Organocatalytic Enantioselective Synthesis of Bioactive Macro-lactones and Development of Synthetic Methodologies Involving C–C and C–N bond Formations

by

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A thesis submitted to the
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Under the supervision of

Dr. Gurunath Suryavanshi

and under the co-supervision of

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Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, "*Organocatalytic Enantioselective Synthesis of Bioactive Macro-lactones and Development of Synthetic Methodologies Involving C–C and C–N bond Formations*" submitted by *Mr. Satish Govind More* to the Academy of Scientific and Innovative Research (AcSIR), in partial fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in Science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) *etc.*, used in the thesis from other source(s), have also been duly cited and acknowledged.

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Date: 29/11/2022	Date: 29/11/2022	Date: 29/11/2022

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I Mr. Satish Govind More, a Ph. D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC17J26028 hereby undertake that, the thesis entitled "Organocatalytic Enantioselective Synthesis of Bioactive Macro-lactones and Development of Synthetic Methodologies Involving C–C and C–N bond Formations" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)*".

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CONTENTS

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their continuous showering of boundless affection on me and supporting me in whatever I choose or do. The warmth and moral value of my parents have stood me in good stead throughout my life, and I would always look up to them for strength no matter what I have to go through. This Ph. D. thesis is a result of my families extraordinary will, efforts, and sacrifices.

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Satish G. More

2022

ABBREVIATIONS AND CHEMICAL FORMULAS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N*-tert-Butoxycarbonyl
Bz	Benzoyl
BBr_3	Boron tribromide
Br_2	Bromine
$(Boc)_2O$	Di-tert-butyl dicarbonate
n-Bu	n-Butyl
n-BuLi	n-Butyl lithium
t-Bu	*tert*-Butyl
CDC	Cross Dehydrogenative Coupling
CSA	Camphorsulfonic acid
CH_3CN	Acetonitrile
CH_2Cl_2	Dichloromethane
EtOH	Ethanol
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutyl aluminium hydride
DMP	Dess–Martin periodinane
DMF	Dimethyl formamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulphoxide
DMAP	N,N-dimethyl-4-aminopyridine
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl

EtOAc	Ethyl acetate
g	Grams
h	Hours
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
I_2	Iodine
imid.	Imidazole
K_2CO_3	Potassium carbonate
IR	Infra-red
IBX	2-Iodoxybenzoic acid
LAH	Lithium aluminum hydride
LiHMDS	Lithium hexamethyldisilazide
M^+	Molecular ion
Me	Methyl
MOM	Methoxymethyl
*m*CPBA	meta-Chloroperoxybenzoic acid
min	Minutes
mg	Miligram
mL	Milliliter
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
NBS	*N*-Bromosuccinimide
NaOH	Sodium Hydroxide
$NaHCO_3$	Sodium bicarbonate
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
PCC	Pyridinium chlorochromate
Pd/C	Palladium on activated charcoal
PDC	Pyridinium dichromate

DCC	Dicyclohexylcarbodiimide
Ph	Phenyl
p-Ts	*p*-Tosyl
p-TSA	*p*-Toluene sulfonic acid
Py	Pyridine
PhI	Iodobenzene
PIDA	(Diacetoxyiodo)benzene
DMAP	4-(N,N-Dimethylamino)pyridine
HTIB	Hydroxy(tosyloxy)iodobenzene
PPh_3	Triphenylphosphine
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethyl-1-piperidinyl)oxyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
TBACl	Tetrabutyl ammonium chloride
TBAB	Tetrabutyl ammonium bromide
p-QMs	*para*-Quinone methides
QIK's	Quinone Imine Ketals
D-A Cyclopropanes	Donor-acceptor cyclopropanes
SET	Single Electron Transfer

GENERAL REMARKS

1. All reagents and starting materials from commercial suppliers were used as such without further purification.
2. Solvents were distilled and dried using standard protocols. Reactions were carried out in anhydrous solvents under argon, nitrogen atmosphere in oven-dried glassware.
3. Petroleum ether refers to the fraction collected in the boiling range 60-80 ^{0}C.
4. Organic layers after every extraction were dried over anhydrous sodium sulphate.
5. Air sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa.
6. Column Chromatography was performed over silica gel (100-200 mesh and 230-400 mesh size).
7. All evaporations were carried out under reduced pressure on Heidolph rotary evaporator below 50 °C unless otherwise specified.
8. All reactions are monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated E-Merck silica gel plates (60F-254). Visualization was accomplished with either UV light, Iodine adsorbed on silica gel or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), p-anisaldehyde or $KMnO_4$ followed by heating with a heat gun for ~15 sec.
9. ^{1}H and ^{13}C NMR spectra were recorded on Brucker FT AC-200 MHz, Brucker Advance 400 MHz, Brucker Advance 500 MHz and JEOL ECX 400 instruments using TMS as an internal standard. The following abbreviations were used: s=singlet, d=doublet, t=triplet, q=quartet, m multiplet, br. s.=broad singlet, dd=doublet of doublet, dt=doublet of triplet and ddd=doublet of doublet of doublet, app=apparent.
10. Chemical nomenclature (IUPAC) and structures were generated using Chem Draw Professional 21.0.0.28 software.

11. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and EI Mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 eV using a direct inlet system.
12. UV-vis absorption spectra were measured with a UV-Vis spectrum were recorded with a Shimadzu 1800 spectrophotometer.
13. All the melting points are uncorrected and were recorded using a scientific melting point apparatus (Buchi B-540) and the temperatures are in centigrade scale.
14. The compounds, scheme and reference numbers given in each chapter refers to that chapter only.

AcSIR	**Synopsis of the thesis to be submitted to the Academy of Scientific and Innovative Research for award of the degree of Doctor of philosophy in Chemical Sciences**
Name of the Candidate	Mr. More Satish Govind
Enrollment No. and Date	Ph. D in Chemical Sciences (10CC17J26028); January 2017
Title of the Thesis	Organocatalytic Enantioselective Synthesis of Bioactive Macro-lactones and Development of Synthetic Methodologies Involving C-C and C-N Bond Formations
Research Supervisor	Dr. Gurunath Suryavanshi
Research Co-Supervisor	Dr. Shafeek A. R. Mulla

1. Introduction

Natural products are the key source in medicine due to its massive structural and chemical diversity.[1] Many drugs which are isolated from natural products having biological activity. Macrolides are one of the major classes of the natural product isolated from various fungal metabolites and having considerable attention due to their stimulating pharmacological features such as antitumoral, antibacterial, or hypolipidemic properties.[2] In particular,12 membered macrolides attracted chemist much because of their prominent biological activities such as antimicrobial, anti-bacterial and anti-malarial. [3] The natural product Phaseolide A and Balticolid are the 12 membered macrolactones showed the versatile biological activity. In particular, Phaseolide A was isolated by Yohei Morishita and co-workers in 2020 from *Macrophomina phaseolina,*and which showed the antimicrobial activity.[4] Similarly, the novel marine macrolide Balticolid was isolated in 2011 by Shushni and coworkers from the marine fungus which belongs to *Ascomycetous* species *via* EtOAc extraction process, and having antiviral as well as anti-HSV-1 activity with an IC_{50} value of 0.45 μM. Additionally, Carbon–carbon (C–C) , and Carbon–Nitrogen (C–N) bond-forming reactions are key steps for the construction of complex molecular frameworks in many syntheses of natural products and organic compounds, as well as in a variety of industrial applications.[5] In this context, diaryl methine cyclic ethers compound and Hemiaminals are gain much more interest in the organic synthesis due to presence of ether moieties.[6] Furthermore, the Sulfoximine are monoaza analog of sulfone is the attractive synthone widely present in natural products, and synthesized compounds.[7] Owing the importance of sulfoximines and *N*-alkyl sulfoximines many natural and unnatural compound synthesized using sulfoximines.[8]

2. Statement of Problem

Due to biological activity of 12-membered macrolactones, there are always need to develop new route for the twelve membered macrolacones, However, Phaseolide A and Balticolid are marine 12-membered macrolactones having attractive structural property and important biological activities. and its necessary to developed new syntheytic route. The Cyclic ethers are having gained importance due

to the abundance in biomass, and many natural products containing the cyclic ethers showed the biological importance. Sulfoximines, *N*-alkyl sulfoximes, and its derivatives are core structure of various natural products and biologically active molecules. Therefore, new methods are for synthesis of these core structure need to develop.

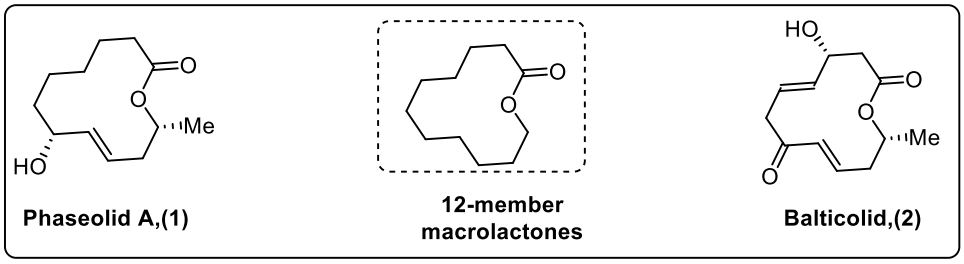
3. Objectives

1) Total Synthesis of 12 membered macro lactones Phaseolide A, and Balticolid.
2) Metal free and radical mediated conjugate addition of cyclic ether on *p*-QMs, and Quinone imine ketals (QIKs).
3) Metal free nucleophilic addition of *N*H- sulfoximines on *p*-QMs, and aza-oxyallyl cations.
4) Lewis acid catalysed *N*-alkylation of sulfoximine and C-alkylation of Indolizines from ring opening of D-A cyclopropanes.

4. Methodology

1) The thesis is divided into four chapters. Chapter 1: Total Synthesis of 12 membered macro lactones Phaseolide A, and Balticolid. Chapter 2: Metal free and radical mediated conjugate addition of cyclic ether on *p*-QMs and Quinone imine ketals (QIKs). Chapter 3: Metal free nucleophilic addition of *N*H- sulfoximines on *p*-QMs and aza-oxyallyl cations. Chapter 4: Lewis acid catalysed *N*-alkylation of sulfoximine and C-alkylation of Indolizines from ring opening D-A cyclopropanes.

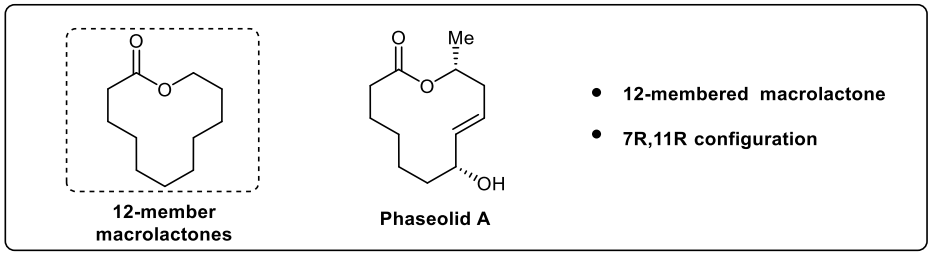
Chapter 1: Total Synthesis of 12 membered macrolactones Phaseolide A, and Balticolid



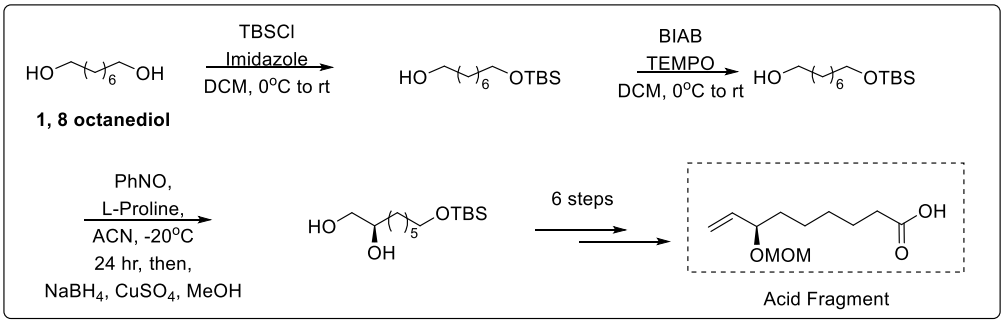
Section I: Synthetic Efforts Towards first total synthesis of Phaseolid A

Natural products are the key source in medicine due to its massive structural and chemical diversity. Many drugs which are isolated from natural products having biological activity. Macrolides are one of the major classes of the natural product isolated from various fungal metabolites and having considerable attention due to their stimulating pharmacological features such as antitumoral, antibacterial, or hypolipidemic properties. In particular,12 membered macrolides attracted chemist much because of their prominent biological activities such as antimicrobial, anti-bacterial and anti-malarial. A novel 12 membered macrolactone Phaseolide A is a fungal macrolide *Macrophomina phaseolina* was isolated by Yohei Morishita and co-workers in 2020. Its structural identified by

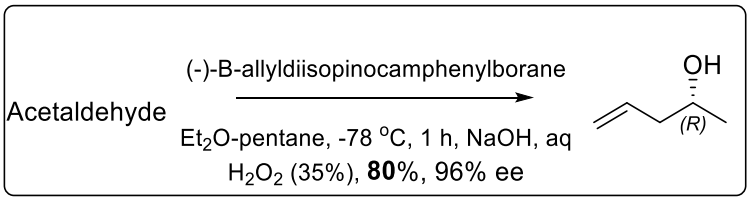
NMR, VCD spectral analysis, and the crystalline sponge method. Phaseolide A macrolactone containing two.



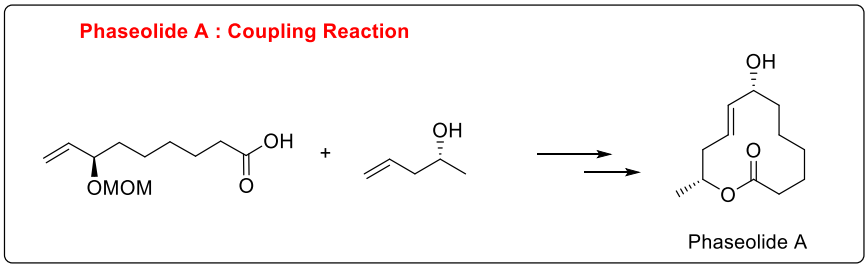
chiral centers at C-7 and C-11. possessed a 7R,11R configuration. Hence due to structural complexity and biological importance of macrolactone many research groups are interested to synthesis the different macrolides Initially we have started our synthesis toward acid fragment of Phaseolide A, Phaseolide starting from the commercially available starting material 1,8 octane-diol. The first diol protected TBS protection followed by the aldehyde formation of 1^{o} alcohol by standard TEMPO BIAB condition. Next, we performed our key step i.e., α- aminoxylation followed by reduction to formation of chiral diol in 63% yield. Then by performing several steps to obtained acid fragment in overall 9% yield.



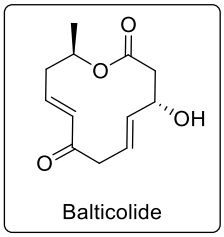
Next, we synthesized the allyl alcohol fragment from acetaldehyde by well-known Brown allylation.



Finally, coupling between acid fragment and alcohol fragment to formed di-olefinic ester which undergoes Grubbs metathesis and deprotection leads to formation of desired Target molecule Phaseolid A.

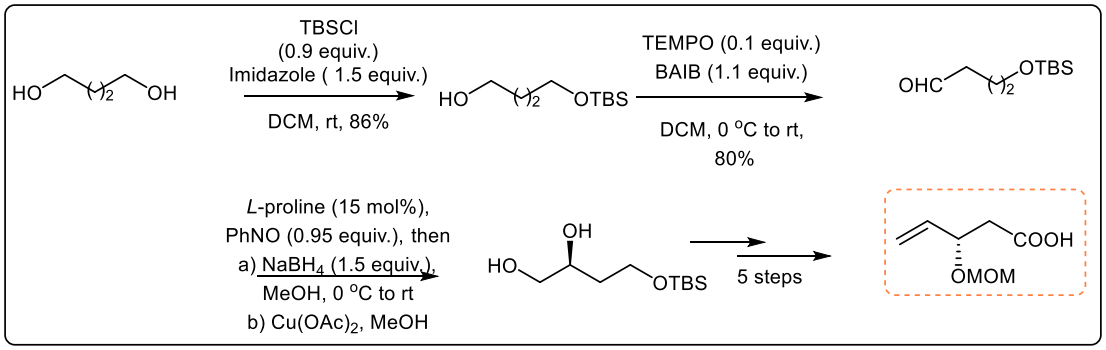


Section II: Section I: Synthetic Efforts Towards total synthesisof Balticolid



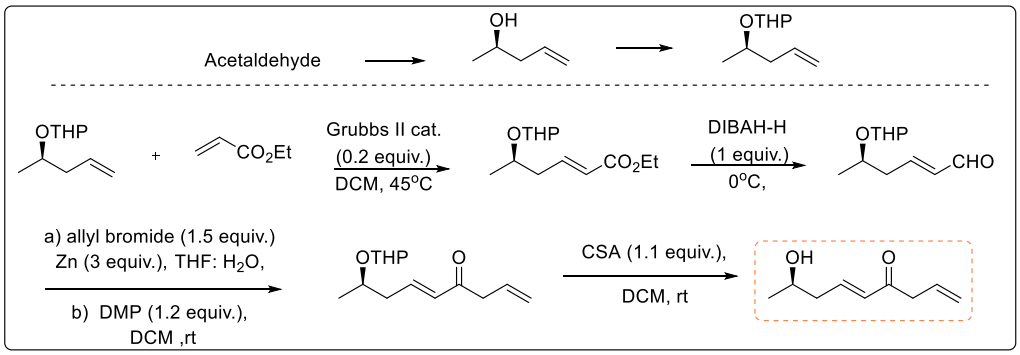
Marine microorganisms are identified as prosperous source of pharmaceutical active metabolites as numbers of secondary metabolites are isolated from these microorganisms. In particular, 12-membered macrolides isolated from fungal metabolites of marine microorganism significantly shows biological and pharmaceutical activities.

As a part of our ongoing research on the synthesis of 12 membered macro-lactone natural products in line with antimicrobial, anti-bacterial and anti-malarial, herein we plan our synthesis of Balticolid by proline catalysed aminoxylation, esterification and Grubb's metathesis sequences.



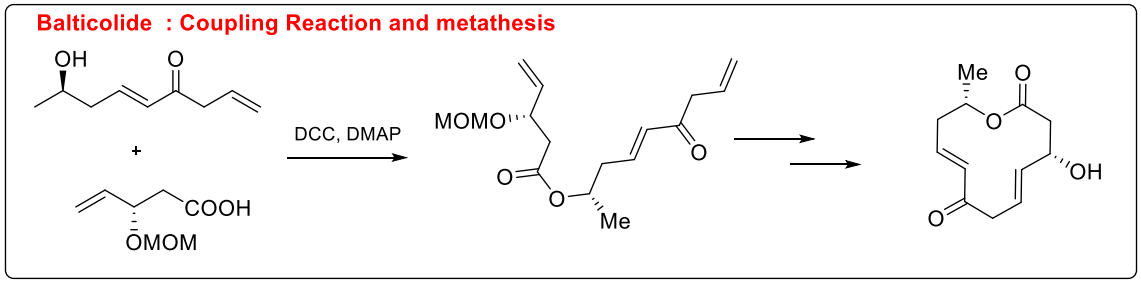
1,4-butanediol was subjected for mono-silylation reaction using TBSCl and imidazole in DCM at 0 °C followed by oxidation of primary alcohol using well known TEMPO-BAIB oxidation conditions, Next the chiral diol was prepared by *α*- amino-oxylation with two consequent steps. Next by performing several steps to obtained the acid fragment.

When, acid fragment in our hand next we synthesized the alcohol from chiral protected allyl alcohol and ethyl crotylate. The allyl alcohol and ethyl crotylate undergoes cross metathesis by grubbs (II)



generation catalyst to formed α- β unsaturated ester. Then, next *α, β*-unsaturated ester was reduced to give aldehyde (DIBAL-H, Toluene, -78 °C) which was then subjected to Barbier allylation followed by DMP mediated oxidation to give ketone. Finally, deprotection of THP under hydrolysis condition

(CSA) gave alcohol fragment. Finally, coupling between acid fragment and alcohol fragments coupled by steglich esterification process to obtained the di-olefinic ester which undergoes Grubb's metathesis followed by deprotection will give Balticolid.

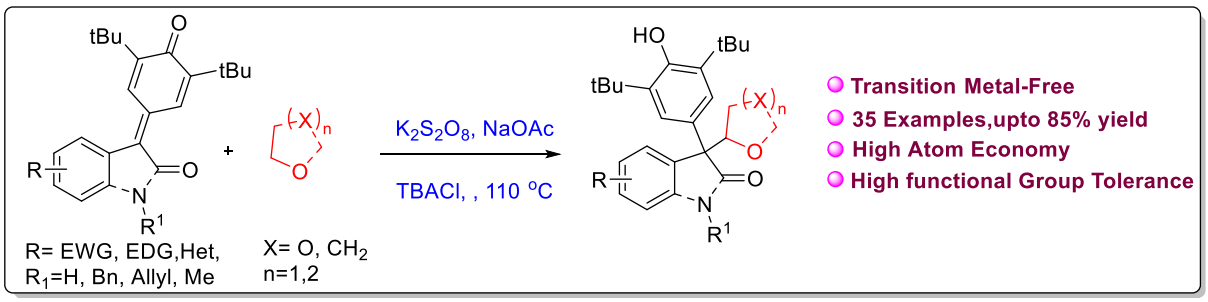


We have synthesised total synthesis of Balticolid from commercially available 1,4 butanediol, acetaldehyde and ethyl acrylate. The proline catalysed *α*–aminoxylation, Brown allylation and Grubbs metathesis are the key steps of the synthesis.

Chapter 2: Metal free and radical mediated conjugate addition of cyclic ether on *p*-QMs and Quinone imine ketals (QIKs).

Section I: Metal-free, radical 1,6-conjugated addition of cyclic ethers with *para*-quinone methides (*p*-QMs)

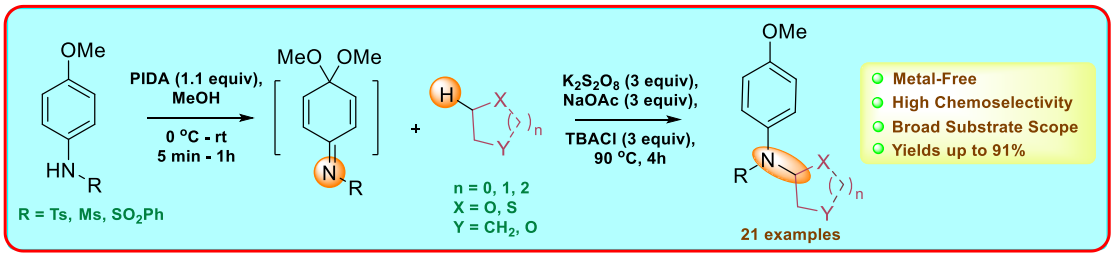
Carbon–carbon (C–C) bond-forming reactions are key steps for the construction of complex molecular frameworks in many syntheses of natural products and organic compounds, as well as in a variety of industrial applications. C–C bond formation under free radical reactions have emerged as a powerful tool for the synthesis of complex molecular frameworks. addition reactions of carbon-centered



cyclic ether radicals to electrophilic carbon acceptors have gained importance due to the abundance of these ethers in biomass. *p*-QMs are inherently found in natural products and pharmaceutical ingredients which possess broad spectrum biological activities. These activities mainly include antitumor, anticancer, antimicrobial, anti-inflammatory and antiviral effects. We have developed an efficient, metal-free, radical C–C bond formation reaction for cyclic ethers with *p*-QMs to afford diarylmethanes containing phenols functionalized with cyclic ethers in excellent yield and with high atom economy. We have elaborated our hypothesis relating to *p*-QMs derived from isatin to establish 3,3′-disubstituted oxindoles with quaternary stereogenic carbon centers. The formed products have been successfully utilised in various transformations such as dihydroxylation and dealkylation reactions.

Section II: Oxidative Radical-Mediated Addition of Ethers to Quinone Imine Ketals: An Access to Hemiaminals

The construction of C−N bonds has been a major research topic in organic synthesis. Nitrogen-containing frameworks are the backbone of around 25% biologically active compounds and synthetic intermediates. Among the various compounds containing C−N bonds having the hemiaminal moiety represents the core structure in many biologically active natural products and pharmaceutical agents. The typical example that includes Aspidophylline A, an alkaloid from the Apocynaceae family, displays



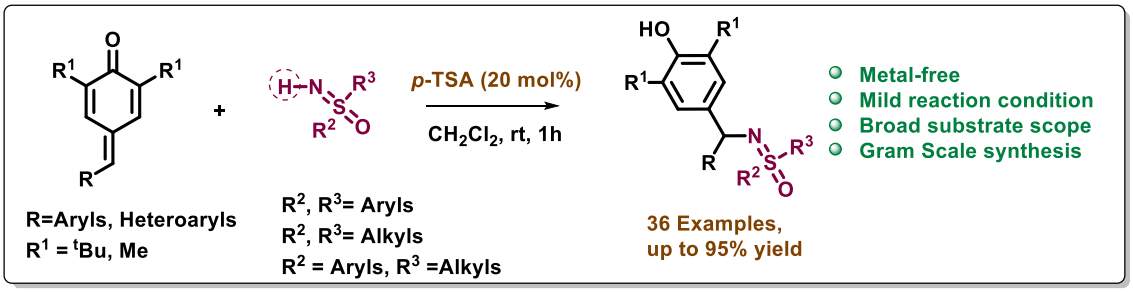
an antiviral activity. However, (−)-physovenine shows anti-cholinergic and miotic activities, while the indole nitrogen-bearing tetrahydrofuran (THF) ring acts as an HCV inhibitor, In particular, hemiaminal ether with sulfonamide as the core structure shows an interesting antitumor activity against the MGC-803 cell line with an IC_{50} value 1.06. Also, the substituted *N*-sulfonamides were present in a large number of bioactive molecules.

The study established an efficient metal-free approach for the synthesis of hemiaminals from QIK and various ethers. Further, this strategy highlights the optimized reaction conditions to obtain the desired products in good to excellent yields and shows the broad substrate scope and high functional grouptolerance with hemiaminals. Also, the formation of the α-oxyalkyl radical in the reaction was confirmed by radical scavenger experiments, and the C-centered radical was confirmed by the EPR spectroscopy experiment.

Chapter 3: Metal free nucleophilic addition of *N*H- sulfoximines on *p*-QMs and aza-oxyallyl cations.

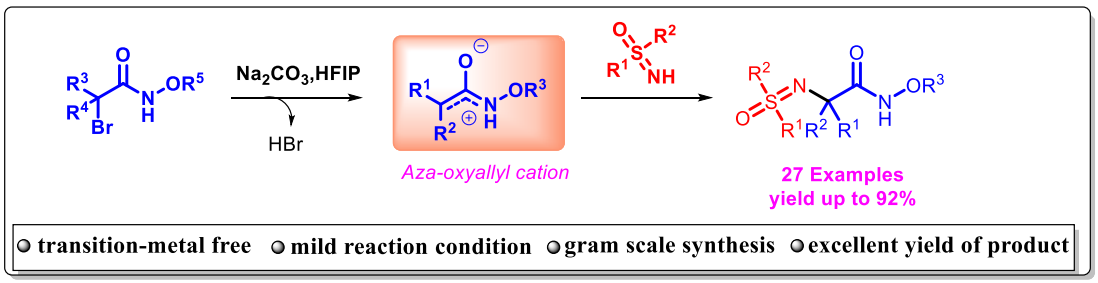
Section I: Metal-Free, Acid-Catalyzed 1,6-Conjugate Addition of NH-Sulfoximines to *para*-Quinone Methides: Accessing to Diarylmethine Imino Sulfanone

Diaryl methane is an interesting pharmacophore possessing a wide range of the biological spectrum. Further, sulfoximidoyl scaffolds have considerable significance in pharmaceutical and medicinal chemistry due to their exceptional structure. In particular, the sulfoximine pharmacophore is a flexible synthetic intermediate that plays a vital role in drug discovery owing to its structural diversity, hydrogen-bonding capability, high metabolic stability, and interesting physicochemical properties. In organic synthesis, the sulfoximine derivative has been used as the key intermediate found in active pharmaceutical ingredients, natural products, crop protection, and in medicinal chemistry with a wide range of biological activity.



We are developed a convenient, metal-free protocol for the synthesis of diverse range of diarylmethine imino sulfanones using *p*-QMs and bench-stable sulfoximines in the presence of a catalytic amount of *p*-TSA. A mild reaction condition, less reaction time, broad substrate scope, high atom economy, and excellent yield of products are the key features of the present methodology.

Section II: Metal-Free and Mild Synthesis of Congested *N*-Alkyl Sulfoximines *via* In-situ Generated Aza-Oxyallyl Cations from Functionalized Alkyl Bromide

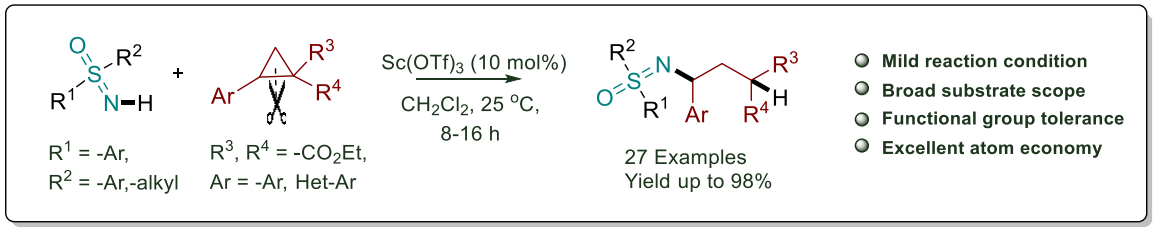


Sulfoximines are the mono-aza analogues of sulfones, having attractive structural properties frequently used in worldwide from last decade. Besides, it significantly used as a privileged ntermediate for the construction of heterocyclic core. Due to the high metabolic stability, hydrogen-bonding capability, structural diversity, and interesting physicochemical properties of sulfoximine make it an exciting pharmacophore. Sulfoximine moiety has been used for stability/oral bioavailability, enhancing specificity, and reducing undesired toxicity in drug discovery.

Herein, we have reported metal-free and mild approach for synthesis of a diverse range of novel congested *N*-alkylation of sulfoximine from *α*-halo hydroxamates via in-situ generated aza-oxyallyl cations pathway. Using a simple and general method, we achieved potential synthesis of active *N*-alkyl sulfoximines. This protocol exhibits construction of wide range of hindered di-alkyl sulfoximines in good to excellent yield.

Chapter 4: Metal catalysed *N*- alkylation of sulfoximine from D-A cyclopropanes and cyclic ethers

Section I: Lewis Acid Triggered *N*-Alkylation of Sulfoximines through Nucleophilic Ring Opening of Donor-Acceptor Cyclopropanes: Synthesis of *γ*-Sulfoximino Malonic Diesters

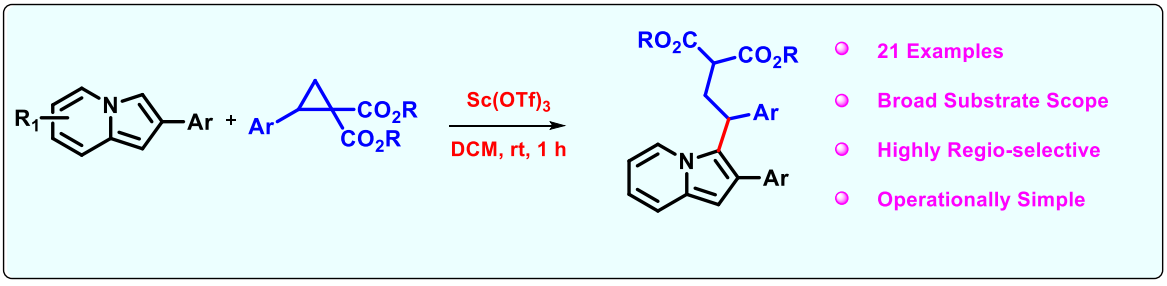


Sulfoximines were discovered in late 1940's, since then it emerged as a valuable moiety in the broad range of applications. 2-5 The interesting properties of sulfoximines in particular its high stability, good physicochemical property, functional groups with hydrogen bonding property, and also its structural diversity makes them important pharmacophore in the medicinal and agro chemistry. The sulfoximines are also used as a functional group in asymmetric catalysis8 as chiral auxiliary and ligand for C-H activation, due to their stable configuration and chemical stability.

Herein, we have developed scandium triflate ($Sc(OTf)_3$) catalyzed mild and regioselective ring-opening reaction of Donor-Acceptor (D-A) cyclopropanes with sulfoximines for the synthesis of γ-sulfoximino malonic diesters. This protocol exhibits the synthesis of different *N*-alkyl sulfoximines in good to excellent yields (up to 98%) with broad functional group tolerance. Herein, N-H and C-C bonds are cleaved to form a new C-N and C-H bond in this cascade process. The feasibility of the method is supported by a gram-scale reaction and synthetic elaboration of obtained product.

Section II: Scandium Triflate Catalyzed Regioselective C-3 Functionalization of Indolizines via Ring-Opening of Donor-Acceptor Cyclopropanes

Nitrogen heterocyclic compounds play a central role in the development of new drugs and materials Indolizines and their derivatives are present in a number of molecules and show a wide range of



biological activities and fluorescence properties. Natural and synthetic derivatives of indolizine have been found to exhibit a variety of biological activities. we have developed an Lewis acid catalyzed convenient protocol for synthesis of C-3 alkylation of indolizines under mild reaction condition for the synthesis of biologically active γ-hetroaryl malonic diesters in good yield.

5. Summary

1) We have targeted the first total synthesis of Phaseolide-A in 11 steps with 8% overall yield from commercially available 1,8- octane diol and acetaldehyde. The Mac-millan α-aminoxylation reaction, brown allylation, steglich esterification are the keys steps of current synthesis.

2) We also accomplished organocatalysed total synthesis of 12- membered macrolide Balticolid in 17 steps with 5% overall yield from commercially available acetaldehyde and 1, 4 butanediol. The Mac-millan α-aminoxylation reaction, brown allylation, steglich esterification are the keys steps of current synthesis.
3) We have developed an efficient, metal-free, radical C–C bond formation reaction for cyclic ethers with p-QMs to afford diarylmethanes and 3, 3 oxindole containing phenols functionalized with cyclic ethers in excellent yield and with high atom economy.
4) We have developed an efficient metal-free approach for the synthesis of hemiaminals from QIK and various ethers. Further, this strategy highlights the optimized reaction conditions to obtain the desired products in good to excellent yields and shows the broad substrate scope and high functional group tolerance with hemiaminals.
5) We have demonstrated a convenient, metal-free protocol for the synthesis of diverse range of diarylmethine imino sulfanones using *p*-QMs and bench-stable sulfoximines in the presence of a catalytic amount of p-TSA. A mild reaction condition, less reaction time, broad substrate scope, high atom economy, and excellent yield of products are the key features of the present methodology.
6) we have developed an efficient, metal-free, and convenient protocol for developing a novel congested, diverse range of dialkyl sulfoximines from sulfoximines and *α*-halo hydroxamates. The reaction proceeds via an azaoxyallyl cation is the key step.
7) we have developed facile and efficient Sc(III) catalyzed ring opening reaction of D-A cyclopropanes from weak nucleophilic sulfoximines for the synthesis of diverse range of novel *γ*-sulfoximino malonic diesters in excellent yields. In this strategy cleavage of old C-C bond from cyclopropane followed by formation of new C-N and C-H bond between sulfoximine and cyclopropane is achieved in a single step.
8) we have developed an Lewis acid catalyzed convenient protocol for synthesis of C-3 alkylation of indolizines under mild reaction condition for the synthesis of biologically active γ-hetroaryl malonic diesters in good yield.

6. Future directions

1) We have targeted to complete the total synthesis of Phaseolide-A, and Balticolid
2) Also, we have to complete the C-3 functionalized indolizines scheme and communicated in due course.

7. Publications

1) **More, S. G.;** Suryavanshi, G. Metal-free, Radical 1,6- Conjugated Addition of Cyclic Ethers with *para*-Quinone Methides (*p*-QMs). *Org. Biomol. Chem.* **2019**, *17*, 3239−3248.
2) **More, S. G.;** Kamble, R. B.; Suryavanshi, G. Oxidative Radical-Mediated Addition of Ethers to Quinone Imine Ketals: An Access to Hemiaminals. *J. Org. Chem.* **2021**, *86*, 2107−2116.

3) **More, S. G.;** Rupanawar, B. D.; Suryavanshi, G. Metal-Free, Acid-Catalyzed 1,6-Conjugate Addition of *N*H-Sulfoximines to para- Quinone Methides: Accessing to Diarylmethine Imino Sulfanone. *J. Org. Chem*, **2021**, *86*, 15, 10129−10139.
4) **More, S. G.;** Suryavanshi, G. Lewis Acid Triggered *N*-Alkylation of Sulfoximines through Nucleophilic Ring-Opening of Donor-Acceptor Cyclopropanes: Synthesis of *γ*-Sulfoximino Malonic Diesters, *Org. Biomol. Chem.*, **2022**, *20*, 2518–2529.
5) **More, S. G.;** Suryavanshi, G. Metal-Free and Mild Synthesis of Congested *N*-Alkyl Sulfoximines *via* In-situ Generated Aza-Oxyallyl Cations from Functionalized Alkyl Bromide *(Manuscript under preparation*)

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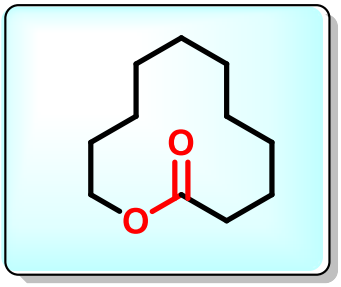
Chapter I

Organocatalysed Total Synthesis of Twelve Membered Macro-lactones: Phaseolide A and Balticolid

1. "Organocatalytic First Total Synthesis of Phaseolide A" **More, S. G.;** Suryavanshi, G. *(Manuscript under preparation)*
2. "Organocatalyzed Total Synthesis of Marine Natural Product 12- membered Macro-lactone Balticolid" **More, S. G.;** Suryavanshi, G. *(Manuscript under preparation)*

1.1.1. Introduction:

Natural products are generally produced as secondary metabolites of various microorganisms and plants, representing a diverse range of chemical compounds. Indeed, the diversity of natural products makes them an attractive goal for both chemists and biologists. However, researchers have already discovered lead drug compounds and new biological targets using 12-membered macro-lactones; as a result, diverted total synthetic routes to libraries of analogs have been developed. Marine microorganisms are a significant interest in natural product research and are a great source of novel and bioactive compounds. The natural products found in the marine environment have great biological activities. Several of them are passed clinical trials. Also, they are the key source of medicine due to their massive structural and chemical diversity.[1, 2]



Common Structure of 12- membered Macrolactone

Marine diversity is a rich source of secondary metabolites. However, 12-membered macrolactones are the secondary metabolites isolated from marine microorganisms. Naturally obtaining 12-membered macrolactones are a family of fungal hexaketide-derived metabolites that contain a simple 12- membered lactone core and an 11-methyl group. The chemical diversity of 12- membered macrolides depend on the hydroxy group, keto group, and the olefines in the macrolactones. Several 12-membered macrolactones are isolated from fungal metabolites. Due to the structural diversity of 12- membered macro-lactones (containing lactone core), it possesses

potent biological activities such as antibacterial, antifungal, cytotoxic, phytotoxic, etc.[3, 4] The first example of 12- membered macrolactones is recifeiolide, isolated from the terrestrial fungus Ceplialosporium recifei in 1971. Then after that, numerous 12- membered macrolactones are isolated and synthesized such as (s)-hydroxyrecifeiolide (**1**), Balticolid (**2**), Cladospolide B (**4**), 10-deoxymethynolide (**5**), Dendrodolide **(6)**,[5-9] have been isolated from fungal metabolites having an interesting biological activity as shown in **Figure 1.**

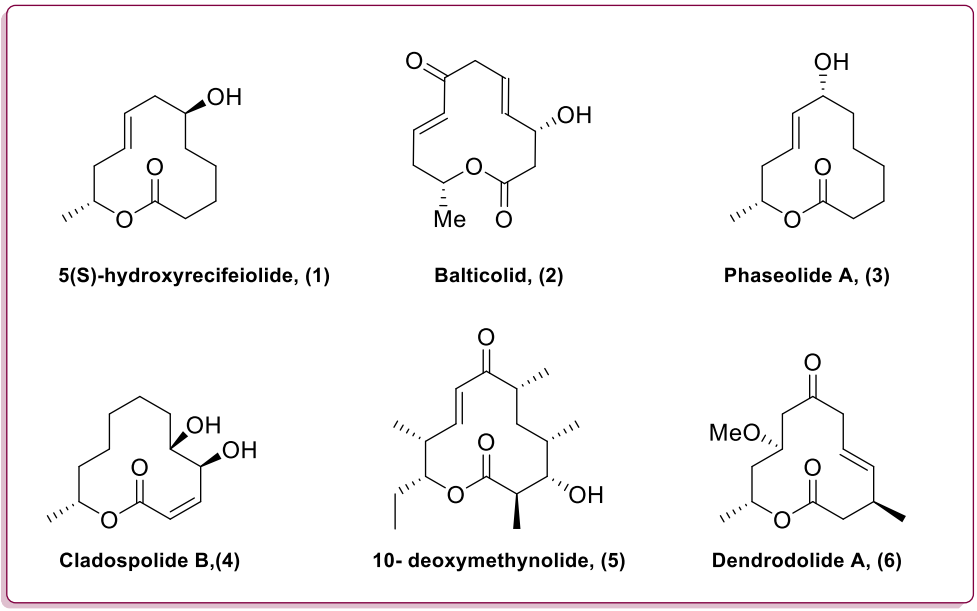


Figure 1. 12 membered macro-lactones containing biologically active natural products

In particular, The Balticolid and Phaseolide A are a new class of 12-membered macro-lactones showing potent biological activity isolated from marine fungal micro-organisms. Both Macrolides have lactone and methyl groups at the C-11 position. Due to the similarity in chemical diversity, both macrolides have promising antiviral and anti-HSV activity.

Phaseolide A was isolated in 2020 by Morishita and a co-worker from Macrophomina phaseolina *via* the crystalline sponge method. The synthesis of Phaseolide A has not been reported in the literature. At the same time, Morishita and co-workers showed the biosynthetic routes for

synthesis of Phaseolide A. and Balticolid. Also 12-membered Shushni and Co-workers synthesized macrolactone in 2011 by modifying Mosher's method. Various convergent synthetic ways of Balticolid synthesis are known in the literature, such as synthesizing acid and alcohol fragments. These fragments are synthesized from commercially available starting material using the Hydrolytic Kinetic Resolution (HKR) technique and Sharpless epoxidation to introduce the chirality. Also, chirality was introduced *via* the chiral pool approach.

In contrast, esterification and metathesis to synthesize Balticolid and related macrolactones, herein, we have synthesized Phaseolid A and Balticolide using the Macmillan α- aminoxylation and keck allylation approach to get chirality in the molecule. Furher, the Steglich Esterification for acid-alcohol coupling and ring-closing metathesis using Grubbs catalyst is employed to reach the target molecules

Section I

Organocatalytic First Total Synthesis of Phaseolide A

1.1.2. Introduction and Pharmacology

Natural products are the key source of medicine due to their massive structural and chemical diversity. Many drugs that are isolated from natural products have biological activity. Macrolides are one of the significant natural products isolated from various fungal metabolites. They have received considerable attention due to their exciting pharmacological features, such as antitumoral, antibacterial, or hypolipidemic properties. Macrolactons are secondary metabolites that were isolated from the marine microorganism. Phaseolide A is a new class of 12-membered macrolides with some common interesting structural features isolated from fungal macrolide *Macrophomina phaseolina* by Yohei Morishita and co- workers in 2020 (**Figure 2**).[10]

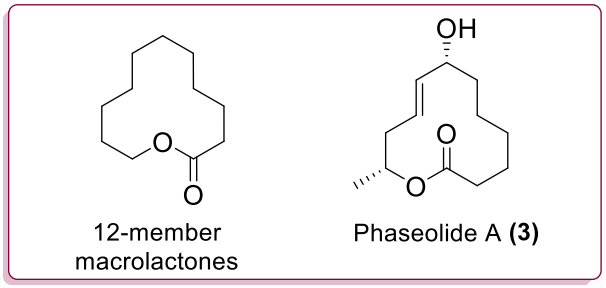


Figure 2: General Structure of 12-membered macrolactone and structure of Phaseolide A

Its structure was identified by NMR, VCD spectral analysis, and the crystalline sponge method. Phaseolide A macrolactone containing two chiral centers at C-7 and C-11 possessed a 7-R and 11-R configuration.

1.1.2. Review of Literature

Phasolide A was isolated in 2020, and there have been no reports, including its synthesis in the

Morishita's Biosynthetic Pathway of Phaseolide A (2020)

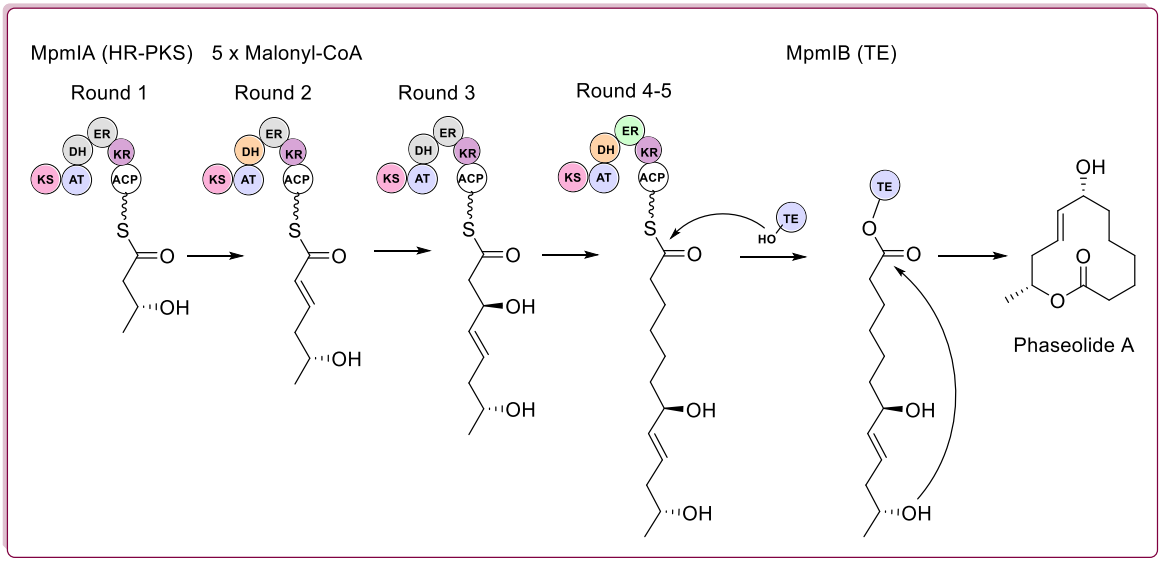


Figure 3: Proposed Biosynthetic Pathways of Phaseolide A

literature until now. Herein we discuss the biosynthetic pathway of Phaseolide A In 2020 Morishita and co-workers isolated Phaseolide A from the marine fungus Macrophomina

phaseolina by crystalline sponge. Based on chemical structure, the author proposed a possible biosynthesis pathway of Phaseolide A, as shown in **Figure 3**. The backbone of the polyketide was amassed using a highly reducing polyketide synthase (HR-PKS) gene, 5 malonyl-CoAs, and MpmlA as extension units, and the hydroxyl groups were produced by a single ketoreductase (KR) unit. The absolute configuration of Phaseolide A proposed that the KR domain of MpmlA reduced a β-ketone to D or L-OH, based on the extension round and ApmlA. As a result, the mature polyketide chain was transferred to a serine residue in MpmlB and released through macro-lactonization.

1.1.3. Present Work

1.1.3.1. Objective

The basis of ongoing work on the synthesis of biologically active natural products and synthetic compounds[11] herein, we have reported the stereoselective first total synthesis of Phaseolide A (**3**) (Figure 1). The total synthesis of Phaseolide A consisted of Macmillan *α*-aminoxylation, Brown allylation, and Grubb's metathesis reaction pathway.

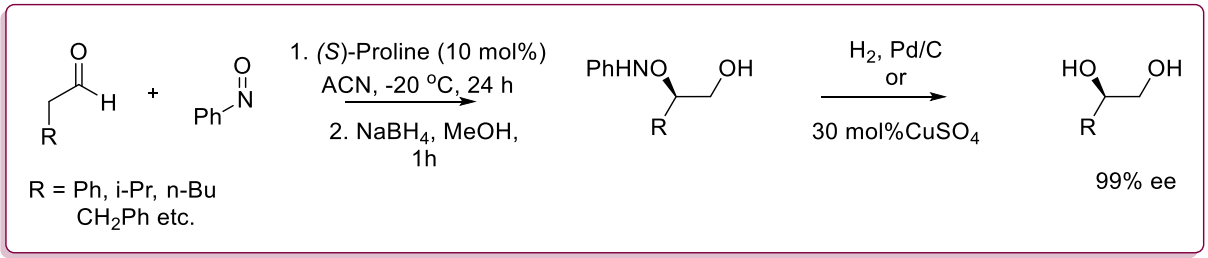
We selected Phaseolide A as a target molecule for synthesis to explore the developments of synthesis of natural products and the enhancement of our interest in synthesis in the view of biological importance. As per our knowledge, there is no report on the synthesis of Phaseolide A in the laboratory.

1.1.3.2. Proline-catalyzed *α*-aminoxylation

Enantiomerically pure *α*-hydroxy aldehydes, ketones, and alcohols (chiral 1,2 diol) are the prominent precursors in asymmetric organic chemistry for synthesizing natural products, drugs, and the development of synthetic methodologies. Conversely, the enantioselective *α*-hydroxy reactions are well developed in the literature, such as Davis Oxaziridine,[12] Sharpless

Dihydroxylation reactions,[13] and Shi epoxidation reactions are the more prominent examples of the α-hydroxylation reactions. Although a method for synthesis of the enantiomerically pure hydroxylation reaction exists, there are some limitations, including multiple manipulations, metal catalysts, and low enantiomeric excess.

Macmillan and coworkers developed an organocatalytic amino-oxylation method and used a proline catalyst for the asymmetric hydroxylation reaction. In this strategy, aldehyde with no substitution at *α* position reacted with aminoxylation precursor (Nitroso-benzene) in the presence of the catalytic amount of s-proline in ACN solvent to furnished the *α*- aminoxylated aldehyde adduct. In the next step, the carbonyl group is reduced in the presence of sodium borohydride ($NaBH_4$) to obtain the *α*-aminoxylated alcohol, and the aminoxyl moiety undergoes hydrolysis in the presence of H_2, Pd/C, or cat. $CuSO_4$ gives corresponding chiral diol in excellent enantiomeric excess (99% ee).



Scheme 1: *α*- aminoxylation of aldehyde

The proposed catalytic cycle of the *α*-aminoxylation reaction is depicted in **Figure 4**. The enantioselectivity of the catalytic *α*- aminoxylation of aldehyde is observed through an enamine mechanism. Enamine, formed from aldehyde and L- proline, operates a chair-like transition state where it approaches through the less-hindered (si-face) oxygen atom of nitrosobenzenene to furnish a chiral *α*- amino aldehyde with R- configuration with the regeneration of proline catalyst

for further catalytic cycle. Then next, in-situ reduction of amino-aldehyde with $NaBH_4$ to produce the chiral S or R diol.

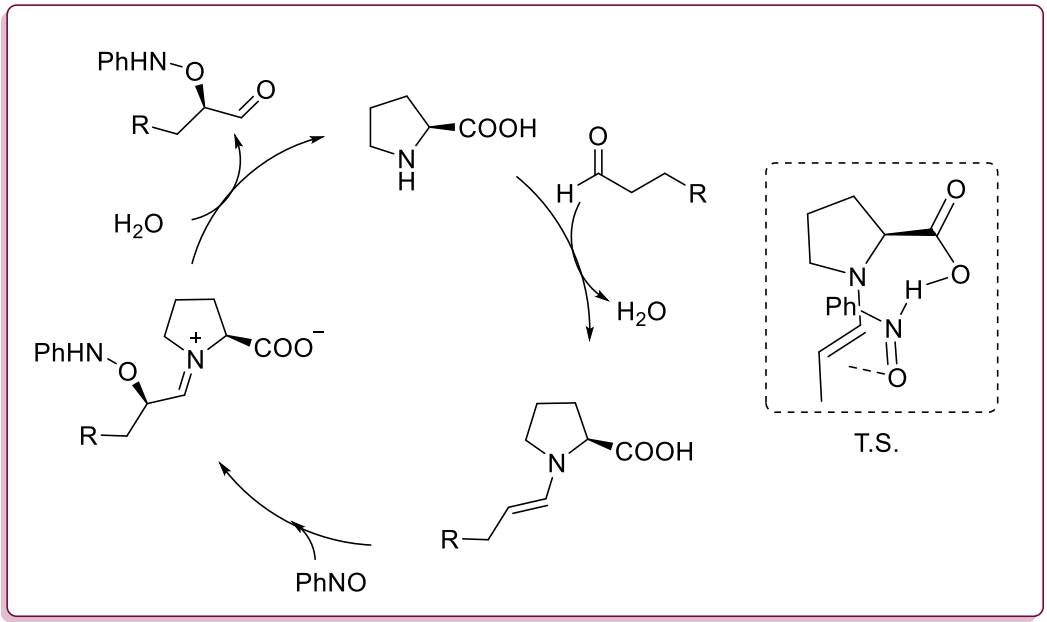
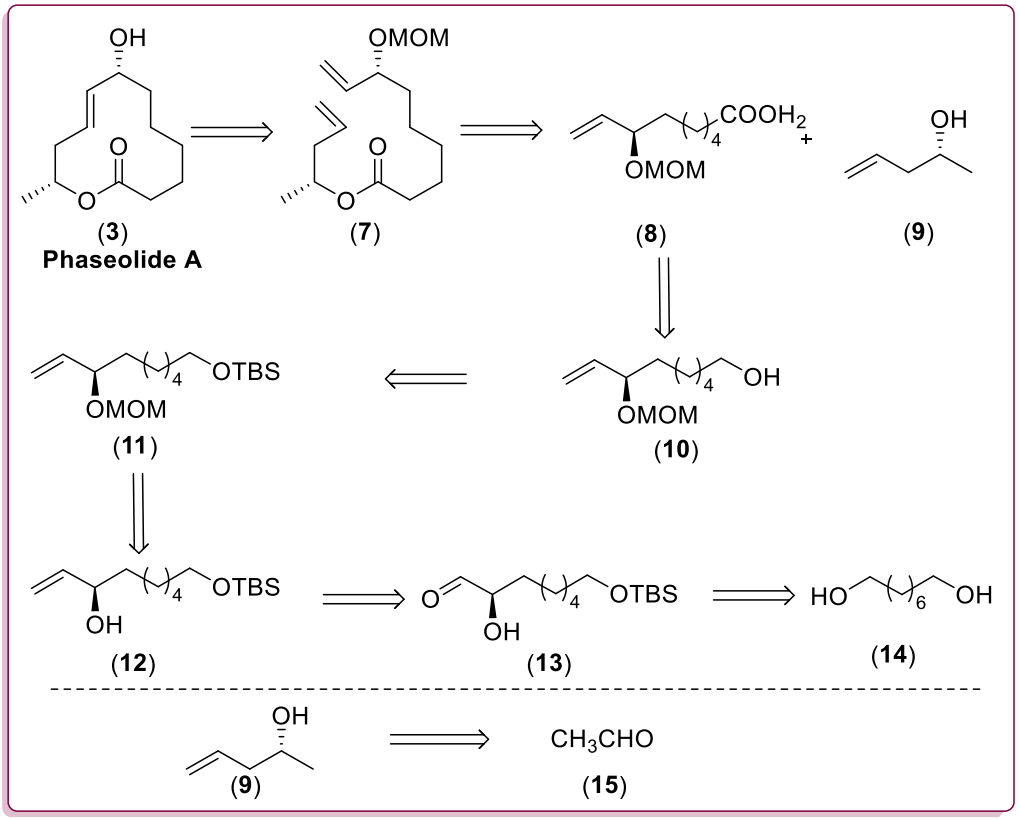


Figure 4. Proposed mechanism of α- aminoxylation of aldehyde

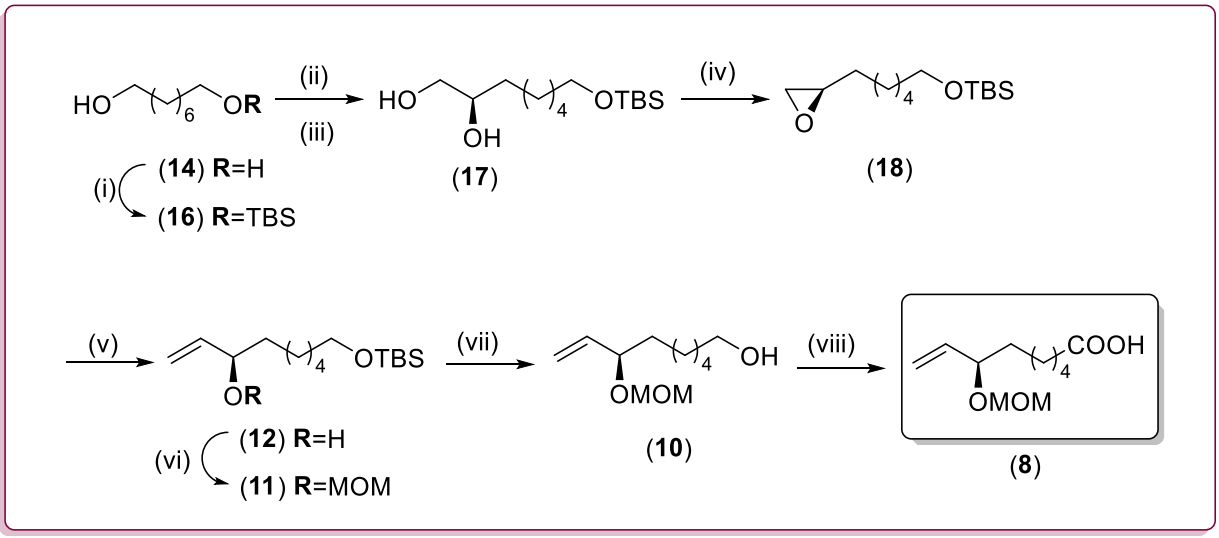
1.1.4. Result and Discussion

The retrosynthesis approach of Phaseolide A is depicted in Scheme 2. The target molecule (**3**) was achieved by the Grubbs ring-closing metathesis of di-olephynic intermediate and deprotection of secondary alcohol. The esterification of alkenoic acid synthesized by the external di-olefin and homoallylic alcohol fragment could be easily accessed by the Brown allylation strategy from commercially available acetaldehyde (**15**). The acid fragment could be synthesized from 1, 8 octane diol (**14**) as commercially available starting material via proline catalyzed mac-Millan α-aminoxylation and variously known transformations.



Scheme 2: Retrosynthetic analysis of Phaseolide A

Based on the retrosynthesis analysis, we visualized the Phaseolide A synthesized from acid and alcohol fragments. First, the synthesis of acid fragment started with commercially available 1,8 octane-diol (**14**). The diol undergoes mono-silyl protection with TBS-Cl obtained corresponding mono-silyl protected product in 88% yield (**16**). Their ^{1}H and ^{13}C spectra unambiguously confirmed the obtained mono-silylated 1, 8 octane-diol 16. In ^{1}H spectroscopy, the peak at δ -0.03 singlet for 6-**H** corresponds to the protons of two methyl groups present in the silyl group, and the peak at δ 0.88 singlet 9-**H** corresponds to the *t*-Butyl of TBS protecting group. The compound **16** was also confirmed by the ^{13}C NMR spectrum; in the ^{13}C NMR spectrum,



Scheme 3: Synthesis of acid fragment (**8**) : **Reagent and conditions:** (i) TBSCl (1 equiv.), imidazole(1.5 equiv.), CH_2Cl_2, 0-25 °C, 8 h, 88%; (ii) $PhI(OAc)_2$ (1 equiv.), TEMPO (10 mol%) CH_2Cl_2, 0-25 °C, 3 h, 84%; ((iii) (a) PhNO (1 equiv.), L-proline (20 mol %), ACN, −20 °C, 24 h, then $NaBH_4$ (1 equiv.), MeOH, 0 °C, 10 min; (b) $CuSO_4.5H_2O$ (0.5 equiv.), MeOH (72% over two steps); (iv) TsCl (1 equiv.), Et_3N (2.5 equiv.), Bu_2SnO (0.3 equiv.), DMAP (0.1 equiv.); (b) K_2CO_3 (1.1 equiv.), MeOH, 30 min., 90% (over two steps); (v) $S^+Me_3I^-$(3 equiv.), nBuLi (2.5 equiv.), THF, −40 °C to 0 °C , 4 h, 86%;(vi) MOMCl (2 equiv.), DIPEA (4 equiv.), CH_2Cl_2, 25 °C, 12h, 84%; (vii) TBAF (1.0M THF) (1.5 equiv.), THF, , 0-25 °C, 3 h, 90%; (viii) $PhI(OAc)_2$ (2 equiv.), TEMPO (0.2 equiv.), CH_3CN/H_2O (4:1), 0-25 °C, 4 h, 72%.

the peak at δ -5.33 the carbons for the methyl of the silyl group. Furthermore, the peak at δ 25.92 corresponds to the *t*-Butyl of the silyl protecting group, as shown in **Figure 5**. The mono-silylated diol **16** was subsequently oxidized using BIAB and TEMPO to obtain the aliphatic aldehyde, which was then further reacted with known Mac-millan *α*- aminoxylation reaction followed by the reduction to obtainthe corresponding terminal chiral diol (**17**) in 72% yield over two-step reaction sequence. [12] The diol formation (**17**) was confirmed by its ^1H and ^{13}C NMR spectra. In the ^1H NMR spectrum, the peak at *δ* 2.53 broad singlet corresponding to O**H** protons

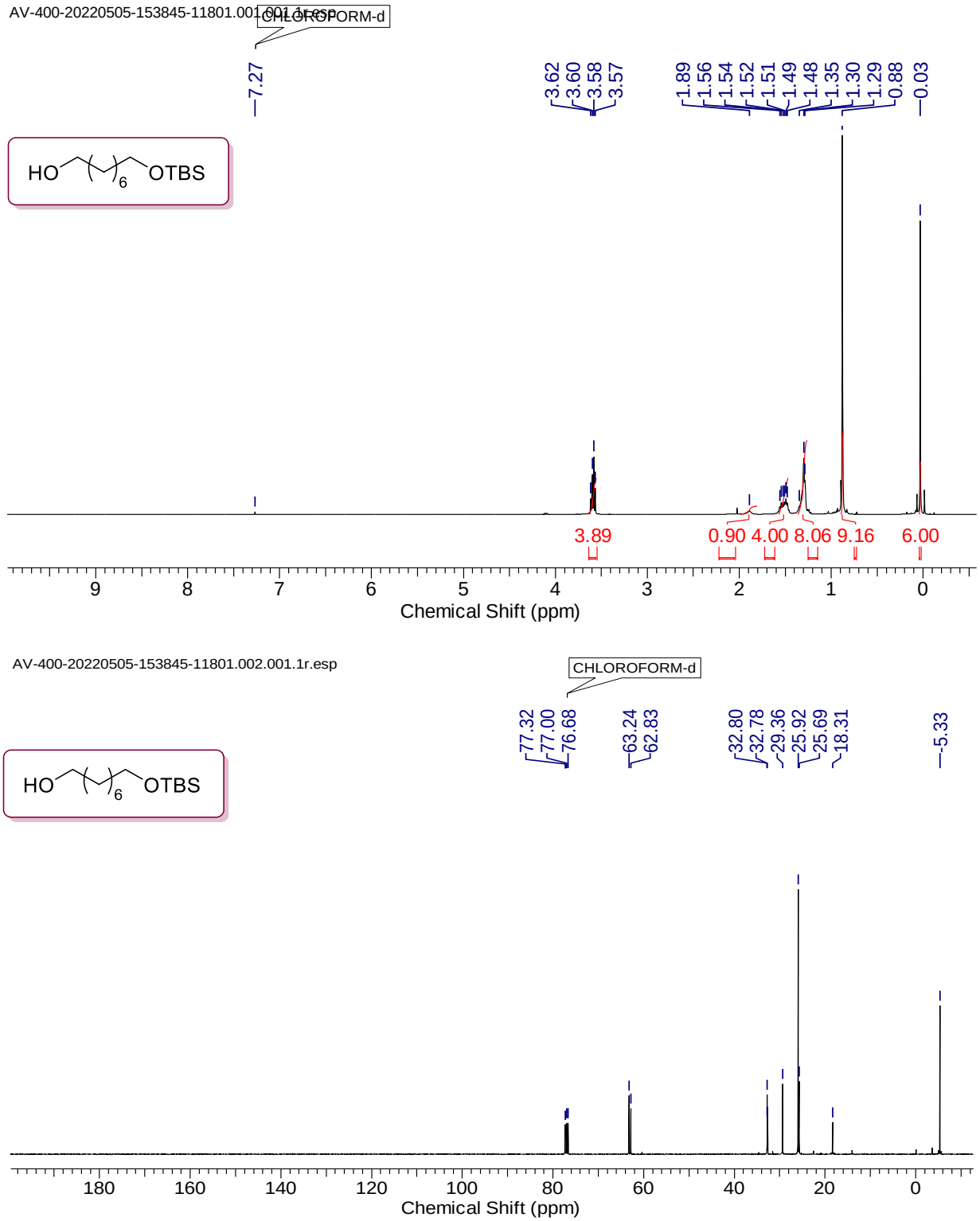


Figure 5: ^{1}H and ^{13}C spectra of 8-((tert-butyldimethylsilyl) oxy) octan-1-ol **(16)**

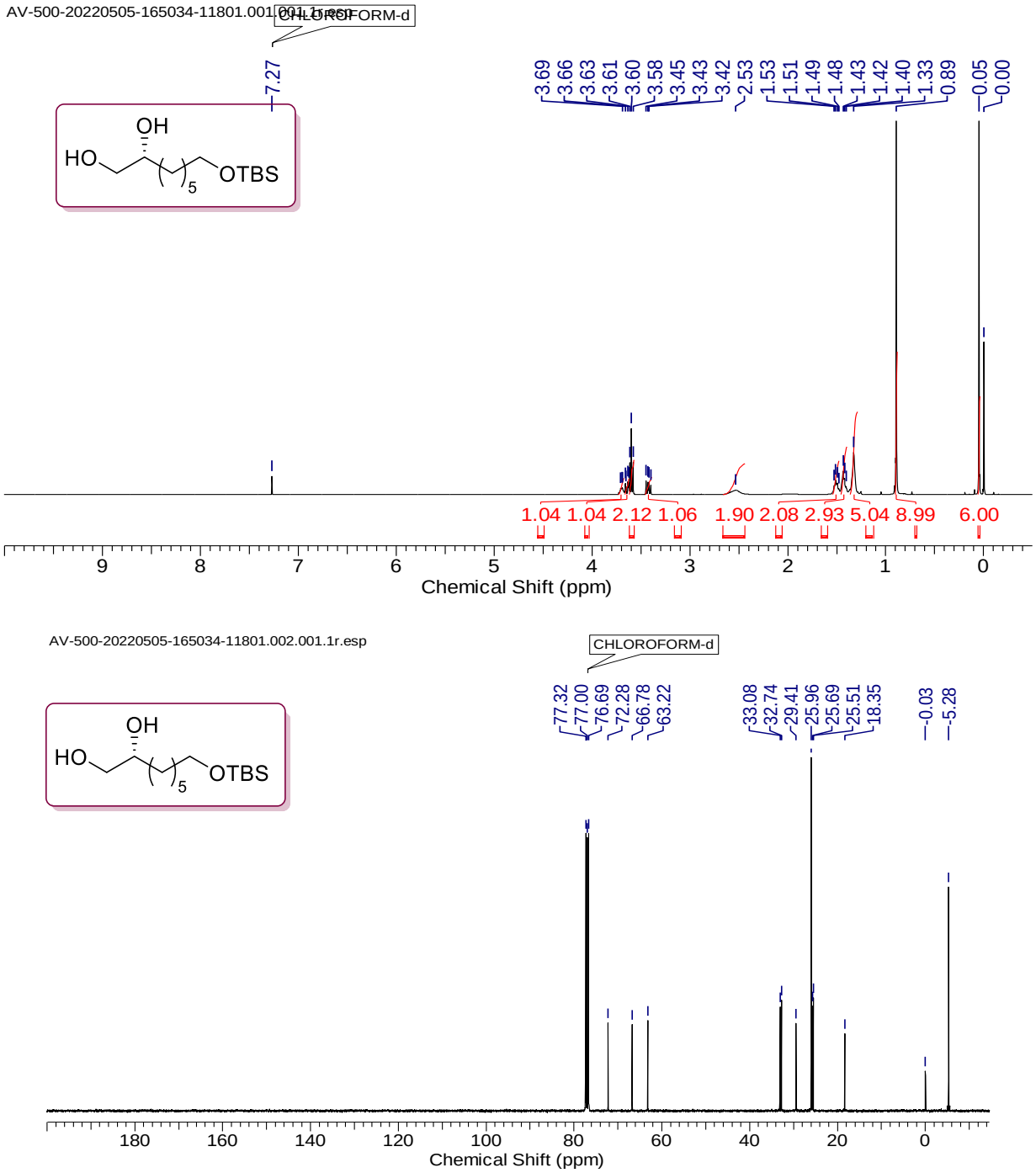


Figure 6: (R)-8-((tert-butyldimethylsilyl) oxy) octane-1,2-diol (**17**)

of diol, while the peak at δ 3.67-3.73, 1-H multiplet corresponding to the methine (CH_2-C**H**OH) proton near to the secondary alcohol, and the peak at δ 3.62 - 3.66 (m, 1 H), and 3.42 (dd, J = 11.1, 7.7 Hz, 1 H) diastereomeric protons (OH-C**H_2**-CHOH) of diol. The compound (**17**) was

also predicted by ^{13}C NMR spectroscopic method. In the ^{13}C NMR spectrum, peaks at 72.3 and 66.8 for the methylene (-**C**H_2-), and methine (-**C**H-) of diol moiety, respectively (**Figure 6)**.

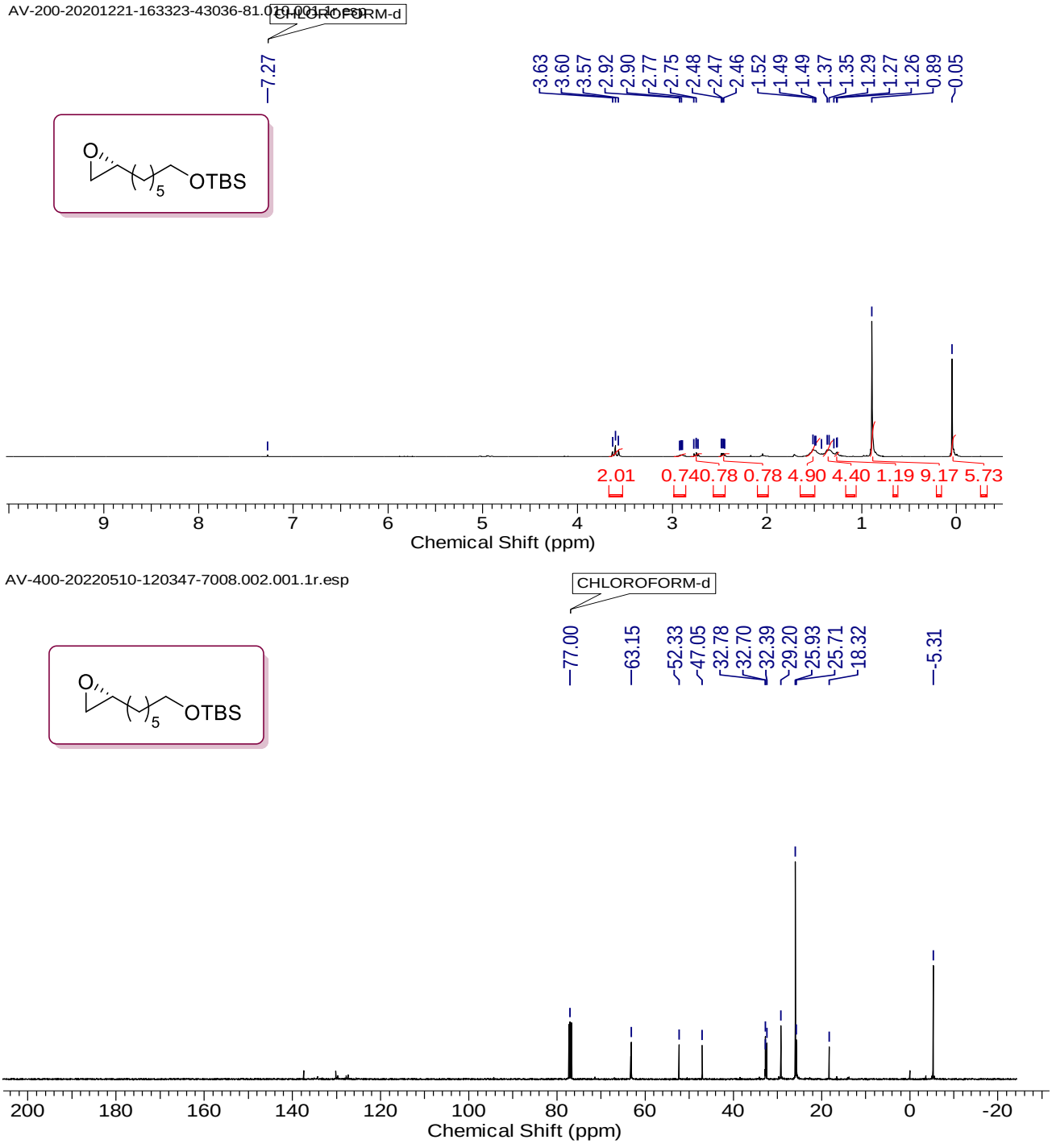


Figure 7: (R)-tert-butyl dimethyl((6-(oxiran-2-yl) hexyl) oxy) silane

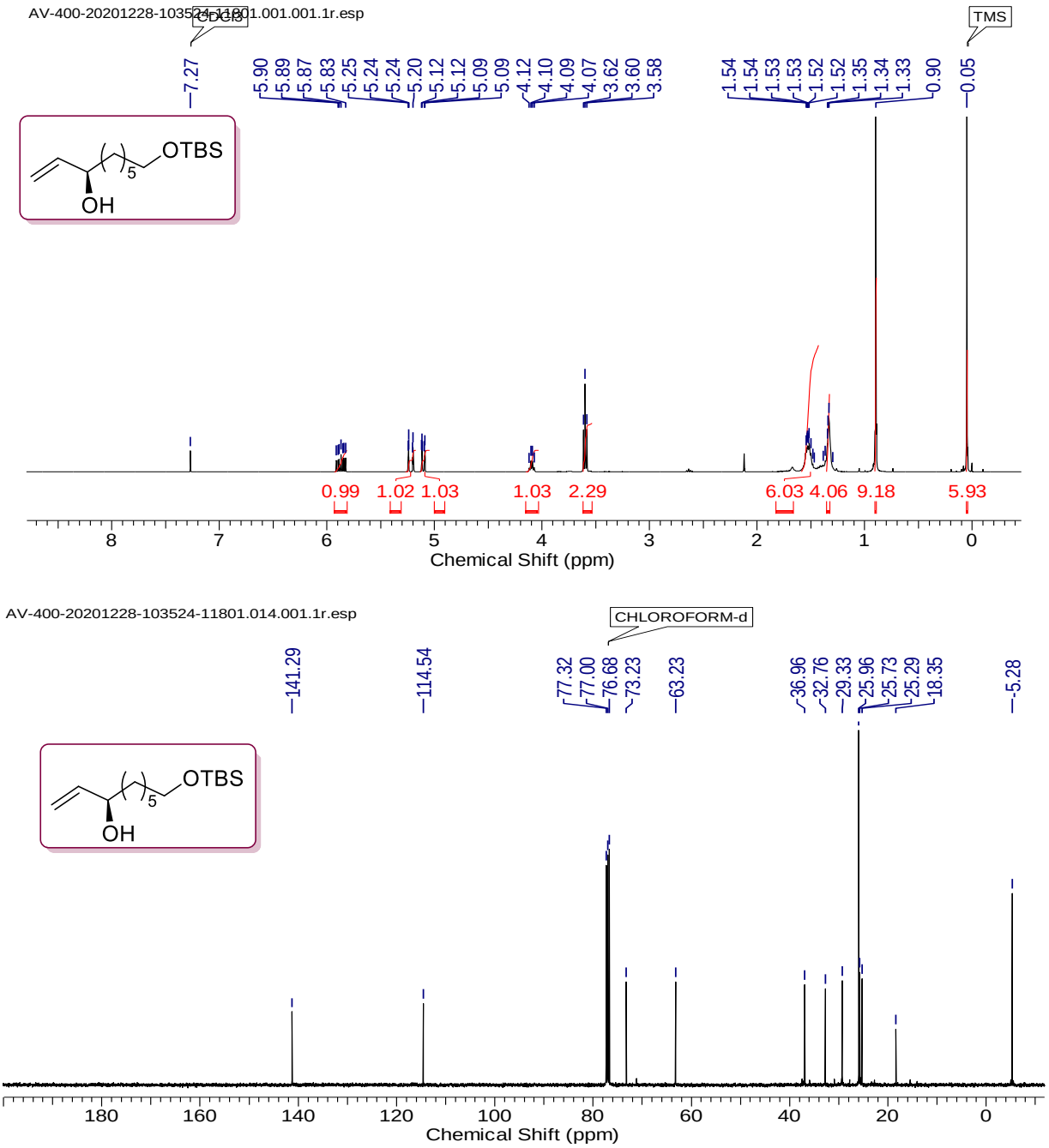


Figure 8: (R)-9-((tert-butyldimethylsilyl) oxy) non-1-en-3-ol

Then the diol was selectively primary alcohol tosylated and followed by treated with K_2CO_3 to obtained the chiral epoxide (**18**) in 90% yield over two steps.[13] The obtained epoxide **18** was confirmed by ^{1}H and ^{13}C spectral analysis, the typical protons at δ 2.86-2.98 multiplet for 1-H

and at δ 2.46 dd, J = 5.02, 2.70 Hz, ^{1}H corresponding to the diastereomeric protons of terminal epoxide carbon. The peak appears at δ 2.75, dd, J = 4.96, 4.08 Hz, for 1-H, corresponding to the proton of internal epoxide carbon. The chiral epoxide also further confirmed by the ^{13}C NMR spectroscopy,

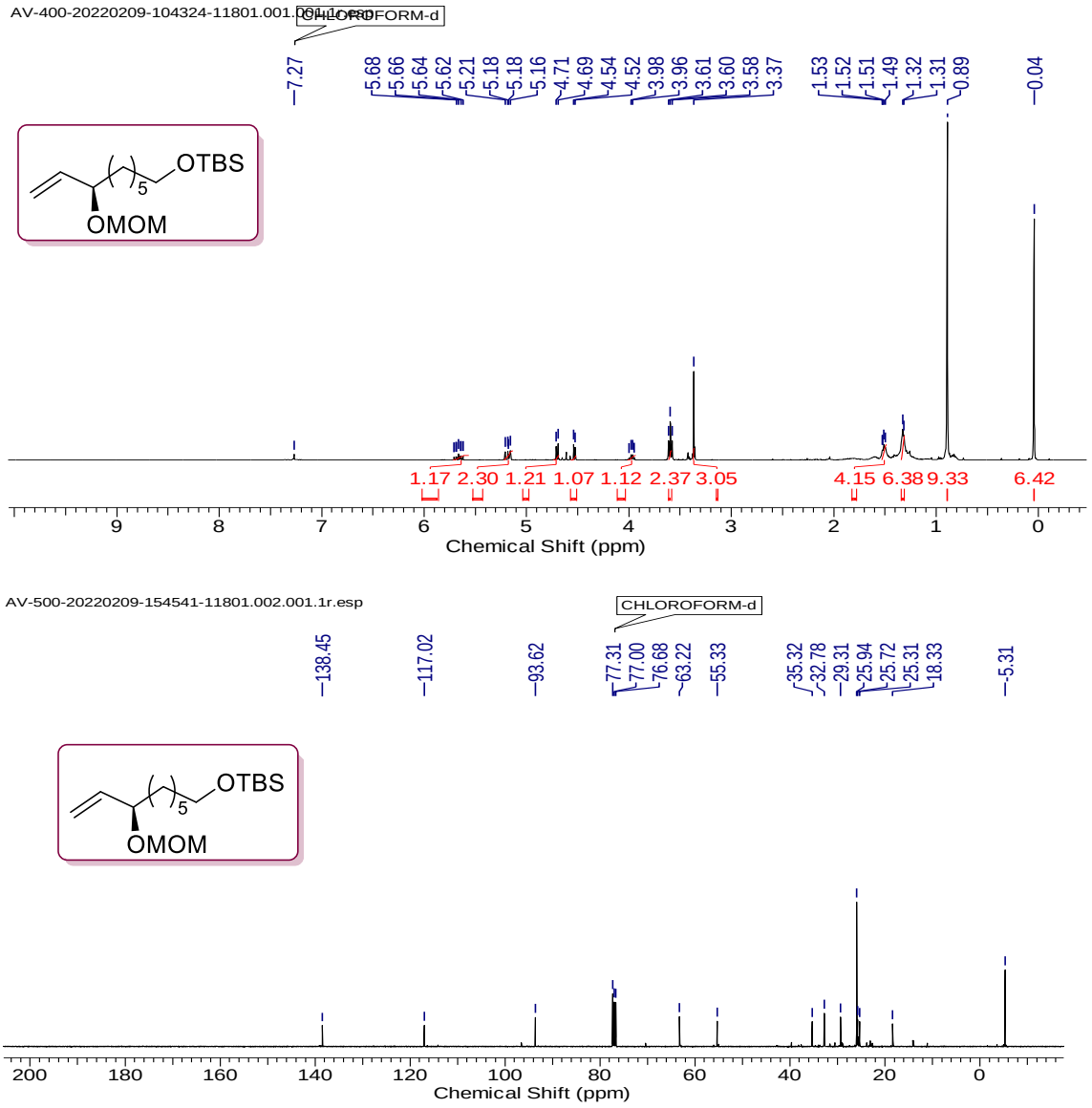


Figure 9: ^{1}H and ^{13}C NMR spectra of (R)-13,13,14,14-tetramethyl-5 -vinyl-2,4,12-trioxa-13-silapentadecane (**8**)

the peak at δ 47.05 and 52.33 corresponding to the terminal methylene (-C**H₂**-) and internal methine (-C**H**-) carbon respectively (**Figure 7**)**.** Furthermore, the regioselective opening of chiral epoxide from the less hindered side with Corey–Chaykovsky reagent ($S^{+}Me_3I^{-}$, NaH, THF) condition obtained the corresponding chiral vinyl-alcohol ((**12**) in 86% yield.[14] The formation of vinylic alcohol is confirmed by the ^{1}H and ^{13}C NMR spectra, as depicted in **figure 8.** In ^{1}H NMR, the peak at δ 5.90-5.87 multiplet for 1 H corresponds to the internal olefinic proton, while the peak at δ 5.25, dt, (J = 17.17, 1.42 Hz), 1H, and a peak at δ 5.20 dt, (J = 10.44, 1.34 Hz), 1H corresponding to the olefinic terminal protons. At the same time ^{13}C NMR spectrum displayed a typical carbon signal at δ 141.3, corresponding to internal olefinic carbon, and a peak at δ 114.5 due to terminal olefinic carbon. The secondary alcohol (**12**) was subsequently methoxymethyl protected with MOM-Cl and DIPEA in DCM solvent to furnish the corresponding to the MOM-protected secondary alcohol (**11**) in 84% yield at ambient temperature within 12 h reaction time. The MOM-protected alcohol **11** was confirmed by its ^{1}H and ^{13}C NMR spectroscopic methods. In ^{1}H NMR, the peak at δ 4.70, doublet (J = 6.6 Hz, 1H), and δ 4.53 (d, J = 6.8 Hz, 1H) are the diastereomeric methylene protons of methoxymethyl group, and the peak at δ 3.37, singlet 3-H for the methyl (O-C**H₃**) of MOM group. In the ^{13}C spectrum, the peak at δ 93.6 for methylene (O-**C**H_2-O) and δ 55.3 for methyl (O-**C**H_3) of the MOM group (**Figure 9**).

Next, the chemo-selective 1°-silylated was alcohol deprotected in the presence of 1.5 equiv. of TBAF (1.0M THF), THF solvent to obtain the corresponding 1° alcohol (**10)** in 90% yield within 3 h The ^{1}H spectrum (**figure 10**) shows the disappearance of peaks at δ -0.04 (singlet for 6-H and 0.89 (singlet for 9-H) for the silyl group. The formed primary alcohol (**10**) was further supported

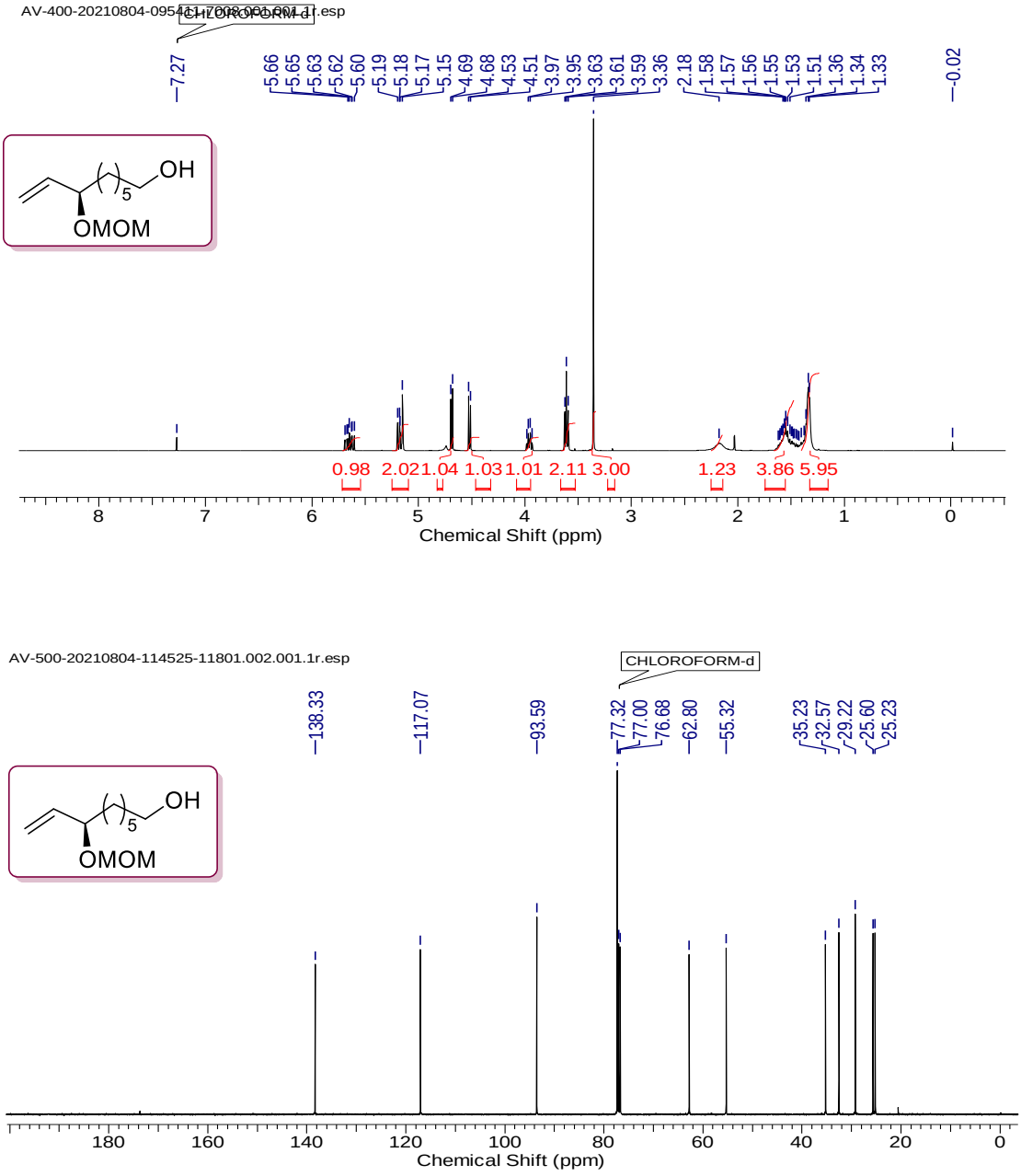


Figure 10: ^{1}H and ^{13}C spectra of (R)-7-(methoxy methoxy) non-8-en-1-ol (**10**)

by the ^{13}C spectrum, which showed the desertion of the peak at δ -5.31 and δ 25.94 confirmed the formation of silyl deprotected compound **10**. Finally, the alcohol was subjected to over oxidation in the presence of TEMPO/BIAB condition (in Acetonitrile: H_2O solvent) to furnish the aliphatic acid fragment (**8**) in 72% yield. The established carboxylic acid was confirmed by

its ^{1}H and ^{13}C spectra. The carboxylic acid proton in the ^{1}H NMR spectrum, appeared as a broad singlet at δ 8.83 for the carboxylic O-**H** proton. While in the ^{13}C spectrum, the carboxylic acid carbon (-**C**OOH) peak appeared at δ 179.45 (**figure 11**).

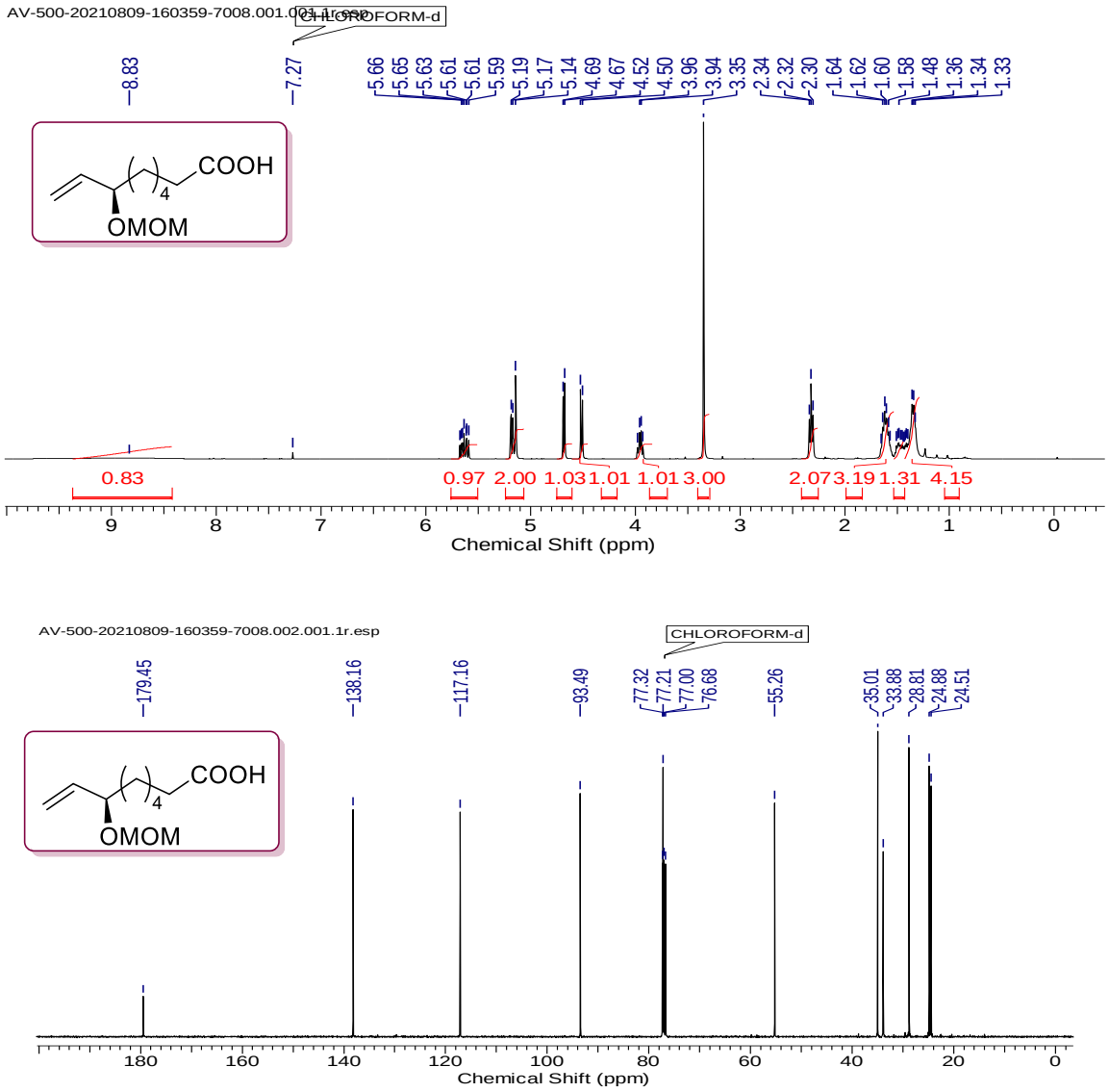
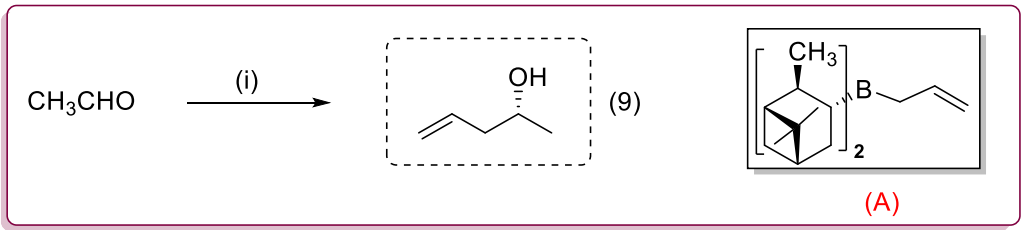


Figure 11: ^{1}H and ^{13}C spectra of (R)-7-(methoxy methoxy) non-8-enoic acid (**8**)

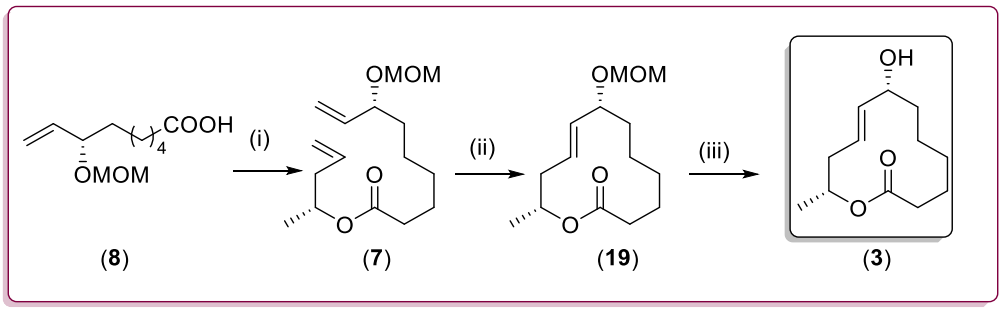
Then, next, we synthesized the one-step chiral alcohol fragment from commercially available acetaldehyde by the well-known Brown allylation reaction condition. In this, the acetaldehyde

reacted with Allyl diisopinocampheylborane, Et_2O-pentane, followed by the addition of NaOH and aqueous H_2O_2 to provide the chiral alcohol (**9**) in 88% yield (Scheme 3). [16]



Scheme 4: Synthesis of alcohol fragment (**9**) **: Reagent and conditions:** A, Et_2O-pentane, -78 °C, 1h, NaOH, aq H_2O_2 (35%), 77%, $[\alpha]_{25}^{D}$ =+8.9 (c=3.00 Et_2O)

With both fragments (**8**) and (**9**) now in hand, we then carried out the coupling of these two fragments in the Steglich esterification condition, which obtained the corresponding ester product (**7**) in 74% yield (Scheme 5). The ester product **7** was unambiguously confirmed by its



Scheme 5: Synthesis of target molecule Phaseolide A (**3**): **Reagent and conditions:** (i) **9 (**1.1 equiv.**),** DCC (1.5 equiv.), DMAP (0.11 equiv.), CH_2Cl_2, 0-25 °C, 12 h, 74%; (ii) Grubb's II generation catalyst (0.2 equiv.), CH_2Cl_2, refluxed, 12 h, 56% yield; (iii) 2N HCl (methanol), 25 °C, 1 h, 92%.

^1H and ^{13}C NMR spectroscopic methods.In the ^1H NMR spectrum, the typical multiplet at δ 4.92-5.01, 1H corresponding to the methine proton (-C**H**-OCO) attached to the ether site (**figure 12**). Also, the compound (**7**) inveterate by ^{13}C NMR spectrum, the peak for ester carbon (R_1-OR_2) appears at δ 173.27, which proves the formation of the ester group as shown in **Figure 12**.

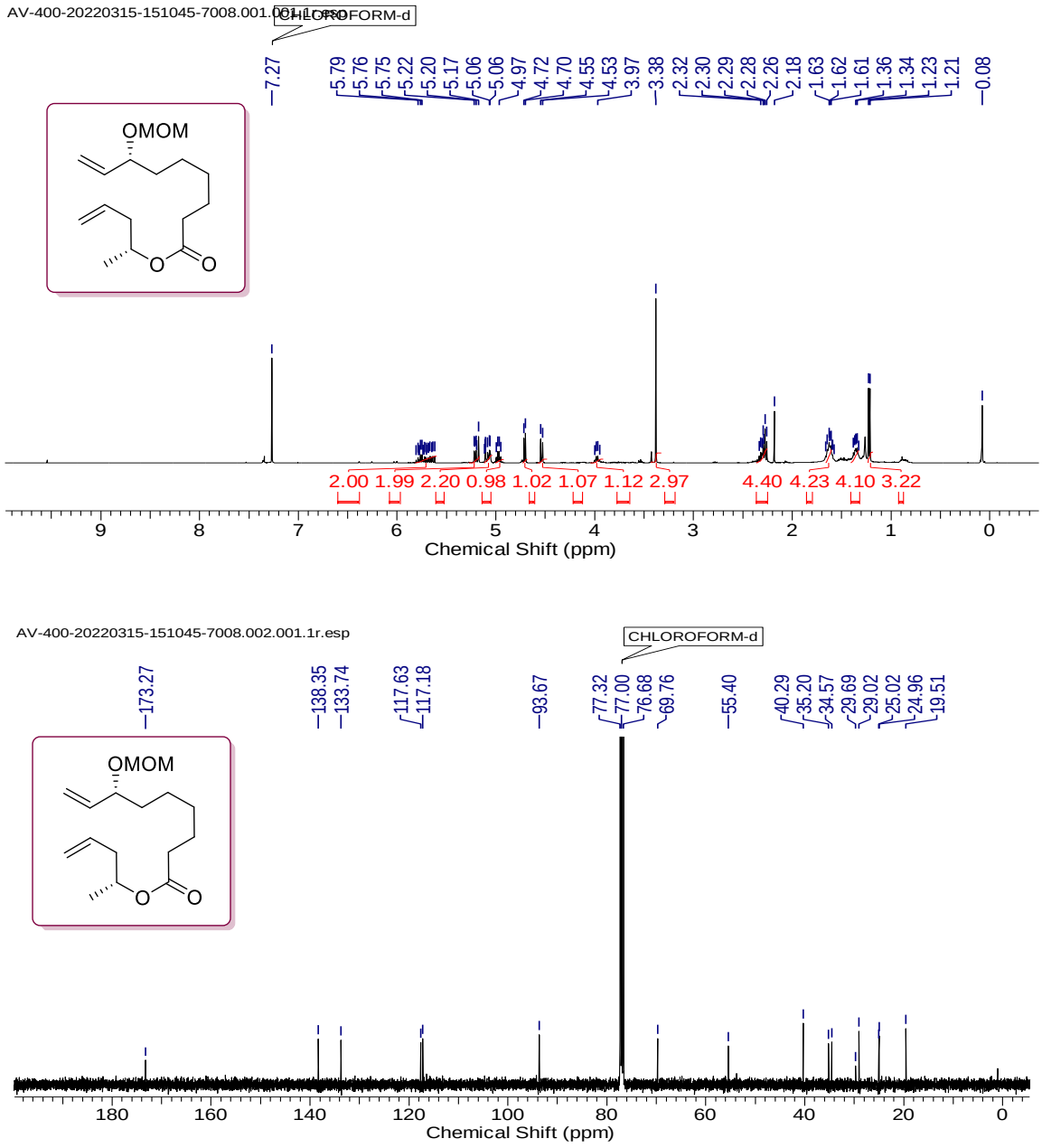


Figure 12: ^{1}H and ^{13}C spectra of (R)-pent-4-en-2-yl (R) -7-(methoxy methoxy) non-8-enoate (**7**)

Then, the ester condition with di-olefin cross couples using Grubb's ring closing metathesis condition formed the desired 12-membered macro-lactone product (**19**) in 56% yield. [19] Finally,

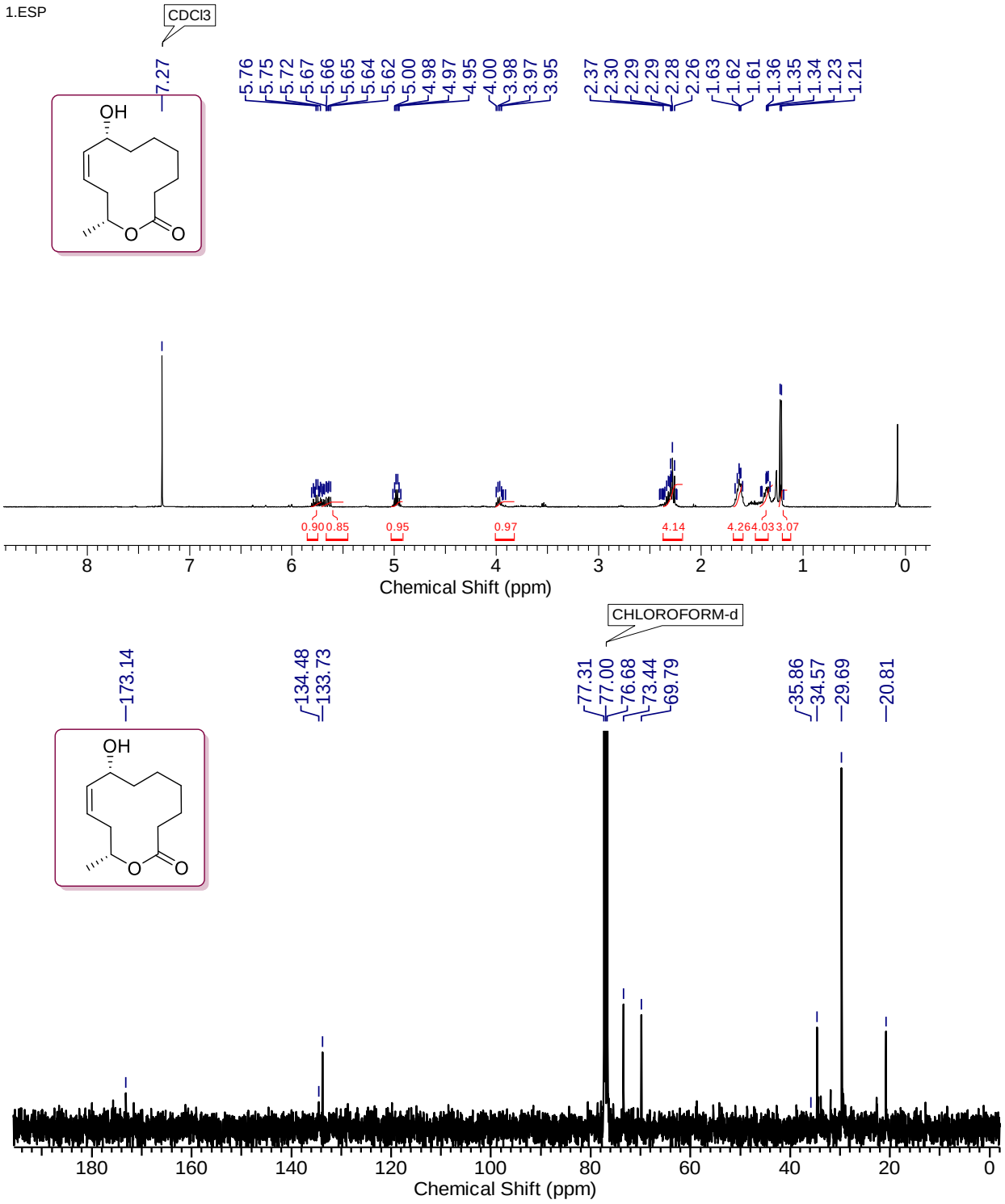


Figure 13: (8R,12R,Z)-8-hydroxy-12-methyloxacyclododec-9-en-2-one (Phaseolide A) (**3**)

the MOM ether was deprotected using 2N HCl in methanol (1:1) to obtain the target molecule Phaseolide A (**3**) in 92% yield. However, the -MOM deprotection in the presence of 2N HCl in methanol obtained our target molecule Phaseolide A within 1h with a 92% yield. The disappearance of the Me group in ^{1}H NMR spectra unambiguously confirmation of deprotection of the MOM group, as depicted in **Figure 13.**

1.1.5. Conclusion

We have successfully synthesized the first total synthesis of macrolide Phaseolide A in 11 steps with an overall 8% yield. The Macmillan α- aminoxylation for chiral diol, keck allylation for chiral 2 ^{o} alcohol, Steglich esterification, and the Grubbs ring closing metathesis are the key features of the current synthesis.

1.1.6. Experimental Section

8-((tert-butyldimethylsilyl)oxy)octan-1-ol (16)

To a cooled solution of 1, 8 octane diol **14** (5.0 g, 34.24 mmol) and Imidazole (3.5 g, 51.36 mmol) in anhydrous DCM (70 mL) was then added, a solution of TBSCl (5.1 g, 34.24 mmol) in anhydrous DCM (50 mL). The resultant mixture was stirred at room temperature for 4 h The reaction was quenched with water (50 mL) and extracted with diethyl ether (3 x 60 mL). The combined organic extracts were washed with brine solution (50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography (2% EtOAc /n-hexane) to give the mono-TBS protected 1, 8 octane diol **16** (7.8 g, 88% yield) as a colorless liquid.

Yield: 88% (7.8 g); colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.59 (q, J = 6.9 Hz, 4H), 1.89 (br. s., 1H), 1.52 (td, J = 13.1, 6.8 Hz, 4H), 1.26-1.36 (m, 8H), 0.88 (s, 9H), 0.03 (s, 6H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 63.3, 63.2, 62.8, 32.8, 32.8, 32.7, 29.4, 29.3, 25.9, 25.7, 25.7, 18.3, -5.3; **HRMS** (m/z): calculated $[M+H]^+$ for $C_{14}H_{33}O_2Si$: 261.2244 found: 261.2234.

(R)-8-((tert-butyldimethylsilyl) oxy) octane-1,2-diol (17)

To a stirred pre-cooled (-20 °C) acetonitrile (100 mL) solution of aldehyde prepared from TBS protected 1,8 octane-diol (6.0 g, 23.25 mmol, 1 equiv.) and nitroso-benzene (2.4 g, 23.25 mmol) was added L-proline (534 mg, 20 mol%). The reaction mixture was allowed to stir at the same temperature for 24 h, followed by adding MeOH (60 mL) and $NaBH_4$ (0.9 g, 23.25 mmol) to the reaction mixture, which was stirred for 10 min. After the reaction (monitored by TLC), the resulting mixture was extracted with EtOAc (3 × 60 mL), and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude aminooxy alcohol, which was directly taken up for the next step without purification. A well-stirred solution of crude aminooxy alcohol in methanol was added with 10% $CuSO_4$. $5H_2O$ and the reaction mixture stirred overnight at 25 ^oC. After completion of the reaction (monitored by TLC), it was filtered through celite (MeOH eluent) and the solvent evaporated under reduced pressure to afford the crude diol. Purification by column chromatography with petroleum ether/ethyl acetate (5:5 v/v) gave the diol **17** (4.6 g) as a colorless liquid.

Yield: 72%; $[\alpha]_D^{25}$ = +7.2 (*c* 1.8, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1376, 1466, 2872, 2969, 3381 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.67-3.73 (m, 1H), 3.62-3.66 (m, 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 3.42 (dd, *J* = 11.1, 7.7 Hz, 1H), 2.53 (br. s., 2H), 1.48-1.54 (m, 2H), 1.39-1.46 (m, 3H), 1.33 (br. s., 5H), 0.89 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 72.3, 66.8, 63.2, 33.1, 32.7, 29.4, 26.0, 25.7, 25.5, 18.4, -5.3; **HRMS** (m/z): calculated $[M+H]^+$ for $C_{14}H_{33}O_3Si$: 277.2093 found: 277.2085.

(R)-tert-butyl dimethyl((6-(oxiran-2-yl) hexyl) oxy) silane (18)

A solution of diol 1**7** (4.0 g, 14.49 mmol) in CH_2Cl_2 (50 mL) was treated with TsCl (2.75 g, 14.49 mmol), Bu_2SnO (1.07 g, 30 mol %), Et_3N (4.5 mL, 30 mmol) and DMAP (cat.) at 0 °C. After being stirred for 1 h, the mixture was extracted with CH_2Cl_2 (3 × 100 mL), washed with water, and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude tosylate. A solution of crude tosylate in MeOH (50 mL) was added to K_2CO_3 (2.1 g, 15.93 mmol), and the mixture was stirred at 0 °C for 30 min. After the reaction was complete (monitored by TLC), the solvent was evaporated, and the residue was extracted with diethyl ether (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography using petroleum ether/EtOAc (8:2 v/v) to give epoxide **18** (3.3 g) as a colorless oil.

Yield: 90%; $[\alpha]_D^{25}$ = +5.0 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1102, 1222, 1255, 2930, 2955 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.60 (t, *J* = 6.34 Hz, 2H), 2.86-2.98 (m, 1H), 2.75 (dd, *J* = 4.96, 4.08 Hz, 1H), 2.46 (dd, *J* = 5.02, 2.70 Hz, 1H), 1.43-1.59 (m, 5H), 1.36 (d, *J* = 4.19 Hz, 4H), 1.24-1.29 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 63.1, 52.3, 47.0, 32.832.7, 32.4 29.2, 25.9, 25.7, 18.3, -5.3; **HRMS** (m/z): calculated $[M+H]^+$ for $C_{14}H_{31}O_2Si$: 259.2088 found: 259.2084.

(R)-9-((tert-butyldimethylsilyl) oxy) non-1-en-3-ol (12)

To a stirred suspension of trimethyl sulfonium iodide (TMSI) (7.1 g, 34.88 mmol, 3 equiv) in a dry THF (50 mL) was added *n*-BuLi (2.5 equiv, 29.05 mmol, 28.3 mL of 1.6 M hexane solution) at -40 °C. After 30 min, epoxide **18** (3 g, 11.62 mmol) in dry THF (30 mL) was added dropwise, and the reaction mixture was slowly warmed to 0 °C and stirred for 2 h. After the reaction (monitored by TLC), the reaction mixture was quenched with water and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried over

anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by column chromatography using petroleum ether/EtOAc (7:3 v/v) to give vinyl alcohol **12** (2.7 g).

Yield: 86% (2.7 g); colourless liquid; $[\alpha]_D^{25}$ = +5.0 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1102, 1222, 1255, 2930, 2955 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.80-5.94 (m, 1H), 5.22 (dt, *J* = 17.17, 1.42 Hz, 1H), 5.10 (dt, *J* = 10.44, 1.34 Hz, 1H), 4.10 (d, *J* = 6.50 Hz, 1H), 3.60 (t, *J* = 6.57 Hz, 2H), 1.50-1.58 (m, 4H), 1.28-1.40 (m, 6H), 0.90 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): *δ* 141.3, 114.5, 73.2, 63.2, 37.0, 32.8, 29.3, 26.0, 25.7, 25.3, 18.4, -5.3; **HRMS** (m/z): calculated [M+H]+ for $C_{15}H_{33}O_2Si$: 273.2244 found: 273.2231.

(R)-13,13,14,14-tetramethyl-5-vinyl-2,4,12-trioxa-13-silapentadecane (11)

To a stirred solution of compound **12** (1.0 g, 3.6 mmol, 1.0 equiv) in dry CH_2Cl_2 (10 mL) was added DIPEA (2.5 mL, 14.70 mmol, 4.0 equiv) at room temperature and stirred for 15 min. The reaction mixture was cooled to 0 °C and then to this solution added dropwise methoxymethyl chloride (0.55 mL, 7.35 mmol, 2.0 equiv) over 5 min. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was washed with aqueous saturated $CuSO_4$ (3 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a crude material, which was purified by column chromatography to obtain compound **11** as a yellowish liquid.

Yield: 84% (0.97 g); Yellowish liquid; $[\alpha]_D^{25}$ = -6.2 (*c* 1.8, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3018, 2927, 2854, 1216, 1033, 929 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 5.66 (ddd, *J*=17.4, 10.1, 7.6 Hz, 1 H), 5.13 - 5.22 (m, 2 H), 4.70 (d, *J*=6.6 Hz, 1 H), 4.53 (d, *J*=6.8 Hz, 1 H), 3.97 (q, *J*=7.0 Hz, 1 H), 3.60 (s, 2 H), 3.37 (s, 3 H), 1.48 - 1.53 (m, 4 H), 1.31 - 1.34 (m, 6 H), 0.89 (s, 9 H),

0.04 (s, 6 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 138.5, 117.0, 93.6, 63.2, 55.3, 35.3, 32.8, 29.3, 25.9, 25.7, 25.3, 18.3, -5.3; **HRMS** (m/z): calculated $[M+H]^+$ for $C_{17}H_{37}O_3Si$: 317.2506 found: 317.2492.

(R)-7-(methoxy methoxy) non-8-en-1-ol (10)

To a stirred solution of **11** (900 mg, 2.84 mmol) in dry THF (20 mL) was added TBAF (6 mg, 1 mol%) dropwise over 5 min., and the reaction mixture was stirred at room temperature for another 3 h. After completion of the reaction (monitored by TLC), H_2O (1 mL) was added, and extraction was done with Ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Column chromatographic purification of the crude product using petroleum ether/EtOAc (8:2 v/v) gave alcohol **10** (517 mg) as a colorless liquid.

Yield: 90%; Colorless liquid; $[\alpha]_D^{25}$ = +9.2 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3441, 2957, 1215, 836, 775 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.6 (ddd, *J* = 17.42, 10.16, 7.69 Hz, 1H), 5.1-5.2 (m, 2H), 4.7 (d, *J* = 6.75 Hz, 1H), 4.5 (d, *J* = 6.75 Hz, 1H), 4.0 (q, *J* = 7.09 Hz, 1H), 3.6 (t, *J* = 6.63 Hz, 2H), 3.4 (s, 3H), 2.2 (br. s., 1H), 1.5-1.7 (m, 4H), 1.2-1.4 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 138.3, 117.1, 93.6, 62.8, 55.3, 35.2, 32.6, 29.2, 25.6, 25.2; **HRMS** (m/z): calculated $[M+Na]^+$ for $C_{11}H_{22}O_3Na$: 225.1461; found, 225.1458.

(R)-7-(methoxy methoxy) non-8-enoic acid (8)

To a solution of alcohol **10** (450 mg, 2.2 mmol) in CH_3CN/H_2O (4:1) was added (diacetoxyiodo)benzene in one portion (1.5 g, 4.90 mmol), and then TEMPO (68 mg, 0.44 mmol) was added. The reaction mixture was then allowed to stir at 25 ^oC for 4 h. After the reaction (monitored by TLC), was completed, the reaction was quenched by adding Na_2SO_4 (aq.). The organic layer was separated, washed with brine, and subjected to column

chromatographic purification with petroleum ether/EtOAc (7:3 v/v) to afford the carboxylic acid **8** (346 mg) as a colorless gummy liquid.

Yield: 72%; Colorless gummy liquid; $[\alpha]_D^{25}$ +6.5 (*c* 1.0, $CHCl_3$) {lit.[3] $[\alpha]_D^{25}$ +6.6 (*c* 1.15, $CHCl_3$)}; **IR** ($CHCl_3$): υ_{max} 3444, 3070, 2931, 2858, 1707, 1462, 1425, 1257, 1109 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.63 (ddd, *J* = 17.39, 10.07, 7.69 Hz, 1H), 5.06-5.24 (m, 2H), 4.68 (d, *J* = 6.75 Hz, 1H), 4.51 (d, *J* = 6.75 Hz, 1H), 3.95 (q, *J* = 7.05 Hz, 1H), 3.35 (s, 3H), 2.32 (t, *J* = 7.44 Hz, 2H), 1.61 (dq, *J* = 14.09, 7.02 Hz, 3H), 1.43-1.53 (m, 1H), 1.28-1.43 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 179.5, 138.2, 117.2, 93.5, 77.2, 55.3, 35.0, 33.9, 28.8, 24.9, 24.5; **HRMS** (m/z): calculated [M+Na]+ for $C_{11}H_{20}O_4Na$, 239.1254; found, 239.1252.

(R)-pent-4-en-2-yl (R)-7-(methoxy methoxy) non-8-enoate (7)

The acid 8 (200 mg, 0.92 mmol, 1 eq.) was dissolved in anhydrous DCM (10 mL), cooled to 0 ^oC then added DCC (286 mg, 1.38 mmol, 1.5 eq.), DMAP (11 mg, 0.513 mmol, 0.11 eq) and stirred for 10 min. The chiral secondary alcohol **9** (87 mg, 1.01 mmol, 1.1 eq.) in 3 mL dry DCM was added at 0 ^oC, and the reaction mixture was stirred for 12 h at 30 ^oC. Then after filtration through a celite pad, it was washed with ether, extracted with 1N HCl, and dried over $MgSO_4$. All the combined organic layer was concentrated under reduced pressure, followed by silica gel (100–200 mesh) column chromatography (eluent 5–10% ethyl acetate: hexane) provided required ester **7** (1.01 g) in 74% as a light-yellow liquid.

Yield: 74%; Light yellow liquid; $[\alpha]_D^{25}$ = +7.2 (*c* 1.8, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1376, 1466, 2872, 2969, 3381 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.60 - 5.82 (m, 2 H), 5.16 - 5.27 (m, 2 H), 5.03 - 5.12 (m, 2 H), 4.92 - 5.01 (m, 1 H), 4.71 (d, *J*=6.8 Hz, 1 H), 4.54 (d, *J*=6.8 Hz, 1 H), 3.98 (q, *J*=7.0 Hz, 1 H), 3.38 (s, 3 H), 2.25 - 2.36 (m, 5 H), 1.60 - 1.66 (m, 4 H), 1.32 - 1.41 (m, 4 H), 1.22 (d, *J*=6.3 Hz, 3 H);0.05 (s, 6H), 0.89 (s, 9H), 1.44-1.58 (m, 6H), 2.50 (br s , 2H), 3.38-

3.48 (m, 1H), 3.59-3.73 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): 173.3 , 138.4, 133.7, 117.6, 117.2, 93.7, 69.8, 55.4, 40.3, 35.2, 34.6, 29.7, 29.0, 25.0, 25.0, 19.5 ; **HRMS** (m/z): calculated [M+Na]+ for $C_{16}H_{28}NaO_4$: 307.1880 found: 307.1871.

(8R,12R, Z)-8-hydroxy-12-methyloxacyclododec-9-en-2-one (Phaseolide A) (3)

2N HCl (1 ml) was added to 0 ^oC cooled solution of compound 19 in 1 ml methanol and stirred the reaction mass for 1h at 30 ^oC, added 3 ml water, extracted with ethyl acetate washed with aqueous bicarbonate (3ml * 3), dried over magnesium sulphate, filtered, concentrated under reduced pressure followed by silica gel (100-200 mesh) column chromatography (with eluent 3%-10% ethyl acetate :hexane) to afford natural product Phaseolide A.

Yield: 92% (38 mg); Light yellow liquid; $[\alpha]_D^{25}$ = +7.2 (*c* 1.8, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1376, 1466, 2872, 2969, 3381 cm^{-1}; **^{1}H NMR** 1H-NMR (400 MHz, CDCl3) δ 5.38-5.28 (m, 2H,), 5.18 (m, 1H), 3.76 (tt, 1H, J = 9.6, 3.8 Hz), 2.44-2.38 (m, 1H), 2.34-2.25 (m, 2H), 2.21 (m, 1H), 2.14-1.99 (m, 2H), 1.86-1.77 (m, 3H), 1.68 (m, 1H), 1.48 (m, 1H), 1.24 (d, 3H, J = 6.3 Hz), 1.17 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 173.1, 132.5,127.3, 68.4, 67.6, 40.9, 34.2, 32.2, 30.3, 28.07, 20.4, 20.1 ; **HRMS** (m/z): calculated [M+Na]+ for $C_{21}H_{21}O_3$: 213.1485 found: 213.1470.

Section II

Organocatalyzed Total Synthesis of Marine Natural Product 12- membered Macro-lactone Balticolid

1.2.1. Introduction and Pharmacology

Marine microorganisms are identified as the prosperous source of active pharmaceutical metabolites as several secondary metabolites are isolated from these microorganisms.[19,20] In particular, 12-membered macrolides isolated from fungal metabolites of marine microorganism significantly shows biological and pharmaceutical activities. All such 12-membered macrolactones includes Cladospolides A and B,[21] Dendrodolides,[22] Patulolides A and C,[23] Pandangolide,[24] and Chloriolide[25] with enormous biological activities like antibacterial,[26] antifungal,[27] cytotoxic,[28] and phytotoxic properties.[29]

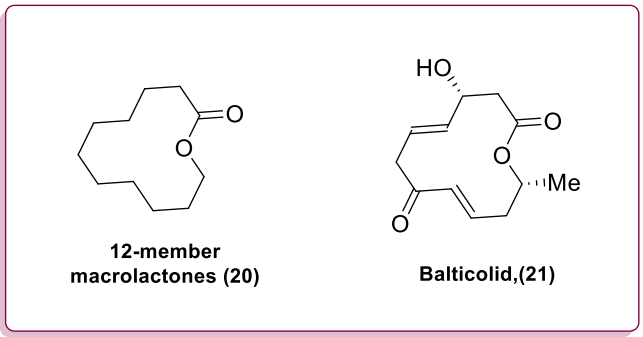


Figure 14: Structure of 12-membered macrolactone and Balticolid

Balticolid **21** is one of the macrolides from the class of 12-membered macro lactone with antiviral and anti-HSV-1 activity with an IC_{50} value of 0.45 μM. Balticolid **21** was isolated in 2011 by Shushni and coworkers from the marine fungus, which belongs to *the Ascomycetous* species, *via* the EtOAc extraction process.[30] The structural determination of Balticolid to be (3*R*,11*R*), (4*E*,8*E*)-3-hydroxy-11-methyloxacyclododeca-4,8-diene-1,7-dione and is well supported with the help of spectral data as well as the modified Mosher ester method. Due

to the different positioning of the functional group than relevant 12-membered macro lactones, it attracts much more attention.

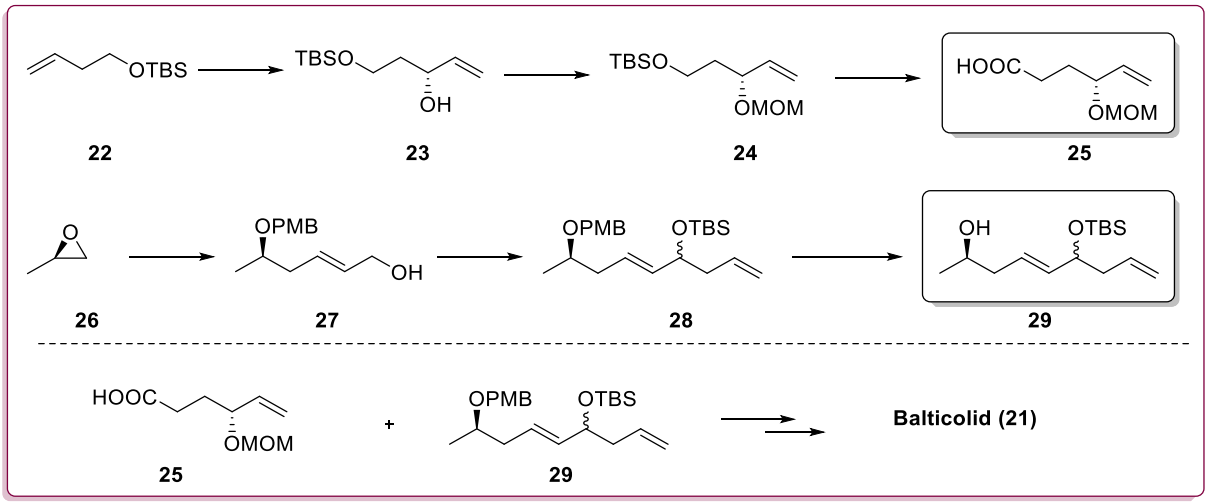
1.2.2. Review of Literature

Considering the biological importance and novelty of Balticolid, many research groups were devoted to synthesizing the target molecule. It was isolated in 2011, and three different chemical routes for synthesizing Balticolid have been reported.

Krishna's Approach (2012)[31]

Radha Krishna and a co-worker (2012) achieved a convergent synthesis of Balticolid from acid and alcohol fragments *via* Hydrolytic Kinetic Resolution (HKR) strategy. From protected butenol, the necessary acid fragment was synthesized. Butenol was having olefine subjected for epoxidation reaction. The epoxide was further resolved using Hydrolytic Kinetic Resolution to yield enantiopure epoxide. The chiral vinylic alcohol was then obtained by opening the enantiopure epoxide with Corey Chavosky's reagent. As a next step, the protection of 2^o alcohol and deprotection of 1^o alcohol was followed by over-oxidation to obtain chiral acid fragments.

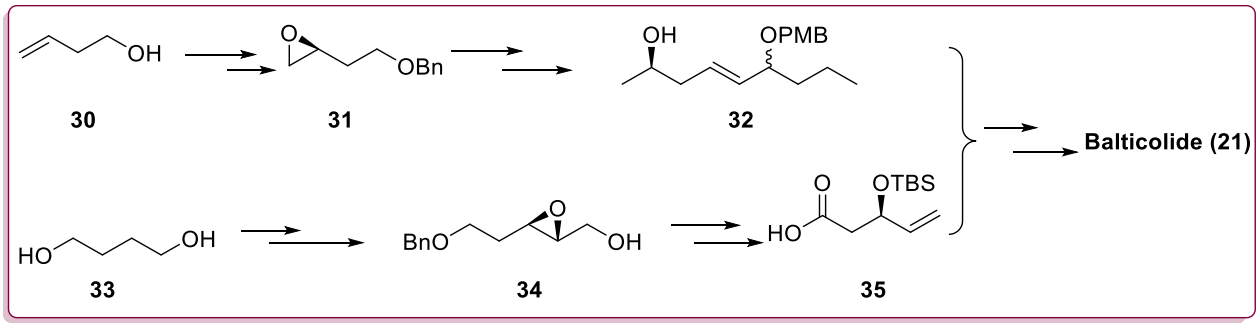
In contrast, the alcohol fragment was synthesized from propylene oxide. The alkylated propargylic alcohol fragment was obtained by carrying a ring-opening reaction of propylene oxide with protected propargylic alcohol under primary conditions. Alcohol is subjected to some chemical transformation to obtain the needed alcohol fragment. The obtained acid and alcohol fragment was coupled and employed by Steglich esterification, followed by Grubb's ring closing metathesis to furnish the macro-lactone. At the end of synthesis, the deprotection, and oxidation of secondary alcohol to get Balticolid (**Scheme 6**).



Scheme 6: Radha Krishna approach (2012)

J. S. Yadav's Approach (2017)[32]

Yadav *et al.* reported the synthesis of Balticolid by using commercially available homoallylic alcohol and 1, 3 propane diol. In this approach author used Sharpless asymmetric epoxidation, Jacobsen's hydrolytic kinetic resolution, Barbier allylation, Yamaguchi esterification, and Grubbs ring-closing metathesis (RCM) to accomplish the total synthesis of Balticolide. The total synthesis of Balticolid was accomplished by coupling acid and alcohol fragments. The required alcohol fragment was synthesized from readily available 3-butene-1-ol. The 3-butene-1-ol containing primary alcohol was initially benzyl protected, then the olefin was epoxidized and resolved via the HKR strategy. The corresponding alcohol fragment was synthesized from chiral epoxide by following steps. i) reduction of epoxide, ii) protection of secondary alcohol, iii) deprotection of primary alcohol, iv) oxidation followed by Wittig reaction, v) reduction of ester, vi) oxidation of primary alcohol and Barbier allylation followed by PMB protection, vii) Then the TBS deprotection to obtained the chiral alcohol fragment.



Scheme 7: J. S Yadav's approach (2017)

In comparison, the acid fragment was synthesized from 1,4 butanediol by various chemical transformations such as i) mono -Bn protection. ii) oxidation of primary alcohol followed by 2-carbon Wittig reaction, iii) then reduction of ester to homoallylic alcohol, iv) homo allylic alcohol transformed to chiral epoxide using Sharpless asymmetric epoxidation, v) further, epoxide opened to obtained vinylic alcohol, vi) TBS protection of secondary alcohol followed by benzyl deprotection of primary alcohol, vii) primary alcohol oxidized to obtained acid.

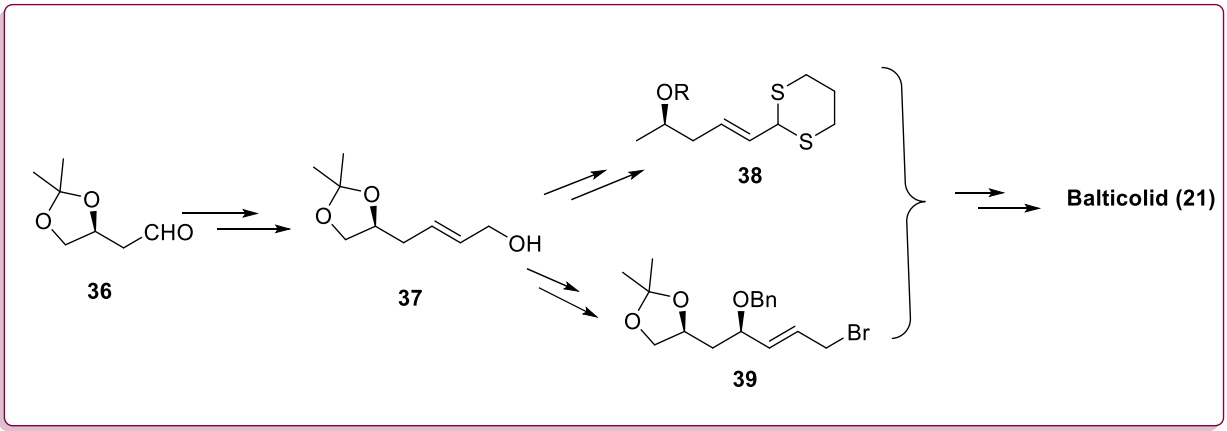
Acid and alcohol fragments were in hand; then, both fragments were coupled with Steglich esterification and Grubbs ring closing reaction to furnish the protected macro-lactone. The deprotection and oxidation sequences did at a late stage to obtain corresponding Balticolid (Scheme 7).

Alapati's Approach (2019) [33]

Srinivasa Rao Alapati and co-workers (2019) accomplished an efficient stereoselective total synthesis of Balticolid from known aldehyde. Sharpless asymmetric epoxidation, Wittig olefination, alkylation of 1,3-dithiane, and Yamaguchi macro-lactonization are the key steps involved in the total synthesis of Balticolid. The total synthesis of Balticolid started from the available starting material, i.e., known aldehyde, which was synthesized from L-malic acid. The actual synthesis of Balticolid started from protected aliphatic aldehyde. It was treated with a 2-C

Wittig reaction to form an unsaturated ester, and the ester was then reduced to obtained homoallylic alcohol. The synthesized homoallylic alcohol is a common intermediate for both fragments. The alcohol fragment is first synthesized from homoallylic alcohol with various chemical steps such as oxidation of homoallylic alcohol to obtain aldehyde. Aldehyde was subjected to 1,3 di-thione protection to furnish the corresponding protected diol. Then diol was subjected to deprotection to obtain the corresponding chiral diol. Then the diol having 1o was subjected to reduction to alkane to formed secondary functionalized alcohol. Alcohol is then protected to TBSCl to complete the alcohol fragment.

However, another fragment allyl bromide fragment was synthesized from the same homoallyl alcohol fragment. The homoallyl alcohol was subjected to Sharpless asymmetric epoxidation. Then the epoxide was treated with I_2 and PPh_3 to obtain the iodo-epoxidized adduct. Iodo epoxidized adduct then reduced to furnish the chiral homoallylic alcohol. Then, the terminal olefin is converted into aldehyde using the ozonolysis process. Further, the aldehyde was subjected to a 2-C Wittig reaction to derive the ester moiety, which was then reduced to formed alcohol. At the late stage, alcohol was replaced by bromide via the known Appel reaction, as shown in Scheme 8.



Scheme 8: Alapati approach (2019)

With both fragments in hand, it was coupled through a nucleophilic substitution reaction. Then acetonide was deprotected to obtain diol, which was further cleaved and over-oxidized to the formed acid fragment. Moreover the secondary alcohol deprotected followed by intramolecular coupled with acid furnished the diathione protected macrolactone. At the same time, deprotection took place at a late stage to deliver the corresponding target molecule.

1.2.3. Present Work

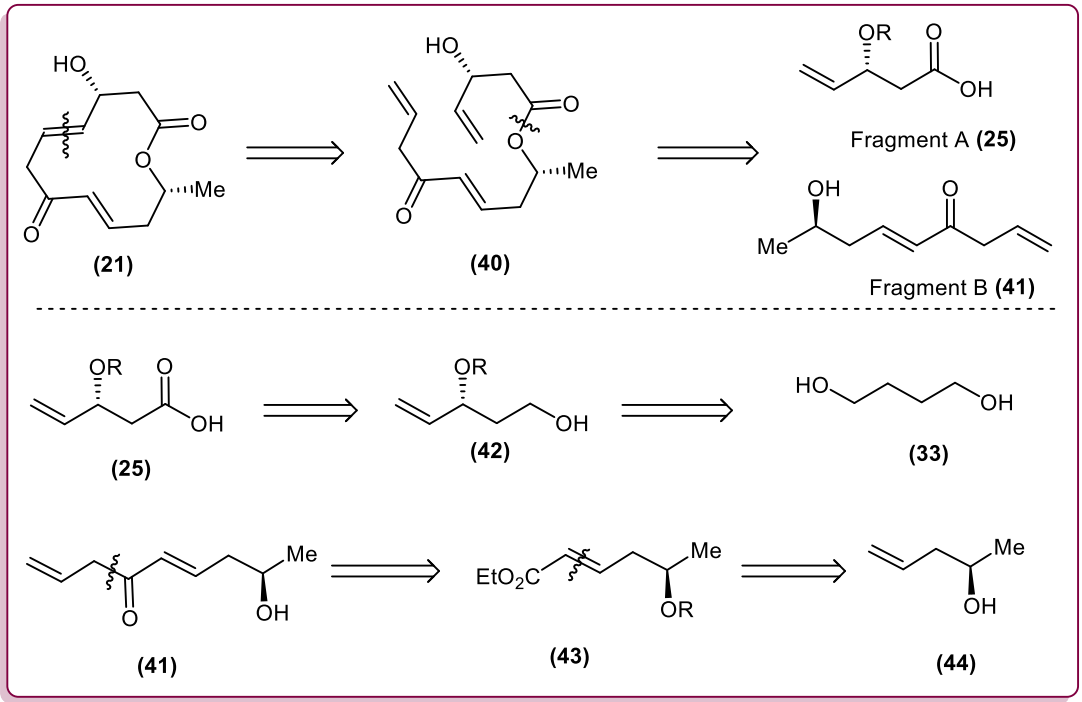
1.2.3.1. Objective

Recently, proline and its derivatives have been extensively utilized for the asymmetric synthesis of bioactive molecules. Our continuous efforts towards its utilization in α-aminoxylation reaction inspired us to use this approach to synthesize Balticolid. Herein, we reported the efficient total synthesis of Balticolid starting from commercially available 1,4-butanediol and acetaldehyde.

1.2.4. Result and Discussion

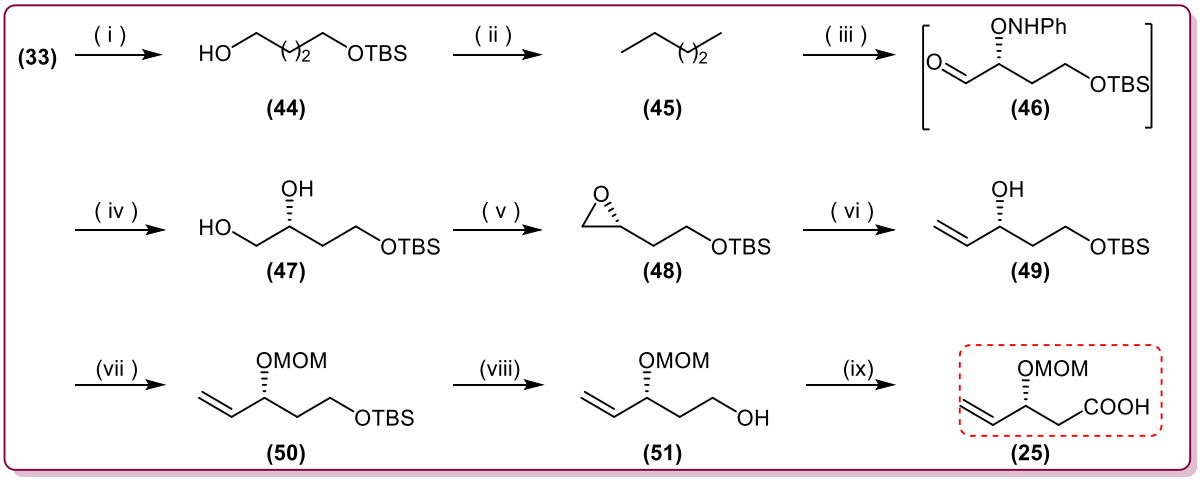
Recently, proline and its derivatives have been extensively utilized for the asymmetric synthesis of bioactive molecules. Our continuous efforts towards its utilization in α-aminoxylation reaction inspired us to use this approach to synthesize Balticolid. Herein, we reported the efficient total synthesis of Balticolid starting from commercially available 1,4-butanediol and acetaldehyde.

Based on the retrosynthetic analysis shown in Scheme 9, Balticolid could be obtained from intramolecular RCM reaction of ester. Further, the ester could be synthesized from Yamaguch esterification of enantiopure acid and alcohol fragments. Then the acid fragment could be obtained from the α-aminoxylation reaction of 1,4-butadiene. In contrast, hydroxyl fragments could be obtained from Keck allylation of acetaldehyde. We commenced our synthesis of Balticolid **21** with the preparation of enantiopure acid fragment A as shown in Scheme 5.



Scheme 9: Retrosynthetic analysis of Balticolid

Initially, 1,4-butanediol was subjected to a monosilylation reaction using 1.0 equivalents of TBSCl and 1.5 equivalents of imidazole in DCM at 0 °C to obtain the corresponding mono TBS protected 1,4 butanediol (**44**) in 86% yield.



Scheme 10: Synthesis of acid fragment (**25**): **Reagent and conditions:** (i) TBSCl (0.9 equiv.) Imidazole (1.5 equiv.) DCM, rt, 86%; (ii) TEMPO (0.1 equiv.), BAIB (1.1 equiv.), DCM, 0 ^{o}C to rt, 80%; (iii) L-proline (15 mol%), PhNO (0.95 equiv.) -20 ^{o}C 24 hr; (iv) a) $NaBH_4$ (1.5 equiv.), MeOH, 0 ^{o}C to rt, b) $Cu(OAc)_2$, MeOH, 62% over three steps; (v) (a) TsCl, Et_3N, Bu_2SnO, DMAP, DCM, 0 ^{o}C, 3h; (b) K_2CO_3, MeOH, 0 ^{o}C, 2 h, 76% over two steps. (vi) $ISMe_3$ (3 equiv.), n-BuLi (2.5 equiv.), THF, 76%; (vii) MOMCl (1.2 equiv.), DIPEA (2 equiv.), DCM, 0 ^{o}C to rt, 82%; (viii) TBAF (1.5 equv.), THF, 90% (viii) TEMPO (0.2 equiv.), BAIB (2.2 equiv.) ACN; H_2O (4:1), rt, 68%.

Its ^{1}H, ^{13}C NMR spectra confirmed the formed mono-silylated butane-diol (44). In the ^{1}H NMR spectra, the peak appears at δ 0.04 and δ 0.87, corresponding to the 6 and 9 protons of the silyl group. However, the same compound was solely confirmed in its ^{13}C NMR spectra. In ^{13}C NMR, the peak appears at δ -5.46 and δ 25.85 for the carbon of the TBS group's respective methyl and *tert* methylene (**Figure 15**). The oxidation of primary alcohol using well-known TEMPO-BAIB oxidation conditions furnished aliphatic aldehyde (**45**) in an 80% yield. The formed aldehyde was then used for *L*-proline mediated α-aminoxylation reaction[34] using 0.95 equivalents of PhNO and 15 mol% of *L*-proline as organocatalyst in ACN at -20 ^{o}C for 24 hours. After 24 hours, 1.5 equivalents of $NaBH_4$ were added to the reaction mixture, followed by the addition of 1.2 equivalents of $Cu(OAc)_2$ in MeOH at room temperature. The corresponding enantiopure diol (**47**) was isolated in the 62% yield over two steps with 98% *ee*. The obtained compound was then unambiguously confirmed by their corresponding ^{1}H and ^{13}C spectra. In the ^{1}H NMR spectra, the peak at δ 3.73 - 3.93, 4H corresponding to the two terminal CH_2 groups, i.e., C**H**$_2$-OH and C**H**$_2$-OTBS group while the peak appeared at δ 3.57 dd for 1H corresponding to the characteristic chiral methylene carbon proton (-C**H**(OH)-). Furthermore in the ^{13}C NMR spectrum, the peak at the δ 71.7 is the typical chiral methylene carbon, as shown in **figure 16**.

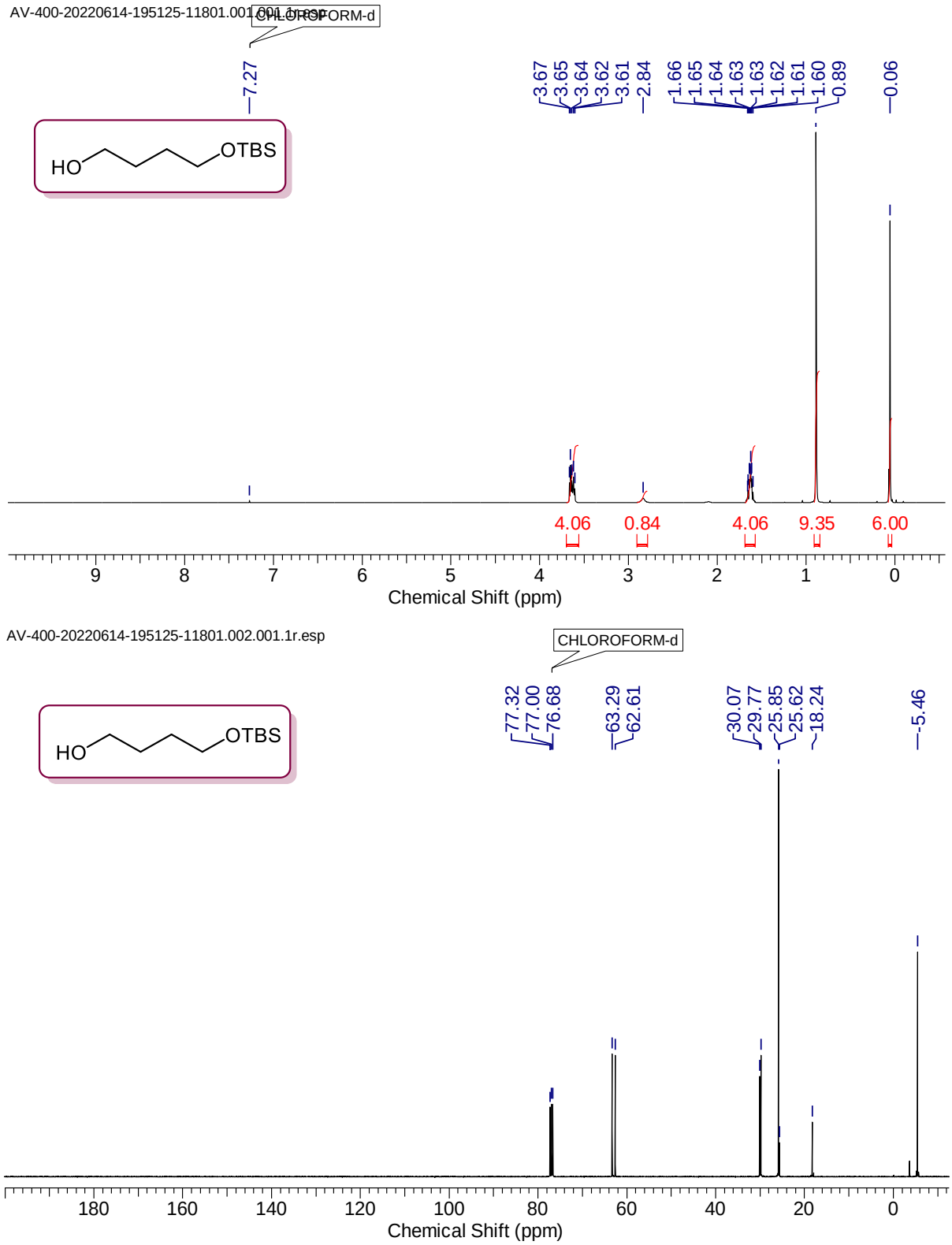


Figure 15: ^{1}H and ^{13}C spectra of 4-((tert-butyldimethylsilyl) oxy) butan-1-ol (44)

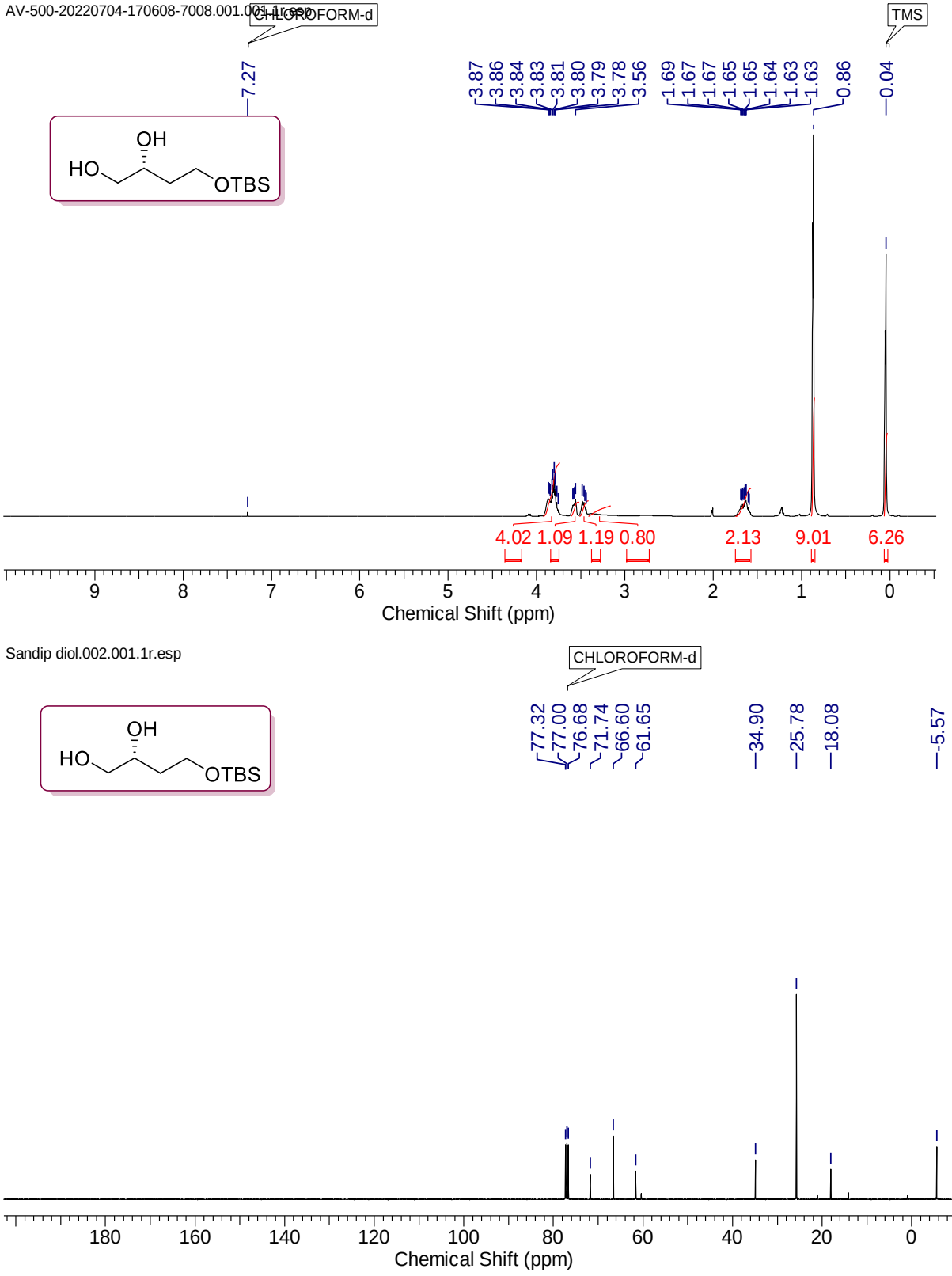


Figure 16: (R)-4-((tert-butyldimethylsilyl) oxy) butane-1,2-diol (47)

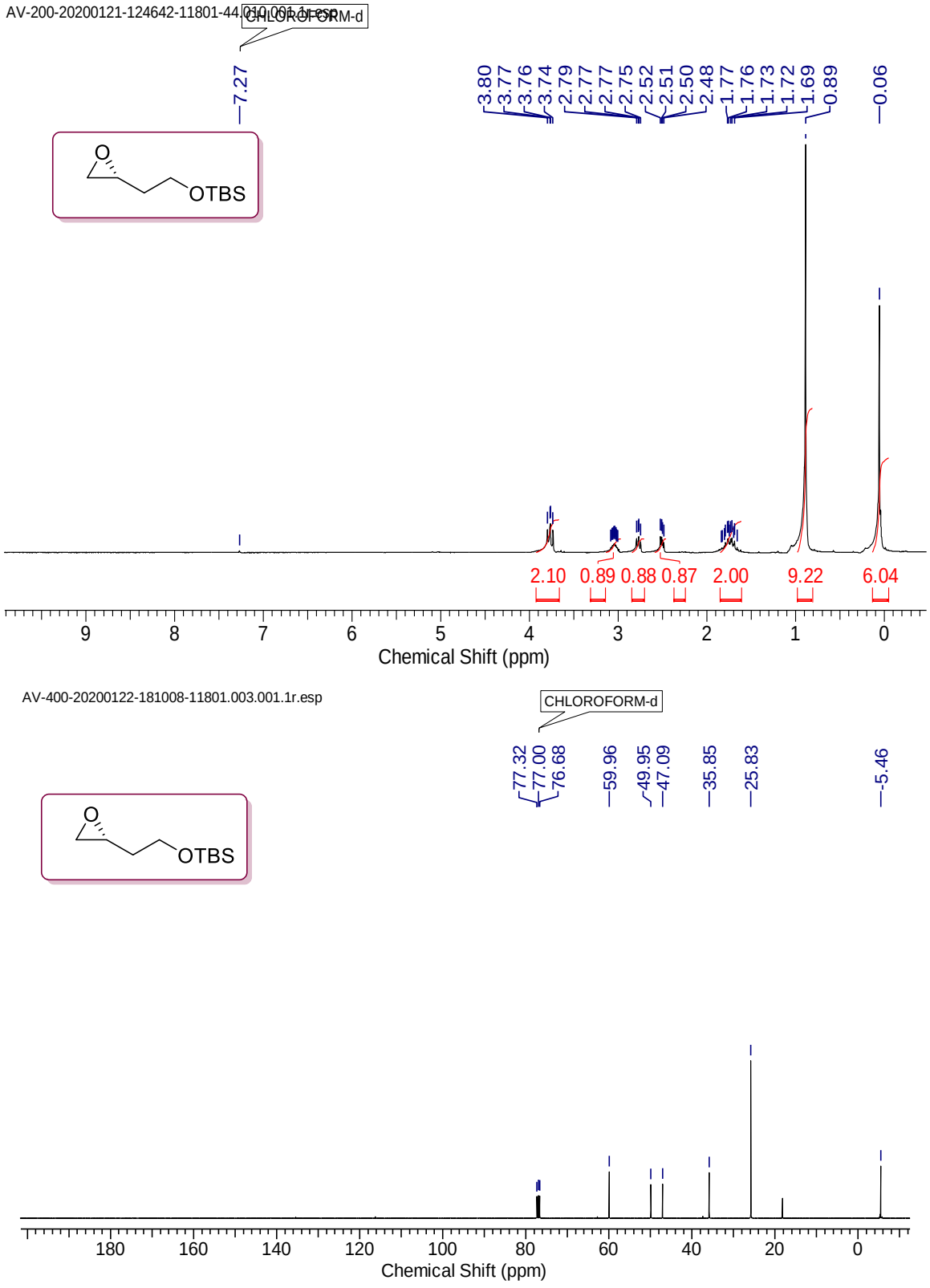


Figure 17: (R)-tert-butyldimethyl(2-(oxiran-2-yl) ethoxy) silane (48)

After the enantiopure diol (**47**) was formed, it was further utilized to synthesize the epoxide. The diol was subjected to a mono-tosylation reaction using 0.99 equivalents of TsCl, and 0.3 equivalents of n-Bu_2SnO and cat. DMAP in DCM. The formed monotosyl group was subjected to base-mediated epoxidation using K_2CO_3 (2.0 equiv.) as the base in MeOH leads to the desired epoxide (**48**) in 76% yield over two steps. The obtained desired epoxide was confirmed by its ^1H and ^{13}C NMR spectra. In the 1H NMR, the peak at δ 2.97-3.14, multiplet for 1-H corresponding to the methylene (-C**H**-) carbon of epoxide, while the peak at δ 2.77 and 2.50 are two diastereomeric protons of terminal epoxide carbon are showed there is the formation of an epoxide. However, in the ^{13}C NMR spectra, the peak at δ 49.95 and δ 47.09 are the epoxide carbons, as shown in **Figure 17**. Moreover, the opening reaction of epoxide using the Corey-Chaykovsky reagent ($S^+Me_3I^-$) gave the corresponding vinylic alcohol (**49**) in 76% yield. The formed homoallylic alcohol was confirmed by its ^1H and ^{13}C NMR spectra. The ^1H NMR, the peak at δ 5.86, ddd for 1-**H** corresponds to the internal olefinic carbon. The peak appears at δ 5.19-5.34, multiplet for 1-**H** and δ 4.98 - 5.17 multiplet for 1-**H** corresponding to the terminal olefinic carbon. Also, in the ^{13}C NMR spectrum, the peak at δ 114.05 and δ 140.60 are the olefinic carbon peaks. Due to the appearance of this peak, we conclude that there is olefin formation in the respective compound, as shown in **Figure 18.**

The obtained secondary alcohol was subjected to MOM protected in the presence of MOM-Cl, and DIPEA in DCM solvent to furnish the corresponding MOM protected compound (**50**) in 82% yield. The NMR spectroscopic technique confirmed the isolated MOM-protected secondary alcohol. In the ^1H NMR, the characteristic protons appeared at δ 4.69 (d, J=6.6 Hz, 1H) and δ 4.53 (d, J = 6.6 Hz, 1H) are the diastereomeric methylene (-C**H**$_2$-) protons, as well as the peak,

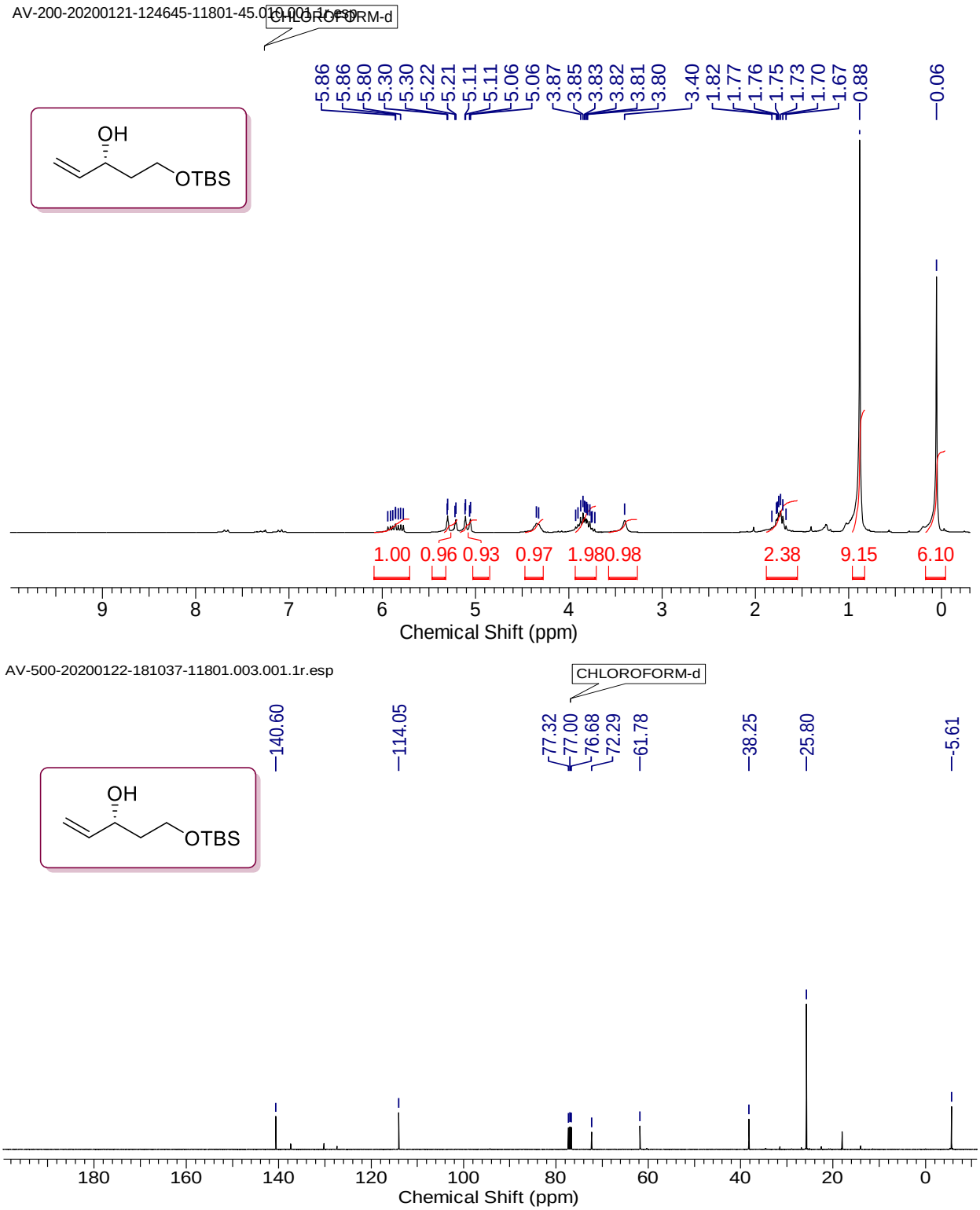


Figure 18: (R)-5-((tert-butyldimethylsilyl) oxy) pent-1-en-3-ol (49)

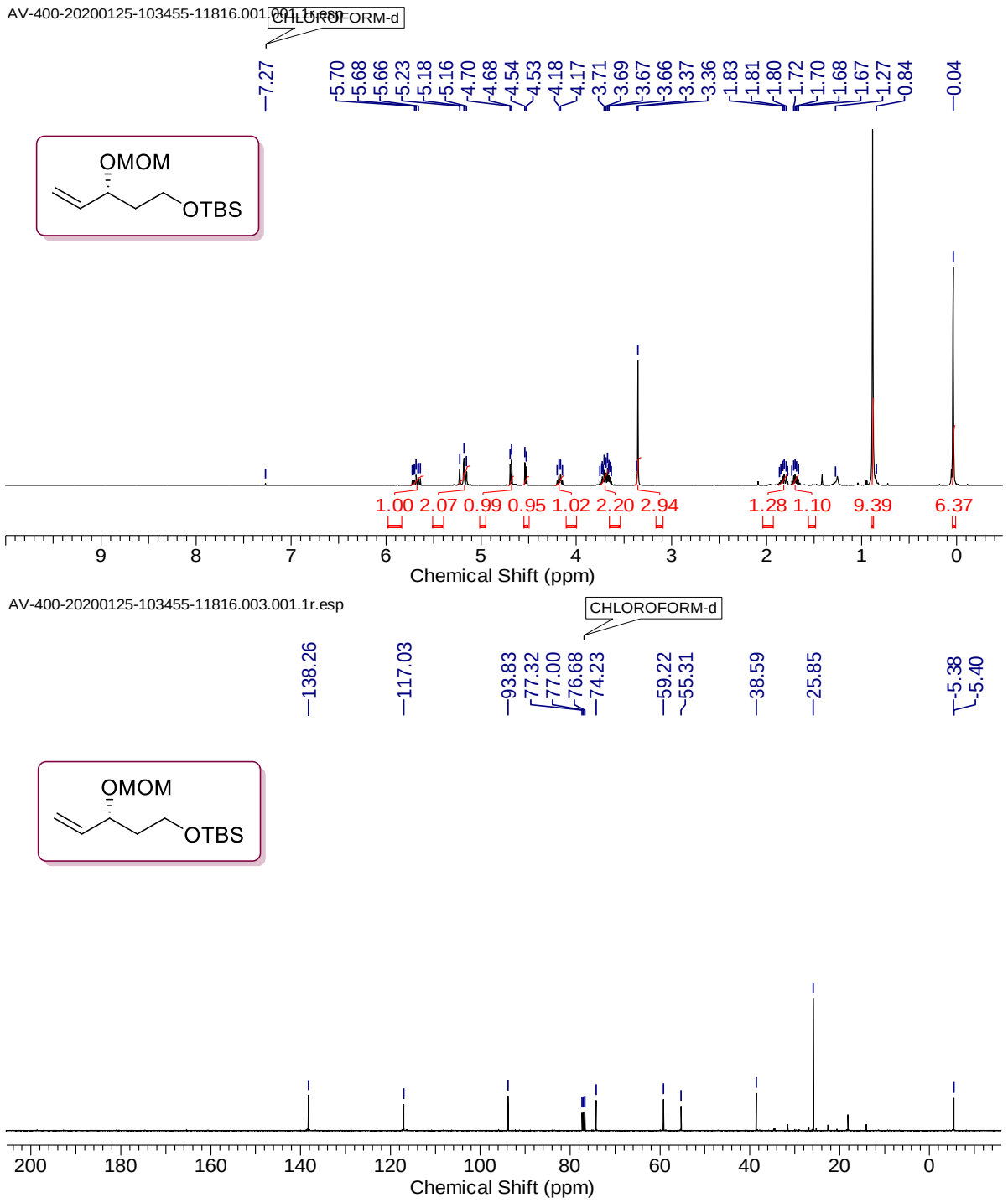


Figure 19: (R)-9,9,10,10-tetramethyl-5-vinyl-2,4,8-trioxa-9-silaundecane (50)

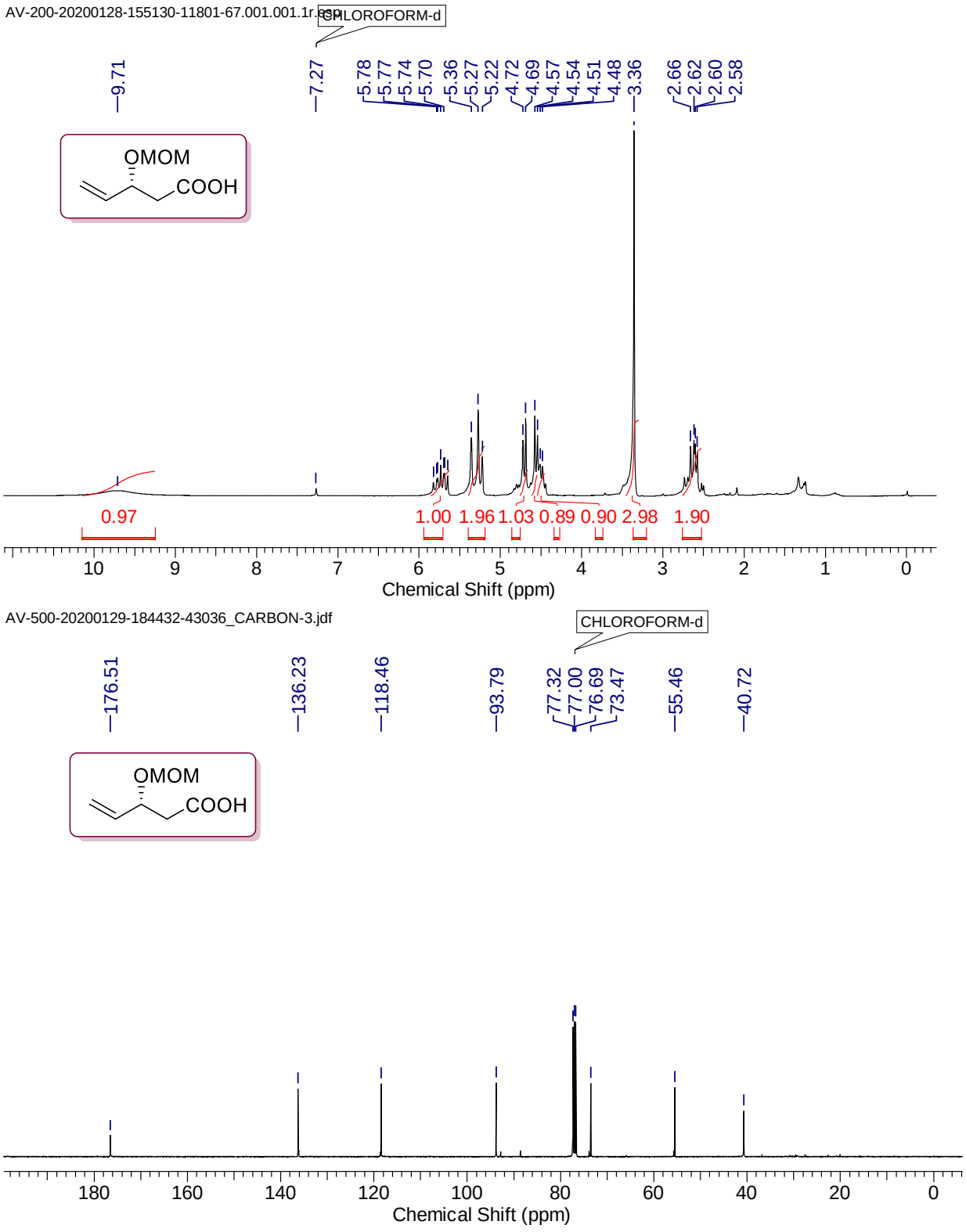
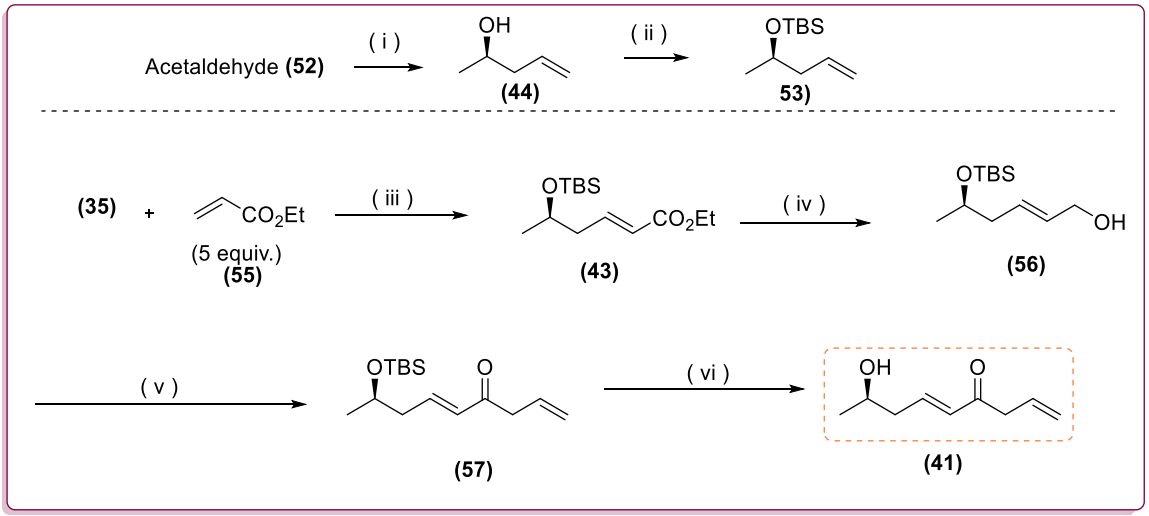


Figure 20: (R)-3-(methoxy methoxy) pent-4-enoic acid (25)

appeared at δ 3.32-3.39 (m, 3H) is the methyl (-C**H**$_3$) protons of MOM group. The same structure was also confirmed by its ^{13}C NMR spectra. The ^{13}C NMR peak at δ 93.8 and δ 55.3 are the carbon peaks of methylene and methyl carbon of the MOM protecting group, as depicted in **Figure 19.**

In the subsequent reaction sequence, the primary alcohol was deprotected, followed by over oxidization in the presence of TEMPO/BIAB in ACN and H_2O conditions to obtain our acid fragment **(25)** in 68% yield. The precise structure of acid was confirmed by ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectrum, the peak found at δ 9.99 sharp singlet for the characteristic acid proton (-COO**H).** However, in the ^{13}C NMR spectrum, the peak at δ 176.51 is the typical acid carbon, as shown in **Figure 20.**



Scheme 6: Synthesis of alcohol fragment (**41**): **Reagent and conditions:** (i) Diisopinacocamponylborane, Et_2O-pentane, -78 ^{o}C, 1h, NaOH, aq H_2O_2 (35%), 77%, $[\alpha]^{25}_D$ =+8.9 (c=3.00 Et_2O; (ii) TBSCl (0.9 equiv.) Imidazole (1.5 equiv.) DCM, rt, 86%; (iii) Grubbs II cat. (0.2 equiv.), DCM, 45^{o}C; 74%; (iv) DIBAL-H (1 equiv.), DCM, 0^{o}C to rt, (v) a) TEMPO (Cat.), BIAB (1.2 equiv.), DCM, rt, b) allyl bromide (1.5 equiv.) Zn (3 equiv.), THF: H_2O, b) DMP (1.2 equiv.), DCM, rt (65% Over two steps); (vi) TBAF (1.5 equv.), THF, 90%

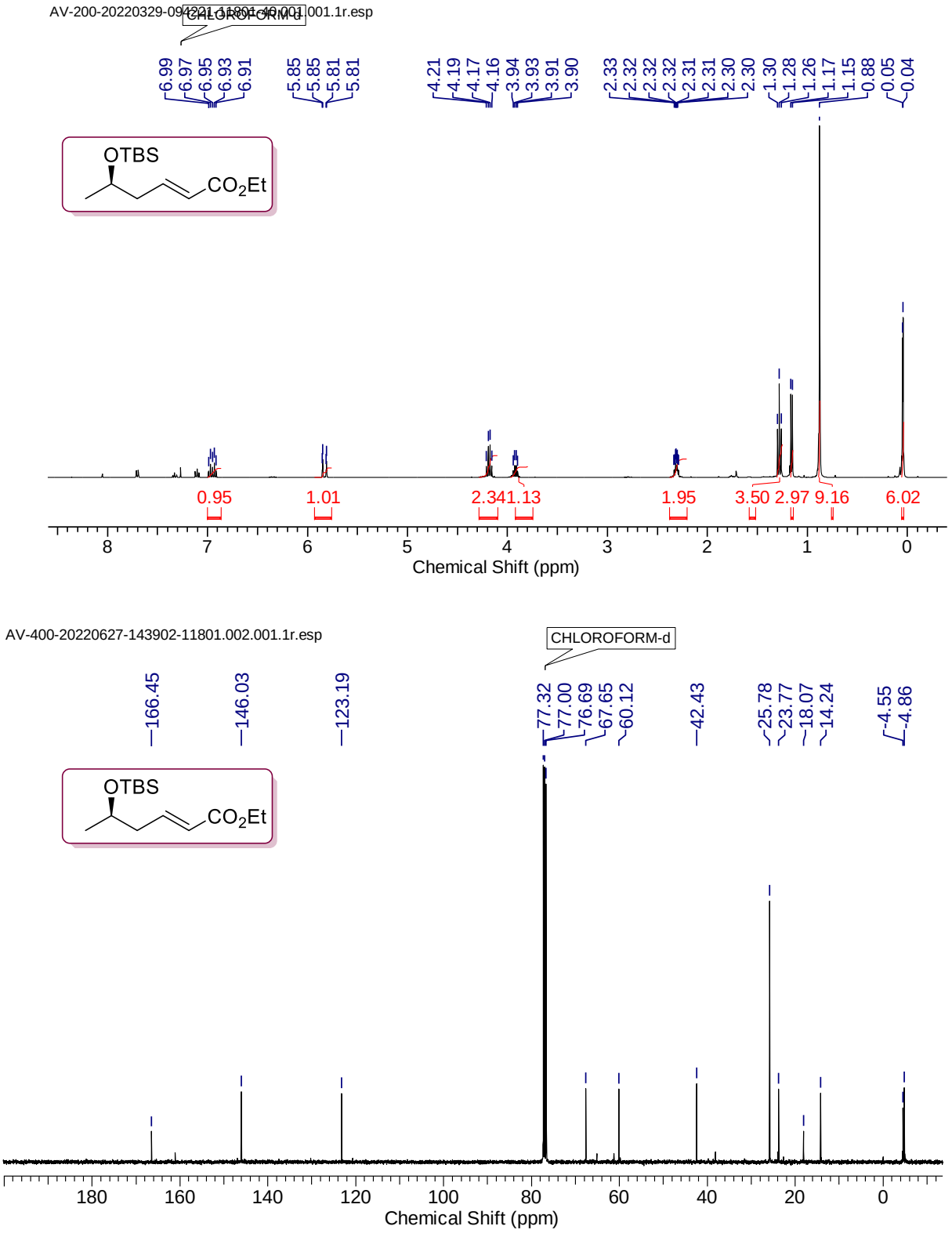


Figure 21: Ethyl (R, E)-5-((tert-butyldimethylsilyl) oxy) hex-2-enoate (43)

After achieving the acid fragment, we focus on synthesizing the alcohol fragment. The acetaldehyde was subjected to the Brown allylation reaction condition (Diisopinacocamponylborane, Et_2O-pentane, -78 ^oC, 1h, NaOH, aq H_2O_2 (35%)), which gave enantiopure alcohol in 77%.[35] as shown in **Scheme 18.** The formed alcohol was then protected as

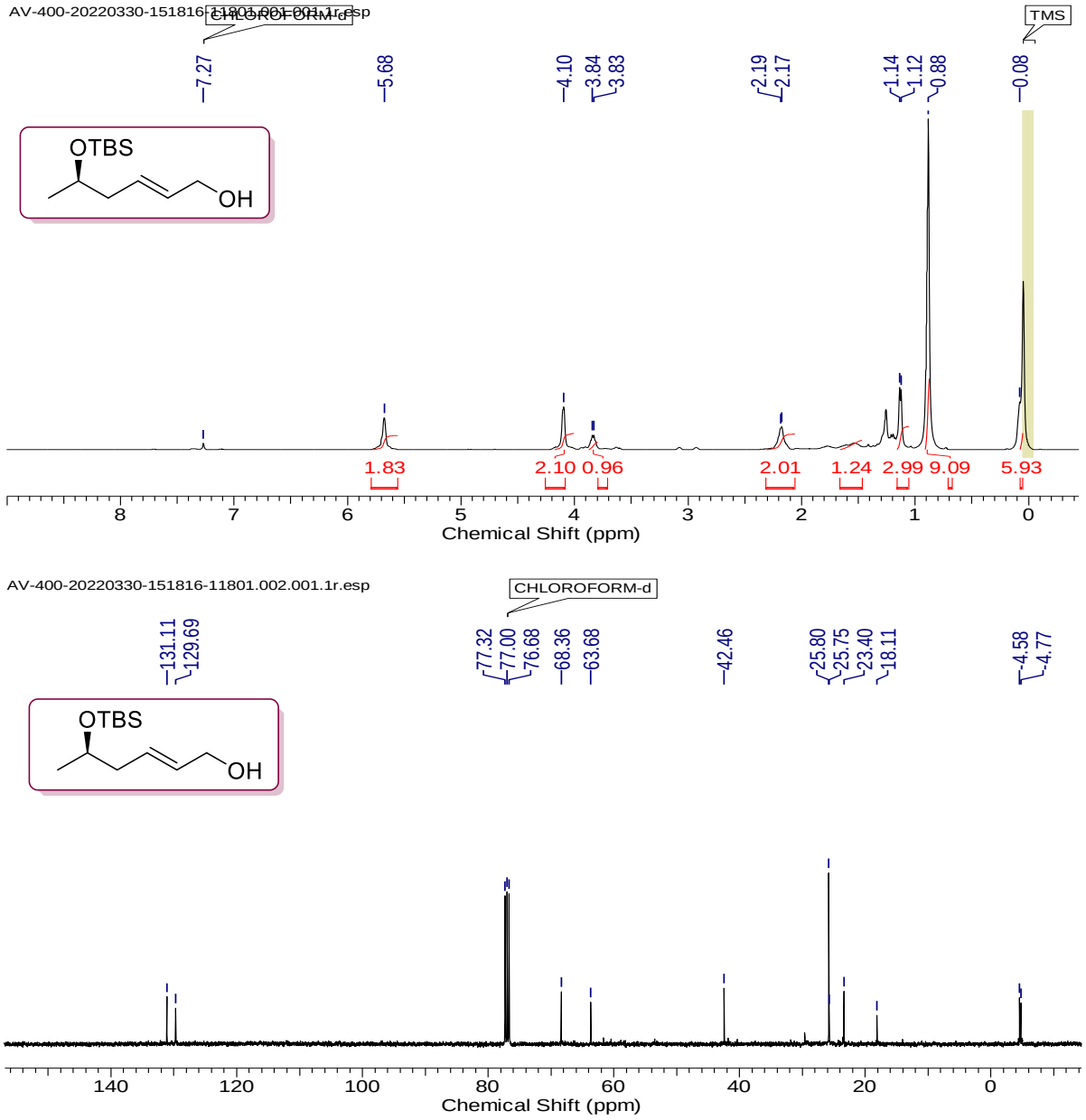


Figure 22: (R, E)-5-((tert-butyldimethylsilyl) oxy) hex-2-en-1-ol (56)

a TBS group to obtain the TBS-protected alcohol fragment (**53**). Then, the protected homoallylic alcohol was subjected to the Grubbs-cross metathesis[36] reaction with commercially available ethyl acrylate (5 Equiv.) (**55**) to furnishes the corresponding *α-β* unsaturated ester fragment (**43**)

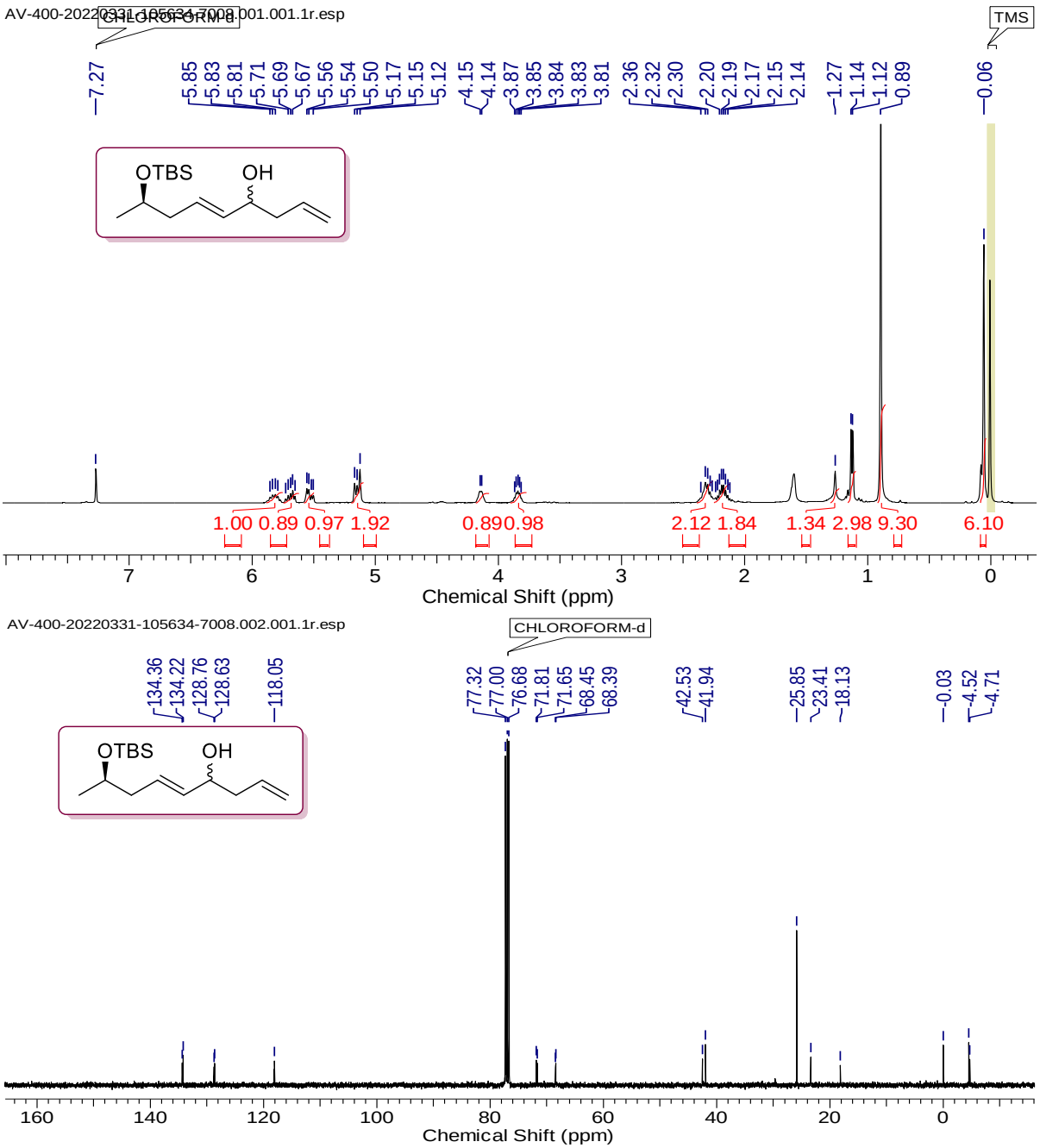


Figure 23: (8R, E)-8-((tert-butyldimethylsilyl) oxy) nona-1,5-dien-4-ol

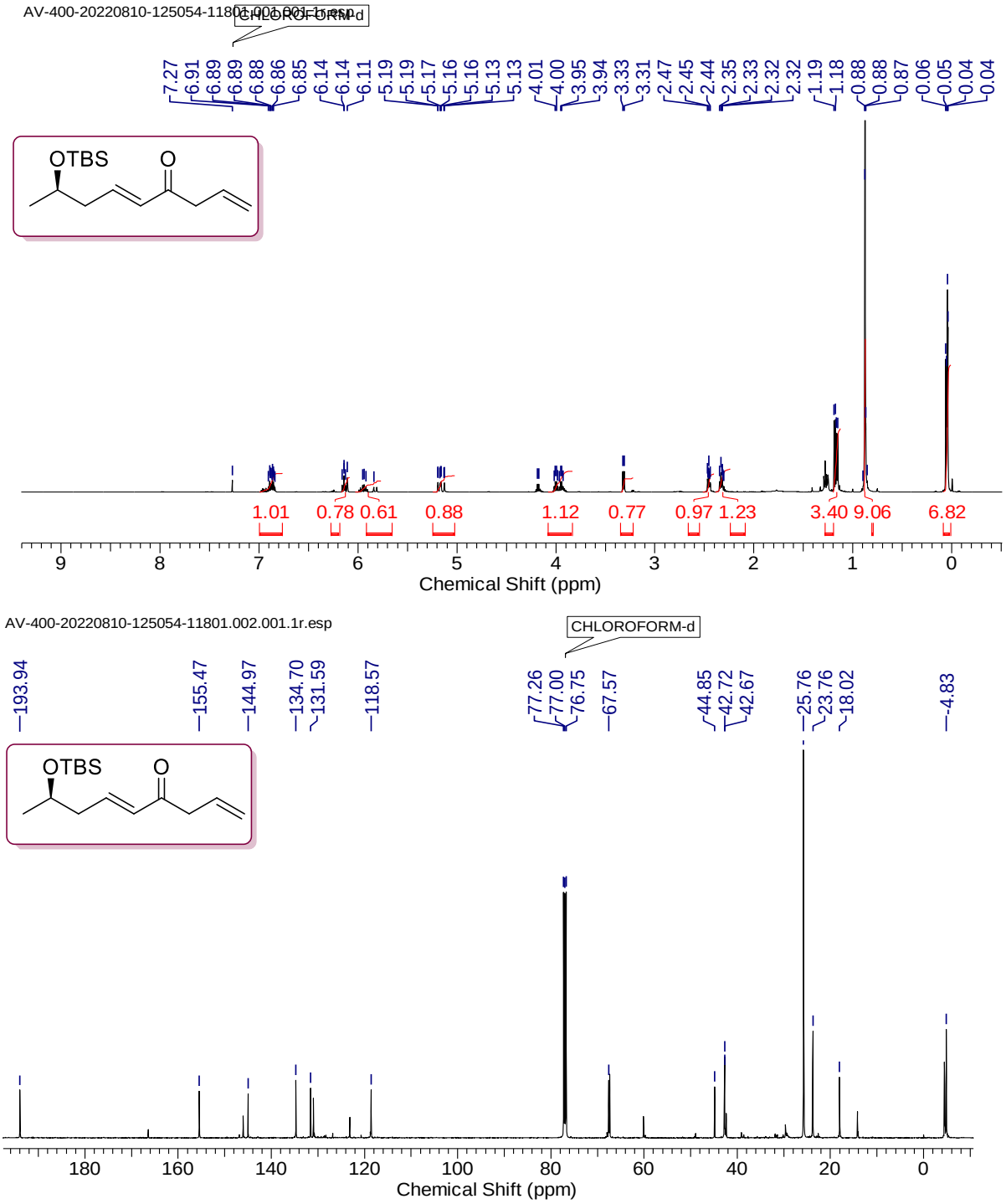
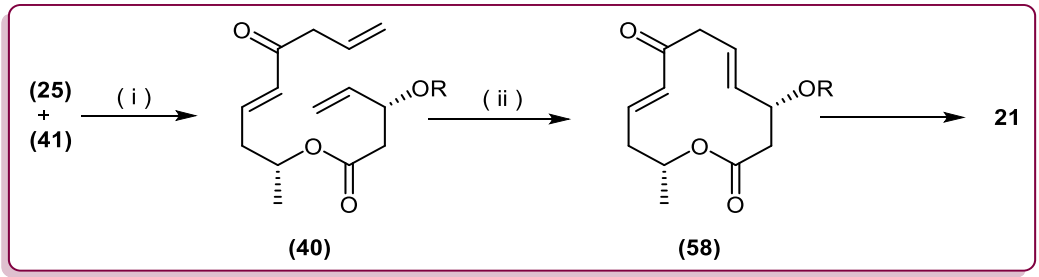


Figure 24: (E)-8-((tert-butyldimethylsilyl) oxy) nona-1,5-dien-4-one (57)

in 74% yield. The formed acid fragment was then confirmed by ^{1}H and ^{13}C NMR specta. In

the ^{1}H NMR spectrum, the peak appears at δ 6.86-7.00 multiplet for ^{1}H, and the δ 5.83 (dt, *J*=15.6, 1.4 Hz, 1H) are the characteristic olefinic protons. And in the ^{13}C NMR spectrum, the peak appears at δ 166.4 for the carbonyl of ester (-**CO**OEt-), and the peak at δ 146.0 and δ 123.1 are the olefinic carbons of α-β unsaturated ester as shown in **Figure 21.** However, the α, β-unsaturated ester was reduced to alcohol (DIBAL-H, DCM, 0 ^{o}C). The formed alcohol product was characterized by ^{1}H and ^{13}C NMR spectroscopy. In ^{1}H NMR, the disappearance of methyl (-**CH$_3$**) and (-**CH$_2$**) peaks confirms the reduction of the ester group. The reduction of ester was confirmed by the ^{13}C NMR spectrum with the disappearance of ester carbon, as shown in **Figure 22**.

The obtained primary alcohol was further subjected to oxidation, and then homoallylation using the known Barbier allylation condition to form the required homoallylic alcohol fragment. The formed product was precisely confirmed to its ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR, the peak appears at δ 5.82 (dd, J=16.7, 7.8 Hz, 1H, δ 5.09 - 5.20 (m, 2H) olefinic protons of external alkene, which was formed by allylation condition. However, the same intermediate was confirmed by ^{13}C NMR spectroscopic method. Which peaks shown at δ 118.05 and δ 134.22 are the characteristic terminal olefinic carbons of the homoallylic alcohol fragment, as depicted in **Figure 23.**



Scheme 12: Synthesis of Balticolid (**21**): (i) PCC (1.0 equiv.) DMAP (0.1 equiv.) DCM, rt, (ii) Grubbs II gen. Catalyst (0.1 equiv.), DCM, 45 ^{o}C, 70% (for two steps);

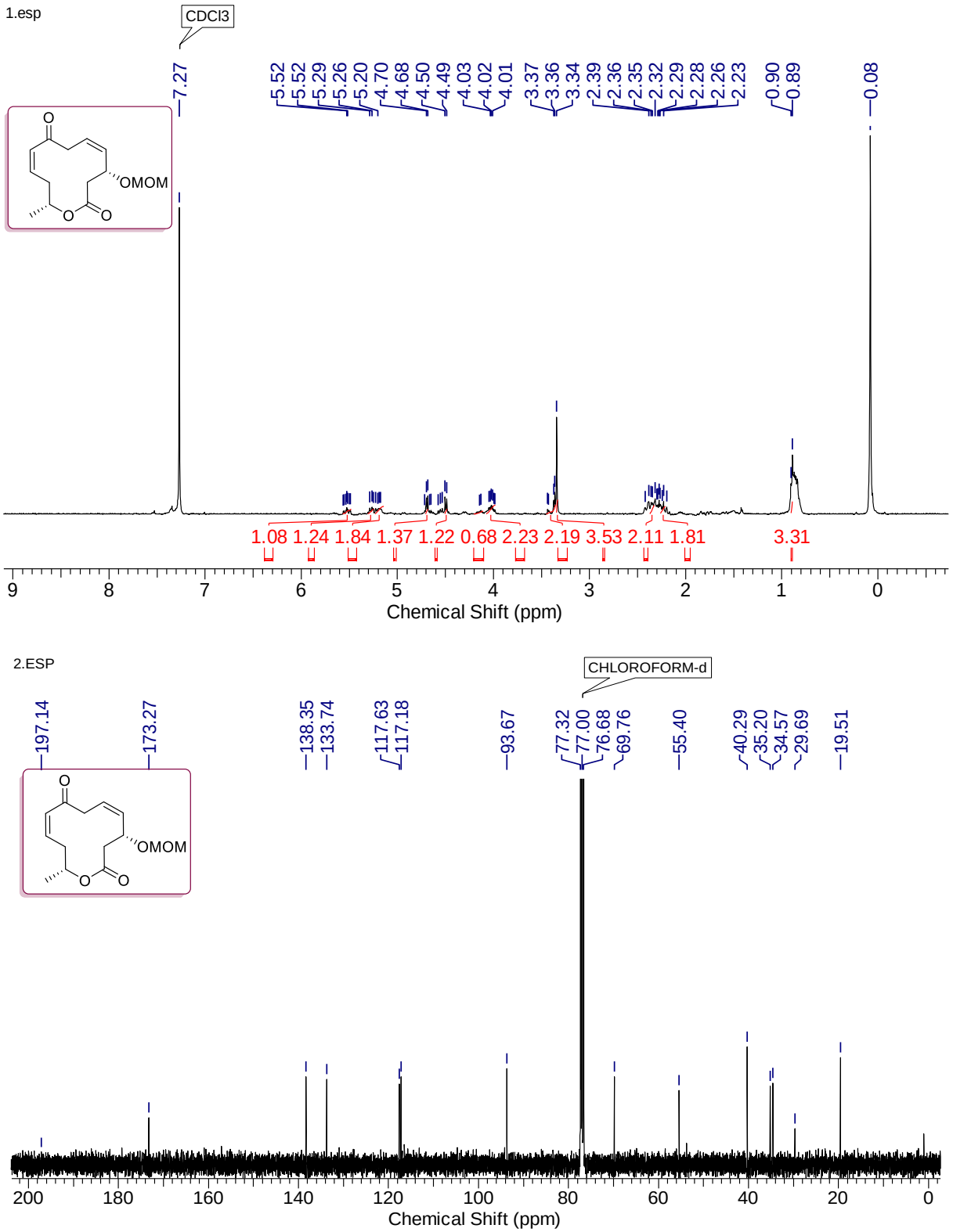


Figure 25: (4R,5E,9E,12R)-4-(methoxymethoxy)-12-methyloxacyclododeca-5,9-diene-2,8-dione (58)

Finally, the homoallylic alcohol was subjected to DMP-mediated oxidation to give ketone 65% yields. The NMR analysis technique confirmed the appearance of the keto group. The peak at δ 193.94 confirms the formation of the ketone group from secondary alcohol, as shown in **Figure 24**. When the both acid and alcohol fragment in hand further they coupled with known steglich esterification to obtained the corresponding crude diolefinic ester 40. further diolefin of ester was treated with Grubbs II generation catalyst to obtained the ring closing product 58 in 70% yield. While deprotection of MOM group to obtained the corresponding target molecule Balticolid **2**[14].

1.2.5 Conclusion

We have accomplished the formal synthesis of Balticolid in 14 steps from commercially available 1,4 butanediol, acetaldehyde, and ethyl acrylate. The proline-catalyzed α – aminoxylation, Brown allylation, and Grubb's metathesis are the key steps of the current synthesis.

1.2.6. Experimental Section

4-((tert-butyldimethylsilyl) oxy) butan-1-ol (44)

To a cooled solution of 1, 4 butane diol **33** (7.0 g, 77.78 mmol) and Imidazole (7.9 g, 116.67 mmol) in anhydrous DCM (70 mL) was then added, a solution of TBSCl (10.5 g, 34.24 mmol) in anhydrous DCM (80 mL). The resultant mixture was stirred at room temperature for 4 h; then, the reaction was quenched with water (50 mL) and extracted with DCM (3 x 60 mL). The combined organic extracts were washed with brine solution (50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography (2% EtOAc /n-hexane) to give the mono-TBS protected 1, 4 butane diol **44** (13 g, 86% yield) as a colorless liquid.

Yield: 86% (13 g); colourless liquid; **^{1}H NMR** (400 MHz, CDCl3): δ 3.56-3.70 (m, 4H), 2.84 (br. s., 1H), 1.57-1.69 (m, 4H), 0.89 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (101 MHz, CDCl3): δ 63.3, 62.6, 30.1, 29.8, 25.8, 25.6, 18.2, -5.5; HRMS (m/z): calculated $[M+H]^+$ for $C_{10}H_{25}O_2Si^+$: 205.1618 found: 205.1630.

(R)-8-((tert-butyldimethylsilyl) oxy) octane-1,2-diol (47)

To a stirred pre-cooled (-20 °C) acetonitrile (100 mL) solution of aldehyde (**45)** prepared from TBS protected 1,4 butane-diol **44** (6.0 g, 29.70 mmol, 1 equiv.) and nitrosobenzene (3.1 g, 23.25 mmol) was added L-proline (594 mg, 20 mol%). The reaction mixture was allowed to stir at the same temperature for 24 h, followed by adding MeOH (60 mL) and $NaBH_4$ (1.6 g, 23.25 mmol) to the reaction mixture, which was stirred for 10 min. After the completion of the reaction (monitored by TLC), the resulting mixture was extracted with EtOAc (3 × 60 mL), and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude aminooxy alcohol, which was directly taken up for the next step without purification. A well-stirred solution of crude aminooxy alcohol in methanol was added 10% $CuSO_4$. $5H_2O$ and the reaction mixture stirred overnight at 25 ^{o}C. After completion of the reaction (monitored by TLC), it was filtered through celite (MeOH eluent) and the solvent evaporated under reduced pressure to afford the crude diol. Purification by column chromatography with petroleum ether/ethyl acetate (5:5 v/v) gave the diol **47** (4.05 g) as a colorless liquid.

Yield: 62%; $[\alpha]_D^{25}$ = -3.4 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1376, 1466, 2872, 2969, 3381 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.73-3.93 (m, 4H), 3.57 (dd, *J* = 7.7, 3.2 Hz, 1H), 3.41-3.52 (m, 1H), 3.38 (br. s., 1H), 1.57-1.75 (m, 2H), 0.86 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): 71.7, 66.6, 61.6, 34.9, 25.8, 18.1, -5.6, -5.6; **HRMS** (m/z): calculated $[M+Na]^+$ for $C_{12}H_{28}NaO_3Si$: 243.1387 found: 243.1380.

(R)-tert-butyldimethyl(2-(oxiran-2-yl) ethoxy) silane (29)

A solution of diol **47** (4.0 g, 18.18 mmol) in CH_2Cl_2 (50 mL) was treated with TsCl (3.8 g, 20 mmol), Bu_2SnO (1.3 g, 30 mol %), Et_3N (4.5 mL, 30 mmol) and DMAP (cat.) at 0 °C. After being stirred for 1 h, the mixture was extracted with CH_2Cl_2 (3 × 100 mL), washed with water, and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude tosylate. A solution of crude tosylate in MeOH (50 mL) was added to K_2CO_3 (3.7 g, 15.93 mmol), and the mixture was stirred at 0 °C for 30 min. After the reaction was complete (monitored by TLC), the solvent was evaporated, and the residue was extracted with diethyl ether (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography using petroleum ether/EtOAc (8:2 v/v) to give epoxide **48** (2.7 g) as a colorless oil.

Yield: 76%; $[\alpha]_D^{25}$ = +5.0 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1102, 1222, 1255, 2930, 2955 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.77 (dd, *J* = 6.6, 5.6 Hz, 2H), 2.97-3.14 (m, 1H), 2.77 (dd, *J* = 5.0, 4.1 Hz, 1H), 2.50 (dd, *J* = 5.1, 2.7 Hz, 1H), 1.61-1.85 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 59.9, 49.9, 47.0, 35.8, 25.8, -5.4; **HRMS** (m/z): calculated [M+Na]+ for $C_{10}H_{23}O_2Si$: 203.1462 found: 203.1458.

(R)-9-((tert-butyldimethylsilyl) oxy) non-1-en-3-ol (49)

To a stirred suspension of trimethylsulfonium iodide (TMSI) (8.1 g, 37.1287 mmol, 3 equiv.) in a dry THF (50 mL) was added *n*-BuLi (2.5 equiv, 30.94 mmol, 38.3 mL of 1.6 M hexane solution) at -40 ^oC. After 30 min, epoxide **48** (2.5 g, 12.37 mmol) in dry THF (30 mL) was added dropwise, and the reaction mixture was slowly warmed to 0 °C and stirred for 2 h. After the reaction (monitored by TLC), the reaction mixture was quenched with water and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over

unhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by column chromatography using petroleum ether/EtOAc (7:3 v/v) to give vinyl alcohol **49** (2.0 g).

Yield: 76% (2.0 g); colourless liquid; $[\alpha]_D^{25}$ = -3.6 (c 0.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 1102, 1222, 1255, 2930, 2955 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.86 (ddd, *J* = 17.0, 10.5, 5.3 Hz, 1 H), 5.19-5.34 (m, 1 H), 4.98-5.17 (m, 1 H), 4.27-4.47 (m, 1H), 3.71-3.93 (m, 2H), 3.40 (br. s., 1 H), 1.55-1.88 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): *δ* 140.6, 114.0, 72.2, 61.8, 38.2, 25.8, -5.6; **HRMS** (m/z): calculated [M+Na]+ for $C_{11}H_{24}NaO_2Si$: 239.1438 found: 239.1440.

(R)-9,9,10,10-tetramethyl-5-vinyl-2,4,8-trioxa-9-silaundecane (50)

To a stirred solution of compound **49** (1.5 g, 6.9 mmol, 1.0 equiv) in dry CH_2Cl_2 (10 mL) was added DIPEA (4 mL, 27.7 mmol, 4.0 equiv) at room temperature and stirred for 15 min. The reaction mixture was cooled to 0 °C and then to this solution added dropwise methoxymethyl chloride (1.03 mL, 7.35 mmol, 2.0 equiv) over 5 min. As a result, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was washed with aqueous saturated $CuSO_4$ (3 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a crude material, which was purified by column chromatography to obtained compound **50** as yellowish liquid.

Yield: 82% (1.4 g); Yellowish liquid; $[\alpha]_D^{25}$ = -1.3(*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3018, 2927, 2854, 1216, 1033, 929 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 5.68 (ddd, *J* = 17.5, 10.1, 7.7 Hz, 1H), 5.12-5.23 (m, 2H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.53 (d, *J* =6.6 Hz, 1H), 4.13-4.24 (m, 1H), 3.64-3.75 (m, 2H), 3.32-3.39 (m, 3H), 1.76-1.87 (m, 1H), 1.70 (dt, *J* = 13.2, 6.6 Hz, 1 H), 0.88

(s, 9 H), 0.04 (s, 6 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 138.3, 117.0, 93.8, 74.2, 59.2, 55.3, 38.6, 25.8, -5.4, -5.4; **HRMS** (m/z): calculated [M+Na]+ for $C_{13}H_{28}NaO_2Si$: 283.1700 found: 283.1714.

(R)-3-(methoxymethoxy)pent-4-en-1-ol (51)

To a stirred solution of **50** (1 gm, 3.84 mmol) in dry THF (20 mL) was added TBAF (10 mg, 1 mol%) dropwise over 5 min. Furtheremore, the reaction mixture was stirred at room temperature for another 3 h. After completion of the reaction (monitored by TLC), H_2O (1 mL) was added, and extraction was done with Ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Column chromatographic purification of the crude product using petroleum ether/EtOAc (8:2 v/v) gave alcohol **51** (507 mg) as a colorless liquid.

Yield: 90%; Colorless liquid; $[\alpha]_D^{25}$ = +1.2 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3441, 2957, 1215, 836, 775 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.64 (ddd, *J* = 17.4, 9.9, 7.8 Hz, 1H), 5.03-5.24 (m, 2H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.47 (d, *J* = 6.6 Hz, 1H), 4.10-4.21 (m, 1H), 3.56-3.74 (m, 2H), 3.31 (s, 3H), 2.90 (br. s., 1H), 1.61-1.82 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 137.5, 117.2, 93.7, 75.5, 60.2, 59.3, 55.3, 37.6, 20.8, 13.9; **HRMS** (m/z): calculated $[M+Na]^+$ for $C_7H_{14}O_3Na$: 169.0835; found, 169.0850.

(R)-3-(methoxymethoxy)pent-4-enoic acid (25)

To a solution of alcohol **51** (450 mg, 3.08 mmol) in CH_3CN/H_2O (4:1) was added (diacetoxyiodo)benzene in one portion (2.3 g, 7.3 mmol), and then TEMPO (70 mg, 0.49 mmol) was added. The reaction mixture was then allowed to stir at 25 ^oC for 4 h. After the reaction (monitored by TLC) was completed, the reaction was quenched by adding Na_2SO_4 (aq.). The organic layer was separated, washed with brine, and subjected to column chromatographic

purification with petroleum ether/EtOAc (7:3 v/v) to afford the carboxylic acid **6** (335 mg) as a colorless gummy liquid.

Yield: 68%; Colorless gummy liquid; $[\alpha]_D^{25}$ -2.3 (*c* 0.55, $CHCl_3$) ; **IR** ($CHCl_3$): υ_{max} 3444, 3070, 2931, 2858, 1707, 1462, 1425, 1257, 1109 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 9.70 (br. s., 1H), 5.74 (ddd, *J* = 17.3, 9.8, 7.7 Hz, 1H), 5.09-5.43 (m, 2 H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.30-4.61 (m, 2H), 3.36 (s, 3H), 2.26-2.83 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 176.5, 136.2, 118.4, 93.7, 73.4, 55.4, 40.7; **HRMS** (m/z): calculated [M+Na]+ for $C_7H_{12}O_4Na$, 183.0628; found, 183.0640.

(R)-tert-butyldimethyl(pent-4-en-2-yloxy)silane (53)

Add a solution of acetaldehyde **52** (6 g, 136.4 mmol) in dry Et_2O (20 ml) to a stirred solution of (allyl)borane (150 mmol) in dry Et_2O (200 mL) at -78 °C. Stir the reaction mixture at -78 °C for 1 h. Add 3 M NaOH (111 mL, 330 mmol) and 30% H_2O_2 (45 mL) to the reaction mixture. Stir the contents at 25 °C for an additional 2 h. Monitor the reaction completion by TLC. Separate the organic layer. Extract the aqueous layer with Et_2O. Wash with brine and dry over anhydrous Na_2SO_4. Remove the solvent. Distill the residue to obtain (R)- (-)-4-penten-2-ol. The crude product was then dissolved in dry DCM and stirred at 0 ^oC. Then Imidazole was added to the solution and stirred for another 5 minutes, and then finally TBSCl was added to the reaction mixture and stirred for another 4 h at room temperature. The reaction was quenched with water (50 mL) and extracted with DCM (3 x 60 mL). The combined organic extracts were washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography (2% EtOAc /n-hexane) to give the (R)-*tert*-butyldimethyl(pent-4-en-2-yloxy) silane (**53**) in 86% yield (4.0. gm) over two steps.

Ethyl (R, E)-5-((tert-butyldimethylsilyl) oxy) hex-2-enoate (43)

Dilute the olefin **53** (4 g, 20.00 mmol) with dry DCM (30 mL) and degas for 15 minutes. Add ethyl acrylate **55** (10 g, 100 mmol, freshly distilled) to the reaction flask, followed by Grubbs' second-generation catalyst (330 mg, 0.20 mmol). Stir the mixture for 20 h under argon at room temperature. Oxidize the mixture by opening the reaction to air and stirring overnight. Concentrate dark brown solution. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (19:1) as eluent to obtain ethyl (R, E)-5-(*tert*-butyldimethylsilyloxy) hex-2-enoate (**43**) (4.0. gm).

Yield: 74%; Light yellow liquid; $[\alpha]_D^{25}$ = -8.90 (c = 1.02 in $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3444, 3070, 2931, 2858, 1707, 1462, 1425, 1257, 1109 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.68 (br. s., 2H), 4.10 (br. s., 2H), 3.84 (d, *J* = 5.6 Hz, 1H), 2.06-2.32 (m, 2H), 1.13 (d, *J* = 5.6 Hz, 4H), 0.88 (br. s., 9H), 0.08 (S, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 131.1, 129.7, 68.4, 63.7, 42.5, 25.8, 25.7, 23.4, 18.1, -4.6, -4.8; **HRMS** (m/z): calculated [M+Na]+ for $C_{12}H_{26}O_2NaSi$, 253.1594; found, 253.1605.

(R, E)-5-((tert-butyldimethylsilyl) oxy) hex-2-en-1-ol (56)

Add i-Bu_2AlH (6.0 mL (33.82 mmol, 2.3 equivalents) dropwise to a solution of ethyl ester (**43**) (4.0 g) in CH_2Cl_2 (420 mL) at -78 °C over 5 minutes. Stir the reaction mixture at -78 °C for 1 hour. Add a saturated aqueous solution of potassium sodium tartrate (60 mL) to the mixture. Stir the mixture vigorously at 23 °C for 3 hours. Separate the organic layer. Extract the aqueous solution with CH_2Cl_2 (3 × 70 mL). Dry the combined organic layers over Na_2SO_4. Concentrate the combined organic layers to dryness under reduced pressure. Purify the crude product by column chromatography on silica gel using pet ether: ethyl acetate (70:30).

Yield: 84%; Light yellow liquid; $[\alpha]_D^{25}$ = -3.2 (c = 0.5 in $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3444, 3070, 2931, 2858, 1707, 1462, 1425, 1257, 1109 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.86-7.00 (m,

1H), 5.83 (dt, *J* = 15.6, 1.4 Hz, 1H), 4.10-4.29 (m, 2H), 3.79-3.97 (m, 1H), 2.31 (dddd, *J* = 7.4, 5.9, 4.4, 1.4 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 4H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (d, *J* = 2.0 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.4, 146.0, 123.2, 67.7, 60.1, 42.4, 25.9, 25.8, 23.8, 18.1, 14.2, -4.6; **HRMS** (m/z): calculated [M+Na]+ for $C_{12}H_{26}O_2NaSi$, 253.1594; found, 253.1605.

(8R,E)-8-((tert-butyldimethylsilyl)oxy)nona-1,5-dien-4-ol

To a solution of alcohol (3 gm, 13.04 mmol, 1 equiv.) in a dry DCM was added one portion (diacetoxyiodo)benzene (4.6 gm, 1.1 equiv.), and TEMPO (203 mg, 10 mol%). The reaction mixture was then allowed to stir at 25 ^oC for 1 h after completion of the reaction (monitored by TLC). The reaction mixture was quenched by adding a saturated solution of $Na_2S_2O_3$. The organic layer was separated, washed, and dried over Na_2SO_4. After evaporation of the solvent, crude was used for further steps without purification. The obtained Crude was dissolved in THF: NH_4Cl (sat) and added Zinc (2.1 gm, 3 equiv. 32.90 mmol). Stir the mixture for 30 minutes at 0°C and add Allyl bromide (2.6 gm, 2 equiv., 21.92) dropwise over 15 minutes. Stir the mixture at room temperature for 4 h. Quench the mixture with sat. NH_4Cl solution and filter through a small pad of celite. Wash the residue with EtOAc (2x20 mL). Dry the combined organic layers over anhydrous Na_2SO_4. Evaporate the solvent under reduced pressure. Purify the residue by silica gel column chromatography (20% EtOAc: Pet. Ether).

Yield: 80%; Light yellow liquid; $[\alpha]_D^{25}$ = -3.1 (c = 0.5 in $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3444, 3070, 2931, 2858, 1707, 1462, 1425, 1257, 1109 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.82 (dd, *J* = 16.7, 7.8 Hz, 1H), 5.61-5.75 (m, 1H), 5.53 (dd, = 15.4, 6.3 Hz, 1H), 5.09-5.20 (m, 2 H), 4.07-4.18 (m, 1H), 3.77-3.90 (m, 1H), 2.25-2.39 (m, 2H), 2.11-2.25 (m, 2H), 1.27 (br. s., 1H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9 H), 0.06 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 134.4, 134.2, 128.8,

128.6, 118.1, 118.0, 71.8, 71.7, 68.4, 68.4, 42.6, 42.5, 41.9, 25.9, 23.4, 18.1, -4.5, -4.7 **HRMS** (m/z): calculated $[M+Na]^+$ for $C_{15}H_{30}O_2NaSi$, 293.1907; found, 293.1900.

(R,E)-8-((tert-butyldimethylsilyl)oxy)nona-1,5-dien-4-one (57)

To a stirred solution of (8R, E)-8-((*tert*-butyldimethylsilyl)oxy)nona-1,5-dien-4-ol (2 gm, 0.17 mmol) in CH_2Cl_2 (10 mL) Dess Martin periodinate (4.7 gm, 11.12) was added at 0 ^oC. The reaction mixture was allowed to stir at room temperature for 1 h and quenched with sat. $NaHCO_3$ solution (30 mL) and extracted with CH_2Cl_2 (2x30 mL). The combined organic layers were washed with water (5 mL) and brine solution (5 mL), dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by CC (10% EtOAc/n-hexane) to afford compound **57** (1.292 gm)

Yield: 65 %; Light yellow liquid; $[\alpha]_D^{25}$ = -3.1 (c = 0.5 in $CHCl_3$); **IR** ($CHCl_3$): υ_{max} 3444, 3070, 2931, 2858, 1707, 1462, 1425, 1257, 1109 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.77 - 7.00 (m, 1 H), 6.08 - 6.17 (m, 1 H), 5.02 - 5.24 (m, 1 H), 3.83 - 4.08 (m, 1 H), 3.32 (d, J=7.0 Hz, 1 H), 2.40 - 2.52 (m, 1 H), 2.24 - 2.39 (m, 1 H), 1.17 (dd, J=11.9, 6.1 Hz, 3 H), 0.87 - 0.88 (m, 9 H), 0.01 - 0.08 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.9, 155.5, 145.0, 134.7, 131.6, 118.6, 67.6, 44.9, 42.7, 42.7, 25.8, 23.8, 18.0, -4.8; **HRMS** (m/z): calculated $[M+Na]^+$ for $C_{15}H_{29}O_2Si$, 269.1931; found, 269.1941.

(4R,5E,9E,12R)-4-(methoxymethoxy)-12-methyloxacyclododeca-5,9-diene-2,8-dione (58)

Bis olefin **40** (50 mg, 0.16 mmol) was dissolved in freshly distilled degassed anhydrous CH_2Cl_2 (50 mL). The reaction mixture was treated with Grubb's catalyst II (48 mg, 20 mol %) and reflux for 12 h under an inert atmosphere. After completion of the reaction (monitored by TLC), the solvent was then distilled off and the residue was purified by column chromatography with petroleum ether/EtOAc (9:1 v/v) to afford **58** (31 mg) as colorless liquid

Yield: 70 %; Colorless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.52 (ddd, J = 15.0, 11.3, 3.3 Hz, 1H), 5.25-5.31 (m, 1H), 5.14-5.23 (m, 2H), 4.69 (d, J = 6.5 Hz, 1H), 4.49 (d, J = 6.5 Hz, 1H), 4.14 (d, J = 6.0 Hz, 1H), 3.98-4.07 (m, 2H), 3.43 (d, J = 3.0 Hz, 2H), 3.35-3.40 (m, 2H), 3.34 (s, 3H), 2.35 (d, J = 4.5 Hz, 2H), 2.21-2.26 (m, 2H), 0.9 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 197.1, 173.27, 138.3, 133.7, 117.63, 117.1, 93.6, 69.7, 40.2, 35.2, 34.5, 29.6, 19.5; **HRMS** (m/z): calculated [M+Na]+ for $C_{14}H_{20}O_5Na$: 291.1208 found: 291.1200.

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Chapter II

Metal Free and Radical Mediated Conjugated Addition of Cyclic Ethers on *para*-Quinone Methides (*p*-QMs) and Quinone Imine Ketals (QIK's)

1. "Metal Free and Radical 1,6-Conjugated Addition of Cyclic Ethers with *para*-Quinone Methides (*p*-QMs)" **More, S. G.;** Suryavanshi, G. *Org. Biomol. Chem*. **2019,**17, 3239–3248.
2. "Oxidative Radical-Mediated Addition of Ethers to Quinone Imine Ketals: An Access to Hemiaminals" **More, S. G.;** Kamble, R. B.; Suryavanshi, G.; *J. Org. Chem.* **2021,** 86, 3, 2107–2116.

2.1.1 Introduction

Carbon-Carbon bond-forming reactions are key steps for constructing complex molecular frameworks in many syntheses of natural products and organic compounds, as well as in various industrial applications,[1] represents a forefront of research in organic chemistry and essential tools for synthetic chemists as well. Therefore, various methods for C-C bond formation are known in the literature under metal[2] and metal-free conditions.[3]. Among these methods, free radical reactions emerged as a powerful tool for constructing C-C bonds, which are efficiently utilized in synthesizing complex molecular frameworks[4] Recently, the addition of carbon-centered cyclic ether radical to an electrophilic carbon acceptor has gained importance due to the abundance of these ethers in biomass.[5] This method is promisingly utilized in synthesizing complex organic molecules *via* the generation of carbon-centred radicals through Single Electron Transfer (SET) mechanism, which results in this method with a high atom economy.[6] Recently, *p*-QMs have been extensively employed in C-C, C-Hetero bond formation *via* nucleophilic addition on *p*-QMs due to its distinct zwitterionic resonance entities, *i.e.* Michael acceptor in conjugate addition reactions.[7]

In addition, the construction of C-N bonds has been a major research topic in organic synthesis. Nitrogen-containing frameworks are the backbone of around 25% of biologically active compounds and synthetic intermediates. Among the compounds containing C-N bonds having hemiaminals, moiety represents the core structure in many biologically active natural products and pharmaceutical agents.

Section I

Metal Free and Radical 1,6-Conjugated Addition of Cyclic Ethers with *para*-Quinone Methides (*p*-QMs)

p-QMs are inherently found in natural products and pharmaceutical ingredients, which possess a broad spectrum of biological activities. These activities include antitumor,[8] anticancer,[9] antimicrobial,[10] antiinflammatory,[11] and antiviral[12](**Figure 1**). Due to the importance of these moieties, it attracts the chemist's attention for their simple and efficient synthesis.

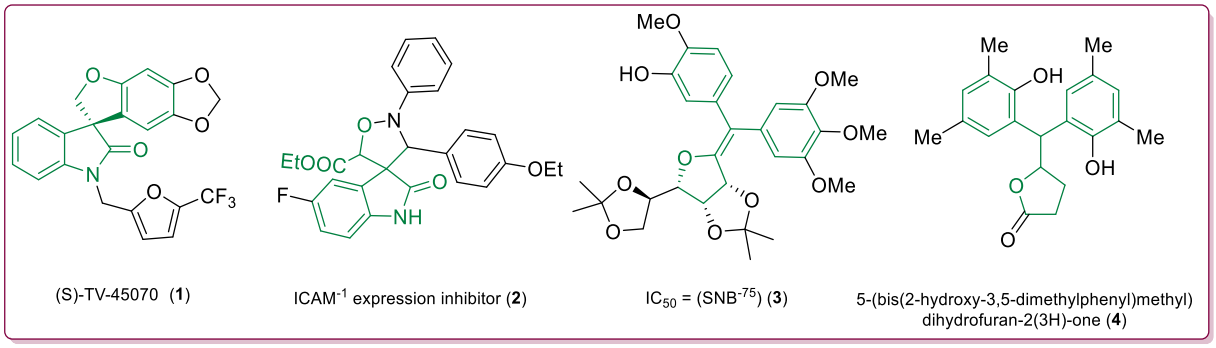


Figure 1. Biologically active 3,3'-oxindole and diarylmethane moiety.

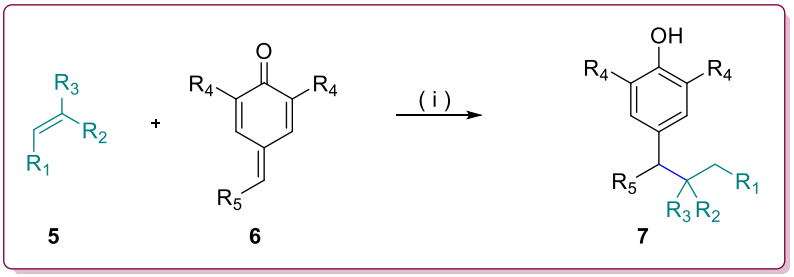
After carefully surveying the literature, numerous metal-catalysed C-C and C-Hetero bond formation reactions of *p*-QMs with different nucleophiles such as C, O, N, S, and P are well known (scheme 1, Eq.1).[13] Though *p*-QMs are reactive intermediate towards nucleophilic addition reaction, and minimal attempts have been made for radical addition reactions.

2.1.2 Review of Literature

In the literature, few methods are known for the radical-mediated conjugate addition on *para*

quinone methide (*p*-QMs).[14,15] Some of the current approaches are described below

Cui's Approach (2016)[14]

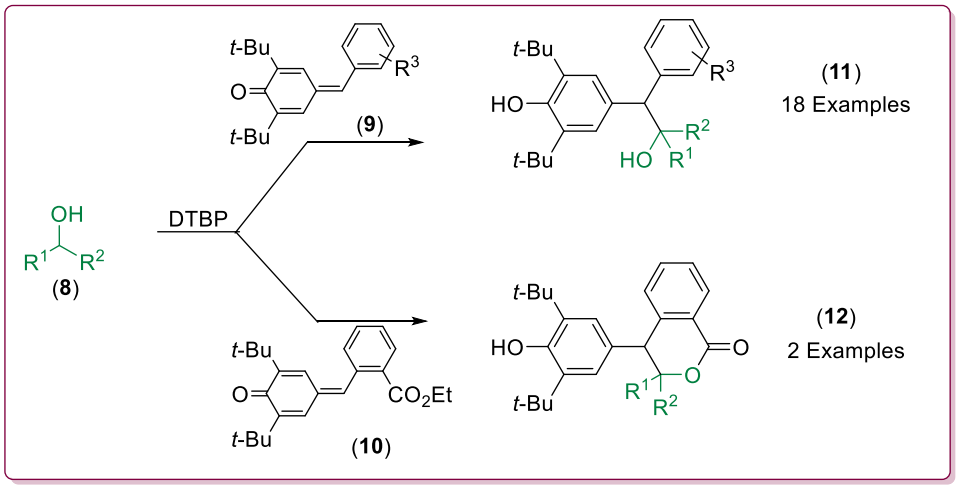


Scheme 1. (i) $Fe(acac)_3$ (30 mol%), $PhSiH_3$, EtOH (2 equiv.), THF, 60 °C, 1 h.

Cui and co-workers 2016, reported a Fe (III) catalyzed hydro alkylation of olefins (**5**) with *para*-quinone methides (*p*-QMs) (**6**) for the synthesis of the diverse range of phenols (**7**). In this report, the author converts different olefins (**5**) to the alkyl radical, which was undergoing conjugate addition with *para*-quinone methide (*p*-QMs) (**6**) in the presence of the catalytic amount of $Fe(acac)_3$ and $PhSiH_3$ in Ethanol as a reductant in THF at 60 °C toward the formation of C-C bond and aromatization of ring. **(Scheme 1).**

Cui's Approach (2018)[15]

The same group in 2018, described metal-free α-alkylation of various 1° and 2° alcohols (**8**) with *para*-quinone methides (*p*-QMs) (**9**) or (**10**) to develop alcohol-containing phenols (**11**) and dihydroisocoumarins (**12**). In this strategy, di-tert-butyl peroxide (DTBP) generated α-oxy alkyl radical of alcohol which reacted with *para*-quinone methides (*p*-QMs) *via* 1, 6 conjugate pathway to establish a new C-C bond. But the method has some limitations like the required high temperature (140 °C), an excess equivalent of oxidant to proceeding the reaction, and limited only to alcohol (**Scheme 2**).

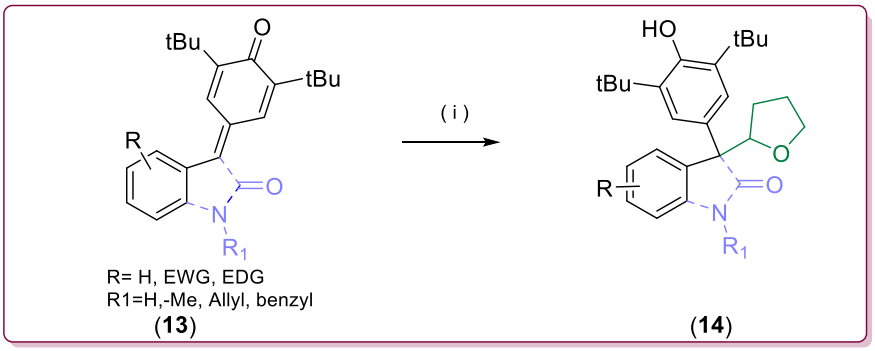


Scheme 2. (i) DTBP (3 equiv.), 140° C, 2 h.

2.1.3 Present Work

2.1.3.1 Objective

p-QMs are the well-known Michel acceptor and are frequently used in synthetic organic chemistry for the develop complex molecule and molecular frameworks. Due to Michel's acceptor ability of *p*-QMs, it is involved in numerous nucleophilic and radical reactions. As part of our interest in developing metal-free and radical reactions,[16] herein, we report a novel 1,6-conjugate radical addition of cyclic ether on p-QMs to establish 3,3 oxindole skeletons.

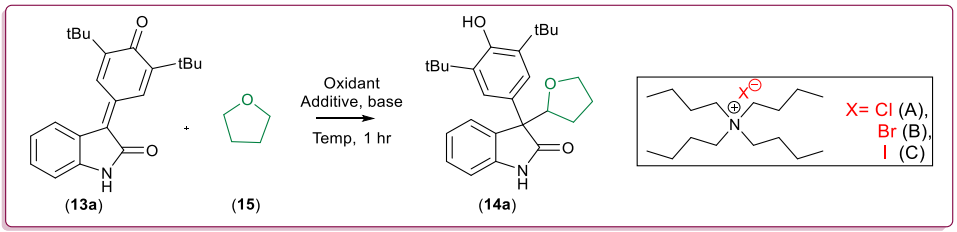


Scheme 3. (i) $K_2S_2O_8$ (3 equiv.), TBACl. H_2O (4 equiv.), NaOAc (3 equiv.), THF, 110 °C, 1 h

2.1.4 Result and Discussion

To investigate our study of a radical addition reaction, we selected *p*-QMs derived from isatin **13a** and cyclic ether (THF) (**15**) as model substrates. We initiated our study by subjecting the addition of ethers to *p*-QMs using oxidant $K_2S_2O_8$ (1 mmol), additive TBACl (1 mmol), and base NaOAc (1 mmol) in THF under air, gratifyingly the desired product **14a** was delivered in 52% yield (Table 1, Entry 1). Next, attempts were made toward yield enhancement by variation in concentration of each reagent at 110 °C, where a slight increase in yield was observed (Entry 2-4). Moreover, variation in additives failed to obtain the desired product **14a** (Entry 5-6). When the reaction was

Table 1. Optimization of Reaction Condition



Sr. No.	Oxidant (Equiv.)	Additive (Equiv.)	Base (Equiv.)	Temp. (°C)	Yield (%)
1	$K_2S_2O_8$(1)	A(1)	NaOAc(1)	110	52
2	$K_2S_2O_8$(2)	A(2)	NaOAc(2)	110	65
3	$K_2S_2O_8$(3)	A(3)	NaOAc(3)	110	72
4	$K_2S_2O_8$(3)	A(4)	NaOAc(2)	110	53
5	$K_2S_2O_8$(3)	B(4)	NaOAc(3)	110	Trace
6	$K_2S_2O_8$(3)	C(4)	NaOAc(3)	110	Trace
7	$K_2S_2O_8$(3)	A(4)	KOAc(3)	110	79
8	$K_2S_2O_8$(3)	A(4)	NH_4OAc(3)	110	30
9	$K_2S_2O_8$(3)	A(4)	NaOAc(3)	110	30
10	$(NH)_4S_2O_8$(3)	A(4)	NaOAc(3)	110	NR
11	$Na_2S_2O_8$(3)	A(4)	NaOAc(3)	110	42

12	$K_2S_2O_8$(3)	A(4)	NaOAc(3)	rt	NR
13	$K_2S_2O_8$(3)	A(4)	NaOAc(3)	90	NR
14	$K_2S_2O_8$(3)	A(4)	NaOAc(3)	140	NR
15 [a]	**$K_2S_2O_8$(3)**	**A(4)**	**NaOAc(3)**	**110**	**85**
16 [b]	$K_2S_2O_8$(3)	A(4)	NaOAc(3)	110	61
17	$K_2S_2O_8$(3)	A(4)	-	110	NR
18	$K_2S_2O_8$(3)	-	NaOAc(3)	110	NR

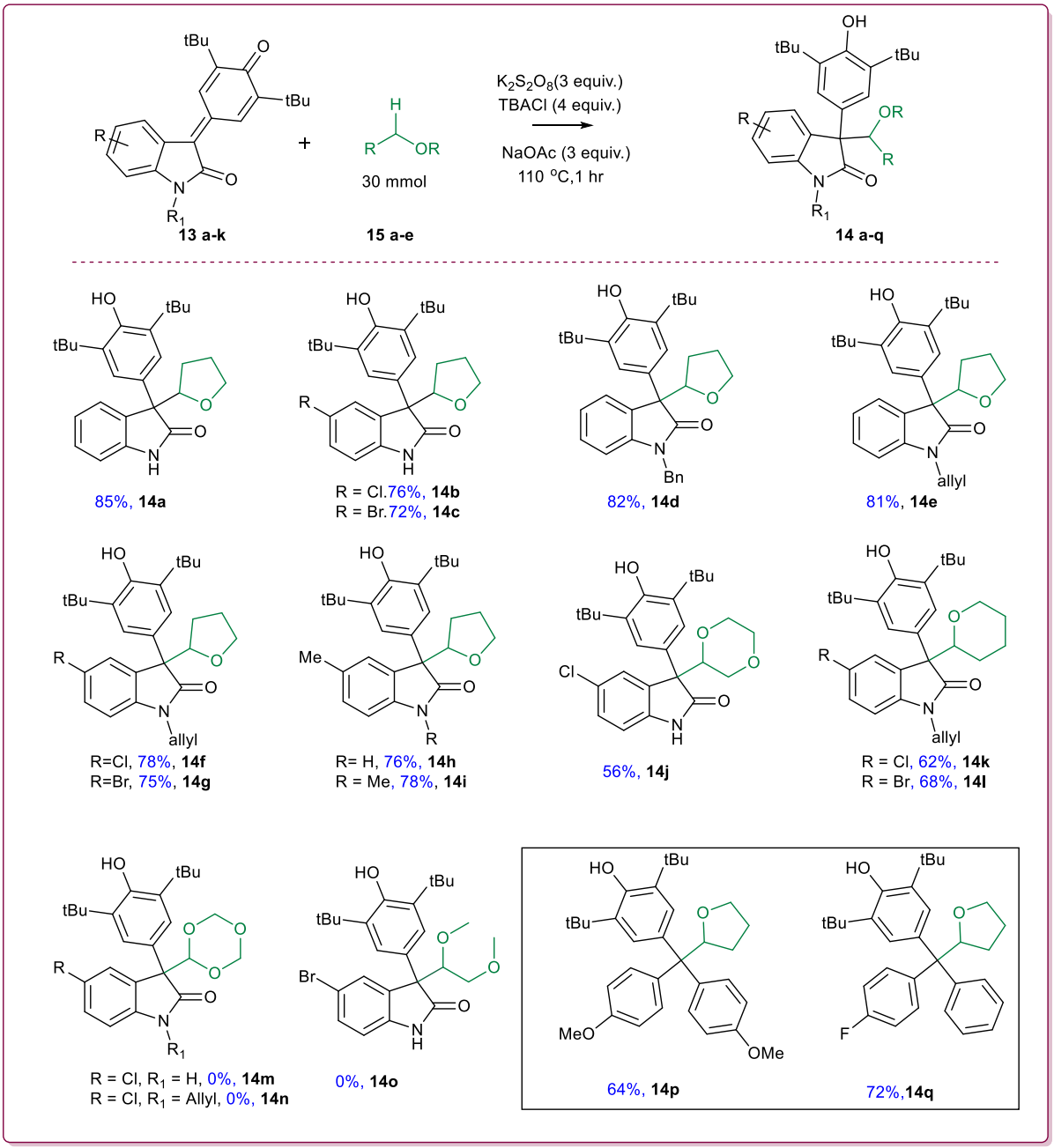
[a] Reaction carried out under N_2; [b] Acetonitrile used as co-solvent, Additive A is 50% in water, NR = No reaction

carried out using 4 equivalent of additive A, it dramatically formed **14a** in 79% yield (Entry 7). Further, changing the oxidant and base did not affect the yield of **14a (**Entry 8-11**).** Also, alteration in reaction temperature failed to give **14a (**Entry 12-14**).** Surprisingly, when reaction was carried out under a nitrogen atmosphere at 110 °C, it achieved the highest yield of product **14a** in **85% (**Entry 15**).** It is noteworthy that the reaction didn't proceed without additive and base **(**Entry 17 & 18**).** With this optimisation study, the best reaction condition for radial addition to *p*-QMs is as per entry 15.

Considering the importance of 3, 3'-oxindole with quaternary stereogenic carbon, we further employed this methodology to various *p*-QMs derived from isatin derivatives. To our delight, wide range of substituted *p*-QMs gives desired 3,3'-oxindole under our standardized reaction condition. *p*-QMs derived from isatin with electron-withdrawing and electron-donating groups such as -Cl, -Br, and -Me substitutions at the 5-position reacted well to give corresponding addition products in excellent yields **(**Table 2, 14b, 14c & 14h**).** There after reaction was performed by protecting isatin with allyl, benzyl and methyl group to attain a-compatible product with good to excellent yields (14d-14g & 14i). Further, the *p*-QMs of isatin were treated with various cyclic ethers such as 1,4 dioxane and tetrahydropyran delivered desired products in good

to excellent yield **(entry 14j-14i).** Unfortunately,1,3,5-trioxane and 1,2-Dimethoxyethane failed to produce corresponding addition products. **(**entries **14m-14o).** Also, high sterically hindered

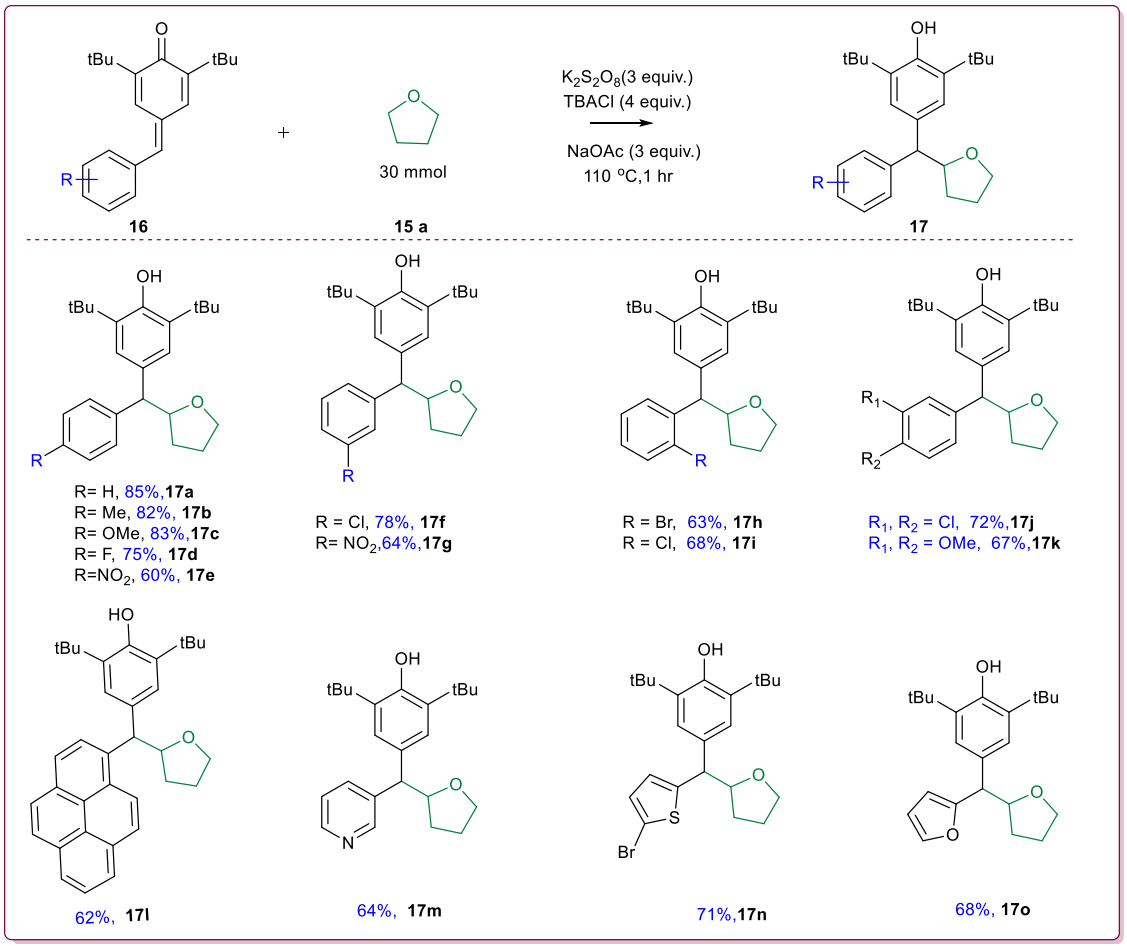
Table 2. Substrate scope of *p*-QMs based Isatin and Fuchsones



[a] **Reaction conditions: 13a-k** (1 mmol), **ethers** (30 mmol), $K_2S_2O_8$ (3 mmol), TBACl (4 mmol), NaOAc (3 mmol), 110 ° C, 1 h, under N_2 atmosphere.

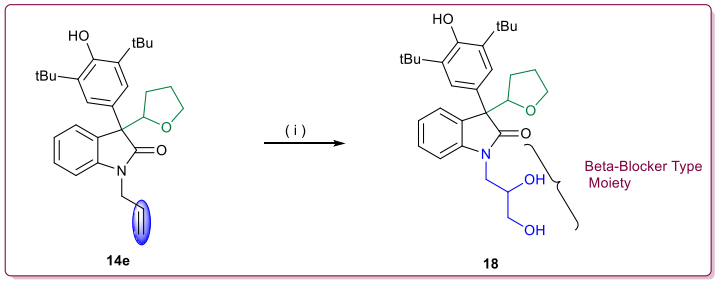
fuchsones were subjected to the desired addition products and were formed smoothly when electron-withdrawing and electro-donating groups were present on fuchsones **(14p & 14q).** The achievement of 1,6-addition of cyclic ether on isatin-based *p*-QMs inspired to do addition of cyclic ether on *p*-QMs for the formation of *α*-alkylated cyclic ether containing diarylmethanes. We further investigated the variety of substrates with electron-withdrawing and electron-donating groups on the aromatic part of *p*-QMs. After careful observation, we conclude that the electron-withdrawing group on *p*-position gave comparatively lower yields to *o*- and *m*-substituent. The electron-donating group such as -OMe, -Me, and unsubstituted aromatic ring delivered additional products in **82 to 85%** yield, respectively **(**Table 3, **17a-17c).** Also, the substrate having electronic withdrawing groups as -Cl, -Br, -F present at *o, m,* and *p*-position gives moderate to good yields **(17d, 17f, 17h & 17i)** of the desired product. Surprisingly, the aromatic ring with -NO_2 group was well tolerated the oxidative reaction conditions afford comparatively lower yields **(17e & 17g).** Moreover, disubstituted *p*-QMs gave the expected product in good yield **(17j-17k).** Also, polycyclic aromatic hydrocarbon, *i.e.*, pyrene-based *p*-QMs, undergo smoothly to give desired product **17l** in 72% yield**.** Further to check the approach's feasibility, we subjected various heterocycle-based *p*-QMs under optimized reaction conditions to get *α*-alkylated cyclic ether. Notably, these heterocyclic systems, such as pyridine, furan, and thiophene, withstand the oxidation conditions to give desired products in good to excellent yield **(17m-17o).** But unfortunately, *p*-QMs of indole failed to give addition product. The utility of this addition reaction, the allyl-protected addition product 6e, was subjected to transformation, as shown in **Table 4.** The **14e** was subjected to dihydroxylation[17] reaction to give the important *β*- blocker type moiety.

Table 3. Substrate Scope of *p*-QMs.



[a] **Reaction conditions: 16** (1 mmol), **THF (5a)** (30 mmol), $K_2S_2O_8$ (3 mmol), TBACl (4 mmol), NaOAc (3 mmol), 110 ° C, 1 h, under N_2 atmosphere.

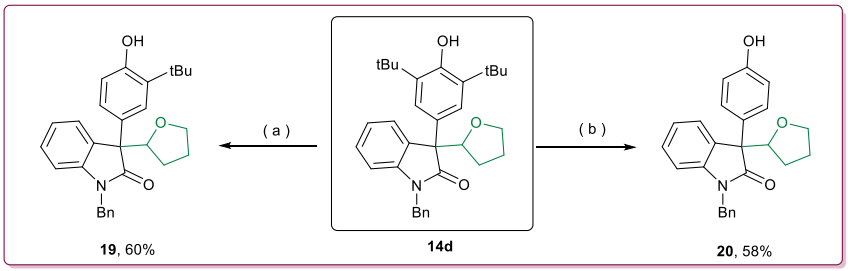
Table 4. Didrohyxylation of terminal olefin of product **(14e)**



Reaction Condition: (i) Olefine (**14e) (**5 mmol**)**, NMO (7.5 mmol), OsO_4 (0.1 mol %), Acetone (2 mL) and water (2 mL), 0 ºC to rt, 2 h.

Also, another transformation of the obtained product is shown in **Table 5.** De-dialkylation of **14d** was carried out by using 6 equiv. of $AlCl_3$ in toluene yields phenol **20** in **58%** whereas, use of 3 equiv. of $AlCl_3$ gives 60% of mono-alkylated product **19.**

Table 5. Mono and Di De-alkylation products



Reaction Condition: (a) **14d (**5 mmol**)**, anhydrous $AlCl_3$ (15 mmol), toluene, N_2 atmosphere, rt, 1 h; (b) **14d (**5 mmol**)**, anhydrous $AlCl_3$ (30 mmol), toluene, N_2 atmosphere, rt, 1 h.

Example 1.

The structure of 3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl) indolin-2-one **14a** was confirmed by ^{1}H NMR spectrum, which showed singlet of 18 hydrogens for the di tert. butyl group of phenol ring at δ 1.31 (s, 18H), triplet hydrogen of α proton of the oxygen atom of ether ring at 4.76 (t, *J* =7.63 Hz, 1H), The singlet of the hydrogen of phenol ring at 5.05 (s, 1 H), The peaks between 6.80- 7.44 corresponding to the aromatic protons 6.81 (d, *J*=7.93 Hz, 1 H), 7.00 (m, 1 H), 7.18 (m, 1 H), 7.30 (s, 2 H), 7.43 (d, *J* =7.32 Hz, 1 H), and the singlet of the hydrogen at 8.54 (m, 1 H) corresponding to free NH of indoli-2-one **(14a).** Also, confirmed the related product from the ^{13}C NMR spectrum, which shows δ 69.10 of quaternary carbon of oxindoline moiety and δ 179.35 due to the presence of the amide group of indoli-2-one is the characteristic carbon of compound **14a** (**Figure 2**).

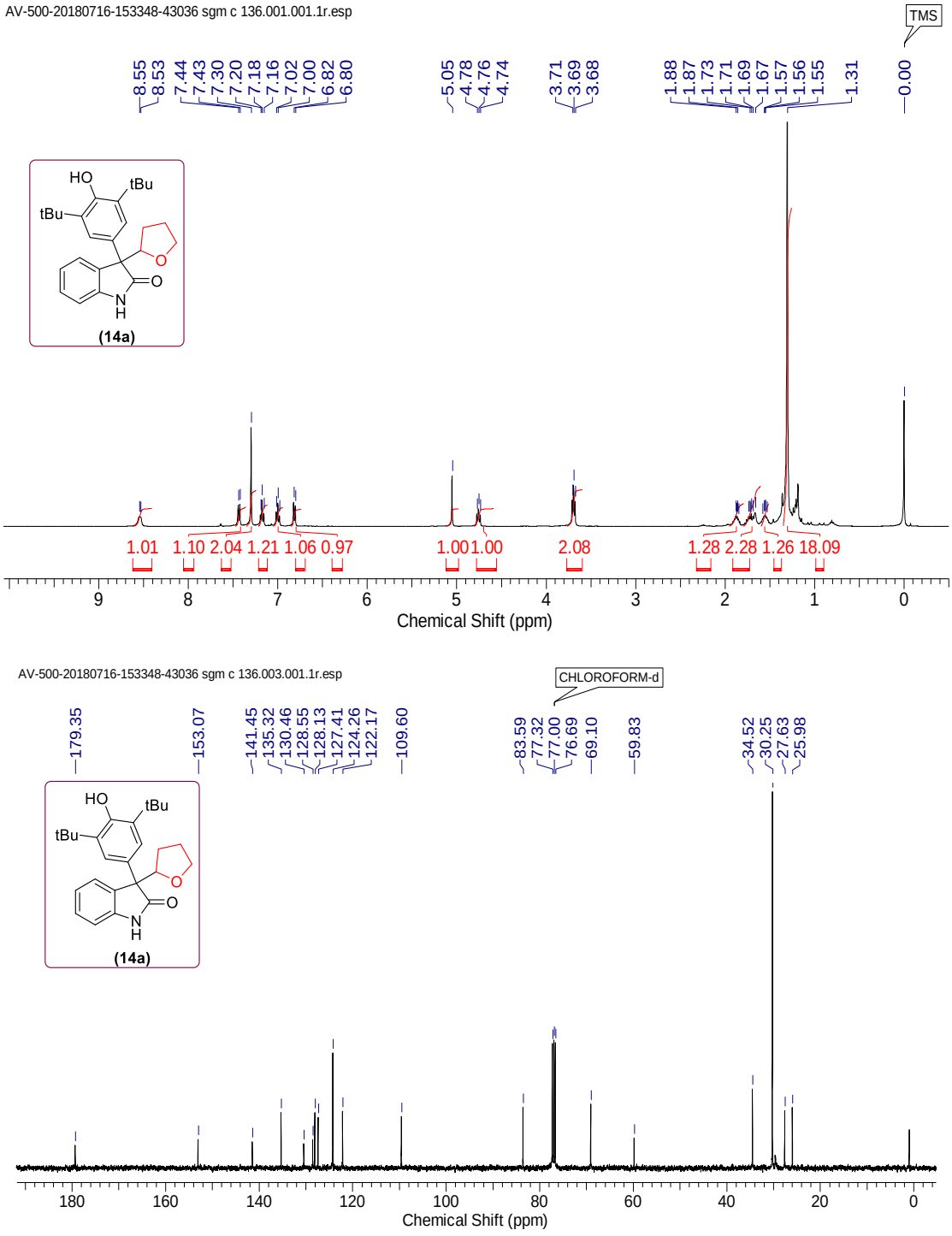
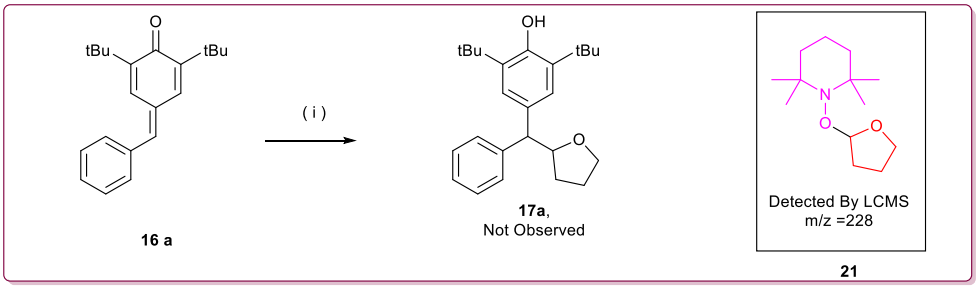


Figure 2. ^{1}H and ^{13}C of 3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl) indolin-2-one (**14a**)

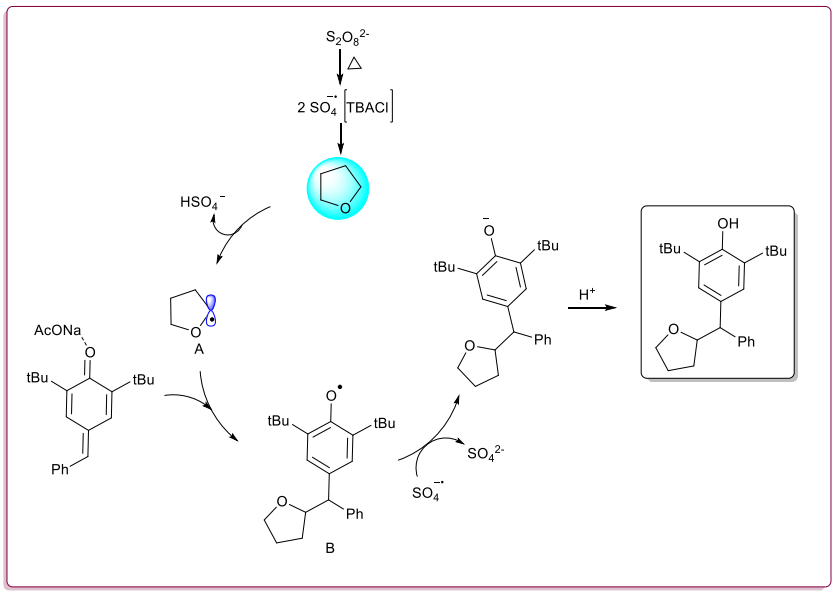
To get an insight into the reaction mechanism, we performed the control experiment using 2 equiv. of TEMPO as a radical scavenger.[18] instead of desired compound **17a.** From the control experiment, it was concluded that the reaction proceeds *via* radical pathway.

Table 4. Control Experiment



[a] **Reaction conditions:** **7** (1 mmol), **THF** (30 mmol), K_2S2O_8 (3 mmol), TBACl (4 mmol), NaOAc (3 mmol), TEMPO (2 mmol), 110 ° C, 1 hr, under N_2 atmosphere.

Based on the control experiment and literature review, [19] we propose the plausible reaction mechanism for the addition reaction. Initially, α-oxyalkyl radical **A** generated via abstracting the



Scheme 4: Plausible Reaction Mechanism

proton from THF by sulfate anion radical, which was developed from the thermal decomposition of persulphate and stabilized by TBACl.[20] Then, the formed α-oxyalkyl radical A undergoes C-C bond formation with O-Chelated *p*-QM, which affords adduct **B.**[21] Furthermore, adduct **B** forms oxyanion by taking radical from sulfate radical anion and undergoes protonation to yield desired product **8a** as shown in **Scheme 4.**

2.1.5. Conclusion

We have developed an efficient, metal-free, radical C-C bond formation reaction of cyclic ether with *p*-QMs to afford the diarylmethane containing functionalized phenol with cyclic ether in excellent yield and high atom economy. We have elaborated our hypothesis on *p*-QMs derived from isatin to establish 3,3'-disubstituted oxindole with quaternary stereogenic carbon. Successfully utilized the formed products in various transformations such as dihydroxylation and dealkyaltion reactions.

2.1.6. Experimental Section

2.1.6.1. General experimental procedure for 3,3 substituted oxindole (14a-14q)

Substituted Isatin based *p*-QMs (**13 a-g**) (0.1 mmol) in THF (3 mL). Were $K_2S_2O_8$ (0.3 mmol), Sodium acetate (0.3 mmol) and TBACl.H_2O (0.4 mmol) added. Then the reaction mixture was refluxed at 110°C under a nitrogen atmosphere for 1 h. After the completion of the reaction (TLC analysis), the reaction mixture was cooled to room temperature and concentrated in a vaccume. The formed residue was extracted with ethyl acetate (3×3ml) and washed with brine (20 ml). Then combined organics dried over anhydrous Na_2SO_4, filtered, and evaporated in vacume. The crude product was purified on flash chromatography (silica gel 100-200 mesh)

using Pet. Ether/Ethyl acetate (v/v, 8:2) as an eluent to afford the 3,3'-substituted oxindole derivatives (**14 a-o**) in high purity.

2.1.6.2. General procedure for the synthesis substituted triaryl methyl ether

To a 25 ml round bottom flask containing fuchsones (**13 p-q**) (0.1 mmol) in THF (3 mL). Were $K_2S_2O_8$ (0.3 mmol), Sodium acetate (0.3 mmol) and TBACl.H_2O (0.4 mmol) added. Then the reaction mixture was refluxed at 110 °C under a nitrogen atmosphere for 1 h. After completion of the reaction (TLC analysis), the resulting mixture is cooled to room temperature and concentrated in a vacuum. The formed residue extracted with ethyl acetate (3×3ml) and washed with brine (20 ml). The combined organic dried over anhydrous Na_2SO_4, filter, and evaporated in vacuum. The crude product was purified on flash chromatography (silica gel 100-200 mesh), Pet. Ether/Ethyl acetate (v/v, 98/2) to give substituted triaryl methyl ethers (**14 p-q**) with high purity.

2.1.6.3. General procedure for the synthesis of substituted diaryl methyl ether

To a 25 ml round bottom flask containing *p*-QMs (**16a-o**) (0.1 mmol) in THF (3 mL) Were $K_2S_2O_8$ (0.3 mmol), Sodium acetate (0.3 mmol) and TBACl.H_2O (0.4 mmol) added. Then the reaction mixture was refluxed at 110°C under a nitrogen atmosphere for 1 h. After completion of the reaction (TLC Analysis), was completed the resulting mixture cooled to room temperature and concentrated in a vacuum. The formed residue was extracted with ethyl acetate (3×3ml) and washed with brine (20 ml). The combined organic phase was dried over anhydrous Na_2SO_4 filters and evaporated in a vacuum. The crude product was purified on flash chromatography (silica gel 100-200 mesh) Pet. Ether/Ethyl acetate (v/v, 98/2) to give diaryl methyl ether (**17 a-o**) with high purity.

2.1.6.4. General procedure for dihydroxylation of alkene (18)

To the solution of olefin (**14e**) (5mmol) in acetone (2ml) and water (2ml) at 25^{o}C, added NMO (7.5mmol) and OsO_4 (0.1 mol %) and stirred the reaction mixture for 2 hr at rt. The reaction mixture was then quenched by sat. aq. $Na_2S_2O_4$ and the biphasic reaction mixture were stirred at 25^{o}C for another 30 min. and extracted with EtOAc. The combined organic layer was awash with brine dried over Na_2SO_4 and concentrated under reduced pressure purified by silica gel column chromatography to afford desired product **18**.

2.1.6.5. General procedure for mono dealkylation (19)

In a 50 mL dry round, bottom flask containing anhydrous $AlCl_3$ in dry toluene under a nitrogen atmosphere and stirred at rt, compound **14d** in toluene was added and stirred for another 1 hr. After completion of the reaction monitor by TLC, the reaction was quenched with ice-cold water. Then the reaction mixture was extracted with EtOAc (3×15 mL) and combined layer dried over anhydrous Na_2SO_4, followed by concentration under reduced pressure to give crude product. The crude product was further purified by flash chromatography to afford desired product **19** in 60% yield.

2.1.6.6. General procedure for di dealkylation (20)

In 50 mL dry round bottom flask containing anhydrous $AlCl_3$ (6 equiv.) in dry toluene under a nitrogen atmosphere and stirred at rt, compound **14d** (50 mg) in toluene was added and stirred for another 1 hr. After completion of the reaction monitor by TLC, the reaction was quenched with ice-cold water. Then the reaction mixture was extracted with EtOAc (3×15 mL) and combined layer dried over anhydrous Na_2SO_4 and followed by concentration under reduced pressure to give crude product. The crude product was further purified by flash chromatography to afford the desired product of **20** in 58% yield.

3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl) indolin-2-one (14a).

Yield: 85% (103 mg); Yellow gummy oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.54 (m, 1H), 7.43 (d, *J* = 7.32 Hz, 1H), 7.30 (s, 2H), 7.18 (m, 1H), 7.00 (m, 1H), 6.81 (d, *J* = 7.93 Hz, 1H), 5.05 (s, 1H), 4.76 (t, *J* = 7.63 Hz, 1H), 3.69 (t, *J* = 6.41 Hz, 2H), 1.87 (dd, *J* = 7.32, 4.88 Hz, 1H), 1.71 (m, 2H), 1.56 (m, 1H), 1.31 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 179.3, 153.1, 141.4, 135.3, 130.5, 128.5, 128.1, 127.4, 124.3, 122.2, 109.6, 83.6, 69.1, 59.8, 34.5, 30.2, 27.6, 26.0; **HRMS** (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{26}H_{33}O_3NNa$, 430.2353; found, 430.2346.

5-chloro-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-((R)-tetrahydrofuran-2-yl) indolin-2-one (14b).

Yield: 76% (90 mg); Yellow gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.67 (br. s., 1H), 7.41 (br. s., 1H), 7.25 (s, 2H), 7.14-7.19 (m, 1H), 6.75 (d, *J* = 8.01 Hz, 1H), 5.09 (s, 1H), 4.72 (t, *J* = 7.44 Hz, 1H), 3.72 (t, *J* = 6.29 Hz, 2H), 1.84-1.92 (m, 1H), 1.71-1.80 (m, 1H), 1.61 (br. s. 1H), 1.31 (s, 18H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 179.1, 153.2, 139.9, 135.5, 132.6 , 128.1, 128.0, 127.7, 127.5, 124.1, 110.5, 83.2, 69.2, 60.1, 34.5, 30.2, 27.6, 25.9; **HRMS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{33}O_3NCl$, 442.2143; found, 442.2138.

5-bromo-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl) indolin-2-one (14c).

Yield: 72% (84 mg); Yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.40 (d, *J* = 2.02 Hz, 1H), 7.01-7.32 (m, 2H), 6.75 (d, *J* = 8.34 Hz, 1H), 5.10 (s, 1H), 4.72 (dd, *J* = 8.53, 6.25 Hz, 2H), 3.47-3.80 (m, 1H), 1.45 1.98 (m, 3H), 1.31 (s, 18H); **^{13}C{^{1}H} NMR** (50 MHz, $CDCl_3$) δ 179.1, 153.2, 140.4, 135.5, 132.9, 131.0, 130.3, 128.0, 124.1, 115.0, 111.0, 83.2, 69.2, 60.1, 34.5, 30.2, 27.6, 25.9; **HRMS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{33}O_3NBr$, 486.1638,; found, 486.1634.

1-benzyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl) indolin-2-one (14d).

Yield: 82% (95 mg); Red gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.36-7.48 (m, 1H), 7.11-7.36 (m, 8H), 6.94-7.10 (m, 1H), 6.70 (d, J = 7.71 Hz, 1H), 5.15 (s, 1H), 4.82-5.08 (m, 3H), 3.62-3.76 (m, 1H), 3.41-3.57 (m, 1H), 2.05 (q, J = 7.28 Hz, 2H), 1.69-1.84 (m, 2H), 1.33-1.44 (m, 18H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 153.0, 178.0, 143.7, 136.0, 135.4, 130.5, 128.6, 128.0, 127.2, 127.0, 125.9, 124.5, 121.7, 109.1, 83.6, 68.7, 59.6, 43.7, 34.5, 30.3, 27.6, 26.0; **HRMS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{33}H_{40}O_3N$, 498.3003; found, 498.2999.

1-allyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl) indolin-2-one (14e).

Yield: 81% (96 mg); Red gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 (d, J = 6.87 Hz, 1H), 7.33-7.39 (m, 2H), 7.30-7.33 (m, 1H), 7.27-7.30 (m, 1H), 7.01-7.14 (m, 1H), 6.78-6.90 (m, 1H), 5.74-5.96 (m, 1H), 5.21-5.29 (m, 1H), 5.16-5.21 (m, 1H), 5.15 (s, 1H), 4.86 (t, J = 7.63 Hz, 1H), 4.33-4.46 (m, 2H), 3.67 (td, J = 7.63, 5.72 Hz, 1H), 3.44-3.52 (m, 1H), 2.00-2.08 (m, 2H), 1.78-1.85 (m, 1H), 1.73 (dd, J = 12.78, 6.29 Hz, 1H), 1.41 (s, 18H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 177.6, 152.9, 143.8, 135.4, 131.3, 130.3, 128.0, 127.9, 126.0, 124.4, 121.6, 116.9, 109.0, 83.7, 68.8, 59.5, 42.2, 34.5, 30.3, 27.6, 25.9; **HRMS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{38}O_3N$, 448.2846; found, 448.2841.

1-allyl-5-chloro-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl) indolin-2-one(14f).

Yield: 78% (91 mg); Brownish red gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.09-7.25 (m, 3H), 6.57-6.77 (m, 1H), 5.14-5.24 (m, 1H), 4.97-5.13 (m, 2H), 4.59-4.78 (m, 1H), 4.18-4.31 (m, 1H), 3.55-3.73 (m, 1H), 3.34-3.53 (m, 1H), 1.81-2.20 (m, 1H), 1.59 -1.76 (m, 1H), 1.23-1.37 (m, 18H); **^{13}C{^{1}H} NMR** (50 MHz, $CDCl_3$) δ 176.3, 153.2, 141.9, 135.5, 132.3, 131.1, 128.4, 127.9,

127.7, 127.1, 124.0, 117.6, 109.6, 83.4, 77.6 , 76.4, 69.1 , 59.4 , 42.3, 34.5, 30.2, 27.6, 25.9; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{29}H_{36}O_3NClNa$, 504.2276; found, 504.2260.

1-allyl-5-bromo-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl) indolin-2-one (14g).

Yield: 75% (86 mg); Brownish red gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 1.91 Hz, 1H); 7.33 (dd, *J* = 8.20, 2.10 Hz, 1H), 7.23 (s, 2H), 6.66 (d, *J* = 8.01 Hz, 1H), 5.72 (ddt, *J* = 17.36, 10.20, 5.10, 5.10 Hz, 1H), 5.13 (m, 2H), 5.07 (s, 1H), 4.73 (dd, *J* = 8.58, 6.29 Hz, 1H), 4.30 (m, 1H), 4.18 (m, 1H), 3.70 (m, 2H), 1.83 (m, 1H), 1.75 (m, 1H), 1.63 (m, 1H), 1.54 (m, 1H), 1.32 (s, 18H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 176.2, 153.2, 142.4, 135.6, 132.7, 131.1, 130.8, 129.9, 128.4, 124.1, 117.6, 115.1, 110.1, 83.5, 69.1, 59.4, 42.3, 34.5, 30.2, 27.6, 26.0; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{37}O_3NBr$, 526.1951; found, 526.1951.

3-(3,5-di-tert-butyl-4-hydroxyphenyl)-5-methyl-3-(tetrahydrofuran-2-yl) indolin-2-one (14h).

Yield: 76% (91 mg); Brownish gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.38 (s, 1H); 7.34 (s, 2H), 7.22 (s, 1H), 7.05 (d, *J* = 7.83 Hz, 1H), 6.81 (d, *J* = 7.83 Hz, 1H), 5.15 (s, 1H), 4.82 (t, *J* = 7.33 Hz, 1H), 3.64-3.78 (m, 1H), 3.45-3.64 (m, 1H), 2.36 (s, 3H), 1.91-2.08 (m, 2H), 1.65-1.84 (m, 3H), 1.40 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 179.9, 152.9, 139.2, 135.3, 130.9, 128.3, 127.8, 127.0, 124.5, 109.6, 83.5 , 68.9, 59.9, 34.5, 30.2, 27.5, 25.9, 21.3; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{27}H_{36}O_3N$, 422.2690; found, 422.2688.

3-(3,5-di-tert-butyl-4-hydroxyphenyl)-1,5-dimethyl-3-(tetrahydrofuran-2-yl) indolin-2-one (14i).

Yield: 78% (93 mg); Red gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.38 (s, 2H), 7.30 (s, 1H), 7.13 (d, *J* = 7.83 Hz, 1H), 6.76 (d, *J* = 7.94 Hz, 1H), 5.13 (s, 1H), 4.78 (t, *J* = 7.44 Hz, 1H),

3.62-3.75 (m, 1H), 3.43-3.60 (m, 1H), 3.21 (s, 3H), 2.39 (s, 3H), 1.90-2.03 (m, 2H), 1.65-1.83 (m, 3H), 1.40 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$) δ 177.7, 152.9, 142.3, 135.2, 130.9, 130.1, 128.3, 127.7, 127.0, 124.5, 107.8, 83.8, 68.9, 59.4, 34.5, 30.3, 27.6, 26.4, 25.9, 21.3; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{38}O_3N$, 436.2846; found, 436.2842.

5-chloro-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(1,4-dioxan-2-yl) indolin-2-one (14j)

Yield: 56% (46 mg); Yellow gummy oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22-7.39 (m, 4H), 6.82-6.92 (m, 1H), 4.74-4.92 (m, 1H), 4.47-4.58 (m, 1H), 3.76 (d, *J* = 8.54 Hz, 2H), 3.65-3.67 (m, 2H), 3.54 (d, *J* = 7.93 Hz, 2H), 1.35 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$) δ 178.6, 152.5, 1439, 128.9, 128.5, 127.4, 126.7, 125.9, 111.0, 99.8, 68.6, 67.6, 66.9, 66.3, 65.8, 36.5, 32.6; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{32}ClNO_4$, 458.2093; found, 458.2082.

1-allyl-5-bromo-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(tetrahydro-2H-pyran-2-yl) indolin-2-one (14k)

Yield: 62% (79 mg); Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.29 Hz, 1H), 7.38-7.46 (m, 1H), 7.24 (d, *J* = 9.62 Hz, 2H), 6.70 (d, *J* = 8.24 Hz, 1H), 5.68-5.83 (m, 1H), 5.10-5.21 (m, 2H), 4.38-4.50 (m, 1H), 4.19-4.31 (m, 1H), 4.12-4.19 (m, 1H), 3.89-4.03 (m, 1H), 3.83 (br. s., 1H), 1.54-1.58 (m, 2H), 1.47-1.52 (m, 3H), 1.45 (d, *J* = 3.21 Hz, 2H), 1.30-1.39 (m, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$) δ 177.6, 153.1, 143.1, 135.6, 131.8, 130.7, 129.8, 126.2, 124.2, 114.1, 110.4, 80.4, 60.6, 42.2, 34.5, 30.2, 27.3, 25.7, 14.1; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{30}H_{38}BrNO_3$, 542.1724; found, 540.2075.

1-allyl-5-chloro-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(tetrahydro-2H-pyran-2-yl) indolin-2-one (14l)

Yield: 64% (68 mg); Brown gummy oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 2.29 Hz, 1H), 7.21-7.28 (m, 3H), 6.73 (d, *J* = 8.70 Hz, 1H), 5.72-5.82 (m, 1H), 5.10-5.22 (m, 3H), 4.38-

4.49 (m, 1H), 4.24 (dd, *J* = 9.62, 2.75 Hz, 1H), 4.07-4.14 (m, 2H), 3.89-4.05 (m, 2H), 3.82 (br. s., 1H), 1.53-1.58 (m, 3H), 1.49 (dd, *J* = 4.58, 2.75 Hz, 2H), 1.43-1.47 (m, 3H), 1.37 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$) δ 177.7, 153.1, 142.6, 135.6, 131.4, 127.0, 127.0, 126.8, 126.3, 124.2, 124.1, 109.8, 80.4, 60.6, 34.5, 31.6, 30.2, 30.2, 27.3, 25.7, 23.9, 23.3; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{30}H_{38}ClNO_3$, 496.2249; found, 496.2609.

4-(bis(4-methoxyphenyl) (tetrahydrofuran-2-yl) methyl)-2,6-di-tert-butylphenol (14p).

Yield: 64% (64 mg); Yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.15-7.27 (m, 5H), 7.02 (s, 1H), 6.78-6.80 (m, 2H), 6.73-6.77 (m, 2H), 5.32 (dd, *J* = 7.71, 5.94 Hz, 1H), 5.06 (s, 1H), 3.78 (d, *J* = 2.40 Hz, 6H), 3.54-3.72 (m, 2H), 1.94-2.28 (m, 1H), 1.61-1.79 (m, 3H), 1.33 (s, 18H), **$^{13}C\{^{1}H\}$ NMR** (126 MHz, $CDCl_3$) δ 157.4, 157, 151.6, 134.1, 131.3, 130.6, 127.1, 112.7, 112.5, 83.2, 68.3, 59.8, 55.1, 55.1, 34.4, 30.4, 29.4, 26.0; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{43}O_4$, 503.2158; found, 503.2153.

2,6-ditertbutyl4((4fluorophenyl) (phenyl)(tetrahydrofuran-2-yl) methyl) phenol (14q).

Yield: 72% (85 mg); Yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.19 - 7.42 (m, 7 H), 6.78 - 7.08 (m, 4 H), 5.20 - 5.53 (m, 1 H), 4.85 - 5.15 (m, 1 H), 3.33 - 3.71 (m, 2 H), 2.11 - 2.25 (m, 1 H), 1.53 - 1.82 (m, 4 H), 1.33 (d, *J* = 1.14 Hz, 18 H); **$^{13}C\{^{1}H\}$ NMR** (126 MHz, $CDCl_3$) δ 162.1, 159.6, 151.9, 134.3, 131.9, 131.3, 130.3, 129.5, 127.6, 127.3, 127.0, 125.8, 114.0, 113.8, 83.0, 68.4, 60.6, 30.4, 29.4, 26.0; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{31}H_{38}O_2F$, 461.2850; found, 461.2848.

2,6-di-tert-butyl-4-(phenyl(tetrahydrofuran-2-yl) methyl) phenol (17a).

Yield: 85% (105 mg); Yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.14-7.35 (m, 5H); 7.08 (s, 1H), 6.97 (s, 1H), 4.95 (d, *J* = 2.65 Hz, 1H), 4.47 (dd, *J* = 5.87, 2.08 Hz, 1H), 3.65-3.84 (m, 3H), 1.60-1.85 (m, 4H), 1.33 (d, *J* = 2.15 Hz, 18H); **$^{13}C\{^{1}H\}$ NMR** (50 MHz, $CDCl_3$) δ

152.1, 143.4, 135.5 , 135.2, 133.5, 133.0, 128.4, 128.3, 128.2, 126.0, 125.0 , 124.7, 81.9, 81.7, 68.3, 57.1, 56.9, 34.3, 31.0, 30.9, 30.3, 25.7; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{35}O_2$, 367.2632; found, 367.2629.

2,6-di-tert-butyl-4-((tetrahydrofuran-2-yl) (p-tolyl) methyl) phenol (17b).

Yield: 82% (82 mg); Yellow gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20-7.28 (m, 1 H), 7.1-7.20 (m, 2H), 7.00-7.12 (m, 3H), 4.99 (d, *J* = 7.25 Hz, 1 H), 4.4-4.59 (m, 1H), 3.82-3.88 (m, 1H), 3.72-3.79 (m, 2H), 2.21-2.33 (m, 3H), 1.71-1.91 (m, 3H), 1.49-1.54 (m, 1H), 1.40 (d, *J* = 4.58 Hz, 18H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 152.1, 140.8 , 140.5, 135.5, 135.4, 135.2, 133.7, 133.3, 129.0, 128.2, 124.9, 124.7, 82.1, 81.9, 68.3, 56.8, 56.6, 34.3, 34.3, 31.0, 30.9, 30.4, 25.7, 25.7, 21.0, 21.0; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{37}O_2$, 381.2788; found, 381.2784.

2,6-di-tert-butyl-4-((4-methoxyphenyl) (tetrahydrofu-ran-2-yl) methyl) phenol (17c).

Yield: 83% (83 mg); Yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.13-7.28 (m, 2H), 7.05-7.12 (m, 2H), 6.72-6.83 (m, 2H), 4.90-5.02 (m, 1H), 5.81 Hz, 1H), 4.46 (dd, *J* = 7.96, 3.83-3.93 (m, 1H), 3.73-3.79 (m, 5H), 1.61-1.94 (m, 4H), 1.40 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 157.9, 152.1, 136.0, 135.1, 133.4, 129.4, 129.3, 125.0, 113.9, 113.7, 81.9 , 68.2, 56.0, 55.0, 34.4, 30.9, 30.5, 25.8; **HRMS** (ESI) *m/z*: $[M+ Na]^+$ calcd for $C_{26}H_{36}O_3Na$, 419.2557; found, 419.2549.

2,6-di-tert-butyl-4-((4-fluorophenyl) (tetrahydrofu-ran-2-yl) methyl) phenol (17d).

Yield: 75% (92 mg); Reddish gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 8.24, 5.80 Hz, 1H), 7.16 (dd, *J* = 8.24, 5.80 Hz, 1H), 7.04 (s, 1H), 6.93 (s, 1H), 6.87 (q, *J* = 8.54 Hz, 2H), 4.97 (d, *J* = 4.88 Hz, 1H), 4.29-4.51 (m, 1H), 3.66-3.80 (m, 3H), 1.54-1.84 (m, 4H), 1.32 (d, *J* = 4.27 Hz, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 160.1, 152.2, 139.5, 135.3, 132.7, 129.8,

129. 7, 125.0, 124.7, 115.0, 114.8, 81.7, 68.3, 55.9, 34.3, 31.0, 30.7, 30.3, 25.7; **HRMS** (ESI) *m/z*: [M+ Na] $^{+}$ calcd for $C_{25}H_{33}O_2FNa$, 407.2357; found, 407.2353.

2,6-di-tert-butyl-4-((4-nitrophenyl) (tetrahydrofuran-2-yl) methyl) phenol (17e).

Yield: 60% (72 mg); Reddish gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 8.72, 3.41 Hz, 2H); 7.51 (t, *J* = 8.08 Hz, 2H), 7.12 (s, 1H), 7.00 (s, 1H), 5.12 (d, *J* = 2.02 Hz, 1H), 4.48-4.65 (m, 1H), 3.72-4.05 (m, 3H), 1.70 1.99 (m, 3H), 1.58-1.69 (m, 1H), 1.41 (d, *J* = 1.52 Hz, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 152.7, 151.5, 151.4, 146.3, 136.0, 135.7, 131.9, 131.0, 129.3, 125.3, 124.7, 123.6, 123.5, 81.4, 81.0, 68.4, 57.0, 56.3, 34.3, 31.1, 30.5, 30.3, 25.7, 25.6; **HRMS** (ESI) *m/z*: [M+ Na]$^{+}$ calcd for $C_{25}H_{33}O_4NNa$, 434.2302; found, 434.2298.

2,6-di-tert-butyl-4-((3-chlorophenyl) (tetrahydrofu-ran-2-yl) methyl) phenol (17f).

Yield: 78% (95 mg); Yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.23-7.28 (m, 1H); 7.0 - 7.23 (m, 3H), 7.02-7.06 (m, 2H), 6.90-6.94 (m, 1H), 4.92-5.00 (m, 1H), 4.35-4.47 (m, 1H), 3.66-3.79 (m, 3H), 1.62-1.81 (m, 3H), 1.42-1.51 (m, 1H), 1.23-1.36 (m, 18H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 152.4, 152.3, 145.8, 145.5 , 135.7, 135.4, 134.0, 133.9, 132.8, 132.1, 129.5, 129.4, 128.8 , 128.6, 126.5, 126.3, 126.2, 125.1, 124.7, 81.6, 81.4, 68.4, 68.3, 56.8, 56.5, 34.3, 31.0 , 30.7 , 30.3, 30.3, 25.6; **HRMS** (ESI) *m/z*: [M+ Na]$^{+}$ calcd for $C_{25}H_{33}O_2ClNa$, 423.2061; found, 423.2059.

2,6-di-tert-butyl-4-((3-nitrophenyl) (tetrahydrofuran-2-yl) methyl) phenol (17g).

Yield: 64% (77mg); Reddish gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.08 Hz, 1H), 7.99-8.11 (m, 1H), 7.64-7.77 (m, 1H), 7.39-7.53 (m, 1H), 7.16 (s, 1H), 7.04 (s, 1H), 5.13 (s, 1H), 4.48-4.69 (m, 1H), 3.75-4.04 (m, 3H), 1.76-1.99 (m, 3H), 1.65-1.76 (m, 1H), 1.40-1.46 (m, 18H), **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 152.6, 152.6, 148.2, 145.8, 145.7, 136.0, 135.6, 134.8, 134.7, 132.0, 131.1, 129.1, 129.0, 125.3, 124.6, 123.5, 123.4, 121.2, 121.2, 81.5, 81.1,

68.4 , 56.7, 56.1, 34.3, 31.1, 30.5, 30.3, 30.2, 25.7, 25.6; **HRMS** (ESI) *m/z*: [M+ Na]$^+$ calcd for $C_{25}H_{33}O_4NNa$, 434.2302; found, 434.2299.

4-((2-bromophenyl) (tetrahydrofuran-2-yl) methyl)-2,6-di-tert-butylphenol (17h).

Yield: 63% (75mg); Yellow gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 - 7.58 (m, 1H), 7.47 (dd, *J* = 4.01, 2.10 Hz, 1H), 7.28 (br. s., 3H), 7.04 (br. s., 1H), 5.07 (br. s., 1H), 4.65 (br. s., 1H), 4.50 (d, *J* = 8.01 Hz, 1H), 3.88-3.94 (m, 1H), 3.78-3.88 (m, 1H), 1.88 (br. s., 3H), 1.45 (br. s., 18H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 152.3, 143.2, 135.1, 132.9, 131.9, 129.3, 127.6, 127.5, 125.2, 124.9, 81.6, 68.5, 54.0, 34.3, 30.6, 30.3, 25.7; **HRMS** (ESI) *m/z*: [M+ Na]$^+$ calcd for $C_{25}H_{33}O_2BrNa$, 467.1556; found, 467.1554.

2,6-di-tert-butyl-4-((2-chlorophenyl) (tetrahydrofu-ran-2-yl) methyl) phenol (17i).

Yield: 68% (82mg); Yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.40-7.68 (m, 1H), 7.28-7.36 (m, 1H), 7.17-7.24 (m, 2H), 7.02-7.17 (m, 2H), 5.03 (d, *J* = 2.91 Hz, 1H), 4.52-4.70 (m, 1H), 4.34-4.51 (m, 1H), 3.70-3.94 (m, 2H), 1.73-2.05 (m, 3H), 1.50 1.73 (m, 2H), 1.40 (d, *J* = 2.53 Hz, 18H); **^{13}C{^{1}H} NMR** (50 MHz, $CDCl_3$) δ 152.3, 141.6 , 140.8, 135.4, 135.2, 133.7, 132.0, 131.8, 129.6, 129.3, 128.7, 127.1, 126.9, 126.6, 125.3, 125.1, 81.6, 81.3, 68.4, 52.1, 51.5, 34.3, 30.9, 30.6, 30.3, 25.7; **HRMS** (ESI) *m/z*: [M+ Na]$^+$ calcd for $C_{25}H_{33}O_2ClNa$, 423.2061; found, 423.2057.

2,6-di-tert-butyl-4-((3,4-dichlorophenyl) (tetrahydro-furan-2-yl) methyl) phenol (17j).

Yield: 72% (86mg); Yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.02 Hz, 1H), 7.24-7.33 (m, 1H), 7.09-7.22 (m, 1H), 6.91 (s, 2H), 5.01 (s, 1H), 4.32-4.47 (m, 1H), 3.59-3.84 (m, 3H), 1.64-1.89 (m, 3H), 1.32-1.37 (m, 18H); **^{13}C{^{1}H} NMR** (50 MHz, $CDCl_3$) δ 152.5, 143.9 , 135.9, 132.4, 130.6, 130.1, 127.8, 124.6, 81.6, 68.4, 56.3, 34.3, 31.1, 30.3, 25.7; **HRMS** (ESI) *m/z*: [M+ Na]$^+$ calcd for $C_{25}H_{32}O_2Cl_2Na$, 457.1672; found, 457.1670.

2,6-di-tert-butyl-4((3,4dimethoxyphenyl) (tetrahydro-furan-2-yl) methyl) phenol (17k).

Yield: 67% (80 mg); Yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.07 (s, 2H), 6.89-6.99 (m, 2H), 6.78-6.86 (m, 1H), 5.05 (s, 1H), 5.81 Hz, 1H), 4.50 (td, *J* = 8.15, 3.47 Hz, 1H), 3.96 (dd, *J* = 5.12, 3.87 (s, 3H), 3.85 (s, 3H), 3.71-3.82 (m, 2H), 1.71-1.95 (m, 4H), 1.42 (s, 18H); **^{13}C{^{1}H} NMR** (50 MHz, $CDCl_3$) δ 152.1, 148.5, 147.3, 136.0, 135.5, 133.6, 124.6, 120.3, 111.9, 111.0, 82.2, 68.5, 56.6, 55.7, 55.7, 34.3, 31.0, 30.1, 25.7; **HRMS** (ESI) *m/z*: $[M+ H]^+$ calcd for $C_{27}H_{39}O_4$, 427.2843; found, 427.2832.

2,6-di-tert-butyl-4-(pyren-1-yl(tetrahydrofuran-2-yl) methyl) phenol (17l).

Yield: 62% (72 mg); Red gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.47-8.76 (m, 1H), 7.91-8.34 (m, 9H), 7.35 (s, 1H), 7.21 (s, 1H), 5.02-5.11 (m, 1H), 5.01 (s, 1H), 4.93 (br. s., 1H), 3.79-4.02 (m, 2H), 1.67-2.18 (m, 5H), 1.39 (d, *J* = 3.16 Hz, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 152.1, 152.1, 138.1, 137.3, 135.5 , 135.3, 133.4, 133.3, 131.4 , 131.4, 130.8 , 130.7, 129.7, 129.5, 129.2, 128.7, 127.6, 127.4, 127.4, 127.1, 126.8, 126.6, 125.8, 125.8, 125.6, 125.2, 125.1, 125.0, 125.0, 124.9, 124.8, 124.6, 124.5, 123.5, 123.3, 82.5, 82.0, 68.5, 51.8, 51.1, 34.3, 34.3, 31.3, 31.1, 30.3, 30.3, 25.9, 25.8; **HRMS** (ESI) *m/z*: $[M+ H]^+$ calcd for $C_{35}H_{39}O_2$, 491.2945; found, 491.2935.

2,6-di-tert-butyl-4-(pyridin-3-yl(tetrahydrofuran-2-yl) methyl) phenol (17m).

Yield: 64% (79 mg); Red gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.44 - 8.57 (m, 1H), 8.35 (d, *J* = 3.16 Hz, 1H), 7.56 (dt, *J* = 7.83, 1.96 Hz, 1H), 7.12-7.22 (m, 1H), 7.00-7.09 (m, 2H), 5.03 (br. s., 1H), 4.45 (dd, *J* = 7.52, 6.00 Hz, 1H), 3.66-3.85 (m, 3H), 1.58-1.92 (m, 4H), 1.28-1.38 (m, 18H); **^{13}C{^{1}H} NMR** (50 MHz, $CDCl_3$) δ 152.5, 149.9, 147.4, 139.2 , 135.8, 135.7, 131.6, 125.1, 123.3, 81.2, 68.3, 54.2, 34.3, 30.6, 30.3, 25.7; **HRMS** (ESI) *m/z*: $[M+ H]^+$ calcd for $C_{24}H_{34}O_2N$, 368.2584; found, 368.2582.

4-((5-bromothiophen-2-yl) (tetrahydrofuran-2-yl) methyl)-2,6-di-tert-butylphenol (17n).

Yield: 71% (84 mg) Reddish gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.13 (s, 2H); 6.84 (d, *J* = 3.79 Hz, 1H), 6.58 (d, *J* = 3.66 Hz, 1H), 5.12 (s, 1H), 4.25-4.47 (m, 1H), 4.13 (d, *J* = 6.19 Hz, 1H), 3.70-3.97 (m, 2H), 1.63-1.92 (m, 4H), 1.44 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 152.7, 148.3, 135.6, 131.1, 128.9, 125.3, 125.2, 110.4, 82.2, 68.4, 52.4, 34.4, 30.4, 29.6, 25; **HRMS** (ESI) *m/z*: $[M+ Na]^+$ calcd for $C_{23}H_{31}O_2BrNaS$, 473.1120; found, 473.1121.

2,6-di-tert-butyl-4-(furan-2-yl(tetrahydrofuran-2-yl) methyl) phenol (17o).

Yield: 68% (68 mg) Red gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.35 (s, 1H); 7.05 (s, 2H), 6.30-6.38 (m, 1H), 6.22 (d, *J* = 3.16 Hz, 1H), 5.08 (s, 1H), 4.32-4.52 (m, 1H), 3.75-3.98 (m, 3H), 1.67-1.93 (m, 4H), 1.42 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 156.4; 152.6, 141.1, 135.6, 130.6, 124.9 , 110.1, 106.0, 81.5, 68.5, 50.7, 34.3, 30.3, 29.7, 25.6; **HRMS** (ESI) *m/z*: $[M+ Na]^+$ calcd for $C_{23}H_{32}O_3Na$, 379.2244; found, 379.2241.

3-(3,5-di-tert-butyl-4-hydroxyphenyl)-1-(2,3-dihydroxypropyl)-3-(tetrahydrofuran-2-yl) indolin-2-one (18)

Yield: 76% (41mg): yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 6.49 Hz, 1H); 7.33-7.38 (m, 3H), 7.16 (t, *J* = 7.06 Hz, 1H), 7.05 (t, *J* = 8.77 Hz, 1H), 5.17 (br. s., 1H), 4.82 (br. s., 1H), 3.99 (br. s., 2H), 3.72-3.80 (m, 3H), 3.57-3.65 (m, 2H), 2.66 (s, 1H), 2.20 (s, 1H), 2.07 (s, 1H), 1.88-1.94 (m, 1H), 1.80-1.85 (m, 1H), 1.69-1.77 (m, 1H), 1.40 (s, 18H); **^{13}C{^{1}H} NMR** (126 MHz, CDCl3) δ 179.0, 178.8, 153.1, 143.1, 135.5, 130.6, 128.3, 128.1, 126.6, 124.1, 122.8, 108.7, 108.5, 84.0, 83.9, 70.0, 69.5, 69.3, 69.0, 63.3, 63.0, 59.2, 53.8, 42.6, 42.1, 34.5, 30.2, 29.7, 29.4, 29.2, 27.6, 27.5, 26.0, 25.9; **HRMS** (ESI) *m/z*: $[M+ H]^+$ calcd for $C_{29}H_{40}O_5N$, 482.2901; found, 482.2899.

1-benzyl-3-(3-(tert-butyl)-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl) indolin-2-one (19).

Yield: 60% (26 mg); Colourless gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (d, J = 7.63 Hz, 1H); 7.25 (s, 1H), 7.22 (br. s., 3H), 7.19 (s, 2H), 7.09-7.17 (m, 3H), 6.97 (t, J = 7.63 Hz, 1H), 6.64 (d, J = 7.63 Hz, 1H), 6.46 (d, J = 8.01 Hz, 1H), 5.23 (br. s., 1H), 4.96 (d, J =15.64 Hz, 1H), 4.78-4.91 (m, 2H), 3.61 (q, J = 6.99 Hz, 1H), 3.40 (q, J = 7.25 Hz, 1H), 1.89-2.02 (m, 2H), 1.70-1.82 (m, 1H), 1.65 (dt, J =12.87, 6.34 Hz, 1H), 1.26 (s, 9H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 178.2; 153.7, 143.8, 135.9, 135.8, 130.3, 129.0, 128.6, 128.1, 127.3, 127.0, 126.6, 126.2, 125.9, 121.9, 116.6, 109.3, 83.6, 68.8, 59.5, 43.8, 34.7, 29.5, 27.5, 26.0; **HRMS** (ESI) *m/z*: $[M+ H]^+$ calcd for $C_{29}H_{32}O_3N$, 442.2377; found, 442.2370.

Benzyl-3-(4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl) indolin-2-one (20).

Yield: 58% (22mg); colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 6.94-7.39 (m, 10H); 6.50-6.69 (m, 2H), 5.83 (br. s., 1H), 4.70-5.06 (m, 3H), 3.49-3.74 (m, 1H), 3.31-3.49 (m, 1H), 1.97 (d, J = 5.31 Hz, 1H), 1.58-1.78 (m, 3 H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 178.4, 155.4, 143.8, 135.6, 130.0, 128.9, 128.8, 128.6, 128.3, 127.3, 127.0, 125.9, 122.1, 115.6, 109.5, 83.4, 68.9, 59.5, 43.8, 29.7, 27.4, 25.9; **HRMS** (ESI) *m/z*: $[M+ H]^+$ calcd for $C_{25}H_{24}O_3N$, 386.1751; found, 386.1744.

Section II

Oxidative Radical Mediated Addition of Ethers to Quinone Imine Ketals (QIK's): An Access to Hemiaminals

2.2.1 Introduction

The construction of C-N bonds has been a major research topic in organic synthesis. Nitrogen-containing frameworks are the backbone of around 25% of biologically active compounds and synthetic intermediates. Among the compounds containing C-N bonds having hemiaminals, moiety represents the core structure in many biologically active natural products and pharmaceutical agents.[24] The typical example that includes Aspidophylline A (**22**), an alkaloid from the Apocynaceae family, displays an antiviral activity.[25a, b] Whereas (-)-physovenine (**25**) shows anti-cholinergic and miotic activities[25c] while indole nitrogen-bearing THF ring acts as HCV inhibitor (**23**) as shown in **Figure 3**.[25d]

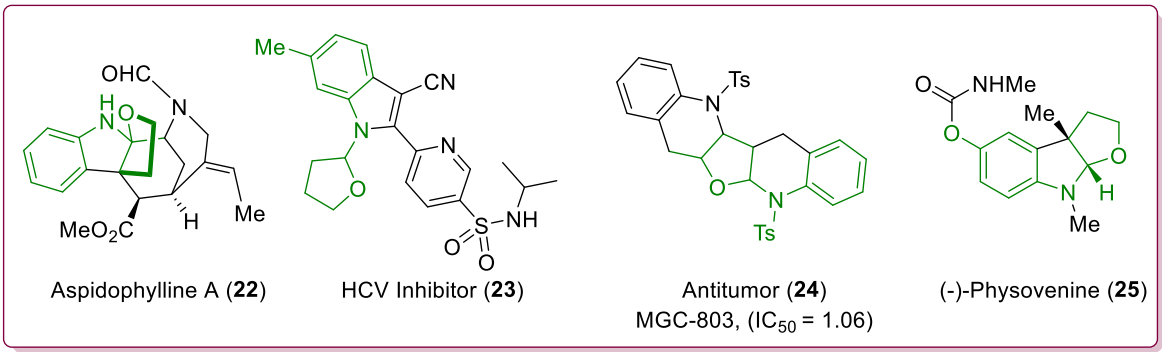


Figure 3. Biologically active cyclic ethers.

In particular, hemiaminal ether with sulfonamide as core structure shows an interesting antitumor activity against MGC-803 (**24**) cell line with an IC_{50} value 1.06.[25e] Also, and the substituted *N*-sulfonamides were present in a large number of bioactive molecules.[25f]

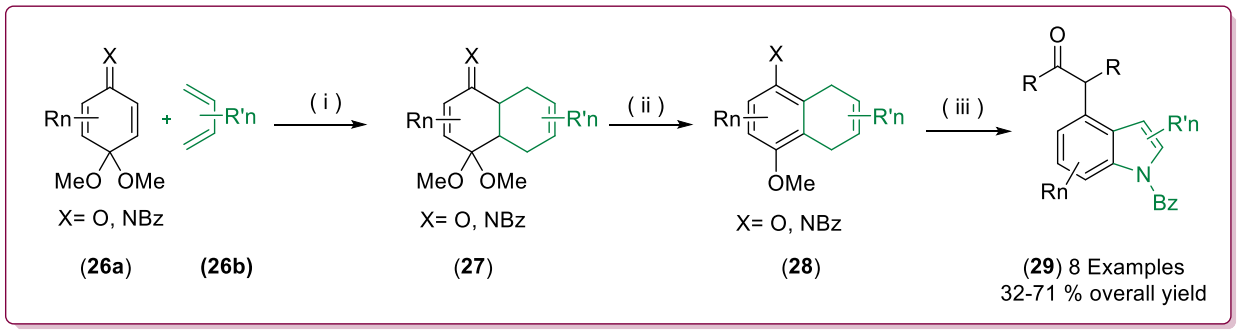
Furthermore, hemiaminal ethers act as key synthons for various organic transformations and also in synthesis of the natural product synthesis.[26,27] Due to the increasing importance of hemiaminals in medicinal and synthetic chemistry, various efforts have been devoted to the development of new methods thereof. Initially, most synthetic endeavors assemble this bioactive core using Pd-mediated reactions.[28] In recent years, immense progress has been made using various metal catalysts such as Cu, Co, Mn, Ru, Ni, and Fe to synthesize hemiaminals from diversified *N*-heterocycles.[29,30] The limited methods were known for synthesizing hemiaminals under metal-free conditions. Therefore, these metal-free reactions attract chemists [31a-i] as these are greener and more eco-friendly approaches to metal-catalyzed reactions. Despite the various methods available for synthesizing hemiaminals, using costly transition metals and hazardous by-products formed in these reactions makes our approach more feasible. Recently, quinone imine ketals (QIK's) are immerging extensively as an electrophilic center for a variety of nucleophilic addition reactions; hence it makes a fascinating target for such addition reactions.[32]

2.2.2 Review of Literature

In the literature, there are so many reports are known for the reactions of Quinone imine ketals due to their reactive sites. It reacts over C-1, C-2, and C-3 reactive sites; due to its reactivity over each position, many research groups are passionate to used QIK's for various nucleophilic reactions. Few reports are known for the reactions on Quinone Imine Ketals (QIK's) [33a-33d]. Some of the latest methods are described below.

Kerr's Approach (2001)[33a]

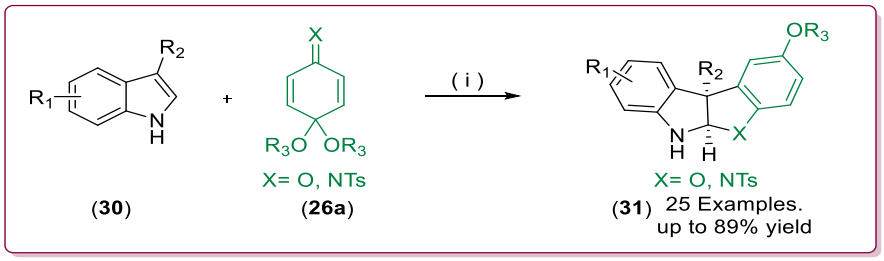
Kerr *et al.* in 2001 have been developed [4+2] Diels-Alder reaction of Quinone Imine ketals (QIK's) (**26a**) and a diene (**26b**) for the construction of the ergot skeleton (**29**). In this report, N-Benzoylated quinone imine ketals reacted with diene undergoes cycloaddition smoothly *via* [4+2] manner to form an adducts (**27** and **28**), which then further performed various steps to formed 5-methoxyindoles in good to excellent yields of the desired product **(Scheme 5).**



Scheme 5. (i) 13 kbar, CH_2Cl_2, 50 °C, 12h. (ii) HCl (cat.) THF, 5 min. (iii) (a) OsO_4 / NMO, (b) $NaIO_2$ on SiO_2, (c) TsOH, $PhCH_3$

Zhang Approach (2014)[33b]

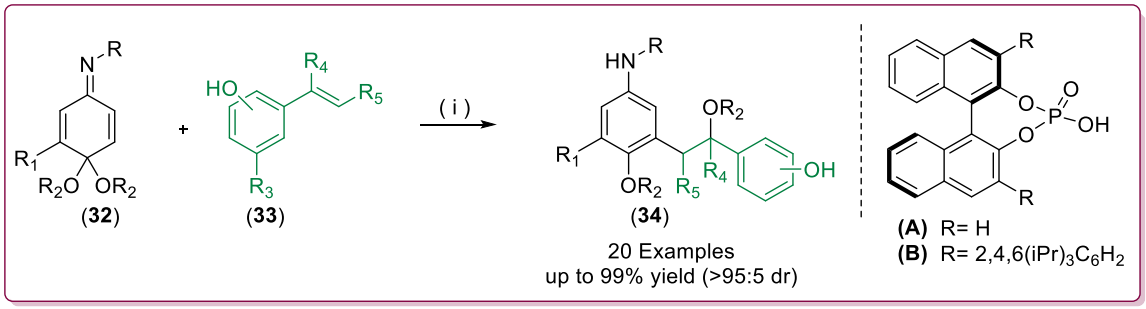
Zhang and a co-worker 2014 achieved a Lewis acid catalyzed [3+2] cycloaddition reaction of 3-methyl-1-indole (**30**) with Quinone Imine Ketal (QIK) (**26a**) for the synthesis of benzofuroindolines and tetra-hydroindolo[2,3-b] indoles (**31**). Here, the QIKs reacted with indoles in the presence of $Zn(OTf)_2$ as a lewis acid in Toluene at 25 °C to form the desired product in moderate to good yield (**Scheme 6**).



Scheme 6. (i) Zn $(OTf)_2$ (10 mol%), Toluene, 25 °C, 24 h.

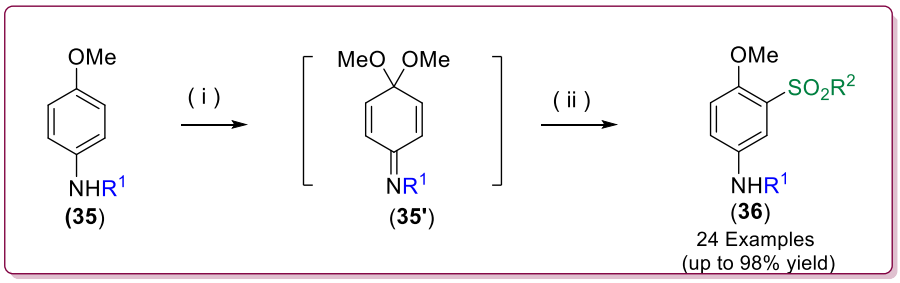
Shi Approach (2014)[33c]

Later on, Shi and co-authors 2014 demonstrated an oxidative rearrangement of QIK (**32**) with styrenes (**33**) to accomplishthe substituted oxyarylation products (**34**). report described the first organocatalytic oxyarylation of styrenes from ortho or para hydroxy styrene and Quinone imine ketals (QIKs). This organocatalysis and cascade reactions approach to access a C−O bond, C−C bond, and a new stereocenter in a single step. This method provides the highly regioselective and chemoselective oxyarylation of styrene to develop the meta-substituted aniline in excellent yield (99%) and high diastereoselectivity (>95:5 dr). (**Scheme 7**).



Scheme 7. (i) BPA (A) or (B) (5 mol%), Toluene, 30 °C, 12 h.

Mhaske Approach (2014)[33d]



Scheme 8. (i) PIDA (1.1 Equiv.), MeOH (0.12 M), 0 °C to rt, 5 min-7 h.
(ii) R^2SO_2Na (2 Equiv.), AcOH (10 Equiv.), THF (0.1 M), rt, 3- 18 h.

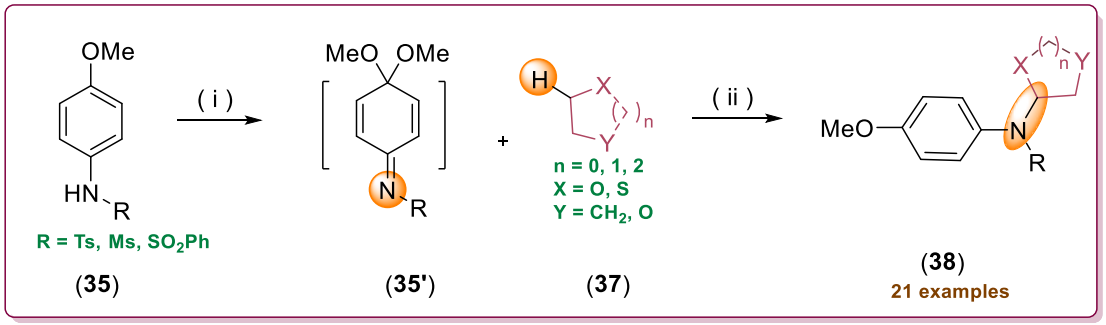
Mhaske and coworkers 2014 prescribed an efficient and regioselective mild, metal-free one-pot development of aryl sulfones (**36**) using in-situ generated reactive Quinone imine ketal (QIKs)

(**35'**) and sulfinate salts as a coupling partner. This mild approach tolerates a wide range of functionality on para-anisidine and sodium sulfinate salts, providing aryl sulfone in excellent yields up to 98%. (**Scheme 8**).

2.2.3 Present Work

2.2.3.1 Objectives

QIK, as well as related cyclohexadienone motifs, served as a useful synthetic intermediate to establish the functionalized aromatic rings as highly reactive key synthons and an important intermediate in various reactions.[34] In addition to these advancements, our continuous efforts toward the generation & utilization of α-oxyalkyl radicals under metal-free conditions have encouraged us to synthesize hemiaminals from QIK. Herein, we are demonstrating an efficient radical-mediated C-N bond formation *via* the addition of ethers (**37**) on QIK (**35**') to accomplish the synthesis of hemiaminals (**Scheme 9**).



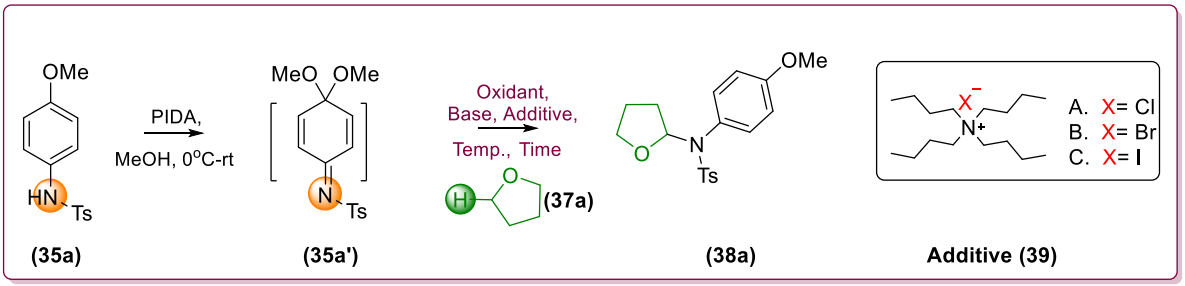
Scheme 9. (i) PIDA (1.1 Equiv.), MeOH, 0 °C to rt, 5 min. to 1 h. (ii) $K_2S_2O_8$ (3 Equiv.), NaOAc (3 Equiv.), TBACl (3 Equiv.), 90 °C, 4 h.

2.2.4 Result and Discussion

We began our investigation using *N*-tosyl QIK **35a'** prepared in situ from *p*-anisidine (**35a**)[33d] employed as a model substrate and THF as a solvent and coupling partner. Based on our previous work, we start with $K_2S_2O_8$ as oxidant, TBACl as an additive, and

NaOAc as a base in 1 equivalent, respectively, to carry out the reaction at ambient temperature (Table 7). Unfortunately, the desired product **38a** was not observed (entry 1).

Table 7. Optimization of Reaction Condition



(35a) (35a') (38a) Additive (39)

Sr. No.	Oxidant (Equiv.)	Additive (Equiv.)	Base (Equiv.)	Temp. (°C)	Time (h)	Yield [b] (%)
1	$K_2S_2O_8$(1)	A(1)	NaOAc(1)	RT	24	NR
2	$K_2S_2O_8$(1)	A(1)	NaOAc(1)	90	4	23
3	$K_2S_2O_8$(2)	A(2)	NaOAc(2)	90	4	64
4[c]	**$K_2S_2O_8$(3)**	**A(3)**	**NaOAc(3)**	**90**	**4**	**91**
5	$K_2S_2O_8$(3)	A(3)	-	90	24	NR
6	$K_2S_2O_8$(3)	-	NaOAc(3)	90	24	NR
7	$K_2S_2O_8$(3)	-	-	90	24	NR
8	$K_2S_2O_8$(3)	B(3)	NaOAc(3)	90	4-24	Trace
9	$K_2S_2O_8$(3)	C(3)	NaOAc(3)	90	4-24	Trace
10	$K_2S_2O_8$(3)	A(3)	NaOAc(3)	110	4	NR[d]
11	$K_2S_2O_8$(3)	A(3)	KOAc(3)	90	24	17
12	$K_2S_2O_8$(3)	A(3)	K_2CO_3(3)	90	24	NR
13	$K_2S_2O_8$(3)	A(3)	NaOEt(3)	90	24	37
14	$K_2S_2O_8$(3)	A(3)	Cs_2CO_3(3)	90	24	NR
15	$K_2S_2O_8$(3)	A(3)	NaO^{t}Bu(3)	90	24	NR
16	$K_2S_2O_8$(3)	A(3)	Bu_4NOH(3)	90	24	NR
17	$Na_2S_2O_8$(3)	A(3)	NaOAc(3)	90	24	35
18	Oxone (3)	A(3)	NaOAc(3)	90	24	NR
19	TBHP (3)	A(3)	NaOAc(3)	90	24	NR
20	DTBP (3)	A(3)	NaOAc(3)	90	24	Trace

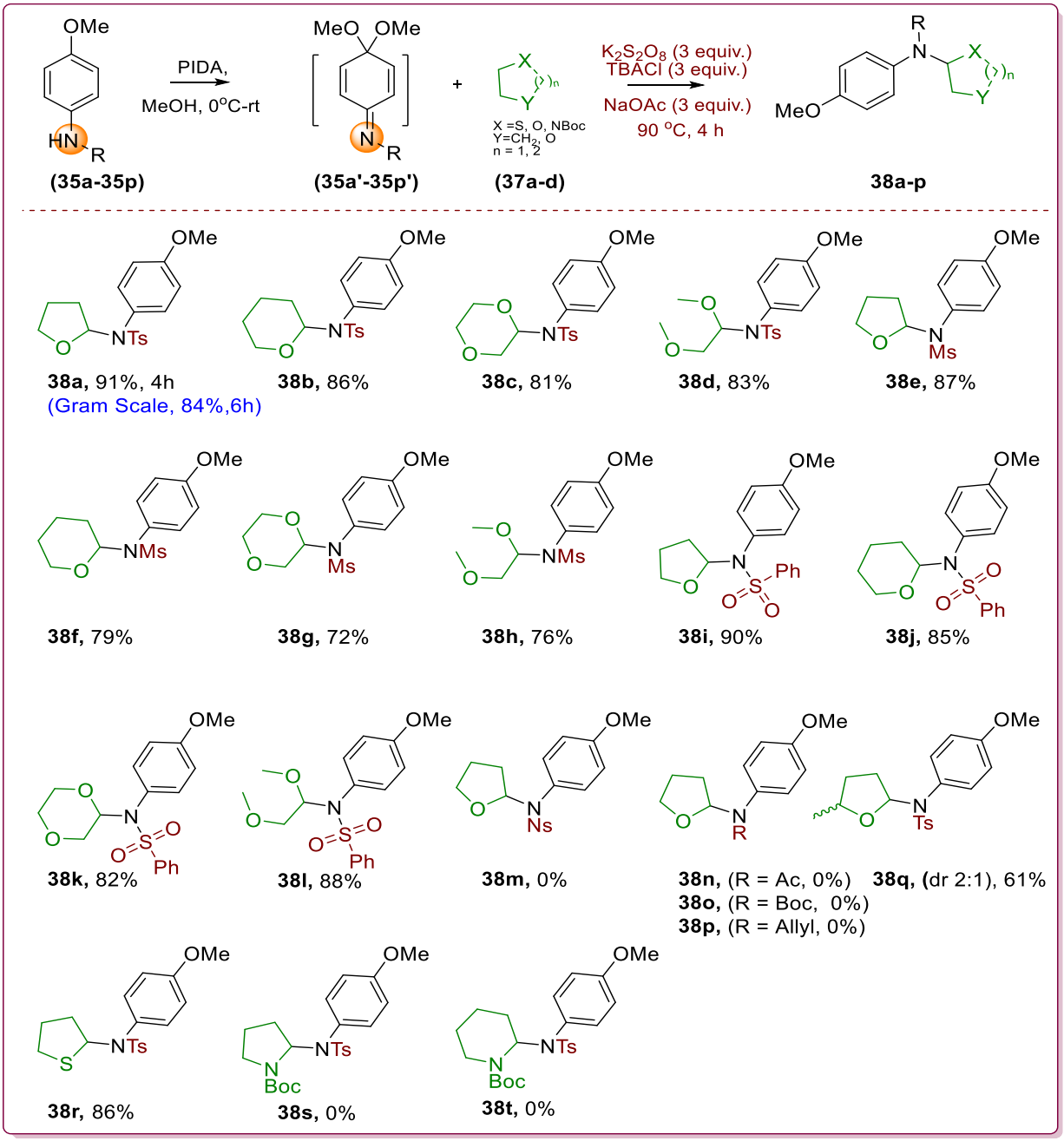
21	BPO (3)	A(3)	NaOAc(3)	90	24	NR

[a] Reaction conditions: **35a** (0.36mmol), **37a** (10 mmol), oxidant, additive and base, [b] Isolated Yields, [c] TBACl in 50% aq. solution; [d] Decomposition of **35a'** was observed, NR=No Reaction.

Whereas, when raised up the reaction temperature to 90 ^{o}C, the desired product **38a** was obtained at 23% within 4 h of reaction time (entry 2). Further, an increase in equivalents of reagent dramatically enhanced the yield of **38a** from 23 to 91% (entry 4). When the reaction was carried out without the additive and base, the reaction ~~fails~~ failed to proceed further, and the starting material remained un-reacted (entries 5-7). Thus, it is confirmed that the base and additive are essential to initiate the reaction. During optimization, TBAB and TBAI were used as an additive, with **38a** observed only in trace amounts (entries 8-9). Enhancement in the temperature of the reaction mixture resulted in the decomposition of the staring material (entry 10). Further, screening of various bases using the same oxidant observed no increment in the yields of hemiaminal **38a** (entries 11-16). Moreover, alteration of various oxidants produced discouraging results in delivering the desired product **38a** (entries 17-21). In conclusion, the best-optimized reaction condition was preferred as entry 4 in Table 7.

With the optimized reaction condition in hand, the study of substrate scope was investigated to justify our approach. Initially, *N*-sulfonates containing QIK (*N*-Ts, *N*-Ms, and *N*-SO_2Ph) subjected to hemiaminal synthesis using our optimized reaction conditions showed the excellent feasibility with various cyclic as well as acyclic ethers, *i.e.*, THF, THP, 1,4-dioxane and DME. *N*-sulfonates containing QIK delivered the desired products **38a** to **38l** in good to excellent yields (72-91%) with various cyclic and acyclic ethers, i.e., THF, THP, 1,4-dioxane, and DME, and **38a** was chromatographic purification are shown.

Table 8. Substrate scope for synthesis of hemiaminals [a, b]



[a] **Reaction conditions: 35a-p** (0.36 mmol), **37a-d** (3.6mmol), $K_2S_2O_8$ (1.08 mmol), TBACl (1.08 mmol, 50% in aq. soln.), NaOAc (1.08 mmol), 90 °C, 4 h, under air; [b] Isolated yields after column

performed on a gram scale to obtain 84% yield (0.840 gm) in 6h, as shown in Table 8. Unfortunately, *N*-Ns, *N*-acetyl, *N*- Boc, and *N*-Allyl (entries **38m-38p**) groups did not lead to giving the corresponding hemiaminal products. Further, 2-Me tetrahydrofuran reacts smoothly

with **35a'** to deliver the corresponding hemiaminal **38q** in 61% yield with a 2:1 diastereomeric ratio under our optimized reaction conditions. In addition, when tetrahydrothiophene was used as the solvent instead of THF along with QIK, it afforded the corresponding thioether amine **38r** in 86% yield. Unfortunately, when the reaction of QIK **35a'** was carried out with *Boc*-protected alkyl amines such as piperidine and pyrrolidine failed to give the expected products **38s-38t.** The formation of the corresponding hemiaminal products was confirmed by their ^{1}H, ^{13}C, HRMS, and FT-IR analysis techniques.

Example 2:

The formed hemiaminal product of the *N*-Ts-protected *p*-anisidine **(38a)** was confirmed from their ^{1}H NMR spectrum. The ^{1}H NMR showed the peak at δ 7.6 doublets (d, J = 8.27 Hz, 2H), δ 7.2 doublets (d, J = 8.05 Hz, 2H), δ 7.0 - 7.1 multiplet 2H (m, 2H) and δ 6.8 and multiplet 2H (m, J = 9.04 Hz, 2H) for corresponding to the aromatic protons. δ 6.2 triplet 1H corresponds to the characteristic hydrogen atom of the hemiaminal product, i.e., the Hydrogen atom between Nitrogen and Oxygen atom of ether (dd, J = 7.28, 4.96 Hz, 1H). The -OMe peak appears at δ 3.8 as a singlet for 3H (s, 3H). Peak at δ 3.6 - 3.7, multiplet 2H for the protons near the oxygen atom of ether (m, 2H), The peak at δ 2.4 singlet 3H for the -*N*Ts group (s, 3H), and remaining multiplet 4 hydrogen comes in between δ 2.0 - 1.2 (m, 4H) for the ether protons in **38a**. It was also confirmed by its ^{13}C NMR spectrum, in which characteristic carbon signal at δ 68.3 hemiaminal carbon of compound **38a** (**Figure 3**).

After a successful approach to synthesizing hemiaminals from different *N*-sulfonates, we further extended the scope of reaction to study the electronic effect of various substituents containing electron-withdrawing and donating groups present on the QIK, as shown in Table 9.

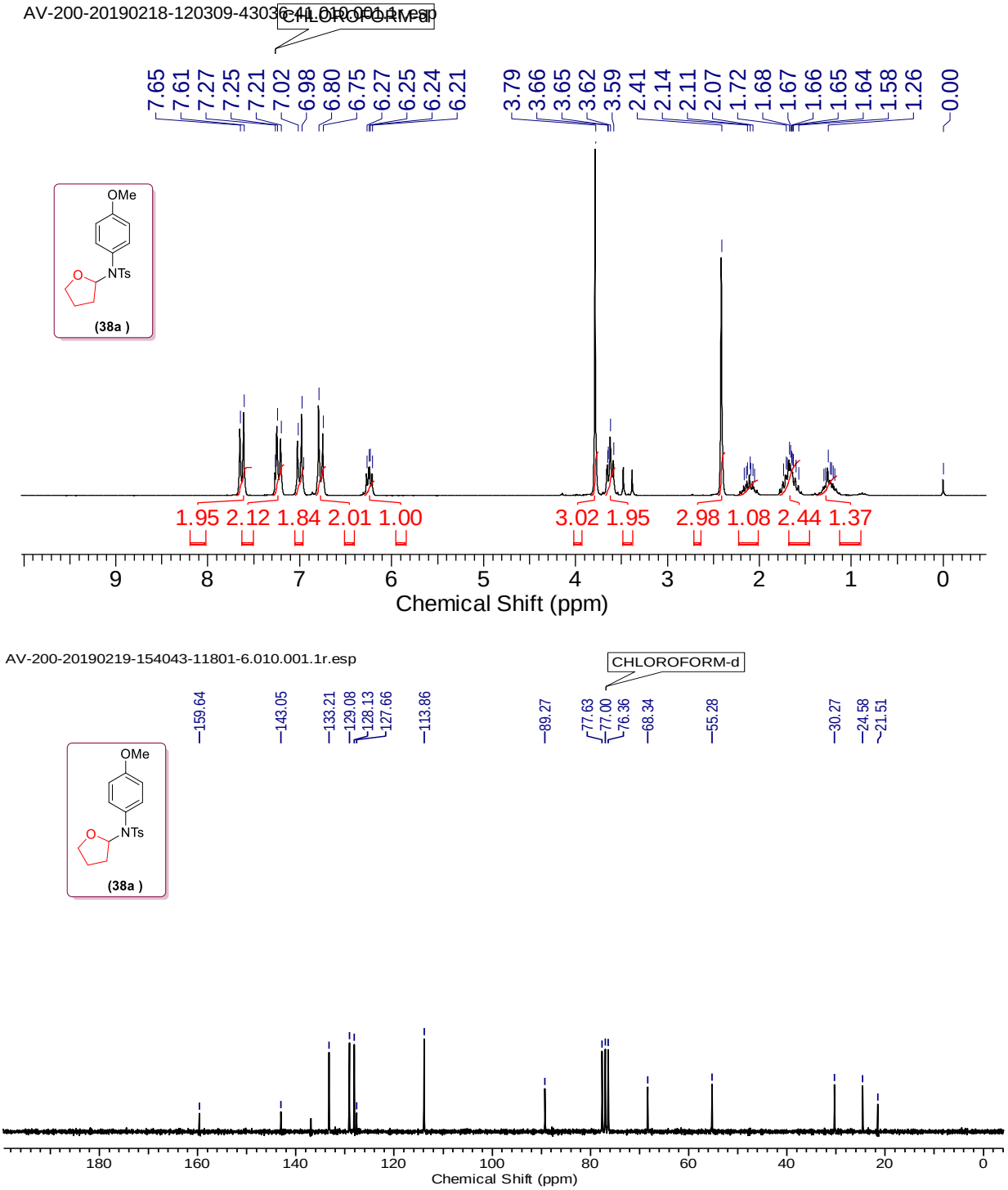
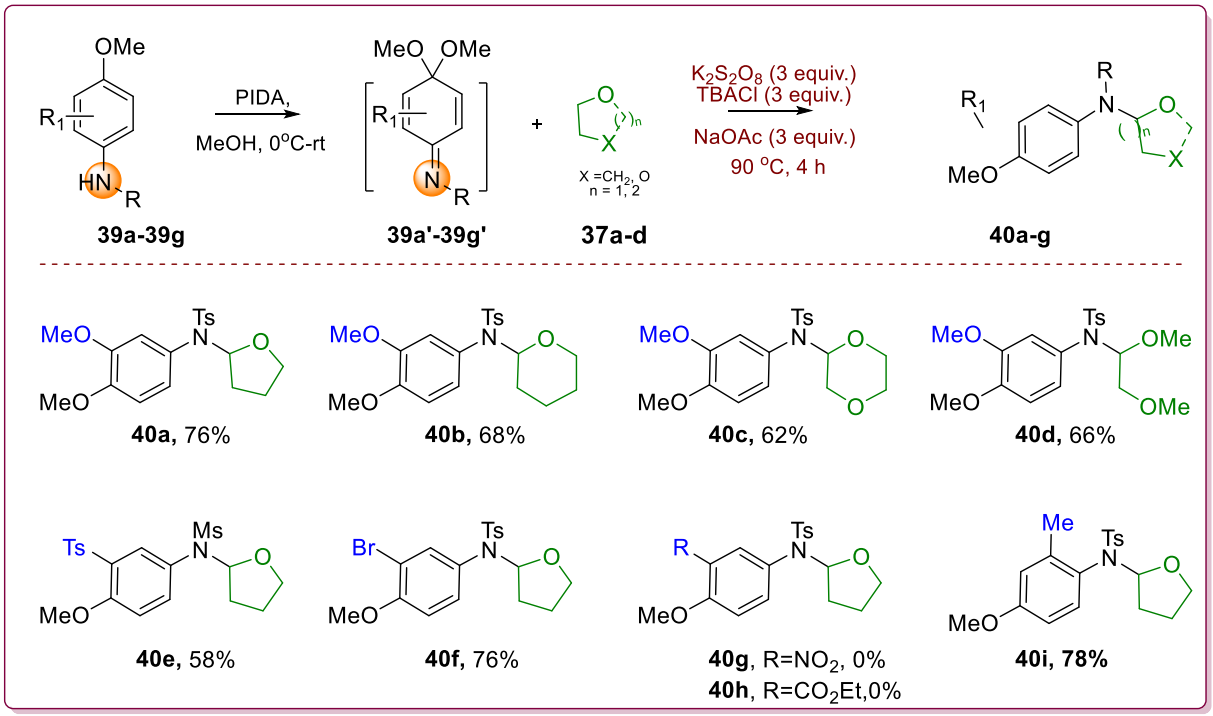


Figure 3: ^{1}H and ^{13}C $\{^{1}H\}$ NMR of *N-(*4-methoxyphenyl)-4-methyl-*N-(*tetrahydrofuran-2-yl) benzenesulfonamide **(38a)**

Table 9. Substrate scope for synthesis of hemiaminals from substituted QIK's [a, b]

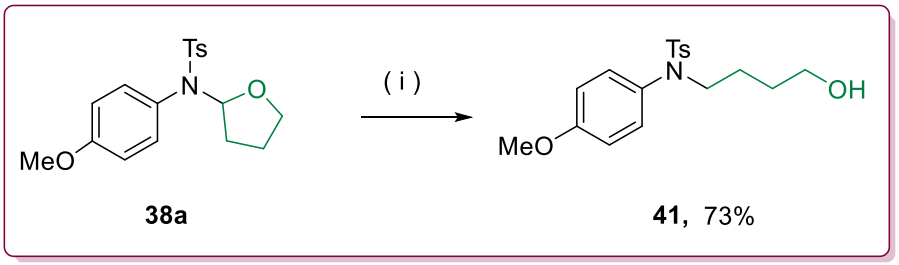


[a] **Reaction conditions: 39a-39g** (0.36 mmol), **37a-d** (3.6 mmol), K_2S_2O8 (1.08 mmol), TBACl (1.08 mmol, 50% in aq. soln.), NaOAc (1.08 mmol), 90 °C, 4 h, under air; [b] Isolated yields after column chromatographic purification are shown.

Interestingly, good yields of hemiaminals (entries **40a-40d**), *i.e.*, 62-76%, were observed when an electron-donating group such as –OMe was present at the *ortho* position of the acetal group. Also, the presence of –Me to *meta*-position of acetal group did not affect the reactivity of QIK to give desired hemiaminal **40i** in 78% yield. In contrast electron-withdrawing groups such as –Br and -Ts *ortho* to acetal of QIK were utilized for C-N bond formation with ethers to give corresponding hemiaminal **40e** and **40f** in moderate yields compared to electron-donating groups (58% and 76%, respectively). However, $-NO_2$ and $-CO_2Et$ substituted QIK **39g'**and **39h'** failed to afford the corresponding hemiaminal **40g** and **40h**, which might be due to the high radical stability of withdrawing groups on QIK which leads to C-N bond cleavageNotably, the reaction of electron-donating groups containing QIK reacts faster than the electron-withdrawing groups.

To check the synthetic utility of our formed key product, the *N*-(4-methoxyphenyl)-4-methyl-*N*-(tetrahydrofuran-2-yl) benzenesulfonamide **38a** was subjected to reduction reaction using 5 equiv. of $NaBH_4$ in EtOH undergoes cleavage of C-O bond to afford amino alcohol **41** in 73% yield as shown in Table 10.[36]

Table 10. Synthetic transformation of formed product [a]

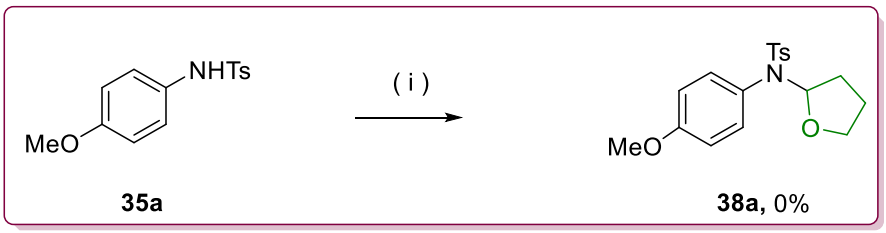


[a] **Reaction conditions:** $NaBH_4$ (5 equiv.), EtOH, rt, 36 h

We conducted a few control experiments to check the reaction pathway, as shown in Table 11. Initially, the reaction of **35a** was carried out in our optimized reaction condition, which failed to give desired product **38a,** and the starting material was recovered.

Moreover, some radical scavenging experiments were done to get more insight into the reaction mechanism, as shown in Table 12. Initially, the reaction was carried out in the presence of 1

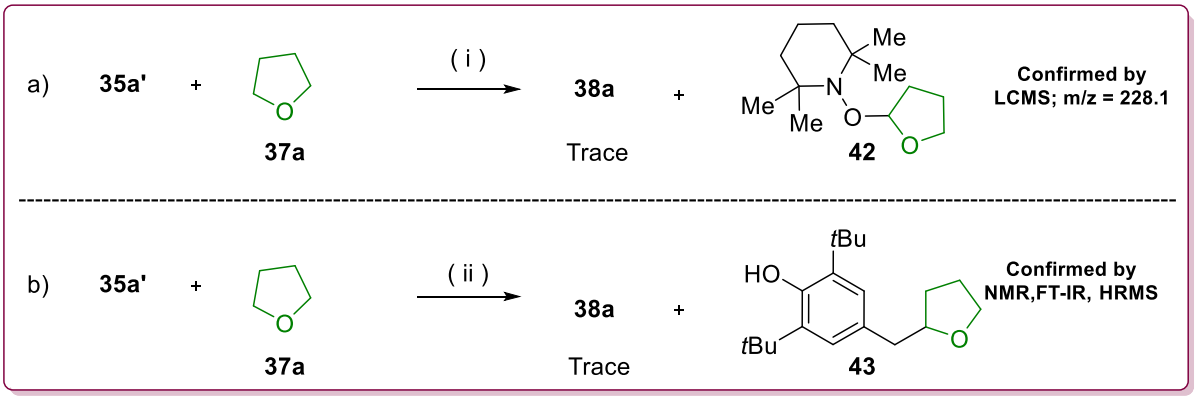
Table 11. Control Experiments [a]



[a] **Reaction conditions:** (i) **35a** (0.36 mmol), 2a (3.6 mmol), K_2S_2O8 (1.08 mmol), TBACl (1.08 mmol, 50% in aq. soln.), NaOAc (1.08 mmol), 90 °C, 4 h, under air

equivalent of TEMPO as a radical scavenger under optimized reaction conditions. The **38a** was formed in trace amounts, whereas the major amount of TEMPO-THF trapped product **42** was observed. LCMS confirmed the formed adduct 42. Additionally, 1 equivalent of butylated hydroxytoluene (BHT) was added to the reaction mixture, which afforded BHT-THF product **43**. The formation of compound **43** was confirmed by ^{1}H, ^{13}C, FT-IR, and HRMS spectroscopy.

Table 12. Control Experiments [a]



[a] **Reaction conditions:** (i) **35a'** (0.36 mmol), **37a** (3.6 mmol), K_2S_2O8 (1.08 mmol), TBACl (1.08 mmol, 50% in aq. soln.), NaOAc (1.08 mmol), TEMPO (0.36 mmol), 90 °C, 4 h, under air; (ii) **35a'** (0.36 mmol), **37a** (3.6 mmol), K_2S_2O8 (1.08 mmol), TBACl (1.08 mmol, 50% in aq. soln.), NaOAc (1.08 mmol), BHT (0.36 mmol), 90 °C, 4 h, under air.

Similarly, The BHT-THF trapped product was confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS spectrum. In ^{1}H NMR spectrum of **43** showed the doublet at δ 7.00 (d, 1H) corresponding to the -O**H** of phenol, and the peak at δ 6.55 - 6.64 (m, 1 H) and 6.39 (d, J = 2.87 Hz, 1 H) for the aromatic proton of phenol. The multiplet 1-H at δ 3.86 - 3.96 (m, 1H) belongs to the proton near the oxygen atom of the THF ring. Multiplet 2-H at δ 3.75 - 3.84 (m, 2H) corresponding methene group of a benzylic ring of compound **43** and the singlet at δ 1.22 (s, 18H) for the corresponding di-tertbutyl group of phenol ring.

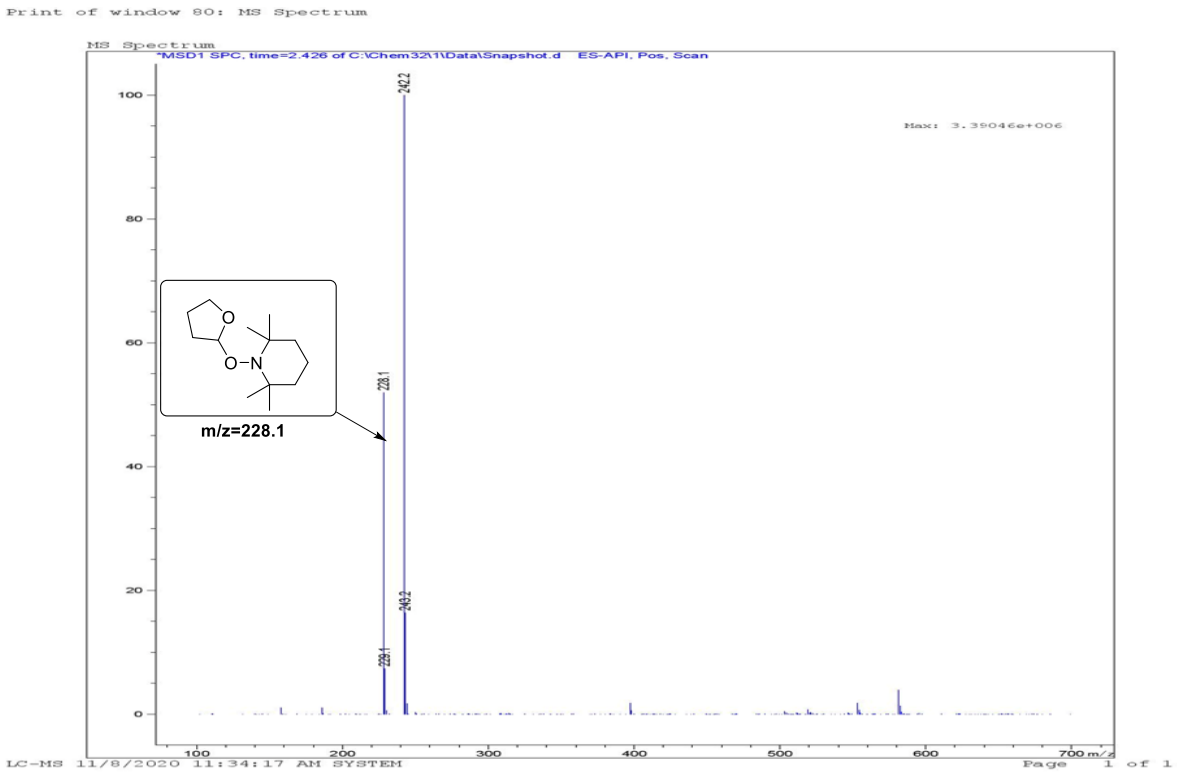


Figure. 4: LCMS spectrum of compound **42**.

The ^{13}C spectrum confirms that the peak showed at δ 43.9 due to methylene carbon (-**C**H_2) of the benzylic position of compound **43** as shown in **Figure 5.** The BHT-THF trapped adduct also confirmed by the HRMS spectrum, the signal at 291. 2328 is an accurate mass of THF-BHT trapped product **43** (**Figure 6**).

The EPR experiments have been carried out on a frozen aliquot of the incomplete reaction mixture of **35a'** (0.36 mmol), 2a (3.6 mmol), K_2S_2O8 (1.08 mmol), TBACl (1.08 mmol, 50% in aq. soln.), NaOAc (1.08 mmol) in THF suggested the presence of a carbon-centric organic radical, as shown in fig. 3. The *g*-factor of the crossover point of the peak was found to be 2.003 (**Figure 7**).

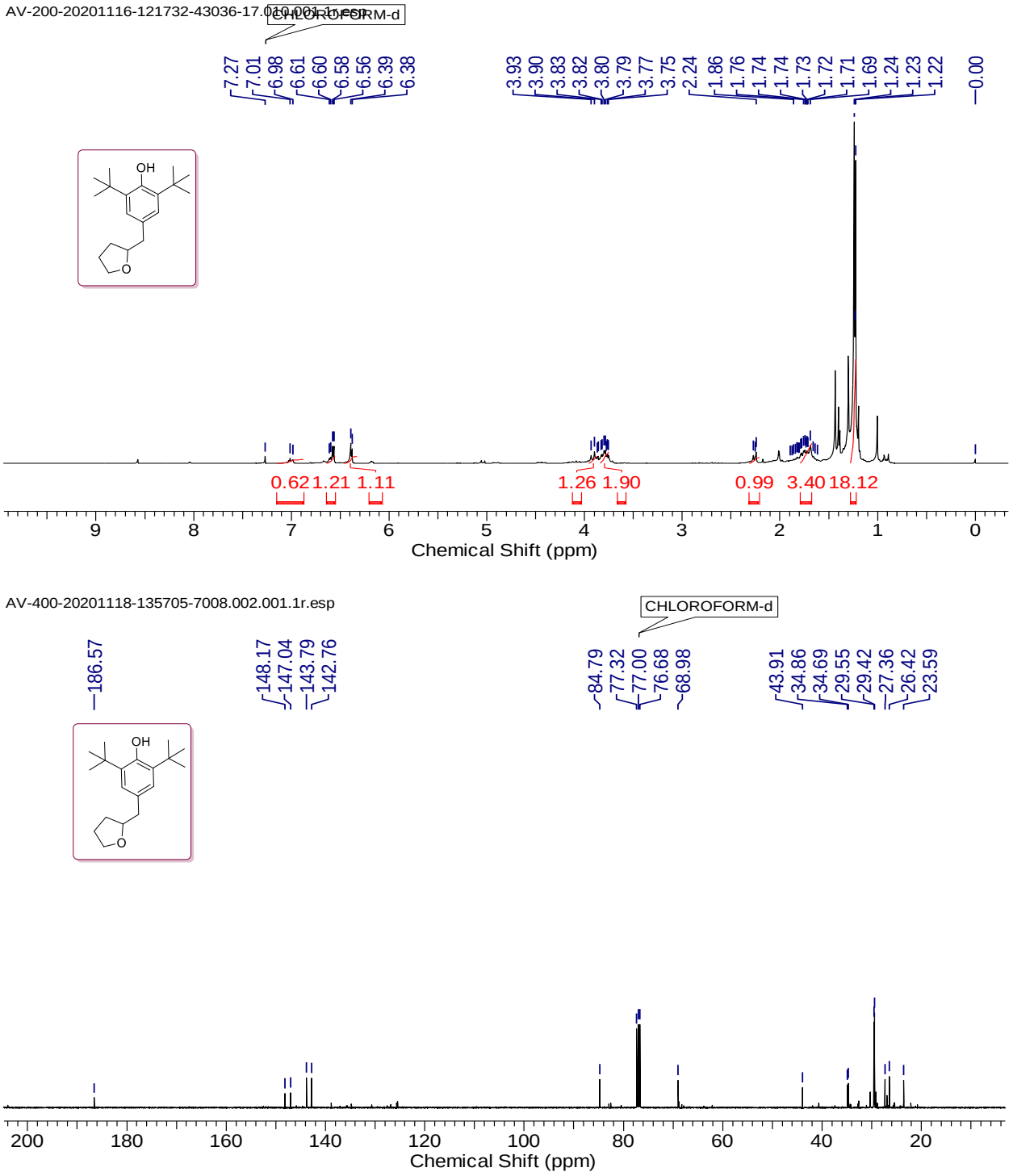


Figure 5: ^{1}H and ^{13}C $\{^{1}H\}$ NMR of BHT-THF Trapped Product **(8)**

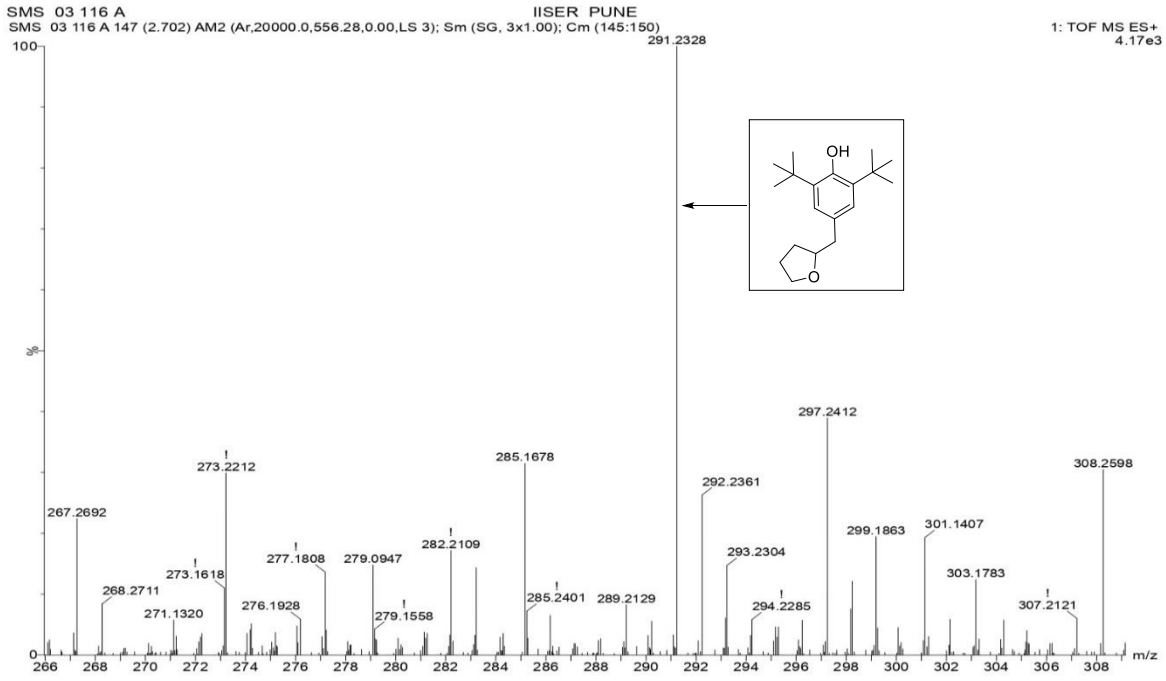


Figure 6: HRMS of BHT-THF Trapped Product **(8)**

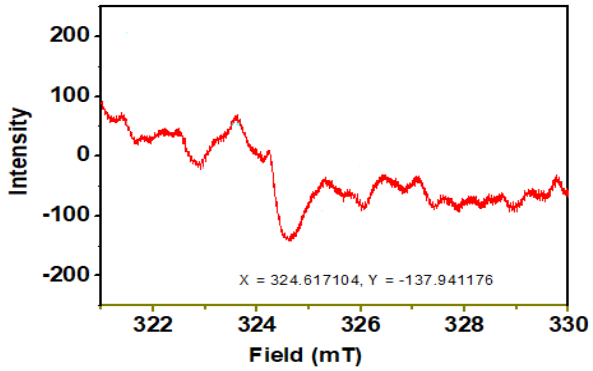
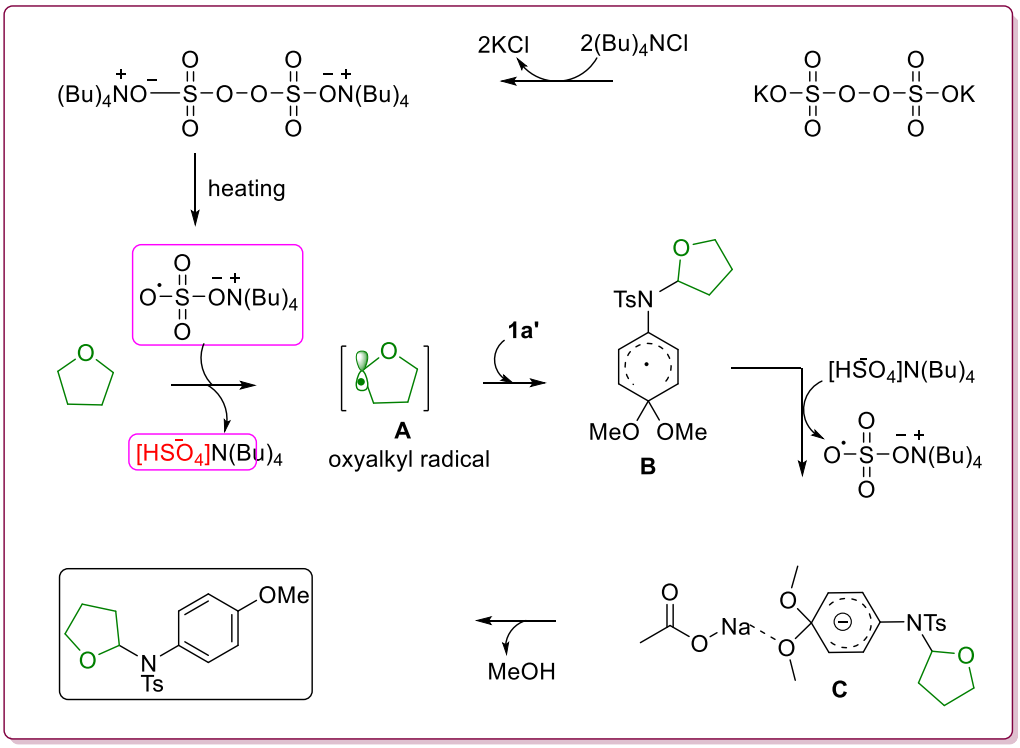


Figure 7: EPR spectrum of an incomplete reaction mixture

Based on literature reports,[37] control experiments, and an EPR study, we believe that the reaction mechanism proceeds *via* radical pathway. The reaction starts with homolytic cleavage of persulfate under thermal conditions in the presence of tetrabutylammonium chloride[38] to form the sulfate radical anion, as shown in **scheme 10**.



Scheme 10: Plausible Reaction Mechanism

The formed sulfate radical anion abstracts a proton from *α*-position to the oxygen of ether and generates *α*-oxyalkyl radical **A** as a reactive intermediate. The reactive radical intermediate **A** undergoes C-N addition through the nitrogen atom of QIK **35a'** to form a C-N bond and the intermediate **B**. Further, the presence of hydrogen sulfate anion leads to the formation of intermediate **C** through single electron transfer (SET)**.**[38a] Then, the intermediate **C** undergoes *O*-chelation with NaOAc,[35a-b] followed by elimination of MeOH, which leads to the formation of desired product **38a**.

2.2.5. Conclusion

In conclusion, the study established an efficient metal-free approach for synthesizing hemiaminals from QIK and various ethers. Further, this strategy highlights the optimized reaction conditions to obtain the desired products in good to excellent yields. It shows the broad

substrate scope and high functional group tolerance with hemiaminals. Also, the formation of α-oxyalkyl radical in the reaction was confirmed by radical scavenger experiments, and the EPR spectroscopy experiment confirmed the C-centered radical.

2.2.6. Experimental Section

2.2.6.1 General Procedure for the Synthesis of *N*-substituted hemiaminals (38a-38t)

In a 25 ml round bottom flask, *N*-substituted *p*-anisidine (**35**) (100 mg, 0.36 mmol, 1 equiv.) was taken in MeOH (3 mL). To this, diacetoxyiodobenzene (PIDA) (0.39 mmol, 1.1 equiv.) was added in portions at 0°C, and the reaction slowly brought to r.t. The progress of the reaction was monitored by the TLC. After completion of the reaction, MeOH was evaporated on a rotary evaporator under reduced pressure. The obtained residue was dissolved in corresponding ether (3.6 mmol, 3 mL) and was added $K_2S_2O_8$ (1.08 mmol, 3 equiv.), Sodium acetate (1.08 mmol, 3 equiv.), and TBACl.H_2O (1.08 mmol, 3 equiv.) sequentially to the reaction mixture. Then the reaction mixture was refluxed in a preheated oil bath at 90 °C for 4h with continuous monitoring of the reaction with TLC. After completion of the reaction, the resulting reaction mixture was cooled to room temperature and concentrated in vacuo. The formed residue was extracted with ethyl acetate (3×3mL) and washed with brine (10 mL). Then combined organic phase dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified on flash chromatography (silica gel 100-200 mesh) using pet ether/ethyl acetate (v/v, 8/2) to afford the corresponding aryl hemiaminals with good to the excellent yield of the desired product.

2.2.6.2 General Experimental procedure for the synthesis of Aryl substituted hemiaminals (40a-40i)

In a 25 ml round bottom flask, Aryl substituted *p*-anisidine (**39**) (100 mg, 0.36 mmol, 1 equiv.) was taken in MeOH (3 mL). To this, diacetoxyiodobenzene (PIDA) (0.39 mmol, 1.1 equiv.) was

added in portions at 0 ^{o}C and brought the reaction mixture to room temperature. The reaction progress was monitored by the TLC. After completion of the reaction, MeOH was evaporated on a rotary evaporator under reduced pressure. Then the residue was dissolved in corresponding ether (3.6 mmol, 3 mL) and followed by sequential addition of $K_2S_2O_8$ (1.08 mmol, 3 equiv.), sodium acetate (1.08 mmol, 3 equiv.), and TBACl.H_2O. The reaction mixture was refluxed a in preheated oil bath at 90 ^{o}C for 4h. After completion of the reaction (with TLC monitoring), the resulting reaction mixture was cooled to room temperature and concentrated in vacuo. The formed residue was extracted with ethyl acetate (3×3 mL) and washed with brine (10 ml). Then combined organic phase dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified on flash chromatography (silica gel 100-200 mesh), Pet. ether/ethyl acetate (v/v, 8/2) to afford the corresponding substituted aryl hemiaminals with good to the excellent yield of the desired product.

2.2.6.3 General Experimental Procedure for Synthetic Transformation of Form Product (41):

To a solution of **38a** (50 mg, 0.14 mmol) in ethanol (5 mL) was added sodium borohydride (27 mg, 0.72 mmol). The resulting suspension was stirred at room temperature for 36 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate = 6:4) to afford **41** (36 mg, 73%).

2..2.6.4. General Procedure for Gram-Scale Synthesis of *N*-(4-methoxyphenyl)-4-methyl-*N*-(tetrahydrofuran-2-yl) benzenesulfonamide (38a)

In 100 ml round bottom flask, *N*-substituted *p*-anisidine (**35a**) (0.800 gm, 2.89 mmol, 1 equiv.) was taken in MeOH (30 mL). To this, diacetoxyiodobenzene (PIDA) (3.17 mmol, 1.1 equiv.) was added in portions at 0 $^{\circ}$C, and the reaction slowly brought to r.t. The progress of the reaction

was monitored by the TLC. After completion of the reaction, MeOH was evaporated on a rotary evaporator under reduced pressure. The obtained residue was dissolved in THF (28.9 mmol, 25 mL) and was added $K_2S_2O_8$ (8.66 mmol, 3 equiv.), Sodium acetate (8.66 mmol, 3 equiv.), and TBACl.H_2O (8.66 mmol, 3 equiv.) sequentially to the reaction mixture. Then the reaction mixture was refluxed in a preheated oil bath at 90 ^oC for 6h with continuous monitoring of the reaction with TLC. After completion of the reaction, the resulting reaction mixture was cooled to room temperature and concentrated in vacuo. The formed residue was extracted with ethyl acetate (30 × 3 mL) and washed with brine (20 mL). Then combined organic phase dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified on flash chromatography (silica gel 100-200 mesh) using pet ether/ethyl acetate (v/v, 8/2) to afford **(38a)** (0.840 gm, 84%) as a colorless oil.

2.2.6.4 General Experimental Procedure for Tempo-THF Trapped Product (42):

A 25 ml round bottom flask containing *N*-Tosyl *p*-anisidine **35a** (100mg, 0.36 mmol, 1 equiv.) was taken in MeOH (3 mL). To this reaction mixture, diacetoxyiodobenzene (PIDA) (0.39, 1.1 equiv.) was added in portions at 0^oC, and the reaction mixture was allowed to stir at room temperature. The reaction was monitored by the TLC. After completion of the reaction, MeOH was evaporated under reduced pressure, and the residue was dissolved in THF (3.6 mmol, 3 mL). To this added sequentially $K_2S_2O_8$ (1.08 mmol, 3 equiv.), sodium acetate (1.08 mmol, 3 equiv.), TBACl.H_2O (1.08 mmol, 3 equiv.) and (2,2,6,6-Tetramethylpiperidin-1-yl) oxyl (TEMPO) (0.36 mmol). Then the reaction mixture was refluxed at 90^oC in an oil bath for 4h. The expected trapped product was detected by the LC-MS of the crude reaction mixture. LCMS (ESI) m/z: 228.1

2.2.6.5 General Experimental Procedure for BHT-THF Trapped Product (43):

A 25 ml round bottom flask containing *N*-Tosyl *p*-anisidine **35a** (100 mg, 0.36 mmol, 1 equiv.) was taken in MeOH (3 mL). To this reaction mixture, diacetoxyiodobenzene (PIDA) (0.39, 1.1 equiv.) was added in portions at 0 ^{o}C, allowing the reaction mixture to stir at room temperature. The reaction was monitored by the TLC. After completion of the reaction, MeOH was evaporated under reduced pressure. Then the residue was dissolved in THF (3.6 mmol, 3 mL). To this added $K_2S_2O_8$ (1.08 mmol, 3 equiv.), sodium acetate (1.08 mmol, 3 equiv.), TBACl. H_2O (1.08 mmol, 3 equiv.) and butylated hydroxytoluene (BHT) (0.36 mmol) sequentially. Then the reaction mixture was refluxed at 90 ^{o}C in an oil bath for 4 h. The reaction was monitored by the TLC; after completion of the reaction resulting mixture cooled to room temperature and concentrated in vacuo. The formed residue was extracted with ethyl acetate (3×3 mL) and washed with brine (20 mL). Then combined organic phase dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified on flash chromatography (silica gel 100-200 mesh), pet. ether/ethyl acetate (v/v, 9/1) to afford BHT- THF trapped product (**43**) in 52% yield.

2.2.6.6 Procedure for EPR Measurement Representative Procedure:

A 25 ml round bottom flask containing *N*-tosyl substituted *p*- anisidine (**35a**) (100 mg, 0.36 mmol, 1 equiv.) was taken in MeOH (3 mL). To this, diacetoxyiodobenzene (PIDA) (0.39 mmol, 1.1 equiv.) was added in portions at 0 ^{o}C, allowing the reaction mixture to stir at room temperature with continuous monitoring by TLC. After completion of the reaction, MeOH was evaporated under reduced pressure. Then the residue was dissolved in THF (3.6 mmol, 3 mL). To this sequential addition of $K_2S_2O_8$ (1.08 mmol, 3 equiv.), sodium acetate (1.08 mmol, 3 equiv.), and TBACl.H_2O (1.08 mmol, 3 equiv.) was done. The reaction mixture was refluxed at 90 ^{o}C in preheated oil bath and stirred for 2 hrs. At ambient temperature, the reaction tube was

transferred to the glove box, and an aliquot of the reaction mixture was transferred to an EPR tube and frozen at 100 K, then subjected to EPR measurement.

***N*-(4-methoxyphenyl)-4-methyl-N-(tetrahydrofuran-2-yl) benzenesulfonamide (38a)**

Yield: 91%, (102 mg) ; Colorless oil; **IR** (Neat, cm^{-1}): υ_{max} 3260.86, 2921.03, 1599.74, 1503.36, 1454.01, 1398.64, 1335.57, 1293.49, 1245.15, 1156.20, 1086.95, 1026.05, 806.10, 663.20, 548.48;**^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.6 (d, J = 8.27 Hz, 2H), 7.2 (d, J = 8.05 Hz, 2H), 7.0-7.1 (m, 2H), 6.8 (m, J = 9.04 Hz, 2H), 6.2 (dd, J = 7.28, 4.96 Hz, 1H), 3.8 (s, 3H), 3.6 - 3.7 (m, 2H), 2.4 (s, 3H), 2.0-2.2 (m, 1H), 1.6 - 1.8 (m, 2H), 1.2-1.4 (m, 1H) ; **^{13}C{^{1}H} NMR** (101 MHz,$CDCl_3$) δ : 159.6, 143.1,133.2, 129.1, 128.1, 127.7, 113.9, 89.3, 68.3, 55.3, 30.3, 24.6, 21.5; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{22}O_4NS$ 348.1264; found348.1264.

***N*-(4-methoxyphenyl)-4-methyl-N-(tetrahydro-2H-pyran-2-yl) benzenesulfonamide (38b)**

Yield: 86% (101 mg); Yellow oil; **IR** (Neat, cm^{-1}): υ_{max} 2918.84, 2839.67, 1602.13, 1447.99, 1328.24, 1244.76, 1158.20, 1115.06, 1009.8, 929.16, 802.62, 650.55, 582.93, 544.44; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.6 (m, J = 8.38 Hz, 2H); 7.2 (m, J = 8.16 Hz, 2H), 7.0-7.1 (m, 2H), 6.7 - 6.8 (m, 2H), 5.5 (dd, J = 10.80, 1.87 Hz, 1H), 3.9 (dt, J = 11.47, 2.09 Hz, 1H), 3.8 (s, 3H), 3.6 (td, J = 11.60, 2.81 Hz, 1H), 2.4 (s, 3H), 1.7-1.8 (m, 1H), 1.5-1.6 (m, 2H), 1.2-1.4 (m, 2H), 0.9-1.1 (m, 1H); **^{13}C{^{1}H} NMR** (50MHz,$CDCl_3$) δ: 159.4, 143, 136.9, 132.8, 128.8, 128.4, 113.6, 86.6, 67.7, 55.3, 30.4, 24.8, 23.4, 21.5; **HRMS** (ESI) *m/z*:$[M+H]^+$ calcd. for $C_{19}H_{24}O_4NS$ 362.1421; found 362.1421.

***N*-(1,4-dioxan-2-yl)-N-(4-methoxyphenyl)-4-methylbenzenesulfonamide (38c)**

Yield: 81% (95 mg); Colorless oil; **IR** (Neat, cm^{-1}): υ_{max} 2916.71, 2851.54, 1724.14, 1599.20, 1455.71, 1390.79, 1329.91, 1156.79, 1110.03, 1026.52, 876.48, 811.73, 664.00, 545.88; **^{1}H NMR** (200 MHz, $CDCl_3$) δ : 7.5-7.8 (m, 2H), 7.2-7.4 (m, 3H), 6.9-7.2 (m, 2H), 6.7 (d, J = 8.49

Hz, 1H), 4.9 (dd, *J* = 9.70, 2.32 Hz, 1H), 3.9 (d, *J* = 7.50 Hz, 4H), 3.7-3.8 (m, 3H), 3.5-3.7 (m, 1H), 3.1 (d, *J* = 10.58 Hz, 1H), 2.4 (s, 3H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$) *δ*: 153.8, 143.3, 135.9, 129.3, 129.2, 127.3, 127.2, 123.6, 122.4, 110.4, 72.0, 70.9, 67.0, 66.2, 55.3, 21.3**; HRMS** (ESI) *m/z*: $[M+Na]^+$calcd. for $C_{16}H_{22}O_5NNaS$ 363.1111, found 363.1113.

***N*-(1,2-dimethoxyethyl)-N-(4-methoxyphenyl)-4-methylbenzenesulfonamide(38d)**

Yield: 83% (98 mg); Colorless oil; **IR** (Neat, cm^{-1}): υ_{max} 2934.06, 1729.54, 1596.96, 1509.87, 1457.27, 1328.24, 1233.26, 1157.80, 1023.74, 811.01, 766.81, 659.03; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ*: 7.60 (m, *J* = 8.25 Hz, 2H),7.22 (m, *J* = 8.25 Hz, 2H), 6.88-6.94 (m, 2H), 6.79 (m, *J* = 8.88 Hz, 2H), 5.57 (dd, *J* = 7.63, 5.25 Hz, 1H), 3.79 (s, 3H), 3.58 (s, 3H), 3.27 (s, 3H), 3.22-3.26 (m, 1H), 3.03 (dd, *J* = 10.26, 7.63 Hz, 1H), 2.42 (s, 3H); **$^{13}C\{^{1}H\}$ NMR** (200 MHz, $CDCl_3$) *δ*: 159.7, 143.2, 137.3, 133.1, 129.0, 128.0, 126.2, 113.9, 87.6, 71.4, 58.6, 56.3, 55.3, 21.5; **HRMS** (ESI) *m/z*: $[M+Na]^+$calcd. for $C_{18}H_{23}O_5NNaS$ 388.1189, found 388.1185.

***N*-(4-methoxyphenyl)-N-(tetrahydrofuran-2-yl) methanesulfonamide(38e)**

Yield: 87% (102 mg); Yellow oil; **IR** (Neat, cm^{-1}): υ_{max} 2941.05, 2872.83, 1608.82, 1493.80, 1392.23, 1317.99, 1249.31, 1145.09, 1029.90, 970.85, 905.61, 761.75, 630.54, 504.64; **^{1}H NMR** (200 MHz, $CDCl_3$) *δ*: 7.2-7.3 (m, 2H), 6.7-6.9 (m, 2H), 5.1 (t, *J* = 6.95 Hz, 1H), 4.1 (q, *J* = 6.84 Hz, 1H), 3.9 (d, *J* = 7.83 Hz, 1H), 3.8 (s, 3H), 2.3-2.5 (m, 1H), 2.9 (s, 3H), 1.5-1.7 (m, 1H), 1.8-2.0 (m, 3H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz,$CDCl_3$) *δ*: 159.9, 132.4, 128.3, 114.4, 89.3, 68.2, 55.4, 39.5, 29.5, 24.7; **HRMS** (ESI) *m/z:*$[M+Na]^+$calcd. for $C_{12}H_{17}O_4NNaS$ 294.0770, found 294.0769.

***N*-(4-methoxyphenyl)-N-(tetrahydro-2H-pyran-2-yl) methane sulfonamide (38f)**

Yield: 79%, 97 mg; Colorless gum; **IR** (Neat, cm^{-1}): υ_{max} 2923.99, 2862.05, 1733.75, 1602.38, 1504.09, 1380.07, 1333.33, 1230.03, 1155.54, 1067.57, 1025.77, 970.84, 733.94, 701.37, 646.82,

592.54; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.4 (m, *J* = 8.55 Hz, 2H), 6.9 (m, *J* = 9.16 Hz, 2H), 5.2-5.3 (m, 1H), 4.0-4.1 (m, 1H), 3.8 (s, 3H), 3.6 (td, *J* = 11.75, 2.75 Hz, 1H), 3.0 (s, 3H), 1.7-1.8 (m, 2H),1.5-1.6 (m, 4H), 1.3-1.4 (m, 1H), 1.0-1.2 (m, 1H); **^{13}C{^{1}H} NMR** (101 MHz,$CDCl_3$) δ: 23.2, 24.9, 29.8, 39.7, 55.3, 67.9, 86.8, 114.0, 128.8, 132.0, 159.6; **HRMS** (ESI) *m/z:* $[M+H]^+$ calcd. for $C_{13}H_{20}O_4NS$ 286.1108, found 286.1107.

***N*-(1,4-dioxan-2-yl)-N-(4-methoxyphenyl) methane sulfonamide (38g)**

Yield: 72% (89 mg); Brown gel; **IR** (Neat, cm^{-1}): υ_{max} 2923.04, 2853.55, 1730.61, 1606.07, 1498.92, 1461.71, 1384.69, 1324.63, 1249.97, 1152.20, 1112.87, 1033.17, 971.80, 877.20, 815.13, 731.59, 523.14; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.29 (br. s., 1 H), 7.24 (s, 1 H), 6.84 (d, *J* = 8.60 Hz, 2 H), 4.93 - 5.00 (m, 1 H), 3.91 - 4.01 (m, 4 H), 3.83 (s, 4 H), 3.72 - 3.79 (m, 2 H), 3.24 (dd, *J* = 11.19, 9.87 Hz, 1 H), 2.96 (s, 3 H); **^{13}C {^{1}H}NMR** (101MHz, $CDCl_3$) δ: 154.3, 129.3, 128.1, 123.5, 121.9, 110.9, 72.5, 71.2, 67.3, 66.4, 55.6, 38.9; **HRMS** (ESI) *m/z*: $[M+Na]^+$calcd. for $C_{12}H_{17}O_5NNaS$ 310.0720, found 310.0707.

***N*-(1,2-dimethoxyethyl)-N-(4-methoxyphenyl) methane sulfonamide (38h)**

Yield: 76% (95 mg); Brown gel; **IR** (Neat, cm^{-1}): υ_{max} 2911.75, 2851.32, 1725.48, 1598.80, 1496.93, 1449.15, 1396.39, 1330.25, 1156.96, 1110.11, 1026.59, 877.0, 811.87, 663.75, 546.49; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.2-7.3 (m, 2H), 6.9-7.0 (m, 2H), 5.4 (dd, *J* = 8.60, 4.52 Hz, 1H), 3.8-3.9 (m, 3H), 3.5-3.6 (m, 3H), 3.4-3.4 (m, 3H), 3.3-3.3 (m, 1H), 3.1-3.2 (m, 1H), 3.0-3.1 (m, 3H); **^{13}C{^{1}H}NMR** (101 MHz,$CDCl_3$) δ: 40.3, 55.4, 55.5, 56.0, 58.7, 70.9, 87.6, 114.4, 114.7, 124.8, 126.3, 132.5, 159.9; **HRMS** (ESI) *m/z*: $[M+Na]^+$calcd. for $C_{12}H_{19}O_5NNaS$ 312.0876, found 312.0865.

***N*-(4-methoxyphenyl)-N-(tetrahydrofuran-2-yl)benzenesulfonamide (38i)**

Yield: 90% (102 mg); Colorless solid; **IR** (Neat, cm^{-1}): υ_{max} 2943.06, 2842.62, 1602.44, 1504.45, 1340.73, 1297.34, 1160.67, 1083.96, 1028.18, 932.47, 888.19, 719.68, 682.03, 637.91; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.8 - 8.0 (m, 1H),7.7 - 7.8 (m, 1H), 7.4 - 7.6 (m, 3H), 6.9 - 7.0 (m, 2H), 6.7 - 6.8 (m, 2H), 6.3 (dd, *J* = 7.22, 4.91 Hz, 1H), 3.7 - 3.8 (m, 3H), 3.5 - 3.7 (m, 2H), 2.0 - 2.3 (m, 1H), 1.5 - 1.8 (m, 2H), 1.2 - 1.3 (m, 1H); **^{13}C{^{1}H}NMR** (101 MHz,$CDCl_3$) δ: 159.7, 139.7, 133.1, 132.4, 128.9, 128.4, 128.1, 127.4, 113.9, 89.3, 68.4, 55.3, 30.3, 24.6; **HRMS** (ESI) *m/z*: $[M+H]^+$calcd. for $C_{17}H_{20}O_4NS$ 334.1108, found 334.1110.

***N*-(4-methoxyphenyl)-N-(tetrahydro-2H-pyran-2-yl) benzenesulfonamide (38j)**

Yield: 85% (100 mg); Brown solid; **IR** (Neat, cm^{-1}): υ_{max} 2939.17, 2842.81, 1731.43, 1601.18, 1504.68, 1445.21, 1298.68, 1212.62, 1161.25, 1083.18, 1030.22, 936.38, 887.55, 800.82, 719.11, 682.35, 637.54, 543.78; **^{1}H NMR** (200 MHz, $CDCl_3$) δ:7.7-7.7 (m, 2H), 7.3-7.6 (m, 3H),7.0-7.1 (m, 2H), 6.7-6.8 (m, 2H), 5.5 (dd, *J* = 10.75, 1.93 Hz, 1H), 3.9-4.0 (m, 1H), 3.7-3.9 (m, 3H), 3.6 (td, *J* = 11.60, 2.92 Hz, 1H), 1.5-1.7 (m, 3H), 1.3-1.4 (m, 1H), 0.9-1.2 (m, 1H), 0.8-0.9 (m, 1H); **^{13}C{^{1}H}NMR** (101 MHz,$CDCl_3$) δ: 159.4, 139.7, 137.4, 132.7, 132.3, 130.2, 128.3, 128.1, 113.6, 86.5, 67.6, 55.2, 30.3, 24.8, 23.4; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{22}O_4NS$ 348.1264, found 348.1263.

***N*-(1,4-dioxan-2-yl)-N-(4-methoxyphenyl) benzenesulfonamide (38k)**

Yield: 82% (97 mg); Yellow gel; **IR** (Neat, cm^{-1}): υ_{max} 2960.91, 2851.72, 1610.36, 1498.21, 1393.38, 1326.26, 1157.11, 1100.23, 1026.85, 877.13, 814.69, 686.24, 630.10, 575.79; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.6-7.8 (m, 2H), 7.4-7.6 (m, 3 H), 7.0-7.1 (m, 2H), 6.9 (s, 1H), 6.7-6.8 (m, 1H), 4.9 (dd, *J* = 9.70, 2.54 Hz, 1H), 3.8-3.9 (m, 4H), 3.7-3.8 (m, 4H), 3.6-3.7 (m, 1H), 3.0-3.1 (m, 1H); **^{13}C{^{1}H}NMR** (101 MHz,$CDCl_3$) δ: 154.2, 138.9, 132.7, 129.1, 128.9, 128.8, 127.6,

127.3, 126.3, 124.3, 122.9, 110.6, 72.1, 71.1, 67.1, 66.3, 55.5; **HRMS** (ESI) *m/z:* $[M+H]^+$ calcd. for $C_{17}H_{20}O_5NS$ 350.1057, found 350.1054.

***N*-(1,2-dimethoxyethyl)-N-(4-methoxyphenyl) benzenesulfonamide (38l)**

Yield: 88% (105 mg); Yellow gel; **IR** (Neat, cm^{-1}): υ_{max} 2934.34, 2836.40, 1605.20, 1505.83, 1448.01, 1335.99, 1247.04, 1161.87, 1111.72, 930.61, 832.27, 801.67, 723.52, 687.51, 588.51; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.6-7.8 (m, 2H),7.4-7.6 (m, 3H), 6.9-6.9 (m, 2H), 6.7-6.8 (m, 2H), 5.6 (dd, *J* = 7.72, 5.07 Hz, 1H), 3.8 (s, 3H), 3.6 (s, 3H), 3.4-3.5 (m, 1H), 3.2 (s, 3H), 3.0-3.1 (m, 1H), **^{13}C{^{1}H}NMR** (101 MHz,$CDCl_3$) δ: 159.7, 140.1, 133.0, 132.5, 128.9, 128.3, 128.0, 125.9, 113.9, 87.7, 71.2, 58.6, 56.2, 55.3; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{17}H_{21}O_5NNaS$ 374.1033, found 374.1027.

***N*-(4-methoxyphenyl)-4-methyl-N-(5-methyltetrahydrofuran-2-yl) benzenesulfonamide (38q)**

Yield: 61% (71 mg); Yellow oil; **IR** (Neat, cm^{-1}): υ_{max} 3252.86, 2965.17, 1599.28, 1498.82, 1458.62, 1390.50, 1326.19, 1246.20, 1154.71, 1088.08, 1027.28, 908.86, 812.33, 664.01; **^{1}H NMR** (200 MHz, $CDCl_3$) δ : 7.55-7.63 (m, 3H), 7.21 (d, *J* = 7.94 Hz, 3H), 6.88-7.04 (m, 2H), 6.67-6.79 (m, 2H), 5.17 (t, *J* = 6.84 Hz, 1H), 3.97-4.18 (m, 1H), 3.76 - 3.79 (m, 3H), 3.23-3.50 (m, 1H), 2.38 (s, 4H), 1.86-2.03 (m, 2H), 1.48-1.59 (m, 2H), 1.24-1.28 (m, 3H); **^{13}C{^{1}H}NMR** (126 MHz, $CDCl_3$) δ : 154.5, 154.3, 143.6, 143.5, 136.3, 136.1, 133.7, 133.5, 129.7, 129.4, 127.5, 127.3, 126.5, 125.5, 123.6, 123.5, 122.0, 121.6, 116.2, 114.4, 110.7, 110.6, 85.0, 84.9, 75.6, 75.3, 55.5, 33.7, 33.7, 33.3, 33.2, 21.5, 21.4, 20.9, 20.7; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{24}O_4N_S$ 362.1421 found 362.1423.

***N*-(4-methoxyphenyl)-4-methyl-N-(tetrahydrothiophen-2-yl) benzenesulfonamide (38r):**

Yield: 86% (101 mg); Yellow oil; **IR** (Neat, cm^{-1}): υ_{max} 3264.19, 2938.07, 1731.05, 1597.31,

1486.58, 1381.98, 1331.83, 1279.66, 1159.27, 1090.24, 1035.21, 907.97, 868.80, 813.00, 728.04, 663.64, 605.93; **^{1}H NMR** (200 MHz, $CDCl_3$) δ :7.50-7.68 (m, 3H), 7.14-7.35 (m, 3H), 6.72-6.90 (m, 2H), 3.75 (s, 3H), 3.44-3.50 (m, 1H), 2.50 (t, *J* =7.22 Hz, 2H), 2.36 (s, 3H), 1.71-1.83 (m, 2H), 1.51-1.67 (m, 2 H); **^{13}C{^{1}H}NMR** (101 MHz, $CDCl_3$) δ : 156.7, 143.8, 136.1, 130.7, 129.5, 127.7, 127.2, 123.1, 118.8, 114.4, 55.4, 44.1, 34.9, 31.2, 26.3, 21.4; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{22}O_3NS_2$ 364.1036 found 364.1038.

***N*-(3,4-dimethoxyphenyl)-4-methyl-N-(tetrahydrofuran-2-yl) benzenesulfonamide (40a)**

Yield: 76% (85 mg); Colourless oil; **IR** (Neat, cm^{-1}): υ_{max} 2923.73, 2851.71, 1710.65, 1597.57, 1510.78, 1457.04, 1394.28, 1332.61, 1233.39, 1157.39, 1089.15, 1022.84, 968.78, 895.01, 810.78, 758.46, 663.25, 545.81; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.6 (m, *J* = 8.27 Hz, 2H), 7.2 (m, *J* = 8.05 Hz, 2H), 6.6-6.8 (m, 2H), 6.5-6.6 (m, 1H), 6.2 (dd, *J* = 7.11, 5.02 Hz, 1H), 3.8-3.9 (m, 3H), 3.5-3.7 (m, 5H), 2.4 (s, 3H), 2.0-2.2(m, 1H), 1.6-1.8 (m, 2H), 1.1-1.3 (m, 2H); **^{13}C{^{1}H}NMR** (101 MHz,$CDCl_3$) δ: 149.2, 136.7, 129.3, 128.9, 128.2, 127.2, 124.7, 115.1, 111.1, 110.3, 107.6, 89.3, 68.3, 55.7, 30.1, 24.5, 21.4; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{24}O_5NS$ 378.1370, found 378.1368.

***N*-(3,4-dimethoxyphenyl)-4-methyl-N-(tetrahydro-2H-pyran-2yl) benzenesulfonamide (40b)**

Yield: 68% (78 mg); White solid; **IR** (Neat, cm^{-1}): υ_{max} 2934.48, 2849.25, 1595.91, 1509.69, 1454.39, 1413.19, 1343.58, 1264.40, 1231.49, 1098.97, 1021.05, 959.50, 926.46, 880.71, 820.25, 766.78, 547.19; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.6 (m, *J* = 8.24 Hz, 2H), 7.2 (m, *J* = 7.79 Hz, 2H), 6.8 (d, *J* = 2.29 Hz, 1H), 6.5 (d, *J* = 2.75 Hz, 1H), 4.6 (dd, *J* = 10.99, 1.83 Hz, 1H), 4.1 (dt, *J* = 11.22, 1.95 Hz, 1H), 3.8 (s, 6H), 3.5 - 3.7 (m, 1H), 2.4 (s, 3H), 1.8 - 1.9 (m, 2H), 1.6 - 1.7 (m, 4H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ: 152.6, 143.6, 143.0, 137.4, 136.1, 132.6, 129.5,

127.3, 112.1, 105.8, 74.2, 68.9, 60.9, 55.8, 33.4, 25.8, 23.9, 21.5; **HRMS** (ESI) *m/z*: $[M+H]^+$calcd. for $C_{20}H_{26}O_5NS$ 392.1527 found 392.1535.

***N*-(3,4-dimethoxyphenyl)-N-(1,4-dioxan-2-yl)-4-methylbenzenesulfonamide (40c)**

Yield: 62% (72 mg); Yellow oil; **IR** (Neat, cm^{-1}): υ_{max} 2930.57, 2849.03, 1689.02, 1595.76, 1509.28, 1453.68, 1343.04, 1230.43, 1161.85, 1097.85, 1020.84, 958.91, 925.35, 879.75, 765.86, 705.17, 545.41; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.6 (d, *J* = 8.16 Hz, 2H),7.2 (d, *J* = 8.05 Hz, 2H), 6.6 (s, 1H), 6.7-6.8 (m, 2H), 5.7 (dd, *J* = 9.65, 2.48 Hz, 1H), 3.8-4.0 (m, 6H), 3.7-3.8 (m, 1H),3.7 (s, 4H), 3.5-3.6 (m, 1H), 3.2-3.4 (m, 1H), 3.0 (t, *J* = 10.36 Hz, 1H), 2.4 (s, 4H); **^{13}C{^{1}H}NMR** (101 MHz, $CDCl_3$) δ: 149.4, 148.4, 143.5, 136.4, 129.0, 128.5, 127.8, 124.0, 114.7, 110.3, 82.6, 68.8, 66.7, 65.5, 55.8, 21.5; **HRMS** (ESI) *m/z*: $[M+H]^+$calcd. for $C_{19}H_{24}O_6NS$ 394.1319, found 394.1317.

***N*-(1,2-dimethoxyethyl)-N-(3,4-dimethoxyphenyl)-4-methylbenzenesulfonamide (40d)**

Yield: 66% (77 mg); Colorless gel; **IR** (Neat, cm^{-1}): υ_{max} 2933.16, 1731.93, 1594.54, 1507.39, 1456.93, 1326.94, 1232.44, 1024.17, 929.37, 848.64, 811.75, 764.93, 657.7; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.6 (d, *J* = 7.83 Hz, 2H), 7.2 (br. s., 2H), 6.7 (d, *J* = 8.49 Hz, 1H), 6.5 - 6.6 (m, 1H), 6.4 (s, 1H), 5.5 - 5.6 (m, 1H), 3.8 (s, 3H), 3.6 (s, 3H), 3.4 (d, *J* = 8.16 Hz, 1H), 3.2 - 3.3 (m, 4H), 2.9 - 3.1 (m, 1H), 2.4 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ: 149.3, 148.4, 143.2, 137.2, 128.9, 128.2, 126.2, 124.6, 114.9, 110.4, 87.7, 71.2, 58.5, 56.2, 55.8, 55.6, 21.5; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{19}H_{25}O_6NNaS$ 418.1295, found 418.1282.

***N*-(4-methoxy-3-tosylphenyl)-N-(tetrahydrofuran-2-yl) methanesulfonamide (40e)**

Yield: 58% (52 mg); Yellow gum; **IR** (Neat, cm^{-1}): υ_{max} 2962.43, 2876.69, 1721.12, 1464.93, 1379.94, 1241.95, 1152.19, 1039.08, 881.21, 814.74, 563.64, 527.65; **^{1}H NMR** (200 MHz, $CDCl_3$) δ : 7.49-7.74 (m, 3H), 7.03-7.46 (m, 3H), 6.79 (d, *J* = 8.82 Hz, 1H), 5.33 (td, *J* = 6.39,

3.09 Hz, 1H), 3.79-3.91 (m, 2H), 3.60-3.76 (m, 3H), 3.07 (s, 3H), 2.39 (s, 3H), 2.13-2.28 (m, 1H), 1.81-1.98 (m, 3H); **$^{13}C\{^{1}H\}$NMR** (101 MHz, $CDCl_3$) δ : 154.7, 144.1, 137.7, 135.5, 129.6, 129.1, 128.3, 127.3, 124.1, 113.3, 84.9, 67.1,56.0, 42.7, 32.0, 24.1, 21.5; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{24}O_6NS_2$ 426.1040 found 426.1034.

***N*-(3-bromo-4-methoxyphenyl)-4-methyl-N-(tetrahydrofuran-2- benzenesulfonamide (40f)**

Yield: 76% (83 mg); Colorless solid; **IR** (Neat, cm^{-1}): υ_{max} 2928.69, 1584.86, 1482.75, 1353.65, 1293.36, 1248.69, 1162.08, 1020.29, 972.66, 908.92, 847.31, 810.85, 738.74, 701.23, 659.18, 542.37; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.8-7.9 (m, 1H), 7.6 (d, *J* = 7.79 Hz, 2H), 7.3 (d, *J* = 8.24 Hz, 1H), 7.2 (s, 1H), 7.3 (s, 1H), 7.1-7.2 (m, 1H), 7.0 (s, 1H), 6.1-6.2 (m, 1H), 3.9-3.9 (m, 3H), 3.6-3.7 (m, 1H), 3.5 (q, *J* = 7.17 Hz, 1H), 2.4 (s, 3H), 2.1-2.2 (m, 1H), 1.6-1.7 (m, 2H), 1.3-1.3 (m, 1H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$) δ: 143.8,136.6,136.2, 129.5, 129.3, 129.2, 128.5, 128.1, 116.2, 109.7, 90.0, 68.4, 56.7, 29.8, 24.7, 21.6; **HRMS** (ESI) *m/z*: $[M+H]^+$ calculated for $C_{18}H_{21}O_4NBrS$ 426.0369, found 426.0366.

***N*-(4-methoxy-2-methylphenyl)-4-methyl-N-(tetrahydrofuran-2-yl) benzenesulfonamide (40i):**

Yield: 78% (87 mg); Red gummy; **IR** (Neat, cm^{-1}): υ_{max} 2930.43, 2872.37, 1651.07, 1602.43, 1497.44, 1457.99, 1388.35, 1303.24, 1221.83, 1159.84, 1035.78, 898.46, 862.56, 812.01, 665.27; **^1H NMR** (400 MHz, $CDCl_3$) δ: 7.57-7.73 (m, 2H), 7.24 (dd, *J* = 8.57, 0.56 Hz, 2H), 6.81 (d, *J* = 3.00 Hz, 1H), 6.60 (d, *J* = 8.75 Hz, 1H), 6.48 (dd, *J* = 8.76, 2.75 Hz, 1 H), 6.24 (t, *J* = 6.44 Hz, 1H), 3.78 (s, 3H), 3.64 (td, *J* = 7.69, 5.25 Hz, 1H), 3.48-3.57 (m, 1 H), 2.43 (s, 3H), 2.38 (s, 3H), 1.60-1.71 (m, 2H), 1.43-1.54 (m, 1H), 1.27- .36 (m, 1H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$) δ : 159.5, 143.1, 142.5, 137.0, 132.3, 129.0, 128.5, 126.7, 115.7, 111.4, 89.7, 68.1, 55.2,

29.4, 24.9, 21.6, 19.2; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{24}O_4N_S$ 362.1421 found 362.1423.

***N*-(4-hydroxybutyl)-N-(4-methoxyphenyl)-4 methylbenzenesulfonamide (41):**

Yield: 73% (73 mg); Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ :7.47 (m, *J* = 8.25 Hz, 2H), 7.24 (m, *J* = 8.13 Hz, 2H), 6.90-6.95 (m, 2H), 6.78-6.83 (m, 2H), 3.80 (s, 3H), 3.61 (t, *J* = 6.32 Hz, 2H), 3.52 (t, *J* = 6.88 Hz, 2H), 2.42 (s, 3H), 1.57-1.66 (m, 2H), 1.44-1.53 (m, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ : 159.0, 143.2, 135.2, 131.4, 129.9, 129.3, 127.7, 114.1, 62.3, 55.4, 50.3, 29.2, 24.5, 21.5; **HRMS** (ESI) *m/z*: $[M+H]^+$ calculated for $C_{18}H_{24}O_4NS$ 350.1421 found 350.1432.

2,6-di-tert-butyl-4-((tetrahydrofuran-2-yl) methyl) phenol (43):

Yield: 52% (73 mg); Yellow liquid; **IR** (Neat, cm^{-1}): υ_{max} 3659.93, 2955.09, 2868.25, 2037.92, 1731.04, 1636.95, 1456.65, 1363.60, 1244.59, 1170.34, 1067.44, 968.77, 913.75, 880.01, 774.24, 733.12, 649.03; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.00 (d, *J* = 5.95 Hz, 1 H), 6.55-6.64 (m, 1H), 6.39 (d, *J* = 2.87 Hz, 1H), 3.86-3.96 (m, 1H), 3.75-3.84 (m, 2H), 2.21-2.32 (m, 1H), 1.67-1.79 (m, 3H), 1.22-1.28 (m, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ : 186.6, 148.2, 147.0, 143.8, 142.8, 84.8, 69.0, 43.9, 34.9, 34.7, 29.5, 29.4, 27.4, 26.4, 23.6; **HRMS** (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{31}O_2$: 291.2319, found 291.2328.

2.2.7. References

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Chapter III

Metal Free Nucleophilic Addition of *N*H- Sulfoximines on *p*-QMs and Aza-Oxyallyl Cations

1. "Metal-Free, Acid-Catalyzed 1,6-Conjugate Addition of *N*H-Sulfoximines to *para*-Quinone Methides (*p*-QMs): Accessing to Diarylmethine Imino Sulfanone." **More, S. G.;** Rupanawar B, D.; Suryavanshi, G. *J. Org. Chem.*, **2021**, *86*, 15, 10129–10139
2. "Metal-Free and Mild Synthesis of Congested *N*-Alkyl Sulfoximines with in Situ-Generated Aza oxyallyl Cations from Functionalized Alkyl Bromide" **More, S. G.**; Mane K, D.; Suryavanshi, G. *Asian J. Org. Chem.*, **2022**, e202200

3.1.1 Introduction:

Diaryl methane is interesting pharmacophore possessing a wide range of the biological spectrum. Further, sulfoximidoyl scaffolds have considerable significance in pharmaceutical and medicinal chemistry due to their unique structure.[1] In particular, sulfoximine pharmacophore is a flexible synthetic intermediate that plays a vital role in drug discovery owing to its structural diversity, hydrogen-bonding capability, high metabolic stability and interesting physicochemical properties.[2] In organic synthesis, the ingredients, natural sulfoximine derivative has been used as a key intermediate found in active pharmaceutical ingredients, natural products, crop protection, and medicinal chemistry with a wide range of biological activity.[3]

Despite these advances in *N*- alkyl sulfoximines in natural products and drug discovery, limited progress has been made towards the *N*- alkylation of sulfoximines because of their low nucleophilicity. Consequently, substantial efforts have been devoted to the synthesis of *N*-alkyl sulfoximines by various routes, including base catalyzed Michael-type additions, Eschweiler- Clark type methylations nucleophilic substitutions, and two-step acylation/reduction sequences.

Section I

Metal-Free, Acid-Catalyzed 1,6-Conjugate Addition of *N*H-Sulfoximines to *para*-Quinone Methides (*p*-QMs): Accessing to Diarylmethine Imino sulfanone.

Sulfoximine is the core structure of the natural product. Many natural and unnatural biological and chemically active compounds contain sulfoximine. For instance, sulfoximine-based rofecoxib analog (**1**), such as (COX inhibitor for both COX-1 and

COX-2 selectivity (shows inhibitory activities of 1% and 48% for COX-1 and COX-2, respectively, at 10 mm concentrations)),[4] proline-rich tyrosine kinase 2 (PYK2) inhibitor (**2**) used in the treatment of osteoporosis,[5] whereas Suloxifen (**3**) used in the polyvalent spasmolytic and antiasthmatic agent,[6] and methyl(phenyl) ((4-(3-(trifluoromethyl)-l,2,4-oxadiazol-5-yl) benzyl) imino)-λ^6 sulfanone (**4**) used as a pesticide[7] are the prominent examples for the *N*-alkyl sulfoximines (**Figure 1**). Additionally, the sulfoximines were

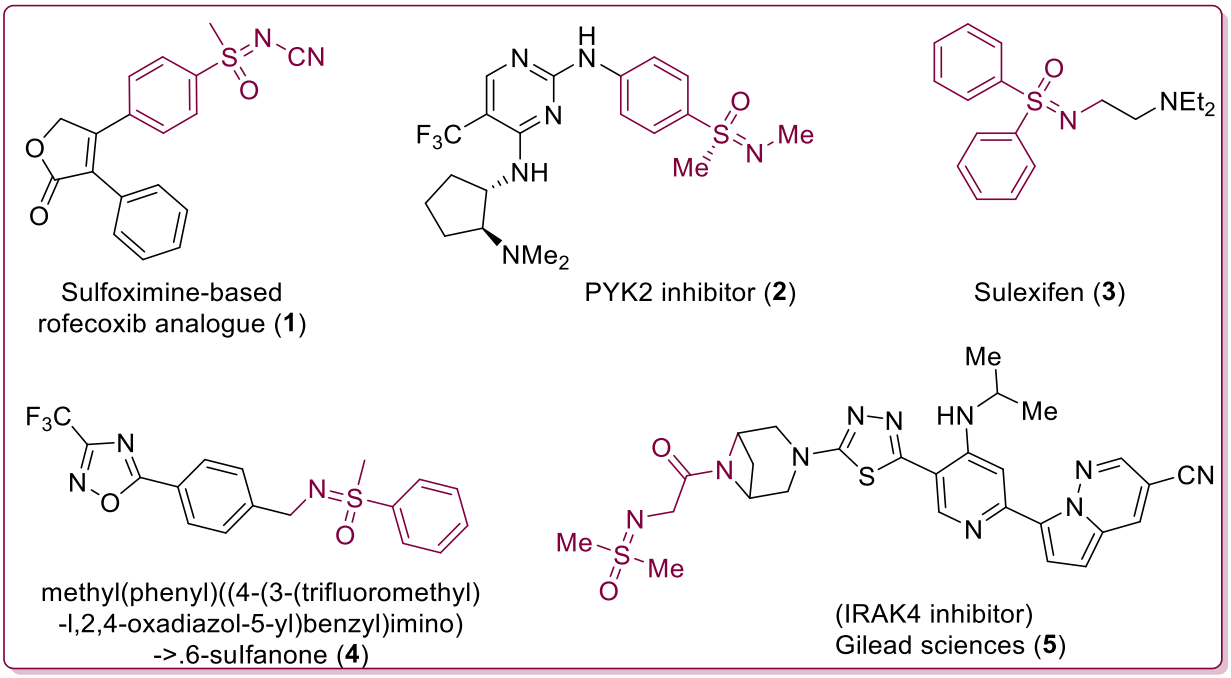


Figure 1. Typical Examples of Biologically active *N*-Alkyl Sulfoximines

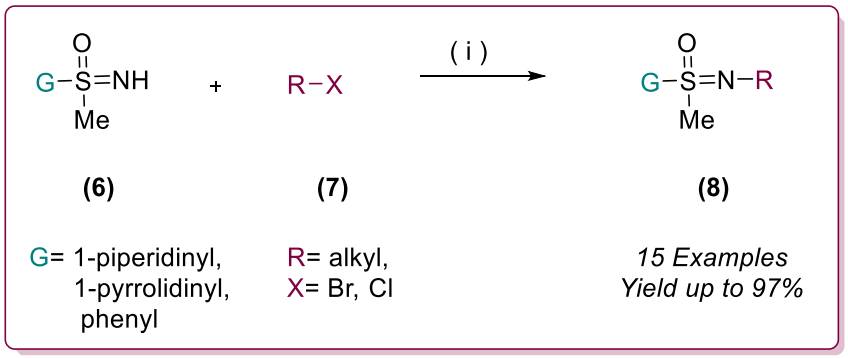
extensively applied for the construction of chiral auxiliaries, ligands as well as in enantioselective catalysis in asymmetric synthesis.[8,9]

3.1.2 Review of Literature

Several synthetic routes for *N*-alkylation of sulfoximines synthesis have been explored, owing to the importance of sulfoximines. Numerous reports for the *N*-alkylation of sulfoximines are described below.[10-13]

Johnson's Approach (1993)[10]

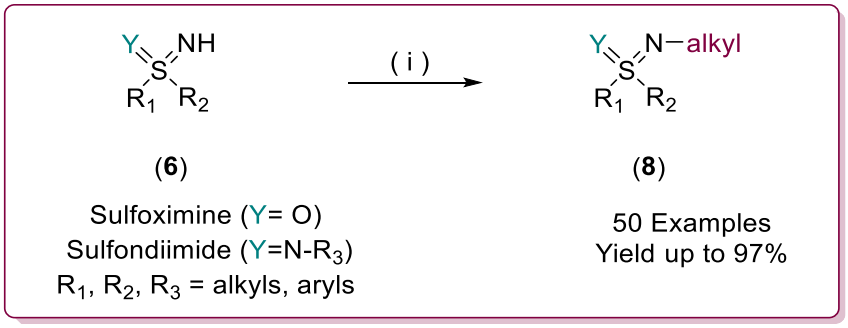
In 1993, Johnson and co-workers developed a method for the direct *N*-alkylation of sulfoximines *via* nucleophilic substitution using alkyl halide and sulfoximines presence of a base. In this report, sulfoximine (**6**) was treated with an alkyl halide (**7**) in the presence of alkali metal hydride base such as KH and NaH, and phase transfer catalyst (PTC) as an additive in DME solvent to obtain corresponding *N*-alkyl sulfoximines (**8**). This method proceeded only in the presence of a strong base and required phase transfer catalyst, the absence of PTC reaction did not proceed or proceed in trace amount. **(Scheme 1).**



Scheme 1. (i) KH (1.2 equiv.), DME, rt, 15 min, then R-X (1.2 equiv.), 5 mol% Bu, NH_4 Br (PTC), rt, 2 h

Bolm Approach (2014)[11]

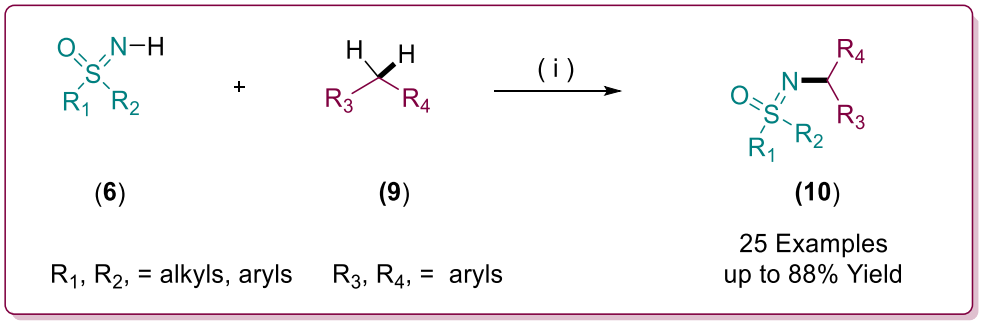
Bolm and co-workers delineated a new procedure for the alkylation of sulfoximine to synthesize of *N*-alkyl-sulfoximine using alkyl halide and base. This report revealed the various *N*-alkyl sulfoximine using alkyl bromides with KOH in DMSO at room temperature. A variety of N-sulfoximes and sulfondiimines was adapted in excellent yield, up to 97%. The Biologically active Suloxifen was readily prepared in a single step. *N*-alkyl sulfoximine transformation required strong base (**Scheme 2**).



Scheme 2. (i) alkyl-Br (1.5 equiv.), KOH (2.0 equiv.), DMSO, 4 h, argon atmosphere.

Bolm Approach (2014)[10]

Bolm *et al.* described an efficient method for C−N bond formation through hetero-cross-dehydrogenative coupling (CDC) reaction between sulfoximines (**6**) and diarylmethanes (**9**) using Fe (III) catalyst. This transformation provides an innovative method for the synthesis of *N*-alkylated sulfoximines (**10**) with α-branched congested substituents. *N*-alkylation of sulfoximes from this method required a high-temperature lengthy reaction time. (**Scheme 3**).

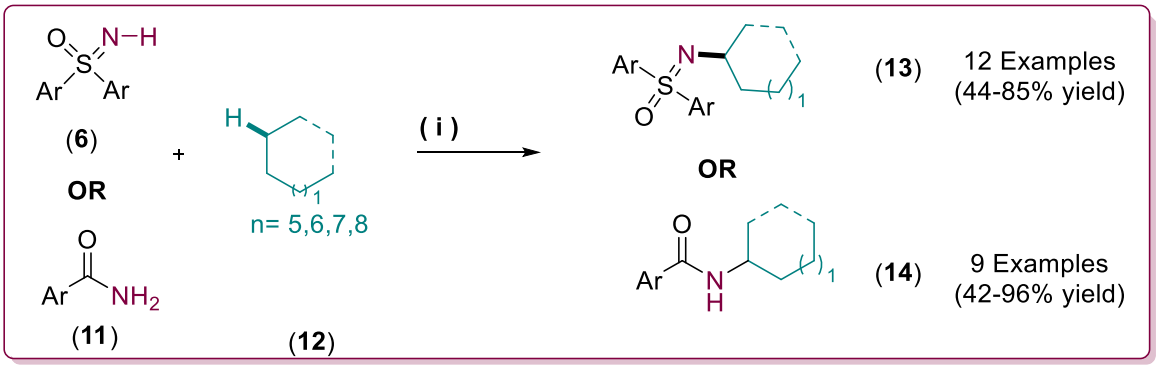


Scheme 3. (i) Fe $(Br)_3$ (20 mol%), DTBP (2.0 equiv.), 4 Å MS (100 mg), neat, 90 °C, 48 h.

Cheng Approach (2015)[13]

Cheng and the co-author developed a copper-catalyzed oxidative coupling of sulfoximines (**6**) with simple alkanes. This approach involved C(sp^3)–N bond formation by a radical pathway using oxidant (di-*tert*-butyl peroxide (DTBP)) and $Cu(acac)_2$ metal catalyst. This method well

tolerated a series of functional groups. Aside from sulfoximines various groups worked well for *N*-alkylation, such as amides, saccharin and aniline. However, this is novel method for C(sp^3)–N bond formation, excess amount of oxidant, and high temperature required for this transformation. (**Scheme 4**).

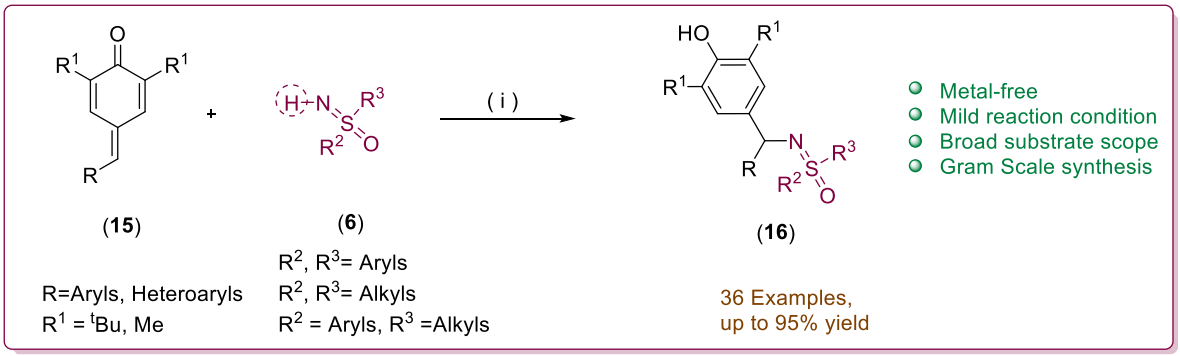


Scheme 4. (i): Sulfoximines/amide (0.2 mmol), $Cu(acac)_2$ (10 mol%), DTBP (4.0 equiv.) in alkanes (2.0 mL), 115 °C, under air for 12 h in a sealed tube.

3.1.3 Present Work

3.1.3.1 Objective

Continuation of our work based on metal-free synthetic methodologies,[21] and the importance of sulfoximes, we are encouraged to utilize *p*-QMs (**15**) and sulfoximines (**6**)



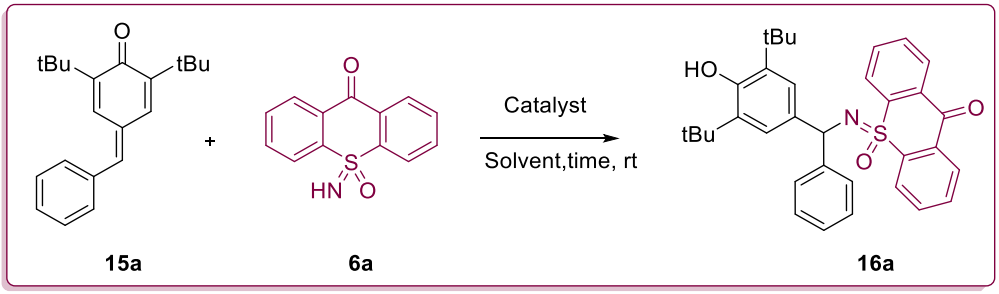
Scheme 5. (i) TsOH (20 mol%), CH_2Cl_2, rt, 1 h.

for the synthesis of diaryl methine moiety (**16**). To our knowledge, there are no reports where sulfoximines are used for conjugate addition on *p*-QMs. We reported a mild and efficient method for *N*- alkylation of sulfoximines (**Scheme 5**).

3.1.4 Result and Discussion

To authenticate our hypothesis, *p*-QM **15a,** and sulfoximine **6a** were selected as model substrates to check the feasibility of our conjugate addition reaction (Table 1). Initially, *p*-QM **15a** (1 equiv.) and sulfoximine **6a** (1.2 equiv.) were subjected to conjugate addition reaction in the presence of NaH (1 equiv.) in acetonitrile at room temperature for 4 h, failed to offered the desired product **16a** (Table 1, entry 1).

Table 1. Optimization of Reaction Condition [a]



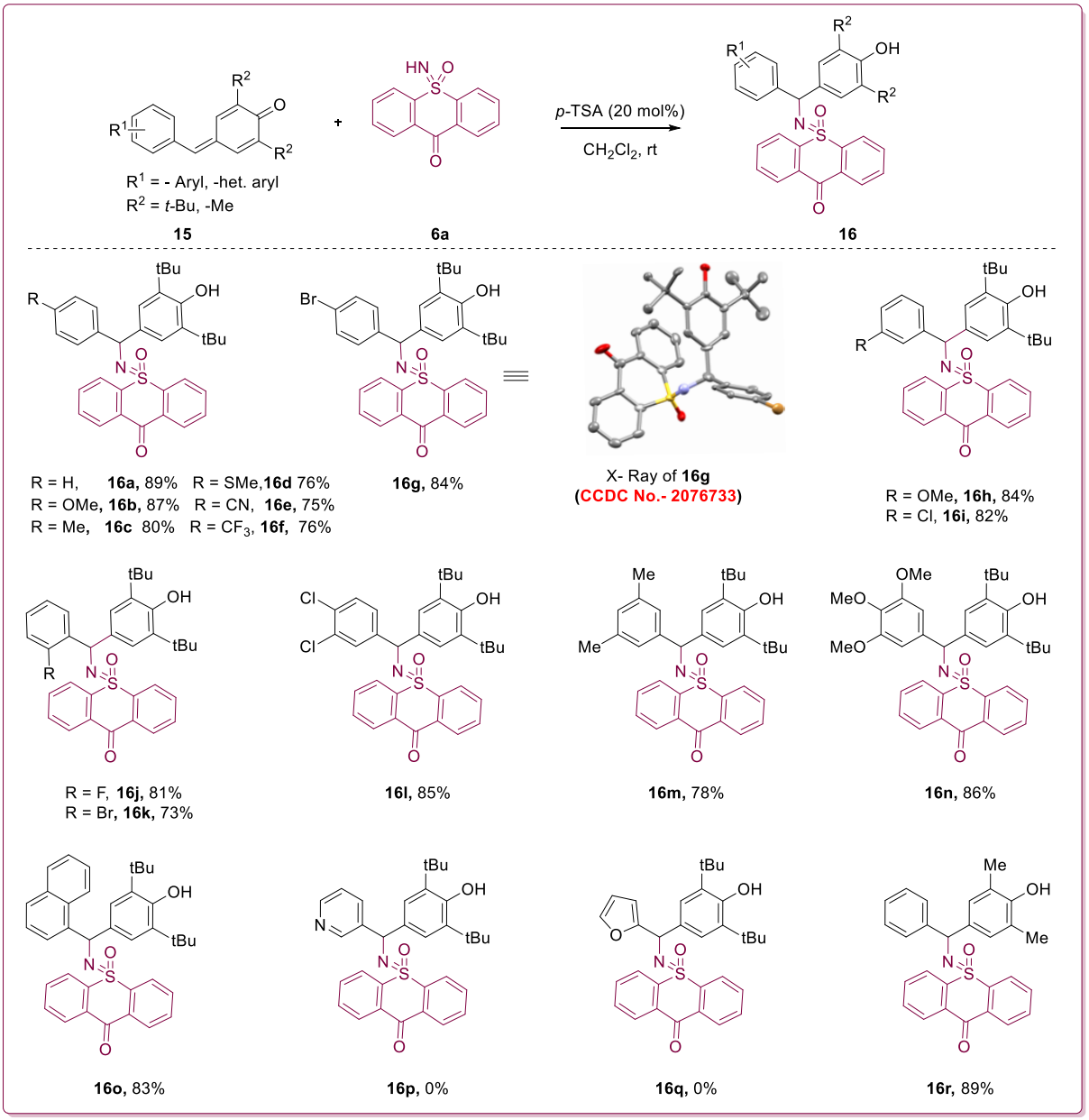
Sr. No.	Catalyst (equiv.)	Solvent	Time (h)	Yield (%) [b]
1	NaH (1)	ACN	4	NR
2	K_2CO_3 (1)	ACN	4	NR
3	Cs_2CO_3 (1)	ACN	4	NR
4	NaOH (1)	ACN	4	NR
5	*p*-TSA (0.1)	ACN	4	38
6	*p*-TSA (0.1)	THF	4	45
7	*p*-TSA (0.1)	EtOAc	4	58
8	*p*-TSA (0.1)	$CHCl_3$	4	64
9	*p*-TSA (0.1)	CH_2Cl_2	4	88

10	***p*-TSA (0.2)**	**CH_2Cl_2**	**1**	**92**
11	TFA (0.2)	CH_2Cl_2	1	85
12	TFOH (0.2)	CH_2Cl_2	1	79
13	CSA (0.2)	CH_2Cl_2	1	80
14	$BF_3.Et_2O$ (0.2)	CH_2Cl_2	1	56
15	*p*-TSA (0.2)	H_2O	1	NR
16	-	CH_2Cl_2	1	NR

[a] Reaction conditions:**15a** (0.1mmol, 1 equiv.), **6a** (0.12 mmol, 1.2 equiv.), catalyst in solvent (2.0 mL) at room temperature under N_2 atmosphere. [b] Isolated yields after column chromatography, NR = No

Further attempts for conjugate addition of sulfoximine on *p*-QM were unsatisfactory under basic conditions with various inorganic bases such as K_2CO_3, Cs_2CO_3, and NaOH (1 equiv. each) in acetonitrile (Table 1, entries 2-4). When the reaction was carried out in the presence of Brønsted acids, such as the catalytic amount of *p*-TSA (10 mol%) in acetonitrile delivered desired product **16a** in 38% yield at room temperature in 4 h of reaction time (Table 1, entry 5), encouraged by this promising result, then we have screened various polar solvents such as THF, EtOAc, $CHCl_3$, and CH_2Cl_2 (entries 6-10). CH_2Cl_2 was the best solvent of all screened solvents and gave an 88% yield of the desired product within 4 h. Furthermore, increasing the catalyst loading from 10 mol% to 20 mol% enhances the yield of desired product **16a** up to 92% yield in 1 h of reaction time (entry 10). Next, we screened different Brønsted acids (20 mol%) such as TFA, TFOH, and CSA (entries 11-13), but the yield of **16a** was not encouraging in all these cases (entries 11-13) as compared to that of entry 10. Further, the use of $BF_3.Et_2O$ did not alter the yield of **16a** (entry 14). Additionally, we tried reaction in aqueous media, but it was found ineffective in getting the corresponding product **16a** (entry 15). However, in the absence of a catalyst, there was no formation of product **16a** (entry 16). Based on the optimization study, **15a** (1.0 equiv.), **6a** (1.2 equiv.),

Table 2. Substrate Scope of the various *p*-QMs [a, b]



[a] **Reaction conditions: 15a-r** (0.17 mmol), **6a (**0.18 mmol), *p*-TSA (20 mol%), room temperature, 1 h, under N_2 atmosphere; [b] Isolated yields after column chromatographic purification are shown.

and *p*-TSA (20 mol%) in CH_2Cl_2 is the best-optimized reaction condition for the addition of sulfoximine to *p*-QMs (Table 1, entry 10).

With the optimal reaction condition in hand, various *p*-QMs (**15**) and sulfoximine (**6a**) were investigated under optimized reaction conditions shown in Table 2. The substrate

containing electron-donating groups (-H, -OMe, -Me, -SMe), electron-withdrawing groups (-CN, -CF_3), and halo group (-Br) on the *para* position of the aryl ring of *p*-QMs (**15a** to **15g**) reacts with sulfoximine derived from thioxanthene-9-one (**6a**) to afford the desire product **16a** to **16g** in good to excellent yield (75% to 89%). The precise structure of **16g** was determined by X-ray crystallography (**CCDC No.- 2076733**). Moreover, *meta* substituted *p*-QMs bearing electron-donating and electron-withdrawing groups on reaction with sulfoximine **6a** leads to the formation of corresponding products **16h** in 84% and **16i** in 82% yields. Also, halogen (-F, -Br), substitution at the *ortho* position of the aryl group of *p*-QMs (**15j** and **15k**) reacted with sulfoximine (**6a**) furnished the corresponding addition products **16j** and **16k** in 81% and 73% yield respectively. Besides that, disubstituted and trisubstituted *p*-QMs (**15l** to **15n**) reacted smoothly and offered the desired product **16l** to **16n** in excellent yield. Next, the reaction proceeds efficiently on sterically hindered *p*-QMs, such as naphthalene-derived *p*-QMs (**15o**), the desired product **16o** obtained in 83% yield. Unfortunately, hetero aryl *p*-QMs such as pyridine and furan containing *p*-QMs did not participate in the reaction with **6a**; subsequently, both the starting materials were recovered (entries **16p** and **16q**), presumably due to heteroatom getting protonated in acidic media to terminate the reaction. To our delight, replacing the *tert*-butyl group with the methyl group of *p*-QM (**15r**) furnishes **16r** with an 89% yield.

Examples 1:

The corresponding addition product (16a) was confirmed by 1H, 13C NMR spectra. In the 1H NMR spectrum, a peak was observed at 8.14 to 7.14 multiplet (8.14-8.23 (m, 2H), 8.02-8.08(m, 1H), 7.94-8.01 (m, 1H), 7.59-7.70 (m, 4H), 7.20-7.24 (m, 2H), 7.15-7.20 (m, 2H), 7.09-7.14 (m, 1H) corresponding to the aromatic protons. The peak δ 6.79 singlet 2H for the corresponding

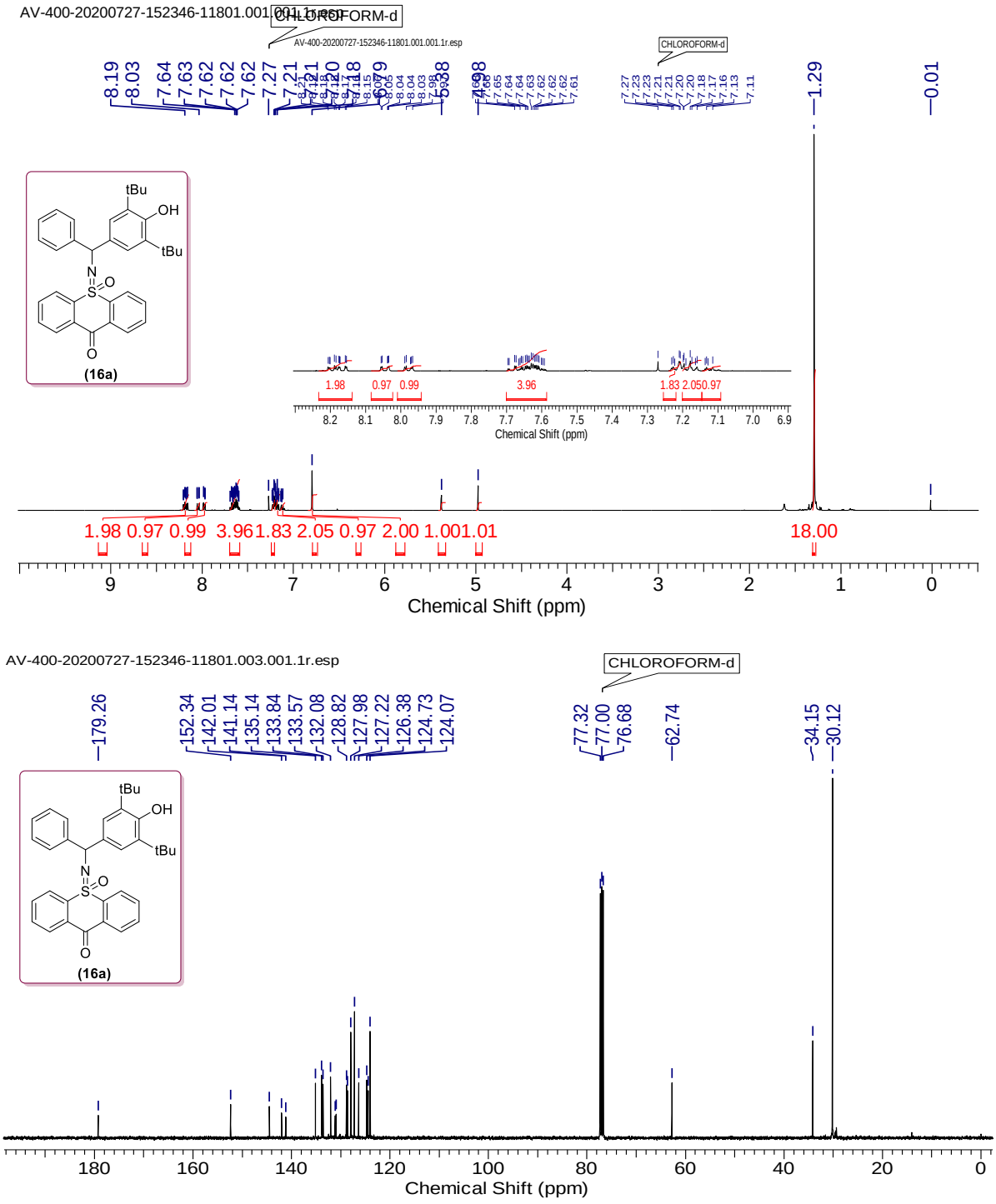
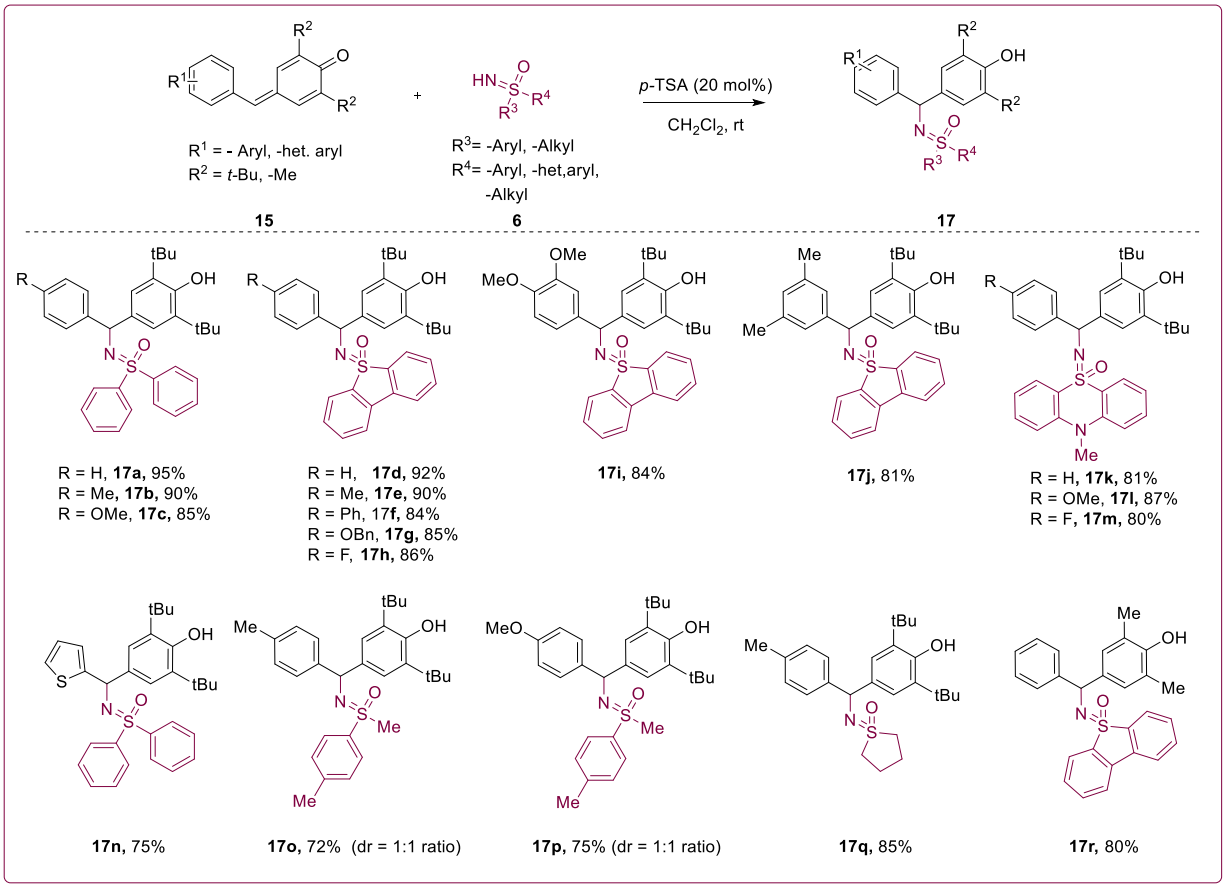


Figure 2: ^{1}H and $^{13}C\{1H\}$ NMR of 10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (phenyl)methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide **(16a)**

Table 3. Substrate Scope of various sulfoximines [a, b]



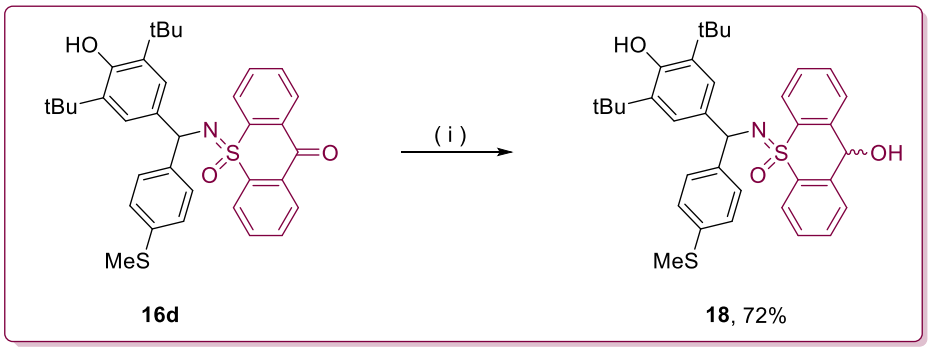
[a] **Reaction conditions: 15** (0.17 mmol), **6 (**0.18 mmol), *p*-TSA (20 mol%), room temperature, 1 h, under N_2 atmosphere; [b] Isolated yields after column chromatographic purification are shown.

aromatic proton of phenol. The peak at δ 5.38 (s, 1H) for the (C-H) methine proton of the characteristic hydrogen atom of benzylic position. The peak at δ 4.98 broad singlets (s, 1H) for the (-O-**H**) proton of phenol. The peak at 1.29 singlet (s, 18H) for two tertiary butyl groups of 3a. It was also confirmed by the ^{13}C NMR spectrum, in which the singlet peak at δ 62.7 characteristic carbon benzylic (-C**H**) of compound **3a** (Figure 2).

Next, the substrate scope of different sulfoximes **(6)** concerning to the *para*-quinone methides was investigated; diaryl, aryl-alkyl sulfoximes, and cyclic sulfoximines were screened with different *p*-QMs, as depicted in Table 3. The addition reaction between symmetrical diaryl

sulfoximines (**6b-6d**) and different *p*-QMs furnished corresponding diarylmethine sulfoximes (1**7a-17c**) in good yields (Table 3). Similarly, dibenzothiophene-derived sulfoximes (**6e-4k**) react smoothly with electron-donating, electron-withdrawing, and multi-substituted groups on *p*-QMs, leading to the formation of diarylmethine sulfoximine **17d-17j** in 81% to 92% yields. Further, *N*-Methyl phenothiazine-derived sulfoximine (**6l-6n**) was also found to be amenable to addition reaction with *p*-QMs bearing electron-donating and withdrawing-group to offer diarylmethine sulfoximines in good yields (entries **17k-17m**, 80%-87%). Heterocyclic *p*-QMs, such as thiophene, react–well with diaryl sulfoximine to furnish the **17n** in 75% yield. Additionally, methyl aryl sulfoximine reacted with *p*-QMs (*p*-Me and *p*-OMe) to obtain**17o** & **17p** in 72% and 75% yields, respectively, with the 1:1 diastereomeric ratio. Next, we applied the tetrahydrothiophene -based sulfoximine on *p*-QM (**15c**) under the optimized reaction condition, which reacted well and furnished the diarylmethine sulfoximine **17q** in 75% yield. In constrast 2,6 dimethyl *p*-QM reacts to get the corresponding product **17r** in 80% yield.

Table 4. Synthetic transformation [a]



16d **18**, 72%

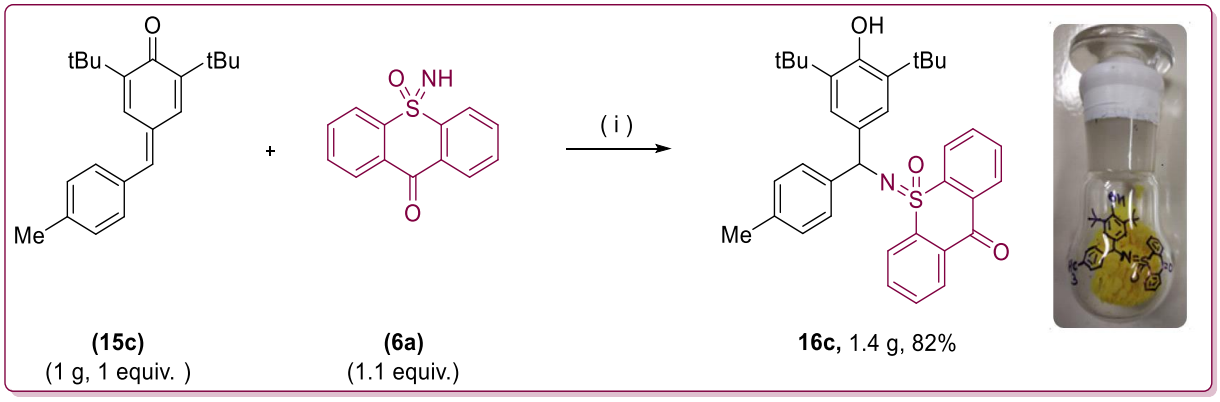
[a] **Reaction condition**: $NaBH_4$ (1 equiv.), MeOH, rt, 1 h

Next, we explored the synthetic transformation of the key product, as shown in Table 4. The keto group of 10-(((3,5-di-*tert*- butyl-4-hydroxyphenyl) (4-(methylthio) phenyl) methyl) imino)-10l4-

thioxanthen-9(10H)-one 10-oxide (**16d**) was selectively reduced with 1 equiv. of $NaBH_4$ afford desired product **18** in 72% yield.[22]

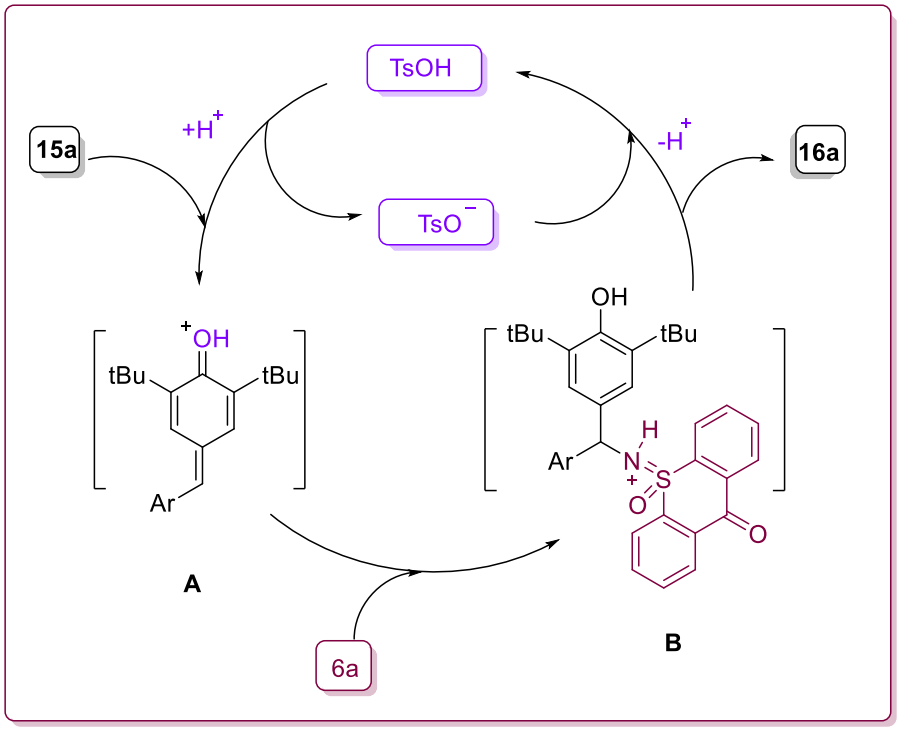
Gram scale reaction was carried out between *p*-QM (**15c**) and sulfoximine (**16a**) to demonstrate the scalability of this method under the optimized conditions obtained 16c in 82% yield (1.4 g) in 1 h, as shown in Table 5.

Table 5. Large scale synthesis [a]



[a] **Reaction conditions:** (i) **15c** (1 equiv.), **6a** (1.1 equiv.), *p*-TSA (20 mol%), CH_2Cl_2, rt, 1 h.

Based on the literature report,[23] we envisaged the plausible reaction pathway as shown in Scheme 6. The reaction was initiated with the activation of *p*-QMs (15a) using *p*-TSA, leading to the formation of highly electrophilic intermediate A for 1,6 conjugate additions. Subsequently, adding sulfoximine (**6a**) in a 1,6 conjugated manner may offer the sulfoximinium ion intermediate **B.** Followed by the deprotonation of intermediate **B** leads to the desired product **16a** with the regeneration of the *p*-TSA catalyst.



Scheme 6: Plausible reaction mechanism.

3.1.5. Conclusion

In conclusion, we have developed a convenient, metal-free protocol for synthesizing a diverse range of diarylmethine imino sulfanones using *p*-Quinone Methide (*p*-QMs) and bench stable sulfoximines in the presence of the catalytic amount of *p*-TSA. The key feature of the methodology are a mild reaction condition, less reaction time, broad substrate scope, high atom economy, and excellent product yield.

3.1.6. Experimental Section

3.1.6.1 General Experimental Procedure for the Synthesis of Diarylmethine sulfoximines (16a-16r)

To a 25 mL round bottom flask with stir bar were added *p*-QMs (**15)** (50 mg, 0.1700 mmol, 1 equiv.), Sulfoximine (**6a**) (0.1870 mmol, 1.1 equiv.) in dry CH_2Cl_2 (2.0 mL) and *p*-TSA (20 mol

%) was added in reaction mixture. The resultant reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the reaction mixture was quenched with water (2 mL) and extracted with CH_2Cl_2 (3×3mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated under a vacuum. The crude was was purified on flash silica gel chromatography (petroleum ether/ethyl acetate = 80:20) to afford Diarylmethine sulfoximines (**16a-16r**).

3.1.6.2. General Experimental Procedure for the Synthesis of Diarylmethine sulfoximines (17a-17r)

To a 25 mL round bottom flask with a stir bar were added *p*-QMs (**15)** (50 mg, 0.34 mmol, 1 equiv.), Sulfoximines (**6)** (0.37 mmol, 1.1 equiv.) in dry CH_2Cl_2 (2.0 mL) and *p*-TSA (20 mol %) was added in reaction mixture. The resultant reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the reaction mixture was quenched with water (2 mL) and extracted with CH_2Cl_2 (3×3mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated under a vacuum. The crude was was purified on flash silica gel chromatography (petroleum ether/ethyl acetate = 80:20) to afford Diarylmethine Sulfoximines**(17a-17s)**.

3.1.6.3. General Experimental Procedure for Synthetic Transformation of Form Product 16d.

To a 25 mL round bottom flask, **16d** (40 mg, 0.068 mmol, 1 equiv.) was taken in Methanol, and $NaBH_4$ (0.068 mmol, 1 equiv.) was added portion-wise at 0 ^oC. The reaction was slowly brought to room temperature, and stirred for 1 h at the same temperature; after completion of the reaction (monitored by TLC), the solvent was evaporated on a rotary evaporator under reduced pressure, and the residue was extracted with Ethyl acetate (3×3mL) and water, washed with brine The

combined organic layer dried over Na_2SO_4, filtered and evaporated under.vaccume. Crude product purified on flash chromatography (silica gel 100-200 mesh), petroleum ether/Ethyl acetate (v/v, 6/4) to afford the corresponding product **18** in 80% yield.

3.1.6.4. General Experimental Procedure for gram scale synthesis of (16c)

To a 100 mL round bottom flask with a stir bar were added *p*-QMs **15c** (1 g, 3.24 mmol, 1 equiv.), Sulfoximine **6a** (3.57 mmol, 1.1 equiv.) in dry CH_2Cl_2 (20 mL) and *p*-TSA (20 mol%) were added to the reaction mixture. The resultant reaction mixture was stirred at room temperature. After completion (monitored by TLC), The reaction mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated under a vaccume. The crude was was purified on flash silica gel chromatography (petroleum ether/ethyl acetate = 80:20) to afford **16c** in 82% yield (1.4 g).

10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (phenyl)methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16a)

Yield: 89% (81 mg); Red solid; **mp** = 98−99 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.14-8.23 (m, 2H), 8.02-8.08 (m, 1H), 7.94-8.01 (m, 1H), 7.59-7.70 (m, 4H), 7.20-7.24 (m, 2H), 7.15-7.20 (m, 2H), 7.09-7.14 (m, 1H), 6.79 (s, 2H), 5.38 (s, 1H), 4.98 (s, 1H), 1.29 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 179.3, 152.3, 144.5, 142.0, 141.1, 135.1, 133.8, 133.6, 132.1, 132.1, 131.2, 131.0, 128.8, 128.6, 128.0, 127.2, 126.4, 124.7, 124.4, 124.1, 62.7, 34.2, 30.1; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{34}H_{35}O_3NNaS$, 560.2230; found, 560.2257.

10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (4-methoxyphenyl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16b):

Yield: 87% (76 mg); Yellow gum; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.15-8.22 (m, 2H), 8.01-8.06 (m, 1H), 7.94-7.99 (m, 1H), 7.59-7.71 (m, 4H), 7.07-7.14 (m, 2H), 6.78 (s, 2H), 6.69-6.74 (m, 2H), 5.33 (s, 1H), 4.96 (s, 1H), 3.75 (s, 3H), 1.29 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 179.3, 158.1, 152.3, 142.1, 141.2, 136.9, 135.1, 134.1, 133.8, 133.6, 132.1, 132.0, 131.2, 131.0, 128.8, 128.6, 128.3, 124.8, 124.5, 124.0, 113.4, 62.2, 55.2, 34.2, 30.2; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{35}H_{36}O_4NS$, 566.2360; found, 566.2379.

10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (p-tolyl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16c):

Yield: 80% (71 mg); Yellow solid; **mp** = 147−148 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.2-8.2 (m, 2H), 8.0 (dd, *J* = 8.01, 1.14 Hz, 1H), 8.0 (dd, *J* = 7.63, 1.53 Hz, 1H), 7.6-7.7 (m, 4H), 7.1 (m, *J* = 8.01 Hz, 2H), 7.0 (m, *J* = 8.01 Hz, 2H), 6.8 (s, 2H), 5.3 (s, 1H), 5.0 (s, 1H), 2.3 (s, 3H), 1.3 (s, 18H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$): δ 179.3, 152.3, 142.1, 141.7, 141.2, 135.8, 135.1, 134.0, 133.8, 133.5, 132.0, 131.1, 131.0, 128.8, 128.7, 128.6, 127.1, 124.8, 124.5, 124.0, 62.7, 34.2, 30.1, 21.0; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{35}H_{38}NO_3S$, 552.2572; found, 552.2570.

10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (4-(methylthio) phenyl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16d):

Yield: 76% (65 mg); Yellow solid; **mp** = 134−135 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.2 (dd, *J* = 9.16, 7.63 Hz, 1H), 8.2 (dd, *J* = 12.21, 7.63 Hz, 1H), 8.0 (dd, *J* = 7.63, 1.14 Hz, 1H), 8.0 (dd, *J* = 7.44, 1.34 Hz, 1H), 7.6-7.7 (m, 4H), 7.1-7.2 (m, 2H), 7.0-7.1 (m, 2H), 6.8 (s, 2 H), 5.3 (s, 1H), 5.0 (s, 1H), 2.4 (s, 3H), 1.3 (s, 18 H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$): δ 179.3, 152.4, 142.0, 141.9, 141.1, 136.0, 135.2, 133.9, 133.7, 133.6, 132.1, 131.2, 131.0, 128.9, 128.6, 127.7, 126.6, 124.7, 124.5, 124.0, 62.4, 34.2, 30.1, 16.2; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{35}H_{37}O_3NNaS_2$, 606.2107; found: 606.2120.

4-((3,5-di-tert-butyl-4-hydroxyphenyl) ((10-oxido-9-oxo-9H-10l4-thioxanthen-10-ylidene) amino) methyl) benzonitrile (16e):

Yield: 75% (66 mg); Yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.1-8.2 (m, 2H), 8.0-8.1 (m, 1H), 7.9 (dd, *J* = 7.25, 1.91 Hz, 1H), 7.7 - 7.7 (m, 1H), 7.7 (dd, *J* = 7.63, 1.14 Hz, 1H), 7.6 (ddd, *J* = 6.87, 4.20, 1.91 Hz, 2H), 7.5 (m, *J* = 8.39 Hz, 2H), 7.4 (m, *J* = 8.01 Hz, 2H), 6.7 (s, 2H), 5.4 (s, 1H), 5.0 (s, 1H), 1.3 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 179.2, 152.7, 150.3, 141.6, 140.7, 135.5, 133.9, 133.6, 132.6, 132.4 , 132.3, 131.9, 131.3, 131.1, 129.0, 128.8, 127.9, 124.6, 124.3, 123.9, 119.1, 110.0, 62.3, 34.2, 30.2, 30.1; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{35}H_{33}O_3N_2S$, 561.2206; found, 561.2225.

10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (4-(trifluoromethyl) phenyl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16f):

Yield: 76% (63 mg); Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.16-8.24 (m, 2H), 7.99-8.11 (m, 1H), 7.93-7.99 (m, 1H), 7.59-7.74 (m, 4H), 7.43 (d, *J* = 8.26 Hz, 2H), 7.34 (d, *J* = 8.50 Hz, 2H), 6.77 (s, 2H), 5.41 (s, 1H), 5.01 (s, 1H), 1.29 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 179.2, 152.6, 148.7, 141.8, 140.9, 135.4, 133.9, 133.6, 133.1, 132.3, 132.2, 131.3, 131.1, 128.9, 128.7, 127.5, 125.0, 125.0, 124.6, 124.4, 123.9, 62.4 , 34.2, 30.1; **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.35; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{35}H_{34}O_3NF_3NaS$, 628.2104; found, 628.2111.

10-(((4-bromophenyl) (3,5-di-tert-butyl-4-hydroxyphenyl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide(16g):

Yield: 84% (69 mg); Yellow solid; **mp** = 177−178 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.15 - 8.22 (m, 2H), 8.01-8.06 (m, 1H), 7.92-7.98 (m, 1H), 7.59-7.72 (m, 4H), 7.28-7.32 (m, 2H), 7.10 (d, *J* = 8.38 Hz, 2H), 6.75 (s, 2H), 5.32 (s, 1H), 4.99 (s, 1H), 1.29 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 179.2, 152.5, 143.8, 141.9, 141.0, 135.3, 133.9, 133.6, 133.4, 132.2, 132.2,

131.2, 131.0, 129.0, 128.9, 128.7, 124.7, 124.4, 123.9, 120.2, 77.2, 62.2, 34.2, 30.1; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{34}H_{34}O_3NBrNaS$, 638.1340; found, 638.1343.

10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (3-methoxyphenyl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16h):

Yield: 84% (73 mg); Red oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.14-8.24 (m, 2H), 7.97-8.07 (m, 2H), 7.54-7.69 (m, 4H), 7.08 (t, *J* = 8.07 Hz, 1H), 6.81 (s, 2H), 6.76 - 6.80 (m, 2H), 6.66 (ddd, *J* = 8.16, 2.53, 0.94 Hz, 1H), 5.35 (s, 1H), 4.97 (s, 1H), 3.70 (s, 3H), 1.29 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 179.3, 159.3, 152.4, 146.0, 142.0, 141.2, 135.1, 133.8, 133.6, 132.1, 131.2, 131.0, 128.9, 128.8, 128.6, 124.7, 124.5, 124.1, 119.8, 112.6, 112.2, 62.7, 55.1, 34.2, 30.2; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{35}H_{36}O4NS$, 566.2360; found, 566.2381.

10-(((3-chlorophenyl) (3,5-di-tert-butyl-4-hydroxyphenyl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16i):

Yield: 82% (71 mg); Red solid; **mp** = 125−126 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.14-8.24 (m, 2H), 8.05 (dd, *J* = 7.69, 1.06 Hz, 1H), 7.90-8.01 (m, 1H), 7.59-7.73 (m, 4H), 7.21-7.25 (m, 1H), 7.02-7.10 (m, 3H), 6.76 (s, 2H), 5.32 (s, 1H), 5.00 (s, 1H), 1.30 (s, 18H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$): δ 179.2, 152.5, 146.7, 141.8, 141.0, 135.3, 133.9, 133.8, 133.6, 133.2, 132.3, 132.2, 131.2, 131.0, 129.2, 128.9, 128.7, 127.4, 126.5, 125.4, 124.7, 124.4, 124.0, 62.3 34.2, 30.1; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{34}H_{33}O_3NClS$, 570.1864; found, 570.1890.

10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (2-fluorophenyl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16j):

Yield: 81% (72 mg); Yellow solid; **mp** = 114−115 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.21-8.25 (m, 1H), 8.16 (dd, *J* = 7.78, 1.37 Hz, 1H), 8.06 (dd, *J* = 8.01, 1.15 Hz, 1H), 7.99-8.04 (m, 1H), 7.60-7.68 (m, 4H), 7.40-7.49 (m, 2H), 7.05-7.13 (m, 1H), 6.98 (td, *J* = 7.44, 1.14 Hz, 1H),

6.81 - 6.89 (m, 3H), 5.73 (s, 1H), 4.99 (s, 1H), 1.29 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 179.3, 158.1, 152.4, 141.7, 140.8, 135.1, 133.9, 133.6, 133.0, 132.2, 132.1, 131.7, 131.5, 131.1, 130.9, 129.3, 129.0, 129.0, 128.9, 128.6, 128.0, 127.9, 124.8, 124.3, 124.0, 123.8, 114.9, 114.7, 55.2, 34.2, 30.1; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{34}H_{35}FNO_3S$, 556.2316; found: 556.2303.

10-(((2-bromophenyl) (3,5-di-tert-butyl-4-hydroxyphenyl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16k):

Yield: 73% (60 mg); Brown gum; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.21-8.27 (m, 1H), 8.15 (dd, 7.69, 1.06 Hz, 1H), 8.07 (dd, *J* = 7.75, 0.88 Hz, 1H), 8.00-8.05 (m, 1H), 7.64-7.72 (m, 3H), 7.57-7.62 (m, 1H), 7.52 (dd, = 7.82, 1.69 Hz, 1H), 7.35 (dd, *J* = 8.00, 1.13 Hz, 1H), 7.11-7.16 (m, 1H), 6.94-6.98 (m, 1H), 6.92-6.94 (m, 2H), 5.80 (s, 1H), 4.99 (s, 1H), 1.30 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (126 MHz, $CDCl_3$): δ 179.3, 152.5, 143.4, 141.7, 140.9, 135.1, 133.9, 133.7, 133.0, 132.2, 132.1, 132.1, 131.1, 130.9, 130.0, 128.9, 128.7, 127.9, 127.5, 124.9, 124.4, 124.0, 122.8, 61.0, 34.2, 30.1; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{34}H_{35}BrNO_3S$, 616.1521; found,616.1509.

10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (3,4-dichlorophenyl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16l):

Yield: 85% (70 mg); Red oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.21-8.26 (m, 1H), 8.15-8.20 (m, 1H), 8.03-8.08 (m, 1H), 7.98-8.02 (m, 1H), 7.62-7.73 (m, 4H), 7.47 (d, *J* = 8.50 Hz, 1H), 7.19 (d, *J* = 2.13 Hz, 1H), 7.08 (dd, *J* = 8.50, 1.88 Hz, 1H), 6.87 (s, 2H), 5.77 (s, 1H), 5.01 (s, 1H), 1.29 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 179.3, 152.6, 141.6, 140.8, 140.7, 135.2, 133.9, 133.7, 132.6, 132.5, 132.4, 132.3, 132.2, 131.2, 130.9, 130.5, 129.0, 128.7, 128.5, 127.2, 124.8,

124.3, 123.9, 77.2, 58.1, 34.2, 30.1; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{34}H_{32}O_3NCl_2S$, 604.1474; found, 604.1498.

10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (3,5-dimethylphenyl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16m):

Yield: 78% (68 mg); Yellow solid; **mp** = 166−167 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.1-8.2 (m, 2H), 7.9-8.1 (m, 2H), 7.6-7.7 (m, 4H), 6.8 (s, 2H), 6.8 (s, 2H), 6.7 (s, 1H), 5.3 (s, 1H), 5.0 (s, 1H), 2.2 (s, 6H), 1.3 (s, 18H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$): δ 179.1, 152.3, 144.0, 141.9, 141.3, 137.3, 135.0, 134.1, 133.8, 133.6, 132.0, 131.1, 131.0, 128.7, 128.5, 128.1, 125.0, 124.7 , 124.5, 124.0, 63.0, 34.2, 30.1, 21.2; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{36}H_{39}O_3NNaS$, 588.2543; found, 588.2560.

10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (3,4,5-trimethoxyphenyl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16n):

Yield: 86% (70 mg); Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13-8.26 (m, 2 H), 7.94-8.10 (m, 2 H), 7.55-7.76 (m, 4H), 6.87 (s, 2H), 6.36 (s, 2H), 5.34 (s, 1H), 5.02 (s, 1H), 3.77 (s, H), 3.71 (s, 6H), 1.31 (s,18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 179.4, 152.7, 152.5, 141.7, 141.4, 139.4, 135.2, 133.9, 133.6, 132.2, 132.2, 128.7, 128.6, 124.6, 124.5, 124.1, 104.5, 62.6, 60.7, 55.9, 34.2, 30.2; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{37}H_{41}O_6NNaS$, 650.2547; found, 650.2554.

10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (naphthalen-1-yl) methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16o):

Yield: 83% (70 mg); Red gum; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19-8.26 (m, 1H), 8.10-8.18 (m, 2H), 7.92-7.99 (m, 1H), 7.84-7.91 (m, 1H), 7.70-7.80 (m, 1H), 7.62 (d, J = 7.88 Hz, 1H), 7.49-7.57 (m, 4H), 7.38-7.44 (m, 2H), 7.29-7.33 (m, 1H), 7.27 (d, J = 7.88 Hz, 1H), 6.96 (s, 2H), 6.21

(s, 1H), 4.99 (s, 1H), 1.27 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 179.2, 152.3,141.5, 141.5, 139.2, 135.1, 133.8, 133.7, 133.3, 133.2, 132.0, 131.8, 131.0, 131.0, 130.7, 128.7, 128.5, 128.4, 127.5, 126.0, 125.5, 125.3, 125.1, 124.6, 124.5, 124.4, 124.4, 59.7, 34.2, 30.2; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{38}H_{36}O_3NS$, 586.2410; found, 586.2431.

10-(((4-hydroxy-3,5-dimethylphenyl) (phenyl)methyl) imino)-10l4-thioxanthen-9(10H)-one 10-oxide (16r):

Yield: 89% (96 mg); Yellow solid; **mp** = 174−175 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10-8.25 (m, 2H), 7.94-8.06 (m, 2H), 7.59-7.70 (m, 4H), 7.04-7.22 (m, 5H), 6.48-6.68 (m, 2H), 5.28 (s, 1H), 4.51 (s, 1H), 2.04 (s, 7H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 179.2, 150.8, 144.2, 141.8, 141.2, 135.2, 133.7, 132.1, 132.0, 131.2, 131.0, 128.7, 128.6, 128.0, 127.5, 127.0, 126.4, 124.7, 124.5, 122.5, 62.4, 15.8; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{28}H_{23}O_3NNaS$, 476.1261; found, 476.1302.

(((3,5-di-tert-butyl-4-hydroxyphenyl) (phenyl)methyl) imino) diphenyl-l6-sulfanone (17a):

Yield: 95% (82 mg); Yellow solid; **mp** =138−139 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94 - 7.98 (m, 2H), 7.81-7.88 (m, 2H), 7.35-7.48 (m, 8H), 7.25-7.30 (m, 2H), 7.17-7.21 (m, 1H), 7.15 (s, 2H), 5.40 (s, 1H), 5.04 (s, 1H), 1.39 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 152.2, 146.0, 141.3, 141.2, 136.0, 135.1, 132.2, 132.0, 128.8, 128.8, 128.7, 128.6, 127.9, 127.5, 126.2, 124.5, 61.6, 34.3, 30.3; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{33}H_{36}O_2NS$, 510.2461; found, 510.2481.

(((3,5-di-tert-butyl-4-hydroxyphenyl) (p-tolyl) methyl) imino) diphenyl-l6-sulfanone (17b):

Yield: 90% (76 mg); Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94-7.98 (m, 2H), 7.81-7.88 (m, 2H), 7.33-7.49 (m, 6H), 7.27-7.31 (m, 3H), 7.15 (s, 2H), 7.07 (d, J = 7.88 Hz, 2H), 5.35 (s, 1H), 5.02 (s, 1H), 2.32 (s, 3H), 1.39 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 152.2,143.1,

141.4, 141.3, 136.2, 135.5, 135.0, 132.1, 132.0, 129.0, 128.8, 128.8, 128.7, 128.6, 127.4, 126.3, 124.4, 123.5, 76.6, 61.5, 34.4, 34.3, 30.4, 21.1; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{34}H_{38}O_2NS$, 524.2618; found, 524.2637.

(((3,5-di-tert-butyl-4-hydroxyphenyl) (4-methoxyphenyl) methyl) imino) diphenyl-l6-sulfanone (17c):

Yield: 85% (71 mg); Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90-8.00 (m, 2H), 7.81-7.89 (m,2H), 7.28-7.50 (m, 8H), 7.15 (s, 2H), 6.82 (d, *J* = 8.76 Hz, 2H), 5.35 (s, 1H), 5.04 (s, 1H), 3.79 (s, 3H), 1.39 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 158.0, 152.2, 141.4, 141.2, 138.4, 136.3, 135.1, 132.2, 132.1, 128.9, 128.8, 128.8, 128.7, 128.6, 124.4, 113.3, 61.1, 55.2, 34.3, 30.4. **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{34}H_{38}O_3NS$, 540.2567; found, 540.2587.

5-(((3,5-di-tert-butyl-4-hydroxyphenyl) (phenyl)methyl) imino)-5H-5l4-dibenzo[b,d]thiophene 5-oxide (17d):

Yield: 92% (79 mg); Yellow gum; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.63 Hz, 2H), 7.50-7.55 (m, 1H), 7.47 (dd, *J* = 7.50, 0.88 Hz, 2H), 7.41 (d, *J* = 7.25 Hz, 2H), 7.34 (td, *J* = 7.57, 0.88 Hz, 1H), 7.15-7.26 (m, 4H), 7.06 (s, 2H), 7.02 (d, *J* = 7.75 Hz, 1H), 5.73 (s, 1H), 5.06 (s, 1H), 1.32 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 152.6,145.3, 139.6, 139.4135.5, 135.0, 132.9, 132.4, 132.2, 131.7, 129.8, 129.6, 128.0, 127.4, 126.4, 124.5, 123.1, 123.1, 121.0, 121.0, 61.6, 34.3, 30.3; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{33}H_{34}O_2NS$, 508.2305; found, 508.2323.

5-(((3,5-di-tert-butyl-4-hydroxyphenyl) (p-tolyl) methyl) imino)-5H-5l4-dibenzo[b,d]thiophene 5-oxide (17e):

Yield: 90% (76 mg); White solid; **mp** = 177−178 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.75 Hz, 2H), 7.50-7.55 (m, 1H), 7.44-7.50 (m, 2H), 7.28-7.35 (m, 3H), 7.21 (td, *J* = 7.57, 1.00 Hz, 1H), 7.04-7.08 (m, 4H), 7.01 (d, *J* = 7.38 Hz, 1H), 5.69 (s, 1H), 5.04 (s, 1H), 2.31 (s, 3H),

1.32 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 152.6, 142.4,139.6, 139.4, 135.8, 135.4, 135.2, 132.9, 132.3, 132.2, 131.7, 129.7, 129.6, 128.7, 127.3, 124.4, 123.2, 123.0, 121.0, 120.9, 61.5, 34.2, 30.3, 21.0; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{34}H_{36}O_2NS$, 522.2461; found, 522.2482.

5-(([1,1'-biphenyl]-4-yl(3,5-di-tert-butyl-4-hydroxyphenyl) methyl) imino)-5H-5l4-dibenzo[b,d]thiophene 5-oxide (17f):

Yield: 84% (66 mg); White solid; **mp** = 151−152 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71-7.76 (m, 2H), 7.56-7.60 (m, 2H), 7.50-7.55 (m, 2H), 7.46-7.50 (m, 5H), 7.40-7.46 (m, 2H), 7.30-7.37 (m, 2H), 7.20-7.25 (m, 1H), 7.11 (s, 2H), 7.03 (d, *J* = 7.50 Hz, 1H), 5.77 (s, 1H), 5.08 (s, 1H), 1.34 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 152.7,144.5, 141.2, 139.5, 139.3, 139.2, 135.6, 134.9, 133.0, 132.4, 132.2, 131.7, 129.8, 129.6, 128.7, 127.8, 127.0, 127.0, 126.8, 124.5, 123.2, 123.0, 121.0, 121.0, 61.5, 34.3, 30.3; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{39}H_{38}O_2NS$, 584.2618; found, 584.2639.

5-(((4-(benzyloxy) phenyl) (3,5-di-tert-butyl-4-hydroxyphenyl) methyl) imino)-5H-5l4-dibenzo[b,d]thiophene 5-oxide (17g):

Yield: 85% (65 mg); Yellow solid; **mp** = 76−77 °C;**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.63 Hz, 2H), 7.52 (td, *J* = 7.57, 1.13 Hz, 1H), 7.41-7.49 (m, 4H), 7.35-7.41 (m, 2H), 7.28-7.35 (m, 4H), 7.21 (td, *J*= 7.60, 0.94 Hz, 1 H), 7.01 - 7.06 (m, 3 H), 6.83 - 6.91 (m, 2 H), 5.69 (s, 1 H), 5.05 (s, 3 H), 1.32 (s, 18 H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$):δ 157.4, 152.6, 139.6, 139.4, 137.9, 137.2, 135.5, 135.2, 132.9, 132.3, 132.2, 131.7, 129.8, 129.6, 128.5, 128.5, 127.8, 127.4, 124.4, 123.1, 123.0, 121.0, 121.0, 114.4, 70.0, 61.0, 34.3, 30.3; **HRMS** (ESI) *m/z*: $[M-H]^+$calcd for $C_{40}H_{42}NO_3S$, 616.2880; found, 616.2880.

5-(((3,5-di-tert-butyl-4-hydroxyphenyl) (4-fluorophenyl) methyl) imino)-5H-5l4-dibenzo[b,d]thiophene 5-oxide (17h):

Yield: 86% (72 mg); Yellow solid; **mp** = 207−208 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71-7.75 (m, 2H), 7.46-7.57 (m, 3H), 7.33-7.40 (m, 3H), 7.22 (td, *J* = 7.57, 1.00 Hz, 1H), 7.02 (s, 2H), 6.90 - 7.00 (m, 3H), 5.70 (s, 1H), 5.08 (s, 1H), 1.32 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 162.8. 160.3, 152.7, 141.1, 141.1, 139.5, 139.2, 135.6, 134.8, 133.1, 132.4, 132.2, 131.7, 129.9, 129.6, 128.9, 128.9, 124.4, 123.1, 123.0, 121.1, 114.8, 114.6, 77.3, 77.2, 76.7, 60.9, 34.3, 30.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ -117.1; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{33}H_{33}O_2NFS$, 526.2211; found, 526.2236.

5-(((3,5-di-tert-butyl-4-hydroxyphenyl) (3,4-dimethoxyphenyl) methyl) imino)-5H-5l4-dibenzo[b,d]thiophene 5-oxide (17i):

Yield: 84% (67 mg); Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (dd, *J* = 7.79, 2.75 Hz, 2H), 7.45-7.53 (m, 2H), 7.24-7.36 (m, 3H), 7.17 (d, *J* = 7.33 Hz, 1H), 7.07 (s, 2H), 6.99 (d, *J* = 1.83 Hz, 1H), 6.85 (dd, *J* = 8.01, 2.06 Hz, 1H), 6.76 (d, *J* = 8.24 Hz, 1H), 5.71 (s, 1H), 5.07 (s, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 1.33 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 152.5, 148.6, 147.6, 139.3, 137.7, 135.3, 135.0, 132.8, 132.5, 132.0, 131.8, 129.7, 129.6, 124.3, 123.0, 123.0, 121.0, 121.0, 119.6, 110.8, 110.6, 61.1, 55.9, 55.7, 34.2, 30.2; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{35}H_{40}NO_4S$, 570.2673; found:570.2680.

5-(((3,5-di-tert-butyl-4-hydroxyphenyl) (3,5-dimethylphenyl) methyl) imino)-5H-5l4-dibenzo[b,d]thiophene 5-oxide(17j):

Yield: 81% (67 mg); Yellow solid; **mp** = 178−179 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71 (dd, *J* = 7.75, 2.88 Hz, 2H), 7.45-7.54 (m, 2H), 7.39-7.43 (m, 1H), 7.33 (dd, *J* = 7.50, 0.88 Hz, 1H), 7.23 (d, *J* = 1.00 Hz, 1H), 7.06 (s, 3H), 7.01 (s, 2H), 6.81 (s, 1H), 5.61 (s, 1H), 5.04 (s, 1H), 2.24

(s, 6H), 1.33 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$):δ 152.5, 145.0, 139.5, 139.3, 137.4, 135.3, 135.2, 132.8, 132.4, 132.1, 131.8, 129.7, 129.5, 128.1, 125.2, 124.4, 123.3, 123.1, 121.0, 120.9, 61.8, 34.3, 30.3, 21.3; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{35}H_{39}O_2NNaS$, 560.2594; found, 560.2603.

5-(((3,5-di-tert-butyl-4-hydroxyphenyl) (phenyl)methyl) imino)-10-methyl-5,10-dihydro-5l4-phenothiazine 5-oxide (17k):

Yield: 81% (74 mg); Yellow solid; **mp** = 147−148 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.0 (dt, *J* = 7.79, 1.61 Hz, 2H), 7.4-7.5 (m, 2H), 7.2-7.2 (m, 4H), 7.1-7.2 (m, 5H), 6.9 (s, 2H), 5.3 (s, 1H), 5.0 (s, 1H), 3.5 (s, 3H), 1.3 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 152.1, 145.2, 141.8, 141.7, 135.3, 134.9, 132.2, 132.2, 127.6, 127.5, 125.9, 124.9, 124.8, 124.6, 124.5, 124.3, 121.5, 121.3, 115.0, 114.9, 61.6, 35.6, 34.2, 30.3; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{34}H_{37}O_2N_2S$, 537.2570; found, 537.2591.

5-(((3,5-di-tert-butyl-4-hydroxyphenyl) (4-methoxyphenyl) methyl) imino)-10-methyl-5,10-dihydro-5l4-phenothiazine 5-oxide (17l):

Yield: 87% (76 mg); Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94 (dd, *J* = 7.75, 1.63 Hz, 2H),7.48 (dddd, *J* = 8.58, 7.18, 4.50, 1.63 Hz, 2H), 7.07 - 7.18 (m, 6H), 6.87 (s, 2H), 6.67 - 6.77 (m, 2H), 5.29 (s, 1H), 4.97 (s, 1H), 3.77 (s, 3H), 3.51 (s, 3H), 1.32 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 157.8, 152.1, 141.8, 137.7, 135.5, 134.8, 132.2, 128.5, 125.0, 124.9, 124.7, 124.4, 124.3, 121.5, 121.3, 115.0,114.9, 113.1, 61.0, 55.2, 35.6, 34.2, 30.3; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{35}H_{39}O_3N_2S$, 567.2676; found, 567.2698.

5-(((3,5-di-tert-butyl-4-hydroxyphenyl) (4-fluorophenyl) methyl) imino)-10-methyl-5,10-dihydro-5l4-phenothiazine 5-oxide (17m):

Yield: 80% (71 mg); Red oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.95 (dt, J = 7.79, 1.61 Hz, 2H), 7.46-7.53 (m, 2H), 7.07-7.19 (m, 6H), 6.81 - 6.87 (m, 4H), 5.32 (s, 1H), 4.98 (s, 1H), 3.51 (s, 3H), 1.32 (s, 18H); **^{13}C{^{1}H}NMR** (101 MHz, $CDCl_3$): δ 152.2, 141.8, 141.1, 135.2, 135.0, 132.3, 129.0, 129.0, 124.9, 124.8, 124.6, 124.5, 124.3, 121.6, 121.4, 115.1, 115.0, 114.4, 114.2, 77.2, 60.8, 35.6, 34.2, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ -117.5; **HRMS** (ESI) m/z: $[M-H]^-$ calcd for $C_{34}H_{36}O_2N_2FS$, 555.2476; found, 555.2502.

(((3,5-di-tert-butyl-4-hydroxyphenyl) (thiophen-2-yl) methyl) imino) diphenyl-l6-sulfanone (17n):

Yield: 75% (64 mg); White solid; **mp** = 180−181°C; **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.95 - 8.01 (m, 2 H),7.87-7.94 (m, 2H), 7.32-7.51 (m, 6H), 7.12-7.20 (m, 3H), 6.88 (dd, *J* = 5.00, 3.50 Hz, 1H), 6.70-6.78 (m, 1H), 5.60 (s, 1H), 5.06 (s, 1H), 1.39 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 152.6, 151.8, 141.1, 140.9, 135.4, 135.1, 132.3, 132.2, 128.9, 128.8, 128.6, 126.3, 124.2, 123.9, 123.8, 77.2, 57.9, 34.3, 30.3; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{31}H_{34}O_2NS_2$, 516.2025; found, 516.2045.

(((3,5-di-tert-butyl-4-hydroxyphenyl) (p-tolyl) methyl) imino) (methyl)(p-tolyl)-l6-sulfanone (17o):

Yield: 72% (55 mg); (dr =1:1); Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67 (d, *J*=8.38 Hz, 2H), 7.62 (d, *J* = 8.25 Hz, 2H), 7.32 (m, *J* = 8.00 Hz, 2H), 7.21 (d, *J* = 7.88 Hz, 2H), 7.19 (s, 2H), 7.16 (dd, *J* = 7.75, 7.00 Hz, 4H), 7.09 (m, *J* = 7.88 Hz, 2H), 7.02 (d, *J* = 7.75 Hz, 2H), 6.96 (s, 2H), 5.30 (s, 1H), 5.28 (s, 1H), 5.03 (s, 1H), 4.98 (s, 1H), 3.07 (s, 3H), 3.05 (s, 3H), 2.41 (s, 3H), 2.38 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H), 1.39 (s, 18H), 1.34 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 152.2, 152.2, 143.2, 143.0, 142.9, 142.6, 136.1, 135.7, 135.5, 135.5, 135.0, 135.0, 129.5, 129.4, 128.6, 128.6, 128.5, 127.5, 127.3, 124.6, 124.3, 61.2, 61.1, 45.7, 45.5, 34.3,

34.2, 30.3, 30.3, 21.4, 21.1; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{30}H_{39}NO_2NaS$, 500.2599; found, 500.2590.

(((3,5-di-tert-butyl-4-hydroxyphenyl) (4-methoxyphenyl) methyl) imino) (methyl)(p-tolyl)-l6-sulfanone (17p):

Yield: 75% (57 mg), (dr = 1:1). Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) : δ 7.62 (d, *J* = 8.24 Hz, 2H), 7.66 (d, *J* = 8.24 Hz, 2H), 7.35 (d, *J* = 8.70 Hz, 2H), 7.14-7.23 (m, 9H), 6.94 (s, 2H), 6.84 (s, 1H), 6.82 (s, 1H), 6.77 (s, 1H), 6.75 (s, 1H), 5.29 (s, 1H), 5.27 (s, 1H), 5.04 (s, 1H), 5.00 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.08 (s, 3H), 3.05 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H), 1.39 (s, 18H), 1.34 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 157.9, 157.9, 152.2, 152.1, 143.2, 142.9, 138.2, 137.9, 137.4, 137.4, 136.1, 135.8, 135.0, 129.5, 129.4, 128.7, 128.6, 128.5, 124.6, 124.3, 113.3, 113.2, 60.7, 60.7, 55.2, 45.8, 45.5, 34.3, 34.2, 30.3, 30.2, 21.4; **HRMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{30}H_{38}O_3NS$, 492.2578; found, 492.2567.

1-(((3,5-di-tert-butyl-4-hydroxyphenyl) (p-tolyl) methyl) imino) tetrahydro-1H-1l6-thiophene 1-oxide (17q):

Yield: 85% (59 mg); Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32 (m, *J* = 8.13 Hz, 2H), 7.19 (s, 2H), 7.10 (m, *J* = 7.75 Hz, 2H), 5.54 (s, 1H), 5.07 (s, 1H), 2.77-2.92 (m, 4H), 2.32 (s, 3H), 2.02-2.14 (m, 4H), 1.40 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 152.5, 142.4, 136.0, 135.5, 135.4, 128.9, 127.5, 124.3, 61.3, 52.8, 52.4, 34.4, 30.3, 23.3, 23.2, 21.1; **HRMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{38}NO_2S$, 428.2623; found, 428.2605.

5-(((4-hydroxy-3,5-dimethylphenyl) (phenyl)methyl) imino)-5H-5l4-dibenzo[b,d]thiophene 5-oxide (17r):

Yield: 80% (81 mg); White solid; **mp** = 186−187 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.24 Hz, 2H), 7.48 - 7.55 (m, 2H), 7.26 - 7.35 (m, 6H), 7.09 - 7.26 (m, 3H), 6.87 (s, 2H), 5.59

(s, 1H), 4.59 (br. s., 1H), 2.12 (s, 6H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 150.9,145.1,139.2,139.0,136.3, 132.8, 132.0, 129.7, 128.1, 127.7, 127.3, 126.4, 123.1, 123.0, 122.5, 121.1, 121.0, 61.2, 15.9; **HRMS** (ESI) *m/z*: $[M-H]^+$ calcd for $C_{27}H_{24}O_2NS$, 426.1523; found, 426.1517.

10-(((3,5-di-tert-butyl-4-hydroxyphenyl) (4-(methylthio) phenyl) methyl) imino)-9-hydroxy-9,10-dihydro-10l4-thioxanthene 10-oxide (18):

Yield: 72% (29 mg); Yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.0-8.1 (m, 1H), 8.0 (dd, *J* = 7.63, 1.14 Hz, 1H), 7.7-7.8 (m, 2H), 7.5-7.6 (m, 1H), 7.4-7.5 (m, 3H), 7.1 (q, *J* = 8.39 Hz, 4H), 6.8 (s, 2H), 5.8 (br. s., 1H), 5.3 (s, 1H), 5.0 (s, 1H), 2.4 (s, 3H), 1.3 (s, 18H); **$^{13}C\{^{1}H\}$ NMR** (126 MHz, $CDCl_3$): δ 152.3, 142.3, 142.0, 141.5, 135.7, 135.1, 134.5, 131.8, 131.6, 128.0, 127.5, 127.3, 126.6, 125.5, 125.1, 124.3, 123.9, 123.9, 67.0, 61.9, 34.2, 30.3, 16.2; **HRMS** (ESI) *m/z:* $[M+H]^+$ calcd for $C_{35}H_{40}O_3NS_2$, 586.2444; found, 586.2463.

Section II

Metal-Free and Mild Synthesis of Congested *N*-Alkyl Sulfoximines with in Situ-Generated Aza oxyallyl Cations from Functionalized Alkyl Bromide

3.2.1 Introduction

Sulfoximines are mono-aza analogs of sulfones with attractive structural properties that have been widely used for the last decade. [26,27] Additionally, it is significantly used as a privileged intermediate for constructing heterocyclic cores.[28] Despite its high metabolic stability, hydrogen-bonding ability, structural diversity, and physicochemical properties, sulfoximine is an intriguing pharmacophore.[29] Furthermore, the sulfoximine

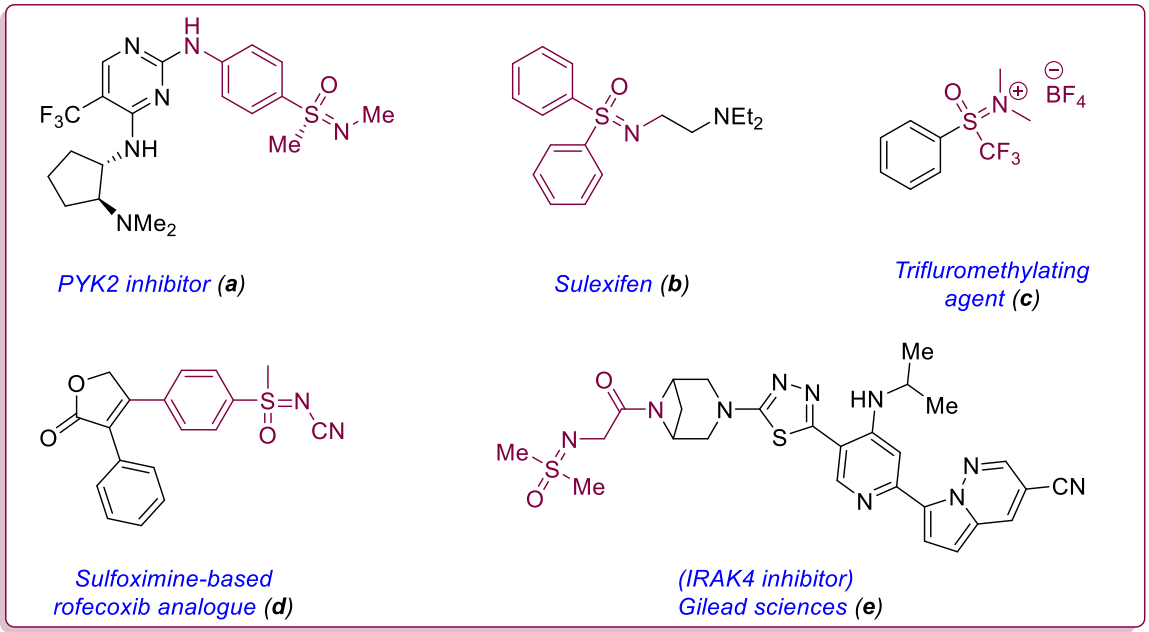


Figure 3. Biologically active sulfoximine and *N*-alkyl sulfoximines.

moiety is employed in drug discovery to enhance specificity, reduce unwanted toxicity, and improve stability/oral bioavailability. [30-32] The chiral auxiliaries and ligands of sulfoximines can also be used in asymmetric syntheses.[33] Moreover, the *N*-alkyl

sulfoximines have attracted considerable interest due to their presence in natural products, and their biologically active properties.[34] For instance, PYK2 inhibitor (**a**) is the analog of *N*-alkyl sulfoximine, which is used to treat osteoporosis.[35] Suloxifen (**b**) is a polyvalent spasmolytic and anti-asthmatic agent and is useful in oral and parenteral dosage.[36] The fluorinated sulfoximine (**c**) acts as an trifluromethylating agent in fluorination chemistry.[37] Similarly, the sulfoximine-based rofecoxib (**d**) analog exhibits 1% and 48% inhibition of COX-1 and COX-2, respectively, at 10 mm concentrations. [38] A sulfoximidoyl-containing scaffold (**e**) is useful as an IRAK4 (interleukin-1 receptor-associated kinase 4) inhibitor, as shown in **Figure 3**. [39]

In contrast, the *α*-bromo amide is the precursor of the aza-oxyallyl cation, a versatile building block for organic synthesis.[45] The functional heterocyclic motifs were developed from highly reactive aza-oxyallyl cations *via* [3+2],[46a] [3+3],[46b] and [4+3][46c] cycloaddition reactions with different dipoles. Furthermore, direct coupling with the various nucleophilic partners such as R–OH, R–NH_2 R–N_3 with *α*-bromo amide with the metal or metal-free condition forms a novel congested C(sp^3)–X bonds (X=N, O) are also known in the literature.[47]

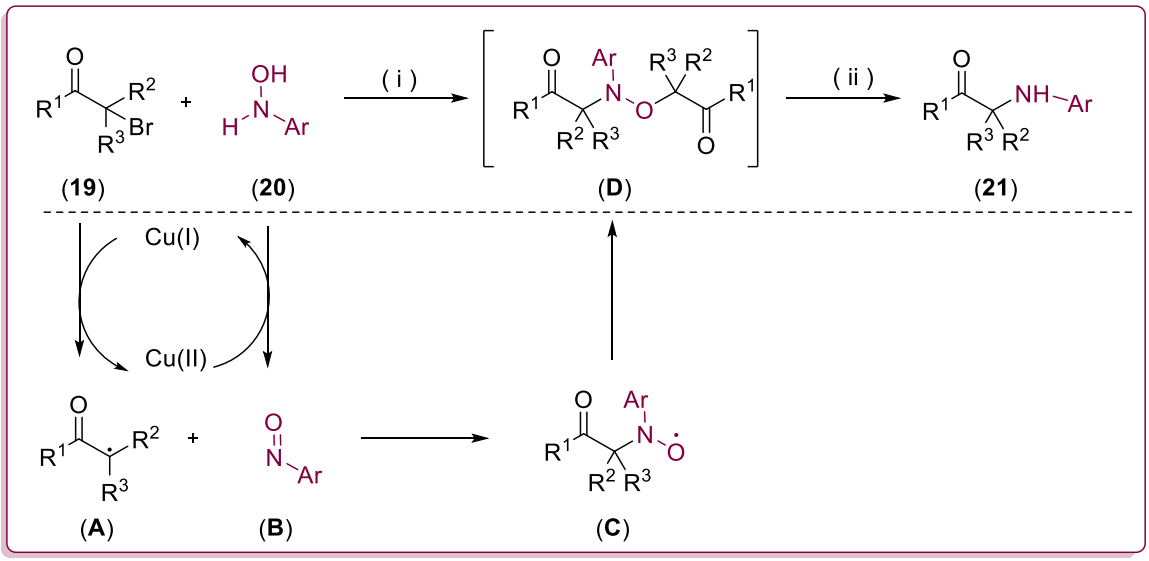
3.2.2 Review of Literature

Many numbers of classical "N" and "O" alkylation reactions of bromo amide with different nucleophiles are known in the literature. Some selective Nucleophilic substitution reactions are depicted below.

Alaniz's Approach (2015)[47a]

In 2015, Alaniz et al. developed a Cu-catalyzed hindered *N*-alkylation reaction of Aryl hydroxylamine (**20**) and α-bromo amide (**19**). The present reaction proceeded through the

radical pathway. The α-alkyl radical (**A**) was generated in the presence of Cu(I) catalyst and the formation of Cu(II). Then subsequently, hydroxyamine was oxidized in the presence of Cu(II) to formed nitrosobenzene (**B**). Then, the α-alkyl radical is trapped by

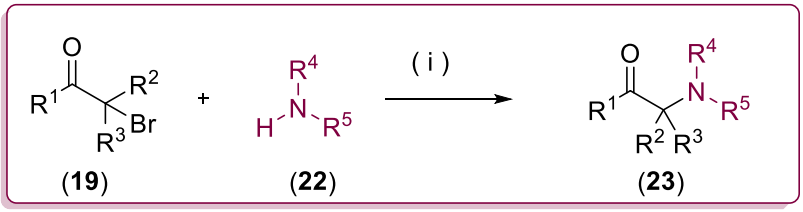


Scheme 7. (i) $CuCl_2$ (5 mol%), PMDTA (1.8 equiv.), THF, N_2, rt. (ii) SmI_2

nitrosobenzene at the N- center to develop nitroxyl radical (**C**), and it is trapped by another α-alkyl radical to obtain the polymerized product (**D** at the end of the N-O bond cleavage presence of SmI_2 to obtaincorresponding hindered α-amino carbonyls (**21**) (**Scheme 7**).

Nishikata's Approach (2017)[47b]

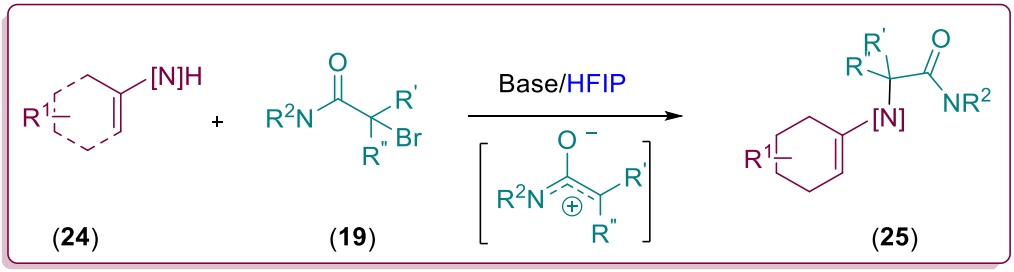
Later in 2017, Nishikata and coworkers also established a method for synthesis of hindered α-Amino acid derivatives (**23**). The generation of Cu-amide intermediates initiated the reaction by oxidative insertion. The developed copper amide intermediate reacted with α-bromoamide (**19**) to furnish the desired product (**Scheme 8**).



Scheme 8. (i) Cu $(Br)_2SMe_2$ (10 mol%), PPh_3(10 mol%), K_3PO_4 (1.2 equiv.), toluene, rt.

Ritesh Singh' Approach (2020)[47c]

Singh and coworkers also established the congested and functionalized alkyl bromide (**25**) from α-bromohydroxymates (**19**) and substituted anilines (**24**) in the presence of HFIP as a fluorinated solvent, as shown in Scheme 9. The presence transformation occurs *via* aza-ooxyallyl cation pathway. Initially, α-bromohydroxymates generate aza-oxyallyl cation presence of HFIP and base. Further, substituted anilines trapped the corresponding aza-oxyallyl cation *via* S_N1 substitution reaction to obtain desired alkylated product in good to excellent yield (up to 91%).



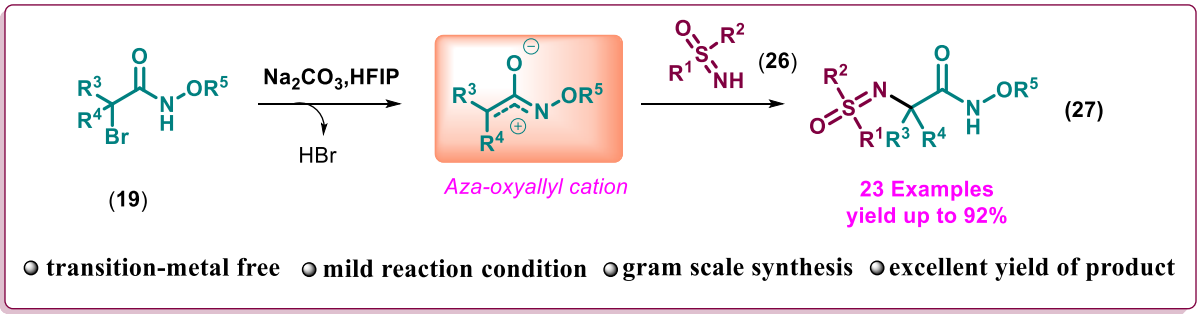
Scheme 9. (i) Na_2CO_3 (2 equiv.), HFIP (0.1 M), rt.

3.2.3 Present Work

3.2.3.1 Objective

Recently, we have developed a method to synthesize diarylmethine imino sulfanones by adding of *N*H-sulfoximines to *para*-quinone methides (*p*-QMs) *via* C–N bond formation.

[48c] Based on this result and our metal-free[48] approaches to construct the C–C and C–N bond formation reactions, here we report an operationally simple and sustainable protocol for synthesizing congested *N*-alkyl sulfoximines at room temperature via aza-oxyallyl cation pathway. (**Scheme 10**)



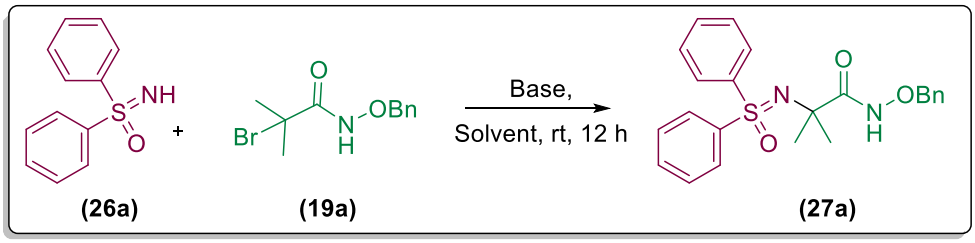
Scheme 10. General Reaction Scheme of Congested N-alkyl Sulfoximines Synthesis via Oxyallyl cation pathway

3.2.4 Result and Discussion

We commenced this study by employing sulfoximine **26a** and *α*-bromo hydroxamate **19a** as a model substrate to check the feasibility of the reaction. With the help of the previous literature report, [22 b-e] we start our investigation with **26a**, **19a** (1 equiv. respectively), 2 equiv. of Na_2CO_3 as a base in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at room temperature; fortunately, the desired product **27a** was obtained in 46% yield in 12 h (Table 6, entry 1). By encouraging this result, we optimized our reaction by varying parameters such as the equivalence of *α*-bromo hydroxamate **19a**, bases, and solvents. First, we changed the equivalent of the *α*-bromo hydroxamate **19a** from 1 to 1.2; we observed a slight increment in the yield of the desired product (Table 6, entries 1-3). However, increasing the equiv. of Na_2CO_3 from 2 to 3; it resulted in the formation of product **27a** in 84% yield. (Table 6, entry 4). Then, we screened various bases, such as K_2CO_3, CS_2CO_3, Et_3N, DBU, and DIPEA, in HFIP solvent, but the yield of the expected product was not satisfactory compared to entry 4 (Table 6, entries 5-9). Furthermore,

we tried the reaction in various routine solvents, such as Acetonitrile and THF, but all these solvents failed to give desired product **27a** (Table 6, entries 10-12). Then we realized the fluorinated solvent was required for the proceeds of the reaction, and we used mixed

Table 6. Optimization of Reaction Condition [a]



(26a) (19a) (27a)

Sr. No.	2a (equiv.)	Base (equiv.)	Solvents	Yield (%) [b]
1.	1.0	Na_2CO_3 (2.0)	HFIP	46
2.	1.1	Na_2CO_3 (2.0)	HFIP	58
3.	1.2	Na_2CO_3 (2.0)	HFIP	66
4.	1.2	Na_2CO_3 (3.0)	HFIP	84
5.	1.2	K_2CO_3 (3.0)	HFIP	78
6.	1.2	Cs_2CO_3 (3.0)	HFIP	74
7.	1.2	Et_3N (3.0)	HFIP	56
8.	1.2	DBU (3.0)	HFIP	58
9.	1.2	DIPEA (3.0)	HFIP	64
10	1.2	Na_2CO_3 (3.0)	ACN	NR
11.	1.2	Na_2CO_3 (3.0)	THF	NR
12.	1.2	Na_2CO_3 (3.0)	DCM	NR
13.[c]	1.2	Na_2CO_3 (3.0)	DCM	82
14.[d]	**1.2**	**Na_2CO_3 (3.0)**	**DCM**	**88**

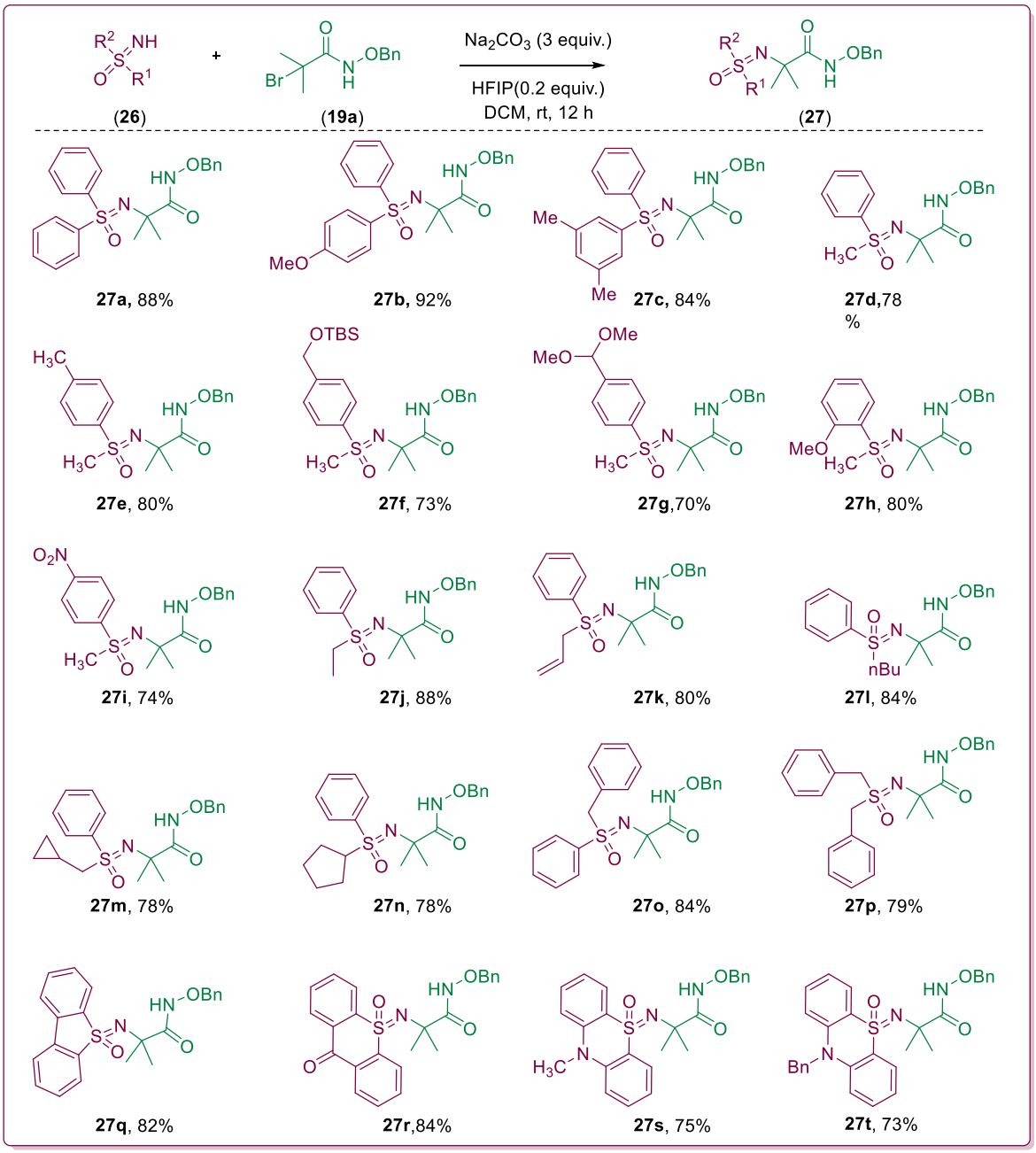
Reaction conditions: a) Reactions were conducted in closed vessel at rt with **1a** (1 equiv.), **2a**, base, and solvent, 12 h; b) Isolated yields after column chromatography, NR = No Reaction; c) used HFIP 0.1 equiv. as co-solvent; d) used HFIP 0.2 equiv. as co-solvent.

solvents such as CH_2Cl_2 and HFIP (0.1 equiv.). Gratifyingly, the reaction works smoothly to obtain the corresponding substitution product **27a** in 82% (Table 6, entry 13). Enhancement of yield (up to 88%) of **27a** was observed with an increasing the loading of co-solvent (HFIP) (0.1 equiv. to 0.2 equiv.) in 12 h of reaction time (Table 6, entry 14). Based on the above optimization study, **26a** (1.0 equiv.), **19a** (1.2 equiv.), HFIP (0.2 equiv.) in CH_2Cl_2 is the excellent optimized reaction condition for the substitution reaction (Table 6, entry 14).

With the optimized condition, we examined the varieties of sulfoximines (**26a**-**26r**) with α-bromo hydroxamate **19a** for substitution reaction, as shown in Table 7. Diaryl-sulfoximines with substitution such as (4-H, 4-OMe, and 3,5 di-Me) on aromatic ring reacted smoothly with **19a** to obtain *N*-alkyl sulfoximine in excellent yields (up to 92%, entries **27a- 27c**). Whereas the aryl-methyl sulfoximines with various substitutions, such as electron-donating and electron-withdrawing on *ortho* (–OMe), and *para* (–H, –Me, –$CH(OMe)_2$, –CH_2OTBS and –NO_2) position reacted well with α-halo hydroxamate **19a** to furnishes the substitution products in excellent yields (70% to 78%, entries **27d**-**27i**). In addition, phenyl-alkyl sulfoximines such as phenyl ethyl (**26j**), (phenyl-allyl (**26k**), phenyl-*n*-butyl (**26l**), phenyl-cyclopropyl (**26m**), and phenyl-cyclopentyl (**26n**) sulfoximine also feasible with our present reaction condition to produce corresponding substitution products (**27j**-**27n**) in good to excellent yield (78%-84%). Moreover, phenyl-benzyl sulfoximine(**26o**) and di-benzyl sulfoximine (**26p**) are also compatible with **19a** to furnish the desired product **27o** and **27p** in 79% and 84%, respectively. Furthermore, the bulky heterocyclic sulfoximine such as thioxanthone sulfoximine (**26q**), dibenzothiophene- sulfoximine (**26r**), –Me and –Bn protected thiazine derived

sulfoximine (**26s** and **26t**) also reacted efficiently with α-bromo amide to obtain the respective substitution products in quantitative yields, i.e., 73% to 84% (**27q-27t**).

Table 7. Substrate Scope of the various *p*-QMs [a, b]



[a] **Reaction conditions: 26a-t** (1 equiv.), **19a** (1.2 equiv.), Na_2CO_3 (3 equiv.), HFIP (0.2 equiv.), DCM, room temperature, 12 h, under N_2 atmosphere. [b] Isolated yields after column chromatographic purification are shown.

Example 1:

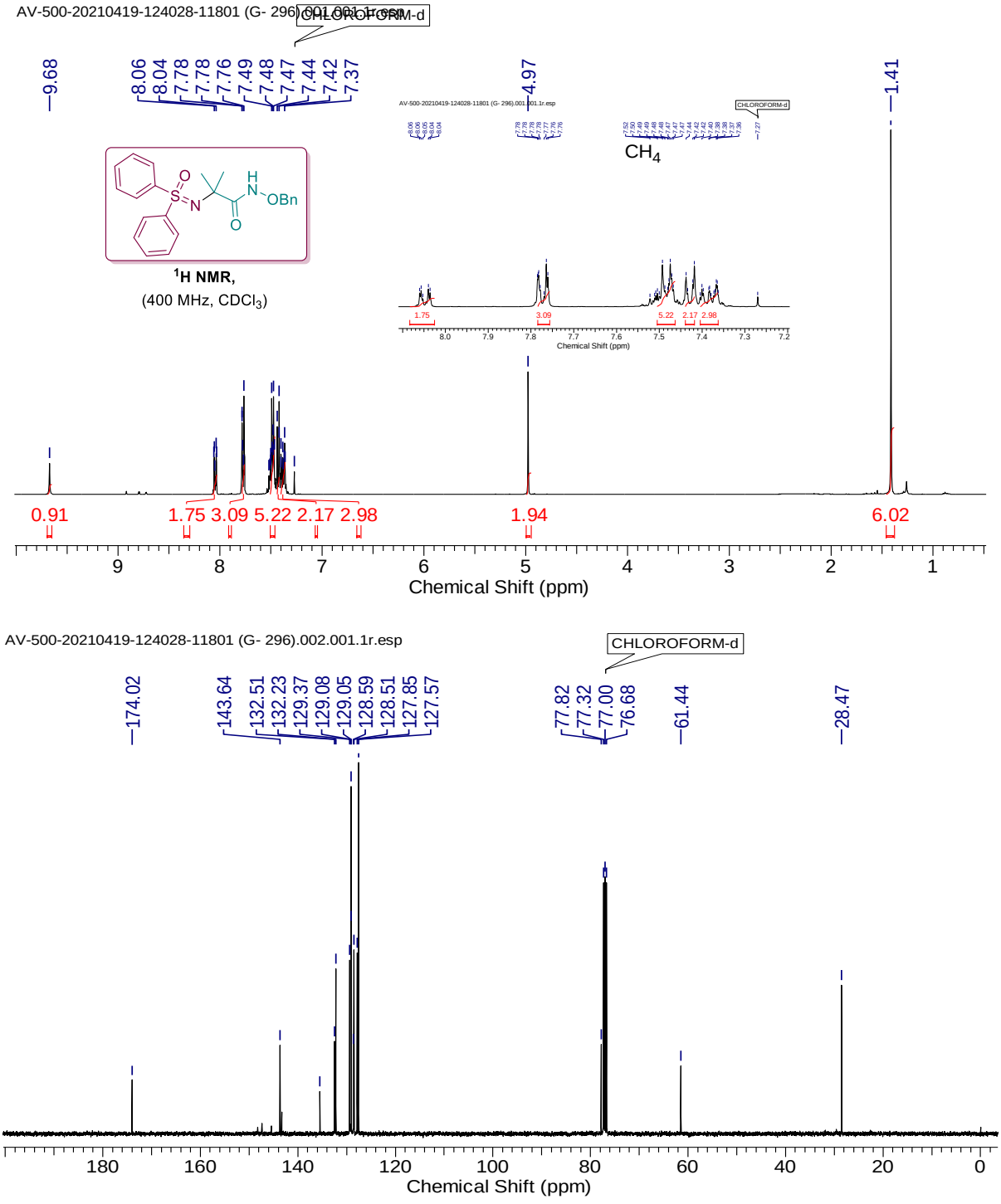


Figure 4: ^{1}H and $^{13}C\{^{1}H\}$ NMR of *N*-(benzyloxy)-2-methyl-2-((oxodiphenyl-l6-sulfaneylidene) amino) propenamide **(27a)**

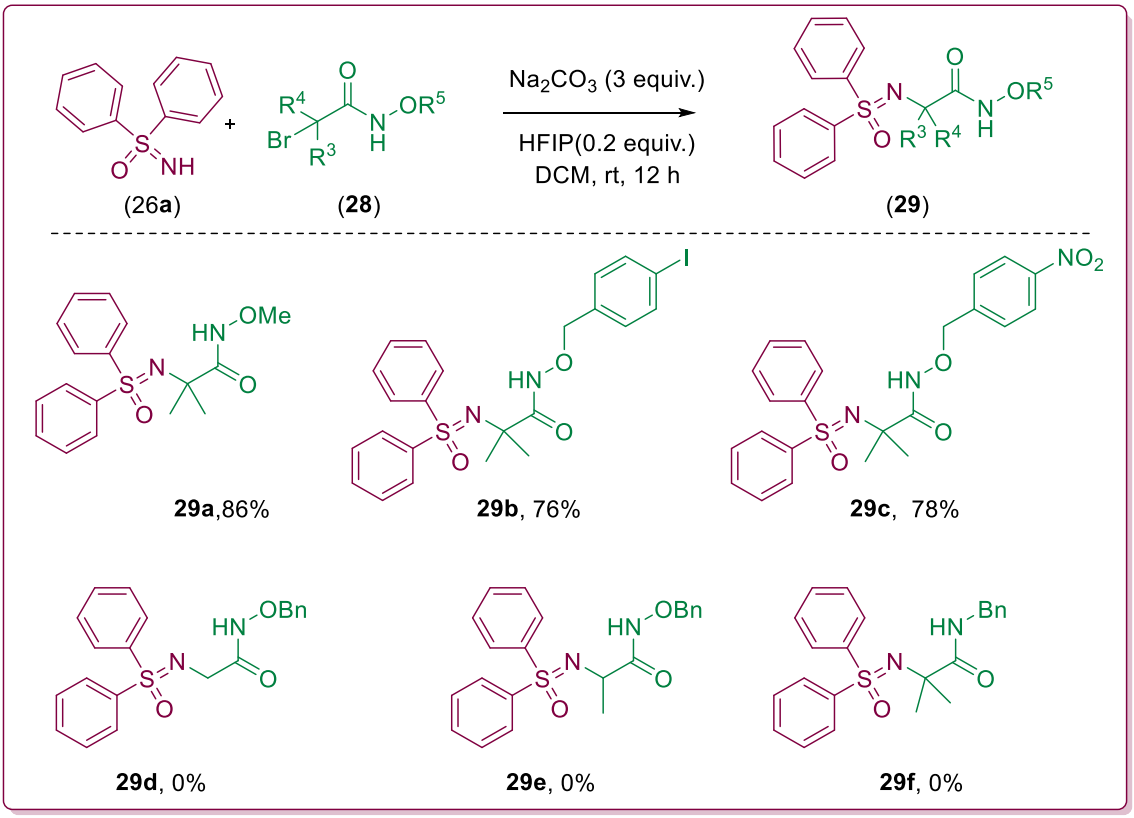
The corresponding hindered *N*-alkylation of Sulfoximine product (**27a**) was confirmed by ^{1}H and ^{13}C NMR Spectrum. The proton (^{1}H) NMR spectrum showed the peak at δ 9.68 singlet proton corresponding to the free (N-**H**) of hydroxyamate. While the peaks come in between δ 8.03- 7.36 (8.03-8.08 (m, 2H), 7.76-7.78 (m, 3H), 7.46-7.50 (m, 5H), 7.42-7.44 (m, 2H), 7.36-7.40 (m, 3H), are the protons of aromatic region. The peak comes at δ 4.97 (s, 2H) singlet for 2-**H** corresponding to the benzylic proton. Whereas the singlet peak at δ 1.41 (s, 6H) for 6 protons of two symmetric methyl groups of hydroxymate group. The ^{13}C spectrum of compound **3a** showed a peak at δ 174.02, corresponding to the amide carbon, whereas, the aromatic carbon comes in between δ 143.64 to 127.57 region in the spectra. The peak at δ 77.82 is the corresponding characteristic quaternary carbon, and the peak appeared at δ 28.47, corresponding to the carbons of two symmetrical methyl groups. (**Figure 4**).

After successfully screening of various *N*-substitutions with sulfoximine, we next vary the different α-halo hydroxamate under standard reaction conditions as depicted in Table 8. While the benzyloxy group in the α-bromo hydroxamates was replaced by other protecting groups such as methoxy, 4-iodo benzyloxy, and 4-nitro benzyloxy, it reacted well with sulfoximine 1a to furnish the desired substitution products (**29a-29c**) in comparative yields. Nevertheless, the α-halo hydroxamates with an absence of alkyl group, mono-alkyl group, and –Bn protected α-bromo amide are not suitable for forming N- alkyl sulfoximines (**29d-29f**).

Example 2:

Next, the representative synthesized compound N-methoxy-2-methyl-2-((oxodiphenyl-l6-sulfaneylidene) amino) propenamide (**29a**) was confirmed by 1H, 13C NMR spectroscopy. The peak appeared at δ 9.80, corresponding to the proton of free N-**H** (s, 1H) of the substituted amide group. 7.95-7.27 are the aromatic ring protons (7.86-8.03 (m, 4H), 7.42-7.57 (m, 6H), and 3.79

Table 8. Substrate scope of different α-bromo hydroxamates.[a, b]



Reaction conditions: **26a** (1 equiv.), **28a-f** (1.2 equiv.), Na_2CO_3 (3 equiv.), HFIP (0.2 equiv.), DCM, room temperature, 12 h, under N_2 atmosphere. [b] Isolated yields after column chromatographic purification are shown.

Example 2:

are the methoxy methyl protons. (-**OMe**) 3.79 (s, 3H), and the peak corresponding to the δ 1.42 for the 6-singlet proton of two methyl groups (1.42 (s, 6H). Moreover, compound **29a** was also confirmed by the 13C spectrum. This peak appears at 64.13, which is the characteristic tertiary carbon of the compound, as shown in **Figure 5**.

To express the practicability and potential synthetic application of *N*-alkyl sulfoximines, we carried out the present reaction on a 1 g. scale for **26a** under standard reaction conditions to obtain 84% yield (1.5 g.) of product **27a** in 12 h of reaction time (**Scheme 11**).

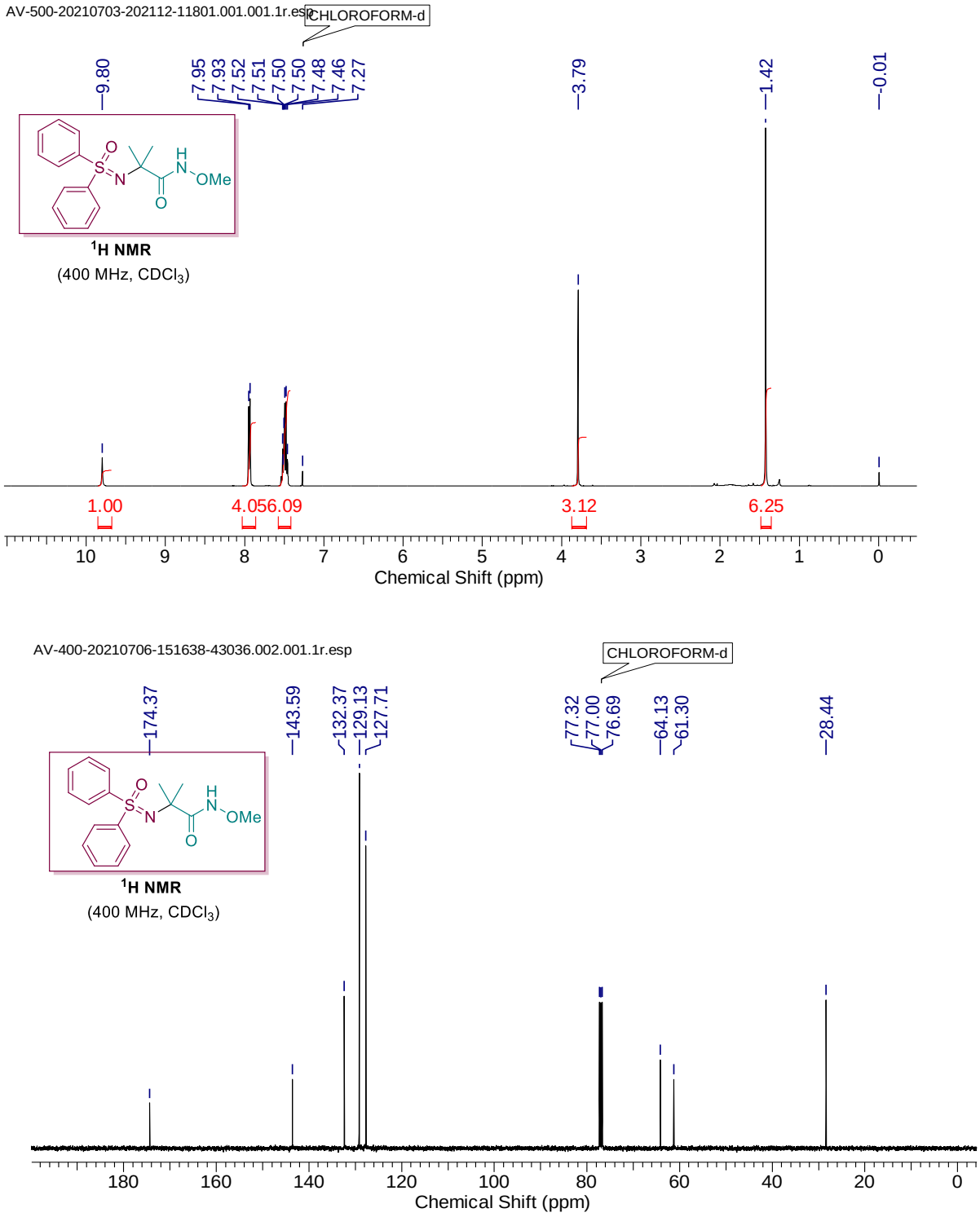
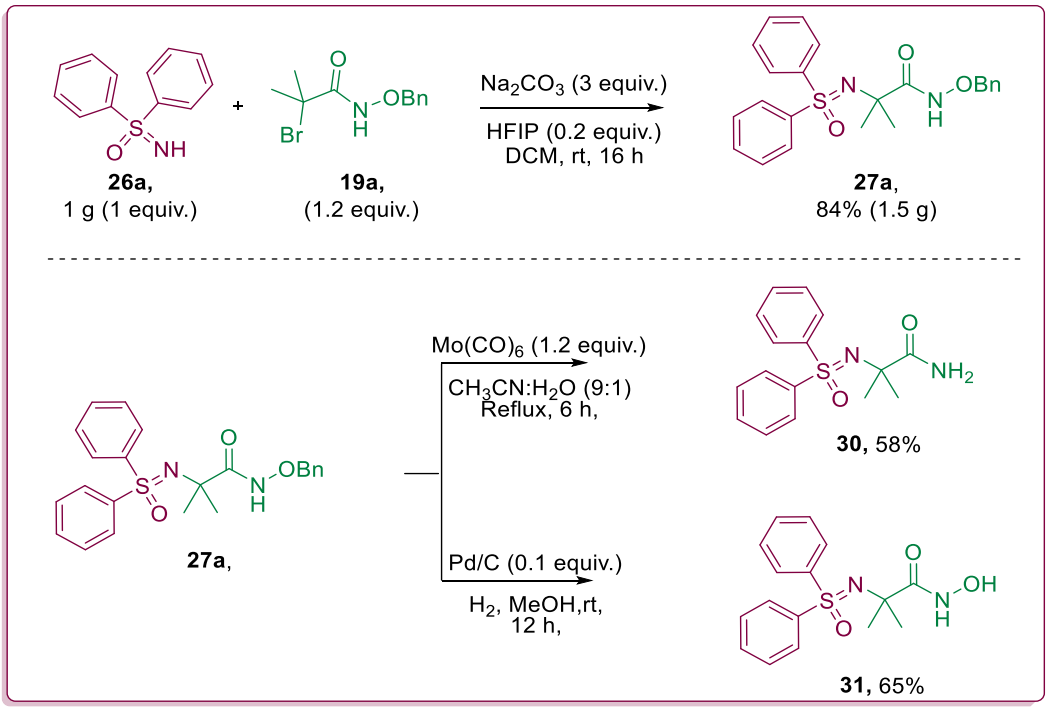


Figure 5: ^{1}H and ^{13}C of *N*-methoxy-2-methyl-2-((oxodiphenyl-l6-sulfaneylidene) amino) propenamide **(5a)**



Scheme 11: Scale-up synthesis and synthetic transformation of product **27a**.

Further, we demonstrate the synthetic utilities of the product as shown in Scheme 4. First, the N–O bond of *α*-sulfoximine hydroxymate **27a** was cleaved by using $Mo(CO)_6$ in the mixture of solvents (Acetonitrile: H_2O in 9:1 proportion) under the refluxed condition to obtain Amide product **30** in 58% yield. Next, the benzyl group was removed under hydrogenation conditions to produce the C–O bond cleaved product **31** in 65% yield.[49]

Example 3:

The formed product 30 was then confirmed by ^1H and ^{13}C and HRMS spectroscopy. In this ^1H NMR spectrum, the disappearance of the peak of the benzylic proton is the clear sign of removal of the -OBn group from the compound, and in the HRMS spectrum, the exact mass of the amide group was found (HRMS (ESI) m/z: [M+H]+ calcd for $C_{16}H_{19}O_2N_2S$, 303.1162; found, 303.1167) as shown in **Figure 6.**

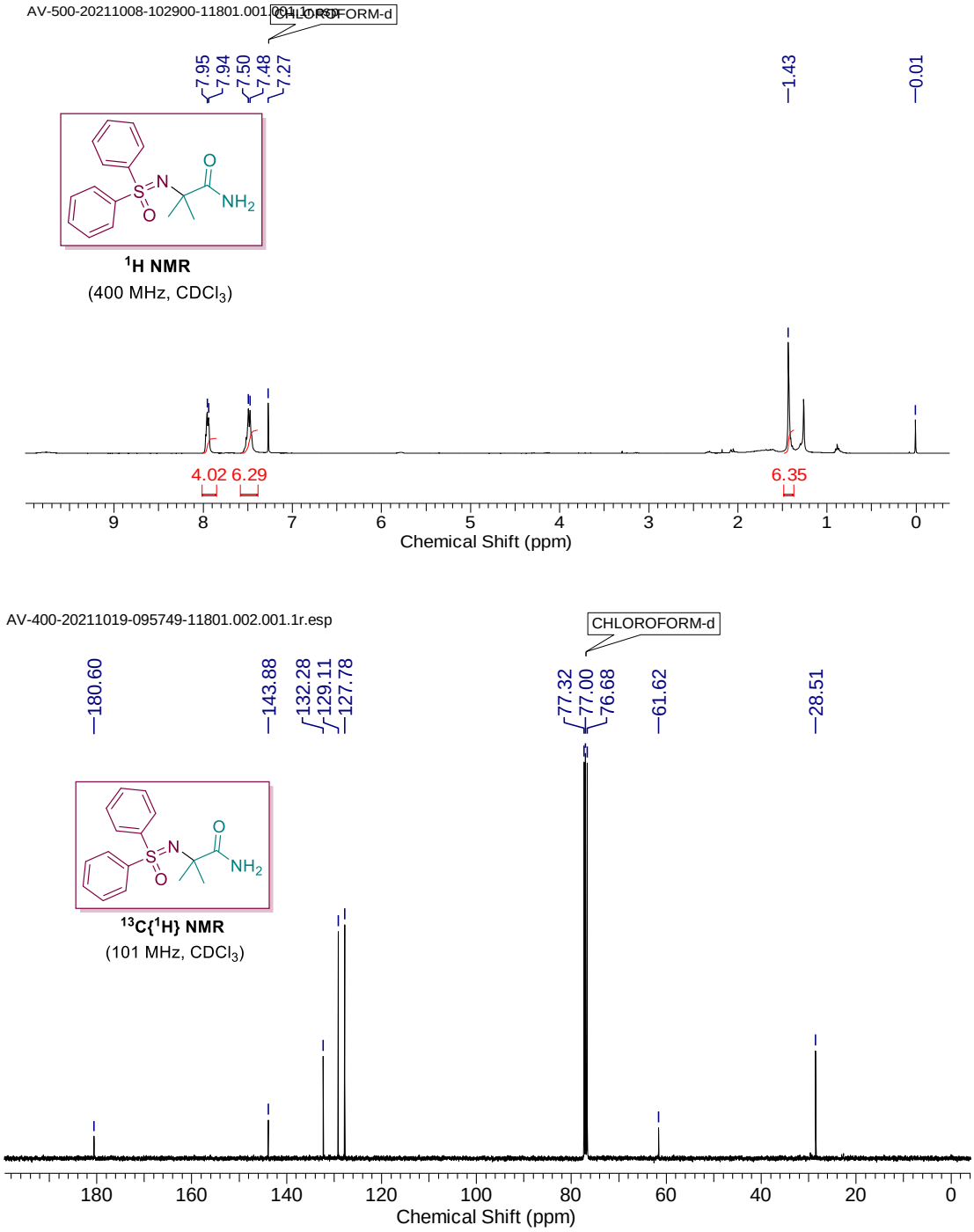
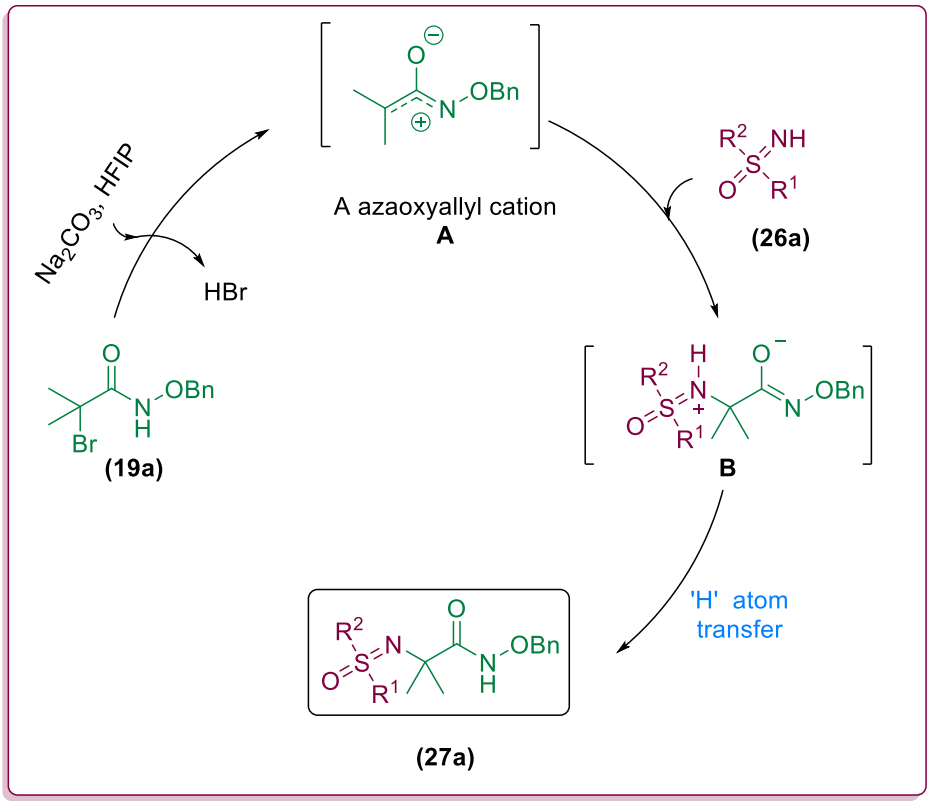


Figure 6: 2-methyl-2-((oxodiphenyl-l6-sulfaneylidene) amino) propenamide (**30**)

Based on the literature report [44, 48, 47 (c)] and controlled experiment, we proposed the plausible reaction mechanism as shown in Scheme 12. Initially, azaoxyallyl cation **A** formed from *α*- halo

hydroxamate **19a** in the presence of HFIP and base with the removal of HBr. Subsequentially, the addition of *N*H-Sulfoximine in in-situ generated azaoxyallyl cationic intermediate **A** *via* the S_N1 displacement pathway to form intermediate **B**. The H- atom transfer at the late step to obtain the desired substitution product **27a**.



Scheme 12: Plausible Reaction Mechanism

3.2.5. Conclusion

In conclusion, we have developed a metal-free and convenient protocol for the *N*-alkylation of sulfoximines using functionalized tertiary halides *via* aza-oxyallyl cations. This process provides a mild and general method to synthesize congested *N*-alkyl sulfoximines by reacting *α*-halo hydroxamates and aryl-alkyl, di-aryl, and hetero-aryl sulfoximines.

3.2.6. Experimental Section

3.2.6.1. General Experimental Procedure for the Synthesis 27 (27a-27t):

Screw-cap reaction vail with a magnetic stir bar was added sulfoximines **26** (50 mg, 1 equiv.) and α- halo hydroxamate **19a** (1.2 equiv.) in DCM under nitrogen atmosphere. In this reaction mixture 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (0.2 equiv.), and Na_2CO_3 (3 equiv.) were added. The mixture was stirred at room temperature until the starting material was completely consumed (by TLC analysis). After completion, the reaction was quenched with water (3 mL) and extracted with DCM (3×3 mL), and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent evaporated on a rotary evaporator under reduced pressure to obtain a crude product, purified by column chromatography on silica gel with petroleum ether and ethyl acetate to afford the desired products **27a-27t**.

3.2.6.2 General Experimental Procedure for the Synthesis 29 (29a-29f):

Screw-cap reaction vail with a magnetic stir bar were added sulfoximine **26a** (1 equiv.) and α-halo hydroxamate **28** (1.2 equiv.) in DCM under a nitrogen atmosphere. In this reaction mixture 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (0.2 equiv.) , and Na_2CO_3 (3 equiv.) were added. The resulting mixture was a stir at room temperature until starting material was completely consumed (by TLC analysis). After completion, the reaction was quenched with water (3 mL) and extracted with DCM (3×3 mL), and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent evaporated on a rotary evaporator under reduced pressure to obtain a crude product, purified by column chromatography on silica gel with petroleum ether and ethyl acetate to offer desired product **29a-29f.**

3.2.6.3 General Experimental Procedure for the Gram Scale Synthesis of 27a

Screw-cap reaction vail with a magnetic stir bar was added Diphenyl-sulfoximine **26a** (1 g., 1 equiv., 4.6082 mmol) and α- bromo hydroxamate **19a** (1.5 g., 1.2 equiv., 5.5299 mmol) in DCM under nitrogen atmosphere. In this reaction mixture 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (0.2 equiv.), and Na_2CO_3 (1.4 g., 3 equiv., 13.8248 mmol) were added. The resulting mixture was stirred at room temperature until the starting material was completely consumed (by TLC analysis). After completion, the reaction was quenched with water (20 mL) and extracted with DCM (30×3 mL), and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent evaporated on a rotary evaporator under reduced pressure to obtain a crude product, purified by column chromatography on silica gel with petroleum ether and ethyl acetate to afford the desired product **27a** in 84% (1.5 g.)

3.2.6.4 General Experimental Procedure for the Synthesis 30

To a solution of **27a** (30.0 mg, 1.0 equiv.) in CH_3CN/H_2O (9:1, degassed under nitrogen) was added Mo $(CO)_6$ (1.2 equiv.) and again degassed under a nitrogen. Then the resulting reaction mixture was stirred and refluxed for 6 hours under nitrogen atmosphere. The complete consumption of **3a** was confirmed by TLC. The crude reaction mixture was filtered through a celite bed and washed with ethyl acetate (50 mL). The collected filtrates were combined and concentrated under reduced pressure. Then the residue was purified by silica gel column chromatography (Pet Ether: Ethyl acetate = 40:60) to afford the desired product **30** (13 mg, 58%).

3.2.6.5 General Experimental Procedure for the Synthesis 31

The Pd/C (20.0 mg, palladium on activated carbon, 10% Pd basis, 0.1 equiv) was added to a solution of **27a** (30 mg, 1.0 equiv) in MeOH (1.5 mL) under N_2 atmosphere. The N_2 balloon was then exchanged for hydrogen balloon. Then the reaction mixture was stirred under an H_2

atmosphere (1 atm) at rt for 12 hr. After the reaction was complete (monitored by TLC), the crude reaction mixture was filtered through celite and washed with EtOAc. The solvent was removed under reduced pressure. Then the residue was purified by silica gel column chromatography (Pet Ether : Ethyl acetate = 50:50) to afford the desired product **31** (14.9 mg, 65%).

***N*-(Benzyloxy)-2-methyl-2-((oxodiphenyl-l6-sulfaneylidene) amino) propenamide (27a):**

Yield: 88% (82 mg); White gum; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.03-8.08 (m, 2H), 7.76-7.78 (m, 3H), 7.46-7.50 (m, 5H), 7.42-7.44 (m, 2H), 7.36-7.40 (m, 3H), 4.97 (s, 2H), 1.41 (s, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 174.0, 143.6, 135.5, 132.5, 132.2, 129.4, 129.1, 129.1, 128.6, 128.5, 127.8, 127.6, 77.8, 61.4, 28.5; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{25}O_3N_2S$, 409.1580; found, 409.1586.

***N*-(Benzyloxy)-2-(((4-methoxyphenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-methylpropanamide (27b):**

Yield: 92% (81 mg); White gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3423.52, 2984.74, 2932.91, 1726.87, 1678.94, 1650.22, 1632.01, 1592.76, 1494.24, 1444.44, 1257.25, 1194.06, 1126.37, 1093.37, 1025.12, 752.46; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.80 (br. s., 1H), 7.73-7.77 (m, 2H), 7.68-7.71 (m, 2H), 7.49 (s, 1H), 7.47 (d, J = 1.13 Hz, 1H), 7.34-7.44 (m, 6H), 6.87-6.92 (m, 2H), 4.97 (s, 2H), 3.83 (s, 3H), 1.41 (d, J = 1.75 Hz, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 174.0, 162.8, 143.8, 135.5, 134.5, 132.1, 129.8, 129.4, 129.3, 129.0, 128.6, 128.5, 127.3, 114.3, 77.8, 61.5, 55.6, 28.4, 28.3; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{27}O_4N_2S$, 439.1686; found, 439.1682.

***N*-(Benzyloxy)-2-(((3,5-dimethylphenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-methylpropanamide (27c):**

Yield: 84% (74 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3021.20, 2400.64, 1850.35, 1616.39, 1518.96, 1422.95, 1332.01, 1216.31, 1152.99, 1109.54, 1040.64, 925.44, 759.59, 669.06; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.06 (dd, *J* = 8.32, 1.31 Hz, 1H), 7.91-7.95 (m, 1H), 7.72-7.80 (m, 2H), 7.68 (s, 1H), 7.51-7.57 (m, 1H), 7.47 (ddd, *J* = 4.88, 3.56, 1.44 Hz, 2H), 7.41-7.42 (m, 2H), 7.34-7.36 (m, 2H), 7.11 (s, 1H), 4.96 (s, 2H), 2.32 (s, 6H), 1.41 (s, 3H), 1.40 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 174.2, 143.8, 143.2, 139.4, 139.1, 135.4, 134.1, 132.1, 129.3, 129.2, 129.0, 128.6, 128.5, 127.9, 127.5, 126.3, 125.5, 125.2, 77.9, 61.4, 28.5, 28.3, 21.3, 21.2; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{27}O_3N_2S$, 437.1893; found, 437.1898.

***N*-(Benzyloxy)-2-methyl-2-((methyl(oxo)(phenyl)-l6-sulfaneylidene) amino) propenamide (27d):**

Yield: 78% (87 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3443.01, 2982.22, 1659.00, 1551.78, 1445.58, 1257.82, 1121.27, 977.05, 744.14, 691.80; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.78-7.83 (m, 2H), 7.57-7.62 (m, 1H), 7.51-7.55 (m, 2H), 7.46-7.50 (m, 2H), 7.37-7.44 (m, 3H), 4.91-5.02 (m, 2H), 2.97 (s, 3H), 1.46 (s, 3H), 1.22 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 174.1, 143.4, 135.5, 132.8, 129.5, 129.4, 128.7, 128.6, 127.6, 77.9, 61.5, 48.2, 29.1, 27.7; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{23}O_3N_2S$, 347.1424; found, 347.1437.

***N*-(Benzyloxy)-2-methyl-2-((methyl(oxo)(p-tolyl)-l6-sulfaneylidene) amino) propenamide (27e):**

Yield: 80% (85 mg); Yellowish white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3628.39, 2926.57, 1666.51, 1494.06, 1454.25, 1376.67, 1257.48, 1120.53, 977.30, 753.00; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.68 (m, *J* = 8.38 Hz, 2H), 7.45-7.50 (m, 2H), 7.36-7.43 (m, 3H), 7.30 (m, *J* = 8.00 Hz, 2H), 4.92-5.00 (m, 2H), 2.94 (s, 3H), 2.44 (s, 3H), 1.45 (s, 3H), 1.21 (s, 3H); **^{13}C{^{1}H} NMR**

(126 MHz, $CDCl_3$) δ 174.1, 143.6, 140.4, 135.5, 129.9, 129.4, 128.6, 128.5, 127.6, 77.8, 61.3, 48.3, 29.0, 27.6, 21.4; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{25}O_3N_2S$, 361.1580; found, 361.1595.

***N*-(Benzyloxy)-2-(((4-(((tert-butyldimethylsilyl) oxy) methyl) phenyl) (methyl)(oxo)-l6-sulfaneylidene) amino)-2-methylpropanamide (27f):**

Yield: 73% (59 mg); White gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3442.81, 2955.15, 2856.42, 1724.58, 1658.85, 1469.34, 1453.48, 1408.35, 1256.33, 1195.30, 1079.66, 838.13, 752.79; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.76 (d, J = 8.38 Hz, 2H), 7.45-7.50 (m, 4H), 7.37-7.44 (m, 3H), 4.97 (d, J = 5.25 Hz, 2H), 4.81 (s, 2H), 2.95 (s, 3H), 1.46 (s, 3H), 1.22 (s, 3H), 0.94-0.99 (m, 9H), 0.13 (s, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ174.07, 146.98, 141.74, 135.53, 129.39, 128.60, 128.50, 127.60, 126.48, 77.84, 64.09, 61.40, 48.27, 29.00, 27.66, 25.85, 18.34, -5.36; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{39}O_4N_2SSi$, 491.2394; found, 491.2413.

***N*-(Benzyloxy)-2-(((4-(dimethoxy methyl) phenyl) (methyl)(oxo)-l6-sulfaneylidene) amino) -2-methylpropanamide (27g):**

Yield: 70% (64 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3393.67, 3065.15, 2983.26, 2929.97, 1705.32, 1666.66, 1595.83, 1469.71, 1378.85, 1261.86, 1197.52, 1121.76, 977.82, 753.98; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.79 (br. s., 1H), 7.84 (m, J = 8.38 Hz, 2H), 7.62 (m, J = 8.25 Hz, 2H), 7.45-7.49 (m, 2H), 7.36-7.42 (m, 3H), 5.44 (s, 1H), 4.93-4.99 (m, 2H), 3.35 (s, 6H), 3.05 (s, 3H), 1.46 (s, 3H), 1.22 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 173.5, 143.6, 135.4, 133.1, 129.4, 128.7, 128.6, 128.5, 128.5, 128.3, 127.9, 127.6, 101.9, 77.9, 61.5, 52.9, 47.8, 47.7, 28.8, 27.4; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{29}O_5N_2S$, 421.1792; found, 421.1787.

***N*-(Benzyloxy)-2-(((2-methoxyphenyl) (methyl)(oxo)-l6-sulfaneylidene) amino)-2-methylpropanamide (27h):**

Yield: 80% (81 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3393.67, 3013.75, 2929.97, 1705.32, 1666.66, 1595.83, 1469.71, 1454.15, 1261.86, 1197.52, 977.82, 753.98; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.00 (br. s., 1H), 7.95 (dd, *J*=7.88, 1.75 Hz, 1H), 7.50-7.61 (m, 1H), 7.42 - 7.48 (m, 2H), 7.33-7.41 (m, 3H), 7.08-7.14 (m, 1H), 6.97 (d, *J* = 8.13 Hz, 1H), 4.83 - 5.00 (m, 2H), 3.82 (s, 3 H), 3.22 (s, 3H), 1.50 (s, 3H), 1.21 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 173.6, 156.4, 135.6, 130.7, 129.5, 128.6, 128.4, 121.3, 112.3, 77.9, 61.3, 56.0, 45.3, 29.2, 26.3; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{25}O_4N_2S$, 377.1530; found, 377.1521.

***N*-(Benzyloxy)-2-methyl-2-((methyl(4-nitrophenyl) (oxo)-l6-sulfaneylidene) amino) propenamide (27i):**

Yield: 74% (72 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3431.46, 2930.94, 2088.80, 1643.23, 1572.85, 1535.88, 1469.06, 1258.88, 1196.39, 753.26; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.53 (br. s., 1 H), 8.24-8.41 (m, 2 H), 7.97-8.07 (m, 2H), 7.35-7.53 (m, 5H), 4.89-5.02 (m, 2H), 3.05 (s, 3H), 1.48 (s, 3H), 1.21 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 173.2, 150.3, 149.2, 135.4, 129.4, 129.0, 128.7, 128.6, 124.6, 77.8, 61.7, 47.6, 29.1, 27.6; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{22}O_5N_2S$, 392.1275; found, 392.1281.

***N*-(Benzyloxy)-2-((ethyl(oxo)(phenyl)-l6-sulfaneylidene) amino)-2-methylpropanamide (27j): Yield:** 88% (93 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3384.68, 3020.47, 2937.09, 1683.77, 1650.22, 1632.01, 1517.62, 1454.79, 1368.12, 1216.99, 1121.39, 1049.33, 923.01, 674.37; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.75 (d, J = 7.63 Hz, 2H), 7.55-7.62 (m, 1H), 7.46-7.52 (m, 4H), 7.34-7.43 (m, 4H), 4.92-5.00 (m, 2H), 2.90-3.05 (m, 2H), 1.45 (s, 3H), 1.20 (s, 3H), 1.07 (t, *J* = 7.38 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 174.3, 141.7, 135.5, 132.7, 129.3, 129.3, 129.2, 128.6, 128.5, 128.3, 77.8, 61.2, 53.4, 29.2, 27.7, 6.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{25}O_3N_2S$, 361.1580; found, 361.1577.

2-((Allyl(oxo)(phenyl)-l6-sulfaneylidene) amino)-N-(benzyloxy)-2-methylpropanamide (27k): Yield: 80% (82 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3744.31, 3423.31, 3019.35, 2114.54, 1723.09, 1641.36, 1551.87, 1513.21, 1445.16, 1253.26, 1215.79, 1121.61, 757.22, 668.33; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.6 (s, 1H), 7.7-7.7 (m, 2H), 7.6-7.6 (m, 1H), 7.4-7.5 (m, 4H), 7.4-7.4 (m, 3 H), 5.5-5.6 (m, 1H), 5.1-5.2 (m, 1H), 4.9-5.0 (m, 3H), 3.6 (dd, *J* = 7.32, 2.81 Hz, 2H), 1.5 (s, 3H), 1.2 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 174.1, 141.7, 135.6, 132.8, 129.4, 129.0, 128.6, 128.5, 124.9, 124.5, 77.7, 63.8, 61.3, 29.2, 27.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{25}O_3N_2S$, 373.1580; found, 373.1597.

***N*-(Benzyloxy)-2-((butyl(oxo)(phenyl)-l6-sulfaneylidene) amino)-2-methylpropanamide (27l): Yield:** 84% (82 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3423.31, 3019.35, 2876.73, 1723.09, 1641.36, 1551.87, 1535.52, 1501.95, 1445.16, 1379.36, 1253.26, 1215.79, 757.22, 699.09; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.73 (br. s., 1H), 7.73-7.78 (m, 2H), 7.56-7.60 (m, 1H), 7.46-7.53 (m, 4H), 7.39-7.43 (m, 2H), 7.34-7.39 (m, 2H), 4.91-5.00 (m, 2H), 3.00-3.13 (m, 1H), 2.90-2.98 (m, 1H), 1.50-1.59 (m, 1H), 1.43 (s, 3H), 1.33-1.41 (m, 1H), 1.24-1.30 (m, 2H), 1.20 (s, 3H), 0.83 (t, *J* = 7.25 Hz, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 173.9, 135.5, 132.9, 129.4, 129.3, 129.2, 128.6, 128.5, 128.2, 77.7, 61.3, 58.6, 29.0, 27.5, 24.3, 23.9, 21.2, 13.4; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{29}O_3N_2S$, 389.1893; found, 389.1891.

***N*-(Benzyloxy)-2-(((cyclopropylmethyl)(oxo)(phenyl)-l6-sulfaneylidene) amino)-2-methylpropanamide (27m):**

Yield: 78% (77 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3378.43, 3010.41, 2931.79, 2866.24, 1681.52, 1454.19, 1365.98, 1252.45, 1120.20, 1059.11, 996.69, 919.03, 696.98, 659.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.74-7.80 (m, 2H), 7.56-7.63 (m, 1H), 7.46-7.55 (m, 4H), 7.36-7.44 (m, 3H), 5.65 (ddt, *J* = 16.9, 10.4, 6.5, 6.5 Hz, 1H), 4.99-5.04 (m,

2H), 4.97 (d, *J* = 5.1 Hz, 2H), 3.08 (ddd, *J* = 13.7, 10.7, 5.5 Hz, 1H), 2.97 (ddd, *J* = 13.8, 10.5, 5.4 Hz, 1H), 2.25-2.42 (m, 1H), 2.12-2.24 (m, 1H), 1.45 (s, 3H), 1.21 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 174.1, 142.3, 135.6, 134.0, 132.8, 129.4, 129.3, 128.7, 128.5, 128.3, 117.0, 77.8, 61.3, 58.1, 29.3, 27.7 , 26.4; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{27}O_3N_2S$, 387.1737; found, 387.1734.

***N*-(Benzyloxy)-2-((cyclo pentyl (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-methylpropanamide (27n):**

Yield: 78% (74 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3389.91, 3031.47, 2876.84, 1768.92, 1704.05, 1632.12, 1459.69, 1328.92, 1230.16, 1152.33, 1110.84, 1042.36, 909.06, 799.51, 750.77, 706.53, 659.61; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.72 (br. s., 1H), 7.78 (d, *J* = 7.38 Hz, 2H), 7.56-7.61 (m, 1H), 7.46-7.54 (m, 4H), 7.36-7.44 (m, 3H), 4.93-5.00 (m, 2H), 3.34-3.64 (m, 1H), 1.93 (d, *J* = 6.75 Hz, 1H), 1.77-1.87 (m, 1H), 1.62-1.71 (m, 3H), 1.48-1.59 (m, 3H), 1.45 (s, 3H), 1.20 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 173.8, 135.7, 132.9, 129.3, 128.6, 128.6, 128.6, 126.4, 77.8, 65.9, 61.3, 26.9, 26.8, 25.9, 25.7; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{22}H_{29}O_3N_3S$, 401.1893; found, 401.1899.

2-((Benzyl(oxo)(phenyl)-l6-sulfaneylidene)amino)-N-(benzyloxy)-2-methylpropanamide (27o):

Yield: 84% (76 mg); Yellow gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3220.79, 3013.48, 2932.25, 1726.26, 1679.03, 1642.62, 1631.92, 1550.23, 1494.98, 1445.52, 1258.47, 1216.61, 1116.62, 754.74; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.42 (br. s., 1H), 7.54-7.61 (m, 3H), 7.40-7.46 (m, 7H), 7.31-7.35 (m, 1H), 7.23 (t, *J* = 7.57 Hz, 2H), 6.99 (d, *J* = 7.13 Hz, 2H), 4.80-4.94 (m, 2H), 4.23 (br. s., 2H), 1.43 (s, 3H), 1.22 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 174.0, 135.5, 133.0, 131.1,

129.4, 129.0, 128.8, 128.6, 128.5, 128.4, 77.7, 65.7, 61.3, 29.0, 27.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{27}O_3N_2S$, 423.1737; found, 424.1787.

***N*-(Benzyloxy)-2-((dibenzyl(oxo)-l6-sulfaneylidene) amino)-2-methylpropanamide (27p):**

Yield: 79% (70 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3744.14, 3443.65, 2114.33, 1723.68, 1642.09, 1552.45, 1513.39, 1483.01, 1453.16, 1276.52, 1217.16, 768.40; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.34-7.41 (m, 12H), 7.28-7.32 (m, 4H), 4.72 (s, 2H), 4.19 (d, J = 13.26 Hz, 2H), 4.04 (d, J = 13.26 Hz, 2H), 1.43 (s, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 174.1, 135.5, 130.9, 129.3, 128.9, 128.9, 128.8, 128.6, 128.4, 77.6, 62.0, 61.1, 29.0; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{29}O_3N_2S$, 437.1893; found, 437.1905.

***N*-(Benzyloxy)-2-methyl-2-((5-oxido-5l4-dibenzo [b, d] thiophen-5-ylidene) amino) propenamide (27q):**

Yield: 82% (77 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3382.45, 2984.56, 1680.09, 1631.66, 1591.66, 1468.53, 1447.73, 1259.15, 1191.74, 1051.22, 910.17, 752.91; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.79 (d, J = 7.63 Hz, 2H), 7.57-7.66 (m, 4H), 7.46-7.51 (m, 2H), 7.31-7.39 (m, 5H), 4.84 (s, 2H), 1.68 (s, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 173.3, 141.0, 135.3, 132.9, 131.4, 130.2, 129.3, 128.6, 128.5, 122.3, 121.5, 77.9, 61.5, 29.3; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{23}O_3N_2S$, 407.1424; found, 407.1440.

***N*-(Benzyloxy)-2-methyl-2-((10-oxido-9-oxo-9H-10l4-thioxanthen-10-ylidene) amino) propanamide (27r):**

Yield: 84% (75 mg); White gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3423.57, 2926.40, 1666.34, 1642.34, 1573.16, 1551.60, 1443.14, 1296.90, 1228.59, 1193.29, 748.58; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.1 (s, 1H), 8.2-8.2 (m, 2H), 8.0-8.1 (m, 2H), 7.7-7.8 (m, 4H), 7.3 (s, 5H), 4.8 (s, 2H), 1.3 (s, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 180.3, 173.0, 143.5, 135.1, 134.6, 133.8, 132.5, 131.8,

129.3, 129.0, 128.6, 128.5, 124.1, 77.9, 77.3, 77.2, 76.7, 62.3, 28.2; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{23}O_4N_2S$, 435.1373; found, 435.1389.

***N*-(Benzyloxy)-2-methyl-2-((10-methyl-5-oxido-10H-5l4-phenothiazin-5-ylidene) amino) propenamide (27s):**

Yield: 75% (66 mg); Colorless gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3451.94, 2928.11, 2088.88, 1642.32, 1587.43, 1535.34, 1462.31, 1350.28, 1257.38, 752.22; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.97 (dd, *J* = 7.75, 1.50 Hz, 2H), 7.57 (ddd, *J* = 8.50, 7.25, 1.50 Hz, 2H), 7.36-7.42 (m, 1H), 7.32 (s, 4H), 7.27-7.29 (m, 1H), 7.26 (s, 1H), 7.21-7.25 (m, 2H), 4.78 (s, 2H), 3.58 (s, 3H), 1.34 (s, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 174.0, 142.2, 135.4, 132.4, 129.3, 128.6, 128.5, 128.4, 126.5, 124.3, 122.1, 115.4, 77.8, 61.4, 35.3, 28.5; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{26}O_3N_3S$, 436.1689; found, 436.1711**.**

2-((10-benzyl-5-oxido-10H-5l4-phenothiazin-5-ylidene) amino)-*N*-(benzyloxy)-2-methylpropanamide (27t):

Yield: 73% (58 mg); Yellow white gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3397.05, 3066.16, 2930.77, 1726.55, 1679.37, 1587.75, 1467.07, 1376.20, 1252.88, 1217.96, 1126.42, 1044.89, 753.03; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.88 Hz, 2H), 7.62 (t, *J* = 7.00 Hz, 2H), 7.30-7.45 (m, 10H), 7.21 (d, *J* = 8.63 Hz, 2H), 7.13 (d, *J* = 6.75 Hz, 2H), 5.57 (br. s., 2H), 4.74 (s, 2H), 1.56 (br. s., 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 173.3, 141.4, 135.4, 134.9, 129.3, 129.2, 129.2, 128.8, 128.6, 128.5, 128.4, 127.7, 125.7, 124.4, 122.8, 117.1, 77.9, 61.6, 29.7, 27.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{30}O_3N_3S$, 512.2002; found, 512.2012.

***N*-methoxy-2-methyl-2-((oxodiphenyl-l6-sulfaneylidene) amino) propenamide (29a):**

Yield: 86% (56 mg); White solid; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3423.18, 3013.55, 2936.27, 1678.63, 1642.03, 1469.15, 1446.47, 1259.46, 1216.57, 1194.17, 1091.25, 754.59, 690.39; **^{1}H NMR** (400

MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.86-8.03 (m, 4H), 7.42-7.57 (m, 6H), 3.79 (s, 3H), 1.42 (s, 6H); **$^{13}C\{^1H\}$ NMR** (101 MHz, $CDCl_3$) δ 174.4, 143.7, 132.4, 129.2, 127.8, 64.2, 61.4, 28.5; **HRMS** (ESI) m/z: $[M+H]^+$calcd for $C_{17}H_{21}O_3N_2S$, 333.1267; found, 333.1265.

***N*-((4-iodobenzyl) oxy)-2-methyl-2-((oxodiphenyl-l6-sulfaneylidene) amino) propenamide (29b):**

Yield: 76% (93 mg); Colorless gum; **^1H NMR** (400 MHz, $CDCl_3$) δ 9.69 (s, 1 H), 8.04 - 8.05 (m, 1 H), 8.02 (d, *J* =1.63 Hz, 1H), 7.80-7.81 (m, 1H), 7.78-7.79 (m, 1H), 7.68 (s, 1H), 7.50-7.53 (m, 2H), 7.49 (t, *J* = 1.50 Hz, 1H), 7.47-7.48 (m, 1H), 7.45-7.46 (m, 2H), 7.42-7.44 (m, 2H), 7.20 (s, 1H), 4.88 (s, 2H), 1.40 (s, 6H); **$^{13}C\{^1H\}$ NMR** (101 MHz, $CDCl_3$) δ 174.2, 143.5, 137.6, 135.0, 132.5, 132.3, 131.1, 129.1, 129.0, 127.8, 127.5, 94.5, 77.1, 61.4, 28.4; **HRMS** (ESI) m/z: $[M+H]^+$calcd for $C_{23}H_{24}O_3N_2IS$, 535.0547; found, 535.0544.

2-Methyl-N-((4-nitrobenzyl) oxy)-2-((oxodiphenyl-l6-sulfaneylidene) amino) propenamide (29c):

Yield: 78% (81 mg); Yellow solid; **^1H NMR** (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.18 (d, *J* = 8.25 Hz, 2H), 7.85 (d, *J* = 7.63 Hz, 4H), 7.63 (d, *J* = 7.50 Hz, 2H), 7.51 (d, *J* = 6.88 Hz, 2H), 7.42-7.48 (m, 4H), 5.05 (s, 2H), 1.41 (s, 6H); **$^{13}C\{^1H\}$ NMR** (101 MHz, $CDCl_3$) δ 174.7, 143.5, 142.7, 132.5, 129.7, 129.4, 129.2, 127.7, 123.7, 123.7, 76.6, 61.4, 28.5; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{24}O_5N_3S$, 454.1431; found, 454.1424.

2-Methyl-2-((oxodiphenyl-l6-sulfaneylidene) amino) propanamide (30):

Yield: 58% (13 mg); White gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3513.17, 3018.94, 2399.48, 1595.97, 1418.85, 1215.82, 1146.57, 757.94, 668.40; **^1H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 5.8 Hz, 4H), 7.49 (d, *J* = 7.6 Hz, 6H), 1.43 (s, 6H); **$^{13}C\{^1H\}$ NMR** (101 MHz, $CDCl_3$) δ 180.6, 143.9,

132.3, 129.1, 127.8, 61.6, 28.5; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{19}O_2N_2S$, 303.1162; found, 303.1167.

***N*-Hydroxy-2-methyl-2-((oxodiphenyl-l6- sulfaneylidene) amino) propanamide (31):**

Yield: 80% (82 mg); White solid; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3021.58, 1797.01, 1715.38, 1616.71, 1516.43, 1421.23, 1330.83, 1215.74, 757.20, 669.38; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93-8.00 (m, 4H), 7.46-7.54 (m, 7H), 7.42 (br. s., 1H), 5.63 (br. s., 1H), 1.44 (s, 7H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 169.6, 142.1, 132.7, 130.0, 129.7, 129.8, 129.1, 128.4, 128.2, 127.8, 54.2, 28.3; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{19}O_3N_2S$, 319.1111; found, 319.1103.

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Chapter IV

Lewis Acid Catalyzed *N*-Alkylation of Sulfoximines and C-3 Alkylation of Indolizine through Nucleophilic Ring-Opening of Donor-Acceptor Cyclopropanes

1. "Lewis Acid Triggered *N*-Alkylation of Sulfoximines through Nucleophilic Ring-Opening of Donor-Acceptor Cyclopropanes: Synthesis of γ-Sulfoximino Malonic Diesters." **More S. G.;** Suryavanshi, G. *Org. Biomol. Chem.*, **2022,** *20*, 2518–2529.
2. "Scandium Triflate Catalyzed Regioselective C-3 Functionalization of Indolizines via Ring- Opening of Donor-Acceptor Cyclopropanes." **More S. G.;** Mane K. D.: Suryavanshi, G. *(Manuscript under preparation.)*

4.1.1 Introduction

Sulfoximines were discovered in the late 1940s;[1] since then, they have emerged as valuable moieties in a broad range of applications.[2,3] The exciting properties of sulfoximines, such as hydrogen bonding (associated with functional groups), high stability, suitable physicochemical properties, and structural diversity, make them essential pharmacophores in medicine and agrochemistry.[2] Due to their stable configuration and chemical stability, sulfoximines can be used as chiral auxiliaries in asymmetric catalysis [4,5] and as ligands in C–H activation.[6] The *N*-functionalization of *N*H-sulfoximines offers molecular diversity through *N*-arylation, *N*-alkylation, *N*-cyanation, *N*-propargylation, and many more.[7] On the other hand, cyclopropane dicarboxylates [8] are simple and commercially available starting materials extensively used to synthesize natural products. The unique D–A characteristics of cyclopropane have made it a valuable component in a wide range of ring-opening,[9] cycloadditions,[10] and rearrangement reactions.[11] As a result, D–A cyclopropane has been studied for several decades, and its applications in natural product synthesis and heterocyclic and medicinal chemistry have been explored.[8]

Section I

Lewis Acid Triggered *N*-Alkylation of Sulfoximines through Nucleophilic Ring-Opening of Donor-Acceptor Cyclopropanes: Synthesis of γ-Sulfoximino Malonic Diesters

There are reports on the successful development of ring-opening strategies for D–A cyclic moieties to its open-chain system with the help of various carbon nucleophiles and heteroatoms (e.g., phenols, amines, indoles, and azides, Scheme 1, eqn (b)).[12] However, there are no reports

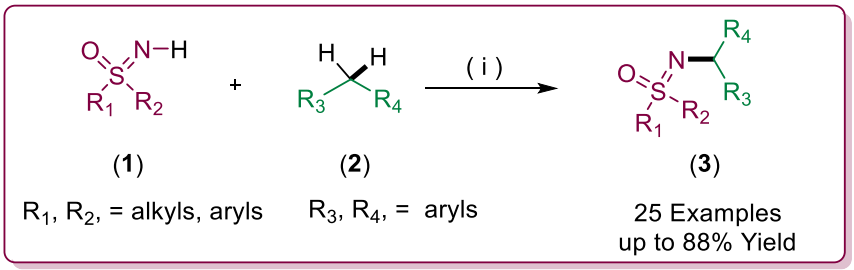
in the literature on the D–A cyclopropane ring opening using sulfoximines. So, we proposed to utilize the nucleophilic properties of *N*H-sulfoximines and the D–A properties of cyclopropane dicarboxylates to form unique *γ*-sulfoximino malonic diesters moieties.

4.1.2 Review of Literature

While reviewing the literature, we noticed that *N*-alkylation of sulfoximines is rarely explored due to their low nucleophilicity of sulfoximines. However, some reports are known in the literature for *N*-alkyl sulfoximines under metal and metal-free conditions. Herein, we have described some literature surveys for the *N*-alkylation sulfoximine reactions.

Bolm's Approach (2014)[13,14]

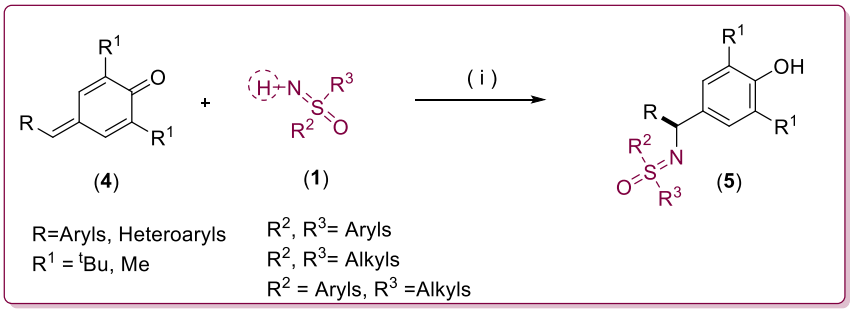
The Bolm group is a front runner in the field of sulfoximines, and they have demonstrated the applications of sulfoximines in a wide range of reactions.[13] In 2014, Bolm and coworkers developed a new strategy for the N-alkylation of sulfoximines with diaryl methane through an iron-catalyzed C–N bond formation reaction.[14] Heteroaryl cross dehydrogenation of diarylmethane and sulfoximines using Fe(III) catalyst furnished the N-alkyl sulfoximines product, in quantitative yields (up to 88%) (up to 88%) (**Scheme 1**).



Scheme 1: (i) Fe $(Br)_3$ (20 mol%), DTBP (2.0 equiv.), 4 Å MS (100 mg), neat, 90 °C, 48 h.

Suryavanshi Approach (2021)[15]

Recently, our group developed an *N*- alkylation of Sulfoximines through acid-catalyzed 1,6-conjugate addition of *N*H-sulfoximines to para-quinone methides (*p*-QMs).[15] In this report, *p*-QMs reacted with different Sulfoximines such as Di-aryl, aryl-alkyl, di-alkyl, and heterocyclic sulfoximines using Bronsted acid (*p*-TSA), to furnish the libraries of different N-alkyl sulfoximines with 95% isolated yield. The Proposed reaction pathway is the nucleophilic attack of sulfoximine on *para*-Quinone Methide (*p*-QMs) via conjugate manner to obtain the corresponding N-alkyl product (**Scheme 2**).

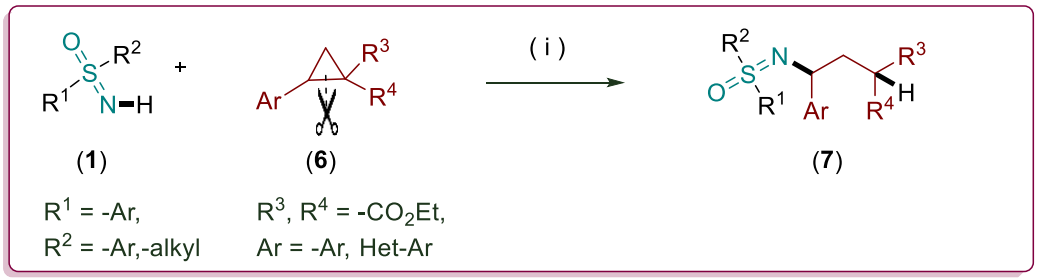


Scheme 2: (i) TsOH (20 mol%), CH_2Cl_2, rt, 1 h.

4.1.3 Present Work

4.1.3.1 Objective

Inspired by the recent advances in sulfoximine synthesis and our ongoing commitment to developing synthetic methodologies,[16] herein, we report the N-alkylation of sulfoximines by



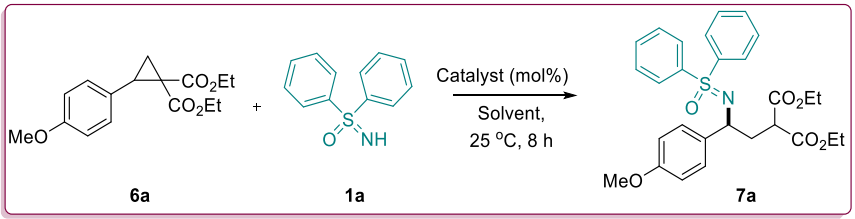
Scheme 3. (i) $Sc(OTf)_3$ (10 mol%), CH_2Cl_2, 25 °C, 8-16 h

a Lewis acid-catalyzed opening of D–A cyclopropane carboxylate, resulting in direct C–N bond formation (**Scheme 3**).

2.1.4 Result and Discussion

Based on our previous report,[15] we have started our investigation to checking the feasibility of reaction with 1 equivalent of D-A cyclopropane (**6a**) and 1.2 equivalents of sulfoximine (**1a**) as a model substrate in the presence of the catalytic amount of Brønsted acid, i.e., *p*-TSA (10 mol%) in CH_2Cl_2. In this reaction, we observed the formation of less amount of the desired product(**7a**) (24% yield) (Table 1, entry 1) within 12 h at room temperature. Then, we varied the Brønsted acids, such as TFA and TfOH, which were observed in low yields (Table 1, entries 2-3). After the unsatisfactory results with Brønsted acids, we turned toward Lewis acids and initially used 10 mol% of $Cu(OTf)_2$; gratifyingly, we obtained the nucleophilic ring-opening product (**7a**) in 85% yield. (Table 1, entry 4). Next, we screened different Lewis acids such as $Bi(OTf)_3$, $Yb(OTf)_3$, $BF_3.Et_2O$, and $Sc(OTf)_3$ (Table 1, entries 4-8) from which $Sc(OTf)_3$ was found to be suitable and

Table 1. Optimization of Reaction Conditions [a]



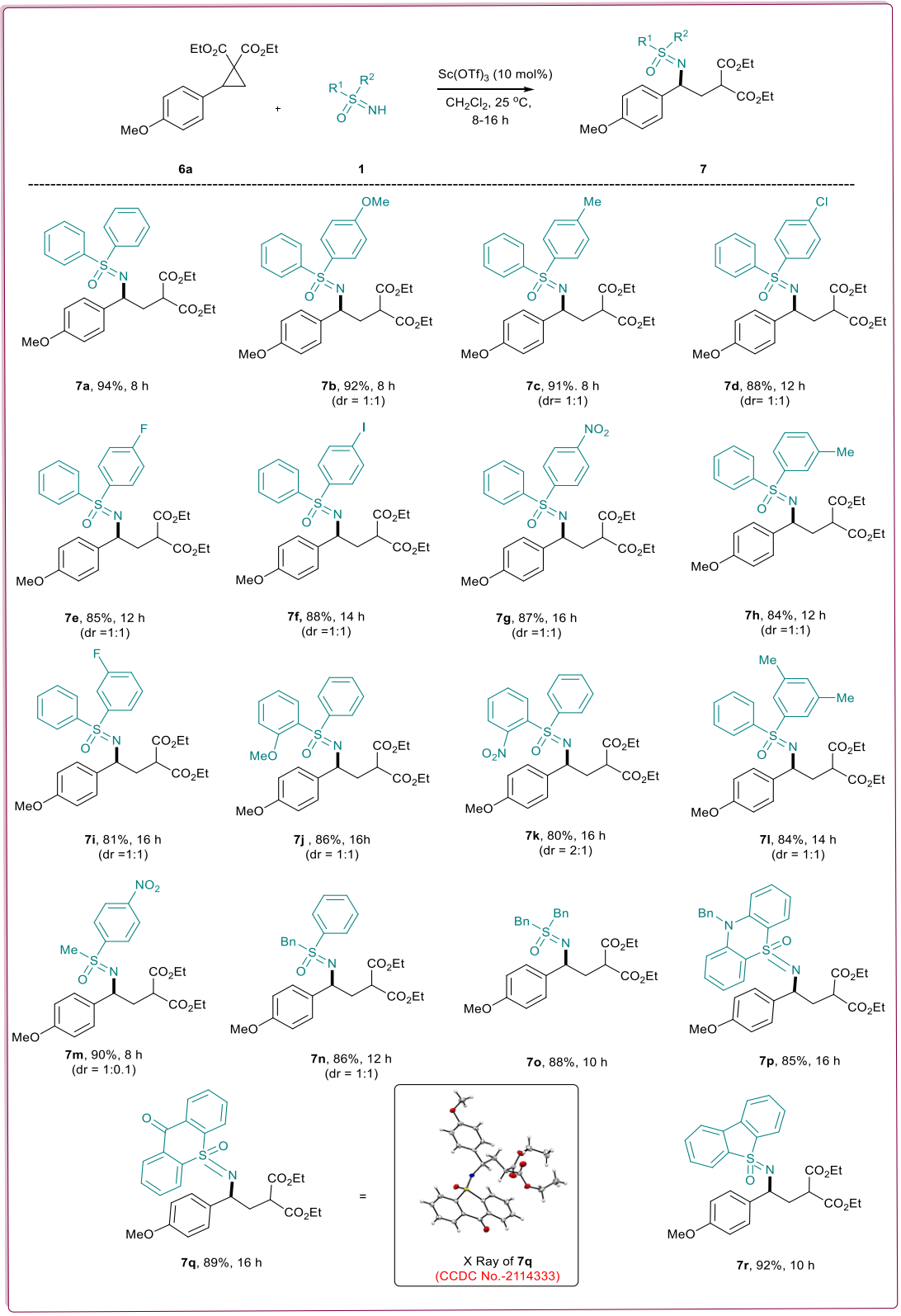
Entry	Catalyst (10 mol%)	Solvent	Yield [b]
1	TsOH	DCM	24
2	TFA	DCM	30
3	TFOH	DCM	34
4	$Cu(OTf)_2$	DCM	85

5	$Bi(OTf)_3$	DCM	83
6	$Yb(OTf)_3$	DCM	65
7	$BF_3.Et_2O$	DCM	40
8	**$Sc(OTf)_3$**	**DCM**	**94**
9	$Sc(OTf)_3$	DCE	90
10	$Sc(OTf)_3$	ACN	60
11	$Sc(OTf)_3$	THF	68
12	$Sc(OTf)_3$	DMF	64
13	-	DCM	NR

[a] = Reaction conditions: **6a** (0.17 mmol, 1 equiv.), **1a** (0.20 mmol, 1.2 equiv.), catalyst in solvent (2.0 mL), 8 h at 25 °C under N_2 atmosphere. b = Isolated yields after column chromatography, NR = No Reaction, DCM= Dichloromethane, ACN= Acetonitrile, THF=Tetrahydrofuran, DMF= Dimethyl formamide

gave a high yield (94%) of corresponding γ-sulfoximino malonic diester **(7a)** within 8 h (Table 1, entry 8). Further, the reaction was carried out in different solvents like 1,2 dichloroethane, acetonitrile, THF, and DMF; however, no improvement in yield was observed (Table 1, entries 9-12). The reaction did not proceed without of Lewis acid, and both the starting materials were recovered (Table 1, entry 13). Based on optimization studies, we confirmed that $Sc(OTf)_3$ (10 mol%), DCM, 25 °C, 8 h is the best reaction condition for Lewis acid-catalyzsed ring-opening reaction of D-A cyclopropane with sulfoximines (Table 1, entry 8). With optimized reaction conditions in hand (Table 1, entry 8), the substrate scope for ring-opening reactions has been evaluated. First, we examined the scope of different sulfoximines, as depicted in Table 2. We varied the di-aryl, aryl-alkyl, di-alkyl, and heteroaryl sulfoximines. The unsubstituted di-aryl sulfoximines, electron-donating and electron-withdrawing sulfoximines, and sulfoximines with halogen groups at the para-position in benzene rings, underwent a smooth reaction with D-A cyclopropane resulting in the formation of the γ-sulfoximino malonic diesters in excellent yields

Table 2. Substrate scope of the various sulfoximines [a, b]



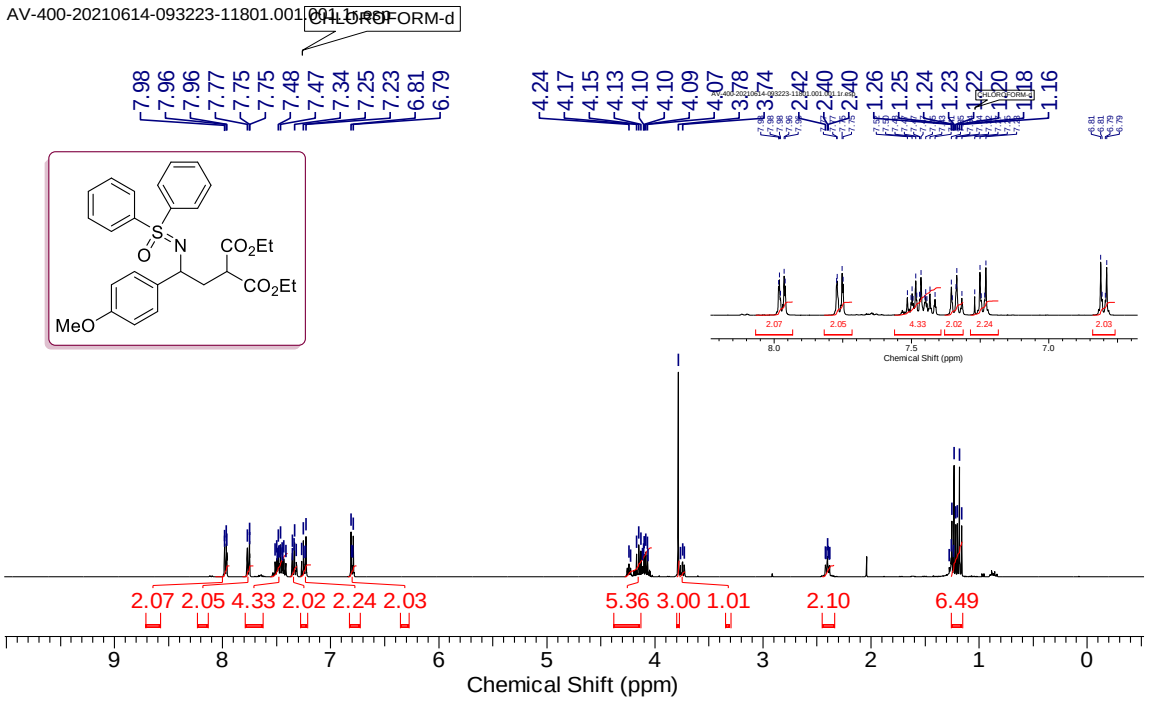
[a] **Reaction conditions:** **1a** (0.17 mmol), **2a-r** (0.20 mmol), $Sc(OTf)_3$ (10 mol%), at 25 °C, 8-16 h, under N_2 atmosphere; [b] Isolated yields after column chromatographic purification are shown.

(85% to 94%) (**7a**-**7g**). Also, the sulfoximines having a substitution at the *meta*- and *ortho*-position of the aryl ring reacted well under the standard reaction conditions and formed the desired product in 80 to 86% yields (**7h**−**7l**). Moreover, aryl-alkyl and di-alkyl sulfoximines are also amenable to ring-opening reactions with D-A cyclopropanes, providing corresponding products (**7m**-**7o**) in good yields (88-90%). The unsymmetrical substitution of di-aryl sulfoximines (**1b**-**1n**) led to the corresponding product (**7b**-**7n**) in a 1:1 diastereomeric ratio (except **7k** and **7m**, which are found in 2:1 and 1:0.1 ratio respectively). Next, the heterocyclic sulfoximines such as *N*-benzyl phenothiazine, thioxanthone, and dibenzyl thiophene derived sulfoximines reacted well to obtain desired products (**7p**-**7r**) in excellent yields (85-92%). The structure of product **3q** was unambiguously confirmed by single-crystal X-ray analysis (**CCDC No. 2114333**, see Supporting Information). The formation of **3a**-**3r** was confirmed by their corresponding ^1H, ^{13}C, and HRMS spectroscopic data.

Example 1:

The synthesized compound Diethyl 2-(2-(4-methoxyphenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (**7a**) was confirmed by their ^1H and ^{13}C NMR spectroscopic method. The peaks come in between δ 8.07 to 6.79, corresponding to the aromatic protons of the aromatic region (7.93-8.07 (m, 2H), 7.76 (dd, J = 8.32, 1.19 Hz, 2H), 7.39-7.56 (m, 4H), 7.31-7.38 (m, 2H), 7.18- 7.28 (m, 2H), 6.76-6.84 (m, 2H), 4.23 (d, J = 7.13 Hz, 1H), while the peak at δ 4.23 equivalent to the proton of quaternary carbon of the in-between two diesters (4.23 (d, J = 7.13 Hz, 1H), then the 4 H peaks come at δ 4.03-4.20 of the methylene proton of diester (4.03-4.20 (m, 4H). Moreover, the singlet peak of 3-H corresponds to the methyl group of the methoxy

group (3.78 (s, 3H). Furthermore, the peak at δ 3.75 dd for 1-H is the characteristic proton peak of methine carbon



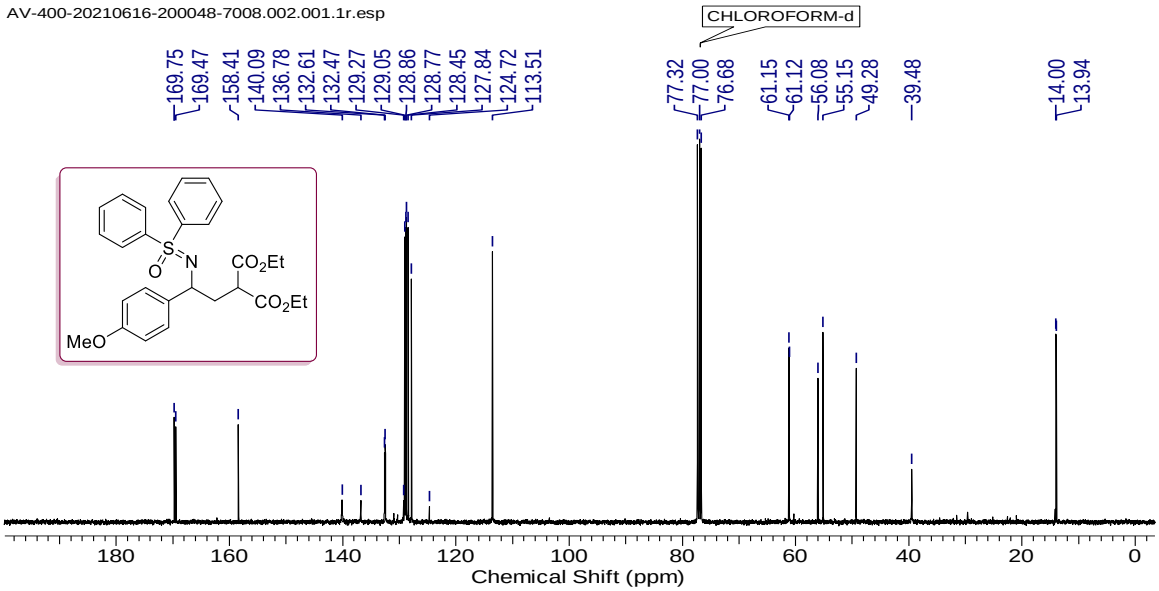


Figure 1. Diethyl 2-(2-(4-methoxyphenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate

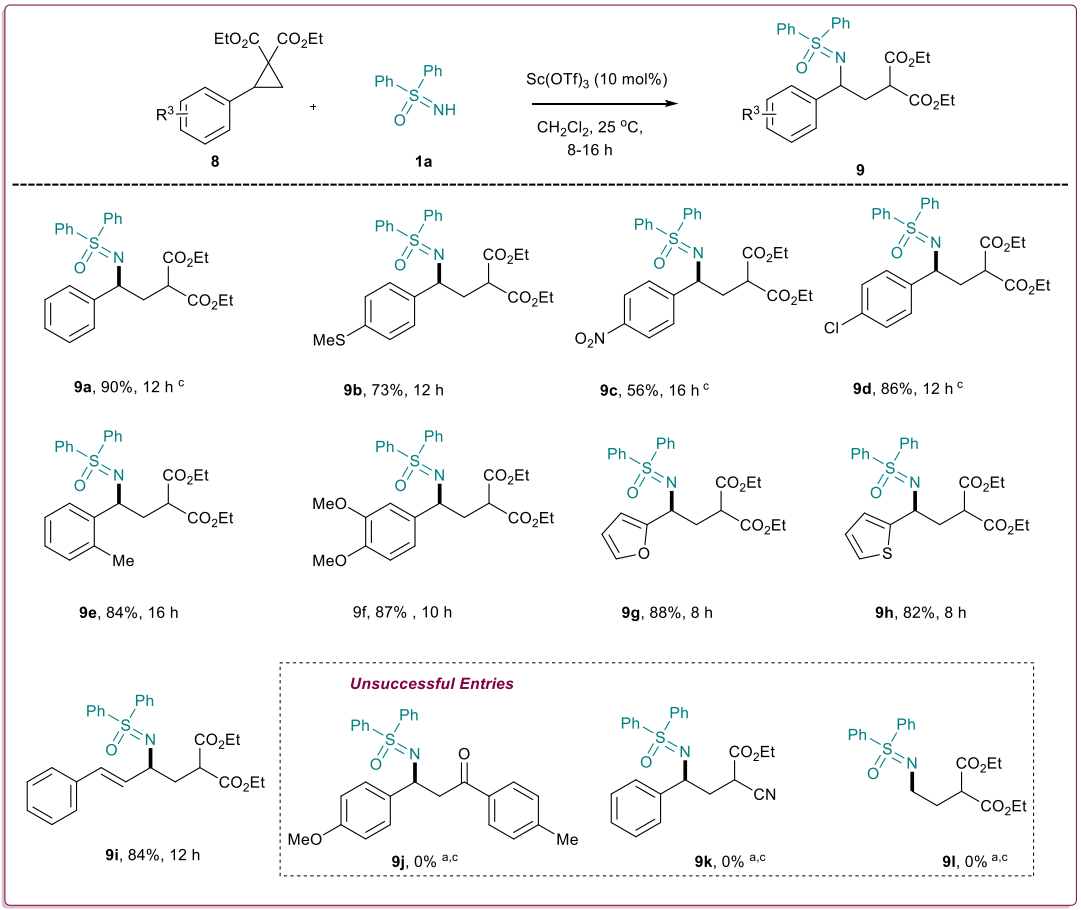
(**7a**)

proton near ~~to~~ the imine of the sulfoximine group (3.75 (dd, J = 7.82, 6.57 Hz, 1H). While the peak appears at δ2.24, the 2 H atom is the methylene proton of the malonic diester group. At the same time the multiplet 6 H comes at δ 1.15-1.26 for the methyl groups of diester moiety (m, 6H). Also, compound **7a** was precisely confirmed by ^{13}C spectroscopy. In the ^{13}C spectrum, the peak appeared at δ49.28 is the characteristic carbon of the C-N bond formation product (**Figure 1**).

After successfully screening (**6a**) with different sulfoximines, we next explored the addition of sulfoximine (**1a**) with substituted D-A cyclopropanes under standard reaction conditions. The results are shown in Table 3. The D-A cyclopropane with neutral (-H), EDG (-SMe), EWG (-NO_2), and halogen group (-Cl) at the *para*-position of aromatic ring reacted well with diphenyl sulfoximine (**1a**) to furnish desired product (**9a**-**9d**) in moderate to excellent yields. In addition, 2- methyl and 3, 4-dimethoxy groups on D-A cyclopropane also participated the ring-opening strategy with sulfoximine to obtain the corresponding product **(9e)** and **(9f)** in 84% and 87% yields, respectively. The formation of compounds **(9a)**, **(9c)**, and **(9d)** was not observed at 25 °C, whereas on warming, the reaction mixture was up to 40 °C; surprisingly, the related products are formed in good yields. Presumably, more activation energy is required to break the cyclopropane bond in compounds (**8a**), (**8c**), and (**8d**), which will be activated by raising the reaction temperature and making it suitable for the addition of weakly nucleophilic sulfoximine. Notably, D−A cyclopropane having heteroaryl groups such as furyl and thienyl are well tolerated in the ring-opening reaction to furnish related product (entries **9g** and **9h**, 88% and 82% yield). Additionally, styryl D-A cyclopropanes reacted smoothly to obtain the related product **(9i)** in 84 yields. Next, we did not observe the formation of desired products **9j** and **9k** from the reaction between sulfoximine with an α-cyclopropyl ketone (**8j)** and cyano-ester

cyclopropane (**8k)** at both reaction temperatures (25 °C as well as 40 °C) due to their lower chelation affinity of these cyclopropanes for Lewis acid. Notably, the aliphatic cyclopropane dicarboxylate (**8l**) remained unreacted under the optimized reaction conditions and recovered both the starting materials. The unreactivity of the aliphatic cyclopropane dicarboxylate (**8l**) is due to the instability of cyclopropane.

Table 3. CDC Reaction between Aromatic Aldehydes and Cyclic Ethers[a]



[a] **Reaction conditions:** **8** (0.19 mmol), **1a** (0.22 mmol), $Sc(OTf)_3$ (10 mol%), 8-16 h at 25 °C, under N_2 atmosphere; [b] Isolated yields after column chromatographic purification are shown. [c] Reaction was carried out at 40 °C

Example 2:

The formed γ-sulfoximino malonic diesters product (**9a**) was then unambiguously confirmed by their ^{1}H, ^{13}C, and HRMS spectroscopic methods. First, the formed compound was verified by the ^{1}H spectrum. In the spectrum, the peak region between the 7.95 to 7.13 comes for the 15-H aromatic protons (7.95 (dd, *J* = 8.19, 1.31 Hz, 2H), 7.66-7.74 (m, 2H), 7.35-7.48 (m, 4H), 7.25-

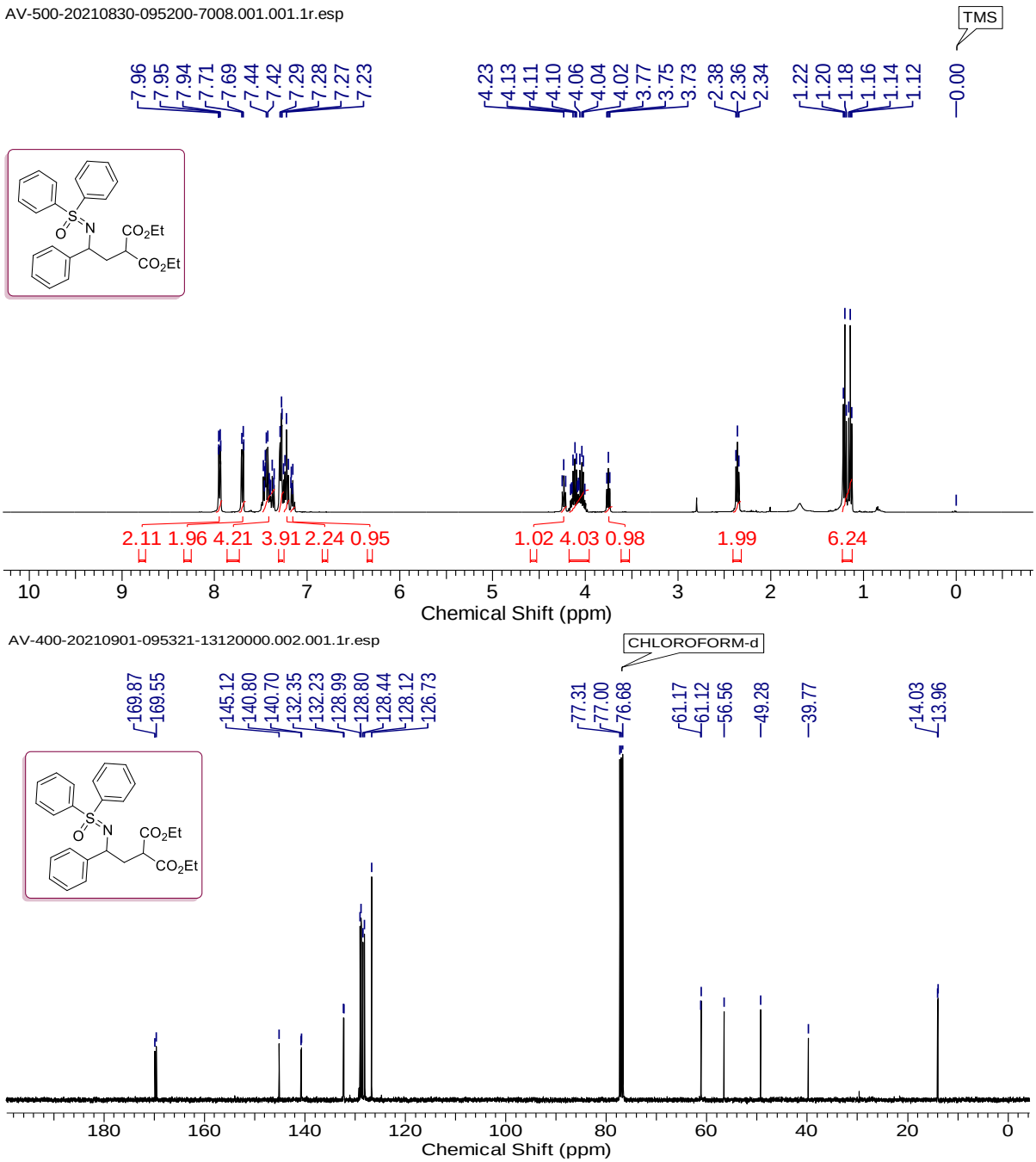
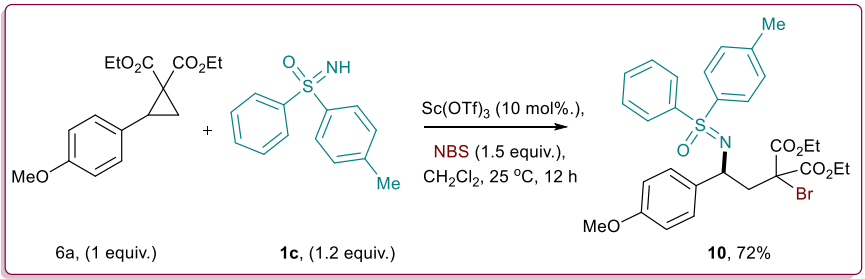


Figure 2. Diethyl 2-(2-(4-nitrophenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (**9a**)

7.31 (m,4H), 7.19-7.25 (m, 2H), 7.13-7.18 (m, 1H), However, the peak at δ 4.23 corresponding to the methine proton of in between diesters group (4.23 (t, J = 6.69 Hz, 1H). The peak at δ 3.96-4.17 multiplet for 4-H corresponds to the methylene protons of ester group. Then, the peak at δ 3. 75 triplet for 1-H is the characteristic methine proton next to the imine group of sulfoximine (3.75 (t, J = 7.13 Hz, 1H). The methylene (-CH_2) group in between two methine carbon comes at δ 2.36, (t, J = 7.00 Hz, 2 H), and the peak at δ 1.12-1.22 (m, 6H) for the two methyl groups protons of diester group. Then, in ^{13}C spectra, the peak appeared at δ 169.87 and δ 169.87 for the two (-C=O) ester groups and the peak at δ 49.28 for the characteristic methine carbon (>CH−) next to the sulfoximine group (**Figure 2**).

After the remarkable success of the achievement of ring-opening of D-A cyclopropane, next, we synthesized γ-sulfoximino, α-bromo malonic diesters **(10)** by adding an appropriate amount of halogenating agent (*N*- Bromo succinimide) using the standard reaction condition as indicated in **Scheme 4**.[17]

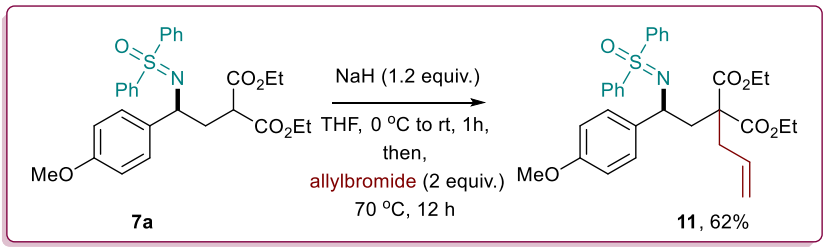


Scheme 4: Synthesis of γ-sulfoximino, α-bromo malonic diesters

Next, the synthetic utility of this reaction was demonstrated through the gram-scale synthesis of (**7a**) (**Scheme 5**) using 1.96 mmol (1.0 g scale) of (**6a**) with 2.35 mmol of (**1a**), which proceeded smoothly and furnished the corresponding product (**7a**) in comparable yield (1.5 g, 88%, 10 h).

Scheme 5: Gram scale synthesis of compound **3a**

Also further, we explored the synthetic expansion of obtained product (**7a**), which was treated with allyl bromide in the presence of NaH in THF to form α-quaternary allylation product (**11**) in 62% yield (**Scheme 6**).[18]

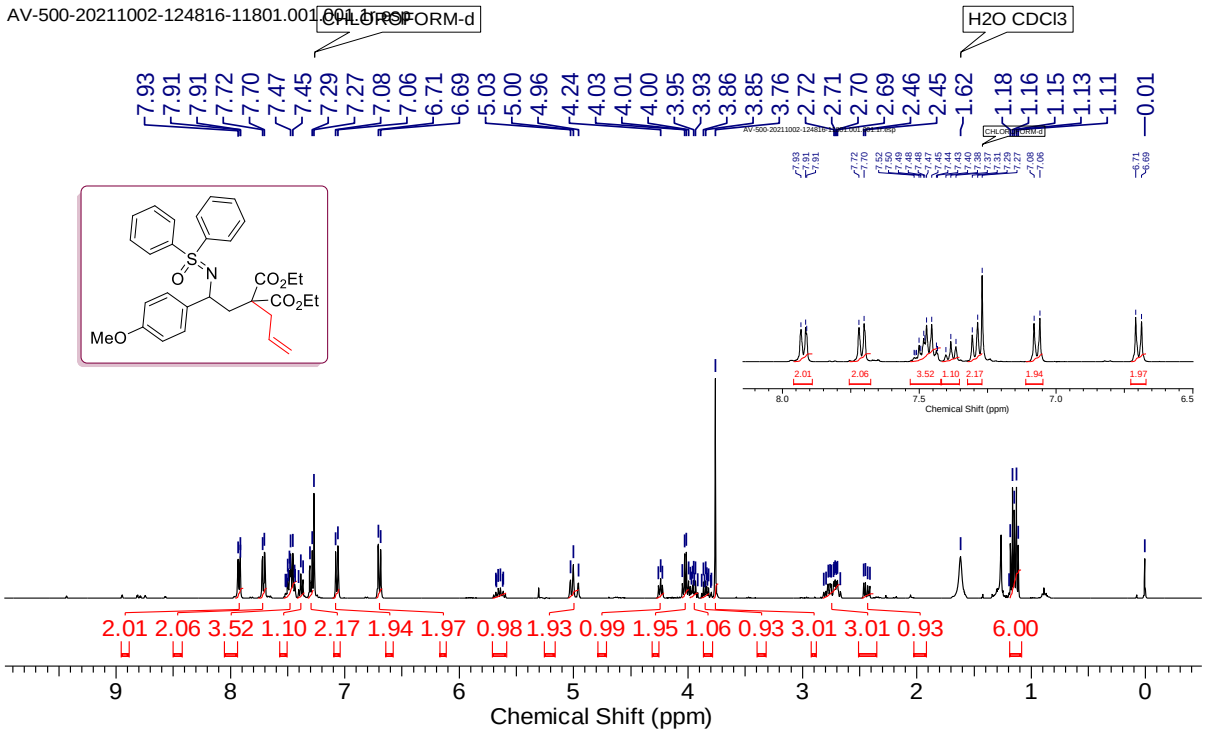


Scheme 6: Synthetic Elaboration of compound **3a**

Example 3:

The formed α-quaternary allylation product (**11**) was confirmed by the respective ^{1}H ^{13}C and HRMS spectroscopy. In the ^{1}H spectra, peaks for allyl compound appeared at δ 5.59-5.71 multiplet 1-H corresponding to the internal olefinic proton, while the peak at δ 4.95-5.05 (m, 2**H**) for terminal olefinic protons and the two methylene (-C**H**$_2$) hydrogen appeared at δ 2.66-2.82. also, the compound was confirmed by its ^{13}C spectra; in the spectra, characteristic quaternary carbon appeared at δ42.50, as shown in **Figure 3**.

To gain insights into the reaction mechanism, we further investigated the reaction pathways by reacting diaryl sulfoximine with enantiopure cyclopropane **6a** (96% *ee*) under optimized reaction



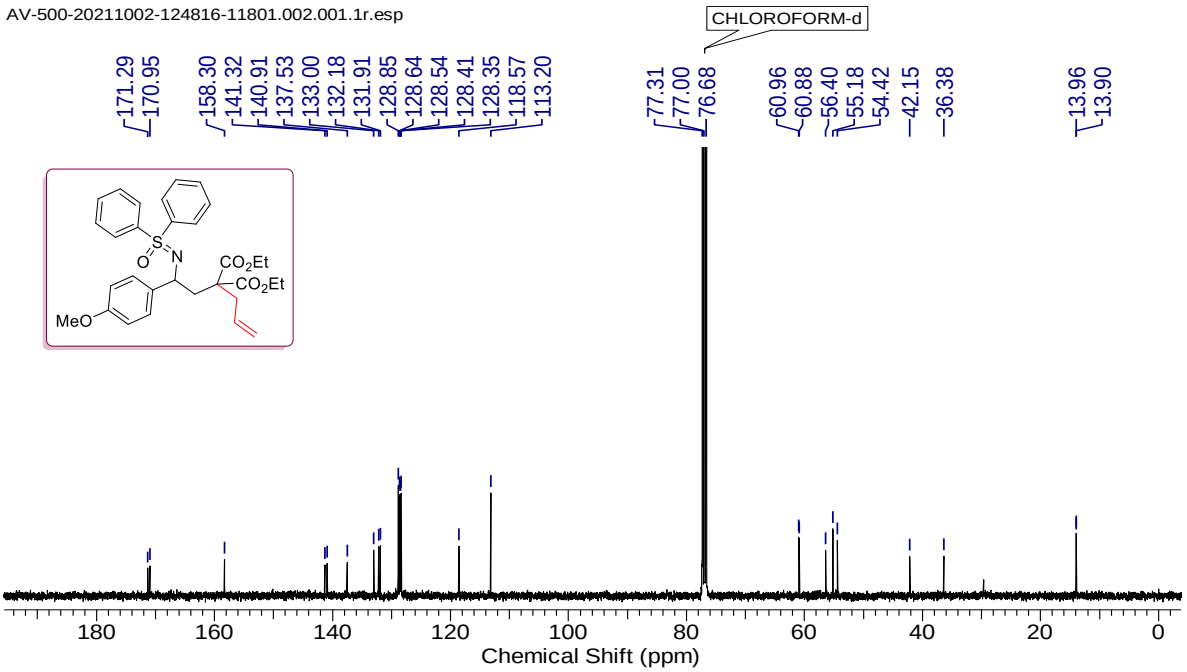
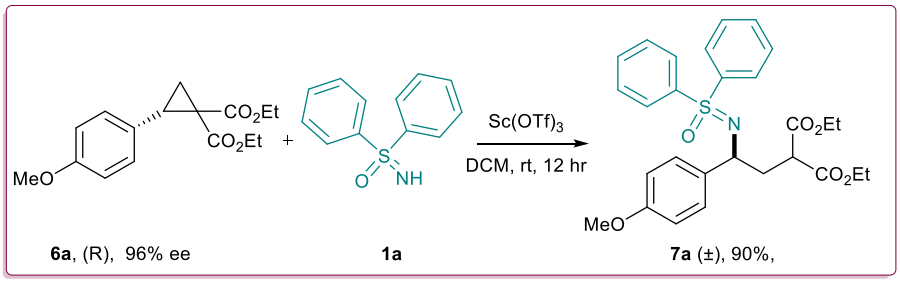


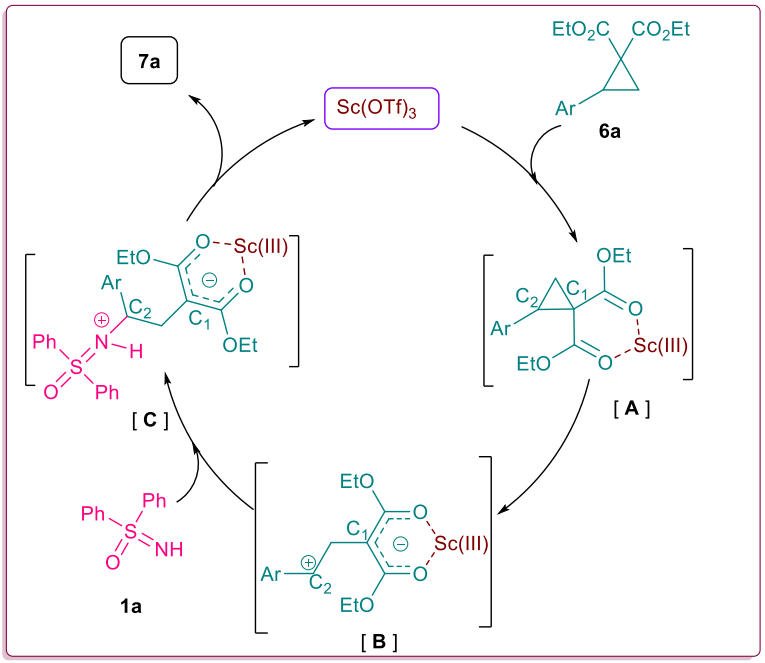
Figure 3: Diethyl 2-allyl-2-(2-(4-methoxyphenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (**11**)

conditions, giving the racemic product **7a** in 90% yield. This result showed the initial ring-opening step with sulfoximine *via* the S_N1 reaction pathway, as shown in **Scheme 7**.



Scheme 7: Synthesis of γ- sulfoximino malonic diesters from enantiomerically pure cyclopropane (**6a**)

Based on the literature report, [8a-b, 8e-g, 12e, 19] and the control experiment, we predicted the possible reaction pathway as delineated in Scheme 8. Sc(III) initially coordinated to diester of D-A cyclopropane (**6a**) to form the Sc-coordinated complex (**A**), which provides the activated cyclopropane complex (**B**) with the formation of a stable benzylic carbocation. [19b] Next, the



Scheme 8: Plausible Reaction Mechanism

nucleophilic addition of sulfoximine (**1a**) at C_2 of cyclopropane *via* the S_N1 pathway leads to forming a ring-opening of cyclopropane intermediate (**C**). Furthermore, the 1, 4-hydrogen atom shift furnishes the construction of desired *γ*-sulfoximino malonic diester (**3a**) with the regeneration of the Sc(III) catalyst.

4.1.5. Conclusion

We have developed a facile and efficient Sc(III) catalyzed ring-opening reaction of D-A cyclopropanes from weak nucleophilic sulfoximines to synthesize a diverse range of novel *γ*-sulfoximino malonic diesters in excellent yields. The old C-C bond from cyclopropane is cleaved, and the C-N and C-H bonds between sulfoximine and cyclopropane are formed in a single step using this strategy. Also, mild reaction conditions, high atom economy, broad substrate scope, and excellent yield of the formed products.

4.1.6. Experimental Section

4.1.6.1 General Experimental Procedure for the Synthesis of Diarylmethine Sulfoximines (7a-7r):

To a 25 mL round bottom flask with a stir bar were added D-A cyclopropanes **6a** (50 mg, 0.1712 mmol, 1 equiv.), Sulfoximines **1** (0.2054, 1.2 equiv.) in dry CH_2Cl_2 (2.0 mL) and $Sc(OTf)_3$ (10 mol %) was added in reaction mixture. The reaction mixture was stirred at room temperature under an N_2 atmosphere for 8 to 16 h. After completion (monitored by TLC), the reaction mixture was quenched with water (2 mL) and extracted with CH_2Cl_2 (3×3mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated under a vacuum. The crude was purified on flash silica gel chromatography (petroleum ether/ethyl acetate = 7:3) to afford γ-sulfoximino malonic diesters (**3a-3r**).

4.1.6.2 General Experimental Procedure for the Synthesis of Diarylmethine Sulfoximines (9a-9r):

To a 25 mL round bottom flask with a stir bar were added D-A cyclopropanes **8** (50 mg, 0.1908 mmol, 1 equiv.), sulfoximine **1a** (0.2290 1.2 equiv.) in dry CH_2Cl_2 (2.0 mL) and $Sc(OTf)_3$ (10 mol %) was added in the reaction mixture. The reaction mixture was stirred at room temperature under an N_2 atmosphere for 8 to 16 h. After completion (monitored by TLC), the reaction mixture was quenched with water (2 mL) and extracted with CH_2Cl_2 (3×3mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated under a vacuum. The crude was purified on flash silica gel chromatography (petroleum ether/ethyl acetate = 70:30) to afford substituted γ-sulfoximino malonic diesters(**9a-9i**)

4.1.6.3 General Experimental Procedure for Synthetic of Synthesis of *γ*-Sulfoximino, *α*-Bromo Malonic Diesters (10):

To a 25 mL round bottom flask with stir bar were added D-A cyclopropane **6a** (50 mg, 0.1712 mmol, 1 equiv.), sulfoximine **1c** (0.2054 mmol, 1.2 equiv.), and NBS (0.2568 mmol,1.5 equiv.) in dry CH_2Cl_2 (20 mL) and $Sc(OTf)_3$ (10 mol%) was added in reaction mixture. The reaction mixture was stirred at room temperature under an N_2 atmosphere for 12 h. After completion (monitored by TLC), The reaction mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated under a vacuum. The crude was purified on flash silica gel chromatography (petroleum ether/ethyl acetate = 80:20) to afford **10** in 72% yield.

4.1.6.4 General Experimental Procedure for Synthetic Utility of Product 3a (11):

Compound **7a** (30 mg, 0.0589 mmol, 1.0 equiv.) was taken in a 25 mL round bottom flask with a stir bar fitted with a water condenser under an N_2 atmosphere, then dry THF was added *via*

cannula. NaH (0.07072 mmol, 1.2 equiv.) was added to this solution at 0 °C and stirred at room temperature for 1 hr. Then added Allyl bromide (0.1178 mmol, 2.0 equiv.) slowly, and the resulting mixture was refluxed at 70 °C for another 12 h under an N_2 atmosphere. After completion (monitored by TLC), The reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with Ethyl acetate (3×10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated under a vacuum. The crude was purified on flash silica gel chromatography (petroleum ether/ethyl acetate = 80:20) to afford **11** in 62% yield.

4.1.6.5 General Experimental Procedure for Gram-Scale Synthesis of Compound 7a:

Compound **7a** (30 mg, 0.0589 mmol, 1.0 equiv.) was taken in a 25 mL round bottom flask with a stir bar fitted with a water condenser under an N_2 atmosphere, then dry THF was added *via* cannula. NaH (0.07072 mmol, 1.2 equiv.) was added to this solution at 0 °C and stirred at room temperature for 1 hr. Then added Allyl bromide (0.1178 mmol, 2.0 equiv.) slowly, and the resulting mixture was refluxed at 70 °C for another 12 h under an N_2 atmosphere. After completion (monitored by TLC), The reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with Ethyl acetate (3×10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated under a vacuum. The crude product was subjected to purification on flash silica gel chromatography (petroleum ether/ethyl acetate = 80:20) to afford **11** in 62% yield.

4.1.6.6 General Experimental Procedure for (±) *γ*-Sulfoximino malonic diester (7a) from chiral D-A cyclopropane (R) (6a):

To a 25 mL round bottom flask with stir bar were added chiral D-A cyclopropane (R) **6a** (> 96% ee) (50 mg, 0.1712 mmol, 1 equiv.), sulfoximine **1a** (0.2054 mmol, 1.2 equiv.), in dry CH_2Cl_2

(20 mL) and $Sc(OTf)_3$ (10 mol%) was added in reaction mixture. The reaction mixture was stirred at room temperature under an N_2 atmosphere for 12 h. After completion (monitored by TLC), the reaction mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated under a vaccum. The crude was purified on flash silica gel chromatography (petroleum ether/ethyl acetate = 80:20) to afford (±) **7a** in 90 % yield.

Diethyl 2-(2-(4-methoxyphenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (7a):

Yield: 94% (81 mg); Colorless gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3443.23, 2087.45, 1723.10, 1642.50, 1551.07, 1481.92, 1284.08, 1195.46, 1010.95, 754.83; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93-8.07 (m, 2H), 7.76 (dd, *J* = 8.32, 1.19 Hz, 2H), 7.39-7.56 (m, 4H), 7.31-7.38 (m, 2H), 7.18-7.28 (m, 2H), 6.76-6.84 (m, 2H), 4.23 (d, *J* = 7.13 Hz, 1H), 4.03-4.20 (m, 4H), 3.78 (s, 3H), 3.75 (dd, *J* = 7.82, 6.57 Hz, 1H), 2.40 (td, *J* = 7.04, 1.56 Hz, 2H), 1.15-1.26 (m, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ169.7, 169.5, 158.4, 140.1, 136.8, 132.6, 132.5, 129.3, 129.0, 128.9, 128.8, 128.5, 127.8, 124.7, 113.5, 61.2, 61.1, 56.1, 55.2, 49.3, 39.5, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{32}O_6NS$, 510.1945; found, 510.1942.

Diethyl 2-(2-(4-methoxyphenyl)-2-(((4-methoxyphenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino) ethyl) malonate (7b):

Yield: 92% (84 mg); Colorless gum; ***dr*** = 1:1; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3423.50, 2088.68, 1724.83, 1641.60, 1550.69, 1534.99, 1511.72, 1494.34, 1443.78, 1242.79, 1172.89, 771.34; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.87-7.98 (m, 2H), 7.66-7.76 (m, 2H), 7.40-7.54 (m, 2H), 7.31-7.37 (m, 1H), 7.24 (d, *J* = 8.63Hz, 1H), 7.27 (d, *J* = 8.63Hz, 1H), 6.95 (d, *J* = 9.01 Hz, 1H), 6.76-6.87 (m, 3H), 4.21-4.28 (m, 1H), 4.03-4.21 (m, 4H), 3.77-3.91 (m, 6H), 3.74 (t, *J* = 7.25Hz, 1H),

2.37-2.46 (m, 2H), 1.17 1.27 (m, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 169.8, 169.5, 158.4, 131.0, 130.7, 129.0, 128.9, 128.6, 128.2, 127.9, 114.4, 114.2, 113.6, 61.2, 61.1, 56.1, 56.1, 55.6, 55.5, 55.2, 49.3, 14.0, 14.0; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{34}O_7NS$, 540.2050; found, 540.2053.

Diethyl 2-(2-(4-methoxyphenyl)-2-((oxo(phenyl)(p-tolyl)-l6-sulfaneylidene) amino) ethyl) malonate (7c):

Yield: 91% (81 mg); Yellowish gum; ***dr*** = 1:1; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3395.18, 2088.24, 1726.79, 1642.07, 1553.27, 1535.67, 1510.97, 1300.32, 1243.71, 1140.68, 771.58; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.91-7.97 (m, 1H), 7.79-7.89 (m, 1H), 7.69-7.79 (m, 1H), 7.64 (d, *J* = 8.38 Hz, 1H), 7.37-7.51 (m, 2H), 7.20-7.35 (m, 4H), 7.13 (d, *J* = 8.00 Hz, 1H), 6.72-6.86 (m, 2H), 4.03-4.26 (m, 5H), 3.78-3.80 (m, 3H), 3.71-3.78 (m, 1H), 2.31-2.41 (m, 5H), 1.18-1.28 (m, 6 H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 169.9, 169.6, 169.6, 158.3, 143.1, 143.0, 141.1, 141.1, 137.7, 137.6, 137.5, 137.4, 132.1, 132.0, 129.6, 129.5, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 127.7, 113.5, 61.1, 61.1, 60.3, 56.0, 56.0, 55.2, 49.3, 39.9, 39.9, 21.4, 21.3, 21.0, 14.1, 14.0, 13.9 ; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{34}O_6NS$, 524.2101; found, 524.2096.

Diethyl 2-(2-(((4-chlorophenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (7d):

Yield: 88% (81 mg); Yellowish gum; ***dr*** = 1:1; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3423.35, 2088.82, 1722.34, 1641.46, 1552.20, 1535.57, 1511.85, 1444.15, 1228.30, 771.18; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93-7.98 (m, 1H), 7.85-7.91 (m, 1H), 7.72-7.77 (m, 1H), 7.61-7.66 (m, 1H), 7.46-7.51 (m, 1H), 7.40-7.44 (m, 1H), 7.32-7.37 (m, 1H), 7.26 (d, *J* = 8.63Hz, 1H), 7.21 (dd, *J* = 8.57, 1.56Hz, 2H), 6.79 (dd, *J* = 8.76, 2.25Hz, 2H), 4.21-4.25 (m, 1H), 4.16-4.20 (m, 1H), 4.11-4.16 (m, 1H), 4.03-4.11 (m, 2H), 3.75-3.81 (m, 3H), 3.71 (td, *J* = 7.19, 1.88 Hz, 1H), 2.32-2.43 (m,

2H), 1.19-1.29 (m, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 169.8, 169.7, 169.5, 166.6, 158.4, 158.4, 140.4, 140.4, 139.5, 139.4, 138.9, 138.7, 137.0, 136.9, 132.5, 132.4, 130.1, 129.9, 129.2, 129.0, 129.0, 128.9, 128.6, 128.3, 127.7, 127.7, 113.5, 61.4, 61.2, 61.1, 61.1, 56.0, 55.9, 55.1, 49.3, 41.6, 39.7, 39.7, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{31}O_6NClS$, 544.1555; found, 554.1550.

Diethyl 2-(2-(((4-fluorophenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (7e):

Yield: 85% (76 mg); Reddish gum; ***dr*** = 1:1; **IR** $CHCl_3$, cm^{-1}) ν_{max}: 3423.23, 2985.52, 1727.80, 1692.03, 1658.23, 1587.39, 1243.23, 1140.19, 1032.01, 835.10, 756.88; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92-8.00 (m, 2H), 7.68-7.77 (m, 2H), 7.39-7.52 (m, 2H), 7.29-7.36 (m, 1H), 7.21 (dd, *J* = 8.50, 1.25 Hz, 2H), 7.07-7.16 (m, 1H), 6.97 (t, *J* = 8.57 Hz, 1H), 6.79 (d, *J* = 8.63 Hz, 2H), 4.18-4.25 (m, 1H), 4.06-4.15 (m, 4 H), 3.77 (s, 3H), 3.72 (s, 1H), 2.37 (t, *J* = 6.94 Hz, 2H), 1.23 (d, *J* = 6.13 Hz, 4 H), 1.15-1.19 (m, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 169.7, 169.7, 169.4, 158.3, 158.3, 140.6, 140.6, 137.0, 136.7, 136.7, 132.4, 132.3, 131.4, 131.3, 131.1, 131.0, 129.0, 128.8, 128.5, 128.2, 127.6, 127.6, 116.2, 116.0, 115.7, 113.4, 61.1, 61.0, 60.2, 56.0, 55.8, 55.0, 49.2, 39.7, 39.7, 14.0, 13.9, 13.9; **^{19}F NMR** (376 MHz, $CDCl_3$): δ -106.4; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{31}O_6NFS$, 528.1851; found, 528.1845.

Diethyl 2-(2-(((4-iodophenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (7f):

Yield: 88% (95 mg); Colorless gum; ***dr*** = 1:1; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3443.49, 2089.03, 1642.49, 1551.63, 1534.49, 1511.83, 1444.44, 1242.66, 1138.57, 769.50; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.88-8.01 (m, 1H), 7.76-7.83 (m, 1H), 7.70-7.76 (m, 1H), 7.61-7.67 (m, 1H), 7.31-7.57 (m, 5H), 7.13-7.26 (m, 2H), 6.75-6.82 (m, 2H), 4.05-4.26 (m, 5H), 3.76-3.81 (m, 3H), 3.68-

3.76 (m, 1H), 2.32-2.44 (m, 2H), 1.16-1.27 (m, 6H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 169.8, 169.8, 169.7, 169.5, 169.5, 158.4, 158.4, 158.3, 158.3, 144.7, 140.8, 140.7, 140.7, 140.4, 140.3, 138.2, 137.9, 137.7, 137.6, 137.2, 137.0, 136.9, 134.1, 133.9, 132.5, 132.4, 132.3, 132.2, 130.2, 129.9, 129.7, 129.6, 129.2, 129.1, 129.0, 129.0, 128.9, 128.8, 128.6, 128.6, 128.3, 127.7, 127.7, 127.4, 127.3, 113.5, 113.4, 100.0, 99.8, 61.2, 61.1, 61.1, 60.3, 56.1, 55.9, 55.9, 55.2, 55.1, 49.3, 39.8, 39.7, 39.6, 14.1, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{31}O_6NIS$, 636.0911; found, 636.0894.

Diethyl 2-(2-(4-methoxyphenyl)-2-(((4-nitrophenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino) ethyl) malonate (7g):

Yield: 87% (82 mg); Yellowish gum; ***dr*** = 1:1; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3423.12, 3022.64, 1726.39, 1691.21, 1641.62, 1610.73, 1530.31, 1511.08, 1445.65, 1368.19, 1349.36, 1291.52, 1245.73, 1142.99, 1093.72, 756.38; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 (d, J = 8.88 Hz, 1H), 8.04-8.15 (m, 2H), 7.95-8.04 (m, 1H), 7.73-7.85 (m, 2H), 7.43-7.60 (m, 2H), 7.34-7.42 (m, 1H), 7.16 (d, J = 8.63 Hz, 1H), 7.21 (d, J = 8.63 Hz, 1H), 6.67-6.84 (m, 2H), 4.22-4.34 (m, 1H), 3.99-4.19 (m, 4H), 3.76 (d, J = 12.26 Hz, 3H), 3.69 (ddd, J = 8.29, 6.03, 3.56 Hz, 1H), 2.30-2.49 (m, 2H), 1.14-1.26 (m, 6H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 169.7, 169.6, 169.4, 158.6, 158.5, 149.8, 149.6, 147.6, 147.0, 139.5, 139.4, 136.5, 136.2, 133.1, 133.0, 129.8, 129.6, 129.3, 129.1, 128.9, 128.5, 127.7, 127.7, 124.1, 123.7, 113.6, 113.5, 61.2, 61.2, 60.3, 56.2, 55.8, 55.1, 49.3, 49.2, 39.6, 39.4, 14.1, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{31}O_8N_2S$, 555.1796; found, 555.1779.

Diethyl 2-(2-(4-methoxyphenyl)-2-((oxo(phenyl)(m-tolyl)-l6-sulfaneylidene) amino) ethyl) malonate (7h):

Yield: 84% (74 mg); Yellowish gum; ***dr*** = 1:1; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3423.67, 3019.93, 2360.90, 1724.41, 1641.41, 1511.00, 1476.68, 1444.51, 1424.55, 1215.09, 928.70, 764.12, 669.32; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.97 (dd, *J* = 8.00, 1.38 Hz, 1H), 7.73-7.80 (m, 2H), 7.40-7.57 (m, 3H), 7.29-7.35 (m, 2H), 7.17-7.25 (m, 3H), 6.80 (d, *J* = 7.88 Hz, 2H), 4.21 (d, *J* = 3.00 Hz, 1H), 4.13-4.17 (m, 1H), 4.05-4.12 (m, 3H), 3.77-3.79 (m, 3H), 3.72-3.77 (m, 1H), 2.36-2.39 (m, 3H), 2.23 (s, 1H), 2.04 (s, 1H), 1.23-1.26 (m, 4H), 1.16-1.21 (m, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$): δ169.9, 169.5, 158.3, 140.9, 140.5, 140.5, 139.1, 138.9, 137.4, 137.3, 133.1, 133.0, 132.2, 132.1, 129.2, 128.9, 128.8, 128.7, 128.7, 128.6, 128.3, 127.7, 127.7, 125.9, 125.5, 113.4, 61.1, 61.0, 56.0, 55.1, 49.3, 39.8, 39.8, 21.3, 21.1, 20.9, 14.1, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{34}O_6NS$, 524.2101; found, 524.2100.

Diethyl 2-(2-(((3-fluorophenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (7i):

Yield: 81% (73 mg); Yellowish gum; ***dr*** = 1:1; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3423.22, 3020.07, 2400.45, 1725.19, 1641.96, 1511.53, 1475.30, 1444.73, 1216.58, 928.79, 773.12, 669.34; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.96 - 8.01 (m, 1H), 7.62 - 7.79 (m, 2H), 7.40 - 7.57 (m, 4 H), 7.32 - 7.40 (m, 1H), 7.15 - 7.26 (m, 3H), 6.76 - 6.84 (m, 2H), 4.05 - 4.26 (m, 5H), 3.79 (d, *J* = 2.00 Hz, 3H), 3.72 (ddd, *J* = 7.82, 6.50, 4.44 Hz, 1H), 2.31 - 2.47 (m, 2H), 1.24 - 1.27 (m, 3H), 1.17 - 1.23 (m, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 169.8, 169.8, 169.5, 169.5, 163.7, 163.5, 161.2, 161.0, 158.4, 143.3, 143.3, 143.2, 143.1, 140.3, 140.3, 137.0, 136.9, 132.7, 132.6, 130.7, 130.6, 130.4, 130.3, 129.3, 129.1, 129.0, 128.8, 128.5, 128.5, 127.8, 127.7, 124.4, 124.4, 124.2, 124.2, 119.6, 119.4, 119.2, 116.1, 115.9, 115.6, 113.6, 61.2, 61.2, 56.1, 56.0, 55.2, 49.3, 49.3, 39.8, 39.6, 14.2, 14.0, 14.0; **^{19}F NMR** (376 MHz, $CDCl_3$): δ-110.33; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{31}O_6NFS$, 528.1851; found, 528.1841.

Diethyl 2-(2-(4-methoxyphenyl)-2-(((2-methoxyphenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino) ethyl) malonate (7j):

Yield: 86% (79 mg); Whitish gum; ***dr*** = 1:1; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3422.19, 3019.94, 2360.82, 1641.16, 1510.88, 1477.73, 1370.32, 1214.46, 1024.20, 850.14, 759.12, 626.58; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.63 Hz, 1 H), 7.94 (d, *J* = 7.13 Hz, 1 H), 7.69 (d, *J* = 8.76 Hz, 1 H), 7.73 (d, *J* = 7.50 Hz, 1 H), 7.37-7.54 (m, 2 H), 7.29-7.36 (m, 1 H), 7.19-7.27 (m, 2 H), 6.94 (d, *J* = 8.63 Hz, 1 H), 6.74-6.85 (m, 3H), 3.97-4.26 (m, 5H), 3.78-3.85 (m, 6 H), 3.75 (t, *J* = 7.13 Hz, 1H), 2.38 (br. s., 2H), 1.17-1.27 (m, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ170.1, 169.6, 169.6, 158.2, 158.0, 156.6, 156.4, 140.8, 140.7, 137.7, 137.7, 134.5, 134.4, 132.1, 131.9, 131.8, 131.7, 129.4, 129.3, 128.0, 127.9, 127.7, 127.5, 127.4, 127.1, 120.3, 120.0, 113.3, 113.0, 112.0, 111.5, 61.0, 61.0, 61.0, 56.5, 55.9, 55.2, 55.2, 55.1, 54.4, 49.3, 49.0, 40.0, 39.9, 14.0, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{34}O_7NS$, 540.2050; found, 540.2054.

Diethyl 2-(2-(4-methoxyphenyl)-2-(((2-nitrophenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino) ethyl) malonate (7k):

Yield: 80% (75 mg); Brown gum; ***dr*** = 2:1; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3422.18, 3020.11, 2400.36, 1724.83, 1641.25, 1545.57, 1445.56, 1218.61, 1033.88, 928.66, 771.98, 669.27; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.0-8.1 (m, 2H), 7.4-7.7 (m, 7H), 7.1-7.2 (m, 2H), 6.7-6.8 (m, 2H), 4.0-4.2 (m, 5H), 3.8 (s, 3H), 3.8 (s, 1H), 2.3-2.5 (m, 2H), 1.2-1.3 (m, 3H), 1.1-1.2 (m, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 169.8, 169.6, 169.4, 169.4, 158.5, 149.6, 140.0, 139.9, 136.1, 136.1, 134.1, 133.6, 133.5, 133.1, 133.0, 132.9, 131.9, 131.8, 131.4, 131.0, 129.0, 128.9, 128.8, 128.4, 127.9, 127.8, 124.2, 124.0, 113.6, 113.5, 61.2, 61.2, 56.4, 55.7, 55.2, 55.1, 49.3, 49.0, 39.3, 14.1, 13.9, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{31}O_8N_2S$, 555.1796; found, 555.1783.

Diethyl 2-(2-(((3,5-dimethylphenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (7l):

Yield: 84% (77 mg); Yellowish gum; ***dr*** = 1:1; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3423.45, 2983.89, 1744.03, 1691.98, 1641.69, 1511.05, 1369.54, 1243.19, 1136.29, 1033.57, 754.86, 688.54; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.96-7.99 (m, 1H), 7.73-7.78 (m, 1H), 7.57 (s, 1H), 7.40-7.52 (m, 2H), 7.30-7.37 (m, 2H), 7.22-7.27 (m, 2H), 7.13 (s, 1H), 7.04 (s, 1H), 6.76-6.84 (m, 2H), 4.20-4.27 (m, 1H), 4.05-4.19 (m, 4H), 3.77-3.80 (m, 3H), 3.71-3.76 (m, 1H), 2.40 (t, *J* = 5.69 Hz, 2H), 2.33-2.36 (m, 3H), 2.20-2.22 (m, 3H), 1.17-1.26 (m, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 169.8, 169.5, 158.3, 139.0, 138.8, 134.3, 134.1, 132.4, 132.2, 129.0, 128.8, 128.7, 128.3, 127.9, 127.8, 126.4, 125.9, 113.5, 113.4, 61.1, 56.0, 55.2, 55.1, 49.3, 49.3, 39.6, 39.5, 21.2, 21.0, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{36}O_6NS$, 538.2258; found, 538.2261.

Diethyl 2-(2-(4-methoxyphenyl)-2-((methyl(4-nitrophenyl) (oxo)-l6-sulfaneylidene) amino) ethyl) malonate (7m):

Yield: 90% (75 mg); Yellow gum; ***dr*** = 0.1:1; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3442.54, 2934.67, 2088.71, 1725.89, 1642.19, 1548.48, 1530.52, 1511.22, 1443.92, 1368.40, 1348.18, 1244.60, 1141.08, 1032.01, 756.78; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.36-8.42 (m, 2H), 8.14-8.19 (m, 2H), 7.21-7.26 (m, 2H), 6.79-6.85 (m, 2H), 4.06-4.20 (m, 5H), 3.78 (s, 3H), 3.46 (t, *J* = 7.13 Hz, 1H), 3.05 (s, 3H), 2.26-2.36 (m, 2H), 1.22 (dt, *J* = 12.26, 7.13Hz, 7H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 169.5, 169.3, 158.7, 150.4, 145.6, 136.0, 129.7, 129.6, 128.1, 127.7, 124.4, 123.8, 113.8, 113.5, 61.3, 61.3, 56.4, 55.2, 49.4, 44.6, 39.0, 14.0, 14.0; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{29}O_8N_2S$, 493.1639; found, 493.1628.

Diethyl 2-(2-((benzyl(oxo)(phenyl)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (7n):

Yield: 86% (77 mg); Colorless gum; ***dr*** = 1:1; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3423.38, 2087.61, 1726.90, 1641.53, 1552.28, 1511.04, 1445.44, 1300.01, 1244.49, 1173.60, 1031.67, 756.30, 696.79; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.59-7.64 (m, 2H), 7.54 (t, *J* = 7.38 Hz, 1H), 7.41 (td, *J* = 7.50, 3.50 Hz, 3H), 7.28-7.34 (m, 3H), 7.16-7.24 (m, 6H), 7.09-7.14 (m, 2H), 7.04 (d, *J* = 7.25Hz, 2H), 6.88 (d, *J* = 7.25Hz, 2H), 6.79-6.86 (m, 2H), 6.67-6.76 (m, 2H), 4.28-4.37 (m, 2H), 4.21-4.27 (m, 2H), 4.17-4.20 (m, 1H), 4.16 (d, *J* = 3.63Hz, 1H), 4.14-4.15 (m, 1H), 4.12-4.13 (m, 1H), 4.08-4.12 (m, 1H), 4.06 (d, *J* = 7.38 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.70 (t, *J* = 7.19 Hz, 1H), 3.58 (t, *J* = 7.13Hz, 1H), 2.36 (t, *J* = 7.00 Hz, 4H), 1.15-1.26 (m, 12H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 169.8, 169.7, 169.5, 169.4, 158.5, 158.4, 137.2, 136.5, 132.8, 131.3, 131.0, 129.6, 129.4, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 113.6, 113.4, 63.1, 62.9, 61.2, 61.1, 61.1, 55.9, 55.6, 55.2, 55.1, 49.4, 49.2, 39.5, 39.2, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{34}O_6NS$, 524.2101; found, 524.2102.

Diethyl 2-(2-((dibenzyl(oxo)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (7o):

Yield: 88% (80 mg); Colorless gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3422.93, 2932.62, 2114.68, 1725.93, 1657.58, 1641.60, 1550.08, 1511.34, 1480.00, 1245.62, 1153.90, 1030.68, 758.72; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.41 (m, 5H), 7.20-7.29 (m, 5H), 7.12 (dd, *J* =7 .75, 1.50 Hz, 2H), 6.76-6.83 (m, 2H), 4.33 (dd, *J* = 8.88, 5.00 Hz, 1H), 4.00-4.18 (m, 6H), 3.79-3.90 (m, 2H), 3.77 (s, 3H), 3.43 (dd, *J* = 8.82, 5.44 Hz, 1H), 2.20 (ddd, *J* = 13.45, 8.63, 5.19 Hz, 2H), 1.22 (q, *J* = 7.13Hz, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 170.0, 169.5, 158.5, 137.6, 131.3, 130.7,

129.5, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 113.6, 61.1, 61.0, 60.1, 58.3, 55.2, 54.3, 49.2, 39.7, 14.0; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{36}O_6NS$, 538.2258; found, 538.2259.

Diethyl 2-(2-((10-benzyl-5-oxido-10H-5l4-phenothiazin-5-ylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (7p):

Yield: 85% (89 mg); Red gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3680.82, 3422.97, 3020.00, 2400.28, 1641.31, 1511.80, 1467.82, 1218.36, 772.12, 669.57; **^{1}H NMR** (400 MHz, $CDCl_3$): δ8.01 (dd, *J* = 7.88, 1.50 Hz, 1H), 7.93 (dd, *J* = 7.88, 1.50 Hz, 1H), 7.28-7.41 (m, 5H), 7.21 (t, *J* = 7.44 Hz, 1H), 7.10-7.17 (m, 3H), 6.96-7.03 (m, 3H), 6.89 (d, *J* = 8.50 Hz, 1H), 6.67 (d, *J* = 8.63Hz, 2H), 5.30 (d, *J* = 18.39 Hz, 1H), 5.18 (d, *J* = 18.39 Hz, 1H), 4.04-4.16 (m, 5H), 3.75 (s, 3H), 3.54 (dd, *J* = 9.38, 4.88 Hz, 1H), 2.01-2.22 (m, 2H), 1.24-1.28 (m, 4H), 1.20 (t, *J* = 7.13Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ169.8, 169.2, 158.1, 140.6, 140.6, 136.9, 135.3, 132.4, 132.4, 129.1, 127.5, 127.3, 125.7, 124.6, 124.4, 123.7, 123.5, 121.8, 121.7, 116.3, 115.9, 113.2, 61.1, 61.0, 55.9, 55.2, 53.1, 49.2, 39.5, 14.0, 14.0; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{35}H_{37}O_6N_2S$, 613.2367; found, 613.2362.

Diethyl 2-(2-(4-methoxyphenyl)-2-((10-oxido-9-oxo-9H-10l4-thioxanthen-10-ylidene) amino) ethyl) malonate (7q):

Yield: 89% (81 mg); White solid; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3435.29, 2089.21, 1723.09, 1642.71, 1536.06, 1510.98, 1468.06, 1442.57, 1369.50, 1301.48, 1220.29, 772.19, 676.29; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.15-8.23 (m, 2H), 8.01-8.06 (m, 1H), 7.85-7.91 (m, 1H), 7.76 (td, *J* = 7.63, 1.38 Hz, 1H), 7.65-7.71 (m, 1H), 7.54-7.64 (m, 2H), 6.91-6.96 (m, 2H), 6.58-6.62 (m, 2H), 4.21 (dd, *J* = 8.44, 5.94 Hz, 1H), 4.12-4.18 (m, 1H), 4.02-4.11 (m, 3H), 3.72 (s, 3H), 3.52 (dd, *J* = 8.25, 6.38 Hz, 1H), 2.17 (ddd, *J* = 8.44, 6.07, 2.25Hz, 2H), 1.25 (t, *J* = 7.13Hz, 3H), 1.18 (t, *J* = 7.13Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 179.1, 169.5, 169.1, 158.3, 141.2, 141.0,

135.2, 133.7, 133.6, 132.2, 131.9, 130.7, 130.6, 128.8, 128.7, 127.4, 124.5, 124.3, 113.5, 61.1, 61.1, 56.9, 55.1, 49.3, 39.5, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{30}O_7NS$, 536.1737; found, 536.1737.

Diethyl 2-(2-(4-methoxyphenyl)-2-((5-oxido-5l4-dibenzo [b, d] thiophen-5-ylidene) amino) ethyl) malonate (7r):

Yield: 92% (79 mg); Yellowish white solid; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3451.97, 2088.34, 1641.52, 1552.65, 1535.56, 1511.83, 1468.05, 1217.53, 769.15; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.75Hz, 1H), 7.58-7.68 (m, 2H), 7.45-7.57 (m, 2H), 7.30 (t, *J* = 7.57 Hz, 2H), 7.21-7.26 (m, 1H), 7.08-7.16 (m, 2H), 6.63-6.70 (m, 2H), 4.63-4.70 (m, 1H), 4.18-4.27 (m, 1H), 4.07-4.16 (m, 3H), 3.75 (s, 3H), 2.94 - 3.04 (m, 1H), 2.49 - 2.58 (m, 1H), 1.18-1.27 (m, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 166.6, 166.4, 158.8, 137.8, 137.5, 135.3, 133.2, 133.1, 132.3, 132.1, 129.6, 129.6, 128.2, 124.1, 124.0, 121.1, 121.0, 113.6, 69.9, 62.7, 55.3, 55.0, 46.0, 13.8, 13.7; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{30}O_6NS$, 508.1788; found, 508.1801.

Diethyl 2-(2-((oxodiphenyl-l6-sulfaneylidene) amino)-2-phenylethyl) malonate (9a):

Yield: 90% (82 mg); Colorless gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3443.01, 2982.22, 1649.00, 1551.78, 1445.58, 1194.63, 1121.27, 977.05, 744.14; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.95 (dd, *J* = 8.19, 1.31 Hz, 2H), 7.66-7.74 (m, 2H), 7.35-7.48 (m, 4H), 7.25-7.31 (m, 4H), 7.19-7.25 (m, 2H), 7.13-7.18 (m, 1H), 4.23 (t, *J* = 6.69 Hz, 1H), 3.96-4.17 (m, 4H), 3.75 (t, *J* = 7.13 Hz, 1H), 2.36 (t, *J* = 7.00 Hz, 2 H), 1.12-1.22 (m, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ169.9, 169.5, 145.1, 140.8, 140.7, 132.3, 132.2, 129.0, 128.8, 128.8, 128.4, 128.1, 126.7, 61.2, 61.1, 56.6, 49.3, 39.8, 14.0, 14.0; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{27}H_{30}O_5NS$, 480.1839; found, 480.1841.

Diethyl 2-(2-(4-(methylthio) phenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (9b):

Yield: 73% (62 mg); Yellowish gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3423.65, 3019.90, 2400.31, 1727.18, 1641.38, 1446.40, 1370.32, 1217.86, 1140.83, 1093.95, 768.30, 687.59; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79-7.85 (m, 2H), 7.58-7.62 (m, 2H), 7.28-7.38 (m, 4H), 7.16-7.22 (m, 2H), 7.11 (d, *J* = 8.63 Hz, 2H), 6.98-7.04 (m, 2H), 4.09 (s, 1H), 3.85-4.03 (m, 4H), 3.60 (t, *J* = 7.25 Hz, 1H), 2.31 (s, 3H), 2.24 (t, *J* = 6.94 Hz, 2H), 1.01-1.10 (m, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 169.7, 169.5, 136.4, 132.6, 132.4, 129.3, 129.0, 128.9, 128.8, 128.7, 128.4, 127.3, 126.6, 61.2, 61.2, 56.2, 49.2, 39.5, 16.0, 14.0, 13.9; **HRMS** (ESI) m/z: [M+H]+ calcd for $C_{28}H_{32}O_5NS_2$, 526.1716; found, 526.1718.

Diethyl2-(2-(4-nitrophenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (9c):

Yield: 56% (47 mg); Yellow liquid; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3642.10, 3423.69, 3020.01, 2361.15, 2096.02, 1724.50, 1641.36, 1522.30, 1424.56, 1217.77, 928.67, 771.92; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.13 Hz, 2H), 7.95 (d, *J* = 7.75 Hz, 2H), 7.76 (d, *J* = 7.75 Hz, 2H), 7.42-7.59 (m, 6 H), 7.32-7.40 (m, 2H), 4.32-4.42 (m, 1H), 4.05-4.25 (m, 4H), 3.80 (t, *J* = 7.00 Hz, 1H), 2.33-2.43 (m, 2H), 1.26 (t, *J* = 7.13 Hz, 4H), 1.20 (t, *J* =7.13 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ169.5, 169.3, 152.9, 146.8, 140.4, 140.1, 132.7, 132.6, 129.2, 129.0, 128.5, 128.4, 128.4, 127.6, 123.5, 61.4, 61.3, 56.0, 49.0, 39.4, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{27}H_{29}O_7N_2S$, 525.1690; found, 525.1688.

Diethyl 2-(2-(4-chlorophenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (9d):

Yield: 86% (74 mg); Colorless gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3423.31, 3019.35, 2114.54, 1723.09, 1641.36, 1551.87, 1501.95, 1468.36, 1379.36, 1215.79, 1121.61, 757.22, 668.33; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 8.07, 1.31 Hz, 2H), 7.61-7.70 (m, 2H), 7.31-7.44 (m, 4H), 7.21-7.27 (m, 2H), 7.19 (m, *J* = 8.38 Hz, 2H), 7.13 (m, *J* = 8.50 Hz, 2H), 4.16 (t, *J* = 6.63

Hz, 1H), 3.95-4.11 (m, 4H), 3.69 (t, *J* = 7.13 Hz, 1H), 2.28 (t, *J* = 7.13 Hz, 2H), 1.12-1.17 (m, 3H), 1.08 (t, *J* = 7.13 Hz, 3H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 169.6, 169.3, 143.6, 140.4, 140.3, 132.4, 132.3, 132.2, 129.0, 128.8, 128.5, 128.3, 128.1, 128.0, 61.1, 61.1, 55.8, 49.0, 39.5, 13.9, 13.8; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{27}H_{29}O_5NClS$, 514.1449; found, 514.1467.

Diethyl 2-(2-((oxodiphenyl-l6-sulfaneylidene) amino)-2-(o-tolyl) ethyl) malonate (9e):

Yield: 84% (75 mg); Colorless gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3683.12, 3433.29, 2984.52, 2400.54, 1724.90, 1603.46, 1521.79, 1464.62, 1218.23, 908.12, 772.01, 690.09; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 8.13, 1.25 Hz, 2 H), 7.83 (d, *J* = 7.38 Hz, 1H), 7.63-7.68 (m, 2H), 7.42-7.53 (m, 3H), 7.35-7.41 (m, 1H), 7.21-7.30 (m, 3H), 7.07-7.13 (m, 1H), 6.96 (d, *J* = 7.50 Hz, 1H), 4.50 (dd, *J* = 9.13, 4.38 Hz, 1H), 4.16-4.24 (m, 2H), 4.04-4.14 (m, 2H), 4.01 (dd, *J* = 9.51, 4.88 Hz, 1H), 2.26 (ddd, *J* = 9.13, 7.32, 4.44 Hz, 2H), 1.92 (s, 3H), 1.27 (t, *J* = 7.19 Hz, 3H), 1.18 (t, *J* = 7.13 Hz, 3H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 170.0, 169.5, 143.7, 140.6, 140.5, 133.8, 132.3, 132.1, 129.7, 128.9, 128.7, 128.6, 128.3, 126.9, 126.3, 126.0, 61.1, 61.0, 49.2, 38.4, 18.6, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{32}O_5NS$, 494.1996; found, 494.2007.

Diethyl 2-(2-(3,4-dimethoxyphenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (9f):

Yield: 87% (72 mg); Colorless gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3423.50, 2088.68, 1724.83, 1641.60, 1534.99, 1511.72, 1443.78, 1242.79, 1172.89, 771.34; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92-8.01 (m, 2H), 7.70-7.78 (m, 2H), 7.40-7.52 (m, 4H), 7.29-7.36 (m, 2H), 6.89 (d, *J*= 1.75 Hz, 1H), 6.81 (dd, *J* = 8.13, 1.75 Hz, 1 H), 6.74 (d, *J* = 8.25 Hz, 1H), 4.22 (t, *J* = 6.75 Hz, 1H), 4.03-4.19 (m, 4H), 3.83 (s, 3H), 3.84 (s, 3H), 3.75 (t, *J* = 7.19 Hz, 1H), 2.39 (t, *J* = 7.00 Hz, 2H), 1.15-1.25 (m, 6H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$): δ 169.8, 169.5, 148.6, 147.7, 140.5,

140.5, 137.6, 132.4, 132.3, 129.0, 129.0, 128.8, 128.7, 128.3, 127.8, 118.7, 110.7, 109.9, 61.1, 61.1, 56.3, 55.8, 55.8, 49.2, 39.6, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{34}O_7NS$, 540.2050; found, 540.2057.

Diethyl 2-(2-(furan-2-yl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (9g):

Yield: 88% (81 mg); Colorless gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3423.55, 3019.97, 2400.39, 1726.05, 1641.58, 1527.39, 1476.55, 1370.95, 1214.35, 1147.83, 1095.31, 928.23 778.80, 688.79; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92-8.00 (m, 2H), 7.80-7.89 (m, 2H), 7.34-7.52 (m, 6H), 7.25 (dd, *J* = 1.81, 0.81 Hz, 1H), 6.19 (dd, *J* = 3.19, 1.81 Hz, 1H), 6.09 (d, *J* = 3.25 Hz, 1H), 4.40 (t, *J* = 6.63 Hz, 1H), 4.01-4.22 (m, 4H), 3.79 (dd, *J* = 7.50, 6.75 Hz, 1H), 2.48-2.58 (m, 2H), 1.18 (t, *J* = 7.19 Hz, 3H), 1.22 (t, *J* = 7.13 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ169.6, 169.4, 156.4, 141.1, 140.7, 140.5, 132.3, 132.2, 129.0, 128.8, 128.5, 128.3, 109.8, 106.0, 61.1, 61.1, 50.0, 48.9, 35.9, 13.9, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{28}O_6NS$, 470.1632; found, 470.1636.

Diethyl 2-(2-((oxodiphenyl-l6-sulfaneylidene) amino)-2-(thiophen-2-yl) ethyl) malonate (9h):

Yield: 82% (74 mg); Yellowish gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3422.70, 3019.92, 2400.40, 1725.67, 1641.33, 1527.14, 1446.70, 1214.82, 1140.93, 928.29, 758.60, 697.82; **^{1}H NMR** (400 MHz, $CDCl_3$): δ7.99-8.11 (m, 2H), 7.81 (dd, *J* = 8.57, 0.94 Hz, 2H), 7.43-7.61 (m, 4H), 7.30-7.43 (m, 2H), 7.17 (dd, *J* = 5.07, 1.19 Hz, 1H), 6.86 (dd, *J* = 5.00, 3.50 Hz, 1H), 6.79 (d, *J* = 3.00 Hz, 1H), 4.65 (dd, *J* = 7.57, 5.82 Hz, 1H), 4.04-4.24 (m, 4H), 3.81 (dd, *J* = 8.25, 6.13 Hz, 1H), 2.52 (dt, *J* = 7.79, 5.49 Hz, 2H), 1.171.27 (m, 6 H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ169.7, 169.4, 149.8, 140.4, 140.0, 132.7, 132.5, 129.1, 128.9, 128.9, 128.7, 128.5, 126.4, 123.7, 123.2,

61.2, 61.2, 52.4, 49.0, 40.1, 14.0, 14.0; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{28}O_5NS_2$, 486.1403; found, 486.1407.

Diethyl (E)-2-(2-((oxodiphenyl-l6-sulfaneylidene) amino)-4-phenylbut-3-en-1-yl) malonate (9i):

Yield: 84% (73 mg); Colorless gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3442.52, 3025.73, 1727.24, 1642.38, 1493.81, 1476.42, 1391.27, 1240.20, 1094.70, 996.06, 754.63, 691.57; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.93 (m, 4H), 7.28-7.46 (m, 6H), 7.15-7.24 (m, 4H), 7.05-7.15 (m, 1H), 6.23 (d, *J* = 15.88 Hz, 1H), 6.12 (dd, *J* = 15.88, 7.00 Hz, 1H), 3.98-4.11 (m, 4H), 3.82 (q, *J* = 6.67 Hz, 1H), 3.75 (t, *J*=7.13 Hz, 1H), 2.21-2.30 (m, 2H), 1.12-1.17 (m, 3H), 1.10 (t, *J* = 7.13 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 169.8, 169.6, 141.0, 140.7, 137.0, 132.8, 132.3, 129.4, 129.0, 128.8, 128.6, 128.3, 128.2, 127.1, 126.3, 61.1, 61.1, 55.2, 48.9, 37.2, 13.9, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{32}O_5NS$, 506.1996; found, 506.2005.

Diethyl 2-bromo-2-(2-(4-methoxyphenyl)-2-((oxo(phenyl)(*p*-tolyl)-l6-sulfaneylidene) amino) ethyl) malonate (10):

Yield: 72% (74 mg); Yellow gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max} : 3422.66, 3019.90, 2400.30, 1723.10, 1641.40, 1503.48, 1218.18, 928.71, 772.18, 669.38; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.96 - 7.97 (m, 1H), 7.94 - 7.95 (m, 1H), 7.85 (d, *J* = 8.38 Hz, 2H), 7.42 - 7.45 (m, 2H), 7.39 - 7.42 (m, 2H), 7.35 (d, *J* = 2.13 Hz, 1H), 7.19 (s, 2H), 7.04 (dd, *J* = 8.25, 2.00 Hz, 1H), 6.72 (d, *J* = 8.50 Hz, 1H), 4.12 - 4.21 (m, 2H), 3.80 - 3.86 (m, 2H), 3.79 (s, 3H), 3.03-3.09 (m, 1H), 2.31 (s, 3H), 2.02 (dd, *J* = 7.88, 5.13 Hz, 1H), 1.61 (dd, *J* = 9.26, 5.25 Hz, 1H), 1.20 - 1.24 (m, 3H), 0.90 (t, *J* = 7.13 Hz, 3 H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 169.6, 166.5, 155.1, 143.6, 133.7, 132.8, 132.5, 129.8, 129.7, 129.2, 129.1, 128.7, 128.4, 128.3, 128.0, 127.9, 127.8, 111.3, 111.1, 61.7,

61.3, 56.2, 37.2, 31.4, 30.9, 29.7, 21.4, 18.8, 14.0, 13.8; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{33}O_6NBrS$, 602.1206; found, 602.1201.

Diethyl 2-allyl-2-(2-(4-methoxyphenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (11):

Yield: 62% (20 mg); Yellow gum; **IR** ($CHCl_3$, cm^{-1}) ν_{max}: 3415.69, 2088.71, 1642.57, 1552.53, 1513.72, 1502.06, 1264.56, 772.04; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89 - 7.96 (m, 2H), 7.71 (d, *J* = 7.50 Hz, 2H), 7.42-7.53 (m, 4 H), 7.35-7.42 (m, 1H), 7.30 (d, *J* = 7.88 Hz, 2H), 7.07 (m, *J* = 8.50 Hz, 2H), 6.70 (m, *J* = 8.50 Hz, 2H), 5.59-5.71 (m, 1H), 4.95-5.05 (m, 2H), 4.24 (t, *J* = 7.07 Hz, 1H), 4.02 (q, *J* = 7.00 Hz, 2 H), 3.91-3.98 (m, 1H), 3.81-3.89 (m, 1H), 3.76 (s, 3H), 2.66-2.82 (m, 3H), 2.44 (dd, *J* = 14.51, 6.25 Hz, 1H), 1.09-1.19 (m, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 171.3, 171.0, 158.3, 141.3, 140.9, 137.5, 133.0, 132.2, 131.9, 128.9, 128.6, 128.5, 128.4, 128.4, 118.6, 113.2, 61.0, 60.9, 56.4, 55.2, 54.4, 42.1, 36.4, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{36}O_6NS$, 550.2258; found, 550.2264.

Section II

Scandium Triflate Catalyzed Regioselective C-3 Functionalization of Indolizines via Ring-Opening of Donor-Acceptor Cyclopropanes

4.1.1 Introduction

Nitrogen heterocyclic compounds are essential in drug discovery and play a vital role in developing new drugs and materials.[22] In particular, Indolizines and their derivatives are a class of fused heterocycles that contain pyridines and pyrroles, forming an imperative class of compounds widely found in natural products and displaying diverse biological activities.[23] Besides indolizines showing their application in materials science,[24] indolizines also play a significant role in forming organic light-emitting devices (OLEDs),[24a] biological markers,[24b] and dyes.[24c] The late-stage C-3 functionalized indolizine is equally important in drug discovery. For instance, Phosphodiesterase IV (**a**) acts as a PDE4 inhibitor. However, C-3 functionalized indolizine derivative (**b**) is used as a potential candidate for liver cancer treatment. The Indolizine derivative (STA-5312) (**c**) exhibits cytotoxic activity against cancer cell lines, and the compound (**d**) shows potent anti-inflammatory activity, as shown in **Figure 4**.[25]

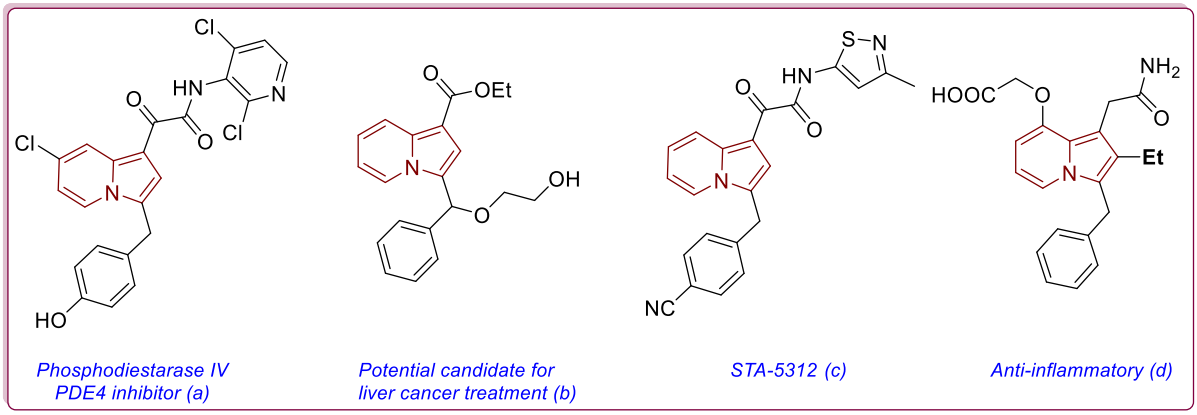


Figure 4: Biological active C-3 Functionalized Indolizines and its Derivatives

Due to the substantial importance of functionalized Indolizines (especially C-3 functionalized), many research groups are devoted to their established methods. In this context, transition metal-catalyzed coupling reactions are general synthetic pathways applied to the C3-functionalization of indolizines via alkylation, alkynylation, arylation, and alkenylation process.[26] However, the direct C-3 alkylation reaction is rarely known in the literature.

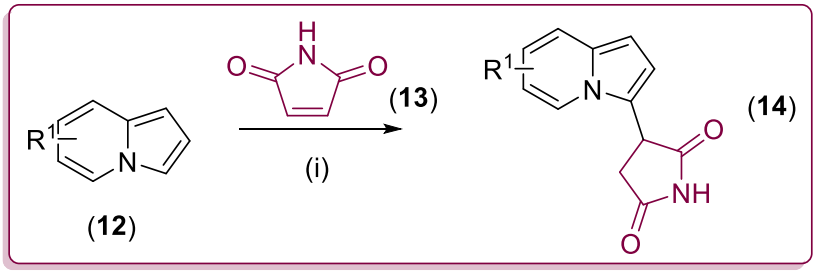
The crucial push-pull property of donor-acceptor (D−A) cyclopropanes, usually considered as 1,3-dipolar zwitterionic synthons, act as the most attractive precursor for many reactions,[27] These reactions are nucleophilic ring-opening reactions,[28] Dipolar-cycloaddition reactions,[29] and rearrangement reactions.[30] For instance, heteroatom nucleophiles (Nu-H= amines,[31a] phenols,[31b] thiols,[31c] azides,[31d] and sulfoximines[31e]) and carbon nucleophiles[32] open the activated D−A cyclopropanes to develop the mono functionalization of D−A cyclopropanes.

2.1.2 Review of Literature

Due to the excellent reactivity of Indolizines towards the different nucleophiles, many reports are known for the N-alkylation of sulfoximines at different carbon positions. However, the C-3 alkylation reactions are commonly known in the literature, and herein, we have described the numerous C-3 alkylation reactions of Indolizines.

Matviiuk Approach (2014)[33]

Matviiuk et al. in 2014 reported C-3 alkylation of Indolizines in the presence of Lewis acid catalyst and maleimide as a reaction partner. In this report, the Michel-type addition of indolizine (**12**) on maleimide (**13**) in the presence of $AlCl_3$ as Lewis acid results in the formation of biologically active C-3 alkyl indolizine (**14**) (**Scheme 9**).

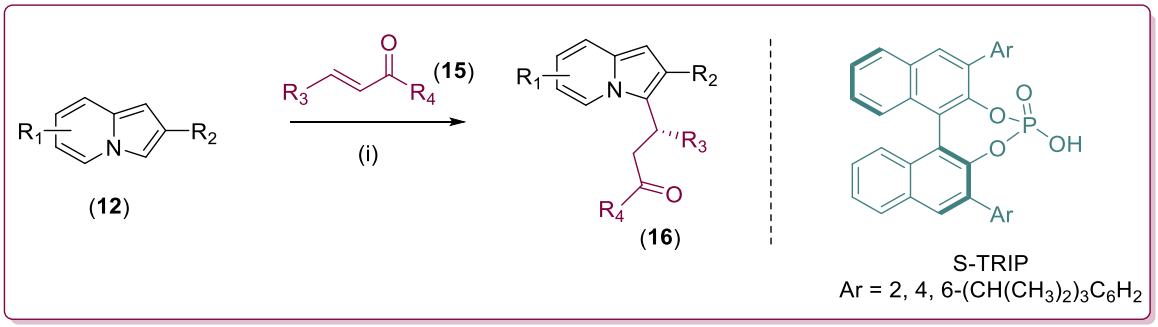


Reaction condition: (i) $AlCl_3$ (cat.), Dioxane.

Scheme 9: C-3 Alkylation of Indolizine

List and Coelho Approach (2017)[34]

In 2017, Benjamin List and Fernando Coelho collaboratively described the highly enantioselective Michel 1,4- addition of indolizines to *α-β* unsaturated ketones to furnished the enantiomerically pure C-3 alkylation of Indolizine product (**16**) in the highest 98% yield with 97% ee. The Indolizine (**12**) reacted with enone (**15**) in the presence of chiral phosphoric acid (S)-TRIP as the organocatalyst (**Scheme 10**).



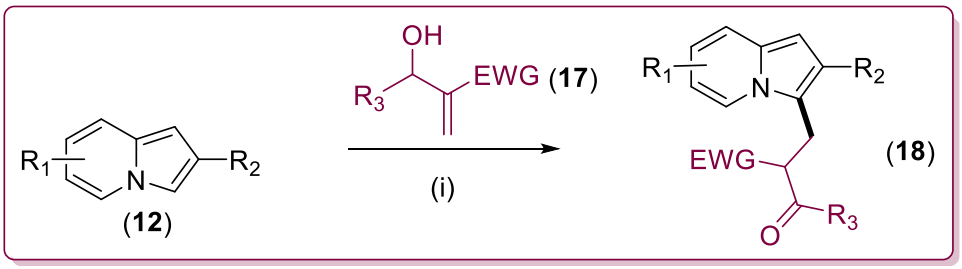
Reaction condition: (i) S-TRIP (10 mol%), Benzene, 5 Å MS (100 mg),

Scheme 10: Enantioselective C-3 alkylation of Indolizines

Coelho's Approach (2020)[35]

Later, in 2020 Same group (Coelho and coworker) established the metal-free C-3 alkylation reaction via conjugate addition of Indolizine (**12**) on Morita− Baylis−Hillman (MBH) adduct (**17**). The broad scope of corresponding functionalized Indolizine products (**18**) was developed from this methodology. This methodology's key feature is the mild reaction condition, broad

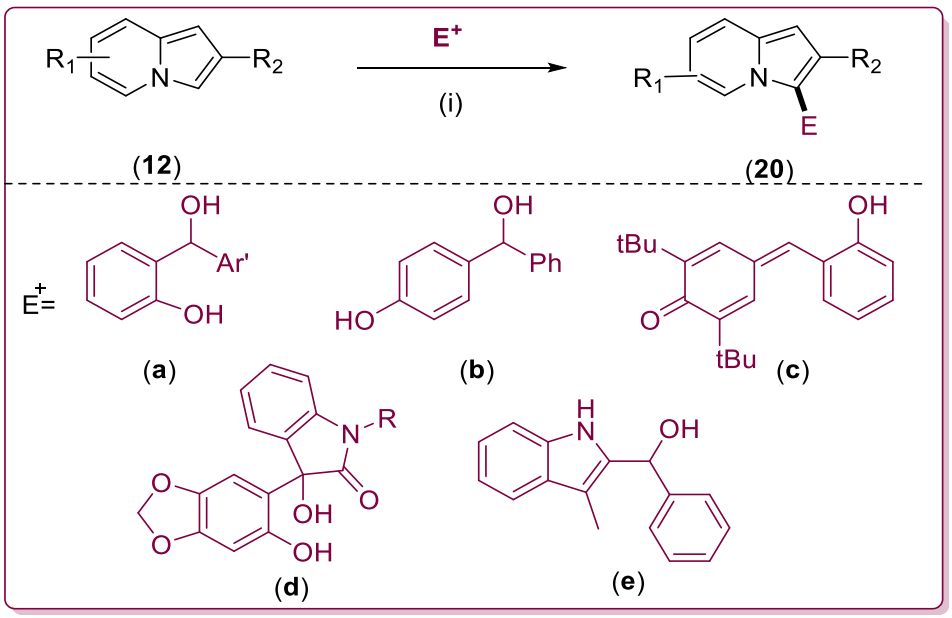
substrate scope, high functional group tolerance, and high atom economy. Also, the author expands this method for synthesizing new heterocyclic moieties with potential biological activity (**Scheme 11**).



Reaction Condition: (i) IBX (1.2 equiv.), ACN (0.2 M), Reflux, 45 min.

Scheme 11. Conjugate Addition of Indolizines to In Situ Generated MBH Ketones for the Synthesis of C-3 Alkylation

Feng Shi's Approach (2020)[36]



Reaction Condition: (i) B.A (20 mol%), Toluene, 30 ºC.

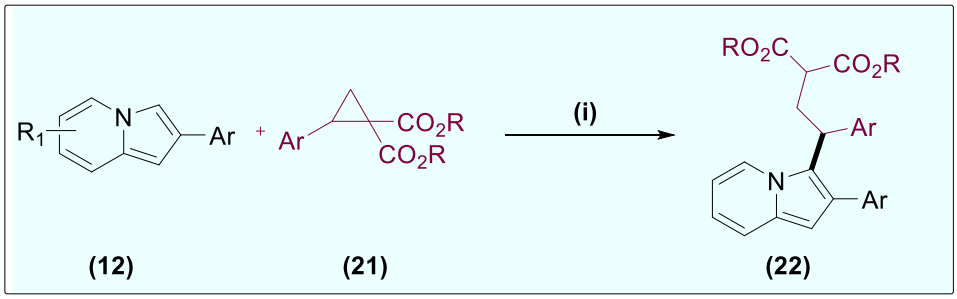
Scheme 12. Bronsted acid catalyzed C-3 alkylation of Indolizines by using different electrophiles

Feng Shi and Coworkers 2020 reported Bronsted acid-driven C-3 alkylation by using different electrophiles. Using this approach, the series of C3-functionalized indolizines obtained an excellent yield (98%). In this report, Indolizine (**12**) reacted with different electrophiles such as ortho-hydroxy benzyl alcohols, para-quinone methides, ortho-quinone methides, and 2-indolylmethanol (**Scheme 12**).

4.1.3 Present Work

4.1.3.1 Objective

With the previous experience and expertise in this work area, [37] and the importance of D-A cyclopropanes in organic synthesis, herein we have reported for the first time the regioselective ring-opening reaction of D-A cyclopropanes (**21**) using nitrogen-containing heterocycles (**12**) (**Scheme 13**).



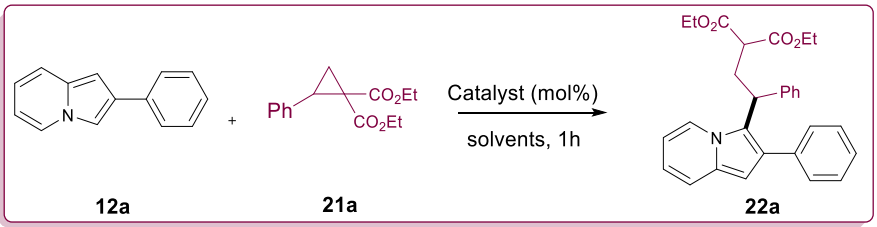
Reaction Condition: (i) $Sc(OTf)_3$ (20 mol%), CH_2Cl_2, 25 °C, 1 h

Scheme 13. General Reaction for the Synthesis of C-3 Alkylation of Indolizines through ring opening of Donor-Acceptor Cyclopropanes

2.1.4 Result and Discussion

Based on Literature reports and our previous work,[31e] we started our investigation by using 2-Phenylindolizine (**12a**) and Diethyl 2-phenylcyclopropane-1,1-dicarboxylate (**21a**) as the reaction partner with ($Sc(OTf)_3$, 5mol%) as Lewis acid catalyst in DCM solvent at room

Table 4. Optimization of Reaction Conditions [a]

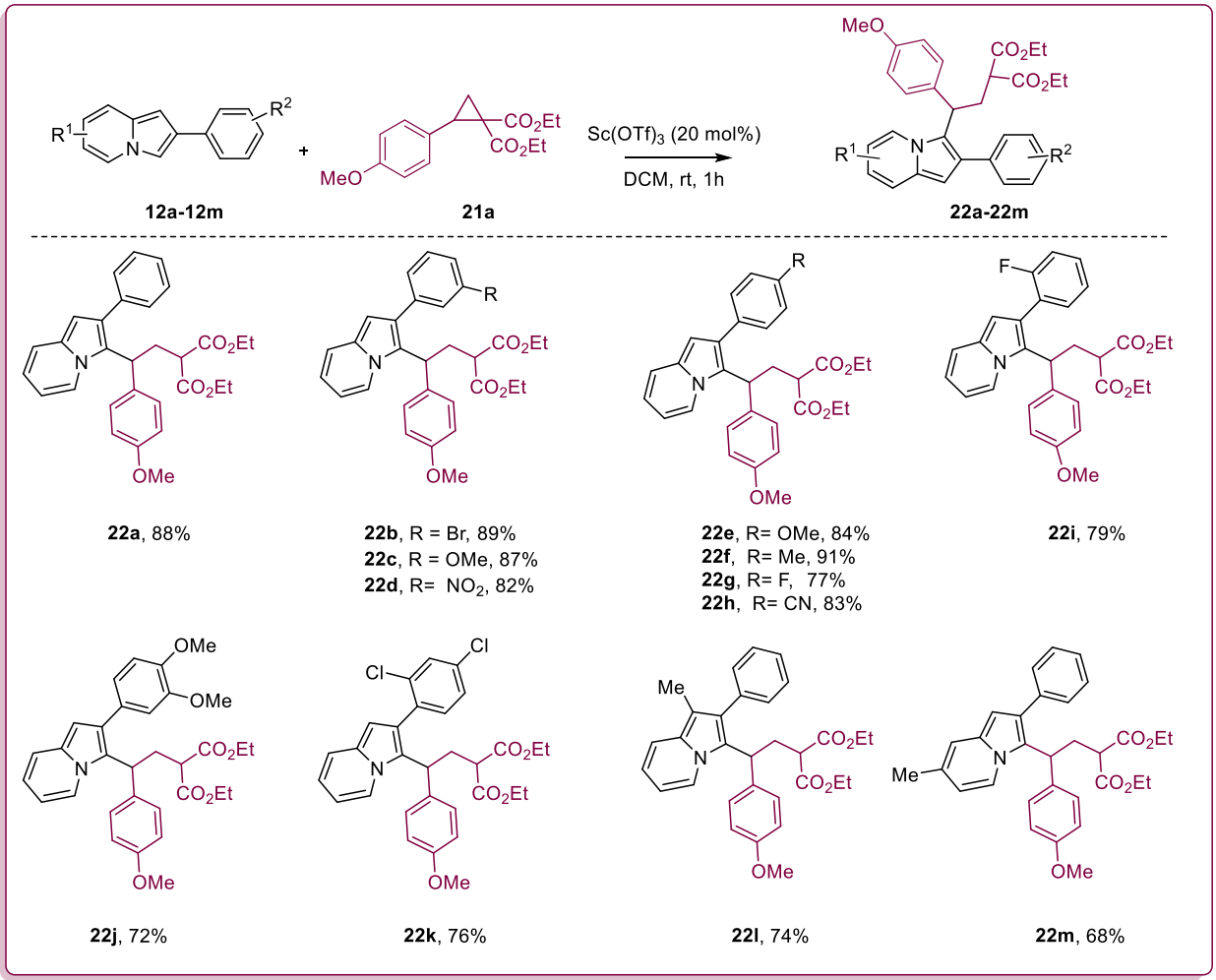


Entry	Catalyst (mol%)	Solvent	Yield [b]
1.	$Sc(OTf)_3$ (5 mol%)	DCM	75
2.	$Sc(OTf)_3$ (10 mol%)	DCM	80
3.	**$Sc(OTf)_3$ (20 mol%)**	**DCM**	**88**
4.	$Cu(OTf)_2$ (20 mol%)	DCM	85
5.	$Bi(OTf)_3$ (20 mol%)	DCM	83
6.	$Yb(OTf)_3$ (20 mol%)	DCM	65
7.	$Sc(OTf)_3$ (20 mol%)	DCE	84
8	$Sc(OTf)_3$ (20 mol%)	ACN	60
9.	$Sc(OTf)_3$ (20 mol%)	THF	68
10.	$Sc(OTf)_3$ (20 mol%)	DMF	64
11	$Sc(OTf)_3$ (20 mol%)	DCE	70
12.	-	DCM	NR

[a] = **Reaction conditions: 12a** (0.17 mmol, 1 equiv.), **21a** (0.20 mmol, 1.2 equiv.), catalyst in solvent (2.0 mL), 1 h at 25 °C under N_2 atmosphere. [b] = Isolated yields after column chromatography, NR = No Reaction

temperature for 1 hr, to our delight, we observed the regioselective ring-opening product **22a** in 75% yield (Table 4, entry 1). Next, we observed the efficiently enhanced yield of **22a** from 80% to 88% upon increasing the catalyst loading from 5 mol% to 20 mol% (entries 2 and 3). Then, we

Table 5. Substrate scope of the various Indolizines [a, b]



a] **Reaction conditions: 12a-12m** (0.17 mmol), **21a** (0.20 mmol), $Sc(OTf)_3$ (20 mol%), at 25 °C, 1 h, under N_2 atmosphere; [b] Isolated yields after column chromatographic purification are shown.

screened the different Lewis acids such as $Cu(OTf)_2$, $Bi(OTf)_3$, and $Yb(OTf)_3$ in DCM solvent, but we observed that the yield of product **22a** is not suitable as compared to entry 3 (entries 3-6). Thus, we conducted further optimization in different routine solvents such as ACN, THF, DMF, and DCE, but all solvents did not give better yields (entries 7-11). However, the reaction does

not proceed without a catalyst (entry 12). We chose entry 3 as the best optimization condition for the regioselective ring-opening reaction from the above optimization study.

With standard reaction conditions in our hand, further, we screen the substrate scope of C-3 alkylation of Indolizines as depicted in Table 5. First, we examined the derivatization of different Substituted Indolizine under optimized reaction conditions. The C-2 phenyl Indolizine and Substituted C-2 phenyl Indolizine at the ortho, meta, and para position with -EWG, -EDG, and -halo substitutions are reacted with Donor-Acceptor cyclopropane (**2a**) to obtain the corresponding ring-opening product **3a**-**3i** in good to excellent yield (79%-91%) (entries **3a**-**3i**). The disubstituted C-2 phenyl Indolizines **1j** and **1k** reacted smoothly with **2a** to furnish the corresponding C-3 alkylation product in 72% and 76% yield, respectively. Moreover, the 2, 3, and 2, 5 disubstituted indolizines are also amenable for regioselective ring-opening reactions to obtain the corresponding products in 74% and 68% yield, respectively (entries **3l**-**3m**). The synthesized compounds were confirmed by known analytical techniques such as NMR and HRMS spectroscopy.

The synthesized C-3 alkylated Indolizine compound, i.e., diethyl 2-(2-(4-methoxyphenyl)-2-(2-phenyl indolizine-3-yl) ethyl) malonate (**22a**) unambiguously established by 1H and 13C NMR spectroscopic method. In ^{1}H NMR spectra, the typical triplet at δ 4.79-4.76 6.36 (t, 1H) corresponds to the characteristic benzylic methine (-C**H**-) proton attached sp^{2} carbon ofindolizine moiety. Also, its ^{13}C spectra showed two peaks near δ 168 for the ester group of malonic diester moiety, and the peak appeared at δ 37.51 for the characteristic benzylic (-**C**H-) carbon, as shown in **Figure 5**.

Example 1:

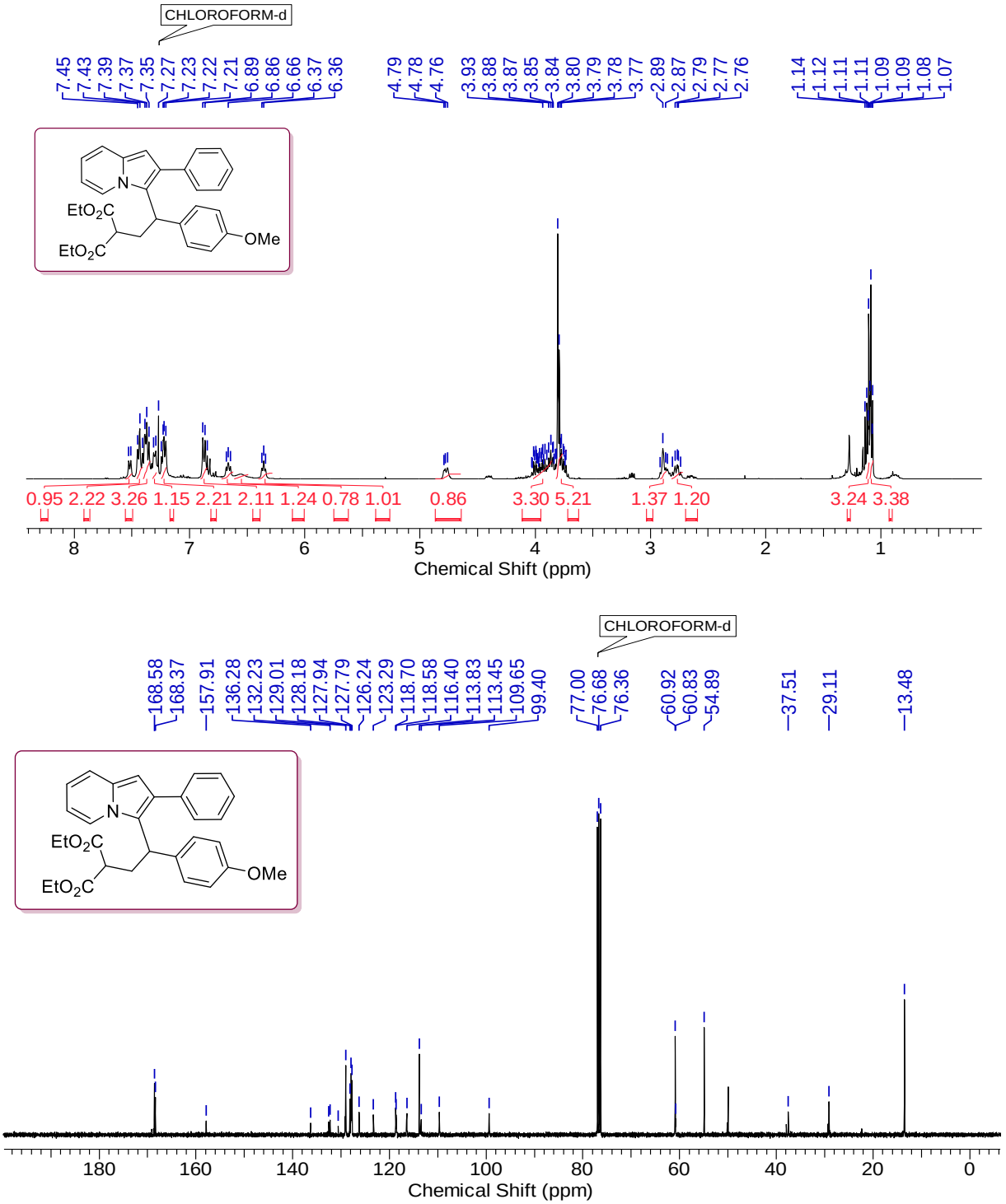
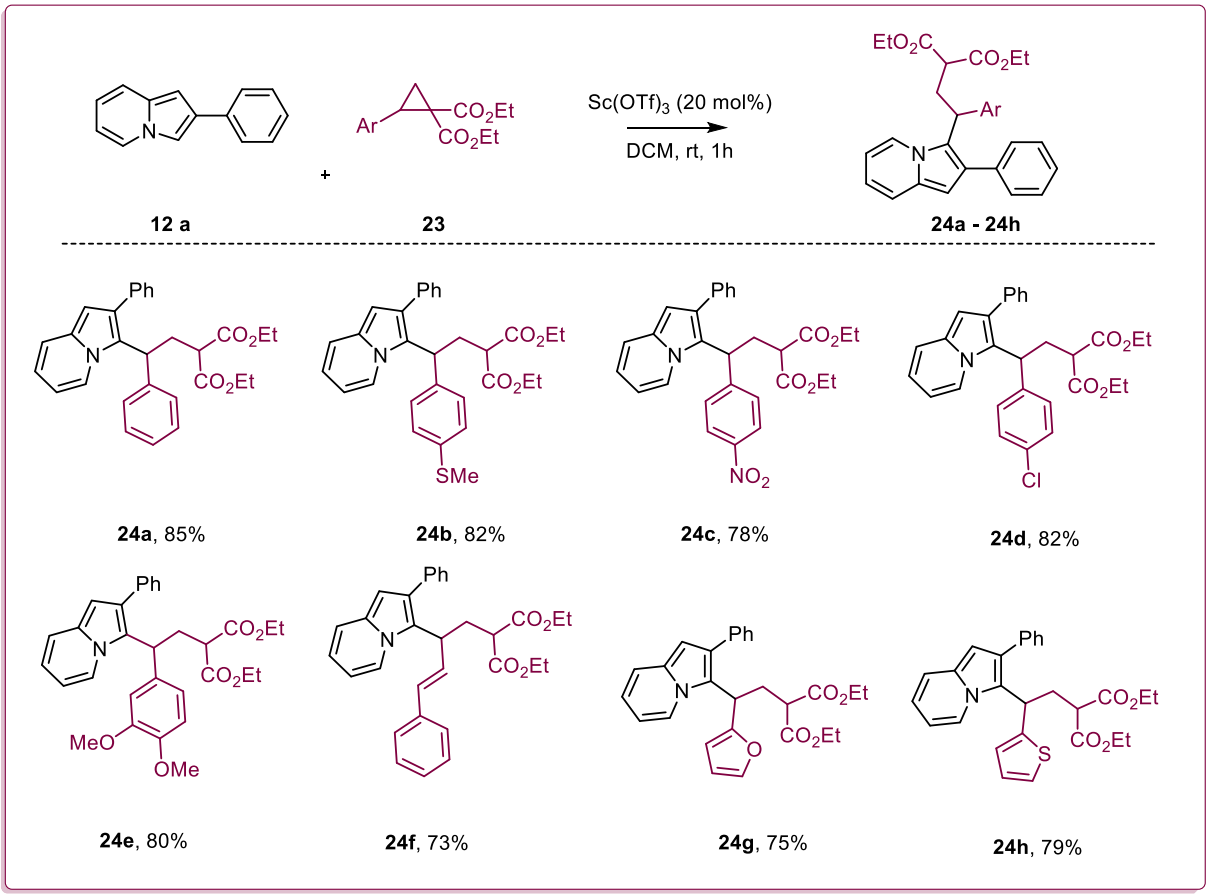


Figure 5: ^{1}H and ^{13}C NMR of diethyl 2-(2-(4-methoxyphenyl)-2-(2-phenylindolizin-3-yl) ethyl) malonate (**22a**)

Next, we investigated the scope of different Donor-Acceptor Cyclopropanes **23** with Indolizine **12a** for C-3 alkylation reaction, as shown in Table 6. A series of Donor-Acceptor cyclopropane containing electron-donating (-H, -SMe), electron-withdrawing ($-NO_2$), and halogen(-Cl) substitution at *para*-position of aryl group reacted well with Nucleophilic Indolizine species to

Table 6. substrate scope of various D-A Cyclopropanes



a] **Reaction conditions: 12a-** (0.17 mmol), **23a-h** (0.20 mmol), $Sc(OTf)_3$ (20 mol%), at 25 °C, 1 h, under N_2 atmosphere; [b] Isolated yields after column chromatographic purification are shown.

furnished the respective ring-opening product **24a** to **24d** in excellent yield (up to 85%). The 3, 4-disubstituted D-A Cyclopropane also tolerated the standard optimization reaction to obtain the respective ring-opening product **5e** in 80% yield. Moreover, the styryl cyclopropane **24f** reacted

smoothly, forming a ring-opening product with a 73% yield. The Heterocyclic D-A cyclopropanes such as furyl and thienyl containing D-A cyclopropanes are also involved in the ring-opening reaction strategy to afford the C-3 alkylation of Indolizine products **24g** and **24h** in 75% and 79% yield respectively. The desired substituted C-3-alkyl indolizine was confirmed by the ^{1}H, ^{13}C, and HRMS spectroscopic methods.

Example 2:

The representative alkylated compound diethyl 2-(2-(4-(methylthio) phenyl)-2-(2-phenyl indolizin-3-yl) ethyl) malonate (**24b**) was verified by ^{1}H and ^{13}C spectra. The characteristic benzylic (-C**H**-) proton next to the indolizine sp^2 carbon appears as a triplet at δ 4.72-4.69 in ^{1}H NMR spectra. In the carbon NMR spectrum, the peak at δ168.57 and δ168.38 for the ester carbon of diesters moiety and the peak at δ35.72 is the characteristic benzylic (-**C**H-) carbon of the compound **5b** (**Figure 6**).

Based on Literature reports[38] and previous reports[39, 31e,] we proposed the plausible reaction mechanism as depicted in **Scheme 14**. Initially, the Scandium triflate Sc (III) coordinated with D-A cyclopropane diesters to form the Sc (III) chelated species **A**. Then due to the push-pull effect in D-A cyclopropane, the cyclopropane ring-opened to obtain the more stable benzylic carbocation intermediate **B**. Subsequentially, the regioselective addition of nucleophilic indolizine compound furnished the desired indolizium ion intermediate **C**. While, the "H" atom transferred as well as the aromatization of indolizine ring to produce the C-3 alkylated product **3a**, with the regeneration of Sc (III) catalyst for next reaction cycle.

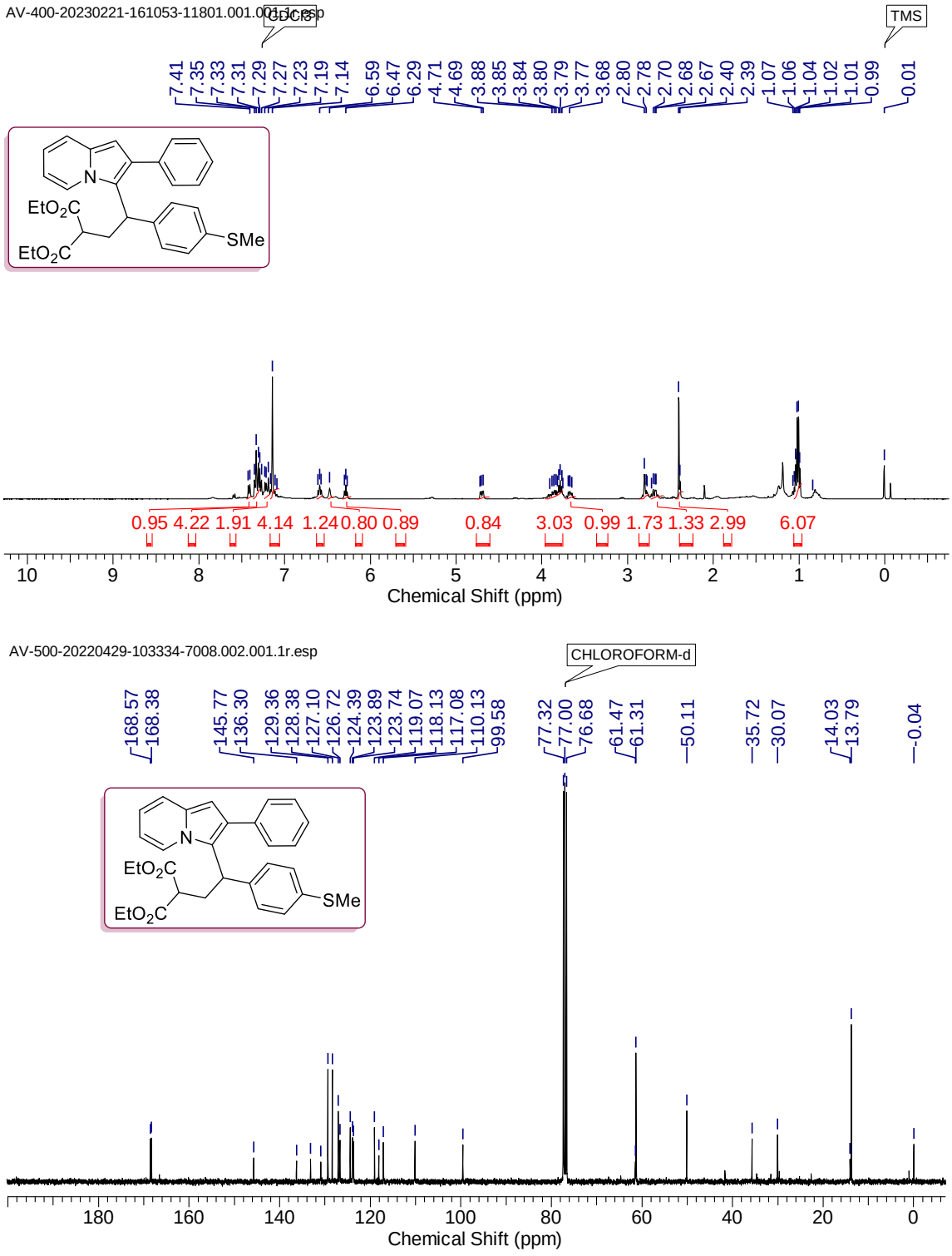
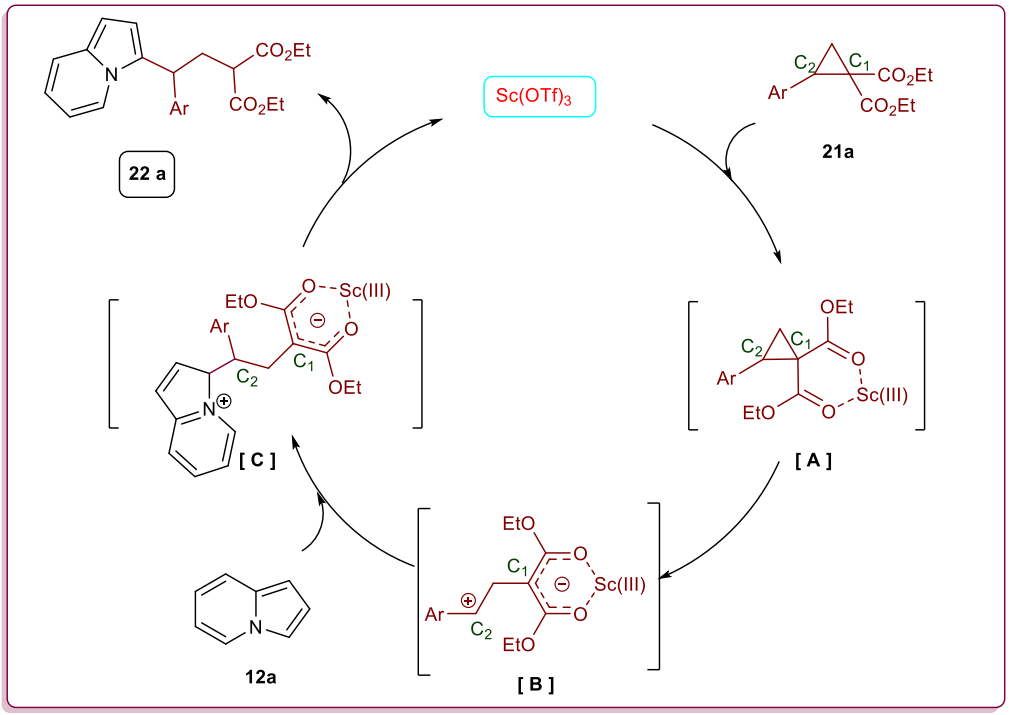


Figure 6: ^{1}H and ^{13}C NMR of diethyl 2-(2-(4-(methylthio) phenyl)-2-(2-phenylindolizin-3-yl) ethyl) malonate (**24b**)



Scheme 14: Plausible Reaction Mechanism

4.1.5. Conclusion

In summary, we have developed a Lewis acid-catalyzed convenient protocol for C-3 alkylation of indolizines under mild reaction conditions for synthesizing biologically active γ-heteroaryl malonic diesters in good yield. We have synthesized the highly regioselective C-3 alkylation through the ring-opening of donor acceptor (D-A) cyclopropanes in an excellent product yield. The further utilization of the method is now ongoing in our laboratory.

4.1.6. Experimental Section

4.2.6.1 General Experimental Procedure for the Synthesis of C-3 alkylated indolizines (22a-22m):

To an oven-dried 25 mL round bottom flask equipped with a magnetic stir bar, substituted Indolizines **(1)** (1 equiv, 0.2 mmol), D-A cyclopropane (**2a**) (1 equiv, 0.2 mmol), were added

DCM solvent (2 mL) under inert atmosphere. The mixture was stirred for 3−5 min at ambient temperature. Then $Sc(OTf)_3$ was added to the reaction mixture and stirred another 1 h at the same temperature. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with DCM (10 mL) and water (~3 mL), the organic layer was separated, and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine (2 × 10 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified using silica gel column chromatography (10% EtOAc/hexane) to afford the corresponding substituted C-3 alkylated indolizines (**22a-22m**).

4.1.6.2 General Experimental Procedure for the Synthesis of C-3 alkylated indolizines (24a-24h):

To an oven-dried 25 mL round bottom flask equipped with a magnetic stir bar, Indolizine (**12a**) (1 equiv, 0.2 mmol), substituted D-A cyclopropanes (**23**) (1 equiv, 0.2 mmol), were added DCM solvent (2 mL) under inert atmosphere. The mixture was stirred for 3−5 min at ambient temperature. Then $Sc(OTf)_3$ was added to the reaction mixture and stirred another 1 h at the same temperature. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with DCM (10 mL) and water (~3 mL), the organic layer was separated, and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine (2 × 10 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10%EtOAc/hexane) to afford the corresponding substituted C-3 alkylated indolizines **(24a-24h).**

4.2.6.5 General Experimental Procedure for Gram-Scale Synthesis of Diethyl 2-(2-(4-methoxyphenyl)-2-(2-phenylindolizin-3-yl) ethyl) malonate 22a:

To an oven-dried 100 mL round bottom flask equipped with a magnetic stir bar, Indolizine (**12a**) (1 gm., 1 equiv, 5.813 mmol), substituted D-A cyclopropanes (**21a**) (1 equiv, 5.813), were added DCM solvent (20 mL) under inert atmosphere. The mixture was stirred for 3−5 min at ambient temperature. Then $Sc(OTf)_3$ was added to the reaction mixture and stirred another 1 h at the same temperature. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with DCM (50 mL) and water (~15 mL), the organic layer was separated, and the aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layer was washed with brine (2 × 50 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant crude product was purified by silica gel column chromatography (10%EtOAc/hexane) to afford the diethyl 2-(2-(4-methoxyphenyl)-2-(2-phenylindolizin-3-yl) ethyl) malonate **(22a)** in 82% yield (2.0 gm).

Diethyl 2-(2-(4-methoxyphenyl)-2-(2-phenylindolizin-3-yl) ethyl) malonate (22a):

Yield: 88% (87 mg); Colorless liquid; **^{1}H NMR** ((400 MHz, $CDCl_3$) δ: 7.52 (d, J = 7.1 Hz, 1H), 7.41-7.46 (m, 2H), 7.34-7.40 (m, 3H), 7.30 (d, J = 7.0 Hz, 1H), 7.20-7.24 (m, 2H), 6.84-6.91 (m, 2H), 6.62-6.72 (m, 1H), 6.36 (t, J = 6.6 Hz, 1H), 4.64-4.87 (m, 1H), 3.85-4.02 (m, 3H), 3.73-3.82 (m, 5H), 2.86-2.92 (m, 1H), 2.72-2.82 (m, 1H), 1.10-1.13 (m, 3H), 1.07-1.10 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 168.6, 168.4, 157.9, 136.3, 132.5, 132.2, 129.0, 128.2, 127.9, 127.8, 126.2, 123.3, 118.7, 118.6, 116.4, 113.8, 113.5, 109.7, 99.4, 60.9, 60.8, 54.9, 37.5, 29.1, 13.5; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{32}O_5N$, 486.2275; found, 486.2269.

Diethyl 2-(2-(2-(3-bromophenyl) indolizin-3-yl)-2-(4-methoxyphenyl) ethyl) malonate (**22b**):

Yield: 89% (87 mg); Colorless liquid; **^{1}H NMR** 1H NMR (400 MHz, $CDCl_3$) δ: 7.56-7.60 (m, 1H), 7.54 (d, J = 7.1 Hz, 2H), 7.34-7.45 (m, 2H), 7.28-7.32 (m, 1H), 7.22 (d, J = 7.9 Hz, 1H), 7.18 (d, J=8.9 Hz, 2H), 6.84-6.91 (m, 2H), 6.68 (dd, J = 8.9, 6.5 Hz, 1H), 6.51 (s, 1H), 6.32-6.42

(m, 1H), 4.73 (dd, J = 11.1, 4.4 Hz, 1H), 3.97-4.02 (m, 1H), 3.89 (dd, J = 7.1, 3.0 Hz, 1H), 3.79-3.82 (m, 3H), 3.75-3.79 (m, 2H), 2.81-2.89 (m, 2H), 2.70-2.79 (m, 1H), 1.08-1.14 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 168.9, 158.3, 138.9, 132.9, 132.3, 129.7, 129.6, 128.1, 127.9, 123.6, 122.3, 119.3, 119.2, 117.1, 114.3, 110.3, 99.7, 61.4, 61.3, 55.3, 50.2, 37.8, 30.9, 29.5, 13.9, 13.8; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{31}O_7BrN$, 564.3080; found, 564.3084.

Diethyl 2-(2-(4-methoxyphenyl)-2-(2-(3-methoxyphenyl) indolizin-3-yl) ethyl) malonate (22c):

Yield: 87% (87 mg); Colorless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ : 7.50 - 7.55 (m, 3 H), 7.39 (d, J = 9.0 Hz, 1H), 7.25 (s, 1H), 7.29 (s, 1H), 7.21 (d, J=8.3 Hz, 2H), 6.97 - 7.04 (m, 2H), 6.83 - 6.89 (m, 3H), 6.66 (ddd, J = 8.9, 6.5, 0.9 Hz, 1H), 6.54 (s, 1H), 6.31 - 6.39 (m, 1H), 4.78 (dd, J = 11.3, 5.1 Hz, 1H), 3.94-4.02 (m, 1H), 3.80-3.91 (m, 3H), 3.80 (s, 3H), 3.77 - 3.79 (s, 6H), 2.72 - 2.94 (m, 3H), 1.07 - 1.12 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 169.0, 168.7, 159.4, 158.2, 138.0, 132.8, 132.6, 130.7, 129.2, 128.6, 128.1, 123.6, 121.8, 119.1, 119.0, 116.8, 115.0, 114.2, 113.6, 112.2, 110.0, 99.7, 61.3, 61.2, 55.2, 55.1, 50.3, 37.9, 29.5, 13.8, 13.8; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{34}O_6N$, 516.2381; found, 516.2391.

Diethyl 2-(2-(4-methoxyphenyl)-2-(2-(3-nitrophenyl) indolizin-3-yl) ethyl) malonate (22d):

Yield: 82% (81 mg); Yellowish gum; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.26 (t, J=1.9 Hz, 1H), 8.14 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.1 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1 H), 7.42 (d, J = 9.0 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 6.85-6.89 (m, 2H), 6.72 (dd, J = 8.9, 6.6 Hz, 1H), 6.56 (s, 1H), 6.40-6.46 (m, 1H), 4.64-4.77 (m, 1H), 3.93-4.00 (m, 1H), 3.89 (qd, J = 7.1, 1.9 Hz, 2H), 3.79-3.81 (m, 3H), 3.74-3.79 (m, 1H), 2.70-2.91 (m, 3H), 1.10 (dt, J = 8.6, 7.1 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 168.8, 168.5, 158.4, 148.2, 138.6, 135.2, 133.1, 131.8, 129.1, 128.2, 128.1, 124.2, 123.6, 121.4, 119.7, 119.3, 117.5, 114.3, 110.8, 99.8,

61.4, 55.3, 50.2, 37.9, 29.6, 13.8, 13.8; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{31}O_7N_2$, 531.2126; found, 531.2120.

Diethyl 2-(2-(4-methoxyphenyl)-2-(2-(4-methoxyphenyl) indolizin-3-yl) ethyl) malonate (22e):

Yield: 84% (76 mg); Reddish gum ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.51 (dd, J=7.2, 0.8 Hz, 1H), 7.31 - 7.40 (m, 3H), 7.17 - 7.24 (m, 2H), 6.92 (d, J=8.8 Hz, 2H), 6.83 - 6.89 (m, 2H), 6.61 - 6.69 (m, 1H), 6.51 (s, 1H), 6.30 - 6.37 (m, 1H), 4.74 (dd, J=11.3, 4.9 Hz, 1H), 3.94 - 4.02 (m, 1H), 3.84 - 3.91 (m, 2H), 3.81 - 3.84 (m, 4H), 3.80 (s, 3H), 3.74 - 3.79 (m, 1H), 2.87 - 2.93 (m, 1H), 2.74 - 2.80 (m, 1H), 1.10 (td, J=7.1, 2.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 169.0, 168.7, 158.5, 158.2, 132.7, 132.7, 130.6, 130.4, 129.1, 128.1, 123.5, 118.9, 118.8, 116.6, 114.2, 113.7, 109.8, 99.7, 61.3, 61.2, 55.2, 50.3, 37.9, 29.5, 13.8; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{34}O_6N$, 516.2381; found, 516.2386.

Diethyl 2-(2-(4-methoxyphenyl)-2-(2-(p-tolyl) indolizin-3-yl) ethyl) malonate (22f):

Yield: 91% (87 mg); Colorless gum; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.50 (d, J = 7.1 Hz, 1 H), 7.38 (d, J = 9.0 Hz, 1H), 7.33 (m, J = 7.9 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 6.87 (m, J = 8.6 Hz, 2H), 6.65 (dd, J = 8.5, 6.8 Hz, 1H), 6.53 (br. s., 1H), 6.34 (t, J = 6.4 Hz, 1H), 4.76 (dd, J = 11.3, 4.8 Hz, 1H), 3.94-4.01 (m, 1H), 3.69-3.92 (m, 7H), 2.87-2.93 (m, 1H), 2.72-2.80 (m, 1H), 2.38 (s, 3H), 1.07-1.14 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 168.7, 168.4, 157.9, 135.8, 133.3, 132.5, 132.3, 130.6, 128.9, 128.6, 127.8, 123.3, 118.6, 116.3, 113.8, 109.5, 99.4, 60.9, 60.9, 54.9, 50.0, 37.5, 29.1, 20.8, 13.5, 13.4; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{34}O_5N$, 500.2431; found, 500.2441.

Diethyl 2-(2-(2-(4-fluorophenyl) indolizin-3-yl)-2-(4-methoxyphenyl) ethyl) malonate (22g):

Yield: 77% (82%); Yellowish gum; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.49 (d, J=8.6 Hz, 1H), 7.52 (d, J=7.3 Hz, 1 H), 7.32 - 7.42 (m, 1H), 7.18 (d, J=8.6 Hz, 1H), 7.06 (t, J=8.7 Hz, 1H), 6.87 (d, J=8.8 Hz, 1H), 6.74 - 6.83 (m, 2H), 6.67 (dd, J=8.8, 6.4 Hz, 4 H), 6.50 (s, 1H), 6.31 - 6.39 (m, 1H), 6.23 - 6.31 (m, 1H), 4.20 - 4.33 (m, 1H), 3.98 (dd, J=10.8, 7.1 Hz, 2H), 3.82 - 3.89 (m, 2H), 3.80 (s, 3H), 2.81 - 2.92 (m, 1H), 2.60 - 2.81 (m, 1 H), 1.06 - 1.19 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 168.9, 168.7, 158.7, 144.2, 130.8, 129.7, 128.1, 119.0, 115.2, 115.0, 114.2, 113.9, 110.1, 61.3, 55.3, 50.3, 37.9, 29.5, 13.8; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{31}O_5NF$, 504.2181; found, 504.2179.

Diethyl 2-(2-(2-(4-cyanophenyl) indolizin-3-yl)-2-(4-methoxyphenyl) ethyl) malonate (22h):

Yield: 83% (74 mg); Yellowish gum; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.65 (d, J = 8.3 Hz, 2H), 7.47 - 7.56 (m, 3H), 7.41 (d, J = 9.0 Hz, 1H), 7.17 (d, J = 8.5 Hz, 2H), 6.88 (d, J=8.8 Hz, 2H), 6.71 (dd, J = 8.7, 6.8 Hz, 1H), 6.54 (s, 1H), 6.41 (t, J=6.8 Hz, 1H), 4.71 (dd, J=10.6, 5.3 Hz, 1H), 3.95 (dd, J=10.8, 7.1 Hz, 1H), 3.83 - 3.91 (m, 2H), 3.79 - 3.82 (m, 3H), 3.76 (dd, J=10.8, 7.1 Hz, 1H), 2.70 - 2.95 (m, 3H), 1.10 (t, J = 7.1 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ : 168.7, 168.5, 158.4, 141.7, 133.2, 132.1, 131.7, 129.9, 128.9, 128.0, 123.7, 119.4, 119.3, 119.1, 117.5, 114.3, 110.7, 110.0, 99.5, 61.4, 61.4, 55.3, 50.2, 37.8, 29.4, 13.8; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{31}O_5N_2$, 511.2227; found, 511.2240.

Diethyl 2-(2-(2-(2-fluorophenyl) indolizin-3-yl)-2-(4-methoxyphenyl) ethyl) malonate (22i):

Yield: 79% (73 mg); Yellowish gum; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.52 (d, J = 7.3 Hz, 1H), 7.33 - 7.42 (m, 2H), 7.28 - 7.31 (m, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.07 - 7.16 (m, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.67 (dd, J = 8.9, 6.5 Hz, 1H), 6.54 (s, 1H), 6.36 (t, J = 6.8 Hz, 1H), 4.55 (dd, J = 10.8, 5.7 Hz, 1H), 3.95 - 4.04 (m, 1H), 3.81 - 3.92 (m, 3H), 3.79 (s, 3H), 2.92 - 2.99 (m, 1H), 2.82 (ddd, J = 13.8, 7.8, 5.9 Hz, 1H), 2.71 (ddd, J = 13.8, 10.9, 6.3 Hz, 1H), 1.07 - 1.15 (m, 6H);

^{13}C NMR (101 MHz, $CDCl_3$) δ:169.0, 168.8, 158.1, 132.7, 132.4, 132.4, 132.0, 128.3, 126.3, 125.5, 123.9, 123.5, 119.1, 116.8, 115.5, 114.0, 110.1, 105.4, 100.6, 61.3, 55.2, 50.2, 38.3, 30.9, 13.8 ; **^{19}F NMR** (376 MHz, $CDCl_3$) δ : -113.80 (s, 1F); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{31}O_5NF$, 504.2181; found, 504.2190

Diethyl 2-(2-(2-(3,4-dimethoxyphenyl) indolizin-3-yl)-2-(4-methoxyphenyl) ethyl) malonate (22j):

Yield: 72% (79 mg); Whitish gum; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.54 (d, J = 7.1 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 6.93-7.00 (m, 2H), 6.81-6.93 (m, 3H), 6.66 (dd, J = 8.7, 6.3 Hz, 1H), 6.52 (s, 1H), 6.29-6.42 (m, 1H), 4.75 (dd, J = 11.2, 5.3 Hz, 1H), 3.98 (dd, J = 10.8, 7.2 Hz, 2H), 3.87-3.91 (m, 3H), 3.82-3.87 (m, 2H), 3.77-3.82 (m, 6H), 2.90-3.00 (m, 1H), 2.70-2.87 (m, 2H), 1.09 (t, J = 7.1 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 169.0, 168.7, 158.2, 148.6, 147.9, 132.8, 132.7, 130.6, 129.5, 128.1, 123.4, 121.4, 119.0, 118.9, 116.7, 114.1, 113.0, 111.0, 110.0, 99.7, 61.3, 61.2, 55.9, 55.7, 55.2, 50.4, 38.0, 29.6, 13.8; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{32}H_{35}O_7N$, 545.2414; found, 545.2424.

Diethyl 2-(2-(2-(2,4-dichlorophenyl) indolizin-3-yl)-2-(4-methoxyphenyl) ethyl) malonate (22k):

Yield: 76% (75 mg); Brown gum ; **^{1}H NMR** ((400 MHz, $CDCl_3$) δ : 7.65 - 7.75 (m, 1H), 7.32 - 7.52 (m, 2H), 7.12 - 7.19 (m, 2H), 7.07 (d, J=8.5 Hz, 2H), 6.75 - 6.81 (m, 2H), 6.69 (dd, J=8.8, 6.3 Hz, 1H), 6.38 - 6.51 (m, 2H), 4.34 - 4.48 (m, 1H), 4.06 - 4.17 (m, 1H), 3.92 - 4.02 (m, 3H), 3.75 - 3.80 (m, 3H), 3.14 (t, J = 7.1 Hz, 1H), 2.75 (dt, J = 14.1, 7.1 Hz, 1H), 2.63 (ddd, J = 14.0, 9.4, 6.9 Hz, 1H), 1.17 (dt, J = 11.2, 7.1 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ : 169.1 , 158.3 , 135.2 , 133.3 , 132.3 , 131.5 , 129.7 , 129.1 , 128.6 , 126.4 , 123.3 , 119.2 , 116.9 , 114.3 , 113.9 ,

110.4 , 101.0 , 61.5 , 61.4 , 55.2 , 50.0 , 38.6 , 30.9 , 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{29}Cl_2O_5N$, 553.1423; found, 553.1440.

Diethyl 2-(2-(4-methoxyphenyl)-2-(1-methyl-2-phenylindolizin-3-yl) ethyl) malonate (22l):

Yield: 74% (77 mg); Yellowish gum; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.96-7.99 (m, 1H), 7.73-7.78 (m, 1H), 7.57 (s, 1H), 7.40-7.52 (m, 2H), 7.30-7.37 (m, 2H), 7.22-7.27 (m, 2H), 7.13 (s, 1H), 7.04 (s, 1H), 6.76-6.84 (m, 2H), 4.20-4.27 (m, 1H), 4.05-4.19 (m, 4H), 3.77-3.80 (m, 3H), 3.71-3.76 (m, 1H), 2.40 (t, *J* = 5.69 Hz, 2H), 2.33-2.36 (m, 3H), 2.20-2.22 (m, 3H), 1.17-1.26 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.8, 169.5, 158.3, 139.0, 138.8, 134.3, 134.1, 132.4, 132.2, 129.0, 128.8, 128.7, 128.3, 127.9, 127.8, 126.4, 125.9, 113.5, 113.4, 61.1, 56.0, 55.2, 55.1, 49.3, 49.3, 39.6, 39.5, 21.2, 21.0, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{33}O_5N$, 499.2359; found, 499.2364.

Diethyl 2-(2-(4-methoxyphenyl)-2-(7-methyl-2-phenylindolizin-3-yl) ethyl) malonate (22m):

Yield: 68% (75 mg); Yellow gum; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.36-8.42 (m, 2H), 8.14-8.19 (m, 2H), 7.21-7.26 (m, 2H), 6.79-6.85 (m, 2H), 4.06-4.20 (m, 5H), 3.78 (s, 3H), 3.46 (t, *J* = 7.13 Hz, 1H), 3.05 (s, 3H), 2.26-2.36 (m, 2H), 1.22 (dt, *J* = 12.26, 7.13Hz, 7H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.5, 169.3, 158.7, 150.4, 145.6, 136.0, 129.7, 129.6, 128.1, 127.7, 124.4, 123.8, 113.8, 113.5, 61.3, 61.3, 56.4, 55.2, 49.4, 44.6, 39.0, 14.0, 14.0; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{33}O_5N$, 499.2359; found, 499.2366.

diethyl 2-(2-phenyl-2-(2-phenylindolizin-3-yl) ethyl) malonate (24a):

Yield: 85% (82 mg); Colourless gum; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.95 (dd, *J* = 8.19, 1.31 Hz, 2H), 7.66-7.74 (m, 2H), 7.35-7.48 (m, 4H), 7.25-7.31 (m, 4H), 7.19-7.25 (m, 2H), 7.13-7.18 (m, 1H), 4.23 (t, *J* = 6.69 Hz, 1H), 3.96-4.17 (m, 4H), 3.75 (t, *J* = 7.13 Hz, 1H), 2.36 (t, *J* = 7.00 Hz, 2 H), 1.12-1.22 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.9, 169.5, 145.1, 140.8, 140.7,

132.3, 132.2, 129.0, 128.8, 128.8, 128.4, 128.1, 126.7, 61.2, 61.1, 56.6, 49.3, 39.8, 14.0, 14.0; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{30}O_4N$, 456.2169; found, 456.2163.

Diethyl 2-(2-(4-(methylthio) phenyl)-2-(2-phenylindolizin-3-yl) ethyl) malonate (24b):

Yield:82% (85 mg); Yellowish gum; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.1 Hz, 1H), 7.28 - 7.37 (m, 4H), 7.17 - 7.24 (m, 2H), 7.06 - 7.17 (m, 4H), 6.59 (t, *J* = 7.6 Hz, 1H), 6.47 (br. s., 1H), 6.29 (t, *J* = 6.8 Hz, 1H), 4.61-4.76 (m, 1H), 3.76-3.96 (m, 3H), 3.67 (dd, *J* = 10.3, 7.1 Hz, 1H), 2.75-2.87 (m, 2H), 2.58-2.73 (m, 1H), 2.35-2.44 (m, 3H), 0.96-1.06 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ168.6, 168.4, 145.8, 136.3, 133.2, 130.9, 129.4, 128.4, 127.1, 126.7, 124.4, 123.9, 123.7, 119.1, 118.1, 117.1, 110.1, 99.6, 61.5, 61.3, 50.1, 35.7, 30.1, 14.0, 13.8; **HRMS** (ESI) m/z: [M+H]+ calcd for $C_{30}H_{32}O_4NS$, 502.2047; found, 502.2067.

Diethyl 2-(2-(4-nitrophenyl)-2-(2-phenylindolizin-3-yl) ethyl) malonate (24c):

Yield:78% (85 mg); colourless gum; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.13 Hz, 2H), 7.95 (d, *J* = 7.75 Hz, 2H), 7.76 (d, *J* = 7.75 Hz, 2H), 7.42-7.59 (m, 6 H), 7.32-7.40 (m, 2H), 4.32-4.42 (m, 1H), 4.05-4.25 (m, 4H), 3.80 (t, *J* = 7.00 Hz, 1H), 2.33-2.43 (m, 2H), 1.26 (t, *J* = 7.13 Hz, 4H), 1.20 (t, *J* =7.13 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ169.5, 169.3, 152.9, 146.8, 140.4, 140.1, 132.7, 132.6, 129.2, 129.0, 128.5, 128.4, 128.4, 127.6, 123.5, 61.4, 61.3, 56.0, 49.0, 39.4, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{29}O_6N_2$, 501.2020; found, 501.2000.

diethyl 2-(2-(4-chlorophenyl)-2-(2-phenylindolizin-3-yl) ethyl) malonate (24d):

Yield: 82% (85 mg); colourless gum; **^{1}H NMR** (400 MHz, $CDCl_3$): δ7.87 (dd, *J* = 8.07, 1.31 Hz, 2H), 7.61-7.70 (m, 2H), 7.31-7.44 (m, 4H), 7.21-7.27 (m, 2H), 7.19 (m, *J* = 8.38 Hz, 2H), 7.13 (m, *J* = 8.50 Hz, 2H), 4.16 (t, *J* = 6.63 Hz, 1H), 3.95-4.11 (m, 4H), 3.69 (t, *J* = 7.13 Hz, 1H), 2.28 (t, *J* = 7.13 Hz, 2H), 1.12-1.17 (m, 3H), 1.08 (t, *J* = 7.13 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.6, 169.3, 143.6, 140.4, 140.3, 132.4, 132.3, 132.2, 129.0, 128.8, 128.5,

128.3, 128.1, 128.0, 61.1, 61.1, 55.8, 49.0, 39.5, 13.9, 13.8; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{29}O_4NCl$, 490.1780; found, 490.1800.

diethyl 2-(2-(3,4-dimethoxyphenyl)-2-(2-phenylindolizin-3-yl) ethyl) malonate (24e):

Yield: 80% (85 mg); Yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 8.13, 1.25 Hz, 2 H), 7.83 (d, *J* = 7.38 Hz, 1H), 7.63-7.68 (m, 2H), 7.42-7.53 (m, 3H), 7.35-7.41 (m, 1H), 7.21-7.30 (m, 3H), 7.07-7.13 (m, 1H), 6.96 (d, *J* = 7.50 Hz, 1H), 4.50 (dd, *J* = 9.13, 4.38 Hz, 1H), 4.16-4.24 (m, 2H), 4.04-4.14 (m, 2H), 4.01 (dd, *J* = 9.51, 4.88 Hz, 1H), 2.26 (ddd, *J* = 9.13, 7.32, 4.44 Hz, 2H), 1.92 (s, 3H), 1.27 (t, *J* = 7.19 Hz, 3H), 1.18 (t, *J* = 7.13 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.0, 169.5, 143.7, 140.6, 140.5, 133.8, 132.3, 132.1, 129.7, 128.9, 128.7, 128.6, 128.3, 126.9, 126.3, 126.0, 61.1, 61.0, 49.2, 38.4, 18.6, 14.0, 13.9; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{34}O_6N$, 516.2381; found, 516.2376.

Diethyl 2-(2-(2-phenylindolizin-3-yl)-2-(thiophen-2-yl) ethyl) malonate (24h):

Yield: 79% (85 mg); Yellowish gum; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.1 Hz, 1H), 7.46-7.51 (m, 2H), 7.36-7.43 (m, 3H), 7.28-7.35 (m, 1H), 7.24 (d, *J* = 5.1 Hz, 1H), 7.01 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.89-6.95 (m, 1H), 6.66-6.72 (m, 1H), 6.54 (s, 1H), 6.36-6.43 (m, 1H), 4.89-4.98 (m, 1H), 3.68-3.97 (m, 4H), 2.84-2.95 (m, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.9, 168.7, 136.6, 132.9, 129.4, 128.7, 128.3, 127.7, 127.1, 126.5, 126.2, 125.1, 123.6, 119.0, 117.3, 116.9, 110.5, 110.1, 96.7, 61.3, 50.2, 38.2, 29.7, 29.3, 15.9, 13.8; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{27}H_{28}O_4NS$, 462.1734; found, 462.1750.

4.2.7. References

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ABSTRACT

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CSIR-National Chemical Laboratory, Pune **Name of the Co-Supervisor:** Dr. S. A. R. Mulla

Title of the thesis: Organocatalytic Enantioselective Synthesis of Bioactive Macro-lactones and Development of Synthetic Methodologies Involving C–C and C–N bond Formations**.**

Natural products are the key source of medicine due to their massive structural and chemical diversity. Many drugs that are isolated from natural products have biological activity. Macrolides are one of the significant natural products isolated from various fungal metabolites. Carbon-carbon bond-forming reactions are vital steps for constructing complex molecular frameworks in many syntheses of natural products and organic compounds, as well as in various industrial applications, and represent a forefront of research in organic chemistry and essential tools for synthetic chemists as well. Sulfoximine is the core structure of the natural product. Many natural and unnatural biological and chemically active compounds contain sulfoximine.

Chapter 1 includes the organocatalyzed total synthesis of twelve membered macro-lactones: Phaseolide A and Balticolid. However, Chapter 2 describes the metal-free and radical-mediated conjugated addition of cyclic ethers on *para*-quinone methides (*p*-QMs) and Quinone Imine Ketals (QIK's). Chapter 3 contains the metal-free, nucleophilic Addition of *N*H- sulfoximines on *p*-QMs and Aza-oxyallyl cations. In chapter 4, we have developed Lewis acid catalyzed *N*-alkylation of sulfoximines and C-3 alkylation of indolizine through nucleophilic ring-opening of donor-acceptor cyclopropanes.

List of Publications Emanating from the Thesis Work

1. **More, S. G.;** Suryavanshi, G. Metal-free, Radical 1,6- Conjugated Addition of Cyclic Ethers with *para*-Quinone Methides (*p*-QMs). *Org. Biomol. Chem.* **2019**, *17*, 3239−3248.

2. **More, S. G.;** Kamble, R. B.; Suryavanshi, G. Oxidative Radical-Mediated Addition of Ethers to Quinone Imine Ketals: An Access to Hemiaminals. *J. Org. Chem.* **2021**, *86*, 2107−2116.

3. **More, S. G.;** Rupanawar, B. D.; Suryavanshi, G. Metal-Free, Acid-Catalyzed 1,6-Conjugate Addition of *N*H-Sulfoximines to *para*- Quinone Methides: Accessing to Diarylmethine Imino Sulfanone. *J. Org. Chem,* **2021**, *86*, 15, 10129−10139.

4. **More, S. G.;** Suryavanshi, G. Lewis Acid Triggered N-Alkylation of Sulfoximines through Nucleophilic Ring-Opening of Donor-Acceptor Cyclopropanes: Synthesis of *γ*-Sulfoximino Malonic Diesters, *Org. Biomol. Chem.*, **2022**, *20*, 2518–2529.

5. **More, S. G.;** Suryavanshi, G. Metal-Free and Mild Synthesis of Congested N-Alkyl Sulfoximines via In-situ Generated Aza-Oxyallyl Cations from Functionalized Alkyl Bromide, *Asian J. Org. Chem.* **2022**,*11*, e20220021.

6. **More, S. G.;** Suryavanshi, G. Organocatalyzed Enantioselective Total Synthesis of Phaseolide A and Balticolid. (*Manuscript under preparation*)

7. **More, S. G.** Mane, K. D. Suryavanshi. G. Scandium Triflate Catalyzed Regioselective C-3 Functionalization of Indolizines via Ring-Opening of Donor-Acceptor Cyclopropanes**.** (*Manuscript under preparation*).

List of Publications Non-Emanating from the Thesis Work

8. Ramavath, V. Rupanawar, B. D. **More, S. G.** Bansode A. B. Hypervalent Iodine (III) Induced Oxidative Olefination of Benzylamines Using Wittig Reagents, *New J. Chem.*, 2021, 45, 8806-8813

9. K. D. Mane, S. B. Bhagve, **S. G. More,** G. Suryavanshi, Metal-free Regioselective C-3 Alkylation of Indolizines via in situ Generated Aza oxyallyl Cations (*Manuscript under preparation*)

List of Posters Presented with Details

1. National Science Day Poster Session at CSIR-National Chemical Laboratory, Pune (February 25-27, **2019**)

   Title: Metal-Free, Radical 1,6-Conjugated Addition of Cyclic Ethers with *para*-Quinone Methides (*p*-QMs).

   Abstract: An efficient metal free C-C bond formation between *para*-Quinone methides (*p*-QMs) and Cyclic Ethers *via* radical pathway to afford the substituted diarylmethanes, triarylmethanes or α-alkylation of Cyclic Ethers has been developed. Also, synthesis of 3,3'-substituted Oxindoles with quaternary stereo genic carbon centre were well achieved under mild reaction conditions.

2. National Science Day Poster Session at CSIR-National Chemical Laboratory, Pune (February 25-27, **2020**)

   Title: Oxidative Radical Mediated Addition of Ethers to Quinone Imine Ketals (QIK's): A Facile Access to Hemiaminals

   Abstract: A highly regioselective, efficient and metal free radical mediated addition of ethers to QIK has been developed. This method offers easy access to substituted hemiaminal ethers with high functional group tolerance in good to excellent yields.

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Metal-free, radical 1,6-conjugated addition of cyclic ethers with *para*-quinone methides (*p*-QMs)†

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An efficient method for metal-free C–C bond formation between *p*-quinone methides (*p*-QMs) and cyclic ethers *via* a radical pathway to afford substituted diarylmethanes and triarylmethanes or to effect the α-alkylation of the cyclic ethers has been developed. Also, the synthesis of 3,3′-disubstituted oxindoles with stereogenic quaternary carbon centers was successfully achieved under mild reaction conditions.

Introduction

Carbon–carbon (C–C) bond-forming reactions are key steps for the construction of complex molecular frameworks in many syntheses of natural products and organic compounds, as well as in a variety of industrial applications.[1] C–C bond formation hence represents a forefront of research in organic chemistry and provides important tools for synthetic chemists as well. Therefore, various methods for C–C bond formation are described in the literature under metal[2] and metal-free conditions.[3] Among these methods, free radical reactions have emerged as a powerful tool for the construction of C–C bonds and are efficiently utilized in the synthesis of complex molecular frameworks.[4] Recently, addition reactions of carbon-centered cyclic ether radicals to electrophilic carbon acceptors have gained importance due to the abundance of these ethers in biomass.[5]

This method has been promisingly utilized in the synthesis of complex organic molecules *via* the generation of carbon centered radicals through a single electron transfer (SET) mechanism which results in a high atom economy.[6] Recently *p*-quinone methides (*p*-QMs) have been extensively employed in C–C and C–hetero bond formation *via* nucleophilic addition due to their characteristic zwitterionic resonance entities (*i.e.* Michael acceptor characteristics) in conjugate addition reactions.[7] *p*-QMs are inherently found in natural products and pharmaceutical ingredients which possess broad spectrum biological activities. These activities mainly include antitumor,[8] anticancer,[9] antimicrobial,[10] antiinflammatory[11] and antiviral[12] effects (Fig. 1). Due to the importance of these moieties, their simple and efficient synthesis attracts the attention of chemists. After a careful survey of the literature, numerous metal catalysed C–C and C–hetero bond formation reactions of *p*-QMs with different nucleophiles such as C, O, N, S and P were identified (Scheme 1, eqn (1)).[13] However, although *p*-QMs are reactive intermediates in nucleophilic addition reactions, minimal attempts have been made to use them for radical addition reactions so far. Recently, Cui *et al.* developed the Fe(III) catalysed hydro alkylation of *p*-QMs *via* a radical conjugate addition reaction.[14] Furthermore, the same group carried out the metal-free α-alkylation of alcohols with *p*-QMs using di-*tert*-butyl peroxide (DTBP) as an oxidant (Scheme 1).[15] To establish new C–C bonds, it is inherent that the coupling

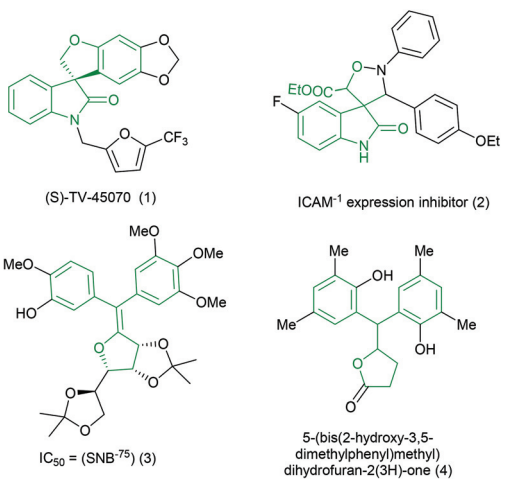

Fig. 1 Biologically active 3,3′ oxindole and diarylmethane moieties.

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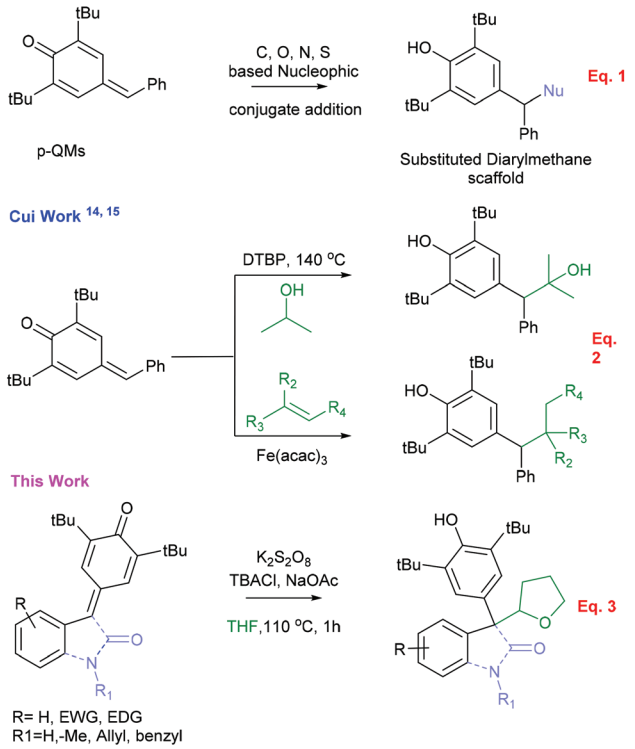


Scheme 1 Nucleophilic addition involving *p*-QMs.

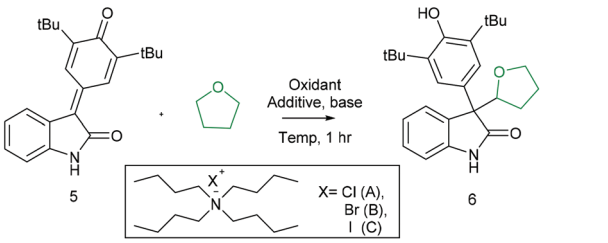
carbons differ in their electronic nature. As a part of our interest in the development of metal-free reactions,[16] herein we report a novel 1,6-conjugate radical addition reaction of cyclic ethers on *p*-QMs.

Results and discussion

To investigate radical addition reactions, we selected *p*-QMs derived from isatin **5a**, and cyclic ether (THF) as model substrates.

We initiated our study by investigating the addition of ethers to *p*-QMs using the oxidant $K_2S_2O_8$ (1 mmol), additive TBACl (1 mmol) and base NaOAc (1 mmol) in THF in air, and gratifyingly the desired product **6a** was delivered in 52% yield (Table 1, entry 1). Next, attempts were made to enhance the yield by varying the concentration of each reagent at 110 °C, whereby a slight increase in yield was observed (entries 2–4). However, variation of the additive failed to produce the desired product **6a** (entries 5 and 6). When the reaction was conducted in the presence of 4 equiv. of additive A, there was a dramatic improvement, with the formation of **6a** in 79% yield (entry 7). Further, changing the oxidant and base did not affect the yield of **6a** (entries 8–11). Also, an alteration in the reaction temperature failed to give **6a** (entries 12–14). Surprisingly, when the reaction was carried out under a nitrogen atmosphere at 110 °C, the highest yield of 85% for product **6a** was achieved (entry 15). It is noteworthy that the reaction did not proceed in the absence of additive or base

Table 1 Optimization of reaction conditions



Entry	Oxidant	Additive	Base (equiv.)	Temp. (°C)	Yields %
1	$K_2S_2O_8$(1)	A (1)	NaOAc (1)	110	52
2	$K_2S_2O_8$(2)	A (2)	NaOAc (2)	110	65
3	$K_2S_2O_8$(3)	A (3)	NaOAc (3)	110	72
4	$K_2S_2O_8$(3)	A (4)	NaOAc (2)	110	53
5	$K_2S_2O_8$(3)	B (4)	NaOAc (3)	110	Trace
6	$K_2S_2O_8$(3)	C (4)	NaOAc (3)	110	Trace
7	$K_2S_2O_8$(3)	A (4)	NaOAc (3)	110	79
8	$K_2S_2O_8$(3)	A (4)	KOAc (3)	110	30
9	$K_2S_2O_8$(3)	A (4)	NH_4OAc (3)	110	30
10	$(NH_4)_2S_2O_8$(3)	A (4)	NaOAc (3)	110	NR
11	$Na_2S_2O_8$(3)	A (4)	NaOAc (3)	110	42
12	$K_2S_2O_8$(3)	A (4)	NaOAc (3)	rt	NR
13	$K_2S_2O_8$(3)	A (4)	NaOAc (3)	90	NR
14	$K_2S_2O_8$(3)	A (4)	NaOAc (3)	140	NR
15[a]	**$K_2S_2O_8$(3)**	**A (4)**	**NaOAc (3)**	**110**	**85**
16[b]	$K_2S_2O_8$(3)	A (4)	NaOAc (3)	110	61
17	$K_2S_2O_8$(3)	A (4)	—	110	NR
18	$K_2S_2O_8$(3)	—	NaOAc (3)	110	NR

[a] Reaction carried out under N_2. [b] Acetonitrile used as co-solvent; Additive A is mixed with water at a w/v ratio of 1 : 1.

(entries 17 and 18). On the basis of this optimisation study, the best reaction conditions for radical addition of cyclic ethers to *p*-QMs are those given in entry 15.

Considering the importance of 3,3′-oxindoles with quaternary stereogenic carbon centers, we further employed our methodology to various *p*-QMs derived from isatin.

To our delight, a wide range of substituted *p*-QMs gave the desired 3,3′-oxindoles under our standardized reaction conditions. *p*-QMs derived from isatin with electron withdrawing as well as electron donating groups (such as, –Cl, –Br and –Me substitutions at the 5-position) reacted well to give the corresponding addition products in excellent yields (Table 2, **6b**, **6c** & **6h**). Thereafter the reaction was performed by protecting the isatin with allyl, benzyl and methyl groups to attain compatible products with good to excellent yields (**6d–6g** & **6i**). Further, the *p*-QMs of isatin were treated with various cyclic ethers (such as 1,4-dioxane and tetrahydropyran) and delivered the desired products in good to excellent yields (**6j–6l**). Unfortunately, 1,3,5-trioxane and 1,2-dimethoxyethane failed to produce the corresponding addition products (**6m–6o**). Also, fuchsones with high steric hindrance formed the desired addition products, when electron withdrawing as well as donating groups were present (**6p** & **6q**).

After successful achievement of 1,6-addition of cyclic ethers to isatin-based *p*-QMs, we were inspired to try the addition of cyclic ethers to *p*-QMs for the formation of α-alkylated cyclic

Table 2 Substrate scope of *p*-QM-based isatins and fuchsones

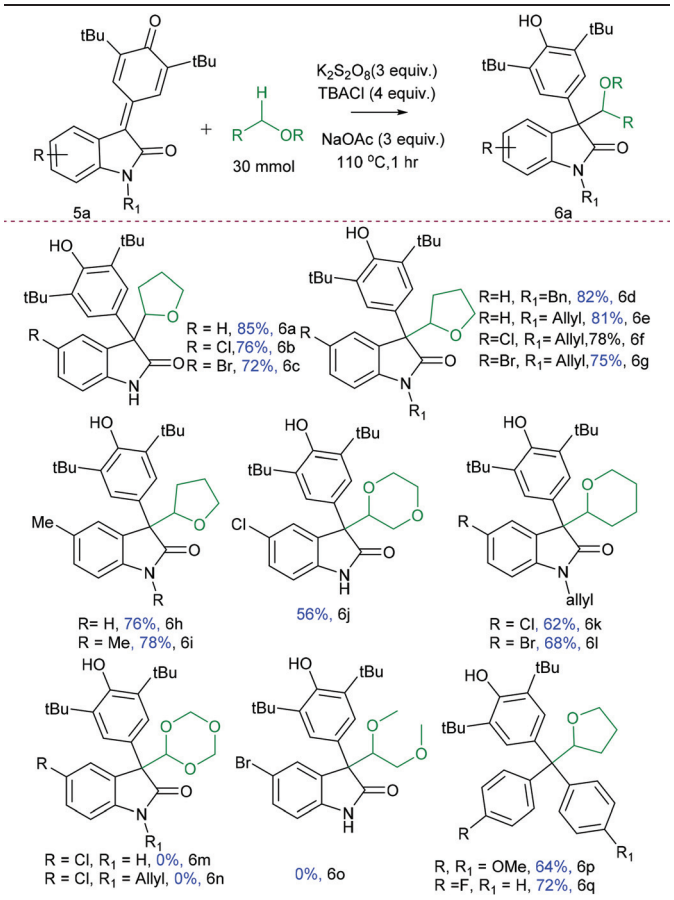
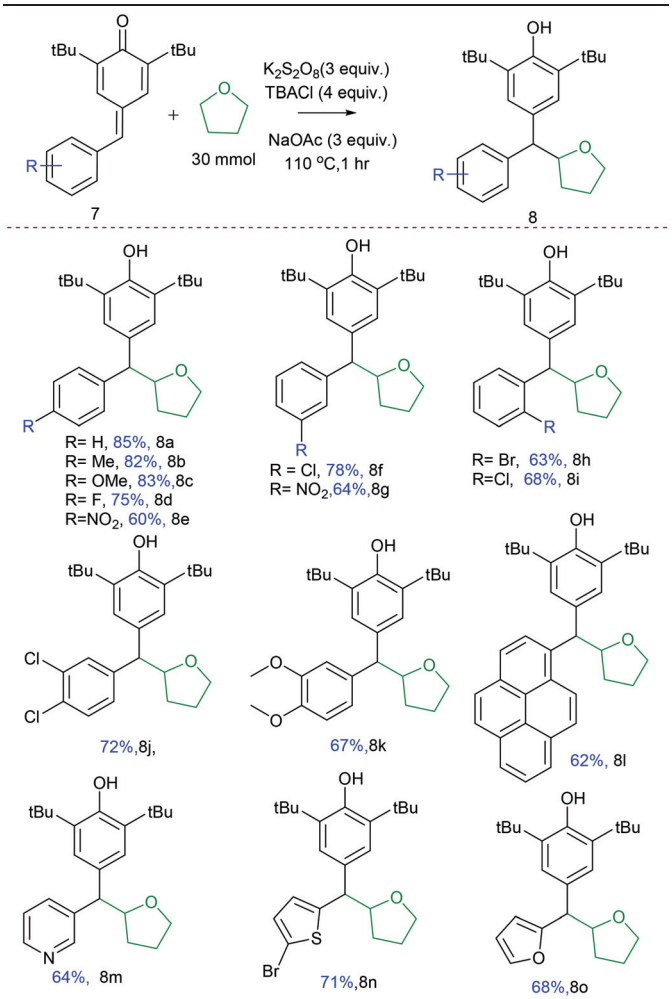


Table 3 Substrate scope of *p*-QMs

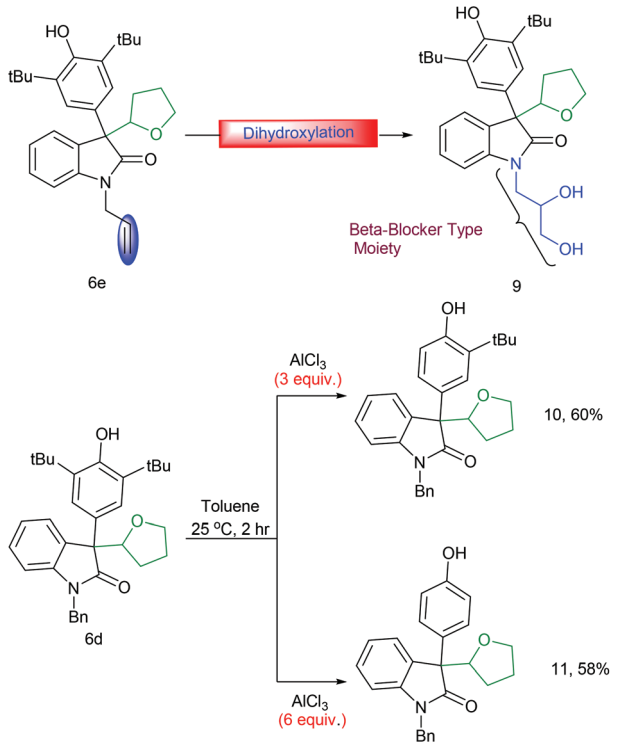


ethers containing diarylmethanes. We further investigated the variety of substrates with electron withdrawing as well as electron donating groups present on the aromatic part of the *p*-QMs.

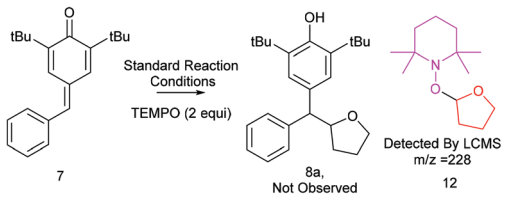
After careful observation we concluded that electron withdrawing groups present at the *p*-position gave comparatively lower yields than those with *o*- and *m*-substituents. The electron donating groups such as –OMe, –Me and the unsubstituted aromatic ring delivered addition products in 82 to 85% yields (Table 3, **8a–8c**). Also, the substrates having electronic withdrawing groups (–Cl, –Br, –F) present at the *o*, *m* and *p* positions gave moderate to good yields of the desired products (**8d**, **8f**, **8h** & **8i**). Surprisingly, although the aromatic ring with the $-NO_2$ group was well tolerated in the oxidative reaction conditions, it afforded comparatively lower yields (**8e** & **8g**). Disubstituted *p*-QMs gave the expected products in good yields (**8j–8k**). Also, the polycyclic aromatic hydrocarbon (*i.e.* pyrene-based *p*-QM) reacted smoothly to give the desired product **8l** in 72% yield. To check the feasibility of the approach further, we reacted various heterocycle-based *p*-QMs under optimized reaction conditions to get α-alkylated cyclic ethers. It is noteworthy that these heterocyclic systems such as pyridine, furan and thiophene withstood the oxidation conditions to give the desired products in good to excellent yields (**8m–8o**). Unfortunately, *p*-QMs of indole failed to give addition products.

To show the utility of this addition reaction, the allyl protected addition product **6e** was subjected to transformation as shown in Scheme 2. The compound **6e** was subjected to dihydroxylation[17] to give the important β-blocker type moiety. Also, di dealkylation of **6d** was carried out by using 6 equiv. of $AlCl_3$ in toluene to give phenol 11 in 58% yield, whereas, use of 3 equiv. of $AlCl_3$ gave 60% of the monoalkylated product **10**.

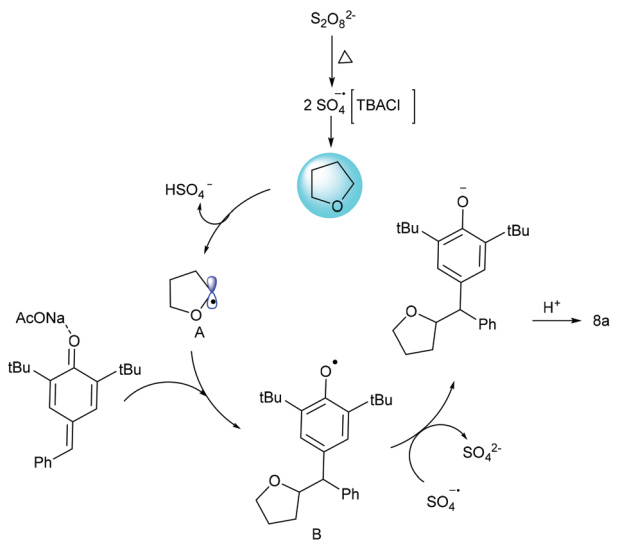
To get insight into the reaction mechanism, we performed a control experiment using 2 equiv. of TEMPO as a radical scavenger.[18] The reaction failed to produce the desired compound **8a** (Scheme 3), and so it was concluded that the reaction proceeds *via* a radical pathway. On the basis of the control experiment and a literature review,[19] we are proposing a plausible reaction mechanism for the addition reaction: Initially the α-oxyalkyl radical **A** is generated *via* abstraction of the proton from THF by a sulfate anion radical which is generated from the thermal decomposition of persulfate and stabilized by TBACl.[20] Then the formed α-oxyalkyl radical **A** forms a C–C bond with *O*-chelated *p*-QM to afford adduct **B**.[21] Further,



Scheme 2 The synthetic transformation.



Scheme 3 The control experiment.



Scheme 4 A plausible reaction mechanism.

adduct **B** forms an oxyanion by taking an electron from the sulfate radical anion and undergoes protonation to yield the desired product **8a** as shown in Scheme 4.

Conclusions

We have developed an efficient, metal-free, radical C–C bond formation reaction for cyclic ethers with *p*-QMs to afford diarylmethanes containing phenols functionalized with cyclic ethers in excellent yield and with high atom economy. We have elaborated our hypothesis relating to *p*-QMs derived from isatin to establish 3,3′-disubstituted oxindoles with quaternary stereogenic carbon centers. The formed products have been successfully utilised in various transformations such as dihydroxylation and dealkylation reactions.

Experimental section

General information

Most of the reagents and starting materials were purchased from commercial sources and used as received. *p*-QMs, including *p*-QMs derived from isatins and fuchsones, were prepared using previously reported procedures.[22–24] All solvents were thoroughly dried and purified before use. Petroleum ether with a boiling point of 60–80 °C was used. ^{1}H and ^{13}C spectra were recorded on 200, 400 and 500 MHz NMR spectrometers. HRMS data for all compounds were recorded using an Orbitrap mass analyser with an Accela 1250 pump. Purification of compounds was done using column chromatography (100–200 mesh). All reactions were carried out under a nitrogen atmosphere in thoroughly dried round bottom flasks. The reactions were monitored by thin layer chromatography (TLC). Coupling constants are given in hertz (Hz) and the classical abbreviations are used to describe the signal multiplicities.

General experimental procedure for synthesis of *p*-QM isatins 5f, 5g

In a Dean–Stark apparatus, di-tertbutyl phenol (10 mmol) and the corresponding isatin (10 mmol) in toluene (50 mL) were refluxed. Piperidine (20.0 mmol, 2.6 mL) was then added dropwise over the course of 1 h. The reaction suspension was further refluxed for 3 h. After cooling to just below the boiling point of the reaction mixture, acetic anhydride (25.0 mmol, 1.2 g) was added and stirring was continued for 15 min. Then the reaction mixture was poured onto ice-water (500 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent of the filtrate was removed under reduced pressure. The crude *p*-QMs were purified by flash column chromatography to give the desired products.

The isatin-based *p*-QMs were further *N*-alkylated using a known procedure.[22a]

1-Allyl-5-bromo-3-(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene) indolin-2-one (5f). Yield: 70%, 87 mg; brown oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.39 (s, 9 H), 1.35 (s, 9 H), 4.38 (d, J = 4.96 Hz, 2 H), 5.13–5.33 (m, 2 H), 5.73–5.90 (m, 1 H), 6.71 (d, J = 8.39 Hz, 1 H), 7.36–7.50 (m, 1 H), 7.75 (d, J = 2.29 Hz, 1 H), 7.85 (s, 1 H), 9.09 (d, J = 2.67 Hz, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 29.7, 36.0, 36.2, 42.0, 110.7, 115.0, 117.7, 124.2, 127.3, 127.5, 128.3, 128.8, 130.8, 133.3, 139.2, 142.6, 151.8, 153.1, 167.2, 186.7; **HRMS** (ESI) calculated for $C_{25}H_{29}BrNO_2$ $[M + H]^+$: 454.1376, found: 454.1374.

1-Allyl-5-chloro-3-(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)indolin-2-one (5g). Yield: 76%, 84 mg; red brown oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.39 (s, 10 H), 1.35 (s, 9 H), 4.30–4.44 (m, 2 H), 5.13–5.27 (m, 2 H), 5.77–5.88 (m, 1 H), 6.75 (d, J = 8.39 Hz, 1 H), 7.22–7.33 (m, 1 H), 7.69 (d, J = 1.91 Hz, 1 H), 7.76 (d, J = 2.29 Hz, 1 H), 9.09 (d, J = 2.67 Hz, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 29.7, 36.1, 36.2, 42.1, 110.2, 117.7, 123.7, 126.0, 127.5, 127.7, 128.4, 130.4, 130.8, 139.2, 142.2, 151.8, 153.1, 167.3, 186.8; **HRMS** (ESI) calculated for $C_{25}H_{29}ClNO_2$ $[M + H]^+$: 410.1881, found: 410.1858.

General experimental procedure for synthesis of *p*-QM 7n

p-QM **7n** was prepared according to a known procedure.[21]

4-((5-Bromothiophen-2-yl)methylene)-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (7n). Yield: 86%, 171 mg; gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.28 (s, 8 H), 1.34 (s, 10 H), 6.89 (d, J = 2.67 Hz, 1 H), 6.99–7.07 (m, 3 H), 7.62 (d, J = 2.29 Hz, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 29.6 and 30.3, 35.1 and 35.7, 118.7, 124.1, 126.0 and 126.5, 129.3 and 130.8, 132.8, 133.7 and 134.9, and 140.9, 147.8 and 149.8, 186.1; **HRMS** (ESI) calculated for $C_{19}H_{23}BrOS$ $[M + H]^+$: 379.0726, found: 379.0722.

General experimental procedure for synthesis of 3,3 substituted oxindoles

$K_2S_2O_8$ (0.3 mmol), sodium acetate (0.3 mmol) and $TBACl{\cdot}H_2O$ (0.4 mmol) were added to a 25 mL round bottom flask containing *p*-QMs of substituted isatin (0.1 mmol) in THF (3 mL). Then the reaction mixture was refluxed at 110 °C under a nitrogen atmosphere for 1 h. After the completion of the reaction (as determined by TLC analysis), the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The formed residue was extracted with ethyl acetate (3 × 3 mL) and washed with brine (20 mL). Then the combined organic phases were dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated *in vacuo*. The crude products were purified by flash chromatography (silica gel 100–200 mesh) using petroleum ether/ethyl acetate (v/v, 9 : 1) to afford the 3,3′-substituted oxindole derivatives with high purity.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl) indolin-2-one (6a). Yield: 85%, 103 mg; yellow gummy oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.31 (s, 18 H), 1.56 (m, 1 H), 1.71 (m, 2 H), 1.87 (dd, J = 7.32, 4.88 Hz, 1 H), 3.69 (t, J = 6.41 Hz, 2 H), 4.76 (t, J = 7.63 Hz, 1 H), 5.05 (s, 1 H), 6.81 (d, J = 7.93 Hz, 1 H), 7.00 (m, 1 H), 7.18 (m, 1 H), 7.30 (s, 2 H), 7.43 (d, J = 7.32 Hz, 1 H), 8.54 (m, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 26.0, 27.6, 30.2, 34.5, 59.8, 69.1, 83.6, 109.6, 122.2, 124.3, 127.4, 128.1, 128.5, 130.5, 135.3, 141.4, 153.1, 179.3; **HRMS** (ESI) calculated for $C_{26}H_{33}O_3NNa$ $[M + Na]^+$: 430.2353, found: 430.2346.

5-Chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-((*R*)-tetrahydrofuran-2-yl)indolin-2-one (6b). Yield: 76%, 90 mg; yellow gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.31 (s, 18 H), 1.61 (br. s., 1 H), 1.71–1.80 (m, 1 H), 1.84–1.92 (m, 1 H), 3.72 (t, J = 6.29 Hz, 2 H), 4.72 (t, J = 7.44 Hz, 1 H), 5.09 (s, 1 H), 6.75 (d, J = 8.01 Hz, 1 H), 7.14–7.19 (m, 1 H), 7.25 (s, 2 H), 7.41 (br. s., 1 H), 8.67 (br. s., 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 25.9, 27.6, 30.2, 34.5, 60.1, 69.2, 83.2, 110.5, 124.1, 127.5, 127.7, 128.0, 128.1, 132.6, 135.5, 139.9, 153.2, 179.1; **HRMS** (ESI) calculated for $C_{26}H_{33}O_3NCl$ $[M + H]^+$: 442.2143, found: 442.2138.

5-Bromo-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl)indolin-2-one (6c). Yield: 72%, 84 mg; yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.31 (s, 59 H), 1.45–1.98 (m, 13 H), 3.47–3.80 (m, 6 H), 4.72 (dd, J = 8.53, 6.25 Hz, 2 H), 5.10 (s, 2 H), 6.75 (d, J = 8.34 Hz, 3 H), 7.01–7.32 (m, 9 H), 7.40 (d, J = 2.02 Hz, 3 H), 8.80 (s, 2 H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 25.9, 27.6, 30.2, 34.5, 60.1, 69.2, 83.2, 111.0, 115.0, 124.1, 128.0, 130.3, 131.0, 132.9, 135.5, 140.4, 153.2, 179.1; **HRMS** (ESI) calculated for $C_{26}H_{33}O_3NBr$ $[M + H]^+$: 486.1638, found: 486.1634.

1-Benzyl-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl)indolin-2-one (6d). Yield: 82%, 95 mg; red gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.33–1.44 (m, 18 H), 1.69–1.84 (m, 2 H), 2.05 (q, J = 7.28 Hz, 2 H), 3.41–3.57 (m, 1 H), 3.62–3.76 (m, 1 H), 4.82–5.08 (m, 3 H), 5.15 (s, 1 H), 6.70 (d, J = 7.71 Hz, 1 H), 6.94–7.10 (m, 1 H), 7.11–7.36 (m, 8 H), 7.36–7.48 (m, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 26.0, 27.6, 30.3, 34.5, 43.7, 59.6, 68.7, 83.6, 109.1, 121.7, 124.5, 125.9, 127.0, 127.2, 128.0, 128.6, 130.5, 135.4, 136.0, 143.7, 153.0, 178.0; **HRMS** (ESI) calculated for $C_{33}H_{40}O_3N$ $[M + H]^+$: 498.3003, found: 498.2999.

1-Allyl-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl)indolin-2-one (6e). Yield: 81%, 96 mg; red gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.41 (s, 19 H), 1.73 (dd, J = 12.78, 6.29 Hz, 1 H), 1.78–1.85 (m, 1 H), 2.00–2.08 (m, 2 H), 3.44–3.52 (m, 1 H), 3.67 (td, J = 7.63, 5.72 Hz, 1 H), 4.33–4.46 (m, 2 H), 4.86 (t, J = 7.63 Hz, 1 H), 5.15 (s, 1 H), 5.16–5.21 (m, 1 H), 5.21–5.29 (m, 1 H), 5.74–5.96 (m, 1 H), 6.78–6.90 (m, 1 H), 7.01–7.14 (m, 1 H), 7.27–7.30 (m, 1 H), 7.30–7.33 (m, 1 H), 7.33–7.39 (m, 2 H), 7.47 (d, J = 6.87 Hz, 1 H); **^{13}C NMR** (126 MHz, MHz, $CDCl_3$) δ: 25.9, 27.6, 30.3, 34.5, 42.2, 59.5, 68.8, 83.7, 109.0, 116.9, 121.6, 124.4, 126.0, 127.9, 128.0, 130.3, 131.3, 135.4, 143.8, 152.9, 177.6; **HRMS** (ESI) calculated for $C_{29}H_{38}O_3N$ $[M + H]^+$: 448.2846, found: 448.2841.

1-Allyl-5-chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl)indolin-2-one (6f). Yield: 78%, 91 mg; brownish-red gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.23–1.37 (m, 17 H), 1.59–1.76 (m, 1 H), 1.81–2.20 (m, 1 H), 3.34–3.53 (m, 1 H), 3.55–3.73 (m, 1 H), 4.18–4.31 (m, 1 H), 4.59–4.78 (m, 1 H), 4.97–5.13 (m, 2 H), 5.14–5.24 (m, 1 H), 6.57–6.77 (m, 1 H), 7.09–7.25 (m, 3 H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 25.9, 27.6, 30.2, 34.5, 42.3, 59.4, 69.1, 76.4, 77.6, 83.4, 109.6, 117.6, 124.0, 127.1, 127.7, 127.9, 128.4, 131.1, 132.3, 135.5, 141.9, 153.2,

176.3; **HRMS** (ESI) calculated for $C_{29}H_{36}O_3NClNa$ $[M + Na]^+$: 504.2276, found: 504.2260.

1-Allyl-5-bromo-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl)indolin-2-one (6g). Yield: 75%, 86 mg; brownish-red gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.32 (s, 18 H), 1.54 (m, 1 H), 1.63 (m, 1 H), 1.75 (m, 1 H), 1.83 (m, 1 H), 3.70 (m, 2 H), 4.18 (m, 1 H), 4.30 (m, 1 H), 4.73 (dd, J = 8.58, 6.29 Hz, 1 H), 5.07 (s, 1 H), 5.13 (m, 2 H), 5.72 (ddt, J = 17.36, 10.20, 5.10, 5.10 Hz, 1 H), 6.66 (d, J = 8.01 Hz, 1 H), 7.23 (s, 2 H), 7.33 (dd, J = 8.20, 2.10 Hz, 1 H), 7.57 (d, J = 1.91 Hz, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 26.0, 27.6, 30.2, 34.5, 42.3, 59.4, 69.1, 83.5, 110.1, 115.1, 117.6, 124.1, 128.4, 129.9, 130.8, 131.1, 132.7, 135.6, 142.4, 153.2, 176.2; **HRMS** (ESI) calculated for $C_{29}H_{37}O_3NBr$ $[M + H]^+$: 526.1951, found: 526.1951.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-methyl-3-(tetrahydrofuran-2-yl)indolin-2-one (6h). Yield: 76%, 91 mg; brownish gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.40 (s, 18 H), 1.65–1.84 (m, 3 H), 1.91–2.08 (m, 2 H), 2.36 (s, 3 H), 3.45–3.64 (m, 1 H), 3.64–3.78 (m, 1 H), 4.82 (t, J = 7.33 Hz, 1 H), 5.15 (s, 1 H), 6.81 (d, J = 7.83 Hz, 1 H), 7.05 (d, J = 7.83 Hz, 1 H), 7.22 (s, 1 H), 7.34 (s, 2 H), 8.38 (s, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 21.3, 25.9, 27.5, 30.2, 34.5, 59.9, 68.9, 83.5, 109.6, 124.5, 127.0, 127.8, 128.3, 130.9, 135.3, 139.2, 152.9, 179.9; **HRMS** (ESI) calculated for $C_{27}H_{36}O_3N$ $[M + H]^+$: 422.2690, found: 422.2688.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1,5-dimethyl-3-(tetrahydrofuran-2-yl)indolin-2-one (6i). Yield: 78%, 93 mg; red gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.40 (s, 19 H), 1.65–1.83 (m, 3 H), 1.90–2.03 (m, 2 H), 2.39 (s, 3 H), 3.21 (s, 3 H), 3.43–3.60 (m, 1 H), 3.62–3.75 (m, 1 H), 4.78 (t, J = 7.44 Hz, 1 H), 5.13 (s, 1 H), 6.76 (d, J = 7.94 Hz, 1 H), 7.13 (d, J = 7.83 Hz, 1 H), 7.30 (s, 1 H), 7.38 (s, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 21.3, 25.9, 26.4, 27.6, 30.3, 34.5, 59.4, 68.9, 83.8, 107.8, 124.5, 127.0, 127.7, 128.3, 130.1, 130.9, 135.2, 142.3, 152.9, 177.7; **HRMS** (ESI) calculated for $C_{28}H_{38}O_3N$ $[M + H]^+$: 436.2846, found: 436.2842.

5-Chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(1,4-dioxan-2-yl)indolin-2-one (6j). Yield: 56%, 46 mg; yellow gummy oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.35 (s, 18 H), 3.54 (d, J = 7.93 Hz, 2 H), 3.65–3.67 (m, 2 H), 3.76 (d, J = 8.54 Hz, 2 H), 4.47–4.58 (m, 1 H), 4.74–4.92 (m, 1 H), 6.82–6.92 (m, 1 H), 7.22–7.39 (m, 4 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 32.6, 36.5, 65.8, 66.3, 66.9, 67.6, 68.6, 99.8, 111.0, 125.9, 126.7, 127.4, 128.5, 128.9, 143.9, 152.5, 178.6; **HRMS** (ESI) calculated for $C_{26}H_{32}ClNO_4$ $[M + H]^+$: 458.2093, found: 458.2082.

1-Allyl-5-bromo-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(tetrahydro-2*H*-pyran-2-yl)indolin-2-one (6k). Yield: 62%, 79 mg; yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.30–1.39 (m, 18 H), 1.45 (d, J = 3.21 Hz, 2 H), 1.47–1.52 (m, 3 H), 1.54–1.58 (m, 2 H), 3.83 (br. s., 1 H), 3.89–4.03 (m, 1 H), 4.12–4.19 (m, 1 H), 4.19–4.31 (m, 1 H), 4.38–4.50 (m, 1 H), 5.10–5.21 (m, 2 H), 5.68–5.83 (m, 1 H), 6.70 (d, J = 8.24 Hz, 1 H), 7.24 (d, J = 9.62 Hz, 2 H), 7.38–7.46 (m, 1 H), 7.53 (d, J = 2.29 Hz, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 14.1, 25.7, 27.3, 30.2, 34.5, 42.2, 60.6, 80.4, 110.4, 114.1, 124.2, 126.2, 129.8, 130.7, 131.8, 135.6, 143.1, 153.1, 177.6; **HRMS** (ESI) calculated for $C_{30}H_{38}BrNO_3$ $[M + H]^+$: 542.1724, found: 540.2075.

1-Allyl-5-chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(tetrahydro-2*H*-pyran-2-yl)indolin-2-one (6l). Yield: 68%, 64 mg; brown gummy oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.37 (s, 19 H), 1.43–1.47 (m, 3 H), 1.49 (dd, J = 4.58, 2.75 Hz, 2 H), 1.53–1.58 (m, 3 H), 3.82 (br. s., 1 H), 3.89–4.05 (m, 2 H), 4.07–4.14 (m, 2 H), 4.24 (dd, J = 9.62, 2.75 Hz, 1 H), 4.38–4.49 (m, 1 H), 5.10–5.22 (m, 3 H), 5.72–5.82 (m, 1 H), 6.73 (d, J = 8.70 Hz, 1 H), 7.21–7.28 (m, 3 H), 7.39 (d, J = 2.29 Hz, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 23.3, 23.9, 25.7, 27.3, 30.2, 30.2, 31.6, 34.5, 60.6, 80.4, 109.8, 124.1, 124.2, 126.3, 126.8, 127.0, 127.0, 131.4, 135.6, 142.6, 153.1, 177.7; **HRMS** (ESI) calculated for $C_{30}H_{38}ClNO_3$ $[M + H]^+$: 496.2249, found: 496.2609.

General experimental procedure for synthesis of substituted triaryl methyl ethers

$K_2S_2O_8$ (0.3 mmol), sodium acetate (0.3 mmol) and $TBACl{\cdot}H_2O$ (0.4 mmol) were added to a 25 mL round bottom flask containing fuchsones (0.1 mmol) in THF (3 mL). Then the reaction mixture was refluxed at 110 °C under a nitrogen atmosphere for 1 h. After completion of the reaction (as determined by TLC analysis), the resulting mixture was cooled to room temperature and concentrated *in vacuo*. The formed residue was extracted with ethyl acetate (3 × 3 mL) and washed with brine (20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated *in vacuo*. The crude products were purified by flash chromatography (silica gel 100–200 mesh) using petroleum ether/ethyl acetate (v/v, 98 : 2) to give the substituted triaryl methyl ethers with high purity.

4-(Bis(4-methoxyphenyl)(tetrahydrofuran-2-yl)methyl)-2,6-di-*tert*-butylphenol (6p). Yield: 64%, 74 mg; yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.33 (s, 19 H), 1.61–1.79 (m, 3 H), 1.94–2.28 (m, 1 H), 3.54–3.72 (m, 2 H), 3.78 (d, J = 2.40 Hz, 6 H), 5.06 (s, 1 H), 5.32 (dd, J = 7.71, 5.94 Hz, 1 H), 6.73–6.77 (m, 2 H), 6.78–6.80 (m, 2 H), 7.02 (s, 1 H), 7.15–7.27 (m, 5 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 26.0, 29.4, 30.4, 34.4, 55.1, 55.1, 59.8, 68.3, 83.2, 112.5, 112.7, 127.1, 130.6, 131.3, 134.1, 151.6, 157.2, 157.4; **HRMS** (ESI) calculated for $C_{33}H_{43}O_4$ $[M + H]^+$: 503.2158, found: 503.2153.

2,6-Di-*tert*-butyl-4-((4fluorophenyl)(phenyl)(tetrahydrofuran-2-yl)methyl)phenol (6q). Yield: 72%, 85 mg; yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.33 (d, J = 1.14 Hz, 18 H), 1.53–1.82 (m, 4 H), 2.11–2.25 (m, 1 H), 3.33–3.71 (m, 2 H), 4.85–5.15 (m, 1 H), 5.20–5.53 (m, 1 H), 6.78–7.08 (m, 4 H), 7.19–7.42 (m, 7 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 26.0, 29.4, 30.4, 60.6, 68.4, 83.0–83.1 (d, J = 10.02 Hz), 113.8, 114.0–114.2 (d, J = 21.58 Hz), 125.8–125.9 (d, J = 15.41 Hz), 127.0–127.2 (d, J = 16.18 Hz), 127.3, 127.6, 129.5, 130.3, 131.3–131.3 (d, J = 6.97 Hz), 131.9, 134.3–134.3 (d, J = 3.08 Hz), 151.9–151.9 (J = 3.08 Hz), 159.6–159.9 (d, J = 23.12 Hz), 162.1–162.3 (d, J = 22.35 Hz); **HRMS** (ESI) calculated for $C_{31}H_{38}O_2F$ $[M + H]^+$: 461.2850, found: 461.2848.

General experimental procedure for the synthesis of substituted diaryl methyl ethers

$K_2S_2O_8$ (0.3 mmol), sodium acetate (0.3 mmol) and $TBACl{\cdot}H_2O$ (0.4 mmol) were added to a 25 mL round bottom flask contain-

ing *p*-QMs (0.1 mmol) in THF (3 mL). Then the reaction mixture was refluxed at 110 °C under a nitrogen atmosphere for 1 h. After completion of the reaction (as determined by TLC analysis), the resulting mixture was cooled to room temperature and concentrated *in vacuo*. The formed residue was extracted with ethyl acetate (3 × 3 mL) and washed with brine (20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (silica gel 100–200 mesh) using petroleum ether/ethyl acetate (v/v, 98 : 2) to give diaryl methyl ethers with high purity.

2,6-Di-*tert*-butyl-4-(phenyl(tetrahydrofuran-2-yl)methyl)phenol (8a). Yield: 85%, 105 mg; yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.33 (d, J = 2.15 Hz, 18 H), 1.60–1.85 (m, 4 H), 3.65–3.84 (m, 3 H), 4.47 (dd, J = 5.87, 2.08 Hz, 1 H), 4.95 (d, J = 2.65 Hz, 1 H), 6.97 (s, 1 H), 7.08 (s, 1 H), 7.14–7.35 (m, 5 H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 25.7, 30.3, 30.9 and 31.0, 34.3, 56.9 and 57.1, 68.3, 81.7 and 81.9, 124.7 and 125.0, 126.0, 128.2 and 128.3, 128.4, 133.0, 133.5 and 135.2 and 135.5, 143.4, 152.1; **HRMS** (ESI) calculated for $C_{25}H_{35}O_2$ $[M + H]^+$: 367.2632, found: 367.2629.

2,6-Di-*tert*-butyl-4-((tetrahydrofuran-2-yl)(*p*-tolyl)methyl)phenol (8b). Yield: 82%, 82 mg; yellow gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.40 (d, J = 4.58 Hz, 19 H), 1.49–1.54 (m, 1 H), 1.71–1.91 (m, 3 H), 2.21–2.33 (m, 3 H), 3.72–3.79 (m, 2 H), 3.82–3.88 (m, 1 H), 4.45–4.59 (m, 1 H), 4.99 (d, J = 7.25 Hz, 1 H), 7.00–7.12 (m, 3 H), 7.12–7.20 (m, 2 H), 7.20–7.28 (m, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 21.0 and 21.0, 25.7 and 25.7, 30.4, 30.9 and 31.0, 34.3 and 34.3, 56.6 and 56.8, 68.3, 81.9 and 82.1, 124.7 and 124.9, 128.2, 129.0, 133.3 and 133.7, 135.2, 135.4 and 135.5, 140.5 and 140.8, 152.1; **HRMS** (ESI) calculated for $C_{26}H_{37}O_2$ $[M + H]^+$: 381.2788, found: 381.2784.

2,6-Di-*tert*-butyl-4-((4-methoxyphenyl)(tetrahydrofuran-2-yl)methyl)phenol (8c). Yield: 83%, 83 mg; yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.40 (s, 18 H), 1.61–1.94 (m, 4 H), 3.73–3.79 (m, 5 H), 3.83–3.93 (m, 1 H), 4.46 (dd, J = 7.96, 5.81 Hz, 1 H), 4.90–5.02 (m, 1 H), 6.72–6.83 (m, 2 H), 7.05–7.12 (m, 2 H), 7.13–7.28 (m, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 25.8, 30.5, 30.9, 34.4, 55.0, 56.0, 68.2, 81.9, 113.7, 113.9, 125.0, 129.3, 129.4, 133.4, 135.1, 136.0, 152.1, 157.9; **HRMS** (ESI) calculated for $C_{26}H_{36}O_3Na$ $[M + Na]^+$: 419.2557, found: 419.2549.

2,6-Di-*tert*-butyl-4-((4-fluorophenyl)(tetrahydrofuran-2-yl)methyl)phenol (8d). Yield: 75%, 92 mg; reddish gummy oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.32 (d, J = 4.27 Hz, 18 H), 1.54–1.84 (m, 4 H), 3.66–3.80 (m, 3 H), 4.29–4.51 (m, 1 H), 4.97 (d, J = 4.88 Hz, 1 H), 6.87 (q, J = 8.54 Hz, 2 H), 6.93 (s, 1 H), 7.04 (s, 1 H), 7.16 (dd, J = 8.24, 5.80 Hz, 1 H), 7.23 (dd, J = 8.24, 5.80 Hz, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 25.7, 30.3, 30.7, 31.0, 34.3, 55.9–56.2 (d, J = 29.28 Hz), 68.3–68.3 (d, J = 4.62 Hz), 81.7–81.9 (d, J = 23.12 Hz), 114.8–114.9 (d, J = 7.71 Hz), 115.0–115.1 (d, J = 7.71 Hz), 124.7, 125.0, 129.7–129.8 (d, J = 4.63 Hz), 129.8–129.9 (d, J = 5.39 Hz), 132.7–133.3 (d, J = 61.65 Hz), 135.3–135.6 (d, J = 30.83 Hz), 139.5–139.5 (d, J = 36.99 Hz), 152.2–152.2 (d, J = 3.85 Hz), 160.1–162.5 (d, J = 243.52 Hz) 139.5–139.5 (d, J = 36.99 Hz), 152.2–152.2 (d, J = 3.85 Hz), 160.1–162.5 (d, J = 243.52 Hz); **HRMS** (ESI) calculated for $C_{25}H_{33}O_2FNa$ $[M + Na]^+$: 407.2357, found: 407.2353.

2,6-Di-*tert*-butyl-4-((4-nitrophenyl)(tetrahydrofuran-2-yl)methyl)phenol (8e). Yield: 60%, 72 mg; reddish gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.41 (d, J = 1.52 Hz, 18 H), 1.58–1.69 (m, 1 H), 1.70–1.99 (m, 3 H), 3.72–4.05 (m, 3 H), 4.48–4.65 (m, 1 H), 5.12 (d, J = 2.02 Hz, 1 H), 7.00 (s, 1 H), 7.12 (s, 1 H), 7.51 (t, J = 8.08 Hz, 2 H), 8.15 (dd, J = 8.72, 3.41 Hz, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 25.6 and 25.7, 30.3, 30.5 and 31.1, 34.3, 56.3 and 57.0, 68.4, 81.0 and 81.4, 123.5 and 123.6, 124.7 and 125.3, 129.3, 131.0 and 131.9, 135.7 and 136.0, 146.3, 151.4 and 151.5, 152.7; **HRMS** (ESI) calculated for $C_{25}H_{33}O_4NNa$ $[M + Na]^+$: 434.2302, found: 434.2298.

2,6-Di-*tert*-butyl-4-((3-chlorophenyl)(tetrahydrofuran-2-yl)methyl)phenol (8f). Yield: 78%, 95 mg; yellow gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.23–1.36 (m, 19 H), 1.42–1.51 (m, 1 H), 1.62–1.81 (m, 3 H), 3.66–3.79 (m, 3 H), 4.35–4.47 (m, 1 H), 4.92–5.00 (m, 1 H), 6.90–6.94 (m, 1 H), 7.02–7.06 (m, 2 H), 7.07–7.23 (m, 3 H), 7.23–7.28 (m, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 25.6, 30.3, 30.3 and 30.7, 31.0, 34.3, 56.5 and 56.8, 68.3 and 68.4, 81.4 and 81.6, 124.7 and 125.1, 126.2 and 126.3, 126.5, 128.6 and 128.8, 129.4 and 129.5, 132.1 and 132.8, 133.9 and 134.0, 135.4 and 135.7, 145.5, 145.8, 152.3 and 152.4; **HRMS** (ESI) calculated for $C_{25}H_{33}O_2ClNa$ $[M + Na]^+$: 423.2061, found: 423.2059.

2,6-Di-*tert*-butyl-4-((3-nitrophenyl)(tetrahydrofuran-2-yl)methyl)phenol (8g). Yield: 64%, 77 mg; reddish gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.40–1.46 (m, 18 H), 1.65–1.76 (m, 1 H), 1.76–1.99 (m, 3 H), 3.75–4.04 (m, 3 H), 4.48–4.69 (m, 1 H), 5.13 (s, 1 H), 7.04 (s, 1 H), 7.16 (s, 1 H), 7.39–7.53 (m, 1 H), 7.64–7.77 (m, 1 H), 7.99–8.11 (m, 1 H), 8.25 (d, J = 8.08 Hz, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 25.6 and 25.7, 30.2 and 30.3, 30.5 and 31.1, 34.3, 56.1 and 56.7, 68.4, 81.1 and 81.5, 121.2 and 121.2, 123.4 and 123.5, 124.6 and 125.3, 129.0 and 129.1, 131.1, 132.0, 134.7 and 134.8, 135.6, 136.0, 145.7 and 145.8, 148.2, 152.6 and 152.6; **HRMS** (ESI) calculated for $C_{25}H_{33}O_4NNa$ $[M + Na]^+$: 434.2302, found: 434.2299.

4-((2-Bromophenyl)(tetrahydrofuran-2-yl)methyl)-2,6-di-*tert*-butylphenol (8h). Yield: 63%, 75 mg; yellow gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.45 (br. s., 18 H), 1.88 (br. s., 3 H), 3.78–3.88 (m, 1 H), 3.88–3.94 (m, 1 H), 4.50 (d, J = 8.01 Hz, 1 H), 4.65 (br. s., 1 H), 5.07 (br. s., 1 H), 7.04 (br. s., 1 H), 7.28 (br. s., 3 H), 7.47 (dd, J = 4.01, 2.10 Hz, 1 H), 7.54–7.58 (m, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 25.7, 30.3, 30.6, 34.3, 54.0, 68.5, 81.6, 124.9, 125.2, 127.5, 127.6, 129.3, 131.9, 132.9, 135.1, 143.2, 152.3; **HRMS** (ESI) calculated for $C_{25}H_{33}O_2BrNa$ $[M + Na]^+$: 467.1556, found: 467.1554.

2,6-Di-*tert*-butyl-4-((2-chlorophenyl)(tetrahydrofuran-2-yl)methyl)phenol (8i). Yield: 68%, 82 mg; yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.40 (d, J = 2.53 Hz, 18 H), 1.50–1.73 (m, 2 H), 1.73–2.05 (m, 3 H), 3.70–3.94 (m, 2 H), 4.34–4.51 (m, 1 H), 4.52–4.70 (m, 1 H), 5.03 (d, J = 2.91 Hz, 1 H), 7.02–7.17 (m, 2 H), 7.17–7.24 (m, 2 H), 7.28–7.36 (m, 1 H), 7.40–7.68 (m, 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 25.7, 30.3, 30.6 and 30.9, 34.3, 51.5 and 52.1, 68.4, 81.3 and 81.6, 125.1 and 125.3, 126.6, 126.9 and 127.1, 128.7, 129.3 and 129.6, 131.8 and 132.0, 133.7, 135.2 and 135.4, 140.8, 141.6, 152.3; **HRMS** (ESI) calculated for $C_{25}H_{33}O_2ClNa$ $[M + Na]^+$: 423.2061, found: 423.2057.

2,6-Di-*tert*-butyl-4-((3,4-dichlorophenyl)(tetrahydrofuran-2-yl)methyl)phenol (8j). Yield: 72%, 86 mg; yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.32–1.37 (m, 19 H), 1.64–1.89 (m, 3 H), 3.59–3.84 (m, 3 H), 4.32–4.47 (m, 1 H), 5.01 (s, 1 H), 6.91 (s, 2 H), 7.09–7.22 (m, 1 H), 7.24–7.33 (m, 1 H), 7.36 (d, J = 2.02 Hz, 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 25.7, 30.3, 31.1, 34.3, 56.3, 68.4, 81.6, 124.6, 127.8, 130.1, 130.6, 132.4, 135.9, 143.9, 152.5; **HRMS** (ESI) calculated for $C_{25}H_{32}O_2C_{l2}Na$ $[M + Na]^+$: 457.1672, found: 457.1670.

2,6-Di-*tert*-butyl-4((3,4-dimethoxyphenyl)(tetrahydrofuran-2-yl)methyl)phenol (8k). Yield: 67%, 80 mg; yellow gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.42 (s, 19 H), 1.71–1.95 (m, 4 H), 3.71–3.82 (m, 2 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 3.96 (dd, J = 5.12, 3.47 Hz, 1 H), 4.50 (td, J = 8.15, 5.81 Hz, 1 H), 5.05 (s, 1 H), 6.78–6.86 (m, 1 H), 6.89–6.99 (m, 2 H), 7.07 (s, 2 H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 25.7, 30.1, 31.0, 34.3, 55.7, 55.7, 56.6, 68.3, 82.2, 111.0, 111.9, 120.3, 124.6, 133.6, 135.5, 136.0, 147.3, 148.5, 152.1; **HRMS** (ESI) calculated for $C_{27}H_{39}O_4[M + Na]^+$: 427.2843, found: 427.2832.

2,6-Di-*tert*-butyl-4-(pyren-1-yl(tetrahydrofuran-2-yl)methyl)phenol (8l). Yield: 62%, 72 mg; red gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.39 (d, J = 3.16 Hz, 19 H), 1.67–2.18 (m, 5 H), 3.79–4.02 (m, 2 H), 4.93 (br. s., 1 H), 5.01 (s, 1 H), 5.02–5.11 (m, 1 H), 7.21 (s, 1 H), 7.35 (s, 1 H), 7.91–8.34 (m, 9 H), 8.47–8.76 (m, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 25.8 and 25.9, 30.3 and 30.3, 31.1 and 31.3, 34.3 and 34.3, 51.1 and 51.8, 68.5, 82.0 and 82.5, 123.3 and 123.5, 124.5 and 124.6, 124.8 and 124.9, 125.0 and 125.0, 125.1 and 125.2, 125.6, 125.8 and 125.8, 126.6, 126.8, 127.1, 127.4 and 127.4, 127.6, 128.7 and 129.2, 129.5 and 129.7, 130.7 and 130.8, 131.4 and 131.4, 133.3 and 133.4, 135.3, 135.5, 137.3 and 138.1, 152.1 and 152.1; **HRMS** (ESI) calculated for $C_{35}H_{39}O_2$ $[M + H]^+$: 491.2945, found: 491.2935.

2,6-Di-*tert*-butyl-4-(pyridin-3-yl(tetrahydrofuran-2-yl)methyl)phenol (8m). Yield: 64%, 79 mg; red gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.28–1.38 (m, 18 H), 1.58–1.92 (m, 4 H), 3.66–3.85 (m, 3 H), 4.45 (dd, J = 7.52, 6.00 Hz, 1 H), 5.03 (br. s., 1 H), 7.00–7.09 (m, 2 H), 7.12–7.22 (m, 1 H), 7.56 (dt, J = 7.83, 1.96 Hz, 1 H), 8.35 (d, J = 3.16 Hz, 1 H), 8.44–8.57 (m, 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 25.7, 30.3, 30.6, 34.3, 54.2, 68.3, 81.2, 123.3, 125.1, 131.6, 135.7, 135.8, 139.2, 147.4, 149.9, 152.5; **HRMS** (ESI) calculated for $C_{24}H_{34}O_2N$ $[M + H]^+$: 368.2584, found: 368.2582.

4-((5-Bromothiophen-2-yl)(tetrahydrofuran-2-yl)methyl)-2,6-di-*tert*-butylphenol (8n). Yield: 71%, 84 mg; reddish gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.44 (s, 18 H), 1.63–1.92 (m, 4 H), 3.70–3.97 (m, 2 H), 4.13 (d, J = 6.19 Hz, 1 H), 4.25–4.47 (m, 1 H), 5.12 (s, 1 H), 6.58 (d, J = 3.66 Hz, 1 H), 6.84 (d, J = 3.79 Hz, 1 H), 7.13 (s, 2 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 25.9, 29.6, 30.4, 34.4, 52.4, 68.4, 82.2, 110.4, 125.2, 125.3, 128.9, 131.1, 135.6, 148.3, 152.7; **HRMS** (ESI) calculated for $C_{23}H_{31}O_2BrNaS$ $[M + Na]^+$: 473.1120, found: 473.1121.

2,6-Di-*tert*-butyl-4-(furan-2-yl(tetrahydrofuran-2-yl)methyl)phenol (8o). Yield: 68%, 68 mg; red gummy oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.42 (s, 18 H), 1.67–1.93 (m, 4 H), 3.75–3.98 (m, 3 H), 4.32–4.52 (m, 1 H), 5.08 (s, 1 H), 6.22 (d, J = 3.16 Hz, 1 H), 6.30–6.38 (m, 1 H), 7.05 (s, 2 H), 7.35 (s, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 25.6, 29.7, 30.3, 34.3, 50.7, 68.5, 81.5, 106.0, 110.1, 124.9, 130.6, 135.6, 141.1, 152.6, 156.4; **HRMS** (ESI) calculated for $C_{23}H_{32}O_3Na$ $[M + Na]^+$: 379.2244, found: 379.2241.

General procedure for dihydroxylation of alkene 9

NMO (7.5 mmol) and OsO_4 (0.1 mol%) were added to the solution of olefin (5 mmol) in acetone (2 mL) and water (2 mL) at 25 °C. The reaction mixture was stirred for 2 h at room temperature and then quenched with saturated aqueous $Na_2S_2O_4$. The biphasic reaction mixture was stirred at 25 °C for another 30 min and then it was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the desired product **9**.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1-(2,3-dihydroxypropyl)-3-(tetrahydrofuran-2-yl)indolin-2-one (9). Yield: 76%, 41 mg; yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.40 (s, 18 H), 1.69–1.77 (m, 1 H), 1.80–1.85 (m, 1 H), 1.88–1.94 (m, 1 H), 2.07 (s, 1 H), 2.20 (s, 1 H), 2.66 (s, 1 H), 3.57–3.65 (m, 2 H), 3.72–3.80 (m, 3 H), 3.99 (br. s., 2 H), 4.82 (br. s., 1 H), 5.17 (br. s., 1 H), 7.05 (t, J = 8.77 Hz, 1 H), 7.16 (t, J = 7.06 Hz, 1 H), 7.33–7.38 (m, 3 H), 7.56 (d, J = 6.49 Hz, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 25.9 and 26.0, 27.5 and 27.6, 29.2 and 29.4, 29.7, 30.2, 34.5, 42.1 and 42.6, 53.8, 59.2, 63.0 and 63.3, 69.0, 69.3, 69.5, 70.0, 83.9 and 84.0, 108.5 and 108.7, 122.8, 124.1, 126.6, 128.1 and 128.3, 130.6, 135.5, 143.1, 153.1, 178.8 and 179.0; **HRMS** (ESI) calculated for $C_{29}H_{40}O_5N$ $[M + H]^+$: 482.2901, found: 482.2899.

General procedure for mono dealkylation 10

Anhydrous $AlCl_3$ (3 equiv.) was stirred in dry toluene under a nitrogen atmosphere at room temperature in a 50 mL dry round bottom flask, and then compound **6d** (50 mg, 1 equiv.) in toluene was added, and stirring was continued for another 1 h. After completion of the reaction (as determined by TLC), the reaction was quenched with ice cold water. Then the reaction mixture was extracted with ethyl acetate (3 × 15 mL) and the combined layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude product was further purified by flash chromatography to afford the desired product **10** in 60% yield.

1-Benzyl-3-(3-(*tert*-butyl)-4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl)indolin-2-one (10). Yield: 60%, 26 mg; colourless gummy oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.26 (s, 9 H), 1.65 (dt, J = 12.87, 6.34 Hz, 1 H), 1.70–1.82 (m, 1 H), 1.89–2.02 (m, 2 H), 3.40 (q, J = 7.25 Hz, 1 H), 3.61 (q, J = 6.99 Hz, 1 H), 4.78–4.91 (m, 2 H), 4.96 (d, J = 15.64 Hz, 1 H), 5.23 (br. s., 1 H), 6.46 (d, J = 8.01 Hz, 1 H), 6.64 (d, J = 7.63 Hz, 1 H), 6.97 (t, J = 7.63 Hz, 1 H), 7.09–7.17 (m, 3 H), 7.19 (s, 2 H), 7.22 (br. s., 3 H), 7.25 (s, 1 H), 7.34 (d, J = 7.63 Hz, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 26.0, 27.5, 29.5, 34.7, 43.8, 59.5, 68.8, 83.6, 109.3, 116.6, 121.9, 125.9, 126.2, 126.6, 127.0, 127.3, 128.1, 128.6, 129.0, 130.3,

135.8, 135.9, 143.8, 153.7, 178.2; **HRMS** (ESI) calculated for $C_{29}H_{32}O_3N$ $[M + H]^+$: 442.2377, found: 442.2370.

General procedure for di dealkylation 11

Anhydrous $AlCl_3$ (6 equiv.) was stirred in dry toluene under a nitrogen atmosphere at room temperature in a 50 mL dry round bottom flask, and then compound **6d** (50 mg) in toluene was added, and stirring was continued for another 1 h. After completion of the reaction (as determined by TLC), the reaction was quenched with ice cold water. Then the reaction mixture was extracted with ethyl acetate (3 × 15 mL) and the combined layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude product was further purified by flash chromatography to afford the desired product **11** in 58% yield.

Benzyl-3-(4-hydroxyphenyl)-3-(tetrahydrofuran-2-yl)indolin-2-one (11). Yield: 58%, 22 mg; colourless oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.58–1.78 (m, 3 H), 1.97 (d, J = 5.31 Hz, 1 H), 3.31–3.49 (m, 1 H), 3.49–3.74 (m, 1 H), 4.70–5.06 (m, 3 H), 5.83 (br. s., 1 H), 6.50–6.69 (m, 2 H), 6.94–7.39 (m, 10 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 25.9, 27.4, 29.7, 43.8, 59.5, 68.9, 83.4, 109.5, 115.6, 122.1, 125.9, 127.0, 127.3, 128.3, 128.6, 128.8, 128.9, 130.0, 135.6, 143.8, 155.4, 178.4; **HRMS** (ESI) calculated for $C_{25}H_{24}O_3N$ $[M + H]^+$: 386.1751, found: 386.1744.

Conflicts of interest

There are no conflicts to declare.

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Oxidative Radical-Mediated Addition of Ethers to Quinone Imine Ketals: An Access to Hemiaminals

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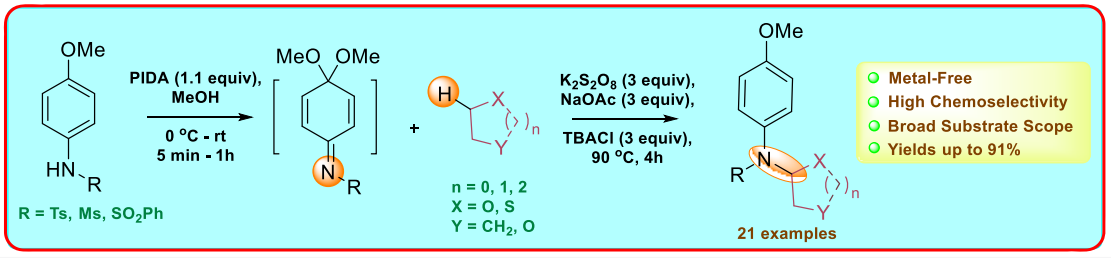

ABSTRACT: The highly regioselective synthesis of substituted hemiaminal *via* addition of ethers to quinone imine ketals (QIKs) has been developed under metal-free conditions. In the presence of tetrabutylammonium chloride and potassium persulfate ($K_2S_2O_8$), QIKs couple efficiently with cyclic and acyclic ethers to give hemiaminals. This strategy offers an easy access to substituted hemiaminal ethers with high functional group tolerance in good to excellent yields.

INTRODUCTION

The construction of C−N bonds has been a major research topic in organic synthesis. Nitrogen-containing frameworks are the backbone of around 25% biologically active compounds and synthetic intermediates. Among the various compounds containing C−N bonds having the hemiaminal moiety represents the core structure in many biologically active natural products and pharmaceutical agents.[1] The typical example that includes Aspidophylline A, an alkaloid from the Apocynaceae family, displays an antiviral activity.[2a,b] However, (−)-physovenine shows anti-cholinergic and miotic activities,[2c] while the indole nitrogen-bearing tetrahydrofuran (THF) ring acts as an HCV inhibitor, as shown in Figure 1.[2d] In particular, hemiaminal ether with sulfonamide as the core structure shows an interesting antitumor activity against the MGC-803 cell line with an IC_{50} value 1.06.[2e] Also, the substituted *N*-sulfonamides were present in a large number of bioactive molecules.[2f] Furthermore, hemiaminal ethers act as key synthons for various organic transformations and also in the synthesis of natural products.[3,4] Due to the increasing importance of hemiaminals in medicinal and synthetic chemistry, various efforts have been made for the development of new methods thereof. Initially, most of the synthetic endeavors to assemble this bioactive core using Pd-mediated reactions.[5] In recent years, there was immense progress made using various metal catalysts such as Cu, Co, Mn, Ru, Ni, and Fe utilized for the synthesis of hemiaminals from diversified N-heterocycles.[6,7] The limited methods were known for the synthesis of hemiaminals under metal-free conditions. Therefore, these metal-free reactions attract much attention of chemists[8a−i] as these are greener and more eco-friendly approaches over metal-catalyzed reactions. Despite the various methods available for the synthesis of hemiaminals, use of costly transition metals and hazardous byproducts formed in these reactions makes our approach more feasible.

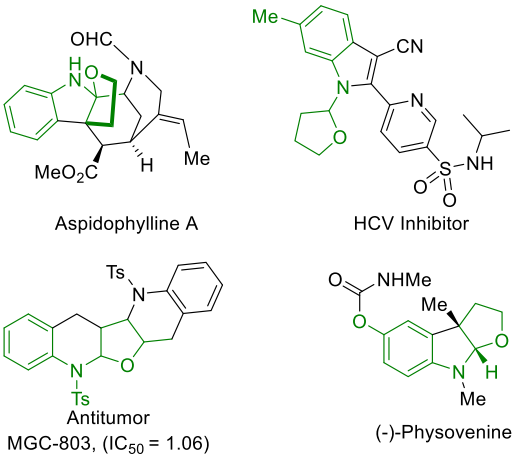

Figure 1. Biologically active cyclic ethers.

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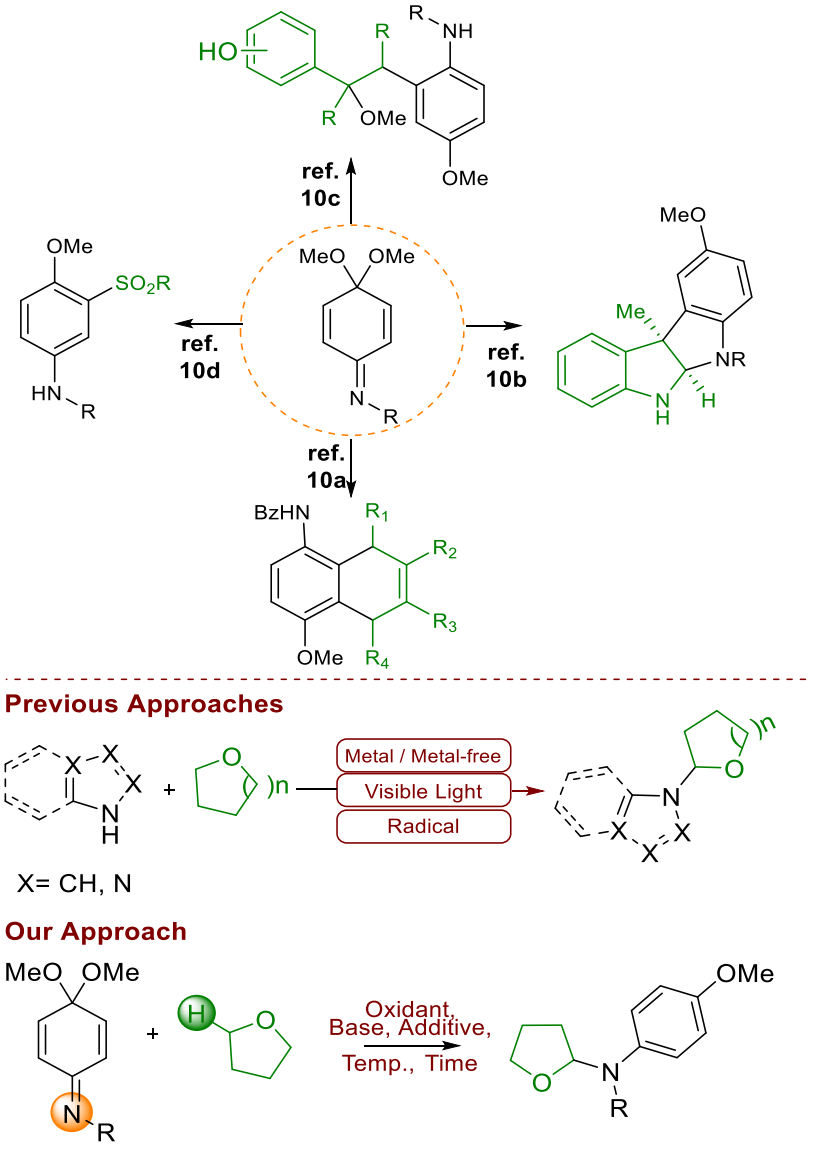
Scheme 1. Utilization of QIK



Recently, quinone imine ketals (QIKs) have emerged extensively as an electrophilic center for a variety of nucleophilic addition reactions, hence making a fascinating target for such addition reactions.[9] In 2001, Banfield and Kerr developed [4 + 2] Diels–Alder reaction of QIKs and diene,[10a] which leads to the formation of the ergot skeleton. In continuation, Zhang and co-workers in 2014 achieved Lewis acid-catalyzed [3 + 2] cycloaddition reaction of 3-methyl-1-indole with QIK.[10b] Further, in 2014, Shi et al. demonstrated an oxidative rearrangement of QIK with styrenes to accomplish the oxyarylation products.[10c] Recently, Mhaske and co-workers achieved C–S bond formation *via* nucleophilic addition of phenyl sodium sulfinate salts on QIK as depicted in Scheme 1.[10d]

QIK as well as related cyclohexadienone motifs served as a useful synthetic intermediate to establish the functionalized aromatic rings as being a highly reactive key synthon and an important intermediate in various reactions.[11] In addition to these advancements, our continuous efforts toward generation and utilization of the α-oxyalkyl radical[12] under metal-free conditions have encouraged us to synthesize hemiaminals from QIK. To the best of our knowledge, herein, for the first time, we demonstrate an efficient radical-mediated C–N bond formation *via* addition of ethers on QIK to accomplish the synthesis of hemiaminals.

RESULTS AND DISCUSSION

We began our investigation using *N*-tosyl QIK **1a′** prepared in situ from *p*-anisidine (**1a**)[10d] employed as a model substrate and THF as a solvent as well as a coupling partner. On the basis of our previous work, we start with $K_2S_2O_8$ as an oxidant, tetrabutylammonium chloride (TBACl) as an additive, and NaOAc as a base in 1 equiv to carry out the reaction at ambient temperature (Table 1). Unfortunately, the desired product **3a** was not observed (entry 1). However, when the reaction temperature was raised up to 90 °C, the desired product **3a** was obtained in 23% within 4 h of reaction time (entry 2). Further, with the increase in equivalents of the reagent, the yield of **3a** was dramatically enhanced from 23 to 91% (entry 4). When the reaction was carried out in the absence of the additive and base, the reaction failed to proceed further, and the starting material remained unreacted (entries

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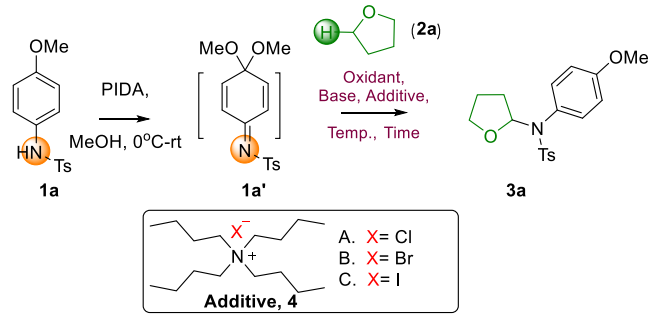
Table 1. Optimization Conditions for Addition of Ethers to QIKs[a]



entry	oxidant (equiv)	additive (equiv)	base (equiv)	temperature (°C)	time (h)	yield (%)[b]
1	$K_2S_2O_8$ (1)	A (1)	NaOAc (1)	RT	24	NR
2	$K_2S_2O_8$ (1)	A (1)	NaOAc (1)	90	4	23
3	$K_2S_2O_8$ (2)	A (2)	NaOAc (2)	90	4	64
4[c]	**$K_2S_2O_8$ (3)**	**A (3)**	**NaOAc (3)**	**90**	**4**	**91**
5	$K_2S_2O_8$ (3)	A (3)		90	24	NR
6	$K_2S_2O_8$ (3)		NaOAc (3)	90	24	NR
7	$K_2S_2O_8$ (3)			90	24	NR
8	$K_2S_2O_8$ (3)	B (3)	NaOAc (3)	90	4−24	trace
9	$K_2S_2O_8$ (3)	C (3)	NaOAc (3)	90	4−24	trace
10	$K_2S_2O_8$ (3)	A (3)	NaOAc (3)	110	4	NR[d]
11	$K_2S_2O_8$ (3)	A (3)	KOAc (3)	90	24	17
12	$K_2S_2O_8$ (3)	A (3)	K_2CO_3 (3)	90	24	NR
13	$K_2S_2O_8$ (3)	A (3)	NaOEt (3)	90	24	37
14	$K_2S_2O_8$ (3)	A (3)	Cs_2CO_3 (3)	90	24	NR
15	$K_2S_2O_8$ (3)	A (3)	NaO^{t}Bu (3)	90	24	NR
16	$K_2S_2O_8$ (3)	A (3)	Bu_4NOH (3)	90	24	NR
17	$Na_2S_2O_8$ (3)	A (3)	NaOAc (3)	90	24	35
18	Oxone (3)	A (3)	NaOAc (3)	90	24	NR
19	TBHP (3)	A (3)	NaOAc (3)	90	24	NR
20	DTBP (3)	A (3)	NaOAc (3)	90	24	trace
21	BPO (3)	A (3)	NaOAc (3)	90	24	NR

[a]Reaction conditions: **1a** (0.36 mmol), **2a** (10 mmol), oxidant, additive, and base. [b]Isolated yields. [c]TBACl in 50% aq solution. [d]Decomposition of **1a′** was observed, NR=no reaction.

5−7). Thus, it is confirmed that the base and additive are essential to initiate the reaction. During optimization, tetrabutylammonium bromide and tetrabutylammonium iodide were used as additives, and **3a** was observed only in a trace amount (entries 8−9). Enhancement in the temperature of the reaction mixture resulted in the decomposition of the staring material (entry 10). Further, screening of various bases using the same oxidant observed no increment in the yields of hemiaminal **3a** (entries 11−16). Moreover, alteration of various oxidants produced discouraging results to deliver the desired product **3a** (entries 17−21). In conclusion, the best optimized reaction condition was preferred as entry 4 in Table 1.

With the optimized reaction conditions in hand, the study of the substrate scope was investigated to justify our approach. Initially, *N*-sulfonates containing QIK (*N*-Ts, *N*-Ms, and *N*−SO_2Ph) subjected to hemiaminal synthesis using our optimized reaction conditions showed the excellent feasibility with various cyclic as well as acyclic ethers, that is, THF, tetrahydropyran, 1,4-dioxane, and 1,2-dimethoxyethane, to deliver the desired products **3a** to **3l** in good to excellent yields (72−91%), and **3a** was performed on a gram scale to obtain 84% yield (0.840 gm) in 6 h, as shown in Scheme 2. Unfortunately, *N*-Ns, *N*-acetyl, *N*-Boc, and *N*-Allyl (entries **3m−3p**) groups did not lead to give the corresponding hemiaminal products. Further, 2-Me THF reacts smoothly with **1a′** under optimized reaction conditions to deliver the corresponding hemiaminal **3q** in 61% yield with a 2:1 diastereomeric ratio. In addition, when tetrahydrothiophene was used as a solvent instead of THF along with QIK, it afforded the corresponding thioether amine **3r** in 86% yield. Unfortunately, when reaction of QIK **1a′** was carried out with *Boc*-protected alkyl amines such as piperidine and pyrrolidine, it failed to give the expected products **3s−3t**.

After the successful approach to synthesize hemiaminals from different *N*-sulfonates, further, we extended the scope of the reaction to study the electronic effect of various substituents containing electron-withdrawing as well as electron-donating groups present on the QIK as shown in Scheme 3. Interestingly, good yields of hemiaminals (entries **5a−5d**), that is, 62−76%, were observed, when electron-donating groups such as −OMe were present at the ortho position of the acetal group. Also, the presence of −Me to the meta position of the acetal group did not affect the reactivity of QIK to give desired hemiaminal **5i** in 78% yield. However, electron-withdrawing groups such as −Br and −Ts groups ortho to acetal of QIK were utilized for C−N bond formation with ethers to give the corresponding hemiaminal **5e** and **5f** in moderate yields compared to electron-donating groups (58% and 76%, respectively). However, $-NO_2$ and $-CO_2$Et-

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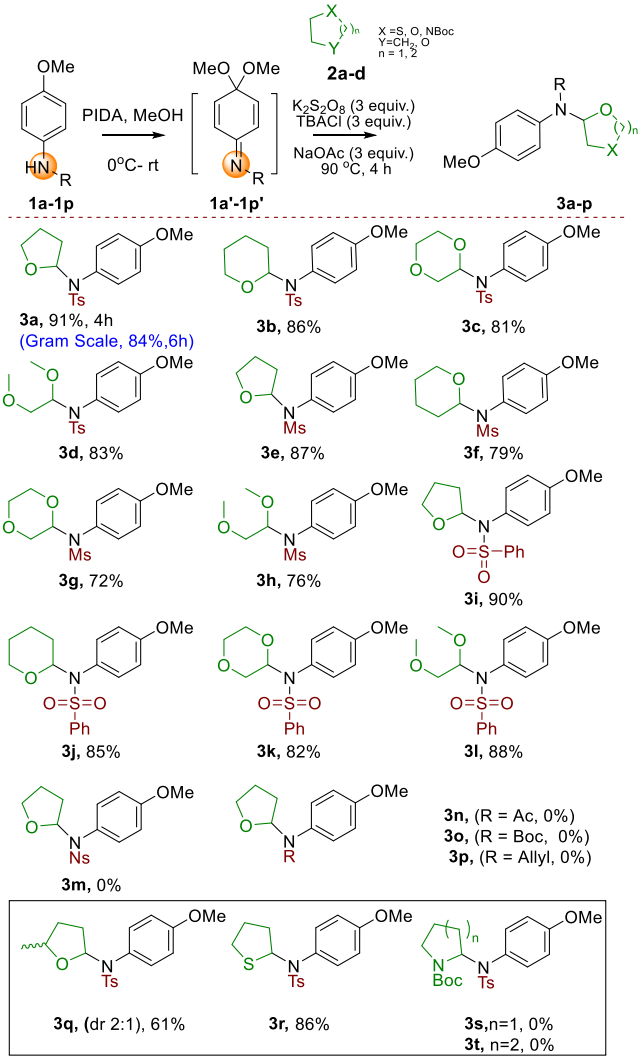
Scheme 2. Substrate Scope for the Synthesis of Hemiaminals[a,b]



[a]Reaction conditions: **1a−p** (0.36 mmol), **2a−d** (3.6 mmol), $K_2S_2O_8$ (1.08 mmol), TBACl (1.08 mmol, 50% in aq soln.), NaOAc (1.08 mmol), 90 °C, 4 h, under air; [b] isolated yields after column chromatographic purification are shown.

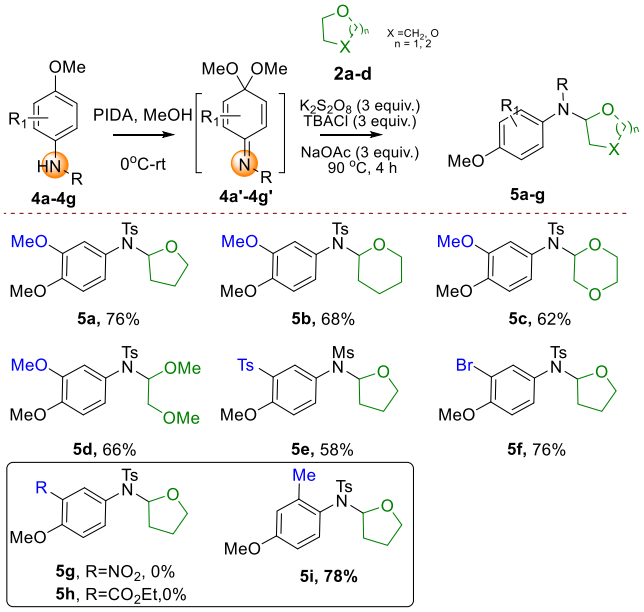
substituted QIK **4g′**and **4h′** failed to afford the corresponding hemiaminal **5g** and **5h**. This might be due to high radical stability of withdrawing groups on QIK which leads to C−N bond cleavage. It is noteworthy that the reaction of electron-donating groups containing QIK is faster than that of the electron-withdrawing groups.

To check the synthetic utility of our formed key product, *N*-(4-methoxyphenyl)-4-methyl-*N*-(tetrahydrofuran-2-yl) benzenesulfonamide **3a** was subjected to reduction reaction using 5 equiv of $NaBH_4$ in EtOH, which undergoes cleavage of the C−O bond to afford amino alcohol **6** in 73% yield, as shown in Scheme 4.[13]

To check the reaction pathway, we carried out few control experiments as shown in Scheme 5. Initially, the reaction of **1a** was carried out under our optimized reaction conditions which failed to give the desired product **3a**, and the starting material was recovered.

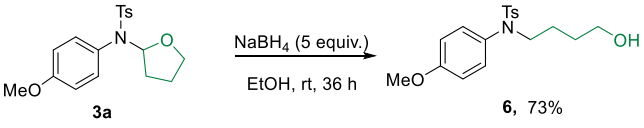
Moreover, to get more insight into the reaction mechanism, some radical scavenging experiments were done, as shown in

Scheme 3. Substrate Scope for the Synthesis of Hemiaminals from Substituted QIKs[a,b]

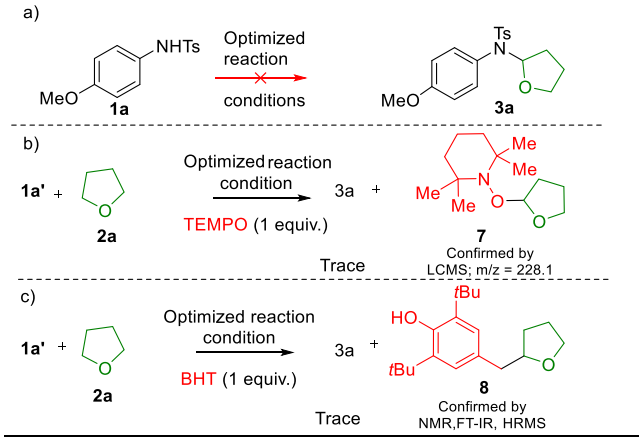


[a]Reaction conditions: **4a−4g** (0.36 mmol), **2a−d** (3.6 mmol), $K_2S_2O_8$ (1.08 mmol), TBACl (1.08 mmol, 50% in aq soln.), NaOAc (1.08 mmol), 90 °C, 4 h, under air; [b] isolated yields after column chromatographic purification are shown.

Scheme 4. Synthetic Transformation of the Formed Product



Scheme 5. Control Experiments



Scheme 5b,c. Initially, the reaction was carried out in the presence of 1 equiv of (2,2,6,6-tetramethylpiperidin-1-yl) oxyl (TEMPO) as a radical scavenger under optimized reaction conditions, and **3a** was formed in trace amounts, whereas the major amount of TEMPO−THF-trapped product **7** was observed. The formed adduct **7** was confirmed by *liquid chromatography−mass spectrometry* (LCMS). Additionally, 1 equiv of butylated hydroxytoluene (BHT) was added in the reaction mixture which afforded BHT−THF product **8**. The formation of compound **8** was confirmed by ^1H, ^{13}C, Fourier

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transform infrared (IR) (FT-IR) spectroscopy, and high-resolution mass spectrometry (HRMS).

The electron paramagnetic resonance (EPR) experiments have been carried out on a frozen aliquot of the incomplete reaction mixture of **1a′**, $K_2S_2O_8$, TBACl, and NaOAc in THF, suggesting the presence of a carbon-centric organic radical, as shown in Figure 2. The *g*-factor of the crossover point of the peak was found to be 2.003.

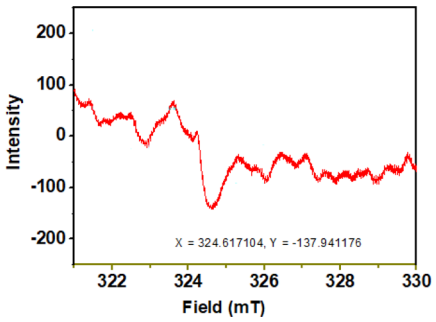


Figure 2. EPR spectrum of an incomplete reaction mixture.

On the basis of literature reports,[14] control experiments, and the EPR study, we believe that the reaction mechanism proceeds *via* the radical pathway. The reaction starts with homolytic cleavage of persulfate under thermal conditions in the presence of tetrabutylammonium chloride[15] to form the sulfate radical anion as shown in Scheme 6. The formed sulfate radical anion abstracts the proton from the α-position to oxygen of ether and generates α-oxyalkyl radical **A** as a reactive intermediate. The reactive radical intermediate **A** undergoes C−N addition through the nitrogen atom of QIK **1a′** to form the C−N bond and forms intermediate **B**. Further, the presence of the hydrogen sulfate anion leads to the formation of intermediate **C** through single electron transfer.[15a] Then, intermediate **C** undergoes *O*-chelation with NaOAc,[12a,b] followed by elimination of MeOH, and leads to the formation of desired product **3a**.

CONCLUSIONS

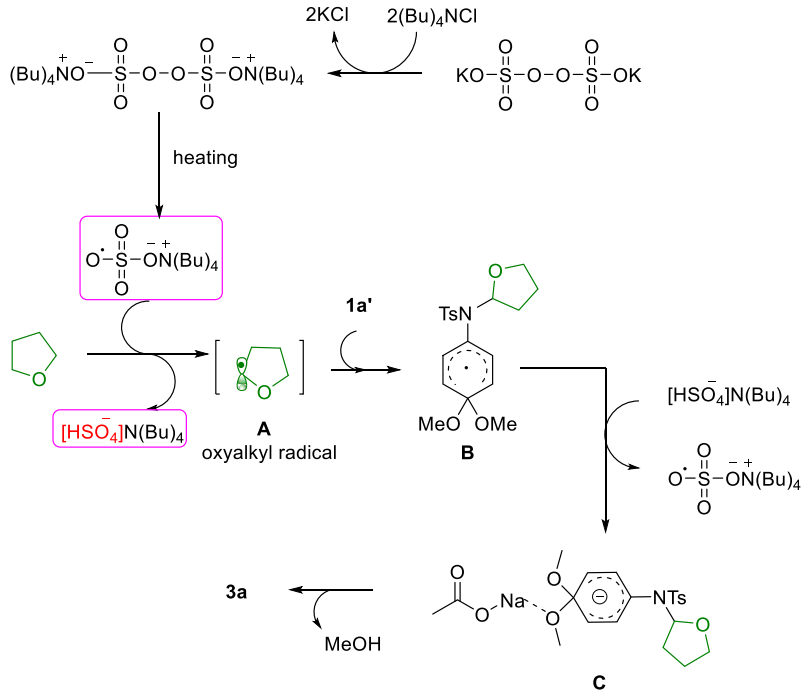
The study established an efficient metal-free approach for the synthesis of hemiaminals from QIK and various ethers. Further, this strategy highlights the optimized reaction conditions to obtain the desired products in good to excellent yields and shows the broad substrate scope and high functional group tolerance with hemiaminals. Also, the formation of the α-oxyalkyl radical in the reaction was confirmed by radical scavenger experiments, and the C-centered radical was confirmed by the EPR spectroscopy experiment.

EXPERIMENTAL SECTION

General Information. Most of the starting materials and reagents used were purchased from commercial sources and used as such. All N-substituted *p*-anisidine compounds were prepared using known literature procedures.[10d,16] QIKs were prepared as per the reported procedure.[10d,11] All solvents were highly purified before use. Petroleum ether (boiling point: 60−80 °C) was used for column chromatography. ^{1}H and ^{13}C spectra were recorded on a 200, 400, and 500 MHz NMR spectrometer. HRMS data were recorded on an Orbitrap mass analyzer associated with an Accela 1250 pump. IR spectra were recorded using a Bruker FT-IR and are reported in terms of frequency of absorption (cm^{-1}). EPR spectra were recorded on a JES—FA200 ESR Spectrometer with the X- and Q-bands [Standard Frequency (X-band)—8.75−9.65 GHz] at 100 K. All compounds were purified by column chromatography (silica of 100−200 mesh). All reactions were carried out in a highly predried round-bottom flask. The reactions were monitored by thin-layer chromatography (TLC). Coupling constants are given in hertz (Hz), and the classical abbreviations are used to describe the signal multiplicities.

*General Experimental Procedure for the Synthesis of N-Substituted Hemiaminals (**3a−3t**).* In a 25 mL round-bottom flask, N-substituted *p*-anisidine (100 mg, 0.36 mmol, 1 equiv) was

Scheme 6. Proposed Reaction Mechanism



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taken in MeOH (3 mL). To this, diacetoxyiodobenzene [phenyliodine(III) diacetate (PIDA)] (0.39 mmol, 1.1 equiv) was added in portions at 0 °C, and the reaction was slowly brought to room temperature (rt). The progress of the reaction was monitored by TLC. After completion of the reaction, MeOH was evaporated on a rotary evaporator under reduced pressure. The obtained residue was dissolved in the corresponding ether (3.6 mmol, 3 mL), and $K_2S_2O_8$ (1.08 mmol, 3 equiv), sodium acetate (1.08 mmol, 3 equiv), and TBACl·H_2O (1.08 mmol, 3 equiv) were added sequentially to the reaction mixture. Then, the reaction mixture was refluxed in a preheated oil bath at 90 °C for 4 h with continuous monitoring of the reaction with TLC. After completion of the reaction, the resulting reaction mixture was cooled to rt and concentrated in vacuo. The formed residue was extracted with ethyl acetate (3 × 3 mL) and washed with brine (10 mL). Then, the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by flash chromatography (silica gel 100−200 mesh) using petroleum ether/ethyl acetate (vol/vol, 8/2) to afford the corresponding aryl hemiaminals with good to excellent yields of the desired product.

*N-(4-Methoxyphenyl)-4-methyl-N-(tetrahydrofuran-2-yl) Benzenesulfonamide (**3a**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 91%, 102 mg; colorless oil; IR (neat, cm^{-1}) ν_{max}: 3260.86, 2921.03, 1599.74, 1503.36, 1454.01, 1398.64, 1335.57, 1293.49, 1245.15, 1156.20, 1086.95, 1026.05, 806.10, 663.20, 548.48; ^1H NMR (200 MHz, $CDCl_3$): δ 7.6 (d, J = 8.27 Hz, 2H), 7.2 (d, J = 8.05 Hz, 2H), 7.0−7.1 (m, 2H), 6.8 (m, J = 9.04 Hz, 2H), 6.2 (dd, J = 7.28, 4.96 Hz, 1H), 3.8 (s, 3H), 3.6−3.7 (m, 2H), 2.4 (s, 3H), 2.0−2.2 (m, 1H), 1.6−1.8 (m, 2H), 1.2−1.4 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 159.6, 143.1,133.2, 129.1, 128.1, 127.7, 113.9, 89.3, 68.3, 55.3, 30.3, 24.6, 21.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{22}O_4NS$, 348.1264; found, 348.1264.

*N-(4-Methoxyphenyl)-4-methyl-N-(tetrahydro-2H-pyran-2-yl) Benzenesulfonamide (**3b**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 86%, 101 mg; yellow oil; IR (neat, cm^{-1}) ν_{max}: 2918.84, 2839.67, 1602.13, 1447.99, 1328.24, 1244.76, 1158.20, 1115.06, 1009.8, 929.16, 802.62, 650.55, 582.93, 544.44; ^1H NMR (200 MHz, $CDCl_3$): δ 7.6 (m, J = 8.38 Hz, 2H); 7.2 (m, J = 8.16 Hz, 2H), 7.0−7.1 (m, 2H), 6.7−6.8 (m, 2H), 5.5 (dd, J = 10.80, 1.87 Hz, 1H), 3.9 (dt, J = 11.47, 2.09 Hz, 1H), 3.8 (s, 3H), 3.6 (td, J = 11.60, 2.81 Hz, 1H), 2.4 (s, 3H), 1.7−1.8 (m, 1H), 1.5−1.6 (m, 2H), 1.2−1.4 (m, 2H), 0.9−1.1 (m, 1H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 159.4, 143, 136.9, 132.8, 128.8, 128.4, 113.6, 86.6, 67.7, 55.3, 30.4, 24.8, 23.4, 21.5; HRMS (ESI) m/z:$[M + H]^+$ calcd for $C_{19}H_{24}O_4NS$, 362.1421; found, 362.1421.

*N-(1,4-Dioxan-2-yl)-N-(4-methoxyphenyl)-4-methylbenzenesulfonamide (**3c**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 81%, 95 mg; colorless oil; IR (neat, cm^{-1}) ν_{max}: 2916.71, 2851.54, 1724.14, 1599.20, 1455.71, 1390.79, 1329.91, 1156.79, 1110.03, 1026.52, 876.48, 811.73, 664.00, 545.88; ^1H NMR (200 MHz, $CDCl_3$): δ 7.5−7.8 (m, 2H),7.2−7.4 (m, 3H), 6.9−7.2 (m, 2H), 6.7 (d, J = 8.49 Hz, 1H), 4.9 (dd, J = 9.70, 2.32 Hz, 1H), 3.9 (d, J = 7.50 Hz, 4H), 3.7−3.8 (m, 3H), 3.5−3.7 (m, 1H), 3.1 (d, J = 10.58 Hz, 1H), 2.4 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 153.8, 143.3, 135.9, 129.3, 129.2, 127.3, 127.2, 123.6, 122.4, 110.4, 72.0, 70.9, 67.0, 66.2, 55.3, 21.3; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{22}O_5NNaS$, 363.1111; found, 363.1113.

*N-(1,2-Dimethoxyethyl)-N-(4-methoxyphenyl)-4-methylbenzenesulfonamide (**3d**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 83%, 98 mg; colorless oil; IR (neat, cm^{-1}) ν_{max}: 2934.06, 1729.54, 1596.96, 1509.87, 1457.27, 1328.24, 1233.26, 1157.80, 1023.74, 811.01, 766.81, 659.03; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (m, J = 8.25 Hz, 2H),7.22 (m, J = 8.25 Hz, 2H), 6.88−6.94 (m, 2H), 6.79 (m, J = 8.88 Hz, 2H), 5.57 (dd, J = 7.63, 5.25 Hz, 1H), 3.79 (s, 3H), 3.58 (s, 3H), 3.27 (s, 3H), 3.22−3.26 (m, 1H), 3.03 (dd, J = 10.26, 7.63 Hz, 1H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$): δ 159.7, 143.2, 137.3, 133.1, 129.0, 128.0, 126.2, 113.9, 87.6, 71.4, 58.6, 56.3, 55.3, 21.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{18}H_{23}O_5NNaS$, 388.1189; found, 388.1185.

*N-(4-Methoxyphenyl)-N-(tetrahydrofuran-2-yl) Methanesulfonamide (**3e**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 87%, 102 mg; yellow oil; IR (neat, cm^{-1}) ν_{max}: 2941.05, 2872.83, 1608.82, 1493.80, 1392.23, 1317.99, 1249.31, 1145.09, 1029.90, 970.85, 905.61, 761.75, 630.54, 504.64; ^1H NMR (200 MHz, $CDCl_3$): δ 7.2−7.3 (m, 2H),6.7−6.9 (m, 2H), 5.1 (t, J = 6.95 Hz, 1H), 4.1 (q, J = 6.84 Hz, 1H), 3.9 (d, J = 7.83 Hz, 1H), 3.8 (s, 3H), 2.3−2.5 (m, 1H), 2.9 (s, 3H), 1.5−1.7 (m, 1H), 1.8−2.0 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 159.9, 132.4, 128.3, 114.4, 89.3, 68.2, 55.4, 39.5, 29.5, 24.7; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{12}H_{17}O_4NNaS$, 294.0770; found, 294.0769.

*N-(4-Methoxyphenyl)-N-(tetrahydro-2H-pyran-2-yl)methanesulfonamide (**3f**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 79%, 97 mg; colorless gum; IR (neat, cm^{-1}) ν_{max}: 2923.99, 2862.05, 1733.75, 1602.38, 1504.09, 1380.07, 1333.33, 1230.03, 1155.54, 1067.57, 1025.77, 970.84, 733.94, 701.37, 646.82, 592.54; ^1H NMR (400 MHz, $CDCl_3$): δ 7.4 (m, J = 8.55 Hz, 2H), 6.9 (m, J = 9.16 Hz, 2H), 5.2−5.3 (m, 1H), 4.0−4.1 (m, 1H), 3.8 (s, 3H), 3.6 (td, J = 11.75, 2.75 Hz, 1H), 3.0 (s, 3H), 1.7−1.8 (m, 2H), 1.5−1.6 (m, 4H), 1.3−1.4 (m, 1H), 1.0−1.2 (m, 1H); $^{13}C\{^1H\}$ NMR(101 MHz, $CDCl_3$): δ 23.2, 24.9, 29.8, 39.7, 55.3, 67.9, 86.8, 114.0, 128.8, 132.0, 159.6; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{20}O_4NS$, 286.1108; found, 286.1107.

*N-(1,4-Dioxan-2-yl)-N-(4-methoxyphenyl)methanesulfonamide (**3g**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 72%, 89 mg; brown gel; IR (neat, cm^{-1}) ν_{max}: 2923.04, 2853.55, 1730.61, 1606.07, 1498.92, 1461.71, 1384.69, 1324.63, 1249.97, 1152.20, 1112.87, 1033.17, 971.80, 877.20, 815.13, 731.59, 523.14; ^1H NMR (200 MHz, $CDCl_3$): δ 7.29 (br s, 1H), 7.24 (s, 1H), 6.84 (d, J = 8.60 Hz, 2H), 4.93−5.00 (m, 1H), 3.91−4.01 (m, 4H), 3.83 (s, 4H), 3.72−3.79 (m, 2H), 3.24 (dd, J = 11.19, 9.87 Hz, 1H), 2.96 (s, 3H); ^{13}C $\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.3, 129.3, 128.1, 123.5, 121.9, 110.9, 72.5, 71.2, 67.3, 66.4, 55.6, 38.9; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{12}H_{17}O_5NNaS$, 310.0720; found, 310.0707.

*N-(1,2-Dimethoxyethyl)-N-(4-methoxyphenyl) Methanesulfonamide (**3h**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 76%, 95 mg; brown gel; IR (neat, cm^{-1}) ν_{max}: 2911.75, 2851.32, 1725.48, 1598.80, 1496.93, 1449.15, 1396.39, 1330.25, 1156.96, 1110.11, 1026.59, 877.0, 811.87, 663.75, 546.49; ^1H NMR (200 MHz, $CDCl_3$): δ 7.2−7.3 (m, 2H), 6.9−7.0 (m, 2H), 5.4 (dd, J = 8.60, 4.52 Hz, 1H), 3.8−3.9 (m, 3H), 3.5−3.6 (m, 3H), 3.4−3.4 (m, 3H), 3.3−3.3 (m, 1H), 3.1−3.2 (m, 1H), 3.0−3.1 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 40.3, 55.4, 55.5, 56.0, 58.7, 70.9, 87.6, 114.4, 114.7, 124.8, 126.3, 132.5, 159.9; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{12}H_{19}O_5NNaS$, 312.0876; found, 312.0865.

*N-(4-Methoxyphenyl)-N-(tetrahydrofuran-2-yl)benzenesulfonamide (**3i**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 90%, 102 mg; colorless solid; IR (neat, cm^{-1}) ν_{max}: 2943.06, 2842.62, 1602.44, 1504.45, 1340.73, 1297.34, 1160.67, 1083.96, 1028.18, 932.47, 888.19, 719.68, 682.03, 637.91; ^1H NMR (200 MHz, $CDCl_3$): δ 7.8−8.0 (m, 1H),7.7−7.8 (m, 1H), 7.4−7.6 (m, 3H), 6.9−7.0 (m, 2H), 6.7−6.8 (m, 2H), 6.3 (dd, J = 7.22, 4.91 Hz, 1H), 3.7−3.8 (m, 3H), 3.5−3.7 (m, 2H), 2.0−2.3 (m, 1H), 1.5−1.8 (m, 2H), 1.2−1.3 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 159.7, 139.7, 133.1, 132.4, 128.9, 128.4, 128.1, 127.4, 113.9, 89.3, 68.4, 55.3, 30.3, 24.6; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}O_4NS$, 334.1108; found, 334.1110.

*N-(4-Methoxyphenyl)-N-(tetrahydro-2H-pyran-2-yl) Benzenesulfonamide (**3j**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 85%, 100 mg; brown solid; IR (neat, cm^{-1}) ν_{max}: 2939.17, 2842.81, 1731.43, 1601.18, 1504.68, 1445.21, 1298.68, 1212.62, 1161.25, 1083.18, 1030.22, 936.38, 887.55, 800.82, 719.11, 682.35, 637.54, 543.78; ^1H NMR (200 MHz, $CDCl_3$): δ 7.7−7.7 (m, 2H), 7.3−7.6 (m, 3H),7.0−7.1 (m, 2H), 6.7−6.8 (m, 2H), 5.5 (dd, J = 10.75, 1.93 Hz, 1H), 3.9−4.0 (m, 1H),3.7−3.9 (m, 3H), 3.6 (td, J = 11.60, 2.92 Hz, 1H), 1.5−1.7 (m, 3H), 1.3−1.4 (m, 1H), 0.9−1.2 (m, 1H), 0.8−0.9 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 159.4, 139.7, 137.4, 132.7, 132.3, 130.2, 128.3, 128.1, 113.6, 86.5, 67.6, 55.2, 30.3, 24.8, 23.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{22}O_4NS$, 348.1264; found, 348.1263.

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*N-(1,4-Dioxan-2-yl)-N-(4-methoxyphenyl) Benzenesulfonamide (**3k**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 82%, 97 mg; yellow gel; IR (neat, cm^{-1}) ν_{max}: 2960.91, 2851.72, 1610.36, 1498.21, 1393.38, 1326.26, 1157.11, 1100.23, 1026.85, 877.13, 814.69, 686.24, 630.10, 575.79; ^1H NMR (200 MHz, $CDCl_3$): δ 7.6−7.8 (m, 2H), 7.4−7.6 (m, 3H), 7.0−7.1 (m, 2H), 6.9 (s, 1H), 6.7−6.8 (m, 1H), 4.9 (dd, J = 9.70, 2.54 Hz, 1H), 3.8−3.9 (m, 4H), 3.7−3.8 (m, 4H), 3.6−3.7 (m, 1H), 3.0−3.1 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.2, 138.9, 132.7, 129.1, 128.9, 128.8, 127.6, 127.3, 126.3, 124.3, 122.9, 110.6, 72.1, 71.1, 67.1, 66.3, 55.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}O_5NS$, 350.1057; found, 350.1054.

*N-(1,2-Dimethoxyethyl)-N-(4-methoxyphenyl) Benzenesulfonamide (**3l**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 88%, 105 mg; yellow gel; IR (neat, cm^{-1}) ν_{max}: 2934.34, 2836.40, 1605.20, 1505.83, 1448.01, 1335.99, 1247.04, 1161.87, 1111.72, 930.61, 832.27, 801.67, 723.52, 687.51, 588.51; ^1H NMR (200 MHz, $CDCl_3$): δ 7.6−7.8 (m, 2H),7.4−7.6 (m, 3H), 6.9−6.9 (m, 2H), 6.7−6.8 (m, 2H), 5.6 (dd, J = 7.72, 5.07 Hz, 1H), 3.8 (s, 3H), 3.6 (s, 3H), 3.4−3.5 (m, 1H), 3.2 (s, 3H), 3.0−3.1 (m, 1H), $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 159.7, 140.1, 133.0, 132.5, 128.9, 128.3, 128.0, 125.9, 113.9, 87.7, 71.2, 58.6, 56.2, 55.3; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{17}H_{21}O_5NNaS$, 374.1033; found, 374.1027.

*N-(4-Methoxyphenyl)-4-methyl-N-(5-Methyltetrahydrofuran-2-yl) Benzenesulfonamide (**3q**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 61%, 71 mg, yellow oil; IR (neat, cm^{-1}) ν_{max}: 3252.86, 2965.17, 1599.28, 1498.82, 1458.62, 1390.50, 1326.19, 1246.20, 1154.71, 1088.08, 1027.28, 908.86, 812.33, 664.01; ^1H NMR (200 MHz, $CDCl_3$): δ 7.55−7.63 (m, 3H), 7.21 (d, J = 7.94 Hz, 3H), 6.88−7.04 (m, 2H), 6.67−6.79 (m, 2H), 5.17 (t, J = 6.84 Hz, 1H), 3.97−4.18 (m, 1H), 3.76−3.79 (m, 3H), 3.23−3.50 (m, 1H), 2.38 (s, 4H), 1.86−2.03 (m, 2H), 1.48−1.59 (m, 2H), 1.24−1.28 (m, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 154.5, 154.3, 143.6, 143.5, 136.3, 136.1, 133.7, 133.5, 129.7, 129.4, 127.5, 127.3, 126.5, 125.5, 123.6, 123.5, 122.0, 121.6, 116.2, 114.4, 110.7, 110.6, 85.0, 84.9, 75.6, 75.3, 55.5, 33.7, 33.7, 33.3, 33.2, 21.5, 21.4, 20.9, 20.7; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{24}O_4N_S$, 362.1421; found, 362.1423.

*N-(4-Methoxyphenyl)-4-methyl-N-(tetrahydrothiophen-2-yl) Benzenesulfonamide (**3r**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 86%, 101 mg, yellow oil; IR (neat, cm^{-1}) ν_{max}: 3264.19, 2938.07, 1731.05, 1597.31, 1486.58, 1381.98, 1331.83, 1279.66, 1159.27, 1090.24, 1035.21, 907.97, 868.80, 813.00, 728.04, 663.64, 605.93; ^1H NMR (200 MHz, $CDCl_3$): δ 7.50−7.68 (m, 3H), 7.14−7.35 (m, 3H), 6.72−6.90 (m, 2H), 3.75 (s, 3H), 3.44−3.50 (m, 1H), 2.50 (t, J = 7.22 Hz, 2 H), 2.36 (s, 3H), 1.71−1.83 (m, 2H), 1.51−1.67 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 156.7, 143.8, 136.1, 130.7, 129.5, 127.7, 127.2, 123.1, 118.8, 114.4, 55.4, 44.1, 34.9, 31.2, 26.3, 21.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{22}O_3NS_2$, 364.1036; found, 364.1038.

*General Experimental Procedure for the Synthesis of Aryl-Substituted Hemiaminals (**5a**−**5i**).* In a 25 mL round-bottom flask, aryl-substituted *p*-anisidine (100 mg, 0.36 mmol, 1 equiv) was taken in MeOH (3 mL). To this, diacetoxyiodobenzene (PIDA) (0.39 mmol, 1.1 equiv) was added in portions at 0 °C, and the reaction mixture was brought to room temperature. The reaction progress was monitored by TLC. After completion of the reaction, MeOH was evaporated on a rotary evaporator under reduced pressure. Then, the residue was dissolved in the corresponding ether (3.6 mmol, 3 mL), followed by sequential addition of $K_2S_2O_8$ (1.08 mmol, 3 equiv), sodium acetate (1.08 mmol, 3 equiv), and TBACl·H_2O. The reaction mixture was refluxed in a preheated oil bath at 90 °C for 4 h. After completion of the reaction (with TLC monitoring), the resulting reaction mixture was cooled to room temperature and concentrated in vacuo. The formed residue was extracted with ethyl acetate (3 × 3 mL) and washed with brine (10 mL). Then, the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by flash chromatography (silica gel 100−200 mesh) and petroleum ether/ethyl acetate (vol/vol, 8/2) to afford the corresponding substituted aryl hemiaminals with good to excellent yields of the desired product.

*N-(3,4-Dimethoxyphenyl)-4-methyl-N-(tetrahydrofuran-2-yl) Benzenesulfonamide (**5a**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 76%, 85 mg; IR (neat, cm^{-1}) ν_{max}: 2923.73, 2851.71, 1710.65, 1597.57, 1510.78, 1457.04, 1394.28, 1332.61, 1233.39, 1157.39, 1089.15, 1022.84, 968.78, 895.01, 810.78, 758.46, 663.25, 545.81; ^1H NMR (200 MHz, $CDCl_3$): δ 7.6 (m, J = 8.27 Hz, 2H), 7.2 (m, J = 8.05 Hz, 2H), 6.6−6.8 (m, 2H), 6.5−6.6 (m, 1H), 6.2 (dd, J = 7.11, 5.02 Hz, 1H), 3.8−3.9 (m, 3H), 3.5−3.7 (m, 5H), 2.4 (s, 3H),2.0−2.2 (m, 1H), 1.6−1.8 (m, 2H), 1.1−1.3 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 149.2, 136.7, 129.3, 128.9, 128.2, 127.2, 124.7, 115.1, 111.1, 110.3, 107.6, 89.3, 68.3, 55.7, 30.1, 24.5, 21.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{24}O_5NS$, 378.1370; found, 378.1368.

*N-(3,4-Dimethoxyphenyl)-4-methyl-N-(tetrahydro-2H-pyran-2yl) Benzenesulfonamide (**5b**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 68%, 78 mg; white solid; IR (neat, cm^{-1}) ν_{max}: 2934.48, 2849.25, 1595.91, 1509.69, 1454.39, 1413.19, 1343.58, 1264.40, 1231.49, 1098.97, 1021.05, 959.50, 926.46, 880.71, 820.25, 766.78, 547.19; ^1H NMR (400 MHz, $CDCl_3$): δ 7.6 (m, J = 8.24 Hz, 2H), 7.2 (m, J = 7.79 Hz, 2H), 6.8 (d, J = 2.29 Hz, 1H), 6.5 (d, J = 2.75 Hz, 1H), 4.6 (dd, J = 10.99, 1.83 Hz, 1H), 4.1 (dt, J = 11.22, 1.95 Hz, 1H), 3.8 (s, 6H), 3.5−3.7 (m, 1H), 2.4 (s, 3H), 1.8−1.9 (m, 2H), 1.6−1.7 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 152.6, 143.6, 143.0, 137.4, 136.1, 132.6, 129.5, 127.3, 112.1, 105.8, 74.2, 68.9, 60.9, 55.8, 33.4, 25.8, 23.9, 21.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{26}O_5NS$, 392.1527; found, 392.1535.

*N-(3,4-Dimethoxyphenyl)-N-(1,4-dioxan-2-yl)-4-methylbenzenesulfonamide (**5c**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 62%, 72 mg; yellow oil; IR (neat, cm^{-1}) ν_{max}: 2930.57, 2849.03, 1689.02, 1595.76, 1509.28, 1453.68, 1343.04, 1230.43, 1161.85, 1097.85, 1020.84, 958.91, 925.35, 879.75, 765.86, 705.17, 545.41; ^1H NMR (200 MHz, $CDCl_3$): δ 7.6 (d, J = 8.16 Hz, 2H),7.2 (d, J = 8.05 Hz, 2H), 6.6 (s, 1H), 6.7−6.8 (m, 2H), 5.7 (dd, J = 9.65, 2.48 Hz, 1H), 3.8−4.0 (m, 6H), 3.7−3.8 (m, 1H),3.7 (s, 4H), 3.5−3.6 (m, 1H), 3.2−3.4 (m, 1H), 3.0 (t, J = 10.36 Hz, 1H), 2.4 (s, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 149.4, 148.4, 143.5, 136.4, 129.0, 128.5, 127.8, 124.0, 114.7, 110.3, 82.6, 68.8, 66.7, 65.5, 55.8, 21.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{24}O_6NS$, 394.1319; found, 394.1317.

*N-(1,2-Dimethoxyethyl)-N-(3,4-dimethoxyphenyl)-4-methylbenzenesulfonamide (**5d**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 66%, 77 mg; colorless gel; IR (neat, cm^{-1}) ν_{max}: 2933.16, 1731.93, 1594.54, 1507.39, 1456.93, 1326.94, 1232.44, 1024.17, 929.37, 848.64, 811.75, 764.93, 657.7; ^1H NMR (200 MHz, $CDCl_3$): δ 7.6 (d, J = 7.83 Hz, 2H), 7.2 (br s, 2H), 6.7 (d, J = 8.49 Hz, 1H), 6.5−6.6 (m, 1H), 6.4 (s, 1H), 5.5−5.6 (m, 1H), 3.8 (s, 3H), 3.6 (s, 3H), 3.4 (d, J = 8.16 Hz, 1H), 3.2−3.3 (m, 4H), 2.9−3.1 (m, 1H), 2.4 (s, 3H), $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ:149.3, 148.4, 143.2, 137.2, 128.9, 128.2, 126.2, 124.6, 114.9, 110.4, 87.7, 71.2, 58.5, 56.2, 55.8, 55.6, 21.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{19}H_{25}O_6NNaS$, 418.1295; found, 418.1282.

*N-(4-Methoxy-3-tosylphenyl)-N-(tetrahydrofuran-2-yl) Methanesulfonamide (**5e**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 58%, 52 mg; yellow gum; IR (neat, cm^{-1}) ν_{max}: 2962.43, 2876.69, 1721.12, 1464.93, 1379.94, 1241.95, 1152.19, 1039.08, 881.21, 814.74, 563.64, 527.65; ^1H NMR (200 MHz, $CDCl_3$): δ 7.49−7.74 (m, 3 H), 7.03−7.46 (m, 3 H), 6.79 (d, J = 8.82 Hz, 1 H), 5.33 (td, J = 6.39, 3.09 Hz, 1 H), 3.79−3.91 (m, 2 H), 3.60−3.76 (m, 3 H), 3.07 (s, 3 H), 2.39 (s, 3 H), 2.13−2.28 (m, 1H), 1.81−1.98 (m, 3 H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.7, 144.1, 137.7, 135.5, 129.6, 129.1, 128.3, 127.3, 124.1, 113.3, 84.9, 67.1,56.0, 42.7, 32.0, 24.1, 21.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{24}O_6NS_2$, 426.1040; found, 426.1034.

*N-(3-Bromo-4-methoxyphenyl)-4-methyl-N-(tetrahydrofuran-2-yl) Benzenesulfonamide (**5f**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 76%, 83 mg; colorless solid; IR (neat, cm^{-1}) ν_{max}: 2928.69, 1584.86, 1482.75, 1353.65, 1293.36, 1248.69, 1162.08, 1020.29, 972.66, 908.92, 847.31, 810.85, 738.74, 701.23,

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659.18, 542.37; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.8−7.9 (m, 1H), 7.6 (d, J = 7.79 Hz, 2H), 7.3 (d, J = 8.24 Hz, 1H), 7.2 (s, 1H), 7.3 (s, 1H), 7.1−7.2 (m, 1H), 7.0 (s, 1H), 6.1−6.2 (m, 1H), 3.9−3.9 (m, 3H), 3.6−3.7 (m, 1H), 3.5 (q, J = 7.17 Hz, 1H), 2.4 (s, 3H), 2.1−2.2 (m, 1H), 1.6−1.7 (m, 2H), 1.3−1.3 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.8,136.6,136.2, 129.5, 129.3, 129.2, 128.5, 128.1, 116.2, 109.7, 90.0, 68.4, 56.7, 29.8, 24.7, 21.6; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{21}O_4NBrS$, 426.0369; found, 426.0366.

*N-(4-Methoxy-2-methylphenyl)-4-methyl-N-(tetrahydrofuran-2-yl) Benzenesulfonamide (**5i**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) yield: 78%, 87 mg; red gum; IR (neat, cm^{-1}) ν_{max}: 2930.43, 2872.37, 1651.07, 1602.43, 1497.44, 1457.99, 1388.35, 1303.24, 1221.83, 1159.84, 1035.78, 898.46, 862.56, 812.01, 665.27; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57−7.73 (m, 2H), 7.24 (dd, J = 8.57, 0.56 Hz, 2H), 6.81 (d, J = 3.00 Hz, 1H), 6.60 (d, J = 8.75 Hz, 1H), 6.48 (dd, J = 8.76, 2.75 Hz, 1H), 6.24 (t, J = 6.44 Hz, 1H), 3.78 (s, 3H), 3.64 (td, J = 7.69, 5.25 Hz, 1H), 3.48−3.57 (m, 1H), 2.43 (s, 3H), 2.38 (s, 3H), 1.60−1.71 (m, 2H), 1.43−1.54 (m, 1H), 1.27−1.36 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.5, 143.1, 142.5, 137.0, 132.3, 129.0, 128.5, 126.7, 115.7, 111.4, 89.7, 68.1, 55.2, 29.4, 24.9, 21.6, 19.2; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{24}O_4N_S$, 362.1421; found, 362.1423.

*General Experimental Procedure for Synthetic Transformation of the Formed Product (**6**).* To a solution of **3a** (50 mg, 0.14 mmol) in ethanol (5 mL) was added sodium borohydride (27 mg, 0.72 mmol). The resulting suspension was stirred at rt for 36 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate = 6:4) to afford 6 (36 mg, 73%).

*N-(4-Hydroxybutyl)-N-(4-methoxyphenyl)-4methylbenzenesulfonamide (**6**).* Purification on silica gel (petroleum ether/EtOAc = 6:4) yield: 73%, 73 mg; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (m, J = 8.25 Hz, 2H), 7.24 (m, J = 8.13 Hz, 2H), 6.90−6.95 (m, 2H), 6.78−6.83 (m, 2H), 3.80 (s, 3H), 3.61 (t, J = 6.32 Hz, 2H), 3.52 (t, J = 6.88 Hz, 2H), 2.42 (s, 3H), 1.57−1.66 (m, 2H), 1.44−1.53 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.0, 143.2, 135.2, 131.4, 129.9, 129.3, 127.7, 114.1, 62.3, 55.4, 50.3, 29.2, 24.5, 21.5; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{24}O_4NS$, 350.1421; found, 350.1432.

General Procedure for Gram-Scale Synthesis of *N*-(4-Methoxyphenyl)-4-methyl-*N*-(tetrahydrofuran-2-yl) Benzenesulfonamide (3a). In a 100 mL round-bottom flask, N-substituted *p*-anisidine (0.800 g, 2.89 mmol, 1 equiv) was taken in MeOH (30 mL). To this, diacetoxyiodobenzene (PIDA) (3.17 mmol, 1.1 equiv) was added in portions at 0 °C, and the reaction was slowly brought to rt. The progress of the reaction was monitored by TLC. After completion of the reaction, MeOH was evaporated on a rotary evaporator under reduced pressure. The obtained residue was dissolved in THF (28.9 mmol, 25 mL), and $K_2S_2O_8$ (8.66 mmol, 3 equiv), sodium acetate (8.66 mmol, 3 equiv), and TBACl·H_2O (8.66 mmol, 3 equiv) were added sequentially to the reaction mixture. Then, the reaction mixture was refluxed in a preheated oil bath at 90 °C for 6 h with continuous monitoring of the reaction with TLC. After completion of the reaction, the resulting reaction mixture was cooled to rt and concentrated in vacuo. The formed residue was extracted with ethyl acetate (30 × 3 mL) and washed with brine (20 mL). Then, the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by flash chromatography (silica gel 100−200 mesh) using petroleum ether/ethyl acetate (vol/vol, 8/2) to afford **3a** (0.840 g, 84%) as a colorless oil.

General Procedure for Control Experiments and the EPR Study. *General Experimental Procedure for the TEMPO−THF-Trapped Product (**7**).* To a 25 mL round-bottom flask containing *N*-tosyl *p*-anisidine, **1a** (100 mg, 0.36 mmol, 1 equiv) was taken in MeOH (3 mL). To this reaction mixture, diacetoxyiodobenzene (PIDA) (0.39, 1.1 equiv) was added in portions at 0 °C, and the reaction mixture was allowed to stir at rt. The reaction was monitored by TLC. After completion of the reaction, MeOH was evaporated under reduced pressure and the residue was then dissolved in THF (3.6 mmol, 3 mL). To this, $K_2S_2O_8$ (1.08 mmol, 3 equiv), sodium acetate (1.08 mmol, 3 equiv), TBACl·H_2O (1.08 mmol, 3 equiv), and TEMPO (0.36 mmol) were added sequentially. Then, the reaction mixture was refluxed at 90 °C in an oil bath for 4 h. The expected trapped product was detected by LCMS of the crude reaction mixture. LCMS (ESI) m/z: 228.1 (please see the Supporting Information).

*General Experimental Procedure for the BHT−THF-Trapped Product (**8**).* To a 25 mL round-bottom flask containing *N*-tosyl *p*-anisidine, **1a** (100 mg, 0.36 mmol, 1 equiv) was taken in MeOH (3 mL). To this reaction mixture, diacetoxyiodobenzene (PIDA) (0.39, 1.1 equiv) was added in portions at 0 °C, and the reaction mixture was allowed to stir at rt; the reaction was monitored by TLC. After completion of the reaction, MeOH was evaporated under reduced pressure. Then, the residue was dissolved in THF (3.6 mmol, 3 mL). To this, $K_2S_2O_8$ (1.08 mmol, 3 equiv), sodium acetate (1.08 mmol, 3 equiv), TBACl·H_2O (1.08 mmol, 3 equiv), and BHT (0.36 mmol) were added sequentially. Then, the reaction mixture was refluxed at 90 °C in an oil bath for 4 h. The reaction was monitored by TLC; after completion of the reaction, the resulting mixture was cooled to rt and concentrated in vacuo. The formed residue was extracted with ethyl acetate (3 × 3 mL) and washed with brine (20 mL). Then, the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by flash chromatography (silica gel 100−200 mesh) and petroleum ether/ethyl acetate (vol/vol, 9/1) to afford the BHT−THF-trapped product in 52% yield.

*2,6-Di-tert-butyl-4-((tetrahydrofuran-2-yl) Methyl) Phenol (**8**).* Purificationon silica gel (petroleum ether/EtOAc = 9:1) yield: 52%, 73 mg; yellow liquid; IR (neat, cm^{-1}) ν_{max}: 3659.93, 2955.09, 2868.25, 2037.92, 1731.04, 1636.95, 1456.65, 1363.60, 1244.59, 1170.34, 1067.44, 968.77, 913.75, 880.01, 774.24, 733.12, 649.03; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.00 (d, J = 5.95 Hz, 1H), 6.55−6.64 (m, 1H), 6.39 (d, J = 2.87 Hz, 1H), 3.86−3.96 (m, 1H), 3.75−3.84 (m, 2H), 2.21−2.32 (m, 1H), 1.67−1.79 (m, 3H), 1.22−1.28 (m, 18 H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 186.6, 148.2, 147.0, 143.8, 142.8, 84.8, 69.0, 43.9, 34.9, 34.7, 29.5, 29.4, 27.4, 26.4, 23.6; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{31}O_2$, 291.2319; found, 291.2328.

Procedure for the EPR Measurement, Representative Procedure. To a 25 mL round-bottom flask, *N*-tosyl-substituted *p*-anisidine (100 mg, 0.36 mmol, 1 equiv) was taken in MeOH (3 mL). To this, diacetoxyiodobenzene (PIDA) (0.39 mmol, 1.1 equiv) was added in portions at 0 °C, and the reaction mixture was allowed to stir at rt with continuous monitoring by TLC. After completion of the reaction, MeOH was evaporated under reduced pressure. Then, the residue was dissolved in THF (3.6 mmol, 3 mL). To this, sequential addition of $K_2S_2O_8$ (1.08 mmol, 3 equiv), sodium acetate (1.08 mmol, 3 equiv), and TBACl·H_2O (1.08 mmol, 3 equiv) was done. The reaction mixture was refluxed at 90 °C in a preheated oil bath and stirred for 2 h. At ambient temperature, the reaction tube was transferred to the glovebox, and an aliquot of the reaction mixture was transferred to an EPR tube and frozen at 100 K, which was then subjected to the EPR measurement.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02254.

^{1}H and ^{13}C{^{1}H} NMR spectra of all compounds, LCMS spectrum of compound **7**, HRMS spectrum of compound **8**, and EPR spectrum (PDF)

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Notes

The authors declare no competing financial interest.

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Metal-Free, Acid-Catalyzed 1,6-Conjugate Addition of NH-Sulfoximines to *para*-Quinone Methides: Accessing to Diarylmethine Imino Sulfanone

Satish G. More, Bapurao D. Rupanawar, and Gurunath Suryavanshi*

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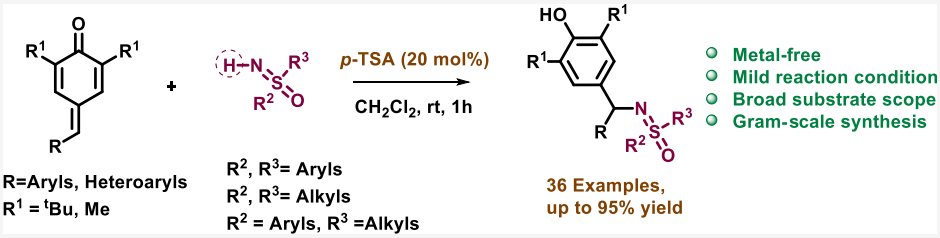

ABSTRACT: We have reported an efficient and metal-free method for the construction of α-diarylmethine imino sulfanone using acid-catalyzed 1,6-conjugate addition of sulfoximines on *para*-quinine methides (*p*-QMs). This method showed broad functional group tolerance and a wide range of substrate scope with good to excellent yield. The excellent protocol exhibits mild reaction conditions with high atom economy. The practicability of the present method was supported by a Gram-scale reaction.

INTRODUCTION

Diaryl methane is an interesting pharmacophore possessing a wide range of the biological spectrum. Further, sulfoximidoyl scaffolds have considerable significance in pharmaceutical and medicinal chemistry due to their exceptional structure.[1] In particular, the sulfoximine pharmacophore is a flexible synthetic intermediate that plays a vital role in drug discovery owing to its structural diversity, hydrogen-bonding capability, high metabolic stability, and interesting physicochemical properties.[2,6] In organic synthesis, the sulfoximine derivative has been used as the key intermediate found in active pharmaceutical ingredients, natural products, crop protection, and in medicinal chemistry with a wide range of biological activity.[3,4] For instance, sulfoximine-based rofecoxib analogues [COX inhibitor for both COX-1 and COX-2 selectivity (shows inhibitory activities of 1% and 48% for COX-1 and COX-2, respectively, at 10 mm concentrations]][4] and the proline-rich tyrosine kinase 2 (PYK2) inhibitor are used in treatment of osteoporosis,[5] whereas sulexifens are used as polyvalent spasmolytic and antiasthmatic agents,[6] and methyl(phenyl) ((4-(3-(trifluoromethyl)-l,2,4-oxadiazol-5-yl) benzyl) imino)-λ^6 sulfanone is used as a pesticide;[7] these are the prominent examples for the *N*-alkyl sulfoximines (Figure 1). Additionally, the sulfoximines were extensively applied for the construction of chiral auxiliaries, ligands, as well as in enantioselective catalysis in asymmetric synthesis.[1b,8,9] Owing the importance of sulfoximines, several synthetic routes for *N*-alkylation of sulfoximines synthesis have been explored. In 1993, Johnson and Lavergne developed the direct *N*-alkylation of sulfoximines

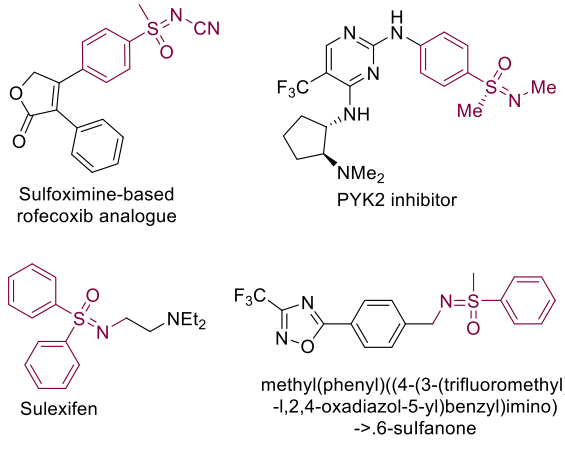

Figure 1. Typical examples of biologically active *N*-alkyl sulfoximines.

via nucleophilic substitution using alkyl halide and sulfoximines in the presence of a base.[10] Later, Bolm et al. in 2014 delineated alkylation of sulfoximine for the synthesis of *N*-alkyl-sulfoximine using alkyl halide and a base.[11] Interestingly, diaryl methine sulfoximines were first explored by the same

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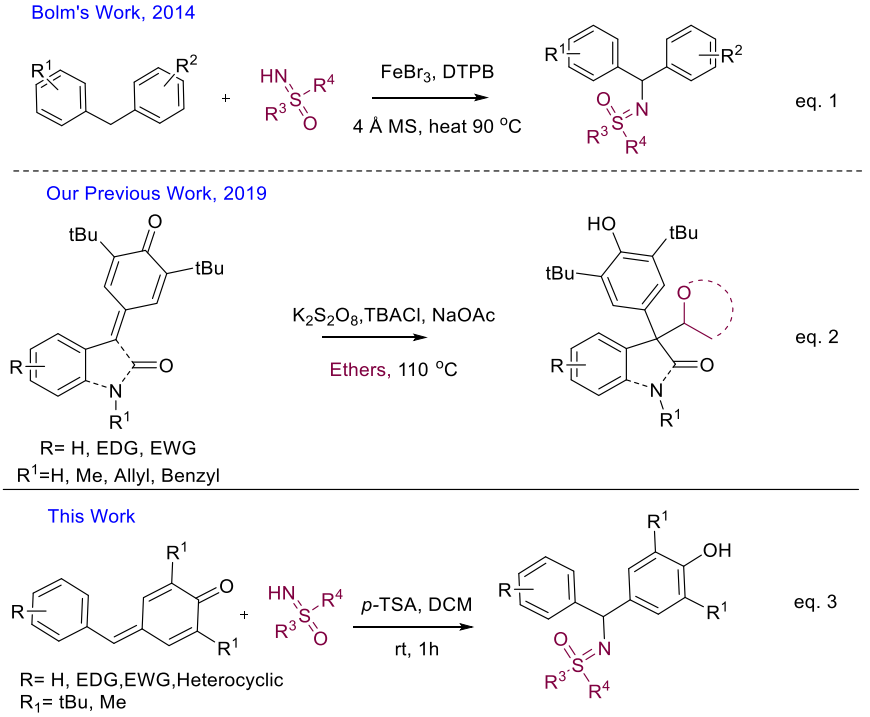
Scheme 1. Reactions of Sulfoximines, *p*-QMs, and the Present Work



group using iron-catalyzed hetero cross-dehydrogenated coupling reactions (Scheme 1, eq 1).[12] Recently, Cheng and co-workers described copper-catalyzed oxidative C(sp^3)−H/N−H coupling of sulfoximines and amides with simple alkanes *via* a radical process.[13]

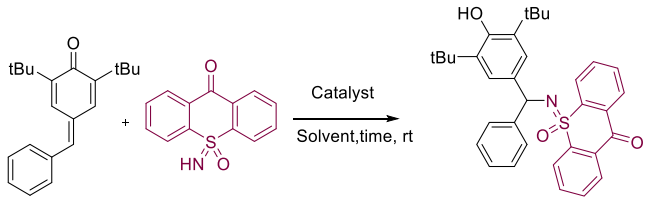
In the past decade, *para*-quinone methides (*p*-QMs) were extensively used as a versatile Michael acceptor for the construction of C−C, C−N, and C−S bond formation reactions.[14] Also, *p*-QMs are used as a precursor in numerous organic reactions such as 1,6-conjugate addition reaction,[15] [4 + 2],[16] [3 + 2],[17] and [2 + 1] annulation reactions.[18] The unique property of *p*-QMs gained attention among many research groups to utilize it for the construction complex building blocks and the core structure of natural products.[19]

In our previous approach, we have effectively utilized *p*-QMs for the C−C bond formation reaction with cyclic ethers using $K_2S_2O_8$, TBACl, and NaOAc (Scheme 1, eq 2),[20] and as a continuation of our work based on metal-free synthetic methodologies[21] and the importance of sulfoximes, we are encouraged to utilize *p*-QMs and sulfoximines for the synthesis of diaryl methine moiety. To the best of our knowledge, there are no reports where sulfoximines are used for conjugate addition on *p*-QMs.

RESULTS AND DISCUSSION

To authenticate our hypothesis, *p*-QM **1a** and sulfoximine **2a** were selected as a model substrate to check the feasibility of our conjugate addition reaction (Table 1). Initially, *p*-QM **1a** (1 equiv) and sulfoximine **2a** (1.2 equiv) were subjected to a conjugate addition reaction in the presence of NaH (1 equiv) in acetonitrile at room temperature for 4 h, which failed to offer the desired product **3a** (Table 1, entry 1). Further attempts for conjugate addition of sulfoximine on *p*-QM were unsatisfactory under basic conditions with various inorganic bases such as K_2CO_3, Cs_2CO_3, and NaOH (1 equiv each) in acetonitrile (Table 1, entries 2−4). When the reaction was carried out in the presence of Brønsted acids such as a catalytic amount of *p*-TSA (10 mol %) in acetonitrile, it delivered the desired product **3a** in 38% yield at room temperature in 4 h of reaction time (Table 1, entry 5). Encouraged by this promising

Table 1. Optimization of Reaction Conditions[a]



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

entry	catalyst (equiv)	solvent	time (h)	yield (%)[b]
1.	NaH (1)	ACN	4	NR
2.	K_2CO_3 (1)	ACN	4	NR
3.	Cs_2CO_3 (1)	ACN	4	NR
4.	NaOH (1)	ACN	4	NR
5.	*p*-TSA (0.1)	ACN	4	38
6.	*p*-TSA (0.1)	THF	4	45
7.	*p*-TSA (0.1)	EtOAc	4	58
8.	*p*-TSA (0.1)	$CHCl_3$	4	64
9.	*p*-TSA (0.1)	CH_2Cl_2	4	88
10.	***p*-TSA (0.2)**	**CH_2Cl_2**	**1**	**92**
11.	TFA (0.2)	CH_2Cl_2	1	85
12.	TFOH (0.2)	CH_2Cl_2	1	79
13.	CSA (0.2)	CH_2Cl_2	1	80
14.	$BF_3{\cdot}Et_2O$ (0.2)	CH_2Cl_2	1	56
15.	*p*-TSA (0.2)	H_2O	1	NR
16.		CH_2Cl_2	1	NR

[a]Reaction conditions: **1a** (0.1 mmol, 1 equiv), **2a** (0.12 mmol, 1.2 equiv), catalyst in solvent (2.0 mL) at room temperature under a N_2 atmosphere. [b]Isolated yields after column chromatography, NR = no reaction.

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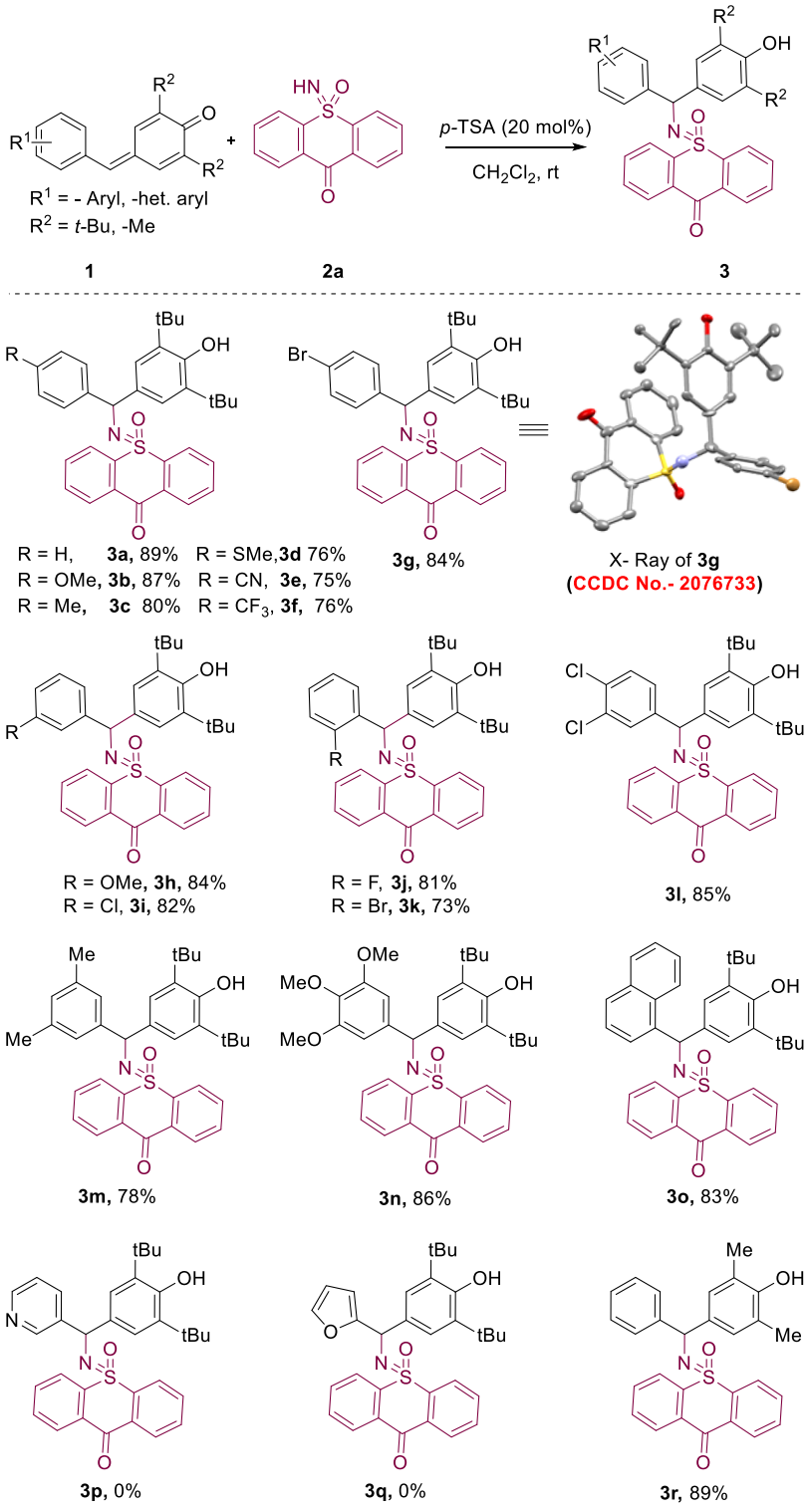
Scheme 2. Substrate Scope of Various *p*-QMs[a,b]



[a]Reaction conditions: **1a−r** (0.17 mmol), **2a** (0.18 mmol), *p*-TSA (20 mol %), room temperature, 1 h, under a N_2 atmosphere. [b]Isolated yields after column chromatographic purification are shown.

result, we then screened various polar solvents such as tetrahydrofuran (THF), EtOAc, $CHCl_3$, and CH_2Cl_2 (entries 6−10). Out of all screened solvents, CH_2Cl_2 was found to be the best solvent giving 88% yield of the desired product within 4 h. Furthermore, increasing the loading of the catalyst from 10 to 20 mol % enhanced the yield of the desired product **3a** up to 92% yield in 1 h of reaction time (entry 10). Next, we screened different Brønsted acids (20 mol %) such as tetrafluoroacetic acid (TFA), TFOH, and CSA (entries 11−13), but the yields of **3a** were not encouraging in all these cases (entries 11−13) as compared to that of entry 10. Further, use of $BF_3{\cdot}Et_2O$ did not alter the yield of **3a** (entry 14). Additionally, we tried the

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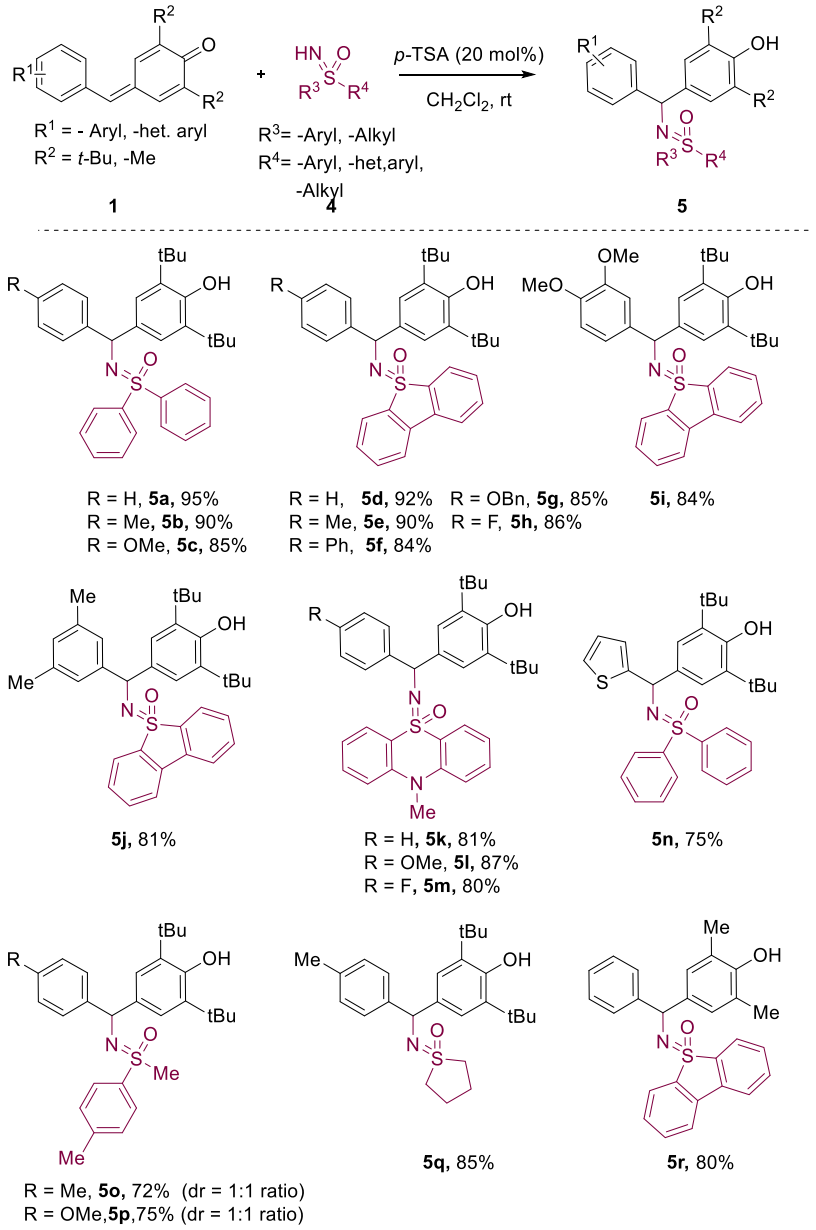
Scheme 3. Substrate Scope of Various Sulfoximines[a,b]



[a]Reaction conditions: **1** (0.17 mmol), **4** (0.18 mmol), *p*-TSA (20 mol %), room temperature, 1 h, under a N_2 atmosphere. [b]Isolated yields after column chromatographic purification are shown.

reaction in aqueous media, but it was found to be ineffective to get the corresponding product **3a** (entry 15). However, in the absence of a catalyst, there was no formation of product **3a** (entry 16). On the basis of the optimization study, **1a** (1.0 equiv), **2a** (1.2 equiv), and *p*-TSA (20 mol %) in CH_2Cl_2 is the best optimal reaction condition for the addition of sulfoximine to *p*-QMs (Table 1, entry 10).

Having the optimal reaction condition in hand, various *p*-QMs (**1a**) and sulfoximines (**2a**) were investigated under optimal reaction conditions, and the results are shown in Scheme 2. The substrate containing electron-donating groups (−H, −OMe, −Me, and −SMe), electron-withdrawing groups (−CN and $-CF_3$), and the halo group (−Br) on the *para* position of aryl ring of *p*-QMs (**1a**−**1g**) reacts with sulfoximine derived from thioxanthene-9-one to afford the desired product **3a**−**3g** in good to excellent yield (75−89%). The precise structure of **3g** was determined by X-ray crystallography (CCDC no. 2076733, see Supporting Information). Moreover, *meta*-substituted *p*-QMs bearing electron-donating and electron-withdrawing groups on reaction with sulfoximine **2a** lead to the formation of corresponding products **3h** in 84% and **3i** in 82% yields. Also, halogen (−F and −Br) substitution at the *ortho* position of the aryl group of *p*-QMs (**1j** and **1k**) reacted with sulfoximine (**2a**) furnished the corresponding addition products **3j** and **3k** in 81 and 73% yields, respectively. Besides this, disubstituted and trisubstituted *p*-QMs (**1l**−**1n**) reacted smoothly and offered the desired products **3l**−**3n** in excellent yield. Next, the reaction proceeds efficiently on sterically hindered *p*-QMs, such as naphthalene-derived *p*-QMs (**1o**); the desired product **3o** was obtained in 83% yield. Unfortunately, hetero aryl *p*-QMs such as pyridine and furan containing *p*-QMs did not participate in the reaction with **2a**;

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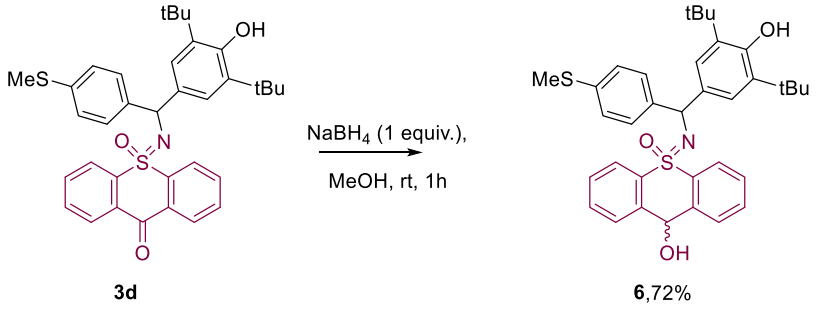
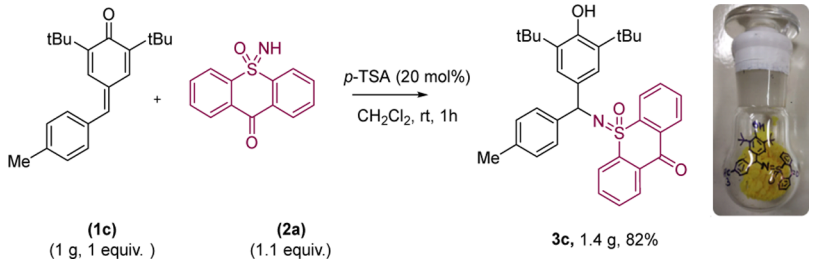
Scheme 4. Synthetic Transformation



Scheme 5. Large-Scale Reaction



subsequently, both the starting materials were recovered (entries **3p** and **3q**), presumably due to the heteroatom being protonated in acidic media to terminate the reaction. To our delight, replacing the *tert*-butyl group with the methyl group of *p*-QM (**1r**) furnishes **3r** in 89% yield.

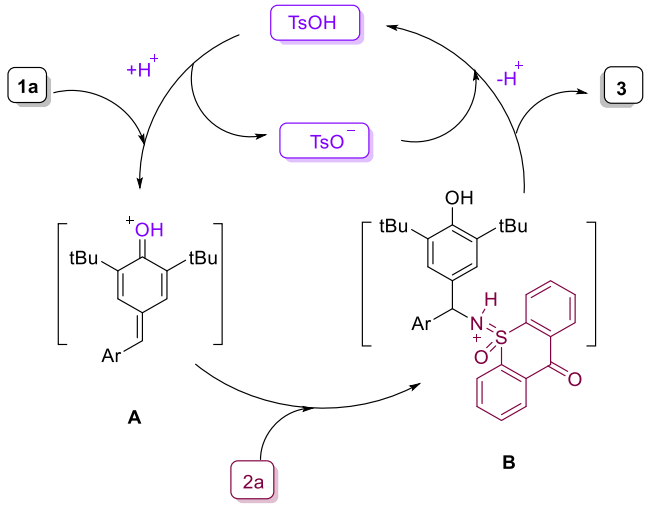
Next, the substrate scope of different sulfoximes (**4**) with respect to the *para*-quinone methides was investigated; all diaryl, aryl−alkyl sulfoximes, and cyclic sulfoximines were screened with different *p*-QMs. The addition reaction between symmetrical diaryl sulfoximines (**4a**−**4c**) and different *p*-QMs furnished corresponding diarylmethine sulfoximes (**5a**−**5c**) in good yields (Scheme 3). Similarly, dibenzothiophene-derived sulfoximes (**4d**−**4j**) reacted smoothly with electron-donating, electron-withdrawing, as well as multisubstituted groups on *p*-QMs, leading to the formation of diarylmethine sulfoximine **5d**−**5j** in 81−92% yields. Further, *N*-methyl phenothiazine-derived sulfoximines (**4k**−**4m**) were also found to be amenable to the addition reaction with *p*-QMs bearing electron-donating and -withdrawing group to offer diarylmethine sulfoximines in good yields (entries **5k**−**5m**, 80−87%). Heterocyclic *p*-QMs, such as thiophene, react well with diaryl sulfoximine to furnish **5n** in 75% yield. Additionally, methyl aryl sulfoximine reacted with *p*-QMs (*p*-Me and *p*-OMe) to obtain **5o** and **5p** in 72 and 75% yields, respectively, with a 1:1 diastereomeric ratio. Next, we applied the tetrahydrothiophene-based sulfoximine on *p*-QM (**2c**) under the optimized reaction condition, which reacted well and furnished the diarylmethine sulfoximine **5q** in 75% yield, whereas 2,6-dimethyl *p*-QM was reacted to get the corresponding product **5r** in 80% yield.

Next, we explored the synthetic transformation of the key product, as shown in scheme 4. The keto group of 10-(((3,5-di-*tert*-butyl-4-hydroxyphenyl) (4-(methylthio) phenyl) methyl) imino)-10l4-thioxanthen-9(10*H*)-one 10-oxide (**3d**) was selectively reduced with 1 equiv of $NaBH_4$, affording the desired product **6** in 72% yield.[22]

To demonstrate the scalability of the method, a Gram-scale reaction was carried out between *p*-QM (**1c**) and sulfoximine (**2a**) under the optimized conditions obtained **3c** in 82% yield (1.4 g) in 1 h, as shown in Scheme 5.

Based on the literature report,[11,23] we envisaged the plausible reaction pathway, as shown in Scheme 6. The

Scheme 6. Plausible Reaction Mechanism



reaction was initiated with activation of *p*-QMs (**1a**) using *p*-TSA, which leads to formation of the highly electrophilic intermediate **A** for 1,6-conjugate addition. Subsequently, the addition of sulfoximine (**2a**) in the 1,6-conjugated manner might have offered the sulfoximinium ion intermediate **B**, followed by the deprotonation of intermediate **B**, which leads to the desired product **3a** with regeneration of the *p*-TSA catalyst.

CONCLUSIONS

In conclusion, we have developed a convenient, metal-free protocol for the synthesis of diverse range of diarylmethine imino sulfanones using *p*-QMs and bench-stable sulfoximines

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in the presence of a catalytic amount of *p*-TSA. A mild reaction condition, less reaction time, broad substrate scope, high atom economy, and excellent yield of products are the key features of the present methodology.

EXPERIMENTAL SECTION

General Information. The solvents were purified and dried using a standard protocol before use. Moisture- and air-sensitive reactions were carried out in oven-dried glassware under nitrogen atmosphere using standard techniques. Commercially available chemicals were used without further purification. For moisture-sensitive reactions, toluene, THF, and dichloromethane (CH_2Cl_2) were dried using a standard solvent purification system. The following dry solvents are commercially available and were used without further purification: acetonitrile, Acros Organics, 99.9% extra-dry, over molecular sieves; methanol, Acros Organics, 99.8% extra-dry, over molecular sieves. Solvents (pet ether, ethyl acetate, CH_2Cl_2, Et_3N) for column chromatography were used after simple distillation. The reactions were monitored by thin-layer chromatography (TLC) visualized by UV (254 nm). The purification was done using column chromatography on silica (Merck, 100−200 mesh) with the specified eluent mixtures (v/v). ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded at room temperature on Bruker AV-200, AV-400, and AV-500 spectrometers in appropriate solvents using TMS as an internal standard, and the chemical shifts are shown in δ scales. Coupling constants (J) are given in hertz (Hz), and the standard abbreviations are used to describe the signal multiplicities. The following abbreviations for single multiplicities are used: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra for all new compounds were recorded based on an ESI+ method and Orbitrap mass analyzer (Thermo Scientific Q-Exactive, Accela 1250 pump). The crystal structure analysis of **3g** was performed on a Bruker KAPPA APEX II CCD Duo diffractometer. All chemicals were purchased from Sigma-Aldrich and used without further purification. The *p*-QMs and sulfoximines were prepared using known literature procedures.[24,25]

General Experimental Procedure for the Synthesis of Diarylmethine Sulfoximines (3a−3r). To a 25 mL round-bottom flask with stir bar were added *p*-QMs **1** (50 mg, 0.1700 mmol, 1 equiv) and sulfoximine **2** (0.1870 mmol, 1.1 equiv) in dry CH_2Cl_2 (2.0 mL), and *p*-TSA (20 mol %) was added in the reaction mixture. The resultant reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the reaction mixture was quenched with water (2 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated in vacuo. The crude was subjected to purification on flash silica gel chromatography (petroleum ether/ethyl acetate = 80:20) to afford diarylmethine sulfoximines (**3a−3r**).

*10-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3a**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3a** as a red solid (81 mg, 89% yield); mp = 98−99 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14−8.23 (m, 2H), 8.02−8.08 (m, 1H), 7.94−8.01 (m, 1H), 7.59−7.70 (m, 4H), 7.20−7.24 (m, 2H), 7.15−7.20 (m, 2H), 7.09−7.14 (m, 1H), 6.79 (s, 2H), 5.38 (s, 1H), 4.98 (s, 1H), 1.29 (s, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 179.3, 152.3, 144.5, 142.0, 141.1, 135.1, 133.8, 133.6, 132.1, 132.1, 131.2, 131.0, 128.8, 128.6, 128.0, 127.2, 126.4, 124.7, 124.4, 124.1, 62.7, 34.2, 30.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{34}H_{35}O_3NNaS$, 560.2230; found, 560.2257.

*10-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-methoxyphenyl)-ethyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3b**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3b** as a yellow gum (76 mg, 87% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.15−8.22 (m, 2H), 8.01−8.06 (m, 1H), 7.94−7.99 (m, 1H), 7.59−7.71 (m, 4H), 7.07−7.14 (m, 2H), 6.78 (s, 2H), 6.69−6.74 (m, 2H), 5.33 (s, 1H), 4.96 (s, 1H), 3.75 (s, 3H), 1.29 (s, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 179.3, 158.1, 152.3, 142.1, 141.2, 136.9, 135.1, 134.1, 133.8, 133.6, 132.1, 132.0, 131.2, 131.0, 128.8, 128.6, 128.3, 124.8, 124.5, 124.0, 113.4, 62.2, 55.2, 34.2, 30.2; HRMS (ESI) m/z: $[M−H]^−$ calcd for $C_{35}H_{36}O_4NS$, 566.2360; found, 566.2379.

*10-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(p-tolyl)methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3c**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3c** as a yellow solid (71 mg, 80% yield); mp = 147−148 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.2−8.2 (m, 2H), 8.0 (dd, J = 8.01, 1.14 Hz, 1H), 8.0 (dd, J = 7.63, 1.53 Hz, 1H), 7.6−7.7 (m, 4H), 7.1 (m, J = 8.01 Hz, 2H), 7.0 (m, J = 8.01 Hz, 2H), 6.8 (s, 2H), 5.3 (s, 1H), 5.0 (s, 1H), 2.3 (s, 3H), 1.3 (s, 18H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 179.3, 152.3, 142.1, 141.7, 141.2, 135.8, 135.1, 134.0, 133.8, 133.5, 132.0, 131.1, 131.0, 128.8, 128.7, 128.6, 127.1, 124.8, 124.5, 124.0, 62.7, 34.2, 30.1, 21.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{35}H_{38}NO_3S$, 552.2572; found, 552.2570.

*10-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-(methylthio)phenyl)-methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3d**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3d** as a yellow solid (65 mg, 76% yield); mp = 134−135 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.2 (dd, J = 9.16, 7.63 Hz, 1H), 8.2 (dd, J = 12.21, 7.63 Hz, 1H), 8.0 (dd, J = 7.63, 1.14 Hz, 1H), 8.0 (dd, J = 7.44, 1.34 Hz, 1H), 7.6−7.7 (m, 4H), 7.1−7.2 (m, 2H), 7.0−7.1 (m, 2H), 6.8 (s, 2 H), 5.3 (s, 1H), 5.0 (s, 1H), 2.4 (s, 3H), 1.3 (s, 18 H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 179.3, 152.4, 142.0, 141.9, 141.1, 136.0, 135.2, 133.9, 133.7, 133.6, 132.1, 131.2, 131.0, 128.9, 128.6, 127.7, 126.6, 124.7, 124.5, 124.0, 62.4, 34.2, 30.1, 16.2; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{35}H_{37}O_3NNaS_2$, 606.2107; found: 606.2120.

*4-((3,5-Di-tert-butyl-4-hydroxyphenyl)((10-oxido-9-oxo-9H-10l4-thioxanthen-10-ylidene)amino)methyl) Benzonitrile (**3e**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3e** as a yellow oil (66 mg, 75% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 8.1−8.2 (m, 2H), 8.0−8.1 (m, 1H), 7.9 (dd, J = 7.25, 1.91 Hz, 1H), 7.7−7.7 (m, 1H), 7.7 (dd, J = 7.63, 1.14 Hz, 1H), 7.6 (ddd, J = 6.87, 4.20, 1.91 Hz, 2H), 7.5 (m, J = 8.39 Hz, 2H), 7.4 (m, J = 8.01 Hz, 2H), 6.7 (s, 2H), 5.4 (s, 1H), 5.0 (s, 1H), 1.3 (s, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 179.2, 152.7, 150.3, 141.6, 140.7, 135.5, 133.9, 133.6, 132.6, 132.4, 132.3, 131.9, 131.3, 131.1, 129.0, 128.8, 127.9, 124.6, 124.3, 123.9, 119.1, 110.0, 62.3, 34.2, 30.2, 30.1; HRMS (ESI) m/z: $[M−H]^−$ calcd for $C_{35}H_{33}O_3N_2S$, 561.2206; found, 561.2225.

*10-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-(trifluoromethyl)-phenyl)methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3f**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3f** as a yellow oil (63 mg, 76% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.16−8.24 (m, 2H), 7.99−8.11 (m, 1H), 7.93−7.99 (m, 1H), 7.59−7.74 (m, 4H), 7.43 (d, J = 8.26 Hz, 2H), 7.34 (d, J = 8.50 Hz, 2H), 6.77 (s, 2H), 5.41 (s, 1H), 5.01 (s, 1H), 1.29 (s, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 179.2, 152.6, 148.7, 141.8, 140.9, 135.4, 133.9, 133.6, 133.1, 132.3, 132.2, 131.3, 131.1, 128.9, 128.7, 127.5, 125.0, 125.0, 124.6, 124.4, 123.9, 62.4, 34.2, 30.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.35; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{35}H_{34}O_3NF_3NaS$, 628.2104; found, 628.2111.

*10-(((4-Bromophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)-methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3g**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3g** as a yellow solid (69 mg, 84% yield); mp = 177−178 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15−8.22 (m, 2H), 8.01−8.06 (m, 1H), 7.92−7.98 (m, 1H), 7.59−7.72 (m, 4H), 7.28−7.32 (m, 2H), 7.10 (d, J = 8.38 Hz, 2H), 6.75 (s, 2H), 5.32 (s, 1H), 4.99 (s, 1H), 1.29 (s, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 179.2, 152.5, 143.8, 141.9, 141.0, 135.3, 133.9, 133.6, 133.4, 132.2, 132.2, 131.2, 131.0, 129.0, 128.9, 128.7, 124.7, 124.4, 123.9, 120.2, 77.2, 62.2, 34.2, 30.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{34}H_{34}O_3NBrNaS$, 638.1340; found, 638.1343.

*10-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(3-methoxyphenyl)-methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3h**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3h** as a red oil (73 mg, 84% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.14−8.24 (m, 2H), 7.97−8.07 (m, 2H), 7.54−7.69

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(m, 4H), 7.08 (t, J = 8.07 Hz, 1H), 6.81 (s, 2H), 6.76−6.80 (m, 2H), 6.66 (ddd, J = 8.16, 2.53, 0.94 Hz, 1H), 5.35 (s, 1H), 4.97 (s, 1H), 3.70 (s, 3H), 1.29 (s, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 179.3, 159.3, 152.4, 146.0, 142.0, 141.2, 135.1, 133.8, 133.6, 132.1, 131.2, 131.0, 128.9, 128.8, 128.6, 124.7, 124.5, 124.1, 119.8, 112.6, 112.2, 62.7, 55.1, 34.2, 30.2; HRMS (ESI) m/z: $[M-H]^-$ calcd for $C_{35}H_{36}O_4NS$, 566.2360; found, 566.2381.

*10-(((3-Chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)-methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3i**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3i** as a red solid (71 mg, 82% yield); mp = 125−126 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14−8.24 (m, 2H), 8.05 (dd, J = 7.69, 1.06 Hz, 1H), 7.90−8.01 (m, 1H), 7.59−7.73 (m, 4H), 7.21−7.25 (m, 1H), 7.02−7.10 (m, 3H), 6.76 (s, 2H), 5.32 (s, 1H), 5.00 (s, 1H), 1.30 (s, 18H); ^{13}C {^1H} NMR (101 MHz, $CDCl_3$): δ 179.2, 152.5, 146.7, 141.8, 141.0, 135.3, 133.9, 133.8, 133.6, 133.2, 132.3, 132.2, 131.2, 131.0, 129.2, 128.9, 128.7, 127.4, 126.5, 125.4, 124.7, 124.4, 124.0, 62.3, 34.2, 30.1; HRMS (ESI) m/z: $[M-H]^-$ calcd for $C_{34}H_{33}O_3NClS$, 570.1864; found, 570.1890.

*10-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(2-fluorophenyl)-methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3j**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3j** as a yellow solid (72 mg, 81% yield); mp = 114−115 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.21−8.25 (m, 1H), 8.16 (dd, J = 7.78, 1.37 Hz, 1H), 8.06 (dd, J = 8.01, 1.15 Hz, 1H), 7.99−8.04 (m, 1H), 7.60−7.68 (m, 4H), 7.40−7.49 (m, 2H), 7.05−7.13 (m, 1H), 6.98 (td, J = 7.44, 1.14 Hz, 1H), 6.81−6.89 (m, 3H), 5.73 (s, 1H), 4.99 (s, 1H), 1.29 (s, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 179.3, 158.1, 152.4, 141.7, 140.8, 135.1, 133.9, 133.6, 133.0, 132.2, 132.1, 131.7, 131.5, 131.1, 130.9, 129.3, 129.0, 129.0, 128.9, 128.6, 128.0, 127.9, 124.8, 124.3, 124.0, 123.8, 114.9, 114.7, 55.2, 34.2, 30.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{35}FNO_3S$, 556.2316; found: 556.2303.

*10-(((2-Bromophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)-methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3k**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3k** as a brown gum (60 mg, 73% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 8.21−8.27 (m, 1H), 8.15 (dd, 7.69, 1.06 Hz, 1H), 8.07 (dd, J = 7.75, 0.88 Hz, 1H), 8.00−8.05 (m, 1H), 7.64−7.72 (m, 3H), 7.57−7.62 (m, 1H), 7.52 (dd, = 7.82, 1.69 Hz, 1H), 7.35 (dd, J = 8.00, 1.13 Hz, 1H), 7.11−7.16 (m, 1H), 6.94−6.98 (m, 1H), 6.92−6.94 (m, 2H), 5.80 (s, 1H), 4.99 (s, 1H), 1.30 (s, 18H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 179.3, 152.5, 143.4, 141.7, 140.9, 135.1, 133.9, 133.7, 133.0, 132.2, 132.1, 132.1, 131.1, 130.9, 130.0, 128.9, 128.7, 127.9, 127.5, 124.9, 124.4, 124.0, 122.8, 61.0, 34.2, 30.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{35}BrNO_3S$, 616.1521; found, 616.1509.

*10-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(3,4-dichlorophenyl)-methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3l**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3l** as a red oil (70 mg, 85% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.21−8.26 (m, 1H), 8.15−8.20 (m, 1H), 8.03−8.08 (m, 1H), 7.98−8.02 (m, 1H), 7.62−7.73 (m, 4H), 7.47 (d, J = 8.50 Hz, 1H), 7.19 (d, J = 2.13 Hz, 1H), 7.08 (dd, J = 8.50, 1.88 Hz, 1H), 6.87 (s, 2H), 5.77 (s, 1H), 5.01 (s, 1H), 1.29 (s, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 179.3, 152.6, 141.6, 140.8, 140.7, 135.2, 133.9, 133.7, 132.6, 132.5, 132.4, 132.3, 132.2, 131.2, 130.9, 130.5, 129.0, 128.7, 128.5, 127.2, 124.8, 124.3, 123.9, 77.2, 58.1, 34.2, 30.1; HRMS(ESI) m/z: $[M-H]^-$ calcd for $C_{34}H_{32}O_3NCl_2S$, 604.1474; found, 604.1498.

*10-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(3,5-dimethylphenyl)-methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3m**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3m** as a yellow solid (68 mg, 78% yield); mp = 166−167 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.1−8.2 (m, 2H), 7.9−8.1 (m, 2H), 7.6−7.7 (m, 4H), 6.8 (s, 2H), 6.8 (s, 2H), 6.7 (s, 1H), 5.3 (s, 1H), 5.0 (s, 1H), 2.2 (s, 6H), 1.3 (s, 18H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 179.1, 152.3, 144.0, 141.9, 141.3, 137.3, 135.0, 134.1, 133.8, 133.6, 132.0, 131.1, 131.0, 128.7, 128.5, 128.1, 125.0, 124.7, 124.5, 124.0, 63.0, 34.2, 30.1, 21.2; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{36}H_{39}O_3NNaS$, 588.2543; found, 588.2560.

*10-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(3,4,5-trimethoxy-phenyl)methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3n**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3n** as a yellow oil (70 mg, 86% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.13−8.26 (m, 2 H), 7.94−8.10 (m, 2 H), 7.55−7.76 (m, 4H), 6.87 (s, 2H), 6.36 (s, 2H), 5.34 (s, 1H), 5.02 (s, 1H), 3.77 (s, H), 3.71 (s, 6H), 1.31 (s, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 179.4, 152.7, 152.5, 141.7, 141.4, 139.4, 135.2, 133.9, 133.6, 132.2, 132.2, 128.7, 128.6, 124.6, 124.5, 124.1, 104.5, 62.6, 60.7, 55.9, 34.2, 30.2; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{37}H_{41}O_6NNaS$, 650.2547; found, 650.2554.

*10-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(naphthalen-1-yl)-methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3o**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3o** as a red gum (70 mg, 83% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.19−8.26 (m, 1H), 8.10−8.18 (m, 2H), 7.92−7.99 (m, 1H), 7.84−7.91 (m, 1H), 7.70−7.80 (m, 1H), 7.62 (d, J = 7.88 Hz, 1H), 7.49−7.57 (m, 4H), 7.38−7.44 (m, 2H), 7.29−7.33 (m, 1H), 7.27 (d, J = 7.88 Hz, 1H), 6.96 (s, 2H), 6.21 (s, 1H), 4.99 (s, 1H), 1.27 (s, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 179.2, 152.3, 141.5, 141.5, 139.2, 135.1, 133.8, 133.7, 133.3, 133.2, 132.0, 131.8, 131.0, 131.0, 130.7, 128.7, 128.5, 128.4, 127.5, 126.0, 125.5, 125.3, 125.1, 124.6, 124.5, 124.4, 124.4, 59.7, 34.2, 30.2; HRMS (ESI) m/z: $[M-H]^-$ calcd for $C_{38}H_{36}O_3NS$, 586.2410; found, 586.2431.

*10-(((4-Hydroxy-3,5-dimethylphenyl)(phenyl)methyl)imino)-10l4-thioxanthen-9(10H)-one 10-Oxide (**3r**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **3r** as a yellow solid (96 mg, 89% yield); mp = 174−175 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10−8.25 (m, 2H), 7.94−8.06 (m, 2H), 7.59−7.70 (m, 4H), 7.04−7.22 (m, 5H), 6.48−6.68 (m, 2H), 5.28 (s, 1H), 4.51 (s, 1H), 2.04 (s, 7H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 179.2, 150.8, 144.2, 141.8, 141.2, 135.2, 133.7, 132.1, 132.0, 131.2, 131.0, 128.7, 128.6, 128.0, 127.5, 127.0, 126.4, 124.7, 124.5, 122.5, 62.4, 15.8; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{28}H_{23}O_3NNaS$, 476.1261; found, 476.1302.

General Experimental Procedure for the Synthesis of Diarylmethine Sulfoximines (5a−5r). To a 25 mL round-bottom flask with a stir bar were added *p*-QMs **1** (50 mg, 0.34 mmol, 1 equiv) and sulfoximine **4** (0.37 mmol, 1.1 equiv) in dry CH_2Cl_2 (2.0 mL), and *p*-TSA (20 mol %) was added in the reaction mixture. The resultant reaction mixture was stirred at room temperature for 1 h. After completion (monitored by TLC), the reaction mixture was quenched with water (2 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layer washed with brine (10 mL), dried over Na_2SO_4, and evaporated under vacuo. The crude was subjected to purification on flash silica gel chromatography (petroleum ether/ethyl acetate = 80:20) to afford diarylmethine sulfoximines (**5a−5s**).

*(((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)imino) Diphenyl-l6-sulfanone (**5a**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5a** as a yellow solid (82 mg, 95% yield); mp = 138−139 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94−7.98 (m, 2H), 7.81−7.88 (m, 2H), 7.35−7.48 (m, 8H), 7.25−7.30 (m, 2H), 7.17−7.21 (m, 1H), 7.15 (s, 2H), 5.40 (s, 1H), 5.04 (s, 1H), 1.39 (s, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 152.2, 146.0, 141.3, 141.2, 136.0, 135.1, 132.2, 132.0, 128.8, 128.8, 128.7, 128.6, 127.9, 127.5, 126.2, 124.5, 61.6, 34.3, 30.3; HRMS (ESI) m/z: $[M-H]^-$ calcd for $C_{33}H_{36}O_2NS$, 510.2461; found, 510.2481.

*(((3,5-Di-tert-butyl-4-hydroxyphenyl)(p-tolyl)methyl)imino) Diphenyl-l6-sulfanone (**5b**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5b** as a yellow oil (76 mg, 90% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.94−7.98 (m, 2H), 7.81−7.88 (m, 2H), 7.33−7.49 (m, 6H), 7.27−7.31 (m, 3H), 7.15 (s, 2H), 7.07 (d, J = 7.88 Hz, 2H), 5.35 (s, 1H), 5.02 (s, 1H), 2.32 (s, 3H), 1.39 (s, 18H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 152.2, 143.1, 141.4, 141.3, 136.2, 135.5, 135.0, 132.1, 132.0, 129.0, 128.8, 128.8, 128.7, 128.6, 127.4, 126.3, 124.4, 123.5, 76.6, 61.5, 34.4, 34.3, 30.4, 21.1; HRMS (ESI) m/z: $[M-H]^-$ calcd for $C_{34}H_{38}O_2NS$, 524.2618; found, 524.2637.

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*(((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl)-imino) Diphenyl-l6-sulfanone (**5c**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5c** as a yellow oil (71 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90−8.00 (m, 2H), 7.81−7.89 (m, 2H), 7.28−7.50 (m, 8H), 7.15 (s, 2H), 6.82 (d, J = 8.76 Hz, 2H), 5.35 (s, 1H), 5.04 (s, 1H), 3.79 (s, 3H), 1.39 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.0, 152.2, 141.4, 141.2, 138.4, 136.3, 135.1, 132.2, 132.1, 128.9, 128.8, 128.8, 128.7, 128.6, 124.4, 113.3, 61.1, 55.2, 34.3, 30.4. HRMS (ESI) m/z: [M−H]$^-$ calcd for $C_{34}H_{38}O_3NS$, 540.2567; found, 540.2587.

*5-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)imino)-5H-5l4-dibenzo[b,d]thiophene 5-Oxide (**5d**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5d** as a yellow gum (79 mg, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 7.63 Hz, 2H), 7.50−7.55 (m, 1H), 7.47 (dd, J = 7.50, 0.88 Hz, 2H), 7.41 (d, J = 7.25 Hz, 2H), 7.34 (td, J = 7.57, 0.88 Hz, 1H), 7.15−7.26 (m, 4H), 7.06 (s, 2H), 7.02 (d, J = 7.75 Hz, 1H), 5.73 (s, 1H), 5.06 (s, 1H), 1.32 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.6, 145.3, 139.6, 139.4135.5, 135.0, 132.9, 132.4, 132.2, 131.7, 129.8, 129.6, 128.0, 127.4, 126.4, 124.5, 123.1, 123.1, 121.0, 121.0, 61.6, 34.3, 30.3; HRMS (ESI) m/z: [M−H]$^-$ calcd for $C_{33}H_{34}O_2NS$, 508.2305; found, 508.2323.

*5-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(p-tolyl)methyl)imino)-5H-5l4-dibenzo[b,d]thiophene 5-Oxide (**5e**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5e** as a white solid (76 mg, 90% yield); mp = 177−178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.75 Hz, 2H), 7.50−7.55 (m, 1H), 7.44−7.50 (m, 2H), 7.28−7.35 (m, 3H), 7.21 (td, J = 7.57, 1.00 Hz, 1H), 7.04−7.08 (m, 4H), 7.01 (d, J = 7.38 Hz, 1H), 5.69 (s, 1H), 5.04 (s, 1H), 2.31 (s, 3H), 1.32 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.6, 142.4, 139.6, 139.4, 135.8, 135.4, 135.2, 132.9, 132.3, 132.2, 131.7, 129.7, 129.6, 128.7, 127.3, 124.4, 123.2, 123.0, 121.0, 120.9, 61.5, 34.2, 30.3, 21.0; HRMS (ESI) m/z: [M−H]$^-$ calcd for $C_{34}H_{36}O_2NS$, 522.2461; found, 522.2482.

*5-(([1,1′-biphenyl]-4-yl(3,5-di-tert-butyl-4-hydroxyphenyl)-methyl)imino)-5H-5l4-dibenzo[b,d]thiophene 5-Oxide (**5f**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5f** as a white solid (66 mg, 84% yield); mp = 151−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71−7.76 (m, 2H), 7.56−7.60 (m, 2H), 7.50−7.55 (m, 2H), 7.46−7.50 (m, 5H), 7.40−7.46 (m, 2H), 7.30−7.37 (m, 2H), 7.20−7.25 (m, 1H), 7.11 (s, 2H), 7.03 (d, J = 7.50 Hz, 1H), 5.77 (s, 1H), 5.08 (s, 1H), 1.34 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.7, 144.5, 141.2, 139.5, 139.3, 139.2, 135.6, 134.9, 133.0, 132.4, 132.2, 131.7, 129.8, 129.6, 128.7, 127.8, 127.0, 127.0, 126.8, 124.5, 123.2, 123.0, 121.0, 121.0, 61.5, 34.3, 30.3; HRMS (ESI) m/z: [M−H]$^-$ calcd for $C_{39}H_{38}O_2NS$, 584.2618; found, 584.2639.

*5-(((4-(Benzyloxy) phenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)-methyl)imino)-5H-5l4-dibenzo[b,d]thiophene 5-Oxide (**5g**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5g** as a yellow solid (65 mg, 85% yield); mp = 76−77 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 7.63 Hz, 2H), 7.52 (td, J = 7.57, 1.13 Hz, 1H), 7.41−7.49 (m, 4H), 7.35−7.41 (m, 2H), 7.28−7.35 (m, 4H), 7.21 (td, J = 7.60, 0.94 Hz, 1 H), 7.01−7.06 (m, 3 H), 6.83−6.91 (m, 2 H), 5.69 (s, 1H), 5.05 (s, 3H), 1.32 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):δ 157.4, 152.6, 139.6, 139.4, 137.9, 137.2, 135.5, 135.2, 132.9, 132.3, 132.2, 131.7, 129.8, 129.6, 128.5, 128.5, 127.8, 127.4, 124.4, 123.1, 123.0, 121.0, 121.0, 114.4, 70.0, 61.0, 34.3, 30.3; HRMS (ESI) m/z: [M−H]$^+$calcd for $C_{40}H_{42}NO_3S$, 616.2880; found, 616.2880.

*5-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-fluorophenyl)methyl)-imino)-5H-5l4-dibenzo[b,d]thiophene 5-Oxide (**5h**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5h** as a yellow solid (72 mg, 86% yield); mp = 207−208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71−7.75 (m, 2H), 7.46−7.57 (m, 3H), 7.33−7.40 (m, 3H), 7.22 (td, J = 7.57, 1.00 Hz, 1H), 7.02 (s, 2H), 6.90−7.00 (m, 3H), 5.70 (s, 1H), 5.08 (s, 1H), 1.32 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.8. 160.3, 152.7, 141.1, 141.1, 139.5, 139.2, 135.6, 134.8, 133.1, 132.4, 132.2, 131.7, 129.9, 129.6, 128.9, 128.9, 124.4, 123.1, 123.0, 121.1, 114.8, 114.6, 77.3, 77.2, 76.7, 60.9, 34.3, 30.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ −117.1; HRMS (ESI) m/z: [M−H]$^-$ calcd for $C_{33}H_{33}O_2NFS$, 526.2211; found, 526.2236.

*5-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(3,4-dimethoxyphenyl)-methyl)imino)-5H-5l4-dibenzo[b,d]thiophene 5-Oxide (**5i**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5i** as a yellow oil (67 mg, 84% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (dd, J = 7.79, 2.75 Hz, 2H), 7.45−7.53 (m, 2H), 7.24−7.36 (m, 3H), 7.17 (d, J = 7.33 Hz, 1H), 7.07 (s, 2H), 6.99 (d, J = 1.83 Hz, 1H), 6.85 (dd, J = 8.01, 2.06 Hz, 1H), 6.76 (d, J = 8.24 Hz, 1H), 5.71 (s, 1H), 5.07 (s, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 1.33 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.5, 148.6, 147.6, 139.3, 137.7, 135.3, 135.0, 132.8, 132.5, 132.0, 131.8, 129.7, 129.6, 124.3, 123.0, 123.0, 121.0, 121.0, 119.6, 110.8, 110.6, 61.1, 55.9, 55.7, 34.2, 30.2; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{35}H_{40}NO_4S$, 570.2673; found, 570.2680.

*5-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(3,5-dimethylphenyl)-methyl)imino)-5H-5l4-dibenzo[b,d]thiophene 5-Oxide (**5j**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5j** as a yellow solid (67 mg, 81% yield); mp = 178−179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (dd, J = 7.75, 2.88 Hz, 2H), 7.45−7.54 (m, 2H), 7.39−7.43 (m, 1H), 7.33 (dd, J = 7.50, 0.88 Hz, 1H), 7.23 (d, J = 1.00 Hz, 1H), 7.06 (s, 3H), 7.01 (s, 2H), 6.81 (s, 1H), 5.61 (s, 1H), 5.04 (s, 1H), 2.24 (s, 6H), 1.33 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):δ 152.5, 145.0, 139.5, 139.3, 137.4, 135.3, 135.2, 132.8, 132.4, 132.1, 131.8, 129.7, 129.5, 128.1, 125.2, 124.4, 123.3, 123.1, 121.0, 120.9, 61.8, 34.3, 30.3, 21.3; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{35}H_{39}O_2NNaS$, 560.2594; found, 560.2603.

*5-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)imino)-10-methyl-5,10-dihydro-5l4-phenothiazine 5-Oxide (**5k**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5k** as a yellow solid (74 mg, 81% yield); mp = 147−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (dt, J = 7.79, 1.61 Hz, 2H), 7.4−7.5 (m, 2H), 7.2−7.2 (m, 4H), 7.1−7.2 (m, 5H), 6.9 (s, 2H), 5.3 (s, 1H), 5.0 (s, 1H), 3.5 (s, 3H), 1.3 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.1, 145.2, 141.8, 141.7, 135.3, 134.9, 132.2, 132.2, 127.6, 127.5, 125.9, 124.9, 124.8, 124.6, 124.5, 124.3, 121.5, 121.3, 115.0, 114.9, 61.6, 35.6, 34.2, 30.3; HRMS (ESI) m/z: [M−H]$^-$ calcd for $C_{34}H_{37}O_2N_2S$, 537.2570; found, 537.2591.

*5-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-methoxyphenyl)-methyl)imino)-10-methyl-5,10-dihydro-5l4-phenothiazine 5-Oxide (**5l**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5l** as a yellow oil (76 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, J = 7.75, 1.63 Hz, 2H),7.48 (dddd, J = 8.58, 7.18, 4.50, 1.63 Hz, 2H), 7.07−7.18 (m, 6H), 6.87 (s, 2H), 6.67−6.77 (m, 2H), 5.29 (s, 1H), 4.97 (s, 1H), 3.77 (s, 3H), 3.51 (s, 3H), 1.32 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.8, 152.1, 141.8, 137.7, 135.5, 134.8, 132.2, 128.5, 125.0, 124.9, 124.7, 124.4, 124.3, 121.5, 121.3, 115.0, 114.9, 113.1, 61.0, 55.2, 35.6, 34.2, 30.3; HRMS (ESI) m/z: [M−H]$^-$ calcd for $C_{35}H_{39}O_3N_2S$, 567.2676; found, 567.2698.

*5-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-fluorophenyl)methyl)-imino)-10-methyl-5,10-dihydro-5l4-phenothiazine 5-Oxide (**5m**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5m** as a red oil (71 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dt, J = 7.79, 1.61 Hz, 2H), 7.46−7.53 (m, 2H), 7.07−7.19 (m, 6H), 6.81−6.87 (m, 4H), 5.32 (s, 1H), 4.98 (s, 1H), 3.51 (s, 3H), 1.32 (s, 18H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$): δ 152.2, 141.8, 141.1, 135.2, 135.0, 132.3, 129.0, 129.0, 124.9, 124.8, 124.6, 124.5, 124.3, 121.6, 121.4, 115.1, 115.0, 114.4, 114.2, 77.2, 60.8, 35.6, 34.2, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ −117.5; HRMS (ESI) m/z: [M−H]$^-$ calcd for $C_{34}H_{36}O_2N_2FS$, 555.2476; found, 555.2502.

*(((3,5-Di-tert-butyl-4-hydroxyphenyl)(thiophen-2-yl)methyl)-imino) Diphenyl-l6-sulfanone (**5n**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5n** as a white solid (64 mg, 75% yield); mp = 180−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95−8.01 (m, 2 H),7.87−7.94 (m, 2H), 7.32−7.51 (m, 6H), 7.12−7.20 (m, 3H), 6.88 (dd, J = 5.00, 3.50 Hz, 1H), 6.70−6.78 (m, 1H), 5.60 (s, 1H), 5.06 (s, 1H), 1.39 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.6, 151.8, 141.1, 140.9, 135.4, 135.1, 132.3,

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132.2, 128.9, 128.8, 128.6, 126.3, 124.2, 123.9, 123.8, 77.2, 57.9, 34.3, 30.3; HRMS (ESI) m/z: $[M-H]^-$ calcd for $C_{31}H_{34}O_2NS_2$, 516.2025; found, 516.2045.

*(((3,5-Di-tert-butyl-4-hydroxyphenyl)(p-tolyl)methyl)imino) (Methyl)(p-tolyl)-l6-sulfanone (**5o**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5o** as a yellow oil (55 mg, 72% yield, dr = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.38 Hz, 2H), 7.62 (d, J = 8.25 Hz, 2H), 7.32 (m, J = 8.00 Hz, 2H), 7.21 (d, J = 7.88 Hz, 2H), 7.19 (s, 2H), 7.16 (dd, J = 7.75, 7.00 Hz, 4H), 7.09 (m, J = 7.88 Hz, 2H), 7.02 (d, J = 7.75 Hz, 2H), 6.96 (s, 2H), 5.30 (s, 1H), 5.28 (s, 1H), 5.03 (s, 1H), 4.98 (s, 1H), 3.07 (s, 3H), 3.05 (s, 3H), 2.41 (s, 3H), 2.38 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H), 1.39 (s, 18H), 1.34 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.2, 152.2, 143.2, 143.0, 142.9, 142.6, 136.1, 135.7, 135.5, 135.5, 135.0, 135.0, 129.5, 129.4, 128.6, 128.6, 128.5, 127.5, 127.3, 124.6, 124.3, 61.2, 61.1, 45.7, 45.5, 34.3, 34.2, 30.3, 30.3, 21.4, 21.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{30}H_{39}NO_2NaS$, 500.2599; found, 500.2590.

*(((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl)-imino) (Methyl)(p-tolyl)-l6-sulfanone (**5p**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5p** as a yellow oil (57 mg, 75% yield, dr = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.24 Hz, 2H), 7.66 (d, J = 8.24 Hz, 2H), 7.35 (d, J = 8.70 Hz, 2H), 7.14−7.23 (m, 9H), 6.94 (s, 2H), 6.84 (s, 1H), 6.82 (s, 1H), 6.77 (s, 1H), 6.75 (s, 1H), 5.29 (s, 1H), 5.27 (s, 1H), 5.04 (s, 1H), 5.00 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.08 (s, 3H), 3.05 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H), 1.39 (s, 18H), 1.34 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.9, 157.9, 152.2, 152.1, 143.2, 142.9, 138.2, 137.9, 137.4, 137.4, 136.1, 135.8, 135.0, 129.5, 129.4, 128.7, 128.6, 128.5, 124.6, 124.3, 113.3, 113.2, 60.7, 60.7, 55.2, 45.8, 45.5, 34.3, 34.2, 30.3, 30.2, 21.4; HRMS (ESI) m/z: $[M-H]^-$ calcd for $C_{30}H_{38}O_3NS$, 492.2578; found, 492.2567.

*1-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(p-tolyl)methyl)imino) Tetrahydro-1H-1l6-thiophene 1-Oxide (**5q**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5q** as a yellow oil (59 mg, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, J = 8.13 Hz, 2H), 7.19 (s, 2H), 7.10 (m, J = 7.75 Hz, 2H), 5.54 (s, 1H), 5.07 (s, 1H), 2.77−2.92 (m, 4H), 2.32 (s, 3H), 2.02−2.14 (m, 4H), 1.40 (s, 18H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.5, 142.4, 136.0, 135.5, 135.4, 128.9, 127.5, 124.3, 61.3, 52.8, 52.4, 34.4, 30.3, 23.3, 23.2, 21.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{38}NO_2S$, 428.2623; found, 428.2605.

*5-(((4-Hydroxy-3,5-dimethylphenyl)(phenyl)methyl)imino)-5H-5l4-dibenzo[b,d]thiophene 5-Oxide (**5r**).* Purification on silica gel (petroleum ether/EtOAc = 8:2) afforded compound **5r** as a white solid (81 mg, 80% yield); mp = 186−187 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.24 Hz, 2H), 7.48−7.55 (m, 2H), 7.26−7.35 (m, 6H), 7.09−7.26 (m, 3H), 6.87 (s, 2H), 5.59 (s, 1H), 4.59 (br s, 1H), 2.12 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 150.9, 145.1, 139.2, 139.0, 136.3, 132.8, 132.0, 129.7, 128.1, 127.7, 127.3, 126.4, 123.1, 123.0, 122.5, 121.1, 121.0, 61.2, 15.9; HRMS (ESI) m/z: $[M-H]^+$ calcd for $C_{27}H_{24}O_2NS$, 426.1523; found, 426.1517.

General Experimental Procedure for Synthetic Transformation of Formed Product 3d. To a 25 mL round-bottom flask, **3d** (40 mg, 0.068 mmol, 1 equiv) was added to methanol, $NaBH_4$ (0.068 mmol, 1 equiv) was added portion-wise at 0 °C, and the reaction slowly brought to room temperature and stirred for 1 h at the same temperature; after completion of the reaction (monitored by TLC), the solvent was evaporated on a rotary evaporator under reduced pressure and the residue was extracted with ethyl acetate (3 × 3 mL) and water and washed with brine. The combined organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified on flash chromatography (silica gel 100−200 mesh) with petroleum ether/ethyl acetate (v/v, 6/4) to afford the corresponding product **6** in 80% yield.

*10-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-(methylthio)phenyl)-methyl)imino)-9-hydroxy-9,10-dihydro-10l4-thioxanthene 10-Oxide (**6**).* Purification on silica gel (petroleum ether/EtOAc = 6:4) afforded compound **6** as a yellow oil (29 mg, 72% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.0−8.1 (m, 1H), 8.0 (dd, J = 7.63, 1.14 Hz, 1H), 7.7−7.8 (m, 2H), 7.5−7.6 (m, 1H), 7.4−7.5 (m, 3H), 7.1 (q, J = 8.39 Hz, 4H), 6.8 (s, 2H), 5.8 (br s, 1H), 5.3 (s, 1H), 5.0 (s, 1H), 2.4 (s, 3H), 1.3 (s, 18H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.3, 142.3, 142.0, 141.5, 135.7, 135.1, 134.5, 131.8, 131.6, 128.0, 127.5, 127.3, 126.6, 125.5, 125.1, 124.3, 123.9, 123.9, 67.0, 61.9, 34.2, 30.3, 16.2; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{35}H_{40}O_3NS_2$, 586.2444; found, 586.2463.

General Experimental Procedure for Gram-Scale Synthesis of (3c). To a 100 mL round-bottom flask with a stir bar were added p-QMs **1c** (1 g, 3.24 mmol, 1 equiv) and sulfoximine **2a** (3.57 mmol, 1.1 equiv) in dry CH_2Cl_2 (20 mL), and p-TSA (20 mol %) was added in the reaction mixture. The resultant reaction mixture was stirred at room temperature. After completion (monitored by TLC), the reaction mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer washed with brine (30 mL), dried over Na_2SO_4, and evaporated in vacuo. The crude product was subjected to purification on flash silica gel chromatography (petroleum ether/ethyl acetate = 80:20) to afford **3c** in 82% yield (1.4 g).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00869.

^{1}H, ^{13}C{^{1}H}, and ^{19}F NMR spectra of synthesized compounds, and X-ray crystallographic data of compound **3g** (PDF)

Accession Codes

CCDC 2076733 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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Lewis acid triggered *N*-alkylation of sulfoximines through nucleophilic ring-opening of donor–acceptor cyclopropanes: synthesis of γ-sulfoximino malonic diesters†

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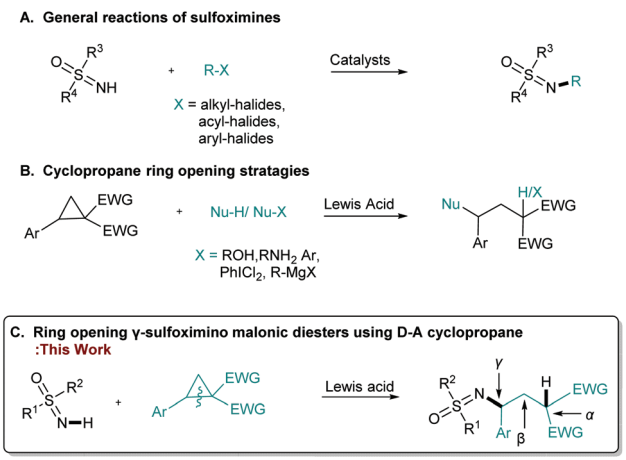
Scandium triflate ($Sc(OTf)_3$) catalyzed, mild, and regioselective ring-opening reaction of donor–acceptor (D–A) cyclopropanes has been developed using sulfoximines for the synthesis of γ-sulfoximino malonic diesters. This protocol allows the synthesis of different *N*-alkyl sulfoximines in good to excellent yields (up to 94%) with broad functional group tolerance. In this process, N–H and C–C bonds are cleaved to form new C–N and C–H bonds. The feasibility of this method is supported by a gram-scale reaction and synthetic elaboration of the obtained product.

Introduction

Sulfoximines were discovered in the late 1940s;[1] since then, they have emerged as valuable moieties in a broad range of applications.[2,3] The exciting properties of sulfoximines, such as hydrogen bonding (associated with functional groups), high stability, suitable physicochemical properties, and structural diversity, make them essential pharmacophores in medicine and agrochemistry.[2] Due to their stable configuration and chemical stability, sulfoximines can be used as chiral auxiliaries in asymmetric catalysis[4,5] and as ligands in C–H activation.[6] The *N*-functionalization of *N*H-sulfoximines offers molecular diversity through *N*-arylation, *N*-alkylation, *N*-cyanation, *N*-propargylation, and many more.[7]

On the other hand, cyclopropane dicarboxylates[8] are simple and commercially available starting materials extensively used to synthesize natural products. The unique D–A characteristics of cyclopropane have made it a valuable component in a wide range of ring-opening,[9] cycloaddition,[10] and rearrangement reactions.[11] As a result, D–A cyclopropane has been studied for several decades and its applications in natural product synthesis, and heterocyclic and medicinal chemistry have been explored.[8] There are reports in the literature on the successful development of ring-opening strategies for D–A cyclic moieties to its open-chain system with the help of various carbon nucleophiles and heteroatoms (*e.g.*, phenols, amines, indoles, and azides, Scheme 1, eqn (b)).[12] However, there are no reports in the literature on the D–A cyclopropane ring opening using sulfoximines. So, we proposed to utilize the nucleophilic properties of *N*H-sulfoximines and the D–A properties of cyclopropane dicarboxylates to form unique γ-sulfoximino malonic diesters moieties.

The Bolm group is a front runner in the field of sulfoximines and they have demonstrated the applications of sulfoximines in a wide range of reactions.[13] In 2014, Bolm and co-workers developed a new strategy for the *N*-alkylation of sulfoximines with diaryl methanes through an iron-catalyzed C–N



Scheme 1 Reactions of sulfoximines, D–A cyclopropane, and present work.

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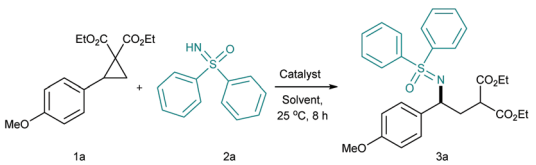
bond formation reaction.[14] Recently, we have developed an acid-catalyzed 1,6-conjugate addition of *N*H-sulfoximines to *para*-quinone methides (*p*-QMs) *via* C–N bond formation to synthesize diarylmethine imino sulfanones.[15] Inspired by the recent advances in sulfoximine synthesis and our ongoing commitment to developing synthetic methodologies,[16] herein, we report the *N*-alkylation of sulfoximines by a Lewis acid-catalysed opening of D–A cyclopropane carboxylate, resulting in direct C–N bond formation (Scheme 1, eqn (c)).

Results and discussion

Based on our previous report,[15] we started our investigation on the feasibility of the reaction using 1 equivalent of D–A cyclopropane **1a** and 1.2 equivalents of sulfoximine **2a** as model substrates in the presence of a catalytic amount of a Brønsted acid (*i.e.*, *p*-TSA, 10 mol%) in CH_2Cl_2. In this reaction, we observed the formation of a smaller amount of the desired product **3a** (24% yield) (Table 1, entry 1) within 12 h at room temperature. Then, we varied the Brønsted acids used, such as TFA and TfOH, which resulted in low yields (Table 1, entries 2 and 3). After the disappointing results with Brønsted acids, we turned our attention toward Lewis acids and initially used 10 mol% of $Cu(OTf)_2$; surprisingly, we obtained the nucleophilic ring-opening product **3a** in 85% yield (Table 1, entry 4). Next, we screened different Lewis acids such as $Bi(OTf)_3$, $Yb(OTf)_3$, $BF_3{\cdot}Et_2O$ and $Sc(OTf)_3$ (Table 1, entries 4–8) and among these, $Sc(OTf)_3$ was found to be most suitable and gave a high yield (94%) of the corresponding γ-sulfoximino malonic diester **3a** within 8 h (Table 1, entry 8). Furthermore, this reaction was carried out in different solvents like 1,2 dichloroethane, acetonitrile, THF, and DMF; however, no improvement in yield was observed (Table 1, entries 9–12). The reaction did not proceed in the absence of Lewis acids, and both the starting materials were recovered (Table 1, entry 13). Based on optimization studies, we confirmed that $Sc(OTf)_3$ (10 mol%), DCM, 25 °C, 8 h are the best reaction conditions for the Lewis acid-catalysed ring-opening reactions of D–A cyclopropane with sulfoximines (Table 1, entry 8).

Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

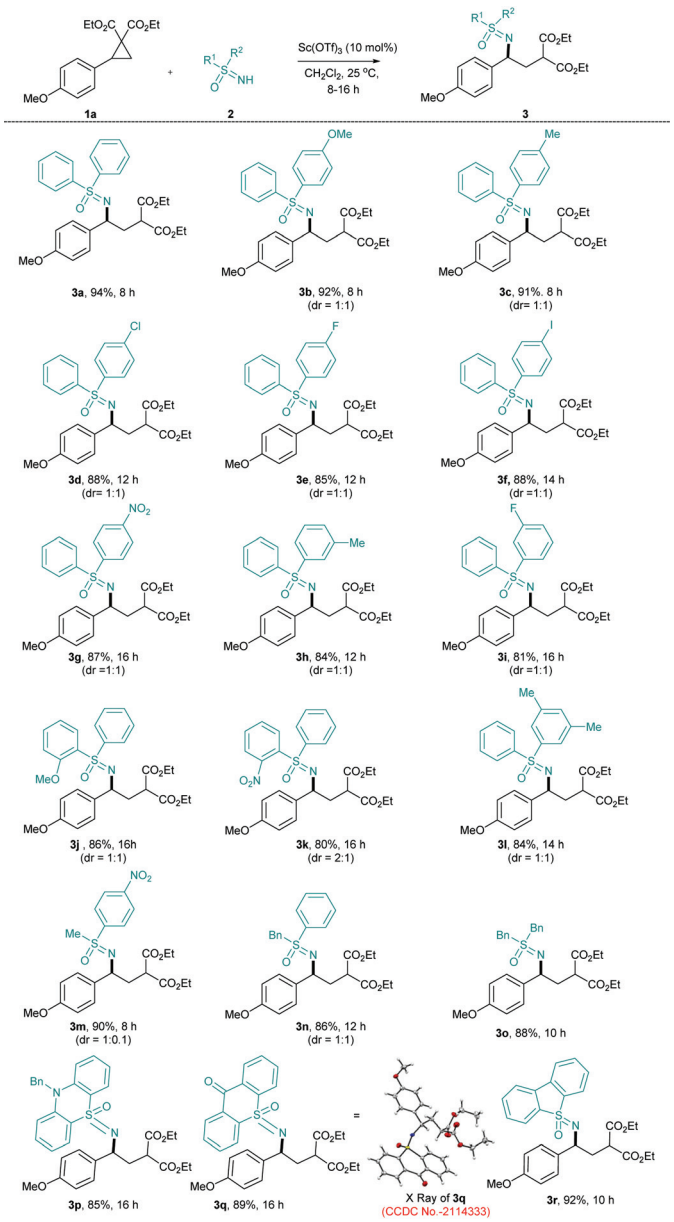
Entry	Catalyst (10 mol%)	Solvent	Yield[b] (%)
1	TsOH	DCM	24
2	TFA	DCM	30
3	TFOH	DCM	34
4	$Cu(OTf)_2$	DCM	85
5	$Bi(OTf)_3$	DCM	83
6	$Yb(OTf)_3$	DCM	65
7	$BF_3.Et_2O$	DCM	40
8	**$Sc(OTf)_3$**	**DCM**	**94**
9	$Sc(OTf)_3$	DCE	90
10	$Sc(OTf)_3$	ACN	60
11	$Sc(OTf)_3$	THF	68
12	$Sc(OTf)_3$	DMF	64
13	—	DCM	NR

[a] Reaction conditions: **1a** (0.17 mmol, 1 equiv.), **2a** (0.20 mmol, 1.2 equiv.), catalyst in solvent (2.0 mL), 8 h at 25 °C under a N_2 atmosphere. [b] Isolated yields after column chromatography, NR = no reaction, DCM = dichloromethane, ACN = acetonitrile, THF = tetrahydrofuran, DMF = dimethyl formamide.

With the optimized reaction conditions in hand (Table 1, entry 8), the substrate scope for the ring-opening reactions was evaluated. First, we examined a range of different sulfoximines, as shown in Table 2. We tested various di-aryl, aryl-alkyl, di-alkyl, and heteroaryl sulfoximines. Unsubstituted di-aryl sulfoximines and sulfoximines with electron-donating and electron-withdrawing groups underwent smooth reaction with D–A cyclopropane; also, the sulfoximines with a halogen at the *para*-position on one of the benzene rings of sufoximines gave the γ-sulfoximino malonic diesters in excellent yields (85% to 94%) (**3a–3g**). Also, the sulfoximines having a substitution at the *meta*- and the *ortho*-position of the aryl ring reacted well under the standard reaction conditions and formed the desired product in 80 to 86% yields (**3h–3l**). Moreover, aryl-alkyl sulfoximines and di-alkyl sulfoximines are also amenable for the ring-opening reactions with D–A cyclopropanes, providing the corresponding products (**3m–3o**) in good yields (88–90%). The unsymmetrical substitution of di-aryl sulfoximines (**2b–2n**) led to the corresponding product (**3b–3n**) in a 1 : 1 diastereomeric ratio (except **3k** and **3m**, which were obtained in a 2 : 1 and 1 : 0.1 ratio, respectively). Next, heterocyclic sulfoximines such as *N*-benzyl phenothiazine, thioxanthone, and dibenzyl thiophene derived sulfoximines reacted well to afford the desired products (**3p–3r**) in excellent yields (85–92%). The structure of product **3q** was unambiguously confirmed by single-crystal X-ray analysis (CCDC no. 2114333, see the ESI†).

After the successful screening of **1a** with different sulfoximines, we explored the addition of sulfoximine **2a** with substituted D–A cyclopropanes under the standard reaction conditions (Table 3). The D–A cyclopropane with neutral (–H), electron-donating (–SMe), electron-withdrawing ($-NO_2$), and halogen (–Cl) groups at the *para*-position of the aromatic ring reacted well with diphenyl sulfoximine **2a** to furnish the desired products (**5a–5d**) in moderate to excellent yields. In addition, the 2-methyl and the 3,4-dimethoxy groups on D–A cyclopropane also participated in the ring-opening strategy with sulfoximine to afford the corresponding products **5e** and **5f** in 84% and 87% yields, respectively. The formation of compounds **5a**, **5c**, and **5d** was not observed at 25 °C, whereas on warming the reaction mixture to 40 °C, surprisingly, the related products were formed in good yields. Because, more energy required to break the cyclopropane bond for compounds **4a**, **4c**, and **4d**. While, increasing the reaction temperature will break the cyclopropane bond, making it suitable for the addition of the weakly nucleophilic sulfoximine. Notably, D–A cyclopropanes having heteroaryl groups such as furyl and

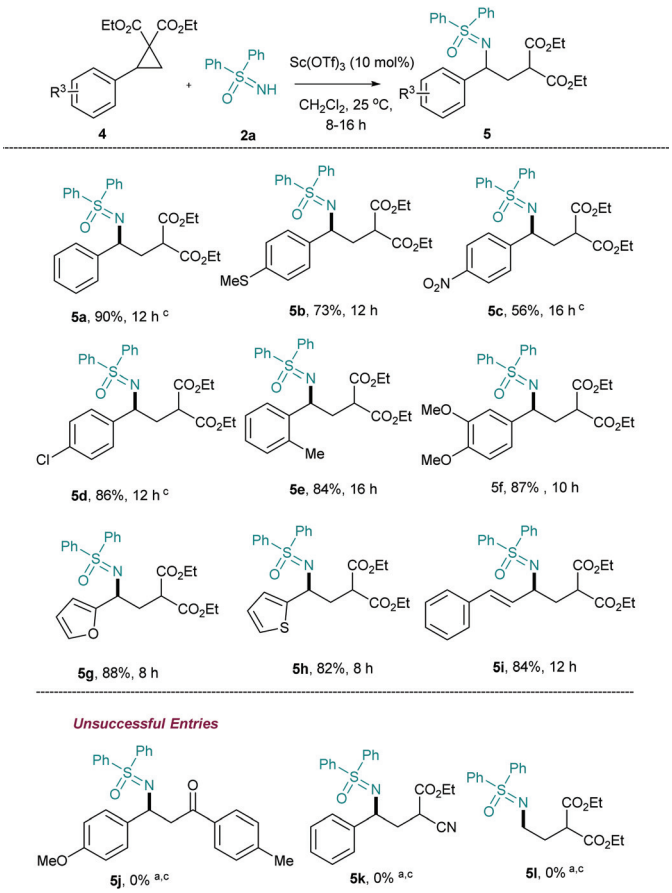
Table 2 Substrate scope of the various sulfoximines[a,b]



[a] Reaction conditions: **1a** (0.17 mmol), **2a-r** (0.20 mmol), $Sc(OTf)_3$ (10 mol%), at 25 °C, 8–16 h, under a N_2 atmosphere. [b] Isolated yields after column chromatographic purification are shown.

thienyl are well tolerated in the ring-opening reaction to furnish the related product (entries **5g** and **5h**, 88% and 82% yield). In addition, styryl D–A cyclopropanes reacted smoothly to afford the related product **5i** in a yield of 84%. We did not observe the formation of the desired products **5j** and **5k** when sulfoximines reacted with the α-cyclopropyl ketone **4j** and the cyano-ester cyclopropane **4k** at 25 °C as well as 40 °C, due to the lower chelation affinity of these cyclopropanes for Lewis acids. In addition, the aliphatic cyclopropane dicarboxylate **4l** remains unreacted under the optimized reaction conditions. The starting materials were recovered because the simple

Table 3 Substrate scope of various D–A cyclopropanes[a,b]

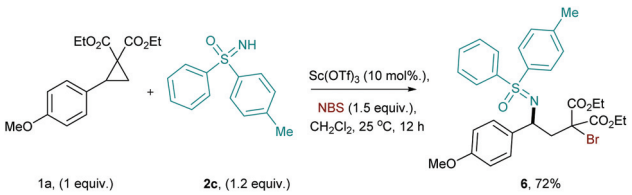


[a] Reaction conditions: **4** (0.19 mmol), **2a** (0.22 mmol), $Sc(OTf)_3$ (10 mol%), 8–16 h at 25 °C, under a N_2 atmosphere. [b] Isolated yields after column chromatographic purification are shown. [c] Reaction was carried out at 40 °C.

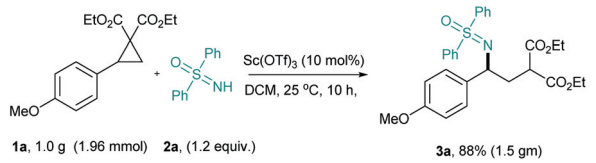
cyclopropane could not stabilize the positive charge that developed in the ring-opening transition state.

After the remarkable achievement of ring-opening of D–A cyclopropane, next, we synthesized γ-sulfoximino, α-bromo malonic diesters **6** by adding an appropriate amount of a halogenating agent (*N*-bromo succinimide) using the standard reaction conditions, as shown in Scheme 2.[17]

Next, the synthetic utility of this reaction was demonstrated through the gram-scale synthesis of **3a** (Scheme 3) using 1.96 mmol (1.0 g scale) of **1a** with 2.35 mmol of **2a**, which pro-



Scheme 2 Synthesis of γ-sulfoximino, α-bromo malonic diesters.

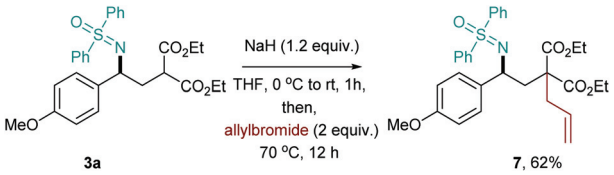


Scheme 3 Gram scale synthesis.

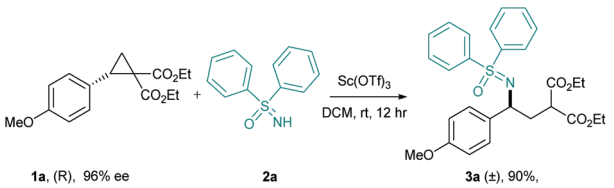
ceeded smoothly and furnished the corresponding product (**3a**) in comparable yields (1.5 g, 88%, 10 h).

Furthermore, we also explored the synthetic expansion of the obtained product **3a**, which was treated with allyl bromide in the presence of NaH in THF to form the α-quaternary allylation product **7** in 62% yield (Scheme 4).[18]

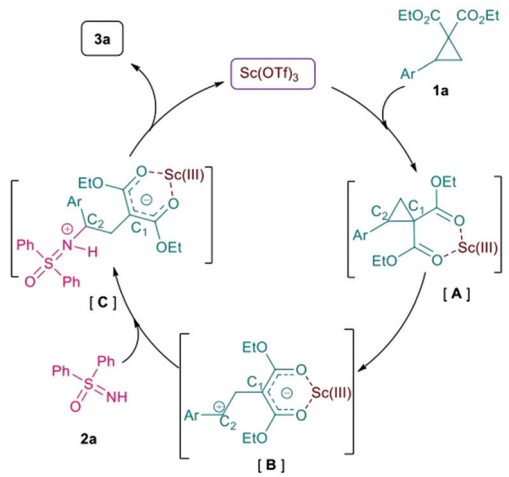
We next investigated the reaction pathways by reacting enantiopure cyclopropane **1a** (96% ee) with diaryl sulfoximine under the optimized reaction conditions to gain insight into



Scheme 4 Further expansion of the substrate scope.



Scheme 5 Synthesis of γ-sulfoximino malonic diesters from enantiomerically pure cyclopropane (**1a**).



Scheme 6 Plausible reaction mechanism.

the reaction mechanism; the reaction proceeded smoothly and racemic **3a** was obtained in 90% yield. This result showed the initial ring-opening step with sulfoximine *via* the S_N1 reaction pathway, as shown in Scheme 5.

Based on literature reports[8a,b,e–g,12e,19] and control experiments, we predicted the possible reaction pathway, as shown in Scheme 6. Sc(III) initially coordinated with the diester of D–A cyclopropane **1a** to form the Sc-coordinated complex (**A**), which provides the activated cyclopropane complex (**B**) with the formation of a stable benzylic carbocation.[19b] Next, the nucleophilic addition of sulfoximine **2a** at the C_2 of cyclopropane *via* the S_N1 pathway leads to the ring-opening of the cyclopropane intermediate (**C**). Furthermore, the 1, 4-hydrogen atom shift leads to the construction of desired γ-sulfoximino malonic diester **3a** with the regeneration of the Sc(III) catalyst.

Conclusions

We have developed a facile and efficient Sc(III) catalyzed ring-opening reaction of D–A cyclopropanes from weak nucleophilic sulfoximines to synthesize a diverse range of novel γ-sulfoximino malonic diesters in excellent yields. The old C–C bond from cyclopropane is cleaved, and the C–N and C–H bonds between sulfoximine and cyclopropane are formed in a single step. Also, mild reaction conditions, high atom economy, broad substrate scope, and excellent product yields are the advantages of this protocol.

Experimental section

General information

Solvents were purified and dried using standard techniques before use. Air-sensitive and moisture-sensitive reactions were carried out in oven-dried glassware under a nitrogen atmosphere using the standard protocol. Commercially available chemicals were used without further purification. For all moisture-sensitive reactions, tetrahydrofuran (THF), *N*,*N*-dimethyl formamide (DMF), MeOH, and di-chloromethane (CH_2Cl_2) were dried using a standard solvent purification system. The following dry solvents are commercially available and were used without further purification: acetonitrile, Acros Organics, 99.9% extra dry, over molecular sieves; methanol, Acros Organics, 99.8% extra dry, over molecular sieves; and benzene, Acros Organics, 99% extra dry, over molecular sieves. Solvents (pet ether, ethyl acetate, CH_2Cl_2, and Et_3N) for column chromatography were used after simple distillation. The reactions were monitored by TLC visualized by UV (254 nm). The purification was done using column chromatography on silica gel (Merck, 100–200 mesh) with the specified eluent mixtures (v/v). ^1H, ^{13}C, and ^{19}F NMR spectra were recorded at room temperature on Bruker AV-200, AV-400, and AV-500 spectrometers in appropriate solvents using TMS as an internal standard, and the chemical shifts are shown in δ scales. Coupling constants (J) are given in hertz (Hz), and the

standard abbreviations describe the signal multiplicities. The following abbreviations were used for single multiplicities: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. High-resolution mass spectra (HRMS) for all new compounds were recorded on an ESI+ method and Orbitrap mass analyzer (Thermo Scientific Q-Exactive, Accela 1250 pump). FT-IR spectra were recorded using a Bruker FT-IR and reported in terms of absorption frequency (cm^{-1}). The crystal structure analysis of **3q** was performed on a BRUKER KAPPA APEX II CCD Duo diffractometer. All chemicals were purchased from Sigma-Aldrich and used without further purification. The D–A cyclopropanes[20] and sulfoximines[21] were prepared using known literature procedures.

General experimental procedure for the synthesis of diarylmethine sulfoximines (3a–3r)

To a 25 mL round bottom flask with a stir bar were added D–A cyclopropane **1a** (50 mg, 0.1712 mmol, 1 equiv.), sulfoximines **2** (0.2054, 1.2 equiv.) in dry CH_2Cl_2 (2.0 mL) and $Sc(OTf)_3$ (10 mol%). The resultant reaction mixture was stirred at room temperature under an N_2 atmosphere for 8 to 16 h. After the completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (2 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated under vacuum. The crude product was subjected to purification using silica gel flash chromatography (petroleum ether/ethyl acetate = 7 : 3) to obtain γ-sulfoximino malonic diesters (**3a–3r**).

Diethyl 2-(2-(4-methoxyphenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (3a). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), iminodiphenyl-l6-sulfanone **2a** (44 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 8 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3a** as a colourless gum (81 mg, 94% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3443.23, 2087.45, 1723.10, 1642.50, 1551.07, 1481.92, 1284.08, 1195.46, 1010.95, 754.83; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93–8.07 (m, 2H), 7.76 (dd, J = 8.32, 1.19 Hz, 2H), 7.39–7.56 (m, 4H), 7.31–7.38 (m, 2H), 7.18–7.28 (m, 2H), 6.76–6.84 (m, 2H), 4.23 (d, J = 7.13 Hz, 1H), 4.03–4.20 (m, 4H), 3.78 (s, 3H), 3.75 (dd, J = 7.82, 6.57 Hz, 1H), 2.40 (td, J = 7.04, 1.56 Hz, 2H), 1.15–1.26 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.7, 169.5, 158.4, 140.1, 136.8, 132.6, 132.5, 129.3, 129.0, 128.9, 128.8, 128.5, 127.8, 124.7, 113.5, 61.2, 61.1, 56.1, 55.2, 49.3, 39.5, 14.0, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{32}O_6NS$, 510.1945; found, 510.1942.

Diethyl 2-(2-(4-methoxyphenyl)-2-(((4-methoxyphenyl) (oxo) (phenyl)-l6-sulfaneylidene) amino) ethyl) malonate (3b). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), imino(4-methoxyphenyl) (phenyl)-l6-sulfanone **2b** (50 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 8 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3b** as a mixture of diastereomers (dr = 1 : 1) as a colorless gum (84 mg, 92% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3423.50, 2088.68, 1724.83, 1641.60, 1550.69, 1534.99, 1511.72, 1494.34, 1443.78, 1242.79, 1172.89, 771.34; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87–7.98 (m, 2H), 7.66–7.76 (m, 2H), 7.40–7.54 (m, 2H), 7.31–7.37 (m, 1H), 7.24 (d, J = 8.63 Hz, 1H), 7.27 (d, J = 8.63 Hz, 1H), 6.95 (d, J = 9.01 Hz, 1H), 6.76–6.87 (m, 3H), 4.21–4.28 (m, 1H), 4.03–4.21 (m, 4H), 3.77–3.91 (m, 6H), 3.74 (t, J = 7.25 Hz, 1H), 2.37–2.46 (m, 2H), 1.17 1.27 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 169.5, 158.4, 131.0, 130.7, 129.0, 128.9, 128.6, 128.2, 127.9, 114.4, 114.2, 113.6, 61.2, 61.1, 56.1, 56.1, 55.6, 55.5, 55.2, 49.3, 14.0, 14.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{34}O_7NS$, 540.2050; found, 540.2053.

Diethyl 2-(2-(4-methoxyphenyl)-2-((oxo(phenyl)(*p*-tolyl)-l6-sulfaneylidene) amino) ethyl) malonate (3c). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), imino(phenyl)(*p*-tolyl)-l6-sulfanone **2c** (47 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 8 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3c**, a mixture of diastereomers (dr = 1 : 1), as a yellowish gum (81 mg, 91% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3395.18, 2088.24, 1726.79, 1642.07, 1553.27, 1535.67, 1510.97, 1300.32, 1243.71, 1140.68, 771.58; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.97 (m, 1H), 7.79–7.89 (m, 1H), 7.69–7.79 (m, 1H), 7.64 (d, J = 8.38 Hz, 1H), 7.37–7.51 (m, 2H), 7.20–7.35 (m, 4H), 7.13 (d, J = 8.00 Hz, 1H), 6.72–6.86 (m, 2H), 4.03–4.26 (m, 5H), 3.78–3.80 (m, 3H), 3.71–3.78 (m, 1H), 2.31–2.41 (m, 5H), 1.18–1.28 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 169.6, 169.6, 158.3, 143.1, 143.0, 141.1, 141.1, 137.7, 137.6, 137.5, 137.4, 132.1, 132.0, 129.6, 129.5, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 127.7, 113.5, 61.1, 61.1, 60.3, 56.0, 56.0, 55.2, 49.3, 39.9, 39.9, 21.4, 21.3, 21.0, 14.1, 14.0, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{34}O_6NS$, 524.2101; found, 524.2096.

Diethyl 2-(2-(((4-chlorophenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (3d). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), (4-chlorophenyl) (imino)(phenyl)-l6-sulfanone **2d** (51 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 12 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3d**, a mixture of diastereomers (dr = 1 : 1), as a yellowish gum (81 mg, 88% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3423.35, 2088.82, 1722.34, 1641.46, 1552.20, 1535.57, 1511.85, 1444.15, 1228.30, 771.18; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93–7.98 (m, 1H), 7.85–7.91 (m, 1H), 7.72–7.77 (m, 1H), 7.61–7.66 (m, 1H), 7.46–7.51 (m, 1H), 7.40–7.44 (m, 1H), 7.32–7.37 (m, 1H), 7.26 (d, J = 8.63 Hz, 1H), 7.21 (dd, J = 8.57, 1.56 Hz, 2H), 6.79 (dd, J = 8.76, 2.25 Hz, 2H), 4.21–4.25 (m, 1H), 4.16–4.20 (m, 1H), 4.11–4.16 (m, 1H), 4.03–4.11 (m, 2H), 3.75–3.81 (m, 3H), 3.71 (td, J = 7.19, 1.88 Hz, 1H), 2.32–2.43 (m, 2H), 1.19–1.29 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 169.7, 169.5, 166.6, 158.4, 158.4, 140.4, 140.4, 139.5,

139.4, 138.9, 138.7, 137.0, 136.9, 132.5, 132.4, 130.1, 129.9, 129.2, 129.0, 129.0, 128.9, 128.6, 128.3, 127.7, 127.7, 113.5, 61.4, 61.2, 61.1, 61.1, 56.0, 55.9, 55.1, 49.3, 41.6, 39.7, 39.7, 14.0, 13.9; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{31}O_6NClS$, 544.1555; found, 554.1550.

Diethyl 2-(2-(((4-fluorophenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (3e). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), (4-fluorophenyl) (imino)(phenyl)-l6-sulfanone **2e** (48 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 12 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3e**, a mixture of diastereomers (dr = 1 : 1), as a reddish gum (76 mg, 85% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3423.23, 2985.52, 1727.80, 1692.03, 1658.23, 1587.39, 1243.23, 1140.19, 1032.01, 835.10, 756.88; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92–8.00 (m, 2H), 7.68–7.77 (m, 2H), 7.39–7.52 (m, 2H), 7.29–7.36 (m, 1H), 7.21 (dd, *J* = 8.50, 1.25 Hz, 2H), 7.07–7.16 (m, 1H), 6.97 (t, *J* = 8.57 Hz, 1H), 6.79 (d, *J* = 8.63 Hz, 2H), 4.18–4.25 (m, 1H), 4.06–4.15 (m, 4H), 3.77 (s, 3H), 3.72 (s, 1H), 2.37 (t, *J* = 6.94 Hz, 2H), 1.23 (d, *J* = 6.13 Hz, 4H), 1.15–1.19 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.7, 169.7, 169.4, 158.3, 158.3, 140.6, 140.6, 137.0, 136.7, 136.7, 132.4, 132.3, 131.4, 131.3, 131.1, 131.0, 129.0, 128.8, 128.5, 128.2, 127.6, 127.6, 116.2, 116.0, 115.7, 113.4, 61.1, 61.0, 60.2, 56.0, 55.8, 55.0, 49.2, 39.7, 39.7, 14.0, 13.9, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ −106.4; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{31}O_6NFS$, 528.1851; found, 528.1845.

Diethyl 2-(2-(((4-iodophenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (3f). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), imino(4-iodophenyl) (phenyl)-l6-sulfanone **2f** (70 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 14 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3f**, a mixture of diastereomers (dr = 1 : 1), as a colorless gum (95 mg, 88% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3443.49, 2089.03, 1642.49, 1551.63, 1534.49, 1511.83, 1444.44, 1242.66, 1138.57, 769.50; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88–8.01 (m, 1H), 7.76–7.83 (m, 1H), 7.70–7.76 (m, 1H), 7.61–7.67 (m, 1H), 7.31–7.57 (m, 5H), 7.13–7.26 (m, 2H), 6.75–6.82 (m, 2H), 4.05–4.26 (m, 5H), 3.76–3.81 (m, 3H), 3.68–3.76 (m, 1H), 2.32–2.44 (m, 2H), 1.16–1.27 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 169.8, 169.7, 169.5, 169.5, 158.4, 158.4, 158.3, 158.3, 144.7, 140.8, 140.7, 140.7, 140.4, 140.3, 138.2, 137.9, 137.7, 137.6, 137.2, 137.0, 136.9, 134.1, 133.9, 132.5, 132.4, 132.3, 132.2, 130.2, 129.9, 129.7, 129.6, 129.2, 129.1, 129.0, 129.0, 128.9, 128.8, 128.6, 128.6, 128.3, 127.7, 127.7, 127.4, 127.3, 113.5, 113.4, 100.0, 99.8, 61.2, 61.1, 61.1, 60.3, 56.1, 55.9, 55.9, 55.2, 55.1, 49.3, 39.8, 39.7, 39.6, 14.1, 14.0, 13.9; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{31}O_6NIS$, 636.0911; found, 636.0894.

Diethyl 2-(2-(4-methoxyphenyl)-2-(((4-nitrophenyl) (oxo) (phenyl)-l6-sulfaneylidene) amino) ethyl) malonate (3g). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), imino(4-nitrophenyl) (phenyl)-l6-sulfanone **2g** (54 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 16 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3g**, a mixture of diastereomers (dr = 1 : 1), as a yellowish gum (82 mg, 87% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3423.12, 3022.64, 1726.39, 1691.21, 1641.62, 1610.73, 1530.31, 1511.08, 1445.65, 1368.19, 1349.36, 1291.52, 1245.73, 1142.99, 1093.72, 756.38; ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.88 Hz, 1H), 8.04–8.15 (m, 2H), 7.95–8.04 (m, 1H), 7.73–7.85 (m, 2H), 7.43–7.60 (m, 2H), 7.34–7.42 (m, 1H), 7.16 (d, *J* = 8.63 Hz, 1H), 7.21 (d, *J* = 8.63 Hz, 1H), 6.67–6.84 (m, 2H), 4.22–4.34 (m, 1H), 3.99–4.19 (m, 4H), 3.76 (d, *J* = 12.26 Hz, 3H), 3.69 (ddd, *J* = 8.29, 6.03, 3.56 Hz, 1H), 2.30–2.49 (m, 2H), 1.14–1.26 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.7, 169.6, 169.4, 158.6, 158.5, 149.8, 149.6, 147.6, 147.0, 139.5, 139.4, 136.5, 136.2, 133.1, 133.0, 129.8, 129.6, 129.3, 129.1, 128.9, 128.5, 127.7, 127.7, 124.1, 123.7, 113.6, 113.5, 61.2, 61.2, 60.3, 56.2, 55.8, 55.1, 49.3, 49.2, 39.6, 39.4, 14.1, 14.0, 13.9; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{31}O_8N_2S$, 555.1796; found, 555.1779.

Diethyl 2-(2-(4-methoxyphenyl)-2-((oxo(phenyl)(*m*-tolyl)-l6-sulfaneylidene) amino) ethyl) malonate (3h). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), imino(phenyl)(m-tolyl)-l6-sulfanone **2h** (47 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 12 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3h**, a mixture of diastereomers (dr = 1 : 1), as a yellowish gum (74 mg, 84% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3423.67, 3019.93, 2360.90, 1724.41, 1641.41, 1511.00, 1476.68, 1444.51, 1424.55, 1215.09, 928.70, 764.12, 669.32; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (dd, *J* = 8.00, 1.38 Hz, 1H), 7.73–7.80 (m, 2H), 7.40–7.57 (m, 3H), 7.29–7.35 (m, 2H), 7.17–7.25 (m, 3H), 6.80 (d, *J* = 7.88 Hz, 2H), 4.21 (d, *J* = 3.00 Hz, 1H), 4.13–4.17 (m, 1H), 4.05–4.12 (m, 3H), 3.77–3.79 (m, 3H), 3.72–3.77 (m, 1H), 2.36–2.39 (m, 3H), 2.23 (s, 1H), 2.04 (s, 1H), 1.23–1.26 (m, 4H), 1.16–1.21 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.9, 169.5, 158.3, 140.9, 140.5, 140.5, 139.1, 138.9, 137.4, 137.3, 133.1, 133.0, 132.2, 132.1, 129.2, 128.9, 128.8, 128.7, 128.7, 128.6, 128.3, 127.7, 127.7, 125.9, 125.5, 113.4, 61.1, 61.0, 56.0, 55.1, 49.3, 39.8, 39.8, 21.3, 21.1, 20.9, 14.1, 14.0, 13.9; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{29}H_{34}O_6NS$, 524.2101; found, 524.2100.

Diethyl 2-(2-(((3-fluorophenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (3i). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), (3-fluorophenyl) (imino)(phenyl)-l6-sulfanone **2i** (48 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 16 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3i**, a mixture of diastereomers (dr = 1 : 1), as a yellowish gum (73 mg, 81% yield); FTIR ($CHCl_3$, cm^{-1})

ν_{max}: 3423.22, 3020.07, 2400.45, 1725.19, 1641.96, 1511.53, 1475.30, 1444.73, 1216.58, 928.79, 773.12, 669.34; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96–8.01 (m, 1H), 7.62–7.79 (m, 2H), 7.40–7.57 (m, 4H), 7.32–7.40 (m, 1H), 7.15–7.26 (m, 3H), 6.76–6.84 (m, 2H), 4.05–4.26 (m, 5H), 3.79 (d, J = 2.00 Hz, 3H), 3.72 (ddd, J = 7.82, 6.50, 4.44 Hz, 1H), 2.31–2.47 (m, 2H), 1.24–1.27 (m, 3H), 1.17–1.23 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 169.8, 169.5, 169.5, 163.7, 163.5, 161.2, 161.0, 158.4, 143.3, 143.3, 143.2, 143.1, 140.3, 140.3, 137.0, 136.9, 132.7, 132.6, 130.7, 130.6, 130.4, 130.3, 129.3, 129.1, 129.0, 128.8, 128.5, 128.5, 127.8, 127.7, 124.4, 124.4, 124.2, 124.2, 119.6, 119.4, 119.2, 116.1, 115.9, 115.6, 113.6, 61.2, 61.2, 56.1, 56.0, 55.2, 49.3, 49.3, 39.8, 39.6, 14.2, 14.0, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −110.33; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{31}O_6NFS$, 528.1851; found, 528.1841.

Diethyl 2-(2-(4-methoxyphenyl)-2-(((2-methoxyphenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino) ethyl) malonate (3j). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), imino(2-methoxyphenyl) (phenyl)-l6-sulfanone **2j** (50 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 16 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3j**, a mixture of diastereomers (dr = 1 : 1), as a whitish gum (79 mg, 86% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3422.19, 3019.94, 2360.82, 1641.16, 1510.88, 1477.73, 1370.32, 1214.46, 1024.20, 850.14, 759.12, 626.58; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.63 Hz, 1H), 7.94 (d, J = 7.13 Hz, 1H), 7.69 (d, J = 8.76 Hz, 1H), 7.73 (d, J = 7.50 Hz, 1H), 7.37–7.54 (m, 2H), 7.29–7.36 (m, 1H), 7.19–7.27 (m, 2H), 6.94 (d, J = 8.63 Hz, 1H), 6.74–6.85 (m, 3H), 3.97–4.26 (m, 5H), 3.78–3.85 (m, 6H), 3.75 (t, J = 7.13 Hz, 1H), 2.38 (br. s., 2H), 1.17–1.27 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1, 169.6, 169.6, 158.2, 158.0, 156.6, 156.4, 140.8, 140.7, 137.7, 137.7, 134.5, 134.4, 132.1, 131.9, 131.8, 131.7, 129.4, 129.3, 128.0, 127.9, 127.7, 127.5, 127.4, 127.1, 120.3, 120.0, 113.3, 113.0, 112.0, 111.5, 61.0, 61.0, 61.0, 56.5, 55.9, 55.2, 55.2, 55.1, 54.4, 49.3, 49.0, 40.0, 39.9, 14.0, 14.0, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{34}O_7NS$, 540.2050; found, 540.2054.

Diethyl 2-(2-(4-methoxyphenyl)-2-(((2-nitrophenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino) ethyl) malonate (3k). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), imino(2-nitrophenyl) (phenyl)-l6-sulfanone **2k** (54 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 16 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3k**, a mixture of diastereomers (dr = 2 : 1), as a brown gum (75 mg, 80% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3422.18, 3020.11, 2400.36, 1724.83, 1641.25, 1545.57, 1445.56, 1218.61, 1033.88, 928.66, 771.98, 669.27; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0–8.1 (m, 2H), 7.4–7.7 (m, 7H), 7.1–7.2 (m, 2H), 6.7–6.8 (m, 2H), 4.0–4.2 (m, 5H), 3.8 (s, 3H), 3.8 (s, 1H), 2.3–2.5 (m, 2H), 1.2–1.3 (m, 3H), 1.1–1.2 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 169.6, 169.4, 169.4, 158.5, 149.6, 140.0, 139.9, 136.1, 136.1, 134.1, 133.6, 133.5, 133.1, 133.0, 132.9, 131.9, 131.8, 131.4, 131.0, 129.0, 128.9, 128.8, 128.4, 127.9, 127.8, 124.2, 124.0, 113.6, 113.5, 61.2, 61.2, 56.4, 55.7, 55.2, 55.1, 49.3, 49.0, 39.3, 14.1, 13.9, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{31}O_8N_2S$, 555.1796; found, 555.1783.

Diethyl 2-(2-(((3,5-dimethylphenyl) (oxo)(phenyl)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (3l). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), (3,5-dimethyl phenyl) (imino)(phenyl)-l6-sulfanone **2l** (52 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 14 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3l**, a mixture of diastereomers (dr = 1 : 1), as a yellowish gum (77 mg, 84% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3423.45, 2983.89, 1744.03, 1691.98, 1641.69, 1511.05, 1369.54, 1243.19, 1136.29, 1033.57, 754.86, 688.54; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96–7.99 (m, 1H), 7.73–7.78 (m, 1H), 7.57 (s, 1H), 7.40–7.52 (m, 2H), 7.30–7.37 (m, 2H), 7.22–7.27 (m, 2H), 7.13 (s, 1H), 7.04 (s, 1H), 6.76–6.84 (m, 2H), 4.20–4.27 (m, 1H), 4.05–4.19 (m, 4H), 3.77–3.80 (m, 3H), 3.71–3.76 (m, 1H), 2.40 (t, J = 5.69 Hz, 2H), 2.33–2.36 (m, 3H), 2.20–2.22 (m, 3H), 1.17–1.26 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 169.5, 158.3, 139.0, 138.8, 134.3, 134.1, 132.4, 132.2, 129.0, 128.8, 128.7, 128.3, 127.9, 127.8, 126.4, 125.9, 113.5, 113.4, 61.1, 56.0, 55.2, 55.1, 49.3, 49.3, 39.6, 39.5, 21.2, 21.0, 14.0, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{36}O_6NS$, 538.2258; found, 538.2261.

Diethyl 2-(2-(4-methoxyphenyl)-2-((methyl(4-nitrophenyl) (oxo)-l6-sulfaneylidene) amino) ethyl) malonate (3m). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), imino(methyl)(4-nitrophenyl)-l6-sulfanone **2m** (41 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 8 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3m**, a mixture of diastereomers (dr = 1 : 0.1), as a yellow gum (75 mg, 90% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3442.54, 2934.67, 2088.71, 1725.89, 1642.19, 1548.48, 1530.52, 1511.22, 1443.92, 1368.40, 1348.18, 1244.60, 1141.08, 1032.01, 756.78; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36–8.42 (m, 2H), 8.14–8.19 (m, 2H), 7.21–7.26 (m, 2H), 6.79–6.85 (m, 2H), 4.06–4.20 (m, 5H), 3.78 (s, 3H), 3.46 (t, J = 7.13 Hz, 1H), 3.05 (s, 3H), 2.26–2.36 (m, 2H), 1.22 (dt, J = 12.26, 7.13 Hz, 7H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.5, 169.3, 158.7, 150.4, 145.6, 136.0, 129.7, 129.6, 128.1, 127.7, 124.4, 123.8, 113.8, 113.5, 61.3, 61.3, 56.4, 55.2, 49.4, 44.6, 39.0, 14.0, 14.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{29}O_8N_2S$, 493.1639; found, 493.1628.

Diethyl 2-(2-((benzyl(oxo)(phenyl)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (3n). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), benzyl(imino)(phenyl)-l6-sulfanone **2n** (47 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 12 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3n**, a mixture of diastereomers (dr = 1 : 1), as a colourless gum (77 mg, 86% yield);

FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3423.38, 2087.61, 1726.90, 1641.53, 1552.28, 1511.04, 1445.44, 1300.01, 1244.49, 1173.60, 1031.67, 756.30, 696.79; ^1H NMR (400 MHz, $CDCl_3$): δ 7.59–7.64 (m, 2H), 7.54 (t, J = 7.38 Hz, 1H), 7.41 (td, J = 7.50, 3.50 Hz, 3H), 7.28–7.34 (m, 3H), 7.16–7.24 (m, 6H), 7.09–7.14 (m, 2H), 7.04 (d, J = 7.25 Hz, 2H), 6.88 (d, J = 7.25 Hz, 2H), 6.79–6.86 (m, 2H), 6.67–6.76 (m, 2H), 4.28–4.37 (m, 2H), 4.21–4.27 (m, 2H), 4.17–4.20 (m, 1H), 4.16 (d, J = 3.63 Hz, 1H), 4.14–4.15 (m, 1H), 4.12–4.13 (m, 1H), 4.08–4.12 (m, 1H), 4.06 (d, J = 7.38 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.70 (t, J = 7.19 Hz, 1H), 3.58 (t, J = 7.13 Hz, 1H), 2.36 (t, J = 7.00 Hz, 4H), 1.15–1.26 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 169.7, 169.5, 169.4, 158.5, 158.4, 137.2, 136.5, 132.8, 131.3, 131.0, 129.6, 129.4, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 113.6, 113.4, 63.1, 62.9, 61.2, 61.1, 61.1, 55.9, 55.6, 55.2, 55.1, 49.4, 49.2, 39.5, 39.2, 14.0, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{34}O_6NS$, 524.2101; found, 524.2102.

Diethyl 2-(2-((dibenzyl(oxo)-l6-sulfaneylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (3o). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), dibenzyl(imino)-l6-sulfanone **2o** (52 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 10 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3o** as a colourless gum (80 mg, 88% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3422.93, 2932.62, 2114.68, 1725.93, 1657.58, 1641.60, 1550.08, 1511.34, 1480.00, 1245.62, 1153.90, 1030.68, 758.72; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.41 (m, 5H), 7.20–7.29 (m, 5H), 7.12 (dd, J = 7.75, 1.50 Hz, 2H), 6.76–6.83 (m, 2H), 4.33 (dd, J = 8.88, 5.00 Hz, 1H), 4.00–4.18 (m, 6H), 3.79–3.90 (m, 2H), 3.77 (s, 3H), 3.43 (dd, J = 8.82, 5.44 Hz, 1H), 2.20 (ddd, J = 13.45, 8.63, 5.19 Hz, 2H), 1.22 (q, J = 7.13 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 169.5, 158.5, 137.6, 131.3, 130.7, 129.5, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 113.6, 61.1, 61.0, 60.1, 58.3, 55.2, 54.3, 49.2, 39.7, 14.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{36}O_6NS$, 538.2258; found, 538.2259.

Diethyl 2-(2-((10-benzyl-5-oxido-10*H*-5l4-phenothiazin-5-ylidene) amino)-2-(4-methoxyphenyl) ethyl) malonate (3p). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), 10-benzyl-5-imino-5,10-dihydro-5l4-phenothiazine 5-oxide **2p** (65 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 16 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3p** as a red gum (89 mg, 85% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3680.82, 3422.97, 3020.00, 2400.28, 1641.31, 1511.80, 1467.82, 1218.36, 772.12, 669.57; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (dd, J = 7.88, 1.50 Hz, 1H), 7.93 (dd, J = 7.88, 1.50 Hz, 1H), 7.28–7.41 (m, 5H), 7.21 (t, J = 7.44 Hz, 1H), 7.10–7.17 (m, 3H), 6.96–7.03 (m, 3H), 6.89 (d, J = 8.50 Hz, 1H), 6.67 (d, J = 8.63 Hz, 2H), 5.30 (d, J = 18.39 Hz, 1H), 5.18 (d, J = 18.39 Hz, 1H), 4.04–4.16 (m, 5H), 3.75 (s, 3H), 3.54 (dd, J = 9.38, 4.88 Hz, 1H), 2.01–2.22 (m, 2H), 1.24–1.28 (m, 4H), 1.20 (t, J = 7.13 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 169.2, 158.1, 140.6, 140.6, 136.9, 135.3, 132.4, 132.4, 129.1, 127.5, 127.3, 125.7, 124.6, 124.4, 123.7, 123.5, 121.8, 121.7, 116.3, 115.9, 113.2, 61.1, 61.0, 55.9, 55.2, 53.1, 49.2, 39.5, 14.0, 14.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{35}H_{37}O_6N_2S$, 613.2367; found, 613.2362.

Diethyl 2-(2-(4-methoxyphenyl)-2-((10-oxido-9-oxo-9*H*-10l4-thioxanthen-10-ylidene) amino) ethyl) malonate (3q). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), 10-imino-10l4-thioxanthen-9(10*H*)-one 10-oxide **2q** (50 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 16 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3q** as a white solid (81 mg, 89% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3435.29, 2089.21, 1723.09, 1642.71, 1536.06, 1510.98, 1468.06, 1442.57, 1369.50, 1301.48, 1220.29, 772.19, 676.29; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15–8.23 (m, 2H), 8.01–8.06 (m, 1H), 7.85–7.91 (m, 1H), 7.76 (td, J = 7.63, 1.38 Hz, 1H), 7.65–7.71 (m, 1H), 7.54–7.64 (m, 2H), 6.91–6.96 (m, 2H), 6.58–6.62 (m, 2H), 4.21 (dd, J = 8.44, 5.94 Hz, 1H), 4.12–4.18 (m, 1H), 4.02–4.11 (m, 3H), 3.72 (s, 3H), 3.52 (dd, J = 8.25, 6.38 Hz, 1H), 2.17 (ddd, J = 8.44, 6.07, 2.25 Hz, 2H), 1.25 (t, J = 7.13 Hz, 3H), 1.18 (t, J = 7.13 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.1, 169.5, 169.1, 158.3, 141.2, 141.0, 135.2, 133.7, 133.6, 132.2, 131.9, 130.7, 130.6, 128.8, 128.7, 127.4, 124.5, 124.3, 113.5, 61.1, 61.1, 56.9, 55.1, 49.3, 39.5, 14.0, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{30}O_7NS$, 536.1737; found, 536.1737.

Diethyl 2-(2-(4-methoxyphenyl)-2-((5-oxido-5l4-dibenzo [*b*,*d*] thiophen-5-ylidene) amino) ethyl) malonate (3r). The compound was synthesized from the reaction of ethyl 1-ethoxy-2-(4-methoxyphenyl) cyclopropane-1-carboxylate **1a** (50 mg, 0.1712 mmol), 5-imino-5*H*-5l4-dibenzo [*b*,*d*] thiophene 5-oxide **2r** (44 mg, 0.2054 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 10 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **3r** as a yellowish white solid (79 mg, 92% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3451.97, 2088.34, 1641.52, 1552.65, 1535.56, 1511.83, 1468.05, 1217.53, 769.15; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.75 Hz, 1H), 7.58–7.68 (m, 2H), 7.45–7.57 (m, 2H), 7.30 (t, J = 7.57 Hz, 2H), 7.21–7.26 (m, 1H), 7.08–7.16 (m, 2H), 6.63–6.70 (m, 2H), 4.63–4.70 (m, 1H), 4.18–4.27 (m, 1H), 4.07–4.16 (m, 3H), 3.75 (s, 3H), 2.94–3.04 (m, 1H), 2.49–2.58 (m, 1H), 1.18–1.27 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 166.4, 158.8, 137.8, 137.5, 135.3, 133.2, 133.1, 132.3, 132.1, 129.6, 129.6, 128.2, 124.1, 124.0, 121.1, 121.0, 113.6, 69.9, 62.7, 55.3, 55.0, 46.0, 13.8, 13.7; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{30}O_6NS$, 508.1788; found, 508.1801.

General experimental procedure for the synthesis of diarylmethine sulfoximines (5a–5r)

To a 25 mL round bottom flask with stir bar were added D–A cyclopropanes **4** (50 mg, 0.1908 mmol, 1 equiv.), sulfoximine **2a** (0.2290 1.2 equiv.) in dry CH_2Cl_2 (2.0 mL) and $Sc(OTf)_3$ (10 mol%). The resultant reaction mixture was stirred at room temperature under an N_2 atmosphere for 8 to 16 h. After completion of the reaction (monitored by TLC), the reaction

mixture was quenched with water (2 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated under vacuum. The crude product was subjected to purification using silica gel flash chromatography (petroleum ether/ethyl acetate = 70 : 30) to obtain the substituted γ-sulfoximino malonic diesters (**5a–5i**).

Diethyl 2-(2-((oxodiphenyl-l6-sulfaneylidene) amino)-2-phenylethyl) malonate (5a). The compound was synthesized from the reaction of diethyl 2-phenylcyclopropane-1,1-dicarboxylate **4a** (50 mg, 0.1908 mmol), iminodiphenyl-l6-sulfanone **2a** (49 mg, 0.2290 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 12 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **5a** as a colourless gum (82 mg, 90% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3443.01, 2982.22, 1649.00, 1551.78, 1445.58, 1194.63, 1121.27, 977.05, 744.14; ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, J = 8.19, 1.31 Hz, 2H), 7.66–7.74 (m, 2H), 7.35–7.48 (m, 4H), 7.25–7.31 (m, 4H), 7.19–7.25 (m, 2H), 7.13–7.18 (m, 1H), 4.23 (t, J = 6.69 Hz, 1H), 3.96–4.17 (m, 4H), 3.75 (t, J = 7.13 Hz, 1H), 2.36 (t, J = 7.00 Hz, 2H), 1.12–1.22 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 169.5, 145.1, 140.8, 140.7, 132.3, 132.2, 129.0, 128.8, 128.8, 128.4, 128.1, 126.7, 61.2, 61.1, 56.6, 49.3, 39.8, 14.0, 14.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{30}O_5NS$, 480.1839; found, 480.1841.

Diethyl 2-(2-(4-(methylthio) phenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (5b). The compound was synthesized from the reaction of diethyl 2-(4-(methylthio) phenyl) cyclopropane-1,1-dicarboxylate **4b** (50 mg, 0.1623 mmol), iminodiphenyl-l6-sulfanone **2a** (42 mg, 0.1948 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 12 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **5b** as a yellowish gum (62 mg, 73% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3423.65, 3019.90, 2400.31, 1727.18, 1641.38, 1446.40, 1370.32, 1217.86, 1140.83, 1093.95, 768.30, 687.59; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79–7.85 (m, 2H), 7.58–7.62 (m, 2H), 7.28–7.38 (m, 4H), 7.16–7.22 (m, 2H), 7.11 (d, J = 8.63 Hz, 2H), 6.98–7.04 (m, 2H), 4.09 (s, 1H), 3.85–4.03 (m, 4H), 3.60 (t, J = 7.25 Hz, 1H), 2.31 (s, 3H), 2.24 (t, J = 6.94 Hz, 2H), 1.01–1.10 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.7, 169.5, 136.4, 132.6, 132.4, 129.3, 129.0, 128.9, 128.8, 128.7, 128.4, 127.3, 126.6, 61.2, 61.2, 56.2, 49.2, 39.5, 16.0, 14.0, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{32}O_5NS_2$, 526.1716; found, 526.1718.

Diethyl2-(2-(4-nitrophenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (5c). The compound was synthesized from the reaction of diethyl 2-(4-nitrophenyl) cyclopropane-1,1-dicarboxylate **4c** (50 mg, 0.1628 mmol), iminodiphenyl-l6-sulfanone **2a** (42 mg, 0.1954 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 16 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **5c** as a yellow liquid (47 mg, 56% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3642.10, 3423.69, 3020.01, 2361.15, 2096.02, 1724.50, 1641.36, 1522.30, 1424.56, 1217.77, 928.67, 771.92; ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.13 Hz, 2H), 7.95 (d, J = 7.75 Hz, 2H), 7.76 (d, J = 7.75 Hz, 2H), 7.42–7.59 (m, 6H), 7.32–7.40 (m, 2H), 4.32–4.42 (m, 1H), 4.05–4.25 (m, 4H), 3.80 (t, J = 7.00 Hz, 1H), 2.33–2.43 (m, 2H), 1.26 (t, J = 7.13 Hz, 4H), 1.20 (t, J = 7.13 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.5, 169.3, 152.9, 146.8, 140.4, 140.1, 132.7, 132.6, 129.2, 129.0, 128.5, 128.4, 128.4, 127.6, 123.5, 61.4, 61.3, 56.0, 49.0, 39.4, 14.0, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{29}O_7N_2S$, 525.1690; found, 525.1688.

Diethyl 2-(2-(4-chlorophenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (5d). The compound was synthesized from the reaction of diethyl 2-(4-chlorophenyl) cyclopropane-1,1-dicarboxylate **4d** (50 mg, 0.1689 mmol), iminodiphenyl-l6-sulfanone **2a** (44 mg, 0.2027 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 12 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **5d** as a colorless gum (74 mg, 86% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3423.31, 3019.35, 2114.54, 1723.09, 1641.36, 1551.87, 1501.95, 1468.36, 1379.36, 1215.79, 1121.61, 757.22, 668.33; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, J = 8.07, 1.31 Hz, 2H), 7.61–7.70 (m, 2H), 7.31–7.44 (m, 4H), 7.21–7.27 (m, 2H), 7.19 (m, J = 8.38 Hz, 2H), 7.13 (m, J = 8.50 Hz, 2H), 4.16 (t, J = 6.63 Hz, 1H), 3.95–4.11 (m, 4H), 3.69 (t, J = 7.13 Hz, 1H), 2.28 (t, J = 7.13 Hz, 2H), 1.12–1.17 (m, 3H), 1.08 (t, J = 7.13 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 169.3, 143.6, 140.4, 140.3, 132.4, 132.3, 132.2, 129.0, 128.8, 128.5, 128.3, 128.1, 128.0, 61.1, 61.1, 55.8, 49.0, 39.5, 13.9, 13.8; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{29}O_5NClS$, 514.1449; found, 514.1467.

Diethyl 2-(2-((oxodiphenyl-l6-sulfaneylidene) amino)-2-(*o*-tolyl) ethyl) malonate (5e). The compound was synthesized from the reaction of diethyl 2-(*o*-tolyl) cyclopropane-1,1-dicarboxylate **4e** (50 mg, 0.1811 mmol), iminodiphenyl-l6-sulfanone **2a** (47 mg, 0.2173 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 16 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **5e** as a yellow liquid (75 mg, 84% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3683.12, 3433.29, 2984.52, 2400.54, 1724.90, 1603.46, 1521.79, 1464.62, 1218.23, 908.12, 772.01, 690.09; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (dd, J = 8.13, 1.25 Hz, 2H), 7.83 (d, J = 7.38 Hz, 1H), 7.63–7.68 (m, 2H), 7.42–7.53 (m, 3H), 7.35–7.41 (m, 1H), 7.21–7.30 (m, 3H), 7.07–7.13 (m, 1H), 6.96 (d, J = 7.50 Hz, 1H), 4.50 (dd, J = 9.13, 4.38 Hz, 1H), 4.16–4.24 (m, 2H), 4.04–4.14 (m, 2H), 4.01 (dd, J = 9.51, 4.88 Hz, 1H), 2.26 (ddd, J = 9.13, 7.32, 4.44 Hz, 2H), 1.92 (s, 3H), 1.27 (t, J = 7.19 Hz, 3H), 1.18 (t, J = 7.13 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 169.5, 143.7, 140.6, 140.5, 133.8, 132.3, 132.1, 129.7, 128.9, 128.7, 128.6, 128.3, 126.9, 126.3, 126.0, 61.1, 61.0, 49.2, 38.4, 18.6, 14.0, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{32}O_5NS$, 494.1996; found, 494.2007.

Diethyl 2-(2-(3,4-dimethoxyphenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (5f). The compound was synthesized from the reaction of diethyl 2-(3,4-dimethoxyphenyl) cyclopropane-1,1-dicarboxylate **4f** (50 mg, 0.1552 mmol), iminodiphenyl-l6-sulfanone **2a** (40 mg, 0.1863 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 10 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **5f** as a colourless gum

(72 mg, 87% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3423.50, 2088.68, 1724.83, 1641.60, 1534.99, 1511.72, 1443.78, 1242.79, 1172.89, 771.34; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92–8.01 (m, 2H), 7.70–7.78 (m, 2H), 7.40–7.52 (m, 4H), 7.29–7.36 (m, 2H), 6.89 (d, J = 1.75 Hz, 1H), 6.81 (dd, J = 8.13, 1.75 Hz, 1H), 6.74 (d, J = 8.25 Hz, 1H), 4.22 (t, J = 6.75 Hz, 1H), 4.03–4.19 (m, 4H), 3.83 (s, 3H), 3.84 (s, 3H), 3.75 (t, J = 7.19 Hz, 1H), 2.39 (t, J = 7.00 Hz, 2H), 1.15–1.25 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 169.5, 148.6, 147.7, 140.5, 140.5, 137.6, 132.4, 132.3, 129.0, 129.0, 128.8, 128.7, 128.3, 127.8, 118.7, 110.7, 109.9, 61.1, 61.1, 56.3, 55.8, 55.8, 49.2, 39.6, 14.0, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{34}O_7NS$, 540.2050; found, 540.2057.

Diethyl 2-(2-(furan-2-yl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (5g). The compound was synthesized from the reaction of diethyl 2-(furan-2-yl) cyclopropane-1,1-dicarboxylate **4g** (50 mg, 0.1984 mmol), iminodiphenyl-l6-sulfanone **2a** (51 mg, 0.2380 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 8 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **5g** as a colourless gum (81 mg, 88% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3423.55, 3019.97, 2400.39, 1726.05, 1641.58, 1527.39, 1476.55, 1370.95, 1214.35, 1147.83, 1095.31, 928.23 778.80, 688.79; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92–8.00 (m, 2H), 7.80–7.89 (m, 2H), 7.34–7.52 (m, 6H), 7.25 (dd, J = 1.81, 0.81 Hz, 1H), 6.19 (dd, J = 3.19, 1.81 Hz, 1H), 6.09 (d, J = 3.25 Hz, 1H), 4.40 (t, J = 6.63 Hz, 1H), 4.01–4.22 (m, 4H), 3.79 (dd, J = 7.50, 6.75 Hz, 1H), 2.48–2.58 (m, 2H), 1.18 (t, J = 7.19 Hz, 3H), 1.22 (t, J = 7.13 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 169.4, 156.4, 141.1, 140.7, 140.5, 132.3, 132.2, 129.0, 128.8, 128.5, 128.3, 109.8, 106.0, 61.1, 61.1, 50.0, 48.9, 35.9, 13.9, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{28}O_6NS$, 470.1632; found, 470.1636.

Diethyl 2-(2-((oxodiphenyl-l6-sulfaneylidene) amino)-2-(thiophen-2-yl) ethyl) malonate (5h). The compound was synthesized from the reaction of diethyl 2-(thiophen-2-yl) cyclopropane-1,1-dicarboxylate **4h** (50 mg, 0.1865 mmol), iminodiphenyl-l6-sulfanone **2a** (48 mg, 0.2238 mmol), and 10 mol% Sc $(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 8 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded compound **5h** as a yellowish gum (74 mg, 82% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3422.70, 3019.92, 2400.40, 1725.67, 1641.33, 1527.14, 1446.70, 1214.82, 1140.93, 928.29, 758.60, 697.82; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99–8.11 (m, 2H), 7.81 (dd, J = 8.57, 0.94 Hz, 2H), 7.43–7.61 (m, 4H), 7.30–7.43 (m, 2H), 7.17 (dd, J = 5.07, 1.19 Hz, 1H), 6.86 (dd, J = 5.00, 3.50 Hz, 1H), 6.79 (d, J = 3.00 Hz, 1H), 4.65 (dd, J = 7.57, 5.82 Hz, 1H), 4.04–4.24 (m, 4H), 3.81 (dd, J = 8.25, 6.13 Hz, 1H), 2.52 (dt, J = 7.79, 5.49 Hz, 2H), 1.171.27 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.7, 169.4, 149.8, 140.4, 140.0, 132.7, 132.5, 129.1, 128.9, 128.9, 128.7, 128.5, 126.4, 123.7, 123.2, 61.2, 61.2, 52.4, 49.0, 40.1, 14.0, 14.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{28}O_5NS_2$, 486.1403; found, 486.1407.

Diethyl (*E*)-2-(2-((oxodiphenyl-l6-sulfaneylidene) ami-no)-4-phenylbut-3-en-1-yl) malonate (5i). The compound was synthesized from the reaction of diethyl (*E*)-2-styrylcyclopropane-1,1-dicarboxylate **4i** (50 mg, 0.1736 mmol), iminodiphenyl-l6-sulfanone **2a** (48 mg, 0.2083 mmol), and 10 mol% $Sc(OTf)_3$ in unhyd. CH_2Cl_2 solvent (2 mL). Reaction time: 12 h. Purification using silica gel (petroleum ether/EtOAc = 7 : 3) afforded com-pound **5i** as a colorless gum (73 mg, 84% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3442.52, 3025.73, 1727.24, 1642.38, 1493.81, 1476.42, 1391.27, 1240.20, 1094.70, 996.06, 754.63, 691.57; ^1H NMR (400 MHz, $CDCl_3$): δ 7.84–7.93 (m, 4H), 7.28–7.46 (m, 6H), 7.15–7.24 (m, 4H), 7.05–7.15 (m, 1H), 6.23 (d, J = 15.88 Hz, 1H), 6.12 (dd, J = 15.88, 7.00 Hz, 1H), 3.98–4.11 (m, 4H), 3.82 (q, J = 6.67 Hz, 1H), 3.75 (t, J = 7.13 Hz, 1H), 2.21–2.30 (m, 2H), 1.12–1.17 (m, 3H), 1.10 (t, J = 7.13 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 169.6, 141.0, 140.7, 137.0, 132.8, 132.3, 129.4, 129.0, 128.8, 128.6, 128.3, 128.2, 127.1, 126.3, 61.1, 61.1, 55.2, 48.9, 37.2, 13.9, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{32}O_5NS$, 506.1996; found, 506.2005.

General experimental procedure for the synthesis of γ-sulfoximino, α-bromo malonic diesters (6)

To a 25 mL round bottom flask with stir bar were added D–A cyclopropane **1a** (50 mg, 0.1712 mmol, 1 equiv.), sulfoximine **2c** (0.2054 mmol, 1.2 equiv.), NBS (0.2568 mmol, 1.5 equiv.) in dry CH_2Cl_2 (20 mL) and $Sc(OTf)_3$ (10 mol%). The resultant reaction mixture was stirred at room temperature under an N_2 atmosphere for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated under a vacuum. The crude product was subjected to purification using silica gel flash chromatography (petroleum ether/ethyl acetate = 80 : 20) to afford **6** in 72% yield.

Diethyl 2-bromo-2-(2-(4-methoxyphenyl)-2-((oxo(phenyl)(*p*-tolyl)-l6-sulfaneylidene) amino) ethyl) malonate (6). Purification using silica gel (petroleum ether/EtOAc = 8 : 2) afforded compound **6** as a yellow gum (74 mg, 72% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3422.66, 3019.90, 2400.30, 1723.10, 1641.40, 1503.48, 1218.18, 928.71, 772.18, 669.38; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96–7.97 (m, 1H), 7.94–7.95 (m, 1H), 7.85 (d, J = 8.38 Hz, 2H), 7.42–7.45 (m, 2H), 7.39–7.42 (m, 2H), 7.35 (d, J = 2.13 Hz, 1H), 7.19 (s, 2H), 7.04 (dd, J = 8.25, 2.00 Hz, 1H), 6.72 (d, J = 8.50 Hz, 1H), 4.12–4.21 (m, 2H), 3.80–3.86 (m, 2H), 3.79 (s, 3H), 3.03–3.09 (m, 1H), 2.31 (s, 3H), 2.02 (dd, J = 7.88, 5.13 Hz, 1H), 1.61 (dd, J = 9.26, 5.25 Hz, 1H), 1.20–1.24 (m, 3H), 0.90 (t, J = 7.13 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 166.5, 155.1, 143.6, 133.7, 132.8, 132.5, 129.8, 129.7, 129.2, 129.1, 128.7, 128.4, 128.3, 128.0, 127.9, 127.8, 111.3, 111.1, 61.7, 61.3, 56.2, 37.2, 31.4, 30.9, 29.7, 21.4, 18.8, 14.0, 13.8; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{33}O_6NBrS$, 602.1206; found, 602.1201.

General experimental procedure for the synthetic utility of product 3a (7)

Compound **3a** (30 mg, 0.0589 mmol, 1.0 equiv.) was taken in a 25 mL round bottom flask with a stir bar fitted with a water

condenser under an N_2 atmosphere; then dry THF was added *via* a cannula. NaH (0.07072 mmol, 1.2 equiv.) was added to this solution at 0 °C and stirred at room temperature for 1 h. Then allyl bromide (0.1178 mmol, 2.0 equiv.) was added slowly, and the resulting mixture was refluxed at 70 °C for another 12 h under an N_2 atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated under vacuum. The crude product was subjected to purification using silica gel flash chromatography (petroleum ether/ethyl acetate = 80 : 20) to afford 7 in 62% yield.

Diethyl 2-allyl-2-(2-(4-methoxyphenyl)-2-((oxodiphenyl-l6-sulfaneylidene) amino) ethyl) malonate (7). Purification using silica gel (petroleum ether/EtOAc = 8 : 2) afforded compound 7 as a yellow gum (20 mg, 62% yield); FTIR ($CHCl_3$, cm^{-1}) ν_{max}: 3415.69, 2088.71, 1642.57, 1552.53, 1513.72, 1502.06, 1264.56, 772.04; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89–7.96 (m, 2H), 7.71 (d, J = 7.50 Hz, 2H), 7.42–7.53 (m, 4H), 7.35–7.42 (m, 1H), 7.30 (d, J = 7.88 Hz, 2H), 7.07 (m, J = 8.50 Hz, 2H), 6.70 (m, J = 8.50 Hz, 2H), 5.59–5.71 (m, 1H), 4.95–5.05 (m, 2H), 4.24 (t, J = 7.07 Hz, 1H), 4.02 (q, J = 7.00 Hz, 2H), 3.91–3.98 (m, 1H), 3.81–3.89 (m, 1H), 3.76 (s, 3H), 2.66–2.82 (m, 3H), 2.44 (dd, J = 14.51, 6.25 Hz, 1H), 1.09–1.19 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 171.0, 158.3, 141.3, 140.9, 137.5, 133.0, 132.2, 131.9, 128.9, 128.6, 128.5, 128.4, 128.4, 118.6, 113.2, 61.0, 60.9, 56.4, 55.2, 54.4, 42.1, 36.4, 14.0, 13.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{31}H_{36}O_6NS$, 550.2258; found, 550.2264.

General experimental procedure for the gram-scale synthesis of compound 3a

To a 100 mL round bottom flask with a stir bar were added D–A cyclopropane **1a** (1 g, 1.96 mmol, 1 equiv.), sulfoximine **2a** (2.35 mmol, 1.2 equiv.) in dry CH_2Cl_2 (20 mL), and $Sc(OTf)_3$ (10 mol%). The resultant reaction mixture was stirred at room temperature under an N_2 atmosphere for 10 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated under vacuum. The crude product was purified using silica gel flash chromatography (petroleum ether/ethyl acetate = 70 : 30) to afford **3a** in 88% yield (1.5 g).

General experimental procedure for the synthesis of (±) γ-sulfoximino malonic diester (3a) from chiral D–A cyclopropane (*R*) 1a

To a 25 mL round bottom flask with stir bar were added chiral D–A cyclopropane (*R*) **1a** (>96% ee) (50 mg, 0.1712 mmol, 1 equiv.), sulfoximine **2a** (0.2054 mmol, 1.2 equiv.) in dry CH_2Cl_2 (20 mL) and $Sc(OTf)_3$ (10 mol%). The resultant reaction mixture was stirred at room temperature under an N_2 atmosphere for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and evaporated under vacuum. The crude product was subjected to purification using silica gel flash chromatography (petroleum ether/ethyl acetate = 80 : 20) to afford (±) **3a** in 90% yield.

Conflicts of interest

There are no conflicts to declare.

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A Metal-free Access to Hindered *N*-Alkyl Sulfoximines via In-Situ Generated Aza-Oxyallyl Cations from Functionalized Alkyl Bromide

Satish G. More,[a, b] Kishor D. Mane,[a, b] and Gurunath Suryavanshi*[a, b]

Abstract: Herein, we report a catalyst-free and mild synthetic method for the construction of hindered *N*-alkyl sulfoximines derivative. A wide range of hindered di-alkyl sulfoximines can be readily obtained from the reaction of α-bromo-hydroxamates with a variety of sulfoximines, including diaryl, aryl-alkyl, di-alkyl and heteroaryl sulfoximines.

Introduction

Sulfoximines are mono-aza analogs of sulfones with attractive structural properties that have been extensively used since the last decade.[1,2] Additionally, it serves as a privileged intermediate for constructing heterocyclic cores.[3] Its chemical diversity, strong hydrogen bonding ability, and high metabolic stability make it an intriguing pharmacophore.[4] Furthermore, the sulfoximine moiety is employed in drug discovery to enhance specificity, reduce unwanted toxicity, and improve stability/oral bioavailability.[5–7] Moreover, the chiral auxiliaries and ligands of sulfoximines can also be used in asymmetric syntheses.[8] Besides, the *N*-alkyl sulfoximines have attracted considerable interest due to their presence in natural products, as well as their biologically active properties.[9] For instance, PYK2 inhibitor (**a**) is the analog of *N*-alkyl sulfoximine, which is used to treat osteoporosis.[10] Suloxifen (**b**) is used as a polyvalent spasmolytic and anti-asthmatic agent and is useful by oral and parenteral dosage.[11] The fluorinated sulfoximine (**c**), is acts as an triflurometh ylating agent in florination chemistry.[12] Similarly, the sulfoximine-based rofecoxib (**d**) analog exhibits 1% and 48% inhibition of COX-1 and COX-2, respectively, at 10 mm concentrations.[13] A sulfoximidoyl-containing scaffold (**e**) is useful as an IRAK4 (interleukin-1 receptor-associated kinase 4) inhibitor, are the prominent examples of *N*-Alkyl sulfoximine scaffolds (figure 1).[14]

Despite these advances of *N*- alkyl sulfoximines in natural product and drug discovery,[9] limited progress has been made towards the *N*- alkylation of sulfoximines due to their low nucleophilicity.[15] Consequently, substantial efforts have been devoted to the synthesis of *N*-alkyl sulfoximines by various routes, including base catalyzed Michael-type additions,[16] Eschweiler- Clark type methylations[17] nucleophilic substitutions,[18] and two step acylation/reduction sequences[19] (Scheme 1, equation 1).

In contrast, α-bromo amide is the precursor of the aza-oxyallyl cation, which is a versatile building block for organic synthesis.[20] The useful heterocyclic motifs were developed

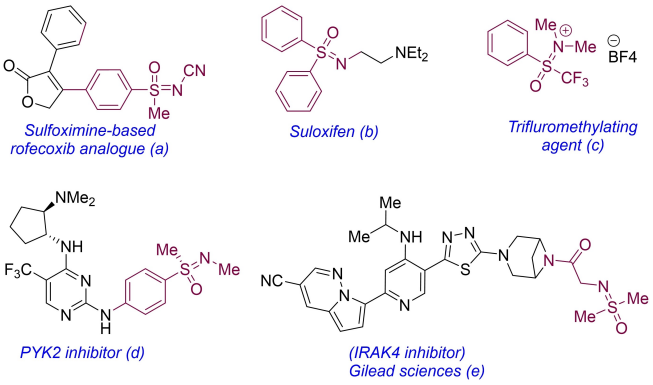
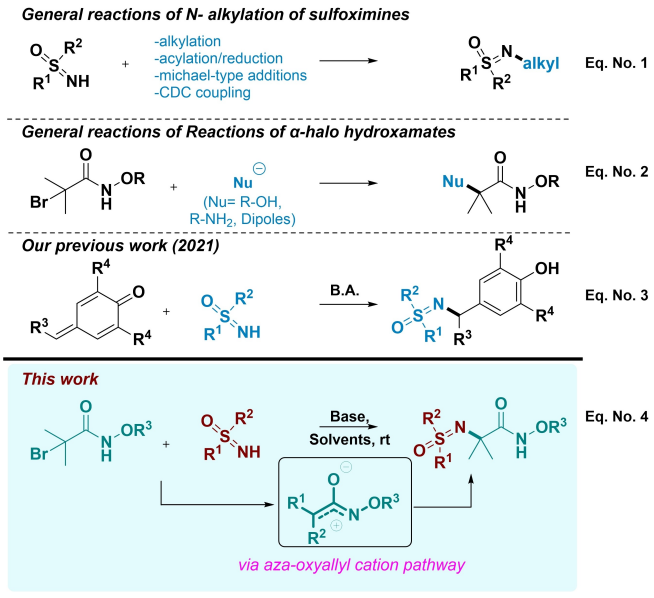


Figure 1. Examples of useful biologically active *N*-Alkyl sulfoximine scaffolds.



Scheme 1. The reactions of sulfoximines, α-halo hydroxamates, our previous work, and present work.

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from highly reactive aza-oxyallyl cations *via* [3 + 2],[21a] [3 + 3],[21b] and [4 + 3][21c] cycloaddition reactions with different dipoles. Furthermore, direct coupling with the various nucleophilic partners such as R–OH, R–NH_2 R–N_3 with α-bromo amide with the metal or metal-free condition to forming a novel congested C(sp^3)–X bonds (X=N, O) are also known in the literature. (Scheme 1, equation 2)[22]

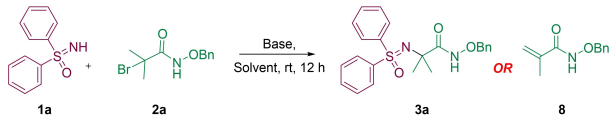
Recently, we have developed a method to synthesize diarylmethine imino sulfanones through the addition of *N*H-sulfoximines to *para*-quinone methides (*p*-QMs) *via* C–N bond formation. (Scheme 1, equation 3).[23c] Based on this result and our metal-free[23] approaches to construct the C–C and C–N bond formation reactions, here we report operationally simple and sustainable protocol for the synthesis of congested *N*-alkyl sulfoximines at room temperature (Scheme 1, equation 4).

Results and Discussion

We commenced this study by employing the sulfoximine **1a** and α-bromo hydroxamate **2a** as a model substrate to check the feasibility of the reaction. With the help of the previous literature report,[22b–e] we start our investigation with **1a** and **2a** (1 equiv. respectively), 2 equiv. of Na_2CO_3 as a base in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at room temperature, to our delight, the desired *N*-alkyl sulfoximine product **3a** was obtained in 46% yield in 12 h (Table 1, entry 1). Inspired by this promising result, different reaction parameters such as the equivalence of α-bromo hydroxamate **2a** bases, and solvents were investigated to improve the efficiency of our reaction. First, we changed the equivalent of the α-bromo hydroxamate **2a** from 1 to 1.2; we observed a slight increment in yield of the desired product (Table 1, entries 1–3). However, increasing the equiv. of Na_2CO_3 from 2 to 3 equiv. resulting in the formation of product **3a** obtained in 84% yield. (Table 1, entry 4). Then, we screened various bases, such as K_2CO_3, CS_2CO_3, Et_3N, DBU, and DIPEA, in HFIP solvent, but the yield of the expected product was not satisfactory compared to entry 4 (Table 1, entries 5–9). Furthermore, we tried the reaction in various routine solvents such as Acetonitrile, THF, and DCM, instead of desired product **3a** we got elimination product **8** (Table 1, entries 10–12). According to literature,[25] we found that the HFIP solvent may be required owing to its strong hydrogen bonding properties and excellent solvation properties to stabilize cationic species in the reaction. Then, we used mixed solvents such as CH_2Cl_2 and HFIP (0.1 equiv.). Gratifyingly, the reaction works smoothly to obtain corresponding substitution product **3a** in 82% (Table 1, entry 13). An increasing the loading of co-solvent (HFIP) (0.1 equiv. to 0.2 equiv.), significantly enhance the yield of **3a** (up to 88%) with in 12 h of reaction time (Table 1, entry 14). Based on the above optimization study, **1a** (1.0 equiv.), **2a** (1.2 equiv.), HFIP (0.2 equiv.) in CH_2Cl_2 is the excellent optimized reaction condition for the substitution reaction (Table 1, entry 14).

With the optimized condition, we studied the varieties of sulfoximines **1a-1r** with α-bromo hydroxamate **2a** for substitution reaction, as outlined in Table 2. Diaryl-sulfoximines with substitution such as (4-H, 4-OMe, and 3,5 di-Me) on aromatic ring reacted smoothly with **1a** to obtain *N*-alkyl sulfoximine in excellent yields (up to 92%, entries **3a**–**3c**). Whereas the aryl-methyl sulfoximines with various substitutions, such as elec-

Table 1. Optimization table for synthesis of 3a.[a]

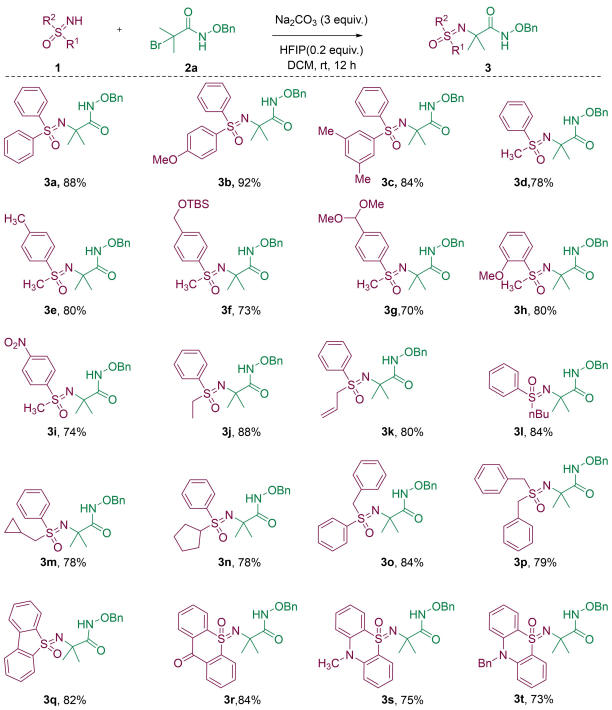


1a 2a 3a 8

Entry	2a [equiv.]	Base [equiv.]	Solvent	Yield of 3a [%][b]
1.	1.0	Na_2CO_3 (2.0)	HFIP	46
2.	1.1	Na_2CO_3 (2.0)	HFIP	58
3.	1.2	Na_2CO_3 (2.0)	HFIP	66
4.	1.2	Na_2CO_3 (3.0)	HFIP	84
5.	1.2	K_2CO_3 (3.0)	HFIP	78
6.	1.2	Cs_2CO_3 (3.0)	HFIP	74
7.	1.2	Et_3N (3.0)	HFIP	56
8.	1.2	DBU (3.0)	HFIP	58
9.	1.2	DIPEA (3.0)	HFIP	64
10.	1.2	Na_2CO_3 (3.0)	ACN	0[c]
11.	1.2	Na_2CO_3 (3.0)	THF	0[c]
12.	1.2	Na_2CO_3 (3.0)	DCM	0[c]
13.[d]	1.2	Na_2CO_3 (3.0)	DCM	82
14.[e]	**1.2**	**Na_2CO_3 (3.0)**	**DCM**	**88**

[a] Reactions were conducted in closed vessel at rt with **1a** (1 equiv.), **2a**, base, and solvent, 12 h; [b] Isolated yields after column chromatography; [c] Undesired elimination product **8** obtained; [d] used HFIP 0.1 equiv. as co-solvent; [e] used HFIP 0.2 equiv. as co-solvent.

Table 2. Substrate scope of different sulfoximines [a,b]

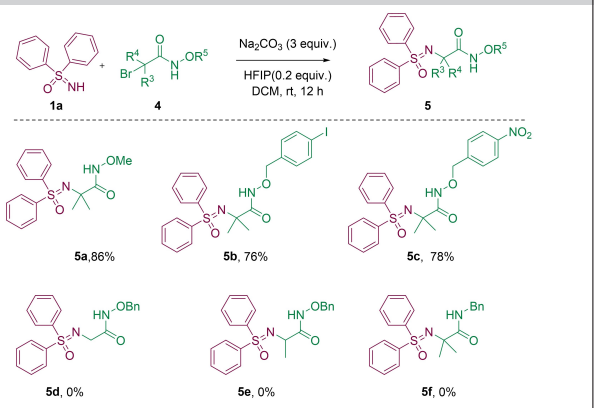


[a] Reaction conditions: **1a-t** (1 equiv.), **2a** (1.2 equiv.), Na_2CO_3 (3 equiv.), HFIP (0.2 equiv.), DCM, room temperature, 12 h, under N_2 atmosphere; [b] Isolated yields after column chromatographic purification are shown.

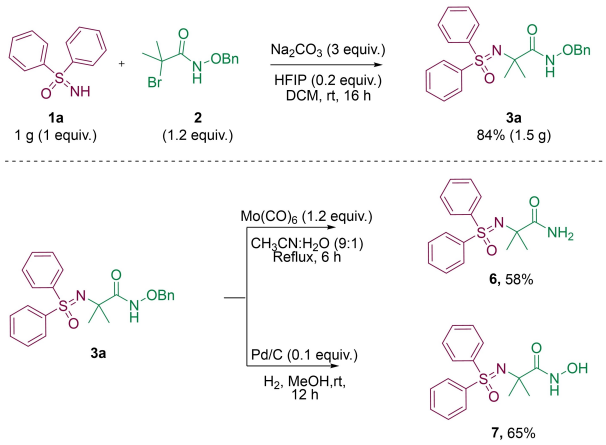
tron-donating and electron-withdrawing on *ortho* (–OMe), and *para* (–H, –Me, $–CH(OMe)_2$, $–CH_2OTBS$ and $–NO_2$) position reacted well with α-halo hydroxamate **1a** to furnishes the substitution products were obtained with attractive yields (70% to 78%, entries **3d**–**3i**). In addition, phenyl-alkyl sulfoximines such as phenyl ethyl **1j**, phenyl-allyl **1k**, phenyl-*n*-butyl **1l**, phenyl-cyclopropyl **1m**, and phenyl-cyclopentyl **1n** sulfoximine also feasible with our present reaction condition to produce corresponding substitution products **3j**–**3n** in good yields (78%–84%). Moreover, phenyl-benzyl sulfoximine **1o** and di-benzyl sulfoximine **1p** are also compatible with **1a** to furnish the desired product **3o** and **3p** in 79% and 84%, respectively. Furthermore, the bulky heterocyclic sulfoximine such as thio-xanthone sulfoximine **1q**, dibenzothiophene- sulfoximine **1r**, –Me and –Bn protected thiazine derived sulfoximine **1s** and **1t** also reacted efficiently with α-bromo amide to obtain the respective substitution products in good yields, i.e., 73% to 84% **3q**–**3t**.

After the successful screening of various *N*-substitutions with sulfoximine, we next vary the different α-halo hydroxamate under standard reaction condition as depicted in Table 3.

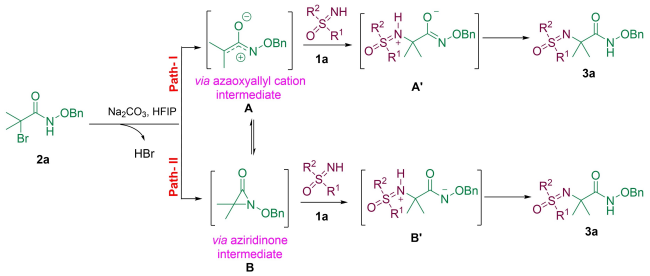
Table 3. Substrate scope of different α-bromo hydroxamates [a,b]



[a] Reaction conditions: **1a** (1 equiv.), **4a**–**f** (1.2 equiv.), Na_2CO_3 (3 equiv.), HFIP (0.2 equiv.), DCM, room temperature, 12 h, under N_2 atmosphere; [b] Isolated yields after column chromatographic purification are shown.



Scheme 2. Scale-up synthesis and synthetic transformation of product **3a**.



Scheme 3. Plausible Reaction Mechanism

While, the benzyloxy group in the α-bromo hydroxamates was replaced by other protecting groups such as methoxy, 4-iodo benzyloxy, and 4-nitro benzyloxy, reacted well with sulfoximine **1a** to furnish the desired substitution products **5a**–**5c** in comparative yields. Nevertheless, the α-halo hydroxamates with an absence of alkyl group, mono-alkyl group, and –Bn protected α-bromo amide are not suitable for forming *N*- alkyl sulfoximines (**5d**–**5f**).

To express the practicability and potential synthetic application of *N*-alkyl sulfoximines, we carried out the present reaction on a 1 g. scale with respect to **1a** under standard reaction condition to obtain 84% yield (1.5 g.) of product **3a** in 12 h of reaction time (Scheme 2).

Further, we demonstrated the synthetic utilities of the product as shown in Scheme 2. First, the N–O bond of α-sulfoximine hydroxymate **3a** was cleaved by using $Mo(CO)_6$ in the mixture of solvents (Acetonitrile: H_2O in 9:1 proportion) under the refluxed condition to obtain Amide product **6** in 58% yield. Also, the benzyl group was removed under hydrogenation conditions to produce the C–O bond cleaved product **7** in 65% yield.[24]

Based on the literature reports[20,24,23c] and control experiments, we proposed the two plausible reaction mechanism pathways as shown in Scheme 3. In the path I, azaoxyallyl cation **A** formed from α- bromo hydroxamate **2a** in the presence of HFIP and base with the removal of HBr. Subsequentially, the addition of *N*H-Sulfoximine on in-situ generated azaoxyallyl cationic intermediate **A** *via* S_N1 displacement pathway to form sulfoxinium ion intermediate **A'**. However, in path II, the reaction may proceed via aziridinone intermediate **B**. followed by the nucleophilic addition of sulfoximine through S_N2 displacement reaction to produce the intermediate **B'**. In both cases the transfer of the H- atom at the late step to obtain the substitution product **3a**.

Conclusion

We have developed a metal-free, and convenient protocol for *N*-alkylation of sulfoximines using functionalized tertiary halides via the aza-oxyallyl cations pathway. This process provides a mild and general method for the synthesis of congested *N*-alkyl sulfoximines from the reaction of α-halo hydroxamates and a variety of aryl-alkyl, di-aryl, and hetero-aryl sulfoximines. Further

application of this in-situ generated aza-oxyallyl cation on another nucleophile is underway.

Experimental Section

Representative Experimental Procedure for the Synthesis **3**:

Screw-cap reaction vail with a magnetic stir bar was added sulfoximines **1** (50 mg, 1 equiv.) and α- halo hydroxamate **2a** (1.2 equiv.) in DCM under nitrogen atmosphere. In this reaction mixture 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (0.2 equiv.), and Na_2CO_3 (3 equiv.) were added. The resulting mixture was stirred at room temperature until the starting material was completely consumed (by TLC analysis). After completion, the reaction was quenched with water (3 mL) and extracted with DCM (3×3 mL), and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent evaporated on a rotary evaporator under reduced pressure to obtain a crude product, purified by column chromatography on silica gel with petroleum ether and ethyl acetate to afford the desired products **3a**–**3t**.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Aza-oxyallyl cations · α-Bromo hydroxamates · Dialkyl sulfoximines · Metal-free · Sulfoximines

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