Sulfoximine: A Reusable Directing Group for C–O, C–N and C–C Bond Formation *via* C–H Bond Activation of Arenes

A Thesis
Submitted for the Degree of
DOCTOR OF PHILOSOPHY

By

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To

My Family

&

Well-Wishers

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STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigation carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India, under the supervision of **Dr. Akhila Kumar Sahoo**.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made on the basis of the findings of other investigators. Any omission, which might have occurred by oversight or error, is regretted.

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CERTIFICATE

Certified that the work contained in the thesis entitled "***Sulfoximine: A Reusable Directing Group for C–O, C–N and C–C Bond Formation via C–H Bond Activation of Arenes***" has been carried out by ***Mr. M. Ramu Yadav*** under my supervision and the same has not been submitted elsewhere for a degree.

Dr. Akhila Kumar Sahoo
(Supervisor)

Dean
School of Chemistry

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University of Hyderabad

June, 2014

List of Abbreviations

AcOH	acetic acid
Ac	acetyl
α	alpha
aq	aqueous
β	beta
Bn	benzyl
Bz	benzoyl
br	broad
^{t}Bu	^{t}butyl
Boc	*tert*-butyloxycarbonyl
^{13}C NMR	carbon-13 nuclear magnetic resonance spectroscopy
^{o}C	degree celsius
CH_3CN	acetonitrile
$CHCl_3$	chloroform
m-CPBA	*m*-chloroperbenzoic acid
d	doublet
dd	doublet of doublet
dt	doublet of triplet
DG	directing group
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DCM	dichloromethane
1,2-DCE	1,2-dichloroethane
DMAP	4-dimethylaminopyridine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
EDC.HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	electron-spray ionization
FT-IR	fourier transform infrared spectroscopy
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HRMS	high-resolution mass spectroscopy
Hz	hertz

J	coupling constant in hertz
$K_2S_2O_8$	potassium persulfate
LDA	lithium diisopropylamide
MPS	methyl phenyl sulfoximine
NS	nosyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
Oxone	potassium peroxymonosulfate
$PhI(OAc)_2$	phenyl iodo diacetate
Piv	pivaloyl
^{i}Pr	*iso*-propyl
TBHP	*tert*-butyl hydroperoxide
THF	tetrahydrofuran
Ts	tosyl
TMS	trimethylsilyl
TBDMS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxy

SYNOPSIS

The thesis entitled "**Sulfoximine: A Reusable Directing Group for C–O, C–N and C–C Bond Formation *via* C–H Bond Activation of Arenes**" consists four chapters: (1) Introduction: The C–H Bond Activation, (2) Sulfoximines: A Reusable Directing Group for Chemo- and Regioselective *ortho*-C–H Oxidation of Arenes, (3) Sulfoximine Directed Intermolecular *ortho*-C–H Amidation of Arenes with Sulfonyl Azides (Section A) and Sulfoximine Directed Ruthenium Catalyzed *ortho*-C–H Amidation of Arenes with N-Arenesulfonated Imides (Section B), (4) Sulfoximine-Directed Ruthenium-Catalyzed *ortho*-C–H Alkenylation of (Hetero)Arenes: Synthesis of EP3 Receptor Antagonist Analogue.

Except chapter 1, each chapter in this thesis is subdivided into three parts: (a) Introduction (literature survey), (b) Results and Discussion, and (c) Experimental Section. The compounds obtained in the present study are generally characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS spectral techniques followed by elemental analyses. Some of the representative compounds are unambiguously characterized by X-ray crystallography.

Chapter 1

Introduction: The C–H Bond Activation

Chapter 1 provides a brief outlook on the evolution of directing group assisted C–H functionalization and its potential utility to modern synthetic chemistry. The advantages and importance of C–H functionalization over coupling reactions is narrated at the beginning of the chapter. The tentative mechanistic paths involved in the C–H functionalization are also discussed. The importance of directing groups to the regioselective C–H activation is also highlighted. In the final part, special attention has been paid highlighting the synthetic potential of the reusable directing groups in C–H activations (Figure 1).

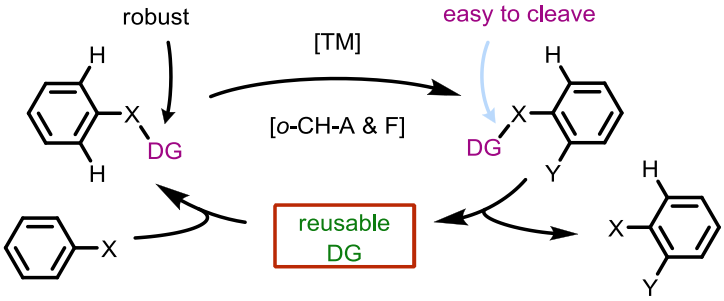


Figure 1. The reusable directing group for *ortho*-C–H activation of arenes

Chapter 2

Sulfoximines: A Reusable Directing Group for Chemo- and Regioselective *ortho*-C–H Oxidation of Arenes

Chapter 2 describes a new protocol for chemo and regioselective *ortho*-C–H acetoxylation of arenes in *N*-aroylated sulfoximines (Figure 2). The sulfoximine directing group is easily detached from the C–H oxidation product through acid promoted hydrolysis, isolated and re-used (Figure 2). *meta*-Substituted phenols are synthesized following this strategy. Stereointegrity of the sulfoximine is preserved in this transformation.

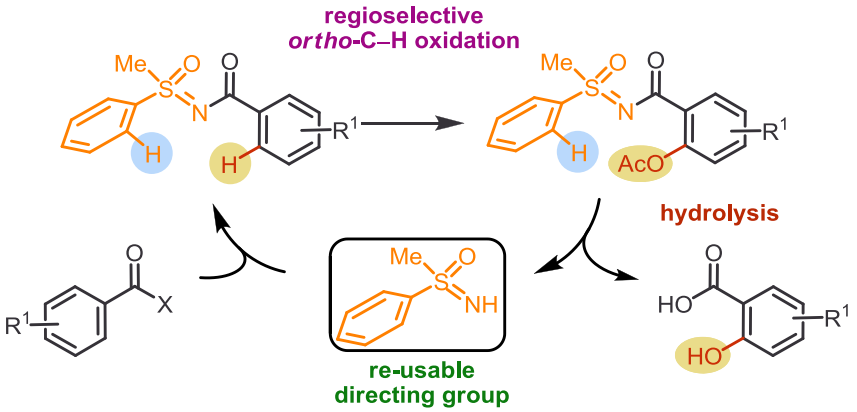
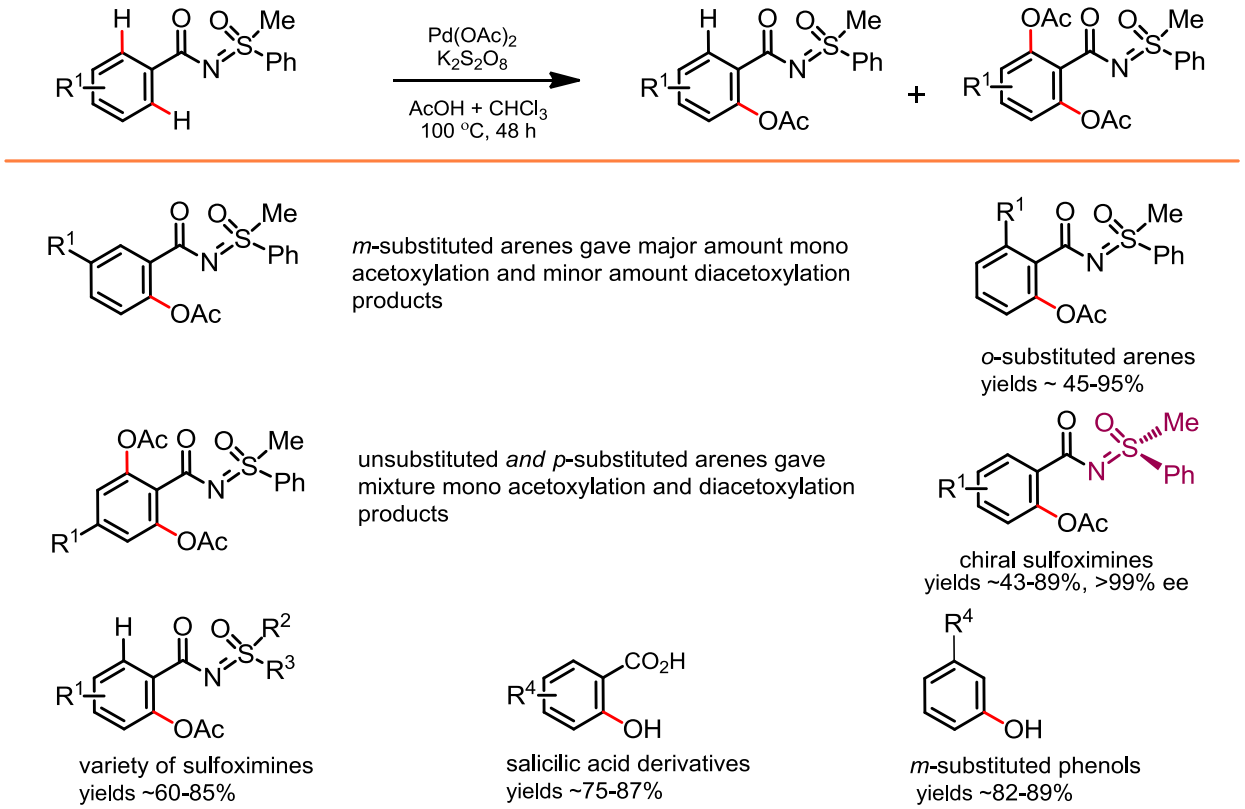


Figure 2. Metal catalyzed reusable sulfoximine directed *ortho*-C–H oxidation of arenes

The use of non-removable and non-modifiable directing group to the C–H oxidations limits the broad synthetic application. Owing to the importance of the C–H oxidations of arenes, the palladium-catalyzed *chemo- and regioselective ortho-acetoxylation of arenes with the aid of a new and potential directing group sulfoximine is demonstrated*. The results are briefed in Scheme 1. Among various sulfoximine derivatives screened, the methyl phenyl sulfoximine (MPS) directing group is found to be effective to the C–H oxidation. The robust sulfoximine directing group is easy to attach in the starting material and rapidly detach from the C–H oxidation product. *It is worth mentioning that the sulfoximine group has been successfully and efficiently re-used*. Based on the *effective cleavability and re-usability of the sulfoximine directing group*, we believe this strategy *would be useful in fabricating complex phenol derivatives*. The hitherto difficult *m*-substituted phenols are also synthesized. Interestingly, the *stereointegrity of the chiral sulfoximine is preserved* during the C–H oxidation.

To the best of our knowledge, the sulfoximine directed C–H oxidation of arenes is reported for the first time.



Scheme 1: Substrate scope for *o*-C–H oxidation of N-aroyl methyl phenyl sulfoximine derivatives.

Chapter 3

This chapter is divided in two sections. The section A entails "Sulfoximine Directed Intermolecular *ortho*-C–H Amidation of Arenes with Sulfonyl Azides". The section B depicts the preliminary results of "Sulfoximine Directed Ruthenium Catalyzed *ortho*-C–H Amidation of Arenes with N-Arenesulfonated Imides".

Section A: Sulfoximine Directed Intermolecular *ortho*-C–H Amidation of Arenes with Sulfonyl Azides

This section describes the cationic Ru(II)-catalyzed chemo and regioselective intermolecular *ortho*-C–H amidation of arenes in *N*-aroylated sulfoximine with sulfonyl azides. The reaction proceeds with broad substrate scope and tolerates various functional groups. Base hydrolysis of the amidation products provide anthranilic acid derivatives and methyl phenyl sulfoximine (MPS) directing group. This method is successfully employed for the divergent synthesis of HMR 1766 (Figure 3).

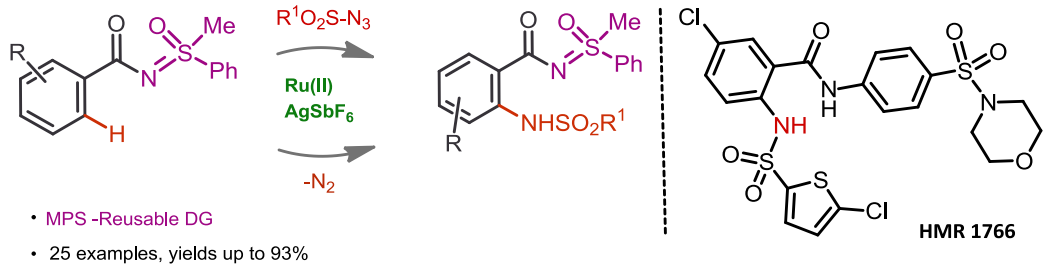
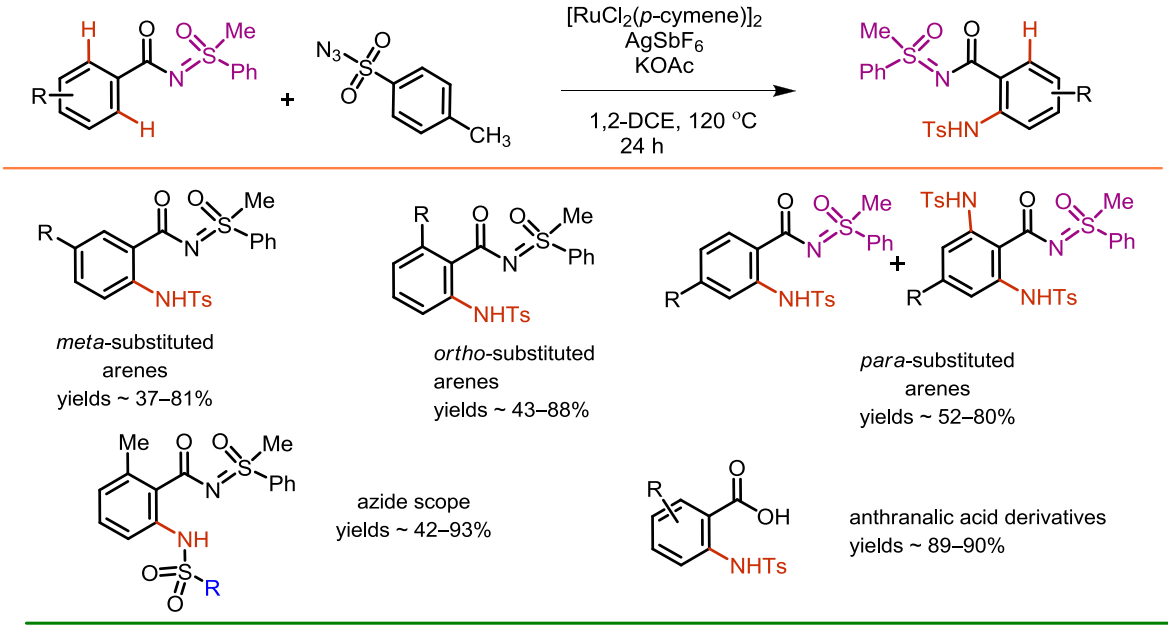


Figure 3. Schematic representation of Ru(II)-catalyzed *o*-C–H amidation of N-aroyl sulfoximines with sulfonyl azides

The amination of C–H bond of arenes is a unique method that creates direct C–N bond in the molecule; more importantly this method does not require the pre-functionalized arenes. Various research groups have independently shown amination of benzamides/aryl ketones using electrophilic aminating reagent as amine source. Recently, Chang group reported an elegant approach Rh(III) catalyzed pyridyl and/or oxime directed amidation of arene C–H bonds using sulfonyl azides; *this process produces the benign N_2 gas byproduct*. The *ortho*-C–H amination on arenes has been achieved with the assistance of modifiable directing groups (DG's), while the identical reaction with the aid of reusable DG is yet to be investigated. Furthermore, the use of Ru-catalysts for the intermolecular *ortho*-C–H amination is rare.



Scheme 2: Substrate scope for the synthesis of *ortho*-amido N-aroyl methyl phenyl sulfoximine derivatives.

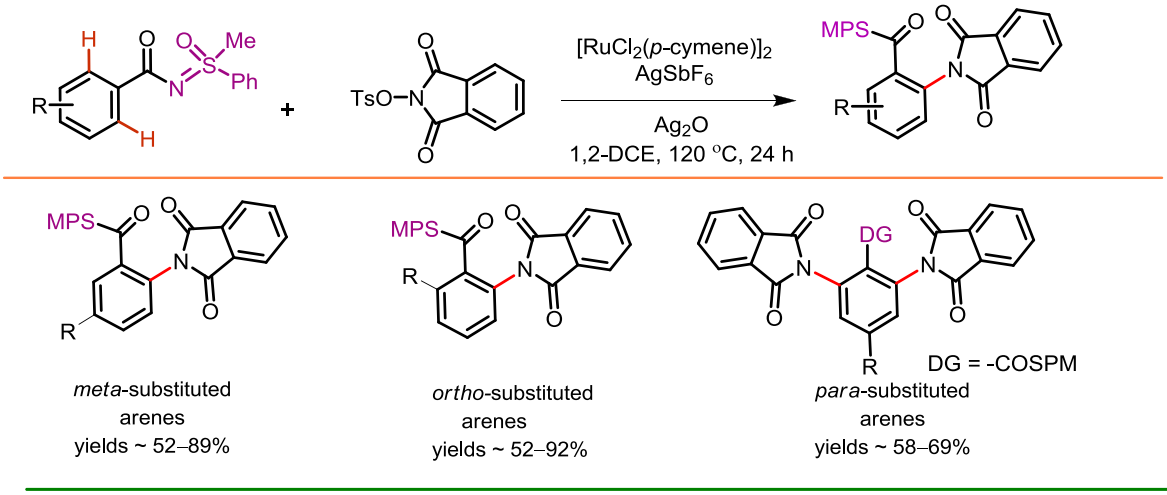
The reaction scope, the synthesis of array of anthanilic acid derivatives, and the isolation of directing groups from the products are broadly sketched in Scheme 2. *To the best of our*

knowledge, the Ru(II)-catalyzed ortho-C–H amidation of arenes with sulfonyl azides is the first result.

Section B: Sulfoximine Directed Ruthenium Catalyzed *ortho*-C–H Amidation of Arenes with N-Arenesulfonated Imides

The current research interest in C–N bond formation through C–H activation motivated us finding *ortho*-C–H amidations of arenes with electrophilic aminating agents.

This section entails the preliminary results of Ru(II)-catalyzed *ortho*-C–H amidation of N-aroyl methyl phenyl sulfoximine derivatives with N-arenesulfonated imides. The reaction of *meta* and *ortho* substitued arenes gave good to excellent yields of amidation products, whereas *para*-substituted arenes furnished synthetically important di-amidation products in moderate to good yields. The results are shown in Scheme 3.



Scheme 3: *ortho*-C–H amidation of N-aroyl methyl phenyl sulfoximine derivatives with N−arenesulfonated Imides.

Chapter 4

Sulfoximine-Directed Ruthenium-Catalyzed *ortho*-C–H Alkenylation of (Hetero)Arenes: Synthesis of EP3 Receptor Antagonist Analogue

Chapter **4** describes the reusable sulfoximine directing group assisted Ru(II)-catalyzed chemo and regioselective *o*-C–H alkenylation of arenes and heteroarenes with acrylates, and α,β-unsaturated ketones/vinyl sulfone (Figure 4). The N-aroyl sulfoximine undergoes annulation with diphenylacetylene delivering isoquinolinones and methyl phenyl sulfoxide.

The present protocol is successfully employed for the synthesis of EP3 receptor antagonist analogue (Figure 4).

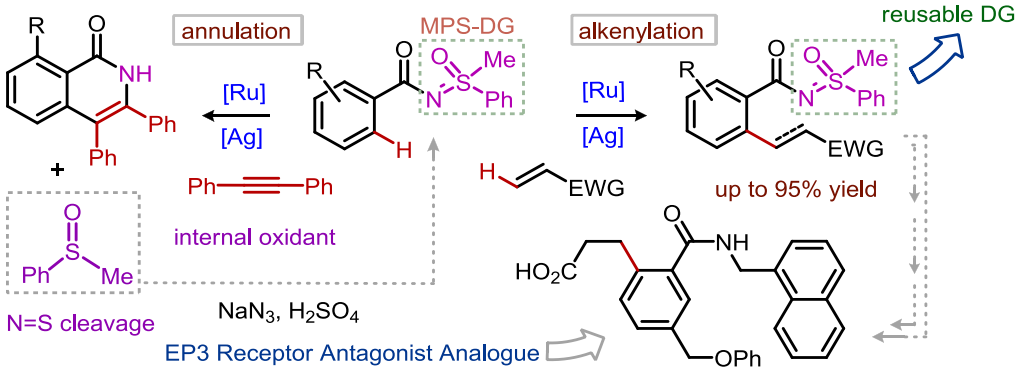
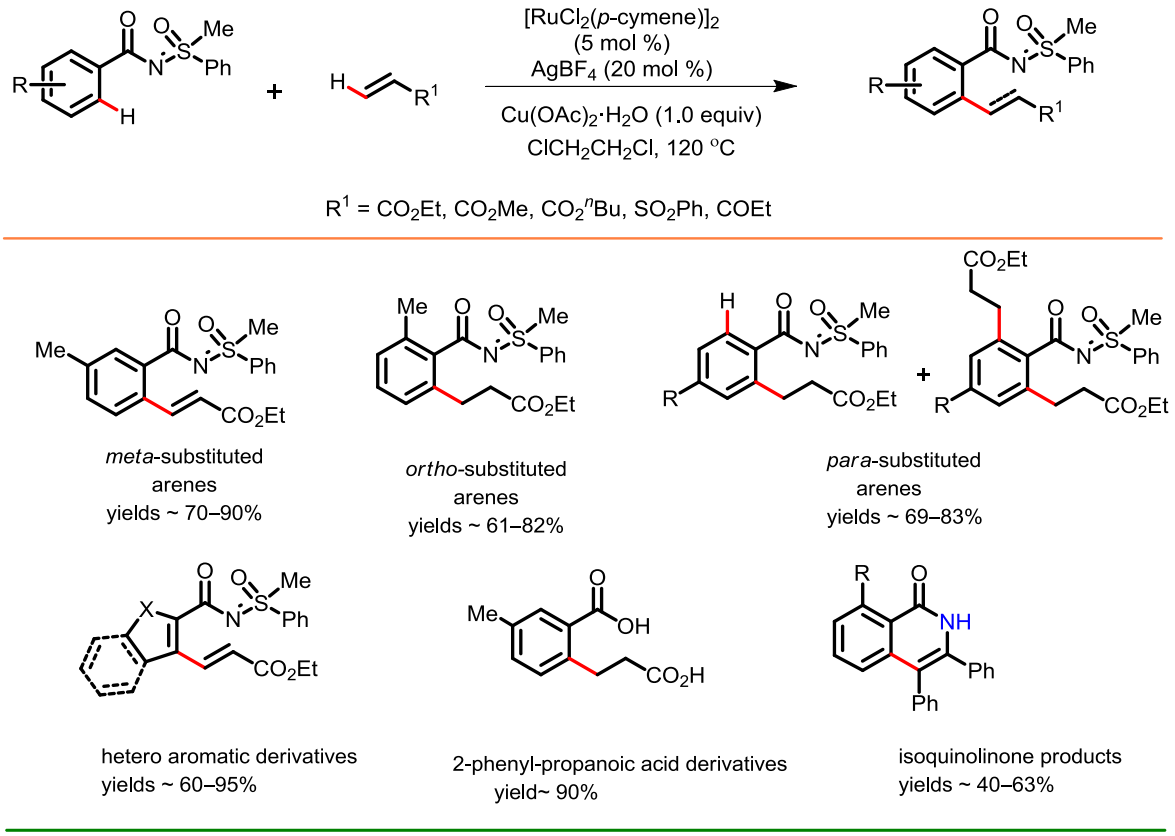


Figure 4. Schematic representation of Ru(II)-catalyzed *o*-C–H alkenylation of N-aroyl sulfoximines

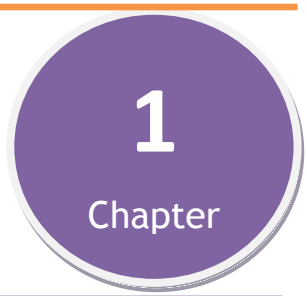
This chapter begins highlighting the metal-catalyzed chelation assisted activation of arene C–H bonds for direct formation of chemo- and regioselective styrene derivatives. The reduced variant of styrene entity, 3-(2-carbamoylphenyl)-propionic acid is a key structural component found in many biologically active and pharmaceutically important molecules. The Miura, Dixneuf, Ackermann, Jaganmohan and others have independently developed the Ru(II)-catalyzed modifiable/non-modifiable DG assisted *o*-C–H alkenylation of arenes. However, the identical reaction with the aid of reusable DG is scarce. Our group recently demonstrated the sp^2 C–H oxidation (*Chem.–Eur. J.***2012**, *18*, 5541) and amidation (*Org. Lett*. **2013**, *15*, 3724) of arenes with the aid of the reusable methyl phenyl sulfoximine (MPS) DG. To further broaden the utility of reusable MPS-DG, the alkenylation on unactivated arenes under the influence of robust Ru-catalyst is detailed in this chapter.

The reaction proceeds with broad substrate scope and tolerates various functional groups. The robust methyl phenyl sulfoximine (MPS) directing group is easily attached to the substrates and rapidly detached from the *o*-C–H alkenylation product (Scheme 4). Surprisingly, the reaction of N-aroyl methyl phenyl sulfoximine with diphenyl acetylene delivered isoquinolinone derivative through an unprecedented cleavage of sulfur-nitrogen double bond in sulfoximine (Scheme 4). The isolation of MPS and the phenyl methyl sulfoxide make these strategies synthetically viable and useful. *It is worth mentioning that the* o-C–H alkenylation of arene *methodology is successfully employed for the synthesis EP3 receptor antagonist analogue (Figure 4).*



Scheme 4: Substrate scope for the synthesis of *ortho*-C–H alkenylation and alkylation of N-(hetero)aroyl methyl phenyl sulfoximine.

Introduction: The C–H Bond Activation



Abstract

The origin of C–H activation and its potential utility to modern synthetic chemistry is briefly discussed in this chapter. The advantage and importance of C–H functionalization over coupling reactions is narrated. The mechanistic paths involved in the C–H functionalization are discussed. The importance of directing groups in the regioselective C–H activation is shown. In the final part, the synthetic potential of reusable directing group in the C–H activation is highlighted.

1.1. Introduction

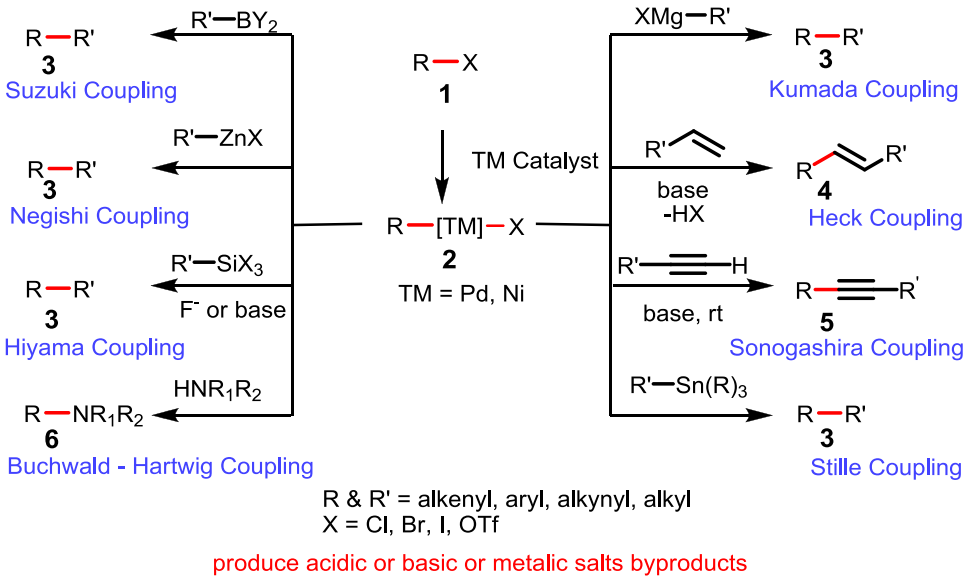
The invention and improvement of new carbon–carbon and carbon–heteroatom bond forming synthetic methods is always demanding. Thus, the focus of the synthetic community has seen great changes in recent decades. For instance, chemists are searching for a novel process that use simple starting materials, give access to more complex and varied products, and generate little or no waste. The development of new catalytic methods is considered to be the best way of achieving these goals.

The transition-metal catalyzed synthetic procedures for C–C and C–X (X = heteroatom) bond formations revolutionized discovering novel reactions with efficiency and yield. Especially, cross-coupling reactions have made great impact on organic chemistry by making molecules in easier manner otherwise difficult to access. Despite this fact, cross-coupling methods require pre-functionalized precursors, obtained through multiple synthetic manipulations from readily available materials, and produce hazardous by products.

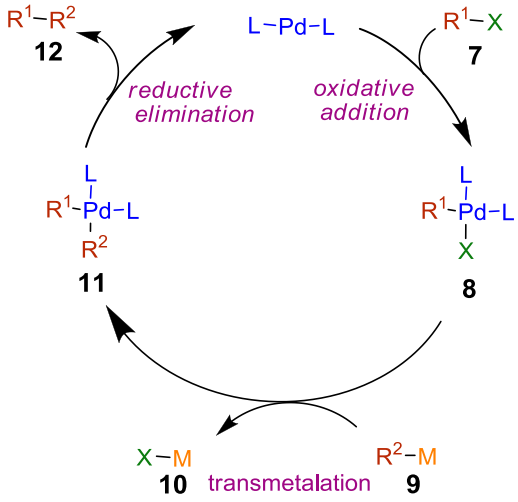
Alternatively, the direct utilization of inert C–H bonds in chemical transformations is highly beneficial in terms of atom and step economy. However, the high bond dissociation energies of C–H bonds require harsh reaction conditions for the cleavage. In addition, the chemo, regio, and stereoselective C–H bond functionalization of specific C–H bond remains challenging. Interestingly, the presence of heteroatom bearing directing group in the molecule enables regioselective functionalization of C–H bond. Moreover, most of the notable directing groups are neither removable nor modifiable.

1.1.1. The Cross-Coupling Reactions

The transition-metal catalyzed cross-couplings are synthetically viable methods broadly useful for carbon-carbon and carbon-heteroatom bond formations.[1,2] In general, cross-coupling reactions essentially require halides or pseudo halides **1** and organometallic nucleophilic reagents; the known cross-coupling methods are sketched in Scheme 1.1. The cross-coupling reactions are broadly useful for the synthesis of pharmaceutically active molecules, agrochemicals and organic materials.[3] Based on the strong impact of these reactions, Heck, Negishi, and Suzuki received Nobel Prize in 2010 for their pioneer discovery of cross-coupling reactions.



Scheme 1.1: Representative cross-coupling reactions



Scheme 1.2: General mechanism of cross-coupling reactions

A general mechanism of cross-coupling reaction is shown in Scheme 1.2. The reaction begins with the oxidative addition of an organic electrophile **7** to the metal to give intermediate **8**. Next, the transmetalation of organometallic reagent **9** with **8** furnished the intermediate **10**. Finally, reductive elimination of **11** affords the desired C–C coupled product **12** along with the regeneration of the catalyst.

In spite of the significant discoveries and developments, the cross-coupling reactions possess the following limitations, i.e. 1) the mandatory requirement of pre-functionalized starting materials, 2) the use of bulky and costly ligands, and 3) the production of stoichiometric amount of hazardous acidic or basic or metal salts byproducts. Therefore, development of an alternate, energy efficient and environmentally benign method is always desirable.

Gratifyingly, the formation of C–C and C–heteroatom bond through the activation of C–H bond is considered effective.

1.1.2. The C–H Bond Activation

The carbon-hydrogen bond is ubiquitous, largely found in organic molecule. However, the utility of C–H bonds as reactive functional group is rare. Significantly, C–H activation protocol avoids the use of pre-functionalized precursors and does not produce environmentally hazardous byproducts. Despite the ready accessibility, the C–H bonds possess high bond dissociation energy (85–120 Kcal/mol), and non-polarized in nature (pK_a > 35). The bond strength and pK_a values of various C–H bonds of alkane, alkene and arenes are listed in Scheme 1.3.

Bond	Bond Dissociation Energy (Kcal/mol)	pK_a (water)
CH_3–H	103	48
$(CH_3)_2HC$–H	95	51
$(CH_3)_3C$–H	93	53
CH_2=CH–H	112	50
C_6H_5–H	110	43
CH_2=$CHCH_2$–H	88	43
$C_6H_5CH_2$–H	85	41

Scheme 1.3: C–H Bond strengths and pK_a's of C–H bonds of alkane, alkene and arenes

Due to the high bond dissociation energies, C–H bonds are thermodynamically stable and least reactive. Thus, direct utilization of C–H bonds for the C–C and C–X bond formation is a challenging task.[4,5] The classical methods use activated or highly acidic C–H bonds. This can be easily achieved under the influence of a base or an electrophile or *via* a free radical. Moreover, metalloproteins/enzymatic systems i.e. cytochrome P450 and methane monooxygenase undergo easy C–H oxidation.[6] Furthermore, the electrophilic transition metals enable C–H functionalization by decreasing the activation energy of C–H bonds. The C–H bond interaction with electrophilic metal is better explained by frontier molecular orbital approach (Fig 1.1). The low energy, sigma symmetry, and low polarizability of the

HOMO C–H bond and high energy, sigma symmetry, and polarizable LUMO of electrophilic metals are involved in C–H bond activation.

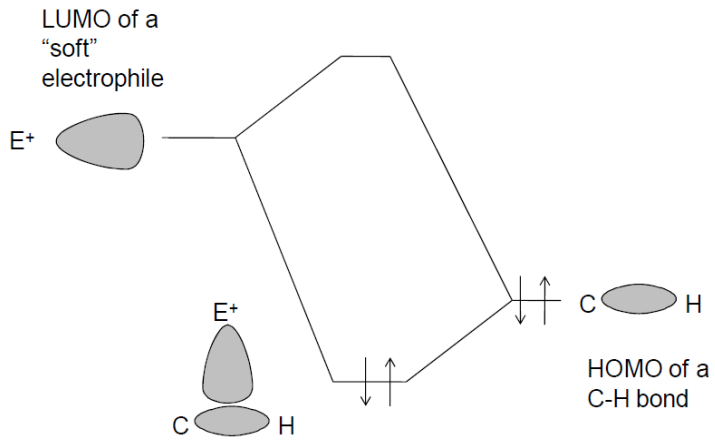
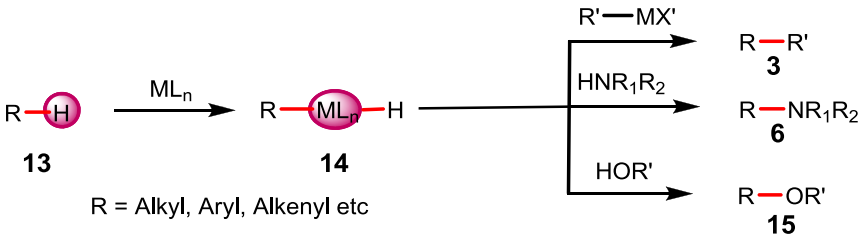


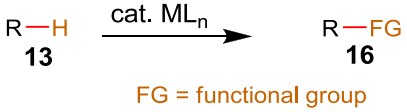
Figure1.1: Molecular orbital diagram of C–H interaction with metal

*The C–H activation can be defined as catalytic or stoichiometric reactions of transition metal complexes with the unreactive C–H bonds of alkanes, arenes, or alkyl chains (**13**) to form a more reactive new metal-carbon bond **14** (Scheme 1.4).* Subsequently, the newly generated C–M intermediate **14** is more reactive than corresponding C–H bond and it readily undergo reactions with a range of electrophiles or nucleophiles to form diverse C–C, C–O, and C–N bonds (Scheme 1.4). [4,7]



Scheme 1.4: General representation of C–H activation/bond formation

Broadly the transformation of C–H bond **13** to C–FG **16** is termed C–H bond functionalization (Scheme 1.5). *Thus, Fiedel-Crafts alkylation reactions or aromatic nitrations or ortho lithiation belongs to C–H functionalization rather C–H activations.*



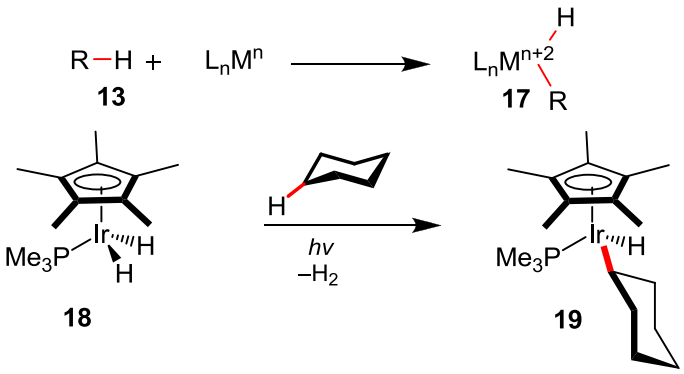
Scheme 1.5: General representation of C–H functionalization

1.2. Mechanism of C–H Activation

On the basis of nature of C–H bond, and use of transition metal catalyst, and ligands the activation of C–H bond occurs through the following ways; oxidative addition, sigma bond metathesis and electrophilic activation.[7a,8]

1.2.1. Oxidative addition

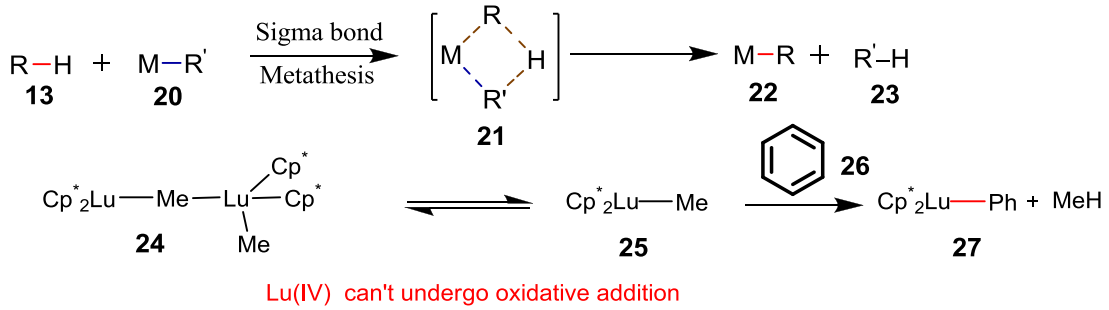
The coordination of transition metal to the C–H bond is the first step. This process primarily proceeds through agostic interaction i.e. distortion of organometallic moiety bringing the appended C–H bond to the close proximity to transition-metal center. The transition-metal insertion to the C–H bond through agostic interaction is termed oxidative insertion. In this case, the electron rich low valent late transition metal (Re, Fe, Ru, Os, Rh, Ir, Pt) is susceptible for the direct insertion to the unactivated C–H bond. The reaction proceeds via co-ordinatively unsaturated intermediates generated *in-situ* by thermal or photochemical decomposition (Scheme 1.6).



Scheme 1.6: C–H Activation *via* oxidative addition

1.2.2. Sigma bond metathesis

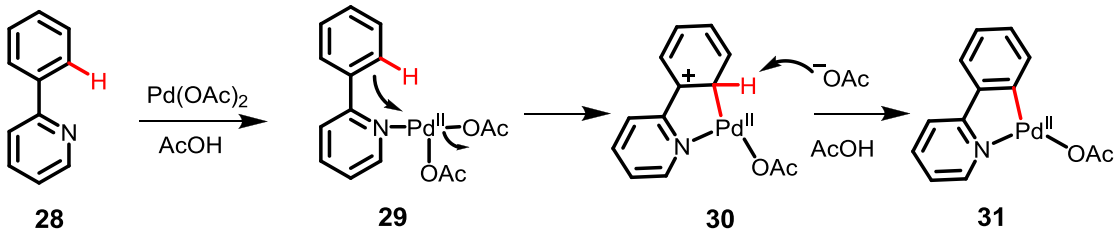
The early transition metal alkyls **20** having d^0 electronic configuration, most commonly the group 3 elements (Sc, lanthanides and actinides), undergo sigma-bond metathesis reactions with inert C–H bonds of **13** to form the alkyl or hydride complexes **22** (Scheme 1.7). The reaction participates a probable four-centred transition state **21**.



Scheme 1.7: C–H Activation *via* sigma bond metathesis

1.2.3. Electrophilic activation

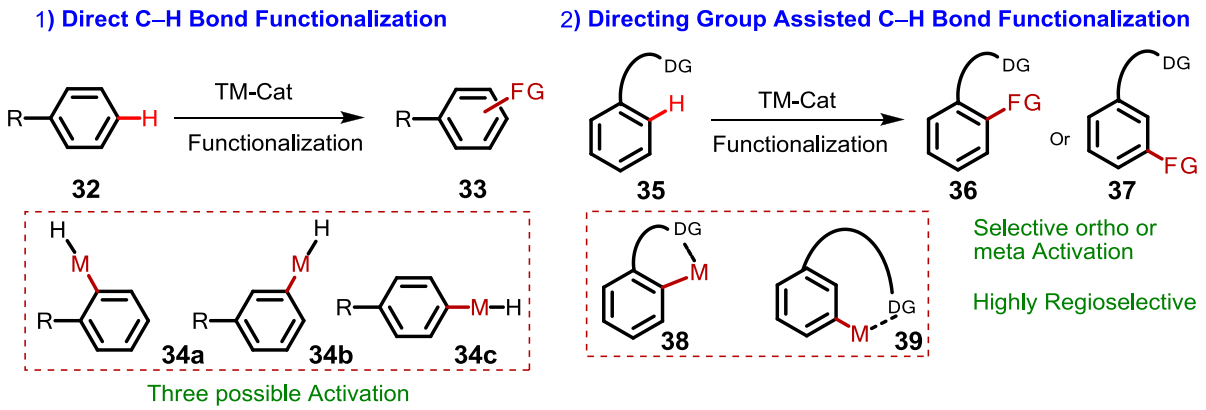
Generally, the late- or post-transition metals (Pd(II), Pt(II) and/or Pt(IV), Hg (II), Tl(III)) participate in direct electrophilic attack with alkanes or arenes (Scheme 1.8). These reactions are favorably proceeds in strong polar medium (water or an anhydrous strong acid). For instance; cyclopalladation of **28** successfully occurs through electrophilic activation of arene C–H bond. The initial co-ordination of nitrogen atom to $Pd(OAc)_2$ in AcOH forms intermediate **29,** subsequent π-attack of arene to metal and the removal of proton finally delivers the cyclopalladated species **31**.



Scheme 1.8: C–H Activation *via* electrophilic activation

1.3. Different Methods of C–H Functionalization

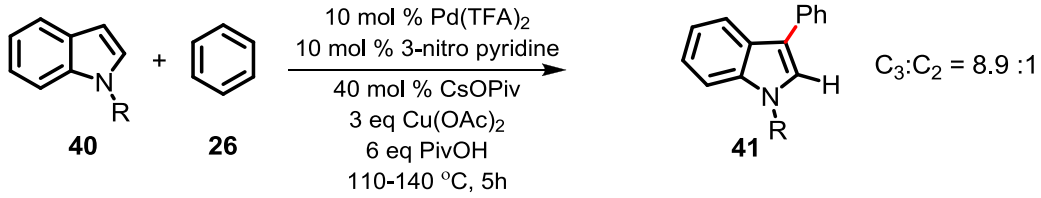
The C–H functionalization can be carried out in two ways (Scheme 1.9): 1) the direct functionalization of inert C–H bond[9] and 2) the chelation or directing group assisted C–H functionalization.[4h] The first approach involves the direct insertion of electrophilic metal to the inert C–H bonds. However, the large number C–H bonds in the molecule get equal opportunity for activation, making this process non-regioselective. Whereas the chelation assisted C–H bond functionalization operates through the coordination of heteroatom to the metal; therefore activates the proximal C–H bond leaving other C–H unreactive.



Scheme 1.9: Different methods of C–H activation of arenes

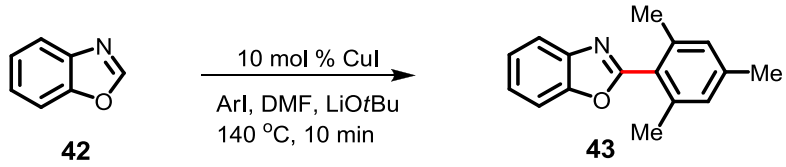
1.3.1. Direct C–H Bond Functionalization

In 2007, Fagnou and coworkers demonstrated an interesting regioselective cross-dehydrogenative arylation of N-protected indoles **40** with arenes **26** under the influence of $Pd(TFA)_2$ catalyst, terminal oxidant $Cu(OAc)_2$ in PivOH (Scheme 1.10).[10] The catalytic condition enabled C3-arylation product **41**. The high selectivity is accountable due to the nucleophilicity at C3 position of indole. Notably, no homocoupling product among indoles or arenes was observed.



Scheme 1.10: Pd-Catalyzed direct arylation of N-protected indole with arenes

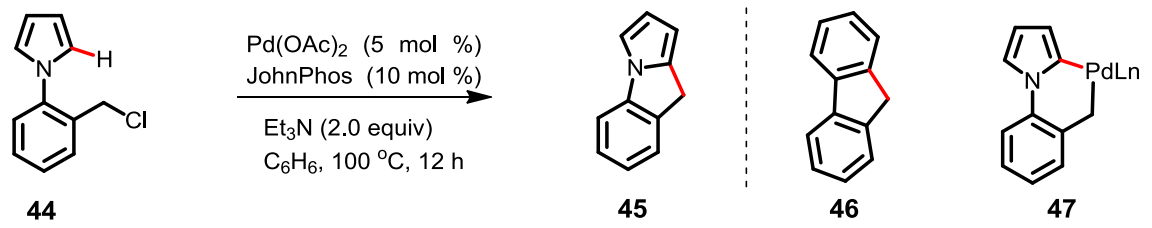
The Daugulis group developed a Cu-catalyzed arylation of acidic C2–H bond of benzoxazole **42** with aryl halide (Scheme 1.11).[11] The lithium *tert*-butoxide base is essential in this reaction. It is noteworthy that the electron-poor pyridine oxide participated in this reaction.



Scheme 1.11: Pd-Catalyzed direct arylation of benzoxzoles

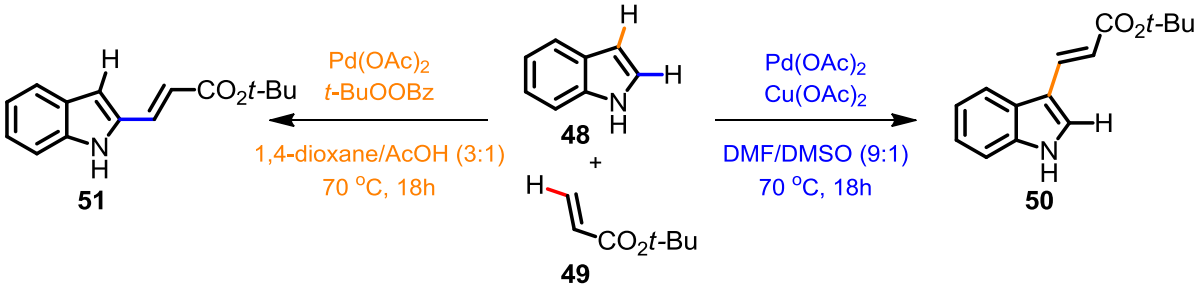
In 2008, Chang group reported a novel strategy for the synthesis of condensed hetero- or carbocycles pyrroloindoles (**45**) or fluorenes (**46**) (Scheme 1.12).[12] The reaction involves Pd-

catalyzed cyclization of readily available *N*-(2-halobenzyl)pyrroles or the phenyl derivatives *via* a base-assisted deprotonative metalation pathway.



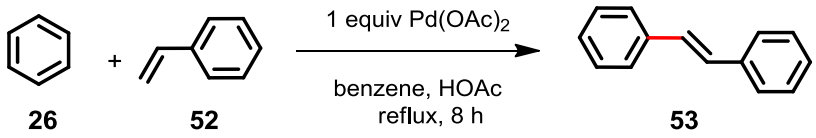
Scheme 1.12: Pd-Catalyzed intermolecular C–H functionalization/cyclization

Gaunt and co-workers showed Pd-catalyzed highly regioselective C2 or C3 olefination of indole **48**; the oxidant and solvent plays vital role to this selectivity (Scheme 1.13).[13] The coordinating polar solvents DMF or DMSO in combination with terminal oxidant $Cu(OAc)_2$ allowed selective insertion of olefins at C3-position producing **50**, whereas peroxide oxidant in an acidic co-solvent enabled C2-olefination product **51**.



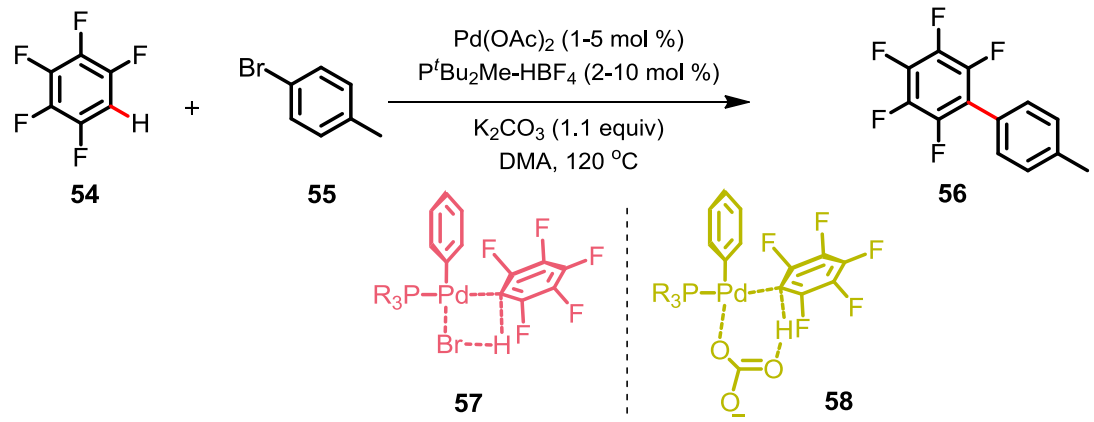
Scheme 1.13: Pd-Catalyzed regioselective alkenylation of indoles

Moritani and Fujiwara demonstrated oxidative coupling between benzene **26** and styrene **52**, when reacted with stoichiometric $PdCl_2$ in acetic acid (Scheme 1.14).[14] The use of silver salts reduces the loading of palladium catalyst.



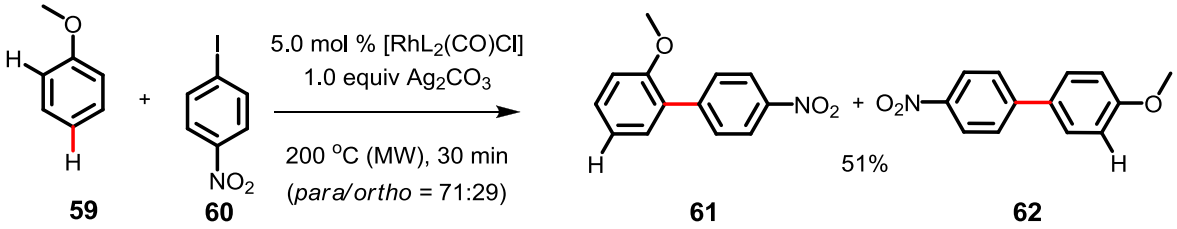
Scheme 1.14: Pd-Catalyzed oxidative alkenylation of arenes

The pentafluorobenzenes **54** underwent direct arylation with a wide range of arylhalides **55** in high yield (Scheme 1.15).[15] The computational study reveals that the carbonate (**58**) or a bromide ligand (**57**) assists cleaving the C–H bond through a concerted carbon–palladium and carbon–hydrogen bond.



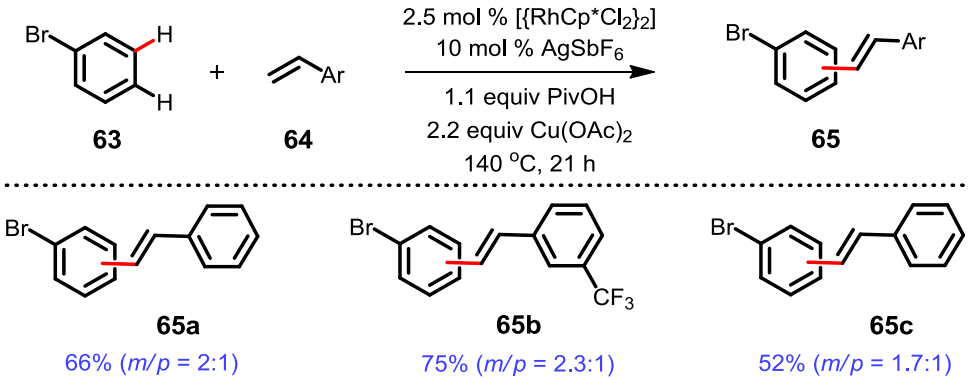
Scheme 1.15: Pd-Catalyzed direct arylation of fluorobenzenes with arylhalides

Itami and co-workers reported a rhodium catalyzed direct arylation of anisoles **59** with *para*-nitrophenyl iodide **60** in the presence of Ag_2CO_3. Unfortunately, the reaction affords non-selective *ortho/para substituted* products **61** & **62** when heated at 200 °C under microwave (Scheme 1.16).[16]



Scheme 1.16: Rh-Catalyzed direct arylation of anisoles with aryliodides

Glorious group demonstrated a Rh(III)-catalyzed oxidative Heck reaction between bromo benzene **63** and styrene derivative **64** (Scheme 1.17).[17]



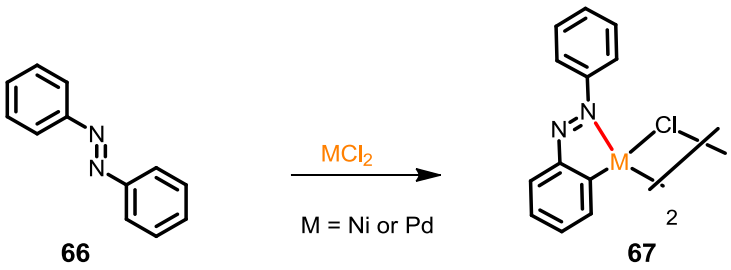
Scheme 1.17: Rh(III)-Catalyzed oxidative Heck reaction between bromobenzene and styrene

Notably, the C–Br bond is inert under the catalytic conditions [Rh-catalyst, $AgSbF_6$, PivOH, and $Cu(OAc)_2$] to produce **65**. Unfortunately, the reaction is not regioselective giving a mixture of *meta* and *para* C–H alkenylation products (Scheme 1.17).

A detailed survey of these reports suggests that the selectivity largely depends on acidity of C–H bond of the heterocyclic compounds or arenes. While a mixture of regioisomeric products is observed through the competitive activation of *ortho*, *meta* and *para* C–H bonds of arenes as discussed in Scheme 1.16 and 1.17. The introduction of a heteroatom chelating group would direct activating the close-proximity C–H bond and produce a regioselective C–H functionalized products. Few cases of directed C–H activations are briefly discussed.

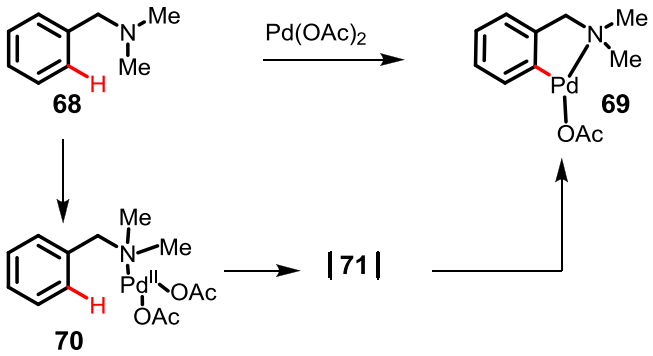
1.3.2. Synthesis of Chelation Assisted Cyclometalated Complexes

The first cyclometalation complex **67** was synthesized from azobenzene **66** and stoichiometric nickel or palladium compounds under reflux. The complex **67** was obtained through C–H activation (Scheme 1.18).[18]



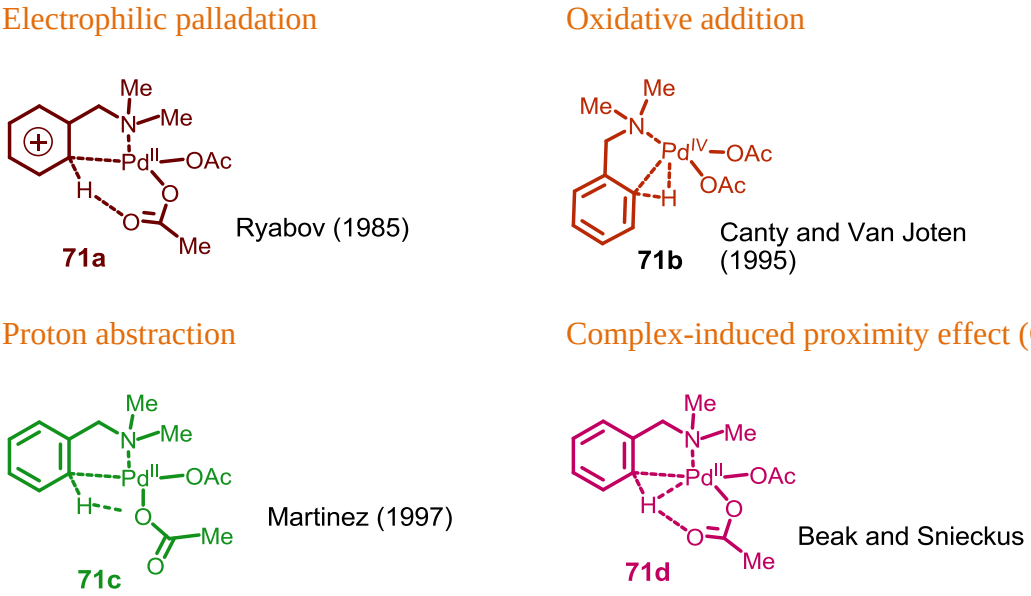
Scheme 1.18: Cyclometalation of azobenzene

A tentative mechanism for cyclometalation of aryl C–H bonds sketched in Scheme 1.19.[19] Importantly, the heteroatom in the molecule promotes facile cyclometalation *via* C–H bond activation.



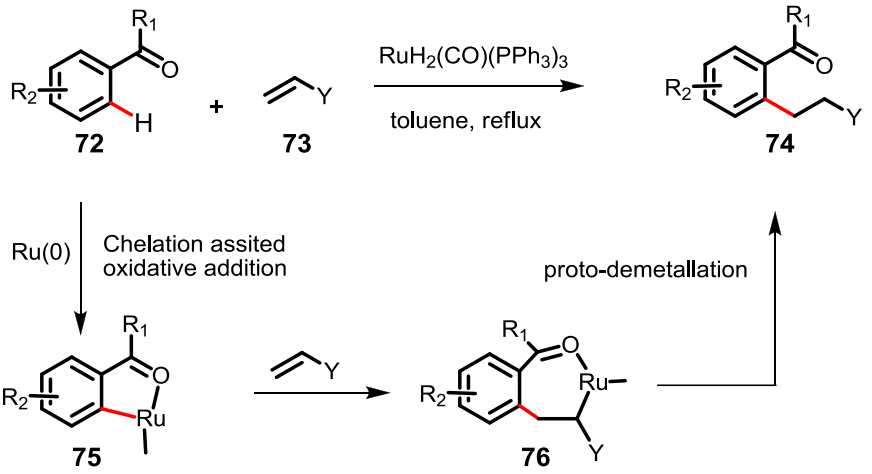
Scheme 1.19: Cyclopalladation of N,N-dimethyl benzyl amine

For instance: initial co-ordination of nitrogen atom in benzyl amine **68** to the transition-metal delivers the **70**, a common intermediate responsible for the formation of cyclopalladation species **69** (Scheme 1.19). Ryabov group postulated the formation of species **71a** through electrophilic substitution of intermediate **70** to metal would produce **71a** (Scheme 1.20), finally removal of proton from **71a** would lead to the cyclopalladation intermediate **69**. Later in 1995, Canty and Van joten described the oxidative addition of arene C–H bond to Pd-centre resulting higher oxidation state Pd(IV)-species **71b** (Scheme 1.20). The elimination of AcOH from **71b** affords the desired cyclopalladation species **69**. Martinez group proposed participation of intermediate **71c** (Scheme 1.20), where the AcO^- co-ordinates to Pd-centre triggering the proton abstraction directly from arene C–H bond responsible for the formation of **69**. The desired metal complex **69** can be obtained through complex-induced proximity effect (CIPE) of the species **71d** (Scheme 1.20).



Scheme 1.20: Intermediates responsible for the formation of cyclometalation species

In 1993, Murai group discovered ruthenium-catalyzed carbonyl directed regioselective *o*-C–H alkylation of arene **72** for the first time (Scheme 1.21).[20] The reaction proceeds through the initial co-ordination of carbonyl oxygen atom to the ruthenium metal, followed by the C–H activation to result the ruthenacycle **75**. Further, the binding of alkene to the ruthenium metal followed by oxidative insertion to C–M bond would lead to the intermediate **76**. Finally proto-demetalation of **76** gave the desired product **74** in good yield.



Scheme 1.21: Ru-Catalyzed carbonyl directed regioselective *o*-C–H alkylation of arenes

The Ru-catalyzed C–H alkenylation inspired the synthetic chemists to develop and investigate different chelating groups for direct construction of C–C, C–hetero bonds *via* C–H bond activation under the influence of transition metal catalysts, external oxidants and additives.

1.3.3. Directing Group (Chelation)-Assisted C–H Bond Activation

Directing groups (DG) assist in achieving the regioselective functionalization of arenes. Directing groups initially co-ordinate to the transition metal and brings the coordinating-metal species to the close proximity to the C–H bond, resulting a substantial enhancement of reactivity as well as selectivity.[4,21] Accordingly, various types of directing groups have been developed and deployed for the construction of C–C and C–X bonds. Some of the notable directing groups, for example: pyridines, pyridine *N*-oxides, pyrazole, pyrimidine, acetanilides, oxime, esters, carbamates, imines, and amides are effectively used for C–H bond functionalization.

Based on the utility, the DGs are classified as follows:

1) Non-modifiable directing groups

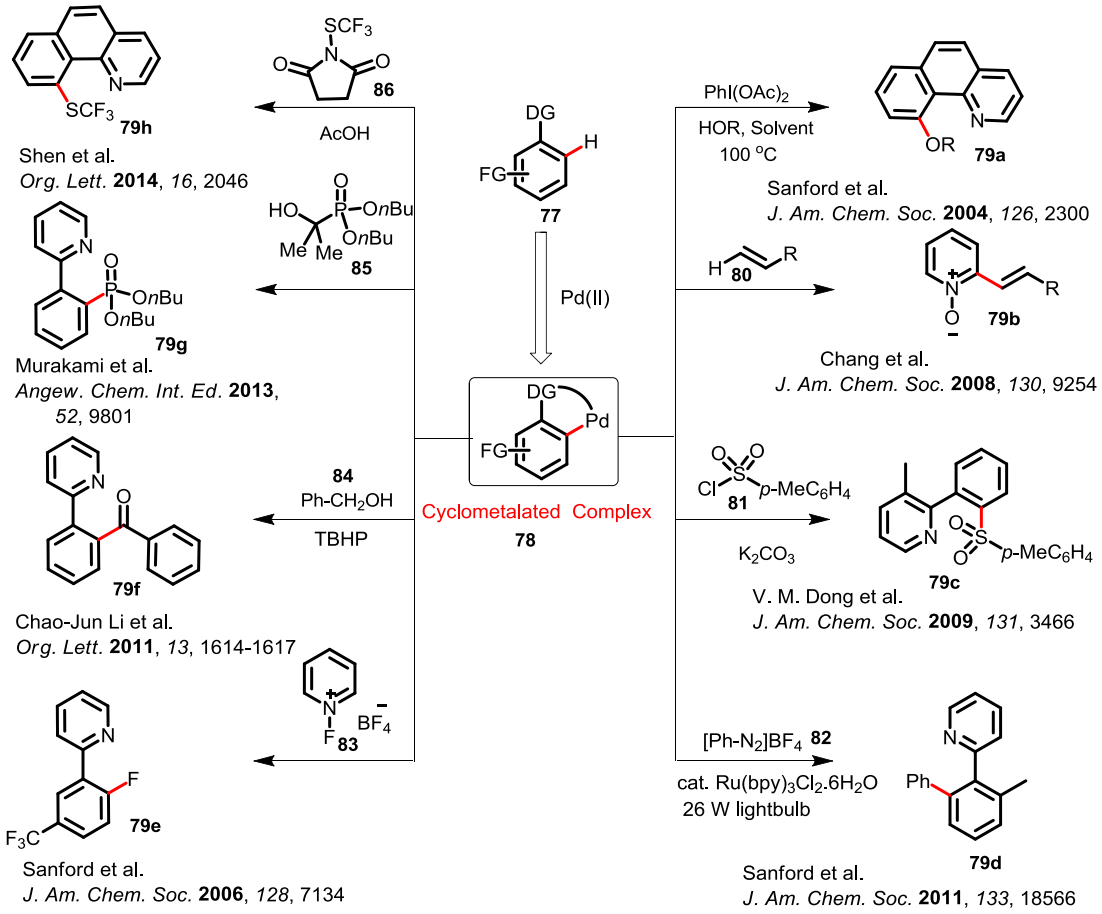
2) Modifiable/transformable directing groups

3) Reusable directing groups

1.3.3.1. Non-Modifiable Directing Groups

The non-Modifiable DGs can't be modified or transformed into different functionality after the reaction.

In 2004, Sanford group reported Pd-catalyzed N-bearing ligand-directed intramolecular sp^2 C–H bond oxidation of arenes **77a** in the presence of oxidant $PhI(OAc)_2$ for the synthesis of **79a** (Scheme 1.22). This discovery led to the development of C–S, C–C, and C–F bond formations involving C–H activation (Scheme 1.22). Chang group demonstrated synthesis of **79b** through Pd-catalyzed alkenylation of pyridine N-oxide. Dong group showed $Pd(MeCN)_2Cl_2$ catalyzed oxidative coupling of $ArSO_2Cl$ **81** with 2-arylpyridine, arylpyrazole, aryloxime ethers for C–S bond formation **79c**.



Scheme 1.22: Transition metal catalyzed non-modifiable directing group assisted regioselective *o*-C–H functionalization of arenes

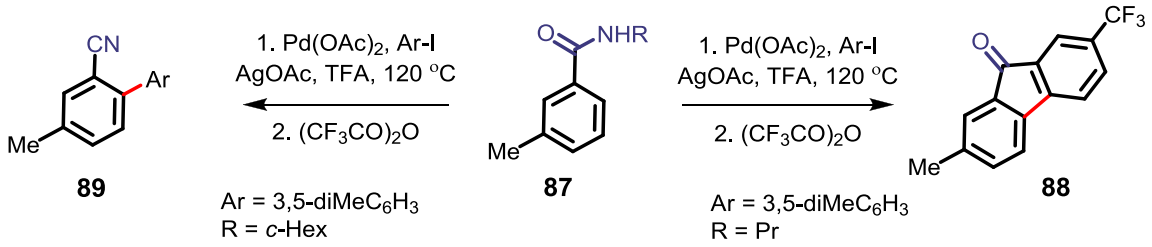
The ligand-directed *ortho*-C–H arylation using aryldiazonium salts **82** under the successful merger of Pd-catalyzed C–H activation and visible-light photoredox catalysis is an interesting result; the reaction proceeds at room-temperature. The *ortho*-C–H fluorination (**79e**),

benzoylation (**79f**), phosphorylation (**79g**), and trifluoro thiomethylation (**79h**) using N-fluoro pyridinium salts (**83**), benzyl alcohol (**84**), α-hydroxyphosphonate (**85**) and/or 1-(trifluoromethylthio)pyrrolidine-2,5-dione (**86**) on 2-phenyl pyridines and benzo[h]quinoline under the influence of palladium catalyst and bases are reported by various research groups (Scheme 1.22). However, the removal of DG from the C–H functionalized products seems to be a difficult task, restricting the broad synthetic applications of these methodologies.

1.3.3.2. Modifiable Directing Groups

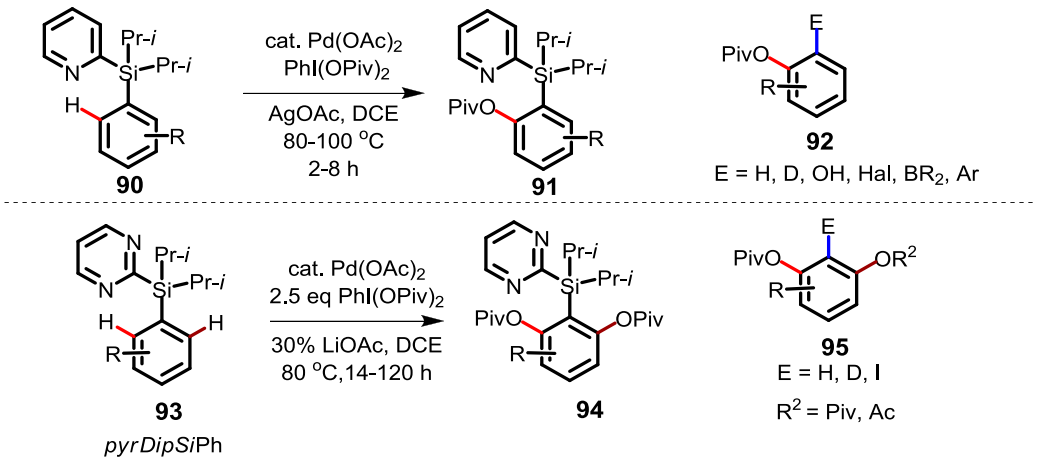
The pre-installed directing groups in the C–H functionalized products can be easily transformable/modifiable to various functional groups.[22]

The synthesis of *ortho*-arylated benzonitriles **89** and fluorenone derivatives **88** from benzamide **87** is an interesting manifestation of the utility of modifiable amide-DG (Scheme 1.23);[23] the *N*-alkyl substituent in amide is responsible for the formation of specific product. For instance, the *ortho*-arylated *N*-cyclohexyl-benzamides with $(CF_3CO)_2O$ delivered the corresponding benzonitrile **89** through dehydration, whereas *o*-arylated *N*-propylbenzamides furnished fluorenone derivatives **88**.



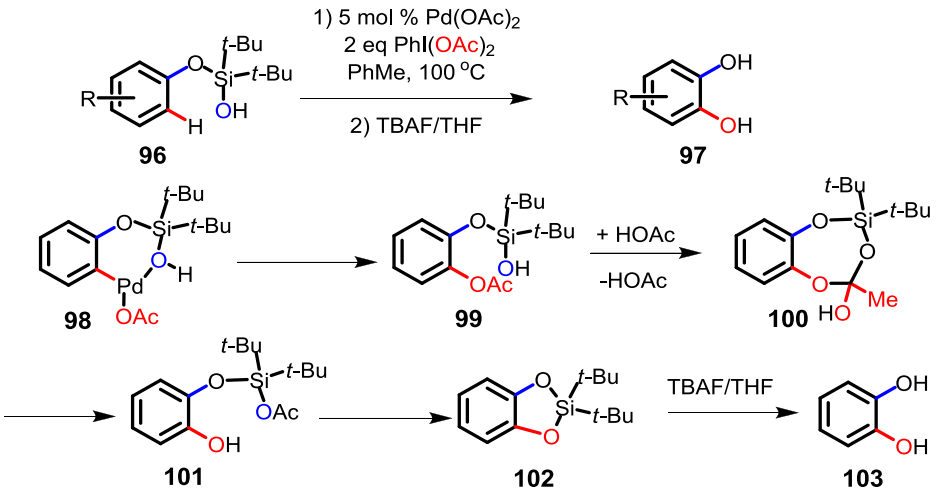
Scheme 1.23: Pd-Catalyzed *o*-C–H arylation of benzamide derivatives

Gevorgyan and co-workers employed a novel easily attachable silicon-tethered pyridyl-containing directing group (PyDipSi) for the regioselective *ortho*-C–H acyloxylation of arenes **90** (Scheme 1.24).[24] The designed directing group can be readily converted to halo, hydroxy, boron bearing derivatives **92**. With the assistance of modifiable PyrDipSi chelating group, double *o*-C–H oxidations occur efficiently in a single step producing resorcinol derivatives **94** and **95**.



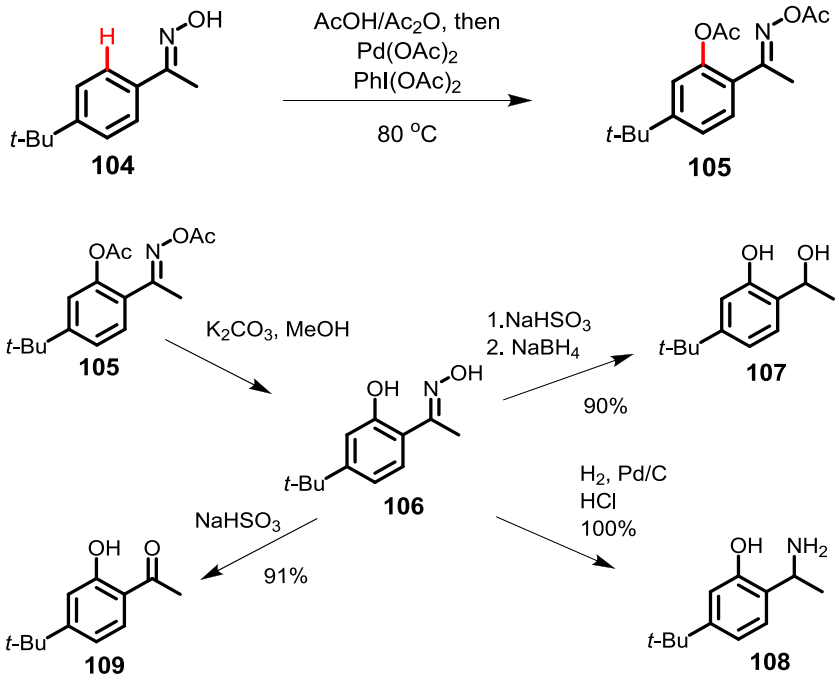
Scheme 1.24: Pd-Catalyzed *o*-C–H oxidation of silicon-tethered arenes

A removable silanol-directed Pd-catalyzed highly regioselective *o*-C–H oxygenation of phenol allows the preparation of catechols **97** (Scheme 1.25).[25] The oxygenation reaction successfully occurs on electron-neutral and electron-poor silanol-bearing phenols **96** in the presence of oxidant. The acid-catalyzed cyclization of **101** forms cyclized silicon-protected catechol intermediate **102**. Finally, TBAF-assisted desilylation of the silacyle **101** furnishes the desired catechol product **103**. On the basis of isotope labeling experiments, the oxygen source comes from $PhI(OAc)_2$ rather than silanol.



Scheme 1.25: Pd-Catalyzed removable silanol-directed *o*-C–H oxygenation of phenols

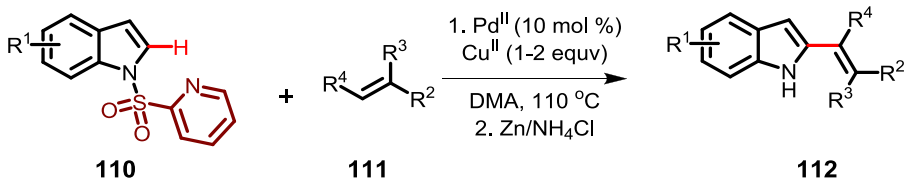
Sanford and coworkers reported the easily modifiable *O*-acetyl oxime directing group assisted acetoxylation of sp^2 C–H bonds. The reaction of compound **104** with $Pd(OAc)_2$ and $PhI(OAc)_2$ in $AcOH/Ac_2O$ gave the desired acetoxylate product **105** in good yield (Scheme 1.26).[26]



Scheme 1.26: Pd-Catalyzed modifiable *o*-acetyl oxime directing group assisted acetoxylation of arenes

The *o*-acetyl oxime products **105** can be easily modified to diverse products. The removal of acetate group furnished oxime **106**, which is readily converted to ketone **109** upon treatment with $NaHSO_3$. Similarly, reduction and hydrogenation of oxime **106** furnished alcohol **107** and amine **108** products.

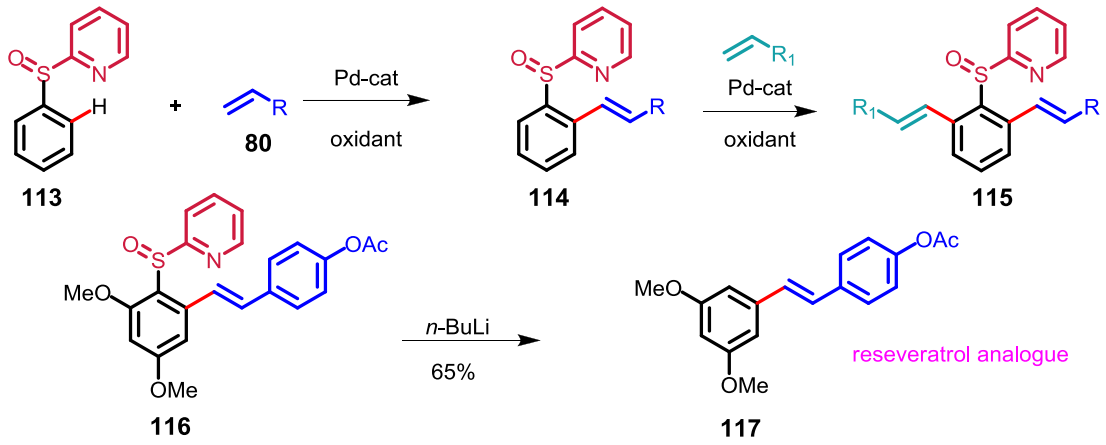
The Pd(II)-catalyzed C2 selective alkenylation of N-(2-pyridyl)sulfonyl protected indole **110** was successfully carried out in the presence of oxidant $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv) in DMA at 110 °C (Scheme 1.27).[27] The C2 selectivity in **112** was controlled by the use of easily removable directing group N-(2-pyridyl)sulfonyl group. The directing group was readily removed from the final product under Zn metal in NH_4Cl. In contrast, the C3 alkenylation on indole exclusively occurred in the absence of pyridine directing group.



Scheme 1.27: Pd-Catalyzed modifiable N-(2-pyridyl)sulfonyl directing group assisted C2 alkenylation of indoles

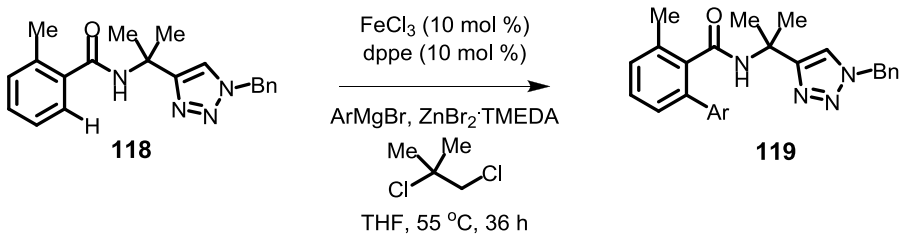
The removable 2-pyridyl sulfinyl directing group also assists the *ortho*-C–H olefination of arenes **113** under the influence of Pd(II)-catalyst with electron-deficient alkenes and styrenes

80 (Scheme 1.28).[28] The directing group efficiently enables sequential double C–H alkenylation to provide di-*ortho*-alkenylated products **115**. Moreover, the 2-pyridylsulfinyl group was readily removed from the C–H olefination products. This method is successfully employed for the synthesis of reseveratrol analogue **117**.



Scheme 1.28: Pd-Catalyzed removable 2-pyridyl sulfinyl directing group assisted alkenylation of arenes

Recently, Ackermann group reported an interesting 1,2,3-triazoles tethered bidentate directing group assisted iron-catalyzed C–H arylations of benzoic acid derivatives **118** (Scheme 1.29).[29] The developed reaction conditions allows C(sp^2)–H arylation of arenes and alkenes, and the rather challenging C(sp^3)–H bonds. The triazole auxiliary is easily removed from arylated product **119**.

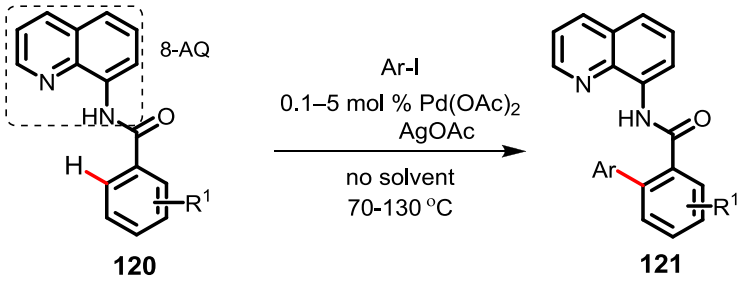


Scheme 1.29: Fe-Catalyzed removable 1,2,3-triazole tethered bidentate directing group enabled arylations of benzoic acid derivatives

1.3.3.3. Reusable Directing Groups

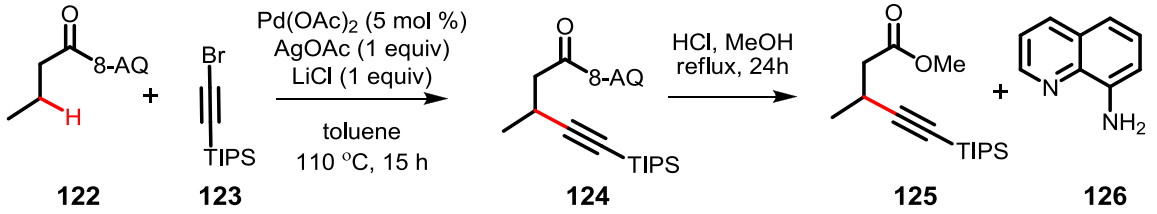
The chelating groups that can easily introduced to the starting materials and readily recovered from the products after C–H bond functionalization are notified as reusable directing groups. The potential utility of some of the notable reusable DG's are briefly discussed.

In 2005, Daugulis group reported Pd-catalyzed 8-amino quinoline (8-AQ) directed *o*-C–H arylation of unactivated C(sp^2)–H bond of arene **120** with aryl iodides (Scheme 1.30).[30] The directing group is also effective for the activation of methylene C(sp^3)–H bonds.



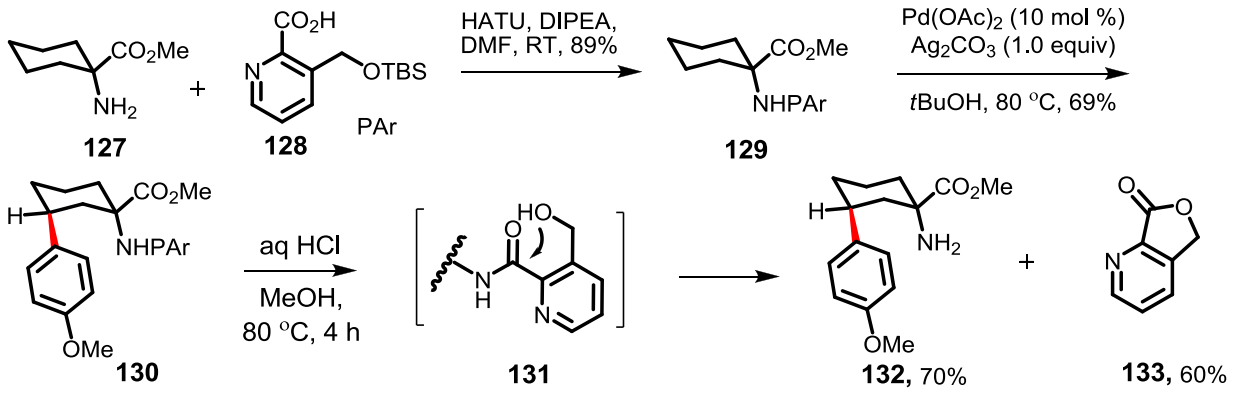
Scheme 1.30: Pd-Catalyzed 8-AQ directed *o*-C–H arylation arenes with aryl iodides

Subsequently, 8-AQ directing group has successfully been employed for C–C and C–hetero atom bond forming reactions. For instance, Chatani group developed Pd-catalyzed direct ethynylation of C(sp^3)–H bonds of aliphatic carboxylic acid derivatives **122** with bromoalkyne **123** (Scheme 1.31).[31] Notably, the directing group was readily removed from the C–H activation products by acid hydrolysis and efficiently recovered in good yields.



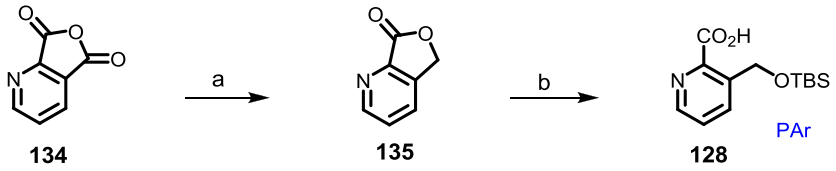
Scheme 1.31: Pd-Catalyzed 8-AQ directed ethynylation of C(sp^3)–H bonds of aliphatic carboxylic acid derivatives

Picolinamide directed remote C(sp^3)–H bond functionalization of **129** was described by Chen group (Scheme 1.32).[32] The coupling between picolinic acid **128** and amine **127** produced **129**. The Pd-catalyzed C–H bond activation and arylation sequence of **129** delivers **130**. Unfortunately, the acid hydrolysis of unsubstituted picolinamide directing group was unsuccessful. Interestingly, introduction of *ortho*-methylene hydroxy group on picolinic acid **131** readily cleaves the amide group through intramolecular acyl transfer (Scheme 1.32).



Scheme 1.32: Pd-Catalyzed picolinamide directed remote C(sp^3)–H bond arylation

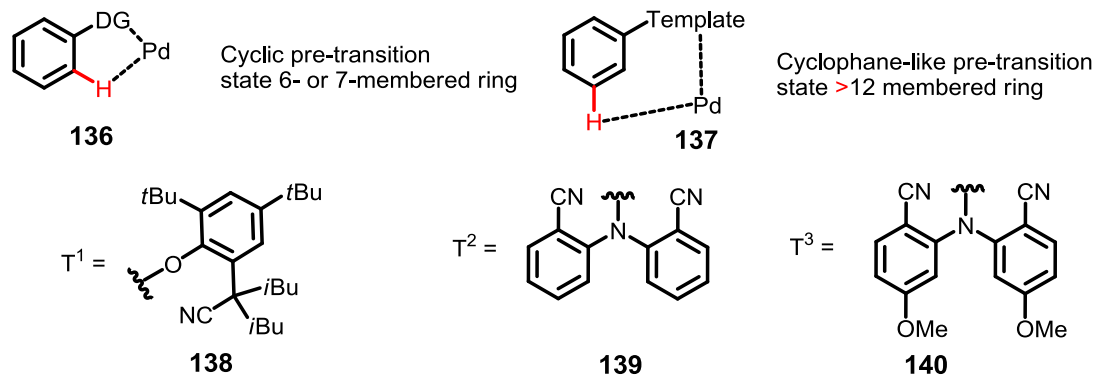
The synthesis of *ortho*-methylene hydroxy group bearing picolinic acid **128** is shown in Scheme 1.33.



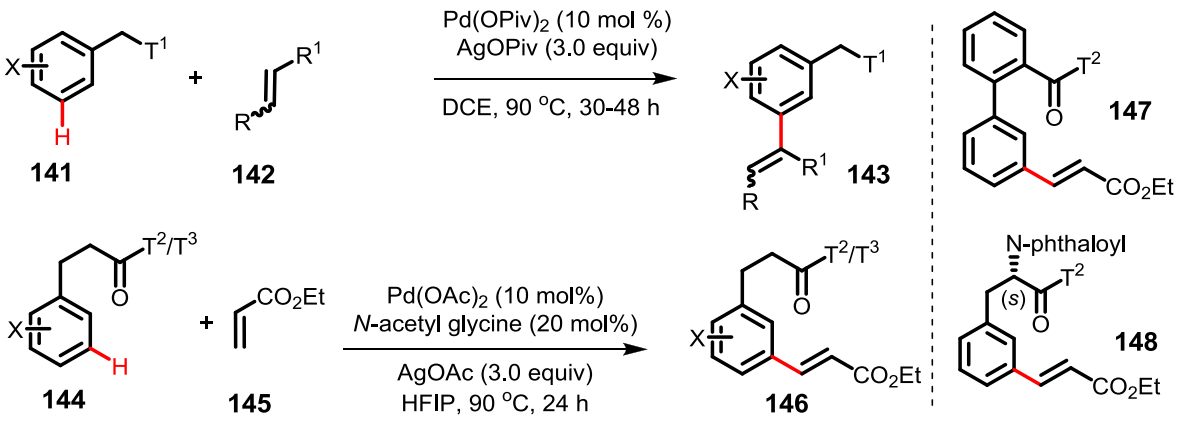
a) 1. MeOH, 90 °C, 84%; 2. CDI, THF, room temperature, then $NaBH_4$ in MeOH/H_2O, room temperature, 65% (2 steps); b) 1. NaOH, THF/H_2O, room temperature; 2. benzyl bromide, DMF, 34% (2 steps); 3. TBDMSCl, imidazole, DMF, room temperature, 92%; 4. Pd/C, H_2, EtOAc, room temperature, quantitative; CDI = 1,1'-carbonyldiimidazole

Scheme 1.33: Preparation of *ortho*-methylene hydroxy group bearing picolinic acid

The Yu group developed end-on nitrile-based DGs **138**, **139**, and **140** to regioselectively activate the distal *meta*-C–H bonds (Scheme 1.34).[33] This is an important achievement as the DGs generally activate the *ortho*-C–H bond in **136** leaving *meta* and *para* unreactive. The newly designed end-on nitrile DG forms 12 membered cyclic transition state with Pd-catalyst through the activation of remote *meta*-C–H bonds **137** (Scheme 1.35). Significantly the present DG overrides the *ortho*-directing effect, electronic and steric bias present on arenes. The new DG and reaction conditions enable synthesis of toluene derivatives **143**, hydrocinnamic acids **146**, 2-biphenylcarboxylic acids **147**, unnatural amino acids **148**, and drug molecules.

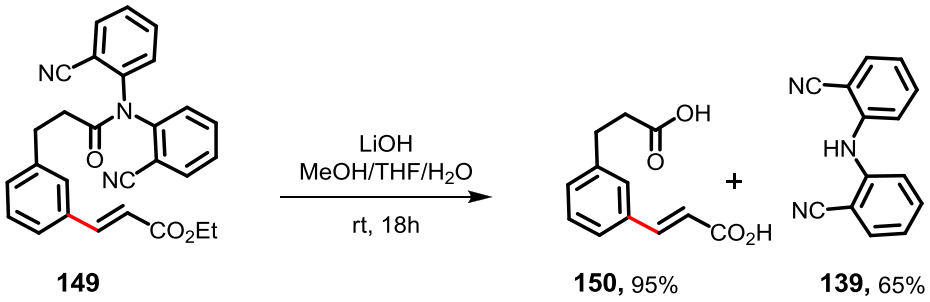


Scheme 1.34: Design of end-on nitrile-based directing groups T^1, T^2 and T^3 for remote *meta* C–H functionalization of arenes



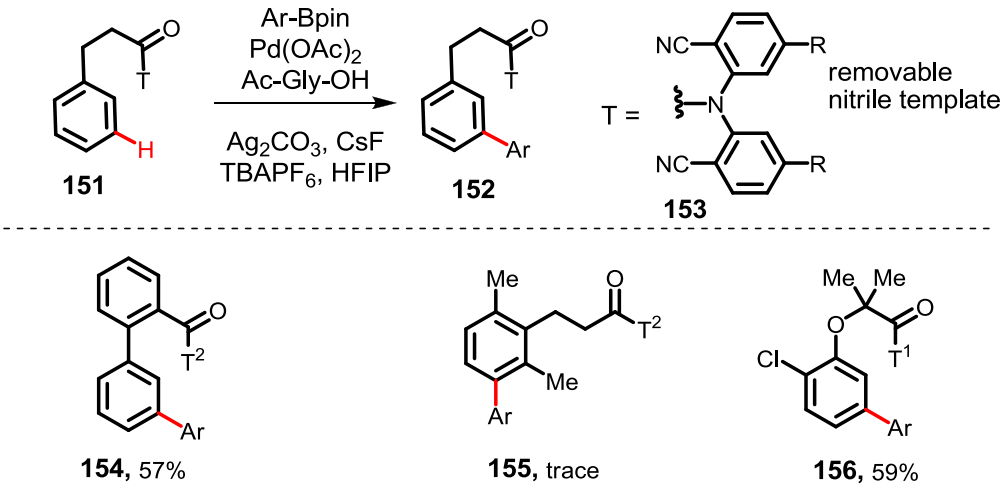
Scheme 1.35: Pd-Catalyzed *meta*-C–H alkenylation of toluene and hydrocinnamic acid derivatives

The LiOH promoted hydrolysis easily knocks out the directing group from the product at room temperature furnishing diacid **150** in 95% yield and recovering the directing group **139** in 65% yield (Scheme 1.36).



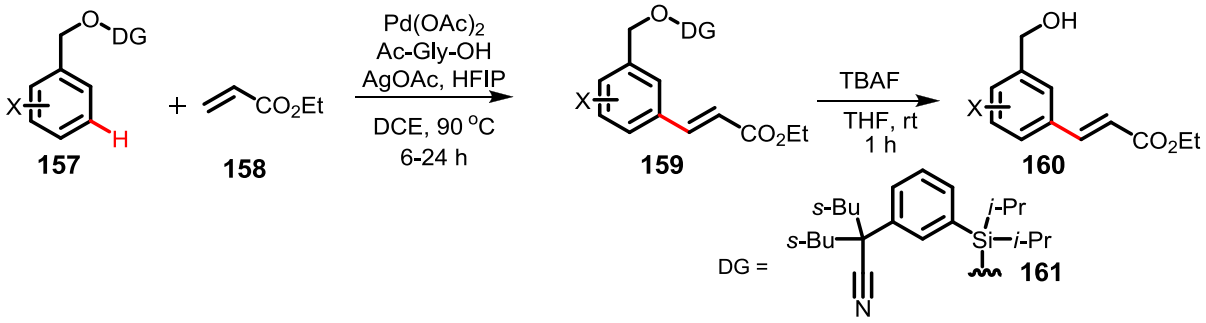
Scheme 1.36: Removal of the directing group

The same authors reported the Pd-catalyzed *meta*-C–H arylation of 3-phenyl propanoic acid **151** and phenol derivatives **156** with organoborons in presence of removable U-shaped template **153** for the first time (Scheme 1.37).[34]



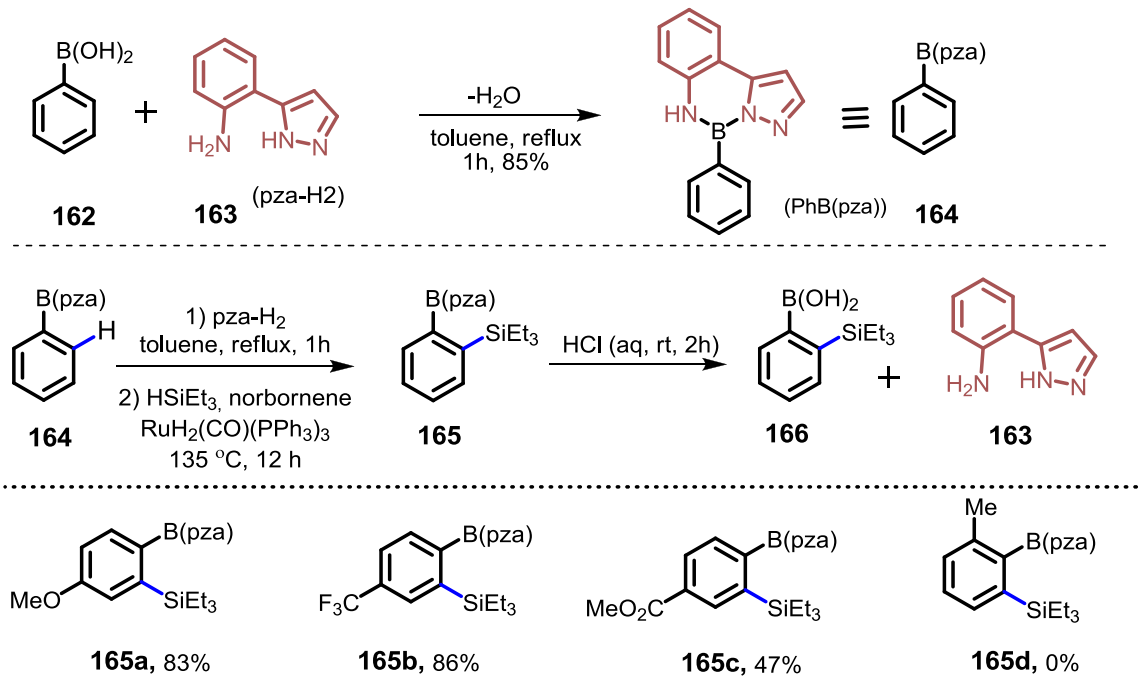
Scheme 1.37: Pd-catalyzed *meta*-C–H arylation of 3-phenyl propanoic acid and phenol derivatives

Tan and coworkers developed Pd-catalyzed silicon tethered nitrile-based template **161** enabled regioselective *meta*-C–H alkenylation of **157** for the synthesis of **159**. Interestingly, the DG is easily attachable to starting precursors and readily cleaved from products (Scheme 1.38). [35]



Scheme 1.38: Pd-Catalyzed *meta*-C–H alkenylation of benzyl alcohol derivatives

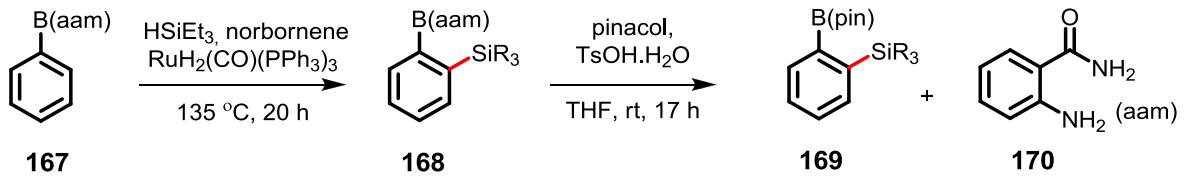
Suginome and coworkers developed an easily attachable and removable 2-pyrazol-5-ylaniline (pza, **163**) and anthranilamide (AAM, **170**) groups for *ortho*-C–H silylation of readily available arylboronic acids **162** (Scheme 1.39 and 1.40).[36] The boronic acids are readily protected with pza group under the reflux conditions in toluene to produce ArB(pza) **164**. The compounds **164** effectively participated in *o*-C–H silylation under the influence of Ru-catalyst with silylhydrides as coupling partners to produce *o*-silylated ArB(pza) derivatives **165**. Interestingly, the protection of arylboronic acids and subsequent *o*-silylation were performed in one-pot.



Scheme 1.39: Ru-Catalyzed pyrazolyl aniline directing group *o*-silylation of arylboronic acids

The *ortho*-C–H silylation is successfully occurred on electron-donating and withdrawing substituted pza protected arylboronic acid derivatives. Notably, the reaction condition is very selective to mono silylation; the reaction did not provide the double silylation product. In contrast, the *ortho*-tolyl boronic acid didn't participate in silylation. Gratifyingly, the acid hydrolysis removes pza DG and provides the corresponding *o*-silylated boronic acid derivatives **166**.

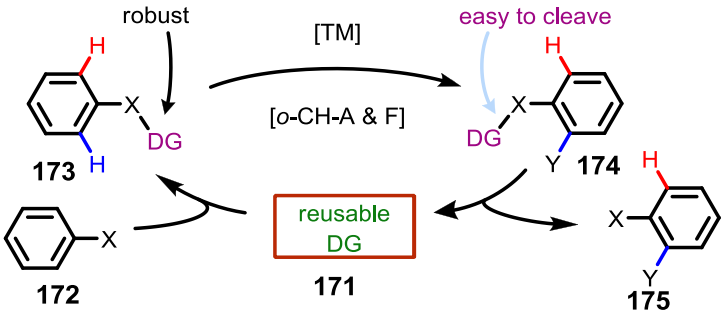
The same authors reported a novel and efficient *o*-C-H silylation of anthranilamide (AAM, **170**) auxillary bearing arylboronic acid derivatives **167** (Scheme 1.40). The AAM auxillary exhibited high reactivity for the activation of *o*-C–H bond over the previously employed pza directing group. The acid hydrolysis of **168** readily delivers **169** and recovering the anthranilamide DG **170** (Scheme 1.40).



Scheme 1.40: Ru-Catalyzed anthranilamide directing group *o*-silylation of arylboronic acids

1.4. Motivation and Design Plan

The DG strategy has successfully been employed to the regioselective functionalization of inactive C–H bonds. However, the removal of DG from the C–H functionalization product is challenging and therefore restricts the broad synthetic application of this methodology. The extensive survey of literature on directing group assisted C–H functionalization revealed that most of the synthetic methods employed non-modifiable/modifiable directing groups. The identical reactions using the reusable directing groups are limited. Therefore, developments of novel easily accessible and reusable DGs, which can readily be attachable to the molecule and easily removable from the products and finally recoverable, for C–H functionalizations is always demanding. Moreover, a reusable DG should be easily attachable to substrate and allows providing high level of regioselective products, and also readily cleaved from the product; over all this process makes the reusability of the DG (Scheme 1.41).



Scheme 1.41: Concept of reusable directing group for C–H activation

This thesis aims in the development of new reusable directing groups for transition-metal catalyzed chemo and regioselective C(sp^2)–H bond functionalization of arenes. A new directing group methyl phenyl sulfoximine (MPS) is developed and employed for the *ortho*-C–O, C–N and C–C bond formation of arenes. Notably, the MPS group is easily cleaved from the products and recovered.

1.5. References

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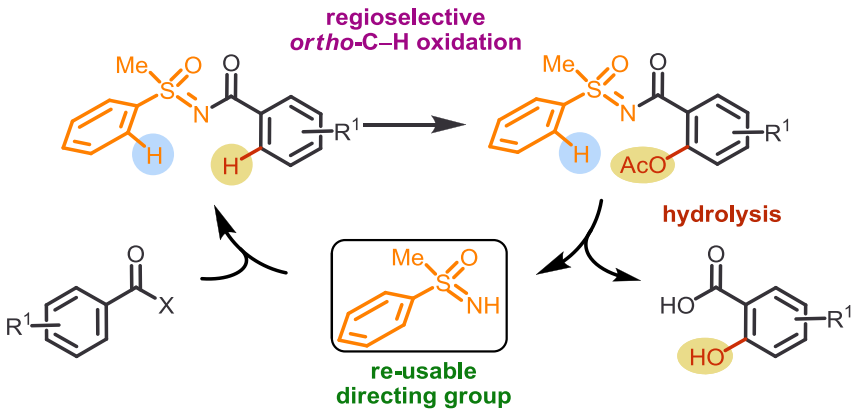
Sulfoximine: A Reusable Directing Group for Chemo- and Regioselective *ortho*-C–H Oxidation of Arenes

2 Chapter

Abstract



A new protocol for chemo and regioselective *ortho*-C–H acetoxylation of arenes in *N*-aroylated sulfoximine is reported. The sulfoximine directing group is easily detached from the C–H oxidation product through acid promoted hydrolysis, isolated and re-used. *meta*-Substituted phenols are synthesized following this strategy. Stereointegrity of the sulfoximine is preserved in this transformation.

Reference:

M. Ramu Yadav, Raja K. Rit, and Akhila K. Sahoo, *Chem. Eur. J.* **2012**, *18*, 5541–5545.

2.1. Introduction

The transition metal catalyzed synthesis of sp^2 C–O bond in arenes is of great interest in organic chemistry, as these motifs are widely present in phenols, catechols and salicylic acids. Importantly, these molecules play an important role in biology, pharmaceutical and material chemistry (Fig. 2.1).[1] As a result, development of simple and convenient methods for the construction of C–O units are highly desirable.

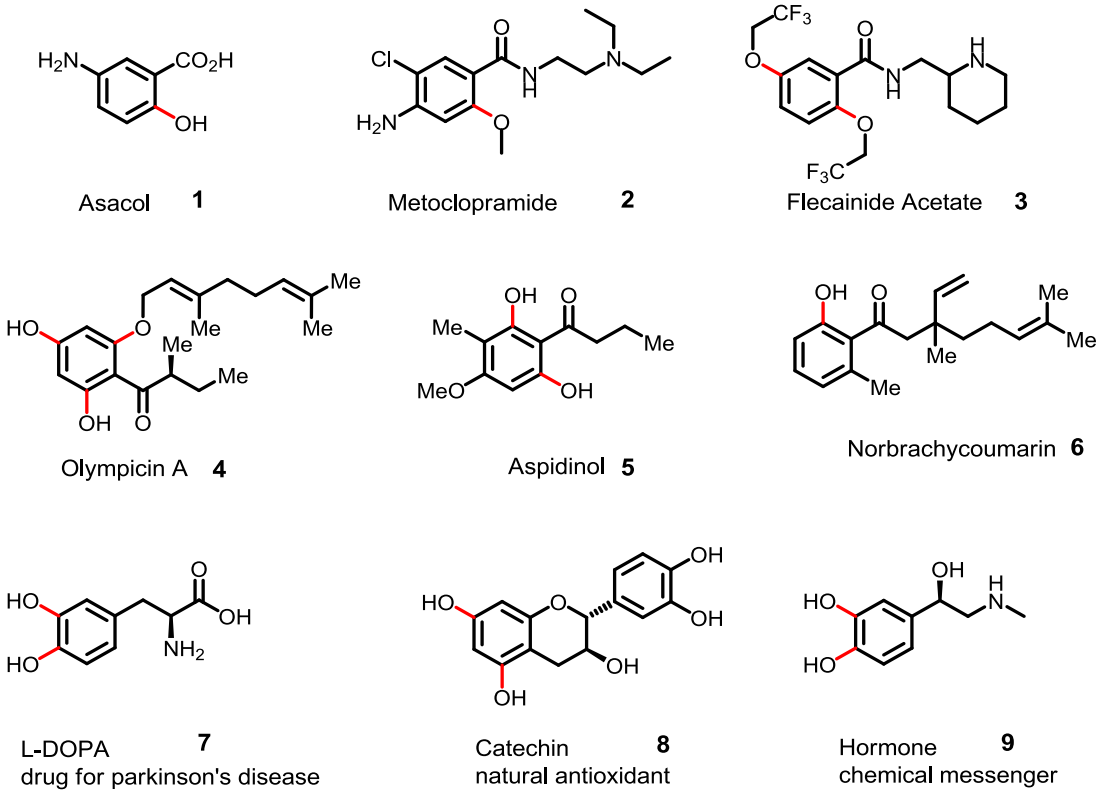


Figure 2.1: Biologically active molecules containing C–O motif.

Owing to the importance of C–O bond, many protocols have been reported towards the direct formation of phenols from arenes. The conventional cross-coupling methods generally require pre-functionalized starting materials and specially designed ligands; in addition, this strategy produces environmentally hazardous byproducts (discussed in Chapter 1).[2] Therefore, development of novel synthetically viable and environmentally benign methods for the functionalization of un-activated C–H bonds to C–O bonds is always demanding. Directing group assisted transition-metal-catalyzed C–H oxidation of arenes is recognized as an elegant and versatile approach for the direct synthesis of phenol derivatives.[3,4] Interestingly, the

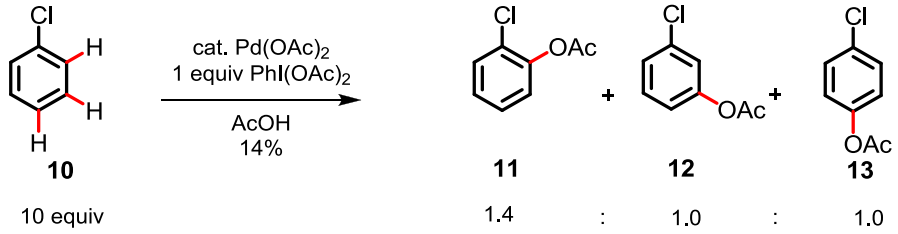
coordination of directing group (DG) to the transition-metal, triggers the activation of the proximal C–H bond and facilitates the formation of product with better regioselectivity.[5]

2.1.1. Precedents and Strategies for C(sp^2)–O Bond Formation of Arene through C–H Activation

The C–H oxidation of arenes was initially studied by Crabtree et al. [3b] under the influence of stoichiometric as well as catalytic amount of $Pd(OAc)_2$. Later, Sanford[6] and Yu[7] groups have independently explored the issues of regioselectivity and the mechanism involved in the DG assisted C–H oxidation of arenes. However, over the last decade a variety of DG's have been developed and successfully deployed investigating *ortho*-C–H oxidation of arenes.

2.1.2. Palladium-Catalyzed sp^2 C–H Oxidation of Arenes

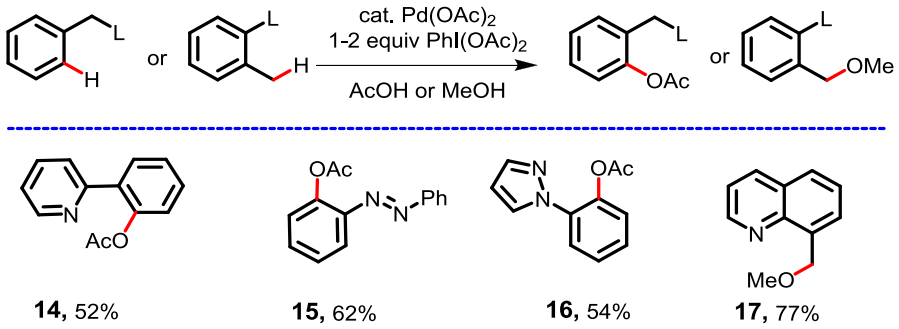
Crabtree group reported an important protocol for direct transformation of arene C–H to C–OAc bond in the presence of Pd(II)-catalyst and $PhI(OAc)_2$ oxidant in AcOH solvent.[3b] For instance, C–H bond functionalization of chlorobenzene **10** gave regioisomeric mixture of *ortho* **11**, *meta* **12** and *para* **13** C-acetoxylation products in overall low yield. The $PhI(OAc)_2$ oxidizes carbon-palladium bond resulting from C–H functionalization of arenes and also acts as the source acetate to give desired acetoxylation product. However, the requirement of large amount of starting material, lack of broad substrate scope and formation of regioisomeric mixture of products are the major drawbacks (Scheme 2.1).



Scheme 2.1: Pd-Catalyzed sp^2 C–H acetoxylation of arenes

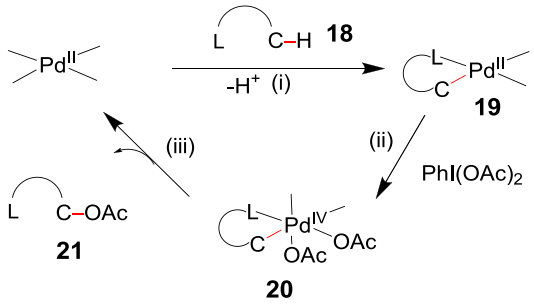
In 2004, Sanford and co-workers made an important discovery on Pd(II)-catalyzed ligand directed acetoxylation of arene C–H bonds (Scheme 2.2).[6a] The presence of N-bearing directing groups in the substrates allowed the regioselective C–H oxidation of arenes. A variety of directing groups, such as pyridyl **14**, azo **15**, pyrazole **16**, etc have successfully been employed; the reaction is general and broad providing ready access of phenol

derivatives. In similar way benzylic sp^3 C–H bond etherification **17** was achieved with methanol in the presence of $PhI(OAc)_2$ oxidant.



Scheme 2.2: Pd-Catalyzed chelation assisted sp^2 and sp^3 C–H acetoxylation of arenes

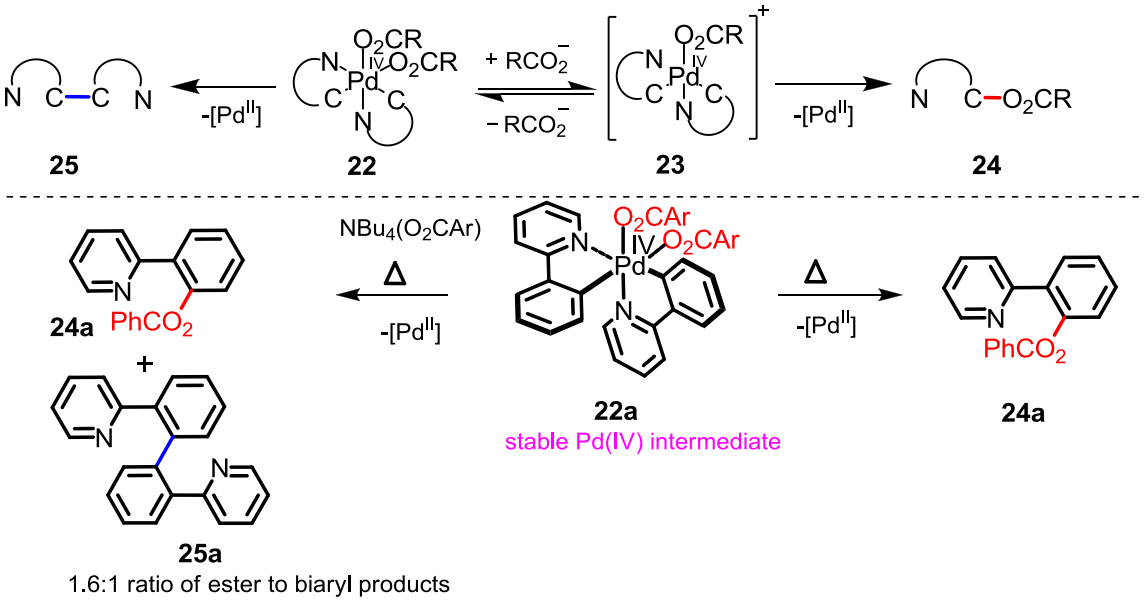
A plausible general reaction mechanism for the ligand directed C–H acetoxylation is shown in Scheme 2.3. [6a] At first co-ordination of hetero atom bearing directing group in **18** to transition metal, for example Pd(II)-center, assists activating the proximal C–H bond and forms the cyclopalladated complex **19** (step i). Oxidation of complex **19** to Pd(IV) intermediate **20** occurs in the presence of oxidant $PhI(OAc)_2$ (step ii). Finally, reductive elimination of **20** produces the desired acetoxylation product **21**, regenerating the active catalyst for next cycle.



Scheme 2.3: Plausible mechanism for Pd-catalyzed sp^2 C–H acetoxylation of arenes

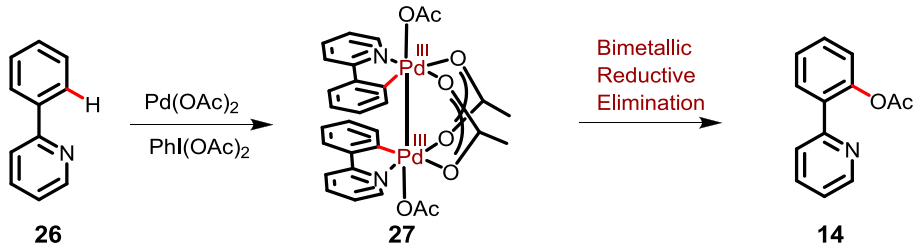
Later, Sanford [6f-g] and Ritter[8] group independently studied the complete mechanistic details of acetoxylation of arene C–H bond. Sanford and co-workers prepared a series of Pd(IV) complexes of general structure $(N\sim C)_2Pd^{IV}(O_2CR)_2$ **22** (N~C = a rigid cyclometalated ligand; O_2CR = carboxylate) from $(N\sim C)_2Pd^{II}$ **19** (Scheme 2.4). Oxidation of **19** with $PhI(O_2CR)_2$ led to **22**. The kinetic experiments revealed that the reductive elimination step proceeds through a 5-coordinate cationic Pd(IV) intermediate **23** to deliver C–O bond formation **24**, While the

competing C−C bond-forming product **25** obtained via the reductive elimination from the octahedral Pd(IV) center **22**.



Scheme 2.4: The reductive elimination study of Pd(IV) complexes

Ritter and coworkers isolated bimetallic Pd(III) complex **27** for the first time, upon reaction of 2-phenyl pyridine with $Pd(OAc)_2$ and $PhI(OAc)_2$ oxidant (Scheme 2.5).[9] Accordingly, authors proposed the participation of bimetallic Pd(III) complexes for the C(sp^2)–H oxidation, although the involvement of proposed Pd(II)/Pd(IV) species in the redox cycles cannot completely be ruled out.

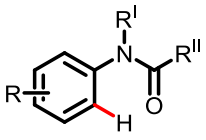
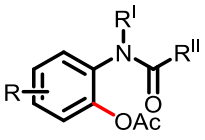
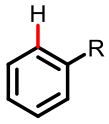
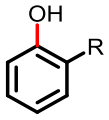
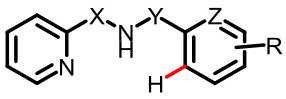
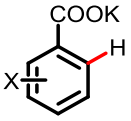
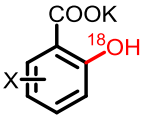
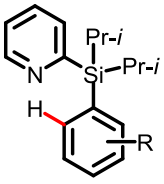
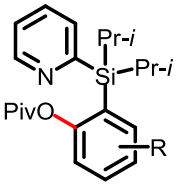


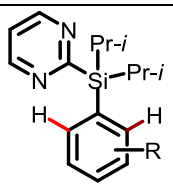
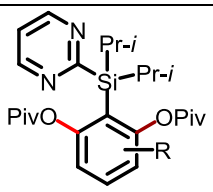
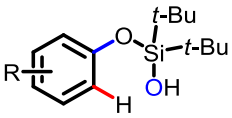
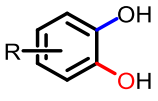
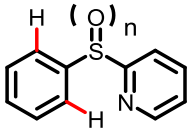
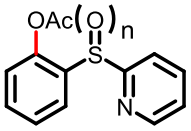
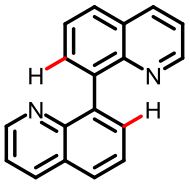
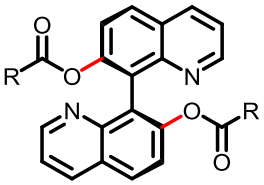
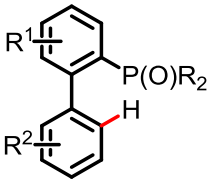
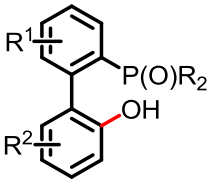
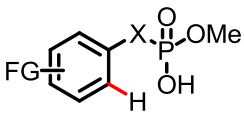
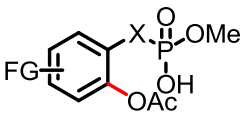
Scheme 2.5: Pd(II)-catalyzed acetoxylation of arenes through bimetallic Pd(III) intermediate

The successful demonstration of transition-meal-catalyzed directing group assisted C–H oxidation of arenes with different oxidants inspired the researcher examining the effect of various easily accessible directing groups for the C(sp^2)–H oxidations, some of the notable strategies are sketched herewith. The known methods for the Pd-catalyzed oxidation of C(sp^2)–H bonds are summarized briefly in Table 2.1. A general and efficient Pd(II) catalyzed regioselective introduction of oxygen atom on *ortho*-C–H bond of arenes, aryl ketones,

benzoates, benzamides, acetanilides, and sulfonamides in the presence of oxidants and acid solvent is reported (entries 1 and 2, Table 2.1). Liang et al. employed N,N-bidentate directing groups **32** i.e. picolinamide and 8-aminoquinoline for the *ortho*-C–H acetoxylation reaction (entry 3). A direct and elegant approach to the *ortho*-hydroxylation of benzoic acid **34** in the presence of O_2 has been demonstrated by Yu (entry 4).

Table 2.1: Chelation assisted Pd(II)-catalyzed acetoxylation of arenes

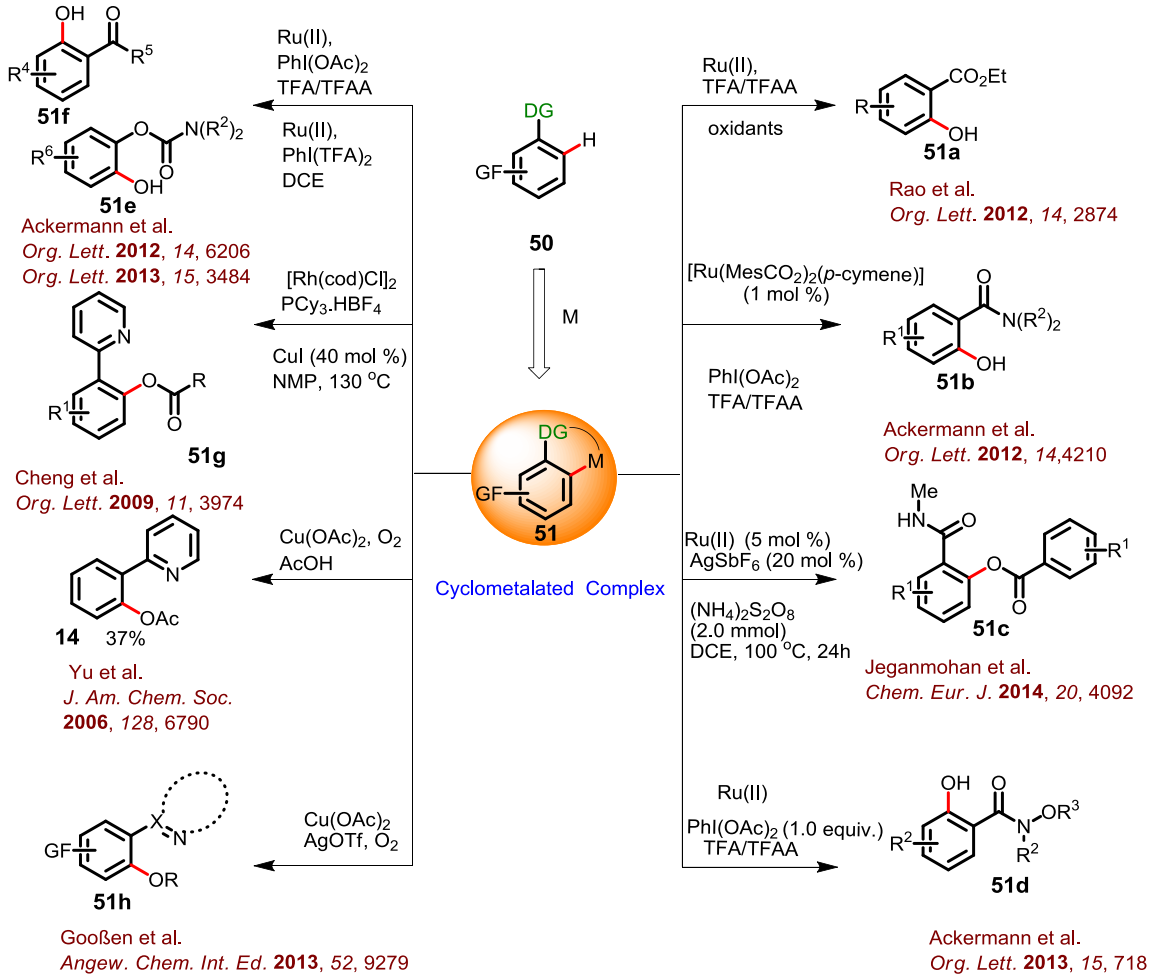
entry	Substrate	Product	Condition
1	 **28**	 **29**	$Pd(OAc)_2$ (5 mol %) $K_2S_2O_8$ (2 equiv) AcOH/DCE (1:1) 100 °C, 48 h Wang et al. *J. Org. Chem.* **2008**, *73*, 4717
2	 **30** R = COR^1, CO_2Et, CH_2CO_2Et, $CONHR^2$, $NHCOR^3$, SO_2NHR^4	 **31**	5 mol % Pd(OAc)$_2$ TFA/TFAA oxidants, 50-100 °C or rt Rao et al. *Angew. Chem. Int. Ed.* **2012**, *51*, 13070
3	 **32** X = CO, aromatic tether Y = CH_2, CO Z = CH, N	**33**	$Pd(OAc)_2$ $PhI(OAc)_2$, toluene $HOAc/Ac_2O$, 150 °C Liang et al. *Org. Lett.* **2009**, *11*, 5726
4	 **34**	 **35**	cat $Pd(OAc)_2$ 1 atm $^{18}O_2$ DMA, 15 h, 115 °C Yu et al. *J. Am. Chem. Soc.* **2009**, *131*, 14654
5	 **36**	 **37**	cat. $Pd(OAc)_2$ $PhI(OPiv)_2$ AgOAc, DCE 80-100 °C 2-8 h Gevorgyan et al. *J. Am. Chem. Soc.* **2010**, *132*, 8270

6	 **38**	 **39**	cat. $Pd(OAc)_2$ 2.5 eq.$PhI(OPiv)_2$ 30% LiOAc, DCE 80 °C,14-120 h Gevorgyan et al. *J. Am. Chem. Soc.* **2012**, 134, 5528
7	 **40**	 **41**	1) 5 mol % $Pd(OAc)_2$ 2 eq. $PhI(OAc)_2$ PhMe, 100 °C 2) TBAF/THF Gevorgyan et al. *J. Am. Chem. Soc.* **2011**, *133*, 17630
8	 **42**	 **43**	$Pd(OAc)_2$ (5-10 mol %) $K_2S_2O_8$ (1.2-4 equiv) DCE/AcOH, 80 °C Mancheño et al. *Adv. Synth. Catal.* **2011**, *353*, 295
9	 **44** tropos (achiral)	 (±)-atropos (chiral) **45**	cat. $Pd(OAc)_2$ $PhI(OAc)_2$ RCO_2H-$CHCl_3$ Blakemore et al. *Org. Lett.* **2011**, *13*, 4024
10	 **46**	 **47**	$Pd(TFA)_2$ (5 mol %) $PhI(OTFA)_2$ (1.5 equiv) CH_3NO_2, 60 °C, air Yang et al. *Org. Lett.* **2013**, *15*, 6186
11	 **48** X = CH_2, O	 **49** X = CH_2, O	$Pd(OAc)_2$ $PhI(OAc)_2$ Kim et al. *J. Org. Chem.* **2013**, *78*, 8826

Gevorgyan and co-workers employed easily attachable and readily removable silicon-tethered pyridyl-containing directing groups 2-pyridine diisopropylsilyl (PyDipSi), 2-pyrimidyl diisopropylsilyl (PyrDipSi) attached arenes **36** & **38** for the regioselective C−H acyloxylation of arenes under the influence of Pd(II)-catalysts (entries 5 and 6). The silyl

tethered directing groups are readily converted to other valuable functional groups e.g., halogen, hydroxyl, boronate etc. The same group developed a silanol directing group assisted regioselective Pd-catalyzed *ortho*-C−H acyloxylation, accomplishing the synthesis of catechol derivatives **41** easily (entry 7). Mancheño and coworkers reported a new class of modifiable sulfur tether directing group **42** for Pd(II)-catalyzed acetoxylation of aromatic C–H bonds (entry 8). Blakemore and co-workers demonstrated an efficient and shortest route for the synthesis of 7,7′-dihydroxy-8,8′-biquinolyl (azaBINOL) in high yield from 2-chloroaniline in four steps (entry 9). Furthermore, the phosphine oxide and phosphoric monoacids worked as effective directing groups for C(aryl)–H acetoxylation reaction (entries 10 and 11).

2.1.3. Ru(II), Rh(III) and Cu(II)-Catalyzed sp² C–H Oxidation of Arenes:

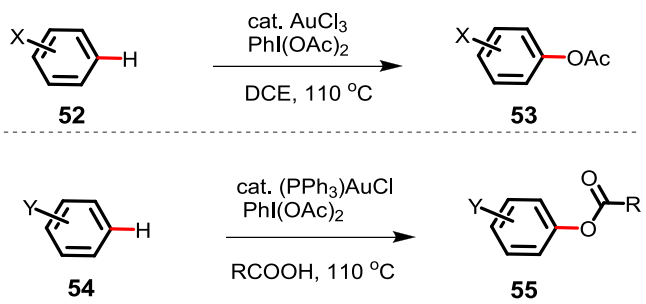


Scheme 2.6: *Ortho* C–H acetoxylation and hydroxylation of arene derivatives.

In 2012, Rao and coworkers revealed the Ru(II) catalyzed, weakly coordinating ester directing group **50a** assisted *ortho*-hydroxylation of ethyl benzoates to produce **51a**. The

TFA/TFAA solvent system and potassium persulfate, selectfluor, or iodic acid oxidants plays vital role in achieving these transformations. Subsequently, Ackermann and coworkers developed ruthenium catalyzed *ortho*-C–H oxidation of arenes bearing weakly coordinating amides **50b**, aryl weinreb amides **50d** and aromatic ketones **50f** in the presence of $PhI(OAc)_2$ oxidant. Similarly, a mild ruthenium catalyzed oxygenation conditions have been developed for aryl carbamates **50e** by the same group. Notably, under similar catalytic conditions anisole gave *para*-selective hydroxylation without any Lewis basic directing group. The Jeganmohan group demonstrated *ortho*-benzoxylation of *N*-alkyl benzamides **50c** with benzoic acid derivatives in the presence of $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$, and $(NH_4)_2S_2O_8$ in 1,2-dichloroethane at 100 °C *via* C–H bond activation. Rhodium-catalyzed *ortho*-benzoxylation of sp^2 C−H bond of carboxylic acids is described by Cheng group. The developed conditions tolerate carbomethoxy, formyl, bromo, chloro, and nitro groups, and provide the benzoxylated products **51g** in moderate to good yields. Importantly, no external oxidant is required for this transformation. In 2006, Yu and co-workers reported copper catalyzed regioselective hydroxylation, acetoxylation and phenoxylation of arene C–H bonds in presence of molecular oxygen. A co-operative bimetallic copper/silver catalyst system for the oxidative dehydrogenative cross-coupling of arene derivatives with directing groups and alcohols was developed by Gooßen and co-workers; this strategy allows the synthesis of aryl and benzyl ethers **51h**.

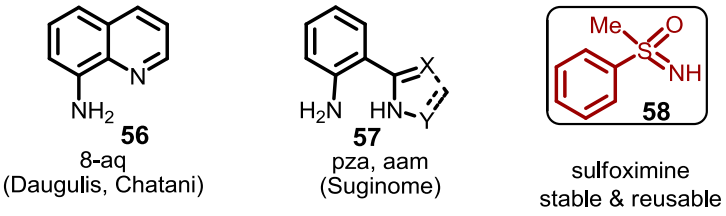
Wang et al. disclosed an efficient direct Au(III)-catalyzed acetoxylation of arenes **52** with iodobenzene diacetate in DCE at 110 °C; this method did not require any chelating group.[10] However, this catalytic system works fine mostly to electron-rich aromatic arenes. A seminal work reported by Michelet reveals that non-activated hindered aromatic rings **54** are efficiently acyloxylated in the presence of Ph_3PAuCl catalyst and $PhI(OAc)_2$ oxidant.[11] The carboxy moieties are especially inserted when reacted with carboxylic acids (Scheme 2.7).



Scheme 2.7: Au(I) and Au(III)-catalyzed acyloxylation of arenes

2.2. Motivation and Design Plan

In spite of these significant advances, the use of non-removable DG's limits the broad synthetic application of this transformation. Recently, the easily modifiable DG's, sulfur[11] and Si[12] tethered pyridyl derivatives have been deployed for the efficient C–H oxidation of arenes. In addition, highly chemoselective C–H functionalization in the presence of variety of C–H bonds remains challenging.[13] We therefore presume that the incorporation of easily removable robust DG's can overcome some of these limitations. So far, the attachable and detachable directing groups, 8-aminoquinoline[14a-b] **56**, pza[14c] and aam[14d] **57** have been used in the C–H functionalization of arenes (Scheme 2.8).



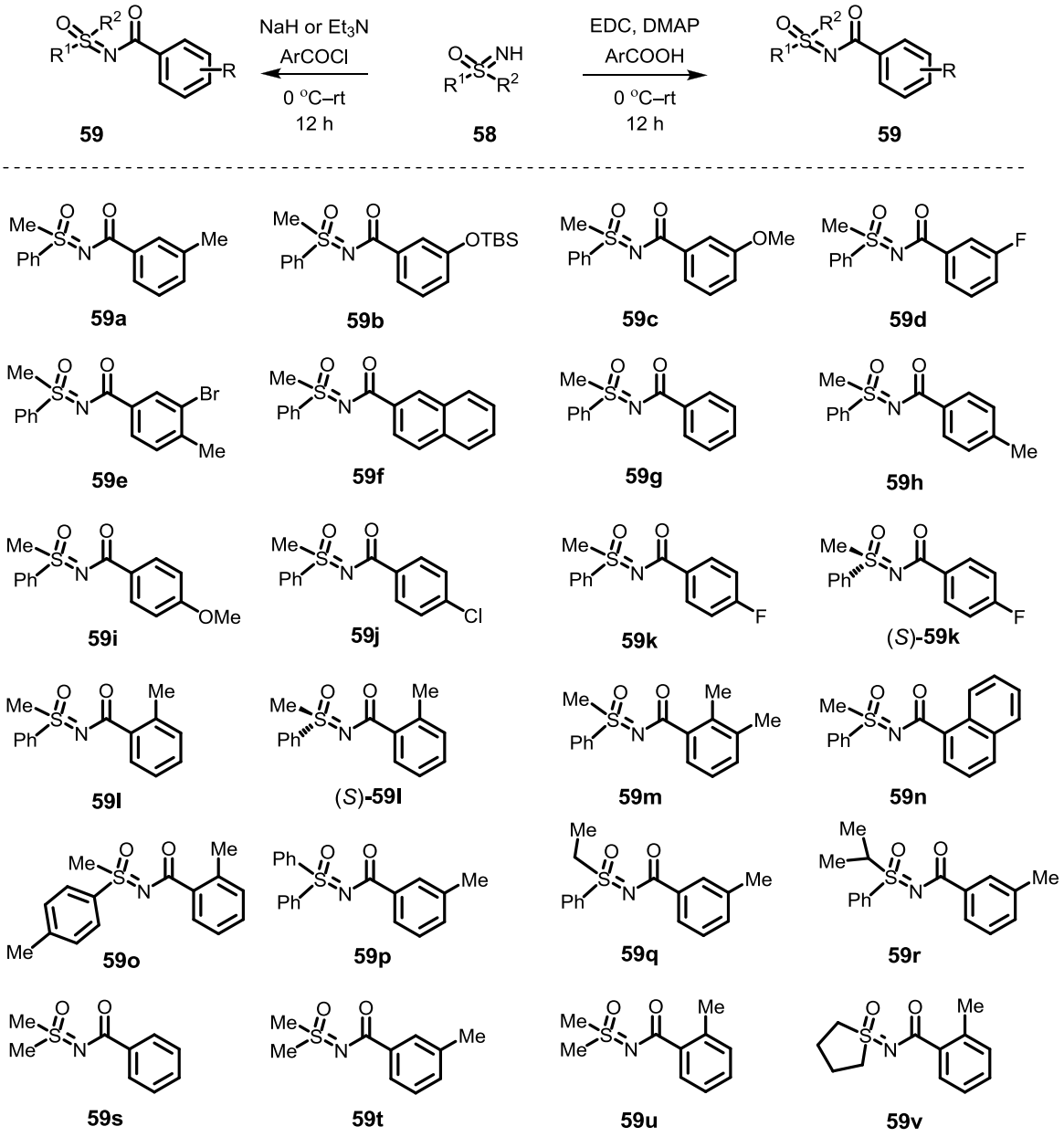
Scheme 2.8: Reusable directing groups in *ortho*-C–H functionalization

Inspired by the previous results and the concerns pertaining to this transformation, we envisioned the use of sulfoximine[15] **58** as an easily attachable and detachable DG for the C–H functionalizations. The initial results on the chemo- and regioselective *ortho*-C–H acetoxylation of *N*-aroyl methyl phenyl sulfoximine is discussed herewith; the directing group is easily detached from the C–H oxidation product and reused.

2.3. Results and Discussion

2.3.1. Synthesis of Precursors

Following the known procedures, various *N*-aroyl derivatives of sulfoximines were prepared (Scheme 2.9). The reaction of sulfoximines with sodium hydride or triethylamine base in DCM solvent at 0 °C followed by quenching the reaction with corresponding aroyl chlorides gave a wide range of the *N*-protected sufoximines in above 80% yields. The EDC.HCl coupling protocol was employed for coupling of benzoic acid derivatives (the procedure is detailed in the experimental section).



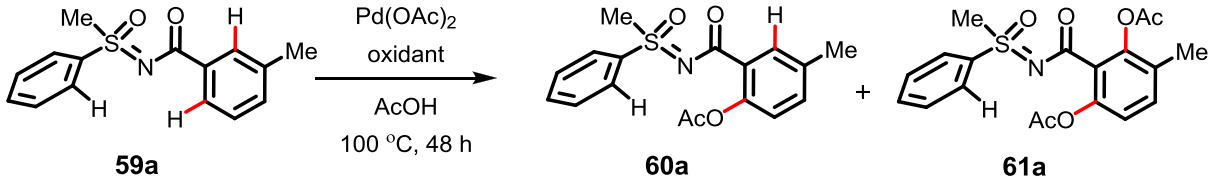
Scheme 2.9: Preparation of *N*-aroyl sulfoximines

2.3.2. Reaction Optimization

To test the hypothesis, compound **59a** was subjected to the known reaction conditions [$Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$, in AcOH] at 100 °C for 48 h (entry 1, Table 2.2.1).[6a] Interestingly, formation of *ortho*-acetoxylation products **60a** and **61a** along with a small amount of mono-deacylated compound was observed in 57% yield by NMR (Table 2.2.1). It is highly intriguing that the *ortho*-C–H bonds of the *N*-aroylated aryl ring has been exclusively functionalized among two different arenes of **59a**. Even though *ortho*-hydrogens of both the aromatic rings are present at the same proximity to the metal-coordinating nitrogen atom, the factors responsible to this chemoselective sp^2 C–H oxidation are unclear.

The acidic sp^3 S-methyl hydrogen did not participate to the oxidation reaction. No trace of the mono-acetoxylation product from selective replacement of more-hindered *o*-C–H bond was detected in crude NMR. These results clearly demonstrate the chemo- as well as regioselective C–H oxidation of arenes. Further screening of various oxidants (entries 2–11), $K_2S_2O_8$ was turned out to be superior (entry 3) forming the analogues phenol as major product; whereas benzoquinone, $Cu(OAc)_2$, and H_2O_2 were completely ineffective (entries 4, 5, 7). To reduce the formation of deacylated product in entry 3, Table 2.2.1, various combinations of solvents (entries 2-14, Table 2.2.2) with AcOH were tested. Chlorinated solvents appeared effective (entries 2–4); chloroform was found to be the best (entry 3). Among the amounts of solvent screened, AcOH:$CHCl_3$ (2:3, 1.5 mL) for 0.2 mmol of substrate resulted optimum. Other Pd-catalysts were found to be similarly efficient except $PdCl_2(CH_3CN)_2$ (entries 1–4, Table 2.2.3). No product was detected in the absence of either Pd-catalysts or oxidant. Gratifyingly, presence of air/moisture did not affect the reaction efficiency.

Table 2.2: Optimization of reaction conditions



59a **60a** **61a**

Table 2.2.1: Oxidant screening [a]

entry	oxidant (2.0 equiv)	yield (%)[b] **(60a : 61a)**	entry	oxidant (2.0 equiv.)	yield (%)[b] **(60a : 61a)**
1	$PhI(OAc)_2$	57 (10:1:3[c])	7	30% H_2O_2	NR
2	Oxone	19 (**60a**)	8	NaOAc	NR
3	$K_2S_2O_8$	70 (1:1:8[c])	9	$Na_2S_2O_8$	Complex mixture
4	BQ	NR	10	Lauroyl peroxide	NR
5	$Cu(OAc)_2$	NR	11	Dicumyl peroxide	NR
6	TBHP	NR			

[a]Reaction conditions: **59a** (50 mg, 0.183 mmol), $Pd(OAc)_2$ (10 mol %), and oxidant (2.0 equiv) in acetic acid (1.0 mL) at 100 °C for 48 h. [b]Conversion based on crude ^{1}H NMR. [c]Formation of mono-deacylated product. NR = no reaction.

Table 2.2.2: Solvent screening[a]

entry	AcOH : solvent (1.0 mL)	yield (%)[b] **(60a : 61a)**	entry	AcOH : solvent (1.0 mL)	yield (%)[b] **(60a : 61a)**
1	-	70 (1:1:8[c])	8	Toluene	78 (20:1:4[c])
2	CH_2Cl_2	83 (3:1:10[c])	9	Acetone	15
3	$CHCl_3$	95 (14:1:1[c])	10	EtOH	36 (0:1:19[c])
4	DCE	90 (13:1:1[c])	11	EtOAc	86 (8:1:3[c])
5	DMF	18	12	Ac_2O	57 (18:1:2[c])
6	DMSO	NR	13	PivOH/ CH_2Cl_2	80 (23:1:9[c])
7	DME	89 (3:1:2[c])	14	PivOH	39 (15:1:10[c])

[a]Reaction conditions: **59a** (50 mg, 0.183 mmol), $Pd(OAc)_2$ (10 mol %), and $K_2S_2O_8$ (2.0 equiv) in a mixture of AcOH and other solvent heated at 100 °C for 48 h. [b]Conversion based on crude ^{1}H NMR. [c]Formation of mono-deacylated product. NR = no reaction.

Table 2.2.3: Catalyst screening[a]

entry	catalyst	yield (%)[b] **(60a : 61a)**
1	$Pd(OAc)_2$	95 (14:1:1[c])
2	$PdCl_2$	90 (4:1:2[c])
3	$PdCl_2(CH_3CN)_2$	69 (1: 2.5[c])
4	$Pd(TFA)_2$	91 (2:1:0.6[c])

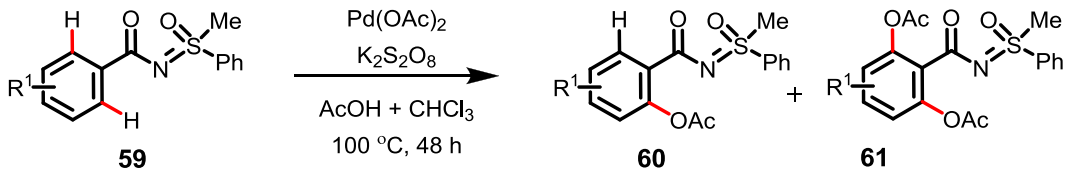
[a]Reaction conditions: **59a** (50 mg, 0.183 mmol), catalyst (10 mol %), and $K_2S_2O_8$ (2.0 equiv) in a mixture of AcOH and $CHCl_3$ (1.0 mL) solvent heated at 100 °C for 48 h. [b]Conversion based on crude ^{1}H NMR. [c]Formation of mono-deacylated product.

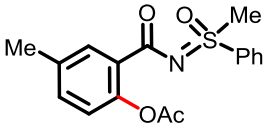
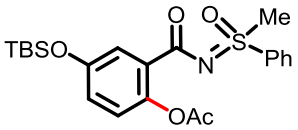
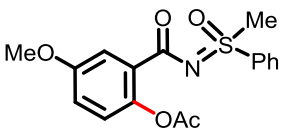
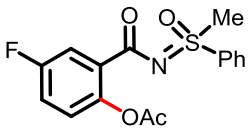
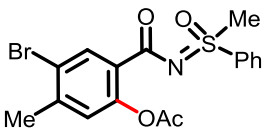
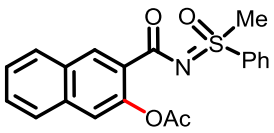
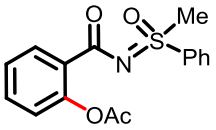
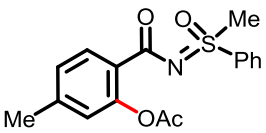
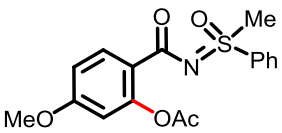
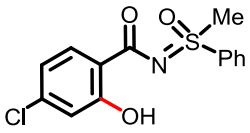
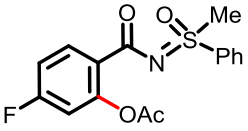
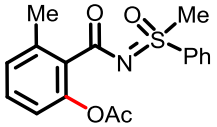
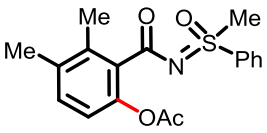
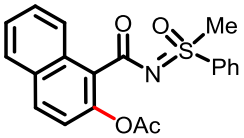
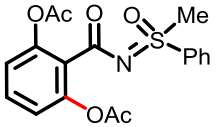
2.3.3. Scope of the Reaction

To probe the effect of *S*-methyl-*S*-phenylsulfoximine (MPS) directing group for chemo- and regioselective *ortho*-C–H acetoxylation of arenes, the optimized reaction condition ($Pd(OAc)_2$ (10 mol%), and $K_2S_2O_8$ (2.0 equiv) in a mixture of AcOH and $CHCl_3$ was surveyed to various *N*-aroylated-MPS (Table 2.3). At first, the regioselective *ortho*-acetoxylation of the *meta*-substituted *N*-aroylated sulfoximines **59** was investigated. The reaction of *N*-[*m*-methylbenzoyl]-MPS (**59a**) gave **60a** as a single regioisomer in 65% yield; the *ortho*-di-acetoxylated **61a** and the mono-deacylated products were also isolated in small

amount. We believe that the compound **61a** is obtained from **60a**. To verify this observation, **6oa** was subjected to the optimized condition and **61a** was isolated albeit in poor yield. Interestingly, the TBS group was tolerated to this reaction condition and the product **60b** was obtained in 47% yield. *m*-Methoxy group did not exhibit the secondary directing effect and produced **60c** exclusively;[6c] the bulky methoxy group inhibits the formation of di-acetoxylated product **61c**. However, poor-level of regioselectivity was observed in the case of *N*-[*m*-F-benzoylated]-MPS (**60d**).[6c] Unfortunately, the bromo-substituted **60e** was obtained in poor-yield, even though the reaction continued for 96 h; the precursor **59e** was recovered in 42% yield. The corresponding de-bromination product was observed in negligible amount (<5%) by crude NMR. Reaction of β-naphthyl derivative **59f** under the catalytic condition gave **60f** (56%) and **61f** (15%). These results suggest that the selectivity is governed by the steric as well as electronic effect of the *m*-substituent.[6c] The electronically neutral **59g** and *p*-substituted *N*-aroylated-MPS (**59h**–**k**) gave the desired mono- and di-acetoxylated products in moderate to good overall yields. However, reaction of *N*-[4-Cl-benzoylated]-MPS (**59j**) gave the mono-deacylated compound as a major product. The halo-groups in **60e** and **60j'** can be amenable to further synthetic transformations. Acetoxylation products **60l** and **60m** were isolated in excellent yields from electron-rich *ortho*-substituted *N*-aroylated-MPS (**59l** and **59m**).[3e,7b] Similarly, the less-hindered *ortho*-C–H bond was replaced with –OAc group in **60n**. Gratifyingly, moderate yield of the di-acetoxylated product **61g** was isolated from **60g**. This reaction cleanly delivers two new molecules of mono and diacetoxylated products. In case of moderate yield of the products formation, the mass-balance is justified with the recovery of the precursors.

Table 2.3: *ortho*-Acetoxylation of *N*-aroylated sulfoximines.[a,b]



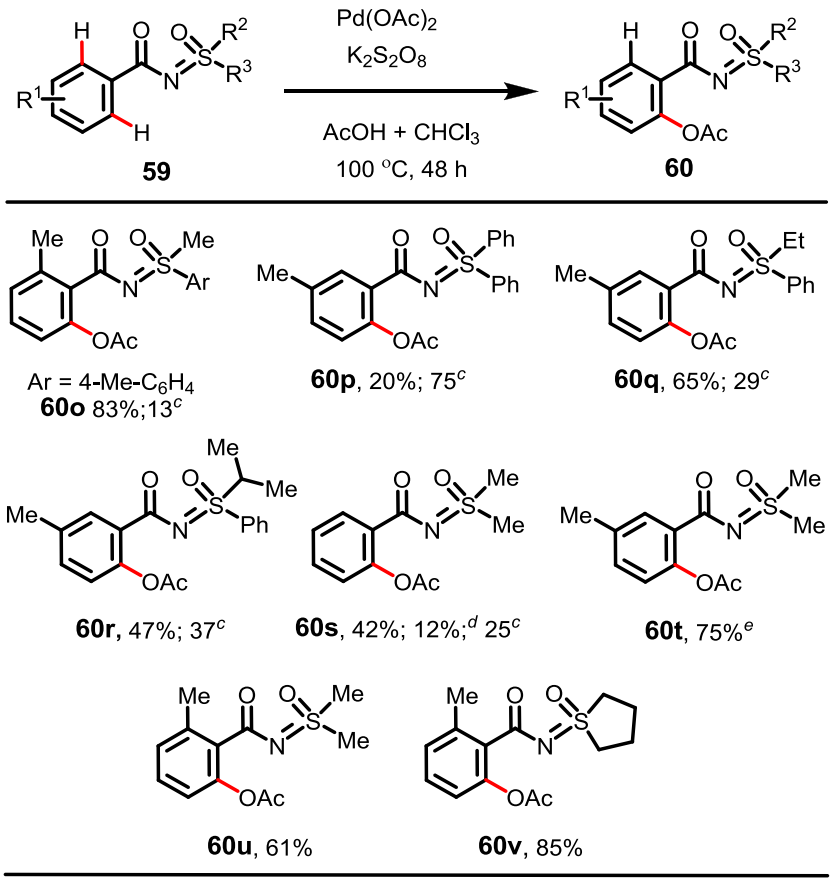
 **60a**, 65%; **61a**, 13%; 4%[c]; 5%[d]	 **60b**, 47%	 **60c**, 53%;[e] 20%[d]
 **60d**, 48% (3:1);[f] 5%[d]	 **60e**, 27%;[g] 42%[d]	 **60f**, 56%; **61f**, 15%; 9%[d]
 **60g**, 54%; **61g**, 12%; 30%[d]	 **60h**, 57%;**61h**, 32%; 10%[d]	 **60i**, 43%; **61i**, 31%; 8%;[c] 10%[d]
 **60j'**, 40%;[c] 25%[d]	 **60k**, 45%;**61k**, 8%; 42%[d]	 **60l**, 95%
 **60m**, 83%	 **60n**, 65%; 25%[d]	 **61g**, 43%;[h] 42%[d]

[a]Reaction conditions: **59** (1.0 mmol), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (2.0 mmol), AcOH:$CHCl_3$ (3:5, 8.0 mL). [b]Isolated yields. [c]Formation of mono de-acetylated product. [d]Starting material recovered. [e]72 h. [f]Regio-isomeric mixture. [g]**59e** (0.57 mmol) at 120 °C for 96 h. [h]96 h.

We next investigated the steric and electronic effects of sulfoximine derivatives to the *ortho*-acetoxylation of arenes (Table 2.4). Electron-rich S-methyl-S-4-(methyl)-phenyl sulfoximine impart slightly lower efficiency resulting **60o** in 83% yield when compared to **60l** (95% yield, Table 2.3). Poor reactivity was noticed in the case of *S*,*S*-diphenyl-substituted sulfoximine (**59p**).The bulkiness on sulfur retards the reaction efficiency: the *S*-ethyl-

substituted sulfoximine (**59q**) shows identical reactivity in comparison to **60a** and delivered **60q** in 65% yield, whereas *S*-*iso*-propyl-substituted sulfoximine resulted **60r** in poor yield. Moreover, a similar trend of selectivity and reactivity were observed in the *o*-acetoxylation products of *N*-benzoylated-*S*,*S*-dimethyl-sulfoximines (**60s-u**) comparable to **60g**, **60a**, and **60l**, respectively. The cyclic *S*,*S*-tetramethylenesulfoximine showed analogous reactivity with respect to *S*-methyl-*S*-phenyl sulfoximine and gave **60v** in 85% yield. Based on these experimental results, the *S*-methyl-*S*-phenylsulfoximine is conceived potential directing group to the *o*-acetoxylation of arenes.

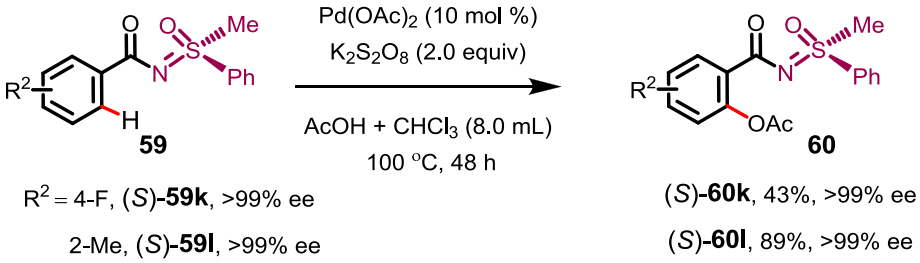
Table 2.4: Steric and electronic effects of sulfoximine derivatives.[a,b]



[a]Reaction conditions: **59** (1.0 mmol), $Pd(OAc)_2$ (10 mol %), $K_2S_2O_8$ (2.0 mmol), AcOH:$CHCl_3$ (3:5, 8.0 mL). [b]Isolated yields. [c]Starting material recovered. [d]Formation of mono-deacetylated product. [e]**59t** (100 mg, 0.47 mmol) is used.

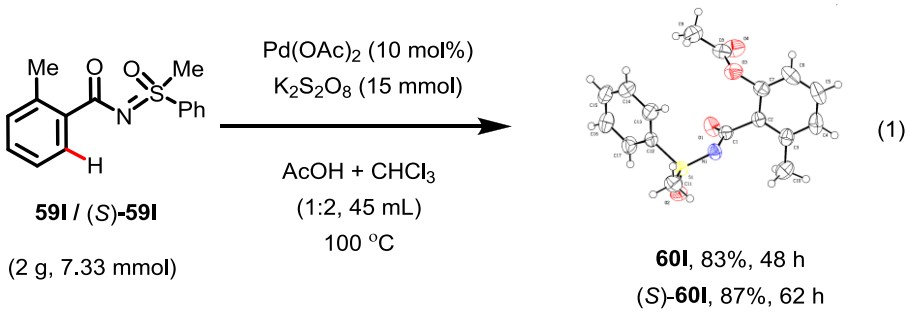
Sulfoximines serve as potential chiral ligands for asymmetric synthesis.[16d,17] Therefore, we intend to examine the effect of the catalytic conditions to the acetoxylation of the chiral *N*-aroylated sulfoximines. Gratifyingly, acetoxylation of (*S*)-**59k** and (*S*)-**59l** gave (*S*)-**60k** and (*S*)-**60l** with >99% ee in 43% and 89% yields, respectively (Scheme 2.10). This

observation reveals that the stereointegrity of the sulfoximine moiety is preserved in this transformation. We believe that this strategy would create a wide array of new optically active sulfoximine bearing complex molecules efficiently.[17]



Scheme 2.10: Pd-Catalyzed acetoxylation of chiral N-aroylated MPS

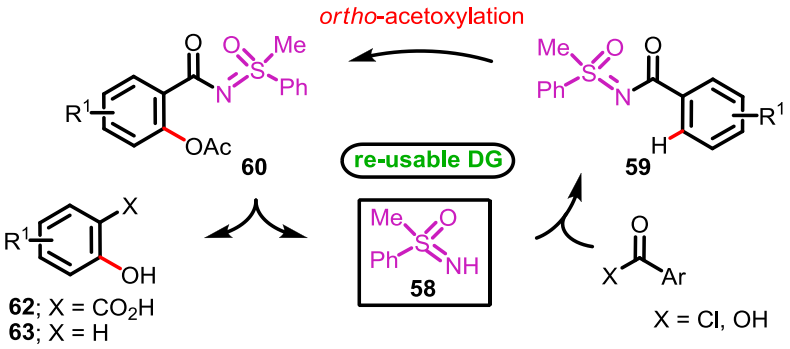
Finally, the robustness of this reaction was demonstrated through gram-scale *ortho*-acetoxylation of arenes. Thus, reaction of **59l** and (*S*)-**59l** was independently performed under the optimized catalytic conditions and the products **60l** and (*S*)-**60l** are obtained in 83% and 87% yields, respectively [eq. (1)].



To show the practical utility of this strategy, we embarked examining the re-usability of the directing group. Thus, hydrolysis of the *N*-benzoyl moiety of **60** was investigated (Table 2.5). Unfortunately, the *N*-benzoyl moiety of **60a** did not cleave under base-induced hydrolysis.[18,19a] However, hydrolysis of **60a** with HCl (12 N) at 80 °C was found successful and the desired 2-hydroxy-5-methyl benzoic acid (**62a**) was extracted in 79% yield (entry 1). Neutralization of the acidic mother liquor followed by standard work-up delivered the S-methyl-S-phenylsulfoximine (**58**) in good yield. Reaction of crude **58** afforded **59a** efficiently. Similarly, the corresponding *o*-hydroxy benzoic acids **62g** and **62k** were obtained from **60g** and **60k**, respectively and **58** was successfully recovered and reused (entries 2 and 3). Surprisingly, the *o*-substituted-*o′*-acetoxylated compounds **60m** and (*S*)-**60l** underwent decarboxylation during hydrolysis and the corresponding 3,4-dimethyl phenol (**63m**) and 3-methyl phenol (**63l**) were isolated in 89% and 82% yield, respectively (entry 4 and 5).

Following this method, the hitherto difficult *m*-substituted phenols can be synthesized.[19b] Interestingly, configuration of the chiral **58** was retained in the acid-mediated hydrolysis of (*S*)-**60l**; (*S*)-**58** was obtained in 85% yield with >99% ee (entry 5). Looking into the effective cleavability and re-usability of the sulfoximine directing group, we hope this strategy would be useful in fabricating complex phenol derivatives of pharmaceutical interest.

Table 2.5: Reusability of the sulfoximine directing group[a]



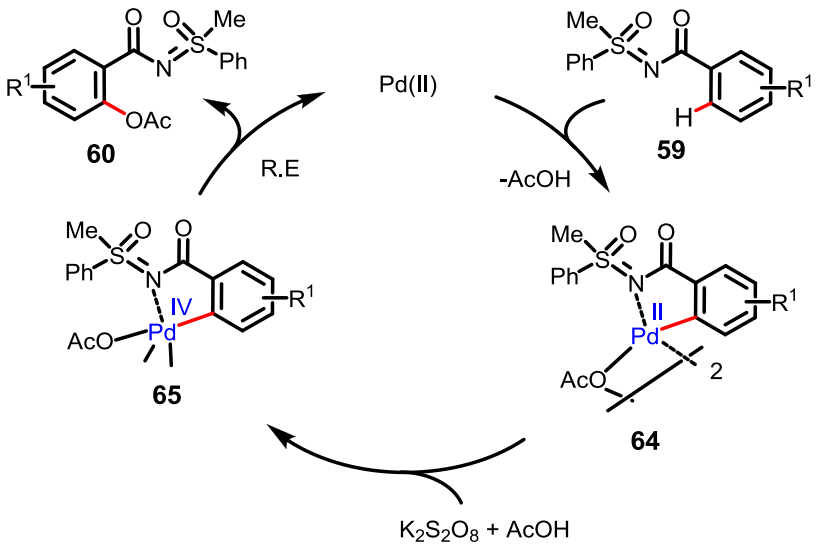
entry	**60**	yield of **62/63** (%)[b]	yield of **58** (%)[c]	yield of **59** (%)[d]
1	**60a**	79	71	87
2	**60g**[e]	87	74	84
3	**60k**	75	61	73
4	**60m**	89[f]	73	68
5	**(S)-60l**	82[f]	85	92

[a]Reaction conditions: **60** (100 mg), HCl (12 N, 5.0 mL), 80 °C, 48 h. [b]Pure crude products. [c]Isolated yields of **58**. [d]Isolated yields of the corresponding **59** from **58**. [e]**60g** (1.0 mmol). [f]Formation of the corresponding decarboxylated product **63**.

2.3.4. Mechanistic Studies

Based on the previous findings on Pd-catalyzed oxidative C–H functionalizations of arenes with $K_2S_2O_8$ oxidant, the proposed catalytic cycle is likely to proceed involving $Pd^{II/IV}$ species, as shown in Scheme 2.11. Interestingly, the heteroatom such as: S, S=O, C=O, and S=N in *N*-benzoylated sulfoximines **59** have the ability to co-ordinate to the Pd-species. Owing to the oxidation state of S (+VI) and the polarization of S=O bond in sulfoximine, co-ordination of S to Pd^{II} is ruled out. Similarly, the chelation of O-atom of the polarized S=O is also believed unlikely because it involves 7-membered transition state. The spectroscopic and theoretical studies revealed that the conjugate delocalization of the nitrogen lone pair is

prohibited due to its orthogonal orientation to the N–C(O) bond.[20] Among the nitrogen and carbonyl-oxygen, we presume that the chelation of N to Pd^{II} is more susceptible due to the localized electron density,[21] however, the coordination of carbonyl-oxygen cannot be completely ruled out. Thus, the first step in the catalytic cycle involves the chelation of N to Pd^{II} followed by palladation of *ortho*-C–H bond of arenes to produce the crucial five-membered cyclopalladated intermediate **64**. Next, the oxidation of Pd(II)-species of **64** with $K_2S_2O_8$ in the presence of AcOH gives the Pd(IV)-species (**65**).[22] Finally, reductive elimination of **65** furnishes the desired *ortho*-acetoxylated product **60** and generates the active Pd(II) species for the next catalytic cycle.



Scheme 2.11: Proposed catalytic cycle

2.4. Conclusion

In conclusion, we have shown that the use of sulfoximine as a directing group exemplifies a novel approach to chemo- and regioselective *ortho*-acetoxylation of arenes. Even though our initial results are not comparable with the Yu's approach to the C–H oxidation of aromatic carboxylic acids, we hope the sulfoximine directing group would contribute to the development of new and useful C–H functionalizations. Notably, stereointegrity of chiral sulfoximine is preserved. The facile attachment and detachment of the robust sulfoximine moiety makes it highly re-usable. Realization of milder reaction conditions for sp^2 and sp^3 C–H functionalizations, unravelling of the mechanistic details, generation of axial chirality

through asymmetric C–H activation, and exploration of novel synthetic applications are being actively pursued in our laboratory.

2.5. Experimetal

2.5.1. General Experimental Information for the Work Presented in this Thesis

All the reactions were performed in an oven-dried Schlenk flask. Commercial grade solvents were distilled prior to use. Column chromatography was performed using either 100-200 Mesh or 230-400 Mesh silica gel. Thin layer chromatography (TLC) was performed on silica gel GF254 plates. Visualization of spots on TLC plate was accomplished with UV light (254 nm) and staining over I_2 chamber.

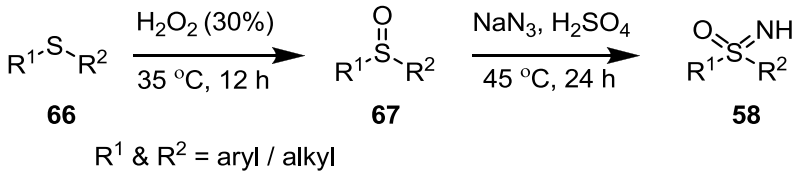
Proton, carbon, and fluorine nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were recorded based on the resonating frequencies as follows: (^{1}H NMR, 400 MHz; ^{13}C NMR, 101 MHz; ^{19}F NMR, 376 MHz) and (^{1}H NMR, 500 MHz; ^{13}C NMR, 126 MHz; ^{19}F NMR, 470 MHz) having the solvent resonance as internal standard (^{1}H NMR, $CDCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.0 ppm). Few cases tetramethylsilane (TMS) at 0.00 ppm was used as reference standard. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet; bs = broad singlet; d = doublet; bd = broad doublet, t = triplet; bt = broad triplet; q = quartet; m = multiplet), coupling constants, *J*, in (Hz), and integration. Data for ^{1}H NMR, ^{13}C NMR, ^{19}F NMR were reported in terms of chemical shift (ppm). IR spectra were reported in cm^{-1}. LC–MS spectra were obtained with ionization voltage of 70ev; data was reported in the form of *m/z* (intensity relative to base peak = 100). High resolution mass spectra were obtained in (ESI-TOF analyzer) equipment. HPLC analysis of the samples was performed using Chiralpak cellulose-1 column/ cellulose-2 column, hexanes–*i*-PrOH as eluent, flow rate = 0.3-1.0 mL/min at λ = 254 nm. Elemental (C, H, N) analysis were carried out using FLASH EA 1112 analyzer. Melting points were determined by electro-thermal heating and are uncorrected. X-ray data was collected at 298 K using graphite monochromated Mo-Kα radiation (0.71073 Å),

2.5.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Dichloromethane (DCM) and chloroform were distilled over CaH_2. Acetic acid was distilled over $KMnO_4$ and THF was freshly distilled over sodium/benzophenone ketyl under dry nitrogen. $Pd(OAc)_2$, $PdCl_2$, $Pd(OTFA)_2$ were purchased from Sigma Aldrich Ltd, and used as received. Oxidants such as $Na_2S_2O_8$, $PhI(OAc)_2$, BQ, TBHP, lauroyl peroxide were purchased from Aldrich Ltd. and $K_2S_2O_8$ was purchased from Merck Ltd and used as received. Analytical and spectral data of all those known compounds are exactly matching with the reported values.

2.5.3. Experimental Procedures

2.5.3.1. Preparation of Sulfoximines; General Procedure (GP-1):



Scheme 2.12: Synthesis of sulfoximines from sulfides

Following the literature procedure,[23a,b] sulfoximines (**58**) are prepared from the commercially available sulfides (**66**) in good yields over two steps.

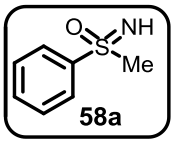
Step-I. Oxidation of Sulfides to Sulfoxides: [23a]

A heterogeneous mixture of the commercially available sulfides **66** (1.0 equiv) and aqueous 30% H_2O_2 (1.1 equiv) was heated at 40 °C for about 12–20 h. The resulting homogeneous reaction mixture was saturated with NaCl and extracted with ethyl acetate (3 × 5 mL, for 5 mmol sulfide). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (~3 mL, for 5 mmol sulfide) and the organic layer was dried over Na_2SO_4. Solvent was filtered and evaporated under reduced pressure to provide the desired sulfoxide **67** in excellent yields. The crude sulfoxides were subsequently used for the imination reaction (Scheme 2.12).

Step-II. Imination of Sulfoxides: [23b]

A solution of crude sulfoxide **67** (1.0 equiv) and sodium azide (1.2 equiv) in $CHCl_3$ (~8–10 mL for 5.0 mmol of sulfoxide) was stirred in an oven-dried three-necked round bottom flask equipped with a reflux condenser and an addition funnel. Concentrated sulphuric acid (~2.0 mL for 1.0 g of sulfoxide) was introduced over 5–10 minutes at 0 °C. The resulting mixture was slowly warmed up to 45 °C and the same temperature was maintained until nitrogen gas evolution subsides. The reaction was continued for an additional 12 h at 45 °C. The reaction mixture was cooled and the pasty-mass was dissolved with ice-water. The organic layer was decanted and the aqueous layer was washed with minimum amount of $CHCl_3$. The aqueous layer was made slightly alkaline using 20% NaOH solution and extracted with $CHCl_3$ (3 × 5 mL, for 5 mmol sulfoxide). The combined organic extracts were dried over Na_2SO_4. Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography on silica gel to afford the desired sulfoximines **58** in good yields.

***S*-Methyl-*S*-phenylsulfoximine (58a):** [23a,b]



58a

Following the literature procedure and GP-1, oxidation followed by imination of methyl phenyl sulfide (25.0 g, 201 mmol, **66a**) afforded *S*-methyl-*S*-phenylsulfoximine (25.6 g, **58a**) in 82% yield over two steps as pale yellow oil. R_f = 0.26 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.2 Hz, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.56 (t, J = 7.2 Hz, 2H), 3.12 (s, 3H), 2.68 (bs, 1H, –NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 133.0, 129.2, 127.6, 46.2.

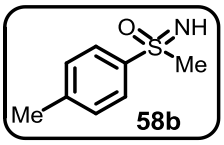
***(S)*-*S*-Methyl-*S*-phenylsulfoximine (*S*-58a):** [23c]

***S*-58a**

Following the known procedure,[23c] A solution of *S*-(+)-camphorsulfonic acid ((+)-CSA) (3.7 g, 16.1 mmol) in dry acetone (200 mL) was added gradually at room temperature under stirring to a solution of racemic *S*-methyl-*S*-phenylsulfoximine (**58a**; 5.0 g, 32.2 mmol) in dry acetone (430 mL). After the addition of about one-third of the solution of (+)-CSA, fine white crystals of the salt (+)-**58a**/(+)-CSA began to precipitate. The resulting suspension was stirred at room temperature for 12 h. The crystals were filtered with the aid of a glass filter, washed thoroughly with dry acetone (4 x 100 mL) and dried in vacuum to give the salt (+)-**58a**/(+)-CSA (58.0 g, 80%) of >99% de as colorless crystals. Base hydrolysis of the resulting S-solid produced *(S)*-*S*-methyl-*S*-phenylsulfoximine (***S*-58a**, 1.9 g) in 76% with >99% ee (determined by chiral HPLC) as

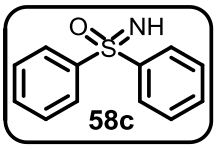
colorless viscous oil. Analytical data of ***S*-58a** exactly matching with the reported value. Optical rotation of (***S*)-58a** (c = 0.005 in $CHCl_3$) was found; $[\alpha]_D = 21.8$ at 28 °C. HPLC: cellulose-2 column [hexane/*i*-PrOH 50:50; 1.0 mL/min; 254 nm; (*S*)-**58a** t_R = 11.39 min (99.65); (*R*)-**58a** t_R = 15.02 min (0.35)].

S-Methyl-*S*-(4-methylphenyl)sulfoximine (58b): [24a,b,25]



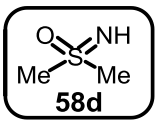
Following the literature procedure and GP-1, oxidation followed by imination of methyl-4-(methyl)phenyl sulfide (1.0 g, 7.2 mmol, **66b**) afforded *S*-methyl-*S*-(4-methylphenyl)sulfoximine (0.831 g, **58b**) in 68% yield over two steps as colorless oil. R_f = 0.30 (EtOAc): [Silica, UV and I_2]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 3.09 (s, 3H), 2.45 (s, 3H), 2.43 (bs, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 140.6, 129.9, 127.7, 46.3, 21.5.

S,S-Diphenylsulfoximine (58c): [24a,b]



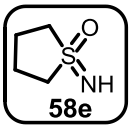
Following the literature procedure and GP-1, imination of diphenyl sulfoxide (5.0 g, 24.75 mmol, **67c**) afforded *S*,*S*-diphenylsulfoximine (2.0 g, **58c**) in 37% yield as colorless solid. R_f = 0.52 (7:13 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 6.8 Hz, 4H), 7.49–7.43 (m, 6H), 3.08 (bs, 1H, –NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 132.4, 129.0, 127.8.

S,S-Dimethylsulfoximine (58d): [24b,c]

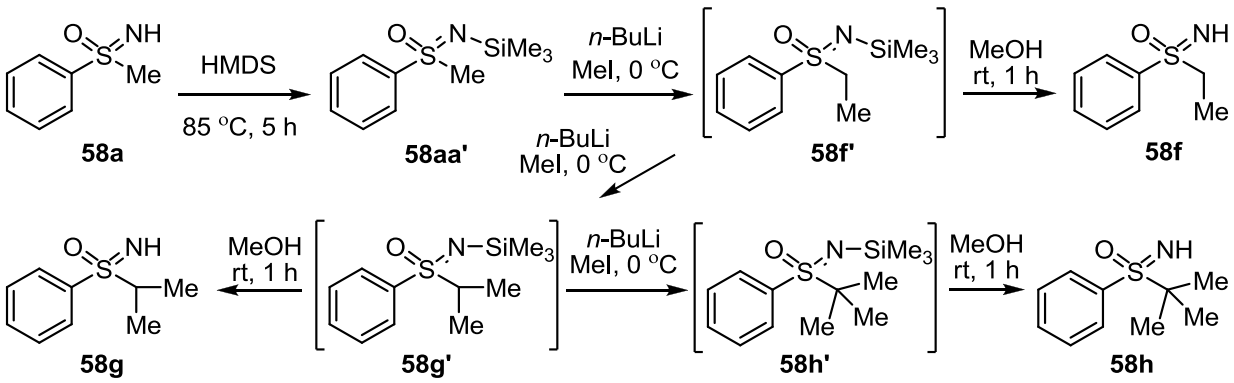


Following the literature procedure and GP-1, imination of dimethyl sulfoxide (14 mL, 192 mmol, **67d**) afforded *S*,*S*-dimethylsulfoximine (8.01 g, **58d**) in 45% yield as hygroscopic solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (s, 6H), 2.61 (bs, 1H, -NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 45.5.

S,S-Tetramethelenesulfoximine (58e): [24b,25]



Following the literature procedure and GP-1, imination of *S*,*S*-tetramethelene sulfoxide (1.0 g, 9.6 mmol, **67e**) afforded *S*,*S*-tetramethelenesulfoximine (0.45 g, **58e**) in 39% yield as pale yellow oil. R_f = 0.63 (MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14–3.10 (m, 4H), 2.70 (bs, 1H, -NH), 2.27–2.23 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.4, 24.0.



Scheme 2.13: Preparation of **58f**, **58g**, **58h** [26]

Step-III. Preparation of TMS protected *NH*-sulfoximine (58aa'):

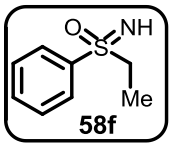
A mixture of methyl phenyl sulfoximine (**58a**, 5.0 g, 32.15 mmol) and hexamethyldisilazane (HMDS, 33.70 mL, 161 mmol) was heated at 85 °C under an inert atmosphere for 5 h. Excess amount of HMDS was removed under reduced pressure to afford quantitative amount of *N*-TMS-sulfoximine (**58aa′**) as pale yellow oil. The crude material was used for the alkylation reaction subsequently.

Step-IV. Methylation of *N*-TMS sulfoximine:

A solution of *N*-TMS-sulfoximine (**58aa′**, 1.0 mmol) in THF (5.0 mL) was stirred in an oven-dried two-neck round bottom flask under an argon atmosphere at 0 °C. *n*-BuLi (1.0 equiv, 1.60 M in THF) was introduced over 30 minutes at 0 °C. After an additional 30 minutes stirring, MeI (1.0 equiv) was added at 0 °C. The resulting mixture was stirred for 30 minutes and warmed to room temperature slowly and continued for 2 h. Methanol (2.0 mL) was added to the reaction mixture and stirred for 1 h to carry out desilylation of the resulting product. The reaction mixture was quenched with saturated aqueous solution NH_4Cl (20 mL). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried over Na_2SO_4. Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography on silica gel to afford *S*-ethyl-*S*-phenyl sulfoximine (**58f**).

Repeating the identical reaction conditions sequentially on **58f′ (**use of *n*-BuLi and MeI), *S*-*iso*-propyl-*S*-phenyl sulfoximine (**58g**) and *S*-*tert*-butyl-*S*-phenyl sulfoximine (**58h**) are prepared in moderate yields.

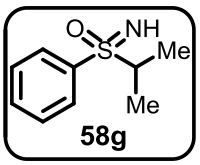
Preparation of *S*-ethyl-*S*-phenylsulfoximine (58f): [26]



Following the literature procedure and step-IV in GP-1, reaction of *N*-TMS-sulfoximine (**58aa′**, 1g, 4.40 mmol), *n*-BuLi (1.60 M, 2.75 mL, 4.40 mmol) and MeI (0.27 mL, 4.40 mmol) afforded *S*-ethyl-*S*-phenylsulfoximine (602 mg, **58f**) in 84% yield as pale yellow oil.

R_f = 0.33 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.0 Hz, 2H), 7.65 (t, J = 8.0 Hz, 1H), 7.57 (t, J = 8.0 Hz, 2H), 3.21 (q, J = 8.0 Hz, 2H), 2.72 (bs, 1H, NH), 1.28 (t, J = 8.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2, 133.1, 129.2, 128.6, 51.7, 7.8.

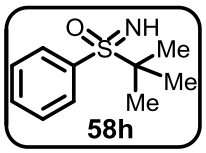
Preparation of *S*-*iso*-propyl-*S*-phenylsulfoximine (58g):



Following the literature procedure and step-IV in GP-1, reaction of *N*-TMS-sulfoximine (**58f′,** 4.15 mmol; prepared in-situ) with *n*-BuLi (1.60 M, 2.59 mL, 4.15 mmol) followed by MeI (0.26 mL, 4.15 mmol) gave *S*-*iso*-propyl-*S*-phenylsulfoximine (480 mg, **58g**) in 63% yield as pale yellow oil.

R_f = 0.34 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.4 Hz, 2H), 3.27–3.21 (m, 1H), 2.45 (bs, 1H, –NH), 1.31 (d, J = 6.8 Hz, 3H), 1.26 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7, 133.0, 129.3, 128.9, 56.5, 16.4, 16.0.

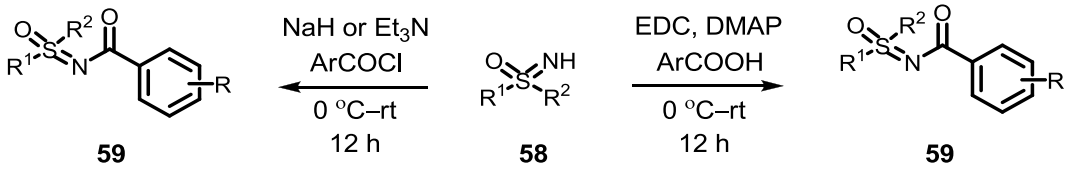
Preparation of *S*-*tert*-butyl-*S*-phenylsulfoximine (58h):[26]



Following the literature procedure and step-IV in GP-1, reaction of *N*-TMS-sulfoximine (**58g',** 4.0 mmol; prepared in-situ) with *n*-BuLi (1.60 M, 2.5 mL, 4.0 mmol) followed by MeI (0.25 mL, 4.0 mmol) gave *S*-*tert*-butyl-*S*-phenylsulfoximine (405 mg, **58h**) in 52% yield as pale yellow oil.

R_f = 0.50 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.2 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.4 Hz, 2H), 3.14 (bs, 1H, –NH), 1.35 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8, 133.0, 130.7, 128.5, 60.4, 20.0.

2.5.3.2. General Procedures (GP-2/-3 and GP-4):



Scheme 2.14: Preparation of *N*-aroylated Sulfoximines

General Procedure (GP-2); Use of sodium hydride base: [19a]

Sodium hydride (NaH; 1.5 equiv, 60% in oil) was taken in a 100 mL oven-dried two necked round bottom flask and was washed with dry hexane (2 × 10 mL) under an inert atmosphere. Dichloromethane (5.0 mL, for 1.0 mmol of sulfoximine) was added. Sulfoximine **58** (1.0 equiv) was charged drop wise at an ambient temperature. After being stirred for about 30 min to 1 h, the reaction mixture was cooled to 0 °C and acid chloride (1.1 equiv) was added drop wise. The resulting mixture was stirred for about 30 minutes and warmed to ambient temperature and continued for overnight. The reaction mixture was quenched with water (10 mL). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3 times). The combined extracts were washed with brine (25 mL) and dried over Na_2SO_4. Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography on silica gel.

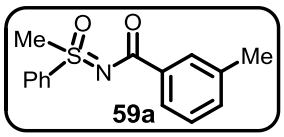
General Procedure (GP-3); Use of triethylamine base: [27]

A solution of sulfoximine **58** (1.0 equiv) in CH_2Cl_2 (5.0 mL, for 1.0 mmol of sulfoximine) was stirred in a 100 mL oven-dried two-necked round bottom flask under an argon atmosphere at an ambient temperature. Triethylamine (1.5 equiv) was introduced drop wise at 0 °C. After an additional 30 minutes stirring, acid chloride (1.1 equiv) was added drop wise at 0 °C. The resulting mixture was stirred for about 1 h at 0 °C and warmed to ambient temperature and continued for overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL) at rt. The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3 times). The combined extracts were washed with brine (25 mL) and dried over Na_2SO_4. Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography on silica gel.

General Procedure (GP-4); EDC-coupling: [28]

A solution of *N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, hydrochloride salt (EDC.HCl) (1.1 equiv), 4-*N*,*N*-dimethylaminopyridine (DMAP) (2.2 equiv) and carboxylic acid (1.1 equiv) in CH_2Cl_2 (5.0 mL, for 1.0 mmol of sulfoximine) was stirred under an argon atmosphere. Sulfoximine **58** (1.0 equiv) was introduced drop wise at 0 °C. The resulting reaction mixture was stirred for about 1 h at 0 °C, and warmed to ambient temperature and continued for overnight. Upon complete consumption of sulfoximine, the reaction mixture was acidified with hydrochloric acid (HCl, 1N). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3 times). The combined extracts were washed with 10% aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4. Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography on silica gel.

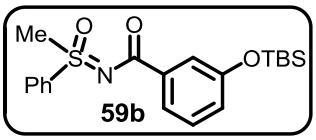
***N*-[3-Methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (59a):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 3.0 g, 19.35 mmol), NaH (60% in mineral oil, 1.16 g, 29 mmol) and *m*-tolyl chloride (3.3 g, 21.3 mmol) afforded **59a** (4.9 g) in 93% yield as colorless crystalline solid.

mp = 75–76 °C; R_f = 0.51 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 2H), 8.01–7.93 (m, 2H), 7.69 (bt, J = 7.2 Hz, 1H), 7.62 (t, J = 8.0 Hz, 2H), 7.37–7.27 (m, 2H), 3.47 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 138.9, 137.6, 135.4, 133.7, 132.8, 129.8, 129.6, 127.8, 127.0, 126.5, 44.2, 21.2; IR (KBr) ν_{max} 3016, 2920, 1626, 1581, 1444, 1224 cm^{-1}; MS (EI) *m/z* (%) 274 (M^+ + 1, 100), 156 (8), 91 (5); Anal. calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found: C, 65.85; H, 5.49; N, 5.22.

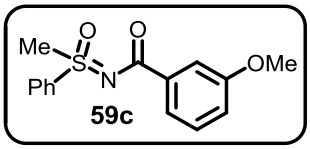
***N*-[3-(*tert*-Butyldiphenylsilyloxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (59b):**



Following the general procedure (GP-4); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 0.68 g, 4.35 mmol), EDC.HCl (0.83 g, 4.35 mmol), DMAP (1.06 g, 8.72 mmol) and 3-(*tert*-butyldiphenylsilyloxy)benzoic acid (1.0 g, 3.96 mmol) afforded **59b** (1.06 g) in 69% yield as colorless viscous oil.

R_f = 0.57 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.6 Hz, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.69(bt, J = 7.2 Hz, 1H), 7.65–7.56 (m, 3H), 7.30–7.21 (m, 1H), 6.99 (dd, J = 8.0 Hz, 1H), 3.46 (s, 3H), 0.98 (s, 9H), 0.20(s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 155.5, 139.1, 137.1, 133.8, 129.7, 129.0, 127.2, 124.1, 122.6, 120.8, 44.4, 25.7, 18.2, –4.4; IR (Neat) ν_{max} 3069, 2920, 1631, 1579, 1286, 1224 cm^{-1}; MS (EI) *m/z* (%) 390 (M^+ + 1, 100); Anal. calcd for $C_{14}H_{12}FNO_2S$: C, 61.66; H, 6.99; N, 3.60. Found: C, 61.45; H, 7.12; N, 3.51.

***N*-[3-Methoxybenzoyl]-*S*-methyl-*S*-phenylsulfoximine (59c):**

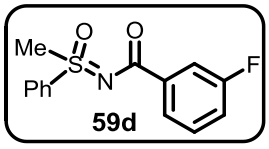


59c

Following the general procedure (GP-4); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 0.5 g, 3.21 mmol), EDC.HCl (0.68 g, 3.54 mmol), DMAP (0.86 g, 7.07 mmol) and 3-methoxybenzoic acid (0.54 g, 3.54 mmol) afforded **59c** (0.77 g) in 83% yield as colorless crystalline solid.

mp = 91–92 °C; R_f = 0.59 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2H), 7.79 (d, J = 7.6 Hz, 1H), 7.71–7.65 (m, 2H), 7.61 (t, J = 7.6 Hz, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.06 (bd, J = 8.0 Hz, 1H), 3.84 (s, 3H), 3.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 159.3, 138.8, 136.9, 133.7, 129.6, 128.9, 127.0, 121.9, 118.6, 113.6, 55.3, 44.2; IR (Neat) ν_{max} 3030, 2930, 1616, 1593, 1277, 1213 cm^{-1}; MS (EI) *m/z* (%) 290 (M^+ + 1, 100), 156 (33); Anal. calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.36; H, 5.31; N, 4.75.

***N*-[3-Fluorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (59d):**

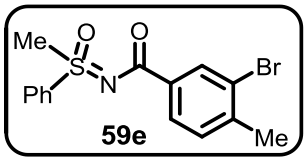


59d

Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 0.5 g, 3.22 mmol), NaH (60% in mineral oil, 0.2 g, 4.83 mmol) and 3-fluorobenzoyl chloride (0.56 g, 3.54 mmol) afforded **59d** (0.84 g) in 93% yield as colorless crystalline solid.

mp = 87–88 °C; R_f = 0.39 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2H), 7.95 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 9.6 Hz, 1H), 7.70 (bt, J = 7.2 Hz, 1H), 7.63 (bt, J = 7.6 Hz, 2H), 7.38 (q, J = 7.2 Hz, 1H), 7.21 (td, J = 8.4, 2.0 Hz, 1H), 3.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 162.6 (d, J = 246.4 Hz), 138.7, 138.0 (d, J = 7.1 Hz), 134.0, 129.8, 129.6 (d, J = 8.1 Hz), 127.1, 125.1 (d, J = 2.0 Hz), 119.1 (d, J = 21.2 Hz), 116.2 (d, J = 22.2 Hz), 44.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –210.75; IR (KBr) ν_{max} 3030, 2932, 1616, 1585, 1446, 1290, 972 cm^{-1}; MS (EI) *m/z* (%) 279 (M^++2, 59), 278 (M^++1, 100), 156 (51), 123 (16); Anal. calcd for $C_{14}H_{12}FNO_2S$: C, 60.64; H, 4.36; N, 5.05. Found: C, 60.55; H, 4.38; N, 5.12.

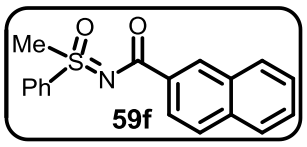
_N_-[3-Bromo-4-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (59e):



Following the general procedure (GP-4); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 0.5 g, 3.22 mmol), EDC.HCl (0.68 g, 3.54 mmol), DMAP (0.84 g, 7.08 mmol) and 3-bromo-4-methylbenzoic acid (0.76 g, 3.54 mmol) afforded **59e** (0.68 g) in 60% yield as colorless crystalline solid.

mp = 75–76 °C; R_f = 0.38 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.04 (d, *J* = 7.2 Hz, 2H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.70 (bt, *J* = 7.2 Hz, 1H), 7.62 (bt, *J* = 7.4 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 1H), 3.46 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ172.7, 142.2, 138.6, 135.0, 133.8, 133.2, 130.3, 129.6, 128.1, 127.0, 124.4, 44.3, 23.0; IR (KBr) ν_{max} 3022, 1633, 1444, 1284, 1255, 1203 cm^{-1}; MS (EI) *m/z* (%) 354 (M^++2, 100), 352 (100), 197 (13), 156 (11); Anal. calcd for $C_{15}H_{14}BrNO_2S$: C, 51.15; H, 4.01; N, 3.98. Found: C, 51.26; H, 4.08; N, 3.89.

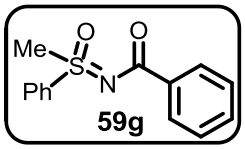
_N_-[β-Naptholoyl]-_S_-methyl-_S_-phenylsulfoximine (59f):



Following the general procedure (GP-4); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 0.8 g, 5.16 mmol), EDC.HCl (1.10 g, 5.68 mmol), DMAP (1.38 g, 11.35 mmol) and β-naphthoic acid (0.98 g, 5.68 mmol) afforded **59f** (1.30 g) in 82% yield as colorless crystalline solid.

mp = 142–143 °C; R_f = 0.41 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 8.10 (d, *J* = 7.6 Hz, 2H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.91–7.83 (m, 2H), 7.70 (bt, *J* = 7.2 Hz, 1H), 7.63 (bt, *J* = 7.4 Hz, 2H), 7.59–7.48 (m, 2H), 3.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.4, 139.0, 135.3, 133.9, 132.9, 132.6, 130.6, 129.7, 129.4, 127.7, 127.2, 126.3, 125.6, 44.4; IR (Neat) ν_{max} 3022, 1608, 1446, 1350, 1304, 1223 cm^{-1}; MS (EI) *m/z* (%) 310 (M^++1, 100), 155 (5), 97 (32); Anal. calcd for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53. Found: C, 69.75; H, 4.82; N, 4.61.

_N_-Benzoyl-_S_-methyl-_S_-phenylsulfoximine (59g):

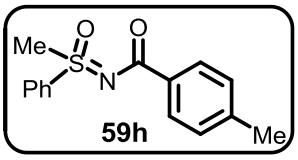


Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 1.55 g, 10 mmol), NaH (60% in mineral oil, 600 mg, 15 mmol) and benzoyl chloride (1.54 g, 11 mmol) afforded **59g** (2.4 g) in 93% yield as colorless solid.

mp = 122–123 °C; R_f = 0.49 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.18 (d, *J* = 7.6 Hz, 2H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.2 Hz,

1H), 7.42 (t, *J* = 7.6 Hz, 2H), 3.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 138.9, 135.5, 133.7, 132.1, 129.6, 129.3, 127.9, 127.1, 44.3; IR (Neat) ν_{max} 3018, 1614, 1446, 1313, 1280, 1213 cm^{-1}; MS (EI) *m/z* (%) 260 (M^++1, 100), 156 (30), 105 (13); Anal. calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40. Found: C, 64.75; H, 5.12; N, 5.51.

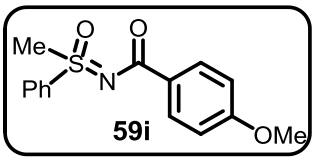
***N*-[4-Methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (59h):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 1.0 g, 6.45 mmol), NaH (60% in mineral oil, 387 mg, 9.67 mmol) and *p*-tolyl chloride (1.09 g, 7.10 mmol) afforded **59h** (1.60 g) in 90% yield as colorless crystalline solid.

mp = 168–169 °C; R_f = 0.42 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.02 (m, 4H), 7.68 (bt, *J* = 7.4 Hz, 1H), 7.60 (bt, *J* = 7.6 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 3.45 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 142.6, 139.0, 133.7, 132.9, 129.6, 129.4, 128.7, 127.1, 44.3, 21.5; IR (Neat) ν_{max} 3020, 2924, 1624, 1444, 1408, 1282, 1221 cm^{-1}; MS (EI) *m/z* (%) 274 (M^++1, 100), 156 (16); Anal. calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found: C, 65.85; H, 5.51; N, 5.22.

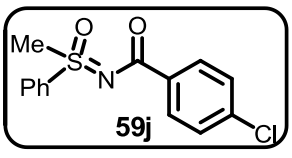
***N*-[4-Methoxybenzoyl]-*S*-methyl-*S*-phenylsulfoximine (59i):**



Following the general procedure (GP-4); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 0.50 g, 3.22 mmol), EDC.HCl (0.68 g, 3.54 mmol), DMAP (0.86 g, 7.08 mmol) and 4-methoxybenzoic acid (0.54 g, 3.54 mmol) afforded **59i** (0.80 g) in 86% yield as colorless crystalline solid.

mp = 138–139 °C; R_f = 0.38 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 2H), 8.03 (d, *J* = 7.6 Hz, 2H), 7.66 (bt, *J* = 6.6 Hz, 1H), 7.59 (bt, *J* = 7.0 Hz, 2H), 6.89 (d, *J* = 7.6 Hz, 2H), 3.83 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 162.8, 139.0, 133.6, 131.4, 129.5, 128.1, 127.0, 113.1, 55.3, 44.3; IR (Neat) ν_{max} 3022, 1609, 1508, 1286, 1255, 1211 cm^{-1}; MS (EI) *m/z* (%) 290 (M^++1, 100), 156 (38), 151 (19), 135 (16); Anal. calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.15; H, 5.28; N, 4.75.

***N*-[4-Chlorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (59j):**

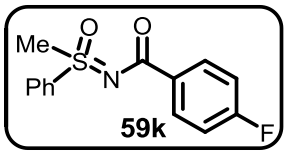


Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 0.5 g, 3.22 mmol), NaH (60% in mineral oil, 0.2 g, 4.83 mmol) and *p*-chlorobenzoyl chloride (0.62 g, 3.54

mmol) afforded **59j** (0.87 g) in 91% yield as colorless crystalline solid.

mp = 113–114 °C. R_f = 0.43 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 7.6 Hz, 2H), 7.71 (bt, J = 7.2 Hz, 1H), 7.63 (bt, J = 7.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 3.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 138.6, 138.3, 134.0, 133.8, 133.7, 129.6, 128.2, 127.0, 44.2; IR (Neat) ν_{max} 3020, 1630, 1398, 1329, 1283, 1221 cm^{-1}; MS (EI) *m/z* (%) 296 (M^++3, 78), 294 (M^++1, 100), 156 (54), 139 (21); Anal. calcd for $C_{14}H_{12}ClNO_2S$: C, 57.24; H, 4.12; N, 4.77. Found: C, 57.35; H, 4.18; N, 4.68.

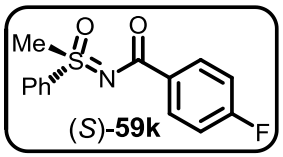
***N*-4-Fluorobenzoyl-*S*-methyl-*S*-phenylsulfoximine (59k):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 0.5 g, 3.22 mmol), NaH (60% in mineral oil, 0.2 g, 4.83 mmol) and *p*-fluorobenzoyl chloride (0.56 g, 3.54 mmol) afforded **59k** (0.81 g) in 90% yield as a colorless crystalline solid.

mp = 128–129 ^{o}C; R_f = 0.41 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 10.5, 5.6 Hz, 2H), 8.06 (d, J = 7.6 Hz, 2H), 7.71 (bt, J = 7.2 Hz, 1H), 7.63 (bt, J = 7.6 Hz, 2H), 7.08 (t, J = 8.6 Hz, 2H), 3.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 165.4 (d, J = 253.5 Hz), 138.8, 133.8, 131.8 (d, J = 9.1 Hz), 129.7, 127.1, 114.9 (d, J = 22.2 Hz), 44.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –205.00; IR (KBr) ν_{max} 3024, 2932, 1616, 1504, 1290, 1217 cm^{-1}; MS (EI) *m/z* (%) 279 (M^++2, 65), 278 (M^++1, 100), 156 (38), 123 (21); Anal. calcd for $C_{14}H_{12}FNO_2S$: C, 60.64; H, 4.36; N, 5.05. Found: C, 60.52; H, 4.31; N, 4.95.

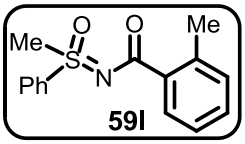
***(S)*-*N*-4-Fluorobenzoyl-*S*-methyl-*S*-phenylsulfoximine (*S*-59k):**



Following the general procedure (GP-2); reaction of (*S*)-*S*-methyl-*S*-phenylsulfoximine (***S*-58a,** 0.5 g, 32.2 mmol), NaH (60% in mineral oil, 0.2 g, 4.83 mmol) and *p*-fluorobenzoyl chloride (0.56 g, 35.4 mmol) afforded ***S*-59k** (0.87 g) in 97% yield with >99% ee (determined by chiral HPLC) as colorless solid. Optical rotation of (***S***)-**59k** (c = 0.007 in $CHCl_3$) was found; $[\alpha]_D$ = + 3.1 at 27 °C.

HPLC: cellulose-2 column [hexane/*i*-PrOH 60:40; 1.0 mL/min; 254 nm; (*S*)-**59K** t_R = 10.23 min (99.72); (*R*)-**59k** t_R = 15.87 min (0.28)].

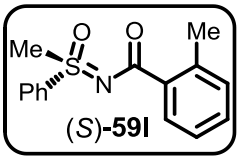
_N_-[2-Methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (59l):



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 5.0 g, 32.2 mmol), NaH (60% in mineral oil, 2.0 g, 48.3 mmol) and *o*-tolyl chloride (5.47 g, 35.4 mmol) afforded **59l** (8.1 g) in 92% yield as colorless solid.

mp = 108–109 °C; R_f = 0.56 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.01 (m, 3H), 7.66 (bt, *J* = 8.0 Hz, 1H), 7.59 (bt, *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 6.0 Hz, 1H), 7.25–7.16 (m, 2H), 3.41 (s, 3H), 2.59 (s, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 139.1, 138.8, 135.2, 133.6, 131.4, 130.8, 130.5, 129.6, 127.0, 125.3, 44.3, 21.6; IR (Neat) ν_{max} 3024, 1610, 1446, 1261 cm^{-1}; MS (EI) *m/z* (%) 274 (M^++1, 100), 156 (5); Anal. calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found: C, 65.71; H, 5.45; N, 5.23.

***(S)*-*N*-[2-Methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (*S*-59l):**

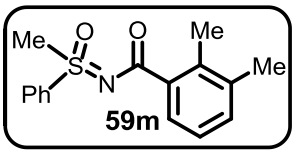


Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 2.0 g, 12.9 mmol), NaH (60% in mineral oil, 0.77 g, 19.4 mmol) and *o*-tolyl chloride (2.2 g, 14.2 mmol) afforded **59l** (2.9 g) in 82% yield with >98% ee (determined by chiral HPLC) as colorless solid.

Optical rotation of (***S***)-**59l** (c = 0.01 in $CHCl_3$) was found; $[\alpha]_D$ = + 6.6 at 27 °C.

HPLC: cellulose-2 column [hexane/*i*-PrOH 60:40; 1.0 mL/min; 254 nm; (*S*)-**59l** t_R = 12.47 min (99.03); (*R*)-**59l** t_R = 19.02 min (0.97)].

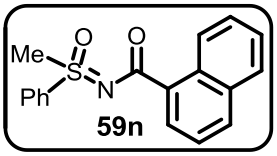
_N_-[2,3-Dimethylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (59m):



Following the general procedure (GP-4); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 0.49 g, 3.16 mmol), EDC.HCl (0.67 g, 3.47 mmol), DMAP (0.85 g, 6.95 mmol) and 2,3-dimethylbenzoic acid (0.50 g, 3.16 mmol) afforded **59m** (0.62 g) in 68% yield as colorless viscous oil.

R_f = 0.61 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.6 Hz, 2H), 7.78–7.67 (m, 2H), 7.63 (bt, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 3.45 (s, 3H), 2.46 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 138.8, 137.7, 136.9, 136.3, 133.7, 131.9, 129.7, 127.2, 127.1, 124.9, 44.4, 20.5, 16.6; IR (KBr) ν_{max} 3065, 2928, 1616, 1585, 1448, 1267 cm^{-1}; MS (EI) *m/z* (%) 288 (M^++1, 100), 156 (11); Anal. calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87.Found: C, 66.75; H, 6.03; N, 4.81.

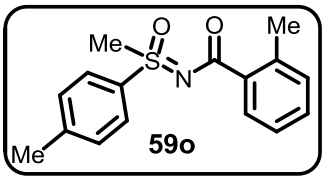
_N_-[_α_-Naptholoyl]-_S_-methyl-_S_-phenylsulfoximine (59n):



Following the general procedure (GP-4); reaction of *S*-methyl-*S*-phenylsulfoximine (**58a,** 0.8 g, 5.16 mmol), EDC.HCl (1.10 g, 5.68 mmol), DMAP (1.38 g, 11.35 mmol) and *α*-naphthoic acid (0.98 g, 5.68 mmol) afforded **59n** (0.76 g) in 49% yield as colorless viscous oil.

R_f = 0.43 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 7.2 Hz, 1H), 8.11 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.70 (bt, J = 7.2 Hz, 1H), 7.63 (bt, J = 7.4 Hz, 2H), 7.58–7.46 (m, 3H), 3.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 138.5, 133.6, 133.5, 132.6, 132.1, 131.0, 129.6, 129.5, 128.1, 126.9, 126.8, 126.2, 125.7, 124.3, 44.1; IR (Neat) ν_{max} 3057, 3013, 1628, 1508, 1404, 1284, 1249 cm^{-1}; MS (EI) *m/z* (%) 310 (M^++1, 100), 155 (19); Anal. calcd for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53. Found: C, 69.75; H, 4.81; N, 4.66.

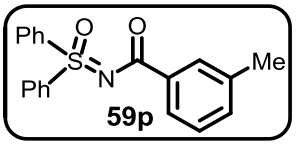
_N_-[2-(Methyl)-benzoyl]-_S_-methyl-_S_-4-(methyl)-phenyl sulfoximine (59o):



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-4-(methyl)-phenyl sulfoximine (**58b,** 0.5 g, 2.96 mmol), NaH (60% in mineral oil, 0.18 g, 4.44 mmol) and *o*-tolyl chloride (0.50 g, 3.25 mmol) afforded **59o (**815 mg) in 96% yield as colorless solid.

mp = 86–88 ^{o}C; R_f = 0.68 (2:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.25–7.18 (m, 2H), 3.42 (s, 3H), 2.60 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 144.7, 139.1, 135.8, 135.3, 131.4, 130.8, 130.4, 130.2, 127.0, 125.3, 44.5, 21.7, 21.5; IR (KBr) ν_{max} 3059, 3018, 2976, 2930, 1631, 1253 cm^{-1}; MS (EI) *m/z* (%) 288 (M^++1, 100), 170 (11), 119 (13); Anal. calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.79; H, 5.88; N, 4.75.

_N_-[3-(Methyl)-benzoyl]-_S,S_-diphenyl sulfoximine (59p):

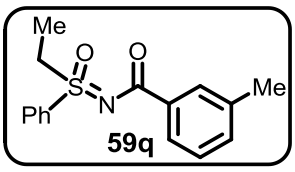


Following the general procedure (GP-2); reaction of *S,S*-diphenyl sulfoximine (**58c**, 1.0 g, 4.61 mmol), NaH (60% in mineral oil, 0.27 g, 6.9 mmol) and *m*-tolyl chloride (0.78 g, 5.07 mmol) afforded **59p** (1.25 g) in 81% yield as colorless solid.

mp = 137–139 ^{o}C; R_f = 0.48 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.02 (m, 6H), 7.63–7.51 (m, 6H), 7.36–7.28 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 139.9,

137.7, 135.7, 133.2, 133.0, 130.0, 129.5, 128.0, 127.6, 126.7, 21.4; IR (KBr) ν_{max} 3069, 2914, 1628, 1448, 1280 cm^{-1}; MS (EI) *m/z* (%) 336 (M^++1, 100), 218 (27), 111 (11); Anal. calcd for $C_{20}H_{17}NO_2S$: C, 71.62; H, 5.11; N, 4.18. Found: C, 71.48; H, 5.15; N, 4.07.

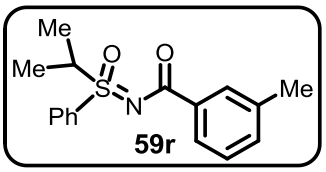
_N_-[3-(Methyl)-benzoyl]-_S_-ethyl-_S_-phenyl sulfoximine (59q):



Following the general procedure (GP-2); reaction of *S*-ethyl-*S*-phenyl sulfoximine (**58f,** 1.0 g, 5.9 mmol), NaH (60% in mineral oil, 0.341 g, 8.9 mmol) and *m*-tolyl chloride (1.0 g, 6.5 mmol) afforded **59q** (1.55 g) in 91% yield as colorless crystalline solid.

mp = 86–87 ºC; R_f = 0.50 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.97 (m, 4H), 7.68 (bt, *J* = 7.2 Hz, 1H), 7.60 (bt, *J* = 7.4 Hz, 2H), 7.37–7.27 (m, 2H), 3.61 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 1.31 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 137.7, 136.6, 135.6, 133.7, 132.9, 130.0, 129.6, 128.0, 127.9, 126.6, 50.6, 21.4, 7.3; IR (KBr) ν_{max} 3059, 2972, 1620, 1292, 1205 cm^{-1}; MS (EI) *m/z* (%) 288 (M^++1, 100), 170 (8), 91 (10); Anal. calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.98; H, 5.87; N, 4.75.

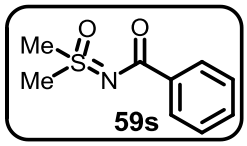
_N_-[3-(Methyl)-benzoyl]-_S_-_iso_-propyl-_S_-phenyl sulfoximine (59r):



Following the general procedure (GP-2); reaction of *S*-*iso*-propyl-*S*-phenyl sulfoximine (**58g,** 1.0 g, 5.46 mmol), NaH (60% in mineral oil, 0.33 g, 8.19 mmol) and *m*-tolyl chloride (0.92 g, 6.0 mmol) afforded **59r** (1.5 g) in 91% yield as colorless crystalline solid.

mp = 82–84 °C; R_f = 0.54 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.96 (m, 2H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.63 (bt, *J* = 7.4 Hz, 1H), 7.55 (bt, *J* = 7.6 Hz, 2H), 7.32–7.25 (m, 2H), 3.79–3.68 (m, 1H), 2.38 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 137.6, 135.9, 134.6, 133.7, 132.8, 129.9, 129.4, 128.8, 127.9, 126.6, 56.3, 21.4, 15.8, 15.3; IR (KBr) ν_{max} 3086, 2995, 2862, 1628, 1448, 1211 cm^{-1}; MS (EI) *m/z* (%) 302 (M^++1, 100), 168 (11); Anal. Calcd. for $C_{17}H_{19}NO_2S$: C, 67.74; H, 6.35; N, 4.65. Found: C, 67.85; H, 6.23; N, 4.51.

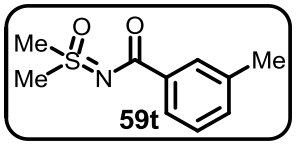
_N_-(Benzoyl)-_S,S_- dimethyl sulfoximine (59s):



Following the general procedure (GP-3); reaction of *S,S*-dimethyl sulfoximine (**58d**; 1.0 g, 10.7 mmol), Et_3N (1.63 g, 16.1 mmol) and benzoyl chloride (1.66 g, 11.8 mmol) afforded **59s** (1.82 g) in 86% yield as colorless solid.

mp = 106–108 °C; R_f = 0.52 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.6 Hz, 2H), 7.50 (bt, J = 6.8 Hz, 1H), 7.40 (bt, J = 7.4 Hz, 2H), 3.37 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 135.3, 132.1, 129.1, 128.0, 41.7; IR (Neat) ν_{max} 3026, 2926, 1608, 1572, 1452, 1292 cm^{-1}; MS (EI) *m/z* (%) 198 (M^++1, 100), 105 (11), 94(10). Anal. Calcd. for $C_{13}H_{20}O_4$: C, 54.80; H, 5.62; N, 7.10. Found: C, 54.68; H, 5.57; N, 7.31.

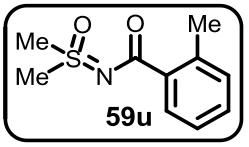
_N_-[3-(Methyl)-benzoyl]-_S,S_-dimethylsulfoximine (59t):



Following the general procedure (GP-3); reaction of *S,S*-dimethylsulfoximine (**58d**; 1.0 g, 10.7 mmol), Et_3N (1.36 g, 16.1 mmol) and *m*-tolyl chloride (1.82 g, 11.8 mmol) afforded **59t** (1.9 g) in 85% yield as colorless solid.

mp = 67–69 °C; R_f = 0.44 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (bs, 1H), 7.91 (bd, J = 8.0 Hz, 1H), 7.35–7.27 (m, 2H), 3.38 (s, 6H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 137.8, 135.3, 133.0, 129.8, 128.0, 126.4, 41.7, 21.3; IR (Neat) ν_{max} 3013, 2930, 1618, 1425, 1292 cm^{-1}; MS (EI) *m/z* (%) 212 (M^++1,100), 119 (27), 91 (19); Anal. Calcd. for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.91; H, 6.16; N, 6.75.

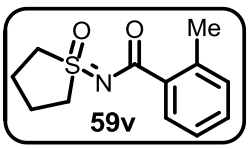
_N_-[2-(Methyl)-benzoyl]-_S,S_-dimethylsulfoximine (59u):



Following the general procedure (GP-2); reaction of *S,S*-dimethylsulfoximine (**58d**; 1.0 g, 10.7 mmol), NaH (60% in mineral oil, 0.64 g, 16.1 mmol) and *o*-tolyl chloride (1.85 g, 11.8 mmol) afforded **59u** (1.8 g) in 82% yield as pale yellow viscous oil.

R_f = 0.52 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.4 Hz, 1H), 7.30 (bt, J = 6.6 Hz, 1H), 7.17 (bt, J = 6.2 Hz, 2H), 3.32 (s, 6H), 2.57 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 138.6, 135.1, 131.3, 130.7, 130.1, 125.2, 41.5, 21.4; IR (Neat) ν_{max} 3020, 2966, 1622, 1216, 1026 cm^{-1}; MS (EI) *m/z* (%) 212 (M^++1,100), 119 (13), 91 (10); Anal. Calcd. for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.68; H, 6.29; N, 6.57.

_N_-[2-(Methyl)-benzoyl]-_S,S_-tetramethylenesulfoximine (59v):



Following the general procedure (GP-2); reaction of *S,S*-tetramethylenesulfoximine (**58e;** 0.5 g, 4.2 mmol), NaH (60% in mineral oil, 0.25 g, 6.3 mmol) and *o*-tolyl chloride (0.71 g, 4.62 mmol) afforded **59v** (0.81 g) in 81% yield as colorless crystalline solid.

mp = 72–73 °C; R_f = 0.44 (1:4 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.6 Hz, 1H), 7.34 (bt, J = 7.4 Hz, 1H), 7.21 (bt, J = 6.8 Hz, 2H), 3.76–3.66 (m, 2H), 3.42–3.32 (m, 2H), 2.63 (s, 3H), 2.44–2.28 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 139.0, 134.8, 131.5, 130.9, 130.5, 125.4, 52.7, 23.7, 21.7; IR (Neat) ν_{max} 3016, 2961, 1620, 1568, 1412, 1265 cm^{-1}; MS (EI) *m/z* (%) 238 (M^++1, 100), 161 (19), 119 (20); Anal. Calcd. for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found: C, 60.85; H, 6.31; N, 5.85.

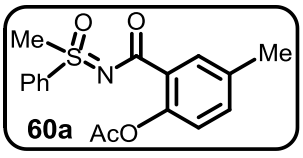
2.5.3.3. General Procedure for the Optimization of Reaction Conditions (GP-5):

N-Aroylated sulfoximine (**59**; 1.0 equiv), $Pd(OAc)_2$ (10 mol %), oxidant (2.0 equiv), and the solvents (~8.0 mL for 1.0 mmol of **59**) were introduced to the Schlenk tube in the presence of air. The reaction mixture was stirred at 100 °C for about 48 h. The reaction mixture was cooled to ambient temperature and the solvent was evaporated under reduced pressure.

2.5.3.4. General Procedure for C–H Oxidation Reaction (GP-6):

The C–H oxidation reactions were carried out in a 50 mL Schlenk tube with high pressure valve and side arm. The tube was charged with *N*-aroylated sulfoximine (**59a**–**v,** 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %), $K_2S_2O_8$ (540 mg, 2.0 mmol), AcOH (3.0 mL), and $CHCl_3$ (5.0 mL) in air. The reaction was stirred at 100 °C for 48 h. The reaction mixture was cooled to ambient temperature and the solvents were evaporated under reduced pressure. The crude material was purified using column chromatography on silica gel.

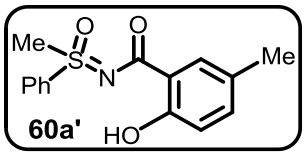
***N*-[2-Acetoxy-5-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (60a):**



Following the general procedure (GP-6); reaction of a mixture of *N*-[3-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**59a**; 273 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60a** (218 mg, 65%), **60a'** (13 mg, 4%) as colorless crystalline solids and **61a** (50 mg, 13%) as brown viscous oil.

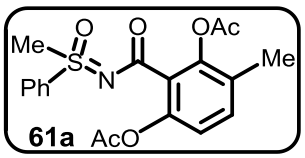
mp = 129–131 °C; R_f = 0.45 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 2H), 7.92 (s, 1H), 7.68 (bt, J = 8.0 Hz, 1H), 7.60 (bt, J = 6.0 Hz, 2H), 7.28 (bd, J = 8.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 3.42 (s, 3H), 2.36 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 170.2, 147.7, 138.5, 135.4, 133.8, 133.2, 132.1, 129.6, 128.1, 127.1, 123.0, 44.1, 21.1, 20.7; IR (Neat) ν_{max} 3027, 2924, 1765, 1637, 1217 cm^{-1}; MS (EI) *m/z* (%) 332 (M^++1, 100), 290 (94), 156 (39); Anal. Calcd. for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23. Found: C, 61.75; H, 5.08, N, 4.31.

_N_-[2-Hydroxy-5-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (60a'):



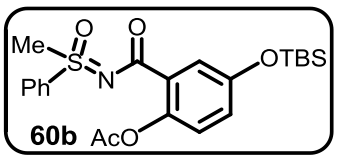
mp = 113–114 °C; R_f = 0.68 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.65 (s, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.87 (s, 1H), 7.68 (bt, J = 7.0 Hz, 1H), 7.60 (bt, J = 7.4 Hz, 2H), 7.19 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 3.43 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0, 159.8, 138.1, 135.8, 134.0, 130.7, 129.7, 127.5, 126.9, 117.0, 116.8, 44.6, 20.3; IR (Neat) ν_{max} 3022, 2928, 1631, 1568, 1225 cm^{-1}; MS (EI) *m/z* (%) 291 (M^++1, 90), 274 (24), 156 (100); Anal. calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.36; H, 5.28, N, 4.79.

_N_-[2,6-Diacetoxy-5-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (61a):



R_f = 0.36 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.6 Hz, 2H), 7.69 (bt, J = 7.4 Hz, 1H), 7.61 (bt, J = 7.6 Hz, 2H), 7.26 (d, J = 9.2 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.38 (s, 3H), 2.17 (s, 3H), 2.14 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 169.4, 168.7, 147.2, 146.7, 138.0, 133.9, 131.7, 129.6, 129.2, 127.3, 124.9, 120.5, 44.0, 20.8, 20.6, 16.0; IR (Neat) ν_{max} 3025, 2930, 1765, 1634, 1294, 1197 cm^{-1}; MS (EI) *m/z* (%) 390 (M^++1, 100), 348 (26), 198 (23), 173 (22), 156 (49); Anal. Calcd. for $C_{19}H_{19}NO_6S$: C, 58.60; H, 4.92; N, 3.60. Found: C, 58.45; H, 4.88, N, 3.51.

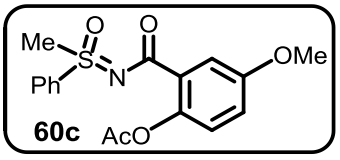
_N_-[2-Acetoxy-5-(*tert*-butyldiphenylsilyloxy)benzoyl]-_S_-methyl-_S_-phenylsulfoximine (60b):



Following the general procedure (GP-6); reaction of a mixture of *N*-[3-(*tert*-butyldiphenylsilyloxy)benzoyl]-*S*-methyl-*S*-phenyl sulfoximine (**59b**; 389 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60b** (210 mg, 47%) as pale brown viscous oil.

R_f = 0.48 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.6 Hz, 2H), 7.68 (t, J = 7.2 Hz, 1H), 7.65–7.55 (m, 3H), 6.95–6.87 (m, 2H), 3.43 (s, 3H), 2.16 (s, 3H), 0.98 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 170.3, 153.0, 144.0, 138.7, 133.9, 129.6, 129.3, 127.3, 124.1, 124.0, 122.6, 44.2, 25.7, 21.2, 18.2, –4.4; IR (KBr) ν_{max} 3069, 2932, 2858, 1763, 1635, 1489, 1307, 1269, 1221, 1184, 1099, 841 cm^{-1}; MS (EI) *m/z* (%) 448 (M^++1, 100); Anal. Calcd. for $C_{17}H_{17}NO_5S$: C, 59.03; H, 6.53; N, 3.13. Found: C, 59.15; H, 6.48; N, 3.18.

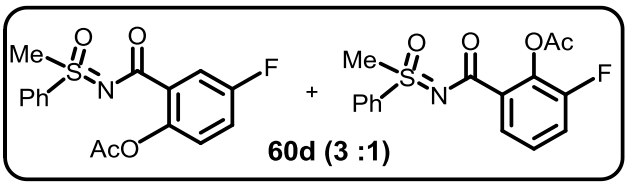
***N*-[2-Acetoxy-5-methoxybenzoyl]-*S*-methyl-*S*-phenylsulfoximine (60c):**



Following the general procedure (GP-6); reaction of a mixture of *N*-[3-methoybenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**59c**; 289 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol%) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60c** (183 mg, 53%) as pale brown viscous oil.

R_f = 0.45 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.6 Hz, 2H), 7.65–7.58 (m, 2H), 7.54 (bt, J = 7.4 Hz, 2H), 6.99–6.90 (m, 2H), 3.75 (s, 3H), 3.37 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 170.1, 156.6, 143.2, 138.1, 133.6, 129.4, 129.1, 126.8, 124.0, 118.1, 115.8, 55.4, 43.9, 20.8; IR (KBr) ν_{max} 3016, 2932, 1761, 1634, 1491 cm^{-1}; MS (EI) *m/z* (%) 348 (M^++1, 100), 306 (100), 197 (57), 156 (56); Anal. Calcd. for $C_{17}H_{17}NO_5S$: C, 58.78; H, 4.93; N, 4.03. Found: C, 58.67; H, 4.88; N, 4.12.

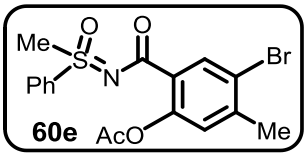
***N*-[2-Acetoxy-5-fluorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (60d):**



Following the general procedure (GP-6); reaction of a mixture of *N*-[3-fluorobenzoyl]-*S*-methyl-*S*-phenyl sulfoximine (**59d**; 277 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave in-separable mixture of regioisomers of **60d** (3:1, 0.162 g, 48%) as colorless crystalline solid.

R_f = 0.46 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–7.99 (m, 3H), 7.91–7.80 (m, 2H), 7.70 (t, J = 6.8 Hz, 2H), 7.63 (t, J = 7.6 Hz, 3H), 7.32–7.13 (m, 3H), 7.06–6.98 (m, 1H), 3.45 (s, 4H), 2.22 (s, 1H), 2.19 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 171.4, 170.0, 168.8, 159.6 (d, J = 244 Hz), 154.8 (d, J = 257 Hz), 145.9, 138.4, 138.3, 134.0, 131.0, 130.1 (d, J = 6.0 Hz), 129.7, 127.1, 126.6, 125.9 (d, J = 8 Hz), 124.8 (d, J = 8.0 Hz), 119.4, 119.3, 119.2, 118.4, 118.2, 44.1, 21.0, 20.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ 213.77; IR (Neat) ν_{max} 2934, 1757, 1630, 1585, 1211 cm^{-1}; Anal. Calcd. for $C_{16}H_{14}FNO_4S$: C, 57.30; H, 4.21; N, 4.18. Found: C, 57.18; H, 4.27; N, 4.23.

***N*-[2-Acetoxy-5-bromo-4-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (60e):**

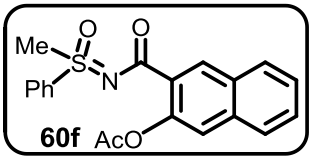


Following the general procedure (GP-6); reaction of a mixture of *N*-[3-bromo-4-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**59e**; 200 mg, 0.57 mmol), $Pd(OAc)_2$ (12.7 mg, 10 mol %) and $K_2S_2O_8$

(307 mg, 1.14 mmol) in AcOH (2.0 mL) and $CHCl_3$ (3.0 mL) was heated at 120 ^oC for 96 h and gave **60e** (63 mg, 27%) as brown solid.

mp = 140–141 ^oC; R_f = 0.70 (3:7 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.67 (bt, *J* = 7.0 Hz, 1H), 7.60 (bt, *J* = 7.4 Hz, 2H), 6.92 (s, 1H), 3.41 (s, 3H), 2.39 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 169.9, 149.1, 143.3, 138.4, 135.4, 134.0, 129.7, 127.6, 127.2, 125.6, 121.2, 44.3, 23.0, 21.1; IR (Neat) ν_{max} 2978, 1761, 1633, 1226 cm^{-1}; MS (EI) *m/z* (%) 412 (M^++2, 70), 410 (62), 370 (98), 368 (100), 156 (22); Anal. Calcd. for $C_{17}H_{16}BrNO_4S$: C, 49.77; H, 3.93;N, 3.41.Found: C, 49.58; H, 3.86; N, 3.51.

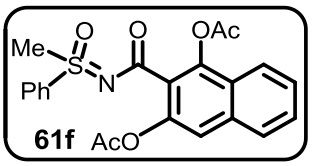
***N*-[3-Acetoxy-β-naptholoyl]-*S*-methyl-*S*-phenylsulfoximine (60f):**



Following the general procedure (GP-6); reaction of a mixture of *N*-β-naptholoyl-*S*-methyl-*S*-phenyl sulfoximine (**59f**; 309 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60f** (205 mg, 56%) as yellowish semi-solid and **61f** (63 mg, 15%) as pale brown viscous oil.

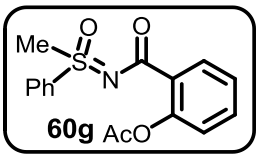
R_f = 0.46 (3:7 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.07 (d, *J* = 7.2 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.69 (bt, *J* = 7.4 Hz, 1H), 7.62 (bt, *J* = 7.4 Hz , 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.53–7.45 (m, 2H), 3.47 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 170.4, 146.8, 138.6, 135.2, 133.8, 133.3, 130.7, 129.6, 128.9, 128.2, 127.5, 127.2, 127.1, 126.1, 120.5, 44.2, 21.2; IR (Neat) ν_{max} 3059, 2932, 1761, 1633, 1211cm^{-1}; MS (EI) *m/z* (%) 368 (M^++1, 62), 326 (100), 214 (27), 213 (40), 198 (29, 171(56), 156 (32), 115 (25), 65 (12); Anal. Calcd. for $C_{20}H_{17}NO_4S$: C, 65.38; H, 4.66; N, 3.81.Found: C, 65.48; H, 4.61; N, 3.75.

***N*-[1,3-Diacetoxy-β-naptholoyl]-*S*-methyl-*S*-phenylsulfoximine (61f):**



R_f = 0.34 (3:7 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.71 (bt, *J* = 7.2 Hz, 1H), 7.62 (bt, *J* = 7.6 Hz , 2H), 7.59–7.49 (m, 2H), 7.50 (s, 1H), 3.44 (s, 3H), 2.29 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 169.5, 169.1, 146.0, 145.3, 138.2, 134.0, 133.9, 129.6, 128.1, 127.6, 127.4, 126.7, 125.6, 122.8, 122.4, 118.5, 44.0, 21.0, 20.9; IR (Neat) ν_{max} 2928, 1770, 1637, 1367, 1292, 1226 cm^{-1}; MS (EI) *m/z* (%) 426 (M^++1, 65), 384 (29), 353 (18), 219 (39), 198 (86), 187 (14), 156 (100); Anal. calcd for $C_{22}H_{19}NO_6S$: C, 62.11; H, 4.50; N, 3.29. Found: C, 62.25; H, 4.55; N, 3.36.

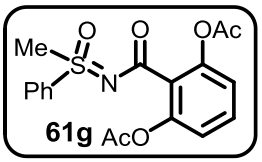
***N*-[2-Acetoxybenzoyl]-*S*-methyl-*S*-phenylsulfoximine (60g):**



Following the general procedure (GP-6); reaction of a mixture of *N*-benzoyl-*S*-methyl-*S*-phenylsulfoximine (**59g**; 259 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60g** (172 mg, 54%) as colorless crystalline solid and **61g** (45 mg, 12%) as brown viscous oil.

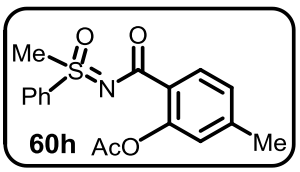
mp = 81–82 ^{o}C; R_f = 0.54 (7:13 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.64 (bt, J = 7.4 Hz, 1H), 7.57 (bt, J = 7.4 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 3.39 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 169.8, 149.8, 138.3, 133.7, 132.5, 131.7, 129.5, 128.6, 127.0, 125.5, 123.2, 44.0, 21.0; IR (Neat) ν_{max} 3024, 1749, 1633, 1479 cm^{-1}; MS (EI) *m/z* (%) 318 (M^++1, 94), 276 (100), 196 (18), 173 (9), 156 (73); Anal. calcd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41. Found: C, 60.32; H, 4.82; N, 4.51.

***N*-[2,6-Diacetoxybenzoyl]-*S*-methyl-*S*-phenylsulfoximine (61g):**



R_f = 0.32 (7:13 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 2H), 7.70 (bt, J = 7.2 Hz, 1H), 7.61 (bt, J = 7.6 Hz, 2H), 7.40 (t, J = 8.2 Hz, 1H), 7.01 (d, J = 8.0 Hz, 2H), 3.39 (s, 3H), 2.14 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 169.2, 148.9, 138.1, 134.0, 130.2, 129.6, 127.3, 125.1, 120.7, 44.0, 20.9; IR (Neat) ν_{max} 3025, 2930, 1768, 1633, 1460, 1294 cm^{-1}; MS (EI) *m/z* (%) 374 (M^+–1, 46), 360 (20), 318 (100), 276 (17), 256 (24); Anal. Calcd. for $C_{18}H_{17}NO_6S$: C, 57.59; H, 4.56; N, 3.73. Found: C, 57.48; H, 4.51; N, 3.65.

***N*-[2-Acetoxy-4-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (60h):**

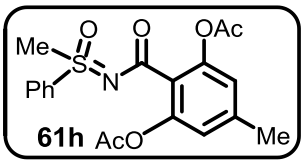


Following the general procedure (GP-6); reaction of a mixture of *N*-[4-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**59h**; 273 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60h** (189 mg, 57%) as pale yellow viscous oil and **61h** (125 mg, 32%) as brown viscous oil.

R_f = 0.57 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.6 Hz, 2H), 7.92 (s, 1H), 7.67 (bt, J = 7.2 Hz, 1H), 7.60 (bt, J = 7.4 Hz, 2H), 7.28 (d, J = 7.2 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.42 (s, 3H), 2.36 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 170.2, 147.8, 138.6, 135.4, 133.9, 133.3, 132.1, 129.7, 128.3, 127.2, 123.1, 44.2, 21.2, 20.8; IR (Neat) ν_{max} 3023, 2930,

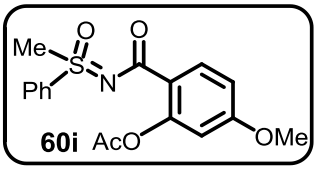
1765, 1630, 1219 cm^{-1}; MS (EI) *m/z* (%) 332 (M^++1, 100), 290 (85), 156 (63); Anal. Calcd. for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23. Found: C, 61.55; H, 5.08; N, 4.32.

_N_-[2,6-Diacetoxy-4-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (61h):



R_f = 0.47 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.65 (bt, *J* = 7.0 Hz, 1H), 7.57 (bt, *J* = 7.4 Hz, 2H), 6.79 (s, 2H), 3.36 (s, 3H), 2.32 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 169.2, 148.8, 141.2, 138.1, 133.8, 129.4, 127.2, 122.0, 121.3, 43.8, 21.1, 20.7; IR (Neat) ν_{max} 3025, 2932, 1757, 1634, 1367 cm^{-1}; MS (EI) *m/z* (%) 390 (M^++1, 100), 348 (19), 306 (25), 156 (89); Anal. Calcd. for $C_{19}H_{19}NO_6S$: C, 58.60; H, 4.92; N, 3.60. Found: C, 58.75; H, 4.88; N, 3.56.

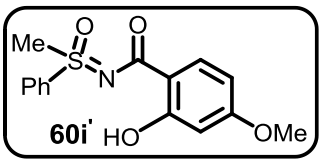
_N_-[2-Acetoxy-4-methoxybenzoyl]-_S_-methyl-_S_-phenylsulfoximine (60i):



Following the general procedure (GP-6); reaction of a mixture of *N*-[4-methoxybenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**59i**; 289 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60i** (148 mg, 43%) as colorless crystalline solid, **60i'** (24 mg, 8%) as colorless crystalline solid and **61i** (124 mg, 31%) as yellow viscous oil.

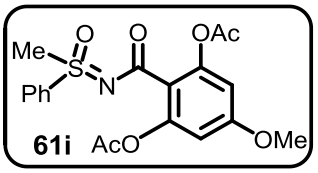
mp = 91–92 °C; R_f = 0.40 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.8 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 2H), 7.63 (bt, *J* = 7.4 Hz, 1H), 7.56 (bt, *J* = 7.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.54 (s, 1H), 3.79 (s, 3H), 3.38 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 169.7, 163.0, 151.8, 138.7, 133.6, 133.5, 129.4, 127.0, 120.7, 111.2, 108.6, 55.4, 44.1, 21.1; IR (KBr) ν_{max} 3017, 2932, 1766, 1614, 1221, 1153 cm^{-1}; MS (EI) *m/z* (%) 348 (M^++1, 100), 306 (91), 156 (42); Anal. Calcd. for $C_{17}H_{17}NO_5S$: C, 58.78; H, 4.93; N, 4.03. Found: C, 58.63; H, 4.88; N, 4.12.

_N_-[2-Hydroxy-4-methoxybenzoyl]-_S_-methyl-_S_-phenylsulfoximine (60i'):



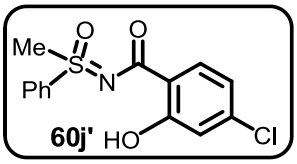
mp = 139–140 °C. R_f = 0.37 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.11 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.70 (bt, *J* = 7.2 Hz, 1H), 7.62 (bt, *J* = 7.8 Hz, 2H), 6.45–6.37 (m, 2H), 3.80 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 165.1, 164.2, 138.5, 134.0, 132.5, 129.8, 127.0, 110.7, 106.7, 100.5, 55.4, 44.8; IR (KBr) ν_{max} 3450, 3016, 2924, 1633, 1589, 1217 cm^{-1}; MS (EI) *m/z* (%) 306 (M^++1, 100), 208 (19), 157(43), 111 (53), 97 (48); Anal. Calcd. for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59. Found: C, 59.21; H, 4.88; N, 4.51.

_N_-[2,6-Diacetoxy-4-methoxybenzoyl]-_S_-methyl-_S_-phenyl sulfoximine (61i) :



R_f = 0.28 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 2H), 7.65 (bt, J = 7.2 Hz, 1H), 7.56 (bt, J = 7.6 Hz, 2H), 6.50 (s, 2H), 3.76 (s, 3H), 3.36 (s, 3H), 2.08 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 169.0, 160.9, 150.5, 138.2, 133.8, 129.4, 127.2, 117.4, 106.8, 55.6, 43.8, 20.8; IR (Neat) ν_{max} 3020, 2932, 1769, 1623, 1367 cm^{-1}; MS (EI) *m/z* (%) 406 (M^++1, 92), 364 (11), 329 (17), 199 (100), 156 (61), 97 (67); Anal. Calcd. for $C_{19}H_{19}NO_7S$: C, 56.29; H, 4.72; N, 3.45. Found: C, 56.38; H, 4.68; N, 3.41.

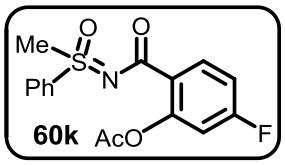
_N_-[2-Hydroxy-4-chlorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (60j'):



Following the general procedure (GP-6); reaction of a mixture of *N*-[4-chlorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**59j**; 293 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60j'** (124 mg, 40%) as colorless crystalline solid.

mp = 118–119 ^{o}C; R_f = 0.46 (2:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.97 (s, 1H), 8.07–7.98 (m, 3H), 7.74 (bt, J = 7.2 Hz, 1H), 7.66 (bt, J = 7.4 Hz, 2H), 6.94 (s, 1H), 6.83 (bd, J = 8.4 Hz, 2H), 3.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 162.6, 140.4, 138.0, 134.3, 132.1, 129.9, 127.1, 127.0, 119.1, 117.5, 116.0, 44.7; IR (Neat) ν_{max} 3021, 2926, 1624, 1579 cm^{-1}; MS (EI) *m/z* (%) 312 (M^++3, 16), 310 (M^++1, 42), 156 (35), 97 (100); Anal. Calcd. for $C_{14}H_{12}ClNO_3S$: C, 54.28; H, 3.90; N, 4.52. Found: C, 54.38; H, 3.85; N, 4.61.

_N_-[2-Acetoxy-4-fluorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (60k):

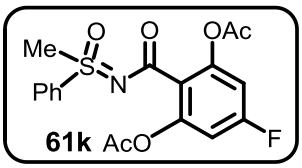


Following the general procedure (GP-6); reaction of a mixture of *N*-[4-fluorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**59k**; 277 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60k** (152 mg, 45%) as colorless crystalline solid and **61k** (33 mg, 8%) as pale brown viscous oil.

mp = 116–117 ^{o}C; R_f = 0.50 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, J = 9.4, 8.8 Hz, 1H), 8.03 (d, J = 7.4 Hz, 2H), 7.70 (bt, J = 7.4 Hz, 1H), 7.62 (bt, J = 7.6 Hz, 2H), 6.99 (td, J = 8.4, 2.1 Hz, 1H), 6.80 (dd, J = 9.0, 2.6 Hz, 1H), 3.44 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 169.6, 164.7 (d, J = 256 Hz), 151.7 (d, J = 11 Hz), 138.6, 134.0–133.7 (m), 129.7, 127.2, 125.0, 112.8 (d, J = 20 Hz), 111.2 (d, J = 24 Hz), 44.2, 21.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –203.13;

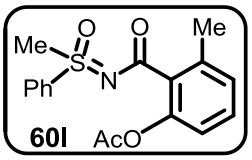
IR (Neat) ν_{max} 3069, 1772, 1635, 1211, 1136 cm^{-1}; MS (EI) *m/z* (%) 336 (M^++1, 100), 294 (44), 198 (18), 197 (53), 156 (47); Anal. Calcd. for $C_{16}H_{14}FNO_4S$: C, 57.30; H, 4.21; N, 4.18. Found: C, 57.21; H, 4.28; N, 4.25.

***N*-[2,6-Diacetoxy-4-fluorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (61k):**



R_f = 0.37 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.70 (bt, *J* = 7.4 Hz, 1H), 7.61 (bt, *J* = 7.6 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 3.40 (s, 3H), 2.13 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 168.8, 162.5 (d, *J* = 252 Hz), 150.1 (d, *J* = 13 Hz), 138.1, 134.1, 129.7, 127.3, 109.0 (d, *J* = 23), 44.0, 20.9; IR (Neat) ν_{max} 2926, 1774, 1620, 1224 cm^{-1}; MS (EI) *m/z* (%) 394 (M^++1, 88), 352 (20), 310 (16), 239 (39), 198 (100), 197 (100), 156 (100); Anal. Calcd. for $C_{18}H_{16}FNO_6S$: C, 54.96; H, 4.10; N, 3.56. Found: C, 54.85; H, 4.06; N, 3.48.

***N*-[2-Acetoxy-6-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (60l):**

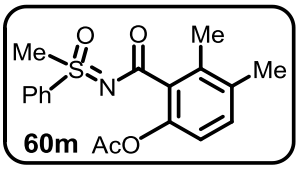


Following the general procedure (GP-6); reaction of a mixture of *N*-[2-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**59l**; 273 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol%) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60l** (314 mg, 95%) as yellow crystalline solid.

Gram scale synthesis of this reaction was performed using *N*-[2-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**59l**; 2.0 g, 7.3 mmol), $Pd(OAc)_2$ (164 mg, 10 mol%) and $K_2S_2O_8$ (3.94 g, 14.6 mmol) in AcOH (15 mL) and $CHCl_3$ (30 mL) gave **60l** (2.02 g, 83%) as colorless crystalline solid.

mp = 108–110 ^{o}C; R_f = 0.36 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.6 Hz, 2H), 7.72 (bt, *J* = 7.2 Hz, 1H), 7.65 (bt, *J* = 7.4 Hz, 2H), 7.26 (bs, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 3.44 (s, 3H), 2.47 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 169.3, 147.4, 138.3, 136.7, 133.8, 131.8, 129.5, 129.1, 127.9, 127.0, 120.1, 44.2, 20.8, 19.6; IR (Neat) ν_{max} 3271, 1738, 1466, 1369, 1230, 1014 cm^{-1}; MS (EI) *m/z* (%) 332 (M^++1, 100), 290 (16), 173 (24), 156 (43), 97 (13); Anal. Calcd. for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23. Found: C, 61.72; H, 5.08; N, 4.27.

***N*-[2-Acetoxy-5,6-dimethyl)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (60m):**

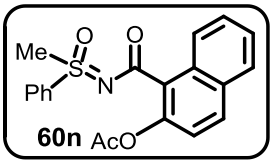


Following the general procedure (GP-6); reaction of a mixture of *N*-[2,3-dimethyl-benzoyl]-*S*-methyl-*S*-phenylsulfoximine (**59m**;

287 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60m** (286 mg, 83%) as pale brown crystalline solid.

mp = 160–162 °C; R_f = 0.52 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.6 Hz, 2H), 7.69 (bt, J = 7.4 Hz, 1H), 7.61 (bt, J = 7.6 Hz, 2H), 7.12 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 3.40 (s, 3H), 2.29 (s, 3H), 2.24 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 169.7, 145.3, 138.5, 135.0, 134.4, 134.0, 132.3, 130.4, 129.7, 127.2, 119.8, 44.4, 21.0, 19.8, 16.7; IR (Neat) ν_{max} 3009, 2926, 1761, 1635, 1288, 1176, 1738, 1510, 1367, 1230, 1051 cm^{-1}; MS (EI) *m/z* (%) 345 (M, 100), 214 (27), 173 (27), 156 (57), 149 (19), 136 (13); Anal. Calcd. for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.46; H, 5.51; N, 4.15.

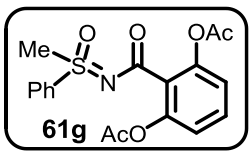
_N_-[2-Acetoxy-_α_-naptholoyl]-_S_-methyl-_S_-phenylsulfoximine (60n):



Following the general procedure (GP-6); reaction of a mixture of *N*-*α*-naptholoyl-*S*-methyl-*S*-phenylsulfoximine (**59n**; 309 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60n** (241 mg, 65%) as colorless crystalline solid.

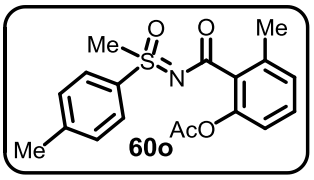
mp = 147–148 °C; R_f = 0.43 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 7.6 Hz, 2H), 7.91–7.82 (m, 2H), 7.72 (bt, J = 7.2 Hz, 1H), 7.65 (bt, J = 7.6 Hz, 2H), 7.56–7.44 (m, 2H), 7.29–7.24 (m, 2H), 3.48 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 169.6, 145.4, 138.4. 134.0, 131.7, 130.7, 130.4, 129.8, 128.1, 127.6, 127.3, 127.2, 125.9, 125.5, 121.7, 44.5, 21.0; IR (Neat) ν_{max} 3063, 2930, 1770, 1633, 1510 cm^{-1}; MS (EI) *m/z* (%) 368 (M^++1, 84), 198 (38), 173 (22), 171 (26), 158 (57), 156 (100), 115 (10); Anal. Calcd. for $C_{20}H_{17}NO_4S$: C, 65.38; H, 4.66; N, 3.81. Found: C, 65.26; H, 4.61; N, 3.91.

_N_-[2,6-Diacetoxybenzoyl]-_S_-methyl-_S_-phenylsulfoximine (61g):



Following the general procedure (GP-6); reaction of a mixture of *N*-[2-acetoxybenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**60g**; 317 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **61g** (160 mg, 43%) as brown viscous oil. Analytical data exactly matching with the compound **61g** reported previously**.**

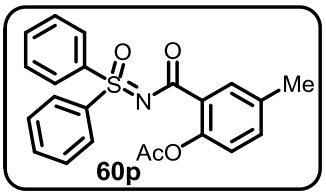
_N_-[2-Acetoxy-6-methylbenzoyl]-_S_-methyl-_S_-4-(methyl)phenylsulfoximine (60o):



Following the general procedure (GP-6); reaction of a mixture of *N*-[2-methylbenzoyl]-*S*-methyl-*S*-4-(methyl)phenylsulfoximine (**59o**; 287 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %), and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60o** (286 mg, 83%) as pale brown solid.

mp = 131–132 °C; R_f = 0.41 (2:3 hexane/EtOAc): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 7.6 Hz, 2H), 7.20 (bt, J = 7.4 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 3.34 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 169.3, 147.3, 144.9, 136.5, 135.0, 131.8, 130.1, 128.9, 127.7, 126.9, 120.0, 44.2, 21.4, 20.7, 19.5; IR (Neat) ν_{max} 3017, 2918, 1763, 1649, 1282, 1199 cm^{-1}; MS (EI) *m/z* (%) 346 (M^++1, 100), 304 (10), 167 (11), 170 (38); Anal. Calcd. for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06; Found: C, 62.45; H, 5.48; N, 4.12.

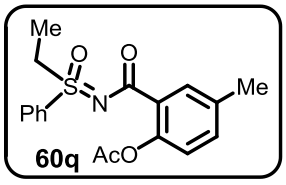
_N_-[2-Acetoxy-5-methylbenzoyl]-_S,S_-diphenylsulfoximine (60p):



Following the general procedure (GP-6); reaction of a mixture of *N*-[3-methylbenzoyl]-*S,S*-diphenylsulfoximine (**59p;** 335 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %), and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) afforded **60p** (77 mg, 20%) as colorless solid.

mp = 155–156 °C; R_f = 0.33 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.6 Hz, 4H), 7.95 (s, 1H), 7.58–7.51 (m, 6H), 7.29 (bd, J = 8.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 2.38 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 170.3, 147.7, 139.5, 135.4, 133.2, 133.1, 132.0, 129.5, 128.7, 127.6, 123.1, 21.1, 20.8; IR (Neat) ν_{max} 3065, 1765, 1633, 1101 cm^{-1}; MS (EI) *m/z* (%) 394 (M^++1, 100), 352 (83), 260 (14), 235 (29), 218 (93), 203 (20); Anal. Calcd. for $C_{22}H_{19}NO_4S$: C, 67.16; H, 4.87; N, 3.56. Found: C, 67.22; H, 4.81; N, 3.48.

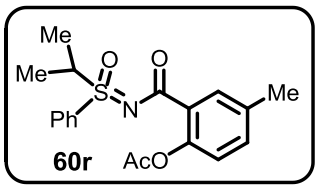
_N_-[2-Acetoxy-5-methylbenzoyl]-_S_-ethyl-_S_-phenylsulfoximine (60q):



Following the general procedure (GP-6); reaction of a mixture of *N*-[3-methylbenzoyl]-*S*-ethyl-*S*-phenylsulfoximine (**59q**; 287 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %), $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60q** (224 mg, 65%) as colorless crystalline solid.

mp = 114–116 °C; R_f = 0.31 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 2H), 7.93 (s, 1H), 7.68 (bt, J = 7.6 Hz, 1H), 7.60 (bt, J = 7.6 Hz, 2H), 7.27 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 3.65–3.50 (m, 2H), 2.37 (s, 3H), 2.16 (s, 3H), 1.28 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 170.2, 147.8, 136.2, 135.4, 133.8, 133.2, 132.2, 129.5, 128.5, 128.1, 123.1, 50.5, 21.2, 20.9, 7.1; IR (Neat) ν_{max} 2935, 1755, 1626, 1267, 1195 cm^{-1}; MS (EI) *m/z* (%) 346 (M^++1, 100), 304 (45), 170 (21), 79 (10); Anal. Calcd. for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.45; H, 5.51; N, 4.15.

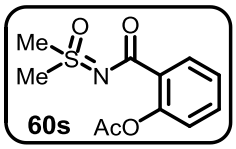
_N_-[2-Acetoxy-5-methylbenzoyl]-_S_-_iso_-propyl-_S_-phenylsulfoximine (60r):



Following the general procedure (GP-6); reaction of a mixture of *N*-[3-methylbenzoyl]-*S*-*iso*-propyl-*S*-phenylsulfoximine (**59r**; 301 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %), $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60r** (169 mg, 47%) as light brown solid.

mp = 130–131 °C; R_f = 0.38 (3:2 hexane/EtOAc): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.91 (m, 3H), 7.67 (bt, J = 7.4 Hz,1H), 7.60 (bt, J = 7.6 Hz, 2H), 7.27 (bd, J = 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz,1H), 3.84–3.70 (m, 1H), 2.38 (s, 3H), 2.14 (s, 3H), 1.44 (d, J = 6.8 Hz, 3H), 1.28 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 170.2, 147.8, 135.3, 134.3, 133.6, 133.0, 132.1, 129.3, 129.0, 128.7, 123.0, 56.2, 21.2, 20.9, 15.8, 15.3; IR (Neat) ν_{max} 2922, 1766, 1633, 1305, 1211 cm^{-1}; MS (EI) *m/z* (%) 360 (M^++1, 100), 318 (59), 184 (16), 152 (13); Anal. Calcd. for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90; Found: C, 63.59; H, 5.84; N, 3.83.

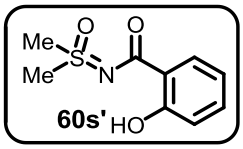
_N_-[2-Acetoxybenzoyl]-_S,S_-dimethylsulfoximine (60s):



Following the general procedure (GP-6); reaction of a mixture of *N*-benzoyl-*S*,*S*-dimethylsulfoximine (**59s**; 197 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %), and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60s** (108 mg, 42%) as pale yellow solid and **60s'** (26 mg, 12%) as pale yellow semi-solid.

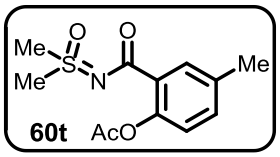
R_f = 0.48 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 6.8 Hz, 1H), 7.46 (bt, J = 7.2 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 3.29 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 169.9, 149.8, 132.6, 131.6, 128.3, 125.6, 123.2, 41.3, 21.2; IR (Neat) ν_{max} 3483, 2932, 1753, 1624, 1448, 1307, 1028 cm^{-1}; MS (EI) *m/z* (%) 256 (M^++1, 73), 214 (100), 94 (7); Anal. Calcd. for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.62; H, 5.18; N, 5.41.

_N_-[2-Hydroxybenzoyl]-_S,S_-dimethylsulfoximine (60s'):



R_f = 0.65 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.88 (bs, 1H, –OH), 7.98 (d, J = 7.6 Hz, 1H), 7.39 (bt, J = 7.2 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.83 (t, J = 7.4 Hz, 1H), 3.41 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 162.0, 135.0, 131.0, 118.6, 117.5, 117.2, 42.1; IR (Neat) ν_{max} 3022, 2930, 1628, 1483, 1163 cm^{-1}; MS (EI) *m/z* (%) 212 (M^+–1, 87), 198 (100), 183 (5); Anal. Calcd. for $C_9H_{11}NO_3S$: C, 50.69; H, 5.20; N, 6.57; Found: C, 50.48; H, 5.31; N, 6.48.

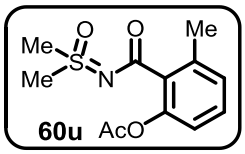
_N_-[2-Acetoxy-5-methylbenzoyl]-_S,S_-dimethylsulfoximine (60t):



Following the general procedure (GP-6); reaction of a mixture of *N*-[3-methylbenzoyl]-*S,S*-dimethylsulfoximine (**59t**; 100 mg, 0.47 mmol), $Pd(OAc)_2$ (10.62 mg, 10 mol %), and $K_2S_2O_8$ (255 mg, 0.94 mmol) in AcOH (1.0 mL) and $CHCl_3$ (3.0 mL) gave **60t** (96 mg, 75%) as brown viscous oil.

R_f = 0.31 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.26 (d, J = 7.2 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 3.31 (s, 6H), 2.34 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 170.2, 147.7, 135.4, 133.3, 132.0, 127.8, 122.9, 41.4, 21.2, 20.6; IR (Neat) ν_{max} 3022, 2930, 1761, 1626, 1491, 1221 cm^{-1}; MS (EI) *m/z* (%) 270 (M^++1, 96), 228 (100), 157 (22), 135 (15), 111(22), 94 (22), 79 (33); Anal. Calcd. for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20. Found: C, 53.42; H, 5.68; N, 5.31.

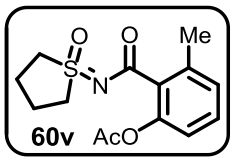
_N_-[2-Acetoxy-6-methylbenzoyl]-_S,S_-dimethylsulfoximine(60u):



Following the general procedure (GP-6); reaction of a mixture of *N*-[2-methylbenzoyl]-*S,S*-dimethylsulfoximine (**59u**; 211 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %), and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave **60u** (165 mg, 61%) as colorless solid.

mp = 118–120 °C; R_f = 0.29 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (bt, J = 7.8 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 3.29 (s, 6H), 2.39 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 169.3, 147.3, 136.5, 131.7, 129.1, 127.9, 120.0, 41.6, 20.9, 19.5; IR (Neat) ν_{max} 3022, 2930, 1766, 1608, 1462, 1369 cm^{-1}; MS (EI) *m/z* (%) 270 (M^++1, 45), 228 (14), 177 (11), 167 (10), 135 (100); Anal. Calcd. for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20. Found: C, 53.41; H, 5.58; N, 5.31.

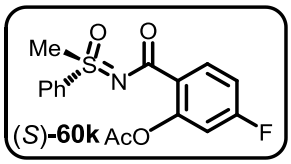
***N*-[2-Acetoxy-6-methylbenzoyl]-*S*,*S*-tetramethylenesulfoximine (60v):**



Following the general procedure (GP-6); reaction of a mixture of *N*-[2-methylbenzoyl]-*S*,*S*-tetramethylenesulfoximine (**59v**; 237 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %), and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) afforded **60v** (250 mg, 85%) as pale brown solid.

mp = 97–98 °C; R_f = 0.3 (1:4 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.21 (m, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.73–3.62 (m, 2H), 3.41–3.30 (m, 2H), 2.43 (s, 3H), 2.41–2.29 (m, 4H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 169.4, 147.4, 136.6, 131.3, 129.2, 127.9, 120.0, 52.7, 23.5, 20.9, 19.5; IR (Neat) ν_{max} 3007, 2953, 1766, 1612, 1464, 1304, 1205 cm^{-1}; MS (EI) *m/z* (%) 296 (M^++1, 100), 254 (18), 135 (29), 120 (18), 105 (10); Anal. Calcd. for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.78; H, 5.88; N, 4.65.

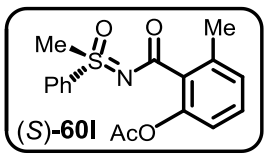
***(S)*-*N*-[2-Acetoxy-4-fluorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-60k]:**



Following the general procedure (GP-6); reaction of a mixture of (*S*)-*N*-[4-fluorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine **[**(*S*)-**59k**; 277 mg, 1.0 mmol], $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave (*S*)-**60k** (144 mg, 43%) as colorless crystalline solid with >99% ee (determined by chiral HPLC) as colorless oil. Optical rotation of (***S***)-**60k** (c = 0.007 in $CHCl_3$) was found; $[\alpha]_D = +29.5$ at 27 °C and a minor amount of diacetoxylation (*S*)-**61k** is observed.

HPLC: cellulose-2 column [hexane/*i*-PrOH 60:40; 1.0 mL/min; 254 nm; (*S*)-**60k** t_R= 12.50 min (99.89); (*R*)-**60k** t_R= 18.04 min (0.11)].

***(S)*-*N*-[2-Acetoxy-6-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-60l]:**



Following the general procedure (GP-6); reaction of a mixture of ***(S)*-*N*-**[2-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (*S*-**59l**; 273 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 10 mol %) and $K_2S_2O_8$ (540 mg, 2.0 mmol) in AcOH (3.0 mL) and $CHCl_3$ (5.0 mL) gave (*S*)-**60l** (295 mg, 89%) with 99% ee (determined by chiral HPLC) as colorless crystalline solid.

Gram scale synthesis of this reaction was performed using *(S)-N*-[2-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (*S*-**59l**; 2.0 g, 7.3 mmol), $Pd(OAc)_2$ (164 mg, 10 mol%) and

$K_2S_2O_8$ (3.9 g, 14.6 mmol) in AcOH (15 mL) and $CHCl_3$ (30 mL) gave (*S*)-**60l** (2.1 g, 87%) with >99% ee (determined by chiral HPLC) as colorless crystalline solid.

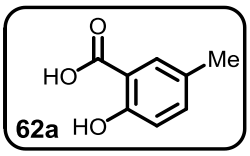
Optical rotation of (***S***)-**60l** (c = 0.01 in $CHCl_3$) was found; $[\alpha]_D = +23.7$ at 27 °C.

HPLC: cellulose-2 column [hexane/*i*-PrOH 60:40; 1.0 mL/min; 254 nm; (*S*)-**60l** $t_R = 20.87$ min (99.87); (*R*)-**60l** $t_R = 29.37$ min (0.13)].

2.5.3.5. General Procedure for the Hydrolysis of *N*-Aroylated Sulfoximines (60); (GP-7):

Compound **60a** (0.2–1.0 mmol) was dissolved in 12 N HCl (3-5 mL) and heated at 80 ^oC for about 48 h. The reaction mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under vacuum to give the sulfoximine. The acid layer was basified with 40% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum to give the corresponding *o*-hydroxy benzoic acid. In the case of substrates **60m** and **(*S*)-60l**, corresponding decarboxylated products **63m** and **63l** were isolated, respectively.

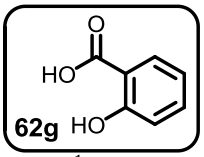
2-Hydroxy-5-methylbenzoic acid (62a): [7b]



Following the general procedure (GP-7); reaction of a mixture of *N*-[2-acetoxy-5-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**60a**; 100 mg, 0.3 mmol) and 12 N HCl (5.0 mL) gave **62a** (36 mg, 79%) as colorless solid and **58a** (33 mg, 71%).

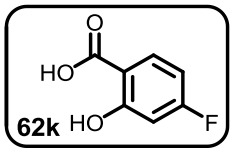
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.47 (bs, 1H), 7.71 (s, 1H), 7.32 (d, J = 7.6 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 160.1, 138.0, 130.5, 128.8, 117.6, 111.0, 20.3.

2-Hydroxybenzoic acid (62g): [7b]



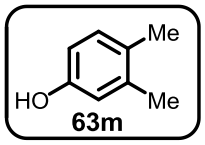
Following the general procedure (GP-7); reaction of a mixture of *N*-[2-acetoxybenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**60g**; 317 mg, 1.0 mmol) and 12 N HCl (5.0 mL) afforded **62g** (120 mg, 87%) as colorless solid and **58a** (116 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (bs, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 162.2, 137.0, 131.0, 119.6, 117.9, 111.3.

2-Hydroxy-4-Fluoro benzoic acid (62k):[7b]



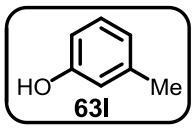
Following the general procedure (GP-7); reaction of a mixture of *N*-[2-acetoxy-4-fluorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**60k;** 50 mg, 0.15 mmol) and 12 N HCl (3.0 mL) afforded **62k** (17 mg, 75%) as colorless solid and **58a** (14 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (t, J = 8.0 Hz, 1H), 6.91–6.62 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 166.7 (d, $J_{C\text{-}F}$ = 249.0 Hz), 163.7 (d, $J_{C\text{-}F}$ = 15.0 Hz), 133.2 (d, $J_{C\text{-}F}$ = 11.0 Hz), 110.6, 107.4 (d, $J_{C\text{-}F}$ = 23.0 Hz), 104.2 (d, $J_{C\text{-}F}$ = 24.0 Hz).

3,4-Dimethyl phenol (63m): [29]



Following the general procedure (GP-7); reaction of a mixture of *N*-[2-acetoxy-5,6-dimethylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**60m**; 100 mg, 0.29 mmol) and 12N HCl (5.0 mL) afforded **63m** (31 mg, 89%) as colorless solid and **58a** (33 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 8.0 Hz, 1H), 6.66 (s, 1H), 6.60 (d, J = 7.6 Hz, 1H), 5.15 (bs, 1H, OH), 2.22 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 137.9, 130.4, 128.5, 116.6, 112.3, 19.8, 18.70.

3-Methyl phenol (63l): [29,30]



Following the general procedure (GP-7); reaction of a mixture of (*S*)-*N*-[2-acetoxy-6-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine [**(*S*)-60l**; 100 mg, 0.35 mmol] and 12 N HCl (5.0 mL) afforded **63l** (27 mg, 82%) as colorless solid and (*S*)-**58a** (40 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.70–6.64 (m, 2H), 5.26 (bs, 1H, OH), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 139.8, 129.4, 121.6, 116.0, 112.3, 21.3.

2.5.3.6. X-ray Crystallographic Data

Single crystal X-ray data for the compound **(*S*)-60k** and **60l** were collected using the detector system [λ(Mo-Kα) = 0.71073 Å] at 298K, graphite monochromator with a ω scan width of 0.3^o, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software was used for the intensity data acquisition and the SAINTPLUS Software was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program, an empirical absorption correction using equivalent reflections was performed with the program. The structure was solved using SHELXS-97, and full-matrix least-squares refinement against F^2 was carried out using SHELXL-97. All non-hydrogen atoms were refined anisotropically. Aromatic and methyl hydrogens were introduced on calculated positions and included in the refinement riding on their respective parent atoms.

Table 2.6. Crystal data for **(*S*)-60k, 60l**

	Compound	**Compound**
Identification code	**(*S*)-60k**	**60l**
Formula	$C_{16}H_{14}FNO_4S$	$C_{17}H_{17}NO_4S$
F_w	335.34	331.38
T (K)	298(2)	298(2)
λ (Å)	0.71073	1.54184
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a (Å)	9.0147(4)	7.58754(15)
b (Å)	10.2380(3)	16.0547(3)
c (Å)	9.5144(5)	13.8265(3)
α (°)	90	90
β (°)	114.991(6)	103.884(2)
γ (°)	90	90
V (Å^3)	795.89(6)	1635.08(5)
Z	2	4
ρ_{calcd} (Mg m^{-3})	1.399	1.346
μ (mm^{-1})	0.233	1.932
F (000)	348	696
Crystal Size (mm)	0.24 × 0.36 × 0.48	0.24 × 0.36 × 0.48
2θ range/deg	3.08 / 26.30	2.75 / 71.55
Reflections collected	5636	10637
Unique reflections	3242	3166
Completeness to 2θ (%)	26.37 (99.8)	71.70 (99.0)
T_{max}, T_{min}	0.9463, 0.8965	0.6542, 0.4573
Parameters	210	276
GOF (F^2)	1.041	1.060
R1, *wR2* $[I>2\sigma(I)]$	0.0340, 0.0847	0.0520, 0.1415
R1, *wR2* (all data)	0.0388, 0.0888	0.0605, 0.1526
Largest diff. Peak and hole (e·Å^{-3})	0.167 and -0.254	0.328 and -0.438

2.6. References

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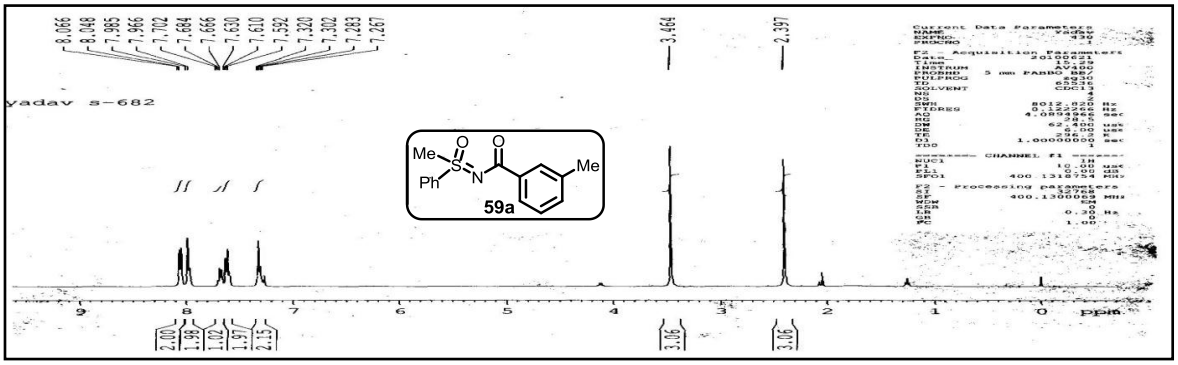
2.7 Spectra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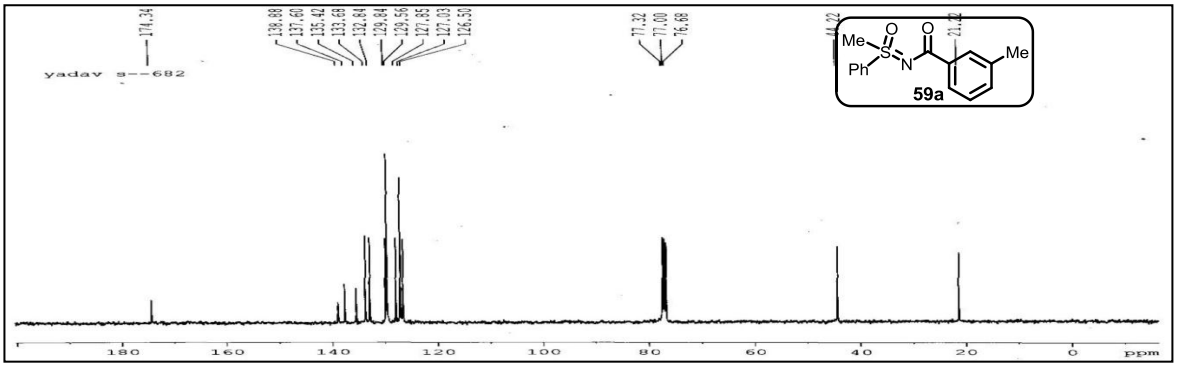
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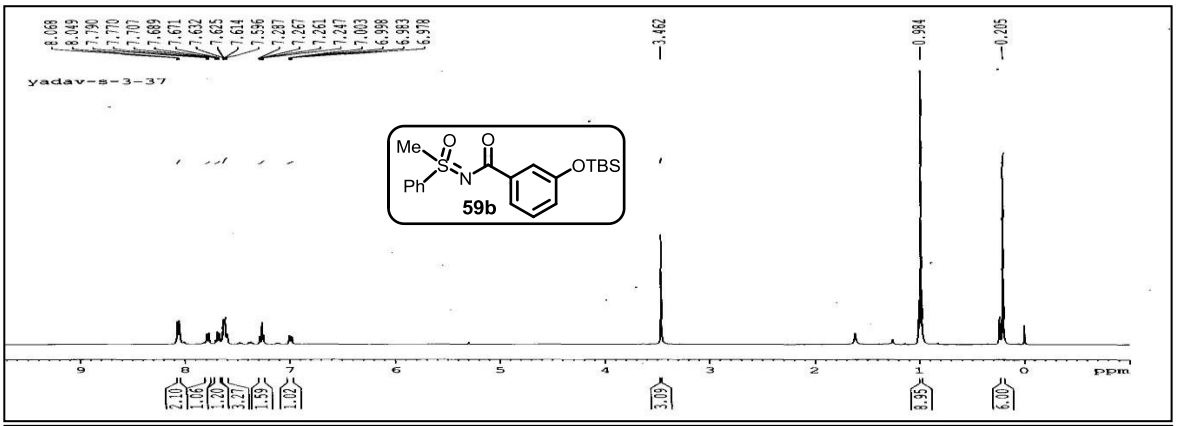
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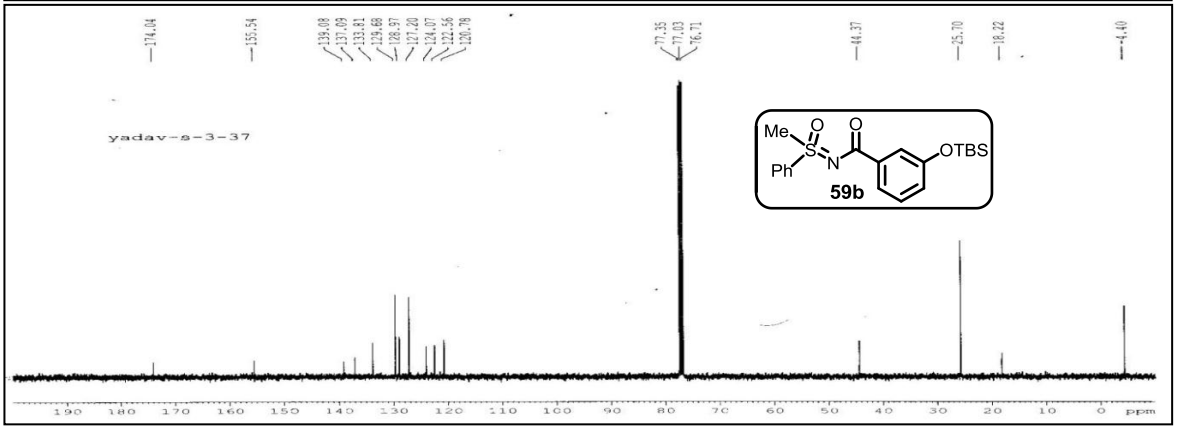
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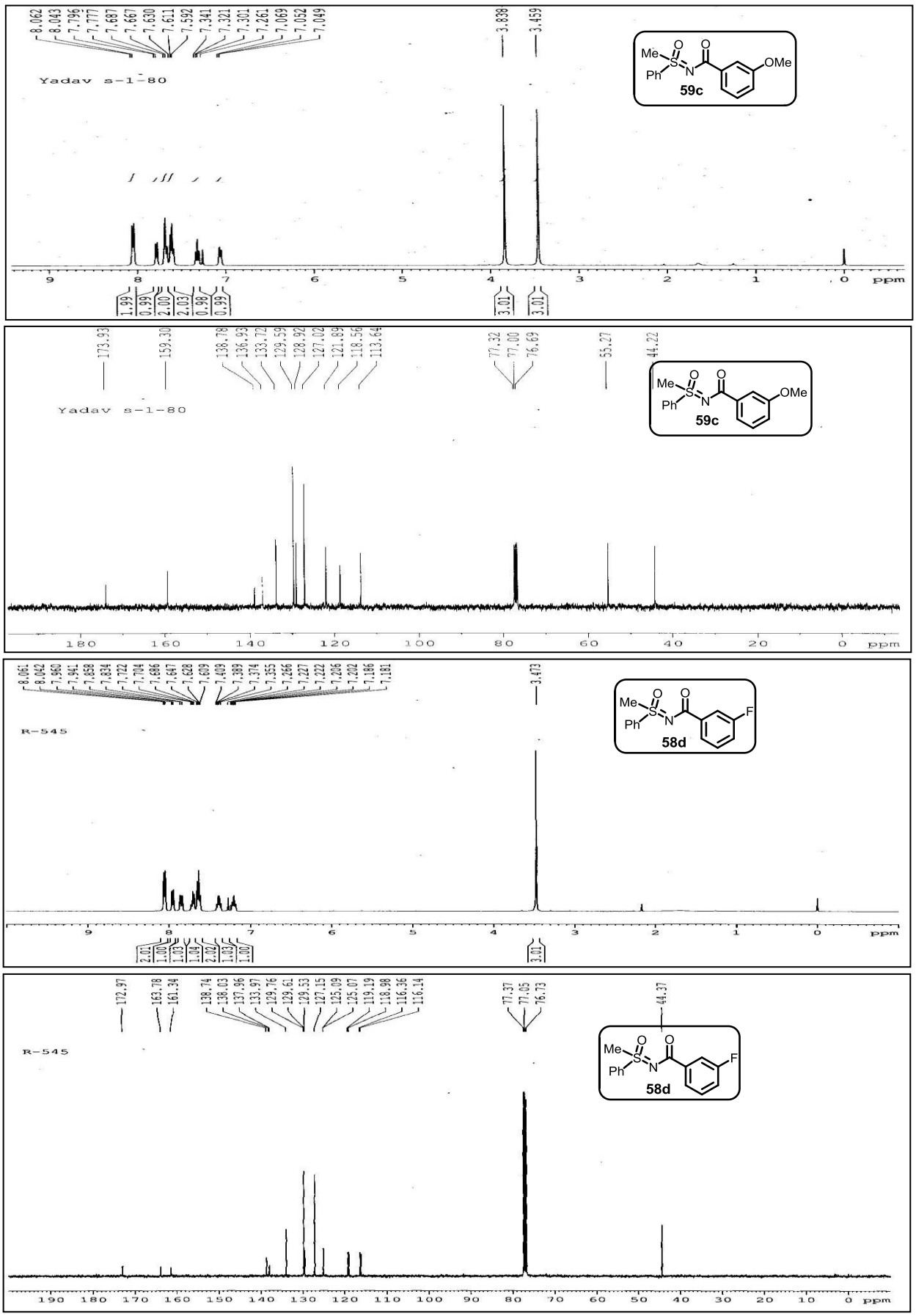
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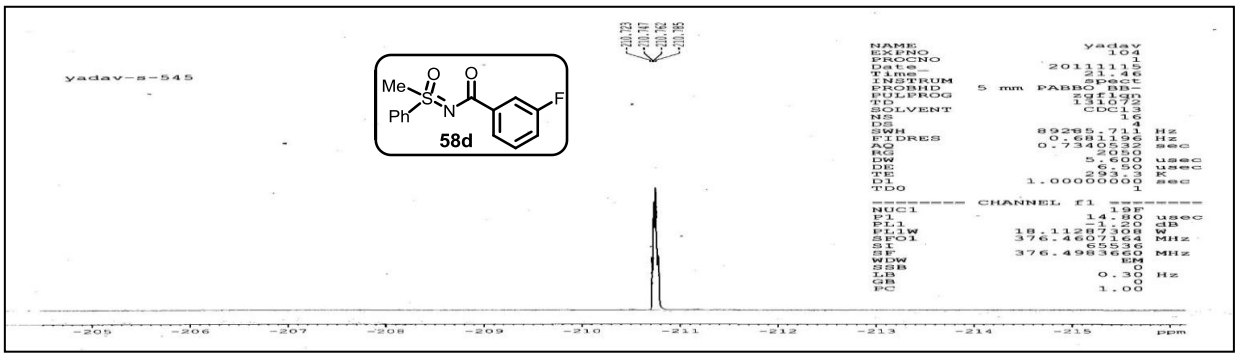
58d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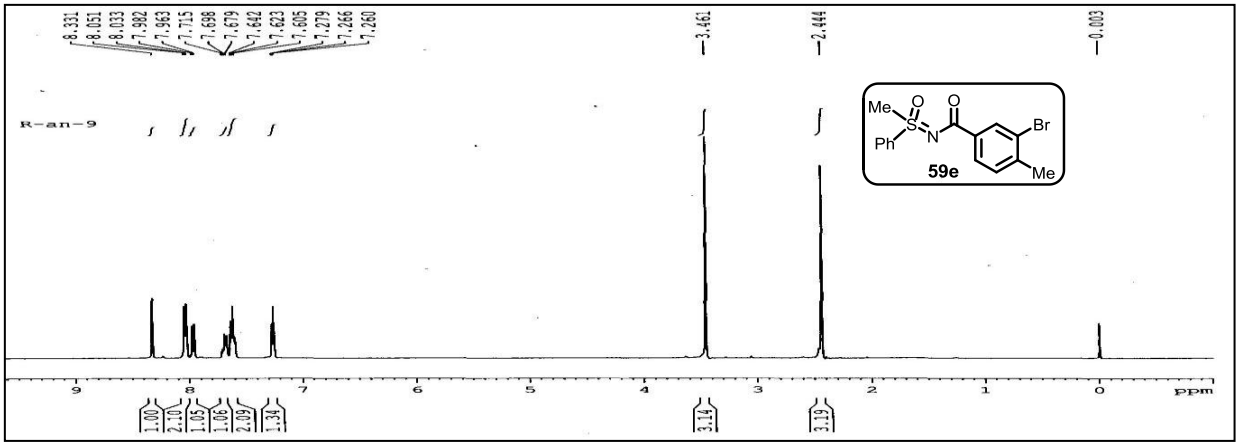
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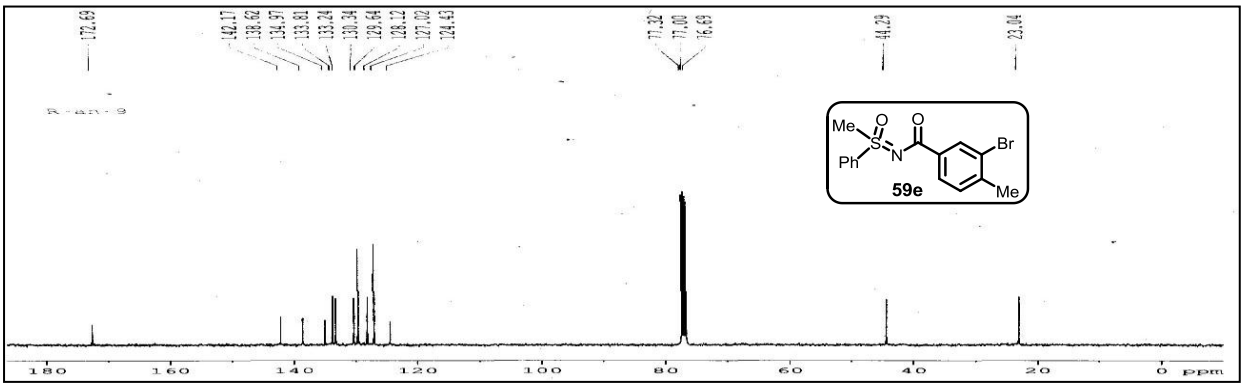
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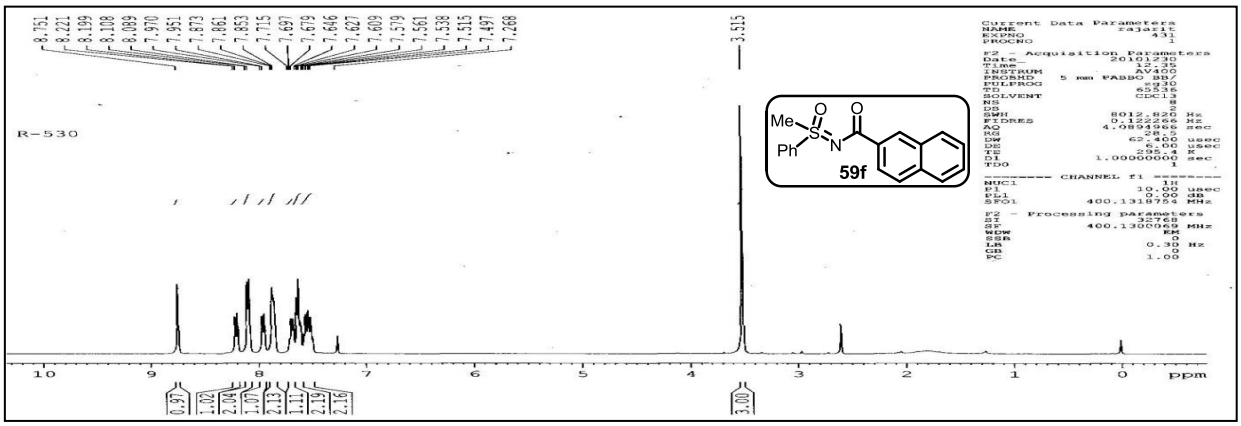
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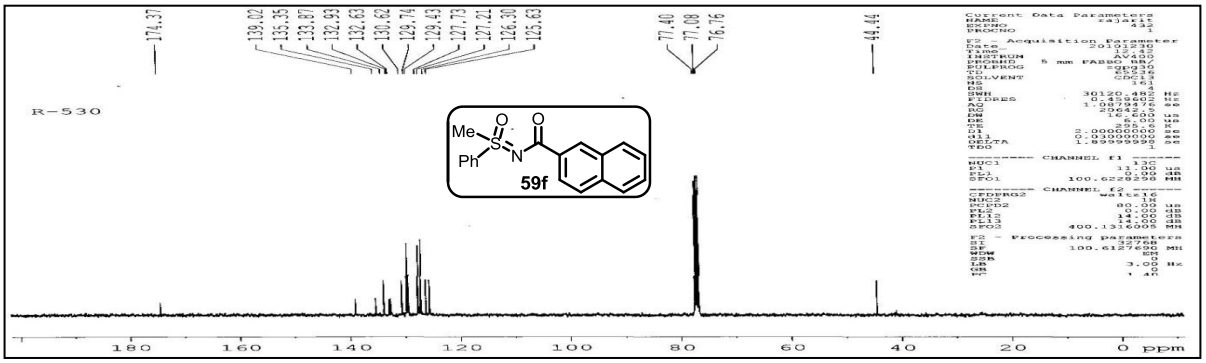
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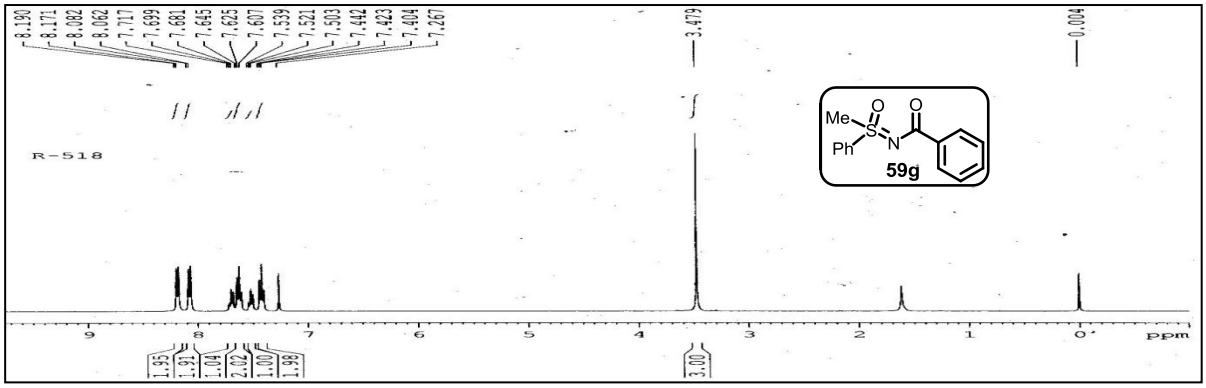
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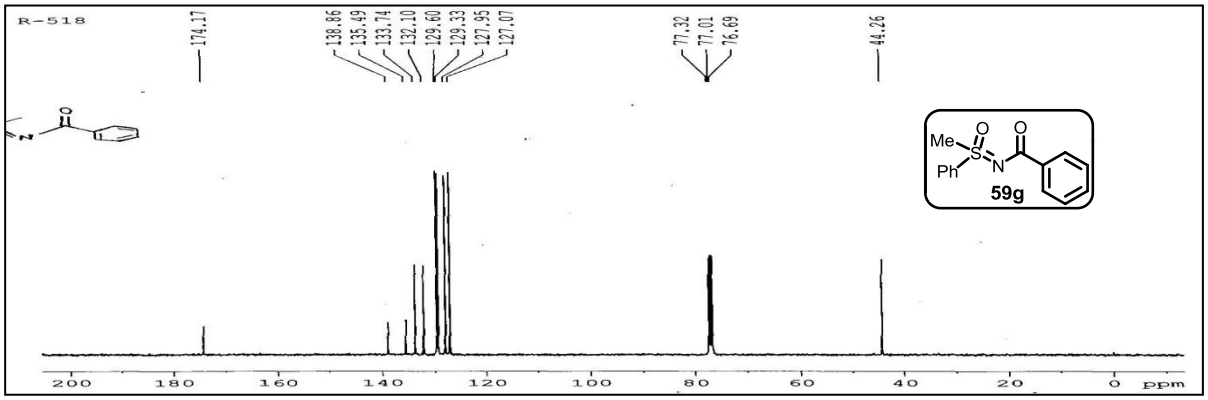
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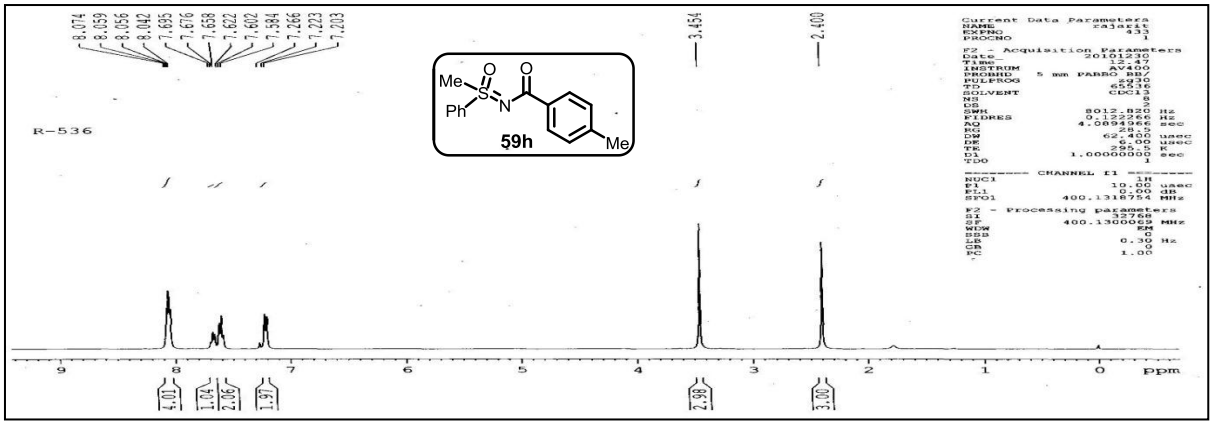
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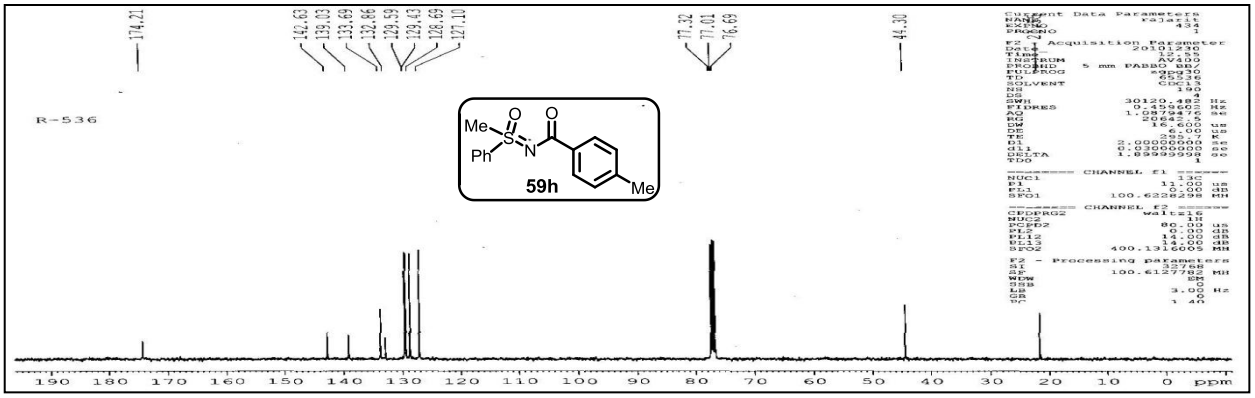
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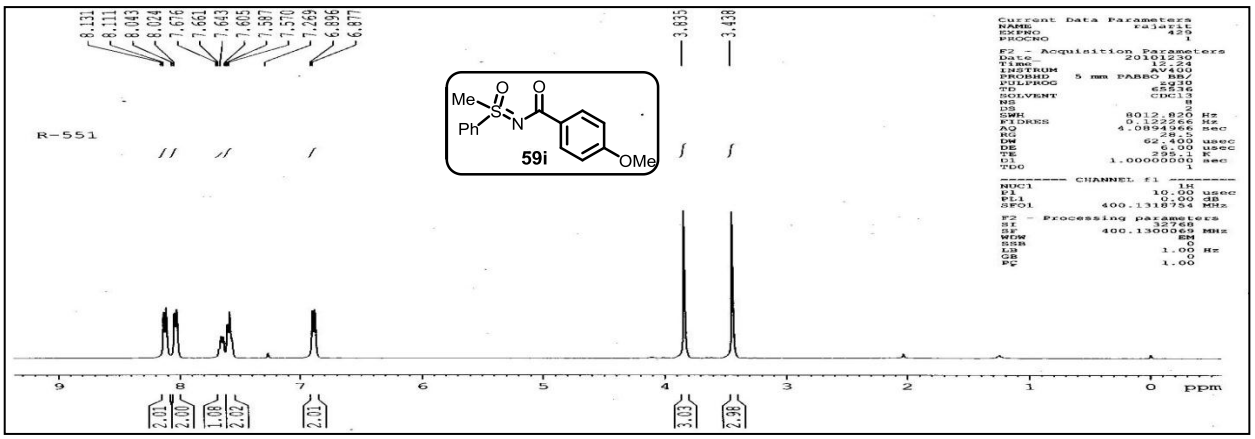
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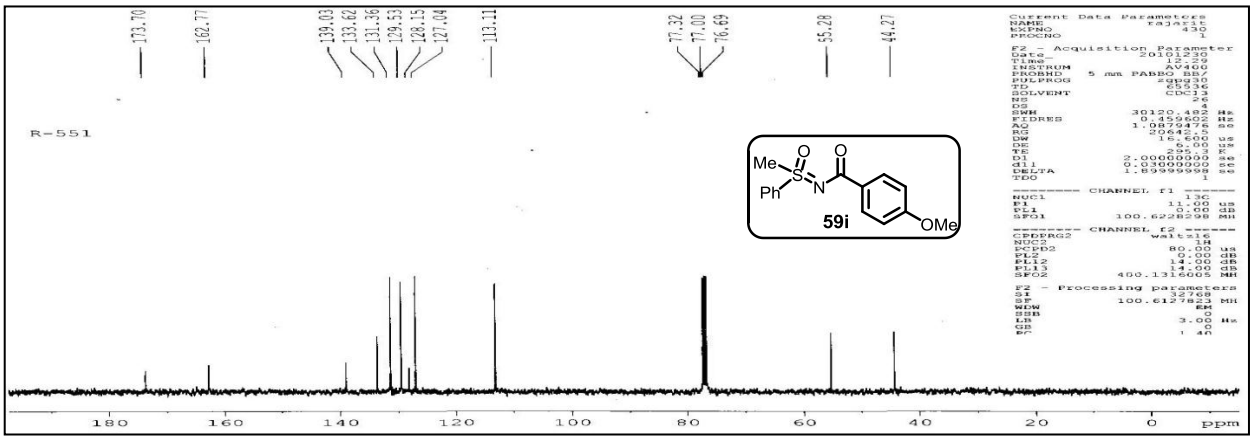
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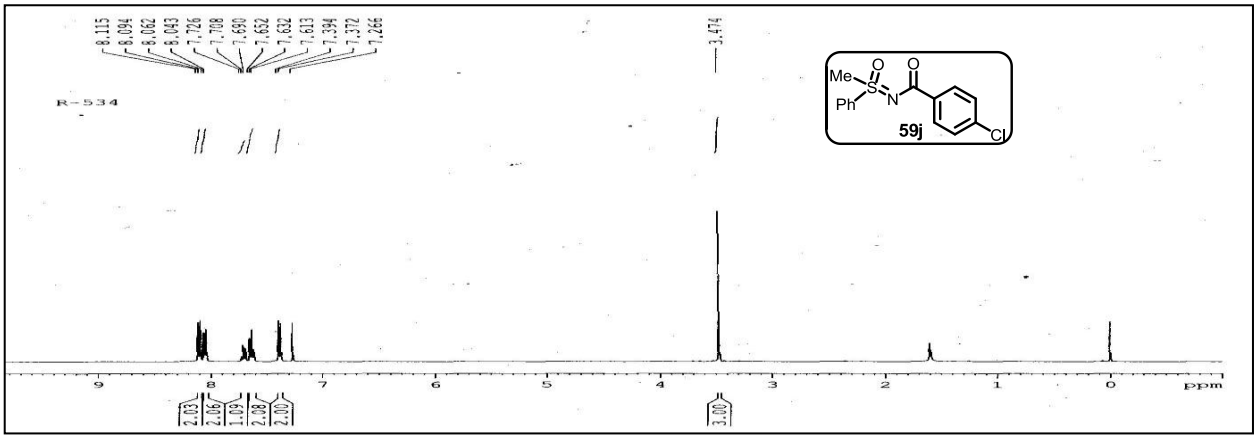
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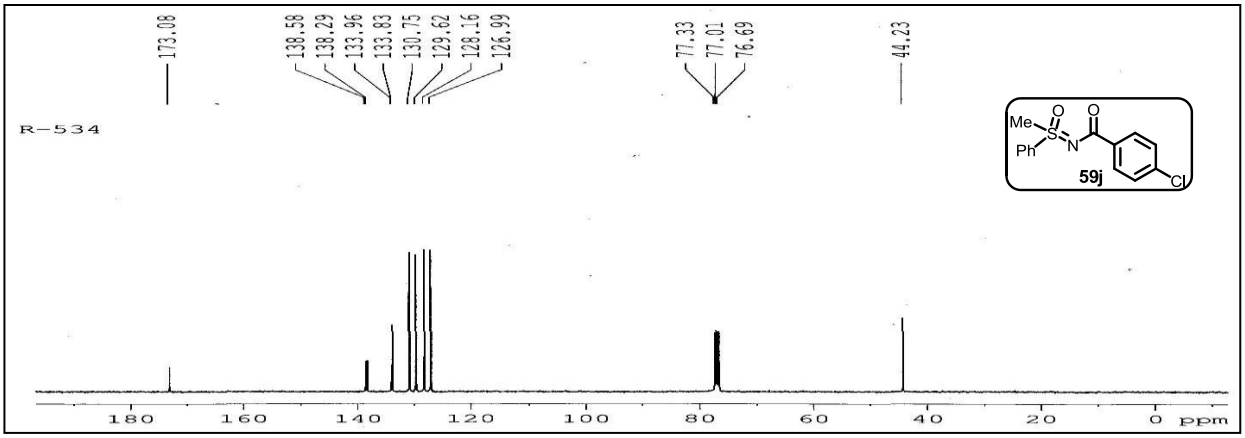
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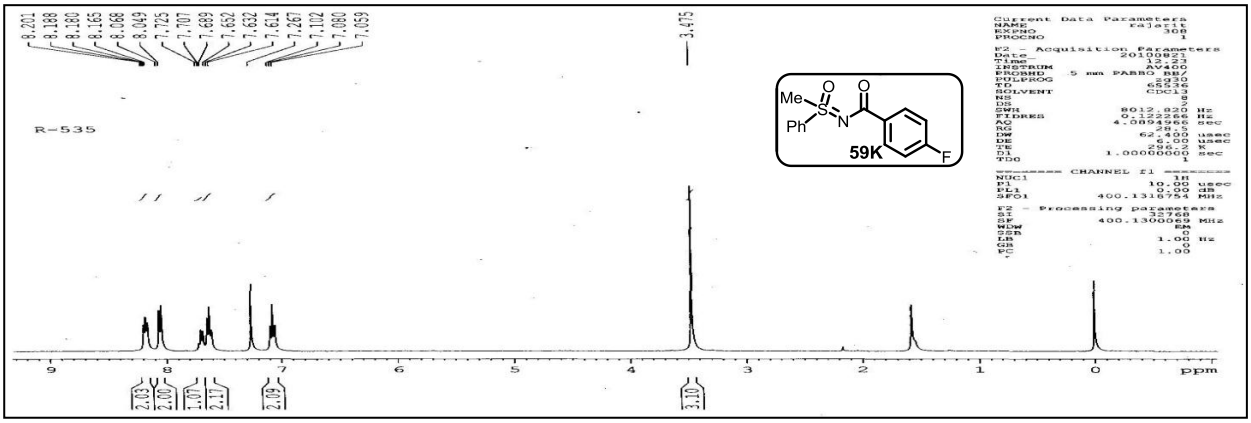
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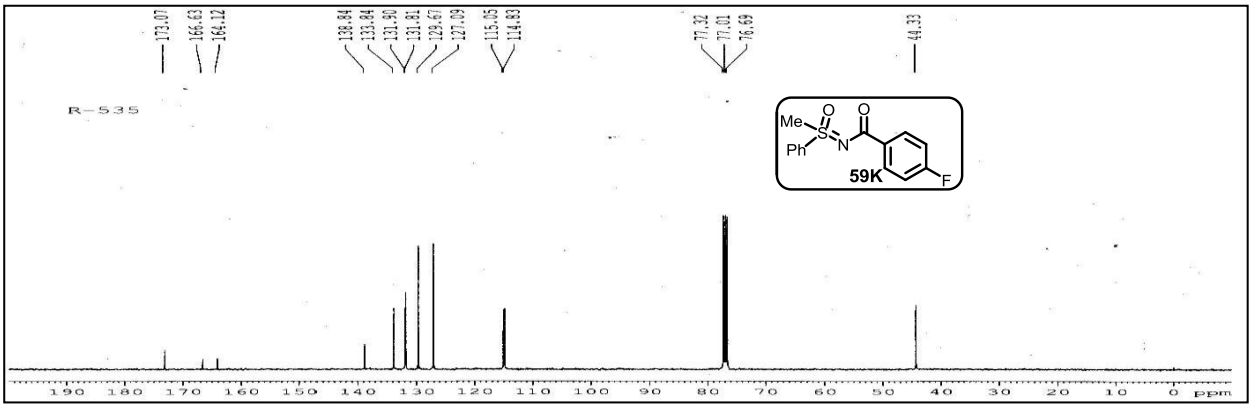
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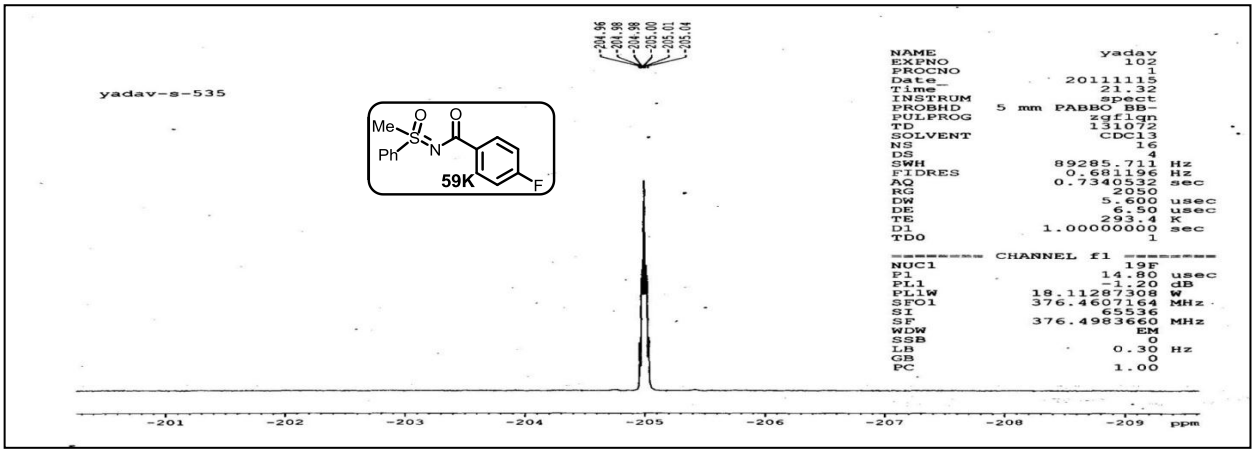
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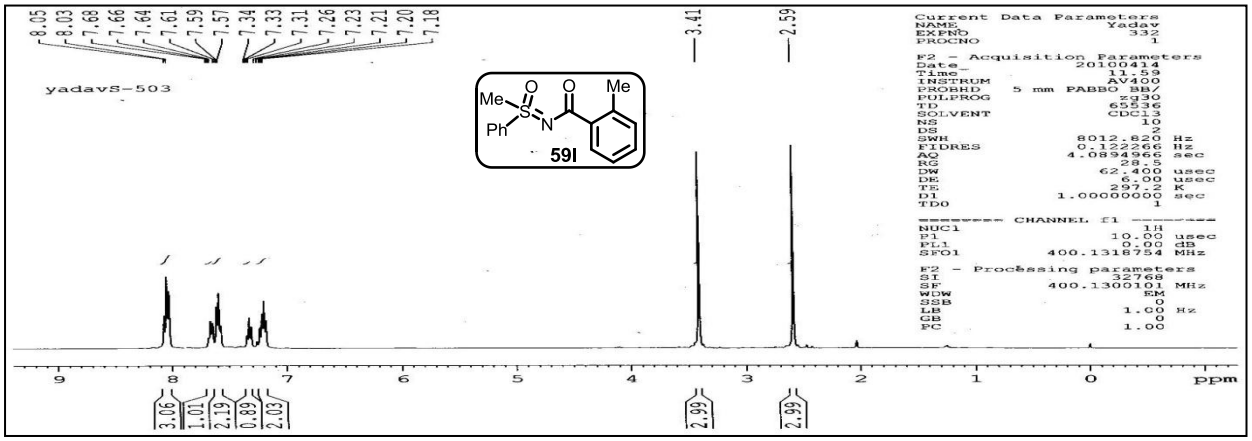
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PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 10
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894966 sec
RG 28.5
DW 62.400 usec
DE 6.00 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 10.000 usec
PL1 0.00 dB
SFO1 400.1318754 MHz
F2 - Processing parameters
SI 32768
SF 400.1300110 MHz
WDW EM
SSB 0
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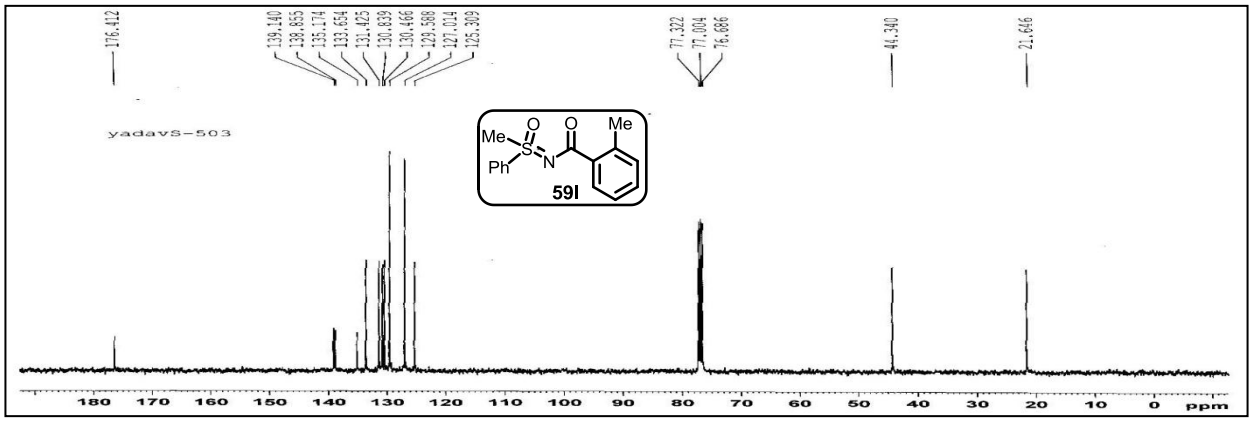
GB 0
PC 1.00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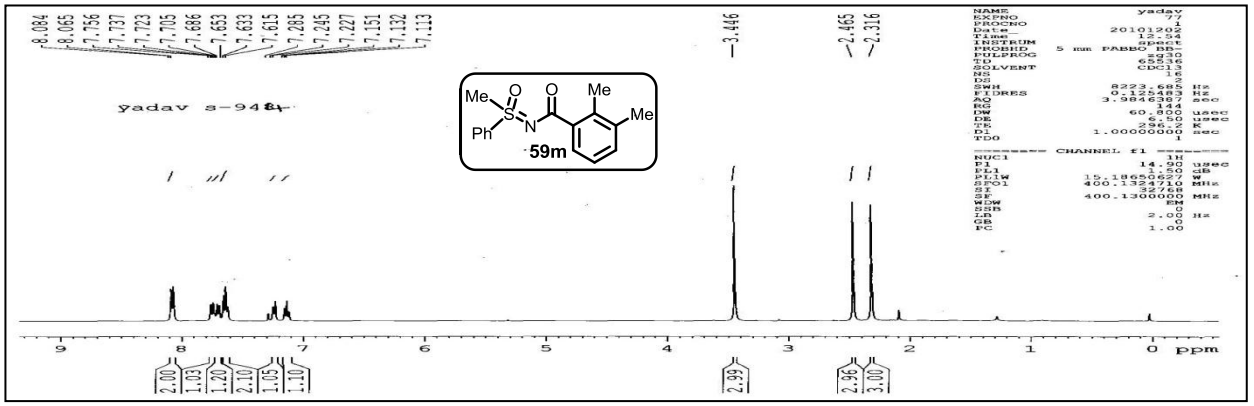
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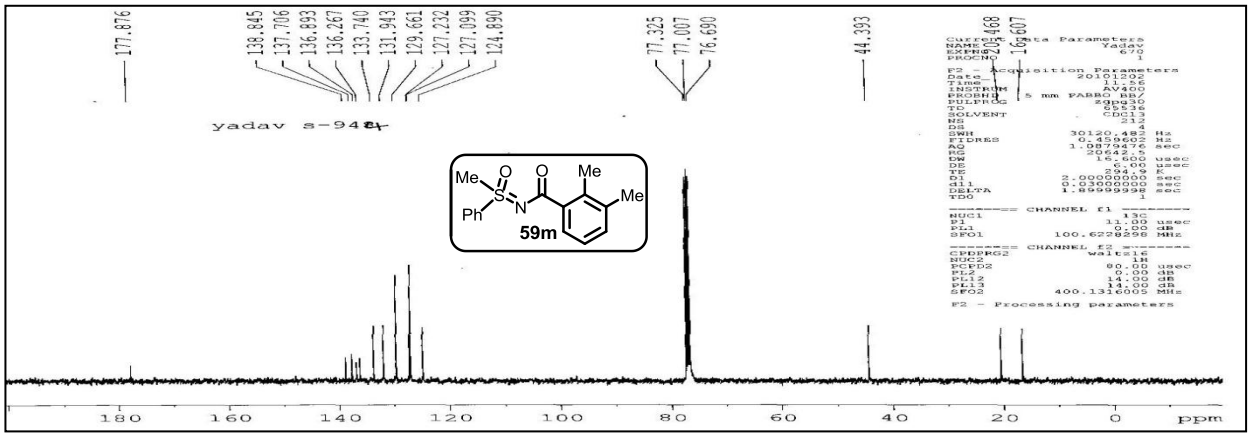
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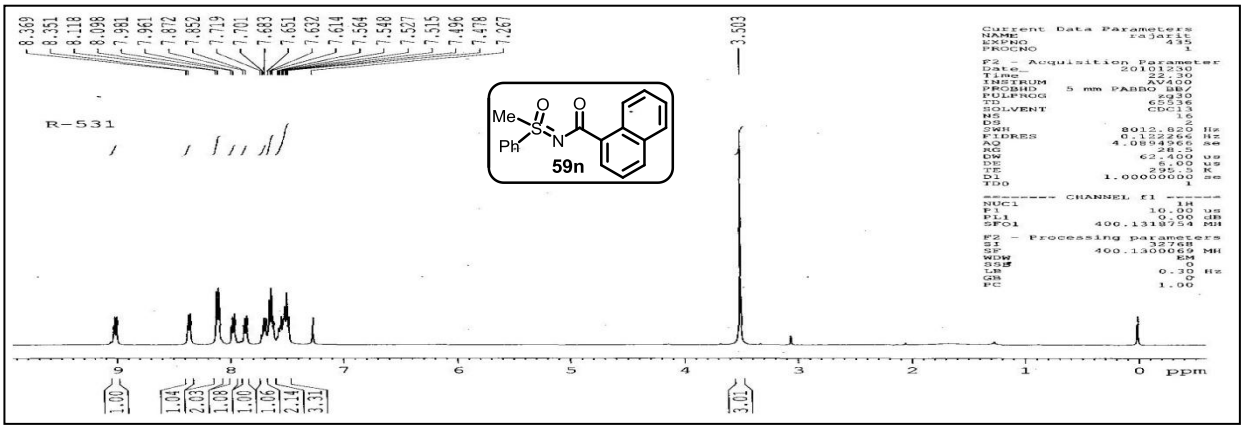
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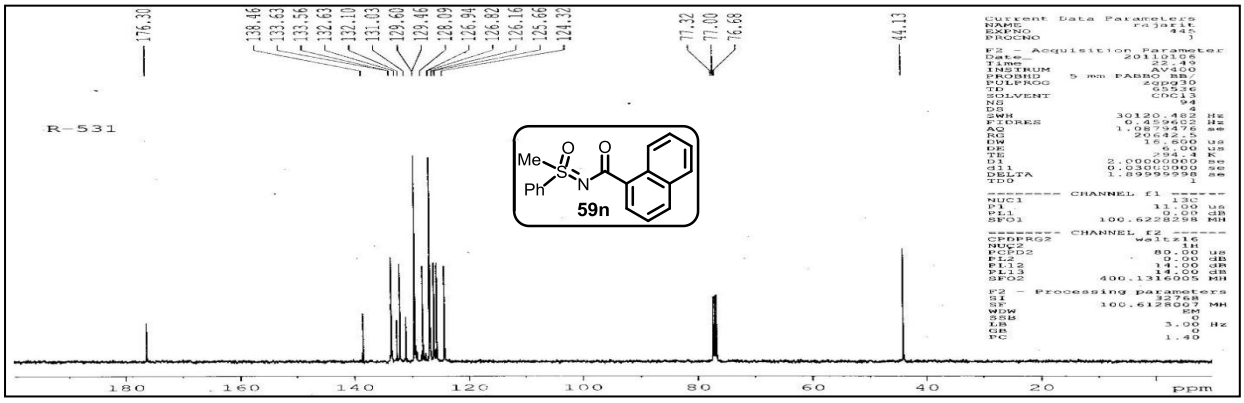
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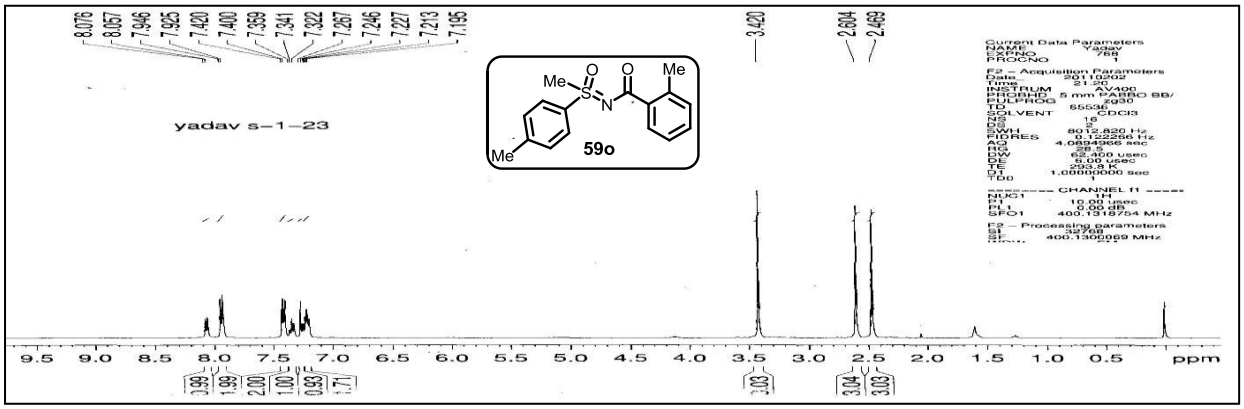
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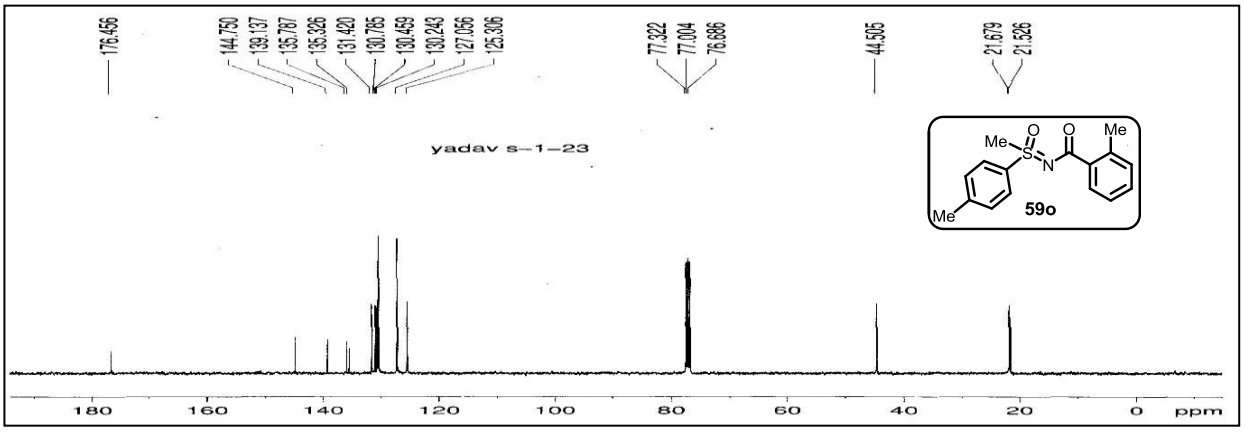
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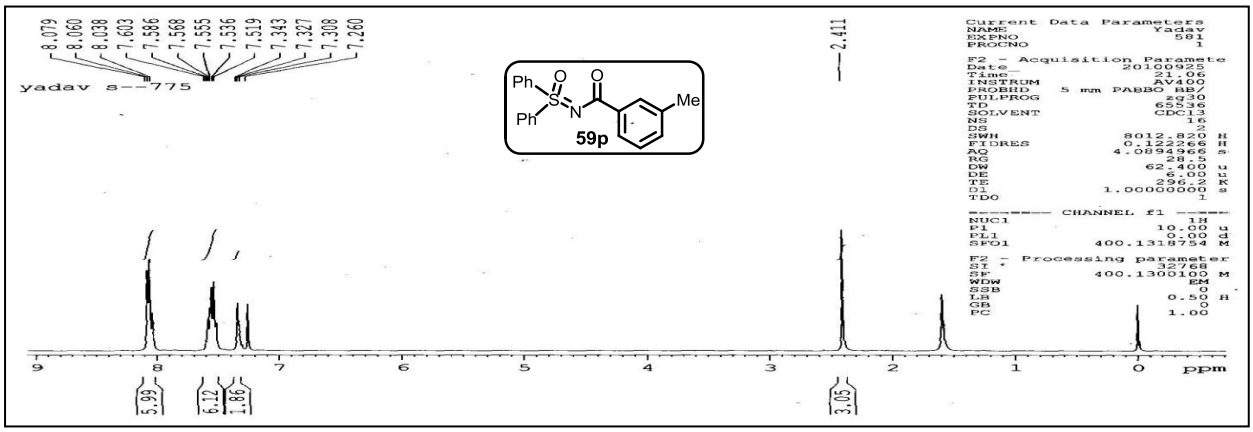
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7.603
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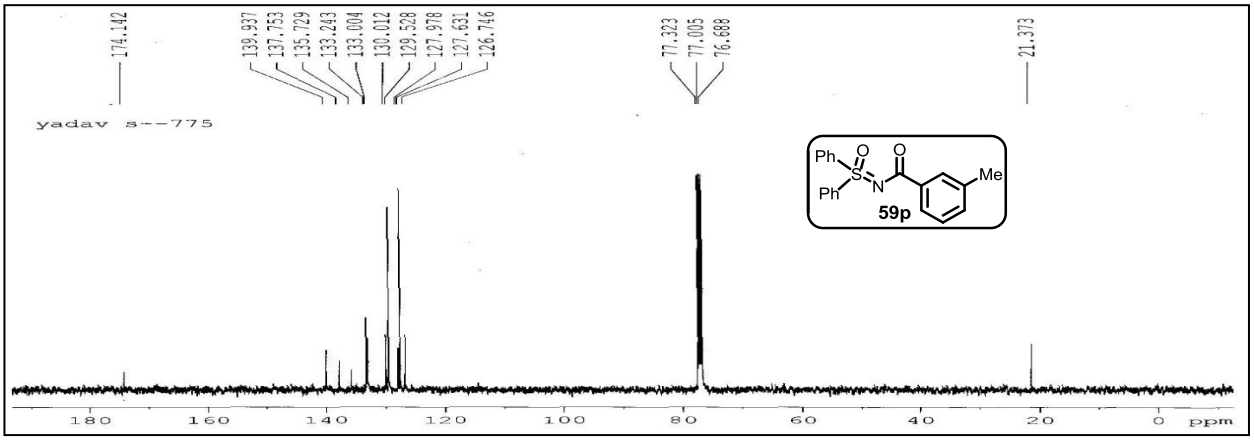
7.260
yadav s--775
2.411
59p
5.99
6.12
1.86
3.05
ppm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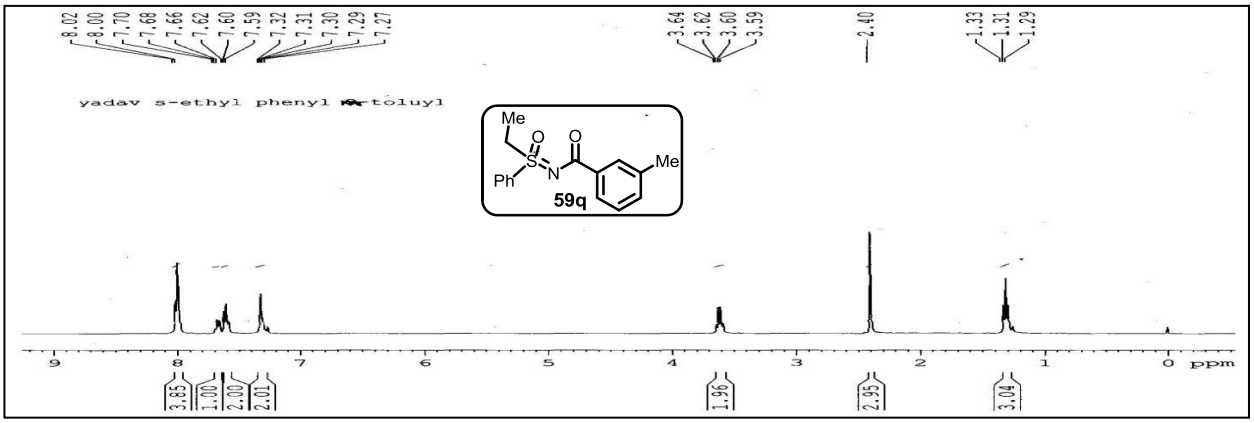
77.005
76.688
21.373
yadav s--775
59p
ppm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8.00
7.70
7.68
7.66
7.62
7.60
7.59
7.32
7.31
7.30
7.29
7.27
3.64
3.62
3.60
3.59
2.40
1.33
1.31
1.29
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59q
3.85
1.00
2.00
2.01
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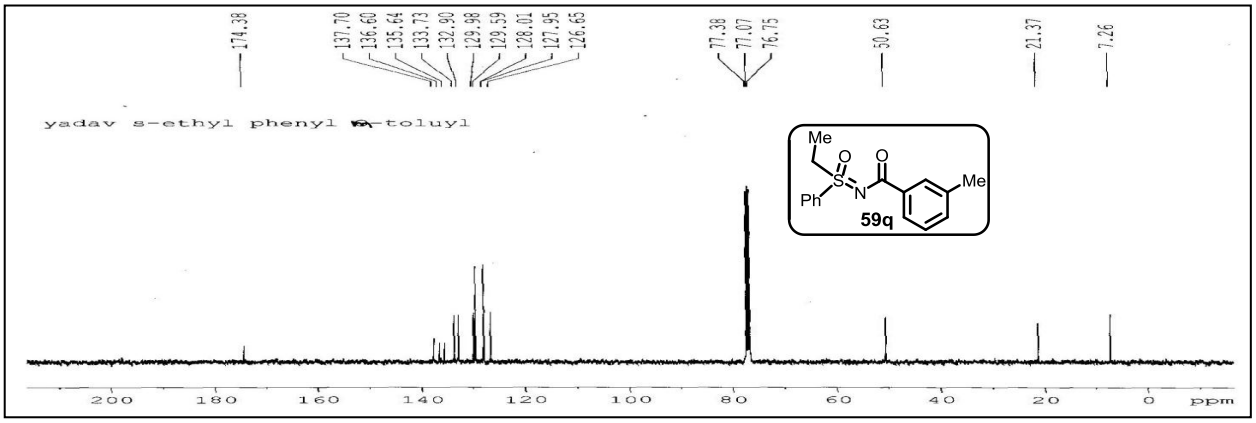
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135.64
133.73
132.90
129.98
129.59
128.01
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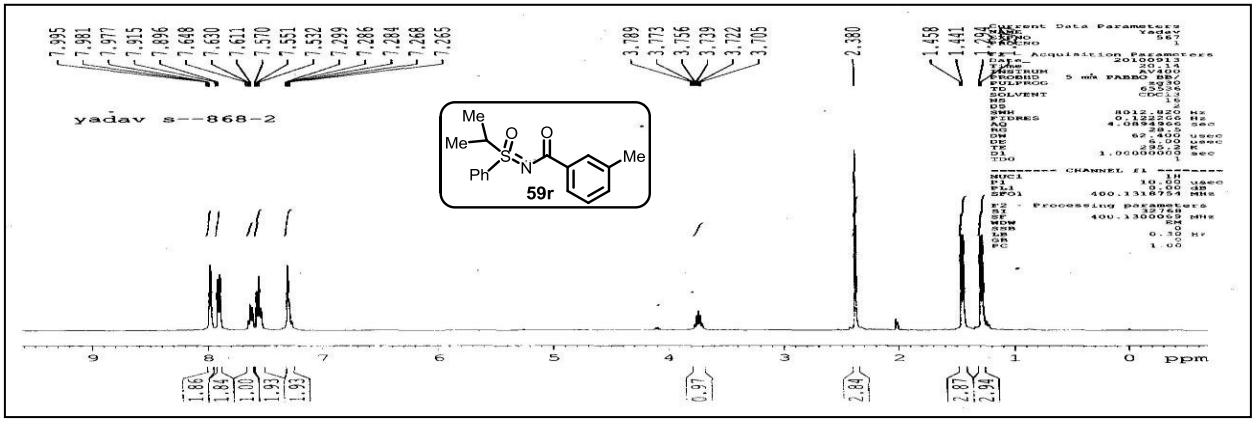
77.07
76.75
50.63
21.37
7.26
yadav s-ethyl phenyl -toluyl
59q
ppm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7.915
7.896
7.648
7.630
7.611
7.570
7.551
7.532
7.289
7.286
7.284
7.268
7.265
3.789
3.773
3.756
3.739
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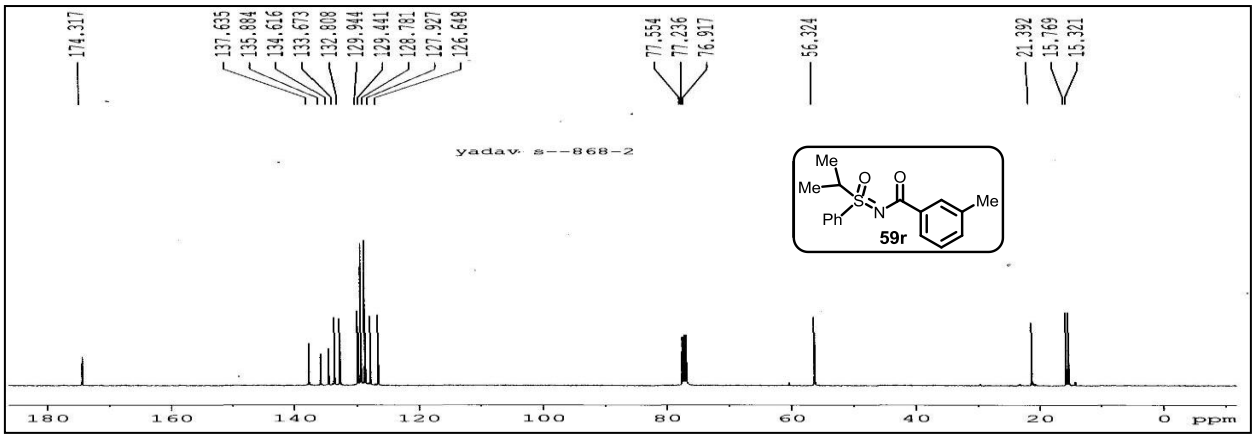
3.705
2.380
1.458
1.441
1.424
yadav s--868-2
Me
Me
Ph
59r
ppm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126.648
77.554
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56.324
21.392
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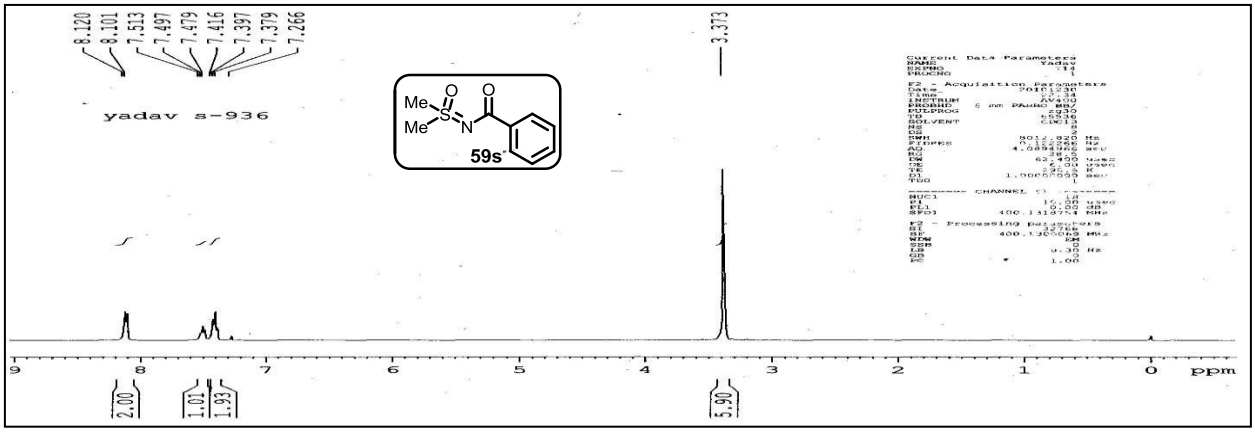
Me
Me
Ph
59r
ppm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8.101
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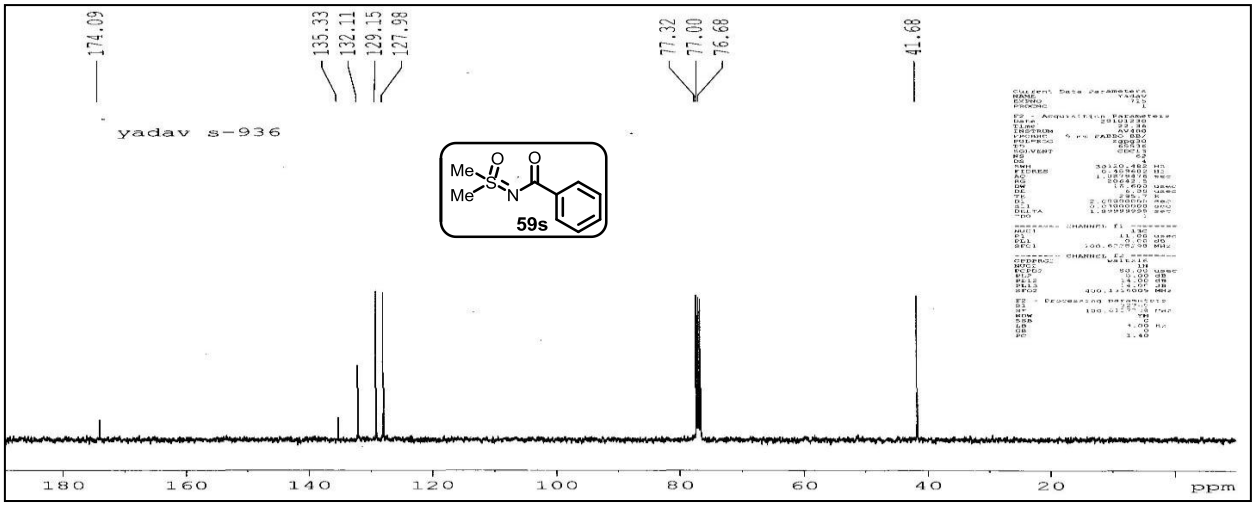
Me
Me
59s
ppm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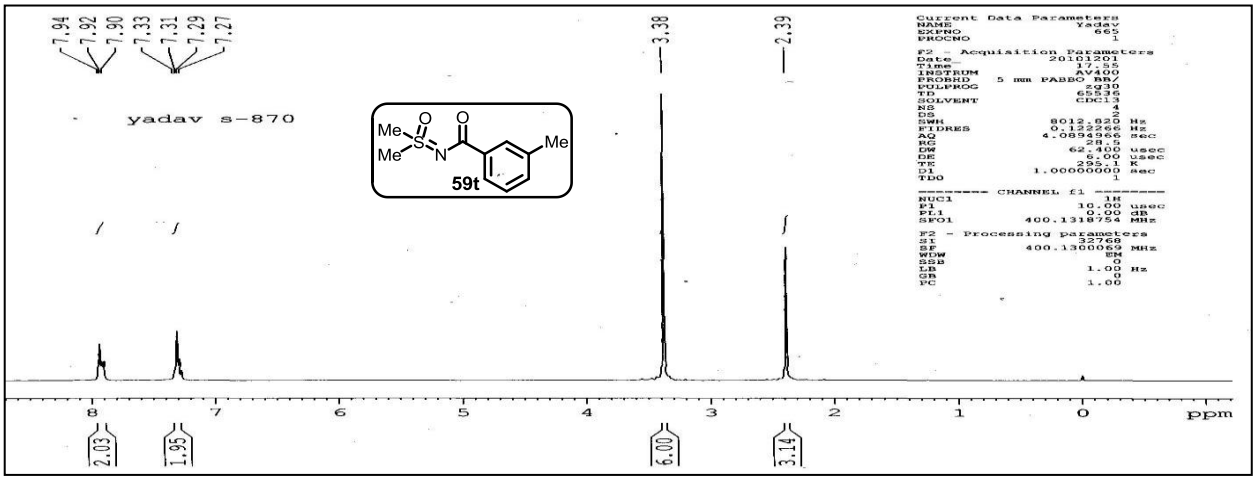
Me
Me
59s
ppm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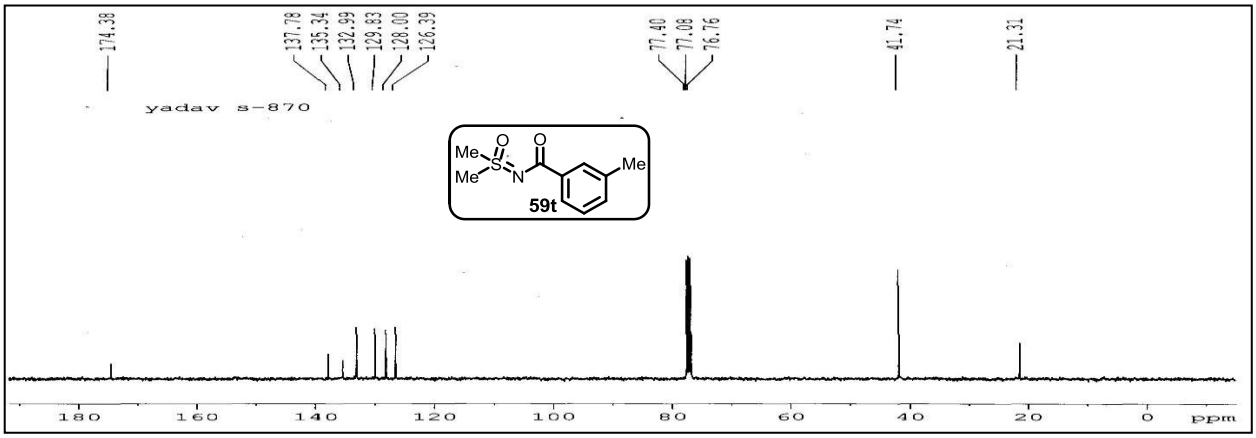
59t
ppm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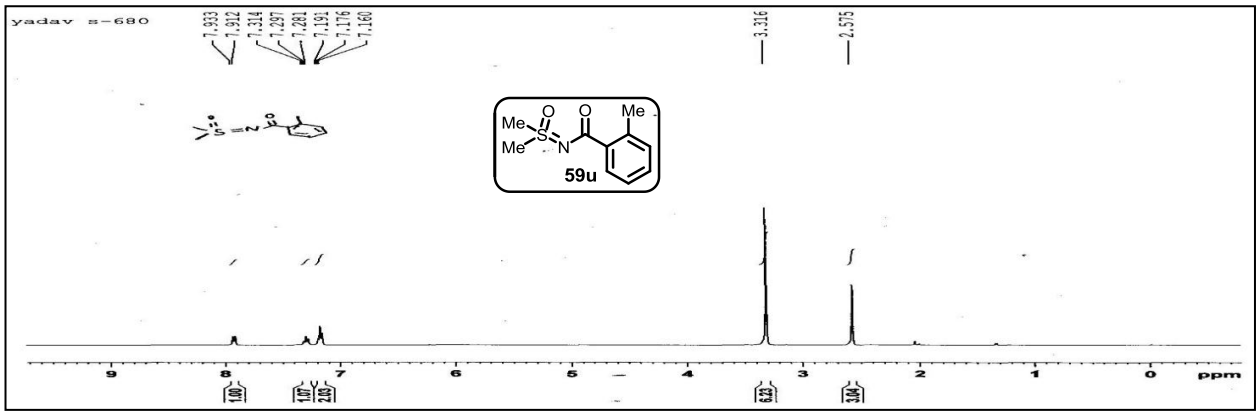
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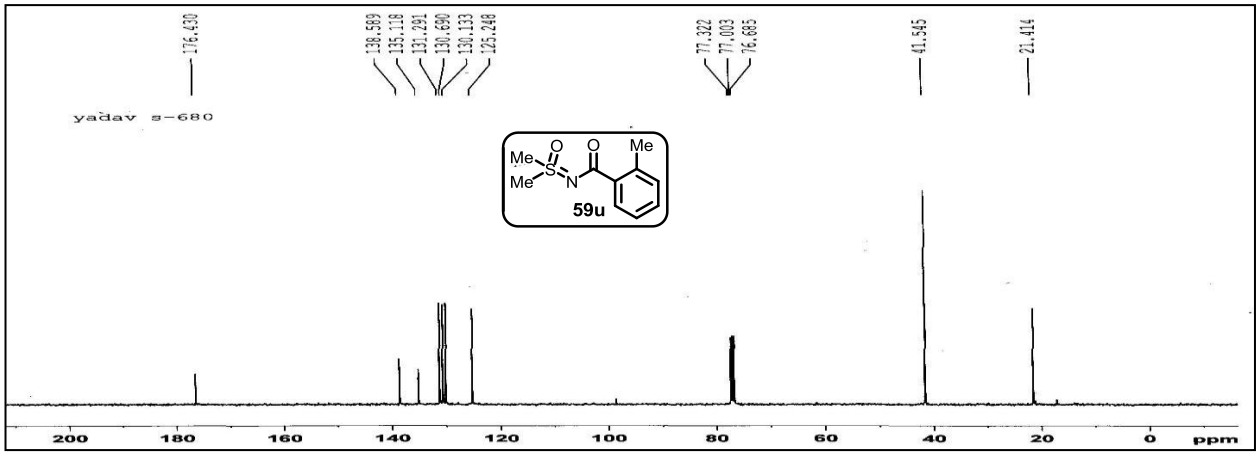
ppm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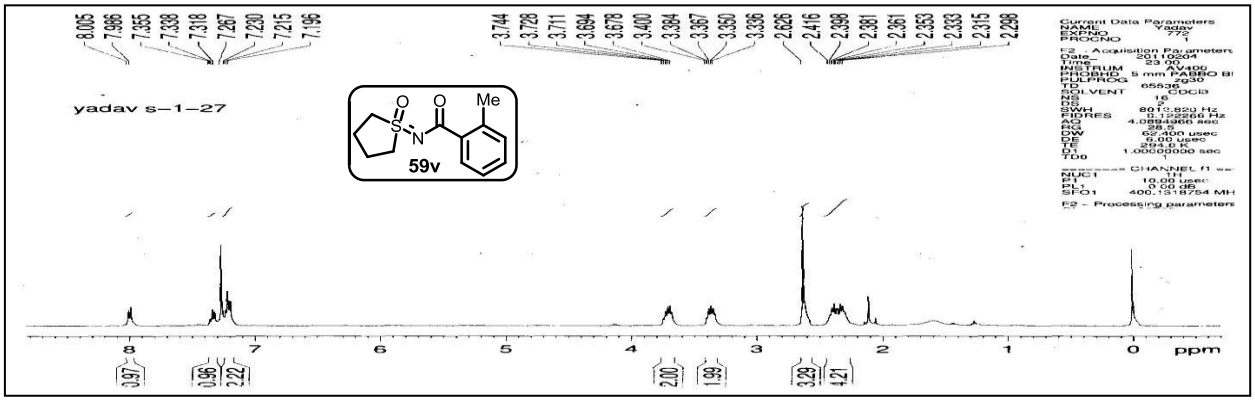
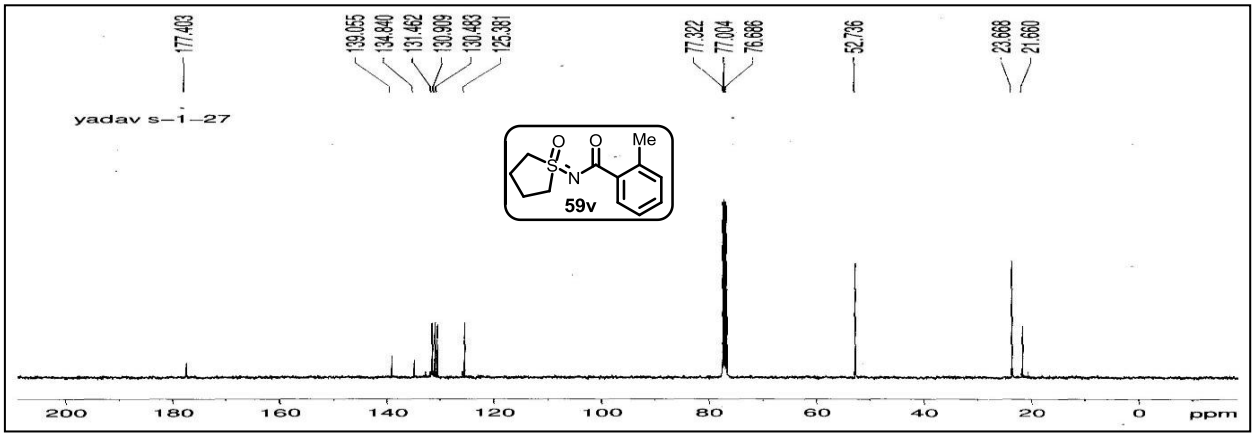
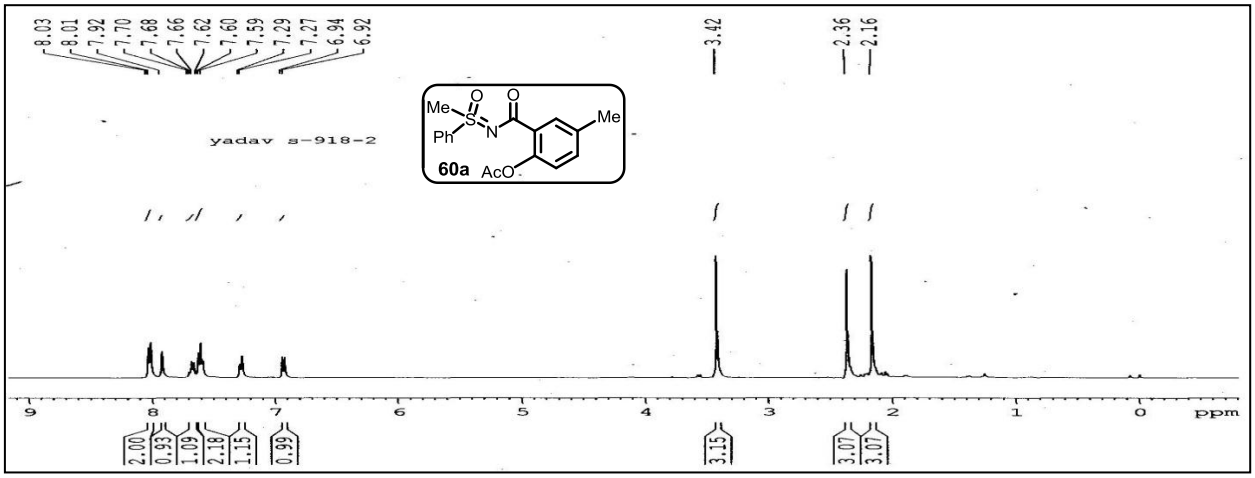

yadav s-1-27
59v
Me


yadav s-1-27
59v
Me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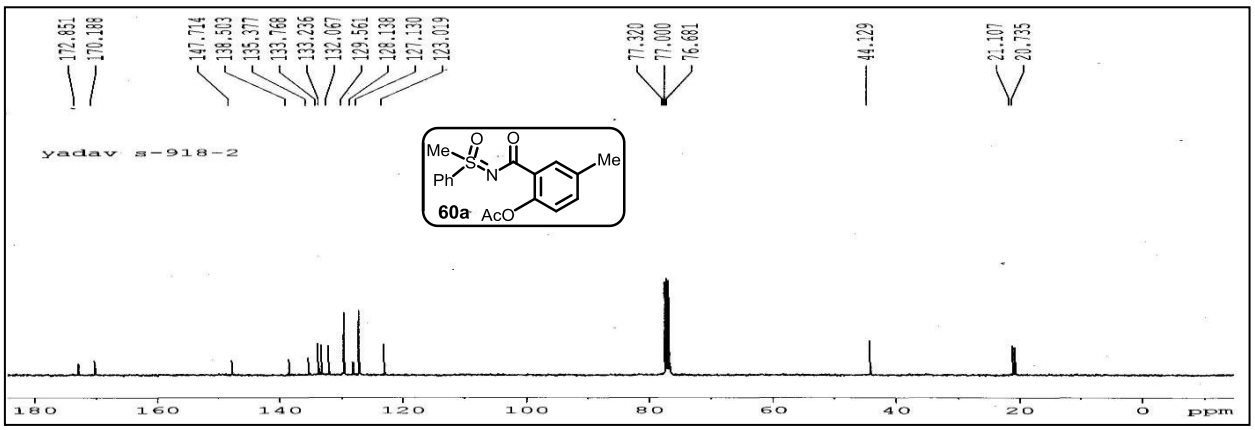
Ph
AcO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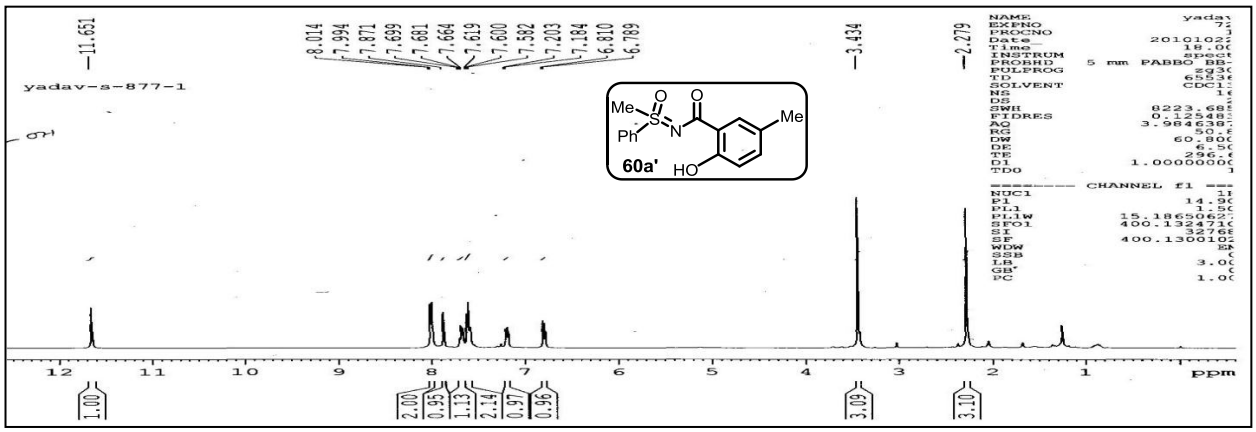
Me
Ph
AcO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7.871
7.699
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7.619
7.600
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7.203
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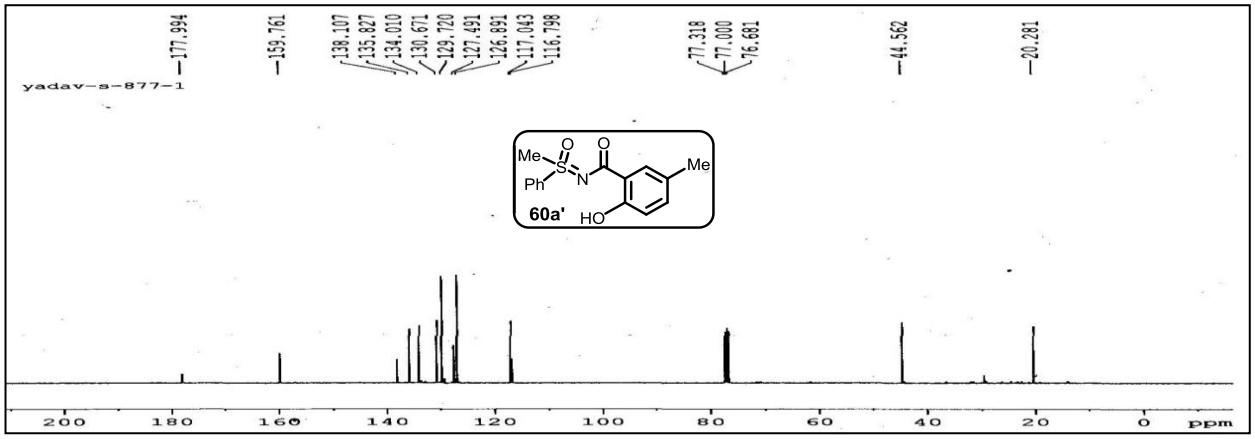
6.810
6.789
3.434
2.279
Me
Ph
S
O
N
O
Me
HO
60a'
ppm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S
O
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O
Me
HO
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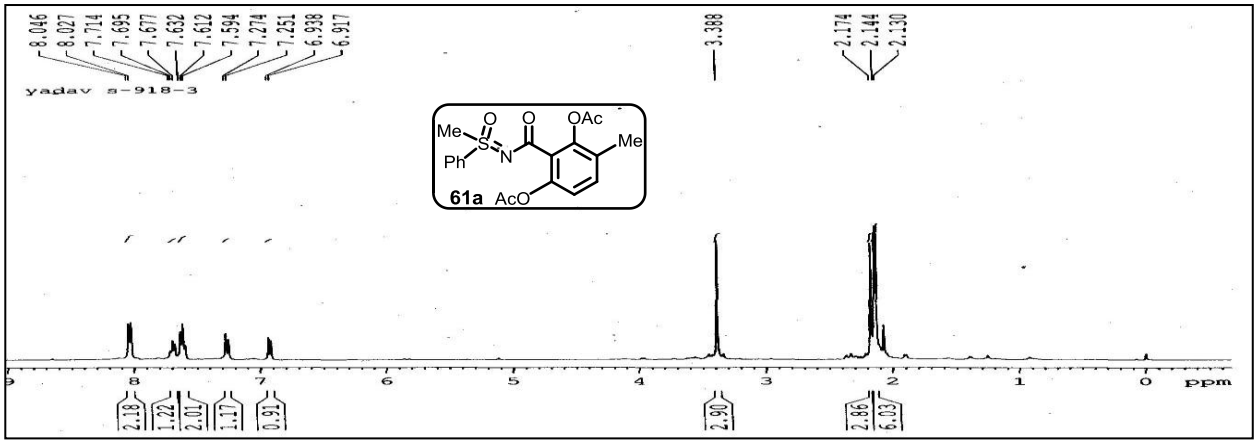
ppm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Me
Ph
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N
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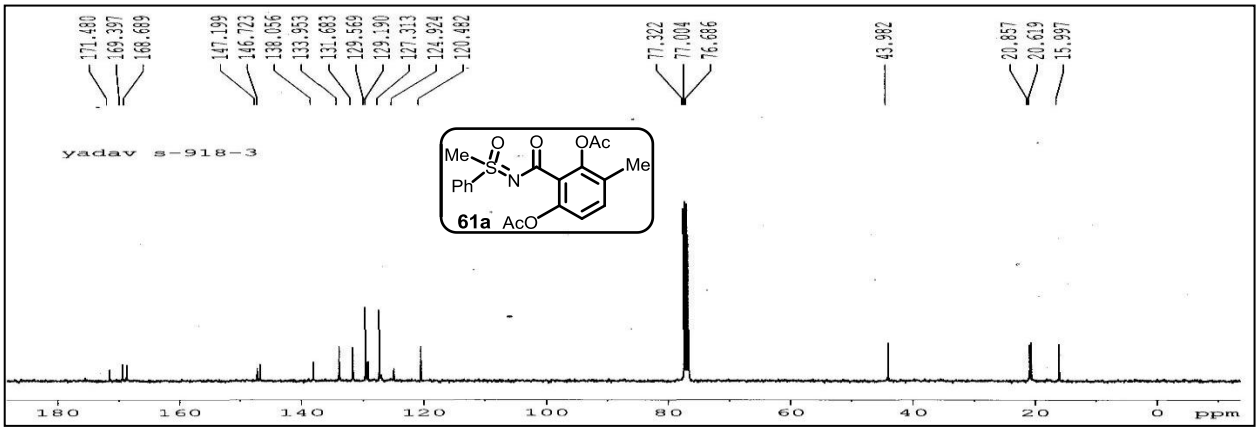
AcO
61a
ppm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77.004
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AcO
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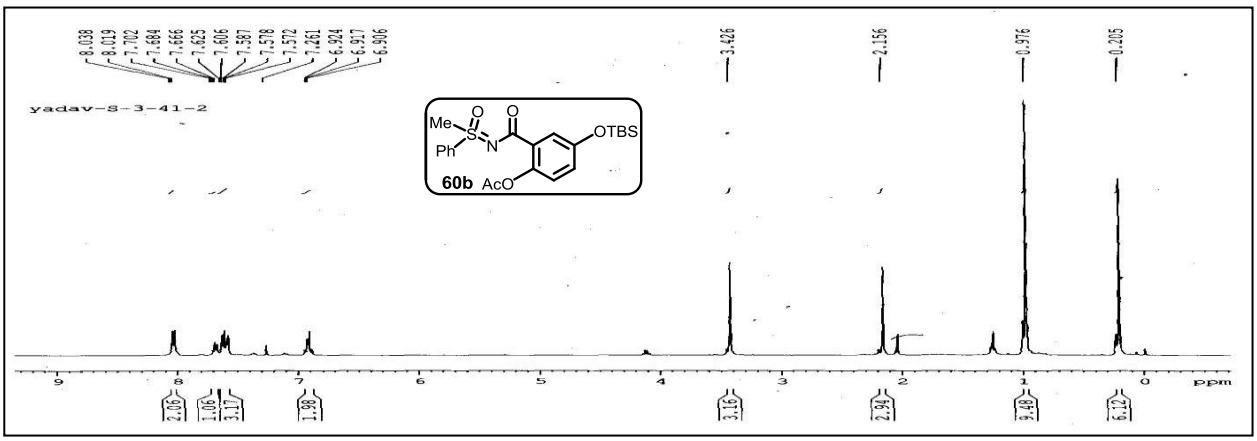
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AcO
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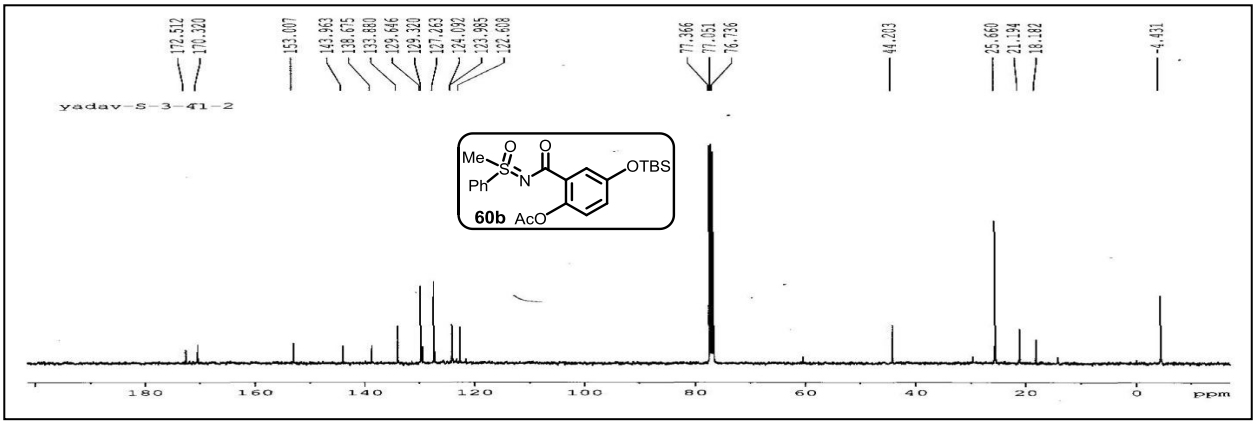
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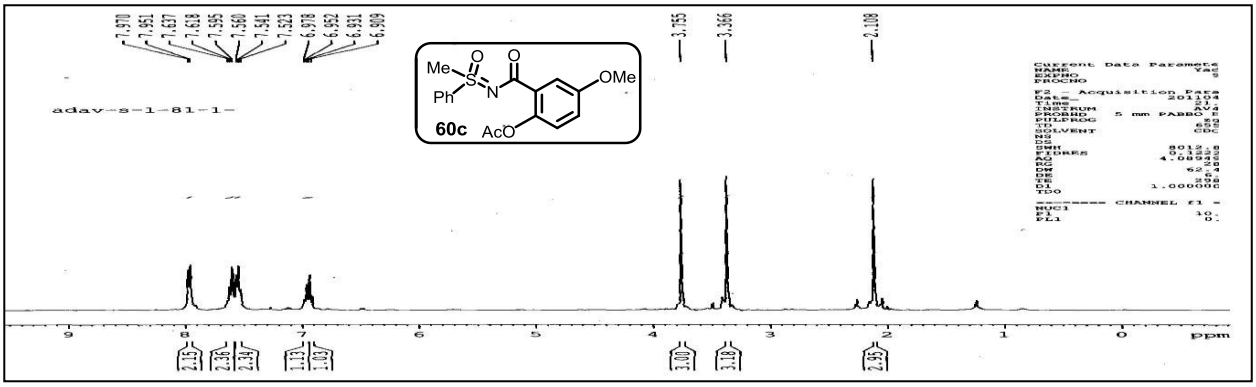
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AcO
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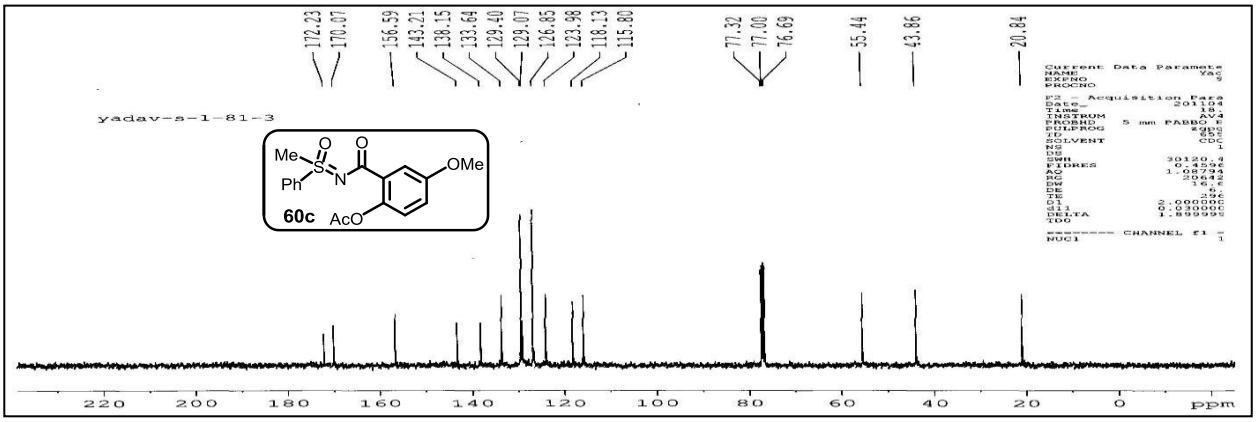
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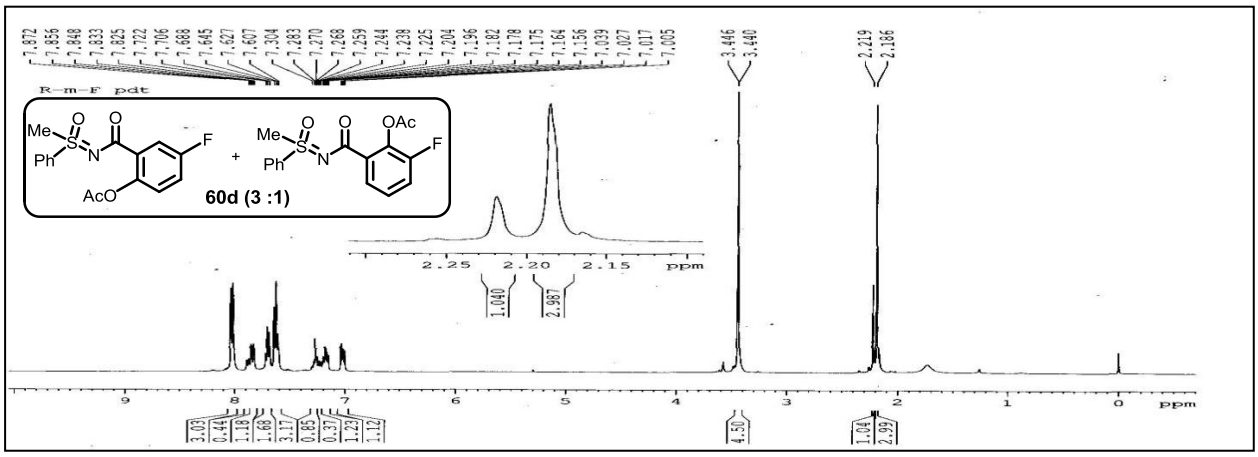
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60d (3 :1)
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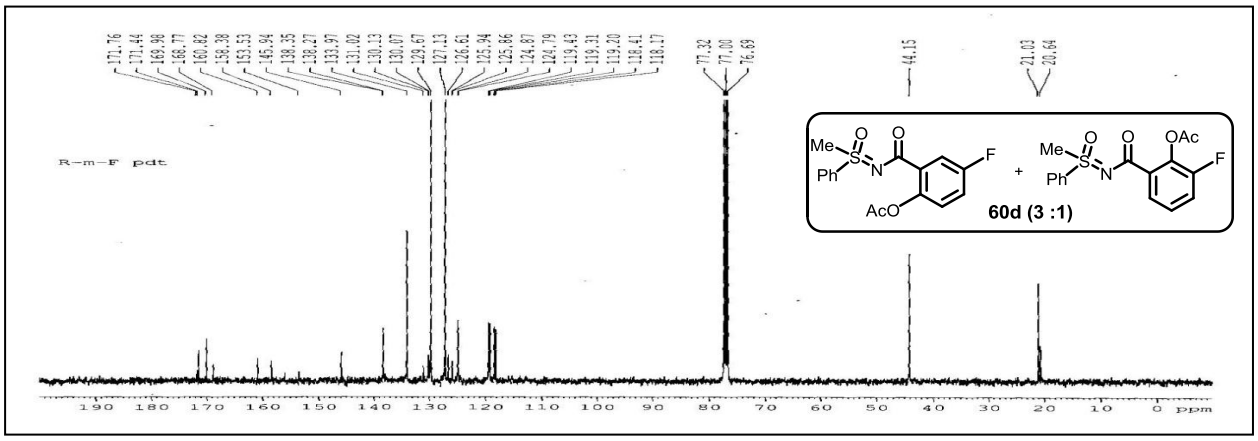
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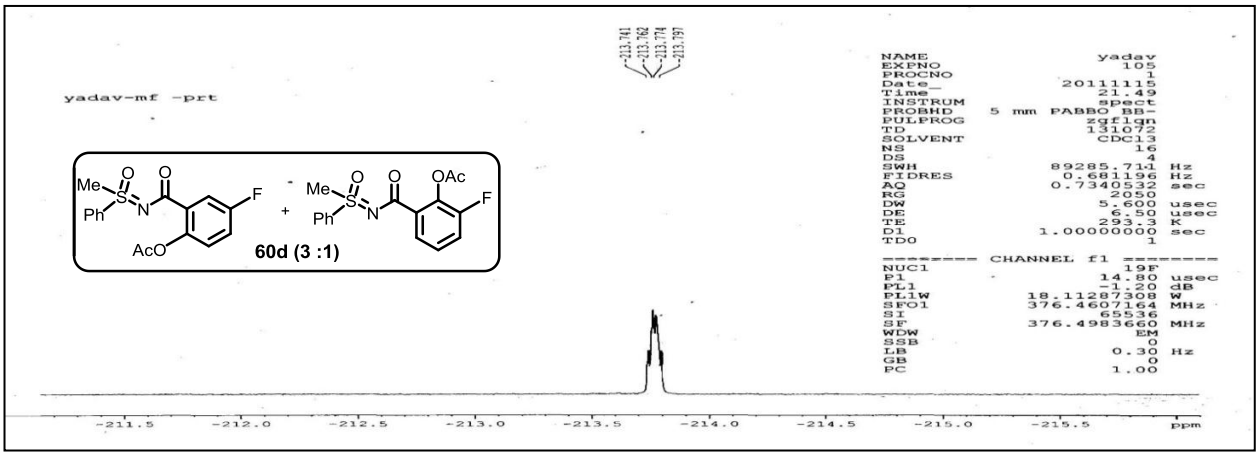
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PROCNO 1
Date_ 20111115
Time 21.49
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PULPROG zgflqn
TD 131072
SOLVENT CDCl3
NS 16
DS 4
SWH 89285.714 Hz
FIDRES 0.681196 Hz
AQ 0.7340532 sec
RG 2050
DW 5.600 usec
DE 6.50 usec
TE 293.3 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 19F
P1 14.80 usec
PL1 -1.20 dB
PL1W 18.11287308 W
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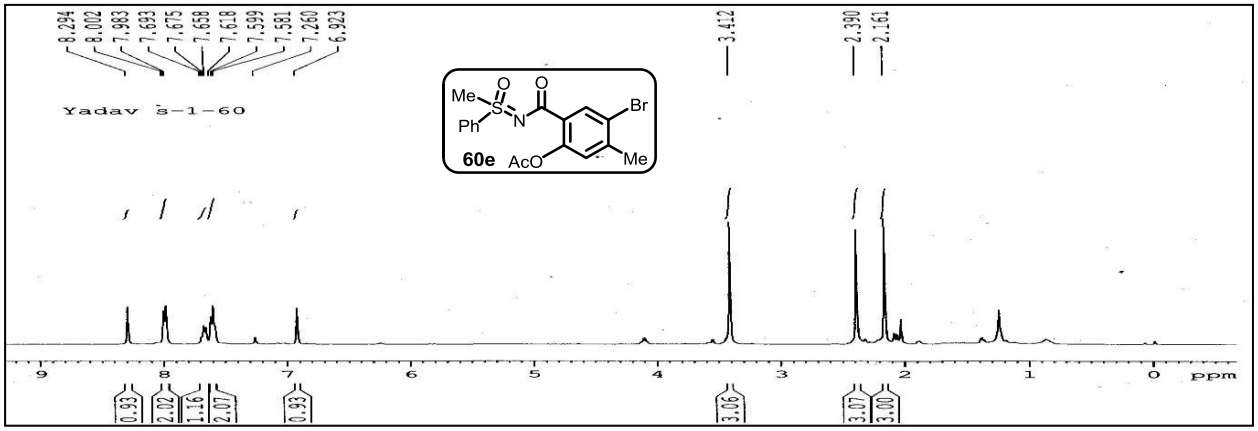
SF 376.4983660 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm


Yadav s-1-60
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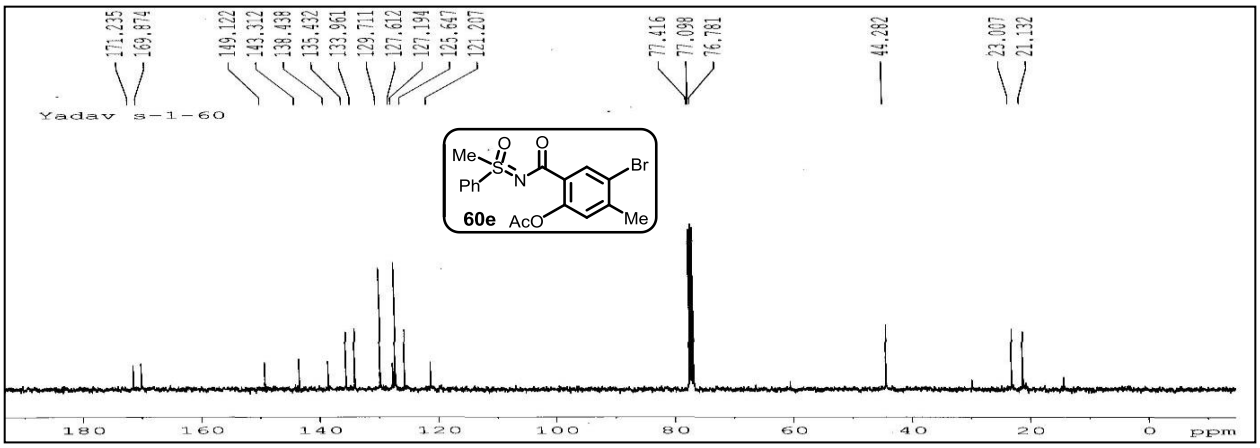
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127.194
125.647
121.207
77.416
77.098
76.781
44.262
23.007
21.132
Yadav s-1-60
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S
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O
Br
Me
60e AcO
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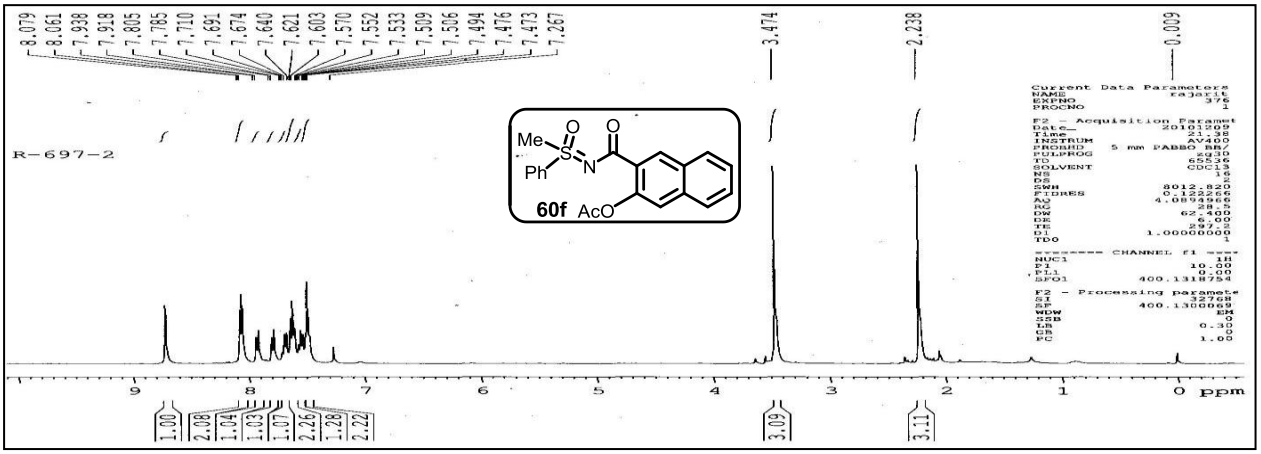
ppm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7.473
7.267
3.474
2.238
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R-697-2
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Ph
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N
O
O
60f AcO
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1.03
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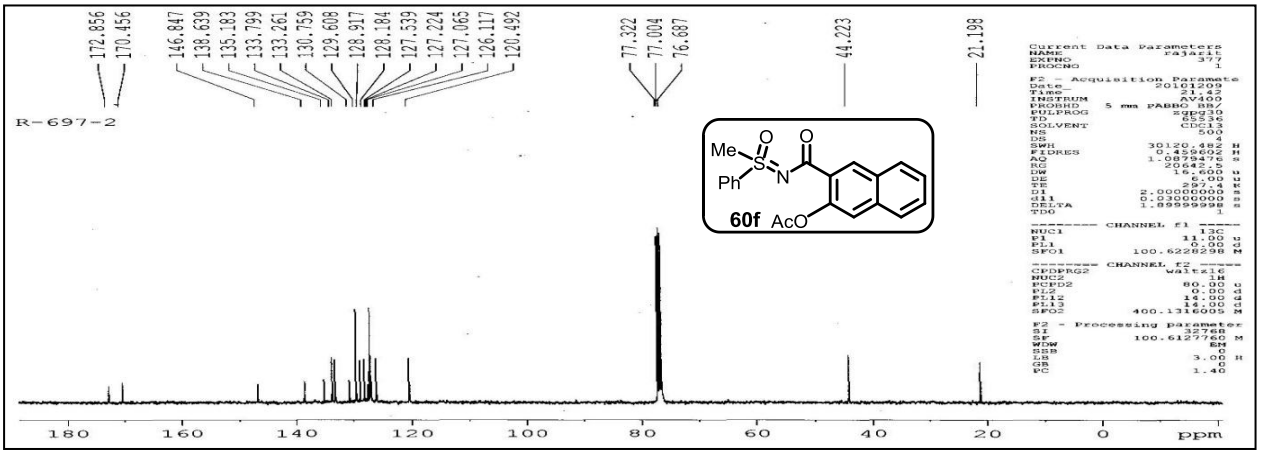
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44.223
21.198
R-697-2
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Ph
S
O
N
O
O
60f AcO
180
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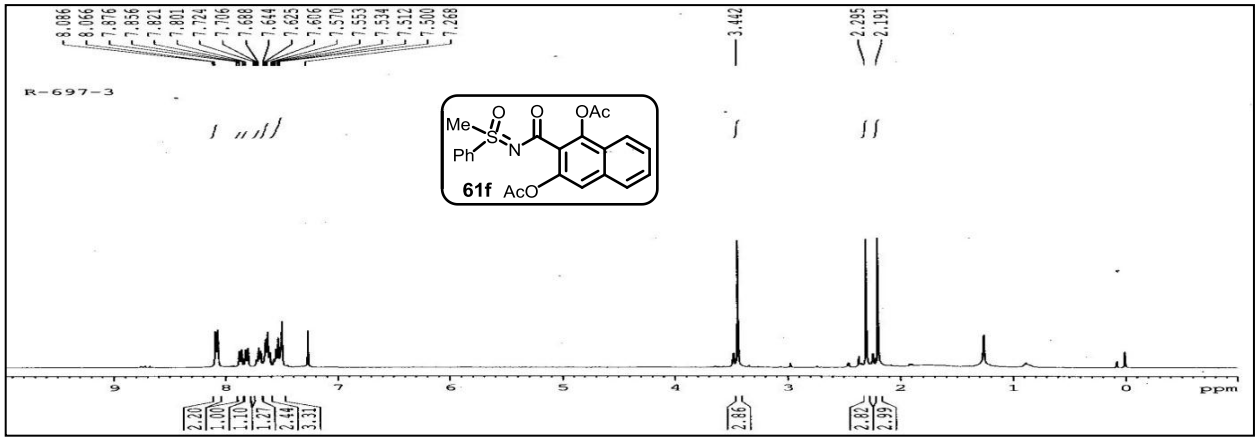
60
40
20
0
ppm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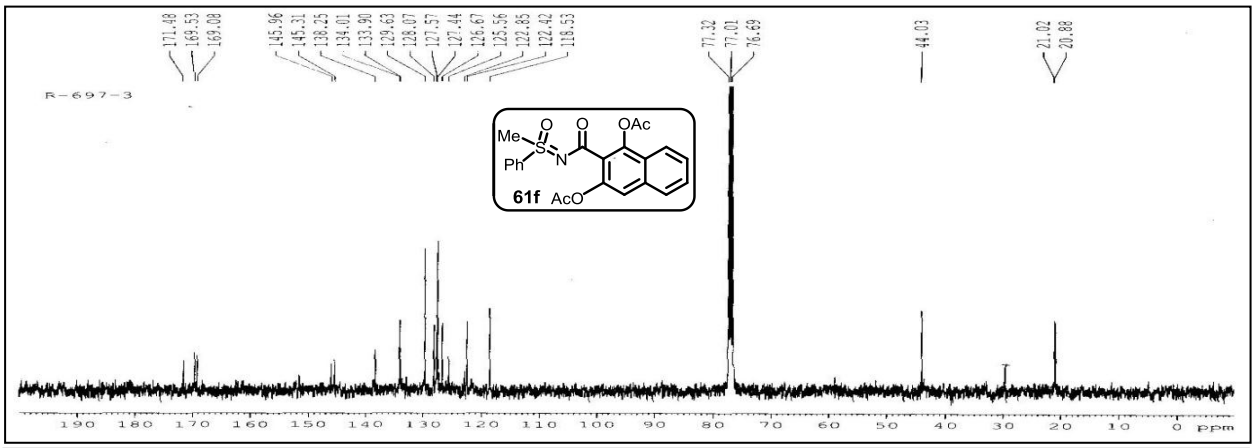
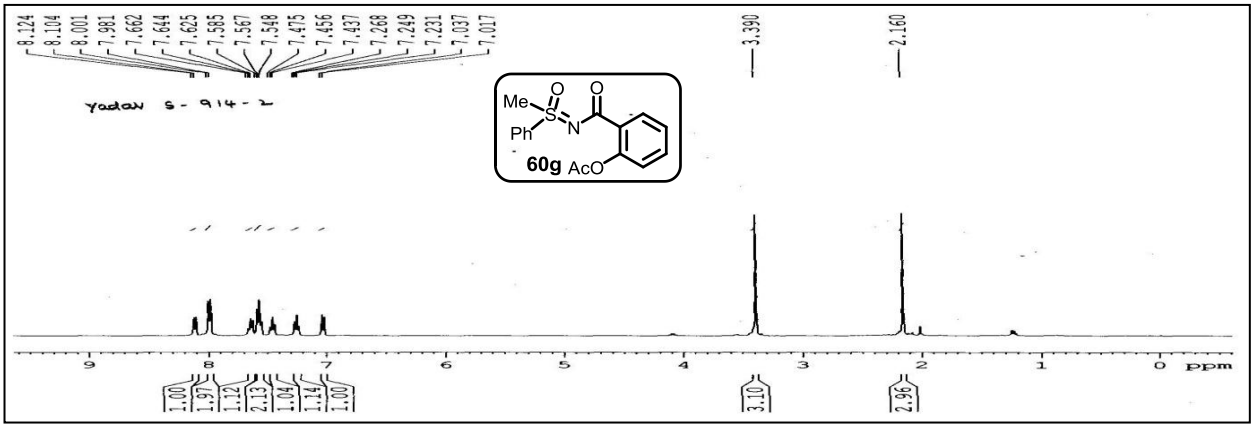
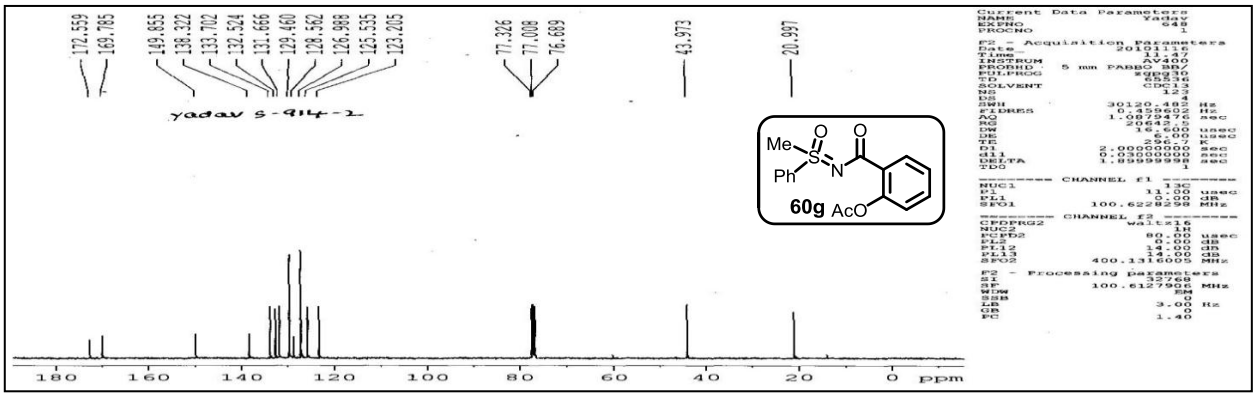
8.066
7.876
7.856
7.821
7.801
7.724
7.706
7.688
7.644
7.625
7.606
7.570
7.553
7.534
7.512
7.500
7.268
3.442
2.295
2.191
R-697-3
Me
Ph
S
O
N
O
O
OAc
61f AcO
2.20
1.00
1.10
1.27
2.44
3.31
2.86
2.82
2.99
9
8
7
6
5
4
3
2
1
0
ppm


R-697-3
61f AcO


yadav s-914-2
60g AcO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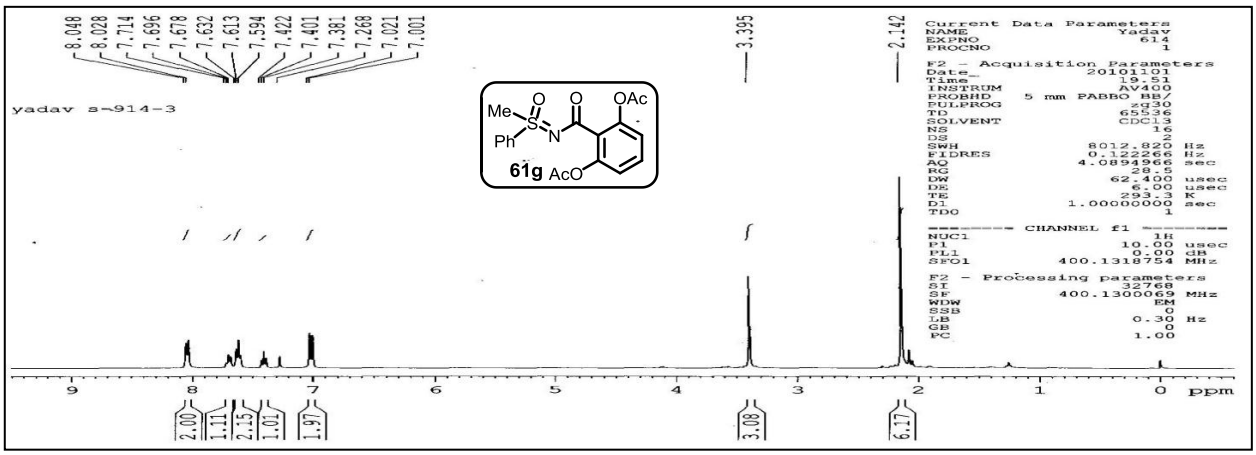
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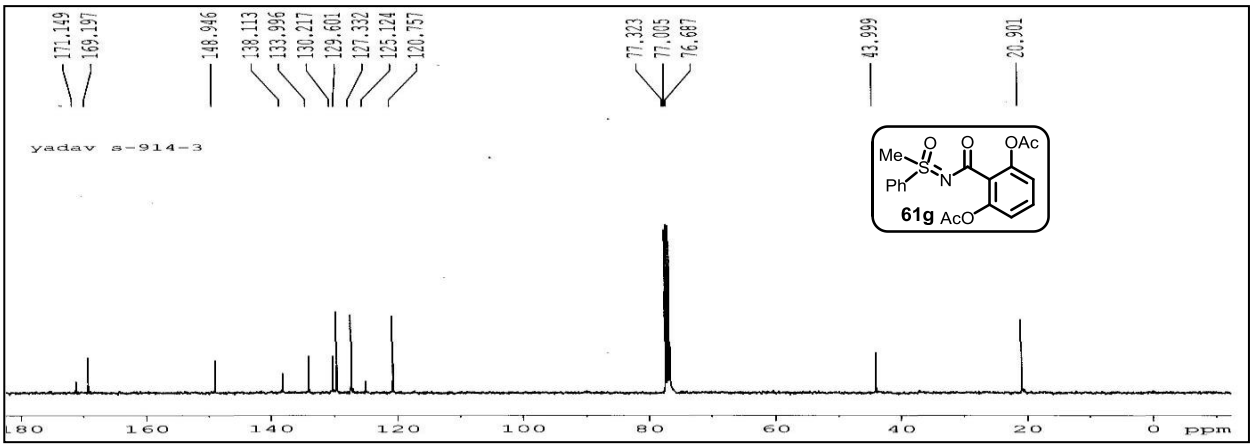
61g AcO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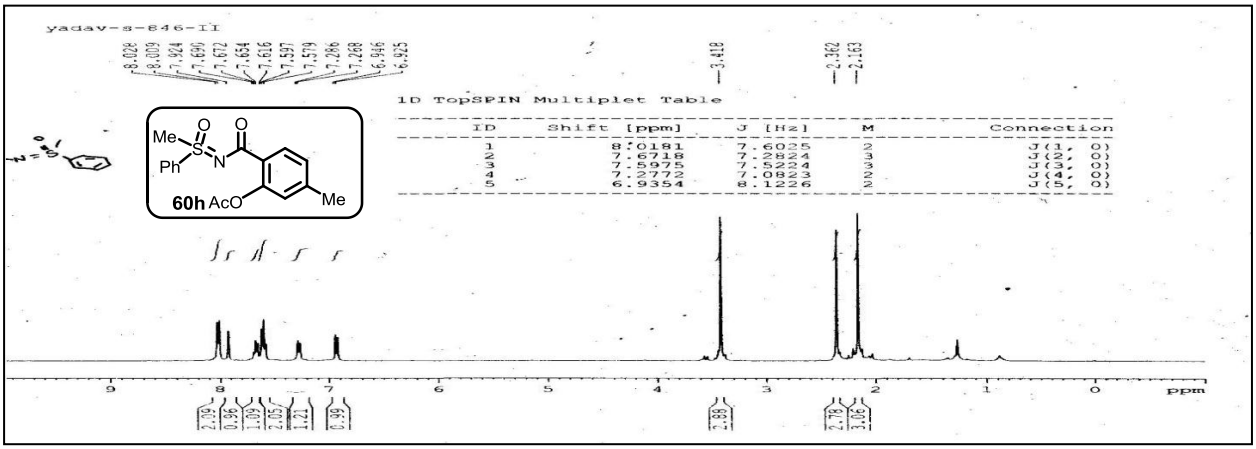
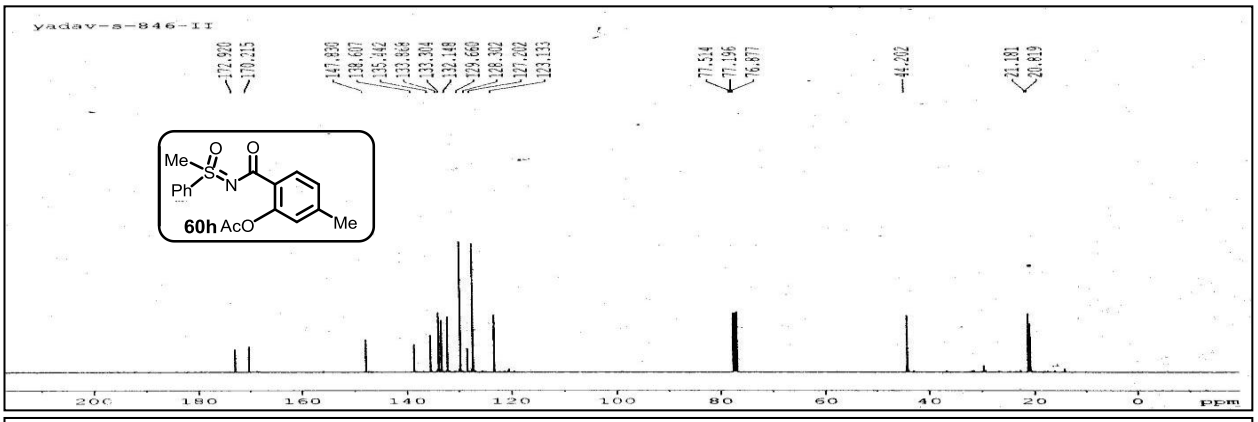
169.197
148.946
138.113
133.996
130.217
129.601
127.332
125.124
120.757
77.323
77.005
76.687
43.999
20.901
yadav s-914-3
Me
Ph
O
O
OAc
61g AcO


yadav-s-846-II
8.028
8.009
7.984
7.669
7.672
7.654
7.616
7.597
7.579
7.206
7.188
6.946
6.925
3.418
2.362
2.163
1D TopSPIN Multiplet Table
ID Shift [ppm] J [Hz] M Connection
1 8.0181 7.6 D J(1, 0)
2 7.6718 7.5 DD J(2, 0)
3 7.5975 7.5 T J(3, 0)
4 7.2775 7.0 DD J(4, 0)
5 6.9354 8.1 D J(5, 0)
Me
Ph
60h AcO
Me
ppm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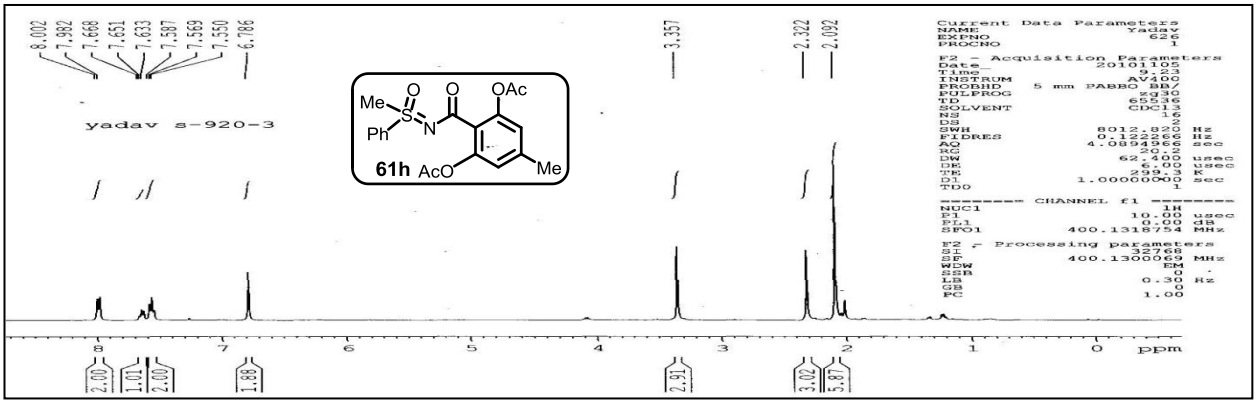
170.215
147.830
138.607
135.442
133.868
133.304
132.148
129.668
128.302
127.202
123.133
77.514
77.196
76.877
44.202
21.181
20.819
Me
Ph
60h AcO
Me
ppm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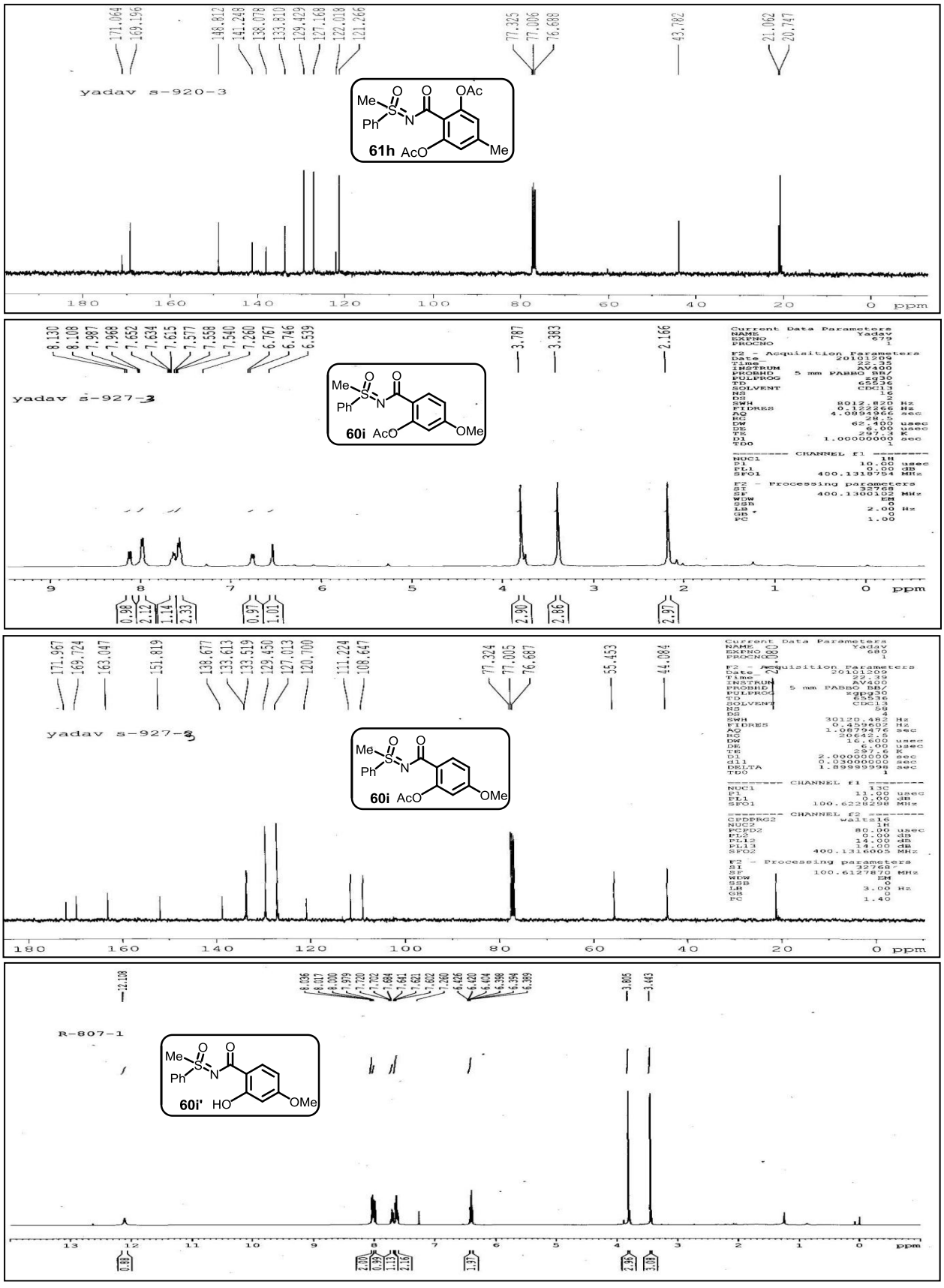
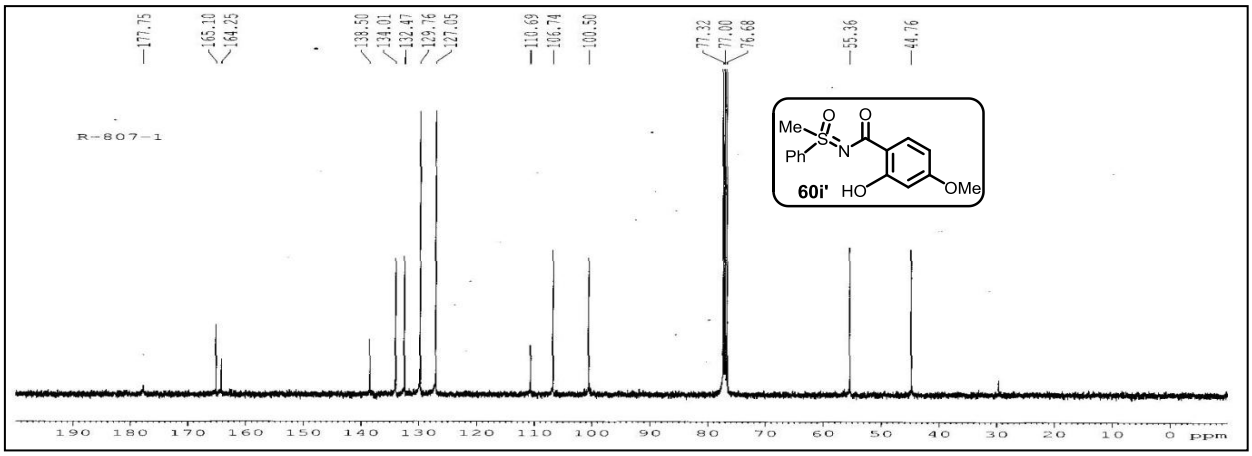
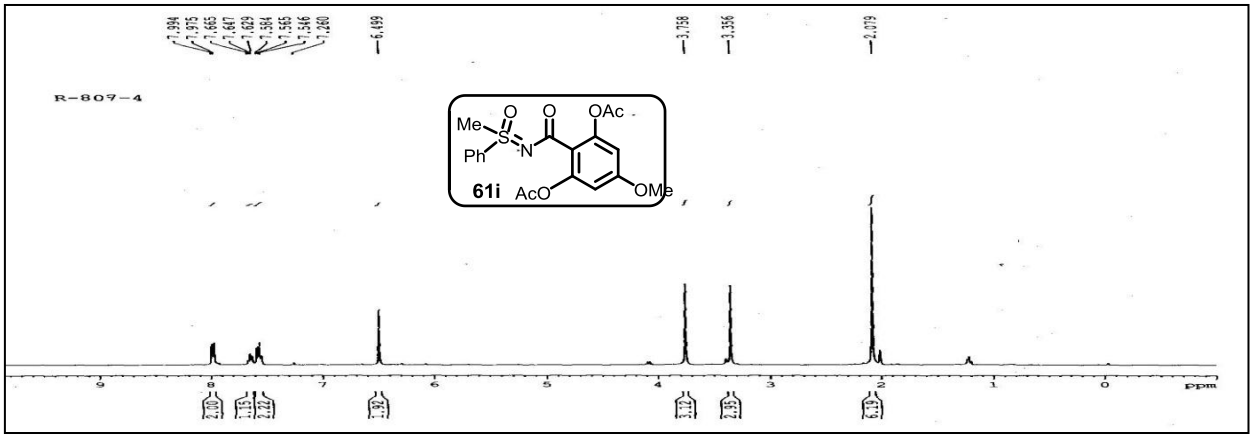
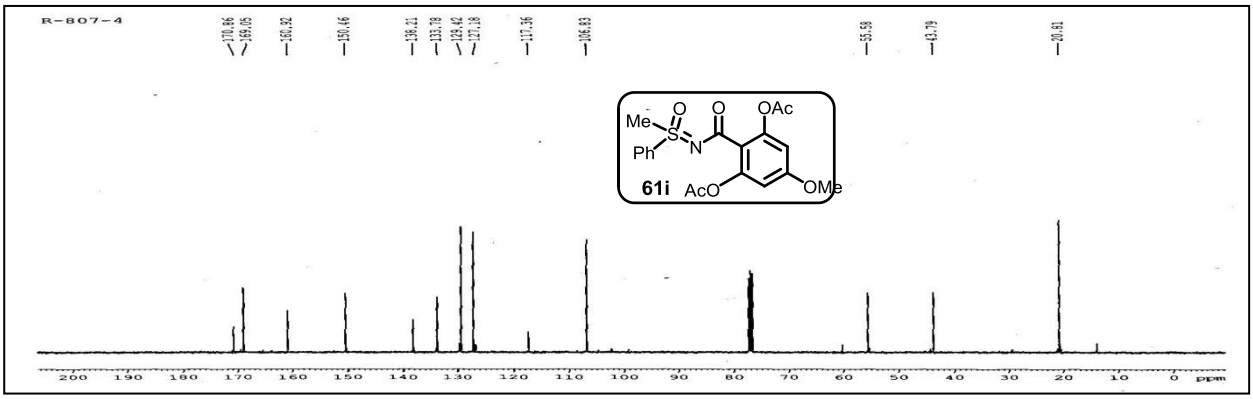
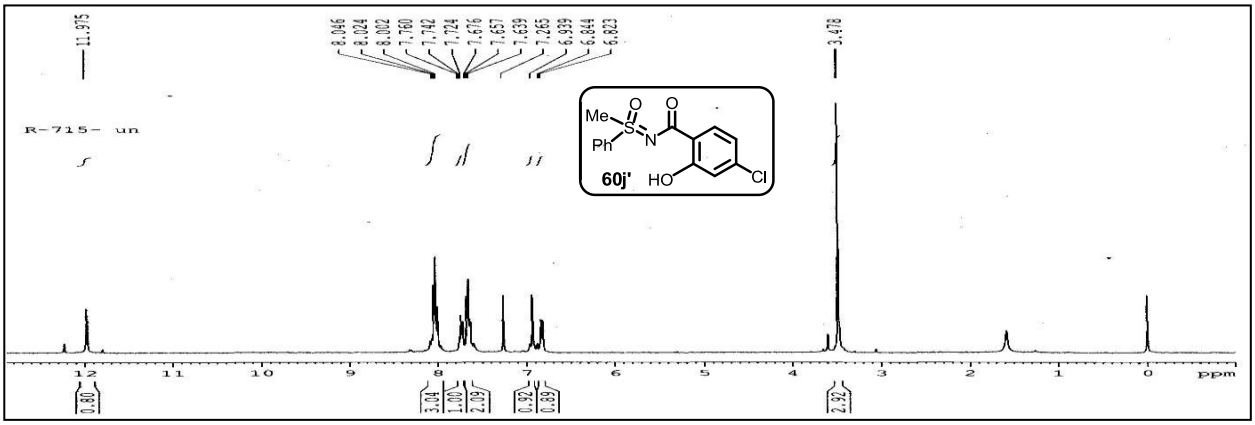
7.982
7.668
7.651
7.633
7.587
7.569
7.550
6.786
3.357
2.322
2.092
yadav s-920-3
Me
Ph
O
O
OAc
61h AcO
Me
Current Data Parameters
NAME Yadav
EXPNO 624
PROCNO 1
F2 - Acquisition Parameters
Date_ 20101105
Time 9.23
INSTRUM AV400
PROBHD 5 mm PABBO BB
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894966 sec
RG 20.2
DW 62.400 usec
DE 6.00 usec
TE 295.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 0.00 dB
SFO1 400.1318754 MHz
F2 - Processing parameters
SI 32768
SF 400.1300069 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm

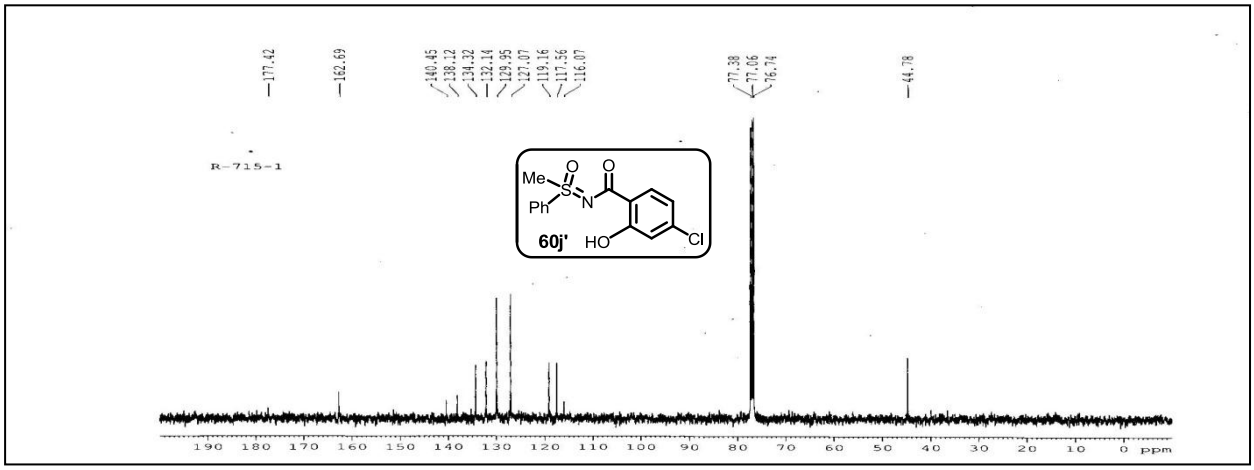

yadav s-920-3
61h
yadav s-927-3
60i
yadav s-927-3
60i
R-807-1
60i'

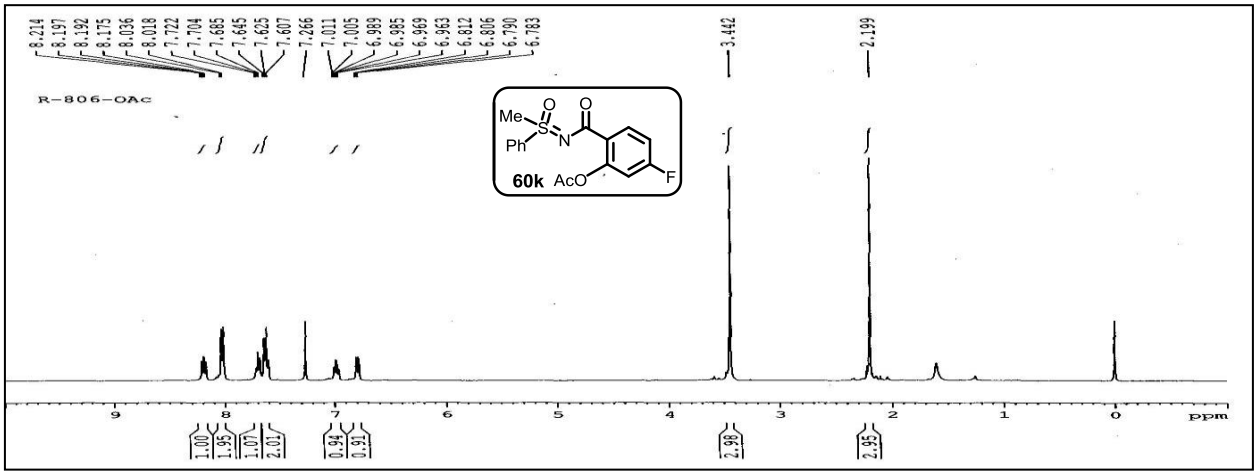

R-807-1
177.75
165.10
164.25
139.50
134.01
132.47
129.76
127.05
110.69
106.74
100.50
77.32
77.00
76.68
55.36
44.76
Me
Ph
O
N
O
60i' HO
OMe
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

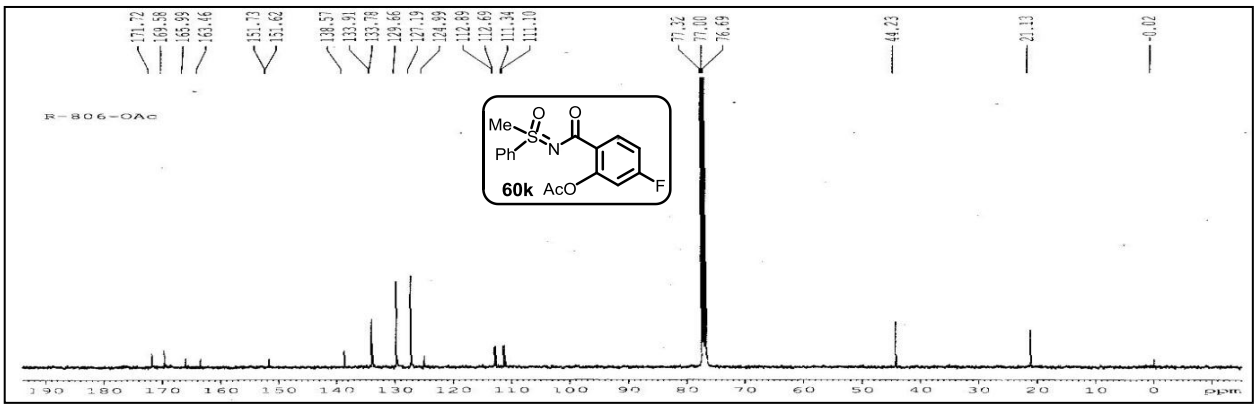

R-807-4
7.394
7.375
7.365
7.347
7.329
7.304
7.295
7.280
6.499
3.738
3.356
2.079
Me
Ph
O
N
O
OAc
61i AcO
OMe
9 8 7 6 5 4 3 2 1 0 ppm


R-807-4
170.86
169.05
160.32
150.46
136.21
133.78
129.42
127.18
117.36
106.83
55.68
43.79
20.81
Me
Ph
O
N
O
OAc
61i AcO
OMe
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


R-715- un
11.975
8.046
8.024
8.002
7.760
7.742
7.724
7.676
7.657
7.639
7.265
6.939
6.844
6.823
3.478
Me
Ph
O
N
O
60j' HO
Cl
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.80
3.04
1.00
2.09
0.92
0.89
2.92


R-715-1
60j' HO Cl


R-806-OAc
60k AcO F


R-806-OAc
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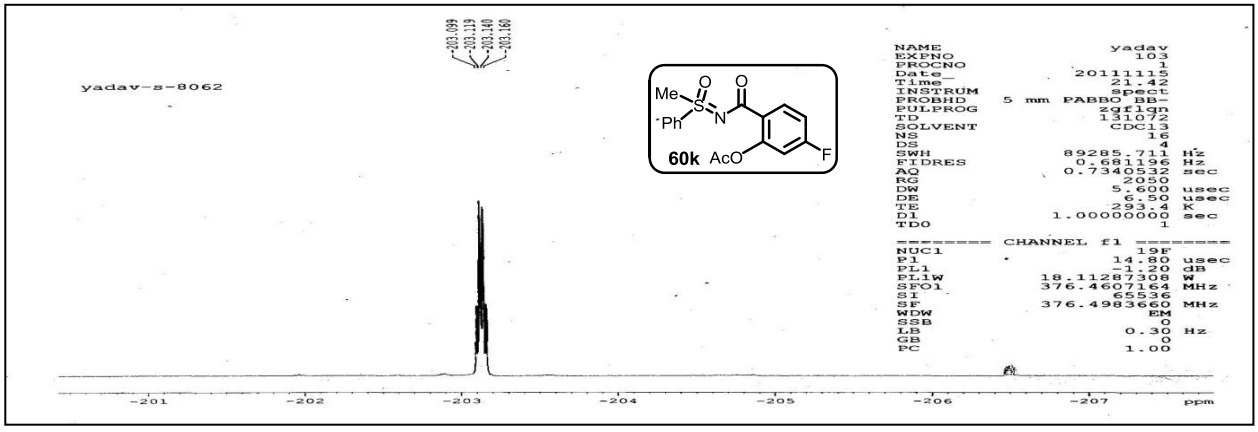
yadav-s-8062
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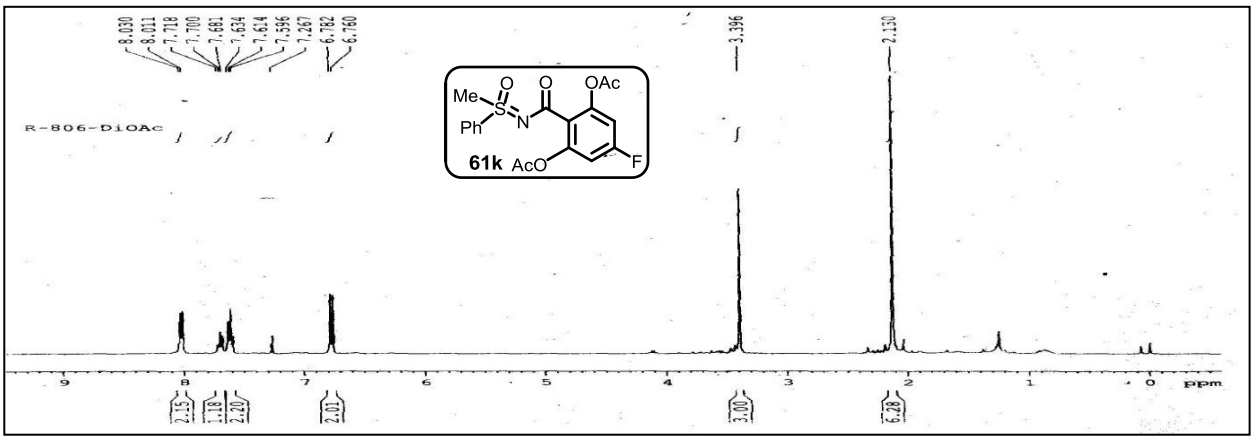
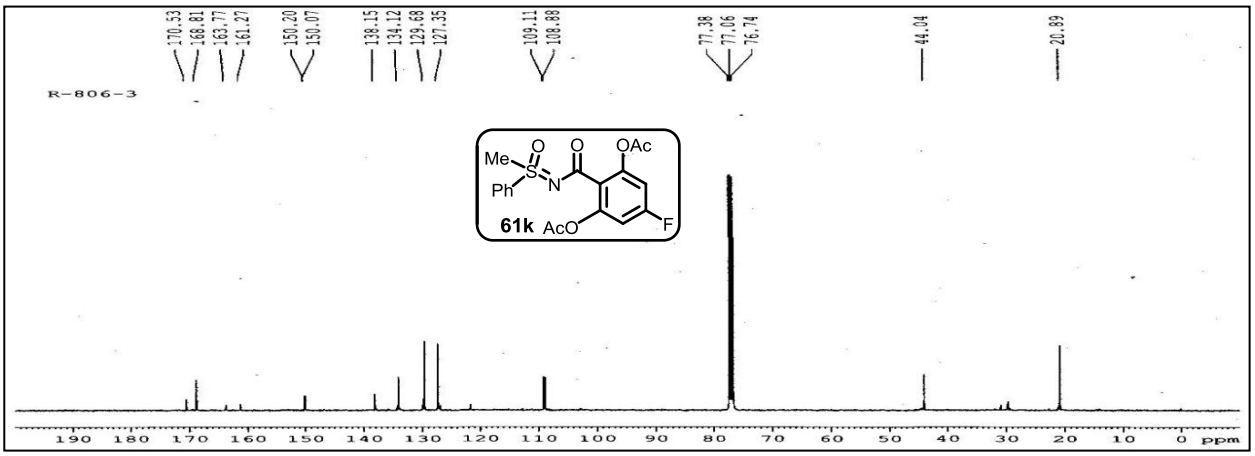
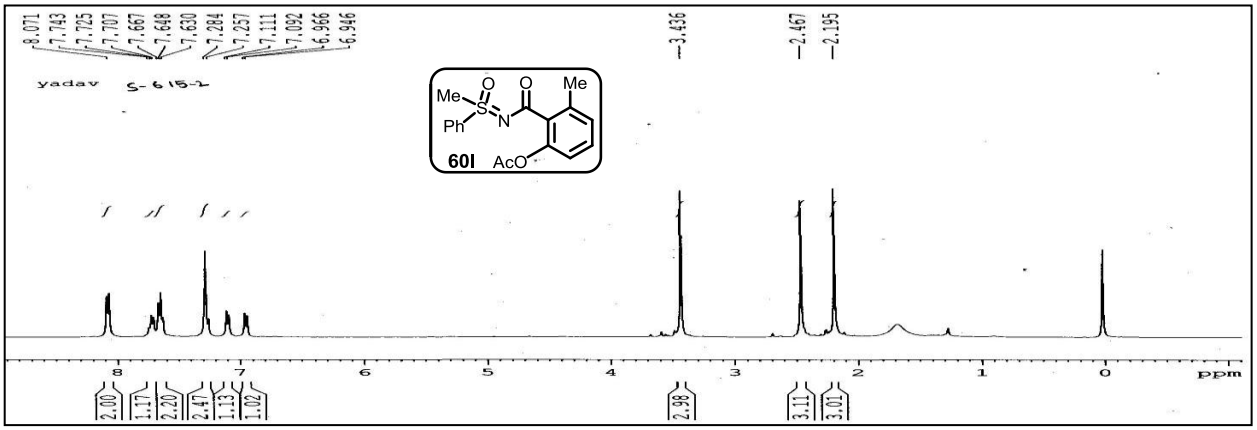
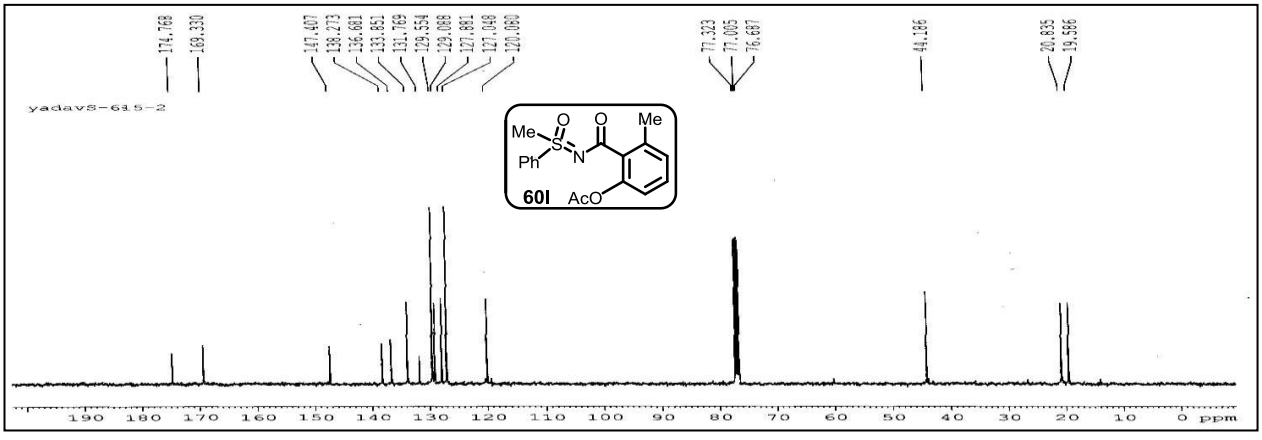

R-806-D1OAc
61k AcO OAc F


R-806-3
61k AcO OAc F


yadav S-615-2
60l AcO Me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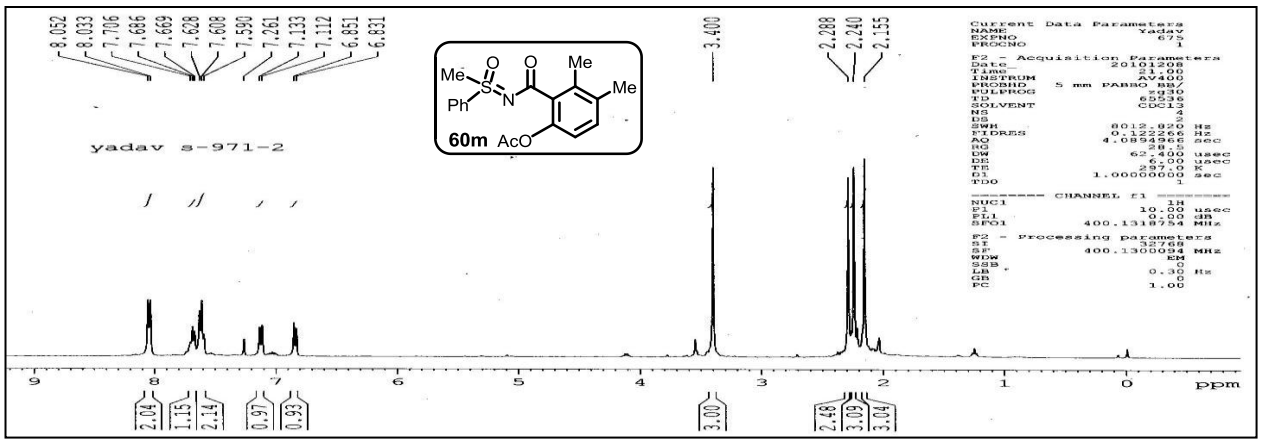
60l AcO Me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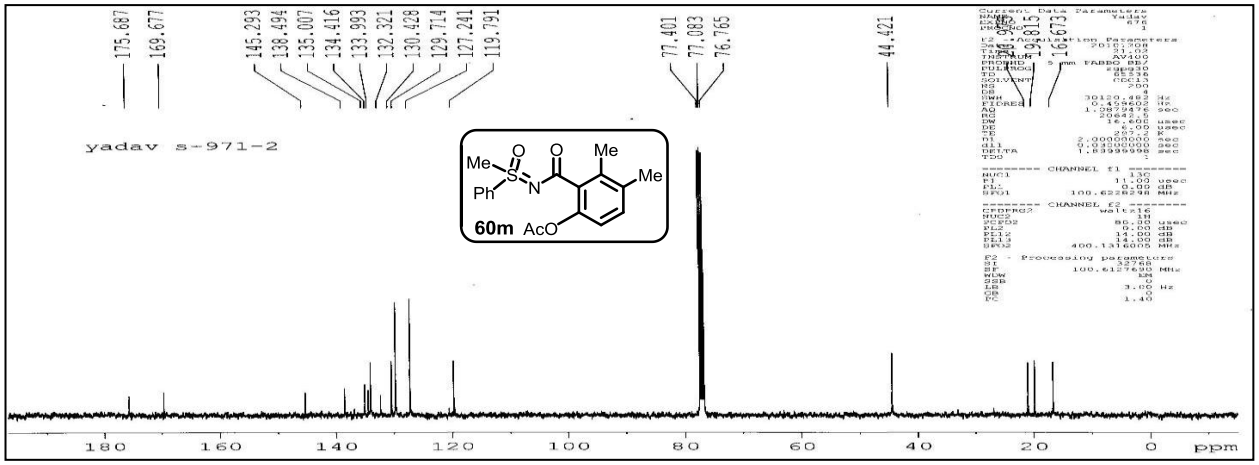
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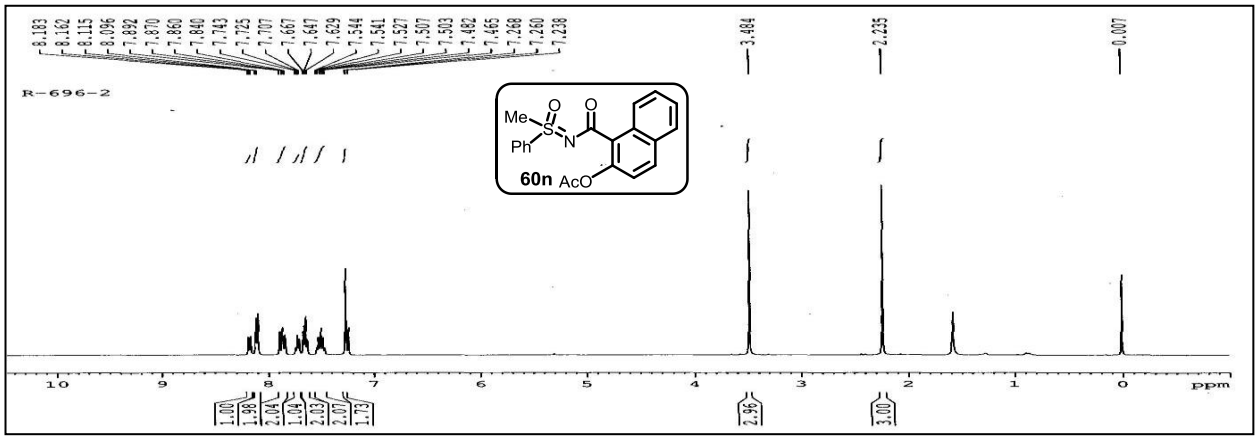
60m AcO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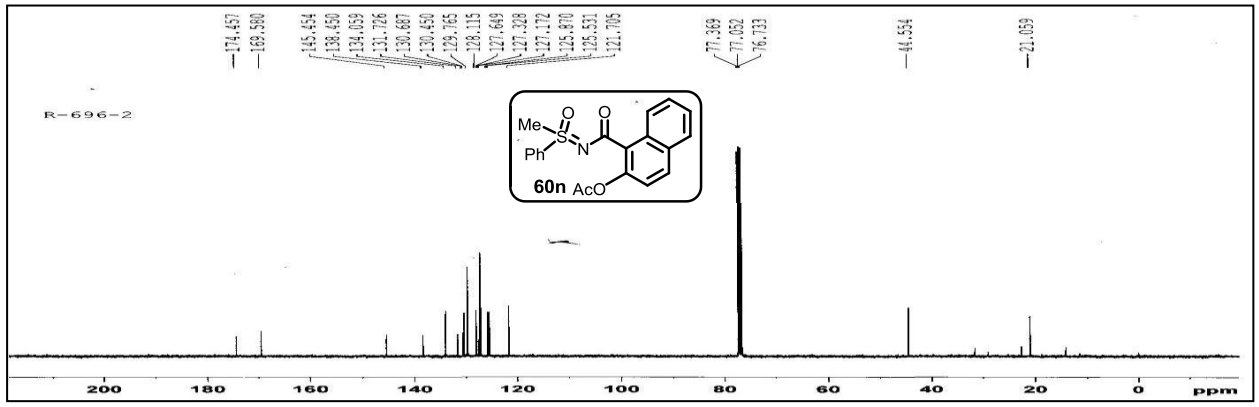
60n AcO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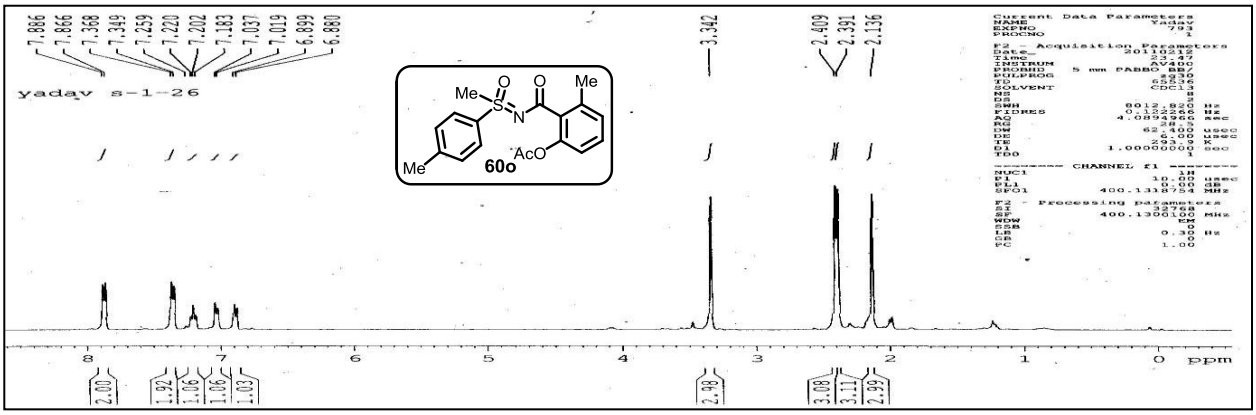
60n AcO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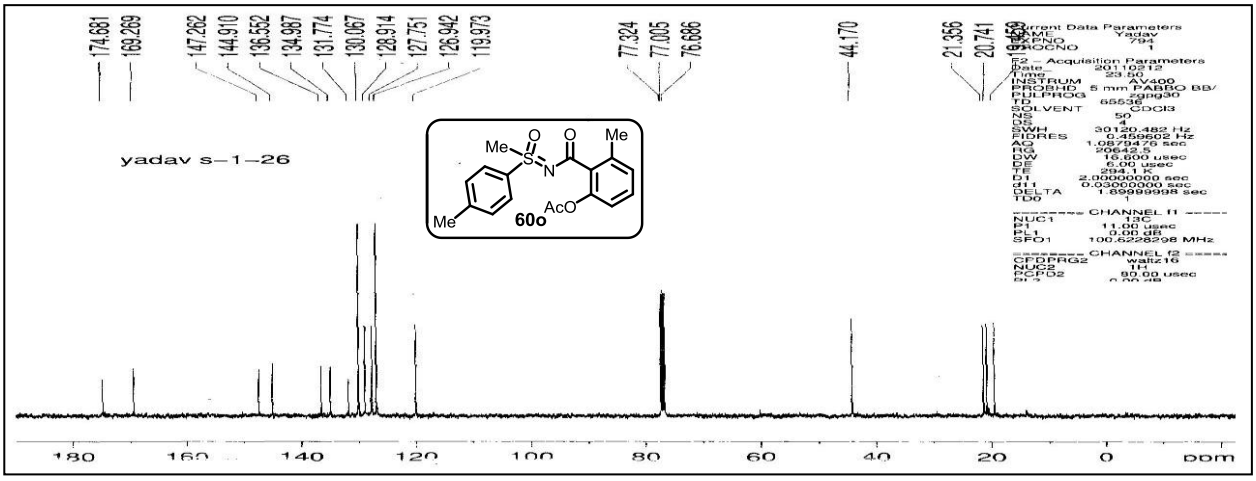
60o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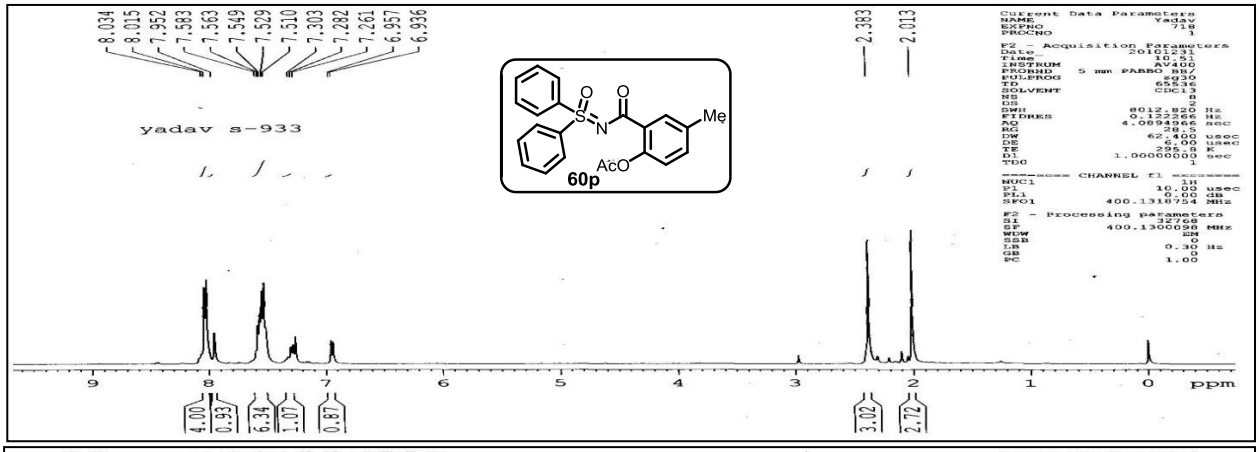
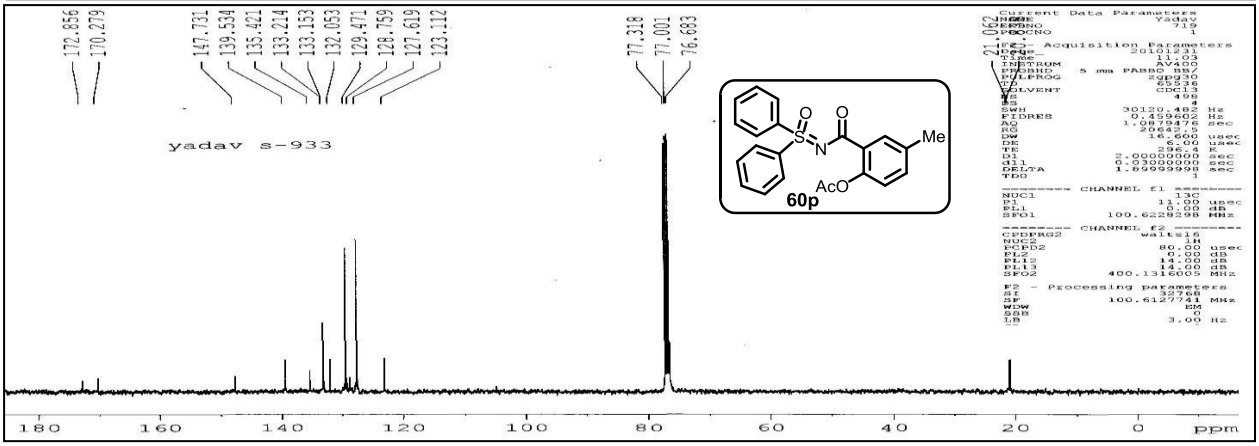
60o


yadav s-933
60p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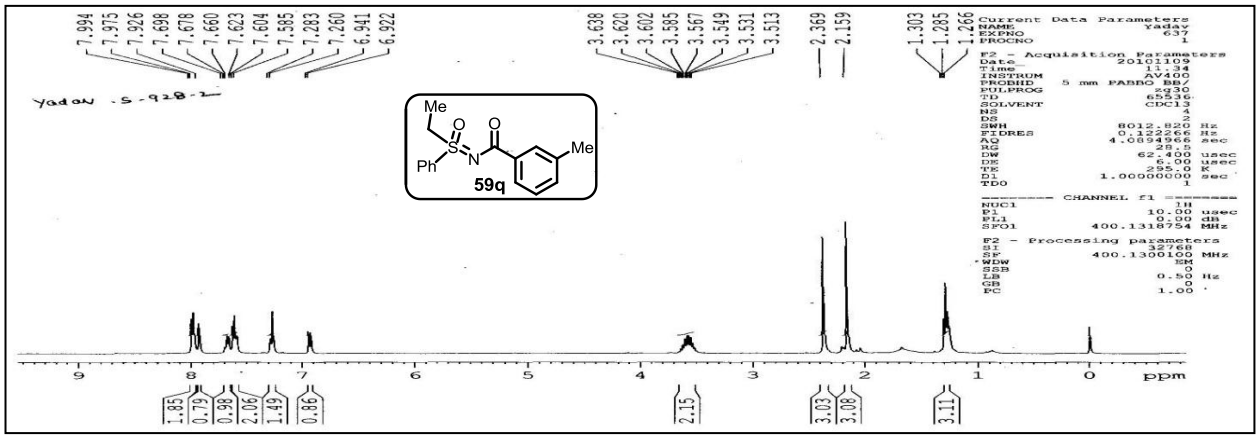
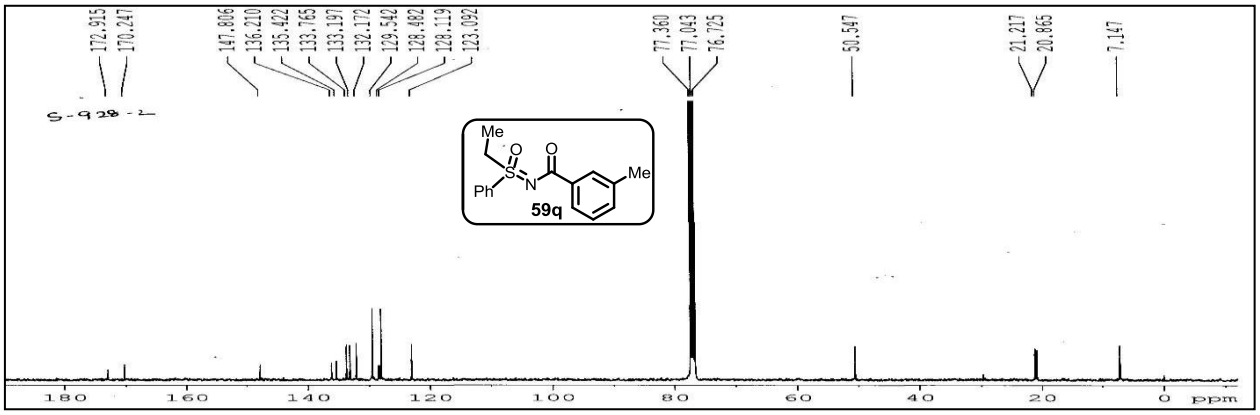

59q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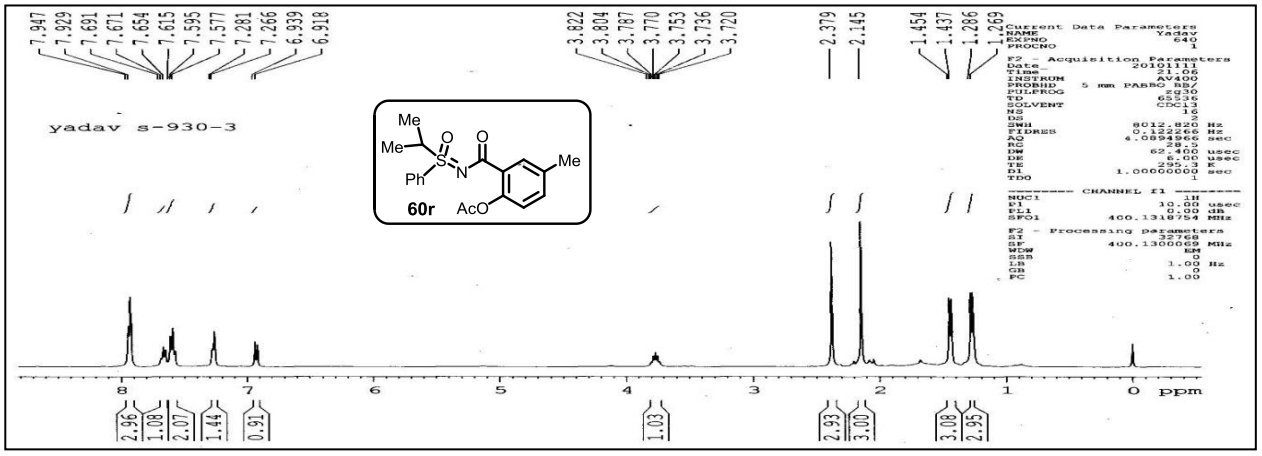
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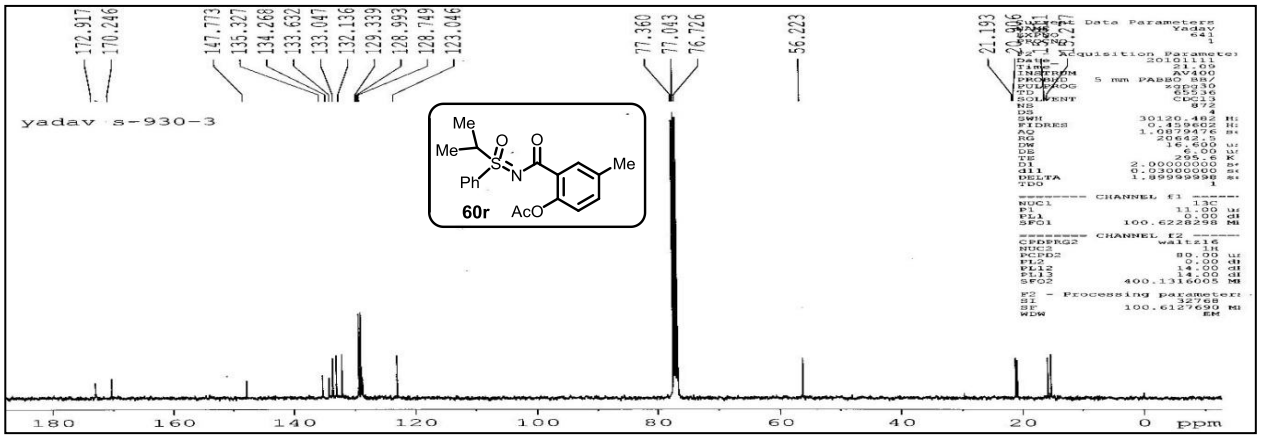
AcO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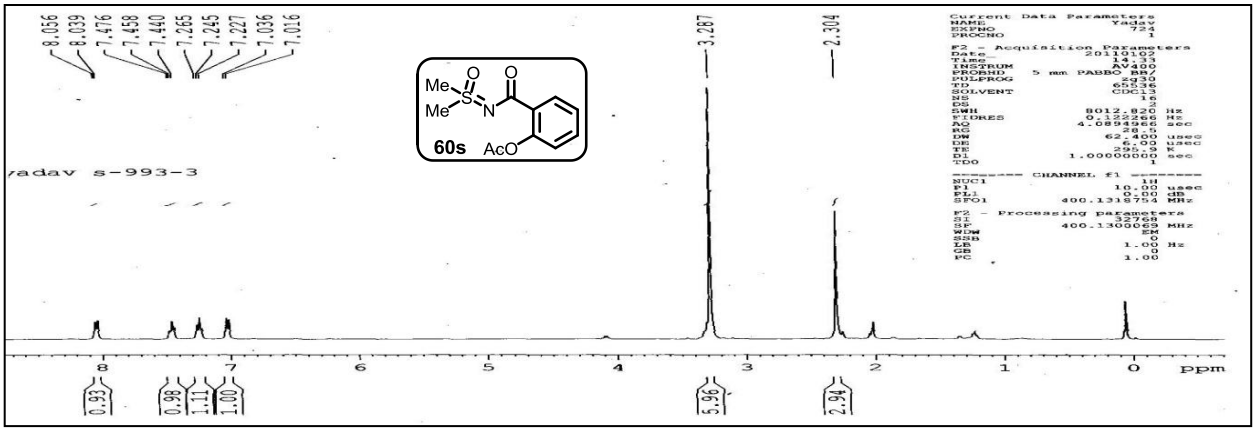
AcO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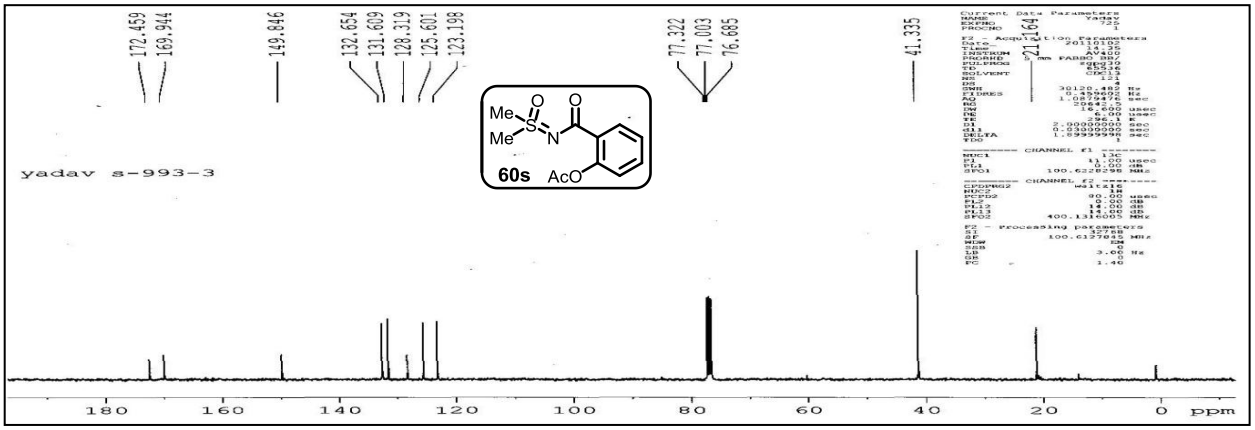
8.039
7.476
7.458
7.440
7.265
7.245
7.227
7.036
7.016
3.287
2.304
yadav s-993-3
60s AcO
0.93
0.98
1.11
1.00
5.96
2.94
ppm


172.459
169.944
149.846
132.654
131.609
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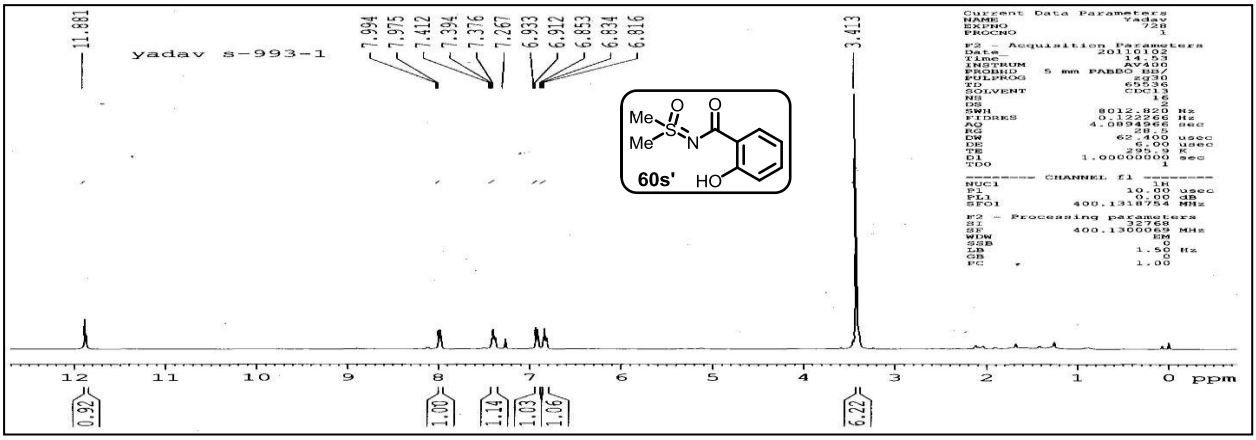
125.601
123.198
77.322
77.003
76.685
41.335
yadav s-993-3
60s AcO
ppm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7.412
7.394
7.376
7.267
6.933
6.912
6.853
6.834
6.816
3.413
60s' HO
0.92
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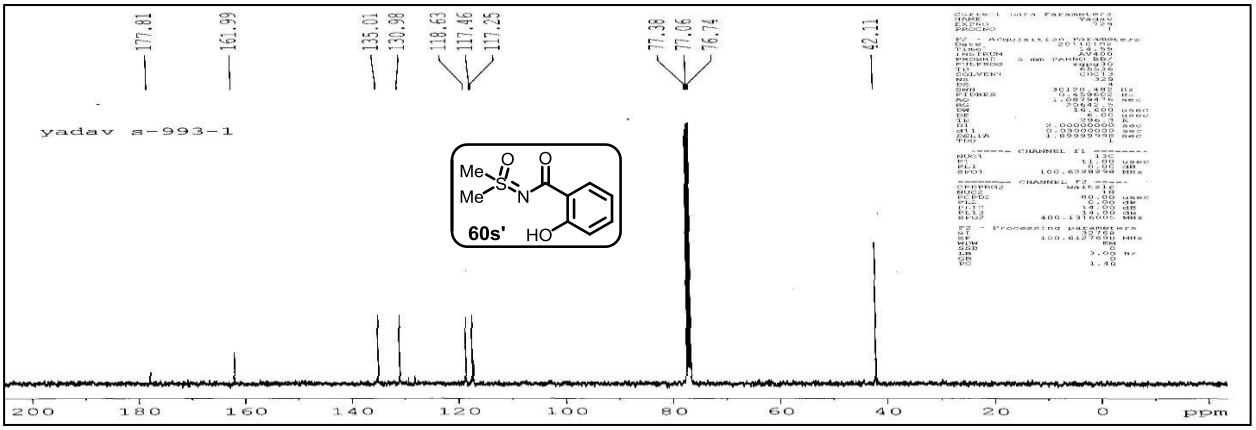
1.14
1.03
1.06
6.22
ppm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161.99
135.01
130.98
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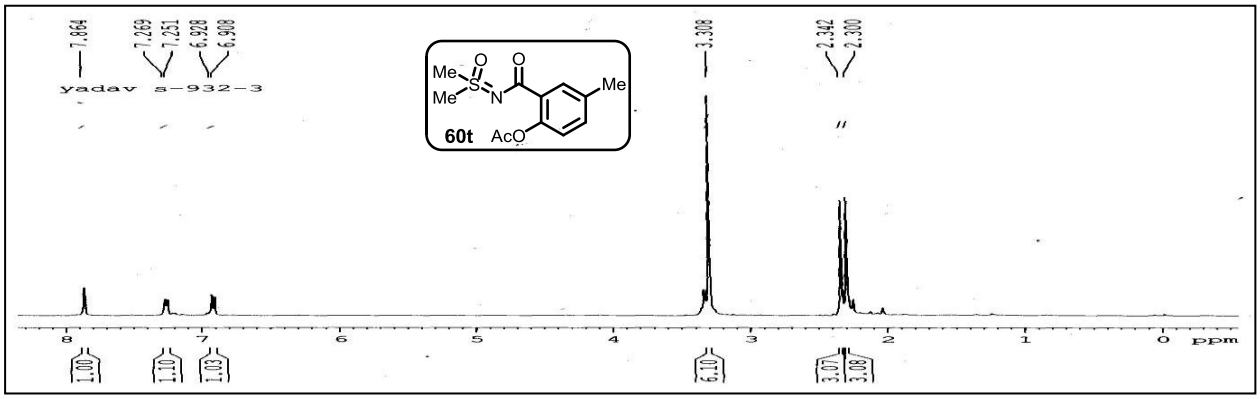
117.46
117.25
77.38
77.06
76.74
42.11
yadav s-993-1
60s' HO
ppm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7.251
6.928
6.908
yadav s-932-3
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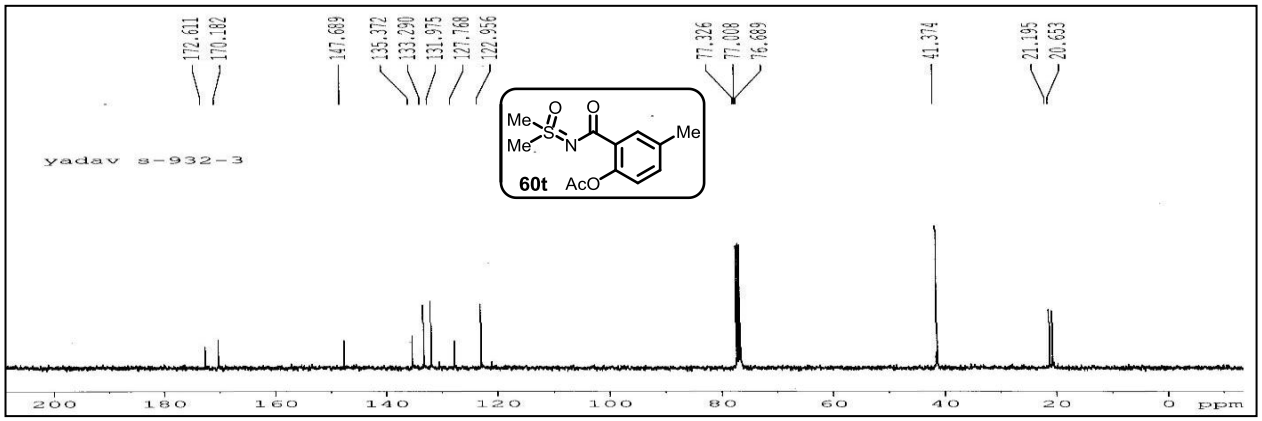
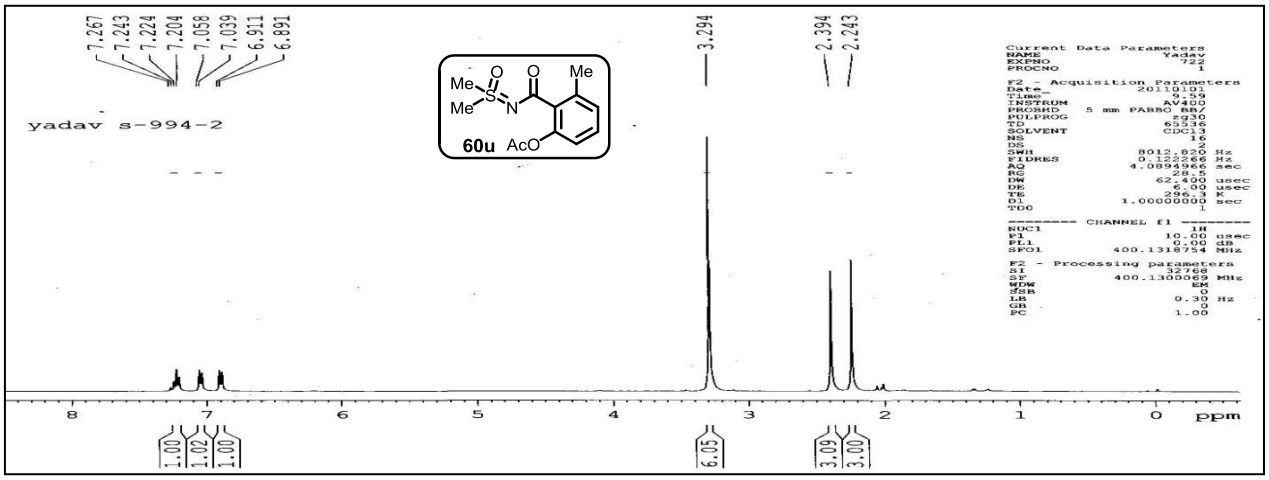
2.300
60t
AcO
1.00
1.10
1.03
6.10
3.07
3.06
ppm


172.611
170.182
147.689
135.372
133.290
131.975
127.768
122.956
77.326
77.008
76.689
41.374
21.195
20.653
yadav s-932-3
60t
AcO
200
180
160
140
120
100
80
60
40
20
0
ppm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2.243
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FIDRES 0.122266 Hz
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RG 28.5
DW 62.400 usec
DE 6.00 usec
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D1 1.00000000 sec
TD0 1
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PL1 0.00 dB
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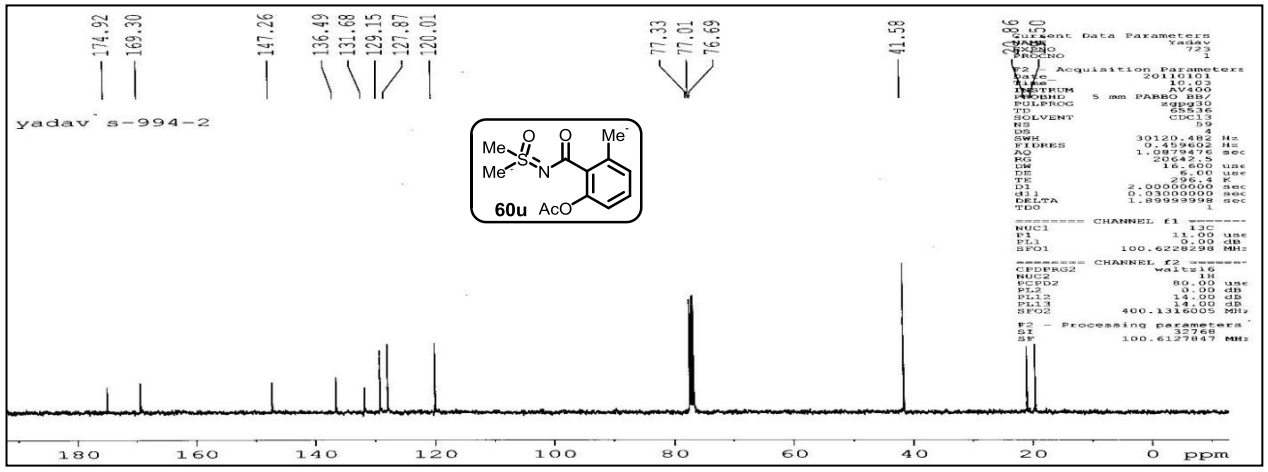
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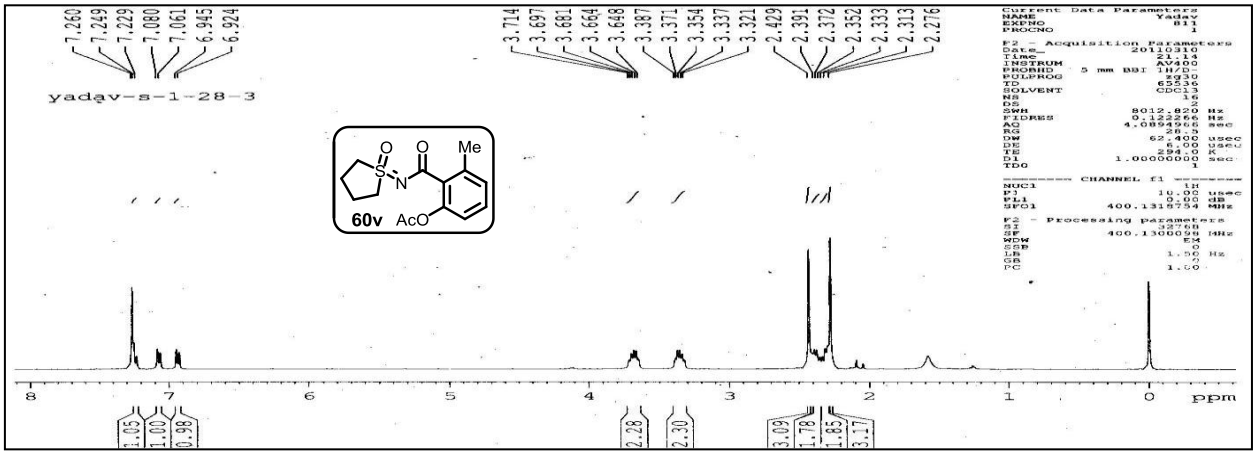
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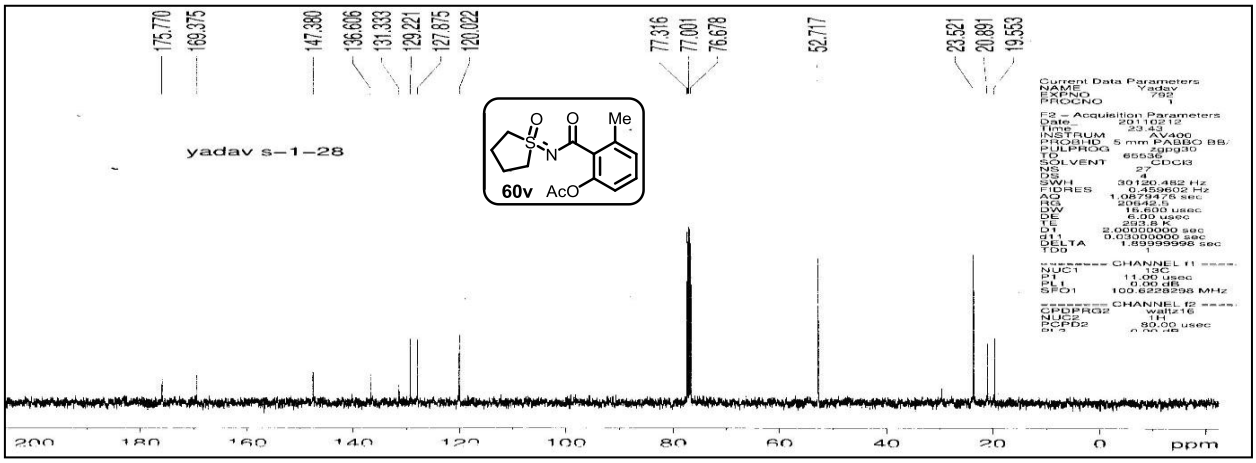
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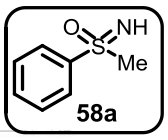
3/7/2011 19:32:29 1 / 1

==== Shimadzu LCsolution Analysis Report ====



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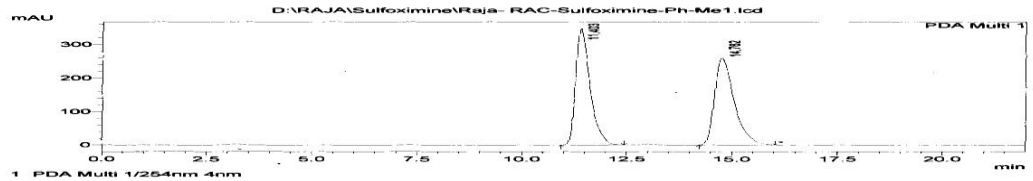

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

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2	14.762	8456626	259447	50.157	42.645
Total		16860185	608380	100.000	100.000

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3/7/2011 19:37:27 1 / 1

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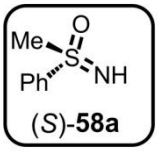

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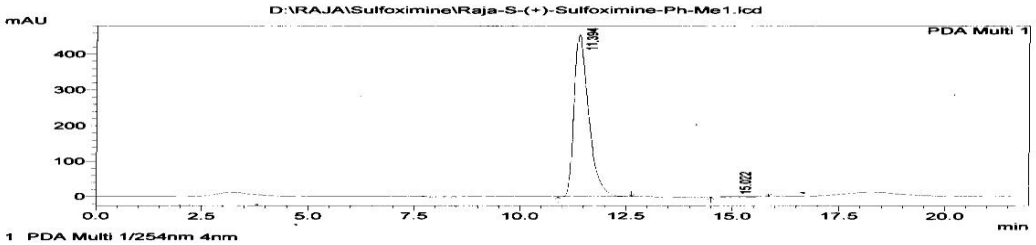

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

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1	11.394	11001708	454800	99.653	99.741
2	15.022	38322	1180	0.347	0.259
Total		11040031	455980	100.000	100.000

D:\RAJA\Sulfoximine\Raja-S-(+)-Sulfoximine-Ph-Me1.lcd

10/27/2011 12:52:04 1 / 1

==== Shimadzu LCsolution Analysis Report ==

D:\RAJA\r-535 Sm\R-535 p-F SM1.lcd

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Sample ID	: R-535 p-F SM
Tray#	: 1
Vail #	: 1
Injection Volume	: 20 uL
Data File Name	: R-535 p-F SM1.lcd
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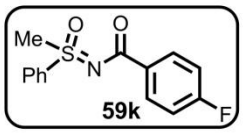

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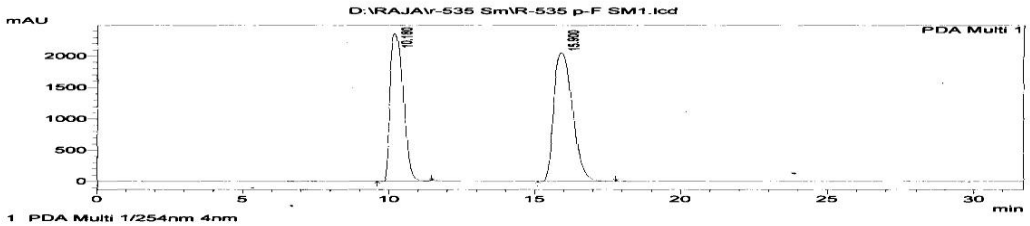

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

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1	10.180	74150703	2357587	44.468	53.422
2	15.900	92598316	2055551	55.532	46.578
Total		166749019	4413137	100.000	100.000

D:\RAJA\r-535 Sm\R-535 p-F SM1.lcd

4/2/2011 00:30:01 1 / 1

==== Shimadzu LCsolution Analysis Report ====

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Acquired by	: Admin
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Sample ID	: R-578-p-F
Tray#	: 1
Vail #	: 1
Injection Volume	: 20 uL
Data File Name	: R-578-p-F1.lcd
Method File Name	: raja-22-02-2011.lcm
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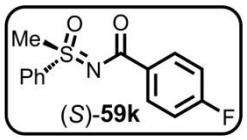

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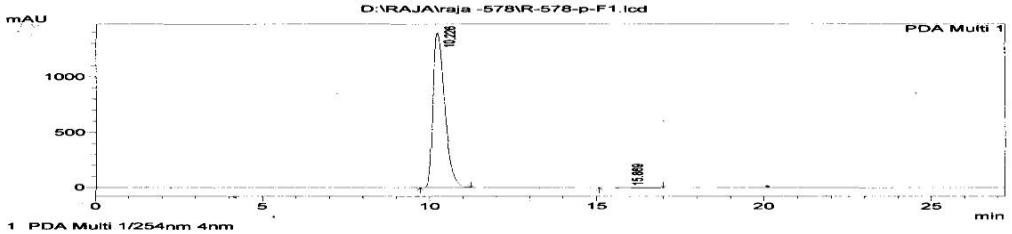

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

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1	10.226	34171576	1396091	99.722	99.798
2	15.869	95278	2828	0.278	0.202
Total		34266854	1398919	100.000	100.000

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4/2/2011 00:26:19 1 / 1

==== Shimadzu LCsolution Analysis Report ====

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Sample ID	: R-806-p-F-o-OAc
Tray#	: 1
Vail #	: 1
Injection Volume	: 20 uL
Data File Name	: R-806-p-F-o-OAc1.lcd
Method File Name	: raja-22-02-2011.lcm
Batch File Name	: SingleRun120110401232314.lcb
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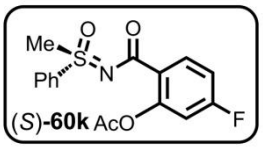

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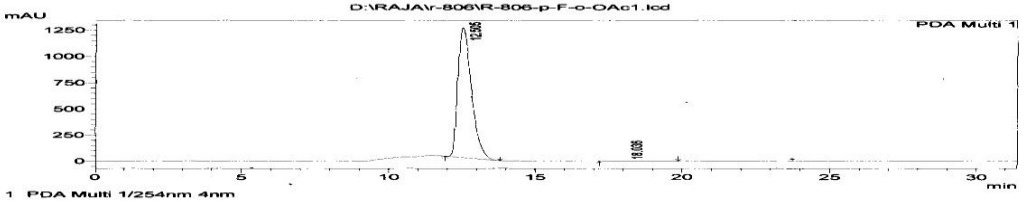

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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2	18.036	41883	859	0.105	0.069
Total		40067520	1241465	100.000	100.000

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==== Shimadzu LCsolution Analysis Report ====

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Sample ID	: R-o-Tolyl-Rac-2
Tray#	: 1
Vail #	: 1
Injection Volume	: 20 uL
Data File Name	: R-o-Tolyl-Rac-3.lcd
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Batch File Name	: SingleRun120110222213853.lcb
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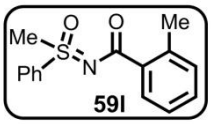

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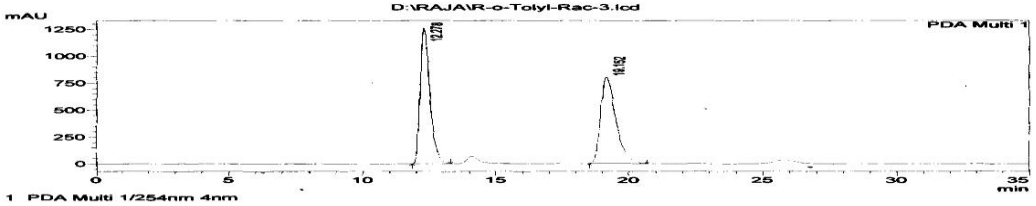

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.278	32365766	1260413	50.140	61.125
2	19.152	32185524	801624	49.860	38.875
Total		64551289	2062037	100.000	100.000

D:\RAJA\R-o-Tolyl-Rac-3.lcd

2/23/2011 21:21:56 1 / 1

==== Shimadzu LCsolution Analysis Report ====

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Sample Name	: R-578-S-(+)-2
Sample ID	: R-578-S-(+)-2
Tray#	: 1
Vail #	: 1
Injection Volume	: 20 uL
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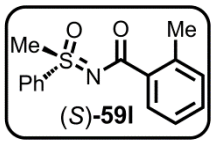

(*S*)-**59l**

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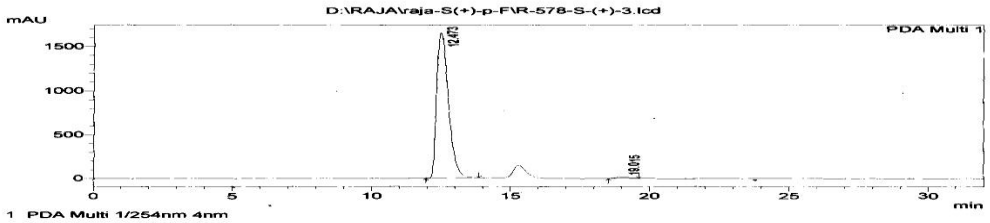

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.473	48374266	1649287	99.028	99.072
2	19.015	474879	15448	0.972	0.928
Total		48849145	1664735	100.000	100.000

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2/22/2011 22:12:29 1 / 1

==== Shimadzu LCsolution Analysis Report ====

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Sample ID	: R-750-OAc-1
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Vail #	: 1
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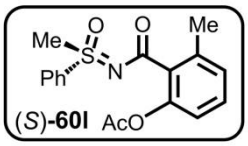

(*S*)-**60l**

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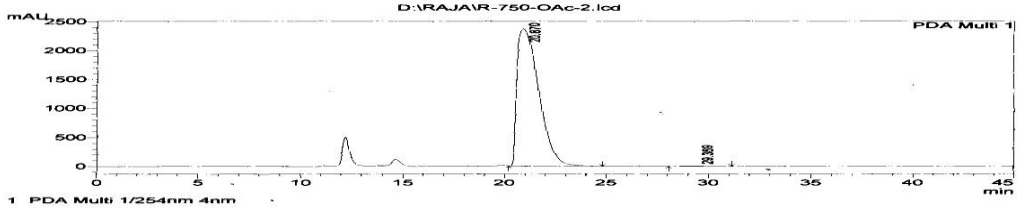


PeakTable

PDA Ch1 254nm 4nm

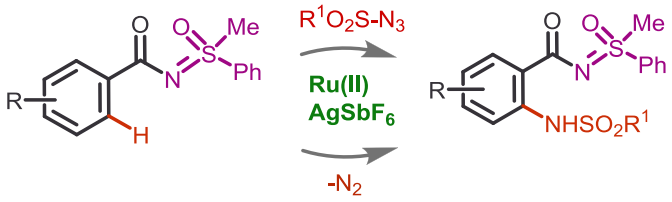
Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.870	175870244	2365599	99.874	99.854
2	29.369	221204	3466	0.126	0.146
Total		176091448	2369065	100.000	100.000

D:\RAJA\R-750-OAc-2.lcd

Sulfoximine Directed Intermolecular *ortho*-C–H Amidation of Arenes [with Sulfonyl Azides (Section-A)] and [with N-Arenesulfonated Imides (Section B)]

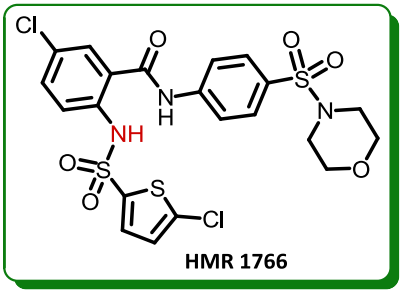
3 Chapter

Abstract

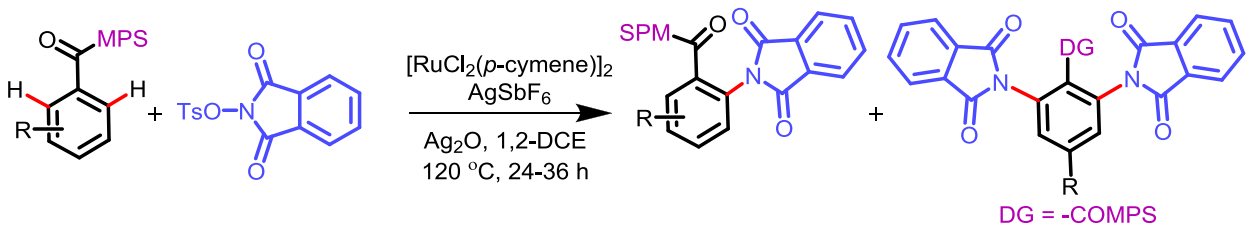


MPS -Reusable DG

25 examples, yields up to 93%



The cationic Ru(II)-catalyzed intermolecular *ortho*-C–H amidation of arenes in *N*-aroylated sulfoximine with sulfonyl azides is demonstrated. The reaction proceeds with broad substrate scope and tolerates various functional groups. Base hydrolysis of the amidation product provides anthranilic acid derivatives and methyl phenyl sulfoximine (MPS) directing group. This method is successfully employed for the synthesis of HMR 1766.



The cationic Ru(II)-catalyzed methyl phenyl sulfoximine (MPS) directed intermolecular *ortho*-C–H amidation of various *N*-aroyl MPS derivatives with electrophilic aminating agent N-arenesulfonated imides is described for the synthesis of anthranilic acid derivatives in good to excellent yield. The modified condition enables the synthesis of diamidation product.

Reference:

Sulfoximine Directed Intermolecular *ortho*-C–H Amidation of Arenes with Sulfonyl Azides

M. Ramu Yadav, Raja K. Rit, and Akhila K. Sahoo, *Org. Lett.*, **2013**, *15*, 1638.

Sulfoximine Directed Ruthenium Catalyzed *ortho*-C–H Amidation of Arenes with N-Arenesulfonated Imides

M. Ramu Yadav, Majji Shankar, E. Ramesh, Koushik Ghosh and Akhila K. Sahoo

(Communicated)

3.1. Introduction

Carbon-nitrogen bond containing compounds, such as aryl amines, are important motifs found in various pharmaceuticals, agrochemicals, polymers, and biologically active molecules.[1] In particular, anthranilic acid derivatives are potential candidates to biological and pharmaceutical importance.[2] Some of the representative molecules possessing anthranilic acid derivative are shown in Figure 3.1. Therefore, the development of practical and efficient methods for the construction of carbon-nitrogen bonds in benzoic acid derivatives is highly desirable.

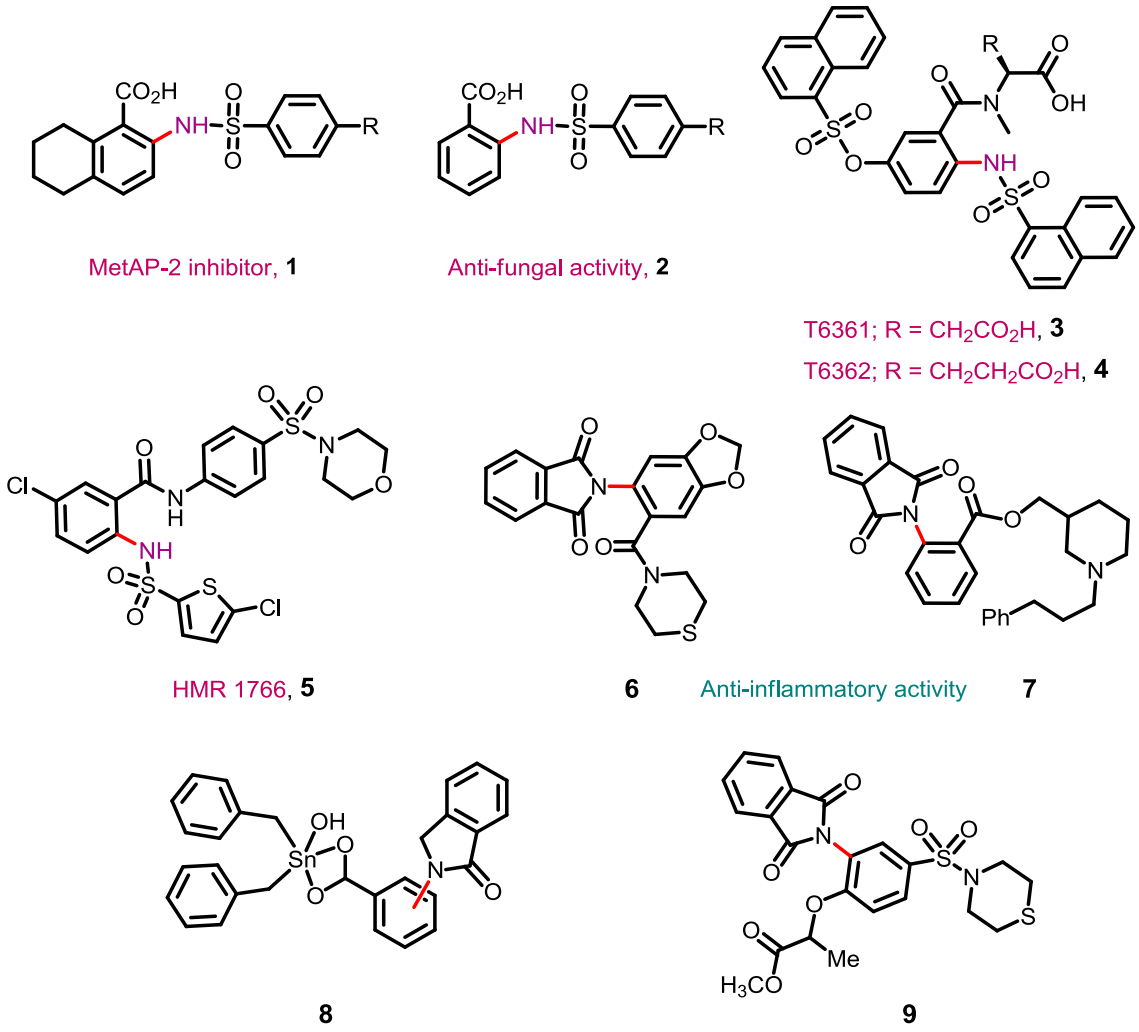
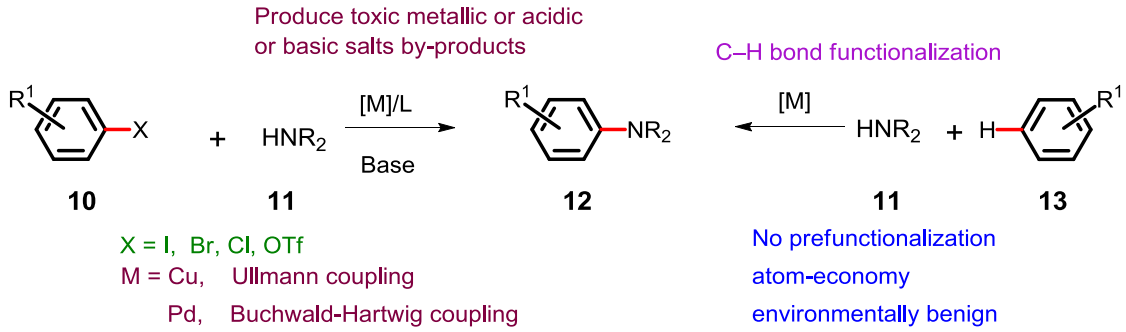


Figure 3.1: Biologically active molecules containing anthranilic acid derivatives

In 1901, Ullmann group demonstrated the first synthesis of arylamines through direct coupling between aryl halides and amines in presence of stoichiometric amount of copper metal (Scheme 3.1).[3] The harsh reaction condition and use of stoichiometric amount of metal

are the inherent limitations. Later, various research groups individually disclosed different strategies for the C–N bond formations using aryl-halides, pseudo-halides and amines under the influence of transition-metal catalysts, Pd, Ni, Cu etc.[3]



Scheme 3.1: Strategies for the synthesis of C–N bond on arenes

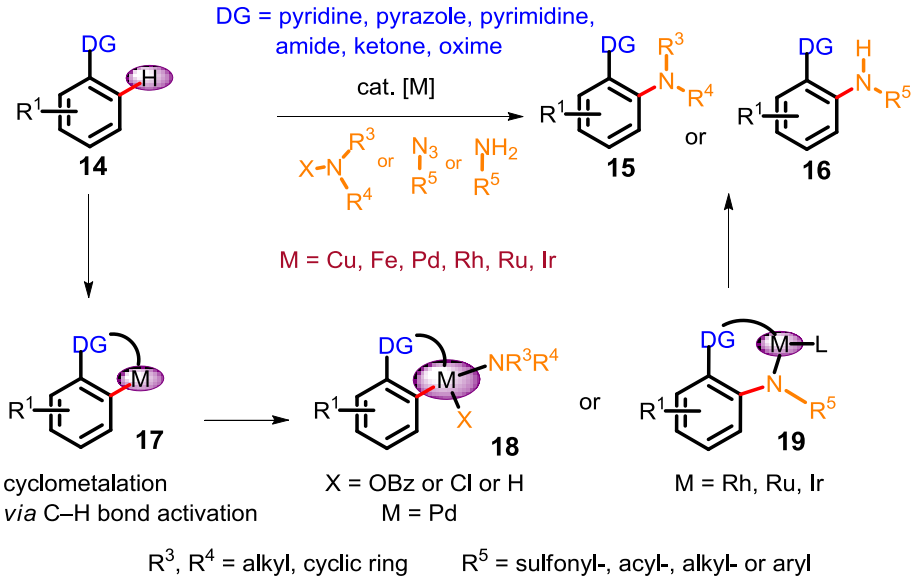
Among the strategies developed for C–N bond formations on arenes, the Buchwald-Hartwig amination protocol is considered versatile and notable (Scheme 3.1).[4] However, the coupling partners used for these reactions are pre-functionalized arenes, obtained from arenes through multiple synthetic manipulations. In addition, these processes produce hazardous wastes such as acids and quaternary amines. Consequently, exploration of atom/step-economical and environmentally benign protocols for C–N bond formations are highly desirable.

The transition-metal-catalyzed coupling between unactivated arene C–H bonds with various N-bearing nucleophiles for the construction of C–N bonds is an atom-economical approach.[5,6] Notably, this process does not require pre-functionalized precursors and produce minimum amount of waste. As a consequence, direct C(aryl)–N bond formation through the amination of C–H bonds is step, cost, and atom efficient. For instance, the transition-metal catalyzed *ortho*-C–H amination of benzoic acid derivatives enables the synthesis of structurally diverse anthranilic acids in a straightforward manner.

As discussed in chapter 1, the ubiquitous C–H bonds offer cumulative challenges for chemo-, regio-, and stereoselective functionalization of these unactivated bonds. Nevertheless, the strongly coordinating nitrogen or oxygen-bearing directing groups (DG) triggers activating the close proximity arene C–H bond in high site selectively. Representative examples of directing or chelating group assisted *o*-C–H amidation/amination are discussed in the next section.

3.1.1. Precedents for Transition-Metal-Catalyzed Chelation Assisted *o*-C–H Amination/Amidation of Benzoic Acid Derivatives

The transition-metal-catalyzed chelation assisted direct intermolecular regioselective amination/amidation of arene C–H bonds is emerged as most powerful and straightforward method for the synthesis of aryl amines **15/16**.[7] The readily accessible amino sources, such as electrophilic aminating agents[7] or aryl/alkyl amines/amides[8] or aryl/alkyl/sulfonyl azides[9] have successfully been employed for the C–N bond formations (Scheme 3.2). The amination reaction generally proceeds through the chelation of DG to metal centre to form the cyclometalated intermediate **17** through C–H bond activation of arene.



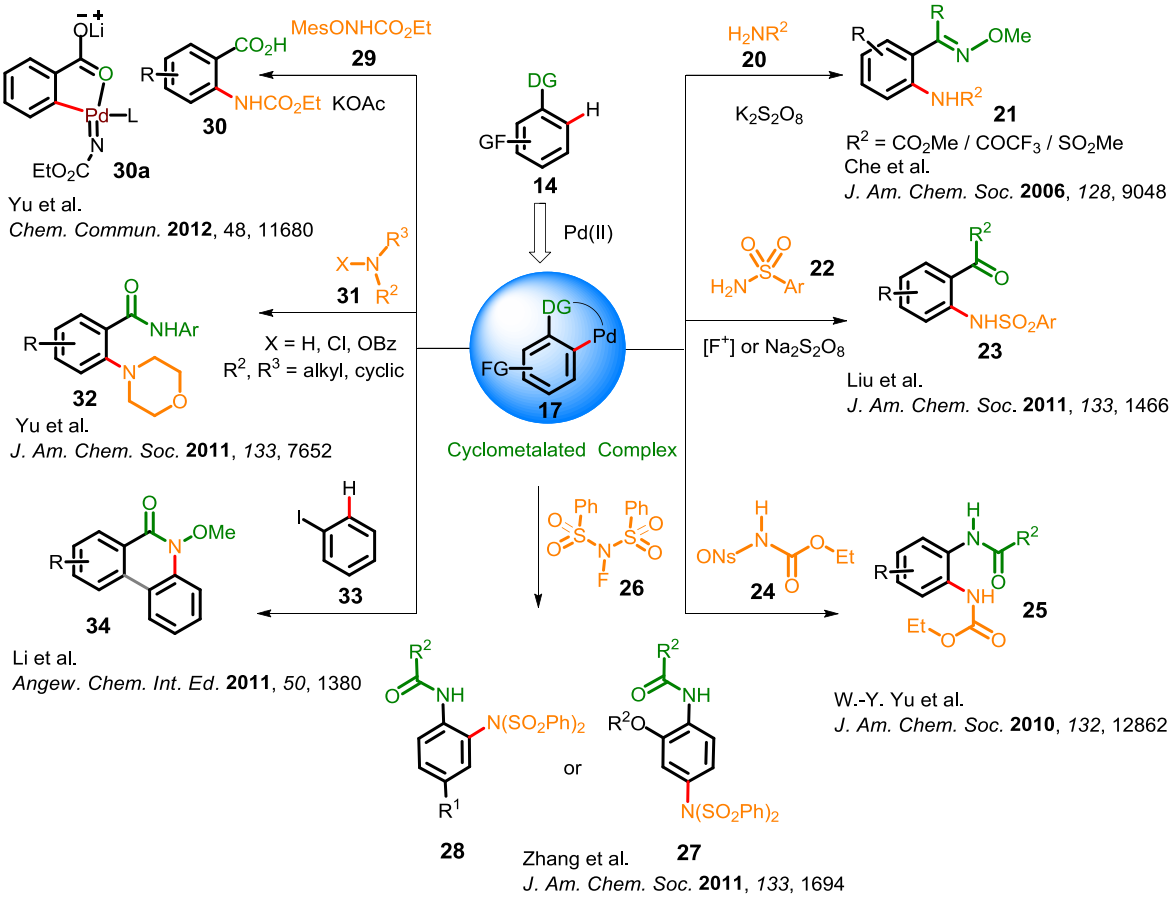
Scheme 3.2: Transition-metal catalyzed chelation assisted synthesis of C–N bond of arenes

Next, oxidative addition of electrophilic aminating agents to the metal or insertion of nitrene (generated from azide/amides) between C–metal bond furnishes intermediates **18**[7] or **19**[8,9], respectively. Finally, reductive elimination/protodemetalation affords the desired amination /amidation product **15/16** and regenerates the active catalyst for next catalytic cycle.

3.1.2. Palladium-Catalyzed sp² C–H Amination/Amidation of Arenes

The palladium-catalyzed intermolecular C–H amination/amidation of unactivated sp² C–H bonds is an important method for the synthesis of aryl amines (Scheme 3.3).[7] Over the years, various research groups investigated in the development of novel methods for C(sp²)–H

amidation and explored the utility of this strategy for broad synthetic applications. A wide range of amides: carbamate, acetamide, and sulfonamide amino sources **20** are successfully inserted on arenes to furnish the *o*-C–H amidation products **21**. A direct approach for the synthesis of *o*-amidated aromatic ketones **23** are accessed by the Pd-catalyzed carbonyl-group assisted *o*-amidation of arene C–H bonds with sulfonamides **22**. The oxidant *N*-fluoro-2,4,6-trimethyl-pyridinum triflate is used in this reaction.



Scheme 3.3: Pd-Catalyzed chelation assisted direct amination/amidation of unactivated sp^2 C–H bonds of arenes

The Pd(II)-catalyzed intermolecular *ortho*-C–H amidation of anilides with electrophilic aminating agent, *N*-nosyloxycarbamate (**24**) or *N*-fluorobenzenesulfonamide (**26**) is also demonstrated. Surprisingly, the presence of –OR group at the *ortho*-position on anilide selectively delivered the *para*-amidation product **27**; while *para*-substituted anilide gave *ortho*-amidation product **28** with *N*-fluorobenzenesulfonamide. Interestingly, the Pd-catalyzed *ortho*-C–H amidation of benzoic acids with ethyl mesityloxycarbamate **29** allows the direct synthesis of anthranalic acid derivatives **30**. The intermediate **30a**, realized through

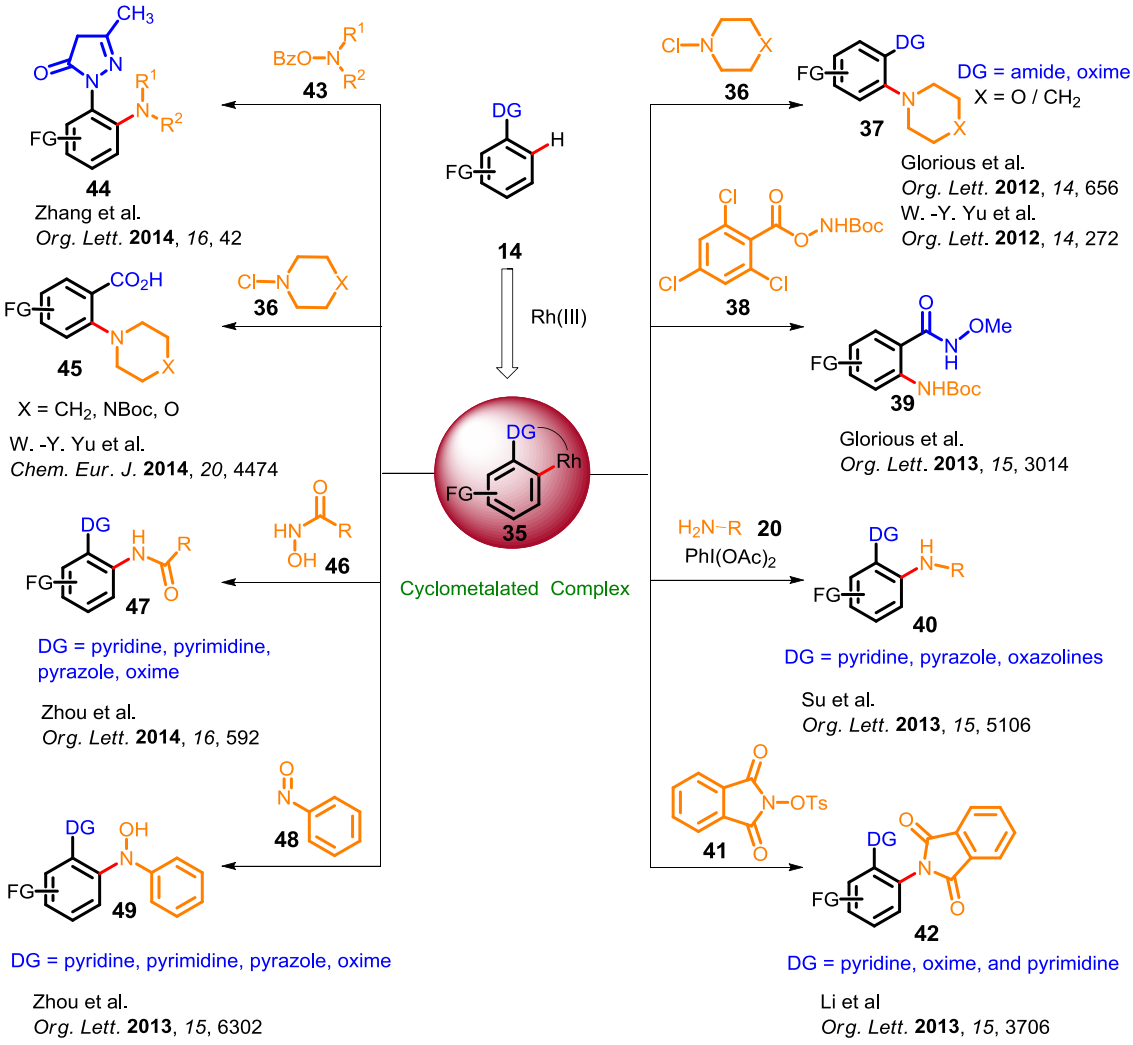
the weakly co-ordinating carboxylate-assisted *ortho*-C–H palladation followed by nitrene insertion, participated in this reaction.

In 2011, the Yu group reported Pd(II) catalyzed *ortho*-C–H amination of *N*-aryl benzamides with electrophilic amino source O-benzoyl hydroxylamine (**31**) in presence of dibenzoylperoxide. Notably, the directing group was successfully cleaved through the hydrolysis of the products with TFA to provide the synthetically useful *o*-amino benzoic acid derivatives. Further, the Li group developed a unique dual C–H activation process for the synthesis of biologically important phenanthridinones **34**; the reaction involves one-pot sequential C–C and C–N bonds formations.

3.1.3. Rhodium-Catalyzed sp^2 C–H Amination/Amidation of Arenes

An overview of the Rh-catalyzed C(sp^2)–H amination/amidation of arenes is sketched in Scheme 3.4. Glorius group demonstrated an efficient and mild Rh(III)-catalyzed direct C–H amination of *N*-pivaloyloxy/methoxy benzamides with electrophilic aminating partners *N*-chloroamines **36** and aroyloxycarbamates **38**; the aminating agents did not affect the ester/alkene functional groups. Dissapointingly, the *o*-substituted benzamides reacted sluggishly under the catalytic conditions. Rh(III)-Catalyzed N-chelating assisted intermolecular direct aromatic C–H bond amidation with aromatic and aliphatic sulfonamides **20** have been developed under mild reaction conditions to produce the corresponding products **40**. Li and coworkers reported Rh(III)-catalyzed chelation assisted intermolecular *o*-C–H amidation of arenes using electrophilic amidating agents *N*-arenesulfonated imides **41**. *The reaction proceeds without the need of the base additive*. Furthermore pyridine, oxime, and pyrimidine directing group bearing arenes are successfully amidated providing the desired products **42**. *Due to less coordinating ability and high electrophilicity of imide, the reaction presumably involves oxidative addition of imide to metal and participation of Rh(III)/Rh(V) species.* A Rh(III)-catalyzed intermolecular *o*-C−H amination of 1-aryl-1*H*-pyrazol-5(4H) with a range of electrophilic aminating agents like **43** directed by an intrinsic functionality of the substrate/product is described. The structural morphology of the aminated products **44** resembles to various pharmaceutical drug candidates. A direct approach for the synthesis of anthranalic acid derivatives **45**, the important precursors for medicinally active heterocycles, is demonstrated through Rh(III)-catalyzed direct C–H amidation/amination of benzoic acids. A wide range of aminating and amidating reagents $NHCO_2Me$, NHCbz, and

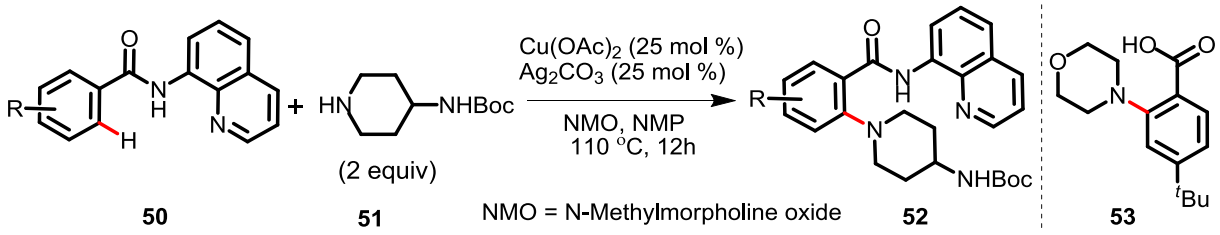
NHTroc (Cbz = carbobenzyloxy; troc = trichloroethyl chloroformate), as well as secondary amines morpholines, piperizines, and piperidines are successfully inserted on *o*-C–H bond of benzoic acid to provide highly functionalized anthranilic acids. Zhou group demonstrated an unprecedented Rh(III)-catalyzed direct intermolecular C−H amidation with N-hydroxycarbamates (**46**) or addition of aryl C–H bonds to nitrosobenzenes (**48**). The pyridine, pyrimidine, pyrazole, and N-OMe oxime directing group also assists in accomplishing the C−H amidations.



Scheme 3.4: Rh(III)-Catalyzed chelation assisted direct amination/amidation of unactivated sp^2 C–H bonds of arenes

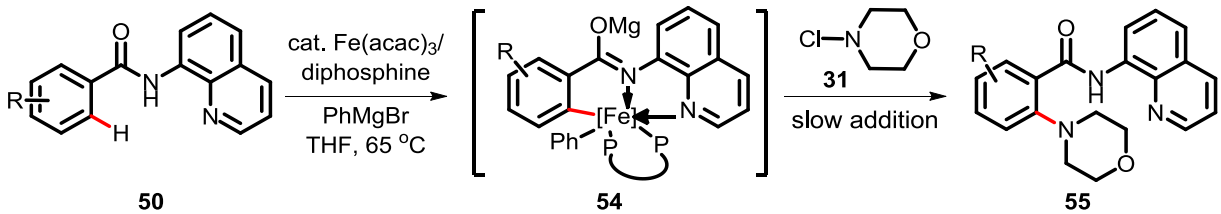
3.1.4. Cu(II), Fe(III) and Ru(II)-Catalyzed sp² C–H Amination of Arenes

Daugulis group achieved the copper-catalyzed 8-amino quinoline (8-Aq) directed intermolecular amination of β-C(sp²)–H bonds of arene derivatives **50** with morpholine **51** and secondary amines.[8f] The hydrolysis of the amination product **52** furnished *ortho*-amino benzoic acid derivative **53**. It has been speculated that aryl-Cu(III) intermediate, obtained through the activation of aryl C–H bond by Cu(II), is actively participated in this transformation.[10] Finally, attack of N-nucleophiles to aryl-Cu(III) species led to the desired amination products (Scheme 3.5).[11]



Scheme 3.5: Cu(II)-Catalyzed 8-amino quinoline directed amination of arenes

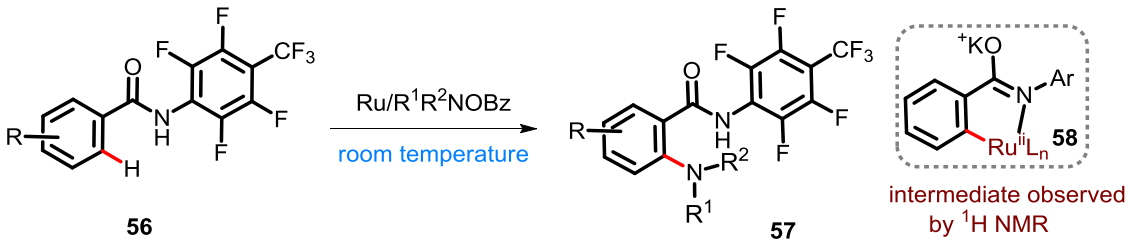
Recently, Nakamura group reported iron catalyzed 8-Aq assisted *o*-C–H amination of arenes **50** with *N*-chloro amines **31** and *N*-benzoyloxyamines to produce anthranilic acid derivatives **55** in high yield (Scheme 3.6).[12] The choice of directing group and diphosphine ligand is crucial to this Fe-catalyzed C–H activation. The reaction begins with the co-ordination of Fe-metal to DG to the formation of Fe-cyclometalation intermediate **54** via C–H activation. Subsequent *in situ* attack of N-chloroamine to the intermediate **54** followed by reductive elimination affords the desired product.



Scheme 3.6: Fe(III)-Catalyzed 8-amino quinoline directed amination of arenes

An interesting example of Ru(II)-catalyzed intermolecular *ortho*-C–H amination of arenes **56** directed by a weakly coordinating amide auxiliary with electrophilic aminating agent *O*-benzoyl hydroxylamines have been successfully accomplished, it is worthy to mention that

the reaction proceeds at room temperature.[13a] The electron-deficient (fluoro-bearing aryl) amide **56** auxiliary enables ready generation of imidate with metal and thus assists cleaving the close-proximity C–H bond by facile orientation between directing atom and target C–H bond; in addition, the weakly bound aryl-N-metal intermediate **58** offers better reactivity to electrophilic or nucleophilic partners used in these reactions. A wide range of acidic C–H containing heteroaryls i.e. pyrazole, thiophene, benzothiophene, furan, benzofuran, and indole were readily produced heteroaryl amines in good yields. The cyclo-ruthenium complex **58** (observed by ^{1}HNMR), obtained *in situ* from aryl amide and $[RuCl_2(p\text{-cymene})]_2$ in presence of K_2CO_3, is the active intermediate participated in this reaction. The attack of aminating agent oxidizes Ru(II)-species **58** to Ru(IV); finally reductive elimination produces the desired product **57** (Scheme 3.7).

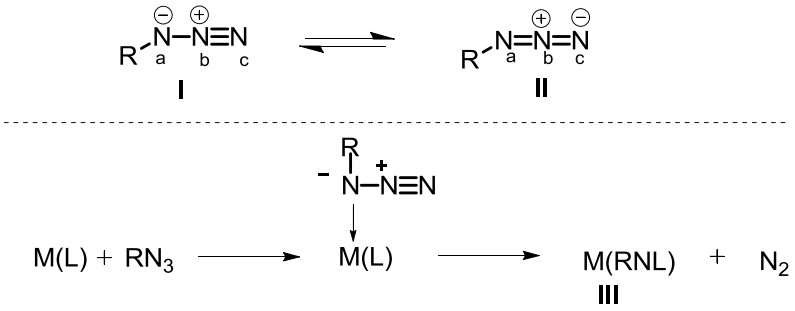


Scheme 3.7: Ru(II)-Catalyzed amide directed amination of arenes

3.1.5. Rh(III) and Ru(II)-Catalyzed sp^2 C–H Amination/Amidation of Arenes with Azides[9]

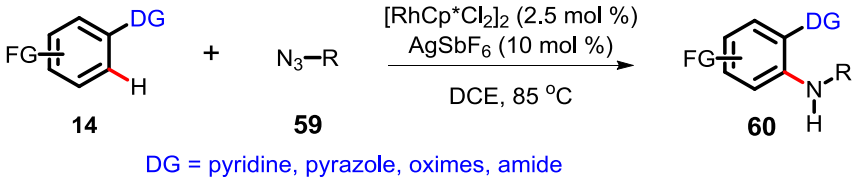
The Pd or Rh catalyzed C–H amination of arenes has extensively been performed in presence of electrophilic aminating reagents. Moreover, the reagents required for these reactions are prepared through multiple synthetic steps; in addition, the N-bearing oxidants are expensive, hazardous and produce acidic salts by-products. Thus, development of an alternate environmentally benign method for C–H amidation of arenes using inexpensive reagents without the production of hazardous by-products is of great interest. Azides are versatile functional groups in organic chemistry, widely employed constructing carbon–nitrogen or nitrogen–heteroatom bonds.[14] The organic azides have the following advantages: (1) ready availability from sodium azide, (2) require no additive besides catalyst to form nitrenoid reactive intermediate, and (3) produce N_2 gas by-product through *N*-atom transfer reaction.[14] The organic azides possess possible resonance structures (Scheme 3.8). The lone pair carrying electron rich N-a atom is sp^2 hybridized. The dipolar character and the relative

instability make the azido group react differently to the reagents used and the conditions employed. For instance: thermal or photochemical activation of azides provides nitrene by releasing dinitrogen gas. Thus, use of readily accessible inexpensive amino source sulfonyl azides for the C–H amidation reaction is highly desirable.



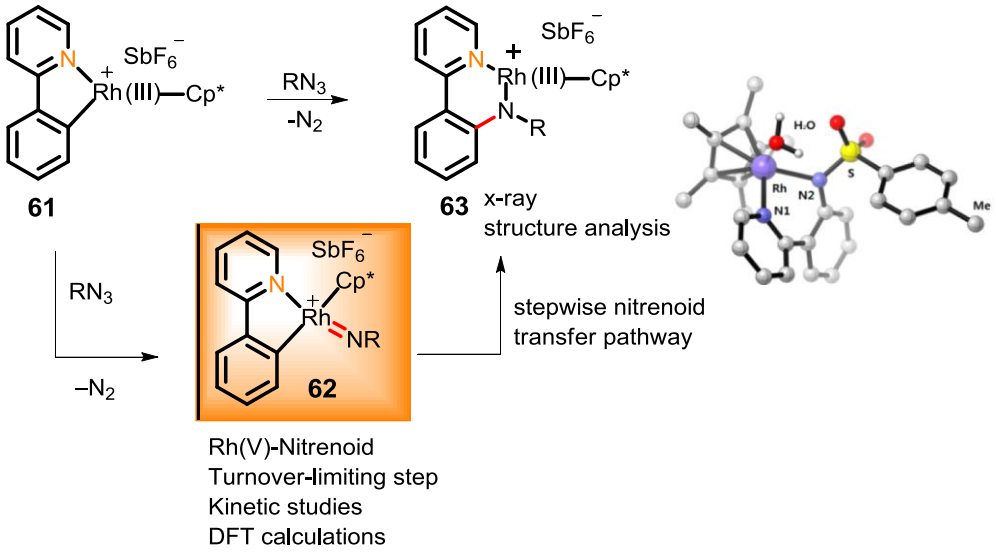
Scheme 3.8: Structure and reactivity of organic azides

An elegant approach, Rh(III) catalyzed pyridyl/amide/oxime directed amination/amidation of arene C–H bonds with sulfonyl azides or aryl azides has recently been elucidated by Chang group (Scheme 3.9).[9j] Importantly, this reaction produces the environmentally benign N_2 byproduct.



Scheme 3.9: Rh-Catalyzed direct C–H amination/ amidation of benzamides with azides

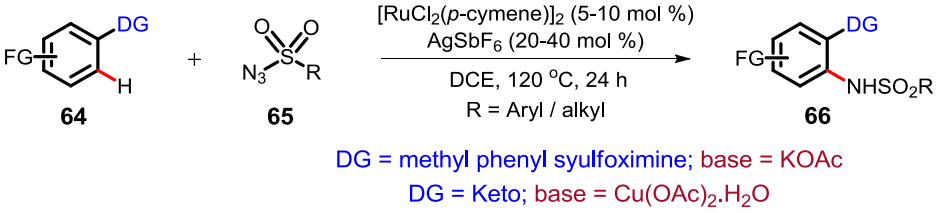
Furthermore, the Chang group thoroughly investigated the mechanistic details of this C–H amidation reaction.[15] First, chelation of pyridyl-DG in 2-phenylpyridine to cationic Rh(III) followed by *ortho*-C–H bond activation of arene affords a five-membered rhodacycle intermediate **61**. Coordination of azide to **61** and subsequent insertion of sulfonamido moiety into the rhodacycle provides Rh(III) amido complex **63** (structure is confirmed by X-ray crystallographic analysis) with the elimination of N_2 gas. The insertion of coordinated azide into the Rh–C bond possibly takes place in two ways: i) a concerted direct insertion or ii) a step wise pathway involving a rhodium-nitrenoid intermediate **62**. The kinetic and DFT calculations suggested that the involvement of rhodium-nitrenoid intermediate **62** is more preferable. Finally, protonolysis of **63** delivers the desired amidation product (Scheme 3.10).



Scheme 3.10: Mechanism of Rh-catalyzed direct C–H amination of benzamides with azides

The Ru-catalyzed C–H bond activation strategy has extensively been studied for the C–C bond formation i.e. introduction of alkyl, vinyl, or aryl groups on *o*-position of arenes.[16] However, to the best of our knowledge, the use of Ru-catalysts for the C–H amidation of arenes using the amino source sulfonyl azides is unprecedented until our report appeared.[17]

Recently, our group independently demonstrated the Ru(II)-catalyzed reusable sulfoximine directed (my thesis work) and weakly coordinating keto directed *o*-C–H amidation of arenes **64** with tosyl azide (**65**).[9c-d] The *o*-amino ketones **66** are obtained in good to excellent yields, and the reaction exhibit broad substrate scope (Scheme 3.11). The sulfoximine directing group assisted reactions require KOAc base, whereas keto directing group reactions proceed efficiently with $Cu(OAc)_2 \cdot H_2O$ base.

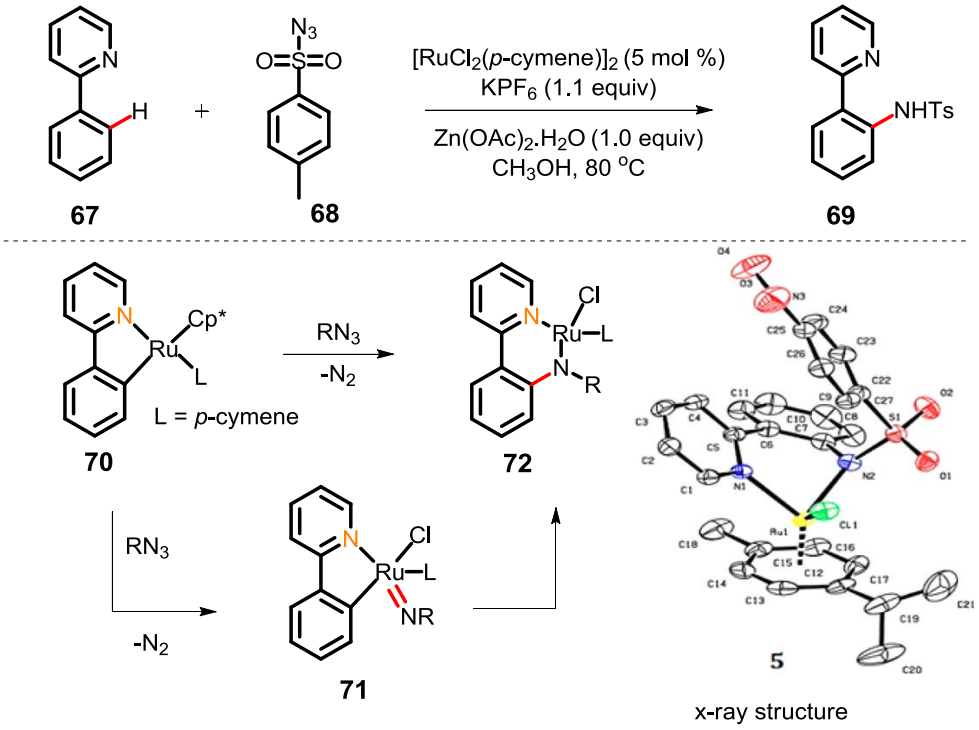


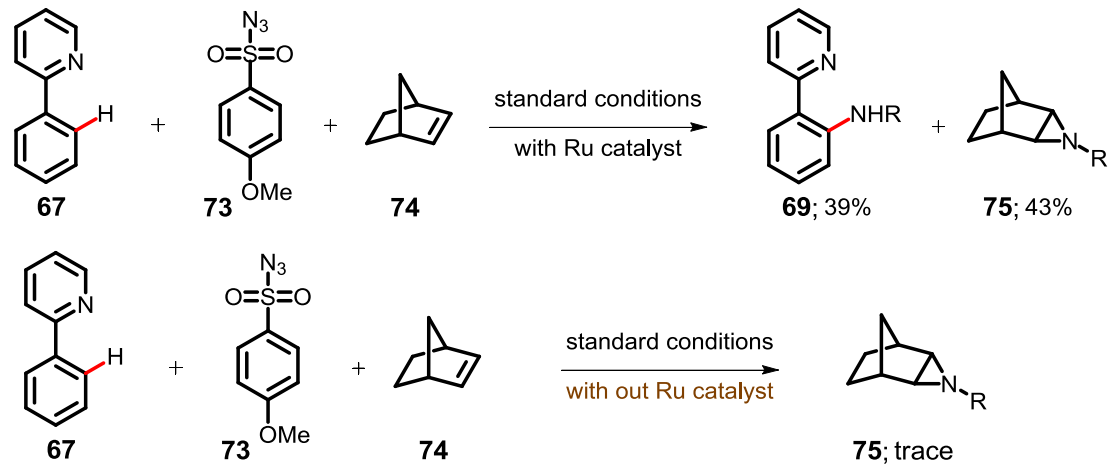
Scheme 3.11: Ru-Catalyzed direct C–H amination of arylketones with azides

Recently, Liang and coworkers studied the mechanistic details of Ru-catalyzed C–H activation/amidation reactions using azides as amino source.[18] Notably, two intermediates in the catalytic cycle $(C_5H_4NC_6H_4)$Ru(*p*-cymene)Cl **70** and $(C_5H_4NC_6H_4)$NArRu(*p*-cymene)Cl

72 (Ar = $NO_2C_6H_4SO_2$) were isolated and the structures were elucidated by X-ray analysis (Scheme 3.12).

On the basis of the experimental facts, the proposed reaction mechanism is detailed in Scheme 3.12. At first, reaction between $[RuCl_2(p\text{-cymene})]_2$ and KPF_6 generates a cationic Ru(III) species; this facilitates activating the key C–H bond to afford the five membered ruthenium intermediate **70**. X-Ray crystallography analysis confirms the structure of intermediate **70**. Next, the coordination of azide to **70** provides ruthenium−imido complex **71** by releasing nitrogen gas. Then, ruthenium−imido complex **71** rearranges to afford six-membered ruthenium intermediate **72**. The amido insertion proceeds via a transition state involving three centered interaction between ruthenium, phenyl carbon, and azide nitrogen atoms. The participation of ruthenium−imido complex **71** is corroborated through the capture of norbornylene for the formation of **75**. Finally, reductive elimination of the intermediate **72** affords the desired C–N bond forming product **69**.

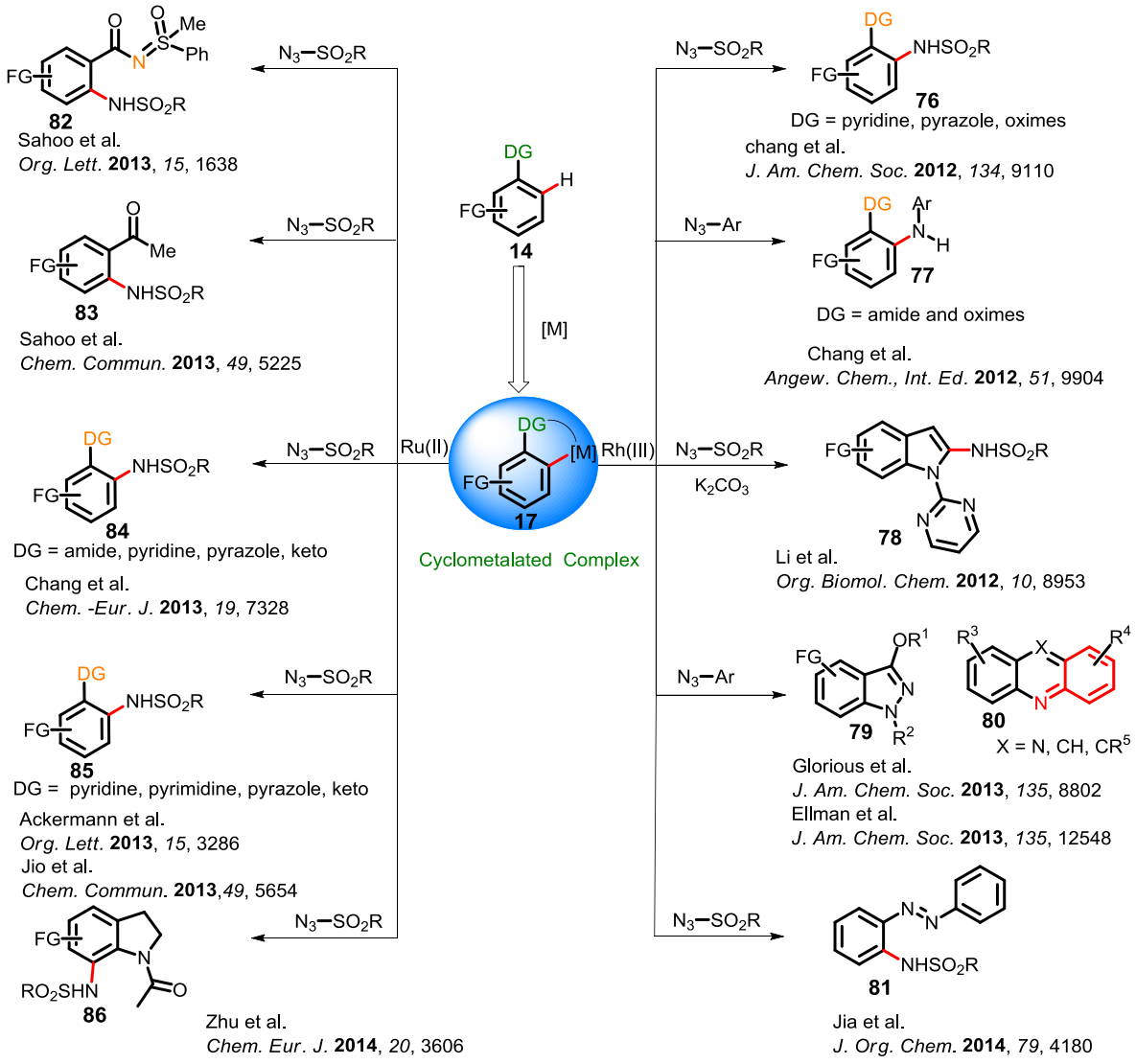




Scheme 3.12: Mechanistic study of Ru-catalyzed direct C–H amination of arenes with azides

These preliminary reports inspired examining the effect of various directing groups (DG = pyridine, pyrazole, pyrimidine, keto, azo, amide etc.) for the *o*-C–H amidation/amination of arenes with azides under the influence of rhodium or ruthenium catalysts; Scheme 3.13 highlights some of the results in this area. Chang and coworkers successfully employed sulfonyl and aryl azides for the synthesis of *o*-amido/amino arenes **76**/**77**. The regioselective C2 amidation of indole with sulfonyl azide produced **78** with the aid of pyrimidine directing group. Glorious group reported the synthesis of 1H-indazoles **79** from readily accessible arylimidates and aryl azides through C−H activation/C−N bond formation under the influence of Rh(III)-catalysts. In a similar way, Ellman group described rhodium catalyzed synthesis acridines and phenazines **80** involving formal [3+3] annulations of arylazides with aromatic imines and azobenzenes. The Rh-catalyzed azobenzene directed *o*-C–H amidation product **81** was synthesized by Jia.

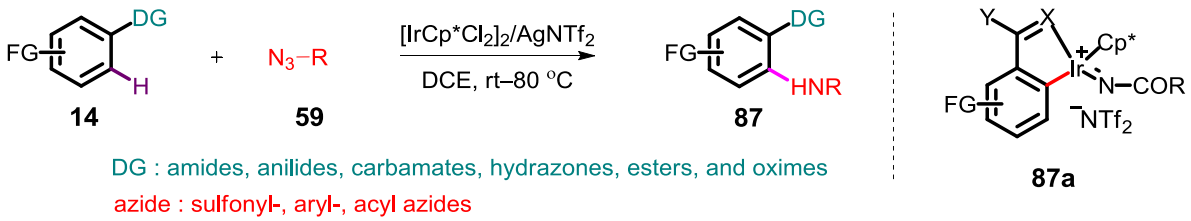
Recently, our group reported the Ru(II)-catalyzed sulfoximine (my thesis work) and weakly coordinating keto directed intermolecular *o*-C–H activation/ amidation of arenes with tosyl azide to furnished *o*-amido arenes **82** & **83** in good yield. Further, Chang, Ackermann and Jio have independently described the synthesis of *o*-amido arenes **84** & **85** with pyridine or pyrazole or amide or keto directed Ru-catalyzed C–H amidations. Zhu group demonstrated Ru-catalyzed intermolecular C–H amidation of N-acetyl indoles to accomplish the selective C7 amidation product **86** (Scheme 3.13).



Scheme 3.13: Rh & Ru-Catalyzed direct C–H amination/amidation of arenes with azides

3.1.6. Iridium-Catalyzed sp² C–H Amination/Amidation of Arenes

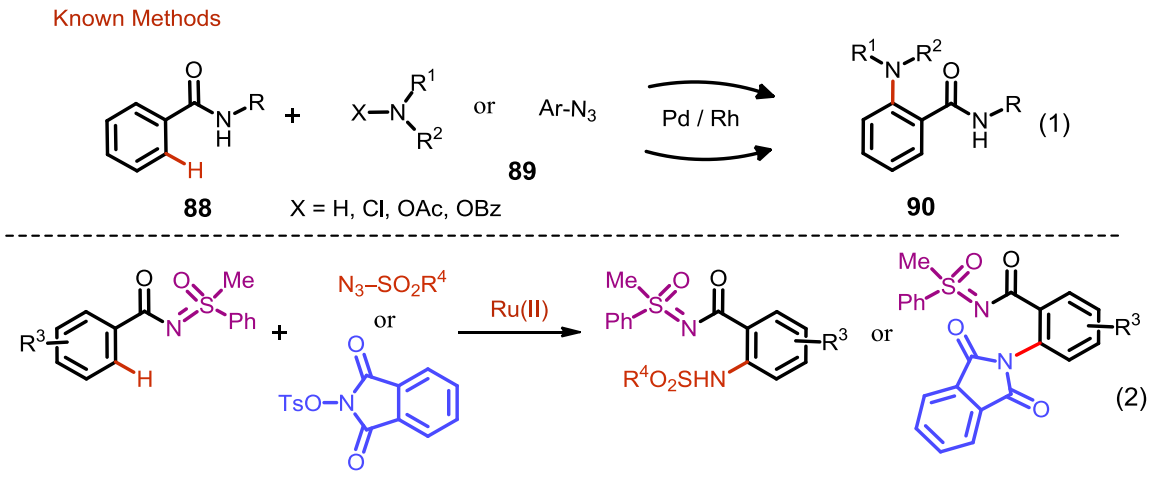
The *o*-C–H amidation/amination of arene moiety **14** from amides, ketones, esters, anilides with sulfonyl-, aryl-, and/or acyl azides **59** were successfully performed under the influence of iridium catalysts at milder conditions. The *o*-C−H amidation products **87** can be obtained from nitrene intermediate **87a** (Scheme 3.14).[90-q]



Scheme 3.14: Ir-Catalyzed direct C–H amination/amidation of arenes with azides

3.2. Motivation and Design Plan

A detailed survey of these reports reveal that the *ortho*-C–H amination of arenes has been achieved with the assistance of modifiable directing groups (DG's), while the identical reaction with the aid of reusable DG is yet to be investigated (Scheme 3.15, eq. 1). Furthermore, the Ru-catalyzed intermolecular *ortho*-C–H amination is rare. Our interest to explore the synthetic utility of reusable sulfoximine[19] DG's for the development of novel C–H functionalizations led us to discover the Ru(II)-catalyzed intermolecular direct chemo- and regioselective *ortho*-C–H amidation of arenes in *N*-aroylated methyl phenyl sulfoximine (MPS) with tosyl azide (Scheme 3.15, eq. 2) or N-arenesulfonated imides amino/amido source (Scheme 3.15, eq. 2). The MPS-DG can be cleaved from the product and recovered. This method can further be employed for the synthesis of natural products and pharmacogically active molecules.



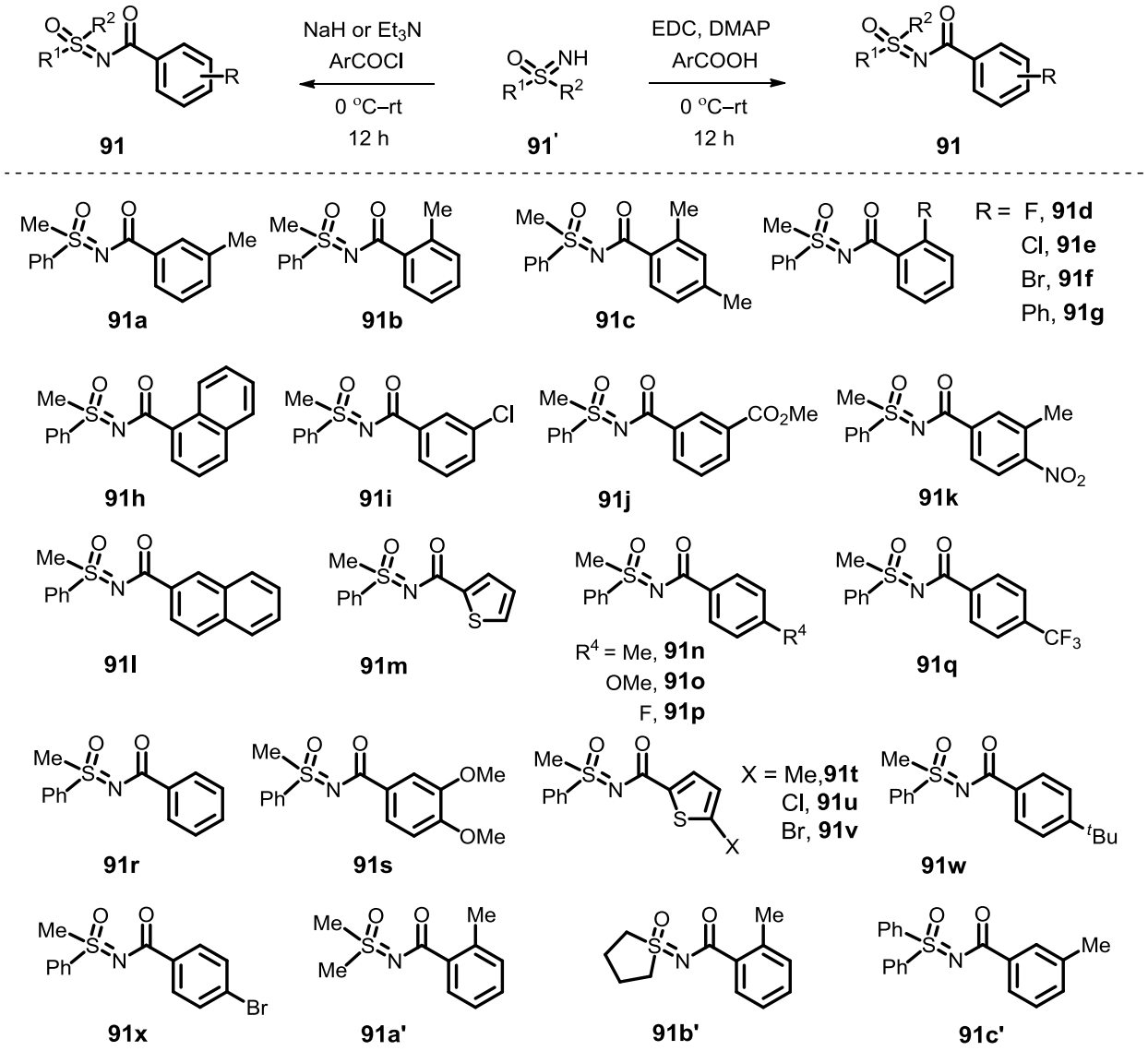
Scheme 3.15: Amide directed *ortho*-C–N bond formation

Section A: Sulfoximine Directed Intermolecular *ortho*-C–H Amidation of Arenes with Sulfonyl Azides

3.3. Results and Discussion

3.3.1. Synthesis of Precursors

Following the known procedures, various *N*-aroyl derivatives of sulfoximines were prepared (Scheme 3.16).



Scheme 3.16: Preparation of *N*-aroyl sulfoximines

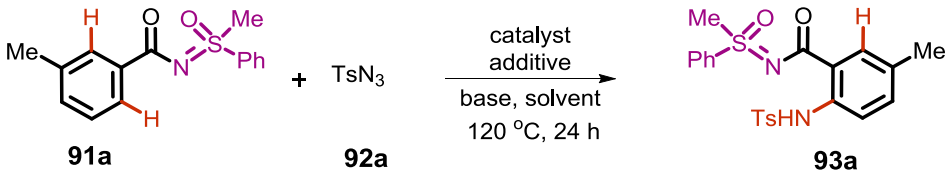
The reaction of sulfoximines with sodium hydride or triethylamine base in DCM solvent at 0 °C followed by quenching the reaction with corresponding benzoyl chlorides gave a wide

range of the *N*-aroylated sufoximines in above 80% yields. The EDC·HCl coupling protocol was employed for coupling of benzoic acid derivatives (the procedure is detailed in experimental section). Synthesis of the following compounds **91a**, **91b**, **91h**, **91l**, **91n-p**, **91r,** and **91a–c** is discussed in Chapter 2 (page no. 39).

3.3.2. Reaction Optimization:

To find the general reaction conditions for the *ortho*-C–H amidation of arenes, compound *N*-[*m*-methylbenzoyl]-MPS (**91a**) was subjected to the known reaction conditions [$(Cp^*RhCl_2)_2$ (5.0 mol %) / $AgSbF_6$ (0.4 equiv) in $ClCH_2CH_2Cl$ (DCE) with tosyl azide at 120 ^oC] reported by Chang.[9j] We are pleased noticing a trace amount of the desired product **93a** (entry 1, Table 3.1). Interestingly, the *ortho*-C–H amidation product **93a** was observed in 41% yield by NMR, when $[RuCl_2(p\text{-cymene})]_2$ was employed in combination with $AgSbF_6$ (entry 2). Among the two different arenes of **91a**, the less hindered *ortho*-C–H bonds of the *N*-benzoylated aryl ring has been exclusively functionalized; demonstrating chemo- as well as regioselective C–H amidation of arenes. Screening of other Ag/K salts did not show satisfactory results (entries 3–5). Among various solvents examined, DCE was found to be the best compared with CH_2Cl_2, $CHCl_3$ and toluene (entries 6–8). The enhanced catalyst loading produced improved yield of **93a** (entry 9). Base plays an important role in the case of C–H functionalizations;[8] thus, exploration of different bases is investigated. Among AgOAc, NaOAc, KOAc, and $Cu(OAc)_2{\cdot}H_2O$ screened, KOAc was found effective and afforded **93a** in 81% yield (entries 10–13). The use of KOAc (0.25 mmol) did not affect the product yield (entry 14). Moderate amount of **93a** was obtained, when the reaction conducted at lower temperature (entries 15–16). Thus, the optimized condition in entry 14, Table 3.1 {$[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %) and KOAc (50 mol %) in DCE at 120 ^oC for 24 h} has been chosen for the *ortho*-C–H amidation of arenes.

Table 3.1: Screening of *ortho*-C–H amidation with tosyl azide[a]



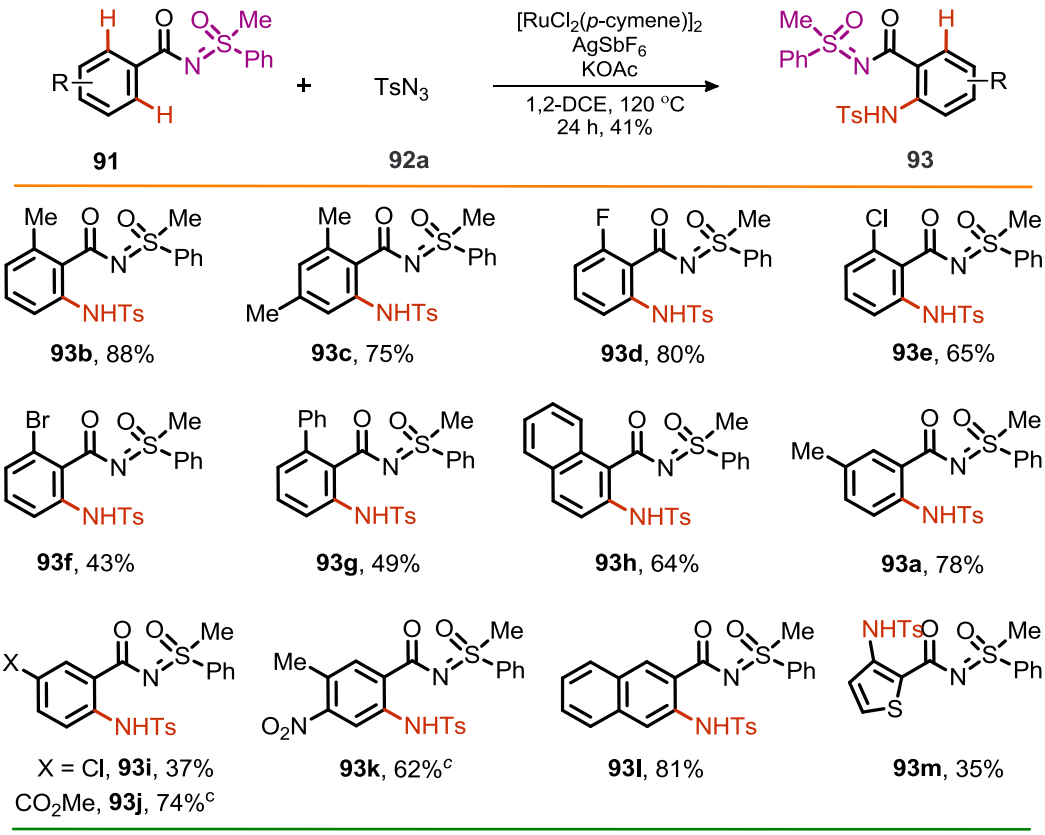
entry	additive (40 mol %)	base (0.1 mmol)	solvent (1.0 mL)	yield (%)[b]
1[c]	$AgSbF_6$		$ClCH_2CH_2Cl$	<5
2	$AgSbF_6$	-	$ClCH_2CH_2Cl$	41
3	$AgBF_4$	-	$ClCH_2CH_2Cl$	32
4	$AgPF_6$	-	$ClCH_2CH_2Cl$	<5
5	KPF_6	-	$ClCH_2CH_2Cl$	<5
6	$AgSbF_6$	-	CH_2Cl_2	37
7	$AgSbF_6$	-	$CHCl_3$	38
8	$AgSbF_6$	-	Toluene	9
9[d]	$AgSbF_6$	-	$ClCH_2CH_2Cl$	56[e]
10[d]	$AgSbF_6$	$Cu(OAc)_2.H_2O$	$ClCH_2CH_2Cl$	60[e]
11[d]	$AgSbF_6$	NaOAc	$ClCH_2CH_2Cl$	76[e]
12[d]	$AgSbF_6$	KOAc	$ClCH_2CH_2Cl$	81[e]
13[d]	$AgSbF_6$	AgOAc	$ClCH_2CH_2Cl$	59[e]
14[d,f]	$AgSbF_6$	**KOAc**	$ClCH_2CH_2Cl$	**78**[e]
15[b,d]	$AgSbF_6$	KOAc	$ClCH_2CH_2Cl$	56[g]
16[b,d]	$AgSbF_6$	KOAc	$ClCH_2CH_2Cl$	69[h]

[a]Reaction conditions: **91a** (0.1 mmol), **92a** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %). [b]Crude ^1H NMR conversion based on the ratio of starting material to product. [c]$[RhCp^*Cl_2)]_2$ (5.0 mol %). [d]$[RuCl_2(p\text{-cymene})]_2$ (10 mol %). [e]**91a** (0.5 mmol), $ClCH_2CH_2Cl$ (2.0 mL), isolated yields. [f]KOAc (0.25 mmol). [g]80 °C. [h]100 °C.

3.3.3. Scope of the Reaction

We then studied the scope and generality of the C–H amidation reaction by exposing various *N*-aroylated-MPS with tosyl azide (**92a**) under the optimized conditions (Table 3.2). The steric and electronic nature of the *ortho*-substituted arenes was probed first. The amidation of *N*-[*o*-methylbenzoyl]-MPS (**91b**) gave the desired **93b** in 88% yield. Similarly, **93c** was obtained in good yield from 2,4-dimethyl-substituted **91c**. Importantly, the halo substituted arenes successfully underwent C–H amidation reaction and the corresponding **93d–f** were isolated in 80%, 65%, and 43% yields, respectively. Interestingly, the electron-deficient fluoro group on arene did not affect the reaction efficiency.

Table 3.2: Substrate scope of *N*-benzoylated sulfoximines [a,b]



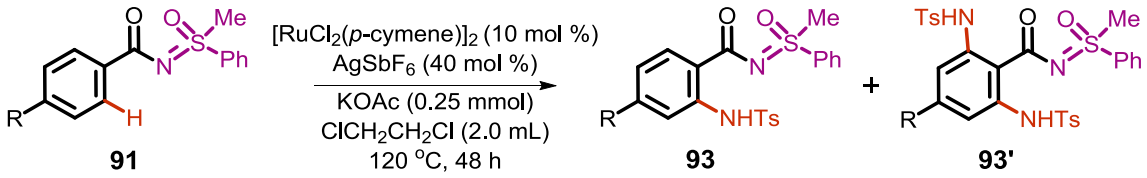
[a]Reaction conditions: **91** (0.5 mmol), azide **92a** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %), KOAc (0.25 mmol), $ClCH_2CH_2Cl$ (2.0 mL). [b]Isolated yields. [c]$Cu(OAc)_2 \cdot H_2O$ (1.0 mmol) was used instead of KOAc.

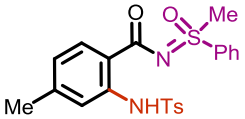
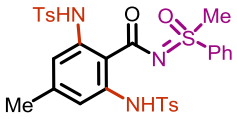
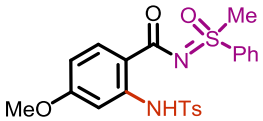
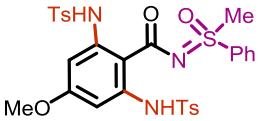
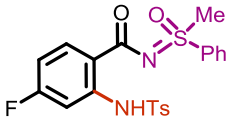
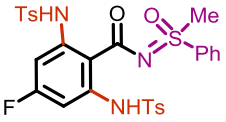
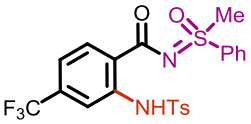
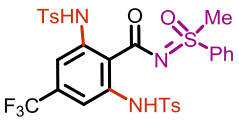
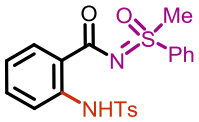
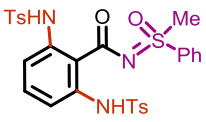
However, the sterically demanding *o*-phenyl group in **91g** hindered the reaction and afforded **93g** in moderate yield. Reaction of α-naphthyl derivative **91h** with **92a** produced **93h** in good yield.

The *meta*-substituted substrates regioselectively underwent amidation in the sterically less hindered position. The chloro and methyl substituted products **93i** and **93a** were obtained in moderate to good yields. The electron withdrawing ester and nitro groups did not affect efficiency, and the corresponding products **93j** and **93k** were isolated in 74% and 62% yields, respectively, when the reaction performed in presence of $Cu(OAc)_2 \cdot H_2O$. The β-naphthyl derivative **91l** under the catalytic conditions gave **93l** in 81% yield. Gratifyingly, reaction of 2-thienyl substituted **91m** with **92a** afforded **93m** albeit in poor yield.

The reaction of *p*-substituted *N*-aroylated-MPS with TsN_3 provided the mono- and di-amidation products (Table 3.3). At first, the *p*-Me-substituted *N*-benzoylated-MPS (**91n**) was

Table 3.3: Scope of *p*-substituted-*N*-benzoylated-sulfoximines [a,b]



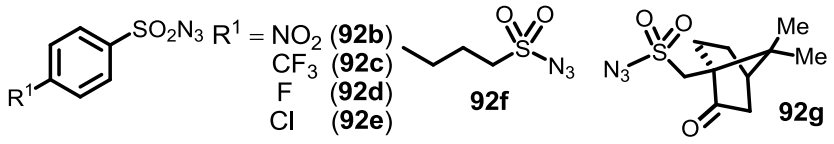
entry	R	TsN_3 (equiv)	yield of **93** (%)	yield of **93′** (%)
			 **93n**	 **93n′**
1	Me (**91n**)	1.0	30 [c]	22 [c]
		1.5	43 [c]	28 [c]
		2.0	49	32
		2.5	14	66
		3.0	10	73
		4.0	16 [c]	59 [c]
			 **93o**	 **93o′**
2	OMe (**91o**)	2.0	55	28
		3.0	<5	71
			 **93p**	 **93p′**
3	F (**91p**)	2.0	49	40
		3.0	12	68
			 **93q**	 **93q′**
4	CF_3 (**91q**)	2.0	50	25
		3.0	48	30
			 **93r**	 **93r′**
5	H (**91r**)	2.0	37	28
		3.0	20	52

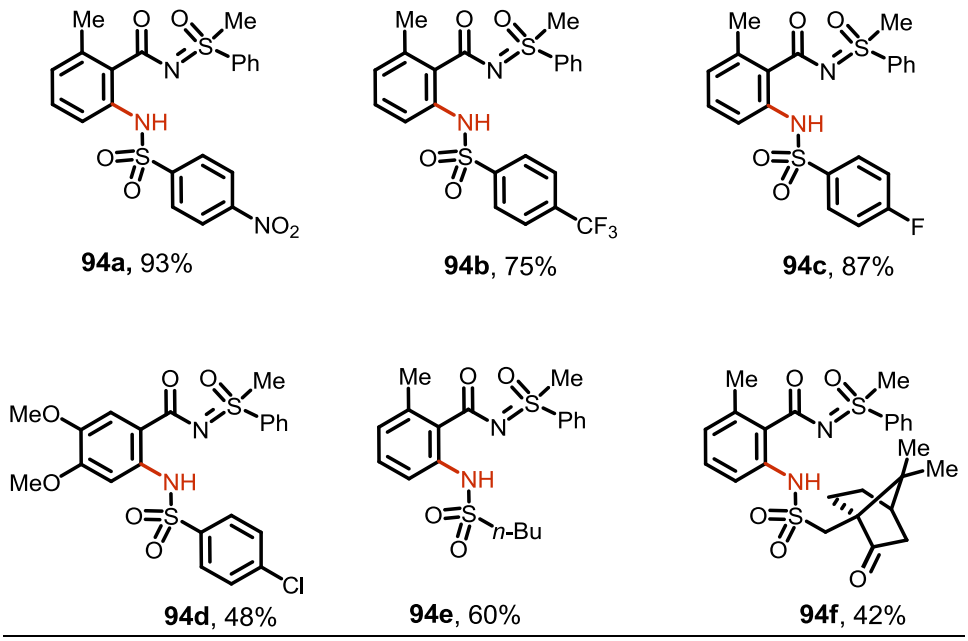
[a]Reaction conditions: **91** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %), KOAc (0.25 mmol), $ClCH_2CH_2Cl$ (2.0 mL).[b]Isolated yields. [c]Crude ^1H NMR conversion based on the ratio of starting material to product.

exposed to different amount of TsN_3 under the optimized conditions.[11] However, the use of **92a** (2.0 equiv) was found optimium affording **93n** (major) and **93n′**(minor) in 49%, 32%

yields, respectively (entry 1). Interestingly, an excess amount of **92a** (2.5/3.0/4.0 equiv) led to produce **93n′** as major product; in particular, the reaction of **91n** with 3.0 equiv of **92a** resulted **93n′** in 73% yield (entry 1). This modified conditions was then applied to various *p*-substituted *N*-aroylated-MPS compounds (**91o–r**).

Table 3.4: Scope of azides[a,b]



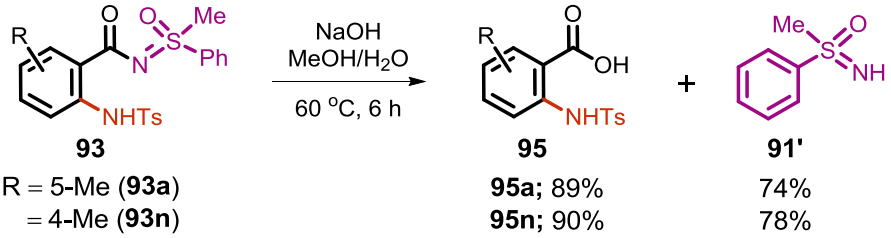


[a]Reaction conditions: **91** (0.5 mmol), azide (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %), KOAc (0.25 mmol), $ClCH_2CH_2Cl$ (2.0 mL). [b]Isolated yields.

The reaction of electron-rich *p*-OMe substituted **91o** with **92a** (2.0 equiv) gave 55% of **93o** as major product; while di-amidation **93o′** (71%) was isolated, when **92a** (3.0 equiv) employed (entry 2).[11] The mono- and di-amidation products **93p** and **93p′** were obtained in 49%, 40% yields, respectively, from the reaction of F-group bearing electron deficient **91p** with **92a** (2.0 equiv); whereas 3.0 equiv of TsN_3 yielded **93p′** in 68% yield (entry 3). Surprisingly, use of enhanced amount of TsN_3 did not affect the reactivity of *p*-CF_3 substituted **91q**, producing the mono-amidation **93q** as major product (entry 4). The electron neutral *N*-benzoylsulfoximine **91r** gave a moderate amount of **93r**/**93r′** in the presence of 2.0/3.0 equiv of **92a** (entry 5).

We next examined the scope of different sulfonyl azides with **91** (Table 3.4). Electron withdrawing substituted aryl-sulfonyl azides **92b**, **92c**, **92d** effectively participated; the corresponding *ortho*-C–H amidation products **94a–c** were obtained in good yields. Similarly, amidation of *N*-[3,4-dimethoxybenzoyl]-MPS (**91s**) with **92e** yielded 48% of **94d**. Pleasingly, the reaction of aliphatic sulfonyl azides **92f**/**92g** with **91b** produced moderate amount of the desired amidation products **94e** and **94f**.

Cleavage of the MPS-directing group from the product would broaden the synthetic versatility of the method. To our delight, **93a** was hydrolyzed under the base hydrolysis conditions (NaOH in MeOH/H_2O at 60 ^oC in 6 h), providing the corresponding anthranilic acid **95a** and MPS in 89% and 74% yield, respectively (Scheme 3.17). Following the same conditions, **93n** was successfully hydrolyzed and the MPS moiety was recovered in 78% yield.



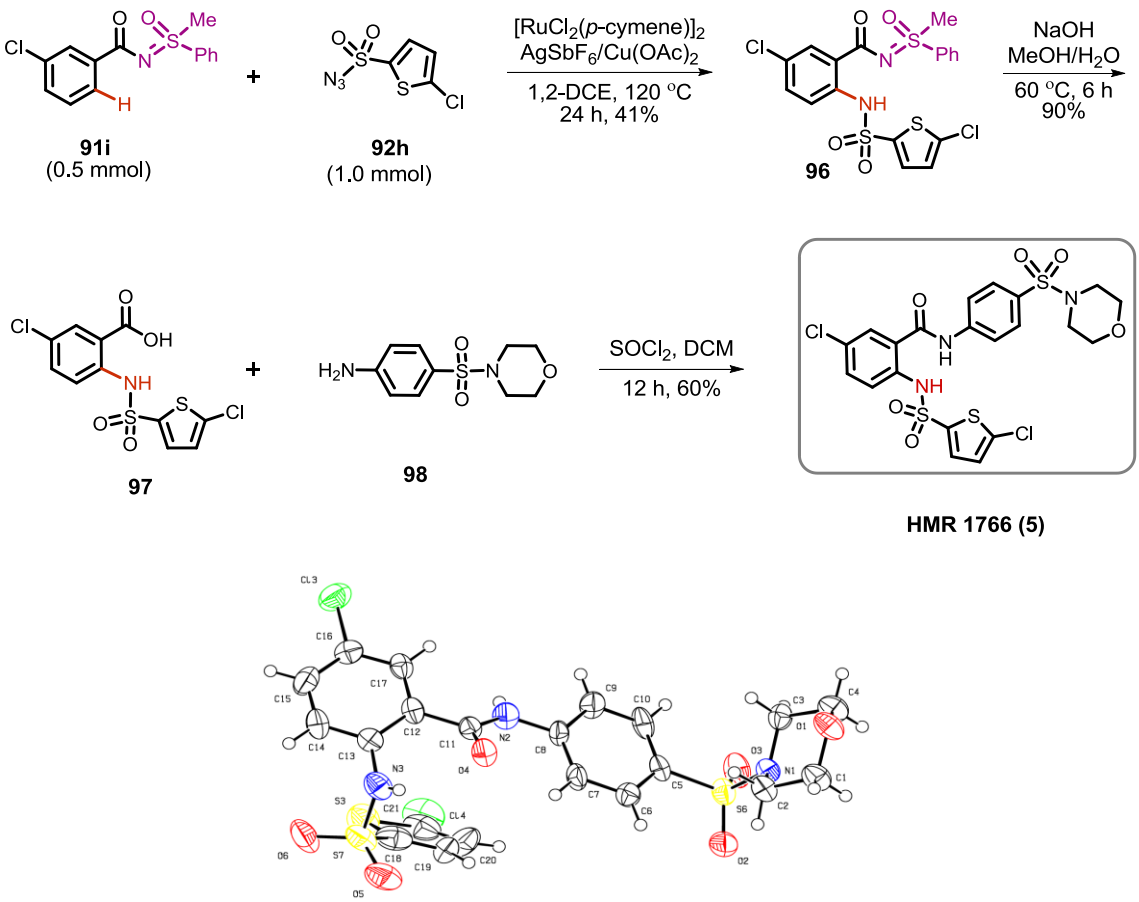
93
R = 5-Me (**93a**)
= 4-Me (**93n**)

95
95a; 89%
95n; 90%

91'
74%
78%

Scheme 3.17: Recovery of the sulfoximine directing group

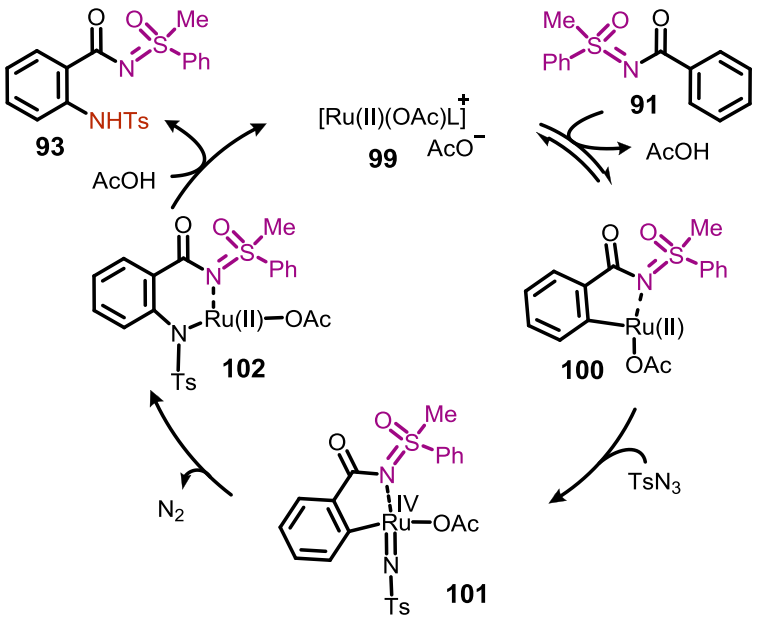
Next, we envisioned the synthesis of HMR 1766 (**5**) involving the reusable MPS-directed C–H amidation protocol as a key step. HMR 1766, named as ataciguat, is a class of sGC activators useful in targeting deficient NO signaling in hypertension, peripheral and coronary artery disease, heart failure etc.[20] The campaign for the synthesis of **5** commenced by inserting the Cl-thienyl-sulfonyl amido group at the less hindered *ortho*-C–H bond on **91i** (Scheme 3.18); the desired product **96** was produced in 41% yield. Hydrolysis of **96** delivered the corresponding acid **97** in 90% yield. Finally, coupling of **97** with amine **98** resulted HMR 1766 (**5**) in 60% yield. X-Ray crystallographic analysis unambiguously confirms the structure of **5**.



Scheme 3.18: Synthesis of HMR 1766

3.3.4. Mechanistic Studies

Although the detailed mechanism of Ru(II)-catalyzed C–H amidation of arenes is yet to be established, the proposed mechanism is outlined in Scheme 3.19 on the basis of Liang's proposal.[18b] The combination of $[RuCl_2(p\text{-cymene})]_2$, acetate-source, and $AgSbF_6$ generates the active cationic Ru(II)-catalyst **99**. The coordination of sulfoximine nitrogen to the cationic Ru-catalyst triggers activating the less-hindered *ortho*-C–H bond and delivers the metallacycle intermediate **100**. Coordination of azide to **100** to give ruthenium−nitrenoid complex **101** by releasing nitrogen gas, the migratory insertion of nitrenoid moiety would then lead to the six membered intermediate **102**. Finally, protonolysis of **102** provides the desired product and generates the cationic ruthenium-complex for the next catalytic cycle.



Scheme 3.19: Proposed catalytic cycle

3.4. Conclusion

In summary, Ru-catalyzed sulfoximine directed chemo- and regioselective *ortho*- C–N bond formation of arenes with broad substrate scope is developed. The reaction of *p*-substituted *N*-benzoylated-MPS with excess amount of tosyl azide delivered major amount of *ortho*-di-amidation product. Anthranilic acid derivatives and recovery of MPS-DG are realized through the base hydrolysis of amidation products. The utility of this method is demonstrated in the synthesis of HMR 1766.

Section B: Sulfoximine-Directed Ruthenium-Catalyzed *ortho*-C–H Amidation of Arenes with N-Arenesulfonated Imides

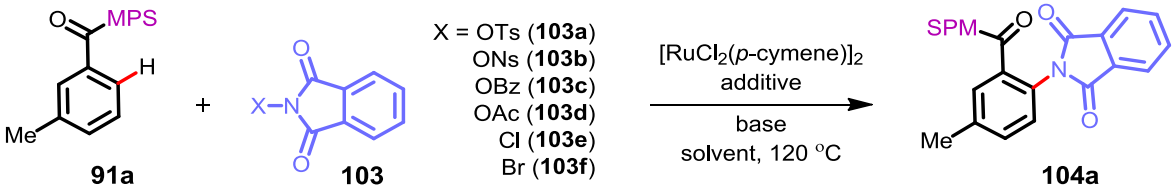
3.5. Results and Discussion

3.5.1. Reaction Optimization

To find a suitable condition for *o*-C–H amidation of N-aroyl MPS with electrophilic aminating agent, the reaction between N-(*m*-methylbenzoyl)MPS (**91a**) and aminiating agent *N*-OTs phthalimide (**103a**) was conducted under different catalytic conditions (Table 3.5). Initially, the reaction was tested with $[RuCl_2(p\text{-Cymene})]_2$ and $AgSbF_6$ in 1,2-dichloroethane (1,2-DEC) at 120 °C for 24 h; a trace amount of the desired *o*-C–H amidation product **104a** was detected by 1H NMR (entry 1, Table 3.5). Surprisingly, addition of $Cu(OAc)_2{\cdot}H_2O$

improved the formation of **104a** up to 52% yield (entry 2). Effort to increase the yield of **104a** failed, when additives $AgBF_4$, $NaBF_4$ and KPF_6 were employed (entries 3–5). The use of $Cu(OAc)_2$, AgOAc or NaOAc led to lower yield of **104a** (entries 6–8). To our delight, the additive Ag_2O drastically improved the yield of **104a** to 82% yield (entry 9). Furthermore, enhancing the catalyst loading from 5 to 10 mol % produced the desired amidation product in excellent yield with complete consumption of **91a** (entry 10). Other solvents DCM, $CHCl_3$,

Table 3.5: Screening of *ortho*-C–H amidation with *N*-OTs phthalimide.[a]



entry	additive (20 mol %)	base (1.0 equiv)	aminating agent	solvent (1.0 mL)	yield (%)[b]
1	$AgSbF_6$	-	**103a**	$ClCH_2CH_2Cl$	8
2	$AgSbF_6$	$Cu(OAc)_2{\cdot}H_2O$	**103a**	$ClCH_2CH_2Cl$	52
3	$AgBF_4$	$Cu(OAc)_2{\cdot}H_2O$	**103a**	$ClCH_2CH_2Cl$	32
4	NaBF4	$Cu(OAc)_2{\cdot}H_2O$	**103a**	$ClCH_2CH_2Cl$	NR
5	KPF_6	$Cu(OAc)_2{\cdot}H_2O$	**103a**	$ClCH_2CH_2Cl$	7
6	$AgSbF_6$	$Cu(OAc)_2$	**103a**	$ClCH_2CH_2Cl$	47
7	$AgSbF_6$	AgOAc	**103a**	$ClCH_2CH_2Cl$	10
8	$AgSbF_6$	NaOAc	**103a**	$ClCH_2CH_2Cl$	21
9	$AgSbF_6$	Ag_2O	**103a**	$ClCH_2CH_2Cl$	82
10	**$AgSbF_6$**	**Ag_2O**	**103a**	**$ClCH_2CH_2Cl$**	**95[d](70%)[e]**
11	$AgSbF_6$	Ag_2O	**103a**	$CHCl_3$	20[d]
12	$AgSbF_6$	Ag_2O	**103a**	toluene	13[d]
13	$AgSbF_6$	Ag_2O	**103a**	CH_2Cl_2	84
14	$AgSbF_6$	Ag_2O	**103a**	1,4-dioxane	36[d]
15	$AgSbF_6$	Ag_2O	**103a**	$ClCH_2CH_2Cl$	NR[f,g,h]
16	$AgSbF_6$	Ag_2O	**103b**	$ClCH_2CH_2Cl$	85
17	$AgSbF_6$	Ag_2O	**103c**	$ClCH_2CH_2Cl$	35
18	$AgSbF_6$	Ag_2O	**103d**	$ClCH_2CH_2Cl$	<5
19	$AgSbF_6$	Ag_2O	**103e**	$ClCH_2CH_2Cl$	NR
20	$AgSbF_6$	Ag_2O	**103f**	$ClCH_2CH_2Cl$	NR

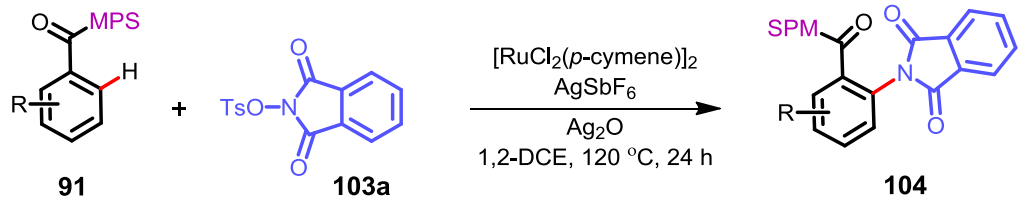
[a]Reaction conditions: **91a** (0.1 mmol), **103a** (0.15 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), 24 h. [b]Conversion based on crude ^1H NMR of starting material. [d]$[RuCl_2(p\text{-cymene})]_2$ (10 mol %). [e]**91a** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $ClCH_2CH_2Cl$ (2.0 mL), isolated yield. [f]$[RhCl_2Cp^*]_2$(10 mol %). [g]$Pd(OAc)_2$ (10 mol %). [h]$[IrCl_2Cp^*]_2$ (5.0 mol %).

toluene, and/or 1, 4-dioxane resulted **104a** in 13–84% product yields (entries 11–14). Screening of Rh(III), Ir(III), and Pd(II) catalysts failed to deliver the desired amidation product (entry 15). Not surprisingly in the absence of Ru(II)-catalyst, the reaction was completely failed to provide even trace amount of the product.To find feasibility of other amido source, the reaction was surveyed with other electrophilic aminating N–X reagents under the optimized condition. The strong electron withdrawing N-ONS phthalimide (**103b**) group gave 85% yield of **104a** (entry 16). However, poor yield of **104a** was noticed, when N-OBz (**103c**), N-OAc (**103d**) compounds were employed (entries 17 and 18). The N-Cl and N-Br phthalimide (**103e–f**) were unsuccessful aminating agents (entries 19 and 20). On the basis of these results, N-OTs phthalimide (**103a**) was found superior in perusing C–H amidation reaction. Finally, the conditions in entry 10, Table 3.5, was considered optimum for the *o*-C–H amidation of N-aroyl MPS with *N*-OTs phthalimide.

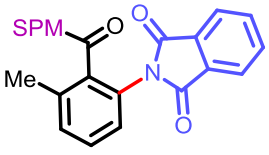
3.5.2. Scope of the Reaction

With the optimized condition in hand, the generality of the *o*-C–H amidation reaction of N-aroyl slulfoximine **91** with **103a** was investigated (Table 3.6). The steric *ortho*-substitution effect in **91b-f** and **91g** (see: Scheme 3.16, page 133) was first examined. The *o*-methyl substituted **104b** and 2,4-dimethyl substituted **104c** were isolated in 77% and 83% yields, respectively. The F, Cl groups bearing compounds **91d** and **91e** delivered the corresponding amidation product **104d** and **104e** in excellent yields. In contrast, the bromo containing **91f** gave poor yield of **104f**. The α-napthyl compound furnished the C–H amidation product **104g** in 72% yield. Next, the regioselective amidation of *m*-substituted N-aroyl slulfoximines was explored. To our delight, the amidation products **104a** and **104h–i** were exclusively obtained by replacing the regioselective less hindered *o*-C–H bond of arenes. The -NO_2 group did not affect the reaction efficiency, delivering **104i** in 86% yield. In case of β-napthyl derivative, the amidation product **104j** was obtained from **91l** in moderate yield. The thiophene derivative **91m** produced the amidation product **104k** in 90% yield. Similarly, the 5- Me, Cl or Br bearing thiophene derivatives **91t–v** afforded **104l–n** in 85–92% yields.

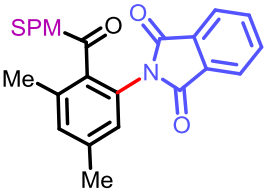
Table 3.6: Substrate scope of *N*-aroylated sulfoximines. [a,b]



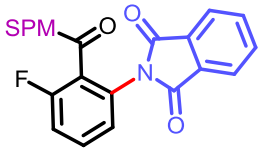
91 **103a** **104**



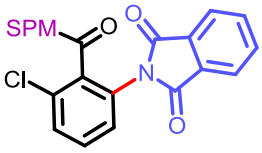
104b, 77%



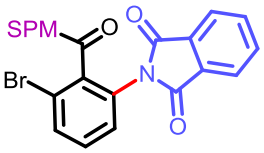
104c, 83%



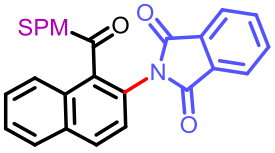
104d, 93%



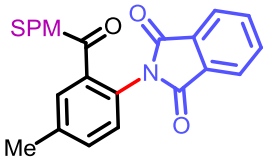
104e, 82%



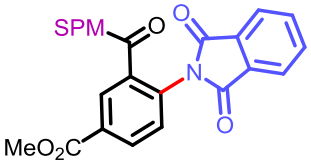
104f, 31%



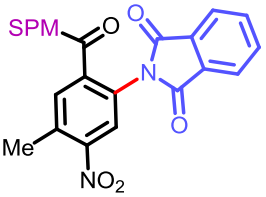
104g, 72%



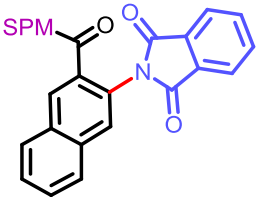
104a, 70%



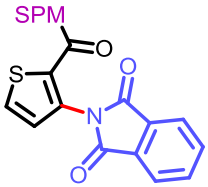
104h,85%



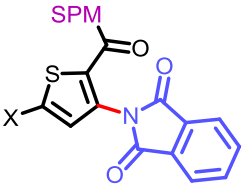
104i, 86%



104j, 61%



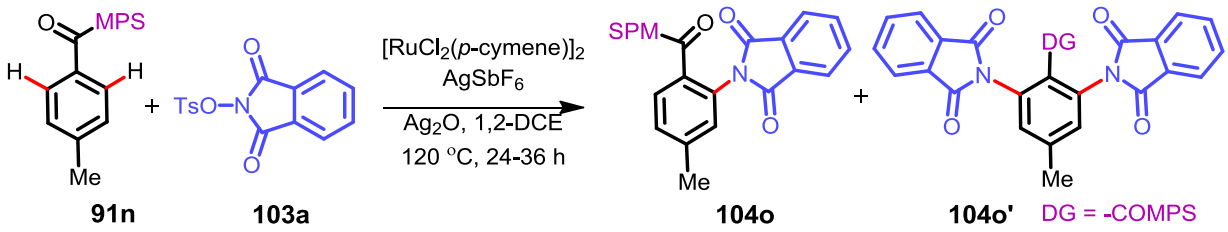
104k, 90%



X = Me,**104l**, 85%
Cl, **104m**, 92%
Br, **104n**, 92%

[a]Reaction conditions: **91** (0.5 mmol), **103a** (0.75 mmol), $RuCl_2$(*p*-cymene)]$_2$ (10 mol %), $AgSbF_6$ (40 mol %), Ag_2O (0.5 mmol), $ClCH_2CH_2Cl$ (2.0 mL) at 120 °C, 24 h. [b]Isolated yields.

Table 3.7: Optimization of diamiation condition [a,b]

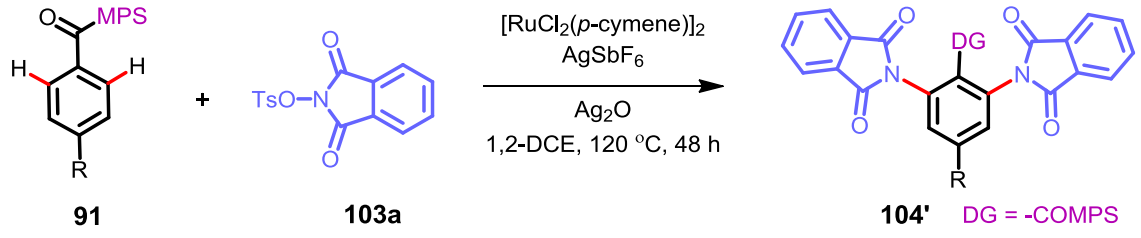


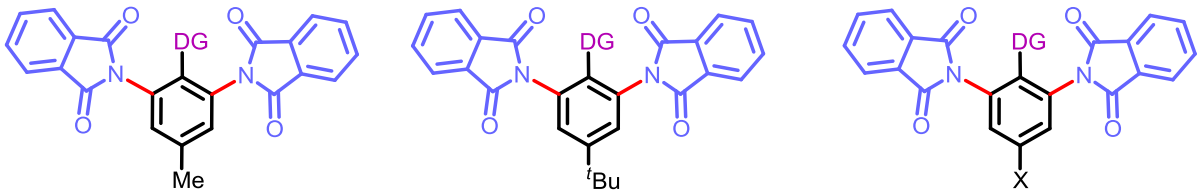
entry	**103a** (equiv)	yield of **104o** (%)	yield of **104o′** (%)
1	1.5	23%	77%
2	2.0	15%	85%
3	**3.0**	**0%**	**>95% (62%)**[c]
4	4.0	11%	89%

[a]Reaction conditions: **91n** (0.1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10.0 mol %), $AgSbF_6$ (40 mol %), Ag_2O (0.1 mmol), $ClCH_2CH_2Cl$ (2.0 mL) at 120 °C, 24 h. [b]Conversion based on crude ^1H NMR of starting material. [c]**91n** (0.5 mmol)

Next, the catalytic condition for *p*-substituted N-aroyl sulfoximine derivatives is persued (Table 3.7 & 3.8). The reaction between N-OTs amidating agent **103a** (1.5 equiv) and *p*-methyl substituted **91n** under the optimized conditions shown in entry 10, Table 3.5 gave mixture of mono **104o** and di-amidation **104o′** products in overall good yields. To improve the yield of **104o′**, the reaction was performed with different amount of **103a** (1.5–4.0 equiv, Table 3.7). The best results were obtained, when 3.0 equiv of **103a** was subjected and the reaction continued for 36 h, giving diamidation product **104o′** in 62% yield with minor amount of mono amidation product **104o** (Table 3.8). The bulky electron donating ^{t}Bu-arene containing diamidation product **104p′** was obtained in 69% yield. Interestingly, the halo F, Br groups bearing diamidation products **104q′** and **104r′** were isolated in moderate to good yields.

Table 3.8: Scope of *p*-substituted-*N*-benzoylated-sulfoximines [a,b]

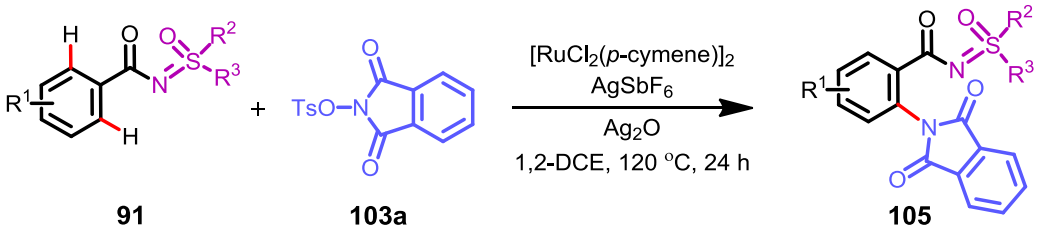


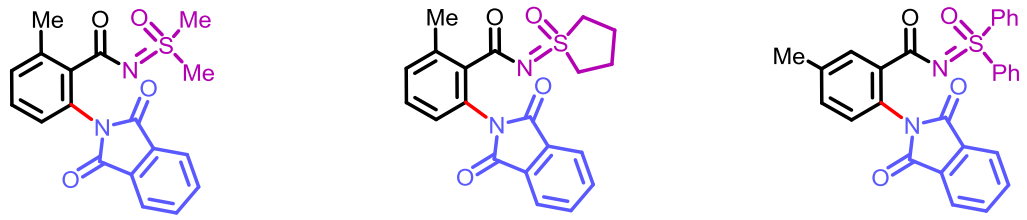


104o', 62% **104p'**, 69% X = F, **104q'**, 65% Br, **104r'**, 60%

[a]Reaction conditions: **91** (0.5 mmol), **103a** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %), Ag_2O (0.5 mmol), $ClCH_2CH_2Cl$ (2.0 mL).[b]Isolated yields.

Table 3.9: Steric and electronic effects of sulfoximine derivatives to the *o*-amidation of arenes[a,b]





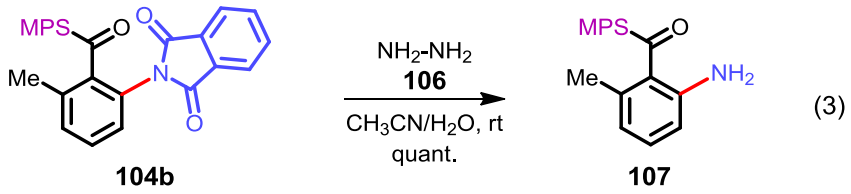
105a, 70% **105b**, 63% **105c**, 12%

[a]Reaction conditions: **91** (0.5 mmol), **103a** (0.75 mmol), $RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %), Ag_2O (0.5 mmol), $ClCH_2CH_2Cl$ (2.0 mL) at 120 °C, 24 h. [b]Isolated yields.

We next investigated the steric and electronic effects of sulfoximine derivatives to the *ortho*-C–H amidation of arenes (Table 3.9). The *N*-benzoylated-*S*,*S*-dimethyl-sulfoximine (**91a′**) and cyclic *S*,*S*-tetramethylene-sulfoximine (**91b′**) afforded the corresponding amidation

products **105a** and **105b** in 70% and 63% yield, respectively. In contrast, sterically demanding *S*,*S*-diphenyl-substituted sulfoximine (**91c′**) showed poor reactivity under the reaction condition. Based on these experimental results, the *S*-methyl-*S*-phenylsulfoximine is conceived potential directing group to the *o*-C–H amidation of arenes.

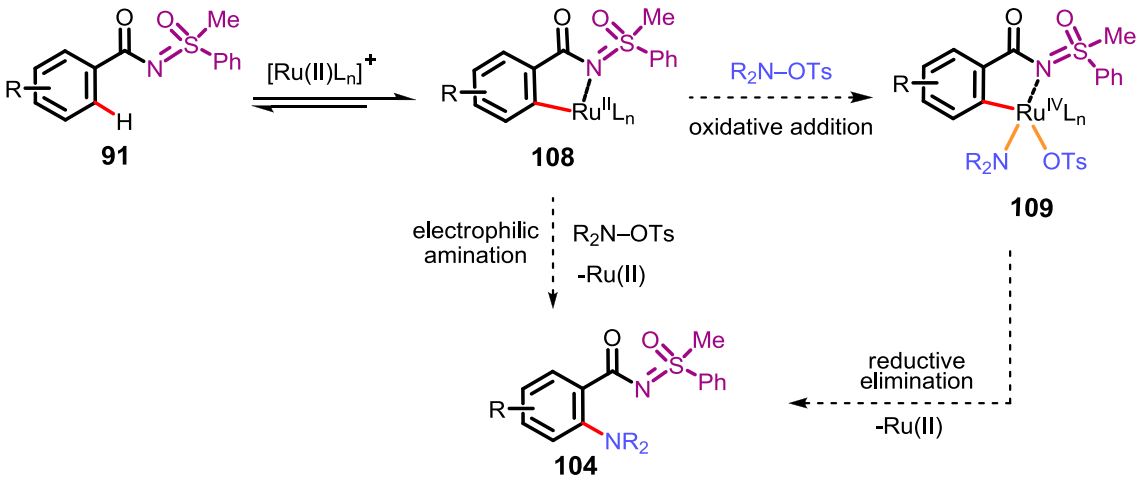
The removal of pthaloyl group from the amidation product would broaden the synthetic potential of the strategy. The reaction of **104b** with NH_2-NH_2 (**106**) in CH_3CN/H_2O readily deprotected the pthaloyl group and furnished free amino compound **107** in quantitative yield (eq. 3).



(3)

3.5.3. Mechanistic Studies

Although the detailed mechanism of Ru(II)-catalyzed C–H amidation of arenes is yet to be established, the proposed mechanism is outlined in Scheme 3.20 based on the observations of Yu and co-workers.[13] The combination of $[RuCl_2(p\text{-cymene})]_2$, acetate-source, and $AgSbF_6$ generates the active cationic Ru(II)-catalyst. The coordination of sulfoximine nitrogen to the cationic Ru-catalyst triggers activating the less-hindered *ortho*-C–H bond and delivers the metalacycle intermediate **108**. Oxidative addition of N-OTs to **108** to give ruthenium (IV) complex **109**.[13] Finally, reductive elimination from **109** provides the desired product **104** and generates the cationic ruthenium-complex for the next catalytic cycle. However, the possible participation of the electrophilic amination from **108** cannot be completely ruled out.[13]



Scheme 3.20: Proposed Catalytic Cycle

3.6. Conclusion

In summary, Ru(II)-catalyzed methyl phenyl sulfoximine (MPS) directed *ortho*-C–H amidation of various substituted N-aroyl MPS derivatives with electrophilic aminating agent N-arenesulfonated imides for the synthesis of anthranilic acid derivatives is reported. This strategy enables the synthesis of diamidation product in moderate to good yields. The reductive cleavage of phthloyl group from amidation products is successfully demonstrated.

3.7. Experimetal

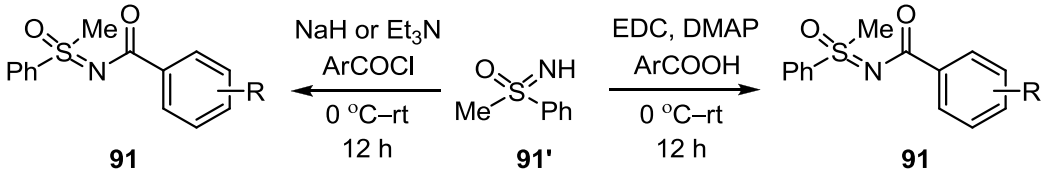
3.7.1. General Experimental Information is shown in Chapter 1.

3.7.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Dichloromethane (DCM) and 1,2-dichloroethane (DCE) were distilled over CaH_2. $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$, $AgBF_4$, $AgPF_6$, and KPF_6 were purchased from Sigma Aldrich Ltd, and used as received. Analytical and spectral data of all the known compounds are exactly matching with the reported values.

3.7.3. Experimental Procedures

3.7.3.1. Preparation of *N*-Protected Sulfoximines: General Procedures (GP-1 and GP-2):



Scheme 3.21: Preparation of *N*-aroyl sulfoximines

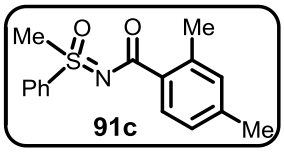
General Procedure (GP-1); Use of sodium hydride base: [22]

Sodium hydride (NaH; 1.5 equiv, 60% in oil) was taken in a 100 mL oven-dried two necked round bottom flask and washed with dry hexane (2 × 10 mL) under an inert atmosphere. Dichloromethane (5.0 mL, for 1.0 mmol of sulfoximine) was added. Sulfoximine (**91′**) (1.0 equiv) was charged drop wise in an ambient temperature. After being stirred for about 30 min to 1 h, the reaction mixture was cooled to 0 °C and acid chloride (1.1 equiv) was added drop wise. The resulting mixture was stirred for about 30 minutes and warmed to ambient temperature and continued for overnight. The reaction mixture was quenched with water (10 mL). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3 times). The combined extracts were washed with brine (25 mL) and dried over Na_2SO_4. Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography on silica gel.

General procedure (GP-2); EDC-coupling: [22a]

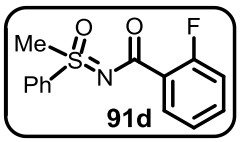
A solution of *N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, hydrochloride salt (EDC.HCl) (1.1 equiv), 4-*N*,*N*-dimethylaminopyridine (DMAP) (2.2 equiv) and carboxylic acid (1.1 equiv) in CH_2Cl_2 (5.0 mL, for 1.0 mmol of sulfoximine) was stirred under an argon atmosphere. Sulfoximine (**91′)** (1.0 equiv) was introduced drop wise at 0 °C. The resulting reaction mixture was stirred for about 1 h at 0 °C, and warmed to ambient temperature and continued for overnight. Upon complete consumption of sulfoximine, the reaction mixture was acidified with hydrochloric acid (HCl, 1N). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3 times). The combined extracts were washed with 10% aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4. Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography on silica gel.

***N*-[2, 4-Dimethylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (91c):**



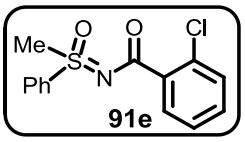
Following the general procedure (GP-2); **91c** (0.47 g) was prepared in 82% yield as colorless solid. mp = 83.8 °C; R_f = 0.36 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.2 Hz, 3H), 7.66 (t, J = 6.8 Hz, 1H), 7.59 (bt, J = 7.0 Hz, 2H), 7.06–6.98 (m, 2H), 3.40 (s, 3H), 2.58 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 141.2, 139.4, 138.9, 133.5, 132.2, 132.1, 130.9, 129.5, 127.0, 126.0, 44.3, 21.7, 21.2; IR (KBr) ν_{max} 3009, 2925, 1624, 1446, 1215 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{17}NO_2S$ $(M+H)^+$: 288.1058, Found: 288.1056.

***N*-[2-Fluorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (91d):**



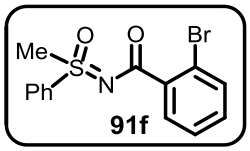
Following the general procedure (GP-1); **91d** (0.87 g) was prepared in 96% yield as colorless solid. mp = 123–124 °C; R_f = 0.30 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (bd, J = 8.0 Hz, 2H), 8.01 (td, J = 7.6 & 1.6 Hz, 1H), 7.70 (bt, J = 7.4 Hz, 1H), 7.62 (bt, J = 7.6 Hz, 2H), 7.49–7.40 (m, 1H), 7.17 (t, J = 7.4 Hz, 1H), 7.10 (dd, J = 11.0 & 8.6 Hz, 2H), 3.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (d, J = 4.0 Hz), 161.7 (d, J = 258.5 Hz), 138.6, 133.9, 133.3 (d, J = 9.1 Hz), 132.1, 129.7, 127.2, 124.4 (d, J = 9.1 Hz), 123.6 (d, J = 4.0 Hz), 116.7 (d, J = 23.2 Hz), 44.3 ; ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.75; IR (Neat) ν_{max} 3008, 2915, 1605, 1298, 1210 cm^{-1}; MS (EI) *m/z* (%) 278 (M^++1, 100); Anal. calcd for $C_{14}H_{12}FNO_2S$: C, 60.64; H, 4.36; N, 5.05. Found: C, 60.52; H, 4.28; N, 5.12.

_N_-[2-Chlorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91e):



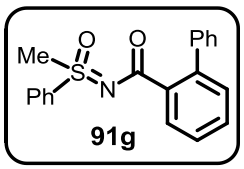
Following the general procedure (GP-1); **91e** (1.43 g) was prepared in 75% yield as colorless solid. mp = 94–95 ^{o}C; R_f = 0.32 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.2 Hz, 2H), 7.85 (dd, J = 7.4 & 1.8 Hz, 1H), 7.70 (bt, J = 7.4 Hz, 1H), 7.63 (t, J = 7.6 Hz, 2H), 7.41 (dd, J = 7.6 & 1.2 Hz, 1H), 7.34 (td, J = 7.5 & 1.9 Hz, 1H), 7.29 (dd, J = 7.4 & 1.4 Hz, 1H), 3.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 138.3, 136.1, 134.0, 132.2, 131.2, 130.7, 130.5, 129.7, 127.2, 126.5, 44.3; IR (Neat) ν_{max} 3013, 2909, 1632, 1216 cm^{-1}; MS (EI) *m/z* (%) 296 (M^+ + 3, 81), 294(M^+ + 1, 100), 156 (57), 139 (21); Anal. calcd for $C_{14}H_{12}ClNO_2S$: C, 57.24; H, 4.12; N, 4.77. Found: C, 57.16; H, 4.08; N, 4.85.

_N_-[2-Bromobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91f): [22b]



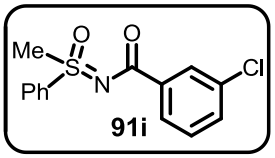
Following the general procedure (GP-1); **91f** (1.06 g) was prepared in 97% yield as colorless solid. mp = 99–100 ^{o}C; R_f = 0.34 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (bd, J = 7.2 Hz, 2H), 7.80 (dd, J = 7.6 & 1.6 Hz, 1H), 7.70 (bt, J = 7.4 Hz, 1H), 7.66–7.57 (m, 3H), 7.33 (td, J = 7.5 & 1.1 Hz, 1H), 7.24 (td, J = 7.7 & 1.8 Hz, 1H), 3.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 138.3, 138.2, 134.0, 133.7, 131.2, 130.5, 129.7, 127.2, 127.1, 120.3, 44.2; IR (Neat) ν_{max} 3028, 2922, 1635, 1215 cm^{-1}; MS (EI) *m/z* (%) 340 (M^++ 2, 100), 338 (M^+, 100), 183 (19), 156 (16); Anal. calcd for $C_{1\ 4}H_{12}BrNO_2S$: C, 49.72; H, 3.58; N, 4.14. Found: C, 49.65; H, 3.51; N, 4.22.

_N_-[2-Phenylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91g):



Following the general procedure (GP-2); **91g** (0.69g) was prepared in 64% yield as colorless crystalline solid. mp = 123.4–124.2 ^{o}C; R_f = 0.31 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (bd, J = 7.6 Hz, 1H), 7.59 (bt, J = 7.4 Hz, 1H), 7.54–7.34 (m, 12H), 3.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0, 142.5, 140.5, 138.2, 137.5, 133.7, 130.3, 130.0, 129.2, 129.0, 128.1, 127.3, 127.2, 127.0, 42.9; IR (KBr) ν_{max} 3003, 2920, 1622, 1304 cm^{-1}; MS (EI) *m/z* (%) 336 (M^++ 1, 100); Anal. calcd for $C_{20}H_{17}NO_2S$: C, 71.62; H, 5.11; N, 4.18. Found: C, 71.52; H, 5.12; N, 4.25.

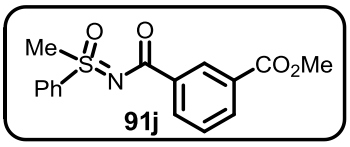
_N_-[3-Chlorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91i):



Following the general procedure (GP-1); **91i** (0.89 g) was prepared in 94% yield as colorless solid. mp = 92–95 ^{o}C; R_f = 0.32 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (t, J = 1.8 Hz, 1H), 8.06–8.00 (m, 3H),

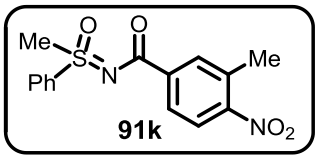
7.69 (t, *J* = 7.4 Hz, 1H), 7.62 (bt, *J* = 7.4 Hz, 2H), 7.50–7.43 (m, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 3.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 138.5, 137.3, 134.0, 133.9, 132.0, 129.7, 129.4, 129.3, 127.4, 127.0, 44.3; IR (KBr) ν_{max} 3024, 2937, 1616, 1561, 1293 cm^{-1}; MS (EI) *m/z* (%) 296 (M^++ 3, 81), 294 (M^++ 1, 100), 156 (57), 139 (21); Anal. calcd for $C_{14}H_{12}ClNO_2S$: C, 57.24; H, 4.12; N, 4.77. Found: C, 57.32; H, 4.06; N, 4.85.

_N_-[3-Methoxycarbonylbenzoyl]-_S_-methyl-_S_-phenyl sulfoximine (91j):



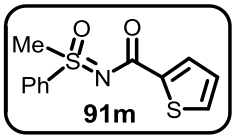
Following the general procedure (GP-2); **91j** (0.51 g) was prepared in 80% yield as colorless solid. mp = 153.8 °C; R_f = 0.28 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.33 (d, *J* = 7.6 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 7.6 Hz, 2H), 7.70 (bt, *J* = 7.2 Hz, 1H), 7.62 (bt, *J* = 7.4 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 3.93 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 166.7, 1387, 136.0, 133.9, 133.7, 133.0, 130.6, 130.1, 129.7, 128..2, 127.1, 52.2, 44.4; IR (KBr) ν_{max} 3021, 2951, 1720, 1629, 1245 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{15}NO_4S$ $(M+H)^+$: 318.0800, Found: 318.0800.

_N_-[3-Methyl-4-nitrobenzoyl]-_S_-methyl-_S_-phenylsulfoxi-mine (91k):



Following the general procedure (GP-2); **91k** (0.56 g) was prepared in 64% yield as colorless solid. mp = 84–85 °C; R_f = 0.31 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.06 (m, 2H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.72 (t, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 2H), 3.49 (s, 3H), 2.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 151.2, 139.2, 138.3, 134.1, 133.7, 133.1, 129.8, 127.8, 127.1, 124.3, 44.3, 20.2; IR (KBr) ν_{max} 3036, 2926, 1627, 1589, 1293, 1216 cm^{-1}; MS (EI) *m/z* (%) 319 (M^++ 1, 100); Anal. calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.68; H, 4.38; N, 8.72.

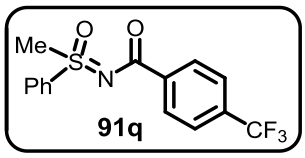
_N_-Thenoyl-_S_-methyl-_S_-phenylsulfoximine (91m):



Following the general procedure (GP-2); **91m** (0.41 g) was prepared in 47% yield as colorless crystalline solid. mp = 134.8–135.9 °C; R_f = 0.32 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.2 Hz, 2H), 7.81 (dd, *J* = 3.6 & 1.2 Hz, 1H), 7.70 (bt, *J* = 7.4 Hz, 1H), 7.62 (bt, *J* = 7.4 Hz, 2H), 7.49 (dd, *J* = 5.0 & 1.0 Hz, 1H), 7.07 (dd, *J* = 4.8 & 4.0 Hz, 1H), 3.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 141.1, 138.7, 133.9, 132.1, 131.6, 129.7, 127.7, 127.2, 44.4; IR (KBr) ν_{max} 3068, 2920, 1611, 1221 cm^{-1}; MS

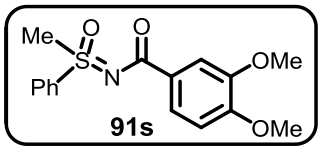
(EI) *m/z* (%) 266 (M^++ 1, 100); Anal. calcd for $C_{12}H_{11}NO_2S_2$: C, 54.32; H, 4.18; N, 5.28. Found: C, 54.26; H, 4.23; N, 5.21.

_N_-[4-Trifluoromethylbenzoyl]-_S_-methyl-_S_-phenyl sulfoximine (91q):



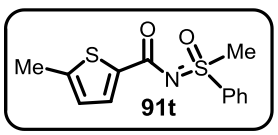
Following the general procedure (GP-2); **91q** (0.71 g) was prepared in 68% yield as colorless crystalline solid. mp = 117–118 ^oC; R_f = 0.39 (1:1 hexane /EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 8.0 Hz, 2H), 7.75–7.60 (m, 5H), 3.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ172.8, 138.7, 138.4, 134.0, 129.7, 129.6, 127.0, 125.0, 124.9, 44.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.84; IR (Neat) ν_{max} 3014, 2920, 1627, 1573, 1320, 1210, 1101 cm^{-1}; MS (EI) *m/z* (%) 328 (M^++ 1, 100), 296 (43), 183 (15); Anal. calcd for $C_{15}H_{12}F_3NO_2S$: C, 55.04; H, 3.70; N, 4.28;. Found: C, 55.12; H, 3.75; N, 4.21.

_N_-[3,4-Dimethoxybenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91s):



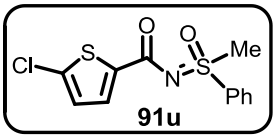
Following the general procedure (GP-2); **91s** (0.48 g) was prepared in 75% yield as colorless solid. mp = 105–106 ^oC; R_f = 0.17 (1:1 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08–8.02 (m, 2H), 7.84 (dd, J = 8.4 & 2.0 Hz, 1H), 7.71–7.64 (m, 2H), 7.63–7.57 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 152.5, 148.4, 139.2, 133.7, 129.6, 128.4, 127.1, 123.5, 111.8, 109.9, 55.9, 44.4; IR (KBr) ν_{max} 3047, 2931, 1621, 1578, 1509, 1264 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{17}NO_4S$ $(M+H)^+$: 320.0956, Found: 320.0952.

_N_-[5-Methylthenoyl]-_S_-methyl-_S_-phenylsulfoximine (91t):



Following the general procedure (GP-2); **91t** (0.65 g) was prepared in 72% yield as colorless crystalline solid. mp = 129–131 ^oC; R_f = 0.30 (2:3 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$)δ 8.04 (d, J = 7.6 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.64–7.56 (m, 3H), 6.73 (d, J = 3.2 Hz, 1H), 3.44 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 168.7, 146.9, 138.7, 138.4, 133.7, 132.4, 129.5 (2C), 127.0 (2C), 126.2, 44.3, 15.7; IR (KBr) ν_{max} 3030, 2926, 1610, 1282 cm^{-1}; HRMS (ESI) for $C_{13}H_{13}NO_2S_2$ $(M+Na)^+$: calcd. 302.0286, found 302.0282.

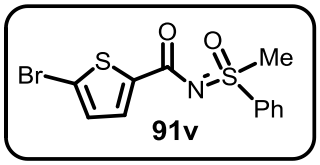
_N_-[5-Chlorothenoyl]-_S_-methyl-_S_-phenylsulfoximine (91u):



Following the general procedure (GP-2); **91u** (0.80 g) was prepared in 82% yield as colorless crystalline solid. mp = 120–121 ^oC; R_f = 0.35 (3:2

hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.6 Hz, 2H), 7.71 (bt, J = 7.4 Hz, 1H), 7.63 (bt, J = 7.6 Hz, 2H), 7.57 (d, J = 4.0 Hz, 1H), 6.90 (d, J = 3.6 Hz, 1H), 3.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 139.2, 138.5, 136.1, 134.0, 131.4, 129.7 (2C), 127.2, 127.1 (2C), 44.4; IR (KBr) ν_{max} 3024, 2931, 1610, 1435, 1221 cm^{-1}; HRMS (ESI) for $C_{12}H_{10}ClNO_2S_2$ $(M+Na)^+$: calcd. 321.9739, found 321.9740.

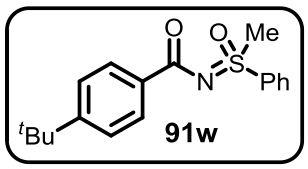
_N_-[5-Bromothenoyl]-_S_-methyl-_S_-phenylsulfoximine (91v):



91v

Following the general procedure (GP-1); **91v** (1.89 g) was prepared in 86% yield as colorless crystalline solid. mp = 137–139 °C; R_f = 0.52 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.6 Hz, 2H), 7.70 (t, J = 7.4 Hz 1H), 7.62 (t, J = 7.6 Hz, 2H), 7.53 (d, J = 4.0 Hz 1H), 7.03 (d, J = 3.6 Hz 1H), 3.44 (s, 3H) ;^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 142.1, 138.4, 134.0, 132.1, 130.8, 129.7, 127.1, 119.1, 44.4; IR (KBr) ν_{max} 3019, 2926, 1605, 1216 cm^{-1}; MS (EI) *m/z* (%) 345 (M^+ + 2, 100); Anal. Calcd. for $C_{12}H_{10}BrNO_2S_2$: C, 41.87; H, 2.93; Br, 23.21; N, 4.07. Found: C, 41.76; H, 2.89; N, 4.12.

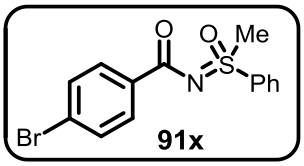
_N_-[4-^{t}Butylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91w):



91w

Following the general procedure (GP-1); **91w** (1.85 g) was prepared in 92% yield as colorless crystalline solid. mp = 142–143 °C; R_f = 0.51 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 7.2 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 3.45 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 155.7, 139.1, 133.7, 132.8, 129.6, 129.3, 127.1, 125.0, 44.3, 34.9, 31.1; IR (Neat) ν_{max} 3024, 2958, 1616, 1446, 1221 cm^{-1}; MS (EI) *m/z* (%) 316 (M^+ + 1, 100); Anal. Calcd. for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44. Found: C, 68.41; H, 6.76; N, 4.52.

_N_-[4-Bromobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91x):

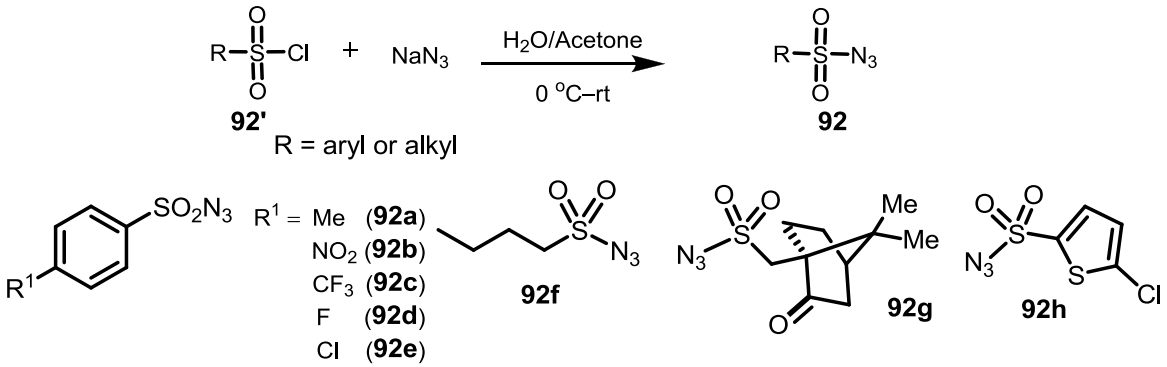


91x

Following the general procedure (GP-1); **91x** (0.89 g) was prepared in 82% yield as colorless crystalline solid. mp = 127–129 °C; R_f = 0.48 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–7.98 (m, 4H), 7.70 (t, J = 7.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 2H), 7.54 (d, J = 7.6 Hz, 2H), 3.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 138.7, 134.5, 133.9, 131.2, 131.0, 129.7, 127.1, 44.3 (one peak merged); IR (KBr) ν_{max} 3068, 2931, 1621, 1397, 1287 cm^{-1}; MS (EI) *m/z* (%) 339 (M^+ + 2, 100); Anal. Calcd. for $C_{14}H_{12}BrNO_2S$: C, 49.72; H, 3.58; N, 4.14. Found: C, 49.65; H, 3.51; N, 4.21.

3.7.3.2. Synthesis of Azides [23a]

The azides **92a, 92b, 92c, 92d, 92e, 92f,** and **92g** are prepared following the known procedure.

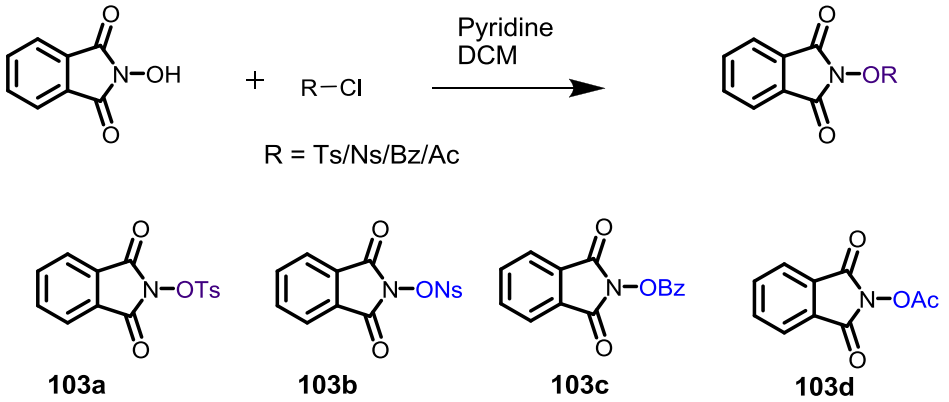


Scheme 3.22: Preparation of sulfonyl azides

To a solution of sodium azide (1.99 g, 30 mmol) in water (10 mL) was added a solution of *p*-toluenesulfonyl chloride (3.85 g, 20 mmol) in acetone (20 mL) dropwise at 0 °C. The reaction was warmed up to room temperature and stirred overnight. Acetone was removed under reduced pressure and the reaction mixture was extracted with EtOAc for three times. The combined organic layers were washed with water and saturated Na_2CO_3 solution, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product is subsequently used without further purification.

3.7.3.3. Synthesis of N-arenesulfonated imides [23b]

The N-arenesulfonated imides **103a, 103b, 103c,** and **103d** were prepared following the known procedure.



Scheme 3.23: Preparation of N-arenesulfonated imides

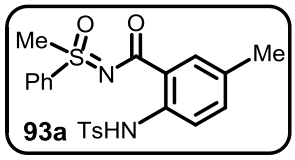
To a solution of 2-hydroxy-1H-isoindole-1,3(2H)-dione (1.00 g, 6.1 mmol) and *p*-toluenesulfonic chloride (1.1 equiv.) in DCM (20 mL) was added pyridine (2.0 mL) dropwise for 15 minutes. The solvent was removed in vacuo after performing the reaction for 4 h. Subsequently, 30 mL distilled water with a drop of concentrated 1N hydrochloric acid was added to the crude mixture. The solid product was filtered and washed with water (twice) to produce pure compound **103a–c** (70-90% yield).

The compound **103d** was prepared from 2-hydroxy-1H-isoindole-1,3(2H)-dione (1.5 g, 9.2 mmol) by reacting with Ac_2O (20 mL) after stirring for 12 h. Upon the completion, the crude mixture was kept at –10 ^oC over night. The desired compound was precipated; the solid prodcuct filtered, washed with water, and dried to afford **103d** as colourless solid.

3.7.3.4. General Procedure for C–H Amidation Reaction (GP-3)

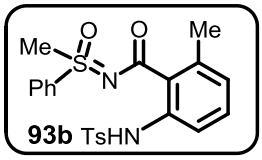
The C–H amidation reactions were carried out in a 50 mL Schlenk tube having high pressure value and side arm. The tube was charged with *N*-aroylated sulfoximine (**91a**–**91s,** 0.5 mmol), sulfonyl azide (**92a–f**, 1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (30.5 mg, 10 mol %), and KOAc (24 mg, 50 mol%). Subsequently, $AgSbF_6$ (69 mg, 40 mol %) was introduced to the flask in a glovebox. 1,2-DCE (2.0 mL) was added to the mixture and the resulting mixture was stirred at 120 ^oC for 24 h. The reaction mixture was cooled to ambient temperature, filtered through a plug of Celite and then washed with dichloromethane (3 × 10 mL). Solvents were evaporated under reduced pressure and the crude material was purified using column chromatography on silica gel (30–40% *n*-hexane/EtOAc eluent) to give the desired product.

_N_-[2-(4′-Methylbenzenesulfonamido)-5-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (93a):



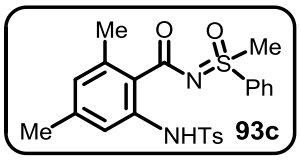
93a (173 mg, 78%) as light brown viscous thick liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 11.35 (s, 1H, NH), 8.02–7.94 (m, 3H), 7.73 (bt, J = 7.4 Hz, 1H), 7.70–7.58 (m, 4H), 7.51 (d, J = 7.6 Hz, 1H), 7.21–7.13 (m, 3H), 3.43 (s, 3H), 2.33 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 143.4, 138.1, 137.9, 136.6, 134.4, 134.1, 132.2, 132.0, 129.8, 129.5, 127.2, 127.0, 120.8, 118.8, 44.5, 21.5, 20.5; IR (Neat) ν_{max} 3063, 2920, 1621, 1577, 1259 cm^{-1}; MS (EI) *m/z* (%) 444 (M^++ 1,100), 412 (37); Anal. Calcd. for $C_{22}H_{22}N_2O_4S_2$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.67; H, 5.12, N, 6.43.

_N_-[2-(4′-Methylbenzenesulfonamido)-6-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (93b):



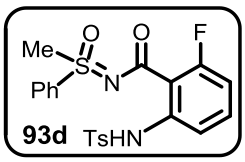
93b (194 mg, 88%) as colorless crystalline solid; mp = 115–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H, NH), 7.99 (d, J = 7.6 Hz, 2H), 7.70 (bt, J = 7.4 Hz, 1H), 7.66–7.58 (m, 4H), 7.36 (d, J = 8.0 Hz, 1H), 7.18–7.10 (m, 3H), 6.87 (d, J = 7.6 Hz, 1H), 3.41 (s, 3H), 2.40 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 143.4, 139.1, 137.7, 136.5, 136.4, 134.2, 130.4, 129.8, 129.5, 127.3, 127.1, 126.8, 126.7, 118.6, 44.3, 22.2, 21.3; IR (Neat) ν_{max} 3232, 2920, 1632, 1599, 1221, 1155 cm^{-1}; MS (EI) *m/z* (%) 444 (M^++ 2, 100), 412 (40); Anal. Calcd. for $C_{22}H_{22}N_2O_4S_2$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.62; H, 5.08; N, 6.43.

_N_-[2-(4′-Methylbenzenesulfonamido)-4,6-dimethylbenz-oyl]-_S_-methyl-_S_-phenylsulfoximine (93c):



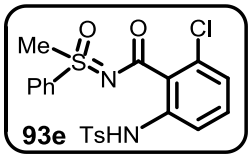
93c (171 mg, 75%) as colorless viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H, NH), 7.97 (d, J = 7.6 Hz, 2H), 7.69 (bt, J = 7.2 Hz, 1H), 7.66–7.56 (m, 4H), 7.23 (s, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.69 (s, 1H), 3.40 (s, 3H), 2.38 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 143.3, 141.0, 139.4, 137.7, 137.1, 136.3, 134.1, 129.7, 129.5, 128.3, 127.0, 126.8, 123.2, 118.9, 44.3, 22.5, 21.31, 21.28.; IR (Neat) ν_{max} 3441, 2929, 1614, 1293, 1164 cm^{-1}; MS (EI) *m/z* (%) 457 (M^++ 1, 100), 297 (19), 229 (11); Anal. Calcd. for $C_{23}H_{24}N_2O_4S_2$: C, 60.50; H, 5.30; N, 6.14. Found: C, 60.41; H, 5.25; N, 6.23.

_N_-[2-(4′-Methylbenzenesulfonamido)-6-fluorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (93d):



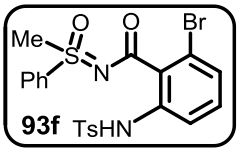
93d (179 mg, 80%) as pale brown viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H, NH), 8.04 (d, J = 7.6 Hz, 2H), 7.72 (bt, J = 7.2 Hz, 1H), 7.68–7.58 (m, 4H), 7.41 (d, J = 8.4 Hz, 1H), 7.32–7.26 (m, 1H), 7.19 (d, J = 8.0 Hz, 2H), 6.76 (dd, J = 10.0 & 8.8 Hz, 1H), 3.43 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 161.9 (d, J = 256 Hz), 143.7, 140.0, 137.6, 136.0, 134.3, 132.7 (d, J = 10.1 Hz), 129.8, 129.6, 127.1, 115.7, 113.6 (d, J = 12.1 Hz), 111.6 (d, J = 24.2 Hz), 44.4, 21.4; ^{19}F (470 MHz, $CDCl_3$) δ –105.02; IR (Neat) ν_{max} 3236, 2927, 1618, 1588, 1311, 1222, 1159 cm^{-1}; MS (EI) *m/z* (%) 447 (M^++ 1, 100), 312 (24); Anal. Calcd. for $C_{21}H_{19}FN_2O_4S_2$: C, 56.49; H, 4.29; N, 6.27. Found: C, 56.38; H, 4.23; N, 6.32.

_N_-[2-(4′-Methylbenzenesulfonamido)-6-chlorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (93e):



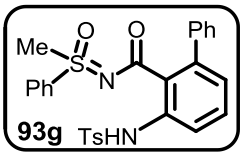
93e (150 mg, 65%) as colorless solid; mp = 133–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H, NH), 8.05 (d, J = 8.0 Hz, 2H), 7.73 (bt, J = 7.4 Hz, 1H), 7.69–7.58 (m, 4H), 7.55 (d, J = 8.4 Hz, 1H), 7.21 (t, J = 8.2 Hz, 1H), 7.18–7.09 (m, 3H), 3.42 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 143.7, 137.4, 137.1, 135.9, 134.4, 132.4, 130.7, 129.9, 129.8, 127.8, 127.2, 126.6, 120.5, 44.3, 21.4; IR (KBr) ν_{max} 3281, 3022, 2929, 1604, 1583, 1293, 1164 cm^{-1}; MS (EI) *m/z* (%) 463 (M^++ 1, 100), 369 (16), 265 (11), 94 (24); Anal. Calcd. for $C_{21}H_{19}ClN_2O_4S_2$: C, 54.48; H, 4.14; N, 6.05. Found: C, 54.32; H, 4.21; N, 6.15.

_N_-[2-(4′-Methylbenzenesulfonamido)-6-bromobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (93f):



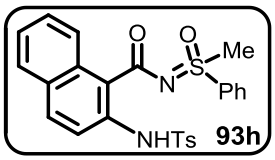
93f (108 mg, 43%) as colorless solid; mp = 145–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (bs, 1H, NH), 8.07 (d, J = 8.0 Hz, 2H), 7.73 (bt, J = 7.4 Hz, 1H), 7.68–7.55 (m, 5H), 7.31 (d, J = 8.0 Hz, 1H), 7.15–7.09 (m, 3H), 3.43 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 143.7, 137.4, 136.6, 135.9, 134.4, 130.9, 130.1, 129.9, 129.8, 129.7, 127.2, 121.3, 120.6, 44.1, 21.3; IR (Neat) ν_{max} 3256, 2925, 1644, 1607, 1264 cm^{-1}; MS (EI) *m/z* (%) 509 (M^++ 2, 97), 507 (M^+, 100), 493 (55), 435 (67), 253 (16); Anal. Calcd. for $C_{21}H_{19}BrN_2O_4S_2$: C, 49.71; H, 3.77; N, 5.52. Found: C, 49.65; H, 3.72; N, 5.61.

_N_-[2-(4′-Methylbenzenesulfonamido)-6-phenylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (93g):



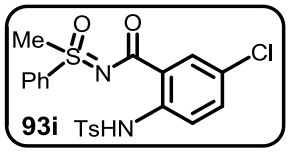
93g (124 mg, 49%) as colorless crystalline solid; mp = 173–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (bs, 1H, NH), 7.70 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.60 (bt, J = 7.4 Hz, 1H), 7.48–7.29 (m, 8H), 7.21 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 7.6 Hz, 1H), 3.16 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 143.3, 142.5, 142.0, 137.5, 136.6, 136.2, 133.9, 130.3, 129.7, 129.3, 128.8, 128.1, 127.2, 126.9, 126.5, 120.2, 42.8, 21.3; IR (KBr) ν_{max} 3231, 2925, 1600, 1584, 1289 cm^{-1}; MS (EI) *m/z* (%) 506 (M^+ + 2, 100), 402(68), 359 (5); Anal. Calcd. for $C_{27}H_{24}N_2O_4S_2$: C, 64.26; H, 4.79; N, 5.55. Found: C, 64.35; H, 4.72; N, 5.61.

_N_-[2-(4′-Methylbenzenesulfonamido)-_α_-naptholoyl]-_S_-methyl-_S_-phenylsulfoximine (93h):



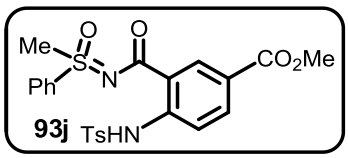
93h (153 mg, 64%) as colorless viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H, NH), 8.48 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 7.6 Hz, 2H), 7.79 (s, 2H), 7.77–7.61 (m, 6H), 7.44 (td, J = 7.7 & 1.3 Hz, 1H), 7.37 (t, J = 7.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 3.50 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 143.7, 137.6, 136.3, 135.6, 134.3, 132.2, 131.3, 130.7, 129.9, 129.7, 128.1, 127.3, 127.1, 127.0, 126.1, 125.1, 121.7, 119.6, 44.4, 21.4 ; IR (Neat) ν_{max} 3063, 2926, 1622, 1594, 1408, 1353, 1233 cm^{-1}; MS (EI) *m/z* (%) 480 (M^++ 2, 84), 234 (11); Anal. Calcd. for $C_{25}H_{22}N_2O_4S_2$: C, 62.74; H, 4.63; N, 5.85. Found: C, 62.81; H, 4.61; N, 5.76.

_N_-[2-(4′-Methylbenzenesulfonamido)-5-chlorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (93i):



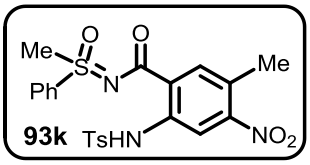
93i (87 mg, 37%) as light brown viscous thick liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (s, 1H, NH), 8.15 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.74 (bt, J = 7.4 Hz, 1H), 7.70–7.60 (m, 4H), 7.56 (d, J = 8.8 Hz, 1H), 7.34–7.27 (m, 1H), 7.18 (d, J = 8.0 Hz, 2H), 3.44 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 143.8, 139.0, 137.6, 136.2, 134.3, 133.4, 131.7, 129.9, 129.6, 127.1, 126.9, 126.3, 121.8, 119.8, 44.5, 21.5; IR (Neat) ν_{max} 3057, 2931, 1616, 1578, 1479, 1244, 1085 cm^{-1}; MS (EI) *m/z* (%) 464 (M^++ 1,100), 372 (16), 350 (42); Anal. Calcd. for $C_{21}H_{19}ClN_2O_4S_2$: C, 54.48; H, 4.14; N, 6.05;. Found: C, 54.38; H, 4.23, N, 6.12.

_N_-[3-methoxycarbonyl-6-(4′-Methylbenzenesulfo-namido)benzoyl]-_S_-methyl-_S_-phenyl sulfoximine (93j):



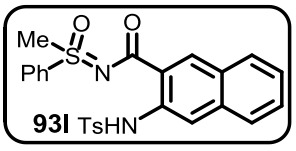
93j (180 mg, 74%) as light brown solid; mp = 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.93 (s, 1H, NH), 8.86 (s, 1H), 8.01–7.94 (m, 3H), 7.74–7.66 (m, 3H), 7.65–7.56 (m, 3H), 7.18 (d, J = 7.6 Hz 2H), 3.84 (s, 3H), 3.44 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 165.9, 144.3, 144.0, 137.6, 136.2, 134.4, 134.2, 134.1, 129.8, 129.6, 127.1, 126.9, 123.4, 119.5, 117.0, 52.0, 44.5, 21.4; IR (Neat) ν_{max} 3078, 3024, 2928, 1718, 1619, 1335 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{22}N_2O_6S_2$ $(M+Na)^+$: 509.0817, Found: 509.0814.

_N_-[2-(4′-Methylbenzenesulfonamido)-5-methyl-4-nitrobenzoyl]-_S_-methyl-_S_-phenylsulfoxi mine (93k):



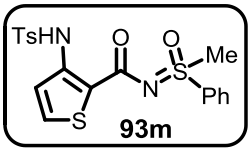
93k (150 mg, 62%) as brown thick liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (s, 1H, NH), 8.13 (d, J = 7.2 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H), 7.75 (bt, J = 7.4 Hz, 1H), 7.72–7.61 (m, 4H), 7.20 (d, J = 8.0 Hz, 2H), 3.48 (s, 3H), 2.43 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 151.2, 144.1, 138.8, 137.3, 136.4, 135.8, 134.4, 129.9, 129.7, 127.2, 126.9, 126.0, 123.7, 113.8, 44.4, 21.4, 19.2; IR (Neat) ν_{max} 3062, 2929, 1630, 1595, 1218 cm^{-1}; MS (EI) *m/z* (%) 488 (M^++ 1, 58), 487 (M^+, 100); Anal. Calcd. for $C_{22}H_{21}N_3O_6S_2$: C, 54.20; H, 4.34; N, 8.62. Found: C, 54.32; H, 4.31; N, 8.56.

_N_-[3-(4′-Methylbenzenesulfonamido)-β-naptholoyl]-_S_-methyl-_S_-phenylsulfoximine (93l):



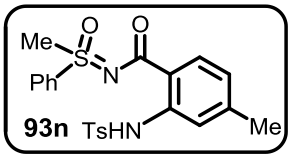
93l (193 mg, 81%) as pale brown viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.43 (s, 1H, NH), 8.79 (s, 1H), 8.05 (bd, J = 7.6 Hz, 2H), 7.97 (s, 1H), 7.82–7.70 (m, 5H), 7.67 (t, J = 7.6 Hz, 2H), 7.51 (td, J = 7.5 & 1.1 Hz, 1H), 7.37 (bt, J = 7.4 Hz, 1H), 7.14 (bd, J = 8.0 Hz, 2H), 3.50 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 143.4, 138.1, 136.5, 135.9, 135.8, 134.2, 129.9, 129.5, 129.0, 128.9, 128.6, 127.3, 127.1, 127.0, 125.2, 121.2, 115.6, 44.6, 21.4; IR (Neat) ν_{max} 3425, 3063, 1640, 1609, 1293, 1221 cm^{-1}; MS (EI) *m/z* (%) 480 (M^++1, 100), 234 (11); Anal. Calcd. for $C_{25}H_{22}N_2O_4S_2$: C, 62.74; H, 4.63; N, 5.85. Found: C, 62.85; H, 4.58; N, 5.81.

_N_-[3-(4′-Methylbenzenesulfonamido)-thenoyl]-_S_-methyl-_S_-phenylsulfoximine (93m):



93m (76 mg, 35%) as pale brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H, NH), 7.99 (d, J = 7.2 Hz, 2H), 7.76–7.66 (m, 3H), 7.63 (bt, J = 8.0 Hz, 2H), 7.35–7.28 (m, 2H), 7.21 (d, J = 7.6 Hz, 2H), 3.41 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 143.8, 138.0, 136.5, 134.2, 130.8, 129.8, 129.6, 127.1, 126.9, 120.4, 44.7, 21.5; IR (Neat) ν_{max} 3167, 2926, 1614, 1589, 1380, 1162 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{18}N_2O_4S_3$ $(M+H)^+$: 435.0507, Found: 435.0507.

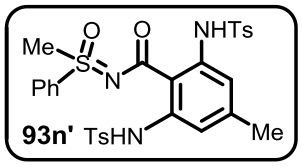
_N_-[2-(4′-Methylbenzenesulfonamido)-4-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (93n):



93n (108 mg, 49%) as pale brown viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (s, 1H, NH), 8.07 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 7.6 Hz,

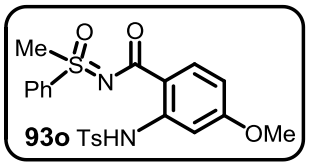
2H), 7.73–7.67 (m, 3H), 7.63 (bt, *J* = 7.6 Hz, 2H), 7.41 (s, 1H), 7.18 (d, *J* = 7.6 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 3.43 (s, 3H), 2.33 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 144.8, 143.5, 140.5, 138.2, 136.8, 134.2, 132.3, 129.9, 129.6, 127.2, 127.1, 123.3, 118.8, 118.1, 44.6, 22.0, 21.5; IR (Neat) ν_{max} 3060, 2926, 1618, 1590, 1255, 1153 cm^{-1}; MS (EI) *m/z* (%) 443 (M^++1, 100), 393 (13); Anal. Calcd. for $C_{22}H_{22}N_2O_4S_2$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.65; H, 5.12; N, 6.43.

_N_-[2,6-Di(4′-methylbenzenesulfonamido)-4-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (93n'):



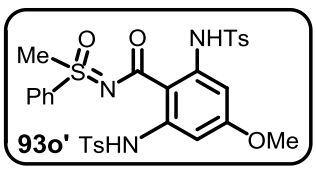
93n' (98 mg, 32%) as colorless solid; mp = 180–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.57 (s, NH, 2H), 7.95 (d, *J* = 7.6 Hz, 2H), 7.75 (bt, *J* = 7.4 Hz, 1H), 7.66 (bt, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 4H), 7.17 (d, *J* = 8.0 Hz, 4H), 7.00 (s, 2H), 3.49 (s, 3H), 2.34 (s, 6H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 144.5, 143.7, 141.0, 136.6, 136.3, 134.7, 130.1, 129.5, 127.0, 126.8, 114.7, 107.3, 44.6, 22.0, 21.4; IR (Neat) ν_{max} 3053, 2985, 1614, 1590, 1399, 1291 cm^{-1}; MS (EI) *m/z* (%) 612 (M^+, 44), 592 (26), 335 (26), 189 (100); Anal. Calcd. for $C_{29}H_{29}N_3O_6S_3$: C, 56.94; H, 4.78; N, 6.87. Found: C, 56.85; H, 4.72; N, 6.81.

_N_-[2-(4′-Methylbenzenesulfonamido)-4-methoxybenzoyl]-_S_-methyl-_S_-phenylsulfoximine (93o):



93o (126 mg, 55%) as colorless viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.82 (s, 1H, NH), 8.13 (d, *J* = 8.8 Hz, 1H), 8.00 (d, *J* = 7.6 Hz, 2H), 7.76–7.68 (m, 3H), 7.63 (bt, *J* = 7.4 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.12 (s, 1H), 6.49 (d, *J* = 8.8 Hz, 1H), 3.78 (s, 3H), 3.43 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 163.7, 143.6, 142.7, 138.4, 136.7, 134.1, 129.9, 129.6, 127.3, 127.1, 113.3, 108.8, 102.4, 55.5, 44.7, 21.5; IR (Neat) ν_{max} 3053, 2928, 1614, 1589, 1259 cm^{-1}; MS (EI) *m/z* (%) 458 (M^+, 100); Anal. Calcd. for $C_{22}H_{22}N_2O_5S_2$: C, 57.62; H, 4.84; N, 6.11. Found: C, 57.48; H, 4.76; N, 6.16.

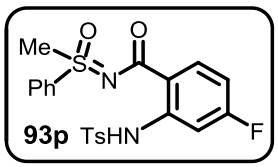
_N_-[2,6-Di(4′-methylbenzenesulfonamido)-4-methoxybenzoyl]-_S_-methyl-_S_-phenyl sulfoxim ine (93o'):



93o' (89 mg, 28%) as pale brown viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 2H, NH), 7.97 (d, *J* = 8.0 Hz, 2H), 7.77 (bt, *J* = 7.2 Hz, 1H), 7.72–7.61 (m, 6H), 7.19 (d, *J* = 8.0 Hz, 4H), 6.71 (s, 2H), 3.68

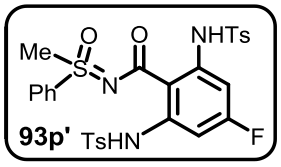
(s, 3H), 3.51 (s, 3H), 2.36 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 163.0, 143.9, 143.5, 136.8, 136.4, 134.8, 130.2, 129.7, 127.3, 127.0, 102.2, 99.1, 55.4, 44.9, 21.6; IR (Neat) ν_{max} 3025, 2926, 1613, 1579, 1229, 1155 cm^{-1}; MS (EI) *m/z* (%) 627 (M^++1, 100), 626 (M^++2, 98); Anal. Calcd. for $C_{29}H_{29}N_3O_7S_3$: C, 55.49; H, 4.66; N, 6.69. Found: C, 55.36; H, 4.72; N, 6.61.

_N_-[2-(4′-Methylbenzenesulfonamido)-4-fluorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (93p):



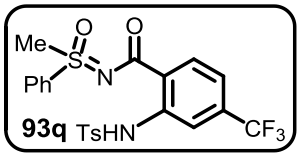
93p (110 mg, 49%) as colorless viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.83 (s, 1H, NH), 8.23 (dd, *J* = 8.8 & 6.8 Hz, 1H), 8.00 (bd, *J* = 7.6 Hz, 2H), 7.76–7.70 (m, 3H), 7.65 (bt, *J* = 7.6 Hz, 2H), 7.33 (dd, *J* = 10.8 & 2.4 Hz, 1H), 7.21 (bd, *J* = 8.4 Hz, 2H), 6.69–6.61 (m, 1H), 3.45 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 165.5 (d, *J* = 254 Hz), 143.9, 142.7 (d, *J* = 12.1 Hz), 137.9, 136.3, 134.7 (d, *J* = 11.1 Hz), 134.2, 129.8, 129.6, 127.2, 127.0, 116.4, 109.3 (d, *J* = 21.2 Hz), 104.9 (d, *J* = 27.3 Hz), 44.5, 21.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.47; IR (Neat) ν_{max} 3456, 3058, 2928, 1625, 1588, 1262 cm^{-1}; MS (EI) *m/z* (%) 448 (M^++2, 51), 447 (M^++1, 100), 417 (15); Anal. Calcd. for $C_{21}H_{19}FN_2O_4S_2$: C, 56.49; H, 4.29; N, 6.27. Found: C, 56.62; H, 4.35; N, 6.19.

_N_-[2,6-Di(4′-methylbenzenesulfonamido)-4-fluorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (93p'):



93p' (122 mg, 40%) as colorless viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.00 (s, 2H, NH), 7.99 (d, *J* = 8.0 Hz, 2H), 7.79 (bt, *J* = 7.4 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 4H), 7.22 (d, *J* = 8.4 Hz, 4H), 6.90 (d, *J* = 10.4 Hz, 2H), 3.55 (s, 3H), 2.37 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 164.7 (d, *J* = 252 Hz), 144.2, 143.8 (d, *J* = 14.1 Hz), 136.3, 135.9, 134.9, 130.2, 129.7, 127.1, 126.8, 104.9, 100.2 (d, *J* = 27.3 Hz), 44.7, 21.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −100.31; IR (Neat) ν_{max} 3063, 2928, 1609, 1433, 1288, 1236 cm^{-1}; MS (EI) *m/z* (%) 617 (M^++1, 35), 541 (100), 499 (19); Anal. Calcd. for $C_{28}H_{26}FN_3O_6S_3$: C, 54.62; H, 4.26; N, 6.82. Found: C, 54.71; H, 4.21; N, 6.75.

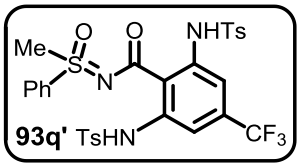
_N_-[2-(4′-Methylbenzenesulfonamido)-4-trifluoromethylbenzoyl]-_S_-methyl-_S_-phenylsulfoxi mine (93q):



93q (124mg, 50%) as pale brown viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.65 (s, 1H, NH), 8.30 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.89 (s, 1H), 7.76–7.68 (m, 3H), 7.68–7.62 (m, 2H), 7.23–7.17 (m, 3H),

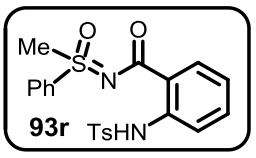
3.47 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 144.2, 140.9, 137.7, 136.2, 134.6, 133.1, 130.1, 129.8, 127.4, 127.1, 126.4, 123.2, 118.6, 115.1, 44.6, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –64.29; IR (Neat) ν_{max} 3101, 2920, 1627, 1600, 1249, 1156 cm^{-1}; MS (EI) *m/z* (%) 496 (M^+, 100), 463 (16), 301 (13); Anal. Calcd. for $C_{22}H_{19}F_3N_2O_4S_2$: C, 53.22; H, 3.86; N, 5.64. Found: C, 53.15; H, 3.92; N, 5.56.

_N_-[2,6-Di(4′-methylbenzenesulfonamido)-4-trifluoromethylbenzoyl]-_S_-methyl-_S_-phenyl sulfoximine (93q'):



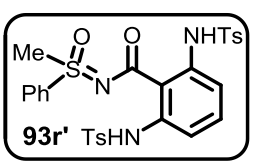
93q' (83 mg, 25%) as pale brown viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (s, 2H, NH), 7.99 (d, *J* = 8.0 Hz, 2H), 7.81 (bt, *J* = 7.0 Hz, 1H), 7.71 (bt, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 4H), 7.42 (s, 2H), 7.21 (d, *J* = 7.6 Hz, 4H), 3.55 (s, 3H), 2.36 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 144.3, 141.8, 136.1, 135.7, 135.0, 130.3, 129.8, 127.2, 126.8, 111.5, 109.8, 44.6, 21.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ–63.46; IR (Neat) ν_{max} 3065, 2928, 1629, 1596, 1249, 1158 cm^{-1}; MS (EI) *m/z* (%) 667 (M^++1, 55), 391 (67), 268 (100), 236 (100), 157 (100); Anal. Calcd. for $C_{29}H_{26}F_3N_3O_6S_3$: C, 52.32; H, 3.94; N, 6.31. Found: C, 52.21; H, 3.89; N, 6.43.

_N_-[2-(4′-Methylbenzenesulfonamido)benzoyl]-_S_-methyl-_S_-phenylsulfoximine (93r):



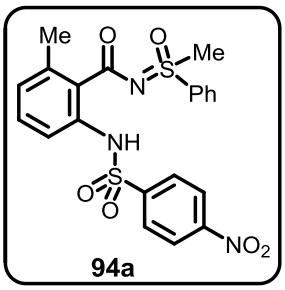
93r (76 mg, 37%) as pale brown viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.58 (s, NH, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.76–7.68 (m, 3H), 7.67–7.56 (m, 3H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 3.45 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 143.5, 140.5, 138.0, 136.6, 134.2, 133.7, 132.2, 129.8, 129.5, 127.2, 127.0, 122.2, 120.6, 118.3, 44.5, 21.5; IR (Neat) ν_{max} 3059, 2926, 1612, 1587, 1157 cm^{-1}; MS (EI) *m/z* (%) 429 (M^++1, 100). Anal. calcd for $C_{21}H_{20}N_2O_4S_2$: C, 58.86; H, 4.70; N, 6.54. Found C, 58.76; H, 4.72; N, 6.61.

_N_-[2,6-Di(4′-methylbenzenesulfonamido)benzoyl]-_S_-methyl-_S_-phenylsulfoximine (93r'):



93r' (84 mg, 28%) as brown viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (s, NH, 2H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.78 (bt, *J* = 7.4 Hz, 1H), 7.69 (bt, *J* = 7.8 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 4H), 7.21–7.12 (m, 7H), 3.51 (s, 3H), 2.35 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 143.8, 141.1, 136.5, 136.5, 134.8, 133.3, 130.2, 129.6, 127.1, 126.9, 114.1, 110.0, 44.7, 21.5; IR (Neat) ν_{max} 3057, 2924, 1608, 1591, 1157 cm^{-1}; MS (EI) *m/z* (%) 599 (M^++2, 33), 491 (100), 473 (100), 333 (89); Anal. Calcd. for $C_{28}H_{27}N_3O_6S_3$: C, 56.26; H, 4.55; N, 7.03. Found: C, 56.15; H, 4.48; N, 7.12.

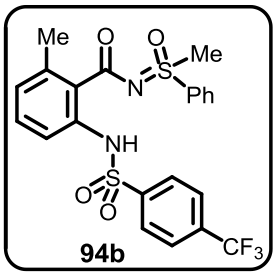
_N_-[2-(4′-Nitrobenzenesulfonamido)-6-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (94a):



94a

94a (220 mg, 93%) as colorless crystalline solid; mp = 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H, NH), 8.19 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 7.6 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.75 (bt, J = 7.0 Hz, 1H), 7.66 (bt, J = 7.2 Hz, 2H), 7.47 (bd, J = 7.6 Hz, 1H), 7.28–7.21 (m, 1H), 7.00 (d, J = 7.2 Hz, 1H), 3.41 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 75.6, 150.0, 144.7, 138.7, 137.5, 135.3, 134.4, 130.7, 130.0, 128.6, 128.5, 128.3, 126.8, 124.3, 120.9, 44.4, 22.1; IR (Neat) ν_{max} 3249, 2927, 1625, 1590, 1220, 1164 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{19}N_3O_6S_2$ $(M+H)^+$: 474.0793, Found: 474.0793.

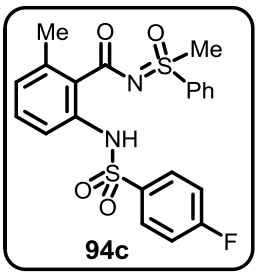
_N_-[2-(4′-Trifluoromethylbenzenesulfonamido)-6-methylbenzoyl]-_S_-methyl-_S_-phenyl sulfoximine (94b):



94b

94b (186 mg, 75%) as colorless solid; mp = 128–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H, NH), 7.97 (d, J = 7.6 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 7.71 (bt, J = 7.4 Hz, 1H), 7.67–7.59 (m, 4H), 7.42 (bd, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.94 (bd, J = 7.6 Hz, 1H), 3.39 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 142.7, 138.9, 137.5, 135.8, 134.2, 130.6, 129.9, 128.1, 127.7, 127.6, 126.8, 126.2, 126.1, 119.8, 44.3, 22.2; ^{19}F (376 MHz, $CDCl_3$) δ –63.02: IR (Neat) ν_{max} 3233, 2929, 1637, 1591, 1321 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{19}F_3N_2O_4S_2$ $(M+Na)^+$: 519.0636, Found: 519.0637.

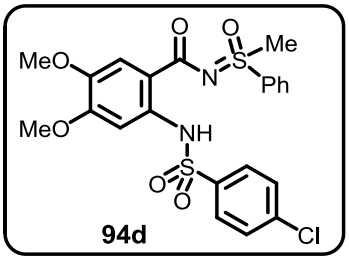
_N_-[2-(4′-Fluorobenzenesulfonamido)-6-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (94c):



94c

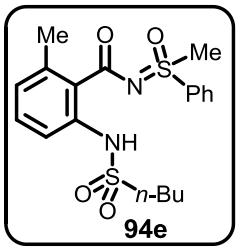
94c (195 mg, 87%) as pale brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H, NH), 8.00 (d, J = 7.6 Hz, 2H), 7.78–7.69 (m, 3H), 7.66 (bt, J = 7.6 Hz, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.04 (bt, J = 8.4 Hz, 2H), 6.93 (d, J = 7.6 Hz, 1H), 3.43 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 165.1 (d, J = 255 Hz), 139.1, 137.8, 136.3, 135.3 (d, J = 4.0 Hz), 134.3, 130.6, 130.1, 130.0, 127.9, 127.5, 127.0, 119.7, 116.3 (d, J = 22.2 Hz), 44.5, 22.2; ^{19}F (376 MHz, $CDCl_3$) δ –105.11; IR (Neat) ν_{max} 3243, 2927, 1635, 1589, 1221 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{19}FN_2O_4S_2$ $(M+H)^+$: 447.0848, Found: 447.0848.

_N_-[2-(4-Chlorobenzenesulfonamido)-4,5-dimethoybenzoyl]-_S_-methyl-_S_-phenyl sulfoximine (94d):



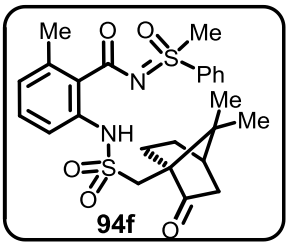
94d (123 mg, 48%) as brown viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.43 (s, 1H, NH), 7.96 (d, J = 7.2 Hz, 2H), 7.75 (bt, J = 7.4 Hz, 1H), 7.69–7.61 (m, 4H), 7.61 (s, 1H), 7.32 (d, J = 8.8 Hz, 2H), 7.24 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 153.3, 144.6, 139.1, 138.2, 137.8, 135.1, 134.2, 129.9, 129.1, 128.6, 126.9, 114.0, 113.6, 103.2, 56.2, 56.0, 44.6; IR (Neat) ν_{max} 3084, 2926, 1616, 1589, 1517, 1364, 1217, 1090 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{21}ClN_2O_6S_2$ $(M+H)^+$: 509.0608, Found: 509.0609.

_N_-[2-(_n_-Butanesulfonamido)-6-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (94e):



94e (122 mg, 60%) as colorless solid; mp = 84–85 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H, NH), 8.03 (d, J = 7.2 Hz, 2H), 7.73 (bt, J = 7.4 Hz, 1H), 7.65 (bt, J = 7.2 Hz, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.28–7.21 (m, 1H), 6.98 (d, J = 7.2 Hz, 1H), 3.47 (s, 3H), 3.04 (bt, J = 7.6 Hz, 2H), 2.50 (s, 3H), 1.73 (quint, J = 7.3 Hz, 2H), 1.40–1.30 (m, 2H); 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 139.2, 137.7, 136.5, 134.2, 130.7, 129.9, 127.3, 126.9, 118.3, 51.5, 44.4, 25.2, 22.1, 21.3, 13.4; IR (Neat) ν_{max} 3246, 2931, 1636, 1600, 1264, 1146 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}N_2O_4S_2$ $(M+Na)^+$: 431.1075, Found: 431.1078.

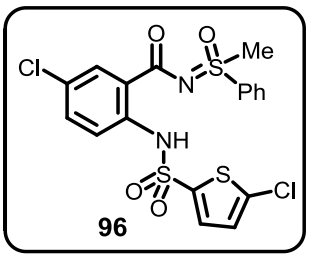
_N_-[2-(1-[(1S)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methanesulfonamido)-6-methyl benzoyl]-_S_-methyl-_S_-phenylsulfoximine (94f):



A mixture of inseparable diastereomers **94f** (105 mg, 42%, 1:1) was obtained as pale yellow viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ [9.38 & 9.25 (s, 1H, NH, 1:1)], 8.08–8.01 (m, 2H), 7.75–7.66 (m, 1H), 7.64 (bt, J = 7.4 Hz, 2H), 7.51 (t, J = 7.2 Hz, 1H), 7.32–7.22 (m, 1H), 6.98 (d, J = 7.6 Hz, 1H), 3.57 (dd, J = 14.8 & 9.6 Hz, 1H), [3.51 & 3.49 (s, 3H, 1:1)], 3.01 (dd, J = 1.6, 14.8 Hz, 1H), 2.49 (s, 3H), 2.47–2.28 (m, 2H), 2.10–1.97 (m, 2H), 1.85–1.68 (m, 2H), 1.46–1.35 (m, 1H), [1.07 & 1.05 (s, 3H, 1:1)], [0.84 & 0.81 (s, 3H, 1:1)]; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 175.6, [139.3 & 139.0 (1C)], 138.1, [136.7 & 136.3 (1C)], 134.2, [130.7 & 130.5 (1C)], 129.9, 127.3, 127.0, [118.7 & 118.3 (1C)], [58.8 & 58.6 (1C)], [49.6 & 49.2 (1C)], [48.1 & 48.0 (1C)], 44.4, 42.9, [42.7 & 42.6 (1C)], [27.0 & 26.9 (1C)], [25.6 & 25.4 (1C)], 22.1, 21.9, [19.9 &

19.8 (1C)], 19.7; IR (Neat) ν_{max} 3271, 2959, 2931, 1753, 1633, 1600, 1468, 1386, 1222, 1145, 981, 734 cm^{-1}; MS (EI) *m/z* (%) 503 (M^+, 100); Anal. Calcd. for $C_{25}H_{30}N_2O_5S_2$: C, 59.74; H, 6.02; N, 5.57. Found: C, 59.85; H, 6.12; N, 5.65.

_N_-[2-(5-Chlorothiophene-2-sulfonamido]-5-chlorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (96):

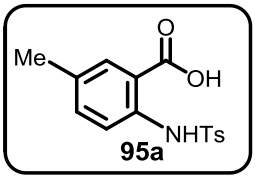


96 (101 mg, 41%) as colorless crystalline solid; mp = 111–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.6 (s, 1H, NH), 8.22 (s, 1H), 7.98 (bd, *J* = 7.6 Hz, 2H), 7.75 (bt, *J* = 7.2 Hz, 1H), 7.70–7.60 (m, 3H), 7.41 (bd, *J* = 8.8 Hz, 1H), 7.30 (bd, *J* = 3.6 Hz, 1H), 6.81 (bd, *J* = 3.6 Hz, 1H), 3.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 138.4, 137.9, 137.7, 137.6, 134.5, 133.7, 132.1, 132.0, 130.0, 128.6, 127.0, 126.7, 122.6, 120.5, 44.6; IR (KBr) ν_{max} 3084, 2915, 2877, 1691, 1402, 1167, 992, 608 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{14}Cl_2N_2O_4S_3$ $(M+H)^+$: 488.9571, Found: 488.9584.

3.7.3.5. General Procedure for the Hydrolysis of 93 (GP-4)

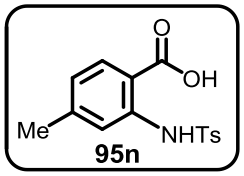
Compound **93** (0.2–1.0 mmol) was dissolved in aq. NaOH / MeOH and heated at 60 ^oC for about 6 h. The reaction mixture was extracted with CH_2Cl_2 (3×10 mL), dried over Na_2SO_4, and concentrated under vacuum to give the sulfoximine. The basic layer was acidified with 1N HCl and extracted with CH_2Cl_2 (5×10 mL). The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum to give the corresponding *o*-sulfonamide benzoic acid.

5-Methyl-2-(4-methylphenylsulfonamido)benzoic acid (95a): [24]



Following the general procedure (GP-4); reaction of a mixture of *N*-[2-(4′-methylbenzenesulfonamide)-5-methylbenzoyl]-*S*-methyl-*S*-phenyl sulfoximine (**93a**; 100 mg, 0.3 mmol) and aq. NaOH in MeOH gave **95a** (36 mg, 89%) as colorless solid and **91′** (33 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.69 (bd, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.20 (bd, *J* = 8.0 Hz, 1H), 7.05 (bd, *J* = 7.6 Hz, 2H), 2.24 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 143.8, 138.1, 135.9, 135.3, 132.6, 132.2, 129.6, 127.2, 118.8, 116.5, 21.4, 20.4; IR (Neat) ν_{max} 3262, 3047, 2925, 1683, 1496, 1264, 731 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{15}NO_4S$ $(M+H)^+$: 306.0800, Found: 306.0803.

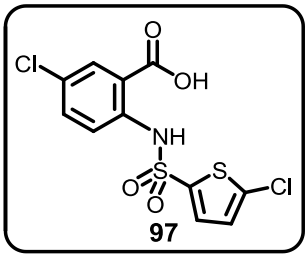
4-Methyl-2-(4-methylphenylsulfonamido)benzoic acid (95n):[25]



95n

Following the general procedure (GP-4); reaction of a mixture of *N*-[2-(4′-methylbenzenesulfonamide)-4-methylbenzoyl]-*S*-methyl-*S*-phenyl sulfoximine (**93n**; 40 mg, 0.09 mmol) and aq. NaOH in MeOH gave **95n** (25 mg, 90%) as colorless solid and **91′** (11 mg, 78%). ^{1}H NMR (400 MHz, DMSO-D6) δ 11.12 (s, 1H, COOH), 7.76 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.36–7.30 (m, 3H), 6.91 (d, J = 8.4 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 170.3, 145.7, 144.6, 140.5, 136.1, 131.9, 130.4, 127.4, 124.6, 118.9, 114.2, 21.9, 21.4.

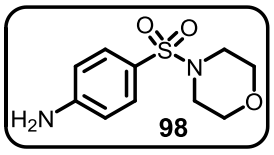
5-Chloro-2-(5-chlorothiophene-2-sulfonamido)benzoic acid (97):



97

Following the general procedure (GP-4); reaction of a mixture of *N*-[2-(5-chlorothiophene-2-sulfonamido)-5-chlorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (**96**; 100 mg, 0.2 mmol) and aq. NaOH in MeOH gave **97** (65 mg, 90%) as colorless solid. ^{1}H NMR (400 MHz, DMSO–D_6) δ 11.58 (bs, 1H, COOH), 7.78 (d, J = 2.0 Hz, 1H), 7.66 (dd, J = 8.8 & 2.4 Hz, 1H), 7.57–7.50 (m, 2H), 7.22 (bd, J = 4.0 Hz, 1H), 4.36 (bs, 1H, NH); ^{13}C NMR (101 MHz, DMSO–D_6) δ 168.6, 138.4, 137.8, 136.5, 134.4, 133.8, 131.2, 128.8, 128.4, 122.1, 121.0; IR (Neat) ν_{max} 3104, 2922, 2852, 1666, 1573, 1159, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_7Cl_2NO_4S_2$ $(M+H)^+$: 373.9092, Found: 373.9092.

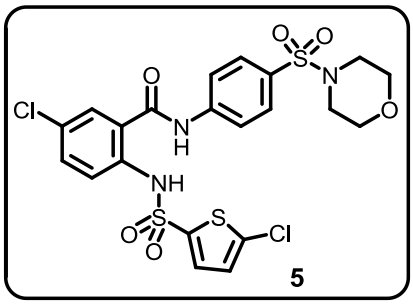
4-(Morpholine-4-sulfonyl)-phenylamine (98): [26]



98

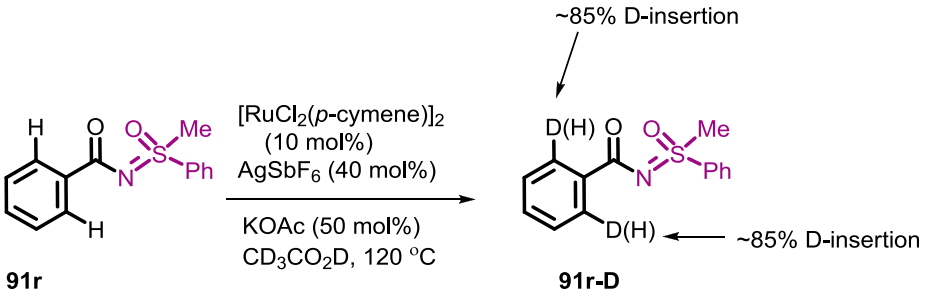
To a stirred solution of 4-(4-nitro-benzenesulfonyl)-morpholine (1.0 mmol) in ethanol (25 mL) was added iron powder (5.0 mmol) and a solution of ammonium chloride (10 mmol) in water (10 mL). The reaction mixture was refluxed for 3 h. Upon completion, iron powder was filtered off and the filtrate was basified with aqueous sodium carbonate solution. The reaction mixture was extracted with ethyl acetate (2×20 mL). The organic extracts were washed with water (2×10 mL) and brine, dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel to afford 4-(morpholine-4-sulfonyl)-phenylamine (**98**) as a colorless solid.

5-Chloro-2-(5-chlorothiophene-2-sulfonamido)-N-[4-(morpholine-4-sulfonyl)phenyl] benzamide (HMR 1766; 5):



Reaction of a mixture of 5-chloro-2-(5-chloro-2-thiophene-2-sulfonamido)benzoic acid (**97**; 100 mg, 0.28 mmol) and 4-(morpholinosulfonyl)aniline (**98**; 81 mg, 0.34 mmol) in CH_2Cl_2 (2 mL) was added $SOCl_2$ (0.5 mL) and the resulting mixture was refluxed for 12 h. Upon completion, excess $SOCl_2$ was removed under reduced pressure. The crude residue was purified using column chromatography on silica gel and the desired product **5** (98 mg) was isolated in 60% yield as colorless crystalline solid. ^{1}H NMR (400 MHz, Acetone–D_6) δ 10.18 (s, 2H, NH), 8.03 (bd, J = 8.4 Hz, 2H), 7.94 (s, 1H), 7.81 (bd, J = 8.4 Hz, 2H), 7.75–7.65 (m, 1H), 7.36 (bd, J = 3.2 Hz, 1H), 6.99 (bd, J = 3.6 Hz, 1H), 3.70 (bt, J = 4.2 Hz, 3H), 2.96 (bt, J = 4.6 Hz, 3H); ^{13}C NMR (101 MHz, Acetone–D_6)δ [165.9 & 165.8 (CO)], [142.4 & 142.3 (1C)], 137.2, 133.1, 132.7, 130.8, 130.3, 129.0, 128.5, 127.8, 126.4, 125.2, 120.5, 120.4, 65.7, 46.2; IR (Neat) ν_{max} 3337, 2909, 2855, 1671, 1589, 1529, 1348, 1172, 1151 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{19}Cl_2N_3O_6S_3$ $(M+Na)^+$: 597.9711, Found: 597.9734.

The low intensity of the NH proton is due to the exchange of the NH proton with the D_2O present in acetone-D_6 solvent.



Scheme 3.25: Deuteration experiments

Deuterium labeling experiment was carried out in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with *N*-benzoyl methyl phenyl sulfoximine (**91r,** 0.08 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (4.7 mg, 10 mol %), and KOAc (4.0 mg, 0.038 mmol). Subsequently, $AgSbF_6$ (10.6 mg, 40 mol %) was introduced to the flask in a glovebox. CD_3CO_2D (0.5 mL) was added to the mixture and the resulting mixture was stirred at 120 ^{o}C for 18 h. The reaction mixture was cooled to ambient temperature, filtered through a small

plug of Celite and then washed with dichloromethane (3×10 mL). The solvents were evaporated under reduced pressure. The ^{1}H NMR showed the > 85% deuterium insertion on the *ortho*-C–H bonds of **91r**.

This preliminary deuterium scrambling data suggests that the reaction presumably proceeds involving the Ru-mediated C–H bond activation.

3.7.3.6. X-ray Crystallography

Single crystal X-ray data for the compound **5** were collected using the detector system [λ(Mo-Kα) = 0.71073 Å] at 298K, graphite monochromator with a ω scan width of 0.3^o, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software was used for the intensity data acquisition and the SAINTPLUS Software was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program, an empirical absorption correction using equivalent reflections was performed with the program. The structure was solved using SHELXS-97, and full-matrix least-squares refinement against F^2 was carried out using SHELXL-97. All non-hydrogen atoms were refined anisotropically. Aromatic and methyl hydrogens were introduced on calculated positions and included in the refinement riding on their respective parent atoms.

Table 3.10: Crystal data for **5**

	Compound
Identification code	**5**
Formula	$C_{21}H_{19}Cl_2N_3O_6S_3$
F_w	576.47
T (K)	293(2)
λ (Å)	0.71073
Crystal system	monoclinic
Space group	*P 1 21/c 1*
a (Å)	11.5332(7)
b (Å)	14.9254(10)
c (Å)	17.4658(13)
α (°)	90
β (°)	125.386(5)
γ (°)	90
V (Å^3)	2451.1(3)
Z	4
ρ_{calcd} (Mg m^{-3})	1.562
μ (mm^{-1})	0.565
F (000)	1184.0
Crystal Size (mm)	0.30 × 0.26 × 0.18
2θ range/deg	2.73 / 25.00
Reflections collected	8782
Unique reflections	4257
Completeness to 2θ (%)	25.00 (98.7)
T_{max}, T_{min}	0.9052, 0.8400
Parameters	316
GOF (F^2)	0.934
R1, *wR2 [I>2σ(I)]*	0.0722, 0.1502
R1, *wR2* (all data)	0.1594, 0.1924
Largest diff. Peak and hole (e·Å^{-3})	1.013 and -0.467

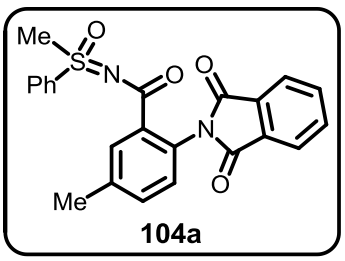
3.7.3.7. Optimization for *ortho*-C–H Amidation of N-Aroylated MPS (GP-5)

The *ortho* C–H amidation reaction was conducted in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with *N*-(*m*-methylbenzoyl)-MPS (**91a,** 27.3 mg, 0.1 mmol), *N*-OTs phthalimide (**103a**–**f**, 0.15 mmol), catalyst (5.0 mol %), and base (0.1 mmol). Subsequently, the additives were introduced to the flask in a glovebox. The corresponding solvent (0.5 mL) was added to the mixture and the resulting mixture was stirred at 120 ^{o}C for 24 h. The reaction mixture was cooled to ambient temperature, filtered through a plug of Celite and washed with dichloromethane (3 × 5.0 mL). The solvents were evaporated under reduced pressure and the crude material was analyzed based on ^{1}H NMR spectroscopy.

3.7.3.8. General Procedure for *ortho*-C–H Amidation of N-Aroylated MPS (GP-6)

The C–H amidation reactions were carried out in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with *N*-aroylated sulfoximine (**91,** 0.5 mmol), *N*-OTs phthalimide (**103a**, 0.75 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (31.0 mg, 10 mol%), and Ag_2O (100 mg, 0.5 mmol). Subsequently, $AgSbF_6$ (69 mg, 40 mol %) was introduced to the flask in a glovebox. The solvent 1,2-dichloroethane (DCE, 2.0 mL) was added to the mixture and the resulting mixture was stirred at 120 ^{o}C for 24 h. The reaction mixture was cooled to ambient temperature, filtered through a small plug of Celite and then washed with dichloromethane (3 × 10 mL). The solvents were evaporated under reduced pressure and the crude material was purified using column chromatography on silica gel (40–60% *n*-hexane/EtOAc eluent) to give the desired product.

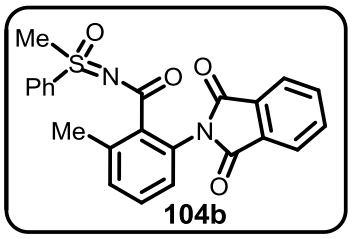
***N*-[2-Phthalimido-5-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (104a):**



104a

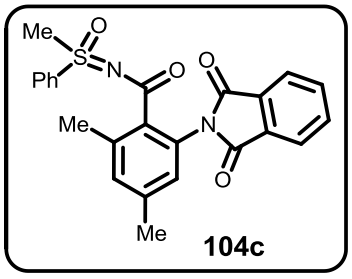
104a (146 mg, 70%) as colorless crystalline solid. mp = 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.89–7.74 (m, 4H), 7.65 (bs, 2H), 7.58 (bt, *J* = 7.0 Hz, 1H), 7.49 (bt, *J* = 7.2 Hz, 2H), 7.39 (bd, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 2.99 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 168.2, 167.9, 139.2, 138.3, 134.0, 133.7, 133.3, 132.9, 132.5, 132.3, 129.9, 129.6, 128.4, 127.0, 123.5, 123.4, 43.9, 21.2; IR (KBr) ν_{max} 3030, 2931, 1715, 1632, 1391, 1210 cm^{-1}; HRMS (ESI) for $C_{23}H_{18}N_2O_4S$ (M+Na)$^{+}$: calcd. 441.0885, found 441.0885.

_N_-[2-Phthalimido-6-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (104b):



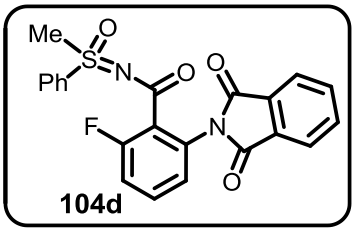
104b (161 mg, 77%) as colorless crystalline solid. mp = 235–237 °C; ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.92–7.78 (m, 4H), 7.70 (bd, J = 3.6 Hz, 2H), 7.58 (t, J = 7.4 Hz 1H), 7.46 (bt, J = 7.8 Hz, 2H), 7.40 (bt, J = 7.8 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 3.16 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ174.6, 167.6, 138.1, 138.0, 136.2, 134.1, 133.7, 132.1, 131.9, 129.7, 129.4 (2C), 126.9 (3C), 123.5, 43.7, 20.7; IR (KBr) ν_{max} 3057, 2926,1720, 1627, 1380, 1221 cm^{-1}; HRMS (ESI) for $C_{23}H_{18}N_2O_4S$ $(M+H)^+$: calcd. 419.1065, found 419.1066.

***N*-[2-Phthalimido-4,6-dimethylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (104c):**



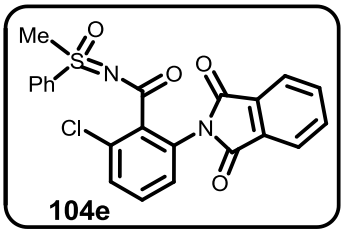
104c (180 mg, 83%) as light brown viscous thick liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (bs, 1H), 7.77 (d, J = 7.6 Hz, 3H), 7.68 (bs, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.11 (s, 1H), 6.95 (s, 1H), 3.11 (s, 3H), 2.47 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.6, 167.6, 139.9, 138.0, 137.9, 134.0, 133.6, 133.1, 132.6, 131.9, 129.4, 129.3, 127.3, 126.7, 123.3, 43.5, 20.9, 20.7; IR (KBr) ν_{max} 3013, 2926, 1715, 1610, 1375, 1282 cm^{-1}; HRMS (ESI) for $C_{24}H_{20}N_2O_4S$ $(M+H)^+$: calcd. 433.1222, found 433.1222.

***N*-[2-Phthalimido-6-fluorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (104d):**



104d (196 mg, 93%) as light brown viscous thick liquid; ^{1}H NMR (400 MHz, DMSO-D6) δ7.97–7.82 (m, 4H), 7.75 (d, J = 8.0 Hz, 2H), 7.69–7.60 (m, 2H), 7.56 (bt, J = 7.6 Hz, 2H), 7.45 (t, J = 9.2 Hz, 1H), 7.34 (bd, J = 7.6 Hz, 1H), 3.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ169.3, 167.2, 160.1 (d, J = 252 Hz), 138.0, 135.3, 134.2, 132.0, 131.7 (d, J = 6.1 Hz), 129.9, 128.3, 127.2, 126.7, 125.8 (d, J = 16.2 Hz), 124.0, 117.8 (d, J = 22.2 Hz), 43.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.41; IR (KBr)ν_{max} 3084, 2931, 1715, 162, 1391, 1216 cm^{-1}; HRMS (ESI) for $C_{22}H_{15}FN_2O_4S$ $(M+H)^+$: calcd. 445.0635, found 445.0635.

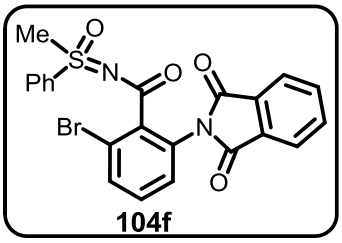
***N*-[2-Phthalimido-6-chlorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (104e):**



104e (180 mg, 82%) as colorless crystalline solid. mp = 234–236 °C; ^{1}H NMR (400 MHz, DMSO-D6) δ7.91 (bd, J = 10.8 Hz, 4H), 7.77 (d, J = 7.2 Hz 2H), 7.65 (bt, J = 6.8 Hz, 2H), 7.57 (bt, J = 7.4 Hz, 1H),

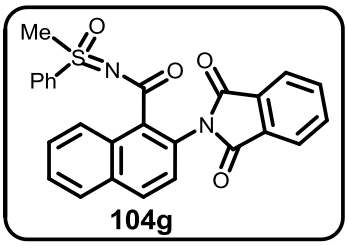
7.51 (bt, *J* = 7.2 Hz, 3H), 3.32 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 170.9, 167.1, 138.0, 137.8, 135.3, 134.3, 132.0, 131.3, 131.2, 131.1, 130.9, 129.6, 127.2, 124.1, 124.0, 43.2; IR (KBr) ν_{max} 3013, 2920, 1726, 1632, 1380, 1221 cm^{-1}. HRMS (ESI) for $C_{22}H_{15}ClN_2O_4S$ (M+H)$^+$: calcd. 439.0519, found 439.0519.

_N_-[2-Phthalimido-6-bromobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (104f):



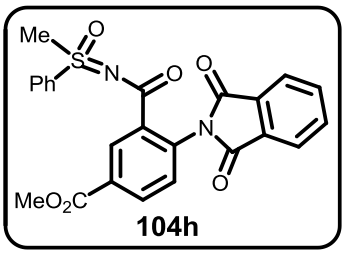
104f (74 mg, 31%) as as pale yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.81 (m, 4H), 7.79–7.68 (m, 3H), 7.61 (bt, *J* = 7.2 Hz, 1H), 7.49 (bt, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.29 (bd, *J* = 7.6 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 167.0, 138.7, 137.7, 134.3, 134.2, 133.9, 131.9, 130.6, 130.3, 129.5, 128.8, 127.1, 123.7, 120.7, 43.8; IR (KBr) ν_{max} 3019, 2926, 1720, 1638, 1369, 1227 cm^{-1}; MS (EI) *m/z* (%) 484 (M$^+$ + 2, 28), 97 (100); Anal. Calcd. for $C_{22}H_{15}BrN_2O_4S$: C, 54.67; H, 3.13; N, 5.80. Found: C, 54.72; H, 3.18; N, 5.91.

_N_-[2-Phthalimido-α-naptholoyl]-_S_-methyl-_S_-phenylsulfoximine (104g):



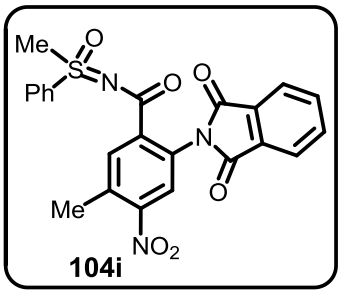
104g (163 mg, 72%) as a viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50–8.42 (m, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.92–7.86 (m, 2H), 7.84 (d, *J* = 8.0 Hz, 3H), 7.72 (bs, 2H), 7.61–7.50 (m, 3H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 1H), 3.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 167.5, 138.1, 134.2, 133.7, 133.5, 132.1, 130.75, 130.68, 129.4, 128.0, 127.3, 127.2, 126.9, 126.4, 125.9, 123.5, 43.8 (2 carbon 13C peak values are merged with other peak); IR (Neat) ν_{max} 3063, 2926, 1715, 1627, 1254 cm^{-1}; HRMS (ESI) for $C_{26}H_{18}N_2O_4S$ (M+Na)$^+$: calcd. 477.0885, found 477.0886.

_N_-[3-Methoxycarbonyl-6-(phthalimido)methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (104h):



104h (197 mg, 85%) as colorless crystalline solid. mp = 195–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (bd, *J* = 2.0 Hz, 1H), 8.26 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.91 (bd, *J* = 7.6 Hz, 3H), 7.82 (bs, 1H), 7.72 (bs, 2H), 7.65 (bt, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 3.96 (s, 3H), 3.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 167.3, 165.8, 138.0, 134.7, 134.1, 134.0, 133.7, 132.8, 132.7, 132.2, 130.4, 130.0, 129.5, 127.0, 123.6, 52.4, 43.9; IR (KBr) ν_{max} 3024, 2920, 1715, 1627, 1386, 1221 cm^{-1}; HRMS (ESI) for $C_{24}H_{18}N_2O_6S$ (M+H)$^+$: calcd. 463.0964, found 463.0964.

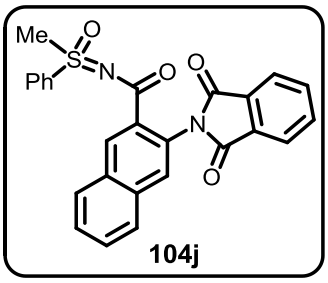
***N*-[2-Phthalimido-5-methyl-4-nitrobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (104i):**



104i

104i (202 mg, 87%) as colorless crystalline solid. mp = 200–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.01 (s, 1H), 7.86 (d, J = 7.6 Hz, 4H), 7.77–7.69 (m, 2H), 7.64 (bt, J = 7.2 Hz, 1H), 7.55 (bt, J = 7.6 Hz, 2H), 3.11 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 167.3, 150.1, 137.7, 137.6, 136.0, 134.4, 134.0, 132.1, 129.7, 129.4, 127.0, 126.4, 123.8, 43.8, 20.4 (one 13C peak value is merged with other peak); IR (KBr) ν_{max} 3063, 2926, 1726, 1632, 1523, 1227 cm^{-1}; HRMS (ESI) for $C_{23}H_{17}N_3O_6S$ $(M+H)^+$: calcd. 464.0916, found 464.0917.

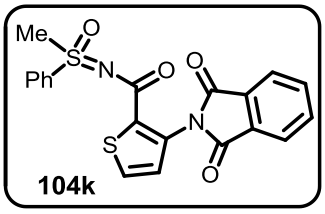
***N*-[2-Phthalimido-β-naptholoylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (104j):**



104j

104j (139 mg, 61%) as colorless crystalline solid. mp = 262–264 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 7.2 Hz, 4H), 7.85 (s, 2H), 7.72 (bs, 2H), 7.71–7.49 (m, 5H), 3.09 (s, 3H); ^{13}C NMR (101 MHz, DMSO-D_6) δ 172.4, 168.1, 168.0, 138.3, 135.2, 134.3, 134.1, 132.4, 132.2, 131.7, 130.3, 130.0, 129.4, 129.2, 128.3, 128.1, 128.0, 127.3, 124.0, 123.9, 43.6; IR (KBr) ν_{max} 2915, 1720, 1616, 1391, 1210 cm^{-1} ; HRMS (ESI) for $C_{26}H_{18}N_2O_4S$ $(M+H)^+$: calcd. 455.1065, found 455.1065.

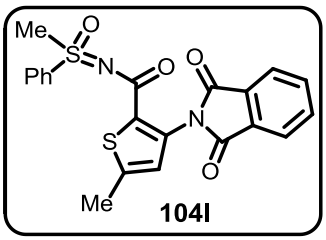
***N*-[3-Phthalimido-thenoyl]-*S*-methyl-*S*-phenylsulfoximine (104k):**



104k

104k (184 mg, 90%) as colorless crystalline solid. mp = 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.87 (m, 4H), 7.76–7.70 (m, 2H), 7.63 (bt, J = 7.4 Hz, 1H), 7.58–7.50 (m, 3H), 7.10 (d, J = 5.2 Hz, 1H), 3.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 167.0, 138.1, 135.6, 134.2, 133.9, 132.4, 131.3, 129.7, 129.5, 128.4, 127.1, 123.7, 44.3; IR (KBr) ν_{max} 3024, 2926, 1786, 1616, 1430, 1265; HRMS (ESI) for $C_{20}H_{14}N_2O_4S_2$ $(M+H)^+$: calcd. 411.0473, found 411.0475.

***N*-[3-Phthalimido-5-methylthenoyl]-*S*-methyl-*S*-phenylsulfoximine (104l):**

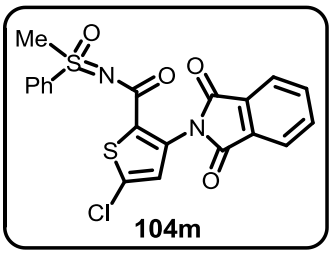


104l

104l (180 mg, 85%) as colorless crystalline solid. mp = 193–195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.81 (m, 4H), 7.73–7.65 (m, 2H), 7.58 (bt, J = 7.2 Hz, 1H), 7.48 (bt, J = 7.6 Hz, 2H), 6.76 (s, 1H), 3.02 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (3CO), 144.6,

138.0, 134.1, 133.7, 133.2, 132.1, 130.8, 129.5, 126.9, 126.6, 123.5, 44.1, 16.0 (Three CO 13C values are merged); IR (KBr) ν_{max} 3019, 2931, 1715, 1594, 1419, 1112 cm^{-1}; HRMS (ESI) for $C_{21}H_{16}N_2O_4S_2$ $(M+H)^+$: calcd. 425.0629, found 425.0630.

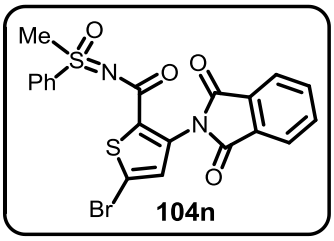
_N_-[3-Phthalimido-5-chlorothenoyl]-_S_-methyl-_S_-phenylsulfoximine (104m):



104m

104m (205 mg, 92%) as colorless crystalline solid. mp = 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.84 (m, 4H), 7.72–7.70 (m, 2H), 7.63 (bt, J = 7.4 Hz, 1H), 7.54 (bt, J = 7.6 Hz, 2H), 6.94 (s, 1H), 3.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 166.0, 137.8, 134.8, 134.3, 134.0, 132.1, 130.1, 129.7, 127.5, 127.0, 123.7, 44.3 (one cabon 13C value is merged); IR (Neat) ν_{max} 3101, 2926, 1720, 1632, 1260 cm^{-1}; HRMS (ESI) for $C_{20}H_{13}ClN_2O_4S_2$ $(M+H)^+$: calcd. 445.0083, found 445.0085.

_N_-[3-Phthalimido-5-bromothenoyl]-_S_-methyl-_S_-phenylsulfoximine (104n):



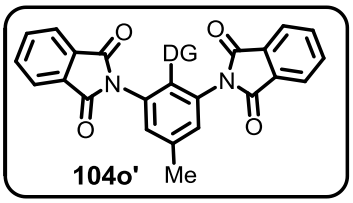
104n

104n (225 mg, 92%) as colorless crystalline solid. mp = 197–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.87 (m, 4H), 7.78–7.71 (m, 2H), 7.64 (bt, J = 7.4 Hz, 1H), 7.54 (bt, J = 7.6 Hz, 2H), 7.07 (s, 1H), 3.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 165.9, 137.8, 137.0, 134.2, 134.0, 132.1, 131.0, 130.8, 129.7, 127.0, 123.7, 44.3 (one cabon 13C value is merged); IR (KBr) ν_{max} 3013, 2926, 1786, 1610, 1539, 1320 cm^{-1}; MS (EI) *m/z* (%) 489 (M^+, 100), 491 (M^+ + 2, 53); Anal. Calcd. for $C_{20}H_{13}BrN_2O_4S_2$: C, 49.09; H, 2.68; N, 5.72. Found: C, 49.15; H, 2.61; N, 5.65.

3.7.3.9. General Procedure for *ortho*-C–H Di-Amidation of N-Aroylated MPS (GP-7)

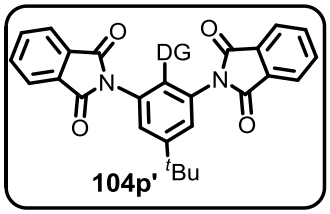
The C–H amidation reactions were carried out in a 50 mL Schlenk tube with high pressure valve and side arm. The tube was charged with *N*-aroylated sulfoximine (**91,** 0.5 mmol), *N*-OTs phthalimide (**103a**, 1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31.0 mg, 10 mol %), and Ag_2O (100 mg, 0.5 mmol). Subsequently, $AgSbF_6$ (69 mg, 40 mol %) was introduced to the flask in a glovebox. The solvent 1,2-dichloroethane (DCE, 2.0 mL) was added to the mixture and the resulting mixture was stirred at 120 ^{o}C for 48 h. The reaction mixture was cooled to ambient temperature, filtered through a small plug of Celite and then washed with dichloromethane (3×10 mL). The solvents were evaporated under reduced pressure and the crude material was purified using column chromatography on silica gel (30–40% *n*-hexane/EtOAc or 1–10% $CHCl_3$/THF an eluent) to give the desired product.

_N_-[2,6-Diphthalimido-4-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (104o′):



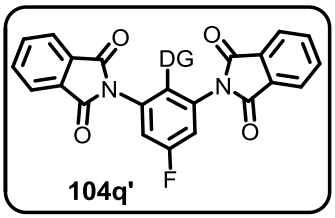
104o′(175 mg, 62%) as colorless crystalline solid. mp = 290–292 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (bs, 2H), 7.70–7.58 (m, 8H), 7.54 (bt, J = 7.2 Hz, 1H), 7.40 (bt, J = 7.4 Hz, 2H), 7.28 (s, 2H), 3.02 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 171.3, 167.6, 167.4, 141.6, 138.0, 134.0, 133.4, 132.2, 131.6, 131.1, 130.4, 129.2, 127.1, 123.5, 43.1, 21.2; IR (Neat) ν_{max} 3063, 2926, 1709, 1643, 1375, 1227cm^{-1}; MS (EI) *m/z* (%) 564 (M^+ + 1, 100); Anal. Calcd. for $C_{31}H_{21}N_3O_6S$: C, 66.07; H, 3.76; N, 7.46. Found: C, 66.21; H, 3.71; N, 7.56.

_N_-[2,6-Diphthalimido-4-^{t}butylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (104p′):



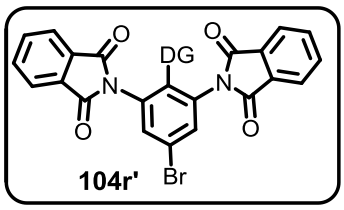
104p′ (209 mg, 69%) as light brown viscous thick liquid; ^{1}H NMR (400 MHz, DMSO-D_6) δ 7.96–7.91 (m, 2H), 7.85 (bs, 6H), 7.67 (bs, 2H), 7.64–7.54 (m, 3H), 7.50 (bt, J = 7.8 Hz, 2H), 2.85 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 167.6, 154.5, 137.7, 135.2, 134.1, 132.1, 131.6, 129.7, 128.5, 127.0, 124.0, 123.8, 42.8, 35.4, 31.1; IR (Neat) ν_{max} 2964, 1720, 1616, 140, 1024 cm^{-1}; HRMS (ESI) for $C_{34}H_{27}N_3O_6S$ $(M+H)^+$: calcd. 628.1519, found. 628.1518.

_N_-[2,6-Diphthalimido-4-fluorobenzoyl]-_S_-methyl-_S_-phenylsulfoxi-mine (104q′):



104q′(184 mg, 65%) as light brown viscous thick liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (bs, 2H), 7.73–7.62 (m, 8H), 7.56 (bt, J = 7.4 Hz, 1H), 7.42 (bt, J = 7.8 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 3.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 170.6, 167.0, 162.4 (d, J = 253 Hz), 137.8, 134.2, 133.5, 133.3 (d, J = 12.1 Hz), 132.0, 129.7 (d, J = 10.1 Hz), 129.2, 127.0, 123.6, 117.9 (d, J = 22.2 Hz), 43.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –107.37; IR (Neat) ν_{max} 3084, 2926, 1791, 1621, 1297 cm^{-1}; MS (EI) *m/z* (%) 567 (M^+, 100); Anal. Calcd. for $C_{30}H_{18}FN_3O_6S$: C, 63.49; H, 3.20; N, 7.40. Found: C, 63.38; H, 3.26; N, 7.51.

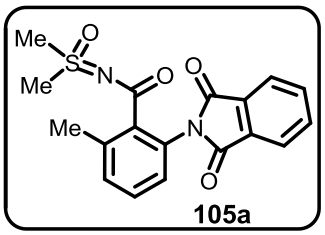
_N_-[2,6-Diphthalimido-4-bromobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (104r′):



104r′ (188 mg, 60%) as light brown viscous thick liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (bs, 2H), 7.73–7.60 (m, 10H), 7.56 (bt, J = 7.4 Hz, 1H), 7.42 (bt, J = 7.8 Hz, 2H), 3.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 167.1, 166.9, 137.6, 134.2, 133.6, 133.3, 132.6, 132.2, 131.9, 129.2, 127.0, 123.7, 123.6, 43.0; IR (KB r) ν_{max}

3073, 2926, 1720, 1632, 1419 cm^{-1}; HRMS (ESI) for $C_{30}H_{18}BrN_3O_6S$ $(M+H)^+$: calcd. 628.0178, found 628.0180.

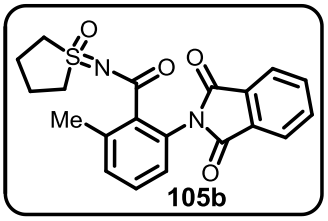
***N*-[2-Phthalimido-6-methylbenzoyl]-*S,S*-dimethyl (105a):**



105a

105a (125 mg, 70%) as colorless crystalline solid. mp = 285–287 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.90 (m, 2H), 7.81–7.75 (m, 2H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.32 (bd, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 3.06 (s, 6H), 2.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ174.7, 167.5, 138.1, 135.7, 134.3, 132.2, 131.9, 129.7, 129.6, 126.9, 123.6, 41.4, 20.8 ; IR (KBr) ν_{max} 3002, 2926, 1715, 1610, 1375 cm^{-1}; MS (EI) *m/z* (%) 355 (M^+–1, 100); Anal. Calcd. for $C_{18}H_{16}N_2O_4S$: C, 60.66; H, 4.53; N, 7.86. Found: C, 60.52; H, 4.51; N, 7.76.

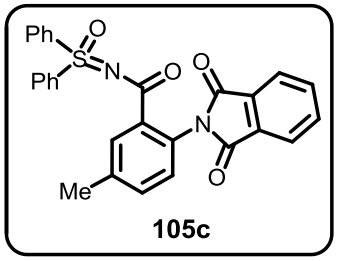
***N*-[2-Phthalimido-6-methylbenzoyl]-*S,S*-tetramethylenesulfoximine (105b):**



105b

105b (121 mg, 63%) as colorless crystalline solid. mp = 241–243 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–7.89 (m, 2H), 7.80–7.74 (m, 2H), 7.40 (bt, *J* = 7.8 Hz 1H), 7.35–7.30 (m, 1H), 7.15 (bd, *J* = 8.4 Hz, 1H), 3.40–3.30 (m, 2H), 3.15–3.04 (m, 2H), 2.55 (s, 3H), 2.17–2.12 (m, 2H), 1.99–1.93 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$)δ175.5, 167.5, 138.2, 135.8, 134.3, 132.2, 131.9, 129.7, 129.5, 126.8, 123.6, 52.6, 23.5, 20.8; IR (KBr) ν_{max} 3090, 1715, 1632, 1386, 1221 cm^{-1}; MS (EI) *m/z* (%) 383 (M^+ + 1, 100); Anal. Calcd. for $C_{20}H_{18}N_2O_4S$: C, 62.81; H, 4.74; N, 7.33. Found: C, 62.76; H, 4.68; N, 7.41.

***N*-[2-Phthalimido-5-methylbenzoyl]-*S,S*-diphenylsulfoximine (105c):**



105c

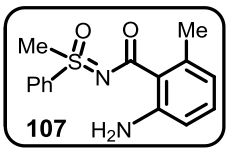
105c (29 mg, 12%) as colorless viscous thick liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.88 (bd, *J* = 8.0 Hz, 4H), 7.74–7.68 (m, 2H), 7.61–7.54 (m, 2H), 7.53–7.47 (m, 2H), 7.46–7.40 (m, 5H), 7.28–7.21 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.1, 167.9, 139.3, 139.1, 133.9, 133.6, 133.0, 132.8, 132.4, 132.3, 129.8, 129.4, 128.3, 127.5, 123.3, 21.2; IR (KBr) ν_{max} 3063, 2915, 1715, 1643, 1380 cm^{-1}; MS (EI) *m/z* (%) 480 (M^+ + 2, 100); Anal. Calcd. for $C_{28}H_{20}N_2O_4S$: C, 69.98; H, 4.20; N, 5.83. Found: C, 69.91; H, 4.16; N, 5.91.

3.7.3.10. General Procedure for the Deprotection of Phthaloyl Group (GP-8)

N-Hydrazine hydrate (0.1 mL) and 0.5 mL of water was added to a solution of **104b** (50 mg, 0.12 mmol) in 1.0 mL acetonitrile. The mixture was stirred for 6 h at room temperature until TLC shows the complete conversion of **104**. To this solution 5 mL of water was added and

the resulting mixture was extracted with CH_2Cl_2 solvent (3 × 10 mL). The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum to give the corresponding free amine derivatives.

***N*-[2-Amino-6-methyl benzoyl]-*S*-methyl-*S*-phenylsulfoximine (107):**



107 as colorless viscous thick liquid; ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.05 (d, J = 7.2 Hz, 2H), 7.67 (bt, J = 7.4 Hz, 1H), 7.60 (bt, J = 7.4 Hz, 2H), 7.04 (bt, J = 7.8 Hz, 1H), 6.64 (bd, J = 8.0 Hz, 1H), 6.61 (bd, J = 7.6 Hz, 1H), 4.62 (bs, 2H, NH_2), 3.43 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 177.0, 145.1, 138.9, 138.7, 133.8, 130.6, 129.7, 127.2, 122.3, 121.9, 115.4, 44.7, 22.3.

3.8. References

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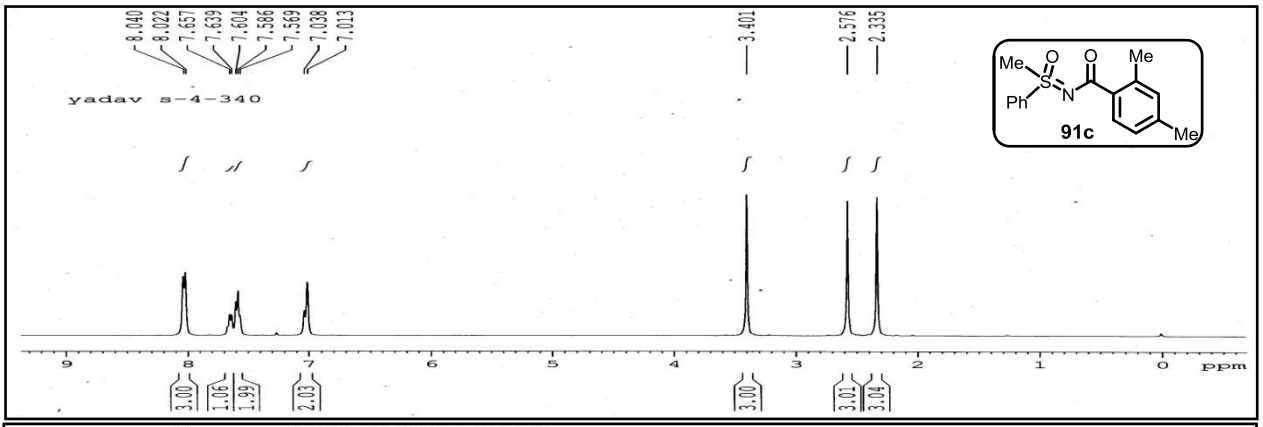
3.9 Spectra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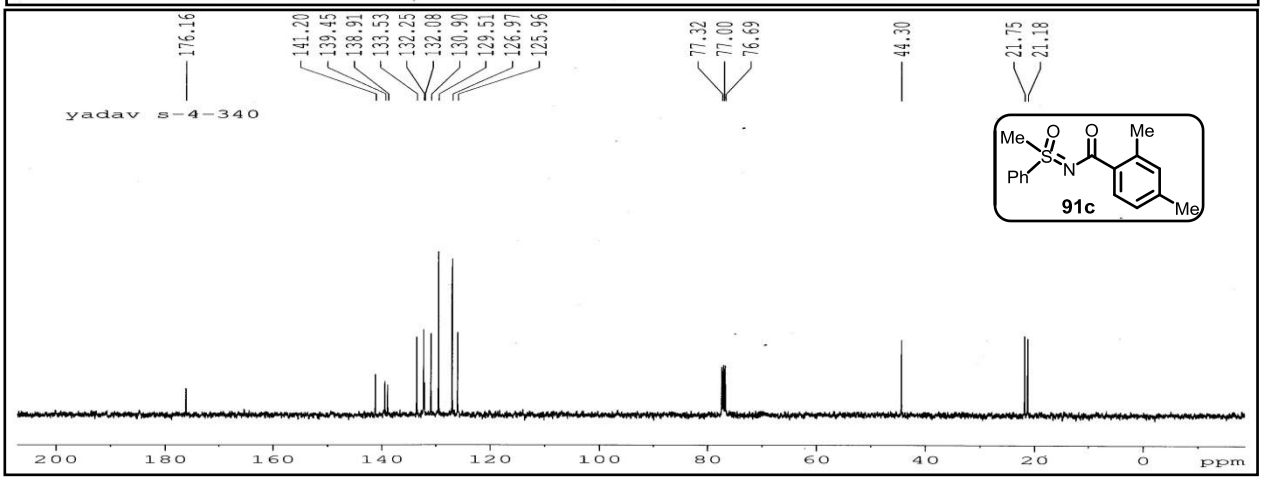
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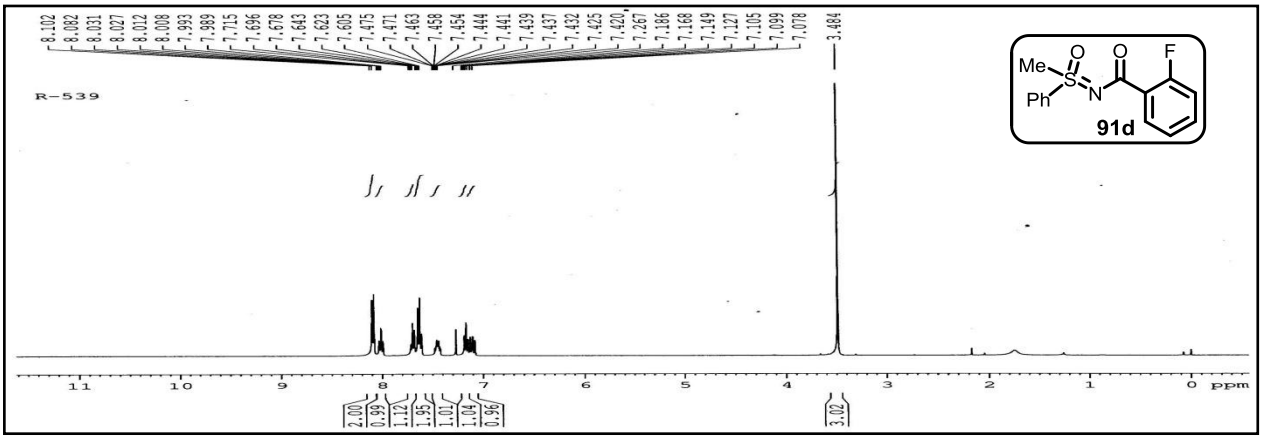
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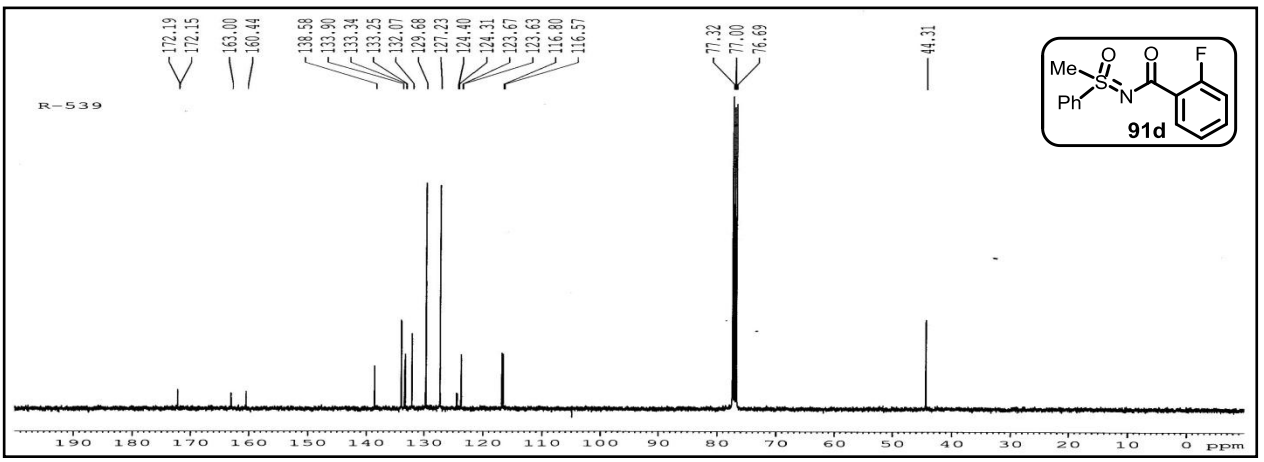
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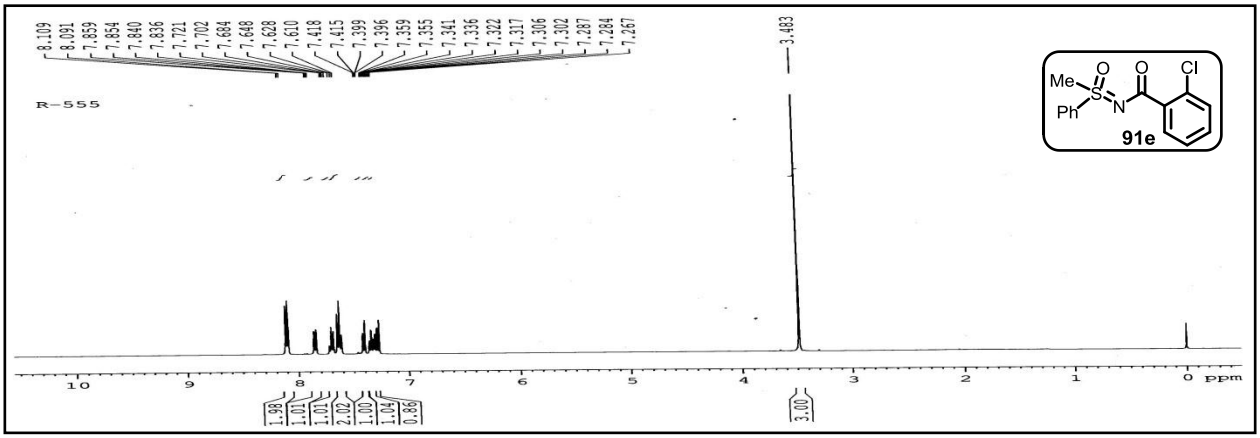
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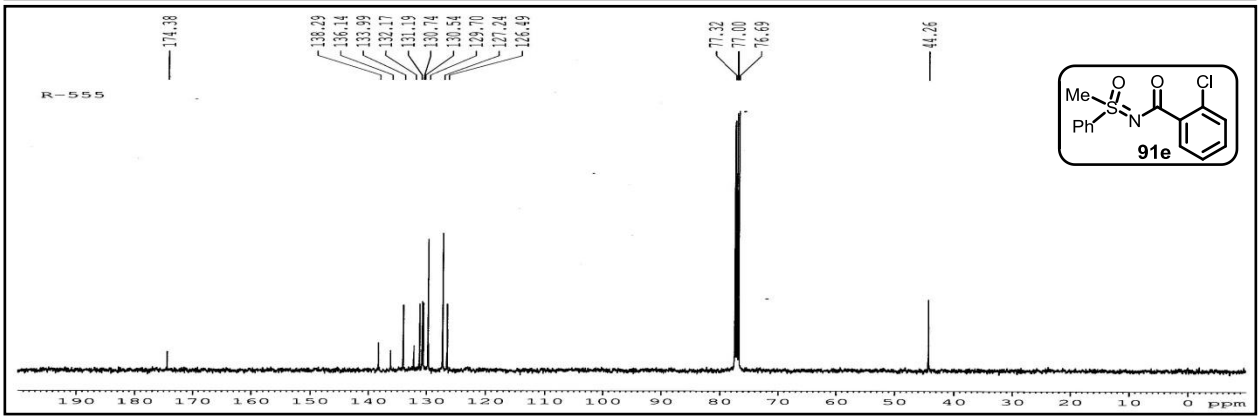
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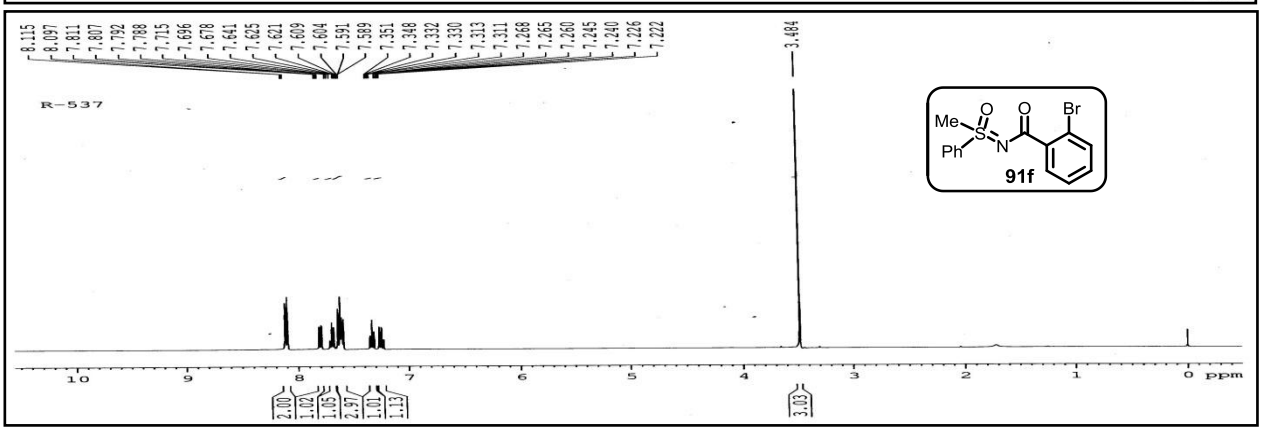
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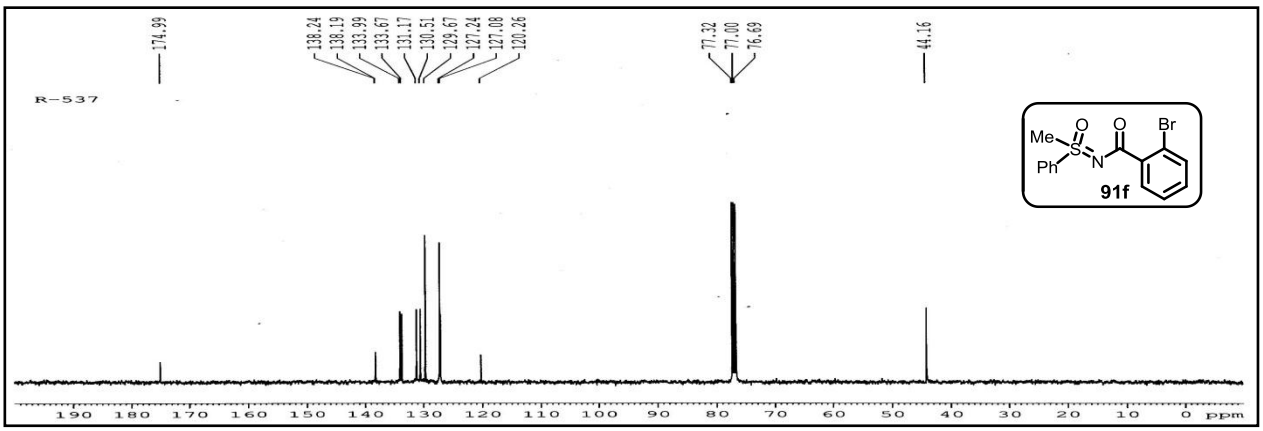
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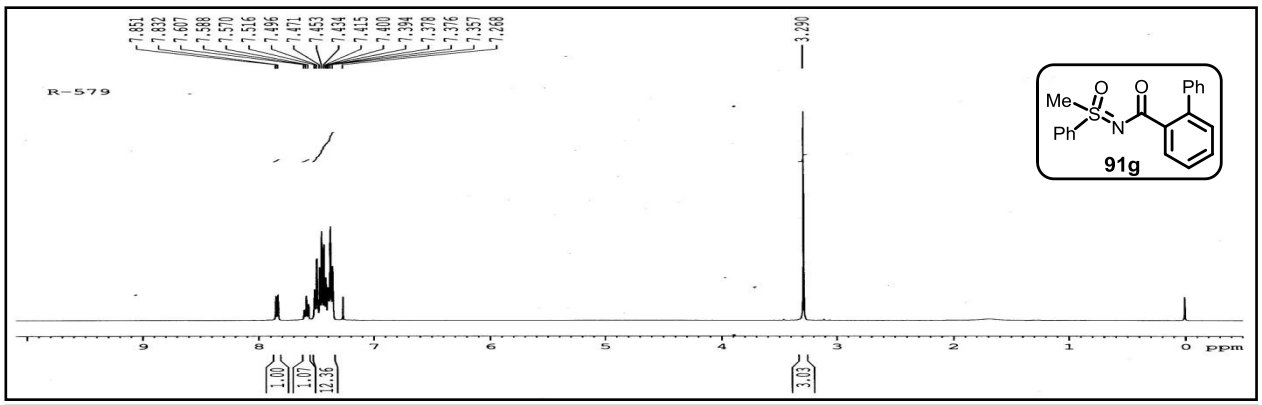
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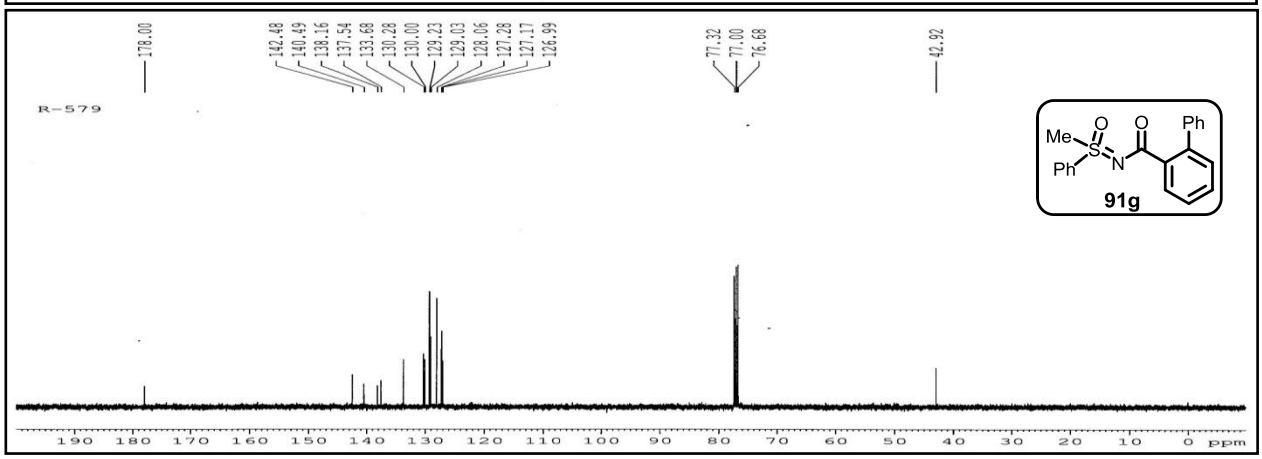
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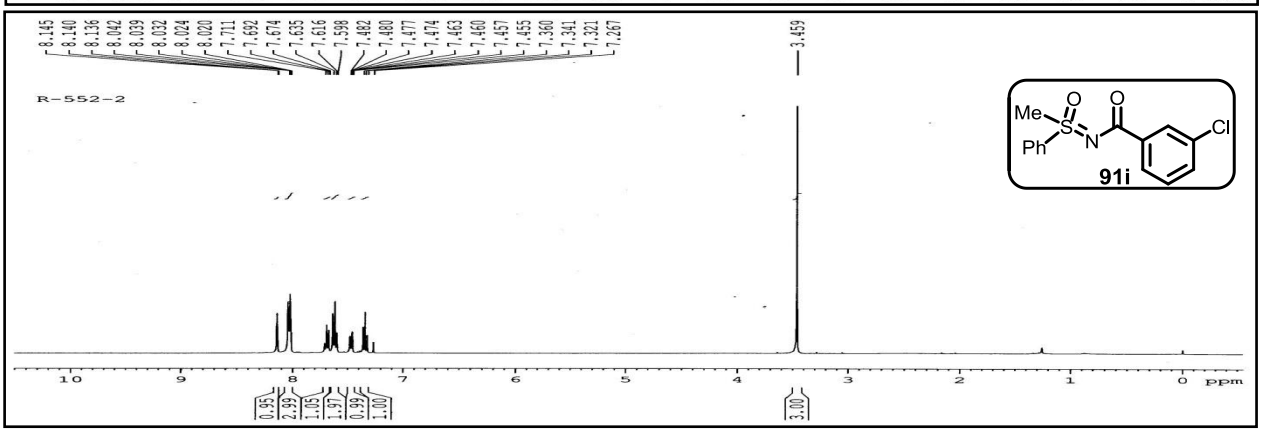
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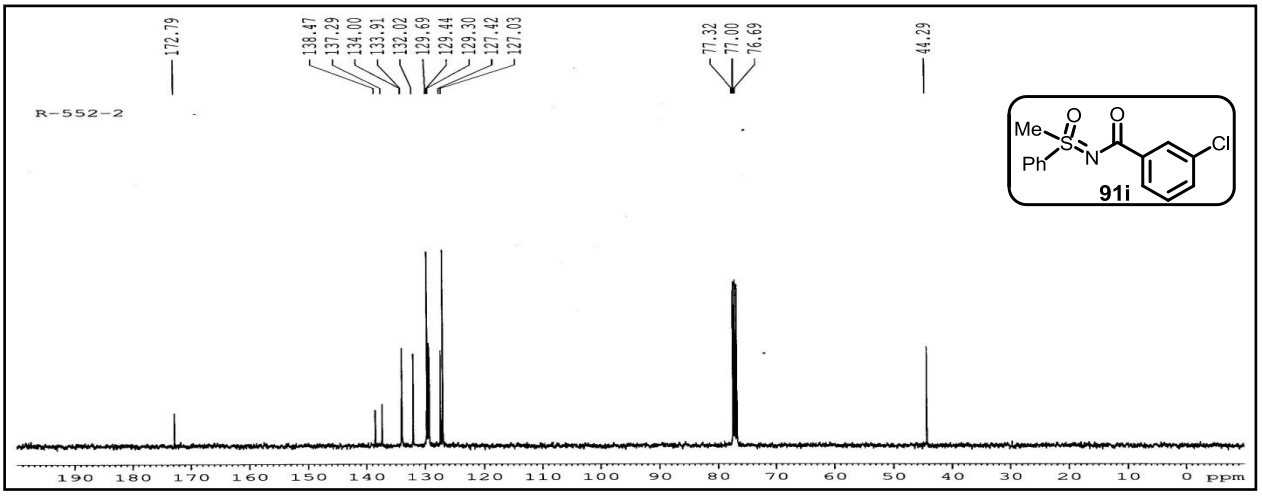
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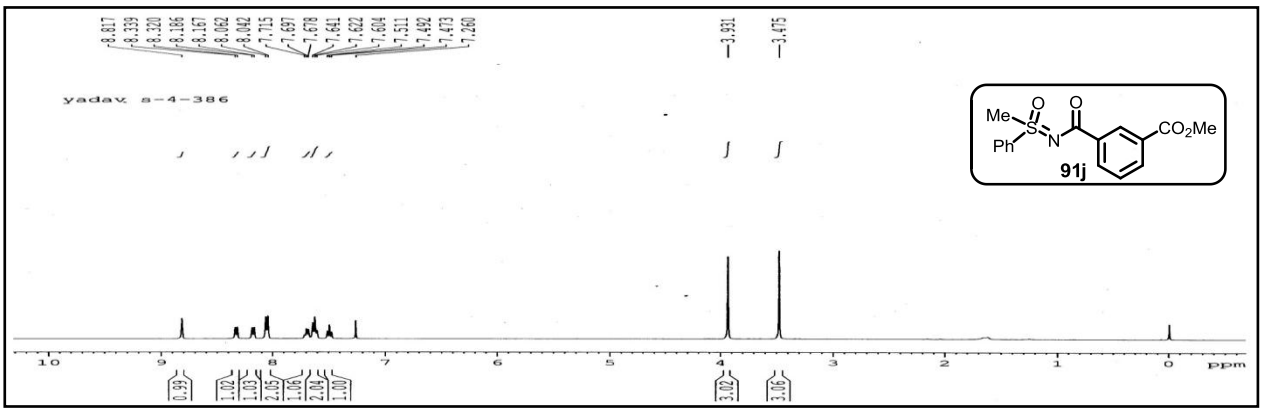
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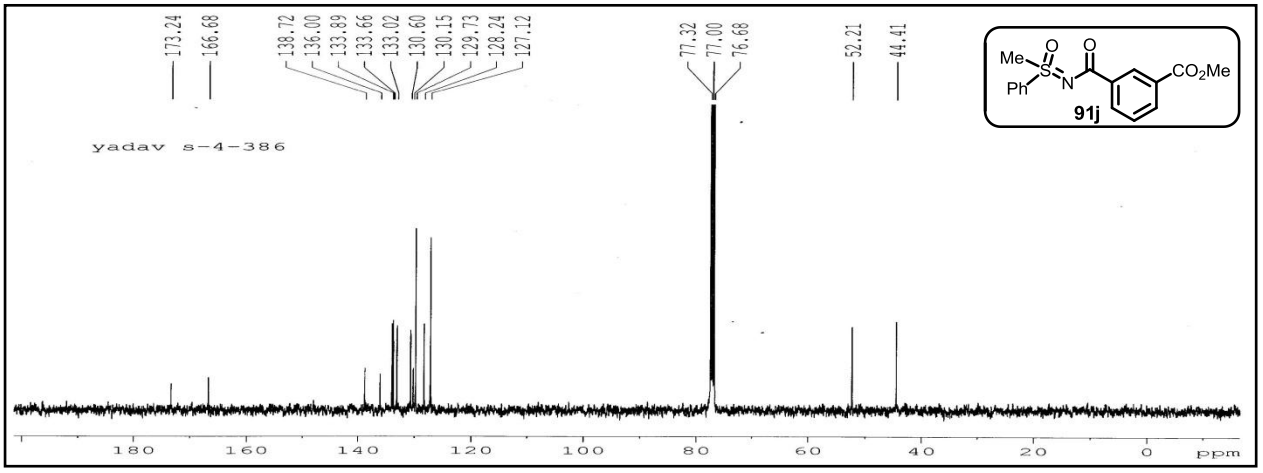
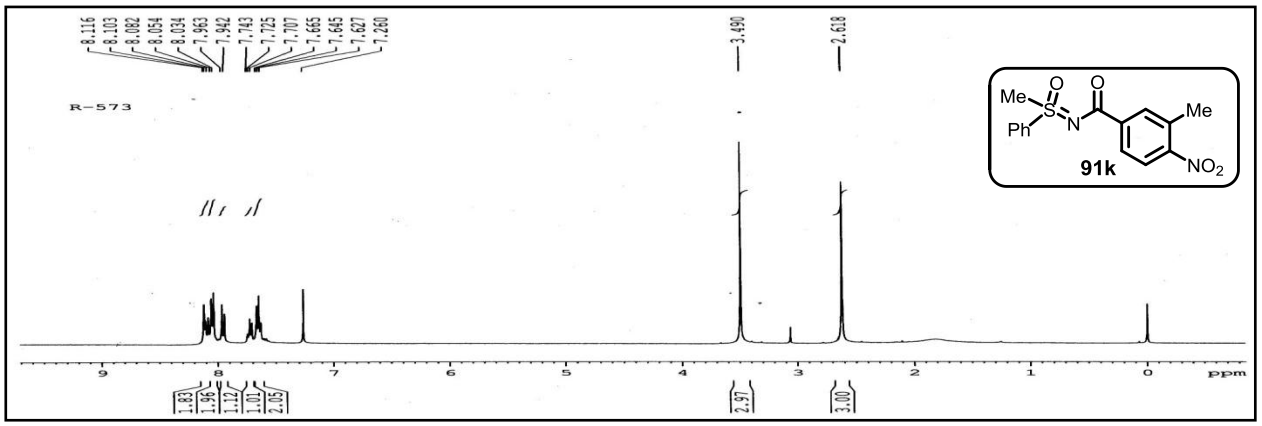
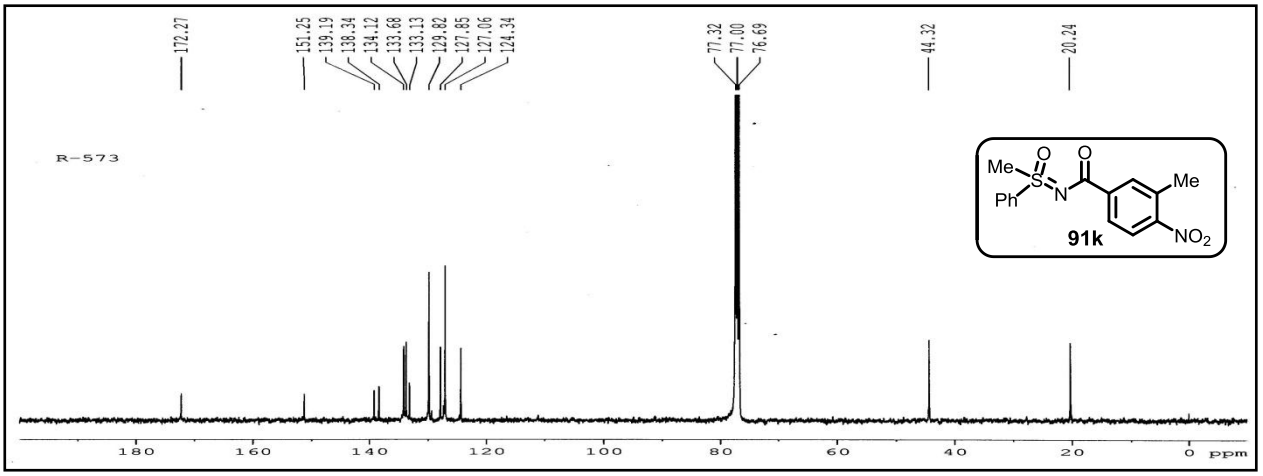
8.339
8.320
8.186
8.167
8.062
8.042
7.715
7.697
7.678
7.641
7.622
7.604
7.511
7.492
7.473
7.260
3.931
3.475
yadav s-4-386
Me
Ph
O
S
N
O
CO2Me
91j
10
9
8
7
6
5
4
3
2
1
0
ppm
0.99
1.02
1.03
2.05
1.06
2.04
1.00
3.02
3.06


173.24
166.68
138.72
136.00
133.89
133.66
133.02
130.60
130.15
129.73
128.24
127.12
77.32
77.00
76.68
52.21
44.41
yadav s-4-386
Me
Ph
O
S
N
O
CO2Me
91j
180
160
140
120
100
80
60
40
20
0
ppm


8.116
8.103
8.082
8.054
8.034
7.963
7.942
7.743
7.725
7.707
7.665
7.645
7.627
7.260
3.490
2.618
R-573
Me
Ph
O
S
N
O
Me
NO2
91k
9
8
7
6
5
4
3
2
1
0
ppm
1.83
1.96
1.12
1.01
2.05
2.97
3.00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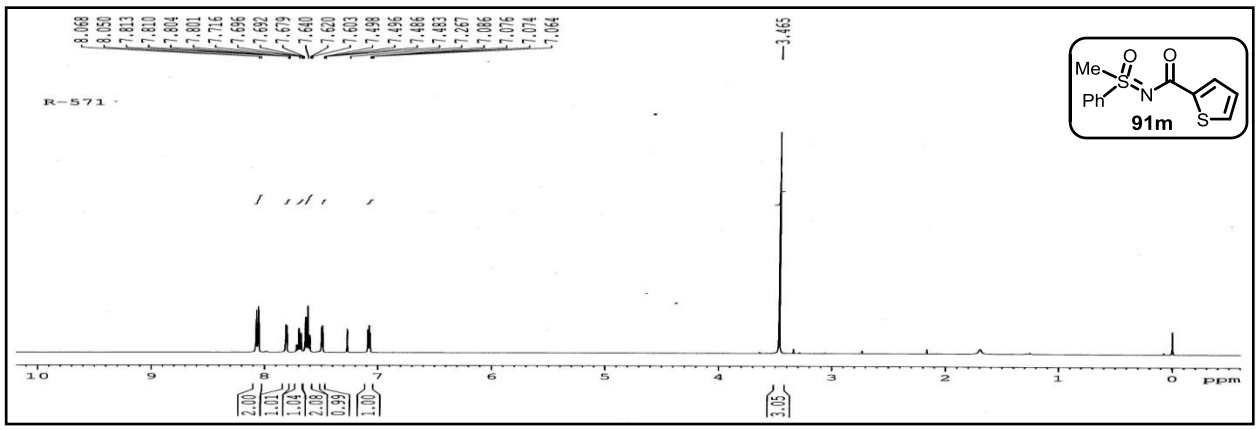
151.25
139.19
138.34
134.12
133.68
133.13
129.82
127.85
127.06
124.34
77.32
77.00
76.69
44.32
20.24
R-573
Me
Ph
O
S
N
O
Me
NO2
91k
180
160
140
120
100
80
60
40
20
0
ppm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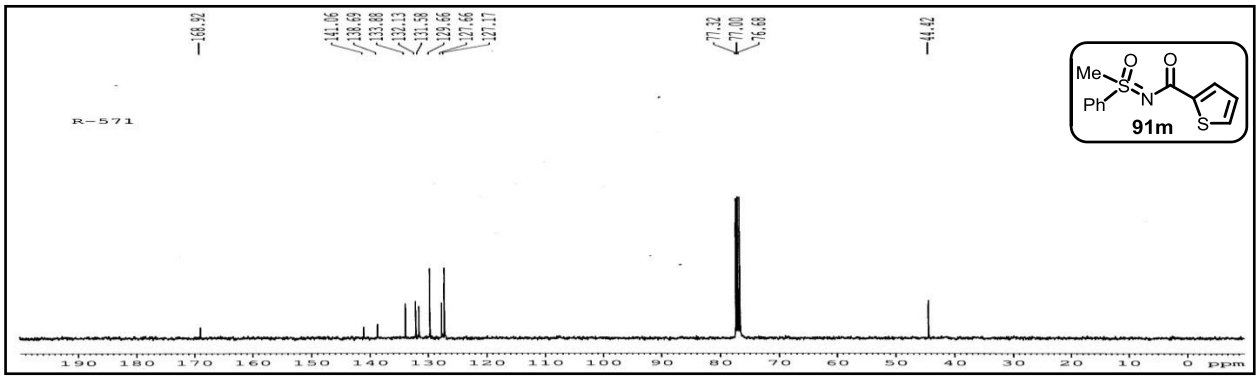
91m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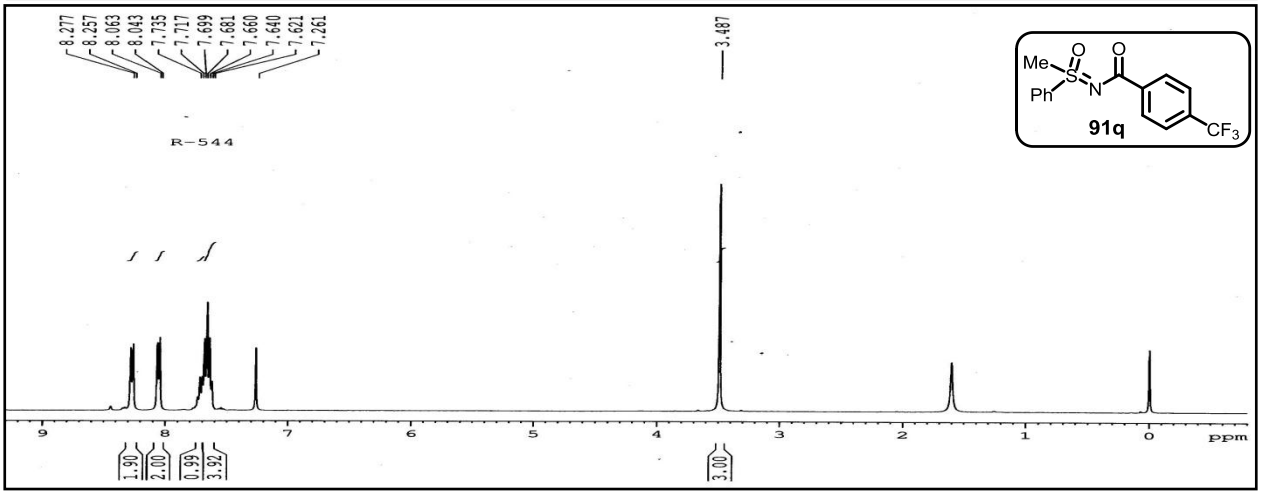
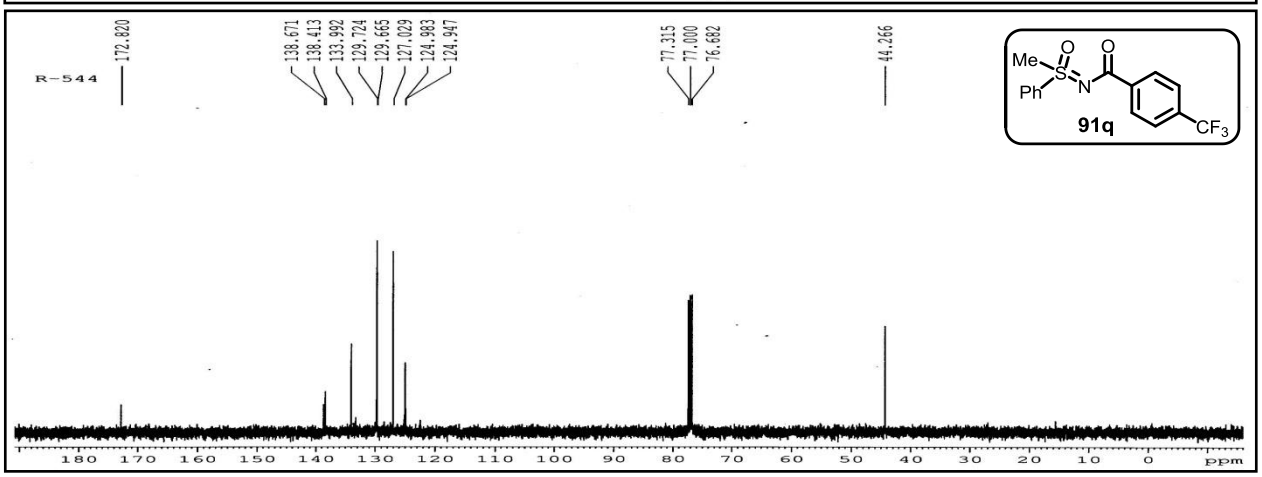
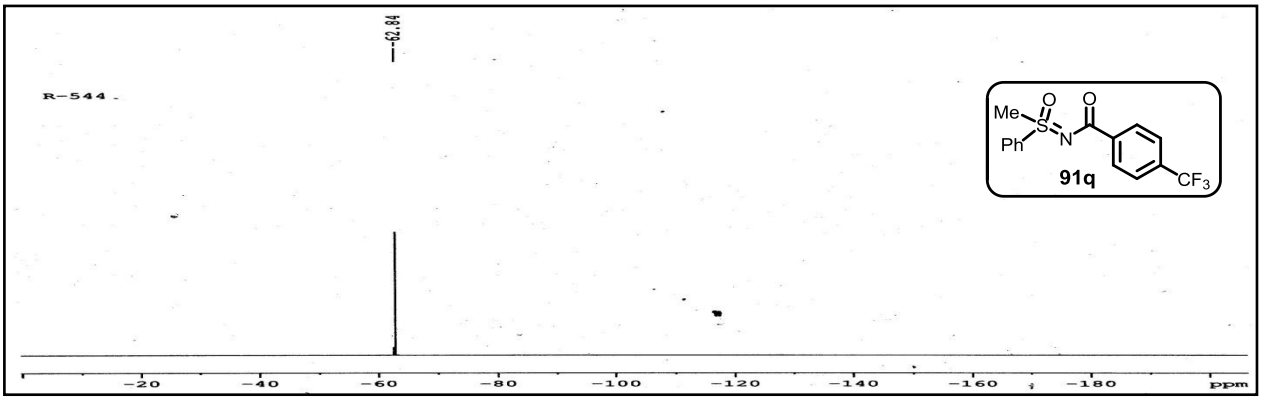
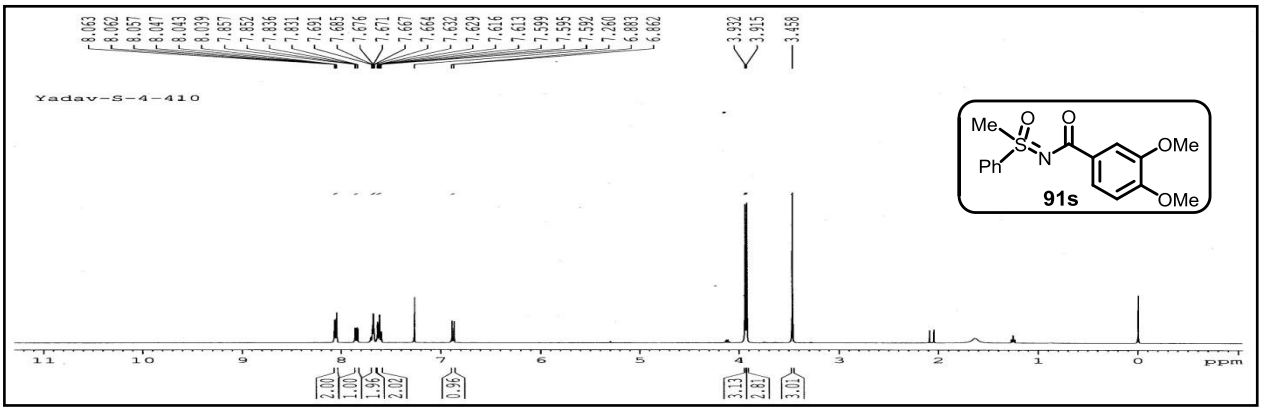
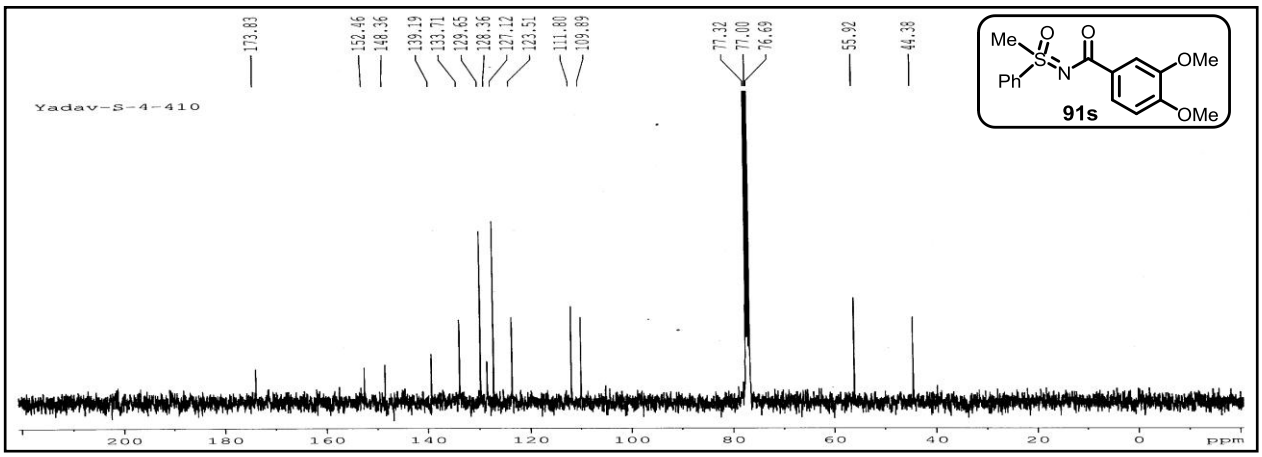
91m

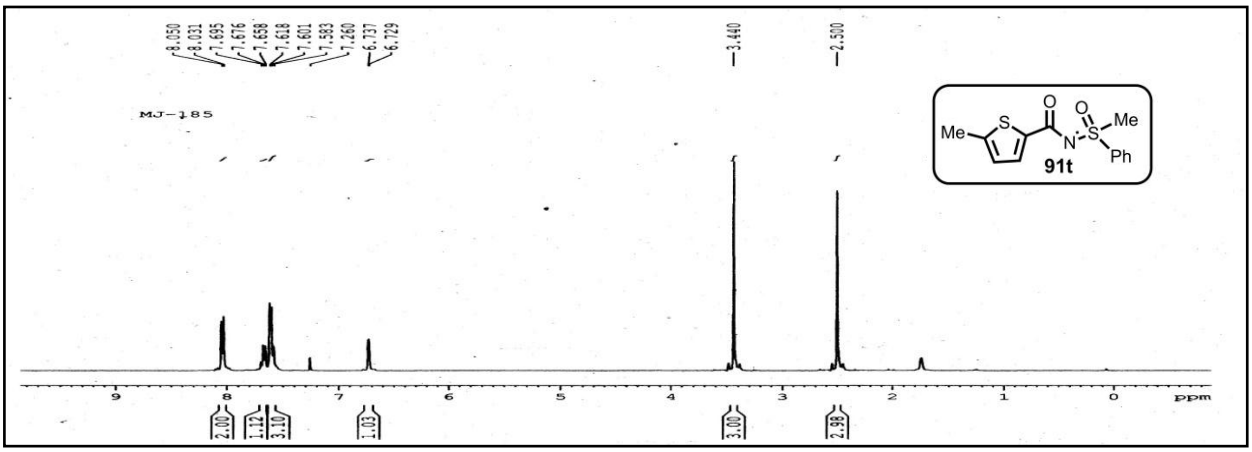

R-544
91q
CF3

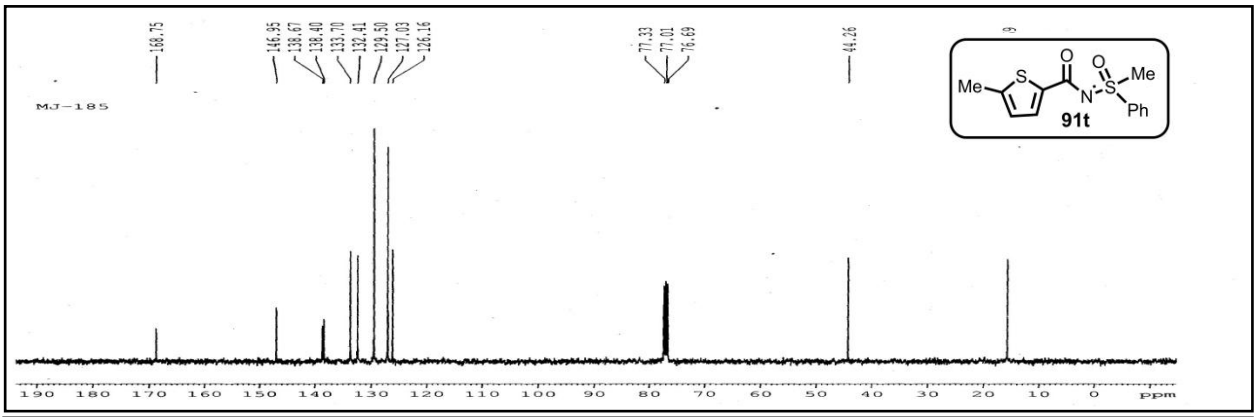

R-544
91q
CF3

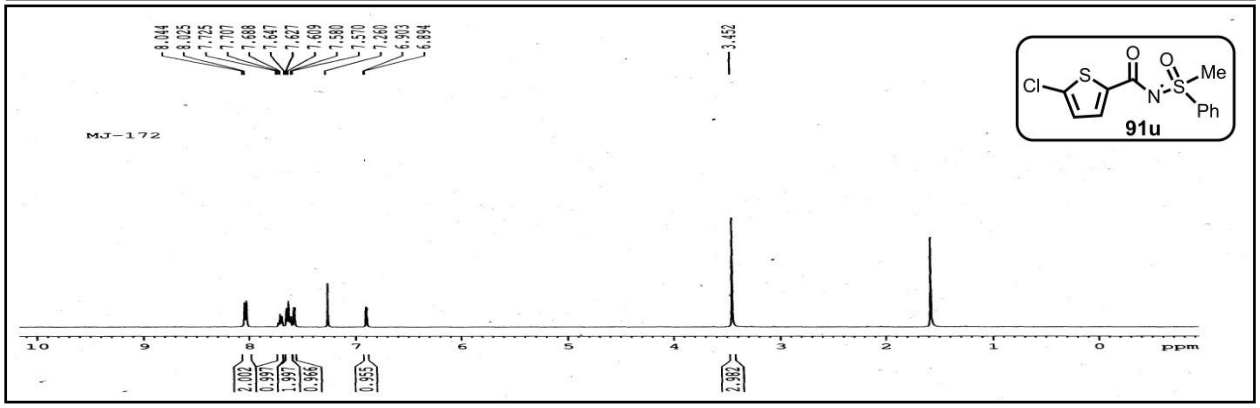

R-544
-62.84
Me
Ph
O
O
N
S
91q
CF3
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm

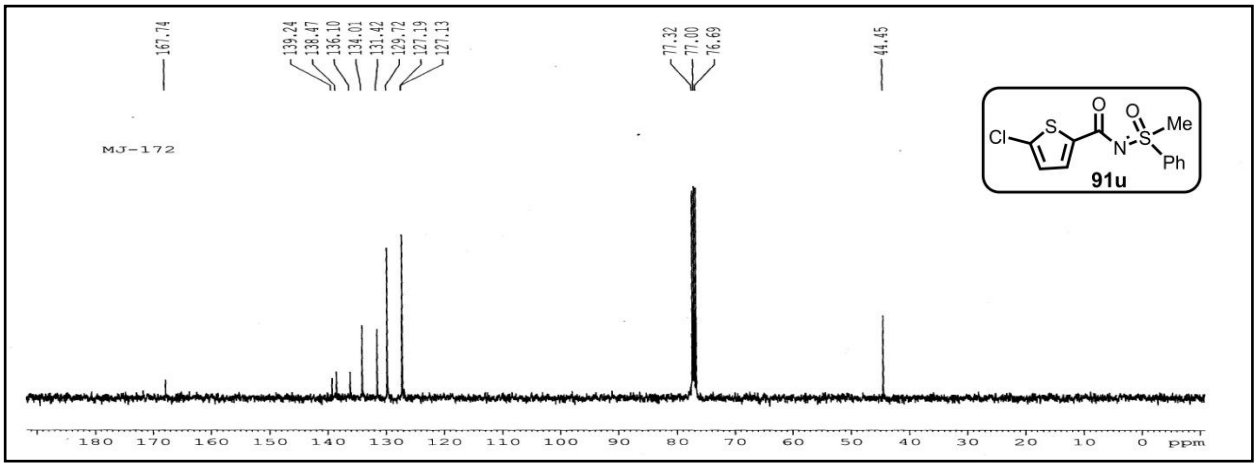

Yadav-S-4-410
8.063
8.062
8.057
8.047
8.043
8.039
7.857
7.852
7.836
7.831
7.691
7.685
7.676
7.671
7.667
7.664
7.632
7.629
7.616
7.613
7.599
7.595
7.592
7.260
6.883
6.862
3.932
3.915
3.458
Me
Ph
O
O
N
S
OMe
OMe
91s
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.00
1.96
2.02
0.96
3.13
2.81
3.01

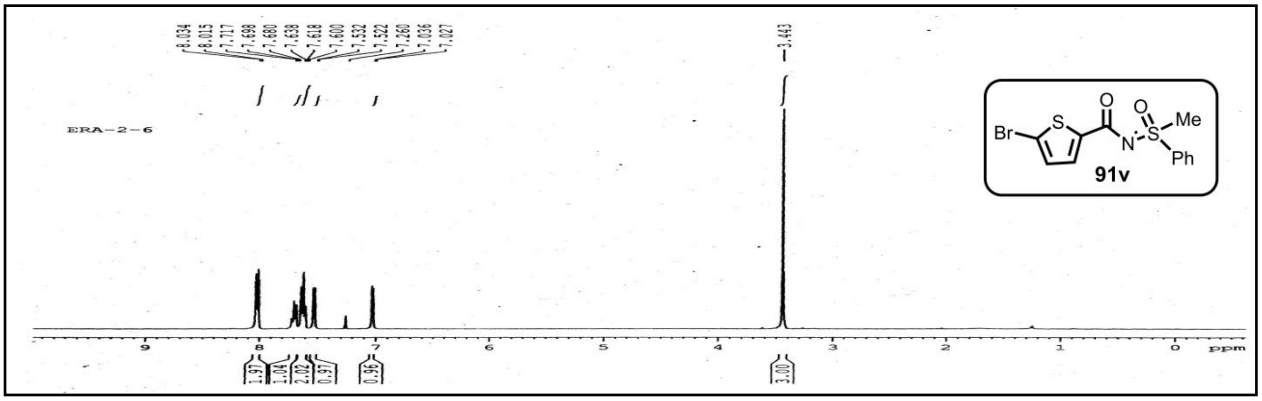

Yadav-S-4-410
173.83
152.46
148.36
139.19
133.71
129.65
128.36
127.12
123.51
111.80
109.89
77.32
77.00
76.69
55.92
44.38
Me
Ph
O
O
N
S
OMe
OMe
91s
200
180
160
140
120
100
80
60
40
20
0
ppm

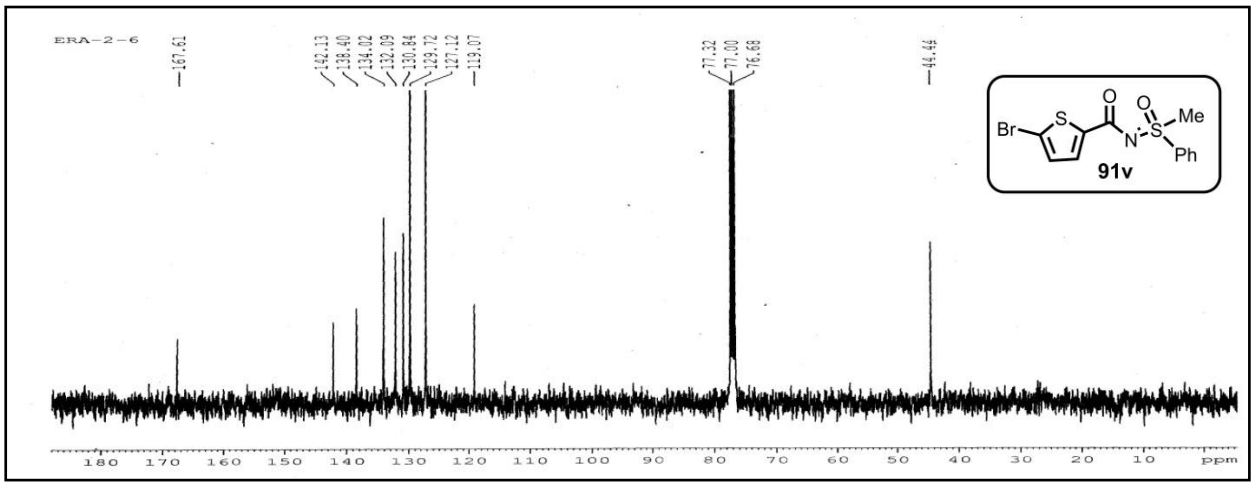

MJ-185
8.050
8.031
7.695
7.676
7.658
7.618
7.601
7.583
7.260
6.737
6.129
3.440
2.500
Me
S
O
N
O
S
Me
Ph
91t
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.14
3.10
1.03
3.00
2.98

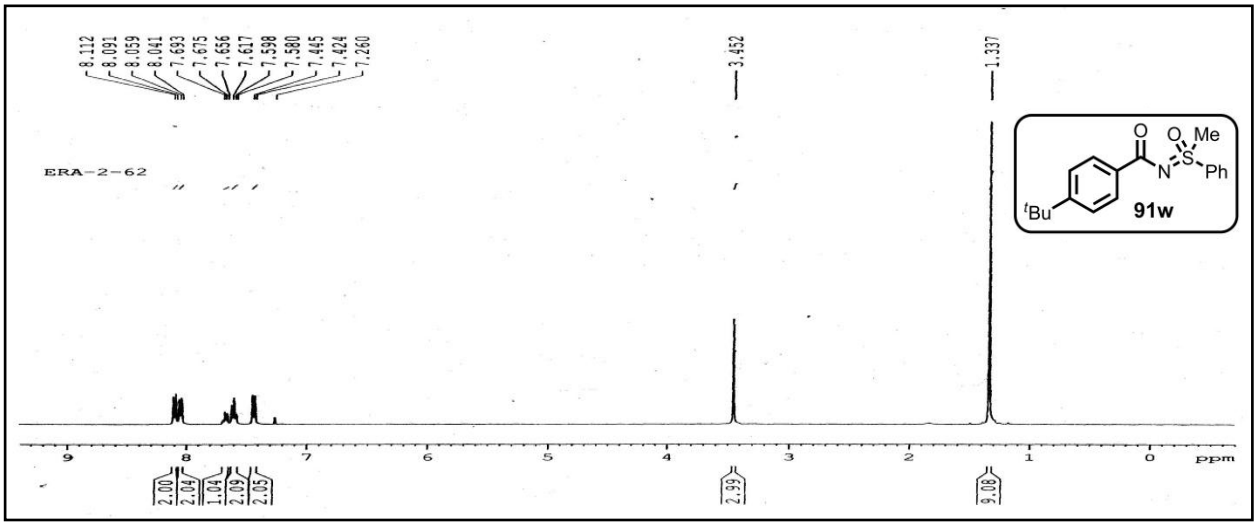

MJ-185
168.75
146.95
138.67
138.40
133.70
132.41
129.50
127.03
126.16
77.33
77.01
76.69
44.26
Me
S
O
N
O
S
Me
Ph
91t
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

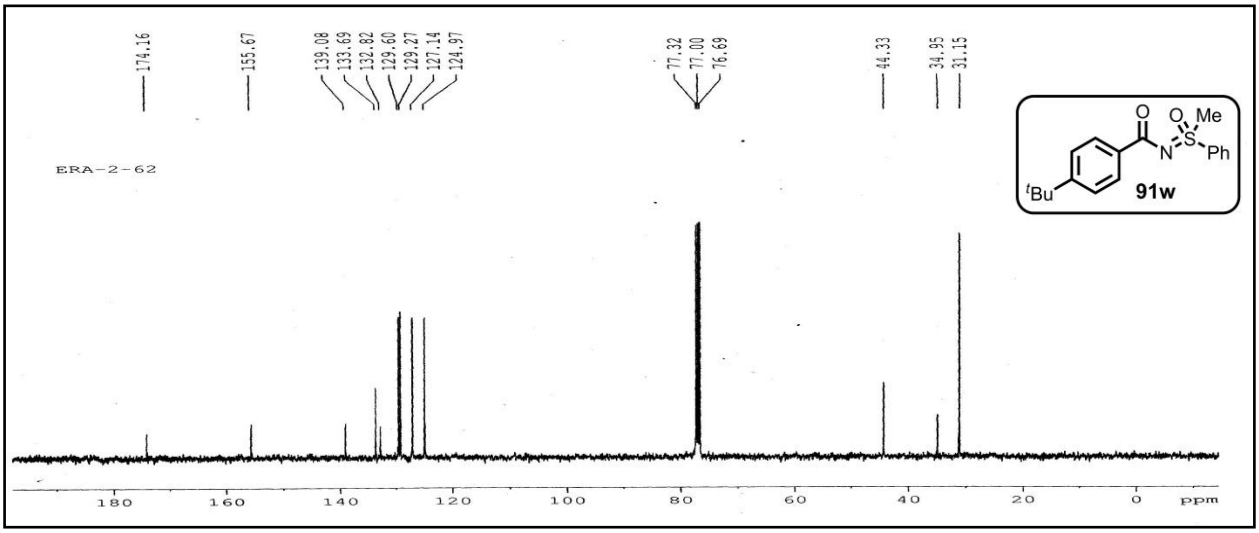

MJ-172
8.044
8.025
7.725
7.707
7.688
7.647
7.627
7.609
7.580
7.570
7.260
6.903
6.894
3.452
Cl
S
O
N
O
S
Me
Ph
91u
10 9 8 7 6 5 4 3 2 1 0 ppm
2.002
0.991
1.993
0.866
0.855
2.982

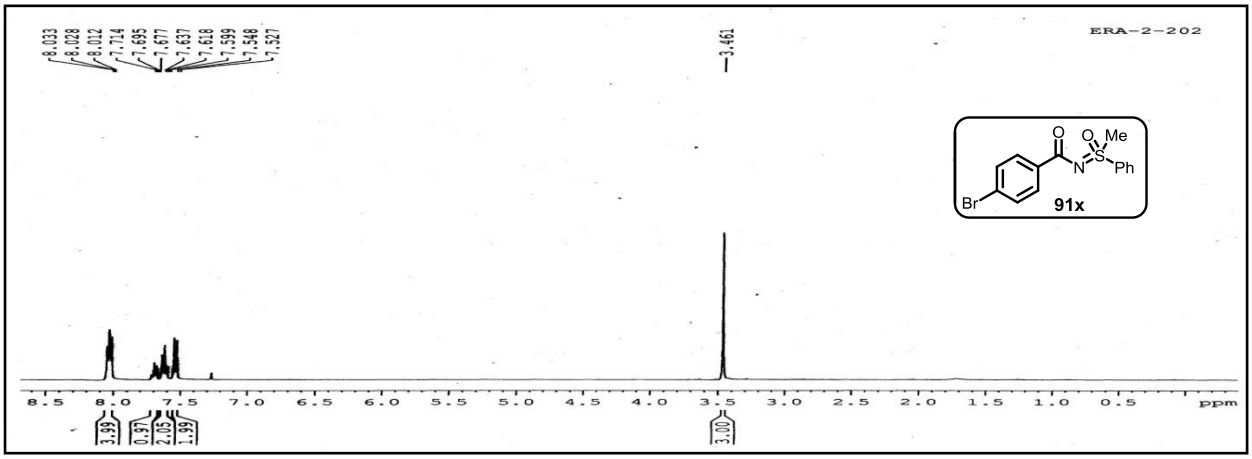

MJ-172
167.74
139.24
138.47
136.10
134.01
131.42
129.72
127.19
127.13
77.32
77.00
76.69
44.45
Cl
S
O
N
O
S
Me
Ph
91u
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

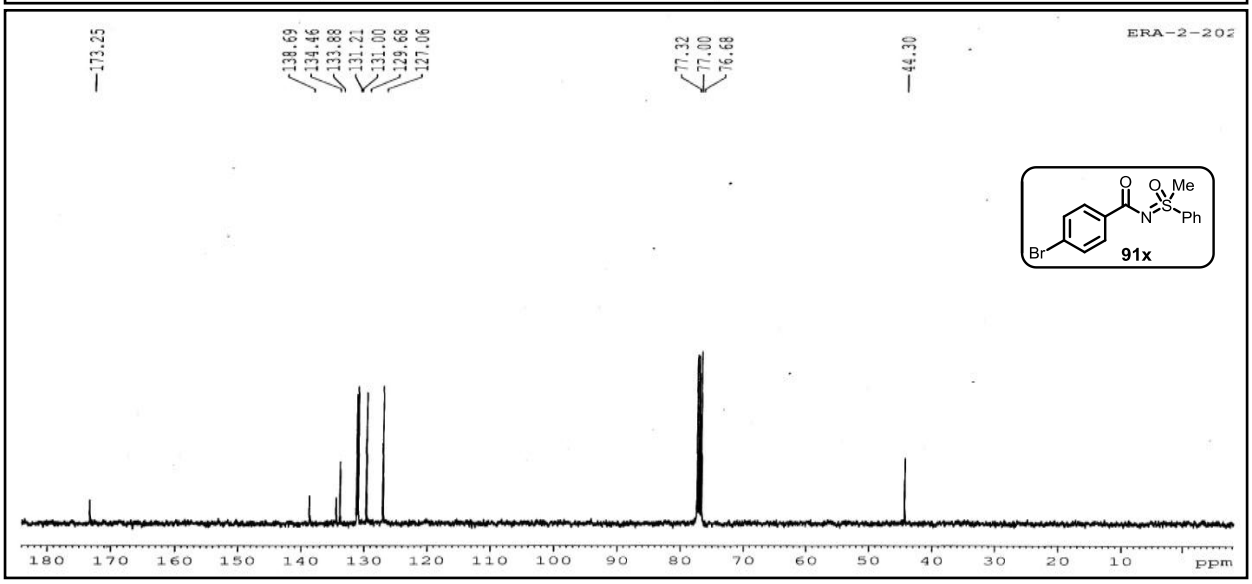

ERA-2-6
8.034
8.015
7.717
7.699
7.680
7.639
7.618
7.600
7.532
7.522
7.260
7.036
7.027
3.443
Br
S
O
N
O
S
Me
Ph
91v
9 8 7 6 5 4 3 2 1 0 ppm
1.97
1.04
2.02
0.97
0.96
3.00

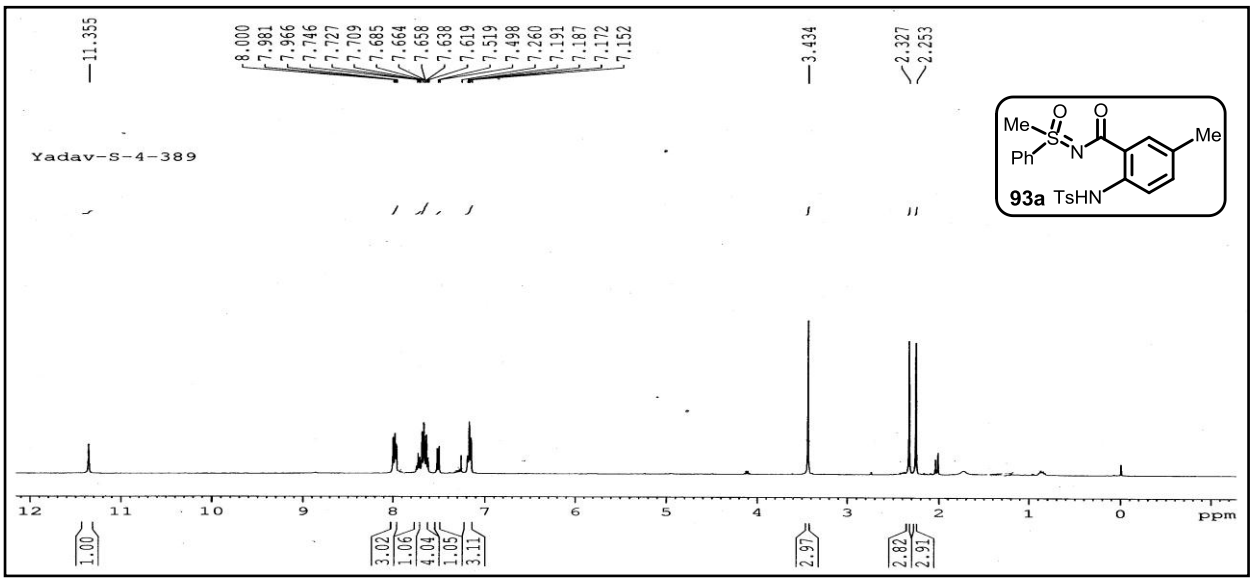

ERA-2-6
167.61
142.13
138.40
134.02
132.09
130.84
129.72
127.12
119.07
77.32
77.00
76.68
46.44
Br
S
O
N
O
S
Me
Ph
91v
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

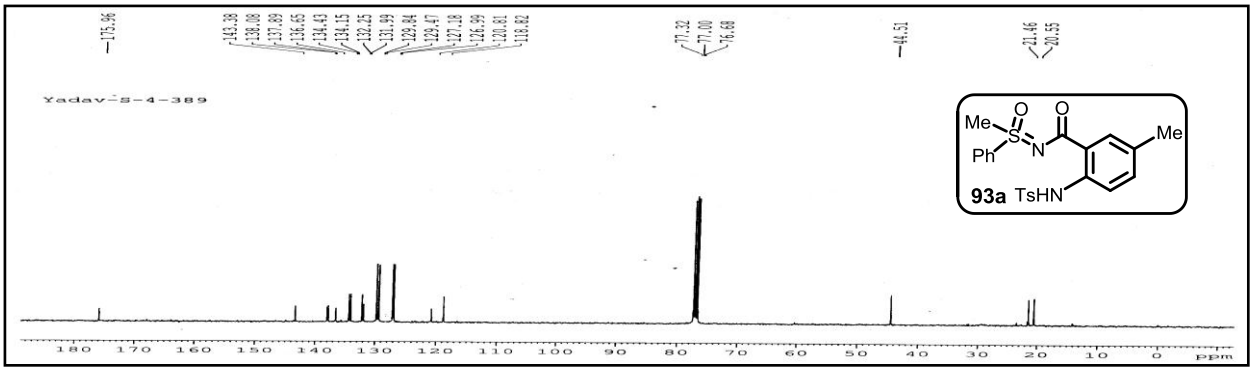

8.112
8.091
8.059
8.041
7.693
7.675
7.656
7.617
7.598
7.580
7.445
7.424
7.260
3.452
1.337
ERA-2-62
O
N
O
S
Me
Ph
tBu
91w
9 8 7 6 5 4 3 2 1 0 ppm
2.00
2.04
1.04
2.09
2.05
2.39
9.08

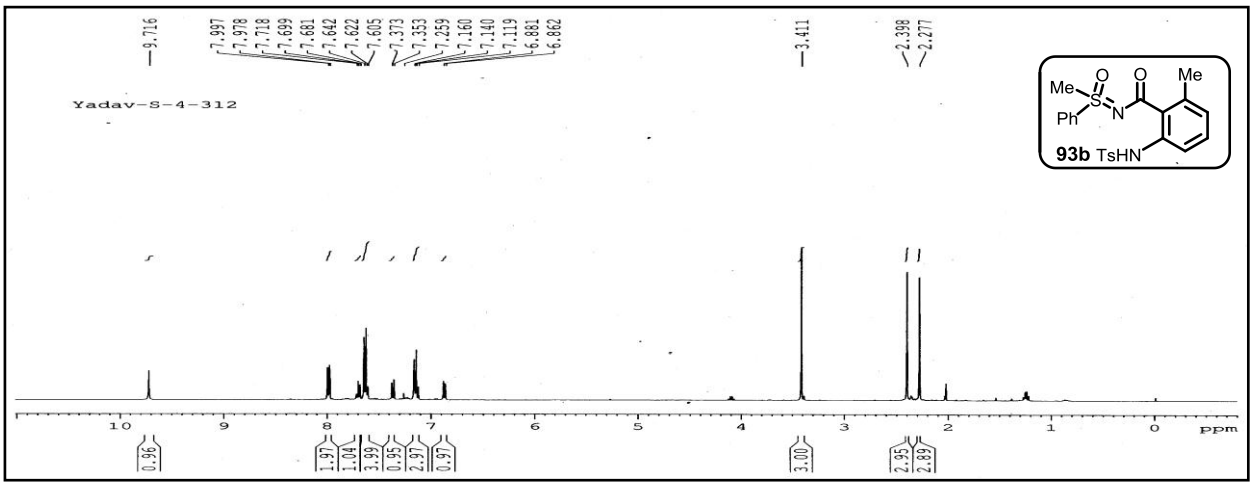

174.16
155.67
139.08
133.69
132.82
129.60
129.27
127.14
124.97
77.32
77.00
76.69
44.33
34.95
31.15
ERA-2-62
O
N
O
S
Me
Ph
tBu
91w
180 160 140 120 100 80 60 40 20 0 ppm

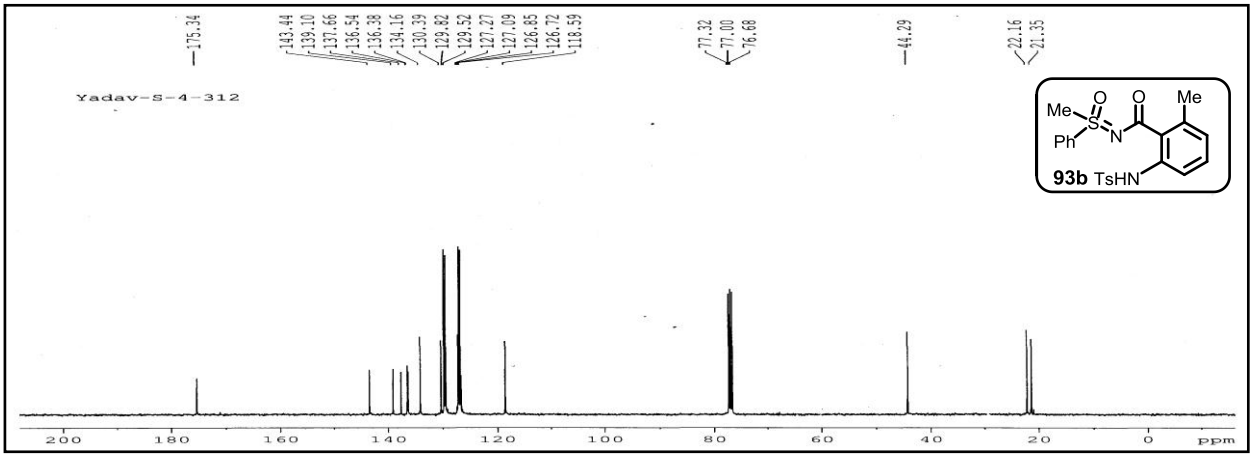

ERA-2-202
8.033
8.028
8.012
7.714
7.695
7.677
7.637
7.618
7.599
7.548
7.527
3.461
Me
O
S
N
Ph
Br
91x
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.99
0.87
2.05
1.99
3.00

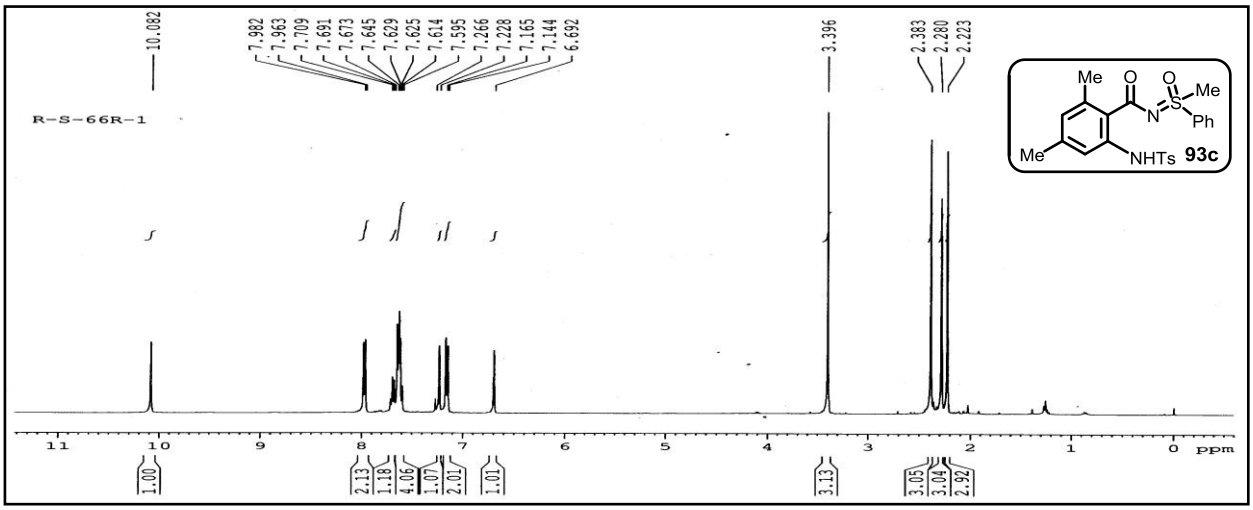

ERA-2-202
173.25
138.69
134.46
133.88
131.21
131.00
129.68
127.06
77.32
77.00
76.68
44.30
Me
O
S
N
Ph
Br
91x
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

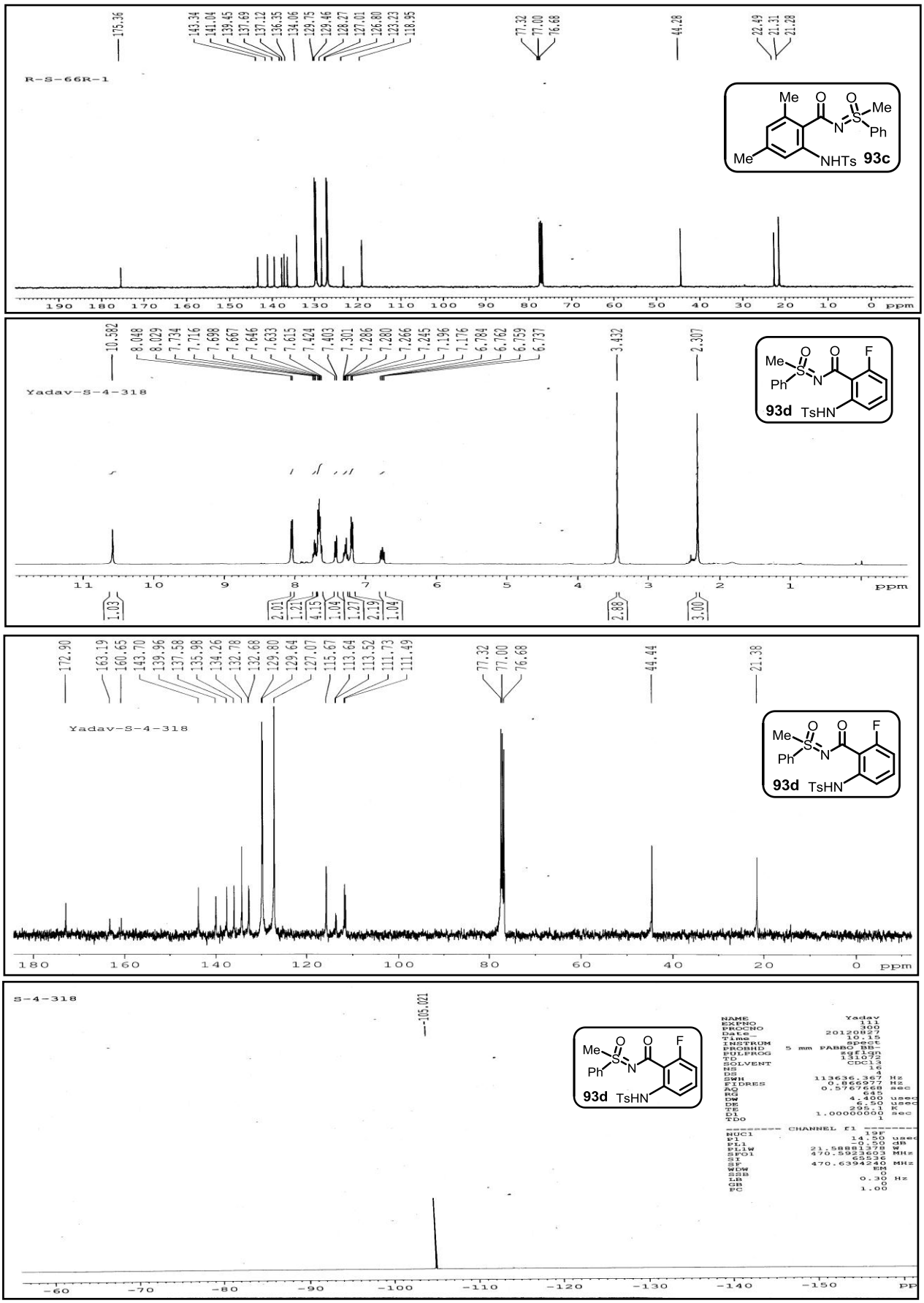

11.355
8.000
7.981
7.966
7.746
7.727
7.709
7.685
7.664
7.658
7.638
7.619
7.519
7.498
7.260
7.191
7.187
7.172
7.152
3.434
2.327
2.253
Yadav-S-4-389
Me
Ph
S
N
O
O
Me
93a TsHN
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
3.02
1.06
4.04
1.05
3.11
2.97
2.82
2.91

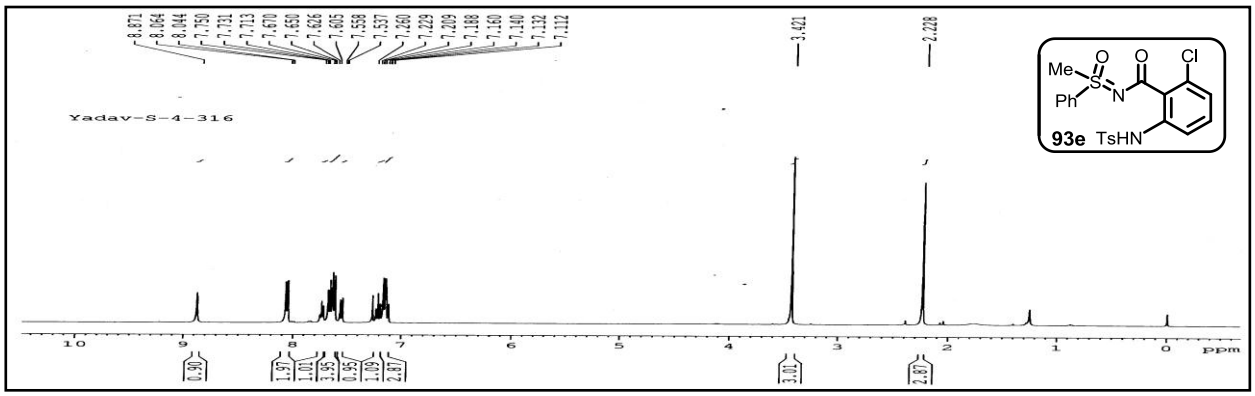

Yadav-S-4-389
93a TsHN

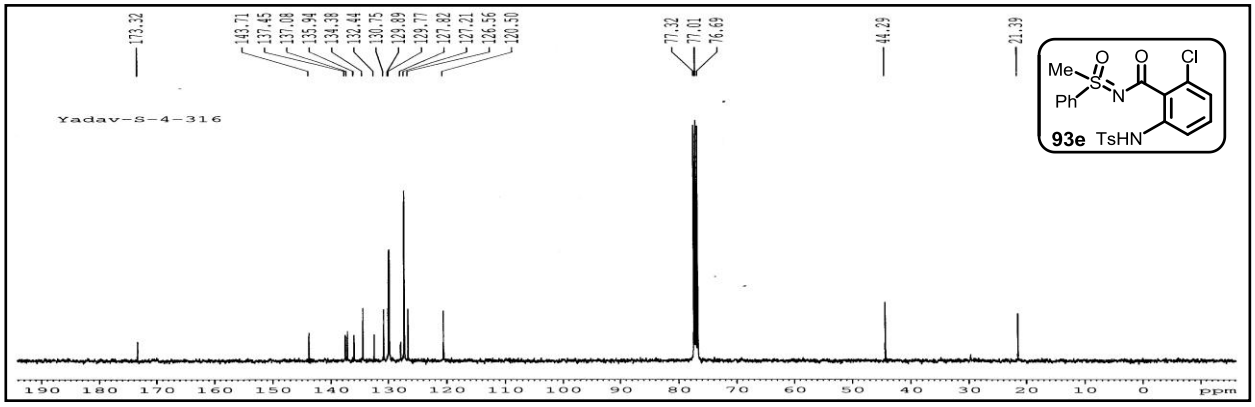

Yadav-S-4-312
93b TsHN

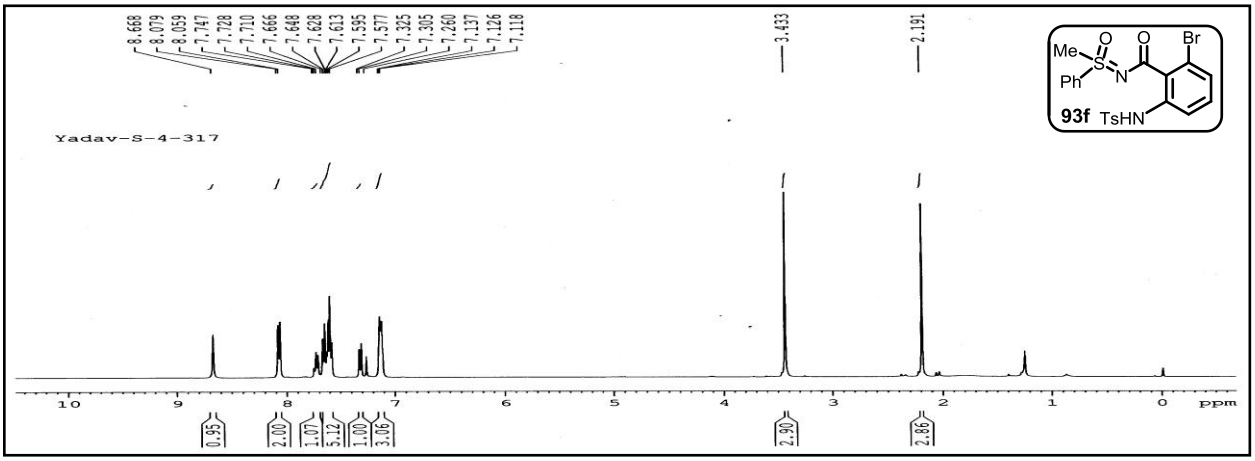

Yadav-S-4-312
93b TsHN

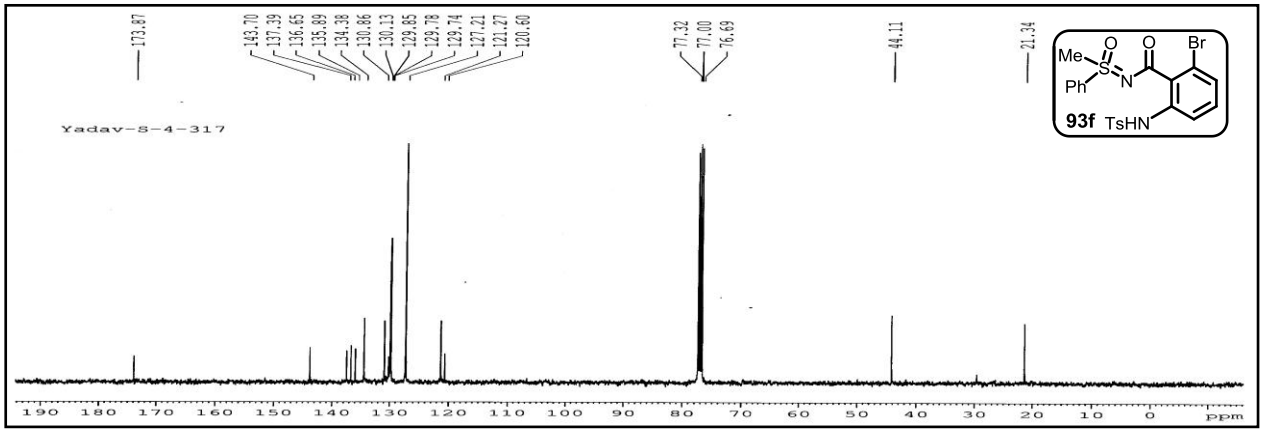

R-S-66R-1
NHTs 93c

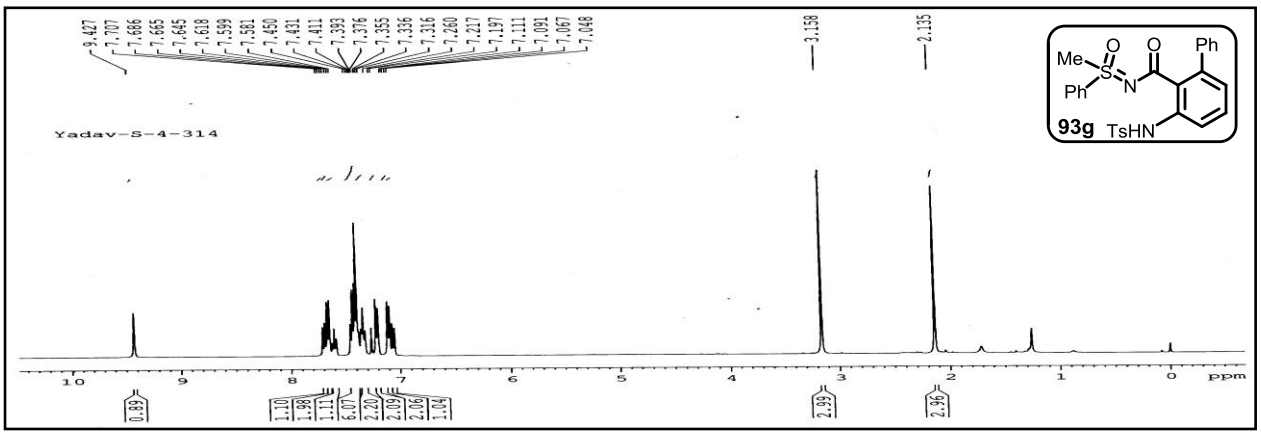

R-S-66R-1
93c
Yadav-S-4-318
93d TsHN
Yadav-S-4-318
93d TsHN
S-4-318
93d TsHN

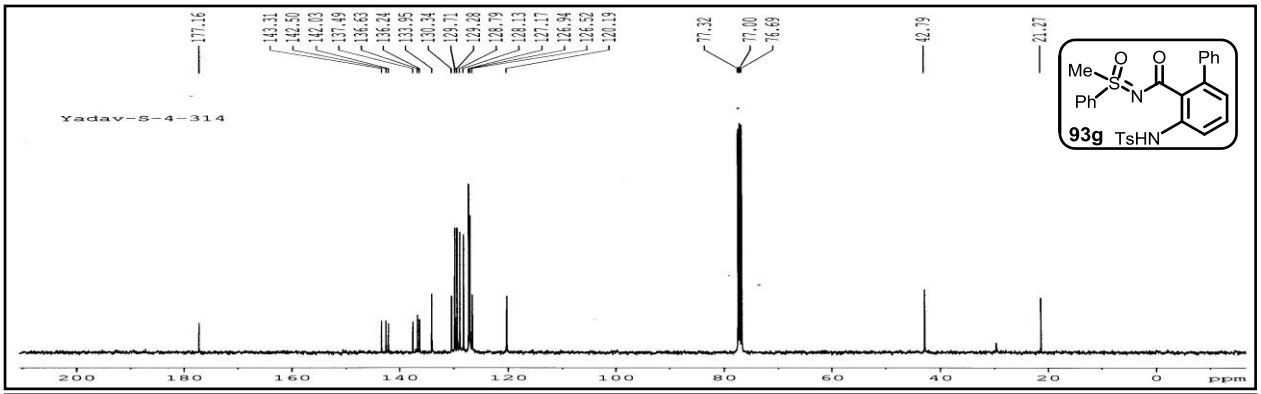

Yadav-S-4-316
93e TsHN

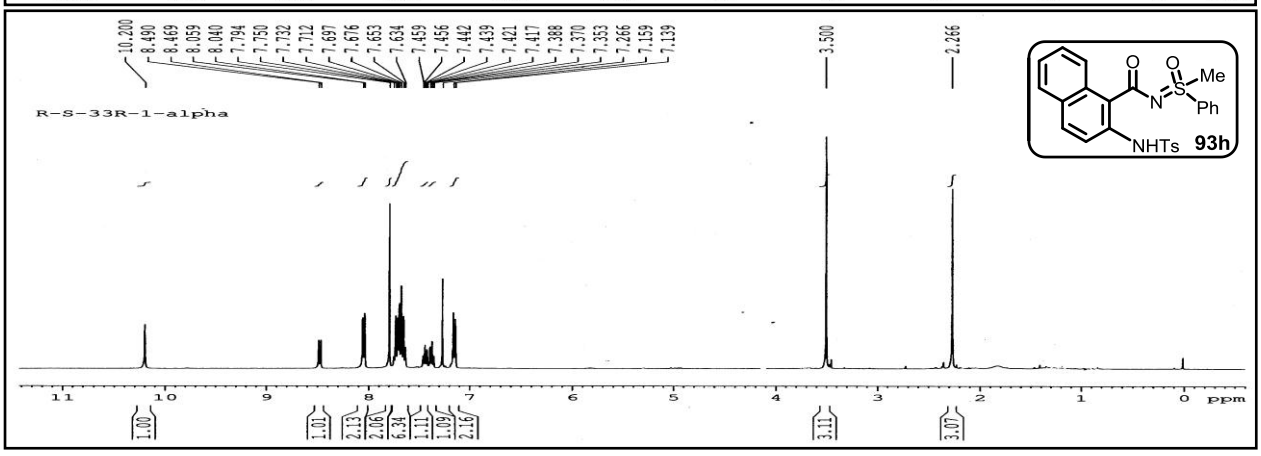

Yadav-S-4-316
93e TsHN

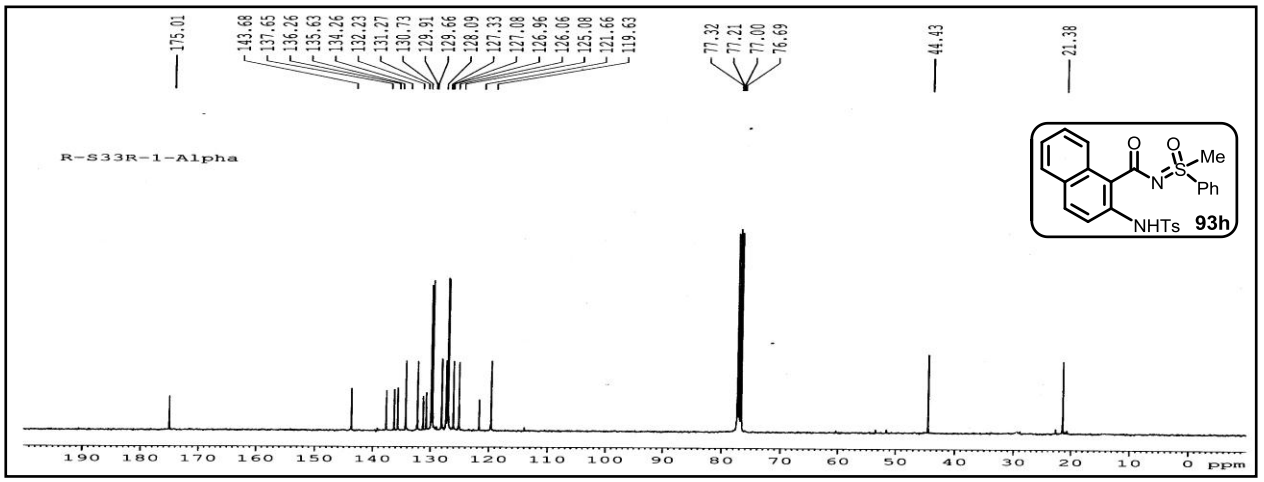

Yadav-S-4-317
93f TsHN

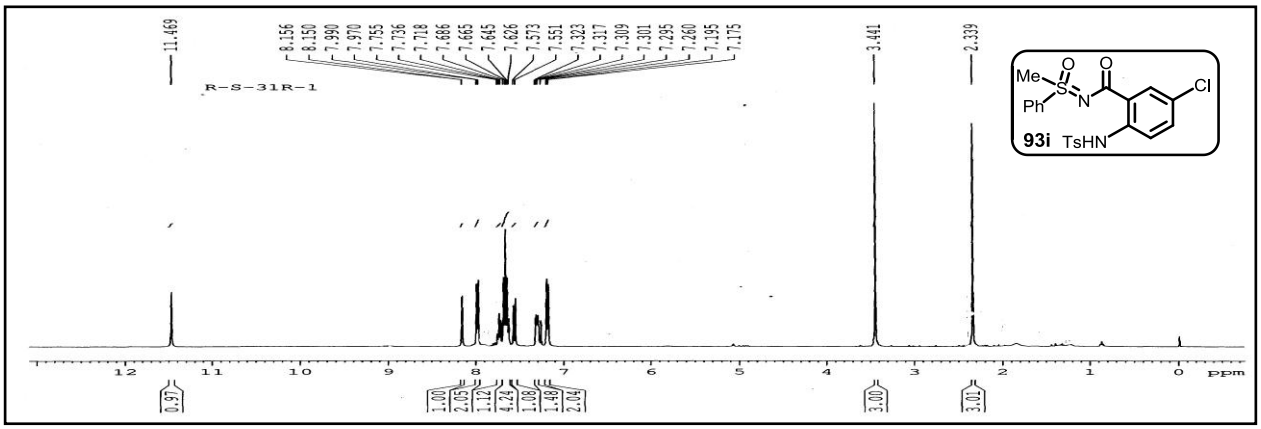

Yadav-S-4-317
93f TsHN

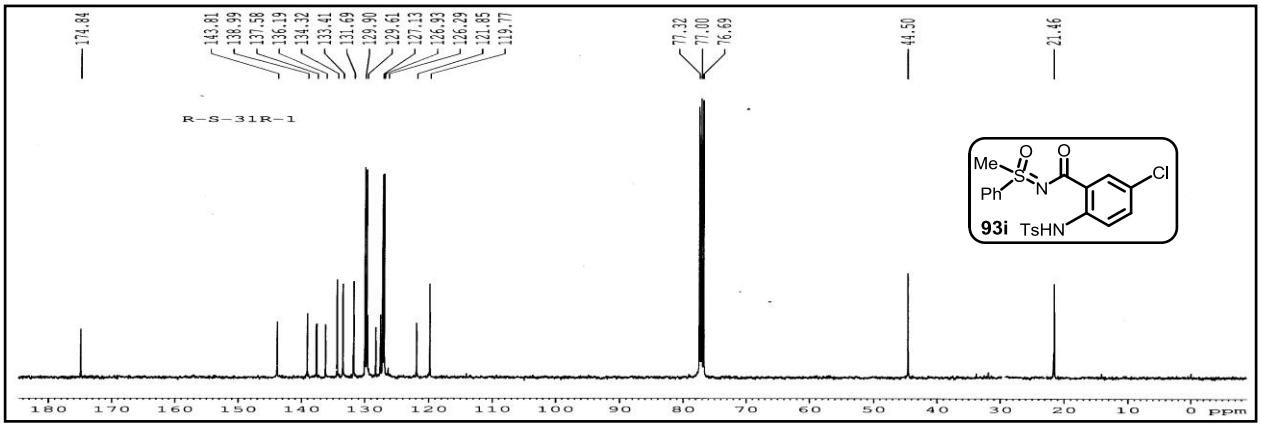

Yadav-S-4-314
93g TsHN


Yadav-S-4-314
93g TsHN


R-S-33R-1-alpha
NHTs 93h


R-S33R-1-Alpha
NHTs 93h


R-S-31R-1
93i TsHN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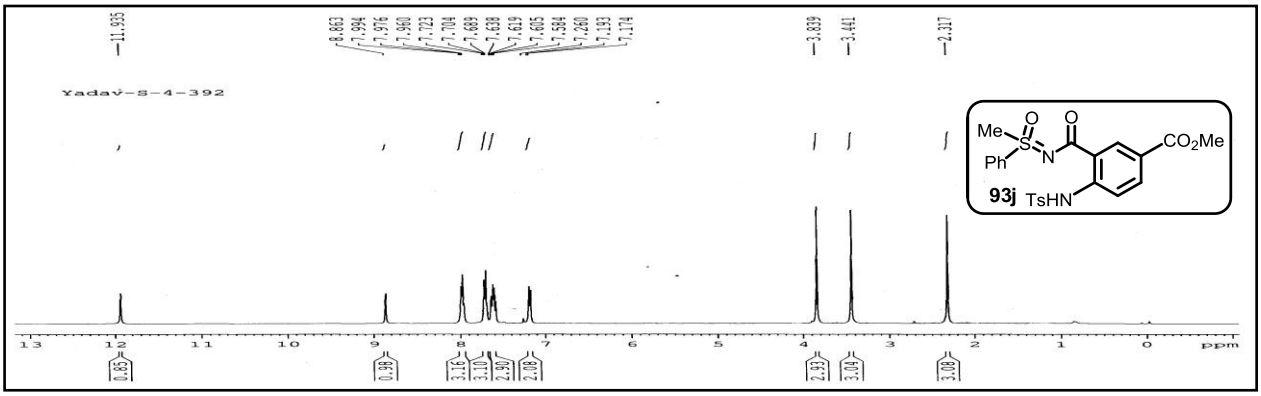
93i TsHN


Yadav-S-4-392
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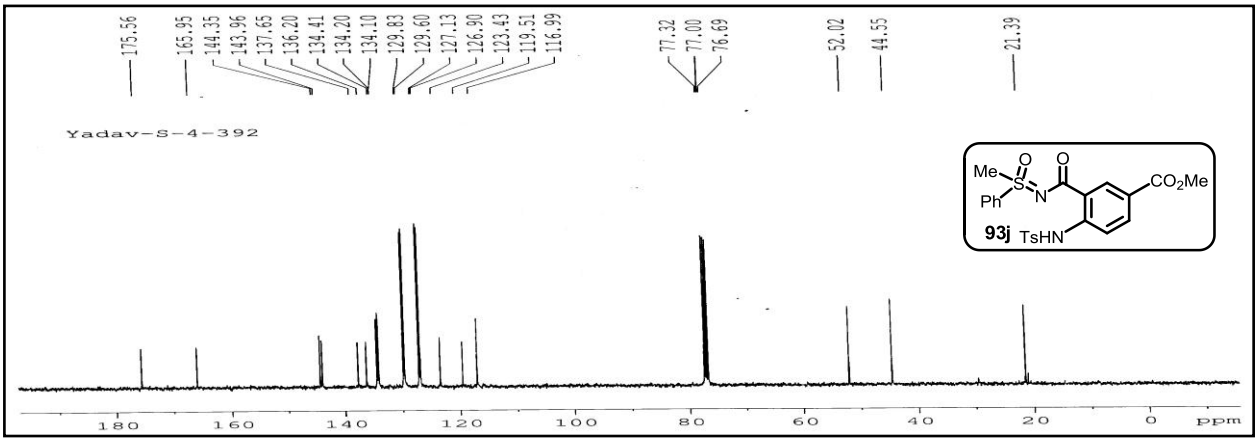
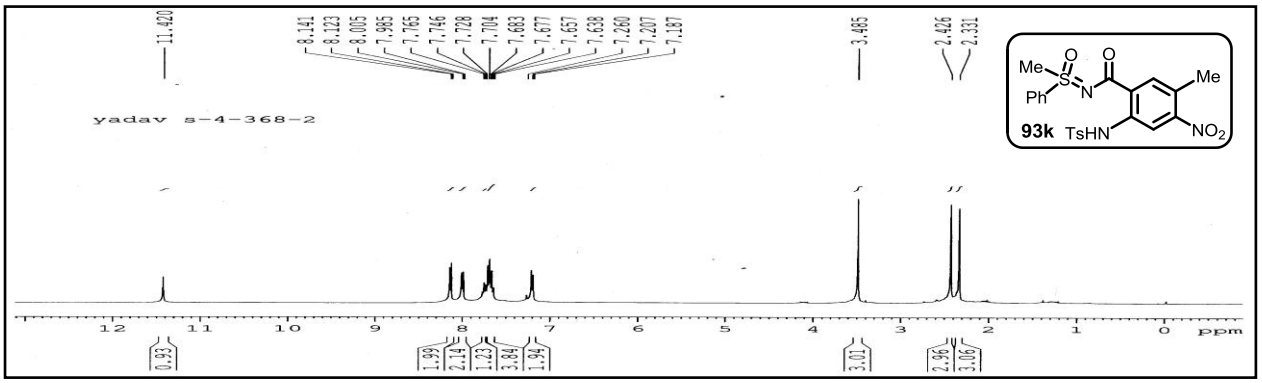
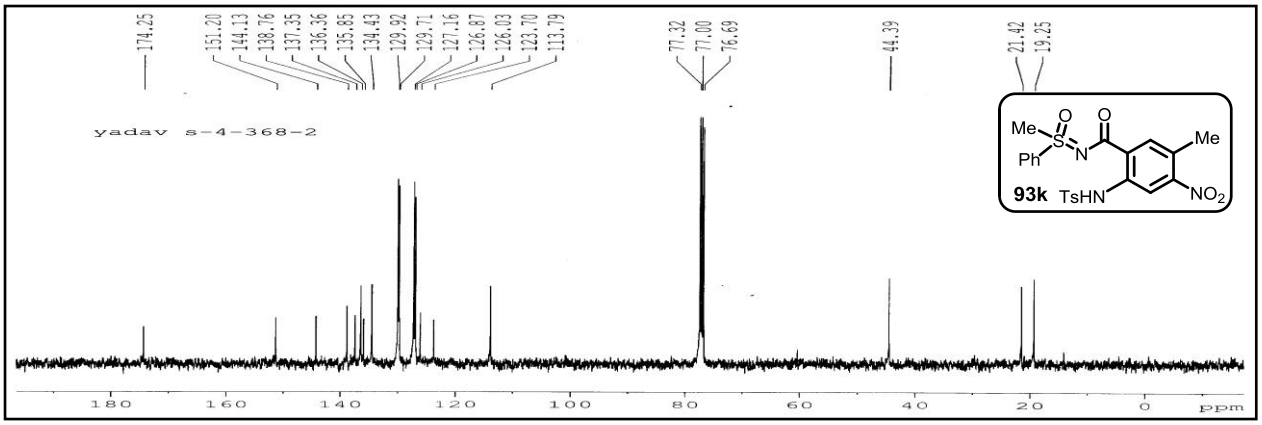

Yadav-S-4-392
93j TsHN


yadav s-4-368-2
93k TsHN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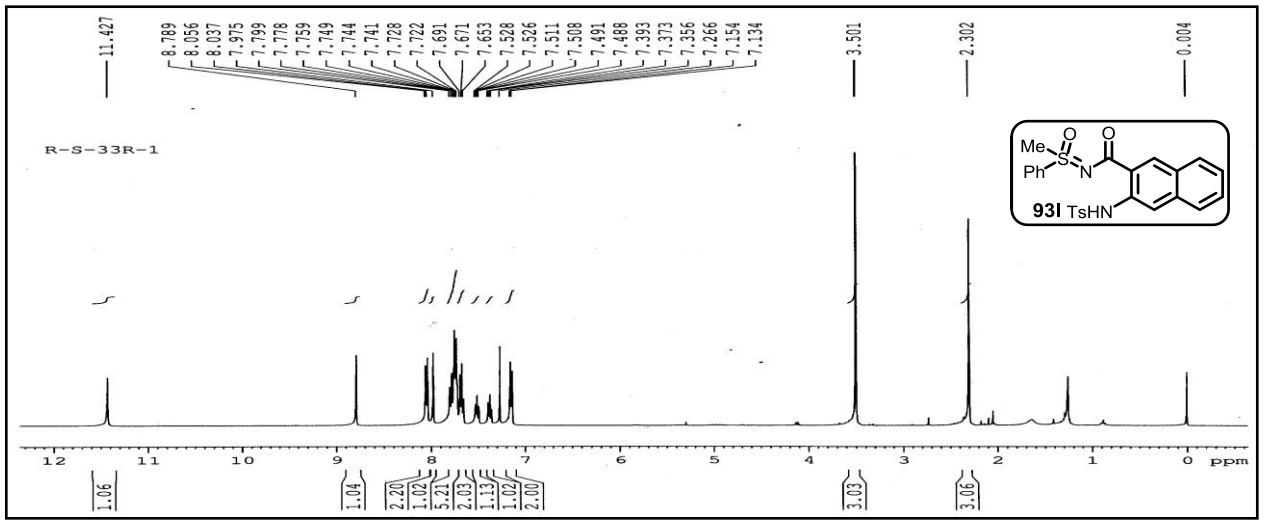
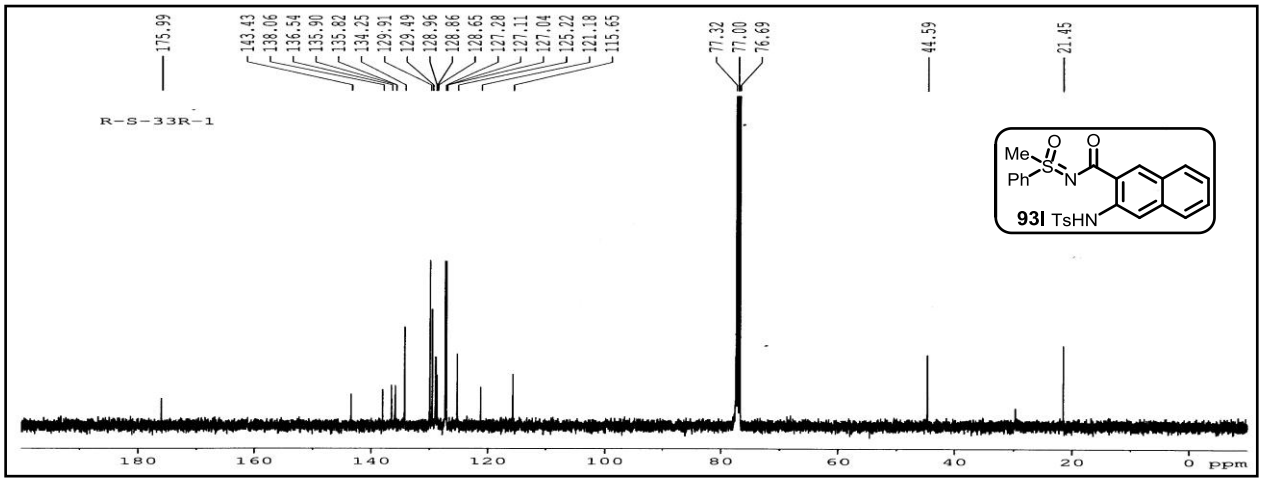

R-S-33R-1
93l TsHN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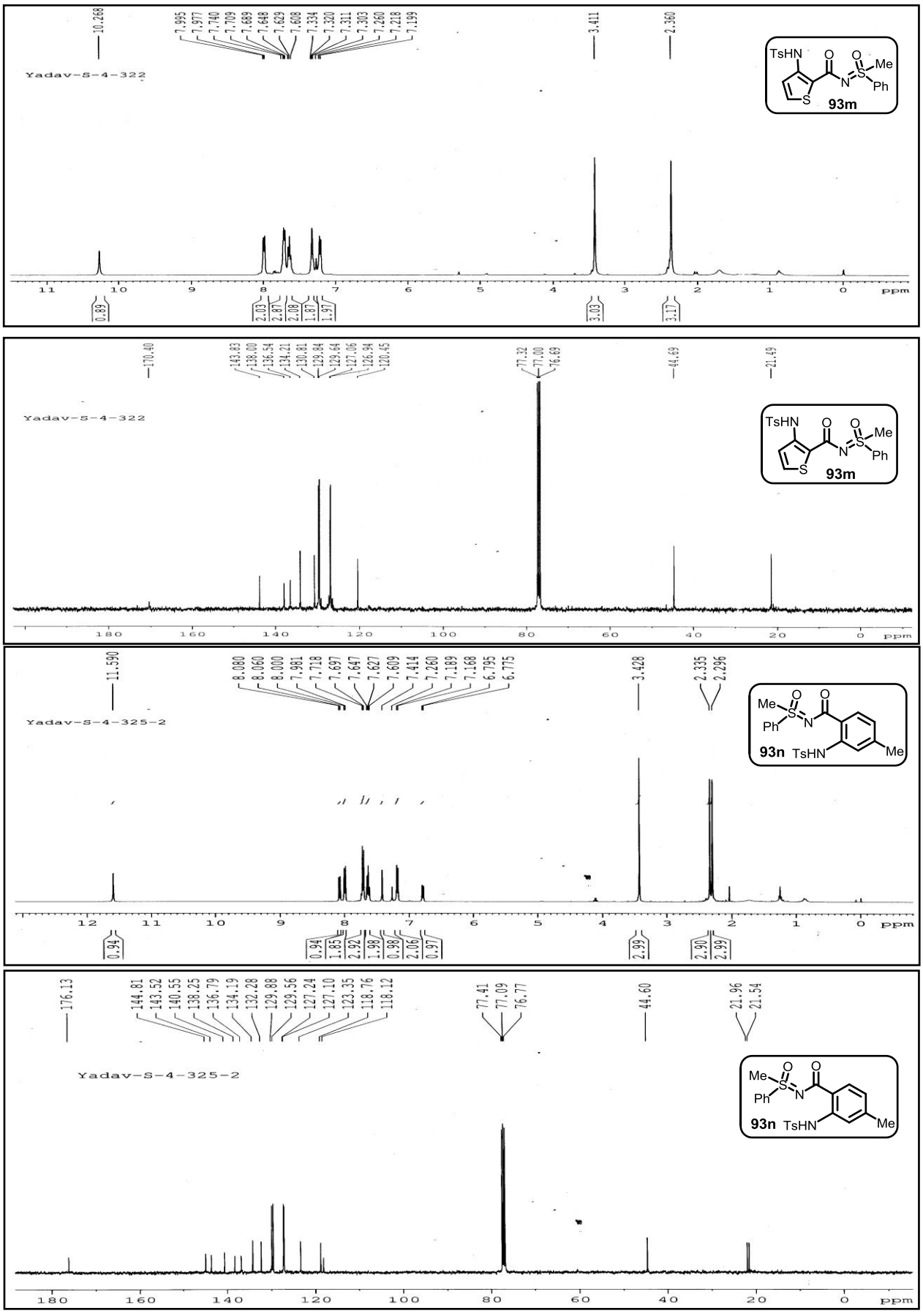
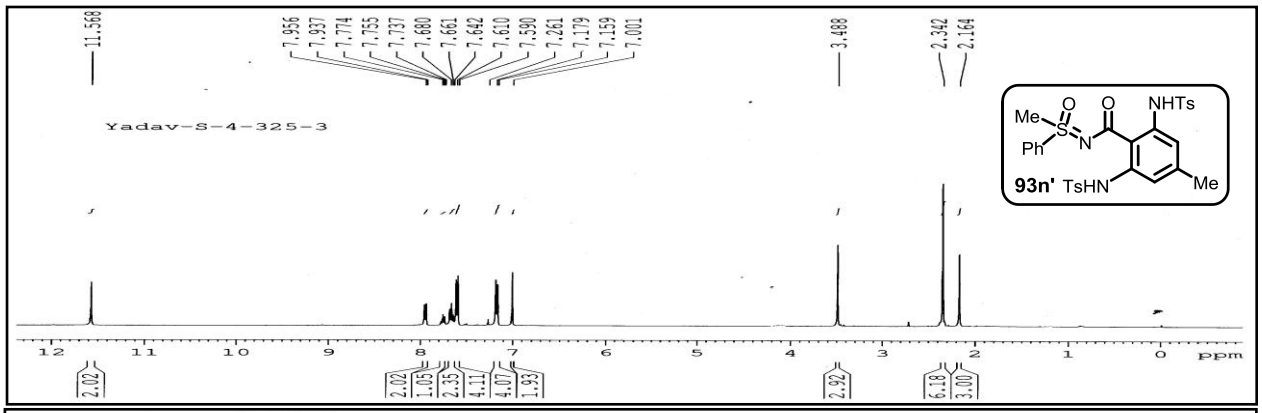
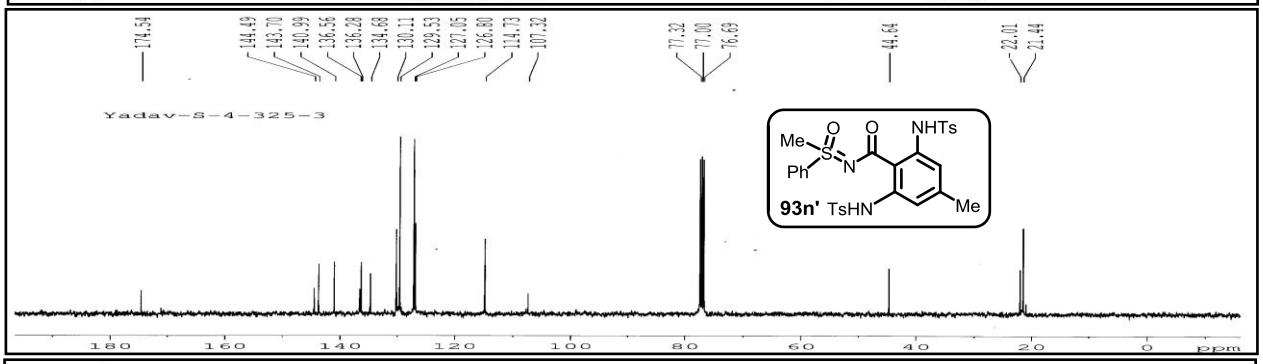

Yadav-S-4-322
93m
Yadav-S-4-322
93m
Yadav-S-4-325-2
93n
Yadav-S-4-325-2
93n


Yadav-S-4-325-3
93n' TsHN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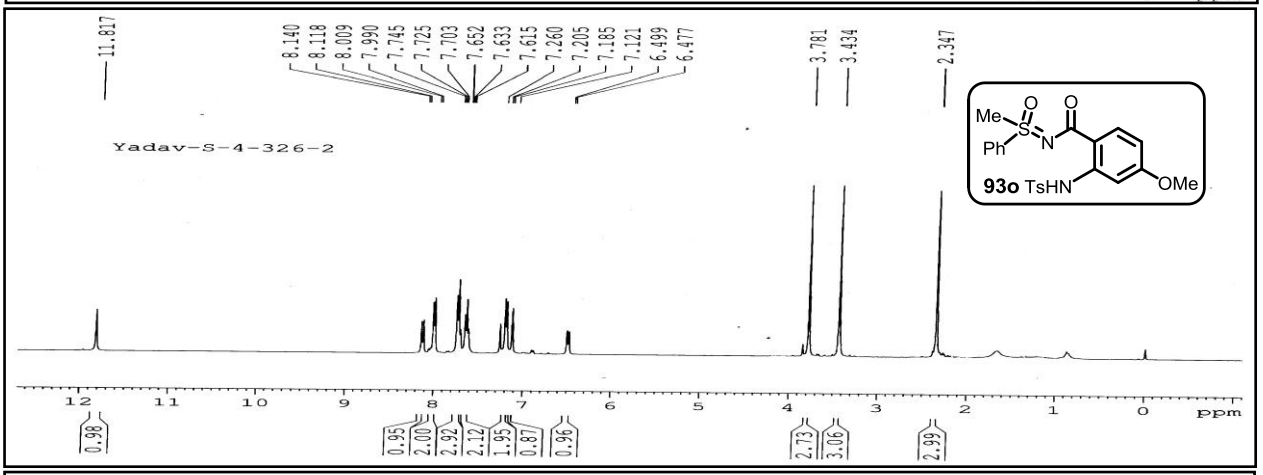
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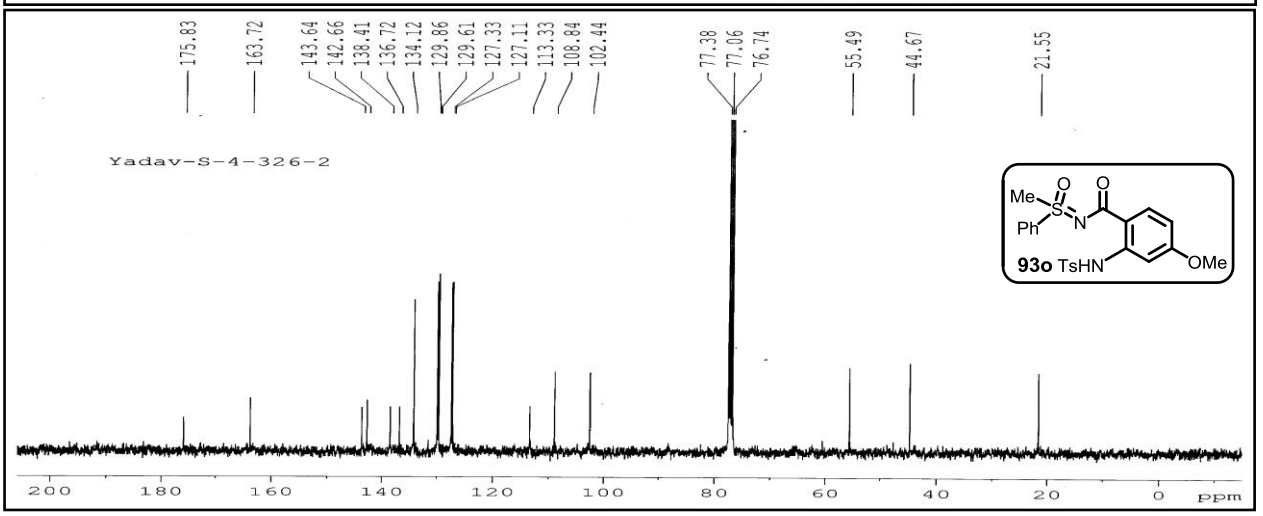
93o TsHN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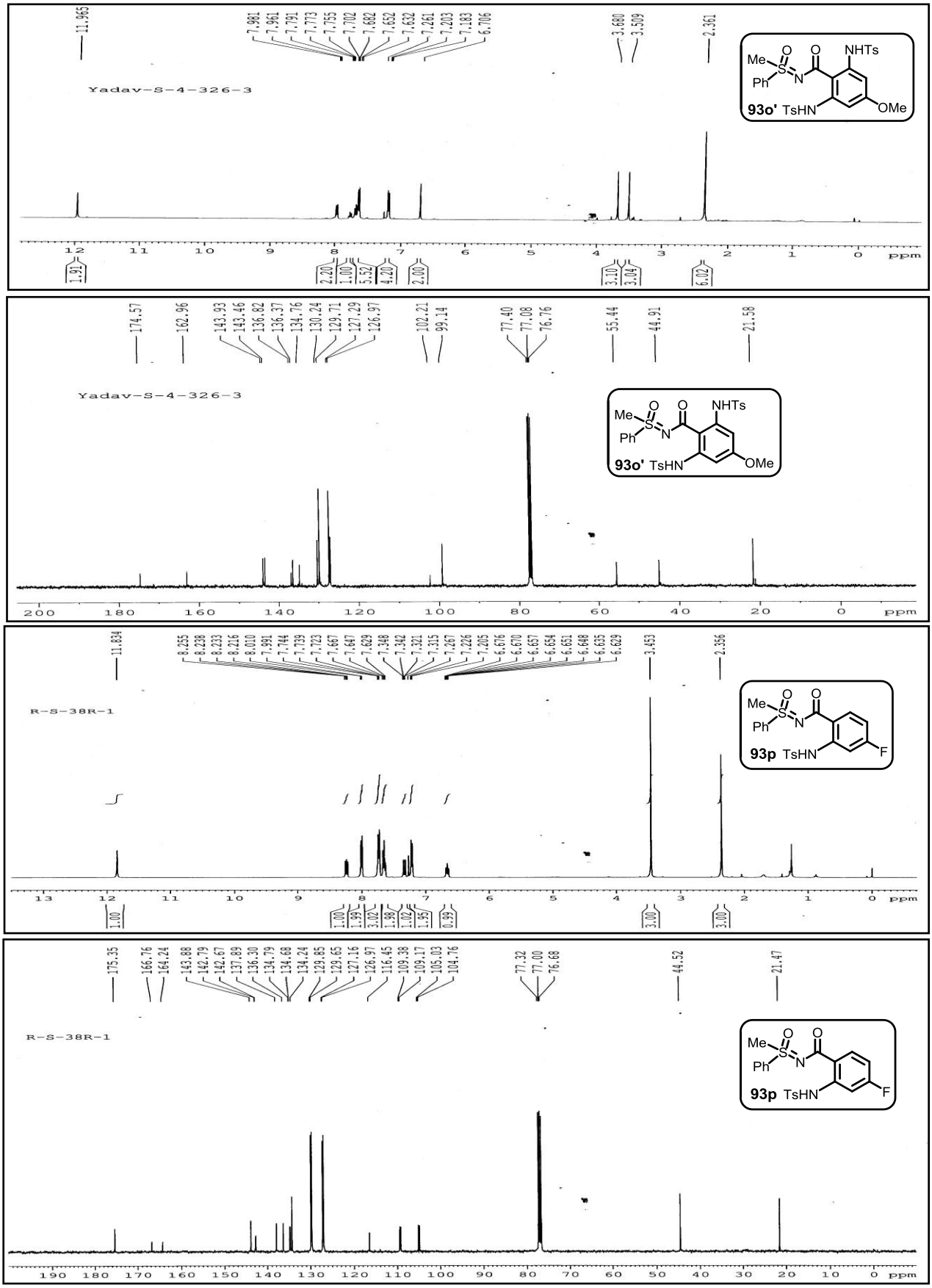
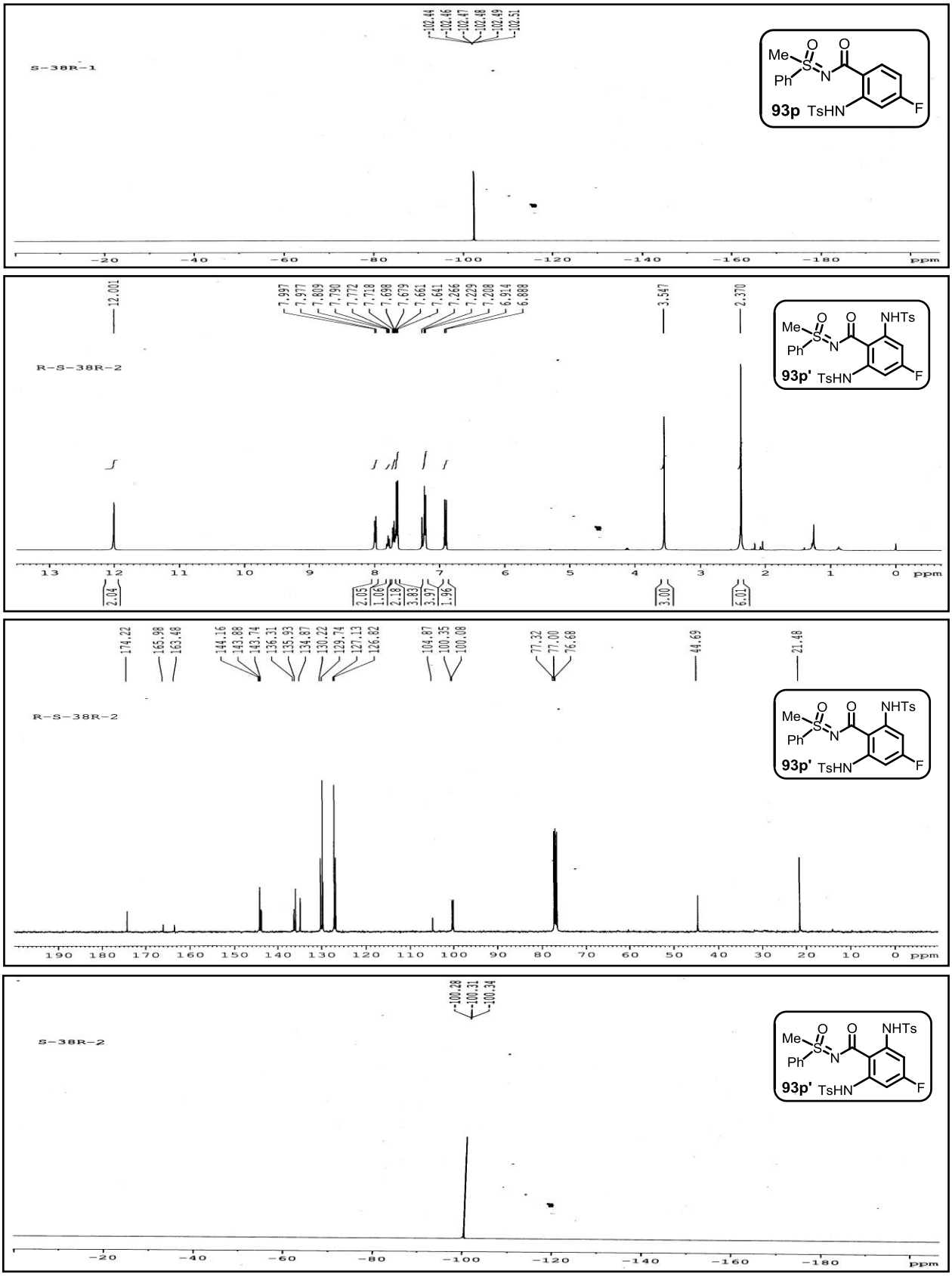

Yadav-S-4-326-3
93o' TsHN
Yadav-S-4-326-3
93o' TsHN
R-S-38R-1
93p TsHN
R-S-38R-1
93p TsHN


S-38R-1
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-102.49
-102.51
93p TsHN
R-S-38R-2
12.001
7.997
7.977
7.809
7.790
7.772
7.718
7.698
7.679
7.661
7.641
7.266
7.229
7.208
6.914
6.888
3.547
2.370
93p' TsHN
R-S-38R-2
174.22
165.98
163.48
144.16
143.88
143.74
136.31
135.93
134.87
130.22
129.74
127.13
126.82
104.87
100.35
100.08
77.32
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76.68
44.69
21.48
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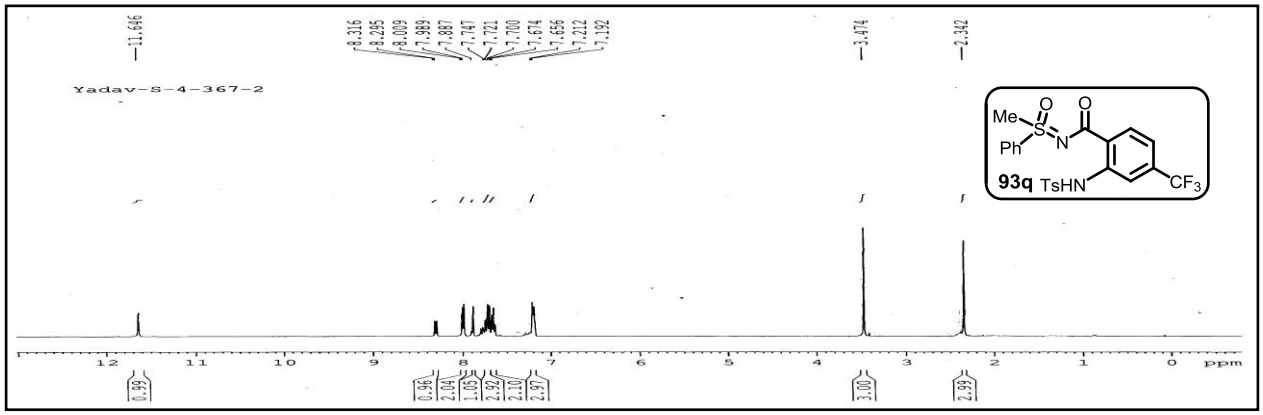
93p' TsHN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7.747
7.721
7.700
7.674
7.656
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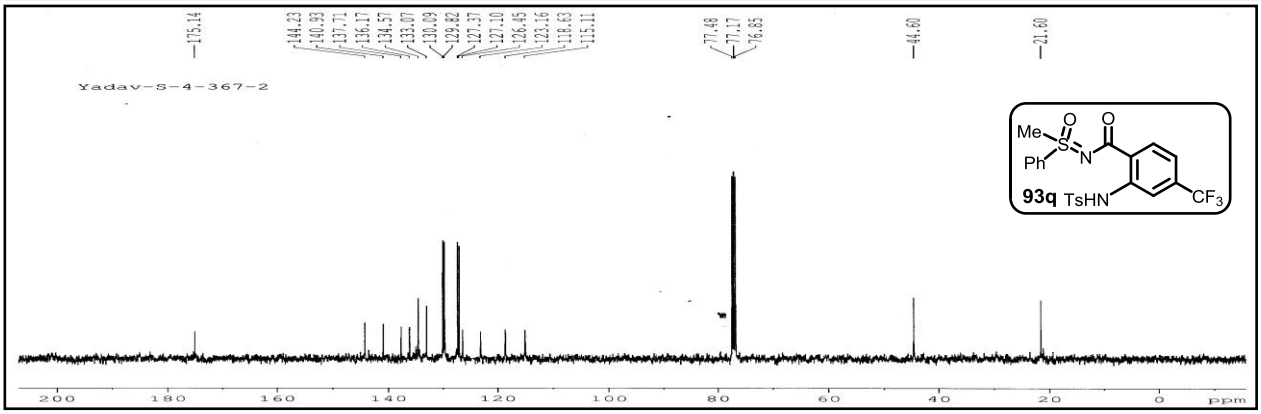
7.192
3.474
2.342
Me
Ph
O
S
N
O
O
93q TsHN
CF3
ppm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140.93
137.71
136.17
134.57
133.07
130.09
129.82
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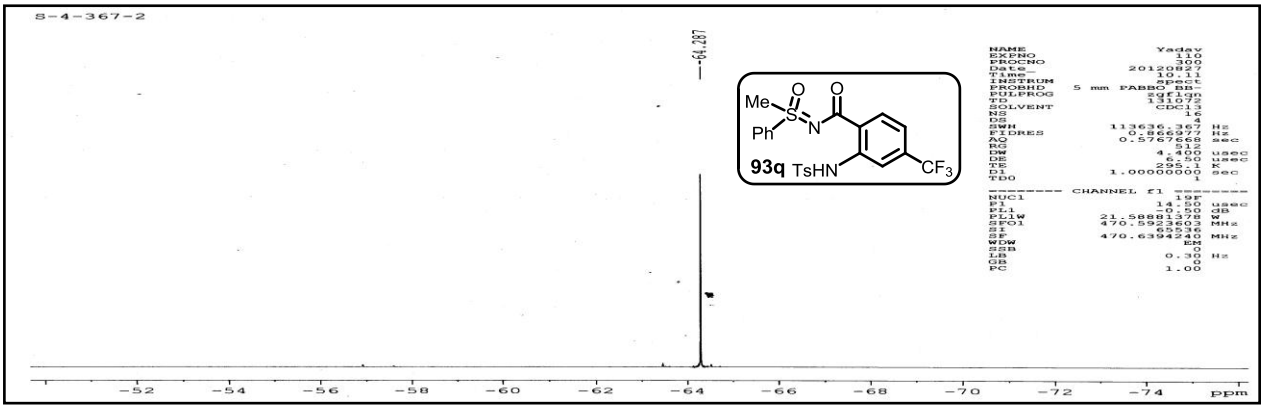
127.10
126.45
123.16
118.63
115.11
77.48
77.17
76.85
44.60
21.60
Me
Ph
O
S
N
O
O
93q TsHN
CF3
ppm


S-4-367-2
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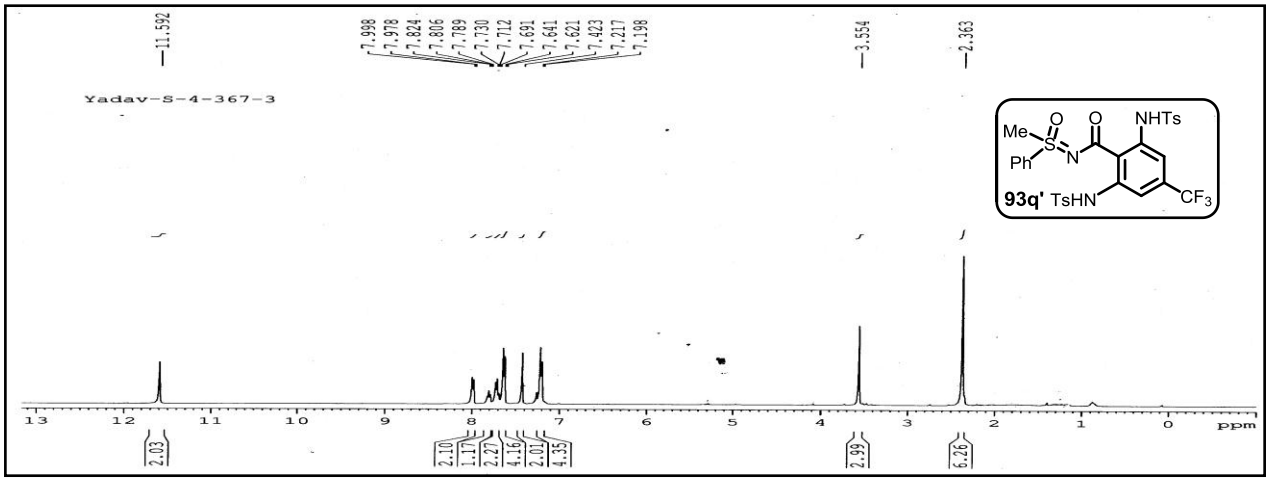
Ph
O
S
N
O
O
93q TsHN
CF3
NAME Yadav
EXPNO 11
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120309
Time 10.31
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgflqn
TD 131072
SOLVENT CDCl3
NS 16
DS 4
SWH 113636.367 Hz
FIDRES 0.866977 Hz
AQ 0.5767648 sec
RG 512
DW 4.400 usec
DE 6.50 usec
TE 298.1 K
D1 1.0000000 sec
TD0 1
CHANNEL f1
NUC1 19F
P1 14.50 usec
PL1 -10.00 dB
PLW 21.58881378 W
SFO1 470.5923603 MHz
SI 65536
SF 470.6394241 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm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7.712
7.691
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7.621
7.423
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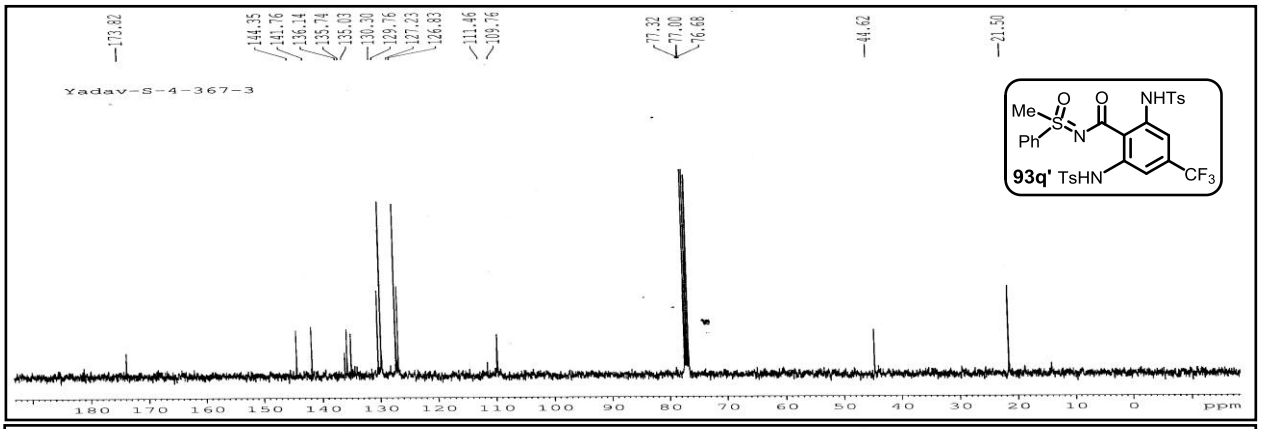
7.198
3.554
2.363
Me
Ph
O
S
N
O
O
NHTs
93q' TsHN
CF3
ppm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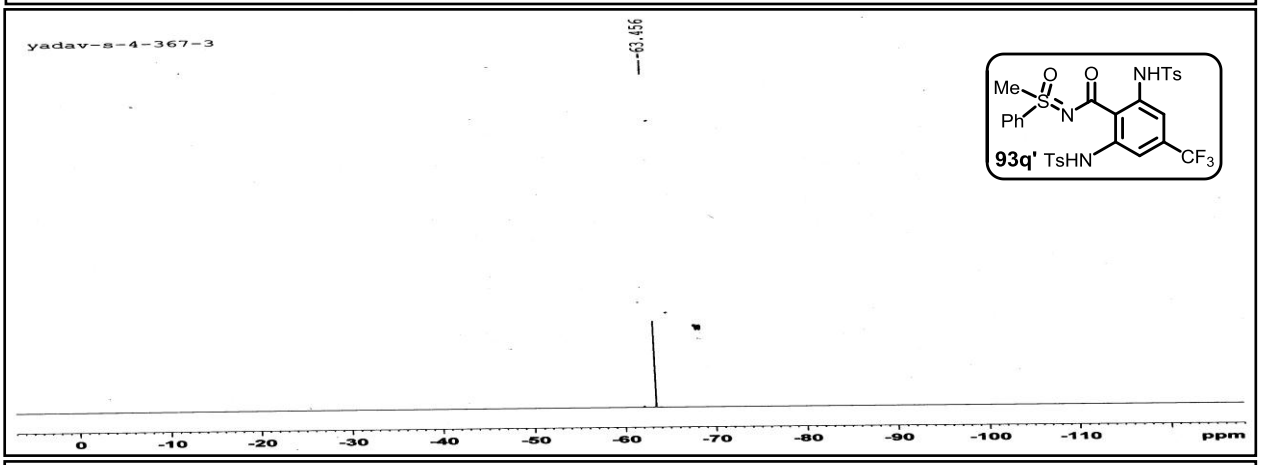
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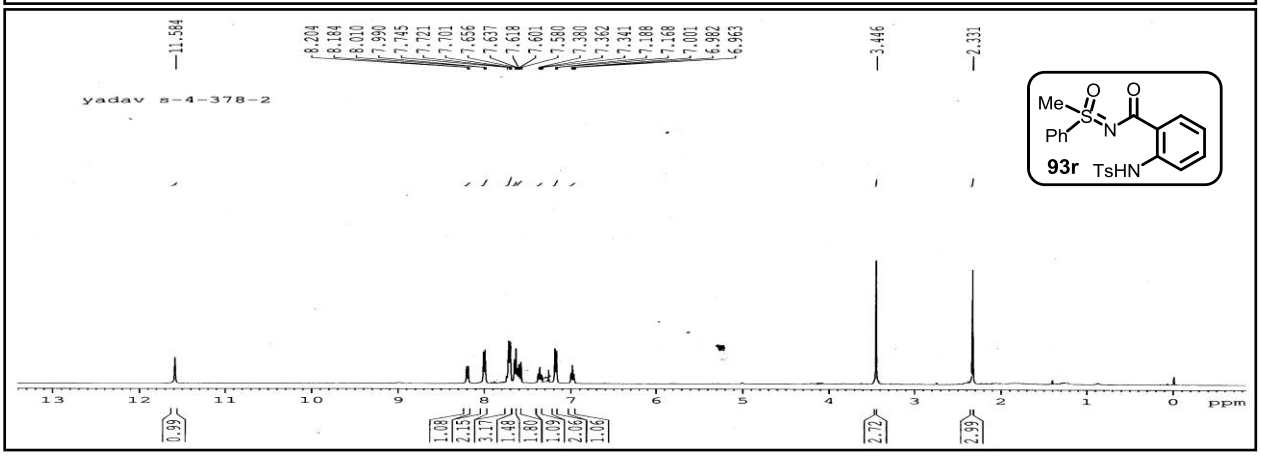
93q' TsHN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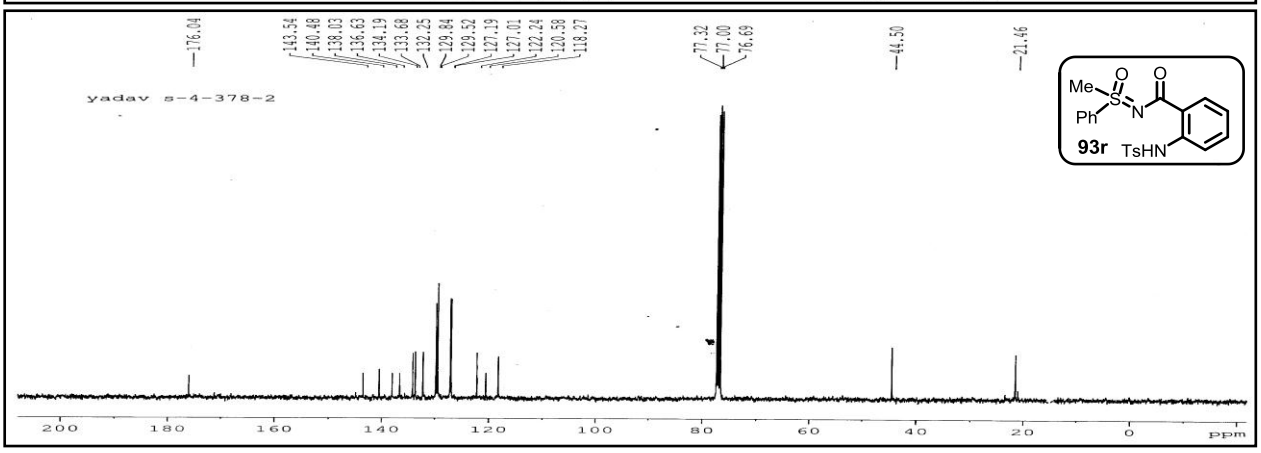
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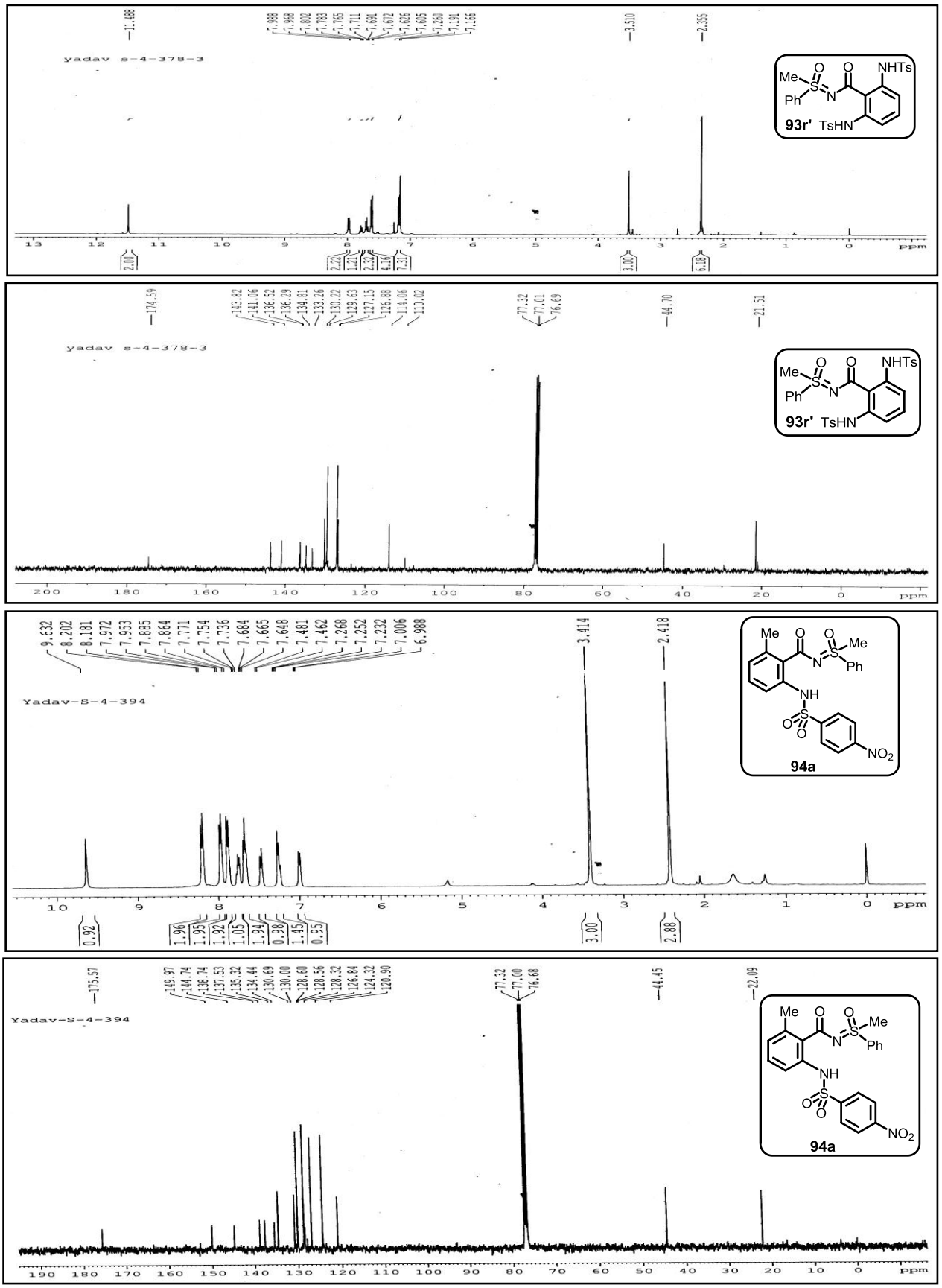
93r TsHN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93r' TsHN
NHTs
Me
Ph
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93r' TsHN
NHTs
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94a
Me
Ph
NH
NO2
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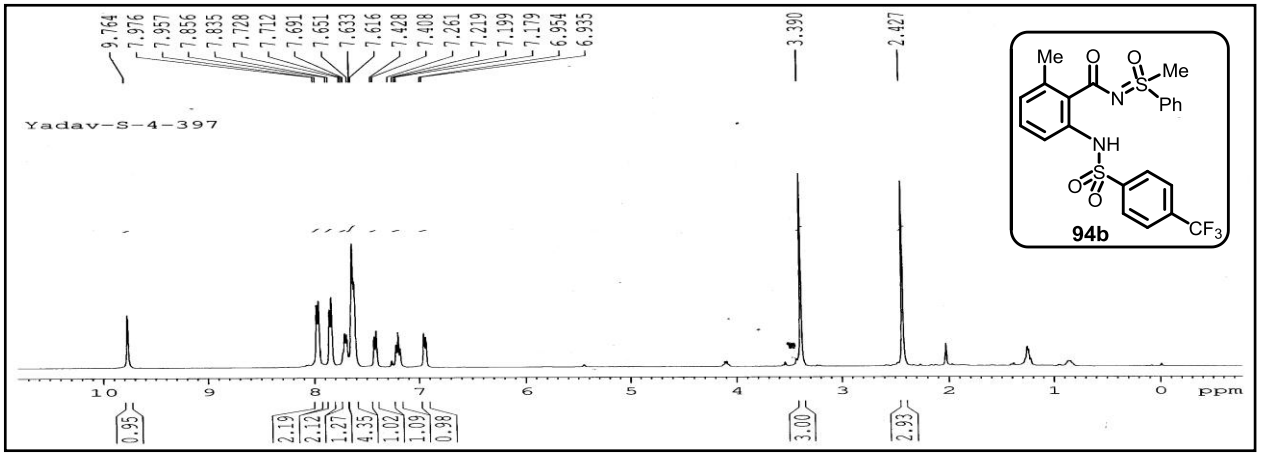
94a
Me
Ph
NH
NO2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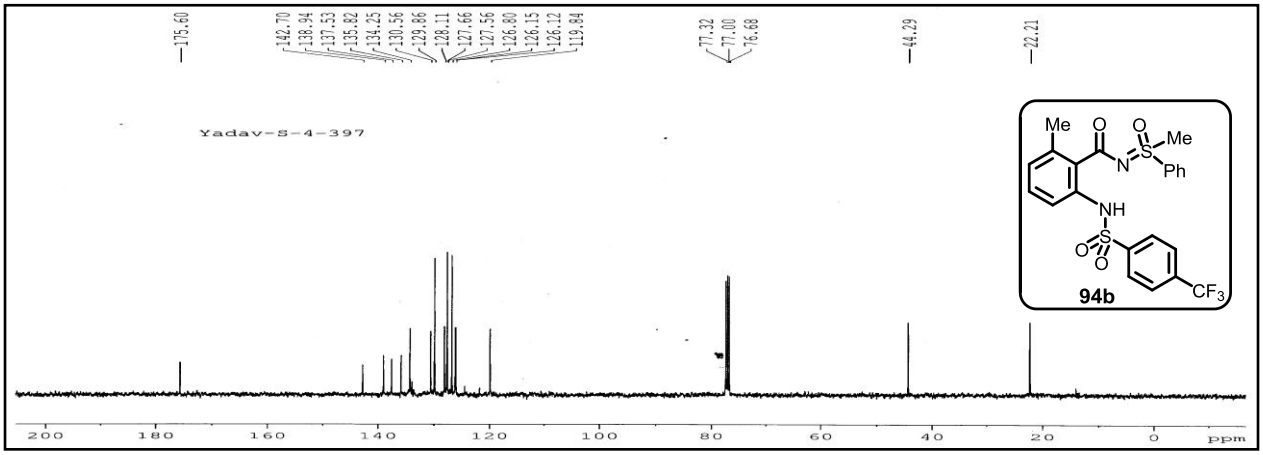
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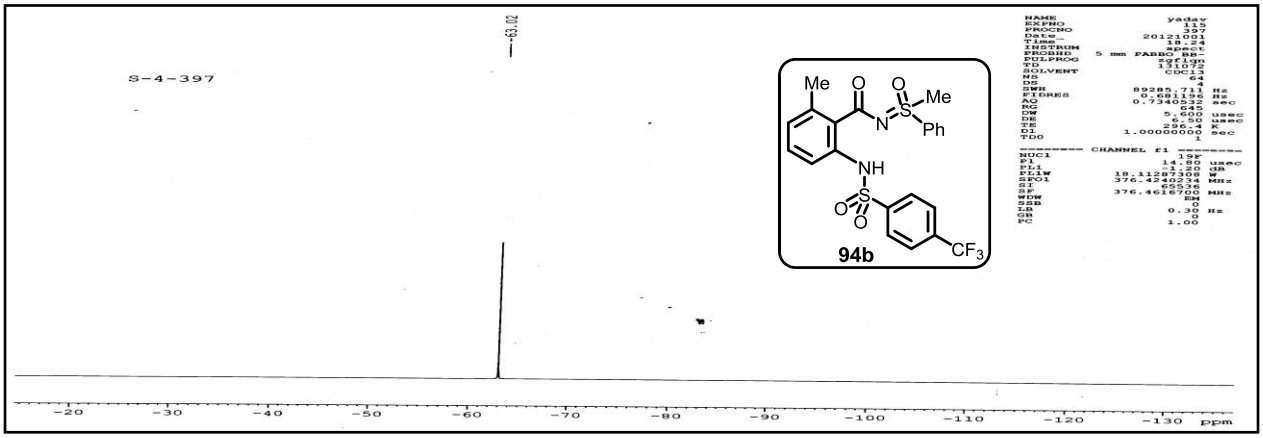
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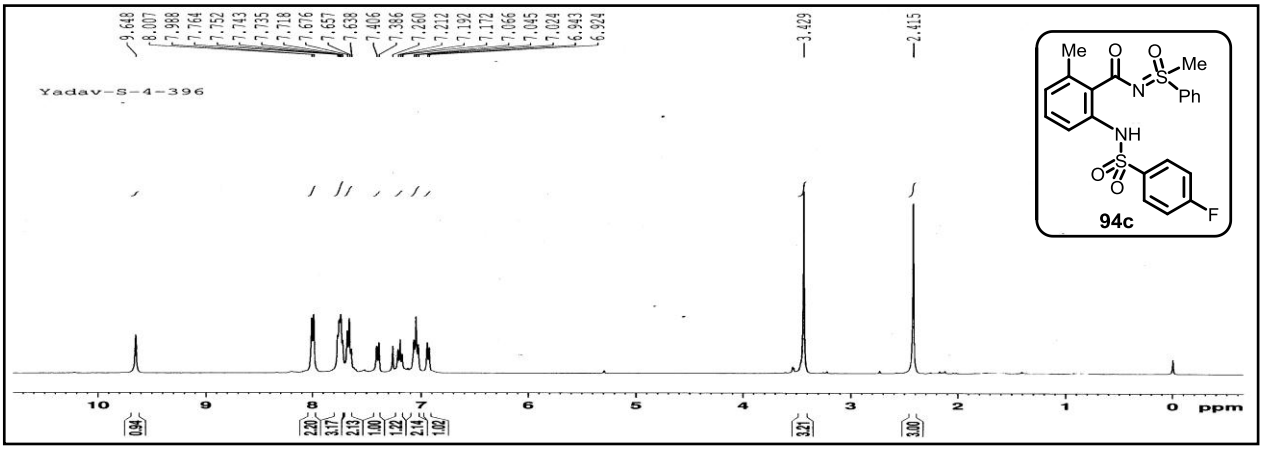
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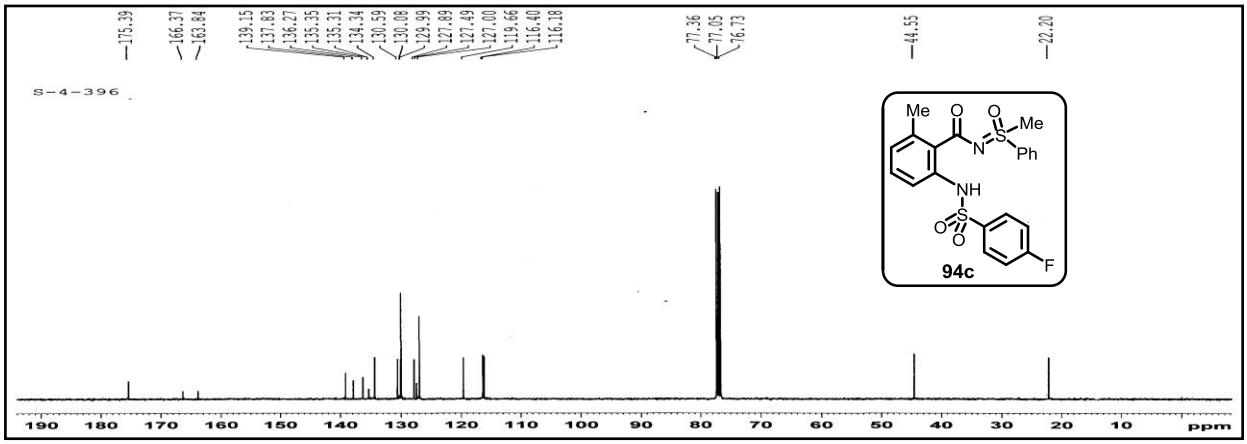
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134.34
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127.00
119.66
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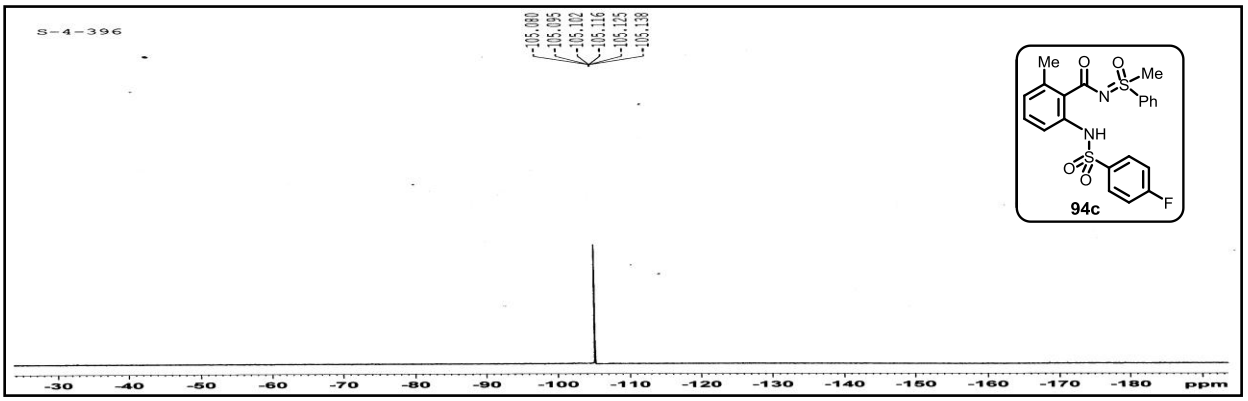
O
N
S
Ph
NH
F
94c
ppm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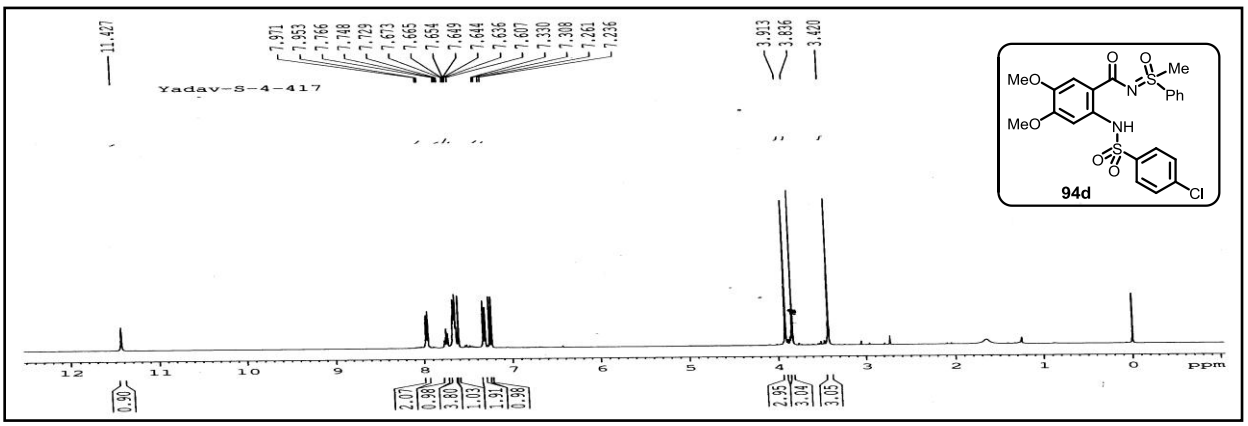
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7.665
7.654
7.649
7.644
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7.308
7.261
7.236
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3.836
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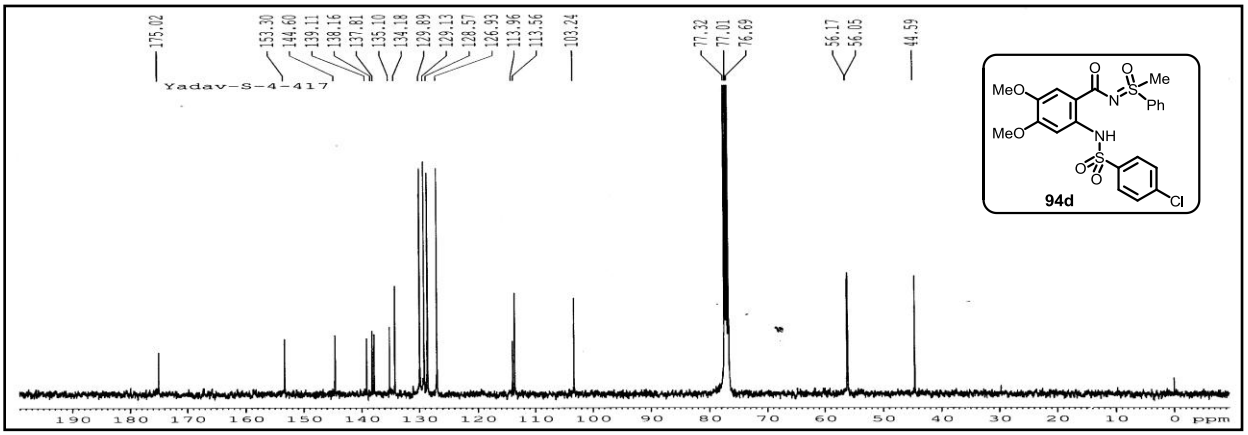
MeO
94d
Cl
ppm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77.01
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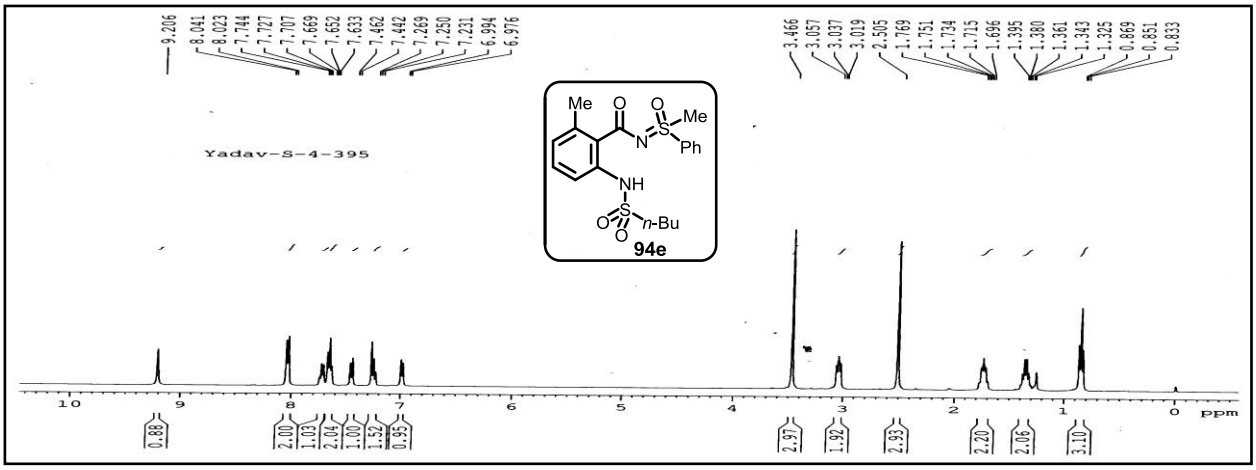
56.17
56.05
44.59
94d
ppm


Yadav-S-4-395
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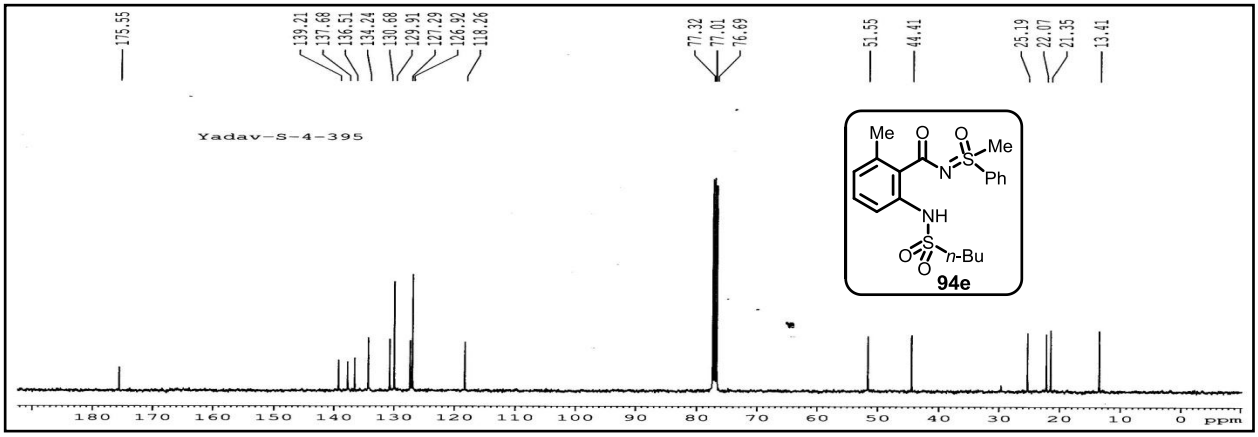
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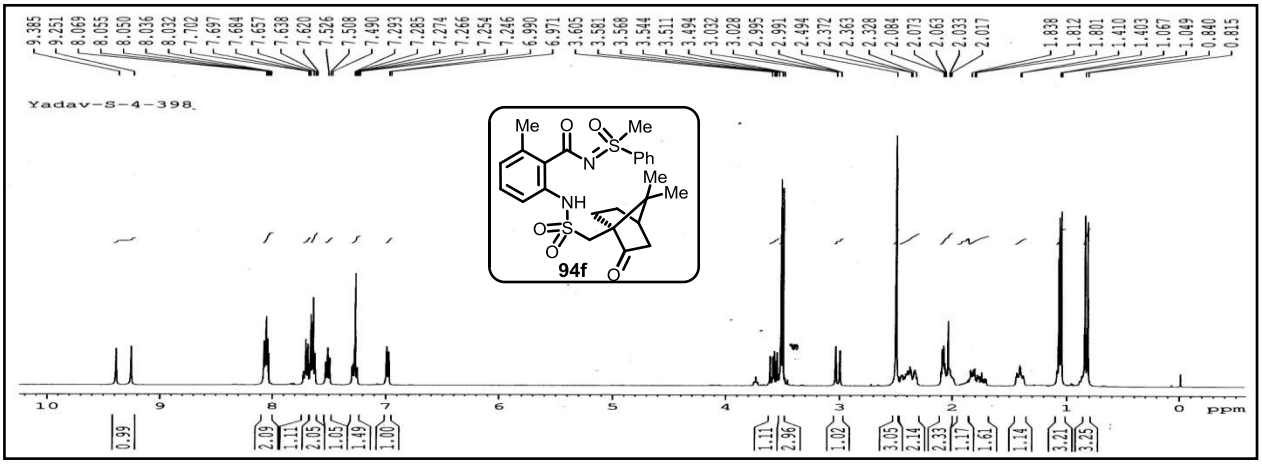
Yadav-S-4-398
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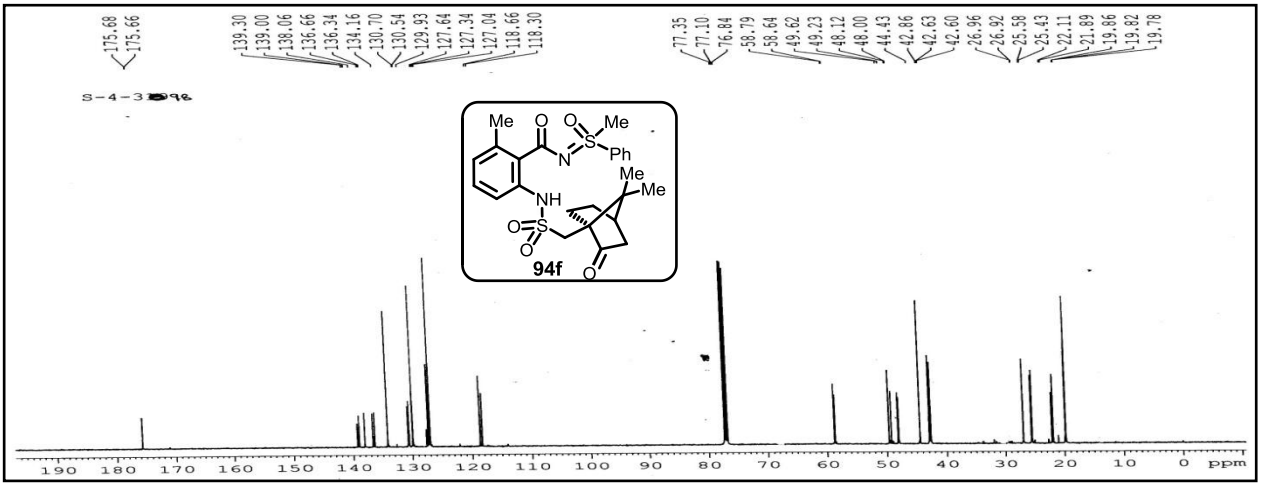
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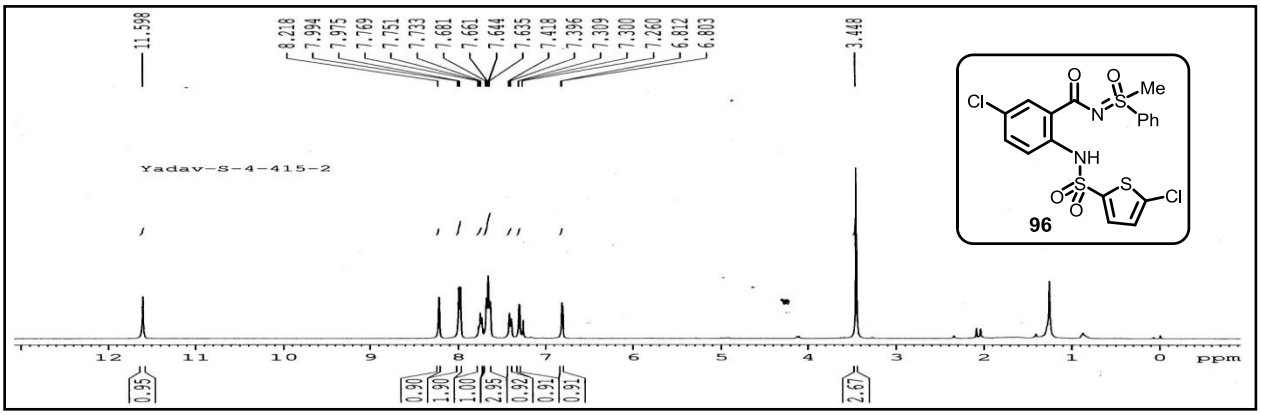
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6.803
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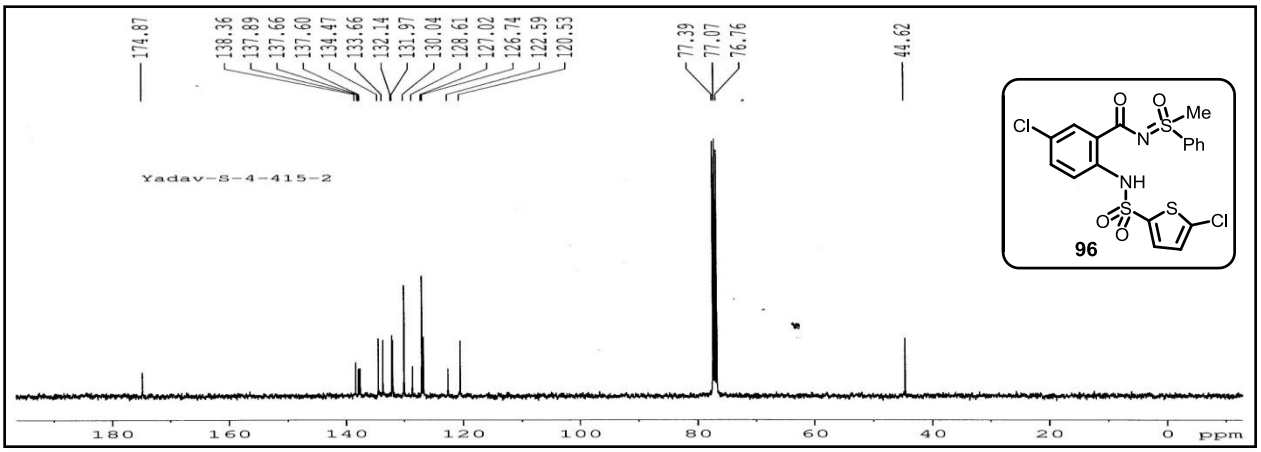
Yadav-S-4-415-2
96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76.76
44.62
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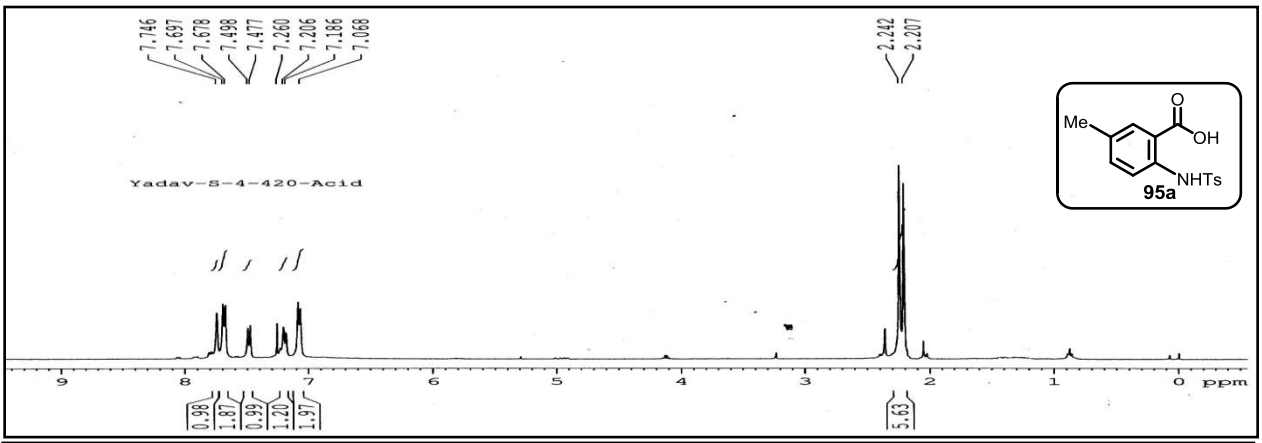
96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2.207
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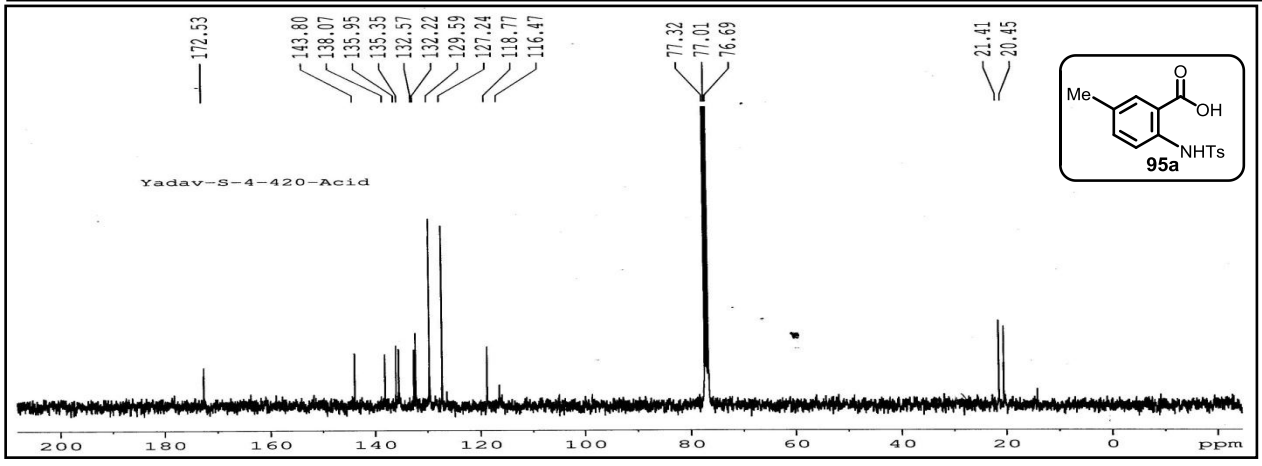
95a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143.80
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132.57
132.22
129.59
127.24
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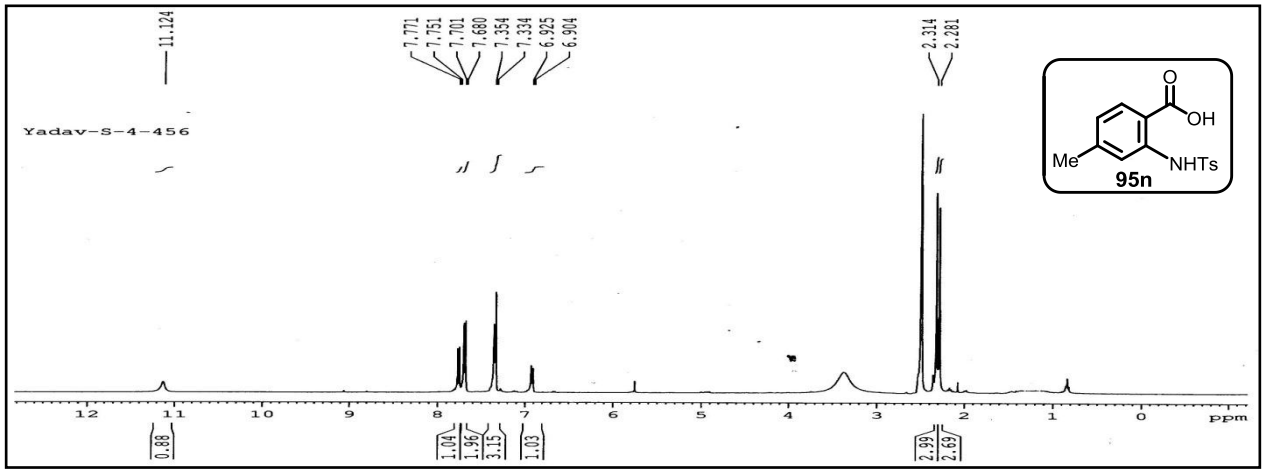
77.01
76.69
21.41
20.45
Yadav-S-4-420-Acid
95a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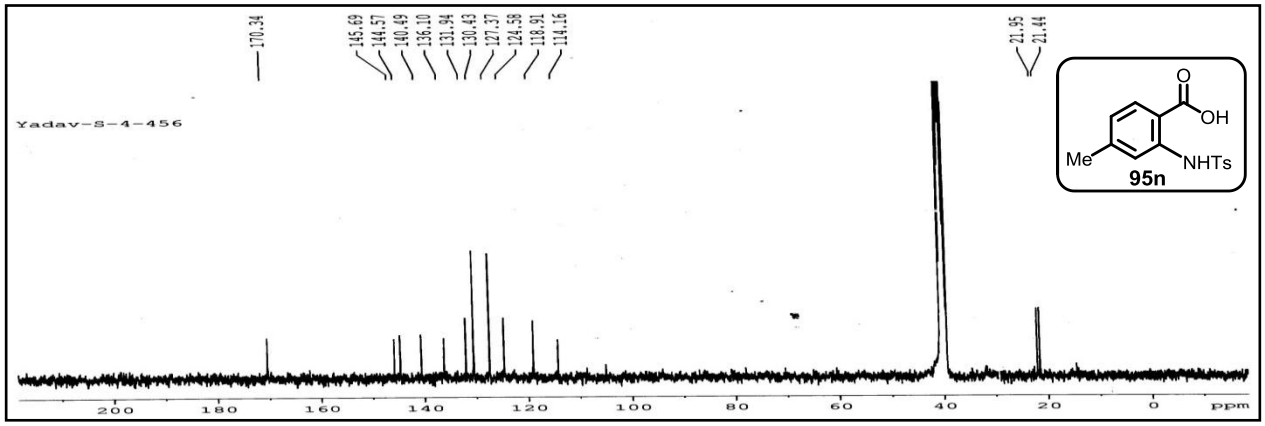
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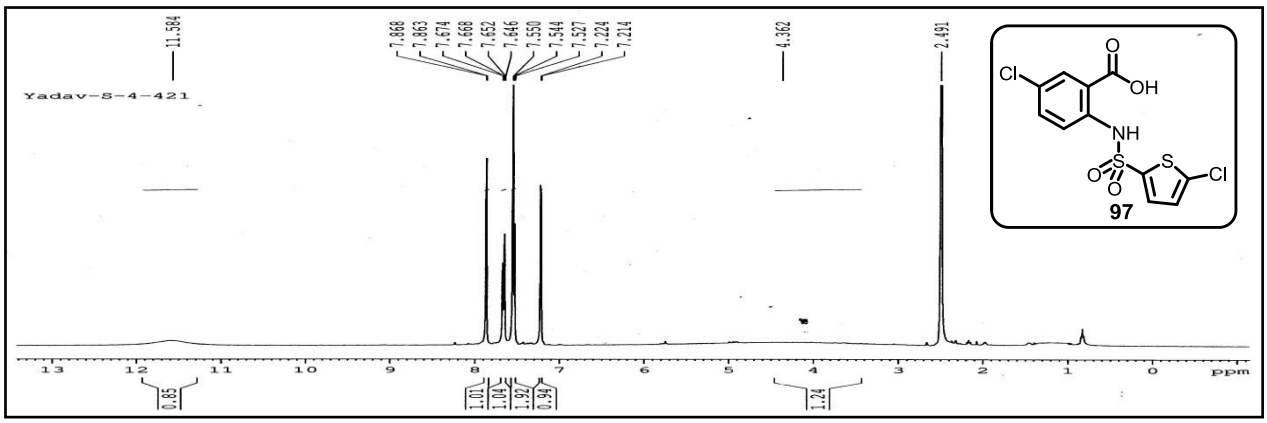
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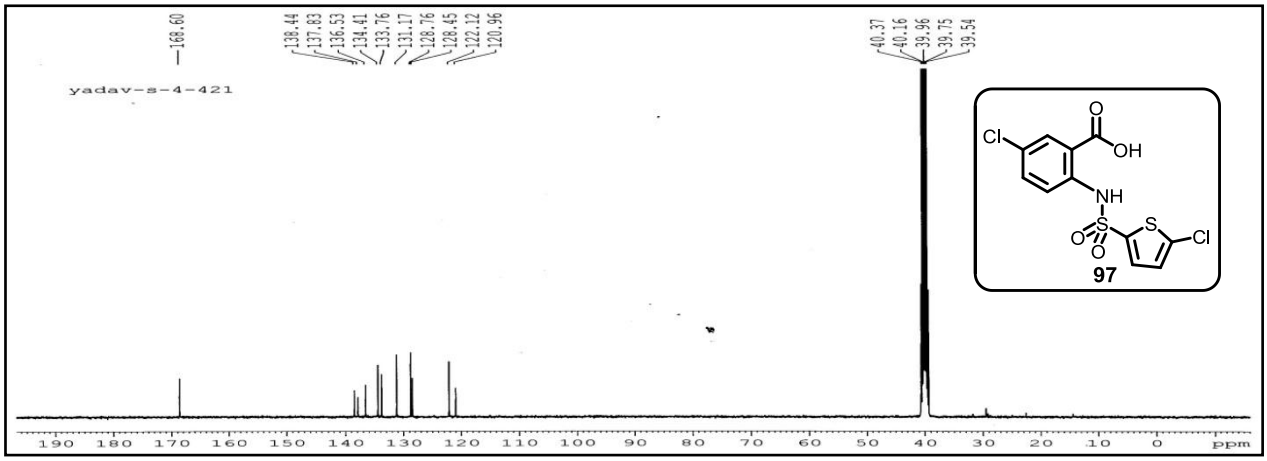
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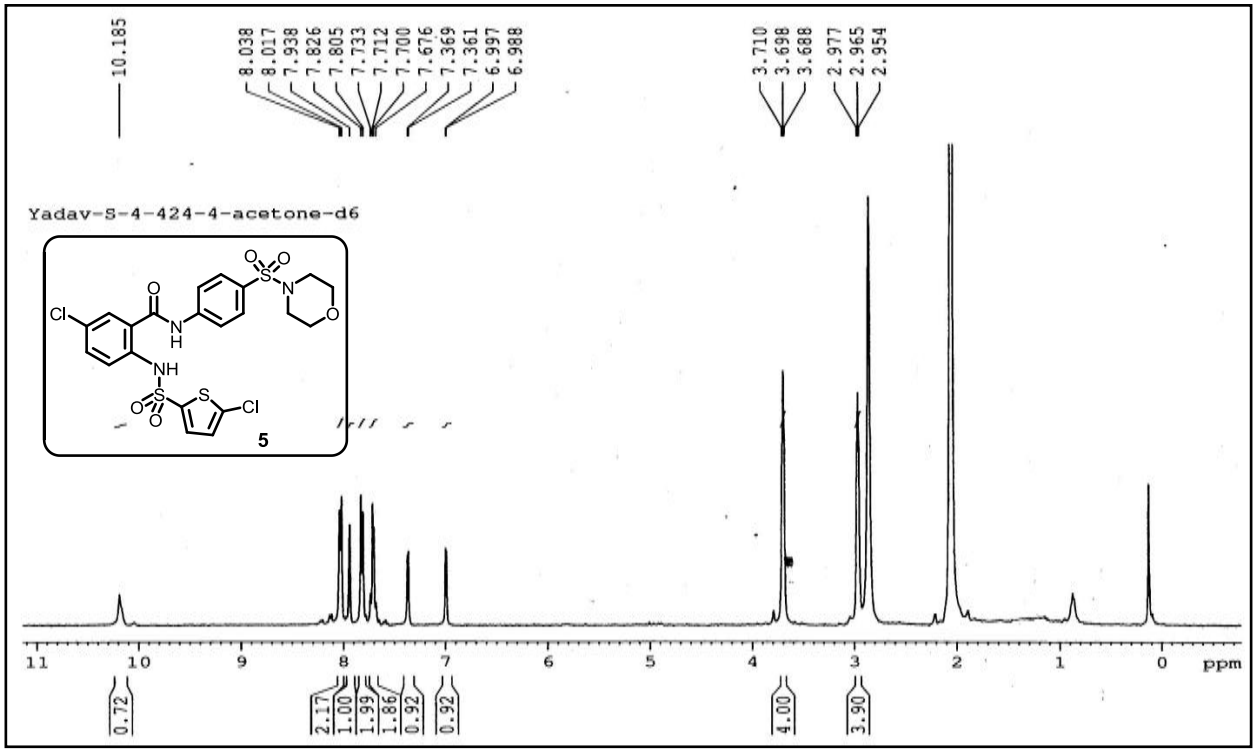
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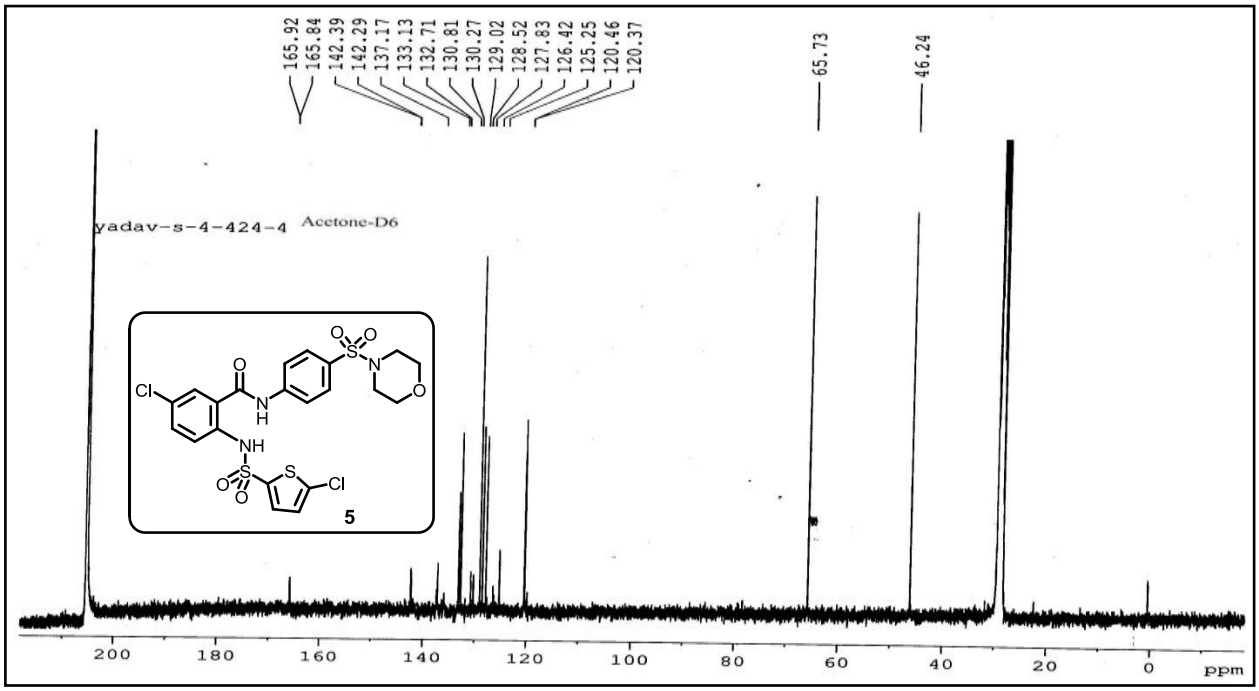
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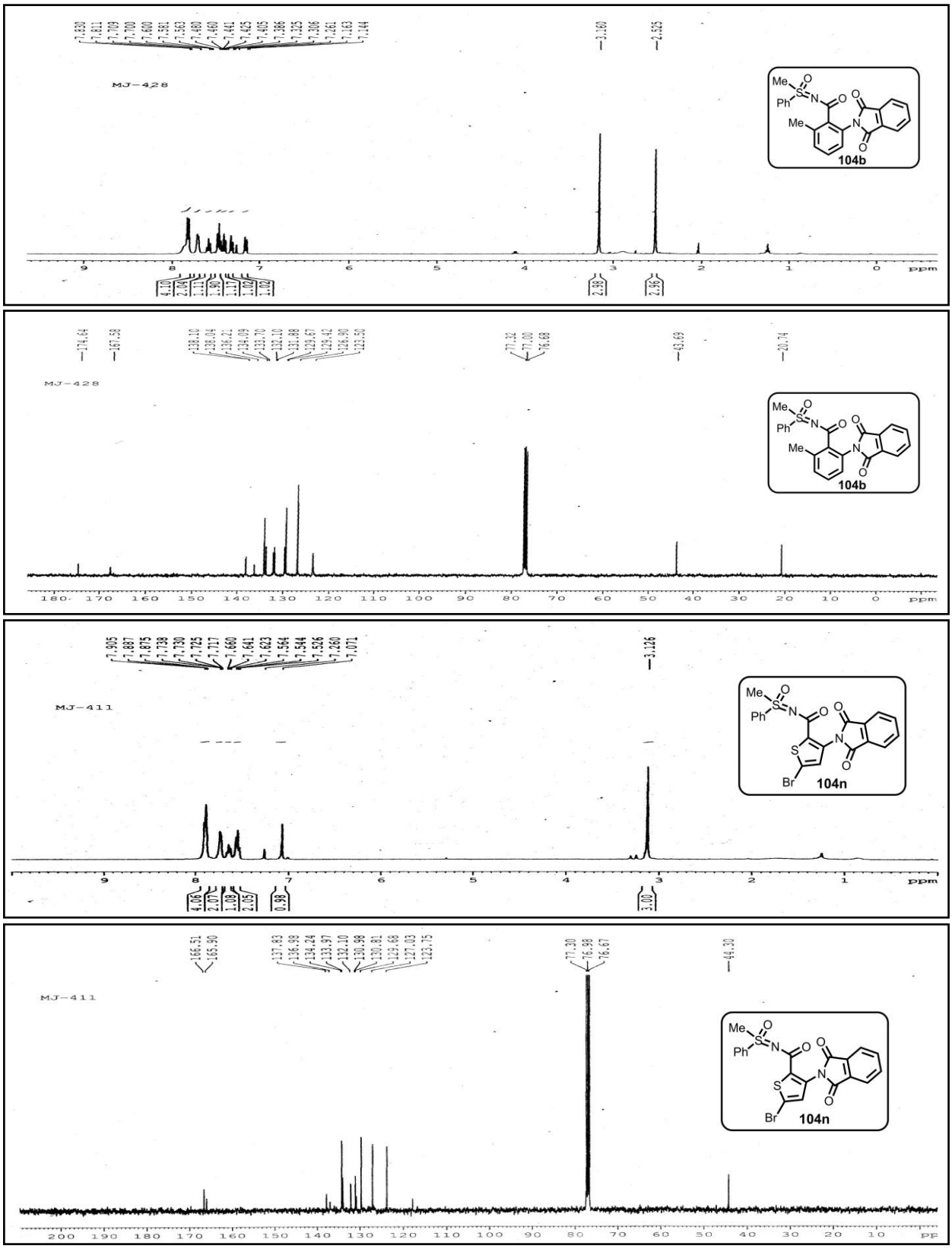
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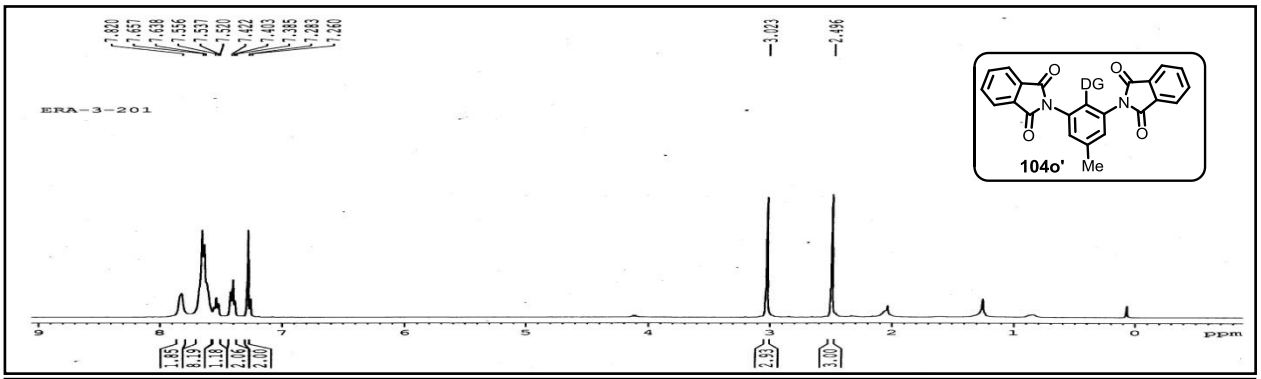
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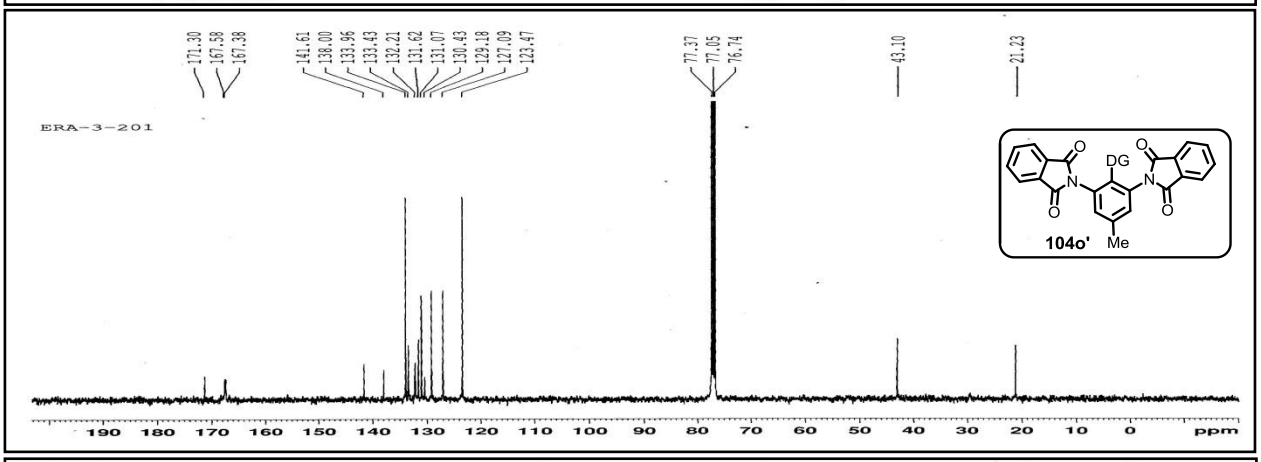
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129.18
127.09
123.47
77.37
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76.74
43.10
21.23
DG
Me
104o'
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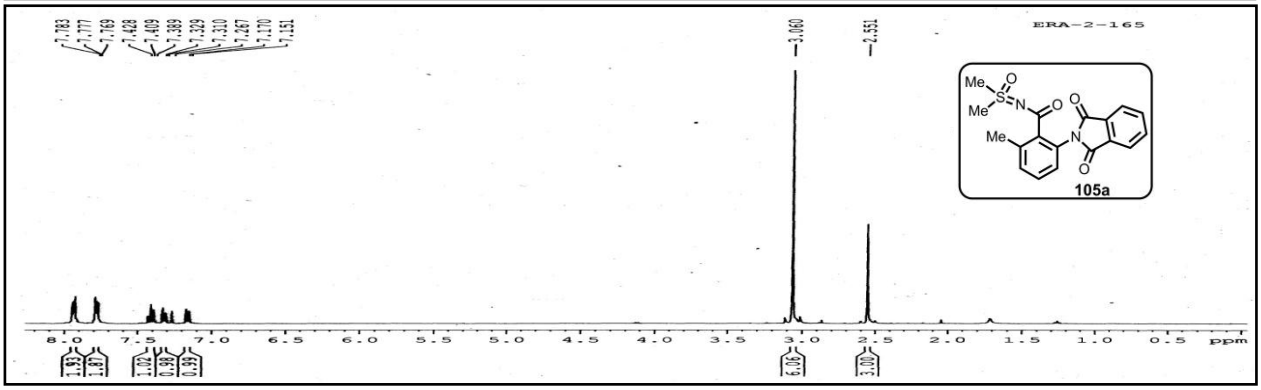
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3.060
2.551
Me
Me
Me
105a
1.92
1.80
1.04
0.94
0.89
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3.00
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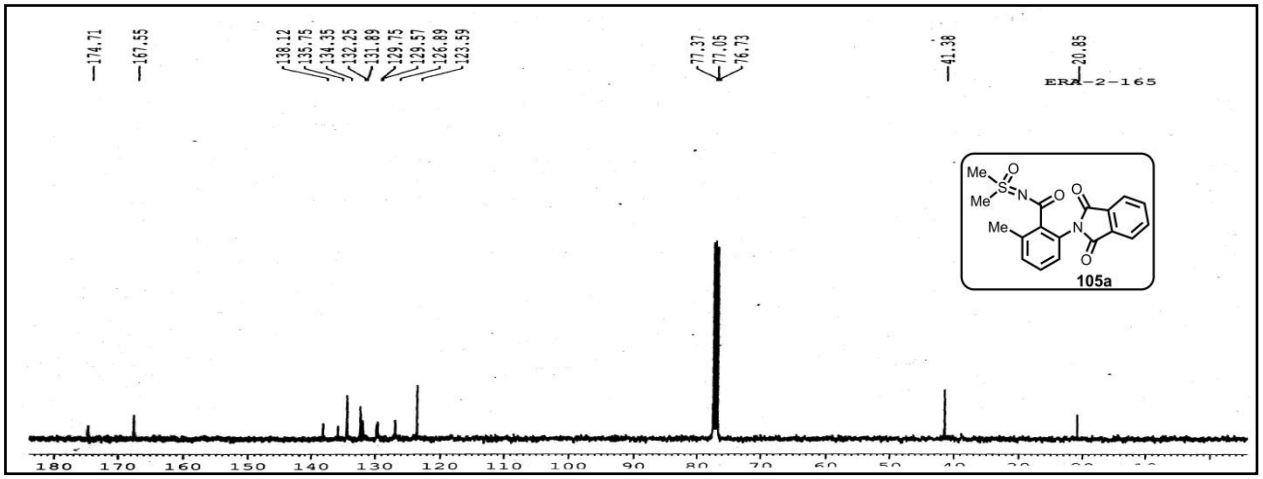
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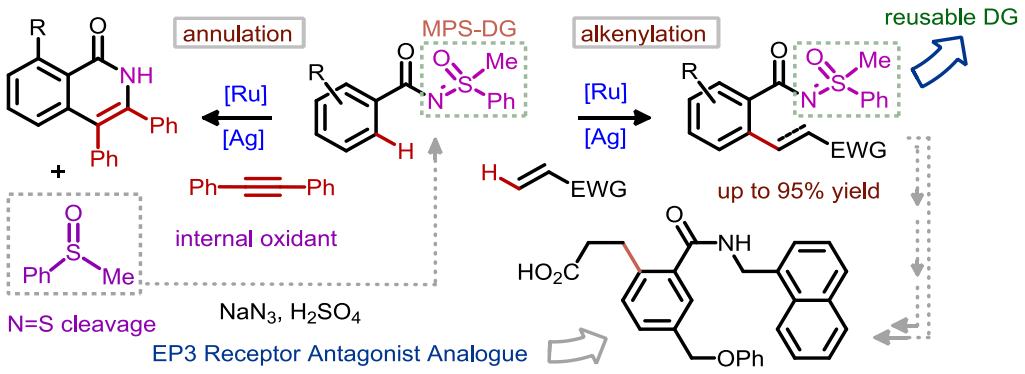
126.89
123.59
77.37
77.05
76.73
41.38
20.85
Me
Me
Me
105a
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

Sulfoximine-Directed Ruthenium-Catalyzed *ortho*-C–H Alkenylation of (Hetero)Arenes: Synthesis of EP3 Receptor Antagonist Analogue

4 Chapter

Abstract



The reusable sulfoximine directing group assisted Ru(II)-catalyzed chemo and regioselective *o*-C–H alkenylation of arenes and heteroarenes with acrylates, and α,β-unsaturated ketones/vinyl sulfone is shown. The N-aroyl sulfoximine undergo annulation with diphenylacetylene delivering isoquinolinones and methyl phenyl sulfoxide. The present protocol is successfully employed for the synthesis of EP3 receptor antagonist analogue.

Reference:

M. Ramu Yadav, Raja K. Rit, Majji Shankar, and Akhila K. Sahoo, *J. Org. Chem.* **2014**, 10.1021/jo5008465.

4.1. Introduction

Aromatic alkenes or styrene derivatives are important functional groups in organic chemistry, as these motifs are extensively used in the synthesis of biologically active and pharmaceutically important molecules. In addition, the alkene bearing extended π-conjugated molecular entities are broadly applicable in optical and electronic materials.[1] Moreover, the styrene derivatives can be transformed to diverse functionality; for instance: the hydrogenated acrylate derivative 3-(2-carbamoyl-phenyl)-propionic acid is a key structural component found in many biologically active and pharmaceutically important molecules (Fig. 4.1).[2]

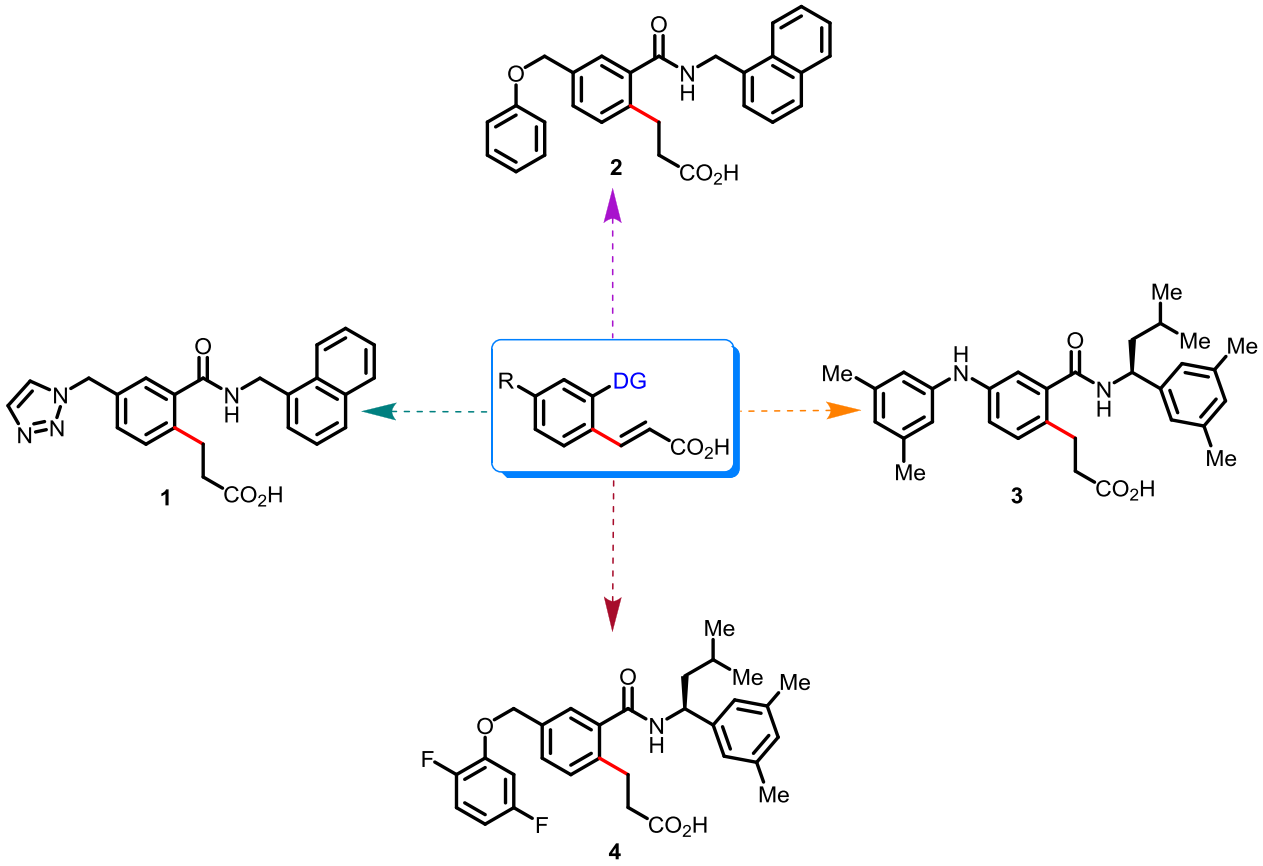
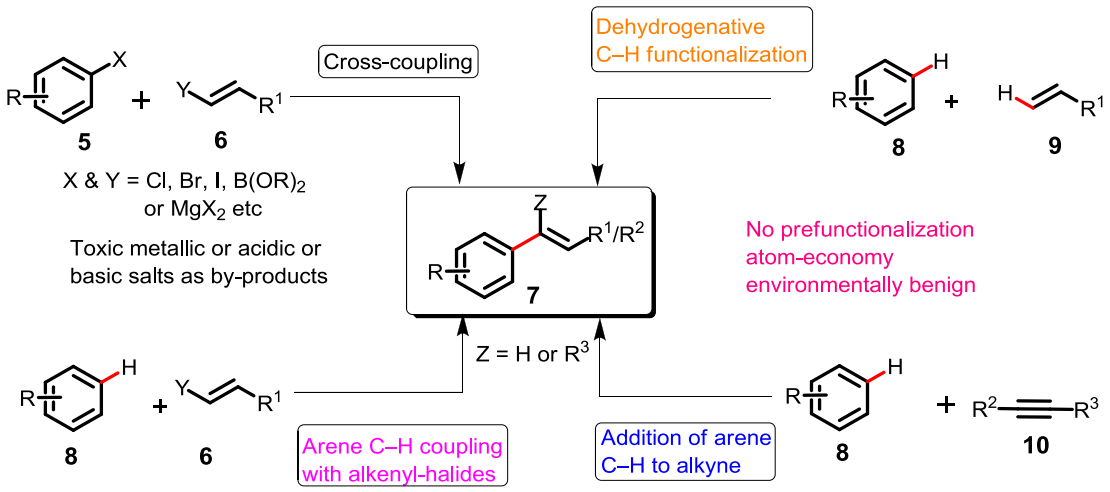


Figure 4.1: Biologically active molecules containing 3-(2-carbamoyl-phenyl)-propionic acid derivative

In general, the coupling between pre-activated aryl-electrophiles with alkenes under the influence of metal-catalysts construct aryl-alkene moiety; a unique strategy discovered by Mizoroki-Heck.[3] The broad synthetic potential of this reaction crowned Richard. F. Heck with noble prize in 2010. Despite, the wide applicability of this method, Heck reaction

exclusively requires the pre-activated aryl halides/tosylates and produce stoichiometric amount of environmentally hazardous acidic or basic salt by-products. Therefore, development of alternate method to Heck-coupling is desirable. Recently, transition-metal-catalyzed direct formation of carbon-carbon bond through dehydrogenative coupling of unactivated carbon-hydrogen (C–H) bonds has been emerged as an attractive alternate strategy to cross-couplings.[4] Thus, synthesis of styrene derivatives through C–H bond activation of arenes becomes widely recognized in terms of atom-efficiency and step-economy.[5] An overview of the olefination of arenes involving direct C–H bond functionalization is sketched in Scheme 4.1. The olefination processes primarily proceed either through (1) oxidative or cross-dehydrogenative coupling of alkenes,[5] (2) arene C–H bond addition to alkynes,[6] and/or (3) arene C–H coupling with alkenyl-halides and pseudohalides.[7]



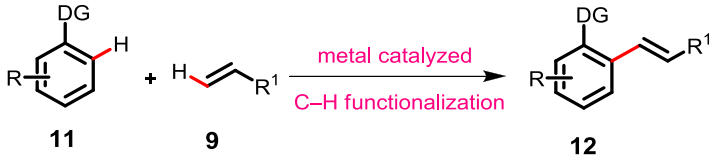
Scheme 4.1: Strategies for synthesis of styrene derivatives

4.1.1. Precedents for the Synthesis of *o*-C–H Alkenylation of Arenes

The transition-metal-catalyzed chelation assisted activation of arene C–H bond is a straightforward method broadly useful for the regioselective functionalization of unactivated C–H bond; one of the elegant manifestation of this strategy is expressed in the formation of chemo- and regioselective C–olefin bond. These strategies do not require pre-activated precursor, provides broad and ready access of a wide range of substrates. Therefore, the utility of modifiable and non-modifiable directing groups (DG's) for *o*-C–H alkenylation of

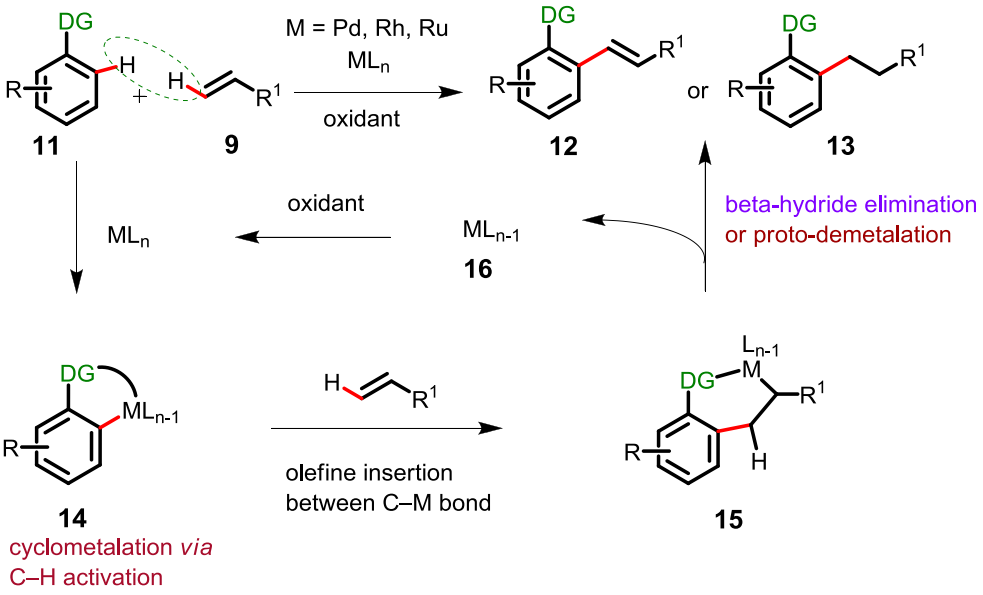
arenes have successfully been investigated under the influence of Pd(II),[5a,f] Rh(III)[8]and/or Ru(II)[9]-catalysts and oxidants.

4.1.2. Oxidative-Heck or Cross-Dehydrogenative Coupling of Alkenes



Scheme 4.2: Directing group assisted oxidative alkenylation of arenes

The transition-metal catalyzed oxidative Heck or cross-dehydrogenative couplings enables the intermolecular coupling between two un-activated C–H bonds instead of C–X bonds as shown in Scheme 4.2. Fujiwara and Moritani are the pioneers, engaged in the development of this reaction.



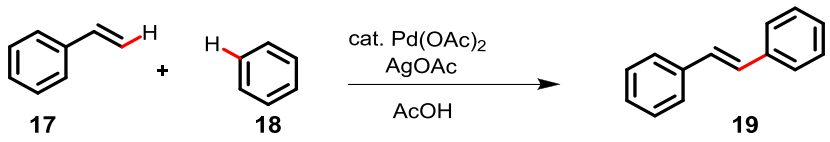
Scheme 4.3: Mechanism of oxidative alkenylation of arenes

A plausible mechanistic pathway for oxidative-Heck reaction is shown in Scheme 4.3.[9p] At first, the cyclometalated intermediate **14** is formed through the co-ordination of DG to transition-metal followed by activation of close-proximity C–H bond. Next, the resulting intermediate **14** coordinates to an olefin and subsequent migratory insertion of alkene furnishes the intermediate **15**. Finally, beta-hydride elimination affords the desired product

12, while producing the metal-catalyst. In the presence of oxidant, the active catalyst is regenerated with the completion of catalytic cycle. However, proto-demetalation provides the alkane products **13** from intermediate **15**.

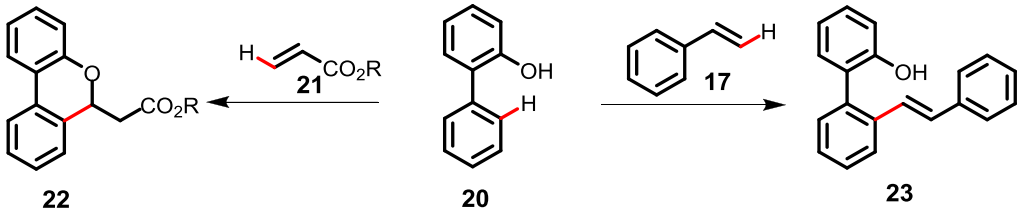
4.1.3. Palladium-Catalyzed Oxidative-Heck or Cross-Dehydrogenative Alkenylation of Arenes

In 1968, Fujiwara group reported an unprecedented oxidative Heck reaction for the synthesis styrene derivatives through C–H functionalization of arenes with alkenes in presence of $Pd(OAc)_2$ catalyst (Scheme 4.4).[3] The reaction proceeds in the presence of AgOAc oxidant in AcOH; these reagents are useful regenerating the active Pd(II)-catalyst. In spite of the significant development, the reaction suffers with broad scope and selectivity.



Scheme 4.4: Oxidative Heck reaction

Miura and coworkers described the palladium-catalyzed oxidative coupling of 2-phenylphenols (**20**) with olefins.[10] The reaction of activated acrylate esters **21** with **20** gave the cyclized product 6H-dibenzo[b,d]pyran derivatives **22**, whereas styrene **17** afforded 2'-alkenylation product **23** in moderate yield (Scheme 4.5).



Conditions: $Pd(OAc)_2$ (5.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (5.0 mol %), 4 Å MS, DMF, air, 120 °C

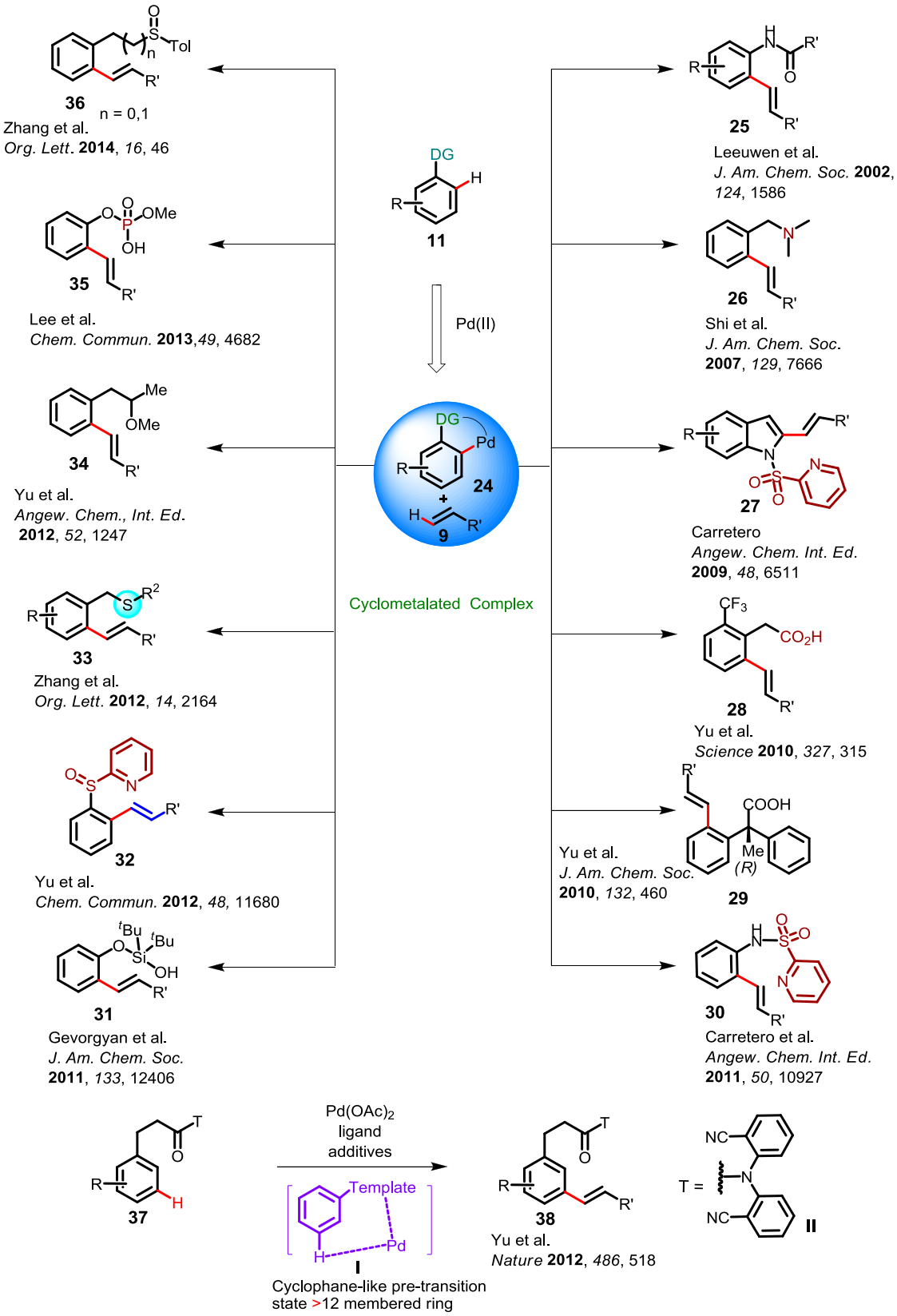
Scheme 4.5: Pd-Catalyzed oxidative coupling of 2-phenylphenols with olefins

The Pd-catalyzed chelation assisted oxidative alkenylation of arenes through C–H activation is briefly summarized in Scheme 4.6. Interestingly, Leeuwen et al. developed chelation assisted Pd-catalyzed highly chemo- and regioselective *o*-C–H olefination of anilide derivatives with acrylates to afford *o*-alkenylated products **25** (Scheme 4.6). The reaction was performed in acidic solvent at room temperature in presence of benzoquinone. The acetyl

group is crucial for *ortho* C–H functionalization, while benzoquinone ligand stabilizes Pd(II)-center. The possibility of electrophilic attack of π-system of the arenes to cationic $[PdOAc]^+$ species can't be ruled out. The readily accessible benzyl amines underwent dehydrogenative cross-coupling with activated olefins to produce desired alkenylated product **26**.

The Pd(II)-catalyzed C2 selective alkenylation of indoles and pyrroles using $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv) oxidant in DMA at 110 °C is reported. The C2 selectivity was controlled by the use of easily removable N-(2-pyridyl)sulfonyl directing group in **27**. The directing group was readily removed from the final product **27** with Zn metal in NH_4Cl. In contrast, regioselective C3 alkenylation of indole is achieved in the absence of directing group. The 2-pyridylsulfonyl group was proved efficient inserting alkenes on *o*-C–H bond of aniline, benzylamine, and phenethylamine derivatives in presence of Pd(II) catalyst. Yu and coworkers exploited the oxidative alkenylation of readily available phenyl acetic acid derivatives with olefins to furnish products **28**. The same group reported the more challenging enantioselective C–H alkenylation of phenylacetic acid derivatives to provide chiral alkenylation products **29** employing chiral mono-protected (*R)*-amino acid ligands. Gevorgyan et al. reported a novel and traceless silanol directing group assisted *o*-C–H alkenylation of phenol to furnish product **31**. The Pd(II)-catalyzed *ortho*-C–H olefination of arenes with electron-deficient alkenes and styrene-type olefins is reported with the aid of 2-pyridyl sulfinyl directing group. The directing group is efficient for sequential double C–H alkenylation to provide *di-ortho-alkenylated products*. Notably, the 2-pyridylsulfinyl group was readily removed from the C–H olefination products **32**. Recently, transition-metal catalyzed thioether-directed C–H activation of arenes with alkenes has been described. This method allows the synthesis of a variety of *o*-alkenylated products **33** with high efficiency. In addition, the tethered sulfoxide DG also shows high performance towards *o*- C–H alkenylation of arenes. Furthermore, ethers and mono-phosphoric acid motifs are also realized efficient directing groups in oxidative alkenylation of arenes.

The Yu group developed an end-on nitrile-based DG **II** to activate regioselective distal *meta* C–H bonds in **37** by overriding *ortho*-directing effect in **24**, electronic and steric biases present on arenes. Whereas the traditional DG's regioselectively activate *ortho*-C–H bond leaving *meta* and *para*-C–H unreactive. *The authors proposed participation of a 12 membered cyclic transition state* **I** *via the remote distal meta-C–H bond activation with Pd-catalyst.*

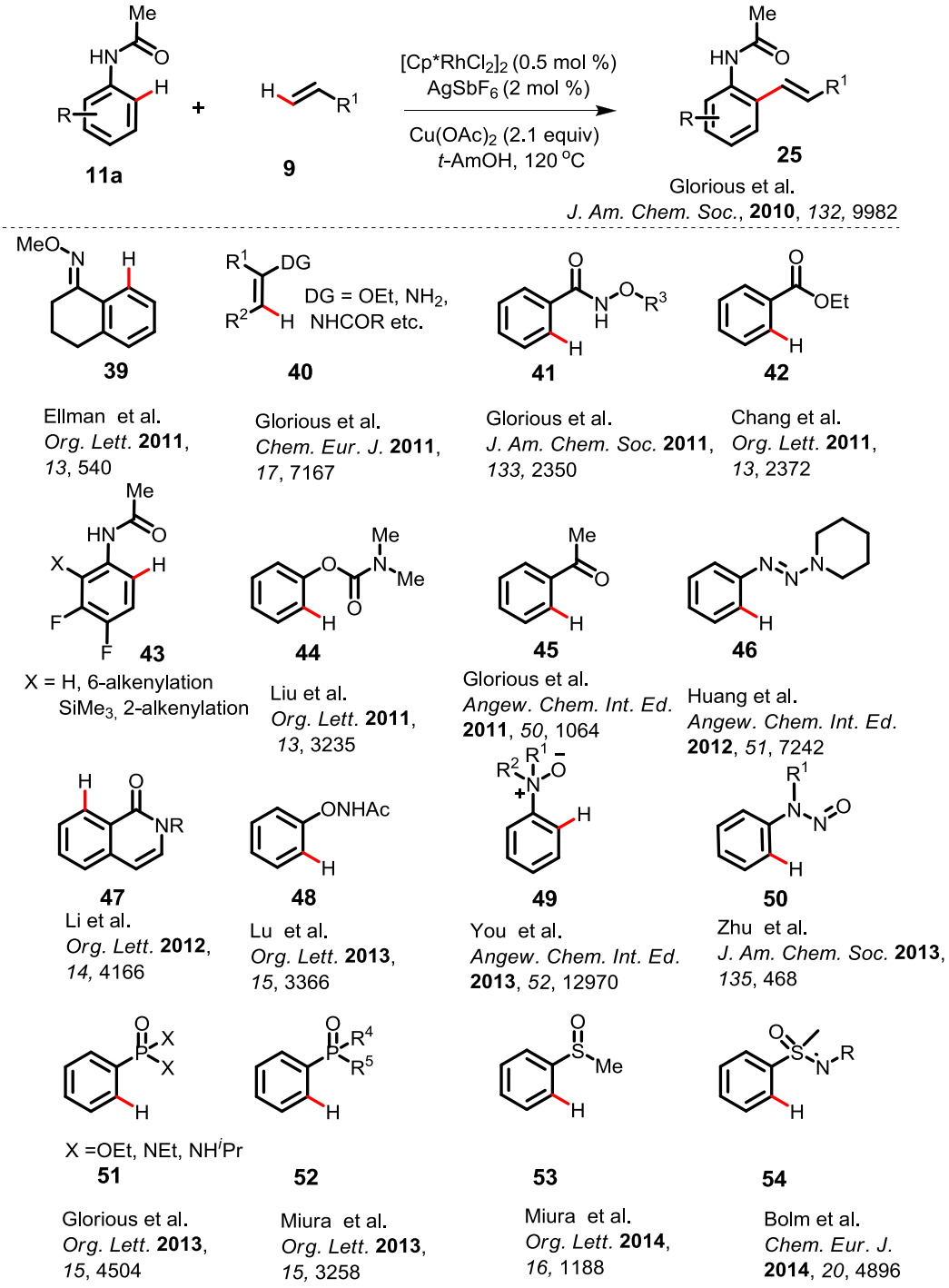


Scheme 4.6: Pd-Catalyzed chelation assisted oxidative coupling of arenes with olefins

4.1.4. Rhodium-Catalyzed Oxidative-Heck or Cross-Dehydrogenative Alkenylation of Arenes[8]

The Rh-catalyzed DG-assisted alkenylation of arenes is briefed in Scheme 4.7. Glorious and coworkers reported Rh(III)-catalyzed oxidative olefination of acetanilides **11a** (Scheme 4.7). The reaction condition exhibited broad functional group tolerance. The other directing groups oximines (**39**), *N*-methoxybenzamides (**41**), esters (**42**), carbamate (**44**), ketones (**45**), nitroso (**50**) etc were successfully employed for the Rh(III)-catalyzed oxidative olefinations.

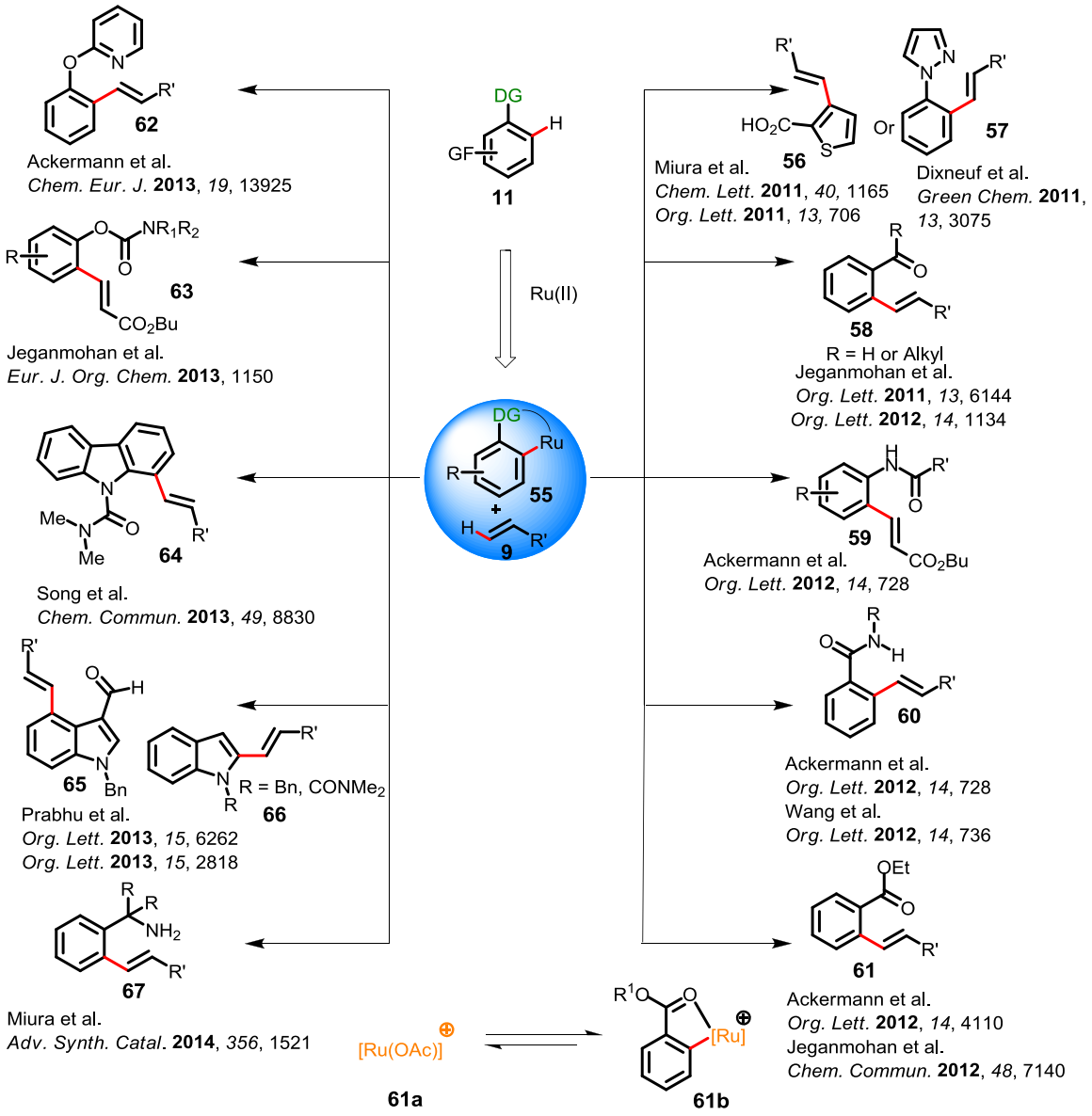
Ellman and co-workers reported oxime directed C–H olefination of arenes **39**. The sp^2 C–H bonds of arenes **40** and **41** are functionalized to C-olefin bond with the aid of chelating groups. In 2011, Chang et al. showed Rh(III)-catalyzed alkenylation of arenes **42** with the assistance of weakly coordinating ester directing group. The Rh(III)-catalyzed C–H activation/alkenylation of fluorinated acetanilide **43** and phenol carbamate derivatives **44** is achieved. Glorious et al. reported ketone directed regioselective *o*-alkenylation of arenes **45**. The use of traizene derivatives **46** for alkenylation is notable, as this group can easily be transformed to amide, free amine and iodo functionality with ease. The Rh(III)-catalyzed amide directed oxidative olefination N-protected isoquinolones furnished regioselective alkenylation at the 8-position of **47**. The O-NHAc (**48**), N-oxide (**49**), and nitroso (**50**) chelating groups have successfully been employed achieving the *ortho*-C–H functionalization with olefins; the internal oxidant of these DGs allows completing the catalytic cycle. Miura and Glorious groups have independently reported the oxidative olefination on phosphorous **51** & **52** and sulfur **53** directing group tethered arenes. More recently, Bolm et al. described C–H alkenylation of S-aryl ring in N-protected methyl phenyl sulfoximine **54**.



Scheme 4.7: Rh-Catalyzed directing group assisted oxidative coupling of arenes with olefins

4.1.5. Ruthenium-Catalyzed Oxidative-Heck or Cross-Dehydrogenative Alkenylataion of Arenes.

The chelation-assisted ruthenium-catalyzed C–H alkenylation of arenes is sketched in Scheme 4.8.



Scheme 4.8: Ru-Catalyzed directing group assisted oxidative coupling of arenes with olefins

In 2011, Miura group demonstrated Ru-catalyzed oxidative coupling of thiophene-2-carboxylic acids with alkenes to provide 3-vinylated heteroarene products **56** (Scheme 4.8). Importantly, the reaction condition is successfully applicable to benzothiophene-, benzofuran-, pyrrole-, and indole carboxylic acids for C–H olefination. Later, Miura and Dixneuf independently reported pyrazole directed oxidative olefination of arenes.

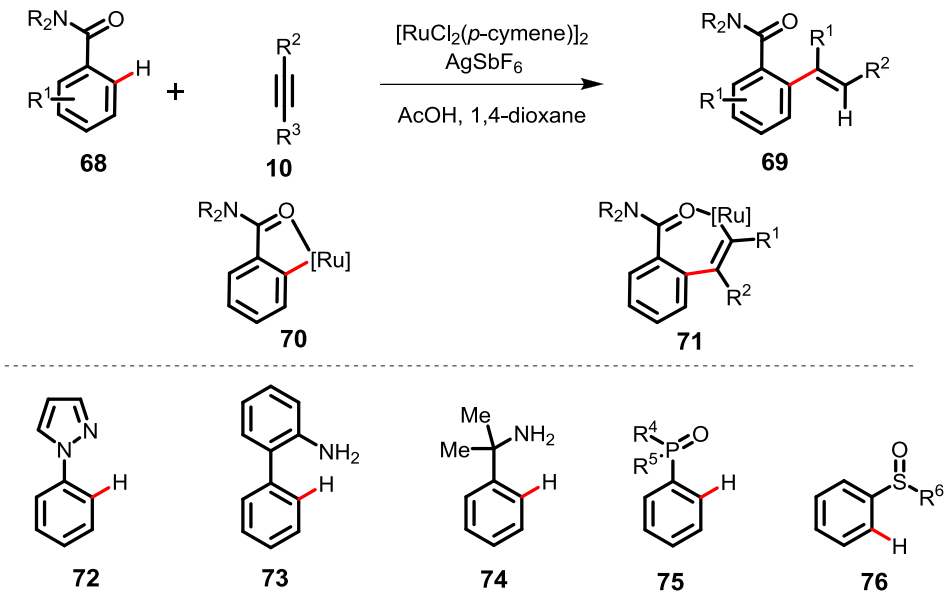
Recently, Jeganmohan group developed a Ru-catalyzed *ortho*-C–H functionalization of aromatic and heteroaromatic carbonyl compounds with alkenes to furnish styrene derivatives **58** in good to excellent yields. The developed catalytic system {[$RuCl_2$(*p*-cymene)]$_2$, $AgSbF_6$, and $Cu(OAc)_2.3H_2O$} gave oxidative Heck-type alkenylation products; while use of $RuH_2(CO)(PPh_3)_3$ catalyst produced Michael-type alkylation products. Similarly, Ackermann group demonstrated Ru-catalyzed oxidative olefination of acetanilide and benzamide derivatives.

Ackermann and Jeganmohan groups independently reported the cationic Ru(II)-catalyzed alkenylation of weakly coordinating aromatic esters with activated alkenes to furnish *o*-C–H alkenylated aromatic esters **61**. The authors revealed the reversible formation of acetate-assisted ruthenacycle **61b**. Despite having these interesting results, the *o*-substituted esters afford lower yields of the alkenylation products. The authors did not examine the alkenylation of heteroaryl esters.

To expand the synthetic potential of the Ru-catalyzed C–H olefinations, a variety of chelating group's pyrazole, 2-O-pyridyl, carbamate induced alkenylation of arenes has successfully been examined. A regioselective alkenylation of indole derivatives has been shown by Prabhu group. Miura and co-workers employed free 2,2-disubstituted benzylamines for *o*-C–H alkenylations.

4.1.6. Arene C–H Bond Addition to Alkynes

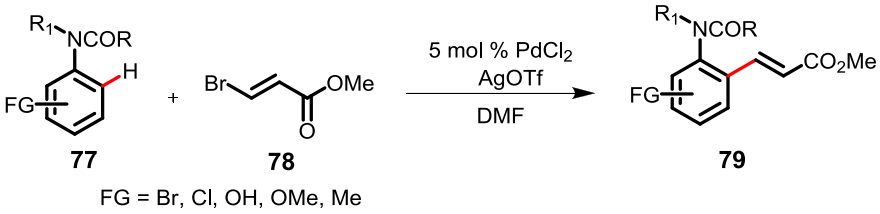
Recently, Miura group reported Ru-catalyzed regio- and stereoselective hydroarylation of alkynes **10** with benzamide **68** for the synthesis of tri-substituted alkenylation product **69** (Scheme 4.9).[6] The reaction initiates with the participation of cycloruthenation **70**, obtained through amide-directed *ortho*-C–H activation. Next, insertion of alkynes to **70** generates carbometalation intermediate **71**. Finally, protonolysis of **71** affords the desired product **69**. Subsequently, various chelating groups pyrazole (**72**), 2-aminobiphenyls (**73**), cumylamine (**74**), phenylphosphine oxides (**75)** and phenyl sulfoxides (**76**) enabled hydroarylation of alkynes has successfully been accomplished (Scheme 4.9).[6]



Scheme 4.9: Metal catalyzed directing group assisted arene C–H bond addition to alkyne

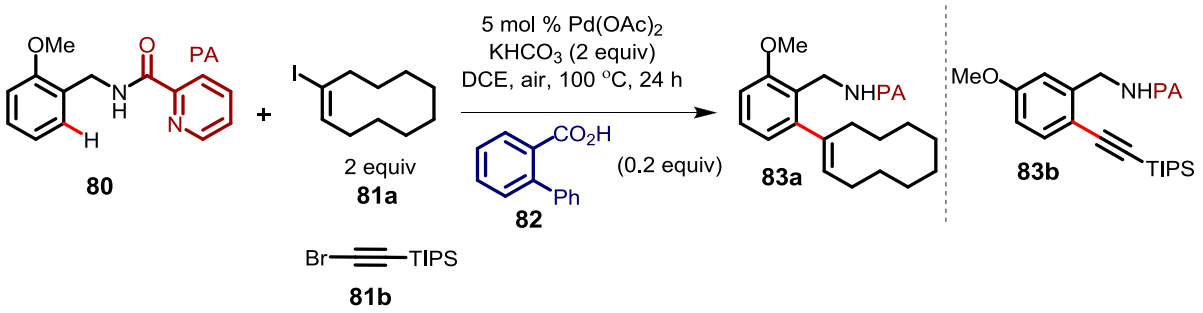
4.1.7. Coupling with Alkenyl-Halides or Pseudohalides

Daugulis group reported palladium catalyzed coupling between acetanilide derivatives **77** and haloacrylates **78** through C−H activation (Scheme 4.10).[7a] Interestingly, single oxidation state of Pd-metal is presumably involved in this transformation.



Scheme 4.10: Pd-Catalyzed anilide assisted *o*-C–H alkenylation of arenes with bromo-acrylates

Chen and co-workers synthesized *ortho*-C–H alkenylation and alkynylation benzylamine products **83a** and **83b** from picolinamide tether derivative **80** and cyclic vinyl iodides (**81a**), or acetylene bromide (**81b**) through Pd-catalyzed C(sp^2)–H functionalization (Scheme 4.11).[7c] Interestingly, the use of *ortho*-phenyl benzoic acid (*o*PBA, **82**) instead of PivOH promotes the reactivity and produce better yield of the product. The role of *o*PBA in this reaction remains elusive.



Scheme 4.11: Pd-Catalyzed picolinamide assisted *o*-C–H alkenylation and alkynylation of benzylamine substrates with vinyl iodides

A Rh(III)-catalyzed direct olefination of benzamide derivative **84** with allyl acetate **85** through C–H bond activation selectively furnished the desired *trans*-alkenylation product **86** (Scheme 4.12).[7d]

Scheme 4.12: Rh-Catalyzed amide assisted *o*-C–H alkenylation of arenes with allyl acetate

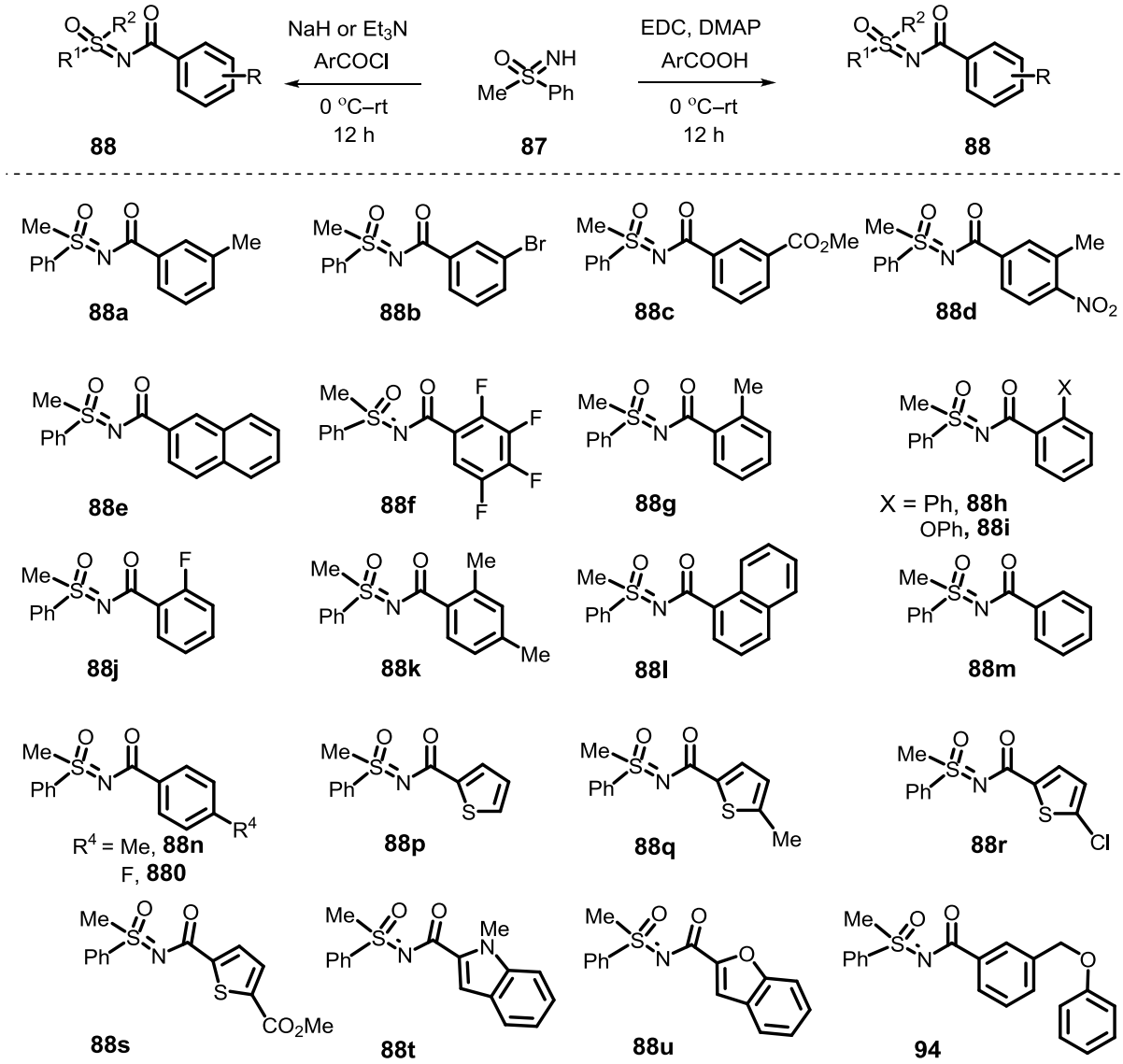
4.2. Motivation and Design Plan

The use of inexpensive, air stable Ru(II)-catalysts under the coordination ability of reusable DG for the *o*-C–H olefination of arene would promote widening the synthetic utility of this approach.[9] Dixneuf,[9a,c,n] Miura,[9f,o,s] Ackermann,[9e,h,m,p] Jaganmohan[9d,j,q], and others have contributed significantly in the development of Ru-catalyzed modifiable/non-modifiable DG assisted *o*-C–H alkenylation of arenes. We have recently demonstrated sp^2 C–H oxidation and amidation of arenes with the aid of reusable S-methyl-S-phenylsulfoximine (MPS) DG (Chapter 2 and 3 in this thesis).[11,12] To further broaden the synthetic utility of reusable MPS-DG, we envisioned performing alkenylation on unactivated arenes under the influence of robust Ru-catalyst; the results are detailed in this chapter. The application of the current method for the synthesis of EP3 antagonist analogue is also shown.

4.3. Results and Discussion

4.3.1. Synthesis of Precursors

Following the known procedures, various *N*-aroyl derivatives of sulfoximines were prepared (Scheme 4.13). The reaction of sulfoximines with sodium hydride or triethylamine base in DCM solvent at 0 °C followed by quenching the reaction with corresponding benzoyl chlorides gave a wide range of the *N*-aroylated sufoximines in above 80% yields.



Scheme 4.13: Preparation of *N*-aroyl sulfoximines

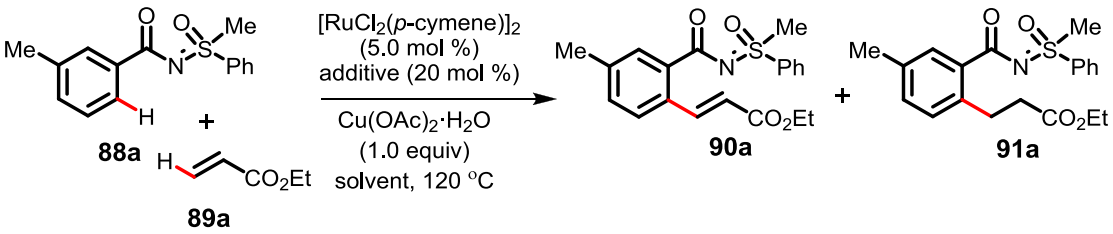
The EDC·HCl coupling protocol was employed accomplishing the *N*-aroyl derivatives of sulfoximines from benzoic acid derivatives (the procedure is detailed in the experimental

section). The preparation of the following compounds **88a**, **88c–e, 88g–h,** and **88j–r** is discussed in Chapter 2 and 3 (page no. 39 & 133).

4.3.2. Reaction Optimization

To begin with, the dehydrogenative alkenylation of *N*-(*m*-methylbenzoyl)-MPS (**88a**) with ethyl acrylate (**89a**) was investigated under the influence of Ru(II)-catalyst, silver salts, $Cu(OAc)_2 \cdot H_2O$, and solvents (Table 4.1). The reaction between **88a** and **89a** with 5.0 mol % $[RuCl_2(p\text{-cymene})]_2$ and $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv) in 1,2-dichloroethane (DCE) at 120 °C

Table 4.1: Optimization of reaction conditions[a]



entry	additive (20 mol %)	solvent	yield (%)[b] **90a**	**91a**
1	-	$ClCH_2CH_2Cl$	<5	-
2	$AgSbF_6$	$ClCH_2CH_2Cl$	90	<10
3	$NaPF_6$	$ClCH_2CH_2Cl$	74	20
4	KPF_6	$ClCH_2CH_2Cl$	37	-
5	$NaBF_4$	$ClCH_2CH_2Cl$	22	-
6	**$AgBF_4$**	**$ClCH_2CH_2Cl$**	**92 (84)[c]**	**-**
7	$AgBF_4$	$ClCH_2CH_2Cl$	54[d]	-
8	$AgBF_4$	CH_2Cl_2	42	14
9	$AgBF_4$	$CHCl_3$	85	-
10	$AgBF_4$	toluene	21	-
11	$AgSbF_6$	1,4-dioxane	43	25[d,e]

[a]Reaction conditions: **88a** (0.1 mmol), **89a** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv), solvent (0.5 mL), 24 h. [b]Crude ^1H NMR conversion based on of the ratio of starting material to product. [c]**88a** (0.5 mmol), $ClCH_2CH_2Cl$ (2.0 mL) was used, isolated yield in parenthesis. [d]In the absence of $Cu(OAc)_2 \cdot H_2O$. [e]AcOH (1.0 equiv) was used. The experiments in dichloromethane, chloroform, and toluene were run at 120 °C in a sealed tube.

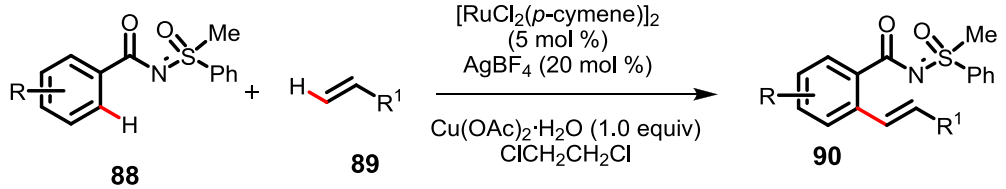
produced a trace amount of *N*-[(*E*)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)-5-methyl-benzoyl]-MPS (**90a**), regioselectively functionalizing the sterically less hindered *o*-C–H bond of **88a**. The yield of **90a** was enhanced to 90% when $AgSbF_6$ employed; formation of a minor amount of hydroarylation product **91a** was also observed by ^{1}HNMR (entry 2). Screening of $NaPF_6$, KPF_6, and $NaBF_4$ salts in this reaction turned unsatisfactory (entries 3–5). The $AgBF_4$

was equally efficient, delivering **90a** in 92% yield (entry 6). To our delight, we observed the formation of *o*-C–H *E*-alkenylation products. The absence of $Cu(OAc)_2 \cdot H_2O$ led to lower yield of **90a** (entry 7). Upon careful scrutiny of various solvents, DCE was found best (entries 8–10). The reaction of **88a** with **89a** under Miura conditions [$\{RuCl_2(p\text{-cymene})\}_2$ (5.0 mol %), $AgSbF_6$ (20 mol%), AcOH (1.0 equiv), 1,4-dioxane] led to the formation of **90a** in only 43% yield (entry 11). Thus, the condition shown in entry 6, Table 4.1 was realized optimum for the sulfoximine directed oxidative *o*-C–H alkenylation of arenes in **88a**. To our disappointment, **88a** did not undergo alkenylation with unactivated alkene (e.g., styrene) under the present reaction conditions.[13]

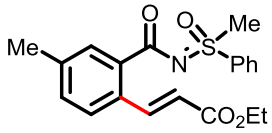
4.3.3. Scope of the Reaction

The optimized condition was explored examining the scope and generality of *o*-C–H alkenylation of arenes **88** with activated olefins **89**. The results are summarized in Table 4.2. The less hindered *o*-C–H bond in electron-rich and deficient *m*-substituted arenes selectively alkenylated, affording **90a–d** in 71–86% yield; the Br, ester, and $–NO_2$ groups did not affect the reaction outcome. The ester group did not assist the *o*-C–H alkenylation in **88c**,[9p-q] witnessing the effective directing group ability of the sulfoximine moiety. The olefinated product **90e** was exclusively obtained from β-naphthyl substrate **88e** in good yield. The alkenylation was effectively conducted between **88a** and other electron-deficient alkenes; methyl acrylate (**89b**), *n*-butyl acrylate (**89c**) and phenyl vinyl sulfone (**89d**) readily coupled with **88a** producing the corresponding *o*-C–H alkenylation products **90f–h** in good to excellent yields. The oxidative alkenylation of *m*-substituted electron-rich and -poor substrates **88a** and **88c** with ethyl vinyl ketone (**89e**) led to **90i** and **90j** in 70% and 72% yield, respectively. Even more electron deficient tetrafluoro substituted arene **88f** was compatible, furnishing **90k** and **90l** in 79% and 81% yield, respectively. In some cases, the formation of minor amount of hydroarylation product along with the desired alkenylation compound was observed in ^1H NMR; the ratio of alkenylation and hydroarylation products is shown in parenthesis.

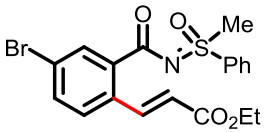
Table 4.2: *o*-C–H Alkenylation of *meta*- and fluoro substituted *N*-aroyl derivatives[a,b]



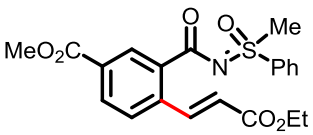
R^1 = CO_2Et (**89a**), CO_2Me (**89b**), $CO_2{}^nBu$ (**89c**), SO_2Ph (**89d**), COEt (**89e**)



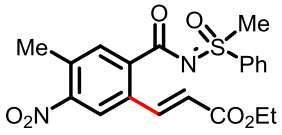
90a, 84%[c]



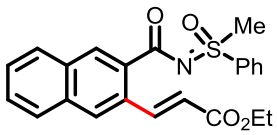
90b, 71%[c]



90c, 79% (5:1)[d]

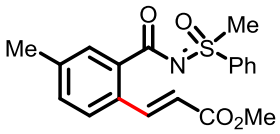


90d, 86% (10:1)[d]

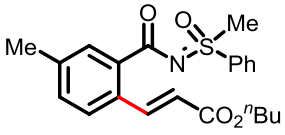


90e, 83% (6:1)[d]

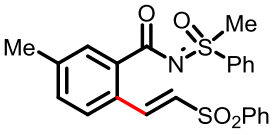
Different electron deficient alkenes



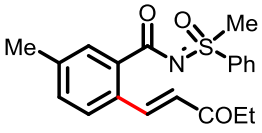
90f, 79%



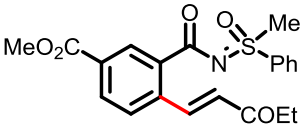
90g, 84%[c]



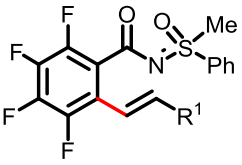
90h, 90%[c]



90i, 70%



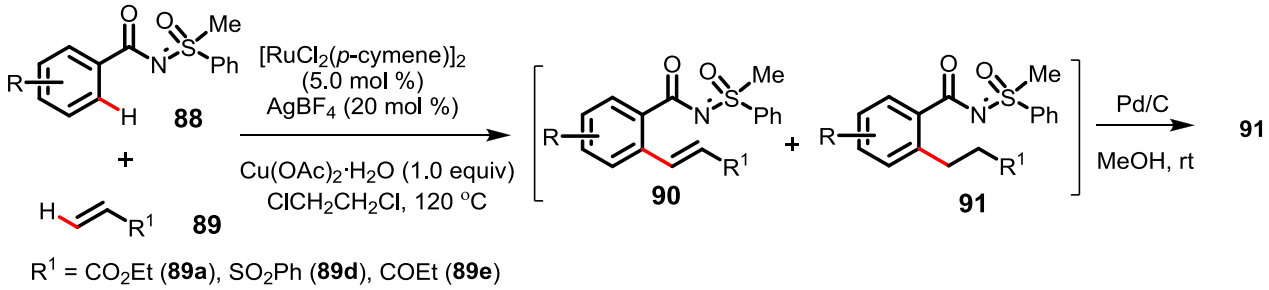
90j, 72% (4:1)[d]

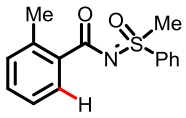
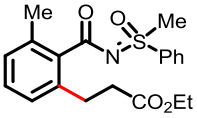
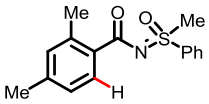
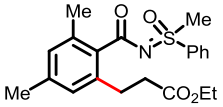
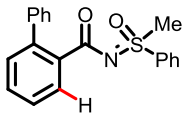
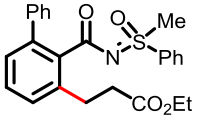
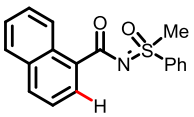
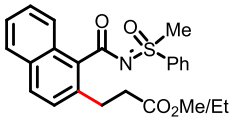
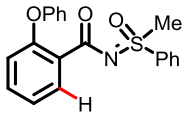
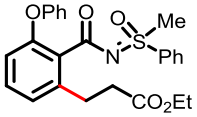
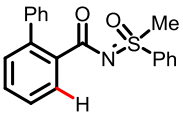
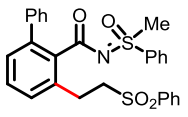
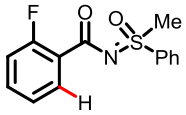
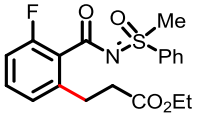
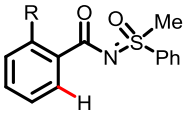
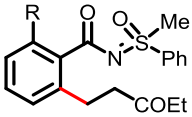


R^1 = CO_2Et, **90k**, 79% (10:3)[d]
SO_2Ph, **90l**, 81% (6:1)[d,e]

[a]Reaction conditions: **88** (0.5 mmol), alkene **89** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgBF_4$ (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv), $ClCH_2CH_2Cl$ (2.0 mL), 120 °C for 24 h. [b]Isolated yields. [c]Minor amount of hydroarylation product (<5%) observed by ^1H NMR; the corresponding alkenylation product **90** is ~95% pure. [d]Ratio of alkenylation and hydroarylation product observed by ^1H NMR; in case of **90l**, ratio is detected by ^{19}F NMR. [e]**88f** (0.15 mmol) was employed.

Table 4.3: Alkylation of *o*-substituted arenes[a,b]



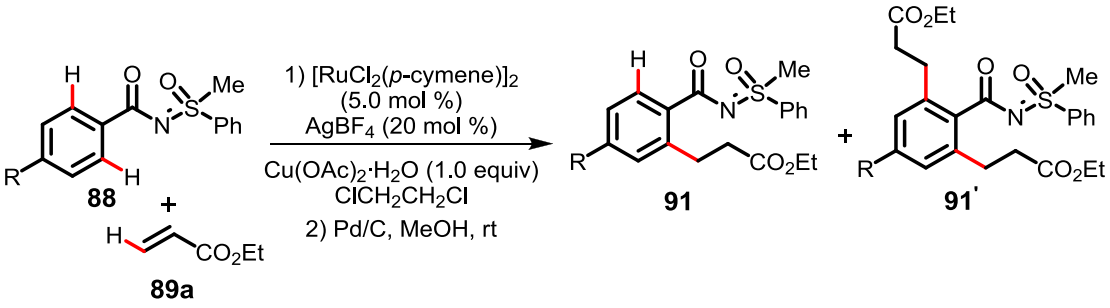
entry	88	90:91	91	entry	88	90:91	91
1		1:2		5		1:3	
	88g		**91b**, 80%		**88k**		**91f**, 78%
2		2:1		6		1:2	
	88h		**91c**, 87%		**88l**		**91g**, 73% (14:3)[c]
3		2:1		7		4:3	
	88i		**91d**, 74%		**88h**		**91h**, 82%
4		2:3					
	88j		**91e**, 70%	8	R = OPh, **88i**	2:1	**91i**, 61%
				9	R = F, **88j**	3:1	**91j**, 64%

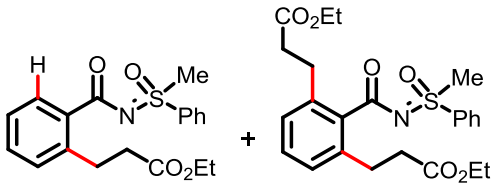
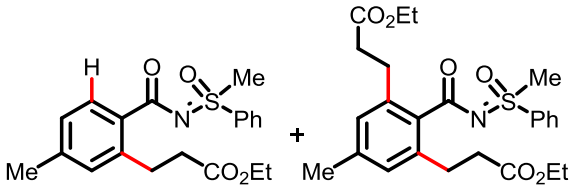
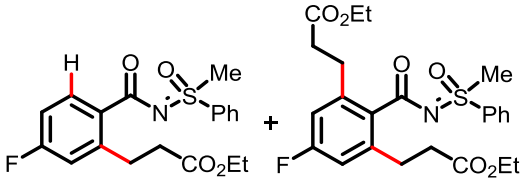
[a]Reaction conditions: **88** (0.5 mmol), alkene **89** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgBF_4$ (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv) and $ClCH_2CH_2Cl$ (2.0 mL). [b]Isolated yields. [c]**88l** (0.32 mmol) was employed.

The coupling of *o*-substituted *N*-aroyl-MPS **88** with **89** was next investigated (Table 4.3). The reaction between *N*-(*o*-methylbenzoyl)-MPS (**88g**) and **89a** surprisingly produced a major amount of *o*-hydroarylation product **91b** over the desired alkenylation compound **90m** (by ^{1}H NMR), suggesting the occurrence of proto-demetallation over β-hydride elimination.[14] The inseparable hydroarylation and alkenylation products render the purification extremely difficult. To validate product isolation ease, the non-purified mixture of compounds was subjected to hydrogenation with Pd/C in methanol, converting the alkenylation product to the hydroarylation compound with the survival of MPS-DG.[15] Following these procedures, a

wide variety of *o,o′*-disubstituted *N*-aroyl MPS products **91b–j** were synthesized in overall good yields (Table 4.3). The *o*-alkenylation followed by hydrogenation of *o*-Me/Ph/OPh substituted compounds **88g–i** with **89a** furnished **91b–d** in 74–87% yield. The fluoro-bearing product **91e** was isolated in 70% yield. The desired 2-alkyl-4,6-dimethyl derivative **91f** was obtained from **88k** in good yield. The α-naphthyl substrate **88l** reacted well, affording 73% of product **91g**. The alkenylation and hydrogenation sequence on **88h** with phenyl vinyl sulfone

Table 4.4: *o*-C–H Alkylation of unsubstituted and *p*-substituted arene derivatives[a,b]



entry	**88**	**91/91′**
1	R = H, **88m**	 **91k** 69% (1:1)[b] **91′k**
2	R = Me, **88n**	 **91l** 71% (1:1)[b] **91′l**
3	R = F, **88o**	 **91m** 83% (9:4)[b] **91′m**

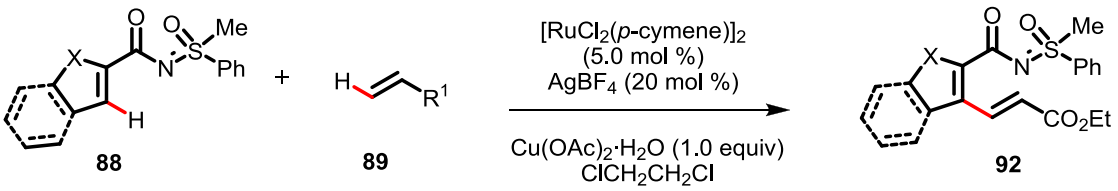
[a]Reaction conditions: **88** (0.5 mmol), **89a** (3.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgBF_4$ (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv), $ClCH_2CH_2Cl$ (2.0 mL), 120 °C for 24 h and Pd/C (50 mg, 20 wt%). [b]Combined yield of isolated mono- and dialkylation products (the mono/di ratio is indicated in the parentheses).

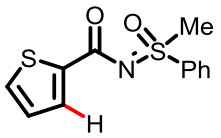
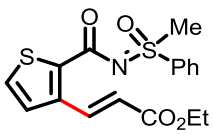
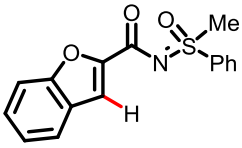
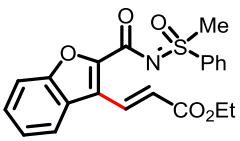
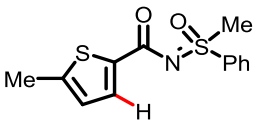
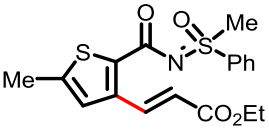
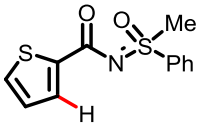
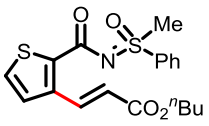
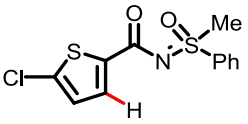
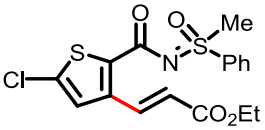
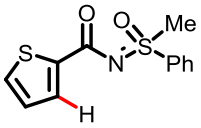
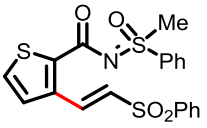
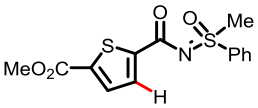
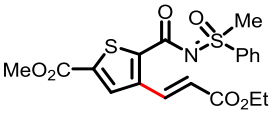
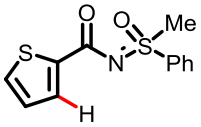
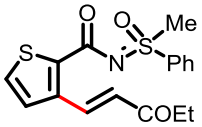
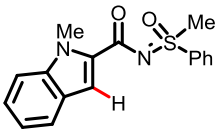
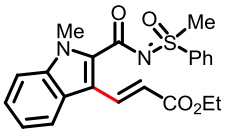
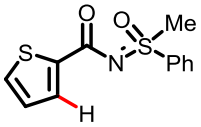
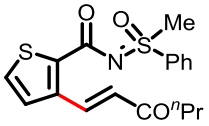
delivered **91h** in 82% yield. The α,β-unsaturated ketones smoothly participated, and the desired products **91i** and **91j** were prepared in moderate yields.

In contrast, the reaction of electron neutral **88m** or *p*-Me/F substituted *N*-aroylated sulfoximines **88n/88o** with **89a** showed a complex mixture (by ^{1}H NMR), displaying the possible formation of a non-separable mixture of *o*-C–H mono-, di-alkenylation, and their corresponding hydroarylation products; subsequent hydrogenation of the non-purified mixture of compounds exhibited the corresponding mono- (**91k–m**) and di-hydroarylation (**91'k–m**) products in overall good yields (entries 1–3, Table 4.4). The formation of di-hydroarylation product enables accessing highly peripheral decorated benzoic acid derivatives.

The utility of the catalytic conditions to the introduction of an olefin moiety on heteroarenes is further examined (Table 4.5). The unsubstituted and 5-substituted thienyl derivatives **88p–s** smoothly underwent oxidative alkenylation, affording the desired products **92a–d** in excellent yields (entries 1–4); the chloro and ester functional groups did not interfere with the reaction efficiency. However, the *N*-methyl indole derivative **88t** furnished a mixture of alkenylation **92e** and hydroarylation **92′e** at the electron rich C3 position in a 2:3 ratio (entry 5); while, the reaction of benzofuran derivative **88u** with **89a** exclusively produced **92f** (entry 6). Other activated alkenes **89c** and **89d** were effective coupling partners and the C–C coupled products **92g** and **92h** were isolated good to excellent yields (entries 7 and 8). The reaction of **88p** with activated ketones (**89e** and **89f)** is no exception, providing **92i** and **92j** in 91% and 86% yield, respectively (entries 9 and 10). The inseparable mixture of alkenylation and hydroarylation products in **92j** is observed 3:1 ratio.

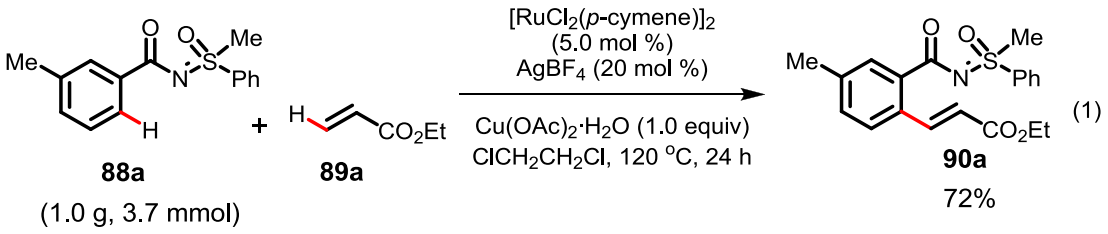
Table 4.5: Alkenylation of heteroarene derivatives[a,b]



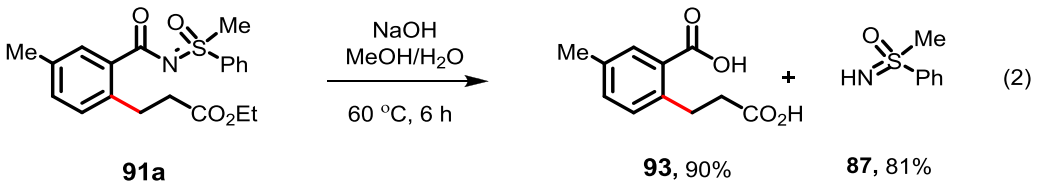
entry	88	92	entry	88	92
1			6		
	88p	**92a**, 88%		**88u**	**92f**, 88%
2			7		
	88q	**92b**, 90%		**88p**	**92g**, 82%
3			8		
	88r	**92c**, 85%		**88p**	**92h**, 95%
4			9		
	88s	**92d**, 84%		**88p**	**92i**, 91%
5			10		
	88t	**92e**, 60% (2:3)[c]		**88p**	**92j**, 86% (3:1)[c]

[a]Reaction conditions: **88** (0.5 mmol), alkene **89** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgBF_4$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv), $ClCH_2CH_2Cl$ (2.0 mL), 120 °C for 24 h. [b]Isolated yields. [c]Ratio of alkenylation and hydroarylation product observed by ^1H NMR.

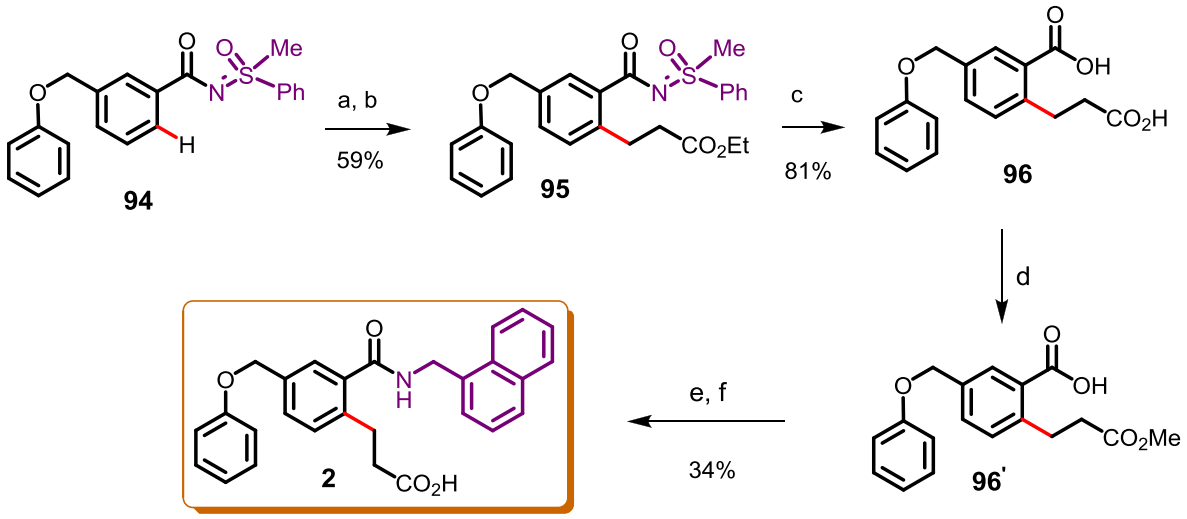
The robustness of this reaction was demonstrated through gram-scale *ortho*-C–H alkenylation of arenes **88a** affording **90a** in 72% yield (eq 1).



The practical utility of the present protocol is demonstrated with the ready cleavage of amide-linkage and recovery of methyl phenyl sulfoximine. Gratifyingly, the base promoted (NaOH in MeOH/H_2O solvent at 60 °C for 6 h) saponification of **91a** yielded **93** (90%) with recovery of 81% of methyl phenyl sulfoximine **87** (eq 2).



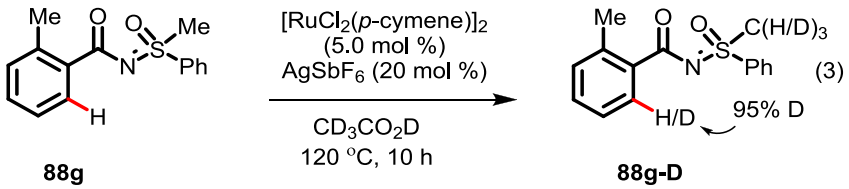
The EP receptor which responds to PGE_2 is divided into four subtypes EP1, EP2, EP3 and EP4. The EP3 antagonist drug is useful for the treatment of pain, pyrexia, threatened abortion and peripheral occupied arterial disease (PAOD).[2] Recently, Merck, de CODE and GlaxoSmithKline reported the synthesis of potential utility of various types EP3 antagonists. The current protocol has successfully been applied in the synthesis of EP3 antagonist analogue 3-(2-(naphthalen-1-ylmethylcarbamoyl)-4-(phenoxymethyl)phenyl)propanoic acid (**2**) (Scheme 4.14).[2] The synthesis is begun by reacting **94** and **89a** under the optimized conditions shown in entry 6, Table 1, producing the *o*-C–H alkenylation product **95′** along with a minor amount hydroarylation compound **95** (4:1 ratio by ^1H NMR). The reduction of activated olefin with $NiCl_2{\cdot}6H_2O/NaBH_4$ in MeOH/THF gave the hydrogenated product **95** in 59% overall yield from **94**. Base mediated hydrolysis of **95** led to the dicarboxylic acid derivative **96** with the recovery of methyl phenyl sulfoximine. The selective esterification of aliphatic acid, EDC-mediated amide formation between naphthalen-1-ylmethanamine **97** and benzoic acid moiety, and finally hydrolysis of ester group delivered the desired EP3 antagonist molecule **2** in 34% overall yield from **96**.



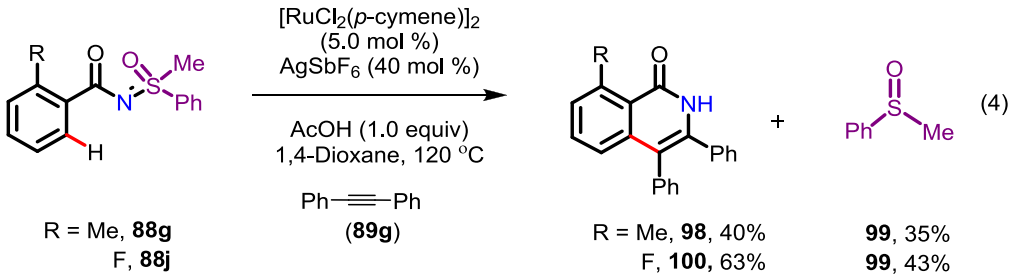
Reaction conditions: a) **94** (2.5 g, 6.8 mmol), **89a** (13.7 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv), $ClCH_2CH_2Cl$ (10.0 mL), 120 °C for 24 h; 66%. b) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH/THF, 0 °C to rt, overnight; 89%. c) NaOH, MeOH/H_2O, 60 °C, 4 h. d) cat. H_2SO_4, MeOH (1.0 equiv), 20 min; 85%. e) EDC·HCl, HOBt, naphthalen-1-ylmethanamine (**97**), DMF, rt, 24 h; 64%. f) $LiOH \cdot H_2O$, MeOH/THF, 60°C, 4 h; 62%.

Scheme 4.14: Synthesis of EP3 antagonist analogue

To understand the mechanistic insights, a deuterium labeling experiment was performed on **88g** (eq 3). Gratifyingly, 95% deuterium incorporation at the *ortho*-C–H in **88g** occurred,[16] when **88g** exposed to Ru(II)-catalyst, $AgSbF_6$ in CD_3COOD at 120 °C for 10 h. In addition, the acidic s-methyl protons underwent deuterium exchange. These results presumably suggest that the insertion of Ru to the *o*-C–H bond is reversible.



The hydroarylation outcome from *o*-substituted N-aroylated sulfoximine and the activated olefin (Table 4.3) prompted us to examine the reaction between *N*-(*o*-methylbenzoyl)-MPS (**88g)** and internal unactivated alkyne, as this would result trisubstituted olefin. To our surprise, we noticed the formation of isoquinolinone **98** (40%) and 35% of methyl phenyl sulfoxide (**99**) from **88g** and diphenylacetylene (**89g**) under the Miura conditions (eq 4).[17,18,19] Furthermore, the annulation between **88j** and **89g** gave product **100** in 63% yield (eq 4). The compound **99** is useful for the synthesis of MPS-DG.



4.4. Conclusion

In summary, Ru(II)-catalyzed *o*-C–H alkenylation and hydroarylation of (hetero)arenes with activated olefins: acrylates, vinyl sulfones, and ketones with the aid of *reusable methyl phenyl sulfoximine directing group* is reported. Isoquinolinone derivatives are synthesized from N-aroylated sulfoximines and diphenylacetylene. The isolation of MPS and the methyl phenyl sulfoxide make these strategies synthetically viable and useful. The utility of this transformation enables the synthesis of EP3 receptor antagonist analogue.

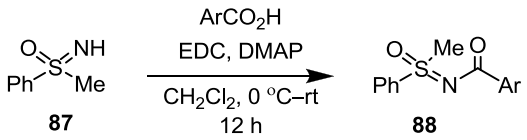
4.5. Experimental

4.5.1. General Experimental Information for this Chapter is same as mentioned in Chapter 1.

4.5.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Dichloromethane (DCM) and 1, 2-dichloroethane (DCE) were distilled over CaH_2. $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$, $AgBF_4$, $AgPF_6$ and KPF_6 were purchased from Sigma Aldrich Ltd, and used as received. Analytical and spectral data of all the known compounds are exactly matching with the reported values.

4.5.3. Experimental Procedures

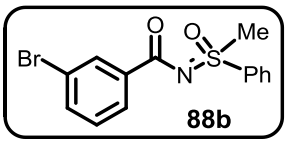


Scheme 4.15: Preparation of *N*-aroylated sulfoximines

4.5.3.1. General Procedure (GP-1); EDC-Coupling[11a]

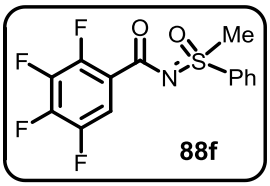
A solution of *N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, hydrochloride salt (EDC·HCl) (2.0 equiv), 4-*N*,*N*-dimethylaminopyridine (DMAP) (2.2 equiv) and benzoic acids (1.1 equiv) in CH_2Cl_2 (5.0 mL, for 1.0 mmol of sulfoximine) was stirred under an argon atmosphere. Sulfoximine (**87**; 1.0 equiv) was introduced drop wise at 0 °C. The resulting reaction mixture was stirred for about 1 h at 0 °C, and warmed to ambient temperature and continued for overnight. Upon complete consumption of sulfoximine, the reaction mixture was acidified with hydrochloric acid (HCl, 1N). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3 times). The combined extracts were washed with 10% aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4. Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography on silica gel using hexane/ ethyl acetate (3:2).

_N_-[3-Bromobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (88b):



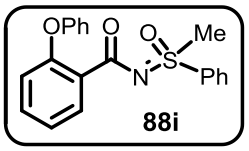
0.76 g, 70% yield; colorless solid; mp = 99–100 °C; R_f = 0.34 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.07 (d, J = 7.6 Hz, 1H), 8.03 (d, J = 7.6 Hz, 2H), 7.69 (bt, J = 7.2 Hz, 1H), 7.65–7.58 (m, 3H), 7.28 (t, J = 7.8 Hz, 1H), 3.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 138.5, 137.5, 134.9, 133.9, 129.7, 129.6, 127.9 (2C), 127.0 (3C), 122.1, 44.3; IR (Neat) ν_{max} 3028, 2922, 1635, 1215 cm^{-1}; HRMS (ESI) for $C_{14}H_{12}BrNO_2S$ $(M+H)^+$: calcd. 337.9850, found 337.9850.

_N_-[2,3,4,5-Tetrafluorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (88f):



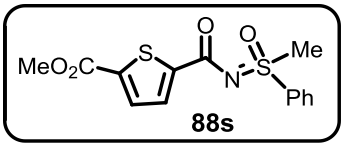
0.42 g, 40% yield, colorless crystalline solid; mp = 104–106 °C; R_f = 0.50 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2H), 7.72 (bt, J = 7.4 Hz, 1H), 7.68–7.60 (m, 3H), 3.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 147.5 (dd, J = 260, 11 Hz), 146.1 (dd, J = 248, 11 Hz), 142.6 (dt, J = 261, 14 Hz), 141.0 (dt, J = 255, 14 Hz), 137.9, 134.2, 129.8 (2C), 127.1 (2C), 120.5, 112.9 (d, J = 20 Hz), 44.3; ^{19}F (376 MHz, $CDCl_3$) δ –135.90 (m), –139.01 (m), –149.81 (m), –154.61 (m); IR (KBr) ν_{max} 3030, 2936, 1649, 1632, 1468, 1216 cm^{-1}; HRMS (ESI) for $C_{14}H_9F_4NO_2S$ $(M+Na)^+$: calcd. 354.0188, found 354.0189.

_N_-[2-Phenoxybenzoyl]-_S_-methyl-_S_-phenylsulfoximine (88i):



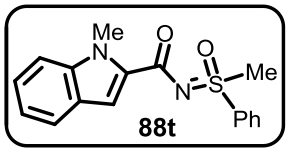
0.73 g, 65% yield; colorless crystalline solid; mp = 120–122 °C; R_f = 0.42 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.50–7.40 (m, 3H), 7.29 (t, J = 7.6 Hz, 2H), 7.21 (t, J = 7.6 Hz, 1H), 7.07–7.00 (m, 2H), 6.96 (d, J = 8.0 Hz, 2H), 3.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 158.7, 154.1, 138.3, 133.6, 132.4, 131.5, 130.2 (2C), 129.6 (2C), 129.4, 127.1 (2C), 124.2, 122.1, 121.8, 117.0 (2C), 43.9; IR (KBr) ν_{max} 3063, 2926, 1621, 1309, 1232 cm^{-1}; HRMS (ESI) for $C_{20}H_{17}NO_3S$ $(M+Na)^+$: calcd. 374.0827, found 374.0820.

_N_-[5-Methoxycarbonylthenoyl]-_S_-methyl-_S_-phenylsulfoximine (88s):



0.71 g, 68% yield; colorless crystalline solid; mp = 152–154 °C; R_f = 0.32 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2H), 7.75–7.68 (m, 3H), 7.64 (t, J = 7.6 Hz, 2H), 3.90 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 162.5, 146.5, 138.3, 137.6, 134.1, 133.2, 131.6, 129.8 (2C), 127.2 (2C), 52.4, 44.4; IR (KBr) ν_{max} 3024, 2926, 1720, 1610, 1254 cm^{-1}; HRMS (ESI) for $C_{14}H_{13}NO_4S_2$ $(M+Na)^+$: calcd. 346.0184, found 346.0187.

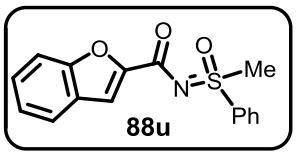
_N_-[N-Methyl-2-indoloyl]-_S_-methyl-_S_-phenylsulfoximine (88t):



88t

0.73 g, 73% yield; colorless crystalline solid; mp = 153–155 °C; R_f = 0.38 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.2 Hz, 2H), 7.73–7.65 (m, 2H), 7.63 (t, J = 7.4 Hz, 2H), 7.45 (s, 1H), 7.39–7.28 (m, 2H), 7.13 (t, J = 7.2 Hz, 1H), 4.07 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 139.8, 139.0, 133.8, 133.3, 129.7 (2C), 127.2 (2C), 125.9, 124.5, 122.4, 120.2, 110.3, 110.1, 44.8, 31.7; IR (KBr) ν_{max} 3008, 2920, 1616, 1468, 1260 cm^{-1}; HRMS (ESI) for $C_{17}H_{16}N_2O_2S$ $(M+Na)^+$: calcd. 335.0830, found 335.0829.

_N_-[2-Benzofuronoyl]-_S_-methyl-_S_-phenylsulfoximine (88u):



88u

1.51 g, 79% yield; colorless crystalline solid; mp = 130–131 °C; R_f = 0.31 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.6 Hz, 2H), 7.72–7.57 (m, 5H), 7.53 (s, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.31–7.25 (m, 1H), 3.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 155.4, 150.7, 138.2, 133.9, 129.6 (2C), 127.3, 127.0 (2C), 126.8, 123.3, 122.5, 112.5, 112.2, 44.3; IR (KBr) ν_{max} 3024, 2920, 1643, 1616, 1572, 1216 cm^{-1}; HRMS (ESI) for $C_{16}H_{13}NO_3S$ $(M+H)^+$: calcd. 300.0694, found 300.0697.

4.5.3.2. Optimization for *ortho*-C–H Alkenylation

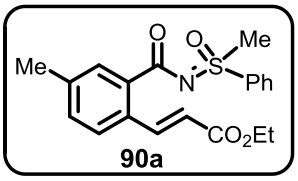
The C–H alkenylation reaction was conducted in a 50 mL Schlenk tube with high pressure valve and side arm. The tube was charged with *N*-(*m*-methylbenzoyl)-MPS (**88a**, 27.3 mg, 0.1 mmol), ethyl acrylate (**89a**, 21 μL, 0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3.1 mg, 5.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol). Subsequently, the reaction tube was taken to the glove box and the additives were introduced. The corresponding solvent (0.5 mL) was added to the mixture and the resulting mixture was stirred at 120 °C for 24 h. The reaction mixture was cooled to ambient temperature, filtered through a plug of Celite and then washed with CH_2Cl_2 (3 × 5 mL). The solvents were evaporated under reduced pressure and the crude material was analyzed based on ^{1}H NMR spectroscopy.

4.5.3.3. General Procedure for *ortho*-C–H Alkenylation Reaction (GP-2)

The C–H alkenylation reactions were carried out in a 50 mL Schlenk tube with high pressure valve and side arm. The tube was charged with *N*-aroylated sulfoximine (**88a–u**, 0.5 mmol), alkene (**89a–f**, 1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.0 mg, 5.0 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (100 mg, 1.0 mmol). Subsequently, the reaction tube was taken to the glove box and $AgSbF_6/AgBF_4$ (20 mol %) was introduced. The solvent 1,2–dichloroethane (DCE, 2.0 mL)

was added to the mixture and the resulting mixture was stirred at 120 ^{o}C for 24 h. The reaction mixture was cooled to ambient temperature, filtered through a small plug of Celite and then washed with CH_2Cl_2 (3 × 10 mL). The solvents were evaporated under reduced pressure and the crude material was purified using column chromatography on silica gel (30–40% *n*-hexane/EtOAc as an eluent) to give the desired product.

_N_-[(_E_)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-5-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (90a):

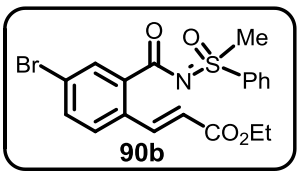


90a

156 mg, 84% yield; colorless crystalline solid; mp = 95–97 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 15.2 Hz, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.83 (s, 1H), 7.69 (bt, J = 7.4 Hz, 1H), 7.62 (bt, J = 7.8 Hz, 2H), 7.47 (d, J = 7.6 Hz, 1H), 7.27 (bd, J = 7.6 Hz, 1H), 6.26 (d, J = 15.6 Hz, 1H), 4.24 (q, J = 6.9 Hz, 2H), 3.50 (s, 3H), 2.39 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 167.1, 144.9, 139.6, 138.4, 136.2, 133.9, 132.3, 132.0, 131.0, 129.7 (2C), 127.5, 127.2 (2C), 118.7, 60.3, 44.4, 21.2, 14.3; IR (KBr) ν_{max} 2980, 2931, 1719, 1615, 1308, 1210 cm^{-1}; HRMS (ESI) for $C_{20}H_{21}NO_4S$ $(M+H)^+$: calcd. 372.1269, found 372.1269.

The same reaction was carried out in bulk scale using **88a** (1.0 g, 3.7 mmol), ethyl acrylate (**89a**, 0.55 g, 5.55 mmol), $[RuCl_2(p\text{-cymene})]_2$ (113 mg, 5.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (736 mg, 3.7 mmol), $AgSbF_6$ (254 mg, 0.74 mmol) in 1,2-DCE (10.0 mL) at 120 ^{o}C for 24 h. The product **90a** (0.98 g) was obtained in 72% yield.

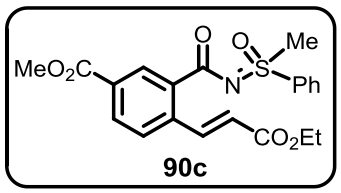
_N_-[(_E_)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-5-bromobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (90b):



90b

155 mg, 71% yield; colorless crystalline solid; mp = 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 15.6 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.06 (d, J = 7.2 Hz, 2H), 7.70 (t, J = 7.4 Hz, 1H), 7.63 (t, J = 7.4 Hz, 2H), 7.58 (dd, J = 8.0, 2.0 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 6.25 (d, J = 16.0 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.48 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 166.6, 143.8, 138.1, 137.5, 134.2, 134.1, 134.0, 133.5, 129.7 (2C), 129.1, 127.1 (2C), 123.3, 120.1, 60.4, 44.3, 14.2; IR (KBr) ν_{max} 3018, 2980, 2936, 1719, 1621, 1100 cm^{-1}; HRMS (ESI) for $C_{19}H_{18}BrNO_4S$ $(M+H)^+$: calcd. 436.0218, found 436.0223.

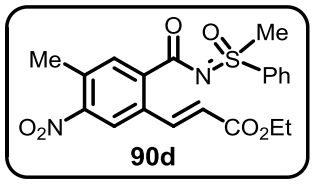
_N_-[3-Methoxycarbonyl-(_E_)-6-(3-ethoxy-3-oxoprop-1-en-1-yl)-benzoyl]-_S_-methyl-_S_-phenylsulfoximine (90c):



90c

164 mg, 79% yield; colorless crystalline solid; mp = 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.54 (d, J = 16.0 Hz, 1H), 8.13–8.05 (m, 3H), 7.70 (t, J = 7.2 Hz, 1H), 7.67–7.57 (m, 3H), 6.32 (d, J = 16.0 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 3.49 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 166.4, 165.9, 143.8, 139.5, 138.0, 136.1, 133.9, 131.8 (2C), 130.5, 129.6 (2C), 127.8, 127.0 (2C), 121.3, 60.4, 52.2, 44.2, 14.1; IR (KBr) ν_{max} 3019, 2926, 1704, 1632, 1200 cm^{-1}; HRMS (ESI) for $C_{21}H_{21}NO_6S$ $(M+Na)^+$: calcd. 438.0988, found 438.1006.

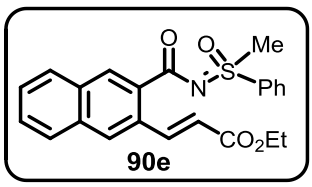
_N_-[(_E_)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-5-methyl-4-nitrobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (90d):



90d

180 mg, 86% yield; yellow crystalline solid; mp = 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 16.0 Hz, 1H), 8.12 (s, 1H), 8.06 (d, J = 7.6 Hz, 2H), 7.96 (s, 1H), 7.71 (t, J = 7.4 Hz, 1H), 7.64 (t, J = 7.6 Hz, 2H), 6.34 (d, J = 16.0 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.50 (s, 3H), 2.61 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 166.3, 149.9, 142.2, 139.6, 137.8, 134.9, 134.1 (2C), 133.9, 129.8 (2C), 127.0 (2C), 123.5, 121.1, 60.6, 44.2, 20.1, 14.2; IR (KBr) ν_{max} 2997, 2931, 1715, 1638, 1523, 1221, 1189 cm^{-1}; HRMS (ESI) for $C_{20}H_{20}N_2O_6S$ $(M+H)^+$: calcd. 417.1120, found 417.1121.

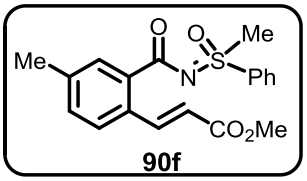
_N_-[(_E_)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-β-naptholoyl]-_S_-methyl-_S_-phenylsulfoximine (90e):



90e

170 mg, 83% yield; viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (bd, J = 15.6 Hz, 1H), 8.61 (bs,1H), 8.09 (d, J = 7.6 Hz, 2H), 7.97 (s, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.66 (bt, J = 7.2 Hz, 1H), 7.59 (t, J = 7.2 Hz, 2H), 7.57–7.46 (m, 2H), 6.36 (d, J = 15.6 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.50 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 166.9, 145.7, 138.4, 134.1, 133.8, 133.2, 132.8, 132.5, 131.6, 129.6 (2C), 128.7, 128.0, 127.9, 127.5, 127.1 (3C), 119.0, 60.3, 44.3, 14.2; IR (Neat) ν_{max} 3063, 2980, 1709, 1638, 1282, 1221 cm^{-1}; HRMS (ESI) for $C_{23}H_{21}NO_4S$ $(M+Na)^+$: calcd. 430.1089, found 430.1090.

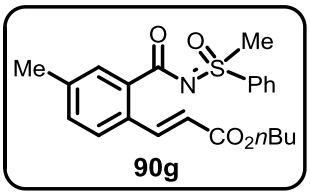
_N_-[(_E_)-2-(3-Methoxy-3-oxoprop-1-en-1-yl)-5-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (90f):



90f

141 mg, 79% yield; colorless crystalline solid; mp = 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 16.0 Hz, 1H), 8.07 (d, J = 7.6 Hz, 2H), 7.84 (s, 1H), 7.68 (t, J = 7.4 Hz, 1H), 7.61 (t, J = 7.6 Hz, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 6.25 (d, J = 16.0 Hz, 1H), 3.75 (s, 3H), 3.47 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 167.4, 145.1, 139.6, 138.3, 136.0, 133.8, 132.2, 131.9, 131.0, 129.6 (2C), 127.4, 127.1 (2C), 118.2, 51.5, 44.3, 21.2; IR (Neat) ν_{max} 3013, 2947, 1704, 1627, 1210 cm^{-1}; HRMS (ESI) for $C_{19}H_{19}NO_4S$ $(M+Na)^+$: calcd. 380.0933, found 380.0937.

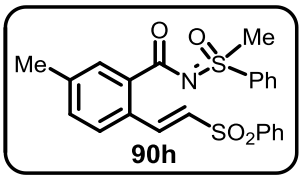
_N_-[(_E_)-2-(3-_n_-Butoxy-3-oxoprop-1-en-1-yl)-5-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (90g):



90g

167 mg, 84% yield; viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 15.6 Hz, 1H), 8.09 (d, J = 8.0 Hz, 2H), 7.82 (s, 1H), 7.69 (t, J = 7.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.25 (bd, J = 5.2 Hz, 1H), 6.27 (d, J = 16.0 Hz, 1H), 4.17 (t, J = 6.6 Hz, 2H), 3.49 (s, 3H), 2.38 (s, 3H), 1.70–1.59 (m, 2H), 1.47–1.36 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 167.3, 145.0, 139.7, 138.5, 136.3, 133.9, 132.3, 132.0, 131.1, 129.7 (2C), 127.5, 127.2 (2C), 118.7, 64.3, 44.4, 30.8, 21.3, 19.2, 13.8; IR (Neat) ν_{max} 2964, 2926, 1704, 1627, 1315, 1210 cm^{-1}; HRMS (ESI) for $C_{22}H_{25}NO_4S$ $(M+H)^+$: calcd. 400.1582, found 400.1583.

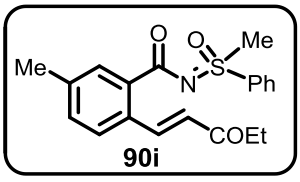
_N_-[(_E_)-2-(2-(Phenylsulfonyl)vinyl)-5-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (90h):



90h

198 mg, 90% yield; colorless crystalline solid; mp = 157–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 15.2 Hz, 1H), 8.09 (d, J = 7.6 Hz, 2H), 7.91 (d, J = 7.6 Hz, 2H), 7.82 (s, 1H), 7.70–7.53 (m, 4H), 7.49 (t, J = 7.6 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 15.2 Hz, 1H), 3.50 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 143.4, 140.7, 138.1, 136.4, 133.8, 133.1, 131.9, 131.2, 129.8, 129.7 (2C), 129.1 (2C), 127.5, 127.4 (2C), 127.0 (2C), 126.9, 44.2, 21.1 (one 13C–value is merged with other peak); IR (KBr) ν_{max} 3052, 2920, 1621, 1221 cm^{-1}; HRMS (ESI) for $C_{23}H_{21}NO_4S_2$ $(M+H)^+$: calcd. 440.0990, found 440.0990.

_N_-[(_E_)-2-(3-Oxopent-1-enyl)-5-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (90i):

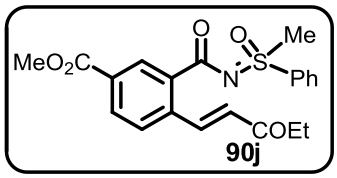


90i

124 mg, 70% yield; colorless viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 17.2 Hz, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.89 (s, 1H), 7.71 (t,

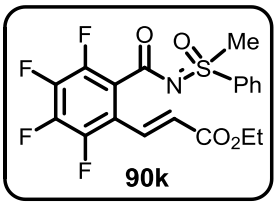
J = 7.8 Hz, 1H), 7.63 (bt, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 8.4 Hz , 1H), 7.32–7.26 (m, 1H), 6.53 (d, *J* = 16.4 Hz , 1H), 3.49 (s, 3H), 2.72–2.61 (m, 2H), 2.41 (s, 3H), 1.11 (t, *J* = 7.2 Hz , 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 175.5, 142.8, 139.7, 138.4, 136.0, 133.9, 132.7, 132.1, 131.2, 129.7 (2C), 127.4, 127.1 (3C), 44.4, 33.2, 21.2, 8.2; IR (KBr) ν_{max} 3013, 2920, 1665, 1621, 1276, 1210 cm^{-1}; HRMS (ESI) for $C_{20}H_{21}NO_3S$ $(M+H)^+$: calcd. 356.1320, found 356.1322.

_N_-[3-Methoxycarbonyl-(_E_)-6-(3-oxopent-1-enyl)-5-methylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (90j):



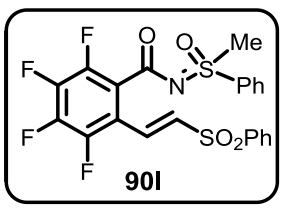
Following GP-2, reaction between **88c** and **89e** gave the inseparable alkenylation **90j** and hydroarylation products (4:1 by ^{1}H NMR; 144 mg, 72% yield) as colorless crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.45 (d, *J* = 16.4 Hz, 1H), 8.15–8.03 (m, 3H), 7.72 (bt, *J* = 7.6 Hz, 1H), 7.64 (bt, *J* = 8.4 Hz, 3H), 6.57 (d, *J* = 16.4 Hz, 1H), 3.95 (s, 3H), 3.49 (s, 3H), 2.70–2.65 (m, 2H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3, 174.4, 166.1, 141.7, 140.1, 138.2, 136.1, 134.0, 132.0, 130.6, 129.8 (2C), 129.4, 127.8, 127.1 (3C), 52.3, 44.4, 28.8, 8.0; IR (Neat) ν_{max} 2926, 1720, 1671, 1627, 1315 cm^{-1}; HRMS (ESI) for $C_{21}H_{21}NO_5S$ $(M+H)^+$: calcd. 400.1218, found 400.1223.

_N_-[(_E_)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-tetrafluorobenzoyl]-_S_-methyl-_S_-phenylsulfoximi- ne (90k):



Following GP-2, reaction between **88f** and **89a** gave the inseparable alkenylation **90k** and hydroarylation products (3.3:1 by ^{1}H NMR; 170 mg, 79% yield) as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.77–7.62 (m, 4H), 6.60 (d, *J* = 16.0 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.49 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 169.7, 166.2, 137.4, 134.4, 133.5, 130.0 (2C), 127.2 (2C), 60.9, 44.2, 14.1 (*The large number of less-intense 13C values arising from ^{19}F and C coupling are omitted due to lack of clarity*); ^{19}F (470 MHz, $CDCl_3$)δ –137.46, –141.04, –152.26, –154.52; IR (KBr) ν_{max} 3013, 2926, 1715, 1632, 1512, 1473, 1232 cm^{-1}; HRMS (ESI) for $C_{19}H_{15}F_4NO_4S$ $(M+Na)^+$: calcd. 452.0556, found 452.0556.

_N_-[(_E_)-2-(2-(Phenylsulfonyl)vinyl)-tetrafluorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (90l):



Following GP-2, reaction between **88f** and **89d** gave the inseparable alkenylation **90l** and hydroarylation products (6:1 by ^{19}F NMR; 60 mg, 81% yield) as yellow viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (bd, *J* = 7.2 Hz, 2H), 7.89 (bd, *J* = 7.6 Hz, 2H), 7.80 (bd, *J* = 15.6

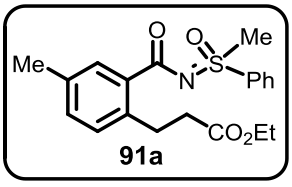
Hz, 1H), 7.76–7.60 (m, 4H), 7.55 (bt, *J* = 7.4 Hz, 2H), 7.10 (d, *J* = 16.0 Hz, 1H), 3.54 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 139.5, 137.2, 134.5, 133.8, 131.5, 130.0 (2C), 129.5 (2C), 127.8 (2C), 127.1 (3C), 44.0 (*The large number of less-intense 13C values arising from* ^{19}*F and C coupling are omitted due to lack of clarity*); ^{19}F (470 MHz, $CDCl_3$) δ –136.13, –139.85, –149.83, –153.74; IR (Neat) ν_{max} 3079, 2926, 1627, 1506, 1369, 1238 cm^{-1}; HRMS (ESI) for $C_{22}H_{15}F_4NO_4S_2$ $(M+H)^+$: calcd. 498.0457, found 498.0457.

4.5.3.4. General Procedure for *ortho*-C–H Alkenylation and Hydrogenation on *ortho* and *para*-substituted *N*-Aroylated MPS derivatives (GP-3)

Following GP-2, the C–H alkenylation on *ortho*-substituted-*N*-aroyl-MPS derivatives gave non-separable mixture of alkenylation and hydroarylation products. To make the purification ease, the non-purified mixture of compounds were subjected to hydrogenation.

Accordingly, a solution of non-purified mixture of compounds in methanol was subjected to hydrogenation in the presence of Pd/C (50 mg, 20 wt%) under hydrogen balloon for overnight at room temperature. The solvent was evaporated under reduced pressure and the crude material was purified using column chromatography on silica gel (30–40% *n*-hexane/EtOAc as eluent) to give the desired hydroarylation product.

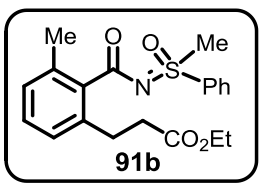
***N*-[2-(3-Ethoxy-3-oxopropyl)-5-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (91a):**



91a

Following GP-3, hydrogenation of **3a** (1.0 g, 2.7 mmol) with Pd/C (270 mg) in MeOH gave **91a** (830 mg, 83%) as colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.81 (s, 1H), 7.67 (bt, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.41 (s, 3H), 3.28–3.19 (m, 2H), 2.67–2.58 (m, 2H), 2.33 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 173.5, 138.9, 138.3, 135.7, 135.2, 133.8, 131.8, 131.2, 130.9, 129.7 (2C), 127.1 (2C), 60.2, 44.4, 36.3, 29.5, 20.9, 14.2; IR (Neat) ν_{max} 2975, 2926, 1726, 1632, 1298, 1221 cm^{-1}; HRMS (ESI) for $C_{20}H_{23}NO_4S$ $(M+Na)^+$: calcd. 396.1246, found 396.1249.

***N*-[2-(3-Ethoxy-3-oxopropyl)-6-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (91b):**

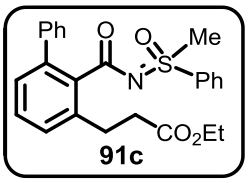


91b

150 mg, 80% yield; colorless crystalline solid; mp = 95–97 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.2 Hz, 2H), 7.66 (bt, *J* = 7.2 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.47 (s, 3H), 3.06–2.96 (m, 2H), 2.70–2.60 (m, 2H), 2.35 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 173.1, 139.0, 138.4, 135.9, 134.0,

133.8, 129.6 (2C), 128.24, 128.18, 127.0 (2C), 126.3, 60.3, 43.9, 36.1, 29.0, 19.4, 14.1; IR (KBr) ν_{max} 3030, 2926, 1731, 1632, 1293,1216 cm^{-1}; HRMS (ESI) for $C_{20}H_{23}NO_4S$ $(M+H)^+$: calcd. 374.1426, found 374.1426.

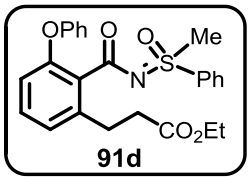
_N_-[2-(3-Ethoxy-3-oxopropyl)-6-phenylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91c):



91c

190 mg, 87% yield; colorless viscous liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.50 (m, 3H), 7.45–7.28 (m, 8H), 7.28–7.22 (m, 1H), 7.21 (d, J = 7.2 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.21 (s, 3H), 3.20–3.01 (m, 2H), 2.78–2.69 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.2, 173.0, 141.9, 138.8, 138.4, 138.0, 137.4, 133.6, 129.2 (2C), 129.1 (2C), 128.6, 128.4, 128.0 (2C), 127.8, 127.0, 126.9 (2C), 60.2, 42.8, 35.8, 28.8, 14.1; IR (Neat) ν_{max} 3063, 2980, 1726, 1627, 1221 cm^{-1}; HRMS (ESI) for $C_{25}H_{25}NO_4S$ $(M+H)^+$: calcd. 436.1582, found 436.1581.

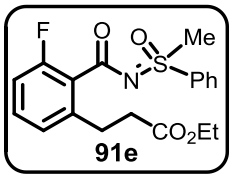
_N_-[2-(3-Ethoxy-3-oxopropyl)-6-phenoxybenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91d):



91d

166 mg, 74% yield; colorless crystalline solid; mp = 146–148 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.8 Hz, 1H), 7.10–7.00 (m, 4H), 6.82 (d, J = 8.4 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.23 (s, 3H), 3.09 (t, J = 7.8 Hz, 2H), 2.71 (t, J = 8.0 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 172.9, 157.9, 152.7, 139.4, 138.0, 133.7, 132.1, 129.6 (2C), 129.5, 129.4 (2C), 127.2 (2C), 124.9, 122.7, 117.9 (2C), 117.8, 60.2, 43.9, 35.7, 28.5, 14.1; IR (KBr) ν_{max} 3024, 2926, 1736, 1638, 1216 cm^{-1}; HRMS (ESI) for $C_{25}H_{25}NO_5S$ $(M+H)^+$: calcd. 452.1531, found 452.1532.

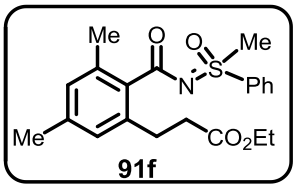
_N_-[2-(3-Ethoxy-3-oxopropyl)-6-fluorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91e):



91e

132 mg, 70% yield; colorless crystalline solid; mp = 64–66 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.6 Hz, 2H), 7.68 (bt, J = 7.4 Hz, 1H), 7.61 (bt, J = 7.4 Hz, 2H), 7.29–7.18 (m, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.93 (t, J = 9.0 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.43 (s, 3H), 3.06 (t, J = 7.8 Hz, 2H), 2.65 (td, J = 2.2, 7.8 Hz, 2H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 172.7, 159.3 (d, J = 248 Hz, 1C), 140.2, 138.0, 134.0, 129.9 (d, J = 9.1 Hz, 1C), 129.7 (2C), 127.2 (2C), 127.0, 125.0, 113.6 (d, J = 22 Hz, 1C), 60.3, 44.2, 35.7, 28.4, 14.1; ^{19}F (470 MHz, $CDCl_3$) δ −115.82; IR (Neat) ν_{max} 2975, 2936, 1731, 1627, 1287, 1227 cm^{-1};HRMS (ESI) for $C_{19}H_{20}FNO_4S$ $(M+H)^+$: calcd. 378.1175, found 378.1178.

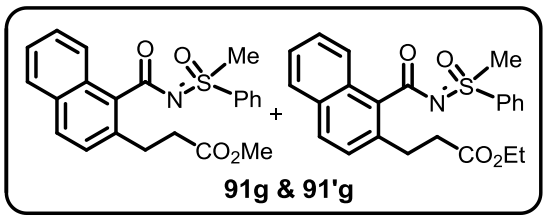
_N_-[2-(3-Ethoxy-3-oxopropyl)-4,6-dimethylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91f):



91f

151 mg, 78% yield; colorless crystalline solid; mp = 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.6 Hz, 2H), 7.68 (bt, J = 6.8 Hz, 1H), 7.61 (bt, J = 7.6 Hz, 2H), 6.85 (bd, J = 2.4 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.48 (s, 3H), 3.07–2.91 (m, 2H), 2.70–2.61 (m, 2H), 2.35 (s, 3H), 2.26 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 173.3, 138.7, 138.0, 136.3, 136.2, 134.2, 133.8, 129.6 (2C), 129.1, 127.2 (2C), 127.1, 60.3, 44.0, 36.3, 29.1, 21.1, 19.5, 14.2; IR (Neat) ν_{max} 3019, 2931, 1715, 1605, 1287, 1216 cm^{-1}; HRMS (ESI) for $C_{21}H_{25}NO_4S$ $(M+H)^+$: calcd. 388.1582, found 388.1577.

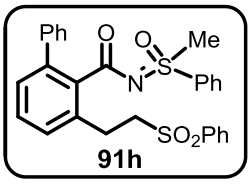
_N_-[2-(3-Ethoxy-3-oxopropyl)-_α_-naphtholoyl]-_S_-methyl-_S_-phenylsulfoximineand _N_-[2-(3-Methoxy-3-oxopropyl)-_α_-naphtholoyl]-_S_-methyl-_S_-phenylsulfoximine (91g & 91'g):



91g & 91'g

Following GP-3, reaction between **88l** (100 mg, 0.32 mmol) and ethyl acrylate (**89a**, 69 µL,0.65 mmol) under the optimized conditions followed by hydrogenation in MeOH afforded the inseparable mixture of products **91g & 91′g** (94 mg, 4.6:1; ^{1}H NMR) in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.6 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H), 7.81–7.73 (m, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 2H), 7.51–7.38 (m, 2H), 7.36–7.29 (m, 1H), 4.14 (q, J = 7.1 Hz, 0.5 H), 3.68 (s, 2.3H), 3.53 (s, 3H), 3.25–3.16 (m, 2H), 2.80–2.72 (m, 2H), 1.24 (t, J = 7.2 Hz, 0.75H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3, 173.5, 173.1, 138.4, 135.7, 133.9, 133.5, 132.1, 129.8, 129.7, 128.8, 127.8, 127.1, 126.6, 125.5, 125.1, 60.4, 51.6, 44.2, 36.1, 35.9, 29.4, 14.2.

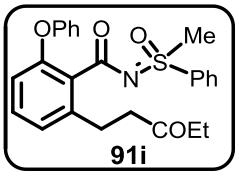
_N_-[2-(2-(Phenylsulfonyl)ethyl)-6-phenylbenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91h):



91h

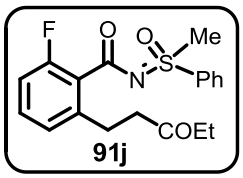
206 mg, 82% yield; colorless viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.6 Hz, 2H), 7.68–7.59 (m, 2H), 7.55 (bt, J = 7.2 Hz, 2H), 7.50–7.28 (m, 10H), 7.21 (bt, J = 8.6 Hz, 2H), 3.55 (bt, J = 8.0 Hz, 2H), 3.33–3.19 (m, 4H), 3.18–3.08 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 141.2, 139.1, 138.6, 138.3, 137.7, 134.1, 133.6, 133.4, 129.2 (2C), 129.0 (2C), 128.72 (3C), 128.68, 128.5, 128.0 (2C), 127.8 (2C), 127.1, 126.7 (2C), 56.8, 42.6, 27.1; IR (neat) ν_{max} 3068, 2920, 1626, 1451, 1308, 1150 cm^{-1}; HRMS (ESI) for $C_{28}H_{25}NO_4S_2$ $(M+Na)^+$: calcd. 526.1123, found 526.1125.

_N_-[2-(3-Oxopentyl)-6-phenoxybenzoyl]-_S_-methyl-_S_-phenylsulfoximine(91i):



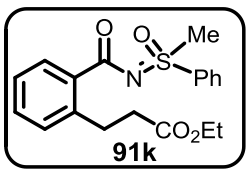
134 mg, 61% yield; colorless viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (bd, J = 7.6 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.19 (t, J = 8.0 Hz, 1H), 7.12–6.97 (m, 4H), 6.80 (d, J = 8.0 Hz, 1H), 3.21 (s, 3H), 3.06–2.97 (m, 2H), 2.90–2.77 (m, 2H), 2.37 (q, J = 6.9 Hz, 2H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.8, 175.9, 157.9, 152.6, 140.0, 137.9, 133.7, 132.0, 129.6 (2C), 129.4 (3C), 127.2 (2C), 125.2, 122.6, 117.9 (2C), 117.6, 43.9, 43.8, 35.8, 27.6, 7.6; IR (neat) ν_{max} 3057, 2931, 1709, 1632, 1451, 1226 cm^{-1}; HRMS (ESI) for $C_{25}H_{25}NO_4S$ $(M+Na)^+$: calcd. 458.1402, found 458.1402.

_N_-[2-(3-Oxopentyl)-6-fluorobenzoyl]-_S_-methyl-_S_-phenylsulfoximine (91j):



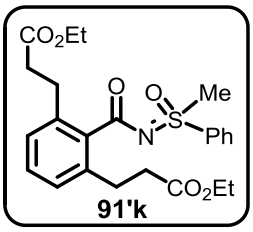
117 mg, 64% yield; colorless viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (bd, J = 8.0 Hz, 2H), 7.68 (bt, J = 7.0 Hz, 1H), 7.62 (bt, J = 7.2 Hz, 2H), 7.25–7.16 (m, 1H), 6.98 (bd, J = 7.6 Hz, 1H), 6.91 (t, J = 8.8 Hz, 1H), 3.42 (s, 3H), 3.05–2.95 (m, 2H), 2.75 (bt, J = 7.6 Hz, 2H), 2.35 (q, J = 7.2 Hz, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.6, 174.1, 159.2 (d, J = 247 Hz), 140.8, 137.9, 134.0, 130.0 (d, J = 9.1 Hz), 129.7 (2C), 127.2 (2C), 127.0 (d, J = 17 Hz), 125.3, 113.5 (d, J = 22 Hz), 44.3, 43.7, 35.8, 27.5, 7.6; ^{19}F (470 MHz, $CDCl_3$) δ –116.0; IR (Neat) ν_{max} 3018, 2975, 2931, 1709, 1637, 1287, 1226, 1133 cm^{-1}; HRMS (ESI) for $C_{19}H_{20}FNO_3S$ $(M+Na)^+$: calcd. 384.1046, found 384.1051.

_N_-[2-(3-Ethoxy-3-oxopropyl)-benzoyl]-_S_-methyl-_S_-phenylsulfoximine (91k):



Following GP-3, reaction between **88m** (129 mg, 0.5 mmol) and **89a** (0.19 mL, 1.75 mmol) under the optimized conditions followed by flash column chromatography purification of crude material on silica gel eluting with 1–10% $CHCl_3$/THF gave **91k** (61 mg, 34%) and **91′k** (80 mg, 35%) as pale brown viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (bd, J = 7.6 Hz, 2H), 8.04 (bd, J = 7.6 Hz, 1H), 7.70 (bt, J = 7.4 Hz, 1H), 7.63 (bt, J = 7.2 Hz, 2H), 7.37 (t, J = 7.4 Hz, 1H), 7.30–7.22 (m, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.44 (s, 3H), 3.39–3.22 (m, 2H), 2.77–2.60 (m, 2H),1.21 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 173.4, 141.4, 138.8, 135.4, 133.8, 131.1, 130.9, 129.7, 127.1, 126.2, 60.2, 44.4, 36.1, 29.9, 14.2; IR (Neat) ν_{max} 3063, 2931, 1726, 1632, 1260 cm^{-1}; HRMS (ESI) for $C_{19}H_{21}NO_4S$ $(M+H)^+$: calcd. 360.1269, found 360.1269.

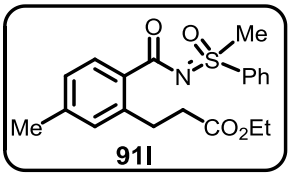
***N*-[2,6-Di(3-ethoxy-3-oxopropyl)-benzoyl]-*S*-methyl-*S*-phenylsulfoximine (91′k):**



91′k

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.6 Hz, 2H), 7.68 (bt, J = 7.4 Hz, 1H), 7.62 (bt, J = 7.4 Hz, 2H), 7.19 (t, J = 7.6 Hz, 1H), 7.08 (bd, J = 7.6 Hz, 2H), 4.11 (q, J = 7.1 Hz, 4H), 3.52 (s, 3H), 3.08–2.97 (m, 4H), 2.72–2.60 (m, 4H), 1.22 (t, J = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 173.1, 139.0, 138.5, 136.6, 133.8, 129.7, 128.5, 127.3, 127.0, 60.3, 43.8, 36.0, 29.0, 14.2; IR (Neat) ν_{max} 3068, 2980, 2926, 1726, 1627, 1293, 1221 cm^{-1}; HRMS (ESI) for $C_{24}H_{29}NO_6S$ $(M+H)^+$: calcd. 460.1794, found 460.1796.

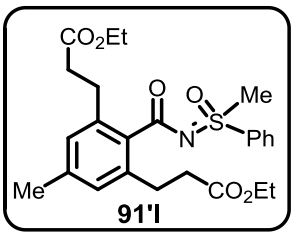
***N*-[2-(3-Ethoxy-3-oxopropyl)-4-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (91l):**



91l

Following GP-3, reaction between **88n** (136 mg, 0.5 mmol) and **89a** (0.19 mL, 1.75 mmol) under the optimized conditions followed by flash column chromatography purification of crude material on silica gel eluting with 1–10% $CHCl_3$/THF gave **91l** (66 mg, 35%) and **91′l** (85 mg, 36%) as pale brown viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2H), 7.97 (d, J = 8.0 Hz, 1H), 7.68 (bt, J = 7.2 Hz, 1H), 7.60 (bt, J = 7.6 Hz, 2H), 7.08–7.02 (m, 2H), 4.08 (q, J = 7.2 Hz, 2H), 3.42 (s, 3H), 3.34–3.20 (m, 2H), 2.69–2.60 (m, 2H), 2.33 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 173.5, 141.7, 141.5, 138.9, 133.7, 132.2, 131.7, 131.3, 129.7, 127.1, 126.8, 60.1, 44.4, 36.1, 30.0, 21.3, 14.2; IR (Neat) ν_{max} 3063, 2920, 2854, 1726, 10627, 1446, 1221 cm^{-1}; HRMS (ESI) for $C_{20}H_{23}NO_4S$ $(M+H)^+$: calcd. 374.1426, found 374.1427.

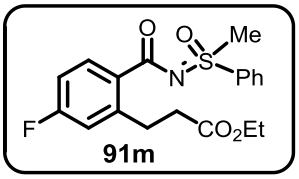
***N*-[2,6-Di(3-ethoxy-3-oxopropyl)-4-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (91′l):**



91′l

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.6 Hz, 2H), 7.67 (bt, J = 7.2 Hz, 1H), 7.61 (bt, J = 7.4 Hz, 2H), 6.89 (s, 2H), 4.11 (q, J = 6.9 Hz, 4H), 3.50 (s, 3H), 3.05–2.90 (m, 4H), 2.67–2.60 (m, 4H), 2.27 (s, 3H), 1.22 (t, J = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 173.1, 138.5, 138.2, 136.2, 133.7, 129.6, 128.0, 127.0, 60.2, 43.8, 36.1, 29.0, 21.1, 14.1; IR (Neat) ν_{max} 3057, 2931, 2854, 1731, 1627, 1106 cm^{-1}; HRMS (ESI) for $C_{25}H_{31}NO_6S$ $(M+H)^+$: calcd. 474.1950, found 474.1950.

***N*-[2-(3-Ethoxy-3-oxopropyl)-4-fluorobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (91m):**

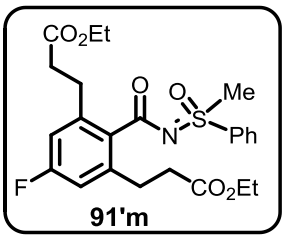


91m

Following GP-3, reaction between **88o** (139 mg, 0.5 mmol) and **89a** (0.19 mL, 1.75 mmol) under the optimized conditions followed by flash column chromatography purification of crude material on silica gel eluting with 1–10% $CHCl_3$/THF gave **91m** (107 mg, 57%)

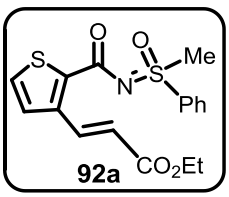
and **91′m** (63 mg, 26%) as pale brown viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 6.4, 2.4 Hz, 1H), 8.03 (d, J = 7.6 Hz, 2H), 7.68 (bt, J = 7.4 Hz, 1H), 7.60 (bt, J = 7.6 Hz, 2H), 6.97–6.86 (m, 2H), 4.07 (q, J = 7.2 Hz, 2H), 3.41 (s, 3H), 3.37–3.23 (m, 2H), 2.71–2.59 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 173.0, 163.9 (d, J = 252 Hz, 1C), 144.9 (d, J = 8.0 Hz, 1C), 138.6, 133.7, 133.6 (d, J = 9.1 Hz, 1C), 131.2, 129.6 (2C), 127.0 (3C), 117.5 (d, J = 21.2 Hz, 1C), 112.9 (d, J = 21.2 Hz, 1C), 60.2, 44.3, 35.6, 29.8, 14.1; ^{19}F (470 MHz, $CDCl_3$) δ –109.0; IR (Neat) ν_{max} 2931, 2854, 1720, 1627, 1221 cm^{-1}; HRMS (ESI) for $C_{19}H_{20}FNO_4S$ $(M+H)^+$: calcd. 378.1175, found 378.1175.

***N*-[2,6-Di(3-ethoxy-3-oxopropyl)-4-fluorobenzoyl]-*S*-methyl-*S*-phenylsulfoxi-mine (91′m):**



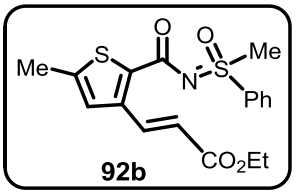
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.0 Hz, 2H), 7.69 (bt, J = 6.8 Hz, 1H), 7.63 (bt, J = 7.4 Hz, 2H), 6.79 (d, J = 9.6 Hz, 2H), 4.12 (q, J = 7.1 Hz, 4H), 3.51 (s, 3H), 3.08–2.97 (m, 4H), 2.69–2.60 (m, 4H), 1.23 (t, J = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 172.8 (2CO-), 162.2 (d, J = 247 Hz, 1C), 139.6 (d, J = 8.1 Hz, 1C), 138.4, 135.2, 133.9, 129.7 (2C), 127.0 (3C), 114.0 (d, J = 21.2 Hz, 2C), 60.4 (2C), 43.8, 35.6 (2C), 28.9 (2C), 14.2 (2C); ^{19}F (470 MHz, $CDCl_3$)δ –113.0; IR (Neat) ν_{max} 2924, 1727, 1626, 1290, 1140 cm^{-1}; HRMS (ESI) for $C_{24}H_{28}FNO_6S$ $(M+H)^+$: calcd. 478.1699, found 478.1699.

***N*-[(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)-thenoyl]-*S*-methyl-*S*-phenylsulfoximine (92a):**



Following GP-2, **92a** (160 mg) was obatined in 88% yield as colorless crystalline solid. mp = 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 16.4 Hz, 1H), 8.06 (bd, J = 7.6 Hz, 2H), 7.69 (bt, J = 7.2 Hz, 1H), 7.62 (bt, J = 7.4 Hz, 2H), 7.38 (d, J = 5.2 Hz, 1H), 7.31 (d, J = 5.2 Hz, 1H), 6.31 (d, J = 16.4 Hz, 1H), 4.21 (q, J = 6.9 Hz, 2H), 3.47 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 166.9, 140.0, 139.0, 138.3, 137.6, 134.0, 129.8 (2C), 129.7, 127.2 (2C), 126.7, 120.8, 60.4, 44.5, 14.2; IR (KBr) ν_{max} 3101, 2931, 1698, 1627, 1282 cm^{-1}; HRMS (ESI) for $C_{17}H_{17}NO_4S_2$ $(M+Na)^+$: calcd. 386.0497, found 386.0499.

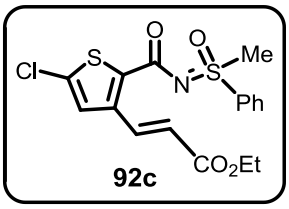
***N*-[5-Methyl-(*E*)-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-thenoyl]-*S*-methyl-*S*-phenylsulfoximine (92b):**



Following GP-2, **92b** (169 mg) was obtained in 90% yield as colorless crystalline solid. mp = 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (b, J = 16.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.63 (bt, J = 7.0 Hz, 1H), 7.56 (t, J = 7.6 Hz, 2H), 6.95 (s, 1H), 6.20 (d, J = 16.4 Hz, 1H), 4.16 (q, J

= 7.1 Hz, 2H), 3.41 (s, 3H), 2.41 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 166.8, 144.5, 140.1, 138.2, 137.5, 136.7, 133.8, 129.5 (2C), 127.0 (2C), 124.9, 120.4, 60.1, 44.3, 15.4, 14.1; IR (KBr) ν_{max} 3063, 2931, 1709, 1610, 1463, 1276 cm^{-1}; HRMS (ESI) for $C_{18}H_{19}NO_4S_2$ $(M+H)^+$: calcd. 378.0833, found 378.0828.

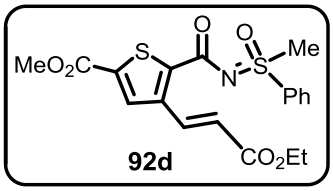
_N_-[5-Chloro-(_E_)-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-thenoyl]-_S_-methyl-_S_-phenylsulfoximine (92c):



92c

Following GP-2, **92c** (169 mg) was obtained in 85% yield as colorless crystalline solid. mp = 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 16.0 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 2H), 7.71 (bt, *J* = 7.2 Hz, 1H), 7.64 (bt, *J* = 7.4 Hz, 2H), 7.13 (s, 1H), 6.23 (d, *J* = 16.4 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.46 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 166.7, 139.8, 138.1, 137.3, 136.5, 135.2, 134.2, 129.8 (2C), 127.2 (2C), 125.8, 121.8, 60.6, 44.6, 14.3; IR (KBr) ν_{max} 3035, 2931, 1698, 1605, 1435, 1293 cm^{-1}; HRMS (ESI) for $C_{17}H_{16}ClNO_4S_2$ $(M+H)^+$: calcd. 398.0287, found 398.0285.

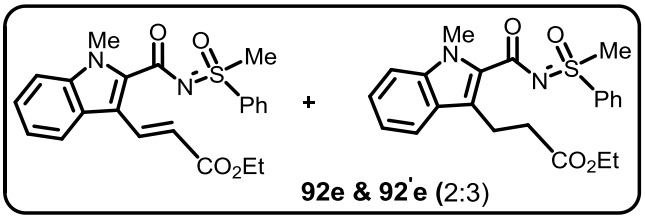
_N_-[2-Methoxycarbonyl-(_E_)-4-(3-ethoxy-3-oxoprop-1-en-1-yl)-thenoyl]-_S_-methyl-_S_-phenylsulfoximine (92d):



92d

Following GP-2, **92d** (178 mg) was obtained in 84% yield as colorless crystalline solid. mp = 185–187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 16.4 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.94 (s, 1H), 7.72 (bt, *J* = 7.0 Hz, 1H), 7.64 (bt, *J* = 7.4 Hz, 2H), 6.34 (d, *J* = 16.4 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.48 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 166.6, 162.0, 143.4, 139.8, 138.0, 136.8, 135.6, 134.2, 131.9, 129.9 (2C), 127.2 (2C), 121.8, 60.5, 52.6, 44.5, 14.3; IR (KBr) ν_{max} 3019, 2931, 1704, 1632, 1221 cm^{-1}; HRMS (ESI) for $C_{19}H_{19}NO_6S_2$ $(M+H)^+$: calcd. 422.0732, found 422.0734.

_N_-[1-Methyl-(_E_)-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-indoloyl]-_S_-methyl-_S_-phenylsulfoximi-ne (92e) and _N_-[1-Methyl-3-(3-ethoxy-3-oxopropyl)-2-indoloyl]-_S_-methyl-_S_-phenylsulfoximine (92′e):



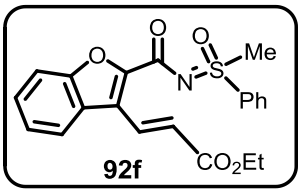
92e & 92′e (2:3)

Following GP-2, reaction between **88t** and **89a** gave the inseparable mixture of alkenylation **92e** and hydroarylation products (2:3 by ^{1}H NMR;122 mg, 60%) as colorless crystalline solid.

Data for **92e** and **92′e:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 16.4 Hz, 0.65H), 8.15 (d, *J* = 7.6 Hz, 1.4H), 8.07 (d, *J* = 6.8 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 0.73H), 7.74–7.59 (m, 6.3H), 7.41–7.36 (m,

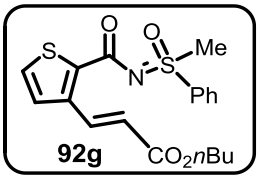
1.4H), 7.35–7.30 (m, 2H), 7.18–7.10 (m, 1H), 6.60 (d, J = 16.4 Hz, 0.65H), 4.28 (q, J = 6.8 Hz, 1.4H), 4.12 (q, J = 7.1 Hz, 2H), 4.00 (s, 2H), 3.99 (s, 3H), 3.65–3.53 (m, 2H), 3.52 (s, 2H), 3.44 (s, 3H), 2.86–2.64 (m, 2H), 1.34 (t, J = 7.0 Hz, 2H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 169.6, 168.9, 168.3, 139.6, 138.74, 138.69, 138.4, 137.9, 134.8, 134.0, 133.7, 130.0, 129.9, 129.7, 127.3, 127.1, 126.3, 125.0, 124.8, 124.6, 121.9, 121.6, 120.2, 119.6, 116.2, 115.5, 110.6, 110.0, 60.2, 60.1, 44.8, 36.0, 32.2, 32.1, 21.7, 14.4, 14.2.

_N_-[(_E_)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)-benzofuranoyl]-_S_-methyl-_S_-phenylsulfoximine (92f):



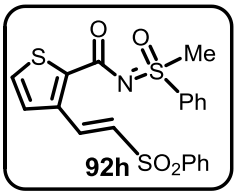
Following GP-2, **92f** (175 mg) was obtained in 88% yield as light brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 16.4 Hz, 1H), 8.08 (d, J = 7.6 Hz, 2H), 7.89 (d, J = 8.0 Hz, 1H), 7.68 (bt, J = 7.4 Hz, 1H), 7.65–7.54 (m, 3H), 7.43 (t, J = 7.8 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 6.67 (d, J = 16.8 Hz, 1H), 4.28–4.19 (m, 2H), 3.52 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 166.0, 154.2, 148.5, 137.9, 136.0, 134.1, 129.7 (2C), 127.5, 127.1 (2C), 125.5, 124.1, 122.1, 121.9, 121.0, 112.5, 60.4, 44.5, 14.2; IR (KBr) ν_{max} 3063, 2926, 1709, 1627, 1271 cm^{-1}; HRMS (ESI) for $C_{21}H_{19}NO_5S(M+Na)^+$: calcd. 420.0882, found 420.0881.

_N_-[(_E_)-3-(3-_n_-Butoxy-3-oxoprop-1-en-1-yl)-thenoyl]-_S_-methyl-_S_-phenylsulfoximine (92g):



Following GP-2, **92g** (161 mg) was obtained in 82% yield as light brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 16.4 Hz, 1H), 8.07 (d, J = 7.6 Hz, 2H), 7.70 (bt, J = 7.2 Hz, 1H), 7.63 (t, J = 7.4 Hz, 2H), 7.38 (d, J = 5.2 Hz, 1H), 7.32 (d, J = 4.4 Hz, 1H), 6.32 (d, J = 16.0 Hz, 1H), 4.22–4.12 (m, 2H), 3.47 (s, 3H), 1.70–1.59 (m, 2H), 1.46–1.35 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 166.9, 139.8, 138.9, 138.1, 137.5, 133.9, 129.7, 129.6 (2C), 127.0 (2C), 126.6, 120.7, 64.2, 44.3, 30.5, 18.9, 13.6; IR (neat) ν_{max} 3013, 2947, 1704, 1638, 1424, 1232 cm^{-1}; HRMS (ESI) for $C_{19}H_{21}NO_4S_2$ $(M+Na)^+$: calcd. 414.0810, found 414.0819.

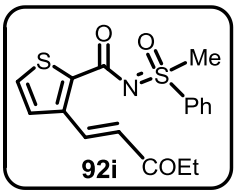
_N_-[(_E_)-3-(2-(Phenylsulfonyl)vinyl)-thenoyl]-_S_-methyl-_S_-phenylsulfoximine (92h):



Following GP-2, **92h** (206 mg) was obtained in 95% yield as colorless crystalline solid. mp = 128–130 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 15.6 Hz, 1H), 8.08 (bd, J = 7.2 Hz, 2H), 7.89 (bd, J = 7.2 Hz, 2H), 7.71 (bt, J = 7.0 Hz, 1H), 7.65 (bt, J = 7.4 Hz, 2H), 7.58 (bt, J = 7.2 Hz, 1H), 7.50 (bt, J = 7.6 Hz, 2H), 7.37 (d, J = 5.2 Hz, 1H), 7.19 (d, J = 5.2 Hz, 1H), 6.77 (d, J = 15.6 Hz, 1H), 3.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 141.5, 140.8, 138.1, 136.9, 136.0, 134.2, 133.3, 130.2, 130.0

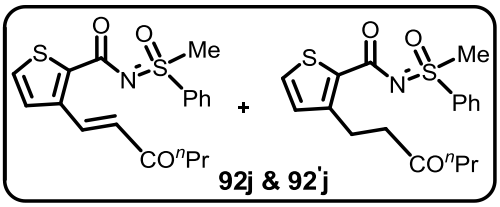
(2C), 129.3 (3C), 127.7 (2C), 127.3 (2C), 126.7, 44.7; IR (KBr) ν_{max} 3052, 2920, 1638, 1260, 1221 cm^{-1}; HRMS (ESI) for $C_{20}H_{17}NO_4S_3$ $(M+H)^+$: calcd. 432.0398, found 432.0399.

_N_-[(_E_)-3-(3-Oxopent-1-enyl)-thenoyl]-_S_-methyl-_S_-phenylsulfoximine (92i):



Following GP-2, **92i** (159 mg) was obtained in 91% yield as light brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 16.8 Hz, 1H), 8.04 (d, J = 7.6 Hz, 2H), 7.68 (bt, J = 7.4 Hz, 1H), 7.61 (t, J = 7.4 Hz, 2H), 7.37 (d, J = 5.2 Hz, 1H), 7.31 (d, J = 5.2 Hz, 1H), 6.51 (d, J = 16.8 Hz, 1H), 3.46 (s, 3H), 2.67 (q, J = 7.2 Hz, 2H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 168.9, 140.6, 138.7, 138.2, 135.8, 134.0, 129.8, 129.7 (2C), 129.2, 127.1 (2C), 126.5, 44.5, 32.2, 8.1; IR (KBr) ν_{max} 3084, 3024, 2926, 1676, 1616,1419, 1287 cm^{-1}; HRMS (ESI) for $C_{17}H_{17}NO_3S_2$ $(M+H)^+$: calcd. 348.0728, found 348.0730.

_N_-[(_E_)-3-(3-Oxohex-1-enyl)-thenoyl]-_S_-methyl-_S_-phenylsulfoximine (92j):



Following GP-2, reaction between **88p** and **89f** gave the inseparable mixture of alkenylation **92j** and hydroarylation products (3:1 by ^{1}H NMR; 156 mg, 86%) as colorless crystalline solid.

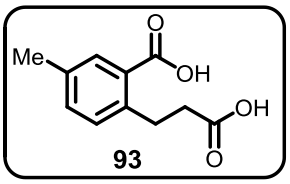
Data for **92j:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 16.4 Hz, 1H), 8.05 (d, J = 7.6 Hz, 2H), 7.70 (bt, J = 7.4 Hz, 1H), 7.62 (bt, J = 7.4 Hz, 2H), 7.38 (d, J = 5.2 Hz, 1H), 7.32 (d, J = 5.2 Hz, 1H), 6.52 (d, J = 16.4 Hz, 1H), 3.47 (s, 3H), 2.64 (t, J = 7.4 Hz, 2H), 1.68–1.58 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.8, 168.9, 140.6, 138.8, 138.2, 135.9, 134.0, 129.8, 129.7, 127.1, 126.5, 44.5, 40.8, 17.6, 13.7.

4.5.3.5. General Procedure for the Hydrolysis of Hydroarylation Product (GP-4)

A solution of **91a** (0.3 mmol) in MeOH (2.0 mL) was added aq. NaOH (5.0 M, 2.0 mL). The reaction mixture was heated at 60 ^{o}C for 6 h. The crude mixture was extracted with CH_2Cl_2 (5 × 10 mL), and the combined extracts were dried over Na_2SO_4. The solvent was filtered and evaporated under vacuum to give the methyl phenyl sulfoximine.

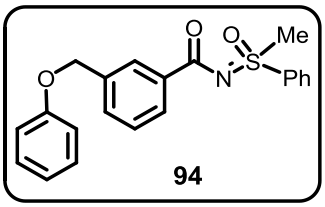
The aqueous layer was acidified with 1N HCl and extracted with CH_2Cl_2 (7 × 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum to give the corresponding benzoic acid derivatives.

2-(2-Carboxyethyl)-5-methylbenzoic acid (93):



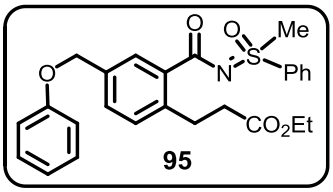
Following GP-4, hydrolysis of **91a** (124 mg, 0.33 mmol) with aq. NaOH afforded **93** (62 mg, 90%) and sulfoximine (42 mg, 81%).^{1}H NMR (400 MHz, DMSO-D_6) δ 12.45 (bs, 2H), 7.60 (s, 1H), 7.26 (d, J = 7.2 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 3.06 (bt, J = 7.6 Hz, 2H), 2.48–2.42 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, DMSO-D_6) δ 174.3, 169.2, 139.3, 135.9, 132.8, 131.2 (2C), 130.6, 35.9, 29.2, 20.8; IR (KBr) ν_{max} 3030, 2920, 1693, 1309, 1276 cm^{-1}; HRMS (ESI) for $C_{11}H_{12}O_4$ $(M+Na)^+$: calcd. 231.0634, found 231.0636.

Synthesis of *N*-[3-(phenoxymethyl)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (94):



Following GP-1, **94** (4.6 g) was prepared in 65% yield as viscous liquid. R_f = 0.38 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.14 (d, J = 7.6 Hz, 1H), 8.06 (d, J = 7.6 Hz, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.66–7.58 (m, 3H),7.45 (t, J = 7.6 Hz, 1H), 7.30 (t, J = 7.8 Hz, 2H), 7.02–6.93 (m, 3H), 5.11 (s, 2H), 3.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 158.6, 138.8, 137.0, 135.8, 133.8, 131.2, 129.7 (2C), 129.4 (2C), 129.0, 128.43, 128.37, 127.1 (2C), 121.0, 114.8 (2C), 69.5, 44.3; IR (Neat) ν_{max}3057, 2926, 1632, 1594, 1287, 1227 cm^{-1}; HRMS (ESI) for $C_{21}H_{19}NO_3S$ $(M+H)^+$: calcd. 366.1164, found 366.1161.

***N*-[2-(3-Ethoxy-3-oxopropyl)-5-(phenoxymethyl)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (95):**



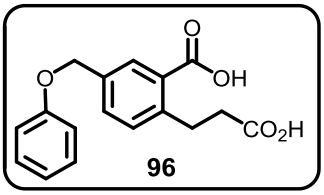
Following GP-2, the reaction of **94** (2.5 g, 6.8 mmol) with **89a** (1.46 mL, 13.7 mmol) was conducted in the presence of $[RuCl_2(p\text{-cymene})]_2$ (416.0 mg, 10 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.35 g, 6.8 mmol), $AgSbF_6$ (933 mg, 2.72 mmol) in 1,2-DCE (10.0 mL) at 120 ^{o}C for 24 h. Upon completion, the inseparable regioisomeric mixture of alkenylation **95′** (major) and hydroarylation **95** (minor) products were isolated [2.1 g (4:1), 66%] as yellow viscous oil. This mixture of compounds was subsequently used for the hydrogenation reaction.

To a solution of **95′**and **95** (2.0 g, 4.3 mmol) in THF (15 mL) and MeOH (10 mL) was added $NiCl_2{\cdot}6H_2O$ (2.0 g, 8.6 mmol) and $NaBH_4$ (0.82 g, 21.5 mmol) at 0 ^{o}C under an argon atmosphere. The resulting mixture was stirred overnight and then quenched with acetone (5.0 mL) and water (5.0 mL). The crude mixture was diluted with Et_2O and filtered through a pad of Celite. The filtrate was separated and the organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was evaporated and the crude mixture was purified by

column chromatography eluting with 3:2 hexane/EtOAc to afford **95** (1.78 g, 89%) as colorless oil.

For product **95**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.05 (d, J = 7.6 Hz, 2H), 7.69 (bt, J = 7.2 Hz, 1H), 7.61 (bt, J = 7.6 Hz, 2H), 7.46 (d, J = 7.6 Hz, 1H), 7.33–7.26 (m, 3H), 7.02–6.93 (m, 3H), 5.06 (s, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.43 (s, 3H), 3.37–3.24 (m, 2H), 2.71–2.62 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 173.3, 158.6, 141.1, 138.6, 135.4, 134.9, 133.7, 131.3, 130.1, 130.0, 129.7 (2C), 129.4 (2C), 127.0 (2C), 120.9, 114.7 (2C), 69.3, 60.2, 44.3, 36.0, 29.6, 14.1; IR (Neat) ν_{max} 3452, 3347, 2986, 2926, 1736, 1627, 1594, 1490, 1227 cm^{-1}; HRMS (ESI) for $C_{26}H_{27}NO_5S$ $(M+Na)^+$: calcd. 488.1508, found 488.1509.

2-(2-Carboxyethyl)-5-(phenoxymethyl)benzoic acid (96):

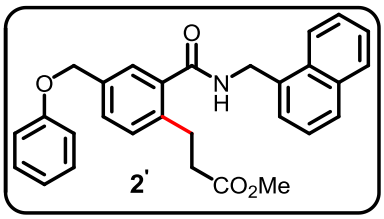


96

Following GP-4, hydrolysis of **95** (1.5 g, 3.2 mmol) afforded **96** (0.79 g) in 81% yield as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$/DMSO-D_6) δ 11.86 (bs, 2H), 7.90 (s, 1H), 7.40 (bd, J = 7.6 Hz, 1H), 7.28–7.14 (m, 3H), 6.91–6.83 (m, 3H), 4.95 (s, 2H), 3.18 (bt, J = 7.4 Hz, 2H), 2.62–2.45 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$/DMSO-D_6) δ 174.9, 169.0, 158.5, 142.3, 135.1, 131.3, 130.9, 130.5, 130.2, 129.5 (2C), 121.0, 114.7 (2C), 69.1, 35.7, 29.5; IR (KBr) ν_{max} 2964, 2926, 1726, 1687, 1238 cm^{-1}; HRMS (ESI) for $C_{17}H_{16}O_5$ $(M+Na)^+$: calcd. 323.0896, found 323.0898.

The reaction of **96** (300 mg) with catalytic amount of H_2SO_4 (0.15 mL) in methanol (1.2 mL) in 30 min afforded the mono-esterification product 2-(3-methoxy-3-oxopropyl)-5-(phenoxymethyl) benzoic acid (**96′**, 85%) and the di-esterification compound (**96″**, 10%). The mixture of crude compounds was subjected to the EDC-coupling for the amide formations in the next step.

Methyl-3-(2-(naphthalen-1-ylmethylcarbamoyl)-4-(phenoxymethyl)phenyl)propanoate (2′):

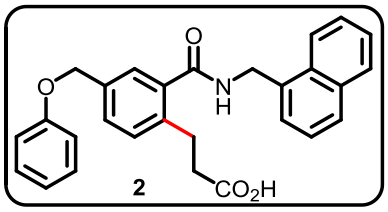


2′

A solution of *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodimide, hydrochloride salt (EDC·HCl) (99 mg, 0.64 mmol), hydroxybenzotriazole (HOBt) (98 mg, 0.64 mmol) and **96′+96″** (100 mg, 0.32 mmol) in DMF (15 mL) was stirred under an argon atmosphere. The naphthalen-1-ylmethanamine **97** (56 μL, 0.38 mmol) was introduced drop wise at 0 °C. The resulting reaction mixture was stirred for about 1 h at 0 °C, and warmed to ambient temperature and continued for overnight. Upon completion, the reaction mixture was acidified with HCl (1N). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3 × 5.0 mL). The combined extracts were washed with 10%

aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4. Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography on silica gel furnishing **2′** (92 mg, 64%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.62–7.51 (m, 3H), 7.49–7.36 (m, 3H), 7.31–7.23 (m, 3H), 6.99–6.88 (m, 3H), 6.53 (bs, 1H), 5.10 (bd, J = 5.2 Hz, 2H), 4.97 (s, 2H), 3.60 (s, 3H), 3.09 (t, J = 7.4 Hz, 2H), 2.71 (t, J = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 169.2, 158.5, 138.4, 136.6, 135.4, 133.9, 133.3, 131.4, 130.2 (2C), 129.5, 129.2, 128.8 (2C), 127.0, 126.7, 126.3, 126.1, 125.4, 123.6, 121.1, 114.8 (2C), 69.1, 51.7, 42.3, 35.3, 27.9; IR (KBr) ν_{max} 3293, 2947, 2920, 1753, 1632, 1517, 1249 cm^{-1}; HRMS (ESI) for $C_{29}H_{27}NO_4$ $(M+H)^+$: calcd. 454.2018, found 454.2017.

3-(2-(Naphthalen-1-ylmethylcarbamoyl)-4-(phenoxymethyl)phenyl)propanoic acid (2):[1]



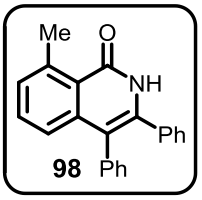
A solution of **2′** (50 mg, 0.11 mmol), $LiOH{\cdot}H_2O$ (5.0 mg, 0.11 mmol) in THF/MeOH (4.0 mL, 1:1) was heated at 60 ^{o}C for about 4 h. The solvent was evaporated. The crude mixture was diluted with CH_2Cl_2 (10 mL) and acidified with 1N HCl; the mixture was extracted with CH_2Cl_2 (5 × 5.0 mL). The combined organic layers were dried over Na_2SO_4, and concentrated to give **2** (30 mg, 62%) as colorless solid. ^{1}H NMR (500 MHz, DMSO-D_6) δ 12.15 (bs, 1H, OH), 8.99 (bt, J = 5.7 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.62–7.40 (m, 6H), 7.35–7.25 (m, 3H), 6.99 (d, J = 8.5 Hz, 2H), 6.94 (t, J = 7.2 Hz, 1H), 5.07 (s, 2H), 4.92 (bd, J = 6.0 Hz, 2H), 2.94 (bt, J = 8.0 Hz, 2H), 2.54 (bt, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-D_6) δ 174.2, 169.2, 158.7, 138.7, 137.4, 135.3, 135.0, 133.8, 131.4, 130.2, 130.0 (2C), 129.1, 129.0, 128.0, 127.0, 126.7, 126.3, 126.0, 125.9, 124.0, 121.2, 115.2 (2C), 69.0, 41.1, 35.8, 28.4; HRMS (ESI) for $C_{28}H_{25}NO_4$ $(M+H)^+$: calcd. 440.1862, found 440.1861.

4.5.3.6. General Procedure for Annulation of *N*-Aroylated MPS with Diphenyl Acetylene (GP-5)

A mixture of *N*-protected sulfoximine (0.5 mmol), diphenylacetylene (178 mg, 1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.0 mg, 5.0 mol %), and $AgSbF_6$ (69 mg, 40 mol %) in AcOH (28.0 µL, 1.0 equiv) & 1,4-dioxane (2.0 mL) was taken in a Schelenk tube under an argon atmosphere. The resulting mixture was stirred at 120 ^{o}C for 24 h. Subsequently, the reaction mixture was cooled to ambient temperature, filtered through a small plug of Celite and then washed with CH_2Cl_2 (3 × 10 mL). The solvents were evaporated under reduced pressure and

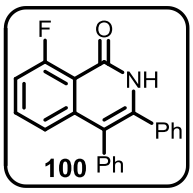
the crude material was purified using column chromatography on silica gel (10-40% *n*-hexane/EtOAc) as an eluent.

8-Methyl-3,4-diphenylisoquinolin-1(2H)-one (98):[20]



63 mg, 40% yield; colorless crystalline solid; ^{1}H NMR (400 MHz, DMSO-D_6) δ 11.27 (s, 1H, NH), 7.43 (t, J = 7.2 Hz, 1H), 7.32–7.19 (m, 9H), 7.14–7.08 (m, 2H), 6.93 (d, J = 7.6 Hz, 1H), 2.88 (s, 3H); ^{13}C NMR (101 MHz, DMSO-D_6) δ 163.2, 141.1, 140.4, 139.0, 137.0, 135.0, 132.3, 132.0, 130.2, 129.6, 128.7, 128.6, 128.1, 127.4, 123.8, 116.0, 24.1 (one peak is missing due to overlap).

8-Fluoro-3,4-diphenylisoquinolin-1(2H)-one (**100**):



Following GP-5, reaction between **88j** (55.4 mg, 0.2 mmol) and diphenylacetylene (71 mg, 0.4 mmol), in the presence of [$RuCl_2$(*p*-cymene)]$_2$ (6.0 mg, 5.0 mol %), and $AgSbF_6$ (14 mg, 40 mol %) in AcOH (11.0 μL) & 1,4-dioxane (1.0 mL) at 120 ^{o}C for 24 h afforded **100** (40 mg) in 63% yield as yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H, NH), 7.54–7.46 (m, 1H), 7.36–7.29 (m, 3H), 7.28–7.22 (m, 5H), 7.20–7.14 (m, 2H), 7.14–7.10 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 160.8 (d, J = 108 Hz, 1C), 141.5, 138.4, 135.6, 134.4, 133.4 (d, J = 9.0 Hz, 1C), 131.8, 129.1, 128.9, 128.5, 128.4, 127.5, 121.6 (d, J = 4.0 Hz, 1C), 116.5, 113.4 (d, J = 21 Hz, 1C); ^{19}F (470 MHz, $CDCl_3$) δ −110.4; IR (KBr) ν_{max} 3183, 3035, 1649, 1473 cm^{-1}; HRMS (ESI) for $C_{21}H_{14}FNO$ $(M+H)^+$: calcd. 316.1137, found 316.1138.

4.6. References

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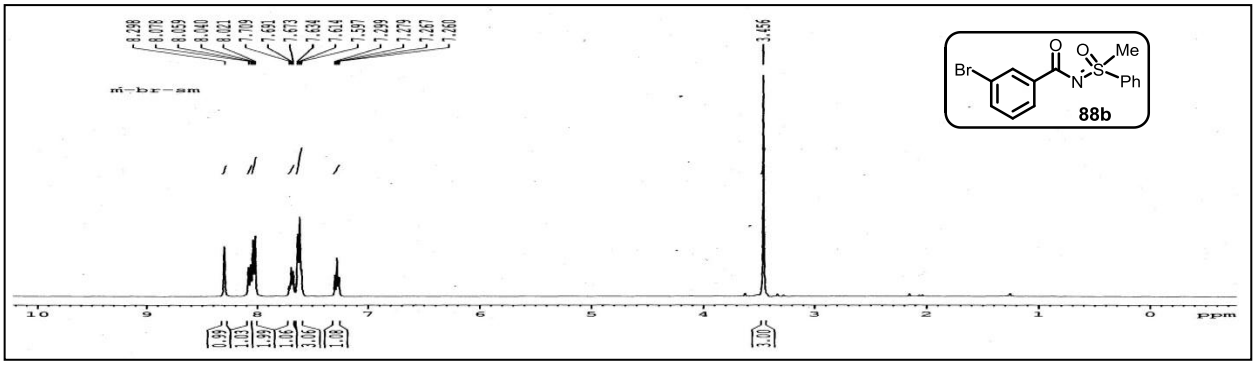
4.7. Spectra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7.267
7.260
3.455
m-br-sm
Br
O
O
N
S
Me
Ph
88b
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9
8
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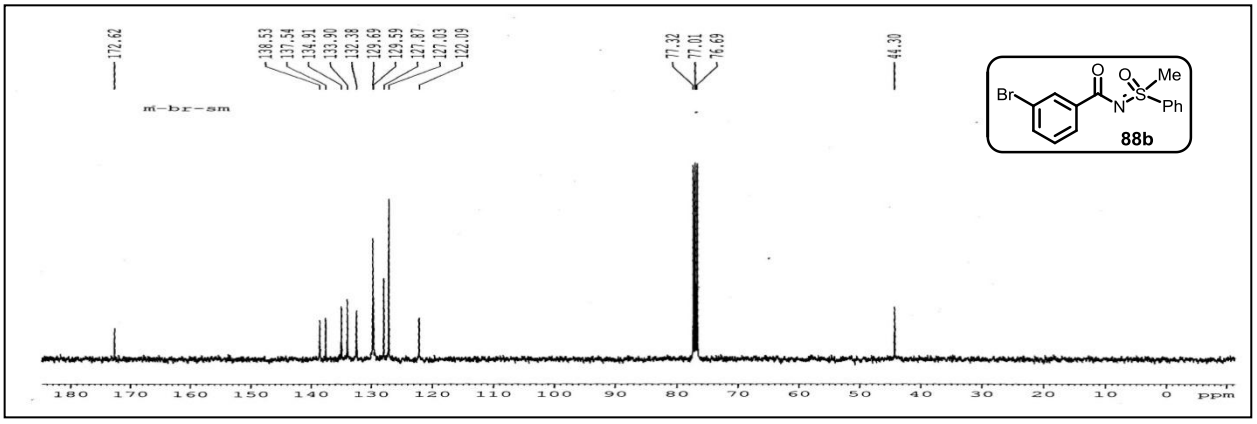
1.00
3.00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m-br-sm
Br
O
O
N
S
Me
Ph
88b
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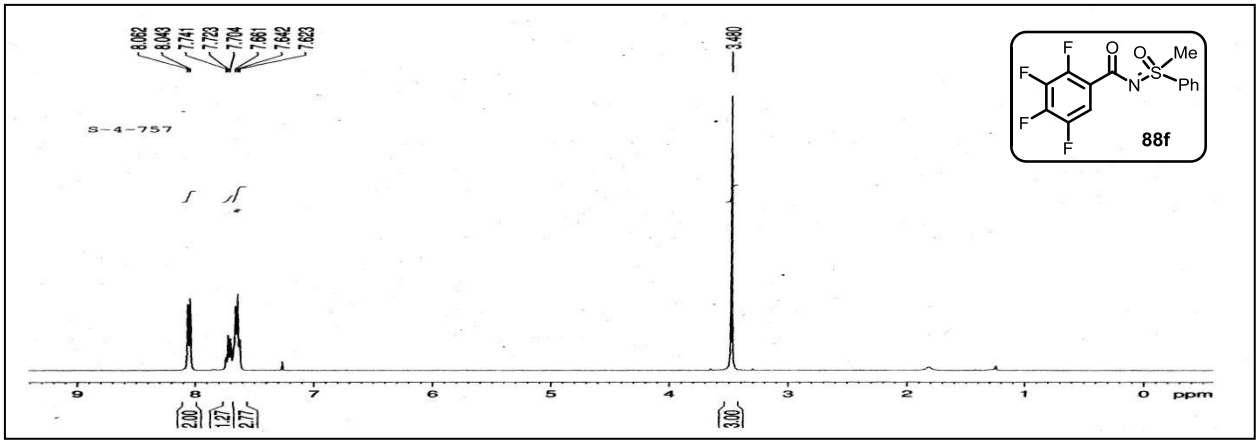
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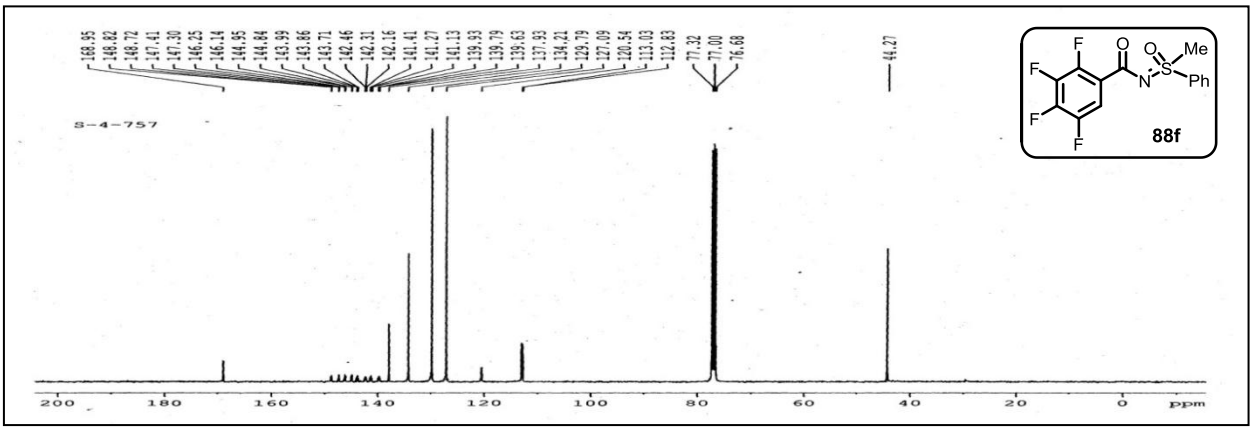
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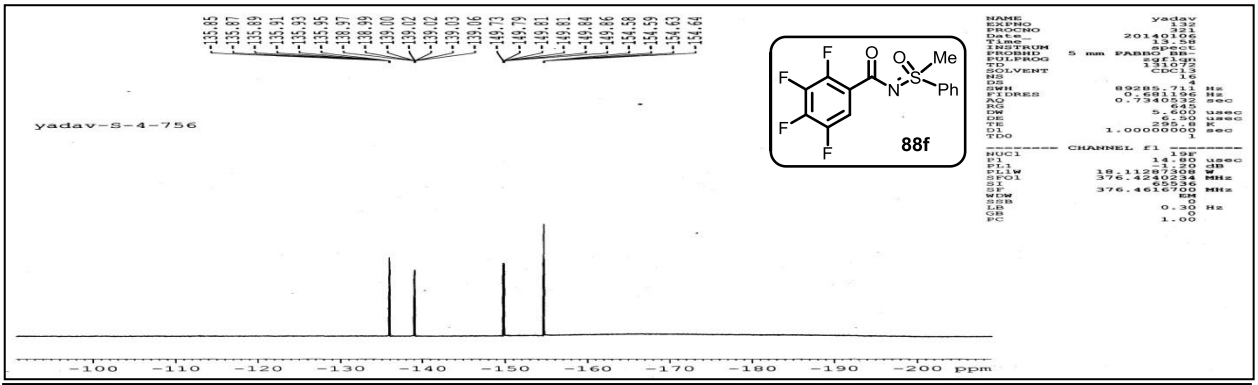
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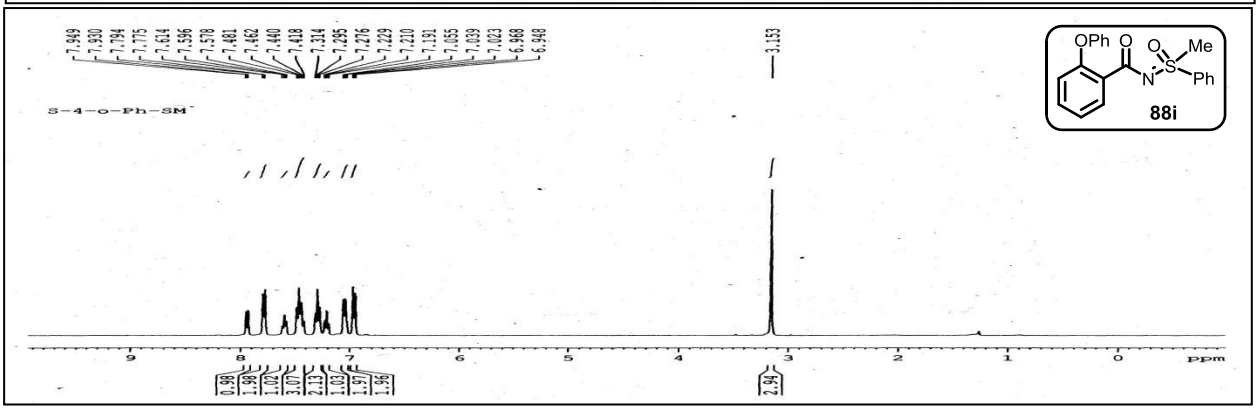
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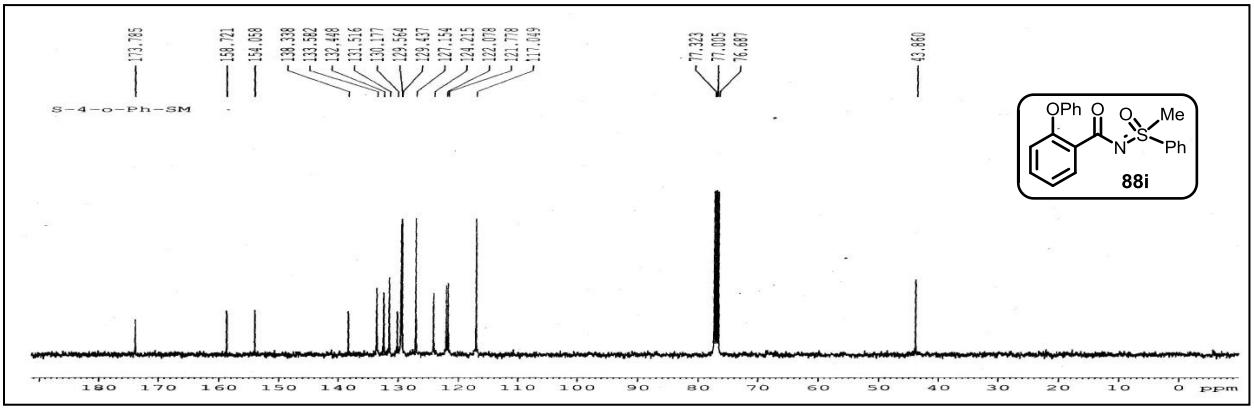
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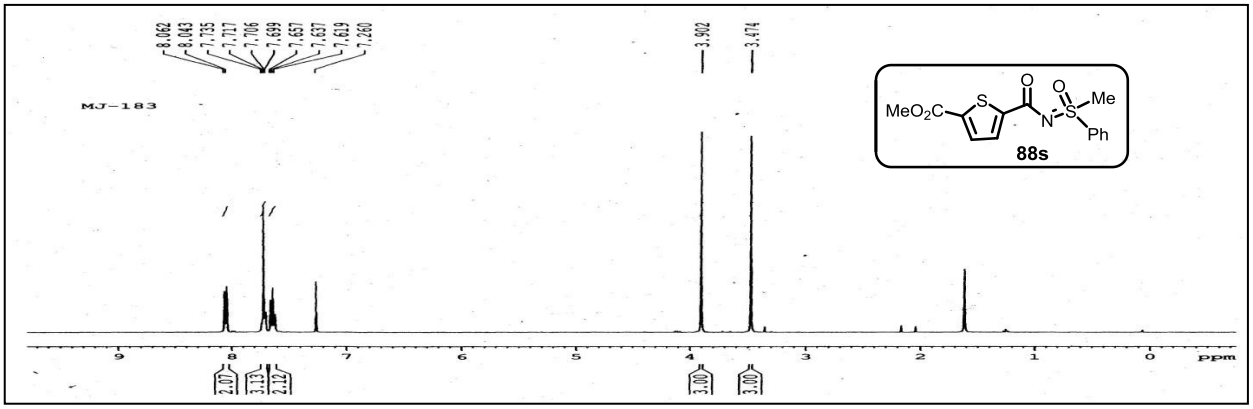
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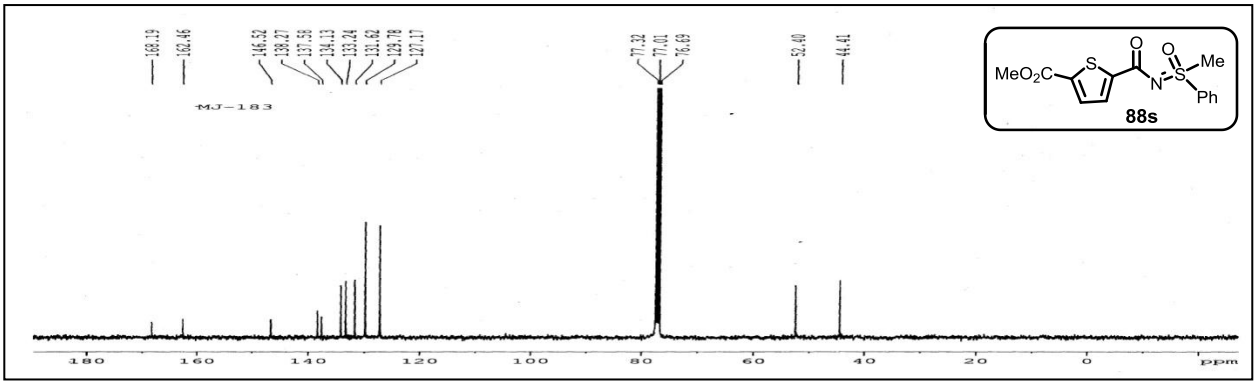
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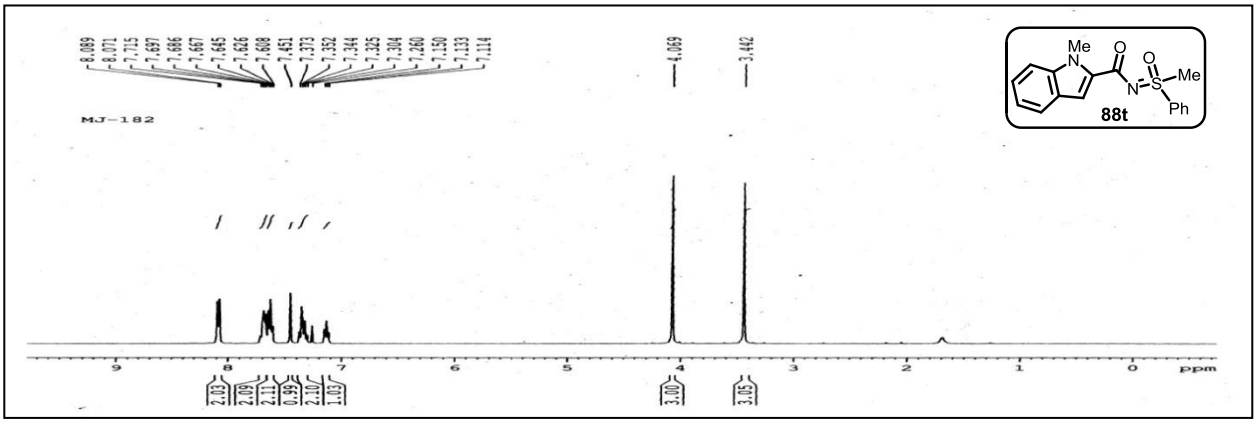
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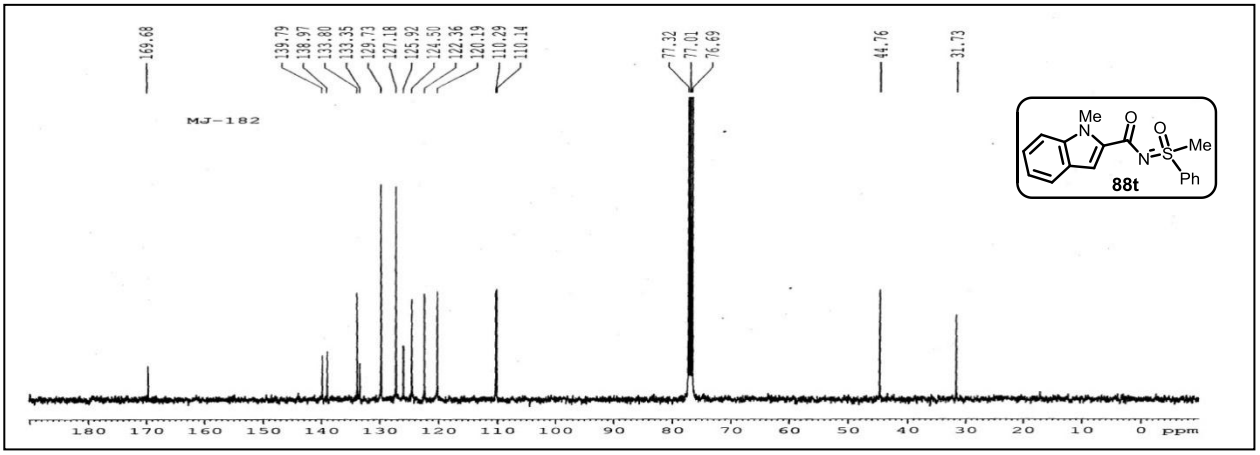
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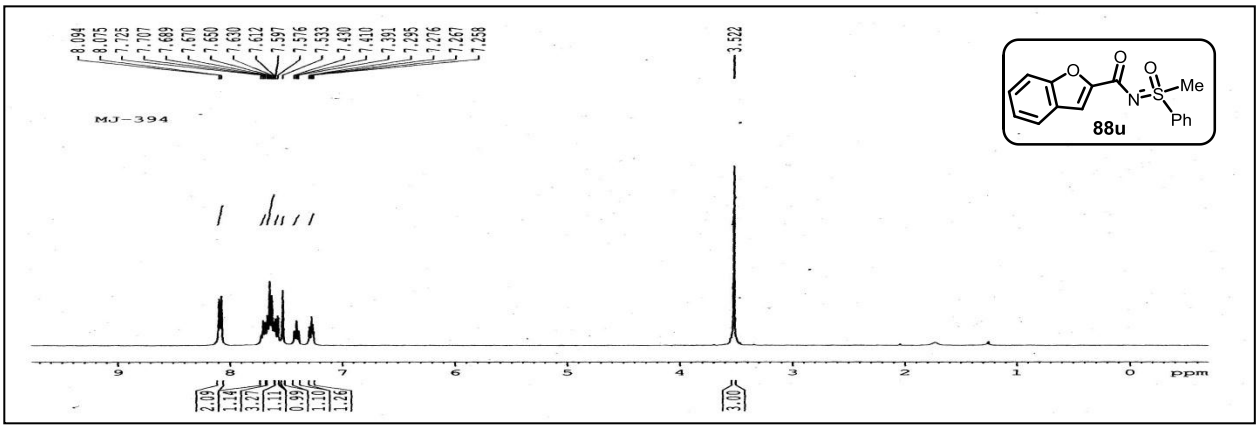
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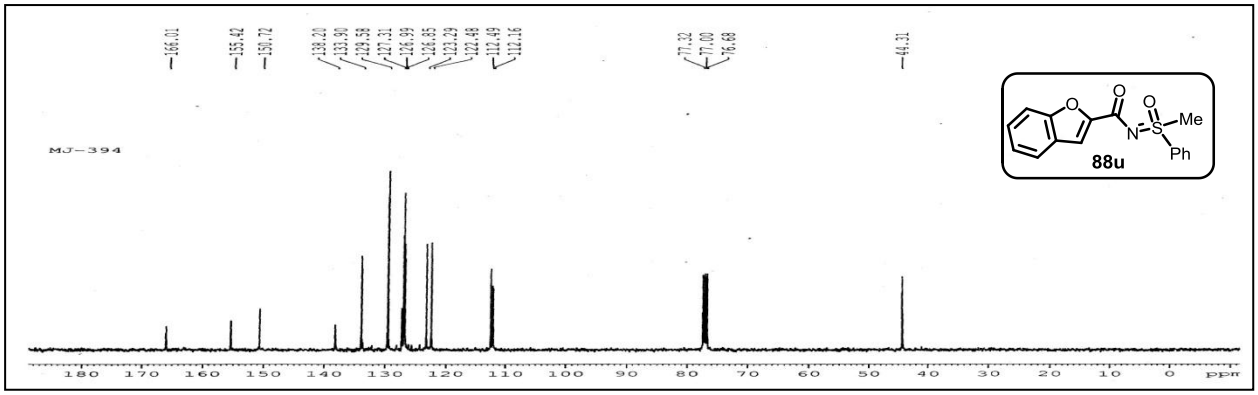
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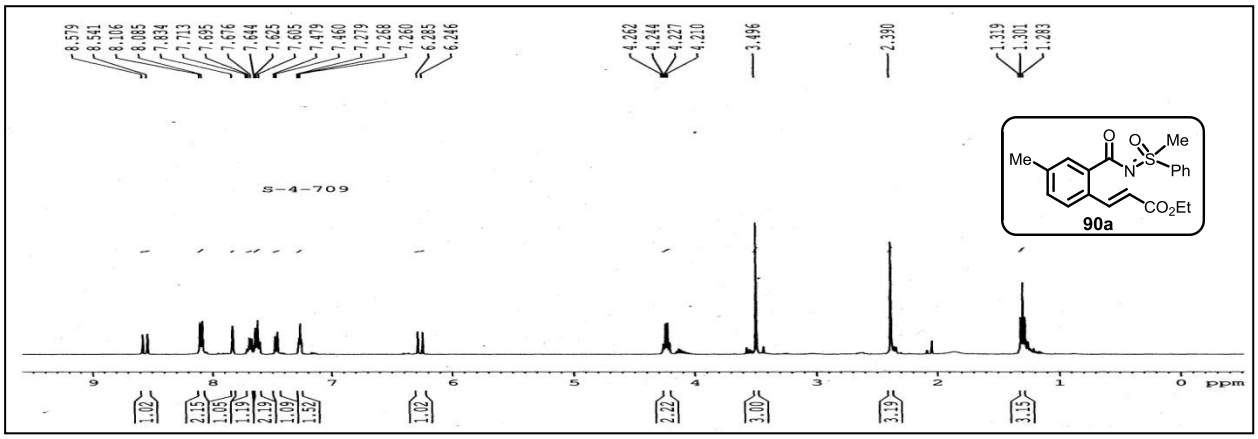
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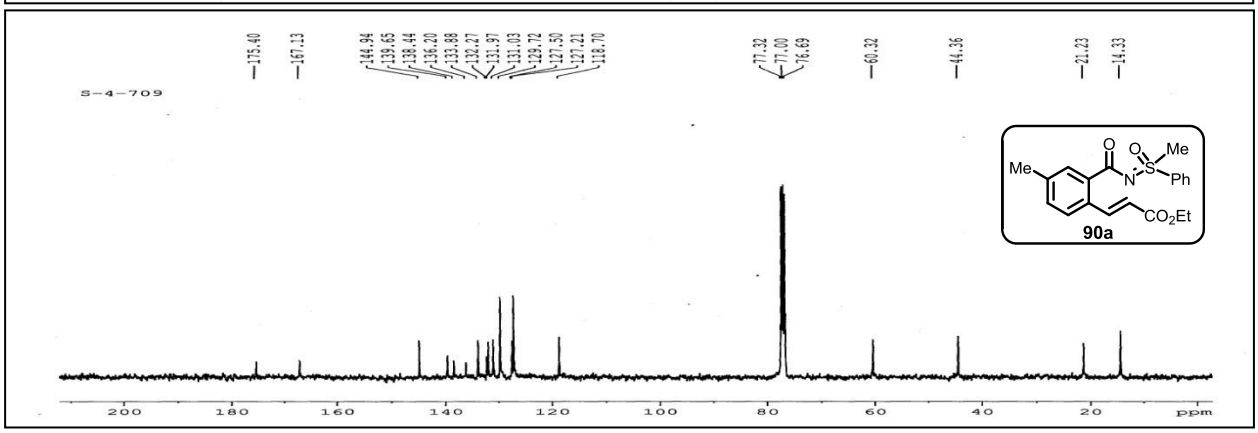
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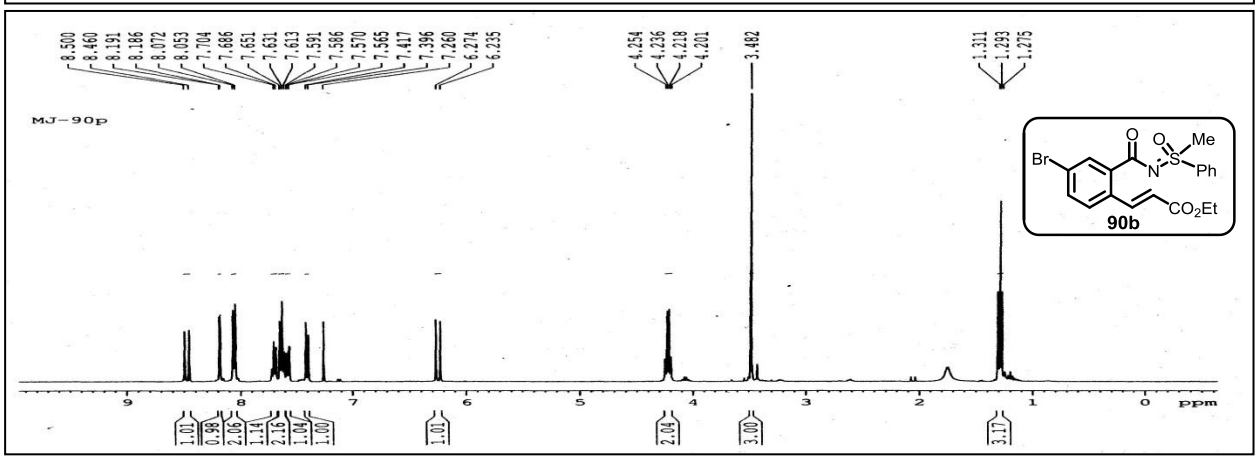
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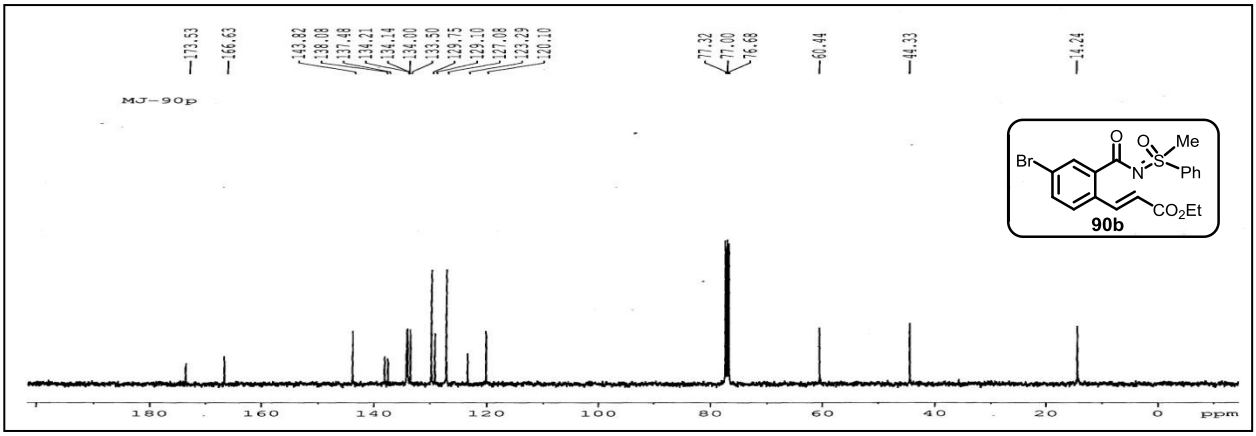
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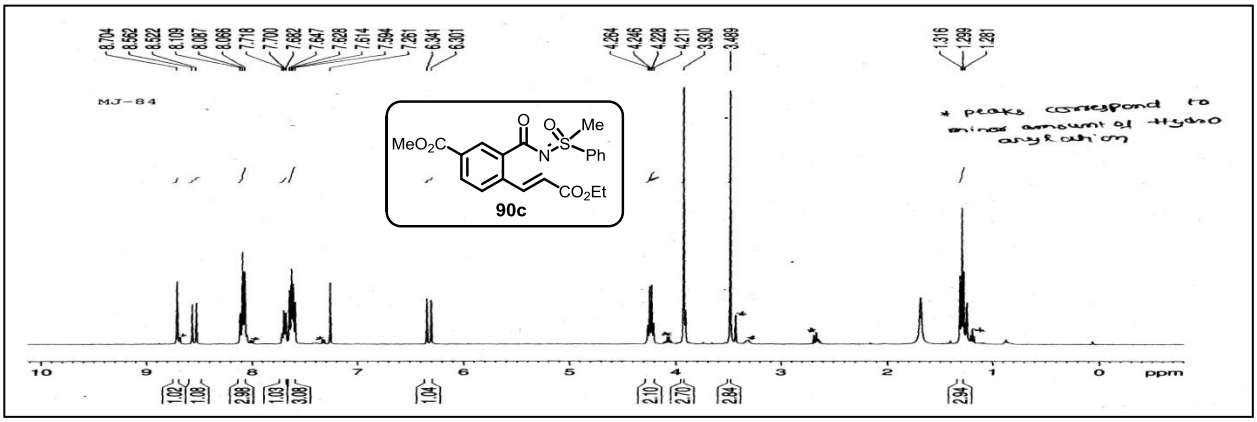
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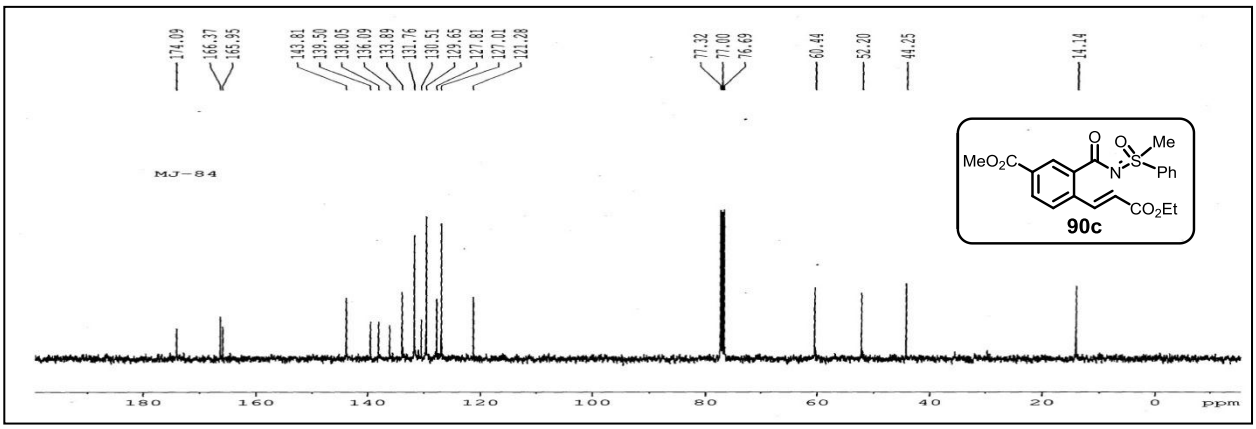
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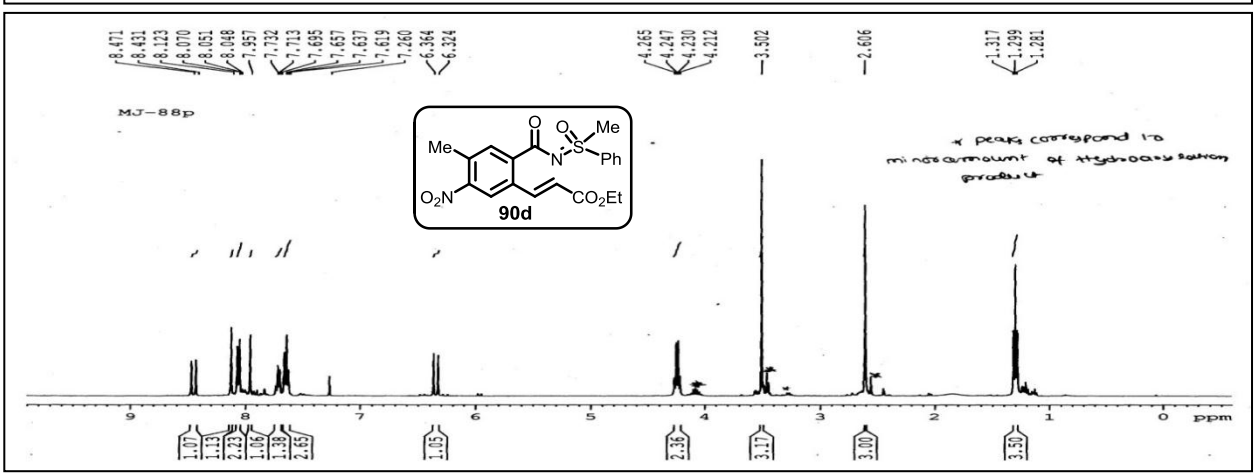
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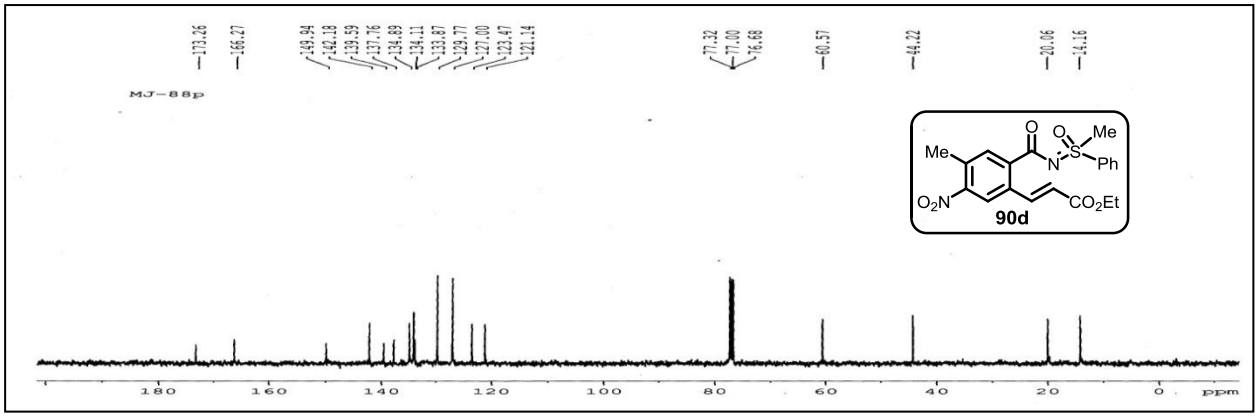
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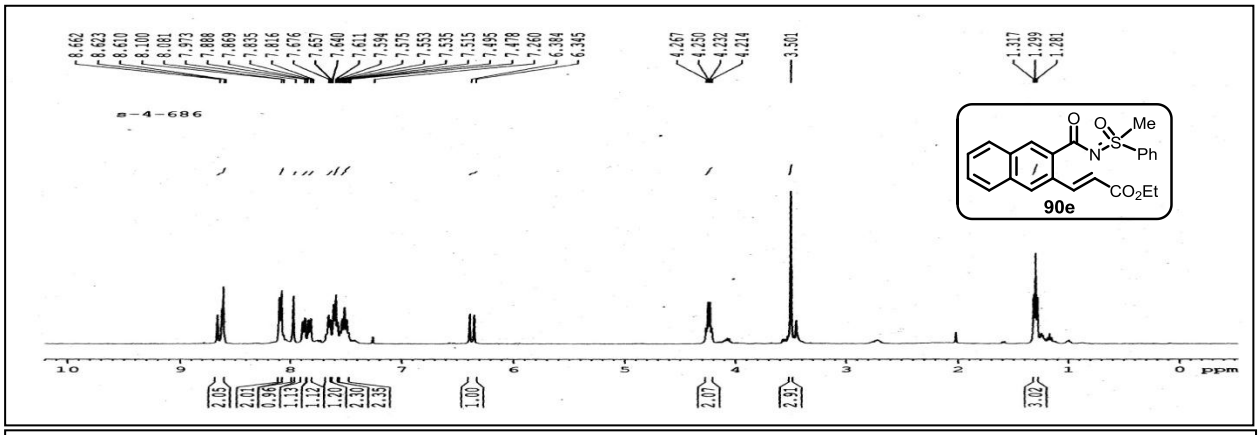
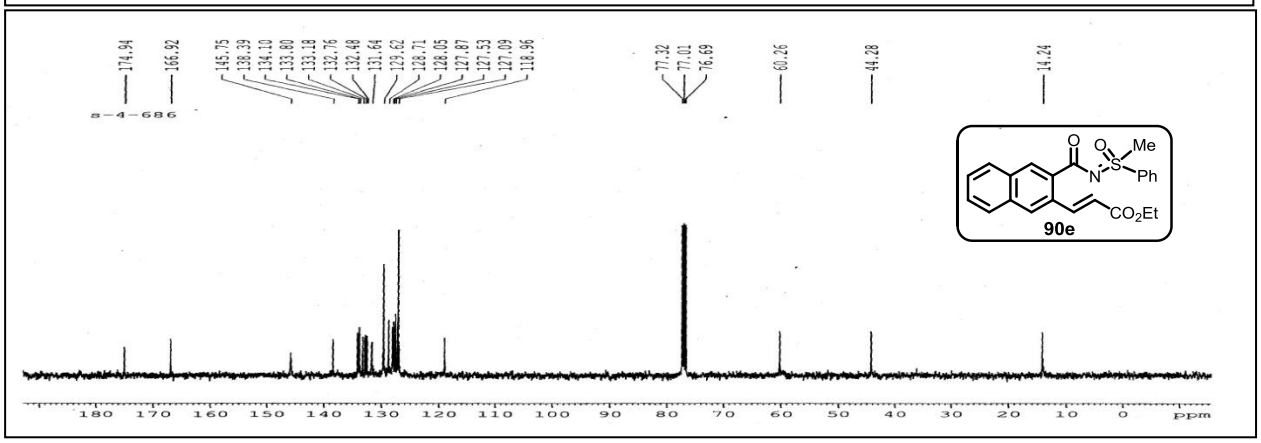
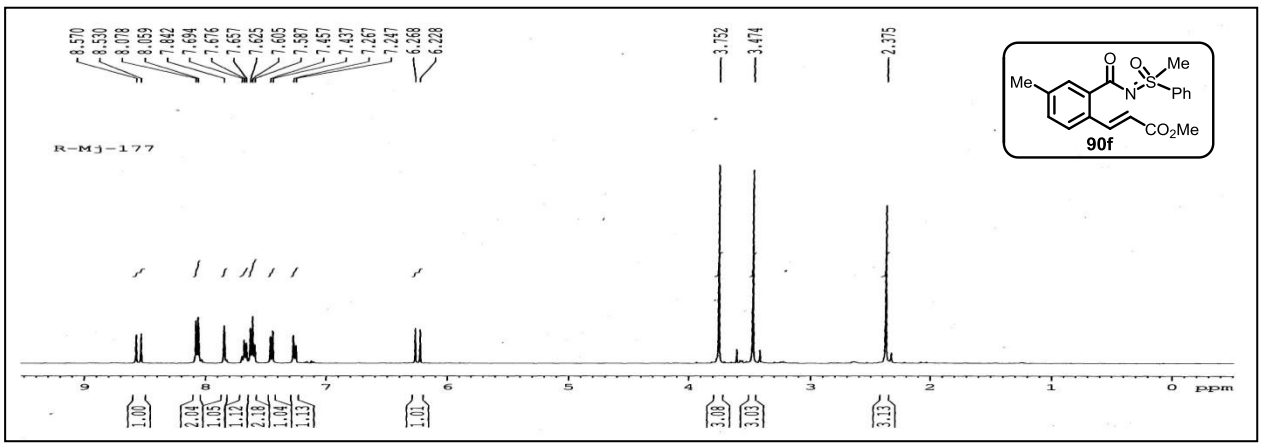
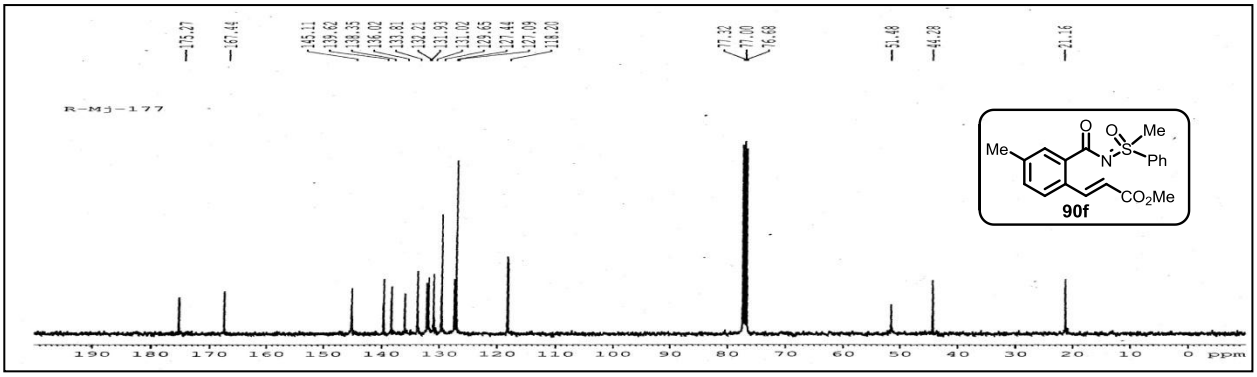
90d


s-4-686
90e


s-4-686
90e


R-Mj-177
90f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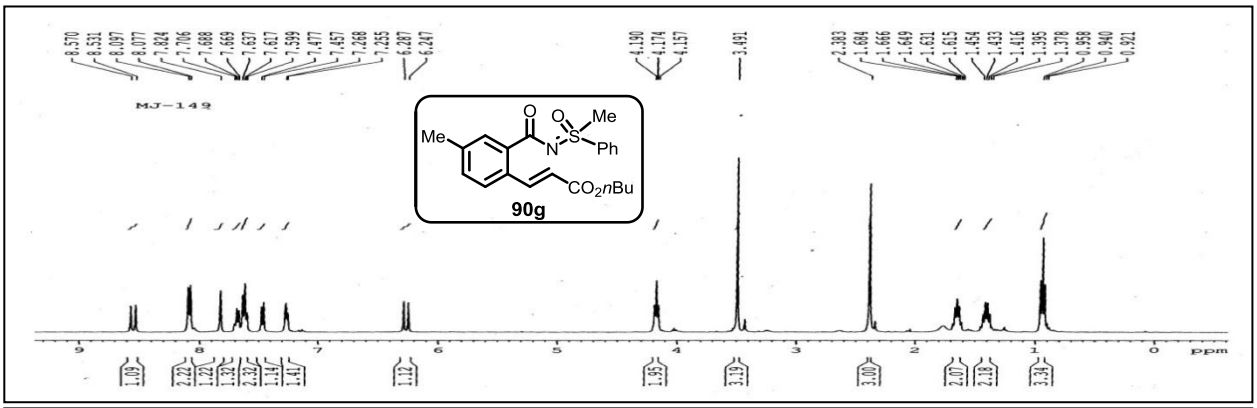
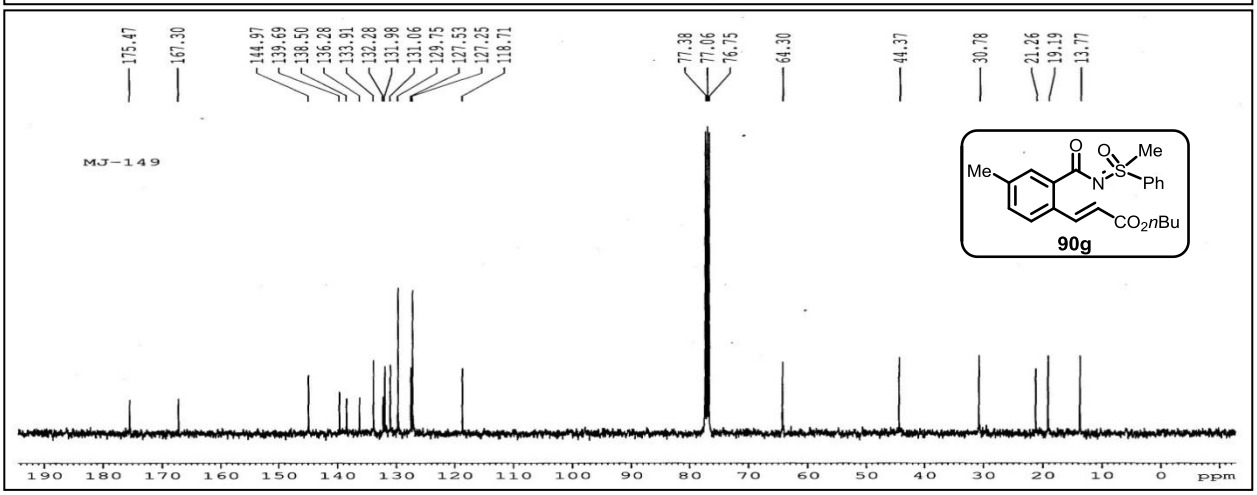
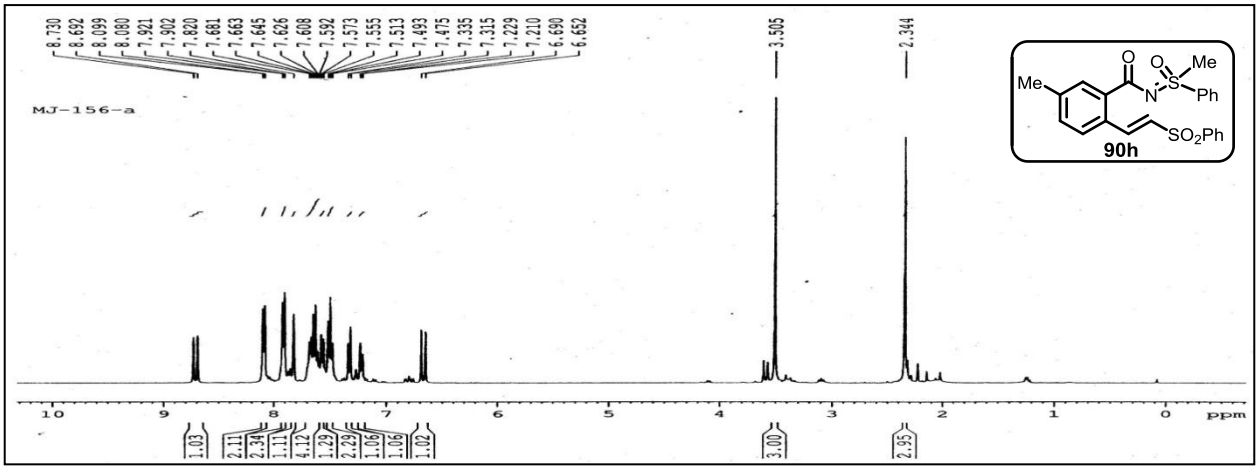
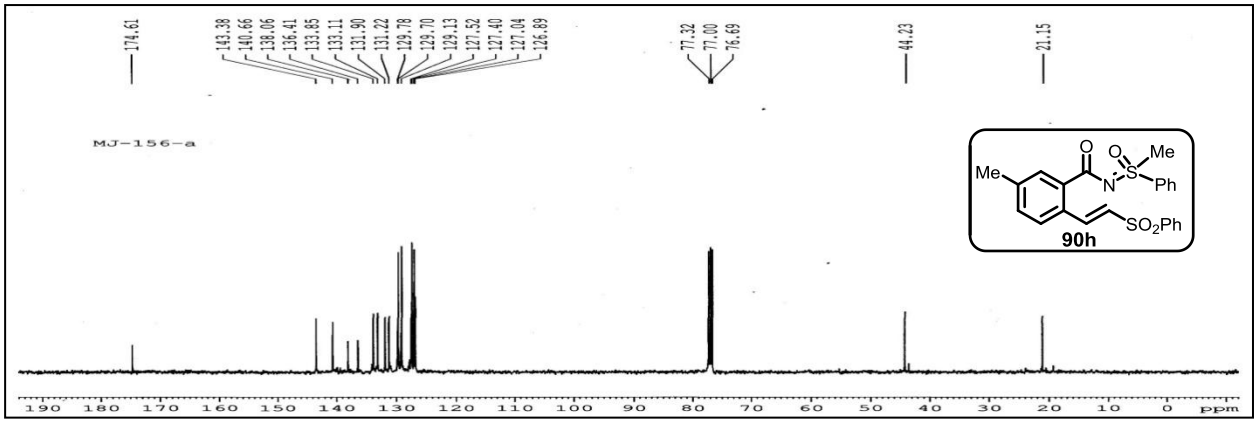
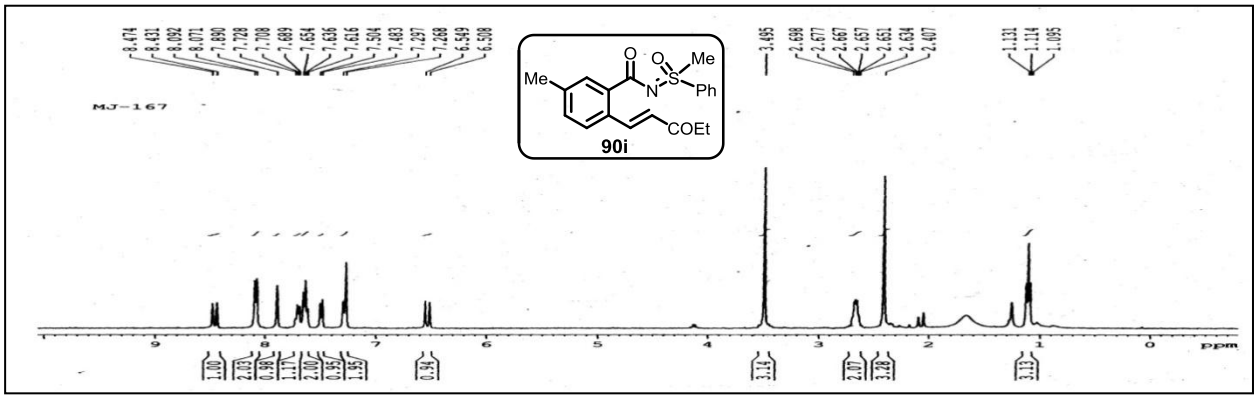
90f

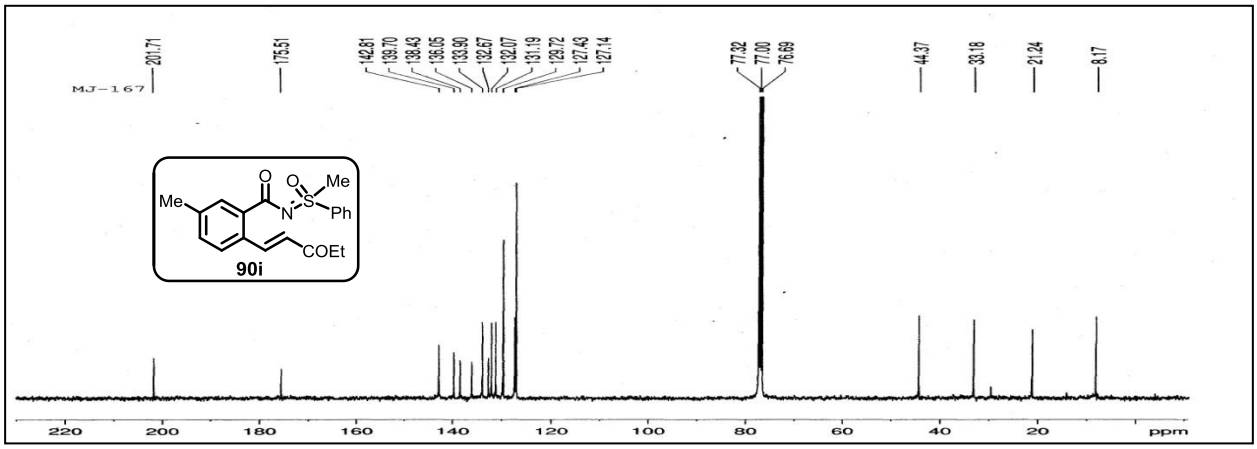

MJ-149
90g

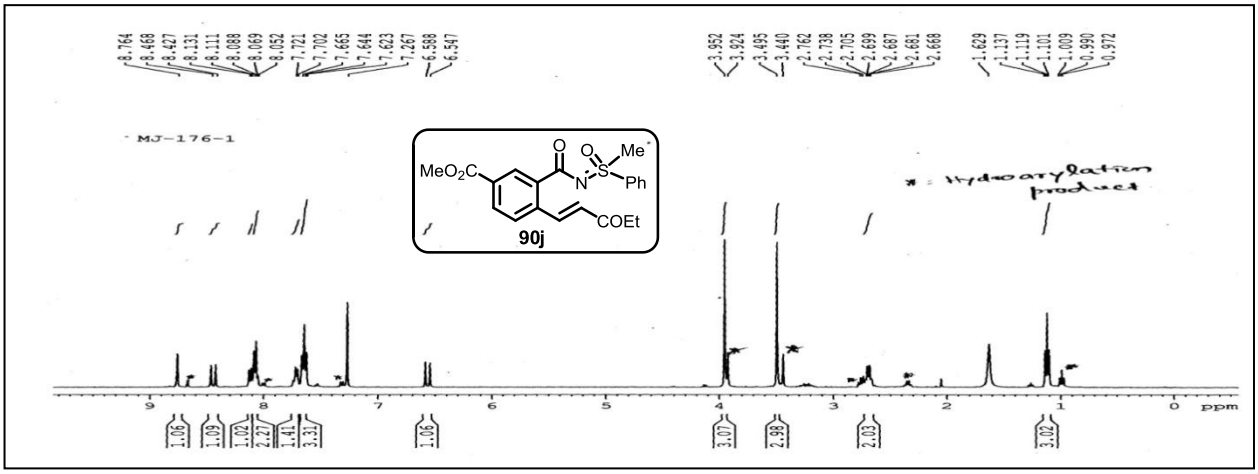

MJ-149
90g

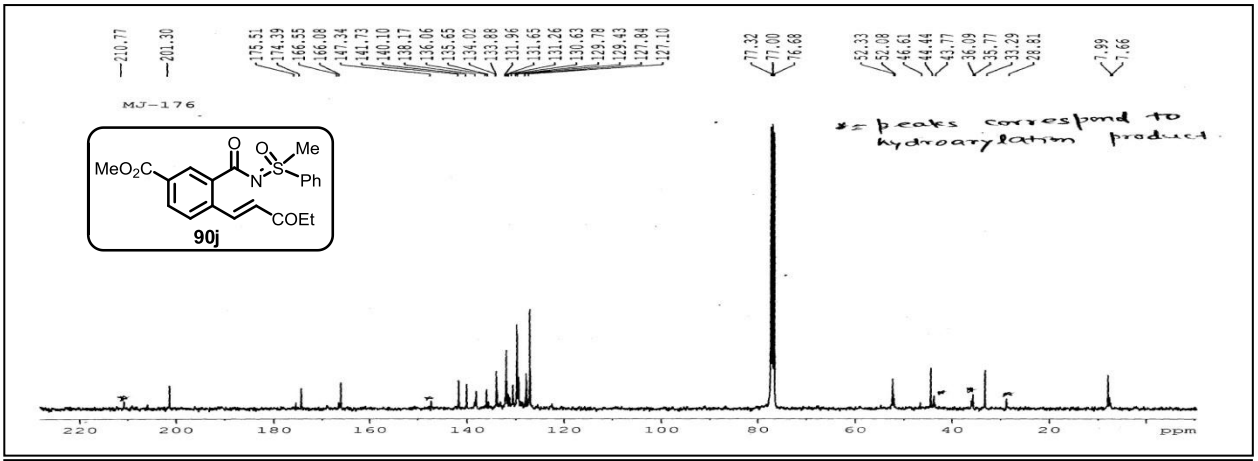

MJ-156-a
90h

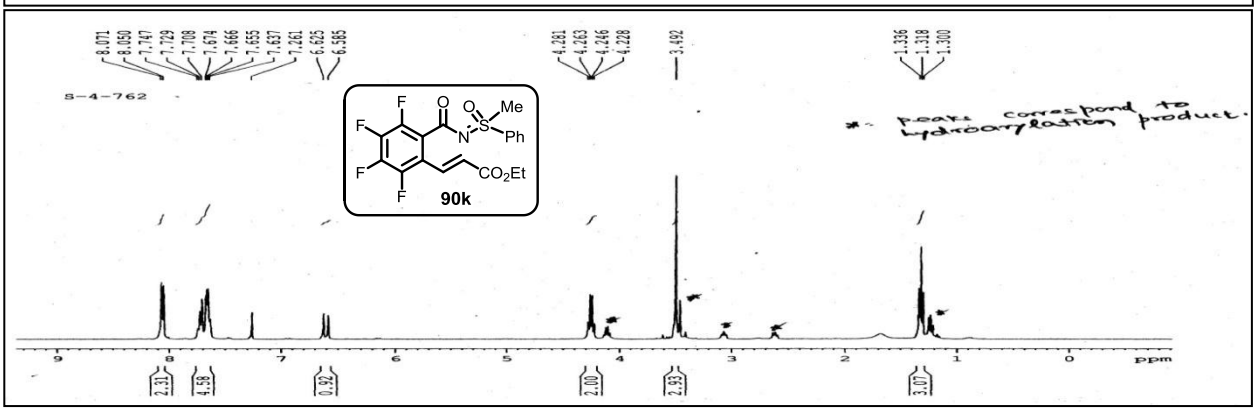

MJ-156-a
90h

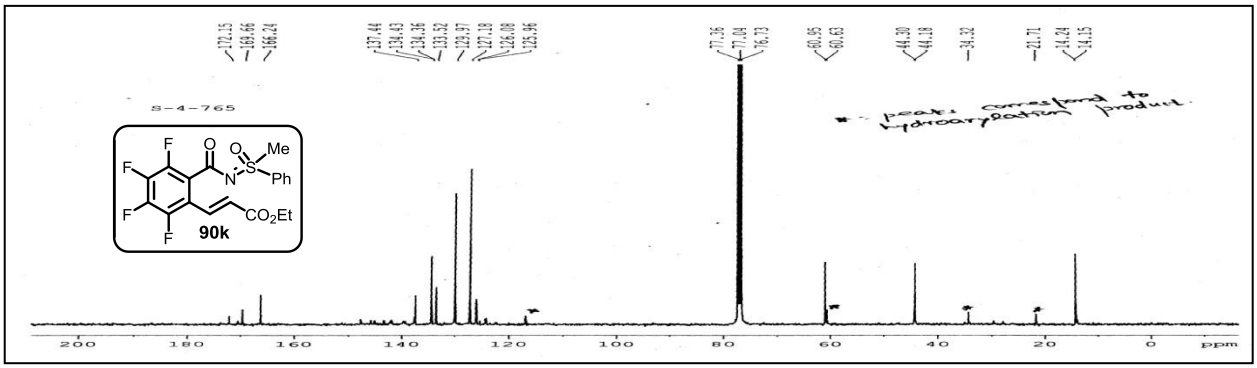

MJ-167
90i

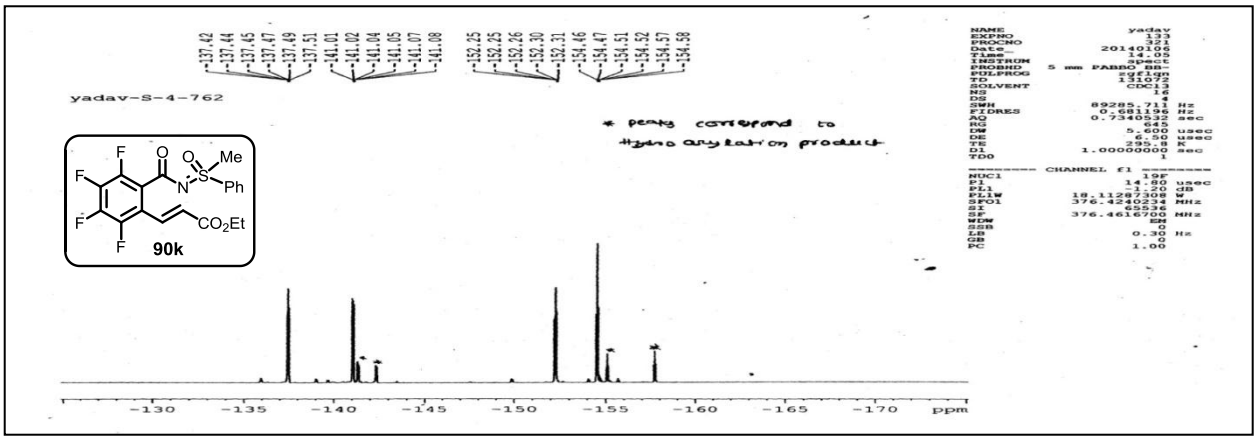

MJ-167
90i

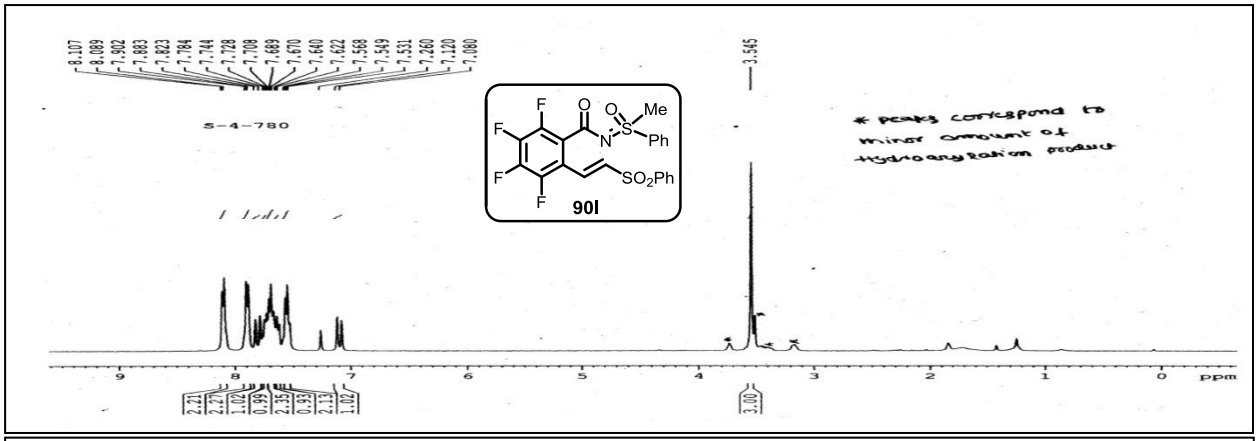

MJ-176-1
90j
* : Hydroarylation product

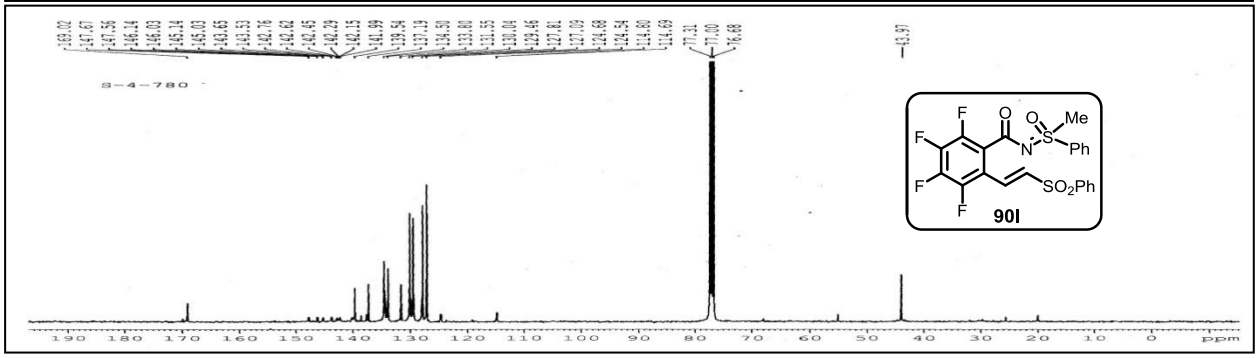

MJ-176
90j
* = peaks correspond to hydroarylation product

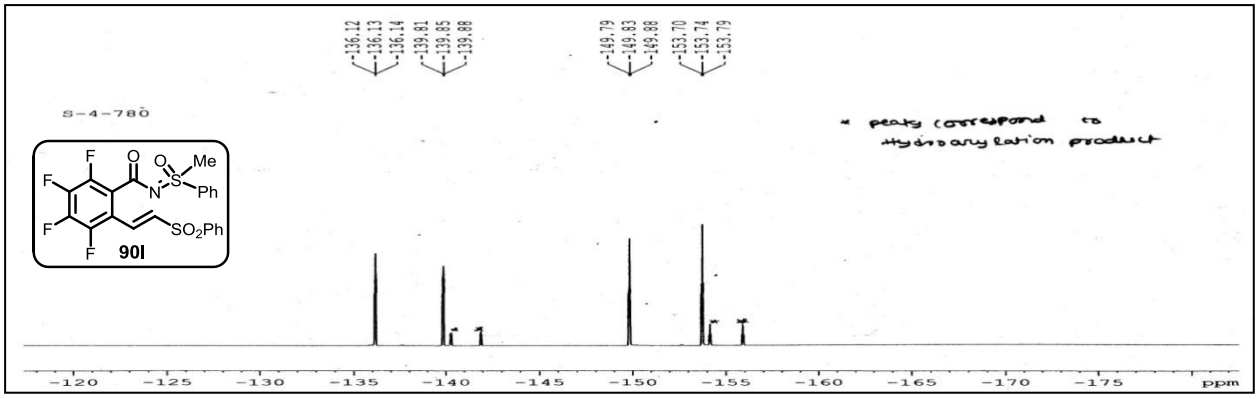

S-4-762
90k
* = peaks correspond to hydroarylation product.

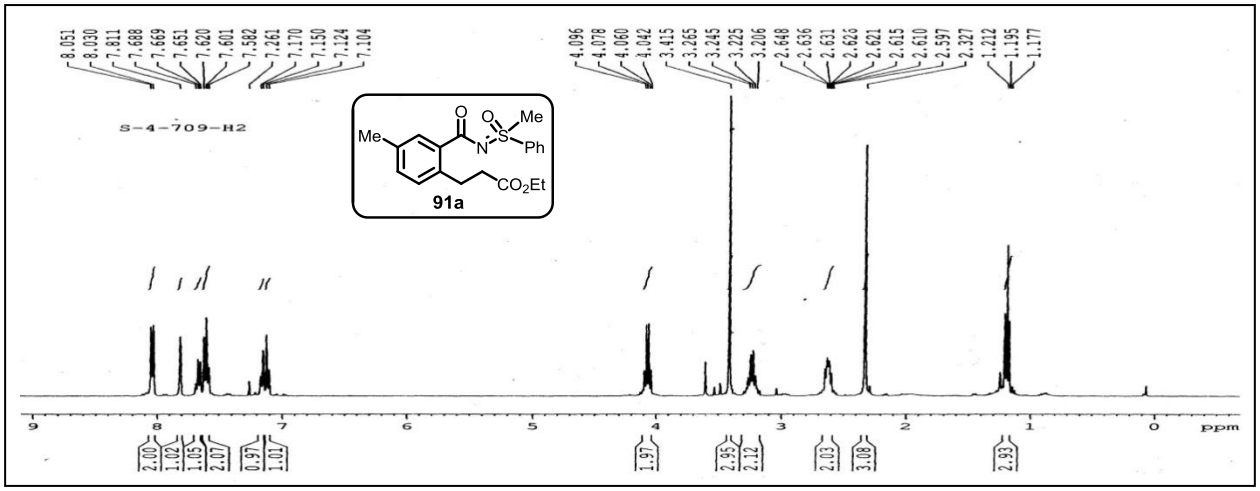

S-4-765
90k
* = peaks correspond to hydroarylation product.

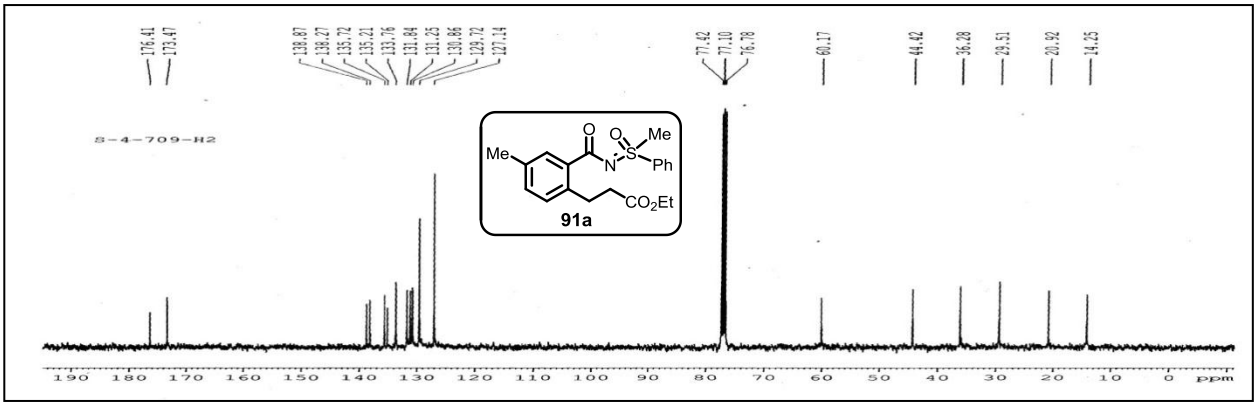

yadav-S-4-762
90k
* peaks correspond to hydroarylation product

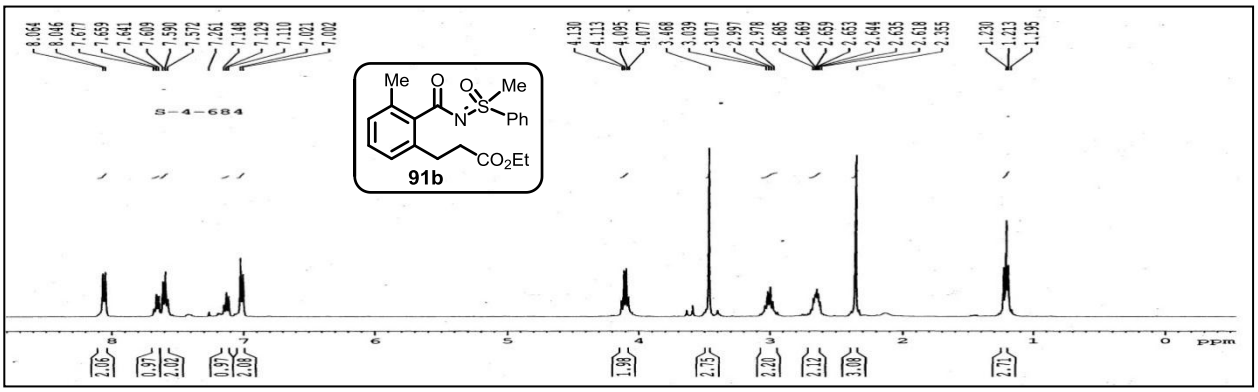

S-4-780
90l
* peaks correspond to minor amount of hydroarylation product
ppm

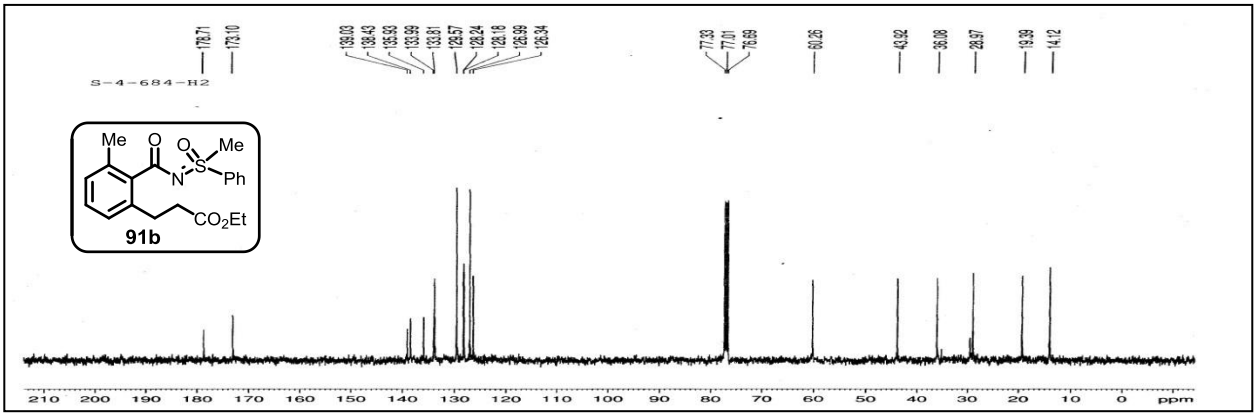

S-4-780
90l
ppm

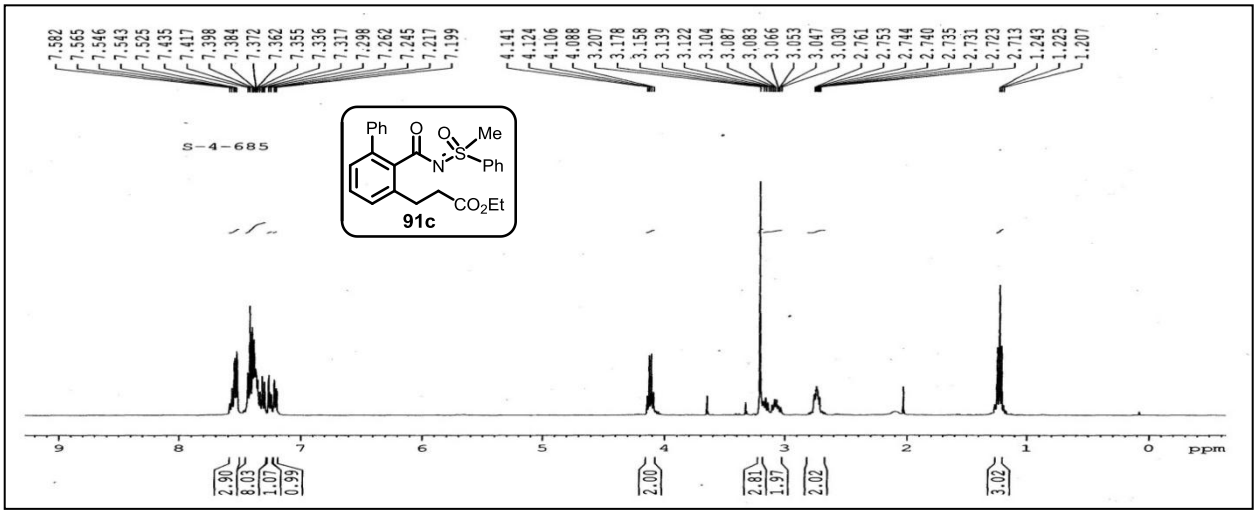

S-4-780
90l
* peaks correspond to hydroarylation product
ppm


S-4-709-H2
91a
ppm


S-4-709-H2
91a


S-4-684
91b


S-4-684-H2
91b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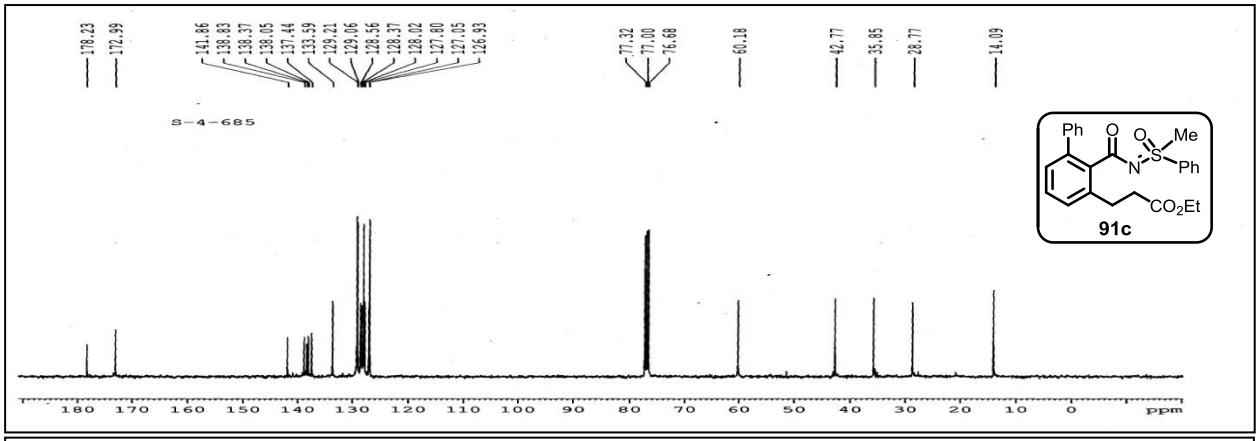
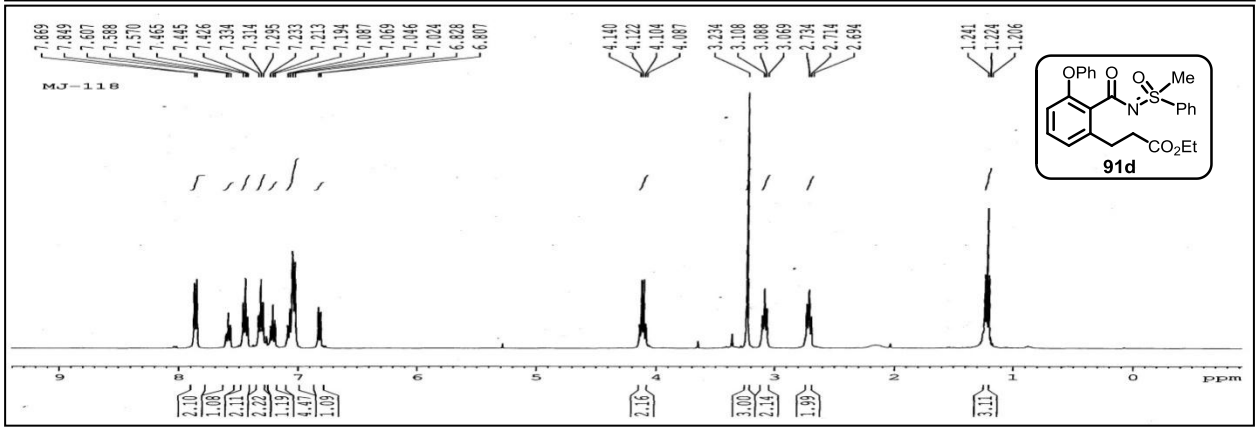
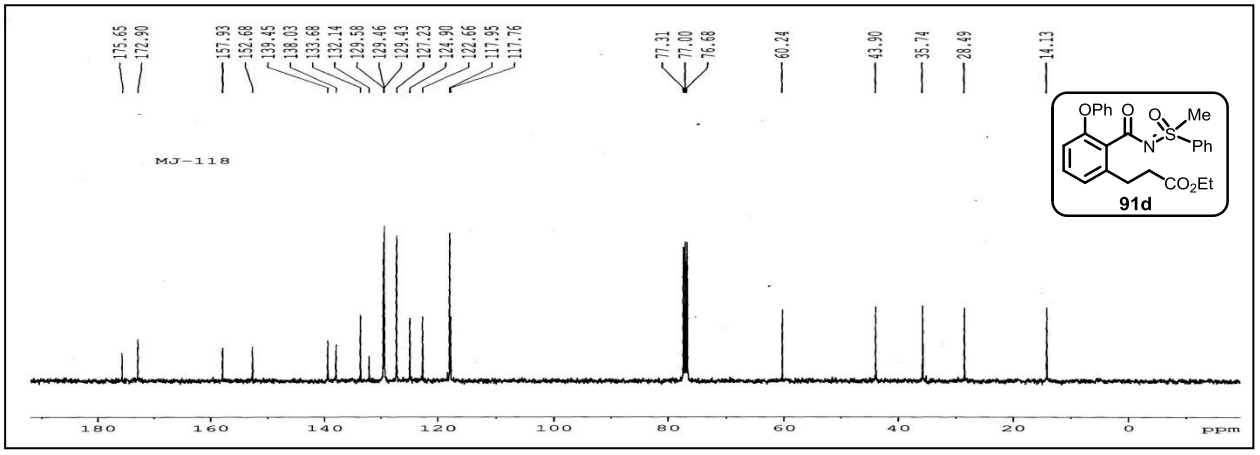
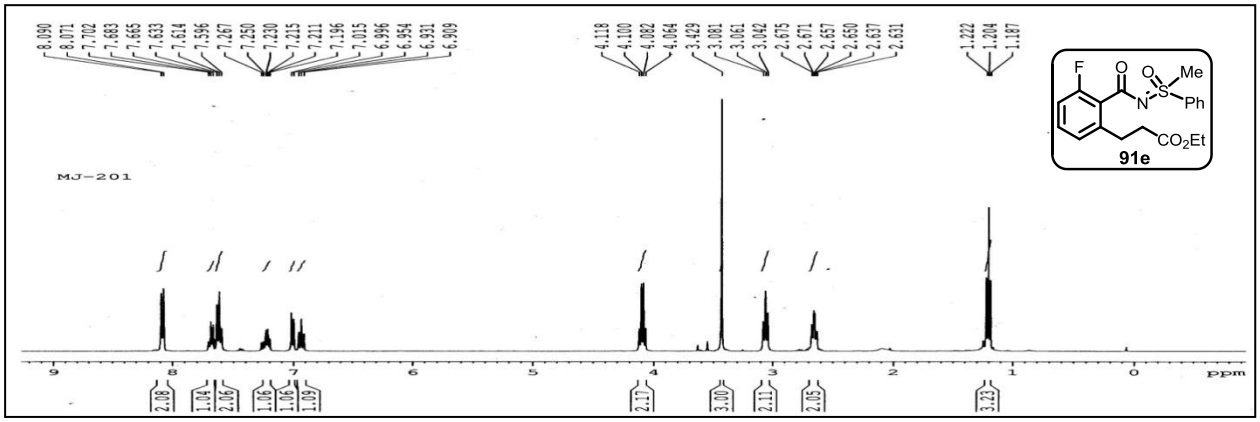
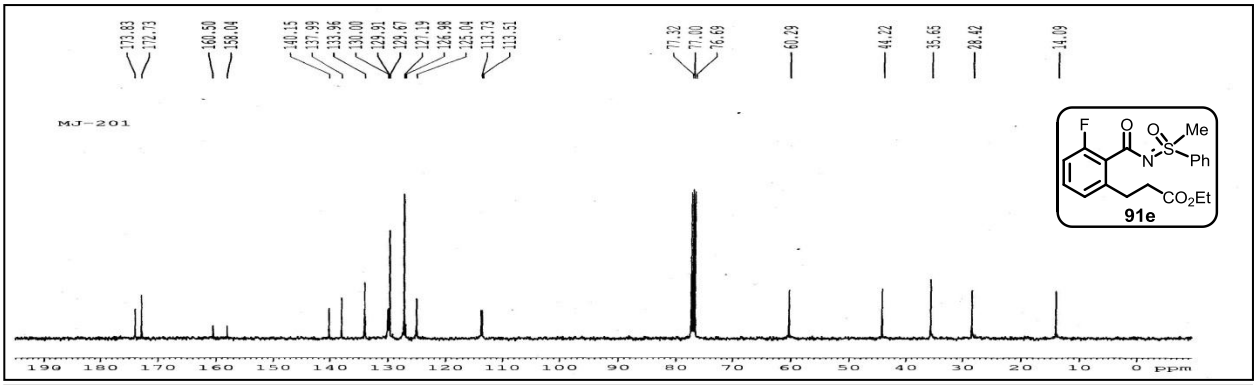
91c


S-4-685
91c


MJ-118
91d


MJ-118
91d


MJ-201
91e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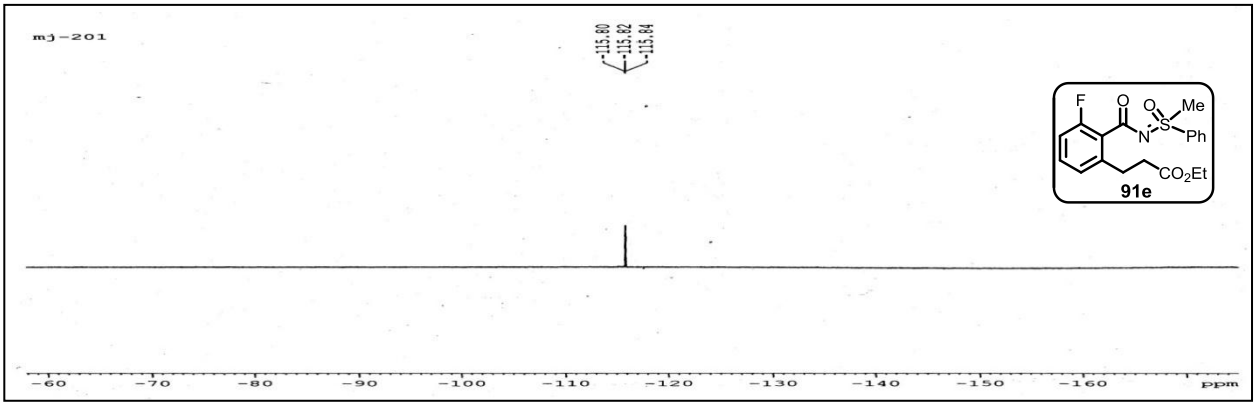
91e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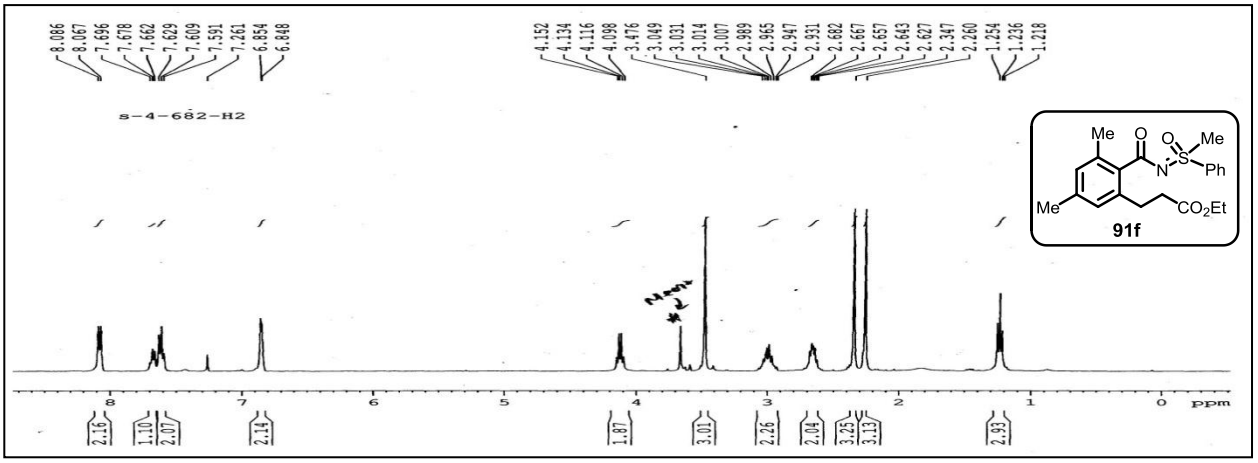
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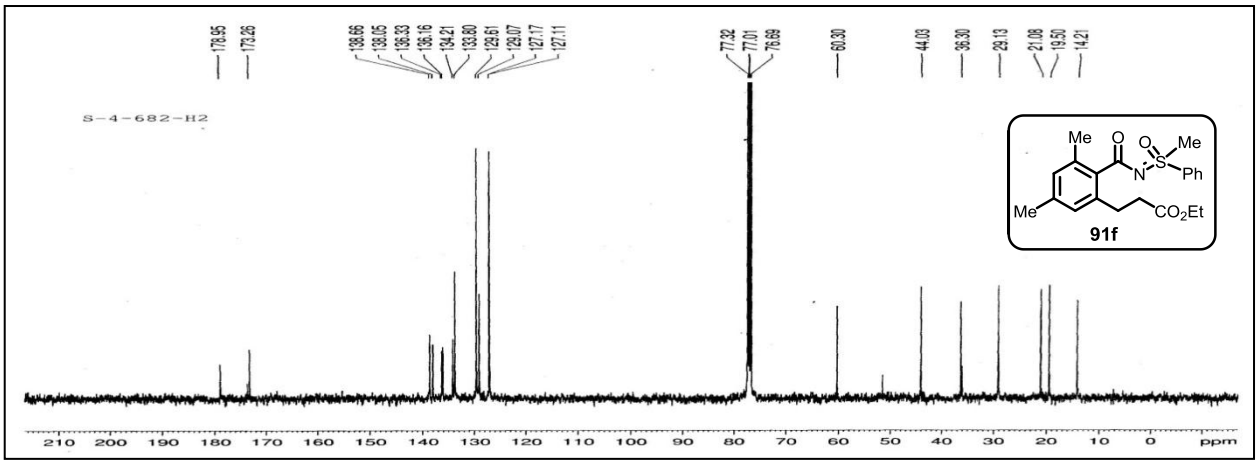
91f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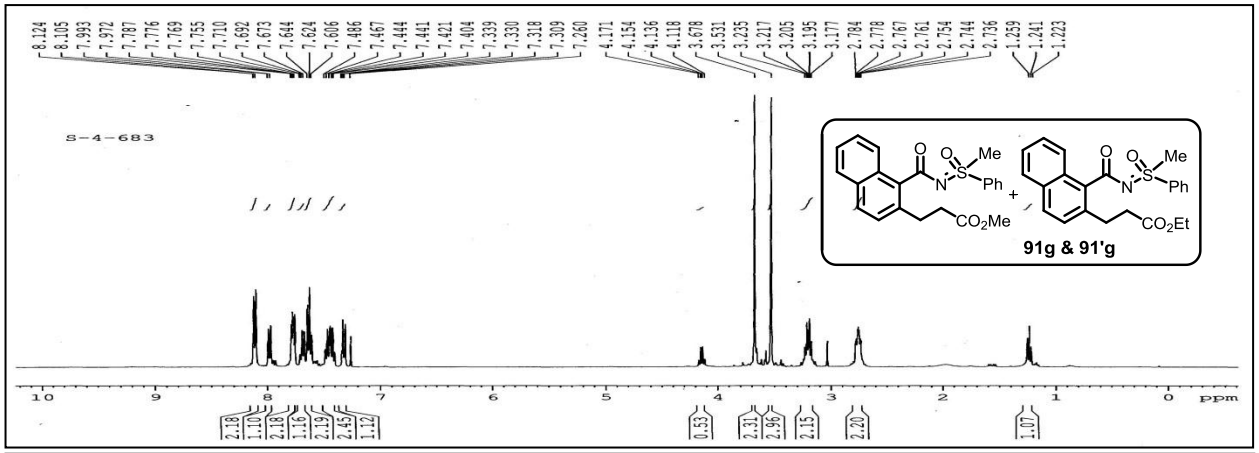
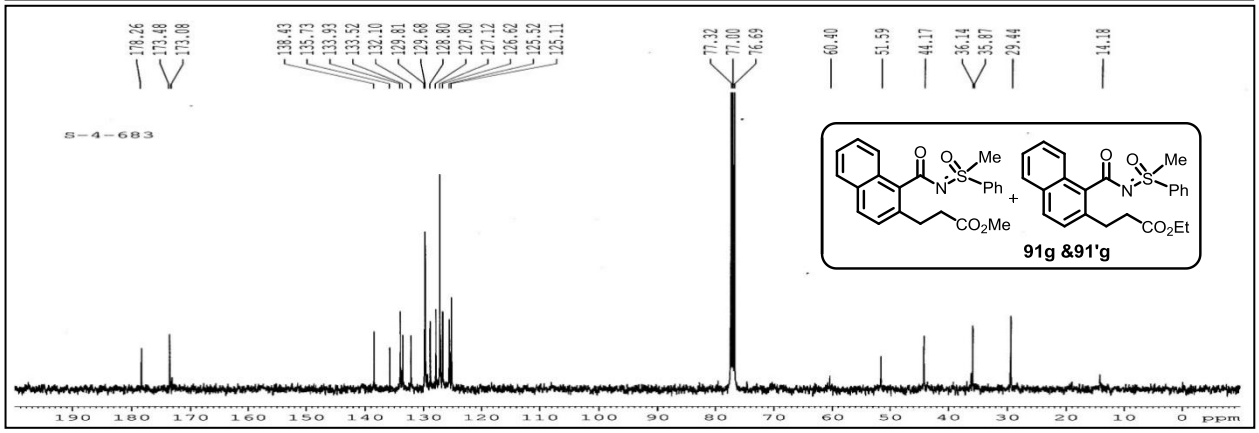
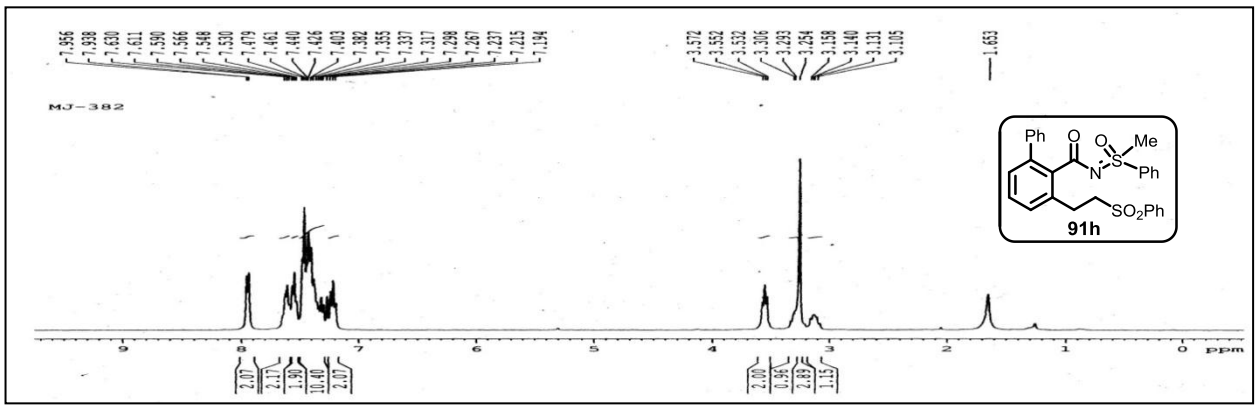
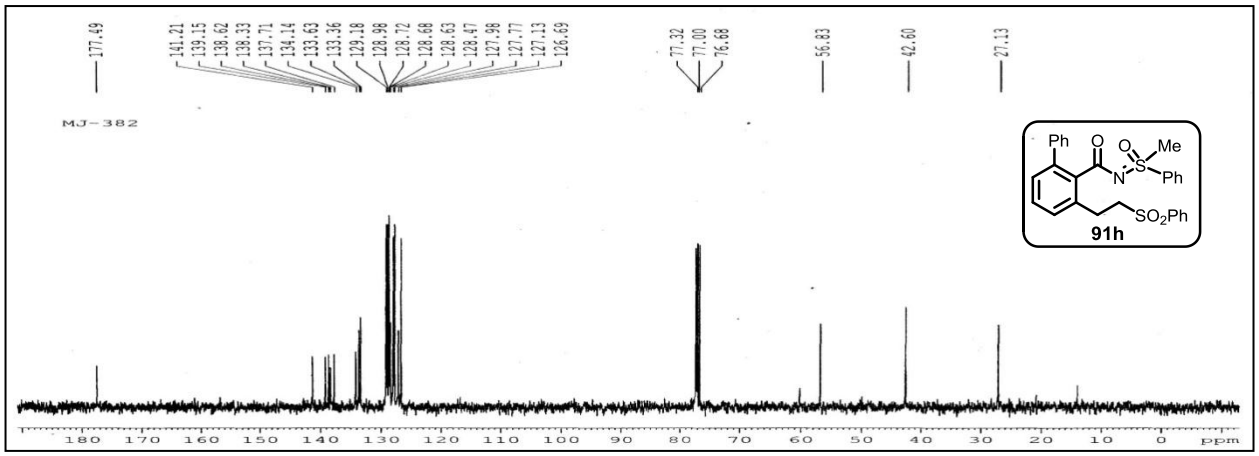
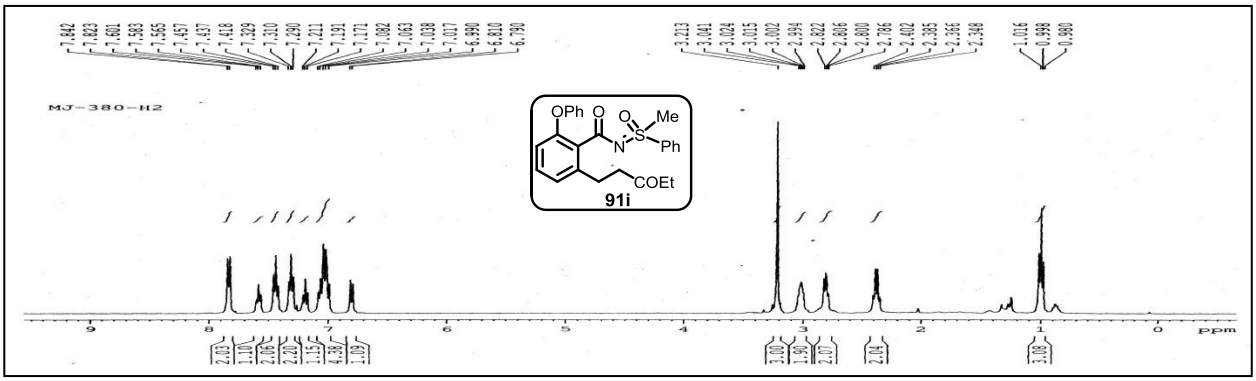
91f

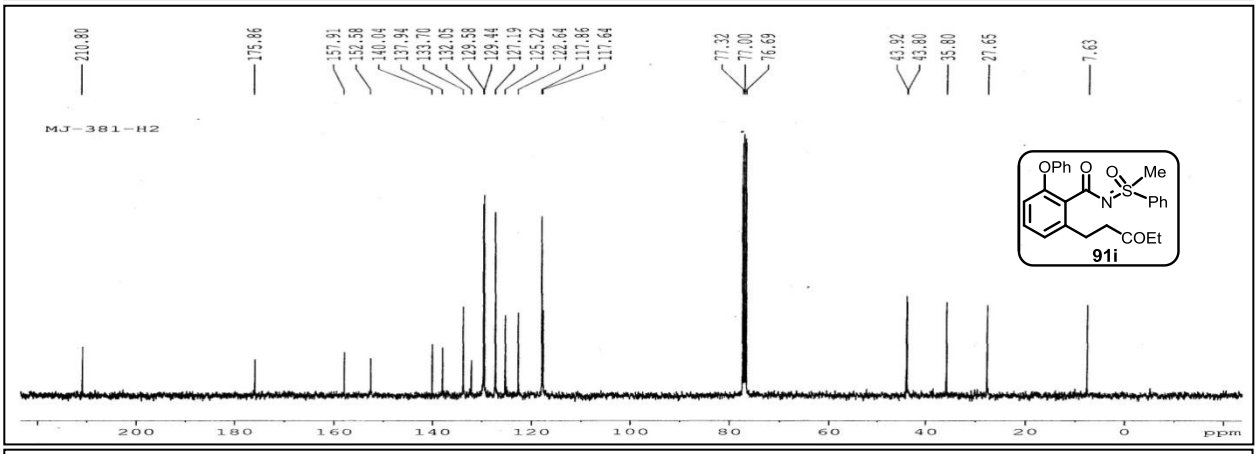

S-4-683
91g & 91'g


S-4-683
91g &91'g


MJ-382
91h


MJ-382
91h


MJ-380-H2
OPh
O
O
Me
N
S
Ph
COEt
91i
ppm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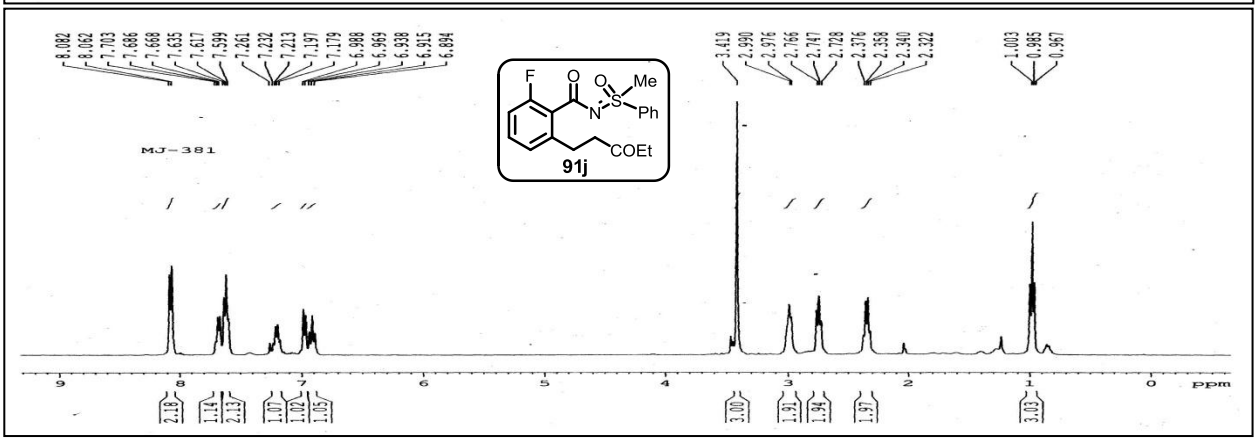
COEt
91i
ppm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O
O
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COEt
91j
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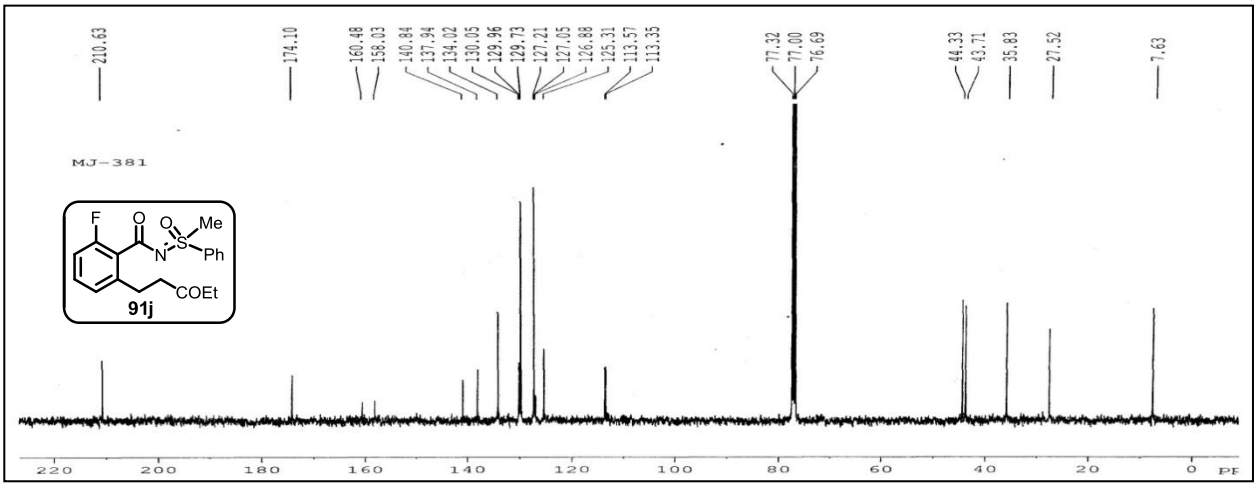
MJ-381
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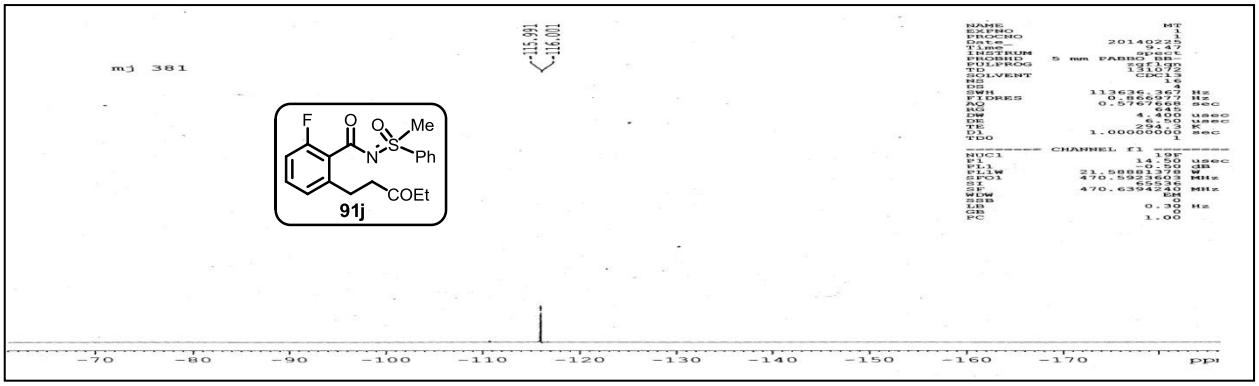
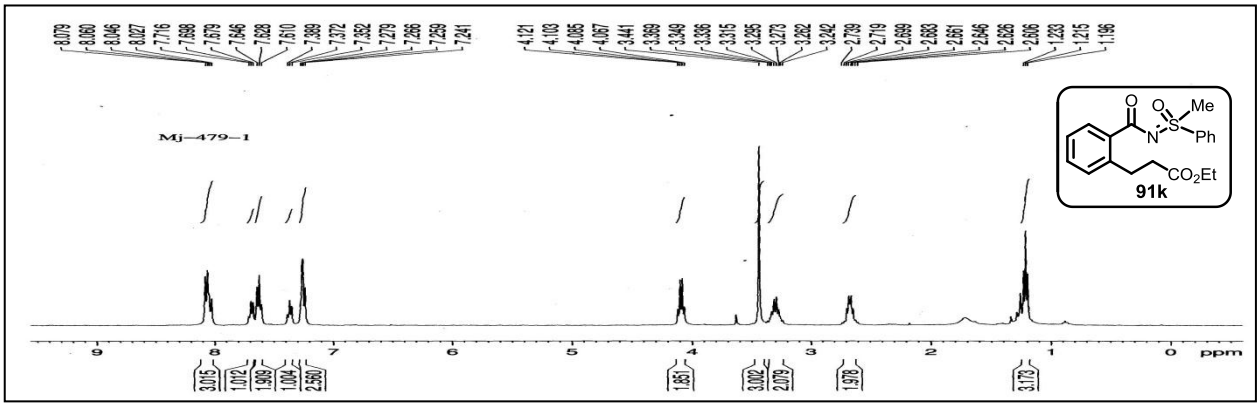
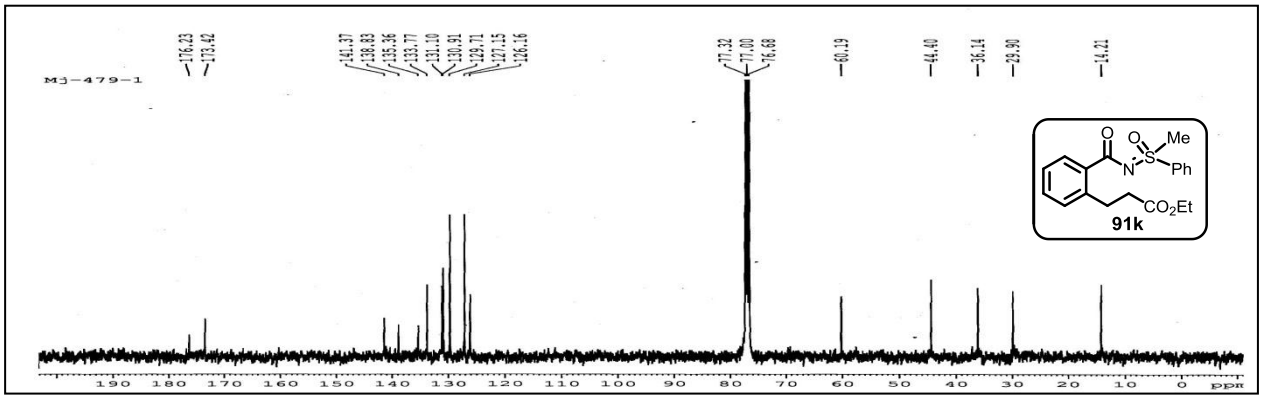
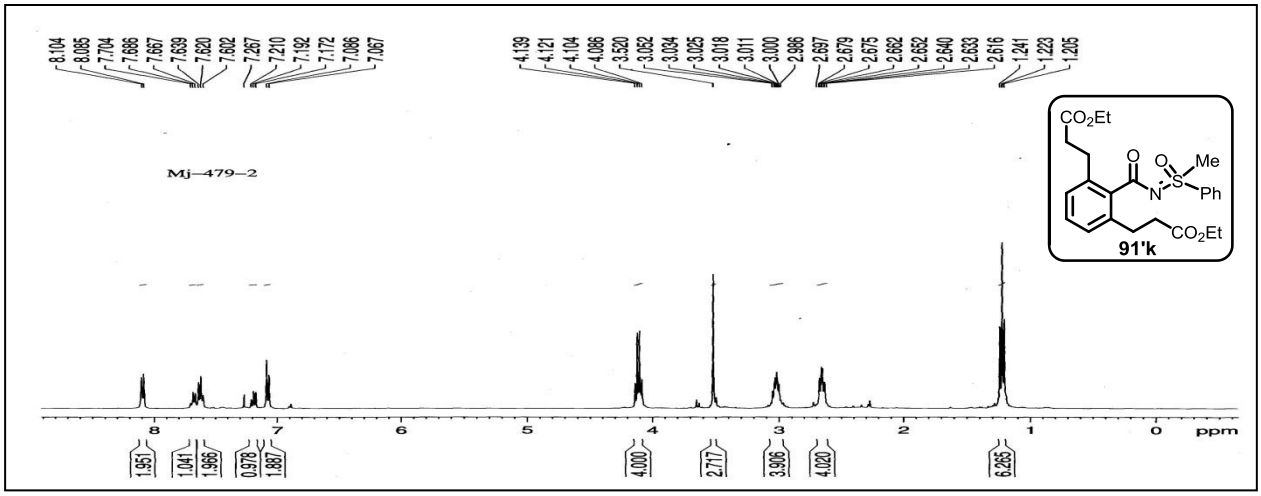
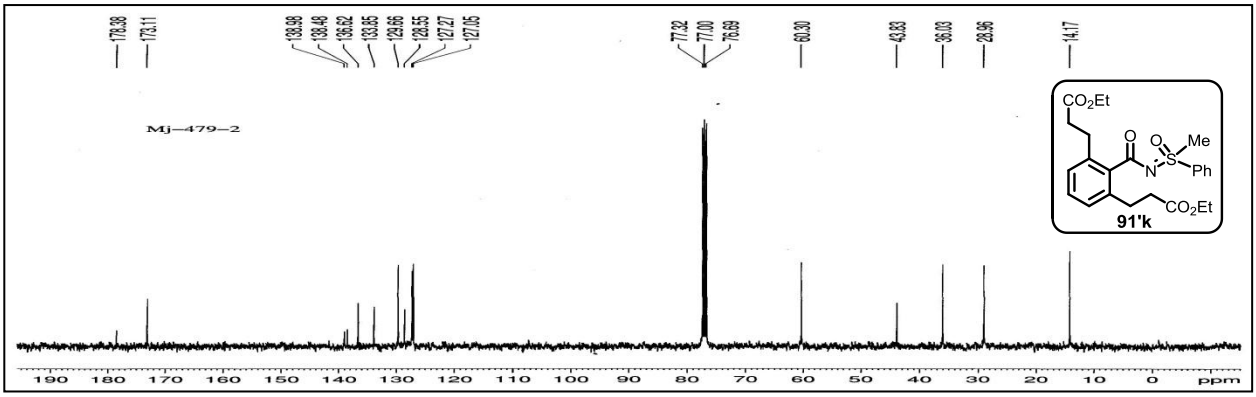

mj 381
91j


Mj-479-1
91k


Mj-479-1
91k


Mj-479-2
91'k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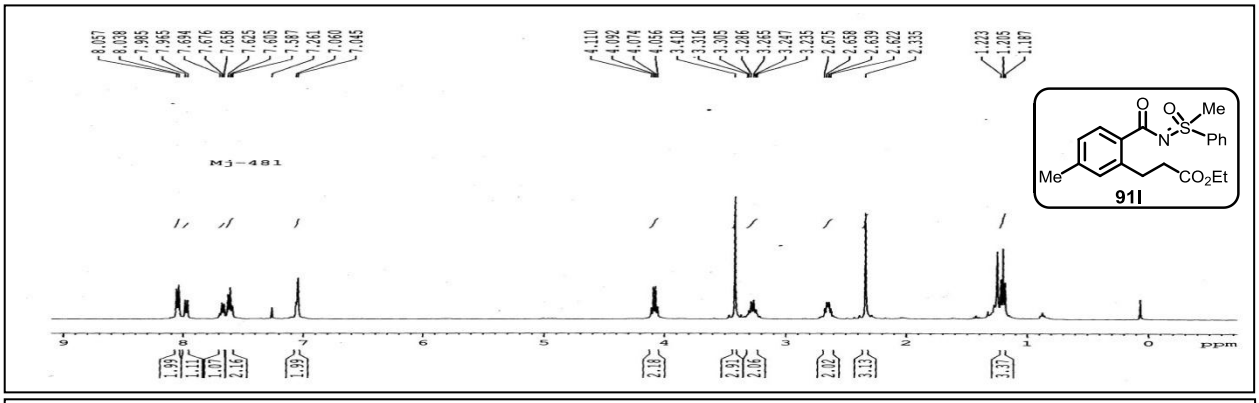
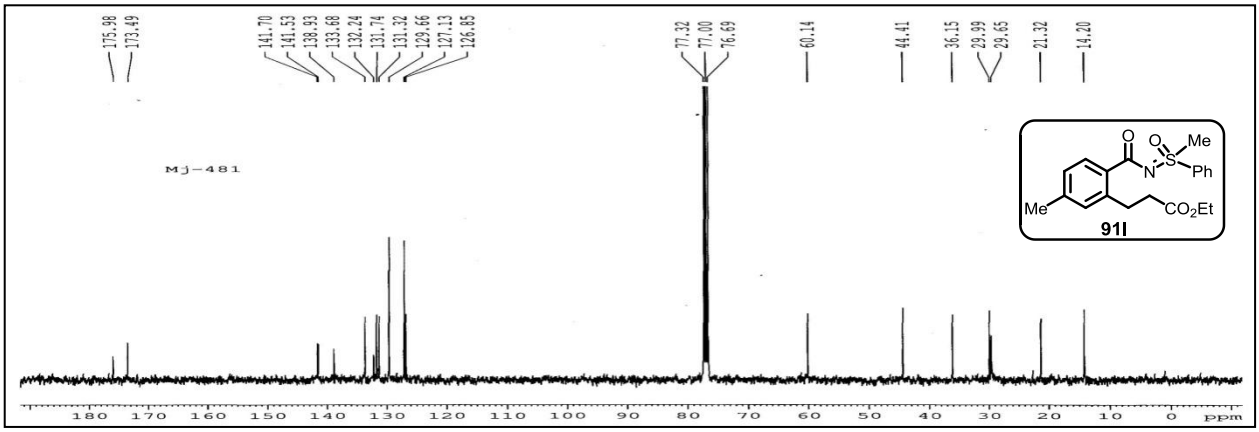
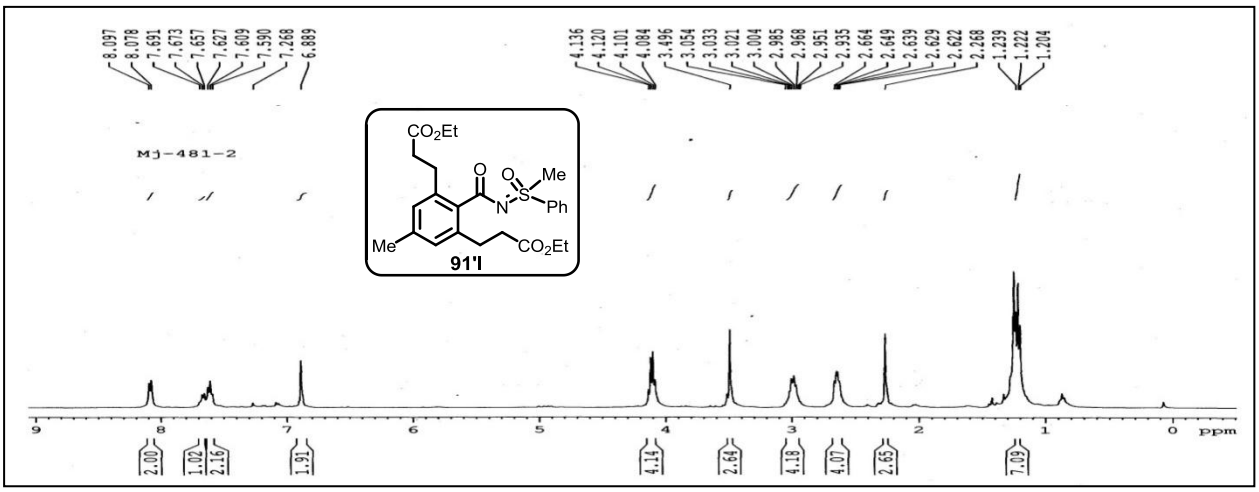
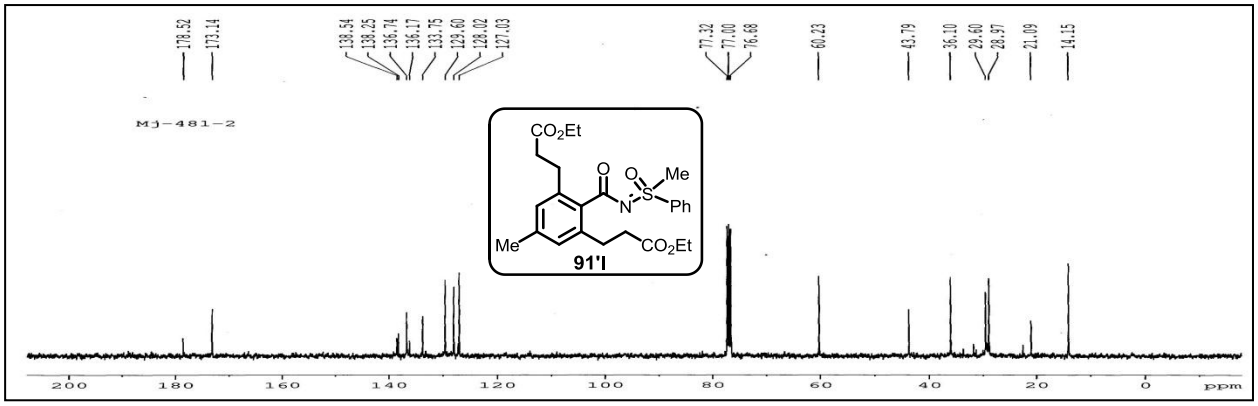
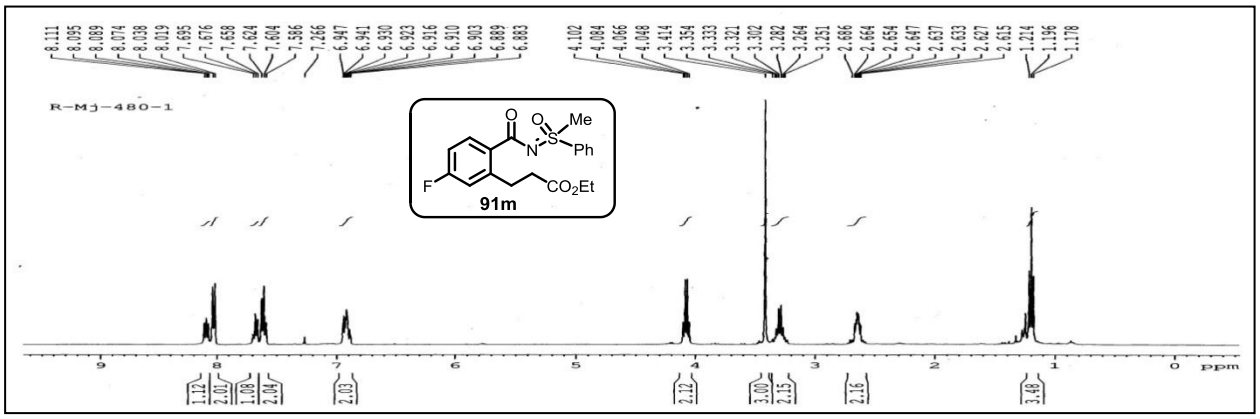
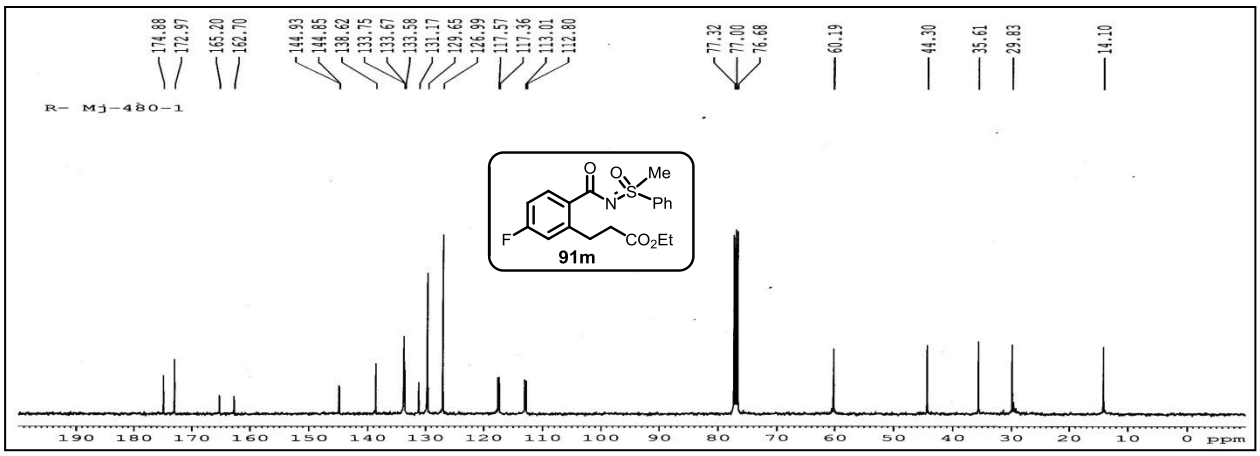

Mj-481
91l

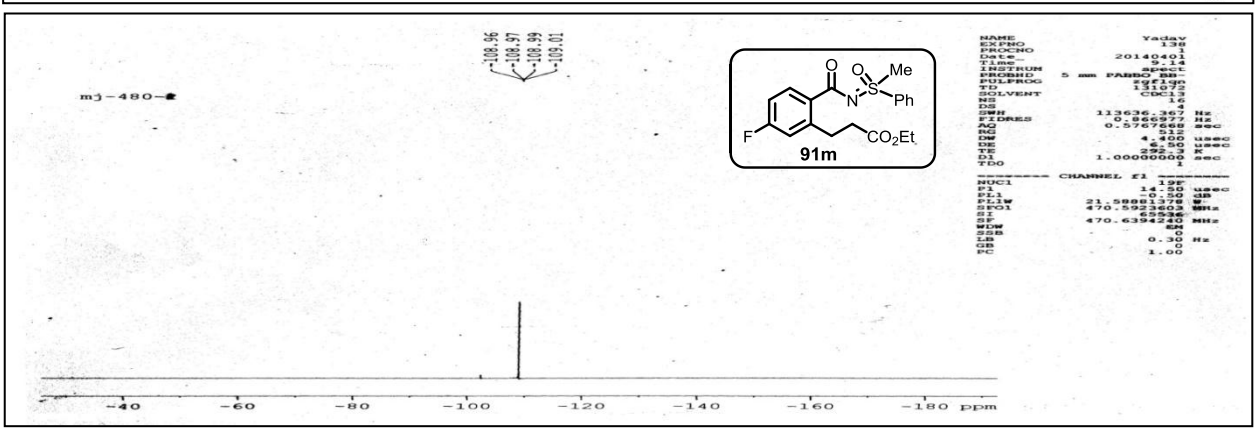

Mj-481
91l

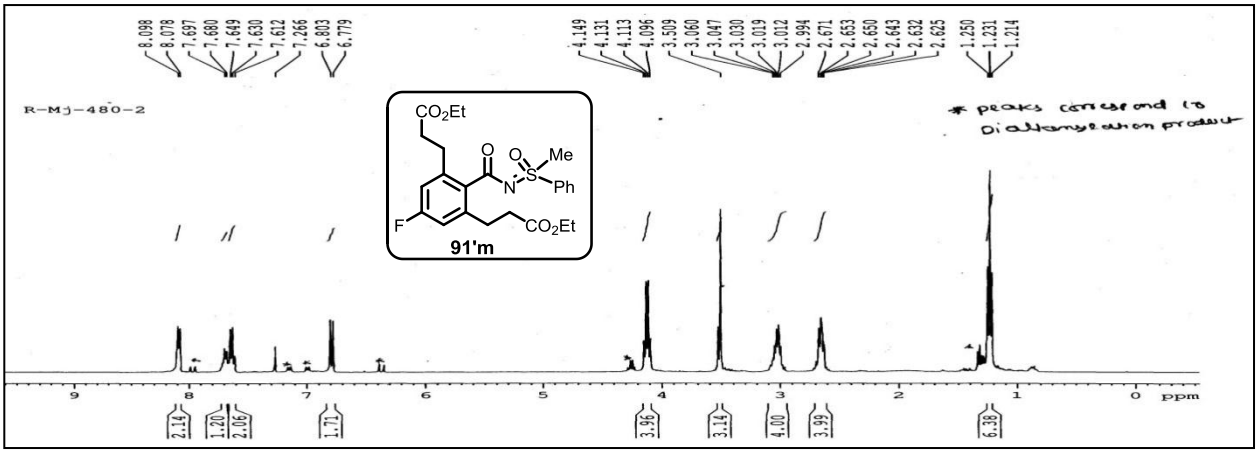

Mj-481-2
91'l

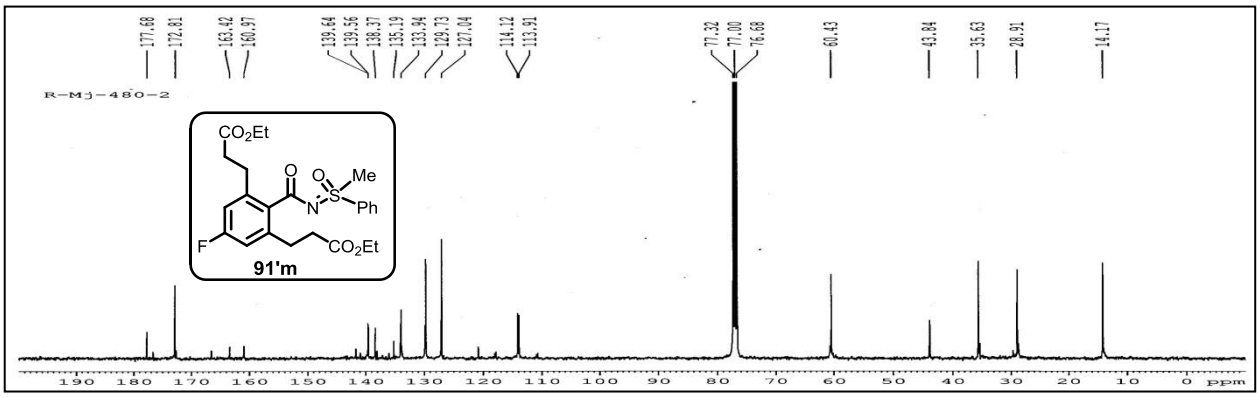

Mj-481-2
91'l

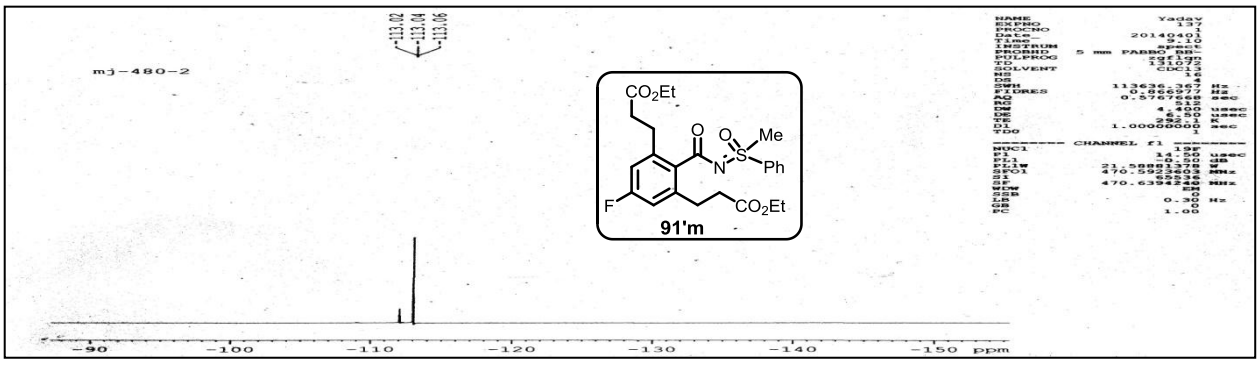

R-Mj-480-1
91m


R- Mj-480-1
91m


mj-480-
91m


R-MJ-480-2
* peaks correspond to Di alkenylation product
91'm


R-MJ-480-2
91'm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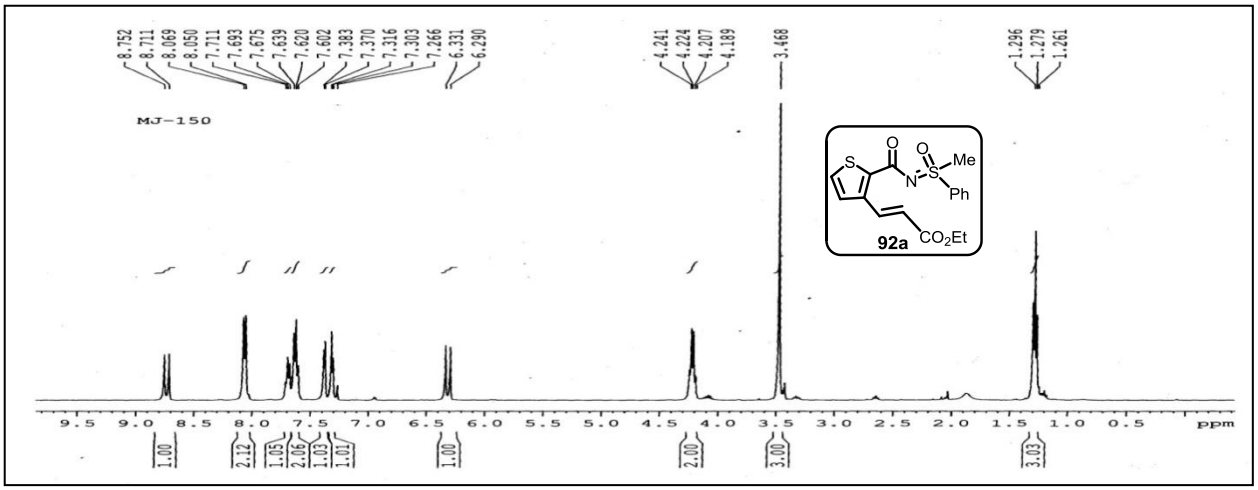
91'm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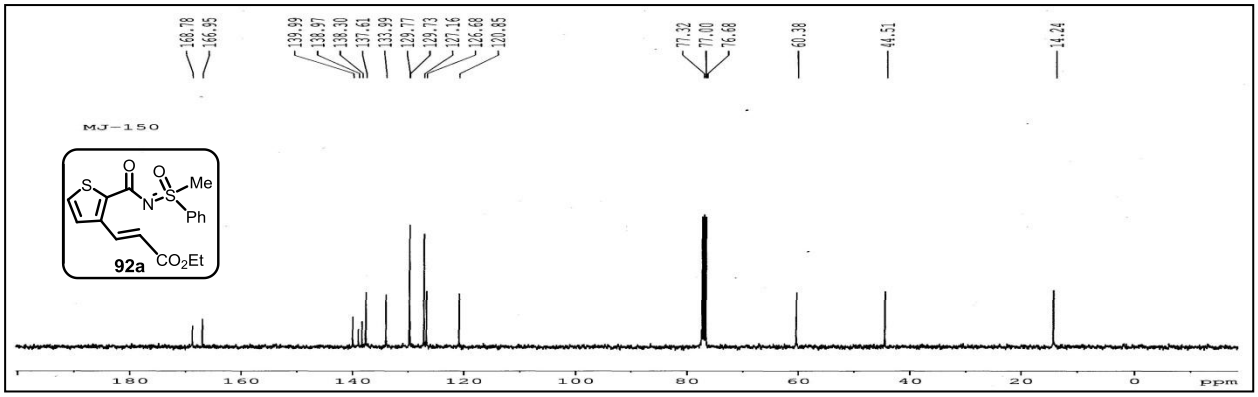
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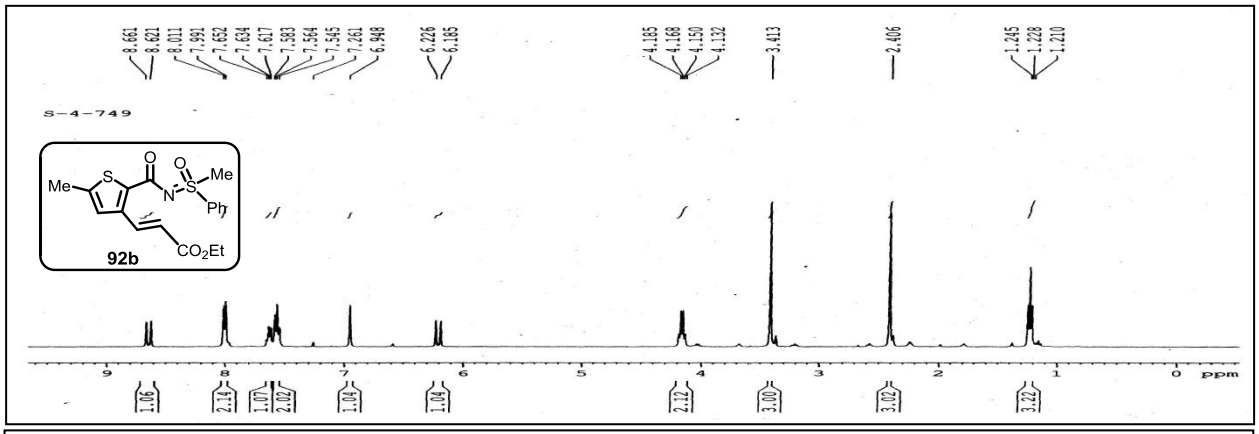
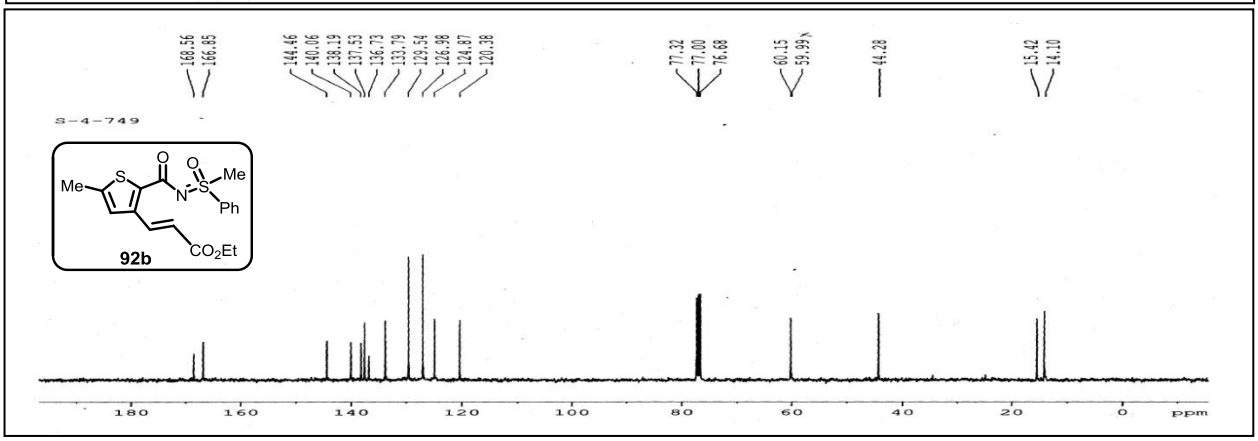

S-4-749
92b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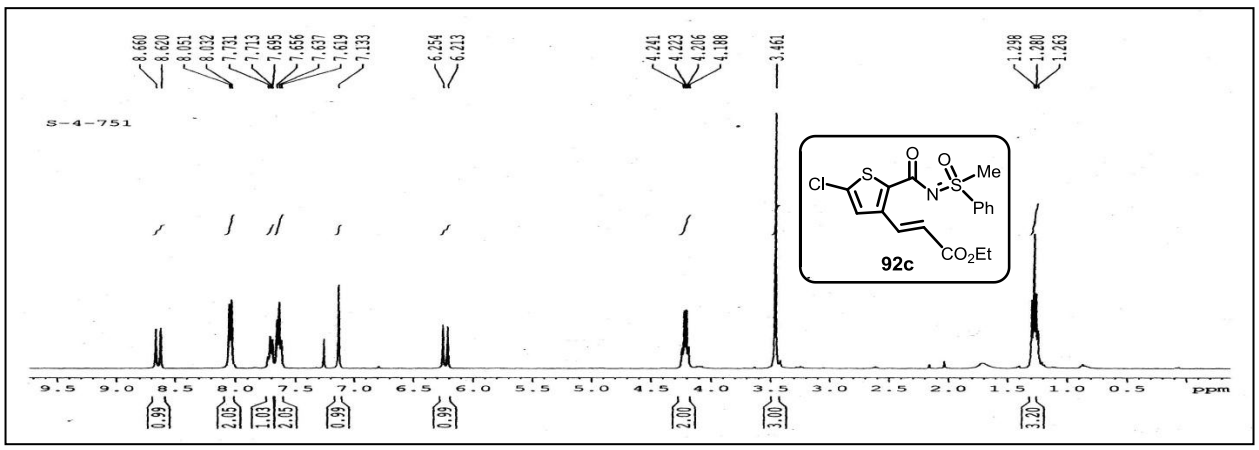
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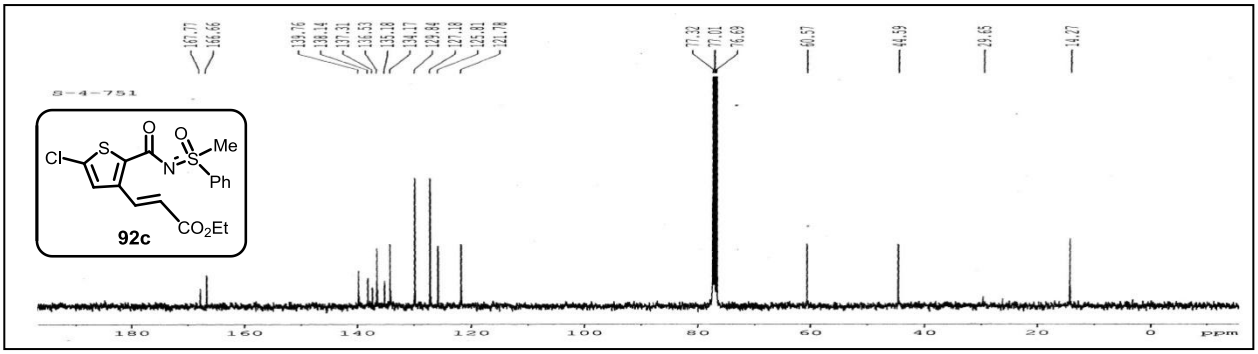
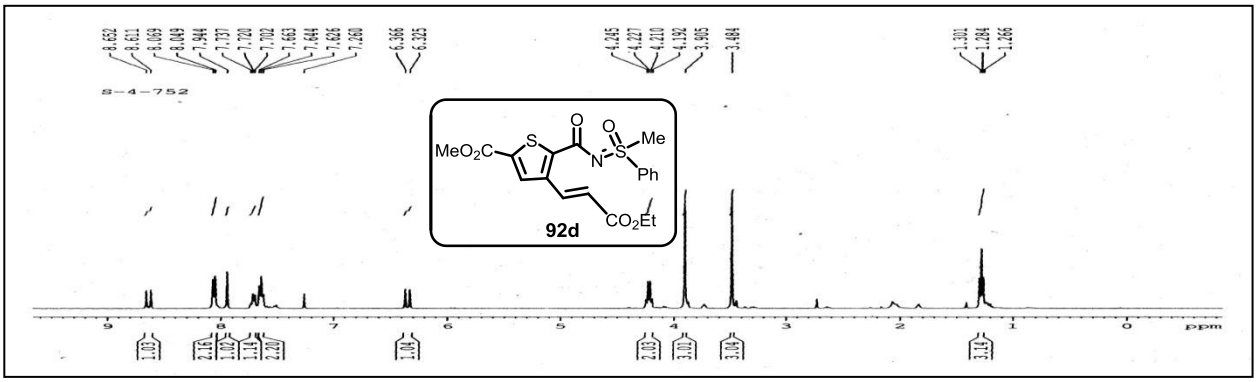
92c


S-4-751
92c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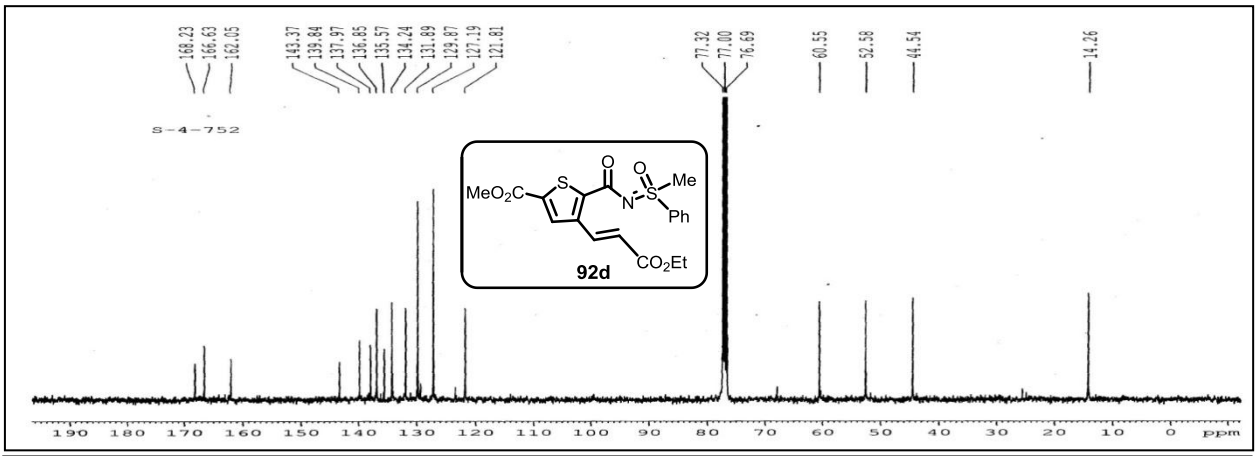
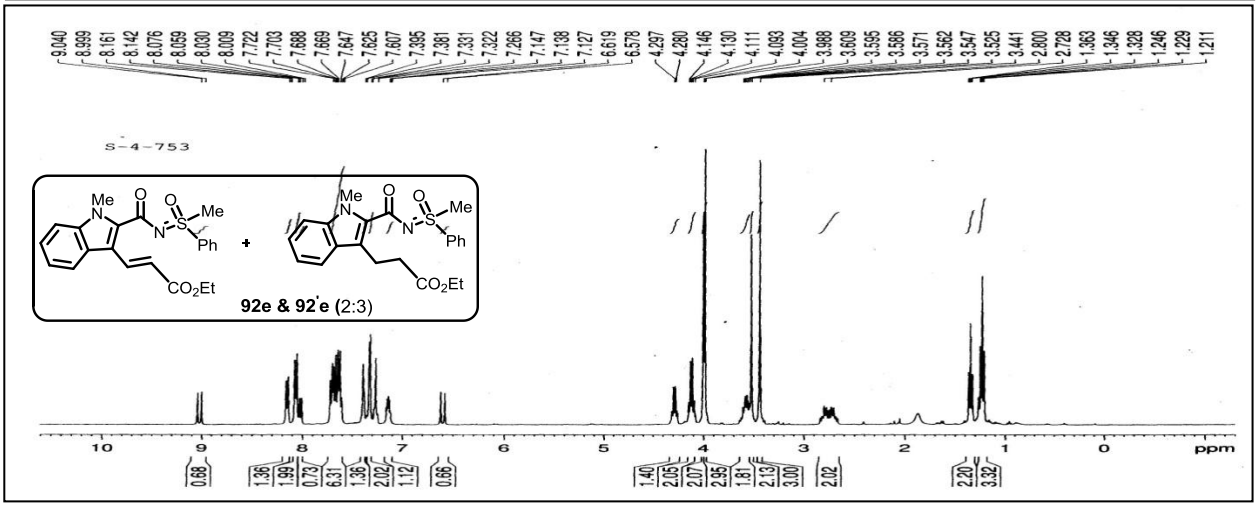
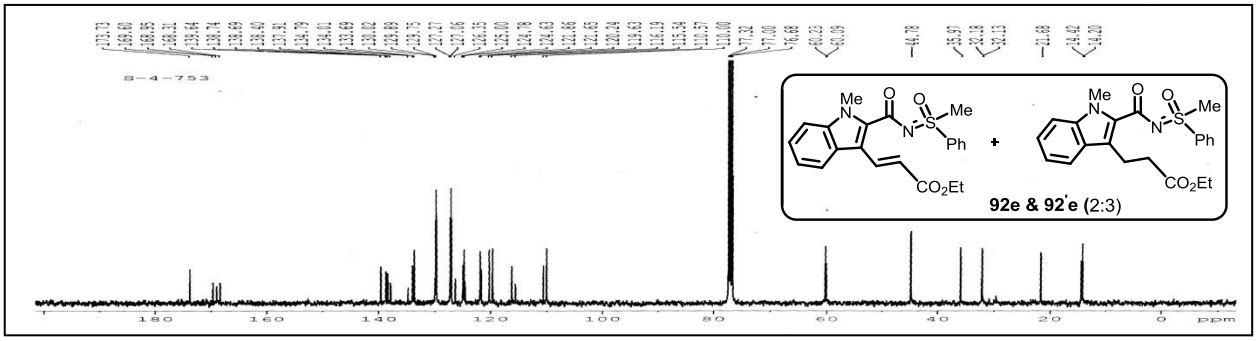
92d


S-4-752
92d


S-4-753
92e & 92'e (2:3)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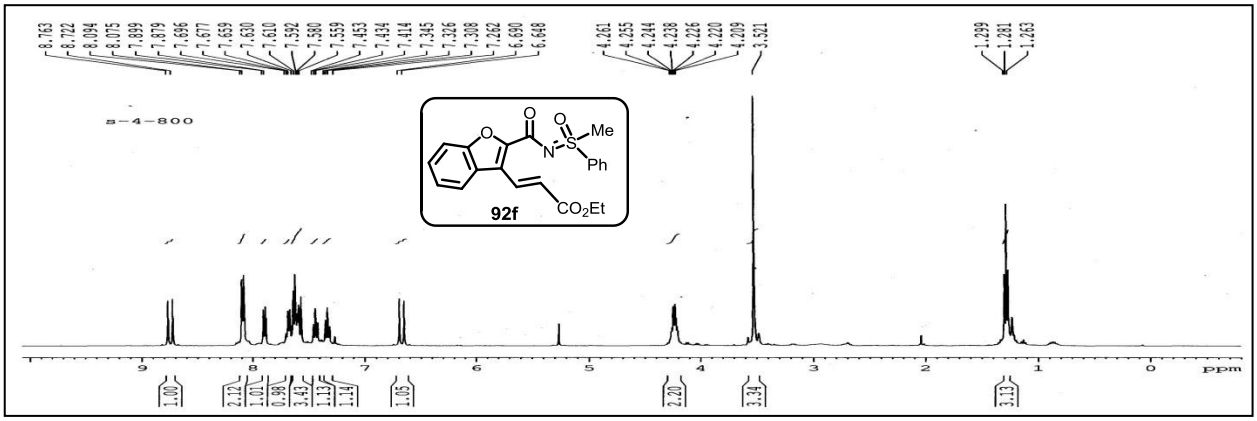
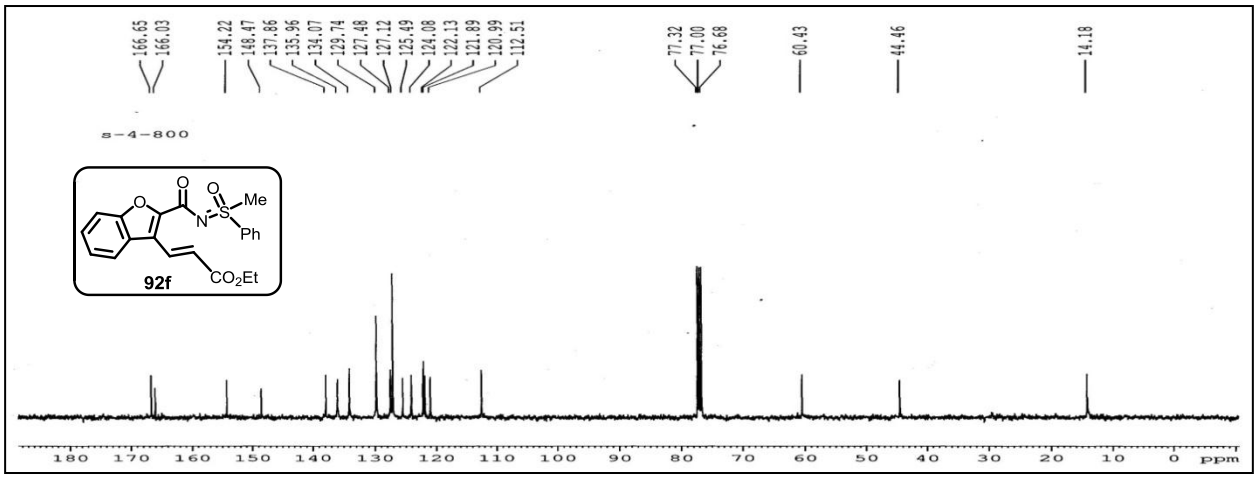
92e & 92'e (2:3)


s-4-800
92f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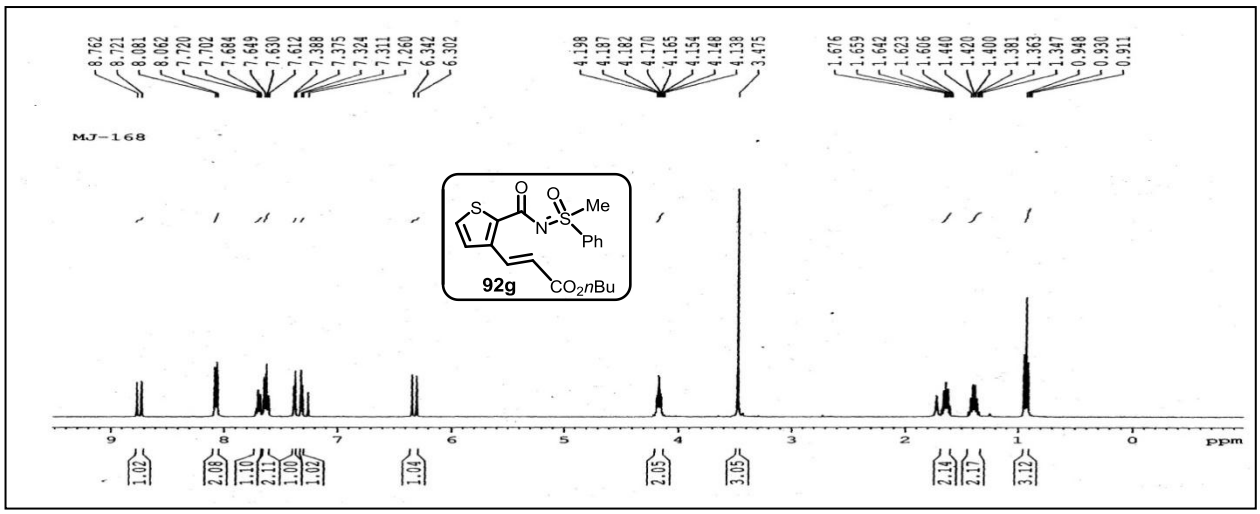
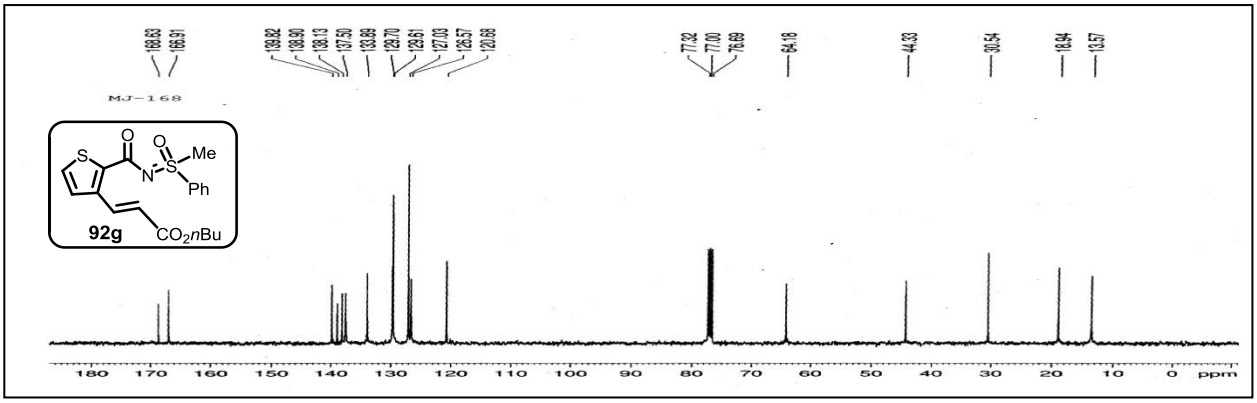
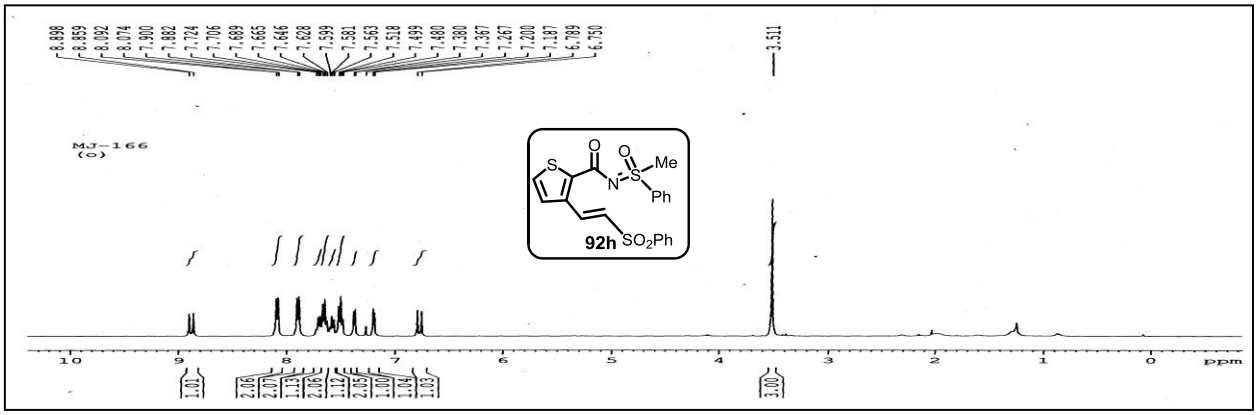
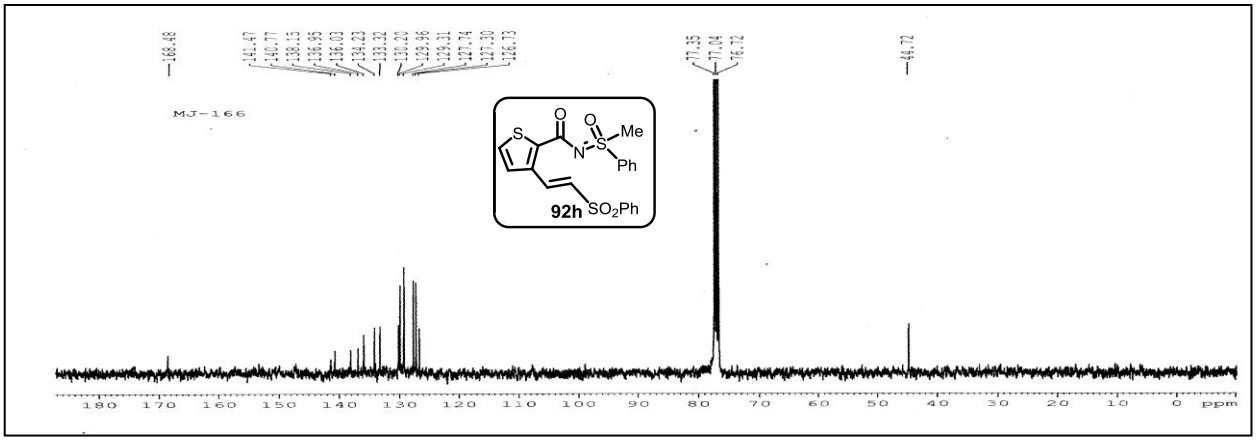
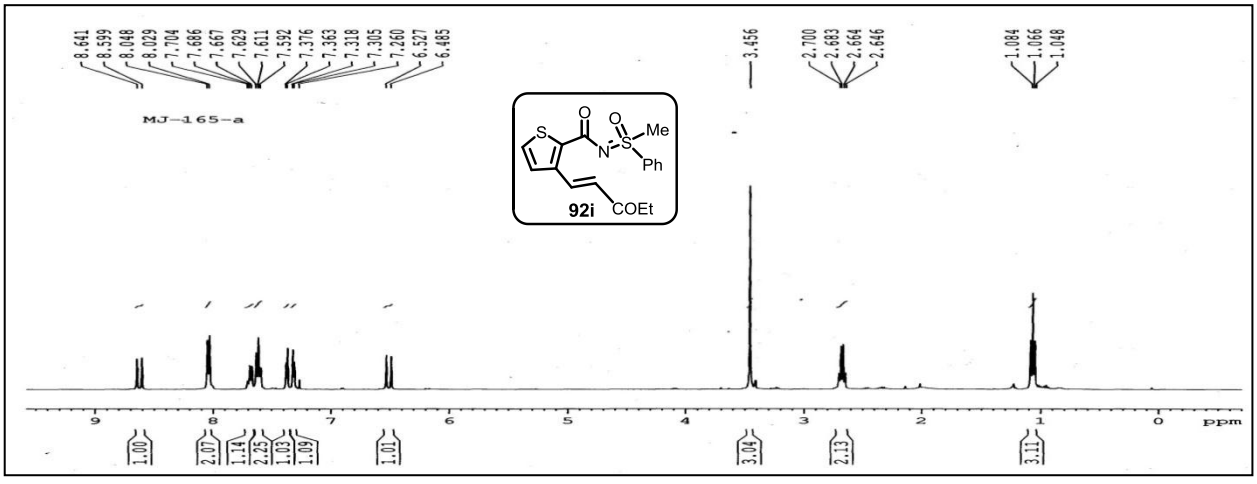
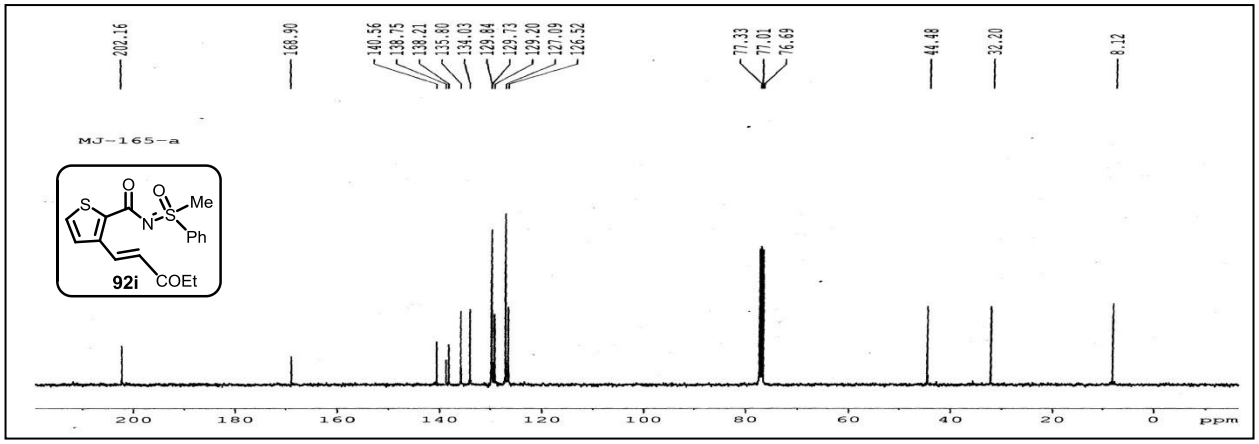

MJ-168
92g


MJ-168
92g
CO2nBu
Me
Ph


MJ-166
(c)
92h
SO2Ph
Me
Ph


MJ-166
92h
SO2Ph
Me
Ph


MJ-165-a
92i
COEt
Me
Ph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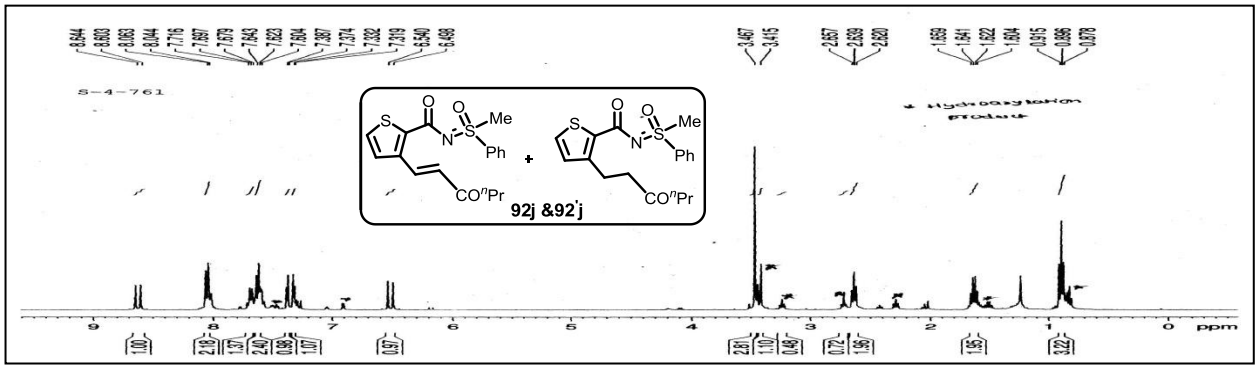
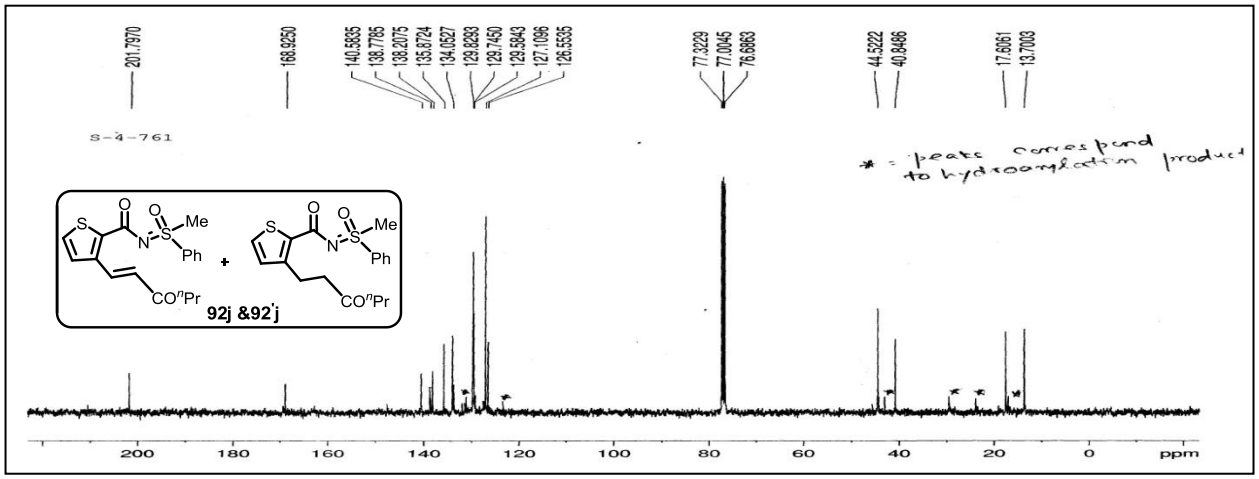
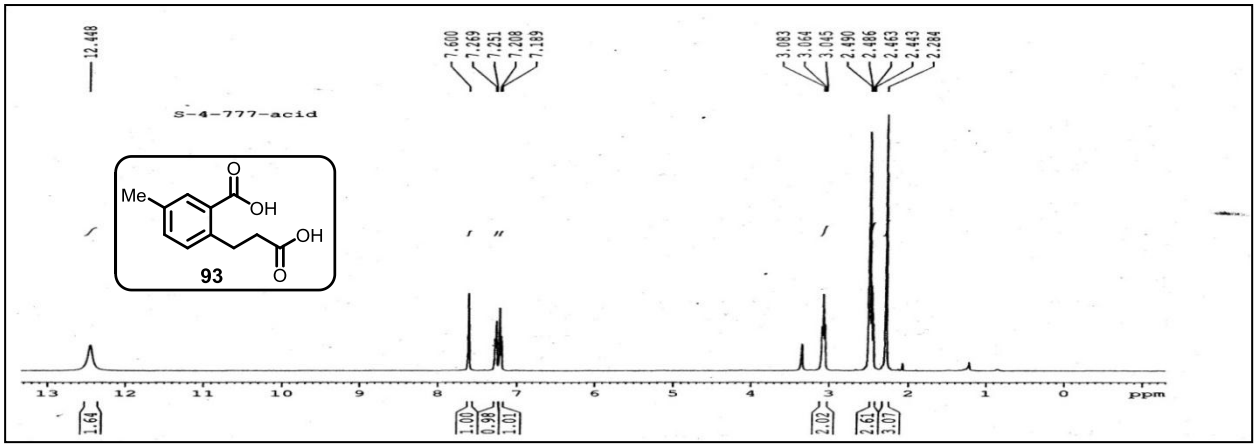
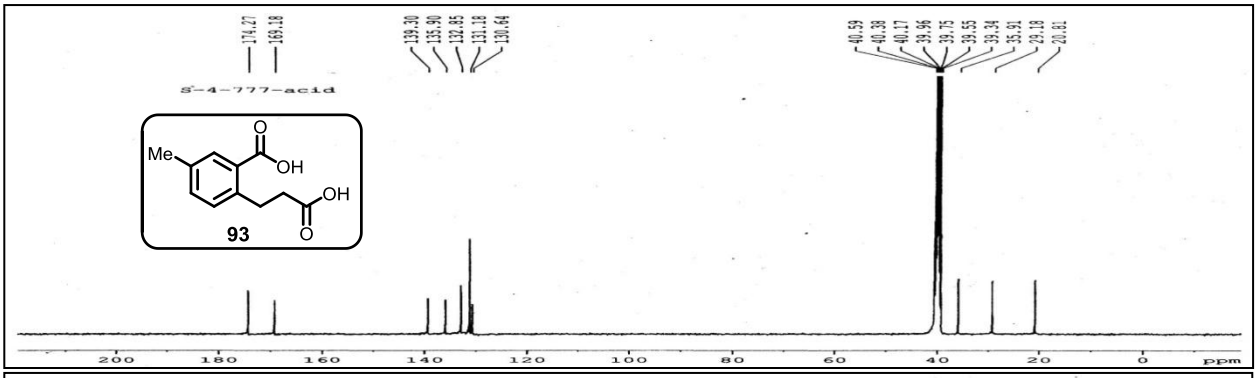
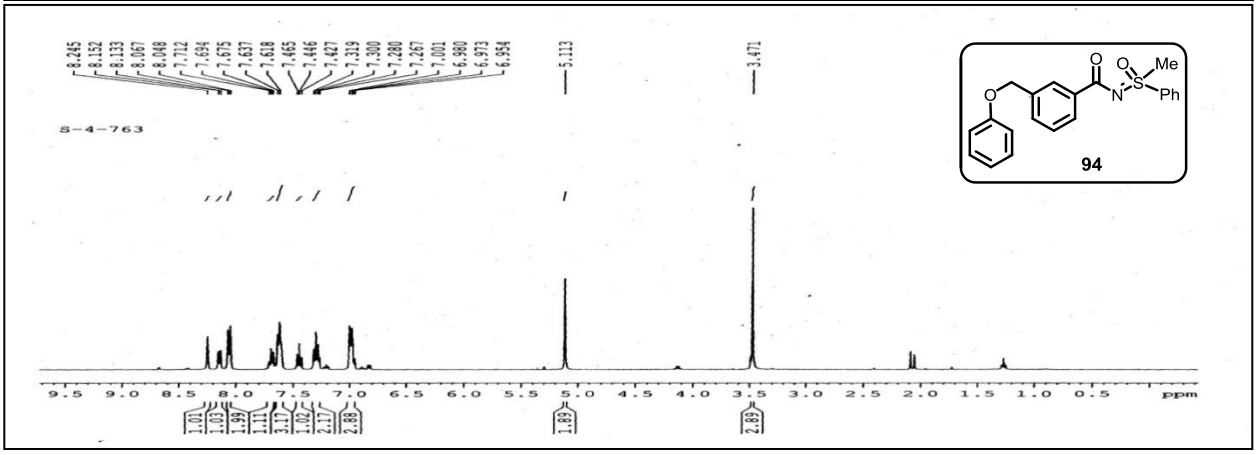
92i
COEt

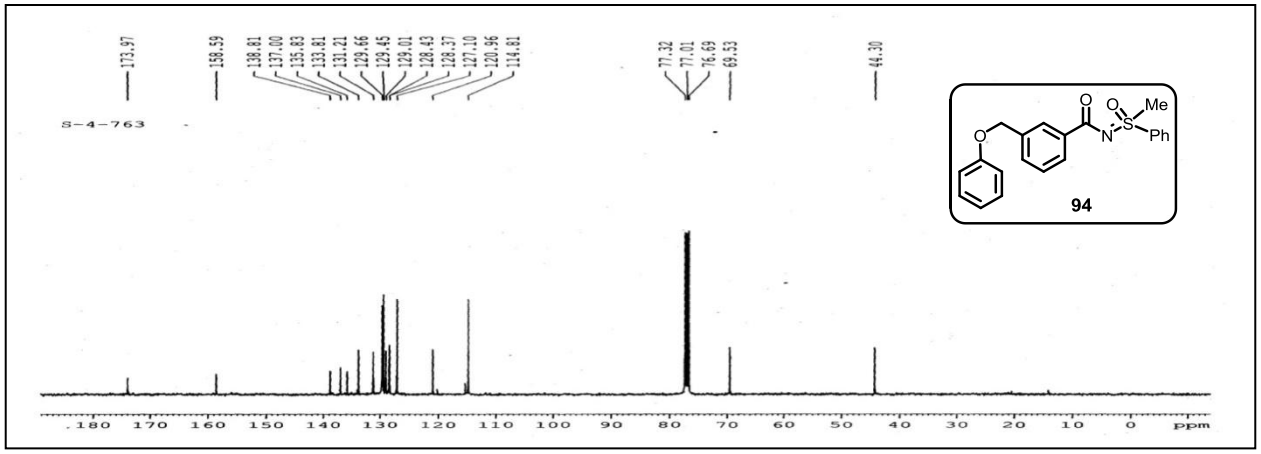

S-4-761
92j &92'j

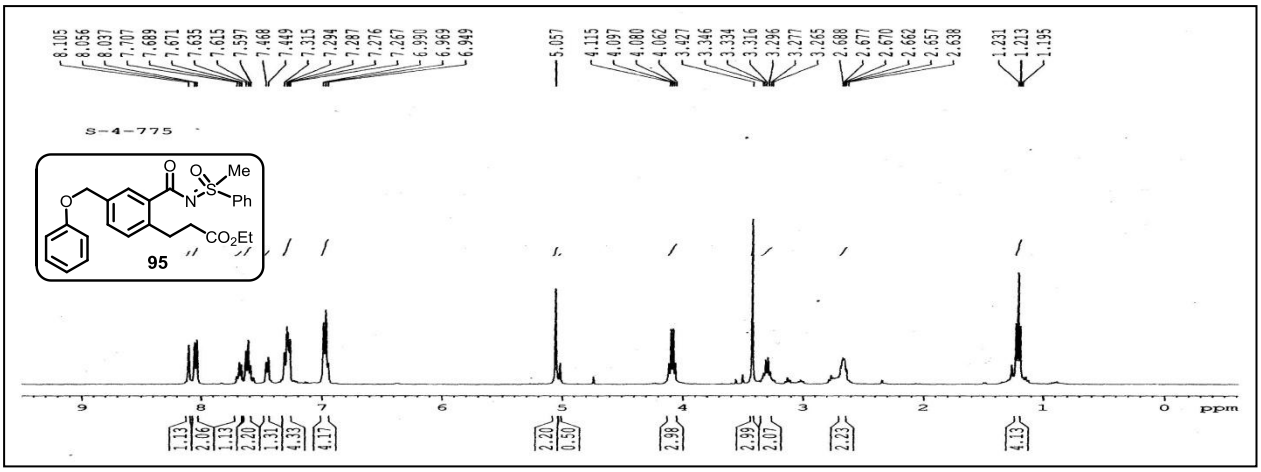

S-4-761
92j &92'j

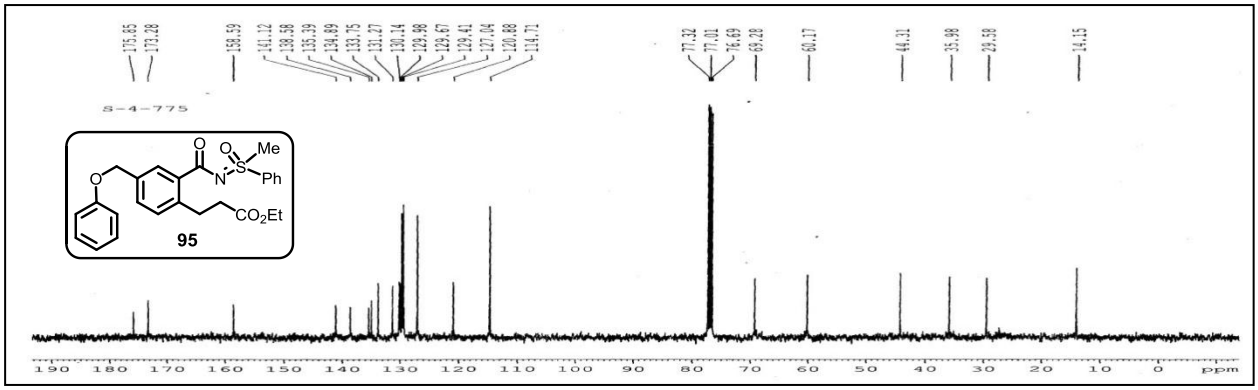

S-4-777-acid
93


S-4-777-acid
Me
OH
OH
O
O
93


S-4-763
Me
Ph
O
N
S
O
O
94


S-4-763
Me
Ph
O
N
S
O
O
94


S-4-775
Me
Ph
O
N
S
O
O
CO2Et
95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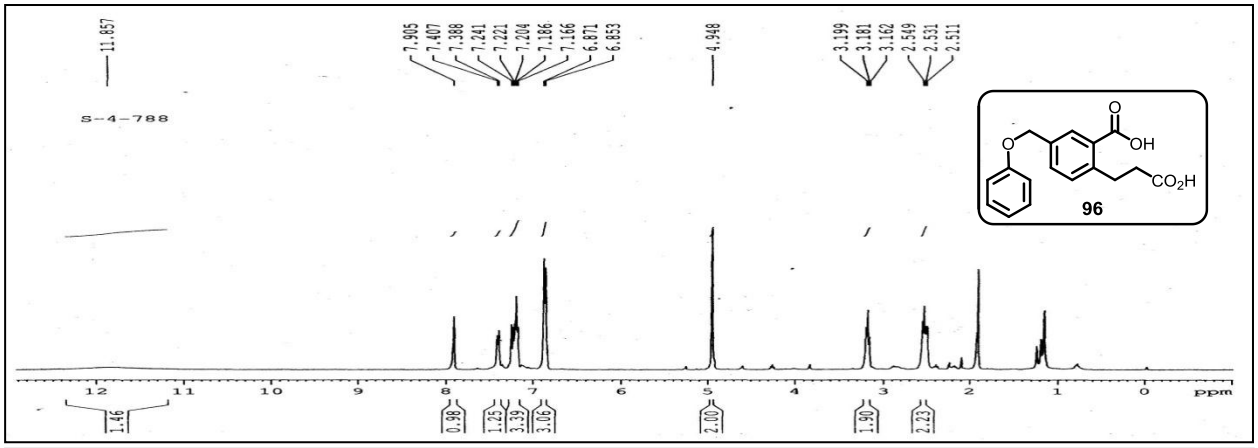
S-4-788
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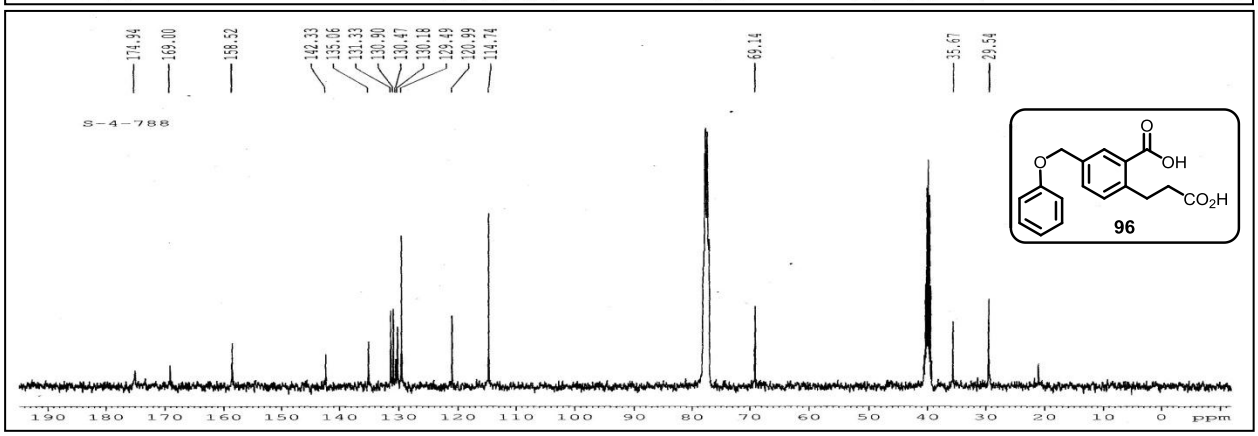
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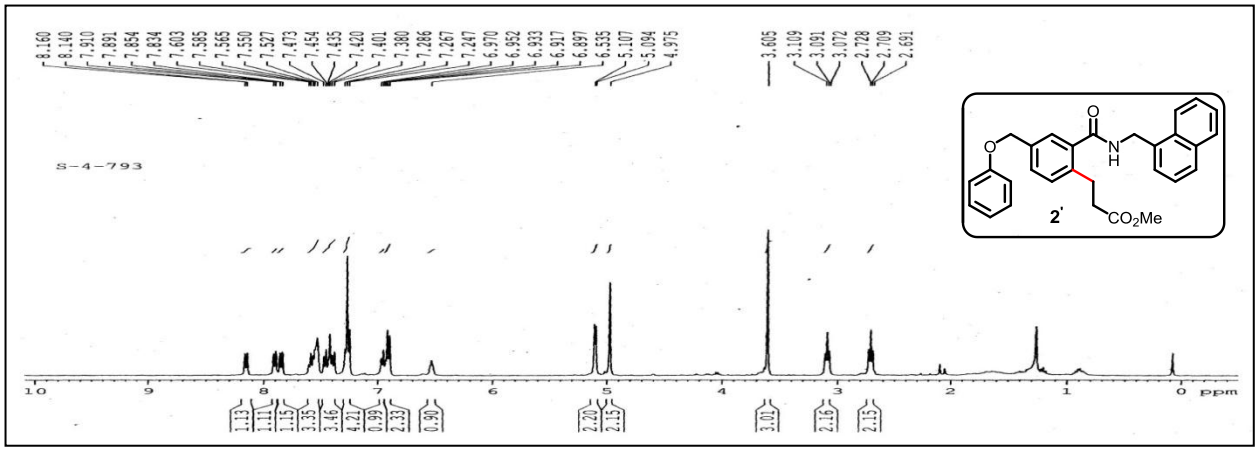
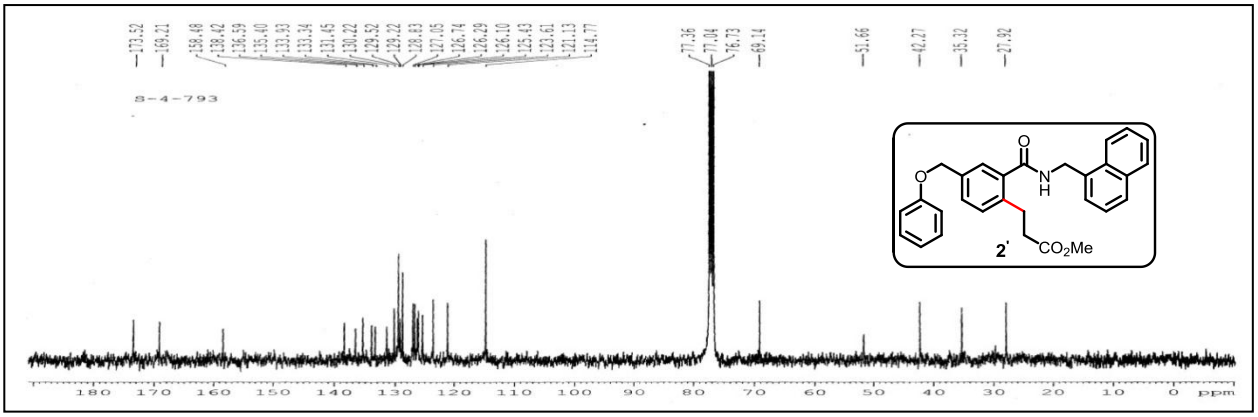
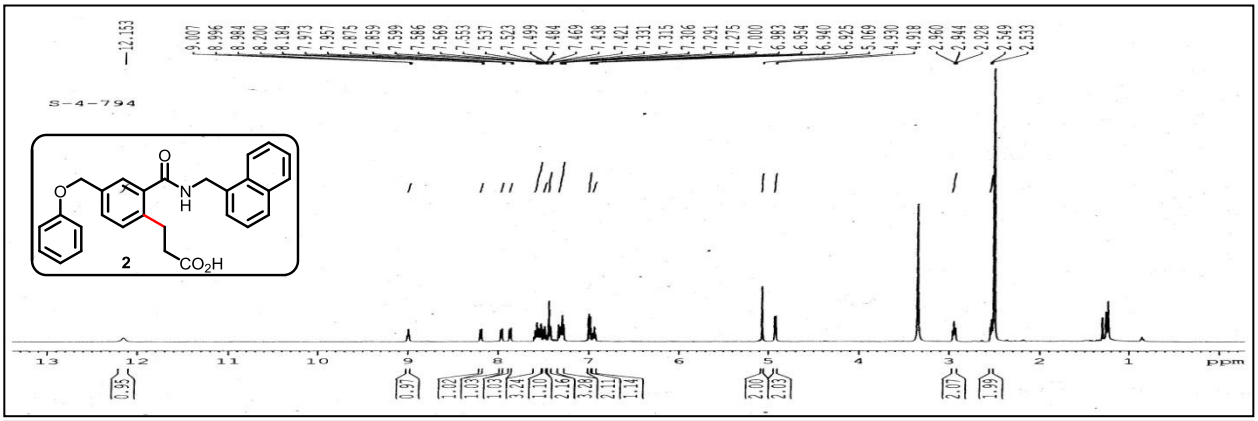
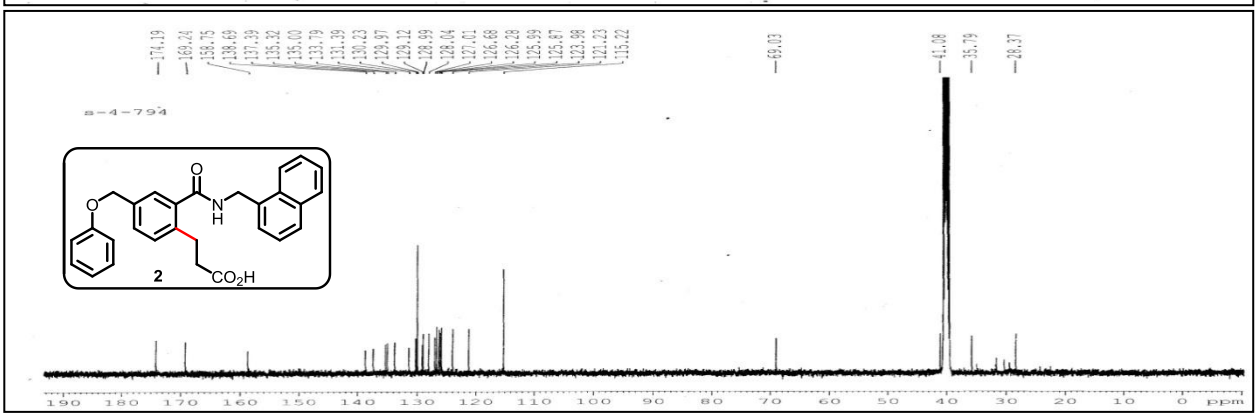
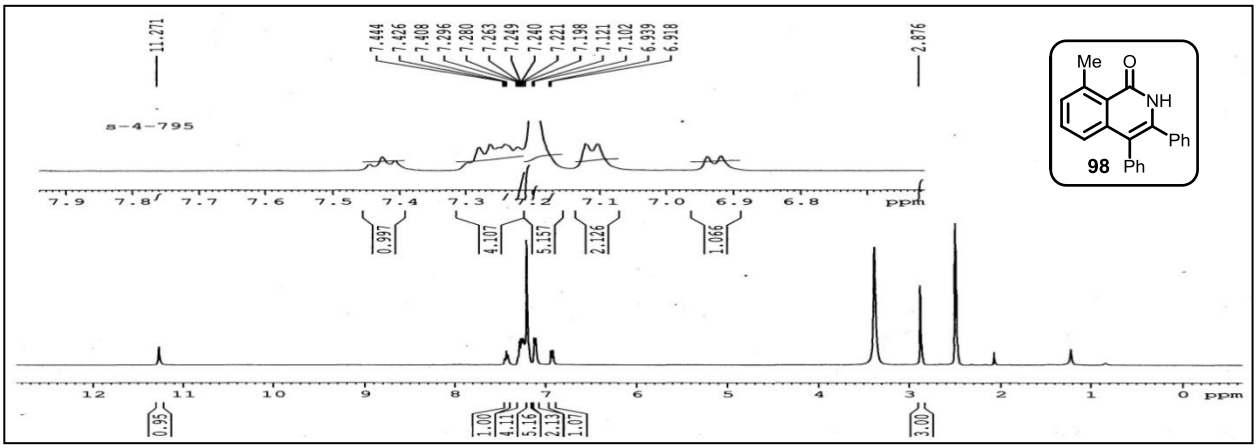
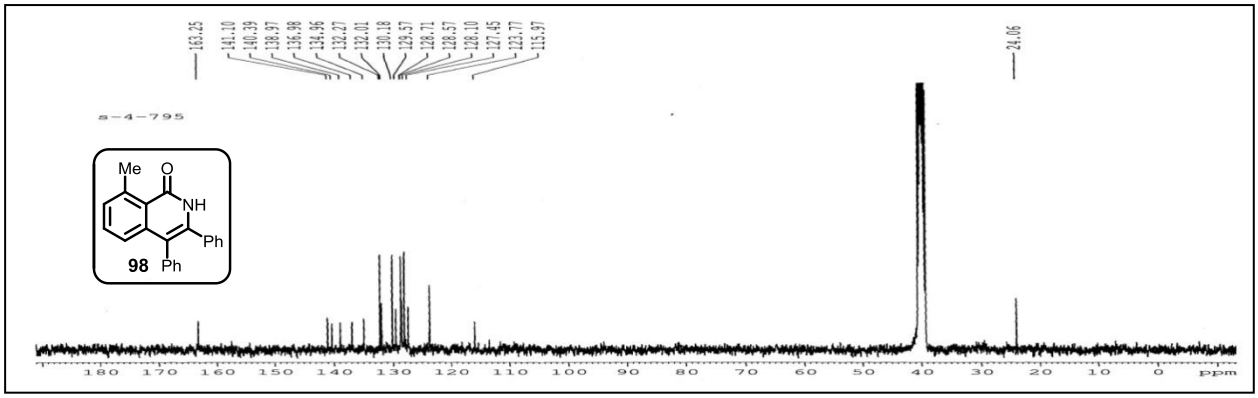

S-4-793
2'

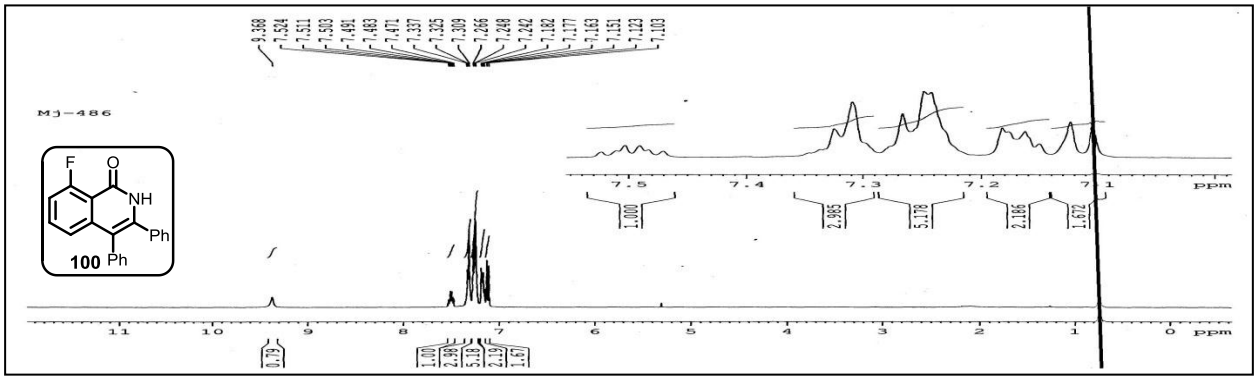

s-4-793
2'
CO2Me

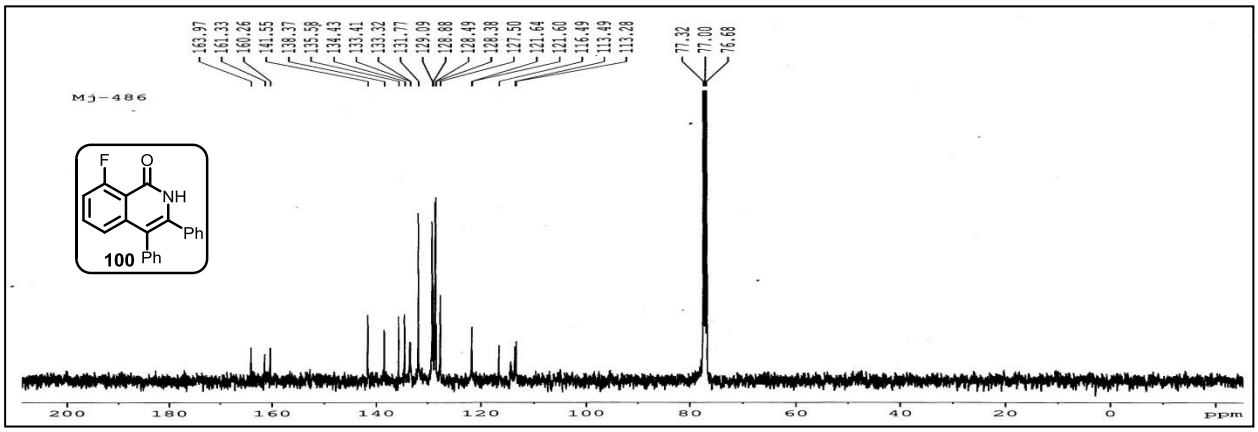

s-4-794
2
CO2H

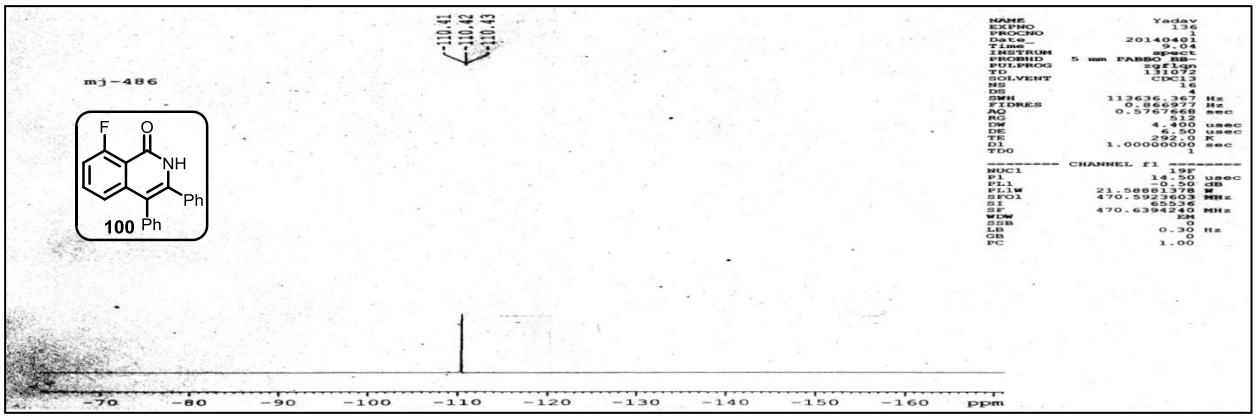

s-4-794
2
CO2H

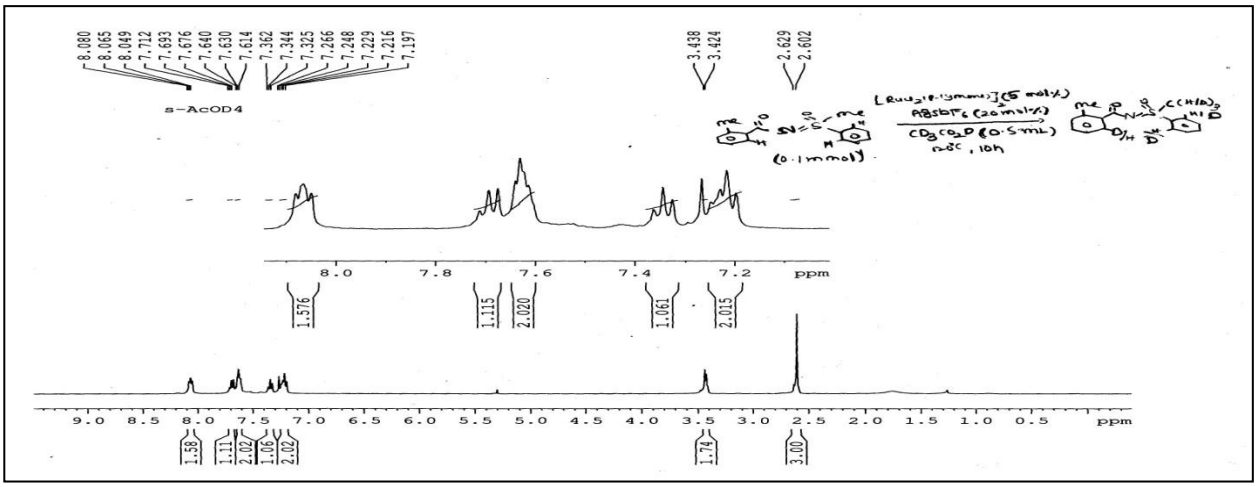

s-4-795
Me
NH
Ph
98 Ph


s-4-795
Me
O
NH
Ph
98 Ph


Mj-486
F
O
NH
Ph
100 Ph


Mj-486
F
O
NH
Ph
100 Ph


mj-486
F
O
NH
Ph
100 Ph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8.065
8.049
7.712
7.693
7.676
7.640
7.630
7.614
7.362
7.344
7.325
7.266
7.248
7.229
7.216
7.197
s-AcOD4
3.438
3.424
2.629
2.602
(0.1mmol)
8.0
7.8
7.6
7.4
7.2
ppm
1.576
1.115
2.020
1.061
2.015
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.58
1.11
2.02
1.06
2.02
1.74
3.00

List of Publications

1. Sulfoximines: A Reusable Directing Group for Chemo- and Regioselective *ortho* C–H Oxidation of Arenes

   M. Ramu Yadav, Raja K. Rit and Akhila K. Sahoo, *Chem.–Eur. J.* **2012**, *18*, 5541.

2. Pd(II)-Catalyzed Primary-C(sp^3)–H Acyloxylation at Room Temperature

   Raja K. Rit, **M. Ramu Yadav** and Akhila K. Sahoo, *Org. Lett*. **2012**, *14*, 3724.

3. Sulfoximine Directed Intermolecular *o*-C–H Amidation of Arenes with SulfonylAzides

   M. Ramu Yadav, Raja K. Rit and Akhila K. Sahoo, *Org. Lett*. **2013**, *15*, 1638.

4. Ru(II)-Catalyzed Intermolecular *Ortho*-C–H Amidation of Aromatic Ketones with SulfonylAzides

   M. Bhanuchandra, **M. Ramu Yadav,** Raja K. Rit, Malleswara Rao Kuram and Akhila K. Sahoo, *Chem. Commun*. **2013**, *49*, 5225.

5. Pd(II)-Catalyzed C(sp^2)–H Acyloxylation of Arylacetic Acid Derivatives: An Access to Benzolactone

   Raja K. Rit, **M. Ramu Yadav** and Akhila K. Sahoo, *Org. Lett*. **2014**, *16*, 968.

6. Sulfoximine-Directed Ruthenium-Catalyzed *ortho*-C–H Alkenylation of (Hetero)Arenes: Synthesis of EP3 Receptor Antagonist Analogue

   M. Ramu Yadav, Raja K. Rit, Majji Shankar and Akhila K. Sahoo, *J. Org. Chem.* (DOI: 10.1021/jo5008465).

7. Sulfoximine Assisted Pd(II)-Catalyzed Bromination, Chlorination and Lactonization of Primary-C(sp^3)–H Bond

   Raja K. Rit, **M. Ramu Yadav**, Koushik Ghosh, Majji Shankar and Akhila K. Sahoo, (Communicated).

8. Sulfoximine-Directed Ruthenium-Catalyzed *o*-C–H Amidation of Arenes with N-Arenesulfonated Imides

   M. Ramu Yadav, Majji Shankar, E. Ramesh, Koushik Ghosh and Akhila K. Sahoo, (Communicated).

Presentations

1. Sulfoximines: A Reusable Directing Group for Chemo- and Regioselective *ortho*-C–H Oxidation of Arenes

   M. Ramu Yadav, Raja K. Rit and Akhila K. Sahoo

   (i) Oral Presentation at "**7th J-NOST Conference**" held at Indian Institute of Science Education and Research (IISER), Mohali, India on December, **2011**.

   (ii) Poster Presentation at "**CHEM-FEST 2012**" held at School of Chemistry, University of Hyderabad, Hyderabad, India on February, **2012**.

2. Sulfoximine Directed Intermolecular *o*-C–H Amidation of Arenes with Sulfonyl Azides

   M. Ramu Yadav, Raja K. Rit and Akhila K. Sahoo

   (i) Oral Presentation at "**CHEM-FEST 2013**", held at School of Chemistry, University of Hyderabad, Hyderabad, India on February, **2013**.

   (ii) Poster Presentation at "**OMCOS 17 (17th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis)**" held at Colorado state university, Ft. Collins, USA on July, **2013.**

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