Lewis Acid-catalyzed [4+3] Cyclization of *para*-Quinone Methides and 1,3-Dipolarophiles to Construct Benzofused Seven-membered Heterocycles

M.Sc. Thesis

by

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DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY INDORE

May 2025

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A THESIS

Submitted in partial fulfillment of the
requirements for the award of the degree
of
Master of Science

by

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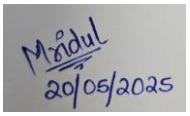
CANDIDATE'S DECLARATION

This is to certify that the work presented in this report, titled **"Lewis Acid-catalyzed [4+3] Cyclization of *para*-Quinone Methides and 1,3-Dipolarophiles to Construct Benzofused Seven-membered Heterocycles"** in the partial fulfillment of the requirements for the award of the Degree of Masters of Science and submitted to the Department of Chemistry, Indian Institute of Technology Indore, is an authentic record of my own work carried out during the period from **July 2024** to **May 2025** under the supervision of **Dr. Selvakumar Sermadurai**, Assistant professor, Department of Chemistry, IIT Indore. The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

The findings and insights documented in this report are the result of my dedicated efforts and have not been copied from any other source. Proper acknowledgment has been given wherever external ideas or contributions have been referenced.



(Mridul Shyam Singhal)
Signature of the student with date

This is to certify that the statements provided by the candidate in this document are true and accurate to the best of my knowledge and belief.

(Dr. Selvakumar Sermadurai)
Signature of Supervisor with date

Mridul Shyam Singhal has successfully given his M.Sc. Oral Examination held on **May 16, 2025**.

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Mridul Shyam Singhal

M.Sc. 2nd Year

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DEDICATED TO MY TEACHERS, FAMILY

AND

FRIENDS….

ABSTRACT

This study presents a Lewis acid-catalyzed [4+3] cyclization approach for synthesizing benzofused seven-membered heterocycles using *para*-quinone methides (*p*-QMs) and 1,3-dipolarophiles such as aziridines and donor–acceptor cyclopropanes. Various Lewis acids and conditions were screened, with yielding the desired benzoxazepine in moderate yield and good diastereoselectivity. Mechanistic insights suggest a Lewis acid-promoted *aza*-Michael addition pathway and highlight conditions leading to by-product formation. This work advances the construction of nitrogen–oxygen-containing heterocycles, offering a promising method for accessing complex scaffolds relevant to medicinal chemistry and synthetic organic applications.

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NOMENCLATURE

δ	Delta (chemical shift)
nm	Nanometer
mL	Milliliter
ppm	Parts per million
Hz	Hertz
g	Gram
mg	Milligram
K	Kelvin
℃	Degree Celsius
α	Alpha

ACRONYMS

The abbreviations used for substituents, reagents, and other terms align with the IUPAC-IUC Commission on Biochemical Nomenclature recommendations (1974, Pure and Applied Chemistry, 40, 315-331). Additional abbreviations specific to this thesis are listed below.

Ac_2O	Acetic anhydride
$CDCl_3$	Chloroform-d
d	Doublet
dd	Doublet of doublet
DMAP	Dimethylaminopyridine
DCM	Dichloromethane
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
HR-MS	High Resolution Mass Spectrometry
m	Multiplet
M.P.	Melting point
MeOH	Methanol
NMR	Nuclear magnetic resonance
p-QMs	*p*-Quinone Methides
q	Quartet
s	Singlet
Na_2SO_4	Sodium sulfate
NEt_3	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TBAF	Tetrabutylammonium fluoride

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Chapter 1

1.1. Introduction

Benzoxazepines and benzoxazines are *N*- and *O*-containing six and seven membered heterocyclic frameworks fused with benzene rings, are crucial in drug discovery due to their broad pharmacological potential, especially in cancer treatment.[3,9] These seven- and six-membered ring structures serve as essential pharmacophores and have been widely studied in pharmaceutical chemistry for their diverse biological properties. Notably, benzoxazepine-based compounds have shown efficacy in treating central nervous system disorders, exhibiting antipsychotic effects, and displaying anticancer activity, particularly against breast cancer cells.[9] Among their isomers, 1,4- and 1,5-benzoxazepines stand out due to their significant therapeutic properties.[3] Additionally, benzoxazepines and benzoxazines are adaptable components for organic synthesis, such as documented in various studies, making them valuable scaffolds in medicinal chemistry. Some important benzoxazepine-containing bioactive drugs are shown in the figure below.[3]

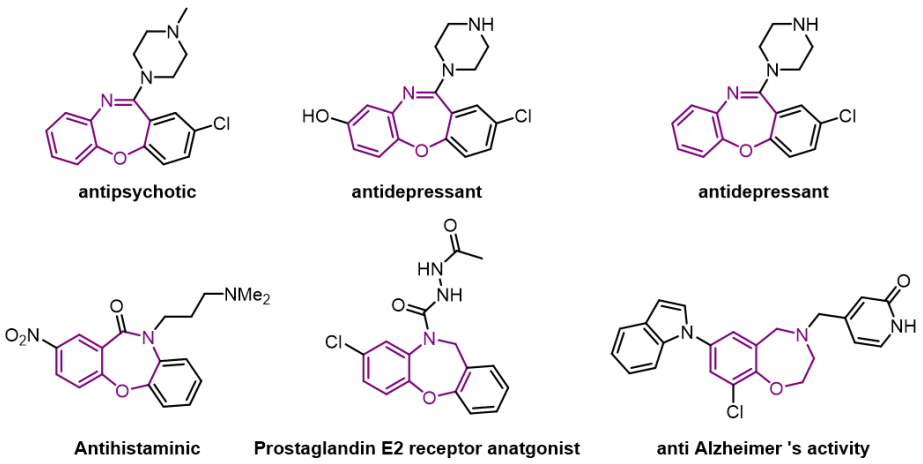
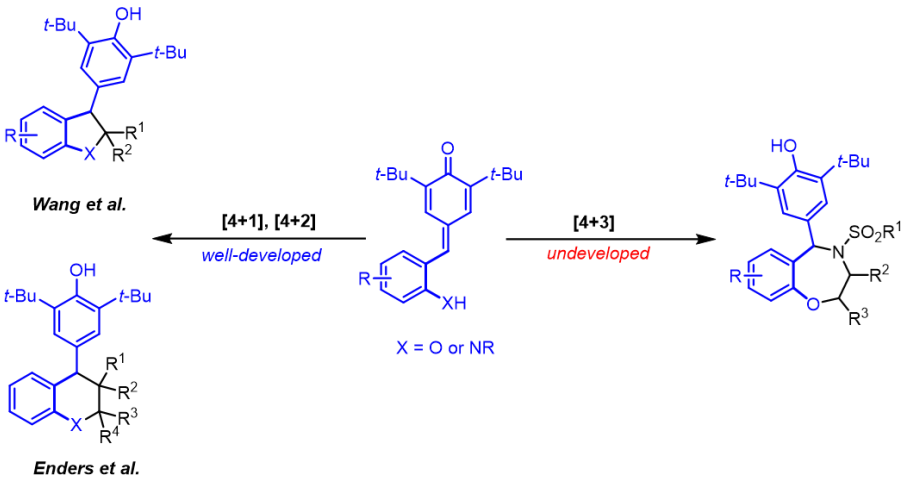


Figure 1: Biological active 1,4-benzoxazepine compounds[3,9]

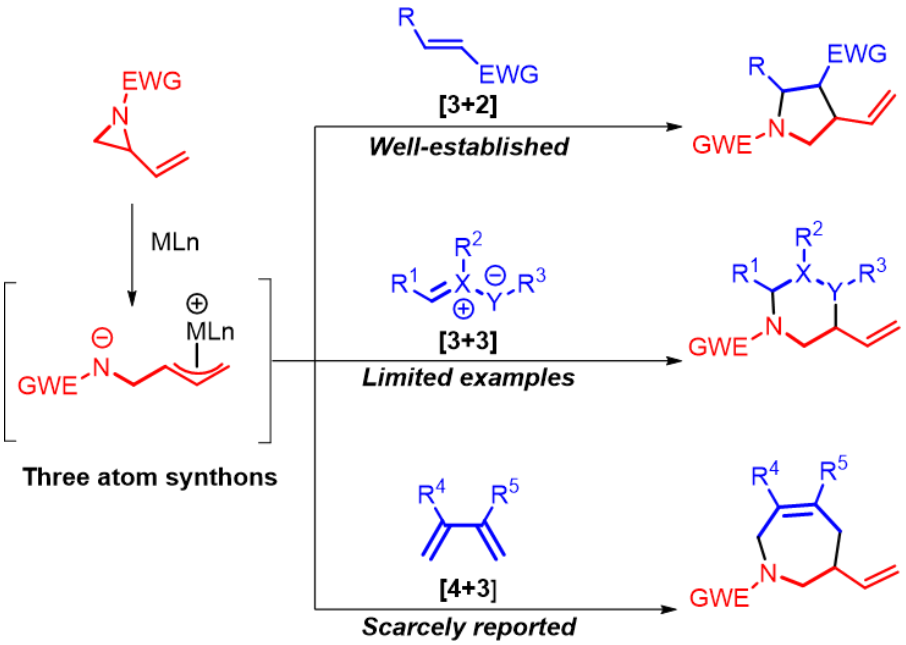
Building on these advances, the development of seven-membered benzo fused frameworks, particularly 1,4-benzoxazepines, through cycloaddition reactions has garnered significant attention. Cycloaddition methods, especially [4+3] cyclizations, are less frequently explored for synthesizing seven-membered heterocyclic rings due to inherent challenges such as unfavourable entropy and transannular strain.[2] Nonetheless, 2-hydroxyphenyl-substituted *para*-Quinone Methides (*p*-QMs) have proven to be proficient four-atom synthons, allowing controlled formation of diverse structures.[1,3,9] Following Enders et al [4+2] cycloaddition using these *p*-QMs and isatin-derived enoates to generate chroman derivatives, researchers have progressively applied these methods to other cycloaddition strategies, achieving notable success with [4+1] and [4+2] processes.[2] Inspite of the challenges, innovative approaches continue to make seven-membered rings more accessible for synthesis, further expanding their potential in medicinal applications.[9]



Scheme 1: Profile of cycloaddition reactions involving *p*-QMs derivatives[2]

The unique reactivity of aziridines, particularly vinyl aziridines, enables the synthesis of nitrogenous heterocycles in innovative ways, with a focus on constructing larger ring systems.[1,2] Although [3+2] cyclizations of vinyl aziridines with electron-deficient alkenes are well-established, primarily yielding five-membered nitrogenous frameworks, further

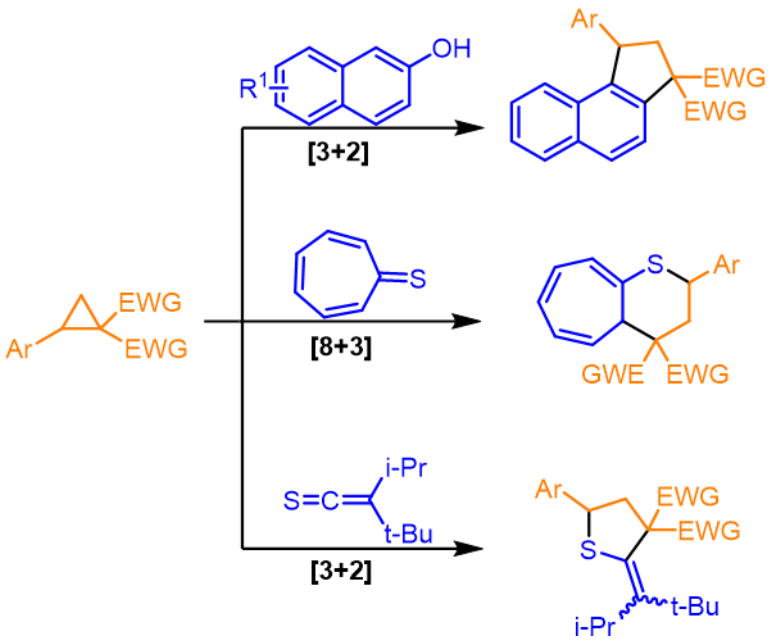
exploration into [3+3] and [4+3] cyclization pathways are still in its early stages.[1] These latter cyclizations hold significant potential for creating six- and seven-membered nitrogen-containing rings, a structural class valuable in medicinal and synthetic chemistry.[9] The underdevelopment of these pathways highlights the ongoing need for innovative synthetic strategies that can overcome challenges such as ring strain and complex intermediate formation, ultimately broadening the scope of aziridine-based cyclizations for diverse applications in heterocyclic chemistry.[1,15]



Scheme 2: Profile of cycloaddition reactions involving vinyl aziridine derivatives[1]

Building upon the utility of donor–acceptor (DA) cyclopropanes as 1,3-dipolarophiles, akin to the established reactivity of vinyl aziridines, recent studies have demonstrated their exceptional versatility in cycloaddition chemistry.[5] The reactivity of DA cyclopropanes, particularly those bearing electron-withdrawing groups (EWGs) and aryl substituents, enables the efficient construction of complex molecular frameworks through diverse cycloaddition pathways.[5,6] The

schematic presented illustrates three distinct cycloaddition modes: [3+2] cycloadditions with naphthol derivatives afford highly functionalized fused carbocycles.[22] In contrast [8+3] cycloadditions with thiopyran-2-one scaffolds yield sulfur-containing eight-membered heterocycles, an area of growing synthetic interest.[23] Additionally, [3+2] cycloadditions with thioketone derivatives expand the chemical space accessible from these systems, producing unique sulfur-functionalized products with potential applications in medicinal chemistry and materials science.[5] The ability to fine-tune the electronic properties of DA cyclopropanes offers significant control over regio-, chemo-, and stereoselectivity, thereby underscoring their potential as powerful intermediates in the development of novel synthetic methodologies.[5,6] Furthermore, their compatibility with different functional groups enhances their appeal for complex molecule synthesis.



Scheme 3: Profile of cycloaddition reactions involving D-A cyclopropane derivatives[22,23,24]

The development of heterocyclic frameworks such as benzoxazepines and benzoxazines has garnered significant attention due to their important roles in medicinal chemistry. The synthesis of these complex structures through cycloaddition reactions, especially those involving

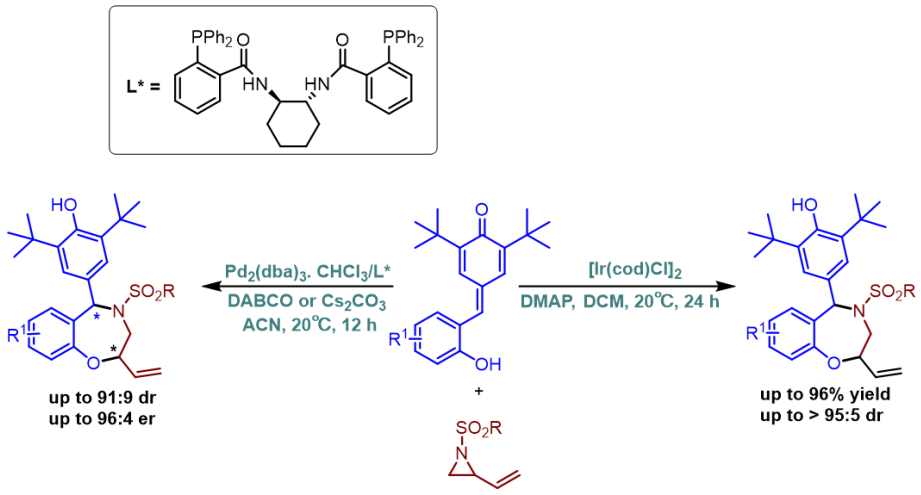
para-quinone methides (*p*-QMs), has become a major area of research, although the construction of seven-membered rings remains challenging due to unfavorable entropic and strain factors.[2,3,9]

Parallel to these efforts, vinyl aziridines have emerged as valuable three-atom synthons for the creation of nitrogen-containing heterocycles, particularly through [3+2] cycloadditions with electron-deficient partners.[2] However, exploration of larger ring systems through [3+3] and [4+3] cyclizations is still under development, signaling the need for new strategies. In a similar vein, donor–acceptor (DA) cyclopropanes have proven to be versatile 1,3-dipolarophiles.[5] Their reactions with various dipolar species have expanded the diversity of accessible molecular scaffolds through distinct [3+2] and [8+3] cycloaddition modes, offering significant promise for advancing synthetic methodologies.[22,23] Ongoing innovation aids drug discovery by enabling efficient synthesis of selective therapeutic heterocycles.

Chapter 2

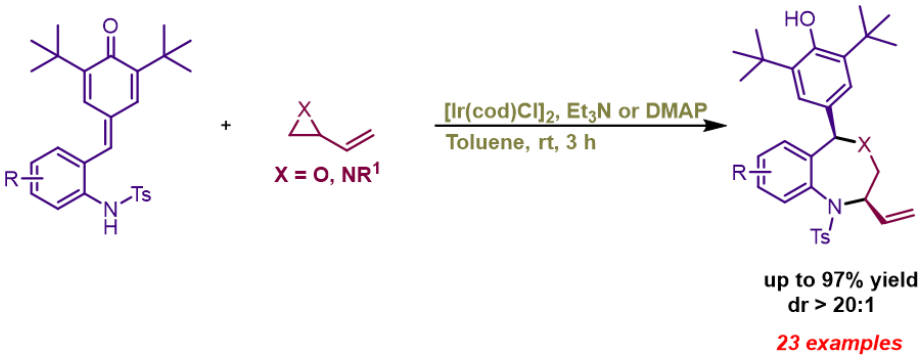
2.1. Literature Review:

In 2018, Shi *et. al.* pioneered the metal-catalyzed [4+3] using vinyl aziridines to cyclize *ortho*-hydroxyphenyl-substituted *para*-quinone methides to synthesize 1,4-benzoxazepines. This reaction achieved yields of up to 96% with excellent diastereoselectivity (dr > 20:1). Additionally, they developed a catalytic asymmetric variant employing palladium and chiral ligands, demonstrating moderate diastereoselectivity up to 91:9 dr and high enantioselectivity up to 96:4 er. These findings highlight a significant advancement in synthesizing complex heterocycles through efficient asymmetric cyclization methodologies.[1]



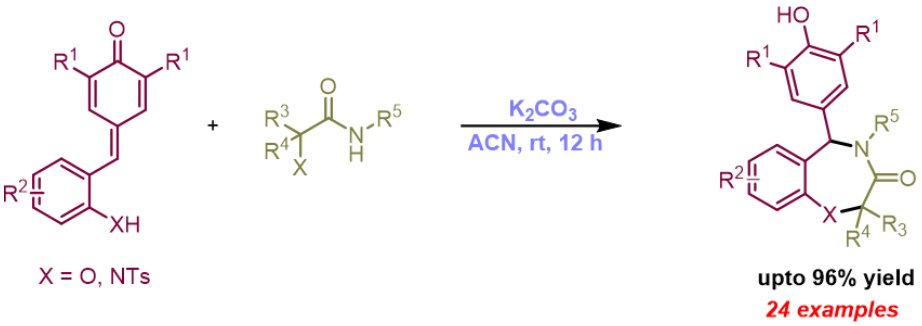
Scheme 4: Iridium-catalyzed and palladium-catalyzed in (presence of chiral ligand) [4+3] cyclization reactions[1]

Hu *et. al.* introduced a regioselective and efficient *ortho*-tosylaminophenyl-substituted *para*-quinone methides with vinylic oxiranes or aziridines undergo metal-catalyzed [4+3] cyclization. This cascade reaction achieved remarkable yields of up to 97% and exhibited excellent diastereoselectivity (dr > 20:1), showcasing its utility in constructing complex seven-membered heterocycles through a streamlined, highly selective synthetic approach.[2]



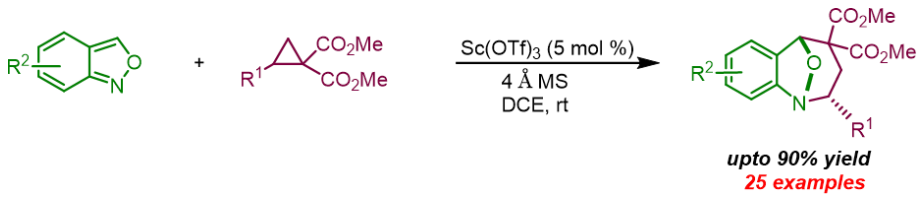
Scheme 5: Iridium catalyzed and base -promoted [4+3] cyclization reactions[2]

In 2021, a transition metal free [4+3] *ortho*-hydroxyphenyl-substituted *para*-quinone methides and *in situ*-generated azaoxyallyl cations was demonstrated by Xuan *et. al*. via a cycloaddition method. This method offers an efficient and straightforward approach to synthesizing 1,4-benzoxazepine derivatives, highlighting its significance in developing complex heterocycles without the need for metal catalysts.[3]



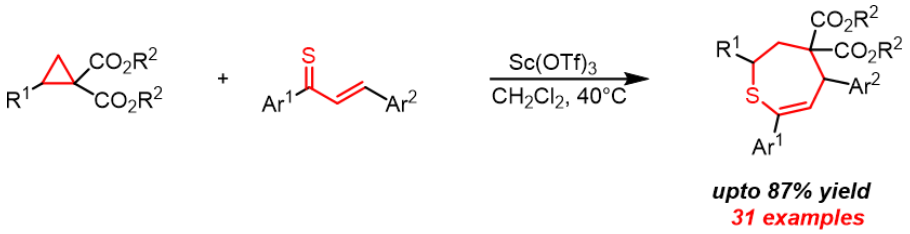
Scheme 6: Transition metal free [4+3] cycloaddition reactions[3]

Luo and co-workers have developed a highly efficient [4+3]-annulation strategy catalyzed by Lewis's acids, which involves the reaction of donor-acceptor (DA) cyclopropanes with anthranils. This transformation proceeds through a sequence of ring opening, aromatization, and nucleophilic addition steps. Notably, the aromatization step is the principal thermodynamic driving force for the overall process. This methodology enables the straightforward synthesis of 8-oxa-1-azabicyclo[3.2.1]octane derivatives with outstanding diastereoselectivity.[6]



Scheme 7: Cycloaddition between donor–acceptor (DA) cyclopropane with anthranil[6]

Werz and co-workers introduced a versatile method for synthesizing tetrahydrothiepine frameworks through the use of donor–acceptor cyclopropanes. In this Lewis acid-catalyzed formal [4+3]-cycloaddition, thiochalcones act as four-atom, sulfur-containing building blocks, reacting efficiently with donor–acceptor cyclopropanes, which serve as the three-atom components in the annulation process.[5]



Scheme 8: Lewis's acid-catalyzed [4+3] cycloaddition reaction to construct seven-membered heterocycles[5]

2.2. Motivation:

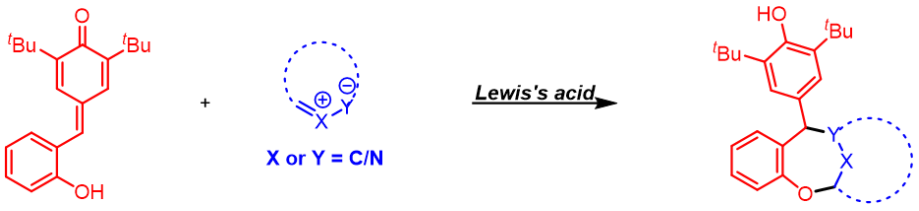
The synthesis of benzoxazepines, particularly seven-membered benzo-fused heterocycles, is significant in pharmaceutical development.[3] Prior studies on metal-catalyzed [4+3] cyclization using vinylic aziridines have shown potential for constructing 1,4 and 1,5 benzoxazepines, using catalysts like palladium and iridium.[1,2] This report aims to advance the synthesis of 1,4 benzoxazepines by exploring Lewis's acid catalysis with aziridine derivatives. Initial research efforts will concentrate on optimizing reaction conditions and proposing a plausible reaction mechanism, contributing to efficient routes for benzoxazepine synthesis in drug discovery.

Chapter 3

3.1. Our Hypothesis:

We hypothesize that Lewis acid catalysis can effectively promote [4+3] cycloaddition reactions between *para*-quinone methides and aziridine derivatives—beyond the traditionally used vinyl aziridines—to construct 1,4-benzoxazepine frameworks under milder and more sustainable conditions. Reported literature[1,2] predominantly focuses on metal-catalyzed processes involving vinyl aziridines, often requiring transition metals like palladium or iridium in combination with chiral ligands. Our proposed method not only seeks to eliminate the reliance on costly and sensitive metal catalysts but also expands the scope of applicable aziridine substrates. By exploring a broader range of aziridine derivatives under Lewis acid catalysis, our approach aims to improve substrate diversity, operational simplicity, and atom economy. This research could lead to more versatile and practical synthetic pathways for accessing structurally diverse benzoxazepine derivatives with potential medicinal relevance.

General Reaction Scheme:



Chapter 4

4.1. General Information

All experiments were performed using glassware dried in an oven, with continuous stirring provided by a magnetic stirrer. The reactions carried out under Argon atmosphere. All the reaction required heating were performed using magnetic stirrer (IKEA C-MAG HS7) with oil bath. With Merck silica gel plates, thin-layer chromatography (TLC) was used to track the reaction's progress. The plates were visible at 254 nm under UV light. A rotating evaporator operating at 40 °C and low pressure was used to extract volatile solvents. Using distilled solvents as eluents, column chromatography on silica gel of 100-200 mesh was used to purify the reaction products. All ^{1}H-NMR, ^{13}C-NMR spectra (NMR) spectra were captured using a Bruker AV 500 MHz and 400 MHz NMR spectrometer. Nuclear magnetic resonance (NMR) analyses were performed utilizing deuterated chloroform ($CDCl_3$) and deuterated dimethyl sulfoxide (DMSO-d_6) as solvents., and chemical shifts (δ) were expressed in parts per million (ppm) with the internal standard, Tetramethylsilane (TMS). High-resolution mass spectrometry (HRMS) was measured by the ESI-TOF method. Every reagent was used just as it was supplied by commercial vendors, without any additional purification. Following recognized literature methodologies, key starting ingredients such as *p*-QMs and 1,3-dipolarophiles were synthesized.

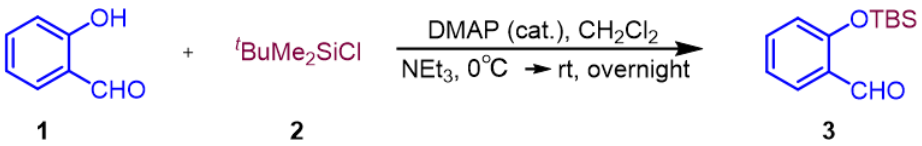
4.2 Experimental Procedures of *p*-QMs and 1,3-dipolarophiles:

4.2.1 Synthesis of 2-((*tert*-butyldimethylsilyl)oxy)benzaldehyde[8] (3):

4.2.1.1 Chemicals required

1. 2-hydroxybenzaldehyde (1)
2. *tert*-butyldimethylsilyl chloride (2)
3. *N*, *N*-dimethylpyridin-4-amine
4. Triethylamine
5. Dichloromethane

4.2.1.2 General Reaction scheme



1 2 3

4.2.1.3 Experimental procedure

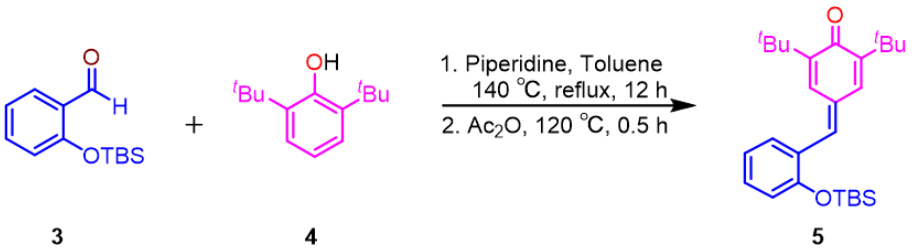
In a round-bottom flask, placed in ice-bath to maintain the temperature 0 °C inside the flask, added 2-hydroxybenzaldehyde (1.5 g, 12.2 mmol) and *tert*-butyldimethylsilyl chloride (2.2 g, 14.7 mmol) were taken and to this mixture, added 4-dimethylaminopyridine (DMAP) (0.3 g, 2.45 mmol) as a catalyst. The reaction constituents were stirred at 0 °C using DCM (6 mL) as a solvent. After stirred for 5 minutes triethylamine (2.0 mL, 14.7 mmol) was introduced in a dropwise manner to the reaction flask at 0 °C. The reaction flask was then allowed to warm to room temperature continuously stirred for overnight. Afterward, Workup have been done by adding water to the reaction mixture with dichloromethane (3 × 15 mL). The combined organic layer were dried over anhydrous sodium sulfate (Na_2SO_4), and the solvent was removed under reduced pressure using a rotary evaporator to obtain the crude residue was obtained **3** in 93% (2.7 g) yield; White viscous liquid; directly used further without purification.

4.2.1 Synthesis of 2,6-di-*tert*-butyl-4-(2-((*tert*-butyldimethylsilyl)oxy)benzylidene)cyclohexa-2,5-dien-1-one[8] (5):

4.2.1.1 Chemicals required

1. 2-((*tert*-butyldimethylsilyl)oxy)benzaldehyde (3)
2. 2,6-di-*tert*-butylphenol (4)
3. Piperidine
4. Acetic anhydride
5. Toluene

4.2.1.2 General Reaction scheme



3 4 5

4.2.1.3 Experimental procedure

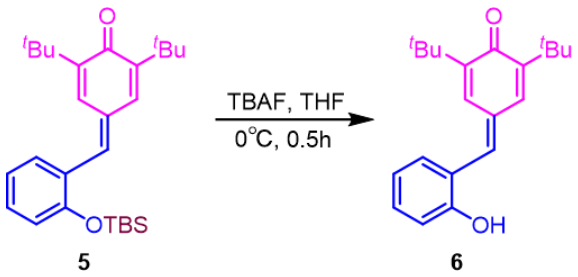
In a 250 ml Two neck round bottom flask, a mixture of **3** (2.7 g, 11.4 mmol) and **4** (2.6 g, 12.5 mmol) was taken and toluene (73 mL) was added to the flask, and fitted the reaction flask with Dean Stark apparatus and transferred to preheated silicon oil bath at 140 °C and stirred for 12 h under reflux conditions. Piperidine (2.2 mL, 22.8 mmol) was added via syringe in a dropwise manner within one hour, followed by stirring. After this step, the temperature was brought to 120 °C, and acetic anhydride (2.1 mL, 22.8 mmol) was added. Stirring was continued at 120 °C for 30 minutes. The mixture was cooled to room temperature gradually and poured into ice-cold water (3 × 25 mL). The aqueous phase was extracted with dichloromethane (3 × 25 mL), and the organic fractions were dried by using anhydrous sodium sulfate (Na_2SO_4). The solvent was removed under reduced pressure using a rotavap, and the crude product was purified by column chromatography on silica gel using a hexane/EtOAc mixture as the eluent to afford the pure **5** in 37% (1.7 g) yield; Yellow solid; $\mathbf{R_f}$ = 0.7(1% EtOAc in Hexane); **M.P.**: 60-62 °C ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2.4 Hz, 1H), 7.29 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.20 (td, *J* = 7.8, 1.8 Hz, 1H), 7.18 (s, 1H), 6.95 (td, *J* = 7.5, 1.2 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.81 (dd, *J* = 8.2, 1.2 Hz, 1H), 1.25 (s, 9H), 1.21 (s, 9H), 0.93 (s, 9H), 0.12 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 186.8, 155.0, 149.1, 147.6, 139.7, 135.3, 131.9, 131.6, 130.8, 128.4, 127.9, 121.5, 119.9, 35.5, 35.1, 29.7, 29.7, 25.8, 18.4, -4.1; **IR (neat)**: 2954, 1610, 1550, 1358, 1256, 1110 cm^{-1}.

4.2.2 Synthesis of 2,6-di-*tert*-butyl-4-(2-hydroxybenzylidene)cyclohexa-2,5-dien-1-one[8] (6):

4.2.2.1 Chemicals required

1. 2,6-di-*tert*-butyl-4-(2-((*tert*-butyldimethylsilyl)oxy)benzylidene)cyclohexa-2,5-dien-1-one (5)
2. Tetrabutylammonium fluoride
3. Tetrahydrofuran

4.2.2.2 General Reaction scheme



5 6

4.2.2.3 Experimental procedure

O-silylated-*p*-quinone methide (1.7 g, 4.1 mmol) was added to a round-bottom flask, followed by the addition of solvent, tetrahydrofuran (41 mL). Tetrabutylammonium fluoride, (1.32 mL, 4.5 mmol). as a reagent was introduced to the reaction flask, which was kept in the ice bath, drop-by-drop and stirring was continued until completion of the reaction, as monitored by thin-layer chromatography (TLC). Once the reaction was complete, it was quenched by carefully adding an aqueous solution of ammonium chloride dropwise. The mixture was then transferred to separating funnel and extracted with diethyl ether (3 × 25 mL) and water (3 × 25 mL). The organic portions were dried over anhydrous sodium sulfate (Na_2SO_4), and the crude was obtained by removing the solvent after dried over drying agent. The resulting crude product was purified through column chromatography on silica gel (100–200 mesh). with a hexane/EtOAc gradient as the eluent, yielding the pure **6** in 73% (0.9 g) yield; Yellow solid; $\mathbf{R_f}$ = 0.5 (10% EtOAc in Hexane); **M.P.**: 158-160 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.4 Hz, 1H), 7.34 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.32 (s, 1H), 7.29 (td, *J* = 7.9, 1.7 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 7.02 (td, *J* = 7.5, 1.1 Hz, 1H), 6.91 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.31 (s, 1H), 1.34 (s, 9H), 1.29 (s, 9H);

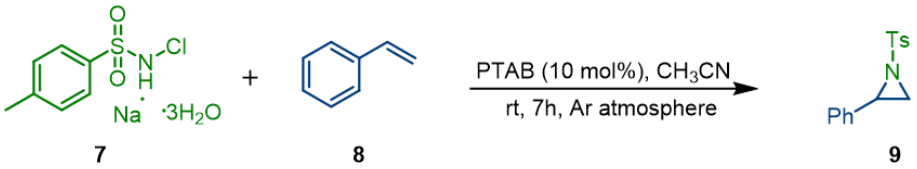
^{13}C NMR (125 MHz, $CDCl_3$) δ 186.8, 154.4, 149.5, 147.9, 137.5, 135.1, 132.5, 131.8, 131.0, 128.2, 123.2, 121.1, 116.1, 35.6, 35.1, 30.4, 29.7; **IR (neat)**: 3313, 2992, 1588, 1544, 1448, 1391, 1256, 1159, 1097, 1026 cm^{-1}.

4.2.3 Synthesis of 2-phenyl-1-tosylaziridine[7] (9):

4.2.3.1 Chemicals required

1. *N*-chloro-4-toluenesulfonamide sodium salt (7)
2. Styrene (8)
3. Mono(*N*,*N*,*N*-trimethylbenzenaminium) tribromide (PTAB)
4. Acetonitrile

4.2.3.2 General Reaction scheme



7 8 9

4.2.3.3 Experimental procedure

A two-neck round-bottom flask was charged with *N*-chloro-4-toluenesulfonamide sodium salt (1.9 g, 6.9 mmol) and PTAB (0.2 g, 0.6 mmol) under an inert argon atmosphere. Acetonitrile (11 mL) was added as the reaction solvent, and the mixture was stirred at room temperature for 30 minutes. Subsequently, styrene (0.7 mL, 6.3 mmol) was introduced into the reaction mixture, and stirring was continued for 7 hours at ambient temperature. Upon completion, the reaction was quenched by adding water (3 × 15 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried over anhydrous sodium sulfate (Na_2SO_4), and the solvent was evaporated under reduced pressure using a rotary evaporator. The resulting crude product was purified by silica gel column chromatography (100–200 mesh) using a hexane/ethyl acetate mixture as the eluent to obtain pure **9** in 29% (0.54 g) yield; White solid; $\mathbf{R_f}$ = 0.4 (5% EtOAc in Hexane); **M.P.**: 76-78 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.23 (m, 3H), 7.20 (dd, *J* = 7.4, 2.1 Hz, 2H), 3.76 (dd, *J*

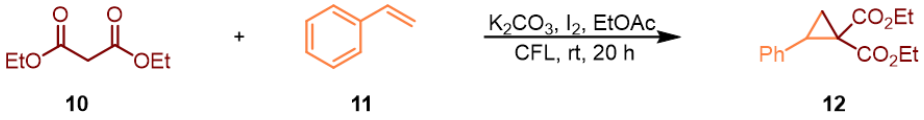
= 7.2, 4.5 Hz, 1H), 2.96 (d, *J* = 7.2 Hz, 1H), 2.41 (s, 3H), 2.37 (d, *J* = 4.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 145.0, 135.4, 135.4, 130.1, 128.9, 128.7, 128.3, 126.9, 126.4, 74.2, 41.4, 36.3, 22.0; **IR (neat)**: 2921, 1592, 1455, 1311, 1190, 1157, 1092 cm^{-1}.

4.2.3 Synthesis of diethyl 2-phenylcyclopropane-1,1-dicarboxylate[18] (12)

4.2.3.1 Chemicals required

1. Diethyl Malonate
2. Styrene
3. Potassium Carbonate
4. Iodine
5. EtOAc

4.2.3.2 General Reaction scheme



10 **11** **12**

4.2.3.3 Experimental procedure

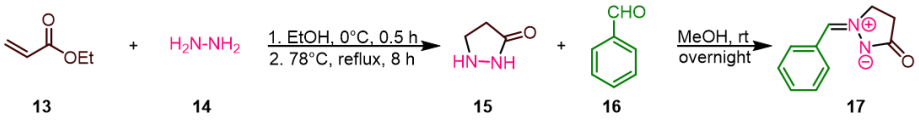
To a solution of Diethyl malonate (0.9 mL, 6.2 mmol) in EtOAc (100 ml) was added Styrene (0.7 mL, 6.2 mmol) at room temperature. Potassium carbonate (0.8 g, 6.28 mmol) and Iodine (0.8 g, 6.28 mmol) were added to the round-bottom flask and irradiated with CFL light (2 × 25W) at room temperature for 20 h under an Argon atmosphere. The mixture was washed with aq. $Na_2S_2O_3$ extracted with Et_2O (3 × 25 ml). The combined organic layers were dried over Na_2SO_4, resulting crude product was purified through column chromatography on silica gel (100–200 mesh). with a hexane/EtOAc gradient as the eluent, yielding the pure **12** in 15% (0.2 g) yield; Colorless oil; $\mathbf{R_f}$ = 0.4 (20% EtOAc in Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33–7.23 (m, 5H), 4.35–4.24 (m, 2H), 3.89 (q, *J* = 7.1 Hz, 2H), 3.27 (t, *J* = 8.6 Hz, 1H), 2.22 (dd, *J* = 8.0, 5.2 Hz, 1H), 1.75 (dd, *J* = 9.3, 5.2 Hz, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 189.9, 164.7, 163.0, 162.4, 135.0, 134.6, 129.0, 128.7, 63.5, 63.4, 63.3, 62.7, 60.9, 60.0, 14.0; **IR (neat)**: 2921, 1760, 1460, 1243, 1103, 1053 cm^{-1}.

4.2.4 Synthesis of (*Z*)-2-benzylidene-5-oxopyrazolidin-2-ium-1-ide[19,20] (17)

4.2.4.1 Chemicals required

1. Hydrazine
2. Ethyl acrylate
3. EtOH
4. MeOH
5. EtOAc

4.2.4.2 General Reaction scheme



13 14 15 16 17

4.2.4.3 Experimental procedure

In a 50 mL round-bottom flask, a solution of Hydrazine (1.1 mL, 10 mmol) in EtOH (10 mL) was added Ethyl acrylate (0.5 mL, 10.5 mmol) in a dropwise manner at 0 ℃. The reaction flask was continued to stir at 0 ℃ for 30 minutes, and after that, transferred to a preheated silicon oil bath, and refluxed for 8 h. After the reaction's completion, the solvent was removed under reduced pressure to obtain 15 as a crude Pale-yellow oil compound and was used further without purification.[19]

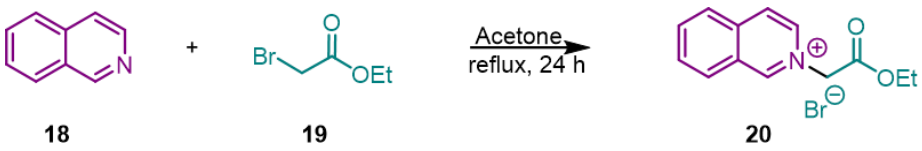
Dissolved the crude reaction mixture (0.7 g, 8.9 mmol) in MeOH (6 mL) and subsequently added Benzaldehyde (1.0 mL, 9.8 mmol) to the reaction flask and allowed to stir overnight at 25 ℃. After that, solvent was evaporated under reduced pressure. Recrystallized using ethanol and washed with EtOAc to yield the pure **17** in 14% (0.2 g) yield; Pale white crystals;[20] **M.P.**: 212-214 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.30 – 8.27 (m, 1H), 7.65 (s, 1H), 7.56 – 7.48 (m, 2H), 4.59 – 4.55 (m, 1H), 2.59 – 2.53 (m, 1H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 184.4, 131.9, 131.0, 130.9, 130.0, 128.7, 57.4, 29.2; **IR (neat)**: 3000, 1663, 1588, 1563, 1455, 1336, 1276, 1246, 1100 cm^{-1}.

4.2.3 Synthesis of 2-(2-ethoxy-2-oxoethyl)isoquinolin-2-ium bromide[21][20]

4.2.3.1 Chemicals required

1. Isoquinoline
2. Ethyl 2-bromoacetate
3. Acetone
4. Diethyl ether

4.2.3.2 General Reaction scheme



18 19 20

4.2.3.3 Experimental procedure

A pressure tube was charged with a mixture of isoquinoline (1.0 mL, 9.0 mmol) and ethyl 2-bromoacetate (1.0 mL, 9.0 mmol), and subsequently, Acetone (9 mL) was added to it. The reaction mixture was allowed to stir at reflux temperature for 24 h. After the completion of reaction, reaction mixture was cooled to room temperature and filtered it by using vaccum filtration setup. The filter cake was washed with Et_2O (3 × 5 mL), followed by acetone (3 × 5 mL) and dried in vaccum to yield the pure **20** in 68% (1.8 g) yield; Light green solid; **M.P.**: 202-204 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.78 (dd, *J* = 6.8, 1.5 Hz, 1H), 8.67 (d, *J* = 6.8 Hz, 1H), 8.54 (d, *J* = 8.2 Hz, 1H), 8.40 (d, *J* = 8.3 Hz, 1H), 8.35–8.31 (m, 1H), 5.82 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 166.6, 151.8, 137.8, 137.3, 136.2, 131.5, 130.7, 127.4, 126.8, 125.5, 62.4, 60.2, 14.0; **IR (neat)**: 2990, 1738, 1643, 1510, 1471, 1391, 1230, 1152 cm^{-1}.

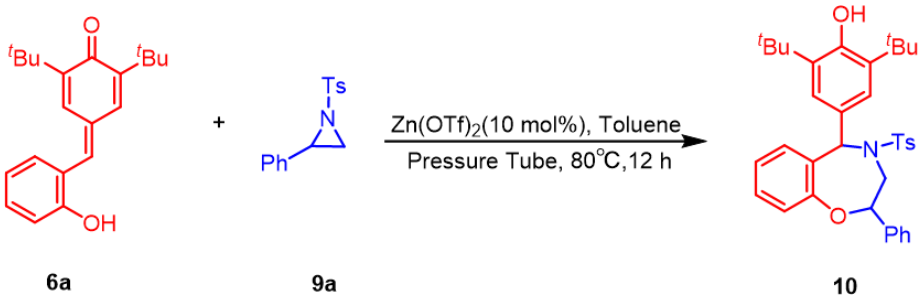
4.3. Synthesis of 2,6-di-*tert*-butyl-4-(2-phenyl-4-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl)phenol (10)

4.3.1.1 Chemicals required

1. 2,6-di-*tert*-butyl-4-(2-hydroxybenzylidene)cyclohexa-2,5-dien-1-one (6a)
2. 2-phenyl-1-tosylaziridine (9a)
3. Zinc trifluomethanesulfonate (Lewis's acid)

4. Toluene

4.3.1.2 General Reaction scheme



6a **9a** **10**

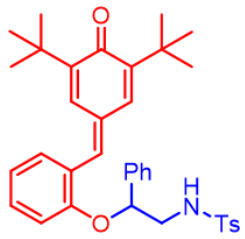
4.3.1.3 Experimental procedure

A pressure tube was charged with 2,6-di-*tert*-butyl-4-(2-hydroxybenzylidene)cyclohexa-2,5-dien-1-one (0.031 g, 0.1 mmol), 2-phenyl-1-tosylaziridine (0.032 g, 0.12 mmol), and zinc(II) trifluoromethanesulfonate (0.003 g, 0.01 mmol). Toluene (1 mL) was added as the reaction solvent. The reaction mixture was placed in a preheated silicone oil bath and heated at 80 °C for 12 hours. After the reaction was complete (monitored by the TLC), the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (3 × 5 mL) and water (5 mL). The combined organic extracts were dried over anhydrous sodium sulfate (Na_2SO_4), and the solvent was evaporated using a rotary evaporator. The crude product was purified by column chromatography on silica gel (100–200 mesh) using a hexane/ethyl acetate mixture as the eluent to obtain pure **10** in 31% (0.018 g) yield; Pale white solid; $\mathbf{R_f}$ = 0.4 (10% EtOAc in Hexane); **M.P.**: 164-166 °C; **dr:** 2.9:1; **^{1}H NMR** (400 MHz, $CDCl_3$) δ {7.69 (d, *J* = 7.9 Hz, 1.7H); 7.51 (d, *J* = 8.1 Hz, 0.3H), {7.39 (d, *J* = 4.3 Hz, 0.7H); 6.96 (d, *J* = 7.8 Hz, 0.3H)}, 7.33 (t, *J* = 6.8 Hz, 3H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.24 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 6.6 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.89 (s, 2H), {6.48 (s, 0.2H); 6.30 (s, 0.8H)}, {5.25 (s, 0.2H); 5.16 (s, 0.8H)}, {4.95 (m, 0.5H); 2.68 – 2.59 (m, 0.5H)}, {4.63 (d, *J* = 9.9 Hz, 0.8H); 3.65 (dd, *J* = 10.4, 3.2 Hz, 0.2H)}, {3.86 (d, *J* = 15.4 Hz, 0.8H); 3.57 (d, *J* = 9.5 Hz, 0.2H)}, {3.29 (dd, *J* = 15.6, 9.7 Hz, 0.5H); 3.25 (dd, *J* = 15.6, 9.7 Hz, 0.5H)}, {2.38 (s, 2.4H) 2.33 (s, 0.6H)},

{1.37 (s, 4H); 1.30 (s, 14H)}; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.7, 157.4, 153.2, 153.2, 143.3, 142.8, 139.4, 138.4, 138.3, 136.7, 136.2, 135.7, 133.3, 131.3, 130.7, 130.5, 129.7, 129.5, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.2, 127.1, 126.0, 125.8, 125.6, 125.6, 125.2, 124.5, 124.4, 122.8, 121.9, 120.5, 82.6, 80.5, 73.8, 64.6, 62.3, 52.6, 51.8, 51.4, 51.3, 40.3, 34.4, 34.3, 30.3, 30.2, 21.5, 21.4; **IR (neat)**: 3613, 2926, 1524, 1486, 1435, 1336, 1225, 1160, 1112 cm^{-1}.

HRMS (ESI) calculated for [$C_{36}H_{40}NO_4S+H^+$] 606.2638, found 606.2649.

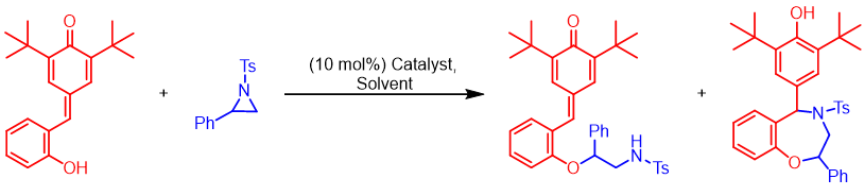
Compound **3a** was confirmed by Mass-Spectrometry:



3a

HRMS (ESI) calculated for [$C_{36}H_{40}NO_4S+H^+$] 606.2649, found 606.2648.

4.4. Table 1: Optimization of Reaction conditions

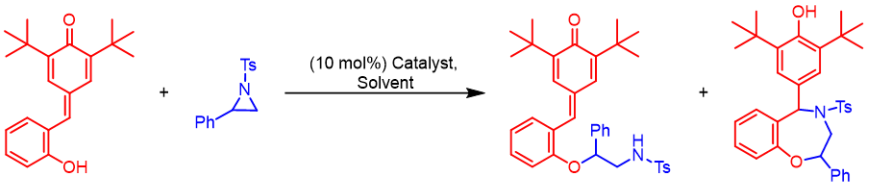


1a **2a** **3a** **4a**

Entry	Catalyst	Solvent	Temp.	3a[b]	4a[b]	dr[e]
1.	$Zn(OTf)_2$	DCM	rt	6%	ND	ND
2.	$Zn(OTf)_2$	Toluene	rt	Trace	ND	ND
3.	$BF_3.(OEt)_2$	DCM	rt	ND	ND	NA
4.	$Zn(OTf)_2$	DCE	80°C	ND	18%	2.6:1
5.	$Zn(OTf)_2$	Toluene	108°C	ND	15%	2.8:1
6.	$Zn(OTf)_2$	DCM	50°C	5%	ND	NA
7.	$Zn(OTf)_2$	Toluene	80°C	ND	31%	2.9:1
8.	$Bi(OTf)_3$	DCM	rt	ND	13%	6.7:1
9.	$Sn(OTf)_2$	DCM	rt	ND	12%	3.7:1
10.	$Bi(OTf)_3$	Toluene	rt	ND	7%	5:1
11.	$Sn(OTf)_2$	Toluene	rt	ND	7%	4.7:1
12[c].	$Zn(OTf)_2$	Toluene	80°C	ND	21%	7:1
13[d].	$Sc(OTf)_3$	DCM	rt	ND	15%	3:1
14.	$Yb(OTf)_3$	DCM	rt	2%	ND	NA

[a]Reaction conditions: compound 1a (0.1 mmol), compound 2a (0.12 mmol), and a solvent (1 mL) stir for 12 h respectively. [b]Isolated yields. ND = not detected. [c]compound 1a (0.12 mmol), compound 2a (0.1 mmol), and a solvent (1 mL). [d]Reaction time is 3 h.[e]The diasteromeric ratio is calculated by ^{1}H-NMR spectroscopy.

4.5. Table 2: Investigation of reaction conditions by changing temperature, solvent etc.

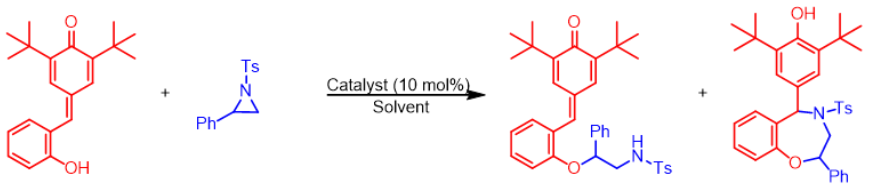


1a 2a 3a 4a

Entry	Catalyst	Solvent	Temp.	3a[b]	4a[b]	dr[e]
15[c].	$Sc(OTf)_3$	DCM	0°C	ND	13%	3.2:1
16[c].	$Bi(OTf)_3$	DCM	0°C	Trace	10%	4.8:1
17.	$[Cu(CH_3CN)_4]BF_4$	DCM	rt	Trace	ND	NA
18.	$Sc(OTf)_3$	Toluene	rt	ND	Trace	NA
19.	$Bi(OTf)_3$	Toluene	rt	Trace	ND	NA
20.	$Bi(OTf)_3$	Toluene	80°C	ND	ND	NA
21.	$Sc(OTf)_3$	Toluene	80°C	ND	9%	4:1
22[d].	$Zn(OTf)_2$	Toluene	80°C	ND	31%	2.9:1
23.	$Sc(OTf)_3$	DCE	50°C	ND	10%	4:1
24.	$Zn(OTf)_2$	Ph-CF_3	80°C	ND	Trace	NA
25.	$Zn(OTf)_2$	Xylene	80°C	ND	ND	NA

[a]Reaction conditions: compound 1a (0.1 mmol), compound 2a (0.12 mmol), and a solvent (1 mL) stir for 12 h respectively. [b]Isolated yields. ND = not detected. [c]Reaction time is 3 h. [d]compound 1a (0.1 mmol), compound 2a (0.2 mmol). [e]The diasteromeric ratio is calculated by ^{1}H-NMR spectroscopy.

4.6 Table 3: Screening of stronger Lewis's acids

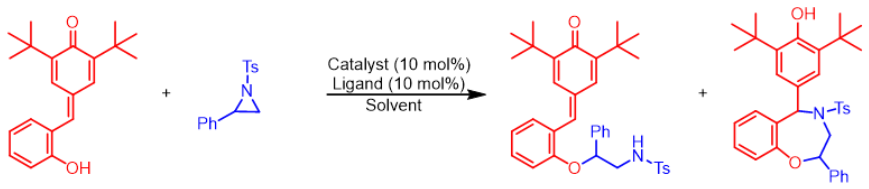


1a **2a** **3a** **4a**

Entry	Catalyst	Solvent	Temp.	3a[b]	4a[b]	dr[k]
26[c].	$Zn(OTf)_2$	Toluene	80°C	ND	28%	4:1
27[d].	$Zn(OTf)_2$	Toluene	80°C	ND	30%	3:1
28[e].	$Zn(OTf)_2$	Toluene	80°C	ND	31%	2.9:1
29[f].	$Sc(OTf)_3$	DCM	-40°C	ND	ND	NA
30[f].	$Bi(OTf)_3$	DCM	-40°C	ND	ND	NA
31.	$Zn(NTf_2)_2$	Toluene	80°C	ND	ND	NA
32.	$Zn(NTf_2)_2$	DCM	rt	ND	13%	7.1:1
33[g].	$Zn(NTf_2)_2$	Toluene	rt	ND	ND	NA
34[h].	$Co(OTf)_2$	DCM	rt	ND	18%	5.9:1
35[h].	$Co(OTf)_2$	Toluene	80°C	ND	9%	5.7:1
36[h].	$Cu(NTf_2)_2$	DCM	rt	ND	ND	NA
37[i].	$Ni(OTf)_2$	DCM	rt	ND	ND	NA
38[i].	$Zn(OTf)_2$	Toluene	80°C	ND	ND	NA

[a]Reaction conditions: compound 1a (0.1 mmol), compound 2a (0.12 mmol), catalyst (10 mol%) and a solvent (1 mL) stir for 12 h respectively. [b]Isolated yields. ND = not detected. [c]Catalyst loading (20 mol%). [d]compound 2a (0.15 mmol).[e]compound 2a (0.2 mmol). [f]Reaction time is 6 h. [g]Reaction continued for 48 h. [h]Starting material consumed in 4 h. [i]Reaction continued for 24 h. [j]Reaction continued for 24 h in presence of Molecular seives. [k]The diasteromeric ratio for 4a is calculated by ^{1}H-NMR spectroscopy.

4.7. Table 4: Screening of ligands:



1a **2a** **3a** **4a**

Entry	Catalyst	Ligand	Solvent	Temp.	3a[b]	4a[b]	dr[g]
39[c].	$Zn(OTf)_2$	dtbpy	Toluene	80°C	ND	ND	ND
40[c].	$Zn(OTf)_2$	1,10-phen	Toluene	80°C	ND	ND	ND
41[d].	$Sc(OTf)_3$	dtbpy	DCM	rt	ND	9%	2.9:1
42[d].	$Sc(OTf)_3$	1,10-phen	DCM	rt	ND	10%	2.4:1
43.	$Cu(OTf)_2$	dtbpy	DCM	rt	ND	22%	3:1
44.	$Cu(OTf)_2$	1,10-phen	DCM	rt	ND	Trace	----
45.	$Cu(NTf_2)_2$	dtbpy	DCM	rt	ND	19%	5:1
46.	$Cu(NTf_2)_2$	1,10-phen	DCM	rt	ND	Trace	----
47.	$Cu(OTf)_2$	dtbpy	Toluene	rt	ND	ND	NA
48.	$Cu(OTf)_2$	1,10-phen	Toluene	rt	ND	Trace	----
49[e].	$Cu(OTf)_2$	dtbpy	CH_3CN	rt	ND	ND	NA
50[e].	$Cu(NTf_2)_2$	dtbpy	CH_3CN	rt	ND	ND	NA
51[f].	$Cu(OTf)_2$	dtbpy	$CHCl_3$	rt	ND	11%	2.9:1
52[f].	$Cu(NTf_2)_2$	dtbpy	$CHCl_3$	rt	ND	14%	3:1

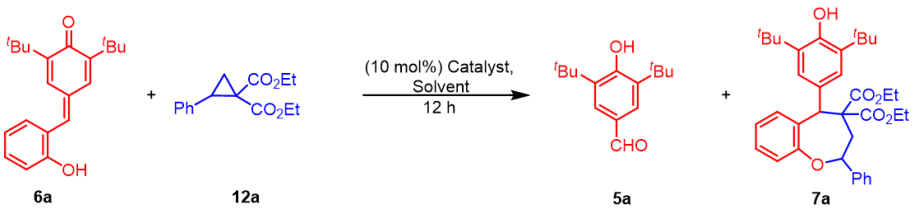
[a]Reaction conditions: compound 1a (0.1 mmol), compound 2a (0.12 mmol), catalyst (10 mol%) and a solvent (1 mL) stir for 12 h respectively. [b]Isolated yields. ND = not detected. [c]Reaction continued for 48 h. [d]Reaction time is 3 h.[e]Reaction continued for 72 h. [f]Reaction time is 6 h. [g]The diasteromeric ratio for 4a is calculated by ^{1}H-NMR spectroscopy.

4.8. Synthesis of diethyl 5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenyl-2,3-dihydrobenzo[*b*]oxepine-4,4(5*H*)-dicarboxylate (7a)

4.8.1.1 Chemicals required

1. 2,6-di-*tert*-butyl-4-(2-hydroxybenzylidene)cyclohexa-2,5-dien-1-one (6)
2. diethyl 2-phenylcyclopropane-1,1-dicarboxylate (12a)
3. Lewis Acid (Catalyst)
4. DCM

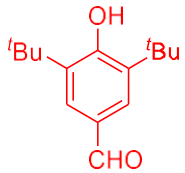
4.8.1.2 General Reaction scheme



4.8.1.3 Experimental procedure

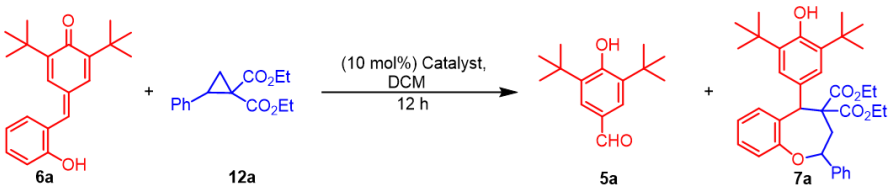
A reaction vial was charged with reaction partners **6a** (0.031 g, 0.1 mmol), **12a** (0.031 g, 0.12 mmol), and Lewis acid catalyst (10 mol%), used DCM as the solvent for the reaction, and the mixture was stirred at room temperature for 12 h. Upon completion of the reaction, the solvent was removed under reduced pressure. Water was added to the residue and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate (Na_2SO_4), and the solvent was removed using a rotary evaporator. The crude product was purified via column chromatography on silica gel with a hexane/ethyl acetate mixture as the eluent to isolate the pure compound **5a** and **7a** remained undetectable.

NMR Data for by-product **5a**.



White solid; $\mathbf{R_f}$ = 0.6 (10% EtOAc in Hexane); **M.P.**: 178-180°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.73 (s, 2H), 5.84 (s, 1H), 1.48 (s, 18H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.0, 159.8, 136.7, 128.9, 127.8, 34.5, 30.2; **IR (neat)**: 3420, 2917, 1663, 1580, 1426, 1370, 1254, 1194, 1092 cm^{-1}.

4.9. Screening of various Lewis's acids:



Entry	Catalyst	5a[b]	7a[b]
1.	$Sc(OTf)_3$	21%	ND
2[c].	$Mg(OTf)_2$	ND	ND
3.	$Yb(OTf)_3$	20%	ND
4.	$Bi(OTf)_3$	21%	ND
5.	$Sn(OTf)_2$	18%	ND
6.	$Zn(OTf)_2$	15%	ND
7.	$Cu(OTf)_2$	15%	ND
8.	$[Cu(CH_3CN)_4BF_4]$	ND	ND
9.	$Zn(NTf_2)_2$	10%	ND
10.	$Cu(NTf_2)_2$	15%	ND
11.	$Ni(OTf)_2$	7%	ND
12.	$Co(OTf)_2$	23%	ND

[a]Reaction conditions: compound 1a (0.1 mmol), compound 2a (0.12 mmol), and a solvent (1 mL) stir for 12 h respectively. [b]Isolated yields. ND = not detected. [c]1a and 2a remain unreacted after 24 h.

Chapter 5

5.1. Characterization / Supporting data

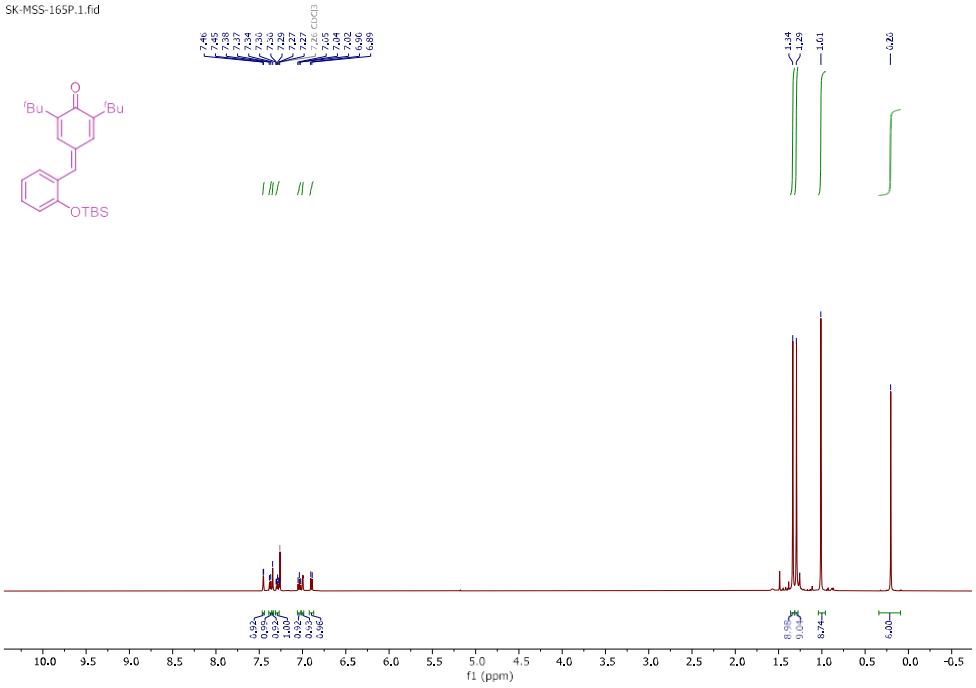


Figure 2: ^{1}H- NMR spectrum of **5** in $CDCl_3$

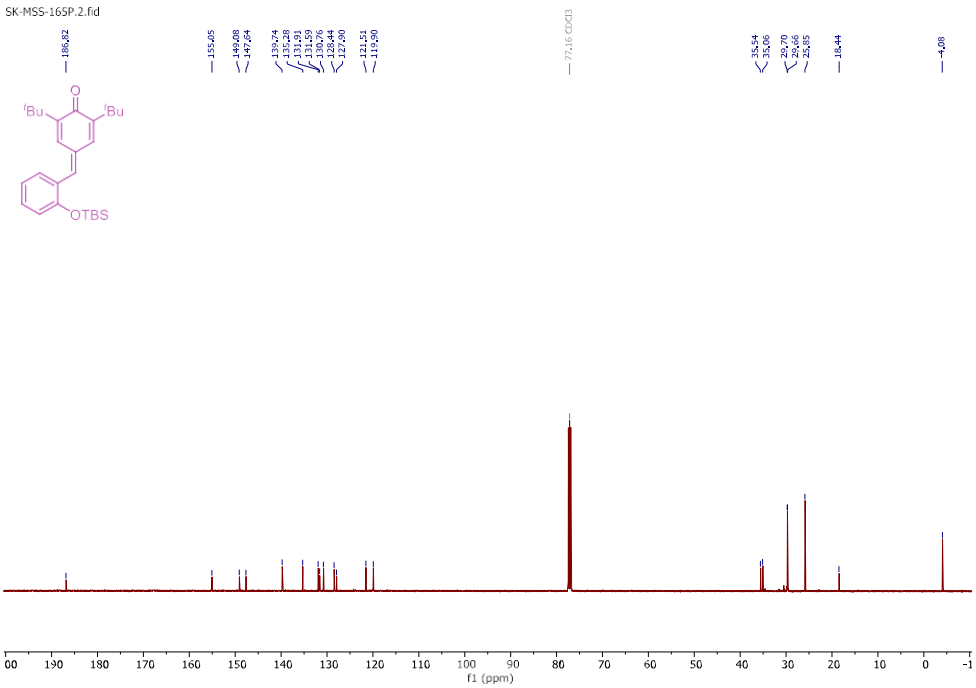


Figure 3: ^{13}C- NMR spectrum of **5** in $CDCl_3$

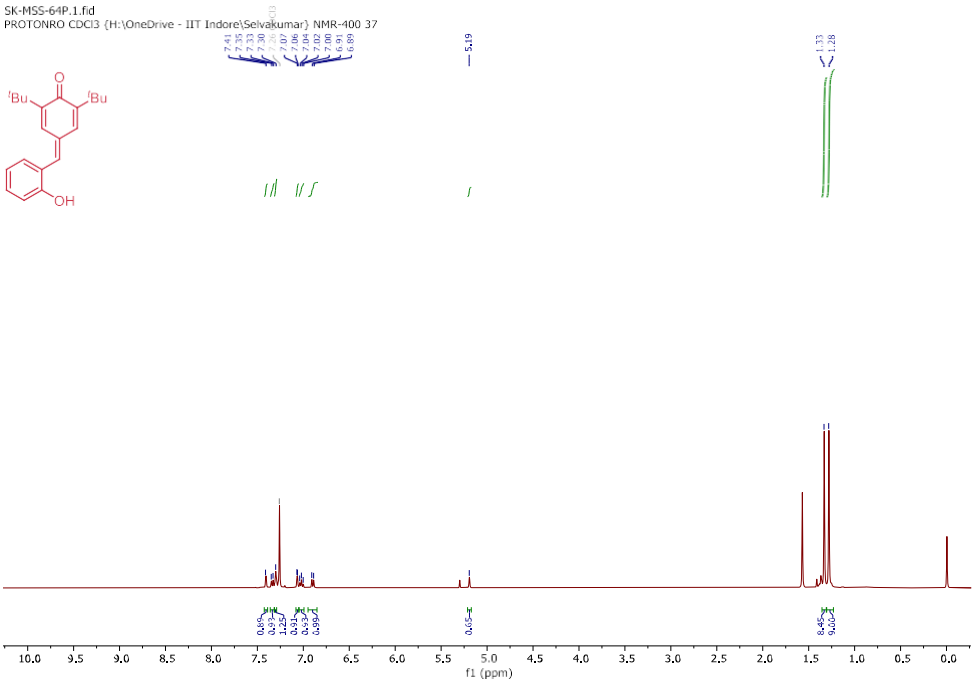


Figure 4: ^{1}H- NMR spectrum of **6** in $CDCl_3$

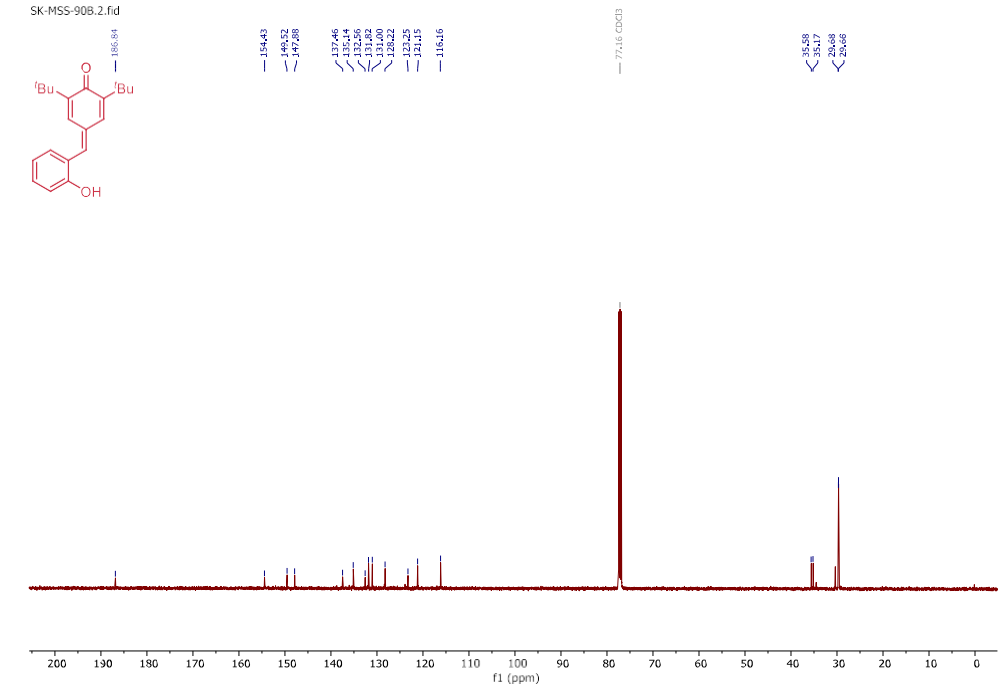


Figure 5: ^{13}C- NMR spectrum of **6** in $CDCl_3$

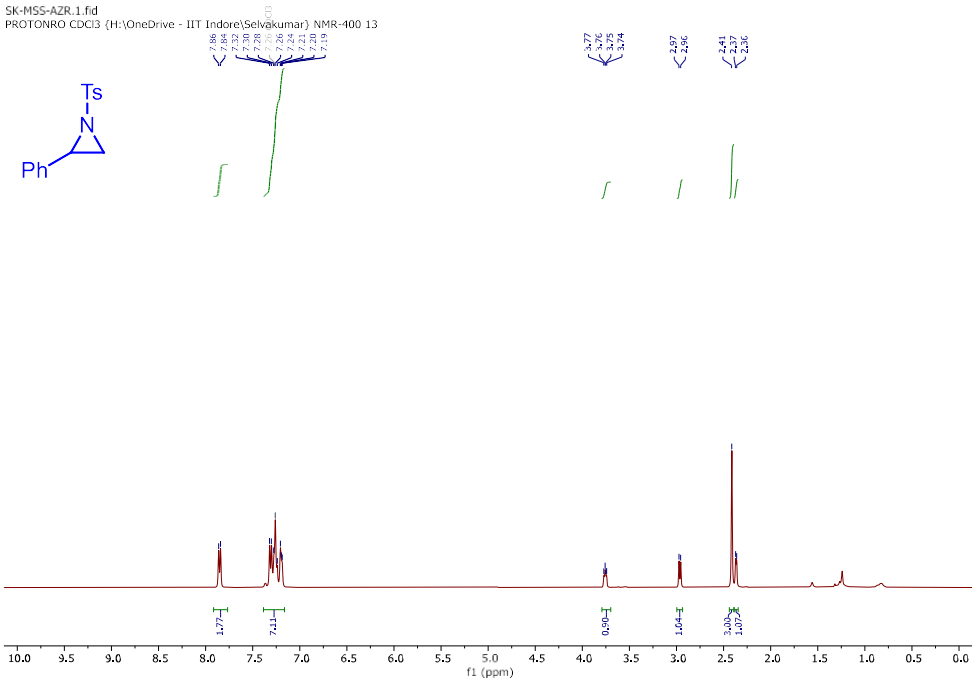


Figure 6: ^{1}H- NMR spectrum of **9** in $CDCl_3$

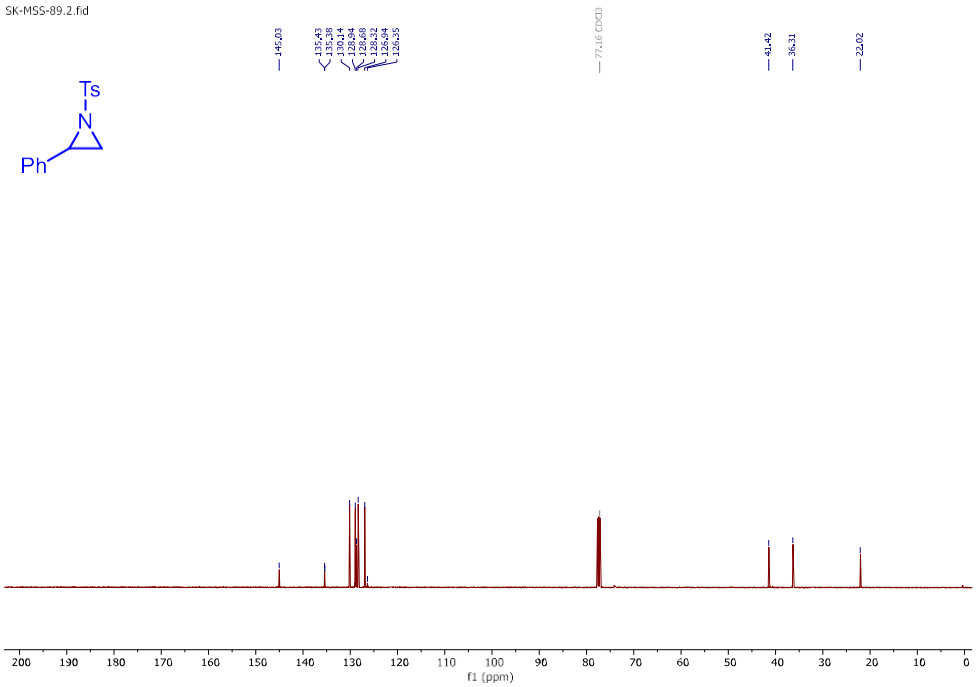


Figure 7: ^{13}C- NMR spectrum of **9** in $CDCl_3$

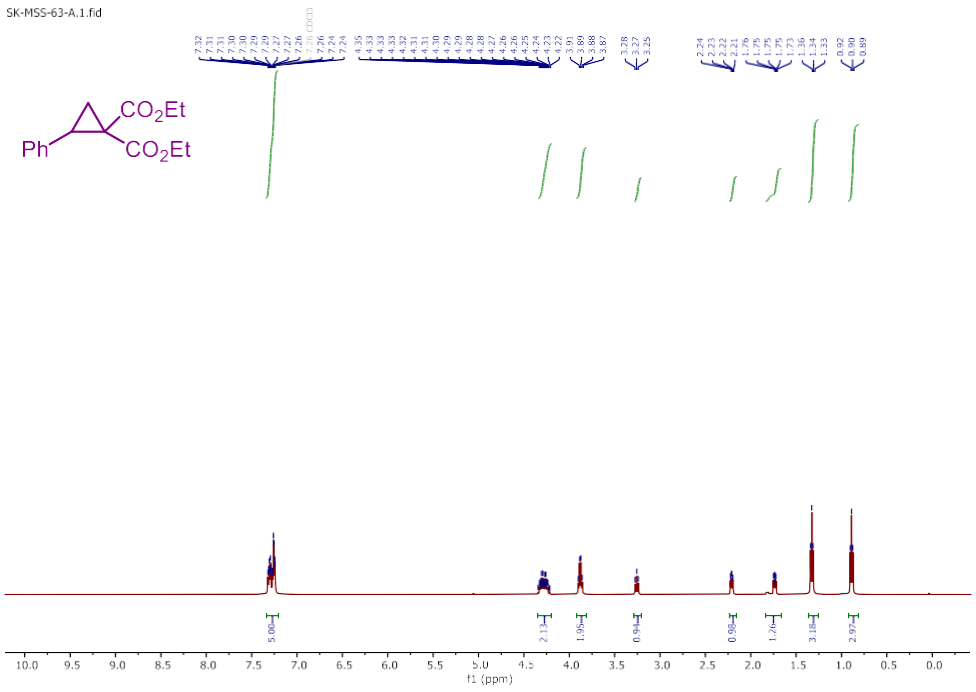


Figure 8: ^{1}H- NMR spectrum of **12** in $CDCl_3$

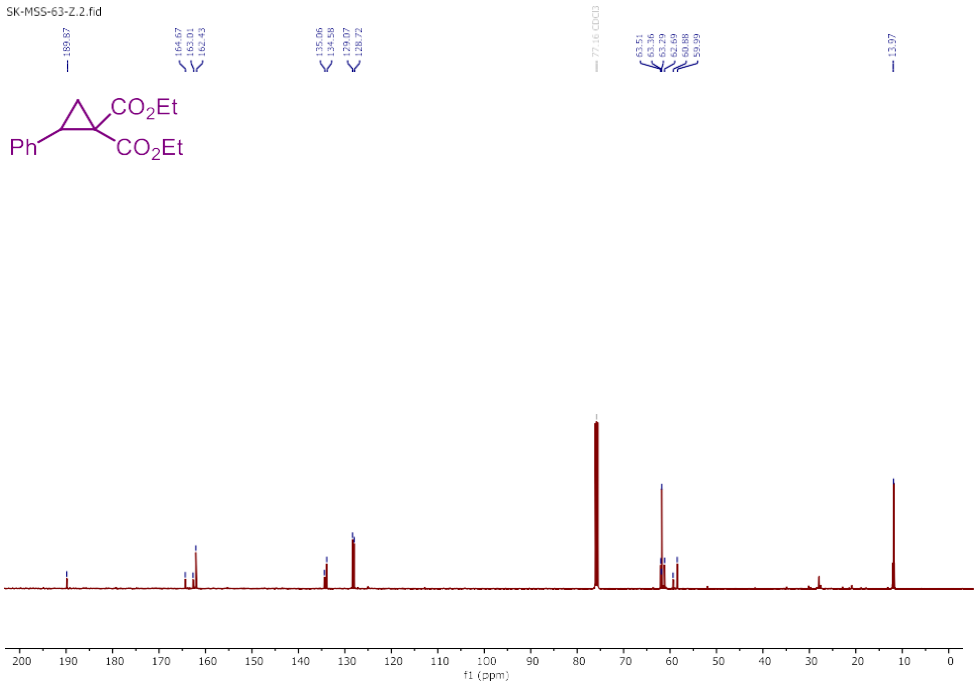


Figure 9: ^{13}C- NMR spectrum of **12** in $CDCl_3$

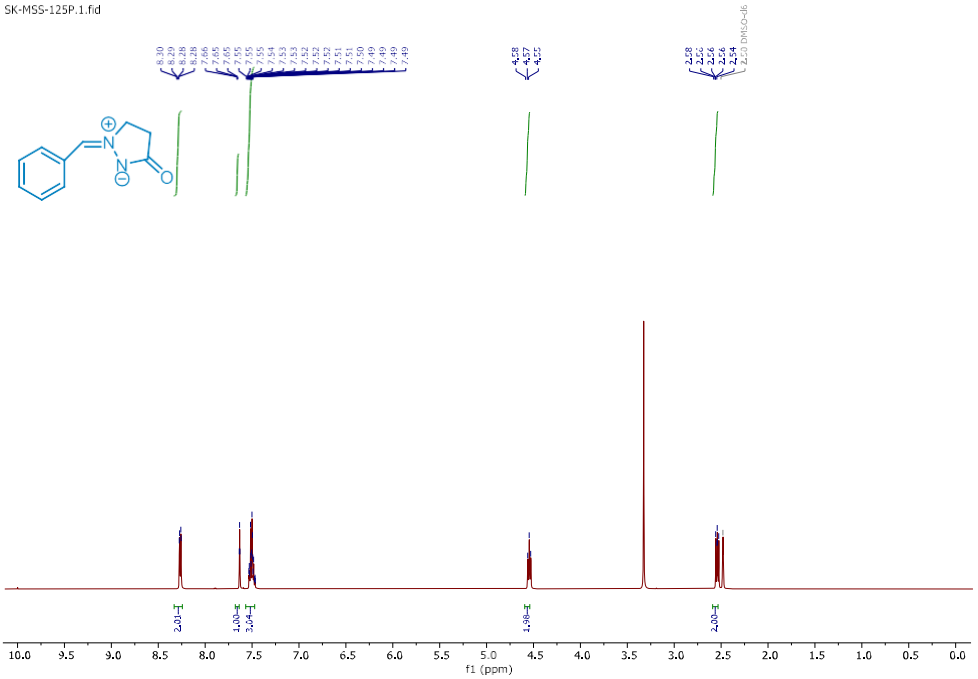


Figure 10: ^{1}H- NMR spectrum of **17** in DMSO-d_6

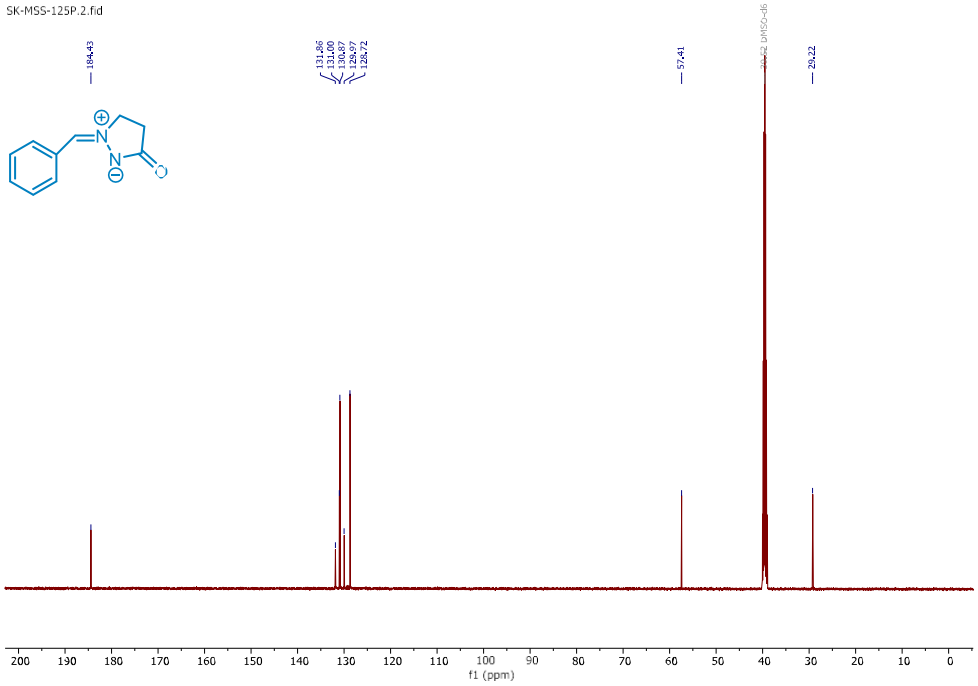


Figure 11: ^{13}C- NMR spectrum of **17** in DMSO-d_6

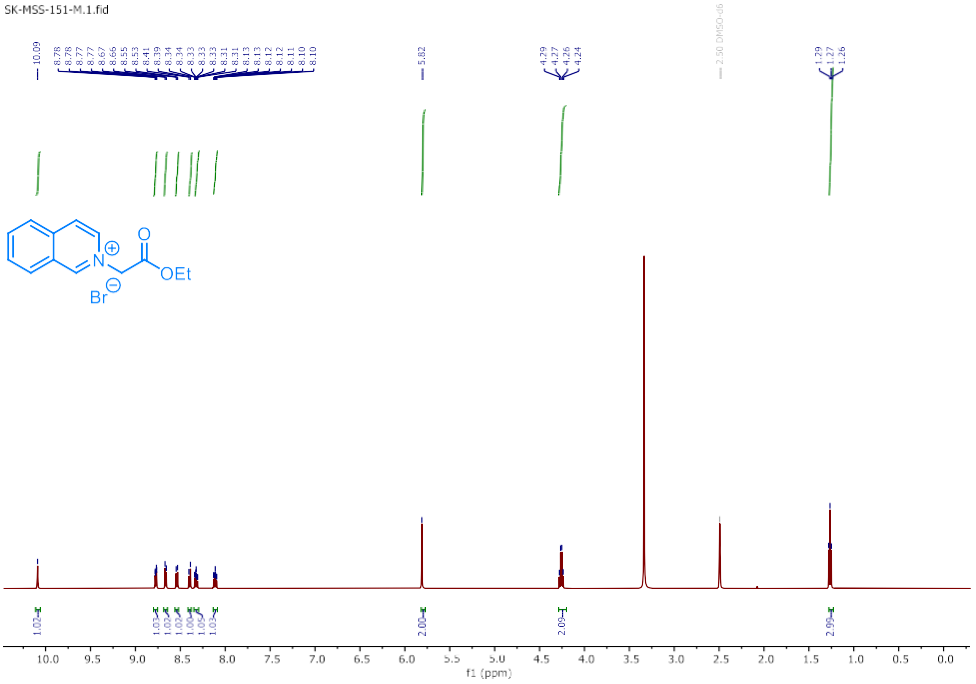


Figure 12: ^{1}H- NMR spectrum of **20** in DMSO-d_6

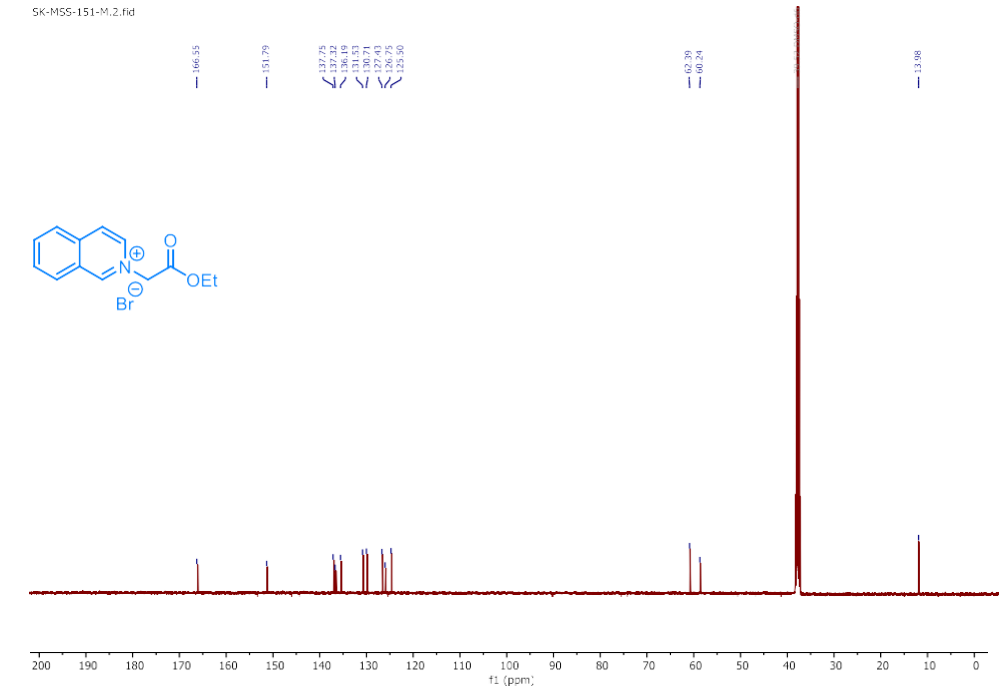


Figure 13: ^{13}C- NMR spectrum of **20** in DMSO-d_6

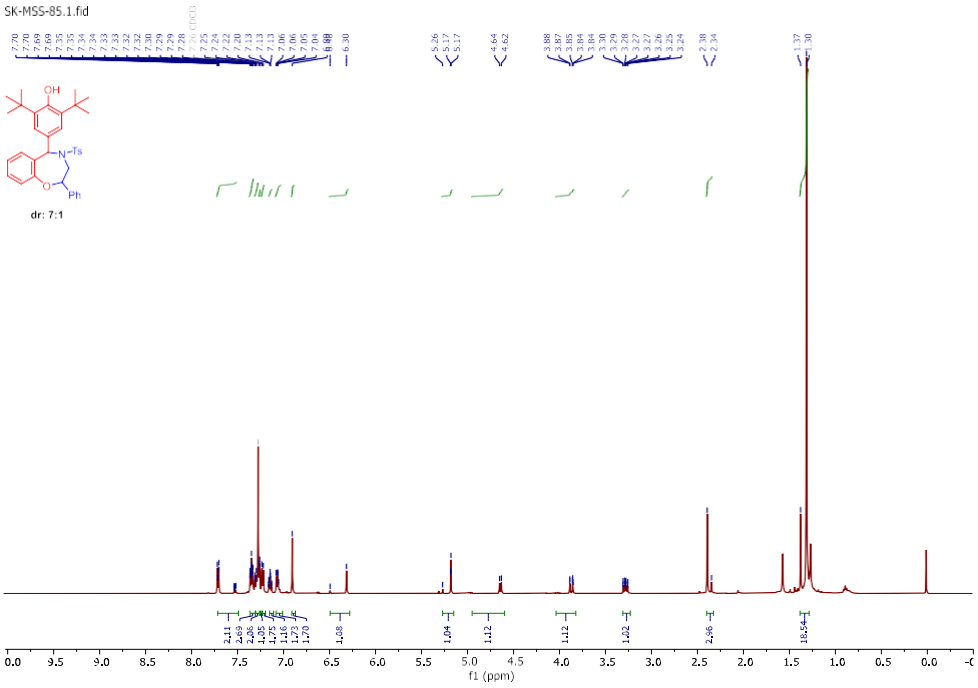


Figure 14: ^{1}H- NMR spectrum of **4a** in $CDCl_3$

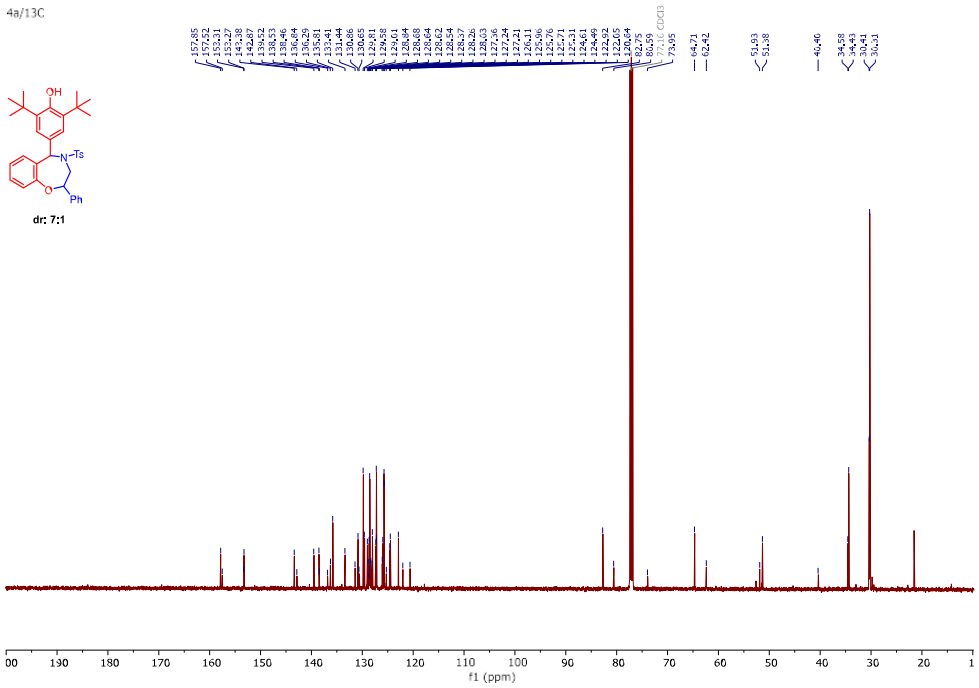


Figure 15: ^{13}C- NMR spectrum of **4a** in $CDCl_3$

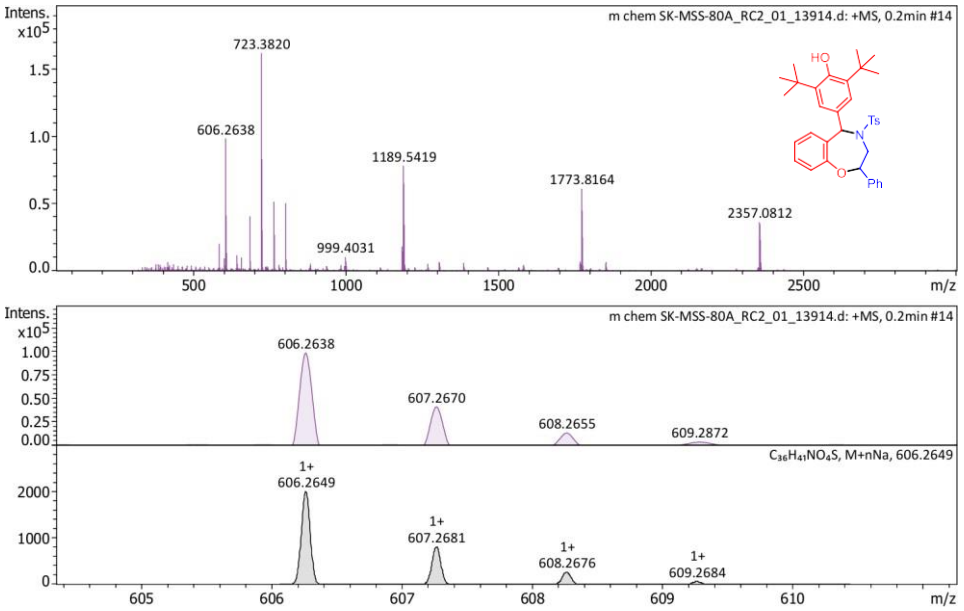


Fig.16: HR-MS data of **4a** in MeOH

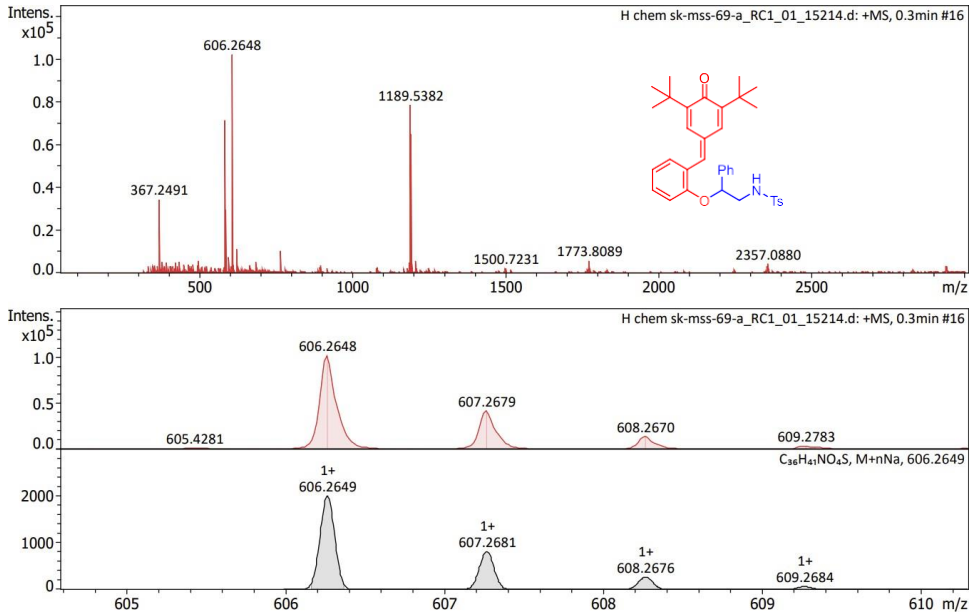


Fig.17: HR-MS data of **3a** in MeOH

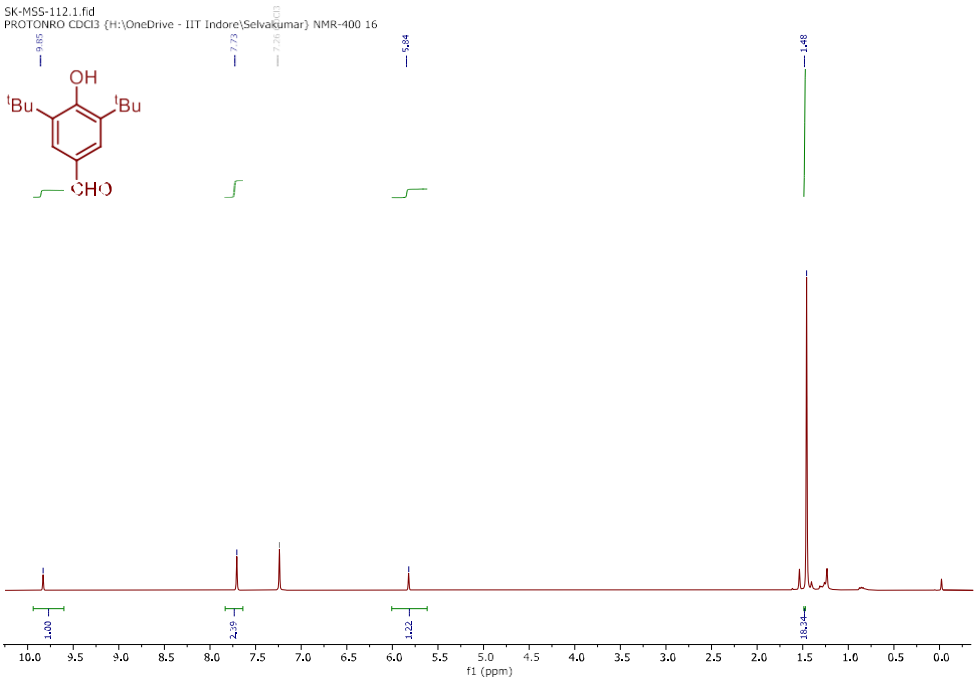


Fig.18: ^{1}H- NMR spectrum of **5a** in $CDCl_3$

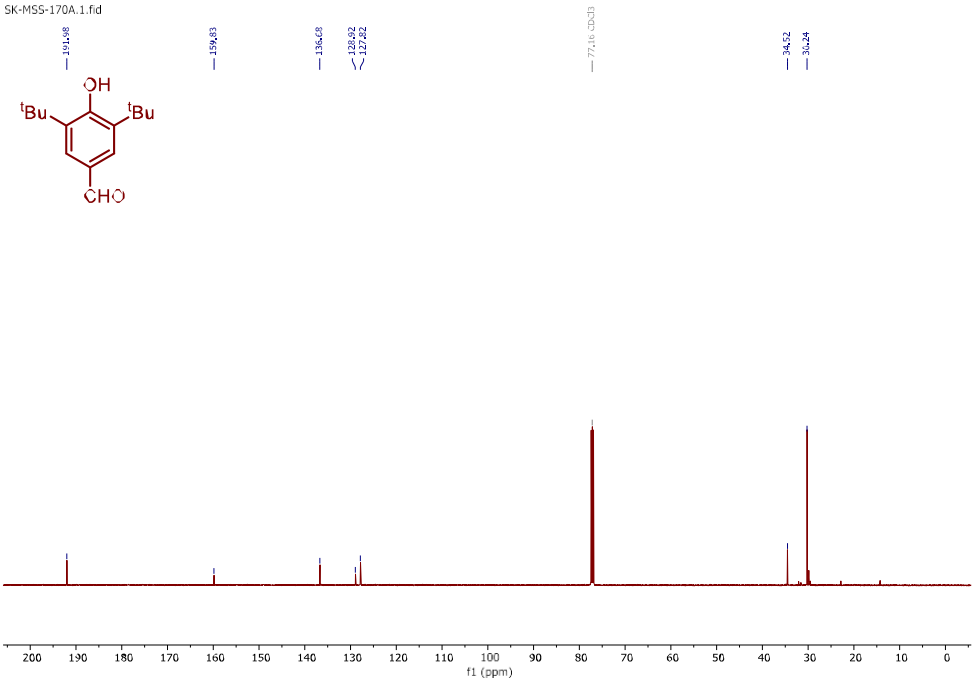


Fig.19: ^{13}C- NMR spectrum of **5a** in $CDCl_3$

Chapter 6

6.1 Results and Discussion:

6.1.1 Optimization of reaction conditions for *N*-tosyl aziridine

A systematic study was undertaken to evaluate the effect of various Lewis acid catalysts and reaction conditions on the regioselective ring-opening of *N*-tosylated aziridines with phenolic substrates.

Catalyst and solvent screening (initial phase)

Initial experiments employed $Zn(OTf)_2$ as the Lewis acid catalyst due to its established efficacy in ring-opening reactions. At room temperature in DCM, compound **3a** was obtained in 6% yield, with no trace of cyclized product **4a** (Entry 1, Table 1). Switching the solvent to toluene led to only trace formation of **3a**, indicating solvent polarity plays a crucial role in stabilizing transition states or intermediates.

Notably, when the temperature was elevated to 80°C using DCE as the solvent (Entry 4), **4a** was obtained in an 18% yield, accompanied by a measurable diastereomeric ratio. (dr) of 2.6:1. Similarly, in toluene at 80°C (Entry 7, Table 1), **4a** was isolated in 31% yield (dr 2.9:1), showing enhanced activity under thermal conditions. These results highlight temperature as a critical factor in activating the catalyst-substrate complex.

Among the catalysts screened (Entries 8–14, Table 1), $Bi(OTf)_3$ and $Sn(OTf)_2$ showed comparable yields (12–13%) for **4a** at room temperature, but $Bi(OTf)_3$ afforded the highest diastereoselectivity of 6.7:1. This suggests that the geometry or steric bulk of the metal center influences the transition state, affecting stereochemical outcomes.

Temperature effect and extended catalyst comparison

Subsequent entries (15–25, Table 2) explored a wider array of Lewis acids under varied thermal conditions. $Sc(OTf)_3$ and $Bi(OTf)_3$ at 0°C

produced only modest yields (9–13%) but improved dr up to 4.8:1. However, in general, lowering the temperature reduced conversion, suggesting that ring strain release requires a thermal push.

Attempts with $[Cu(CH_3CN)_4BF_4]$, $Zn(OTf)_2$ in polar solvents, and various catalysts in high-boiling solvents like xylene or Ph-CF_3(Entries 17–25, Table 2) largely failed to produce significant yields of **4a**. The poor outcomes could be attributed to solubility limitations or rearrangement reactions of *p*-QMs under Lewis acid conditions.

Further optimization and ligand influence

The next phase (Entries 26–38, Table 3) assessed alternate Zn-based catalysts and different metal triflates at varying temperatures. $Zn(NTf_2)_2$ (Entry 32) in DCM at room temperature yielded 13% of **4a** with exceptional diastereoselectivity (7.1:1). $Co(OTf)_2$ (Entry 34, Table 3) and $Cu(NTf_2)_2$ (Entry 36, Table 3) also showed moderate yields (9–18%) with acceptable dr values, highlighting their potential as alternative Lewis acids.

However, $Sc(OTf)_3$ and $Bi(OTf)_3$ at sub-zero temperatures did not promote product formation, indicating temperature constraints on these catalysts' activity.

Incorporating ligands such as 1,10-phenanthroline (*o*-phen) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) in metal-catalyzed reactions (Entries 39–52, Table 4) yielded minimal improvements. Only $Cu(OTf)_2$with dtbpy (Entry 43) led to 22% of **4a** with a dr of 3:1, while others produced negligible yields. Ligands may interfere with substrate coordination or increase Lewis's acidity, increased catalytic turnover.

6.1.2 Reactions with diester-substituted cyclopropanes (12a)

An alternative substrate, diethyl 2-phenylcyclopropane-1,1-dicarboxylate (**12a**), was also investigated. Under similar Lewis acid catalysis conditions, the major product observed was the aldehyde **5a**, with cyclized product **7a** remain undetectable. For example, $Sc(OTf)_3$ and $Bi(OTf)_3$ in DCM at room temperature gave 21% yields of **5a**, while

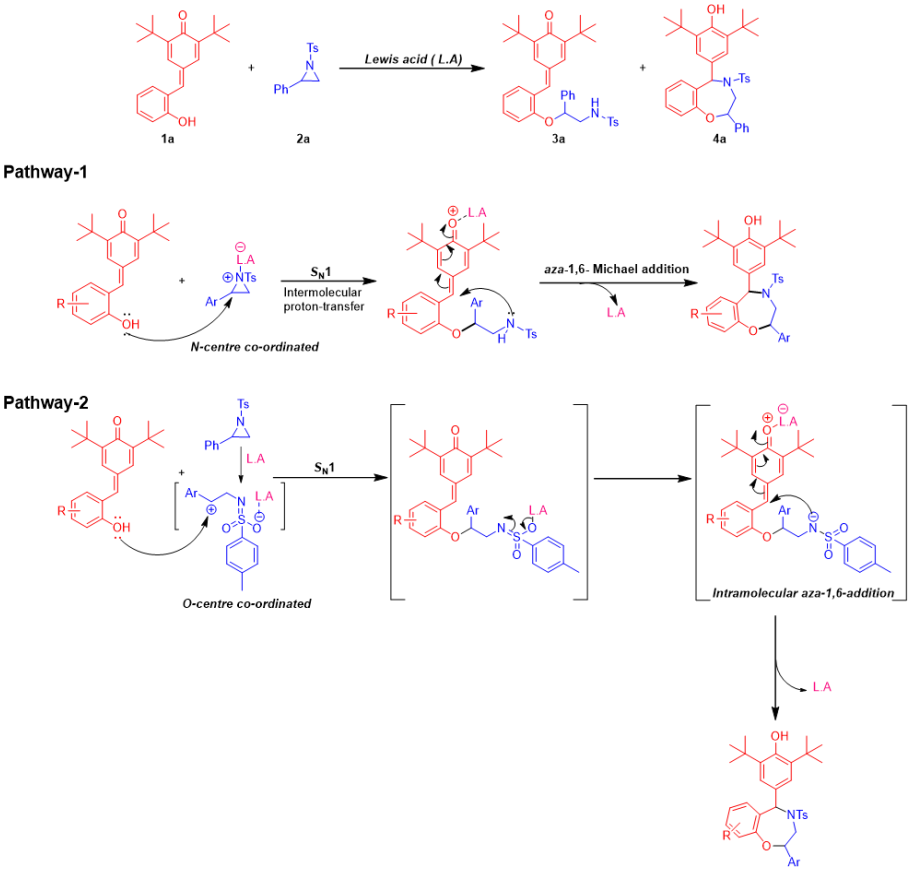
no corresponding **7a** was isolated (entries 1 and 4). This suggests that the steric and electronic demands of the diester moiety may hinder cyclization or divert the pathway toward alternative reaction channels.

6.1.3 Summary of optimization conditions

- **Best catalyst/solvent system** for **4a** formation: $Zn(OTf)_2$ in toluene at 80°C (Entry 7, Table 1) yielded 31% with 2.9:1 dr.
- **Highest diastereoselectivity** was obtained with $Zn(NTf_2)_2$ in DCM (Entry 32, Table 3), giving a dr of 7.1:1.
- **Ligand-assisted catalysis** with $Cu(OTf)_2$ and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) showed improved yields and moderate dr values.
- **Donor-acceptor (DA) Cyclopropanes (12a)** led predominantly to by-product **5a**, indicating poor compatibility under current catalytic conditions.

These findings provide a foundation for future mechanistic exploration and potential structural modifications to enhance product yields and selectivity.

6.2. Plausible reaction mechanism:



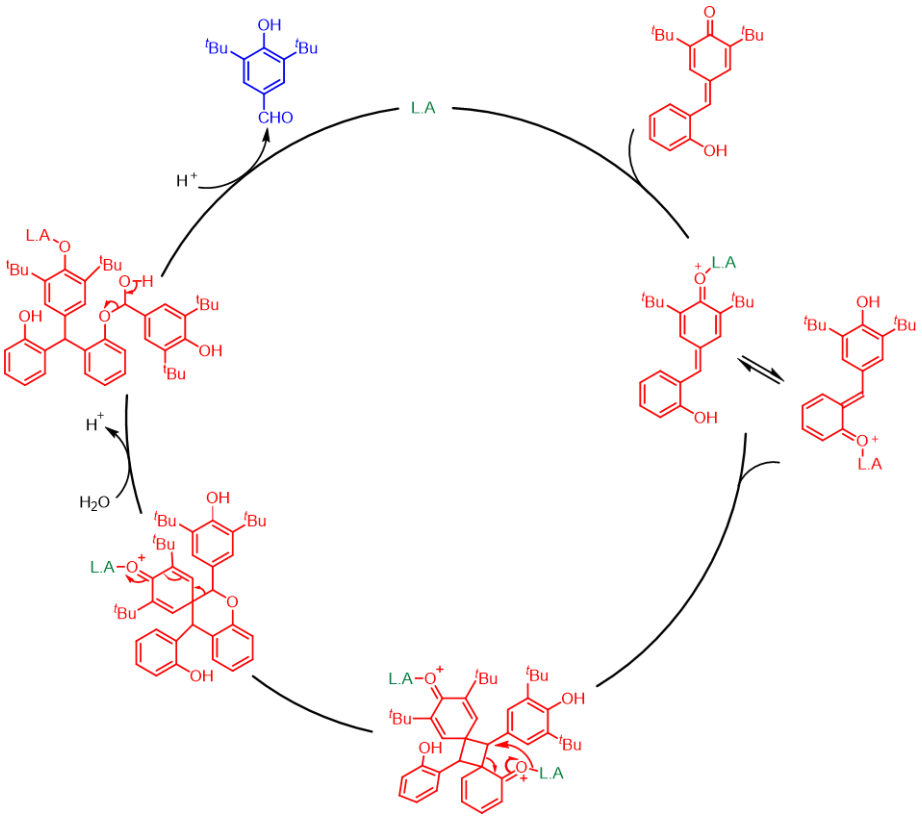
Scheme 9: Plausible mechanism of our hypothesis.

Lewis's acid (L.A.)-catalyzed reaction mechanism between compound **1a**, featuring a hydroxyl group, and aziridine derivatives **2a**. The pathways outlined involve the synthesis of benzoxazepine derivatives via distinct mechanistic routes. Pathway 1 begins with the activation of **2a** by the Lewis acid, generating an electrophilic intermediate. A proton transfer enables the formation of an aza-Michael adduct through a 1,6-addition to **1a**, yielding structures **3a** and **4a**. This pathway emphasizes the stepwise activation of reactants, highlighting the role of intermolecular proton transfer in forming the product. Pathway 2 employs a similar activation strategy but diverges mechanistically with the formation of a 1,3-dipolarophilic species. This intermediate undergoes an intramolecular nucleophilic attack facilitated by Lewis acid producing the final benzoxazepine structure. The nucleophilic

hydroxyl group on **1a** is critical in driving the reaction forward through successive proton exchanges and bond rearrangements.

Both pathways demonstrate the pivotal role of Lewis acids in stabilizing intermediates, enhancing electrophilicity, and promoting cyclization. These proposed mechanisms underline the complexity of regioselectivity and stereochemical control during the cyclization of aziridine derivatives to form benzo-fused seven-membered heterocycles. Further optimization and experimental validation of these pathways are required to understand their efficiency.

6.3. Plausible mechanism of by-product:



Scheme 10: Plausible mechanism of by-product[25]

Mechanistic insight into by-product formation[25]

During our studies on Lewis's acid-catalyzed cyclopropane ring-opening reactions, a side product was consistently observed under specific conditions. Mechanistic studies and structural elucidation,

supported by literature precedent, suggest that this by-product arises via a distinct reaction pathway involving quinone methide (QM) intermediates and Lewis's acid-mediated transformations.

Formation of quinone methide intermediates

The initial step involves the Lewis acid (L.A.) activation of the phenolic starting material, generating both *para*-quinone methide (*p*-QM, denoted as **1a**) and *ortho*-quinone methide (*o*-QM, **1a′**) species *via* proton loss and rearrangement. These electrophilic intermediates are known to engage in cycloaddition reactions due to their electron-deficient diene character.[25]

[2+2] *Ipso*-cycloaddition and ring expansion

The activated QMs (**1a** and **1a′**) subsequently undergo a formal [2+2] *ipso*-cycloaddition with a phenolic nucleophile. This interaction leads to the formation of a highly strained spirobutane intermediate, wherein the two aromatic fragments are bridged *via* a four-membered ring. This transient species undergoes ring expansion under the influence of Lewis acid, affording a more stable six-membered chroman framework. The resultant compound features a spiro-connected dienone system, with a *para*-hydroxyaryl moiety retained on the chroman ring.[25]

Retro-Friedel–Crafts reaction and hemiacetal formation

Upon formation of the intermediate, Lewis's acid facilitates retro-Friedel–Crafts-type cleavage to take place in the presence of trace water. This leads to the opening of the chroman ring and the generation of a hemiacetal intermediate. Protonation and subsequent hydrolytic cleavage of C-O bond result in the dissociation into two discrete products: the Triarylmethanes (TRAMs) compound and an aldehyde-functionalized phenol (**5a**).[25]

Mechanistic illustration and role of Lewis acid

The overall transformation is summarized in the proposed catalytic cycle, where the Lewis acid facilitates multiple key steps: activation of

QMs, stabilization of transition states during cycloaddition and ring rearrangement, and promotion of retro-Friedel–Crafts cleavage. The presence of water plays a crucial role in the final hydrolysis, indicating that moisture control is critical for suppressing or promoting by-product formation, depending on the desired outcome.

This mechanistic pathway illustrates a complex yet elegant sequence of events, highlighting how minor changes in catalytic or environmental parameters can shift reaction outcomes toward undesired yet mechanistically insightful products. Understanding such pathways is vital for refining selectivity and designing improved synthetic protocols in heterocyclic chemistry.

6.4. Conclusion:

This study successfully demonstrates the potential of Lewis acid-catalyzed [4+3]-cyclization between *para*-Quinone methides (*p*-QMs) and aziridine derivatives as a strategic method for constructing benzofused seven-membered *N*-heterocycles, specifically benzoxazepines. Through the systematic evaluation of a broad array of Lewis acids, solvents, and temperature, the catalytic performance of $Zn(OTf)_2$ in toluene at elevated temperature emerged as the most effective, affording the target compound **4a** in a 31% yield with favorable diastereoselectivity. The reaction's sensitivity to temperature and solvent underscores the importance of precise condition optimization in achieving selective product formation.

Furthermore, mechanistic studies provided insights into the plausible pathways leading to both desired cyclization products and undesired by-products, reinforcing the complexity and significance of Lewis acid activation in heterocycle synthesis. The reactivity pattern observed with donor–acceptor cyclopropanes also broadened the understanding of substrate compatibility, although these systems favored alternative reaction outcomes under the tested conditions.

Overall, the research contributes a valuable advancement to synthetic heterocyclic chemistry by expanding the toolbox for generating bioactive benzoxazepine scaffolds. The methodologies and findings reported herein establish a foundation for future studies aimed at improving reaction efficiency, extending substrate scope, and applying this strategy to the synthesis of Active Pharmaceutical Ingredient (APIs).

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