Use of 3-Halobut-3-en-1-ol and N-(3-Halobut-3-en-1-yl)-4-Methylbenzenesulfonamide in the Prins Reaction: Access to Oxygen and Nitrogen Heterocycles

A Dissertation Submitted in Partial Fulfilment for the

Degree of

Doctor of Philosophy

Submitted by

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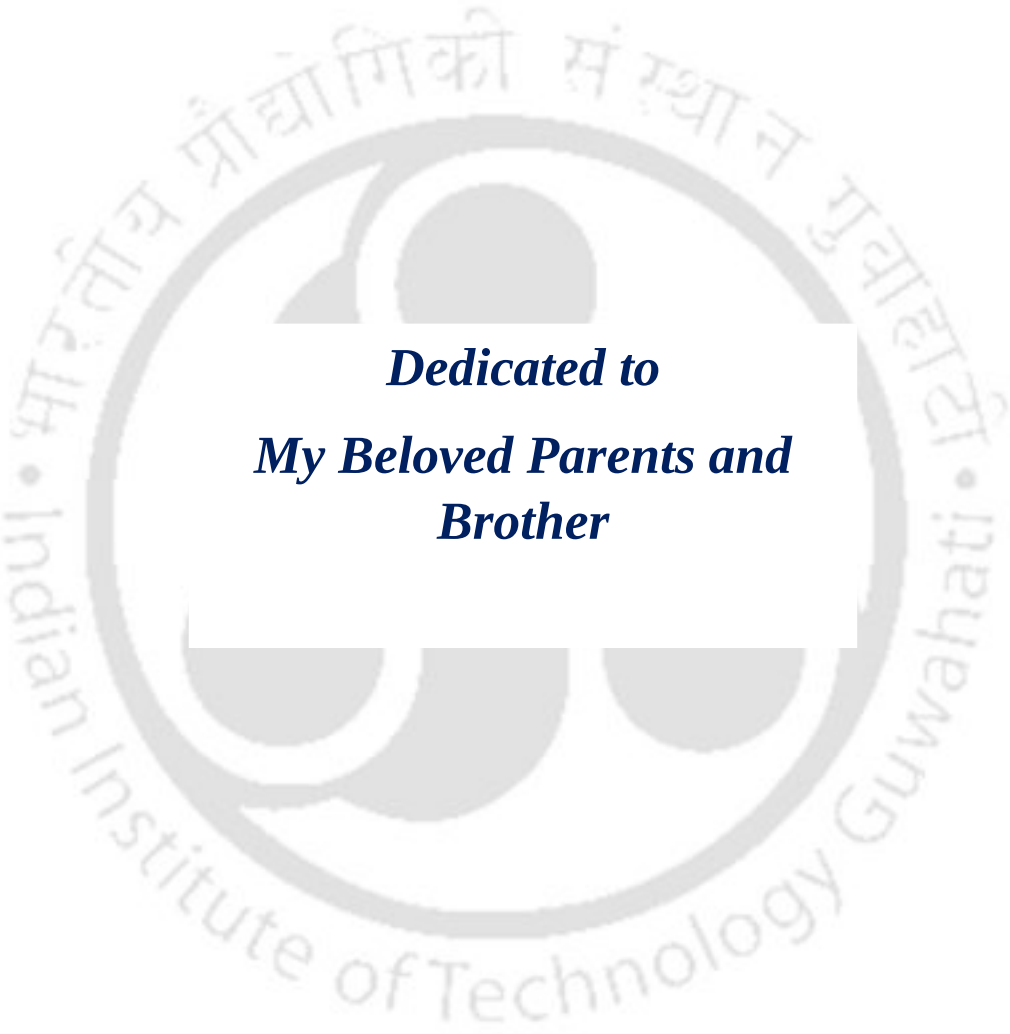

Dedicated to

My Beloved Parents and Brother

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "***Use of 3-Halobut-3-en-1-ol and N-(3-Halobut-3-en-1-yl)-4-Methylbenzenesulfonamide in the Prins Reaction: Access to Oxygen and Nitrogen Heterocycles"*** is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Prof. 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.

July, 2025

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CERTIFICATE

This is to certify that **Surjya Kumar Bora** has been working under my supervision since July 2019 as a regular registered Ph. D. student. I am forwarding his thesis entitled "***Use of 3-Halobut-3-en-1-ol and N-(3-Halobut-3-en-1-yl)-4-Methylbenzenesulfonamide in the Prins Reaction: Access to Oxygen and Nitrogen Heterocycles***" being submitted to the Indian Institute of Technology, Guwahati for the award of Doctor of Philosophy in Chemistry. I certify that he has fulfilled all the requirement 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.

July, 2025
IIT Guwahati

Prof. Anil K. Saikia
Supervisor

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Above all, I owe it all to the Almighty Lord for granting me the wisdom, health, and strength to undertake this research life and the completion of this difficult yet fulfilling journey.

Sincerely,

Surjya

LIST OF ABBREVIATIONS

Ac	Acetyl	HMPA	Hexamethylphosphoramide
AcOH	Acetic acid	$HNTf_2$	Bis(trifluoromethane-sulfonyl)imide
AIBN	Azobisisobutyronitrile		
AR grade	Analytical Reagent grade	HRMS	High resolution mass spectrometry
Bn	benzyl		
Boc	*tert*-Butyloxycarbonyl	IR	Infrared
Bu	Butyl	*m*-CPBA	*meta*-chloroperbenzoic acid
Cbz	Carboxybenzyl	mp	melting point
CCDC	Cambridge Crystallographic Data Centre	m/z	mass to charge ratio
		NaHDMS	Sodium bis(trimethylsilyl)-amide
c.HCl	Concentrate HCl		
CoPc	Cobalt Phthalocyanine	NCS	*N*-chlorosuccinimide
CSA	camphorsulfonic acid	NHC	N-heterocyclic carbene
Cy	cyclohexyl	Ph	Phenyl
DABCO	1,4-diazabicyclo-[2.2.2]octane	ppm	parts per million
		p-TSA	p-toluenesulfonic acid
DBU	1,8-Diazabicyc-lo(5.4.0)undec-7-ene	Q-TOF	Quadrupole Time-of-Flight
		R_f	Retention Factor
DCM	Dichloromethane	SSRI	Selective Serotonin Reuptake Inhibitors
DCE	1,2-dichloroethane		
de	diastereomeric excess	TBHP	*tert*-Butyl hydroperoxide
DFT	Density Functional Theory	^{t}Bu	*tert*- Butyl
DMF	N, N-Dimethylformamide	TBHP	*tert*-Butyl hydroperoxide
DMSO	Dimethyl Sulfoxide	TfOH	trifluoromethanesulfonyl acid
ee	enantiomeric excess	TFA	Trifluoroacetic acid
Et	Ethyl	THF	Tetrahydrofuran
$Fe(TMHD)_3$	Tris(2,2,6,6-tetramethyl-3,5- heptanedionato)iron(III)	TLC	Thin layer chromatography
		TMS	trimethylsilyl
FTIR	Fourier Transform Infrared Spectroscopy	Ts	*p*-toluenesulfonyl
		XRD	X-ray Diffraction
GF254	Gypsum and Fluorescent 254		

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

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

Abstract

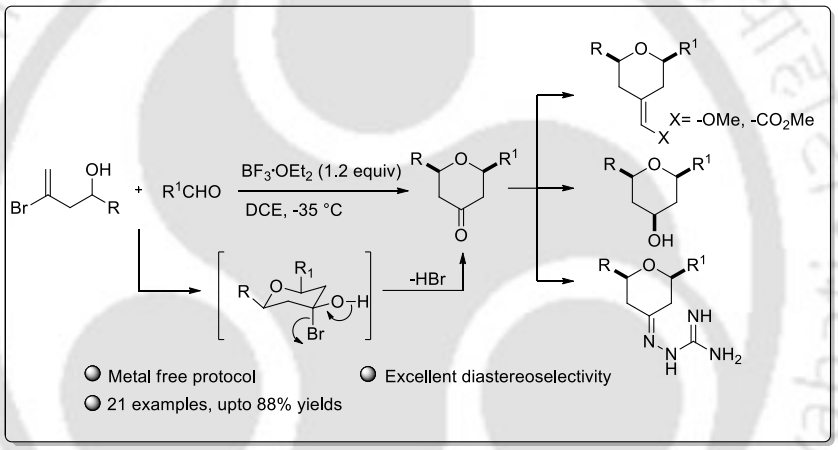
The content of this thesis, entitled "Use of 3-Halobut-3-en-1-ol and *N*-(3-Halobut-3-en-1-yl)-4-Methylbenzenesulfonamide in the Prins Reaction: Access to Oxygen and Nitrogen Heterocycles," is systematically organized into five chapters, each reflecting the outcomes of the experimental investigations conducted throughout the research period. Chapter **1** provides an overview of heterocyclic compounds and their biological significance and summarizes the reported methodologies for their synthesis. Chapter **2** focuses on the diastereoselective synthesis of 2,6-disubstituted tetrahydropyranones through Prins cyclization of 3-bromobut-3-en-1-ols and aldehydes. Chapter **3** describes the stereoselective synthesis of *gem*-dihalopiperidines through halo-aza-Prins cyclization reaction of halogenated homoallylic amine and aldehydes. Chapter **4** presents $BF_3{\cdot}OEt_2$ mediated cascade synthesis of 4*H*-3,1-Benzoxazines from 2-azidobenzaldehydes and homoallylic alcohols. Finally, Chapter **5** elaborates on the use of halogenated homoallylic amine for the highly diastereoselective synthesis of gem-dihalopiperidines and regioselective synthesis of 4-halo-1,2,3,6-tetrahydropyridines.

Chapter 1: Introduction to Heterocycles and Prins Reaction

Heterocyclic compounds are commonly found in a wide range of natural products and serve as valuable synthetic intermediates. Many vitamins, alkaloids, proteins, natural dyes, enzymes, drugs, etc. contain oxygen or nitrogen heterocyclic moieties. Various strategies for the construction of oxygen- and nitrogen-containing heterocycles are present in the literature, mostly including Diels-Alder reaction, oxonium-ene, Prins cyclizations, transition metal catalyzed cyclization, radical cyclization reactions, reductive amination, etc. Out of these stated methods, this thesis mainly focuses on Prins cyclization and retro-Prins reaction for the construction of six-membered oxygen and nitrogen heterocycles.

Chapter 2: Diastereoselective Synthesis of 2,6-Disubstituted Tetrahydro-pyranones *via* Prins Cyclization of 3-Bromobut-3-en-1-ols and Aldehydes

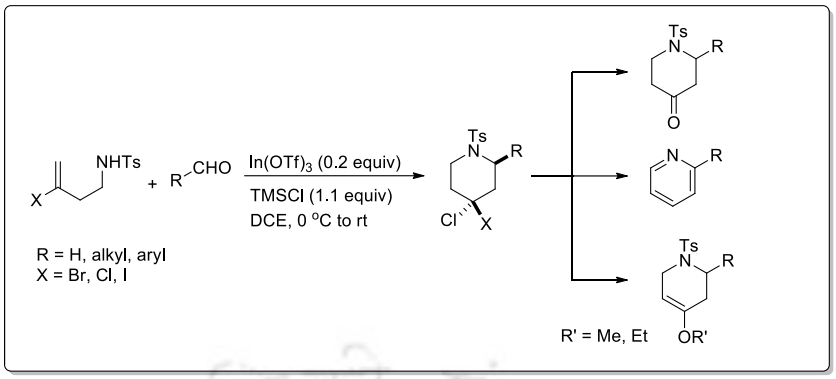
Chapter-2 describes an efficient synthetic strategy for accessing 2,6-disubstituted tetrahydropyranones from 3-bromobut-3-en-1-ols and aldehydes *via* Prins cyclization reactions. Late-stage modification was carried out for the synthesis of enol ether, ester derivatives, and 4-hydroxy 2,6-disubstituted tetrahydropyran with 2,4- and 4,6-*cis* configuration. The methodology is further extended for the synthesis of aminoguanidine derivatives, which are considered as anticancer agents.



J. Org. Chem. **2023,** *88,* 3012-3021

Chapter 3: Stereoselective Synthesis of gem-Dihalopiperidines *via* Halo-Aza-Prins Cyclization Reaction: Access to Piperidin-4-ones and Pyridines

Chapter-3 highlights an efficient methodology for the synthesis of 4,4-dihalopiperidine derivatives that has been developed from *N*-(3-halobut-3-en-1-yl)-4-methylbenzenesulfonamide and aldehyde, catalyzed by $In(OTf)_3$ in excellent yields. The dihalopiperidine is converted to tetrahydropiperidinone using Ac_2O/Et_3N in DCM/H_2O (1:1). It is also utilized for the synthesis of pyridine scaffold by treatment with DBU. Further, the dihalopiperidine is transformed to its enol ether derivatives using KOH in alcohol.



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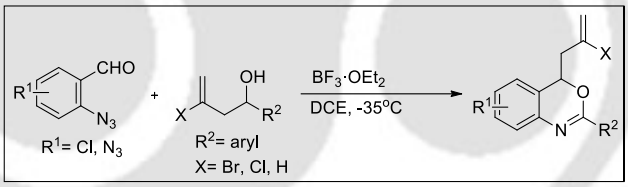
Chapter 4: $BF_3{\cdot}OEt_2$ Mediated Cascade Synthesis of 4*H*-3,1-Benzoxazines from 2-Azidobenzaldehydes and Homoallylic Alcohols

In this chapter, we developed a methodology for the synthesis of 4*H*-3,1-benzoxazine derivatives by utilizing 2-azidobenzaldehydes and homoallylic alcohols in the presence of $BF_3{\cdot}OEt_2$ in moderate to good yields. In addition, the method was successfully applied for the synthesis of triazole compounds *via* click reaction.

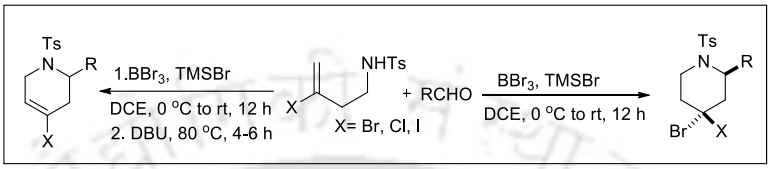


J. Org. Chem. **2025**, *90*, 6443−6453

Chapter 5: Selective Synthesis of *gem*-Dihalopiperidines and 4-Halo-1,2,3,6-Tetrahydropyridines from Halogen Substituted Homoallylic Benzene-sulfonamides and Aldehydes

In Chapter-5, we established an effective approach for the diastereoselective synthesis of gem-dihalopiperidine derivatives *via* aza Prins cyclization and also regioselective synthesis of 4-halo-1,2,3,6-tetrahydropyridines *via* a one-pot process involving aza Prins cyclization followed by elimination using halogen-substituted homoallylic benzenesulfonamide and aldehyde. The

dihalogen moiety of gem-dihalopiperidines can be easily converted to ketone, giving good yields. Additionally, gem-dihalopiperidines can be converted into a pyridine scaffold by the use of DBU, and also 4-halo-1,2,3,6-tetrahydropyridines can be employed to afford their corresponding Sonogashira coupling products.



RSC Adv. **2025**, *15*, 21257

CONTENTS

Chapter 1:

1. Introduction to Heterocycles and Prins Cyclization Reaction

1.1 General Background

Organic molecules are classified into two main categories: acyclic and cyclic compounds. Cyclic compounds that consist solely of a carbon framework are referred to as carbocyclic, while those with a carbon skeleton and at least one heteroatom (commonly nitrogen (N), oxygen (O), and sulfur (S)) are referred to as heterocyclic. Many vitamins, alkaloids, proteins, natural dyes, enzymes and drugs contain oxygen- or nitrogen-heterocyclic moieties. Based on their electronic and structural arrangements, heterocycles are categorized as aromatic and aliphatic heterocycles. Aromatic heterocycles are those heterocycles that follow Huckel's rule. According to this rule, the compounds are said to be aromatic if it is cyclic, planar geometry, fully conjugated and contain (4n+2) π electrons in their system. Examples include pyrrole **I**, furan **II**, thiophene **III**, thiazole **IV**, imidazole **V**, pyridine **VI**, pyridone **VII,** pyridazine **VIII**, pyrimidine **IX**, and pyrazine **X** (*Figure 1.1.1*).

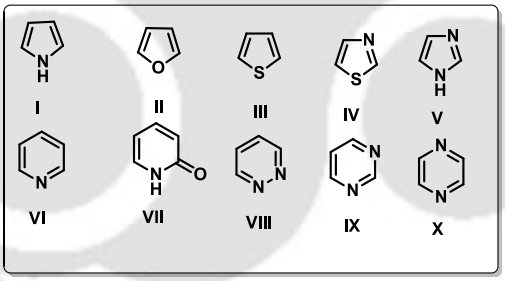


Figure 1.1.1

Conversely, aliphatic heterocycles are heterocycles that lack any double bonds. e.g., such as aziridine **XI**, oxirane **XII**, thiirane **XIII**, azetidine **XIV**, oxetane **XV**, thietene **XVI**, pyrrolidine **XVII**, tetrahydrofuran **XVIII**, tetrahydrothiophene **XIX**, piperidine **XX**, tetrahydropyran **XXI**, tetrahydrothiopyran **XXII** (*Figure 1.1.2*).

Heterocycles are a fundamental area of organic chemistry, with increasing research interest due to their antimicrobial, medicinal and industrial applications. They are essential in the synthesis of various natural compounds such as nucleic acids, the oxygen-transport protein haemoglobin and

the photosynthetic pigment chlorophyll.[1] Due to their prevalence, the synthesis of these compounds remains a significant area of interest for chemists.

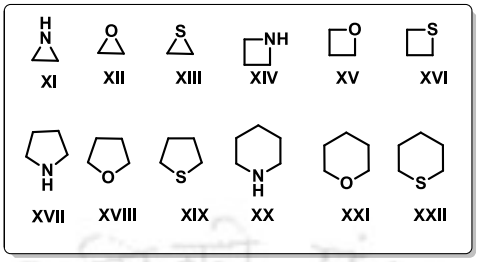


Figure 1.1.2

1.2 Importance of Tetrahydropyran, Piperidine and Benzoxazines

The pyran is a six-membered heterocycle that contains oxygen (O). The terms tetrahydro and dihydro are commonly used to indicate fully or partially reduced forms of unsaturated compounds. Most pharmaceuticals and natural products contain a functionalized tetrahydropyran moiety.[2] For

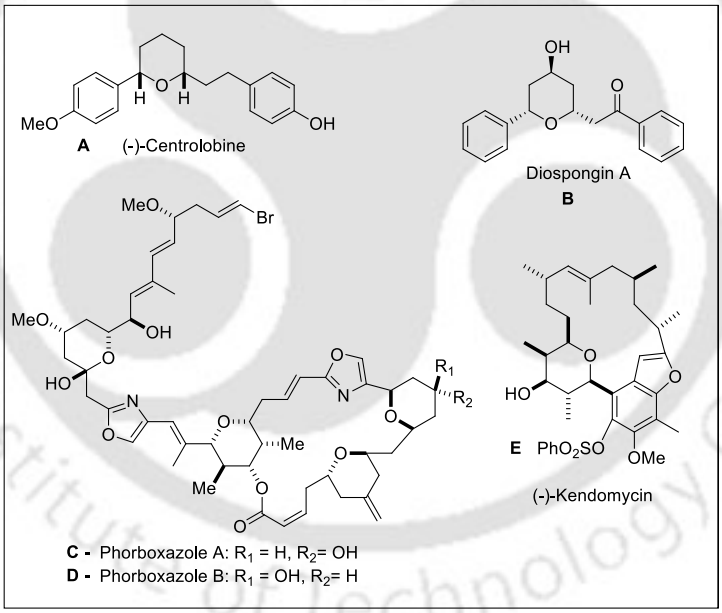


Figure 1.2.1: Some bio-active tetrahydropyrans.

example, tetrahydropyran-based compounds like (–)-centrolobine (**A**), isolated from the stem of *Brosinum potabile* and heartwood of *Centrolobium robustum* tree, show activity against Leishmania amazonensis promastigotes.[3] Similarly, Diospongin A (**B**), extracted from *Discorea spongiosa* rhizomes has been identified for its anti-osteoporotic effects.[4] Phorboxazoles A (**C**) & Phorboxazoles B (**D**) are also effective antineoplastic and antifungal agents.[5] Another

compound (-)-Kendomycin (**E**) shows anti-osteoporotic properties and serves as a potent antagonist of the endothelin receptor (*Figure 1.2.1*).[6]

Similarly, the piperidine motif is a six-membered saturated nitrogen-containing heterocycle. They are highly present in drug molecules and natural products, which makes their synthesis more demanding.[7] For example, Pergolide (**F**) provides clinical benefits in Parkinson's disease through the stimulation of dopamine D1 and D2 receptors.[8a-b] The Next one is a commonly used painkiller, morphine (**G**).[8c] (-)-Pelletierine (**H**), derived from the root bark of pomegranate (Punica granatum), is effective due to its anthelmintic properties.[9] Similar kind of piperidine alkaloid, α-conine (**I**), isolated from hemlock Conium maculatum, is a powerful poison.[10] Prosophylline (**J**), extracted from different species of Prosopis, has demonstrated anaesthetic and antibiotic properties.[11] Indalpine(**K**) is an SSRI antidepressant, developed by the Paris-based firm Pharmuka in 1977 (*Figure 1.2.2*).[12]

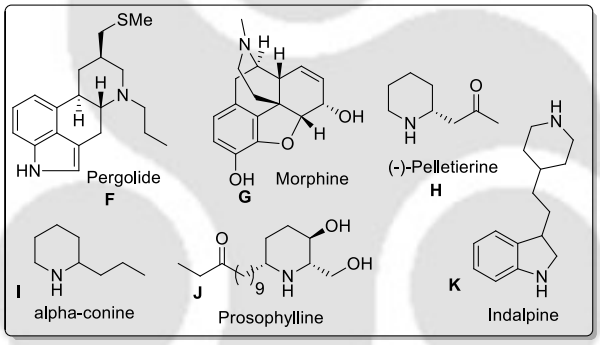


Figure 1.2.2: Some bio-active piperidine-containing molecules.

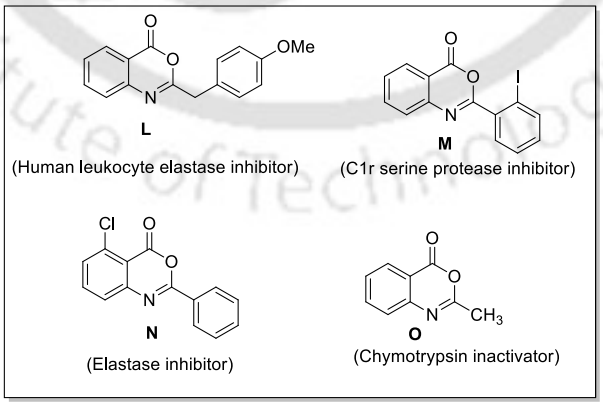
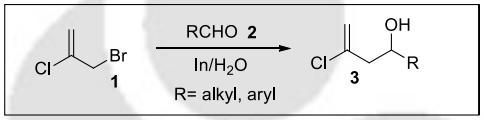


Figure 1.2.3: Some bio-active benzoxazines *containing molecules.*

Benzoxazines are bicyclic compounds that have a benzene ring fused to an oxazine ring. They are present in many bioactive molecules and various natural products. This scaffold has been used as a fungicide, a progesterone, and an anticonvulsant drug.[13] They are prevalent in various biologically active molecules, such as human leukocyte elastase inhibitors **L**,[14] C1r serine protease inhibitors **M**,[15] elastase inhibitors **N**,[15a,16] chymotrypsin inactivators **O**,[17] and others (*Figure 1.2.3).*

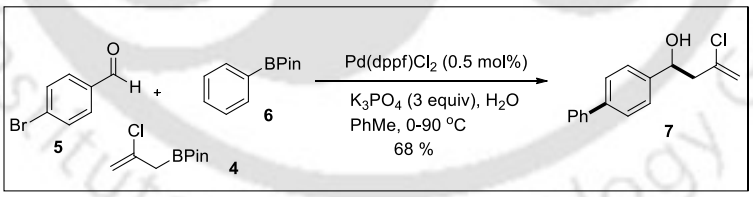
1.3 An Overview for the Synthesis of 3-Halobut-3-en-1-ol Derivatives Because of their widespread applications

Yi and colleagues documented the synthesis of 3-chloro-1-substituted-but-3-en-1-ol (**1**) by using 3-bromo-2-chloro-l-propene (**1**) and aldehydes (**2**) with Indium in water at ambient temperature (*Scheme 1.3.1*).[18]



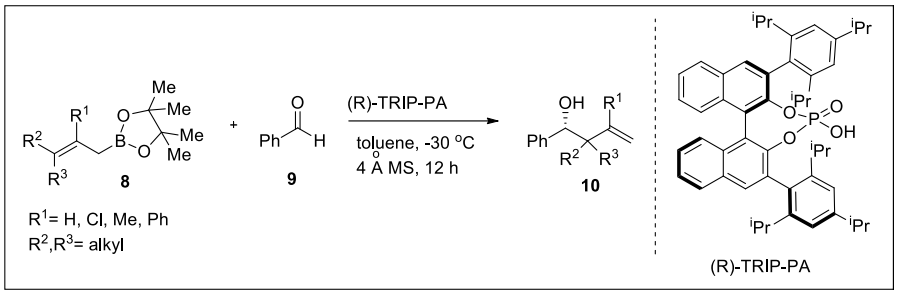
Scheme 1.3.1

In 2017, Watson and co-worker synthesized 1-([1,1'-biphenyl]-4-yl)-3-chlorobut-3-en-1-ol (**7**) by the reaction of 2-(2-chloroallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4**), 4-bromobenzaldehyde (**5**), and 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6**) promoted by $Pd(dppf)Cl_2$ and K_3PO_4 (*Scheme 1.3.2*).[19]



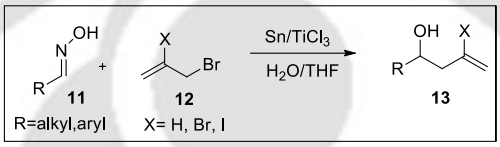
Scheme 1.3.2

In 2022, Yuan and colleagues documented the formation of 3,4-anti/syn homoallylic alcohols (**10**) in a manner that exhibits high enantioselectivity and diastereoselectivity, utilizing *β,γ*-substituted allylboronates (**8**) and aldehydes (**9**) catalyzed by chiral phosphoric acid (*Scheme 1.3.3*).[20]



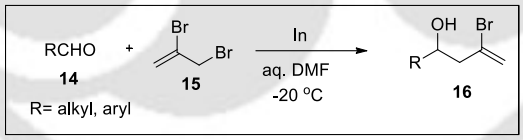
Scheme 1.3.3

Lin *et al.* synthesized homoallylic alcohols (**13**) from aldoximes (**11**) and other allylic halides (**12**), mediated by Sn/$TiCl_3$ in H_2O/THF (*Scheme 1.3.4*).[21]



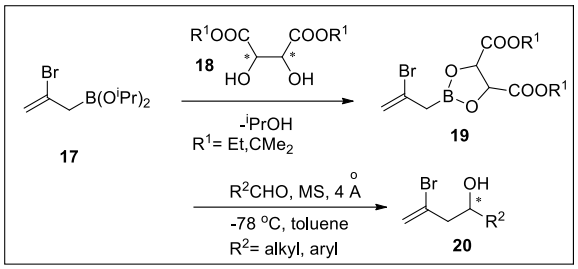
Scheme 1.3.4

In 2011, Kim *et al*. developed an efficient methodology for synthesizing 2-bromohomoallylic alcohols (**16**) using 2,3-dibromopropene (**15**) and aldehydes (**14**), mediated by indium *via* Barbier reaction. To prevent the decomposition of the 2-bromoallylindium intermediate into allene, the reactions were carried out at low temperature (*Scheme 1.3.5*).[22]



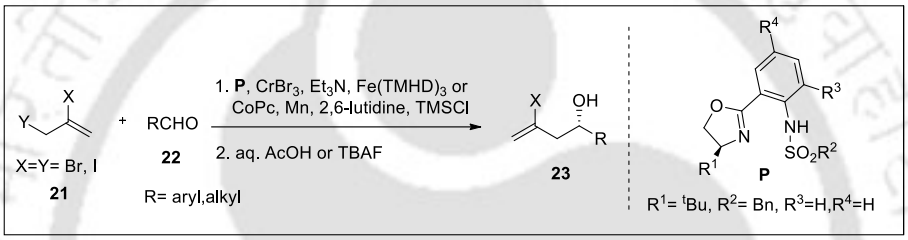
Scheme 1.3.5

Hara *et al.* synthesized 2-halohomoallylic alcohols (**20**) in an asymmetric manner through a two-step process. First, they prepared tartrate ester of (2-bromoallyl)boronic acid (**19**) from (2-bromoallyl)boronic acid (**17**) and dialkyl tartrates (**18**); these intermediates subsequently reacted with aldehydes to give the desired chiral 2-halohomoallylic alcohols (**20**) (*Scheme 1.3.6*).[23]



Scheme 1.3.6

Kishi and group reported the enantioselective synthesis of 3-halohomoallylic alcohols (**23**) mediated by Fe/Cr and Co/Cr systems, using 2-haloallyl halides (**21**) and aldehydes (**22**) as starting materials (*Scheme 1.3.7*).[24]



Scheme 1.3.7

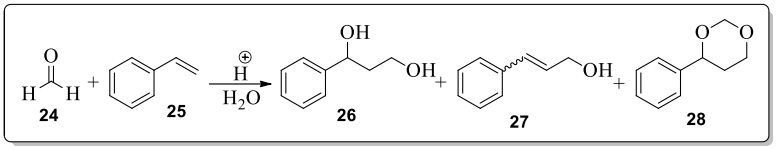
1.4 A Comprehensive Review of the Synthesis of oxygen and nitrogen heterocycles

The existence of oxygen and nitrogen heterocycles in natural products makes their synthesis a valuable area of interest for many researchers. Multiple strategies for the development of oxygen- and nitrogen heterocycles are present in the literature, including Diels-Alder reaction, oxonium-ene, Prins cyclizations, reductive amination, etc.[25] Out of these stated methods, this thesis mainly concentrates on Prins and aza-Prins cyclization for the synthesis of six-membered oxygen and nitrogen heterocycles.

1.4.1. Prins reaction

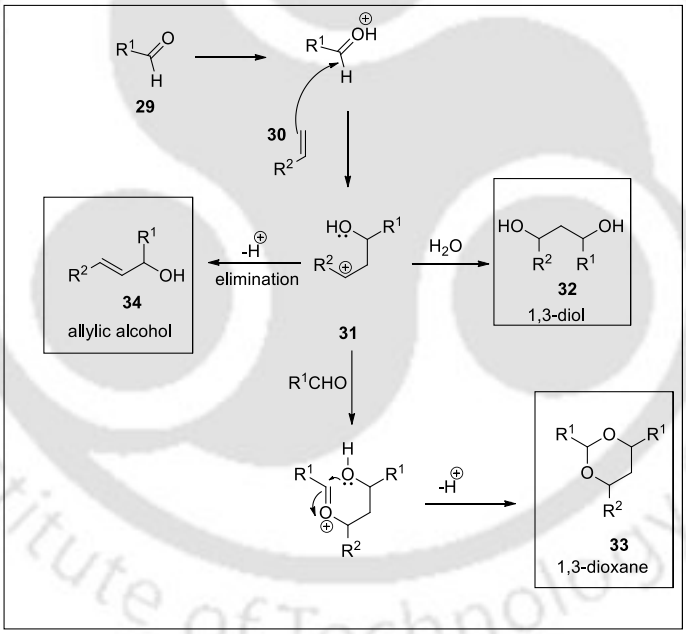
Hendrik Jacobus Prins, a Dutch chemist, first reported the Prins reaction in 1919. It is the electrophilic addition of a carbonyl compound to an alkene or alkyne under acidic conditions. Initially, he conducted the reaction between formaldehyde (**24**) and styrene (**25**) in water, resulting in the formation of 1,3-butane diol **26**, an unsaturated alcohol **27**, and 1,3-dioxane **28** (*Scheme 1.4.1.1*).[26] Depending on the reaction conditions, the Prins reaction can give various products.

Therefore, it is essential to maintain the experimental parameters to ensure the selective formation of the desired product.



Scheme 1.4.1.1

The overall mechanism is illustrated in *Scheme 1.4.1.2*. Under acidic conditions, an alkene **30** reacts with a carbonyl compound **29** to generate a stable intermediate, *β*-hydroxy carbocation **31**. This intermediate **31** can then interact with an additional molecule of aldehyde to yield 1,3-dioxane **33**, lose a proton to yield the unsaturated alcohol **34,** or react with a solvent such as water to give 1,3-diol adduct **32.**

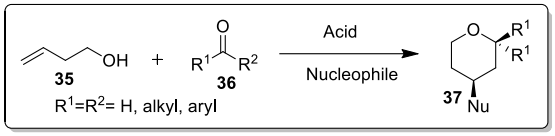


Scheme 1.4.1.2

1.4.2 Prins cyclization reaction

Initially, the Prins reaction was limited by its low chemo- and regio-selectivity, leading to the generation of numerous products. Therefore, its use in organic synthesis is limited compared to other well-developed selective reagents.[27] So, Prins reaction has been largely replaced by its

modified version, the Prins cyclization. In recent years, it has become a valuable method for the stereoselective construction of the tetrahydropyran scaffold, a prevalent structural feature in

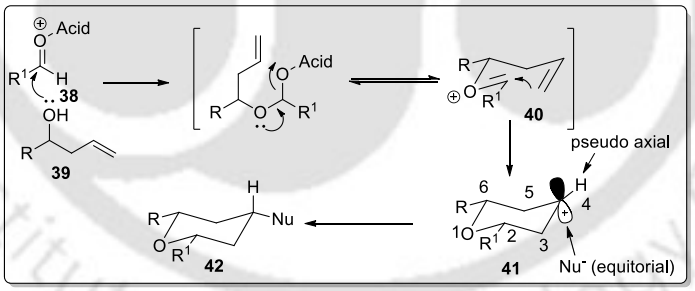


Scheme 1.4.2.1: Prins cyclization

numerous natural products.[28] In 1955, Hanschke was the first, who was able to show that 3-buten-1-ol (**35**) reacts with different aldehydes and ketones **36** by using either a Lewis or Brønsted acid to obtain stereochemically defined tetrahydropyran rings **37** by Prins cyclization (*Scheme 1.4.2.1*).[29] Subsequent research identified homoallylic alcohol as a crucial intermediate in this reaction, which has gradually developed into a powerful tool for synthesizing tetrahydropyran moieties.

1.4.3 Mechanistic studies for Prins cyclization

In most cases, the Prins cyclization reaction offers very high diastereoselectivity, resulting in the formation of 2,4,6-substituted tetrahydropyrans **42** with all substituents occupying equatorial positions. The diastereoselectivity observed is detailed below (*Scheme 1.4.3.1*).[30]



Scheme 1.4.3.1: Mechanism of Prins cyclization

The general mechanism is depicted in *Scheme 1.4.3.1*. Under the influence of an acid, homoallylic alcohol **39** interacts with aldehyde **38** to generate oxocarbenium ion **40**, which serves as a key intermediate. This intermediate undergoes a 6-endo-trig cyclization to produce a chair-like tetrahydropyranyl cation **41**. Based on Alder's DFT calculations,[30a] the chair conformation of carbocation (**44**) is 56.0 kJ/mol more stable than the staggered conformation of cation (**45**). This

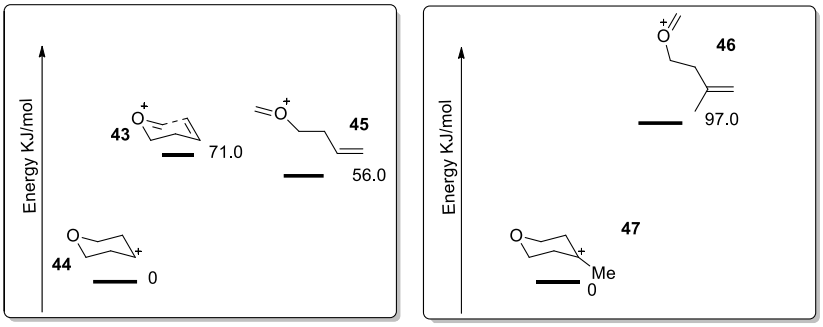


Figure 1.4.3.1

suggests the reaction is expected to proceed through a chair-like transition state that closely resembles structure (**43**) (*Figure 1.4.3.1*). It was observed that the stability of the cyclic carbocation is affected by substituents at the C-4 position. As a result, the tertiary carbocation (**47**) exhibits greater stability compared to the most stable open-chain conformation (**46**) by an energy difference of 97 kJ/mol.

According to this calculation, the chair conformation of secondary carbocation (**A**) is stabilized by stereoelectronic effects. This stabilization seems due to the interaction between the σ* and σ orbitals of the C2-C3 and C5-C6 bonds with the equatorial lone pair of the oxygen atom, as well as with the vacant p orbital at C4. Maximum stabilization occurs when the hydrogen atom at C4 adopts a pseudo-axial orientation. This stabilization promotes nucleophilic attack at the equatorial position, resulting in the formation of tetrahydropyran. (*Figure 1.4.3.2*). However, the tertiary cation (**B**) is planar because of stereoelectronic factors, and in this situation, axial trapping, which experiences less steric hindrance, would be preferred.

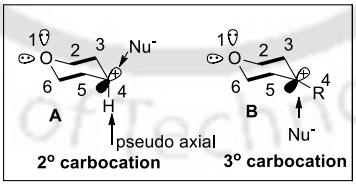


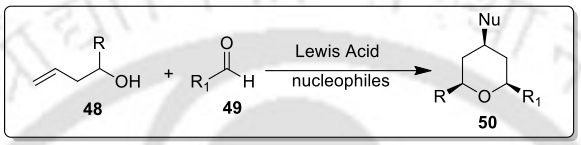
Figure 1.4.3.2

1.4.4 Scope of the Prins cyclization

In the last six decades, the modification of the Prins reaction has been widely improved. These developments include the generation of oxocarbenium ions from simple homoallylic alcohols and carbonyl compounds, as well as from a variety of substrates, including end ethers, ene-carbamates,

and benzylic homoallyl ethers. A wide range of nucleophiles has been utilized to add different substituents at the C4 position. Furthermore, several research groups have employed halogenated Lewis acids to entrap the tetrahydropyranyl carbocation with halide nucleophiles.[31a] In addition to halides, these carbocations have also been captured with other nucleophiles including acetate (-OCOMe), hydroxide (-OH), alkynes, azide (-N_3), and sulfur-containing nucleophiles, etc (*Table 1.4.4.1*).[31]

Table 1.4.4.1: Scope of the Prins cyclization with different 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	I
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
$BF_3{\cdot}OEt_2/CH_3CN$, $CeCl_3{\cdot}7H_2O$-AcCl/CH_3CN	$NHCOCH_3$
$BF_3{\cdot}OEt_2$/Arene	Ar
$BF_3{\cdot}OEt_2$/CuI/ Ph—≡—H	$PhCOCH_3$

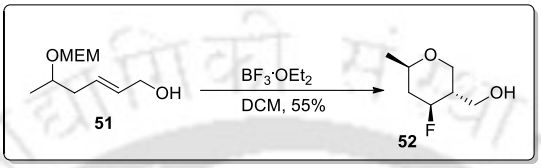
1.4.5 Prins cyclization utilizing derivatives of homoallylic alcohols.

The Prins cyclization of homoallylic alcohols to aldehyde or ketone is one of the most preferred methods for producing 4-substituted tetrahydropyrans, particularly functionalized at the C4 position with such groups as halogen, amide, oxygen, or azide.

1.4.5.1 Halo Prins Cyclization

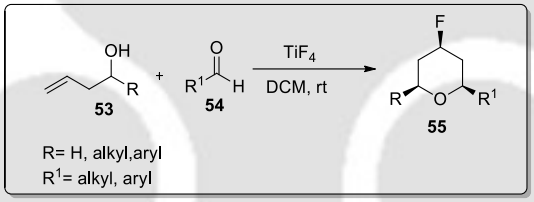
1.4.5.1.1 Synthesis of 4-Fluoro-tetrahydropyrans

Al-Mutairi *et al.* have successfully synthesized 2,6-substituted 4-fluorotetrahydropyrans (**52**) by the reaction of acetal (**51**) with $BF_3 \cdot Et_2O$, achieving a 55% yield with excellent diastereoselectivity (*Scheme 1.4.5.1.1.1*).[32]



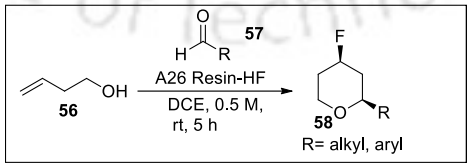
Scheme 1.4.5.1.1.1

Saikia and coworkers developed a TiF_4 facilitated Prins cyclization for producing 4-fluorotetrahydropyran (**55**).[33] Here, TiF_4 serves both as a fluorinating agent and a Lewis acid. The method is general and provides high yields with excellent stereoselectivity (*Scheme 1.4.5.1.1.2*).



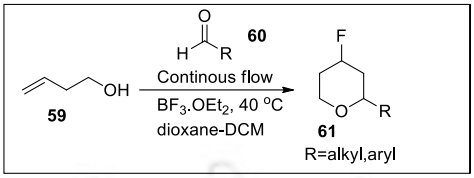
Scheme 1.4.5.1.1.2

In 2019, Lu *et al.* prepared A26 Resin-HF by mixing inexpensive anion exchange resin with hydrogen fluoride gas. This reagent enabled the synthesis of fluorinated tetrahydropyrans **58** *via* a fluoro-Prins cyclisation reaction, providing high selectivity (*Scheme 1.4.5.1.1.3*).[34]



Scheme 1.4.5.1.1.3

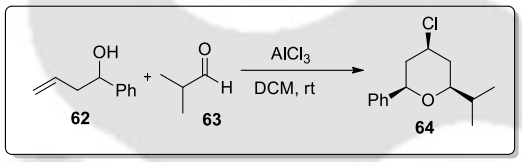
Recently, Talavera-Alemán *et al.* have successfully synthesized fluorinated tetrahydropyrans (**61**) through an oxa-Prins cyclization, achieving good selectivity toward the *anti*-configuration (*Scheme 1.4.5.1.1.4*).[35]



Scheme 1.4.5.1.1.4

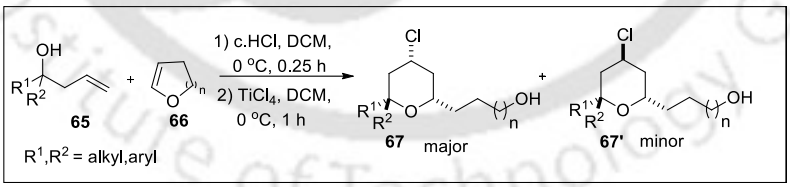
1.4.5.1.2 Synthesis of 4-Chloro-tetrahydropyrans

Taddei and group reported a stereoselective approach for synthesizing 4-halotetrahydropyrans (**64**) using homoallylic alcohols **62** and aldehydes **63** under the influence of $AlCl_3$ (*Scheme 1.4.5.1.2.1*).[36]



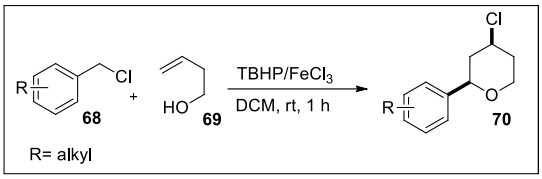
Scheme 1.4.5.1.2.1

Trevorrow *et al.* devised an innovative approach for synthesizing α,ω-hydroxy-tetrahydropyrans **67** by employing a double-Prins cyclisation strategy (*Scheme 1.4.5.1.2.2*).[37]



Scheme 1.4.5.1.2.2

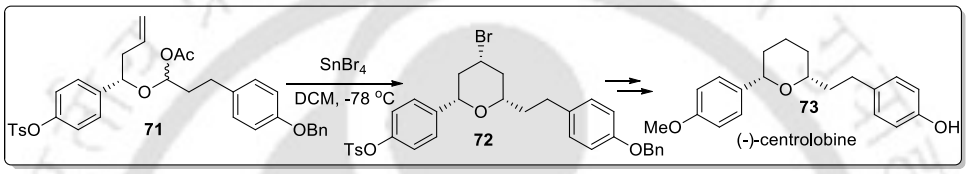
In the same year, Reddy and colleagues established an effective procedure for the high-yielding formation of 2-aryl-4-chlorotetrahydropyrans **70** from homoallylic alcohols and benzyl chlorides utilizing TBHP/$FeCl_3$ in a sequential oxidation/Prins cyclization pathway (*Scheme 1.4.5.1.2.3*).[38]



Scheme 1.4.5.1.2.3

1.4.5.1.3 Synthesis of 4-Bromotetrahydropyrans

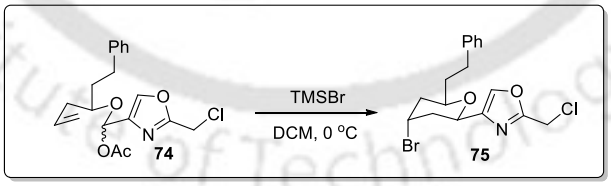
Rychnovsky and group found that the cyclization process of α-acetoxyether **71** mediated by $SnBr_4$ led to the formation of the all-equatorial 4-bromotetrahydropyran **72**. Subsequent substitution of



Scheme 1.4.5.1.3.1

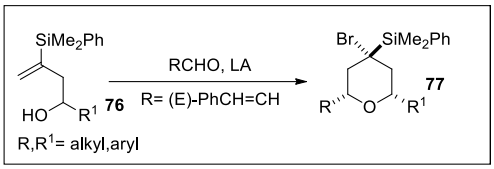
the tosylate by a methyl ether group, along with the elimination of the bromide and benzyl groups, afforded (-)-centrolobine (*Scheme 1.4.5.1.3.1*).[39]

On the other hand, they also discovered that under specific conditions, a Prins cyclization selectively produced tetrahydropyrans with axial 4-bromosubstituent **75**. When the α-acetoxy ether (**74**) was reacted with TMSBr in DCM at 0 °C, it produced tetrahydropyran (**75**) as the sole axial-bromide configuration (*Scheme 1.4.5.1.3.2*).[40]



Scheme 1.4.5.1.3.2

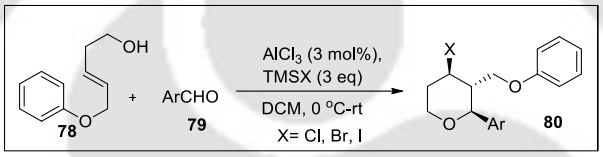
Very recently, González-Andrés *et al.* reported a silyl-Prins cyclization of *gem*-vinylsilyl alcohols **76** with TMSBr, yielding 4-bromodimethyl (phenyl)silane derivatives **77** with excellent diastereoselectivity at -78 °C (*Scheme 1.4.5.1.3.3*).[41]



Scheme 1.4.5.1.3.3

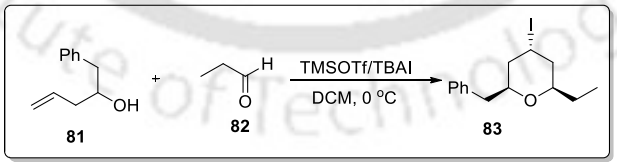
1.4.5.1.4 Synthesis of 4-Iodo-tetrahydropyrans

Recently, Satteyyanaidu and colleagues documented the synthesis of 4-halo-3-(phenoxymethyl) tetrahydro-2*H*-pyran derivatives **80** from alcohol **78** and aldehydes **79**, facilitated by the combination of TMSX and $AlCl_3$. Notably, the reaction gives products with excellent diastereoselectivity, affording a single *trans-trans* diastereomer (*Scheme 1.4.5.1.4.1*).[42]



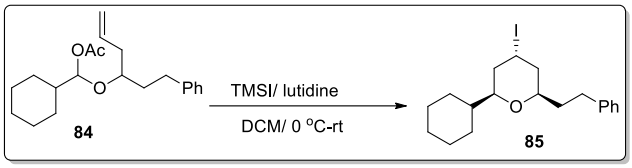
Scheme 1.4.5.1.4.1

According to the Alder model, the halogen functionality in these reactions is positioned in the equatorial position. However, only a limited number of methods are available for the production of 4-axial halotetrahydropyrans. Saikia and colleagues described an axial-selective Prins cyclization method to synthesize 4-axial-iodotetrahydropyran (**83**) from homoallylic alcohol (**81**) and aldehyde (**82**), employing TMSOTf and tetrabutylammonium iodide (TBAI) as catalysts (*Scheme 1.4.5.1.4.2*).[43]



Scheme 1.4.5.1.4.2

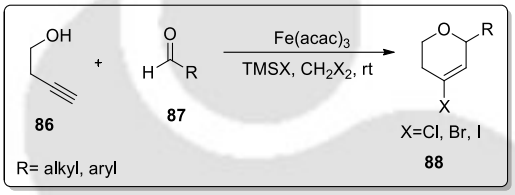
Rychnovsky and colleagues reported the synthesis of 4-axial iodo tetrahydropyran **85** from acetoxy ether **84** using TMSI and lutidine in DCM at 0 °C-rt (*Scheme 1.4.5.1.4.3*).[40]



Scheme 1.4.5.1.4.3

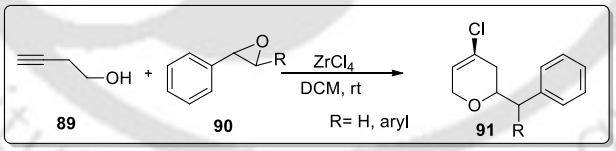
1.4.5.2 Cyclization involving Homopropargylic alcohol

Miranda *et al.*[44] reported a novel approach for synthesizing dihydropyran derivatives (**88**) *via* alkyne-Prins cyclizations. This method uses relatively inexpensive iron sources such as $FeBr_3$, FeI_3, $FeCl_3$, or $Fe(acac)_3$, in combination with TMSX to form the corresponding six-membered oxa-cycles (**88)** (*Scheme 1.4.5.2.1*).



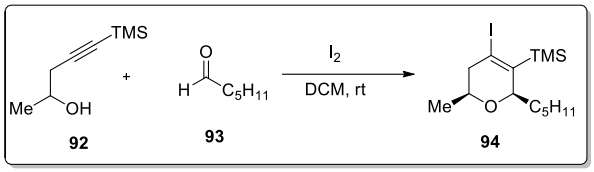
Scheme 1.4.5.2.1

Yadav and colleagues used epoxides (**90**) as aldehyde equivalents with homopropargylic alcohol (**89**) under the influence of $ZrCl_4$, leading to the creation of the corresponding dihydropyran derivatives (**91**) (*Scheme 1.4.5.2.2*).[45]



Scheme 1.4.5.2.2

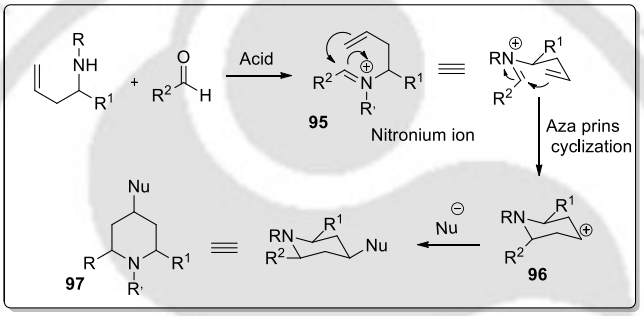
The same group detailed the reaction of silylated secondary homopropargylic alcohols (**92**) with aldehydes (**93**) *via* silyl alkyne-Prins cyclization. They used molecular iodine to generate 4-iododihydropyrans (**94**) in high yields with high stereoselectivity (*Scheme 1.4.5.2.3*). In this reaction, molecular iodine serves as both the catalyst and the halide source.[46]



Scheme 1.4.5.2.3

1.5 Aza-Prins cyclization

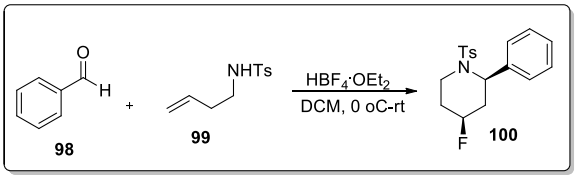
This represents the nitrogen variant of the Prins cyclization, where a nitronium ion **95** is formed instead of an oxocarbenium ion. This ion, after cyclisation, gives a piperidine unit **97** in place of tetrahydropyran units. Due to the lower electrophilicity of iminium ions, there has been less



Scheme 1.5.1

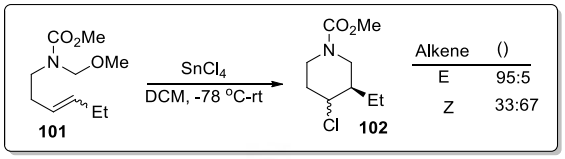
extensive research on aza-Prins cyclization involving iminium ions for the formation of nitrogen-containing heterocycles (*Scheme 1.5.1*). In contrast, to higher electrophilicity of *N*-acyliminium ions has resulted in more extensive research on aza-Prins cyclization involving both cyclic and acyclic *N*-acyliminium ions for the formation of mono- and bicyclic piperidine ring compounds.[47]

In 2010, Yadav *et al.* described the synthesis of *cis*-4-fluoropiperidines (**100**) through the interaction of *N*-tosyl homoallylamine (**99**) with aldehydes (**98**), utilizing tetrafluoroboric acid-diethyl ether complex solution (*Scheme 1.5.2*).[48]



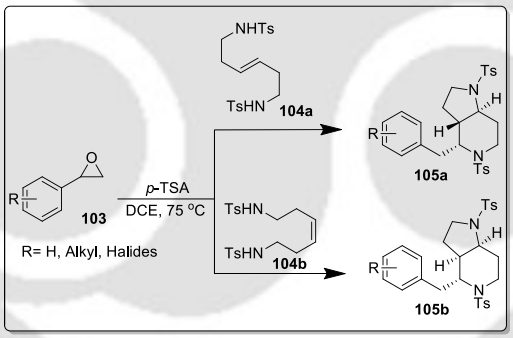
Scheme 1.5.2

Speckamp's group documented the synthesis of diverse substituted piperidines by employing the concept of *N*-acyliminium ions. At -78 °C, the *N*-acyliminium ion precursor **101** underwent aza-Prins cyclization with $SnCl_4$, gave a mixture of 4-chloro piperidines **102** (*Scheme 1.5.3*).[49]



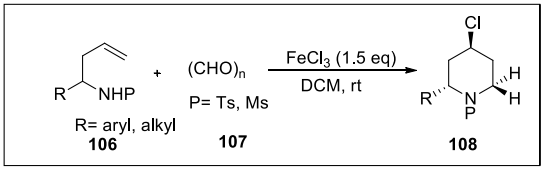
Scheme 1.5.3

Yadav and group described the formation of fused aza-bicyclic systems through intramolecular aza-Prins cyclization reaction.[50] Here, styrene oxide **103** reacts with (E)-ditosylamide **104a**, using *p*-TSA in DCE, resulting in the formation of octahydro-1*H*-pyrrolidino[3,2-*c*]pyridines **105a**, favoring the *trans*-configuration at the ring system. Conversely, the reaction involving (Z)-ditosylamide **104b** primarily yielded *cis*-octahydro-1*H*-pyrrolidino[3,2-*c*]pyridines **105b** (*Scheme 1.5.4*).



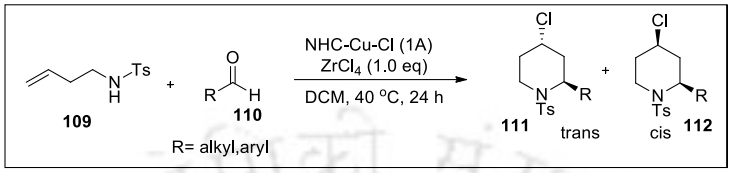
Scheme 1.5.4

Recently, Padron and co-worker described the synthesis of homoallyl sulfonyl amides **108** through an aza-Prins cyclization reaction involving formaldehyde **107** (*Scheme 1.5.5*).[51]



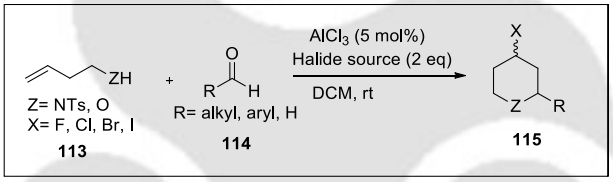
Scheme 1.5.5

Duan and colleagues disclosed the preparation of 4-chloro-1-tosylpiperidine frameworks from *N*-(but-3-enyl)-4-methylbenzenesulfonamide (**109**) and aldehydes (**110**), catalyzed by $ZrCl_4$ and NHC-Cu Complex. Under mild reaction conditions, the NHC–Cu complex acts as the catalyst while $ZrCl_4$ serves as the chloride source (*Scheme 1.5.6*).[52]



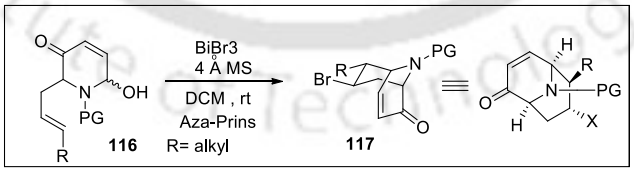
Scheme 1.5.6

Li and group described the formation of *trans*-2-substituted-4-halopiperidines (**115**) with high diastereoselectivity, employing $AlCl_3$ and trimethylsilyl halides (TMSX). Here, $AlCl_3$ functions as the catalyst, while TMSX serves as a halide source (*Scheme 1.5.7*).[53]



Scheme 1.5.7

Cheng and colleagues reported aza-Achmatowicz rearrangement products **117** through intramolecular aza-Prins cyclization facilitated by $BiBr_3$, functioning as both a catalyst and a source of bromide nucleophiles (*Scheme 1.5.8*).[54]

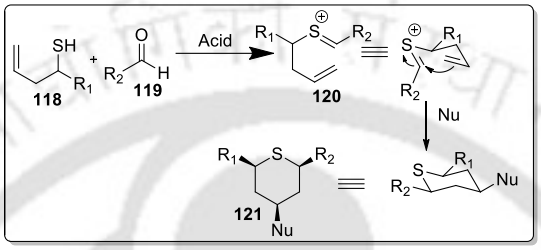


Scheme 1.5.8

1.6 Thia-Prins cyclization reaction

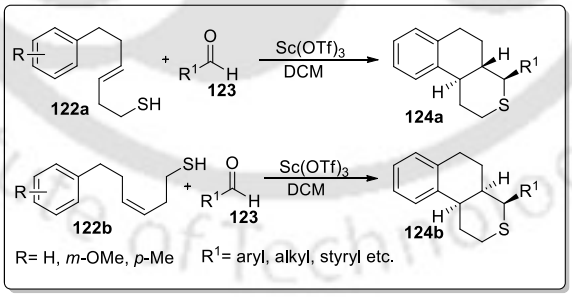
This represents the sulfur variant of the Prins cyclization. It involves the acid-promoted or acid-catalyzed reaction of carbonyl compounds with homoallylic thiols. In comparison to the oxa- and

aza-Prins cyclizations, its use in organic synthesis is more restricted. Similar to the Prins cyclization, a thiocarbenium ion **120** is formed through the reaction of aldehyde **119** and homoallylic thiol **118** when acid is present. This intermediate undergoes 6-endo trig cyclization to generate a secondary carbocation, which is subsequently attacked equatorially by nucleophiles, resulting in the production of 2,4-*cis*-tetrahydrothiopyran derivatives (**121**), as illustrated in *Scheme 1.6.1*.



Scheme 1.6.1

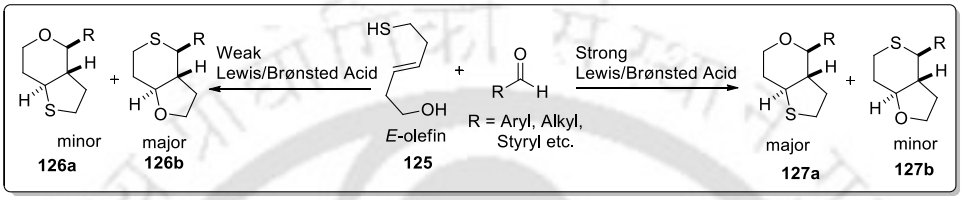
Yadav *et al.* reported the formation of fused hexahydro-1*H*-benzo[*f*]isothiochromenes **124** using a tandem intramolecular thia-Prins/Friedel-Crafts approach. This methodology involved the use of aldehydes **123** and (E/Z)-6-arylhex-3-enyl thiols **122** using $Sc(OTf)_3$ (*Scheme 1.6.2*).[55] The reaction of (E)-thiols **122a** afforded *trans*-fused isothiochromenes **124a**, while (Z)-thiols **122b** yielded the *cis*-fused products **124b**.



Scheme 1.6.2

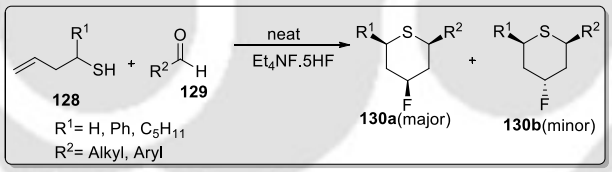
In 2014, Reddy *et al.* systematically studied the selectivity between sulfur ("S") and oxygen ("O") in Prins cyclization.[56] They conducted the reaction of 6-mercaptohex-3-en-1-ol **126** with aldehydes using strong Lewis or Brønsted acids, resulting in the predominant formation of hexahydro-2*H*-

thieno[3,2-*c*]pyrans **127**. But, when they used catalytic amounts, hexahydro-2*H*-thiopyrano[4,3-*b*]furans **126** emerged as the primary product. It indicates that selectivity depends on the complexation tendencies of the acids. Strong Lewis acids, like $BF_3.OEt_2$ favors complexation with sulfur, resulting in the oxonium-Prins product being the major product. Conversely, weak Lewis acids, such as $InCl_3$, preferentially complex with oxygen, resulting in the thionium-Prins product as the predominant outcome (*Scheme 1.6.3*).



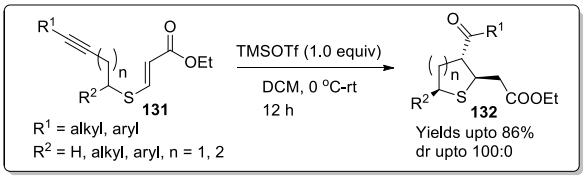
Scheme 1.6.3

Kishi *et al.* synthesized 4-fluoro-tetrahydrothiopyrans **130** *via* thia-Prins cyclization of homoallylic thiols **128** with aldehydes **129** using $Et_4NF{\cdot}5HF$.[57] In this process, $Et_4NF{\cdot}5HF$ serves both as the reaction medium and a fluorine source. This synthetic route proceeds with excellent diastereoselectivity, predominantly yielding the *cis* products **130a** (*Scheme 1.6.4*).



Scheme 1.6.4

Saikia's group demonstrated a thia-Prins cyclization reaction that successfully synthesized functionalized tetrahydrothiophenes (n=1) and thiopyrans (n=2) **132** in significant yield and with

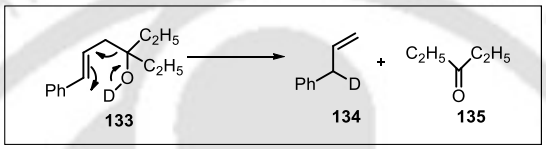


Scheme 1.6.5

excellent diastereoselectivity[58] (*Scheme 1.6.5*).

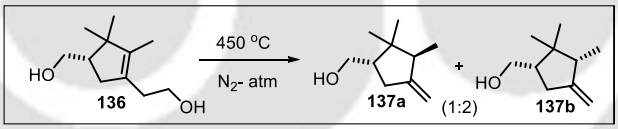
1.7 Retro-Prins reaction

The retro-Prins reaction is the reverse of the Prins reaction. In this process, a carbon–carbon bond is broken to regenerate the corresponding aldehydes or ketones **135** along with alkenes **134** (*Scheme 1.7.1*).[59] It is extensively used in organic synthesis. Initially, it was known to proceed only *via* a thermal route, but recent studies have shown that it can also be achieved under catalytic conditions without the need for high temperatures.[59]



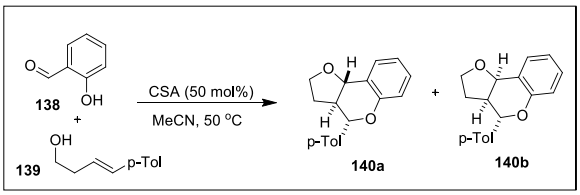
Scheme 1.7.1: Mechanism of retro-Prins reaction

Schulte-Eke *et al*. reported the synthesis of C3-epimeric alcohols **137** in a 1:2 ratio from a diacetate precursor **136** by heating at 450 °C under an inert nitrogen atmosphere, proceeding through a retro-Prins reaction (*Scheme 1.7.2*).[60]

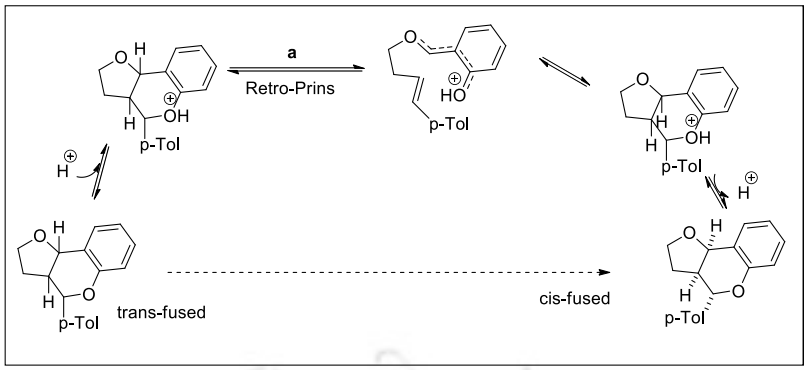


Scheme 1.7.2

In 2019, Spivey and his group investigated the formation of furanochromanes **140** through the reaction of salicylaldehyde **138** and styrenyl homoallylic alcohols **139** (*Scheme 1.7.3*). DFT



Scheme 1.7.3



Scheme 1.7.4

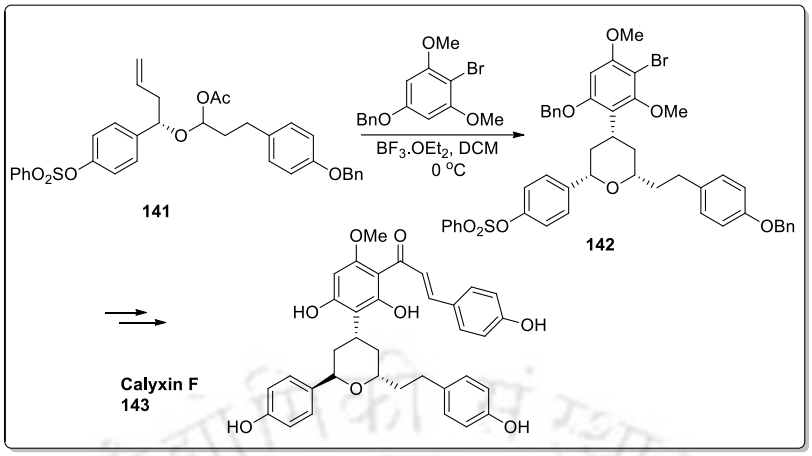
calculations revealed that the reaction initially favoured *trans*-fused products, suggesting a thermodynamically driven *trans*-to-*cis* isomerization. The greater stability of the *cis* isomer (ΔG = –3.9 kcal/mol), likely due to destabilizing orbital interactions present in the *trans* isomer. The isomerization was hypothesized to proceed *via* reversible pathways, including retro-Prins/Prins or retro-cycloaddition/cycloaddition pathways (path a, *Scheme 1.7.4*).[61]

1.8 Prins reaction approach in natural product development

It is well known from the literature that piperidine and tetrahydropyran moieties exhibit diverse biological activities and are found in many natural products. Among several methods, Prins cyclization is widely used in synthesis due to its diastereoselectivity and one-step synthesis of highly functionalized tetrahydropyran units. So, it can be used for the production of many natural products.

1.8.1 Synthesis of Calyxin F

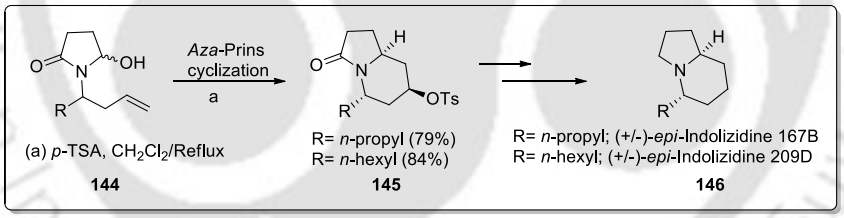
Calyxin F is used for treating stomach disorders. Rychnovsky successfully synthesized these compounds through a Prins/Friedel-Crafts reaction, in which the tetrahydropyran ring in compound **142** was formed by the reaction of starting materials **141** and 5-(benzyloxy)-2-bromo-1,3-dimethoxybenzene, catalyzed by $BF_3 \cdot OEt_2$ (*Scheme 1.8.1.1*).[62]



Scheme 1.8.1.1

1.8.2 Synthesis of (±)-epi-indolizidine 167B and 209D

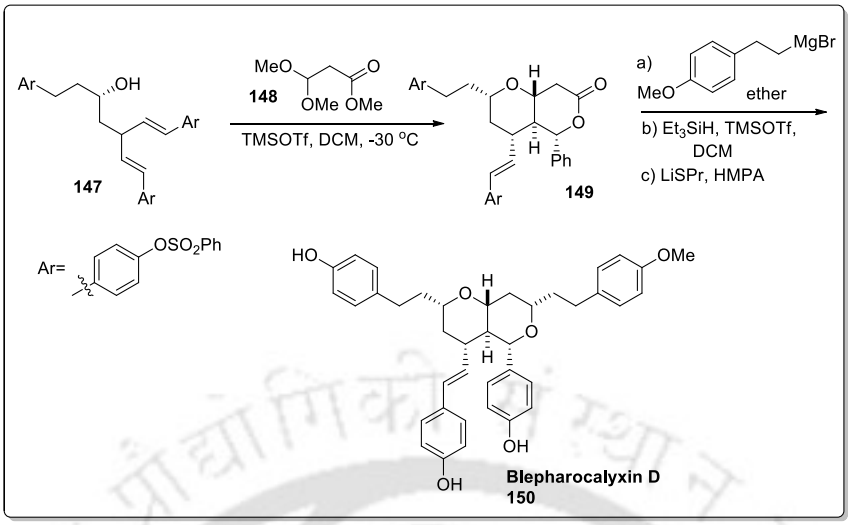
Saikia and his team reported the synthesis of o-tosyl aza-bicyclic heterocycles *via* the aza-Prins cyclization of endocyclic *N*-acyliminium ions.[63] This approach was further expanded to synthesize the piperidine alkaloids (±)-epi-indolizidine 209D (±)-and epi-indolizidine 167B (**146**). (*Scheme 1.8.2.1*).



Scheme 1.8.2.1

1.8.3 Synthesis of Blepharocalyxin D

In 2013, Willis and his colleagues reported the formation of blepharocalyxin D using the Prins bicyclization strategy. The acid-catalyzed cascade reaction between methyl 3,3-dimethoxypropanoate **148** and unsaturated alcohol **147** led to the formation of *trans*-fused bicyclic lactone **149**. Then, it was converted into blepharocalyxin D **150** using a Grignard protocol (*Scheme 1.8.3.1*).[64]



Scheme 1.8.3.1

1.9 Concluding remarks:

The preceding discussion emphasized that the Prins reaction methodology utilizing Lewis acid has garnered considerable interest and established itself as an essential strategy for producing oxygen and nitrogen heterocycles. These heterocycles are crucial components in the creation of natural products and therapeutic agents. In recent years, a significant number of reports have documented the application of the Prins reaction with homoallylic alcohols and carbonyl compounds under acidic conditions. In the present century, substantial efforts have been directed toward the introduction of diverse functionalities into oxygen and nitrogen heterocycle moieties *via* the Prins reaction, especially for the assembly of different components of complex natural products. In the course of the literature review, it was noted that substituents at the C-4 position significantly impact the stability of the cyclic carbocation. To address this issue, we introduced a halogen at the C-4 position of the ring. Following this approach, we chose 3-halobut-3-en-1-ol as the starting material for the oxygen variant and *N*-(3-halobut-3-en-1-yl)-4-methylbenzenesulfonamide for the nitrogen variant.

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Chapter 2:

Diastereoselective Synthesis of 2,6-Disubstituted Tetrahydropyranones *via* Prins Cyclization of 3-Bromobut-3-en-1-ols and Aldehydes

2.1 Importance and Applications

Tetrahydropyrans are among the most common heterocyclic structures ubiquitously present in bioactive molecules and natural products.[1] Substituted pyran motifs are the structural core unit of numerous biologically active natural products. For example, calixyn L (**I**), a natural diarylheptanoid isolated from the seeds of *Alpinia blepharocalyx*,[2] and Diosniponol A (**II**), a natural diarylheptanoid isolated from the rhizomes of *Dioscorea nipponica*,[3] are natural products; exiguolide (**III**) is a complex macrolide isolated from the marine sponge *Geodia exigua*. It exhibits notable biological activities, particularly in terms of its anticancer properties.[4] Bryostatin 1 (**IV**) is a macrolide lactone isolated from the marine bryozoan *Bugula neritina*. It has shown activity against various conditions, including cancer and Alzheimer's disease[5](Figure 2.1).

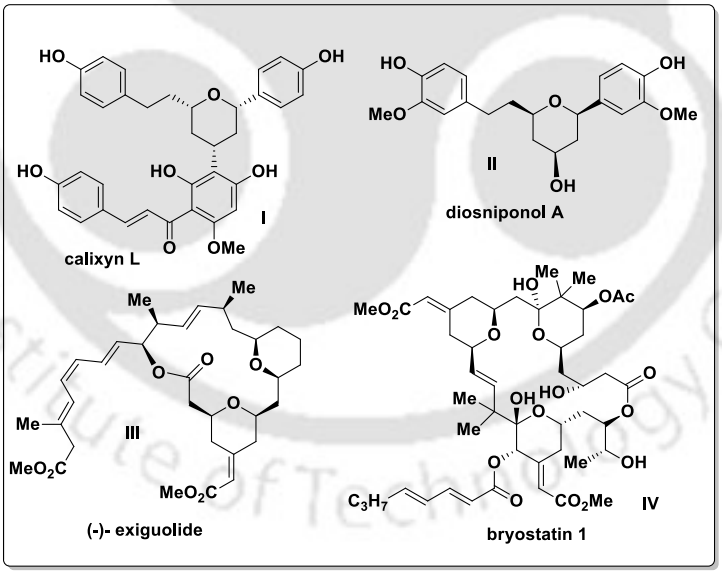
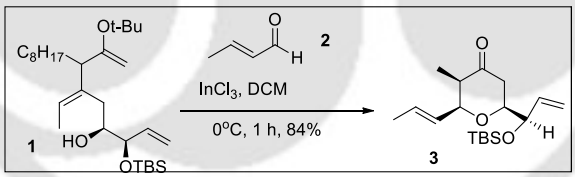


Figure 2.1: *Biologically active molecules.*

2.2. An Overview of Relevant Synthetic Methods

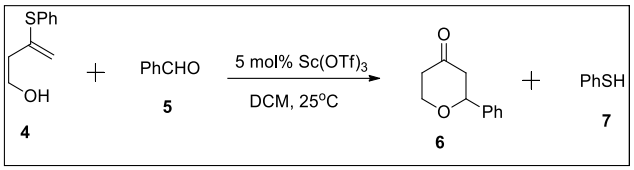
Due to the significant importance of tetrahydropyrans, numerous methodologies have been established over the years for the synthesis of tetrahydropyran rings, including the hetero-Diels−Alder reaction,[6] manipulations of carbohydrates,[7] intramolecular oxa-Michael reaction,[4b,8] cyclization of epoxy alcohols,[9] Prins cyclization[10] and others.[11] Among the various methods available, Prins cyclization is considered to be the most convenient tool as it forms carbon−carbon and carbon−heteroatom bonds in a single step with high diastereoselectivity.[11c,12] The introduction of various functionalities into a tetrahydropyran moiety is crucial for constructing complex natural product units. Incorporating a carbonyl group into the tetrahydropyran framework is a valuable method for achieving such functionality. It may be noted that the carbonyl moiety may be manipulated to transform into other functional groups using different strategies, such as reduction by borohydride to alcohols, reaction with amine to form imine, Wittig reaction to form olefins, etc. Therefore, the synthesis of tetrahydropyranones plays a significant role in organic synthesis.

In 2004, Funk and co-workers reported the formation of tetrahydropyran-4-one *via* Prins cyclization of enecarbamates.[13] As demonstrated in *Scheme 2.2.1*, the reaction of compound **1** with crotonaldehyde gives the trisubstituted 2,3,6-*cis*,*cis*-tetrahydropyran-4-one (**3**) ***(****Scheme 2.2.1*).



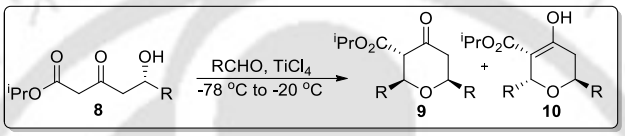
Scheme 2.2.1

In 2016, Reddy and co-workers reported the synthesis of tetrahydropyran-4-one derivatives using phenylthiophene-substituted homoallylic alcohols.[14] In this method, 3-(phenylthio)but-3-en-1-ol (**4**) reacts with carbonyl compounds in the presence of 5 mol% $Sc(OTf)_3$ as a catalyst, leading to the formation of tetrahydropyran-4-one (*Scheme 2.2.2*).



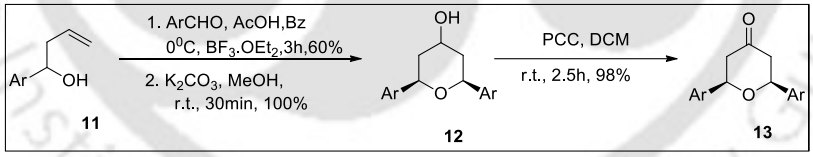
Scheme 2.2.2

Clarke emphasized the green synthesis of tetrahydropyran-4-ones from diketone and aldehydes using pot, atom and step economy (PASE) protocol.[15] Here, diketone (**8**) reacts with aldehydes in the presence of $TiCl_4$ in DCM to give the tetrahydropyran products *(Scheme 2.2.3*).



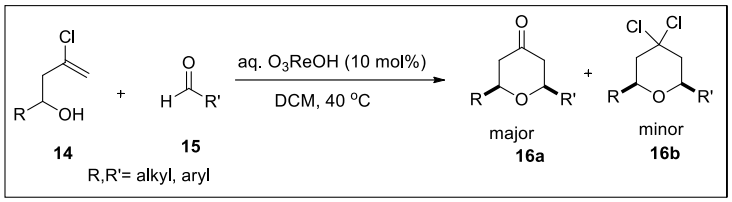
Scheme 2.2.3

Silva *et al*. reported the synthesis of tetrahydropyran-4-ones in two steps: first, the formation of alcohols, followed by oxidation.[16] They synthesized 2,6-diphenyl tetrahydro-2*H*-pyran-4-ol **(11)** through the reaction of homoallylic alcohol with aldehyde. Oxidation of compound **12** with PCC gives 2,6-diphenyltetrahydropyran-4-one **(13)** *(Scheme 2.2.4*).



Scheme 2.2.4

Recently, Tadpetch reported the synthesis of tetrahydropyran-4-ones **16a** as the major product and *gem*-dichloro tetrahydropyran **16b** as a minor product, utilizing 3-chloro homoallylic alcohols **14** and aldehyde **15** catalyzed by O_3ReOH *via* Prins cyclization reaction[17] *(Scheme 2.2.5*).

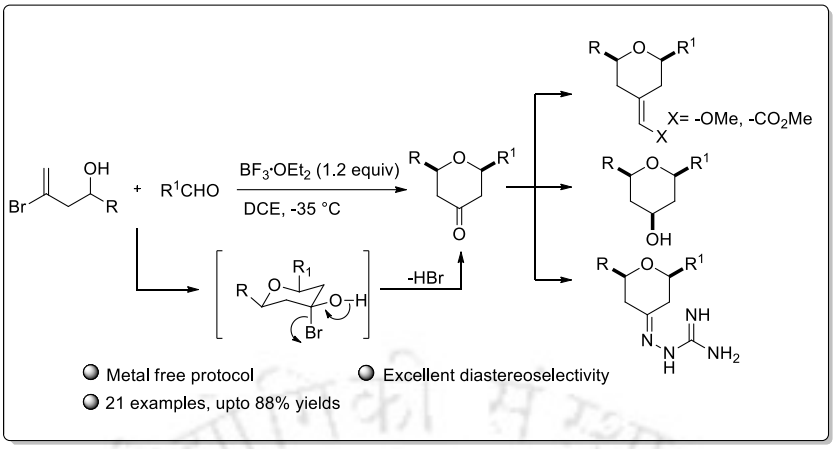


Scheme 2.2.5

2.3 Present Work

Considering the importance of tetrahydropyranones, several chemists have utilized various methods for its synthesis. For instance, Funk reported the formation of tetrahydropyran-4-one *via* Prins cyclizations of enecarbamate,[13] and Subba Reddy synthesized tetrahydropyran-4-one using phenyl thiophene substituted homoallylic alcohols.[14] But the methodology is limited to monosubstituted tetrahydropyran-4-ones. Silva *et al.*, on the other hand, obtained tetrahydropyran-4-ones in two steps, which include the formation of alcohols followed by an oxidation reaction.[16] Very recently, Tadpetch reported the synthesis of tetrahydropyran-4-ones using 3-chlorohomoallylic alcohols catalysed by O_3ReOH *via* Prins cyclization reaction.[17] But the reaction suffers from low yields and side products. Therefore, there is a need for the development of an efficient synthetic methodology for the synthesis of tetrahydropyran-4-one.

In light of this importance, we hereby introduce a novel and efficient methodology for the synthesis of 2,6-disubstituted tetrahydropyranones, achieving good yields and excellent diastereoselectivity from 3-bromobut-3-en-1-ols and aldehydes *via* Prins cyclization reaction. Unlike previous methods, this technique allows for disubstitution rather than being restricted to monosubstituted compounds. Additionally, it is a one-step reaction that offers improved yields compared to earlier approaches. Late-stage modification was carried out for the synthesis of enol ether, ester derivatives, and 4-hydroxy 2,6-disubstituted tetrahydropyran with 2,4- and 4,6-*cis* configuration. The methodology is further extended for the synthesis of aminoguanidine derivatives, which are considered as anticancer agents.



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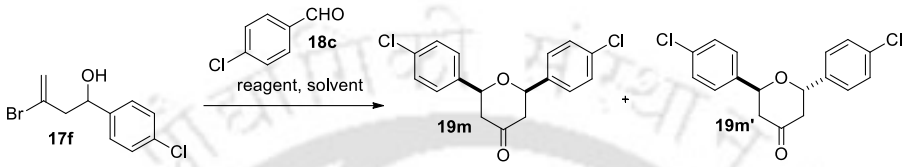
2.4 Results and Discussions

2.4.1 Optimization of the Reaction

To start, 3-bromo-1-(4-chlorophenyl)but-3-en-1-ol (**17f**) was considered as a model substrate and was reacted with 4-chlorobenzaldehyde (**18c**) with one equivalent of $BF_3 \cdot OEt_2$ in dichloromethane (DCM) at 0 °C to room temperature, which produced 2-(4-chlorophenyl)tetrahydro-4*H*-pyran-4-one (**19m**) with 23% yield (Table 2.4.1.1, entry 1) along with some unidentified decomposed products. Therefore, the reaction was performed at lower temperatures such as 0, −20, and −40 °C, and the corresponding yields were 29%, 37%, and 53%, respectively (Table 2.4.1.1, entries 2−4). Further decrease in temperature to −60 °C produced only 15% yield of the desired product, and unreacted starting material was recovered in 52% (Table 2.4.1.1, entry 5). Next, when the reagent loading was increased to 1.2 equiv., the yield increased to 62% (Table 2.4.1.1, entry 6). Further increase in reagent loading to 1.5 equiv. did not improve the reaction yield (Table 2.4.1.1, entry 7). Switching solvent from DCM to slightly polar 1,2-dichloroethane (DCE) at −35 °C resulted in 68% yield (Table 2.4.1.1, entry 8). The reaction was also performed in other solvents, such as less polar toluene and more polar acetonitrile, but the yield was not satisfactory (Table 2.4.1.1, entries 9−10). We then screened the reaction with other Lewis acids. Weak Lewis acids such as $FeCl_3$ produced only 9% yield, whereas $InCl_3$ did not produce any products (Table 2.4.1.1, entries 11−12). On the other hand, TMSOTf gave only decomposed products (Table 2.4.1.1, entry 13). The reaction was also performed with Brønsted acids. Reaction with strong acids like triflic acid gave 48% yield (Table 2.4.1.1, entry 14) accompanied by some decomposed products. On the other

hand, weak acids such as *p*-toluene sulfonic acid (*p*-TSA), trifluoroacetic acid (TFA), and camphor sulfonic acid (CSA)did not produce any products (Table 2.4.1.1, entries 15−17). Open air reaction with $BF_3{\cdot}OEt_2$ in DCE gave only 50% yield (Table 2.4.1.1, entry 18). Finally, 1.2 equiv of $BF_3{\cdot}OEt_2$ in DCE at −35 °C were the optimum conditions for the reaction.

Table 2.4.1.1: Optimization of the reaction[a]



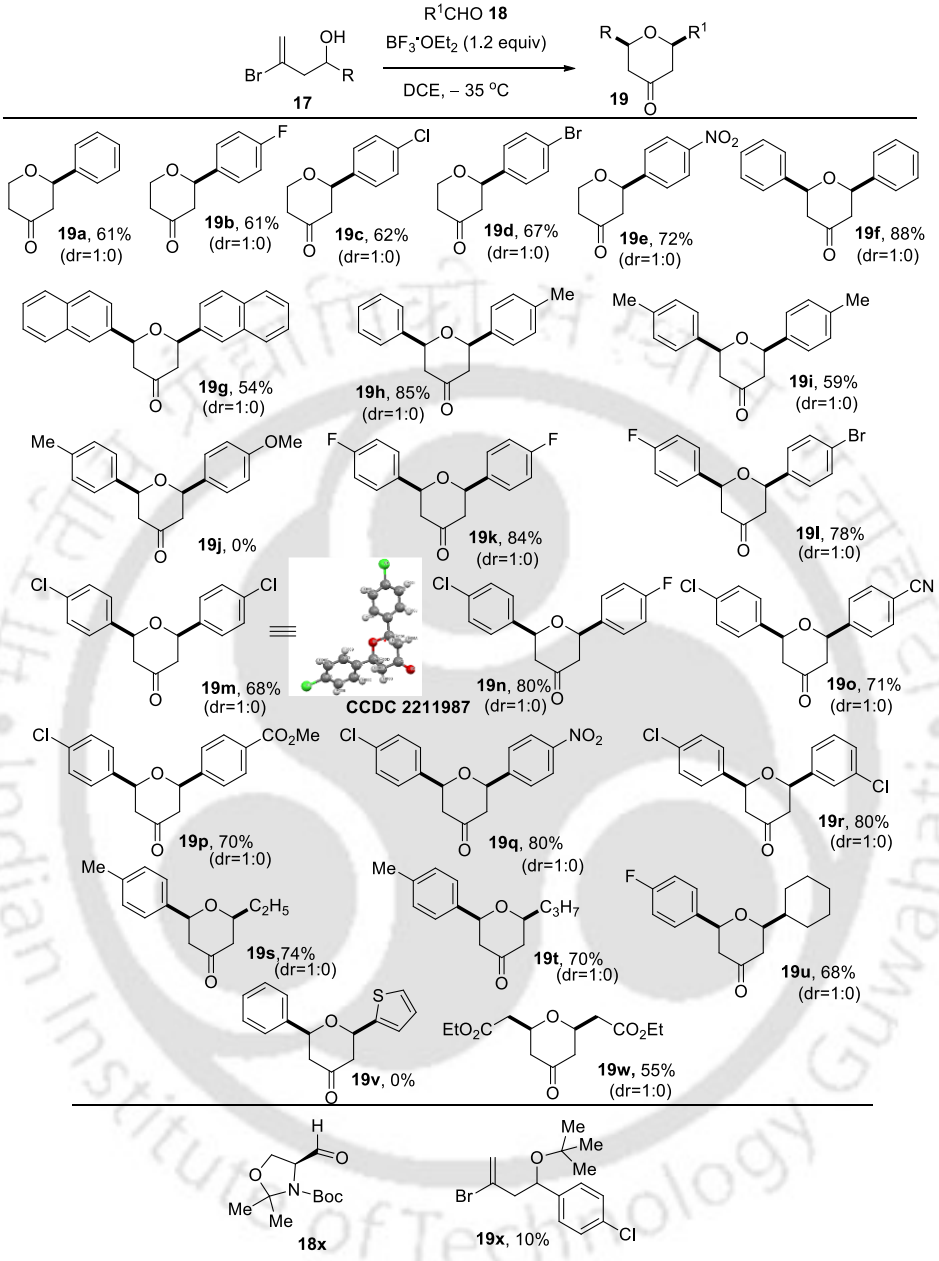
S. No	Lewis acid (equiv.)	Solvent	Temp.	Time/ h	%Yield[bf] (**19m:19m′**) (=1:0)
1	$BF_3{\cdot}OEt_2$ (1.0)	DCM	0 °C-rt	3	23
2	$BF_3{\cdot}OEt_2$ (1.0)	DCM	0	3	29
3	$BF_3{\cdot}OEt_2$ (1.0)	DCM	-20	3	37
4	$BF_3{\cdot}OEt_2$ (1.0)	DCM	-40	3	53
5	$BF_3{\cdot}OEt_2$ (1.0)	DCM	-60	12	15[c]
6	$BF_3{\cdot}OEt_2$ (1.2)	DCM	-40	3.5	62
7	$BF_3{\cdot}OEt_2$ (1.5)	DCM	-40	3.5	60
8	**$BF_3{\cdot}OEt_2$ (1.2)**	**DCE**	**-35**	**3.5**	**68**
9	$BF_3{\cdot}OEt_2$ (1.2)	toluene	-35	3.5	45
10	$BF_3{\cdot}OEt_2$ (1.2)	CH_3CN	-35	4	49
11	$FeCl_3$ (1.2)	DCE	-35	2	9
12	$InCl_3$ (1.2)	DCE	-35	12	NR
13	TMSOTf (1.2)	DCE	-35	2	--[d]
14	TfOH (1.2)	DCE	-35	2	48
15	*p*-TSA (1.2)	DCE	-35	12	NR
16	TFA (1.2)	DCE	-35	12	NR
17	CSA (1.0)	DCE	-35	12	NR
18	$BF_3{\cdot}OEt_2$ (1.2)	DCE	-35	3.5	50[e]

[a]Reaction conditions: all reactions were carried out under a nitrogen atmosphere. **17f** (1.0 mmol) and **18c** (0.67 mmol), Solvent (3.0 mL). [b]Isolated yield. [c]Unreacted starting material (**17f**) (136 mg, 52%) was recovered. [d]Decomposed. [e]Open air condition. NR= No reaction. [f]Diastereoselectivity was measured by ^{1}H NMR spectroscopy and was found to be 1:0.

2.4.2 Substrates Scope of the Reaction:

With these optimum conditions in hand, the reaction was screened with different substrates (*Scheme 2.4.2.1*). Aromatic aldehydes having electron-withdrawing groups in the aromatic ring were reacted with primary and secondary alcohols (*Scheme 2.4.2.1*, **19b**−**19e**, **19k**−**19r**) and gave the products in 61−84% yields. Similarly, aromatic aldehydes with an electron-donating methyl

Scheme 2.4.2.1: Synthesis of Tetrahydropyranones[a]



[a]Reaction conditions: **17** (1.0 mmol), **18** (0.67 mmol), $BF_3{\cdot}OEt_2$ (0.8 mmol), DCE (3 mL), -35 °C, N_2 atmosphere. Diastereoselectivity was determined by ^1H NMR spectroscopy.

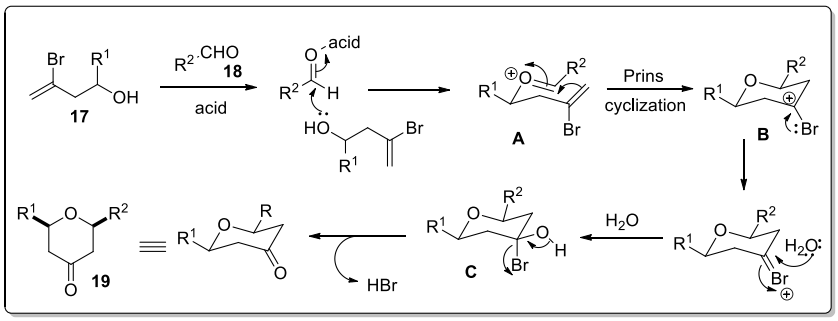
group in the aromatic ring (*Scheme 2.4.2.1*, **19h**–**19i**) also gave good yields. Aromatic aldehydes having electron-donating groups in the aromatic ring gave comparatively better yields than the aromatic aldehydes with electron-withdrawing groups. This is attributed to the stabilization of oxocarbenium ion **A** (*Scheme 2.5.1*) by an electron-donating group. However, the highly electron-

donating methoxy group **18j** gave a decomposed product, as in many Prins cyclization reactions.[18] Aliphatic aldehydes **18s**−**18u**, **18w** gave lower yields compared to aromatic aldehydes, which is due to the low reactivity of aliphatic aldehydes. Unfortunately, heteroatomic aldehyde **18v** did not give any product. Secondary alcohols having aryl and alkyl groups also provided good yields (*Scheme 2.4.2.1*, **19f**−**19i**, **19k**−**19u**, and **19w**). The Garner's aldehyde **18x,** when reacted with bromo alcohol **17f,** provided decomposed products along with 10% of *tert*-butyl protected alcohol **19x** instead of the desired tetrahydropyranone (*Scheme 2.4.2.1*). This indicates that Garner's aldehydes are not compatible under these reaction conditions. The reaction is highly diastereoselective as it is often found in Prins cyclization reactions. The diastereoselectivity in the Prins cyclization reaction is due to the formation of the most stable chair-like intermediate **A** (*Scheme 2.5.1*), occupying both R^1 and R^2 in the equatorial position. The structure of the compounds was determined by ^1H, $^{13}C\{^1H\}$ NMR, IR spectroscopy, HRMS spectrometry, and finally by X-ray crystallographic analysis of **19m**.

2.5 Plausible mechanism of the reaction

The plausible mechanism is proposed in *Scheme 2.5.1*. Initially, 3-bromobut-3-en-1-ols **17** react with aldehyde **18** in the presence of borontrifluoride etherate ($BF_3{\cdot}OEt_2$) to generate oxocarbenium ion **A**, which, after Prins cyclization reaction, produces carbocation **B**, which is stabilized by bromine. This reaction exclusively yields the *cis* isomer. In the course of the Prins cyclization, the tetrahydropyran ring is formed with the R^1 and R^2 groups in equatorial positions, minimizing 1,3-diaxial interactions. The carbocation **B**, then, reacts with water to give intermediate **C**. The intermediate **C**, after eliminating hydrobromic (HBr) acid, would provide the tetrahydropyran-4-ones **19.**

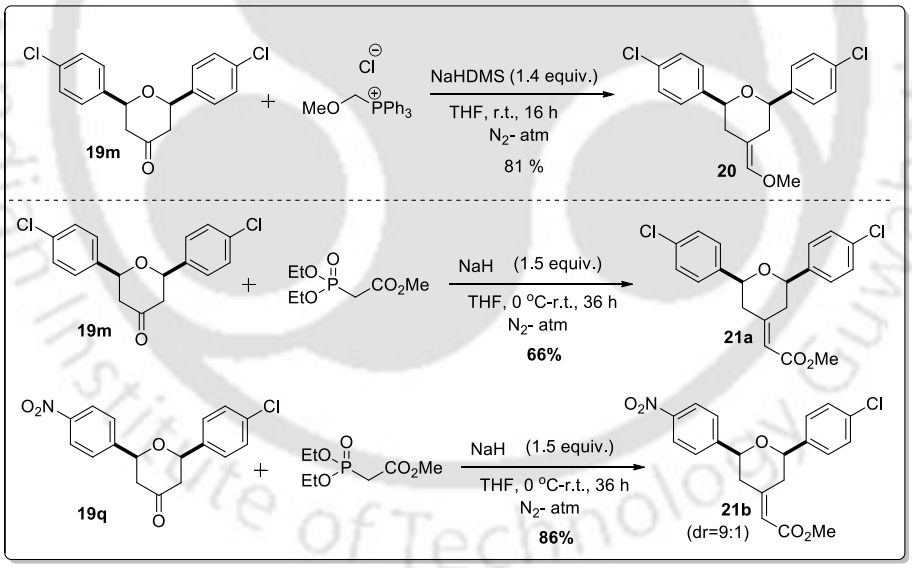
Scheme 2.5.1. *Plausible Mechanism of the Reaction*



2.6 Post-Synthetic Utility of the Reaction:

To explore the synthetic applicability of the products, several transformations were carried out as depicted in *Schemes 2.6.1−2.6.3*. Thus, the reaction of **19m** with (methoxymethyl)-triphenyl-phosphonium chloride in the presence of NaHDMS provided 2,6-bis(4-chlorophenyl)-(methoxymethylene)tetrahydro-2*H*-pyran **20** in 81% yield. Similarly, reaction of **19m** and **19q** with methyl 2-(diethoxyphosphoryl)acetate in the presence of NaH gave corresponding acetates **21a**−**21b** with 66% and 86% yields, respectively (*Scheme 2.6.1*). Compound **21b** is obtained as a diastereomeric mixture with a dr ratio of 9:1, which was confirmed by ^{1}H NMR spectroscopy. This result was determined from the intensity ratio of two peaks, specifically located at 8.22 ppm and 7.82 ppm (see Page 58). Importantly, the tetrahydropyran ring with a vinyl carboxylate group is a basic unit of many biologically active molecules, such as exiguolide[4] and bryostatin 1.[5]

Scheme 2.6.1. Wittig olefination

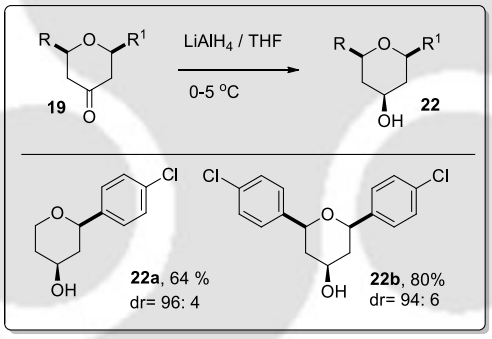


The carbonyl group of the tetrahydropyranones could be reduced by lithium aluminum hydride ($LiAlH_4$) to its hydroxy derivatives (*Scheme 2.6.2*). Thus, the reaction of **19c** and **19m** with $LiAlH_4$ provided **22a** (dr = 96:4) and **22b** (dr = 94:6) with 64% and 80% yields, respectively. Both products are *cis*-configured with respect to the 2,6-disubstituted groups. The small size of $LiAlH_4$ allows the hydride ion (H^-) to attack from the less hindered axial side, resulting in **22a** and **22b** as major

products. The diastereomeric ratio was determined from crude ^{1}H NMR spectroscopy of compound **22b**, where the intensity ratio of the two peaks corresponding to *cis* (H-2 and H-6) and *trans* (H-2 and H-6) protons (δ~5.01 and δ~4.51) for compound **22b** was found to be 94:6 (see Page 59). The *cis*-configuration is determined by NOE experiments (see *Figure 2.6.3.1* and Page 60-61) and X-ray crystallographic data of **22b**. In the NOE experiments, interactions between H-2 (δ=4.54) and H-4 (δ=4.15−4.07) indicate that these protons are on the same face. This observation confirms the presence of a *cis*-configuration. Interestingly, this type of scaffold with *cis*-configuration is present in natural products such as diosniponol **A**.

In order to investigate their utility toward the synthesis of biologically active molecules, the compounds **19f, 19k**, and **19g** were converted to their aminoguanidine derivatives **23a**−**23c** by reaction with aminoguanidine hydrochloride. It may be noted that these compounds possess anticancer activity (*Scheme 2.6.3*).[19]

Scheme 2.6.2. Synthesis of 4-hydroxytetrahydropyrans



Scheme 2.6.3. Synthesis of Anticancer Active Molecules

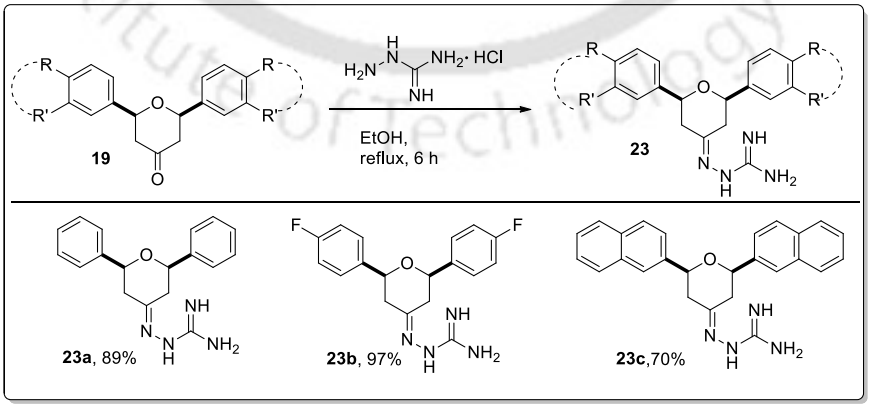
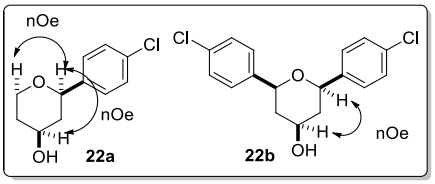


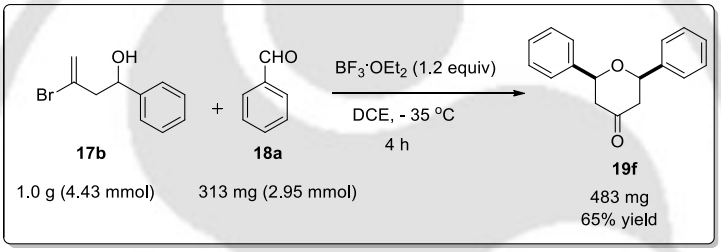
Figure 2.6.3.1. *nOe of compounds* ***22a*** *and* ***22b***



2.7 Gram scale experiment of the reaction

A gram scale experiment was performed between 3-bromo-1-phenylbut-3-en-1-ol **17b** (1.0 g, 4.43 mmol, 1.5 equiv) and benzaldehyde **18a** (313 mg, 2.95 mmol, 1.0 equiv) under standard reaction conditions to provide 65% (483 mg) yield of the corresponding product **19f** (*Scheme 2.7.1*).

Scheme 2.7.1. Gram scale experiment



2.8 Conclusion

In conclusion, an efficient synthesis of tetrahydropyran-4-one has been developed with high yields and excellent diastereoselectivity. The reaction is compatible with many functional groups. The post-synthetic application of the methodology enables it to provide a variety of new structural motifs such as enol ethers, esters, alcohols, and imines by manipulation of the carbonyl moiety, which is crucial for biologically active molecules and natural products. The methodology is extended to the synthesis of aminoguanidine derivatives, which are known as anticancer agents. Therefore, the methodology may be extended for the synthesis of other biologically active molecules where tetrahydropyran moieties are a core structural unit.

2.9 Experimental Section

2.9.1 General Information

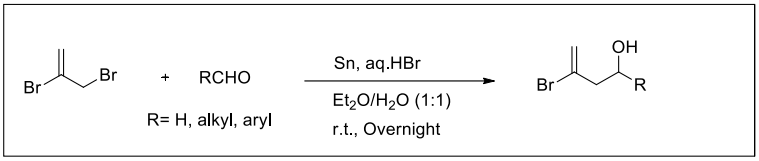
All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60−120 mesh size) was used for column chromatography. Reactions were

monitored by TLC on silica gel GF254 (0.25 mm). The reaction was carried out in Julabo FT903 to maintain a negative temperature. Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infrared (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 with tetramethyl silane as the internal standard for ^1H (600 MHz, 500 and 400 MHz) or $^{13}C\{^1H\}$ (150 MHz, 125 and 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin−spin coupling constants (J) are given in Hz. Structural assignments were made with additional information from NOESY and single-crystal XRD experiments. HRMS spectra were recorded using Q-TOF and micrOTOF-Q II mass spectrometer.

The starting material 3-bromobut-3-en-1-ol (**17a**),[20a] 3-bromo-1-phenylbut-3-en-1-ol (**17b**),[20b] 3-bromo-1-(*p*-tolyl)but-3-en-1-ol(**17d**),[20c] 3-bromo-1-(4-fluorophenyl)but-3-en-1-ol (**17e**),[20a] and 3-bromo-1-(4-chlorophenyl)but-3-en-1-ol (**17f**)[20d] were synthesized according to the reported literatures. The spectroscopic data of the above compounds are in good agreement with the literature values. The experimental procedure and the characterization data of the remaining starting material are given as follows.

2.9.2 General Procedure for the Preparation of Starting Materials (17c, 17g and 17h):

To a mixture of aldehyde (8.3 mmol, 1.0 equiv) and tin powder (1282 mg, 10.8 mmol, 1.3 equiv) in water/Et_2O (1:1, 24 mL) was added HBr (0.5 mL, 48% aq.). After 10 min, 2,3-dibromopropene (2159 mg,10.8 mmol, 1.3 equiv) was added slowly and stirred overnight at room temperature. After completion of the reaction, the reaction mixture was diluted with brine solution and the organic layer was extracted with diethyl ether (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The crude was subjected to column chromatography over silica gel using hexane and ethyl acetate as eluent to get the product up to 96%yield.



2.9.3 General procedure for the synthesis of (19a-19i, 19k-19u and 19w):

To a solution of alcohol (1.0 mmol, 1.5 equiv) and aldehyde (0.67 mmol, 1.0 equiv) in dry DCE (3 mL) was added $BF_3{\cdot}OEt_2$ (113 mg, 0.8 mmol, 1.2 equiv) dropwise at −35 °C under a nitrogen atmosphere. The reaction mixture was then stirred at −35 °C for 2 h, and progress of the reaction was monitored by TLC (ethyl acetate:hexane = 1:9). After completion of the reaction, the organic layer was extracted with ethyl acetate (3 × 10 mL) and washed with saturated sodium bicarbonate and brine solutions. The reaction mixture was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The crude was subjected to column chromatography over silica gel using ethyl acetate and hexane as eluents to get the product up to 88% yield.

2.9.4. Experimental procedure for the synthesis of 20:

To a suspension of (methoxymethyl) triphenyl phosphonium chloride (343mg, 1.0 mmol, 1.5 equiv) in THF (3 mL) was added NaHDMS (0.2 mL, 0.94 mmol, 1.40 equiv) over 10 min at −10 °C. The reaction mixture was stirred for 30 min, and a solution of 2,6-bis(4-chlorophenyl) dihydro-2*H*-pyran-4(3*H*)-one (215 mg, 0.67 mmol,1.0 equiv) in THF (2 mL) was added slowly to the reaction mixture. The reaction mixture was allowed to stir for 16 h at room temperature. After completion of the reaction, the organic layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered, and all volatiles were removed under reduced pressure. The crude was purified by column chromatography over silica gel using hexane and ethyl acetate as eluent to get a colorless solid in 81% yield.

2.9.5 General procedure for the synthesis of 21a-21b

To a suspension of NaH (23 mg, 1.0 mmol, 1.5 equiv, 60 wt % in mineral oil) in THF (2 mL) was added methyl 2-(diethoxyphosphoryl)acetate(317 mg, 1.51 mmol, 2.25 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, and ketone (0.67 mmol, 1.0 equiv) was added with THF (2 mL). The mixture was stirred at room temperature until full conversion of the ketone was detected by TLC. The reaction mixture was washed by brine solution and the organic layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers are dried over anhydrous Na_2SO_4 and filtered, and all volatiles were removed under reduced pressure by rotary evaporator. The crude was purified by column chromatography over silica gel using hexane and ethyl acetate as eluent to get 66−86%yield of the product.

2.9.6 General procedure for the synthesis of 22a-22b

To a suspension of $LiAlH_4$ (76 mg, 2.0 mmol, 2.0 equiv) in THF (2 mL) was added the corresponding ketone (1.0 mmol, 1.0 equiv) in THF (2 mL) at 0−5 °C under a N_2 atmosphere. The resulting solution was stirred for 3 h at 0−5 °C in an ice bath. The reaction mixture was then quenched by the addition of water (3.0 mL), NaOH solution (3.0 mL,1 M), and further diluted by water (7 mL). The organic layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers are dried over anhydrous Na_2SO_4 and filtered, and all volatiles were removed under reduced pressure and purified by column chromatography over silica gel using hexane and ethyl acetate as eluent to get 64−80% yields of the products.

2.9.7 General procedure for the synthesis of 23a-23c

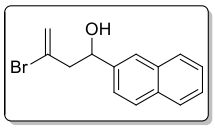
To a solution of ketone (0.5 mmol, 1.0 equiv) in absolute EtOH (3 mL) was added aminoguanidine hydrochloride (56 mg, 0.5 mmol, 1 equiv) at room temperature. The reaction mixture was refluxed at 80 °C in an oil bath until the full conversion of the ketone. After completion of the reaction (determined by TLC), the reaction mixture was allowed to cool to room temperature and concentrated by rotary evaporator. The crude was purified by column chromatography over silica gel by using ethyl acetate and methanol to get 70−97% yield of the product.

2.9.8 Experimental procedure for the gram-scale reaction

To a solution of 3-bromo-1-phenylbut-3-en-1-ol (**17b)** (1.0 g, 4.43 mmol, 1.5equiv) and benzaldehyde (**18a)** (313 mg, 2.95 mmol, 1.0 equiv) in dry DCE (14 mL) was added $BF_3{\cdot}OEt_2$ (500 mg, 3.54 mmol, 1.2 equiv) dropwise at −35 °C under the nitrogen atmosphere. The reaction mixture was then stirred at −35 °C for 4 h, and progress of the reaction was monitored by TLC (ethyl acetate:hexane = 1:9). After completion of the reaction, the organic layer was extracted with ethyl acetate (3 × 30 mL) and washed with saturated sodium bicarbonate and brine solutions. The reaction mixture was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The product **19f** was obtained in a 65% (483 mg, brown solid) yield by column chromatography over silica gel using hexane and ethyl acetate (9:1) as eluents.

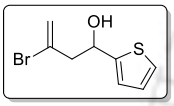
2.9.9 Characterization Data

3-Bromo-1-(naphthalen-2-yl)but-3-en-1-ol (17c):



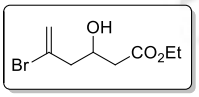
Colourless solid; R_f (hexane/EtOAc, 9:1) 0.55; mp 105–107 °C yield 2215 mg, 96%; mp 105 °C, IR (KBr, neat) ν 3383, 2909, 1630, 1051, 816, 748, 476 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 4 H), 7.40 – 7.38 (m, 2 H), 7.34 (d, *J* = 8.5 Hz, 1 H), 5.50 (s, 1 H), 5.40 (s, 1 H), 5.04 – 5.02 (m, 1 H), 2.92 – 2.83 (m, 1 H), 2.80 – 2.77 (m, 1 H), 2.72 – 2.68 (m, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 140.3, 133.3, 133.1, 130.1, 128.4, 128.1, 127.8, 126.3, 126.0, 124.8, 123.9, 120.0, 71.8, 51.0. HRMS (ESI) calcd. for $C_{14}H_{17}BrNO$ $(M + NH_4)^+$ 294.0488, found 294.0506.

3-Bromo-1-(thiophen-2-yl)but-3-en-1-ol (17g):



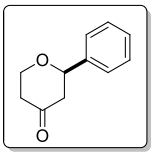
Brown liquid; R_f (hexane/EtOAc, 19:1) 0.48; yield 1572 mg, 81%; IR (KBr, neat) ν 3392, 2909, 1631, 1265, 1036, 893, 735, 553 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 5.0 Hz, 1 H), 6.99 – 6.98 (m, 1 H), 6.96 – 6.94 (m, 1 H), 5.67 (s, 1 H), 5.52 (s, 1 H), 5.27 – 5.24 (m, 1 H), 2.95 – 2.91 (m, 1 H), 2.86 – 2.82 (m, 1 H), 2.60 (s, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 146.7, 129.5, 126.9, 125.0, 124.3, 120.5, 68.0, 51.2. HRMS (ESI) calcd. for $C_8H_{10}BrOS$ $(M + H)^+$ 232.9630, found 232.9637.

Ethyl 5-bromo-3-hydroxyhex-5-enoate (17h):



Pale yellow liquid; R_f (hexane/EtOAc, 7:3) 0.57; yield 296 mg, 15%; IR (KBr, neat) ν 3449, 2925, 1631, 1170, 1030, 893, 537 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.71 (s, 1 H), 5.54 (s, 1 H), 4.38 – 4.34 (m, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 2.70 (dd, *J* = 14.4, 7.7 Hz, 1 H), 2.59 – 2.54 (m, 2 H), 2.48 – 2.43 (m, 1 H), 1.67 (s, 1 H), 1.28 (t, *J* = 7.1 Hz, 3 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 172.6, 129.8, 120.1, 66.1, 61.1, 48.3, 40.4, 14.4. HRMS (ESI) calcd. for $C_8H_{14}BrO_3$ $(M + H)^+$ 237.0121, found 237.0143.

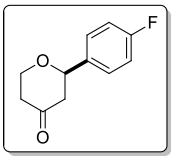
2-Phenyldihydro-2*H*-pyran-4(3*H*)-one (19a):



Pale yellow liquid; R_f (hexane/EtOAc, 9:1) 0.47; yield 72 mg, 61%; IR (KBr, neat) ν 2972, 2868, 1718, 1247, 1076, 822, 700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 4 H), 7.34 – 7.29 (m, 1 H), 4.64 (ddd, *J* = 14.6, 10.2 and 2.2 Hz, 1 H), 4.42 (ddd, *J* = 11.6, 7.4, and 1.6 Hz, 1 H), 3.83 (dt, *J* = 11.6 and 2.8 Hz, 1 H), 2.74 – 2.68 (m, 1

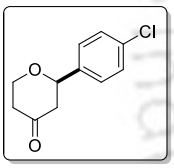
H), 2.66 – 2.60 (m, 2 H), 2.44 – 2.40 (m, 1 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 206.5, 140.8, 128.8, 128.3, 125.8, 79.9, 66.9, 50.1, 42.3. HRMS (ESI) calcd. for $C_{11}H_{16}NO_2$ $(M + NH_4)^+$ 194.1176, found 194.1190.

2-(4-Fluorophenyl)dihydro-2*H*-pyran-4(3*H*)-one (19b):



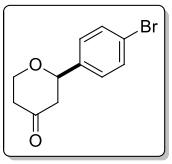
Pale yellow gum; R_f (hexane/EtOAc, 9:1) 0.40; yield 79 mg, 61%; IR (KBr, neat) ν 2969, 2858, 1716, 1602, 1220, 1026, 830, 773, 500 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.32 (m, 2 H), 7.07 – 7.04 (m, 2 H), 4.62 (dd, *J* = 10.3 and 3.9 Hz, 1 H), 4.42 (ddd, *J* = 11.7, 7.4 and 1.6 Hz, 1 H), 3.83 (dt, *J* = 11.7 and 2.9 Hz, 1 H), 2.74 – 2.69 (m, 1 H), 2.64 – 2.56 (m, 2 H), 2.43 (dd, *J* = 12.8 and 2.0 Hz, 1 H).$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 206.2, 162.7 (d, *J* = 245.0 Hz), 136.7 (d, *J* = 3.2 Hz), 127.7 (d, *J* = 8.1 Hz), 115.8 (d, *J* = 21.4 Hz), 79.4, 66.9, 50.2, 42.3. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ 47.86; HRMS (ESI) calcd. for $C_{11}H_{11}FNaO_2$ $(M+ Na)^+$ 217.0635, found 217.0655.

2-(4-Chlorophenyl)dihydro-2*H*-pyran-4(3*H*)-one (19c):



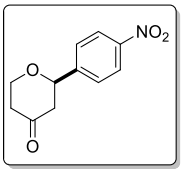
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.40; mp 62–64 °C, yield 88 mg, 62%; IR (KBr, neat) ν 3054, 2860, 1718, 1247, 1084, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.34 (m, 2 H), 7.32 – 7.30 (m, 2 H), 4.62 (dd, *J* = 10.8 and 3.4 Hz, 1 H), 4.43 (ddd, *J* = 11.6, 7.4 and 1.6 Hz, 1 H), 3.84 (ddd, *J* = 14.4, 11.6 and 2.8 Hz, 1 H), 2.77 – 2.68 (m, 1 H), 2.65 – 2.54 (m, 2 H), 2.47 – 2.41 (m, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 206.2, 139.4, 134.1, 129.1, 127.3, 79.3, 67.0, 50.1, 42.3. HRMS (ESI) calcd. for $C_{11}H_{15}ClNO_2$ $(M + NH_4)^+$ 228.0786, found 228.0769.

2-(4-Bromophenyl)dihydro-2*H*-pyran-4(3*H*)-one (19d):



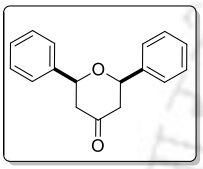
Colourless Solid; R_f (hexane/EtOAc, 9:1) 0.40; mp 96–99 °C, yield 115 mg, 67%; IR (KBr, neat) ν 2986, 2864, 1719, 1263, 1010, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 4.59 (dd, *J* = 11.1 and 3.1 Hz, 1 H), 4.41 (dd, *J* = 11.1 and 7.4 Hz, 1 H), 3.82 (dt, *J* = 11.9 and 2.8 Hz, 1 H), 2.74 – 2.66 (m, 1 H), 2.64 – 2.52 (m, 2 H), 2.44 – 2.40 (m, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 206.0, 139.9, 132.0, 127.5, 122.2, 79.2, 66.9, 50.0, 42.3. HRMS (ESI) calcd. for $C_{11}H_{12}BrO_2$ $(M + H)^+$ 255.0015, found 255.0034.

2-(4-Nitrophenyl)dihydro-2*H*-pyran-4(3*H*)-one (19e):



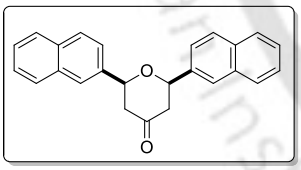
Brown Solid; R_f (hexane/EtOAc, 8:2) 0.40; mp 88–81 °C, yield, 107 mg, 72%; IR (KBr, neat) ν 2921, 2860, 1718, 1517, 1344, 1090, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.8 Hz, 2 H), 7.54 (d, *J* = 8.8 Hz, 2 H), 4.75 (dd, *J* = 11.5 and 2.8 Hz, 1 H), 4.48 (ddd, *J* = 11.6, 6.0 and 1.4 Hz, 1 H), 3.90 – 3.83 (m, 1 H), 2.79 – 2.72 (m, 1 H), 2.71 – 2.67 (m, 1 H), 2.56 – 2.44 (m, 2 H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 205.3, 147.9, 147.8, 126.5, 124.1, 78.7, 67.0, 49.9, 42.2. HRMS (ESI) calcd. for $C_{11}H_{12}NO_4$ $(M + H)^+$ 222.0761, found 222.0783.

2,6-Diphenyldihydro-2*H*-pyran-4(3*H*)-one (19f):



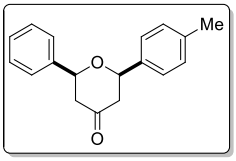
Brown Solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 86-88 °C, yield 149 mg, 88%; IR (KBr, neat) ν 2990, 2858, 1718, 1247, 1061, 754, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.4 Hz, 4 H), 7.41 (t, *J* = 7.4 Hz, 4 H), 7.34 (t, *J* = 7.4 Hz, 2 H), 4.86 (dd, *J* = 11.2 and 3.2 Hz, 2 H), 2.77 – 2.69 (m, 4 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 206.2, 140.9, 128.8, 128.3, 125.8, 79.1, 49.9. HRMS (ESI) calcd. for $C_{17}H_{20}NO_2$ $(M + NH_4)^+$ 270.1489, found 270.1474.

2,6-Di(naphthalen-2-yl)tetrahydro-4*H*-pyran-4-one (19g):



Yellow solid; R_f (hexane/EtOAc, 9:1) 0.47; mp 139–141 °C, yield 128 mg, 54%; IR (KBr, neat) ν 2921, 2853, 1712, 1242, 1051, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.85 (m, 8 H), 7.62 (d, *J* = 8.5 Hz, 2 H), 7.53 – 7.51 (m, 4 H), 5.06 (dd, *J* = 10.1, 4.2 Hz, 2 H), 2.89 – 2.84 (m, 4 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 206.2, 138.3, 133.5, 133.4, 128.8, 128.3, 128.0, 126.6, 126.5, 124.9, 123.9, 79.5, 49.9. HRMS (ESI) calcd. for $C_{25}H_{21}O_2$ $(M + H)^+$ 353.1536, found 353.1543.

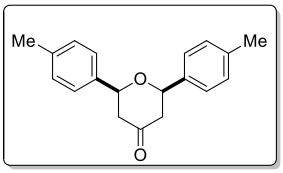
2-Phenyl-6-(*p*-tolyl)dihydro-2*H*-pyran-4(3*H*)-one (19h):



Pale yellow gum; R_f (hexane/EtOAc, 9:1) 0.60; yield 151 mg, 85%; IR (KBr, neat) ν 2957, 2853, 1720, 1616, 1186, 1087, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.5 Hz, 1 H), 7.41 – 7.28 (m, 5 H), 7.22 – 7.20 (m, 3 H), 4.86 – 4.79 (m, 2 H), 2.76 – 2.66 (m, 4 H), 2.37 (s, 3 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ

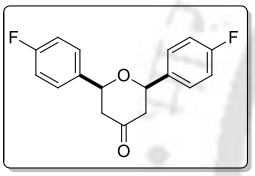
206.5, 141.0, 138.1, 138.0, 129.5, 129.4, 128.8, 128.2, 125.9, 79.1, 79.0, 49.9, 49.8, 21.4. HRMS (ESI) calcd. for $C_{18}H_{18}NaO_2$ $(M + Na)^+$ 289.1199, found 289.1181.

2,6-Di-*p*-tolyldihydro-2*H*-pyran-4(3*H*)-one (19i):



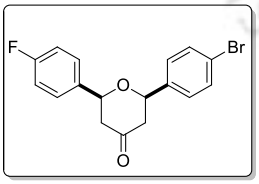
Pale yellow Solid; R_f (hexane/EtOAc, 9:1) 0.60; mp 90-92 °C, yield 111 mg, 59%; IR (KBr, neat) ν 2926, 2858, 1723, 1242, 1059, 812, 587 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.8 Hz, 4 H), 7.20 (d, *J* = 7.8 Hz, 4 H), 4.80 (dd, *J* = 9.1 and 5.1 Hz, 2 H), 2.72 – 2.66 (m, 4 H), 2.36 (s, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 206.8, 138.1, 138.0, 129.5, 125.9, 79.1, 50.0, 21.4. HRMS (ESI) calcd. for $C_{19}H_{21}O_2$ $(M + H)^+$ 281.1536, found 281.1532.

2,6-Bis(4-fluorophenyl)dihydro-2*H*-pyran-4(3*H*)-one (19k):



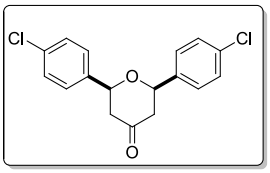
Pale yellow Solid; R_f (hexane/EtOAc, 9:1) 0.40; mp 141-143 °C, yield 162 mg, 84%; IR (KBr, neat) ν 2983, 2880, 1719, 1511, 1265, 1058, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 4 H), 7.10 – 7.05 (m, 4 H), 4.81 (dd, *J* = 10.8 and 3.4 Hz, 2 H), 2.73 – 2.62 (m, 4 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 205.6, 163.6 (d, *J* = 244.9 Hz), 136.6 (d, *J* = 3.2 Hz), 127.6 (d, *J* = 8.1 Hz), 115.7 (d, *J* = 21.4 Hz), 78.5, 49.7. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ 47.90; HRMS (ESI) calcd. for $C_{17}H_{18}F_2NO_2$ $(M + NH_4)^+$ 306.1300, found 306.1294.

2-(4-Bromophenyl)-6-(4-fluorophenyl)dihydro-2*H*-pyran-4(3*H*)-one (19l):



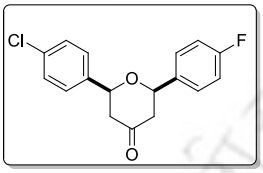
Pale yellow gum; R_f (hexane/EtOAc, 9:1) 0.40; yield 182 mg, 78%; IR (KBr, neat) ν 2921, 2873, 1718, 1224, 1069, 830, 522 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.4 and 1.8 Hz, 2 H), 7.41 (dt, *J* = 8.4 and 1.6 Hz, 2 H), 7.31 (dd, *J* = 8.4 and 1.6 Hz, 2 H), 7.08 (dt, *J* = 8.4 and 1.8 Hz, 2 H), 4.83 – 4.78 (m, 2 H), 2.73 – 2.60 (m, 4 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 206.4, 162.7 (d, *J* = 245.0 Hz), 139.7, 136.6, 132.1, 127.6, 122.3, 115.8 (d, *J* = 22.7 Hz), 78.6, 78.5, 49.8, 49.6. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ 47.85; HRMS (ESI) calcd. for $C_{17}H_{14}BrFKO_2$ $(M + K)^+$ 386.9793, found 386.9780.

2,6-Bis(4-chlorophenyl)dihydro-2*H*-pyran-4(3*H*)-one (19m):



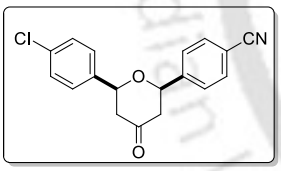
Pale yellow Solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 88-90 °C, yield 146 mg, 68%; IR (KBr, neat) ν 2972, 2860, 1720, 1242, 1087, 824, 517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.29 (m, 8 H), 4.80 (dd, *J* = 11.3 and 2.8 Hz, 2 H), 2.73 – 2.59 (m, 4 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 205.3, 139.2, 134.2, 129.1, 127.2, 78.5, 49.6. HRMS (ESI) calcd. for $C_{17}H_{14}Cl_2NaO_2$ $(M + Na)^+$ 343.0263, found 343.0254.

2-(4-Chlorophenyl)-6-(4-fluorophenyl)dihydro-2*H*-pyran-4(3*H*)-one (19n):



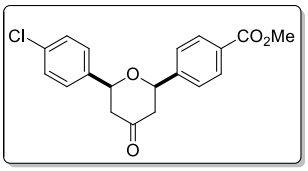
Pale yellow Solid; R_f (hexane/EtOAc, 9:1) 0.40; mp 86-88 °C, yield 163 mg, 80%; IR (KBr, neat) ν 2967, 2876, 1723, 1514, 1222, 1056, 827, 515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 3 H), 7. 37 (s, 2 H), 7.10 – 7.05 (m, 3 H), 4.83 – 4.81 (m, 1 H), 4.80 – 4.79 (m, 1 H), 2.73 – 2.63 (m, 4 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 205.5, 162.7 (d, *J* = 245.0 Hz), 139.3, 136.6, 134.1, 129.1, 127.7, 127.6, 127.2, 115.8 (d, *J* = 21.4 Hz), 78.6, 78.4, 49.8, 49.6. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ 47.89; HRMS (ESI) calcd. for $C_{17}H_{15}ClFO_2$ $(M + H)^+$ 305.0739, found 305.0716.

4-(6-(4-Chlorophenyl)-4-oxotetrahydro-2*H*-pyran-2-yl)benzonitrile (19o):



Brown gum; R_f (hexane/EtOAc, 8:2) 0.40; yield 148 mg, 71%; IR (KBr, neat) ν 2926, 2850, 2229, 1720, 1087, 835, 542 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 7.42 – 7.37 (m, 4 H), 4.90 (d, *J* = 11.7 and 2.6 Hz, 1 H), 4.84 (d, *J* = 11.7 and 3.0 Hz, 1 H), 2.78 – 2.57 (m, 4 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 204.6, 145.8, 138.9, 134.4, 132.8, 129.2, 127.2, 126.4, 118.7, 112.2, 78.6, 78.2, 49.5, 49.3. HRMS (ESI) calcd. for $C_{18}H_{14}ClNNaO_2$ $(M + Na)^+$ 334.0605, found 334.0587.

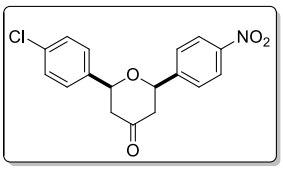
Methyl 4-(6-(4-chlorophenyl)-4-oxotetrahydro-2*H*-pyran-2-yl)benzoate (19p):



Brown gum; R_f (hexane/EtOAc, 8:2) 0.50; yield 162 mg, 70%; IR (KBr, neat) ν 2921, 2870, 1723, 1280, 1018, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 2 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 7.43 – 7.37 (m, 4 H), 4.90 (dd, *J* = 11.7 and 2.7 Hz, 1 H), 4.84 (dd, *J* = 11.7 and 2.8 Hz, 1 H), 3.92 (s, 3 H), 2.78 – 2.72 (m, 2 H), 2.68 – 2.62 (m, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz,

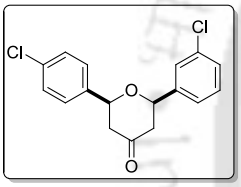
$CDCl_3$) δ 205.2, 166.9, 145.6, 139.2, 134.3, 130.3, 130.2, 129.2, 127.3, 125.7, 78.7, 78.6, 52.5, 49.7, 49.6. HRMS (ESI) calcd. for $C_{19}H_{18}ClO_4$ $(M + H)^+$ 345.0888, found 345.0892.

2-(4-Chlorophenyl)-6-(4-nitrophenyl)dihydro-2*H*-pyran-4(3*H*)-one (19q):



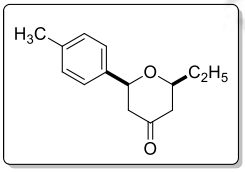
Brown gum; R_f (hexane/EtOAc, 8:2) 0.50; yield 178 mg, 80%; IR (KBr, neat) ν 2978, 2867, 1719, 1596, 1491, 1265, 1012, 733, 514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.6 Hz, 2 H), 7.62 (d, *J* = 8.6 Hz, 2 H), 7.39 (s, 4 H), 4.96 (dd, *J* = 11.8 and 2.8 Hz, 1 H), 4.86 (dd, *J* = 11.8 and 3.1 Hz, 1 H), 2.81– 2.74 (m, 2 H), 2.71 – 2.59 (m, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 204.4, 147.9, 147.7, 138.8, 134.4, 129.2, 127.2, 126.6, 124.3, 78.7, 78.0, 49.5, 49.4. HRMS (ESI) calcd. for $C_{17}H_{14}ClKNO_4$ $(M + K)^+$ 370.0243, found 370.0279.

2-(3-Chlorophenyl)-6-(4-chlorophenyl)dihydro-2*H*-pyran-4(3*H*)-one (19r):



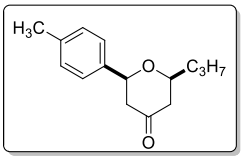
Pale yellow gum; R_f (hexane/EtOAc, 9:1) 0.50; yield 172 mg, 80%; IR (KBr, neat) ν 2986, 2853, 1718, 1336, 1067, 784, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.43 (m, 1 H), 7.38 – 7.34 (m, 3 H), 7.33–7.26 (m, 4 H), 4.80 (dd, *J* = 11.4 and 3.0 Hz, 2 H), 2.75 – 2.59 (m, 4 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 204.9, 142.6, 139.2, 134.9, 134.2, 130.2, 129.1, 128.6, 127.3, 126.1, 124.0, 78.5, 78.4, 49.6, 49.5. HRMS (ESI) calcd. for $C_{17}H_{14}Cl_2KO_2$ $(M + K)^+$ 359.0002, found 359.0009.

2-Ethyl-6-(*p*-tolyl)dihydro-2*H*-pyran-4(3*H*)-one (19s):



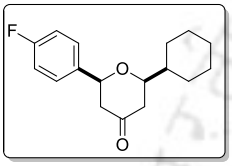
Colourless liquid; R_f (hexane/EtOAc, 9:1) 0.50; yield 108 mg, 74%; IR (KBr, neat) ν 2966, 2872, 1717, 1246, 1061, 807, 551 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.9 Hz, 2 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 4.60 (dd, *J* = 11.2 and 3.1 Hz, 1 H), 3.71 – 3.66 (m, 1 H), 2.63 – 2.54 (m, 2 H), 2.46 (dt, *J* = 14.3 and 2.3 Hz, 1 H), 2.38 (s, 1 H), 2.35 (s, 3 H), 1.80 – 1.75 (m, 1 H), 1.69 – 1.63 (m, 1 H), 1.01 (t, *J* = 7.5 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 207.6, 138.3, 137.9, 129.5, 125.8, 78.8, 78.7, 49.8, 47.6, 29.6, 21.4, 9.9. HRMS (ESI) calcd. for $C_{14}H_{22}NO_2$ $(M+NH_4)^+$ 236.1645, found 236.1662.

2-Propyl-6-(*p*-tolyl)dihydro-2*H*-pyran-4(3*H*)-one (19t):



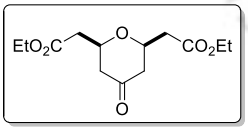
Colourless gum; R_f (hexane/EtOAc, 19:1) 0.40; yield 109 mg, 70%; IR (KBr, neat) ν 2926, 2867, 1716, 1257, 1066, 807, 497 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.7 Hz, 2 H), 7.18 (d, *J* = 7.7 Hz, 2 H), 4.60 (dd, *J* = 11.3 and 3.0 Hz, 1 H), 3.78 – 3.73 (m, 1 H), 2.63 – 2.54 (m, 2 H), 2.45 (dt, *J* = 14.3 and 2.3 Hz, 1 H), 2.35 (s, 3 H), 1.78 – 1.72 (m, 1 H), 1.61 – 1.48 (m, 3 H), 1.46 – 1.41 (m, 1 H), 0.94 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 207.6, 138.3, 137.9, 129.5, 125.9, 78.8, 77.4, 49.8, 48.0, 38.8, 21.4, 18.7, 14.2. HRMS (ESI) calcd. for $C_{15}H_{20}NaO_2$ $(M + Na)^+$ 255.1356, found 255.1374.

2-Cyclohexyl-6-(4-fluorophenyl)dihydro-2*H*-pyran-4(3*H*)-one (19u):



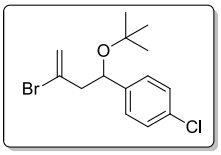
Colourless gum; R_f (hexane/EtOAc, 9:1) 0.60; yield 126 mg, 68%; IR (KBr, neat) ν 2926, 2852, 1716, 1223, 1064, 830, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.33 (m, 2 H), 7.06 (t, *J* = 8.7 Hz, 2 H), 4.59 (dd, *J* = 11.6 and 2.7 Hz, 1 H), 3.54 – 3.50 (m, 1 H), 2.62 (dt, *J* = 14.2 and 2.3 Hz, 1 H), 2.51 – 2.45 (m, 2 H), 2.42 – 2.36 (m, 1 H), 1.98 – 1.94 (m, 1 H), 1.79 – 1.74 (m, 3 H), 1.72 – 1.67 (m, 2 H), 1.63 – 1.57 (m, 1 H), 1.22 – 1.13 (m, 2 H), 1.11 – 1.03 (m, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 207.7, 162.5 (d, *J* = 244.5 Hz) 137.3 (d, *J* = 3.1 Hz), 127.4 (d, *J* = 8.0 Hz), 115.7 (d, *J* = 21.2 Hz), 81.7, 78.0, 50.0, 45.2, 43.4, 29.0, 28.6, 26.7, 26.3, 26.2. ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$) δ 47.23. HRMS (ESI) calcd. for $C_{17}H_{21}FKO_2$ $(M + K)^+$ 315.1157, found 315.1140.

Diethyl 2,2'-(4-oxotetrahydro-2*H*-pyran-2,6-diyl)diacetate (19w):



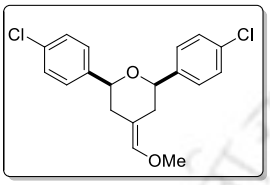
Yellow gum; R_f (hexane/EtOAc, 8:2) 0.42; yield 100 mg, 55%; IR (KBr, neat) ν 2980, 2922, 1723, 1251, 1024, 858 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.15 (q, *J* = 7.1 Hz, 4 H), 4.11 – 4.07 (m, 2 H), 2.67 (dd, *J* = 15.4, 7.4 Hz, 2 H), 2.51 – 2.46 (m, 4 H), 2.32 – 2.27 (m, 2 H), 1.27 – 1.25 (m, 6 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 205.3, 170.2, 73.5, 61.0, 46.9, 41.4, 14.4. HRMS (ESI) calcd. for $C_{13}H_{20}NaO_6$ $(M + Na)^+$ 295.1152, found 295.1146.

1-(3-Bromo-1-(*tert*-butoxy)but-3-en-1-yl)-4-chlorobenzene (19x):



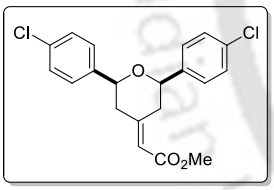
Colourless liquid; R_f (hexane/EtOAc, 19:1) 0.57; yield 21 mg, 10%; IR (KBr, neat) ν 2974, 2854, 1630, 1487, 1364, 1191, 1068, 1012, 822, 573 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 4 H), 5.46 (s, 1 H), 5.38 (d, *J* = 1.6 Hz, 1 H), 4.77 – 4.74 (m, 1 H), 2.76 – 2.72 (m, 1 H), 2.52 – 2.48 (m, 1 H), 1.13 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 143.9, 132.8, 130.5, 128.5, 127.7, 119.9, 74.9, 71.5, 52.6, 28.9. HRMS (ESI) calcd. for $C_{14}H_{18}BrClKO$ $(M + K)^+$ 354.9861, found 354.9840.

2,6-Bis(4-chlorophenyl)-4-(methoxymethylene)tetrahydro-2*H*-pyran (20):



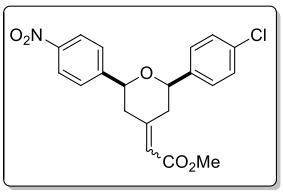
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.60 ; mp 97–99 °C, yield 190 mg, 81%; IR (KBr, neat) ν 2934, 2840, 1690, 1489, 1128, 1084, 817, 723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 4 H), 7.34 – 7.32 (m, 4 H), 6.01 (s, 1 H), 4.48 – 4.45 (m, 2 H), 3.62 (s, 3 H), 3.00 (d, *J* = 13.9 Hz, 1 H), 2.27 – 2.24 (m, 1 H), 2.20 – 2.15 (m, 1 H), 1.96 – 1.90 (m, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 141.6, 141.3, 141.2, 133.3, 133.2, 128.7, 128.6, 127.4, 127.3, 112.2, 80.5, 79.2, 59.8, 38.1, 33.7. HRMS (ESI) calcd. for $C_{19}H_{19}Cl_2O_2$ $(M + H)^+$ 349.0757, found 349.0750.

Methyl-2-(2,6-bis(4-chlorophenyl)dihydro-2*H*-pyran-4(3*H*)-ylidene)acetate (21a):



Colourless gum; R_f (hexane/EtOAc, 9:1) 0.70; yield 167 mg, 66%; IR (KBr, neat) ν 2952, 2853, 1715, 1150, 1056, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.38 (m, 3 H), 7.36 – 7.33 (m, 5 H), 5.85 (s, 1 H), 4.60 – 4.54 (m, 2 H), 4.18 (d, *J* = 14.0 Hz, 1 H), 3.73 (s, 3 H), 2.51–2.46 (m, 2 H), 2.20 – 2.15 (m, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.9, 155.9, 140.3, 140.2, 133.8, 133.7, 128.9, 128.8, 127.5, 127.4, 115.6, 79.9, 79.4, 51.4, 44.8, 37.9. HRMS (ESI) calcd. for $C_{20}H_{19}Cl_2O_3$ $(M + H)^+$ 377.0706, found 377.0697.

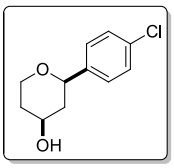
Methyl 2-(2-(4-chlorophenyl)-6-(4-nitrophenyl)dihydro-2*H*-pyran-4(3*H*)-ylidene)acetate (geometric isomers; 9:1, **21b**):



Yellow gum; R_f (hexane/EtOAc, 9:1) 0.52; yield 223 mg, 86%; IR (KBr, neat) ν 2951, 2854, 1712, 1519, 1435, 1292, 1057, 855, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 – 8.21 (m, 2 H, major), 7.82 (d, *J* = 8.1 Hz, 2 H, minor), 7.65 – 7.60 (m, 2 H, major), 7.51 (d, *J* = 8.1 Hz, 2 H, minor), 7.42 – 7.35 (m, 4 H), 5.89 (s, 1 H), 4.74 – 4.67 (m, 1 H), 4.63 – 4.57 (m, 1 H), 4.29–4.19

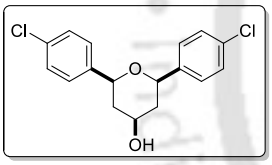
(m, 1 H), 3.74 (s, 3 H), 2.58 – 2.42 (m, 2 H), 2.24 – 2.13 (m, 1 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 166.8, 166.7, 155.0, 154.9, 148.9, 148.7, 147.8, 147.7, 140.0, 139.8, 134.1, 133.9, 131.1, 129.7, 129.0, 128.9, 127.43, 127.38, 126.8, 126.7, 124.0, 123.9, 116.1, 116.0, 80.0, 79.5, 78.5, 51.5, 44.6, 37.7. HRMS (ESI) calcd. for $C_{20}H_{22}ClN_2O_5$ $(M + NH_4)^+$ 405.1212, found 405.1230.

2-(4-Chlorophenyl)tetrahydro-2*H*-pyran-4-ol (22a) :



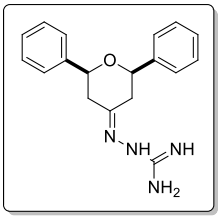
Colourless liquid; R_f (hexane/EtOAc, 8:2) 0.51; yield 136 mg, 64%; IR (KBr, neat) ν 3368, 2944, 1492, 1362, 1066, 1014, 821, 592 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 4 H), 4.28 (dd, *J* = 11.6 and 2.2 Hz, 1 H), 4.16 (ddd, 11.6, 4.8 and 1.8 Hz, 1 H), 3.95 – 3.88 (m, 1 H), 3.56 (dt, *J* = 12.2 and 2.2 Hz, 1 H), 2.17 – 2.12 (m, 1 H), 1.98 – 1.93 (m, 1 H), 1.84 (brs, 1 H), 1.65 – 1.57 (m, 1 H), 1.47 (dd, *J* = 11.6 and 11.6 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 140.7, 133.5, 128.8, 127.5, 77.8, 68.4, 66.5, 43.9, 35.6. HRMS (ESI) calcd. for $C_{11}H_{14}ClO_2$ $(M + H)^+$ 213.0677, found 213.0668.

2,6-Bis(4-chlorophenyl)tetrahydro-2H-pyran-4-ol (22b):



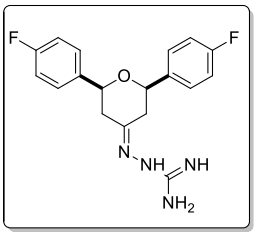
White solid; R_f (hexane/EtOAc, 8:2) 0.52; mp 113–115 ºC, yield 258 mg, 80%; IR (KBr, neat) ν 3367, 2921, 1492, 1378, 1086, 1067, 822, 589 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 8 H), 4.54 (dd, *J* = 11.6 and 2.0 Hz, 2 H), 4.15 – 4.07 (m, 1 H), 2.28 – 2.23 (m, 2 H), 1.72 (brs, 1 H), 1.58 – 1.50 (m, 2 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 140.5, 133.5, 128.8, 127.5, 77.5, 68.6, 43.1. HRMS (ESI) calcd. for $C_{17}H_{16}Cl_2KO_2$ $(M + K)^+$ 361.0159, found 361.0158.

2-(2,6-Diphenyldihydro-2*H*-pyran-4(3*H*)-ylidene)hydrazinecarboximidamide (23a):



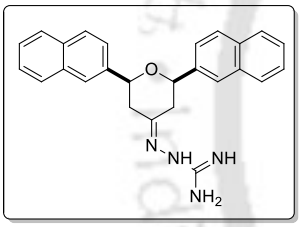
Colorless solid; R_f (EtOAc /MeOH, 19:1) 0.47; mp 75–77 ºC, yield 137 mg, 89%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 2 H), 7.49 (d, *J* = 7.7 Hz, 2 H), 7.45 (d, *J* = 7.7 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.32 (t, *J* = 7.7 Hz, 3 H), 7.25 – 7.23 (m, 1 H), 4.67 (d, *J* = 11.3 Hz, 1 H), 4.61 (d, *J* = 11.2 Hz, 1 H), 3.50 (d, *J* = 14.7 Hz, 1 H), 2.73 (d, *J* = 13.8 Hz, 1 H), 2.51 – 2.46 (m, 1 H), 2.05 – 2.00 (m, 1 H).$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 156.8, 155.9, 141.2, 128.8, 128.7, 128.2, 128.0, 125.9, 125.8, 79.8, 77.9, 42.8, 36.8.

2-(2,6-Bis(4-fluorophenyl)dihydro-2*H*-pyran-4(3*H*)-ylidene)hydrazinecarboximidamide (23b):



Colorless solid; R_f (EtOAc /MeOH, 19:1) 0.49; mp 272–274 °C; yield 167 mg, 97%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.61 (s, 2 H), 7.60 – 7.57 (m, 3 H), 7.52 (t, *J* = 7.1 Hz, 2 H),7.22 (t, *J* = 8.7 Hz, 4 H), 4.79 (d, *J* = 11.2 Hz, 1 H), 4.73 (d, *J* = 11.5 Hz, 1 H), 3.50 (d, *J* = 14.5 Hz, 1 H), 2.66 (d, *J* = 13.6 Hz, 1 H), 2.60 – 2.55 (m, 1 H), 2.29 (t, *J* = 13.0 Hz, 1 H).^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 161.6 (d, *J* = 242.1 Hz), 161.5 (d, *J* = 242.0 Hz), 156.2, 154.1, 137.6, 137.5, 127.9, 127.8, 115.1 (d, *J* = 21.2 Hz), 115.0 (d, *J* = 21.2 Hz), 77.8, 76.3, 41.5, 35.8. ^{19}F NMR (470 MHz, DMSO-d_6) δ 47.93, 47.86.

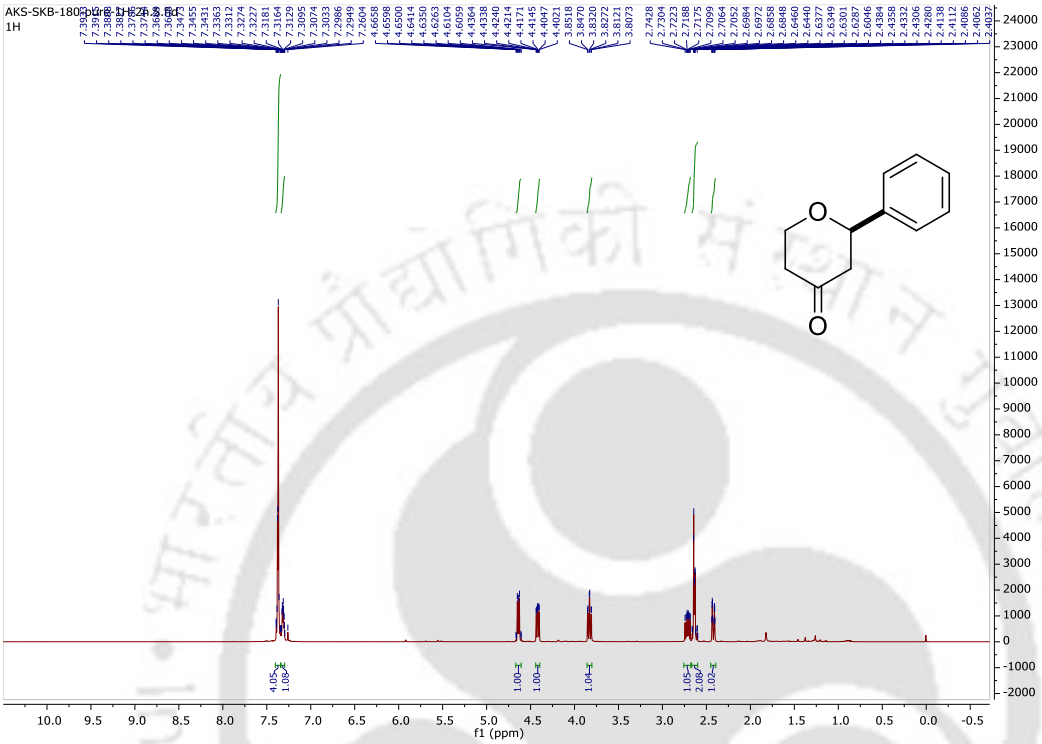
2-(2,6-Di(naphthalen-2-yl)dihydro-2*H*-pyran-4(3*H*)-ylidene)hydrazinecarboximidamide (23c) :

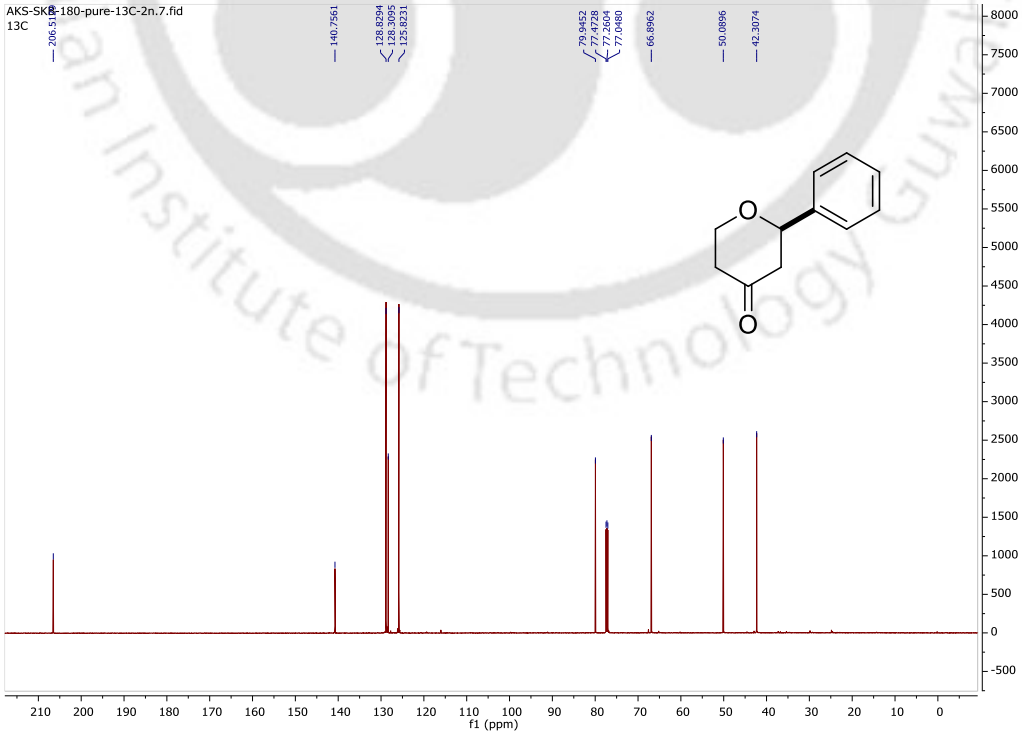


Colorless solid; R_f (EtOAc /MeOH, 7:3) 0.59; mp 183–185 °C; yield 143 mg, 70%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.81 (m, 6 H), 7.74 (s, 1 H), 7.68 (t, *J* = 8.6 Hz, 2 H), 7.50 – 7.46 (m, 3 H), 7.43 – 7.39 (m, 2 H), 7.36 – 7.34 (d, *J* = 7.7 Hz, 1 H), 4.52 (t, *J* = 13.6 Hz, 2 H), 3.35 (d, *J* = 14.6 Hz, 1 H), 2.52 (d, *J* = 13.9 Hz, 1 H), 2.07 – 2.03 (m, 1 H), 1.45 (t, *J* = 13.1 Hz, 1 H).^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 156.7, 155.4, 138.8, 138.5, 133.43, 133.41, 133.3, 133.1, 128.5, 128.4, 128.3, 127.93, 127.85, 126.5, 126.3, 126.2, 124.8, 124.6, 124.09, 124.05, 79.6, 77.7, 42.2, 36.5.

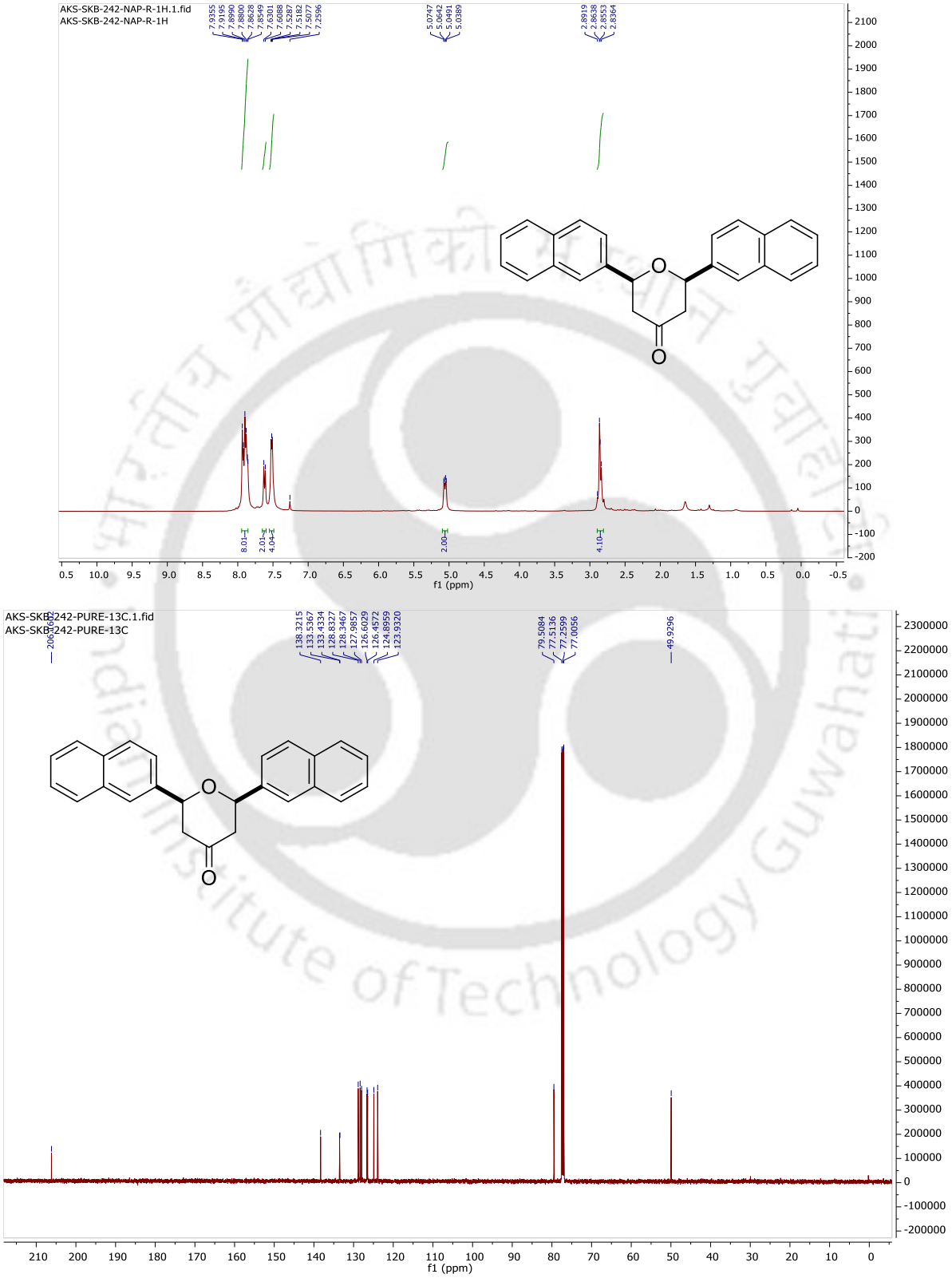
2.9.10 Representative Spectra and crystal parameter

^{1}H(600 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (150 MHz, $CDCl_3$) spectra of **19a**

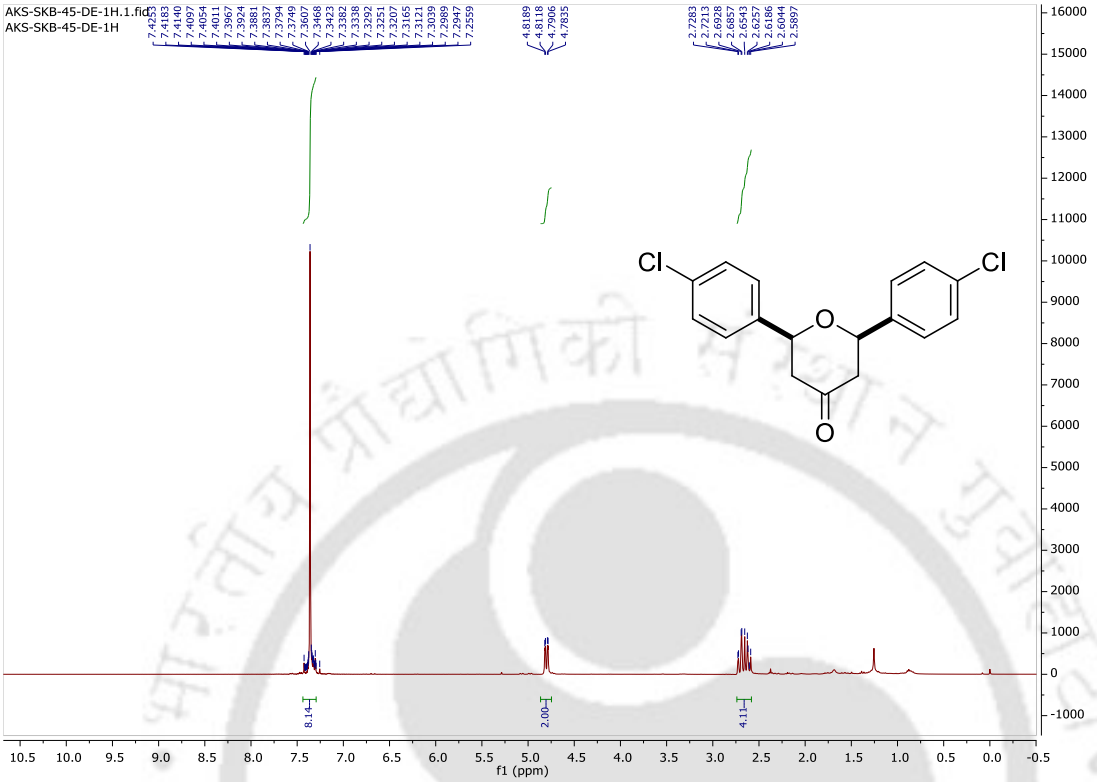


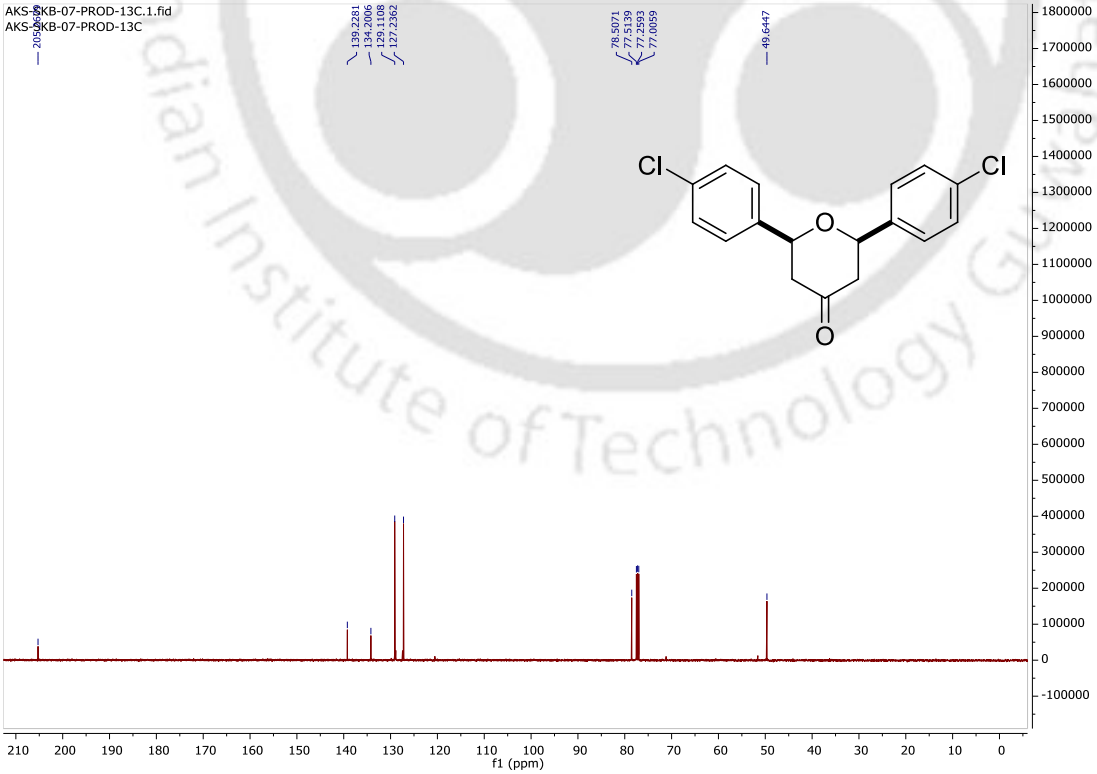


^{1}H (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **19g**

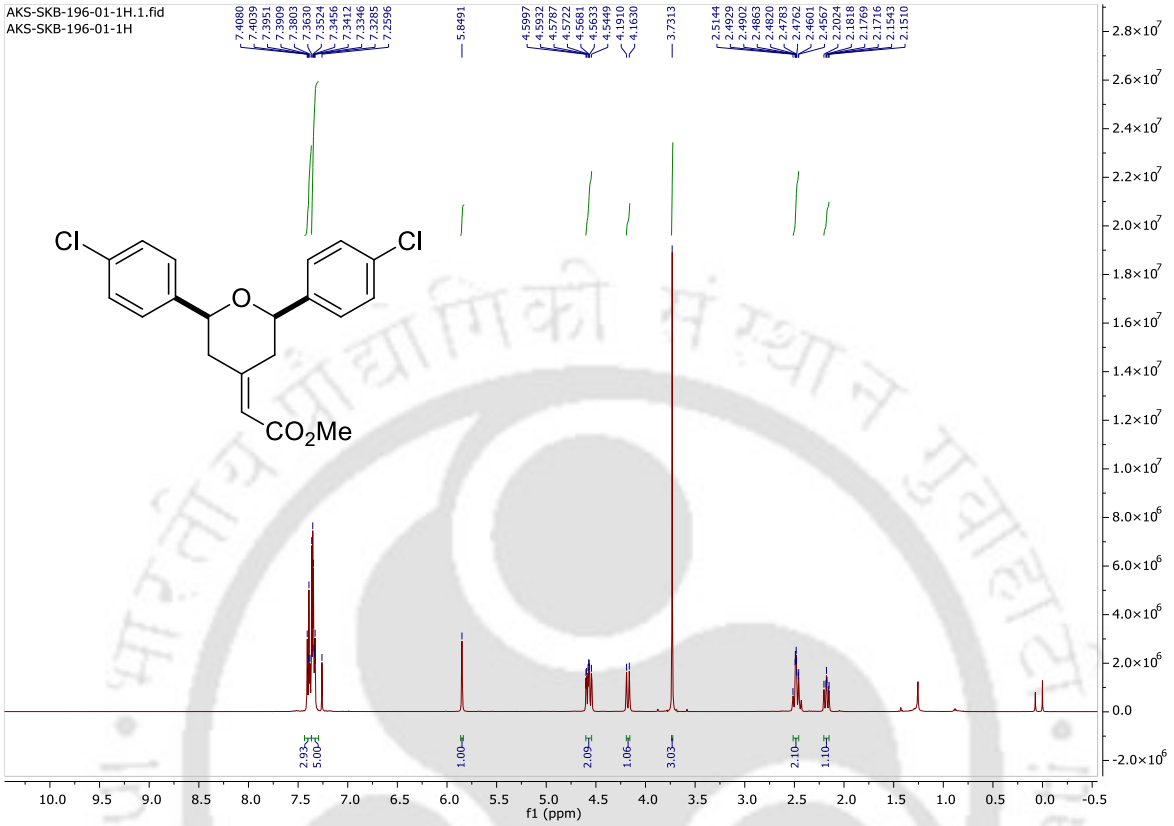


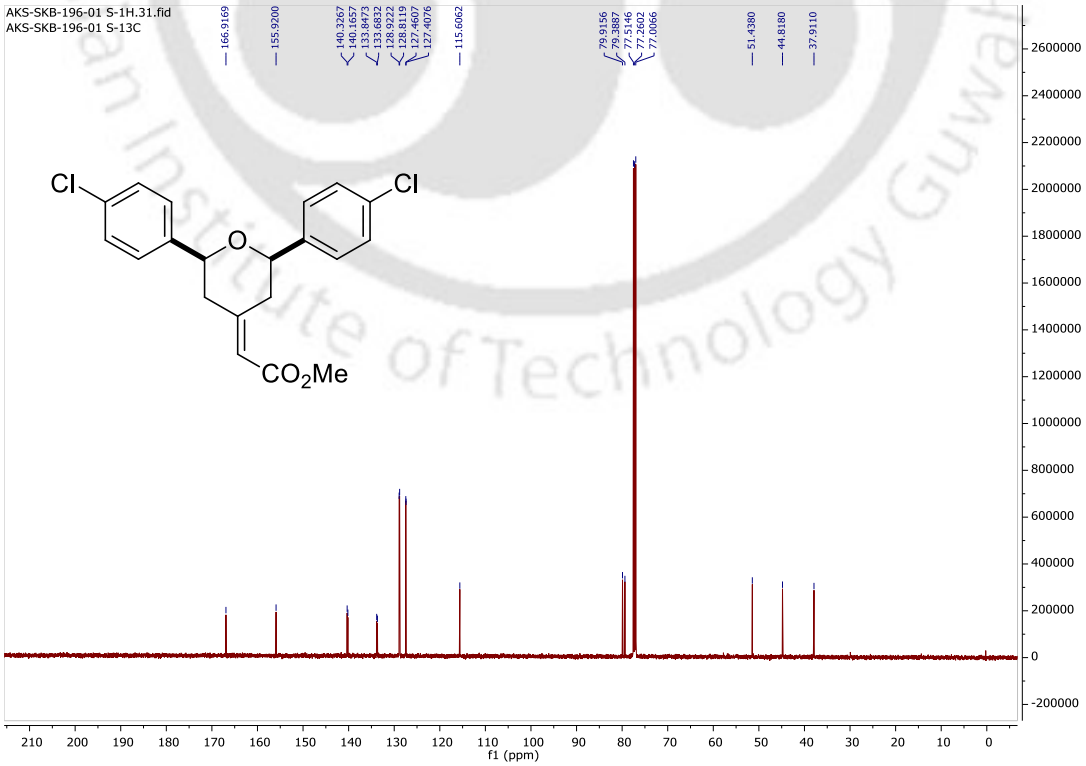
^{1}H (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100 MHz, $CDCl_3$) spectra of **19m**



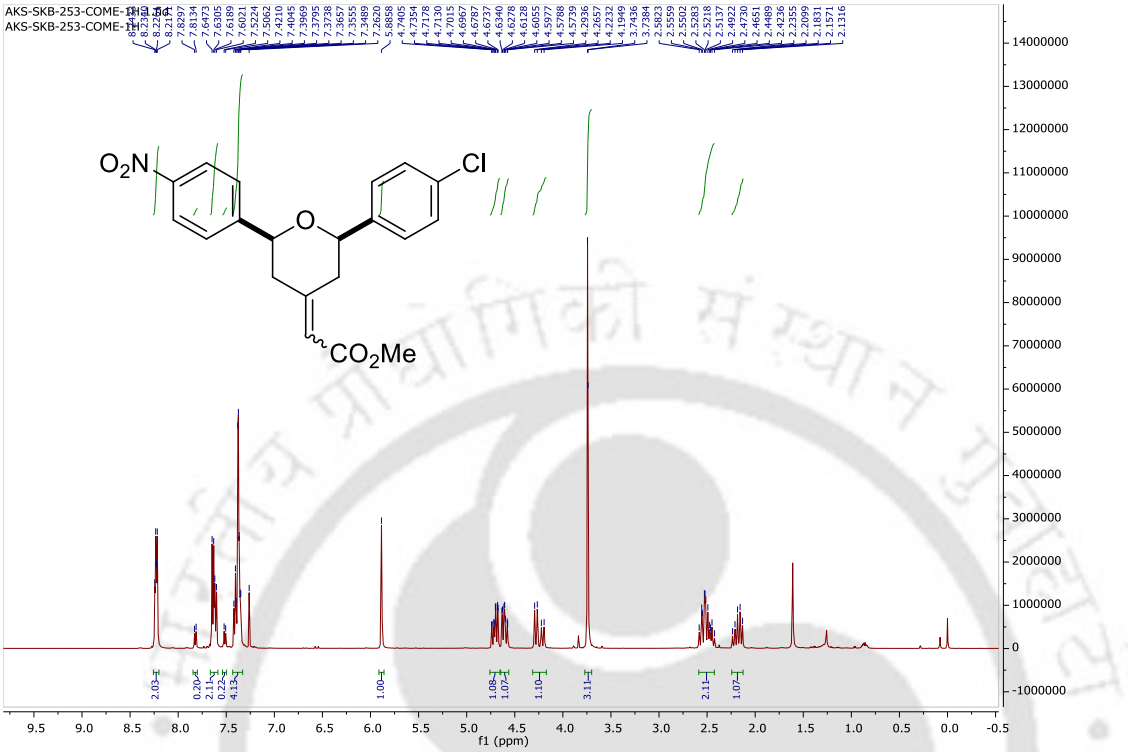


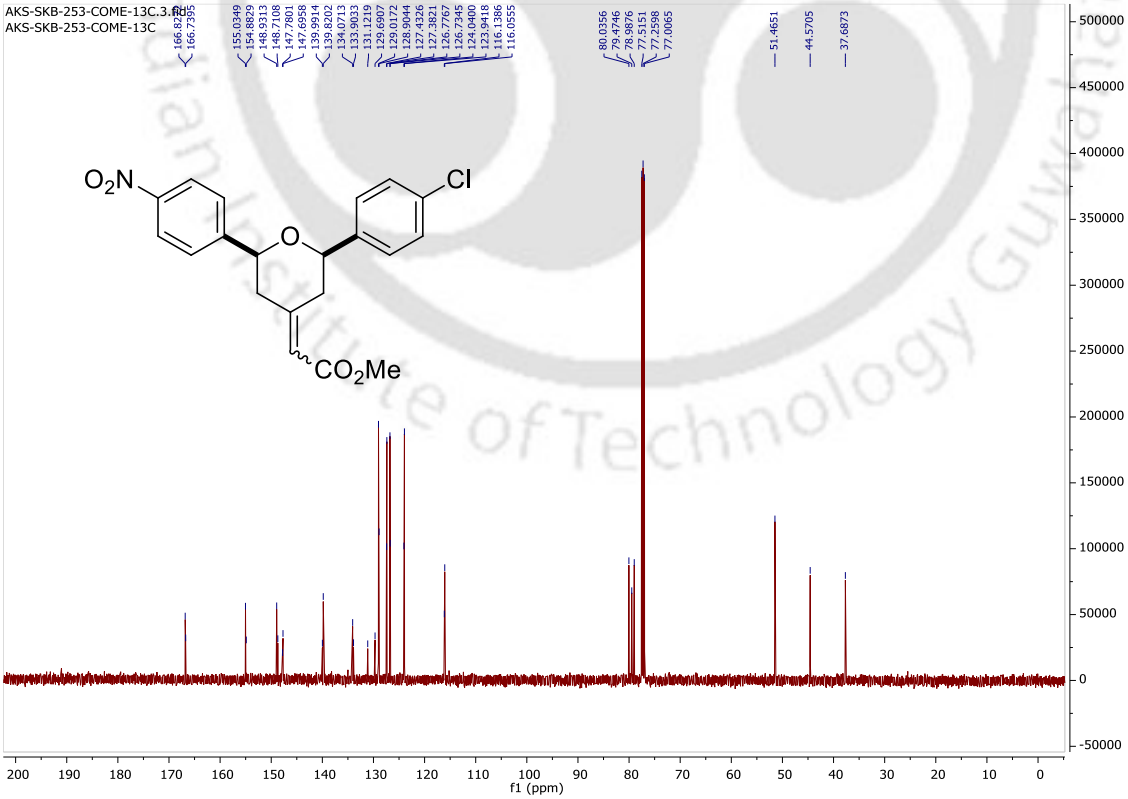
^{1}H (500 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **21a**



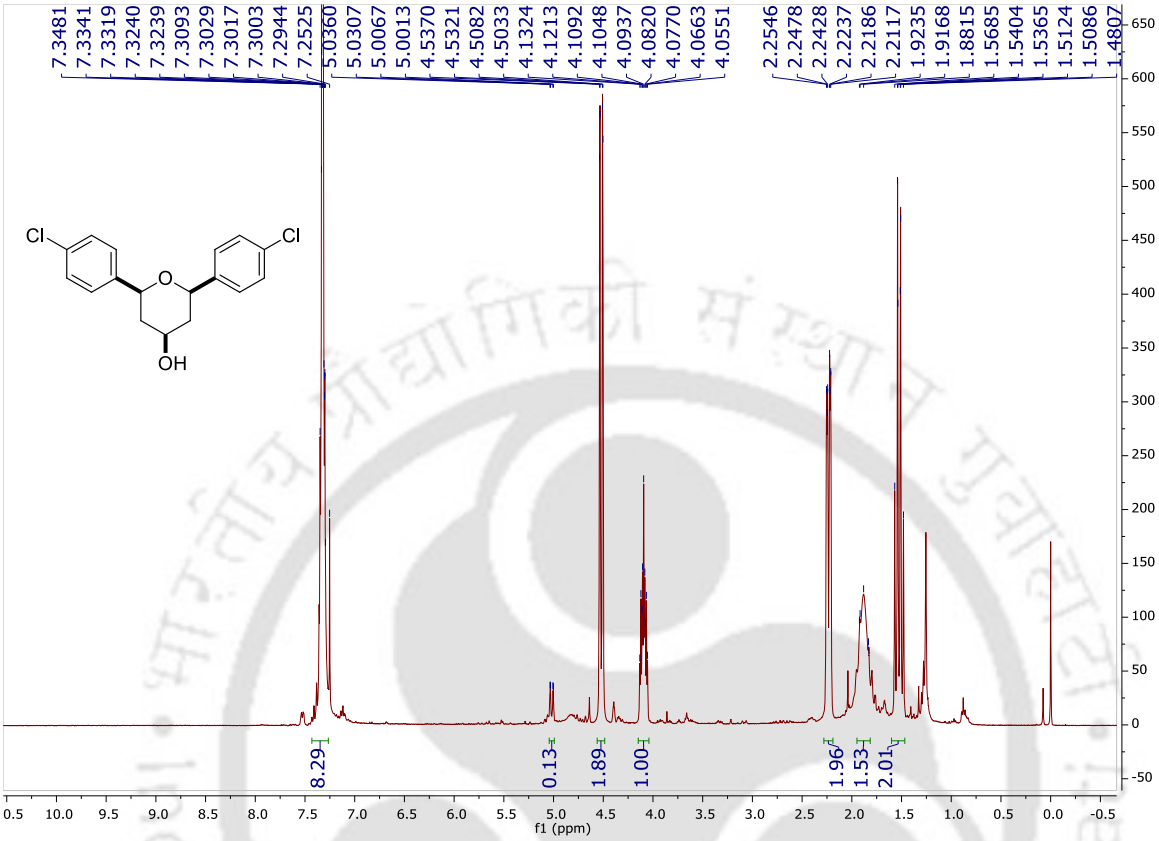


^{1}H (500 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **21b**

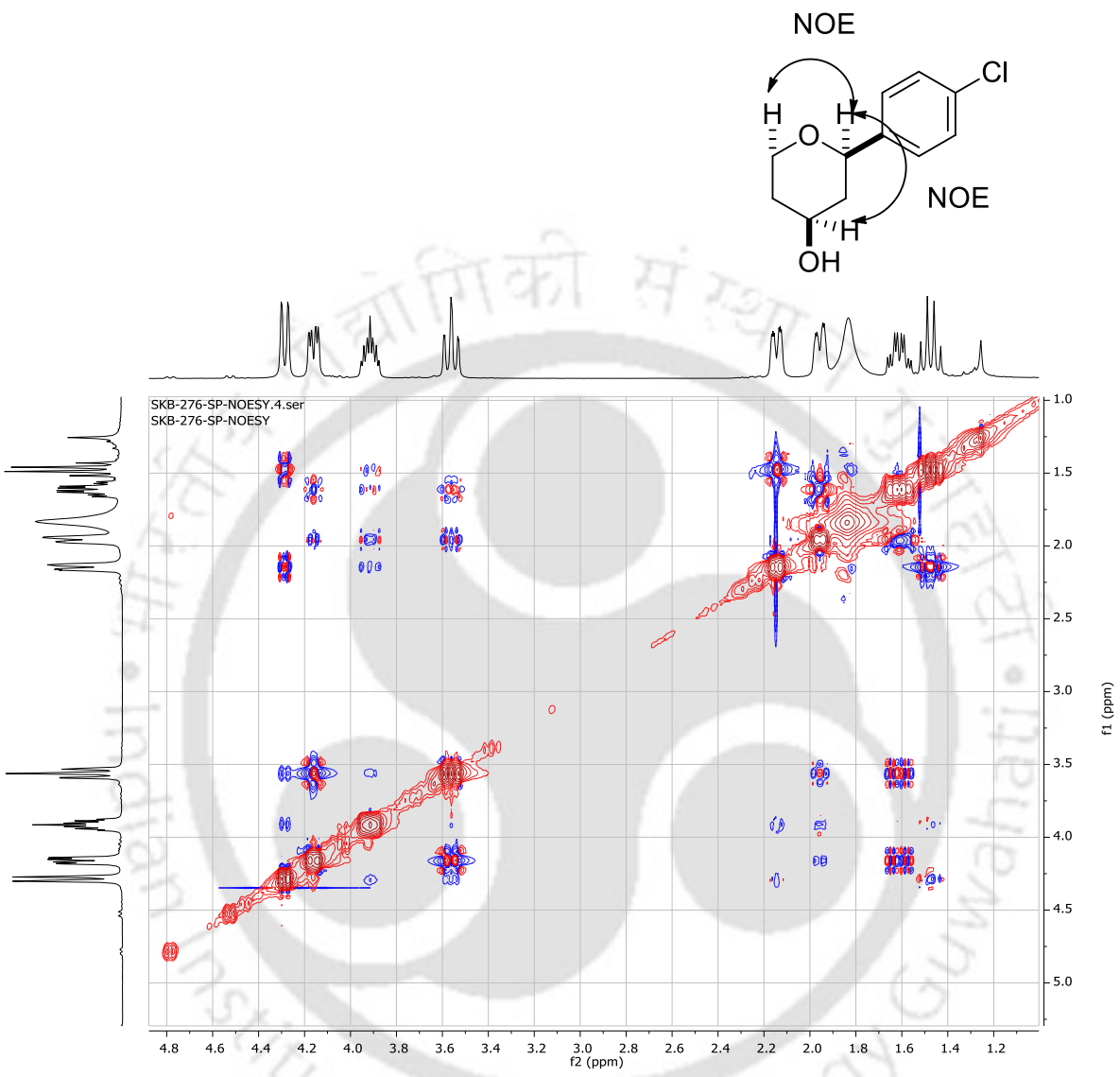




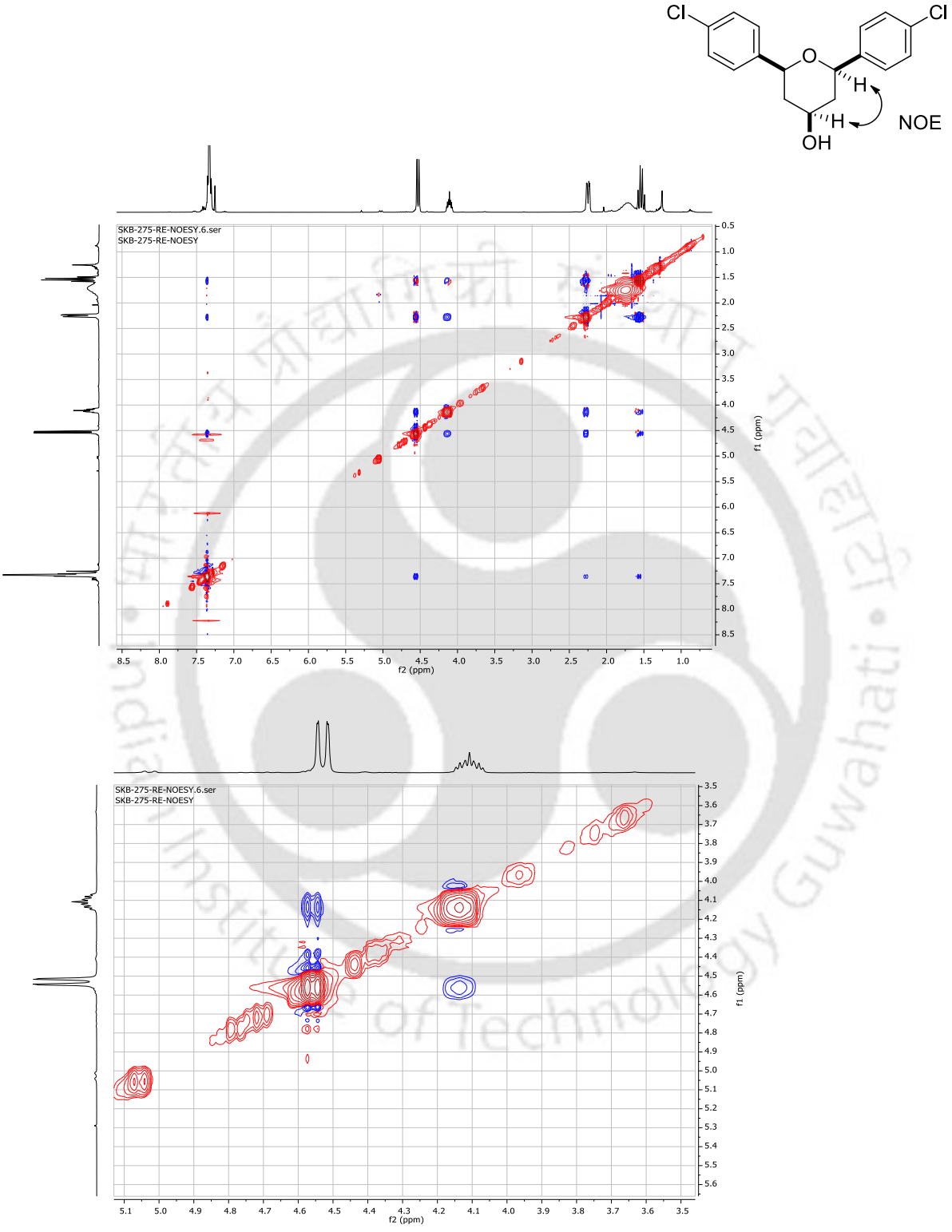
Crude ^{1}H (400 MHz, $CDCl_3$) spectrum of **22b**



NOESY spectrum of compound **22a** (400 MHz, $CDCl_3$)



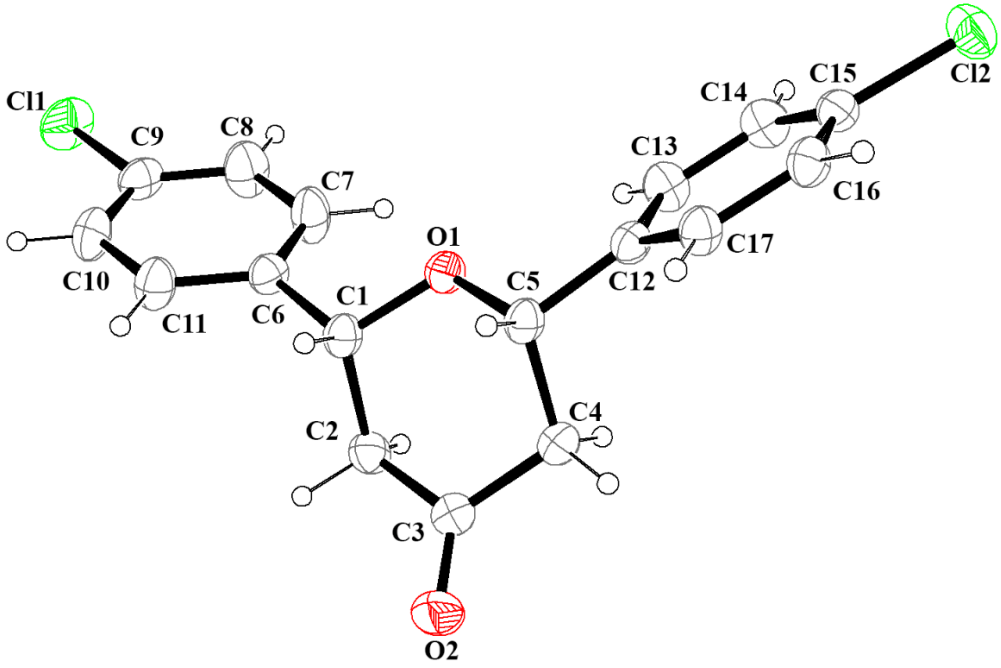
NOESY spectrum of compound **22b** (400 MHz, $CDCl_3$)



The crystal parameters of compound 19m

	CCDC 2211987
Formula	$C_{17}H_{14}Cl_2O_2$
Formula weight	321.18
T/K	273
Crystal system	monoclinic
Space group	P 21/c
• *a*/Å	16.154(5)
• *b*/Å	8.965(3)
• *c*/Å	11.543(4)
• *α*/°	90
• *β*/°	110.700(7)
• *γ*/°	90
• *V*/Å^3	1563.7(8)
• Z	4
Abs. Coeff./mm^{-1}	0.416
Abs. Correction	'none'
GOF on F^2	1.083
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0560 *wR2* = 0.1575
R indices [all data]	*R1* = 0.0617 *wR2* = 0.1675

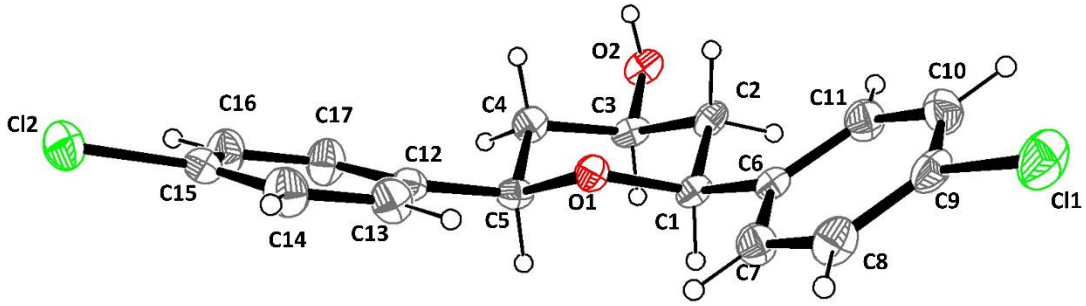
ORTEP diagram of compound **19m** with 30% probability



The crystal parameters of compound 22b

	CCDC 2239584
Formula	$C_{17}H_{16}Cl_2O_2$
Formula weight	323.20
T/K	297
Crystal system	orthorhombic
Space group	P n a 21
• *a*/Å	4.8261(6)
• *b*/Å	28.786(3)
• *c*/Å	11.0636(13)
• *α*/°	90
• *β*/°	90
• *γ*/°	90
• *V*/Å^3	1537.0(3)
• Z	4
Abs. Coeff./mm^{-1}	0.423
Abs. Correction	'none'
GOF on F^2	0.899
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0350 *wR2* = 0.0994
R indices [all data]	*R1* = 0.0380 *wR2* = 0.1078

ORTEP diagram of compound **22b** with 30% probability



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Chapter 3:

Stereoselective Synthesis of *gem*-Dihalopiperidines *via* Halo-Aza-Prins Cyclization Reaction: Access to Piperidin-4-ones and Pyridines

3.1 Importance and Applications

Nitrogen heterocyclic compounds are found in many biologically active molecules and natural products, especially in alkaloids.[1] Among them, the piperidine ring is widely distributed in alkaloids,[2] and is an important scaffold for drug discovery and development.[3] For example, Dienomycin C (**IV**), an alkaloid isolated from the Streptomyces strain MC67-C1, has been identified as possessing antibacterial activity against certain strains of Mycobacterium tuberculosis.[4] Similarly, the piperidinone motif is found in novel monoacylglycerol Lipase inhibitors,[5] α-glucosidase inhibitors,[6] and anticancer agents;[7] such as compounds **I** and **II** exhibit the ability to inhibit both N-myristoyltransferase (NMT) and cellular growth.[7] On the other hand, functionalized pyridine derivatives have long been known as important biologically active compounds.[8] For example, compound **V** functions as a 5-HT1A receptor agonist and acts as an antidepressant, while sulphapyridine (**III**) serves as an antibacterial agent[8c] (Figure 1).

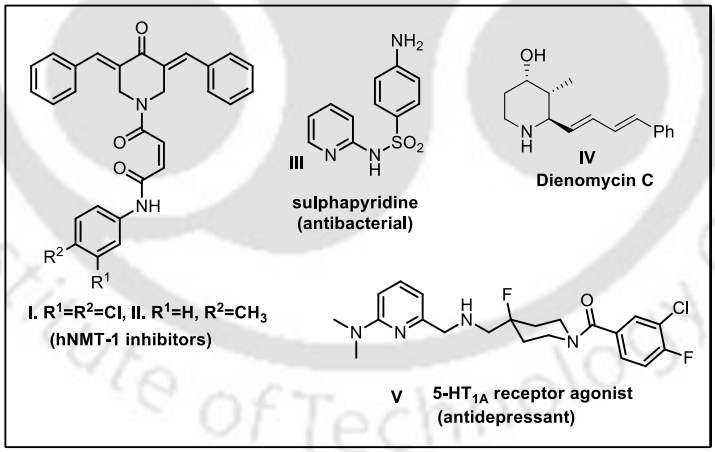
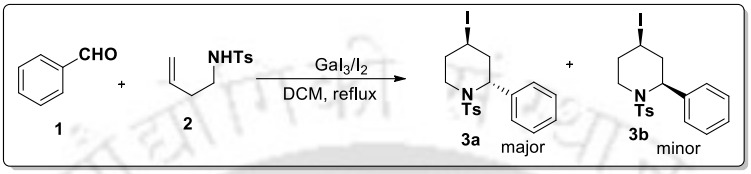


Figure 3.1: *Biologically active molecules.*

3.2 An Overview of Relevant Synthetic Methods

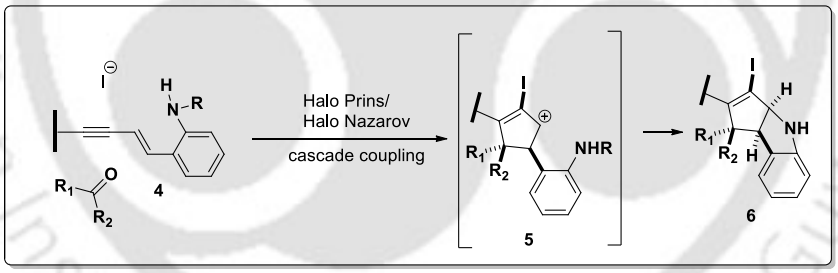
Halo Prins and aza-Prins cyclization are well known for the synthesis of various heterocyclic compounds. The basic overview of Halo Prins and aza-Prins cyclization is described in chapter **1**, sections **1.4.5.1** and **1.5**, along with a brief discussion on the synthesis of halogenated compounds.

Yadav *et al*. synthesized 4-Iodopiperidines with high selectivity through aza-Prins-cyclization utilizing a catalytic amount of gallium(III) iodide and a stoichiometric quantity of iodine.[9] In this method, the reaction of benzaldehyde with *N*-tosylhomoallyl amine in the presence of 10 mol% GaI_3 and a stoichiometric amount of molecular iodine at ambient temperature for 6.5 hours afforded 4-iodo-2-phenylpiperidine (**3**) in 91% yield with *trans*-selectivity (*Scheme 3.2.1*).



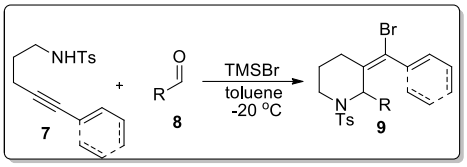
Scheme 3.2.1

Frontier and coworkers reported the synthesis of indolines *via* a halo-Prins/halo-Nazarov cyclization strategy.[10] This involves the assembly of cyclopentannulated indolines through the intramolecular capture of an intermediate halo-cyclopentenyl cation by an aniline moiety (*Scheme 3.2.2*).



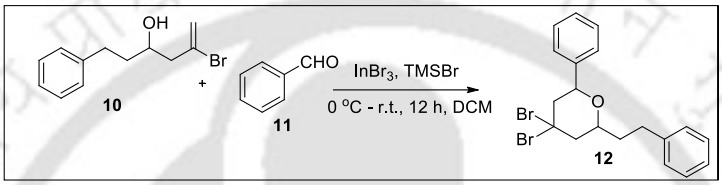
Scheme 3.2.2

The same group synthesized various nitrogen-containing heterocycles through alkynyl aza-Prins cyclization.[11] The reaction involves the synthesis of tosyl-piperidine **9** by the corresponding sulfonamides **7** and aldehyde **8** in the presence of TMSBr in toluene at -20 ^{o}C (*Scheme 3.2.2*).



Scheme 3.2.3

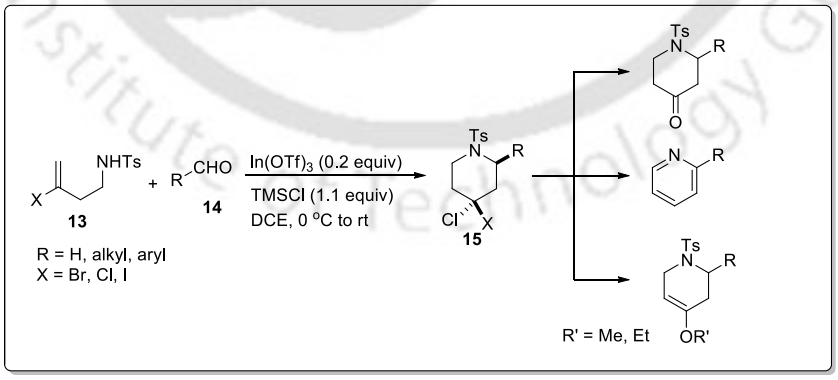
In 2018, Zhou *et al*. reported the synthesis of 4,4-dihalotetrahydropyran (**12**) through the reaction of an aldehyde with a bromo-substituted homoallylic alcohol[12] (*Scheme 3.2.4*).



Scheme 3.2.4

3.3 Present Work

Due to the prevalence of piperidines, piperidinones, and pyridines in pharmaceuticals and natural products, their synthesis remains an area of enormous interest to the synthetic chemist. Therefore, an intensive effort has been made to develop new and innovative synthetic routes for the synthesis of such compounds. Aza-Prins cyclization, which



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involves the in situ generation of an iminium ion followed by a nucleophilic attack of an alkene or an alkyne, is a well-known reaction for the synthesis of nitrogen heterocyclic compounds.[13]

Although halo-Prins/ halo-aza-Prins cyclization, wherein a halide ion acts as a nucleophile to give mono-halogenated compounds, is well established,[14] the halo-aza-Prins reaction, which provides *gem* dihalo compounds, has not yet been reported. Considering the importance of these compounds, we hereby present an efficient method for the synthesis of 4,4-dihalopiperidine derivatives from *N*-(3-halobut-3-en-1-yl)-4-methylbenzenesulfonamide and aldehyde, catalyzed by $In(OTf)_3$, resulting in excellent yields. The dihalopiperidine is converted to tetrahydropiperidinone using Ac_2O/Et_3N in DCM/H_2O (1:1). It is also utilized for the synthesis of pyridine scaffold by treatment with DBU. Further, the dihalopiperidine is transformed to its enol ether derivatives using KOH in alcohol.

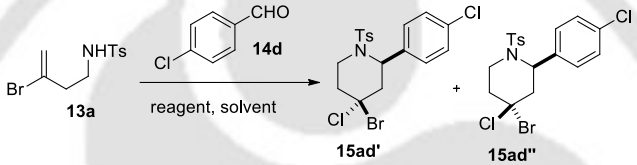
3.4 Results and Discussions

3.4.1 Optimization of the Reaction

Initially, *N*-(3-bromobut-3-en-1-yl)-4-methylbenzenesulfonamide (**13a**) and 4-chloro-benzaldehyde (**14d**) were chosen as model substrates and treated with 1.2 equiv of $BF_3{\cdot}OEt_2$ in dichloromethane (DCM) at 0 ^oC to room temperature for 2 h (Table 3.4.1.1, entry 1). To our dismay, not a trace amount of the product was isolated; instead, some decomposed product was observed on the TLC plate. Therefore, the reaction was performed at 0 ^oC but did not give any product (Table 3.4.1.1, entry 2). However, when the reaction was carried out with 1.2 equiv of $FeCl_3$ in DCM at 0 ^oC to rt for 12 h, 4-bromo-4-chloro-1-tosylpiperidine was isolated with 51% yield (Table 3.4.1.1, entry 3). Inspired by this observation, the reaction was screened with other Lewis acids such as $InCl_3$ and $TiCl_3$ (Table 3.4.1.1, entries 4-5), but was disappointed with no yield for the former and 43% yield for the latter. On the other hand, $FeCl_3$ under reflux conditions gave decomposed products (Table 3.4.1.1, entry 6). In order to observe the effect of the additive, the reaction was performed with a catalytic amount of $FeCl_3$ in the presence of 1.1 equiv of TMSCl in DCM at 0 ^oC to rt (Table 3.4.1.1, entry 7). To our delight, the yield was increased to 79%. When the reaction was performed with 0.2 equiv of indium(III) triflate ($In(OTf)_3$) in the presence of 1.1 equiv of TMSCl gave 88% yield (Table 3.4.1.1, entry 8). Other triflates such as $Bi(OTf)_3$ and $Cu(OTf)_2$ failed to improve the yield (Table 3.4.1.1, entries 9-10). Further changes $In(OTf)_3$ loading to 0.1 and 0.3 equiv did not provide better yield (Table 3.4.1.1, entries 11 and 12). Switching the solvent from DCM to dichloroethane (DCE) and considering 0.2 equivalents of $In(OTf)_3$ with 1.1 equiv of TMSCl at 0 °C to room temperature for 12 h resulted in 93% yield

(Table 3.4.1.1, entry 13). Decreasing the time to 8 h produced only 80% yield with unreacted starting materials (Table 3.4.1.1, entry 14). The reaction was also performed with other solvents like toluene and CH_3CN, but the yield was not improved in all these cases (Table 3.4.1.1, entries 15 and 16). Additive like TMSBr was found to be ineffective in generating the corresponding *gem*-dibromide derivative; this may be due to its less ionic character than TMSCl (Table 3.4.1.1, entry 17). Therefore, 0.2 equiv of $In(OTf)_3$ and 1.1 equiv of TMSCl in DCE at 0 ^oC to rt were found to be the optimal conditions for the reaction. The diastereoselectivity was assessed using ^1H NMR spectroscopy and found to be 9:1, based on the intensity ratio of two peaks located at 4.74 ppm and 4.89 ppm, respectively (see Page 95).

Table 3.4.1.1: Optimization of the reaction[a]



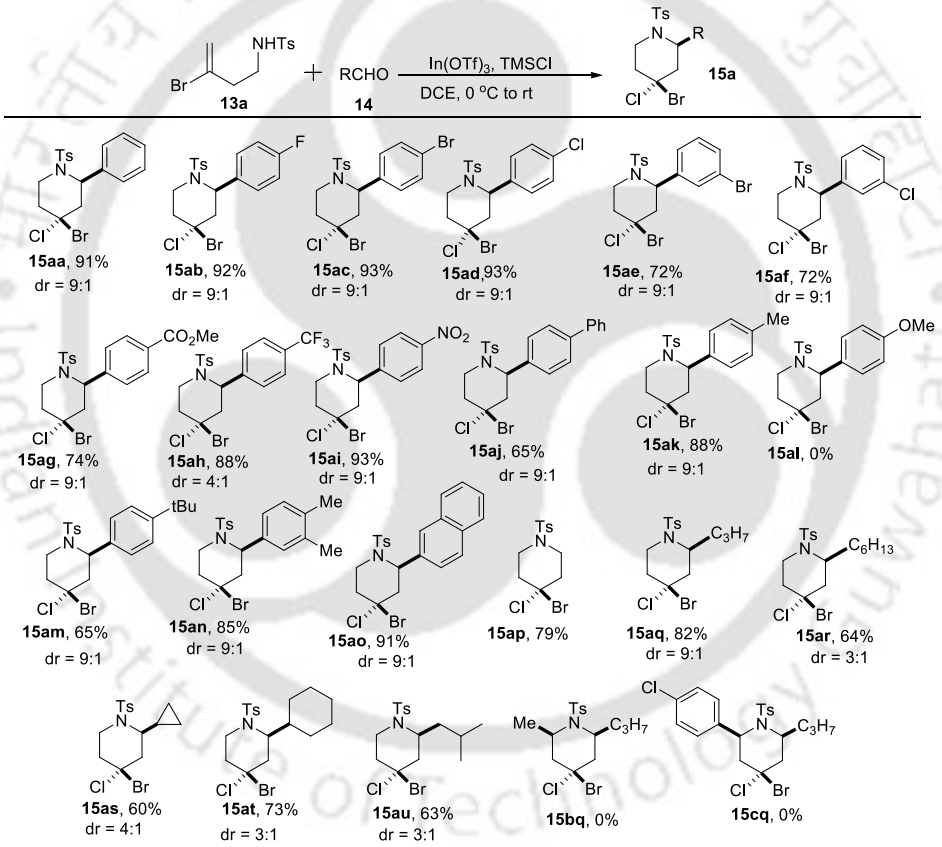
S. No	Reagents (equiv.)	Solvent	Temp.	Time/h	%Yield[bd] (**15ad′**:**15ad′′**)=**15ad** (= 9:1)
1	$BF_3{\cdot}OEt_2$ (1.2)	DCM	0 ^{o}C-rt	2	--[c]
2	$BF_3{\cdot}OEt_2$ (1.2)	DCM	0 ^{o}C	12	NR
3	$FeCl_3$ (1.2)	DCM	0 ^{o}C-rt	12	51
4	$InCl_3$ (1.2)	DCM	0 ^{o}C-rt	12	NR
5	$TiCl_3$ (1.2)	DCM	0 ^{o}C-rt	12	43
6	$FeCl_3$ (1.2)	DCM	40 ^{o}C	2	--[c]
7	$FeCl_3$ (0.2) + TMSCl (1.1)	DCM	0 ^{o}C-rt	12	79
8	$In(OTf)_3$ (0.2) + TMSCl (1.1)	DCM	0 ^{o}C-rt	12	88
9	$Bi(OTf)_3$ (0.2) + TMSCl (1.1)	DCM	0 ^{o}C-rt	12	76
10	$Cu(OTf)_2$ (0.2) + TMSCl (1.1)	DCM	0 ^{o}C-rt	12	74
11	$In(OTf)_3$ (0.1) + TMSCl (1.1)	DCM	0 ^{o}C-rt	12	84
12	$In(OTf)_3$ (0.3) + TMSCl (1.1)	DCM	0 ^{o}C-rt	12	86
13	**$In(OTf)_3$ (0.2) + TMSCl (1.1)**	**DCE**	**0 ^{o}C-rt**	**12**	**93**
14	$In(OTf)_3$ (0.2) + TMSCl (1.1)	DCE	0 ^{o}C-rt	8	80
15	$In(OTf)_3$ (0.2) + TMSCl (1.1)	toluene	0 ^{o}C-rt	12	83
16	$In(OTf)_3$ (0.2) + TMSCl (1.1)	CH_3CN	0 ^{o}C-rt	12	NR
17	$In(OTf)_3$ (0.2) + TMSBr (1.1)	DCM	0 ^{o}C-rt	12	NR

The major isomer product is shown here. [a]Reaction conditions: all reactions were carried out under a nitrogen atmosphere, **13a** (0.5 mmol) and **14d** (0.55 mmol), solvent (3.0 mL). [b]Isolated yield. [c]Decomposed. [d]Diastereoselectivity was measured by ^1H NMR spectroscopy and was found to be 9:1. NR= No reaction.

3.4.2 Substrates Scope of the Reaction:

With these optimal conditions in hand the scope of the reaction was investigated with aromatic and aliphatic aldehydes as shown in *Scheme 3.4.2.1,* Aromatic aldehydes having moderately electron-withdrawing groups (*Scheme 3.4.2.1*, **15ab**-**15af**) such as -F, -Br, -Cl, *m*-Br, *m*-Cl, and highly electron-withdrawing groups (*Scheme 3.4.2.1*, **15ag**-**15ai**) such as -CO_2Me, -CF_3, -NO_2 in the aromatic ring gave excellent yields. On the other hand, electron-donating groups (*Scheme 3.4.2.1,* **15ak**, **15am**-**15an**) gave good to moderate yields, which is due to their low reactivity.

Scheme 3.4.2.1: Synthesis of 4-bromo-4-chloro-1-tosyl piperidine[a]



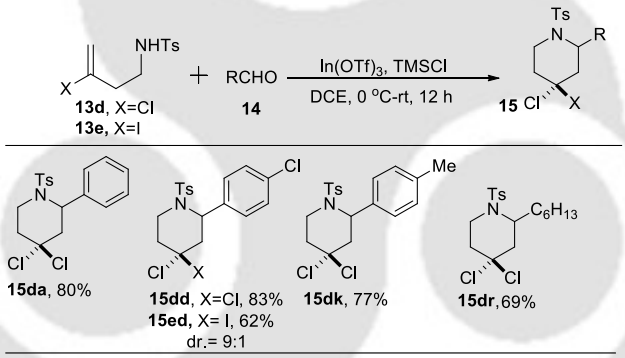
The formula of the major isomer is shown in the scheme. [a]Reaction conditions: **13a** (0.5 mmol), **14** (0.55 mmol), $In(OTf)_3$ (0.1 mmol), TMSCl (0.55 mmol), DCE (3 mL), 0 °C- rt, N_2 atmosphere. Diastereoselectivity was determined by ^{1}H NMR spectroscopy.

However, a highly electron-donating methoxy group **14l** gave a decomposed product, like many Prins cyclisation reactions.[15] Aliphatic aldehydes **14p**-**14u** also resulted in their corresponding products in decent yield. It may be noted that strained cyclopropanecarbaldehyde is compatible

with the reaction conditions, providing **15as** in 60% yield. Unfortunately, α-substituted amides **13b**-**13c** did not give any product.

Similarly, with the same optimal reaction conditions, the scope of this reaction was examined with *N*-(3-chlorobut-3-en-1-yl)-4-methylbenzenesulfonamide (**13d**) and *N*-(3-iodobut-3-en-1-yl)-4-methylbenzenesulfonamide (**13e**), and the results were summarized in *Scheme 3.4.2.2*. It was observed that both electron-donating and electron-withdrawing groups in the aromatic ring provided corresponding products **15dd** and **15dk** in good yields. Aliphatic aldehyde **14r** gave a low yield compared to the others. Iodine-substituted homoallylic methylbenzenesulfonamide gave 62% yield of the corresponding product **15ed**. The structure of all compounds was determined by ^{1}H NMR, ^{13}C{^{1}H} NMR, mass spectrometry and finally, by X-Ray crystallographic analysis of compound **15ad**.

Scheme 3.4.2.2: Synthesis of 4-chloro/iodo-4-chloro-1-tosyl piperidine[a]

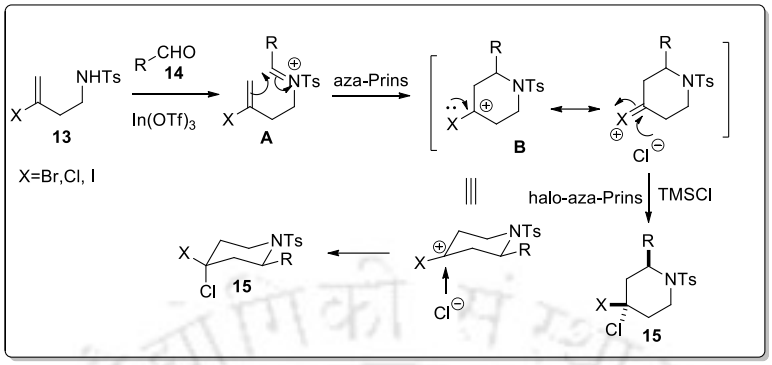


[a]Reaction conditions: **13d/13e** (0.5 mmol), **14** (0.55 mmol), $In(OTf)_3$ (0.1 mmol), TMSCl (0.55 mmol), DCE (3 mL), 0 °C-rt, N_2 atmosphere.Diastereoselectivity was determined by ^{1}H NMR spectroscopy.

3.4.3. Possible mechanism of the reaction

The plausible mechanism is proposed in *Scheme 3.4.3.1*. Initially, alkene sulfonamide **13** reacts with aldehyde **14** to generate iminium ion **A,** which, after aza-Prins cyclization reaction, produces carbocation **B**. Nucleophilic attack by chloride ion from TMSCl gives final product **15**. The diastereoselectivity of the reaction can be explained on the basis of the formation of the six-membered chair conformation **B,** where the substituent halogen is in a pseudo-equatorial position. As a result, the incoming chloride nucleophile attacks from the axial position to give a more stable final product **15** with -R and -Cl groups *trans* to each other.

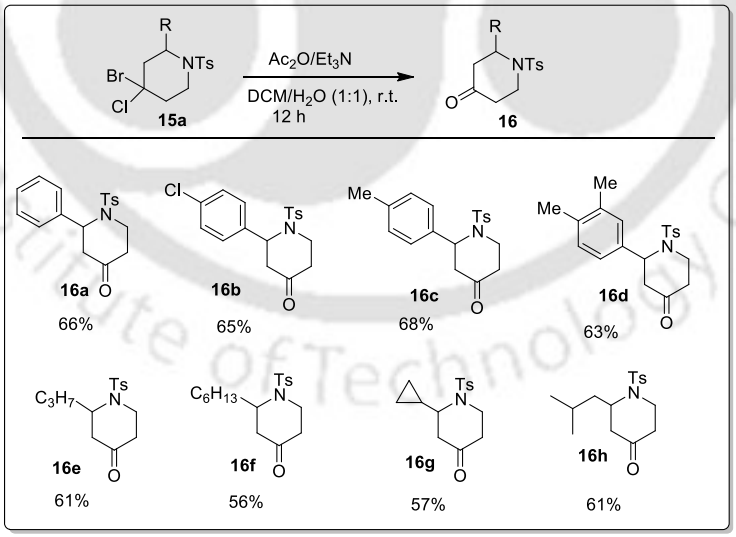
Scheme 3.4.3.1. *Plausible Mechanism of the Reaction*



3.4.4. Post-Synthetic Utility of the Reaction:

In order to investigate the applicability of the reaction, the *gem*-difunctionality was converted to its carbonyl group using a literature procedure.[16] Thus, the reaction of *gem*-dihalocompounds **15a** with acetic anhydride and triethylamine in DCM/H_2O (1:1) at room temperature resulted in piperidinone scaffolds **16a**-**16h** in moderate yields. (*Scheme 3.4.4.1*).

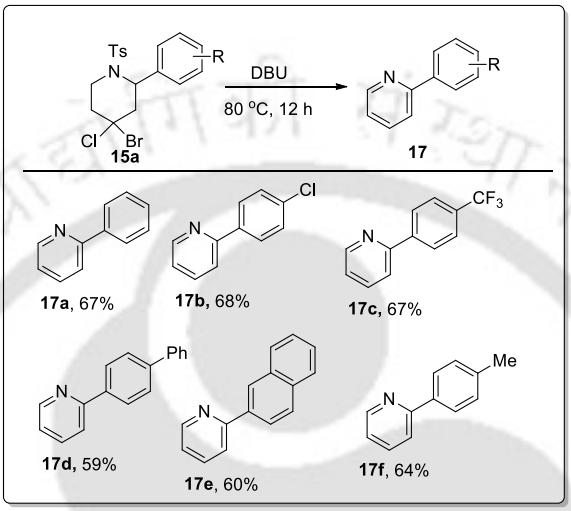
Scheme 3.4.4.1. Synthesis of 2-substituted-1-tosylpiperidin-4-one



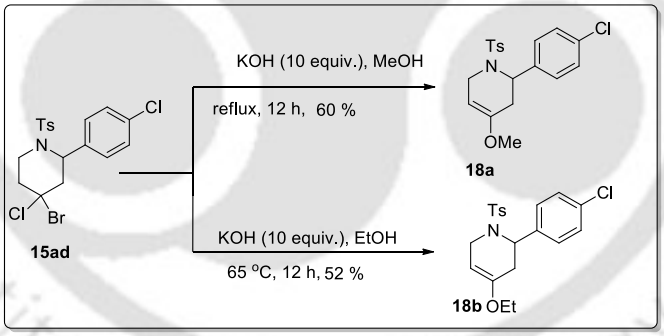
Furthermore, the *gem*-dihalocompounds **15a** were converted to their corresponding pyridine derivatives **17a-17f** in moderate yields by treatment with organic base DBU at 80 ^oC for 12 h (*Scheme 3.4.4.2*).

In an attempt to utilize the reactivity of *gem*-dihalopiperidine compound, **15ad** was subjected to react with KOH in methanol and ethanol at 65 °C. Interestingly, enol ethers **18a** and **18b** were obtained in 60% and 52% yields, respectively (*Scheme 3.4.4.3*).

Scheme 3.4.4.2. *Synthesis of pyridine*



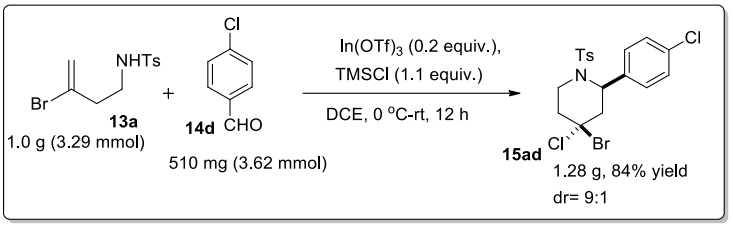
Scheme 3.4.4.3. *Synthesis of enol ether derivatives*



3.4.5. Gram scale experiment of the reaction

The scalability of the reaction was ascertained by performing a gram scale reaction (Scheme 3.4.5.1). Thus, the reaction of **13a** (1.0 g, 3.29 mmol) with **14d** (510 mg, 3.62 mmol) gave 1.28 g of the product **15ad** with 84% yield.

Scheme 3.4.5.1. Gram scale experiment



3.5 Conclusion

In conclusion, we have developed a methodology for the synthesis of *gem*-dihalopiperidine derivatives from alkene sulfonamides and aldehydes *via* halo-aza-Prins cyclization reaction in excellent yields. The reaction is highly diastereoselective. The methodology is further extended to the synthesis of piperidinone and pyridine derivatives in moderate yields. The *gem*-dihalopiperidine can also be converted to its enol ether derivatives.

3.6 Experimental Section

3.6.1 General Information

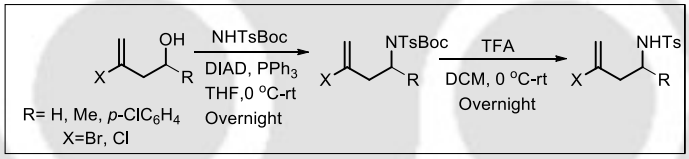
All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infrared (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H (600 MHz, 500 MHz and 400 MHz) or $^{13}C\{^{1}H\}$ (150 MHz, 125 MHz and 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. Structural assignments were made with additional information from single-crystal XRD experiments. HRMS spectra were recorded using Q-TOF mass spectrometer.

The starting material *N*-(3-bromobut-3-en-1-yl)-4-methylbenzenesulfonamide[17a] (**13a**) and *N*-(3-iodobut-3-en-1-yl)-4-methylbenzenesulfonamide[17b] (**13e**) are synthesized according to the reported literatures. The spectroscopic data of the above compound are in good agreement with the literature.

The experimental procedure and the characterization data of the remaining starting material are given as follows:

3.6.2 General Procedure for the Preparation of Starting Materials (13b-13d):

Di-isopropylazodicarboxylate (DIAD) (1.51 g, 7.5 mmol, 1.5 equiv.) was added dropwise to a solution of TsNHBoc (1.86 g, 6.5 mmol, 1.3 equiv.) triphenylphosphine (2.62 g, 10.0 mmol, 2.0 equiv.) and 4-bromopent-4-en-2-ol[17c]/3-bromo-1-(4-chlorophenyl)but-3-en-1-ol[17e]/3-chlorobut-3-en-1-ol[17d] (5.0 mmol, 1.0 equiv.) in THF (15 mL) at 0 °C. The reaction was stirred overnight at room temperature before being concentrated. The crude was subjected to column chromatography over silica gel using ethyl acetate and hexane as eluents to get the *N*-Ts-*N*-Boc amide derivative. This was dissolved in CH_2Cl_2 (9 mL), then TFA (1.5 mL, 19.25 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 12 h at room temperature before being cooled to 0 °C, and slowly quenched by the dropwise addition of $NaHCO_3$ (sat., aq.). The organic layer was extracted with additional CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The crude was subjected to column chromatography over silica gel using ethyl acetate and hexane as eluents to get the product.



3.6.3 General procedure for the synthesis of (15aa-15au,15ba,15bd,15bk,15br,15ed):

To a solution of **15** (0.5 mmol, 1.0 equiv) and aldehyde (0.55 mmol, 1.1 equiv) in dry DCE (3 mL) was added $In(OTf)_3$ (0.1 mmol, 0.2 equiv) and TMSCl (0.55 mmol, 1.1 equiv) at 0 °C under a nitrogen atmosphere. The reaction mixture was then stirred at room temperature overnight, and the progress of the reaction was monitored by TLC (ethyl acetate:hexane = 1:9). After completion of the reaction, the organic layer was extracted with ethyl acetate (3 × 10 mL) and washed with saturated sodium bicarbonate and brine solutions. The reaction mixture was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The crude was subjected to column chromatography over silica gel using ethyl acetate and hexane as eluents to get the product up to 93% yield.

3.6.4. General procedure for the synthesis of (16a-16h):

To a mixture of 4-Bromo-4-chloro-1-tosyl piperidine derivatives (0.22 mmol, 1 equiv.) in DCM (1.0 mL) and H_2O (1.0 mL) were added Ac_2O (4.1 mmol, 19.0 equiv.) and Et_3N (5.7 mmol, 30.0 equiv.) at room temperature under an air atmosphere. The reaction mixture was vigorously stirred overnight at room temperature. After completion of the reaction, H_2O was added, and the organic layer was extracted with DCM (3 × 10 mL). The reaction mixture was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The crude was subjected to column chromatography over silica gel using ethyl acetate and hexane as eluents to get the product.

3.6.5 General procedure for the synthesis of (17a-17f):

The solution of 4-Bromo-4-chloro-1-tosyl piperidine derivatives (0.22 mmol, 1 equiv.) in DBU (10 mmol, 45.45 equiv.) was stirred at 80 ^oC in an oil bath for 12 h. After completion of the reaction (determined by TLC), the reaction mixture was allowed to cool to room temperature, brine was added and the organic layer was extracted with EtOAc (3 x 10 mL). The combined organic layers are dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and purified by column chromatography over silica gel using hexane and ethyl acetate as eluent to get the products.

3.6.6 General procedure for the synthesis of (18a-18b):

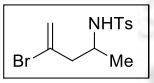
To a suspension of KOH (2.2 mmol, 10.0 equiv.) in anhydrous MeOH/EtOH (3 mL) was added 4-Bromo-4-chloro-1-tosyl piperidine derivatives (0.22 mmol, 1 equiv.) at 65 ^oC. The reaction mixture was stirred at 65 ^oC in an oil bath until the full conversion of the 4-Bromo-4-chloro-1-tosyl piperidine derivatives. After completion of the reaction (determined by TLC), the reaction mixture was allowed to cool to room temperature and concentrated by rotary evaporator. The reaction mixture was then neutralized with 6 M HCl solution (3.0 mL). The organic layer was extracted with DCM (3 x 10 mL). The combined organic layers are dried over anhydrous Na_2SO_4, filtered, and all volatiles are removed under reduced pressure and purified by column chromatography over silica gel using hexane and ethyl acetate as eluent to get the products.

3.6.7 Experimental procedure for the gram-scale reaction

To a solution of *N*-(3-bromobut-3-en-1-yl)-4-methylbenzene-sulfonamide (1.0 g, 3.29 mmol, 1.0 equiv) and 4-chlorobenzaldehyde (510 mg, 3.62 mmol, 1.1 equiv) in dry DCE (15 mL) was added $In(OTf)_3$ (380 mg, 0.66 mmol, 0.2 equiv) and TMSCl (0.46 mL, 1.1 equiv) at 0 °C under a nitrogen atmosphere. The reaction mixture was then stirred at room temperature for overnight and progress of the reaction was monitored by TLC (ethyl acetate : hexane = 1 : 9). After completion of the reaction, the organic layer was extracted with ethyl acetate (3 × 30 mL) and washed with saturated sodium bicarbonate and brine solutions. The reaction mixture was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The product 3ad was obtained in an 84% (1.28 g, colorless solid) yield by column chromatography over silica gel using hexane and ethyl acetate (9:1) as eluents.

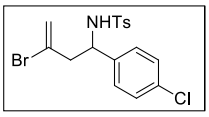
3.6.8 Characterization Data

***N*-(4-Bromopent-4-en-2-yl)-4-methylbenzenesulfonamide (13b)[17f]:**



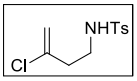
Colorless solid; R_f (hexane/EtOAc, 3:1) 0.52; mp 70 °C, yield 1065mg, 67% (overall); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 5.58 (s, 1 H), 5.41 (s, 1 H), 4.80 – 4.75 (m, 1 H), 3.57 – 3.61 (m, 1 H), 2.56 (ddd, *J* = 14.3, 6.8, 1.1 Hz, 1 H), 2.42 (s, 3 H), 2.38 (dd, *J* = 14.3, 6.8 Hz, 1 H), 1.12 (d, *J* = 6.6 Hz, 3 H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 143.7, 137.7, 129.9, 127.4, 120.4, 120.3, 49.0, 48.4, 21.8, 21.0.

***N*-(3-bromo-1-(4-chlorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide (13c):**



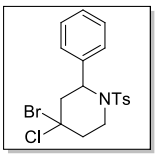
Colorless solid; R_f (hexane/EtOAc, 3:1) 0.53; mp 109 °C, yield 1421mg, 69% (overall); IR (KBr, neat) ν 3262, 2924, 1631, 1598, 1445, 1321, 1155, 1090, 811, 663, 547 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 2 H), 7.16 (d, J = 8.0 Hz, 2 H), 7.13 (d, J = 8.4 Hz, 2 H), 7.04 (d, J = 8.2 Hz, 2 H), 5.49 (d, J = 2.0 Hz, 1 H), 5.41 (s, 1 H), 5.37 (s, 1 H), 4.57 (q, J = 6.8 Hz, 1 H), 2.79 (dd, J = 14.6, 8.0 Hz, 1 H), 2.67 (dd, J = 14.6, 6.6 Hz, 1 H), 2.39 (s, 3 H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 143.8, 138.1, 137.0, 133.8, 129.7, 128.8, 128.5, 128.4, 127.5, 121.3, 55.9, 49.3, 21.7. HRMS (ESI) calcd. for $C_{17}H_{17}BrClNNaO_2S$ $(M + Na)^+$ 435.9745, found 435.9755.

***N*-(3-Chlorobut-3-en-1-yl)-4-methylbenzenesulfonamide (13d):**



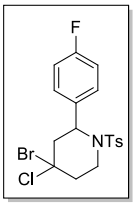
Colorless solid; R_f (hexane/EtOAc, 3:1) 0.51; mp 52 ºC, yield 741 mg, 57% (overall); IR (KBr, neat) ν 3278, 2925, 1636, 1598, 1420, 1322, 1154, 1093, 814, 662, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 7.9 Hz, 2 H), 5.23 (d, *J* = 1.5 Hz, 1 H), 5.15 (d, *J* = 1.3 Hz, 1 H), 4.63 (t, *J* = 6.3 Hz, 1 H), 3.18 (q, *J* = 6.4 Hz, 2 H), 2.49 (td, *J* = 6.4, 1.0 Hz, 2 H), 2.43 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.9, 138.6, 137.1, 130.0, 127.3, 115.8, 40.5, 39.5, 21.8. HRMS (ESI) calcd. for $C_{11}H_{15}ClNO_2S$ $(M + H)^+$ 260.0507, found 260.0520.

4-Bromo-4-chloro-2-phenyl-1-tosylpiperidine (diastereomers, 9:1) (15aa):



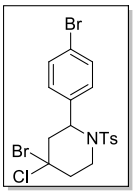
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 131 ºC, yield 195 mg, 91%; IR (KBr, neat) ν 2928, 1598, 1495, 1344, 1157, 663, 556 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.0 Hz, 2 H), 7.22 – 7.17 (m, 7 H), 4.96 (dd, *J* = 5.5, 5.5 Hz, 1 H, minor), 4.78 (dd, *J* = 5.5, 5.5 Hz, 1 H, major), 3.85 – 3.80 (m, 1 H), 3.65 – 3.60 (m, 1 H), 3.13 (dd, *J* = 14.6, 6.8 Hz, 1 H), 2.67 – 2.62 (m, 2 H), 2.50 – 2.45 (m, 1 H), 2.41 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 143.8, 137.6, 136.5, 129.8, 128.3, 127.8, 127.59, 127.57, 74.6, 58.4, 51.7, 46.4, 43.5, 21.7. HRMS (ESI) calcd. for $C_{18}H_{20}BrClNO_2S$ $(M + H)^+$ 428.0082, found 428.0083.

4-Bromo-4-chloro-2-(4-fluorophenyl)-1-tosylpiperidine (diastereomers, 9:1) (15ab):



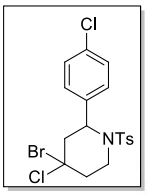
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.51; mp 140 ºC, yield 206 mg, 92%; IR (KBr, neat) ν 2963, 1603, 1509, 1345, 1159, 1093, 740, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.44 (m, 2 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 7.15 – 7.12 (m, 2 H), 6.91 – 6.87 (m, 2 H), 4.88 (dd, *J* = 7.7, 5.8 Hz, 1 H, minor), 4.70 (dd, *J* = 7.7, 5.8 Hz, 1 H, major), 3.87 – 3.81 (m, 1 H), 3.62 – 3.56 (m, 1 H), 3.07 (dd, *J* = 14.5, 7.2 Hz, 1 H), 2.68 – 2.60 (m, 2 H), 2.52 – 2.45 (m, 1 H), 2.41 (s, 3 H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.4 (d, *J* = 245.3 Hz), 143.9, 136.5, 133.3 (d, *J* = 3.2 Hz), 129.8, 129.4 (d, *J* = 8.1 Hz), 127.5, 115.2 (d, *J* = 21.5 Hz), 74.4, 58.1, 51.9, 46.4, 43.6, 21.7. ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$) δ 47.20. HRMS (ESI) calcd. for $C_{18}H_{19}BrClFNO_2S$ $(M + H)^+$ 445.9987, found 445.9988.

4-Bromo-2-(4-bromophenyl)-4-chloro-1-tosylpiperidine (diastereomers, 9:1) (15ac):



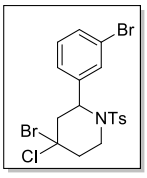
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.51; mp 143 °C, yield 236 mg, 93%; IR (KBr, neat) ν 2928, 1596, 1488, 1344, 1157, 708, 662, 548 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.45 (m, 2 H), 7.32 (d, *J* = 8.5 Hz, 2 H), 7.23 (d, *J* = 8.1 Hz, 2 H), 7.04 (d, *J* = 8.5 Hz, 2 H), 4.87 (dd, *J* = 5.2, 5.2 Hz, 1 H, minor), 4.72 (dd, *J* = 6.9, 4.9 Hz, 1 H, major), 3.83 – 3.77 (m, 1 H), 3.64 – 3.58 (m, 1 H), 3.06 (dd, *J* = 14.6, 6.5 Hz, 1 H), 2.65 – 2.60 (m, 2 H), 2.50 – 2.44 (m, 1 H), 2.42 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.1, 136.7, 136.4, 131.4, 129.8, 129.4, 127.5, 121.9, 74.3, 58.0, 51.5, 46.3, 43.4, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}Br_2ClNO_2S$ $(M + H)^+$ 507.9166, found 507.9158.

4-Bromo-4-chloro-2-(4-chlorophenyl)-1-tosylpiperidine (diastereomers, 9:1) (15ad):



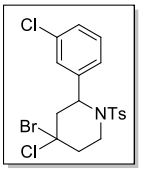
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.51; mp 156 °C, yield 215 mg, 93%; IR (KBr, neat) ν 2925, 1597, 1492, 1344, 1156, 712, 667, 551 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.46 (m, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.18 – 7.16 (m, 2 H), 7.11 – 7.09 (m, 2 H), 4.89 (dd, *J* = 5.4, 5.4 Hz, 1 H, minor), 4.74 (dd, *J* = 5.6, 5.6 Hz, 1 H, major), 3.82 – 3.77 (m, 1 H), 3.63 – 3.58 (m, 1 H), 3.06 (dd, *J* = 14.6, 6.9 Hz, 1 H), 2.65 – 2.59 (m, 2 H), 2.48 – 2.44 (m, 1 H), 2.41 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 144.0, 136.3, 136.2, 133.7, 129.8, 129.0, 128.5, 127.5, 74.3, 57.9, 51.5, 46.2, 43.4, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}BrCl_2NO_2S$ $(M + H)^+$ 461.9692, found 461.9692.

4-Bromo-2-(3-bromophenyl)-4-chloro-1-tosylpiperidine (diastereomers, 9:1) (15ae):



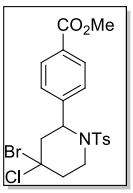
Colorless gum; R_f (hexane/EtOAc, 9:1) 0.51; yield 180 mg, 71%; IR (KBr, neat) ν 2925, 1596, 1475, 1344, 1157, 1092, 733, 659, 562 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.45 (m, 2 H), 7.33 – 7.30 (m, 1 H), 7.23 – 7.21 (m, 2 H), 7.16 – 7.10 (m, 3 H), 4.92 (dd, *J* = 5.3, 5.3 Hz, 1 H, minor), 4.77 (dd, *J* = 7.2, 5.0 Hz, 1 H, major), 3.84 – 3.77 (m, 1 H), 3.68 – 3.62 (m, 1 H), 3.07 (dd, *J* = 14.5, 6.8 Hz, 1 H), 2.67 – 2.61 (m, 2 H), 2.52 – 2.46 (m, 1 H), 2.42 (s, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 144.2, 139.8, 136.5, 131.0, 130.8, 129.93, 129.90, 127.4, 126.5, 122.5, 74.3, 57.9, 51.5, 46.3, 43.4, 21.8. HRMS (ESI) calcd. for $C_{19}H_{19}Br_2ClNO_2S$ $(M + H)^+$ 507.9166, found 507.9165.

4-Bromo-4-chloro-2-(3-chlorophenyl)-1-tosylpiperidine (diastereomers, 9:1) (15af):



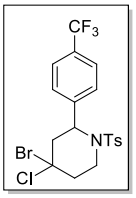
Colorless gum; R_f (hexane/EtOAc, 9:1) 0.48; yield 167 mg, 72%; IR (KBr, neat) ν 2926, 1597, 1575, 1345, 1157, 1093, 733, 663, 564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.3 Hz, 2 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 7.19 – 7.15 (m, 2 H), 7.13 – 7.10 (m, 1 H), 7.03 – 7.02 (m, 1 H), 4.94 (dd, *J* = 5.2, 5.2 Hz, 1 H, minor), 4.79 (dd, *J* = 5.7, 5.7 Hz, 1 H, major), 3.83 – 3.77 (m, 1 H), 3.69 – 3.62 (m, 1 H), 3.07 (ddd, *J* = 14.6, 6.7, 1.1 Hz, 1 H), 2.67 – 2.60 (m, 2 H), 2.51 – 2.46 (m, 1 H), 2.42 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.2, 139.7, 136.5, 134.3, 129.9, 129.7, 128.0, 127.9, 127.5, 125.9, 74.2, 57.9, 51.4, 46.3, 43.4, 21.8 HRMS (ESI) calcd. for $C_{18}H_{19}BrCl_2NO_2S$ $(M + H)^+$ 461.9692, found 461.9687.

Methyl 4-(4-bromo-4-chloro-1-tosylpiperidin-2-yl)benzoate (diastereomers, 9:1) (15ag):



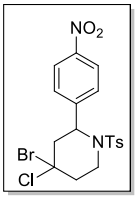
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.47; mp 159 ºC, yield 180 mg, 74%; IR (KBr, neat) ν 2951, 1720, 1611, 1436, 1345, 1279, 1094, 1018, 730, 664, 550 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 2 H), 7.54 (d, *J* = 7.9 Hz, 2 H), 7.28 (d, *J* = 7.9 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 5.07 (dd, *J* = 5.2, 5.2 Hz, 1H, minor), 4.92 (dd, *J* = 5.6, 5.6 Hz, 1 H, major), 3.91 (s, 3 H), 3.75 – 3.69 (m, 2 H), 3.14 (dd, *J* = 14.8, 6.0 Hz, 1 H), 2.68 – 2.59 (m, 2 H), 2.43 (s, 4 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.9, 144.2, 143.1, 136.2, 130.0, 129.7, 129.6, 127.6, 127.3, 74.2, 57.8, 52.3, 51.1, 46.2, 43.1, 21.8. HRMS (ESI) calcd. for $C_{20}H_{22}BrClNO_4S$ $(M + H)^+$ 486.0136, found 486.0139.

4-Bromo-4-chloro-1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidine (diastereomers, 9:1) (15ah):



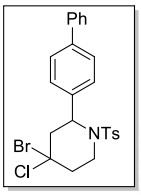
Colorless gum; R_f (hexane/EtOAc, 9:1) 0.52; yield 219 mg, 88%; IR (KBr, neat) ν 2931, 1620, 1598, 1322, 1158, 1116, 1068, 714, 668, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.45 (m, 4 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 5.02 (dd, *J* = 5.7, 5.7 Hz, 1 H, minor), 4.87 (dd, *J* = 5.7, 5.7 Hz, 1 H, major), 3.83 – 3.77 (m, 1 H), 3.70 – 3.64 (m, 1 H), 3.12 (ddd, *J* = 14.7, 6.7, 1.2 Hz, 1 H), 2.68 – 2.61 (m, 2 H), 2.49 – 2.43 (m, 1 H), 2.40 (s, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 144.2, 141.8, 136.4, 130.0, 129.9, 128.0, 127.5, 127.4, 125.3 (q, *J* = 3.7 Hz), 74.1, 58.0, 51.4, 46.2, 43.4, 21.7. ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$) δ 99.27. HRMS (ESI) calcd. for $C_{19}H_{19}BrClF_3NO_2S$ $(M + H)^+$ 495.9955, found 495.9956.

4-Bromo-4-chloro-2-(4-nitrophenyl)-1-tosylpiperidine (diastereomers, 4:1) (15ai):



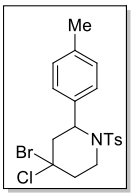
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.45; mp 190 °C, yield 220 mg, 93%; IR (KBr, neat) ν 2926, 1598, 1519, 1344, 1160, 1094, 726, 663, 551 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.11 (m, 2 H), 7.62 (d, *J* = 8.3 Hz, 2 H) (minor), 7.56 (d, *J* = 8.3 Hz, 2 H) (major), 7.41 – 7.39 (m, 2 H), 7.30 – 7.28 (m, 2 H), 5.10 (dd, *J* = 5.2, 5.2 Hz, 1 H, minor), 4.97 (dd, *J* = 5.5, 5.5 Hz, 1 H, major), 3.73 – 3.70 (m, 2 H), 3.12 (ddd, *J* = 14.7, 5.8, 1.4 Hz, 1 H), 2.66 (ddd, *J* = 14.7, 5.3, 1.2 Hz, 1 H), 2.63 – 2.58 (m, 1 H), 2.44 (s, 3 H), 2.42 – 2.37 (m, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.5, 146.0, 145.7, 144.6, 136.5, 136.0, 130.2, 130.1, 128.1, 127.7, 127.5, 127.4, 123.8, 123.7, 74.3, 73.8, 57.4, 51.0, 50.2, 45.9, 45.8, 43.0, 42.0, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}BrClN_2O_4S$ $(M + H)^+$ 472.9932, found 472.9950.

2-([1,1'-Biphenyl]-4-yl)-4-bromo-4-chloro-1-tosylpiperidine (diastereomers, 9:1) (15aj):



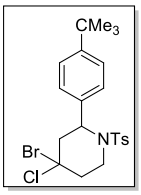
Pale yellow gum; R_f (hexane/EtOAc, 9:1) 0.52; yield 164 mg, 65%; IR (KBr, neat) ν 2925, 1598, 1488, 1344, 1155, 1093, 725, 661, 547 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.56 – 7.55 (m, 2 H), 7.48 – 7.46 (m, 2 H), 7.44 – 7.42 (m, 4 H), 7.37 – 7.34 (m, 1 H), 7.24 – 7.23 (m, 2 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 4.96 (dd, *J* = 5.0, 5.0 Hz, 1 H, minor), 4.80 (dd, *J* = 7.4, 4.4 Hz, 1 H, major), 3.92 – 3.88 (m, 1H), 3.66 – 3.62 (m, 1 H), 3.18 (dd, *J* = 14.6, 7.3 Hz, 1 H), 2.71 – 2.67 (m, 2 H), 2.56 – 2.52 (m, 1 H), 2.40 (s, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 143.7, 140.73, 140.70, 136.8, 136.5, 129.7, 129.0, 128.3, 127.7, 127.6, 127.2, 126.9, 74.7, 58.5, 51.8, 46.5, 43.7, 21.8. HRMS (ESI) calcd. for $C_{24}H_{24}BrClNO_2S$ $(M + H)^+$ 504.0395, found 504.0394.

4-Bromo-4-chloro-2-(p-tolyl)-1-tosylpiperidine (diastereomers, 9:1) (15ak):



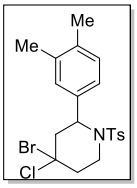
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.51; mp 120 °C, yield 194 mg, 88%; IR (KBr, neat) ν 2924, 1597, 1514, 1344, 1156, 735, 661, 556 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.06–7.05 (m, 2 H), 7.01 (d, *J* = 7.9 Hz, 2 H), 4.86 (dd, *J* = 4.4, 4.4 Hz, 1 H, minor), 4.67 (dd, *J* = 5.7, 5.0 Hz, 1 H, major), 3.87 – 3.82 (m, 1 H), 3.59 – 3.54 (m, 1 H), 3.10 (dd, *J* = 14.6, 7.1 Hz, 1 H), 2.68 – 2.61 (m, 2 H), 2.52 – 2.47 (m, 1 H), 2.41 (s, 3 H), 2.30 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 143.7, 137.6, 136.4, 134.6, 129.6, 129.0, 127.7, 127.6, 74.7, 58.6, 52.0, 46.5, 43.7, 21.8, 21.3. HRMS (ESI) calcd. for $C_{19}H_{22}BrClNO_2S$ $(M + H)^+$ 442.0238, found 442.0237.

4-Bromo-2-(4-(tert-butyl)phenyl)-4-chloro-1-tosylpiperidine (diastereomers, 9:1) (15am):



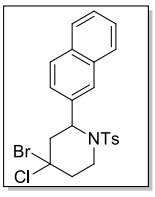
Colorless gum; R_f (hexane/EtOAc, 9:1) 0.53; yield 201 mg, 83%; IR (KBr, neat) ν 2962, 1598, 1494, 1346, 1323, 1155, 1093, 1017, 713, 656, 548 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.36 (m, 2 H), 7.16 – 7.11 (m, 4 H), 7.06 – 7.04 (m, 2 H), 4.84 (dd, *J* = 5.6, 5.6 Hz, 1 H, minor), 4.68 (dd, *J* = 8.2, 4.1 Hz, 1 H, major), 3.96 – 3.90 (m, 1 H), 3.60 – 3.53 (m, 1 H), 3.14 (dd, *J* = 14.4, 8.1 Hz, 1 H), 2.75 – 2.70 (m, 1 H), 2.68 – 2.66 (m, 1 H), 2.64 – 2.57 (m, 1 H), 2.38 (s, 3 H), 1.28 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 150.9, 143.3, 137.1, 133.9, 129.5, 128.0, 127.6, 125.1, 75.0, 58.9, 52.1, 46.7, 44.0, 34.6, 31.5, 21.7. HRMS (ESI) calcd. for $C_{22}H_{28}BrClNO_2S$ $(M + H)^+$ 484.0708, found 484.0715.

4-Bromo-4-chloro-2-(3,4-dimethylphenyl)-1-tosylpiperidine (diastereomers, 9:1) (15an):



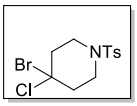
Pale yellow gum; R_f (hexane/EtOAc, 9:1) 0.51; yield 194 mg, 85%; IR (KBr, neat) ν 2922, 1597, 1505, 1344, 1321, 1155, 1093, 731, 662, 547 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 2 H), 7.17 – 7.15 (m, 2 H), 6.97 (d, *J* = 7.8 Hz, 1 H), 6.92 (dd, *J* = 7.8, 2.0 Hz, 1 H), 6.80 (d, *J* = 2.0 Hz, 1 H), 4.82 – 4.79 (dd, *J* = 6.0, 6.0 Hz, 1 H, minor), 4.62 (dd, *J* = 7.8, 4.3 Hz, 1 H, major), 3.92 – 3.85 (m, 1 H), 3.59 – 3.52 (m, 1 H), 3.10 (dd, *J* = 14.5, 7.6 Hz, 1 H), 2.70 – 2.62 (m, 2 H), 2.58 – 2.52 (m, 1 H), 2.40 (s, 3 H), 2.19 (s, 3 H), 2.09 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.5, 136.7, 136.3, 134.7, 129.5, 129.4, 129.3, 127.7, 127.6, 125.5, 75.0, 58.8, 52.2, 46.7, 43.9, 21.7, 19.9, 19.6. HRMS (ESI) calcd. for $C_{20}H_{24}BrClNO_2S$ $(M + H)^+$ 456.0395, found 456.0377.

4-Bromo-4-chloro-2-(naphthalen-2-yl)-1-tosylpiperidine (diastereomers, 9:1) (15ao):



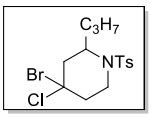
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.49; mp 149 ºC, yield 218 mg, 91%; IR (KBr, neat) ν 2927, 1598, 1508, 1344, 1157, 1093, 732, 664, 559 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.78 (m, 1 H), 7.70 (d, *J* = 8.6 Hz, 1 H), 7.66 – 7.64 (m, 1 H), 7.50 (s, 1 H), 7.47 – 7.44 (m, 3 H), 7.43 – 7.42 (m, 1 H), 7.35 – 7.33 (m, 1 H), 7.09 (d, *J* = 7.9 Hz, 2 H), 5.07 (dd, *J* = 5.4, 5.4 Hz, 1 H, minor), 4.90 (dd, *J* = 6.8, 5.6 Hz, 1 H) (major), 3.96 – 3.91 (m, 1 H), 3.70 – 3.65 (m, 1 H), 3.25 (dd, *J* = 14.6, 7.1 Hz, 1 H), 2.75 – 2.69 (m, 2 H), 2.59 – 2.54 (m, 1 H), 2.34 (s, 3 H).$^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) δ 143.8, 136.5, 135.0, 133.1, 133.0, 129.6, 128.1, 128.0, 127.8, 127.6, 126.8, 126.4, 126.3, 125.6, 74.6, 58.9, 51.9, 46.6, 43.7, 21.7. HRMS (ESI) calcd. for $C_{22}H_{22}BrClNO_2S$ $(M + H)^+$ 478.0238, found 478.0236.

4-Bromo-4-chloro-1-tosylpiperidine (15ap):



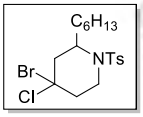
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.52; mp 142 °C, yield 139 mg, 79%; IR (KBr, neat) ν 2926, 1597, 1350, 1165, 937, 716, 546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 2 H), 7.34 (d, *J* = 7.9 Hz, 2 H), 3.24 – 3.16 (m, 4 H), 2.64 – 2.58 (m, 2 H), 2.51 – 2.46 (m, 2 H), 2.44 (s, 3 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 144.2, 133.5, 130.1, 127.7, 46.3, 44.3, 21.8. HRMS (ESI) calcd. for $C_{12}H_{16}BrClNO_2S$ $(M + H)^+$ 351.9769, found 351.9772.

4-Bromo-4-chloro-2-propyl-1-tosylpiperidine (diastereomers, 9:1) (15aq):



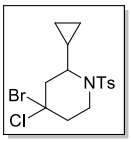
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.53; mp 120 °C, yield 162 mg, 82%; IR (KBr, neat) ν 2961, 1597, 1456, 1343, 1157, 710, 551 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 4.05 – 3.98 (m, 1 H), 3.80 – 3.75 (m, 1H), 3.46 – 3.41 (m, 1 H), 2.67 (dt, *J* = 15.0, 2.3 Hz, 1 H), 2.51 – 2.47 (m, 1 H), 2.42 (s, 3 H), 2.38 (dd, *J* = 15.6, 6.9 Hz, 1 H), 2.20 – 2.14 (m, 1 H), 1.82 (dd, *J* = 7.8, 7.8 Hz, 2 H), 1.32 – 1.24 (m, 2 H), 0.86 (t, *J* = 7.4 Hz, 3 H).$^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) δ 143.8, 138.1, 130.1, 127.2, 75.7, 54.4, 47.6, 46.7, 40.4, 33.6, 21.8, 20.2, 13.9. HRMS (ESI) calcd. for $C_{15}H_{22}BrClNO_2S$ $(M + H)^+$ 394.0238, found 394.0243.

4-Bromo-4-chloro-2-hexyl-1-tosylpiperidine (diastereomers, 3:1) (15ar):



Pale yellow gum; R_f (hexane/EtOAc, 9:1) 0.49; yield 140 mg, 64%; IR (KBr, neat) ν 2926, 1597, 1494, 1321, 1156, 814, 653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2 H), 7.31 – 7.29 (m, 2 H), 4.02 – 3.90 (m, 1 H), 3.79 (dtd, *J* = 14.8, 3.9, 1.3 Hz, 1 H, major), 3.69 (dtd, *J* = 14.6, 3.5, 1.3 Hz, 1 H, minor), 3.47 – 3.40 (m, 1 H), 2.71 – 2.66 (m, 1 H), 2.54 – 2.47 (m, 1 H), 2.43 (s, 3 H), 2.39 – 2.38 (m, 1 H, minor), 2.23 – 2.16 (m, 1 H, major), 1.87 – 1.75 (m, 2 H), 1.28 – 1.17 (m, 9 H), 0.86 (t, *J* = 7.0 Hz, 3 H).$^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 143.6, 137.9, 129.8, 127.1, 75.6, 62.2, 55.4, 54.5, 48.7, 47.4, 46.6, 40.5, 40.2, 31.6, 31.2, 28.8, 26.7, 22.5, 21.5, 14.1. HRMS (ESI) calcd. for $C_{18}H_{28}BrClNO_2S$ $(M + H)^+$ 436.0708, found 436.0727.

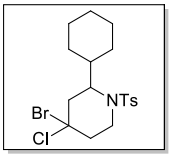
4-Bromo-4-chloro-2-cyclopropyl-1-tosylpiperidine (diastereomers, 4:1) (15as):



Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.52; mp 130 °C, yield 118 mg, 60%; IR (KBr, neat) ν 2925, 1598, 1495, 1341, 1152, 1092, 714, 658, 558 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 3.75 – 3.63 (m, 2 H) (major), 3.61 – 3.55 (m, 2 H) (minor), 3.01 – 2.86 (m, 2 H), 2.83 – 2.50 (m, 3 H), 2.42 (s, 3 H),

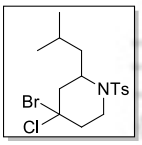
2.41 – 2.36 (m, 1 H), 0.60 – 0.54 (m, 1 H), 0.32 – 0.26 (m, 1 H), 0.20 – 0.10 (m, 2 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 143.6, 138.7, 129.8, 127.4, 76.0, 61.1, 50.5, 48.4, 47.1, 21.8, 13.3, 7.7, 4.7. HRMS (ESI) calcd. for $C_{15}H_{20}BrClNO_2S$ $(M + H)^+$ 392.0082, found 392.0080

4-Bromo-4-chloro-2-cyclohexyl-1-tosylpiperidine (diastereomers, 3:1) (15at):



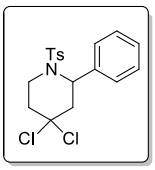
Colorless gum; R_f (hexane/EtOAc, 9:1) 0.52; yield 159 mg, 73%; IR (KBr, neat) ν 2925, 1598, 1494, 1346, 1158, 658, 611 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 6.3, 1.9 Hz, 2 H), 7.32 – 7.30 (m, 2 H), 3.85 – 3.80 (m, 1 H), 3.73 – 3.65 (m, 1 H), 3.34 – 3.27 (m, 1 H), 3.03 (dt, *J* = 15.3, 1.9 Hz, 1 H, minor), 2.91 (dt, *J* = 15.3, 1.9 Hz, 1 H, major), 2.43 (s, 3 H), 2.39 – 2.32 (m, 1 H), 2.31– 2.23 (m, 1 H), 2.16 (dd, *J* = 15.3, 6.7 Hz, 1 H), 2.07 – 2.01 (m, 1 H), 1.94 – 1.90 (m, 1 H), 1.80 – 1.70 (m, 4 H), 1.66 – 1.64 (m, 1 H), 1.13 – 1.08 (m, 2 H), 0.86 – 0.75 (m, 2 H).$^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$) δ 143.9, 138.1, 130.1, 127.4, 75.9, 59.7, 47.6, 46.2, 45.0, 43.7, 40.3, 40.1, 36.0, 31.0, 30.3, 26.3, 26.2, 26.0, 21.8. HRMS (ESI) calcd. for $C_{18}H_{26}BrClNO_2S$ $(M + H)^+$ 434.0551, found 434.0545.

4-Bromo-4-chloro-2-isobutyl-1-tosylpiperidine (diastereomers, 3:1) (15au):



Colorless solid; R_f (hexane/EtOAc, 9:1) 0.56; mp 82 ºC, yield 128 mg, 63%; IR (KBr, neat) ν 2925, 1459, 1345, 1159, 1093, 932, 718, 652, 592, 555 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 4.08 – 4.02 (m, 1 H), 3.69 (dtd, *J* = 14.9, 4.1, 1.3 Hz, 1 H), 3.48 – 3.40 (m, 1 H), 2.78 (t, *J* = 2.3 Hz, 1H, minor), 2.74 (t, *J* = 2.2 Hz, 1 H, major), 2.70 (d, *J* = 6.1 Hz, 1 H, major), 2.66 (d, *J* = 6.1 Hz, 1 H, minor), 2.63 – 2,58 (m, 1 H), 2.49 – 2.45 (m, 1 H), 2.43 (s, 3 H), 1.81 – 1.74 (m, 1 H), 1.64 – 1.58 (m, 2 H), 0.85 (dd, *J* = 6.4, 4.8 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 138.1, 130.1, 127.3, 62.3, 53.5, 48.9, 48.2, 40.6, 40.3, 25.3, 22.7, 22.2, 21.8. HRMS (ESI) calcd. for $C_{16}H_{24}BrClNO_2S$ $(M + H)^+$ 408.0395, found 408.0399.

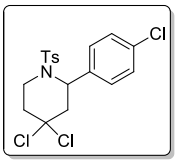
4,4-Dichloro-2-phenyl-1-tosylpiperidine (15da):



Colorless gum; R_f (hexane/EtOAc, 9:1) 0.52; yield 153 mg, 80%; IR (KBr, neat) ν 2927, 1598, 1496, 1346, 1160, 666, 552 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2 H), 7.26 – 7.18 (m, 7 H), 4.96 (dd, *J* = 5.4, 5.4 Hz, 1H), 3.83 – 3.69 (m, 2 H), 3.06 (ddd, *J* = 14.5, 5.5, 1.3 Hz, 1 H), 2.59 (ddd, *J* = 14.5, 5.2, 1.1 Hz, 1 H), 2.48 – 2.43 (m, 1 H), 2.42 (s, 3 H), 2.40 – 2.34 (m, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 143.9, 137.8, 136.8, 129.9, 128.4, 127.6, 127.5, 127.1, 86.3, 57.5,

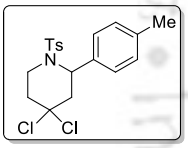
49.6, 44.9, 42.4, 21.8. HRMS (ESI) calcd. for $C_{18}H_{20}Cl_2NO_2S$ $(M + H)^+$ 384.0587, found 344.0557.

4,4-Dichloro-2-(4-chlorophenyl)-1-tosylpiperidine (15dd):



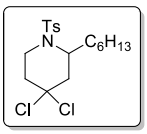
Colorless gum; R_f (hexane/EtOAc, 9:1) 0.53; yield 174 mg, 83%; IR (KBr, neat) ν 2925, 1597, 1493, 1346, 1161, 714, 670, 550 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 2 H),7.26 – 7.25 (m, 2 H), 7.19 (d, *J* = 8.3 Hz, 2 H), 7.11 (d, *J* = 8.3 Hz, 2 H), 4.90 (t, *J* =5.5, 5.5 Hz, 1 H), 3.77 – 3.71 (m, 2 H), 3.00 (dd, *J* = 14.6, 5.7 Hz, 1 H), 2.57 (dd, *J* = 14.5, 5.2 Hz, 1 H), 2.49 – 2.45 (m, 1 H), 2.43 (s, 3 H), 2.40 – 2.35 (m, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 144.1, 136.8, 136.4, 133.6, 130.0, 128.7, 128.6, 127.5, 86.0, 57.1, 49.5, 44.8, 42.4, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}Cl_3NO_2S$ $(M + H)^+$ 418.0197, found 418.0213.

4,4-Dichloro-2-(p-tolyl)-1-tosylpiperidine (15dk):



Colorless liquid; R_f (hexane/EtOAc, 9:1) 0.51; yield 153 mg, 77%; IR (KBr, neat) ν 2924, 1598, 1515, 1345, 1158, 738, 663, 560 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.52 (m, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 7.04 (q, *J* = 8.4 Hz, 4 H), 4.85 (dd, *J* = 5.5, 5.5 Hz, 1 H), 3.85 – 3.78 (m, 1 H), 3.70 – 3.64 (m, 1 H), 3.03 (ddd, *J* = 14.5, 6.0, 1.3 Hz, 1 H), 2.56 (ddd, *J* = 14.5, 5.0, 1.2 Hz, 1 H), 2.46 – 2.43 (m, 1 H), 2.42 (s, 3 H), 2.40 – 2.36 (m, 1 H), 2.30 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.8, 137.4, 136.8, 134.7, 129.8, 129.1, 127.6, 127.2, 86.4, 57.6, 49.8, 45.0, 42.6, 21.8, 21.3. HRMS (ESI) calcd. for $C_{19}H_{22}Cl_2NO_2S$ $(M + H)^+$ 398.0743, found 398.0716.

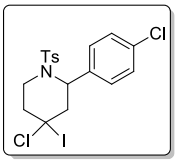
4,4-Dichloro-2-hexyl-1-tosylpiperidine (15dr):



Pale yellow liquid; R_f (hexane/EtOAc, 9:1) 0.51; yield 135 mg, 69%; IR (KBr, neat) ν 2927, 1598, 1495, 1323, 1157, 814, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.06 – 3.99 (m, 1 H), 3.86 – 3.80 (m, 1 H), 3.43 – 3.36 (m, 1 H), 2.57 (dt, *J* = 14.7, 2.2 Hz, 1 H), 2.43 (s, 3H), 2.42 – 2.40 (m, 1 H), 2.38 – 2.31 (m, 2 H), 2.23 – 2.16 (m, 1 H), 1.77 – 1.71 (m, 2 H), 1.25 – 1.19 (m, 7 H), 0.86 (t, *J* = 6.7 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 143.8, 138.1,

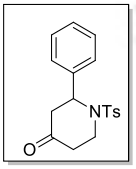
130.1, 127.3, 86.9, 54.3, 46.3, 45.2, 39.3, 31.8, 29.9, 29.0, 27.0, 22.8, 21.8, 14.3. HRMS (ESI) calcd. for $C_{18}H_{28}Cl_2NO_2S$ $(M + H)^+$ 392.1213, found 392.1218.

4-Chloro-2-(4-chlorophenyl)-4-iodo-1-tosylpiperidine (diastereomers, 9:1) (15ed):



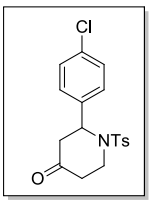
Colorless gum; R_f (hexane/EtOAc, 9:1) 0.53; yield 158 mg, 62%; IR (KBr, neat) ν 2924, 1597, 1492, 1343, 1160, 712, 667, 551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 2 H, minor), 7.57 – 7.54 (m, 2 H, minor), 7.39 (d, J = 8.3 Hz, 2 H, major), 7.30 – 7.28 (m, 2 H, minor), 7.21 (d, J = 8.0 Hz, 2 H, major), 7.18 – 7.15 (m, 2 H, major), 7.11 – 7.09 (m, 2 H), 4.76 (dd, J = 5.1, 5.1 Hz, 1 H, minor), 4.54 (dd, J = 8.2, 4.0 Hz, 1 H, major), 3.70 – 3.65 (m, 1 H), 3.51 – 3.47 (m, 1 H), 3.15 (dd, J = 14.6, 8.2 Hz, 1 H), 2.91 – 2.85 (m, 1 H), 2.65 – 2.60 (m, 1 H), 2.57 – 2.52 (m, 1 H), 2.42 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 144.0, 136.0, 135.9, 134.0, 130.0, 129.7, 129.6, 128.6, 128.5, 127.7, 127.4, 58.8, 55.4, 49.5, 44.6, 44.0, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}Cl_2INO_2S$ $(M + H)^+$ 509.9553, found 509.9572.

2-Phenyl-1-tosylpiperidin-4-one (16a)[17g]:



Yellow gum; R_f (hexane/EtOAc, 4:1) 0.47; yield 48 mg, 66%; IR (KBr, neat) ν 3058, 1720, 1598, 1340, 1154, 1092, 732, 559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.81 (m, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.30 – 7.26 (m, 3 H), 7.24 – 7.22 (m, 2 H), 5.63 (d, *J* = 6.9 Hz, 1 H), 4.04 – 3.97 (m, 1 H), 3.18 – 3.10 (m, 1 H), 2.93 (dt, *J* = 15.4, 1.9 Hz, 1 H), 2.72 (dd, *J* = 15.3, 7.0 Hz, 1 H), 2.45 (s, 3 H), 2.44 – 2.40 (m, 1 H), 2.27 – 2.21 (m, 1 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 206.6, 144.3, 138.6, 137.7, 130.3, 129.1, 128.3, 127.6, 127.4, 56.7, 43.6, 40.6, 40.5, 21.8. HRMS (ESI) calcd. for $C_{18}H_{20}NO_3S$ $(M + H)^+$ 330.1159, found 330.1150.

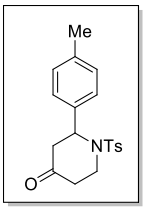
2-(4-Chlorophenyl)-1-tosylpiperidin-4-one (16b):



Brown solid; R_f (hexane/EtOAc, 4:1) 0.47; mp 119 °C, yield 52 mg, 65%; IR (KBr, neat) ν 2924, 1720, 1597, 1340, 1153, 1091, 815, 711, 548 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.81 (m, 2 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.29 – 7.27 (m, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 5.59 (d, *J* = 6.8 Hz, 1 H), 4.06 – 3.99 (m, 1 H), 3.17 – 3.09 (m, 1 H), 2.88 (dt, *J* = 15.2, 1.9 Hz, 1 H), 2.70 (dd, *J* = 15.4, 7.0 Hz, 1 H), 2.46 (s, 3 H), 2.43 – 2.40

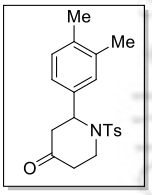
(m, 1 H), 2.27 – 2.21 (m, 1 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 206.2, 144.5, 137.5, 137.2, 134.3, 130.4, 129.2, 128.9, 127.3, 56.2, 43.5, 40.6, 40.4, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}ClNO_3S$ $(M + H)^+$ 364.0769, found 364.0768.

2-(p-Tolyl)-1-tosylpiperidin-4-one (16c):



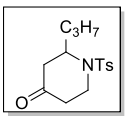
Yellow gum; R_f (hexane/EtOAc, 4:1) 0.47; yield 51 mg, 68%; IR (KBr, neat) ν 2924, 1720, 1598, 1340, 1154, 1092, 733, 550 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.81 (m, 2 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 7.10 (s, 4 H), 5.59 (d, *J* = 6.9 Hz, 1 H), 4.02 – 3.96 (m, 1 H), 3.17 – 3.09 (m, 1 H), 2.90 (dt, *J* = 15.2, 1.8 Hz, 1 H), 2.70 (dd, *J* = 15.3, 7.0 Hz, 1 H), 2.45 (s, 3H), 2.43 – 2.40 (m, 1 H), 2.30 (s, 3H), 2.25 – 2.20 (m, 1 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 206.7, 144.2, 138.1, 137.8, 135.5, 130.3, 129.7, 127.5, 127.4, 56.5, 43.7, 40.6, 40.4, 21.8, 21.2. HRMS (ESI) calcd. for $C_{19}H_{22}NO_3S$ $(M + H)^+$ 344.1315, found 344.1330.

2-(3,4-Dimethylphenyl)-1-tosylpiperidin-4-one (16d):



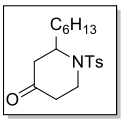
Brown gum; R_f (hexane/EtOAc, 4:1) 0.46; yield 49 mg, 63%; IR (KBr, neat) ν 2923, 1716, 1597, 1339, 1152, 1091, 729, 548 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.04 (d, *J* = 8.2 Hz, 1 H), 6.93 – 6.91 (m, 2 H), 5.55 (d, *J* = 7.0 Hz, 1 H), 4.04 – 3.98 (m, 1 H), 3.19 – 3.11 (m, 1 H), 2.90 (dt, *J* = 15.3, 1.8 Hz, 1 H), 2.69 (dd, *J* = 15.3, 7.0 Hz, 1 H), 2.45 (s, 3 H), 2.44 – 2.39 (m, 1 H), 2.23 – 2.21 (m, 1 H), 2.20 (s, 3 H), 2.17 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 206.8, 144.1, 137.9, 137.3, 136.7, 135.9, 130.2, 130.1, 128.8, 127.4, 124.8, 56.4, 43.7, 40.6, 40.4, 21.8, 20.0, 19.5. HRMS (ESI) calcd. for $C_{20}H_{24}NO_3S$ $(M + H)^+$ 358.1472, found 358.1468.

2-propyl-1-tosylpiperidin-4-one (16e)[17h]:



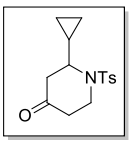
Brown oil; R_f (hexane/EtOAc, 4:1) 0.47; yield 40 mg, 61%; IR (KBr, neat) ν 2930, 1719, 1598, 1338, 1156, 687, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 4.41 – 4.38 (m, 1 H), 4.16 – 4.09 (m, 1 H), 3.30 – 3.22 (m, 1 H), 2.52 (dd, *J* = 14.3, 6.5 Hz, 1 H), 2.43 (s, 3 H), 2.40 – 2.34 (m, 1 H), 2.24 – 2.20 (m, 2 H), 1.39 – 1.33 (m, 2 H), 1.27 – 1.23 (m, 2 H), 0.84 (t, *J* = 7.3 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 206.9, 144.1, 137.8, 130.2, 127.3, 54.6, 45.6, 40.5, 40.3, 34.5, 21.8, 19.3, 13.7. HRMS (ESI) calcd. for $C_{15}H_{22}NO_3S$ $(M + H)^+$ 296.1315, found 296.1327.

2-Hexyl-1-tosylpiperidin-4-one (16f)[17i]:



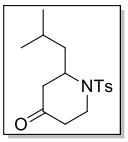
Colorless oil; R_f (hexane/EtOAc, 4:1) 0.46; yield 42 mg, 56%; IR (KBr, neat) ν 2926, 1717, 1597, 1338, 1156, 1091, 688, 550 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 4.36 (dd, *J* = 7.6, 7.4 Hz, 1 H), 4.17 – 4.12 (m, 1 H), 3.28 – 3.22 (m, 1 H), 2.55 (dd, *J* = 14.3, 6.4 Hz, 1 H), 2.43 (s, 3H), 2.42 – 2.37 (m, 1 H), 2.25 – 2.22 (m, 2 H), 1.41– 1.32 (m, 3 H), 1.21 – 1.15 (m, 7 H), 0.85 (t, *J* = 7.0 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 202.0, 139.1, 132.9, 125.2, 122.3, 49.9, 40.7, 35.7, 35.3, 27.4, 26.8, 23.9, 21.0, 17.7, 16.79, 9.3. HRMS (ESI) calcd. for $C_{18}H_{28}NO_3S$ $(M + H)^+$ 338.1785, found 338.1777.

2-Cyclopropyl-1-tosylpiperidin-4-one (16g):



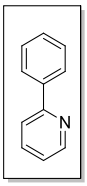
Pale yellow gum; R_f (hexane/EtOAc, 4:1) 0.44; yield 34 mg, 57%; IR (KBr, neat) ν 2925, 1716, 1598, 1335, 1153, 1091, 815, 710, 548 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.77 – 7.75 (m, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 4.13 (ddt, *J* = 14.2, 7.2, 1.9 Hz, 1 H), 3.65 – 3.62 (m, 1 H), 3.56 – 3.51 (m, 1 H), 2.55 (ddd, *J* = 14.2, 6.7, 0.8 Hz, 1 H), 2.45 – 2.43 (m, 1 H), 2.42 (s, 3 H), 2.41 – 2.39 (m, 1 H), 2.32 – 2.28 (m, 1 H), 0.88 – 0.83 (m, 1 H), 0.63 – 0.59 (m, 1 H), 0.48 – 0.44 (m, 1 H), 0.32 – 0.28 (m, 1 H), 0.27 – 0.23 (m, 1 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 206.9, 144.0, 138.0, 130.1, 127.3, 60.1, 45.9, 41.1, 40.8, 21.8, 14.2, 5.4, 4.8. HRMS (ESI) calcd. for $C_{15}H_{20}NO_3S$ $(M + H)^+$ 294.1159, found 294.1155.

2-Isobutyl-1-tosylpiperidin-4-one (16h):



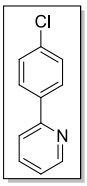
Brown gum; R_f (hexane/EtOAc, 4:1) 0.46; yield 41 mg, 61%; IR (KBr, neat) ν 2926, 1718, 1598, 1338, 1159, 1091, 929, 815, 689, 552 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 4.49 (q, *J* = 7.0, 1 H), 4.15 – 4.09 (m, 1 H), 3.30 – 3.22 (m, 1 H), 2.56 (dd, *J* = 14.3, 6.5 Hz, 1 H), 2.43 (s, 3 H), 2.40 – 2.35 (m, 1 H), 2.23 – 2.16 (m, 2 H), 1.54 – 1.50 (m, 1 H), 1.21 – 1.13 (m, 2 H), 0.84 (dd, *J* = 6.6, 4.0 Hz, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 207.0, 144.1, 137.7, 130.2, 127.4, 53.0, 45.8, 41.4, 40.5, 40.3, 24.6, 22.9, 22.0, 21.8. HRMS (ESI) calcd. for $C_{16}H_{24}NO_3S$ $(M + H)^+$ 310.1472, found 310.1477.

2-Phenylpyridine (17a)[17j]:



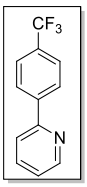
Yellow solid; R_f (hexane/EtOAc, 9:1) 0.53; mp 73 °C, yield 23 mg, 67%; IR (KBr, neat) ν 2924, 1586, 1449, 1424, 1020, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, *J* = 4.3 Hz, 1 H), 7.99 (d, *J* = 7.6 Hz, 2 H), 7.77 – 7.72 (m, 2 H), 7.50 – 7.47 (m, 2 H), 7.44 – 7.40 (m, 1 H), 7.25 – 7.22 (m, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 157.7, 149.9, 139.6, 137.0, 129.2, 129.0, 127.2, 122.3, 120.9. HRMS (ESI) calcd. for $C_{11}H_{10}N$ $(M + H)^+$ 156.0808, found 156.0811.

2-(4-Chlorophenyl)pyridine (17b)[17k]:



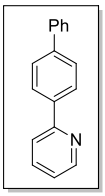
Yellow solid; R_f (hexane/EtOAc, 9:1) 0.54; mp 43 °C, yield 28 mg, 68%; IR (KBr, neat) ν 3005, 1587, 1464, 1435, 1088, 1076, 831, 770 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.69 – 8.68 (m, 1 H), 7.94 – 7.93 (m, 2 H), 7.75 (td, *J* = 7.7, 1.9 Hz, 1 H), 7.69 (dt, *J* = 8.0, 1.1 Hz, 1 H), 7.45 – 7.43 (m, 2 H), 7.25 – 7.23 (m, 1 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 156.5, 150.0, 138.0, 137.1, 135.3, 129.2, 128.4, 122.6, 120.6. HRMS (ESI) calcd. for $C_{11}H_9ClN$ $(M + H)^+$ 190.0419, found 190.0410.

2-(4-(Trifluoromethyl)phenyl)pyridine (17c)[17k]:



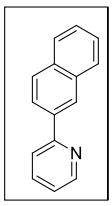
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.54; mp 72 °C, yield 33 mg, 67%; IR (KBr, neat) ν 2926, 1583, 1467, 1404, 1325, 1107,1070, 782, 732, 658, 600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (dt, *J* = 4.9, 1.3 Hz, 1 H), 8.12 (d, *J* = 8.1 Hz, 2 H), 7.83 – 7.78 (m, 2 H), 7.73 (d, *J* = 8.1 Hz, 2 H), 7.32 – 7.29 (m, 1 H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.0, 150.0, 142.7, 137.5, 131.2 (q, *J* = 32.0 Hz), 127.5, 126.0 (q, *J* = 3.9 Hz), 123.3, 121.2. ^{19}F NMR (565 MHz, $CDCl_3/C_6F_6$) δ 99.12. HRMS (ESI) calcd. for $C_{12}H_9F_3N$ $(M + H)^+$ 224.0682, found 224.0685.

2-([1,1'-Biphenyl]-4-yl)pyridine (17d)[17j]:



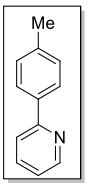
Yellow solid; R_f (hexane/EtOAc, 9:1) 0.53; mp 133 °C, yield 30 mg, 59%; IR (KBr, neat) ν 2926, 1571, 1466, 1449, 1432, 1265, 848, 750 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.8 Hz, 1 H), 8.08 (d, *J* = 8.4 Hz, 2 H), 7.78 – 7.77 (m, 2 H), 7.72 (d, *J* = 7.9 Hz, 2 H), 7.67 (d, *J* = 7.6 Hz, 2 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.37 (t, *J* = 7.3 Hz, 1 H), 7.26 – 7.23 (m, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 157.30, 149.97, 141.97, 140.83, 138.51, 137.03, 129.07, 127.77, 127.71, 127.55, 127.35, 122.37, 120.73. HRMS (ESI) calcd. for $C_{17}H_{14}N$ $(M + H)^+$ 232.1121, found 232.1142.

2-(Naphthalen-2-yl)pyridine (17e)[17j]:



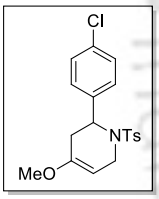
Yellow solid; R_f (hexane/EtOAc, 9:1) 0.51; mp 70 °C, yield 27 mg, 60%; IR (KBr, neat) ν 2918, 1587, 1478, 1440, 1129, 861, 784, 765 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1 H), 8.51 (s, 1 H), 8.14 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.98 – 7.95 (m, 2 H), 7.90 – 7.82 (m, 3 H), 7.54 – 7.50 (m, 2 H), 7.32 – 7.29 (m, 1 H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.5, 149.8, 137.3, 136.6, 133.9, 133.7, 129.0, 128.7, 127.9, 126.8, 126.7, 126.6, 124.8, 122.5, 121.2. HRMS (ESI) calcd. for $C_{15}H_{12}N$ $(M + H)^+$ 206.0965, found 206.0970.

2-(P-tolyl)pyridine (17f)[17l]:



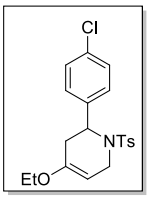
Colorless oil; R_f (hexane/EtOAc, 9:1) 0.53; yield 23 mg, 63%; IR (KBr, neat) ν 2922, 1588, 1466, 1432, 1016, 771, 742, 570 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.5 Hz, 1 H), 7.89 (d, *J* = 8.1 Hz, 2 H), 7.75 – 7.69 (m, 2 H), 7.28 (d, *J* = 7.9 Hz, 2 H), 7.21 – 7.19 (m, 1 H), 2.41 (s, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.7, 149.8, 139.2, 136.9, 136.8, 129.7, 127.0, 122.0, 120.5, 21.5. HRMS (ESI) calcd. for $C_{12}H_{12}N$ $(M + H)^+$ 170.0965, found 170.0981.

2-(4-Chlorophenyl)-4-methoxy-1-tosyl-1,2,3,6-tetrahydropyridine (18a):



Brown gum; R_f (hexane/EtOAc, 4:1) 0.45; yield 50 mg, 60%; IR (KBr, neat) ν 2925, 1588, 1326, 1156, 1090, 814, 696, 657, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.3 Hz, 2 H), 7.32 – 7.30 (m, 2 H), 7.26 – 7.24 (m, 4 H), 5.53 (dd, *J* = 3.9, 1.3 Hz, 1 H), 4.10 (dt, *J* = 14.0, 3.8 Hz, 1 H), 3.56 – 3.53 (m, 1 H), 3.44 – 3.38 (m, 1 H), 3.27 (s, 3 H), 2.42 (s, 3 H), 1.74 – 1.69 (m, 1 H), 1.43 – 1.37 (m, 1 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 144.2, 141.0, 137.5, 136.9, 134.4, 129.8, 129.1, 128.2, 127.7, 117.9, 70.4, 55.9, 44.0, 27.1, 21.8. HRMS (ESI) calcd. for $C_{19}H_{21}ClNO_3S$ $(M + H)^+$ 378.0926, found 378.0924.

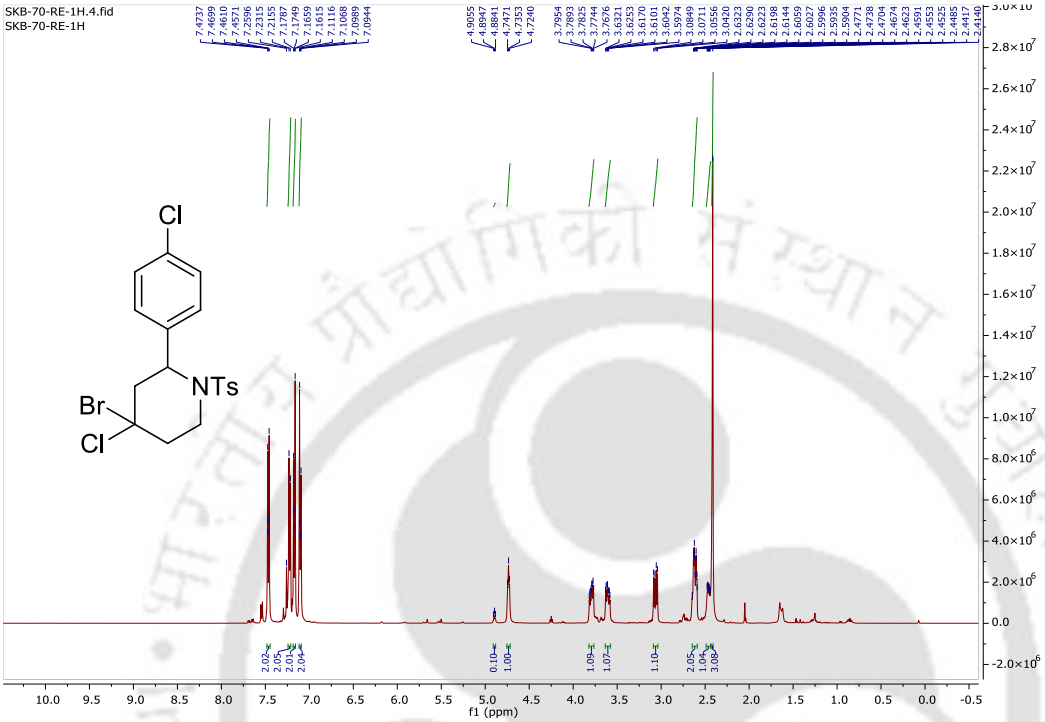
2-(4-Chlorophenyl)-4-ethoxy-1-tosyl-1,2,3,6-tetrahydropyridine (18b):

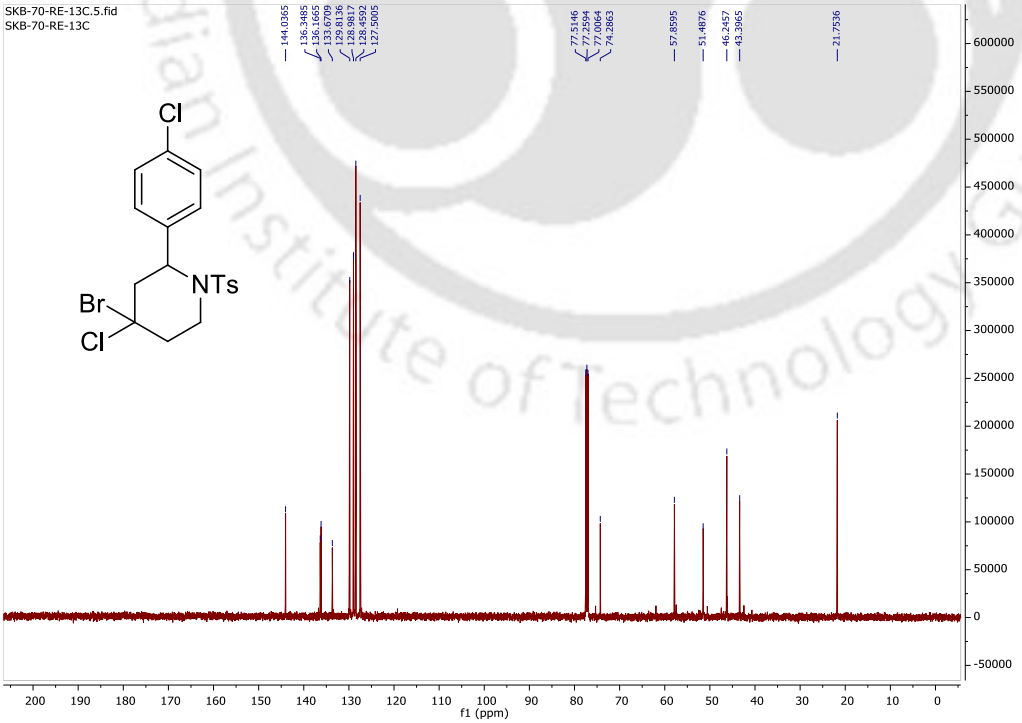


Brown gum; R_f (hexane/EtOAc, 4:1) 0.46; yield 45 mg, 52%; IR (KBr, neat) ν 2928, 1590, 1328, 1158, 1089, 814, 734, 661, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.50 (m, 2 H), 7.32 – 7.29 (m, 2 H), 7.26 – 7.23 (m, 4 H), 5.52 (dd, *J* = 4.0, 1.2 Hz, 1 H), 4.10 (dt, *J* = 14.0, 3.9 Hz, 1 H), 3.64 – 3.62 (m, 1 H), 3.47 – 3.39 (m, 3 H), 2.42 (s, 3 H), 1.73 – 1.68 (m, 1 H), 1.44 – 1.37 (m, 1 H), 1.13 (t, *J* = 7.0 Hz, 3 H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 144.1, 140.7, 137.5, 137.0, 134.4, 129.8, 129.1, 128.2, 127.7, 118.7, 68.8, 63.7, 44.1, 27.7, 21.8, 15.7. HRMS (ESI) calcd. for $C_{20}H_{23}ClNO_3S$ $(M + H)^+$ 392.1082, found 392.1102.

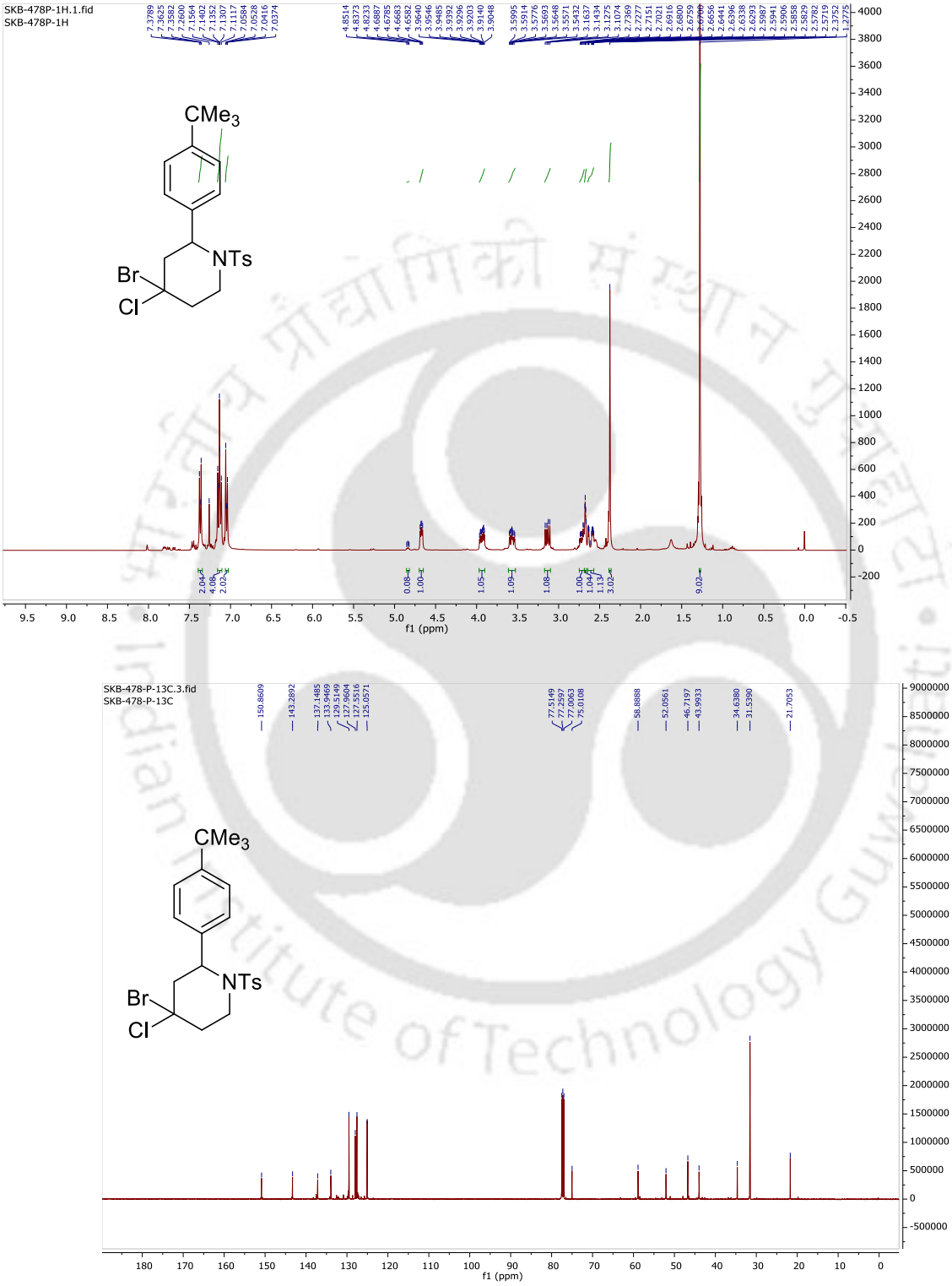
3.6.9 Representative Spectra and crystal parameter

^{1}H(500 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **15ad**

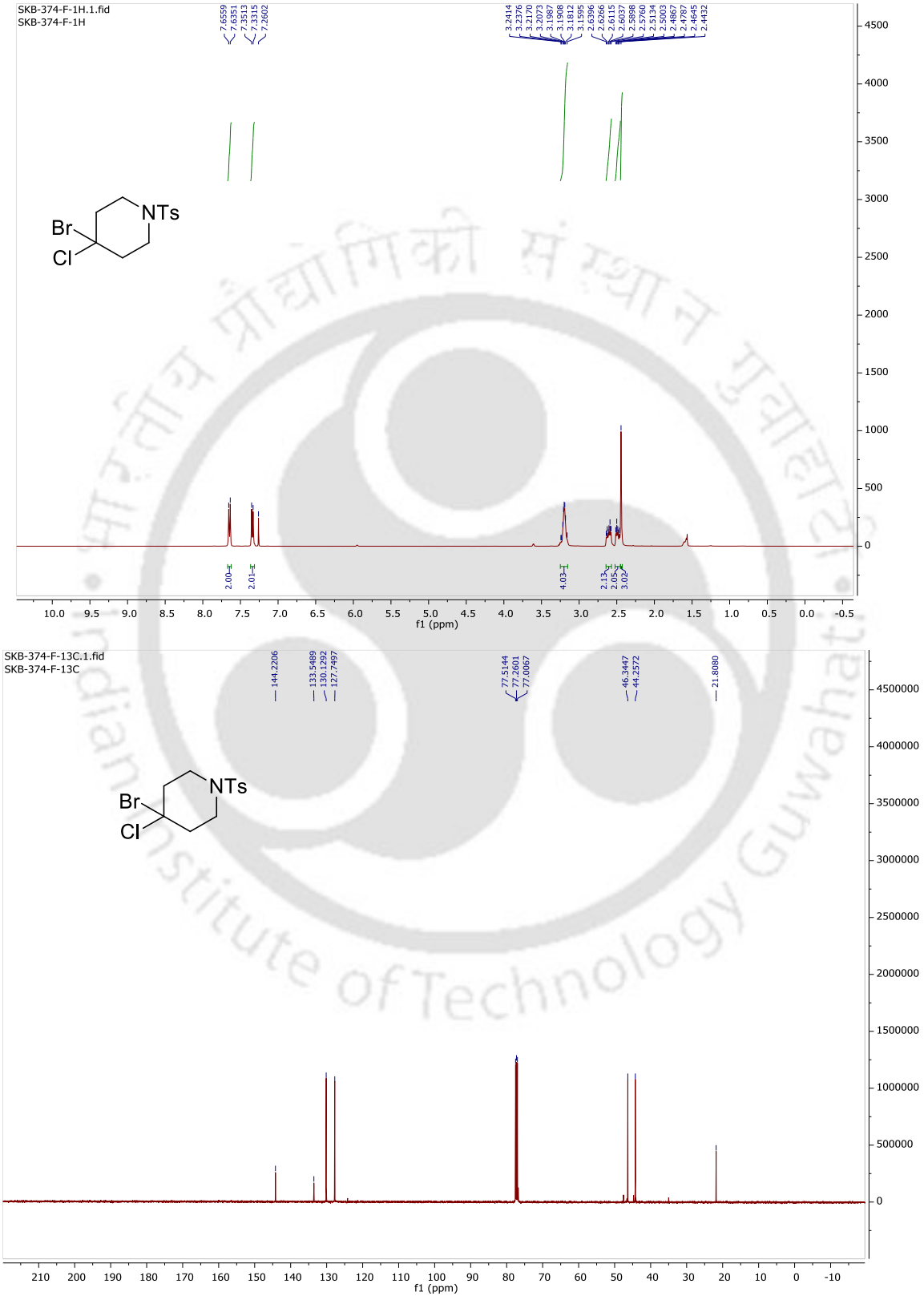




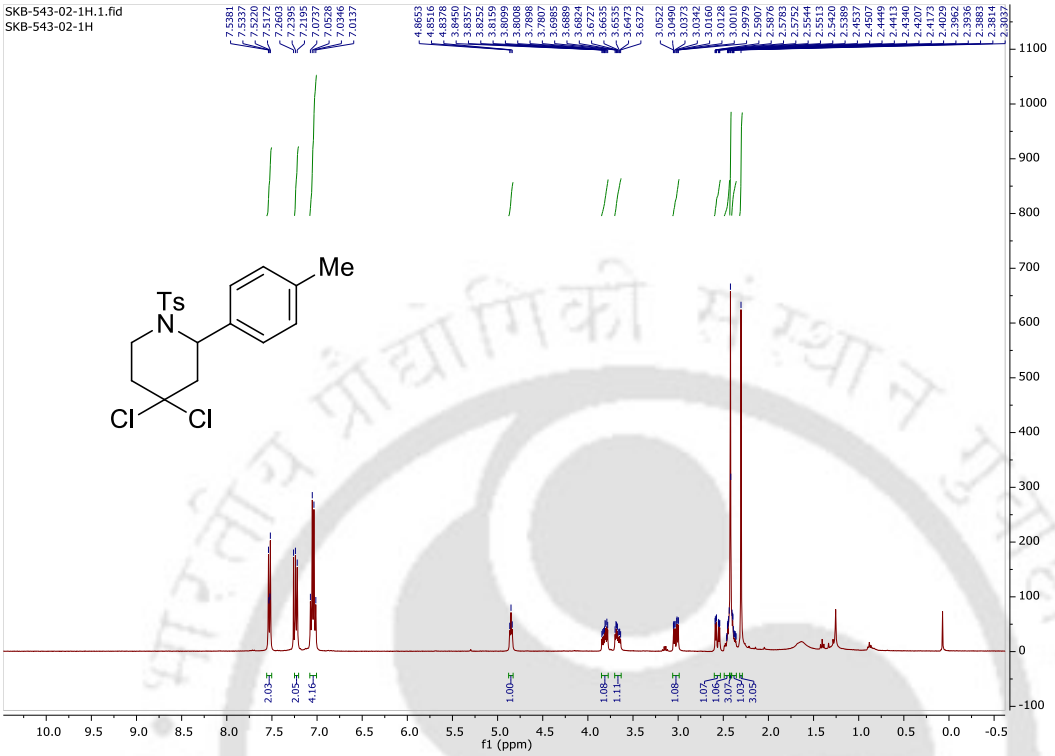
^{1}H(400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **15am**

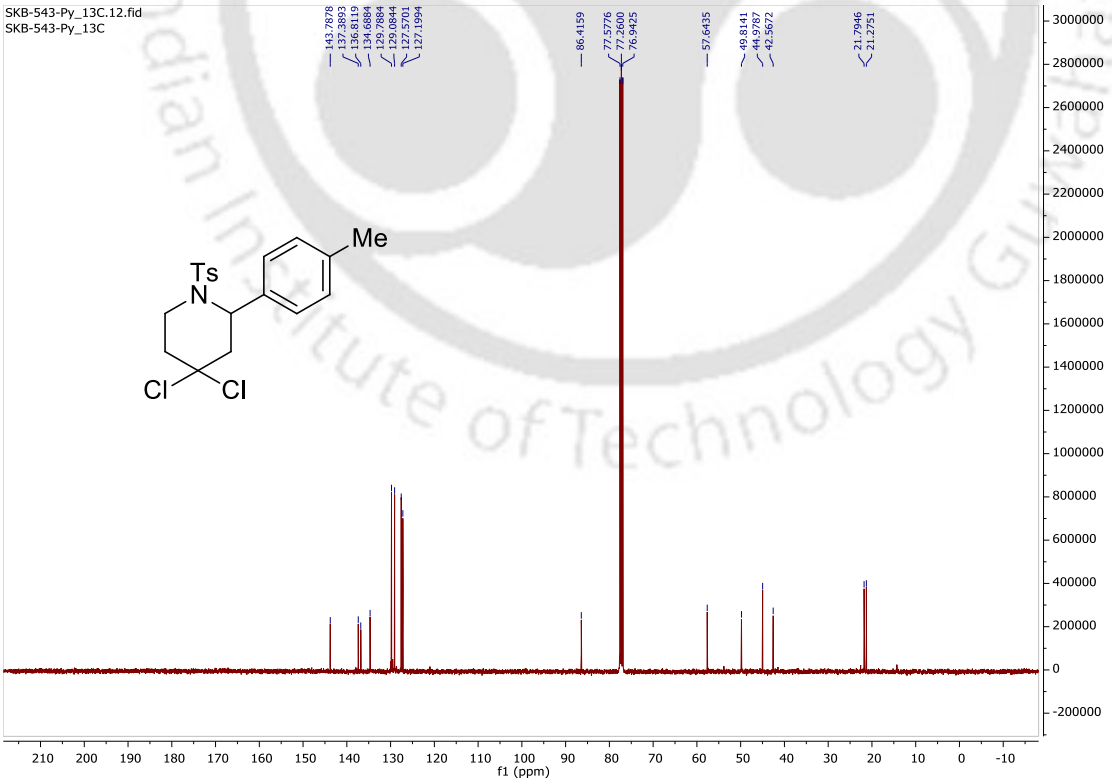


^{1}H (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **15ap**

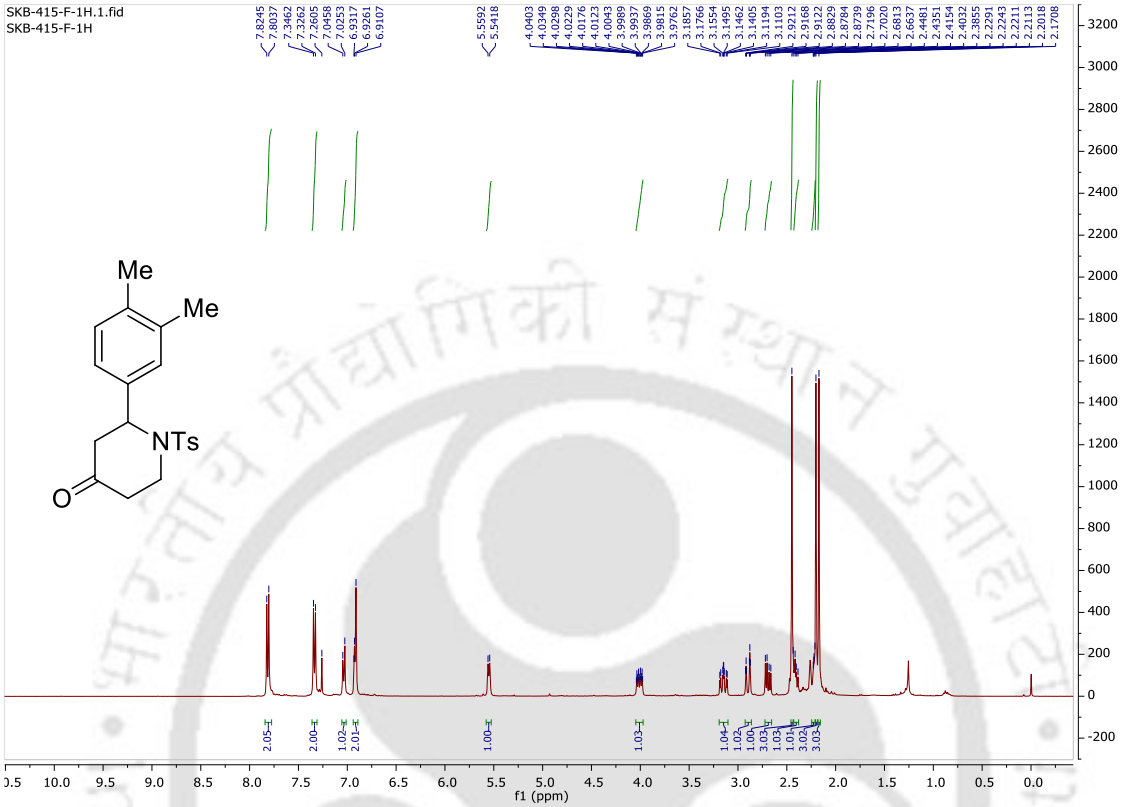


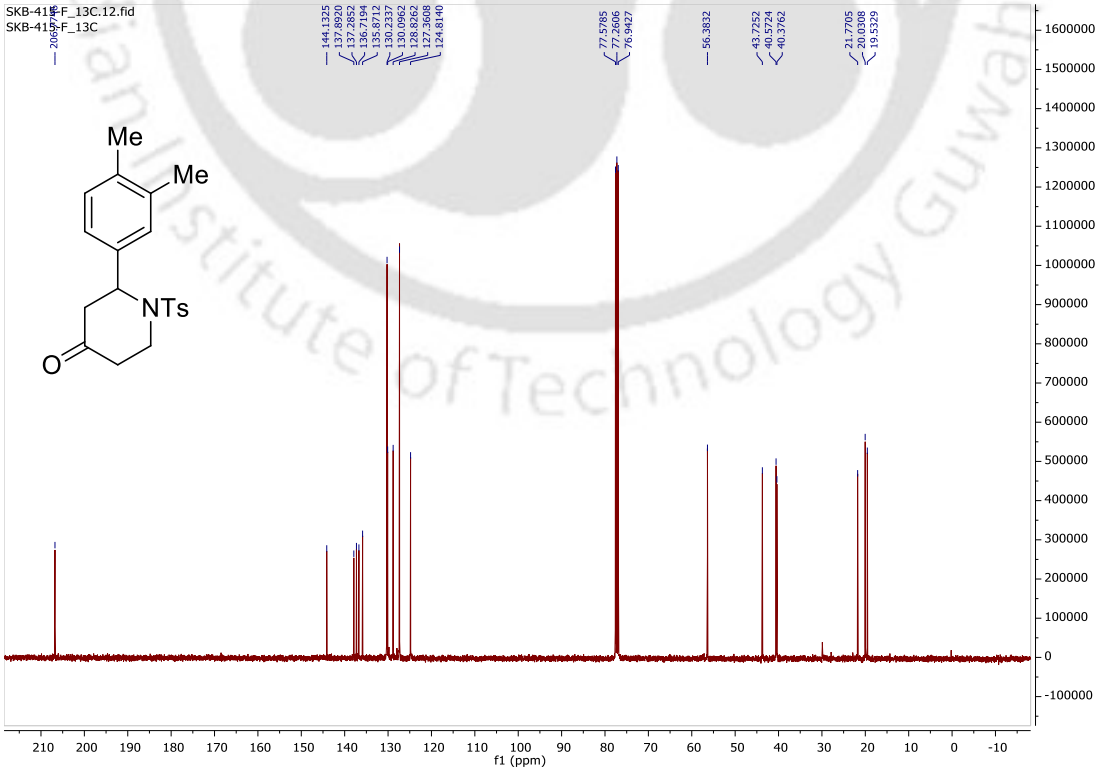
^{1}H (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100 MHz, $CDCl_3$) spectra of **15ck**





^{1}H (600 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (150 MHz, $CDCl_3$) spectra of **16d**

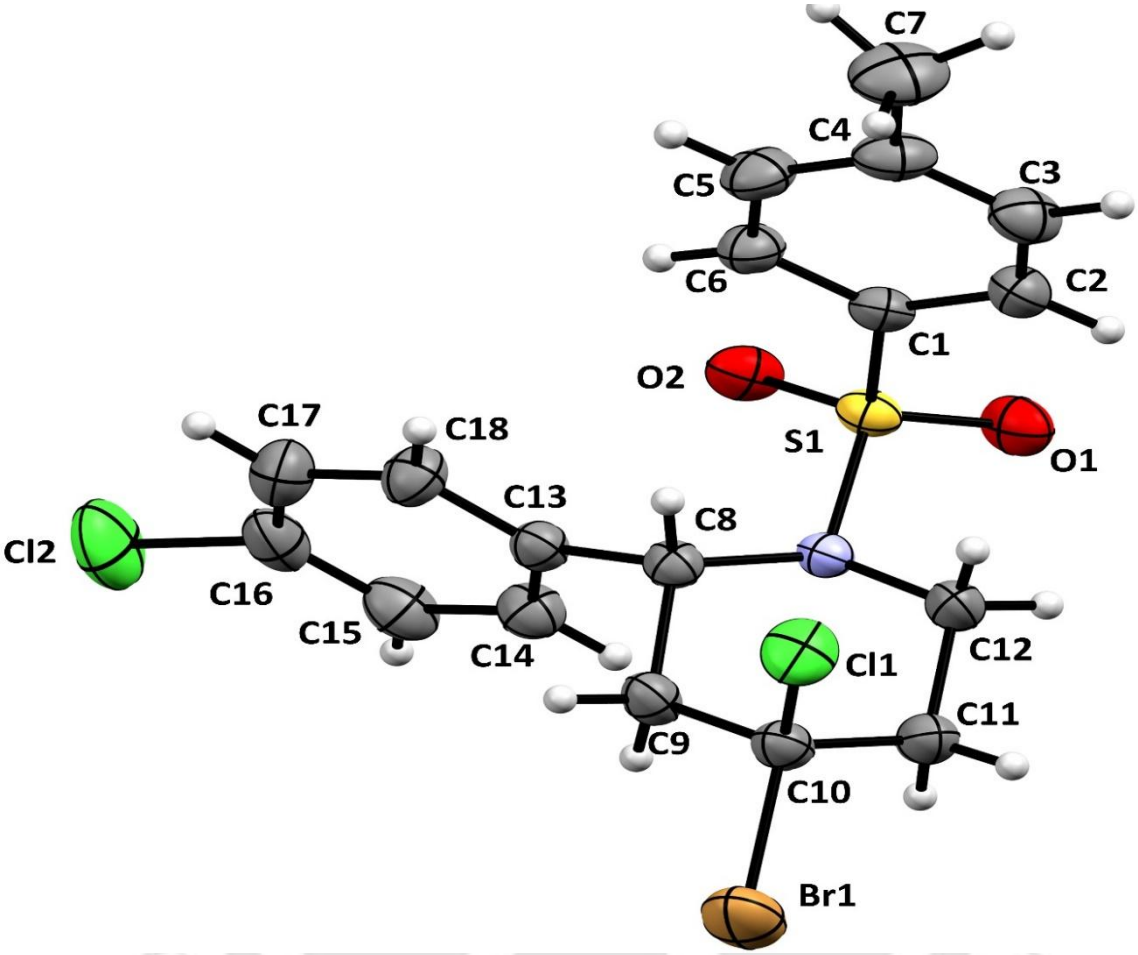




The crystal parameters of compound 15ad

	CCDC 2314309
Formula	$C_{18}H_{18}BrCl_2NO_2S$
Formula weight	463.20
T/K	298(2)
Crystal system	Monoclinic
Space group	P 21/c
a/Å	11.812(2)
b/Å	15.310(3)
c/Å	11.343(2)
α/°	90
β/°	112.195(5)
γ/°	90
V/Å^3	1899.3(6)
Z	4
Abs. Coeff./mm^{-1}	2.567
Abs. Correction	none
GOF on F^2	1.071
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0596 *wR2* = 0.1888
R indices [all data]	*R1* = 0.0746 *wR2* = 0.2070

ORTEP diagram of compound (**15ad**) with 30% probability



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Chapter 4:

$BF_3{\cdot}OEt_2$ Mediated Cascade Synthesis of 4*H*-3,1-Benzoxazines from 2-Azidobenzaldehydes and Homoallylic Alcohols

4.1 Importance and Applications

4*H*-3,1-Benzoxazines are one of the widely recognized structural fragments present in bioactive natural products and synthetically derived pharmaceuticals with notable biological activities.[1] For example, etifoxine (**A**), a gamma-Aminobutyric acid (GABA) receptor inhibitor, serves as an anxiolytic and anticonvulsant;[2] cetilistat (**B**), a pancreatic lipase inhibitor, is used in managing obesity.[3] Additionally, target benzoxazine cell scaffolds are present in diverse bioactive molecules such as a progesterone receptor agonist **C**,[4] human leukocyte elastase inhibitors **D**,[5] high-density lipoprotein elevators **E**,[6] etc. (*Figure 4.1.1*). Because of the importance of benzoxazines, chemists have put a lot of effort into synthesizing them.

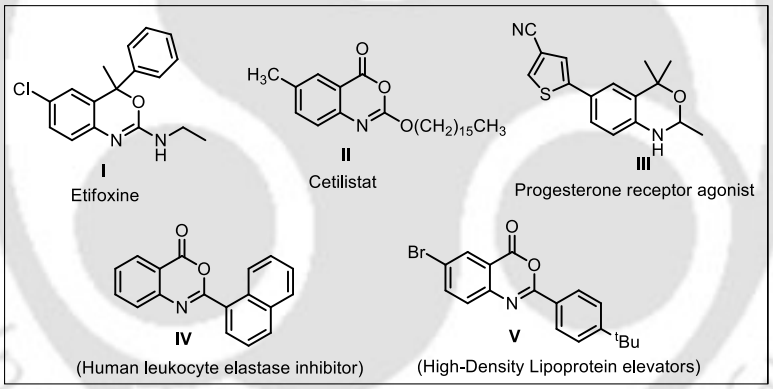
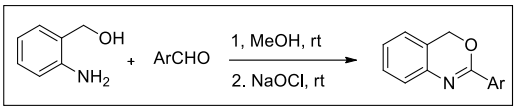


Figure 4.1.1: *Representative examples of biologically active benzoxazines*

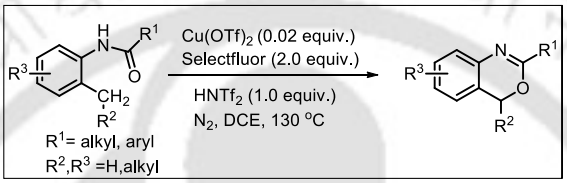
4.2. Literature Survey on the Synthesis of Substituted Benzoxazines

A wide variety of methodologies have been found for the synthesis of substituted benzoxazines in the literature.[7] Furthermore, the condensation of 2-aminobenzyl alcohol with aldehydes, followed by oxidation using strong oxidizing agents such as sodium hypochlorite ($NaClO_4$),[8] gives an efficient and direct method for the synthesis of 4*H*-3,1-benzoxazines (*Scheme 4.2.1*).



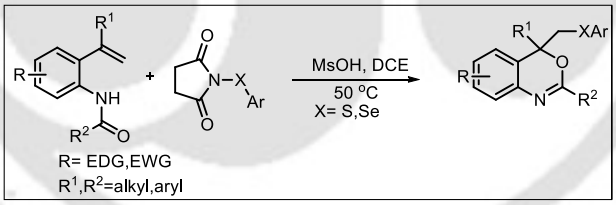
Scheme 4.2.1

In 2012, Zhang's group reported the synthesis of 4*H*-3,1-benzoxazines through a copper-catalyzed, selective benzylic C-O bond formation using ortho-methyl benzanilides as substrates (*Scheme 4.2.2*).[9]



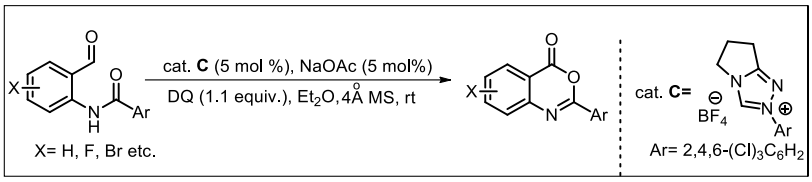
Scheme 4.2.2

In another approach, Anbarasan and co-workers disclosed an efficient and versatile methodology for synthesizing arylthio-/arylseleno tethered benzoxazines through oxychalcogenation of o-vinylanilides (*Scheme 4.2.3*).[10]



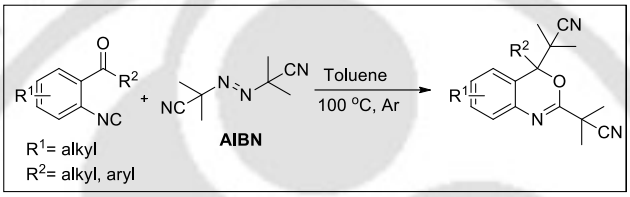
Scheme 4.2.3

Wang and his group recently reported a novel strategy for synthesizing benzoxazinone frameworks, employing an oxidative carbene-catalysed tandem isomerization/cyclization process (*Scheme 4.2.4*).[5a]



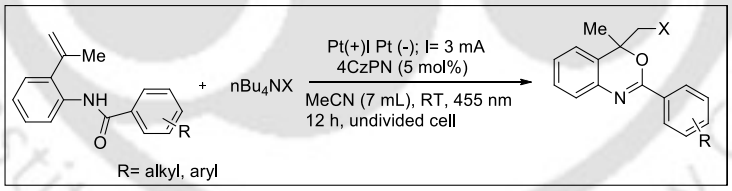
Scheme 4.2.4

Recently, Ding and coworkers synthesized 2,4-Dicyanoalkylated Benzoxazines from aryl isocyanides *via* radical cascade cyclization using AIBN, without the need for metals or additives (*Scheme 4.2.5*).[11]



Scheme 4.2.5

In the same year, Chen *et al.* developed a photoelectrochemical method for producing 4-halomethyl benzoxazines using a halogen anion source (*Scheme 4.2.6*).[12]

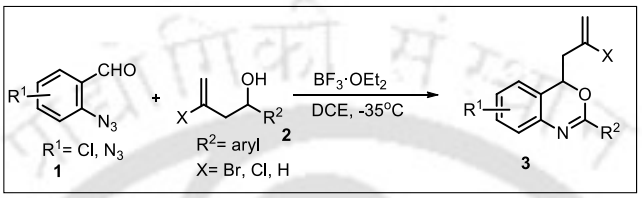


Scheme 4.2.6

4.3 Present Work

Although the benzoxazine moiety is biologically significant, it serves as a crucial component in various thermoset and optoelectronic materials.[13] Because of its importance, numerous dependable methods for synthesizing benzoxazine derivatives have been established.[7] Nevertheless, these methods do not eliminate the difficulty in the efficient and rapid synthesis of benzoxazines. Consequently, developing a more efficient system is required to enhance the synthetic

attractiveness of this approach. In recognition of its significance, we have developed a methodology for the synthesis of 4*H*-3,1-benzoxazine derivatives by utilizing 2-azidobenzaldehydes and homoallylic alcohols in the presence of $BF_3{\cdot}OEt_2$ in moderate to good yields. This reaction proceeds *via* retro-Prins reaction, followed by nucleophilic attack by azide and subsequent elimination of nitrogen and proton. In addition, the method was successfully applied for the synthesis of triazole compounds *via* click reaction.



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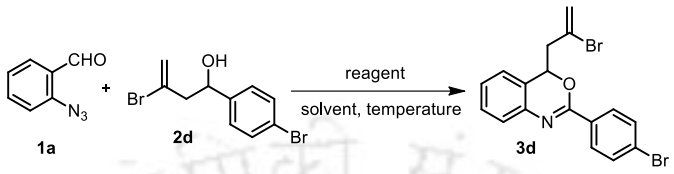
4.4 Results and Discussions

4.4.1 Optimization of the Reaction

Using 3-bromo-1-(4-bromophenyl)but-3-en-1-ol (**2d)** as a model substrate, it was reacted with 2-azidobenzaldehyde (**1a)** in the presence of 1.0 equivalent of $BF_3{\cdot}OEt_2$ in DCM at 0 °C to room temperature. This reaction gave 4-(2-bromoallyl)-2-(4-bromophenyl)-4*H*-benzo[*d*][1,3]oxazine (**3d)** in 24% yield (Table 4.4.1.1, entry 1), accompanied by some decomposed products. To improve the outcome, the reaction was carried out at lower temperatures of 0 °C, −20 °C, and −35 °C, giving yields of 38%, 50%, and 67%, respectively (Table 4.4.1.1, entries 2−4). However, further decreasing the temperature to −50 °C gave only 34% for the desired product, along with unreacted starting material (Table 4.4.1.1, entry 5). The reaction was then tested with various reagents. Lewis acids such as $In(OTf)_3$ and $TiCl_4$ failed to give any product (Table 4.4.1.1, entries 6−7). In contrast, use of TfOH and TMSOTf gave 51% and 63 % yield of product, respectively (Table 4.4.1.1, entries 8-9). Using $BF_3{\cdot}OEt_2$ as a reagent and replacing DCM with the moderately polar DCE at −35 °C, improved the yield to 70% (Table 4.4.1.1, entry 10). The reaction was also tested in other solvents, including the more polar acetonitrile and the less polar toluene; however, these conditions did not improve the yields (Table 4.4.1.1, entries 11−12). Next, increasing the reagent loading of $BF_3{\cdot}OEt_2$ to 1.2 equivalents resulted in a yield of 74% (Table 4.4.1.1, entry 13). However, further increasing the reagent loading to 1.5 equivalents did not lead to any enhancement

of the yield (Table 4.4.1.1, entry 14). Therefore, the optimal conditions for the reaction is 1.2 equivalents of $BF_3 \cdot OEt_2$ in DCE at −35 °C.

Table 4.4.1.1: Optimization of the reaction[a]



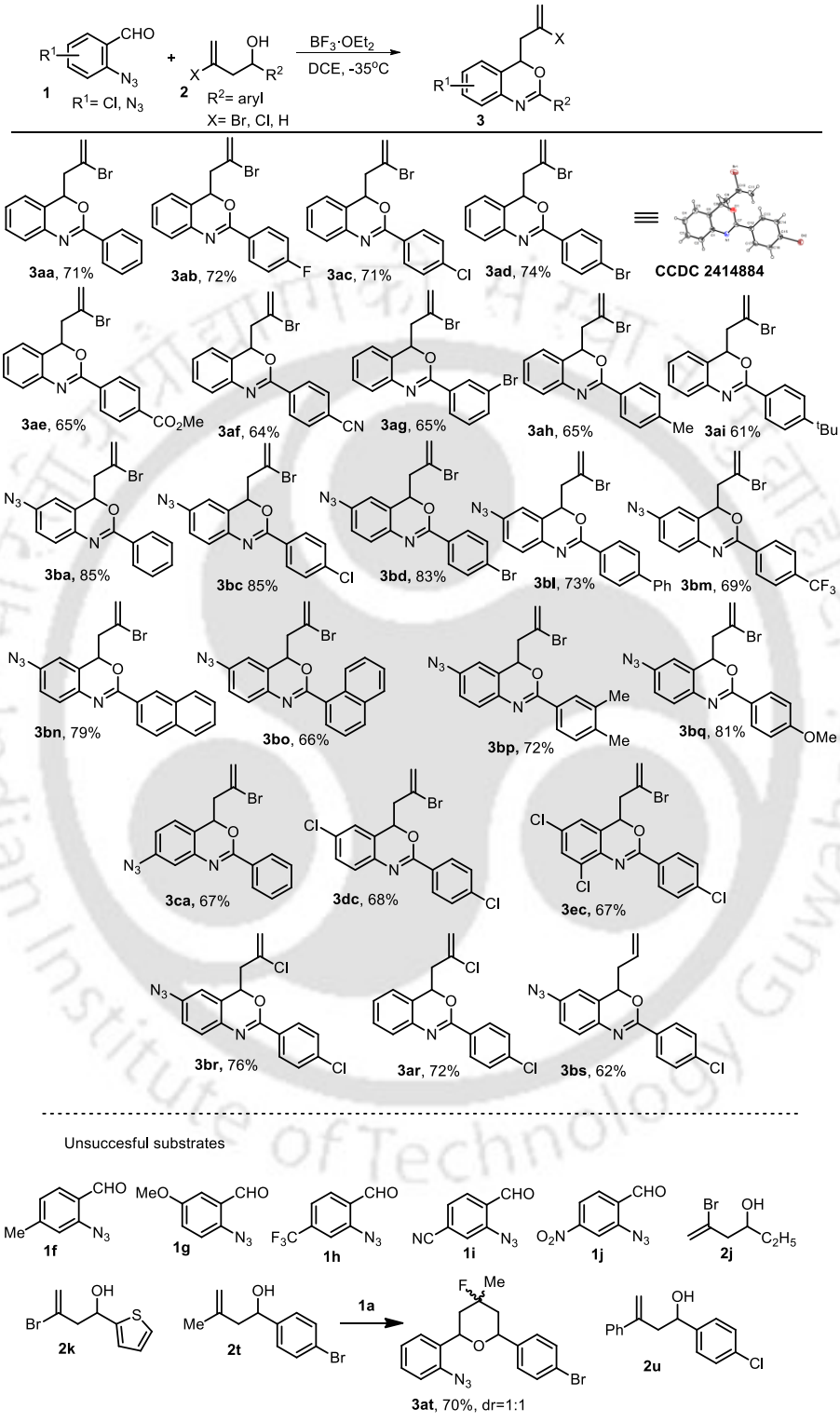
S. No	Reagents (equiv.)	Solvent	Temp.	Time/h	Yield[b] (%)
1	$BF_3 \cdot OEt_2$ (1.0)	DCM	0 °C-rt	2	24
2	$BF_3 \cdot OEt_2$ (1.0)	DCM	0	2	38
3	$BF_3 \cdot OEt_2$ (1.0)	DCM	–20	2	50
4	$BF_3 \cdot OEt_2$ (1.0)	DCM	–35	2	67
5	$BF_3 \cdot OEt_2$ (1.0)	DCM	–50	12	34
6.	$In(OTf)_3$ (1.0)	DCM	–35	12	NR
7.	$TiCl_4$(1.0)	DCM	–35	12	NR
8.	TfOH (1.0)	DCM	–35	2	51
9.	TMSOTf (1.0)	DCM	–35	2	63
10.	$BF_3 \cdot OEt_2$ (1.0)	DCE	–35	2	70
11.	$BF_3 \cdot OEt_2$ (1.0)	Toluene	–35	2	56
12.	$BF_3 \cdot OEt_2$ (1.0)	CH_3CN	–35	2	59
13.	**$BF_3 \cdot OEt_2$ (1.2)**	**DCE**	**–35**	**2**	**74**
14.	$BF_3 \cdot OEt_2$ (1.5)	DCE	–35	2	71

[a]Reaction conditions: all reactions were conducted under open-air atmosphere. **1a** (0.75 mmol) and **2d** (0.50 mmol), solvent (3.0 mL). [b]Isolated yield. NR= No reaction

4.4.2 Substrates Scope of the Reaction:

With this established optimal condition, the reaction was screened with various substrates, as shown in *Scheme 4.4.2.1*. The reaction proceeds efficiently with a variety of homoallylic alcohols, bearing both electron-withdrawing and electron-donating substituents at different positions on the aromatic ring. The reaction of 2-azidobenzaldehydes with homoallylic alcohols containing moderately electron-withdrawing halo groups at the para and meta positions of the aromatic ring yielded the corresponding products **3ab**–**3ad** and **3ag** in good yields. In contrast, homoallylic alcohols with strong electron-withdrawing groups such as $–CO_2Me$ and –CN produced yields of 65% and 64% of the corresponding products **3ae** and **3af**, respectively. Similarly, when the reaction was carried out with homoallylic alcohols bearing a moderate electron-donating methyl group and a strong electron-donating *tert*-butyl group at the para positions provided the products

Scheme 4.4.2.1: Substrate scope of the reaction[a]



[a]Reaction conditions: **1** (0.75 mmol), **2** (0.5 mmol), $BF_3{\cdot}OEt_2$(0.6 mmol), DCE (3 mL).

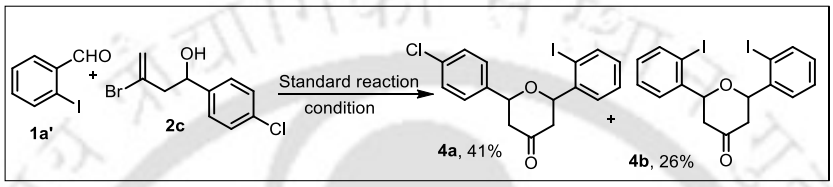
3ah and **3ai** in 65% and 61% yields, respectively. For aliphatic and heteroatomic homoallylic alcohols (**2j**−**2k**), the reaction failed to give the desired products and instead led to decomposition, possibly due to the instability of intermediate **C** (*Scheme 4.5.2b*) for aliphatic compound **2j** and ring opening of the heterocyclic moiety of compound **2k**. On the other hand, when the reaction was conducted with an azide(-N_3) group on the R^1 substituent at the 5-position, the corresponding products (**3ba–3bq)** were obtained in good to excellent yields. The presence of a moderately electron-withdrawing group (**3ba-3bd**) at the R^2 position resulted in an excellent yield of up to 85%. However, the highly electron-withdrawing -CF_3 group gave 69% yield of the corresponding product (**3bm)**. Intriguingly, biphenyl aldehyde **2l** and 2-naphthaldehyde **2n** provided 73% and 79% yields of their corresponding products, while bulky 1-naphthaldehyde **2o** gave the desired product **3bo** in 66% yield, which might be due to the steric hindrance. The presence of the moderately electron-donating 3,4-dimethyl group and the highly electron-donating methoxy (-OMe) group at the para position of the aryl groups on the aromatic ring of homoallylic alcohol afforded the corresponding products **3bp** and **3bq**, with yields of 72% and 81%, respectively. The 4-azido, 5-chloro, and 3,5-dichloro substituents on the aromatic ring of 2-azido benzaldehyde furnished the products **3ca**, **3dc** and **3ec** with 67%, 68% and 67% yields, respectively. However, methyl (**1f**), methoxy (**1g**), cyano (**1h**), nitro (**1i**) and trifluoromethyl (**1j**) substituents on the aromatic ring of 2-azido benzaldehyde failed to give any product and instead resulted in decomposition. The reaction is also compatible with chlorine (Cl) or hydrogen (H), substituents in the homoallylic alcohols yielding products **3br** to **3bs** in moderate to excellent yields (*Scheme 4.4.2.1*). Interestingly, methyl-substituted substrate **2t** provided 2-(2-Azidophenyl)-6-(4-bromophenyl)-4-fluoro-4-methyltetrahydro-2*H*-pyran (**3at**) in 70% yield with dr ratio of 1:1, which was confirmed by ^{1}H NMR spectroscopy. This result was determined from the intensity ratio of two peaks, specifically located at 5.17 ppm and 5.15 ppm (see Page 140). However, when a phenyl substituent (**2u**) was present in the homoallylic alcohol, decomposition occurred. The structure of the compounds was elucidated through ^{1}H, ^{13}C{^{1}H} NMR, IR spectroscopy, HRMS spectrometry, and ultimately by X-ray crystallographic analysis of **3ad**.

4.5 Possible mechanism of the reaction

A control experiment was performed to identify the mechanistic steps involved in this process (*Scheme 4.5.1*). When 2-iodobenzaldehyde was reacted with brominated homoallylic alcohol

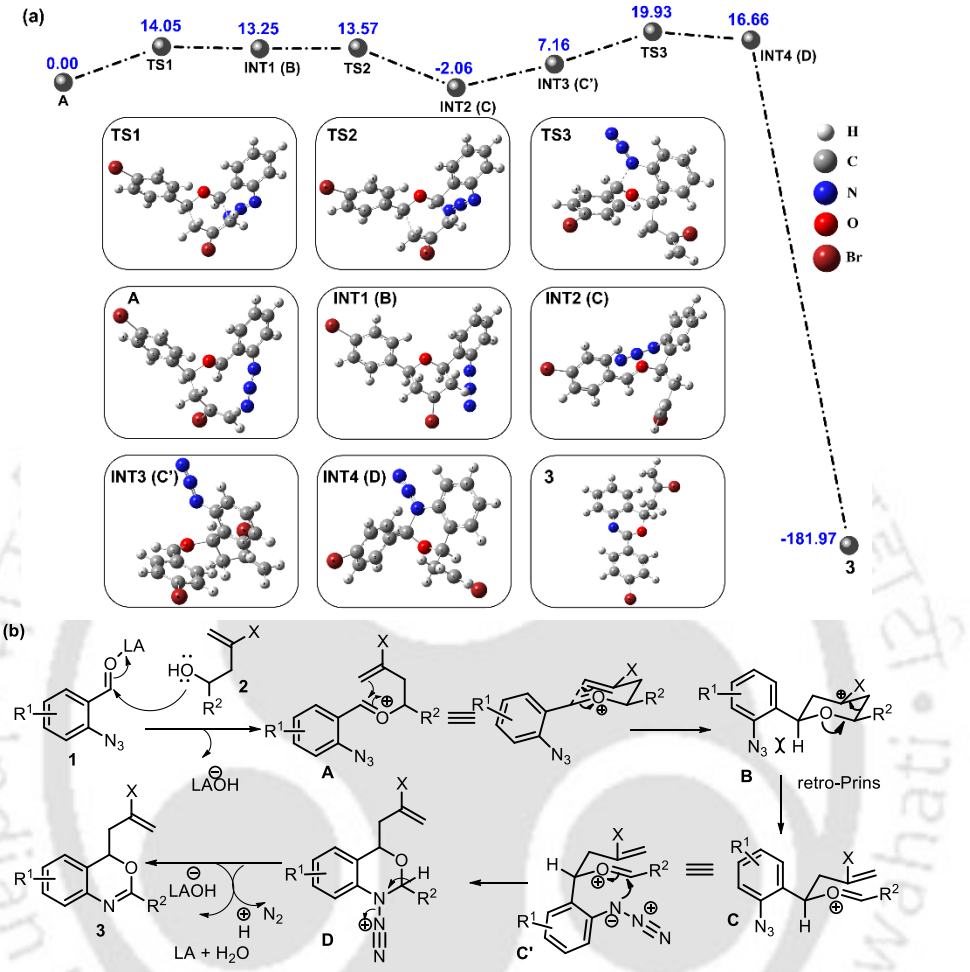
under standard reaction conditions, primarily gave product **4a**, consistent with literature reports;[14] a side product, the retro-Prins product **4b**, was also observed, possibly due to the steric hindrance caused by the bulky iodine atom at the 2-position of the phenyl ring. This suggests that the reaction follows a retro-Prins reaction pathway likely facilitated by the presence of the azide group at the 2-position of the phenyl ring.

Scheme 4.5.1. *Control experiment.*



The reaction pathway and energetics are explored by Density Functional Theory (DFT) calculations, considering the formation of 4-(2-bromoallyl)-2-(4-bromophenyl)-4*H*-benzo[*d*][1,3]oxazine (**3ad**). *Scheme 4.5.2a* shows the energy profile diagram calculated at the DFT-B3LYP/6-311+G(d,p)//B3LYP/6-31G(d,p) level of theory, along with the geometries of reactive chemical species involved in the overall reaction. Based on the experimental results and computational analysis, the reaction mechanism is proposed in *Scheme 4.5.2b*. Under Lewis acidic conditions, halogenated homoallylic alcohol **2** reacts with substituted 2-azido benzaldehyde **1** to form oxocarbenium ion **A.** This oxocarbenium ion **A** has to cross an activation free energy barrier of 14.05 kcal/mol and transform into intermediate **B** (**INT1(B)**) through the transition state **TS1**. Following the retro-Prins reaction, stereoselectively delivered the product-side oxocarbenium ion **C** by reducing the steric repulsion of the initial oxocarbenium ion **B (INT1(B))**, where intermediate **C** (**INT2(C)**) is formed when intermediate **B** (**INT1(B)**) crosses the transition state **TS2**, which has an activation free energy of 0.32 kcal/mol. **INT2(C)** then reorients to another intermediate **C'** (**INT3(C')**) to adopt a favourable geometry for the attack by the azide group on the C-atom of the R−C=O^{+}··· moiety. Following the attack, intermediate **D** (**INT4(D)**) is formed *via* an energy barrier of 12.77 kcal/mol at the transition state **TS3**. Finally, **INT4(D)** releases H^{+} to the $LAOH^{-}$ species, resulting in the formation of H_2O and LA, followed by the removal of N_2 gas. This process results in the formation of the final product 4*H*-3,1-Benzoxazines (**3**). The computational methodology details are presented in the supporting information.

Scheme 4.5.2. *(a) Calculated energy profile diagram[a] and (b) proposed reaction mechanism*



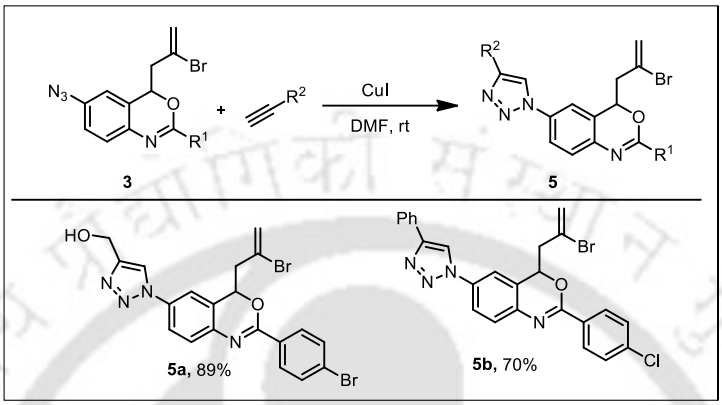
[a]Calculated energy profile diagram for the retro-Prins cyclization pathway for 4*H*-3,1-Benzoxazines formation. The relative energies (blue) from DFT approaches are in kcal mol^{-1}. Stationary points are located by optimization at the DFT-B3LYP/6-31G(d,p) level of theory. Following this, single-point energy calculations are carried out using the DFT-B3LYP/6-311+G(d,p) level of theory.

4.6 Post-Synthetic Utility of the Reaction:

To evaluate the synthetic applicability of the products, several transformations were performed (*Scheme 4.6.1*). The click reaction of the benzoxazine molecule **3** with CuI led to the successful synthesis of its triazole derivative **5**. Thus, the reaction of **3bd** with propagyl alcohol and **3bc** with phenyl acetylene gave products **5a** and **5b** with 89% and 70% yields, respectively. It may be noted that the 1,2,3-triazole moiety holds significant importance in chemistry and chemical biology due

to its unique properties, chemical inertness, and capability to mimic amide bonds. They also display an extensive application in the pharmaceutical and agricultural industries.[15]

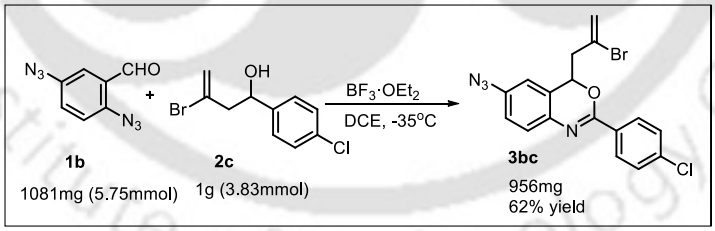
Scheme 4.6.1. Post-synthetic modification



4.7 Gram scale experiment of the reaction

To demonstrate the scalability of the methodology, a scale-up experiment was performed using 2,5-diazidobenzaldehyde **1b** (1081mg, 5.75 mmol) and 3-bromo-1-(4-chlorophenyl)but-3-en-1-ol **2c** (1.0 g, 3.83 mmol) under the standard conditions, yielding 62% (956 mg) of the corresponding product **3bc** (*Scheme 4.7.1*).

Scheme 4.7.1. Gram scale experiment



4.8 Conclusion

In summary, a highly efficient method for synthesizing 4*H*-3,1-benzoxazines has been developed, yielding satisfactory yields. This approach is free from any metal catalyst and involves a retro-Prins reaction, and delivers the product in a short time. The methodology is advantageous for the synthesis of several substituted benzoxazine compounds, which are valuable frameworks in medicinal compounds and can be beneficial for drug discovery and other organic compounds.

4.9 Experimental Section

4.9.1 General Information

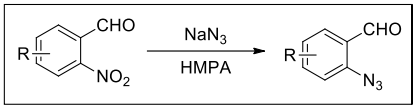
All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). The reaction was carried out in Julabo FT903 to maintain a negative temperature. Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infrared (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as the internal standard for ^1H (600 MHz, 500 MHz and 400 MHz) or $^{13}C\{^1H\}$ (150 MHz, 125 MHz and 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 Q-TOF and micrOTOF-Q II mass spectrometer.

The starting material 2-azidobenzaldehyde **(1a)**,[16h] 2,4-diazidobenzaldehyde **(1c)**,[16h] 2-azido-5-chlorobenzaldehyde **(1d),**[16h] 3-bromo-1-phenylbut-3-en-1-ol **(2a)**,[16a] 3-bromo-1-(4-fluorophenyl)but-3-en-1-ol **(2b)**,[16b] 3-bromo-1-(4-chlorophenyl)but-3-en-1-ol **(2c)**,[16c] 3-bromo-1-(4-bromophenyl)but-3-en-1-ol **(2d)**,[16d] methyl 4-(3-bromo-1-hydroxybut-3-en-1-yl)benzoate **(2e)**,[16c] 3-bromo-1-(p-tolyl)but-3-en-1-ol (**2h**),[16d] 5-bromohex-5-en-3-ol **(2j)**,[16b] 3-bromo-1-(thiophen-2-yl)but-3-en-1-ol **(2k)**,[14] 1-([1,1'-biphenyl]-4-yl)-3-bromobut-3-en-1-ol **(2l)**,[16c] 3-bromo-1-(4-(trifluoromethyl)phenyl)but-3-en-1-ol **(2m)**,[16a] 3-bromo-1-(naphthalen-2-yl)but-3-en-1-ol **(2n)**,[14] 3-bromo-1-(naphthalen-1-yl)but-3-en-1-ol **(2o)**,[16e] 3-bromo-1-(4-methoxyphenyl)but-3-en-1-ol **(2q)**,[16c] 3-chloro-1-(4-chlorophenyl)but-3-en-1-ol **(2r)**,[16f] and 1-(4-chlorophenyl)but-3-en-1-ol **(2s)**,[16g] were synthesized according to the reported literatures. The spectroscopic data of the above compounds are in good agreement with the literature. The experimental procedure and the characterization data of the remaining starting material are given as follows:

4.9.2 General Procedure for the Preparation of Starting Materials (1b-1j):

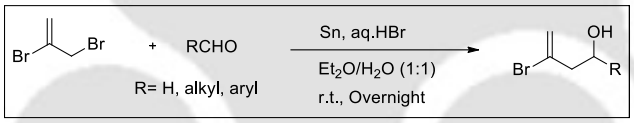
To a stirred solution of substituted 2-nitrobenzaldehyde (13.25 mmol) in HMPA (40 mL) was added NaN_3 (26.50 mmol, 2.0 equiv). The reaction mixture was stirred at 50 ^oC in an oil bath. After completion of the reaction (determined by TLC), the reaction mixture was allowed to cool to room temperature. The organic layer was extracted with ethyl acetate (3 x 30 mL). The

combined organic layers are dried over anhydrous Na_2SO_4, filtered, and all volatiles are removed under reduced pressure and purified by column chromatography over silica gel using hexane and ethyl acetate as eluent to get the products.



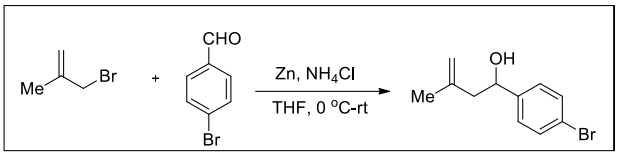
4.9.3 General Procedure for the Preparation of Starting Materials (2f, 2g, 2i and 2p):

To a mixture of aldehyde (8.3 mmol, 1.0 equiv.) and tin powder (10.8 mmol, 1.3 equiv.) in water / Et_2O (1:1, 24 mL) was added HBr (0.5 mL, 48% aq.). After 10 minutes, 2,3-dibromopropene (10.8 mmol, 1.3 equiv.) was added slowly and stirred overnight at room temperature. After completion of the reaction, the reaction mixture was diluted with brine solution and the organic layer was extracted with diethyl ether (3×20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The crude was subjected to column chromatography over silica gel using hexane and ethyl acetate as eluents to get the product.



4.9.4. Experimental procedure for the synthesis of Starting Materials (2t):

Zn dust (7.56 mmol, 3.5 equiv) was slowly added to a stirred solution of the 3-bromo-2-methylprop-1-ene (1021 mg, 7.56 mmol, 3.5 equiv) in dry THF (3 mL) under a N_2 atmosphere at 0 ^oC. A solution of the 4-bromobenzaldehyde (399 mg, 2.16 mmol, 1.0 equiv) in dry THF (4 mL) was added to the reaction mixture. The resulting suspension was stirred at 0 °C for 2 hours, followed by stirring at room temperature overnight. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with aq. NH_4Cl at 0 ^oC, extracted with ethyl acetate (3×10 mL) and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel to get the products.



4.9.5 General procedure for the synthesis of (3aa-3bs):

To a solution of homoallylic alcohols (0.5 mmol, 1.0 equiv) and 2-azido benzaldehyde derivative (0.75 mmol, 1.5 equiv) in dry DCE (3 mL) was added $BF_3 \cdot OEt_2$ (0.6 mmol, 1.2 equiv) was added dropwise at -35 °C under an open-air atmosphere. The reaction mixture was then stirred at -35 °C and the progress of the reaction was monitored by TLC (ethyl acetate: hexane = 1:19). After completion of the reaction, the organic layer was extracted with ethyl acetate (3 × 10 mL) and washed with saturated sodium bicarbonate and brine solutions. The reaction mixture was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The crude was subjected to column chromatography over silica gel using ethyl acetate and hexane as eluents to get the product.

4.9.6 Experimental procedure for the synthesis of 4:

To a solution of 3-bromo-1-(4-chlorophenyl)but-3-en-1-ol (131 mg, 0.5 mmol, 1.0 equiv) and 2-iodo benzaldehyde (174 mg, 0.75 mmol, 1.5 equiv) in dry DCE (4 mL) was added $BF_3 \cdot OEt_2$ (85 mg, 0.6 mmol, 1.2 equiv) dropwise at -35 °C under the nitrogen atmosphere. The reaction mixture was then stirred at -35 °C and the progress of the reaction was monitored by TLC (ethyl acetate:hexane = 1:9). After completion of the reaction, the organic layer was extracted with ethyl acetate (3x10 mL) and washed with saturated sodium bicarbonate and brine solutions. The reaction mixture was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The crude was subjected to column chromatography over silica gel using ethyl acetate and hexane as eluents to get the product.

4.9.7 General procedure for the preparation of (5a and 5b):

To a stirred solution of azide derivative **3** (0.5 mmol, 1.0 equiv) and alkyne (1.0 mmol, 2.0 equiv) in DMF (3 mL) was added CuI (0.05 mmol, 10 mol%). The reaction mixture was stirred at room temperature for 6 hours. After completion of the reaction (monitored by TLC), the reaction mixture was poured out on ice-cooled water, extracted with ethyl acetate (3×10 mL), and washed with water and brine solutions. The reaction mixture was dried over anhydrous Na_2SO_4, filtered, and

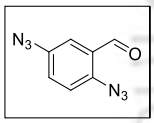
all volatiles were removed under reduced pressure and purified by column chromatography over silica gel to give pure triazole derivatives.

4.9.8 Experimental procedure for the gram-scale reaction

To a solution of 3-bromo-1-(4-chlorophenyl)but-3-en-1-ol **2c** (1.0 g, 3.83 mmol, 1.0 equiv) and 2,5-diazidobenzaldehyde **1b** (1081 mg, 5.75 mmol, 1.5 equiv) in dry DCE (18 mL) was added $BF_3{\cdot}OEt_2$ (648 mg, 4.60 mmol, 1.2 equiv) dropwise at -35 °C under open air atmosphere. The reaction mixture was then stirred at -35 °C for 2.5 hours and progress of the reaction was monitored by TLC (ethyl acetate:hexane = 1:19). After completion of the reaction, the organic layer was extracted with ethyl acetate (3 x 30 mL) and washed with saturated sodium bicarbonate and brine solutions. The reaction mixture was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The product **3bc** was obtained in a 62% (956 mg, brown solid) yield by column chromatography over silica gel using hexane and ethyl acetate as eluents.

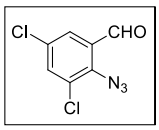
4.9.9 Characterization Data

2,5-diazidobenzaldehyde (1b): Following the general procedure, **1b** was obtained from the



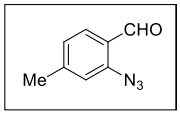
reaction of 5-fluoro-2-nitrobenzaldehyde (2239 mg, 1.0 equiv) after column chromatographic isolation as a brown solid; R_f (hexane/EtOAc, 19:1) 0.49; mp 51 °C, yield 1744 mg, 70%; IR (KBr, neat) ν 3370, 2867, 2110, 1692, 1575, 1432, 1308, 1213, 1075, 843, 722, 532 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 10.30 (s, 1 H), 7.54 (d, *J* = 2.6 Hz, 1 H), 7.24 (s, 1 H), 7.22 (dd, *J* = 8.6, 2.6 Hz, 1 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 187.8, 139.7, 137.7, 128.0, 126.4, 120.9, 118.7. HRMS (ESI) calcd. for $C_7H_5N_6O$ $(M + H)^+$ 189.0520, found 189.0527.

2-azido-3,5-dichlorobenzaldehyde (1e): Following the general procedure, **1e** was obtained from

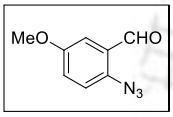


the reaction of 3,5-dichloro-2-nitrobenzaldehyde (2915 mg, 1.0 equiv) after column chromatographic isolation as a brown solid; R_f (hexane/EtOAc, 19:1) 0.48; mp 55 °C, yield 1889 mg, 66%; IR (KBr, neat) ν 3372, 2870, 2433, 2115, 1692, 1578, 1435, 1383, 1308, 1213, 1177, 1075, 849, 728, 532, 411 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.34 (s, 1 H), 7.74 (d, *J* = 2.2 Hz, 1 H), 7.59 (d, *J* = 2.2 Hz, 1 H). $^{13}C\{^1H\}$NMR (125MHz, $CDCl_3$) δ 187.5, 137.5,

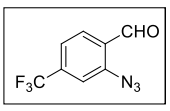
135.8, 132.1, 131.1, 130.8, 127.1. HRMS (ESI) calcd. for $C_7H_7Cl_2N_4O$ $(M + NH_4)^+$ 232.9992, found 232.9992.

2-Azido-4-methylbenzaldehyde (1f)[17a]**:** Following the general procedure, **1f** was obtained from 

the reaction of 4-methyl-2-nitrobenzaldehyde (2186 mg, 1.0 equiv) after column chromatographic isolation as a yellow solid; R_f (hexane/EtOAc, 19:1) 0.43; mp 39 ^oC, yield 1450 mg, 68%; ^1H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1 H), 7.78 (d, *J* = 7.9 Hz, 1 H), 7.06 – 7.02 (m, 2 H), 2.44 (s, 3 H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 188.5, 147.2, 143.1, 129.2, 126.3, 125.0, 119.6, 22.1.

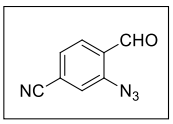
2-Azido-5-methoxybenzaldehyde (1g)[17b]**:** Following the general procedure, **1g** was obtained 

from the reaction of 5-methoxy-2-nitrobenzaldehyde (2398 mg, 1.0 equiv) after column chromatographic isolation as a pale yellow solid; R_f (hexane/EtOAc, 19:1) 0.47; mp 79 ^oC, yield 469 mg, 20%; ^1H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1 H), 7.37 (dd, *J* = 2.2, 1.3 Hz, 1 H), 7.20 – 7.19 (m, 2 H), 3.84 (s, 3 H). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 188.6, 157.1, 136.1, 127.7, 123.8, 120.6, 111.0, 56.0.

2-Azido-4-(trifluoromethyl)benzaldehyde (1h)[17c]**:** Following the general procedure, **1h** was 

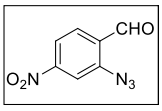
obtained from the reaction of 2-nitro-4-(trifluoromethyl)benzaldehyde (2902 mg, 1.0 equiv) after column chromatographic isolation as a yellow solid; R_f (hexane/EtOAc, 19:1) 0.46; mp 88 ^oC, yield 2365 mg, 83%; ^1H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1 H), 7.91 (d, *J* = 8.1 Hz, 1 H), 7.43 – 7.39 (m, 2 H). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) δ 187.7, 143.7, 137.0 (q, *J* = 33.0 Hz), 130.0, 129.2, 123.1 (q, *J* = 271.7 Hz), 121.8 (q, *J* = 3.6 Hz), 116.5 (q, *J* = 4.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$) δ 98.24.

3-Azido-4-formylbenzonitrile (1i)[17d]**:** Following the general procedure, **1i** was obtained from the



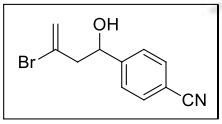
reaction of 3-fluoro-4-formylbenzonitrile (1974 mg, 1.0 equiv) after column chromatographic isolation as a colorless solid; R_f (hexane/EtOAc, 19:1) 0.43; mp 134 °C, yield 1823 mg, 80%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.31 (s, 1 H), 8.15 (d, *J* = 2.6 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 1 H), 7.39 (d, *J* = 8.2 Hz, 1 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 186.6, 147.0, 138.1, 133.4, 127.2, 120.4, 117.5, 109.1.

2-Azido-4-nitrobenzaldehyde (1j): Following the general procedure, **1j** was obtained from the

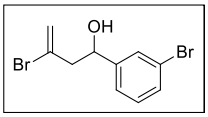


reaction of 2-fluoro-4-nitrobenzaldehyde (2239 mg, 1.0 equiv) after column chromatographic isolation as a yellow solid; R_f (hexane/EtOAc, 19:1) 0.47; mp 135 °C, yield 1984 mg, 78%; IR (KBr, neat) ν 3101, 3041, 2881, 2424, 2217, 2138, 1693, 1608, 1533, 1476, 1394, 1351, 1296, 1189, 1111, 884, 814, 737, 527, 462, 440 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.41 (s, 1 H), 8.13 (s, 1 H), 8.06 – 8.03 (m, 2 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 187.2, 151.9, 144.5, 130.6, 130.5, 119.7, 114.7. HRMS (ESI) calcd. for $C_7H_8N_5O_3$ $(M + NH_4)^+$ 210.0622, found 210.0615.

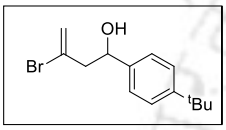
4-(3-Bromo-1-hydroxybut-3-en-1-yl)benzonitrile (2f): Pale yellow solid; R_f (hexane/EtOAc,



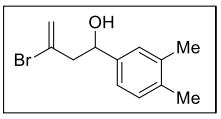
9:1) 0.55; mp 75 °C, yield 1792 mg, 86%; IR (KBr, neat) ν 3430, 2911, 2229, 1631, 1609, 1505, 1266, 1194, 1058, 836, 736, 574, 431 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2 H), 7.49 (d, *J* = 8.1 Hz, 2 H), 5.64 (s, 1 H), 5.53 (s, 1 H), 5.07 (dd, *J* = 8.6, 4.6 Hz, 1 H), 2.78 (dd, *J* = 14.4, 8.6 Hz, 1 H), 2.71 (dd, *J* = 14.4, 4.6 Hz, 1 H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 148.4, 132.5, 129.2, 126.7, 120.9, 118.9, 111.5, 71.0, 51.4. HRMS (ESI) calcd. for $C_{11}H_{11}BrNO$ $(M + H)^+$ 252.0019, found 252.0006.

3-Bromo-1-(3-bromophenyl)but-3-en-1-ol (2g): Pale yellow liquid; R_f (hexane/EtOAc, 9:1) 

0.54; yield 2057 mg, 81%; IR (KBr, neat) ν 3389, 2910, 1630, 1570, 1428, 1264, 1051, 891, 782, 737, 696, 531 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1 H), 7.42 (dd, *J* = 7.7, 1.9 Hz, 1 H), 7.31 – 7.29 (m, 1 H), 7.22 (td, *J* = 7.8, 1.9 Hz, 1 H), 5.68 (s, 1 H), 5.55 (s, 1 H), 5.01 – 4.98 (m, 1 H), 2.82 – 2.77 (m, 1 H), 2.75 – 2.70 (m, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 145.3, 131.1, 130.3, 129.8, 129.2, 124.7, 122.9, 120.7, 71.1, 51.6. HRMS (ESI) calcd. for $C_{10}H_{11}Br_2O$ $(M + H)^+$ 306.9151, found 306.9162.

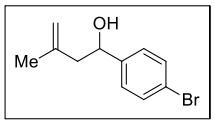
3-Bromo-1-(4-(tert-butyl)phenyl)but-3-en-1-ol (2i): Colourless solid; R_f (hexane/EtOAc, 9:1) 

0.55; mp 80 °C yield 2020 mg, 86%; IR (KBr, neat) ν 3369, 2962, 2904, 1631, 1511, 1407, 1363, 1201, 1108, 1013, 888, 831, 581, 470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.38 (m, 2 H), 7.33 – 7.31 (m, 2 H), 5.71 (s, 1 H), 5.55 (d, *J* = 1.6 Hz, 1 H), 5.04 – 5.00 (m, 1 H), 2.85 (ddd, *J* = 14.5, 9.0, 0.8 Hz, 1 H), 2.75 (ddd, *J* = 14.5, 4.2, 1.2 Hz, 1 H), 2.06 (s, 1 H), 1.32 (s, 9 H).$^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) δ 151.1, 140.1, 130.6, 125.8, 125.7, 120.1, 71.6, 51.4, 34.8, 31.6. HRMS (ESI) calcd. for $C_{14}H_{19}BrNaO$ $(M + Na)^+$ 305.0512, found 305.0493.

3-Bromo-1-(3,4-dimethylphenyl)but-3-en-1-ol (2p): Brown liquid; R_f (hexane/EtOAc, 9:1) 

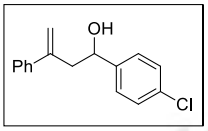
0.52; yield 1834 mg, 87%; IR (KBr, neat) ν 3389, 2920, 1631, 1505, 1452, 1265, 1199, 1116, 1021, 887, 737, 596, 447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 1.6 Hz, 1 H), 7.13 – 7.10 (m, 2 H), 5.70 (s, 1 H), 5.54 (d, *J* = 1.7 Hz, 1 H), 4.97 (dd, *J* = 9.0, 4.1 Hz, 1 H), 2.84 (ddd, *J* = 14.5, 8.9, 0.8 Hz, 1 H), 2.74 (ddd, *J* = 14.5, 4.1, 1.3 Hz, 1 H), 2.28 (s, 3 H), 2.27 (s, 3 H), 2.17 (s, 1 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 140.6, 137.0, 136.4, 130.6, 130.0, 127.3, 123.5, 120.0, 71.7, 51.4, 20.0, 19.7. HRMS (ESI) calcd. for $C_{12}H_{16}BrO$ $(M + H)^+$ 255.0380, found 255.0384.

1-(4-Bromophenyl)-3-methylbut-3-en-1-ol (2t)[17e]**:** Colorless solid; R_f (hexane/EtOAc, 9:1) 0.48;



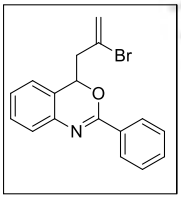
mp 57 °C, yield 406 mg, 78%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.45 (m, 2 H), 7.26 – 7.23 (m, 2 H), 4.93 – 4.92 (m, 1 H), 4.84 – 4.83 (m, 1 H), 4.77 – 4.74 (m, 1 H), 2.38 – 2.36 (m, 2 H), 1.78 (s, 3 H).^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) δ 143.3, 142.2, 131.7, 127.7, 121.4, 114.6, 71.0, 48.5, 22.5.

1-(4-Chlorophenyl)-3-phenylbut-3-en-1-ol (2u)[17f]**:** The compound **2u** was prepared according



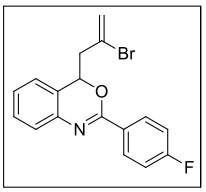
to the literature procedure.[17g] Silica gel column chromatography purification afforded the desired product (70% yield, 392 mg) as pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.33 (m, 2 H), 7.31 – 7.27 (m, 2 H), 7.25 – 7.17 (m, 5 H), 5.33 (d, *J* = 1.4 Hz, 1 H), 5.06 (d, *J* = 1.3 Hz, 1 H), 4.61 (dd, *J* = 8.9, 4.5 Hz, 1 H), 2.88 (ddd, *J* = 14.2, 4.5, 1.3 Hz, 1 H), 2.74 (ddd, *J* = 14.2, 8.9, 0.9 Hz, 1 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.9, 142.5, 140.3, 133.4, 128.8, 128.7, 128.1, 127.4, 126.5, 116.3, 71.6, 46.3.

4-(2-Bromoallyl)-2-phenyl-4*H*-benzo[*d*][1,3]oxazine (3aa):



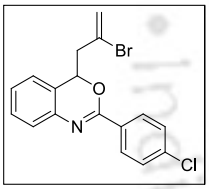
Brown gum; R_f (hexane/EtOAc, 19:1) 0.51; yield 116 mg, 71%; IR (KBr, neat) ν 3067, 2922, 1622, 1596, 1563, 1400, 1359, 1257, 1229, 1089, 1014, 894, 451 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.1 Hz, 2 H), 7.52 – 7.48 (m, 1 H), 7.46 – 7.42 (m, 2 H), 7.35 – 7.33 (m, 2 H), 7.23 – 7.19 (m, 1 H), 7.08 (d, *J* = 7.4 Hz, 1 H), 5.80 (dd, *J* = 9.2, 4.4 Hz, 1 H), 5.58 (s, 1 H), 5.55 (s, 1 H), 3.06 (dd, *J* = 14.8, 9.2 Hz, 1 H), 2.78 (dd, *J* = 14.7, 4.4 Hz, 1 H).^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 156.4, 139.2, 132.6, 131.8, 129.4, 128.5, 128.3, 128.2, 126.7, 125.3, 124.9, 124.3, 121.0, 73.9, 48.3. HRMS (ESI) calcd. for $C_{17}H_{15}BrNO$ $(M + H)^+$ 328.0332, found 328.0354.

4-(2-Bromoallyl)-2-(4-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazine (3ab):



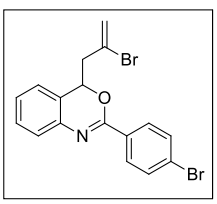
Brown gum; R_f (hexane/EtOAc, 19:1) 0.52; yield 124 mg, 72%; IR (KBr, neat) ν 2927, 1625, 1601, 1580, 1507, 1412, 1360, 1225, 1153, 1076, 844, 766, 509, 409 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 – 8.14 (m, 2 H), 7.36 – 7.30 (m, 2 H), 7.23 – 7.19 (m, 1 H), 7.13 – 7.07 (m, 3 H), 5.79 (dd, *J* = 9.3, 4.3 Hz, 1 H), 5.58 (s, 1 H), 5.54 (s, 1 H), 3.04 (dd, *J* = 14.8, 9.3 Hz, 1 H), 2.78 (dd, *J* = 14.8, 4.3 Hz, 1 H).$^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) δ 165.3 (d, *J* = 250.5 Hz), 155.5, 139.10, 130.6 (d, *J* = 9.0 Hz), 129.5, 128.8 (d, *J* = 3.1 Hz), 128.3, 126.8, 125.3, 124.8, 124.3, 121.0, 115.6 (d, *J* = 21.8 Hz), 74.0, 48.3.^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$) δ 53.63. HRMS (ESI) calcd. for $C_{17}H_{14}BrFNO$ $(M + H)^+$ 346.0238, found 346.0218.

4-(2-Bromoallyl)-2-(4-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazine (3ac):



Brown gum; R_f (hexane/EtOAc, 19:1) 0.53; yield 128 mg, 71%; IR (KBr, neat) ν 3071, 2925, 1726, 1621, 1596, 1567, 1402, 1360, 1257, 1229, 1090, 1075, 1014, 894, 837, 502, 452 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.6 Hz, 2 H), 7.41 (d, *J* = 8.6 Hz, 2 H), 7.36 – 7.30 (m, 2 H), 7.22 (td, *J* = 7.3, 1.5 Hz, 1 H), 7.07 (d, *J* = 7.5 Hz, 1 H), 5.79 (dd, *J* = 9.3, 4.3 Hz, 1 H), 5.57 (s, 1 H), 5.53 (s, 1 H), 3.03 (dd, *J* = 14.8, 9.3 Hz, 1 H), 2.77 (dd, *J* = 14.8, 4.3 Hz, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.4, 139.0, 138.0, 131.1, 129.7, 129.5, 128.8, 128.2, 127.0, 125.4, 124.9, 124.3, 121.0, 74.1, 48.3. HRMS (ESI) calcd. for $C_{17}H_{14}BrClNO$ $(M + H)^+$ 361.9942, found 361.9924.

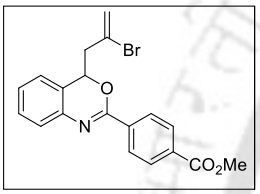
4-(2-Bromoallyl)-2-(4-bromophenyl)-4*H*-benzo[*d*][1,3]oxazine (3ad):



Brown solid; R_f (hexane/EtOAc, 19:1) 0.52; mp 81 ºC yield 151 mg, 74%; IR (KBr, neat) ν 3067, 2925, 2124, 1723, 1621, 1598, 1589, 1567, 1485, 1452, 1397, 1264, 1228, 1072, 1010, 892, 833, 765, 728, 618, 501, 476 cm^{-1}; ^1H NMR

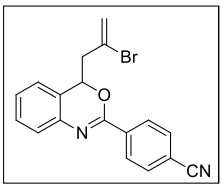
(400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 2 H), 7.57 (d, *J* = 8.7 Hz, 2 H), 7.35 – 7.29 (m, 2 H), 7.22 (td, *J* = 7.2, 1.8 Hz, 1 H), 7.08 – 7.06 (m, 1 H), 5.78 (dd, *J* = 9.3, 4.3 Hz, 1 H), 5.57 (d, *J* = 1.9 Hz, 1 H), 5.53 (s, 1 H), 3.03 (ddd, *J* = 14.7, 9.3, 0.7 Hz, 1 H), 2.77 (ddd, *J* = 14.8, 4.3, 1.3 Hz, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.5, 139.0, 131.8, 131.6, 129.9, 129.5, 128.2, 127.0, 126.6, 125.4, 124.9, 124.4, 121.0, 74.1, 48.3. HRMS (ESI) calcd. for $C_{17}H_{14}Br_2NO$ $(M + H)^+$ 407.9417, found 407.9429.

Methyl 4-(4-(2-bromoallyl)-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzoate (3ae):



Brown gum; R_f (hexane/EtOAc, 19:1) 0.48; yield 125 mg, 65%; IR (KBr, neat) ν 3020, 2921, 2120, 1624, 1599, 1567, 1480, 1397, 1260, 1070, 1010, 892, 830, 767, 729, 475 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.1 Hz, 2 H), 8.09 (d, *J* = 8.1 Hz, 2 H), 7.37 – 7.33 (m, 2 H), 7.25 – 7.22 (m, 1 H), 7.08 (d, *J* = 7.4 Hz, 1 H), 5.82 (dd, *J* = 9.3, 4.4 Hz, 1 H), 5.58 (s, 1 H), 5.53 (s, 1 H), 3.94 (s, 3 H), 3.05 (dd, *J* = 14.8, 9.2 Hz, 1 H), 2.79 (dd, *J* = 14.8, 4.4 Hz, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.8, 155.3, 138.9, 136.7, 132.8, 130.4, 129.7, 129.6, 128.2, 127.3, 125.6, 124.9, 124.4, 121.1, 74.1, 52.6, 48.4. HRMS (ESI) calcd. for $C_{19}H_{17}BrNO_3$ $(M + H)^+$ 386.0387, found 386.0367.

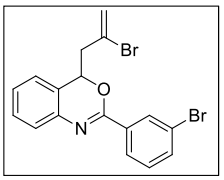
4-(4-(2-Bromoallyl)-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzonitrile (3af):



Brown solid; R_f (hexane/EtOAc, 19:1) 0.49; mp 131 °C, yield 113 mg, 64%; IR (KBr, neat) ν 2919, 2229, 1624, 1599, 1484, 1260, 1077, 766, 552, 488 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.3 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2 H), 7.38 – 7.32 (m, 2 H), 7.25 – 7.24 (m, 1 H), 7.09 (d, *J* = 7.4 Hz, 1 H), 5.83 (dd, *J* = 9.3, 4.3 Hz, 1 H), 5.58 (s, 1 H), 5.53 (s, 1 H), 3.03 (dd, *J* = 14.8, 9.3 Hz, 1 H), 2.80 (dd, *J* = 14.8, 4.3 Hz, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.4, 138.6, 136.8, 132.3, 129.7, 128.7, 128.1,

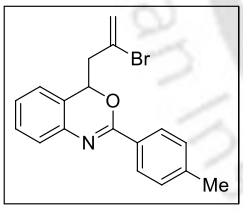
127.7, 125.7, 124.8, 124.4, 121.1, 118.7, 114.9, 74.3, 48.4. HRMS (ESI) calcd. for $C_{18}H_{14}BrN_2O$ $(M + H)^+$ 353.0285, found 353.0266.

4-(2-Bromoallyl)-2-(3-bromophenyl)-4*H*-benzo[*d*][1,3]oxazine (3ag):



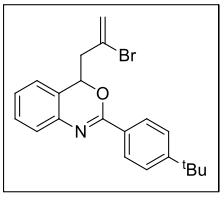
Pale red gum; R_f (hexane/EtOAc, 19:1) 0.51; yield 132 mg, 65%; IR (KBr, neat) ν 2919, 1655, 1630,1589, 1529, 1449, 1276, 1261, 1067, 895, 750, 573 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1 H), 8.06 (d, *J* = 7.8 Hz, 1 H), 7.61 (dd, *J* = 8.1, 2.0 Hz, 1 H), 7.35 – 7.31 (m, 3 H), 7.22 (td, *J* = 7.2, 1.8 Hz, 1 H), 7.08 (d, *J* = 7.4 Hz, 1 H), 5.79 (dd, *J* = 9.1, 4.5 Hz, 1 H), 5.59 (s, 1 H), 5.54 (s, 1 H), 3.04 (dd, *J* = 14.8, 9.1 Hz, 1 H), 2.78 (dd, *J* = 14.7, 4.5 Hz, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.9, 138.8, 134.7, 134.6, 131.1, 130.0, 129.6, 128.1, 127.1, 126.8, 125.5, 124.9, 124.4, 122.7, 121.1, 74.2, 48.4. HRMS (ESI) calcd. for $C_{17}H_{14}Br_2NO$ $(M + H)^+$ 407.9417, found 407.9426.

4-(2-Bromoallyl)-2-(p-tolyl)-4*H*-benzo[*d*][1,3]oxazine (3ah):



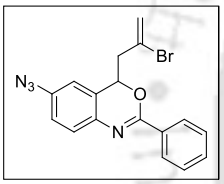
Brown solid; R_f (hexane/EtOAc, 9:1) 0.49; mp 86 ºC yield 111 mg, 65%; IR (KBr, neat) ν 2922, 1720, 1620, 1597, 1568, 1482, 1458, 1275, 1260, 1177, 1074, 892, 764, 750, 574, 499 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.9 Hz, 2 H), 7.34 – 7.32 (m, 2 H), 7.24 (d, *J* = 7.9 Hz, 2 H), 7.21 – 7.18 (m, 1 H), 7.07 (d, *J* = 7.4 Hz, 1 H), 5.78 (dd, *J* = 9.2, 4.4 Hz, 1 H), 5.58 (s, 1 H), 5.54 (s, 1 H), 3.05 (dd, *J* = 14.8, 9.2 Hz, 1 H), 2.77 (dd, *J* = 14.8, 4.4 Hz, 1 H), 2.42 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 156.5, 142.3, 139.4, 129.8, 129.4, 129.2, 128.4, 128.3, 126.5, 125.2, 125.0, 124.3, 121.0, 73.8, 48.2, 21.8. HRMS (ESI) calcd. for $C_{18}H_{17}BrNO$ $(M + H)^+$ 342.0489, found 342.0492.

4-(2-Bromoallyl)-2-(4-(tert-butyl)phenyl)-4*H*-benzo[*d*][1,3]oxazine (3ai):



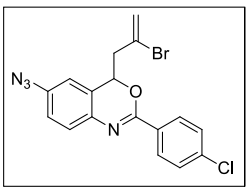
Brown gum; R_f (hexane/EtOAc, 19:1) 0.48; yield 117 mg, 61%; IR (KBr, neat) ν 3315, 2963, 1611, 1533, 1448, 1268, 1188, 1115, 1016, 892, 752, 706, 546 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.5 Hz, 2 H), 7.46 (d, *J* = 8.5 Hz, 2 H), 7.33 – 7.32 (m, 2 H), 7.21 – 7.17 (m, 1 H), 7.07 (d, *J* = 7.5 Hz, 1 H), 5.78 (dd, *J* = 9.1, 4.4 Hz, 1 H), 5.59 (s, 1 H), 5.57 (s, 1 H), 3.05 (dd, *J* = 14.8, 9.1 Hz, 1 H), 2.78 (dd, *J* = 14.8, 4.4 Hz, 1 H), 1.35 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 156.5, 155.3, 139.4, 129.8, 129.4, 128.4, 128.2, 126.5, 125.5, 125.2, 125.0, 124.3, 121.0, 73.9, 48.2, 35.2, 31.4. HRMS (ESI) calcd. for $C_{21}H_{23}BrNO$ $(M + H)^+$ 384.0958, found 384.0971.

6-Azido-4-(2-bromoallyl)-2-phenyl-4*H*-benzo[*d*][1,3]oxazine (3ba):



Brown gum; R_f (hexane/EtOAc, 19:1) 0.51; yield 156 mg, 85%; IR (KBr, neat) ν 2921, 2109, 1621, 1481, 1390, 1298, 1074, 1009, 735, 641, 498, 441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.11 (m, 2 H), 7.52 – 7.48 (m, 1 H), 7.45 – 7.41 (m, 2 H), 7.32 (d, *J* = 8.4 Hz, 1 H), 7.01 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.72 (d, *J* = 2.5 Hz, 1 H), 5.75 (dd, *J* = 9.1, 4.5 Hz, 1 H), 5.60 (d, *J* = 1.9 Hz, 1 H), 5.56 (s, 1 H), 3.07 – 3.01 (m, 1 H), 2.77 (ddd, *J* = 14.7, 4.5, 1.2 Hz, 1 H).$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 156.0, 138.1, 136.5, 132.3, 131.9, 128.5, 128.3, 127.9, 126.8, 126.6, 121.3, 119.8, 115.0, 73.7, 48.1. HRMS (ESI) calcd. for $C_{17}H_{14}BrN_4O$ $(M + H)^+$ 369.0346, found 369.0364.

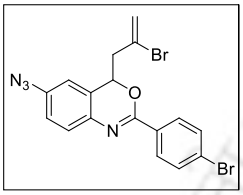
6-Azido-4-(2-bromoallyl)-2-(4-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazine (3bc):



Brown solid; R_f (hexane/EtOAc, 19:1) 0.52; mp 110 °C, yield 171 mg, 85%; IR (KBr, neat) ν 2925, 2112, 1623, 1597, 1491, 1402, 1300, 1090, 1014, 837, 749, 503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.99 (m, 2 H), 7.35 (d, *J* = 8.7 Hz, 2 H), 7.23 (d, *J* = 9.4 Hz, 1 H), 6.96 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.66 (d, *J* = 2.5 Hz, 1

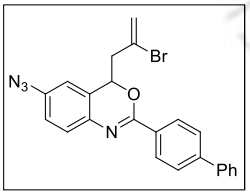
H), 5.69 (dd, *J* = 9.3, 4.4 Hz, 1 H), 5.54 (d, *J* = 1.9 Hz, 1 H), 5.49 (s, 1 H), 2.97 (dd, *J* = 14.7, 9.2 Hz, 1 H), 2.73 – 2.68 (m, 1 H).$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 155.0, 138.4, 138.1, 136.2, 130.8, 129.5, 128.8, 127.8, 126.8, 126.5, 121.3, 119.9, 115.0, 73.8, 48.1. HRMS (ESI) calcd. for $C_{17}H_{13}BrClN_4O$ $(M + H)^+$ 402.9956, found 402.9949.

6-Azido-4-(2-bromoallyl)-2-(4-bromophenyl)-4*H*-benzo[*d*][1,3]oxazine (3bd):



Brown solid; R_f (hexane/EtOAc, 19:1) 0.52; mp 98 ºC yield 186 mg, 83%; IR (KBr, neat) ν 2923, 2421, 2108, 1623, 1488, 1396, 1298, 1074, 1009, 889, 828, 738, 645, 500, 440 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.96 (m, 2 H), 7.58 – 7.54 (m, 2 H), 7.29 (d, *J* = 8.4 Hz, 1 H), 7.00 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.71 (d, *J* = 2.5 Hz, 1 H), 5.73 (dd, *J* = 9.2, 4.4 Hz, 1 H), 5.58 (d, *J* = 1.9 Hz, 1 H), 5.53 (s, 1 H), 3.04 – 2.98 (m, 1 H), 2.75 (ddd, *J* = 14.8, 4.4, 1.2 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 155.1, 138.4, 136.2, 131.8, 131.3, 129.7, 127.8, 126.8, 126.7, 126.5, 121.3, 119.9, 115.0, 73.8, 48.1. HRMS (ESI) calcd. for $C_{17}H_{13}Br_2N_4O$ $(M + H)^+$ 448.9431, found 448.9438.

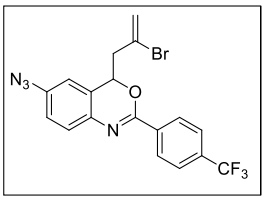
2-([1,1'-Biphenyl]-4-yl)-6-azido-4-(2-bromoallyl)-4*H*-benzo[*d*][1,3]oxazine (3bl):



Brown solid; R_f (hexane/EtOAc, 19:1) 0.53; mp 102 ºC yield 162 mg, 73%; IR (KBr, neat) ν 3030, 2924, 2400, 2108, 1620, 1488, 1405, 1352, 1298, 1078, 1007, 848, 732, 695, 495 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.18 (m, 2 H), 7.69 – 7.64 (m, 4 H), 7.49 – 7.45 (m, 2 H), 7.41 – 7.37 (m, 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 7.02 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.73 (d, *J* = 2.5 Hz, 1 H), 5.77 (dd, *J* = 9.1, 4.5 Hz, 1 H), 5.62 (d, *J* = 1.9 Hz, 1 H), 5.58 (s, 1 H), 3.06 (dd, *J* = 14.7, 9.2 Hz, 1 H), 2.80 – 2.75 (m, 1 H).$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 155.8, 144.5, 140.4, 138.1, 136.5, 131.2, 129.1, 128.8,

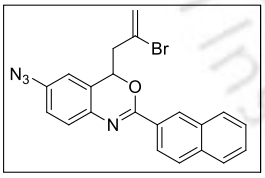
128.2, 127.9, 127.4, 127.2, 126.8, 126.6, 121.3, 119.8, 115.0, 73.7, 48.1. HRMS (ESI) calcd. for $C_{23}H_{18}BrN_4O$ $(M + H)^+$ 445.0659, found 445.0646.

6-Azido-4-(2-bromoallyl)-2-(4-(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]oxazine (3bm):



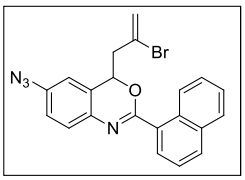
Brown gum; R_f (hexane/EtOAc, 19:1) 0.54; yield 150 mg, 69%; IR (KBr, neat) ν 2921, 2111, 1628, 1599, 1491, 1420, 1455, 1301, 1091, 1010, 831, 509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.22 (m, 2 H), 7.69 (d, *J* = 8.2 Hz, 2 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 7.03 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.73 (d, *J* = 2.5 Hz, 1 H), 5.78 (dd, *J* = 9.2, 4.4 Hz, 1 H), 5.60 (d, *J* = 2.0 Hz, 1 H), 5.55 (s, 1 H), 3.03 (dd, *J* = 14.7, 9.2 Hz, 1 H), 2.81 – 2.76 (m, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.5, 138.9, 136.0, 135.7, 133.3 (q, *J* = 32.4 Hz), 128.5, 127.7, 127.1, 126.5, 125.5 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 270.9 Hz), 123.0, 121.4, 120.0, 115.1, 74.0, 48.2. ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$) δ 98.85. HRMS (ESI) calcd. for $C_{18}H_{13}BrF_3N_4O$ $(M + H)^+$ 437.0220, found 437.0202.

6-Azido-4-(2-bromoallyl)-2-(naphthalen-2-yl)-4*H*-benzo[*d*][1,3]oxazine (3bn):



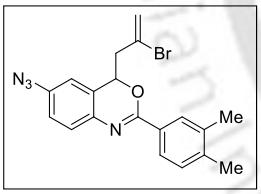
Brown solid; R_f (hexane/EtOAc, 19:1) 0.50; mp 134 ºC, yield 165 mg, 79%; IR (KBr, neat) ν 3212, 3057, 2925, 2106, 1618, 1592, 1488, 1300, 1234, 1127, 1072, 821, 754, 477, 440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1 H), 8.24 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.96 – 7.94 (m, 1 H), 7.89 – 7.86 (m, 2 H), 7.58 – 7.51 (m, 2 H), 7.37 (d, *J* = 8.4 Hz, 1 H), 7.03 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.74 (d, *J* = 2.5 Hz, 1 H), 5.80 (dd, *J* = 9.1, 4.6 Hz, 1 H), 5.61 (d, *J* = 1.9 Hz, 1 H), 5.56– 5.55 (m, 1 H), 3.11 – 3.05 (m, 1 H), 2.79 (ddd, *J* = 14.7, 4.6, 1.2 Hz, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 156.0, 138.2, 136.6, 135.2, 133.0, 129.7, 129.4, 129.0, 128.2, 128.0, 127.9, 126.8, 126.7, 126.6, 124.7, 121.4, 119.9, 115.1, 73.8, 48.1. HRMS (ESI) calcd. for $C_{21}H_{16}BrN_4O$ $(M + H)^+$ 419.0502, found 419.0496.

6-Azido-4-(2-bromoallyl)-2-(naphthalen-1-yl)-4*H*-benzo[*d*][1,3]oxazine (3bo):



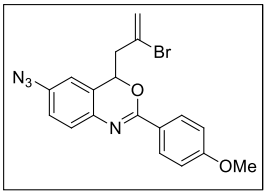
Brown gum; R_f (hexane/EtOAc, 19:1) 0.51; yield 138 mg, 66%; IR (KBr, neat) ν 3050, 2924, 2108, 1714, 1627, 1585, 1487, 1299, 1236, 1125, 1019, 894, 775, 512, 456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, *J* = 8.1 Hz, 1 H), 8.15 (dd, *J* = 7.3, 1.3 Hz, 1 H), 7.98 (d, *J* = 8.2 Hz, 1 H), 7.89 (dd, *J* = 8.2, 1.5 Hz, 1 H), 7.64 – 7.60 (m, 1 H), 7.56 – 7.50 (m, 2 H), 7.45 (d, *J* = 8.4 Hz, 1 H), 7.06 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.77 (d, *J* = 2.5 Hz, 1 H), 5.86 (dd, *J* = 8.6, 4.9 Hz, 1 H), 5.63 (s, 1 H), 5.61 (d, *J* = 2.0 Hz, 1 H), 3.20 – 3.14 (m, 1 H), 2.95 – 2.90 (m, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 157.1, 138.5, 136.2, 134.3, 132.5, 131.4, 129.6, 129.0, 128.8, 127.9, 127.5, 126.8, 126.5, 126.3, 126.1, 124.9, 121.5, 119.9, 115.0, 74.1, 47.9. HRMS (ESI) calcd. for $C_{21}H_{16}BrN_4O$ $(M + H)^+$ 419.0502, found 419.0495.

6-Azido-4-(2-bromoallyl)-2-(3,4-dimethylphenyl)-4*H*-benzo[*d*][1,3]oxazine (3bp):



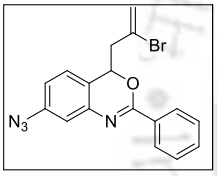
Brown solid; R_f (hexane/EtOAc, 19:1) 0.52; mp 90-94 ºC, yield 143 mg, 72%; IR (KBr, neat) ν 2919, 2400, 1720, 1620, 1487, 1299, 1254, 1080, 1019, 724, 529, 440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 1.9 Hz, 1 H), 7.82 (dd, *J* = 7.8, 1.9 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 7.19 (d, *J* = 7.9 Hz, 1 H), 7.00 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.71 (d, *J* = 2.5 Hz, 1 H), 5.72 (dd, *J* = 9.0, 4.6 Hz, 1 H), 5.58 (d, *J* = 1.9 Hz, 1 H), 5.54 (s, 1 H), 3.03 (dd, *J* = 14.7, 9.0 Hz, 1 H), 2.75 (ddd, *J* = 14.6, 4.6, 1.2 Hz, 1 H), 2.32 (s, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 156.4, 141.2, 137.8, 136.9, 136.7, 129.9, 129.8, 129.4, 127.9, 126.6, 126.5, 125.9, 121.3, 119.8, 115.0, 73.6, 48.0, 20.2, 20.0. HRMS (ESI) calcd. for $C_{19}H_{18}BrN_4O$ $(M + H)^+$ 397.0659, found 397.0685

6-Azido-4-(2-bromoallyl)-2-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazine (3bq):



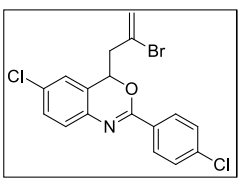
Brown solid; R_f (hexane/EtOAc, 19:1) 0.48; mp 115 °C, yield 161 mg, 81%; IR (KBr, neat) ν 2930, 2839, 2109, 1621, 1597, 1510, 1489, 1168, 1077, 839, 750, 681, 520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.05 (m, 2 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.00 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.95 – 6.92 (m, 2 H), 6.71 (d, *J* = 2.5 Hz, 1 H), 5.71 (dd, *J* = 9.2, 4.4 Hz, 1 H), 5.59 (d, *J* = 1.9 Hz, 1 H), 5.55 (s, 1 H), 3.86 (s, 3 H), 3.05 – 2.99 (m, 1 H), 2.77 – 2.72 (m, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.8, 156.0, 137.6, 136.8, 130.1, 128.0, 126.5, 126.4, 124.8, 121.2, 119.8, 115.0, 113.9, 73.6, 55.6, 48.0. HRMS (ESI) calcd. for $C_{18}H_{16}BrN_4O_2$ $(M + H)^+$ 399.0452, found 399.0456.

7-Azido-4-(2-bromoallyl)-2-phenyl-4*H*-benzo[*d*][1,3]oxazine (3ca):



Brown gum; R_f (hexane/EtOAc, 19:1) 0.52; yield 123 mg, 67%; IR (KBr, neat) ν 2925, 2104, 1622, 1481, 1390, 1298, 1071, 1010, 731, 641, 442 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.13 (m, 2 H), 7.52 – 7.50 (m, 1 H), 7.46 – 7.43 (m, 2 H), 7.06 – 7.03 (m, 2 H), 6.85 (dd, *J* = 8.0, 2.3 Hz, 1 H), 5.78 (dd, *J* = 8.8, 4.7 Hz, 1 H), 5.58 (s, 1 H), 5.55 (s, 1 H), 3.06 – 3.00 (m, 1 H), 2.77 (ddd, *J* = 14.8, 4.7, 1.2 Hz, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 157.3, 141.3, 140.8, 132.2, 132.1, 128.6, 128.5, 127.9, 125.6, 121.5, 121.2, 117.2, 115.6, 73.8, 48.3. HRMS (ESI) calcd. for $C_{17}H_{14}BrN_4O$ $(M + H)^+$ 369.0346, found 369.0347.

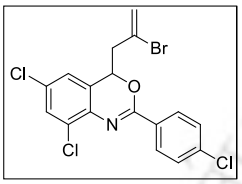
4-(2-Bromoallyl)-6-chloro-2-(4-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazine (3dc):



Brown gum; R_f (hexane/EtOAc, 19:1) 0.51; yield 134 mg, 68%; IR (KBr, neat) ν 2924, 2853, 1618, 1594, 1488, 1402, 1351, 1252, 1088, 1014, 894, 829, 729, 675, 505, 409 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.7 Hz, 2 H), 7.41 (d, *J* = 8.7 Hz, 2 H), 7.30 (dd, *J* = 8.4, 2.3 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 7.06

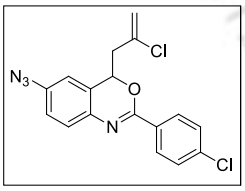
(d, *J* = 2.3 Hz, 1 H), 5.74 (dd, *J* = 9.3, 4.3 Hz, 1 H), 5.59 (d, *J* = 2.0 Hz, 1 H), 5.54 (s, 1 H), 3.02 (d, *J* = 5.4 Hz, 1 H), 2.76 (ddd, *J* = 14.8, 4.3, 1.3 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 155.6, 138.3, 137.7, 132.0, 130.7, 129.7, 129.6, 128.9, 127.7, 126.7, 126.3, 124.4, 121.3, 73.6, 48.1. HRMS (ESI) calcd. for $C_{17}H_{13}BrCl_2NO$ $(M + H)^+$ 395.9553, found 395.9535.

4-(2-Bromoallyl)-6,8-dichloro-2-(4-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazine (3ec):



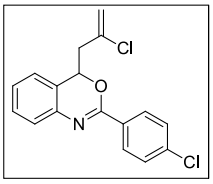
Colorless solid; R_f (hexane/EtOAc, 19:1) 0.52; mp 103 °C, yield 144 mg, 67%; IR (KBr, neat) ν 2924, 1614, 1566, 1489, 1452, 1402, 1352, 1304, 1264, 1191, 1090, 1014, 864, 736, 564, 491, 476 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.10 (m, 2 H), 7.43 – 7.40 (m, 3 H), 6.98 (dd, *J* = 2.2, 0.7 Hz, 1 H), 5.72 (dd, *J* = 9.3, 4.5 Hz, 1 H), 5.59 (d, *J* = 2.0 Hz, 1 H), 5.52 (s, 1 H), 3.01 (ddd, *J* = 14.7, 9.3, 0.7 Hz, 1 H), 2.72 (ddd, *J* = 14.9, 4.5, 1.3 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 156.5, 138.8, 134.9, 131.9, 131.3, 131.2, 130.1, 130.0, 128.9, 127.5, 127.2, 123.1, 121.7, 73.6, 47.9. HRMS (ESI) calcd. for $C_{17}H_{12}BrCl_3NO$ $(M + H)^+$ 429.9163, found 429.9146.

6-Azido-4-(2-chloroallyl)-2-(4-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazine (3br):



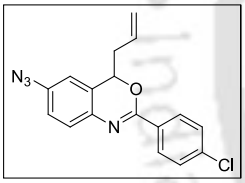
Brown solid; R_f (hexane/EtOAc, 19:1) 0.51; mp 116 °C, yield 136 mg, 76%; IR (KBr, neat) ν 3388, 2920, 1622, 1491, 1402, 1299, 1090, 1014, 888, 822, 750, 511 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 – 8.04 (m, 2 H), 7.41 – 7.39 (m, 2 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 7.01 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.70 (d, *J* = 2.4 Hz, 1 H), 5.74 (dd, *J* = 9.4, 4.4 Hz, 1 H), 5.34 (d, *J* = 1.6 Hz, 1 H), 5.10 (s, 1 H), 2.94 (dd, *J* = 14.7, 9.4 Hz, 1 H), 2.68 (ddd, *J* = 14.7, 4.4, 1.1 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 155.1, 138.4, 138.2, 136.8, 136.1, 130.7, 129.6, 128.8, 126.8, 126.5, 119.9, 116.8, 115.0, 73.4, 46.1. HRMS (ESI) calcd. for $C_{17}H_{13}Cl_2N_4O$ $(M + H)^+$ 359.0461, found 359.0469.

4-(2-Chloroallyl)-2-(4-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazine (3ar):



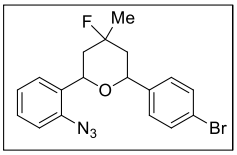
Brown solid; R_f (hexane/EtOAc, 19:1) 0.51; mp 77 °C, yield 114 mg, 72%; IR (KBr, neat) ν 3071, 2924, 1719, 1620, 1595, 1487, 1402, 1360, 1229, 1090, 1074, 1013, 837, 764, 621, 509, 455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.6 Hz, 2 H), 7.41 (d, *J* = 8.6 Hz, 2 H), 7.36 – 7.30 (m, 2 H), 7.22 (td, *J* = 7.2, 1.6 Hz, 1 H), 7.06 (d, *J* = 7.5 Hz, 1 H), 5.79 (dd, *J* = 9.4, 4.3 Hz, 1 H), 5.33 (s, 1 H), 5.10 (s, 1 H), 2.96 (dd, *J* = 14.7, 9.4 Hz, 1 H), 2.69 (dd, *J* = 14.7, 4.3 Hz, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.4, 138.9, 138.0, 137.2, 131.1, 129.6, 129.5, 128.8, 127.0, 125.4, 124.9, 124.3, 116.5, 73.6, 46.3. HRMS (ESI) calcd. for $C_{17}H_{14}Cl_2NO$ $(M + H)^+$ 318.0447, found 318.0441.

4-Allyl-6-azido-2-(4-chlorophenyl)-4*H*-benzo[*d*][1,3]oxazine (3bs):



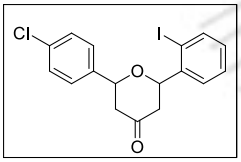
Brown solid; R_f (hexane/EtOAc, 19:1) 0.53; mp 102 °C, yield 100 mg, 62%; IR (KBr, neat) ν 3076, 2925, 2854, 2107, 1621, 1489, 1401, 1297, 1255, 1089, 1013, 836, 749, 650, 506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.6 Hz, 2 H), 7.33 (d, *J* = 8.6 Hz, 2 H), 7.22 – 7.19 (m, 1 H), 6.92 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.60 (d, *J* = 2.5 Hz, 1 H), 5.84 – 5.73 (m, 1 H), 5.40 (dd, *J* = 7.6, 4.8 Hz, 1 H), 5.11 – 5.03 (m, 2 H), 2.65 – 2.49 (m, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.6, 138.2, 137.9, 136.5, 132.2, 131.1, 129.5, 128.8, 127.2, 126.7, 119.6, 119.5, 115.0, 76.1, 41.2. HRMS (ESI) calcd. for $C_{17}H_{14}ClN_4O$ $(M + H)^+$ 325.0851, found 325.0853.

2-(2-Azidophenyl)-6-(4-bromophenyl)-4-fluoro-4-methyltetrahydro-2*H*-pyran (diastereomers, 1:1) (3at):



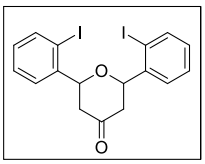
Colorless solid; R_f (hexane/EtOAc, 19:1) 0.49; mp 92 °C, yield 137 mg, 70%; IR (KBr, neat) ν 2975, 2921, 2122, 1583, 1489, 1451, 1379, 1294,1278, 1209, 1072, 1009, 863, 816, 780, 751, 682, 590, 523, 497, 465, 414 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 1.6 Hz, 1 H, isomer-1), 7.62 (d, *J* = 1.6 Hz, 1 H, minor), 7.50 – 7.49 (m, 2 H, isomer-1), 7.48 – 7.47 (m, 2 H, isomer-2), 7.34 – 7.32 (m, 3 H, isomer-1), 7.32 – 7.31 (m, 3 H, isomer-2), 7.19 (td, *J* = 7.6, 1.1 Hz, 2 H, isomer-1), 7.15 (dd, *J* = 8.0, 1.1 Hz, 2 H, isomer-2), 5.17(d, *J* = 2.4Hz, 1 H, isomer-1), 5.15(d, *J* = 2.4Hz,1 H, isomer-2), 4.91(d, *J*=2.4Hz,1 H, isomer-1), 4.89(d, *J* = 2.4Hz,1 H, isomer-2), 2.27 – 2.23 (m, 2 H, isomer-1), 2.16 – 2.12 (m, 2 H, isomer-2), 1.71 – 1.62 (m, 2 H, isomer-1), 1.59 – 1.49 (m, 2 H, isomer-2), 1.46 (s, 3 H, isomer-1), 1.42 (s, 3 H, isomer-2). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 141.5, 136.4, 133.6, 131.7, 128.8, 127.7, 127.1, 125.4, 121.5, 118.1, 93.1 (d, *J* = 167.8 Hz), 75.0, 70.8, 44.3 (d, *J* = 21.3 Hz), 42.9 (d, *J* = 21.3 Hz), 27.6 (d, *J* = 23.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$) δ 10.91, 10.90. HRMS (ESI) calcd. for $C_{18}H_{17}BrFKN_3O$ $(M + K)^+$ 428.0171, found 428.0179.

2-(4-Chlorophenyl)-6-(2-iodophenyl)dihydro-2*H*-pyran-4(3*H*)-one (4a):



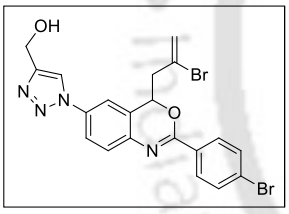
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.47; mp 92 °C, yield 85 mg, 41%; IR (KBr, neat) ν 3055, 2925, 1718, 1492, 1437, 1336, 1264, 1148, 1057, 1013, 829, 733, 646, 482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.9, 1.2 Hz, 1 H), 7.66 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.46 – 7.36 (m, 5 H), 7.04 (td, *J* = 7.6, 1.7 Hz, 1 H), 5.00 (dd, *J* = 11.7, 2.6 Hz, 1 H), 4.90 (dd, *J* = 11.5, 3.0 Hz, 1 H), 2.94 (dt, *J* = 14.5, 2.3 Hz, 1 H), 2.77 – 2.72 (m, 1 H), 2.69 – 2.62 (m, 1 H), 2.52 – 2.45 (m, 1 H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 205.1, 142.8, 139.8, 139.2, 134.2, 130.1, 129.1, 127.3, 127.2, 97.2, 82.4, 78.3, 49.4, 47.9. HRMS (ESI) calcd. for $C_{17}H_{14}ClIKO_2$ $(M + K)^+$ 450.9359, found 450.9367.

2,6-Bis(2-iodophenyl)dihydro-2*H*-pyran-4(3*H*)-one (4b):



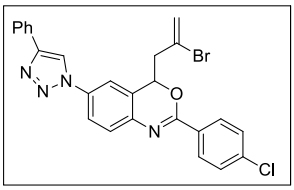
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.46; mp 99 °C, yield 66 mg, 26%; IR (KBr, neat) ν 3050, 2920, 1715, 1492, 1437, 1339, 1264, 1148, 1050, 1013, 829, 733, 485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.9, 1.2 Hz, 2 H), 7.71 (dd, *J* = 7.9, 1.7 Hz, 2 H), 7.45 (td, *J* = 7.6, 1.2 Hz, 2 H), 7.03 (td, *J* = 7.6, 1.7 Hz, 2 H), 5.06 (dd, *J* = 11.5, 2.4 Hz, 2 H), 2.99 – 2.94 (m, 2 H), 2.51 – 2.44 (m, 2 H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 204.9, 143.0, 139.8, 130.1, 129.1, 127.3, 96.8, 82.4, 47.9. HRMS (ESI) calcd. for $C_{17}H_{18}I_2NO_2$ $(M + NH_4)^+$ 521.9422, found 521.9413.

(1-(4-(2-Bromoallyl)-2-(4-bromophenyl)-4*H*-benzo[*d*][1,3]oxazin-6-yl)-1*H*-1,2,3-triazol-5-yl)methanol (5a):



Colorless solid; R_f (DCM/MeOH, 9:1) 0.47; mp 97 °C, yield 224 mg, 89%; IR (KBr, neat) ν 3360, 3055, 2920, 2852, 2120, 1710, 1626, 1492, 1263, 1086, 1014, 890, 731, 693, 504 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.68 (s, 1 H), 7.98 (d, *J* = 8.6 Hz, 2 H), 7.89 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.85 (d, *J* = 2.4 Hz, 1 H), 7.74 (d, *J* = 8.7 Hz, 2 H), 7.41 (d, *J* = 8.3 Hz, 1 H), 5.96 (dd, *J* = 9.3, 3.9 Hz, 1 H), 5.81 (s, 1 H), 5.64 (s, 1 H), 5.37 (s, 1 H), 4.62 (s, 2 H), 3.15 (dd, *J* = 15.1, 9.5 Hz, 1 H), 3.07 (dd, *J* = 15.2, 3.9 Hz, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 155.1, 149.3, 138.2, 134.9, 131.7, 130.8, 129.6, 127.6, 126.0, 125.9, 125.8, 121.5, 120.9, 120.5, 116.5, 73.5, 55.0, 46.7. HRMS (ESI) calcd. for $C_{20}H_{17}Br_2N_4O_2$ $(M + H)^+$ 504.9693, found 504.9668.

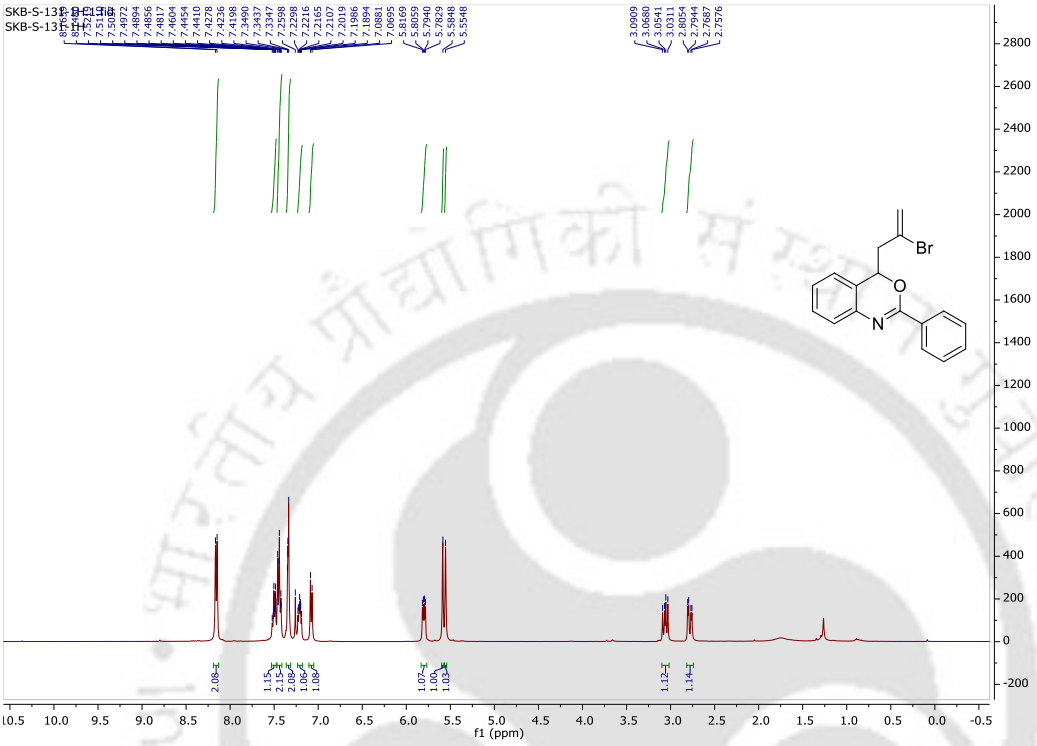
4-(2-Bromoallyl)-2-(4-chlorophenyl)-6-(5-phenyl-1*H*-1,2,3-triazol-1-yl)-4*H*-benzo[*d*][1,3]oxazine (5b):

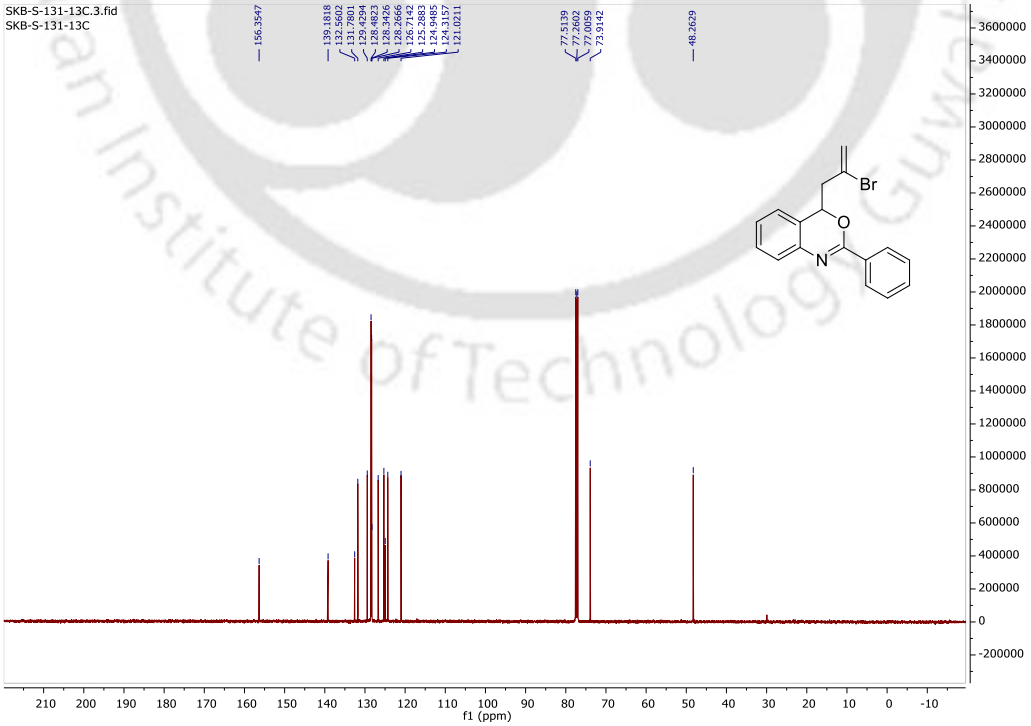


Pale yellow liquid; R_f (hexane/EtOAc, 3:7) 0.49; yield 176 mg, 70%; IR (KBr, neat) ν 3364, 3060, 2922, 2851, 2125, 1718, 1626, 1595, 1492, 1402, 1263, 1089, 1014, 892, 736, 695, 504, 408 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.11 (m, 2 H), 8.01 – 7.99 (m, 2 H), 7.56 – 7.49 (m, 5 H), 7.46 – 7.44 (m, 3 H), 7.31 (d, *J* = 2.2 Hz, 1 H), 5.89 (dd, *J* = 9.1, 4.5 Hz, 1 H), 5.62 (d, *J* = 1.9 Hz, 1 H), 5.59 (d, *J* = 1.9 Hz, 1 H), 3.15 – 3.09 (m, 1 H), 2.87 (dd, *J* = 14.7, 4.4 Hz, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.9, 150.8, 140.7, 138.7, 135.0, 130.4, 130.2, 129.9, 129.1, 129.0, 128.9, 128.0, 127.7, 127.4, 126.1, 125.8, 122.7, 121.7, 73.8, 48.1. HRMS (ESI) calcd. for $C_{25}H_{19}BrClN_4O$ $(M + H)^+$ 505.0426, found 505.0396.

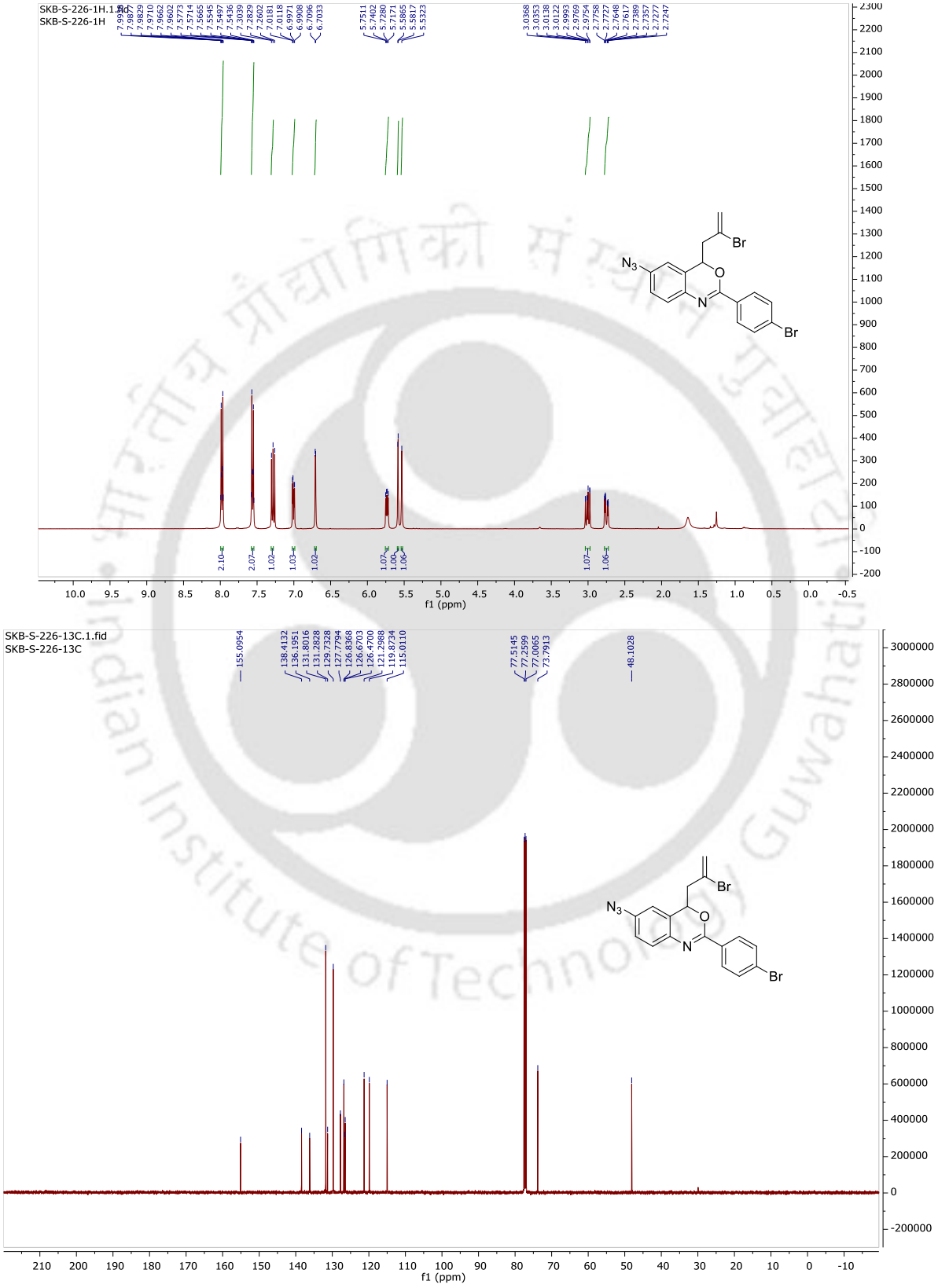
4.9.10 Representative Spectra and crystal parameter

^{1}H(400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **3aa**

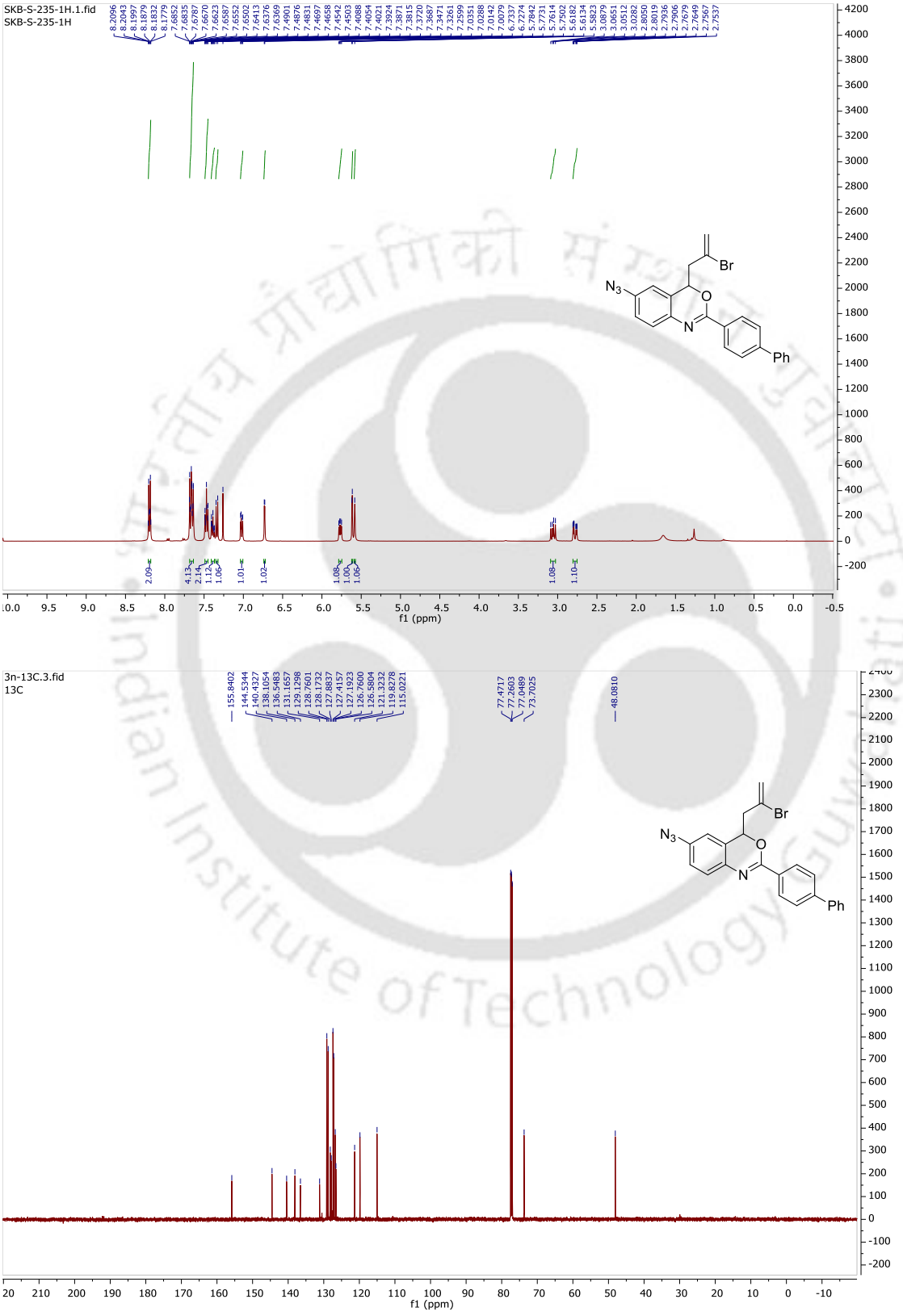




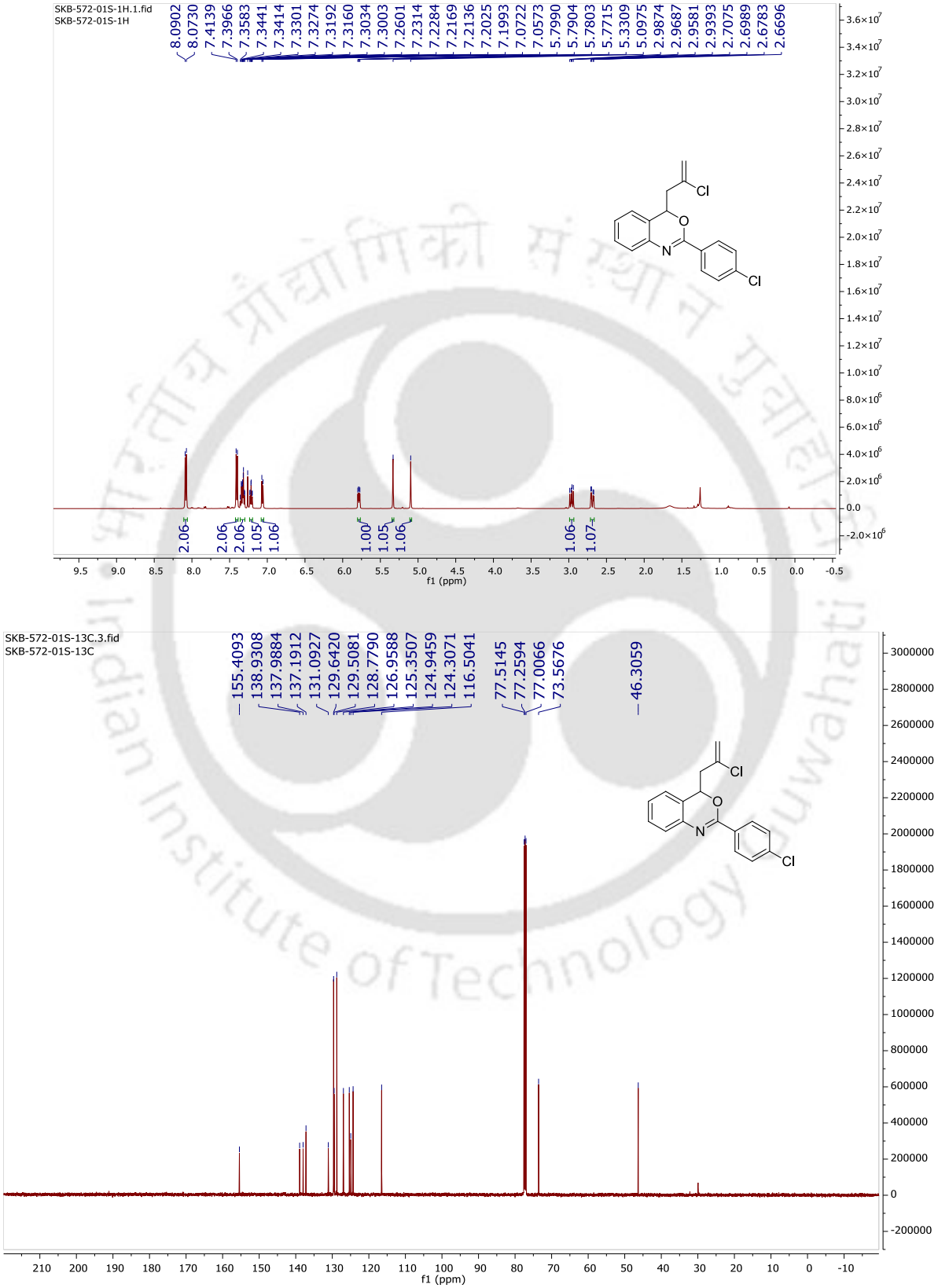
^{1}H (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **3bd**



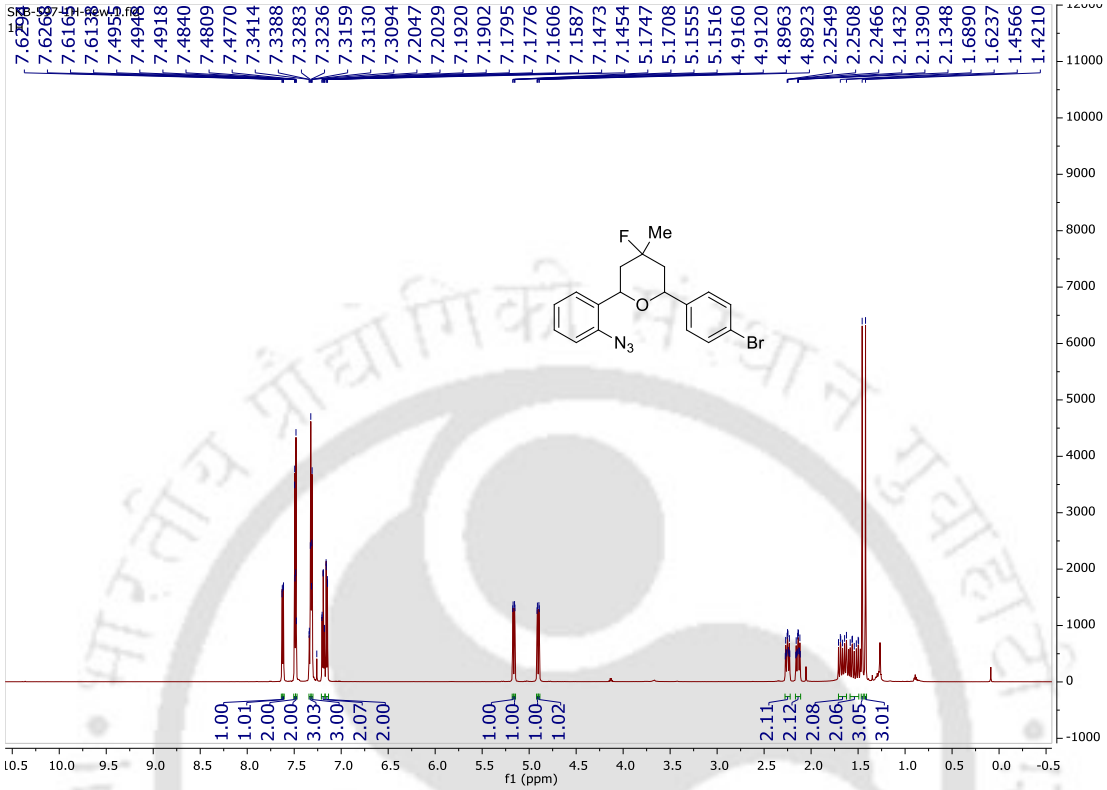
^{1}H (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (150 MHz, $CDCl_3$) spectra of **3bl**

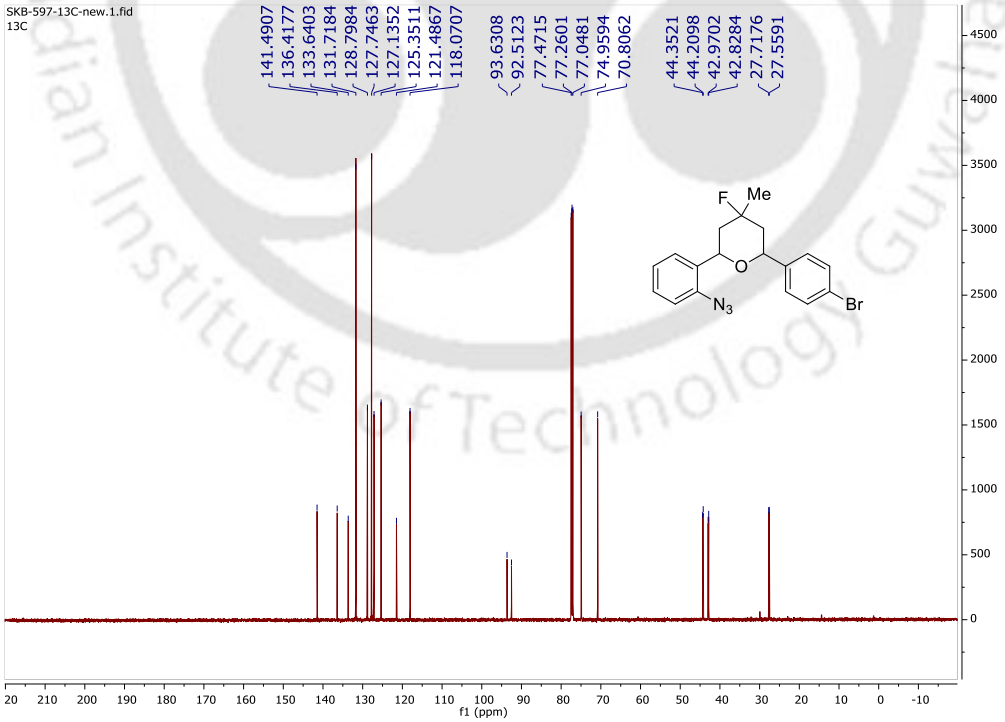


^{1}H (500 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **3ar**



^{1}H (600 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (150 MHz, $CDCl_3$) spectra of **3at**:

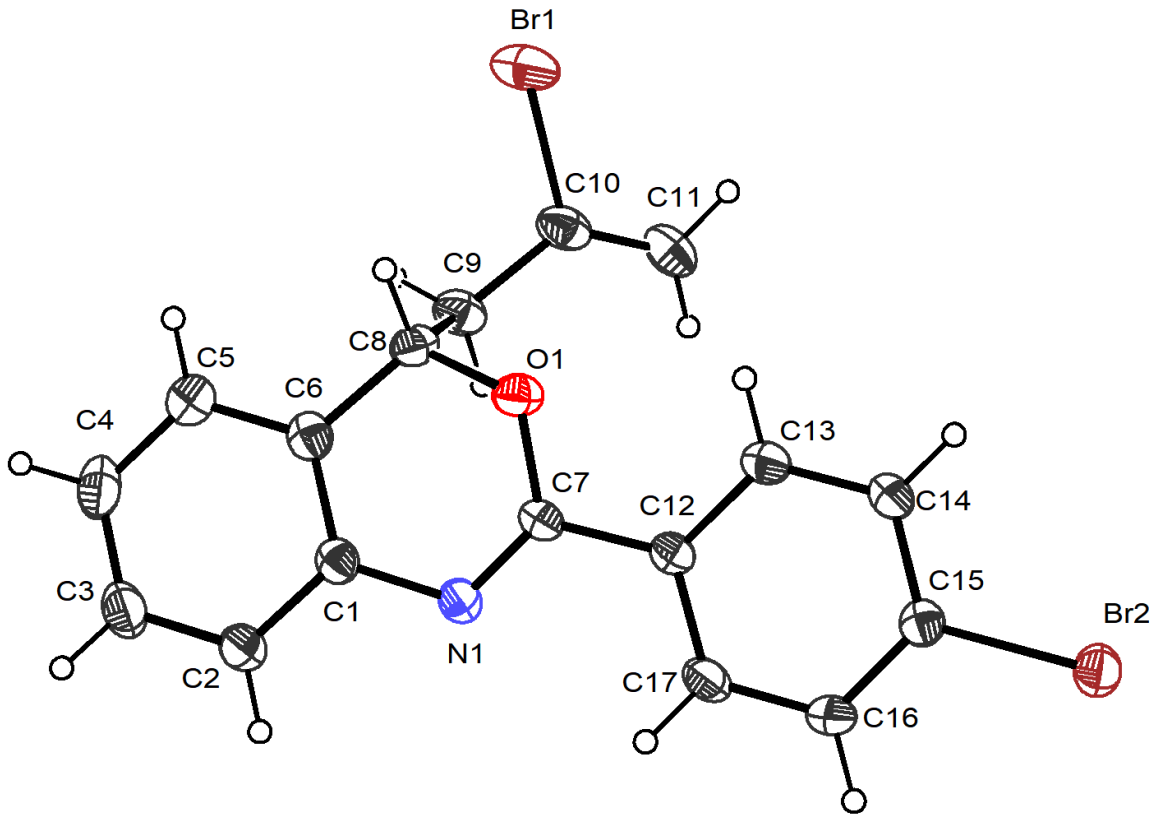




The crystal parameters of compound 3ad

	CCDC 2414884
Formula	$C_{17}H_{13}Br_2NO$
Formula weight	407.10
T/K	297(2)
Crystal system	orthorhombic
Space group	Pbcn
• *a*/Å	15.3968(12)
• *b*/Å	8.9942(7)
• *c*/Å	45.737(4)
• *α*/°	90
• *β*/°	90
• *γ*/°	90
• *V*/Å^3	6333.8(8)
• Z	16
Abs. Coeff./mm^{-1}	5.117
Abs. Correction	'none'
GOF on F^2	1.034
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0490 *wR2* = 0.0954
R indices [all data]	*R1* = 0.0732 *wR2* = 0.1040

ORTEP diagram of compound **3ad** with 30% probability



4.10. References

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Chapter 5:

Selective Synthesis of *gem*-Dihalopiperidines and 4-Halo-1,2,3,6-Tetrahydropyridines from Halogen Substituted Homoallylic Benzenesulfonamides and Aldehydes

5.1 Importance and Applications

Six-membered nitrogen heterocycles serve as key structural units in organic synthesis, as they are found in a wide range of natural products and bioactive compounds.[1] Among these, the piperidine ring is highly prevalent in alkaloids,[2] and serves as a fundamental scaffold in drug discovery and development,[3] e.g., Donepezil (**I**), a widely prescribed medication, is commonly used for the treatment of Alzheimer's disease (AD).[4] Naratriptan (**II**) is utilized for the treatment of migraine headaches,[1d] while Selfotel (**III**) functions as a competitive NMDA receptor agonist.[5] Femoxetine (**IV**) belongs to a significant class of serotonin reuptake inhibitors.[6] Similarly, tetrahydropyridine compounds **V** and **VI** show antiproliferative activity in solid tumour cell lines[7] (*Figure 5.1.1*). Due to their broad spectrum of biological activity in both pharmaceuticals and natural products, the synthesis of these compounds continues to be of significant interest to synthetic chemists. As a result, considerable research efforts have been made toward developing novel and efficient synthetic methodologies for their preparation.

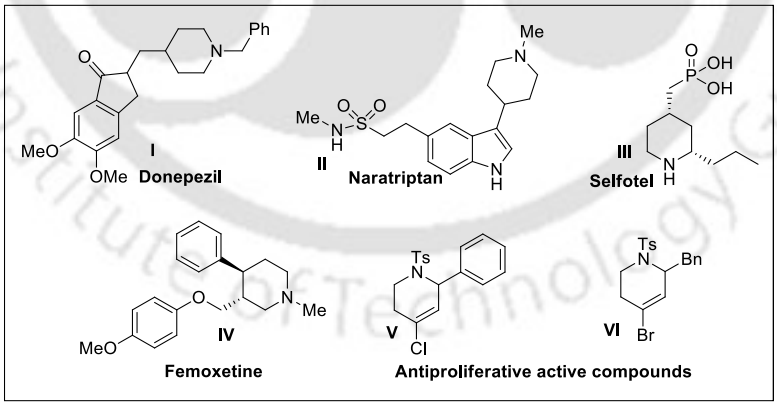
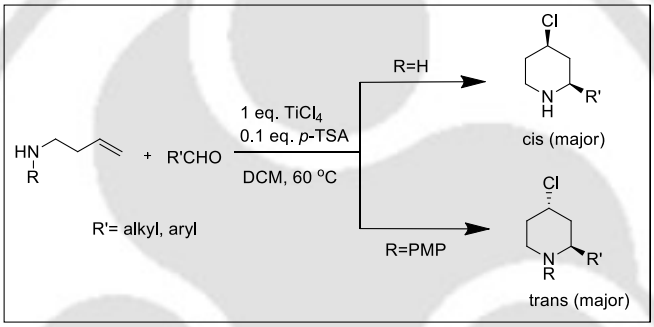


Figure 5.1.1: *Biologically active molecules.*

5.2 An Overview of Relevant Synthetic Methods

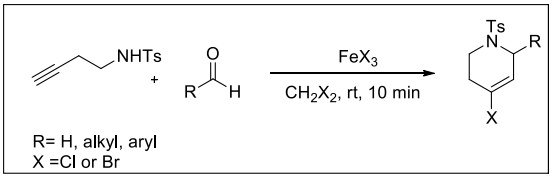
The general overview of halo Prins and aza-Prins cyclization is described in Chapter 1, Sections **1.4.5.1** and **1.5,** which also includes a concise discussion on the synthesis of halogenated compounds.

Durel *et al.* developed a methodology that utilized a synergistic combination of a Lewis acid ($TiCl_4$) and a Brønsted acid (*p*-TsOH) for the synthesis of piperidines.[8] When tosyl and *p*-methoxyphenyl (PMP) were employed as protecting groups, the *trans*-isomer emerged as the primary product, whereas the *cis*-isomer was the major product when no protecting group was used (*Scheme 5.2.2).*



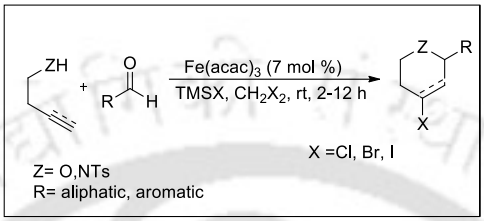
Scheme 5.2.1

The synthesis of *gem*-dihalopiperidines (see chapter 2) and 4-halo-1,2,3,6-tetrahydropyridines has been rarely reported in the literature. In 2006, Carballo *et al.* reported the synthesis of tetrahydropyridines using iron(III) halides as a reagent. The reaction of homopropargyl tosylamine with aldehydes provides 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines through the alkyne aza-Prins cyclization pathway. This reaction is effective with both aliphatic and aromatic substrates, including enolizable and non-enolizable aldehydes (*Scheme 5.2.2*).[9]



Scheme 5.2.2

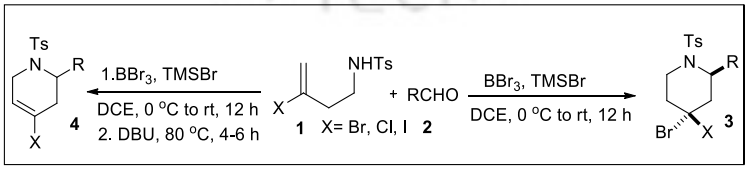
In another study, Miranda *et al.* reported a synthetic strategy of oxa- and azacycles through the combination of an iron(III) source with the corresponding trimethylsilyl halide. They also synthesize bromo, chloro and iodo heterocycles using this methodology. This process constructs one carbon-carbon bond, one halogen-carbon bond, one heteroatom-carbon bond and a ring in a regioselective manner (*Scheme 5.2.3*).[10]



Scheme 5.2.3

5.3 Present Work

One-pot, multi-component, and selective reactions are regarded as environmentally sustainable synthetic methodologies.[11] Additionally, aza-Prins cyclization[12] reactions are recognized for their ability to form C-C and C-N bonds in a single step. Given the significance of these reactions, an efficient synthesis of *gem*-dihalopiperidines and 4-halo-1,2,3,6-tetrahydropyridines *via* aza-Prins cyclization reaction of homoallylic benzenesulfonamides and aldehydes has been described. The reaction proceeds *via* aza-Prins followed by base-mediated elimination reaction, giving moderate to good yields. The reaction is highly diastereo- and regio-selective. Notably, the position of the double bond of tetrahydropyridines **4** in the present case differs from that of the products reported by Carballo[9] and Miranda.[10] Also, in *gem*-dihalopiperidines, Br (axial) acts as a nucleophile, which differs from our



RSC Adv. **2025**, *15*, 21257

previous report (chapter 2) where Cl (axial) acted as a nucleophile. Consequently, the two cases give products with different stereochemistry, particularly in the case of 4-bromo-4-chloro derivatives.

Furthermore, the *gem* dihalopiperidines can be easily converted to 2-substituted-1-tosylpiperidin-4-one and pyridine in good yields. Additionally, 4-halo-1,2,3,6-tetrahydropyridines can be employed to afford their corresponding Sonogashira coupling products in good yield.

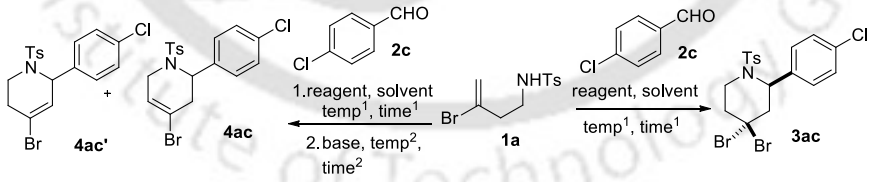
5.4 Results and Discussions

5.4.1 Optimization of the Reaction

Initially, *N*-(3-bromobut-3-en-1-yl)-4-methylbenzenesulfonamide (**1a**) was reacted with 4-chloro-benzaldehyde (**2c**) using 1.1 equiv. of boron trifluoride etherate ($BF_3{\cdot}OEt_2$) in dichloro- methane (DCM) at 0 °C to room temperature under a nitrogen atmosphere for 1.5 hours (Table 5.4.1.1, entry 1). However, this led to the decomposition of the starting material. When the reagent was changed to boron tribromide (BBr_3), it gave 18% of product **3ac** with unreacted starting material (Table 5.4.1.1, entry 2). Changing BBr_3 to indium tribromide ($InBr_3$) did not yield any product (Table 5.4.1.1, entry 3). Therefore, in order to increase the yield, the reaction was performed at 40 °C with BBr_3, which led to the decomposition of the product (Table 5.4.1.1, entry 4). Fortunately, when the reaction was performed using 0.25 equiv. of BBr_3 with 1.2 equiv. of trimethylsilyl bromide (TMSBr) as an additive, the yield of **3ac** increased to 80% (Table 5.4.1.1, entry 5). Other combinations, such as indium triflate ($In(OTf)_3$) and scandium triflate ($Sc(OTf)_3$) with TMSBr, failed to produce **3ac** (Table 5.4.1.1, entries 6 and 7). When the reaction was performed using only 1.2 equiv. of TMSBr resulted in a mere 9% yield of the product with unreacted starting material (Table 5.4.1.1, entry 8). Additionally, decreasing the BBr_3 loading to 0.1 equiv. or increasing it to 0.3 equiv. did not improve the yield (Table 5.4.1.1, entries 9 and 10). However, changing the solvent to 1,2-dichloroethane (DCE) resulted in an improved yield of 83% (Table 5.4.1.1, entry 11). It may be due to its higher polarity than DCM which dissolves both organic substrates and Lewis acids effectively to promote the transformation. Other solvents, such as toluene and acetonitrile, did not improve the yield of product **3ac** (Table 5.4.1.1, entries 12 and 13). Thus, 0.25 equiv. of BBr_3 and 1.2 equiv. of TMSBr in DCE at 0 °C to rt were the optimal conditions for the product **3ac**.

After confirming the formation of product **3ac** by thin layer chromatography (TLC), 1.0 equiv. of 1,8-diazabicyclo-[5.4.0] undec-7-ene (DBU) was added to the reaction mixture at rt and stirred for 12 hours. Interestingly, this resulted in 20% yield of regioisomeric products **4ac** and **4ac′** with a regioselectivity 1:2, along with unreacted **3ac** (Table 5.4.1.1, entry 14). In order to improve the yield and regioselectivity, various reaction conditions were examined (Table 5.4.1.1). However, the use of inorganic base potassium tertiary butoxide (KO^{t}Bu) failed to produce **4ac**, possibly due to solubility issues (Table 5.4.1.1, entry 15). Other organic bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO) and piperidine led to the formation of a complex mixture (Table 5.4.1.1, entries 16–17). Increasing the temperature to 80 °C and using 10.0 equiv. of DBU improved the yield to 68%, but the regioselectivity remains same (Table 5.4.1.1, entry 18). Notably, increasing the loading of DBU to 20.0 equiv. provided **4ac** and **4ac′** with a ratio of 1:1 (Table 5.4.1.1, entry 19). Finally, employing 40.0 equiv. of DBU resulted in the formation of a single regioselective product **4ac** (Table 5.4.1.1, entry 20). Therefore, it was concluded that 0.25 equiv. of BBr_3 and 1.2 equiv. of TMSBr in DCE at 0 °C to rt for 12 h, followed by treatment with 40.0 equiv. of DBU at 80 °C were the optimal conditions for the product **4ac**. The high concentration of DBU may be required to abstract the proton from the less hindered site of the *gem*-dihalopiperidine effectively as DBU is bulky molecule. We attempted to isolate **4ac'** by altering reaction conditions, including lowering the temperature to 0°C and varying the equivalents of DBU (Table 5.4.1.1, entry 21-22). However, these attempts did not yield pure **4ac'**.

Table 5.4.1.1: Optimization of the reaction[a]



S. No	Reagents (equiv.)	Base (eq) (Temp[2]) (Time[2])	Solvent	Temp[1].	Time[1]/ h	**3ac** **%**Yield[b]	**4ac : 4ac′** **%**Yield[be] (**4ac : 4ac′**)
1	$BF_3{\cdot}OEt_2$ (1.1)	-	DCM	0 °C-rt	1.5	--[c]	-
2	BBr_3 (1.1)	-	DCM	0 °C	12	18	-
3	$InBr_3$ (1.1)	-	DCM	0 °C-rt	12	NR	-
4	BBr_3 (1.1)	-	DCM	40 °C	2	--[c]	-
5	BBr_3 (0.25) + TMSBr (1.2)	-	DCM	0 °C-rt	12	80	-
6	$In(OTf)_3$ (0.25) + TMSBr (1.2)	-	DCM	0 °C-rt	12	NR	-
7	$Sc(OTf)_3$(0.25) + TMSBr (1.2)	-	DCM	0 °C-rt	12	NR	-

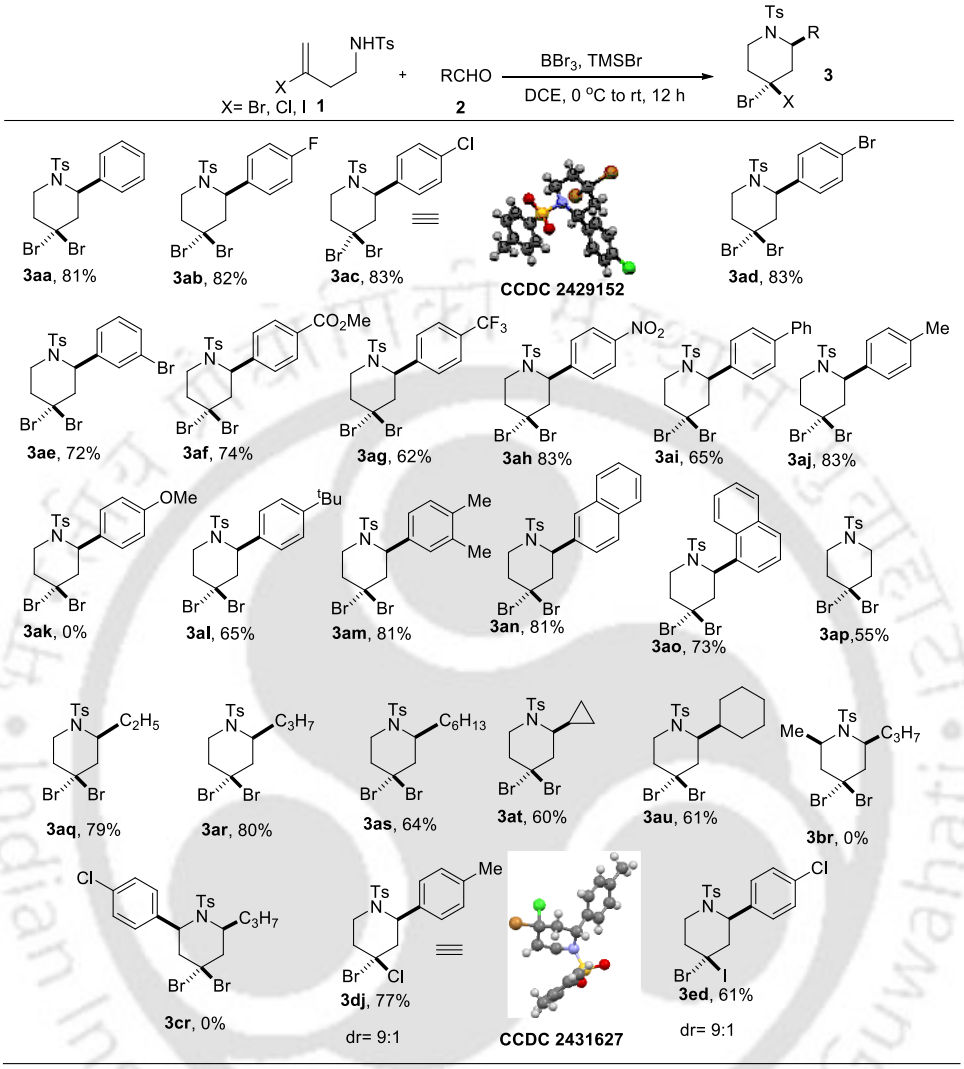
8	TMSBr (1.2)	-	DCM	0 °C-rt	12	9	-
9	BBr_3 (0.1) + TMSBr (1.2)	-	DCM	0 °C-rt	12	76	-
10	BBr_3 (0.3) + TMSBr (1.2)	-	DCM	0 °C-rt	12	78	-
11	**BBr_3 (0.25) + TMSBr (1.2)**	**-**	**DCE**	**0 °C-rt**	**12**	**83**	**-**
12	BBr_3(0.25) + TMSBr (1.2)	-	toluene	0 °C-rt	12	71	-
13	BBr_3(0.25) + TMSBr (1.2)	-	CH_3CN	0 °C-rt	12	NR	-
14	BBr_3 (0.25) + TMSBr (1.2)	DBU (1.0) (rt) (12 h)	DCE	0 °C-rt	12	51	20 (1:2)
15	BBr_3 (0.25) + TMSBr (1.2)	KO^{t}Bu(1.0) (rt) (12 h)	DCE	0 °C-rt	12	74	NR
16	BBr_3 (0.25) + TMSBr (1.2)	DABCO (1.0) (rt) (4 h)	DCE	0 °C-rt	12	-	--[d]
17	BBr_3 (0.25) + TMSBr (1.2)	Piperidine (1.0) (rt) (4 h)	DCE	0 °C-rt	12	-	--[d]
18	BBr_3 (0.25) + TMSBr (1.2)	DBU (10.0) (80) (4 h)	DCE	0 °C-rt	12	-	68 (1:2)
19	BBr_3 (0.25) + TMSBr (1.2)	DBU (20.0) (80) (4 h)	DCE	0 °C-rt	12	-	69 (1:1)
20	**BBr_3 (0.25) + TMSBr (1.2)**	**DBU (40.0) (80) (4 h)**	**DCE**	**0 °C-rt**	**12**	**-**	**70 (1:0)**
21	BBr_3 (0.25) + TMSBr (1.2)	DBU (1.0) (0 °C) (24 h)	DCE	0 °C-rt	12	59	NR
22	BBr_3 (0.25) + TMSBr (1.2)	DBU (0.5) (rt) (12 h)	DCE	0 °C-rt	12	56	Trace

[a]Reaction conditions: all reactions were carried out under a nitrogen atmosphere, **1a** (0.6 mmol) and **2c** (0.66 mmol), solvent (3.0 mL). [b]Isolated yield. [c]Decomposed. NR= No reaction. [d]complex mixture. [e]Regioselectivity was determined by ^{1}H NMR spectroscopy.

5.4.2 Substrates Scope of the Reaction:

Under the first established optimal conditions, the reaction was screened with different aldehydes, as presented in *Scheme 5.4.2.1*. Aldehydes bearing moderately electron withdrawing groups at para and meta positions of the aromatic ring such as–F, –Cl and–Br (*Scheme 5.4.2.1*, **3ab**–**3ae**), as well as those with strongly electron-withdrawing groups, including such as–CO_2Me, –CF_3 and–NO_2 (*Scheme 5.4.2.1*, **3af**–**3ah**), gave good to excellent yields. Similarly, when the reaction was carried out with aldehydes containing a moderately electron-donating group such as–Me, 3,4-dimethyl or a bulky electron-donating tert-butyl group at the para positions, gave the products **3aj**, **3am** and **3al** in 83%, 81% and 65% yields, respectively. However, a highly electron-donating methoxy group on the aromatic ring of aldehyde **2k** led to decomposition, similar to many Prins cyclisation reactions.[13] Intriguingly, biphenyl aldehyde **2i** gave **3ai** in 65% yield, and bulky substrate such as 2-naphthaldehyde **2n** and sterically hindered 1-naphthaldehyde **2o** provided corresponding products **3an** and **3ao** in

Scheme 5.4.2.1: Synthesis of *gem*-Dihalopiperidines[a]



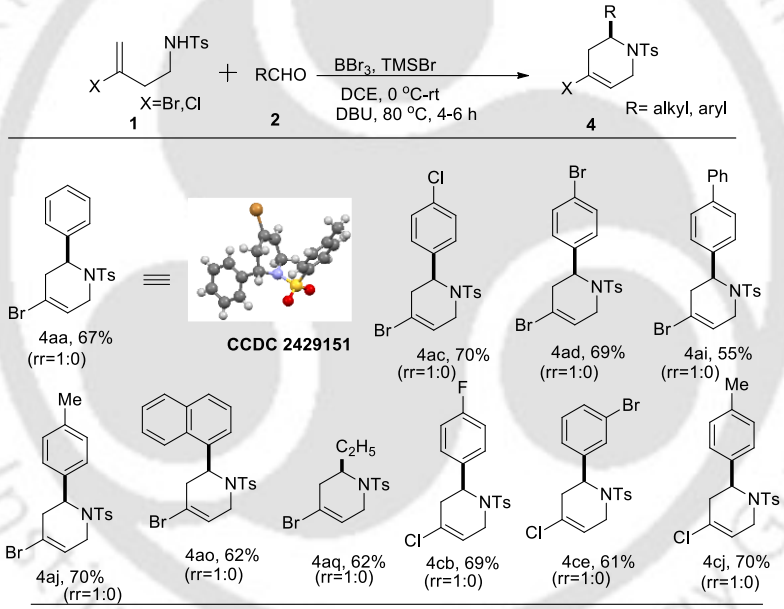
The formula of the major isomer is shown in the scheme. [a]Reaction conditions: **1** (0.6 mmol), **2** (0.66 mmol), BBr_3 (0.15 mmol), TMSBr (0.72 mmol), DCE (3 mL), 0 °C-rt, N_2 atmosphere. Diastereoselectivity was determined by ^1H NMR spectroscopy.

81% and 73% yields, respectively. Aliphatic aldehydes, including–C_2H_5, –C_3H_7, and–C_6H_{13} groups, also furnished their corresponding products in decent yields (**3aq- 3au**). Unfortunately, secondary amide *N*-(4-bromopent-4-en-2-yl)-4-methylbenzenesulfonamide (**1b**) and *N*-(3-bromo-1-(4 chlorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide (**1c**) did not yield the desired products. Under the same optimized reaction conditions, the reaction also proceeded efficiently with halogen-substituted homoallylic benzenesulfonamides bearing chlorine (Cl) or iodine (I), specifically, *N*-(3-chlorobut-3-en-1-yl)-4-methylbenzene-sulfonamide (**1d**) and *N*-(3-iodobut-3-en-1-yl)-4-methylbenzenesulfonamide (**1e**), giving products **3dj**–**3ed** in moderate to good yields

(*Scheme 5.4.2.1*). The structure and stereochemistry of all compounds (**3aa**–**3aj**, **3al**–**3au**, **3dj**, **3ed**) were determined by ^{1}H NMR, ^{13}C{^{1}H} NMR, mass spectrometry, and ultimately by X-ray crystallographic analysis of compounds **3ac** and **3dj**. Diastereoselectivity was evaluated for compounds **3dj** and **3ed** using ^{1}H NMR spectroscopy. For compound **3dj**, the diastereoselectivity was determined to be 9:1, based on the intensity ratio of the peaks at 4.86 ppm and 4.67 ppm (Page 175). In the case of compound **3ed**, the diastereoselectivity was also assessed *via* ^{1}H NMR spectroscopy and found to be 9:1, with peak intensities at 4.52 ppm and 4.60 ppm (see Page 176).

Likewise, under the second set of optimized reaction conditions, the reaction was explored with different aldehydes as shown in *Scheme 5.4.2.2*. Substrates with electron-withdrawing groups, such

Scheme 5.4.2.2: Synthesis of 4-halo-1,2,3,6-tetrahydropyridines[a]



[a]Reaction conditions: **1** (0.6 mmol), **2** (0.66 mmol), BBr_3 (0.15 mmol), TMSBr (0.72 mmol), DCE (3 mL), 0 °C-rt, DBU (24.0 mmol) N_2 atmosphere. Regioselectivity was determined by ^{1}H NMR spectroscopy.

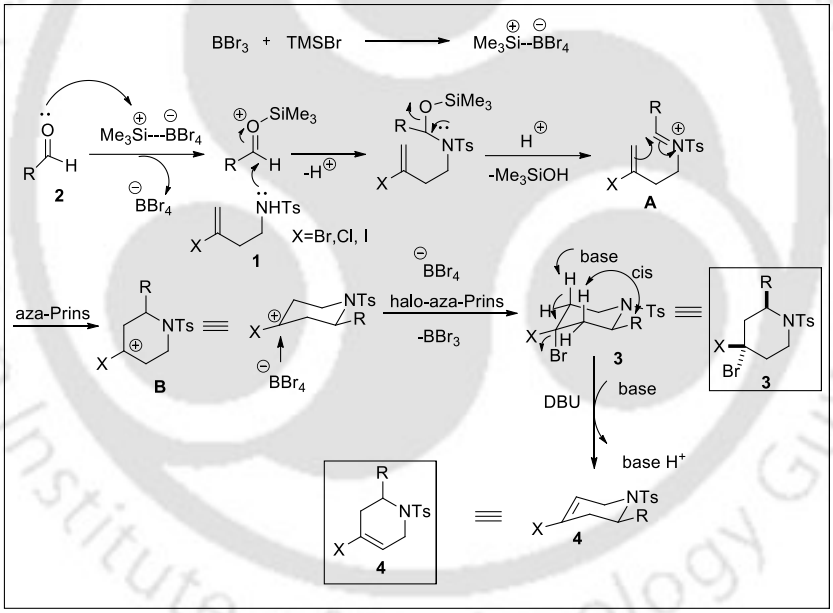
as–Cl, –Br on the aromatic ring, provided products **4ac** and **4ad** in good to moderate yields. Electron-donating group in the aromatic ring of the aldehyde provided a 70% yield of their corresponding product **4aj**. Moreover, biphenyl and sterically hindered 1-naphthyl groups were well tolerated under the reaction conditions. The substrate with an aliphatic group gave 62% of its desired product **4aq**. The reaction of halogen-substituted homoallylic benzenesulfonamides containing chlorine (Cl) with electron-donating and electron-withdrawing groups at the para and meta positions of the aromatic group of the aldehyde gave their corresponding products **4db**, **4de**,

and **4dj** in moderate yields (*Scheme 5.4.2.2*). The structure of all compounds (**4aa**–**4dj**) was determined by ^{1}H NMR, $^{13}C\{^{1}H\}$ NMR, and mass spectrometry. The stereochemistry of the compounds was determined by comparison with the reported ^{1}H NMR data.[9,10] For example, the olefinic proton of **4aa** resonates at 5.92 ppm, whereas the olefinic proton of the corresponding regioisomer of Carballo's group[9] resonates at 6.22 ppm. Finally, the structure and stereochemistry of compounds were determined by X-ray crystallographic analysis of compound **4aa**.

5.4.3. Possible mechanism of the reaction

A plausible mechanism is proposed in *Scheme 5.4.3.1*. First, BBr_3 reacts with TMSBr to generate Me_3Si^{+}–BBr_4^{-} species.[14] In the presence of these species, the halogen-substituted homoallylic

Scheme 5.4.3.1. *Plausible Mechanism of the Reaction*



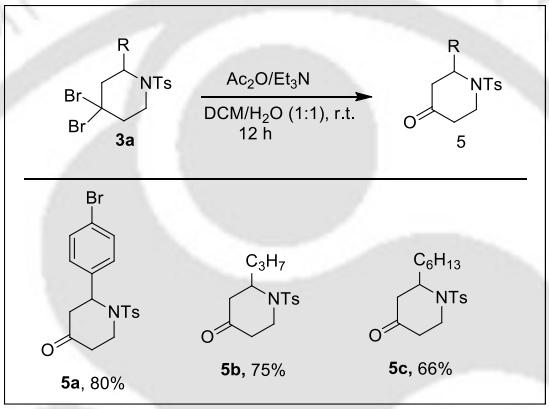
benzenesulfonamide **1** reacts with aldehyde **2** to form the iminium ion intermediate (**A**), which then undergoes aza-Prins cyclisation to produce the tertiary carbocation intermediate (**B**). Stereoelectronic factors favour nucleophilic attack (by Br) from the less hindered axial side. A further axial attack by bromide ion from BBr_4^{-} gives product **3**. After the addition of organic base DBU, its abstract proton from compound **3** to give the final product **4**. The formation of a single regioisomer may be attributed to the selective abstraction of a proton from C-5 of the piperidine

ring. The proton at C-3 is not in a position to be abstracted by bulky DBU as it is sterically hindered due to its *cis* configuration with the bulky substituent "R" at the C-2 position.

5.4.4. Post-Synthetic Utility of the Reaction:

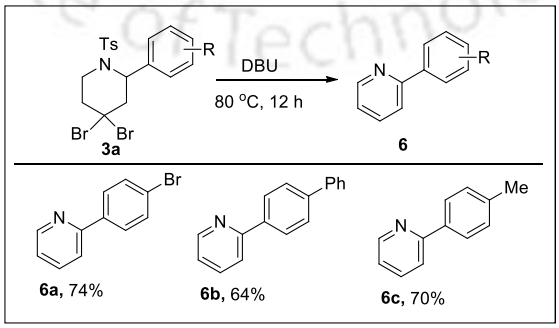
To investigate the utility of this methodology, several reactions were carried out as shown in *Schemes 5.4.4.1-5.4.4.3*. The *gem* dihalogen compounds **3ad**, **3ar** and **3as** were treated with

Scheme 5.4.4.1. Synthesis of 2-substituted-1-tosylpiperidin-4-one



triethylamine and acetic anhydride in DCM/H_2O (1:1), to give corresponding piperidinone compounds 2-(4-bromophenyl)-1 tosylpiperidin-4-one (**5a**), 2-propyl-1-tosylpiperidin-4-one (**5b**) and 2-hexyl-1-tosylpiperidin-4-one (**5c**) in 80%, 75% and 66% yields, respectively, under a previously reported procedure (*Scheme 5.4.4.1*).[15]

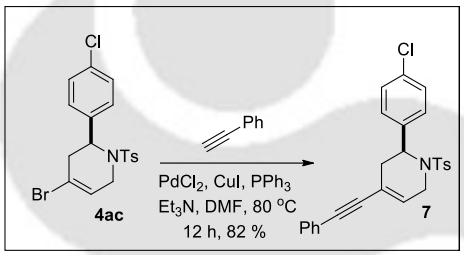
Scheme 5.4.4.2. Synthesis of pyridine



Furthermore, treatment with DBU of *gem*-dihalocompounds **3ad**, **3ai** and **3aj** gave their corresponding pyridine derivatives **6a-6c** in 74%, 64% and 70% yields, respectively (*Scheme 5.4.4.2*).[13]

The reaction of 4-halo-1,2,3,6-tetrahydropyridines gives Sonogashira product using literature precedents.[16] Thus, the reaction of 4-bromo-2-(4-chlorophenyl)-1-tosyl-1,2,3,6-tetrahydropyridine (**4ac**) with phenyl acetylene in the presence of $PdCl_2$, CuI, PPh_3 and Et_3N provided the corresponding Sonogashira product 2-(4-chlorophenyl)-4-(phenylethynyl)-1-tosyl 1,2,3,6-tetrahydropyridine (**7**) (*Scheme 5.4.4.3*).

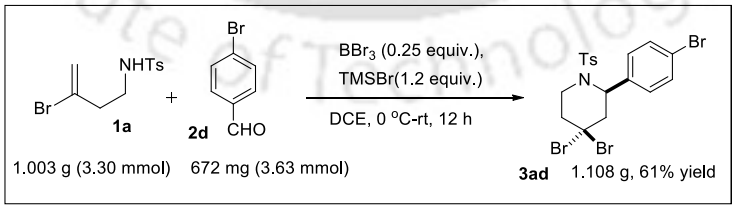
Scheme 5.4.4.3. Synthesis of 2-(4-chlorophenyl)-4-(phenylethynyl)-1-tosyl-1,2,3,6-tetrahydropyridine



5.4.5. Gram scale experiment of the reaction

To evaluate the scalability of this methodology, a gram-scale reaction was performed between *N*-(3-bromobut-3-en-1-yl)-4 methylbenzenesulfonamide **1a** (1.00 g, 3.30 mmol) and 4-bromobenzaldehyde **2d** (0.67 g, 3.63 mmol), which gave 1.11 g of the product **3ad** with 61% yield (*Scheme 5.4.5.1*).

Scheme 5.4.5.1. Gram-scale experiment



5.5 Conclusion

In conclusion, an efficient methodology has been developed that is useful not only for the synthesis of *gem*-dihalopiperidine but also for the synthesis of 4-halo-1,2,3,6-tetrahydropyridine derivatives from alkene sulfonamides and aldehydes in good to moderate yields. The selectivity of the reaction

is particularly notable, as the first pathway gives a diastereoselective product, while the second provides a regioselective product. *Gem*-diha- lopiperidines can be extended to the synthesis of pyridine and piperidinone derivatives in moderate to good yields, whereas 4-halo-1,2,3,6-tetrahydropyridine can be transformed into its corresponding Sonogashira product. However, the enantioselective or chiral induction strategies for the synthesis of its chiral counterpart are a limitation of the current approach and will be explored in the future. Furthermore, the scalability of the reaction is investigated using a gram-scale experiment, and it shows its potential for large-scale applications with industrial relevance.

5.6 Experimental Section

5.6.1 General Information

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H (600 MHz, 500 MHz and 400 MHz) or $^{13}C\{^{1}H\}$ (150 MHz, 125 MHz and 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. Structural assignments were made with additional information from single crystal XRD experiments. HRMS spectra were recorded using Q-TOF mass spectrometer.

The starting material *N*-(3-bromobut-3-en-1-yl)-4-methylbenzenesulfonamide[17a] (**1a**), *N*-(4-bromopent-4-en-2-yl)-4-methylbenzenesulfonamide[13] (**1b**), *N*-(3-bromo-1-(4-chlorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide[13] (**1c**), *N*-(3-chlorobut-3-en-1-yl)-4-methylbenzenesulfonamide[13] (**1d**) and *N*-(3-iodobut-3-en-1-yl)-4-methylbenzenesulfonamide[17b] (**1e**) was synthesized according to the reported literatures. The spectroscopic data of the above compound is in good agreement with the literature one. The experimental procedure and the characterization data of the all compounds are given as follows:

5.6.2 General procedure for the synthesis of (3aa-3ad):

A solution of *N*-(3-bromobut-3-en-1-yl)-4-methylbenzenesulfonamide (0.6 mmol, 1.0 equiv.) and the aldehyde (0.66 mmol, 1.1 equiv.) in dry 1,2-dichloroethane (DCE) (3 mL) was added boron

tribromide (BBr_3) (1 M in DCM) (0.15 mmol, 0.25 equiv.) and trimethylsilyl bromide (TMSBr) (0.72 mmol, 1.2 equiv.) at 0 °C under the nitrogen atmosphere. The reaction mixture was then stirred at room temperature overnight, and the progress of the reaction was monitored by thin-layer chromatography (TLC) (ethyl acetate:hexane = 1:9). Upon completion of the reaction, it was quenched with a saturated sodium bicarbonate solution. A brine solution was then added, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure using a rotary evaporator. The crude product was purified by silica gel column chromatography, employing a mixture of ethyl acetate and hexane (1:9, v/v) as the eluent to obtain the final product.

5.6.3 General procedure for the synthesis of (4aa-4dj):

A solution of N-(3-bromobut-3-en-1-yl)-4-methylbenzene-sulfonamide (0.6 mmol, 1.0 equiv.) and the aldehyde (0.66 mmol, 1.1 equiv.) in dry 1,2-dichloroethane (DCE) (3 mL) was cooled to 0 ° C under a nitrogen atmosphere. To this solution, boron tribromide (BBr_3) (1 M in DCM) (0.15 mmol, 0.25 equiv.) and trimethylsilyl bromide (TMSBr) (0.72 mmol, 1.2 equiv.) were added. The reaction mixture was then stirred at room temperature for overnight, and progress of the reaction was monitored by thin-layer chromatography (TLC) (ethyl acetate: hexane = 1: 9). Once the starting material was fully consumed, 1,8 diazabicyclo[5.4.0]undec-7-ene (DBU) (24 mmol, 40.0 equiv.) was added, and the mixture was stirred in an oil bath at 80 °C for 4 to 6 hours. The progress of the reaction was monitored by TLC (ethyl acetate:hexane = 1:9). After completion, it was allowed to cool to room temperature, brine was added, and the organic layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure by rotary evaporator and purified by column chromatography over silica gel using hexane/ethyl acetate (9:1, v/v) as eluent to get the products.

5.6.4. General procedure for the synthesis of (5a-5c):

A mixture of 4,4-dibromo-1-tosylpiperidine derivatives (0.22 mmol, 1 equiv.) in dichloromethane (DCM) (1.0 mL) and water (1.0 mL) was treated with acetic anhydride (Ac_2O) (4.1 mmol, 19.0 equiv.) and triethylamine (Et_3N) (5.7 mmol, 30.0 equiv.) at room temperature under an air atmosphere. The reaction mixture was vigorously stirred overnight at room temperature. After completion of the reaction, H_2O was added, and the organic layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate (Na_2SO_4),

filtered, and concentrated under reduced pressure by rotary evaporator and purified by column chromatography over silica gel using hexane/ethyl acetate (4:1, v/v) as eluent to get the products.

5.6.5 General procedure for the synthesis of (6a-6c):

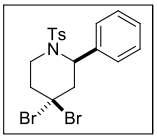
A solution of 4,4-dibromo-1-tosylpiperidine derivatives (0.22 mmol, 1 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (10 mmol, 45.45 equiv.) was stirred in an oil bath at 80 °C for 12 hours. After completion of the reaction, it was allowed to cool to room temperature, brine was added, and the organic layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure by rotary evaporator and purified by column chromatography over silica gel using hexane/ethyl acetate (9:1, v/v) as eluent to get the products.

5.6.6 Experimental procedure for the gram-scale reaction

A solution of *N*-(3-bromobut-3-en-1-yl)-4 methylbenzenesulfonamide (1.0 g, 3.30 mmol, 1.0 equiv.) and 4-bromobenzaldehyde (0.67 g, 3.63 mmol, 1.1 equiv.) in anhydrous 1,2-dichloroethane (DCE) (15 mL) was cooled to 0 °C under a nitrogen atmosphere. To this solution boron tribromide (BBr_3) (1 M in DCM) (0.21 g, 0.83 mmol, 0.25 equiv.) and trimethylsilyl bromide (TMSBr) (0.61 g, 3.96 mmol, 1.2 equiv.) were added. The reaction mixture was stirred at room temperature overnight, and the progress was monitored by thin layer chromatography (TLC) using ethyl acetate/hexane (1:9, v/v) as the eluent. After completion of the reaction, it was quenched with a saturated sodium bicarbonate solution. A brine solution was then added, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure by rotary evaporator. The desired product 3ad was obtained (1.11 g, colorless solid) in 61% yield by silica gel column chromatography using hexane/ ethyl acetate (9:1, v/v) as the eluent.

5.6.7 Characterization Data

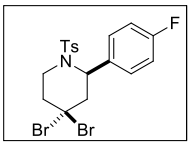
4,4-Dibromo-2-phenyl-1-tosylpiperidine (3aa):



Colorless solid; R_f (hexane/EtOAc, 9:1) 0.51; mp 136 °C, yield 230 mg, 81%; IR (KBr, neat) ν 2924, 1598, 1495, 1450, 1344, 1158, 1094, 950, 719, 660, 559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2 H), 7.24 – 7.17 (m, 7 H), 4.78 (t, *J* = 5.7 Hz, 1 H), 3.84 – 3.78 (m, 1 H), 3.62 – 3.56 (m, 1 H), 3.19 (dd, *J*

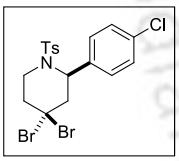
= 14.8, 6.4 Hz, 1 H), 2.81 (ddd, *J* = 14.8, 4.8, 1.1 Hz, 1 H), 2.66 – 2.62 (m, 2 H), 2.42 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 143.8, 137.7, 136.6, 129.8, 128.4, 127.8, 127.6, 127.5, 62.4, 59.0, 52.8, 47.7, 43.9, 21.8. HRMS (ESI) calcd. for $C_{18}H_{20}Br_2NO_2S$ $(M + H)^+$ 473.9556, found 473.9571.

4,4-Dibromo-2-(4-fluorophenyl)-1-tosylpiperidine (3ab):



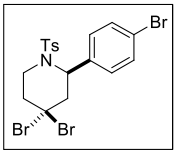
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.52; mp 143 °C, yield 242 mg, 82%; IR (KBr, neat) ν 2944, 1602, 1510, 1443, 1375, 1162, 1095, 1039, 918, 744, 660, 553 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.45 (m, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 7.15 – 7.12 (m, 2 H), 6.91 – 6.87 (m, 2 H), 4.71 (t, *J* = 5.7 Hz, 1 H), 3.86 – 3.79 (m, 1 H), 3.59 – 3.53 (m, 1 H), 3.15 – 3.09 (m, 1 H), 2.80 – 2.75 (m, 1H), 2.67 – 2.62 (m, 2 H), 2.42 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 162.4 (d, *J* = 245.3 Hz), 144.0, 136.6, 133.3 (d, *J* = 3.2 Hz), 129.8, 129.4 (d, *J* = 8.1 Hz), 127.6, 115.3 (d, *J* = 21.5 Hz), 62.2, 58.7, 53.0, 47.7, 44.1, 21.8. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -114.50. HRMS (ESI) calcd. for $C_{18}H_{19}Br_2FNO_2S$ $(M + H)^+$ 491.9462, found 491.9441.

4,4-Dibromo-2-(4-chlorophenyl)-1-tosylpiperidine (3ac):



Colorless solid; R_f (hexane/EtOAc, 9:1) 0.52; mp 159 °C, yield 252 mg, 83%; IR (KBr, neat) ν 2925, 2855, 1597, 1492, 1345, 1162, 1093, 1015, 916, 712, 656, 551 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.8 Hz, 2 H), 7.24 (d, *J* = 7.9 Hz, 2 H), 7.17 (d, *J* = 8.8 Hz, 2 H), 7.10 (d, *J* = 8.1 Hz, 2 H), 4.73 (t, *J* = 5.6 Hz, 1 H), 3.80 – 3.76 (m, 1 H), 3.60 – 3.55 (m, 1 H), 3.12 (dd, *J* = 14.8, 6.5 Hz, 1 H), 2.78 (dd, *J* = 14.8, 4.7 Hz, 1 H), 2.65 – 2.61 (m, 2 H), 2.43 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 144.1, 136.5, 136.2, 133.7, 129.9, 129.0, 128.5, 127.6, 62.0, 58.5, 52.6, 47.6, 43.8, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}Br_2ClNO_2S$ $(M + H)^+$ 507.9166, found 507.9174.

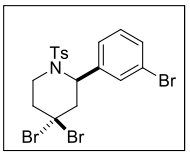
4,4-Dibromo-2-(4-bromophenyl)-1-tosylpiperidine (3ad):



Colorless solid; R_f (hexane/EtOAc, 9:1) 0.52; mp 149 °C, yield 274 mg, 83%; IR (KBr, neat) ν 2924, 1597, 1488, 1341, 1162, 1094, 1011, 915, 709, 661, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.6 Hz, 2 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.04 (d, *J* = 8.3 Hz, 2 H), 4.72 (t, *J* = 5.6 Hz,

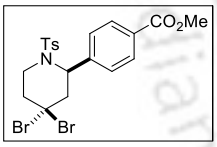
1 H), 3.81 – 3.75 (m, 1 H), 3.61 – 3.55 (m, 1 H), 3.15 – 3.09 (m, 1 H), 2.78 (dd, *J* = 14.8, 4.8, 1.2 Hz, 1 H), 2.65 – 2.61 (m, 2 H), 2.43 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 144.1, 136.7, 136.5, 131.5, 129.9, 129.3, 127.6, 121.9, 61.9, 58.5, 52.5, 47.6, 43.8, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}Br_3NO_2S$ $(M + H)^+$ 551.8661, found 551.8637.

4,4-Dibromo-2-(3-bromophenyl)-1-tosylpiperidine (3ae):



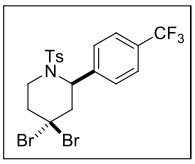
Colorless gum; R_f (hexane/EtOAc, 9:1) 0.52; yield 238 mg, 72%; IR (KBr, neat) ν 2924, 1596, 1475, 1341, 1160, 1091, 1011, 923, 808, 725, 659, 570 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.1 Hz, 2 H), 7.32 – 7.30 (m, 1 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.18 – 7.16 (m, 1 H), 7.15 – 7.10 (m, 2 H), 4.76 (t, *J* = 5.7 Hz, 1 H), 3.81 – 3.77 (m, 1 H), 3.63 – 3.59 (m, 1 H), 3.12 (dd, *J* = 14.7, 6.6 Hz, 1 H), 2.80 (ddd, *J* = 14.8, 4.8, 1.2 Hz, 1 H), 2.66 – 2.60 (m, 2 H), 2.42 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 144.2, 139.9, 136.6, 130.9, 130.8, 130.0, 129.9, 127.4, 126.4, 122.5, 61.9, 58.4, 52.5, 47.6, 43.8, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}Br_3NO_2S$ $(M + H)^+$ 551.8661, found 551.8655.

Methyl 4-(4,4-dibromo-1-tosylpiperidin-2-yl)benzoate (3af):



Colorless solid; R_f (hexane/EtOAc, 9:1) 0.48; mp 169 ºC, yield 236 mg, 74%; IR (KBr, neat) ν 2926, 1718, 1611, 1435, 1344, 1278, 1158, 1094, 1017, 950, 917, 868, 771, 662, 550 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 2 H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.24 (m, 4 H), 4.90 (t, *J* = 5.5 Hz, 1 H), 3.91 (s, 3 H), 3.77 – 3.70 (m, 1 H), 3.68 – 3.62 (m, 1 H), 3.20 (ddd, *J* = 14.8, 5.6, 1.1 Hz, 1 H), 2.84 (ddd, *J* = 14.7, 5.2, 0.9 Hz, 1 H), 2.65 – 2.56 (m, 2 H), 2.43 (s, 3 H).$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 166.9, 144.3, 143.2, 136.3, 130.0, 129.8, 129.6, 127.6, 127.2, 61.6, 58.3, 52.4, 52.2, 47.4, 43.4, 21.8. HRMS (ESI) calcd. for $C_{20}H_{22}Br_2NO_4S$ $(M + H)^+$ 531.9611, found 531.9610.

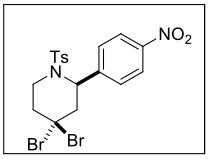
4,4-Dibromo-1-tosyl-2-(4-(trifluoromethyl)phenyl)piperidine (3ag):



Colorless gum; R_f (hexane/EtOAc, 9:1) 0.53; yield 201 mg, 62%; IR (KBr, neat) ν 2926, 1620, 1598, 1324, 1160, 1116, 1123, 1069, 1017, 951, 715, 664, 583, 549 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 – 7.45 (m, 4 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 4.84 (t, *J* = 5.8 Hz, 1 H), 3.81 – 3.77

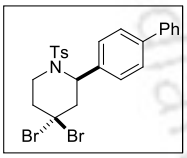
(m, 1 H), 3.64 – 3.60 (m, 1 H), 3.17 (dd, *J* = 14.7, 6.4 Hz, 1 H), 2.82 (ddd, *J* = 14.8, 4.9, 1.3 Hz, 1 H), 2.68 – 2.59 (m, 2 H), 2.42 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 144.2, 141.8, 136.5, 130.1 (q, *J* = 32.2 Hz), 130.0, 127.9, 127.5, 125.3 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 270.4 Hz), 61.6, 58.5, 52.4, 47.5, 43.7, 21.8. ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$) δ -62.50. HRMS (ESI) calcd. for $C_{19}H_{19}Br_2F_3NO_2S$ $(M + H)^+$ 541.9430, found 541.9431.

4,4-Dibromo-2-(4-nitrophenyl)-1-tosylpiperidine (3ah):



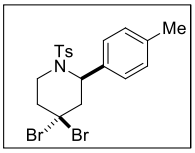
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.46; mp 193 °C, yield 258 mg, 83%; IR (KBr, neat) ν 2927, 1597, 1522, 1349, 1159, 1092, 721, 663, 550 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.8 Hz, 2 H), 7.57 – 7.56 (m, 2 H), 7.40 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 4.96 – 4.94 (m, 1 H), 3.72 – 3.64 (m, 2 H), 3.18 (dd, *J* = 15.0, 5.4 Hz, 1 H), 2.84 (dd, *J* = 14.9, 5.3 Hz, 1 H), 2.65 – 2.60 (m, 1 H), 2.57 – 2.52 (m, 1 H), 2.44 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 147.4, 145.8, 144.6, 136.0, 130.1, 128.0, 127.5, 123.7, 60.9, 57.9, 52.0, 47.1, 43.3, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}Br_2N_2O_4S$ $(M + H)^+$ 518.9407, found 518.9379.

2-([1,1'-Biphenyl]-4-yl)-4,4-dibromo-1-tosylpiperidine (3ai):



Yellow solid; R_f (hexane/EtOAc, 9:1) 0.53; mp 152 °C, yield 214 mg, 65%; IR (KBr, neat) ν 3030, 2924, 1598, 1488, 1343, 1262, 1157, 1093, 1008, 949, 866, 758, 728, 697, 550 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.54 (m, 2 H), 7.50 – 7.421 (m, 6 H), 7.37 – 7.33 (m, 1 H), 7.25 – 7.19 (m, 4 H), 4.82 – 4.79 (m, 1 H), 3.91 – 3.85 (m, 1 H), 3.64 – 3.58 (m, 1 H), 3.22 (dd, *J* = 14.7, 6.9 Hz, 1 H), 2.85 (ddd, *J* = 14.8, 4.6, 1.1 Hz, 1 H), 2.70 – 2.66 (m, 2 H), 2.40 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 143.7, 140.7, 136.8, 136.5, 129.7, 129.0, 128.3, 127.7, 127.6, 127.2, 127.0, 62.6, 59.1, 52.8, 47.8, 44.1, 21.8. HRMS (ESI) calcd. for $C_{24}H_{24}Br_2NO_2S$ $(M + H)^+$ 549.9869, found 549.9863.

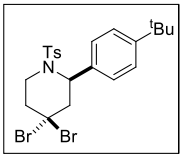
4,4-Dibromo-2-(p-tolyl)-1-tosylpiperidine (3aj):



Brown solid; R_f (hexane/EtOAc, 9:1) 0.52; mp 127 °C, yield 242 mg, 83%; IR (KBr, neat) ν 2923, 1598, 1511, 1343, 1161, 812, 726, 673, 567, 546 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 7.01 (d, *J* = 8.0 Hz, 2 H), 4.68 (t, *J* = 5.6 Hz, 1 H),

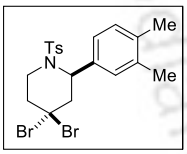
3.85 – 3.81 (m, 1 H), 3.56 – 3.52 (m, 1 H), 3.15 (dd, *J* = 14.7, 6.8 Hz, 1 H), 2.78 (ddd, *J* = 14.8, 4.6, 1.3 Hz, 1 H), 2.68 – 2.62 (m, 2 H), 2.42 (s, 3 H), 2.30 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 143.7, 137.6, 136.6, 134.6, 129.7, 129.0, 127.7, 127.6, 62.7, 59.1, 53.1, 47.8, 44.1, 21.8, 21.3. HRMS (ESI) calcd. for $C_{19}H_{22}Br_2NO_2S$ $(M + H)^+$ 487.9713, found 487.9707.

4,4-Dibromo-2-(4-(tert-butyl)phenyl)-1-tosylpiperidine (3al):



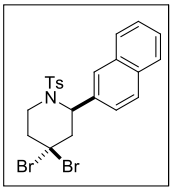
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.52; mp 137 °C, yield 206 mg, 65%; IR (KBr, neat) ν 2961, 1512, 1494, 1345, 1322, 1155, 1092, 1017, 714, 656, 547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2 H), 7.16 – 7.12 (m, 4 H), 7.06 – 7.04 (m, 2 H), 4.67 (dd, *J* = 7.8, 4.1 Hz, 1 H), 3.95 – 3.89 (m, 1 H), 3.57 – 3.51 (m, 1 H), 3.16 (dd, *J* = 14.7, 7.8 Hz, 1 H), 2.81 – 2.76 (m, 1 H), 2.70 – 2.67 (m, 2 H), 2.38 (s, 3 H), 1.27 (s, 9 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 150.9, 143.3, 137.2, 133.9, 129.5, 127.9, 127.6, 125.1, 63.2, 59.5, 53.1, 47.9, 44.5, 34.6, 31.5, 21.7. HRMS (ESI) calcd. for $C_{22}H_{28}Br_2NO_2S$ $(M + H)^+$ 530.0182, found 530.0175.

4,4-Dibromo-2-(3,4-dimethylphenyl)-1-tosylpiperidine (3am):



Colorless gum; R_f (hexane/EtOAc, 9:1) 0.52; yield 243 mg, 81%; IR (KBr, neat) ν 2922, 1597, 1504, 1451, 1342, 1321, 1156, 1092, 1017, 920, 813, 723, 659, 546, 449 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.3 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 6.97 (d, *J* = 7.8 Hz, 1 H), 6.92 (dd, *J* = 7.8, 2.0 Hz, 1 H), 6.83 – 6.78 (m, 1 H), 4.65 – 4.62 (m, 1 H), 3.90 – 3.84 (m, 1 H), 3.57 – 3.51 (m, 1 H), 3.15 (dd, *J* = 14.7, 7.4 Hz, 1 H), 2.82 – 2.76 (m, 1 H), 2.69 – 2.66 (m, 2 H), 2.40 (s, 3 H), 2.19 (s, 3 H), 2.09 (s, 3 H).$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 143.5, 136.8, 136.3, 136.2, 134.6, 129.5, 129.4, 129.2, 127.6, 125.4, 63.0, 59.3, 53.2, 47.9, 44.3, 21.7, 19.9, 19.6. HRMS (ESI) calcd. for $C_{20}H_{24}Br_2NO_2S$ $(M + H)^+$ 501.9869, found 501.9869.

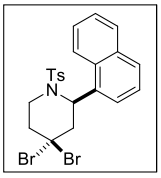
4,4-Dibromo-2-(naphthalen-2-yl)-1-tosylpiperidine (3an):



Colorless solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 159 °C, yield 254 mg, 81%; IR (KBr, neat) ν 3057, 2925, 1598, 1438, 1343, 1158, 1093, 1016, 816, 662, 559, 478 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.77 (m, 1 H), 7.69 (d, *J* = 8.6 Hz, 1 H), 7.65 – 7.62 (m, 1 H), 7.49 – 7.42 (m, 5 H), 7.33 (dd, *J*

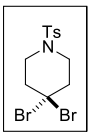
= 8.6, 1.9 Hz, 1 H), 7.15 – 7.04 (m, 2 H), 4.91 – 4.88 (m, 1 H), 3.94 – 3.89 (m, 1 H), 3.68 – 3.62 (m, 1 H), 3.30 (dd, *J* = 14.8, 6.8 Hz, 1 H), 2.89 (dd, *J* = 14.7, 4.6 Hz, 1 H), 2.72 – 2.70 (m, 2 H), 2.35 (s, 3 H).$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 143.9, 136.7, 135.0, 133.2, 133.0, 129.7, 128.1, 128.0, 127.8, 127.6, 126.7, 126.4, 126.3, 125.6, 62.5, 59.5, 53.0, 47.8, 44.1, 21.7. HRMS (ESI) calcd. for $C_{22}H_{22}Br_2NO_2S$ $(M + H)^+$ 523.9713, found 523.9699.

4,4-Dibromo-2-(naphthalen-1-yl)-1-tosylpiperidine (3ao):



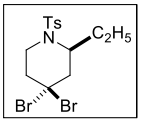
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.51; mp 149 °C, yield 229 mg, 73%; IR (KBr, neat) ν 3051, 1598, 1510, 1494, 1439, 1342, 1316, 1264, 1152, 1088, 1007, 777, 694, 571, 531, 481 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.70 (m, 1 H), 7.66 (d, *J* = 8.2 Hz, 1 H), 7.62 – 7.58 (m, 1 H), 7.53 (d, *J* = 7.2 Hz, 1 H), 7.40 – 7.31 (m, 3 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 6.57 (d, *J* = 8.0 Hz, 2 H), 5.20 (dd, *J* = 10.9, 2.6 Hz, 1 H), 4.34 (dt, *J* = 14.2, 3.7 Hz, 1 H), 3.75 (dd, *J* = 14.2, 10.8 Hz, 1 H), 3.64 (ddd, *J* = 14.1, 10.9, 2.9 Hz, 1 H), 2.98 – 2.90 (m, 2 H), 2.86 (dq, *J* = 14.6, 2.8 Hz, 1 H), 2.10 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 142.4, 135.9, 133.5, 131.7, 131.5, 129.6, 128.7, 128.3, 127.3, 127.0, 126.5, 125.5, 125.0, 123.2, 65.8, 57.5, 51.9, 48.5, 47.0, 21.4. HRMS (ESI) calcd. for $C_{22}H_{22}Br_2NO_2S$ $(M + H)^+$ 523.9713, found 523.9715.

4,4-Dibromo-1-tosylpiperidine (3ap):



Colorless solid; R_f (hexane/EtOAc, 9:1) 0.51; mp 149 °C, yield 131 mg, 55%; IR (KBr, neat) ν 2927, 1598, 1350, 1163, 933, 715, 546 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 3.17 (t, *J* = 5.3 Hz, 4 H), 2.63 (t, *J* = 5.3 Hz, 4 H), 2.44 (s, 3 H).$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 144.2, 133.6, 130.1, 127.7, 64.6, 47.5, 44.7, 21.8. HRMS (ESI) calcd. for $C_{12}H_{16}Br_2NO_2S$ $(M + H)^+$ 397.9243, found 397.9240.

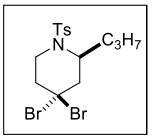
4,4-Dibromo-2-ethyl-1-tosylpiperidine (3aq):



Colorless solid; R_f (hexane/EtOAc, 9:1) 0.52; mp 127 °C, yield 201 mg, 79%; IR (KBr, neat) ν 2970, 2931, 2876, 1597, 1494, 1455, 1341, 1319, 1156, 1092, 1051, 957, 814, 718, 648, 552 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 3.88 – 3.84 (m, 1H), 3.68 (dtd, *J* = 14.8, 3.9, 1.4 Hz, 1 H), 3.45 – 3.41 (m, 1 H), 2.81 (dt, *J* = 15.0, 2.3 Hz, 1 H), 2.65 (dd, *J* = 15.0, 6.3 Hz,

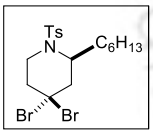
1 H), 2.62 – 2.58 (m, 1 H), 2.47 – 2.44 (m, 1 H), 2.43 (s, 3 H), 1.89 (p, *J* = 7.5 Hz, 2 H), 0.86 (t, *J* = 7.4 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 143.9, 138.1, 130.1, 127.3, 62.3, 57.1, 48.5, 48.1, 40.7, 24.6, 21.8, 11.6. HRMS (ESI) calcd. for $C_{14}H_{20}Br_2NO_2S$ $(M + H)^+$ 425.9556, found 425.9557.

4,4-Dibromo-2-propyl-1-tosylpiperidine (3ar):



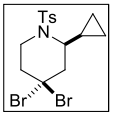
Brown solid; R_f (hexane/EtOAc, 9:1) 0.52; mp 126 °C, yield 211 mg, 80%; IR (KBr, neat) ν 2960, 2931, 2872, 1597, 1494, 1456, 1320, 1157, 1092, 1062, 926, 815, 710, 650, 552 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 3.99 – 3.95 (m, 1 H), 3.67 (dtd, *J* = 14.8, 3.9, 1.4 Hz, 1 H), 3.47 – 3.42 (m, 1 H), 2.78 (dt, *J* = 14.9, 2.2 Hz, 1 H), 2.65 (dd, *J* = 15.0, 6.3 Hz, 1 H), 2.61 – 2.58 (m, 1 H), 2.43 (s, 3 H), 2.42 – 2.41 (m, 1 H), 1.85 – 1.81 (m, 2 H), 1.32 – 1.25 (m, 2 H), 0.87 (t, *J* = 7.4 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 143.9, 138.1, 130.1, 127.3, 62.3, 55.3, 48.9, 48.1, 40.7, 33.7, 21.8, 20.2, 13.9. HRMS (ESI) calcd. for $C_{15}H_{22}Br_2NO_2S$ $(M + H)^+$ 439.9713, found 439.9712.

4,4-Dibromo-2-hexyl-1-tosylpiperidine (3as):



Pale yellow gum; R_f (hexane/EtOAc, 9:1) 0.48; yield 184 mg, 64%; IR (KBr, neat) ν 2927, 15967, 1494, 1322, 1157, 812, 651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 3.96 – 3.90 (m, 1 H), 3.69 (dtd, *J* = 14.8, 3.9, 1.3 Hz, 1 H), 3.47 – 3.40 (m, 1 H), 2.79 (dt, *J* = 15.0, 2.3 Hz, 1 H), 2.67 (dd, *J* = 15.0, 6.2 Hz, 1 H), 2.63 – 2.58 (m, 1 H), 2.49 – 2.45 (m, 1 H), 2.42 (s, 3 H), 1.87 – 1.77 (m, 2 H), 1.25 – 1.17 (m, 8 H), 0.86 (t, *J* = 6.9 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 143.9, 138.1, 130.1, 127.3, 62.4, 55.6, 48.9, 48.2, 40.7, 31.8, 31.5, 29.0, 27.0, 22.8, 21.8, 14.3. HRMS (ESI) calcd. for $C_{18}H_{28}Br_2NO_2S$ $(M + H)^+$ 482.0182, found 482.0181.

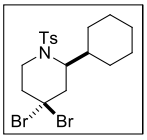
4,4-Dibromo-2-cyclopropyl-1-tosylpiperidine (3at):



Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.53; mp 136 °C, yield 157 mg, 60%; IR (KBr, neat) ν 2962, 1597, 1493, 1383, 1255, 1155, 1093, 755, 711, 649, 553 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2 H), 7.32 (d, *J* = 7.9 Hz, 2 H), 4.03 – 3.95 (m, 1 H), 3.71 (dt, *J* = 14.8, 3.6 Hz, 1 H), 3.47 – 3.42 (m, 1 H), 3.38

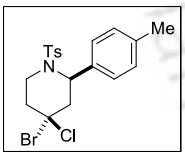
(t, *J* = 6.2 Hz, 2 H), 2.75 (dt, *J* = 15.1, 2.3 Hz, 1 H), 2.65 (dd, *J* = 15.1, 6.4 Hz, 1 H), 2.60 – 2.54 (m, 1 H), 2.43 (s, 3 H), 2.40 – 2.33 (m, 1 H), 2.20 – 2.10 (m, 1 H), 1.89 – 1.81 (m, 2 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 144.2, 137.7, 130.3, 127.3, 61.6, 54.6, 49.2, 47.7, 40.5, 33.3, 30.4, 30.1, 21.8. HRMS (ESI) calcd. for $C_{15}H_{20}Br_2NO_2S$ $(M + H)^+$ 437.9556, found 437.9544.

4,4-Dibromo-2-cyclohexyl-1-tosylpiperidine (3au):



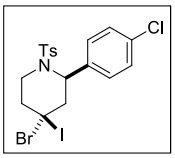
Colorless gum; R_f (hexane/EtOAc, 9:1) 0.51; yield 175 mg, 61%; IR (KBr, neat) ν 2926, 1599, 1494, 1342, 1156, 658, 612 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 3.73 – 3.63 (m, 2 H), 3.35 – 3.28 (m, 1 H), 3.03 (dt, *J* = 15.3, 1.9 Hz, 1 H), 2.53 – 2.44 (m, 2 H), 2.43 (s, 3 H), 2.37 – 2.33 (m, 1 H), 2.31 – 2.25 (m, 1 H), 1.96 – 1.91 (m, 1 H), 1.79 – 1.70 (m, 3 H), 1.66 – 1.58 (m, 2 H), 1.15 – 1.07 (m, 2 H), 0.86 – 0.72 (m, 2 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 143.9, 138.1, 130.1, 127.4, 62.3, 60.6, 47.6, 45.1, 40.4, 36.2, 31.1, 30.3, 26.3, 26.2, 26.0, 21.8. HRMS (ESI) calcd. for $C_{18}H_{26}Br_2NO_2S$ $(M + H)^+$ 480.0026, found 480.0025.

4-Bromo-4-chloro-2-(p-tolyl)-1-tosylpiperidine (diastereomers, 9:1) (3dj):



Colorless solid; Rf (hexane/EtOAc, 9:1) 0.51; mp 102 °C, yield 204 mg, 77%; IR (KBr, neat) ν 2924, 1597, 1512, 1344, 1154, 734, 660, 556 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2 H, major), 7.46 (d, *J* = 8.4 Hz, 2 H, minor), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.08 – 7.01 (m, 4 H), 4.86 (t, *J* = 5.3 Hz, 1 H, major), 4.67 (dd, *J* = 7.4, 4.5 Hz, 1 H, minor), 3.84 – 3.77 (m, 1 H), 3.67 – 3.61 (m, 1 H), 3.13 – 3.08 (m, 1 H), 2.77 – 2.72 (m, 1 H), 2.56 – 2.49 (m, 2 H), 2.42 (s, 3 H), 2.30 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 143.8, 137.3, 136.9, 134.7, 129.8, 129.1, 127.5, 127.1, 76.0, 74.7, 58.6, 58.1, 51.0, 46.5, 46.4, 43.7, 42.8, 21.8, 21.2. HRMS (ESI) calcd. for $C_{19}H_{22}BrClNO_2S$ $(M + H)^+$ 442.0238, found 442.0227.

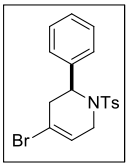
4-Bromo-2-(4-chlorophenyl)-4-iodo-1-tosylpiperidine (diastereomers, 9:1) (3ed):



Colorless gum; R_f (hexane/EtOAc, 9:1) 0.52; yield 202 mg, 61%; IR (KBr, neat) ν 2925, 1597, 1491, 1343, 1161, 712, 666, 551 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.6 Hz, 2 H, minor), 7.50 (d, *J* = 8.2 Hz, 2 H,

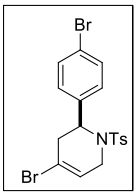
minor), 7.41 (d, *J* = 8.2 Hz, 2 H, major), 7.22 (d, *J* = 8.1 Hz, 2 H, major), 7.17 (d, *J* = 8.6 Hz, 2 H), 7.10 (d, *J* = 8.6 Hz, 2 H), 4.60 (dd, *J* = 5.5, 5.5 Hz, 1 H, minor), 4.52 (dd, *J* = 8.0, 4.1 Hz, 1 H, major), 3.66 – 3.60 (m, 1 H), 3.45 – 3.41 (m, 1 H), 3.17 (dd, *J* = 14.8, 7.9 Hz, 1 H), 2.89 – 2.82 (m, 1 H), 2.76 – 2.71 (m, 1 H), 2.65 – 2.59 (m, 1 H), 2.42 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 144.0, 136.0, 135.8, 133.9, 129.7, 129.6, 128.5, 127.7, 59.4, 56.0, 50.3, 50.0, 45.4, 45.1, 29.3, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}BrClINO_2S$ $(M + H)^+$ 553.9048, found 553.9027.

4-Bromo-2-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine (4aa):



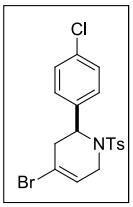
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.52; mp 116 °C, yield 157 mg, 67%; IR (KBr, neat) ν 2926, 2851, 1663, 1597, 1493, 1441, 1343, 1160, 1093, 1011, 912, 811, 731, 571, 492, 444 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2 H), 7.32 – 7.28 (m, 7 H), 5.92 (s, 1 H), 5.30 (d, *J* = 5.9 Hz, 1 H), 4.17 – 4.12 (m, 1 H), 3.34 (dt, *J* = 18.5, 2.1 Hz, 1 H), 2.74 – 2.68 (m, 2 H), 2.44 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 143.9, 138.0, 137.5, 130.0, 128.9, 128.2, 127.4, 127.2, 125.1, 118.5, 54.8, 42.6, 35.9, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}BrNO_2S$ $(M + H)^+$ 392.0315, found 392.0307.

4-Bromo-2-(4-chlorophenyl)-1-tosyl-1,2,3,6-tetrahydropyridine (4ac):



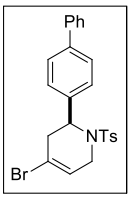
Brown gum; R_f (hexane/EtOAc, 9:1) 0.54; yield 176 mg, 69%; IR (KBr, neat) ν 2925, 2852, 1660, 1597, 1493, 1443, 1346, 1160, 1093, 1015, 911, 814, 733, 711, 654, 573, 491, 444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2 H), 7.31 – 7.28 (m, 4 H), 7.25 – 7.24 (m, 2 H), 5.93 – 5.92 (m, 1 H), 5.26 (t, *J* = 3.9 Hz, 1 H), 4.14 (dd, *J* = 18.6, 4.7 Hz, 1 H), 3.32 (dq, *J* = 18.4, 3.0 Hz, 1 H), 2.70 – 2.68 (m, 2 H), 2.44 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 144.1, 137.3, 136.5, 134.1, 130.1, 129.1, 128.9, 127.2, 125.2, 118.1, 54.2, 42.6, 35.8, 21.8. HRMS (ESI) calcd. for $C_{18}H_{18}BrClNO_2S$ $(M + H)^+$ 425.9925, found 425.9899.

4-Bromo-2-(4-bromophenyl)-1-tosyl-1,2,3,6-tetrahydropyridine (4ad):



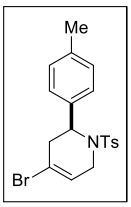
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.54; mp 119 °C, yield 198 mg, 70%; IR (KBr, neat) ν 2922, 2851, 1660, 1596, 1489, 1442, 1344, 1159, 1095, 909, 814, 708, 696, 544, 481, 410 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.68 (m, 2 H), 7.45 – 7.42 (m, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 5.93 – 5.91 (m, 1 H), 5.24 (t, *J* = 3.9 Hz, 1 H), 4.17 – 4.11 (m, 1 H), 3.35 – 3.28 (m, 1 H), 2.70 – 2.68 (m, 2 H), 2.44 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.1, 137.3, 137.0, 132.0, 130.1, 129.2, 127.2, 125.2, 122.3, 118.1, 54.2, 42.6, 35.7, 21.8. HRMS (ESI) calcd. for $C_{18}H_{18}Br_2NO_2S$ $(M + H)^+$ 471.9400, found 471.9387.

2-([1,1'-Biphenyl]-4-yl)-4-bromo-1-tosyl-1,2,3,6-tetrahydropyridine (4ai):



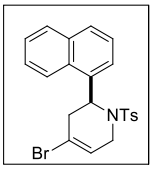
Brown solid; R_f (hexane/EtOAc, 9:1) 0.55; mp 114 °C, yield 154 mg, 55%; IR (KBr, neat) ν 3030, 2922, 2851, 1658, 1598, 1442, 1344, 1159, 1094, 1008, 909, 814, 766, 720, 658, 568, 543 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2 H), 7.58 – 7.54 (m, 4 H), 7.46 – 7.42 (m, 2 H), 7.40 – 7.35 (m, 3 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 5.96 – 5.95 (m, 1 H), 5.35 – 5.33 (m, 1 H), 4.20 – 4.14 (m, 1 H), 3.44 – 3.38 (m, 1 H), 2.83 – 2.70 (m, 2 H), 2.44 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.9, 141.1, 140.6, 137.5, 137.0, 130.0, 129.1, 127.9, 127.7, 127.6, 127.3, 127.2, 125.2, 118.4, 54.6, 42.7, 35.9, 21.8. HRMS (ESI) calcd. for $C_{24}H_{23}BrNO_2S$ $(M + H)^+$ 468.0628, found 468.0603.

4-Bromo-2-(p-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridine (4aj):



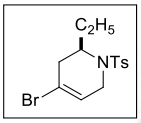
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.54; mp 144 °C, yield 170 mg, 70%; IR (KBr, neat) ν 2922, 1659, 1597, 1514, 1345, 1159, 1095, 909, 813, 725, 657, 575, 550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 8.1 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 5.92 – 5.89 (m, 1 H), 5.26 (d, *J* = 5.7 Hz, 1 H), 4.16 – 4.09 (m, 1 H), 3.37 – 3.30 (m, 1 H), 2.72 – 2.66 (m, 2 H), 2.44 (s, 3 H), 2.32 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.8, 138.0, 137.6, 134.9, 130.0, 129.5, 127.3, 127.2, 125.1, 118.6, 54.5, 42.5, 35.9, 21.8, 21.3. HRMS (ESI) calcd. for $C_{18}H_{21}BrNO_2S$ $(M + H)^+$ 406.0471, found 406.0470.

4-Bromo-2-(naphthalen-1-yl)-1-tosyl-1,2,3,6-tetrahydropyridine (4ao):



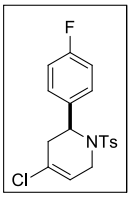
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.52; mp 146 °C, yield, 164 mg, 62%; IR (KBr, neat) ν 3051, 2924, 1656, 1598, 1511, 1439, 1340, 1317, 1159, 1092, 1049, 779, 717, 664, 572, 542 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.6 Hz, 1 H), 7.79 (d, *J* = 8.2 Hz, 1 H), 7.76 – 7.74 (m, 1 H), 7.69 (d, *J* = 7.9 Hz, 2 H), 7.55 (t, *J* = 7.8 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.32 – 7.29 (m, 2 H), 7.20 (d, *J* = 8.1 Hz, 2 H), 6.03 (d, *J* = 7.2 Hz, 1 H), 5.88 (s, 1 H), 3.93 (dd, *J* = 17.5, 4.3 Hz, 1 H), 3.13 (d, *J* = 19.3 Hz, 1 H), 2.90 – 2.84 (m, 1 H), 2.70 (d, *J* = 18.4 Hz, 1 H), 2.36 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 144.2, 136.8, 134.3, 133.3, 131.7, 129.9, 129.8, 128.9, 127.9, 127.1, 126.3, 125.4, 124.9, 124.5, 124.4, 119.5, 52.0, 42.8, 36.5, 21.8. HRMS (ESI) calcd. for $C_{22}H_{21}BrNO_2S$ $(M + H)^+$ 442.0471, found 442.0446.

4-Bromo-2-ethyl-1-tosyl-1,2,3,6-tetrahydropyridine (4aq):



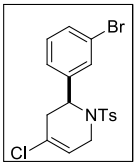
Pale yellow gum; R_f (hexane/EtOAc, 9:1) 0.54; yield 128 mg, 62%; IR (KBr, neat) ν 2968, 2933, 2876, 1654, 1598, 1494, 1454, 1335, 1266, 1155, 1092, 1042, 951, 882, 814, 717, 648, 540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 5.96 – 5.94 (m, 1 H), 4.22 – 4.17 (m, 1 H), 3.80 – 3.75 (m, 1 H), 3.20 – 3.12 (m, 1 H), 2.35 (s, 3 H), 2.09 – 1.96 (m, 2 H), 1.59 – 1.51 (m, 2 H), 0.91 (t, *J* = 7.4 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 143.7, 138.1, 129.9, 129.2, 127.1, 119.5, 57.3, 39.7, 32.9, 27.9, 21.7, 10.9. HRMS (ESI) calcd. for $C_{14}H_{19}BrNO_2S$ $(M + H)^+$ 344.0315, found 344.0316.

4-Chloro-2-(4-fluorophenyl)-1-tosyl-1,2,3,6-tetrahydropyridine (4db):



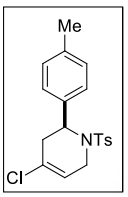
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.55; mp 77 °C, yield, 151 mg, 69%; IR (KBr, neat) ν 2962, 1603, 1510, 1343, 1159, 1484, 1442, 1093, 740, 661, 484, 403 cm−1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2 H), 7.31 – 7.27 (m, 4 H), 7.02 – 6.98 (m, 2 H), 5.72 – 5.70 (m, 1 H), 5.31 (d, *J* = 6.1 Hz, 1 H), 4.22 – 4.16 (m, 1 H), 3.37 – 3.31 (m, 1 H), 2.67 – 2.56 (m, 2 H), 2.43 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.5 (d, *J* = 245.7 Hz), 144.0, 137.4, 133.8 (d, *J* = 3.2 Hz), 130.1, 129.2 (d, *J* = 8.2 Hz), 129.0, 127.2, 121.1, 115.7 (d, *J* = 21.2 Hz), 53.4, 41.4, 33.9, 21.8. ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$) δ -114.01. HRMS (ESI) calcd. for $C_{18}H_{18}ClFNO_2S$ $(M + H)^+$ 366.0726, found 366.0708.

2-(3-Bromophenyl)-4-chloro-1-tosyl-1,2,3,6-tetrahydropyridine (4de):



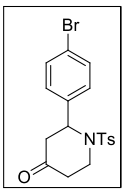
Colorless solid; R_f (hexane/EtOAc, 9:1) 0.54; mp 118 °C, yield 156 mg, 61%; IR (KBr, neat) ν 2924, 1659, 1596, 1488, 1441, 1344, 1159, 1093, 906, 814, 707, 481, 409 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 2 H), 7.40 (d, *J* = 7.9 Hz, 1 H), 7.35 (s, 1 H), 7.30 (d, *J* = 7.9 Hz, 2 H), 7.24 (d, *J* = 7.8 Hz, 1 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 5.73 (s, 1 H), 5.29 (d, *J* = 6.4 Hz, 1 H), 4.23 (d, *J* = 18.2 Hz, 1 H), 3.41 – 3.36 (m, 1 H), 2.67 – 2.61 (m, 1 H), 2.56 (d, *J* = 17.7 Hz, 1 H), 2.44 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 144.1, 140.4, 137.3, 131.4, 130.6, 130.5, 130.1, 128.8, 127.2, 125.9, 123.0, 121.0, 53.7, 41.6, 33.9, 21.8. HRMS (ESI) calcd. for $C_{18}H_{18}BrClNO_2S$ $(M + H)^+$ 425.9925, found 425.9904.

4-Chloro-2-(p-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridine (4dj):



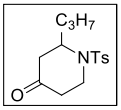
Pale yellow solid; R_f (hexane/EtOAc, 9:1) 0.53; mp 130 °C, yield 152 mg, 70%; IR (KBr, neat) ν 2923, 1658, 1597, 1514, 1342, 1159, 1095, 906, 811, 575, 551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2 H), 7.28 (d, *J* = 7.9 Hz, 2 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 5.69 – 5.67 (m, 1 H), 5.31 – 5.29 (m, 1 H), 4.20 – 4.14 (m, 1 H), 3.40 – 3.33 (m, 1 H), 2.61 – 2.58 (m, 2 H), 2.43 (s, 3 H), 2.32 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 143.8, 137.9, 137.6, 135.0, 130.0, 129.5, 129.3, 127.3, 127.2, 121.0, 53.8, 41.5, 33.9, 21.8, 21.3. HRMS (ESI) calcd. for $C_{19}H_{21}ClNO_2S$ $(M + H)^+$ 362.0977, found 362.0953.

2-(4-Bromophenyl)-1-tosylpiperidin-4-one (5a):



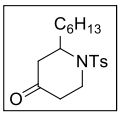
Brown solid; R_f (hexane/EtOAc, 4:1) 0.48; mp 113 °C, yield 72 mg, 80%; IR (KBr, neat) ν 2924, 1721, 1596, 1339, 1153, 1091, 1009, 930, 815, 709, 548 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2 H), 7.42 (d, *J* = 8.5 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.12 (d, *J* = 8.3 Hz, 2 H), 5.56 (d, *J* = 7.0 Hz, 1 H), 4.04 – 3.98 (m, 1 H), 3.16 – 3.08 (m, 1 H), 2.88 – 2.84 (m, 1 H), 2.68 (dd, *J* = 15.3, 7.0 Hz, 1 H), 2.45 (s, 3 H), 2.42 – 2.38 (m, 1 H), 2.26 – 2.21 (m, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 206.2, 144.5, 137.6, 137.4, 132.2, 130.4, 129.3, 127.3, 122.5, 56.2, 43.4, 40.6, 40.4, 21.8. HRMS (ESI) calcd. for $C_{18}H_{19}BrNO_3S$ $(M + H)^+$ 408.0264, found 408.0235.

2-Propyl-1-tosylpiperidin-4-one (5b)[13]:



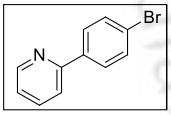
Brown oil; R_f (hexane/EtOAc, 4:1) 0.47; yield 49 mg, 75%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 2 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 4.42 – 4.37 (m, 1 H), 4.15 – 4.10 (m, 1 H), 3.30 – 3.23 (m, 1 H), 2.55 – 2.51 (m, 1 H), 2.43 (s, 3 H), 2.41 – 2.36 (m, 1 H), 2.22 (d, *J* = 14.3 Hz, 2 H), 1.39 – 1.32 (m, 2 H), 1.26 – 1.22 (m, 2 H), 0.85 (q, *J* = 7.2, 3 H).^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 206.9, 144.1, 137.8, 130.2, 127.3, 54.6, 45.6, 40.5, 40.3, 34.6, 21.8, 19.3, 13.7.

2-Hexyl-1-tosylpiperidin-4-one (5c)[13]:



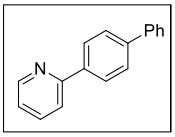
Colorless oil; R_f (hexane/EtOAc, 4:1) 0.46; yield 49 mg, 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 4.39 – 4.33 (m, 1 H), 4.18 – 4.12 (m, 1 H), 3.29 – 3.22 (m, 1 H), 2.54 (dd, *J* = 14.3, 6.5 Hz, 1 H), 2.43 (s, 3 H), 2.41 – 2.36 (m, 1 H), 2.25 – 2.21 (m, 2 H), 1.41 – 1.33 (m, 3 H), 1.22 – 1.15 (m, 7 H), 0.85 (t, *J* = 7.0 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 207.0, 144.0, 137.8, 130.2, 127.3, 54.9, 45.7, 40.6, 40.2, 32.4, 31.8, 28.9, 26.0, 22.7, 21.8, 14.3.

2-(4-Bromophenyl)pyridine (6a):



Colorless gum; R_f (hexane/EtOAc, 9:1) 0.53; yield 38 mg, 74%; IR (KBr, neat) ν 3052, 3008, 2924, 1586, 1463, 1432, 1393, 1153, 1070, 1006, 839, 771 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.8 Hz, 1 H), 7.90 (d, *J* = 8.3 Hz, 2 H), 7.81 – 7.78 (m, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 8.2 Hz, 2 H), 7.30 – 7.28 (m, 1 H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 156.5, 149.9, 138.4, 137.2, 132.2, 128.7, 123.8, 122.7, 120.6. HRMS (ESI) calcd. for $C_{11}H_9BrN$ $(M + H)^+$ 233.9913, found 233.9909.

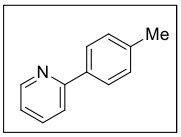
2-([1,1'-Biphenyl]-4-yl)pyridine (6b)[13]:



Yellow solid; R_f (hexane/EtOAc, 9:1) 0.53; mp 133 °C, yield 33 mg, 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (dt, *J* = 4.8, 1.5 Hz, 1 H), 8.10 – 8.06 (m, 2 H), 7.79 – 7.77 (m, 2 H), 7.73 – 7.71 (m, 2 H), 7.67 – 7.65 (m, 2 H), 7.49 – 7.45 (m, 2 H), 7.39 – 7.35 (m, 1 H), 7.26 – 7.24 (m, 1 H). ^{13}C{^{1}H} NMR (100 MHz,

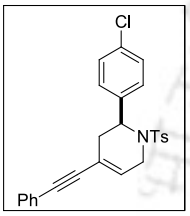
$CDCl_3$) δ 157.2, 149.8, 142.0, 140.8, 138.3, 137.2, 129.1, 127.8, 127.7, 127.6, 127.3, 122.4, 120.8.

2-(p-Tolyl)pyridine (6c)[13]:



Colorless oil; R_f (hexane/EtOAc, 9:1) 0.53; yield 26 mg, 70%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (t, *J* = 4.1 Hz, 1 H), 7.90 – 7.88 (m, 2 H), 7.74 – 7.70 (m, 2 H), 7.30 – 7.26 (m, 2 H), 7.22–7.20 (m, 1 H), 2.41 (s, 3 H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.7, 149.7, 139.3, 137.0, 136.7, 129.7, 127.0, 122.1, 120.6, 21.5.

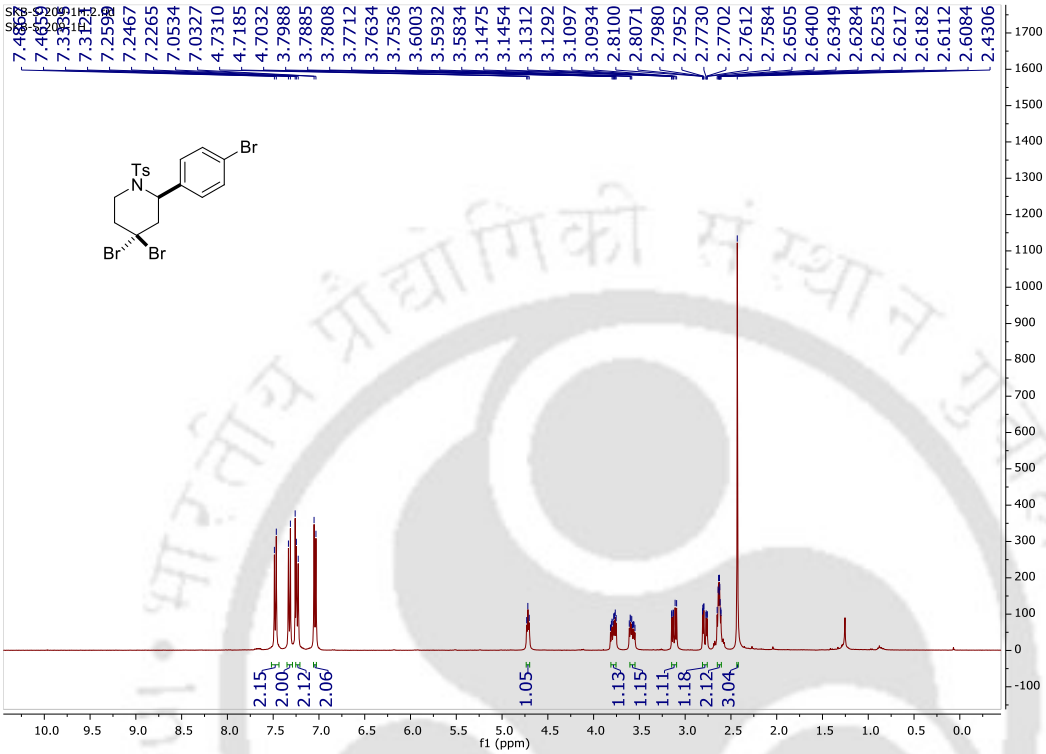
2-(4-Chlorophenyl)-4-(phenylethynyl)-1-tosyl-1,2,3,6-tetrahydropyridine (7):

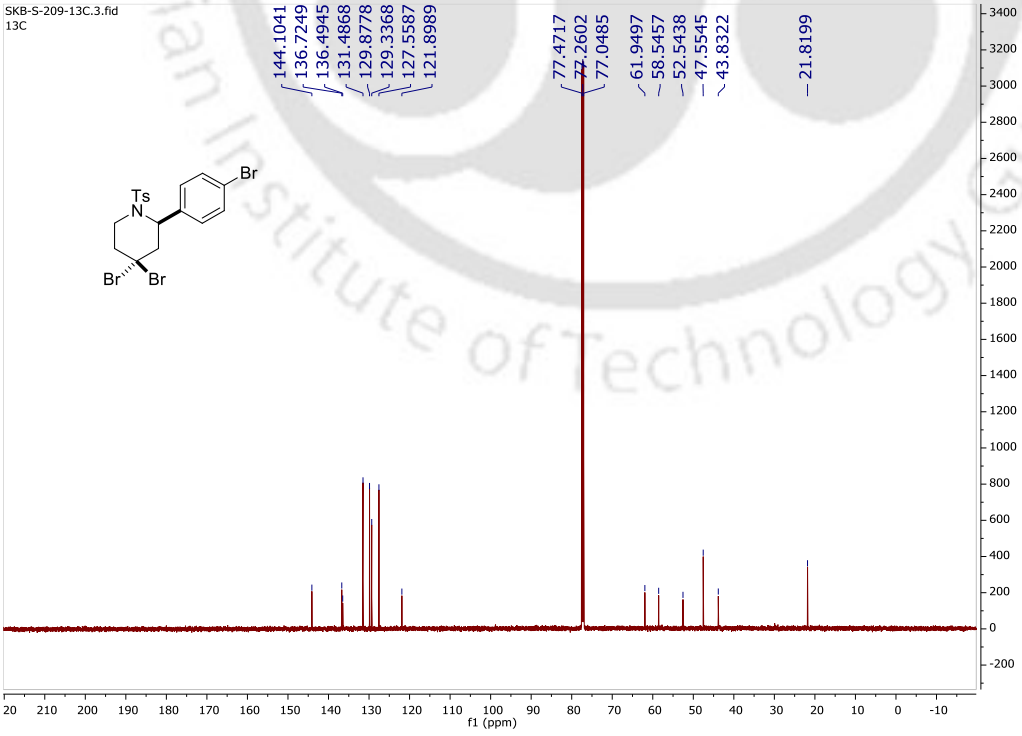


Pale yellow gum; R_f (hexane/EtOAc, 9:1) 0.32; yield 88 mg, 82%; IR (KBr, neat) ν 2921, 2851, 2278, 1659, 1597, 1493, 1441, 1344, 1160, 1093, 1012, 911, 812, 733, 491 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.61 (m, 2 H), 7.35 – 7.32 (m, 2 H), 7.24 – 7.19 (m, 9 H), 5.92 – 5.90 (m, 1 H), 5.24 (dd, *J* = 5.8, 2.0 Hz, 1 H), 4.20 – 4.13 (m, 1 H), 3.43 – 3.36 (m, 1 H), 2.54 – 2.46 (m, 2 H), 2.34 (s, 3 H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 143.8, 137.5, 137.1, 133.8, 131.7, 130.0, 129.5, 129.0, 128.9, 128.7, 128.6, 127.1, 122.9, 118.2, 89.6, 88.8, 52.4, 41.4, 30.5, 21.8. HRMS (ESI) calcd. for $C_{26}H_{22}ClNNaO_2S$ $(M + Na)^+$ 470.0952, found 470.0925.

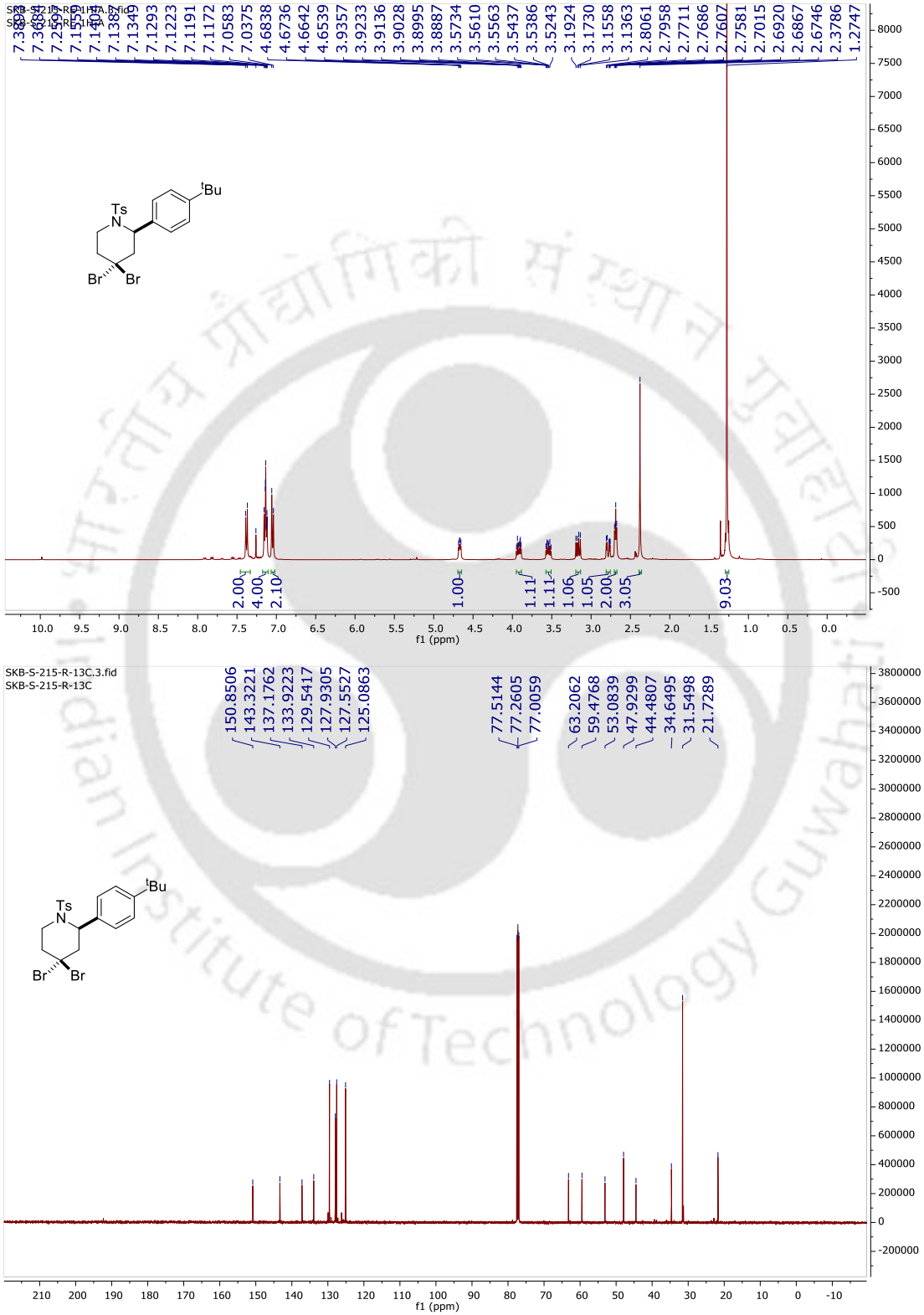
5.6.8 Representative Spectra and crystal parameter

^{1}H(400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (150 MHz, $CDCl_3$) spectra of **3ad**

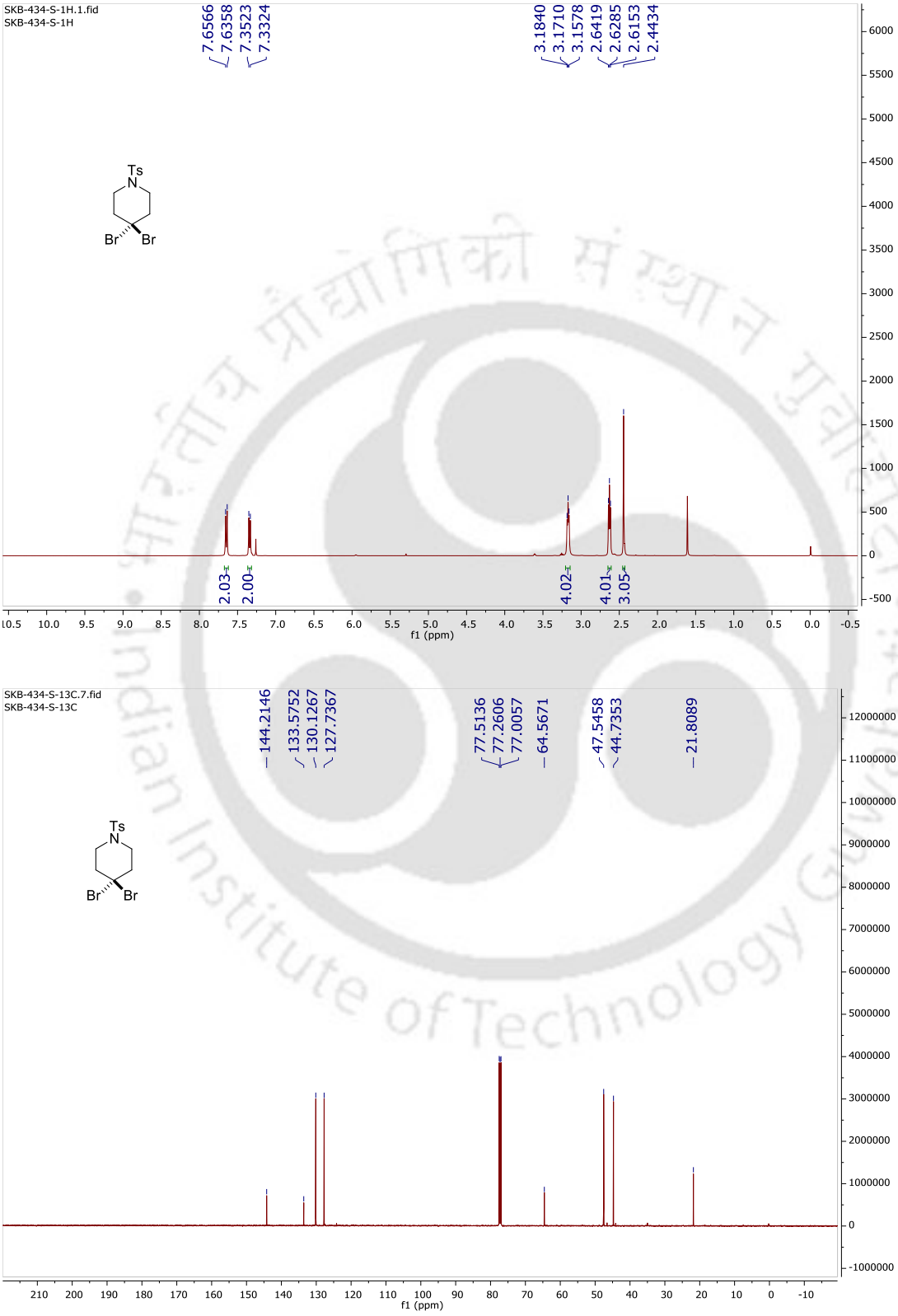




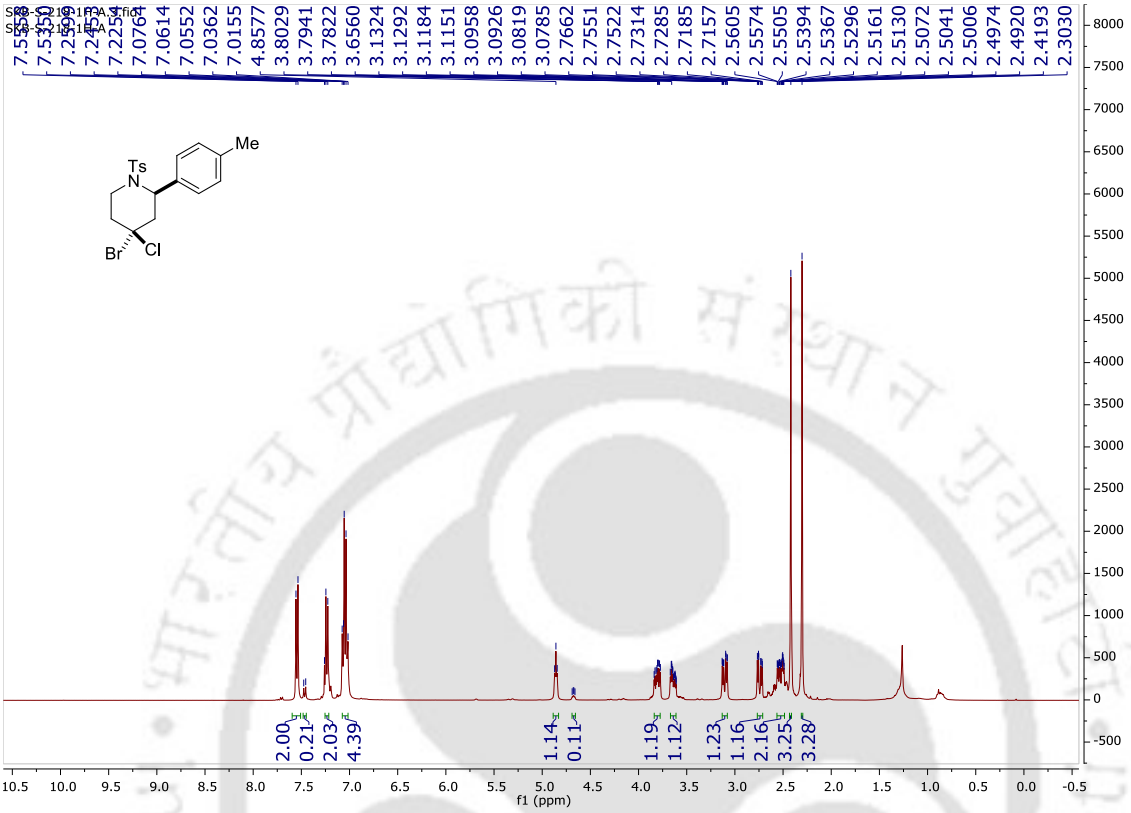
^{1}H (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **3al**

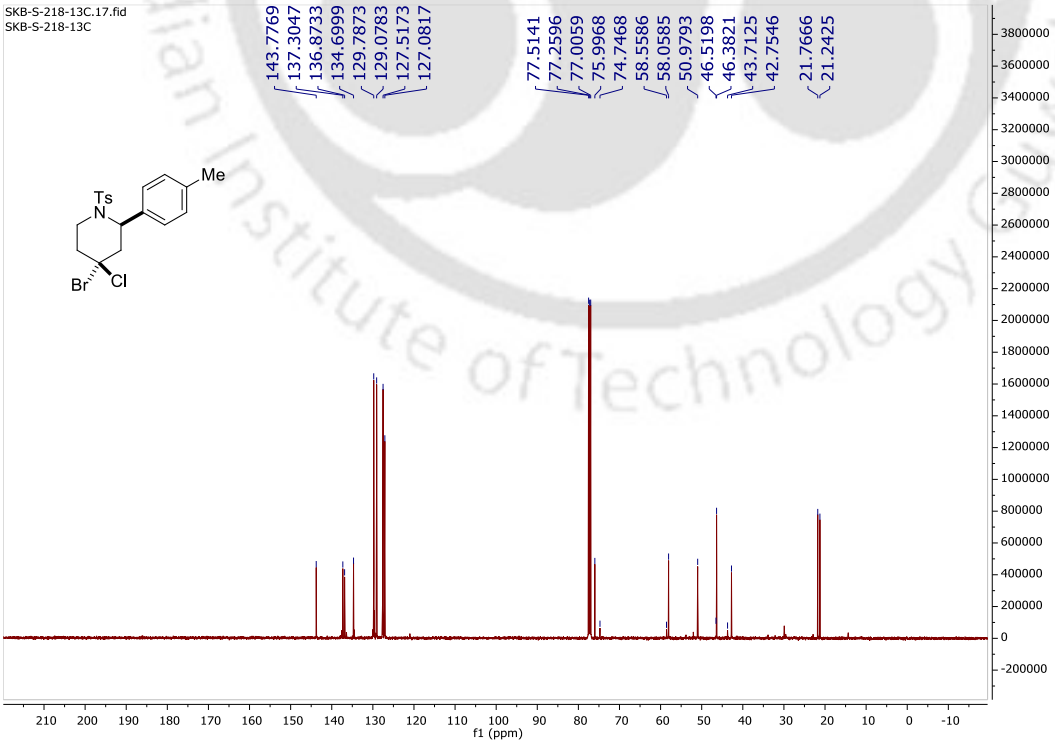


^{1}H (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **3ap**

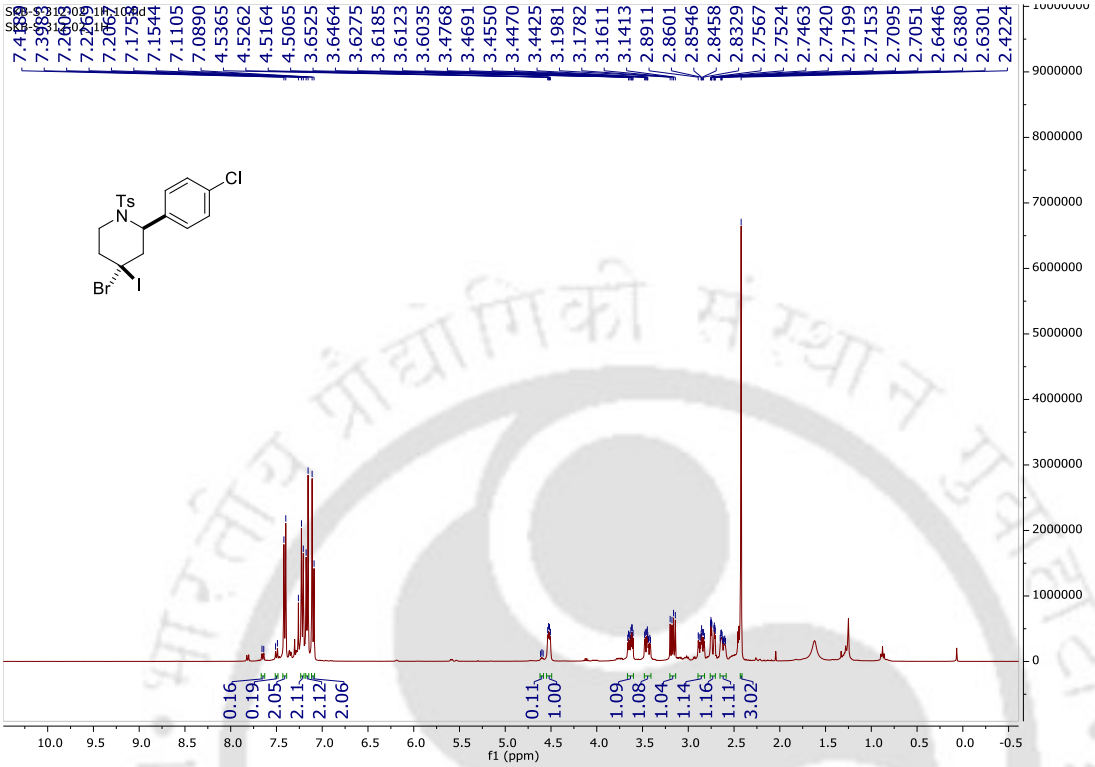


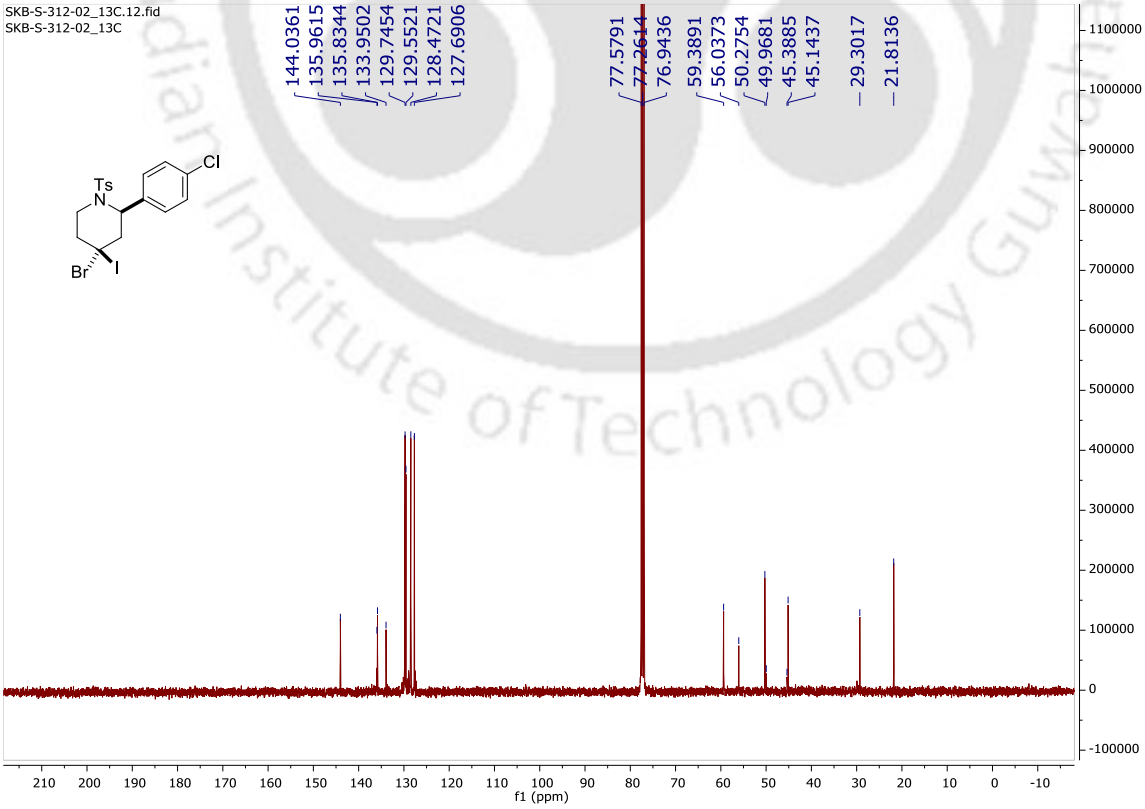
^{1}H (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **3dj**



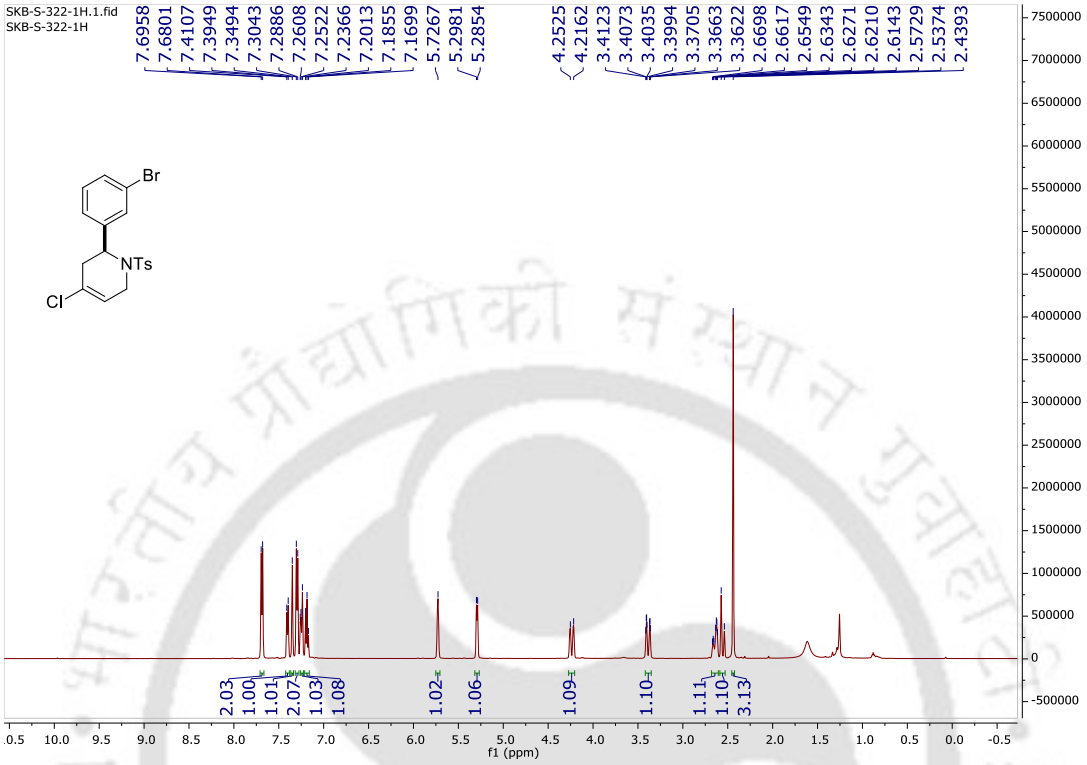


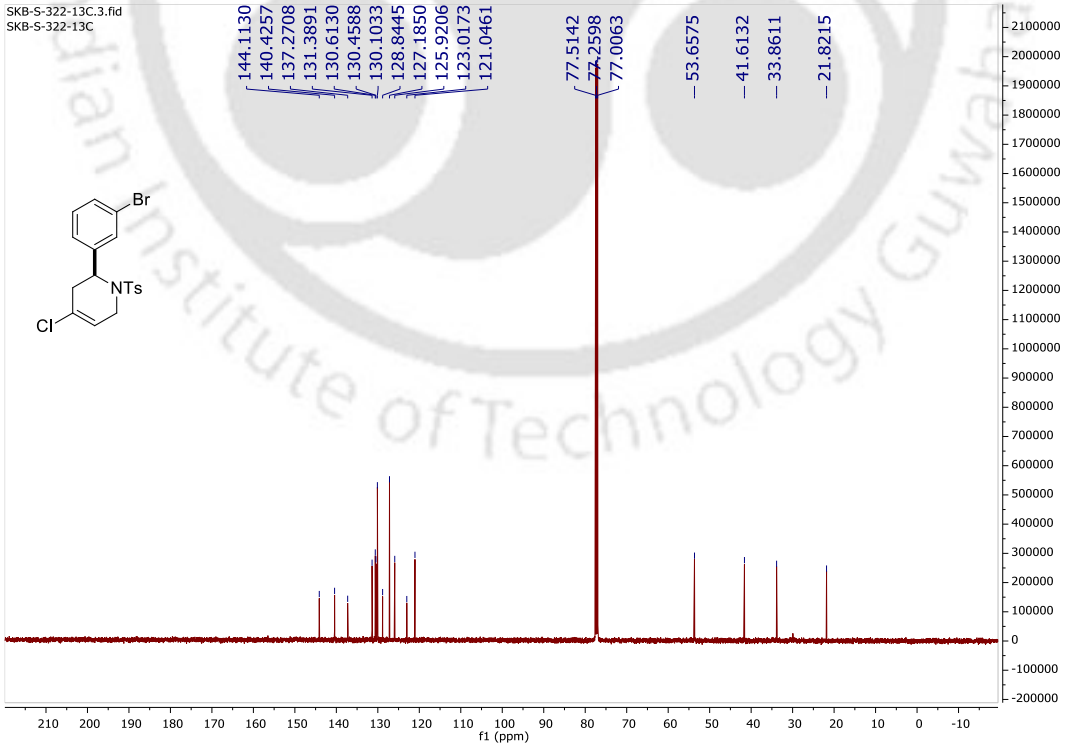
^{1}H (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100 MHz, $CDCl_3$) spectra of **3ed**





^{1}H (500 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) spectra of **4ce**

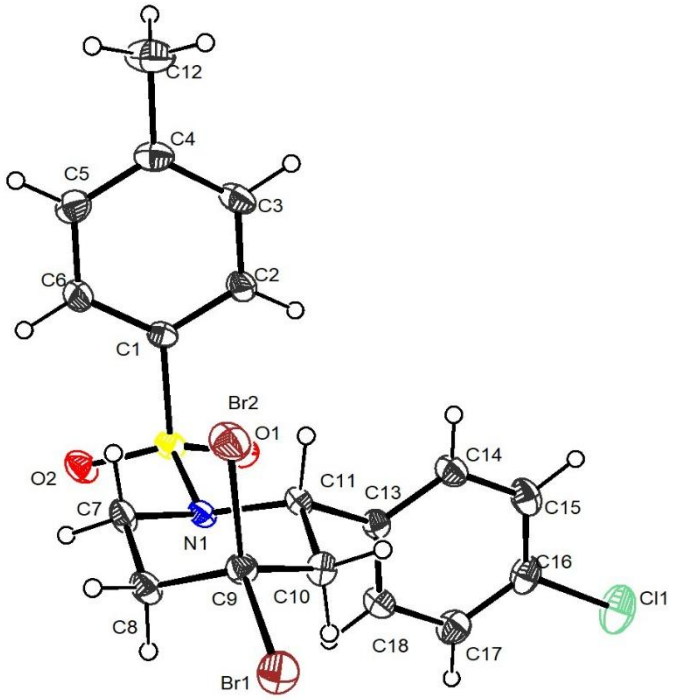




The crystal parameters of compound 3ac

	CCDC 2429152
Formula	$C_{18}H_{18}Br_2ClNO_2S$
Formula weight	507.66
T/K	293(2)
Crystal system	Monoclinic
Space group	P 21/c
a/Å	11.4025(12)
b/Å	15.3012(15)
c/Å	11.8426(12)
α/°	90
β/°	112.487(4)
γ/°	90
V/Å^3	1909.1(3)
Z	4
Abs. Coeff./mm^{-1}	4.507
Abs. Correction	none
GOF on F^2	1.058
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0299 *wR2* = 0.0688
R indices [all data]	*R1* = 0.0406 *wR2* = 0.0726

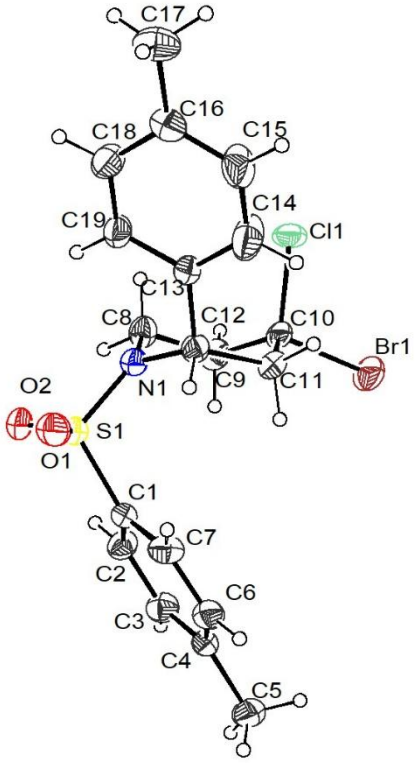
ORTEP diagram of compound **3ac** with 30% probability



The crystal parameters of compound 3dj

	CCDC 2431627
Formula	$C_{19}H_{21}BrClNO_2S$
Formula weight	442.79
T/K	295.00
Crystal system	monoclinic
Space group	Cc
• *a*/Å	20.319(4)
• *b*/Å	10.440(2)
• *c*/Å	9.3782(19)
• *α*/°	90
• *β*/°	100.424(6)
• *γ*/°	90
• *V*/Å^3	1956.6(7)
• Z	4
Abs. Coeff./mm^{-1}	2.356
Abs. Correction	'none'
GOF on F^2	1.025
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0534 *wR2* = 0.1373
R indices [all data]	*R1* = 0.0649 *wR2* = 0.1460

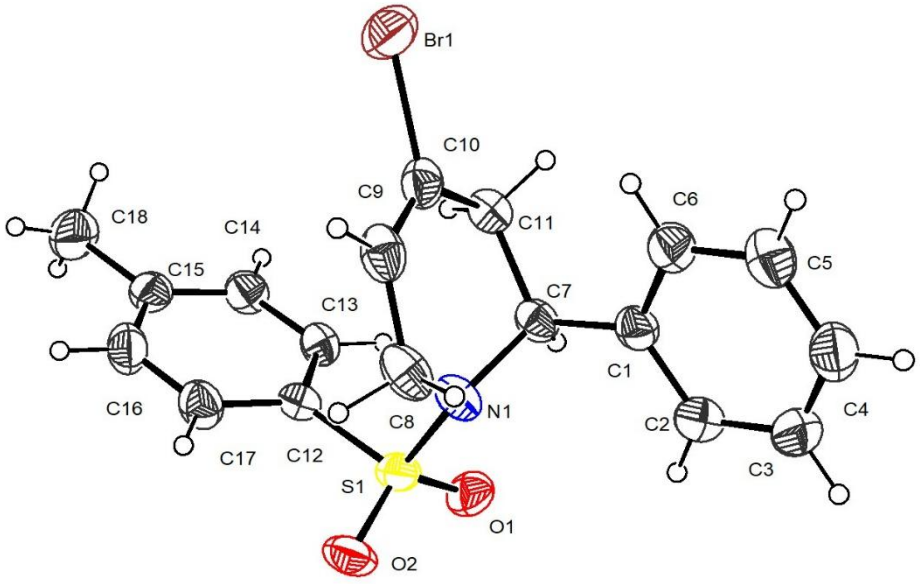
ORTEP diagram of compound **3dj** with 30% probability



The crystal parameters of compound 4aa

	CCDC 2429151
Formula	$C_{18}H_{18}BrNO_2S$
Formula weight	392.30
T/K	295(2)
Crystal system	monoclinic
Space group	P21/c
• *a*/Å	11.378(2)
• *b*/Å	8.0513(15)
• *c*/Å	19.674(4)
• *α*/°	90
• *β*/°	106.635(5)
• *γ*/°	90
• *V*/Å^3	1726.9(5)
• Z	4
Abs. Coeff./mm^{-1}	2.510
Abs. Correction	'none'
GOF on F^2	1.023
Final *R* indices [*I*> 2σ(I)]	R_1 = 0.0493 *wR2* = 0.1183
R indices [all data]	*R1* = 0.0863 *wR2* = 0.1373

ORTEP diagram of compound **4aa** with 30% probability



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List of Publications

1. Diastereoselective Synthesis of 2,6-Disubstituted Tetrahydropyranones *via* Prins Cyclization of 3-Bromobut-3-en-1-ols and Aldehydes.

   Bora, S. K.; Shit, S.; Sahu, A. K.; Saikia, A. K. *J. Org. Chem*. **2023**, *88*, 3012.

2. Stereoselective Synthesis of *gem*-Dihalopiperidines *via* the Halo-aza-Prins Cyclization Reaction: Access to Piperidin-4-ones and Pyridines.

   Bora, S. K.; Biswas, S.; Behera, B. K.; Saikia, A. K. *Org. Biomol. Chem*. **2024**, *22*, 3893.

3. $BF_3.OEt_2$ Mediated Cascade Synthesis of 4*H*-3,1-Benzoxazines from 2-Azidobenzaldehydes and Homoallylic Alcohols.

   Bora, S. K.; Medhi, B.; Sarma, M.; Saikia, A. K. *J. Org. Chem.* ***2025***, *90,* *6443−6453.*

4. Selective Synthesis of *gem*-Dihalopiperidines and 4-Halo-1,2,3,6-tetrahydropyridines from Halogen Substituted Homoallylic Benzenesulfonamide and Aldehyde.

   Bora, S. K.; Saikia, A. K. *RSC Adv.* **2025**, *15*, 21257.

5. Synthesis of 3C-Alkylated Active Methylene Substituted 2*H*-Indazole Derivatives *via* Sequential Ring Opening of Donor–Acceptor Cyclopropanes and Reductive Cyclization Reaction

   Sahu, A. K.; Biswas, S.; **Bora, S. K.**; Saikia, A. K. *New J. Chem*. **2022**, *46*, 12456.

6. Synthesis of Spiro[furan-2,1′-isoindolin]-3′-ones from 2-(4-Hydroxybut-1-yn-1-yl)benzonitriles and Aryl Aldehydes under the Action of Triflic Acid.

   Shit, S.; **Bora, S. K.**; Sahu, A. K.; Saikia, A. K. *J. Org. Chem*. **2022**, *87*, 11634.

7. Base-Promoted [4 + 2] Annulation Reaction of In Situ-Generated Azadienes from N-Propargylamines with Active Methylene Compounds: Access to Highly Functionalized 2-Pyridones.

   Behera, B. K.; Arandhara, P. J.; Porashar, B.; **Bora, S. K.**; Saikia, A. K. *J. Org. Chem*. **2023**, *88*, 15041−15059.

8. Regioselective Synthesis of Spiro Quinazolinones *via* Sequential Hydroalkoxylation and Intramolecular Amide-Cyclization of Alkynol Ureas.

   Biswas, S.; **Bora, S. K.**; Arandhara, P. J.; Saikia, A. K. *New J. Chem*. **2024**, *48*, 10756.