.31-7.35 (m, 2 H), 7.36-7.39 (m, 4 H), 7.59 (d, *J* = 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 28.0, 49.5, 60.5, 84.1, 85.4, 116.0, 123.1, 128.3, 128.4, 129.1, 129.2, 131.8, 134.1, 138.1, 144.8, 165.2; IR (KBr, neat) 2983, 2925, 1705, 1583, 1490, 1254, 1164, 1031, 830, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{20}ClO_2S$ $(M + H)^+$ 371.0867, found 371.0866.

(*E*)-Ethyl 3-((4-(4-chlorophenyl)-1-(*p*-tolyl)but-3-yn-1-yl)thio)acrylate (24k):

Colourless oil; R_f (hexane/EtOAc 9:1) 0.61; yield 599 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3 H), 2.33 (s, 3 H), 3.03 (d, *J* = 6.4 Hz, 2 H), 4.11 (q, *J* =

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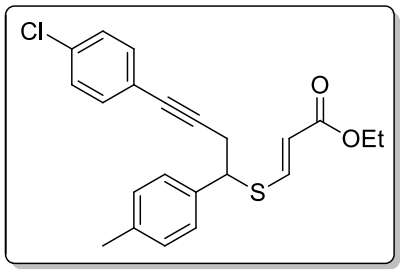
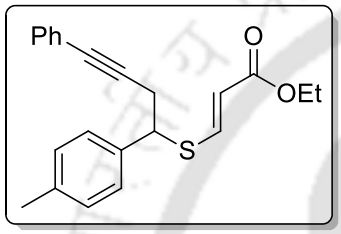


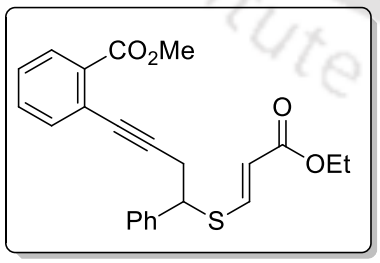
7.2 Hz, 2 H), 4.40 (t, *J* = 7.2 Hz, 1 H), 5.82 (d, *J* = 15.6 Hz, 1 H), 7.16 (d, *J* = 7.2 Hz, 2 H), 7.23-7.26 (m, 4 H), 7.29 (d, *J* = 7.2 Hz, 2 H), 7.64 (d, *J* = 15.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.3, 28.1, 50.0, 60.4, 82.6, 87.1, 115.4, 121.8, 127.6, 128.6, 129.7, 133.0, 134.1, 136.4, 138.1, 145.5, 165.3; IR (KBr, neat) 2982, 2926, 1707, 1580, 1483, 1252, 1164, 1039, 827, 710 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{22}ClO_2S$ $(M + H)^+$ 385.1024, found 385.1025.

(*E*)-Ethyl 3-((4-phenyl-1-(*p*-tolyl)but-3-yn-1-yl)thio)acrylate (24l):



Colourless oil; R_f (hexane/EtOAc 9:1) 0.62; yield 562 mg, 93%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3 H), 2.34 (s, 3 H), 3.04 (dd, *J* = 4.8 and 2.8 Hz, 2 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.40 (t, *J* = 7.2 Hz, 1 H), 5.82 (d, *J* = 15.0 Hz, 1 H), 7.17 (d, *J* = 7.8 Hz, 2 H), 7.24-7.27 (m, 3 H), 7.30-7.34 (m, 4 H), 7.65 (d, *J* = 15.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 21.3, 28.2, 50.2, 60.4, 83.7, 86.1, 115.5, 123.4, 127.7, 128.2, 128.4, 129.7, 131.8, 136.6, 138.1, 145.7, 165.4; IR (KBr, neat) 2983, 22913, 2358, 1706, 1580, 1449, 1302, 1257, 1166, 1040, 829, 694 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{23}O_2S$ $(M + H)^+$ 351.1413, found 351.1411.

(*E*)-Methyl 2-(4-((3-ethoxy-3-oxoprop-1-en-1-yl)thio)-4-phenylbut-1-yn-1-yl)benzoate (24m):



Colourless oil; R_f (hexane/EtOAc 9:1) 0.39; yield 709 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3 H), 3.15 (d, *J* = 7.2 Hz, 2 H), 3.86 (s, 3 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.49 (t, *J* = 7.2 Hz, 1 H), 5.83 (d, *J* = 15.2 Hz, 1 H), 7.28-7.41 (m, 6 H), 7.45 (d, *J* = 7.2 Hz, 2 H), 7.64 (d, *J* = 15.2 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 28.4, 50.2, 52.3, 60.4, 82.3, 91.3, 115.6, 123.7, 127.9, 128.3 (2C), 129.0, 130.4, 131.7, 132.0, 134.6, 139.6, 145.4, 165.3, 166.8; IR (KBr, neat) 2985, 2899, 2230, 1728, 1580, 1440, 1300, 1164, 1036, 755 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{23}O_4S$ $(M + H)^+$ 395.1312, found 395.1312.

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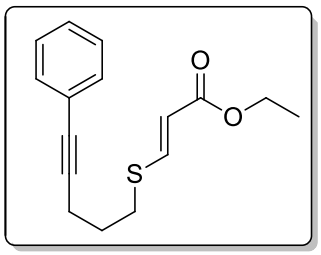
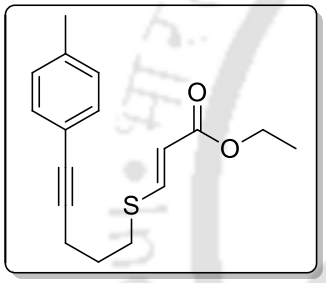
(*E*)-Ethyl 3-((5-phenylpent-4-yn-1-yl)thio)acrylate (24n):



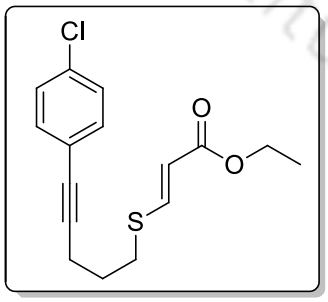
Colourless oil; R_f (hexane/EtOAc 9:1) 0.60; yield 444 mg, 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3 H), 1.93-1.99 (m, 2 H), 2.55 (t, *J* = 7.2 Hz, 2 H), 2.97 (t, *J* = 7.2 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.83 (d, *J* = 15.2 Hz, 1 H), 7.26-7.28 (m, 3 H), 7.40-7.43 (m, 2 H), 7.69 (d, *J* = 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 18.6, 27.7, 30.8, 60.3, 82.0, 88.2, 114.1, 123.6, 127.9, 128.3, 131.7, 146.3, 165.3; IR (KBr, neat) 2984, 2842, 2225, 1708, 1582, 1440, 1256, 1164, 1037, 952, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{19}O_2S$ $(M + H)^+$ 275.1100, found 275.1100.

(*E*)-Ethyl 3-((5-(*p*-tolyl)pent-4-yn-1-yl)thio)acrylate (24o):



Colourless oil; R_f (hexane/EtOAc 9:1) 0.58; yield 548 mg, 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3 H), 1.93-2.00 (m, 2 H), 2.32 (s, 3 H), 2.56 (t, *J* = 6.8 Hz, 2 H), 2.99 (t, *J* = 6.8 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.82 (d, *J* = 15.2 Hz, 1 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.69 (d, *J* = 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 18.7, 21.6, 27.9, 31.0, 60.4, 82.1, 87.5, 114.3, 120.6, 129.2, 131.7, 138.0, 146.5, 165.5; IR (KBr, neat) 2983, 2923, 2358, 1706, 1580, 1446, 1298, 1165, 1038, 825 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{21}O_2S$ $(M + H)^+$ 289.1257, found 289.1251.

(*E*)-Ethyl 3-((5-(4-chlorophenyl)pent-4-yn-1-yl)thio)acrylate (24p):



Colourless oil; R_f (hexane/EtOAc 9:1) 0.60; yield 566 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3 H), 1.94-2.01 (m, 2 H), 2.56 (t, *J* = 6.8 Hz, 2 H), 2.98 (t, *J* = 7.2 Hz, 2 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 5.82 (d, *J* = 14.8 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.69 (d, *J* = 14.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 18.7, 27.7, 30.9, 60.4, 81.0, 89.4, 114.3, 122.1, 128.7, 133.0, 134.0, 146.3, 165.5; IR (KBr, neat) 2925, 2844, 1706, 1581, 1482, 1255, 1164, 1040, 830 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}ClO_2S$ $(M + H)^+$ 309.0711, found 309.0711.

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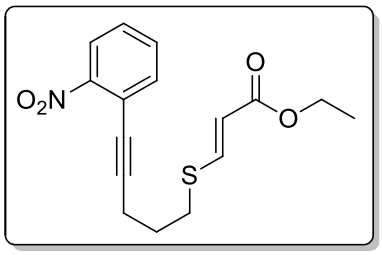
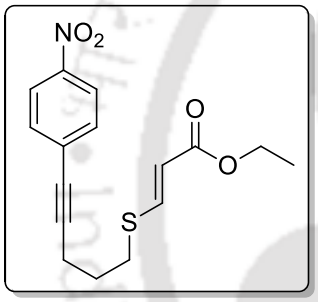
(*E*)-Ethyl 3-((5-(2-nitrophenyl)pent-4-yn-1-yl)thio)acrylate (24q):



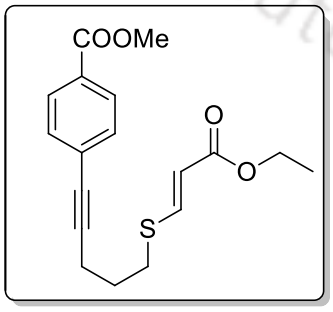
Colourless oil; R_f (hexane/EtOAc 9:1) 0.38; yield 484 mg, 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 6.8 Hz, 3 H), 1.99-2.06 (m, 2 H), 2.66 (t, *J* = 6.8 Hz, 2 H), 3.05 (t, *J* = 7.2 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.83 (d, *J* = 15.2 Hz, 1 H), 7.39-7.45 (m, 1 H), 7.54 (t, *J* = 8.4 Hz, 1 H), 7.61 (d, *J* = 8.4 Hz, 1 H), 7.69 (d, *J* = 15.2 Hz, 1 H), 8.00 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 19.0, 27.5, 30.8, 60.4, 77.5, 97.1, 114.3, 119.0, 121.2, 124.7, 128.4, 132.8, 135.0, 146.4, 165.5; IR (KBr, neat) 2921, 2850, 2230, 1703, 1579, 1460, 1260, 1158, 1032, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}NO_4S$ $(M + H)^+$ 320.0951, found 320.0950.

(*E*)-Ethyl 3-((5-(4-nitrophenyl)pent-4-yn-1-yl)thio)acrylate (24r):



Pale yellow semi-solid; R_f (hexane/EtOAc 9:1) 0.48; yield 530 mg, 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 6.8 Hz, 3 H), 1.98-2.05 (m, 2 H), 2.63 (t, *J* = 6.4 Hz, 2 H), 2.99 (t, *J* = 6.8 Hz, 2 H), 4.19 (q, *J* = 6.8 Hz, 2 H), 5.83 (d, *J* = 15.2 Hz, 1 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 7.69 (d, *J* = 15.2 Hz, 1 H), 8.17 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 18.8, 27.5, 30.9, 60.5, 80.6, 94.4, 114.4, 123.7, 130.7, 132.5, 146.2, 147.0, 165.4; IR (KBr, neat) 2933, 2853, 2228, 1704, 1585, 1518, 1437, 1344, 1254, 1165, 1039, 848, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}NO_4S$ $(M + H)^+$ 320.0951, found 320.0955.

(*E*)-Methyl 4-(5-((3-ethoxy-3-oxoprop-1-en-1-yl)thio)pent-1-yn-1-yl)benzoate (24s):



Pale yellow oil; R_f (hexane/EtOAc 9:1) 0.46; yield 604 mg, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3 H), 1.96-2.02 (m, 2 H), 2.60 (t, *J* = 6.4 Hz, 2 H), 2.99 (t, *J* = 6.8 Hz, 2 H), 3.91 (s, 3 H), 4.18 (q, *J* = 6.8 Hz, 2 H), 5.83 (d, *J* = 15.2 Hz, 1 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 7.69 (d, *J* = 15.2 Hz, 1 H), 7.97 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 18.7, 27.6, 30.9, 52.4, 60.4, 81.5, 91.7, 114.3, 128.4, 129.3, 129.6, 131.7, 146.3, 165.5, 166.8; IR (KBr, neat) 2944, 2358, 2227, 1931, 1722, 1579, 1440, 1298, 1104, 1035, 954, 762 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{21}O_4S$ $(M + H)^+$ 333.1155, found 333.1162.

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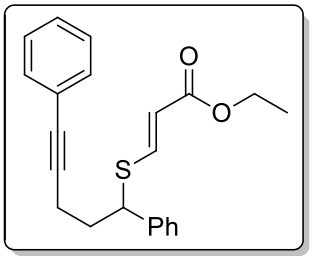
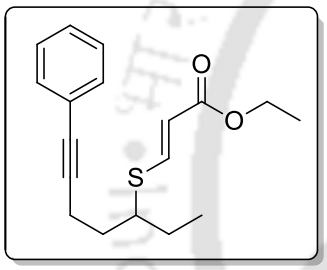
(*E*)-Ethyl 3-((1,5-diphenylpent-4-yn-1-yl)thio)acrylate (24t):



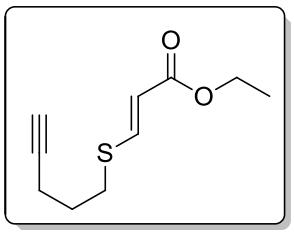
Colourless oil; R_f (hexane/EtOAc 9:1) 0.68; yield 658 mg, 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3 H), 2.15-2.34 (m, 1 H), 2.26-2.37 (m, 2 H), 2.46-2.53 (m, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.42 (dd, *J* = 9.2 and 6.0 Hz, 1 H), 5.88 (d, *J* = 15.6 Hz, 1 H), 7.28-7.30 (m, 4 H), 7.34-7.42 (m, 4 H), 7.42-7.46 (m, 2 H), 7.59 (d, *J* = 15.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 17.7, 35.4, 49.9, 60.4, 82.3, 88.2, 115.3, 123.7, 128.0, 128.1, 128.2, 128.5, 129.2, 131.8, 140.0, 145.5, 165.5; IR (KBr, neat) 2979, 2932, 2358, 1706, 1582, 1444, 1253, 1162, 1037, 758, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{23}O_2S$ $(M + H)^+$ 351.1413, found 351.1413.

(*E*)-Ethyl 3-((7-phenylhept-6-yn-3-yl)thio)acrylate (24u):



Colourless oil; R_f (hexane/EtOAc 9:1) 0.70; yield 562 mg, 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.63-1.73 (m, 1 H), 1.74-1.84 (m, 1 H), 1.86-2.00 (m, 2 H), 2.59 (t, *J* = 6.8 Hz, 2 H), 3.15-3.23 (m, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 5.92 (d, *J* = 15.6 Hz, 1 H), 7.27-7.30 (m, 3 H), 7.40-7.43 (m, 2 H), 7.73 (d, *J* = 15.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 14.5, 17.4, 27.8, 33.5, 48.5, 60.4, 81.9, 88.7, 114.9, 123.7, 128.0, 128.4, 131.8, 146. 5, 165.7; IR (KBr, neat) 2970, 2928, 2313, 1707, 1582, 1452, 1252, 1162, 1038, 950, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{23}O_2S$ $(M + H)^+$ 303.1413, found 303.1413.

(*E*)-Ethyl 3-(pent-4-yn-1-ylthio)acrylate (24v):



Colourless oil; R_f (hexane/EtOAc 9:1) 0.60; yield 608 mg, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3 H), 1.87-1.94 (m, 2 H), 2.03 (t, *J* = 2.8 Hz, 1 H), 3.05 (dt, *J* = 6.4 and 2.4 Hz, 2 H), 2.94 (t, *J* = 6.8 Hz, 2 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 5.79 (d, *J* = 15.2 Hz, 1 H), 7.67 (d, *J* = 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 17.6, 27.4, 30.7, 60.4, 69.8, 82.7, 114.3, 146.3, 165.4; IR (KBr, neat) 2984, 2927, 1708, 1582, 1446, 1253, 1168, 1038, 640 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_{15}O_2S$ $(M + H)^+$ 199.0787, found 199.0787.

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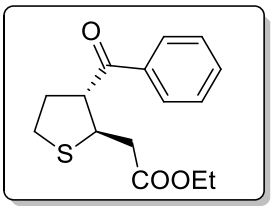
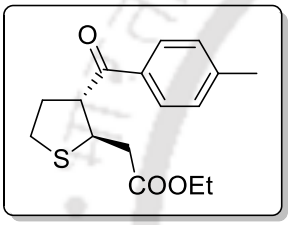
Ethyl 2-((2*R,3*R**)-3-benzoyltetrahydrothiophen-2-yl)acetate (25a):**



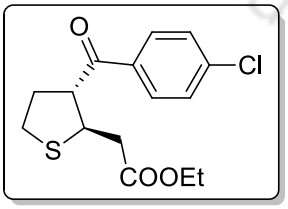
Colourless oil; R_f (hexane/EtOAc 9:1) 0.38; Yield 214 mg, 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.2 Hz, 3 H), 2.21-2.27 (m, 1 H), 2.42-2.47 (m, 1 H), 2.61 (dd, *J* = 15.6 and 8.0 Hz, 1 H), 2.73 (dd, *J* = 15.6 and 6.4 Hz, 1 H), 2.95-3.00 (m, 1 H), 3.02-3.07 (m, 1 H), 3.85-3.91 (m, 1 H), 4.08 (q, *J* = 7.2 Hz, 2 H), 4.20 (q, *J* = 6.8 Hz, 1 H), 7.50 (t, *J* = 7.6 Hz, 2 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.97 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl3) 14.2, 31.4, 35.7, 41.3, 45.6, 55.4, 60.9, 128.5, 128.9, 133.6, 136.5, 171.2, 199.5; IR (KBr, neat) 2932, 2858, 1731, 1679, 1447, 1158, 1027, 698 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{19}O_3S$ $(M + H)^+$ 279.1049 found 279.1049.

Ethyl 2-((2*R,3*R**)-3-(4-Methylbenzoyl)tetrahydrothiophen-2-yl)- acetate (25b):**



Colourless oil; Rf (hexane/EtOAc 9:1) 0.38; Yield 190 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.2 Hz, 3 H), 2.18-2.28 (m, 1 H), 2.39-2.47 (m, 4 H), 2.59 (dd, *J* = 15.6 and 7.6 Hz, 1 H), 2.73 (dd, *J* = 15.6 and 6.0 Hz, 1 H), 2.94-3.00 (m, 1 H), 3.03-3.08 (m, 1 H), 3.81-3.86 (m, 1 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 4.15-4.23 (m, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.87 (t, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl3) 14.3, 21.9, 31.5, 35.9, 41.4, 45.8, 55.3, 60.9, 128.8, 129.7, 134.2, 144.6, 171.3, 199.1; IR (KBr, neat) 2923, 2853, 1733, 1676, 1607, 1447, 1177, 1028, 802, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{21}O_3S$ $(M + H)^+$ 293.1206 found 293.1193.

Ethyl 2-((2*R,3*R**)-3-(4-chlorobenzoyl)tetrahydrothiophen-2-yl)acetate (25c)**



Colourless oil; R_f (hexane/EtOAc 9:1) 0.47; Yield 225 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.2 Hz, 3 H), 2.19-2.29 (m, 1 H), 2.36-2.45 (m, 1 H), 2.61 (dd, *J* = 15.6 and 7.6 Hz, 1 H), 2.70 (dd, *J* = 15.6 and 6.8 Hz, 1 H), 2.94-3.00 (m, 1 H), 3.02-3.08 (m, 1 H), 3.84 (q, *J* = 6.4 Hz, 1 H), 4.08 (q, *J* = 7.2 Hz, 2 H), 4.16 (q, *J* = 7.2 Hz, 1 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.92 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3, 31.4, 35.5, 41.3, 45.6, 55.3, 61.0, 129.3, 130.1, 134.9, 140.1, 171.3, 198.4; IR (KBr, neat) 2976, 2860, 1731, 1681, 1584, 1481, 1213, 1166, 1095, 1021, 851, 745 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{18}ClO_3S$ $(M + H)^+$ 313.0660 found 313.0646.

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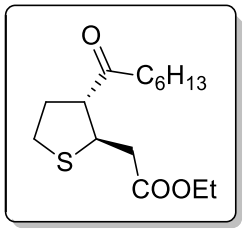
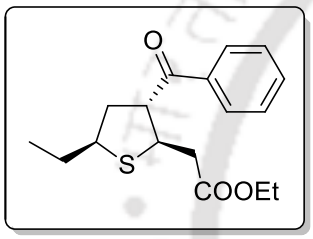
Ethyl 2-((2*R,3*R**)-3-hexanoyltetrahydrothiophen-2-yl)acetate (25d):**



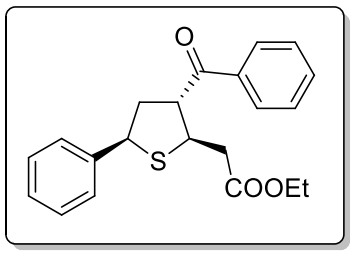
Colourless oil; R_f (hexane/EtOAc 9:1) 0.52; Yield 206 mg, 61%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.24-1.33 (m, 9 H), 1.54-1.62 (m, 2 H), 2.12-2.21 (m, 1 H), 2.27-2.35 (1 H), 2.51 (t, *J* = 7.2 Hz, 2 H), 2.56 (dd, *J* = 16.0 and 7.6 Hz, 1 H), 2.69 (dd, *J* = 16.0 and 6.4 Hz, 1 H), 2.87−2.98 (m, 3 H), 4.01 (q, *J* = 6.8 Hz, 1 H), 4.14 (q, *J* = 7.2 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 14.7, 23.0, 24.1, 29.3, 31.7, 32.1, 34.7, 42.2, 42.3, 45.0, 60.9, 61.3, 171.8, 210.2; IR (KBr, neat) 2964, 2855, 1731, 1708, 1679, 1459, 1165, 1029, 732 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{27}O_3S$ $(M + H)^+$ 287.1675 found 287.1672.

Ethyl 2-((2*R,3*R**,5S)-3-benzoyl-5-ethyltetrahydrothiophen-2-yl)acetate (25f):**



Colourless oil; R_f (hexane/EtOAc 9:1) 0.42; Yield 205 mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.2 Hz, 3 H), 1.20 (t, *J* = 7.2 Hz, 3 H), 1.59-1.67 (m 1 H), 1.71-1.80 (m, 1 H), 2.09-2.16 (m, 1 H), 2.31-2.39 (m, 1 H), 2.61 (dd, *J* = 15.6 and 8.0 Hz, 1 H), 2.73 (dd, *J* = 15.6 and 6.8 Hz, 1 H), 3.34-3.41 (m, 1 H), 3.98 (q, *J* = 7.2 Hz, 1 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 7.96 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.2, 14.3, 31.4, 40.4, 41.9, 45.6, 50.0, 54.0, 60.9, 128.6, 129.0, 133.5, 136.5, 171.3, 199.7; IR (KBr, neat) 2965, 2870, 1738, 1678, 1596, 1449, 1373, 1156, 1028, 694 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{23}O_3S$ $(M + H)^+$ 307.1362 found 307.1366.

Ethyl 2-((2*R,3*R**,5*R**)-3-benzoyl-5-phenyltetrahydrothiophen-2-yl)acetate (25g):**



Colourless oil; R_f (hexane/EtOAc 9:1) 0.40; Yield 269 mg, 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.2 Hz, 3 H), 2.41-2.48 (m, 1 H), 2.62-2.70 (m, 1 H), 2.80 (dd, *J* = 15.6 and 7.6 Hz, 1 H), 2.88 (dd, *J* = 15.6 and 6.8 Hz, 1 H), 4.05-4.15 (m, 3 H), 4.30 (q, *J* = 7.2 Hz, 1 H), 4.69 (t, *J* = 7.2 Hz, 1 H), 7.14-7.28 (m, 1 H), 7.34 (t, *J* = 7.2 Hz, 2 H), 7.44-7.48 (m, 4 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.91 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3, 42.1, 43.1, 46.5, 51.7, 54.2, 61.0, 127.5, 127.8, 128.6, 128.7, 129.0, 133.6, 136.2, 142.0, 171.2,

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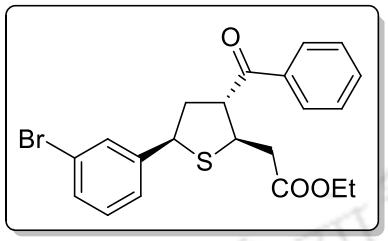
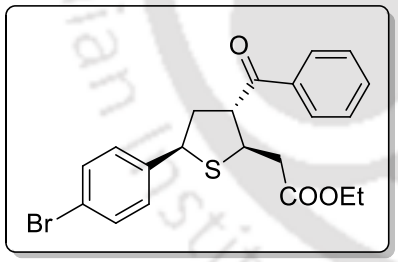
199.5; IR (KBr, neat) 2976, 2930, 1731, 1681, 1590, 1451, 1165, 1023, 944, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}O_3S$ $(M + H)^+$ 355.1362 found 355.1358.

Ethyl 2-((2*R,3*R**,5*R**)-3-benzoyl-5-(3-bromophenyl)tetrahydrothiophen-2-yl)acetate (25h):**



Colourless solid, mp. 87-89 ºC; R_f (hexane/EtOAc 9:1) 0.40; Yield 354 mg, 82%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3 H), 2.36-2.44 (m, 1 H), 2.64-2.70 (m, 1 H), 2.80 (dd, *J* = 15.6 and 7.6 Hz, 1 H), 2.88 (dd, *J* = 15.6 and 6.8 Hz, 1 H), 4.08 (q, *J* = 5.6 Hz, 1 H), 4.14 (q, *J* = 5.6 Hz, 2 H), 4.29 (q, *J* = 7.2 Hz, 1 H), 4.65 (t, *J* = 6.8 Hz, 1 H), 7.21 (t, *J* = 7.2 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.57-7.62 (m, 2 H), 7.92 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3, 42.0, 42.8, 46.7, 51.1, 54.1, 61.1, 122.8, 126.6, 128.5, 128.7, 129.0, 130.3, 130.6, 130.9, 133.7, 144.5, 171.1, 199.2; IR (KBr, neat) 2924, 2856, 1731, 1681, 1585, 1464, 1155, 1025, 784 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{22}BrO_3S$ $(M + H)^+$ 433.0468 found 433.0446.

Ethyl 2-((2*R,3*R**,5*R**)-3-benzoyl-5-(4-bromophenyl)tetrahydrothiophen-2-yl)acetate (25i):**



Colourless solid, mp. 89-91 ºC; R_f (hexane/EtOAc 9:1) 0.45; Yield 359 mg, 83%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.2 Hz, 3 H), 2.35-2.40 (m, 1 H), 2.59-2.67 (m, 1 H), 2.77 (dd, *J* = 15.6 and 7.8 Hz, 1 H), 2.86 (dd, *J* = 15.6 and 6.6 Hz, 1 H), 4.07 (q, *J* = 6.0 Hz, 1 H), 4.12 (q, *J* = 5.6 Hz, 2 H), 4.27 (q, *J* = 7.2 Hz, 1 H), 4.65 (t, *J* = 6.6 Hz, 1 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.43-7.49 (m, 4 H), 7.58 (t, *J* = 7.8 Hz, 1 H), 7.90 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3, 42.0, 43.0, 46.7, 51.1, 54.1, 61.1, 121.3, 128.7, 129.0, 129.6, 131.8, 133.7, 136.1, 141.2, 171.1, 199.3; IR (KBr, neat) 2982, 2926, 1730, 1681, 1587, 1483, 1163, 1015, 699 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{22}BrO_3S$ $(M + H)^+$ 433.0468 found 433.0457.

Ethyl 2-((2*R,3*R**,5*R**)-3-benzoyl-5-(4-chlorophenyl)tetrahydrothiophen-2-yl)acetate (25j):**

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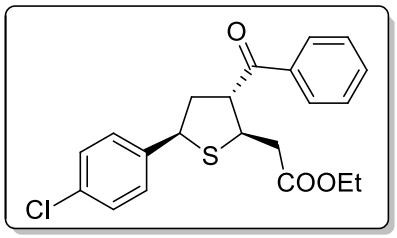
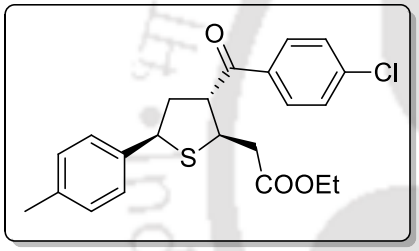


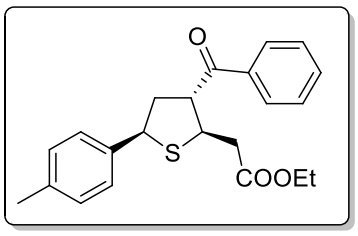
Colourless oil; R_f (hexane/EtOAc 9:1) 0.46; Yield 303 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3 H), 2.35-2.42 (m, 1 H), 2.62-2.69 (m, 1 H), 2.79 (dd, *J* = 15.6 and 7.2 Hz, 1 H), 2.88 (dd, *J* = 15.6 and 6.8 Hz, 1 H), 4.07 (q, *J* = 6.4 Hz, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.27 (q, *J* = 5.6 Hz, 1 H), 4.66 (t, *J* = 7.2 Hz, 1 H), 7.30 (d, *J* = 8.8 Hz, 2 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 7.47 (t, *J* = 6.8 Hz, 1 H), 7.49-7.51 (m, 2 H), 7.91 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3, 42.1, 43.0, 46.7, 51.1, 54.1, 61.1, 128.7, 128.9, 129.0, 129.2, 133.2, 133.7, 136.1, 140.6, 171.2, 199.3; IR (KBr, neat) 2923, 2857, 1710, 1681, 1488, 1093, 1020, 698 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{22}ClO_3S$ $(M + H)^+$ 389.0973 found 389.0968.

Ethyl 2-((2*R,3*R**,5*R**)-3-(4-chlorobenzoyl)-5-(*p*-tolyl)tetrahydrothiophen-2-yl)acetate (25k):**



Colourless solid, mp. 92-94 °C; R_f (hexane/EtOAc 9:1) 0.50; Yield 261 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3 H), 2.33 (s, 3 H), 2.37-2.45 (m, 1 H), 2.57-2.67 (m, 1 H), 2.79 (dd, *J* = 16.0 and 7.2 Hz, 1 H), 2.85 (dd, *J* = 16.0 and 7.6 Hz, 1 H), 4.00-4.07 (m, 1 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 4.23 (q, *J* = 4.8 Hz, 1 H), 4.66 (t, *J* = 6.8 Hz, 1 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.43 (d, *J* = 8.8 Hz, 2 H), 7.87 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3, 21.2, 42.0, 43.0, 46.4, 51.4, 54.2, 61.0, 127.7, 129.3, 129.4, 130.1, 134.5, 137.2, 138.8, 140.0, 171.2, 198.4; IR (KBr, neat) 2976, 2930, 1731, 1680, 1587, 1447, 1160, 1095, 1018, 818, 752 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{24}ClO_3S$ $(M + H)^+$ 403.1129 found 403.1129.

Ethyl 2-((2*R,3*R**,5*R**)-3-benzoyl-5-(*p*-tolyl)tetrahydrothiophen-2-yl)acetate (25l):**



Colourless oil; R_f (hexane/EtOAc 9:1) 0.46; Yield 250 mg, 68%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.2 Hz, 3 H), 2.34 (s, 3 H), 2.44 (p, *J* = 7.2 Hz, 1 H), 2.64 (p, *J* = 6.6 Hz, 1 H), 2.80 (dd, *J* = 15.6 and 7.2 Hz, 1 H), 2.87 (dd, *J* = 15.6 and 6.6 Hz, 1 H), 4.07-4.14 (m, 3 H), 4.30 (q, *J* = 7.2 Hz, 1 H), 4.67 (t, *J* = 6.0 Hz, 1 H), 7.14 (d, *J* = 7.8 Hz, 2 H), 7.35 (d, *J* = 7.8 Hz, 2 H), 7.46 (t, *J* = 7.2 Hz, 2 H), 7.57 (t, *J* = 7.8 Hz, 1 H), 7.93 (d, *J* = 7.8 Hz, 2 H); ^{13}C

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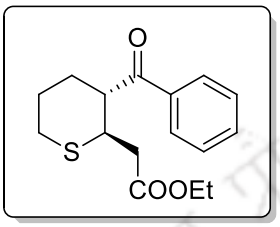
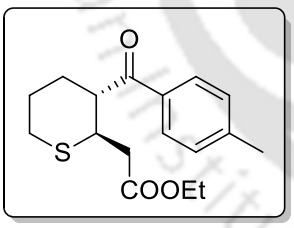
NMR (100 MHz, $CDCl_3$) 14.3, 21.2, 42.0, 43.0, 46.3, 51.3, 54.1, 60.9, 127.6, 128.6, 128.9, 129.3, 133.5, 136.0, 137.1, 138.9, 171.2, 199.4; IR (KBr, neat) 2923, 2858, 1732, 1681, 1588, 1449, 1162, 1026, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{25}O_3S$ $(M + H)^+$ 369.1519 found 369.1514.

Ethyl 2-((*2R,3*R**)-3-benzoyltetrahydro-2*H*-thiopyran-2-yl)acetate (25n, diastereomeric mixture with a ratio of 9:1; data only for major isomer):**



Colourless liquid; R_f (hexane/EtOAc 9:1) 0.48; Yield 201 mg, 69%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.2 Hz, 3 H), 1.48 (q, *J* = 10.4 Hz, 1 H), 1.77 (q, *J* = 9.6 Hz, 1 H), 2.04-2.13 (m, 2 H), 2.37 (dd, *J* = 15.2 and 8.4 Hz, 1 H), 2.56 (dd, *J* = 15.2 and 4.0 Hz, 1 H), 2.59-2.64 (m, 1 H), 2.78-2.85 (m, 1 H), 3.62-3.74 (m 2 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.59 (t, *J* = 7.2 Hz, 2 H), 7.97 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3, 27.0, 29.4, 31.1, 38.7, 39.9, 50.2, 60.8, 128.5, 129.0, 133.6, 136.3, 170.9, 202.7; IR (KBr, neat) 2935, 2853, 2275, 1732, 1682, 1587, 1452, 1156, 1033, 781, 701cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{21}O_3S$ $(M + H)^+$ 293.1206 found 293.1202.

Ethyl 2-((2*R,3*R**)-3-(4-methylbenzoyl)tetrahydro-2*H*-thiopyran-2-yl)acetate (25o, diastereomeric mixture with a ratio of 9:1; data only for major isomer):**



Colourless oil; R_f (hexane/EtOAc 9:1) 0.52; Yield 208 mg, 68%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.2 Hz, 3 H), 1.49 (q, *J* = 10.4 Hz, 1 H), 1.78 (q, *J* = 10.0 Hz, 1 H), 2.02-2.16 (m, 2 H), 2.36 (dd, *J* = 15.2 and 8.4 Hz, 1 H), 2.42 (s, 3 H), 2.54 (dd, *J* = 15.2 and 6.4 Hz, 1 H), 2.58-2.64 (m, 1 H), 2.77-2.85 (m, 1 H), 3.61-3.70 (m, 2 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 7.28 (t, *J* = 8.0 Hz, 2 H), 7.88 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) 14.3, 21.9, 27.1, 29.5, 31.2, 38.8, 40.1, 50.1, 60.8, 128.7, 129.7, 133.9, 144.5, 170.9, 202.3; IR (KBr, neat) 2933, 2853, 1723, 1672, 1605, 1446, 1155, 1028, 825, 740 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{23}O_3S$ $(M + H)^+$ 307.1362 found 307.1354.

Ethyl 2-((2*R,3*R**)-3-(4-chlorobenzoyl)tetrahydro-2*H*-thiopyran-2-yl)acetate (25p, diastereomeric mixture with a ratio of 9:1; data only for major isomer):**

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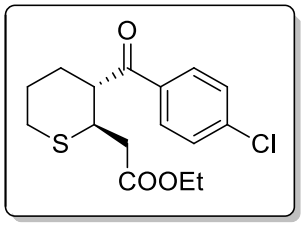
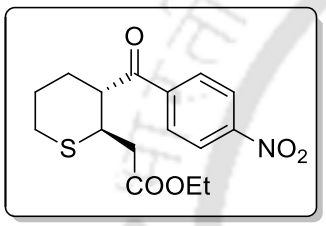


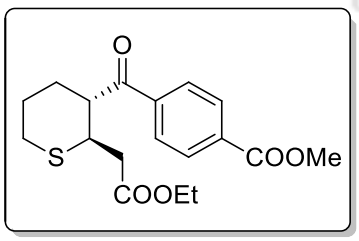
Colourless oil; R_f (hexane/EtOAc 9:1) 0.52; Yield 202 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.2 Hz, 3 H), 1.48 (q, *J* = 12.4 Hz, 1 H), 1.78 (q, *J* = 12.8 Hz, 1 H), 1.98-2.06 (m, 1 H), 2.08-2.20 (m, 1 H), 2.41 (dd, *J* = 15.2 and 8.0 Hz, 1 H), 2.54 (dd, *J* = 15.2 and 3.6 Hz, 1 H), 2.60-2.65 (m, 1 H), 2.77-2.85 (m, 1 H), 3.59-3.71 (m, 2 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 7.46 (d, *J* = 7.6 Hz, 2 H), 7.92 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3, 26.9, 29.3, 31.0, 38.5, 39.8, 50.1, 60.9, 129.3, 129.9, 134.6, 140.1, 170.8, 201.5; IR (KBr, neat) 2925, 2853, 1733, 1677, 1584, 1487, 1180, 1091, 1027, 836, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{20}ClO_3S$ $(M + H)^+$ 327.0816 found 327.0820.

Ethyl 2-((2*R,3*R**)-3-(4-nitrobenzoyl)tetrahydro-2*H*-thiopyran-2-yl)acetate (25r):**



White solid, mp 75-77 ^{o}C; R_f (hexane/EtOAc 9:1) 0.42; Yield 273 mg, 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 6.8 Hz, 3 H), 1.46 (q, *J* = 11.6 Hz, 1 H), 1.78 (q, *J* = 13.6 Hz, 1 H), 1.99-2.05 (m, 1 H), 2.09-2.16 (m, 1 H), 2.46-2.58 (m, 2 H), 2.60-2.67 (m, 1 H), 2.76-2.82 (m, 1 H), 3.58-3.64 (m, 1 H), 3.74-3.81 (m, 1 H), 4.09 (q, *J* = 6.8 Hz, 2 H), 8.13 (d, *J* = 8.4 Hz, 2 H), 8.33 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) 14.3, 26.7, 29.2, 30.6, 38.3, 39.6, 50.4, 61.0, 124.2, 129.6, 140.9, 150.6, 170.9, 201.4; IR (KBr, neat) 2927, 2855, 1726, 1688, 1525, 1455, 1351, 1136, 1030, 852, 710 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{20}NO_5S$ $(M + H)^+$ 338.1057 found 338.1069.

Methyl 4-((2*R,3*R**)-2-(2-ethoxy-2-oxoethyl)tetrahydro-2*H*-thiopyran-3-carbonyl)benzoate (25s):**



Colourless oil; R_f (hexane/EtOAc 9:1) 0.40; Yield 301 mg, 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.6 Hz, 3 H), 1.43-1.54 (m, 1 H), 1.74-1.85 (m, 1 H), 2.02-2.08 (m, 1 H), 2.12 (dt, *J* = 13.6 and 3.2 Hz, 1 H), 2.44 (dd, *J* = 15.2 and 8.0 Hz, 1 H), 2.56 (dd, *J* = 15.2 and 4.4 Hz, 1 H), 2.60-2.67 (m, 1 H), 2.81 (ddd, *J* = 15.2, 14.0 and 2.4 Hz, 1 H), 3.64 (ddd, *J* = 13.6, 9.6 and 4.0 Hz, 1 H), 3.74 (ddd, *J* = 13.6, 11.6 and 2.8 Hz, 1 H), 3.96 (s, 3 H), 4.09 (q, *J* = 6.8 Hz, 2 H), 8.03 (d, *J* = 8.0 Hz, 2 H), 8.15 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3, 26.8, 29.3, 30.9, 38.5, 39.7, 50.4, 52.7, 60.8, 128.4, 130.2, 134.2,

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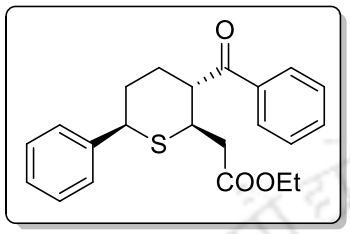
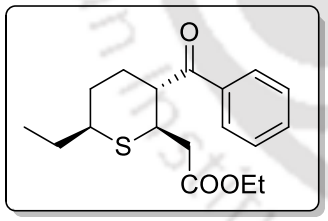
139.5, 166.3, 170.8, 202.3; IR (KBr, neat) 2925, 2856, 1735, 1682, 1569, 1446, 1283, 1107, 1024, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{23}O_5S$ $(M + H)^+$ 351.1261 found 351.1271.

Ethyl 2-((2*R,3*R**,6*R**)-3-benzoyl-6-phenyltetrahydro-2*H*-thiopyran-2-yl)acetate (25t):**



Colourless oil; R_f (hexane/EtOAc 9:1) 0.53; Yield 257 mg, 70%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.2 Hz, 3 H), 1.61-1.72 (m, 1 H), 2.04-2.15 (m, 1 H), 2.20-2.29 (m, 2 H), 2.42 (dd, *J* = 15.2 and 4.4 Hz, 1 H), 2.59 (dd, *J* = 15.2 and 4.0 Hz, 1 H), 3.74-3.80 (m, 1 H), 3.85-3.91 (m, 1 H), 4.03-4.06 (m, 1 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 7.26 (t, *J* = 8.4 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 7.37 (d, *J* = 7.6 Hz, 2 H), 7.37 (t, *J* = 7.6 Hz, 2 H), 7.61 (t, *J* = 7.2 Hz, 1 H), 8.01 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3, 32.1, 34.6, 38.4, 42.0, 48.0, 49.7, 60.9, 127.7, 127.8, 128.5, 128.8, 129.1, 133.7, 136.4, 141.3, 170.7, 202.9; IR (KBr, neat) 2926, 2855, 1734, 1675, 1590, 1447, 1148, 1031, 757, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{25}O_3S$ $(M + H)^+$ 369.1519 found 369.1515.

Ethyl 2-((2*R,3*R**,6*S**)-3-benzoyl-6-ethyltetrahydro-2*H*-thiopyran-2-yl)acetate (25u):**



Colourless oil; R_f (hexane/EtOAc 9:1) 0.55; Yield 208 mg, 65%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.2 Hz, 3 H), 1.17 (t, *J* = 7.2 Hz, 3 H), 1.47-1.52 (m, 2 H), 1.53-1.58 (m, 2 H), 2.07-2.11 (m, 2 H), 2.39 (dd, *J* = 15.0 and 7.8 Hz, 1 H), 2.54 (dd, *J* = 15.0 and 3.0 Hz, 1 H), 2.79-2.84 (m, 1 H), 3.64-3.67 (m, 2 H), 4.05-4.10 (m, 2 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 7.58 (t, *J* = 7.2 Hz, 1 H), 7.97 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 11.6, 14.3, 28.8, 31.9, 33.8, 38.6, 40.8, 45.5, 50.4, 60.8, 128.5, 129.0, 133.6, 136.5, 170.9, 203.1; IR (KBr, neat) 2926, 2853, 1735, 1676, 1588, 1450, 1293, 1155, 1031, 703 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{25}O_3S$ $(M + H)^+$ 321.1519 found 321.1519.

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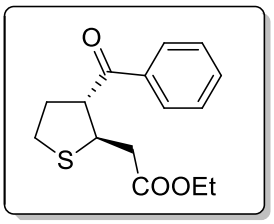
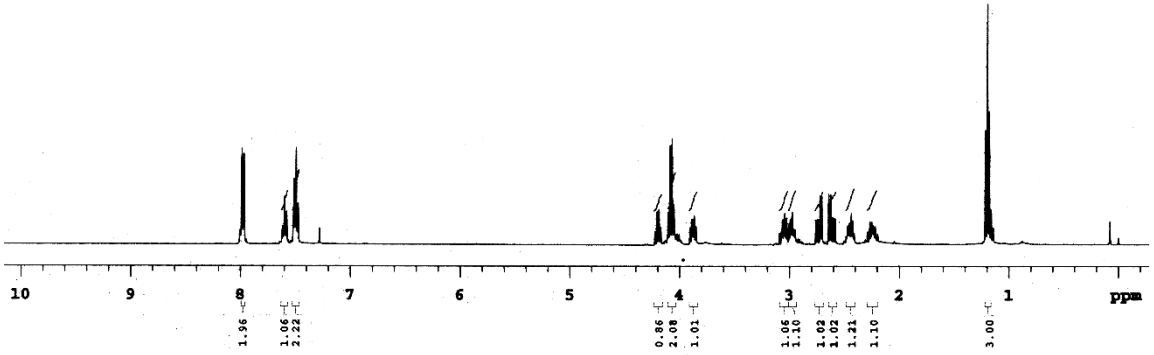
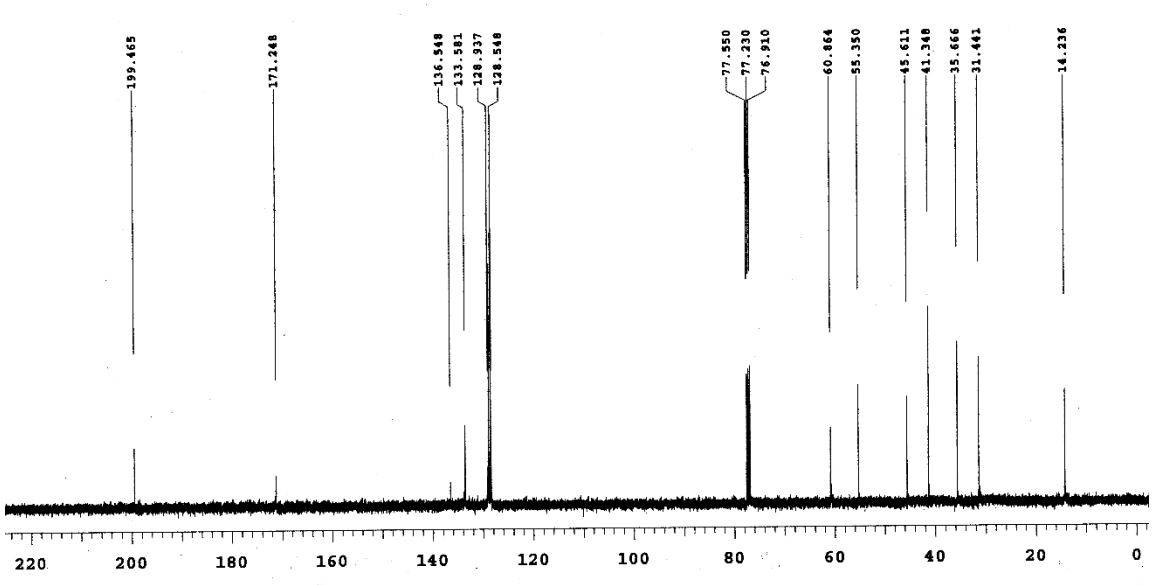
2.8. Selected spectra of substituted tetrahydro-thiophenes and -thiopyrans

Ethyl 2-((2*R,3*R**)-3-benzoyltetrahydrothiophen-2-yl)acetate (25a):**







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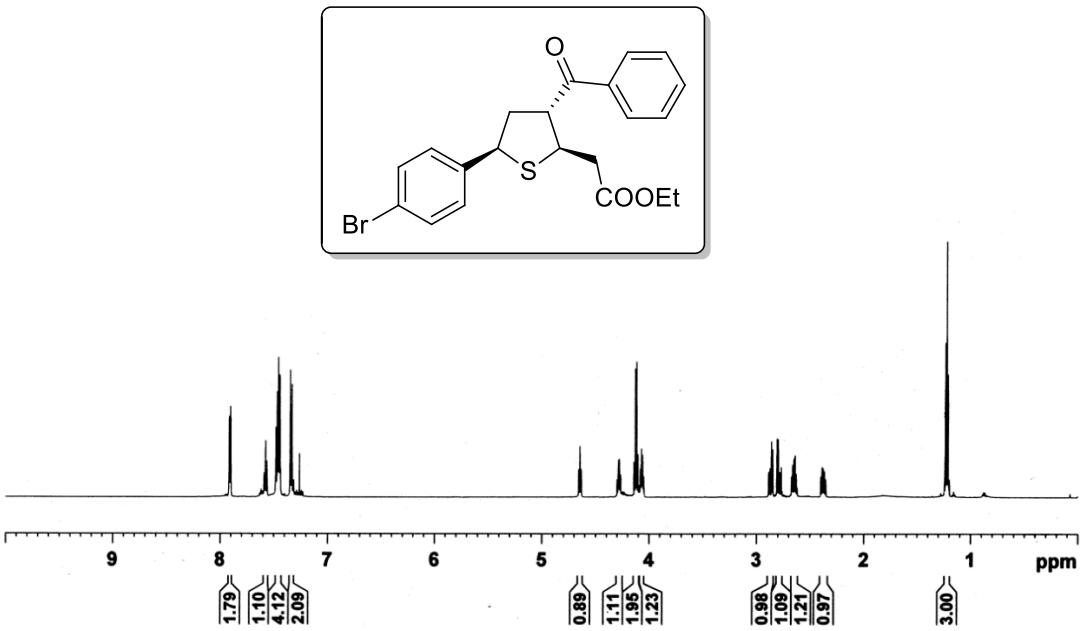
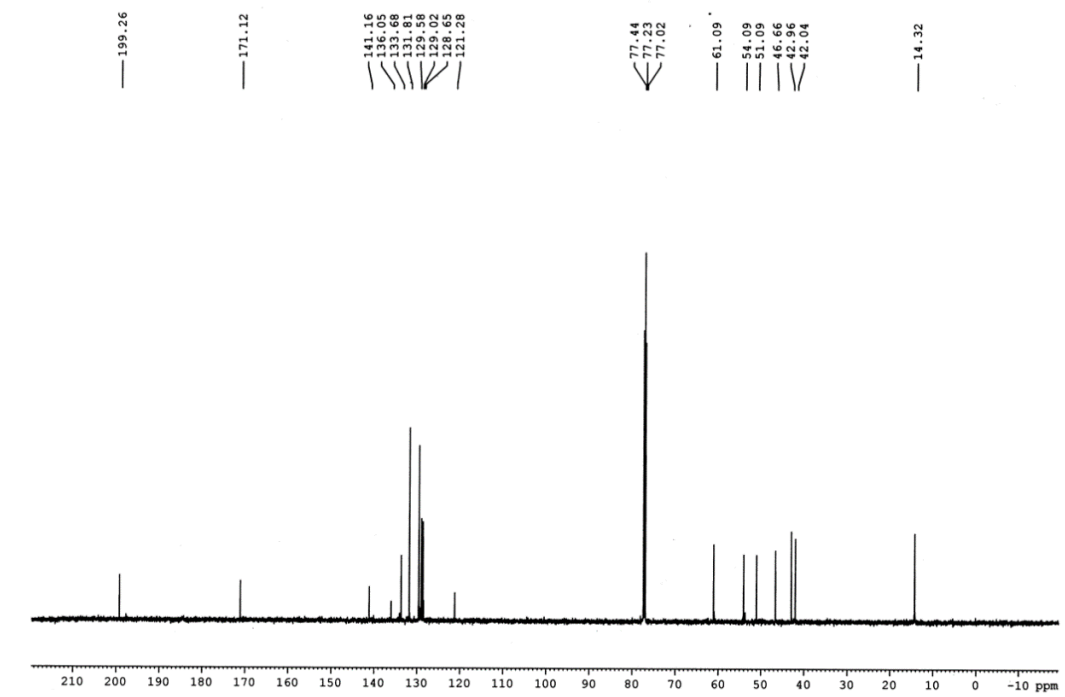
Ethyl 2-((2*R,3*R**,5*R**)-3-benzoyl-5-(4-bromophenyl)tetrahydrothiophen-2-yl)acetate (25i):**





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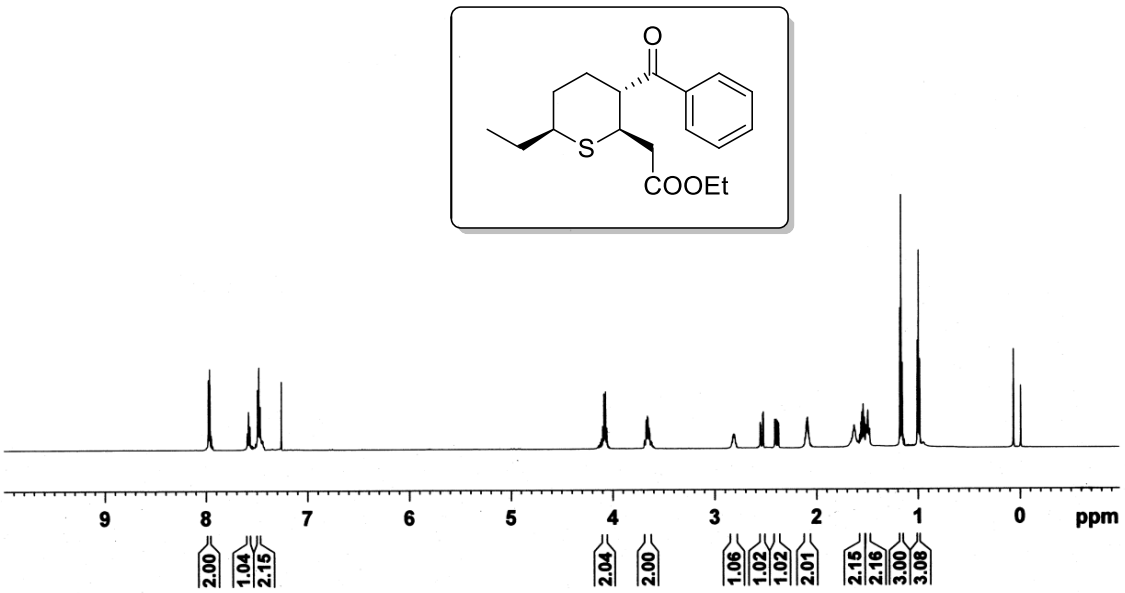
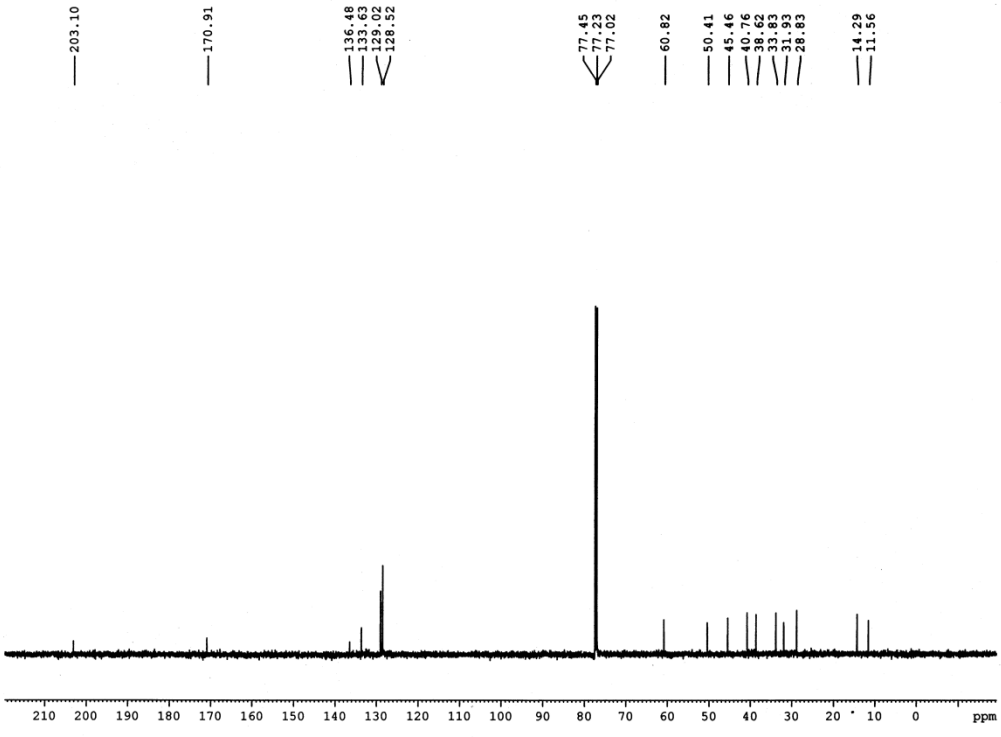
Ethyl 2-((2*R,3*R**,6*S**)-3-benzoyl-6-ethyltetrahydro-2*H*-thiopyran-2-yl)acetate (25u):**





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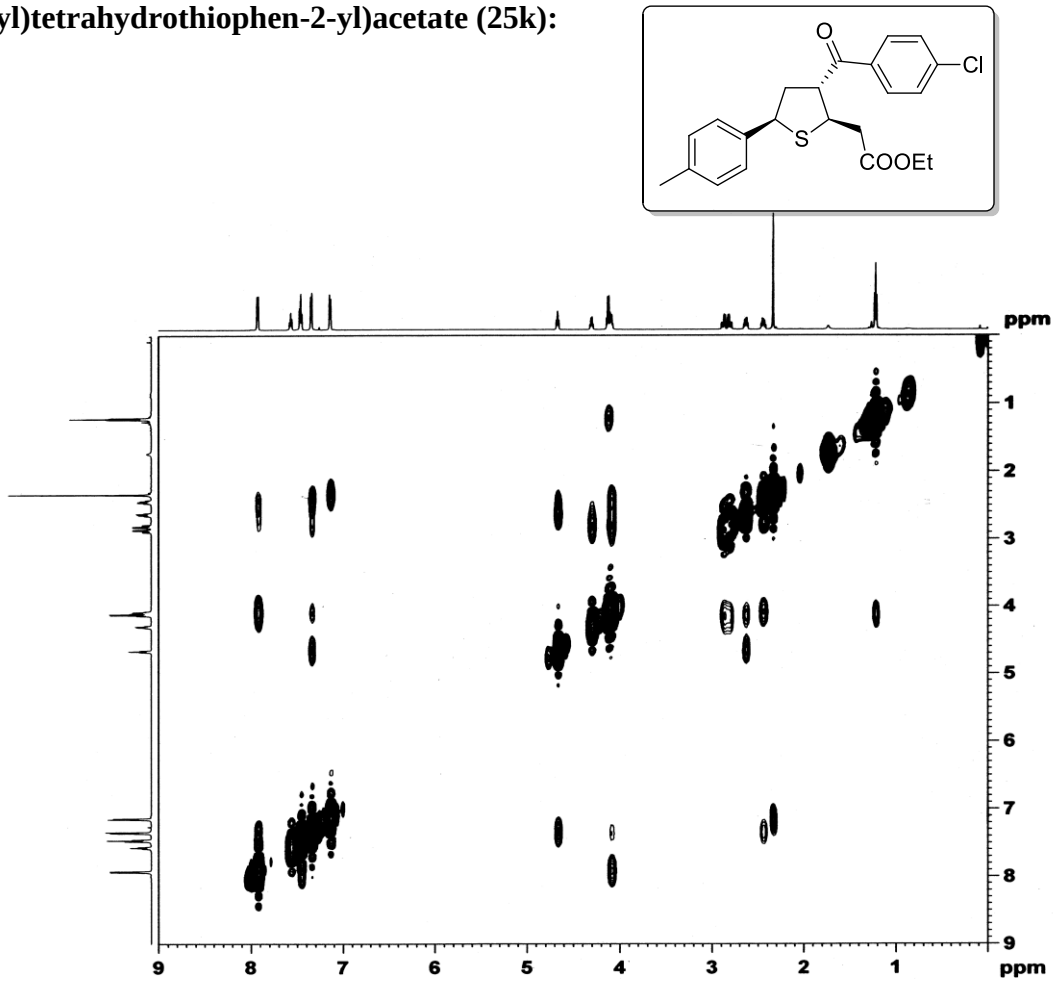
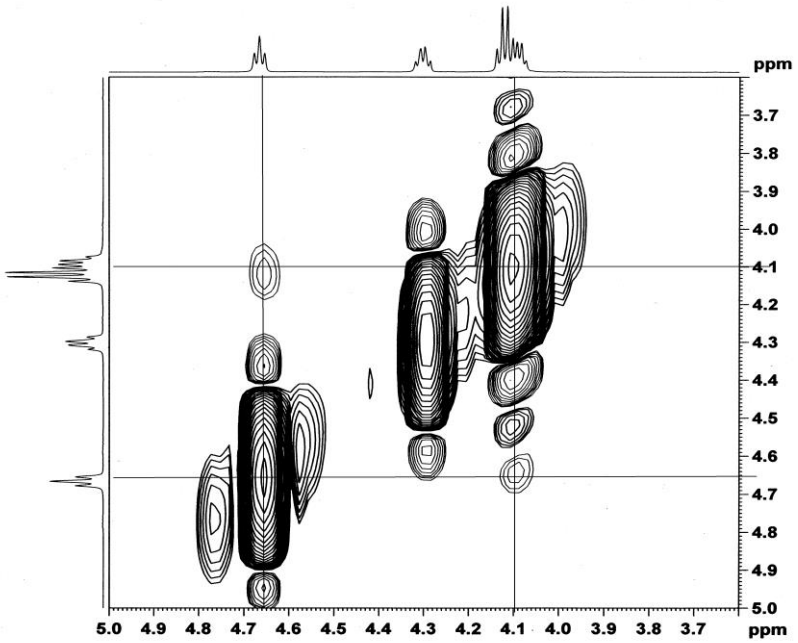
NOE Spectra of compound ethyl 2-((2*R,3*R**,5*R**)-3-(4-chlorobenzoyl)-5-(*p*-tolyl)tetrahydrothiophen-2-yl)acetate (25k):**





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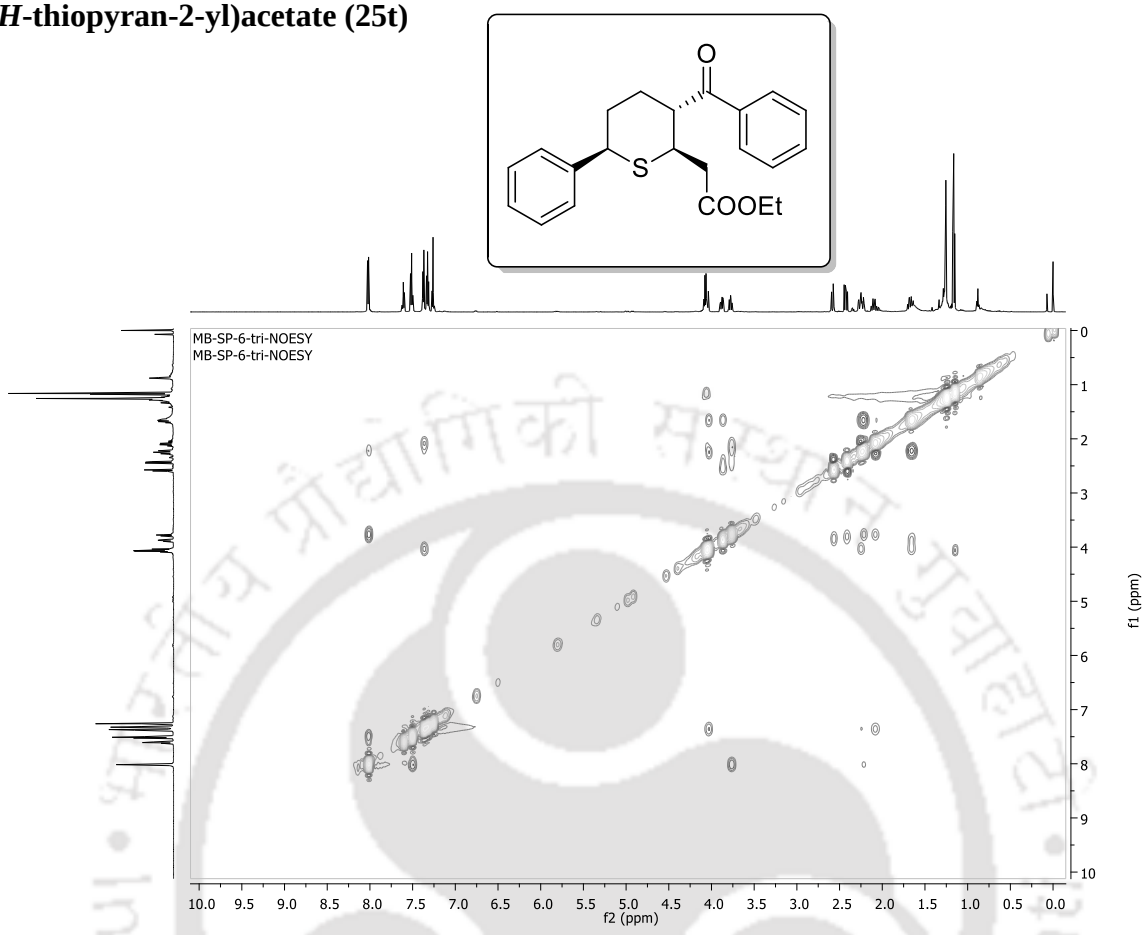
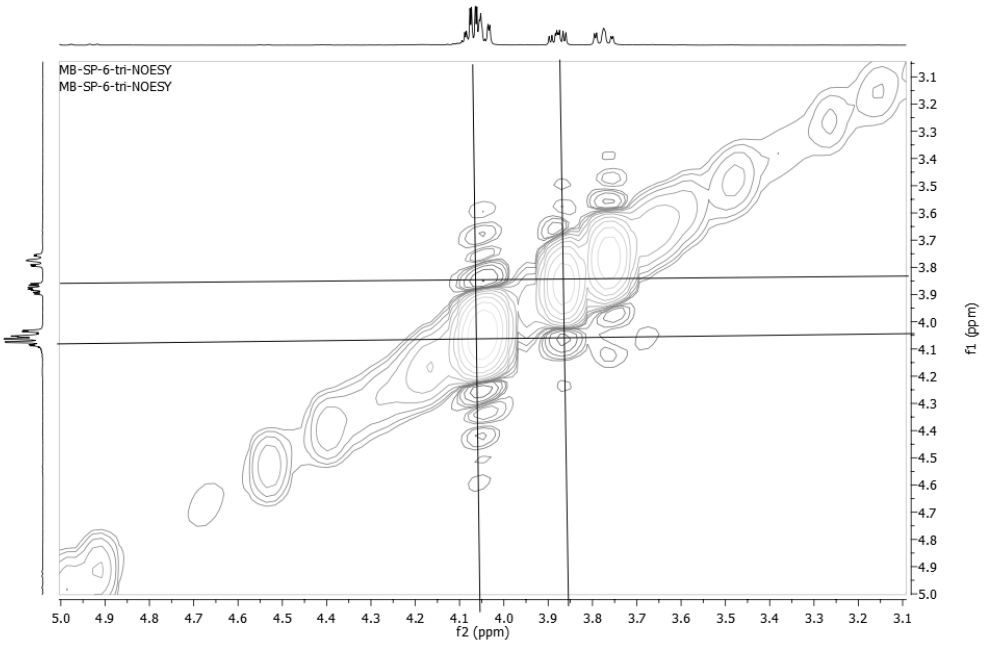
NOE Spectra of compound ethyl 2-((2*R,3*R**,6*R**)-3-benzoyl-6-phenyltetrahydro-2*H*-thiopyran-2-yl)acetate (25t)**





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2.9. Crystal parameters

The crystal parameters of compound 25k

	CCDC 1038837
Formula	$C_{22}H_{23}ClO_3S$
Formula weight	402.91
T/K	293(2)
Crystal system	Orthorhombic
Space group	P212121
a/Å	5.7035(2)
b/Å	7.8753(3)
c/Å	45.6289(15)
α/°	90.00
β/°	90.00
γ/°	90.00
V/Å^3	2049.50(13)
Z	4
Abs. Coeff./mm^{-1}	0.307
Abs. Correction	none
GOF on F^2	1.101
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0422
	wR2 = 0.0491
R indices [all data]	*R1* = 0.0948
	wR2 = 0.1028

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2.10. References

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CHAPTER 3

Diastereoselective Synthesis of Substituted Morpholines from *N*-Tethered Alkenols: Total Synthesis of (±)-Chelonin A

3.1. Importance and applications

Substituted morpholine derivatives are widely distributed in various natural products and biologically relevant compounds. Especially, 2,6-disubstituted and 2,5-disubstituted morpholine derivatives are associated with numerous therapeutic properties. For example, the natural products chelonin A (**1**) and chelonin C (**2**), exhibits antimicrobial activity against *Bacillus subtilis*. Additionally, Chelonin A (**1**) shows *in-vivo* antiinflammatory activity in the mouse. These aromatic alkaloids were isolated from the marine sponge *Chelonaplysilla* sp. collected from a marine lake on Kaibaku Island, Palau in 1991.[1] Similarly, *Cis*-2,6-disubstituted morpholine derivative, fenpropimorph (**3**) is a leaf fungicide, used in agriculture to control fungal diseases in cereals.[2]

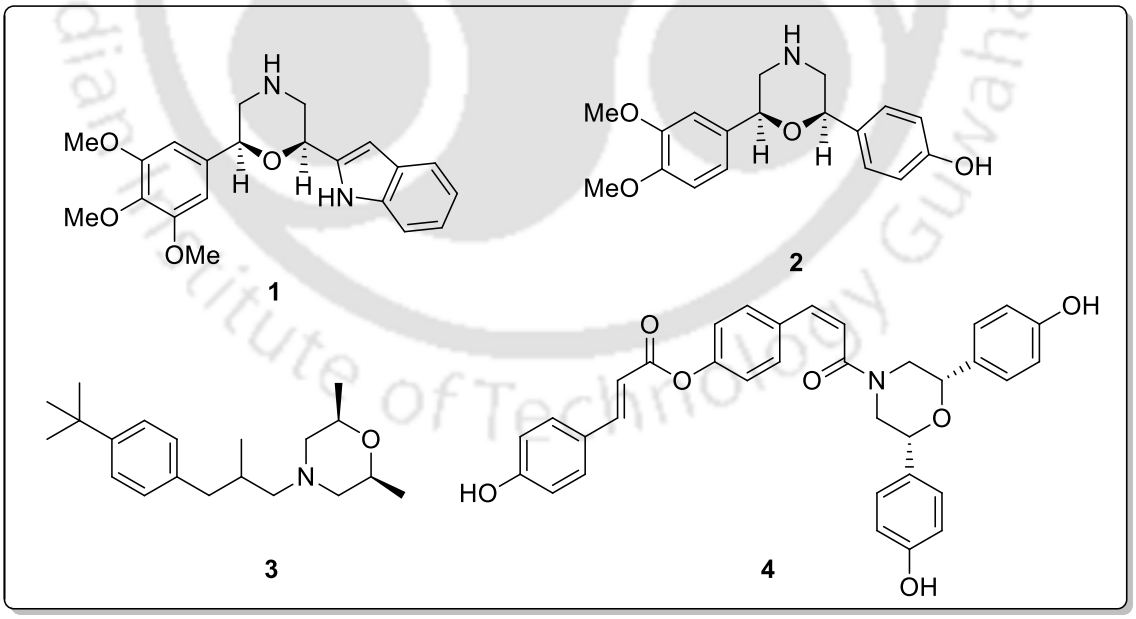

Figure 3.1.1. *Bioactive molecules containing morpholines*

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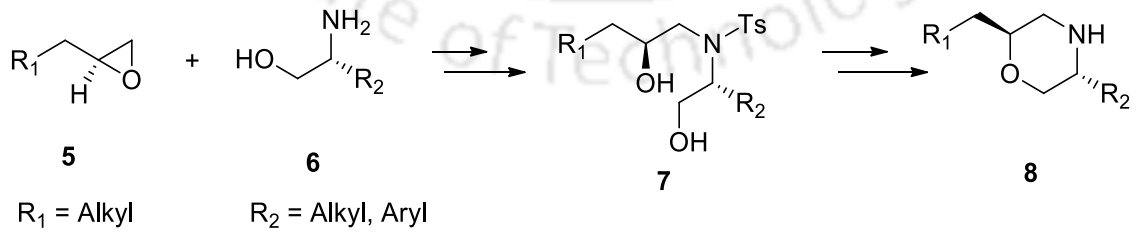
Alkaloid polygonapholine (**4**), which was isolated from the methanol extract of the rhizome of *Polygonatum altelobatum* Hayata, a Formosan endemic plant, has been used as a tonic drug in Taiwan (*Figure 3.1.1*).[3] Apart from these, morpholines are used in organic synthesis as bases or *N*-alkylating agents.[4] Substituted chiral morpholine derivatives have also been used as chiral auxiliaries in numerous asymmetric synthesis.[5] In addition to these, they are used as versatile synthetic units in organic synthesis particularly for the construction of agrochemicals, fungicides and bactericides.[6]

3.2. An overview of relevant synthetic methods

Several synthetic approaches have been developed for the preparation of morpholines such as ring closure of amino diols,[7] ring closure of amino alcohols and bromosulphonium salts,[8] double allylic substitution by amino alcohols,[9] cyclization of *N*-tethered halo-alcohols,[10] reductive amination of diketones,[11] reductive etherification of *N*-tethered ketoalcohols,[12] cyclization of *O*-protected amino alcohols,[13] oxirane ring opening by tosylamide and subsequent cyclization,[14] ring opening of aziridines[15] and intramolecular cyclization of *N*-tethered alkene-alkanols.[16] These methods have their own advantages and disadvantages. Therefore, development of new and efficient methods is imperative especially to address the issue of stereoselectivity.

Myers *et al*. have developed a method for enantio- and diastereo-selective synthesis of *trans*-2,5-disubstituted morpholine derivatives **8** from enantiopure epoxides **5**. The synthesis began with the reaction of enantiopure epoxides **5** with chiral amino alcohols **6** to give amino diol adducts **7**, followed by regioselective hydroxyl activation/ring closure of the resulting amino diol adducts **7** to give morpholine **8** (*Scheme 3.2.1*).[7b]



Scheme 3.2.1

Aggarwal and his group have demonstrated the reaction of bromoethylsulfonium salt **9** with 1,2-/1,3-aminoalcohols/thiols and diamines giving 6- and 7-membered heterocyclic

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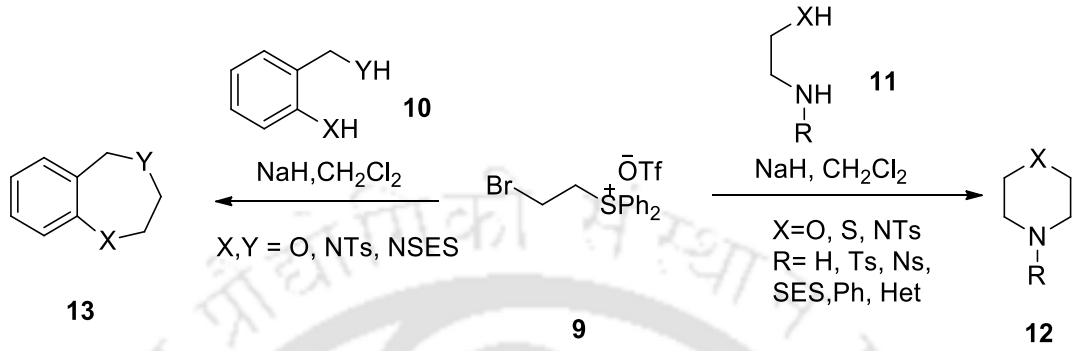
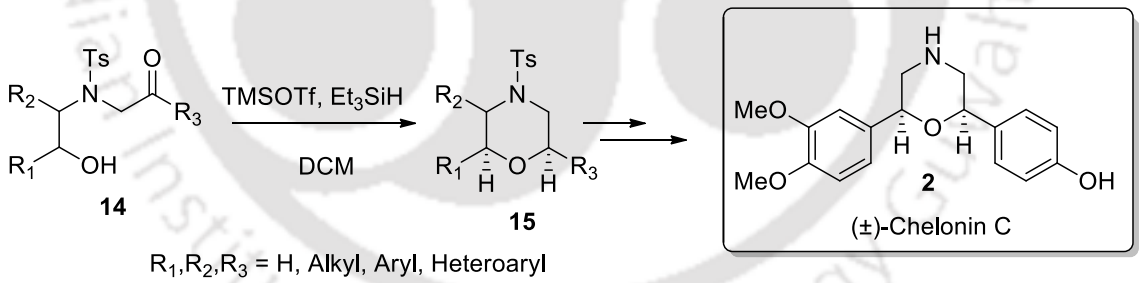
compounds in good-to-excellent yields. The reactions proceed through the generation of a vinyl sulfonium salt in presence of a base (NaH) followed by annulation to give 1,4-heterocyclic compounds such as morpholines, thiomorpholines and piperazines **12** and benzoxazepines **13** (*Scheme 3.2.2*).[8]



Scheme 3.2.2

Gharpure *et al.* have developed a strategy for the stereoselective synthesis of substituted morpholine derivatives **15** *via* intramolecular reductive etherification reaction of *N*-tethered keto-alcohols **14**. The method is highly diastereoselective with dr ≥ 19:1. The methodology was further extended to the first diastereoselective total synthesis of (±)-chelonin C (**2**) (*Scheme 3.2.3*).[12]



Scheme 3.2.3

Young and co-workers developed a methodology for the diastereoselective synthesis of substituted morpholines using intramolecular aza-Michael reactions between *N*-Cbz carbamates and enones **16** catalyzed by Brønsted acids (*Scheme 3.2.4*). It was observed that the Brønsted acids with different strengths produce different diastereomers.[17]

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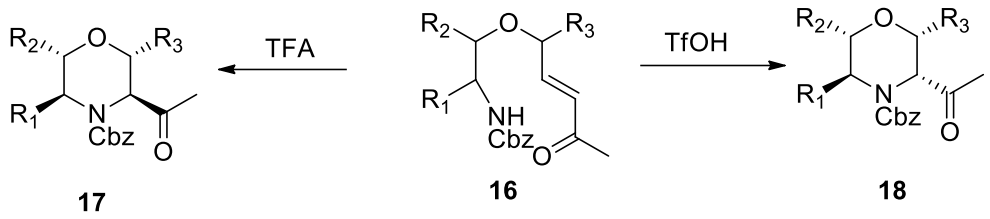
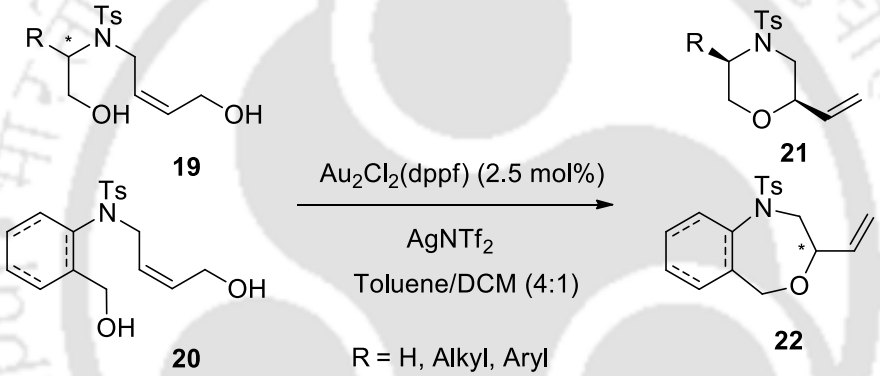


R_1 = H, Alkyl, Aryl; R_2, R_3 = H, Aryl

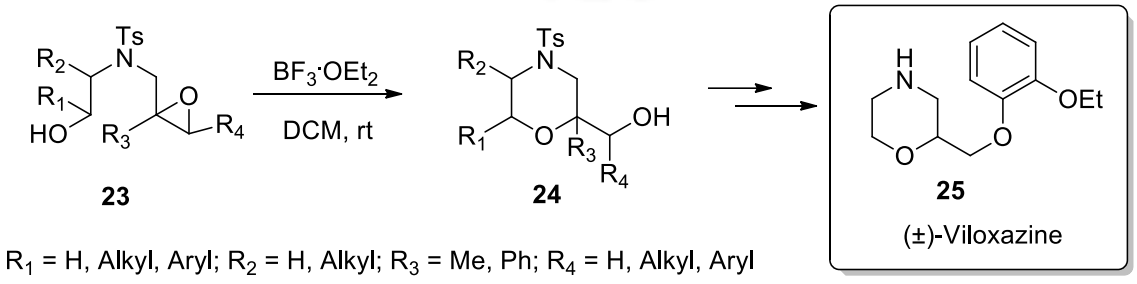
Scheme 3.2.4

Recently, Tragni and co-workers reported an intramolecular gold(I)-catalyzed asymmetric nucleophilic alkoxylation of allylic alcohols for the synthesis of vinyl-substituted morpholines **21** and 1,4-oxazepanes **22** (*Scheme 3.2.5*).[18] The method is highly diastereoselective with dr upto 98:2.



Scheme 3.2.5

In 2016, our group reported a methodology for the synthesis of substituted morpholines **24** *via* $BF_3{\cdot}OEt_2$ mediated intramolecular cyclization reaction of *N*-tethered alkanol-epoxide **23** in good yields (*Scheme 3.2.6*). The methodology was further extended towards the total synthesis of biologically active molecule (±)-viloxazine (**25**).[19]



R_1 = H, Alkyl, Aryl; R_2 = H, Alkyl; R_3 = Me, Ph; R_4 = H, Alkyl, Aryl

Scheme 3.2.6

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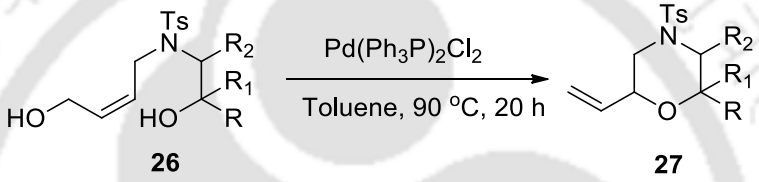
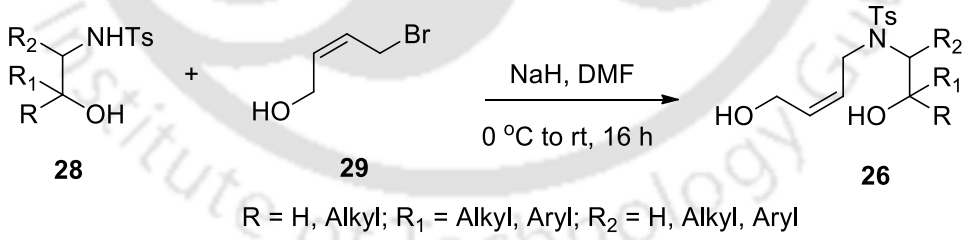
3.3. Present strategy and objective

Palladium(II) salts have been used for the synthesis of oxygen heterocycles *via* intramolecular oxypalladation reaction,[20] but the use of palladium(II) salts in the synthesis of morpholines *via* oxypalladation is not yet reported. Considering the ability of palladium(II) compounds to participate in oxypalladation reaction, we now present in this chapter an efficient method for the diastereoselective synthesis of 2,6-disubstituted and 2,5-disubstituted morpholines using intramolecular C-O bond formation of *N*-tethered diols consisting of alkanol and alkenol catalyzed by palladium(II) chloride. Thus the reaction of *N*-tethered diols **26** in toluene at 90 ^{o}C catalyzed by palladium(II) chloride gave 2-vinyl substituted morpholines **27** in excellent yields (*Scheme 3.3.1*).



Scheme 3.3.1

The *N*-tethered diols **26** were synthesized from *N*-tosylated aminoalcohols **28** and (*Z*)-4-bromobut-2-en-1-ol **29** in presence of sodium hydride (*Scheme 3.3.2*).



Scheme 3.3.2

3.4. Results and discussion

3.4.1. Optimization studies

In order to optimize the reaction condition, (*Z*)-*N*-(4-Hydroxybut-2-en-1-yl)-*N*-(2-hydroxyethyl)-4-methylbenzene-sulfonamide **26a** was treated with 5 mol % of

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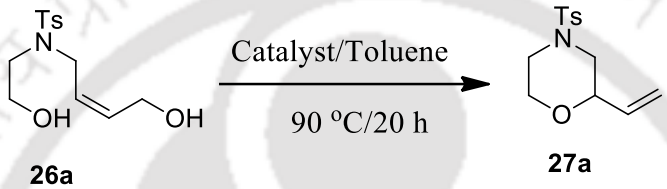
preformed $Pd(Ph_3P)_2Cl_2$ in toluene at 90 °C for 20 h, and 4-tosyl-2-vinylmorpholine **27a** was obtained in 85% yield (Table 3.4.1.1, entry 1). The reaction was also performed in the absence of PPh_3 with 5 mol % of other palladium(II) sources such as $Pd(OAc)_2$ and $PdCl_2$ to give the same product in 20 and 65% yields, respectively (entries 2 & 3). Similarly, reaction with a mixture of $PdCl_2$ (5 mol %) and Ph_3P (10 mol %) gave 85% yield, which suggested that the complex catalyst was formed in situ (entry 4). Reaction was also carried out with 5 mol % of $Pd(Ph_3P)_4$ but resulted in no yield (entry 5). This indicates that the reaction proceeds *via* oxypalladation and elimination processes.

Table 3.4.1.1. Optimization of the reaction



26a **27a**

Entry	Catalyst (mol %)	**27a** Yield (%)[a]
1	$PdCl_2(Ph_3P)_2$ (5)	85
2	$Pd(OAc)_2$ (5)	20
3	$PdCl_2$ (5)	65
4	$PdCl_2$ (5), Ph_3P (10)	85
5	$Pd(Ph_3P)_4$ (5)	No reaction

[a]Yield refers to isolated yield.

3.4.2. Substrate scope of the reaction

Having obtained the optimized conditions in hand, we further examined the scope of the reaction with variety of substrates (**26a**-**26s**). The results are outlined in the Table 3.4.2.1. It was observed from Table 3.4.2.1 that primary (**26a**-**e**), secondary, including benzylic or allylic alcohols (**26f**-**o**, **q**, **r**, and **s**), and tertiary alcohols (**26p**) undergo the reaction smoothly in the optimized reaction conditions and furnished the corresponding cyclized product in good yields. The reaction worked well for both electron-withdrawing and electron-donating groups on the aromatic ring of benzylic alcohol substrates, suggesting little influence of the aryl group, and produced the desired morpholines in good yields. The reaction with substrate having both primary and secondary allylic alcohol groups **26q** (entry 17), primary allylic alcohol coordinates with palladium(II) selectively under these reaction conditions, and this accounts for the observed formation

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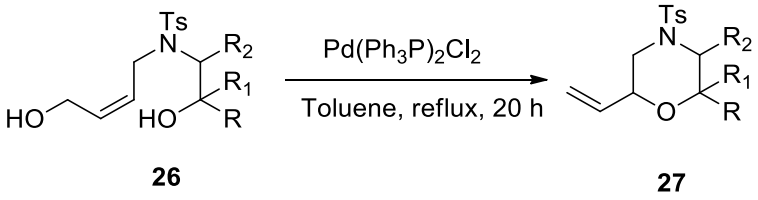
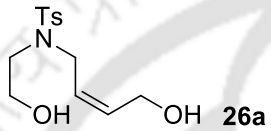
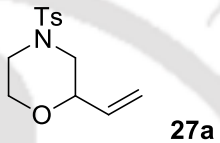
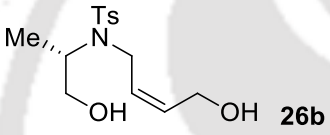
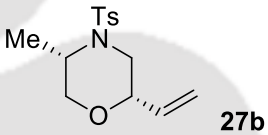
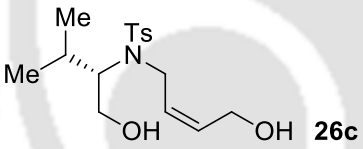
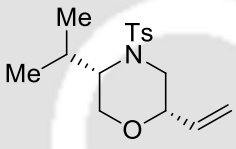
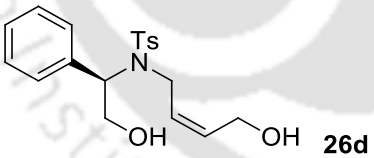
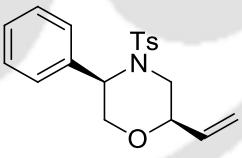
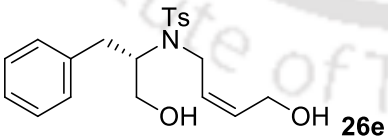
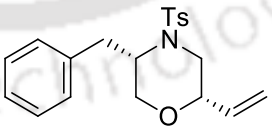
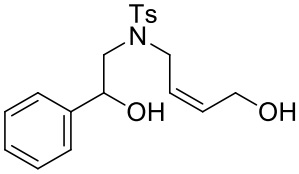
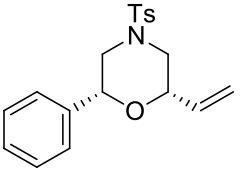
of product **27q**. Sterically hindered tertiary alcohol **26p** (entry 16) gave comparatively lower yield (65%), indicating that nucleophilic addition was rate limiting.

Table 3.4.2.1. Synthesis of morpholines



26 **27**

Entry	Substrate **26**	Product **27**	dr[a]	Yield (%)[b]
1	 **26a**	 **27a**	---	85
2	 **26b**	 **27b**	100:0	88
3	 **26c**	 **27c**	100:0	72
4	 **26d**	 **27d**	97:3	80
5	 **26e**	 **27e**	86:14	78
6	 **26f**	 **27f**	91:9	90

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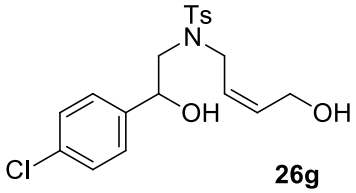
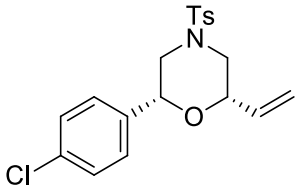
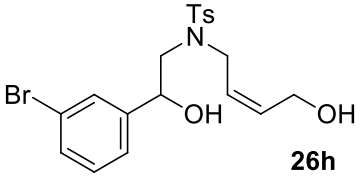
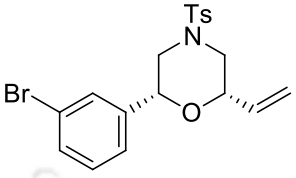
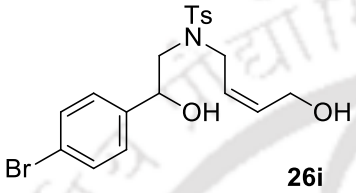
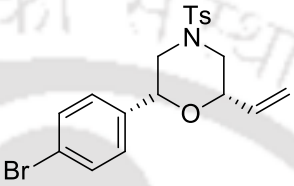
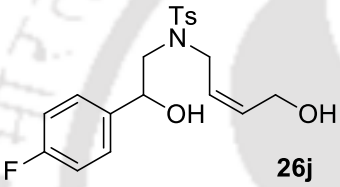
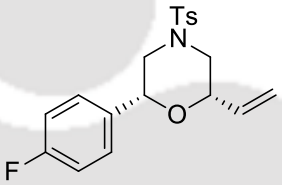
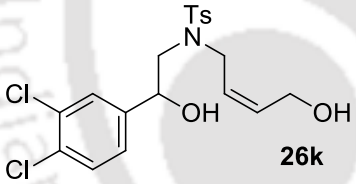
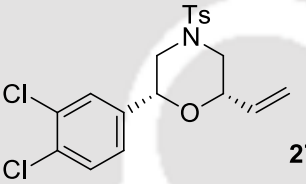
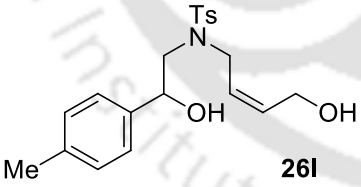
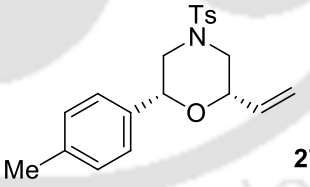
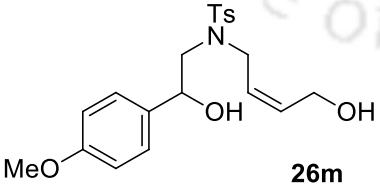
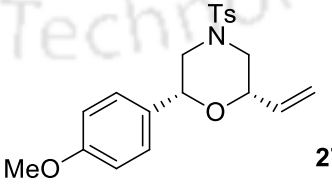
7	 **26g**	 **27g**	100:0	80
8	 **26h**	 **27h**	100:0	85
9	 **26i**	 **27i**	91:9	84
10	 **26j**	 **27j**	72:28	75
11	 **26k**	 **27k**	100:0	74
12	 **26l**	 **27l**	93:7	82
13	 **26m**	 **27m**	97:3	85

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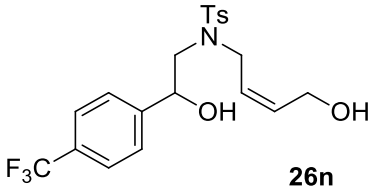
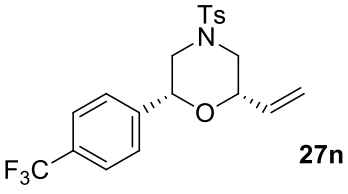
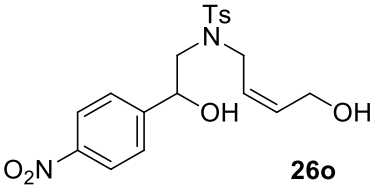
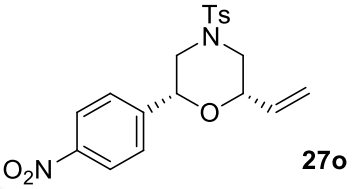
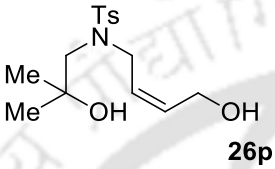
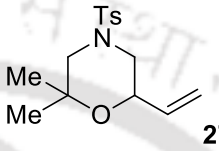
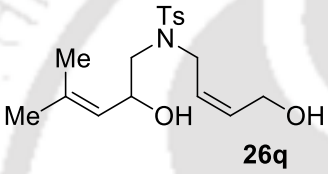
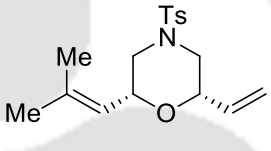
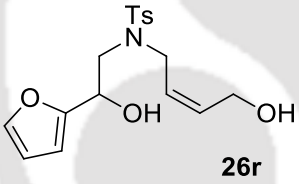
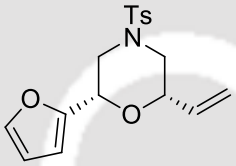
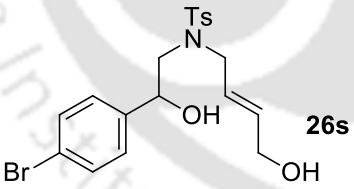
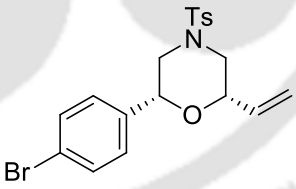
14	 **26n**	 **27n**	100:0	82
15	 **26o**	 **27o**	93:7	84
16	 **26p**	 **27p**	---	65
17	 **26q**	 **27q**	91:9	70
18	 **26r**	 **27r**	90:10	72
19	 **26s**	 **27s**	63:37	70

[a]The ratio was determined by ^{1}H NMR spectroscopy of crude products. [b]Yield refers to isolated yield. All the products were characterized by ^{1}H, ^{13}C NMR and mass spectrometry.

3.4.3. Stereochemistry of the morpholines

The reaction is highly diastereoselective with the predominant formation of *cis* isomers for both 2,6-disubstituted and 2,5-disubstituted morpholines. The relative stereochemistry of the 2,6-disubstituted morpholines was determined by 2D nuclear Overhauser enhancement spectroscopy (NOESY) of compound **27o**. It showed a clear

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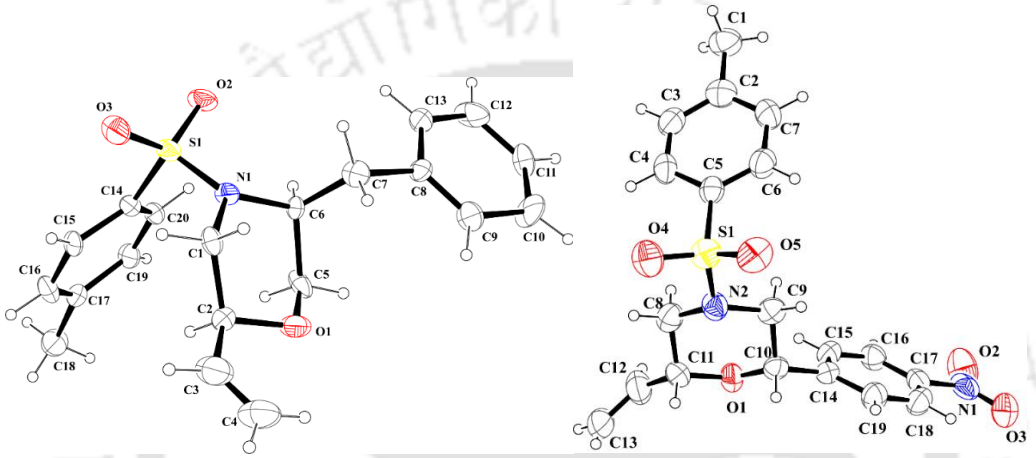
characteristic nOe correlations between the hydrogens C-2H and C-6H, which clearly indicates that the substituents at 2,6 positions are *cis* to each other. The stereochemistry of 2,6-disubstituted morpholines was further confirmed by X-ray crystallographic analysis of compound **27o** (*Figure 3.4.3.1*).[21] Similarly, the relative stereochemistry of the 2,5-disubstituted morpholines was determined by X-ray crystallographic analysis of compound **27e** (*Figure 3.4.3.1*).[21] In contrast, the substrate having an *E*- configured alkene, alcohol **26s** (Table 3.4.2.1, entry 19), showed poor *cis*/*trans* diastereoselectivity (63:37).



27e **27o**

Figure 3.4.3.1. *ORTEP diagram of* **27e** *and* **27o**

3.4.4. Plausible mechanism for the synthesis of *cis*-2,6-disubstituted and *cis*-2,5-disubstituted morpholines

The proposed mechanism of the reaction is similar to that reported by Tragni[18] and others.[20] The reaction proceeds *via* stepwise oxypalladation and elimination processes.[20d] Palladium(II) chloride forms a π-complex with allylic alcohol in an *anti*-fashion to form transition states **A** and **A′**, of which **A′** is unstable due to the presence of the allylic group in the axial position. In the favored transition state **A**, both vinyl and R groups take the equatorial position to minimize the 1,3-diaxial interaction. The stability of the transition state **A** may be further increased by the formation of a second six-membered ring due to the hydrogen bonding between the two hydroxyl groups.[20d] The transition state **A** after nucleophilic attack by the hydroxyl group *via* S_N2' pathway forms intermediate **B**.

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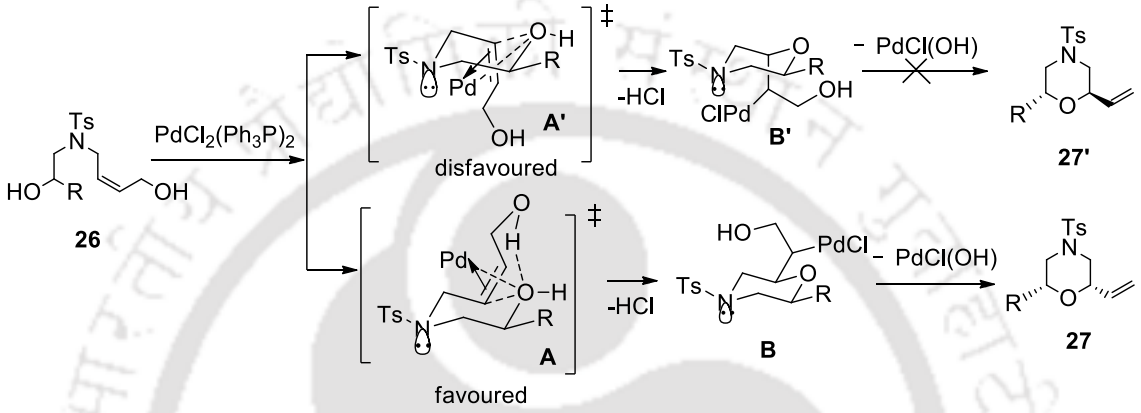
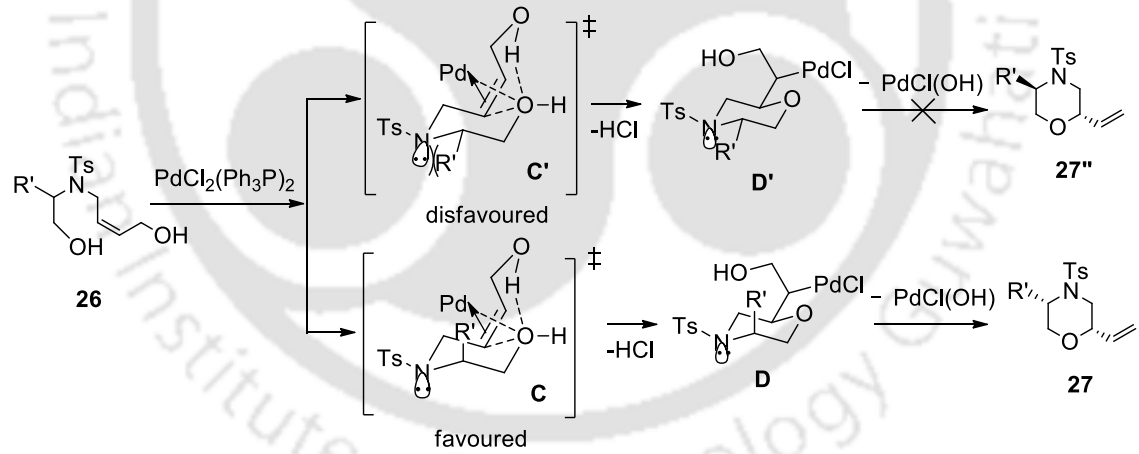
Intermediate **B**, after either *syn*- or *anti*-elimination, forms vinyl substituted morpholines **27a** and **27f-7r** (*Scheme 3.4.4.1a*).[20d] The formation of compounds **27b-7e** can be explained as follows. The R' groups take the axial position in the transition state **C** to minimize the repulsive force between the lone pair over nitrogen and C-C bond pair of R′ group attached to the C-5 position. The nucleophilic attack of the transition state **C** by the hydroxyl group *via* S_N2' pathway forms intermediate **D**, which after either *syn*- or *anti*-elimination, forms vinyl substituted morpholines **27b-7e** (*Scheme 3.4.4.1b*).



Scheme 3.4.4.1a



Scheme 3.4.4.1b

Scheme 3.4.4.1 *Proposed mechanism of the reaction*

3.5. Total synthesis of (±)-chelonin A

Chelonin A is an aromatic alkaloid with tryptophan and tyrosine unit, isolated from the marine sponge *Chelonaplysilla* sp. found in a marine lake in Palau. It was isolated by

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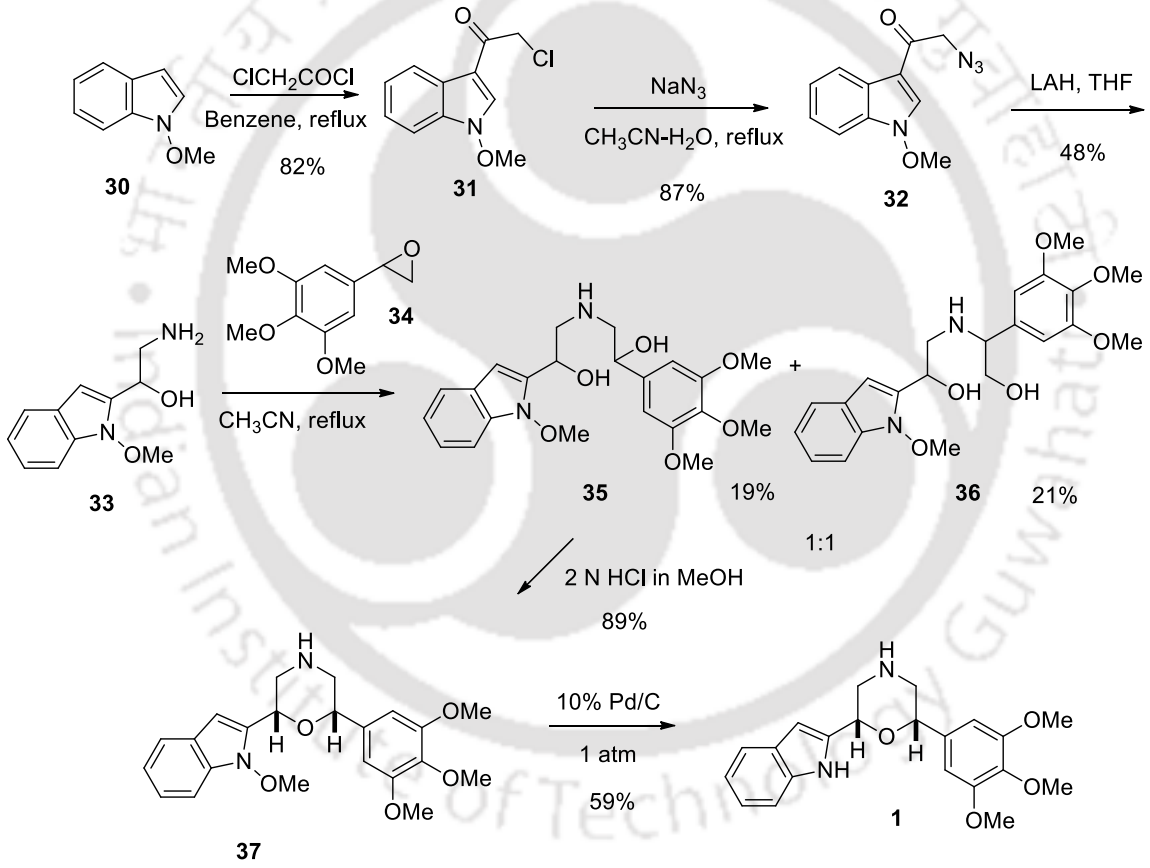
Faulkner and co-workers in 1991. This compound have been reported to exhibit antimicrobial activity against *Bacillus subtilis* and *in-vivo* anti-inflammatory activities.[1]

3.5.1. Literature review on total synthesis of (±)-chelonin A

There are only limited methods available in literature for the total synthesis of (±)-chelonin A. In 1995, Masanori Somei *et al.* have described the first total synthesis of (±)-chelonin A (**1**) starting from 1-methoxyindole **30** followed by six steps as shown in *scheme 3.5.1.1*. The key steps of their synthesis involves the ring opening of the epoxide **34** with amino alcohol **33**, acid catalysed cyclisation of the diol **35** followed by removal of the *N*-methoxy group to furnish the natural product (±)-chelonin A.[22]



Scheme 3.5.1.1

In 2015, Gharpure and co-workers reported the total synthesis of (±)-chelonin A in good yield and excellent diastereoselectivity by starting from *α*-keto amine **37** in three steps as shown in *scheme 3.5.1.2*.[23] The key step of the synthesis involved the TMSOTf catalysed

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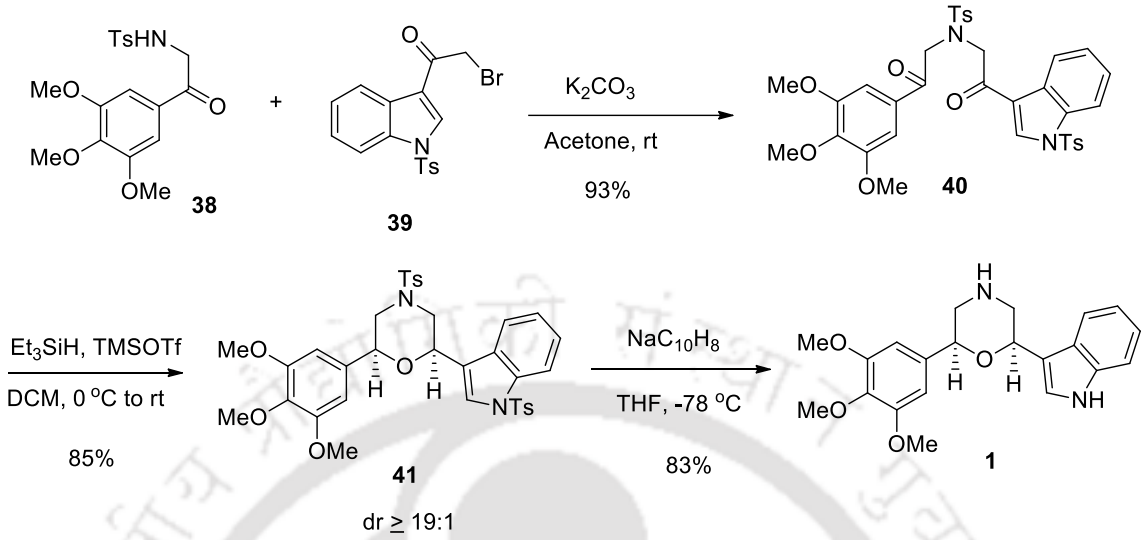
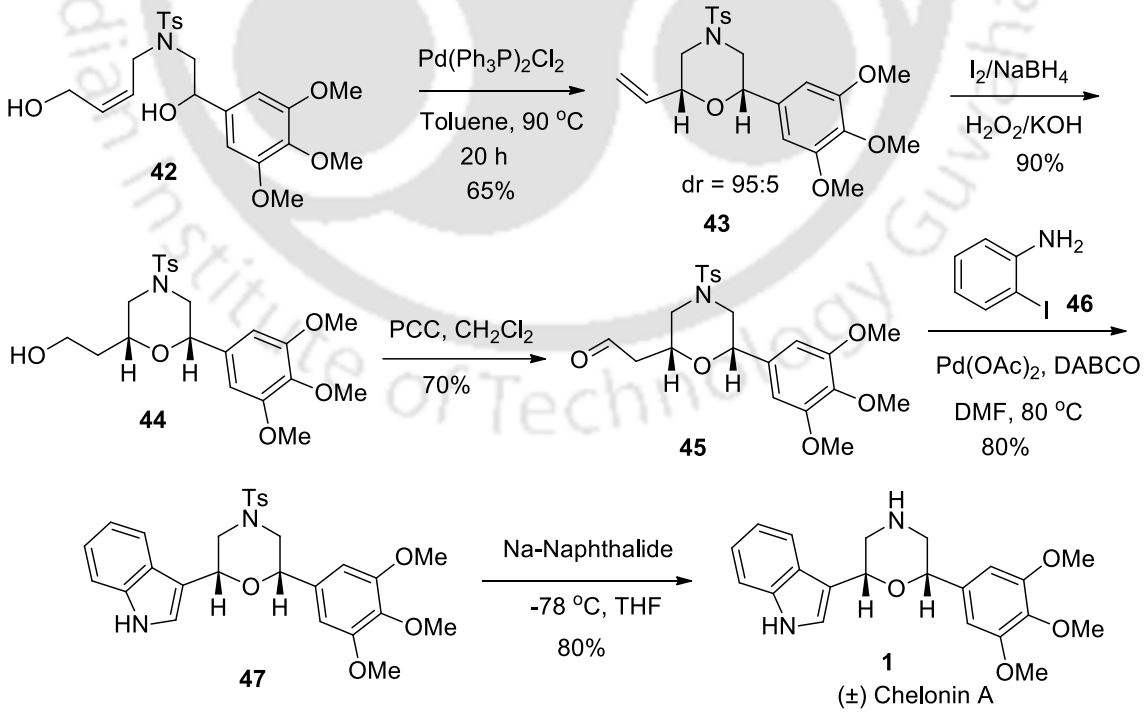
intramolecular reductive etherification of diketone **40** in presence of Et_3SiH to give the corresponding *N*-protected (±)-chelonin A **41**.



Scheme 3.5.1.2

3.5.2. Our strategy on total synthesis of (±)-chelonin A

Here, we have utilized our methodology for the total synthesis of (±)-chelonin A.



Scheme 3.5.2.1

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To start with, the diol **42** was treated with 5 mol % of $Pd(PPh_3)_2Cl_2$ to give diastereomeric mixture of morpholine **43** with a ratio of 95:5 in 65% yield along with 20% unreacted starting material. Conversion of the olefinic group of the major diastereomer of morpholine **43** into alcohol **44** by using $NaBH_4/I_2$ (*via* hydroboration oxidation reaction) followed by PCC oxidation gave aldehyde **45** as a single diastereomer in 70% yield. The aldehyde **45** was treated with 2-iodoaniline **46** in the presence of palladium acetate and DABCO to give tosylated (±)-chelonin A **47** in 80% yield. The final compound **1** was obtained by detosylation with sodium naphthalide at -78 ^oC in 80% yield and 26% overall yield. The ^1H and ^{13}C NMR data were found in good agreement with the literature.

3.6. Conclusion:

In conclusion, we have developed an efficient method for the synthesis of substituted morpholines *via* palladium(II) chloride catalysed intramolecular cyclization reaction of *N*-tethered alkenols in good yields. The reaction is compatible with a wide range of functional groups such as ether, nitro, fluoro, chloro, bromo and furan. The major advantage of this reaction is that it regioselectively generates a vinyl group at position 2 of the morpholine ring, which can be used for the synthesis of natural product (±)-chelonin A.

3.7. Experimental section

3.7.1. Instrumentation and characterization

As described in chapter 2 section 2.6.1.

3.7.2. General procedure for synthesis of *N*-Tethered Alkenols (26a-26s):

To a stirred solution of NaH (2.2 mmol, 60% in mineral oil) in dry DMF (5 mL) was added dropwise a solution of the *N*-tosylated amino alcohol **28** (2.0 mmol) in dry DMF (10 mL) at 0 °C (N_2 atmosphere). After 20 min, a solution of (*Z*)-4-bromobut-2-en-1-ol **29** (2 mmol) in DMF (5 mL) was added, and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, a few drops of methanol were added at 0 °C, and the solution was poured into ethyl acetate (50 mL). The organic phase

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was washed with brine (3 × 30 mL), dried over anhydrous Na_2SO_4. Evaporation of solvent gives the crude product, which was purified by silica gel column chromatography using ethyl acetate and hexane as eluents to give the *N*-tethered alkenol **26a-26s**.

3.7.3. Synthesis of (*Z*)-*N*-(4-Hydroxybut-2-en-1-yl)-*N*-(2-hydroxyethyl)-4-methylbenzene-sulfonamide (26a):

To a stirred solution of NaH (88 mg, 2.2 mmol, 60% in mineral oil) in dry DMF (5 mL) was added dropwise a solution of the *N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (430 mg, 2 mmol) in dry DMF (5 mL) at 0 °C (N_2 atmosphere). After 20 min, a solution of (*Z*)-4-bromobut-2-en-1-ol **29** (300 mg, 2 mmol) in DMF (5 mL) was added, and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, a few drops of methanol were added at 0 °C, and the solution was poured into ethyl acetate (50 mL). The organic phase was washed with brine (3 × 30 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified on silica gel column chromatography using hexane and ethyl acetate (hexane:EtOAc, 3:2) as eluents to give **26a** (342 mg, 60%) as colourless solid.

3.7.4. General procedure for the synthesis of vinylmorpholine (27a-27s):

A solution of *N*-tethered alkenol **26** (0.5 mmol) and $Pd(PPh_3)_2Cl_2$ (0.025 mmol) in 10 mL of toluene was heated at 90 °C for 20 h. The reaction was monitored by TLC. After completion of the reaction, ethyl acetate (15 mL) was poured into the reaction mixture and passed through celite. The filtrate was concentrated in vacuo and purified by column chromatography using ethyl acetate and hexane as eluents to give the morpholine derivatives.

3.7.5. Synthesis of 4-Tosyl-2-vinylmorpholine (27a):

A solution of (*Z*)-*N*-(4-hydroxybut-2-en-1-yl)-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide **26a** (143 mg, 0.5 mmol) and $PdCl_2(PPh_3)_2$ (18 mg, 0.025 mmol) in 10 mL of toluene was heated at 90 °C for 20 h. The reaction was monitored by TLC. After completion of the reaction, ethyl acetate (15 mL) was poured into the reaction mixture and passed through celite. The filtrate was concentrated in vacuo and

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purified by column chromatography using ethyl acetate and hexane as eluents (EtOAc:hexane, 1:4) to give **27a** (114 mg, 85%) as colourless solid.

3.7.6. Syntheis of (*Z*)-*N*-(2-Hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (42):

To a stirred solution of NaH (176 mg, 4.4 mmol, 60% in a mineral oil) in dry DMF (10 mL) was added dropwise a solution of the *N*-(2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)-4-methylbenzenesulfonamide (1.524 g, 4 mmol) in dry DMF (15 mL) at 0 °C (N_2 atmosphere). After 20 min, DMF (5 mL) solution of (*Z*)-4-bromobut-2-en-1-ol **29** (600 mg, 4 mmol) was added, and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, a few drops of methanol were added at 0 °C, and the solution was poured in ethyl acetate (60 mL). The organic phase was washed with brine (3 × 40 mL), dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography using ethyl acetate and hexane as eluents (EtOAc:hexane, 3:2) to give 1.074 g (60% yield) of (*Z*)-*N*-(2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide **42** as light yellow solid.

3.7.7. Synthesis of 4-Tosyl-2-(3,4,5-trimethoxyphenyl)-6-vinylmorpholine (43):

To a solution of (*Z*)-*N*-(2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide **42** (902 mg, 2 mmol) in toluene was added $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol) and the solution was refluxed for 20 h. After completion of the reaction (monitored by TLC), ethyl acetate (20 mL) was poured in to the reaction mixture and passed through celite. The filtrate was concentrated in vacuo and purified by column chromatography using ethyl acetate and hexane as eluents (EtOAc:hexane, 1:3) to give 4-tosyl-2-(3,4,5-trimethoxyphenyl)-6-vinylmorpholine **43** (0.56 g, 65% yield) as white solid.

3.7.8. Synthesis of 2-(4-Tosyl-6-(3,4,5-trimethoxyphenyl)morpholin-2-yl)ethanol (44):

In a two-neck septum-capped round-bottom flask, $NaBH_4$ (87 mg, 2.3 mmol) was added to dry THF (25 mL). Iodine (292 mg, 1.15 mmol) in dry THF (10 mL) was added under

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nitrogen atmosphere over 2.5 h at 0 °C. A THF solution of 4-tosyl-2-(3,4,5-trimethoxyphenyl)-6-vinylmorpholine **43** (500 mg, 1.15 mmol) was added, and the reaction mixture was stirred for 6 h at 25 °C. It was quenched with water (2 mL), THF (10 mL) was added and oxidized using H_2O_2 (30%, 10 mL)/NaOH (3N, 10 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extract was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification by column chromatography using ethyl acetate and hexane as eluents (EtOAc:hexane, 1:1) gives 468 mg (90%) of 2-(4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholin-2-yl)ethanol **44** as a colourless solid.

3.7.9. Synthesis of 2-(4-Tosyl-6-(3,4,5-trimethoxyphenyl)morpholin-2-yl)acetaldehyde (45):

Pyridinium chlorochromate (286 mg, 1.33 mmol) was suspended in DCM (10 mL), and the alcohol **44** (400 mg, 0.89 mmol) in 10 mL of DCM was rapidly added at room temperature. The reaction mixture was stirred for another 2 h. The reaction mixture was diluted with 5 volumes of anhydrous ether and filtered through a short celite pad. Evaporation of the solvent at reduced pressure followed by purification by column chromatography using ethyl acetate and hexane as eluents (EtOAc:hexane, 1:1) gives 280 mg (70%) of 2-(4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholin-2-yl)acetaldehyde as a colourless solid.

3.7.10. Synthesis of 2-(1*H*-Indol-2-yl)-4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholine (47):

A mixture of *o*-iodoaniline **46** (107 mg, 0.49 mmol), aldehyde **45** (200 mg, 0.45 mmol), and DABCO (151.2 mg, 1.35 mmol) in dry DMF (7 mL) was degassed for 20 min. $Pd(OAc)_2$ (5.2 mg, 0.0225 mmol) was added to the reaction, and the resulting reaction mixture was heated at 80 °C until the reaction was complete (12 h). The reaction mixture was cooled to room temperature and diluted with water. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. Purification of the crude product by column chromatography using ethyl acetate and hexane as eluents (EtOAc:hexane, 2:3) gives 188 mg (80%) of 2-(1*H*-indol-2-yl)-4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholine as a colourless solid.

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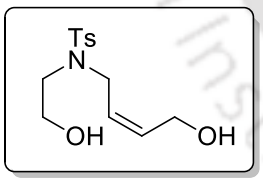
3.7.11. Synthesis of (±) chelonin A (1):

To the solution of 2-(1*H*-indol-2-yl)-4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholine **47** (100 mg, 0.19 mmol) in dry THF (10 mL) at -78 °C was added freshly prepared sodium naphthalenide solution (obtained by addition of naphthalene (245 mg, 1.9 mmol) to the vigorously stirred solution of Na (45.6 mg, 1.9 mmol) in dry THF (4 mL) at room temperature for 2 h) and the resulting solution was stirred at the same temperature for another 1 h. The reaction mixture was quenched by the addition of saturated NH_4Cl solution at -78 °C and slowly warmed to room temperature. Then, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic layer was treated with dil. HCl (3 × 5 mL). The aqueous layer was neutralized with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4, and the solvent was evaporated in vacuo followed by purification by column chromatography using dichloromethane and methanol as eluents (CH_2Cl_2:MeOH, 19:1), which gives (±) chelonin A (56 mg, 80%) as a colourless solid.

3.8. Spectral data

(*Z*)-*N*-(4-Hydroxybut-2-en-1-yl)-*N*-(2-hydroxyethyl)-4-methylbenzene-sulfonamide (26a):



White solid, mp. 48-50 °C; R_f (hexane/EtOAc 3:2) 0.6; yield 342 mg, 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 3.24 (t, *J* = 5.4 Hz, 2 H), 3.73 (t, *J* = 5.4 Hz, 2 H), 3.94 (d, *J* = 7.2 Hz, 2 H), 4.13 (d, *J* = 6.6 Hz, 2 H), 5.35−5.38 (m, 1 H), 5.74−5.79 (m, 1 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.68 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl3) δ 21.7, 46.1, 49.9, 57.7, 61.7, 127.0, 127.3, 130.1, 133.0, 136.4, 143.9; IR (KBr, neat) 3579, 2959, 2853, 1923, 1652, 1593, 1449, 1163, 887, 764 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{20}NO_4S$ $(M+H)^+$ 286.1108, found 286.1119.

(*Z*)-*N*-(4-Hydroxybut-2-en-1-yl)-*N*-(1-hydroxypropan-2-yl)-4-methylbenzenesulfonamide (26b):

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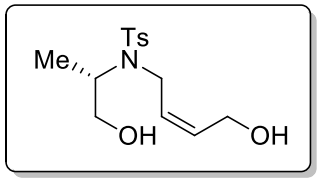
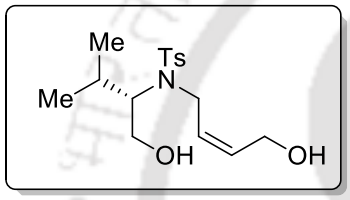


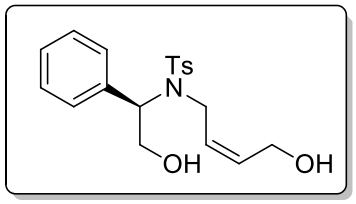
Colourless oil; R_f (hexane/EtOAc 3:2) 0.55; yield 400 mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 7.2 Hz, 3 H), 2.41 (s, 3 H), 3.49-3.57 (m, 2 H), 3.86 (dd, *J* = 16.2 and 7.8 Hz, 1 H), 3.95-3.98 (m, 2 H), 4.21 (d, *J* = 7.2 Hz, 2 H), 5.55-5.60 (m, 1 H), 5.71-5.76 (m, 1 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.71 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 21.7, 40.3, 55.5, 58.0, 64.8, 127.3, 129.5, 130.0, 131.3, 137.8, 143.7; IR (KBr, neat) 3477, 2980, 2856, 1920, 1647, 1599, 1457, 1324, 1153, 1014, 870, 760 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{22}NO_4S$ $(M + H)^+$ 300.1264, found 300.1274. $[\alpha]_D^{20}$ +24.9 (c 1.0 $CHCl_3$).

(*Z*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (26c):



Pale yellow oil; R_f (hexane/EtOAc 3:2) 0.51; yield 405 mg, 62%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.69 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 1.79-1.85 (m, 2 H), 2.20 (brs, 1 H), 2.42 (s, 3 H), 3.44-3.48 (m, 1 H), 3.62 (dd, *J* = 12.0 and 8.4 Hz, 1 H), 3.75 (dd, *J* = 12.0 and 9.6 Hz, 1 H), 3.91 (dd, *J* = 16.2 and 7.2 Hz, 1 H), 4.02 (dd, *J* = 16.2 and 7.2 Hz, 1 H), 4.21 (d, *J* = 7.2 Hz, 2 H), 5.60-5.65 (m, 1 H), 5.72-5.77 (m, 1 H), 7.28 (d, *J* = 7.8 Hz, 2 H), 7.72 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.3, 20.8, 21.7, 28.2, 41.3, 58.1, 62.4, 66.3, 127.6, 129.5, 129.8, 131.1, 138.2, 143.6; IR (KBr, neat) 3468, 2873, 1920, 1654, 1470, 1290, 1170, 1008, 883, 773 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{26}NO_4S$ $(M + H)^+$ 328.1577, found 328.1598. $[\alpha]_D^{20}$-5.7 (c 0.8 $CHCl_3$).

(*Z*)-*N*-(2-Hydroxy-1-phenylethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (26d):



Pale yellow oil; R_f (hexane/EtOAc 3:2) 0.53; yield 404 mg, 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (brs, 1 H), 2.43 (s, 3 H), 2.57 (brs, 1 H), 3.75 (dd, *J* = 16.2 and 7.8 Hz, 1 H), 3.91 (dd, *J* = 16.2 and 6.0 Hz, 1 H), 4.00-4.10 (m, 4 H), 5.03 (t, *J* = 7.2 Hz, 1 H), 5.28-5.32 (m, 1 H), 5.60-5.64 (m, 1 H), 6.99 (d, *J* = 7.2 Hz, 2 H), 7.22-7.26 (m, 3 H), 7.28 (d, *J* = 7.8 Hz, 2 H), 7.72 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 41.7, 57.9, 62.1, 62.4, 127.6, 128.3, 128.5, 128.9,

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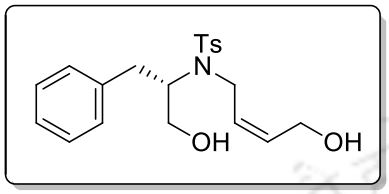
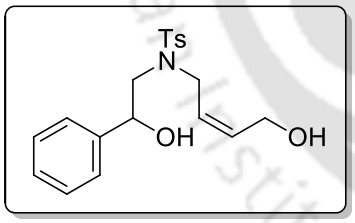
129.0, 129.9, 131.3, 136.0, 137.9, 143.8; IR (KBr, neat) 3528, 2924, 1598, 1496, 1305, 1164, 1017, 891, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421, found 362.1431. $[\alpha]_D^{20}$ -28.4 (c 0.8 $CHCl_3$).

(*Z*)-*N*-(1-Hydroxy-3-phenylpropan-2-yl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (26e):



White solid, mp. 108-110 ^oC; R_f (hexane/EtOAc 3:2) 0.50; yield 450 mg, 60%; ^1H NMR (600 MHz, $CDCl_3$) δ 2.38 (s, 3 H), 2.64 (dd, *J* = 13.8 and 6.0 Hz, 1 H), 2.78 (dd, *J* = 13.8 and 8.4 Hz, 1 H), 2.92 (brs, 1 H), 3.58-3.65 (m, 2 H), 4.00 (d, *J* = 6.6 Hz, 2 H), 4.04-4.09 (m, 1 H), 4.21 (d, *J* = 6.6 Hz, 2 H), 5.54-5.59 (m, 1 H), 5.70-5.73 (m, 1 H), 7.03 (d, *J* = 7.2 Hz, 2 H), 7.18-7.20 (m, 5 H), 7.58 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 36.2, 41.3, 58.0, 61.7, 62.6, 126.7, 127.3, 128.7, 129.1, 129.4, 129.8, 131.2, 137.6, 137.8, 143.6; IR (KBr, neat) 3479, 2967, 1658, 1598, 1496, 1289, 1158, 872, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{26}NO_4S$ $(M + H)^+$ 376.1577, found 376.1576. $[\alpha]_D^{20}$ -28.0 (c 0.9 $CHCl_3$).

(*Z*)-*N*-(2-Hydroxy-2-phenylethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (26f):



Pale yellow oil; R_f (hexane/EtOAc 3:2) 0.52; yield 397 mg, 55%; ^1H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.29 (d, *J* = 6.0 Hz, 2 H) 3.98 (dd, *J* = 15.6 and 7.2 Hz, 1 H), 4.02 (dd, *J* = 15.6 and 7.8 Hz, 1 H), 4.11 (dd, *J* = 12.6 and 6.6 Hz, 1 H), 4.19 (dd, *J* = 12.6 and 6.6 Hz, 1 H), 4.98 (t, *J* = 6.0 Hz, 1 H), 5.34-5.39 (m, 1 H), 5.78-5.83 (m, 1 H), 7.29 (d, *J* = 7.8 Hz, 3 H), 7.30-7.36 (m, 4 H), 7.69 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.5, 55.6, 58.0, 73.8, 126.1, 127.1, 127.5, 128.3, 128.8, 130.1, 133.1, 136.6, 141.5, 143.9; IR (KBr, neat) 3400, 2924, 1640, 1448, 1331, 1155, 1087, 816, 656 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421, found 362.1405.

(*Z*)-*N*-(2-(4-Chlorophenyl)-2-hydroxyethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (26g):

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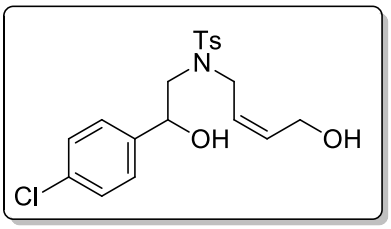
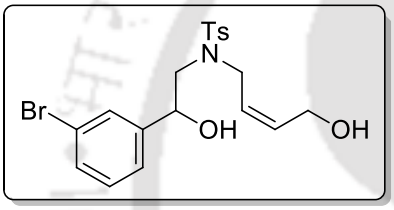


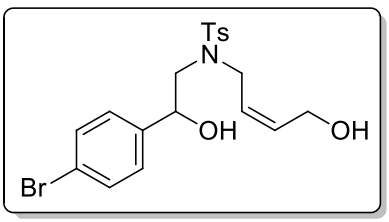
Pale yellow oil; R_f (hexane/EtOAc 3:2) 0.48; yield 482 mg, 61%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.23 (brs, 1 H), 2.42 (s, 3 H), 3.23 (d, *J* = 5.4 Hz, 2 H), 3.38 (brs, 1 H), 3.95-4.03 (m, 2 H), 4.13 (dd, *J* = 13.2 and 7.2 Hz, 1 H), 4.19 (dd, *J* = 13.2 and 6.6 Hz, 1 H), 4.96 (t, *J* = 6.0 Hz, 1 H), 5.33-5.38 (m, 1 H), 5.78-5.83 (m, 1 H), 7.26-7.30 (m, 6 H), 7.67 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.5, 55.5, 57.9, 73.1, 126.9, 127.4, 127.5, 128.9, 130.1, 133.2, 133.9, 136.4, 140.0, 144.1; IR (KBr, neat) 3500, 2924, 2870, 1597, 1492, 1334, 1159, 1090, 817, 658 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}ClNO_4S$ $(M + H)^+$ 396.1031, found 396.1038.

(*Z*)-*N*-(2-(3-Bromophenyl)-2-hydroxyethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (26h):



White solid, mp. 108-110 °C; R_f (hexane/EtOAc 3:2) 0.50; yield 570 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 2.60 (brs, 1 H), 3.24 (d, *J* = 6.0 Hz, 2 H), 3.73 (brs, 1 H), 3.94-4.03 (m, 2 H), 4.11 (dd, *J* = 12.6 and 5.4 Hz, 1 H), 4.17 (dd, *J* = 12.6 and 7.2 Hz, 1 H), 4.93 (t, *J* = 6.0 Hz, 1 H), 5.30-5.35 (m, 1 H), 5.76-5.81 (m, 1 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 7.27-7.30 (m, 3 H), 7.39 (d, *J* = 8.4 Hz, 1 H), 7.49 (s, 1 H), 7.67 (t, *J* = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.4, 55.3, 57.8, 73.0, 122.8, 124.8, 126.8, 127.4, 129.2, 130.1, 130.3, 131.1, 133.2, 136.3, 143.9, 144.0; IR (KBr, neat) 3521, 2922, 2856, 1919, 1596, 1473, 1332, 1161, 889, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}BrNO_4S$ $(M + H)^+$ 440.0526, found 440.0532.

(*Z*)-*N*-(2-(4-bromophenyl)-2-hydroxyethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (26i):



White solid, mp. 111-113 °C; R_f (hexane/EtOAc 3:2) 0.53; yield 570 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.22 (d, *J* = 6.0 Hz, 2 H), 3.96 (dd, *J* = 15.6 and 7.2 Hz, 1 H), 4.00 (dd, *J* = 15.6 and 7.8 Hz, 1 H), 4.10 (dd, *J* = 13.2 and 6.6 Hz, 1 H), 4.16 (dd, *J* = 13.2 and 7.2 Hz, 1 H), 4.92 (t, *J* = 6.0 Hz, 1 H), 5.29-5.33 (m, 1 H), 5.76-5.80 (m, 1 H),

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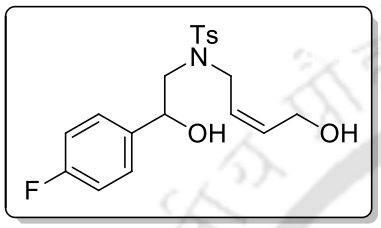
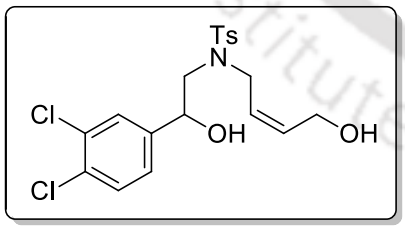
7.21 (d, *J* = 7.8 Hz, 2 H), 7.28 (d, *J* = 7.8 Hz, 2 H), 7.43 (d, *J* = 7.8 Hz, 2 H), 7.65 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.3, 55.1, 57.7, 73.1, 121.9, 126.7, 127.3, 127.8, 130.1, 131.8, 133.2, 136.3, 140.5, 144.0; IR (KBr, neat) 3530, 2925, 2850, 1925, 1590, 1480, 1356, 1156, 878, 755 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}BrNO_4S$ $(M + H)^+$ 440.0526, found 440.0529.

(*Z*)-*N*-(2-(4-Fluorophenyl)-2-hydroxyethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (26j):



Pale yellow oil; R_f (hexane/EtOAc 3:2) 0.50; yield 500 mg, 66%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 3.20-3.26 (m, 2 H), 3.94 (dd, *J* = 15.6 and 6.6 Hz, 1 H), 4.01 (dd, *J* = 15.6 and 7.8 Hz, 1 H), 4.09 (dd, *J* = 12.6 and 7.2 Hz, 1 H), 4.15 (dd, *J* = 12.6 and 6.6 Hz, 1 H), 4.94 (t, *J* = 7.8 Hz, 1 H), 5.27-5.32 (m, 1 H), 5.74-5.78 (m, 1 H), 7.00 (t, *J* = 7.2 Hz, 2 H), 7.27-7.31 (m, 4 H), 7.66 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.3, 55.2, 57.7, 73.0, 115.5 (d, *J* = 22.5 Hz), 126.7, 127.3, 127.7 (d, *J* = 9.0 Hz), 130.1, 133.2, 136.4, 137.3, 144.0, 162.5 (d, *J* = 244.5 Hz, C-F); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 38.05; IR (KBr, neat) 3500, 2926, 2857, 1600, 1450, 1338, 1222, 737 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}FNO_4S$ $(M + H)^+$ 380.1326, found 380.1332.

(*Z*)-*N*-(2-(3,4-Dichlorophenyl)-2-hydroxyethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (26k):



Pale yellow oil; R_f (hexane/EtOAc 3:2) 0.48; yield 549 mg, 64%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 2.55 (brs, 1 H), 3.22 (d, *J* = 6.0 Hz, 2 H), 3.79 (brs, 1 H), 3.96-4.03 (m, 2 H), 4.09-4.20 (m, 2 H), 4.90-4.94 (m, 1 H), 5.32-5.36 (m, 1 H), 5.78-5.82 (m, 1 H), 7.18 (d, *J* = 7.8 Hz, 1 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.37 (dd, *J* = 8.4 and 3.6 Hz, 1 H), 7.44 (s, 1 H), 7.65 (dd, *J* = 7.8 and 1.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 46.5, 55.2, 57.8, 72.5, 125.6, 126.8, 127.3, 128.1, 130.1, 130.7, 131.9, 132.8, 133.2, 136.2, 141.8, 144.2; IR (KBr, neat) 3419, 2925, 2854, 1641, 1470, 1337, 1159, 1089, 820, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{22}Cl_2NO_4S$ $(M + H)^+$ 430.0641, found 430.0643.

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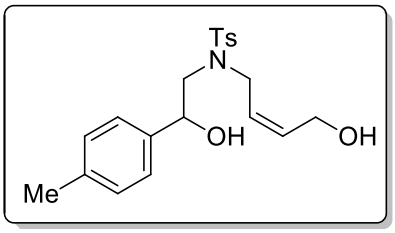
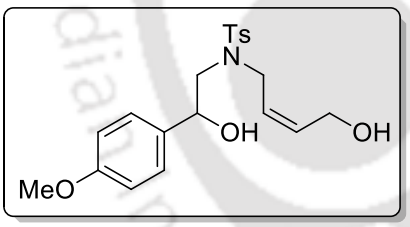
(*Z*)-*N*-(2-Hydroxy-2-(*p*-tolyl)ethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (26l):



Pale yellow oil; R_f (hexane/EtOAc 3:2) 0.51; yield 435 mg, 58%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.32 (s, 3 H), 2.40 (s, 3 H), 2.83 (brs, 1 H), 3.25 (d, *J* = 6.0 Hz, 2 H), 3.54 (brs, 1 H), 3.94 (dd, *J* = 15.6 and 6.6 Hz, 1 H), 4.03 (dd, *J* = 15.6 and 7.8 Hz, 1 H), 4.09 (dd, *J* = 12.6 and 6.6 Hz, 1 H), 4.15 (dd, *J* = 12.6 and 7.2 Hz, 1 H), 4.90 (t, *J* = 5.4 Hz, 1 H), 5.30 (dd, *J* = 17.4 and 7.8 Hz, 1 H), 5.76 (dd, *J* = 17.4 and 6.6 Hz, 1 H), 7.12 (d, *J* = 7.8 Hz, 2 H), 7.21 (d, *J* = 7.8 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.66 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 21.7, 46.2, 55.2, 57.7, 73.6, 126.0, 126.8, 127.3, 129.4, 130.0, 133.1, 136.6, 137.8, 138.5, 143.8; IR (KBr, neat) 3498, 2923, 1640, 1330, 1153, 1086, 939, 816, 754 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{26}NO_4S$ $(M + H)^+$ 376.1577, found 376.1594.

(*Z*)-*N*-(2-hydroxy-2-(4-methoxyphenyl)ethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (26m):



White solid, mp. 79-81 ^oC; R_f (hexane/EtOAc 3:2) 0.45; yield 523 mg, 67%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 2.69 (brs, 1 H), 3.25 (d, *J* = 6.0 Hz, 2 H), 3.43 (brs, 1 H), 3.78 (s, 3 H), 3.94 (dd, *J* = 15.6 and 6.0 Hz, 1 H), 4.03 (dd, *J* = 15.6 and 7.8 Hz, 1 H), 4.07 (dd, *J* = 12.6 and 6.0 Hz, 1 H), 4.16 (dd, *J* = 12.6 and 6.0 Hz, 1 H), 4.90 (t, *J* = 5.4 Hz, 1 H), 5.31 (dd, *J* = 16.2 and 7.8 Hz, 1 H), 5.76 (dd, *J* = 16.2 and 6.0 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 7.24-7.29 (m, 4 H), 7.67 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 46.2, 55.2, 55.5 57.7, 73.4, 114.1, 126.9, 127.3, 127.4, 130.0, 133.1, 133.6, 136.6, 143.8, 159.5; IR (KBr, neat) 3503, 2925, 2839, 1612, 1447, 1334, 1249, 1156, 1032, 835, 745 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{26}NO_5S$ $(M + H)^+$ 392.1526, found 392.1530.

(*Z*)-*N*-(2-Hydroxy-2-(4-(trifluoromethyl)phenyl)ethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (26n):

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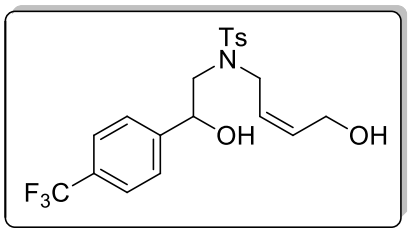
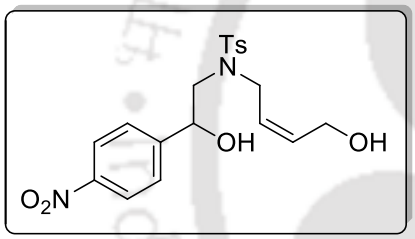


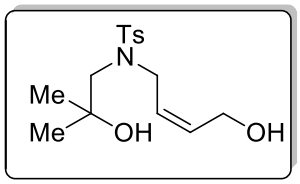
White solid, mp. 78-79 °C; R_f (hexane/EtOAc 3:2) 0.52; yield 506 mg, 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 3.25 (d, *J* = 6.0 Hz, 2 H), 3.95-4.07 (m, 2 H), 4.11-4.22 (m, 2 H), 5.03-5.06 (m, 1 H), 5.34 (dd, *J* = 17.6 and 7.2 Hz, 1 H), 5.77-583 (m, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.0 Hz, 2 H), 7.66 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 46.5, 55.4, 57.8, 73.2, 122.9, 125.7 (q, *J* = 3.8 Hz), 126.46, 126.5, 126.8, 127.4, 127.5, 130.1, 134.7 (q, *J* = 294.4 Hz), 144.2, 145.5; ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 13.4; IR (KBr, neat) 3508, 2926, 2873, 1621, 1599, 1449, 1320, 1169, 1014, 851, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{23}F_3NO_4S$ $(M + H)^+$ 430.1294, found 430.1308.

(*Z*)-*N*-(2-Hydroxy-2-(4-nitrophenyl)ethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (26o):



White solid, mp. 75-77 °C; R_f (hexane/EtOAc 3:2) 0.40; yield 416 mg, 51%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 2.50 (brs, 1 H), 3.25 (d, *J* = 7.8 Hz, 2 H), 3.96 (brs, 1 H), 4.00 (d, *J* = 7.2 Hz, 2 H), 4.12-4.21 (m, 2 H), 5.08-5.10 (m, 1 H), 5.33 (dd, *J* = 18.0 and 7.8 Hz, 1 H), 5.80 (m, 1 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 8.16 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 46.4, 54.9, 57.7, 72.8, 123.8, 126.6, 127.0, 127.3, 130.1, 133.3, 136.0, 144.3, 147.5, 148.9; IR (KBr, neat) 3558, 2923, 2858, 1602, 1529, 1449, 1309, 1160, 1089, 747 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}N_2O_6S$ $(M + H)^+$ 407.1271, found 407.1279.

(*Z*)-*N*-(2-Hydroxy-2-methylpropyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (26p):



White solid, mp. 97-99 °C; R_f (hexane/EtOAc 3:2) 0.50; yield 375 mg, 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.23 (s, 6 H), 2.15 (brs, 1 H), 2.42 (s, 3 H), 2.80 (brs, 1 H), 3.66 (s, 2 H), 4.13 (d, *J* = 6.0 Hz, 2 H), 4.21 (d, *J* = 6.0 Hz, 2 H), 5.67-5.75 (m, 2 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.74 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 25.0, 43.7, 58.3, 63.8, 69.8, 127.3, 129.9, 130.0, 131.3, 140.0, 143.6; IR

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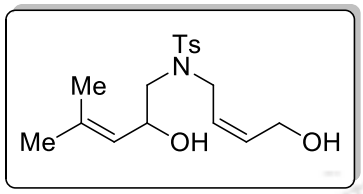
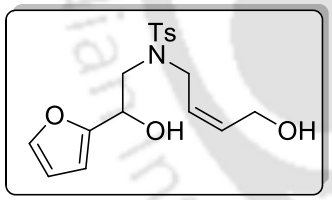
(KBr, neat) 3505, 2926, 2880, 1646, 1472, 1310, 1147, 1090, 879, 736, 660 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{24}NO_4S$ $(M + H)^+$ 314.1421, found 314.1443.

(*Z*)-*N*-(2-Hydroxy-4-methylpent-3-en-1-yl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (26q):



Pale yellow oil; R_f (hexane/EtOAc 3:2) 0.55; yield 325 mg, 48%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.66 (s, 3 H), 1.69 (s, 3 H), 2.41 (s, 3 H), 2.80 (brs, 2 H), 3.07 (d, *J* = 4.2 Hz, 2 H), 3.97 (dd, *J* = 15.6 and 6.0 Hz, 1 H), 4.03 (dd, *J* = 15.6 and 7.8 Hz, 1 H), 4.09 (dd, *J* = 12.6 and 6.0 Hz, 1 H), 4.15 (dd, *J* = 12.6 and 7.2 Hz, 1 H), 4.56-4.61 (m, 1 H), 5.07 (d, *J* = 7.2 Hz, 1 H), 5.32-5.39 (m, 1 H), 5.75-5.80 (m, 1 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.68 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.6, 21.7, 25.9, 46.4, 53.4, 57.7, 68.6, 124.5, 127.1, 127.4, 130.0, 133.0, 136.6, 137.3, 143.8; IR (KBr, neat) 3418, 2922, 1648, 1447, 1335, 1158, 1019, 817, 769 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{26}NO_4S$ $(M + H)^+$ 340.1577, found 340.1598.

(*Z*)-*N*-(2-(Furan-2-yl)-2-hydroxyethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (26r):



Pale yellow oil; R_f (hexane/EtOAc 3:2) 0.50; yield 414 mg, 59%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.44 (d, *J* = 5.2 Hz, 2 H), 3.90 (dd, *J* = 15.6 and 10.2 Hz, 1 H), 4.00 (dd, *J* = 15.6 and 12.0 Hz, 1 H), 4.08 (dd, *J* = 13.2 and 6.8 Hz, 1 H), 4.15 (dd, *J* = 13.2 and 7.6 Hz, 1 H), 4.95 (t, *J* = 6.0 Hz, 1 H), 5.29 (dd, *J* = 17.6 and 7.2 Hz, 1 H), 5.72-5.79 (m, 1 H), 6.29-6.32 (m, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.35 (m, 1 H), 7.69 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 46.3, 52.1, 57.7, 67.5, 107.4, 110.6, 126.6, 127.4, 130.1, 133.2, 136.5, 142.4, 143.9, 153.8; IR (KBr, neat) 3585, 2923, 2870, 1632, 1598, 1449, 1330, 1160, 1094, 917, 749 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{22}NO_5S$ $(M + H)^+$ 352.1213, found 352.1211.

(*E*)-*N*-(2-(4-Bromophenyl)-2-hydroxyethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (26s):

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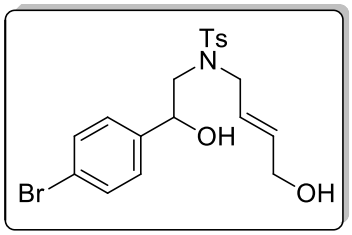
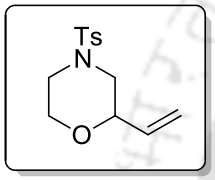


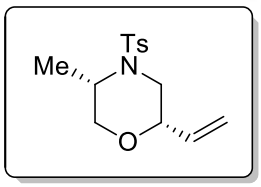
Pale yellow oil; R_f (hexane/EtOAc 3:2) 0.50; yield 518 mg, 59%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 3.06 (dt, *J* = 15.6 and 2.4 Hz, 1 H), 3.16-3.26 (m, 1 H), 3.64-3.69 (m, 1 H), 3.74-3.76 (m, 1 H), 3.96 (brs, 2 H), 4.81-4.86 (m, 1 H), 5.40-5.45 (m, 1 H), 5.62-5.65 (m, 1 H), 7.12-7.14 (m, 1 H), 7.19-7.22 (m, 2 H), 7.25-7.37 (m, 2 H), 7.34-7.37 (m, 1 H), 7.57-7.60 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 51.7, 55.7, 62.6, 72.9, 121.8, 126.2, 127.5, 128.7, 130.0, 131.7, 134.5, 136.0, 141.5, 143.9; IR (KBr, neat) 3604, 2922, 2865, 1597, 1457, 1377, 1164, 1096, 973, 747 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}BrNO_4S$ $(M + H)^+$ 440.0526, found 440.0529.

4-Tosyl-2-vinylmorpholine (27a):



White solid, mp. 126-128 °C; R_f (hexane/EtOAc 4:1) 0.55; yield 114 mg, 85%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.12 (dd, *J* = 11.4 and 10.8 Hz, 1 H), 2.40 (dd, *J* = 11.4 and 3.0 Hz, 1 H), 2.44 (s, 3 H), 3.52 (d, *J* = 11.4 Hz, 1 H), 3.60 (d, *J* = 11.4 Hz, 1 H), 3.72 (dd, *J* = 11.4 and 10.8 Hz, 1 H), 3.95 (d, *J* = 11.4 Hz, 1 H), 4.04-4.06 (m, 1 H), 5.21 (d, *J* = 10.8 Hz, 1 H), 5.33 (d, *J* = 16.8 Hz, 1 H), 5.69-5.75 (m, 1 H), 7.34 (d, *J* = 7.8Hz, 2 H), 7.63 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 45.5, 50.2, 65.9, 75.9, 117.9, 128.0, 130.0, 132.3, 134.8, 144.2; IR (KBr, neat) 2923, 2856, 1651, 1451, 1267, 1163, 1095, 938, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{18}NO_3S$ $(M + H)^+$ 268.1002 found 268.1023.

(2*S,5*S**)-5-Methyl-4-tosyl-2-vinylmorpholine (27b):**



Colourless oil; R_f (hexane/EtOAc 4:1) 0.52; yield 124 mg, 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, *J* = 7.2 Hz, 3 H), 2.43 (s, 3 H), 2.87 (dd, *J* = 12.8 and 10.8 Hz, 1 H), 3.60 (dd, *J* = 12.8 and 2.4 Hz, 1 H), 3.67 (d, *J* = 1.2 Hz, 2 H), 3.83-3.88 (m, 1 H), 3.98 (q, *J* = 6.8 Hz, 1 H), 5.24 (d, *J* = 10.8 Hz, 1 H), 5.35 (d, *J* = 17.6 Hz, 1 H), 5.72-5.80 (m, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.70 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.7, 44.4, 48.4, 71.4, 76.4, 117.9, 127.3, 130.0, 134.9, 137.6, 143.6; IR (KBr, neat) 2982, 2857, 1648, 1598, 1457, 1258, 1183, 927, 764 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{20}NO_3S$ $(M + H)^+$ 282.1158 found 282.1179. $[\alpha]_D^{20}$ +22.9 (c 0.9 $CHCl_3$).

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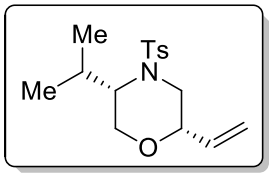
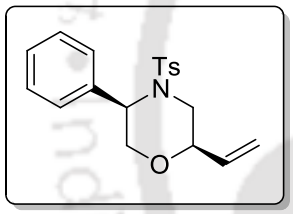
(2*S,5*S**)-5-Isopropyl-4-tosyl-2-vinylmorpholine (27c):**



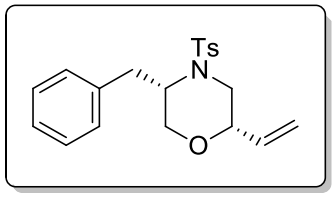
White solid, mp. 100-102 ^{o}C; R_f (hexane/EtOAc 4:1) 0.55; yield 111 mg, 72%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (d, *J* = 7.2 Hz, 3 H), 0.96 (d, *J* = 7.2 Hz, 3 H), 2.19-2.26 (m, 1 H), 2.43 (s, 3 H), 2.92 (dd, *J* = 15.0 and 11.4 Hz, 1 H), 3.28-3.30 (m, 2 H), 3.54-3.58 (m, 1 H), 3.67 (dd, *J* = 15.0 and 4.2 Hz, 1 H), 3.88 (d, *J* = 11.4 Hz, 1 H), 5.17 (d, *J* = 10.8 Hz, 1 H), 5.24 (d, *J* = 17.4 Hz, 1 H), 5.63-5.69 (m, 1 H), 7.30 (d, *J* = 7.8 Hz, 2 H), 7.71 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.9, 20.1, 21.7, 25.5, 45.5, 59.1, 66.2, 75.0, 117.8, 127.1, 130.0, 135.0, 138.8, 143.5; IR (KBr, neat) 2980, 2857, 1649, 1598, 1466, 1277, 1179, 1088, 929, 818, 680 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{24}NO_3S$ $(M + H)^+$ 310.1471 found 310.1460. $[\alpha]_D^{20}$ +3.2 (c 0.9 $CHCl_3$).

(2*R,5*R**)-5-Phenyl-4-tosyl-2-vinylmorpholine (27d, Diastereomeric mixture with a ratio of 97:3; Data only for major isomer):**



Colourless oil; R_f (hexane/EtOAc 4:1) 0.54; yield 137 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 2.91 (dd, *J* = 14.0 and 11.2 Hz, 1 H), 3.65 (dd, *J* = 14.0 and 2.4 Hz, 1 H), 3.82 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 3.85-3.90 (m, 1 H), 4.32 (d, *J* = 12.0 Hz, 1 H), 4.93 (d, *J* = 3.2 Hz, 1 H), 5.20 (d, *J* = 10.4 Hz, 1 H), 5.31 (d, *J* = 17.6 Hz, 1 H), 5.67-5.76 (m, 1 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 7.24-7.30 (m, 3 H), 7.45-7.48 (m, 2 H), 7.59 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 45.5, 54.5, 68.7, 75.7, 117.9, 127.2, 127.8, 128.4, 128.5, 129.8, 134.8, 137.6, 137.9, 143.6; IR (KBr, neat) 2918, 2859, 1649, 1598, 1495, 1338, 1165, 1096, 937, 817, 737 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{22}NO_3S$ $(M + H)^+$ 344.1315 found 344.1313. $[\alpha]_D^{20}$ -17.4 (c 0.8 $CHCl_3$).

(2*S,5*S**)-5-Benzyl-4-tosyl-2-vinylmorpholine (27e, Diastereomeric mixture with a ratio of 97:3; Data only for major isomer):**



White solid, mp. 118-120 ^{o}C; R_f (hexane/EtOAc 4:1) 0.50; yield 139 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 2.68 (dd, *J* = 13.2 and 4.8 Hz, 1 H), 2.96-3.05 (m, 2 H), 3.47 (dd, *J* = 12.0 and 2.0 Hz, 1 H), 3.65 (dd, *J* = 13.2 and

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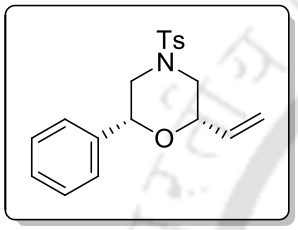
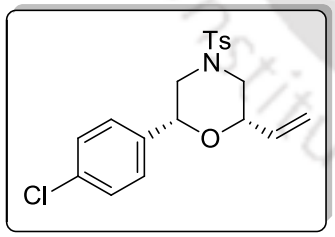
2.8 Hz, 1 H), 3.69 (d, *J* = 12.0 Hz, 1 H), 3.86-3.91 (m, 1 H), 3.97-4.02 (m, 1 H), 5.27 (d, *J* = 10.8 Hz, 1 H), 5.31 (d, *J* = 16.0 Hz, 1 H), 5.76-5.85 (m, 1 H), 7.16-7.20 (m, 2 H), 7.22-7.30 (m, 5 H), 7.63 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 34.1, 45.1, 54.3, 67.3, 76.2, 118.1, 126.8, 127.3, 128.9, 129.7, 130.1, 135.0, 137.7, 138.0, 143.7; IR (KBr, neat) 2921, 2857, 1599, 1495, 1344, 1164, 1090, 1057, 816, 703 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{24}NO_3S$ $(M + H)^+$ 358.1471 found 358.1483. $[\alpha]_D^{20}$ -7.6 (c 0.6 $CHCl_3$).

(2*R,6*S**)-2-Phenyl-4-tosyl-6-vinylmorpholine (27f, Diastereomeric mixture with a ratio of 97:3; Data only for major isomer):**



White solid, mp. 102-104 °C; R_f (hexane/EtOAc 4:1) 0.51; yield 154 mg, 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.12-2.19 (m, 2 H), 2.43 (s, 3 H), 3.73 (d, *J* = 11.4 Hz, 1 H), 3.78 (d, *J* = 10.8 Hz, 1 H), 4.28-4.31 (m, 1 H), 4.71 (dd, *J* = 10.8 and 2.4 Hz, 1 H), 5.24 (d, *J* = 10.2 Hz, 1 H), 5.42 (d, *J* = 17.4 Hz, 1 H), 5.79-5.85 (m, 1 H), 7.29-7.34 (m, 7 H), 7.60 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 49.6, 51.5, 71.2, 76.0, 117.7, 126.1, 127.8, 128.3, 128.5, 129.9, 132.2, 134.6, 138.7, 144.0; IR (KBr, neat) 2925, 2847, 1648, 1598, 1495, 1230, 1170, 1091, 930, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{22}NO_3S$ $(M + H)^+$ 344.1315 found 344.1293.

(2*R,6*S**)-2-(4-Chlorophenyl)-4-tosyl-6-vinylmorpholine (27g):**



White solid, mp. 141-143 °C; R_f (hexane/EtOAc 4:1) 0.50; yield 151 mg, 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.08-2.15 (m, 2 H), 2.43 (s, 3 H), 3.72-3.77 (m, 2 H), 4.27-4.30 (m, 1 H), 4.68 (dd, *J* = 11.4 and 1.8 Hz, 1 H), 5.25 (d, *J* = 10.8 Hz, 1 H), 5.41 (d, *J* = 17.4 Hz, 1 H), 5.77-5.83 (m, 1 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.30-7.33 (m, 4 H), 7.60 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 49.7, 51.6, 76.5, 76.7, 118.0, 127.6, 128.0, 128.9, 130.1, 132.3, 134.3, 134.6, 137.3, 144.3; IR (KBr, neat) 2987, 2852, 1648, 1598, 1491, 1349, 1166, 1087, 1017, 975, 776, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}ClNO_3S$ $(M + H)^+$ 378.0925 found 378.0927.

(2*R,6*S**)-2-(3-Bromophenyl)-4-tosyl-6-vinylmorpholine (27h):**

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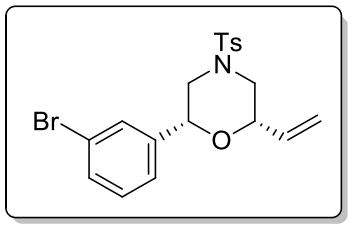
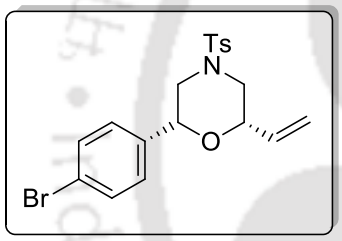


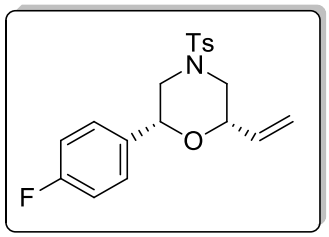
White solid, mp. 115-117 °C; R_f (hexane/EtOAc 4:1) 0.56; yield 179 mg, 85%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.09-2.15 (m, 2 H), 2.43 (s, 3 H), 3.73 (d, *J* = 11.4 Hz, 1 H), 3.76 (d, *J* = 11.4 Hz, 1 H), 4.26-4.29 (m, 1 H), 4.68 (dd, *J* = 10.2 and 1.8 Hz, 1 H), 5.26 (d, *J* = 10.2 Hz, 1 H), 5.41 (d, *J* = 16.8 Hz, 1 H), 5.78-5.84 (m, 1 H), 7.20 (t, *J* = 7.8 Hz, 1 H), 7.25 (d, *J* = 7.8 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.42 (d, *J* = 7.8 Hz, 1 H), 7.50 (s, 1 H), 7.60 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 49.6, 51.5, 76.3, 76.6, 118.1, 122.8, 124.9, 127.9, 129.3, 130.1, 130.2, 131.5, 132.2, 134.5, 141.0, 144.3; IR (KBr, neat) 2923, 2849, 1597, 1570, 1451, 1345, 1169, 1092, 1025, 972, 737, 662 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}BrNO_3S$ $(M + H)^+$ 422.0420 found 422.0414.

(2*R,6*S**)-2-(4-Bromophenyl)-4-tosyl-6-vinylmorpholine (27i, Diastereomeric mixture with a ratio of 97:3; Data only for major isomer):**



White solid, mp. 149-151 °C; R_f (hexane/EtOAc 4:1) 0.60; yield 177 mg, 84%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.07-2.14 (m, 2 H), 2.43 (s, 3 H), 3.71-3.76 (m, 2 H), 4.26-4.32 (m, 1 H), 4.67 (d, *J* = 10.8 Hz, 1 H), 5.25 (d, *J* = 10.8 Hz, 1 H), 5.40 (d, *J* = 17.4 Hz, 1 H), 5.77-5.83 (m, 1 H), 7.21 (d, *J* = 7.8 Hz, 2 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.46 (d, *J* = 7.8 Hz, 2 H), 7.60 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 49.6, 51.5, 76.2, 76.7, 118.1, 122.4, 126.3, 128.0, 130.1, 131.8, 132.2, 134.5, 137.8, 144.3; IR (KBr, neat) 2923, 2849, 1597, 1491, 1348, 1168, 1090, 1012, 975, 818, 670 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}BrNO_3S$ $(M + H)^+$ 422.0420 found 422.0433.

(2*R,6*S**)-2-(4-Fluorophenyl)-4-tosyl-6-vinylmorpholine (27j, Diastereomeric mixture with a ratio of 97:3; Data only for major isomer):**



White solid, mp. 130-132 °C; R_f (hexane/EtOAc 4:1) 0.52; yield 136 mg, 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.11-2.16 (m, 2 H), 2.43 (s, 3 H), 3.72-3.77 (m, 2 H), 4.27-4-30 (m, 1 H), 4.68 (d, *J* = 13.2 Hz, 1 H), 5.25 (d, *J* = 10.8 Hz, 1 H), 5.41 (d, *J* = 17.4 Hz, 1 H), 5.77-5.83 (m, 1 H), 7.02 (t, *J* = 8.4 Hz, 2 H), 7.28-7.34 (m, 4 H), 7.60 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$)

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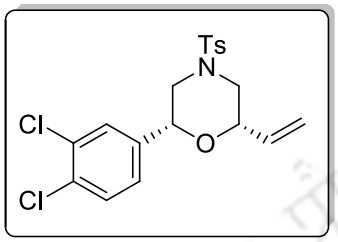
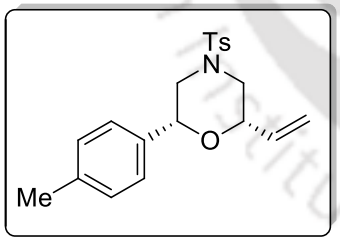
δ 21.7, 49.7, 51.7, 76.3, 76.8, 115.6 (d, *J* = 21.0 Hz), 118.0, 127.9, 128.0, 128.1, 130.1, 132.4, 134.6, 144.3, 162.8 (d, *J* = 246.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 47.99 (t, *J* = 5.26 Hz); IR (KBr, neat) 2850, 1604, 1511, 1348, 1228, 1166, 1088, 975, 762, 667 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}FNO_3S$ $(M + H)^+$ 362.1221 found 362.1252.

(2*R,6*S**)-2-(3,4-Dichlorophenyl)-4-tosyl-6-vinylmorpholine (27k):**



White solid, mp. 117-119 °C; R_f (hexane/EtOAc, 4:1) 0.48; yield 152 mg, 74%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.08 (t, *J* = 10.8 Hz, 1 H), 2.12 (t, *J* = 10.8 Hz, 1 H), 2.43 (s, 3 H), 3.71-3.77 (m, 2 H), 4.25-4.28 (m, 1 H), 4.67 (d, *J* = 10.8 Hz, 1 H), 5.26 (d, *J* = 10.8 Hz, 1 H), 5.40 (d, *J* = 17.4 Hz, 1 H), 5.77-5.83 (m, 1 H), 7.16 (d, *J* = 7.8 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.40 (d, *J* = 7.8 Hz, 1 H), 7.44 (s, 1 H), 7.60 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 49.6, 51.4, 76.1, 76.3, 118.2, 125.6, 127.9, 128.2, 130.1, 130.7, 132.2, 132.4, 133.0, 134.4, 139.0, 144.4; IR (KBr, neat) 2923, 2850, 1646, 1598, 1471, 1350, 1168, 1090, 1030, 977, 820, 704, 670 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{20}Cl_2NO_3S$ $(M + H)^+$ 412.0535 found 412.0547.

(2*R,6*S**)-2-(*p*-Tolyl)-4-tosyl-6-vinylmorpholine (27l, Diastereomeric mixture with a ratio of 97:3; Data only for major isomer):**



White solid, mp 104-106 °C; R_f (hexane/EtOAc 4:1) 0.55; yield 147 mg, 82%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.10-2.17 (m, 2 H), 2.33 (s, 3 H), 2.43 (s, 3 H), 3.71-3.77 (m, 2 H), 4.26-4.29 (m, 1 H), 4.66 (d, *J* = 11.4 Hz, 1 H), 5.23 (d, *J* = 10.8 Hz, 1 H), 5.41 (d, *J* = 17.4 Hz, 1 H), 5.78-5.84 (m, 1 H), 7.14 (d, *J* = 7.8 Hz, 2 H), 7.21 (d, *J* = 7.8 Hz, 2 H), 7.30 (d, *J* = 7.8 Hz, 2 H), 7.60 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 21.7, 49.7, 51.7, 76.2, 77.0, 117.8, 126.2, 128.0, 129.3, 130.0, 132.4, 134.8, 135.9, 138.2, 144.1; IR (KBr, neat) 2924, 2846, 1598, 1353, 1231, 1168, 1087, 818, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{24}NO_3S$ $(M + H)^+$ 358.1471 found 358.1497.

(2*R,6*S**)-2-(4-Methoxyphenyl)-4-tosyl-6-vinylmorpholine (27m, Diastereomeric mixture with a ratio of 97:3; Data only for major isomer):**

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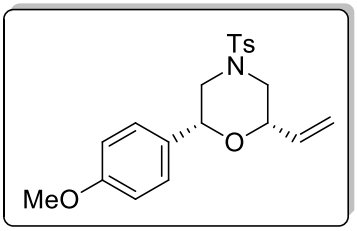
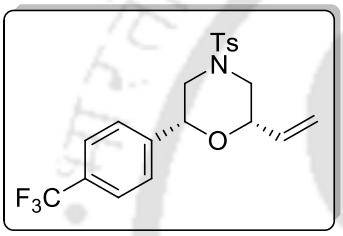


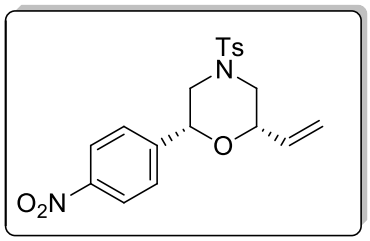
White solid, mp. 109-111 °C; R_f (hexane/EtOAc 4:1) 0.45; yield 158 mg, 85%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.11-2.17 (m, 2 H), 2.43 (s, 3 H), 3.71-3.75 (m, 2 H), 3.79 (s, 3 H), 4.25-4.30 (m, 1 H), 4.65 (d, *J* = 10.8 Hz, 1 H), 5.24 (d, *J* = 10.8 Hz, 1 H), 5.41 (d, *J* = 17.4 Hz, 1 H), 5.77-5.84 (m, 1 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.61 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 49.7, 51.7, 55.5, 76.2, 77.0, 114.1, 117.9, 127.6, 128.0, 130.0, 131.0, 132.4, 134.8, 144.2, 159.8; IR (KBr, neat) 2926, 1612, 1515, 1447, 1250, 1167, 1087, 1031, 831, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{24}NO_4S$ $(M + H)^+$ 374.1421 found 374.1400.

(2*R,6*S**)-4-Tosyl-2-(4-(trifluoromethyl)phenyl)-6-vinylmorpholine (27n):**



White solid, mp. 115-117 °C; R_f (hexane/EtOAc 4:1) 0.55; yield 169 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08-2.18 (m, 2 H), 2.43 (s, 3 H), 3.75 (dt, *J* = 11.4 and 2.4 Hz, 1 H), 3.80 (dt, *J* = 11.6 and 2.4 Hz, 1 H), 4.29-4.34 (m, 1 H), 4.78 (dd, *J* = 11.6 and 2.4 Hz, 1 H), 5.27 (dt, *J* = 11.2 and 1.6 Hz, 1 H), 5.43 (dt, *J* = 17.6 and 1.2 Hz, 1 H), 5.78-5.87 (m, 1 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.60 (d, *J* = 8.4 Hz, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 49.7, 51.5, 76.3, 76.7, 118.1, 124.2 (q, *J* = 271.5 Hz), 125.7, 126.6, 128.0, 130.1, 130.6 (q, *J* = 33.0 Hz), 132.3, 134.4, 142.7, 144.4; ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 99.10 ; IR (KBr, neat) 2924, 2850, 1622, 1598, 1452, 1356, 1171, 1020, 972, 857, 738, 668 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}F_3NO_3S$ $(M + H)^+$ 412.1189 found 412.1198.

(2*R,6*S**)-2-(4-Nitrophenyl)-4-tosyl-6-vinylmorpholine (27o, Diastereomeric mixture with a ratio of 97:3; Data only for major isomer):**



White solid, mp. 128-130 °C; R_f (hexane/EtOAc 4:1) 0.40; yield 163 mg, 84%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.11 (dd, *J* = 11.4 and 10.2 Hz, 1 H), 2.15 (dd, *J* = 11.4 and 10.8 Hz, 1 H), 2.43 (s, 3 H), 3.76 (dd, *J* = 11.4 and 3.0 Hz, 1 H), 3.83 (dd, *J* = 11.4 and 2.4 Hz, 1 H), 4.30-4.34 (m, 1 H), 4.82 (dd, *J* = 10.2 and 2.4 Hz, 1 H), 5.29 (d, *J* = 10.8 Hz, 1 H), 5.45 (d, *J* = 16.2 Hz, 1 H), 5.80-5.85 (m, 1 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.53 (d, *J* = 8.4 Hz, 2 H),

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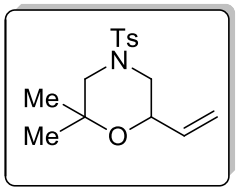
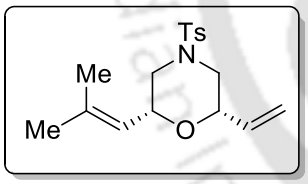
7.60 (d, *J* = 8.4 Hz, 2 H), 8.21 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 49.6, 51.3, 76.3, 76.4, 118.3, 123.9, 127.1, 127.9, 130.1, 132.2, 134.3, 144.4, 145.8, 148.0; IR (KBr, neat) 3082, 2849, 1603, 1522, 1452, 1351, 1168, 1092, 862, 774, 664 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}N_2O_5S$ $(M + H)^+$ 389.1166 found 389.1178.

2,2-Dimethyl-4-tosyl-6-vinylmorpholine (27p):



White solid, mp. 92-94 ºC; R_f (hexane/EtOAc 4:1) 0.50; yield 96 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.14 (s, 3 H), 1.33 (s, 3 H), 2.43 (s, 3 H), 2.96 (t, *J* = 12.0 Hz, 1 H), 3.38 (s, 2 H), 3.77 (d, *J* = 12.0 Hz, 1 H), 4.00-4.10 (m, 1 H), 5.39 (d, *J* = 10.8 Hz, 1 H), 5.41 (d, *J* = 17.4 Hz, 1 H), 5.79-5.85 (m, 1 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.69 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.1, 21.7, 24.8, 47.2, 56.9, 77.4, 77.9, 118.0, 127.4, 129.9, 134.9, 139.3, 143.5; IR (KBr, neat) 2978, 2854, 1646, 1599, 1454, 1330, 1160, 1093, 940, 818, 668 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{22}NO_3S$ $(M + H)^+$ 296.1315 found 296.1338.

(2*R,6*S**)-2-(2-Methylprop-1-en-1-yl)-4-tosyl-6-vinylmorpholine (27q, Diastereomeric mixture with a ratio of 97:3; Data only for major isomer):**



Colourless oil; R_f (hexane/EtOAc 4:1) 0.60; yield 112 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (s, 6 H), 2.00-2.06 (m, 2 H), 2.44 (s, 3 H), 2.96 (dt, *J* = 12.0 and 1.6 Hz, 1 H), 3.62 (dt, *J* = 12.0 and 2.0 Hz, 1 H), 4.12-4.16 (m, 1 H), 4.31-4.37 (m, 1 H), 5.02 (d, *J* = 10.0 Hz, 1 H), 5.20 (d, *J* = 10.4 Hz, 1 H), 5.33 (d, *J* = 17.6 Hz, 1 H), 5.68-5.77 (m, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.9, 21.8, 26.0, 49.4, 49.5, 72.9, 75.9, 118.1, 121.6, 128.0, 130.0, 132.3, 135.0, 139.1, 144.1; IR (KBr, neat) 2924, 2854, 1598, 1453, 1378, 1167, 1078, 971, 818, 778 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{24}NO_3S$ $(M + H)^+$ 322.1471 found 322.1457.

(2*S,6*S**)-2-(Furan-2-yl)-4-tosyl-6-vinylmorpholine (27r, Diastereomeric mixture with a ratio of 97:3; Data only for major isomer):**

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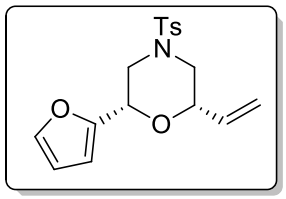
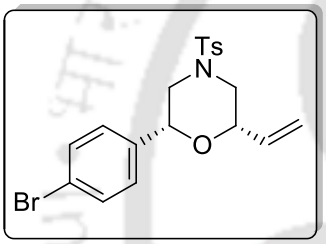


Colourless oil; R_f (hexane/EtOAc 4:1) 0.60; yield 120 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (dd, *J* = 11.2 and 10.8 Hz, 1 H), 2.45 (s, 3 H), 2.53 (dd, *J* = 11.2 and 11.2 Hz, 1 H), 3.70 (dt, *J* = 11.2 and 2.0 Hz, 1 H), 3.81 (dt, *J* = 11.2 and 2.4 Hz, 1 H), 4.23-4.28 (m, 1 H), 4.74 (dd, *J* = 10.8 and 2.8 Hz, 1 H), 5.24 (d, *J* = 10.8 Hz, 1 H), 5.37 (d, *J* = 17.6 Hz, 1 H), 5.71-5.80 (m, 1 H), 6.31 (d, *J* = 3.6 Hz, 1 H), 6.34 (dd, *J* = 3.2 and 1.6 Hz, 1 H), 7.33-7.37 (m, 3 H), 7.64 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 48.2, 49.5, 71.2, 76.5, 108.3, 110.5, 118.6, 128.0, 130.1, 132.2, 134.4, 142.9, 144.3, 151.1; IR (KBr, neat) 2922, 2853, 1648, 1598, 1454, 1344, 1168, 1095, 934, 819, 664 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{20}NO_4S$ $(M + H)^+$ 334.1108 found 334.1111.

(2*R,6*S**)-2-(4-Bromophenyl)-4-tosyl-6-vinylmorpholine and (2*S**,6*S**)-2-(4-bromophenyl)-4-tosyl-6-vinylmorpholine (27s, 27s′:: 63:37):**



Colourless solid, mp (mixed) 150-152 °C; R_f (hexane/EtOAc 4:1) 0.60; yield 147 mg, 70%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.96-2.11 (m, 2 H), 2.35 (s, 3 H), 3.66 (m, 2 H, major), 3.70 (m, 2 H, minor), 4.19-4.23 (m, 1 H), 4.59 (dd, *J* = 10.8 and 2.4 Hz, 1 H, major), 4.63 (dd, *J* = 10.8 and 3.0 Hz, 1 H, minor), 5.17 (dd, *J* = 10.8 and 3.0 Hz, 1 H), 5.33 (d, *J* = 17.4 Hz, 1 H, major), 5.35 (d, *J* = 16.8 Hz, 1 H, minor), 5.70-5.77 (m, 1 H), 7.13 (d, *J* = 8.4 Hz, 2 H, major), 7.22-7.26 (m, 2 H, major and minor), 7.39 (d, *J* = 7.8 Hz, 2 H, major), 7.52 (d, *J* = 7.8 Hz, 2 H, major), 7.53 (d, *J* = 7.8 Hz, 2 H, minor); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 49.6, 49.7, 51.5, 51.7, 76.2, 76.3, 76.7, 77.4, 117.9, 118.0, 122.4, 126.3, 127.9, 128.0, 128.4, 128.7, 130.0, 130.1, 131.8, 132.3, 134.6, 134.8, 137.8, 138.8, 144.2, 144.3; IR (KBr, neat) 3090, 3063, 2847, 1650, 1598, 1492, 1268, 1176, 1097, 929, 852, 775 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}BrNO_3S$ $(M + H)^+$ 422.0420 found 422.0430.

(*Z*)-*N*-(2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (42):

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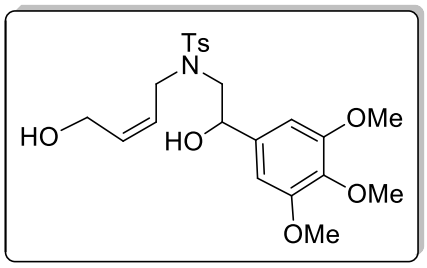
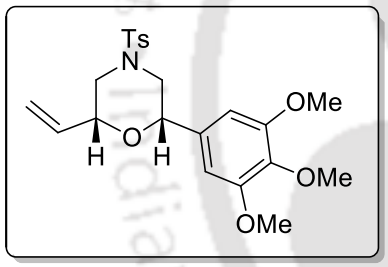


Light yellow solid, mp. 92-93 ^{o}C; R_f (hexane/EtOAc 2:3) 0.50; yield 1074 mg, 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.92 (brs, 2H), 2.41 (s, 3 H), 3.24-3.31 (m, 2 H), 3.81 (s, 3 H), 3.84 (s, 6 H), 3.93 (dd, *J* = 16.2 and 6.6 Hz, 1 H), 3.98 (dd, *J* = 16.2 and 7.8 Hz, 1 H), 4.10 (dd, *J* = 12.6 and 6.6 Hz, 1 H), 4.16 (dd, *J* = 12.6 and 7.2 Hz, 1 H), 4.90 (dd, *J* = 7.2 and 3.6 Hz, 1 H), 5.31 (dd, *J* = 10.8 and 7.8 Hz, 1 H), 5.78 (dd, *J* = 10.8 and 4.8 Hz, 1 H), 6.58 (s, 2 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.68 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 46.3, 55.5, 56.3, 57.8, 61.0, 73.8, 102.9, 126.8, 127.4, 130.1, 133.2, 136.5, 137.3, 144.0, 153.5; IR (KBr, neat) 3475, 2939, 2835, 1596, 1462, 1332, 1232, 1160, 1002, 916, 839, 772 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{30}NO_7S$ $(M + H)^+$ 452.1737 found 452.1733. Anal. calcd for $C_{22}H_{29}NO_7S$: C, 58.52; H, 6.47; N, 3.10. Found: C, 58.45; H, 6.43; N, 3.07.

4-tosyl-2-(3,4,5-trimethoxyphenyl)-6-vinylmorpholine (43):



White solid, mp. 142-144 ^{o}C; R_f (hexane/EtOAc 3:1) 0.50; yield 560 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.13-2.17 (m, 2 H), 2.42 (s, 3 H), 3.72 (d, *J* = 11.4 Hz, 1 H), 3.77 (d, *J* = 11.4 Hz, 1 H), 3.81 (s, 3 H), 3.84 (s, 6 H), 4.27-4.30 (m, 1 H), 4.63 (d, *J* = 11.4 Hz, 1 H), 5.24 (d, *J* = 10.8 Hz, 1 H), 5.40 (d, *J* = 17.4 Hz, 1 H), 5.79-5.85 (m, 1 H), 6.54 (s, 2 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.61 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 49.6, 51.8, 56.4, 61.0, 76.4, 77.6, 103.3, 118.0, 128.0, 130.1, 132.5, 134.4, 134.7, 138.0, 144.2, 153.5; IR (KBr, neat) 3446, 2938, 2844, 1592, 1461, 1341, 1237, 1169, 1089, 973, 839, 776 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{28}NO_6S$ $(M + H)^+$ 434.1632 found 434.1635. Anal. calcd for $C_{22}H_{27}NO_6S$: C, 60.95; H, 6.28; N, 3.23. Found: C, 60.87; H, 6.22; N, 3.21.

2-(4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholin-2-yl)ethanol (44):

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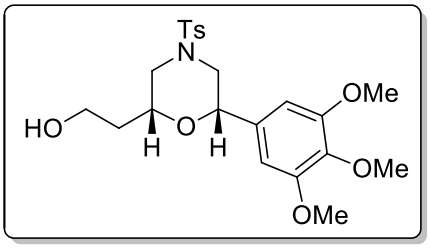
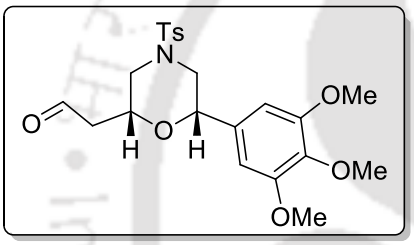


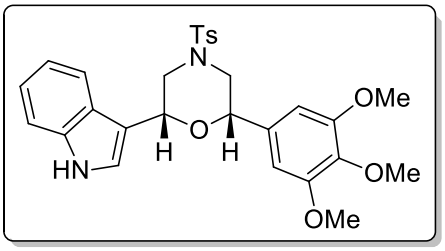
Colourless solid, mp. 93-95 ^{o}C; R_f (hexane/EtOAc: 3:2) 0.45; yield 468 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-1.27 (m, 2 H), 2.16 (dd, *J* = 11.2 and 10.8 Hz, 1 H), 2.24 (dd, *J* = 11.2 and 10.8 Hz, 1 H), 2.44 (s, 3 H), 3.57-3.79 (m, 5 H), 3.83 (s, 3 H), 3.85 (s, 6 H), 4.62 (t, *J* = 9.6 Hz, 1 H), 6.51 (s, 2 H), 7.34 (d, *J* = 7.6 Hz, 2 H), 7.62 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 35.4, 49.8, 51.9, 56.4 (2C), 60.3, 61.0, 75.4, 77.9, 103.1, 127.9, 130.0, 132.4, 134.3, 137.9, 144.2, 153.5; IR (KBr, neat) 3519, 2936, 2842, 1594, 1461, 1342, 1268, 1166, 1091, 977, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{30}NO_7S$ $(M + H)^+$ 452.1737 found 452.1735. Anal. calcd for $C_{22}H_{29}NO_7S$: C, 58.52; H, 6.47; N, 3.10. Found: C, 58.41; H, 6.42; N, 3.12.

2-(4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholin-2-yl)acetaldehyde (45):



Colourless solid, mp. 115-117 ^{o}C; R_f (hexane/EtOAc: 6:4) 0.50; yield 280 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13-2.25 (m, 2 H), 2.44 (s, 3 H), 2.59 (dd, *J* = 16.8 and 6.6 Hz, 1 H), 2.69 (dd, *J* = 16.8 and 6.8 Hz, 1 H), 3.65-3.78 (m, 2 H), 3.82 (s, 3 H), 3.84 (s, 6 H), 4.29-4.36 (m, 1 H), 4.65 (t, *J* = 9.2 Hz, 1 H), 6.50 (s, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 2 H), 9.78 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.7, 49.3, 51.6, 56.4, 61.0, 78.0, 79.3, 103.1, 127.9, 130.1, 132.4, 134.0, 138.0, 144.3, 153.5, 199.2; IR (KBr, neat) 3517, 2844, 1727, 1594, 1462, 1340, 1272, 1121, 1011, 977, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{28}NO_7S$ $(M + H)^+$ 450.1581 found 450.1583. Anal. calcd for $C_{22}H_{27}NO_7S$: C, 58.78; H, 6.05; N, 3.12. Found: C, 58.68; H, 6.00; N, 3.08.

2-(1*H*-indol-2-yl)-4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholine (47):



Colourless Solid, mp. 137-139 ^{o}C; R_f (hexane/EtOAc: 7:4) 0.45; yield 188 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (dd, *J* = 11.2 and 10.8 Hz, 1 H), 2.42 (s, 3 H), 2.63 (dd, *J* = 11.2 and 10.8 Hz, 1 H), 3.82 (s, 3 H), 3.84 (s, 6 H), 3.90-3.98 (m, 2 H), 4.85 (d, *J* = 10.0 Hz, 1 H), 5.17 (d, *J* = 10.8 Hz, 1 H), 6.64 (s, 2 H), 7.11 (t, *J* = 8.0 Hz, 1 H), 7.18-7.22 (m, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.38 (d, *J* = 8.0 Hz, 1

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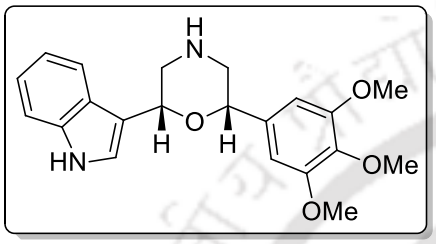
H), 7.61 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 8.29 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 50.8, 52.1, 56.4, 61.0, 73.3, 77.9, 103.3, 111.7, 114.1, 119.9, 120.0, 122.2, 122.6, 125.7, 127.9, 130.1, 134.8, 136.5, 144.1, 153.5; IR (KBr, neat) 3374, 2927, 2852, 1594, 1461, 1342, 1267, 1166, 1090, 976, 743 cm^{-1}; HRMS (ESI) calcd. for $C_{28}H_{31}N_2O_6S$ $(M + H)^+$ 523.1897 found 523.1901. Anal. calcd for $C_{28}H_{30}N_2O_6S$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.31; H, 6.71; N, 5.32.

(±)-Chelonin A (1):



Colourless solid, mp. 180-182 °C; R_f (DCM/MeOH: 9.5:0.5) 0.35; yield 56 mg, 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.90 (dd, *J* = 11.4 and 10.8 Hz, 1 H), 3.15-3.26 (m, 3 H), 3.82 (s, 3 H), 3.85 (s, 6 H), 4.74 (d, *J* = 10.8 Hz, 1 H), 5.06 (d, *J* = 9.0 Hz, 1 H), 6.68 (s, 2 H), 7.12 (t, *J* = 7.2 Hz, 1 H), 7.16-7.20 (m, 2 H), 7.35 (d, *J* = 7.2 Hz, 1 H), 7.84 (d, *J* = 7.2 Hz, 1 H), 8.30 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.1, 52.6, 56.3 (2C), 61.0, 74.5, 79.6, 103.4 (2C), 111.5, 115.6, 119.8, 120.0, 121.9, 122.4, 126.1, 136.3, 136.6, 137.6, 153.4 (2C); IR (KBr, neat) 3371, 2923, 2852, 1593, 1462, 1335, 1235, 1127, 1003, 908, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{25}N_2O_4$ $(M + H)^+$ 369.1803 found 369.1818.

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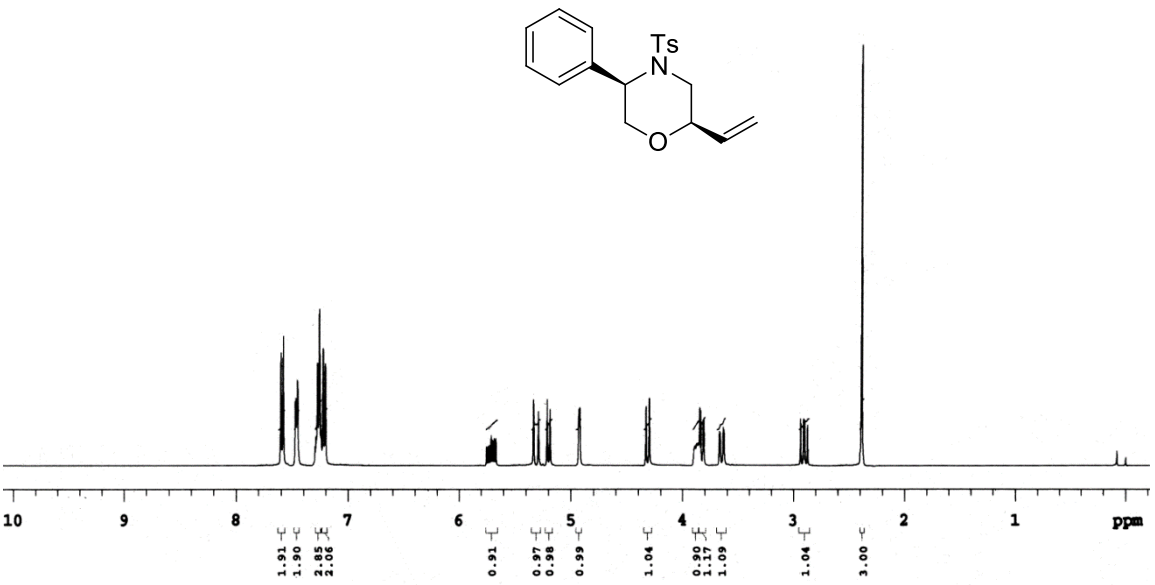
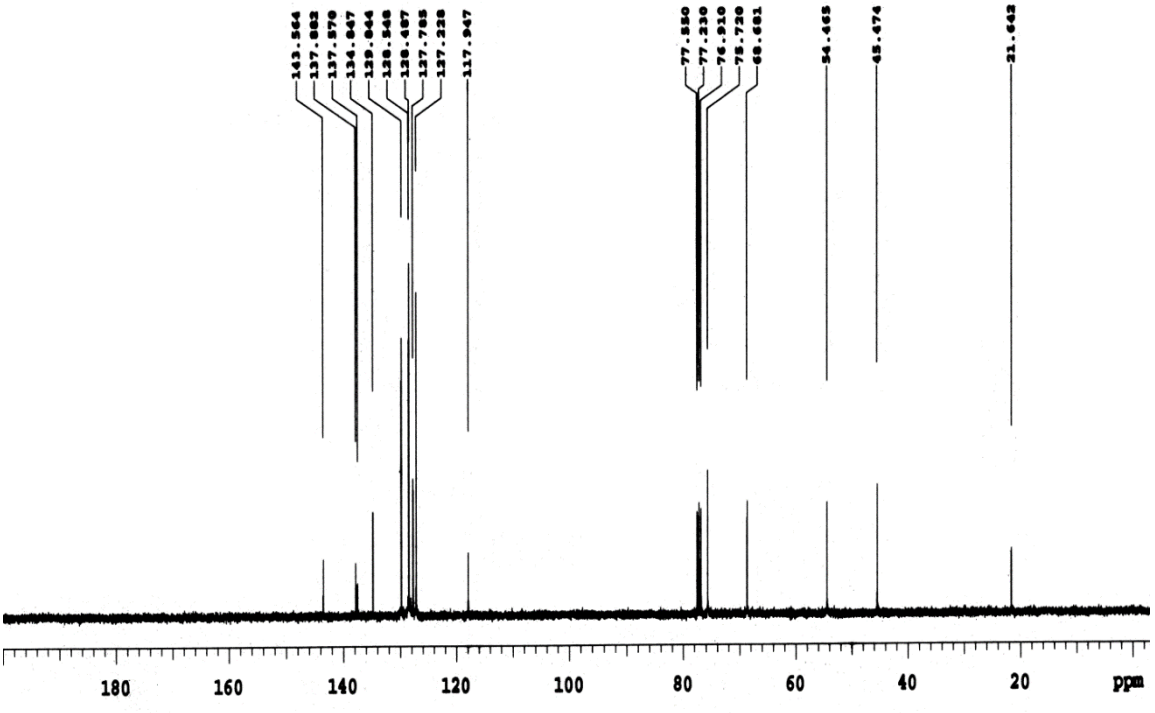
3.9. Selected spectra of substituted morpholines

(2*R,5*R**)-5-Phenyl-4-tosyl-2-vinylmorpholine (27d):**





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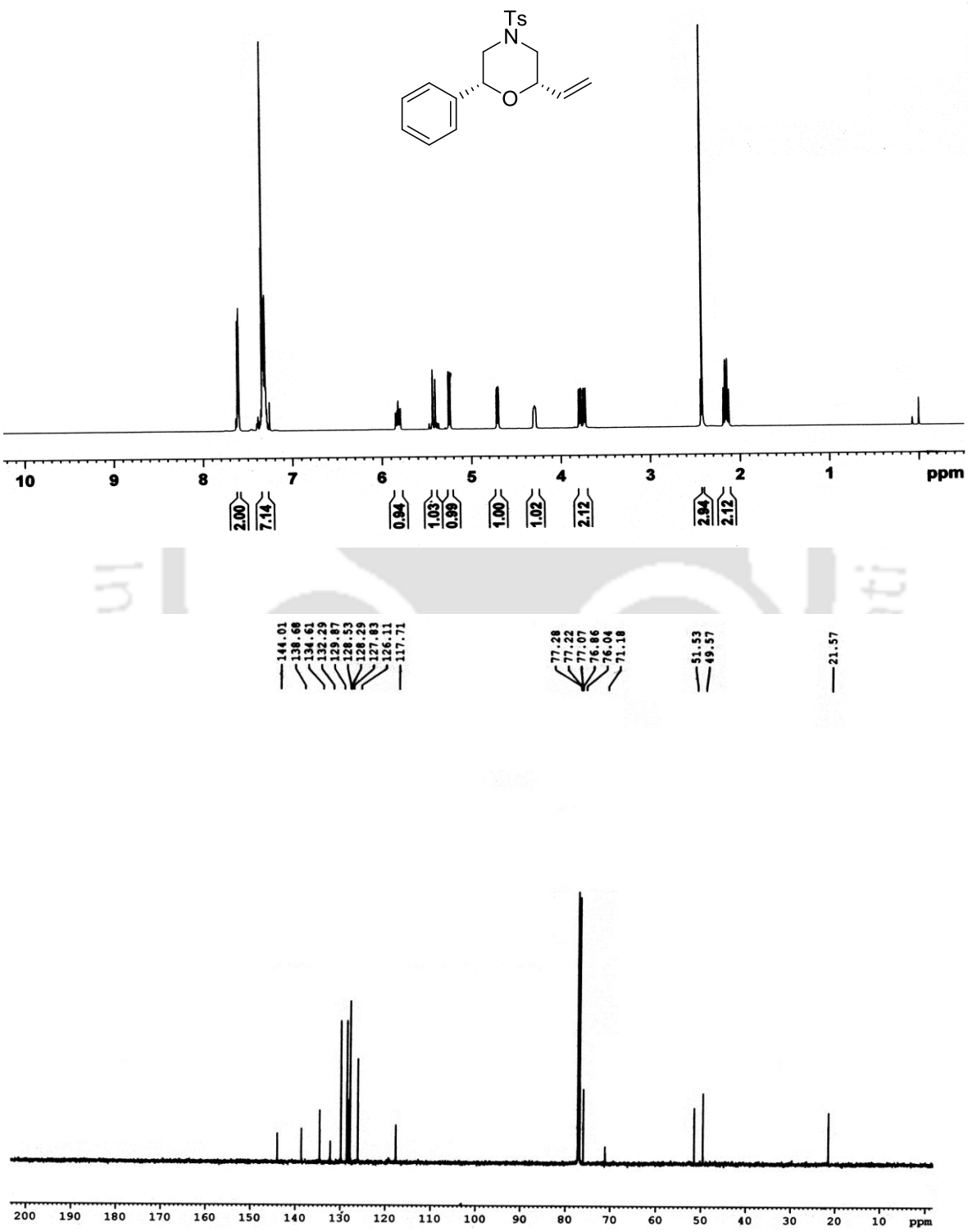
(2*R,6*S**)-2-Phenyl-4-tosyl-6-vinylmorpholine (27f):**



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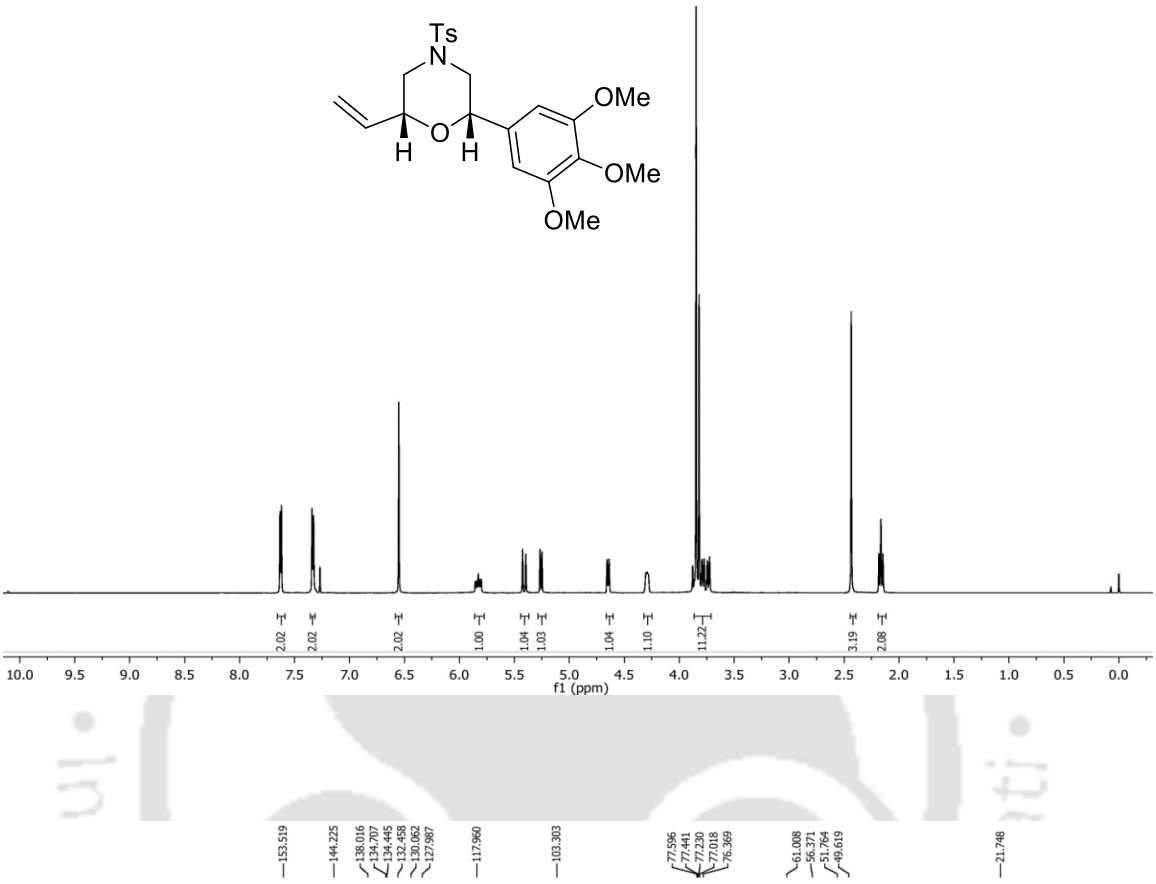
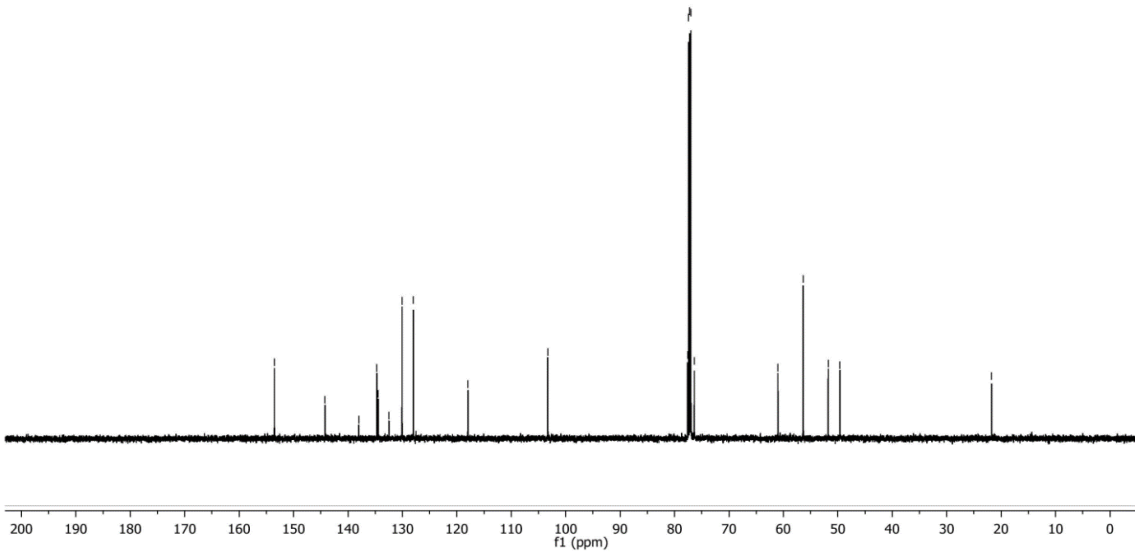
4-tosyl-2-(3,4,5-trimethoxyphenyl)-6-vinylmorpholine (43):





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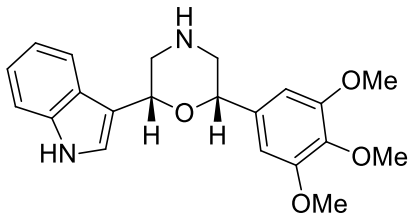
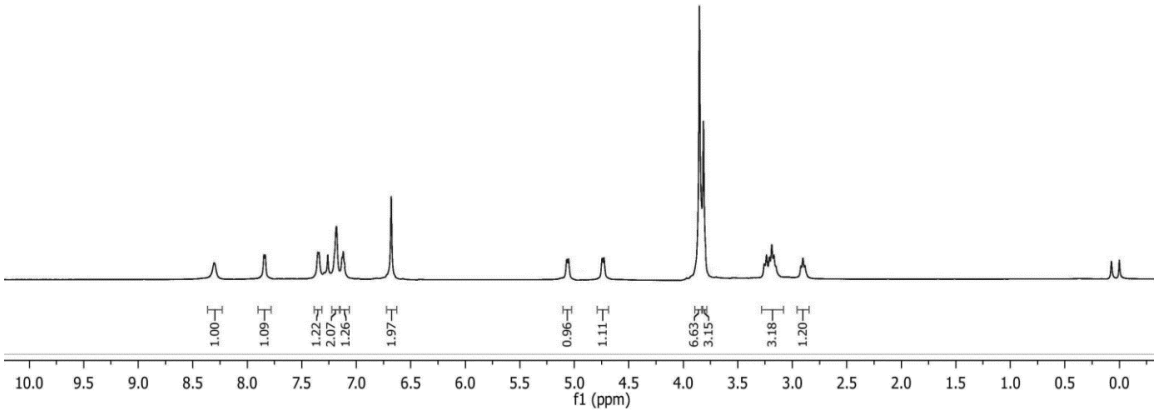
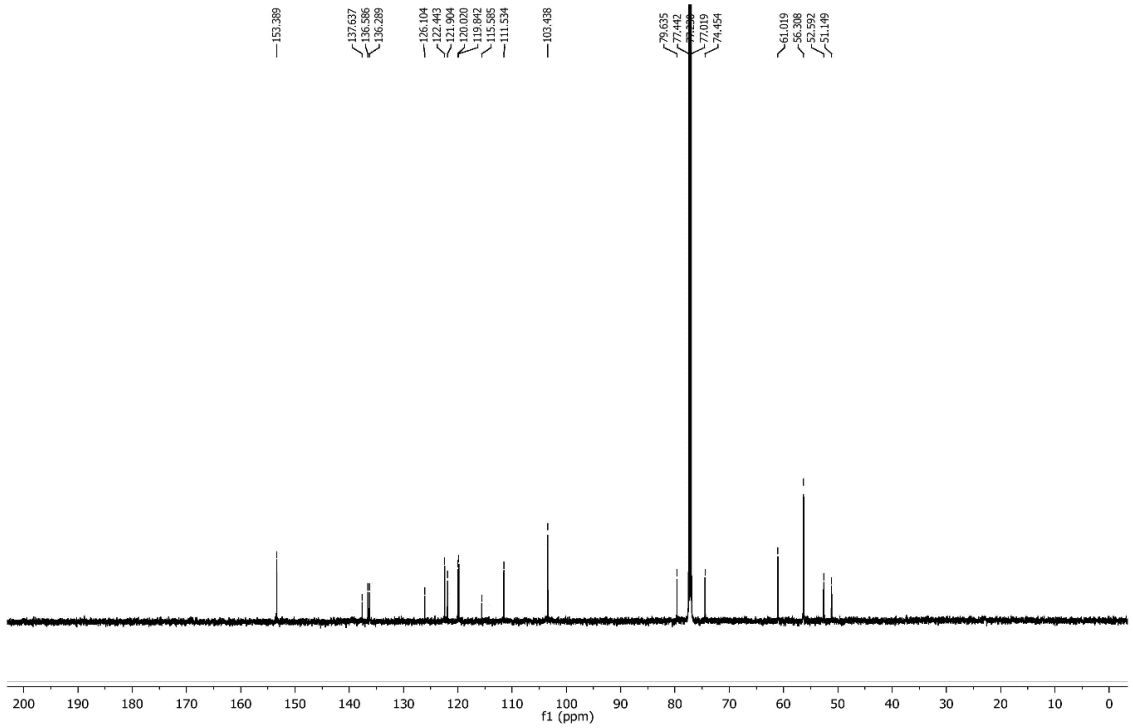
Chelonin A (1):







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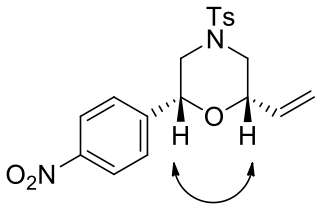
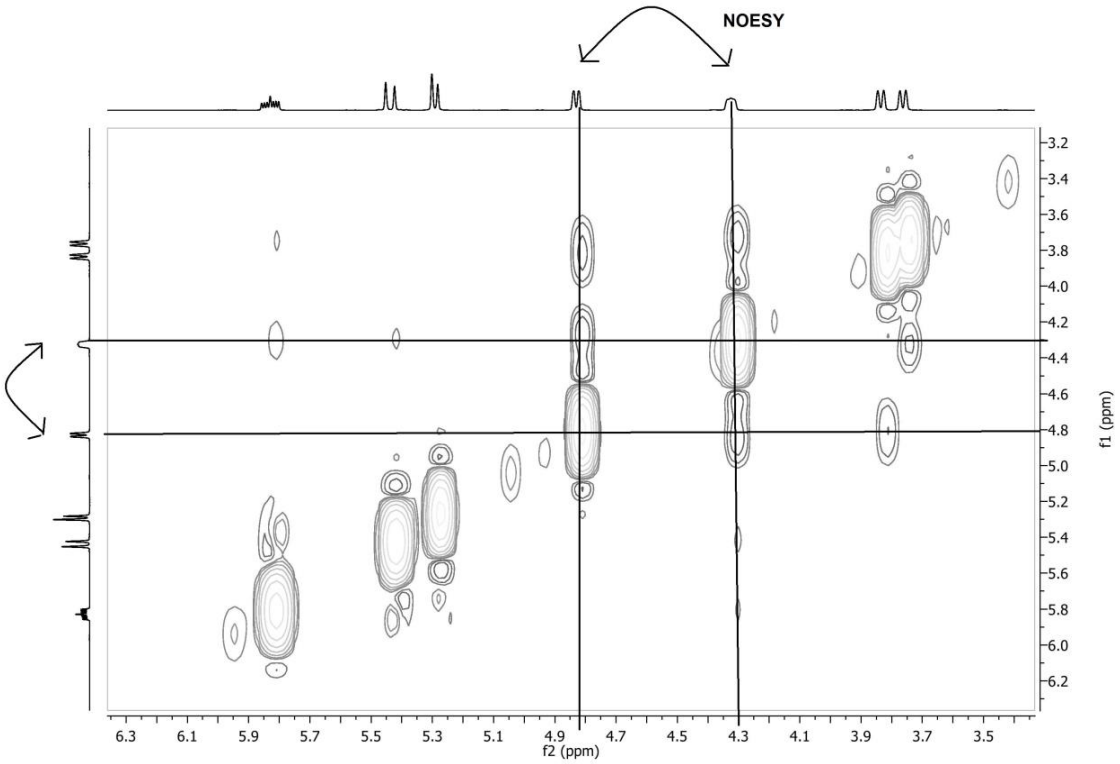
NOE Spectra of compound (2*R,6*S**)-2-(4-Nitrophenyl)-4-tosyl-6-vinylmorpholine (27o):**



NOESY



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3.10. Crystal parameters

The crystal parameters of compound 27e

	CCDC 1515088
Formula	$C_{20}H_{23}NO_3S$
Formula weight	357.45
T/K	296(2)
Crystal system	Orthorhombic
Space group	P_21_21_21
a/Å	6.1952(5)
b/Å	10.7715(8)
c/Å	27.987(3)
α/°	90.00
β/°	90.00
γ/°	90.00
V/Å^3	1867.6(3)
Z	4
Abs. Coeff./mm^{-1}	0.191
Abs. Correction	multi-scan
GOF on F^2	1.108
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.1235
	wR2 = 0.2528
R indices [all data]	*R1* = 0.1895
	wR2 = 0.3338

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The crystal parameters of compound 27o

	CCDC 1515089
Formula	$C_{19}H_{20}N_2O_5S_1$
Formula weight(Sum)	388.43
T/K	296(2)
Crystal system	Triclinic
Space group	P-1
a/Å	8.0238(11)
b/Å	20.185(3)
c/Å	24.621(3)
α/°	96.566(8)
β/°	92.291(7)
γ/°	90.483(7)
V/Å^3	3957.9(9)
Z	8
Abs. Coeff./mm^{-1}	0.195
Abs. Correction	multi-scan
GOF on F^2	1.262
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.1468
	wR2 = 0.3316
R indices [all data]	*R1* = 0.1946
	wR2 = 0.3316

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3.11. References

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CHAPTER 4

$FeCl_3$-Mediated Carbenium-ion Induced Cyclization of *N*-Tethered Alkyne-Benzyl Alkanols

4.1. Importance and applications

N-Heterocycles are a privileged structural moiety present in many biologically active molecules, and are increasingly attractive platform in the development of new pharmaceuticals. Pyrrolidines, a five membered saturated *N*-heterocycle is found in a wide variety of natural products[1] and pharmaceuticals[2] (*Figure 4.1.1*). In particular, functionalized 3,4-disubstituted pyrrolidine derivatives are found to exhibit various pharmacological properties.[3] For example, compound **1** is a direct renin inhibitors (DRIs), which can trigger blood pressure lowering effects.[3a] Similarly compound **2** belongs to a novel class of monoamine transporter inhibitors.[3b] In addition to their importance in medicinal chemistry, enantiomerically pure pyrrolidines are useful chiral auxiliaries.[4] Apart from these, pyrrolidine based organocatalysts[5] and chiral ligands[6] have been employed in a range of organic transformations.

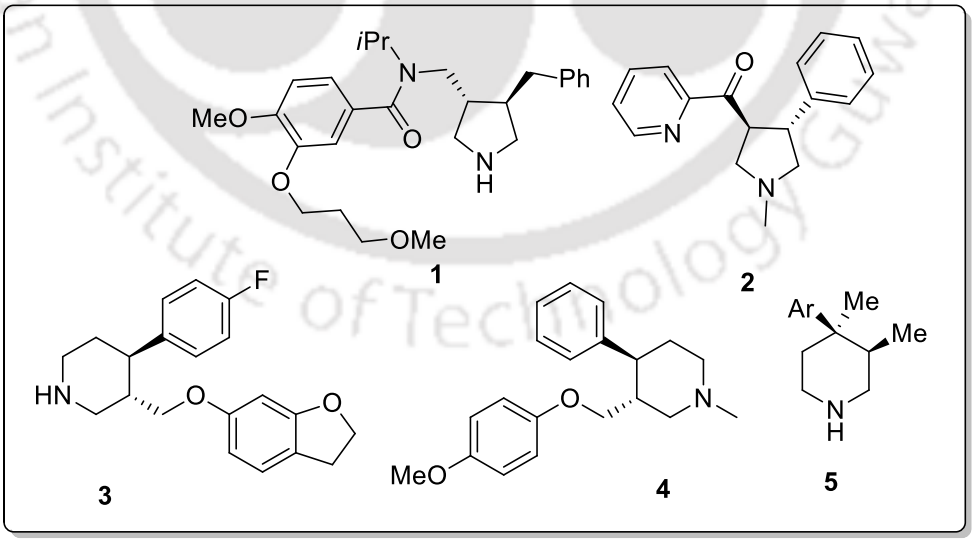

Figure 4.1.1. *Bioactive molecules containing pyrrolidines and piperidines*

On the other hand, piperidine derivatives are popular building blocks in a vast array of natural products and present in many alkaloids.[7] They have also been found widespread

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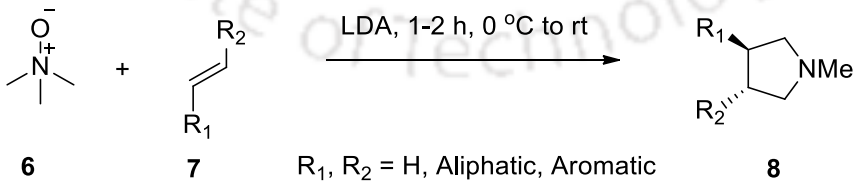
applications in various drugs, with extensive clinical and preclinical studies reported in last decades.[8-11] For example, antidepressant drugs (-)-paroxetine[9] (**3**) and (+)-femoxetine[10] (**4**) are a significantly important class of serotonin (5-hydroxytryptamine) reuptake inhibitors. Compound **5** and their derivatives exhibit pure opioid antagonist activity that may be useful in the treatment of obesity, psychosis, depression and other central nervous system disorders (*Figure 4.1.1*).[11]

4.2. An overview of relevant synthetic methods

The stereoselective synthesis of five- and six-membered saturated *N*-heterocycles has been a subject of great interest for organic chemists owing to their promising pharmaceutical properties. Over the years, many strategies have been developed for the synthesis of pyrrolidine and piperidine heterocycles such as oxidative decarboxylation-*β*-iodination of amino acids,[12] cycloaddition reaction of nitroalkenes,[13] palladium-catalysed carbonylative cyclization and carboamination reaction,[14] ring-closing metathesis (RCM),[15] cycloadditions of azomethine ylides,[16] cyclization of amino chlorides,[17] aza-Prins cyclization reaction,[18] intramolecular cyclization of epoxy and halogenated sulfones under basic conditions[19] etc. Some of the recent methods for the synthesis of pyrrolidine and piperidine derivatives are summarised below.

Davoren and co-workers have developed a methodology for the synthesis of 3,4-disubstituted pyrrolidines **8** from an unstabilized azomethine ylide generated from trimethylamine *N*-oxide **6** which undergoes 1,3-dipolar cycloaddition with electron-rich and unpolarized olefins **7** in good yields (*Scheme 4.2.1*).[16b] A broad range of substituents on the alkenes are tolerated provided they are compatible with excess LDA.



6 **7** **8**

Scheme 4.2.1

Stahl and Scarborough have developed an intermolecular Pd(II) catalysed oxidative coupling of allyl sulfonamides **9** with alkenes **10** to afford 2,4-disubstituted pyrrolidines **11**, **12** in excellent yield with modest diastereoselectivity (*Scheme 4.2.2*).[20] This reaction

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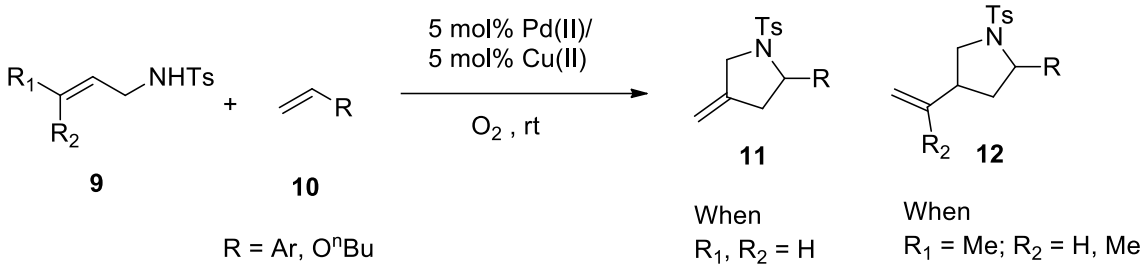
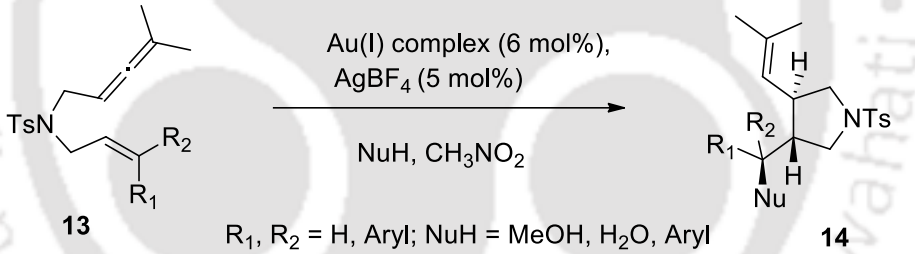
proceeds through intermolecular aminopalladation of olefins **10**, which undergoes alkene insertion, followed by *β*-hydride elimination to generate the product.



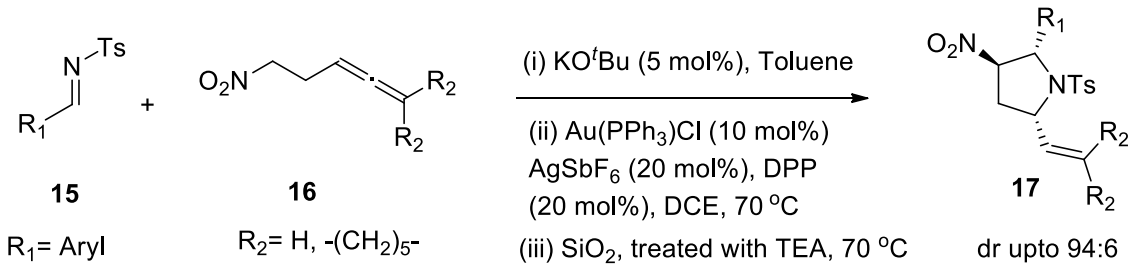
Scheme 4.2.2

Toste *et al.* have developed an efficient phosphoramidite Au(I)-catalyzed diastereo- and enantio-selective synthesis of 3,4-substituted pyrrolidines **14** from *N*-tethered allenenes-alkenes **13** (*Scheme 4.2.3*).[21] The reaction proceeds through the Au(I)-catalysed cyclisation of allenenes to form a carbocationic intermediate which is trapped by an external nucleophile, resulting in the highly diastereoselective construction of substituted pyrrolidines with three stereogenic centers.



Scheme 4.2.3

Dixon and co-workers have developed a diastereoselective one-pot nitro-Mannich/hydroamination cascade reaction for the synthesis of substituted pyrrolidines **17** bearing three stereocentres from aldimine **15** and nitroallene **16** by using a combination



Scheme 4.2.4

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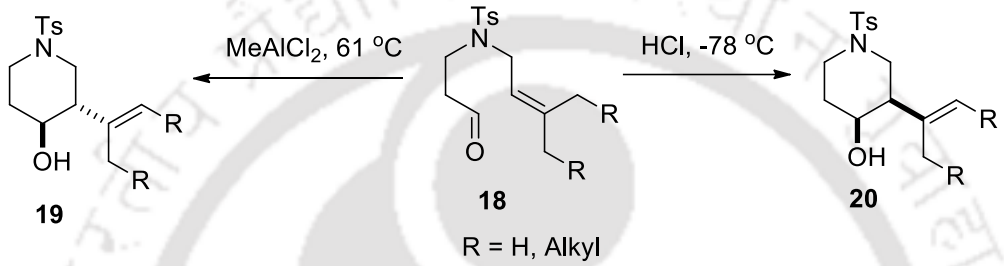
of base (KO^{t}Bu) and Au(I) as catalyst (*Scheme 4.2.4*).[22] The reaction proceeds with moderate to good yields and with excellent diastereoselectivity.

Snaith and co-workers demonstrated a novel diastereoselective method for synthesis of *cis* and *trans* 3,4-disubstituted piperidines *via* carbonyl-ene and Prins cyclizations.[23] In presence of Lewis acid methyl aluminum dichloride, the aldehyde **18** undergoes carbonyl-ene reactions thereby forming *trans* piperidines **19** with dr up to 93:7. However, in presence of hydrochloric acid, the aldehyde **18** affords *cis* products **20** with dr up to 98:2 *via* prins cyclization (*Scheme 4.2.5*).



Scheme 4.2.5

4.3. Present strategy and objective

A carbon-carbon bond formation reaction between R-OH (alcohol) and R'-H (nucleophile) is a powerful strategy for the organic chemists to access wide variety of functionalized derivatives. Direct nucleophilic substitution of an alcohol is a difficult process as hydroxide is a poor leaving group and therefore activation is usually required. However, π-activated alcohols, such as allylic, benzylic and propargylic alcohols can be activated towards nucleophilic attack in the presence of Lewis acids and Brønsted acids.[24] As part of our research interest in synthesis of nitrogen heterocycles[25] and considering the ability of benzyl alcohols to undergo nucleophilic substitution reactions, herein we present a methodology for the synthesis of substituted pyrrolidines and piperidines from *N*-tethered alkyne-benzyl alkanols *via* intramolecular cyclization of alkyne with benzylic electrophile. In this reaction, ferric chloride acts as a Lewis acid to remove hydroxyl group of benzyl alkanol to afford benzyl carbenium-ion followed by nucleophilic attack by alkyne and simultaneous *anti*-addition of chloride ion across the alkyne to form pyrrolidine and piperidine derivatives with exocyclic chloro-alkylidene and -arylidene moiety. Thus, the reaction of *N*-tethered alkyne-benzyl alkanols **21** in

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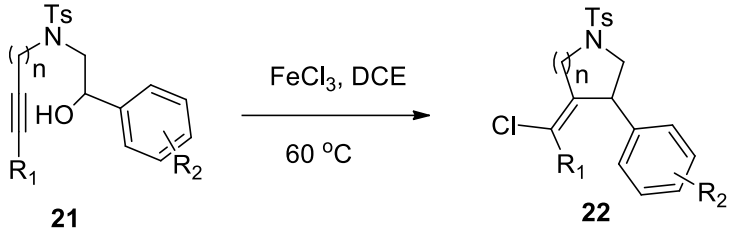
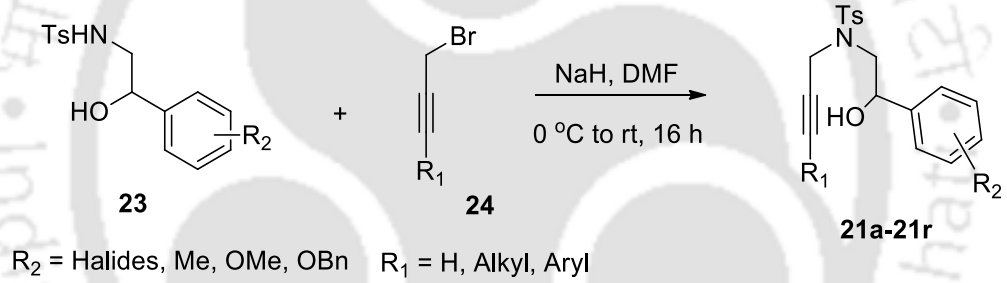
dichloroethane at 60 °C gave substituted pyrrolidines and piperidines **22** in presence of stoichiometric amount of ferric chloride, in good yields (*Scheme 4.3.1*).



R_1 = H, Alkyl, Aryl; R_2 = H, Me, OMe, OBn, Cl, Br, F; n = 1,2

Scheme 4.3.1

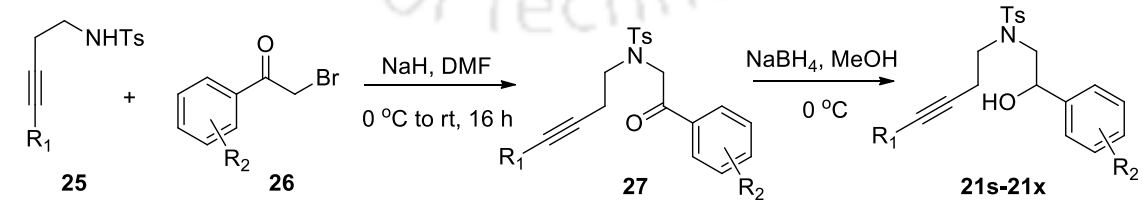
The *N*-tethered alkyne-benzyl alkanols **21a-21r** were synthesized from *N*-tosylated aminoalcohols **23** and propargyl bromide derivative **24** in presence of sodium hydride (*Scheme 4.3.2*).



R_2 = Halides, Me, OMe, OBn R_1 = H, Alkyl, Aryl

Scheme 4.3.2

The *N*-tethered alkyne-benzyl alkanols **21s-21x** were synthesized from *N*-tosylated homopropargyl amine **25** and phenacyl bromide derivative **26** in presence of sodium hydride, followed by $NaBH_4$ reduction of *N*-tethered keto-alkyne **27** (*Scheme 4.3.3*).



R_1 = H, Alkyl, Aryl R_2 = H, Br

Scheme 4.3.3

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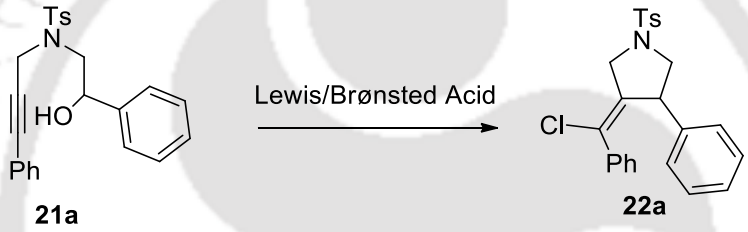
4.4. Results and discussion

4.4.1. Optimization studies

In an initial investigation, *N*-(2-Hydroxy-2-phenylethyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide **21a** was treated with one equivalent of $BF_3{\cdot}OEt_2$ in dichloromethane at 0 °C to room temperature for 24 h, but the reaction produced neither the desired product nor the decomposed product. However, the starting material was recovered in 96% yield. In order to optimize the reaction conditions, the alkyne-benzyl alkanol **21a** was treated with various Lewis acids such as TMSOTf, $FeCl_3$, $InCl_3$ and $In(OTf)_3$ and Brønsted acids such as *p*-TSA and triflic acid (Table 4.4.1.1).

Table 4.4.1.1. Optimization of the reaction



Entry	Lewis/Brønsted Acid (equiv.)	Reaction Conditions[a]	Yield(%)[b]
1	$BF_3{\cdot}OEt_2$ (1.0)	DCM, 0 °C to rt, 24 h	--[c]
2	TMSOTf (1.0)	DCM, 0 °C to rt, 2 h	--[d]
3	$FeCl_3$ (1.0)	DCE, 60 °C, 2 h	71
4	$InCl_3$ (1.0)	DCE, 60 °C, 3 h	70
5	$FeCl_3$ (0.2) + TMSCl (1.0)	DCE, 60 °C, 12 h	15
6	**$FeCl_3$ (1.0)**	**DCE, 60 °C, 2 h**	**76**[e]
7	$FeCl_3$ (1.0)	Toluene, 60 °C, 12 h	45
8	$FeCl_3$ (1.0)	CH_3CN, 60 °C, 12 h	56
9	$In(OTf)_3$ (1.0)	DCE, 60 °C, 12 h	--[d]
10	*p*-TSA (1.0)	DCE, 60 °C, 12 h	--[c]
11	Triflic Acid (1.0)	DCM, 0 °C to rt, 2 h	--[d]

[a]Reaction conditions: 0.4 mmol **21a** in 5 mL of solvent. [b]Yield refers to isolated yield. [c]No reaction, starting material was recovered. [d]Decomposed. [e]Reaction conditions: 0.4 mmol **21a** in 3 mL of DCE (0.13 M solution).

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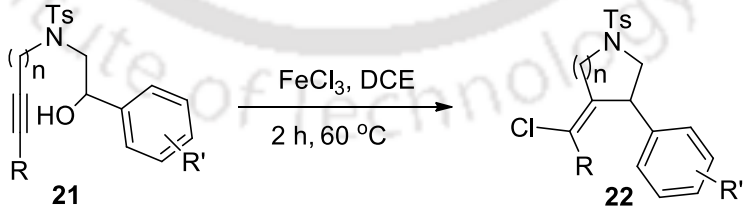
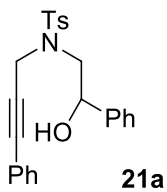
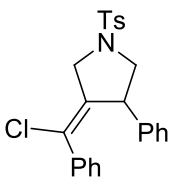
It was observed that the reaction of **21a** with $FeCl_3$ (1 equiv.) in 1,2-dichloeroethane (DCE) at 60 ^oC for 2 h produced the chlorinated pyrrolidine derivative **22a** in 71% yield as a mixture of *Z* and *E* isomers in a ratio of 91:09 (entry 3). The ratio of *Z* and *E* isomers was determined from the ^1H NMR of crude product. In a similar manner, reaction with one equivalent of $InCl_3$ in DCE at 60 ^oC for 3 h gave the same chloride substituted product **22a** in 70% yield with *Z* and *E* ratio 9:1 (entry 4). However, use of an external source of chloride nucleophile (TMSCl, 1 equiv.) in presence of catalytic amount of $FeCl_3$ (20 mol %) gave only 15% yield (entry 5). This indicates that $FeCl_3$ acts both as a Lewis acid as well as chloride nucleophile. Further, increasing the reaction concentration (0.13 M solution in DCE) results in slight increment of the yield to 76% (entry 6). Changing the solvent from DCE to toluene and acetonitrile results in decrease in the yield to 45% and 56%, respectively. Other Lewis acids such as TMSOTf and $In(OTf)_3$ produced decomposed products (entries 2 & 9). On the other hand, Brønsted acids such as *p*-TSA and triflic acid are found to be ineffective for the cyclization reaction. Hence, one equivalent of $FeCl_3$ in DCE at 60 ^oC stands out to be the optimum condition for the reaction.

4.4.2. Substrate scope of the reaction

With these optimized conditions, we further examined the scope of the reaction and limitations with a variety of derivatives (**21a-21r**). The results are outlined in the Table 4.4.2.1.

Table 4.4.2.1. Synthesis of pyrrolidines and piperidines



Entry	**21** (n= 1,2)	**22**	*Z*:*E* ratio[a]	Yield(%)[b]
1	 **21a**	 **22a**	91:9	76

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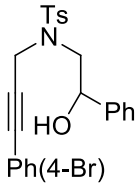
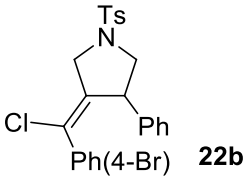
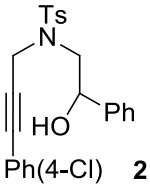
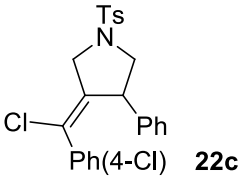
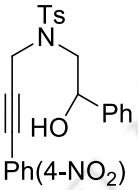
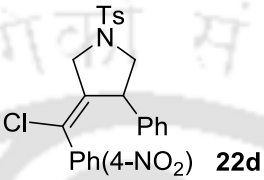
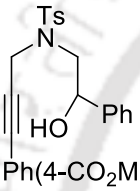
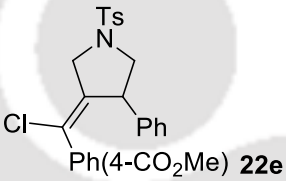
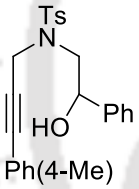
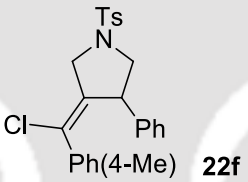
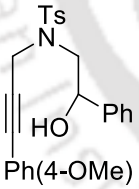
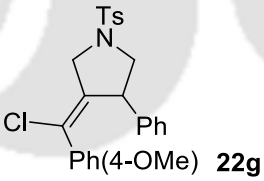
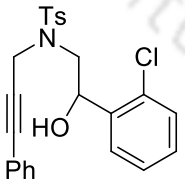
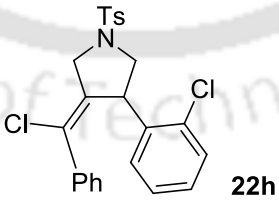
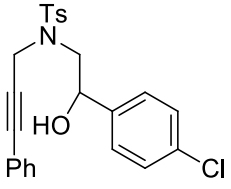
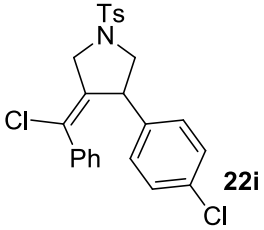
2	 **21b**	 **22b**	92:8	72
3	 **21c**	 **22c**	93:7	74
4	 **21d**	 **22d**	81:19	68
5	 **21e**	 **22e**	84:16	70
6	 **21f**	 **22f**	94:6	72
7	 **21g**	 **22g**	-	d
8	 **21h**	 **22h**	94:6	61
9	 **21i**	 **22i**	88:12	74

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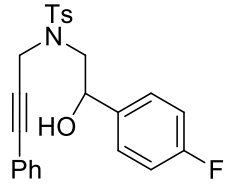
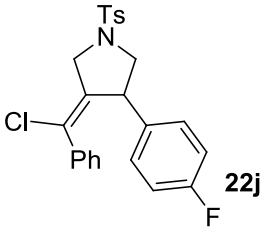
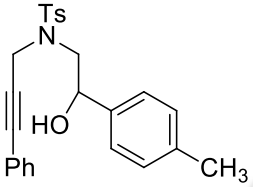
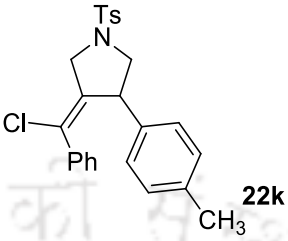
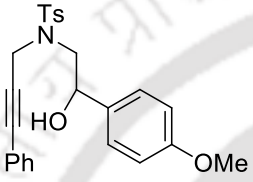
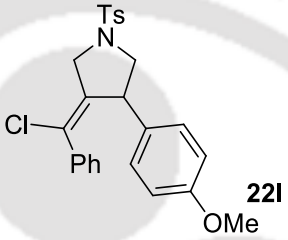
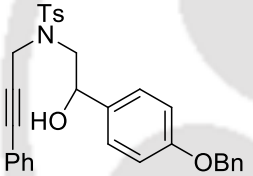
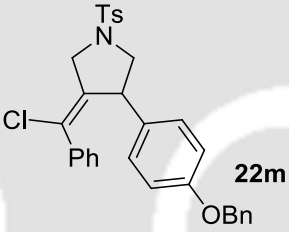
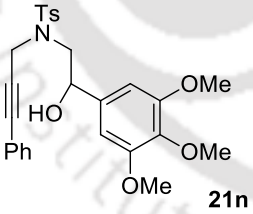
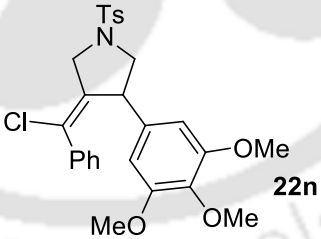
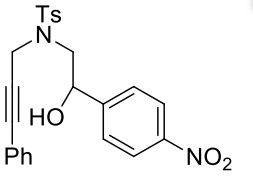
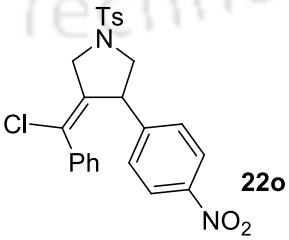
10	 **21j**	 **22j**	89:11	72
11	 **21k**	 **22k**	93:7	78
12	 **21l**	 **22l**	93:7	82
13	 **21m**	 **22m**	93:7	78
14	 **21n**	 **22n**	91:9	77
15	 **21o**	 **22o**	-	d

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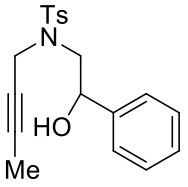
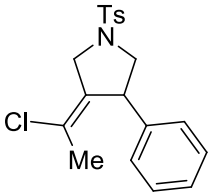
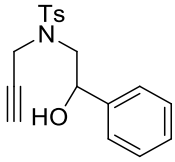
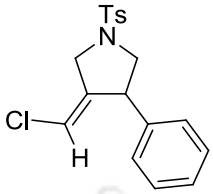
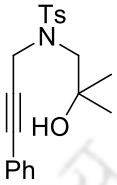
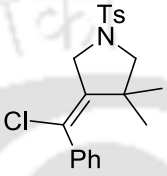
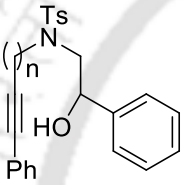
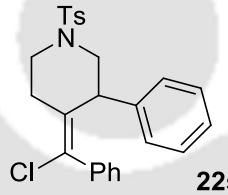
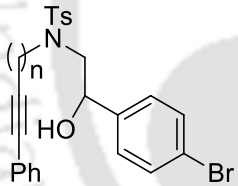
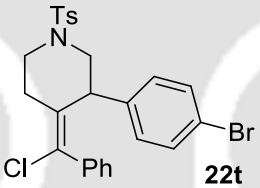
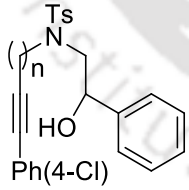
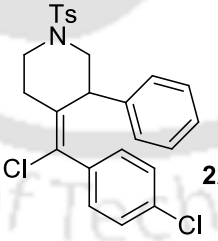
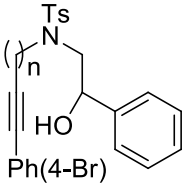
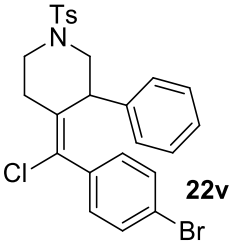
16	 **21p**	 **22p**	86:14	70
17	 **21q**	 **22q**	98:2	65
18	 **21r**	 **22r**	-	d
19	 n=2 **21s**	 **22s**	11:89	71
20	 n=2 **21t**	 **22t**	16:84	70
21	 n=2 **21u**	 **22u**	08:92	72
22	 n=2 **21v**	 **22v**	07:93	73

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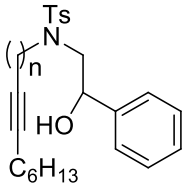
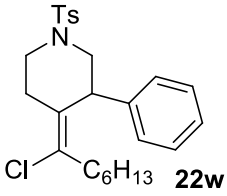
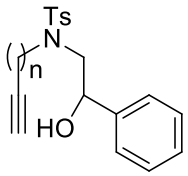
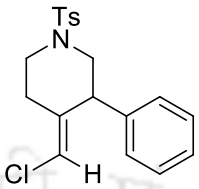
23	 n=2 **21w**	 **22w**	19:81	73
24	 n=2 **21x**	 **22x**	07:93	67

[a]The ratio was determined by ^{1}H NMR spectroscopy of products. [b]Yield refers to isolated yield. The compounds were characterized by IR, NMR and Mass spectrometry. d = Decomposed.

It was observed that the reaction was compatible to both electron-withdrawing and electron-donating groups on the aromatic ring of the alkyne side chain, delivering cyclized products in good yields with *Z* isomer as the major product. However, substrate having a strong electron-donating group (-OMe) on the aromatic ring of the alkyne side chain (entry 7) decomposed during the reaction. It was also observed that methyl substituted alkyne side chain (entry 16) gave the cyclized product in 70% yield with *Z* and *E* ratio 86:14. In addition to these, unsubstituted alkyne **21q** also reacts smoothly under these reaction conditions to furnish the pyrrolidine derivative **22q** in 65% yield. On the other hand, benzyl alcohols with halogen substituents (entries 8-10) gave the desired products in moderate to good yields, whereas benzyl alcohols with electron-donating groups (entries 11-14) produce excellent yields. The low yield for the *ortho* substituted benzyl alcohol **22h** may be attributed to steric hindrance. On the contrary, benzyl alcohols with a strong electron-withdrawing group (entry 15) failed to give the product under the standard reaction conditions, as the electron withdrawing group in the aromatic ring affords insufficient stabilization of the carbocation intermediate **A** (*Scheme 4.4.4.1*). Tertiary aliphatic alcohols (entry 18) found to be unreactive under these reaction conditions as tertiary aliphatic carbocations are not stable enough to facilitate the nucleophilic attack during under the reaction conditions.

This method also worked well for the homologous *N*-tethered alkyne-benzyl alkanols **21s-21x** and gave the desired exocyclic chlorinated piperidine derivatives **22s-22x** in good yields with *E* isomer as the major product. Substrate having alkyl substituted (entry

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23) on the alkyne side chain as well as unsubstituted alkyne (entry 24) also furnished the desired cyclized product in good yields.

4.4.3. Stereochemistry of the pyrrolidines and piperidines

The reaction is highly *Z*-selective for pyrrolidines and *E*-selective for piperidines. The addition reaction to the triple bond proceeds with *anti*-mode in preference to *syn*-mode in both the cases. Therefore, the *E*/*Z* selectivity is just a consequence of the IUPAC nomenclature. The stereochemistry of the pyrrolidine products was confirmed by X-ray crystallographic analysis of **22h** (*Figure 4.4.3.1*).[26]

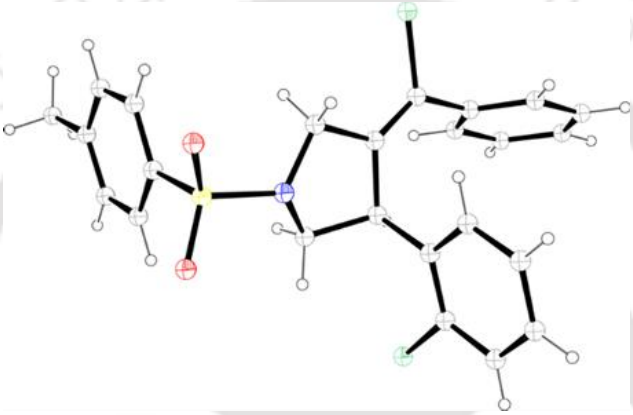

Figure 4.4.3.1. *ORTEP diagram of* ***22h*** *with 50% probability ellipsoid*

4.4.4. Plausible mechanism for the synthesis of pyrrolidines and piperidines

A plausible mechanism explaining the sequence of the events is tailored in *Scheme 4.4.4.1*. It involves the carbenium-ion induced cyclization of benzyl alcohols, followed by quenching of the resulting vinyl cation by chloride ion. Initially, the hydroxyl group of benzyl alcohol is activated by ferric chloride to generate benzyl carbenium-ion **A**. The intermediate **A** is then attacked by the alkyne group to form exocyclic vinyl carbocation **B**, with a five and six membered rings (n = 1 and 2). The intermediate carbocation **B** is trapped by chloride ion from $[FeCl_3(OH)]^-$ species to form pyrrolidine and piperidine derivatives with a chloride substituted exocyclic double bond, respectively. The stereoselectivity can be explained on the basis of attack of the incoming chloride ion. The steric repulsion between the incoming chloride ion and equatorial aromatic ring of the five and six membered ring system (intermediate **B**) makes the pathway "b" less feasible.

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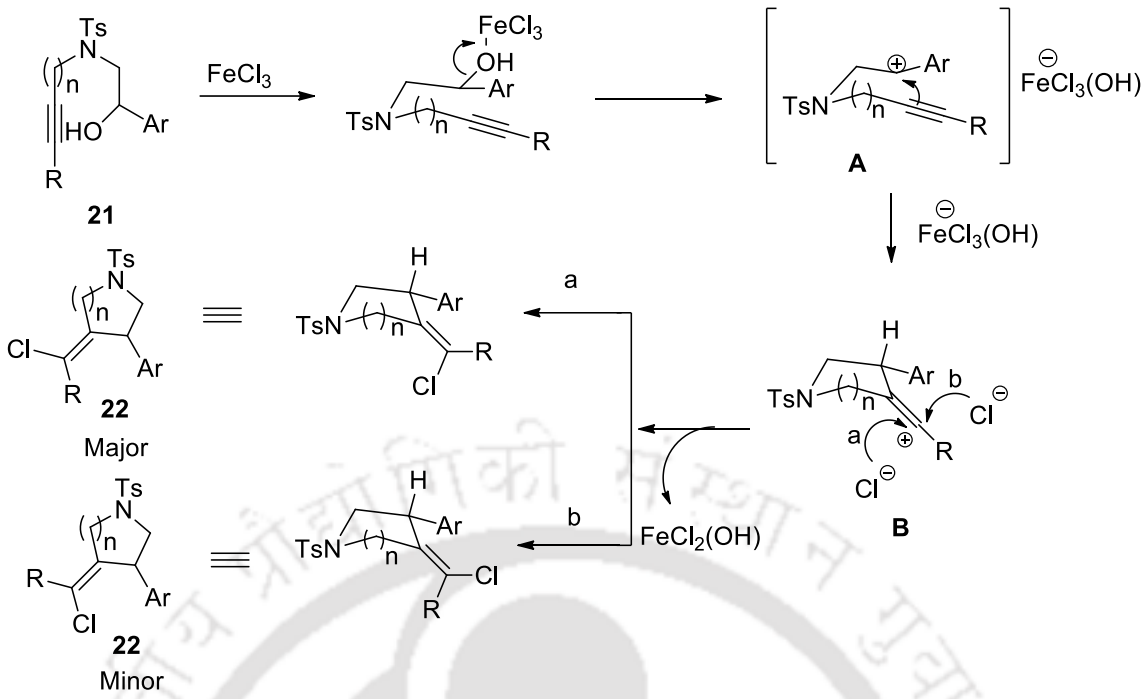

Scheme 4.4.4.1. *Proposed mechanism of the reaction*

4.5. Conclusion:

In conclusion, we have developed an efficient method for the synthesis of substituted pyrrolidine and piperidine derivatives with exocyclic chloro-alkylidene and -arylidene moiety *via* ferric chloride mediated intramolecular carbenium-ion induced cyclization reaction of *N*-tethered alkyne-benzyl alkanols in good yields. The reaction is *Z* selective for pyrrolidines and *E* selective for piperidines. One of the important aspects of the reaction is the dual role exhibited by ferric chloride as Lewis acid as well as chloride nucleophile.

4.6. Experimental section

4.6.1. Instrumentation and characterization

As described in chapter 2 section 2.6.1.

4.6.2. General procedure for preparation of *N*-tethered alkyne-benzyl alkanols (21a-21r):

To a stirred solution of NaH (44 mg, 1.1 mmol, 60% in a mineral oil) in dry DMF (4 mL) was added dropwise solution of the *N*-tosylated amino alcohol **23** (1 mmol) in dry

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DMF (4 mL) at 0 ^{o}C (N_2 atmosphere). After 20 minutes, DMF (4 mL) solution of propargylic bromide derivative **24** (1 mmol) was added and reaction was stirred at room temperature for 16 h. After completion of the reaction, a few drops of methanol was added at 0 ^{o}C and the solution was poured in ethylacetate (50 mL). The organic phase is washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. Evaporation of solvent gave the crude product, which was purified by column chromatography to give the *N*-tethered alkyne-benzyl alkanols **21a**-**21r**.

4.6.3. General procedure for preparation of *N*-tethered alkyne-benzyl alkanols (21s-21x):

To a stirred solution of NaH (44 mg, 1.1 mmol, 60% in a mineral oil) in dry DMF (4 mL) was added dropwise solution of the *N*-tosylated homopropargyl amine **25** (1 mmol) in dry DMF (4 mL) at 0 ^{o}C (N_2 atmosphere). After 20 minutes, DMF (4 mL) solution of phenacyl bromide or substituted phenacyl bromide **26** (1 mmol) was added and reaction was stirred at room temperature for 16 h. After completion of the reaction, a few drops of methanol was added at 0 ^{o}C and the solution was poured in ethylacetate (50 mL). The organic phase is washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by column chromatrography to *N*-tethered alkyne-ketones **27**.

To a stirred solution of *N*-tethered alkyne-ketones **27** in MeOH (15 mL), was added $NaBH_4$ (1 equiv.) at 0 ^{o}C and the mixture was stirred for half an hour. After completion of reaction, aq NH_4Cl (20 mL) is added and the organic layer is extracted with ethylacetate (2 x 30 mL). The organic phase is washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by column chromatrography to give the *N*-tethered alkyne-benzyl alkanols **21s**-**21x**.

4.6.4. Synthesis of *N*-(2-hydroxy-2-phenylethyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (21a):

To a stirred solution of NaH (44 mg, 1.1 mmol, 60% in a mineral oil) in dry DMF (4 mL) was added dropwise solution of the *N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (291 mg, 1 mmol) in dry DMF (4 mL) at 0 ^{o}C (N_2 atmosphere). After 20 minutes, DMF (4 mL) solution of (3-bromoprop-1-yn-1-

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yl)benzene (194 mg, 1 mmol) was added and reaction was stirred at room temperature for 16 h. After completion of the reaction, a few drops of methanol was added at 0 ^{o}C and the solution was poured in ethylacetate (50 mL). The organic phase is washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. Evaporation of solvent gave the crude product, which was purified by column chromatography using hexane and ethyl acetate (hexane:EtOAc, 4:1) as eluents to give *N*-(2-hydroxy-2-phenylethyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide **21a** in 67% yield (265 mg).

4.6.5. General procedure for synthesis of substituted pyrrolidines and piperidines (22a-22x):

To a suspension of ferric chloride (1 equiv.) in dry dichloroethane (1 mL) was added dichloroethane solution (2 mL) of *N*-tethered alkyne-benzyl alkanols **21** (0.4 mmol) dropwise under nitrogen atmosphere. The reaction mixture was heated at 60 ^{o}C. The reaction is monitored by checking TLC. After completion of the reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (5 mL). The product was extracted with CH_2Cl_2 (2 × 20 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 using hexane and ethyl acetate as eluents to afford the title compounds **22a-22x**.

4.6.6. Synthesis of (*Z*)-3-(chloro(phenyl)methylene)-4-phenyl-1-tosylpyrrolidine (22a):

To a suspension of ferric chloride (65 mg, 1 equiv.) in dry dichloroethane (1 mL) was added dichloroethane solution (2 mL) of *N*-(2-hydroxy-2-phenylethyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide **21a** (162 mg, 0.4 mmol) dropwise under nitrogen atmosphere. The reaction mixture was heated at 60 ^{o}C. The reaction is monitored by checking TLC. After completion of the reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (5 mL). The product was extracted with CH_2Cl_2 (2 × 20 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

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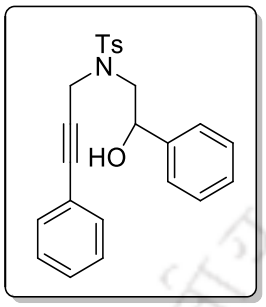
gel column chromatography using hexane and ethyl acetate (hexane:EtOAc, 10:1) as eluents to give **22a** (127 mg, 76% yield) as a colorless solid.

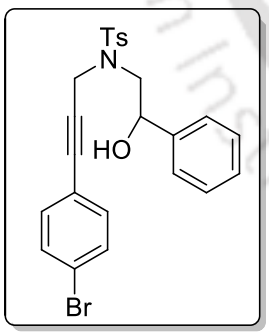
4.7. Spectral data

_N_-(2-Hydroxy-2-phenylethyl)-4-methyl-_N_-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (21a):



White solid, mp. 95-97 ^{o}C; R_f (hexane/EtOAc 4:1) 0.50; yield 265 mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 3.11 (brs, 1 H), 3.37 (dd, *J* = 14.4 Hz and *J* = 3.6 Hz, 1 H), 3.47 (dd, *J* = 14.4 and 8.8 Hz, 1 H), 4.29 (d, *J* = 18.8 Hz, 1 H), 4.42 (d, *J* = 18.8 Hz, 1 H), 5.03 (dt, *J* = 8.8 and 2.8 Hz, 1 H), 7.06-7.09 (m, 2 H), 7.22-7.30 (m, 6 H), 7.35-7.39 (m, 2 H), 7.42-7.45 (m, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 39.5, 54.8, 72.6, 82.1, 86.0, 122.1, 126.2, 128.0, 128.2, 128.3, 128.7, 128.8, 129.8, 131.7, 135.6, 141.3, 144.0; IR (KBr, neat) 3521, 3062, 2923, 2239, 1598, 1492, 1347, 1162, 921, 762, 660 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{24}NO_3S$ $(M + H)^+$ 406.1471, found 406.1476.

_N_-(3-(4-Bromophenyl)prop-2-yn-1-yl)-_N_-(2-hydroxy-2-phenylethyl)-4-methylbenzene-sulfonamide (21b):



Brown solid, mp. 130-132 ^{o}C; R_f (hexane/EtOAc 4:1) 0.50; yield 299 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 3.08 (brs, 1 H), 3.35 (dd, *J* = 14.4 Hz and *J* = 3.6 Hz, 1 H), 3.45 (dd, *J* = 14.4 and 8.8 Hz, 1 H), 4.28 (d, *J* = 18.8 Hz, 1 H), 4.40 (d, *J* = 18.8 Hz, 1 H), 5.02 (dd, *J* = 8.8 and 3.6 Hz , 1 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 7.29-7.37 (m, 5 H), 7.40-7.42 (m, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 39.4, 54.8, 72.7, 83.4, 84.8, 121.0, 122.9, 126.1, 128.0, 128.2, 128.8, 129.7, 131.6, 133.0, 135.6, 141.2, 144.0; IR (KBr, neat) 3513, 3063, 2924, 2214, 1597, 1488, 1346, 1160, 823, 764, 662 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{23}BrNO_3S$ $(M + H)^+$ 484.0582, found 484.0578.

_N_-(3-(4-chlorophenyl)prop-2-yn-1-yl)-_N_-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (21c):

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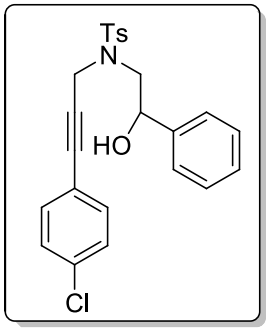
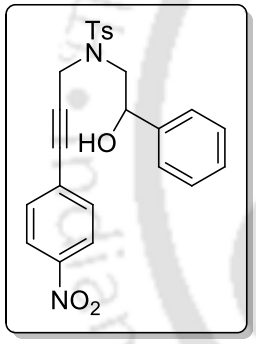


Brown solid, mp. 135-137 ^{o}C; R_f (hexane/EtOAc 4:1) 0.50; yield 272 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 3.09 (d, *J* = 3.2 Hz, 1 H), 3.36 (dd, *J* = 14.4 Hz and *J* = 3.6 Hz, 1 H), 3.45 (dd, *J* = 14.4 and 8.8 Hz, 1 H), 4.29 (d, *J* = 18.8 Hz, 1 H), 4.42 (d, *J* = 18.8 Hz, 1 H), 5.01-5.04 (m, 1 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 7.19-7.23 (m, 4 H), 7.28-7.32 (m, 1 H), 7.34-7.43 (m, 4 H), 7.75 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 39.5, 54.8, 72.7, 83.2, 84.8, 120.6, 126.2, 128.0, 128.2, 128.7, 128.8, 129.8, 132.9, 134.8, 135.7, 141.3, 144.0; IR (KBr, neat) 3519, 3061, 2920, 2219, 1595, 1488, 1346, 1161, 831, 769, 671 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{23}ClNO_3S$ $(M + H)^+$ 440.1082, found 440.1089.

_N_-(2-Hydroxy-2-phenylethyl)-4-methyl-_N_-(3-(4-nitrophenyl)prop-2-yn-1-yl)benzene-sulfonamide (21d):



Pale yellow gum; R_f (hexane/EtOAc 4:1) 0.40; yield 261 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 2.99 (d, *J*= 2.8 Hz, 1 H), 3.38 (dd, *J* = 14.4 and 3.6 Hz, 1 H), 3.45 (dd, *J* = 14.4 and 8.8 Hz, 1 H), 4.35 (d, *J* = 18.8 Hz, 1 H), 4.47 (d, 18.8 Hz, 1 H), 5.05 (dd, *J* = 8.4 and 3.6 Hz, 1 H), 7.19 (d, *J* = 8.8 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H) 7.29-7.43 (m, 5 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 8.10 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 39.5, 54.9, 73.1, 83.9, 87.9, 123.5, 126.1, 128.0, 128.3, 128.8, 128.9, 129.8, 132.4, 135.7, 141.2, 144.1, 147.3; IR (KBr, neat) 3522, 3064, 2923, 2853, 1596, 1522, 1351, 1163, 910, 856, 746, 662 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{23}N_2O_5S$ $(M + H)^+$ 451.1328, found 451.1340.

Methyl 4-(3-(_N_-(2-hydroxy-2-phenylethyl)-4-methylphenylsulfonamido)prop-1-yn-1-yl)benzoate (21e):

White solid, mp. 125-127 ^{o}C; R_f (hexane/EtOAc 4:1) 0.40; yield 278 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 2.98 (brs, 1 H), 3.38 (dd, *J* = 14.4 and 3.2 Hz, 1 H), 3.46 (dd, *J* = 14.4 and 8.8 Hz, 1 H), 3.91 (d, *J* = 2.0 Hz, 3 H), 4.32 (d, *J* = 18.8 Hz, 1 H), 4.45 (d, 18.8 Hz, 1 H), 5.04 (d, *J* = 7.6 Hz, 1 H), 7.10 (dd, *J* = 8.4 and 1.6 Hz, 2 H), 7.23

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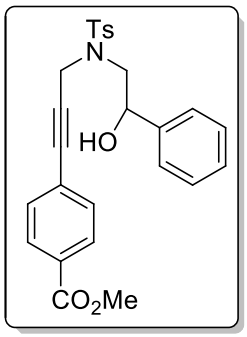
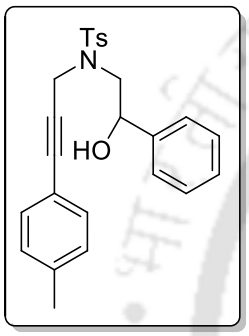


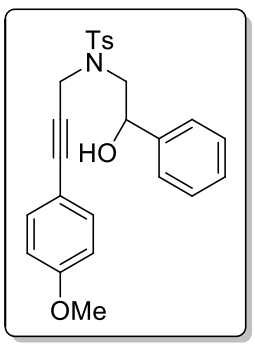
(d, *J* = 8.4 Hz, 2 H), 7.29-7.44 (m, 5 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 7.90 (dd, *J* = 8.4 and 1.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 39.4, 52.5, 54.7, 72.8, 85.1, 85.2, 126.1, 126.7, 128.0, 128.2, 128.7, 129.4, 129.7, 129.9, 131.5, 135.6, 141.3, 144.0, 166.5; IR (KBr, neat) 3508, 3063, 2953, 2849, 1725, 1603, 1495, 1438, 1161, 910, 768, 662 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{26}NO_5S$ $(M + H)^+$ 464.1532, found 464.1546.

_N_-(2-Hydroxy-2-phenylethyl)-4-methyl-_N_-(3-(_p_-tolyl)prop-2-yn-1-yl)benzenesulfonamide (21f):



White solid, mp. 115-116 °C; R_f (hexane/EtOAc 4:1) 0.50; yield 285 mg, 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3 H), 2.33 (s, 3 H), 3.36 (dd, *J* = 14.4 and 3.6 Hz, 1 H), 3.46 (dd, *J* = 14.4 and 8.8 Hz, 1 H), 4.28 (d, *J* = 18.8 Hz, 1 H), 4.41 (d, 18.8 Hz, 1 H), 5.02 (dd, *J* = 8.8 and 3.6 Hz, 1 H), 6.96 (d, *J* = 8.0 Hz, 2 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.25-7.43 (m, 5 H), 7.76 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (2C), 39.5, 54.9, 72.6, 81.4, 86.2, 119.1, 126.2, 128.1, 128.2, 128.8, 129.1, 129.8, 131.6, 135.7, 138.9, 141.3, 144.0; IR (KBr, neat) 3522, 3064, 2923, 2856, 2242, 1599, 1509, 1347, 1163, 923, 816, 766, 671 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{26}NO_3S$ $(M + H)^+$ 420.1633, found 420.1630.

_N_-(2-Hydroxy-2-phenylethyl)-_N_-(3-(4-methoxyphenyl)prop-2-yn-1-yl)-4-methylbenzene-sulfonamide (21g):



White solid, mp. 98-99 °C; R_f (hexane/EtOAc 4:1) 0.45; yield 265 mg, 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 3.36 (dd, *J* = 14.8 and 3.6 Hz, 1 H), 3.45 (dd, *J* = 14.8 and 8.8 Hz, 1 H), 3.79 (s, 3 H), 4.28 (d, *J* = 18.4 Hz, 1 H), 4.41 (d, 18.4 Hz, 1 H), 5.02 (dd, *J* = 8.8 and 3.6 Hz, 1 H), 6.75 (d, *J* = 8.4 Hz, 2 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.28-7.44 (m, 5 H), 7.77 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 39.6, 54.9, 55.5, 72.5, 80.6, 86.0, 114.0, 114.2, 126.2, 128.1, 128.2, 128.8, 129.8, 133.2, 135.6, 141.3, 144.0, 160.0; IR (KBr, neat) 3522, 3064, 2926, 2840, 2239, 1605, 1511, 1350,

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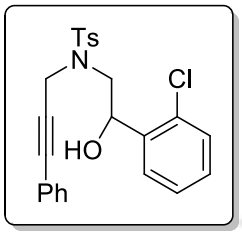
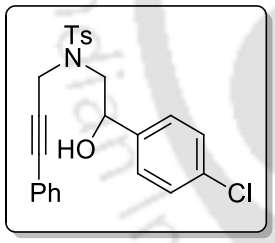
1170, 923, 836, 766, 658 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{26}NO_4S$ $(M + H)^+$ 436.1583, found 436.1579.

_N_-(2-(2-Chlorophenyl)-2-hydroxyethyl)-4-methyl-_N_-(3-phenylprop-2-yn-1-yl)benzene-sulfonamide (21h):



White solid, mp. 100-101 ^oC; R_f (hexane/EtOAc 4:1) 0.50; yield 272 mg, 62%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 3.39 (dd, *J* = 14.8 and 8.8 Hz, 1 H), 3.48 (brs, 1 H), 3.53 (dd, *J* = 14.8 and 2.4 Hz, 1 H), 4.43 (brs, 2 H), 5.38 (d, *J* = 8.8 Hz, 1 H), 7.06-7.08 (m, 2 H), 7.20-7.34 (m, 8 H), 7.73-7.35 (m, 1 H), 7.78 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 39.3, 52.8, 68.8, 82.0, 86.0, 122.1, 127.5, 127.9, 128.1, 128.3, 128.7, 129.2, 129.5, 129.8, 131.7, 131.8, 135.6, 138.4, 144.1; IR (KBr, neat) 3511, 3063, 2924, 2854, 2241, 1597, 1492, 1348, 1162, 916, 815, 761, 659 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{23}ClNO_3S$ $(M + H)^+$ 440.1087, found 440.1096.

_N_-(2-(4-Chlorophenyl)-2-hydroxyethyl)-4-methyl-_N_-(3-phenylprop-2-yn-1-yl)benzene-sulfonamide (21i):



White solid, mp. 106-107 ^oC; R_f (hexane/EtOAc 4:1) 0.50; yield 285 mg, 65%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 3.18 (brs, 1 H), 3.33 (dd, *J* = 14.8 and 3.6 Hz, 1 H), 3.41 (dd, *J* = 14.8 and 8.8 Hz, 1 H), 4.29 (d, *J* = 18.4 Hz, 1 H), 4.39 (d, *J* = 18.4 Hz, 1 H), 5.01 (d, *J* = 8.8 Hz, 1 H), 7.06 (d, *J* = 7.2 Hz, 2 H), 7.22-7.27 (m, 5 H), 7.29-7.38 (m, 4 H), 7.76 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 39.6, 54.8, 72.0, 81.9, 86.1, 122.0, 127.6, 128.0, 128.4, 128.8, 128.9, 129.9, 131.7, 133.9, 135.4, 139.8, 144.2; IR (KBr, neat) 3511, 3060, 2923, 2858, 2241, 1598, 1491, 1331, 1161, 918, 816, 758, 659 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{23}ClNO_3S$ $(M + H)^+$ 440.1087, found 440.1088.

_N_-(2-(4-fluorophenyl)-2-hydroxyethyl)-4-methyl-_N_-(3-phenylprop-2-yn-1-yl)benzene-sulfonamide (21j):

White solid, mp. 90-91 ^oC; R_f (hexane/EtOAc 4:1) 0.50; yield 245 mg, 58%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 3.16 (brs, 1 H), 3.33 (dd, *J* = 14.8 and 3.6 Hz, 1 H), 3.43 (dd, *J* = 14.8 and 8.8 Hz, 1 H), 4.29 (d, *J* = 18.4 Hz, 1 H), 4.42 (d, *J* = 18.4 Hz, 1

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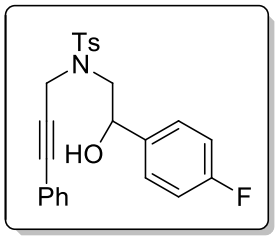
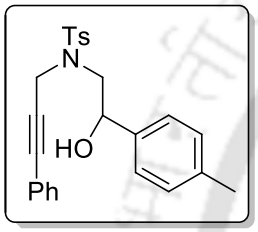


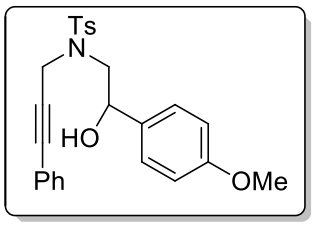
H), 5.01 (dd, *J* = 8.8 and 3.2 Hz, 1 H), 7.02-7.07 (m, 4 H), 7.22-7.31 (m, 5 H), 7.38-7.42 (m, 2 H), 7.77 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 39.6, 54.9, 72.0, 81.9, 86.1, 115.7 (d, *J* = 21.3 Hz), 122.0, 127.9 (d, *J* = 8.2 Hz), 128.0, 128.4, 128.8, 129.9, 131.7, 135.5, 137.0, 144.1, 162.6 (d, *J* = 244.7 Hz, C-F); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 47.44; IR (KBr, neat) 3513, 3062, 2924, 2855, 2241, 1602, 1510, 1348, 1161, 918, 838, 758, 660 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{23}FNO_3S$ $(M + H)^+$ 424.1377, found 424.1384.

_N_-(2-Hydroxy-2-(_p_-tolyl)ethyl)-4-methyl-_N_-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (21k):



White solid, mp. 107-108 °C; R_f (hexane/EtOAc 4:1) 0.50; yield 260 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3 H), 2.32 (s, 3 H), 3.17 (d, *J*= 2.4 Hz, 1 H), 3.35 (dd, *J* = 14.8 and 3.2 Hz, 1 H), 3.45 (dd, *J* = 14.8 and 8.8 Hz, 1 H), 4.28 (d, *J* = 18.4 Hz, 1 H), 4.43 (d, *J* = 18.4 Hz, 1 H), 4.97-4.99 (m, 1 H), 7.03-7.06 (m, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.19-7.27 (m, 5 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 21.5, 39.4, 54.7, 72.4, 82.1, 86.0, 122.1, 126.1, 128.0, 128.3, 128.6, 129.4, 129.7, 131.6, 135.6, 137.9, 138.3, 143.9; IR (KBr, neat) 3511, 3057, 2922, 2863, 2240, 1598, 1491, 1345, 1160, 917, 816, 758, 660 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{26}NO_3S$ $(M + H)^+$ 420.1633, found 420.1630.

_N_-(2-Hydroxy-2-(4-methoxyphenyl)ethyl)-4-methyl-_N_-(3-phenylprop-2-yn-1-yl)benzene-sulfonamide (21l):



White solid, mp. 121-122 °C; R_f (hexane/EtOAc 4:1) 0.44; yield 265 mg, 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 3.05 (brs, 1 H), 3.33 (dd, *J* = 14.4 and 3.6 Hz, 1 H), 3.45 (dd, *J* = 14.4 and 8.8 Hz, 1 H), 3.78 (s, 3 H), 4.26 (d, *J* = 18.8 Hz, 1 H), 4.42 (d, *J* = 18.8 Hz, 1 H), 4.97 (dd, *J* = 8.8 and 3.2 Hz, 1 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 7.04-7.08 (m, 2 H), 7.20-7.29 (m, 5 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 39.4, 54.7, 55.4, 72.2, 82.1, 86.0, 114.1, 122.1, 127.4, 128.0, 128.3, 128.7, 129.7, 131.6, 133.4, 135.7, 144.0, 159.5; IR (KBr, neat) 3520, 3061, 2926, 2834, 2241, 1612, 1514, 1348,

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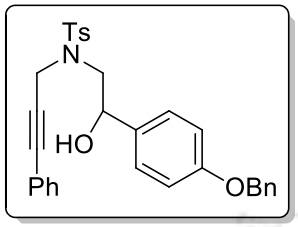
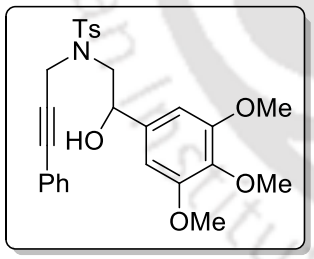
1170, 917, 834, 759, 660 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{26}NO_4S$ $(M + H)^+$ 436.1577, found 436.1572.

_N_-(2-(4-(benzyloxy)phenyl)-2-hydroxyethyl)-4-methyl-_N_-(3-phenylprop-2-yn-1-yl)benzene-sulfonamide (21m):



White solid, mp. 140-142 ^oC; R_f (hexane/EtOAc 4:1) 0.47; yield 301 mg, 59%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 2.95 (brs, 1 H), 3.33 (dd, *J* = 14.4 and 3.6 Hz, 1 H), 3.45 (dd, *J* = 14.4 and 8.8 Hz, 1 H), 4.27 (d, *J* = 18.8 Hz, 1 H), 4.42 (d, *J* = 18.8 Hz, 1 H), 4.97 (dd, *J* = 8.8 and 2.8 Hz, 1 H), 5.05 (s, 2 H), 6.96 (d, *J* = 8.4 Hz, 2 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 7.20-7.28 (m, 5 H), 7.30-7.43 (m, 7 H), 7.76 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 39.5, 54.8, 70.2, 72.2, 82.1, 86.0, 115.2, 122.2, 127.5, 127.6, 128.0, 128.2, 128.3, 128.7, 128.8, 129.8, 131.7, 133.7, 135.7, 137.1, 144.0, 158.8; IR (KBr, neat) 3512, 3062, 2923, 2866, 1609, 1512, 1345, 1160, 916, 834, 757, 660 cm^{-1}; HRMS (ESI) calcd. for $C_{31}H_{30}NO_4S$ $(M + H)^+$ 512.1896, found 512.1900.

_N_-(2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)-4-methyl-_N_-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (21n):



White solid, mp 110-112 ^oC; R_f (hexane/EtOAc 7:3) 0.45; yield 292 mg, 59%; ^1H NMR (600 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 3.08 (brs, 1 H), 3.37 (dd, *J* = 14.4 and 3.6 Hz, 1 H), 3.47 (dd, *J* = 14.4 and 9.0 Hz, 1 H), 3.82 (s, 3 H), 3.82 (s, 6 H), 4.31 (d, *J* = 18.0 Hz, 1 H), 4.42 (d, *J* = 18.0 Hz, 1 H), 4.98 (dt, *J* = 8.4 and 3.0 Hz, 1 H), 6.64 (s, 2 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 7.22-7.30 (m, 5 H), 7.77 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 39.5, 54.9, 56.3, 61.0, 72.8, 82.1, 86.2, 103.0, 122.1, 128.0, 128.4, 128.8, 129.9, 131.6, 135.6, 137.0, 137.7, 144.1, 153.6; IR (KBr, neat) 3521, 3058, 2921, 2841, 2231, 1622, 1517, 1358, 1163, 927, 763, 659 cm^{-1}; HRMS (ESI) calcd. for $C_{27}H_{33}N_2O_6S$ $(M + NH_4)^+$ 513.2054, found 513.2041.

_N_-(2-Hydroxy-2-(4-nitrophenyl)ethyl)-4-methyl-_N_-(3-phenylprop-2-yn-1-yl)benzene-sulfonamide (21o):

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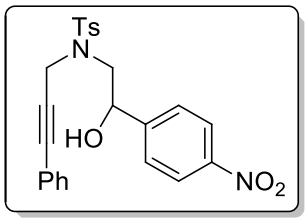
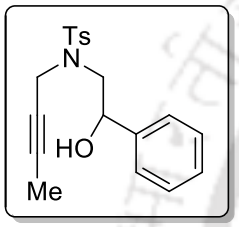


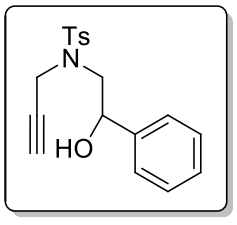
White solid, mp. 143-145 ^{o}C; R_f (hexane/EtOAc 4:1) 0.38; yield 261 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 3.40-3.47 (m, 3 H), 4.33 (d, *J* = 18.4 Hz, 1 H), 4.39 (d, *J* = 18.4 Hz, 1 H), 5.15-5.19 (m, 1 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 7.22-7.32 (m, 5 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 8.21 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 39.9, 54.8, 72.0, 81.6, 86.4, 121.8, 124.0, 127.1, 128.0, 128.4, 129.0, 130.0, 131.7, 135.2, 144.4, 147.8, 148.5; IR (KBr, neat) 3454, 2925, 2852, 1639, 1602, 1518, 1341, 1100, 921, 866, 757, 694 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{23}ClNO_3S$ $(M + H)^+$ 451.1328, found 451.1328.

***N*-(But-2-yn-1-yl)-*N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (21p):**



Colourless liquid; R_f (hexane/EtOAc 4:1) 0.50; yield 223 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (s, 3 H), 2.32 (s, 3 H), 3.10 (brs, 1 H), 3.19 (dd, *J* = 14.4 and 3.0 Hz, 1 H), 3.29 (dd, *J* = 14.4 and 9.0 Hz, 1 H), 3.94 (dd, *J* = 18.0 and 1.2 Hz, 1 H), 4.06 (dd, *J* = 18.0 and 2.4 Hz, 1 H), 4.88 (d, *J* = 8.4 Hz, 1 H), 7.18-7.22 (m, 3 H), 7.28 (t, *J* = 7.8 Hz, 2 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.65 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.4, 21.6, 39.2, 54.8, 72.2, 72.4, 82.1, 126.1, 128.1, 128.7, 129.5, 135.8, 141.4, 143.8; IR (KBr, neat) 3522, 2921, 2224, 1598, 1494, 1347, 1163, 1091, 873, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{22}NO_3S$ $(M + H)^+$ 344.1315, found 344.1333.

***N*-(2-Hydroxy-2-phenylethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (21q):**



Pale yellow liquid; R_f (hexane/EtOAc 4:1) 0.55; yield 230 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (t, *J* = 2.4 Hz, 1 H), 2.40 (s, 3 H), 3.04 (brs, 1 H), 3.29 (dd, *J* = 14.4 and 3.6 Hz, 1 H), 3.39 (dd, *J* = 14.4 and 8.8 Hz, 1 H), 4.09 (dd, *J* = 18.8 and 2.4 Hz, 1 H), 4.22 (dd, *J* = 18.8 and 2.4 Hz, 1 H), 4.97-5.00 (m, 1 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 7.2 Hz, 1 H), 7.34-7.41 (m, 4 H), 7.72 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 38.5, 54.4, 72.5, 74.3, 76.9, 126.1, 127.9, 128.1, 128.7, 129.7, 135.5, 141.3, 144.0; IR (KBr, neat) 3524, 3063, 2924, 2120, 1599, 1451, 1344, 1159, 907, 766, 662 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{20}NO_3S$ $(M + H)^+$ 330.1164, found 330.1168.

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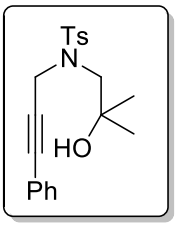
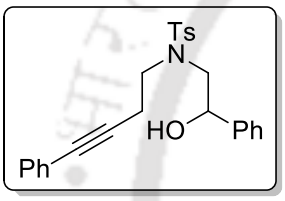
***N*-(2-Hydroxy-2-methylpropyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzene-sulfonamide (21r):**



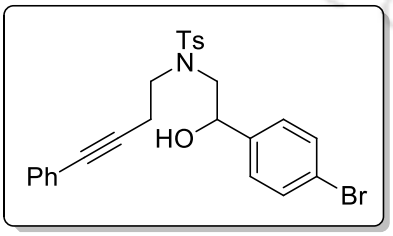
Pale yellow liquid; R_f (hexane/EtOAc 4:1) 0.40; yield 232 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32 (s, 6 H), 2.30 (s, 3 H), 2.55 (brs, 1 H), 3.64 (s, 2 H), 4.47 (s, 2 H), 7.18 (d, *J* = 7.8 Hz, 2 H), 7.22-7.27 (m, 5 H), 7.82 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 25.0, 36.6, 64.0, 70.3, 84.7, 86.8, 122.6, 127.6, 128.5, 128.7, 129.7, 131.7, 139.9, 143.5; IR (KBr, neat) 3528, 2981, 2242, 1598, 1491, 1325, 1151, 1091, 874, 758, 651 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{24}NO_3S$ $(M + H)^+$ 358.1477, found 358.1482.

***N*-(2-Hydroxy-2-phenylethyl)-4-methyl-*N*-(4-phenylbut-3-yn-1-yl)benzenesulfonamide (21s):**



White solid, mp. 76-78 °C; R_f (hexane/EtOAc 4:1) 0.50; yield 276 mg, 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 2.72-2.76 (m, 2 H), 3.13 (d, *J* = 2.8 Hz, 1 H), 3.28-3.35 (m, 2 H), 3.35-3.50 (m, 2 H), 5.04 (dd, *J* = 8.0 and 4.4 Hz, 1 H), 7.26-7.31 (m, 6 H), 7.32-7.40 (m, 6 H), 7.73 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.6, 21.7, 49.4, 57.8, 73.1, 82.9, 86.6, 123.3, 126.2, 127.5, 128.2, 128.4, 128.8, 130.1, 131.8, 136.1, 141.4, 144.0; IR (KBr, neat) 3509, 3061, 2924, 2870, 1599, 1492, 1333, 1160, 971, 815, 759, 658 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{26}NO_3S$ $(M + H)^+$ 420.1633, found 420.1625.

***N*-(2-(4-bromophenyl)-2-hydroxyethyl)-4-methyl-*N*-(4-phenylbut-3-yn-1-yl)benzenesulfonamide (21t):**



Yellow gum; R_f (hexane/EtOAc 4:1) 0.50; yield 293 mg, 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 2.72 (dt, *J* = 7.2 Hz and *J* = 3.0 Hz, 2 H), 3.29 (d, *J* = 6.0 Hz, 2 H), 3.32 (brs, 1 H), 3.39-3.48 (m, 2 H), 5.02 (t, *J* = 6.0 Hz, 1 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.26-7.28 (m, 5 H), 7.33-7.35 (m, 2 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 7.71 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.5, 21.7, 49.4, 57.5, 72.5, 82.9, 86.6, 122.0, 123.2, 127.5, 127.9, 128.3, 128.5, 130.1, 131.7, 131.8, 135.9, 140.4, 144.1; IR (KBr, neat) 3511, 3058,

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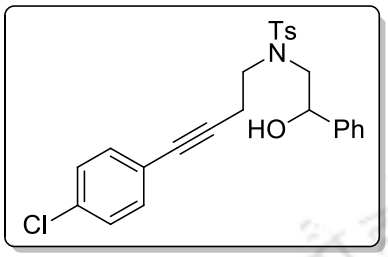
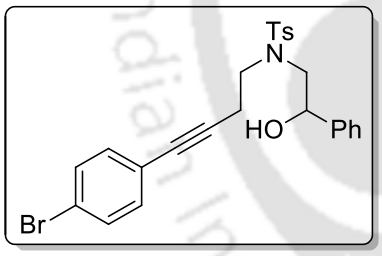
2923, 2237, 1597, 1489, 1450, 1325, 1160, 970, 817, 738, 652 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{25}BrNO_3S$ $(M + H)^+$ 498.0739, found 498.0724.

_N_-(4-(4-Chlorophenyl)but-3-yn-1-yl)-_N_-(2-hydroxy-2-phenylethyl)-4-methylbenzene-sulfonamide (21u):



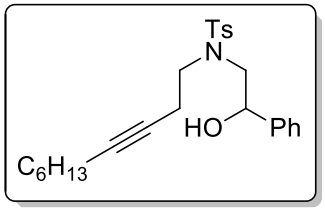
Yellow gum; R_f (hexane/EtOAc 4:1) 0.50; yield 271 mg, 60%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 2.73 (dt, *J* = 7.2 and 2.0 Hz, 2 H), 3.19 (brs, 1 H), 3.27-3.36 (m, 2 H), 3.37-3.50 (m, 2 H), 5.02 (dd, *J* = 8.0 and 4.4 Hz, 1 H), 7.22-7.30 (m, 6 H), 7.31-7.39 (m, 5 H), 7.72 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 21.6, 49.3, 57.7, 73.1, 81.7, 87.7, 121.8, 126.1, 127.4, 128.2, 128.6, 128.7, 130.0, 133.0, 134.0, 135.9, 141.3, 143.9; IR (KBr, neat) 3522, 3062, 2922, 2872, 2237, 1597, 1490, 1452, 1162, 970, 838, 757, 656 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{25}ClNO_3S$ $(M + H)^+$ 454.1244, found 454.1239.

_N_-(4-(4-bromophenyl)but-3-yn-1-yl)-_N_-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (21v):



Yellow gum; R_f (hexane/EtOAc 4:1) 0.50; yield 288 mg, 58%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 2.68-2.78 (m, 2 H), 3.15 (d, *J* = 4.4 Hz, 1 H), 3.26-3.31 (m, 2 H), 3.34-3.50 (m, 2 H), 5.01 (t, *J* = 6.0 Hz, 1 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 7.26-7.40 (m, 9 H), 7.72 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.6, 21.7, 49.4, 57.8, 73.1, 81.8, 88.0, 122.3, 122.4, 126.1, 127.5, 128.2, 128.8, 130.1, 131.7, 133.2, 136.0, 141.3, 144.0; IR (KBr, neat) 3514, 3059, 2921, 2230, 1590, 1479, 1445, 1325, 1160, 973, 819, 748, 652 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{25}BrNO_3S$ $(M + H)^+$ 498.0739, found 498.0715.

_N_-(Dec-3-yn-1-yl)-_N_-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (21w):



Yellow liquid; R_f (hexane/EtOAc 4:1) 0.50; yield 256 mg, 60%; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.2 Hz, 3 H), 1.22-1.34 (m, 6 H), 1.40-1.47 (m, 2 H), 1.69 (brs, 1 H), 2.08-2.12 (m, 2 H), 2.41 (s, 3 H), 2.46-2.50 (m, 2 H), 3.24-3.26

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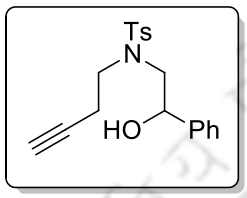
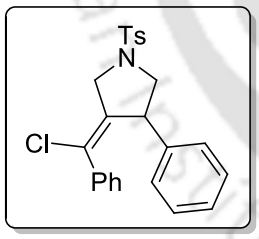
(m, 2 H), 3.28-3.34 (m, 2 H), 4.99 (dt, *J* = 8.8 and 2.8 Hz, 1 H), 7.28-7.30 (m, 3 H), 7.33-7.40 (m, 4 H), 7.71 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 18.9, 20.0, 21.7, 22.7, 28.8, 29.0, 31.5, 49.8, 57.9, 73.0, 76.7, 83.1, 126.1, 127.5, 128.1, 128.7, 130.0, 136.0, 141.3, 143.9; IR (KBr, neat) 3508, 3063, 2852, 1632, 1601, 1454, 1352, 1163, 974, 815, 751, 657 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{34}NO_3S$ $(M + H)^+$ 428.2259, found 428.2263.

***N*-(but-3-yn-1-yl)-*N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (21x):**



Colourless liquid; R_f (hexane/EtOAc 4:1) 0.45; yield 216 mg, 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (s, 1 H), 2.34 (s, 3 H), 2.44 (t, *J* = 6.8 Hz, 2 H), 3.09 (brs, 1 H), 3.18-3.21 (m, 2 H), 3.23-3.32 (m, 2 H), 4.91 (t, *J* = 6.8 Hz, 1 H), 7.18-7.23 (m, 3 H), 7.25-7.31 (m, 4 H), 7.62 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.6, 21.6, 49.2, 57.7, 70.7, 73.0, 81.3, 126.1, 127.4, 128.1, 128.7, 130.0, 135.8, 141.3, 143.9; IR (KBr, neat) 3525, 3289, 2924, 2361, 1598, 1494, 1335, 1162, 972, 756, 658 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{22}NO_3S$ $(M + H)^+$ 344.1315, found 344.1335.

(*Z*)-3-(Chloro(phenyl)methylene)-4-phenyl-1-tosylpyrrolidine (22a, mixture of *Z* and *E* isomers in a ratio of 91:9):



White solid, mp. 167-169 ^{o}C; R_f (hexane/EtOAc 9:1) 0.50; yield 127 mg, 76%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.45 (s, 3 H), 3.45 (dd, *J* = 9.6 and 3.6 Hz, 1 H), 3.54 (dd, *J* = 9.6 and 6.6 Hz, 1 H), 3.87-3.91 (m, 1 H), 4.18 (d, *J* = 15.6 Hz, 1 H), 4.30 (d, *J* = 15.6 Hz, 1 H), 6.87-6.89 (m, 2 H), 6.99 (d, *J* = 7.8 Hz, 2 H), 7.10-7.13 (m, 5 H), 7.16 (t, *J* = 7.2 Hz, 1 H), 7.34 (d, *J* = 7.8 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 48.1, 53.6, 57.4, 127.0, 127.4, 128.1, 128.2, 128.3, 128.7, 128.8, 128.9, 130.0, 132.6, 137.1, 137.5, 141.7, 144.1; IR (KBr, neat) 3061, 2924, 2855, 1641, 1597, 1493, 1347, 1161, 1092, 1024, 892, 754, 698, 663 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{23}ClNO_2S$ $(M + H)^+$ 424.1138, found 424.1135.

(*Z*)-3-((4-Bromophenyl)chloromethylene)-4-phenyl-1-tosylpyrrolidine (22b, mixture of *Z* and *E* isomers in a ratio of 92:8):

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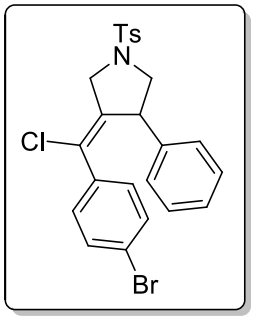
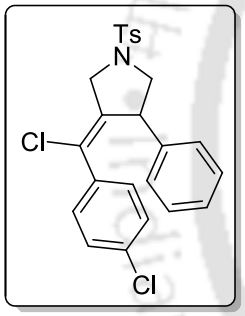


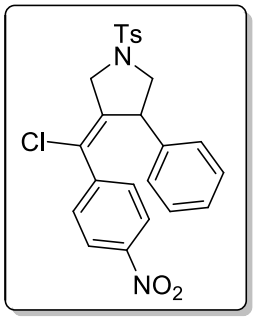
White solid, mp. 135-137 °C; R_f (hexane/EtOAc 9:1) 0.50; yield 144 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 3.44 (dd, *J* = 9.6 and 3.6 Hz, 1 H), 3.54 (dd, *J* = 9.6 and 7.2 Hz, 1 H), 3.82-3.86 (m, 1 H), 4.15 (d, *J* = 15.6 Hz, 1 H), 4.28 (dd, *J* = 15.6 and 1.2 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 6.88-6.90 (m, 2 H), 7.14-7.16 (m, 3 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 48.3, 53.7, 57.4, 123.0, 126.2, 127.2, 127.4, 128.1, 128.8, 129.96, 130.01, 131.4, 132.5, 136.0, 138.4, 141.4, 144.2; IR (KBr, neat) 3062, 2926, 2853, 1658, 1593, 1490, 1352, 1161, 1094, 897, 738, 665 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{22}BrClNO_2S$ $(M + H)^+$ 502.0238, found 502.0240.

(*Z*)-3-(chloro(4-chlorophenyl)methylene)-4-phenyl-1-tosylpyrrolidine (22c, mixture of *Z* and *E* isomers in a ratio of 93:7):



White solid, mp. 114-116 °C; R_f (hexane/EtOAc 9:1) 0.50; yield 135 mg, 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 3.43 (dd, *J* = 9.6 and 4.0 Hz, 1 H), 3.55 (dd, *J* = 9.6 and 7.2 Hz, 1 H), 3.84-3.86 (m, 1 H), 4.16 (d, *J* = 15.6 Hz, 1 H), 4.29 (dd, *J* = 15.6 and 1.6 Hz, 1 H), 6.88-6.94 (m, 4 H), 7.08-7.10 (m, 2 H), 7.15 (t, *J* = 2.8 Hz, 3 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 48.3, 53.8, 57.5, 126.3, 127.2, 127.4, 128.2, 128.4, 128.9, 129.7, 130.0, 132.6, 134.8, 135.5, 138.4, 141.5, 144.2; IR (KBr, neat) 3062, 2926, 2853, 1658, 1593, 1490, 1352, 1161, 1094, 897, 738, 665 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{22}Cl_2NO_2S$ $(M + H)^+$ 458.0743, found 458.0749.

(*Z*)-3-(Chloro(4-nitrophenyl)methylene)-4-phenyl-1-tosylpyrrolidine (22d, mixture of *Z* and *E* isomers in a ratio of 81:19):



White solid, mp. 138-140 °C; R_f (hexane/EtOAc 9:1) 0.40; yield 127 mg, 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 3.38 (dd, *J* = 9.6 and 4.4 Hz, 1 H), 3.64 (dd, *J* = 9.6 and 7.2 Hz, 1 H), 3.87-3.91 (m, 1 H), 4.23 (d, *J* = 16.0 Hz, 1 H), 4.30 (dd, *J* = 16.0 and 2.0 Hz, 1 H), 6.86-6.89 (m, 2 H), 7.11-7.13 (m, 3 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2

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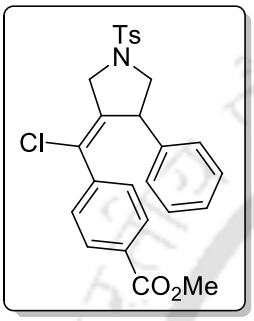
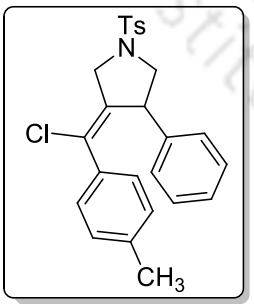
H), 7.95 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 48.6, 54.1, 57.6, 123.4, 124.0, 124.8, 127.5, 128.2, 129.0, 129.5, 130.1, 132.4, 140.7, 140.9, 143.1, 144.4, 147.5; IR (KBr, neat) 3063, 2926, 2854, 1654, 1599, 1525, 1353, 1162, 1094, 907, 855, 738, 665 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{22}ClN_2O_4S$ $(M + H)^+$ 469.0989, found 469.1009.

(*Z*)-Methyl 4-(chloro(4-phenyl-1-tosylpyrrolidin-3-ylidene)methyl)benzoate (22e, mixture of *Z* and *E* isomers in a ratio of 84:16):



White solid, mp. 137-139 °C; R_f (hexane/EtOAc 9:1) 0.40; yield 135 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 3.44 (dd, *J* = 9.6 Hz and *J* = 3.6 Hz, 1 H), 3.57 (dd, *J* = 9.6 Hz and *J* = 6.8 Hz, 1 H), 3.86 (s, 3 H), 3.87-3.90 (m, 1 H), 4.19 (d, *J* = 16.0 Hz, 1 H), 4.32 (dd, *J* = 16.0 and 2.0 Hz, 1 H), 6.87-6.89 (m, 2 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 7.11-7.13 (m, 3 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.78 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 48.3, 52.4, 53.9, 57.5, 126.2, 127.2, 127.4, 128.1, 128.4, 128.8, 129.4, 130.0, 130.2, 132.5, 139.1, 141.29, 141.33, 144.2, 166.5; IR (KBr, neat) 3062, 2952, 2849, 1730, 1602, 1495, 1357, 1159, 1114, 902, 767, 664 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{25}ClNO_4S$ $(M + H)^+$ 482.1187, found 482.1174.

(*Z*)-3-(Chloro(*p*-tolyl)methylene)-4-phenyl-1-tosylpyrrolidine (22f, mixture of *Z* and *E* isomers in a ratio of 94:6):



White solid, mp. 100-101 °C; R_f (hexane/EtOAc 9:1) 0.50; yield 126 mg, 72%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.18 (s, 3 H), 2.38 (s, 3 H), 3.41 (dd, *J* = 9.6 Hz and *J* = 3.0 Hz, 1 H), 3.44 (dd, *J* = 9.6 and 6.6 Hz, 1 H), 3.79-3.82 (m, 1 H), 4.08 (d, *J* = 15.6 Hz, 1 H), 4.23 (d, *J* = 15.6 Hz, 1 H), 6.82-6.87 (m, 6 H), 7.07-7.11 (m, 3 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.64 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 21.8, 48.2, 53.6, 57.4, 127.0, 127.4, 127.7, 128.1, 128.2, 128.8, 128.9, 130.0, 132.8, 134.3, 136.9, 138.9, 142.0, 144.1; IR (KBr, neat) 3061, 2926, 2851, 1658, 1600, 1512, 1354, 1165, 1094, 898, 819, 663 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{25}ClNO_2S$ $(M + H)^+$ 438.1295, found 438.1293.

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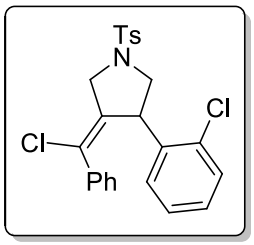
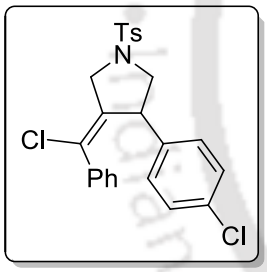
(*Z*)-3-(Chloro(phenyl)methylene)-4-(2-chlorophenyl)-1-tosylpyrrolidine (22h, mixture of *Z* and *E* isomers in a ratio of 94:6):



White solid, mp. 129-130 °C; R_f (hexane/EtOAc 9:1) 0.50; yield 112 mg, 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 3.36 (dd, *J* = 9.6 and 4.0 Hz, 1 H), 3.61 (dd, *J* = 9.6 and 7.2 Hz, 1 H), 4.23 (d, *J* = 16.0 Hz, 1 H), 4.31-4.35 (m, 2 H), 6.96-7.00 (m, 3 H), 7.01-7.12 (m, 5 H), 7.17-7.19 (m, 1 H), 7.35 (d, *J* = 8.4 Hz, 2 H),7.73 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 45.5, 54.3, 56.3, 127.2, 127.7, 127.8, 128.1, 128.2, 128.5, 128.8, 129.1, 129.6, 130.0, 132.5, 133.0, 136.6, 136.8, 138.5, 144.2; IR (KBr, neat) 3062, 2925, 2854, 1657, 1597, 1474, 1353, 1164, 1094, 895, 816, 758, 665 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{22}Cl_2NO_2S$ $(M + H)^+$ 458.0748, found 458.0746.

(*Z*)-3-(Chloro(phenyl)methylene)-4-(4-chlorophenyl)-1-tosylpyrrolidine (22i, mixture of *Z* and *E* isomers in a ratio of 88:12):



White solid, mp. 140-141 °C; R_f (hexane/EtOAc 9:1) 0.50; yield 135 mg, 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 3.42 (dd, *J* = 9.6 and 3.2 Hz, 1 H), 3.52 (dd, *J* = 9.6 and 7.8 Hz, 1 H), 3.85-3.89 (m, 1 H), 4.14 (d, *J* = 16.0 Hz, 1 H), 4.29 (dd, *J* = 16.0 and 1.2 Hz, 1 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 6.98-7.05 (m, 2 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 7.12-7.20 (m, 3 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.70 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 47.5, 53.4, 57.3, 127.9, 128.1, 128.3, 128.4, 128.7, 128.8, 129.1, 130.0, 132.6, 132.9, 137.0, 137.1, 140.2, 144.3; IR (KBr, neat) 3060, 2926, 2854, 1656, 1597, 1490, 1349, 1162, 1093, 816, 752, 668 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{22}Cl_2NO_2S$ $(M + H)^+$ 458.0748, found 458.0748.

(*Z*)-3-(Chloro(phenyl)methylene)-4-(4-fluorophenyl)-1-tosylpyrrolidine (22j, mixture of *Z* and *E* isomers in a ratio of 89:11):

White solid, mp. 129-130 °C; R_f (hexane/EtOAc 9:1) 0.50; yield 127 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 3.41 (dd, *J* = 9.6 and 3.6 Hz, 1 H), 3.52 (dd, *J* = 9.6 and 6.8 Hz, 1 H), 3.86-3.91 (m, 1 H), 4.14 (d, *J* = 15.6 Hz, 1 H), 4.23 (dd, *J* = 15.6 and 1.2 Hz, 1 H), 6.77-6.86 (m, 4 H), 6.99 (d, *J* = 7.2 Hz, 2 H), 7.12-7.20 (m, 3 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 47.4,

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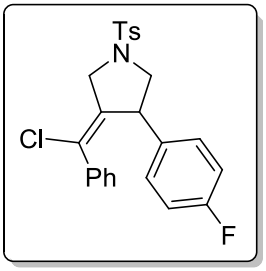
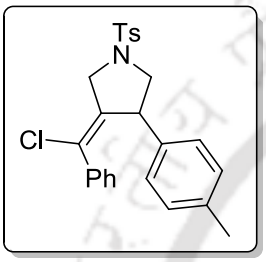


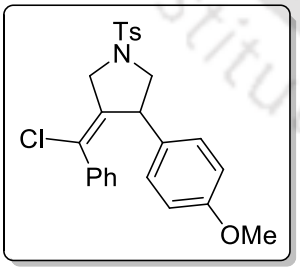
53.5, 57.4, 115.5 (d, *J* = 21.3 Hz), 127.8, 128.1, 128.2, 128.31, 128.33, 128.8, 128.9 (d, *J* = 8.1 Hz), 130.0, 132.6, 137.1, 137.4, 144.2, 161.8 (d, *J* = 244.2 Hz, C-F); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 46.16; IR (KBr, neat) 3060, 2928, 2854, 1647, 1601, 1508, 1349, 1162, 1095, 817, 754, 666 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{22}ClFNO_2S$ $(M + H)^+$ 442.1038, found 442.1025.

(*Z*)-3-(Chloro(phenyl)methylene)-4-(*p*-tolyl)-1-tosylpyrrolidine (22k, mixture of *Z* and *E* isomers in a ratio of 93:07):



White solid, mp. 130-132 °C; R_f (hexane/EtOAc 9:1) 0.50; yield 136 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3 H), 2.47 (s, 3 H), 3.45-3.53 (m, 2 H), 3.85-3.89 (m, 1 H), 4.16 (d, *J* = 15.6 Hz, 1 H), 4.31 (d, *J* = 15.6 Hz, 1 H), 6.80 (d, *J* = 7.6 Hz, 2 H), 6.95 (d, *J* = 7.6 Hz, 2 H), 7.04 (d, *J* = 7.6 Hz, 2 H), 7.11-7.21 (m, 3 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 21.8, 47.8, 53.6, 57.5, 127.2, 127.3, 128.1, 128.2, 128.4, 128.8, 129.4, 130.0, 132.7, 136.6, 137.2, 137.6, 138.8, 144.0; IR (KBr, neat) 3057, 2924, 2855, 1653, 1598, 1513, 1349, 1162, 1094, 1021, 893, 813, 754, 666 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{25}ClNO_2S$ $(M + H)^+$ 438.1295, found 438.1294.

(*Z*)-3-(Chloro(phenyl)methylene)-4-(4-methoxyphenyl)-1-tosylpyrrolidine (22l, mixture of *Z* and *E* isomers in a ratio of 93:07):



White solid, mp. 140-142 °C; R_f (hexane/EtOAc 9:1) 0.45; yield 149 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 3.43 (dd, *J* = 9.6 and 3.6 Hz, 1 H), 3.50 (dd, *J* = 9.6 and 6.8 Hz, 1 H), 3.75 (s, 3 H), 3.82-3.86 (m, 1 H), 4.14 (d, *J* = 15.6 Hz, 1 H), 4.31 (d, *J* = 15.6 Hz, 1 H), 6.66 (d, *J* = 8.4 Hz, 2 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 7.6 Hz, 2 H), 7.12-7.20 (m, 3 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 47.4, 53.5, 55.4, 57.5, 114.1, 127.3, 128.1, 128.2, 128.37, 128.40, 128.8, 130.0, 132.7, 134.0, 137.2, 137.7, 144.1, 158.6; IR (KBr, neat) 3060, 2933, 2834, 1658, 1611, 1512, 1352, 1159, 1032, 893, 820, 736, 666 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{25}ClNO_3S$ $(M + H)^+$ 454.1238, found 454.1227.

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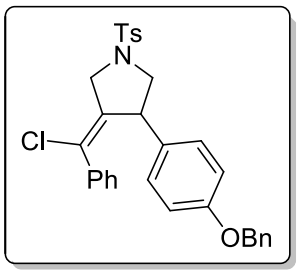
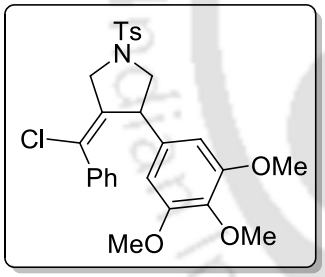
(*Z*)-3-(4-(Benzyloxy)phenyl)-4-(chloro(phenyl)methylene)-1-tosylpyrrolidine (22m, mixture of *Z* and *E* isomers in a ratio of 93:07):



White solid, mp. 159-161 ^{o}C; R_f (hexane/EtOAc 9:1) 0.45; yield 165 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3 H), 3.43 (dd, *J* = 9.6 and 3.6 Hz, 1 H), 3.49 (dd, *J* = 9.6 and 6.8 Hz, 1 H), 3.82-3.86 (m, 1 H), 4.13 (d, *J* = 15.6 Hz, 1 H), 4.28 (d, *J* = 15.6 Hz, 1 H), 4.99 (s, 2 H), 6.73 (d, *J* = 8.4 Hz, 2 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 7.01 (d, *J* = 8.0 Hz, 2 H), 7.10-7.19 (m, 3 H), 7.31-7.42 (m, 7 H), 7.72 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 47.4, 53.5, 57.5, 70.2, 115.1, 127.3, 127.7, 128.16, 128.19, 128.2, 128.37, 128.45, 128.79, 128.83, 130.0, 132.6, 134.2, 137.1, 137.2, 137.7, 144.1, 157.8; IR (KBr, neat) 3061, 2925, 2856, 1656, 1605, 1510, 1349, 1243, 1161, 1021, 816, 736, 666 cm^{-1}; HRMS (ESI) calcd. for $C_{31}H_{29}ClNO_3S$ $(M + H)^+$ 530.1551, found 530.1561.

(*Z*)-3-(chloro(phenyl)methylene)-1-tosyl-4-(3,4,5-trimethoxyphenyl)pyrrolidine (22n, mixture of *Z* and *E* isomers in a ratio of 91:09):



Pale yellow gum; R_f (hexane/EtOAc 8:2) 0.50; yield 158 mg, 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 3.53-3.55 (m, 2 H), 3.69 (s, 6 H), 3.78 (s, 3 H), 3.86 (t, *J* = 4.4 Hz, 1 H), 4.13 (d, *J* = 15.6 Hz, 1 H), 4.30 (dd, *J* = 15.6 and 1.2 Hz, 1 H), 6.09 (s, 2 H), 7.07 (dd, *J* = 8.0 and 2.0 Hz, 2 H), 7.17-7.22 (m, 3 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 48.0, 53.3, 56.2, 57.0, 61.0, 104.4, 127.5, 128.1, 128.3, 128.5, 128.9, 130.0, 132.8, 137.0, 137.26, 137.31, 137.5, 144.2, 153.2; IR (KBr, neat) 3061, 2931, 2828, 1648, 1601, 1521, 1349, 1161, 1032, 893, 820, 741, 666 cm^{-1}; HRMS (ESI) calcd. for $C_{27}H_{29}ClNO_5S$ $(M + H)^+$ 514.1455, found 514.1452.

(*Z*)-3-(1-Chloroethylidene)-4-phenyl-1-tosylpyrrolidine (22p, mixture of *Z* and *E* isomers in a ratio of 86:14):

Colourless liquid; R_f (hexane/EtOAc 9:1) 0.40; yield 101 mg, 70%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.68 (d, *J* = 6 Hz, 3 H), 2.36 (s, 3 H), 3.31 (dd, *J* = 9.6 and 4.2 Hz, 1 H), 3.51 (dd, *J* = 9.6 and 1.8 Hz, 1 H), 3.78-3.82 (m, 1 H), 3.89 (dd, *J* = 15.0 and 1.2 Hz, 1 H), 4.02 (dd, *J* = 15.0 and 1.8 Hz, 1 H), 7.04 (d, *J* = 7.2 Hz, 2 H), 7.12-7.16 (m, 1 H), 7.18-

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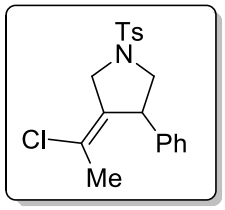
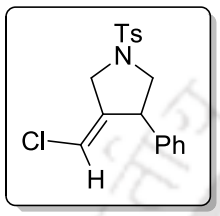


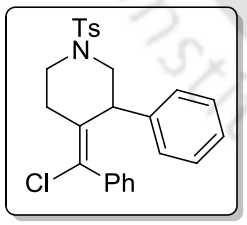
7.20 (m, 2 H), 7.25 (d, *J* = 7.8 Hz, 2 H), 7.62 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 22.9, 47.5, 53.1, 57.5, 125.7, 127.2, 127.3, 128.1,129.0, 129.9, 132.4, 134.8, 141.3, 144.0; IR (KBr, neat) 3028, 2922, 2852, 1598, 1494, 1350, 1164, 1095, 833, 759, 666 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}ClN_2O_2S$ $(M + H)^+$ 362.0976, found 362.0988.

(*Z*)-3-(Chloromethylene)-4-phenyl-1-tosylpyrrolidine (22q, mixture of *Z* and *E* isomers in a ratio of 98:02):



White solid, mp. 106-108 °C; R_f (hexane/EtOAc 9:1) 0.50; yield 90 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 2.57 (dd, *J* = 12.0 and 9.6 Hz, 1 H), 3.47 (d, *J* = 16.2 Hz, 1 H), 3.61-3.64 (m, 1 H), 3.67 (dd, *J* = 12.0 and 4.8 Hz, 1 H), 3.93 (d, *J* = 16.2 Hz, 1 H), 5.86 (s, 1 H), 7.07 (d, *J* = 7.2 Hz, 2 H), 7.18 (t, *J* = 7.2 Hz, 1 H), 7.22-7.24 (m, 4 H), 7.55 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 42.9, 49.2, 49.7, 126.7, 127.6, 127.7, 127.8, 127.9, 129.0, 130.0, 133.5, 140.2, 144.2; IR (KBr, neat) 3063, 2923, 2853, 1675, 1598, 1495, 1352, 1166, 1096, 815, 776, 665 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}ClNO_2S$ $(M + H)^+$ 348.0820, found 348.0823.

(*E*)-4-(Chloro(phenyl)methylene)-3-phenyl-1-tosylpiperidine (22s, mixture of *Z* and *E* isomers in a ratio of 11:89):



White solid, mp. 130-131 °C; R_f (hexane/EtOAc 9:1) 0.50; yield 124 mg, 71%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.36-2.43 (m, 2 H), 2.45 (s, 3 H), 2.54 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 3.04-3.09 (m, 1 H), 3.89-3.92 (m, 2 H), 4.36 (d, *J* = 12.0 Hz, 1 H), 7.25-7.30 (m, 6 H), 7.30-7.34 (m, 6 H), 7.63 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 27.4, 42.5, 47.1, 49.8, 126.8, 127.8, 127.9, 128.2, 128.79, 128.81, 128.83, 128.8, 130.0, 132.8, 134.4, 138.1, 139.6, 143.9; IR (KBr, neat) 3060, 2923, 2848, 1658, 1598, 1493, 1338, 1163, 1096, 935, 738, 699 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{25}ClNO_2S$ $(M + H)^+$ 438.1295, found 438.1296.

(*E*)-3-(4-bromophenyl)-4-(chloro(phenyl)methylene)-1-tosylpiperidine (22t, mixture of *Z* and *E* isomers in a ratio of 16:84):

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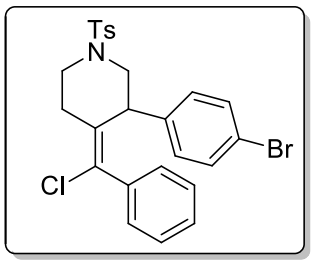
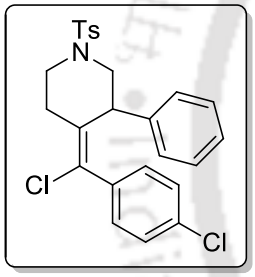


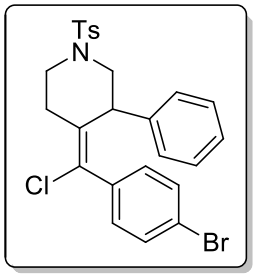
White solid, mp. 105-107 ^{o}C; R_f (hexane/EtOAc 9:1) 0.50; yield 144 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37-2.42 (m, 2 H), 2.46 (s, 3 H), 2.53 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 3.06-3.11 (m, 1 H), 3.80-3.83 (m, 1 H), 3.89-3.92 (m, 1 H), 4.28 (dt, *J* = 12.0 and 1.8 Hz, 1 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.23-7.26 (m, 2 H), 7.31-7.33 (m, 3 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 27.4, 42.2, 47.1, 49.8, 120.9, 127.9, 128.8, 128.9, 129.0, 129.6, 130.0, 131,9, 132.0, 132.8, 133.8, 137.9, 138.7, 144.1; IR (KBr, neat) 3059, 2923, 2850, 1650, 1597, 1489, 1356, 1163, 1096, 928, 821, 760, 699 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{24}BrClNO_2S$ $(M + H)^+$ 516.0400, found 516.0389.

(*E*)-4-(Chloro(4-chlorophenyl)methylene)-3-phenyl-1-tosylpiperidine (22u, mixture of *Z* and *E* isomers in a ratio of 08:92):



White solid, mp. 127-128 ^{o}C; R_f (hexane/EtOAc 9:1) 0.50; yield 136 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36-2.42 (m, 2 H), 2.45 (s, 3 H), 2.52 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 3.05-3.08 (m, 1 H), 3.82-3.86 (m, 1 H), 3.88-3.91 (m, 1 H), 4.35 (d, *J* = 12.0 Hz, 1 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.23-7.35 (m, 9 H), 7.63 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 27.5, 42.7, 47.0, 49.8, 126.9, 127.0, 127.7, 128.0, 128.9, 129.0, 130.0, 130.2, 132.8, 134.8, 135.1, 136.4, 139.3, 144.0; IR (KBr, neat) 3062, 2922, 2846, 1651, 1597, 1492, 1160, 1094, 888, 823, 749, 648 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{24}Cl_2NO_2S$ $(M + H)^+$ 472.0905, found 472.0884.

(*E*)-4-((4-bromophenyl)chloromethylene)-3-phenyl-1-tosylpiperidine (22v, mixture of *Z* and *E* isomers in a ratio of 07:93):



White solid, mp. 158-160 ^{o}C; R_f (hexane/EtOAc 9:1) 0.50; yield 150 mg, 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36-2.44 (m, 5 H), 2.52 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 3.04-3.09 (m, 1 H), 3.84-3.91 (m, 2 H), 4.35 (d, *J* = 12.0, 1 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.20-7.27 (m, 1 H), 7.31-7.34 (m, 6 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 27.5,

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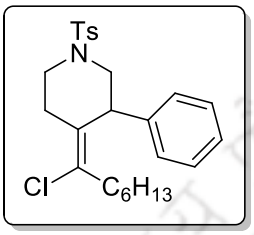
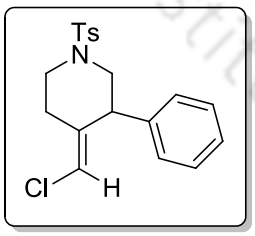
42.7, 47.0, 49.8, 123.0, 126.99, 127.05, 127.7, 127.9, 128.9, 130.0, 130.5, 132.0, 132.8, 135.1, 136.9, 139.3, 143.9; IR (KBr, neat) 3054, 2920, 2851, 1648, 1589, 1491, 1356, 1162, 1090, 928, 827, 763 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{24}BrClNO_2S$ $(M + H)^+$ 516.0400, found 516.0380.

(*E*)-4-(1-Chloroheptylidene)-3-phenyl-1-tosylpiperidine (22w, mixture of *Z* and *E* isomers in a ratio of 19:81):



Pale yellow liquid; R_f (hexane/EtOAc 9:1) 0.50; yield 130 mg, 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 6.8 Hz, 3 H), 1.22-1.28 (m, 6 H), 1.45-1.50 (m, 2 H), 1.71 (t, *J* = 7.2 Hz, 1 H), 2.10 (dt, *J* = 11.6 and 3.6 Hz, 1 H), 2.37 (s, 3 H), 2.44 (t, *J* = 7.6 Hz, 2 H), 2.65 (dt, *J* = 11.6 and 5.6 Hz, 1 H), 3.74-3.78 (m, 1 H), 3.43 (dd, *J* = 11.2 and 6.4 Hz, 1 H), 4.07 (dd, *J* = 11.2 and 6.4 Hz, 1 H), 4.53 (ddd, *J* = 11.2, 6.4 and *J* = 1.6 Hz, 1 H), 7.12-7.16 (m, 1 H), 7.24-7.27 (m, 4 H), 7.30-7.35 (m, 1 H), 7.38-7.40 (m, 1 H), 7.64 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.6, 22.8, 25.0, 26.2, 29.0, 29.4, 31.8, 47.7, 48.1, 51.7, 119.3, 123.1, 124.4, 127.6, 129.8, 135.9, 140.1, 143.1, 143.7, 146.1; IR (KBr, neat) 3064, 2923, 2853, 1639, 1600, 1463, 1347, 1164, 1097, 924, 817, 751, 660 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{33}ClNO_2S$ $(M + H)^+$ 446.1921, found 446.1922.

(*E*)-4-(Chloromethylene)-3-phenyl-1-tosylpiperidine (22x, mixture of *Z* and *E* isomers in a ratio of 07:93):



White solid, mp. 83-85 °C; R_f (hexane/EtOAc 9:1) 0.42; yield 97 mg, 67%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 2.65-2.69 (m, 1 H), 2.84-2.92 (m, 1 H), 2.98 (dd, *J* = 13.2 and 10.2 Hz, 1 H), 3.03-3.08 (m, 1 H), 3.67-3.75 (m, 3 H), 5.93 (d, *J* = 3.6 Hz, 1 H), 7.10 (d, *J* = 7.2 Hz, 2 H), 7.17-7.22 (m, 3 H), 7.24-7.27 (m, 2 H), 7.54 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 39.0, 46.8, 47.0, 54.6, 127.2, 127.5, 127.7, 129.1, 130.0, 131.9, 133.7, 136.2, 141.9, 143.7; IR (KBr, neat) 3028, 2924, 2855, 1645, 1599, 1494, 1452, 1342, 1165, 1095, 949, 845, 701, 550 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}ClNO_2S$ $(M + H)^+$ 362.0976, found 362.0995.

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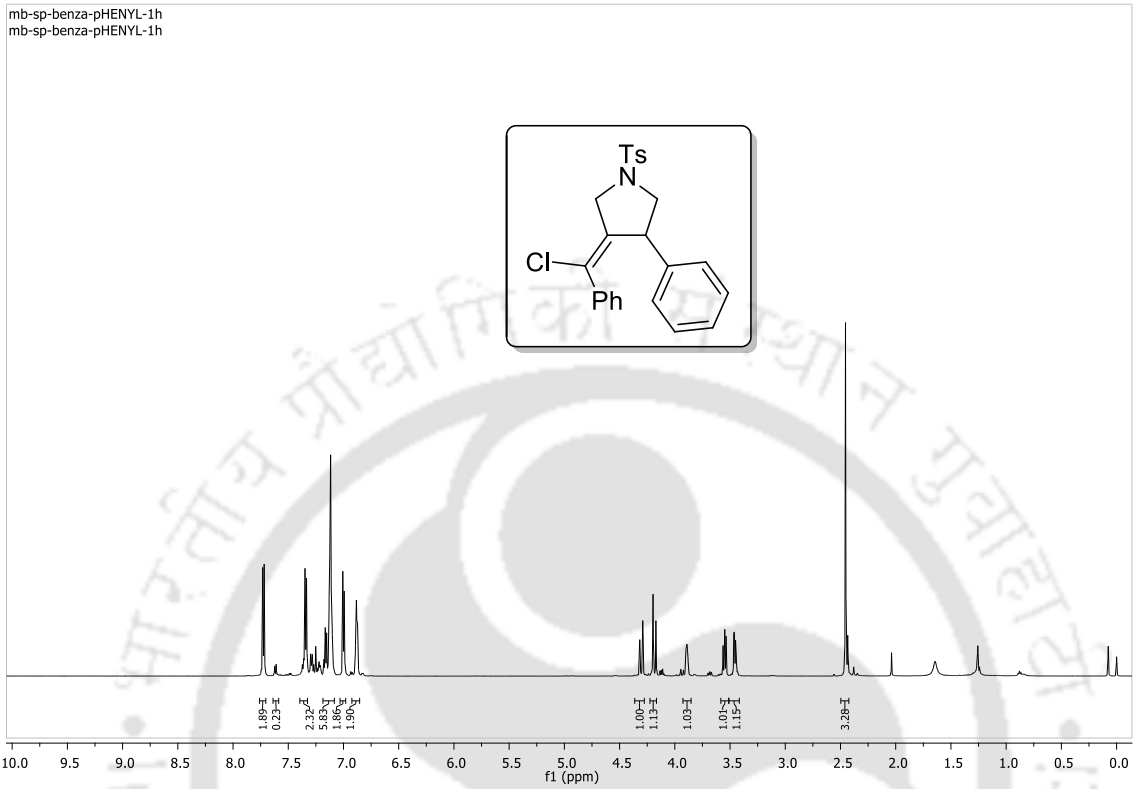
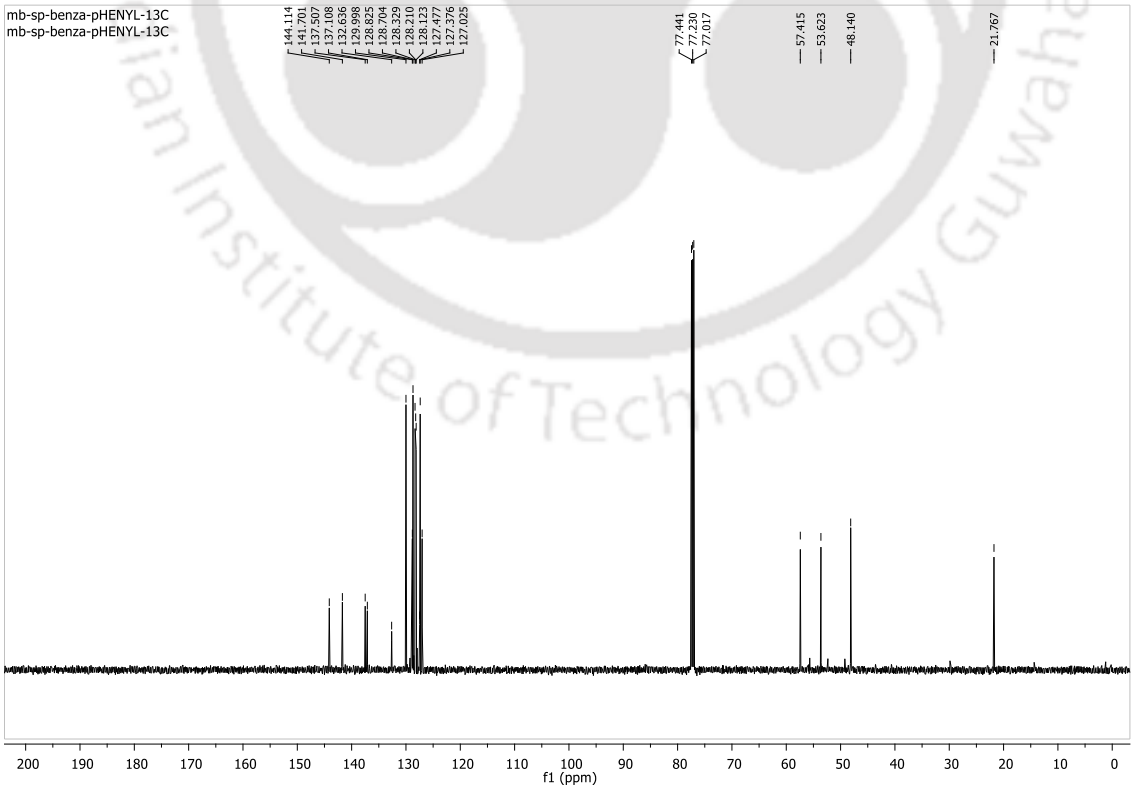
4.8. Selected spectra of substituted pyrrolidines and piperidines

(*Z*)-3-(Chloro(phenyl)methylene)-4-phenyl-1-tosylpyrrolidine





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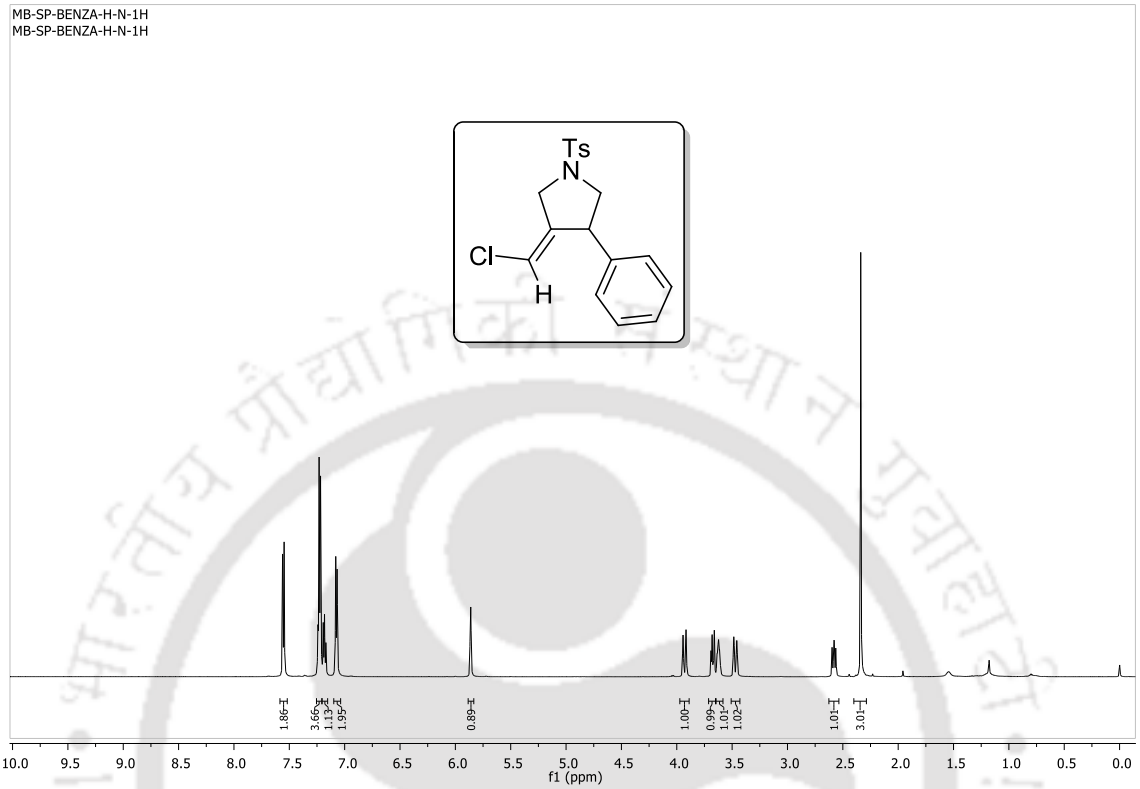
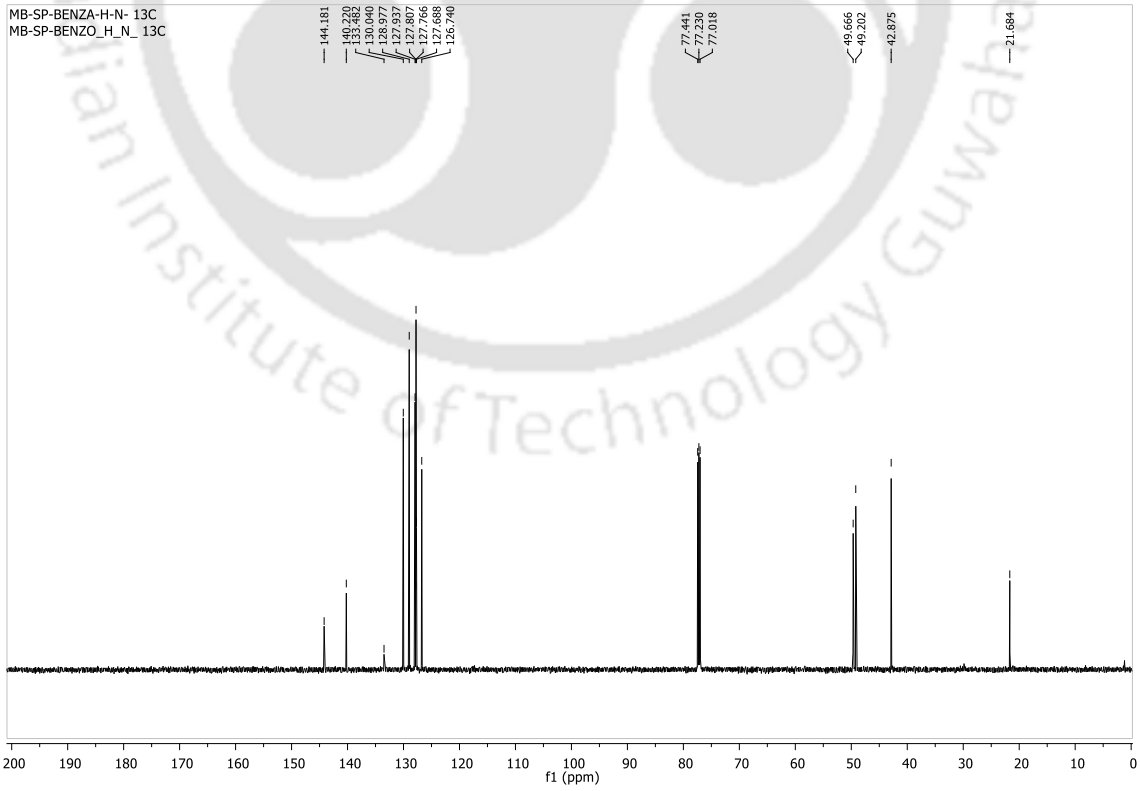
(*Z*)-3-(Chloromethylene)-4-phenyl-1-tosylpyrrolidine





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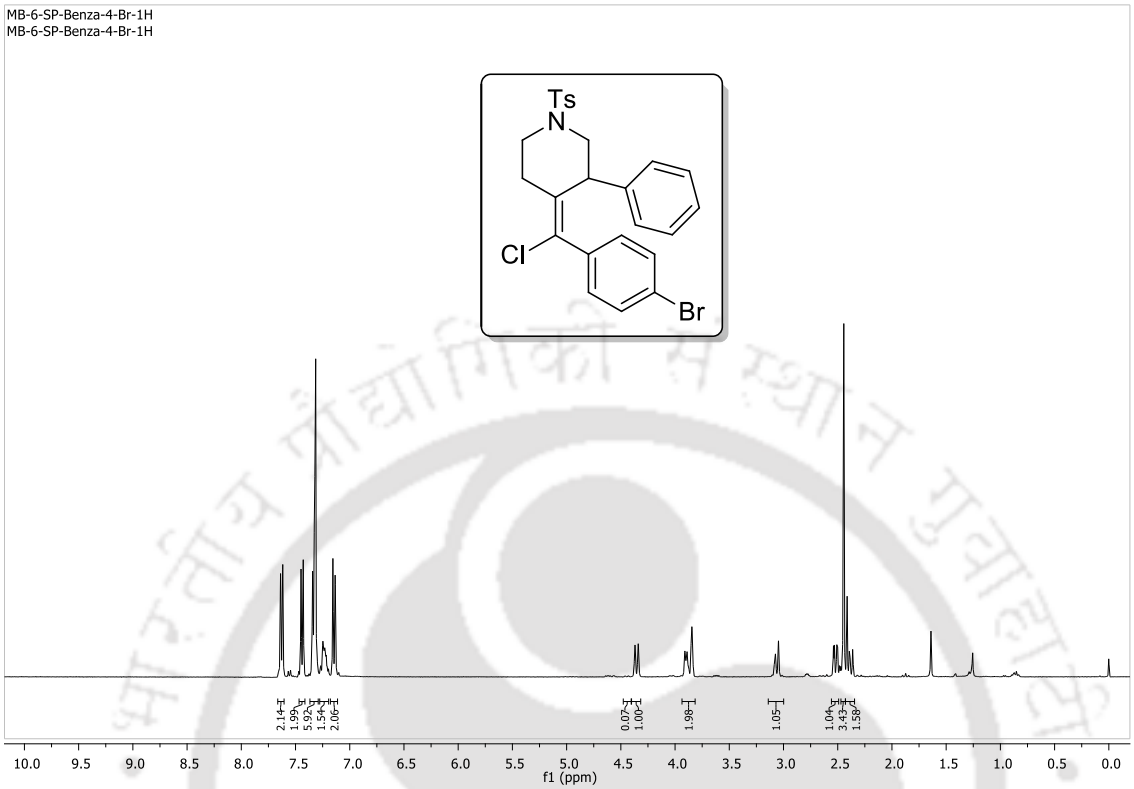
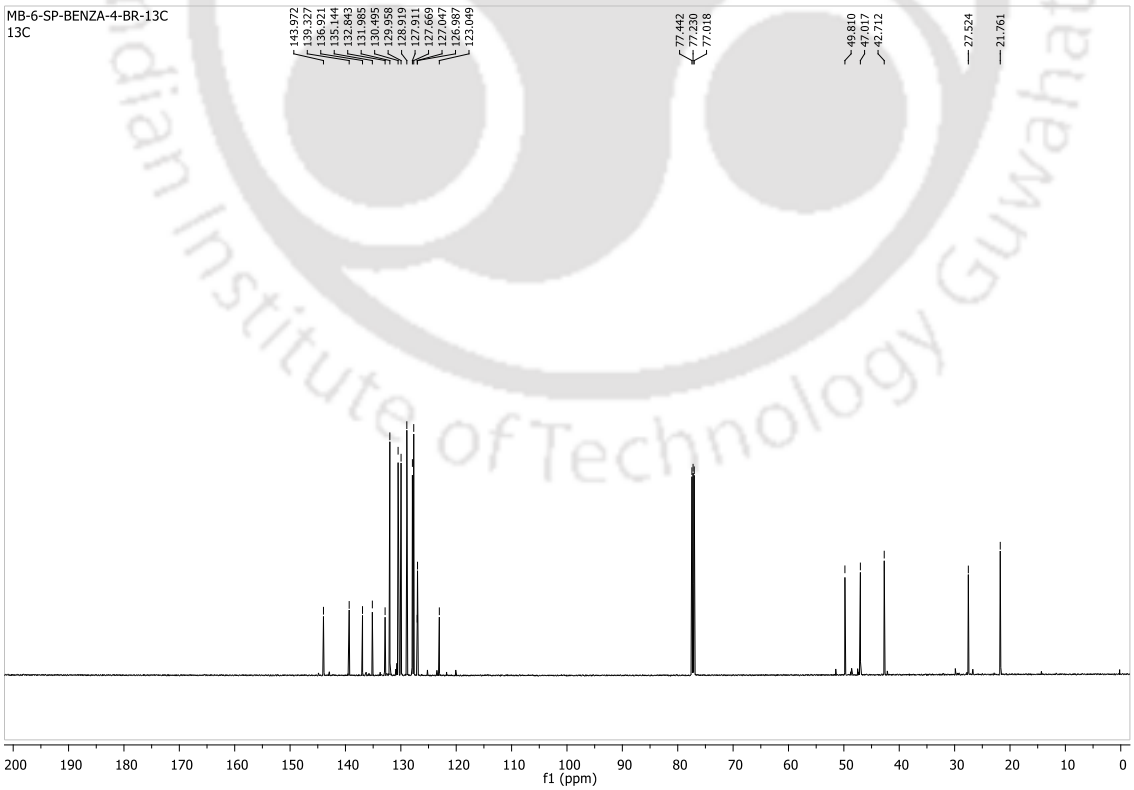
(*E*)-4-((4-bromophenyl)chloromethylene)-3-phenyl-1-tosylpiperidine





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4.9. Crystal parameters

The crystal parameters of compound 22h

	CCDC 1522843
Formula	$C_{24}H_{21}Cl_2NO_2S$
Formula weight	458.38
T/K	296(2)
Crystal system	Monoclinic
Space group	P2(1)/n
a/Å	14.5366(18)
b/Å	10.5212(12)
c/Å	15.794(2)
α/°	90.00
β/°	109.404(7)
γ/°	90.00
V/Å^3	2278.3(5)
Z	4
Abs. Coeff./mm^{-1}	0.397
Abs. Correction	multiscan
GOF on F^2	1.116
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0370
	wR2 = 0.1255
R indices [all data]	*R1* = 0.0447
	wR2 = 0.1371

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4.10. References

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26. The crystallographic data for the compound **22h** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1522843.

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CHAPTER 5

Synthesis of Tetrahydroisoquinolines from *N*-Tethered Aryl-Benzyl Alkanols Mediated by $BF_3{\cdot}OEt_2$

5.1. Importance and applications

Tetrahydroisoquinoline (THIQ) is a privileged substructure found in a number of plant alkaloids as well as in various synthetic compounds, attributed with a broad spectrum of pharmacological properties such as calcium antagonists,[1] antibacterial[2] and antitumor antibiotics,[3] neuoromodulating effects[4] etc. These biological properties are attributed to the substitution pattern on the isoquinoline scaffold. In particular, THIQ derivatives with C4 substitution constitute a large class of compounds with profound biological properties. For example, nomifensine (**1**), a C4-aryl substituted THIQ derivative, is an antidepressant drug.[5] Hamayne (**2**), a crinine alkaloid**,** isolated from the fruit and seeds of *Crinum asiaticum* L. *var. japonicum* Baker by Ochi *et al*. in 1976, inhibits acetylcholinesterase (AChE) and shows antiplasmodial and cytotoxic activities.[6] Similarly, Hexahydropyrrolo[2,1-*a*]isoquinolines (**3**) and their derivatives shows a potential activity in the central nervous system. (*Figure 5.1.1*).[7] In addition to these, THIQs also acts as key intermediates for the synthesis of an array of substances.[8]

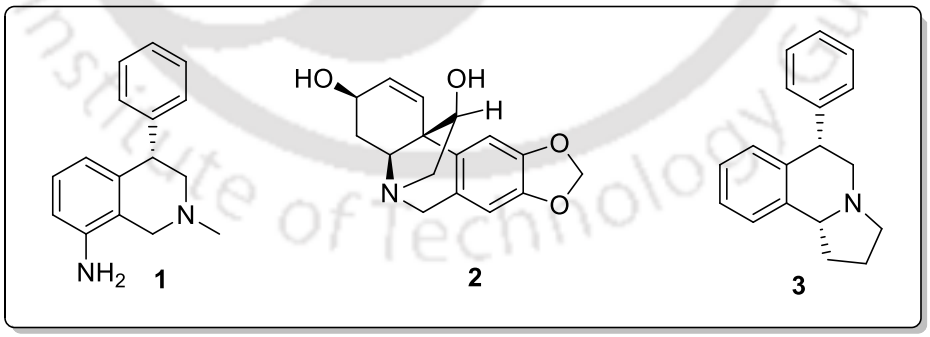

Figure 5.1.1. *Bioactive molecules containing tetrahydroisoquinolines*

5.2. An overview of relevant synthetic methods

The stereoselective synthesis of functionalized THIQs has always attracted significant interest due to their structural diversity and abundance in bioactive natural and unnatural

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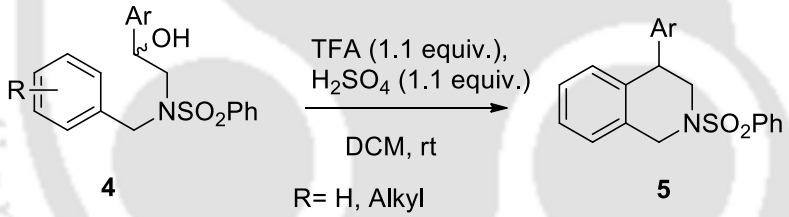
products. Pictet-Spengler,[9] Bischler-Napieralski[10] cyclization/reduction and hydrogenation[11] of isoquinolines are the conventional methods used for the synthesis of THIQs. A variety of synthetic methods have been developed over the years to synthesize THIQ derivatives, but there are lesser known methods for the synthesis of C4-substituted THIQs which includes intramolecular Friedel-Crafts (F-C) cyclization reactions of *N*-tethered amino alcohols promoted by aluminium trichloride,[12] trifluoroacetic acid and H_2SO_4,[13] Pd- and Ir-catalyzed intramolecular F-C type allylic alkylation of phenols,[14] $FeCl_3{\cdot}6H_2O$ catalyzed intramolecular F-C reaction of propargylic alcohols,[15] radical cyclizations,[16] Pd-catalyzed coupling of aryl halide with alkenes[17]and alkynes,[18] Rh(I)-catalyzed intramolecular cyclization of arylboron compounds onto ketones[19] etc. Some of the methods for the synthesis of C4 substituted THIQ derivatives are discussed below.

In 1982, Webb *et al.* developed a methodology for the synthesis of tetrahydroisoquinolines **5** from *N*-tethered amino-alcohols **4** by using combination of H_2SO_4 and TFA (1:1 ratio) in refluxing methylene chloride (*Scheme 5.2.1*).[13b] The reaction pathway involves intramolecular Friedel-Crafts alkylation mechanism.



Scheme 5.2.1

You and co-workers have developed a methodology for the enantioselective synthesis of 4-substituted tetrahydroisoquinolines **7**, **8** *via* iridium-catalyzed intramolecular Friedel-Crafts type allylic alkylation of phenols **6** in presence of phosphoramidite ligand **9** (*Scheme 5.2.2*).[14] The reaction afforded the Friedel-Crafts-type allylic alkylation product in good yield and is highly enantioselective with ee up to 96%. In 2015, the same research group developed a palladium-catalyzed regio- and stereo-selective protocol for the synthesis of tetrahydroisoquinolines starting from phenols in excellent yields.[13]

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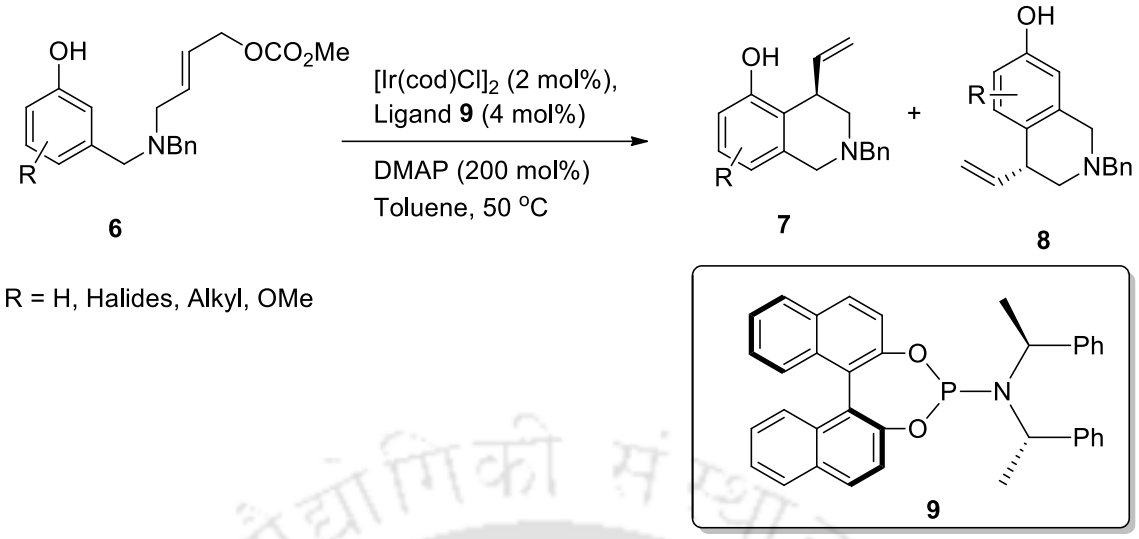
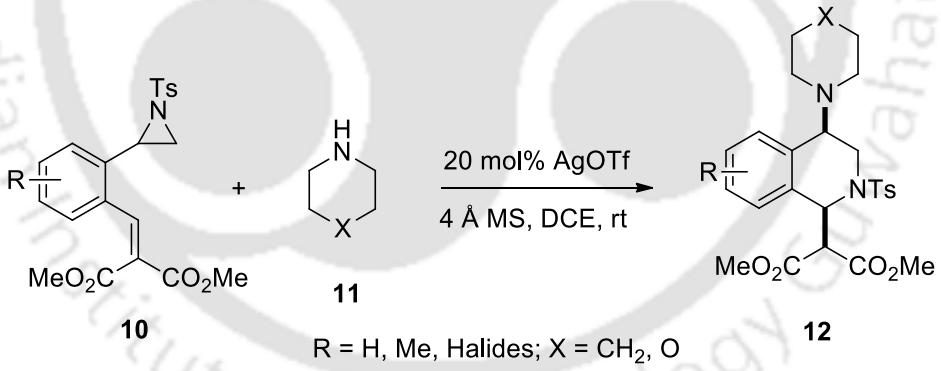


Scheme 5.2.2

In 2016, Li and coworkers reported a methodology for the stereoselective synthesis of substituted *cis*-1,4-tetrahydroisoquinolines **12** *via* silver(I) triflate catalyzed tandem reaction comprising of ring opening of aziridines **10** by secondary amine **11** and a Michael reaction (*Scheme 5.2.3*).[20] The reaction is highly diastereoselective with dr ≥ 99:1 and produced excellent yields.



Scheme 5.2.3

In 2014, Perumal and coworkers reported an intramolecular Pd(0) catalyzed tandem oxoarylation reaction of internal alkynes **13** containing a proximate aryl halide and a hydroxyl nucleophile for the synthesis of tetrahydroisoquinoline derivatives **14** (*Scheme 5.2.4*).[18] The reaction began with the oxidative addition of aryl halide with Pd(0), followed by alkyne insertion to form carbo-palladation complex. The organo-palladium complex undergoes an internal cross-coupling reaction with the nucleophile and subsequent reductive elimination produced the product.

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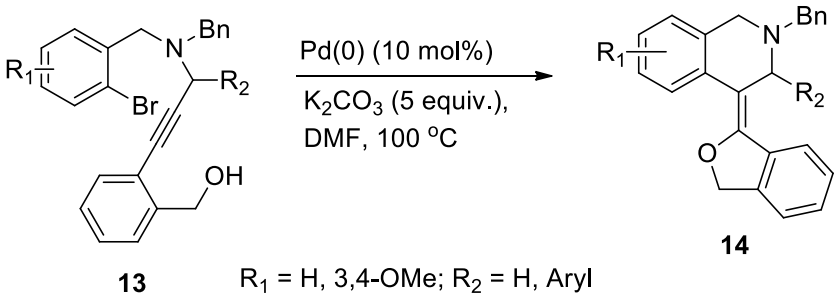
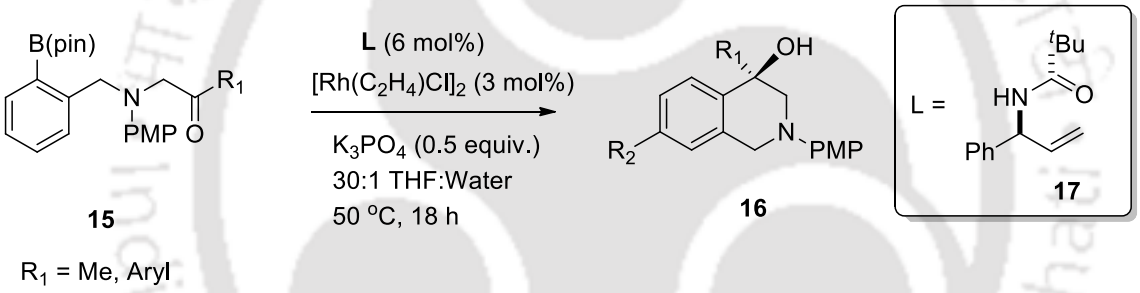


Scheme 5.2.4

Lam *et al*. devised a strategy for the enantioselective synthesis of aza-, oxa-, and carbo-cycles *via* Rh(I)-catalyzed intramolecular cyclization of arylboron compounds onto ketones (*Scheme 5.2.5*).[19] The method was highly enantioselective with ee up to 91%. The process illustrates the utility of chiral sulfinamide-alkene as a ligand in rhodium-catalyzed intramolecular additions of aryl boron compounds.



Scheme 5.2.5

5.3. Present strategy and objective

Friedel-Crafts reaction is one of the most powerful method for the formation of a new carbon-carbon bond in organic synthesis and has been widely used in various industrial processes.[21] Carbocation generated from the treatment of π-activated alcohols with Lewis and Brønsted acids may be used as electrophilic alkyl equivalents in F-C alkylation reactions. A number of research groups have reported the synthesis of C4-substituted THIQs *via* intramolecular Friedel-Crafts reaction of *N*-tethered amino alcohols in the presence of acids such as aluminium trichloride, trifluoroacetic acid and H_2SO_4.[12-13] But these methods suffer from serious problems such as low yield, use of excess reagents and harsh reaction conditions, which limited their application. However, the use of $BF_3{\cdot}OEt_2$ in intramolecular Friedel-Crafts cyclization reaction for the synthesis of C4-substituted THIQs from amino alcohols has not been reported so far. In continuation of our research

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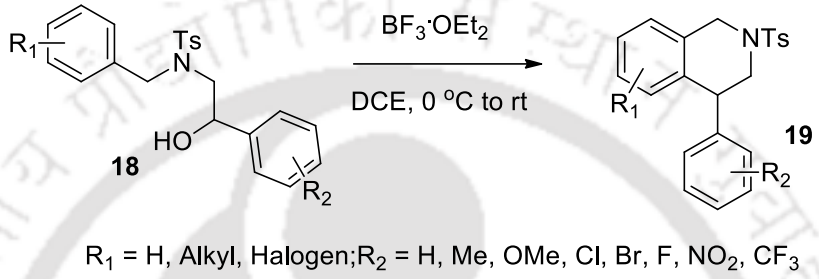
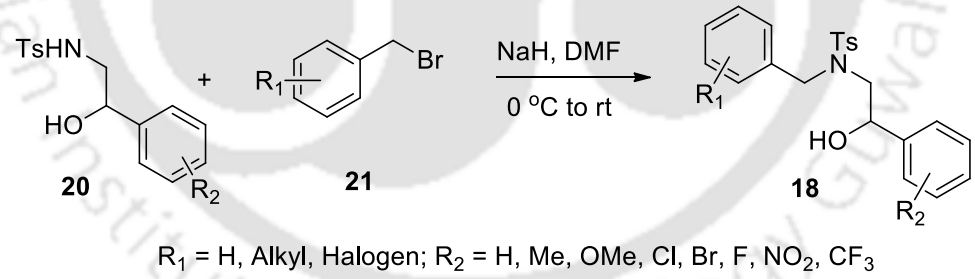
interest in the synthesis of nitrogen heterocycles,[22] we report in this chapter a general methodology for the synthesis of 4-aryl-tetrahydroisoquinolines from *N*-tethered aryl-benzyl alkanols mediated by boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) in good to excellent yields. In the process, benzylic alcohol is used as an electrophilic alkyl equivalent in presence of Lewis acid $BF_3{\cdot}OEt_2$ for the intramolecular F-C alkylation reactions. Thus, the reaction of *N*-tethered aryl-benzyl alkanol **18** in dichloroethane mediated by Boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) gave 4-aryl-tetrahydroisoquinolines **19** in good yields (*Scheme 5.3.1*).



Scheme 5.3.1

The *N*-tethered aryl-benzyl alkanols **18** were synthesized from *N*-tosylated amino alcohols **20** and benzyl bromide derivatives **21** in presence of sodium hydride in DMF solvent (*Scheme 5.3.2*).



Scheme 5.3.2

5.4. Results and discussion

5.4.1. Optimization studies

To start with, *N*-Benzyl-*N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide **18a** was treated with one equivalent of $BF_3{\cdot}OEt_2$ in dichloromethane (5 mL) at 0 °C and allowed the reaction to stir at room temperature. To our delight, the reaction proceeded smoothly to afford the tetrahydroisoquinoline **19a** in 76% yield. The structure of the

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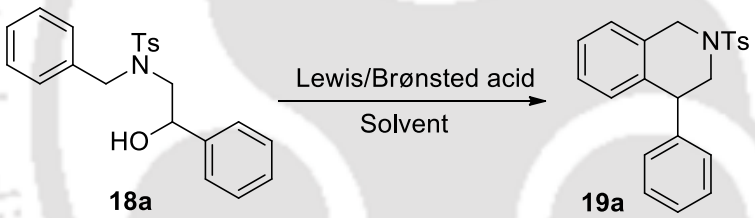
compound was determined by NMR analysis. In order to optimize the reaction conditions, aryl-benzyl alkanol **18a** was treated with various available Lewis and Brønsted acids as well as other parameters such as solvents; reaction time was studied as summarized in Table 5.4.1.1. It was observed that 1,2-dichloroethane (DCE) is the best solvent over dichloromethane and toluene. The reaction of **18a** with TMSOTf (1 equiv.) produced a decomposed result. Upon treatment with metal salts such as $InCl_3$ (20 mol %) and $FeCl_3$ (20 mol %) in 1,2-dichloroethane at 60 ^oC for 2 h gave THIQ derivative **19a** in 64% and 66% yield respectively (entries 5, 6). Other Lewis acid such as AgOTf produced only a trace product, whereas $In(OTf)_3$ gave only 37% yield. The reaction was also screened with Brønsted acids such as *p*-TSA, triflic acid and CSA but resulted in lesser yield. From these observations, it was concluded that 1.1 equivalent of $BF_3{\cdot}OEt_2$ in 1,2-dichloroethane at 0 ^oC is the optimum condition for the reaction for the respective transformation.

Table 5.4.1.1. Optimization of the reaction



18a **19a**

Entry	Lewis/Brønsted acid (equiv.)	Reaction conditions	%Yield[a]
1.	$BF_3{\cdot}OEt_2$ (1.0)	DCM, 0 ^oC to rt, 12 h	76
2.	$BF_3{\cdot}OEt_2$ (1.0)	Toluene, 0 ^oC to rt, 20 h	58
3.	**$BF_3{\cdot}OEt_2$ (1.0)**	**DCE, 0 ^oC to rt, 12 h**	**82**
4.	TMSOTf (1.0)	DCE, 0 ^oC to rt, 12 h	--[d]
5.	$InCl_3$ (0.2)	DCE, 60 ^oC, 2 h	64
6.	$FeCl_3$ (0.2)	DCE, 60 ^oC, 2 h	66
7.	AgOTf (0.2)	DCE, 60 ^oC, 12 h	trace
8.	$In(OTf)_3$ (0.2)	DCE, 60 ^oC, 12 h	37
9	*p*-TSA (1.0)	DCE, 60 ^oC, 12 h	47
10	Triflic Acid (1.0)	0 ^oC to rt, 12 h	65
11	CSA (1.0)	DCE, 60 ^oC, 12 h	25

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

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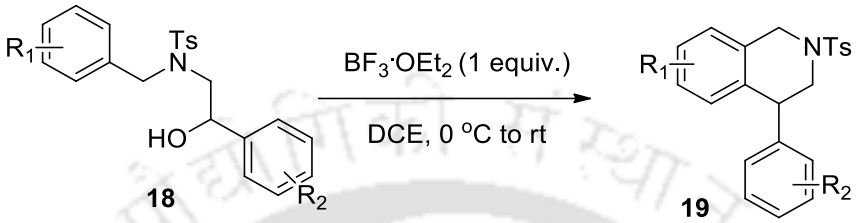
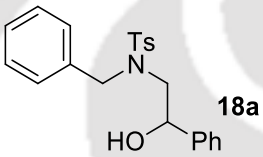
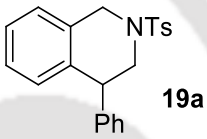
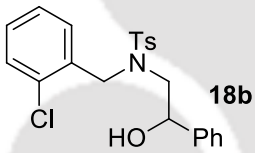
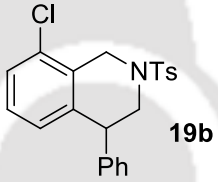
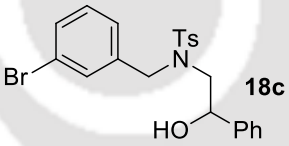
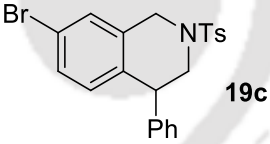
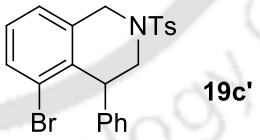
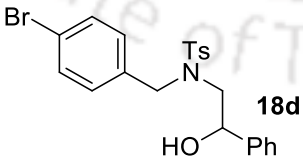
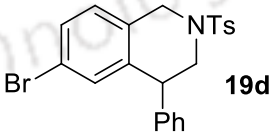
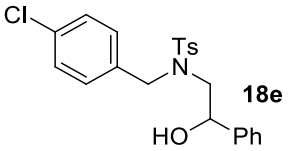
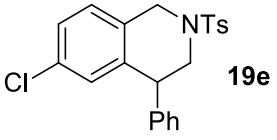
5.4.2. Substrate scope of the reaction

Under the optimized reaction conditions, various substrates were tested to examine the scope and limitation of the reaction in more details. The results are summarised in Table 5.4.2.1.

Table 5.4.2.1. Synthesis of Tetrahydroisoquinolines



Entry	Substrate **18**	Product **19**	Yield (%)[a]
1	 **18a**	 **19a**	82
2	 **18b**	 **19b**	76
3	 **18c**	 **19c**	53
		 **19c'**	26
4	 **18d**	 **19d**	81
5	 **18e**	 **19e**	79

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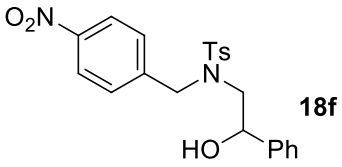
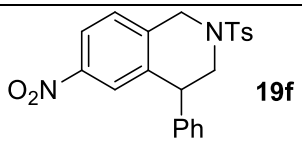
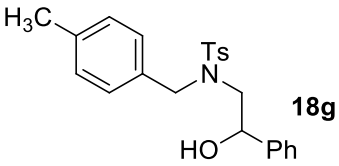
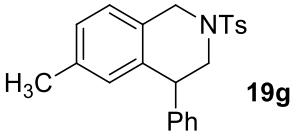
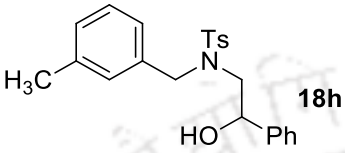
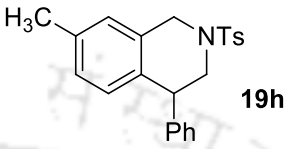
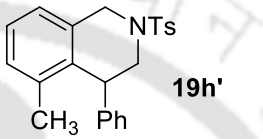
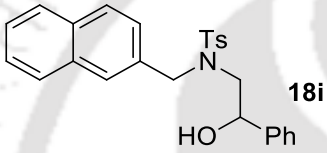
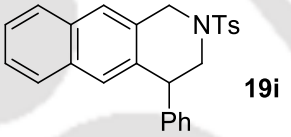
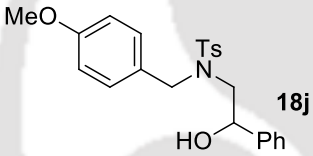
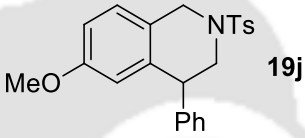
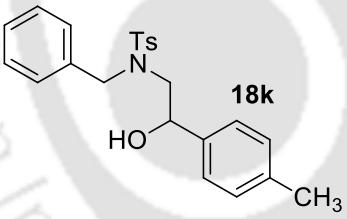
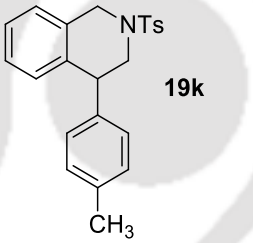
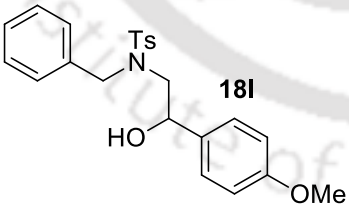
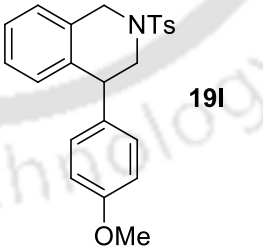
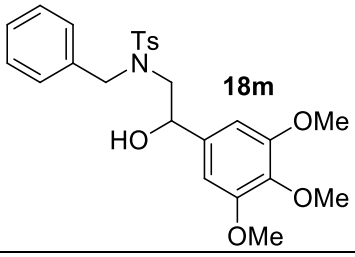
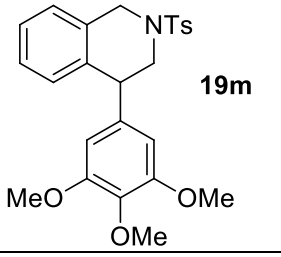
6	 **18f**	 **19f**	d
7	 **18g**	 **19g**	80
8	 **18h**	 **19h**	52
		 **19h'**	26
9	 **18i**	 **19i**	78
10	 **18j**	 **19j**	d
11	 **18k**	 **19k**	84
12	 **18l**	 **19l**	84
13	 **18m**	 **19m**	86

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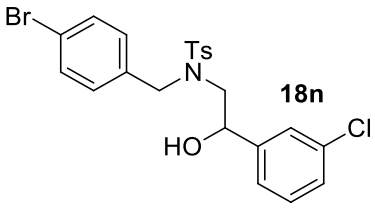
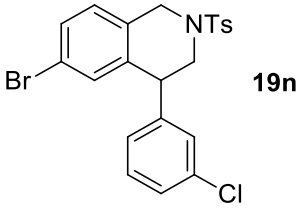
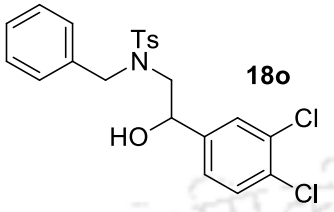
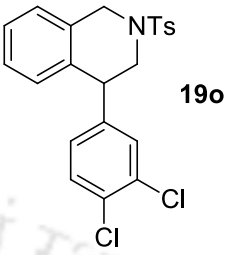
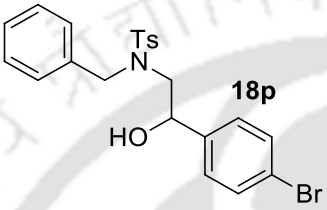
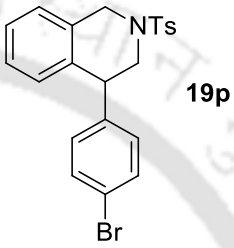
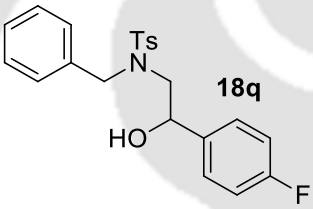
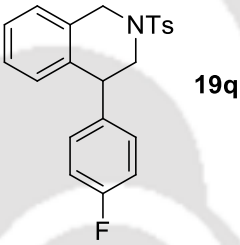
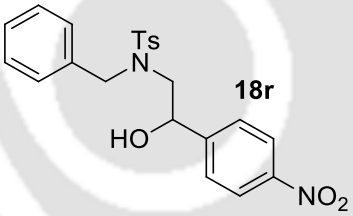
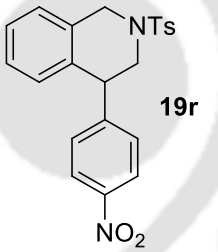
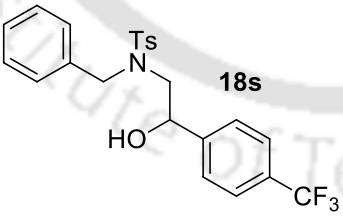
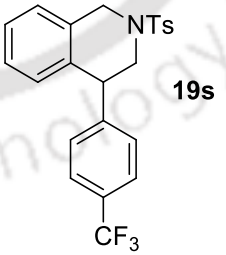
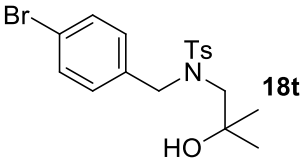
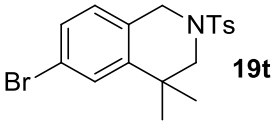
14	 **18n**	 **19n**	71
15	 **18o**	 **19o**	72
16	 **18p**	 **19p**	77
17	 **18q**	 **19q**	73
18	 **18r**	 **19r**	67
19	 **18s**	 **19s**	65
20	 **18t**	 **19t**	d

[a]Yield refers to isolated yield. The compounds were characterized by IR, NMR and Mass spectrometry. d = Decomposed product.

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It was observed from the Table 5.4.2.1 that aryl groups bearing electron-donating and electron-withdrawing substituents reacted smoothly under optimized reaction conditions to give the desired THIQ derivatives in good yields. Substrates having *meta* substituents (entries 3 & 8), both the regioisomeric products were isolated in 2:1 ratio, with sterically hindered regioisomer as the minor product. In addition to these, the 2-naphthyl group also gave the tricyclic tetrahydrobenzo[*g*]isoquinoline derivative **19i** in 78% yield. Presence of a strong electron withdrawing group (-NO_2, entry 6) did not give any product as the highly electron-withdrawing substituent on the benzene ring decreases the electron density on the aromatic ring, which is unfavourable to the Friedel-Crafts reaction. However, aryl group bearing strongly electron donating group (-OMe, entry 10) decomposed under these optimised reaction conditions.

On the other hand, benzyl alcohols with electron-donating groups (entries 11-13) reacted smoothly, affording the Friedel-Crafts adducts in excellent yields. Whereas, benzyl alcohols with halogen substituents (entries 14-17) gave the desired products in moderate to good yields. Presence of strong electron withdrawing groups (-NO_2, -CF_3) in the benzyl scaffold (entries 18-19) failed to give the product under the optimised reaction conditions, but the starting materials were recovered. However, the reaction at elevated temperature (80 ^oC) for 12 h led to the formation of THIQ derivatives **19r** and **19s** with 67% and 65% yields, respectively. This indicates that the formation of benzyl carbenium ion is hampered in these cases due to the presence of electron withdrawing group that destabilize the carbenium ion **A** (*Scheme 5.4.3.1*). Tertiary aliphatic alcohol was found to be unreactive under this reaction condition as tertiary aliphatic carbocation is not stable enough to undergo electrophilic aromatic substitution during the reaction conditions.

5.4.3. Plausible mechanism for the synthesis of 4-aryl-tetrahydroisoquinolines

A plausible mechanism explaining the sequence of the events is tailored in *Scheme 5.4.3.1*. The hydroxyl group of alcohol **18** is activated by Lewis acid ($BF_3{\cdot}OEt_2$) to form benzyl carbenium-ion **A,** which is resonance stabilized. The aromatic ring of *N*-aryl scaffold undergoes electrophilic aromatic substitution leading to the formation of positively charged cyclohexadienyl cation, also known as an arenium-ion **B**, which is also resonance stabilized. Finally, the arenium-ion **B** deprotonates thereby forming C4 substituted THIQ derivatives **19**.

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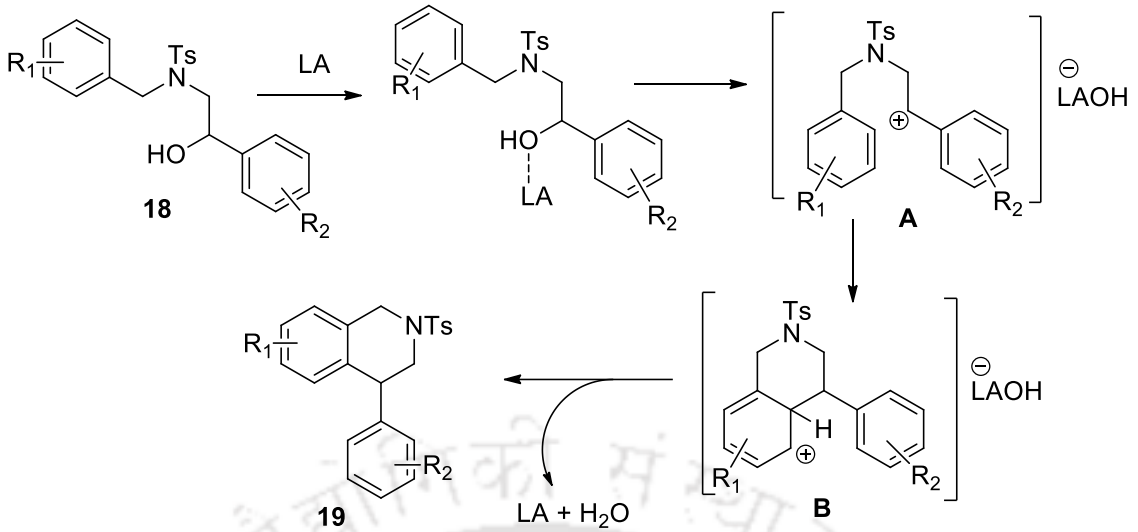

Scheme 5.4.3.1

5.5. Conclusion:

In conclusion, we have developed an alternate methodology for the synthesis of 4-aryl-tetrahydroisoquinoline derivatives from *N*-tethered aryl-benzyl alkanol in good to excellent yields. The reaction is efficient, mild and can be carried out by inexpensive and commercially available boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) as Lewis acid.

5.6. Experimental section

5.6.1. Instrumentation and characterization

As described in chapter 2 section 2.6.1.

5.6.2. General procedure for synthesis of *N*-tethered aryl-benzyl alkanols (18a-18t):

To a stirred solution of NaH (44 mg, 1.1 mmol, 60% in a mineral oil) in dry DMF (4 mL) was added dropwise solution of the *N*-tosylated amino alcohol **20** (1 mmol) in dry DMF (4 mL) at 0 ^oC (N_2 atmosphere). After 20 minutes, DMF (4 mL) solution benzyl bromide derivative **21** (1 mmol) was added and the reaction was stirred at room temperature for 16 h. After completion of the reaction, a few drops of methanol was added at 0 ^oC and the solution was poured in ethylacetate (50 mL). The organic phase is washed with brine (3 x 30 mL), dried over Na_2SO_4. Evaporation of solvent gave the

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crude product, which was purified by column chromatography to give the *N*-tethered aryl-benzyl alkanols (**18a-18t**).

5.6.3. Synthesis of *N*-benzyl-*N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (18a):

To a stirred solution of NaH (44 mg, 1.1 mmol, 60% in a mineral oil) in dry DMF (4 mL) was added dropwise solution of the *N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide **20a** (291 mg, 1 mmol) in dry DMF (4 mL) at 0 ^{o}C (N_2 atmosphere). After 20 minutes, DMF (4 mL) solution benzyl bromide (119 μL, 1 mmol) was added and the reaction was stirred at room temperature for 16 h. After completion of the reaction, a few drops of methanol was added at 0 ^{o}C and the solution was poured in ethylacetate (50 mL). The organic phase is washed with brine (3 x 30 mL), dried over Na_2SO_4. Evaporation of solvent gave the crude product, which was purified by column chromatography to give *N*-benzyl-*N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide **18a** (255 mg, 67% yield) as a white solid.

5.6.4. General procedure for the synthesis of tetrahydroisoquinolines (19a-19s):

To a solution of *N*-tethered aryl-benzyl alkanols (0.5 mmol) in dichloroethane (5 mL), was added $BF_3{\cdot}OEt_2$ (1 equiv.) dropwise at 0 ^{o}C under the nitrogen atmosphere. The reaction mixture was allowed to come to room temperature and the reaction was monitored by checking TLC. After completion of the reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (10 mL). The product was extracted with CH_2Cl_2 (2 × 20 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 using ethyl acetate and hexane as eluents to afford the title compounds **19a-19s.**

5.6.5. Synthesis of 4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19a):

To a solution of *N*-benzyl-*N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide **18a** (191 mg, 0.5 mmol) in dichloroethane (5 mL), was added $BF_3{\cdot}OEt_2$ (62 μL, 0.5 mmol) dropwise at 0 ^{o}C under nitrogen atmosphere. The reaction mixture was allowed to come to room temperature and the reaction was monitored by TLC. After the completion

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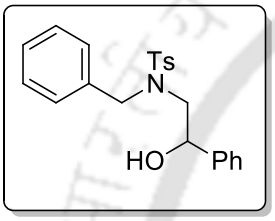
of the reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (10 mL). The product was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layer was washed with brine. The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using a rotary evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluents to give **19a** (149 mg, 82% yield) as a colorless solid.

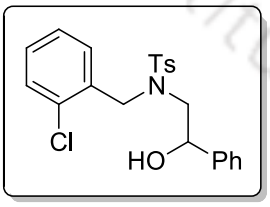
5.7. Spectral data

***N*-Benzyl-*N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (18a):**



White solid, mp. 118-120 °C; R_f (hexane/EtOAc 5:1) 0.50; yield 255 mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 2.98 (dd, *J* = 15.2 and 2.8 Hz, 2 H), 3.27 (dd, *J* = 15.2 Hz and 9.6 Hz, 1 H), 4.06 (d, *J* = 14.4 Hz, 1 H), 4.43 (dd, *J* = 9.6 and 2.8 Hz, 1 H), 4.53 (d, *J* = 14.4 Hz, 1 H), 7.02 (d, *J* = 8.0 Hz, 2 H), 7.11-7.29 (m, 10 H), 7.65 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 54.2, 56.8, 72.7, 125.9, 127.5, 127.9, 128.4, 128.6, 128.9, 129.0, 130.0, 136.0, 136.1, 141.4, 144.0; IR (KBr, neat) 3513, 3030, 2923, 1599, 1452, 1335, 1156, 1092, 771, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{24}NO_3S$ $(M + H)^+$ 382.1471, found 382.1478.

***N*-(2-Chlorobenzyl)-*N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (18b):**



White solid, mp. 84-86 °C; R_f (hexane/EtOAc 5:1) 0.50; yield 261 mg, 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 3.05 (dd, *J* = 15.2 and 2.8 Hz, 2 H), 3.30 (dd, *J* = 15.2 Hz and 9.6 Hz, 1 H), 4.31 (d, *J* = 15.2 Hz, 1 H), 4.44 (d, *J* = 9.6 Hz, 1 H), 4.58 (d, *J* = 15.2 Hz, 1 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 7.10-7.19 (m, 7 H), 7.22-7.25 (m, 1 H), 7.60 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 51.1, 57.4, 72.5, 125.9, 127.4, 127.9, 128.5, 129.4, 129.7, 130.0, 136.7, 133.5, 133.9, 135.9, 141.2, 144.0; IR (KBr, neat) 3521, 3029, 2925, 1598, 1449, 1351, 1154, 1092, 771, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{23}ClNO_3S$ $(M + H)^+$ 416.1082, found 416.1077.

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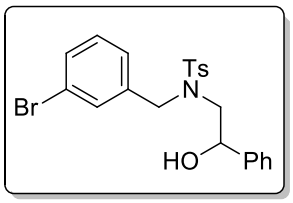
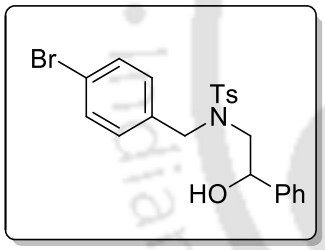
***N*-(3-Bromobenzyl)-*N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (18c):**



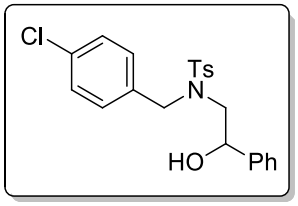
Brown solid, mp. 128-130 ^{o}C; R_f (hexane/EtOAc 5:1) 0.55; yield 285 mg, 62%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 2.83 (brs, 1 H), 3.08 (dd, *J* = 15.0 and 3.0 Hz, 1 H), 3.27 (dd, *J* = 15.0 and 9.0 Hz, 1 H), 4.13 (d, *J* = 15.0 Hz, 1 H), 4.42 (d, *J* = 15.0 Hz, 1 H), 4.58 (d, *J* = 9.0 Hz, 1 H), 7.09-7.11 (m, 4 H), 7.14 (s, 1 H), 7.16-7.18 (m, 1 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.32-7.34 (m, 1 H), 7.63 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 53.1, 56.4, 73.0, 123.0, 126.0, 127.36, 127.44, 128.1, 128.7, 130.1, 130.5, 131.3, 131.6, 136.5, 138.6, 141.4, 144.1; IR (KBr, neat) 3521, 3029, 2924, 1597, 1475, 1336, 1156, 1092, 770, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{23}BrNO_3S$ $(M + H)^+$ 460.0577, found 460.0596.

***N*-(4-Bromobenzyl)-*N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (18d):**



White solid, mp. 104-106 ^{o}C; R_f (hexane/EtOAc 5:1) 0.55; yield 312 mg, 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 2.87 (brs, 1 H), 3.11 (dd, *J* = 15.2 and 3.2 Hz, 1 H), 3.34 (dd, *J* = 15.2 Hz and 9.2 Hz, 1 H), 4.15 (d, *J* = 14.8 Hz, 1 H), 4.51 (d, *J* = 14.8 Hz, 1 H), 4.61 (dd, *J* = 9.2 and 2.8 Hz, 1 H), 7.11-7.16 (m, 4 H), 7.22-7.33 (m, 5 H), 7.44 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 53.4, 56.5, 72.9, 122.3, 126.0, 127.5, 128.1, 128.7, 130.1, 130.4, 132.1, 135.3, 136.4, 141.4, 144.1; IR (KBr, neat) 3521, 3029, 2924, 1597, 1490, 1451, 1340, 1158, 1092, 771, 703 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{23}BrNO_3S$ $(M + H)^+$ 460.0577, found 460.0585.

***N*-(4-Chlorobenzyl)-*N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (18e):**



Pale yellow liquid; R_f (hexane/EtOAc 5:1) 0.52; yield 278 mg, 67%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 2.98 (brs, 1 H), 3.11 (dd, *J* = 15.0 and 3.0 Hz, 1 H), 3.33 (dd, *J* = 15.0 Hz and 9.0 Hz, 1 H), 4.17 (d, *J* = 15.0 Hz, 1 H), 4.50 (d, *J* = 15.0 Hz, 1 H), 4.60 (dd, *J* = 9.0 and 3.0 Hz, 1 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 7.17 (d, *J* = 8.4

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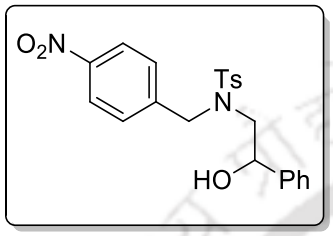
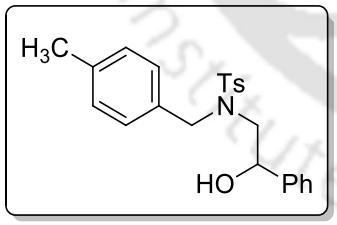
Hz, 2 H), 7.21-7.27 (m, 5 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.70 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 53.2, 56.4, 72.8, 126.0, 127.4, 128.0, 128.6, 129.0, 130.0, 130.1, 134.1, 134.8, 136.2, 141.3, 144.0; IR (KBr, neat) 3512, 3030, 2924, 1598, 1492, 1451, 1336, 1157, 1092, 769, 702, 662 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{23}ClNO_3S$ $(M + H)^+$ 416.1082, found 416.1081.

_N_-(2-Hydroxy-2-phenylethyl)-4-methyl-_N_-(4-nitrobenzyl)benzenesulfonamide (18f):



Pale yellow solid, mp. 95-97 °C; R_f (hexane/EtOAc 5:1) 0.40; yield 257 mg, 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3 H), 2.57 (d, *J* = 2.4 Hz, 1 H), 3.19 (dd, *J* = 15.0 and 3.0 Hz, 1 H), 3.25 (dd, *J* = 15.0 Hz and 9.0 Hz, 1 H), 4.35 (d, *J* = 15.6 Hz, 1 H), 4.53 (d, *J* = 15.6 Hz, 1 H), 4.65-4.66 (m, 1 H), 7.01 (t, *J* = 7.2 Hz, 2 H), 7.18-7.22 (m, 3 H), 7.25 (d, *J* = 7.8 Hz, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.66 (d, *J* = 8.4 Hz, 2 H), 8.07 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 53.3, 56.6, 73.2, 124.0, 126.0, 127.5, 128.4, 128.8, 129.2, 130.2, 136.4, 141.3, 144.3, 147.8; IR (KBr, neat) 3502, 3031, 2924, 1601, 1521, 1345, 1157, 1090, 739, 700 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{23}N_2O_5S$ $(M + H)^+$ 427.1322, found 427.1314.

_N_-(2-Hydroxy-2-phenylethyl)-4-methyl-_N_-(4-methylbenzyl)benzenesulfonamide (18g):



White solid, mp. 89-90 °C; R_f (hexane/EtOAc 5:1) 0.50; yield 273 mg, 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3 H), 2.31 (s, 3 H), 2.95 (dd, *J* = 15.2 and 2.8 Hz, 1 H), 3.04 (brs, 1 H), 3.24 (dd, *J* = 15.2 Hz and 9.2 Hz, 1 H), 3.99 (d, *J* = 14.4 Hz, 1 H), 4.40-4.46 (m, 2 H), 7.01-7.07 (m, 6 H), 7.10-7.17 (m, 3 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 21.6, 53.7, 56.5, 72.5, 125.9, 127.4, 127.8, 128.5, 128.8, 129.6, 130.0, 132.9, 136.1, 138.0, 141.4, 143.8; IR (KBr, neat) 3512, 3029, 2923, 1598, 1451, 1335, 1156, 1092, 768, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{26}NO_3S$ $(M + H)^+$ 396.1628, found 396.1635.

_N_-(2-Hydroxy-2-phenylethyl)-4-methyl-_N_-(3-methylbenzyl)benzenesulfonamide (18h):

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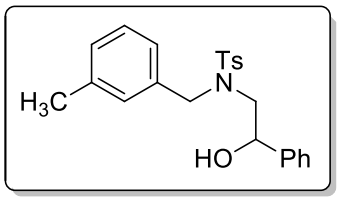
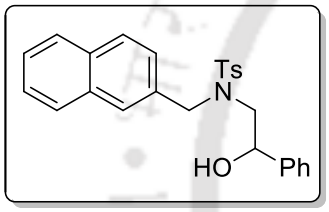


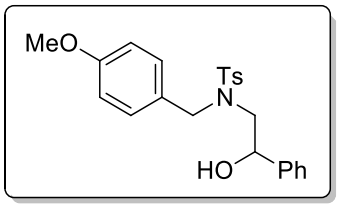
White solid, mp. 90-91 °C; R_f (hexane/EtOAc 5:1) 0.50; yield 253 mg, 64%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.29 (s, 3 H), 2.42 (s, 3 H), 3.07 (dd, *J* = 15.0 and 2.4 Hz, 1 H), 3.10 (brs, 1 H), 3.34 (dd, *J* = 15.0 Hz and 9.6 Hz, 1 H), 4.11 (d, *J* = 14.4 Hz, 1 H), 4.53-4.55 (m, 2 H), 6.99 (s, 1 H), 7.03(d, *J* = 7.8 Hz, 1 H), 7.09-7.12 (m, 3 H), 7.19-7.26 (m, 4 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 21.7, 54.0, 56.3, 72.7, 125.9, 126.0, 127.5, 127.9, 128.5, 128.8, 129.0, 129.5, 130.0, 135.9, 136.2, 138.7, 141.4, 143.9; IR (KBr, neat) 3512, 3029, 2923, 1601, 1452, 1335, 1156, 1091, 766, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{26}NO_3S$ $(M + H)^+$ 396.1628, found 396.1629.

_N_-(2-Hydroxy-2-phenylethyl)-4-methyl-_N_-(naphthalen-2-ylmethyl)benzenesulfonamide (18i):



White solid, mp. 114-116 °C; R_f (hexane/EtOAc 5:1) 0.47; yield 267 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.04 (d, *J* = 2.4 Hz, 1 H), 3.15 (dd, *J* = 15.2 and 2.8 Hz, 1 H), 3.38 (dd, *J* = 15.2 Hz and 9.2 Hz, 1 H), 4.32 (d, *J* = 14.4 Hz, 1 H), 4.55 (d, *J* = 9.2 Hz, 1 H), 4.74 (d, *J* = 14.4 Hz, 1 H), 7.03-7.06 (m, 2 H), 7.17-7.21 (m, 3 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.41 (dd, *J* = 8.4 and 1.6 Hz, 1 H), 7.46-7.50 (m, 2 H), 7.57 (s, 1 H), 7.72-7.83 (m, 5 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 54.1, 56.5, 72.7, 125.9, 126.3, 126.4, 126.6, 127.5, 127.8, 127.87, 127.89, 128.5, 128.7, 128.9, 130.0, 133.1, 133.3, 133.4, 136.3, 141.3, 143.9; IR (KBr, neat) 3511, 3029, 2924, 1599, 1450, 1334, 1156, 1092, 759, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{26}NO_3S$ $(M + H)^+$ 432.1628, found 432.1629.

_N_-(2-Hydroxy-2-phenylethyl)-_N_-(4-methoxybenzyl)-4-methylbenzenesulfonamide (18j):



White solid, mp. 92-93 °C; R_f (hexane/EtOAc 5:1) 0.40; yield 267 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 2.96 (dd, *J* = 14.8 and 2.8 Hz, 1 H), 3.01 (brs, 1 H), 3.25 (dd, *J* = 14.8 Hz and 8.6 Hz, 1 H), 3.72 (s, 3 H), 3.98 (d, *J* = 14.0 Hz, 1 H), 4.41-4.53 (m, 2 H), 6.79 (d, *J* = 8.8 Hz, 2 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 7.11-7.21 (m, 5 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 7.65 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR

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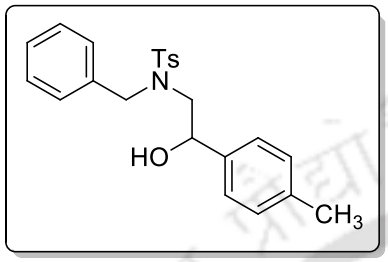
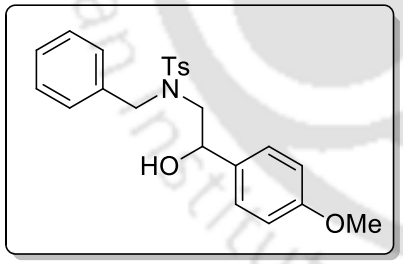
(100 MHz, $CDCl_3$) δ 21.7, 53.7, 55.5, 56.6, 72.7, 114.4, 126.0, 127.5, 127.89, 127.91, 128.6, 130.0, 130.3, 136.1, 141.4, 143.9, 159.7; IR (KBr, neat) 3512, 3029, 2931, 1611, 1512, 1452, 1334, 1250, 1156, 1063, 748, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{26}NO_4S$ $(M + H)^+$ 412.1577, found 412.1577.

_N_-Benzyl-_N_-(2-hydroxy-2-(_p_-tolyl)ethyl)-4-methylbenzenesulfonamide (18k):



White solid, mp. 120-122 °C; R_f (hexane/EtOAc 5:1) 0.50; yield 272 mg, 69%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3 H), 2.33 (s, 3 H), 2.94-2.98 (m, 2 H), 3.25 (dd, *J* = 14.8 Hz and 9.6 Hz, 1 H), 4.05 (d, *J* = 14.4 Hz, 1 H), 4.40 (d, *J* = 9.2 Hz, 1 H), 4.48 (d, *J* = 14.4 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 2 H), 6.96 (d, *J* = 7.6 Hz, 2 H), 7.17-7.24 (m, 7 H), 7.63 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 21.7, 54.0, 56.7, 72.4, 125.8, 127.5, 128.3, 128.9, 129.0, 129.2, 130.0, 136.1, 136.2, 137.6, 138.4, 143.9; IR (KBr, neat) 3513, 3029, 2923, 1599, 1453, 1335, 1156, 1092, 816, 735 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{26}NO_3S$ $(M + H)^+$ 396.1628, found 396.1636.

_N_-Benzyl-_N_-(2-hydroxy-2-(4-methoxyphenyl)ethyl)-4-methylbenzenesulfonamide (18l):



White solid, mp. 90-92 °C; R_f (hexane/EtOAc 5:1) 0.40; yield 275 mg, 67%; ^1H NMR (600 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 2.93 (brs, 1 H), 3.03 (dd, *J* = 15.0 and 2.4 Hz, 1 H), 3.33 (dd, *J* = 15.0 Hz and 9.0 Hz, 1 H), 3.76 (s, 3 H), 4.14 (d, *J* = 14.4 Hz, 1 H), 4.48 (d, *J* = 9.0 Hz, 1 H), 4.57 (d, *J* = 14.4 Hz, 1 H), 6.78 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 7.26-7.35 (m, 7 H), 7.73 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 54.1, 55.4, 56.8, 72.3, 114.0, 127.2, 127.5, 128.3, 128.9, 129.0, 130.0, 133.6, 136.2, 136.3, 143.9, 159.4; IR (KBr, neat) 3520, 3061, 2926, 1612, 1514, 1349, 1170, 917, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{26}NO_4S$ $(M + H)^+$ 412.1577, found 412.1584.

_N_-Benzyl-_N_-(2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)-4-methylbenzenesulfonamide (18m):

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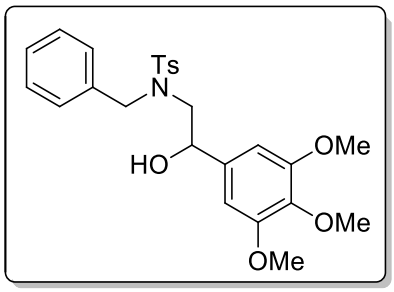
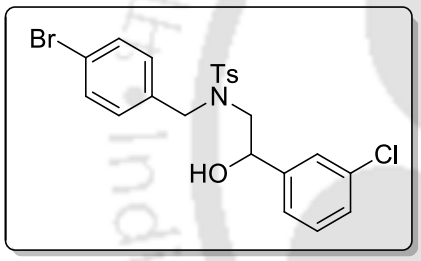


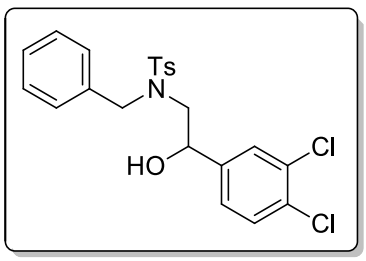
White solid, mp. 146-148 °C; R_f (hexane/EtOAc 5:1) 0.40; yield 325 mg, 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 3.05 (dd, *J* = 14.8 and 2.4 Hz, 1 H), 3.35 (dd, *J* = 14.8 Hz and 8.8 Hz, 1 H), 3.77 (s, 6 H), 3.78 (s, 3 H), 4.07 (d, *J* = 14.0 Hz, 1 H), 4.47 (dd, *J* = 8.8 and 2.8 Hz, 1 H), 4.60 (d, *J* = 14.0 Hz, 1 H), 6.28 (s, 2 H), 7.25 (d, *J* = 6.8 Hz, 2 H), 7.31-7.35 (m, 5 H), 7.75 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 54.3, 56.2, 56.8, 61.0, 73.1, 102.7, 127.6, 128.4, 129.0, 129.1, 130.1, 135.93, 135.94, 137.2, 137.4, 144.1, 153.4; IR (KBr, neat) 3492, 2924, 1594, 1461, 1331, 1156, 1127, 722 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{30}NO_6S$ $(M + H)^+$ 472.1788, found 472.1789.

_N_-(4-Bromobenzyl)-_N_-(2-(3-chlorophenyl)-2-hydroxyethyl)-4-methylbenzenesulfonamide (18n):



White solid, mp. 105-107 °C; R_f (hexane/EtOAc 5:1) 0.50; yield 330 mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.07 (dd, *J* = 15.2 and 3.2 Hz, 1 H), 3.22 (brs, 1 H), 3.28 (dd, *J* = 15.2 and 8.8 Hz, 1 H), 4.09 (d, *J* = 14.8 Hz, 1 H), 4.48 (d, *J* = 14.8 Hz, 1 H), 4.56 (td, *J* = 8.8 and 2.8 Hz, 1 H), 6.97-6.98 (m, 1 H), 7.08-7.10 (m, 3 H), 7.16-7.18 (m, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.41 (d, *J* = 7.6 Hz, 2 H), 7.69 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 53.5, 56.3, 72.3, 122.3, 124.1, 126.1, 127.4, 128.0, 129.9, 130.1, 130.4, 132.0, 134.5, 135.1, 135.9, 143.4, 144.2; IR (KBr, neat) 3505, 3026, 2924, 1597, 1488, 1335, 1157, 1010, 766, 660 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{22}BrClNO_3S$ $(M + H)^+$ 494.0187, found 494.0195.

_N_-Benzyl-_N_-(2-(3,4-dichlorophenyl)-2-hydroxyethyl)-4-methylbenzenesulfonamide (18o):



White solid, mp. 115-117 °C; R_f (hexane/EtOAc 5:1) 0.50; yield 283 mg, 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 2.91 (dd, *J* = 15.2 and 2.8 Hz, 1 H), 3.18 (dd, *J* = 15.2 and 8.8 Hz, 1 H), 3.24 (brs, 1 H), 3.94 (d, *J* = 14.0 Hz, 1 H), 4.35 (d, *J* = 8.8 Hz, 1 H), 4.54 (d, *J* =

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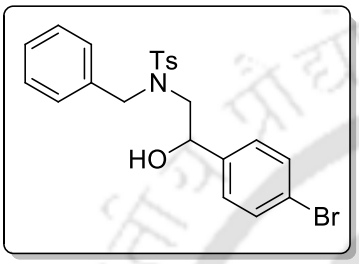
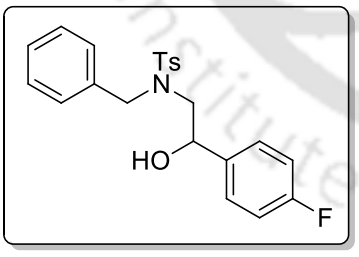
14.0 Hz, 1 H), 6.78 (d, *J* = 8.4 Hz, 1 H), 7.04 (s, 1 H), 7.17-7.20 (m, 3 H), 7.24-7.27 (m, 5 H), 7.64 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 54.7, 56.8, 72.0, 125.4, 127.6, 128.0, 128.7, 129.1, 129.2, 130.2, 130.5, 131.7, 132.7, 135.5, 135.7, 141.7, 144.3; IR (KBr, neat) 3499, 3031, 2924, 1598, 1469, 1335, 1157, 1091, 772, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{22}Cl_2NO_3S$ $(M + H)^+$ 450.0692, found 450.0698.

_N_-Benzyl-_N_-(2-(4-bromophenyl)-2-hydroxyethyl)-4-methylbenzenesulfonamide (18p):



White solid, mp. 130-131 ºC; R_f (hexane/EtOAc 5:1) 0.55; yield 312 mg, 68%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.01 (dd, *J* = 15.0 and 3.0 Hz, 1 H), 3.18 (brs, 1 H), 3.28 (dd, *J* = 15.0 Hz and 9.0 Hz, 1 H), 4.08 (d, *J* = 14.4 Hz, 1 H), 4.45 (dd, *J* = 9.0 and 3.0 Hz, 1 H), 4.59 (d, *J* = 14.4 Hz, 1 H), 6.94 (d, *J* = 8.4 Hz, 2 H), 7.25-7.26 (m, 2 H), 7.31-7.35 (m, 7 H), 7.72 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 54.4, 56.7, 72.3, 121.7, 127.5, 127.7, 128.5, 129.0, 129.1, 130.1, 131.6, 135.8, 135.9, 140.0, 144.1; IR (KBr, neat) 3516, 3030, 2924, 1597, 1490, 1340, 1159, 1092, 771, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{23}BrNO_3S$ $(M + H)^+$ 460.0577, found 460.0578.

_N_-Benzyl-_N_-(2-(4-fluorophenyl)-2-hydroxyethyl)-4-methylbenzenesulfonamide (18q):



White solid, mp. 87-89 ºC; R_f (hexane/EtOAc 5:1) 0.52; yield 259 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.01 (dd, *J* = 14.8 and 3.2 Hz, 1 H), 3.30 (dd, *J* = 14.8 Hz and 9.2 Hz, 1 H), 4.10 (d, *J* = 14.4 Hz, 1 H), 4.48 (dd, *J* = 9.2 and 3.2 Hz, 2 H), 4.59 (d, *J* = 14.4 Hz, 1 H), 6.91 (t, *J* = 8.8 Hz, 2 H), 7.02-7.06 (m, 2 H), 7.24-7.28 (m, 2 H), 7.31-7.34 (m, 5 H), 7.72 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 54.2, 56.7, 72.2, 115.3 (d, *J* = 21.30 Hz), 127.5, 127.58, 127.64, 128.4, 128.9, 129.0, 130.1, 135.9 (d, *J* = 4.8 Hz), 137.1(d, *J* = 3.0 Hz), 144.0, 162.4 (d, *J* = 244.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 47.02; IR (KBr, neat) 3508, 3030, 2924, 1603, 1511, 1337, 1159, 1090, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{23}FNO_3S$ $(M + H)^+$ 400.1377, found 400.1394.

_N_-Benzyl-_N_-(2-hydroxy-2-(4-nitrophenyl)ethyl)-4-methylbenzenesulfonamide (18r):

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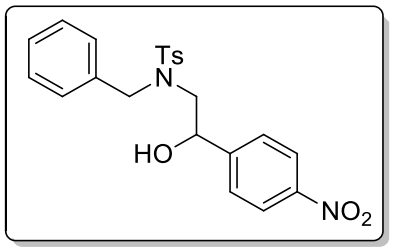
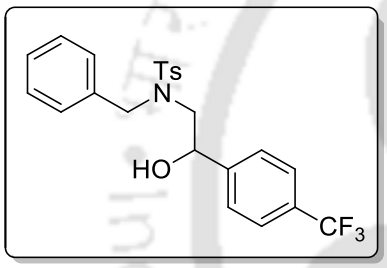


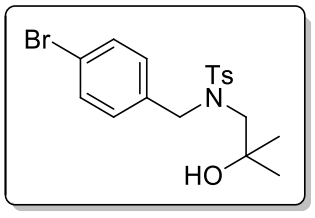
White solid, mp. 105-107 °C; R_f (hexane/EtOAc 5:1) 0.40; yield 256 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 3.05 (dd, *J* = 15.2 and 2.4 Hz, 1 H), 3.30 (dd, *J* = 15.2 Hz and 9.2 Hz, 1 H), 3.51 (brs, 1 H), 4.04 (d, *J* = 14.0 Hz, 1 H), 4.58-4.65 (m, 2 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 7.17-7.35 (m, 7 H), 7.73 (d, *J* = 7.6 Hz, 2 H), 8.05 (d, *J* = 6.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 54.7, 56.6, 72.4, 123.7, 126.8, 127.5, 128.7, 129.1, 129.2, 130.2, 135.3, 135.6, 144.4, 147.5, 148.7; IR (KBr, neat) 3504, 3031, 2924, 1602, 1521, 1347, 1157, 1089, 770, 700 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{23}N_2O_5S$ $(M + H)^+$ 427.1322, found 427.1329.

_N_-Benzyl-_N_-(2-hydroxy-2-(4-(trifluoromethyl)phenyl)ethyl)-4-methylbenzenesulfonamide (18s):



White solid, mp. 109-111 °C; R_f (hexane/EtOAc 5:1) 0.45; yield 283 mg, 63%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 3.03 (dd, *J* = 15.0 and 3.0 Hz, 1 H), 3.30 (dd, *J* = 15.0 Hz and 9.0 Hz, 2 H), 4.07 (d, *J* = 14.4 Hz, 1 H), 4.55 (dd, *J* = 9.0 and 2.4 Hz, 1 H), 4.64 (d, *J* = 14.4 Hz, 1 H), 7.19 (d, *J* = 7.8 Hz, 2 H), 7.26-7.28 (m, 2 H), 7.33-7.36 (m, 5 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 54.6, 56.9, 72.5, 124.2 (q, *J* =270 Hz), 125.5 (q, *J* =3.7 Hz), 126.3, 127.6, 128.6, 129.1, 129.2, 130.1(q, *J* =32.0 Hz), 135.6, 135.8, 144.2, 145.4; ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 99.20; IR (KBr, neat) 3503, 3032, 2925, 1599, 1453, 1327, 1160, 1068, 759, 664 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{23}F_3NO_3S$ $(M + H)^+$ 450.1345, found 450.1364.

_N_-(4-Bromobenzyl)-_N_-(2-hydroxy-2-methylpropyl)-4-methylbenzenesulfonamide (18t):



White solid, mp. 99-100 °C; R_f (hexane/EtOAc 5:1) 0.40; yield 263 mg, 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 6 H), 2.43 (s, 3 H), 2.92 (brs, 1 H), 3.62 (s, 2 H), 4.62 (s, 2 H), 7.29-7.32 (m, 4 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 25.0, 50.0, 64.5, 69.8, 121.0, 127.3, 128.6, 130.0, 131.7, 139.2, 139.4, 143.9; IR (KBr, neat) 3534, 3030, 2924, 1597, 1488,

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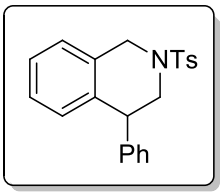
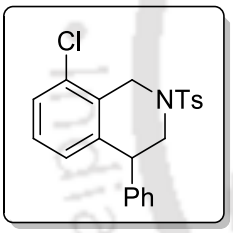
1323, 1151, 1089, 879, 814 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{23}BrNO_3S$ $(M + H)^+$ 412.0577, found 412.0579.

4-Phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19a):



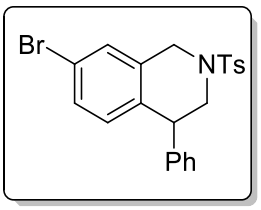
White solid, mp. 138-140 ^oC; R_f (hexane/EtOAc 10:1) 0.50; yield 149 mg, 82%; ^1H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 3.05 (dd, *J* = 11.4 and 8.4 Hz, 1 H), 3.79 (dd, *J* = 11.4 Hz and 5.4 Hz, 1 H), 4.17 (d, *J* = 14.4 Hz, 1 H), 4.29-4.31 (m, 1 H), 4.50 (d, *J* = 14.4 Hz, 1 H), 6.85 (d, *J* = 7.8 Hz, 1 H), 7.07-7.11 (m, 4 H), 7.17 (t, *J* = 7.8 Hz, 1 H), 7.24-7.29 (m, 5 H), 7.66 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 45.5, 48.2, 51.2, 126.4, 126.9, 127.1, 127.3, 128.0, 128.9, 129.2, 129.7, 129.9, 132.2, 133.3, 136.6, 142.6, 143.9; IR (KBr, neat) 3028, 2922, 1599, 1494, 1454, 1351, 1164, 958, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{22}NO_2S$ $(M + H)^+$ 364.1371, found 364.1367.

8-Chloro-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19b):



White solid, mp. 104-105 ^oC; R_f (hexane/EtOAc 10:1) 0.50; yield 151 mg, 76%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3 H), 2.96 (dd, *J* = 12.0 and 8.4 Hz, 1 H), 3.68 (dd, *J* = 12.0 Hz and 5.2 Hz, 1 H), 4.02 (d, *J* = 16.0 Hz, 1 H), 4.19-4.23 (m, 1 H), 4.48 (d, *J* = 16.0 Hz, 1 H), 6.68 (d, *J* = 7.6 Hz, 1 H), 6.92-7.00 (m, 3 H), 7.12 (d, *J* = 8.0 Hz, 1 H), 7.16-7.23 (m, 5 H), 7.58 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 45.6, 46.6, 50.5, 127.4, 127.5, 127.8, 127.9, 128.2, 128.8, 129.0, 129.9, 130.3, 132.1, 133.1, 139.2 141.9, 144.0; IR (KBr, neat) 3028, 2922, 1598, 1444, 1353, 1164, 967, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{21}ClNO_2S$ $(M + H)^+$ 398.0982, found 398.0988.

7-Bromo-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19c):



White solid, mp. 162-164 ^oC; R_f (hexane/EtOAc 10:1) 0.55; yield 116 mg, 53%; ^1H NMR (600 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 2.93 (dd, *J* = 11.4 and 8.4 Hz, 1 H), 3.72 (dd, *J* = 11.4 Hz and 5.84 Hz, 1 H), 4.04 (d, *J* = 15.0 Hz, 1 H), 4.15 (dd, *J* = 8.4 and 5.4 Hz, 1 H), 4.41 (d, *J* = 15.0 Hz, 1 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 7.01 (d, *J* = 7.2 Hz, 2 H), 7.12 (dd, *J* = 7.8 and 1.8 Hz, 1 H), 7.18-7.23 (m, 6 H), 7.57 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR

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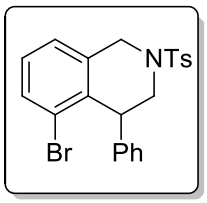
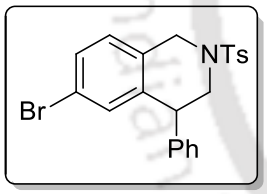
(150 MHz, $CDCl_3$) δ 21.7, 45.1, 47.8, 51.1, 120.6, 127.5,127.9, 128.9, 129.1, 129.2, 130.0, 130.4, 131.5, 133.4, 134.4, 135.8, 141.9, 144.1; IR (KBr, neat) 3028, 2924, 1597, 1486, 1455, 1350, 1164, 958, 770 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{21}BrNO_2S$ $(M + H)^+$ 442.0476, found 442.0490.

5-Bromo-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19c') :



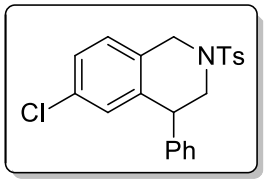
White solid, mp. 153-155 °C; R_f (hexane/EtOAc 10:1) 0.50; yield 58 mg, 26%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 3.11 (dd, *J* = 11.6 and 3.6 Hz, 1 H), 3.92 (d, *J* = 11.6 Hz, 1 H), 4.02 (d, *J* = 15.2 Hz, 1 H), 4.40 (brs, 1 H), 4.67 (d, *J* = 15.2 Hz, 1 H), 6.97-6.99 (m, 2 H), 7.11-7.13 (m, 2 H), 7.21-7.23 (m, 5 H), 7.42-7.44 (m, 1 H), 7.51 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 45.4, 47.4, 50.8, 125.8, 126.3, 126.8, 127.9, 128.4, 128.5, 128.7, 129.8, 132.0, 133.5, 135.02, 135.03, 141.7, 143.8; IR (KBr, neat) 3027, 2923, 1598, 1453, 1353, 1164, 959, 755 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{21}BrNO_2S$ $(M + H)^+$ 442.0476, found 442.0474.

6-Bromo-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19d):



White solid, mp. 148-149 °C; R_f (hexane/EtOAc 10:1) 0.50; yield 178 mg, 81%; ^1H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.01 (dd, *J* = 12.0 and 8.4 Hz, 1 H), 3.77 (dd, *J* = 12.0 Hz and 5.4 Hz, 1 H), 4.10 (d, *J* = 15.0 Hz, 1 H), 4.24-4.26 (m, 1 H), 4.45 (d, *J* = 15.0 Hz, 1 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 6.99 (d, *J* = 0.6 Hz, 1 H), 7.08-7.09 (m, 2 H), 7.28-7.32 (m, 6 H), 7.64 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 45.4, 47.9, 51.0, 121.0, 127.6, 128.0, 128.1, 129.02, 129.11, 129.99, 130.14, 131.3, 132.5, 133.3, 139.0, 141.7, 144.1; IR (KBr, neat) 3028, 2922, 1596, 1486, 1455, 1348, 1164, 1091, 958, 771 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{21}BrNO_2S$ $(M + H)^+$ 442.0476, found 442.0461.

6-Chloro-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19e):



White solid, mp. 93-95 °C; R_f (hexane/EtOAc 10:1) 0.50; yield 157 mg, 79%; ^1H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 3.01 (dd, *J* = 12.0 and 8.4 Hz, 1 H), 3.78 (ddd, *J* = 12.0 Hz, 5.4 Hz and 1.2 Hz, 1 H), 4.11 (d, *J* = 15.0 Hz, 1 H), 4.24-4.26 (m, 1 H), 4.47

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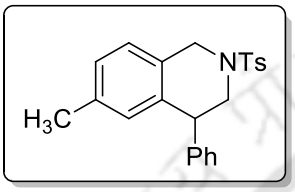
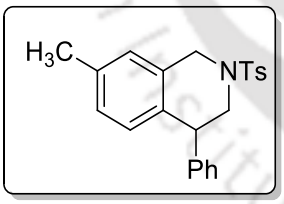
(d, *J* = 15.0 Hz, 1 H), 6.84 (d, *J* = 1.2 Hz, 1 H), 7.03 (d, *J* = 8.4 Hz, 1 H), 7.09 (d, *J* = 7.8 Hz, 2 H), 7.14 (dd, *J* = 8.4 Hz and 2.4 Hz, 1 H), 7.25-7.32 (m, 5 H), 7.65 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 45.4, 47.8, 50.9, 127.2, 127.6, 127.8, 127.9, 129.0, 129.1, 129.5, 130.0, 130.7, 132.18, 133.1, 138.6, 141.7, 144.1; IR (KBr, neat) 3028, 2922, 1598, 1489, 1456, 1351, 1164, 1094, 960, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{21}ClNO_2S$ $(M + H)^+$ 398.0982, found 398.0977.

6-Methyl-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19g):



White solid, mp. 111-112 ºC; R_f (hexane/EtOAc 10:1) 0.50; yield 150 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3 H), 2.33 (s, 3 H), 2.98 (dd, *J* =11.6 and 8.4 Hz, 1 H), 3.66 (dd, *J* = 11.6 Hz and 5.2 Hz, 1 H), 4.07 (d, *J* = 14.4 Hz, 1 H), 4.16-4.19 (m, 1 H), 4.36 (d, *J* = 14.4 Hz, 1 H), 6.58 (s, 1 H), 6.90 (s, 2 H), 7.02-7.42 (m, 2 H), 7.17-7.23 (m, 5 H), 7.57 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 21.7, 45.4, 48.0, 51.3, 126.2, 127.2, 127.8, 127.9, 128.1, 128.7, 129.2, 129.9, 130.1, 133.3, 136.3, 136.7, 142.8, 143.8; IR (KBr, neat) 3026, 2922, 1599, 1498, 1456, 1353, 1164, 962, 773 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{24}NO_2S$ $(M + H)^+$ 378.1528, found 378.1521.

7-Methyl-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19h):



White solid, mp. 112-113 ºC; R_f (hexane/EtOAc 10:1) 0.52; yield 98 mg, 52%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28 (s, 3 H), 2.40 (s, 3 H), 3.03 (dd, *J* = 12.0 and 7.8 Hz, 1 H), 3.66 (ddd, *J* = 12.0 Hz, 5.4 Hz and 1.2 Hz, 1 H), 4.13 (d, *J* = 15.0 Hz, 1 H), 4.25 (dd, *J* = 7.8 and 5.4 Hz, 1 H), 4.46 (d, *J* = 15.0 Hz, 1 H), 6.73 (d, *J* = 7.8 Hz, 1 H), 6.89 (d, *J* = 7.8 Hz, 2 H), 7.09-7.10 (m, 2 H), 7.22-7.29 (m, 5 H), 7.65 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 21.7, 45.1, 48.2, 51.3, 126.8, 127.2, 127.9, 128.1, 128.7, 129.1, 129.5, 129.9, 132.0, 133.3, 133.6, 136.5, 142.7, 143.8; IR (KBr, neat) 3027, 2922, 1599, 1499, 1455, 1350, 1164, 958, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{24}NO_2S$ $(M + H)^+$ 378.1528, found 378.1510.

5-Methyl-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19h'):

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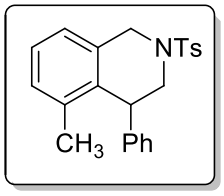
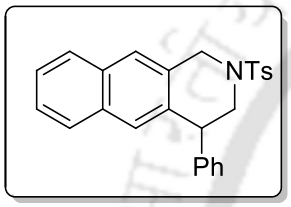


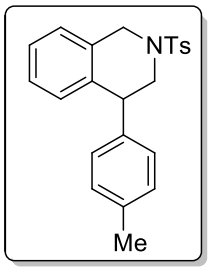
White solid, mp. 148-149 °C; R_f (hexane/EtOAc 10:1) 0.48; yield 49 mg, 26%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.94 (s, 3 H), 2.38 (s, 3 H), 3.16 (dd, *J* = 12.0 and 3.6 Hz, 1 H), 3.83 (ddd, *J* = 12.0 Hz, 2.4 Hz and 1.2 Hz, 1 H), 4.04 (d, *J* = 15.0 Hz, 1 H), 4.19 (t, *J* = 3 Hz 1 H), 4.61 (d, *J* = 15.0 Hz, 1 H), 6.98-7.00 (m, 4 H), 7.12-7.15 (m, 1 H), 7.19-7.23 (m, 5 H), 7.53 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.5, 21.7, 42.9, 47.9, 51.2, 124.3, 126.7, 127.0, 127.9, 128.5, 128.6, 129.2, 129.7, 132.4, 133.6, 133.8, 137.6, 142.5, 143.6; IR (KBr, neat) 3026, 2922, 1598, 1494, 1455, 1352, 1164, 962, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{24}NO_2S$ $(M + H)^+$ 378.1528, found 378.1515.

4-Phenyl-2-tosyl-1,2,3,4-tetrahydrobenzo[*g*]isoquinoline (19i):



White solid, mp. 150-152 °C; R_f (hexane/EtOAc 10:1) 0.49; yield 161 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3 H), 3.24 (dd, *J* = 11.6 and 4.0 Hz, 1 H), 3.99 (dd, *J* = 11.6 Hz and 1.2 Hz, 1 H), 4.18 (d, *J* = 15.2 Hz, 1 H), 4.74 (brs, 1 H), 4.77 (d, *J* = 15.2 Hz, 1 H), 7.05-7.08 (m, 2 H), 7.15-7.25 (m, 6 H), 7.29-7.39 (m, 2 H), 7.57 (d, *J* = 8.0 Hz, 2 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 42.2, 48.0, 51.1,124.1, 124.4, 125.7, 126.7, 126.8, 127.9, 128.0, 128.5, 128.6, 128.7, 129.7, 130.1, 130.2, 131.7, 132.9, 133.5, 143.1, 143.7; IR (KBr, neat) 3027, 2921, 1599, 1494, 1455, 1347, 1164, 970, 759 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{24}NO_2S$ $(M + H)^+$ 414.1528, found 414.1525.

4-(*p*-Tolyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19k):



White solid, mp. 154-156 °C; R_f (hexane/EtOAc 10:1) 0.50; yield 158 mg, 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 2.44 (s, 3 H), 3.02-3.06 (m, 1 H), 3.82 (dd, *J* = 11.4 Hz and 4.8 Hz, 1 H), 4.19 (d, *J* = 14.4 Hz, 1 H), 4.30 (t, *J* = 6.6 Hz, 1 H), 4.55 (d, *J* = 14.4 Hz, 1 H), 6.89 (d, *J* = 7.2 Hz, 1 H), 7.02-7.04 (m, 2 H), 7.09-7.14 (m, 4 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.69-7.71 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 21.7, 45.0, 48.2, 51.3, 126.3, 126.7, 127.0, 127.9, 129.0, 129.4, 129.6, 129.8, 132.0, 133.1, 136.77, 136.81, 139.5, 143.8; IR (KBr, neat) 3025, 2922, 1598, 1494, 1454, 1350, 1164, 958, 760 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{24}NO_2S$ $(M + H)^+$ 378.1528, found 378.1510.

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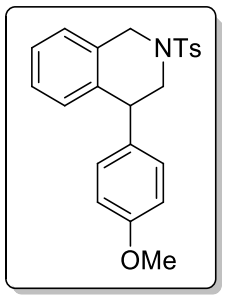
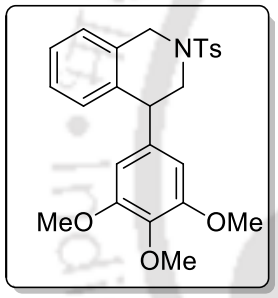
4-(4-Methoxyphenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19l):



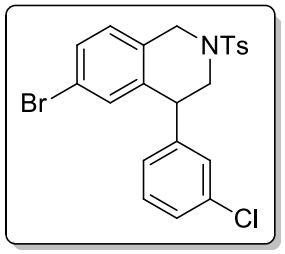
White solid, mp. 127-129 ^{o}C; R_f (hexane/EtOAc 10:1) 0.45; yield 165 mg, 84%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.02-3.06 (m, 1 H), 3.76-3.79 (m, 4 H), 4.19 (d, *J* = 14.4 Hz, 1 H), 4.26-4.28 (m, 1 H), 4.51 (d, *J* = 14.4 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 7.8 Hz, 1 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 7.08-7.10 (m, 2 H), 7.17 (t, *J* = 7.2 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.68 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 44.5, 48.1, 51.2, 55.3, 114.0, 126.3, 126.7, 127.0, 127.9, 129.6, 129.8, 130.0, 132.0, 133.2, 134.5, 136.8, 143.8, 158.7; IR (KBr, neat) 3026, 2925, 1610, 1511, 1457, 1350, 1163, 958, 759 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{24}NO_3S$ $(M + H)^+$ 394.1477, found 394.1460.

2-Tosyl-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (19m):



Pale yellow gummy liquid; R_f (hexane/EtOAc 10:1) 0.38; yield 195 mg, 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.08 (dd, *J* = 12.0 Hz and 8.0 Hz, 1 H), 3.76-3.84 (m, 10 H), 4.17-4.24 (m, 2 H), 4.48 (d, *J* = 14.8 Hz, 1 H), 6.34 (s, 2 H), 6.94 (d, *J* = 7.2 Hz, 1 H), 7.09-7.13 (m, 2 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.68 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6,45.6, 48.0, 51.0, 56.3, 60.9, 106.2, 126.3, 126.9, 127.1, 127.8, 129.6, 129.8, 132.0, 133.4, 136.3, 137.3, 138.2, 143.9, 153.3; IR (KBr, neat) 3014, 2934, 1592, 1505, 1459, 1339, 1163, 958, 760 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{28}NO_5S$ $(M + H)^+$ 454.1688, found 454.1670.

6-Bromo-4-(3-chlorophenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19n):



White solid, mp. 152-154 ^{o}C; R_f (hexane/EtOAc 10:1) 0.50; yield 169 mg, 71%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 3.09 (dd, *J* = 12.0 and 9.0 Hz, 1 H), 3.43 (ddd, *J* = 12.0 Hz, 4.8 Hz and 0.6 Hz, 1 H), 4.16 (d, *J* = 15.0 Hz, 1 H), 4.21-4.23 (m, 1 H), 4.39 (d, *J* = 15.0 Hz, 1 H), 6.98-7.00 (m, 3 H), 7.03 (s, 1 H), 7.22-7.32 (m, 5 H), 7.63 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 44.9, 47.7, 50.6, 121.1, 127.3, 127.8, 127.9, 128.2, 129.0, 130.0, 130.2, 130.4, 131.2, 132.4, 133.1, 134.7, 138.0, 143.9, 144.2; IR (KBr, neat) 3025, 2922, 1595, 1482, 1350, 1164,

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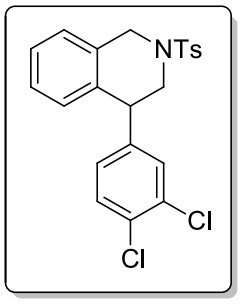
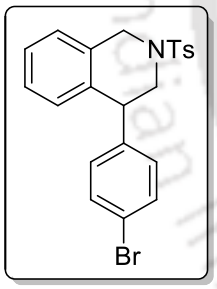
1092, 960, 759 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{20}BrClNO_2S$ $(M + H)^+$ 476.0087, found 476.0091.

4-(3,4-Dichlorophenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19o):



White solid, mp. 143-145 ^oC; R_f (hexane/EtOAc 10:1) 0.50; yield 155 mg, 72%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.21 (dd, *J* = 12.0 and 6.4 Hz, 1 H), 3.61 (dd, *J* = 12.0 Hz and 5.2 Hz, 1 H), 4.23 (t, *J* = 5.6 Hz, 1 H), 4.32 (d, *J* = 15.2 Hz, 1 H), 4.39 (d, *J* = 15.2 Hz, 1 H), 6.86 (d, *J* = 8.0 Hz, 1 H), 6.94 (dd, *J* = 8.4 Hz and 2.0 Hz, 1 H), 7.11-7.15 (m, 3 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 44.5, 47.9, 50.7, 126.7, 127.4, 127.5, 127.9, 128.5, 129.7, 129.9, 130.6, 130.8, 131.3, 132.2, 132.7, 133.3, 135.0, 143.2, 144.1; IR (KBr, neat) 3026, 2924, 1597, 1467, 1352, 1164, 1091, 958, 753 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{20}Cl_2NO_2S$ $(M + H)^+$ 432.0592, found 432.0589.

4-(4-Bromophenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19p):



White solid, mp. 105-107 ^oC; R_f (hexane/EtOAc 10:1) 0.50; yield 170 mg, 77%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 3.04-3.09 (m, 1 H), 3.57 (dd, *J* = 12.0 Hz and 5.2 Hz, 1 H), 4.15-4.20 (m, 2 H), 4.33 (d, *J* = 15.2 Hz, 1 H), 6.76 (d, *J* = 7.6 Hz, 1 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 7.00-7.03 (m, 2 H), 7.10 (t, *J* = 7.2 Hz, 1 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.55 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 44.8, 48.0, 50.9, 121.1, 126.5, 127.1, 127.3, 127.9, 129.7, 129.9, 130.7, 131.8, 132.1, 133.2, 135.7, 141.8, 144.0; IR (KBr, neat) 3028, 2922, 1596, 1487, 1349, 1168, 1091, 959, 772 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{21}BrNO_2S$ $(M + H)^+$ 442.0476, found 442.0467.

4-(4-Fluorophenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19q):

White solid, mp. 127-129 ^oC; R_f (hexane/EtOAc 10:1) 0.50; yield 139 mg, 73%; ^1H NMR (600 MHz, $CDCl_3$) δ 2.40 (s, 3 H), 3.13 (dd, *J* = 12.0 and 7.8 Hz, 1 H), 3.66 (dd, *J* = 12.0 Hz and 5.4 Hz, 1 H), 4.24-4.27 (m, 2 H), 4.41 (d, *J* = 15.0 Hz, 1 H), 6.84 (d, *J* = 7.8 Hz, 1 H), 6.93-6.96 (m, 2 H), 7.05-7.07 (m, 2 H), 7.09 (d, *J* = 7.8 Hz, 2 H), 7.17 (t, *J*

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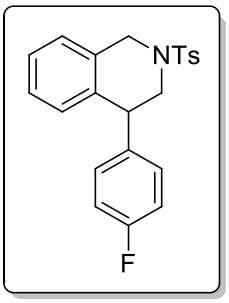
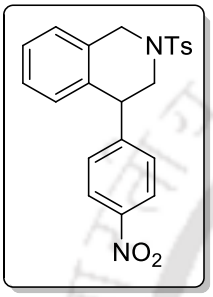


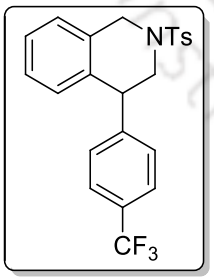
= 7.8 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.65 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 44.5, 48.1, 51.1, 115.5 (d, *J* = 21.15 Hz), 126.4, 127.0, 127.2, 127.8, 129.6, 129.9, 130.5 (d, *J* = 7.95 Hz), 132.0, 143.9, 162.0 (d, *J* = 243.90 Hz); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 46.01; IR (KBr, neat) 3029, 2923, 1602, 1508, 1455, 1350, 1164, 1092, 958, 762 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{21}FNO_2S$ $(M + H)^+$ 382.1277, found 382.1273.

4-(4-Nitrophenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19r):



Pale yellow semi-solid; R_f (hexane/EtOAc 10:1) 0.50; yield 131 mg, 67%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 3.38 (dd, *J* = 12.0 and 6.0 Hz, 1 H), 3.55 (dd, *J* = 12.0 Hz and 4.8 Hz, 1 H), 4.31 (d, *J* = 15.0 Hz, 1 H), 4.37-4.39 (m, 1 H), 4.42 (d, *J* = 15.0 Hz, 1 H), 6.85 (d, *J* = 7.2 Hz, 1 H), 7.12-7.16 (m, 2 H), 7.23 (t, *J* = 7.2 Hz, 1 H), 7.26-7.30 (m, 4 H), 7.63 (d, *J* = 7.8 Hz, 2 H), 8.12 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ21.7, 45.1, 48.0, 50.6, 124.0, 126.8, 127.59, 127.63, 127.9, 129.8, 129.9, 130.0, 132.2, 133.2, 134.6, 144.2, 147.2, 150.5; IR (KBr, neat) 3027, 2925, 1601, 1524, 1345, 1160, 958, 770 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{21}N_2O_4S$ $(M + H)^+$ 409.1222, found 409.1219.

2-Tosyl-4-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (19s):



White solid, mp. 135-137 ^{o}C; R_f (hexane/EtOAc 10:1) 0.50; yield 141 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 3.23 (dd, *J* = 12.0 and 6.8 Hz, 1 H), 3.65 (dd, *J* = 12.0 Hz and 4.8 Hz, 1 H), 4.29-4.36 (m, 2 H), 4.40 (d, *J* = 14.8 Hz, 1 H), 6.84 (d, *J* = 7.6 Hz, 1 H), 7.09-7.13 (m, 2 H), 7.19-7.22 (m, 3 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 45.1, 48.0, 50.8, 125.9 (q, *J* = 213.1 Hz), 125.7 (q, *J* =3.75 Hz), 126.6, 127.3, 127.4, 127.9, 129.4, 129.5 (q, *J* =32.1 Hz), 129.7, 129.9, 132.2, 133.2, 135.4, 144.1, 146.9; ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 99.32; IR (KBr, neat) 3028, 2925, 1618, 1495, 1456, 1325, 1164, 1092, 959, 759 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{21}F_3NO_2S$ $(M + H)^+$ 432.1245, found 432.1221.

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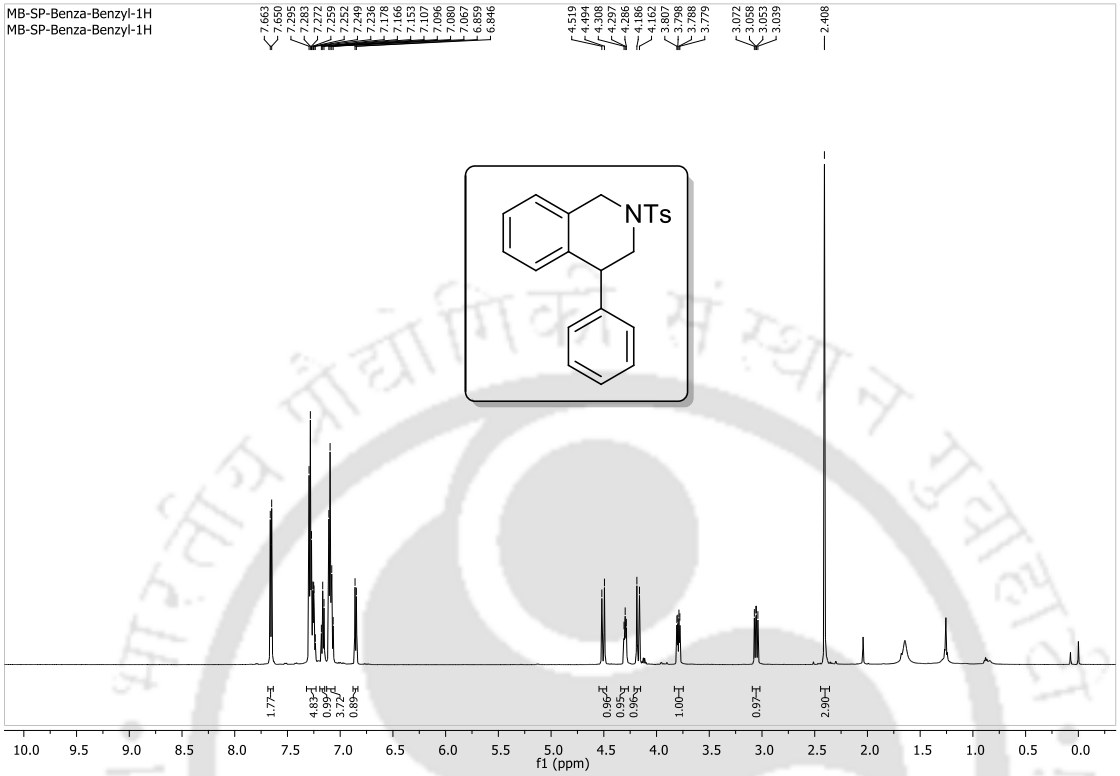
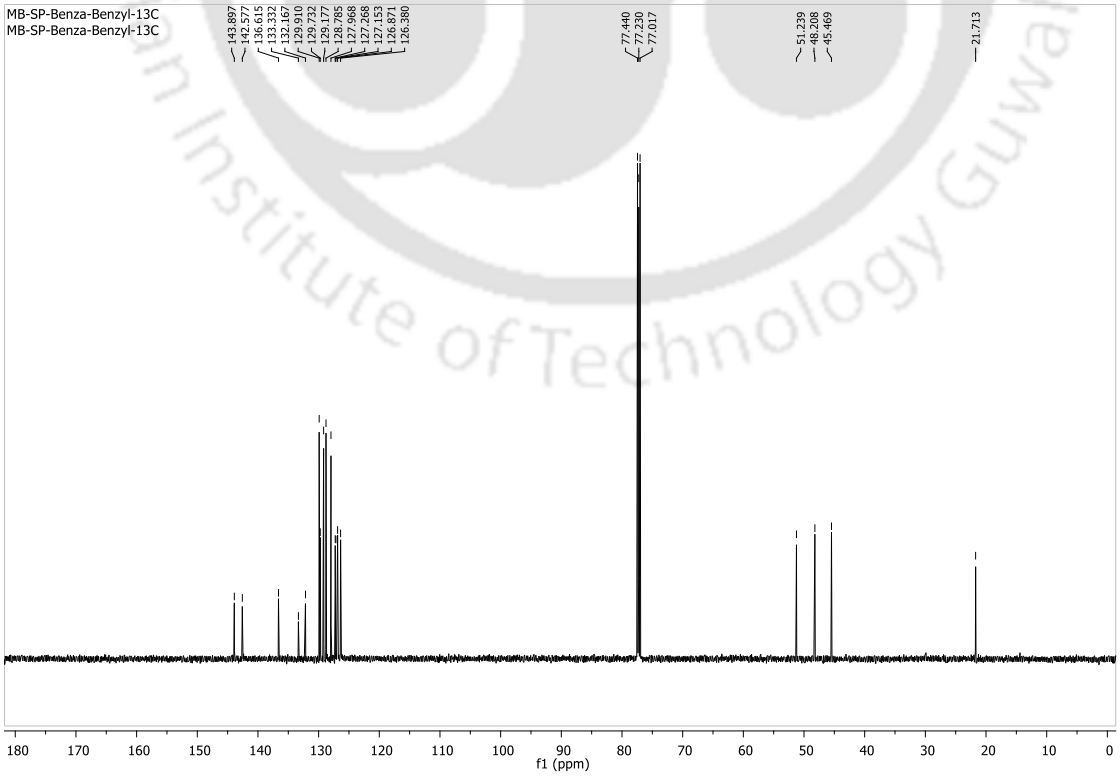
5.8. Selected spectra of substituted tetrahydroisoquinolines

(4-Phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19a):





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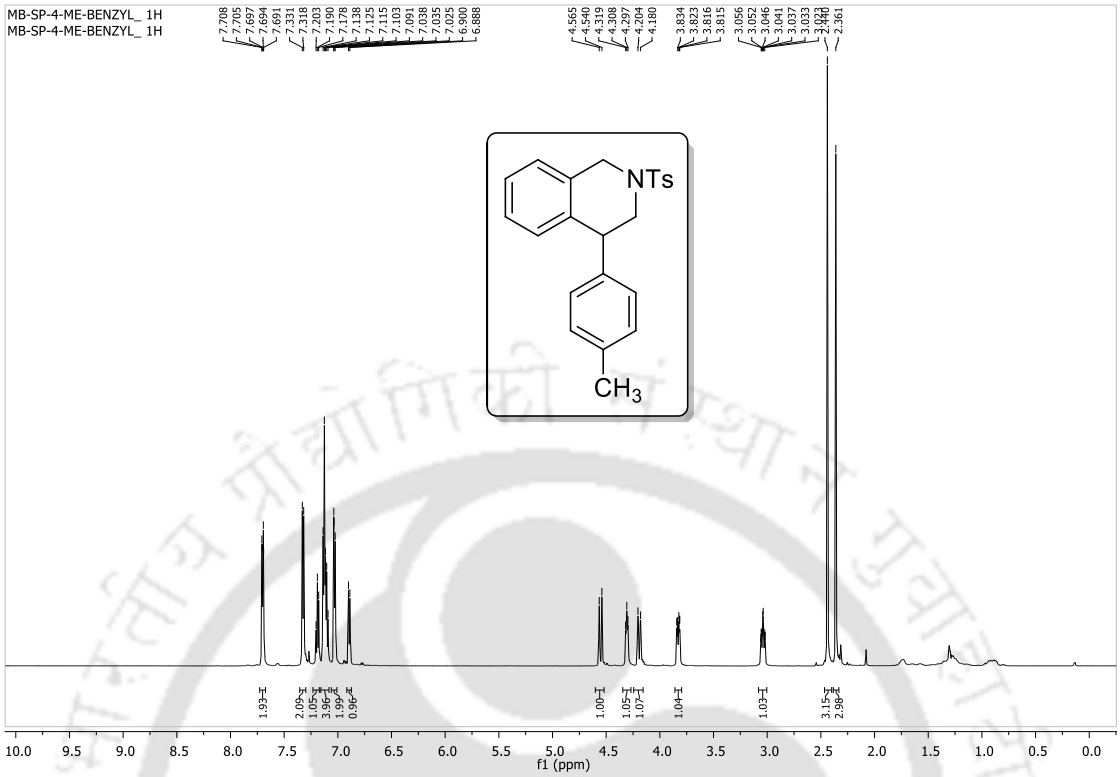
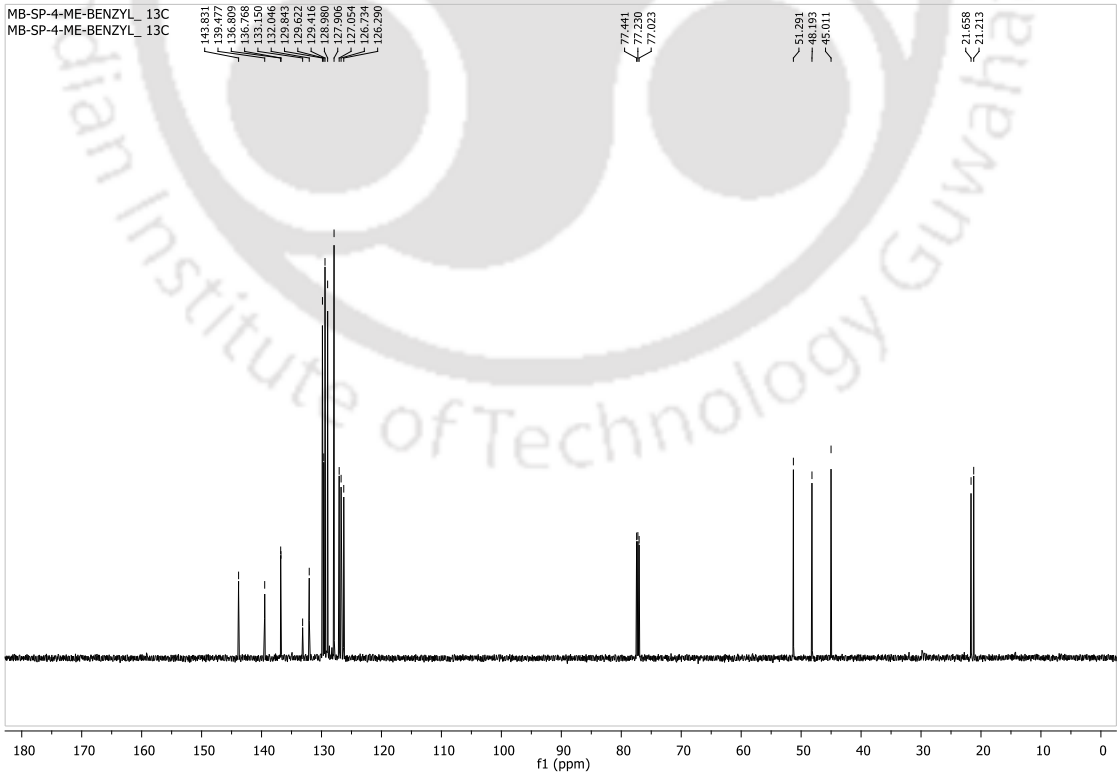
4-(*p*-Tolyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (19k):





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List of Publications

1. "Diastereoselective Synthesis of Substituted Tetrahydro-thiophenes and -thiopyrans *via* Thia-Prins Cyclization Reaction" **Borah, M.**; Gogoi, P.; Indukuri, K.; Saikia, A. K. *J. Org. Chem.* **2015**, *80*, 2641-2648.
2. "Diastereoselective Synthesis of Substituted Morpholines from *N*-Tethered Alkenols: Total Synthesis of (±)-Chelonin A" **Borah, M.**; Borthakur, U.; Saikia, A. K. *J. Org. Chem.* **2017,** *82*, 1330-1339.
3. "$FeCl_3$-Mediated Carbenium Ion Induced Intramolecular Cyclization of *N*-Tethered Alkyne-Benzyl Alkanols" **Borah**, **M.**; Saikia, A. K. *ChemistrySelect*, **2018**, *3*, 2162-2166.
4. "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.
5. "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.
6. "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.
7. "Piper-Betle-Shaped Nano-S-Catalyzed Synthesis of 1-Amidoalkyl-2-naphthols under Solvent-Free Reaction Condition: A Greener "Nanoparticle-Catalyzed Organic Synthesis Enhancement" Approach" Das, V. K.; **Borah, M.**; Thakur, A. J. *J. Org. Chem.* **2013**, *78*, 3361-3366.

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