Hydroarylation and Multiple Functionalization of Unactivated Arene C–H Bonds

A Thesis
Submitted for the Degree of
DOCTOR OF PHILOSOPHY

By

Koushik Ghosh



School of Chemistry
University of Hyderabad
Hyderabad 500 046
Telangana
India

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To

My Family

&

Well-Wishers

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STATEMENT

I hereby declare that the matter embodied in this thesis entitled "Hydroarylation and Multiple Functionalization of Unactivated Arene C–H Bonds" is the result of investigation carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India, under the supervision of **Prof. Akhila Kumar Sahoo**.

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Prof. Akhila Kumar Sahoo
Supervisor

University of Hyderabad

December, 2017



CERTIFICATE

This is to certify that the thesis entitled **"Hydroarylation and Multiple Functionalization of Unactivated Arene C–H Bonds"** submitted by **Koushik Ghosh** bearing registration number **12CHPH11** in partial fulfillment of the requirements for award of Doctor of Philosophy in the School of Chemistry is a bonafide work carried out by him under my supervision and guidance.

This thesis is free from plagiarism and has not been submitted previously in part or in full to this or any other University or Institution for award of any degree or diploma.

Parts of this thesis have been:

A. Published in the following publications:

1. **Koushik Ghosh**, Raja K. Rit, E. Ramesh and Akhila K. Sahoo *Angew. Chem., Int. Ed.* **2016**, *55*, 7821. **(Chapter 2 and 3)**
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University of Hyderabad

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List of Abbreviations

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

ESI	electron-spray ionization
FG	functional group
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
MPyS	methyl-2-pyridyl sulfoximine
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
Ns	nosyl
Oxone	potassium peroxymonosulfate
$PhI(OAc)_2$	phenyl iodo diacetate
Piv	pivaloyl
^{i}Pr	*iso*-propyl
TBHP	*tert*-butyl hydroperoxide
TBDMS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxy
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl

Chapter 1

C–H Activation: An Introduction

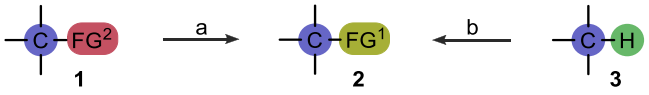
Abstract

The origin, development, and significance of C–H activation in modern synthetic organic chemistry are enumerated in this chapter. The mechanistic details involved in each step of C–H activation are briefly discussed. The use of C–H activation for the synthesis of complex molecular architecture is also highlighted. Finally, the aim of this thesis directed towards the development of new synthetic method for multiple functionalization of readily accessible simple molecules for the construction of complex skeleton is deliberated.

1.1. Introduction

Nature's propensity for selective functionalization of ubiquitous C–H bonds continuously attracts synthetic community to mimic this process. The C–H bonds are pervasive; thus direct use of C–H bonds for the construction of complex molecular entities always attracts attention. In 1968, Jack Halpern, inorganic chemists, stated: "development of a successful approach for the activation of C–H bonds, particularly saturated hydrocarbons, is most important and challenging in the field of homogeneous catalysis."[1] Later, in 1995, a special issue in '*Accounts of Chemical Research*' depicted 8 Holy Grails of chemistry. One of the Holy Grails is homogeneous metal complex guided selective intermolecular C–H bond activation written by Robert G. Bergman. According to Bergman "one Holy Grail is not simply to find new C–H activation reactions, but to obtain an understanding of them that will allow development of reagents for selective transformations of C–H bonds."[2]

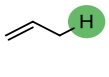
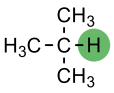
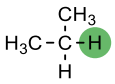
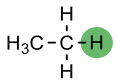
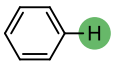
Substantial development in the realm of synthetic chemistry has particularly been witnessed from past 50 years. The strategy of C–H activation stands unique in the domain of synthetic chemistry; as un-functionalized molecules have particularly been functionalized in this study.[3] Generally, a pre-functionalized precursor is necessary for the introduction of new functional group (FG) into the molecule (path a, Scheme 1.1). However, extra steps are always required making the pre-functionalized molecule from readily available material; consequently producing waste in every step of the transformation. For instance, transition-metal-catalyzed cross-coupling reactions of pre-functionalized electrophile and metal-enabled nucleophile always accumulate stoichiometric amount of acids or inorganic salts waste by-products.[4,5] In contrast, the direct conversation/functionalization of inert C–H bond does not essentially require prefunctionalized substrate and therefore this is considered ideal in terms of step and atom-efficiency (path b, Scheme 1.1).[3,6]



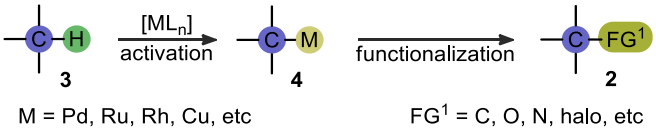
Scheme 1.1. Functionalization of molecule

The large kinetic barrier of isolated C–H bond always possesses low reactivity, as cleavage of C–H is related to apolar nature of the bond. Moreover, the high energy

LUMO and low energy HOMO of C–H bond did not allow proper energy criteria for the construction of new bond with other FGs.[3,7] The bond dissociation energies and pK_a values of various C–H bonds of hydrocarbons are listed below.

Type of C-H	$C(sp^3)_{allylic}$	$C(sp^3)_{3°}$	$C(sp^3)_{2°}$	$C(sp^3)_{1°}$	$C(sp^2)_{vinyl}$	$C(sp^2)_{arene}$	C(sp)
structure							
BDE	361.1	389.9	397.9	410.8	460.2	473.0	552.2
pK_a	43	50	50	50	44	43	25

The BDE increases along the series $C(sp^3)$-H→ $C(sp^2)$-H →C(sp)-H, and from allylic $C(sp^3)$-H bond → 3°→ 2°→ 1°, in line with the notion that this value is proportional to the stability of the radicals obtained from homolysis of C–H bond. On the other hand, the acidity function (pKa) trend goes roughly in the opposite direction (depends on the stability of the corresponding conjugate base).[8] Thus, not only the bond strength but also the pka value controls the activation of C–H bond. The issues can proficiently be addressed forming carbon-metal (C–M) bond intermediate for further transformation (Scheme 1.2).



Scheme 1.2. Inception of C–H bond activation

The C–H activation and functionalization process involve the cleavage of covalent C–H bond under the influence of transition metal for the direct introduction of a functional group by replacing hydrogen (Scheme 1.2).[3,7]

1.2. Mechanism of C–H Activation

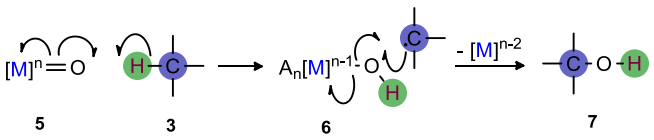
The formation of a new carbon–metal bond through activation of C–H bond depends on, 1) the environment of concerned C–H bond, 2) the use of transition metal catalyst, and 3) the ligands.[3]

The transition metal enabled activation of C–H bond can proceed in two ways. In the first category, the C–H insertion happens into the ligand of a transition metal complex often termed as outer sphere mechanism. On the other side, inner sphere

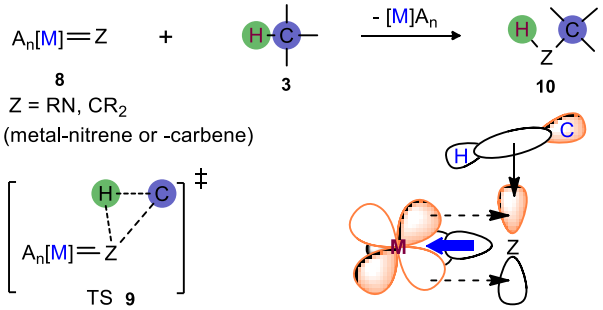
mechanism involves coordination of C–H bond into metal centre to form an organometallic complex where the hydrocarbyl unit sticks into the inner-sphere of the metal during C–H bond cleavage.[9] Although the terminology "C–H functionalization" and "C–H activation"are often used interchangeably, however, the inner-sphere mechanism largely supports the term "C–H activation".

1.2.1. Outer sphere mechanism

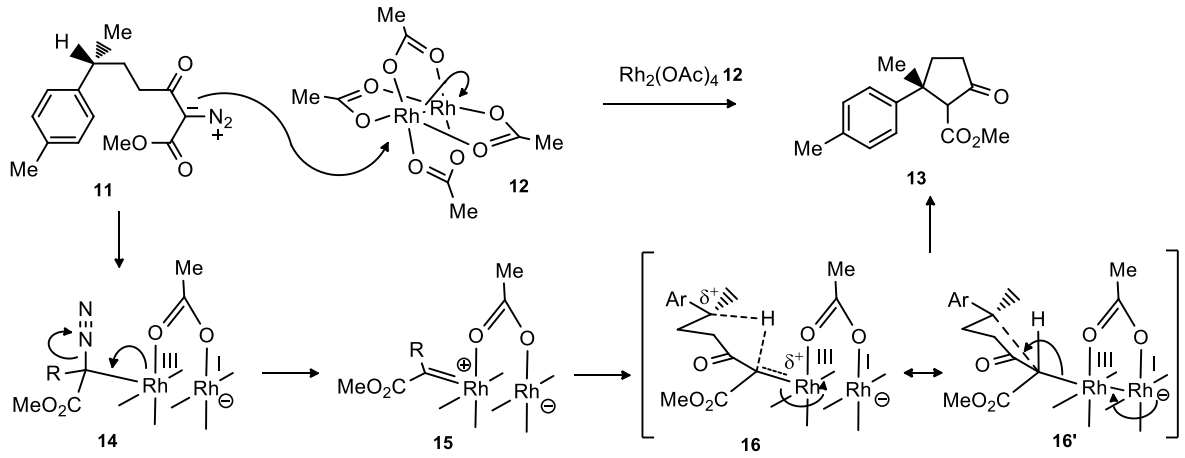
The bio-inspired or enzymatic metal-oxo species are often used promoting the C–H activation of alkane system; the transformation involves metalloradical pathway.[10] The reaction begins with the hydrogen radical abstraction from **3** by the metal oxo species **5**; followed by rapid rebound of radical to the metal hydroxo intermediate **6** occurs (Scheme 1.3). Likewise, the N-atom of metal-nitrenes or the C-atom of metal-carbenes directly interacts with C–H bond via outer sphere mechanism (TS-9); subsequently H–N and C–N bond or H–C and C–C bond formation occurs by dissociating the metal (Scheme 1.4).[11,12] In 1981, the pioneer work of Teyssie's describes Rh(II)-catalyzed C–H bond insertion into carbenes (carbenoids); this transformation follows outer sphere mechanism.[13] The complex natural product smanzacidin A and C were synthesized via Rh-catalyzed nitrene insertion into a C–H bond key step; Du Bios group demonstrated this work. A general mechanism is discussed in Scheme 1.5. The $Rh_2(OAc)_4$, a paddle-wheel shaped compound **12**, has vacant axial coordination site. Nucleophilic attack of **11** to **12** gives intermediate **14**. Nitrogen (N_2) extrusion from **14** generates carbene intermediate **15**. Interaction of carbon of metal carbene with benzylic C–H bond followed by C–H insertion leads to final product **13**.[14]



Scheme 1.3. Radical rebound mechanism



Scheme 1.4. Metal- nitrene and metal-carbene insertions



Scheme 1.5. C–H Bond activation by Rh-carbene insertion

1.2.2. Inner sphere mechanism

The transitional metal catalyzed C–H activation through inner sphere mechanism possibly occurs through three pathways: (a) oxidative addition of C–H bond by electron-rich and low-valent transition metal complexes, (b) σ-bond metathesis by electrophilic early transition metal complexes, and (c) electrophilic activation of C–H bond by electron withdrawing ligand enabled late transition metal species.

On the basis of charge transfer concept, the inner sphere C–H activation processes can suitably be explained. The interaction of metal and C–H bond occurs via two types of charge transfer (CT): (i) from filled dπ orbital metal centre to σ* orbital of the coordinated C–H bond (known as reverse CT) and (ii) from occupied σ orbital of C–H bond to the empty metal-based dσ orbital (known as forward CT).[9] These two interactions make the C–H bond weaker and subsequently the bond is broken. Owing to the electronic character of the transition state, the C–H activation process can be defined either electrophilic or nucleophilic. A qualitative M.O. diagram for the above mentioned process is sketched in Figure 1.1.

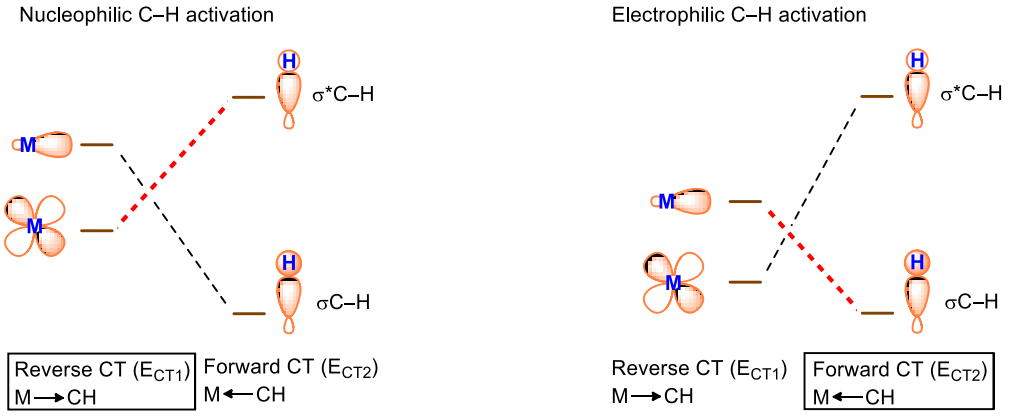
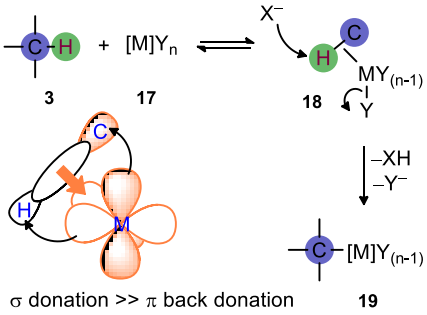
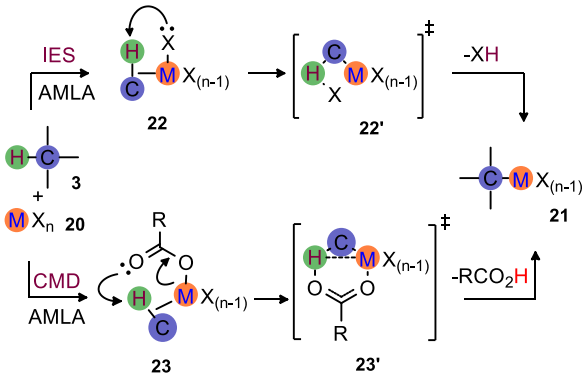


Figure 1.1. Frontier orbital interaction of nucleophilic (left side) and electrophilic (right side) C–H activation

For example, the cationic electron deficient late transition metals have low-lying dσ and dπ electrons. Therefore, forward CT dominates over reverse CT during the interaction of metal to the C–H bond. These types of metal complexes are electrophilic. On the other hand, transition metal complexes with high electron density have high energy dσ and dπ orbital. In this system, the effective frontier orbital interaction is reverse CT, i.e. interaction of σ* C–H with the occupied dπ orbital of metal; this process is nucleophilic C–H activation. Thus, the nature and oxidation state of metal complex determines nucleophilic or electrophilic C–H activation under inner sphere mechanism. Therefore, high oxidation state electron poor late transition metals, such as Ru(II), Pd(II), Pt(II), Rh(III), Ir(III) prefers electrophilic activation. Thus, C–H to metal co-ordination favours a strong σ donation and a weak π back donation from metal;



Scheme 1.6. Mechanism of electrophilic substitution



Scheme 1.7. Ambiphilic concerted mechanism

this intrigues heterolytic cleavage of C–H bond by the assistance of an external anion (Scheme 1.7).

This mechanism proceeds through intramolecular deprotonation via a cyclic, concerted mechanism under the assistance of a heteroatom-based ligand; it may be bridging ligands, like carbonate(CO_3^{2-}), acyloxy (RCO_2^-), halide (X^-), or alkoxy anion (RO^-). These pathways are familiar as: concerted metalation deprotonation (CMD),[15] ambiphilic metal-ligand activation (AMLA),[16] internal electrophilic substitution (IES)[17]etc (Scheme 1.7).

Typically electron-rich, low-valent metal complexes oxidatively inserts to the C–H bond through agostic interaction. The agostic interaction is the electronic distortion of C–H bond to the metal, resulting from the donation of bonding C–H electrons to the vacant d orbital of the transition-metal with the formation of three-centered-two-electron bonds (**24'**).[7,18] The late transition metals: Re, Fe, Ru, Os, Rh, Ir, Pt are susceptible inserting to the unactivated C–H bonds. The coordinatively unsaturated intermediate [LnMx], generated in situ by thermal or photochemical decomposition of suitable precursor, is the reactive species (Scheme 1.8). A qualitative MO interaction of C–H bond activation via oxidative addition is shown in Figure 1.2. For example, under photo irradiation of complex [(η^5-C_5Me_5)(PMe_3)$Ir^{III}H_2$] (**26**) losses H_2 to give the intermediate [(η^5-C_5Me_5)(PMe_3)Ir^{I}], which subsequently activates the C–H bond of cyclohexane to give complex **27**(Scheme 1.8).

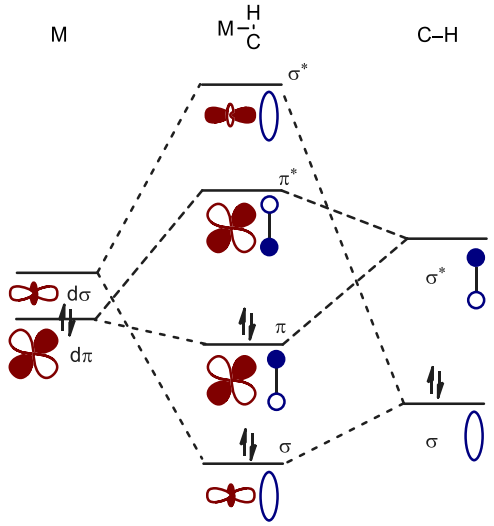
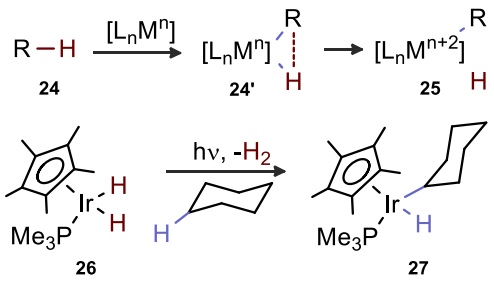
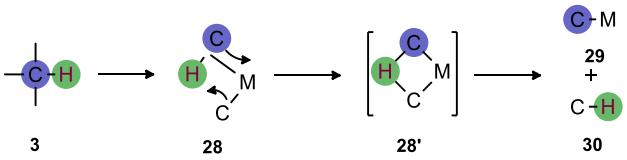


Figure 1.2. MO diagram of oxidative addition



Scheme 1.8. C–H Activation *via* oxidative addition

Low valent, late transition metal complexes could be able to promote the C–H activation spanning from oxidative addition (OA) to σ-bond metathesis, with plenty of subclasses lies between these two mechanisms. Depending on steric and electronic properties of the metal environment, the reaction path can be specified. On the other hand, nucleophilic C–H activation is favored in presence of donating ligands such as bidentate nitrogen-based ligands, N-heterocyclic carbenes (NHCs), or phosphines. In particular, oxidative addition is possible by the electron-rich, nucleophilic, low valent d^8, second- and third-row late transition metal complexes. The change of enthalpy among the breaking of C–H bond with M–H and M–C bond formation is energetically favorable process, consequently metal oxidizes to d^6 configuration. The C–H to metal coordinated species attributed with a weak σ donation and strong π back donation. Thus, metal with high oxidation state and early d^0 transition metals cannot undergo oxidative addition due to lack of d electrons, so they can operate σ-bond metathesis with C–H bonds.[7,19] This process involves concerted four-electron kite-like transition state where the oxidation state of metal remains unchanged (Scheme 1.9). A qualitative M.O. for σ bond metathesis is shown in Figure 1.3.



Scheme 1.9.σ-bond metathesis

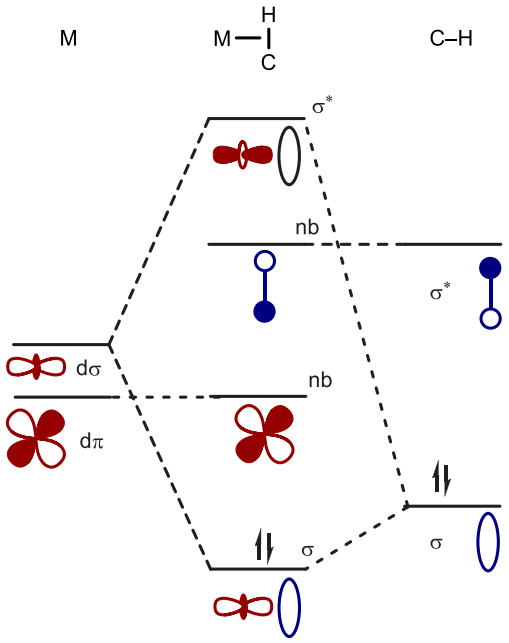
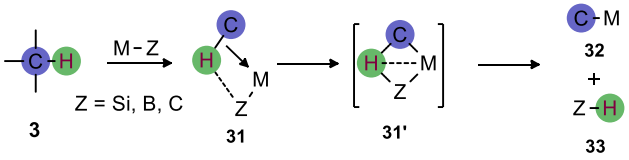


Figure 1.3. MO diagram of sigma bond metathesis

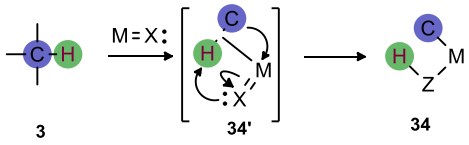
Transition metal fragments with d^4 to d^8 configuration can also undergo σ bond metathesis. The presence of free vacant sites on the fragments, a stable σ adducts after and before the actual metathesis is possible.

This mechanism is known as σ complex assisted metathesis (σ-CAM)[20] (Scheme 1.10).

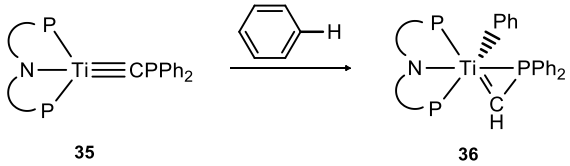


Scheme 1.10. Metathesis by the assistance of σ-complex

The last process of C–H activation termed as 1,2-addition.[7,21] This occurs by the addition of C–H bond of compound **3** across M=X bond and delivers **34** via four centered concerted mechanism. This process is similar to σ-BM; however, the newly generated X–H moiety does not leave the metal center, as the π or lone pair electrons are involved in the activation of C–H bond instead of σ bond. The alkoxy, amido, alkylidene, alkylidyne containing early and middle transition metal complexes undergo this mode of C–H activation (Scheme 1.11). Activation of benzene C–H bond by the reactive transient complex $TiCPPh_2$ **35** involves a 1,2-C–H bond addition to give **36** (Scheme 1.12).[22]

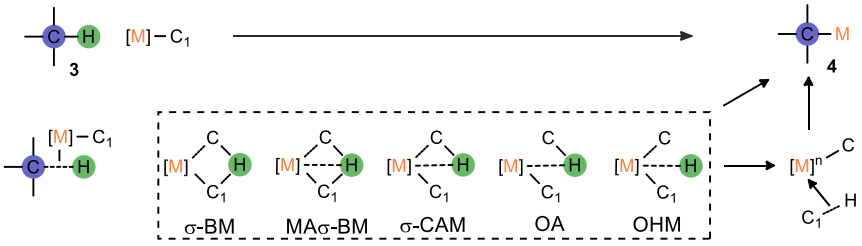


Scheme 1.11. 1,2-Addition mechanism



Scheme 1.12. C-H activation via 1,2-addition

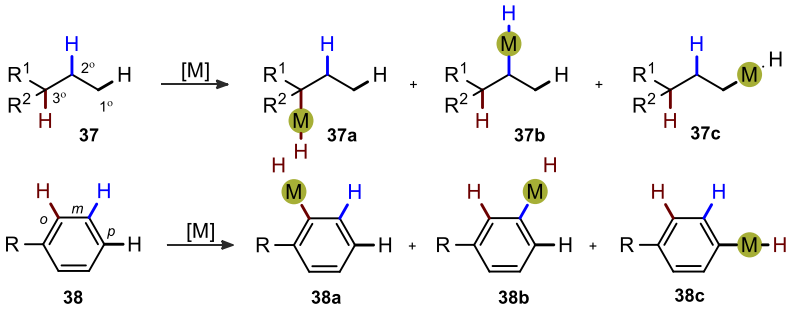
In summary, the nature of metal as well as the co-ordinated ligands decides the type of C–H activation involved in the reaction. The process either involves a two-step oxidative addition-reductive elimination path with discrete AO intermediate or σ bond metathesis with single transition state. All the possible paths are summarized in Scheme 1.13.



Scheme 1.13. Possible paths for the activation of C–H bonds

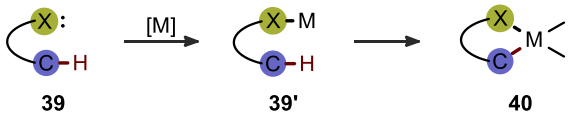
1.3. Selective C–H Functionalization:

Although activation/functionalization of C–H bond is achieved by the transation metal catalysis, but selective functionalization of particular C–H bond among chemically divergent C–H bonds is challenging. This eventually produces mixture of products; consequently, the issue of non-selectivity makes the process cumbersome and tumultuous.



Scheme 1.14. Regioselectivity in C–H activation

In a simplest case, activation of a monosubstituted alkyl chain **37** or arene **38** produce non-regioselective mixture of respective C–H activation complex **37a**–**c** or **38a**–**c** (Scheme 1.14). Thus, selective activation of a specific C-H bond among various indifferent C–H bonds is truly challenging. To overcome the perennial selectivity problem, the likeness between Lewis acidic transition metals and Lewis basic heteroatom for the site-selective activation of specific C–H bond is eventually considered. A number of strategies have been developed and successfully been applied to explore the activation of specific inert C–H bonds.[3,23] The heteroatom-containing moiety (**X**) often termed as directing group that can anchor metal (**M**) and bring the selective C–H bond of **39** to close proximity to metal and finally assists forming the cyclometalated complex **40** (Scheme 1.15).



Scheme 1.15. Chelation directed C–H activation

1.3.1. Direct C–H Bond Functionalization of Arenes

The first report of metal-assisted C–H activation was documented by Volhard in 1892;[24] although C–H activation term was not introduced at that time. Following

similar strategy, Otto Dimroth prepared a number of arylmercury acetate **42** from aromatic hydrocarbons and mercury(II) acetate (Figure 1.4).[25] Later, in 1931 Kharasch and Isbell were able to isolate $PhAuCl_2$ **43** from the reaction of $AuCl_3$ with benzene **41** (Figure 1.4).[26] Shunsuke Murahashi reported the synthesis of phthalimidines via Co-catalyzed chelation-assisted C–H functionalization.[27] Probably, the pioneer study was discovered by Joseph Chatt in 1965, for the metal promoted activation of C–H bond. The insertion of ruthenium(0) from the complex $RuCl_2(dmpe)_2$ (**44**) to the naphthalene C–H bond provides **45** (Figure 1.5).[28]

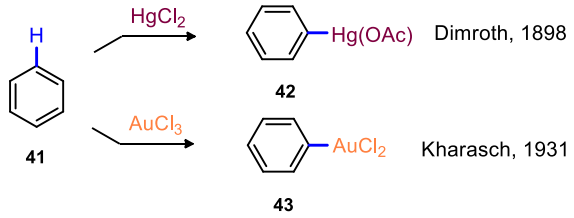


Figure 1.4. First reports of activation of the C–H bonds

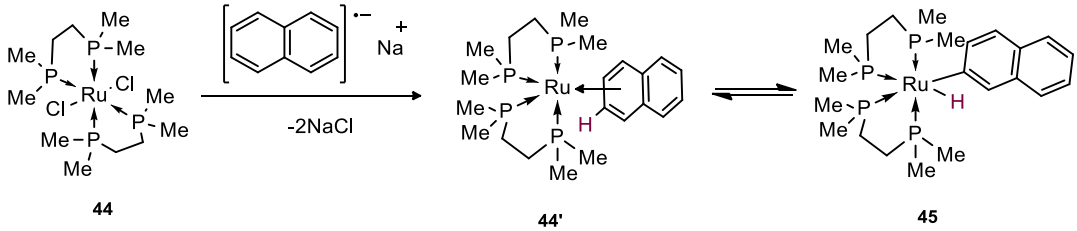
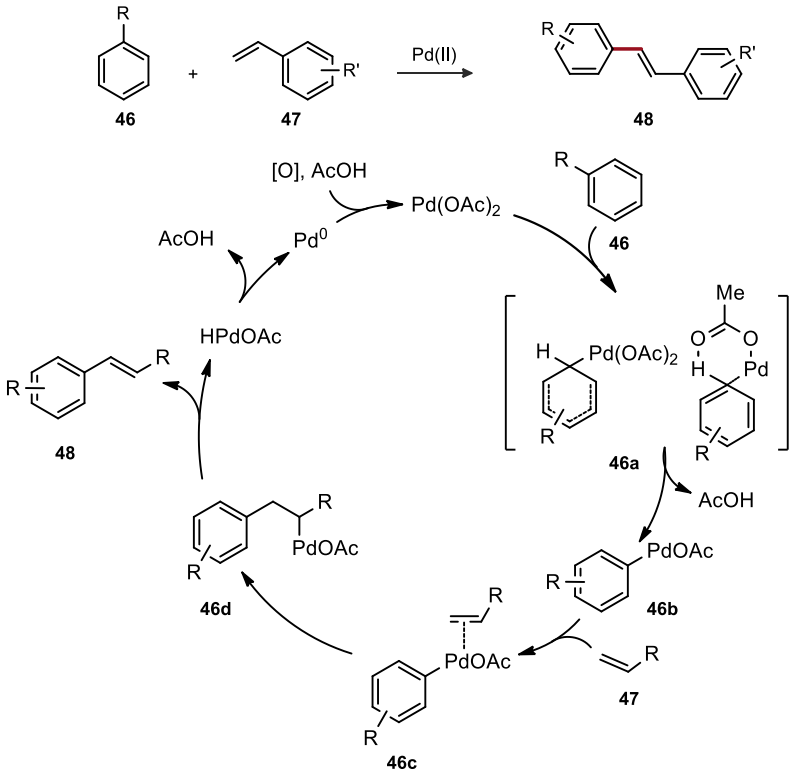


Figure 1.5. Chatt's pioneer work on C–H activation of naphthalene

The path-breaking discovery by Yuzo Fujiwara and Ichiro Moritani demonstrates oxidative cross-dehydrogenative coupling of C–H bonds. This transformation is analogous to the Heck cross-coupling reaction where direct coupling of olefin-C–H bond with aromatic C–H bond occurs for the construction of C–C coupled product. The non-requirement of pre-functionalized precursors makes this process synthetically useful (Scheme 1.16).[29] Despite the potential, this process typically needs harsh reaction conditions and lack of high-selectivity.

Although the mechanism of this reaction is not completely understood but the wider accepted path is described in scheme 1.16. The reaction starts with the formation of palladium–aryl cationic complex **46a** either through concerted deprotonation metallation (CMD) or Friedel-Crafts process; subsequent elimination of acetic acid produces palladium–aryl species **46b**. Next, coordination of olefin to the palladium

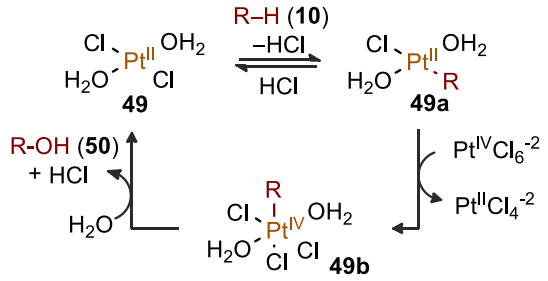
complex **46b** undergoes 1,2-migratory insertion through the formation of C–C bond to give the intermediate **46d**.



Scheme 1.16. Fujiwara-Moritani reaction

Finally, β-hydride elimination of **46d** delivers styrene **48** with the generation of palladium hydride species. This palladium(II) species undergoes deprotonation to yield Pd(0). Further re-oxidation of Pd(0) by oxidant generates Pd(II) and keeps the catalytic cycle alive (Scheme 1.16).[30]

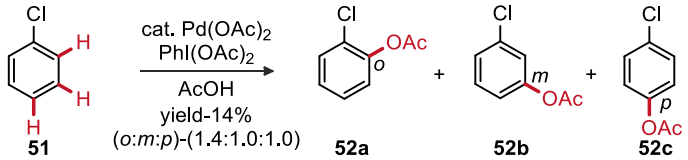
In the twentieth century, a break through by Shilov witnessed the true catalytic C–H activation of alkane. Oxidation of simple alkanes with $K_2Pt^{II}Cl_4$ catalyst and $K_2Pt^{IV}Cl_6$ stoichiometric oxidant delivered the hydroxylation product **50** (Scheme 1.17). The C–H bond activation occurs by Pt^{II} catalyst **49** to generate the activated complex **49a**, which further oxidized with the aid of Pt(IV) to provide **49b**. Finally, the C–H bond oxidized product **50** was obtained with the regeneration of catalyst **49**



Scheme 1.17. Oxidationofalkene (Shilov's catalytic cycle)

(Scheme 1.17). Disappointingly, the requirement of expensive stoichiometric Pt oxidant, decomposition of Pt-catalyst, the formation of undesired side products, low turnover number hinders the broad synthetic application. However, this work opens up a new horizon in understanding the catalytic reaction of C–H activation.[31]

Crabtree group reported the direct C–H oxidation of arenes under the Pd(II)-catalysis. For instance, oxidation of chlorobenzene (**51**) in presence of oxidant $PhI(OAc)_2$ in AcOH delivered a mixture *ortho*, *meta*, and *para* acetoxylation products (**52a**–**c**) (Scheme 1.18).[32] Low product yield and the issue of selectivity causes main problems in this process.

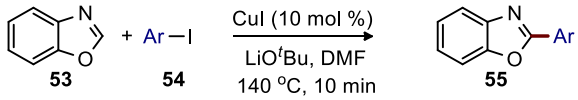


Scheme 1.18. Carbtree's non-regioselective C–H acetoxylation

In 1986, the *ortho*-selective C–H alkylation of phenol was reported by Lewis and Smith. Selective *ortho*-alkylation was achieved by the chelation assisted C–H activation strategy.

1.3.2. Direct C–H Bond Functionalization of Heteroarenes

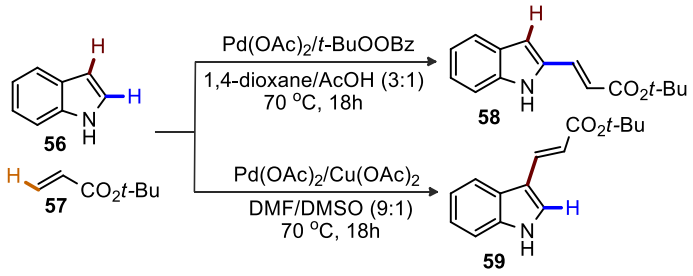
The electronic bias of heteroarene's easily distinguish the reactivity of C–H bonds; hence direct functionalization of heteroarenes occurs with high regioselectivity. For example, Cu-catalyzed regioselective arylation of C2–H of benzoxazole (**53**) is achieved with the coupling of aryl iodide (**54**) (Scheme 1.19).[33] This strategy has successfully been implemented for direct arylation of various heteroarenes.



Scheme 1.19. Regioselective C-H arylation of benzoxazole

Gaunt group demonstrated Pd-catalyzed site-selective C2 or C3 olefinations of indole. The products regioselectivity are tuned on the basis of the use of oxidant and solvent. The C3-olefination product **59** was obtained when the reaction conducted in

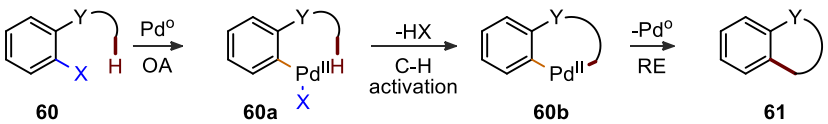
presence of $Cu(OAc)_2$ in DMF/DMSO, while the reaction with peroxide oxidant in dioxane/AcOH provided C2 olefination product **58** (Scheme 1.20).[35,36]



Scheme 1.20. Regioselective olefination of indole

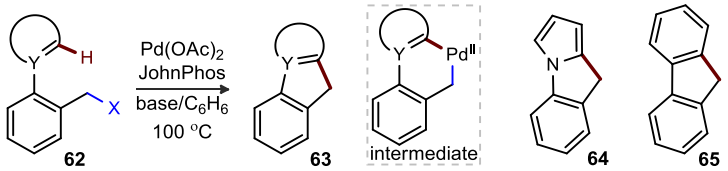
1.3.3. Direct C–H Bond Functionalization: Oxidative Addition-Induced Activation

The C–X (halogen, -OTf) species efficiently assist the functionalization of inert C–H bonds. For instance, transition metal easily undergoes oxidative addition to C–X bond to produce metal embedded activated complex. Thus, the oxidative addition species, obtained in situ through insertion of low valent metal to C–X bond, can selectively activate the internal C–H bond of close proximity. For example, the base-mediated C–H activation involves oxidative insertion of transition-metal to C-X bond of **60** to form **60a** followed by proximal proton abstraction to generate active metallacycle **60b**. Finally, reductive elimination of **60b** produces new C–C bond in **61** (Scheme 1.21). The base and ligand plays crucial in this type of transformation. Dyker group developed one such C–H activation strategy in the early 1990s; this method has been implemented for the synthesis of various polycyclic compounds from tethered aryl iodides in presence of Pd(0) catalyst. Recently, Buchwald, Cramer, Fagnou, Baudoin groups used similar strategy for the construction of novel carbo- and heterocycle skeletons.[37]



Scheme 1.21. Regioselectivity of C(sp^3)–H activation by oxidative addition induced mechanism

Interestingly, a complementary approach from Chang group reveals the synthesis of pyrroloindoles (**64**) and fluorenes (**65**) from tethered benzyl chloride/bromides (**62**) (Scheme 1.22).[38]



Scheme 1.22. Regioselective C(sp^2)–H activation via oxidative addition induced mechanism

These seminal works indulge various research groups to explore this *Holi grail* chemistry of C–H activation. Thus, in the fortress for synthetic chemistry, the activation and functionalization of C–H bonds to carbon-heteroatom or carbon-carbon bonds from non-functionalized precursors attracts significant attention. This process eventually is straight forward and efficient. Despite the progress, the selective C–H bond functionalization is always attractive.[3] Thus, DG enabled functionalization of selective C–H bonds is important.

Chelation assisted C–H activation occurs through the participation of various transition states (discussed earlier). In 1985, Ryabov group postulated electrophilic substitution of metal on aryl ring to form the intermediate **66a**. The oxidative addition to arene C–H bond with Pd(II) provides transient Pd(IV)-species **66b**, as proposed by Canty and Van Koten in 1995. Later, in 1997 Martinez described the acetate (base) assisted proton abstraction and subsequent formation of M–C bond to yield activated metal complex **66c**. Generation of metallacycle **66d** is possible via complex induced activation of proximal C–H bond; Beak and Snieckus described this as CIPE i.e. complex-induced proximity effect (Figure 1.6).[39]

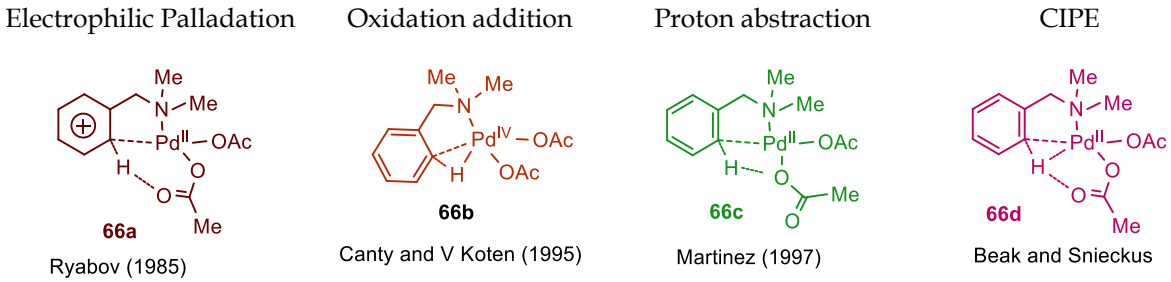


Figure 1.6. Possible participation of transition states for C–H activation

1.3.4. Directing Groups in Chelation Assisted C-H Bond Activation

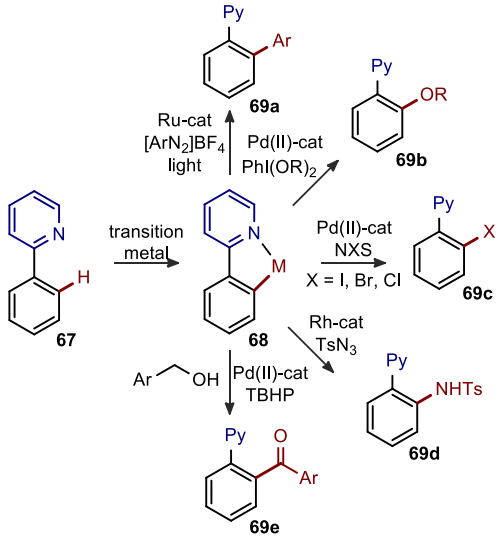
As discussed earlier (Scheme 1.15), the directing group (DG) especially assists the C–H bond activation with high regioselectivity. In the last decades, DG assisted metal catalyzed C–H activation has witnessed tremendous use for selective functionalization of the molecular scaffold.

The Lewis basic heteroatom of the DG is a σ donor, which cohesively binds to the Lewis acidic metal. Simultaneously, DG brings the metal close to the proximal C–H bonds and triggers activating the C–H bond to form cyclometalated or activated complex. Subsequent interactions of specific reagent with the activated complex provide the desired product. The reversible binding ability of metal to the DGs keeps the catalytic cycle alive. A large variety of DGs e.g. pyridine, pyrimidine, pyrazole, oxazole, oxime, amide, imines, acetanilide, ester, carbamate, sulfoxide, sulfonamide, etc. have been deployed from time to time for the activation and functionalization of C–H bonds.[3,40]

The DGs can be (a) non-removable/non-modifiable, (b) modifiable/transformable, (c) traceless, and/or (d) reusable.

1.3.4.1. Non-Modifiable Directing Group:

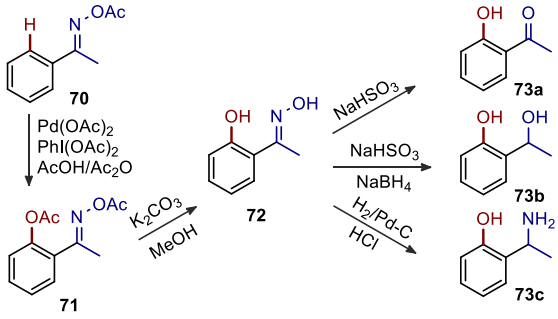
The non-modifiable DGs are robust; these groups strongly facilitate activating inert C–H bonds with ease. However, these groups are not easily transformable or modifiable from the C–H functionalized product. As a result synthetic utility of the strategy is hampered. 2-Pyridyl is a true example of non-modifiable DG. The pyridyl assisted activation of C(sp^2)–H in **67** with transition metal (TM) forms the active metallacycle **68**, which has extensively been trapped with electrophiles and nucleophiles for the construction of C–C and C–heteroatom bond (Scheme 1.23).[41]



Scheme 1.23. C–H activation using non-modifiable DG

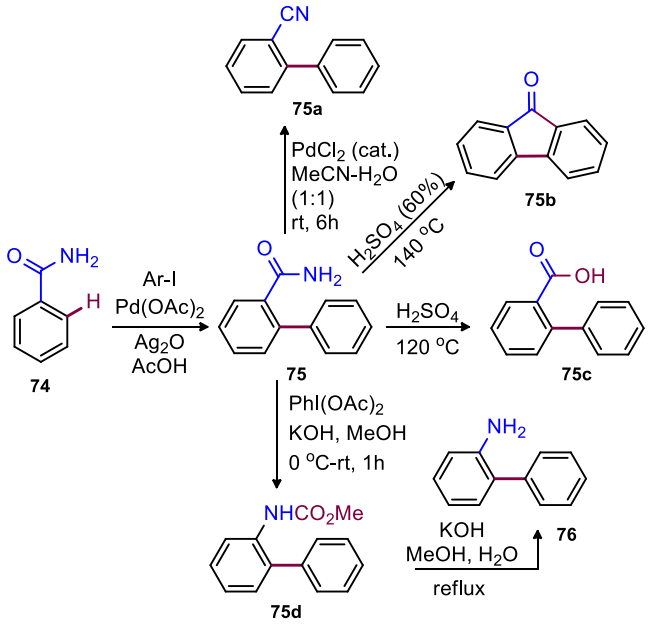
1.3.4.2. Modifiable/Transformable Directing Group

The DG from the C–H functionalized products are easily modifiable or transformable to other functionality are widely termed as modifiable/transformable DG (MDG/T^{f}DG). The MDG possesses strong synthetic utility; as these groups are easily transformable eventually helping further functionalization of the products. Thus, MDG plays vital for the challenging multiple functionalization of C–H bonds (i.e. mono-functionalization assisted by DG and second-functionalization directed by MDG). Accordingly, several modifiable or transformable DGs have been developed and successfully deployed for various C–H functionalization.[42]



Scheme 1.24. C–H activation using modifiable oxime-DG

An interesting protocol from Sanford group entails the oxime directed acetoxylation of C(sp^2)–H bond of arenes **70** in the presence of $Pd(OAc)_2$ and $PhI(OAc)_2$ to give the acetoxylation product **71** (Scheme 1.24). The oxime moiety easily transformed to the corresponding ketone, alcohol, and amine, demonstrating the modifiable nature of oxime DG.[43]



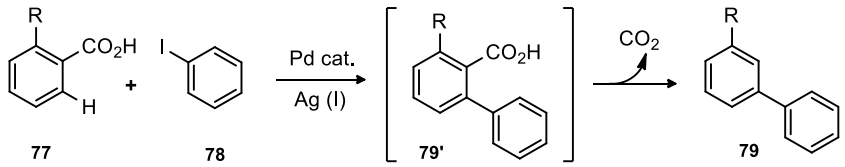
Scheme 1.25. C–H activation using modifiable amide-DG

The amide directed oxidative arylation of benzamide **74** proficiently delivers monoarylation compound **75**. The amide moiety of **75** is readily transformed to cyano **75a**, cyclic ketone **75b**, acid **75c**, and anilide**75d**, showcasing the modifiable nature of amide DG (Scheme 1.25).[44]

1.3.4.3. Traceless Directing Group

The DG is traceless, when the trace of DG is not present in the product after the C–H functionalization. Clearly, cleavage of DG occurs during/after the functionalization of the precursors under the same reaction condition.

Yu and co-workers have shown the traceless carboxylic acid assisted *o*-C–H arylation with aryl iodide. In this process, the carboxylate moiety behaves DG; upon C–H arylation proto-decarboxylation occurs under Ag-catalysis, truly demonstrating traceless nature of carboxylic acid. Larrosa group also reveal the *meta*-selective direct C–H arylation under the influence of carboxylic acid (**77**) as a traceless DG using iodoarenes **78** as coupling partner (Scheme 1.26).[45]



Scheme 1.26. C–H activation using traceless DG

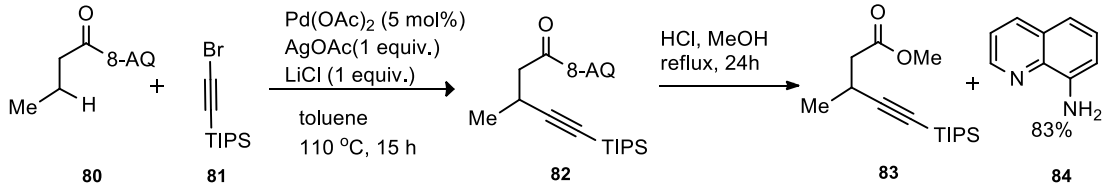
1.3.4.4. Reusable Directing Group

In this category, the DG can easily be incorporated in the starting material, cleaved from the C–H functionalization product and finally recovered, and reused. These groups act as catalytic mimic in the functionalization of C–H bonds. Thus, reusable DG assisted functionalization of C–H bond is atom-economical and the process is synthetically viable.[46]

In 2005, Daugulis group demonstrated the palladium catalyzed 8-amino quinoline (8AQ) directed arylation of inert *o*-C(sp^2)–H with aryl iodides. The 8-AQ directing group has successfully been adopted for the effective functionalization of C(sp^2)–H/C(sp^3)–H and even methylene C(sp^3)–H bonds.[47]

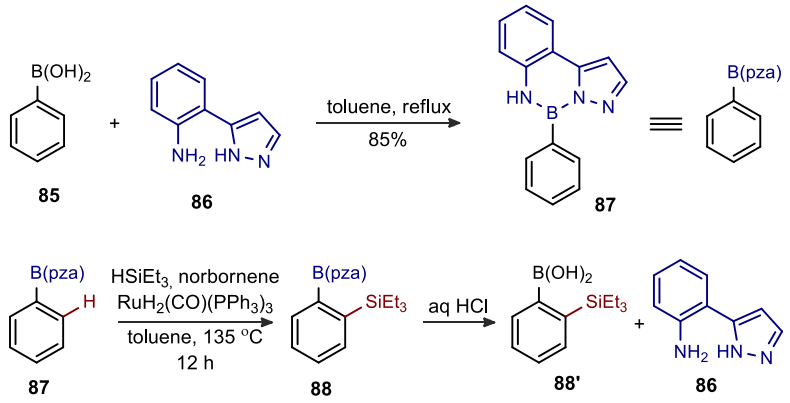
For instance, Pd-catalyzed ethynylation of methylene C(sp^3)–H bonds has been achieved with the aid of 8-AQ DG. The reaction of aliphatic carboxylic acid coupled

8AQ **80** with bromoalkyne **81** delivers the C(sp^3)–H functionalized product **82**. Acid hydrolysis of **82** provides the DG **84** in good yields (Scheme 1.27).[47]



Scheme 1.27. Reusable DG for methylene C(sp^3)–H activation of alkanes

The 2-pyrazol-5-ylaniline (pzaH$_2$, **86**), developed in 2009 by Suginome and coworkers, can easily mount with arylboronic acids **85** to give the precursor **87**. The Ru-catalyzed *ortho*-C–H silylation of **87** successfully affords **88**. Hydrolysis of **88** with aqueous HCl produces pzaH$_2$DG (**86**) along with the desired product *o*-silylated arylboronic acid **88′** (Scheme 1.28). Pleasingly, total sequence was successfully performed in one-pot.[48]



Scheme 1.28. C(sp^2)–H activation of boronic acids using reusable pza DG

The Yu group at first revealed a regioselective *meta*-C–H bond activation of arene with the aid of end-on nitrile-based DGs **89a** and **89b** (Figure 1.7). Interestingly, *meta*-C–H bond is selectively functionalized keeping *ortho* position intact.[49] The amide coupling between hydrocinnamic acid and **89** provides **90**. The *meta*-C–H bond functionalization involves the coordination of end-on nitrile DGs to Pd(II)-catalyst via a 12 membered metallacycle. Finally, reaction of 12-membered palladacycle with olefin **91** proficiently delivers the desired styrene **92** (Scheme 1.29). The large

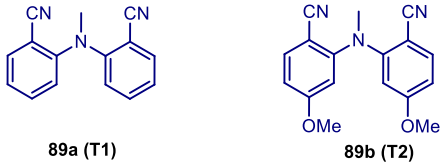
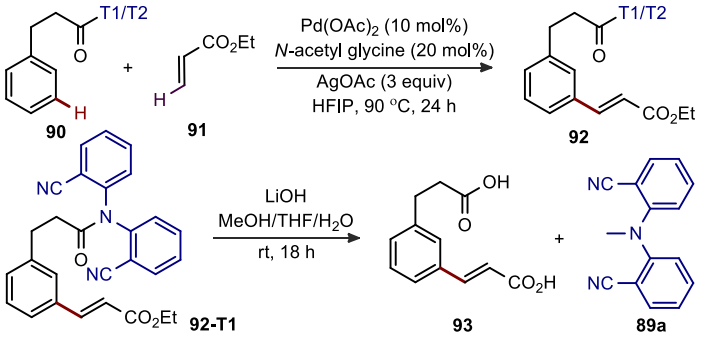


Figure 1.7. End-on nitrile DGs

membered metallacycle with the terminating linear nitrile DG excludes activating *ortho*-C–H bonds. The *meta*-C–H acetoxylation and arylation are also perceived under the influence of end-on nitrile U-shaped DG.[49] The base mediated hydrolysis of amide-motif in **92-T1** at room temperature affords the desired diacid **93,** recovering the DG **89a** in 65% yield (Scheme 1.29).[49]



Scheme 1.29. *meta*-C–H Activation of arenes using reusable end-on-nitrile DG

1.4. Multiple Functionalization of Unactivated C–H Bonds

Transition metal (TM)-catalyzed selective C–H bond functionalization with the aid of DG is a promising tool for the step- and atom-efficient construction of versatile molecular scaffolds from easily accessible precursor.[49,50] Consequently, an appreciable amount of effort has therefore been made for the development of several 'DGs' and 'catalytic systems' for the stereo and regioselective activation of chemically indifferent C–H bonds.[51] In spite of the growth and success in C–H activation, DG-promoted synthetically attractive multiple functionalization of arene C–H bonds are rarely developed, although exceedingly appealing.

Multiple C–H bond functionalization promptly installs various functionalities on the molecular framework and consequently fabricate complex molecular entities with ease. Conventionally, complexities can be introduced in a molecule via multistep synthetic modification of the pre-functionalized substrate, which often suffers from numerous difficulties (discussed below). The multiple functionalization of C–H bonds is referred to the direct replacement of inert C–H bonds with diverse functional groups involving C–H bond activation (Figure 1.8).

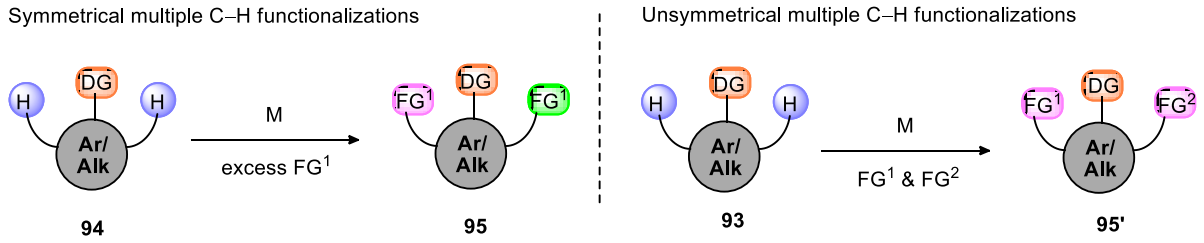
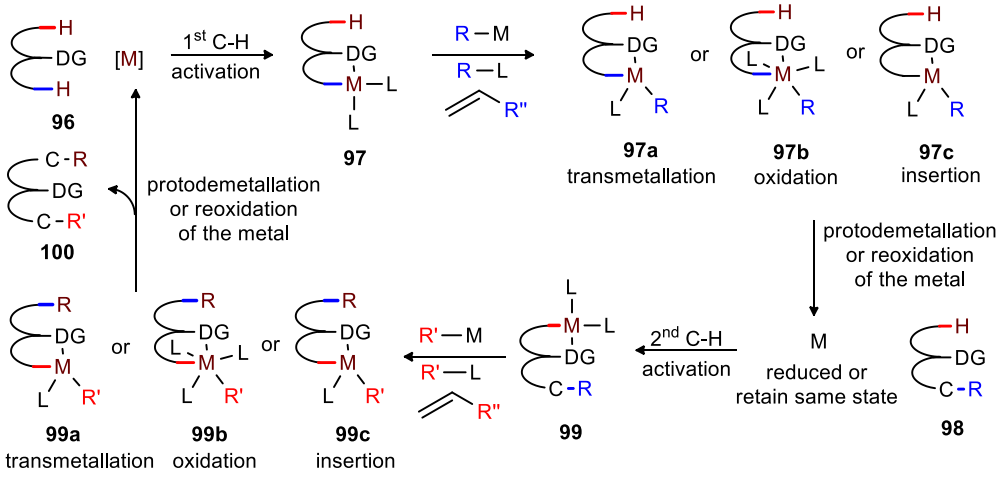


Figure 1.8. Multiple functionalization of C–H bonds

1.4.1. Problems and Solutions of Multiple Functionalization

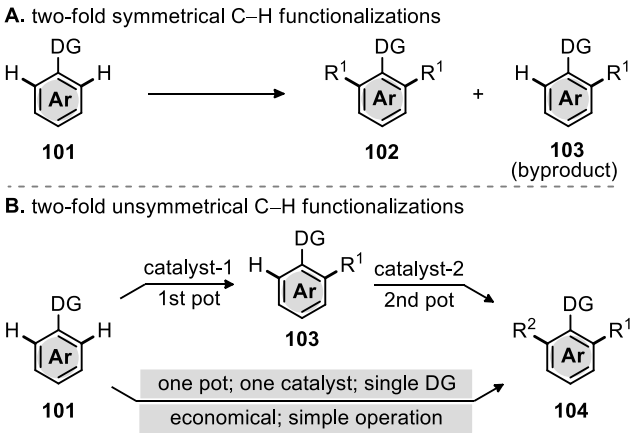
In general, the coordinating/electronic/steric effects of the *o*-substituent in DG-bearing arene have great influence on the activation and functionalization of *o'*-C–H bond. However, presence of *o*-substitution often hampers the efficient introduction of another FG in arene; as a result, effective twofold functionalization of aryl C–H bonds remains challenging.[52] In addition, the catalytic conditions, as well as the DGs, are obliquely selective towards specific bond formations; thus, unsymmetrical functionalization of C–H bonds under one catalyst is mostly turned futile. Moreover, the formation various by-products and incomplete profile of the reaction involved in each step of the transformation makes the whole process cumbersome and unproductive.[53]

Notably, single DG-enabled symmetrical di-functionalization of *o*-C–H bonds of arenes has been well investigated; the product selectivity is greatly influenced by the choice of DG and stoichiometry of the reactants.



Scheme 1.30. Unsymmetrical functionalization of multiple C–H bonds

The general reaction mechanism of symmetrical di-functionalization (Scheme 1.30) involves- (i) co-ordination of metal to the DG, (ii) activation of proximal C–H bond (**97**), (iii) association of the functional group to the activated metal complex by transmetallation (**97a**) or oxidative addition (**97b**) or by substitution (**97c**) and (iv) reductive elimination or β-hydride elimination/protodemetallation delivers the mono-functionalized **98**. Repetition of all these steps with **98** accomplishes dual symmetrical C–H functionalization. In case of unsymmetrical dual functionalization, the system gets complicated. Although the first C–H activation is quite similar to the mechanism proposed in Scheme 1.30, the remaining steps are no longer same in the competitive environment of multiple reagents. The primary challenges are- a) the preferential reactivity of a reagent to the metallacycle over others leading to symmetrical dual functionalization, b) different mode of incorporation of reagent to metallacycle under specific conditions. Therefore, proper reaction condition, appropriate reagents as well as functional group play vital in each reaction step. Next, the catalytic activity with high turnover number (TON), less load of catalyst makes the process economical. Considering all these points, the realization of an efficient unsymmetrical dual C–H functionalization in one pot is extremely challenging. Therefore, development of such a process not only requires in-depth understanding of the reaction path and reagents but also it is necessary to understand the reactivity pattern (even for subtle reacting groups).



Scheme 1.31. Strategies for multiple C–H functionalization of arenes

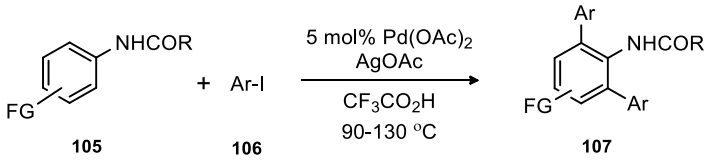
Recently, a handful number of investigations have been disclosed for unsymmetrical *o*-C–H functionalization of arenes under single DG. Although the DG is compatible

to two different reactions, however, the catalytic conditions are truly different. Moreover, purification of the product(s) in each step makes these methods tedious and inefficient (Scheme 1.31).

A one-pot twofold unsymmetrical functionalization of arenes in the presence of a single DG under one catalytic condition would essentially deliver highly functionalized aryl derivatives in a by-product-free and step-efficient fashion. This process would therefore be considered ideal for the synthesis of complex molecular scaffold (Scheme 1.31).

1.4.2. Precedents for Multiple Functionalization of C-H Bonds

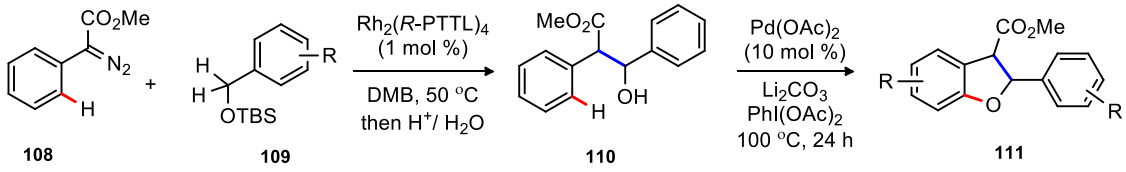
Daugaulis group has shown the Pd-catalyzed symmetrical diarylation of anilide derivative (**105**) in presence of excess amount of aryl iodide (**106**). The turnover number of this reaction is up to 1000 (Scheme 1.32).[54]



Scheme 1.32. Symmetrical diarylation of anilide

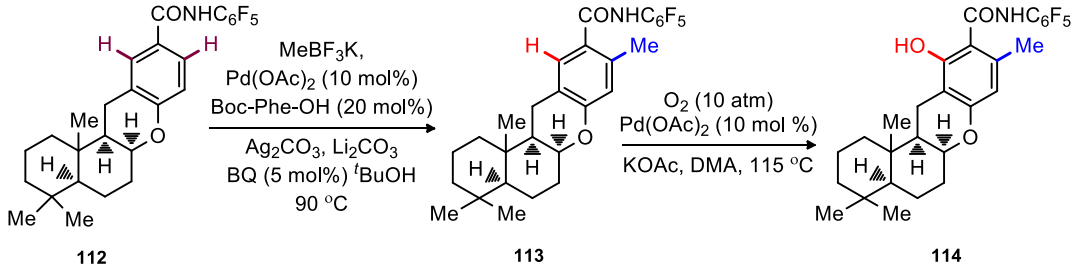
Many reports are also available in the literature for symmetrical multiple functionalization. Whereas, the reactions to introduce different functionality are scarcely explored. (details are *vide infra)*

An enantioselective, highly functionalized 2,3-dihydrobenzofuran synthesis has been demonstrated by Yu and Davis group, using sequential C−H functionalization. The enantioselective C–H insertion to the metal-carbene creates C–C bond under Rh-catalysis delivering **110**. Then Pd(II) catalyzed intramolecular C−H activation/C−O cyclization finally delivers 2,3-dihydrobenzofuran **111**. (Scheme 1.33).[55]



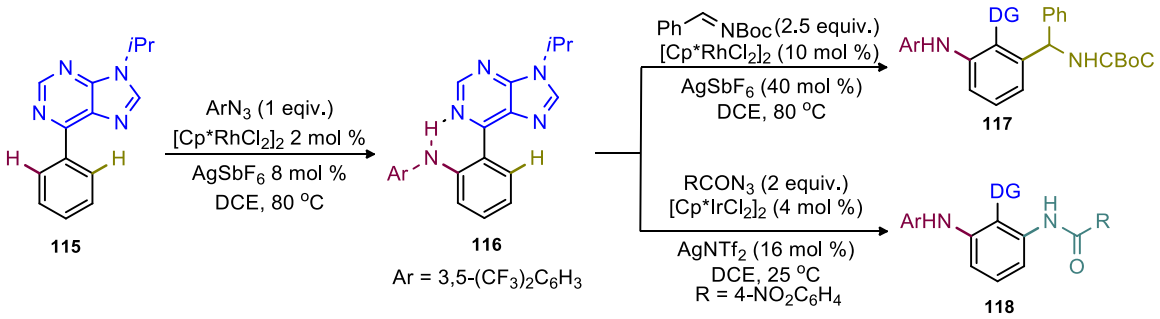
Scheme 1.33. Synthesis of dihydrobenzofuran via multiple C–H functionalization

The sequential two-fold unsymmetrical C–H functionalization has been adopted for the total synthesis of (+)-hongoquercin A; this elegant manifestation emanated from Yu and Baran group. A controlled site-specific methylation of **112** followed by oxygenation of **113** leads to the target molecule (+)-chromazonarol **114** (Scheme 1.34).[56]



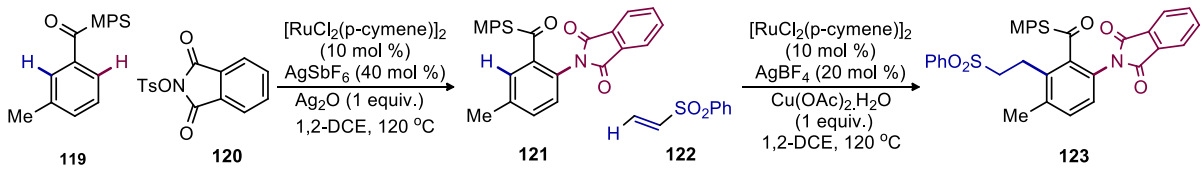
Scheme 1.34. Total synthesis of (+)-hongoquercin A via multiple functionalization

Recently, Chang group described an interesting example of multiple C–H functionalization in 6-arylpurines through the assistance of intramolecular hydrogen bonding. The Rh-catalyzed C–H amination of 6-arylpurines (**115**) delivers **116**. Subsequent C–C bond forming product **117** or amidation product **118** were obtained from the isolated mono-amination product **116**. Intramolecular hydrogen-bonding between N-1 or N-7 of purine helps delivering the desired product (Scheme 1.35).[57]



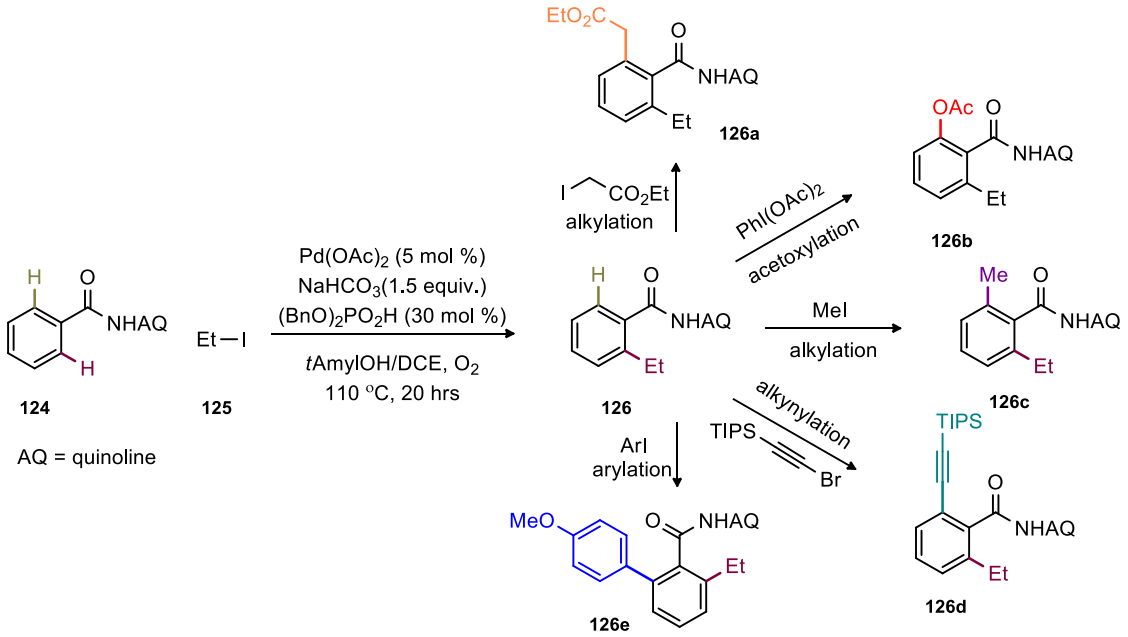
Scheme 1.35. Sequential multiple C–H bond functionalization of 6-arylpurines

A stepwise protocol for unsymmetrical difunctionalization of arene derivatives was developed by our group. Ru(II)-catalyzed methyl phenyl sulfoximine (MPS) aided imidation of arenes **119** with N-tosyloxy-phthalimide gave the imidation product **121**. Next, alkylation of **121** with phenyl vinyl sulfone **122** proficiently delivered unsymmetrical functionalized product **123** (Scheme 1.36).[58]



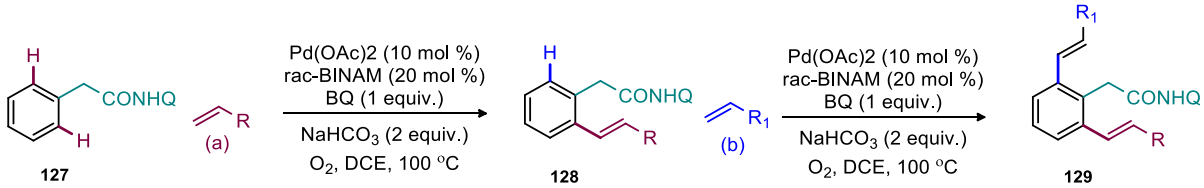
Scheme 1.36. Sequential multiple C–H bond functionalization of N-aroylated-MPS

The Pd-catalyzed mono or di-selective alkylation of N-quinolylbenzamides has been demonstrated by Chen group. The use of $NaHCO_3$ and $(BnO)_2PO_2H$ or $(PhO)_2PO_2H$ controls the selectivity. Sequential C–H functionalization of **126** provides peripheral decorated arenes (Scheme 1.37).[59]



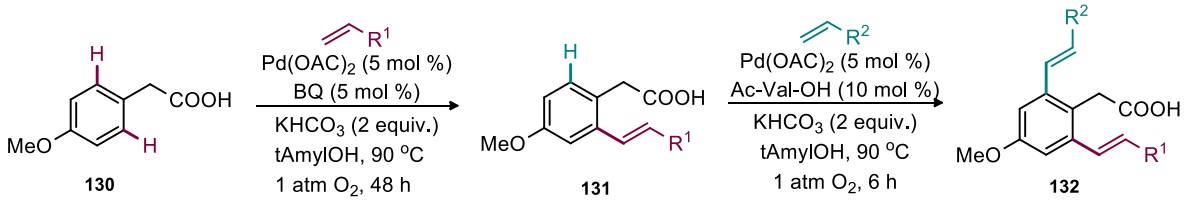
Scheme 1.37. Sequential multiple C–H bond alkenylation of benzamides

The Pd-catalyzed and 8AQ-assisted unsymmetrical sequential di-olefination of phenyl acetic acid derivatives has been reported by Maiti and co-workers. Alkenylation of **127** delivers **128**; second alkenylation under the same condition yielded up unsymmetrical di-vinylation product **129** (Scheme 1.38).[60]



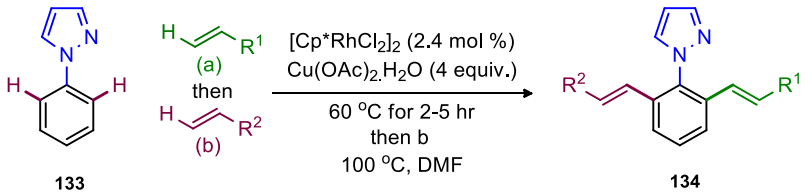
Scheme 1.38. Sequential multiple C–H bond alkenylation of aryl acetic acid derivatives

Yu group demonstrated a sequential multiple C–H olefination for the synthesis of divinylbenzene derivatives. A two-step protocol adopted for the Pd-catalyzed alkenylation of 4-methoxyphenylacetic acid **130**; the first alkenylation proceeds in presence of BQ oxidant and the second alkenylation occurs in presence of gly-ala-val ligand (Scheme 1.39).[61]



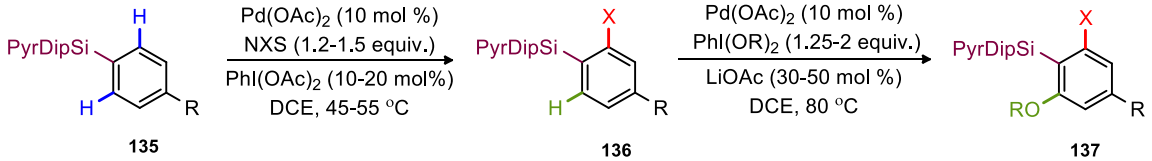
Scheme 1.39. Sequential multiple C–H alkenylation of aryl acetic acid derivative

First time Miura group has uncovered the elegant approach of one pot two-fold functionalization of C–H bonds. The Rh(II) catalyzed unsymmetrical alkenylation of phenyl pyrazole **133** reliably produced divinylated compound **134** by controlling temperature under one set of reaction condition.[62]



Scheme 1.40. One pot two-fold unsymmetrical C–H bond alkenylation

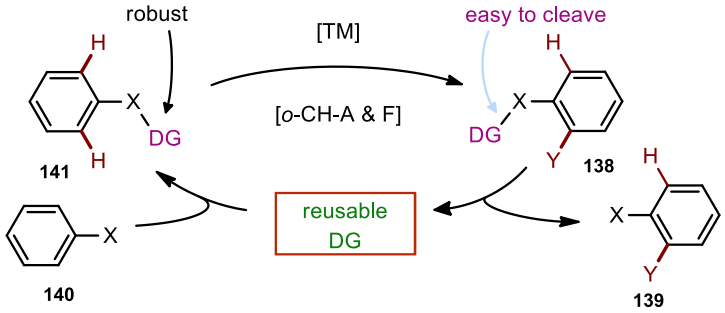
The known reports for multiple C–H functionalization use identical functional groups. Introduction of dissimilar functional groups in different C–H bonds are rare. Gevorgyan group revealed an efficient twofold unsymmetrical functionalization of arene. The two-step protocol delivered polyfunctionalized arene derivative from PyrDipSi-substituted arene involving C–H halogenation and oxygenation reaction. Halogenation of **135** delivered *ortho*-halogenation product **136**; next, the acetoxylation of **136** produced unsymmetrically functionalized **137** (Scheme 1.41).[63]



Scheme 1.41. Two-fold unsymmetrical C–H functionalization

1.5. Motivation, Hypothesis, and Planning

The extensive literature survey suggests that the directing group assisted functionalization of C–H bond involves non-modifiable/modifiable directing groups. Thus, the development of a novel, easily accessible and simultaneously readily recoverable directing groups (DG) has a great impact on the C–H functionalization reactions. An extensive study has therefore been made for the development of new directing groups and new strategies for the functionalization of unactivated C–H bonds. However, most of the directing groups are capable of introducing either selective functionalization of one C−H bond or non-selective single or double C−H functionalization.



Scheme 1.42. Concept of reusable directing group in C–H activation

Along this line, synthetically appealing two-fold symmetrical C−H functionalization has also been developed. All these seminal reports reveal that multiple functionalization of C–H bonds is underdeveloped. However, installation of identical functionality on two C–H bonds is widely adoptable in a stepwise manner. Sporadic reports for unsymmetrical functionalization of C–H bonds under different set of conditions are known. To the best of our knowledge, a one-pot two-fold unsymmetrical functionalization of C–H bonds remains obscure. Finding solution to the perennial problems associated in multiple functionalization (discussed earlier) opens up a new era in the continent of C–H functionalization. We thus believe that judicious planning and proper understanding to the reaction dynamics would help solving the cumulative challenges posed by unsymmetrical functionalization of C–H

bonds. Thus, development of novel DG and optimized procedure for the selective two-fold unsymmetrical C−H functionalization always attracts attention.

This thesis aims in the development of transition-metal-catalyzed site-selective functionalization of C(sp^2)–H bonds under the assistance of reusable directing group. The reactions discussed in this thesis use air stable and inexpensive Ru-catalyst and methyl phenyl sulfoximine (MPS) as reusable/modifiable/traceless DG. After successful functionalization of C-H bonds, the MPS-DG is readily cleaved and recovered from the products and finally reused. Highly challenging one-pot multiple functionalization of C–H bonds has been established for the first time. The entire work force of the thesis is enumerated in the following chapters II, III, and IV.

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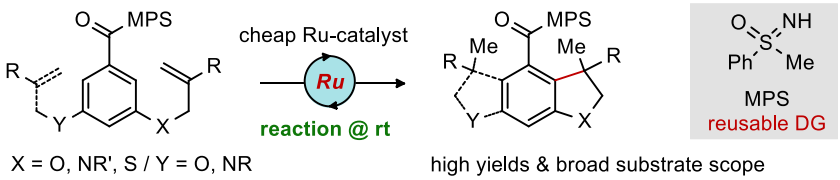
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Chapter 2

Ruthenium-Catalyzed Hydroarylation of Arenes

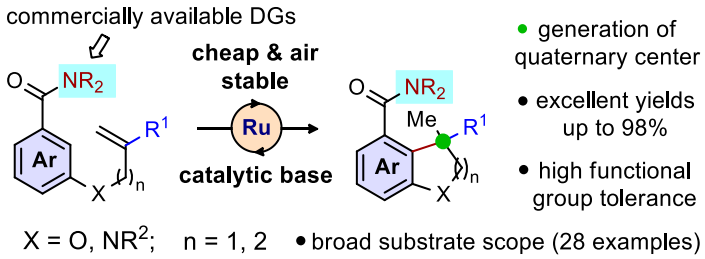
Abstract:

Section A: Reusable Sulfoximine Directed Intramolecular Hydroarylation of Arenes



Ruthenium catalyzed and methyl phenyl sulfoximine (MPS) directing group (DG) aided intramolecular hydroarylation of alkene-tethered benzoic acid derivatives is discussed. Biologically important dihydrobenzofuran, indoline scaffolds are proficiently constructed. The wide tolerance of common functional groups, gram scale synthesis with low-catalyst loading and easy removability as well as recovery of the MPS-DG makes the synthetic model viable and significant. The two-fold symmetrical hydroarylations in one pot reliably create novel densely functionalized arene derivatives. Deuterium scrambling studies unveiled about reaction path.

Section B: Ruthenium Catalyzed Intramolecular Hydroarylation of Arenes and Mechanistic Study: Synthesis of Dihydrobenzofurans, Indolines, and Chromans



Intramolecular hydroarylation of commercially available amide directed alkene-tethered benzamide derivatives is enumerated. The hydroarylation smoothly occurs in the presence of catalytic amount of base under Ru-catalysis. Dihydrobenzofuran, indoline, and chroman skeletons are successfully constructed. This synthetic

transformation has vast substrate scope, tolerating various labile protecting units, common functional groups as well as the heteroaryl motifs. Kinetic studies and deuterium scrambling experiment offer insightful idea deducing reaction path.

Reference:

Koushik Ghosh, Raja K. Rit, E. Ramesh and Akhila K. Sahoo *Angew. Chem., Int. Ed.* **2016**, *55*, 7821.

Raja K. Rit, Koushik Ghosh, R. Mondal, and Akhila K. Sahoo *J. Org. Chem.*, **2016**, 81, 8552.

2.1. Introduction

"*Making and Breaking of Bonds*": the process unequivocally supports the growth of organic chemistry. Strategically, creation of bonds has profound impact building new molecular scaffold. Among various bond formation processes, fabrication of carbon-carbon (C–C) bond is most fundamental in the domain of synthetic organic chemistry.[1] Consequently, the chemistry community unequivocally embrace new synthetic methods developed for the construction of C–C bonds. In this scenario, the transition-metal catalyzed cross-coupling strategy has perceived wider adoptability;[2] although this method essentially requires pre-functionalized precursors, obtained from commercially available source through multiple synthetic variations, specially designed ligands, and the production of environmentally hazardous by-products (discussed in Chapter 1).[3] Hence, synthesis of C–C bonds from un-activated ubiquitous C–H bonds emerges synthetically viable and environmentally benign, offering wider benefit.[4] The transition metal (TM)-catalyzed directing group (DG)-assisted functionalization of inert C–H bonds has particularly been sustainable; as this process directly inducts various functional groups in the molecular template and constructs structurally complex molecules from easily accessible precursor with high level of regio- and stereoselectivity. Interestingly, the annulation strategy has widely been implemented manufacturing complex carbo(hetero)cycles from simple precursors.[5] Notably, intramolecular cyclizations via functionalization of C–H bonds of the heteroatom bearing scaffolds have successfully been delivered heterocyclic motifs, adequately infusing regio-selectivity in the molecule.[6] Therefore, execution of such synthetic technique would coherently add value to the progressing paradigm of C–H functionalization and that is ultimately useful to construct versatile heterocycle motifs.

Dihydrobenzofuran skeletons are widely found in many biologically active compounds and potential drug candidates, such as lithospermic acid, ramelteon, and mesocyperusphenol A (Figure 1).[7] Furthermore, the benzofuran scaffolds, oxidized analog of dihydrobenzofuran, are invariably present in the molecules of diverse

applications. Consequently, demand always remains to find a technique for the construction of such motifs. We envisioned adopting '*Hydroarylation*' method to manufacture heteroatom (O/N/S)-bearing molecular scaffold.

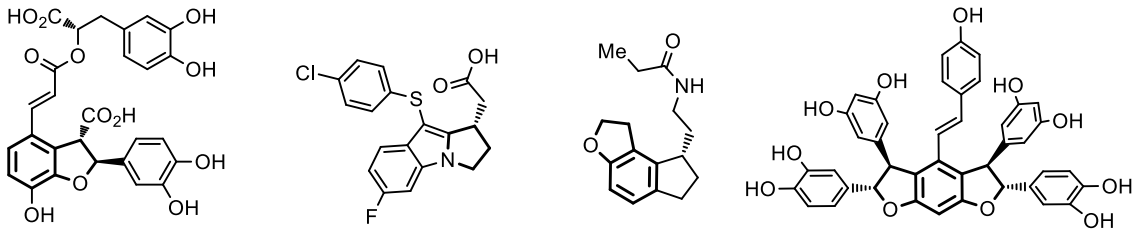
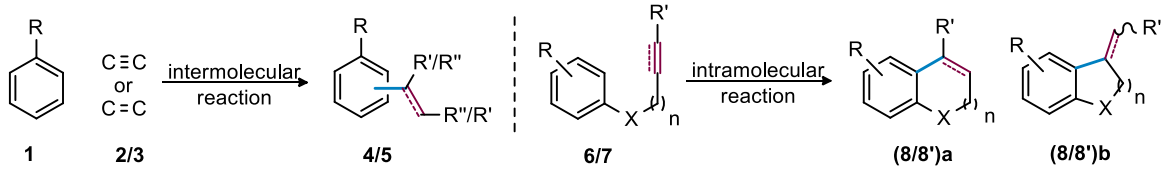


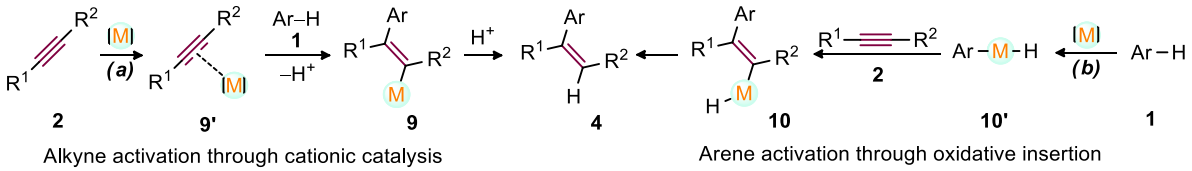
Figure 2.1 Dihydrobenzofuran containing biologically active and drug molecules

Hydroarylation process primarily involves reductive coupling of C–C multiple bond with an aryl coupling partner.[8] The classical hydroarylation reaction generally involves electrophilic aromatic substitution of the Lewis acid activated C–C multiple bonds.[9] Accordingly, coupling partner source decides the mode of hydroarylation (intra-/intermolecular) (Scheme 2.1).



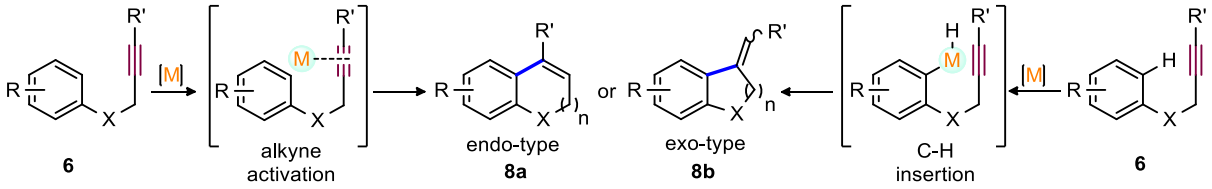
Scheme 2.1. Hydroarylation reaction

The intermolecular hydroarylation of alkyne involves activation of alkyne (**2**) by a cationic metal complex (shown ***a***) followed by the attack of arene to form **9**. Next, the proto-demetalation of intermediate **9** yields the hydroarylation product **4** (Path I).[10,11] The alternate pathway comprises the oxidative insertion of a nucleophilic metal ***b*** to the arene (**1**) C–H bond to form **10′**; subsequent attack of **10′** to alkyne and reductive elimination delivers the hydroarylated product **4** (Scheme 2.2).[10,12]



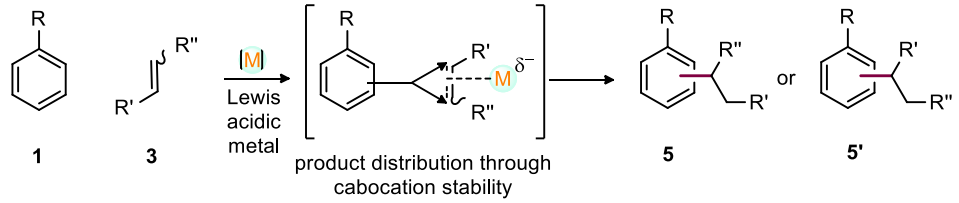
Scheme 2.2. Intermolecular hydroarylation of alkyne

Likewise, the intramolecular hydroarylation of alkyne could provide the product **8a**/**8b** from **6**. These reaction dynamics are judged by the catalyst and the ligand employed in the transformation (Scheme 2.3).[13]



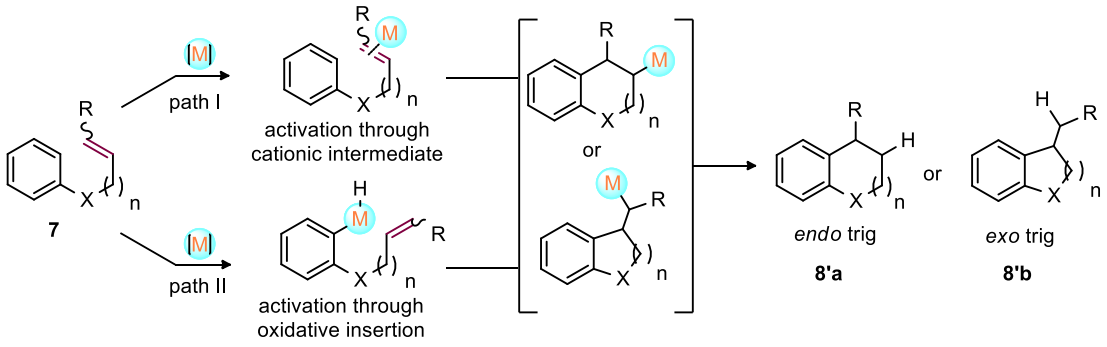
Scheme 2.3. Intramolecular hydroarylation of alkyne

The intermolecular olefin hydroarylation whereas involves Friedel–Crafts type mechanism, where the stability of intermediary carbocation decides the product outcome. Thus, the reaction between **1** and **3** in presence of Lewis acid provides mixture of products **5** or **5'**, predominantly delivering the Markovnikov products. In case of aryl-substituted olefin, the substituents at the *ortho*, *meta*, and/or *para* position of aryl-moiety decides the product selectivity. Overall, these transformations require harsh reaction condition forming several by-products (Scheme 2.4).



Scheme 2.4. Intermolecular hydroarylation of alkene

By contrast, the intramolecular alkene hydroarylation eventually delivers mixture of regioisomers **8'a** or **8'b**. However, the use of transition-metal (TM) catalysts can improve the products regioselectivity.[14] Mechanistic and computational studies indicated that TM-catalyzed alkene hydroarylation involves Friedel–Crafts mode attack of arene to the TM-activated olefin (path I, Scheme 2.5). The insertion of olefin to the in-situ generated oxidative M-hydride complex could lead to **8'b** (path II, Scheme 2.5).

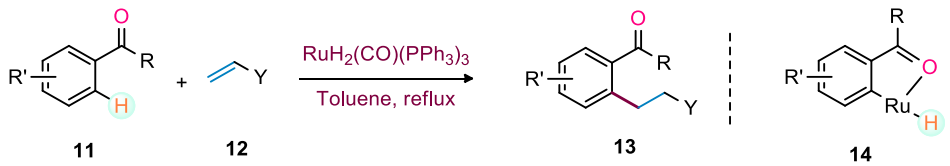


Scheme 2.5. Intramolecular hydroarylation of alkene

It is apparent that the alkyne/alkene hydroarylation process can rationally provide large variety of products (discussed in Scheme 2.2 to 2.5). Incorporation of a DG in the molecule could virtually address such chaos, strategically dictating the hydroarylation to occur with high regioselectivity in the presence of TM catalyst.[6] In addition, hydroarylation process can also be tuned under the mild conditions. Moved with the cumulative challenges involved in the hydroarylation process,[16,17] herein we discuss the effort linked to the discovery of the sulfoximine DG assisted intramolecular hydroarylation of aromatic system under Ru-catalysis; the synthetic procedure is successfully carried out at room temperature and directly builds various fused heteroaryl structures.[18]

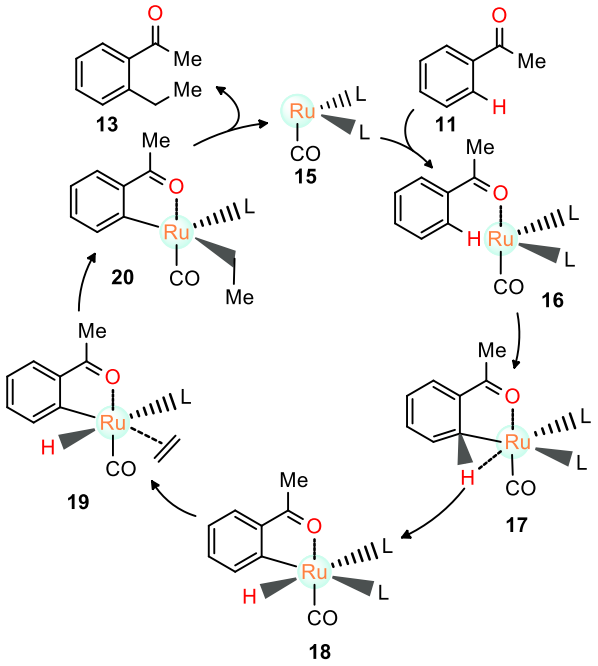
2.1.1. Precedents of Intermolecular Hydroarylation of Arenes

Murai's pioneering discovery of heteroatom guided ruthenium-catalyzed C–C bond formation via *ortho*-C–H activation of aromatic ketones rekindles interest among the synthetic community witnessing the vast development perceived in the area of direct functionalization of unactivated C–H bonds. The reaction of aromatic ketone **11** with alkene **12** produces the product **13**; the reaction involves the intermediate **14**.[19]



Scheme 2.6. Ruthenium-catalyzed intermolecular hydroarylation of arenes

The mechanistic details of Murai's protocol is not fully understood; however, on the basis of computational studies the possible reaction path is deduced (Scheme 2.7). The active catalyst $[Ru(CO)(PPh_3)_n]$ (n = 2, 3), generated in situ from $[Ru(H)_2(CO)(PPh_3)_3]$ at higher temperature, is actively participated.[20] The transformation begins with the coordination of ketone's oxygen to the three-coordinate Ru species to generate **16**; next, the insertion of arene moiety to **16** forms the five-coordinated metallacycle Ru intermediate **17**.



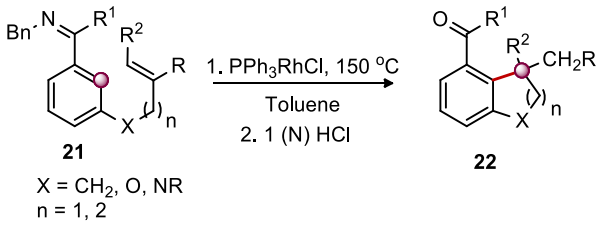
Scheme 2.7. Mechanistic cycle of Murai's reaction

The agostic interaction of the proximal C–H bond with its empty coordination site of Ru in **17** activates the C–H bond; the re-aromatization of **17** then forms **18**. Substitution of ethylene with one of the *cis* phosphine ligands with respect to hydride gives **19**. Migratory insertion of hydride to the olefin delivers **20**. Finally, reductive elimination of **20** affords the functionalized product **13**; simultaneously, the ligand coordination to Ru-species regenerates the active catalyst **15**. The C–C bond formation is found rate limiting step. This concept has been adopted in the development of various C–C hydroarylation transformations.

As this chapter discusses the development of novel synthetic method for the intramolecular hydroarylation of C(sp^2)–H bonds, the known techniques of intramolecular hydroarylation processes are briefly enumerated.

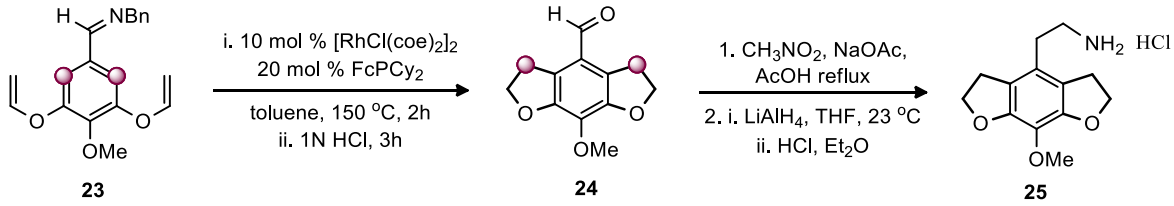
2.1.2. Intramolecular Hydroarylation of Arenes

The Ellman and Bergmann group showcased the intramolecular hydroarylation of aromatic imines **21** (Scheme 2.8).[6a] Wilkinson catalyst has been used in this transformation to produce the carbo(hetero)cycles **22**. This elegant manifestation occurred at high temperature (150 °C), producing moderate yield of the desired products, however with limited scope.



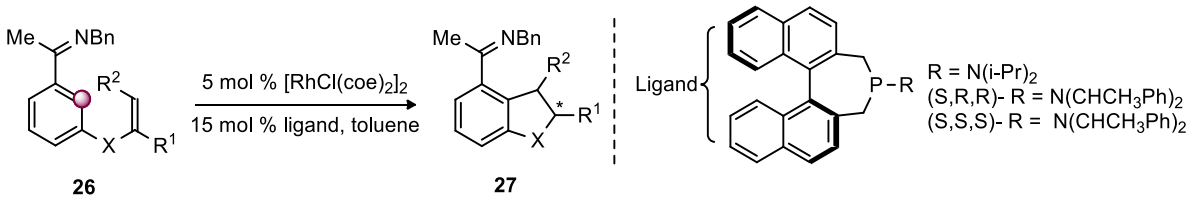
Scheme 2.8. Intramolecular hydroarylation of aromatic imines

The intramolecular hydroarylation of aromatic imines has successfully been implemented for the synthesis of tetrahydrobis(benzofuran) mescaline analogue **25** in overall 38% yield (Scheme 2.9).[6b] The key step for the fabrication of parent molecular template is the tandem double-cyclization of alkene-motif of **23** via two successive C–H activations.



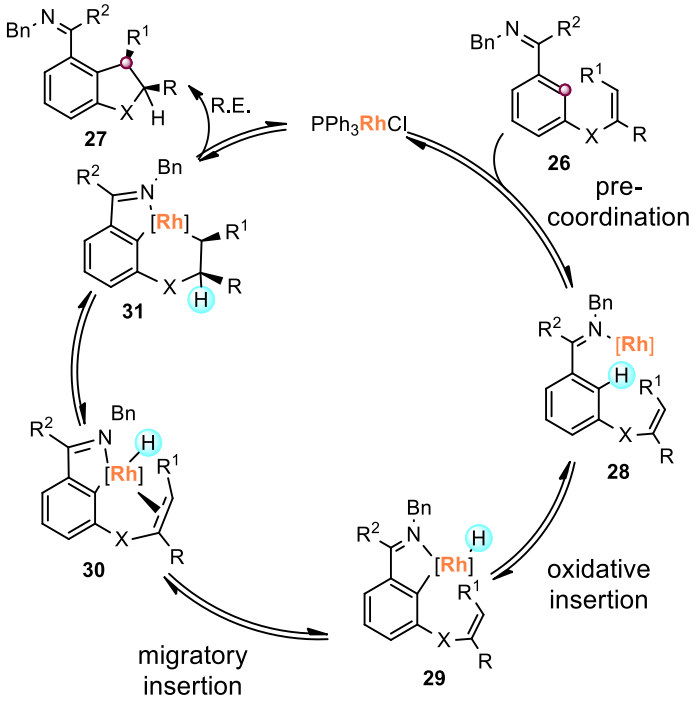
Scheme 2.9. Synthesis of tetrahydrobis(benzofuran) mescaline analogue

With the use of chiral mono-dentate phosphine ligand, the unfolded enantioselective hydroarylation of **26** in the presence of Rh-catalyst has been accomplished delivering **27** (up to 96% ee) (Scheme 2.10).[21]



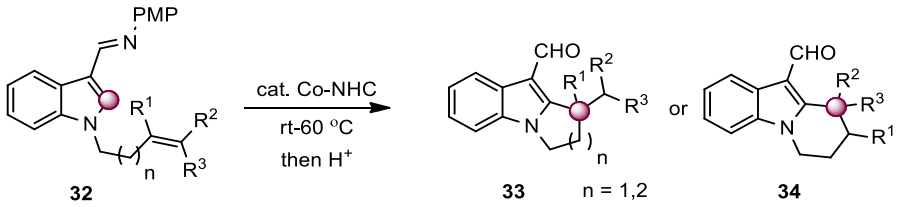
Scheme 2.10. Enantioselective hydroarylation of aromatic imines

The reaction initiates with the chelation of Rh catalyst to the imine-DG to generate **28** which then undergoes successive C–H oxidative addition with the Rh(I) species to form Rh–H rhodacycle **29** (Scheme 2.11). Coordination of alkenyl group to the Rh species affords **30**; subsequent migratory insertion of the double bond in to Rh–H bond provides six-five fused metallacycle **31**. Finally, reductive elimination of **31** delivers the desired hydroarylation product **27** with the expulsion of the active catalyst for the next cycle. The distinct binding properties of the phosphoramidite ligands, which associated with σ donation to the metal and unique π acceptor ability compared to simple phosphine attributes to the observed stereoselectivity. The rate-determining step of this transformation is the reductive elimination, as this has been corroborated by the detailed deuterium (D) scrambling studies.[22]



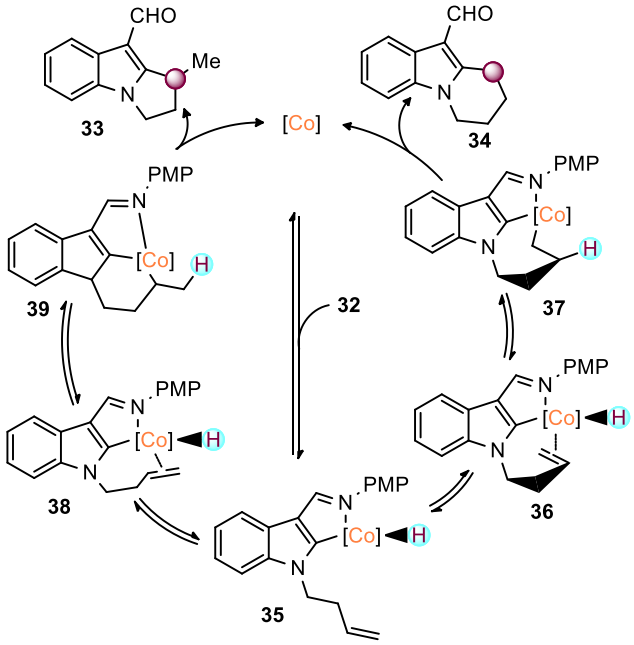
Scheme 2.11. Mechanistic cycle of intramolecular hydroarylation process

Recently, the imine chelation-assisted intramolecular olefin hydroarylation of indole in presence of cobalt-N-heterocyclic carbene (NHC)-catalyst has been developed by Yoshikai group (Scheme 2.12).[23] The NHC ligand plays vital, as it tunes the formation of regio-divergent five- and six membered rings. In addition, the hitherto difficult quaternary carbon center bearing heterocycles are easily constructed.



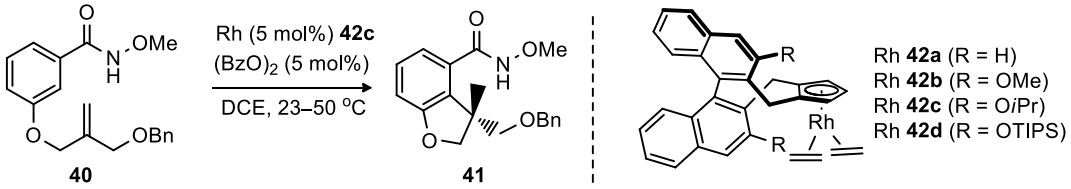
Scheme 2.12. Cobalt catalyzed intramolecular hydroarylation of indoles

The transformation initiates with the chelation-assisted oxidative insertion of low-valent cobalt species in to the C–H bond of **32** to give the intermediate **35** (Scheme 2.13). Next, the insertion of olefin moiety to Co–H bond leads to six-membered **39** or seven-membered **37** cobalt cycle via **38** or **36**, respectively. Finally, reductive elimination of **39**/**37** produces the respective products. On the basis of deuterium scrambling study, the insertion of olefin to Co-species is irreversible; thus, the product regioselectivity is controlled.[23]



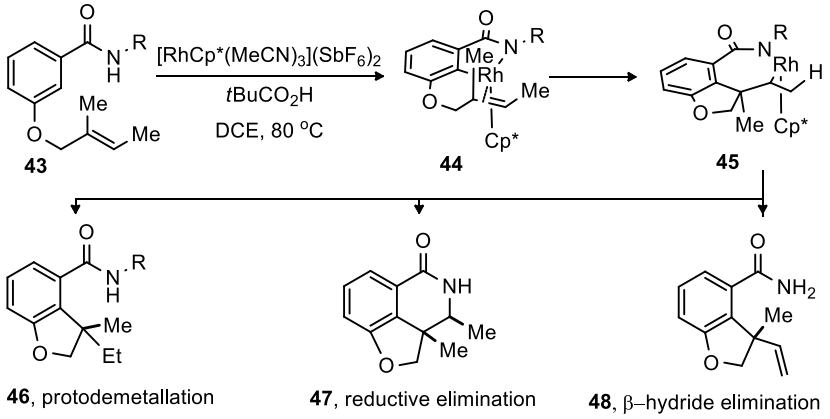
Scheme 2.13. Mechanistic cycle of cobalt catalyzed hydroarylation of indole

The Cramer group showcased an impressive oxidizable amide directed enantioselective hydroarylation of arenes (Scheme 2.14).[15b] The chiral Rh catalyst (**42**), designed by using cyclopentadienyl manifold with an atropchiral biaryl backbone, plays significant. The construction of quaternary stereogenic center bearing dihydrobenzofuran **41** with high enantioselectivity has been reliably accessed via intramolecular hydroarylation.



Scheme 2.14. Cp*-Rh(III)-catalyzed asymmetric hydroarylations

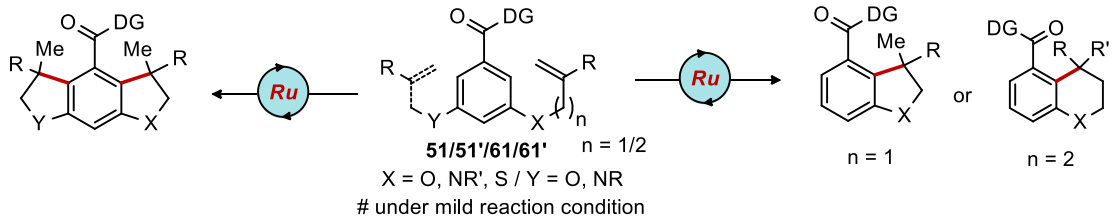
Rovis group demonstrated the Rh-catalyzed amide assisted hydroarylation of **43** to construct dihydrobenzofuran **46** (Scheme 2.15).[15a,15c] Further tuning of the reaction parameters delivers the amidoarylation **47** and dehydrogenative Heck type product **48** (Scheme 2.15).



Scheme 2.15. Rh(III)-catalyzed intramolecular hydroarylation, amidoarylation, and Heck-type reaction

2.2. Motivation, Hypothesis, and Design

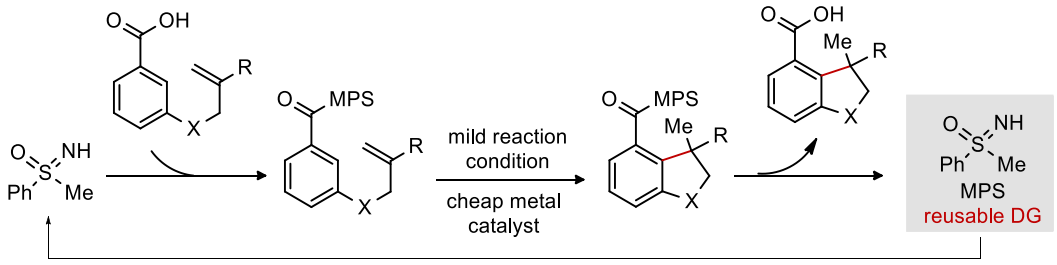
As detailed in the section 2.1, the intramolecular C(sp^2)–H hydroarylation of arenes are successfully carried out under the Rh-catalysis or Co-catalyst in combination with NHC ligands; moreover, the reactions essentially proceed under the harsh conditions. Importantly, DG's employed in these studies are neither modifiable nor reusable. As a result, synthetic utility of this protocol is hampered. Thus, substantial opportunity remains for the development of alternate synthetic technique for the intramolecular hydroarylation of arenes. We therefore envisaged discovering reusable DG assisted hydroarylation of arenes; furthermore, we intend to showcase the use of air stable and relatively inexpensive Ru-catalyst in this study (Scheme 2.16). To the best of our knowledge, the plans highlighted above are so far unprecedented.



Scheme 2.16. Working hypothesis

Section A: Reusable Sulfoximine Directed Intramolecular Hydroarylation of Arenes

The detailed survey of DG assisted intramolecular hydroarylation of olefins revealed that no such synthetic manifestations has been performed under the air stable Ru-catalysis under the directing ability of a reusable group. Accordingly, methyl phenyl sufoximine (MPS) group has been developed and employed for the challenging intramolecular hydroarylation of arenes in presence of Ru-catalysis (Scheme 2.17). Pleasingly, the MPS moiety is detached from the hydroarylation product, recovered and finally reused, authenticating synthetic viability of this demonstration.



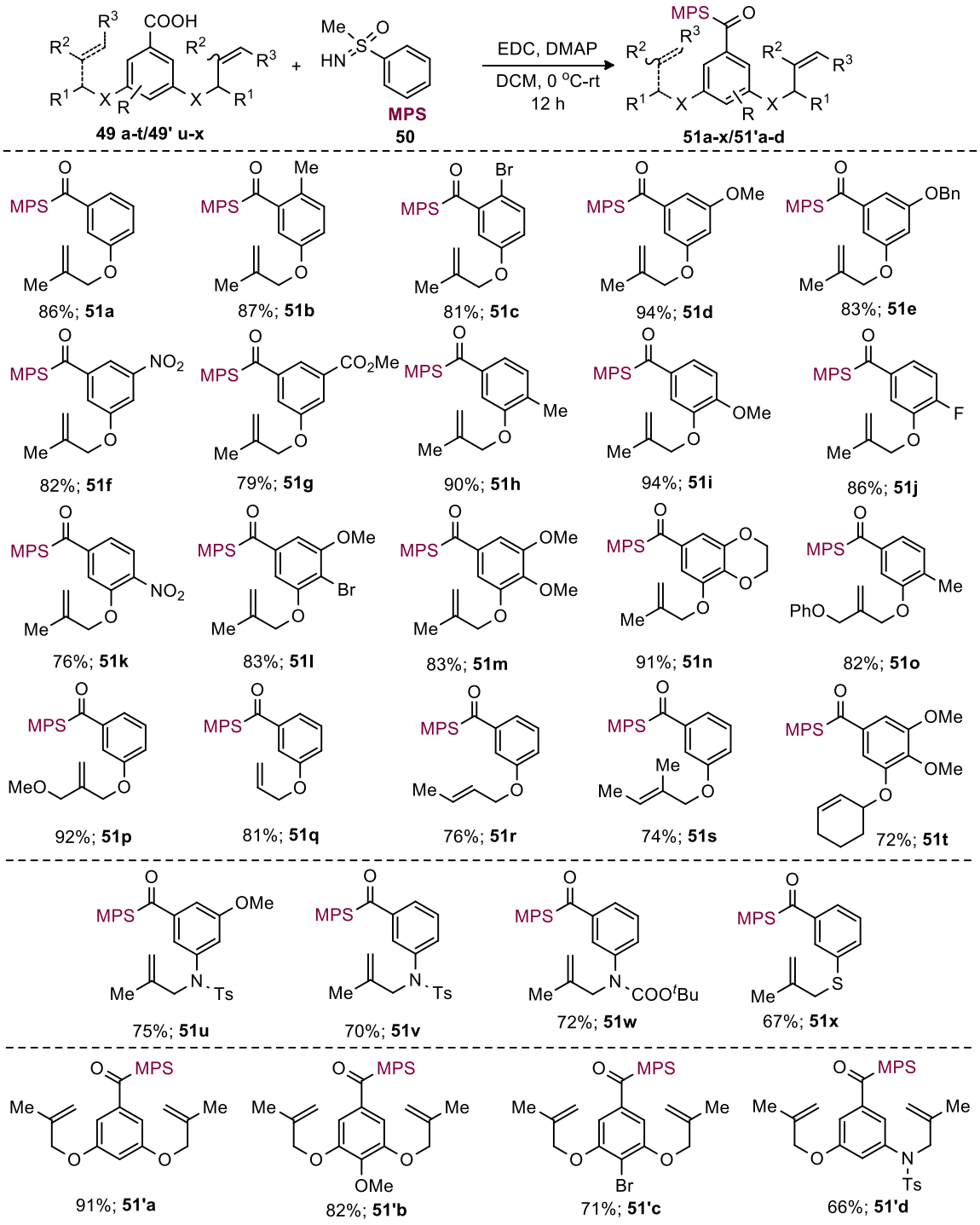
Scheme 2.17. Synthetic design

2.3. Results and Discussion

2.3.1. Synthesis of Precursors:

A large variety of di/tri substituted '*O*'-tethered benzoic acid derivatives (**49a**–**t**) were prepared. Similarly, terminal di-substituted '*N*'/'*S*'-tethered benzoic acid (**49u**–**x**) were synthesized. Following the known synthetic procedures, large varieties of *N*-aroyl sulfoximine derivatives were prepared.[24] The coupling of methyl phenyl sulfoximine with different benzoic acid derivatives were performed using EDC.HCl. Likewise, bis-allyl(oxy/amino) aroyl sulfoximine derivatives (**51'a**–**d**) were also accessed. The entire range of the synthesized precursors are listed in Table 2.1 (the reaction procedure is detailed in the experimental section 2.7.3, page 69).

Table 2.1. Preparation of *N*-aroyl sulfoximine derivatives

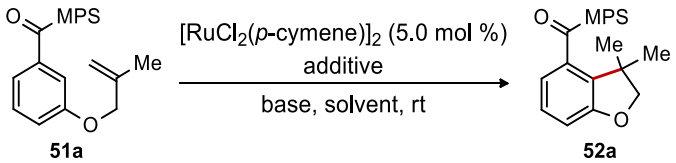


2.3.2. Reaction Condition Optimization

To realize the feasibility of the envisioned process sketched in Scheme 2.16, Ru-catalyzed intramolecular hydroarylation was explored on [3-(2-

methylallyloxy)benzoyl]methyl phenyl sulfoximine (**51a**) (Table 2.2). To begin with, **51a** was at first exposed to $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %) and $Cu(OAc)_2 \cdot H_2O$ in $ClCH_2CH_2Cl$ (DCE). Disappointingly, the expected *N*-[3,3-Dimethyl-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfox -imine (**52a**) was not formed, when the reaction conducted at room temperature (rt) or 80 °C for longer time (entries 1 and 2). The use of $AgSbF_6$ (20 mol %) in combination with Ru-catalyst (in entry 1) worked remarkably well, producing **52a** in 92% yield in 4 h (entry 3). Examination of other acetate-sources led to moderate product yield (entries 4–6); while the reaction in the absence of base was poor (entry 7). Other additives, e.g. $AgBF_4$ and KPF_6 were found inferior (entries 8 and 9). Interestingly, the low loading of catalyst to (2.0 mol % or 1.0 mol %) was equally effective; although the reaction required a little long time for completion (entries 10 and 11). Thus, the conditions in entry 10 $[RuCl_2(p\text{-cymene})]_2$ (2.0 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv) in $ClCH_2CH_2Cl$ at rt for 12 h] was reflected optimum, accessing **52a** (97%) from **51a**.

Table 2.2. Optimization of Reaction Parameters[a]



entry	additive (20 mol %)	base (1.0 equiv)	time (h)	yield of **52a** (%)[b]
1	–	$Cu(OAc)_2 \cdot H_2O$	24	nr
2	–	$Cu(OAc)_2 \cdot H_2O$	24	nr[c]
3	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	04	92
4	$AgSbF_6$	AgOAc	12	42
5	$AgSbF_6$	NaOAc	12	26
6	$AgSbF_6$	KOAc	12	48
7	$AgSbF_6$	–	12	<10[d]
8	$AgBF_4$	$Cu(OAc)_2 \cdot H_2O$	12	49
9	KPF_6	$Cu(OAc)_2 \cdot H_2O$	12	18
10[e]	**$AgSbF_6$**	**$Cu(OAc)_2 \cdot H_2O$**	**12**	**97**
11[f]	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	18	93

[a]Reactions were carried out using **51a** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), base (0.2 mmol), additive (20 mol %) in $ClCH_2CH_2Cl$ (DCE; 1.0 mL). [b]Isolated yields. [c]at 80 °C. [d]^1H NMR yield. [e]$[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %) was used. [f]$[RuCl_2(p\text{-cymene})]_2$ (1.0 mol %) was used.

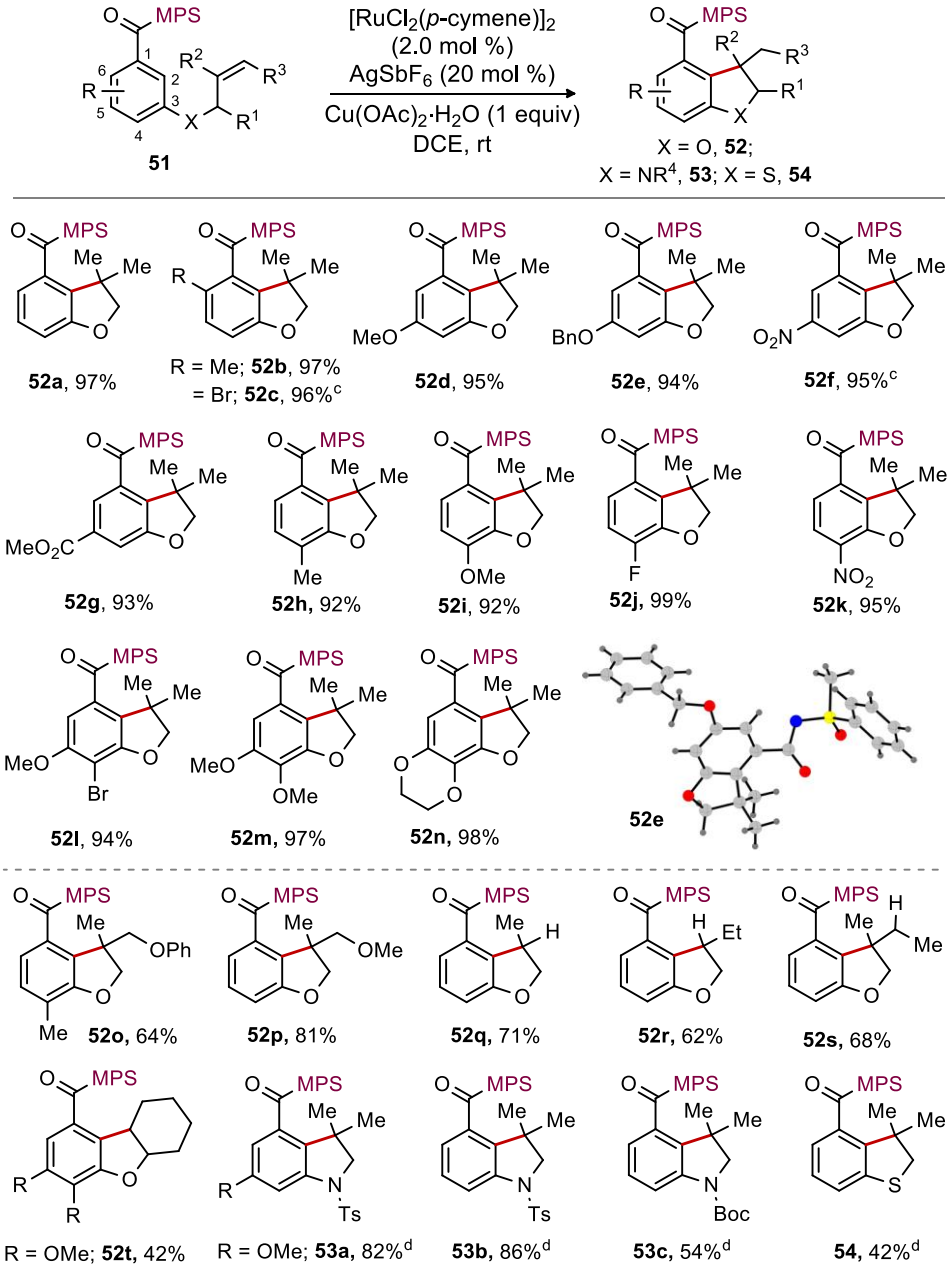
2.3.3. Scope of Ru-Catalyzed MPS-DG Assisted Hydroarylation

Scope of this novel Ru-catalyzed MPS-DG assisted intramolecular hydroarylation reaction for the synthesis of dihydrobenzofuran derivatives is showcased in Table 2.3. The hydroarylation of a broad range of easily accessible **51** (0.5 mmol) under the optimized conditions in entry 10, Table 2.2 was thus scrutinized. The compound **52a** was isolated in 97% yield from **51a**. Gratifyingly, excellent yields were observed for 6-Me (**51b**) and 6-Br (**51c**) bearing sterically encumbered substrates which smoothly resulted the desired hydroarylation products **52b** and **52c**. Electron perturbation by keeping the electron-donating (OMe, OBn) and –withdrawing (NO_2, ester) functional groups at the 5-position of arene moiety did not disturb the reaction efficiency, affording the required dihydrobenzofurans **52d**–**g** in excellent yields. X-ray crystallographic studies established the structure of **52e**. Formation of **52g** from **51g** clearly suggests the superior directing group ability of MPS over the ester group; although the ester group directed C–C bond formations in the arene *o*-C–H bonds under Ru-catalysis is feasible.[25]

Excellent outcome of the products **52h–k** were conquered from 4-substituted MPS-protected benzoic acid derivatives **51h–k**; electronically biased (OMe/NO_2) units did not affect the delivery of the product. Thus, wide arrays of tetra-substituted arenes **52b–k** were reliably manufactured from 3-hydroxy benzoic acid derivatives. Construction of highly-peripheral decorated dihydrobenzofurans **52l–n** was comprehended without compromising the products yield. The bromo group in **52l** (94%) is amenable to further functionalizations and also useful for the induction of axial-chirality through oxidative dimerization.[26] Gratifyingly, compounds **52m** (97%) and **52n** (98%) with three contiguous oxygen-atoms on the arene-periphery were efficiently synthesized. The hydroarylation with di-substituted terminal olefin (other

than a methyl-group) in *m*-allyloxy benzoic acid derivative would create the useful all-carbon quaternary stereocenter. To our satisfaction, the current transformation

Table 2.3. Substrate Scope of Hydroarylation Reaction[a,b]



[a]Reactions were carried out using **51** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.5 mmol) in DCE (2.0 mL) at room temperature for 8–16 h. [b]Isolated yields. [c]Reaction was heated at 50 °C. [d]4.0 mol % $[RuCl_2(p\text{-cymene})]_2$ and reaction was heated at 65 °C.

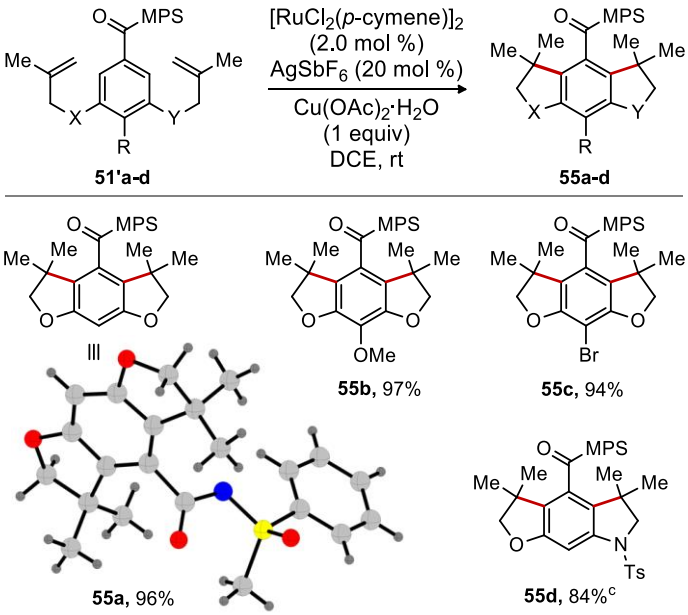
conveniently resulted the phenoxymethyl and methoxymethyl bearing products **52o** (64%, 3:1) and **52p** (81%, 7:1) as inseparable mixture of diastereoisomers. The O-allyl substrate **51q** successfully underwent hydroarylation, delivering 71% of the cyclization product **52q**. Internal alkenes were also participated in the hydroarylation reaction; 3-ethyl-dihydrobenzofuran derivatives **52r** and **52s** were synthesized in 62% and 68% yield, respectively. The substrate with a substituent α to the oxygen was tolerated; accordingly, cyclohexane-fused dihydrobenzofuran **52t** was obtained, albeit in moderate yield. The successful demonstration of Ru-catalyzed and MPS-DG enabled intramolecular hydroarylation of arenes **51a–t** motivated us to investigate the identical reactions with the N and S-tethered substrates. Accordingly, the N/S-tethered olefin bearing benzoic acid derivatives **51u**–**x** were independently subjected to the optimized catalytic conditions at 65 °C; gratifyingly, the reactions were facile and the desired cyclization products were isolated in good to excellent yields (Table 2.3). The N-Tosyl and N-Boc protected indolines **53a**–**c** (54–86% yield) were reliably constructed. Likewise, dihydrobenzothiophene **54** was obtained in 42% yield from **51x** (Table 2.3).

2.3.4. Scope of One Pot Twofold Symmetrical Hydroarylation

The excellent performance of intramolecular hydroarylation (Table 2.3) encouraged us to examine the Ru-catalyzed MPS-DG assisted twofold hydroarylation between aryl *o*-C–H bonds and the spatially configured olefins. To realize this task, the bis-allyloxy bearing benzoic acid derivatives **51'a–d** were easily prepared from the corresponding commercially available 3,5-dihydroxybenzoic acid. Pleasingly, the dicyclization product **55a** was explicitly formed in 96% yield, when **51'a** was exposed to the optimized catalytic conditions in entry 10, Table 2.2 at rt (Table 2.4). The structure of **55a** was unambiguously confirmed by X-ray analysis. The current manifestation of the twofold hydroarylations under the low catalyst loading at rt is a distinct advantage over the previous Rh-catalyzed transformations.[6b] Similarly, 97% (**55b**) and 94% (**55c**) yield were achieved when 4-OMe and 4-Br substituted arene deposited under the same condition. This method readily allowed the construction of modifiable functional groups (OMe

and Br) bearing peripheral decorated arene derivatives. The di-hydroarylation of [3-*O*]-[5-*N*]-allyl tethered benzoic acid skeleton **51′d** proceeded smoothly to exclusively produce 84% of novel molecular framework **55d** (Table 2.4). *Collectively, these data uncover the tenacity of MPS DG-enabled infusion of two heterocycles in the aryl moiety via twofold symmetrical hydroarylation.*

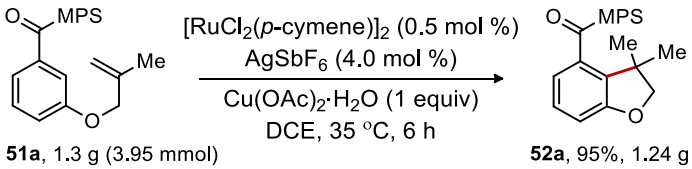
Table 2.4. Substrate Scope of Two-fold Hydroarylation Reaction[a,b]



[a]Reactions were carried out using **51′** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.5 mmol) in DCE (2.0 mL) at room temperature for 10–16 h. [b]Isolated yields. [c]4.0 mol % $[RuCl_2(p\text{-cymene})]_2$ and reaction was heated at 60 °C.

2.3.5. Gram Scale Synthesis

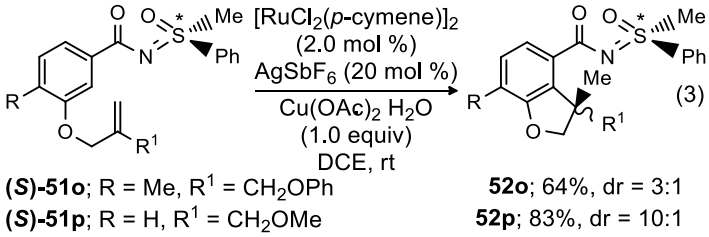
Furthermore, a gram scale hydroarylation experiment was conducted to examine the scalability of the reaction. The reaction of **51a** (1.3 g) with 0.5 mol % Ru-catalyst at 35 °C for 6 h furnished 95% of **52a** (1.24 g), (Scheme 2.18) truly reflecting the influence of MPS-DG and the efficacy of the catalytic conditions in the hydroarylation method. By contrast, the notable other intramolecular hydroarylation strategies invariably requires more amount of catalyst.[6,15]



Scheme 2.18. Gram scale synthesis

2.3.6. Diastereoselective Hydroarylation

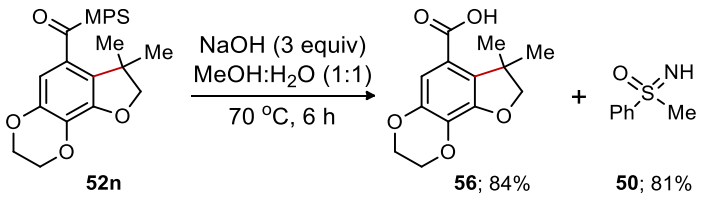
To demonstrate the usefulness of this protocol, diastereoselective hydroarylation was investigated with enantiopure MPS bearing amide substrate. Gratifyingly, optically pure (*S*)-**51o** and (*S*)-**51p** afforded (*S*)-**52o** (3:1) and (*S*)-**52p** (10:1), respectively, under the optimized conditions at rt with moderate diastereoselectivity (Scheme 2.19). These results show the possible chiral induction in the transformation.[27] This unknown Ru-catalyzed diastereoselective hydroarylation requires further detailed investigation, which is currently under investigation.



Scheme 2.19. Diastereoselective hydroarylation

2.3.7. Reusability of Directing Group

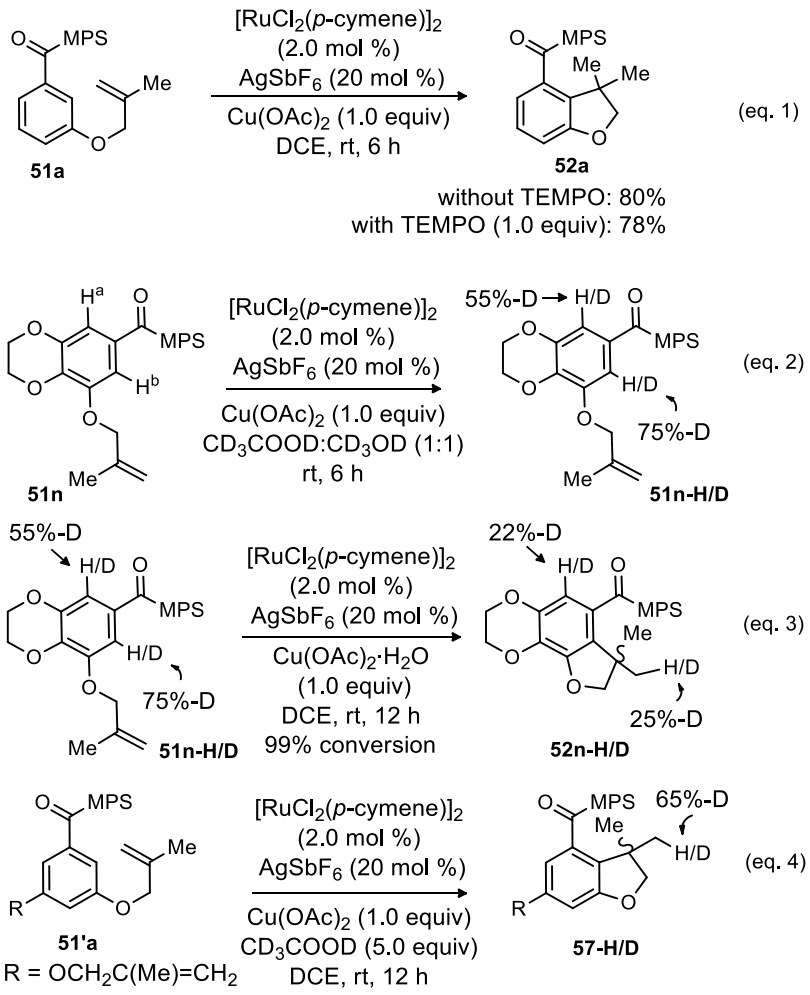
The reusability of MPS-DG was realized hydrolyzing the amide bond with NaOH in MeOH/H_2O.[28,29] The hydrolysis of **52n** led to 7,7-dimethyl-2,3,7,8-tetrahydro-[1,4]dioxino[2,3-g]benzofuran-6-carboxylic acid (**56**) (84%) with the recovery of MPS-DG (81%) (Scheme 2.20).



Scheme 2.20. Recovery of MPS-DG

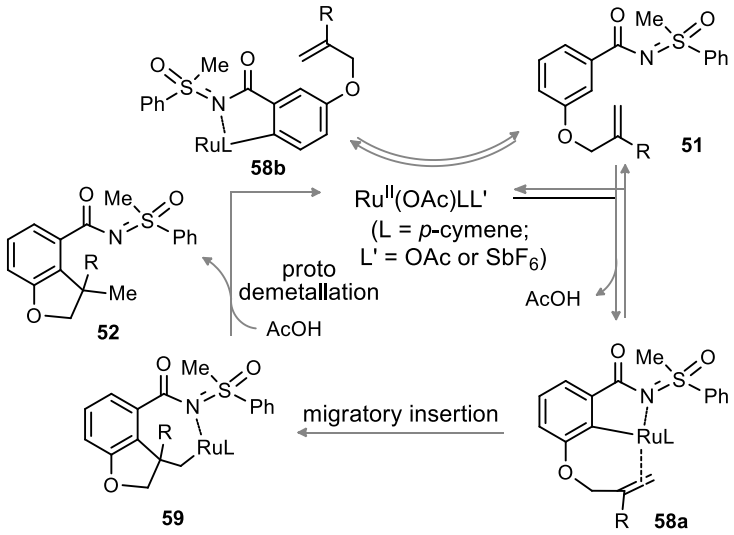
2.3.8. Mechanistic Investigation for Intramolecular hydroarylation

In order to gain insight into the probable mechanistic pathways involved in the DG-promoted Ru-catalyzed hydroarylation reaction, various control experiments and deuterium labelling studies were designed and examined. Interestingly, Ru-catalyzed hydroarylation of **51a** in the presence of TEMPO smoothly delivered **52a** in 78% yield, consequently refuting the possible participation of stable radical species in this reaction (eq 1; Scheme 2.21).[30] To understand the occurrence of site selective cyclometalation, compound **51n** was exposed to the hydroarylation conditions in a 1:1 mixture of CD_3CO_2D and CD_3OD for 6 h. The reaction explicitly provided H/D scrambled products **51n-H/D** (with deuterium incorporation at both *ortho*-positions of the precursor **51n**), without the formation of even a trace of the desired dihydrobenzofuran (eq 2, Scheme 2.21); suggesting that cleavage of the *o*-C–H bond, which generally involves a concerted metalation-deprotonation (CMD) pathway, under the Ru-catalyzed conditions is reversible.[31] Although both the *o*-C–H bonds in **51n**, positioned between the amide and the O-bearing groups, offer equal possibilities for the oxidative insertion of the Ru-catalyst, the incorporation of D into the *o*-C–H^a bond (55%), sandwiched between the DG and the O-allyl moiety over the *o*-C–H^b bond (75%) reveals that the tethered olefin moiety helps the activation of the *o*-C–H^a bond. Interestingly, the hydroarylation of **51n-H/D** under the optimized conditions resulted in **52n-H/D** (eq 3, Scheme 2.21). To our surprise, we observed a significant decrease in deuterium population at the arene *o*'-C–H bond (22%) and incorporation of only 25% of D to 3-methyl (CH_2–D) in **52n-H/D** (eq 3, Scheme 2.21). Furthermore, Ru-catalyzed hydroarylation of **51'a** in the presence of $Cu(OAc)_2$ (1.0 equiv) and CD_3CO_2D (5.0 equiv) afforded **57-H/D** with 65% deuterium incorporation in the newly generated 3-methyl moiety of dihydrobenzofuran (eq 4, Scheme 2.21). These results indicate that the reaction involves a proto-demetalation step.[15a]



Scheme 2.21. Controlled experiments

On the basis of the previous work and the above mentioned control experiments, a plausible reaction pathway for this hydroarylation reaction is outlined in Scheme 2.22. The active catalyst, generated from $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$, and $Cu(OAc)_2$, coordinates to MPS-DG and activates the *o*-C–H bonds to produce cyclometalated complex **58a**/**58b**. The additional interaction of tethered olefin to the metal probably facilitates the activation of sterically encumbered proximal C–H bond to provide **58a** over **58b**. The migratory insertion of **58a** then leads to **59**, which on proto-demetalation produces the desired product **52** with the regeneration of active catalyst (Scheme 2.22).[15a]



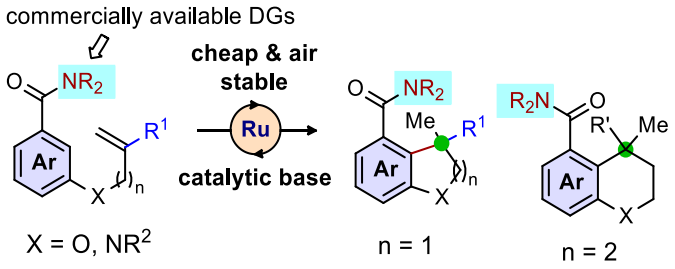
Scheme 2.22. Proposed catalytic cycle for C(sp^2)–H hydroarylation

2.4. Conclusions

In summary, first time we have demonstrated a novel and efficient MPS DG-promoted Ru-catalyzed hydroarylation of benzoic acid derivatives at rt; the reaction exhibits broad scope for manufacturing dihydrobenzofurans, indolines, and dihydrobenzothiophenes derivatives. Efficiency of this catalytic system is authenticated through the one-pot two-fold symmetrical C–H hydroarylation. Preliminary results of diastereoselective hydroarylation with the aid of enantiopure MPS-group is revealed. The success of gram-scale hydroarylation indicates the robustness of the reaction. The cleavage and recovery of the MPS DG from the products makes this strategy synthetically viable. The diastereoselective and multi-fold functionalization of unactivated C–H bonds via hydroarylation method is currently under investigation.

Section B: Ruthenium Catalyzed Intramolecular Hydroarylation of Arenes and Mechanistic Study: Synthesis of Dihydrobenzofurans, Indolines, and Chromans

The successful exploration of the reusable MPS DG promoted hydroarylation of arenes, we next envisioned exploring similar type synthetic method under the assistance of weakly coordinating amide DG. The mechanistic details of the transformation is studied; the validation of catalytic amount of acetate base is clarified. Furthermore, dihydrobenzofuran, indoline, and chroman skeletons are constructed.

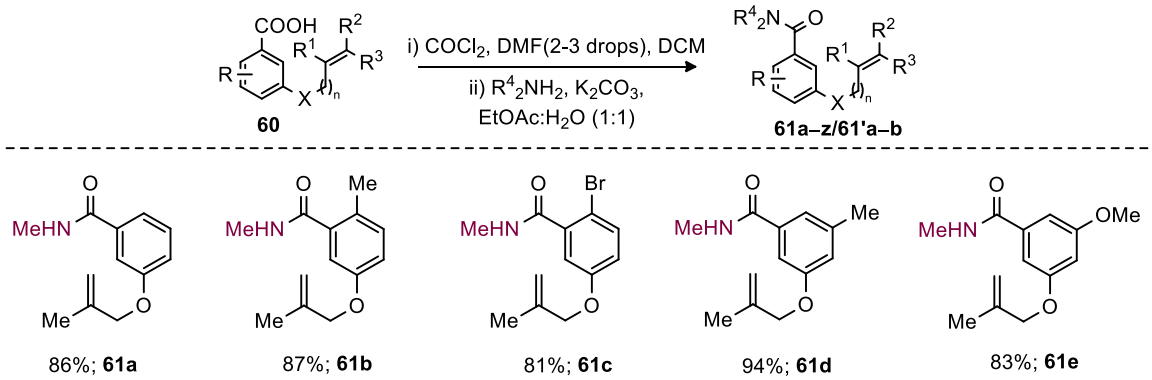


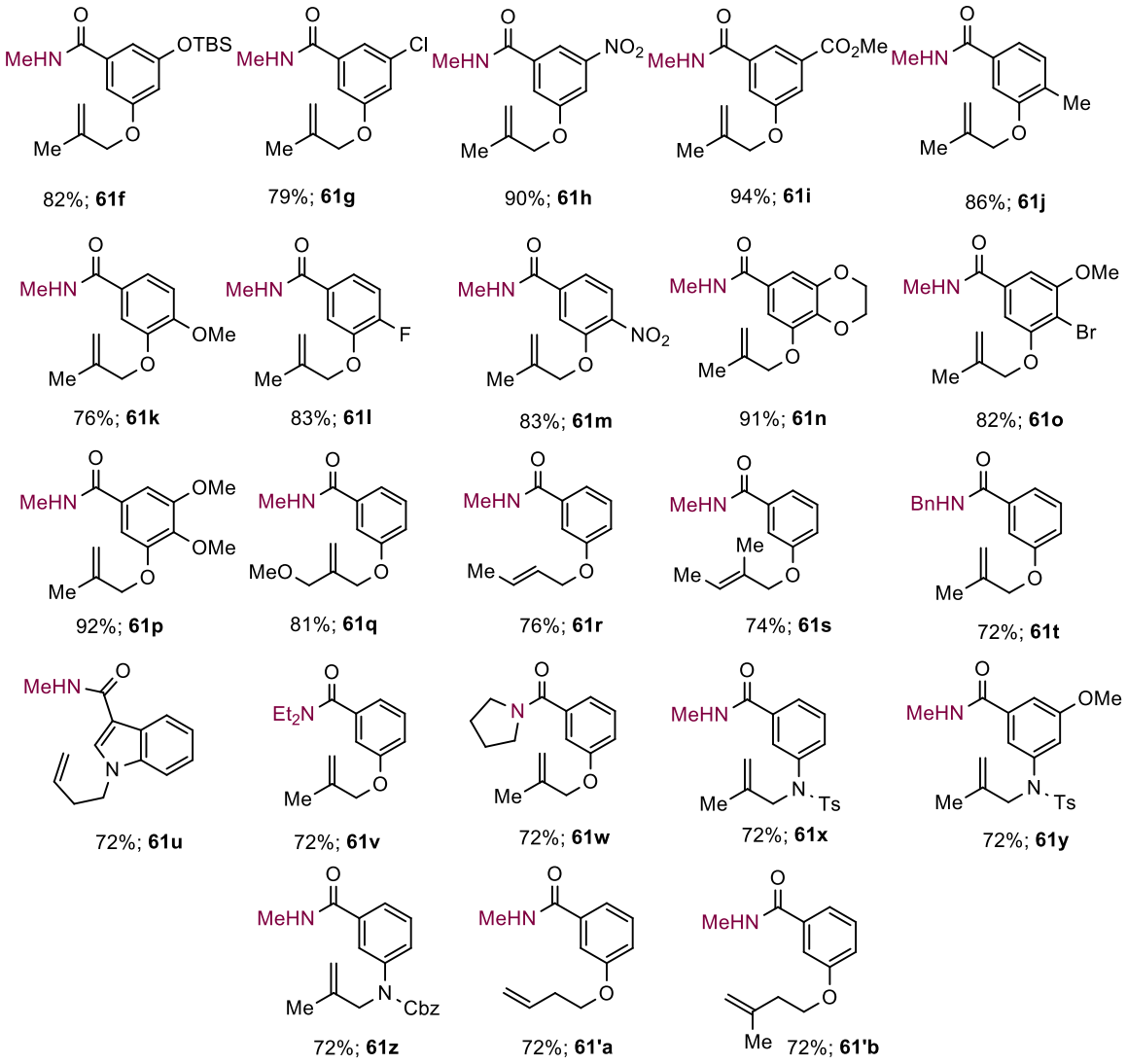
2.5. Results and Discussion

2.5.1. Synthesis of Precursors

Following the known synthetic procedure that involves base mediated amide formation of acid chlorides, obtained in-situ from the carboxylic acids in the presence of oxalyl chloride and DMF, various N-alkylbenzamide derivatives **61** were prepared from the corresponding *meta*-O/N-allyl substituted benzoic acid derivatives (**60**) (Table 2.5) (the reaction procedure is detailed in the experimental section 2.7.3, page 96).[17]

Table 2.5. Preparation of benzamide derivatives



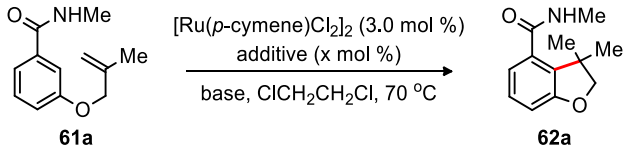


2.5.2. Reaction Optimization

To probe the feasibility of this intramolecular hydroarylation, compound **61a** was exposed to [Ru(*p*-cymene)Cl_2]$_2$ (3.0 mol %), $AgSbF_6$ (12 mol %) in $ClCH_2CH_2Cl$ (1,2-DCE) (Table 2.6); the expected dihydrobenzofuran **62a** was noticed in a trace amount (entry 1). The addition of $Cu(OAc)_2$ (1.0 equiv) enhanced the yield of **62a** (68%) (entry 2), indicating the necessity of base in this current transformation. Other acetate containing bases were found moderate (entries 3–5); while $Zn(OAc)_2$ and $Mn(OAc)_2$ worked remarkably well, affording 92% and 98% of **62a** (entry 6 and 7). Among other additives $AgBF_4$, $AgSbF_6$, KPF_6, or $NaPF_6$ screened, $AgSbF_6$ was found to be the best (entries 8–10). Surprisingly, catalytic amount of $Mn(OAc)_2$ (50 mol % and 25 mol %)

effectively delivered **62a** without hampering the outcome; although the reaction took a little longer time for completion (entries 11 and 12); The use of 10 mol % $Mn(OAc)_2$ provided 74% of **62a** in 20 h (entry 13). Finally, the catalytic conditions in entry 12 for the amide directed intramolecular hydroarylation was optimum.

Table 2.6. Optimization of Reaction Parameters[a]



61a **62a**

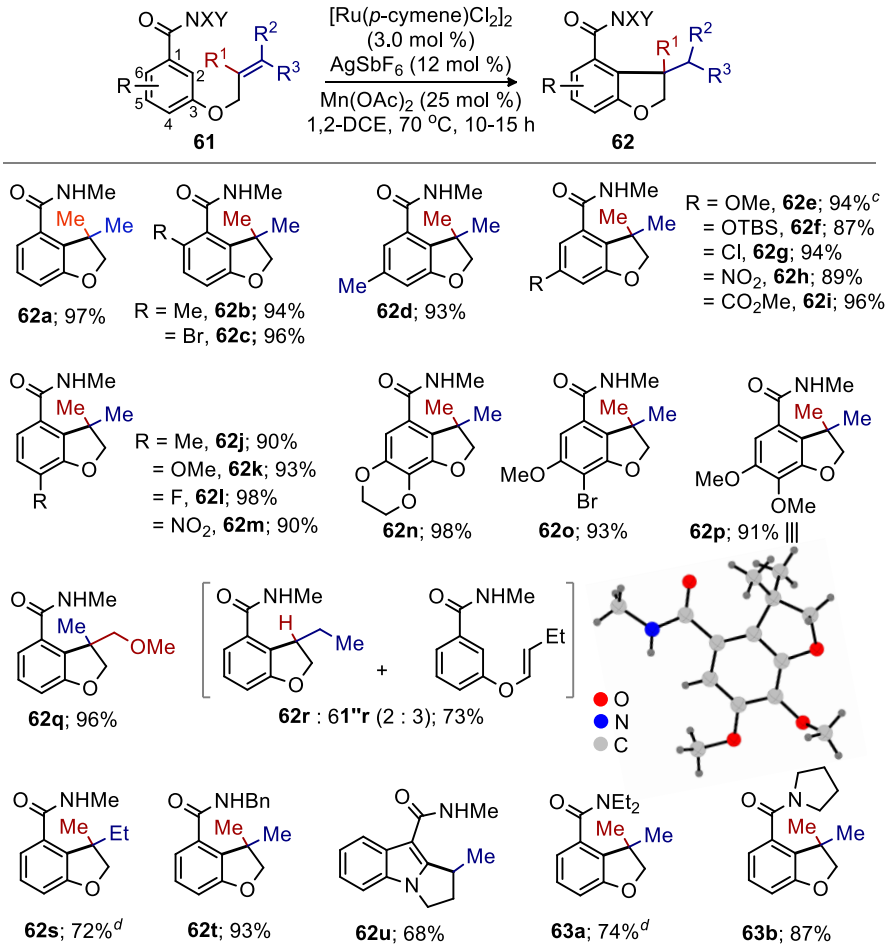
Entry	Additive (12 mol %)	Base (1.0 equiv)	Yield(%)[b] **62a**
1	$AgSbF_6$	–	<5[c]
2	$AgSbF_6$	$Cu(OAc)_2$	68
3	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	56
4	$AgSbF_6$	KOAc	36
5	$AgSbF_6$	NaOAc	21
6	$AgSbF_6$	$Zn(OAc)_2$	92
7	$AgSbF_6$	$Mn(OAc)_2$	98
8	$AgBF_4$	$Mn(OAc)_2$	<10[c]
9	KPF_6	$Mn(OAc)_2$	nr
10	$NaPF_6$	$Mn(OAc)_2$	nr
11[d]	$AgSbF_6$	$Mn(OAc)_2$	96
12[e]	**$AgSbF_6$**	**$Mn(OAc)_2$**	**96**
13[f]	$AgSbF_6$	$Mn(OAc)_2$	74

[a]Reactions were carried out with **61a** (50 mg, 0.24 mmol), Ru-cat. (3.0 mol %), additive (12 mol %), base (1.0 equiv) in $ClCH_2CH_2Cl$ (1,2-DCE) at 70 °C for 5 h. [b]Isolated yield. [c]^1H NMR yield. [d]50 mol % $Mn(OAc)_2$, 5 h. [e]25 mol % $Mn(OAc)_2$, 10 h. [f]10 mol % $Mn(OAc)_2$, 20 h. nr = no reaction.

2.5.3. Scope of Ru-Catalyzed Amide-DG Assisted Hydroarylation

To observe the steric and electronic effect of the amide directed hydroarylation outcome, the reaction of various alkene-tethered benzamide derivatives under the optimized condition was thus pursued. The compound **61a** yielded 97% of **62a**. Sterically encumbered 6-Me (**61b**) and 6-Br (**61c**) containing substrates smoothly produced **62b** and **62c** in excellent yields. Gratifyingly, the substrates having electron-donating (Me, OMe, OTBS; **61d**–**f**) or electron-withdrawing (halo, nitro, ester; **61g**–**i**) groups on arenes did not hamper the reaction, constructing **62d–i** in attractive yields (87–96%). The labile TBS protecting group in **62f** survived in this condition. The hydroarylation was not affected by the directing ability of the ester-moiety (**62i**).[25] Likewise, peripheral decorated dihydrobenzofurans **62j**–**p** were fabricated from the corresponding benzamides **61j**–**p** with substituent at the 4- or 4,5-position on arene in lucrative yield. X-ray crystallographic study unambiguously confirmed the structure of **62p** (Table 2.7). Different terminal olefin bearing compound **61q** (methoxymethyl) delivered the desired **62q** (96%). When internal alkene bearing **61r** was exposed to the optimized condition, an inseparable mixture of **62r** and the isomerized arylvinyl ether **61''r** was obtained. Notably, hydroarylation of tri-substituted internal alkene **61s** produced the desired product **62s** (72%). The N-benzyl-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxamide **62t** was isolated in 93% yield. Thus, wide arrays of highly functionalized dihydrobenzofurans were consequently accessed from the benzamide derivatives. Interestingly, indole skeleton successfully underwent C2-hydroarylation delivering indole-fused-pyrrolidine **62u** (68%), which was otherwise difficult to access (Table 2.7). The acidic N-H moiety of amide-DG plays an essential role in the TM-catalyzed C–H activation.[32,25] We therefore investigated examining the directing group ability of tertiary amides in this intramolecular hydroarylation reaction (Table 2.7). Gratifyingly, the desired products **63a** and **63b** were effectively isolated in 74% and 87% yield, respectively, when Et_2N and pyrrolidine bearing tertiary amides exposed to the reaction (Table 2.7).

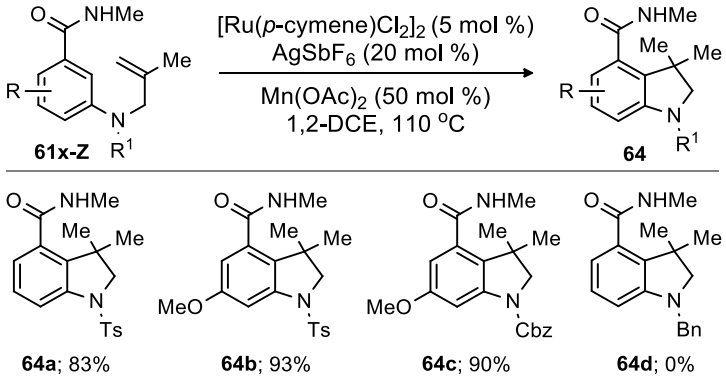
Table 2.7. Substrate scope for amide directed hydroarylation of arenes[a]



[a]Reaction conditions: **61** (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3.0 mol %), $AgSbF_6$ (12.0 mol %), $Mn(OAc)_2$ (25 mol %), 1,2-DCE (1.0 mL) at 70 °C for 10–15 h. [b]Isolated yields. [c]Reaction was continued for 18 h. [d]Reaction at 100 °C.

The successful execution of the intramolecular hydroarylation of 3-*O*-tethered olefin bearing arene amides provoked us to check the same reaction with the N-tethered olefin substrates. Therefore, 3-N-Ts/Cbz protected tethered olefin bearing benzamides **61x–z** were subjected to the optimized conditions in the presence of 50 mol% $Mn(OAc)_2$ at 110 °C. The desired product indolines **64a–c** formed in appreciable amount yields (83–93%; Table 2.8). To our surprise, the N-Bn protected benzamide did not produce the product **64d**; probably the C–H activation step is getting hamper due to the coordination ability of N-Bn to Ru-species.

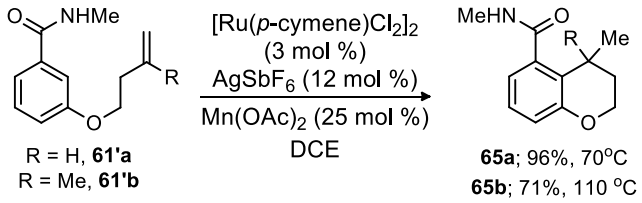
Table 2.8. Synthesis of Indolines[a,b]



[a]Reaction conditions: **61x**–**z** (0.3 mmol), Ru-catalyst (5.0 mol %), Ag-salt (20 mol %), $Mn(OAc)_2$ (50 mol %) in DCE (3.0 mL) at 110 °C for 20–24 h. [b]Isolated yields.

2.5.4. Scope of Ru-Catalyzed Amide-DG Assisted Chromans

The natural occurrences of chroman in various biologically important candidates lead us to think about the hydroarylation of homo-allyl bearing compounds for the synthesis of chroman architecture.[33] Therefore, we envisioned the intramolecular hydroarylation of 3-*O*-homo-allyl tethered benzamides. Gratifyingly, the precursor **61'a** and **61'b** were reliably delivered the corresponding chroman derivatives **65a** (96%) and **65b** (71%), respectively, in good yields under the same catalytic system (Scheme 2.23). To our knowledge, the amide assisted Ru-catalyzed C–H bond functionalization for the construction of chroman derivatives is the first report. We hope this initial result would find a broad applicability for the efficient construction of novel chroman derivatives.

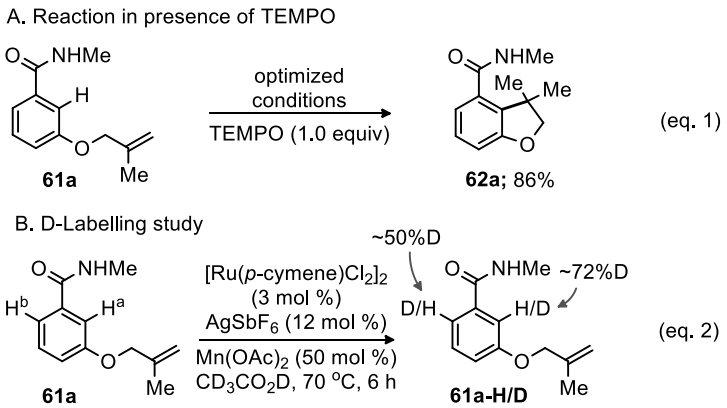


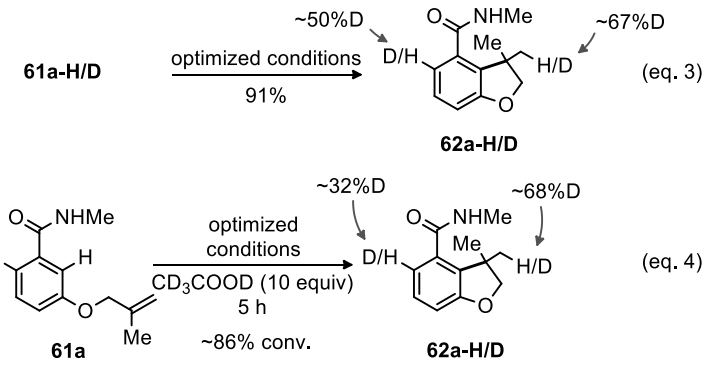
Scheme 2.23. Synthesis of Chromans

2.5.5. Mechanistic Investigation of Intramolecular Hydroarylation

To understand the probable reaction pathways involved in the amide directed intra molecular hydroarylation reaction, various controlled experiments were designed and

executed. Interestingly, hydroarylation of **61a** under the optimized condition in the presence of TEMPO smoothly produced **62a** in 86% yield. Thus, the involvement of stable radical species in this current hydroarylation method is ruled out (eq 1; Scheme 2.24).[30] To gain the idea about preferable site selective metalation, compound **61a** was exposed to the hydroarylation conditions in presence of CD_3CO_2D for 6 h. The incorporation of D-atom at both *ortho*-positions of the compound **61a** (eq 2, Scheme 2.24) definitely indicating the reversible cleavage of the *o*-C–H bond, which generally occurs through a base assisted concerted metalation-deprotonation (CMD) path under the reaction conditions.[31] The deuterium incorporation into the *o*-C–H^a bond (72%) over the *o*-C–H^b bond (50%) in **61a-H/D** clearly suggesting the ancillary effect of a tethered olefin moiety and which of course facilitates the *o*-C–H^a bond activation (eq 2, Scheme 2.24). Next we carried out the hydroarylation of **61a-H/D** (H/D scrambled product) and it produced **62a-H/D** (eq 3, Scheme 2.24). A significant amount of deuterium (67%) incorporation was observed to the newly generated 3-methyl (CH_2–D) in **62a-H/D** (eq 3, Scheme 2.24). Furthermore, hydroarylation of **61a** under optimized conditions in the presence of CD_3CO_2D (10.0 equiv) delivered 68% of D incorporated product at the newly generated 3-methyl moiety of dihydrobenzofuran **62a-H/D** (eq 4, Scheme 2.24). These observations are explicitly suggesting about the involvement of a proto-demetalation step rather than the C–C reductive elimination.[31]

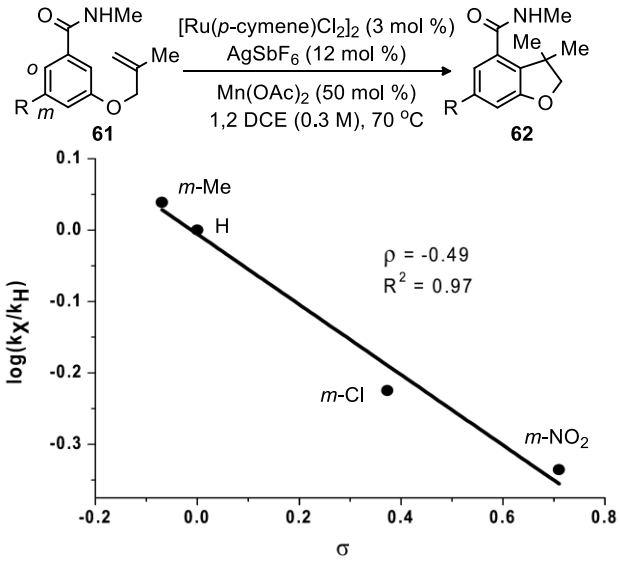




Scheme 2.24. Controlled experiments

2.5.5.1. Hammett Analysis for Intramolecular Hydroarylation

To understand the electronic substituent effect of this hydroarylation reaction, the Hammett study was planned with various *meta*-substituted benzamide derivatives (Scheme 2.25).[34] The negative value of reaction constant (ρ = –0.49) clearly indicates the occurrence of electron diffusion away from the arene ring in the rate determining step. Therefore, we speculate the electron releasing group on arene periphery in benzamides would promote the hydroarylation process; the outcome in scheme 2.25 supports consistently with this fact. The lower magnituted of ρ-value and correct fitting of σ_m-values in the Hammett plot with respect to amide-DG, suggests a probable non-rate limiting C–H activation.



Scheme 2.25. Hammett analysis

2.6. Conclusion

With the aid of commercially accessible amide-DG, an efficient and novel Ru-catalyzed hydroarylation of arenes is demonstrated. This methodology exhibits broad scope, providing dihydrobenzofurans and indolines in good yields. Hammett studies and deuterium labelling experiments offers a keen understanding about the reaction mechanism. Synthesis of chromans is achieved through the hydroarylation of *O*-homoallyl tethered compounds.

2.7. Experimental

2.7.1. General Experimental Information

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 ^{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). Elemental (C, H, N) analysis were carried out using FLASH EA 1112 analyzer. High resolution mass spectra were obtained in ESI mode. Melting points were determined by electro-thermal heating and are uncorrected. X-ray data was collected at 293 K using graphite monochromated Mo-Kα radiation (0.71073 Å).

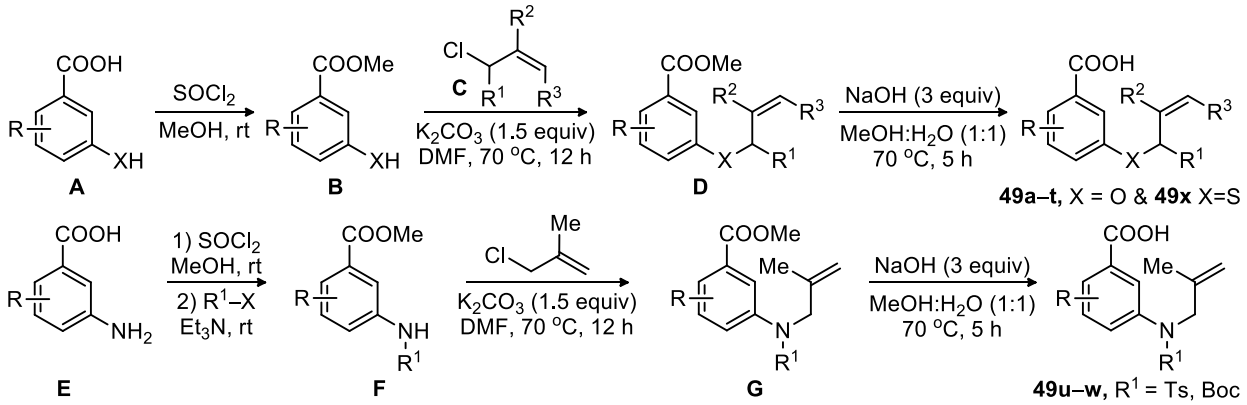
2.7.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Dichloromethane (DCM), 1,2-dichloroethane (DCE), and chloroform were distilled over CaH_2. THF was freshly distilled over sodium/benzophenone ketyl under dry nitrogen. $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$, $AgBF_4$,

KPF_6 were purchased from Sigma Aldrich Ltd, and used as received. Bases such as $Cu(OAc)_2{\cdot}H_2O$, KOAc, NaOAc, AgOAc were purchased from Aldrich Ltd. and used as received. Analytical and spectral data of all those known compounds are exactly matching with the reported values.

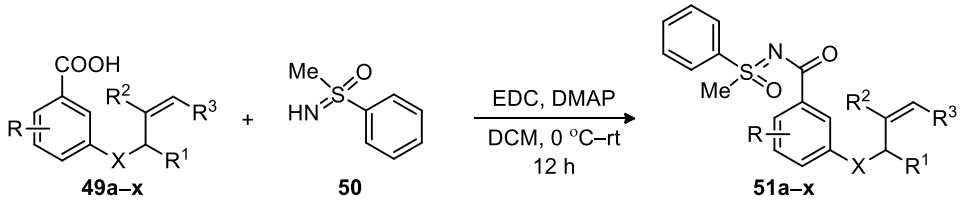
2.7.3. Experimental Procedures and Analytical Data

2.7.3.1. Preparation of carboxylic acid 49a–t: General procedure (GP-1):



Following the above Schemes, corresponding benzoic acid derivatives were prepared and used for the next step. The analytical data of the benzoic acid derivatives are exactly matching with the reported values.

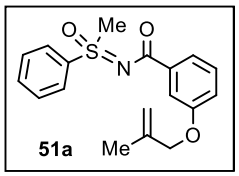
2.7.3.2. Preparation of *N*-Aroyl Sulfoximines (51); General Procedure (GP-2); EDC-coupling:



A solution of *N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodimide, hydrochloride salt (EDC.HCl) (2.0 equiv), 4-*N*,*N*-dimethylaminopyridine (DMAP) (2.2 equiv) and carboxylic acid (**49a–x**) (1.1 equiv) in CH_2Cl_2 (5.0 mL, for 1 mmol of sulfoximine) was stirred under an argon atmosphere. Methyl phenyl sulfoximine (**50)** (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

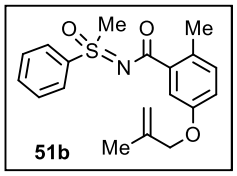
consumption of sulfoximine, the reaction mixture was acidified with hydrochloric acid (HCl, 1N). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3 times). The combined extracts were washed with 10% aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4. Solvent was filtered and evaporated under the reduced pressure. The crude residue was purified using column chromatography on silica gel.

***N*-[3-((2-Methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51a):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.5 g, 3.22 mmol), EDC.HCl (1.23 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-((2-methylallyl)oxy)benzoic acid (0.68 g, 3.54 mmol) afforded **51a** (0.916 g) in 86% yield as colorless solid. m.p. = 85–88 °C; R_f = 0.43 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.04 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 7.6 Hz, 1H), 7.71 (s, 1H), 7.67 (t, J = 7.0 Hz, 1H), 7.60 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 8.0 Hz, 1H), 7.08 (dd, J = 8.0, 2.4 Hz, 1H), 5.10 (s, 1H), 4.98 (s, 1H), 4.47 (s, 2H), 3.45 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.9, 158.5, 140.6, 138.8, 136.9, 133.7, 129.6 (2C), 128.9, 127.0 (2C), 122.0, 119.2, 114.8, 112.7, 71.7, 44.2, 19.3; IR (KBr) ν_{max} 3051, 2920, 1621, 1578, 1453, 1282 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{19}NNaO_3S$ $(M+Na)^+$: calcd. 352.0983, found 352.0981.

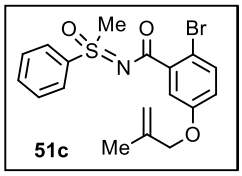
***N*-[2-Methyl-5-((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51b):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.23 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 2-methyl-5-((2-methylallyl)oxy)benzoic acid (0.73 g, 3.54 mmol) afforded **51b** (0.965 g) in 87% yield as colorless solid. m.p. = 99–101 °C; R_f = 0.48 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.04 (d, J = 8.0 Hz, 2H), 7.71–7.56 (m, 4H), 7.09 (d, J = 8.4 Hz, 1H), 6.91 (dd, J = 8.4, 2.8 Hz, 1H), 5.10 (s, 1H), 4.98 (s, 1H), 4.44 (s, 2H), 3.42 (s, 3H), 2.51 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ176.1, 156.3, 140.9, 138.9, 135.9, 133.7, 132.3, 131.3, 129.6 (2C), 127.0 (2C), 117.5, 116.6, 112.6, 71.8, 44.4, 20.8, 19.3; IR (Neat) ν_{max} 3063, 2926,

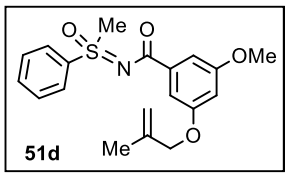
1632, 1495, 1413, 1221, 980 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{21}NNaO_3S$ $(M+Na)^+$: calcd. 366.1140, found 366.1143.

***N*-[2-Bromo-5-((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51c):**



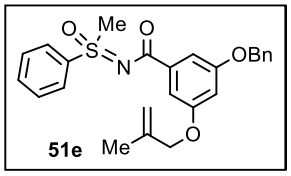
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50,** 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 2-bromo-5-((2-methylallyl)oxy)benzoic acid (0.96 g, 3.54 mmol) afforded **51c** (1.06 g) in 81% yield as colorless solid. m.p. = 129–132 °C; R_f = 0.49 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.10 (d, J = 8.0 Hz, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 3.2 Hz, 1H), 6.83 (dd, J = 8.8, 3.2 Hz, 1H), 5.06 (s, 1H), 4.98 (s, 1H), 4.42 (s, 2H), 3.48 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.7, 157.7, 140.2, 138.9, 138.2, 134.3, 134.0, 129.6 (2C), 127.3 (2C), 118.3, 116.5, 113.0, 110.7, 72.0, 44.2, 19.3; IR (Neat) ν_{max} 3068, 2931, 1632, 1567, 1260, 810 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{19}BrNO_3S$: $(M+H)^+$: calcd. 408.0269, found 408.0272.

***N*-[3-Methoxy-5-((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-2-phenylsulfoximine (51d):**



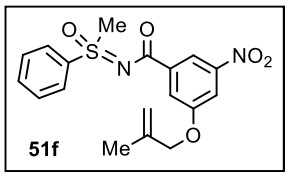
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-methoxy-5-((2-methylallyl)oxy)benzoic acid (0.78 g, 3.54 mmol) afforded **51d** (1.09 g) in 94% yield as colorless solid. m.p. = 101–104 °C; R_f = 0.28 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.6 Hz, 2H), 7.35 (dt, J = 10.4, 1.0 Hz, 2H), 6.64 (bs, 1H), 5.09 (s, 1H), 4.98 (s, 1H), 4.44 (s, 2H), 3.80 (s, 3H), 3.44 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.8, 160.3, 159.5, 140.6, 138.8, 137.6, 133.7, 129.6 (2C), 127.0 (2C), 112.7, 108.0, 107.0, 105.5, 71.8, 55.4, 44.2, 19.3; IR (Neat) ν_{max} 3084, 3019, 2926, 1643, 1435, 1331, 1260, 1205, 1150 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{22}NO_4S$: $(M+H)^+$: calcd. 360.1269, found 360.1264.

***N*-[3-(Benzyloxy)-5-((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-2-phenylsulfoximine (51e):**



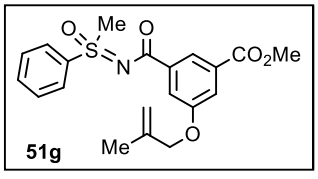
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50,** 0.50 g, 3.22 mmol), EDC.HCl (1.24 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-(benzyloxy)-5-((2-methylallyl)oxy)benzoic acid (1.05 g, 3.54 mmol) afforded **51e** (1.16 g) in 83% yield as colorless solid. m.p. = 154–157 °C; R_f = 0.40 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.06 (d, J = 7.6 Hz, 2H), 7.72 (t, J = 7.2 Hz, 1H), 7.64 (t, J = 7.6 Hz, 2H), 7.49–7.31 (m, 7H), 6.75 (bt, J = 2.4 Hz, 1H), 5.13–5.08 (m, 3H), 5.00 (s, 1H), 4.47 (s, 2H), 3.47 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.7, 159.5, 140.5, 138.8, 137.6, 136.6, 133.7, 129.6 (2C), 128.4 (2C), 127.9, 127.5 (2C), 127.0 (2C), 112.7, 108.2, 107.9, 106.3, 71.8, 70.1, 44.2, 19.3; IR (KBr) ν_{max} 3024, 2926, 1594, 1435, 1358, 1210, 1161 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{26}NO_4S$ $(M+H)^+$: calcd. 436.1582, found 436.1577.

***N*-[3-((2-Methylallyl)oxy)-5-nitrobenzoyl]-*S*-methyl-*S*-2-phenylsulfoximine (51f):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-((2-methylallyl)oxy)-5-nitrobenzoic acid (0.84 g, 3.54 mmol) afforded **51f** (0.989 g) in 82% yield as colorless solid. m.p. = 150–154 °C; R_f = 0.40 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.56 (bd, J = 1.2 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H), 8.00–7.95 (m, 1H), 7.88□7.83 (m, 1H), 7.71 (t, J = 7.4 Hz, 1H), 7.63 (t, J = 7.8 Hz, 2H), 5.10 (s, 1H), 5.02 (s, 1H), 4.53 (s, 2H), 3.48 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 158.9, 148.8, 139.5, 138.24, 138.17, 134.1, 129.8 (2C), 127.0 (2c), 121.4, 116.6, 113.6, 112.8, 72.4, 44.3, 19.2; IR (KBr) ν_{max} 3090, 2926, 1638, 1583, 1534, 1358, 1293, 1227 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{18}N_2NaO_5S$ $(M+Na)^+$: calcd. 397.0834, found 397.0836.

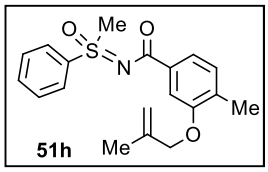
***N*-[3-(Methoxycarbonyl)-5-((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-2-phenylsulfoximine (51g):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g,

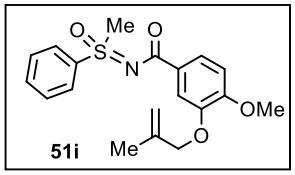
6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-(methoxycarbonyl)-5-((2-methylallyl)oxy)benzoic acid (0.88 g, 3.54 mmol) afforded **51g** (0.980 g) in 79% yield as colorless solid; m.p. = 156–159 °C; R_f = 0.36 (6:4 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.42 (s, 1H), 8.05 (d, J = 7.6 Hz, 2H), 7.88 (s, 1H), 7.75–7.66 (m, 2H), 7.62 (t, J = 7.6 Hz, 2H), 5.11 (s, 1H), 5.00 (s, 1H), 4.50 (s, 2H), 3.92 (s, 3H), 3.47 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 166.5, 158.5, 140.2, 138.6, 137.3, 133.8, 131.2, 129.7, 127.1, 123.1, 119.8, 119.3, 113.0, 72.0, 52.2, 44.4, 19.3; IR (KBr) ν_{max} 3051, 2925, 1725, 1615, 1593, 1445, 1341, 1204 cm^{-1}; **HRMS (ESI)** for $C_{20}H_{22}NO_5S$ $(M+H)^+$: calcd. 388.1219, found 388.1215.

***N*-[4-Methyl-3-((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51h):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 4-methyl-3-((2-methylallyl)oxy)benzoic acid (0.73 g, 3.54 mmol) afforded **51h** (1.00 g) in 90% yield as colorless solid. m.p. = 101–103 °C; R_f = 0.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.06 (dd, J = 8.6, 1.4 Hz, 2H), 7.73 (dd, J = 7.6, 1.2 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.65–7.56 (m, 3H), 7.18 (d, J = 7.6 Hz, 1H), 5.13 (s, 1H), 4.99 (s, 1H), 4.49 (s, 2H), 3.46 (s, 3H), 2.31 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.1, 156.4, 140.9, 139.1, 134.4, 133.7, 131.8, 130.0, 129.6 (2C), 127.1 (2C), 122.0, 112.1, 111.4, 71.4, 44.3, 19.4, 16.5; IR (KBr) ν_{max} 3063, 2926, 1616, 1578, 1413, 1293, 1210 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{21}NNaO_3S$ $(M+Na)^+$: calcd. 366.1140, found 366.1142.

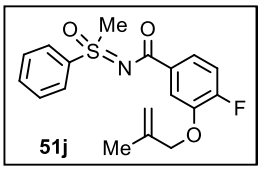
***N*-[4-Methoxy-3-((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51i):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 4-methoxy-3-((2-methylallyl)oxy)benzoic acid (0.78 g, 3.54 mmol) afforded **51i** (1.09 g) in 94% yield as colorless solid. m.p. = 115–117.5 °C; R_f = 0.23; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.02 (bd, J = 7.2 Hz, 2H), 7.81 (bd, J = 6.8 Hz, 1H), 7.70–7.53 (m, 4H), 6.86 (bd, J = 8.0 Hz, 1H), 5.09 (s,

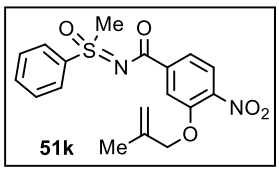
1H), 4.96 (s, 1H), 4.53 (s, 2H), 3.89 (s, 3H), 3.43 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.6, 152.8, 147.3, 140.4, 139.0, 133.5, 129.4 (2C), 128.1, 126.9 (2C), 123.5, 113.9, 112.6, 110.2, 72.3, 55.8, 44.2, 19.2; IR (KBr) ν_{max} 3024, 2920, 1616, 1572, 1309, 1216 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{22}NO_4S$ $(M+H)^+$: calcd. 360.1270, found 360.1264.

***N*-[4-Fluoro-3-((2-methylallyl)oxy)benoyl]-*S*-methyl-*S*-phenylsulfoximine (51j):**



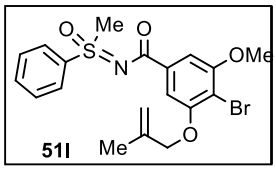
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 4-fluoro-3-((2-methylallyl)oxy)benzoic acid (0.74 g, 3.54 mmol) afforded **51j** (0.967 g) in 86% yield as colorless solid. m.p. = 100–104 °C; R_f = 0.41(7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.0 Hz, 2H), 7.85–7.77 (m, 2H), 7.73 (t, J = 7.4 Hz, 1H), 7.65 (t, J = 7.8 Hz, 2H), 7.11 (dd, J = 10.6, 8.6 Hz, 1H), 5.15 (s, 1H), 5.03 (s, 1H), 4.56 (s, 2H), 3.49 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ173.0, 155.4 (d, J = 253 Hz), 146.3 (d, J = 11 Hz), 140.1, 138.8, 133.8, 132.0, 129.6 (2C), 127.0 (2C), 123.1 (d, J = 7.1 Hz), 116.0, 115.5 (d, J = 19 Hz), 113.2, 72.8, 44.3, 19.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –128.32; IR (KBr) ν_{max} 3073, 2926, 1627, 1600, 1419, 1298, 1216 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{18}FNNaO_3S$ $(M+Na)^+$: calcd. 370.0889, found 370.0884.

***N*-[3-((2-Methylallyl)oxy)-4-nitrobenzoyl]-*S*-methyl-*S*-phenylsulfoximine (51k):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.5 g, 3.20 mmol), EDC.HCl (1.22 g, 6.40 mmol), DMAP (0.863 g, 7.04 mmol) and 3-((2-methylallyl)oxy)-4-nitrobenzoic acid (0.84 g, 3.54 mmol) afforded **51k** (0.912 g) in 76% yield as colorless crystalline solid. m.p. = 112–115 °C; R_f = 0.33 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.6 Hz, 2H), 7.86–7.80 (m, 3H), 7.73 (t, J = 7.4 Hz, 1H), 7.65 (t, J = 7.6 Hz, 2H), 5.15 (s, 1H), 5.02 (s, 1H), 4.60 (s, 2H), 3.48 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ171.9, 151.3, 141.7, 140.4, 139.2, 138.2, 134.1, 129.7, 127.0, 125.0, 121.3, 115.3, 113.5, 72.7, 44.2, 19.1; IR (KBr) ν_{max} 3062, 2931, 1610, 1582, 1522, 1303, 1215 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{18}N_2NaO_5S$ $(M+Na)^+$: calcd. 397.0834, found 397.0831.

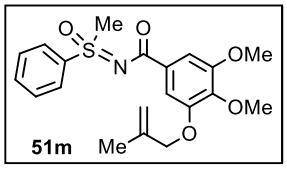
***N*-[4-Bromo-3-methoxy-5-((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51l):**



51l

Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 4-bromo-3-methoxy-5-((2-methylallyl)oxy)benzoic acid (1.06 g, 3.54 mmol) afforded **51l** (1.17 g) in 83% yield as colorless solid. m.p. = 94–97 °C; R_f = 0.32 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.07 (d, J = 8.0 Hz, 2H), 7.73 (t, J = 7.4 Hz, 1H), 7.66 (t, J = 7.6 Hz, 2H), 7.41 (s, 2H), 5.21 (s, 1H), 5.04 (s, 1H), 4.58 (s, 2H), 3.97 (s, 3H), 3.50 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.2, 156.6, 155.6, 140.0, 138.6, 135.6, 133.8, 129.6 (2C), 126.9 (2C), 112.7, 106.7, 106.1, 105.3, 72.5, 56.4, 44.2, 19.3; IR (KBr) ν_{max} 3073, 2931, 1632, 1578, 1419, 1336, 1254, 1216, 1117 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{21}BrNO_4S$ $(M+H)^+$: calcd. 438.0375 found 438.0369.

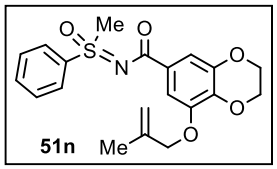
***N*-[3,4-Dimethoxy-5-((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51m):**



51m

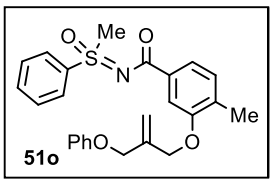
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3,4-dimethoxy-5-((2-methylallyl)oxy)benzoic acid (0.893 g, 3.54 mmol) afforded **51m** (1.04 g) in 83% yield as colorless solid. m.p. = 95–98 °C; R_f = 0.20 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 2H), 7.70 (bt, J = 7.2 Hz, 1H), 7.62 (t, J = 7.8 Hz, 2H), 7.45 (d, J = 4.8 Hz, 2H), 5.13 (s, 1H), 5.00 (s, 1H), 4.54 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.47 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.5, 152.7, 151.7, 142.0, 140.6, 139.0, 133.7, 130.6, 129.6 (2C), 127.0 (2C), 112.7, 108.4, 106.6, 72.6, 60.8, 56.1, 44.2, 19.4; IR (KBr) ν_{max} 3030, 2926, 1578, 1446, 1336, 1216 cm^{-1}; **HRMS (ESI)** for $C_{20}H_{24}NO_5S$ $(M+H)^+$: calcd. 390.1375, found 390.1370.

***N*-[8-((2-Methylallyl)oxy)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (51n):**



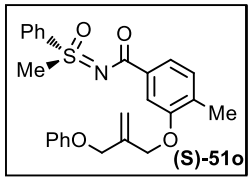
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 8-((2-methylallyl)oxy)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylic acid (0.88 g, 3.54 mmol) afforded **51n** (1.13 g) in 91% yield as colorless solid. m.p. = 123–126 ^{o}C; R_f = 0.23 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.06 (d, J = 7.6 Hz, 2H), 7.70 (t, J = 7.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 1.6 Hz, 1H), 5.13 (s, 1H), 5.01 (s, 1H), 4.55 (s, 2H), 4.41–4.35 (m, 2H), 4.33–4.27 (m, 2H), 3.46 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.5, 147.5, 143.3, 140.4, 139.1, 137.3, 133.7, 129.6 (2C), 127.6, 127.1 (2C), 112.9, 112.2, 106.9, 72.7, 64.7, 64.0, 44.3, 19.3; IR (KBr) ν_{max} 3024, 2926, 1583, 1506, 1358, 1205 cm^{-1}; **HRMS (ESI)** for $C_{20}H_{21}NNaO_5S$ (M+Na)$^+$: calcd. 410.1038, found 410.1037.

***N*-[4-Methyl-3-((2-(phenoxymethyl)allyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51o):**



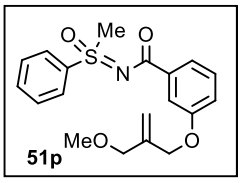
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 4-methyl-3-((2-(phenoxymethyl)allyl)oxy)benzoic acid (1.05 g, 3.54 mmol) afforded **51o** (1.15 g) in 82% yield as colorless viscus liquid. R_f = 0.37 (3:2 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ8.07 (d, J = 7.6 Hz, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.74–7.66 (m, 2H), 7.62 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.8 Hz, 2H), 7.21 (d, J = 7.6 Hz, 1H), 7.01–6.93 (m, 3H), 5.47 (s, 1H), 5.44 (s, 1H), 4.72 (s, 2H), 4.69 (s, 2H), 3.48 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.1, 158.5, 156.2, 140.4, 139.0, 134.5, 133.7, 131.8, 130.2, 129.6 (2C), 129.4 (2C), 127.1 (2C), 122.2, 120.9, 115.2, 114.7 (2C), 111.5, 68.54, 68.47, 44.3, 16.5; IR (Neat) ν_{max} 3062, 2925, 1621, 1572, 1490, 1446, 1413, 1293, 1221, 1117 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{25}NNaO_4S$ (M+Na)$^+$: calcd. 458.1402, found 458.1405.

(*S*)-*N*-[4-Methyl-3-((2-(phenoxymethyl)allyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-51o]:



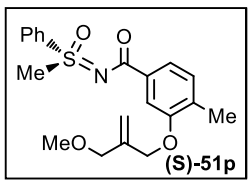
Following the general procedure (GP-2); reaction of (*S*)-*S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 4-methyl-3-((2-(phenoxymethyl)allyl)oxy)benzoic acid (1.05 g, 3.54 mmol) afforded (*S*)-**51o** (1.03 g) in 80% yield as colorless viscus liquid.

***N*-[3-((2-(Methoxymethyl)allyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51p):**



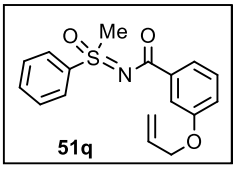
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50,** 0.5 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-((2-(methoxymethyl)allyl)oxy)-4-methylbenzoic acid (0.78 g, 3.54 mmol) afforded **51p** (1.07 g) in 92% yield as yellowish liquid. R_f = 0.28 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.07 (d, J = 7.6 Hz, 2H), 7.80 (d, J = 7.6 Hz, 1H), 7.74 (bs, 1H), 7.71 (bt, J = 7.4 Hz, 1H), 7.63 (t, J = 7.4 Hz, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.11 (dd, J = 8.0, 1.2 Hz, 1H), 5.36 (s, 1H), 5.29 (s, 1H), 4.61 (s, 2H), 4.04 (s, 2H), 3.48 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.7, 158.3, 141.1, 138.7, 136.9, 133.6, 129.5 (2C), 128.8, 126.9 (2C), 122.0, 119.0, 114.8, 114.7, 73.0, 68.4, 57.9, 44.1; IR (Neat) ν_{max} 3068, 2926, 1720, 1627, 1578, 1479, 1452, 1271, 1221, 1117, 1084 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{21}NNaO_4S$ $(M+Na)^+$: calcd. 382.1089, found 382.1090.

(*S*)-*N*-[3-((2-(Methoxymethyl)allyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine [(*S*)-51p]:



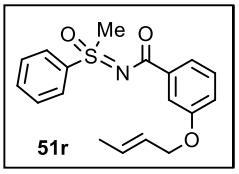
Following the general procedure (GP-2); reaction of (*S*)-*S*-methyl-*S*-phenylsulfoximine (**50,** 0.5 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-((2-(methoxymethyl)allyl)oxy)-4-methylbenzoic acid (0.78 g, 3.54 mmol) afforded (*S*)-**51p** (0.85 g) in 73% yield as yellowish liquid.

***N*-[3-(Allyloxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51q):**



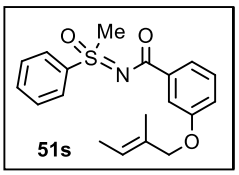
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-(allyloxy)benzoic acid (0.63 g, 3.54 mmol) afforded **51q** (0.82 g) in 81% yield as colorless solid. m.p. = 100-103 ^{o}C; R_f = 0.33 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.6 Hz, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.76–7.68 (m, 2H), 7.64 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.8 Hz, 1H), 7.11 (dd, J = 8.0, 2.4 Hz, 1H), 6.16–6.02 (m, 1H), 5.45 (dd, J = 17.2, 1.2 Hz, 1H), 5.32 (dd, J = 10.4, 0.8 Hz, 1H), 4.60 (d, J = 5.6 Hz, 2H), 3.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 158.3, 138.8, 136.9, 133.7, 133.0, 129.6 (2C), 128.9, 127.0 (2C), 122.0, 119.2, 117.6, 114.6, 68.7, 44.2; IR (KBr) ν_{max} 3063, 3024, 2926, 2860, 1616, 1572, 1484, 1452, 1419, 1304, 1216, 1079, 986, 838, 761, 690 cm^{-1}; **HRMS (ESI)** for $C_{17}H_{18}NO_3S$ $(M+H)^+$: calcd. 316.1007, found 316.1002.

***N*-[(*E*)-3-(but-2-en-1-yloxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51r):**



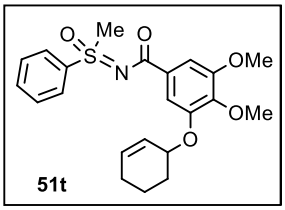
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and (E)-3-(but-2-en-1-yloxy)benzoic acid (predominantly trans) (0.68 g, 3.54 mmol) afforded **51r** (0.81 g) in 76% yield as colorless viscous liquid; R_f = 0.50 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.6 Hz, 2H), 7.76 (d, J = 7.6 Hz, 1H), 7.72–7.63 (m, 2H), 7.59 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.06 (dd, J = 7.8, 1.8 Hz, 1H), [5.92–5.08 (m, 0.8 H), 5.78–5.67 (m, 1.2 H)], [4.62 (d, J = 6.0 Hz, 0.42 H), 4.48 (d, J = 6.0 Hz, 1.6 Hz)], 3.44 (s, 3H), 1.74 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, [158.5, 158.4], 138.8, 136.9, 133.7, 130.7, 129.6 (2C), [128.9, 128.7], 127.0 (2C), [125.8, 125.3], [121.94, 121.90], [119.33, 119.26], [114.6, 114.4], [68.7, 63.7], 44.2, [17.8, 13.3]; IR (Neat) ν_{max} 3019, 2926, 1616, 1572, 1446, 1276, 1227, 1123 cm□1; **HRMS (ESI)** for $C_{18}H_{19}NNaO_3S$ $(M+Na)^+$: calcd. 352.0983, found 352.0988.

***N*-[(*E*)-3-((2-Methylbut-2-en-1-yl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51s):**



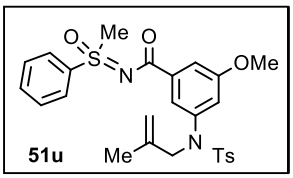
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and (E)-3-((2-methylbut-2-en-1-yl)oxy)benzoic acid (0.73 g, 3.54 mmol) afforded **51s** (0.82 g) in 74% yield as colorless viscous liquid. R_f = 0.43 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 7.6 Hz, 1H), 7.70 (s, 1H), 7.67–7.62 (m, 1H), 7.62–7.56 (m, 2H), 7.29 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 6.8 Hz, 1H), 5.68–5.58 (m, 1H), 4.40 (s, 2H), 3.43 (s, 3H), 1.72 (s, 3H), 1.64 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 158.6, 138.7, 136.8, 133.7, 131.4, 129.5 (2C), 128.8, 127.0 (2C), 123.4, 121.8, 119.2, 114.7, 74.0, 44.2, 13.5, 13.1; IR (Neat) ν_{max} 3068, 2931, 2849, 1616, 1578, 1441, 1282, 1221, 1123 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{22}NO_3S$ $(M+H)^+$: calcd. 344.1320, found 344.1313.

***N*-[3-(Cyclohex-2-enyloxy)-4,5-dimethoxybenzoyl]-*S*-methyl-*S*-phenylsulfoximine (51t):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-(cyclohex-2-en-1-yloxy)-4,5-dimethoxybenzoic acid (0.98 g, 3.54 mmol) afforded **51t** (0.97 g) in 72% yield as colorless viscous liquid. R_f = 0.29 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.6 Hz, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.62 (t, J = 7.8 Hz, 2H), 7.51 (bd, J = 1.6 Hz, 1H), 7.43 (bd, J = 1.6 Hz, 1H), 6.01–5.87 (m, 2H), 4.85 (bs, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.46 (s, 3H), 2.25–1.80 (m, 5H), 1.70–1.55 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 152.9, 150.8, 143.3, 139.0, 133.7, 131.9, 130.5, 129.6 (2C), 127.0 (2C), 126.4, 110.7, 106.6, 72.6, 60.7, 56.1, 44.2, 28.4, 25.0, 18.9; IR (Neat) ν_{max} 2926, 1621, 1572, 1419, 1232, 1106 cm^{-1}; **HRMS (ESI)** for $C_{22}H_{25}NNaO_5S$ $(M+Na)^+$: calcd. 438.1351, found 438.1348.

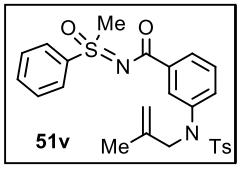
***N*-[3-Methoxy-5-(4-methyl-*N*-(2-methylallyl)phenylsulfonamido)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51u):**



51u

Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-methoxy-5-(4-methyl-N-(2-methylallyl)phenylsulfonamido)benzoic acid (1.33 g, 3.54 mmol) afforded **51u** (1.23 g) in 75% yield as pale yellow viscous liquid. R_f = 0.15 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.6 Hz, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.67–7.57 (m, 3H), 7.48 (d, J = 8.0 Hz, 2H), 7.40 (s, 1H), 7.23 (d, J = 8.0 Hz, 2H), 6.85 (bt, J = 2.0 Hz, 1H), 4.76 (s, 1H), 4.75 (s, 1H), 4.08 (s, 2H), 3.78 (s, 3H), 3.43 (s, 3H), 2.37 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 159.2, 143.4, 139.7, 139.4, 138.5, 137.0, 134.9, 133.8, 129.5 (2C), 129.3 (2C), 127.5 (2C), 126.9 (2C), 121.0, 118.8, 115.1, 113.3, 56.4, 55.4, 44.1, 21.4, 19.8; IR (Neat) ν_{max} 3095, 2942, 1632, 1594, 1462, 1336, 1167, 1090 cm^{-1}; **HRMS (ESI)** for $C_{26}H_{28}N_2NaO_5S_2$ $(M+Na)^+$: calcd. 535.1337, found 535.1335.

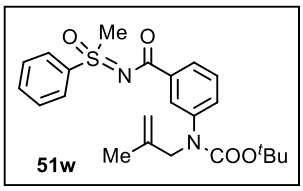
***N*-[3-(4-Methyl-*N*-(2-methylallyl)phenylsulfonamido)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51v):**



51v

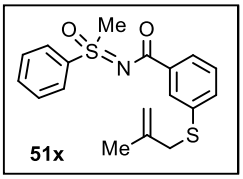
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-(4-methyl-*N*-(2-methylallyl)phenylsulfonamido)benzoic acid (1.22 g, 3.54 mmol) afforded **51v** (1.08 g) in 70% yield as colorless solid. m.p. = 145–149 ^{o}C; R_f = 0.26 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.6 Hz, 1H), 8.02 (d, J = 7.6 Hz, 2H), 7.77 (s, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.62 (t, J = 7.6 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.34 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 4.74 (s, 1H), 4.72 (s, 1H), 4.09 (s, 2H), 3.44 (s, 3H), 2.38 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 143.5, 139.4, 138.8, 138.7, 136.3, 134.9, 133.8, 132.5, 129.6 (2C), 129.4 (2C), 128.60, 128.56, 128.3, 127.5 (2C), 127.0 (2C), 115.3, 56.4, 44.3, 21.5, 19.8; IR (KBr) ν_{max} 3007, 2964, 2914, 1626, 1582, 1445, 1352, 1164, 1089, 870, 684 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{26}N_2NaO_4S_2$ $(M+Na)^+$: calcd. 505.1232, found 505.1233.

***N*-[3-(*tert*-Butoxycarbonyl(2-methylallyl)amino)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51w):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-((*tert*-butoxycarbonyl)(2-methylallyl)amino)benzoic acid (1.03 g, 3.54 mmol) afforded **51w** (0.991 g) in 72% yield as colorless solid. m.p. = 112–115 ^{o}C; R_f = 0.42 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–8.00 (m, 3H), 7.96 (d, J = 7.6 Hz, 1H), 7.67 (bt, J = 7.2 Hz, 1H), 7.59 (bt, J = 7.4 Hz, 2H), 7.39 (bd, J = 7.6 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 4.83 (s, 1H), 4.80 (s, 1H), 4.18 (s, 2H), 3.44 (s, 3H), 1.73 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 154.4, 142.6, 141.3, 138.8, 136.1, 133.8, 129.8, 129.6 (2C), 128.0, 127.1 (2C), 126.6, 126.5, 111.4, 80.4, 55.5, 44.2, 28.1 (3C), 20.1; IR (Neat) ν_{max} 3068, 2975, 2926, 1698, 1621, 1578, 1484, 1369, 1150 cm^{-1}; **HRMS (ESI)** for $C_{23}H_{28}N_2NaO_4S$ $(M+Na)^+$: calcd. 451.1667, found 451.1661.

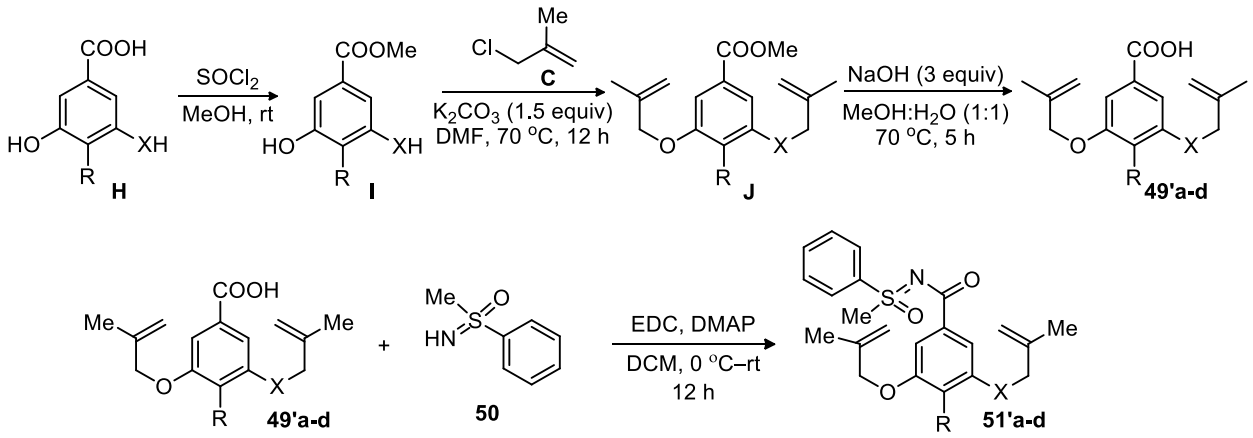
***N*-[3-(2-methylallylthio)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51x):**



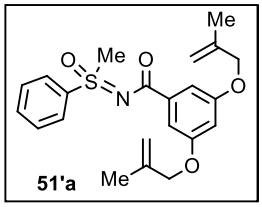
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50,** 0.5 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-((2-methylallyl)thio)benzoic acid (0.74 g, 3.54 mmol) afforded **51x** (0.74 g) in 67% yield as yellow viscous liquid. R_f = 0.44 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (bs, 1H), 8.03 (d, J = 7.6 Hz, 2H), 7.96 (d, J = 7.6 Hz, 1H), 7.68 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.6 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 4.84 (s, 1H), 4.81 (s, 1H), 3.54 (s, 2H), 3.45 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 140.4, 138.7, 136.5, 136.0, 133.8, 133.2, 130.3, 129.6 (2C), 128.3, 127.1, 127.0 (2C), 114.2, 44.3, 41.5, 21.1; IR (KBr) ν_{max} 3063, 3013, 2931, 2854, 1726, 1627, 1561, 1441, 1397, 1282, 1260, 1139 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{20}NO_2S_2$ $(M+H)^+$: calcd. 343.0935, found 343.0934.

Preparation of *N*-Aroyl Sulfoximines (51′):

Following the synthetic procedure of GP-1 and GP-2, corresponding N-aroyl sulfoximines (**51′a**–**d**) were prepared in overall good to excellent yield.

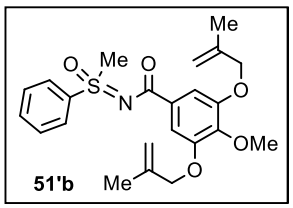


***N*-[3,5-Bis((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51′a):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50,** 0.5 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.856 g, 7.08 mmol) and 3,5-bis((2-methylallyl)oxy)benzoic acid (0.93 g, 3.54 mmol) afforded **51′a** (1.29 g) in 91% yield as colorless solid. m.p. = 85–88 °C; R_f = 0.36 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.07 (bd, J = 7.2 Hz, 2H), 7.71 (bt, J = 7.4 Hz, 1H), 7.63 (bt, J = 7.4 Hz, 2H), 7.39–7.35 (m, 2H), 6.73–6.67 (m, 1H), 5.12 (s, 2H), 5.01 (s, 2H), 4.47 (s, 4H), 3.47 (s, 3H), 1.84 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.8, 159.5 (2C), 140.6 (2C), 138.9, 137.5, 133.7, 129.6 (2C), 127.1 (2C), 112.7 (2C), 108.0 (2C), 106.3, 71.8 (2C), 44.3, 19.4 (2C). IR (Neat) ν_{max} 3057, 3030, 2926, 1583, 1446, 1353, 1304, 1210, 1167 cm^{-1}; **HRMS (ESI)** for $C_{22}H_{26}NO_4S$ $(M+H)^+$: calcd. 400.1583, found 400.1577.

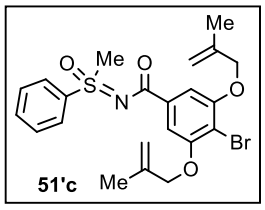
***N*-[4-Methoxy-3,5-bis((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51′b):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.5 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.856 g, 7.08 mmol) and 4-methoxy-3,5-bis((2-

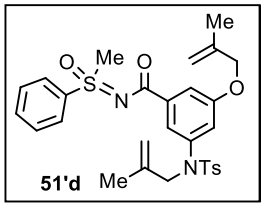
methylallyl)oxy)benzoic acid (1.03 g, 3.54 mmol) afforded **51'b** (1.23 g) in 82% yield as colorless solid. m.p. = 107–110 °C; R_f = 0.35 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.07 (d, J = 8.0 Hz, 2H), 7.72 (bt, J = 7.6 Hz, 1H), 7.64 (t, J = 7.8 Hz, 2H), 7.46 (s, 2H), 5.15 (s, 2H), 5.01 (s, 2H), 4.55 (s, 4H), 3.95 (s, 3H), 3.49 (s, 3H), 1.87 (s, 6H); ^{13}C NMR (101 MHz,$CDCl_3$) δ173.5, 151.9 (2C), 142.5, 140.7 (2C), 139.0, 133.8, 130.5, 129.6 (2C), 127.1 (2C), 112.6 (2C), 108.5 (2C), 72.6 (2C), 60.8, 44.2, 19.4 (2C). IR (Neat) ν_{max} 2920, 2849, 1627, 1583, 1424, 1336, 1221 cm^{-1}; **HRMS (ESI)** for $C_{23}H_{28}NO_5S$ $(M+H)^+$: calcd. 430.1688, found 430.1683.

***N*-[4-Bromo-3,5-bis((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51'c):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**1**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.856 g, 7.08 mmol) and 4-bromo-3,5-bis((2-methylallyl)oxy)benzoic acid (1.2 g, 3.54 mmol) afforded **51'c** (1.20 g) in 71% yield as colorless solid. m.p. = 118–121 °C; R_f = 0.3 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.04 (d, J = 7.2 Hz, 2H), 7.71 (bt, J = 7.4 Hz, 1H), 7.63 (bt, J = 7.4 Hz, 2H), 7.38 (s, 2H), 5.19 (s, 2H), 5.01 (s, 2H), 4.55 (s, 4H), 3.47 (s, 3H), 1.86 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.3, 155.8 (2C), 140.2 (2C), 138.9, 135.5, 133.9, 129.7 (2C), 127.1 (2C), 112.9 (2C), 107.0, 106.8 (2C), 72.7 (2C), 44.3, 19.4 (2C); IR (KBr) ν_{max} 3090, 3013, 2931, 1621, 1572, 1419, 1320, 1249, 1112 cm^{-1}; **HRMS (ESI)** for $C_{22}H_{25}BrNO_4S$ $(M+H)^+$: calcd. 478.0688, found 478.0682.

***N*-[3-(4-Methyl-N-(2-methylallyl)phenylsulfonamido)-5-((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (51'd):**



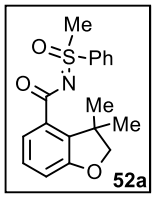
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**50**, 0.50 g, 3.22 mmol), EDC.HCl (1.22 g, 6.44 mmol), DMAP (0.856 g, 7.08 mmol) and 3-(4-methyl-N-(2-methylallyl)phenylsulfonamido)-5-((2-methylallyl)oxy)benzoic acid (1.17 g, 3.54 mmol) afforded **51'd** (1.31 g) in 66% yield as pale yellow high viscous liquid. R_f = 0.24 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.04 (d, J = 8.0 Hz,

2H), 7.73 (t, J = 7.4 Hz, 1H), 7.69–7.61 (m, 3H), 7.51 (d, J = 8.4 Hz, 2H), 7.42 (bt, J = 1.6 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 6.88 (bt, J = 2.0 Hz, 1H), 5.08 (s, 1H), 5.00 (s, 1H), 4.78 (s, 1H), 4.76 (s, 1H), 4.43 (s, 2H), 4.10 (s, 2H), 3.46 (s, 3H), 2.41 (s, 3H), 1.82 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.0, 158.5, 143.5, 140.4, 139.8, 139.5, 138.7, 137.0, 135.0, 133.8, 129.7 (2C), 129.4 (2C), 127.6 (2C), 127.1 (2C), 121.2, 119.5, 115.2, 114.7, 113.0, 71.9, 56.5, 44.3, 21.5, 19.9, 19.3; IR (Neat) ν_{max} 3073, 2920, 1627, 1594, 1446, 1347, 1227, 1172 cm^{-1}; **HRMS (ESI)** for $C_{29}H_{33}N_2O_5S_2$ $(M+H)^+$: calcd. 553.1831, found 553.1825.

2.7.3.3. General Procedure for Hydroarylation of O-Tethered Compounds (51) (GP-3):

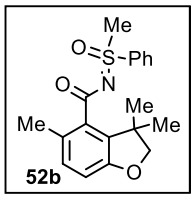
The hydroarylation reactions were conducted in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with (**51**, 0.5 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (6.0 mg, 2.0 mol %), and $Cu(OAc)_2 \cdot H_2O$ (100 mg, 0.5 mmol). Subsequently, the additive $AgSbF_6$ (35 mg, 0.1 mmol) was introduced to the flask in a glove box. 1,2-dichloroethene (DCE) (2.0 mL) was added to the mixture and the resulting mixture was stirred at room temparature for 8–16 h. The reaction mixture was filtered through a small plug of Celite and washed with dichloromethane (3 × 5.0 mL). The solvents were evaporated under the reduced pressure and the crude material was purified using column chromatography on silica gel.

***N*-[3,3-Dimethyl-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52a):**



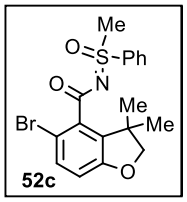
52a (160 mg, 97%) as colourless solid. m.p. = 48–52 °C; R_f = 0.44 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.04 (d, J = 8.0 Hz, 2H), 7.67 (bt, J = 7.4 Hz, 1H), 7.59 (bt, J = 7.8 Hz, 2H), 7.54 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 4.15 (d, J = 8.4 Hz, 1H), 4.13 (d, J = 8.0 Hz, 1H), 3.40 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ175.4, 160.4, 138.7, 135.4, 134.1, 133.7, 129.5 (2C), 127.5, 127.1 (2C), 122.7, 112.6, 85.3, 44.3, 43.3, 25.5, 25.2; IR (Neat) ν_{max} 2953, 2926, 1627, 1435, 1265, 1227 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{19}NNaO_3S$ $(M+Na)^+$: calcd. 352.0983, found 352.0978.

***N*-[3,3,5-Trimethyl-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52b):**



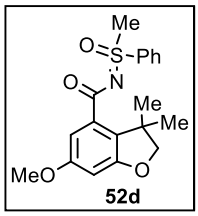
52b (167 mg, 97%) as colorless solid. m.p. = 99–102 °C; R_f = 0.50 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.6 Hz, 2H), 7.70 (bt, J = 7.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 2H), 6.92 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 4.14 (d, J = 8.4 Hz, 1H), 4.12 (d, J = 8.0 Hz, 1H), 3.48 (s, 3H), 2.33 (s, 3H), 1.46 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ177.7, 157.8, 138.5, 135.6, 134.0, 131.5, 129.8, 129.6 (2C), 127.1 (2C), 125.5, 109.8, 84.9, 44.2, 42.9, 26.0, 25.8, 18.6; IR (Neat) ν_{max} 2953, 2920, 1626, 1451, 1276, 1215 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{21}NNaO_3S$ $(M+Na)^+$: calcd. 366.1140, found 366.1142.

***N*-[5-Bromo-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52c):**



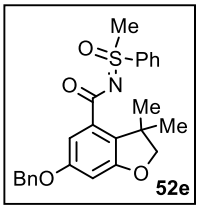
52c (196 mg, 96%) as colourless solid. m.p. = 128–132 °C; R_f = 0.49 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.16 (d, J = 8.0 Hz, 2H), 7.71 (bt, J = 7.4 Hz, 1H), 7.63 (t, J = 7.8 Hz, 2H), 7.29 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 4.20 (d, J = 8.4 Hz, 1H), 4.16 (d, J = 8.0 Hz , 1H), 3.56 (s, 3H), 1.48 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ175.1, 159.1, 138.0, 136.8, 134.1, 134.0, 131.9, 129.6 (2C), 127.3 (2C), 111.4, 108.7, 85.2, 43.9, 43.3, 26.3, 25.4; IR (Neat) ν_{max} 2920, 1626, 1424, 1287, 1221 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{18}BrNNaO_3S$ $(M+Na)^+$: calcd. 430.0089, found 430.0091.

***N*-[6-Methoxy-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52d):**



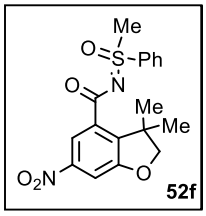
52d (171 mg, 95%) as colourless viscous liquid; R_f = 0.42 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.6 Hz, 2H), 7.71 (bt, J = 7.2 Hz, 1H), 7.63 (t, J = 7.6 Hz, 2H), 7.11 (d, J = 2.0 Hz, 1H), 6.51 (d, J = 2.0 Hz, 1H), 4.19 (d, J = 8.0 Hz, 1H), 4.17 (d, J = 8.8 Hz, 1H), 3.82 (s, 3H), 3.43 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ175.2, 161.7, 159.4, 138.7, 134.1, 133.8, 129.6 (2C), 127.9, 127.1 (2C), 108.2, 99.2, 86.1, 55.6, 44.4, 42.8, 25.8, 25.5; IR (Neat) ν_{max} 2997, 2953, 2926, 1616, 1309, 1221, 1101 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{21}NNaO_4S$ $(M+Na)^+$: calcd. 382.1089, found 382.1092.

***N*-[6-(Benzoyloxy)-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52e):**



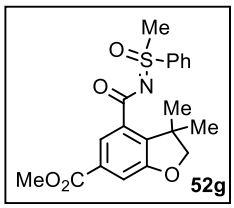
52e (204 mg, 94%) as colourless solid. m.p.= 155–158 °C; R_f = 0.53 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.03 (d, J = 7.2 Hz, 2H), 7.70 (bt, J = 7.4 Hz, 1H), 7.62 (t, J = 7.8 Hz, 2H), 7.47–7.30 (m, 5H), 7.20 (d, J = 2.4 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 5.06 (s, 2H), 4.18 (d, J = 8.0 Hz, 1H), 4.13 (d, J = 8.0 Hz, 1H), 3.40 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ175.2, 161.7, 158.7, 136.9, 134.2, 133.8, 129.7 (2C), 128.6 (2C), 128.2, 128.0, 127.5 (2C), 127.2 (2C), 109.2, 100.1, 86.1, 70.4, 44.5, 42.9, 25.8, 25.6; IR (KBr) ν_{max} 2920, 1605, 1583, 1315, 1216 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{26}NO_4S$ $(M+H)^+$: calcd. 436.1582, found 436.1577.

***N*-[3,3-Dimethyl-6-nitro-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52f):**



52f (178 mg, 95%) as pale yellow viscous liquid. R_f = 0.40 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.39 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 2H), 7.72 (bt, J = 7.4 Hz, 1H), 7.68–7.60 (m, 3H), 4.27 (d, J = 8.4 Hz, 1H), 4.24 (d, J = 8.4 Hz, 1H), 3.45 (s, 3H), 1.49 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ173.4, 161.4, 147.7, 143.2, 138.2, 134.6, 134.1, 129.8 (2C), 127.1 (2C), 118.3, 107.0, 86.3, 44.5, 43.6, 25.3, 25.0; IR (KBr) ν_{max} 2953, 2926, 1632, 1528, 1419, 1336, 1287, 1221 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{18}N_2NaO_5S$ $(M+Na)^+$: calcd. 397.0834, found 397.0837.

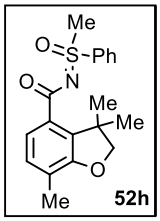
***N*-[6-(Methoxycarbonyl)-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52g):**



52g (180 mg, 93%) as colorless solid. m.p.= 169–173 °C; R_f = 0.46 (6:4 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.21 (d, J = 1.2 Hz, 1H), 8.06 (d, J = 7.6 Hz, 2H), 7.70 (bt, J = 7.4 Hz, 1H), 7.63 (t, J = 7.6 Hz, 2H), 7.49 (d, J = 1.6 Hz, 1H), 4.21 (d, J = 8.4 Hz, 1H), 4.18 (d, J = 8.0 Hz, 1H), 3.91 (s, 3H), 3.42 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 166.4, 160.7, 140.8, 138.4, 134.2, 133.8, 129.9, 129.7 (2C), 127.1 (2C), 124.4, 112.9, 85.6, 52.1,

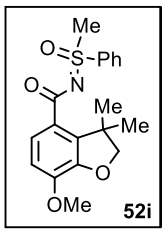
44.5, 43.5, 25.3, 25.0; IR (KBr) ν_{max} 2958, 2925, 1709, 1643, 1407, 1336, 1303, 1237, 991 cm^{-1}; **HRMS (ESI)** for $C_{20}H_{22}NO_5S$ $(M+H)^+$: calcd. 388.1218, found 388.1218.

_N_-[3,3,7-Trimethyl-2,3-dihydrobenzofuran-4-carboxyl]-_S_-methyl-_S_-phenylsulfoximine (52h):



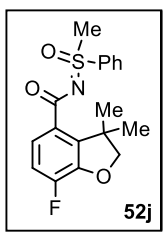
52h (158 mg, 92%) as colorless viscous liquid. R_f = 0.36 (7:3 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.2 Hz, 2H), 7.66 (bt, J = 7.2 Hz, 1H), 7.59 (bt, J = 7.6 Hz, 2H), 7.52 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 4.17 (d, J = 8.4 Hz, 1H), 4.14 (d, J = 8.4 Hz, 1H), 3.40 (s, 3H), 2.23 (s, 3H), 1.48 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 158.5, 138.9, 134.8, 133.6, 131.5, 129.5 (2C), 128.7, 127.1 (2C), 123.5, 123.0, 85.2, 44.3, 43.6, 25.6, 25.3, 15.4; IR (Neat) ν_{max} 2947, 2920, 1632, 1402, 1265. 1215 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{21}NNaO_3S$ $(M+Na)^+$: calcd. 366.1140, found 366.1135.

_N_-[7-Methoxy-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxyl]-_S_-methyl-_S_-phenylsulfoximine (52i):



52i (166 mg, 92%) as colorless solid. m.p.= 49–52 °C; R_f = 0.36 (3:2 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 2H), 7.67 (d, J = 8.4 Hz, 1H), 7.61 (bt, J = 7.4 Hz, 1H), 7.54 (t, J = 7.4 Hz, 2H), 6.71 (d, J = 8.4 Hz, 1H), 4.19 (d, J = 8.4 Hz, 1H), 4.17 (d, J = 8.0 Hz, 1H), 3.85 (s, 3H), 3.35 (s, 3H), 1.45 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 148.1, 147.1, 138.7, 136.8, 133.5, 129.4 (2C), 126.9 (2C), 125.9, 125.0, 109.5, 85.9, 55.6, 44.2, 44.0, 25.4, 25.1; IR (Neat) ν_{max} 2947, 2926, 1627, 1430, 1265, 1221 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{22}NO_4S$ $(M+H)^+$: calcd. 360.1269, found 360.1264.

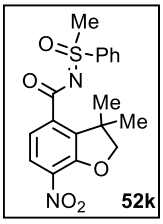
_N_-[7-Fluoro-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxyl]-_S_-methyl-_S_-phenylsulfoximine (52j):



52j (172 mg, 99%) as colourless solid. m.p.= 112–114 °C; R_f = 0.43 (7:3 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 2H), 7.70 (bt, J = 7.4 Hz, 1H), 7.66–7.56 (m, 3H), 6.94 (t, J = 8.6 Hz, 1H), 4.28 (d, J = 8.0 Hz, 1H), 4.25 (d, J = 8.4 Hz, 1H), 3.42 (s, 3H), 1.50 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 149.6 (d, J = 251 Hz), 147.0 (d, J = 11 Hz), 139.8, 138.8,

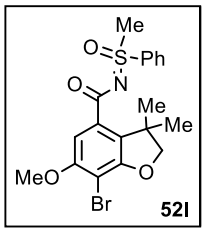
133.8 (2C), 129.7 (2C), 127.1 (2C), 124.3 (d, J = 6.1 Hz), 114.6 (d, J = 17 Hz), 86.7, 44.4 (2C), 25.4, 25.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –134.25; IR (Neat) ν_{max} 3024, 2953, 2936, 1621, 1424, 1287, 1216 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{19}FNO_3S$ $(M+H)^+$: calcd. 348.1069, found 348.1064.

_N_-[3,3-Dimethyl-7-nitro-2,3-dihydrobenzofuran-4-carboxyl]-_S_-methyl-_S_-phenylsulfoximine (52k):



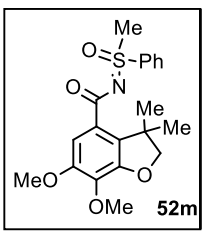
52k (178 mg, 95%) as yellow solid. m.p. = 53–56 °C; R_f = 0.33 (6:4 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.6 Hz, 2H), 7.94 (d, J = 8.8 Hz, 1H), 7.73 (t, J = 7.2 Hz, 1H), 7.65 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 8.8 Hz, 1H), 4.43 (d, J = 8.4 Hz, 1H), 4.40 (d, J = 8.4 Hz, 1H), 3.45 (s, 3H), 1.51 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 155.4, 139.9, 139.7, 138.0, 134.2, 133.8, 129.8 (2C), 127.0 (2C), 123.6, 121.9, 87.3, 44.3, 43.0, 25.4, 25.1; IR (Neat) ν_{max} 3024, 2953, 2925, 1632, 1610, 1522, 1276, 1221, 1040,739 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{18}N_2NaO_5S$ $(M+Na)^+$: calcd. 397.0834, found 397.0836.

_N_-[7-Bromo-6-methoxy-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxyl]-_S_-methyl-_S_-phenylsulfoximine (52l):



52l (206 mg, 94%) as colourless viscous liquid. R_f = 0.34 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.6 Hz, 2H), 7.73 (t, J = 7.4 Hz, 1H), 7.65 (t, J = 7.6 Hz, 2H), 7.12 (s, 1H), 4.31 (d, J = 8.4 Hz, 1H), 4.28 (d, J = 8.4 Hz, 1H) 3.94 (s, 3H), 3.46 (s, 3H), 1.49 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 158.9, 155.5, 138.6, 133.9, 132.6, 129.7 (2C), 129.3, 127.1 (2C), 105.8, 96.6, 86.3, 56.6, 44.4, 44.2, 25.9, 25.4; IR (KBr) ν_{max} 2936, 1632, 1600, 1336, 1254, 1221 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{21}BrNO_4S$ $(M+H)^+$: calcd. 438.0374, found 438.0369.

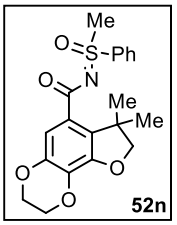
_N_-[6,7-Dimethoxy-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxyl]-_S_-methyl-_S_-phenylsulfoximine (52m):



52m (189 mg, 97%) as colourless solid. m.p. = 134–137 °C; R_f = 0.21 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.2 Hz, 2H), 7.69 (bt, J = 7.4 Hz, 1H), 7.61 (t, J = 7.6 Hz, 2H), 7.18 (s, 1H), 4.21 (d, J = 8.0

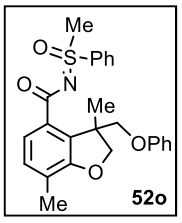
Hz, 1H), 4.19 (d, J = 8.0 Hz, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.42 (s, 3H), 1.46 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.7, 152.3, 151.1, 138.8, 136.2, 133.7, 131.1, 129.6 (2C), 127.3, 127.1 (2C), 107.2, 86.5, 60.6, 56.4, 44.4, 43.4, 25.6, 25.2; IR (KBr) ν_{max} 2958, 2931, 1621, 1506, 1402, 1227, 1106 cm^{-1}; **HRMS (ESI)** for $C_{20}H_{23}NNaO_5S$ $(M+Na)^+$: calcd. 412.1195, found 412.1189.

***N*-[7,7-Dimethyl-2,3,7,8-tetrahydrobenzofuro[6,7-*b*][1,4]dioxine-6-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52n):**



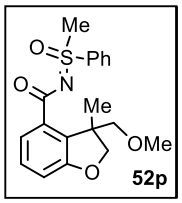
52n (190 mg, 98%) as colorless solid. m.p. = 80–83 ^{o}C; R_f = 0.24 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.03 (d, J = 8.0 Hz, 2H), 7.68 (bt, J = 7.6 Hz, 1H), 7.60 (t, J = 7.8 Hz, 2H), 7.28 (s, 1H), 4.36–4.30 (m, 2H) 4.31–4.26 (m, 2H), 4.26–4.23 (m, 2H), 3.39 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.3, 148.4, 142.7, 139.0, 133.7, 132.2, 130.1, 129.6 (2C), 127.2 (2C), 125.3, 112.6, 87.1, 64.9, 64.4, 44.5, 43.9, 25.8, 25.5; IR (KBr) ν_{max} 2931, 2876, 1627, 1578, 1512, 1309, 1216 cm^{-1}; **HRMS (ESI)** for $C_{20}H_{21}NNaO_5S$ $(M+Na)^+$: calcd. 410.1038, found 410.1033.

***N*-[3-Methyl-3-(phenoxymethyl)-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52o):**



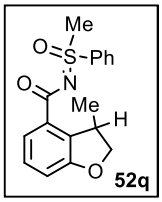
52o (140 mg, 64%) as colourless viscous liquid. R_f = 0.39 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$)δ8.03–7.93 (m, 2H), 7.70–7.53 (m, 2.6H), 7.49–7.43 (m, 1.5H), 7.24–7.15 (m, 2H), [7.05 (dd, J = 7.6, 0.8 Hz) & 7.04 (dd, J = 7.8, 0.6 Hz), 1H], 6.93–6.82 (m, 1.5H), 6.80–6.73 (m, 1.5H), [4.73 (d, J = 8.8 Hz, 0.25H) & 4.70 (d, J = 8.8 Hz, 0.75H)], [4.45 (d, J = 8.8 Hz, 0.25H) & 4.36 (d, J = 8.8 Hz, 0.75H)], 4.29–4.11 (m, 2H), [3.35 (s, 2.2H) & 3.28 (s, 0.8H)], 2.26 (s, 3H), [1.58 (s, 2.2H) & 1.47 (s, 0.8H)]; ^{13}C NMR (101 MHz, $CDCl_3$) δ[175.5, 175.2], [159.6, 159.5], [159.3, 159.2], [138.83, 138.76], [133.7, 133.6], [132.2, 131.9], [130.7, 130.5], [129.64, 129.57] (2C), 129.4, 129.2 (2C), [127.15, 127.06] (2C), [124.2, 124.0], [123.4, 123.2], [120.39, 120.36], 114.7 (2C), [81.0, 80.8], 71.2, [48.4, 48.3], [44.5, 44.2], [21.2, 20.8], [15.54, 15.51]; IR (Neat) ν_{max} 3303, 1632, 1567, 1413, 1265, 1221 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{25}NNaO_4S$ $(M+Na)^+$: calcd. 458.1402, found 458.1400.

***N*-[3-(Methoxymethyl)-3-methyl-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52p):**



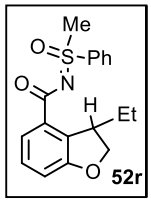
52p (146 mg, 81%) as colourless viscous liquid. R_f = 0.39 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 2H), 7.71 (t, J = 7.0 Hz, 1H), 7.68–7.58 (m, 3H), 7.19 (t, J = 7.8 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 4.61 (d, J = 8.4 Hz 1H), 4.10 (d, J = 8.4 Hz, 1H), 3.71 (d, J = 8.4 Hz, 1H), 3.66 (d, J = 8.8 Hz, 1H), 3.44 (s, 3H), 3.23 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ175.4, 161.2, 138.7, 134.5, 133.8, 131.8, 129.6 (2C), 128.0, 127.1 (2C), 122.8, 112.9, 81.3, 76.6, 59.0, 48.1, 44.4, 21.1; IR (Neat) ν_{max} 3063, 2926, 2843, 2361, 1632, 1578, 1473, 1435, 1271, 1216, 1106 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{21}NNaO_4S$ $(M+Na)^+$: calcd. 382.1089, found 382.1092.

***N*-[3-Methyl-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52q):**



52q (112 mg, 71%) as colourless solid. m.p. = 99–103 ^{o}C; R_f = 0.33 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.6 Hz, 2H), 7.72 (t, J = 8.0 Hz, 2H), 7.64 (t, J = 7.4 Hz, 2H), 7.20 (t, J = 7.8 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 4.54 (t, J = 8.4 Hz, 1H), 4.27 (dd, J = 8.4, 2.4 Hz 1H), 4.05 (bt, J = 6.4 Hz, 1H), 3.46 (s, 3H), 1.32 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 160.0, 138.8, 134.5, 133.8, 132.3, 129.7 (2C), 127.6, 127.1 (2C), 122.7, 113.0, 78.8, 44.5, 37.1, 20.6; IR (KBr) ν_{max} 3030, 2969, 2931, 2882, 1621, 1572, 1446, 1287, 1145 cm^{-1}; **HRMS (ESI)** for $C_{17}H_{17}NNaO_3S$ $(M+Na)^+$: calcd. 338.0827, found 338.08221.

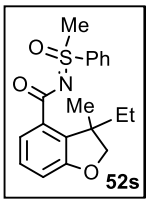
***N*-[3-Ethyl-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52r):**



52r (102 mg, 62%) as colourless viscous liquid. R_f = 0.57 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.02 (d, J = 8.0 Hz, 2H), 7.72–7.63 (m, 2H), 7.59 (t, J = 7.8 Hz, 2H), 7.15 (dt, J = 8.0, 1.3 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 4.47–4.36 (m, 2H), 3.93–3.85 (m, 1H), 3.42 (s, 3H), 1.83–1.66 (m, 1H), 1.60–1.42 (m, 1H), 0.87–0.77 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ [174.3, 174.2], [160.31, 160.29], [138.8, 138.7], [133.73, 133.69], [132.8, 132.7], [132.6, 132.5], [129.6, 129.5] (2C), 127.6, [127.1, 127.0] (2C), [122.6, 122.5], [112.72, 112.67], 75.8, [44.4,

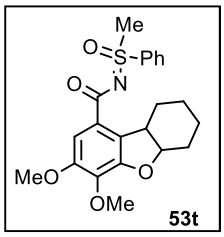
44.3], [43.52, 43.49], [27.03, 26.95], [11.12, 11.08]; IR (Neat) ν_{max} 3441, 2969, 2931, 1672, 1572, 1446, 1276, 1227 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{20}NO_3S$ $(M+H)^+$: calcd. 330.1164, found 330.1160.

***N*-[3-Ethyl-3-methyl-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52s):**



52s (117 mg, 68%) as colourless viscous liquid. R_f = 0.49 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.6 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.63–7.51 (m, 3H), 7.14 (t, J = 7.8 Hz, 1H), 6.86 (dd, J = 8.0, 0.8 Hz, 1H), 4.32 (d, J = 8.4 Hz, 1H), 4.06 (d, J = 8.4 Hz, 1H), 3.39 (s, 3H), 2.16–2.03 (m, 1H), 1.77–1.64 (m, 1H), 1.34 (s, 3H), 0.74 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 160.9, 138.6, 134.5, 133.8, 133.7, 129.6 (2C), 127.6, 127.1 (2C), 122.6, 112.4, 82.3, 47.2, 44.3, 30.6, 24.2, 9.2; IR (Neat) ν_{max} 3446, 3063, 2969, 1632, 1578, 1479, 1441, 1287, 1216, 1095 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{22}NO_3S$ $(M+H)^+$: calcd. 344.1320, found 344.1320.

***N*-[3,4-Dimethoxy-5a,6,7,8,9,9a-hexahydrodibenzo[b,d]furan-1-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (52t):**



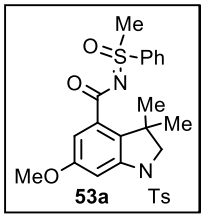
52t (100 mg, 42%) as colourless viscous liquid. R_f = 0.29 (3:2 hexane/EtOAc).The product **52t** and the starting material **51t** were non-seperable and isolated as a mixture of **52t** and **51t** (1:1). The yield of **52t** was calculated based on ^{1}H NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–8.00 (m, 1.8H), 7.69 (t, J = 7.4 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1.8H), 7.50 (d, J = 2Hz, 0.3H), 7.42 (d, J = 1.6 Hz, 0.3H), 7.27 (d, J = 3.2 Hz, 0.5H), 5.95–5.89 (m, 0.6H), 4.84 (bs, 0.3H), 4.58 (bs, 0.5H), 4.01 (s, 1.5H), 3.91–3.85 (m, 3.8H), 3.67–3.57 (m, 0.6H), 3.45 (s, 0.8H), 3.44 (s, 0.5H), 3.42 (s, 1.2H), 2.34 (d, J = 14.4 Hz, 0.5H), 2.23–2.07 (m, 0.8H), 2.01–1.47 (m, 4.9H), 1.18–0.95 (s, 1.6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.64, 173.59, 152.9, 151.0, 155.9, 143.4, 139.1, 137.4, 133.7, 132.6, 132.0, 130.6, 129.7, 127.1, 127.04, 127.01, 126.5, 124.8, 110.9, 106.7, 106.4, 84.1, 72.7, 60.8, 60.5, 56.4, 56.2, 44.5, 44.3, 41.2, 28.7, 28.6, 28.5, 27.4, 25.1, 23.2, 20.5, 19.0; IR (Neat) ν_{max} 3013, 2926, 2854, 1720,

1621, 1578 1501, 1413, 1287, 1227, 1117, 1090 cm^{-1}; **HRMS (ESI)** for $C_{22}H_{26}NO_5S$ $(M+H)^+$: calcd. 416.1532, found 416.1537.

2.7.3.4. General Procedure for Hydroarylation of N/S-Tethered Compounds (51u–x) (GP-4):

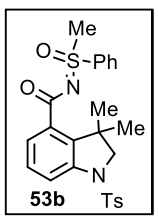
The hydroarylation reaction was conducted in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with (**51u–x,** 0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (12 mg, 4.0 mol %), and $Cu(OAc)_2.H_2O$ (100 mg, 0.5 mmol). Subsequently, the additive $AgSbF_6$ (35 mg, 0.1 mmol) was introduced to the flask in a glove box. 1,2-Dichloroethene (DCE) (2.0 mL) was added to the mixture and the resulting mixture was stirred at 65 °C for 8–16 h. The reaction mixture was filtered through a small plug of Celite and washed with dichloromethane (3 × 5.0 mL). The solvents were evaporated under the reduced pressure and the crude material was purified using column chromatography on silica gel.

***N*-[6-Methoxy-3,3-dimethyl-1-tosylindoline-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (53a):**



53a (210 mg, 82%) as yellow viscous liquid; R_f = 0.15 (3:2 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.6 Hz, 2H), 7.74–7.65 (m, 3H), 7.60 (t, J = 7.6 Hz, 2H), 7.37 (d, J = 2.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 2.4 Hz, 1H), 3.85 (s, 3H), 3.58 (d, J = 9.6 Hz, 1H), 3.54 (d, J = 9.6 Hz, 1H), 3.37 (s, 3H), 2.37 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 159.2, 144.2, 143.3, 138.4, 135.1, 134.0, 133.8, 130.8, 129.72 (2C), 129.67 (2C), 127.4 (2C), 127.1 (2C), 110.4, 102.9, 65.4, 55.8, 44.4, 41.0, 26.4, 26.2, 21.5; IR (Neat) ν_{max} 2969, 2936, 2843, 1638, 1605, 1517, 1473, 1419, 1347, 1227, 1167 cm^{-1}; **HRMS (ESI)** for $C_{26}H_{28}N_2NaO_5S_2$ $(M+Na)^+$: calcd. 535.1337, found 535.1339.

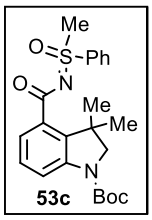
***N*-[3,3-Dimethyl-1-tosylindoline-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (53b):**



53b (207 mg, 86%) as yellow viscous liquid. R_f = 0.33 (7:3 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ8.01(d, J = 7.6 Hz, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.71–7.67 (m, 3H), 7.60 (t, J = 8.0 Hz, 2H), 7.46 (d, J = 7.6 Hz, 1H), 7.25–7.18

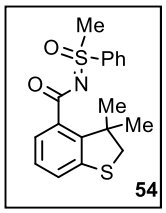
(m, 3H), 3.58 (d, J = 9.6 Hz, 1H), 3.54 (d, J = 9.6 Hz, 1H), 3.38 (s, 3H), 2.36 (s, 3H), 1.30 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 144.1, 142.0, 138.4, 134.8, 133.9, 133.7, 129.7 (2C), 129.6 (2C), 127.6, 127.4, 127.3 (2C), 127.1 (2C), 124.8, 116.4, 64.9, 44.4, 41.6, 26.1, 25.9, 21.5; IR (Neat) ν_{max} 3062, 2953, 2925, 2865, 1632, 1577, 1440, 1352, 1281, 1226, 1166 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{27}N_2O_4S_2$ $(M+H)^+$: calcd. 483.1412, found 483.1412.

***N*-[1-(tert-Butoxycarbonyl)-3,3-dimethylindoline-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (53c):**



53c (116 mg, 54%) as yellow viscous liquid. R_f = 0.56 (6:4 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.6 Hz, 2H), 7.67 (bt, J = 7.4 Hz, 1H), 7.59 (t, J = 7.4 Hz, 2H), 7.46 (bd, J = 7.8 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 3.64 (d, J = 10.4 Hz, 1H), 3.61 (d, J = 10.4 Hz, 1H), 3.40 (s, 3H), 1.55 (s, 9H), 1.46 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 152.6, 138.8, 134.4, 133.8 (2C), 129.6 (2C), 127.2 (2C), 127.1, 123.8, 117.0 (2C), 63.7, 60.3, 44.3, 40.8, 28.4 (3C), 26.6, 26.4; IR (Neat) ν_{max} 3068, 2975, 2926, 1704, 1632, 1441, 1369, 1106 cm^{-1}; **HRMS (ESI)** for $C_{23}H_{28}N_2NaO_4S$ $(M+Na)^+$: calcd. 451.1667, found 451.1669.

***N*-[3,3-Dimethyl-2,3-dihydrobenzo[*b*]thiophene-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (54):**

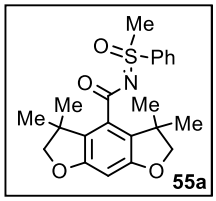


54 (86 mg, 42%) as yellow viscous liquid. R_f = 0.44 (3:2 hexane/EtOAc); The product **54** and the unreacted starting material **51x** were non-seperable and isolated as a mixture of **54** and **51x** (1:1.6). The yield of **54** was calculated based on ^{1}H NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1.4H), 8.09–8.01 (m, 6.2H), 7.95 (t, J = 8 Hz, 1.8H), 7.68 (t, J = 7.2 Hz, 2.9H), 7.61 (t, J = 7.4 Hz, 5.8H), 7.45 (d, J = 8.0 Hz, 1.5H), 7.34–7.27 (m, 2.8H), 7.20 (d, J = 7.6 Hz, 0.9H), 7.11 (t, J = 7.6Hz, 0.9H), 4.84 (s, 1.3H), 4.81 (s, 1.2H), 3.55 (s, 2.5H), 3.45 (s, 5.4H), 3.41 (s, 3.2H), 1.84 (s, 4.1H), 1.53 (s, 3.1H), 1.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 173.7, 140.5, 138.8, 138.5, 136.6, 136.2, 134.0, 133.9, 133.3, 130.5, 129.7 (2C), 128.4, 127.23, 127.17 (2C), 127.0, 124.8, 124.3, 114.3, 48.9, 48.6, 44.4, 41.6, 25.5, 25.4, 21.2; IR (Neat) ν_{max} 3402, 2920, 2087, 1627, 1473, 1452, 1402, 1287, 1265, 1221 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{20}NO_2S_2$ $(M+H)^+$: calcd. 346.0935, found 346.0934.

2.7.3.5. General Procedure for the Dual Hydroarylation Reaction (GP-5):

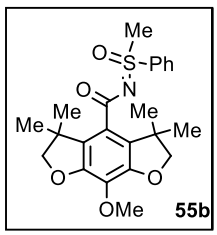
The dual hydroarylation reactions were conducted in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with **51′** (0.5 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (6.0 mg, 2.0 mol %), and $Cu(OAc)_2 \cdot H_2O$ (100 mg, 0.5 mmol). Subsequently, the additive $AgSbF_6$ (35 mg, 0.1 mmol) was introduced to the flask in a glove box. 1,2-Dichloroethene (DCE) (2.0 mL) was added to the mixture and the resulting mixture was stirred at room temparature for 10–16 h. The reaction mixture was filtered through a plug of Celite and washed with CH_2Cl_2 (3 × 5.0 mL). The solvents were evaporated under the 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 **55**.

_N_-[3,3,5,5-Tetramethyl-2,3,5,6-tetrahydrobenzo[1,2-*b*:5,4-*b*']difuran-4-carboxyl]-_S_-methyl-_S_-phenylsulfoximine (55a):



55a (192 mg, 96%) as colourless crystalline solid. m.p. = 229–233 °C; R_f = 0.26 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.05 (bd, J = 7.6 Hz, 2H), 7.70 (bt, J = 7.4 Hz, 1H), 7.61 (t, J = 7.6 Hz, 2H), 6.25 (s, 1H), 4.12 (s, 4H), 3.55 (s, 3H), 1.40 (s, 6H), 1.37 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 160.0 (2C), 138.3, 134.0, 131.9, 129.5 (2C), 127.0 (3C), 123.2 (2C), 93.5 (2C), 85.6 (2C), 43.8, 42.5 (2C), 26.1 (2C); IR (Neat) ν_{max} 2958, 2926, 2860, 1616, 1600, 1468, 1430, 1309, 1254, 1221, 1134 cm^{-1}; **HRMS (ESI)** for $C_{22}H_{26}NO_4S$ $(M+H)^+$: calcd. 400.1582, found 400.1543.

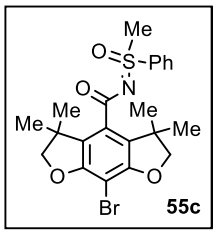
_N_-[8-Methoxy-3,3,5,5-tetramethyl-2,3,5,6-tetrahydrobenzo[1,2-*b*:5,4-*b*']difuran-4-carboxyl]-_S_-methyl-_S_-phenylsulfoximine (55b):



55b (208 mg, 97%) as colourless solid. m.p. = 191–194 °C; R_f = 0.19 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.06 (d, J = 7.6 Hz, 2H), 7.71 (t, J = 7.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 2H), 4.17 (s, 4H), 3.96 (s, 3H), 3.54 (s, 3H), 1.42 (s, 6H), 1.38 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 150.2 (2C), 138.3, 134.0, 129.7, 129.5 (2C), 127.0 (2C), 125.8, 125.5 (2C), 86.1 (2C),

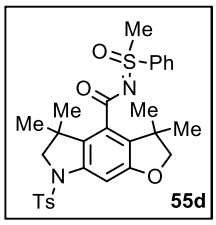
60.3, 43.9, 43.1 (2C), 26.0 (4C); IR (KBr) ν_{max} 2931, 2860, 1632, 1583, 1402, 1326, 1282, 1210, 1057 cm^{-1}; **HRMS (ESI)** for $C_{23}H_{27}NNaO_5S$ $(M+Na)^+$: calcd. 452.1508, found 452.1502.

***N*-[8-Bromo-3,3,5,5-tetramethyl-2,3,5,6-tetrahydrobenzo[1,2-*b*:5,4-*b*']difuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (55c):**



55c (225 mg, 94%) as colourless solid. m.p. = 207–211 °C; R_f = 0.28 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (bd, J = 7.6 Hz, 2H), 7.69 (bt, J = 7.4 Hz, 1H), 7.61 (bt, J = 7.6 Hz, 2H), 4.22 (s, 4H), 3.54 (s, 3H), 1.40 (s, 6H), 1.37 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 156.8 (2C), 138.1 (2C), 134.1, 130.9, 129.6 (2C), 126.9 (2C), 124.3 (2C), 86.2, 86.0, 43.9, 43.8 (2C), 26.2 (2C), 26.1 (2C); IR (KBr) ν_{max} 2958, 2926, 2876, 1616, 1589, 1408, 1320, 1216, 1090 cm^{-1}; **HRMS (ESI)** for $C_{22}H_{25}BrNO_4S$ $(M+H)^+$: calcd. 478.0687, found 478.0682.

***N*-[3,3,5,5-Tetramethyl-7-tosyl-3,5,6,7-tetrahydro-2H-furo[3,2-*f*]indole-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (55d):**

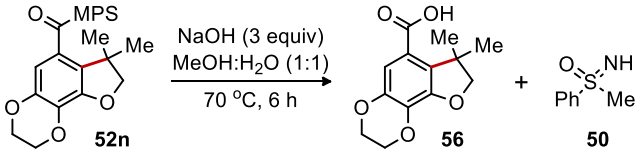


55d (232 mg, 84%) as colourless solid. m.p. = 219–221 °C; R_f = 0.11 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 2H), 7.78–7.68 (m, 3H), 7.63 (t, J = 7.8 Hz, 2H), 7.29 (s, 2H), 7.13 (s, 1H), 4.16 (s, 2H), 3.56 (s, 3H), 3.55 (s, 2H), 2.41 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 159.9, 144.0, 141.5, 138.2, 134.2, 133.9, 132.5, 129.7 (2C), 129.6 (2C), 127.5 (2C), 127.0 (2C), 126.9, 126.0, 97.3, 85.6, 65.1, 43.8, 42.7, 40.8, 26.6 (2C), 26.1 (2C), 21.5; IR (KBr) ν_{max} 2958, 2920, 2865, 1632, 1594, 1468, 1353, 1304, 1232, 1161 cm^{-1}; **HRMS (ESI)** for $C_{29}H_{33}N_2O_5S_2$ $(M+H)^+$: calcd. 553.1831, found 553.1825.

2.7.3.6. General Procedure for the Hydrolysis of 52 (GP-6):

Compound **52n** (0.25 mmol) was dissolved in NaOH in H_2O and MeOH solution (1:1, 2.0 mL) and stirred at 70 °C for 6 h. The reaction mixture was extracted with Et_2O, dried over Na_2SO_4, and concentrated under vacuum to give 7,7-dimethyl-2,3,7,8-tetrahydrobenzofuro[6,7-*b*][1,4]dioxine-6-carboxylic acid (**56**). The basic aqueous-layer was acidified with dil. HCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed

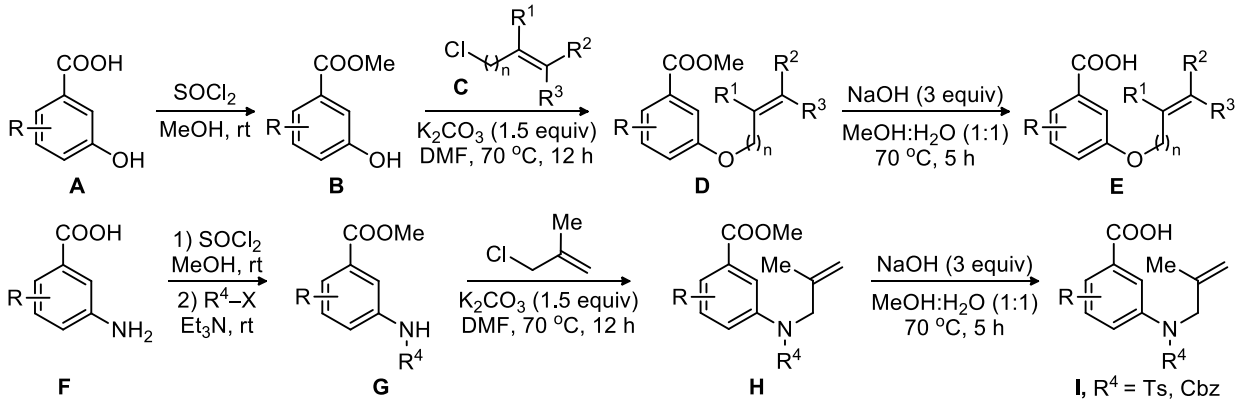
with brine, dried over Na_2SO_4, and concentrated under vacuum to give the methylphenylsulfoximine (**50**).



7,7-Dimethyl-2,3,7,8-tetrahydrobenzofuro[6,7-*b*][1,4]dioxine-6-carboxylic acid (56):

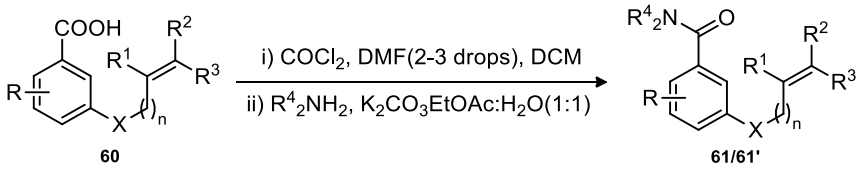
56 (53 mg, 84%) as colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.25 (s, 1H), 4.41–4.28 (m, 6H), 1.53 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ171.2, 148.7, 143.0, 133.8, 131.5, 117.7, 113.5, 87.0, 64.9, 64.2, 44.1, 25.7; IR (KBr) ν_{max} 2920, 2887, 1720, 1676, 1309, 1145 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{15}O_5$ $(M+H)^+$: calcd. 251.0919, found 251.0914.

2.7.3.7. Preparation of Benzoic Acid Derivatives (E and I); General Procedure (GP-7):



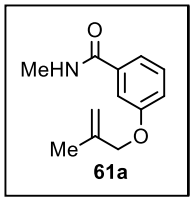
Following the above schemes, corresponding benzoic acid derivatives were prepared and used for the next step.

2.7.3.8. Preparation of *N*-alkyl amide (61); General Procedure (GP-8):



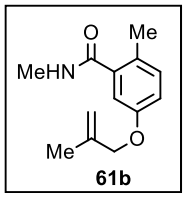
Following the above Schemes, corresponding N-alkylbenzamide derivatives were prepared in excellent yield (80-95% see table 2.5) and used for hydroarylation reaction.

***N*-Methyl-3-((2-methylallyl)oxy)benzamide (61a):**



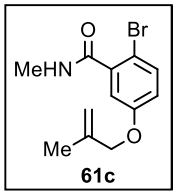
Colourless solid. m.p. = 74–75 °C; R_f = 0.29 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.35 (m, 1H), 7.34–7.23 (m, 2H), 7.05–6.98 (m, 1H), 6.70 (bs, 1H), 5.07 (s, 1H), 4.98 (s, 1H), 4.43 (s, 2H), 2.96 (d, J = 4.8 Hz, 3H), 1.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 158.8, 140.4, 135.9, 129.3, 118.8, 118.0, 113.1, 112.8, 71.6, 26.7, 19.3; IR (KBr) ν_{max} 3320, 3079, 2926, 2860, 1638, 1534, 1304, 1232, 898, 750 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{16}NO_2$ $(M+H)^+$: calcd. 206.1181, found 206.1177.

***N*-2-Dimethyl-5-((2-methylallyl)oxy)benzamide (61b):**



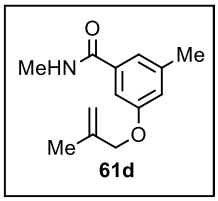
Colourless solid. m.p. = 115–116 °C; R_f = 0.39 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.84 (dd, J = 8.4, 2.8 Hz, 1H), 5.88 (bs, 1H), 5.05 (s, 1H), 4.96 (s, 1H), 4.38 (s, 2H), 3.04 (dd, J = 1.6, 4.8 Hz, 3H), 2.32 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 156.4, 140.6, 137.1, 131.7, 127.6, 116.0, 113.2, 112.5, 71.7, 26.4, 19.2, 18.6; IR (Neat) ν_{max} 3282, 1632, 1539, 1320, 1243, 1167, 1068, 805 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_2$ $(M+H)^+$: calcd. 220.1338, found 220.1334.

2-Bromo-*N*-methyl-5-((2-methylallyl)oxy)benzamide (61c):



Colourless solid. m.p. = 145–146 °C; R_f = 0.19 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 2.8 Hz, 1H), 6.82 (dd, J = 8.8, 3.2 Hz, 1H), 6.12 (bs, 1H), 5.05 (s, 1H), 4.98 (s, 1H), 4.40 (s, 2H), 2.99 (d, J = 4.8 Hz, 3H), 1.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 158.0, 140.1, 138.3, 134.1, 118.3, 115.7, 113.1, 109.4, 72.0, 26.7, 19.2; IR (Neat) ν_{max} 3320, 1638, 1600, 1545, 1397, 1156, 904, 821 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{14}BrNNaO_2$: $(M+Na)^+$: calcd. 306.0106, found 306.0114.

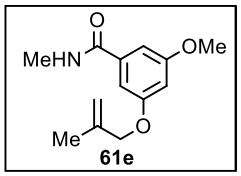
***N*-3-Dimethyl-5-((2-methylallyl)oxy)benzamide (61d):**



Colourless viscous liquid. R_f = 0.32 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.11 (s, 1H), 6.82 (s, 1H), 6.60 (bs, 1H), 5.04

(s, 1H), 4.94 (s, 1H), 4.38 (s, 2H), 2.94 (d, J = 4.8 Hz, 3H), 2.28 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ168.3, 158.8, 140.5, 139.5, 135.7, 119.8, 118.7, 112.6, 110.1, 71.6, 26.7, 21.3, 19.3; IR (Neat) ν_{max} 3315, 3079, 2915, 1643, 1594, 1320, 1063 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_2$: $(M+H)^+$: calcd. 220.1338, found 220.1343.

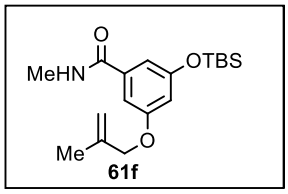
3-Methoxy-*N*-methyl-5-((2-methylallyl)oxy)benzamide (61e):



61e

Colourless viscous liquid. R_f = 0.26 (1:1 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ6.89 (t, J = 1.7 Hz, 1H), 6.88 (t, J = 1.7 Hz, 1H), 6.58–6.53 (m, 1H), 6.49 (bs, 1H), 5.05 (s, 1H), 4.96 (s, 1H), 4.39 (s, 2H), 3.76 (d, J = 1.5 Hz, 3H), 2.94 (dd, J = 4.7, 1.2 Hz, 3H), 1.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ168.1, 160.7, 159.8, 140.4, 136.7, 112.8, 105.6, 104.8, 104.1, 71.8, 55.4, 26.8, 19.3; IR (KBr) ν_{max} 3320, 3079, 2942, 1588, 1352, 1160, 1062 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_3$ $(M+H)^+$: calcd.236.1287, found 236.1290.

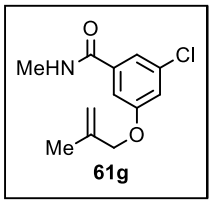
3-((*tert*-Butyldimethylsilyl)oxy)-*N*-methyl-5-((2-methylallyl)oxy)benzamide (61f):



61f

Colourless viscous liquid. R_f = 0.45 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ6.93 (t, J = 1.8 Hz, 1H), 6.78 (t, J = 1.6 Hz, 1H), 6.52 (t, J = 2.2 Hz, 1H), 6.11 (bs, 1H), 5.08 (s, 1H), 4.98 (s, 1H), 4.42 (s, 2H), 2.98 (d, J = 5.2 Hz, 3H), 1.81 (s, 3H), 0.97 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 159.9, 156.8, 140.5, 136.7, 112.9, 111.2, 109.9, 106.4, 71.9, 26.8, 25.6 (3C), 19.3, 18.1, –4.4 (2C); IR (KBr) ν_{max} 3331, 2958, 2849, 1589, 1435, 1156, 832 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{30}NO_3Si$ $(M+H)^+$: calcd. 336.1995, found 336.1996.

3-Chloro-*N*-methyl-5-((2-methylallyl)oxy)benzamide (61g)

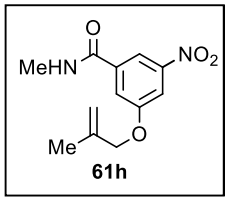


61g

Colourless solid. m.p. = 90–91 ^{o}C; R_f = 0.39 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.30–7.25 (m, 1H), 7.24 (dd, J = 2.4, 1.6 Hz, 1H), 7.01 (t, J = 2.2 Hz, 1H), 6.49 (bs, 1H), 5.07 (s, 1H), 5.00 (s, 1H), 4.43 (s, 2H), 2.98 (d, J = 4.8 Hz, 3H), 1.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ166.9, 159.5,

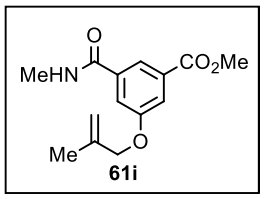
139.9, 137.1, 135.0, 119.1, 118.0, 113.2, 111.9, 72.0, 26.9, 19.3; IR (KBr) ν_{max} 3369, 3315, 3084, 2931, 1654, 1578, 1545, 1243, 1008, 673 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{15}ClNO_2$ $(M+H)^+$: calcd. 240.0791, found 240.0791.

***N*-Methyl-3-((2-methylallyl)oxy)-5-nitrobenzamide (61h):**



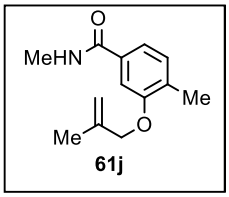
Pale yellow solid. m.p. = 158–159 °C; R_f = 0.19 (1:1 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ8.13 (t, J = 1.6 Hz, 1H), 7.81 (t, J = 2.2 Hz, 1H), 7.74–7.69 (m, 1H), 6.81 (bs, 1H), 5.09 (s, 1H), 5.02 (s, 1H), 4.51 (s, 2H), 3.02 (d, J = 4.8 Hz, 3H), 1.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ165.8, 159.4, 148.9, 139.3, 136.9, 120.2, 113.8, 113.5, 112.1, 72.5, 27.0, 19.2; IR (KBr) ν_{max} 3282, 3101, 2926, 1632, 1528, 1336, 1073, 887 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{15}N_2O_4$ $(M+H)^+$: calcd. 251.1032, found 251.1037.

Methyl 3-((2-methylallyl)oxy)-5-(methylcarbamoyl)benzoate (61i):



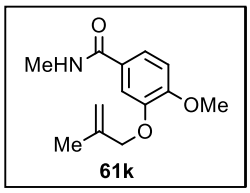
Colourless solid. m.p. = 113–115 °C; R_f = 0.29 (1:1 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ7.90 (t, J = 1.4 Hz, 1H), 7.68 (dd, J = 2.4, 1.2 Hz, 1H), 7.61 (dd, J = 2.4, 1.6 Hz, 1H), 6.36 (bs, 1H), 5.09 (s, 1H), 5.00 (s, 1H), 4.49 (s, 2H), 3.91 (s, 3H), 3.01 (d, J = 4.8 Hz, 3H), 1.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ167.0, 166.2, 158.9, 140.0, 136.1, 131.4, 119.5, 118.4, 118.3, 113.1, 71.9, 52.3, 26.8, 19.3; IR (KBr) ν_{max} 3336, 2953, 2350, 1720, 1643, 1589, 1435, 904 cm^{-1}; **HRMS (ESI)** for $C_{14}H_{18}NO_4$ $(M+H)^+$: calcd. 264.1236, found 264.1233.

***N*-4-Dimethyl-3-((2-methylallyl)oxy)benzamide (61j):**



Colourless solid. m.p. = 139–141 °C; R_f = 0.28 (1:1 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.73 (bs, 1H), 5.07 (s, 1H), 4.95 (s, 1H), 4.39 (s, 2H), 2.94 (d, J = 4.8 Hz, 3H), 2.24 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ168.2, 156.8, 140.6, 133.2, 130.6, 130.2, 118.2, 112.1, 110.0, 71.3, 26.7, 19.3, 16.2; IR (KBr) ν_{max} 3364, 3095, 2915, 1638, 1556, 1506, 1243, 1057, 893 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_2$ $(M+H)^+$: calcd. 220.1338, found 220.1338.

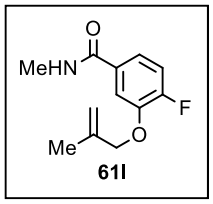
4-Methoxy-*N*-methyl-3-((2-methylallyl)oxy)benzamide (61k):



61k

Colourless solid. m.p. = 114–116 °C; R_f = 0.17 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 2.0 Hz, 1H), 7.26 (dd, J = 8.4, 2.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.12 (bs, 1H), 5.10 (s, 1H), 4.99 (s, 1H), 4.54 (s, 2H), 3.90 (s, 3H), 2.98 (d, J = 4.8 Hz, 3H), 1.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ167.8, 151.9, 147.8, 140.2, 126.9, 119.7, 112.8, 112.4, 110.6, 72.4, 55.8, 26.7, 19.2; IR (KBr) ν_{max} 3331, 3090, 2931, 2356, 1841, 1726, 1506, 1216, 1139, 904 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_3$ $(M+H)^+$: calcd. 236.1287, found 236.1291.

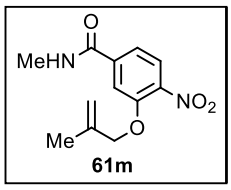
4-Fluoro-*N*-methyl-3-((2-methylallyl)oxy)benzamide (61l):



61l

Colourless solid. m.p. = 121–122 °C; R_f = 0.28 (1:1 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, J = 8.0, 2.0 Hz, 1H), 7.24–7.17 (m, 1H), 7.08 (dd, J = 10.5, 8.5 Hz, 1H), 6.15 (bs, 1H), 5.12 (s, 1H), 5.01 (s, 1H), 4.54 (s, 2H), 2.99 (d, J = 5.0 Hz, 3H), 1.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ167.3, 154.5 (d, J = 252.0 Hz), 146.7 (d, J = 10.1 Hz), 139.9, 130.9 (d, J = 2.5 Hz), 119.4, 115.8 (d, J = 20.2 Hz), 114.6, 113.3, 72.8, 26.8, 19.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –129.3; IR (KBr) ν_{max} 3369, 1873, 1638, 1600, 1501, 1052 cm^{-1}; **HRMS** (**ESI**) for $C_{12}H_{15}FNO_2$ $(M+H)^+$: calcd. 224.1087, found 224.1088.

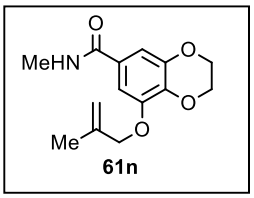
***N*-Methyl-3-((2-methylallyl)oxy)-4-nitrobenzamide (61m):**



61m

Pale yellow solid. m.p. = 133–134 °C; R_f = 0.18 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 7.32–7.26 (m, 1H), 6.49 (bs, 1H), 5.16 (s, 1H), 5.04 (s, 1H), 4.61 (s, 2H), 3.02 (d, J = 4.8 Hz, 3H), 1.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ166.1, 152.0, 141.2, 139.6, 139.0, 125.6, 117.7, 114.2, 113.8, 73.0, 27.0, 19.2; IR (KBr) ν_{max} 3370, 1875, 1678, 1660, 1561, 1161, 865 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{15}N_2O_4$ $(M+H)^+$: calcd. 251.1032, found 251.1026.

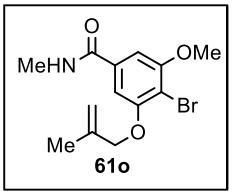
***N*-Methyl-8-((2-methylallyl)oxy)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide (61n):**



61n

Colourless solid. m.p. = 151–153 °C; R_f = 0.20 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 2.0 Hz, 1H), 6.05 (bs, 1H), 5.11 (s, 1H), 4.99 (s, 1H), 4.53 (s, 2H), 4.37–4.31 (m, 2H), 4.29–4.23 (m, 2H), 2.97 (d, J = 4.8 Hz, 3H), 1.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 147.9, 143.5, 140.2, 136.2, 126.4, 113.0, 108.6, 105.2, 72.6, 64.4, 64.0, 26.7, 19.3; IR (KBr) ν_{max} 3287, 3052, 2926, 1758, 1632, 1353, 1134, 882 cm^{-1}; **HRMS (ESI)** for $C_{14}H_{18}NO_4$ $(M+H)^+$: calcd. 264.1236, found 264.1232.

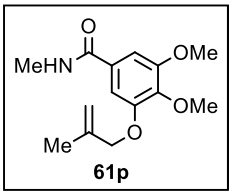
4-Bromo-3-methoxy-N-methyl-5-((2-methylallyl)oxy)benzamide (61o):



61o

Colourless solid. m.p. = 124–126 °C; R_f = 0.40 (1:1 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.91 (s, 1H), 6.26 (bs, 1H), 5.17 (s, 1H), 5.01 (s, 1H), 4.51 (s, 2H), 3.92 (s, 3H), 2.99 (d, J = 4.5 Hz, 3H), 1.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 157.2, 156.2, 139.9, 134.9, 113.0, 105.1, 104.4, 103.2, 72.8, 56.6, 26.9, 19.3; IR (Neat) ν_{max} 3276, 3090, 2942, 1632, 1561, 1419, 1336, 1243, 1123, 1035, 860, 767 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{17}BrNO_3$ $(M+H)^+$: calcd. 314.0392, found 314.0395.

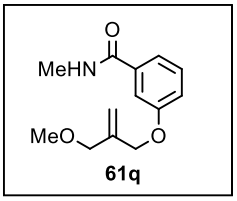
3,4-Dimethoxy-*N*-methyl-5-((2-methylallyl)oxy)benzamide (61p):



61p

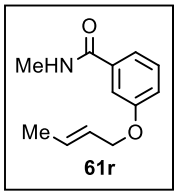
Colourless solid. m.p. = 146–148 °C; R_f = 0.14 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 6.12 (bs, 1H), 5.10 (s, 1H), 4.99 (s, 1H), 4.50 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 2.99 (d, J = 4.8 Hz, 3H) 1.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 153.1, 152.1, 141.0, 140.3, 129.8, 112.7, 105.9, 104.3, 72.6, 60.7, 56.1, 26.8, 19.3; IR (Neat) ν_{max} 3276, 3084, 2936, 1638, 1495, 1342, 1243, 1134, 849 cm^{-1}; **HRMS (ESI)** for $C_{14}H_{20}NO_4$ $(M+H)^+$: calcd. 266.1392, found 266.1392.

3-((2-(Methoxymethyl)allyl)oxy)-*N*-methylbenzamide (61q):



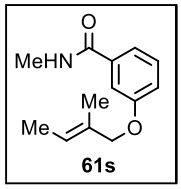
Colourless solid. m.p. = 89–90 °C; R_f = 0.22 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.38 (s, 1H), 7.36–7.27 (m, 2H), 7.09–7.02 (m, 1H), 6.15 (bs, 1H), 5.34 (s, 1H), 5.28 (s, 1H), 4.59 (s, 2H), 4.02 (s, 2H), 3.36 (s, 3H), 3.01 (d, J = 4.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ168.0, 158.8, 141.0, 136.0, 129.5, 118.9, 118.1, 115.1, 113.2, 73.3, 68.5, 58.1, 26.8; IR (KBr) ν_{max} 3326, 3079, 2816, 1643, 1578, 1545, 1304, 920, 756 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{17}NNaO_3$ $(M+Na)^+$: calcd. 258.1106, found 258.1109.

(*E*)-3-(But-2-en-1-yloxy)-*N*-methylbenzamide (61r):



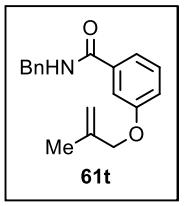
Colourless solid. m.p. = 97–98 °C; R_f = 0.30 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.40–7.33 (m, 1H), 7.33–7.23 (m, 2H), 7.06–6.99 (m, 1H), 6.23 (bs, 1H), [5.93–5.81 (m, 0.8H), 5.78–5.66 (m, 1.2H)], [4.63 (d, J = 6.0 Hz, 0.4H), 4.49 (d, J = 6.0 Hz, 1.6H)], 3.00 (d, J = 4.8 Hz, 3H), 1.79–1.72 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ168.1, 158.8, 135.9, 130.7, [129.4 & 128.9], [125.6 & 125.1], 118.7, 118.2, 112.9, [68.7 & 63.8], 26.7, [17.7 & 13.3]; IR (Neat) ν_{max} 3298, 2915, 1643, 1545, 1479, 1309, 1238, 1013, 805 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{16}NO_2$ $(M+H)^+$: calcd. 206.1181, found 206.1182.

(*E*)-*N*-Methyl-3-((2-methylbut-2-en-1-yl)oxy)benzamide (61s):



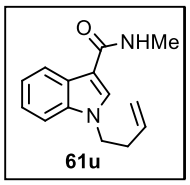
Colourless solid. m.p. = 98–99 °C; R_f = 0.31 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.36 (s, 1H), 7.34–7.23 (m, 2H), 7.06–7.00 (m, 1H), 6.23 (bs, 1H), 5.68–5.59 (m, 1H), 4.41 (s, 2H), 3.00 (d, J = 4.8 Hz, 3H), 1.73 (s, 3H), 1.67 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 159.0, 135.8, 131.2, 129.3, 123.5, 118.7, 118.1, 113.1, 74.0, 26.7, 13.4, 13.1; IR (Neat) ν_{max} 3238, 3073, 2926, 1643, 1578, 1556, 1419, 1238, 997 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{17}NNaO_2$ $(M+Na)^+$: calcd. 242.1157, found 242.1157.

***N*-Benzyl-3-((2-methylallyl)oxy)benzamide (61t):**



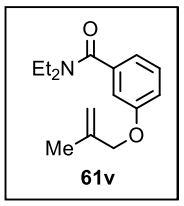
Colourless solid. m.p. = 95–96 °C; R_f = 0.38 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.38 (m, 1H), 7.37–7.34 (m, 4H), 7.32–7.28 (m, 3H), 7.09–7.00 (m, 1H), 6.48 (bs, 1H), 5.09 (s, 1H), 4.99 (s, 1H), 4.63 (d, J = 5.6 Hz, 2H), 4.46 (s, 2H), 1.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 158.9, 140.4, 138.2, 135.7, 129.4, 128.6 (2C), 127.8 (2C), 127.4, 118.9, 118.2, 113.3, 112.8, 71.7, 44.0, 19.3; IR (Neat) ν_{max} 3304, 3057, 2926, 1638, 1587, 1539, 1315, 887 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{19}NNaO_2$ $(M+Na)^+$: calcd. 304.1313, found 304.1314.

1-(But-3-en-1-yl)-*N*-methyl-1H-indole-3-carboxamide (61u):



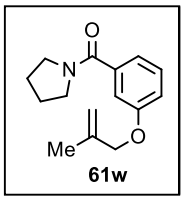
Colourless solid. m.p. = 143–144 °C; R_f = 0.13 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.90 (m, 1H), 7.69 (s, 1H), 7.42–7.36 (m, 1H), 7.32–7.21 (m, 2H), 5.94 (bs, 1H), 5.83–5.68 (m, 1H), 5.10–5.06 (m, 1H), 5.07–5.02 (m, 1H), 4.19 (t, J = 7.0 Hz, 2H), 3.05 (d, J = 4.8 Hz, 3H), 2.64–2.55 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 136.4, 133.9, 131.3, 125.3, 122.4, 121.3, 120.1, 118.0, 111.0, 110.2, 46.3, 34.1, 26.3; IR (KBr) ν_{max} 3331, 3101, 2920, 2361, 1627, 1550, 1282, 750 cm^{-1}; **HRMS (ESI)** for $C_{14}H_{16}N_2NaO$ $(M+Na)^+$: calcd. 251.1160, found 251.1159.

***N*,*N*-Diethyl-3-((2-methylallyl)oxy)benzamide (61v):**



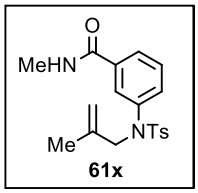
Colourless viscous liquid. R_f = 0.28 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, J = 8.2 Hz, 1H), 6.97–6.90 (m, 3H), 5.08 (s, 1H), 4.98 (s, 1H), 4.44 (s, 2H), 3.53 (bs, 2H), 3.26 (bs, 2H), 1.82 (s, 3H), 1.24 (bs, 3H), 1.10 (bs, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 158.5, 140.4, 138.4, 129.3, 118.4, 115.6, 112.6, 112.4, 71.6, 43.1, 39.0, 19.2, 14.1, 12.7; IR (KBr) ν_{max} 3448, 3079, 2975, 2925, 2876, 1637, 1577, 1440, 1287, 1232 cm^{-1}; **HRMS (ESI)** for $C_{15}H_{22}NO_2$ $(M+H)^+$: calcd. 248.1651, found 248.1652.

(3-((2-Methylallyl)oxy)phenyl)(pyrrolidin-1-yl)methanone (61w):



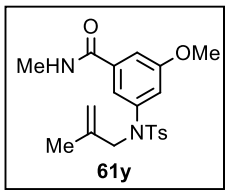
Colourless viscous liquid. R_f = 0.28 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.28 (t, J = 8.2 Hz, 1H), 7.10–7.04 (m, 2H), 6.99–6.92 (m, 1H), 5.08 (s, 1H), 4.98 (s, 1H), 4.44 (s, 2H), 3.63 (t, J = 7.0 Hz, 2H), 3.41 (t, J = 6.6 Hz, 2H), 1.99–1.83 (m, 4H), 1.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ169.3, 158.4, 140.4, 138.2, 129.1, 119.2, 116.3, 113.1, 112.6, 71.6, 49.4, 46.0, 26.2, 24.2, 19.2; IR (KBr) ν_{max} 3462, 3073, 2969, 2870, 2366, 1725, 1621, 1572, 1237 cm^{-1}; **HRMS (ESI)** for $C_{15}H_{20}NO_2$ $(M+H)^+$: calcd. 246.1494, found 246.1496.

***N*-Methyl-3-(4-methyl-*N*-(2-methylallyl)phenylsulfonamido)benzamide (61x):**



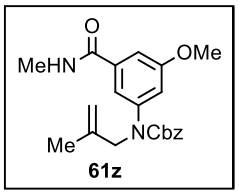
Colourless solid. m.p. = 162–164 ^{o}C; R_f = 0.22 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.68 (d, J = 7.6 Hz, 1H), 7.50–7.41 (m, 3H), 7.33 (t, J = 8.0 Hz, 1H), 7.29–7.22 (m, 2H), 7.19–7.11 (m, 1H), 6.24 (bs, 1H), 4.74 (s, 1H), 4.71 (s, 1H), 4.10 (s, 2H), 2.98 (d, J = 4.8 Hz, 3H), 2.42 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ167.1, 143.8, 139.2, 139.1, 135.3, 134.7, 131.0, 129.5 (2C), 128.8, 127.5 (2C), 126.9, 126.1, 115.5, 56.4, 26.8, 21.5, 19.8; IR (KBr) ν_{max} 3282, 3090, 3057, 2937, 2865, 1632, 1556, 1342, 701 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{22}N_2NaO_3S$ $(M+Na)^+$: calcd. 381.1249, found 381.1249.

3-Methoxy-*N*-methyl-5-(4-methyl-*N*-(2-methylallyl)phenylsulfonamido)benzamide (61y):



Colourless solid. m.p. = 172–173 ^{o}C; R_f = 0.19 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.47 (d, J = 8.0 Hz, 2H), 7.29–7.23 (m, 3H), 7.03 (t, J = 1.4 Hz, 1H), 6.65 (t, J = 2.2 Hz, 1H), 6.19 (bs, 1H), 4.76 (s, 1H), 4.72 (s, 1H), 4.07 (s, 2H), 3.77 (s, 3H), 2.97 (d, J = 4.8 Hz, 3H), 2.43 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ167.0, 159.7, 143.8, 140.1, 139.2, 136.1, 134.7, 129.5 (2C), 127.6 (2C), 118.9, 117.3, 115.4, 111.4, 56.4, 55.5, 26.7, 21.5, 19.8; IR (KBr) ν_{max} 3353, 3101, 2915, 2854, 1632, 1589, 1550, 1342, 1167, 810 cm^{-1}; **HRMS (ESI)** for $C_{20}H_{25}N_2O_4S$ $(M+H)^+$: calcd. 389.1535, found 389.1535.

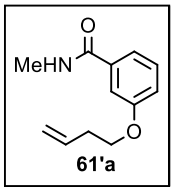
Benzyl (3-methoxy-5-(methylcarbamoyl)phenyl)(2-methylallyl)carbamate (61z):



61z

Colourless viscous liquid. R_f = 0.22 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.38–7.29 (m, 5H), 7.20–7.13 (m, 2H), 6.91 (bs, 1H), 6.08 (bs, 1H), 5.18 (s, 2H), 4.86 (s, 1H), 4.80 (s, 1H), 4.23 (s, 2H), 3.79 (s, 3H), 2.94 (d, J = 4.8 Hz, 3H), 1.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 159.9, 155.2, 143.2, 140.7, 136.23, 136.18, 128.4 (2C), 128.1, 127.9 (2C), 116.7, 115.2, 112.2, 109.8, 67.5, 55.9, 55.5, 26.8, 20.1; IR (KBr) ν_{max} 3358, 3084, 2936, 1709, 1643, 1326, 1232, 1145 cm^{-1}; **HRMS (ESI)** for $C_{21}H_{25}N_2O_4$ $(M+H)^+$: calcd. 369.1814, found 369.1812.

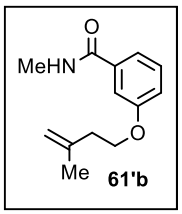
3-(But-3-en-1-yloxy)-*N*-methylbenzamide (61'a):



61'a

Colourless solid. m.p. = 74–75 ^{o}C; R_f = 0.28 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.37–7.32 (m, 1H), 7.33–7.24 (m, 2H), 7.04–6.97 (m, 1H), 6.42 (bs, 1H), 5.96–5.81 (m, 1H), 5.16 (dd, J = 17.2, 1.2 Hz, 1H), 5.11 (d, J = 10 Hz, 1H), 4.03 (t, J = 6.6 Hz, 2H), 2.98 (d, J = 4.8 Hz, 3H), 2.53 (q, J = 6.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$)δ168.1, 159.0, 136.0, 134.2, 129.4, 118.6, 118.0, 117.1, 112.9, 67.3, 33.5, 26.8; IR (KBr) ν_{max} 3358, 1632, 1578, 1534, 1304, 1243, 1030 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{16}NO_2$ $(M+H)^+$: calcd. 206.1181, found 206.1183.

***N*-Methyl-3-((3-methylbut-3-en-1-yl)oxy)benzamide (61'b):**



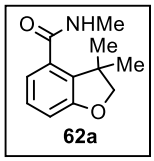
61'b

Colourless viscous liquid. R_f = 0.31 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.38–7.33 (m, 1H), 7.33–7.24 (m, 2H), 7.05–6.98 (m, 1H), 6.43 (bs, 1H), 4.84 (s, 1H), 4.79 (s, 1H), 4.10 (t, J = 6.8 Hz, 2H), 2.98 (d, J = 4.8 Hz, 3H), 2.49 (t, J = 6.8 Hz, 2H), 1.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ168.1, 159.0, 141.9, 136.0, 129.4, 118.6, 118.0, 112.9, 112.0, 66.5, 37.0, 26.8, 22.7; IR (KBr) ν_{max} 3325, 3084, 2931,1648, 1555, 1308, 1243, 892 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{17}NNaO_2$ $(M+Na)^+$: calcd. 242.1157, found 242.1159.

2.7.3.9. General Procedure for Hydroarylation of O-Tethered Compounds (61) (GP-9):

The hydroarylation reactions were conducted in a 20 mL Schlenk tube having high pressure valve and side arm. The tube was charged with (**61**, 0.3 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (5.5 mg, 3.0 mol %), and $Mn(OAc)_2$ (13 mg, 0.075 mmol). Subsequently, the additive $AgSbF_6$ (12 mg, 0.036 mmol) was introduced to the flask in a glove box. 1,2-Dichloroethene (DCE) (1.0 mL) was added to the mixture and the resulting mixture was stirred at 70 °C for 10–15 h. The reaction mixture was filtered through a small plug of Celite and washed with dichloromethane (3 × 5.0 mL). The solvents were evaporated under the reduced pressure and the crude material was purified using column chromatography on silica gel.

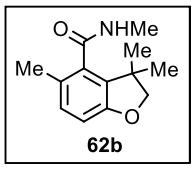
***N*-3,3-Trimethyl-2,3-dihydrobenzofuran-4-carboxamide (62a):**



62a

62a (60 mg, 97%) as colourless solid. m.p. = 116–117 °C; R_f = 0.37 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (t, J = 7.6 Hz, 1H), 6.85–6.79 (m, 2H), 5.98 (bs, 1H), 4.15 (s, 2H), 2.94 (d, J = 4.8 Hz, 3H), 1.42 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ169.6, 160.2, 133.8, 133.6, 128.2, 118.9, 111.7, 85.2, 42.9, 26.6, 25.9 (2C); IR (Neat) ν_{max} 3287, 2926, 2876, 1643, 1545, 1435, 1260, 1057 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{16}NO_2$ $(M+H)^+$: calcd. 206.1181, found 206.1190.

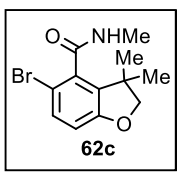
***N*-3,3,5-Tetramethyl-2,3-dihydrobenzofuran-4-carboxamide (62b):**



62b

62b (62 mg, 94%) as colourless solid. m.p. = 176–178 °C; R_f = 0.40 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ6.91 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.81 (bs, 1H), 4.12 (s, 2H), 2.97 (d, J = 4.8 Hz, 3H), 2.20 (s, 3H), 1.34 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 157.6, 133.6, 131.9, 129.8, 126.0, 110.3, 84.8, 42.8, 26.22, 26.17 (2C), 18.0; IR (Neat) ν_{max} 3282, 2964, 2926, 1632, 1457, 1298 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_2$ $(M+H)^+$: calcd. 220.1338, found 220.1328.

5-Bromo-*N*-3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (62c):

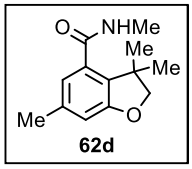


62c

62c (84 mg, 96%) as colourless solid. m.p. = 170–171 °C; R_f = 0.44 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.26 (d, J = 8.4 Hz, 1H),

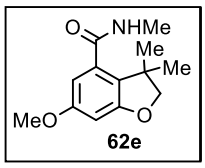
6.66 (d, J = 8.4 Hz, 1H), 5.83 (bs, 1H), 4.17 (s, 2H), 2.99 (d, J = 4.8 Hz, 3H), 1.35 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ167.3, 159.0, 134.84, 134.77, 132.2, 112.2, 109.5, 85.1, 43.2, 26.4, 26.0 (2C); IR (Neat) ν_{max} 3304, 2958, 2882, 1638, 1545, 1287 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{15}BrNO_2$ $(M+H)^+$: calcd. 284.0286, found 284.0284.

_N_-3,3,6-Tetramethyl-2,3-dihydrobenzofuran-4-carboxamide (62d):



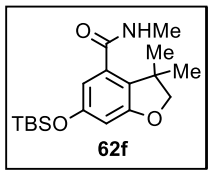
62d (61 mg, 93%) as colourless viscous liquid. R_f = 0.39 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ6.65 (s, 2H), 5.97 (bs, 1H), 4.14 (s, 2H), 2.93 (d, J = 4.8 Hz, 3H), 2.26 (s, 3H), 1.40 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ169.7, 160.4, 138.4, 133.1, 130.9, 119.6, 112.3, 85.4, 42.6, 26.5, 25.9 (2C), 21.2; IR (Neat) ν_{max} 3229, 2952, 1643, 1534, 1435, 1200 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_2$ $(M+H)^+$: calcd. 220.1338, found 220.1342.

6-Methoxy-_N_-3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (62e):



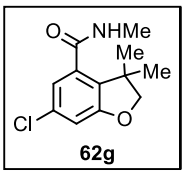
62e (66 mg, 94%) as colourless solid. m.p. = 135–136 ^{o}C; R_f = 0.33 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, J = 2.4 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 5.86 (bs, 1H), 4.18 (s, 2H), 3.75 (s, 3H), 2.96 (d, J = 4.8 Hz, 3H), 1.41 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ169.4, 161.6, 160.0, 133.6, 125.9, 104.9, 97.9, 86.0, 55.6, 42.4, 26.6, 26.1 (2C); IR (Neat) ν_{max} 3304, 2986, 2947, 2865, 2361, 1649, 1550, 1326 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_3$ $(M+H)^+$: calcd. 236.1287, found 236.1284.

6-((_tert_-Butyldimethylsilyl)oxy)-_N_-3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (62f):



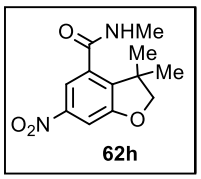
62f (88 mg, 87%) as colourless solid. m.p. = 150–153 ^{o}C; R_f = 0.60 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (d, J = 2.4 Hz, 1H), 6.33 (d, J = 2.0 Hz, 1H), 5.77 (bs, 1H), 4.18 (s, 2H), 2.97 (d, J = 4.8 Hz, 3H), 1.42 (s, 6H), 0.97 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ169.4, 161.4, 155.8, 133.5, 126.7, 110.7, 103.9, 85.9, 42.4, 26.6, 26.2 (2C), 25.6 (3C), 18.1, -4.4 (2C); IR (KBr) ν_{max} 3238, 2958, 2854, 1638, 1473, 1139 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{30}NO_3Si$ $(M+H)^+$: calcd. 336.1995, found 336.1992.

6-Chloro-*N*-3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (62g):



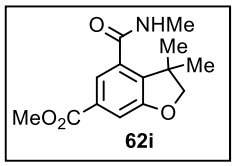
62g (68 mg, 94%) as colourless solid. m.p. = 158–160 °C; R_f = 0.50 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ6.82 (s, 2H), 5.98 (bs, 1H), 4.19 (s, 2H), 2.95 (d, J = 4.8 Hz, 3H), 1.40 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ168.2, 161.2, 134.1, 133.3, 132.7, 118.9, 112.2, 85.9, 42.6, 26.6, 25.8 (2C); IR (KBr) ν_{max} 3243, 3079, 2942, 1638, 1408, 1320, 1243 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{15}ClNO_2$ $(M+H)^+$: calcd. 240.0791, found 240.0781.

***N*-3,3-Trimethyl-6-nitro-2,3-dihydrobenzofuran-4-carboxamide (62h):**



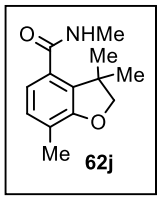
62h (67 mg, 89%) as pale yellow solid. m.p. = 236–238 °C; R_f = 0.38 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.76 (s, 1H), 7.61 (s, 1H), 6.04 (bs, 1H), 4.30 (s, 2H), 3.01 (d, J = 5.2 Hz, 3H), 1.47 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ167.2, 161.2, 148.0, 141.7, 133.6, 114.7, 106.7, 86.2, 43.2, 26.8, 25.5 (2C); IR (KBr) ν_{max} 3232, 3101, 2953, 1638, 1528, 1342 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{15}N_2O_4(M+H)^+$: calcd. 251.1032, found 251.1035.

Methyl-3,3-dimethyl-4-(methylcarbamoyl)-2,3-dihydrobenzofuran-6-carboxylate (62i):



62i (76 mg, 96%) as colourless viscous liquid. R_f = 0.37 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.56 (d, J = 1.2 Hz, 1H), 7.43 (d, J = 1.6 Hz, 1H), 6.01 (bs, 1H), 4.22 (s, 2H), 3.89 (s, 3H), 2.99 (d, J = 5.2 Hz, 3H), 1.45 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ168.5, 166.2, 160.6, 139.4, 133.3, 130.4, 120.8, 112.4, 85.6, 52.3, 43.1, 26.7, 25.6 (2C); IR (KBr) ν_{max} 3293, 2958, 1715, 1638, 1413, 1276, 1238, 1013 cm^{-1}; **HRMS (ESI)** for $C_{14}H_{18}NO_4$ $(M+H)^+$: calcd. 264.1236, found 264.1230.

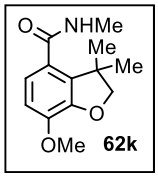
***N*-3,3,7-Tetramethyl-2,3-dihydrobenzofuran-4-carboxamide (62j):**



62j (59 mg, 90%) as colourless viscous liquid. R_f = 0.37 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ6.95 (d, J = 7.6 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 5.81 (bs, 1H), 4.18 (s, 2H), 2.98 (d, J = 4.8 Hz, 3H), 2.22 (s, 3H), 1.45 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ169.7, 158.5, 133.2, 131.1, 129.2, 122.4,

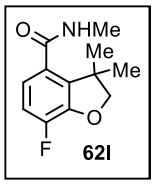
118.8, 85.1, 43.2, 26.6, 25.9 (2C), 15.2; IR (Neat) ν_{max} 3298, 2947, 2865, 1643, 1539, 1408, 1320, 1265 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_2$ $(M+H)^+$: calcd. 220.1338, found 220.1338.

7-Methoxy-*N*-3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (62k):



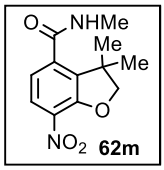
62k (66 mg, 93%) as colourless solid. m.p. = 137–139 °C; R_f = 0.27 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.92 (bs, 1H), 4.23 (s, 2H), 3.86 (s, 3H), 2.94 (d, J = 4.8 Hz, 3H), 1.44 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ169.4, 148.3, 146.1, 135.3, 125.9, 120.1, 110.2, 85.9, 55.9, 43.7, 26.6, 25.7 (2C); IR (Neat) ν_{max} 3282, 3101, 2953, 1643, 1506, 1287, 1057 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_3$ $(M+H)^+$: calcd. 236.1287, found 236.1283.

7-Fluoro-*N*-3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (62l):



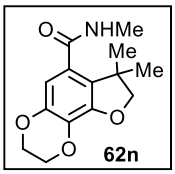
62l (65 mg, 97%) as colourless solid. m.p. = 112–113 °C; R_f = 0.36 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ6.92–6.84 (m, 1H), 6.83□6.76 (m, 1H), 5.95 (bs, 1H), 4.26 (s, 2H), 2.94 (d, J = 4.8 Hz, 3H), 1.44 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 148.6 (d, J = 251 Hz), 146.9 (d, J = 10 Hz), 137.9 (d, J = 2.0 Hz), 129.2 (d, J = 3.0 Hz), 119.7 (d, J = 6.1 Hz), 115.1 (d, J = 17 Hz), 86.5, 43.8, 26.6, 25.6 (2C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –135.8; IR (Neat) ν_{max} 3282, 2958, 1638, 1495, 1265, 997, 953, 821 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{15}FNO_2$ $(M+H)^+$: calcd. 224.1087, found 224.1090.

***N*-3,3-Trimethyl-7-nitro-2,3-dihydrobenzofuran-4-carboxamide (62m):**



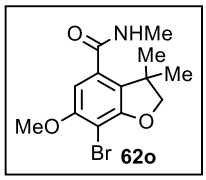
62m (68 mg, 90%) as pale yellow solid. m.p. = 130–132 °C; R_f = 0.23 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.89 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.01 (bs, 1H), 4.44 (s, 2H), 3.00 (d, J = 4.8 Hz, 3H), 1.47 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ167.6, 155.3, 138.82, 138.80, 133.5, 124.3, 119.0, 87.2, 42.7, 26.7, 25.7 (2C); IR (Neat) ν_{max} 3216, 3079, 2964, 1643, 1600, 1523, 1200 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{15}N_2O_4$ $(M+H)^+$: calcd. 251.1032, found 251.1029.

***N*-7,7-Trimethyl-2,3,7,8-tetrahydro-[1,4]dioxino[2,3-g]benzofuran-6-carboxamide(62n):**



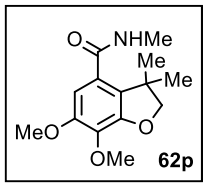
62n (78 mg, 98%) as colourless solid. m.p. = 189–190 °C; R_f = 0.30 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ6.45 (s, 1H), 5.83 (bs, 1H), 4.33–4.26 (m, 2H), 4.27–4.21 (m, 4H), 2.94 (d, J = 4.8 Hz, 3H) 1.43 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 148.3, 143.2, 130.8, 127.9, 124.9, 108.1, 86.9, 64.6, 64.4, 43.3, 26.6, 25.9 (2C); IR (KBr) ν_{max} 3325, 2920, 2312, 1654, 1621, 1501, 1304 cm^{-1}; **HRMS (ESI)** for $C_{14}H_{18}NO_4$ $(M+H)^+$: calcd. 264.1236, found 264.1232.

7-Bromo-6-methoxy-*N*-3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (62o):



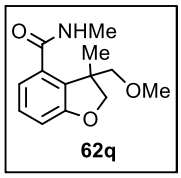
62o (88 mg, 93%) as colourless solid. m.p. = 202–204 °C; R_f = 0.27 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ6.36 (s, 1H), 5.94 (bs, 1H), 4.27 (s, 2H), 3.83 (s, 3H), 2.96 (d, J = 4.8 Hz, 3H), 1.41 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 158.8, 156.0, 132.0, 127.2, 102.4, 94.9, 86.1, 56.7, 43.6, 26.6, 26.1 (2C); IR (KBr) ν_{max} 3293, 2964, 1634, 1463, 1260, 1106 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{17}BrNO_3$ $(M+H)^+$: calcd. 314.0392, found 314.0388.

6,7-Dimethoxy-*N*-3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (62p):



62p (73 mg, 91%) as colourless solid. m.p. = 171–173 °C; R_f = 0.22 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ6.40 (s, 1H), 5.87 (bs, 1H), 4.21 (s, 2H), 3.92 (s, 3H), 3.81 (s, 3H), 2.96 (d, J = 4.8 Hz, 3H), 1.41 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ169.3, 152.2, 151.7, 135.0, 128.8, 127.0, 103.5, 86.3, 60.6, 56.5, 42.9, 26.6, 25.9 (2C); IR (KBr) ν_{max} 3408, 2936, 1665, 1605, 1238, 1106 cm^{-1}; **HRMS (ESI)** for $C_{14}H_{20}NO_4$ $(M+H)^+$: calcd. 266.1392, found 266.1391.

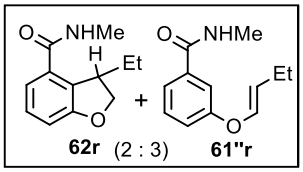
3-(Methoxymethyl)-*N*-3-dimethyl-2,3-dihydrobenzofuran-4-carboxamide (62q):



62q (68 mg, 96%) as colourless solid. m.p. = 150–152 °C; R_f = 0.28 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.60 (bs, 1H), 4.48 (d, J = 8.8 Hz, 1H), 4.06 (d, J = 8.8 Hz, 1H), 3.66 (d, J = 8.8 Hz, 1H), 3.60 (d, J = 8.8 Hz, 1H), 3.33 (s, 3H), 2.96 (d, J = 4.8 Hz, 3H), 1.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 160.9,

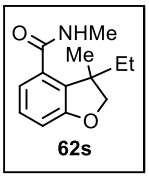
134.5, 129.6, 128.7, 119.7, 111.9, 81.1, 77.5, 59.2, 47.6, 26.5, 20.7; IR (Neat) ν_{max} 3304, 2931, 1649, 1539, 1441, 1101 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_3$ $(M+H)^+$: calcd. 236.1287, found 236.1291.

3-Ethyl-*N*-methyl-2,3-dihydrobenzofuran-4-carboxamide (62r) & (E)-3-(But-1-en-1-yloxy)-*N*-methylbenzamide (61''r):



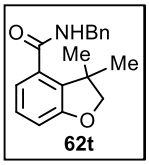
62r & **61''r** (45 mg, 73%) as colourless solid. R_f = 0.30 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.52 (dd, J = 7.6, 1.6 Hz, 1H), 7.46 (s, 1H), 7.31–7.23 (m, 3H), 7.14 (t, J = 7.8 Hz, 1.5H), 6.96 (d, J = 7.6 Hz, 1.5H), 6.87 (d, J = 8.0 Hz, 1.5H), 6.03 (bs, 1.5H), 5.94 (bs, 1H), 4.55 (t, J = 8.2 Hz, 1.5H), 4.40 (dd, J = 8.8, 3.6 Hz, 1.5H), 3.88–3.79 (m, 1.5H), 3.05 (d, J = 4.8 Hz, 3H), 2.99 (d, J = 5.2 Hz, 4.5H), 2.80–2.71 (m, 1.5H), 1.80–1.68 (m, 2H), 1.58–1.46 (m, 1.5H), 1.24 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4Hz, 4.5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 168.6, 160.7, 156.1, 142.2, 132.4, 130.8, 130.6, 128.3, 125.0, 123.6, 122.6, 120.9, 118.2, 113.4, 111.8, 76.2, 42.8, 27.1, 26.8, 26.6, 18.1, 13.5, 11.0; IR (Neat) ν_{max} 3282, 2969, 1632, 1545, 1238, 1095, 1057, 810 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{16}NO_2$ $(M+H)^+$: calcd. 206.1181, found 206.1184.

3-Ethyl-*N*-3-dimethyl-2,3-dihydrobenzofuran-4-carboxamide (62s):



62s (48 mg, 72%) as colourless viscous liquid. R_f = 0.48 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.12 (t, J = 7.8 Hz, 1H), 6.88–6.81 (m, 2H), 5.81 (bs, 1H), 4.36 (d, J = 8.4 Hz, 1H), 4.11 (d, J = 8.8 Hz, 1H), 2.98 (d, J = 4.8 Hz, 3H), 2.03–1.90 (m, 1H), 1.82–1.69 (m, 1H), 1.42 (s, 3H), 0.80 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 160.8, 133.9, 132.5, 128.3, 118.9, 111.6, 82.3, 46.9, 31.5, 26.6, 24.6, 9.2; IR (Neat) ν_{max} 3304, 2926, 1643, 1539, 1441, 1254 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_2$ $(M+H)^+$: calcd. 220.1338, found 220.1332.

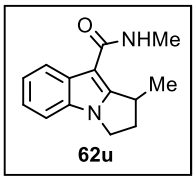
***N*-Benzyl-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxamide (62t):**



62t (79 mg, 93%) as colourless solid. m.p. = 119–120 °C; R_f = 0.42 (7:3) hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.33 (m, 4H), 7.33–7.25

(m, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.89 (d, J = 6.8 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.20 (bs, 1H), 4.61 (d, J = 5.6 Hz, 2H), 4.18 (s, 2H), 1.46 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ168.6, 160.3, 138.0, 134.1, 133.3, 128.7 (2C), 128.2, 127.8 (2C), 127.6, 118.9, 111.9, 85.2, 43.9, 43.0, 25.9 (2C); IR (Neat) ν_{max} IR (Neat) ν_{max} 3276, 2980, 2953, 1649,1627, 1523, 1194 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{20}NO_2$ $(M+H)^+$: calcd. 282.1494, found 282.1490.

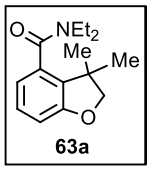
***N*-1-Dimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide (62u):**



62u

62u (47 mg, 68%) as colourless solid. m.p. = 218–220 °C; R_f = 0.19 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.73 (m, 1H), 7.31–7.24 (m, 1H), 7.23–7.17 (m, 2H), 5.87 (bs, 1H), 4.18–4.04 (m, 2H), 3.81–3.71 (m, 1H), 3.05 (d, J = 4.8 Hz, 3H), 2.91–2.78 (m, 1H), 2.32–2.21 (m, 1H), 1.45 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ166.2, 154.4, 132.2, 129.2, 121.3, 121.0, 119.3, 110.3, 102.4, 42.9, 35.6, 33.3, 26.2, 19.2; IR (KBr) ν_{max} 3287, 2926, 2849, 1742, 1621, 1463 cm^{-1}; **HRMS (ESI)** for $C_{14}H_{17}N_2O$ $(M+H)^+$: calcd. 229.1341, found 229.1348.

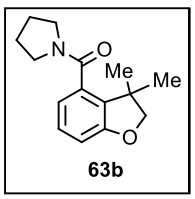
***N*,*N*-diethyl-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxamide (63a):**



63a

63a (55 mg, 74%) as colourless viscous liquid. R_f = 0.29 (7:3 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.10 (bt, J = 7.6 Hz, 1H), 6.77 (bd, J = 8.0 Hz, 1H), 6.66 (bd, J = 7.2 Hz, 1H), 4.17 (bs, 2H), 3.79 (bs, 1H), 3.34 (bs, 1H), 3.16 (bs, 2H), 1.50–1.20 (m, 9H), 1.09 (t, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ169.4, 160.0, 133.4, 131.7, 128.2, 117.9, 110.2, 84.7, 43.0, 42.8, 38.4, 13.8, 12.5; IR (Neat) ν_{max} 2964, 2865, 1632, 1430, 1282, 1117 cm^{-1}; **HRMS (ESI)** for $C_{15}H_{22}NO_2$ $(M+H)^+$: calcd. 248.1651, found 248.1643.

(3,3-Dimethyl-2,3-dihydrobenzofuran-4-yl)(pyrrolidin-1-yl)methanone (63b):



63b

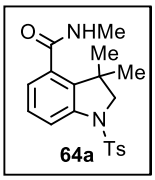
63b (64 mg, 87%) as colourless viscous liquid. R_f = 0.33 (1:1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, J = 7.8 Hz, 1H), 6.79 (dd, J = 8.4, 0.8 Hz, 1H), 6.71 (dd, J = 7.6, 0.8 Hz, 1H), 4.17 (s, 2H), 3.64 (t, J = 7.0 Hz, 2H), 3.21 (t, J = 6.8 Hz, 2H), 2.01–1.91 (m, 2H), 1.90–1.79 (m, 2H), 1.36 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ168.4, 160.1, 134.1, 131.7,

128.4, 118.2, 110.4, 84.9, 49.0, 45.3, 42.7, 26.0, 25.9 (2C), 24.6; IR (Neat) ν_{max} 2969, 2865, 2350, 1627, 1430, 1249, 1189 cm^{-1}; **HRMS (ESI)** for $C_{15}H_{20}NO_2$ $(M+H)^+$: calcd. 246.1494, found 246.1495.

2.7.3.10. General Procedure for Hydroarylation of *N*-Tethered Compounds (61x–z) (GP-10):

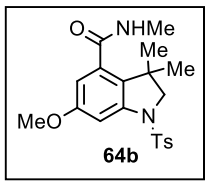
The hydroarylation reaction was conducted in a 20 mL Schlenk tube having high pressure valve and side arm. The tube was charged with (**61**, 0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (9.2 mg, 5.0 mol %), and $Mn(OAc)_2$ (27 mg, 0.15 mmol). Subsequently, the additive $AgSbF_6$ (21 mg, 0.06 mmol) was introduced to the flask in a glove box. 1,2-Dichloroethene (DCE) (1.0 mL) was added to the mixture and the resulting mixture was stirred at 110 °C for 24 h. The reaction mixture was filtered through a small plug of Celite and washed with dichloromethane (3 × 5.0 mL). The solvents were evaporated under the reduced pressure and the crude material was purified using column chromatography on silica gel.

_N_-3,3-Trimethyl-1-tosylindoline-4-carboxamide (64a):



64a (89 mg, 83%) as colourless solid. m.p. = 242–243 °C; R_f = 0.25 (1:1 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–7.66 (m, 3H), 7.28–7.21 (m, 2H), 7.18 (t, J = 8.0, 1H), 6.91 (dd, J = 7.6, 0.8 Hz, 1H), 5.80 (s, 1H), 3.58 (s, 2H), 2.92 (d, J = 4.8 Hz, 3H), 2.37 (s, 3H), 1.22 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 144.3, 141.9, 137.1, 134.0, 133.9, 129.7 (2C), 128.1, 127.2 (2C), 122.0, 115.8, 64.5, 41.3, 26.6, 26.5 (2C), 21.5; IR (Neat) ν_{max} 3287, 2920, 2860, 1638, 1353, 1260 1161 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{23}N_2O_3S$ $(M+H)^+$: calcd. 359.1429, found 359.1430.

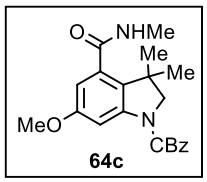
6-Methoxy-*N*-3,3-trimethyl-1-tosylindoline-4-carboxamide (64b):



64b (108 mg, 93%) as colourless solid. m.p. = 230–232 °C; R_f = 0.20 (1:1 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ7.71 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 2.4 Hz, 1H), 7.26 (d, J = 7.6 Hz, 2H), 6.46 (d, J = 2.4 Hz, 1H), 5.74 (bs, 1H), 3.81 (s, 3H), 3.60 (s, 2H), 2.93 (d, J = 4.8 Hz, 3H), 2.39 (s,

3H), 1.20 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 159.5, 144.3, 143.0, 134.2, 134.0, 129.7 (2C), 129.0, 127.2 (2C), 107.6, 102.0, 65.0, 55.6, 40.5, 26.6 (2C), 26.5, 21.5; IR (Neat) ν_{max} 3315, 2931, 1649, 1556, 1347, 1320, 1167 cm^{-1}; **HRMS (ESI)** for $C_{20}H_{25}N_2O_4S$ $(M+H)^+$: calcd. 389.1535, found 389.1535.

6-Methoxy-*N*,3,3-trimethyl-1-tosylindoline-4-carboxamide (64c):



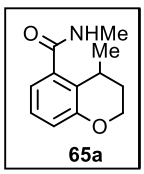
64c

64c (99 mg, 90%) as colourless solid. m.p. = 160–161 °C; R_f = 0.24 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (bs, 1H), 7.41–7.30 (m, 5H), 6.44 (s, 1H), 6.02 (bs, 1H), 5.23 (s, 2H), 3.77–3.70 (m, 5H), 2.93 (d, J = 4.8 Hz, 3H), 1.38 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 159.4, 153.0, 136.0, 133.8, 128.6 (3C), 128.2 (2C), 128.0 (2C), 107.6, 102.0, 63.7, 55.5, 40.1, 29.6, 27.1, 26.6 (2C); IR (Neat) ν_{max} 3320, 2964, 1665, 1600, 1539, 1391, 1221 cm^{-1}; **HRMS (ESI)** for $C_{21}H_{25}N_2O_4$ $(M+H)^+$: calcd. 369.1814, found 369.1813.

2.7.3.11. General Procedure for Hydroarylation of O-Tethered Compounds (61′) (GP-11):

The hydroarylation reactions were conducted in a 20 mL Schlenk tube having high pressure valve and side arm. The tube was charged with (**61′**, 0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.5 mg, 3.0 mol %), and $Mn(OAc)_2$ (13 mg, 0.075 mmol). Subsequently, the additive $AgSbF_6$ (12 mg, 0.036 mmol) was introduced to the flask in a glove box. 1,2-Dichloroethene (DCE) (1.0 mL) was added to the mixture and the resulting mixture was stirred at 70 °C for 10–15 h. The reaction mixture was filtered through a small plug of Celite and washed with dichloromethane (3 × 5.0 mL). The solvents were evaporated under the reduced pressure and the crude material was purified using column chromatography on silica gel.

***N*-4-Dimethylchroman-5-carboxamide (65a):**

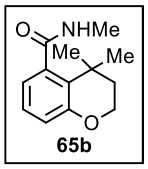


65a

65a (59 mg, 96%) as colourless solid. m.p. = 152–154 °C; R_f = 0.30 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.07 (t, J = 7.8 Hz, 1H), 6.88–6.82 (m, 2H), 5.83 (bs, 1H), 4.26–4.13 (m, 2H), 3.61–3.54 (m, 1H), 2.98 (d,

J = 4.8 Hz, 3H), 2.19–2.06 (m, 1H), 1.73–1.64 (m, 1H), 1.26 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 154.5, 137.0, 126.9, 125.9, 118.9, 118.8, 62.0, 28.8, 26.6, 24.8, 22.6; IR (Neat) ν_{max} 3326, 2953, 2915, 1627, 1523, 1287, 1216 cm^{-1}; **HRMS (ESI)** for $C_{12}H_{16}NO_2$ $(M+H)^+$: calcd. 206.1181, found 206.1184.

***N*-4,4-Trimethylchroman-5-carboxamide (65b):**



65b

65b (47 mg, 71%) as colourless solid. m.p. = 175–177 ^{o}C; R_f = 0.35 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (t, J = 7.8 Hz, 1H), 6.80 (dd, J = 8.2, 1.4 Hz, 1H), 6.73 (dd, J = 7.4, 1.4 Hz, 1H), 5.85 (bs, 1H), 4.25–4.19 (m, 2H), 2.94 (d, J = 4.8 Hz, 3H), 1.80–1.73 (m, 2H), 1.44 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 154.1, 138.0, 128.2, 127.0, 120.1, 118.9, 62.4 , 39.4, 31.5, 29.2 (2C), 26.7; IR (Neat) ν_{max} 3271, 3002, 2931, 1627, 1446, 1243, 1167, 1002 cm^{-1}; **HRMS (ESI)** for $C_{13}H_{18}NO_2$ $(M+H)^+$: calcd. 220.1338 found 220.1340.

2.8. Reference

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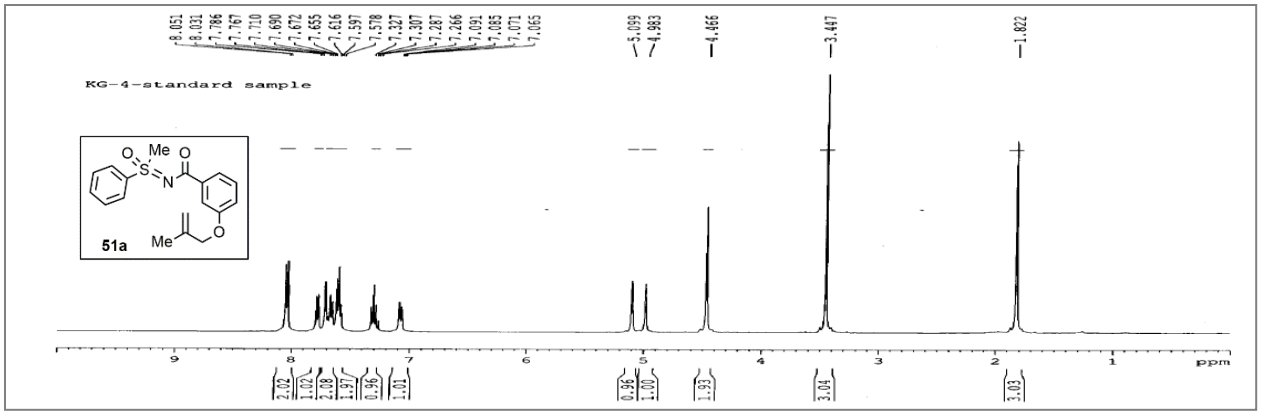
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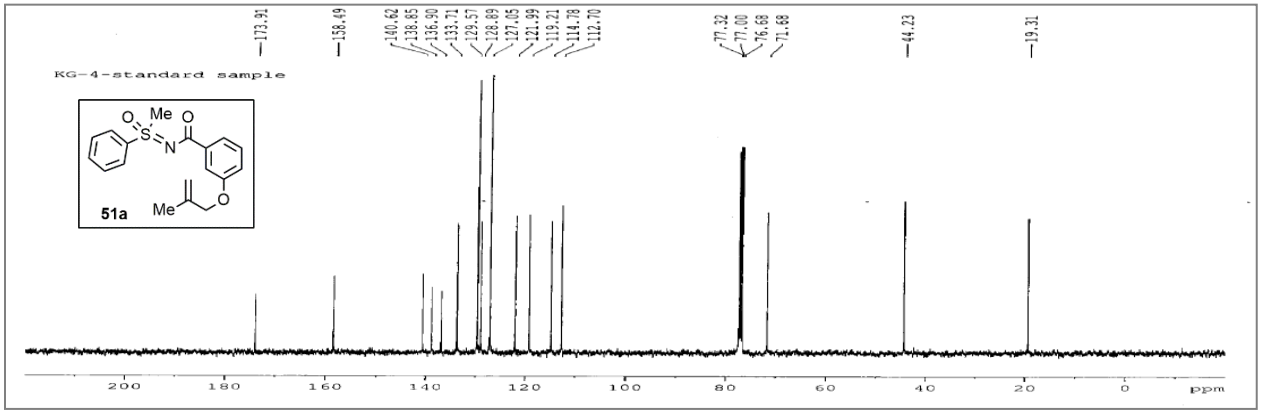
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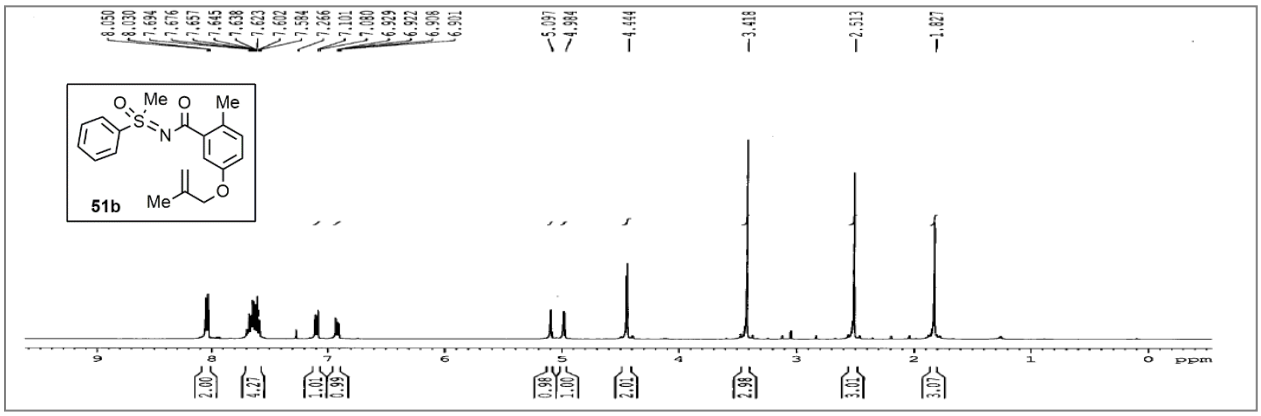
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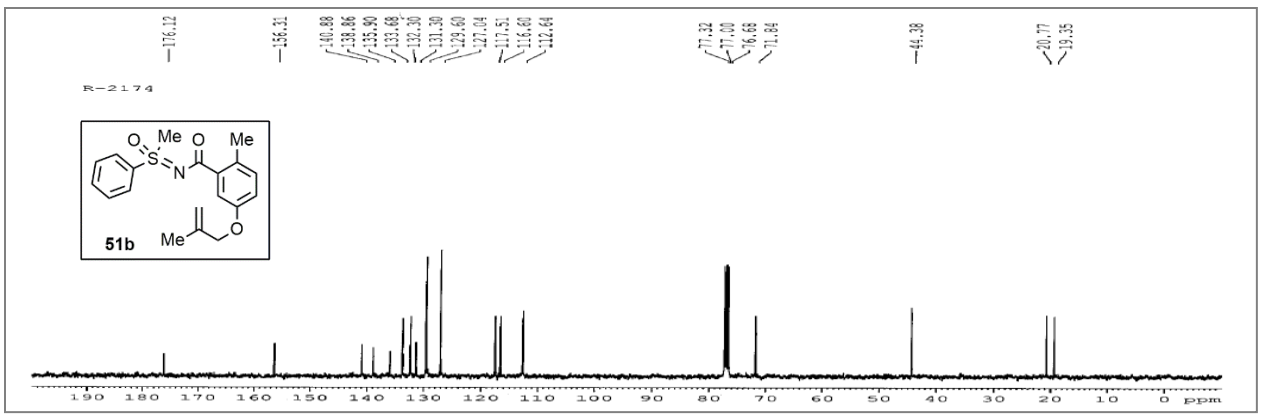
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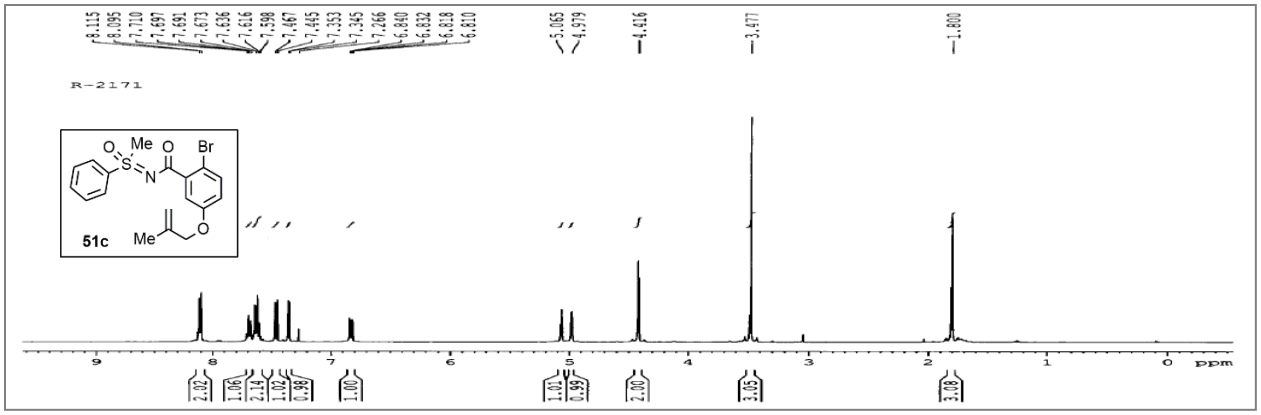
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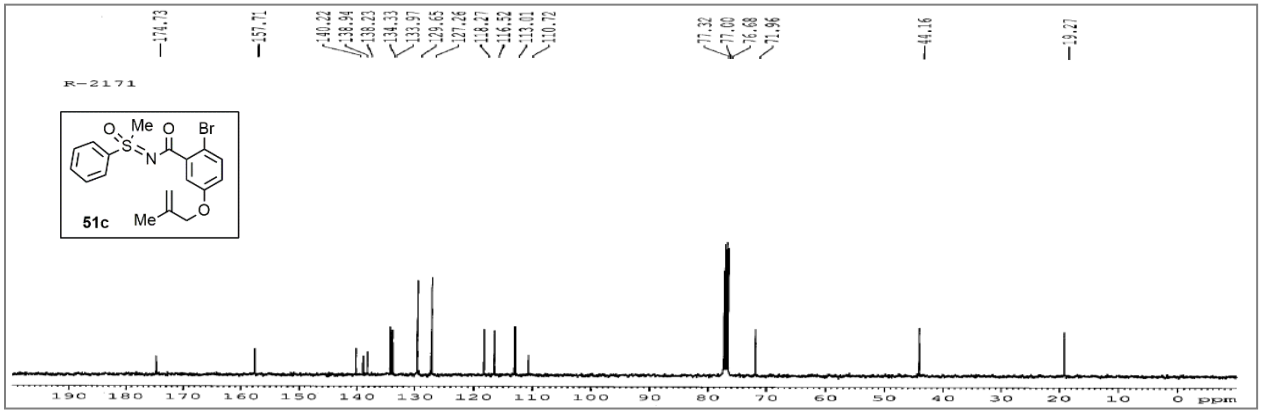

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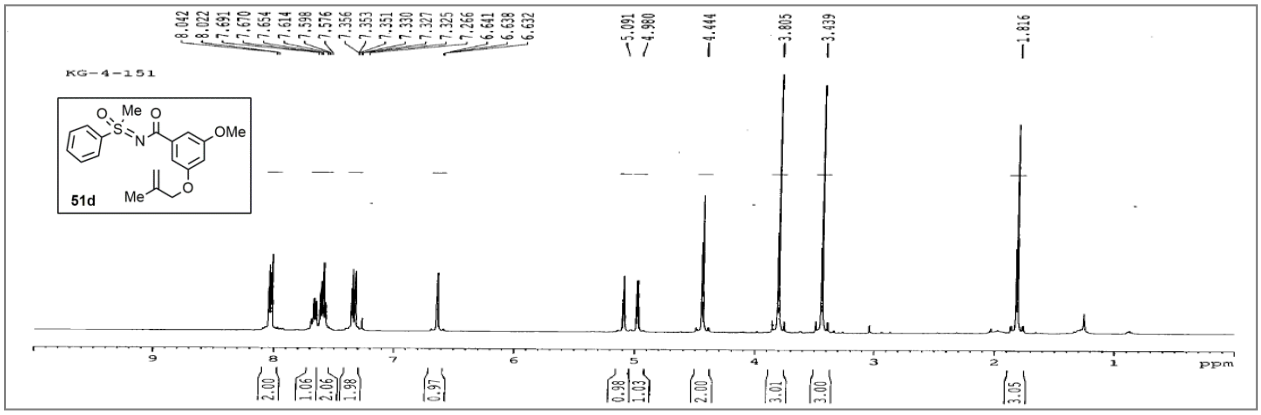

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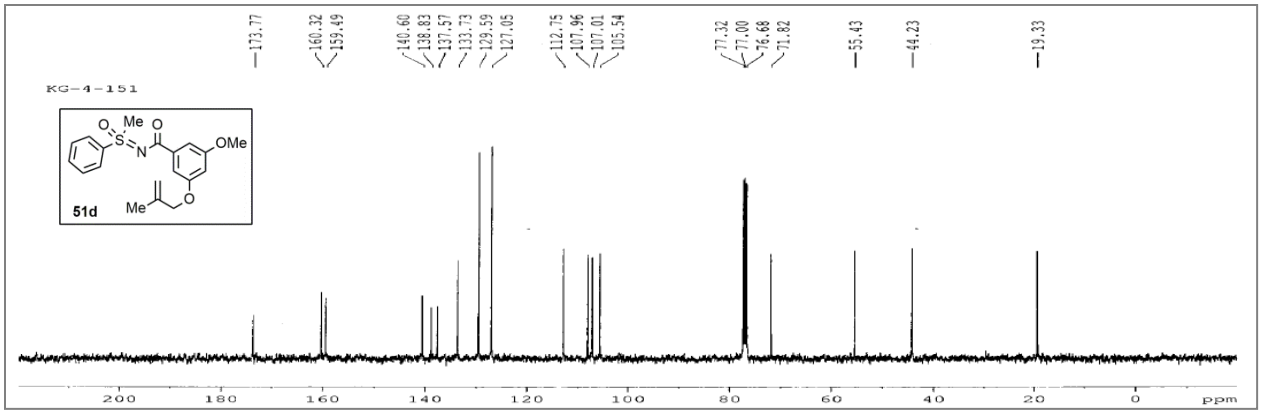

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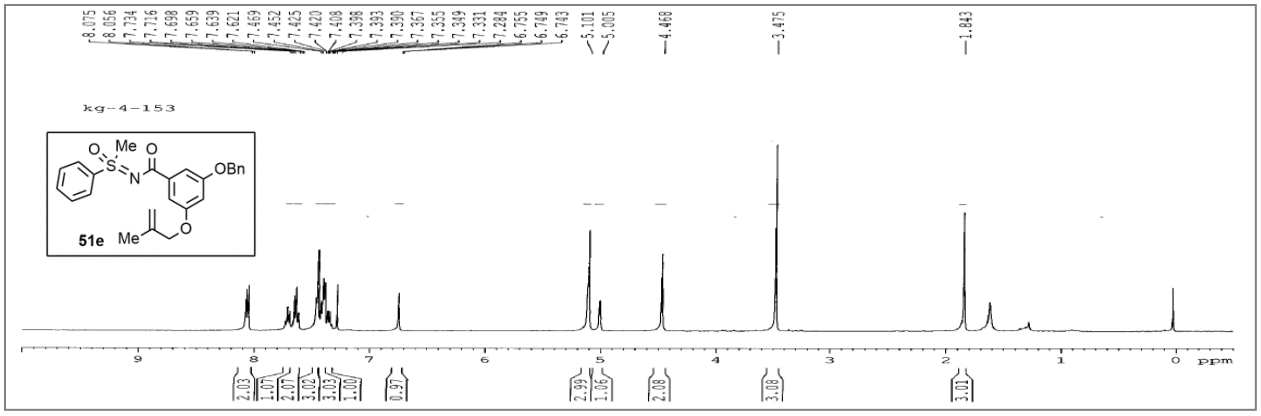

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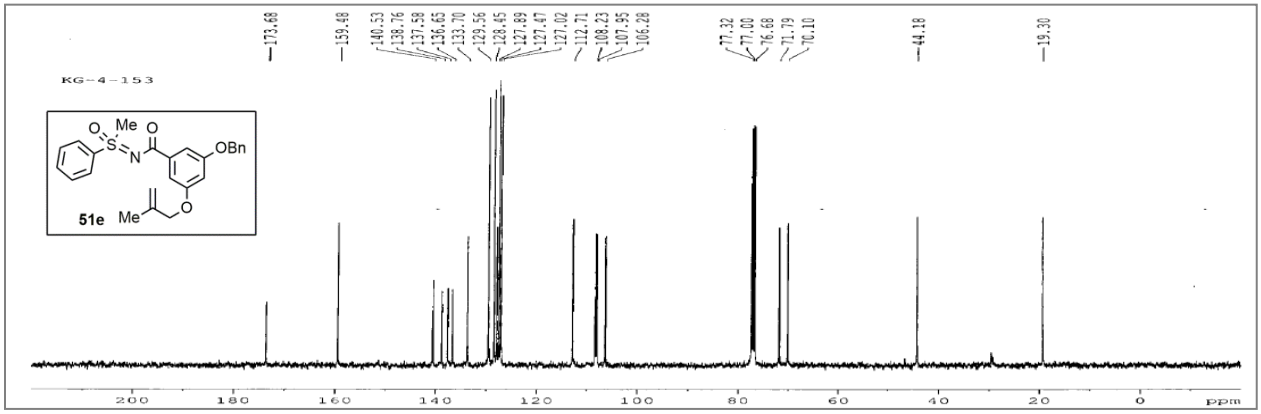

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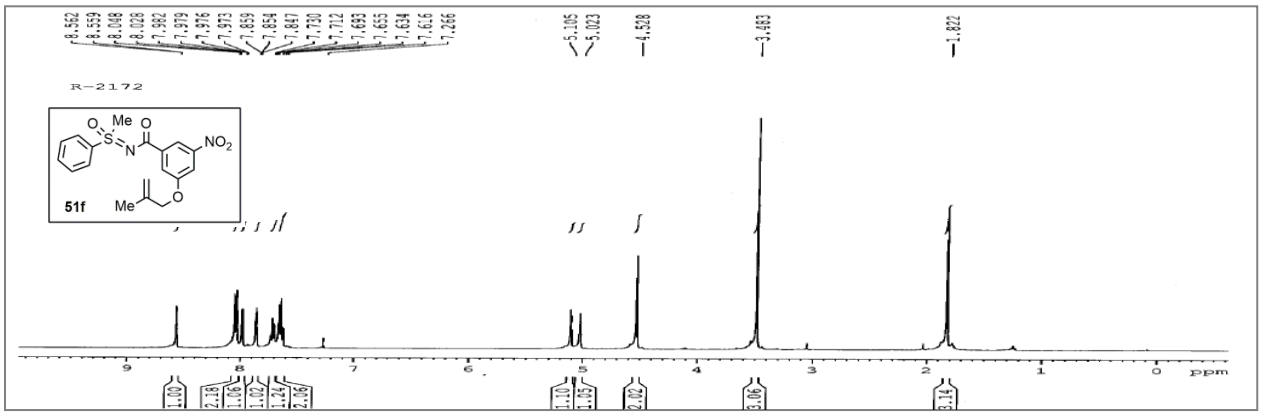

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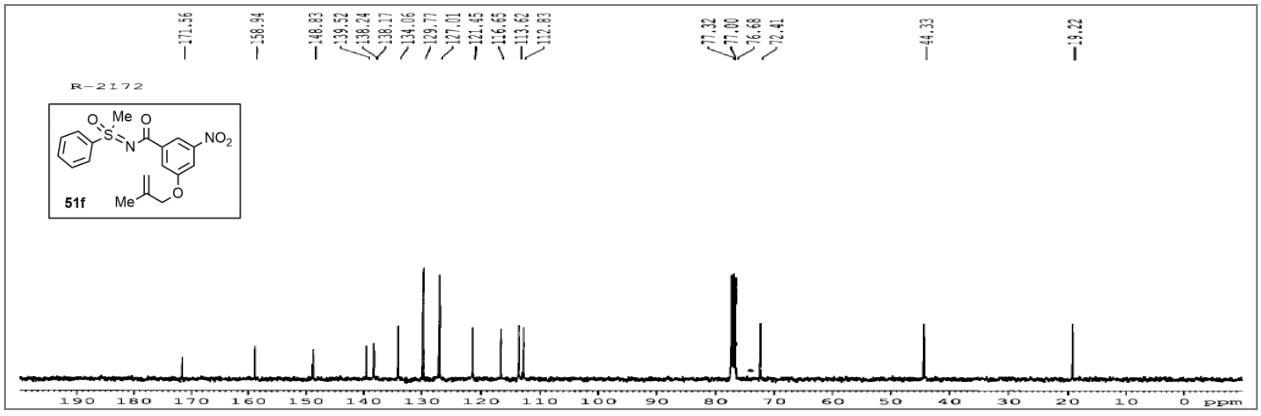

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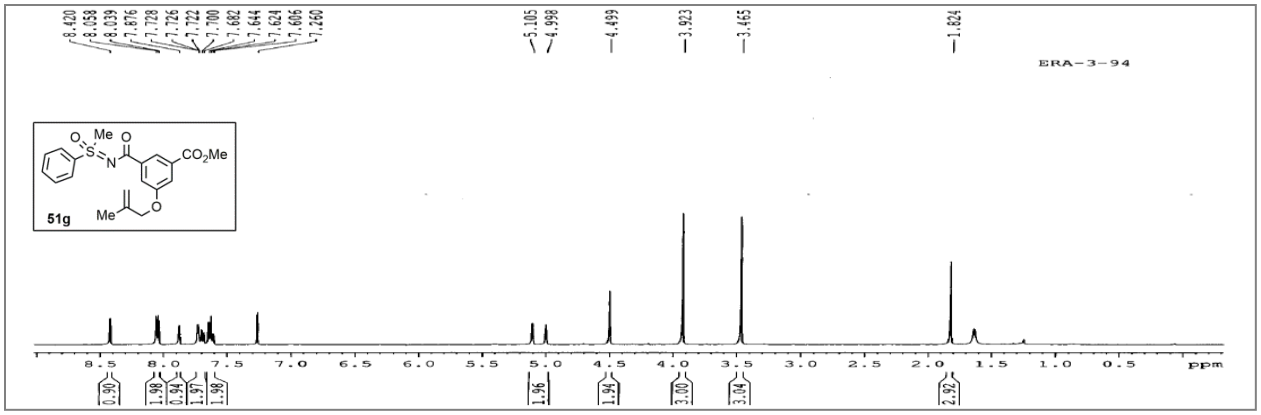

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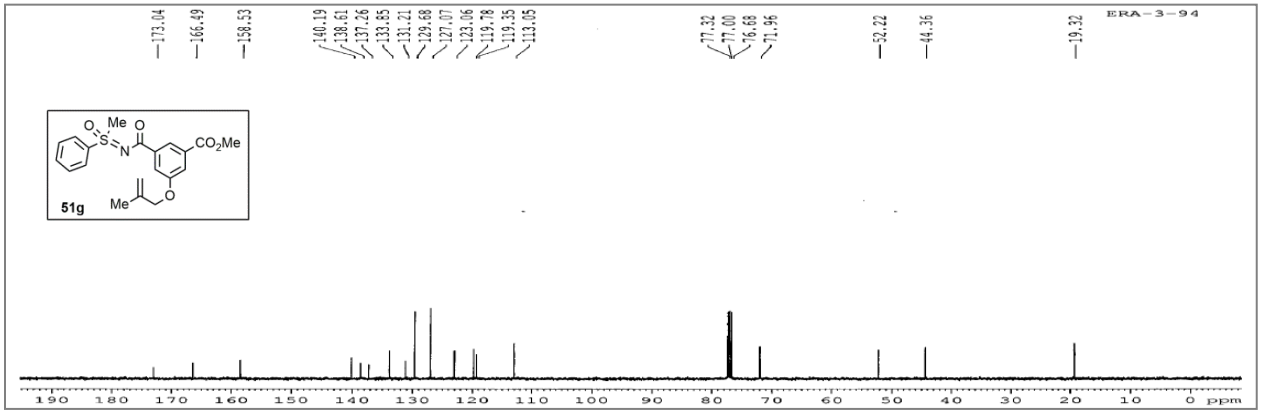

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7.355
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ppm

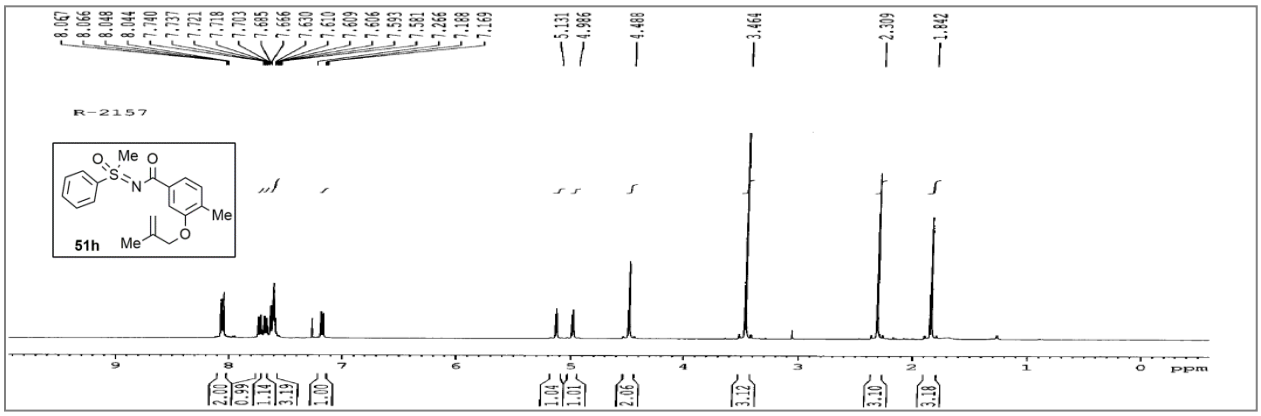

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106.28
77.32
77.00
76.68
71.79
70.10
44.18
19.30
ppm

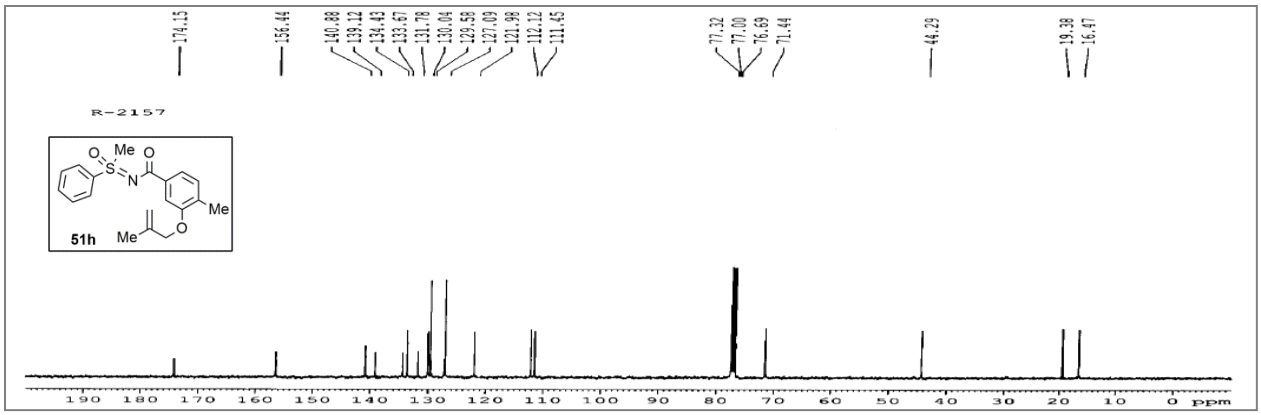

R-2172
51f
8.562
8.559
8.048
8.026
7.982
7.979
7.976
7.973
7.859
7.854
7.847
7.730
7.712
7.693
7.653
7.634
7.616
7.266
5.105
5.023
4.528
3.483
1.822
ppm

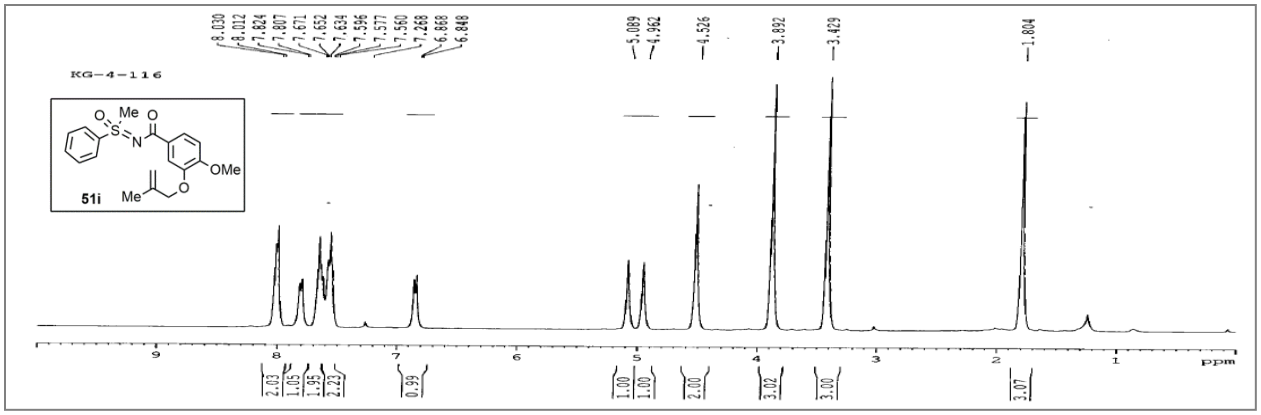

R-2172
51f
171.56
158.94
148.83
139.52
138.24
138.17
134.06
129.77
127.01
121.45
116.65
113.62
112.83
77.32
77.00
76.68
72.41
44.33
19.22
ppm

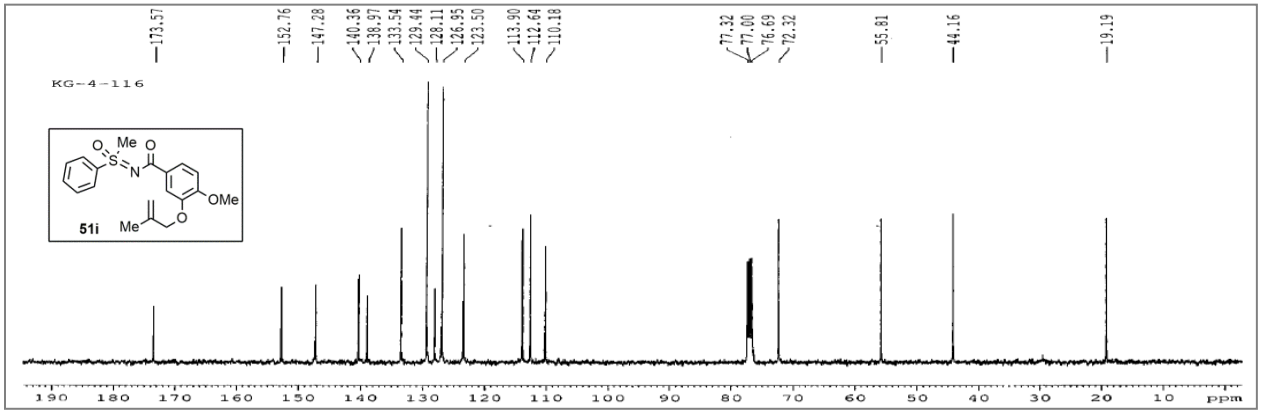

ERA-3-94
51g
ppm

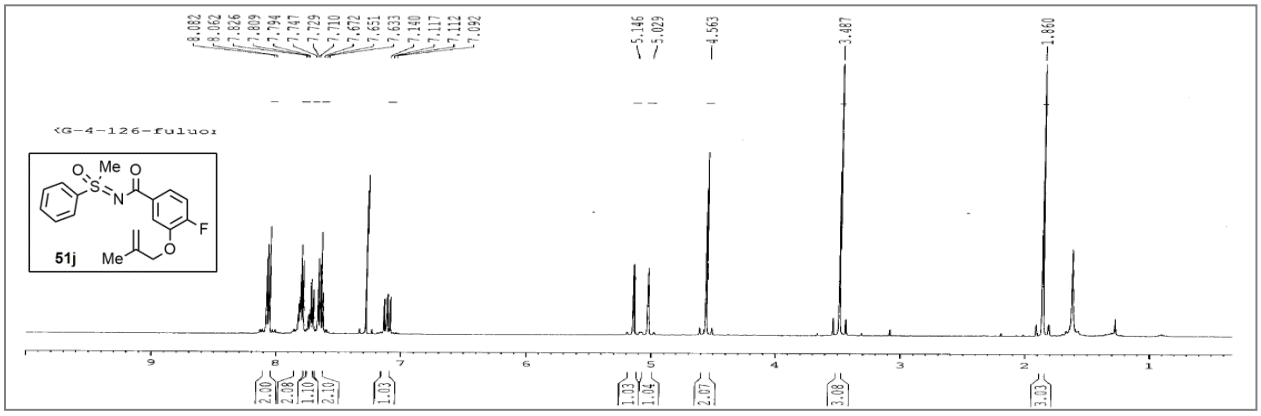

ERA-3-94
51g
ppm

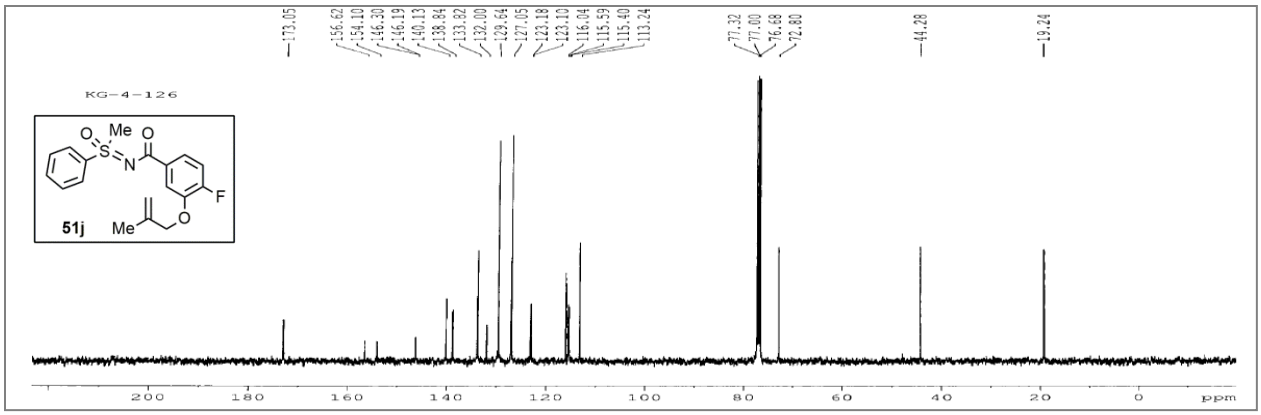

R-2157
51h
ppm

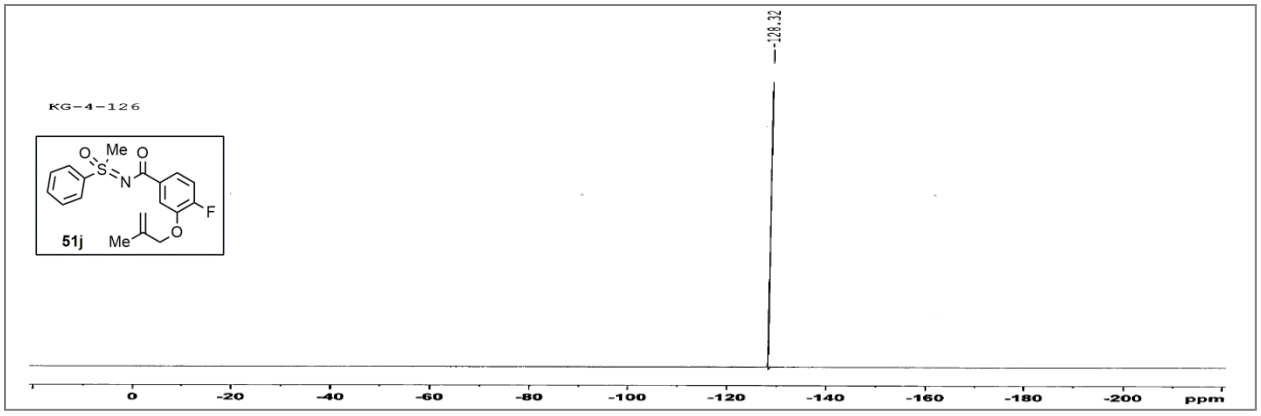

R-2157
51h
ppm

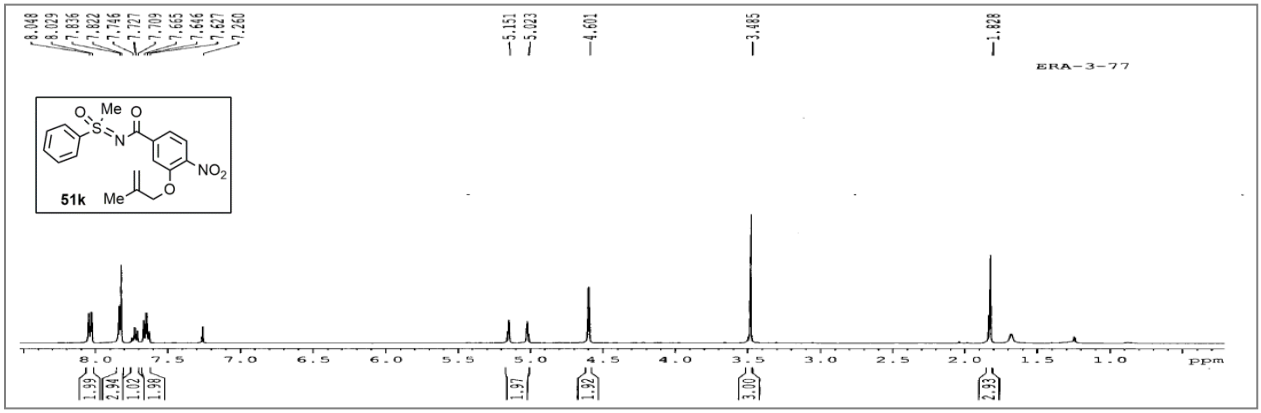

KG-4-116
51i
OMe
Me
ppm

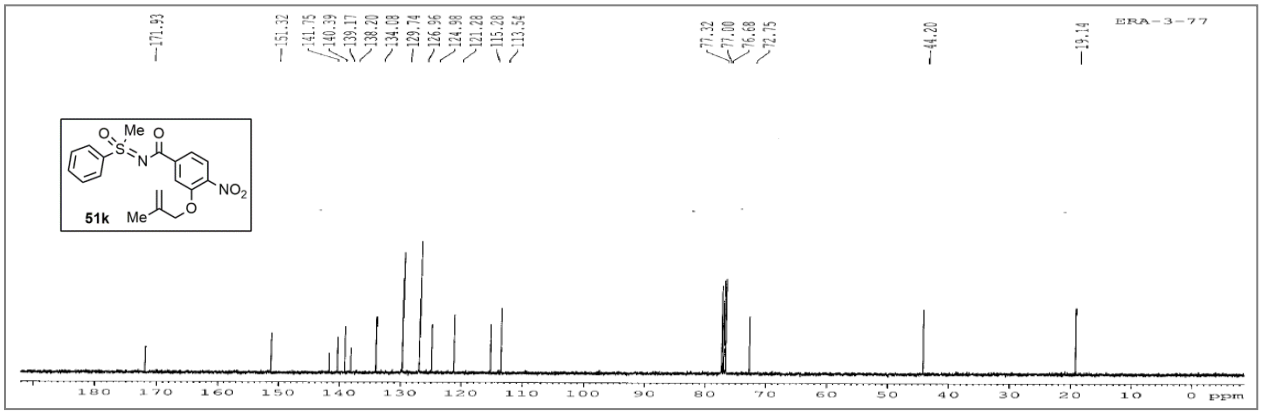

KG-4-116
51i
OMe
Me
ppm

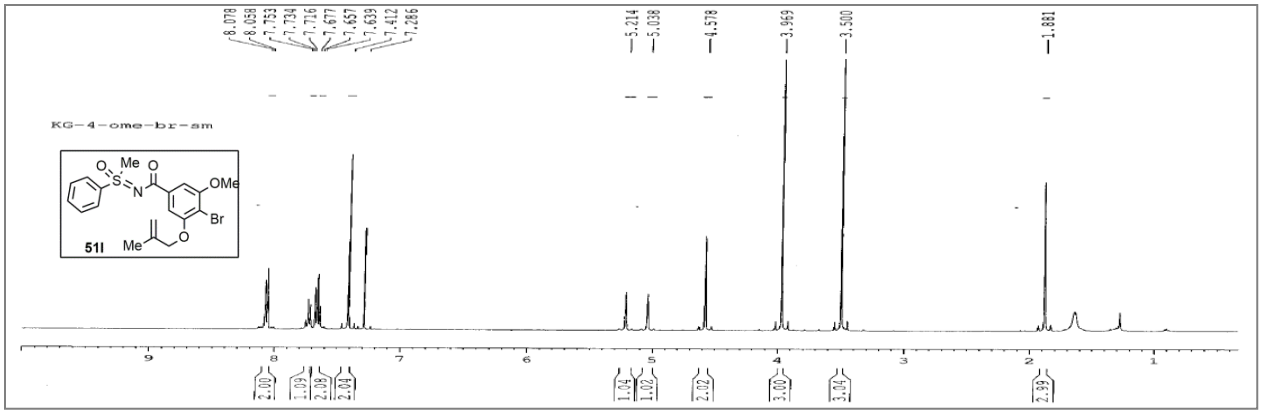

51j
F
Me
ppm

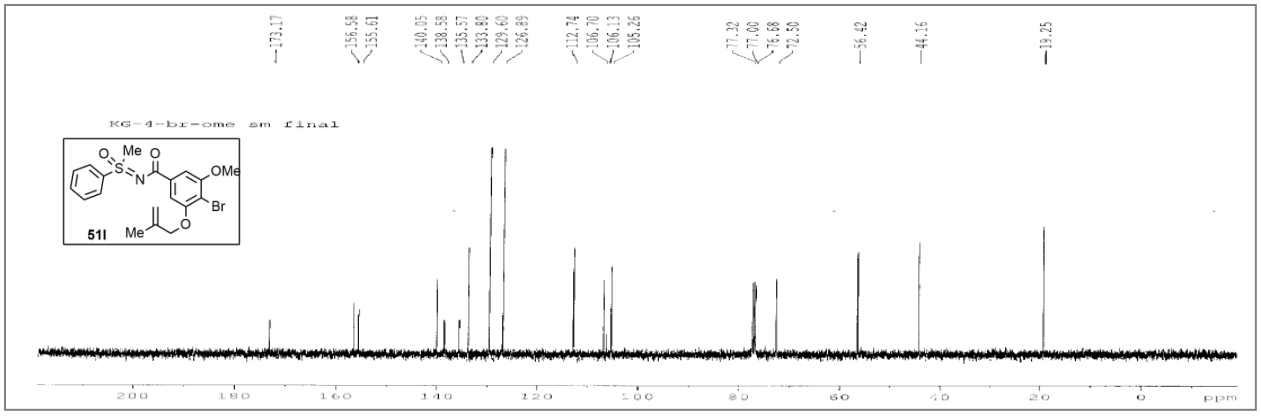

KG-4-126
51j
F
Me
ppm

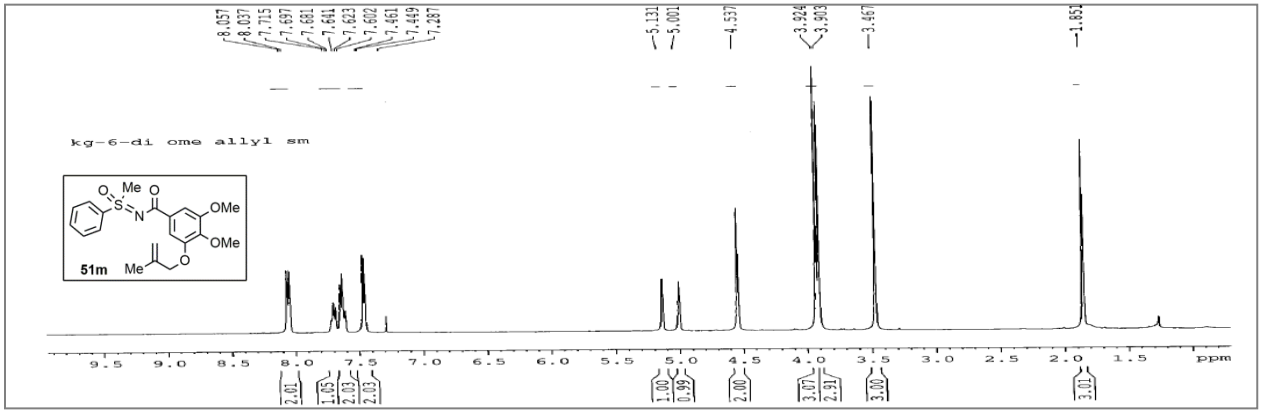

KG-4-126
-128.32
51j
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

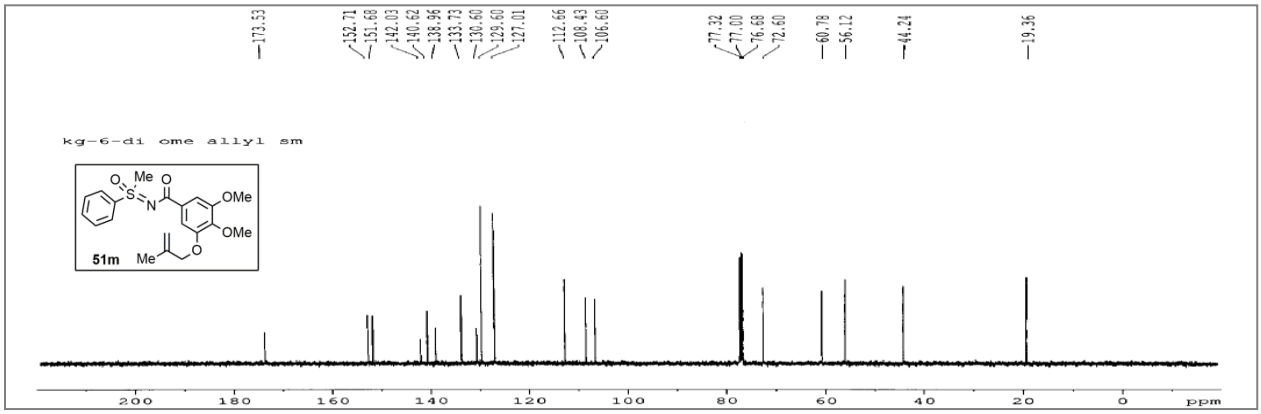

8.048
8.029
7.836
7.822
7.746
7.727
7.709
7.665
7.646
7.627
7.260
5.151
5.023
4.601
3.485
1.828
ERA-3-77
51k
1.99
2.94
1.02
1.98
1.97
1.92
3.00
2.93
ppm

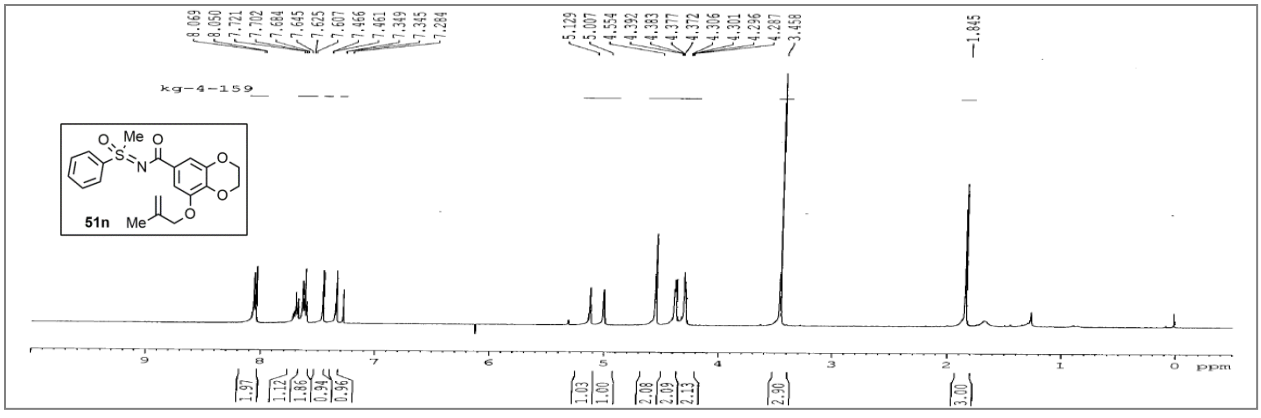

171.93
151.32
141.75
140.39
139.17
138.20
134.08
129.74
126.96
124.98
121.28
115.28
113.54
77.32
77.00
76.68
72.75
44.20
19.14
ERA-3-77
51k
ppm

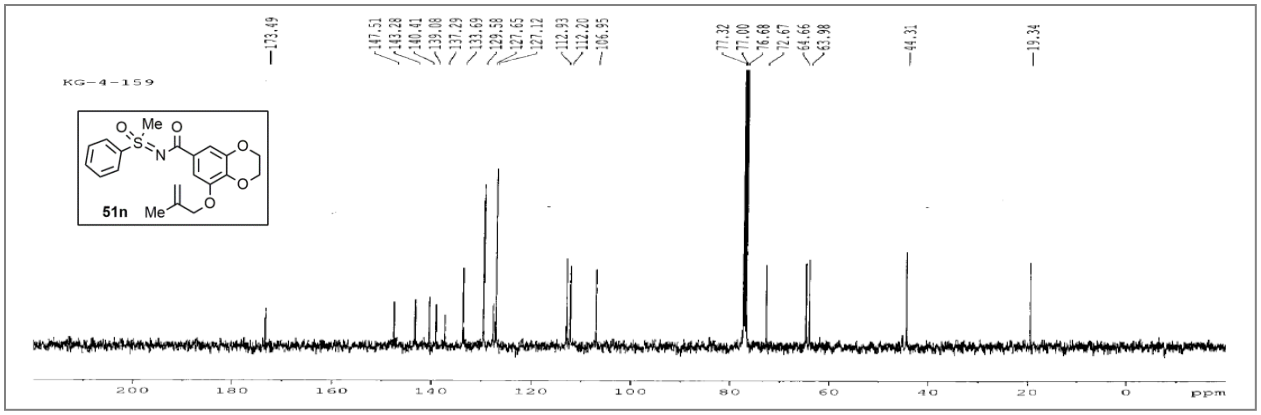

8.078
8.058
7.753
7.734
7.716
7.677
7.657
7.639
7.412
7.286
5.214
5.038
4.578
3.969
3.500
1.881
KG-4-ome-br-sm
51l
2.00
1.09
2.08
2.04
1.04
1.02
2.02
3.00
3.04
2.89

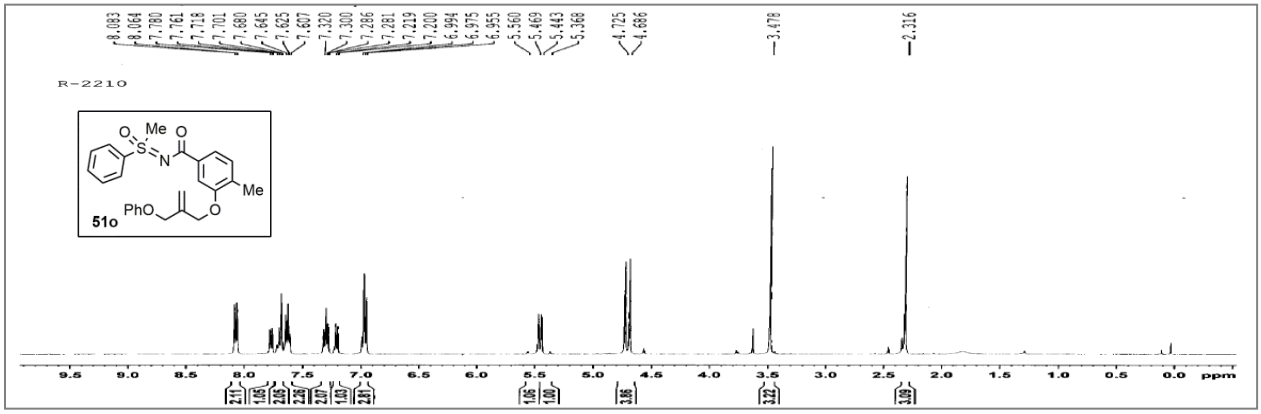

KG-4-br-ome sm final
51l

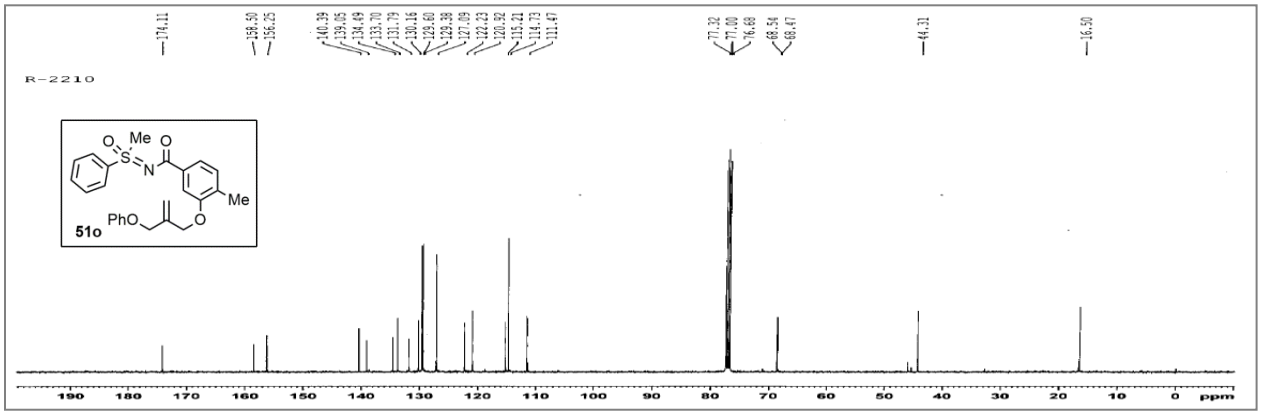

kg-6-di ome allyl sm
51m

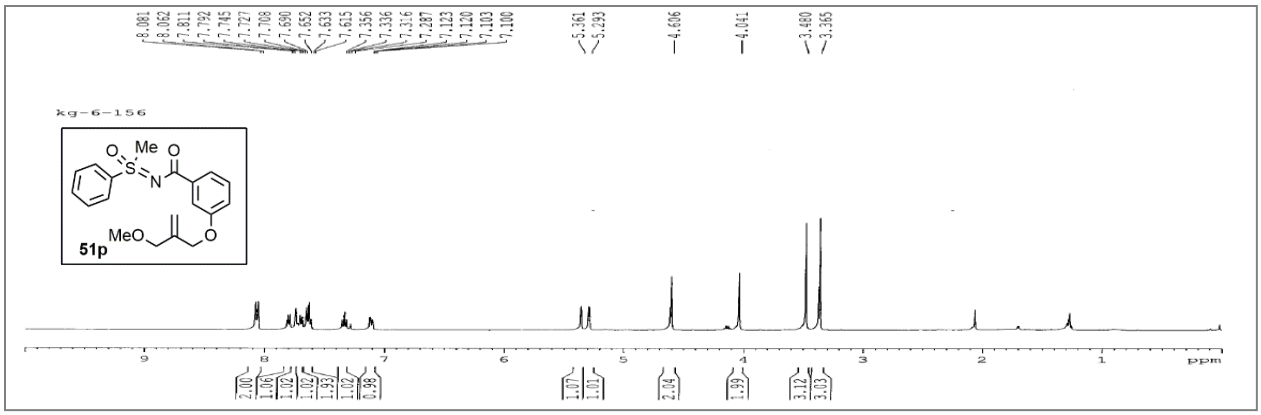

kg-6-di ome allyl sm
51m

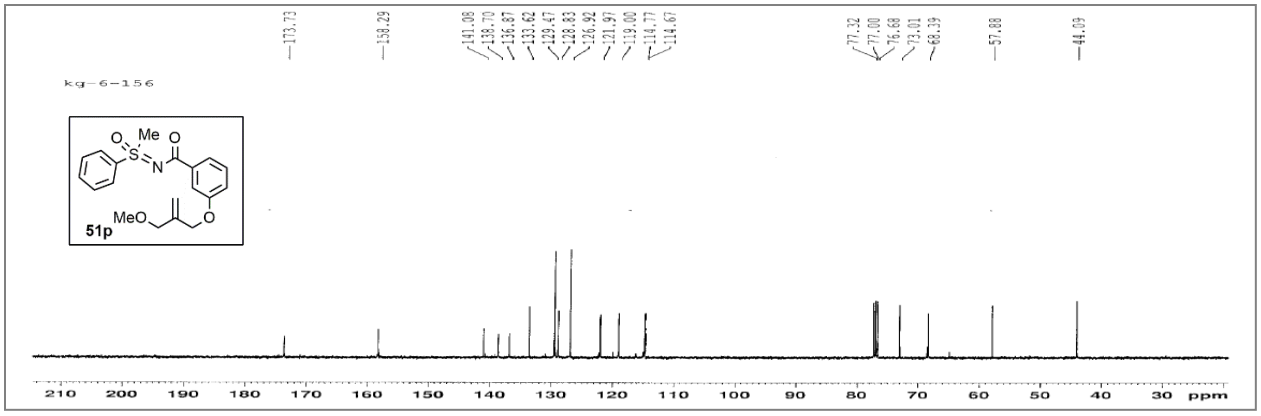

kg-4-159
51n

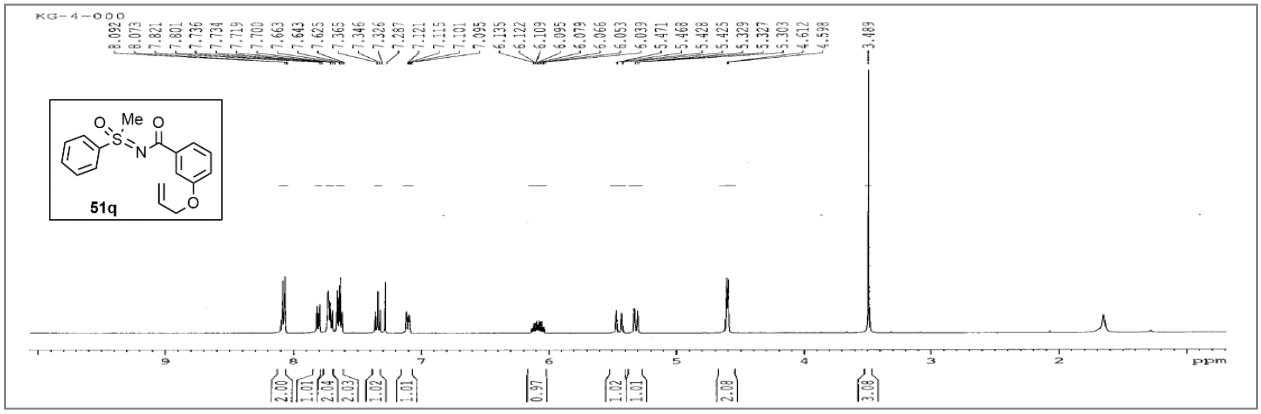

KG-4-159
51n

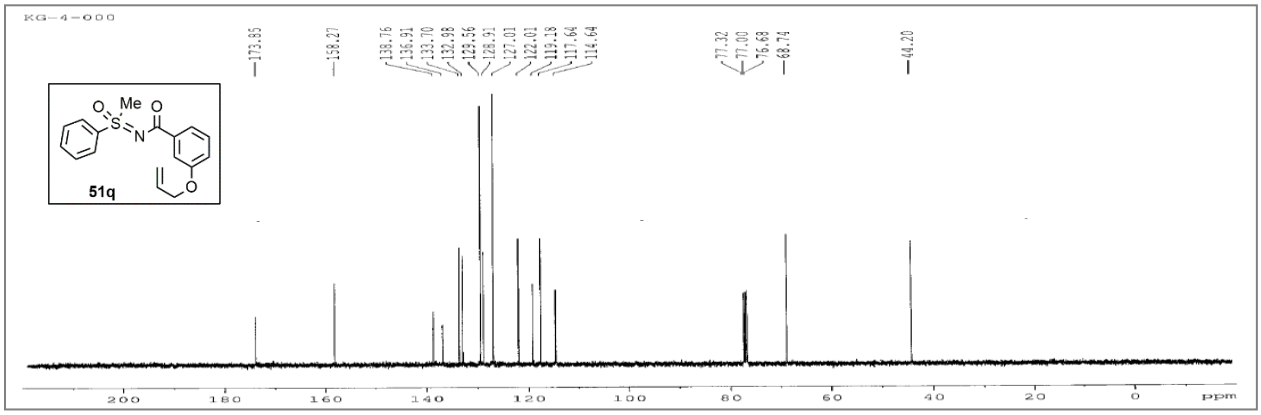

R-2210
51o

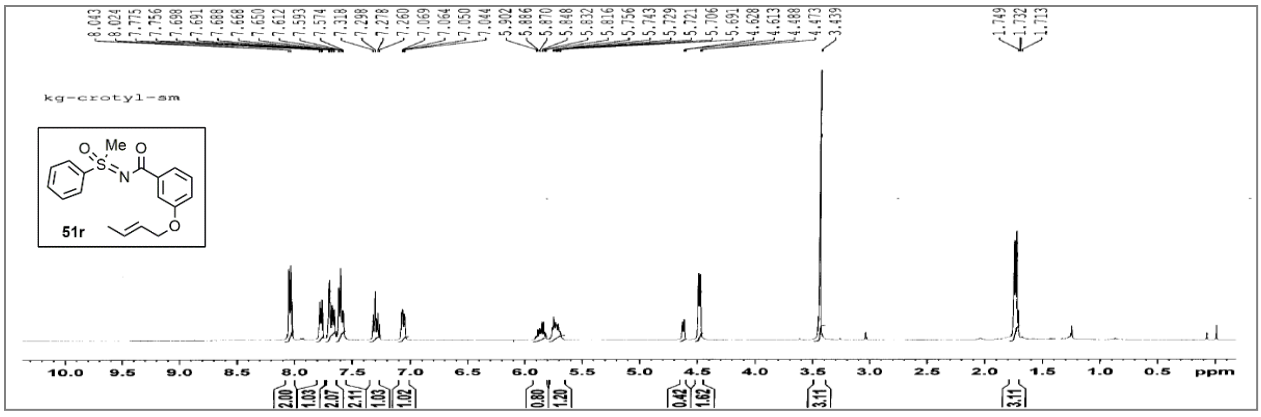

R-2210
51o

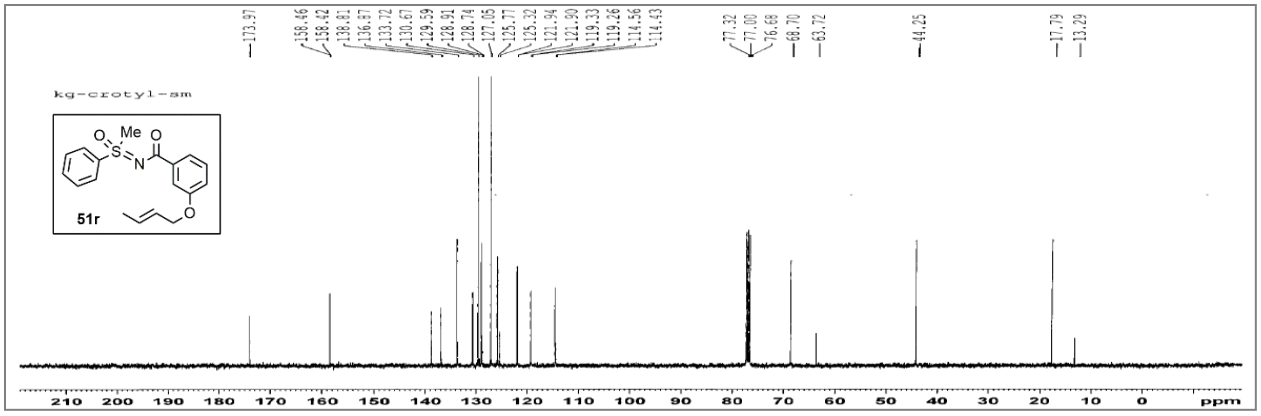

kg-6-156
51p

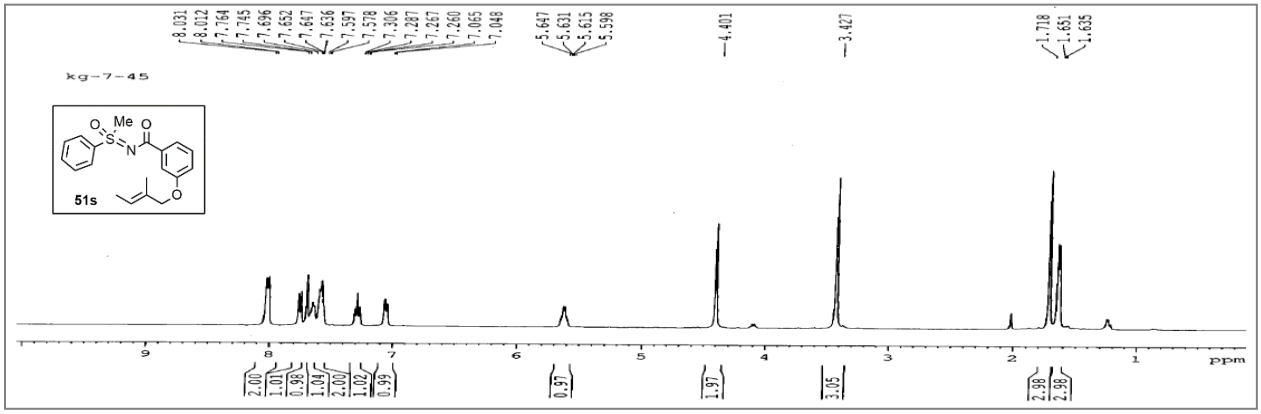

kg-6-156
51p

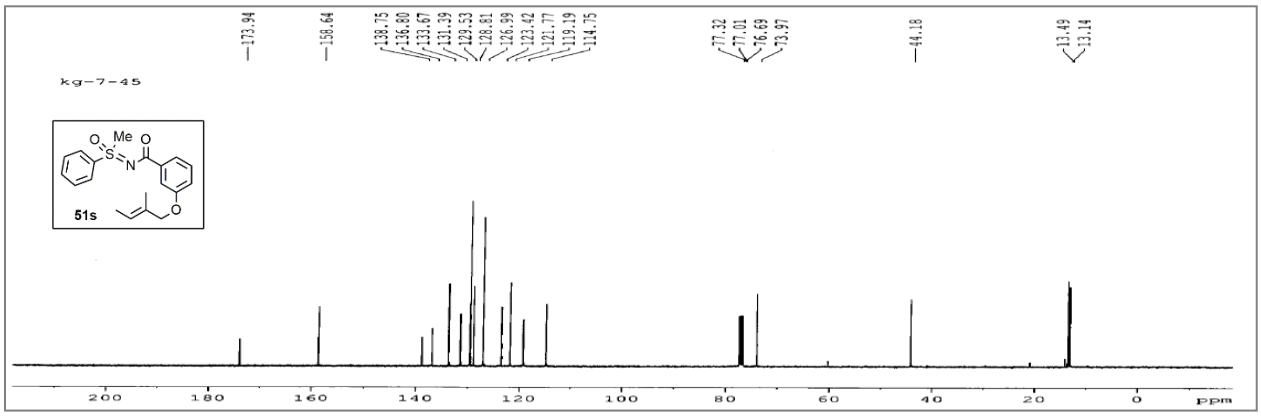

KG-4-000
51q

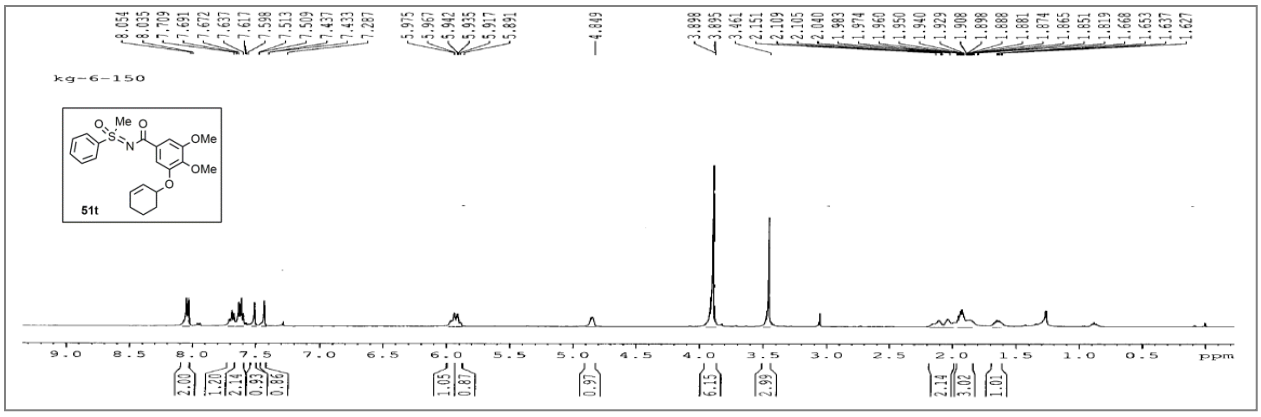

KG-4-000
51q

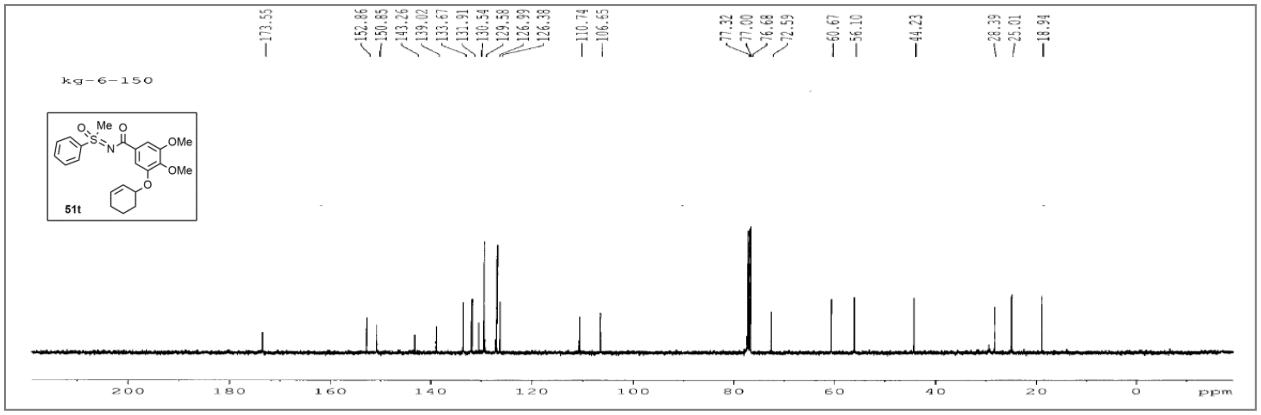

kg-crotyl-sm
51r

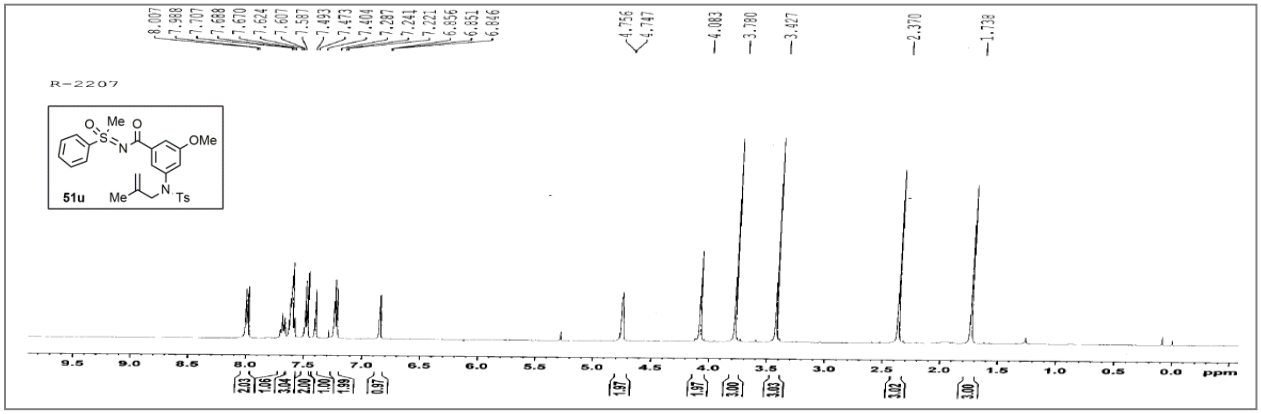

kg-crotyl-sm
51r
ppm

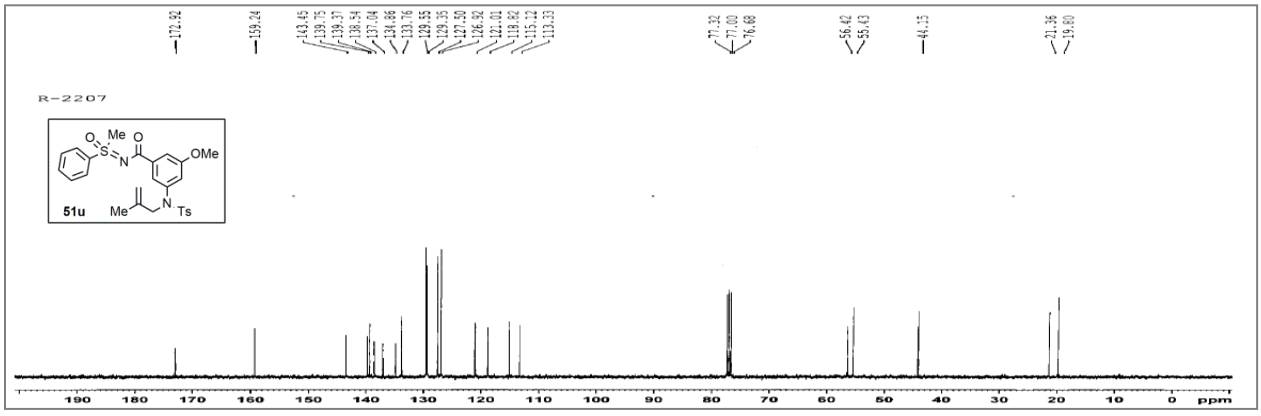

kg-7-45
51s
ppm

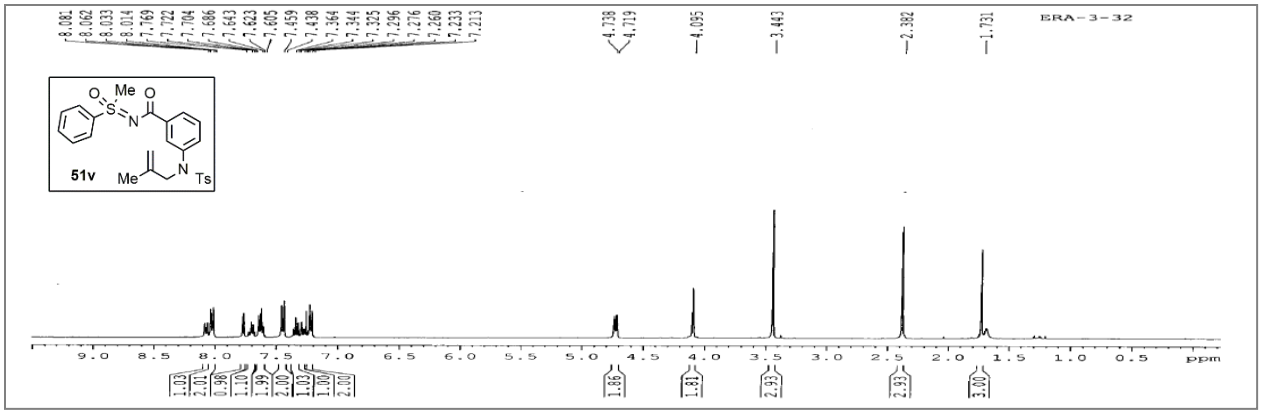

kg-7-45
51s
ppm

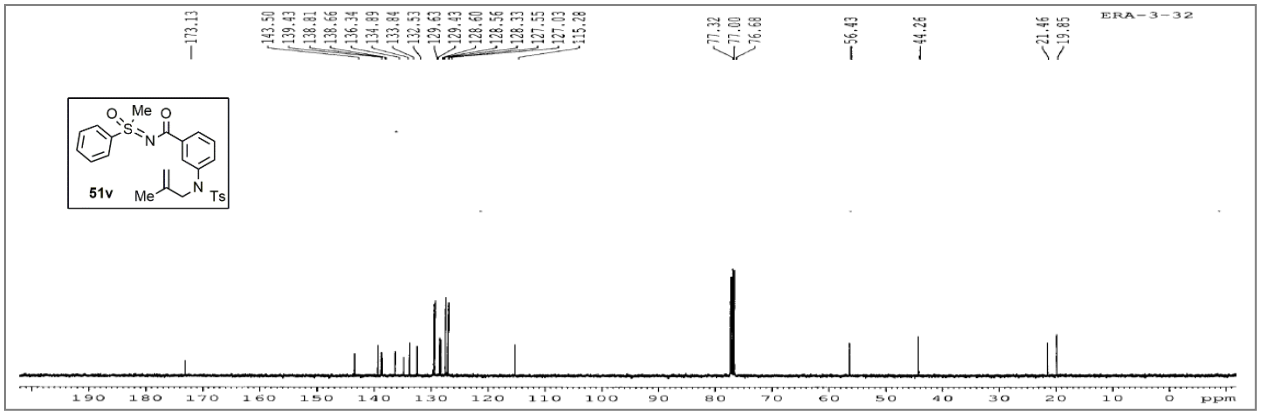

kg-6-150
51t
ppm

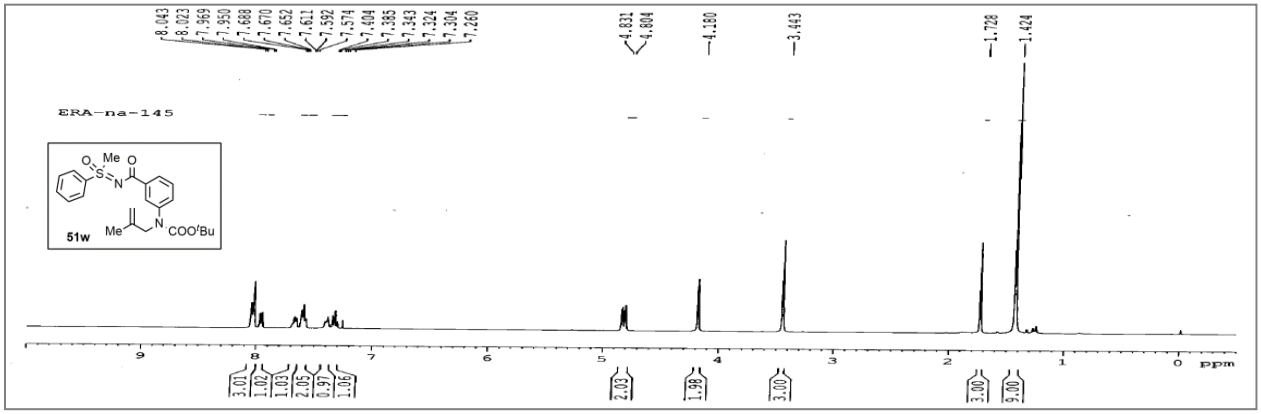

kg-6-150
51t
OMe
OMe
Me
O
S
N
O
O

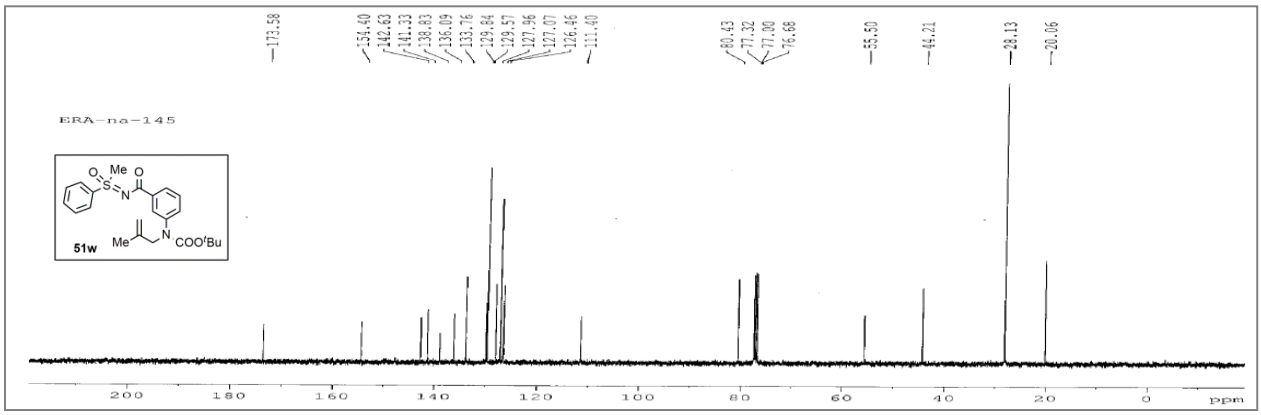

R-2207
51u
OMe
Me
N
Ts
Me
O
S
N
O
O

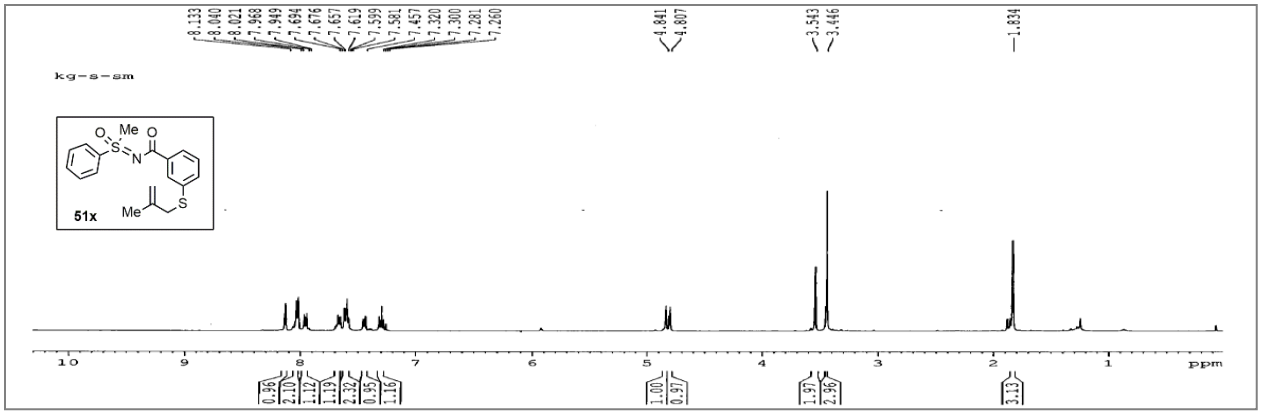

R-2207
51u
OMe
Me
N
Ts
Me
O
S
N
O
O

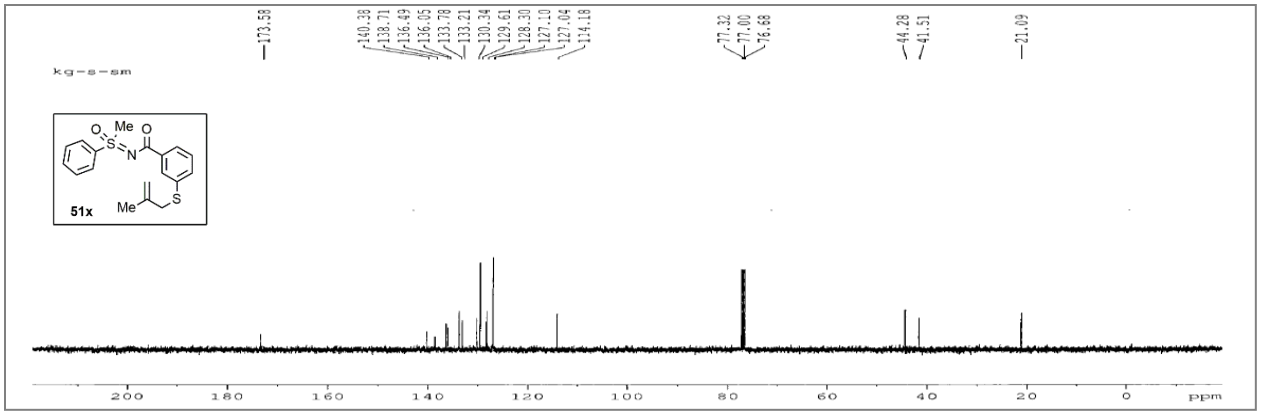

ERA-3-32
51v
Me
N
Ts
Me
O
S
N
O
O

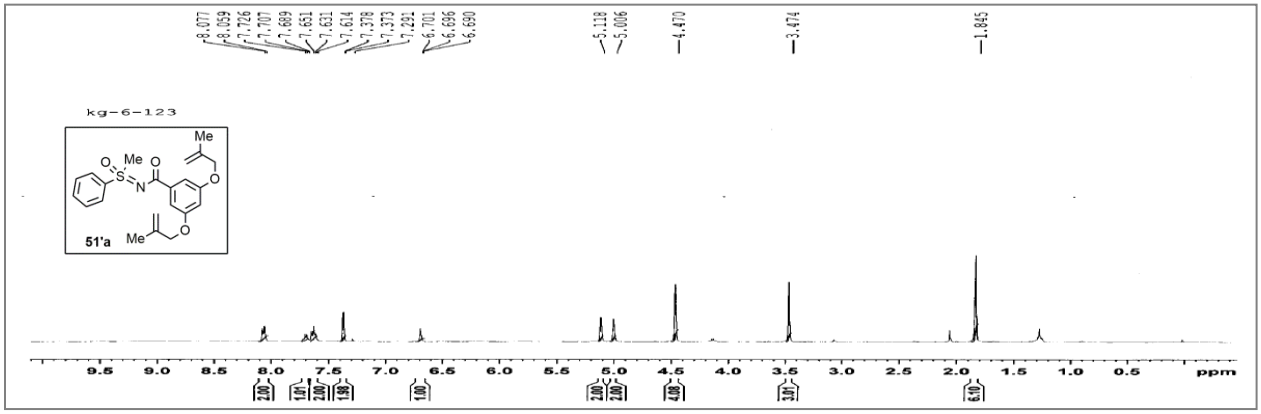

ERA-3-32
51v

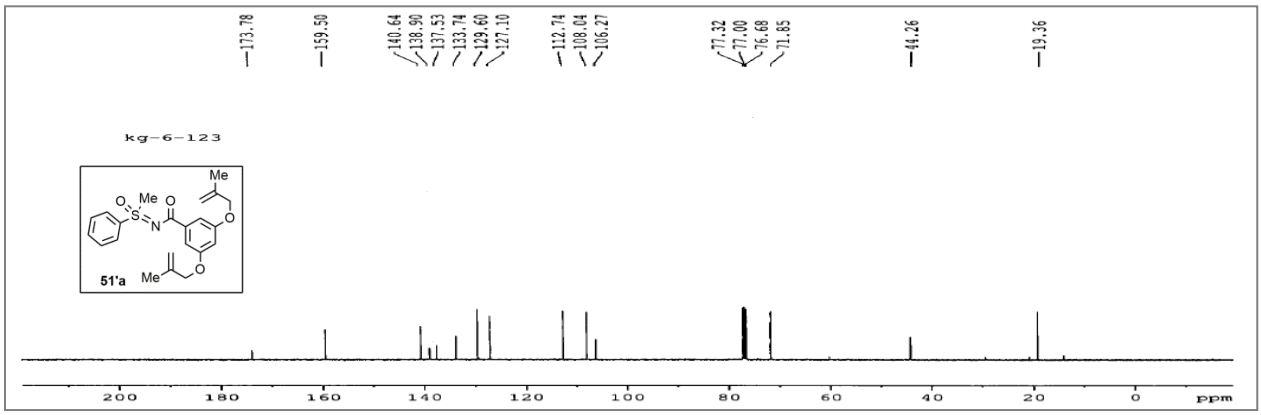

ERA-na-145
51w

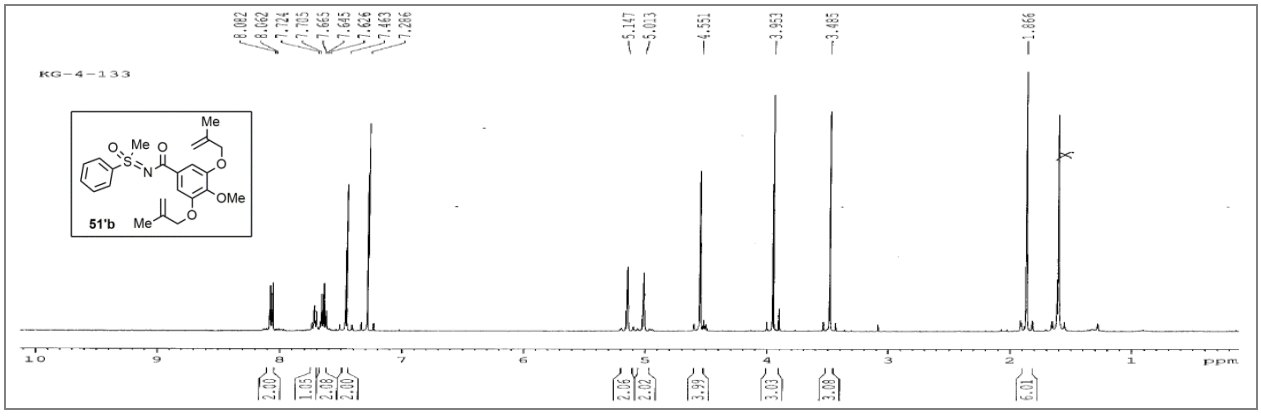

ERA-na-145
51w

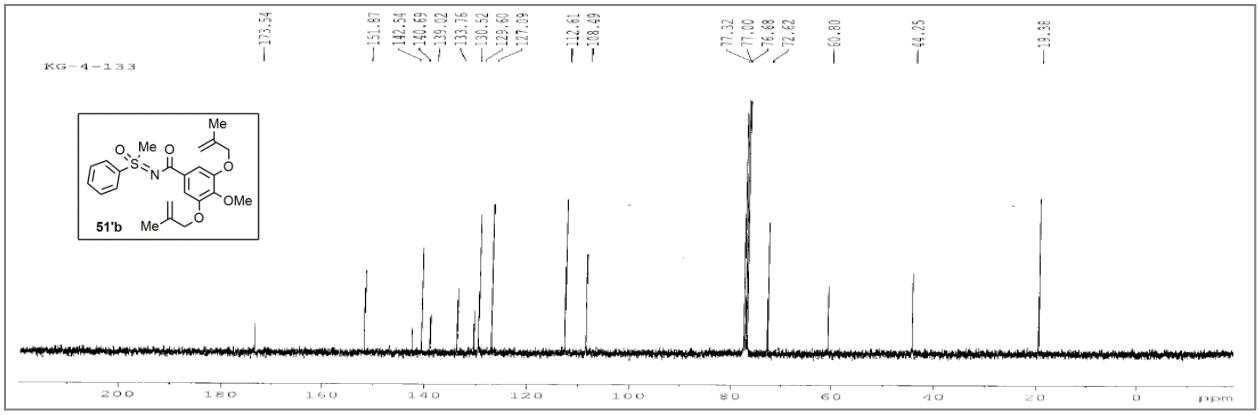

kg-s-sm
51x

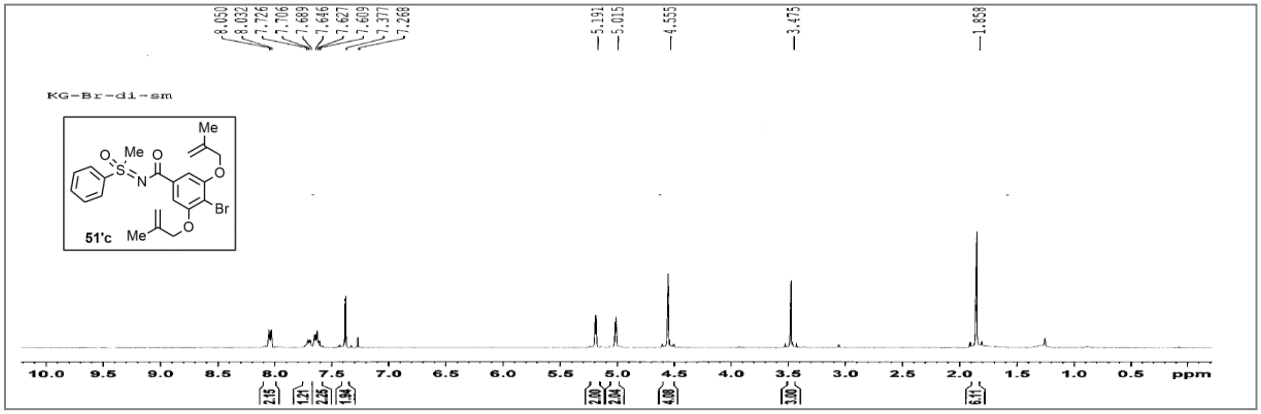

kg-s-sm
51x

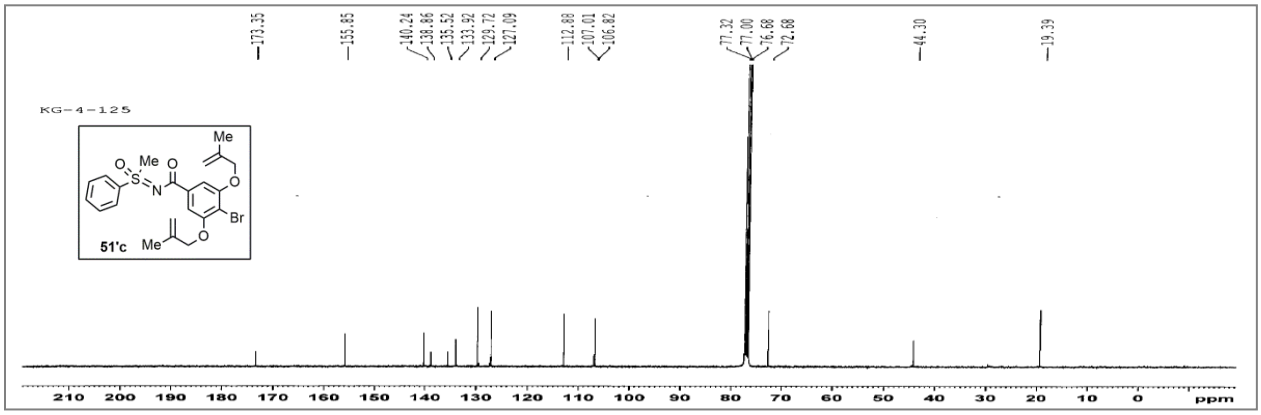

kg-6-123
51'a

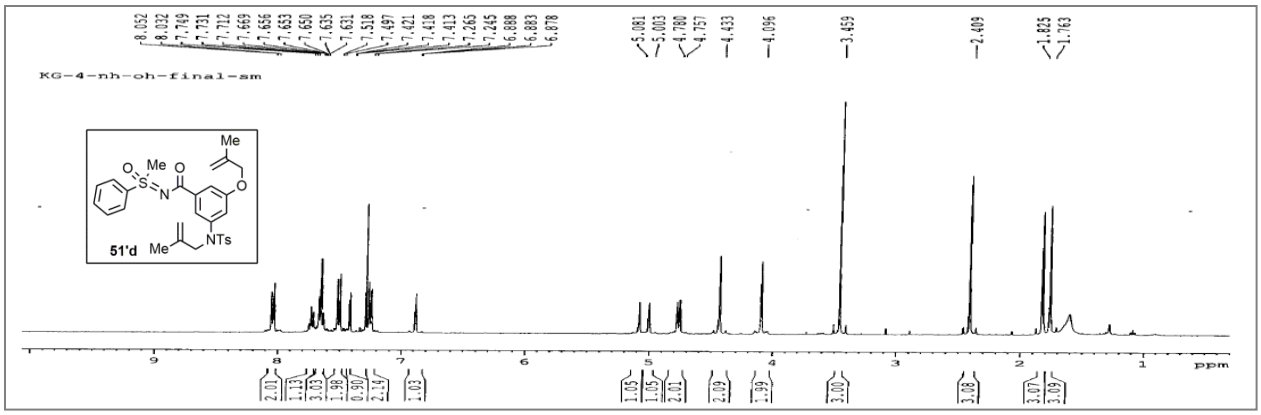

kg-6-123
51'a

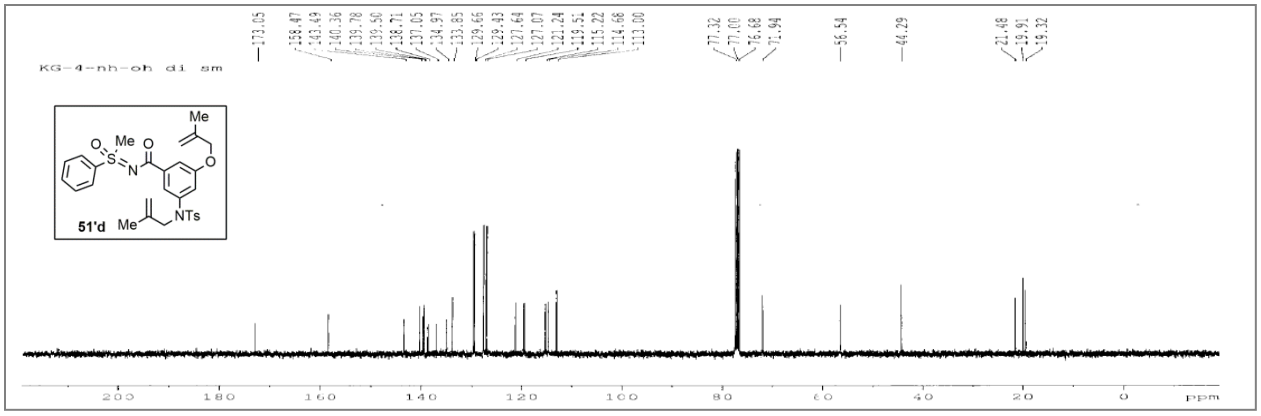

KG-4-133
51'b

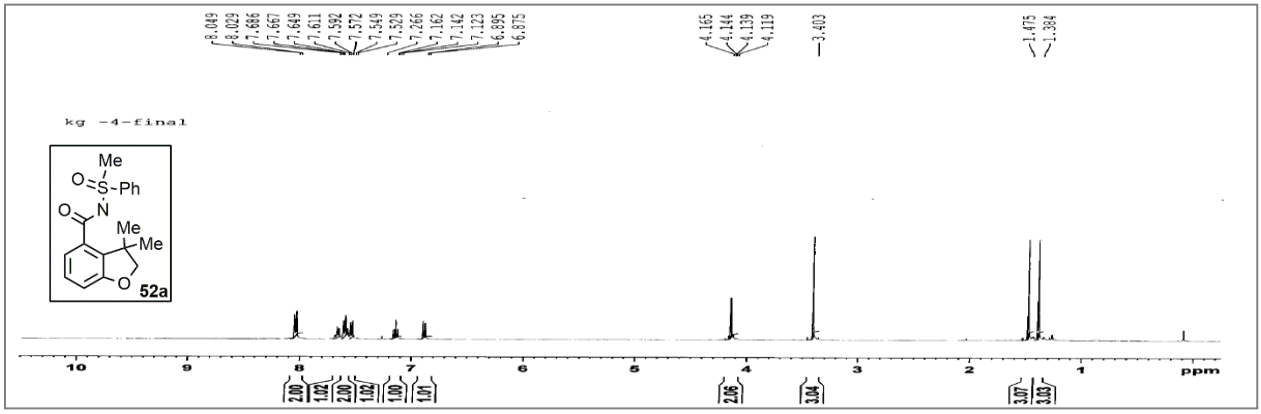

KG-4-133
51'b

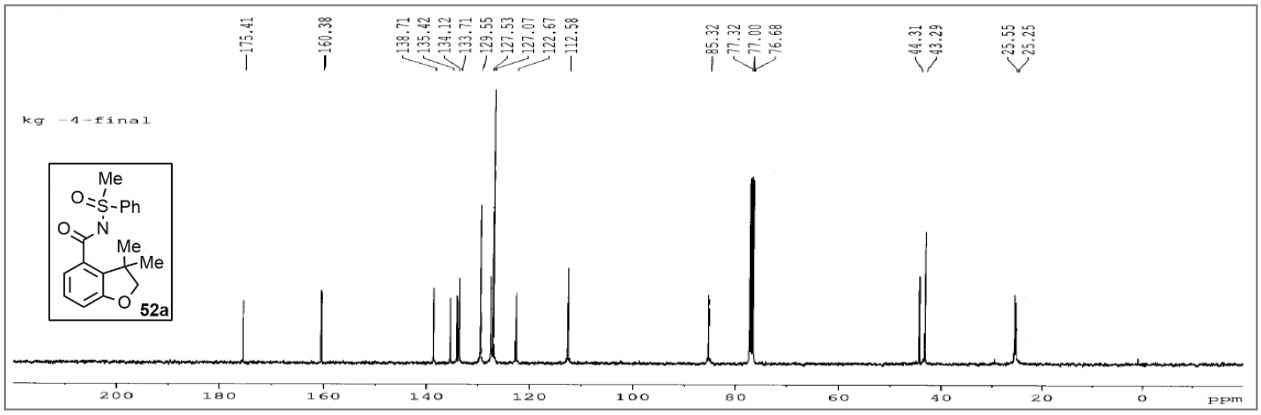

KG-Br-di-sm
51'c

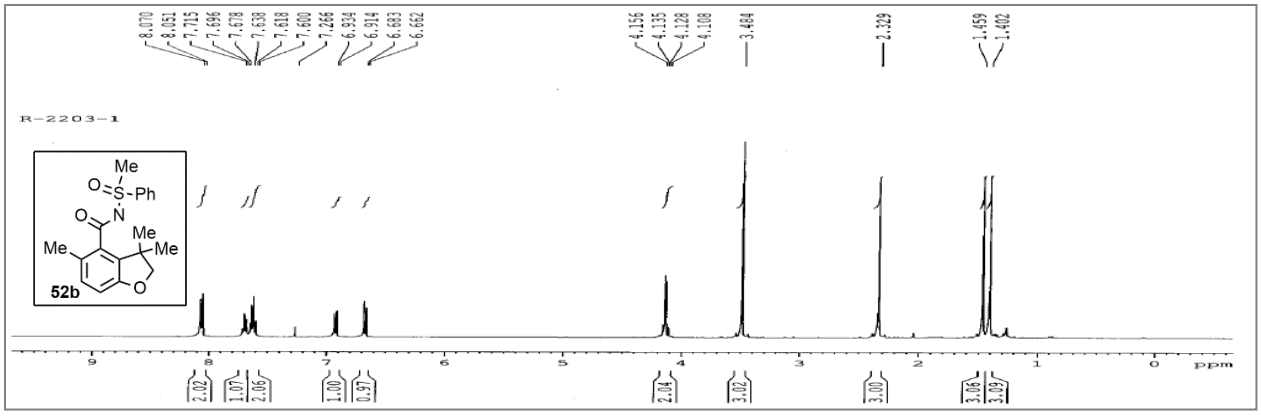

KG-4-125
51'c

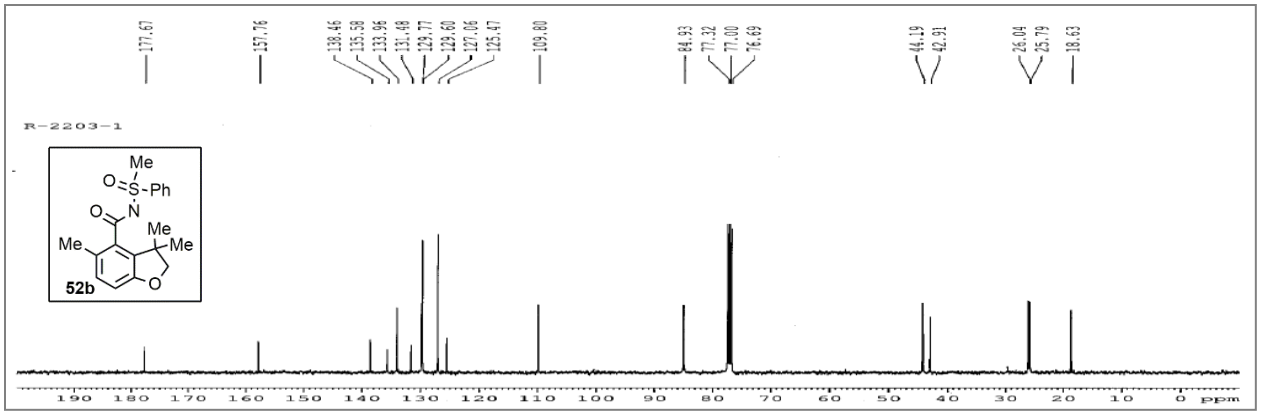

KG-4-nh-oh-final-sm
51'd

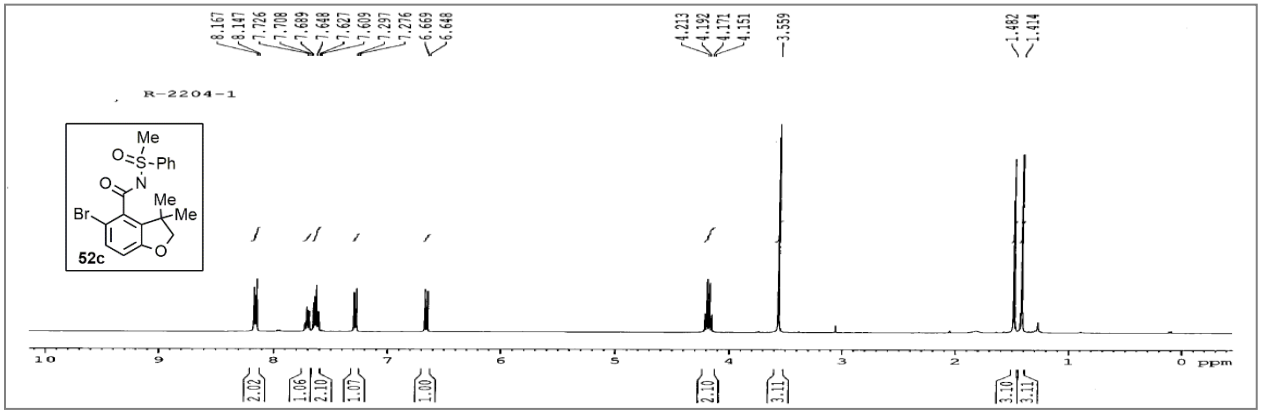

KG-4-nh-oh di sm
51'd

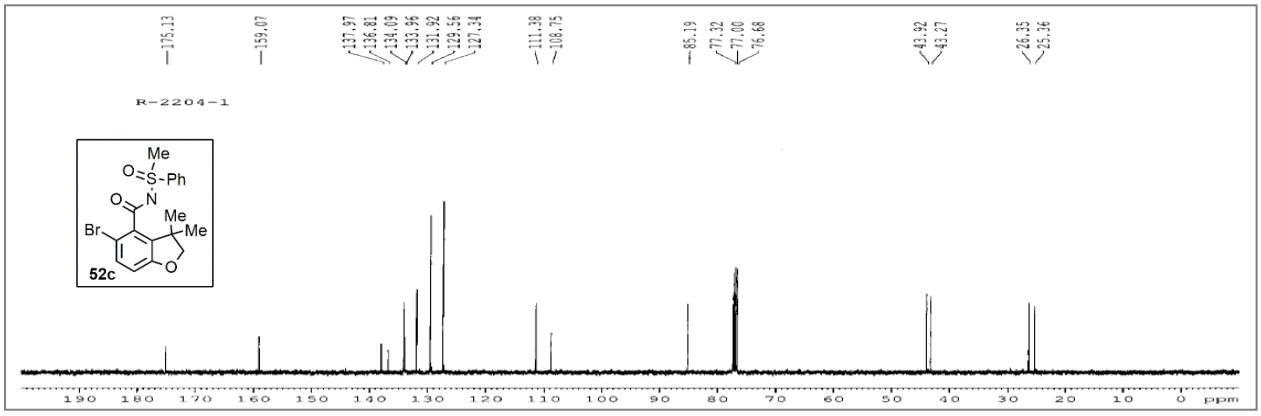

kg -4-final
52a

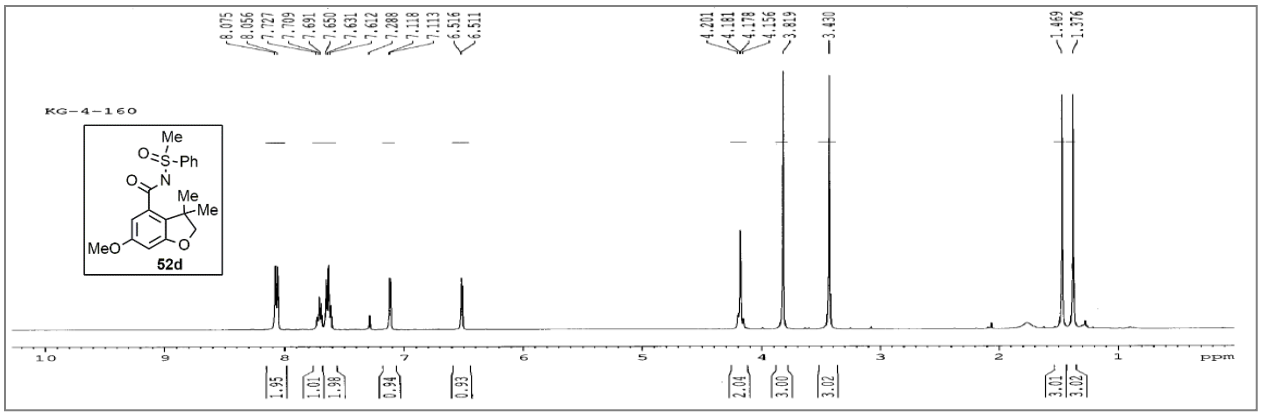

kg -4-final
52a

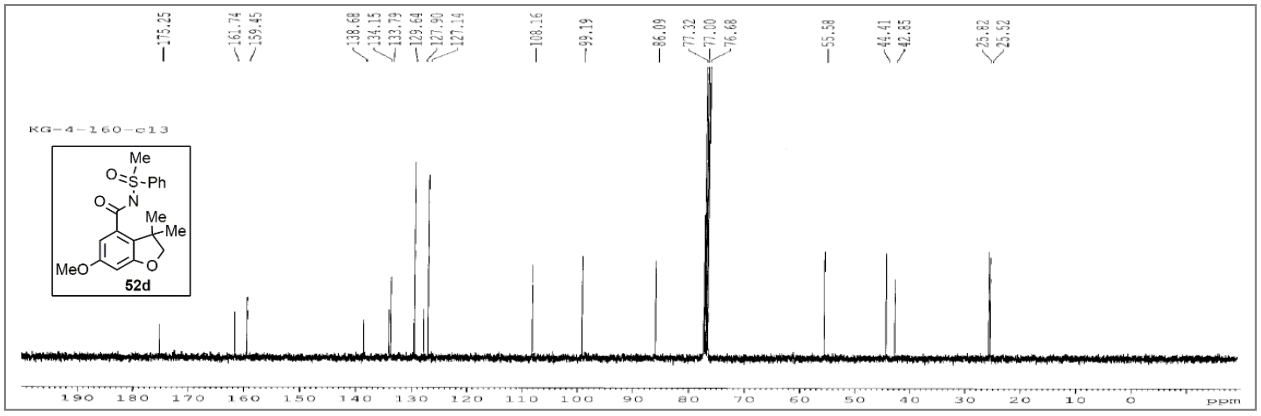

R-2203-1
52b

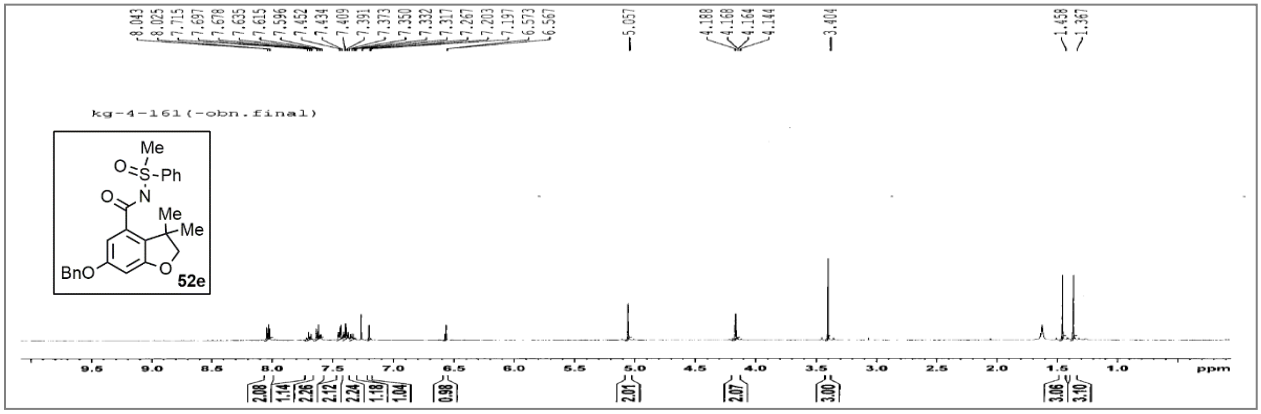

R-2203-1
52b

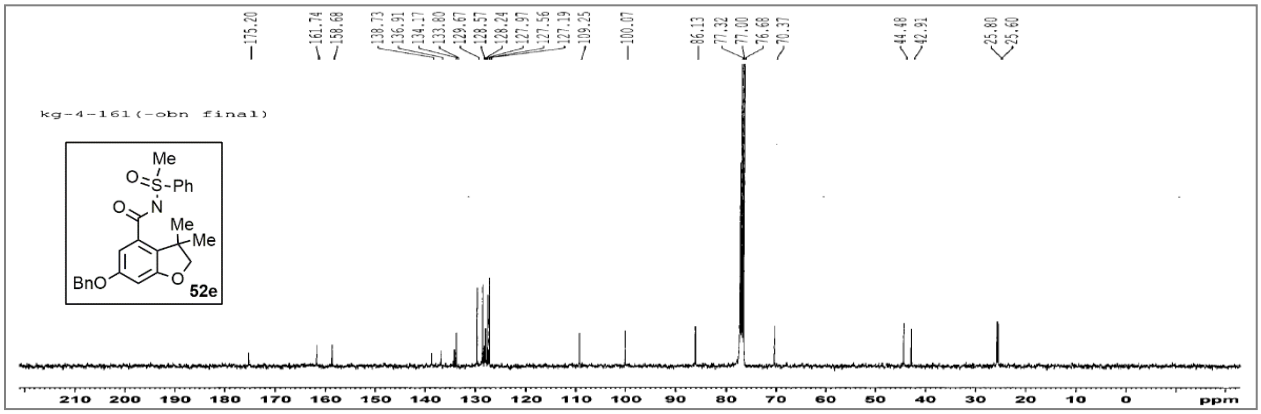

R-2204-1
52c

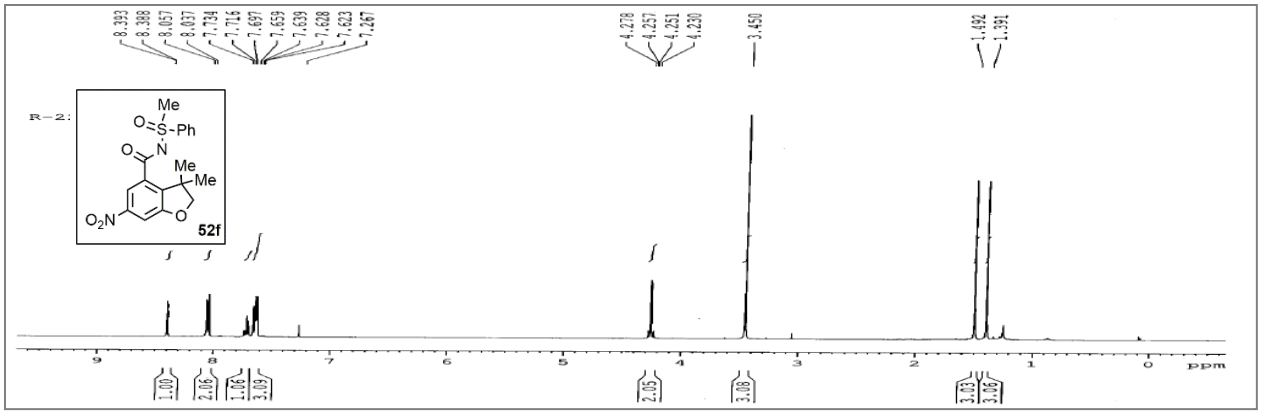

R-2204-1
52c

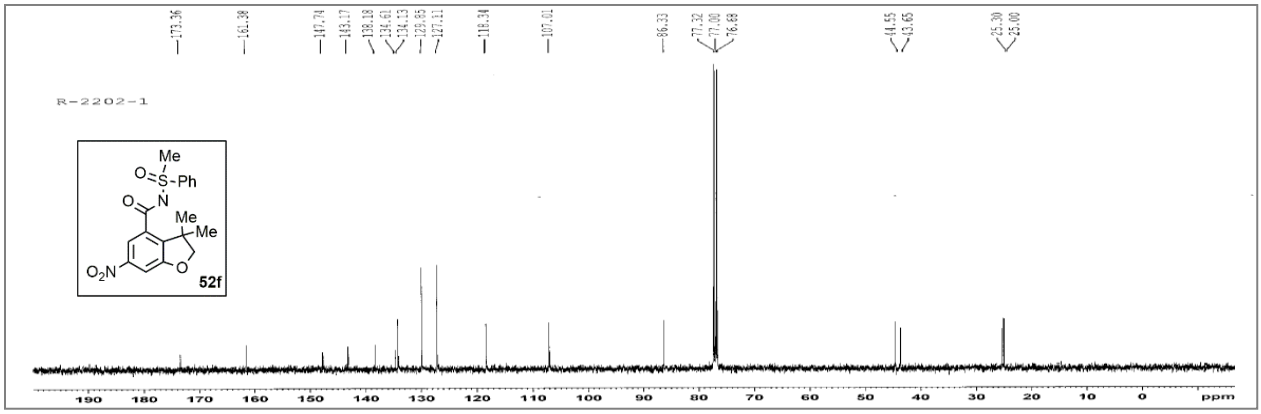

KG-4-160
52d

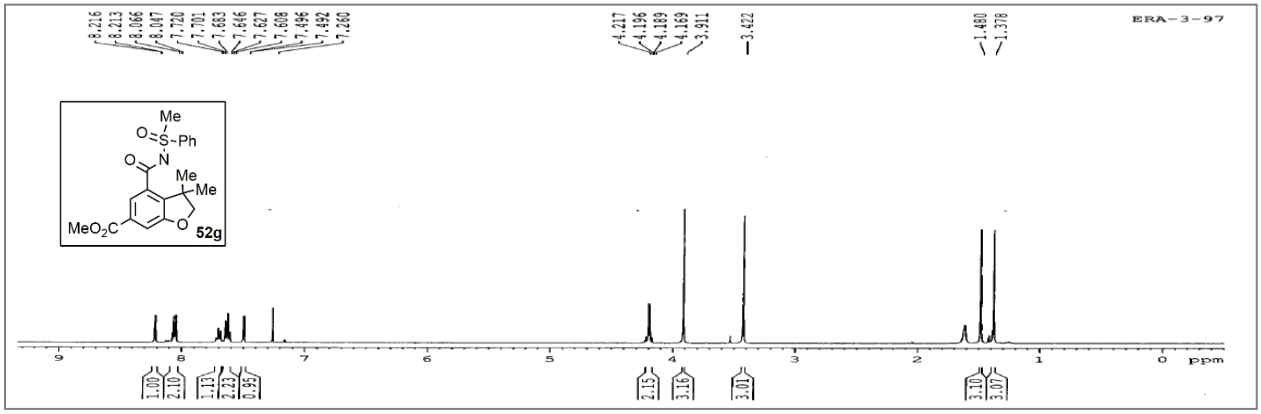

KG-4-160-c13
52d

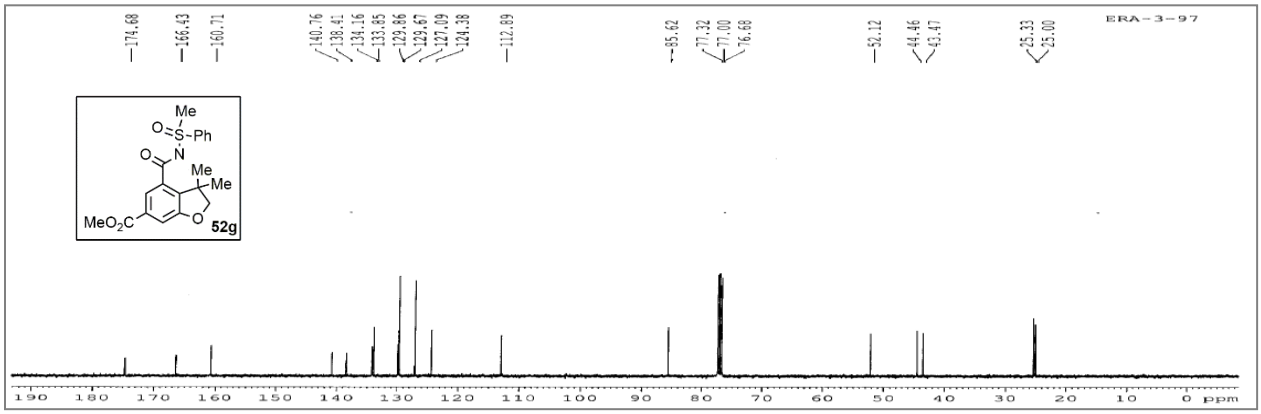

kg-4-161(-obn.final)
52e

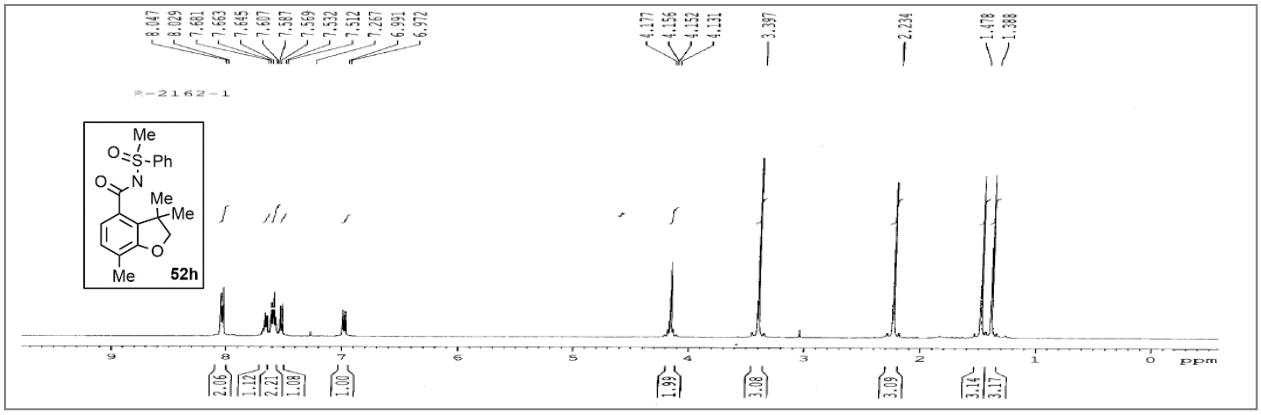

kg-4-161(-obn final)
52e

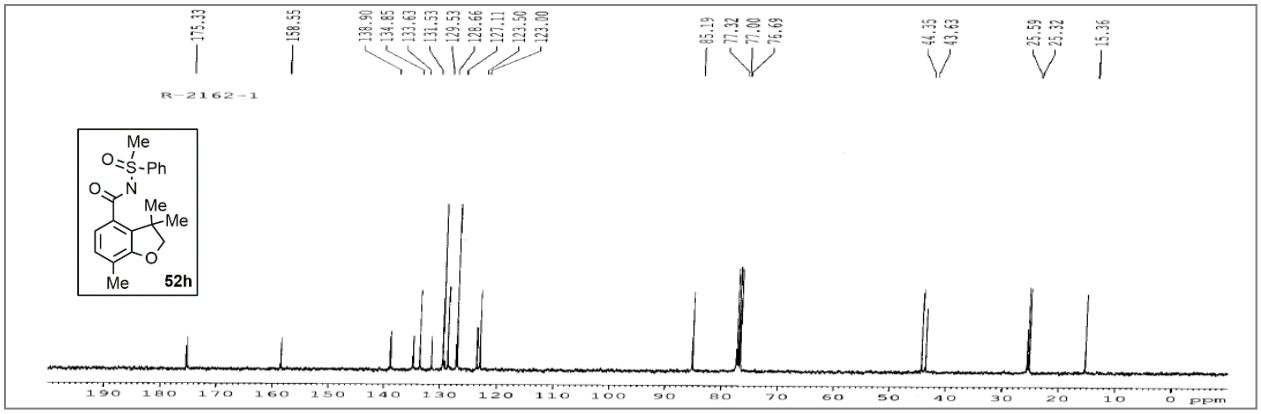

R-2:
52f

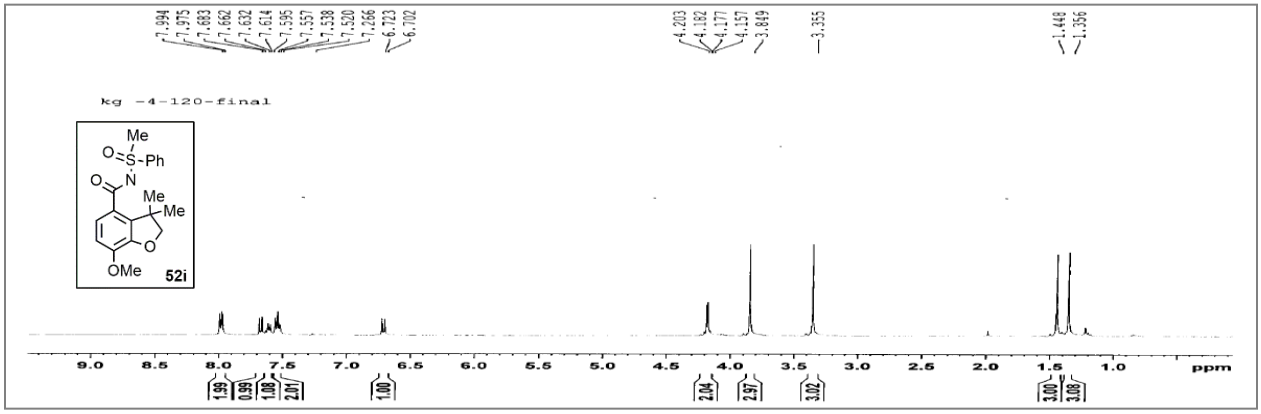

R-2202-1
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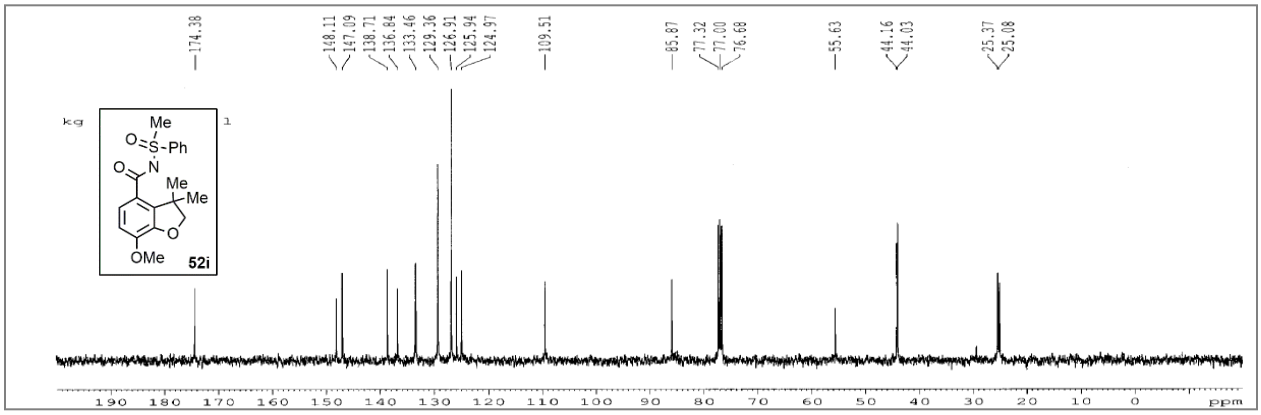

ERA-3-97
52g

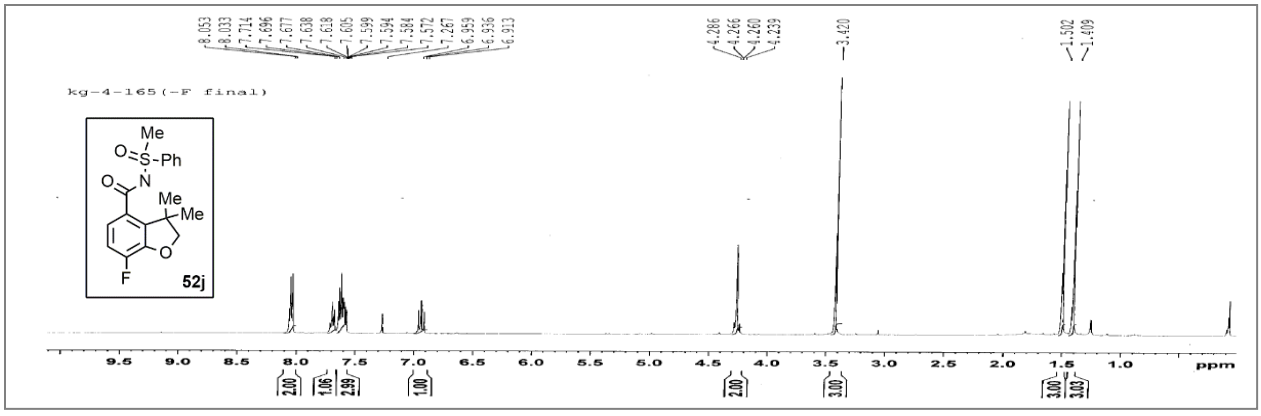

ERA-3-97
52g

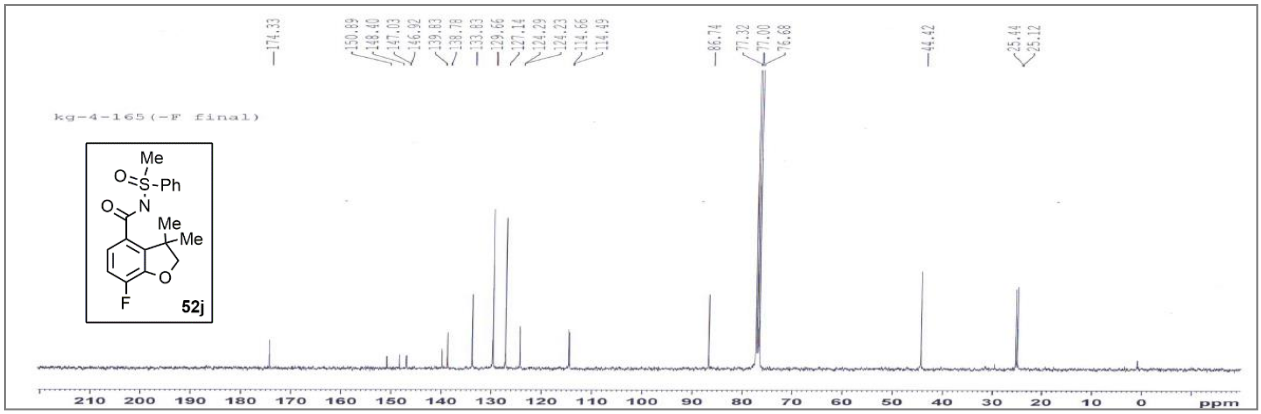

P-2162-1
52h

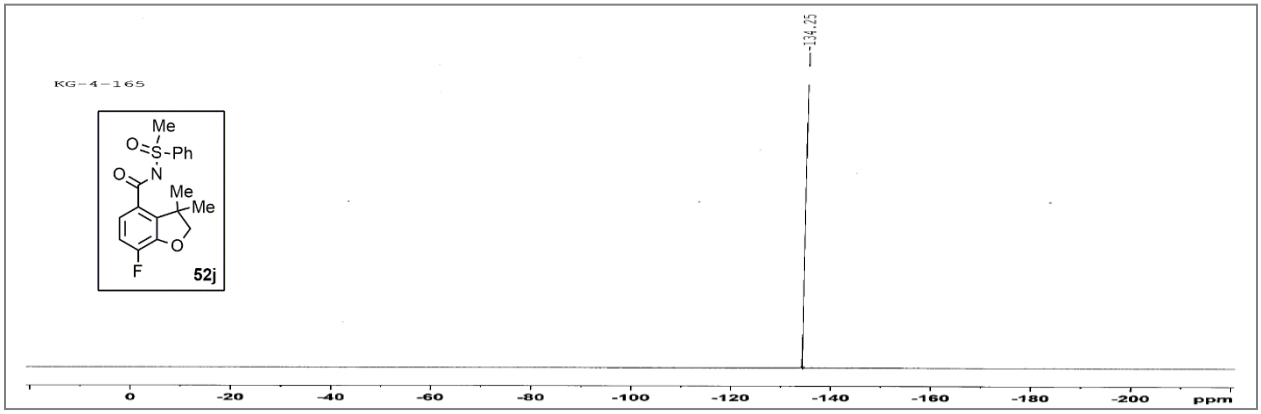

R-2162-1
52h

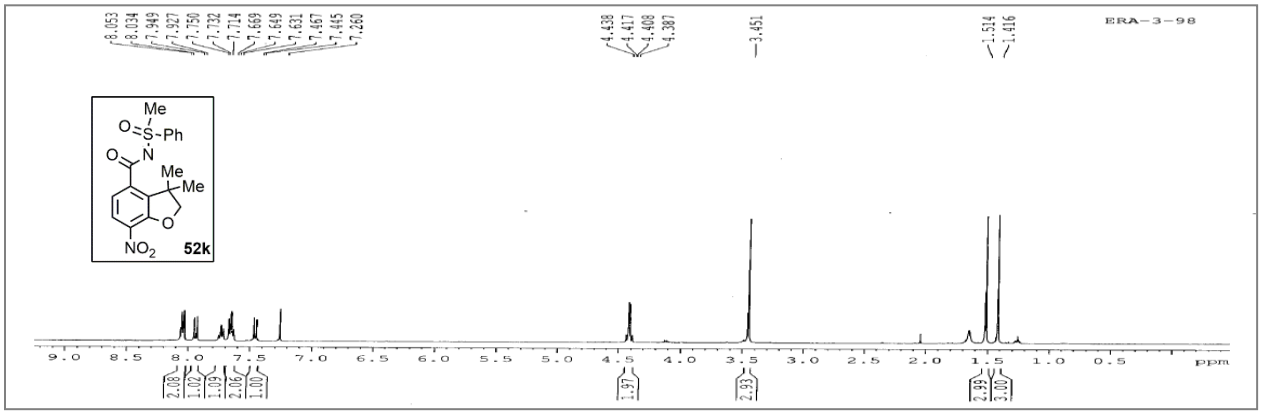

kg -4-120-final
52i

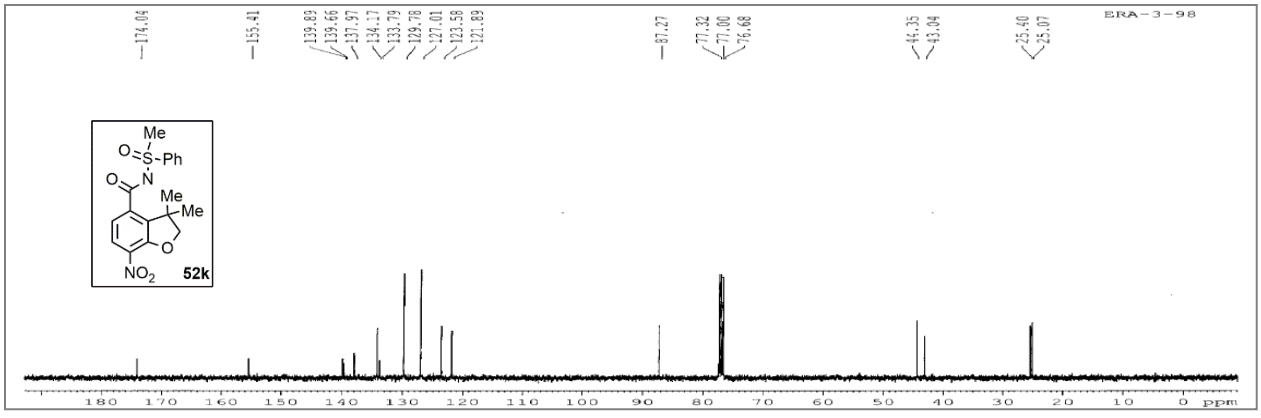

52i

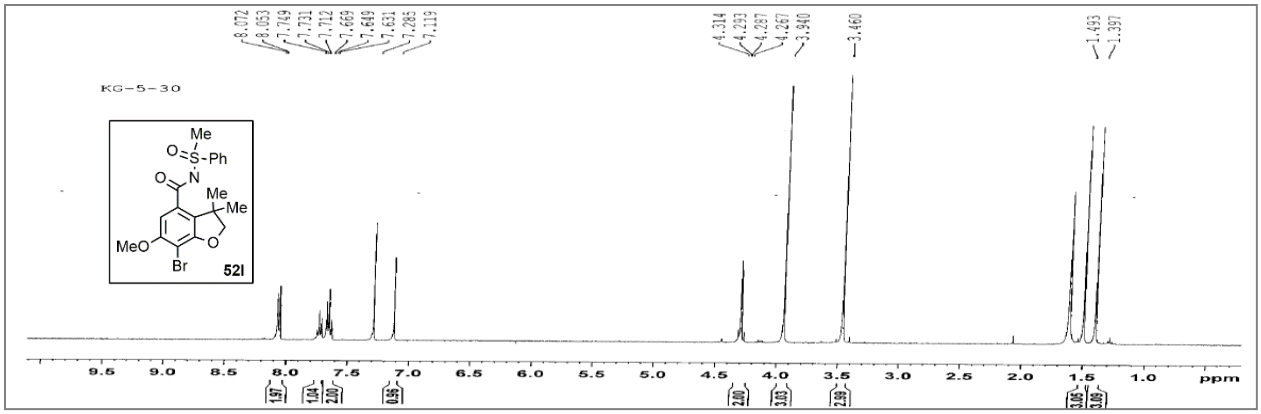

kg-4-165(-F final)
52j

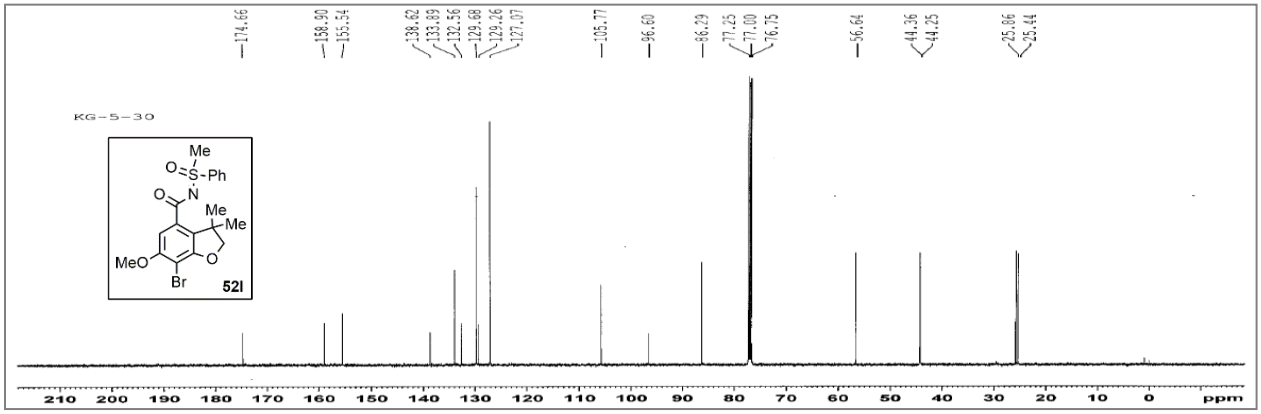

kg-4-165(-F final)
52j
ppm

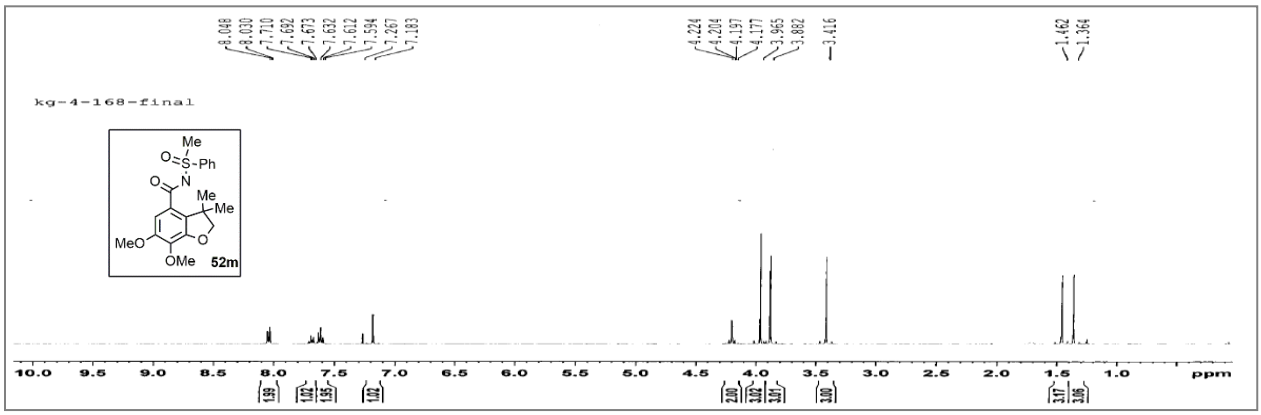

KG-4-165
52j
ppm

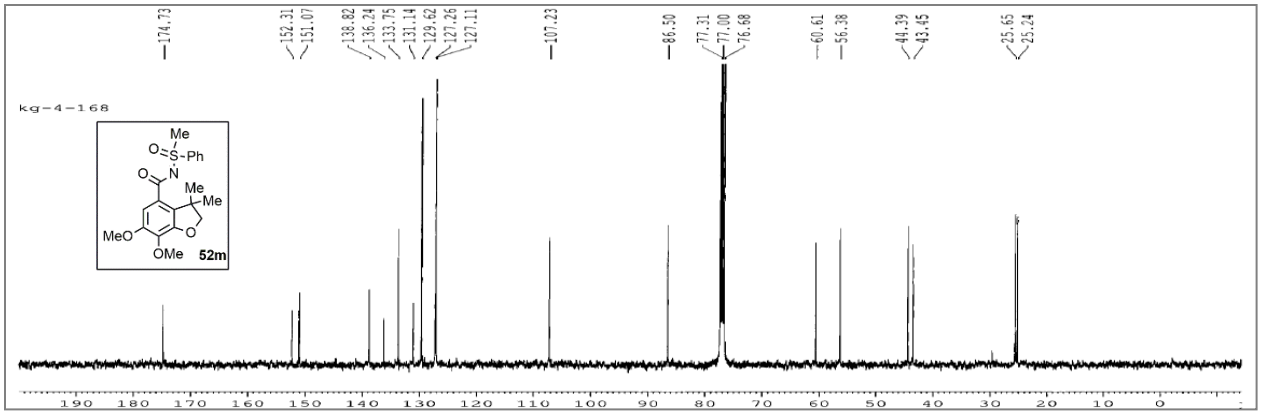

ERA-3-98
52k
ppm

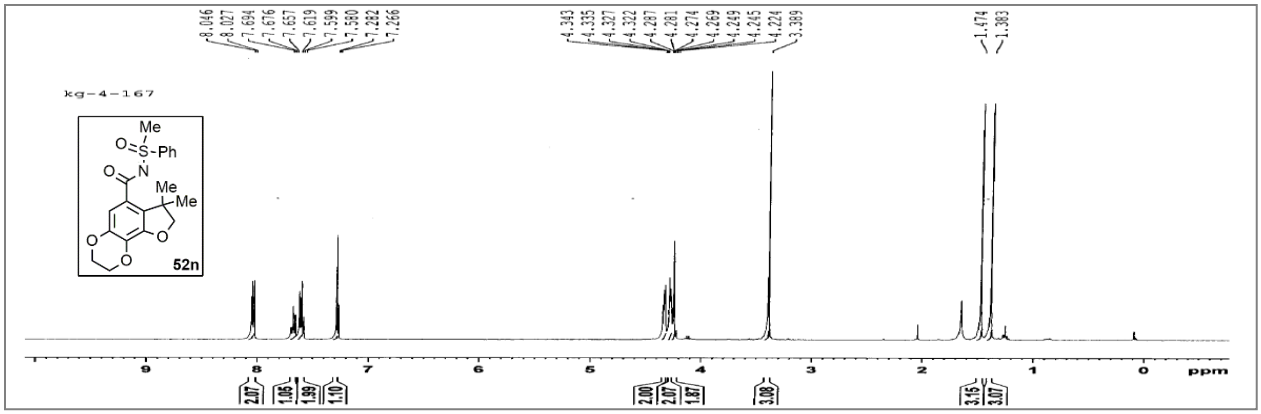

ERA-3-98
52k
ppm

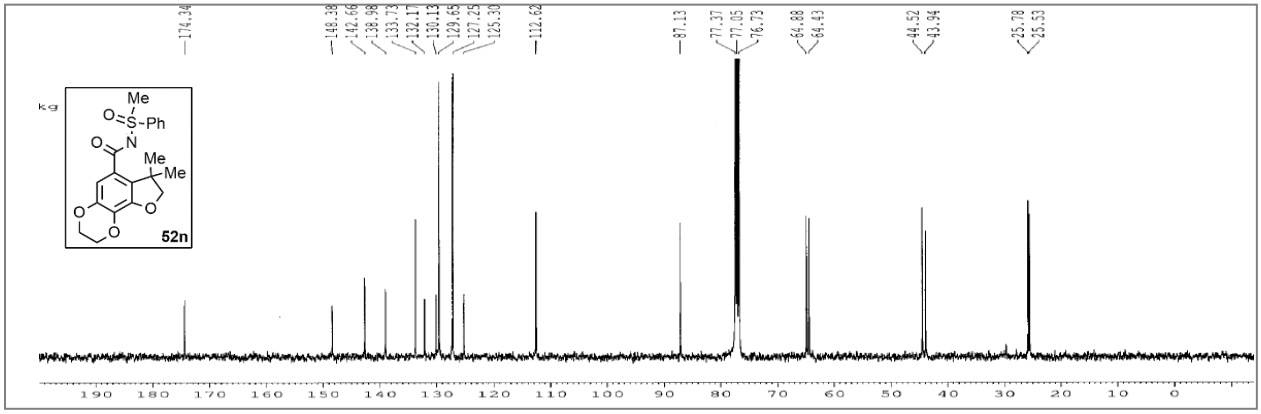

8.072
8.053
7.749
7.731
7.712
7.669
7.649
7.631
7.285
7.119
4.314
4.293
4.287
4.267
3.940
3.460
1.493
1.397
KG-5-30
Me
O
S-Ph
N
Me
Me
MeO
O
Br
52l
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.97
1.04
2.00
0.95
2.00
3.03
2.59
3.05
3.00

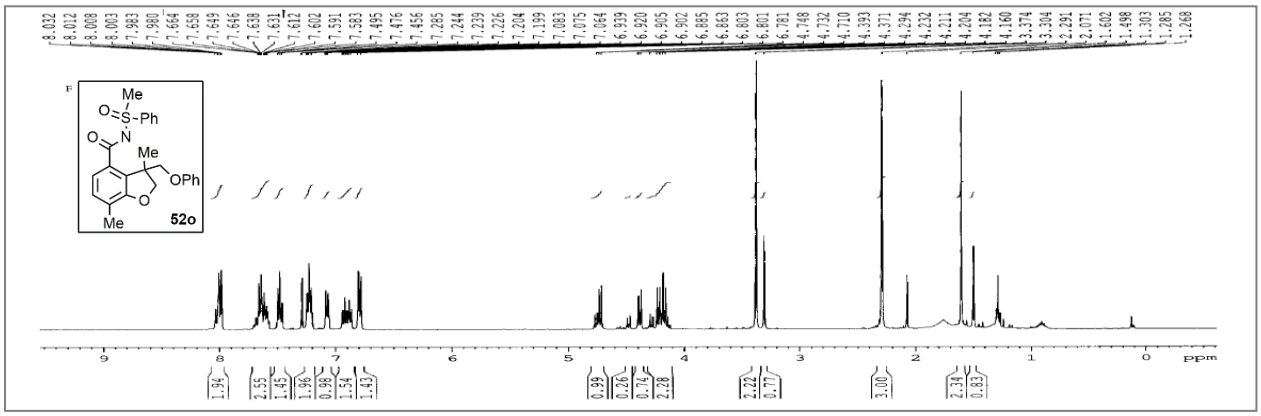

174.66
158.90
155.54
138.62
133.89
132.56
129.68
129.26
127.07
105.77
96.60
86.29
77.25
77.00
76.75
56.64
44.36
44.25
25.86
25.44
KG-5-30
Me
O
S-Ph
N
Me
Me
MeO
O
Br
52l
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

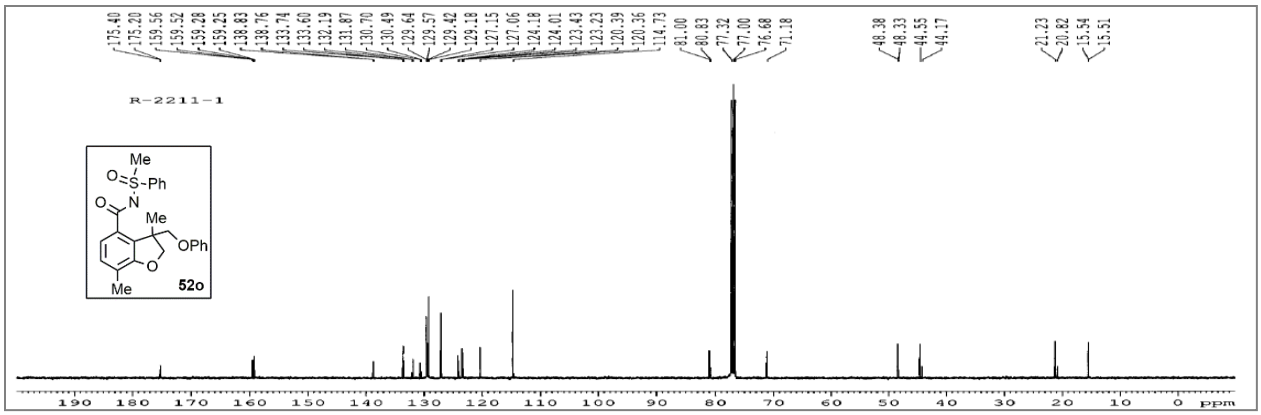

8.048
8.030
7.710
7.692
7.673
7.632
7.612
7.594
7.267
7.183
4.224
4.204
4.197
4.177
3.965
3.892
3.416
1.462
1.364
kg-4-168-final
Me
O
S-Ph
N
Me
Me
MeO
O
OMe
52m
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.58
1.02
1.65
1.02
2.08
3.04
3.07
3.00
3.17
3.06

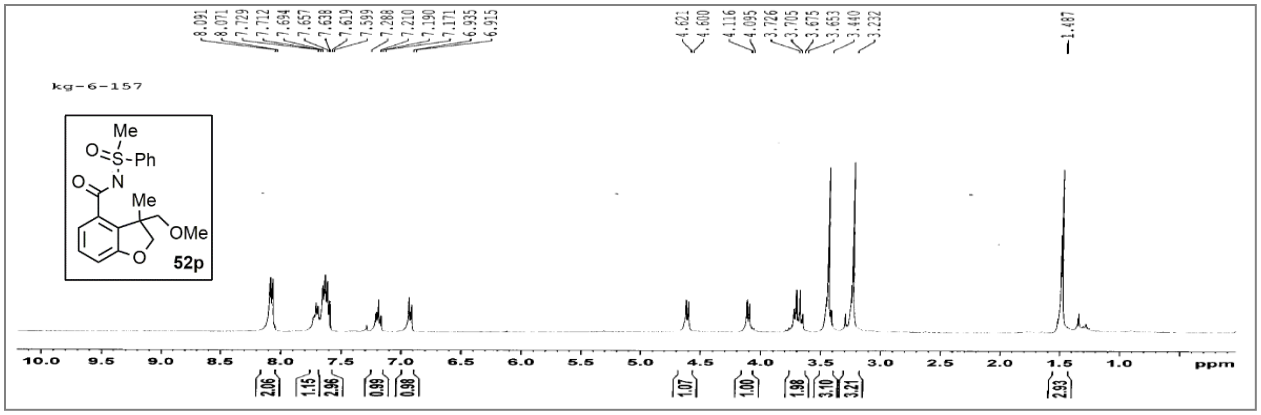

174.73
152.31
151.07
138.82
136.24
133.75
131.14
129.62
127.26
127.11
107.23
86.50
77.31
77.00
76.68
60.61
56.38
44.39
43.45
25.65
25.24
kg-4-168
Me
O
S-Ph
N
Me
Me
MeO
O
OMe
52m
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

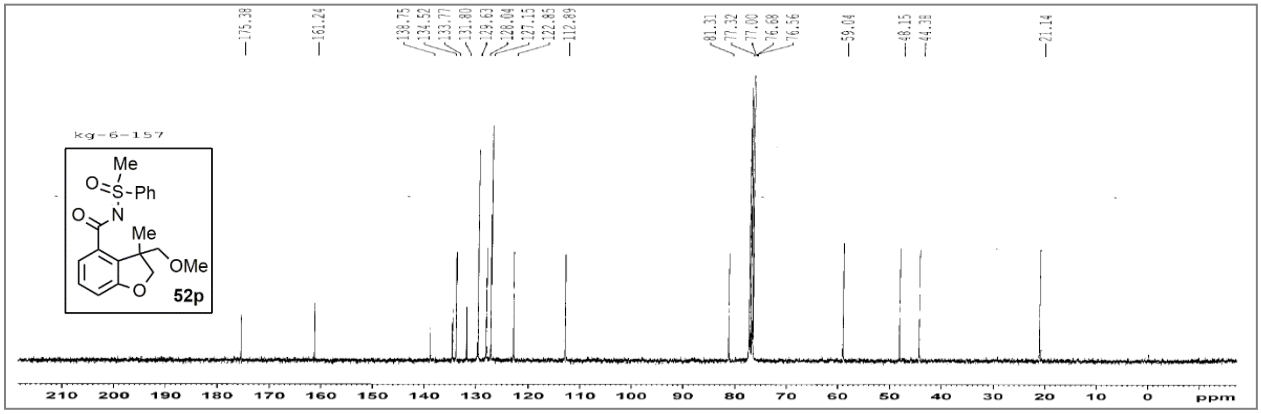

kg-4-167
52n

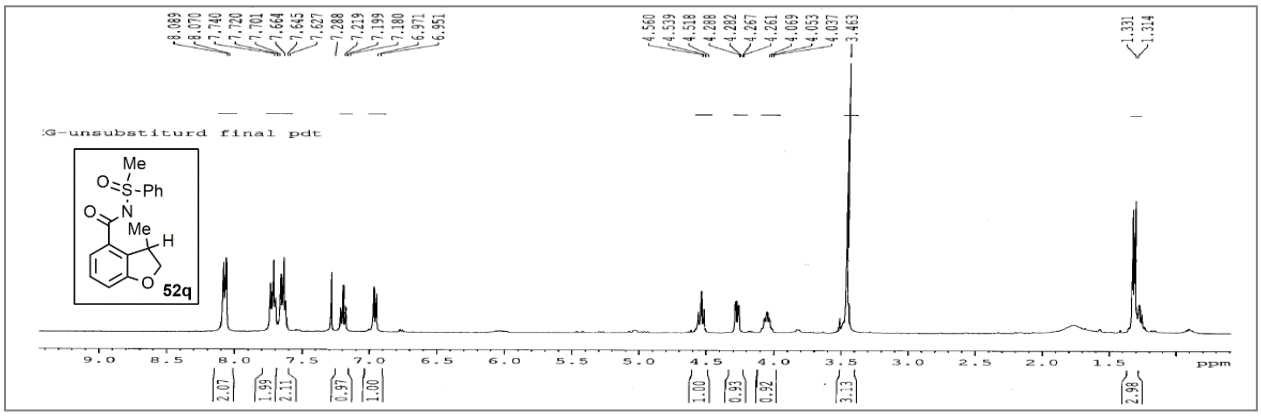

kg
52n

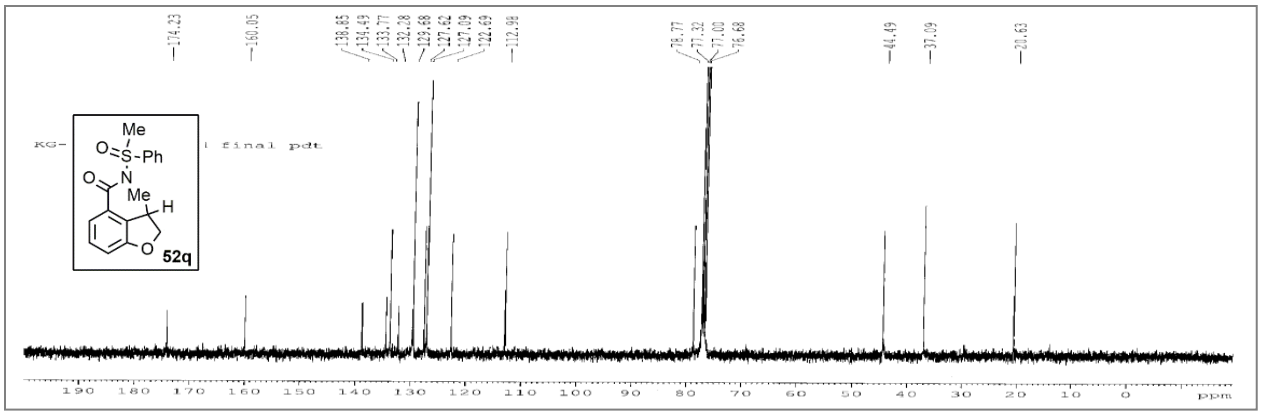

52o

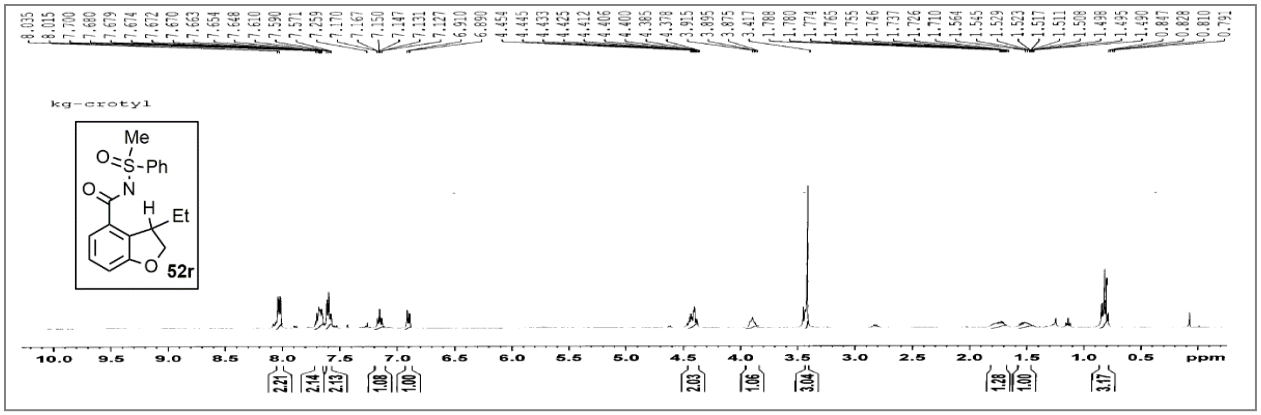

R-2211-1
52o

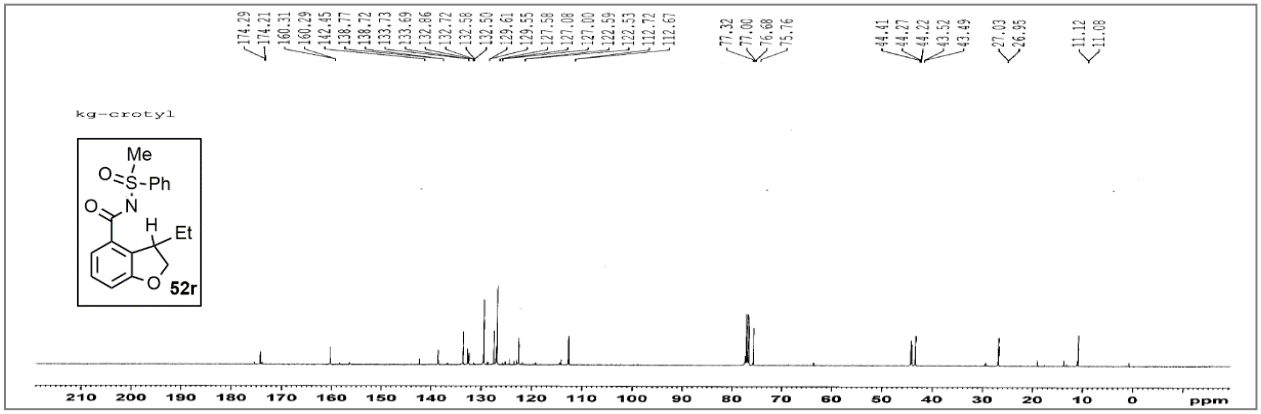

kg-6-157
Me
O=S-Ph
N
O
Me
OMe
52p
ppm

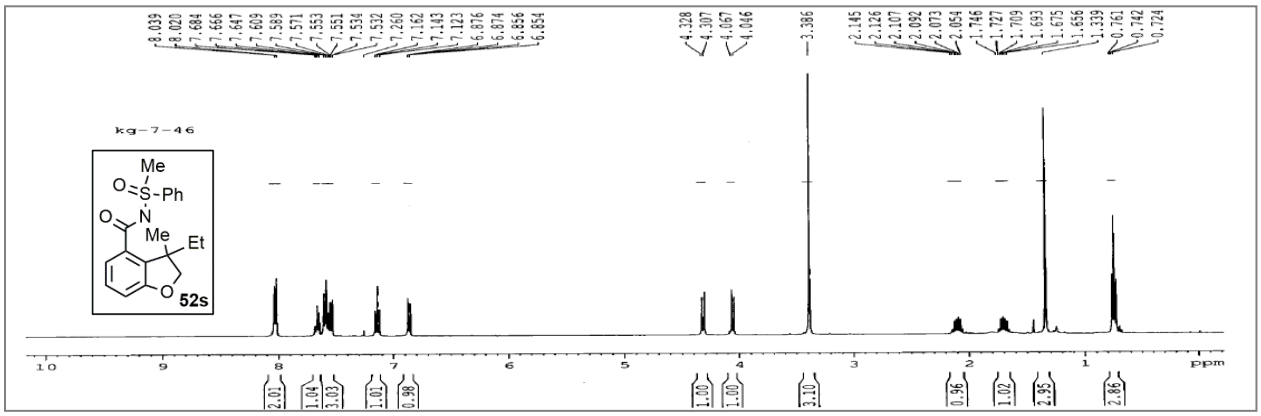

kg-6-157
Me
O=S-Ph
N
O
Me
OMe
52p
ppm

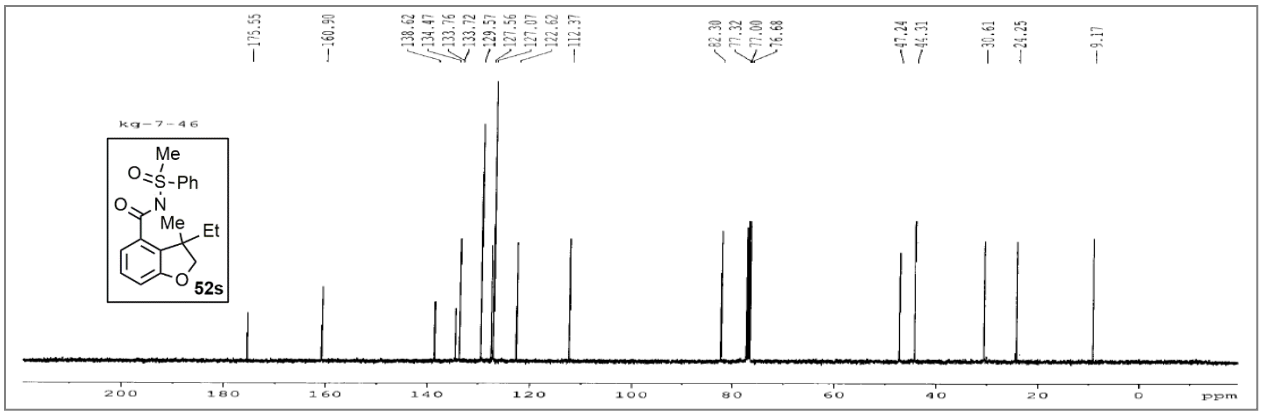

G-unsubstitutd final pdt
Me
O=S-Ph
N
O
Me
H
52q
ppm

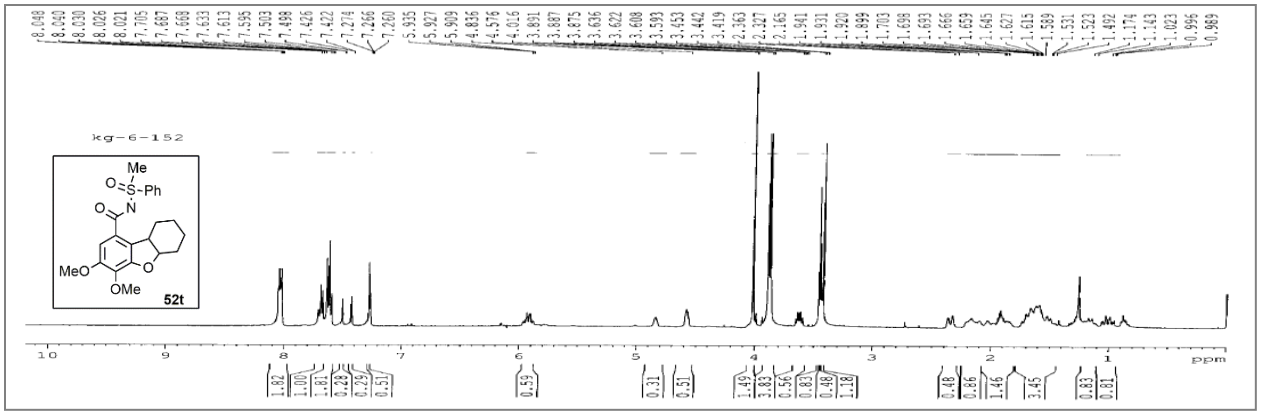

KG-
final pdt
Me
O=S-Ph
N
O
Me
H
52q
ppm

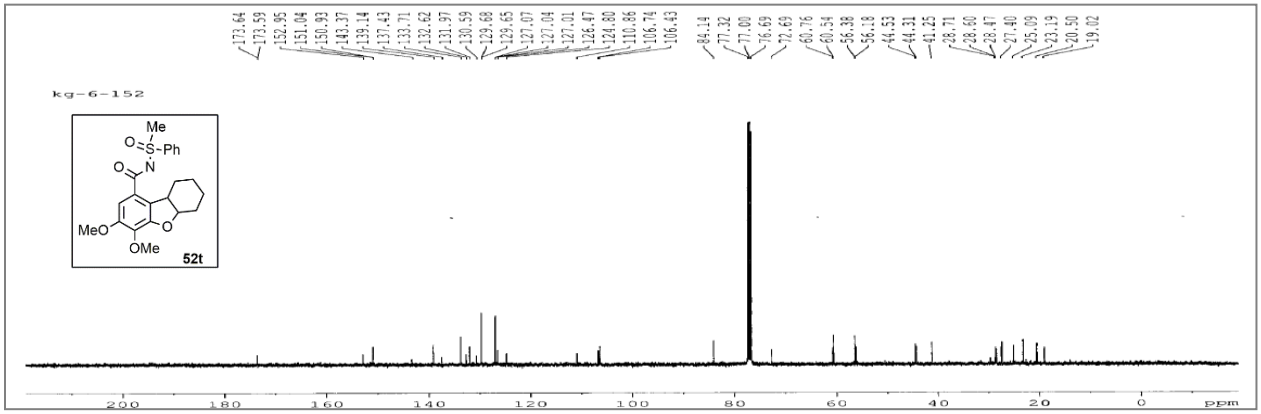

kg-crotyl
52r

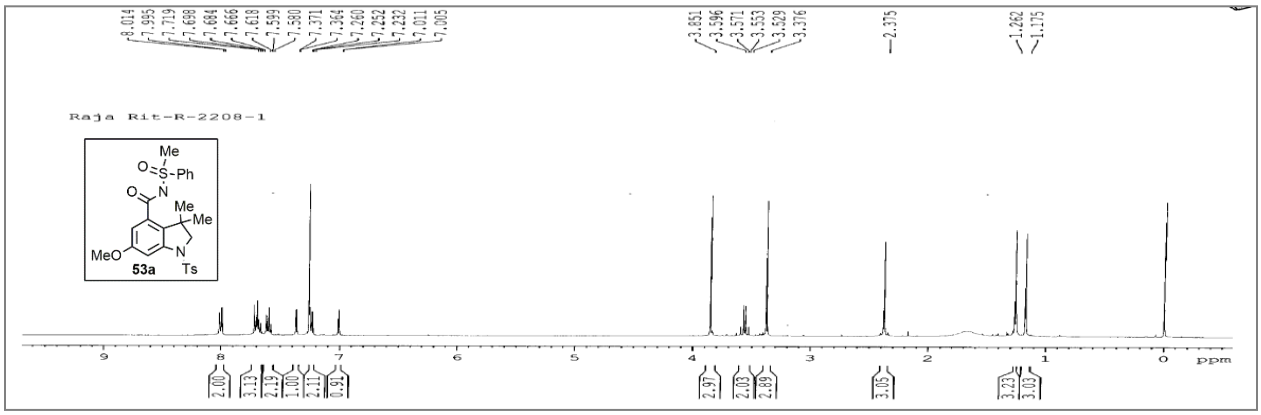

kg-crotyl
52r

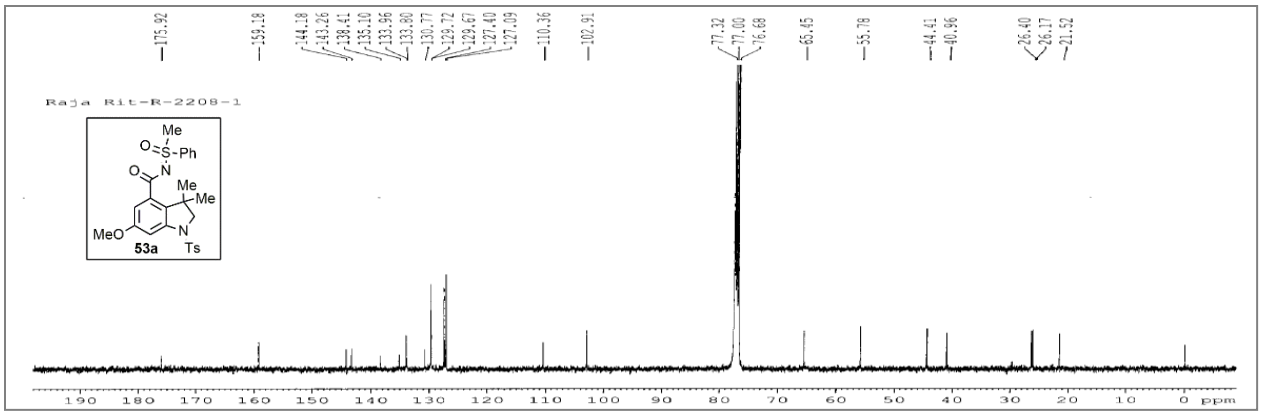

kg-7-46
52s

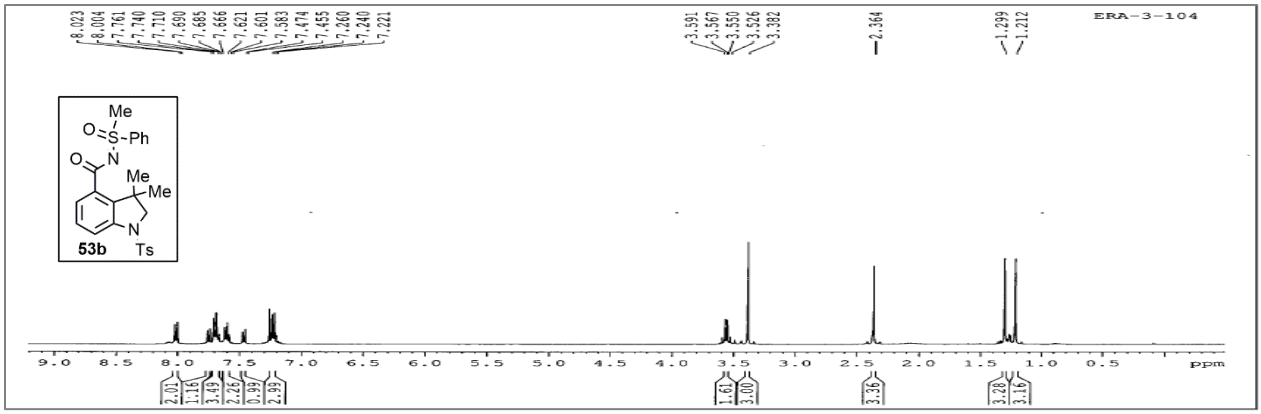

kg-7-46
52s

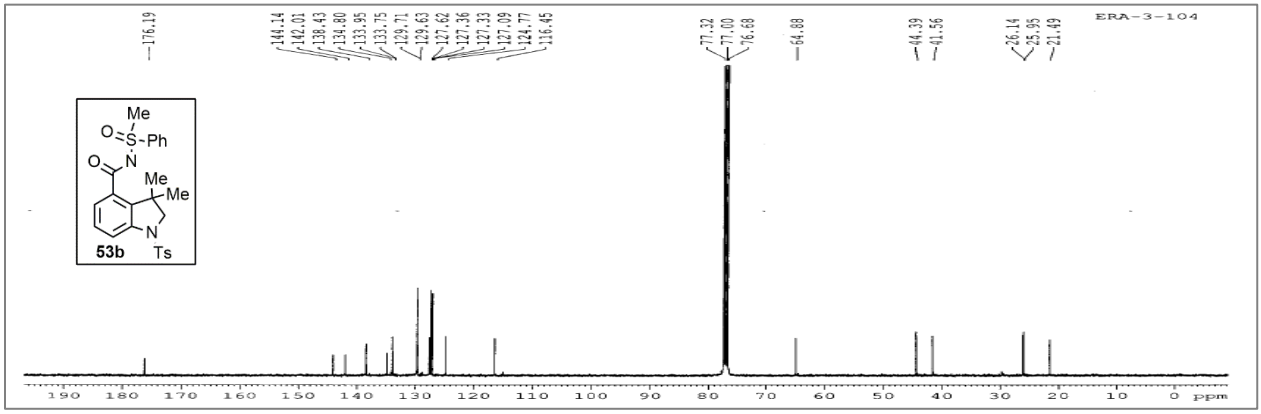

kg-6-152
Me
O
S-Ph
N
O
MeO
OMe
52t
ppm

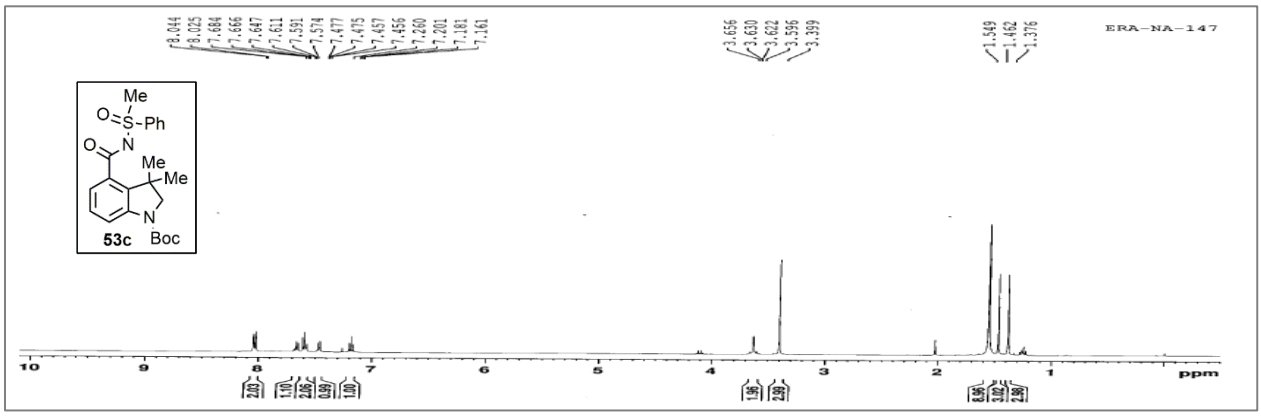

kg-6-152
Me
O
S-Ph
N
O
MeO
OMe
52t
ppm

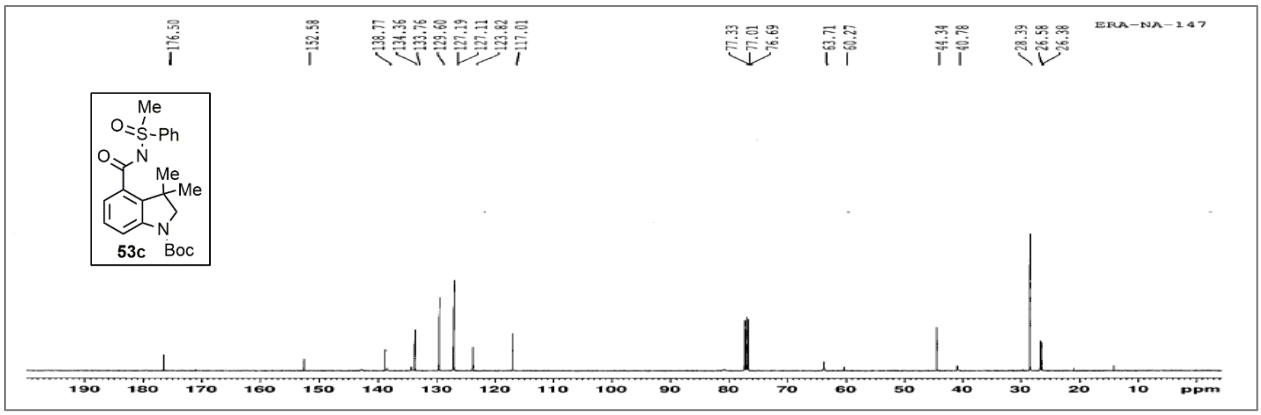

Raja Rit-R-2208-1
Me
O
S-Ph
N
O
Me
Me
MeO
N
53a
Ts
ppm

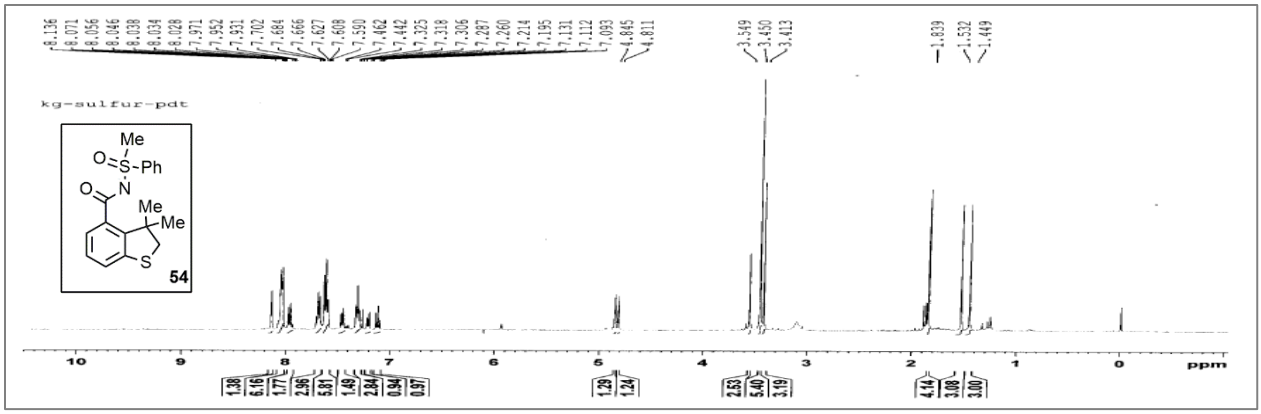

Raja Rit-R-2208-1
Me
O
S-Ph
N
O
Me
Me
MeO
N
53a
Ts
ppm

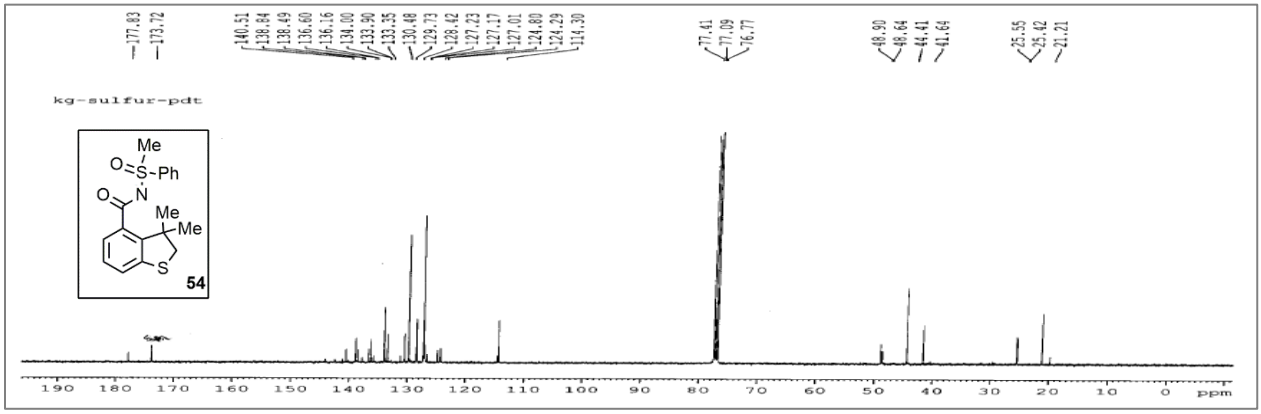

ERA-3-104
53b Ts

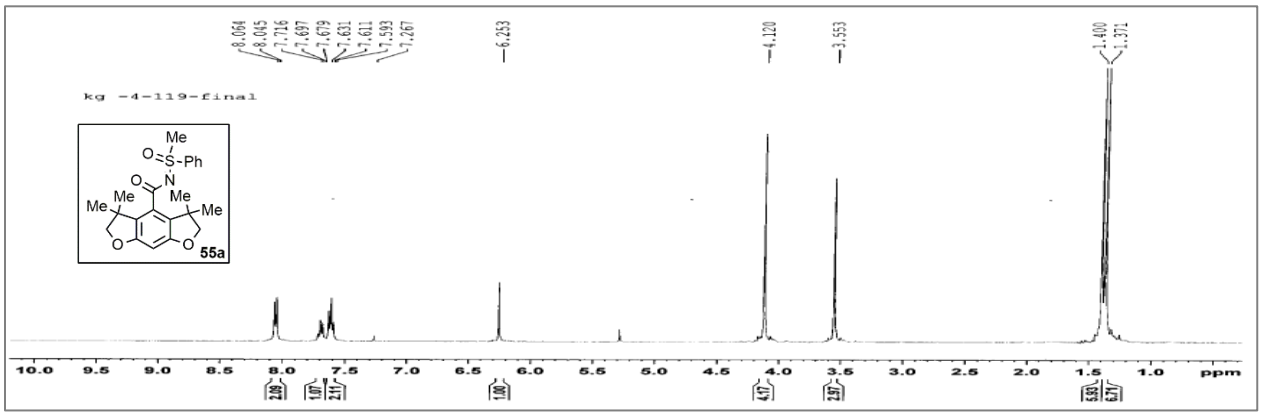

ERA-3-104
53b Ts

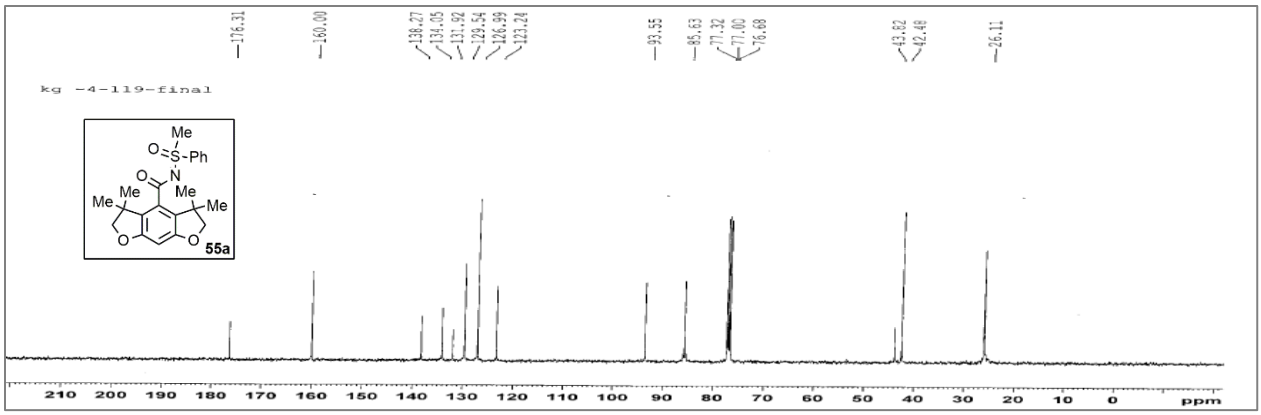

ERA-NA-147
53c Boc

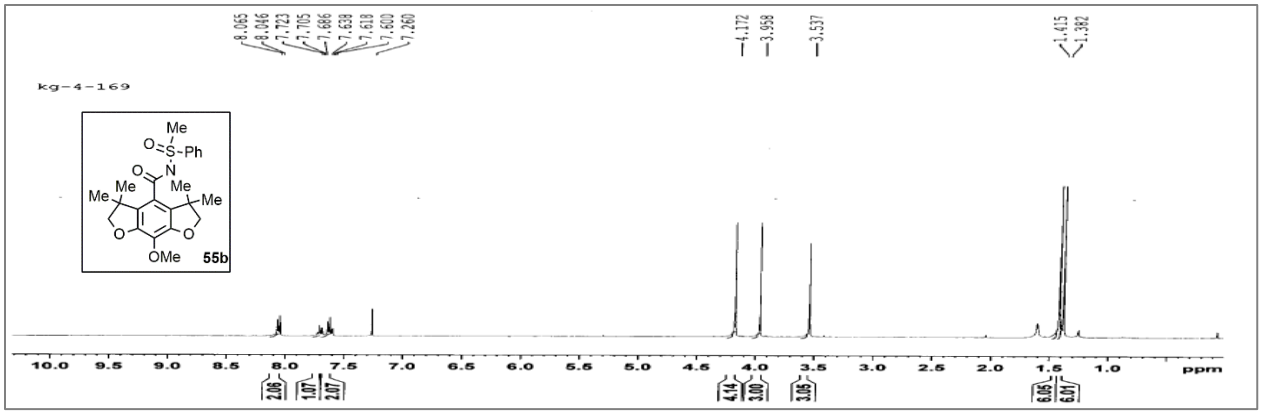

ERA-NA-147
53c Boc

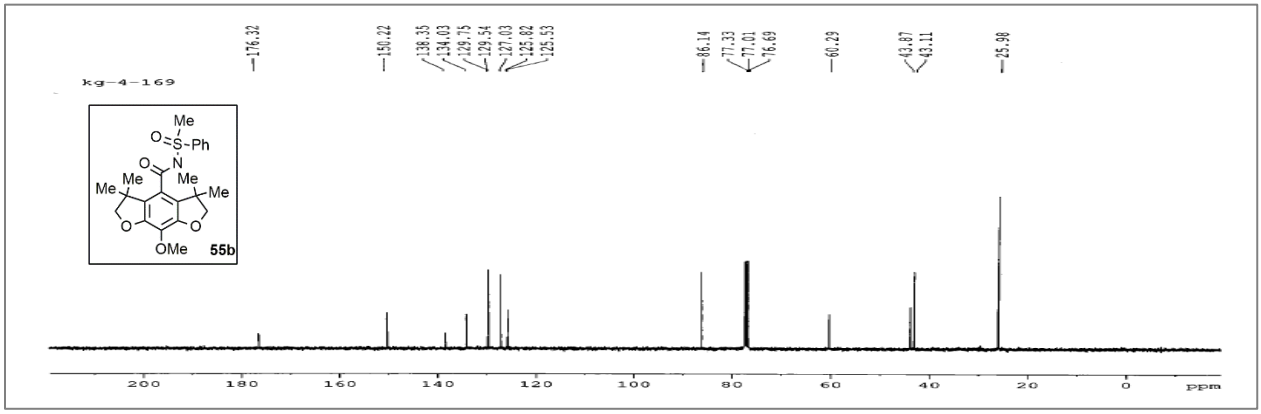

kg-sulfur-pdt
54
ppm

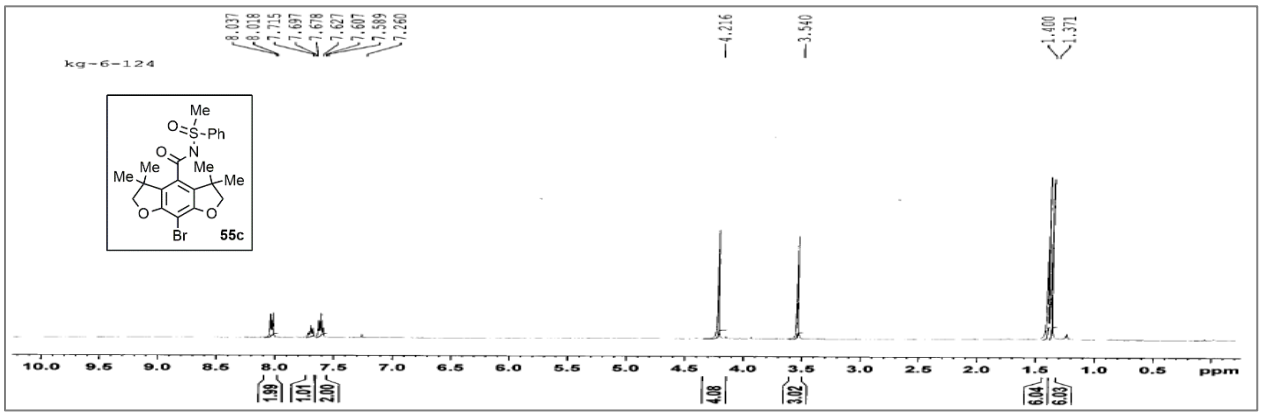

kg-sulfur-pdt
54
ppm

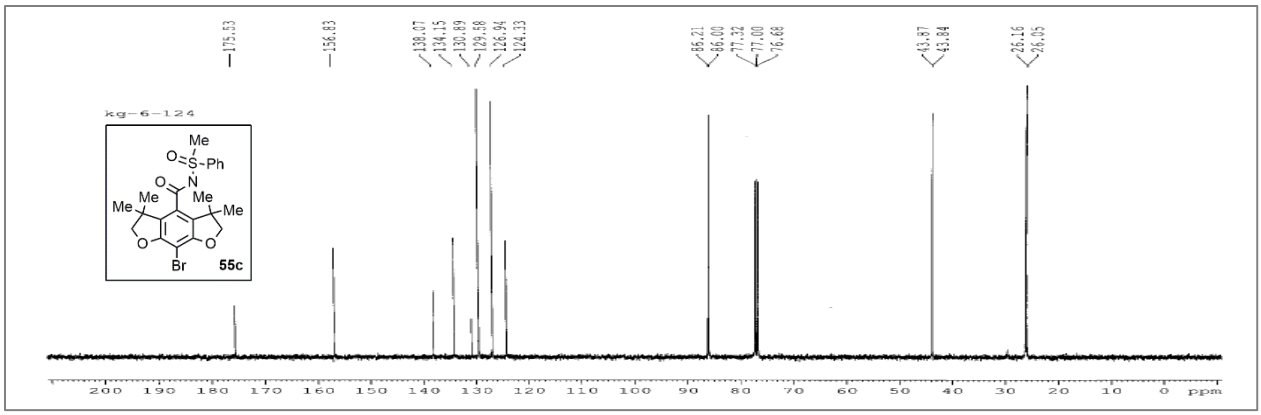

kg -4-119-final
55a
ppm

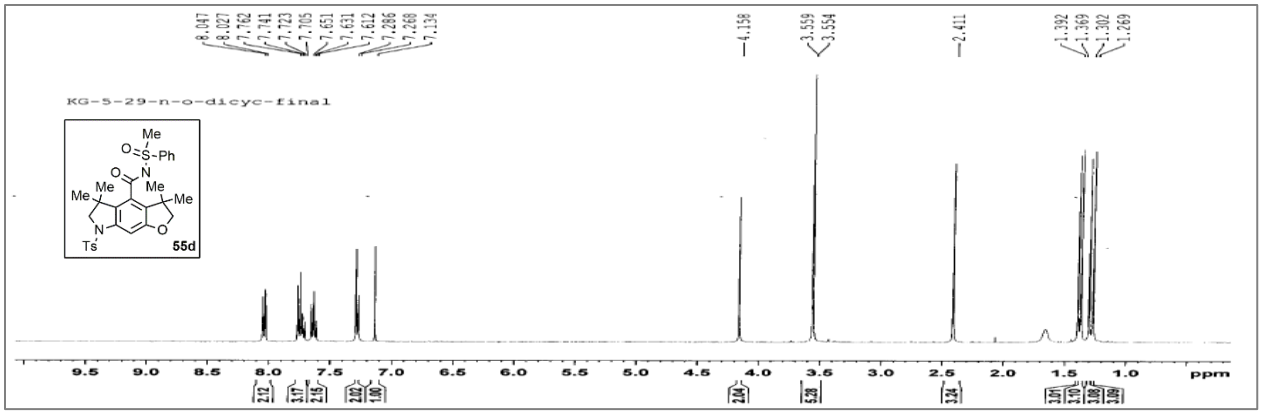

kg -4-119-final
55a
ppm

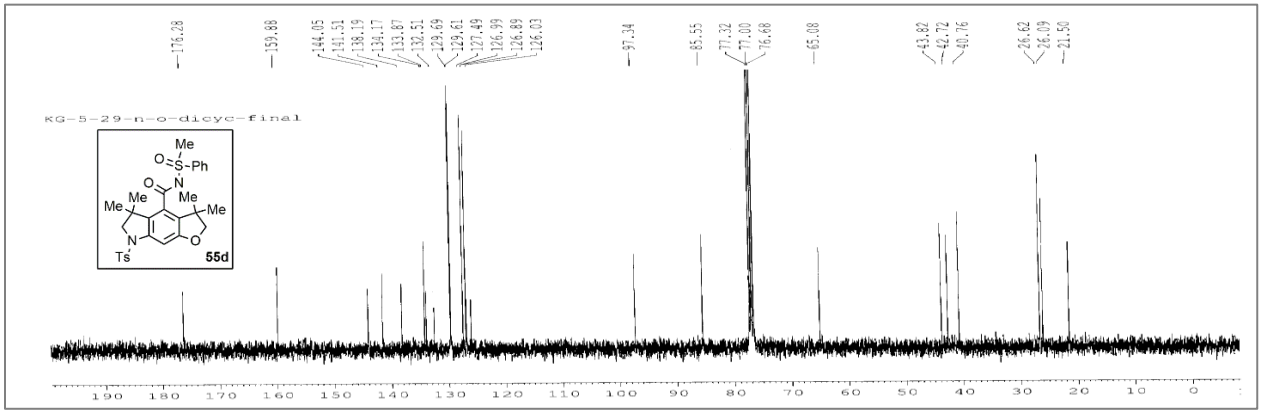

kg-4-169
55b

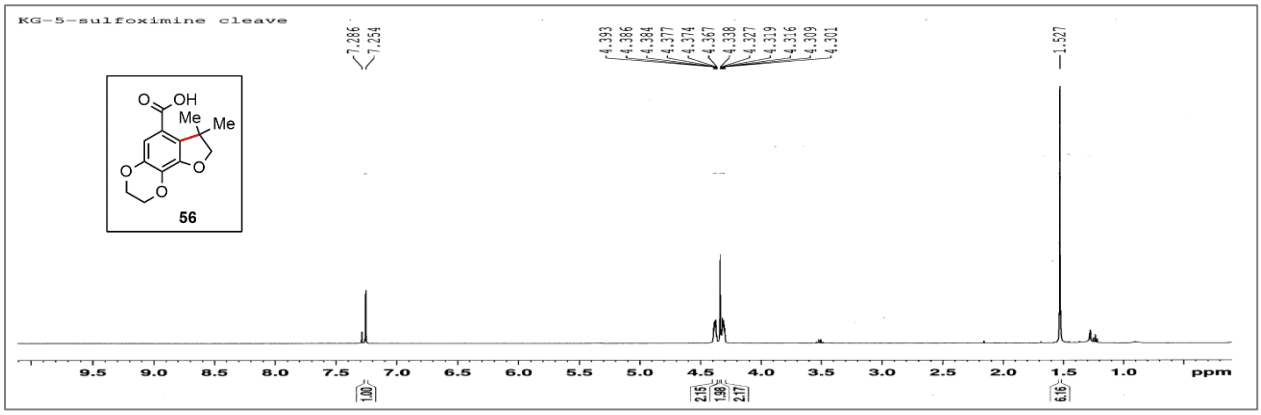

kg-4-169
55b

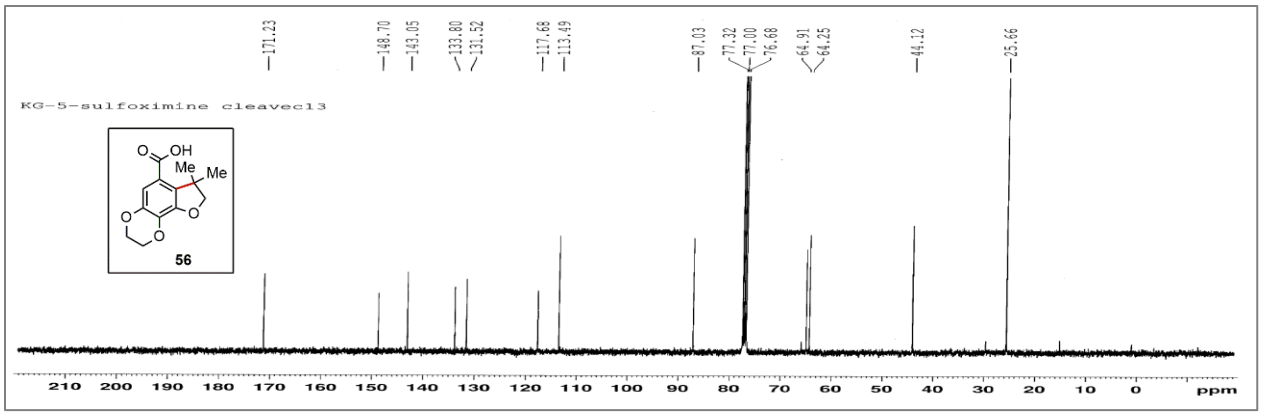

kg-6-124
55c

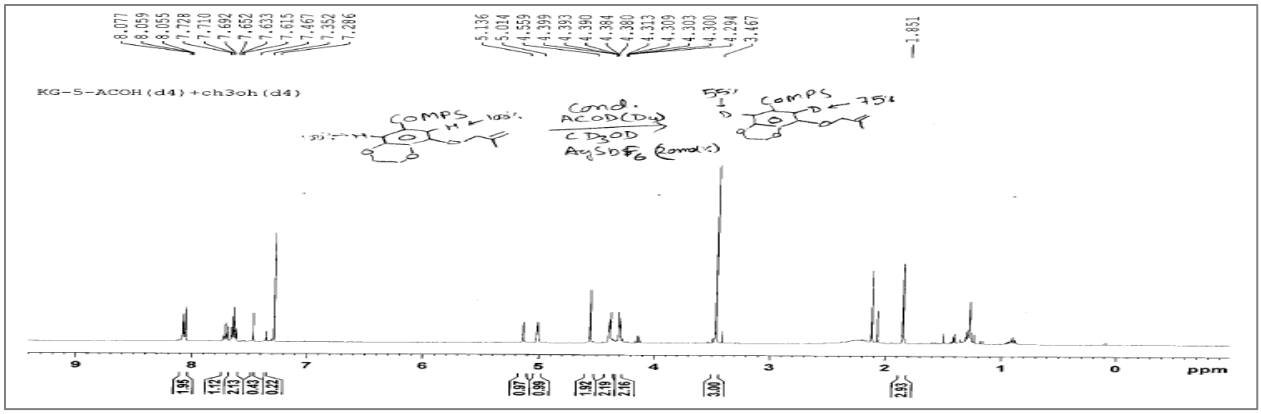

kg-6-124
55c

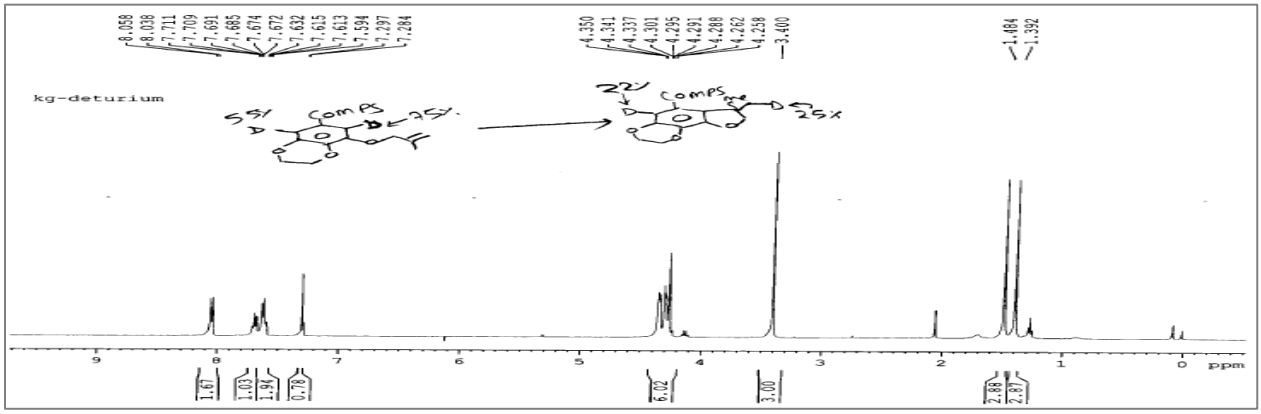

KG-5-29-n-o-dicyc-final
55d

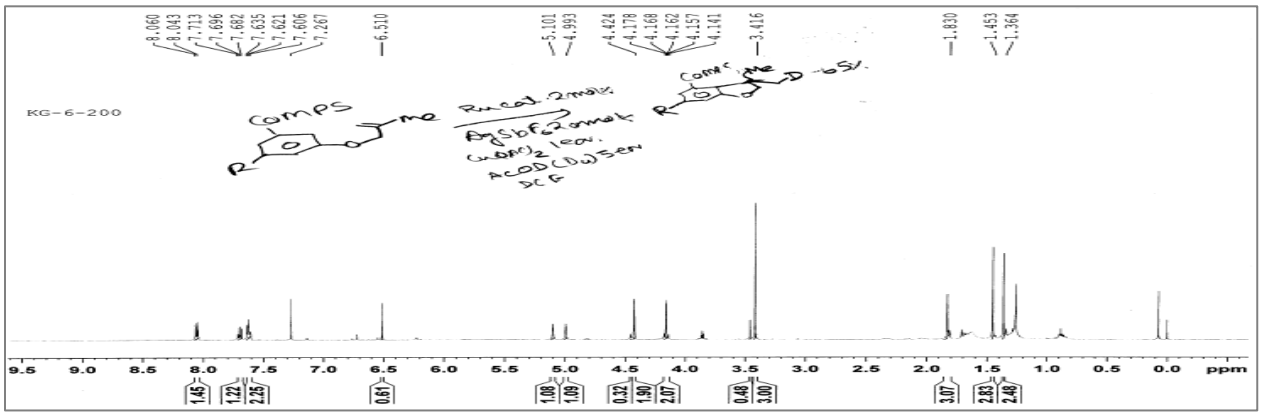

KG-5-29-n-o-dicyc-final
55d

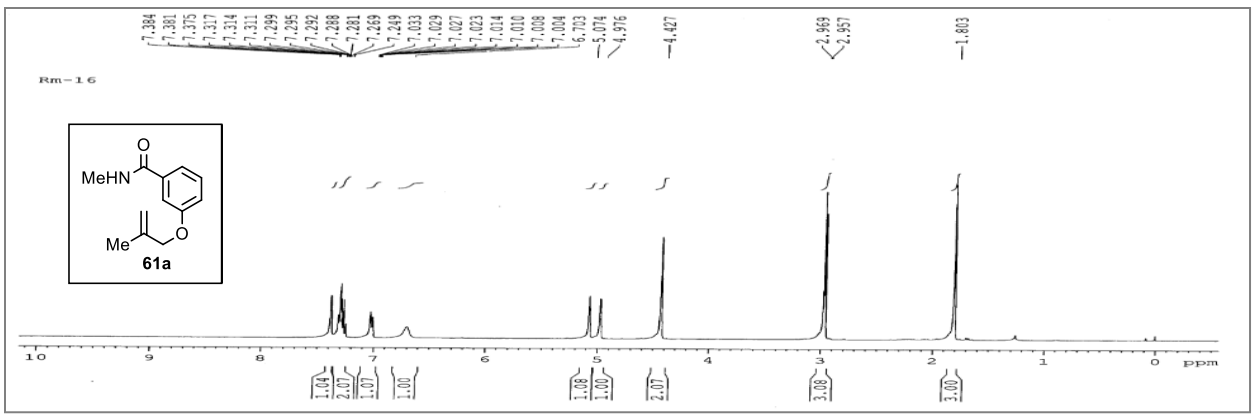

KG-5-sulfoximine cleave
56

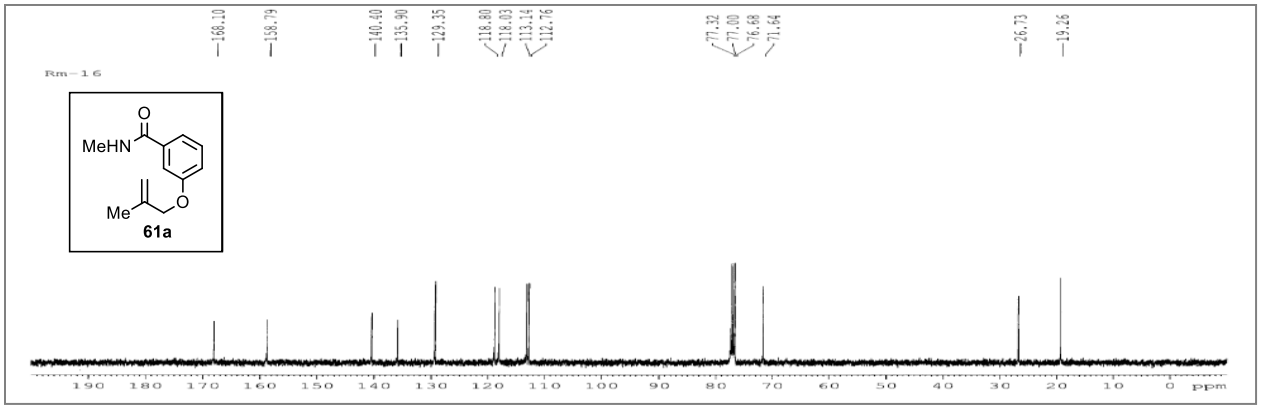

KG-5-sulfoximine cleavec13
56

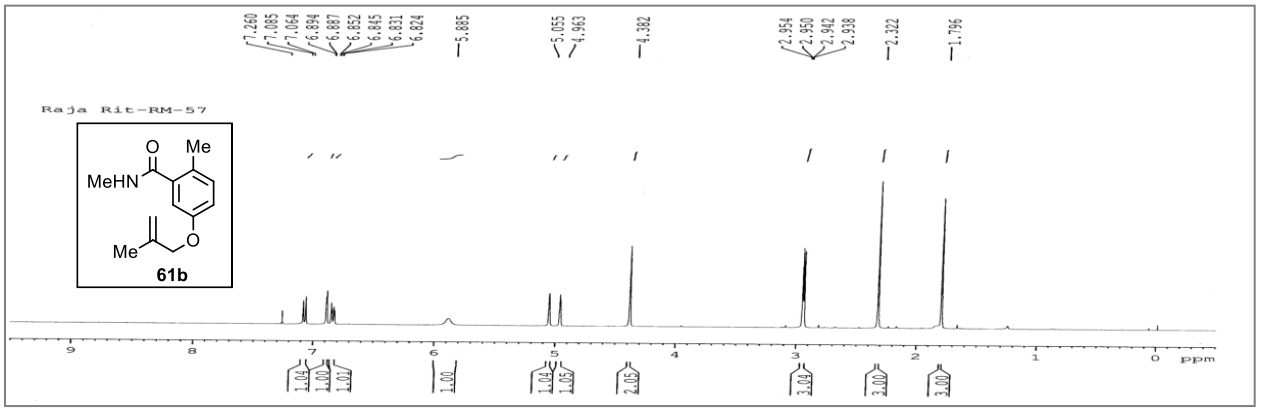

KG-5-ACOH(d4)+ch3oh(d4)
8.077
8.059
8.055
7.728
7.710
7.692
7.652
7.633
7.615
7.467
7.352
7.286
5.136
5.014
4.559
4.399
4.393
4.390
4.384
4.380
4.313
4.309
4.303
4.300
4.294
3.467
1.851
ppm

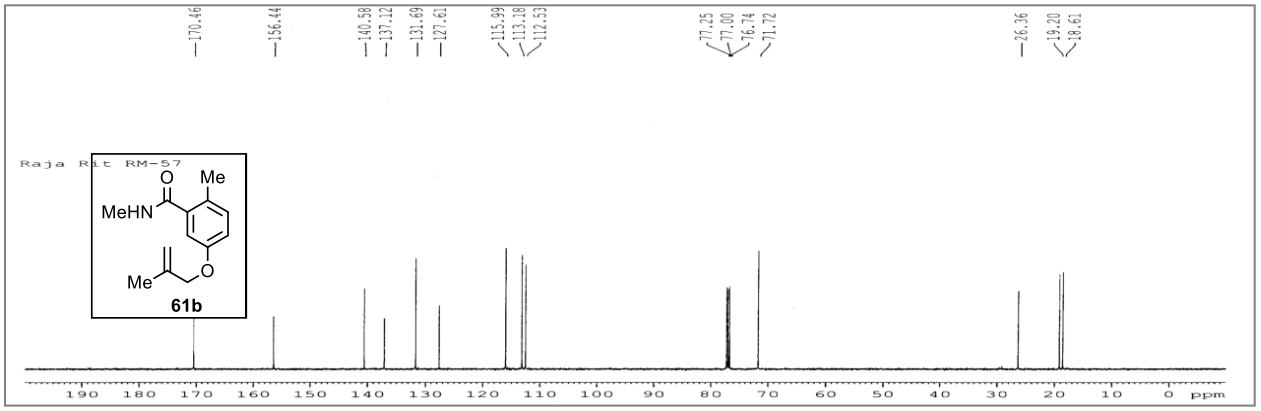

kg-deturium
8.088
8.038
7.711
7.709
7.691
7.685
7.674
7.672
7.632
7.615
7.613
7.594
7.297
7.284
4.350
4.341
4.337
4.301
4.295
4.291
4.288
4.262
4.258
3.400
1.484
1.392
ppm

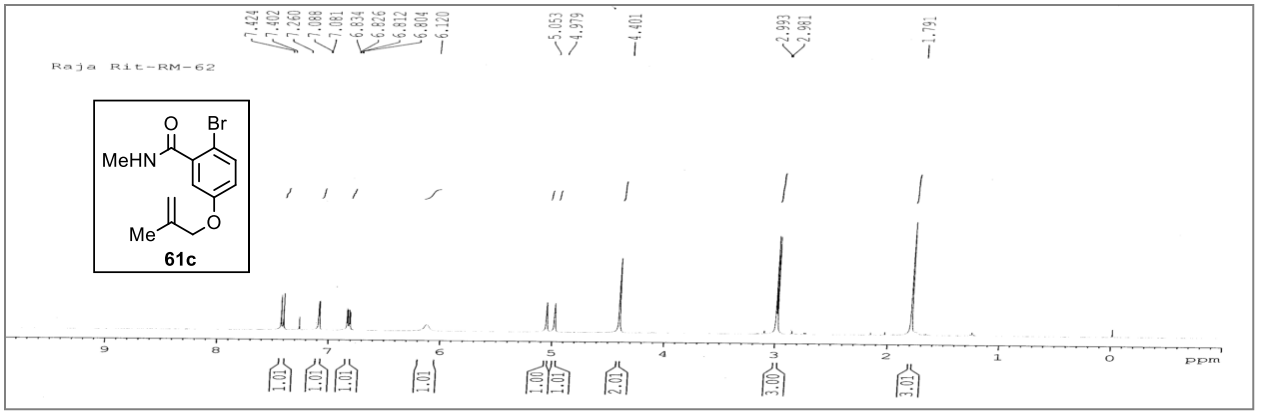

KG-6-200
8.060
8.043
7.713
7.696
7.682
7.635
7.621
7.606
7.267
6.510
5.101
4.993
4.424
4.178
4.168
4.162
4.157
4.141
3.416
1.830
1.453
1.364
ppm

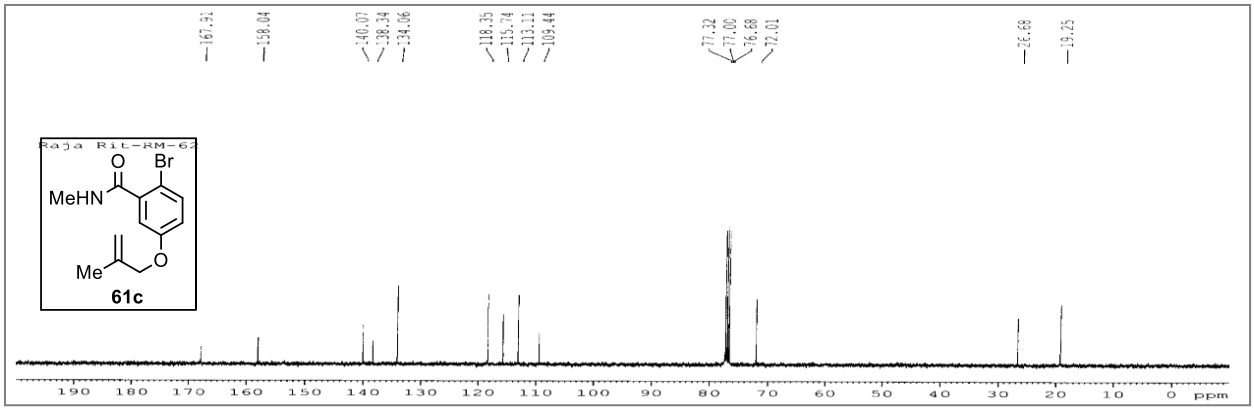

Rm-16
7.384
7.381
7.375
7.317
7.314
7.311
7.299
7.295
7.292
7.288
7.281
7.269
7.249
7.033
7.029
7.027
7.023
7.014
7.010
7.008
7.004
6.703
5.074
4.976
4.427
2.969
2.957
1.803
MeHN
Me
61a
ppm

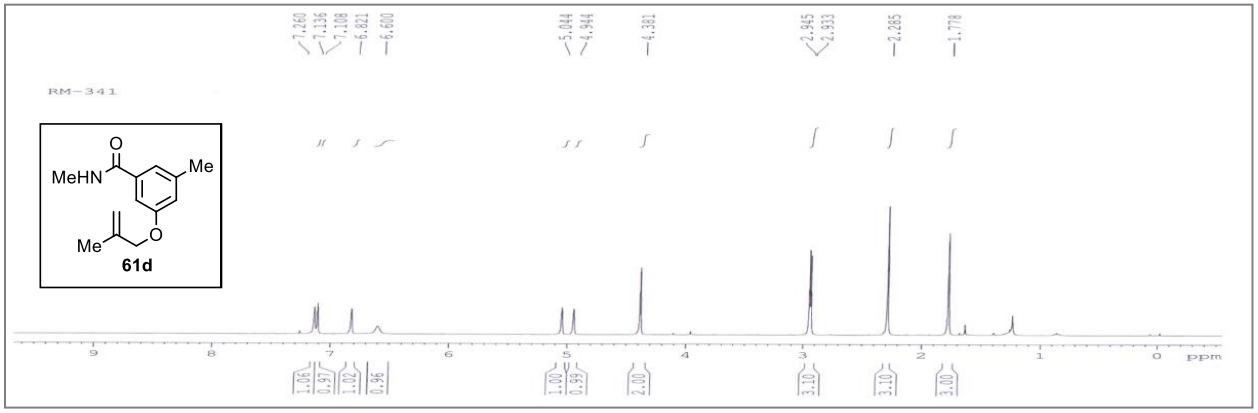

Rm-16
MeHN
Me
61a
168.10
158.79
140.40
135.90
129.35
118.80
118.03
113.14
112.76
77.32
77.00
76.68
71.64
26.73
19.26
ppm

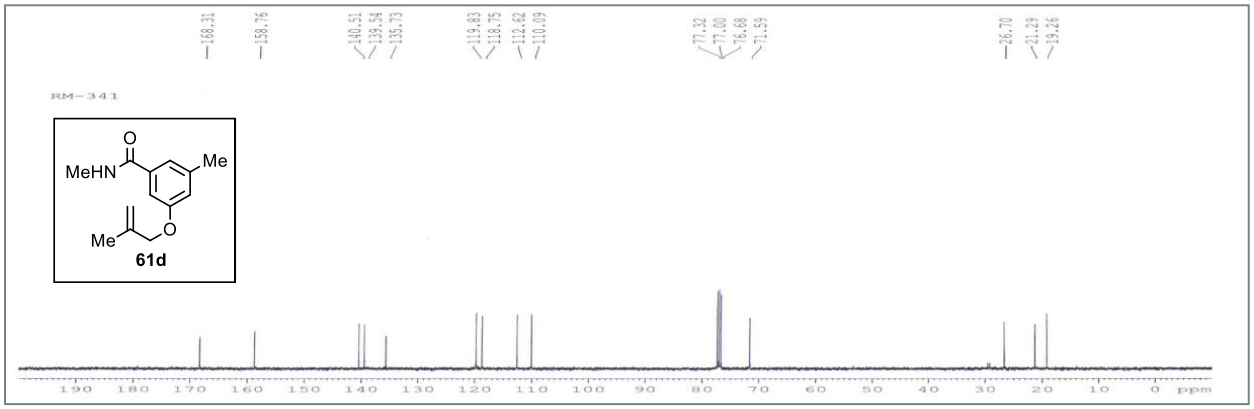

Raja Rit-RM-57
MeHN
Me
Me
61b
7.260
7.085
7.064
6.894
6.887
6.852
6.845
6.831
6.824
5.885
5.055
4.963
4.382
2.954
2.950
2.942
2.938
2.322
1.796
ppm

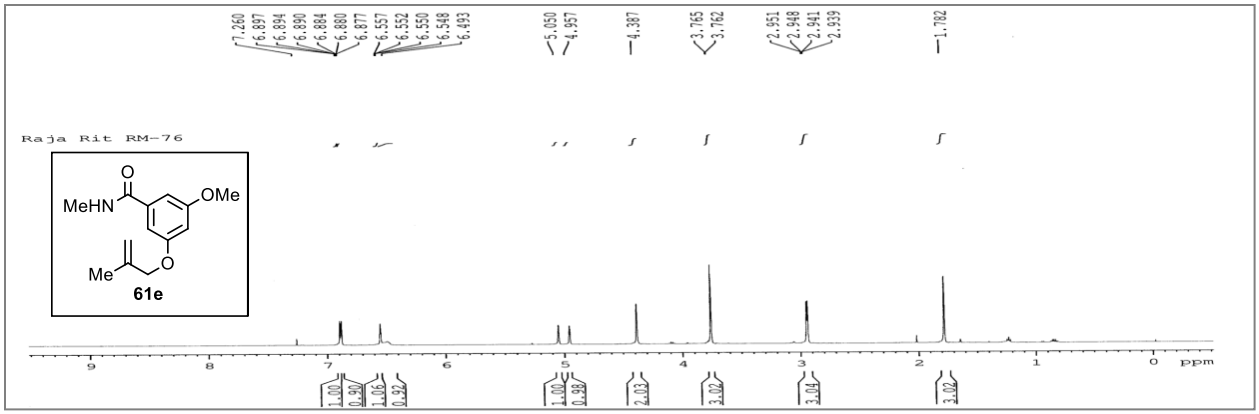

Raja Rit RM-57
MeHN
Me
Me
61b
170.46
156.44
140.58
137.12
131.69
127.61
115.99
113.18
112.53
77.25
77.00
76.74
71.72
26.36
19.20
18.61
ppm

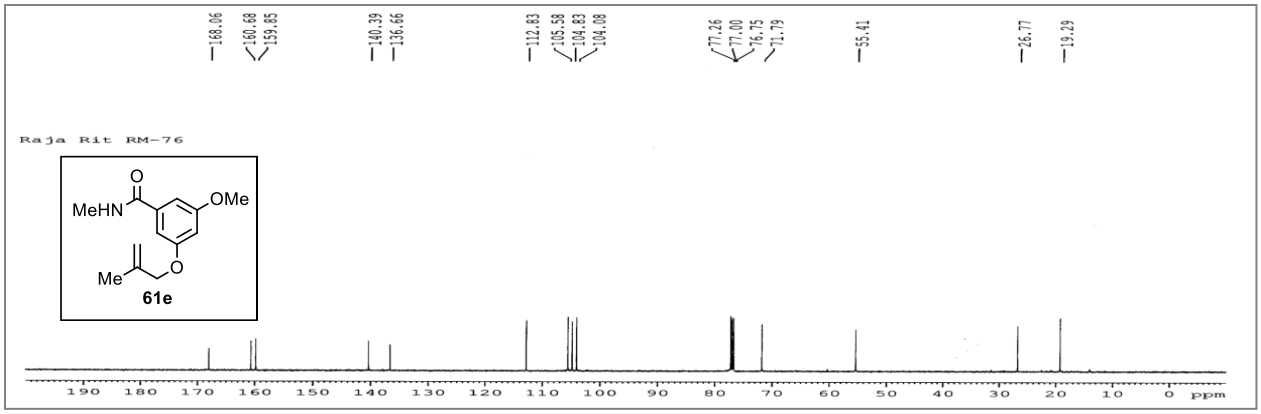

Raja Rit-RM-62
MeHN
Br
Me
61c
7.424
7.402
7.260
7.088
7.081
6.834
6.826
6.812
6.804
6.120
5.053
4.979
4.401
2.993
2.981
1.791
ppm

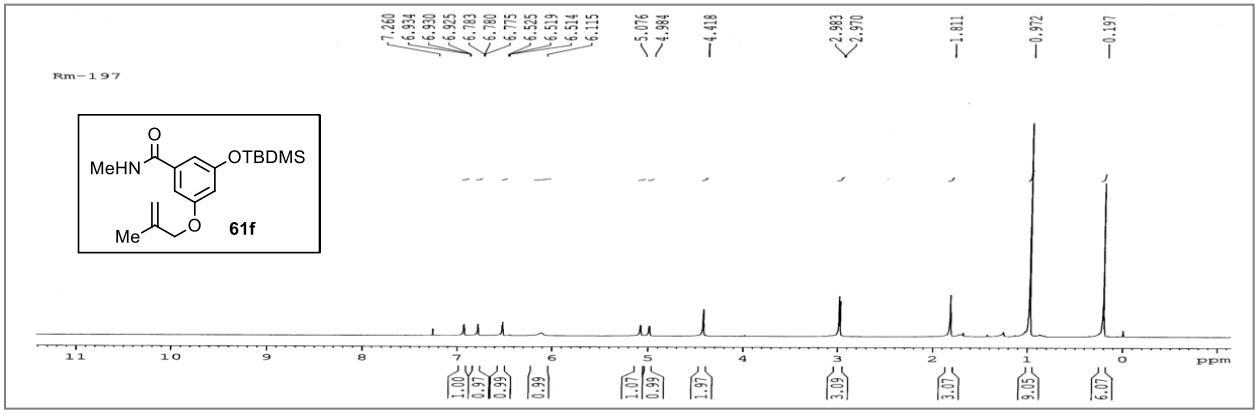

Raja Rit-RM-62
MeHN
Br
Me
61c
ppm

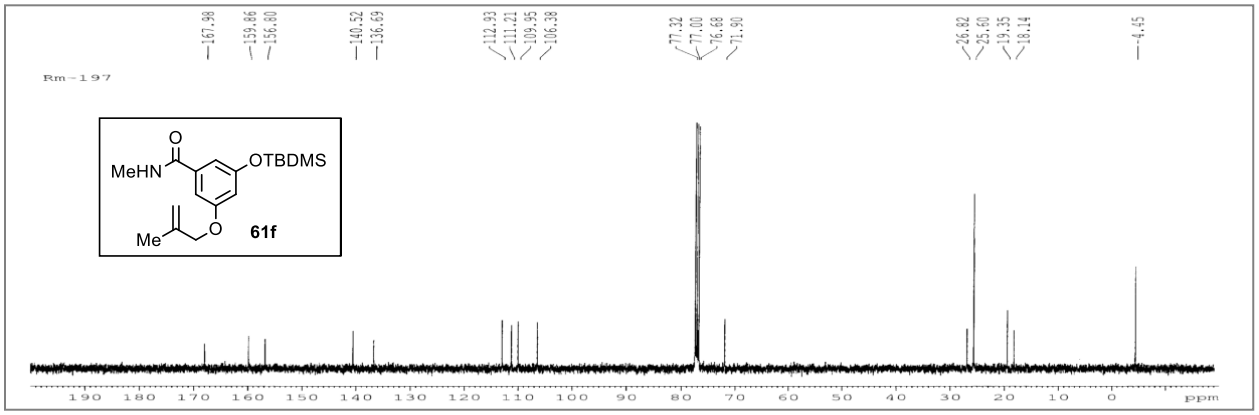

RM-341
MeHN
Me
Me
61d
ppm

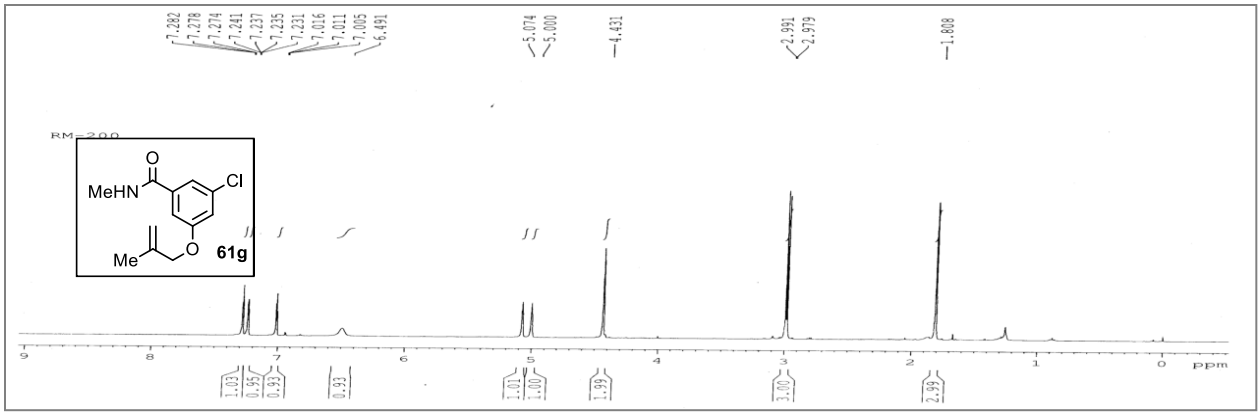

RM-341
MeHN
Me
Me
61d
ppm

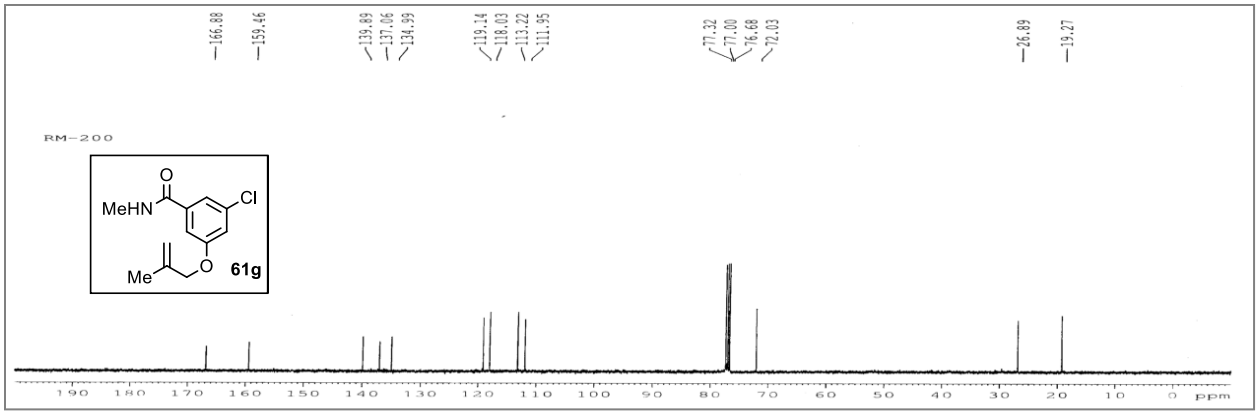

Raja Rit RM-76
MeHN
OMe
Me
61e
ppm

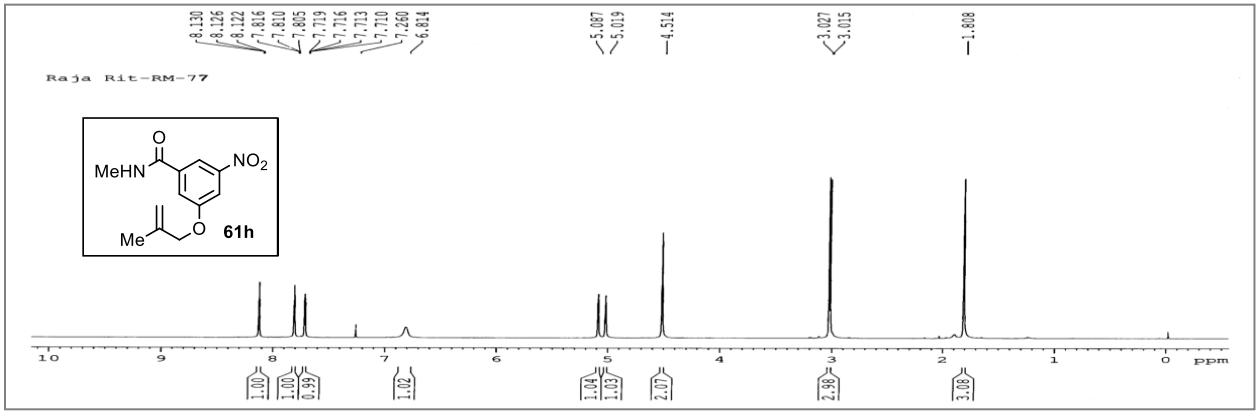

Raja Rit RM-76
MeHN
OMe
Me
61e

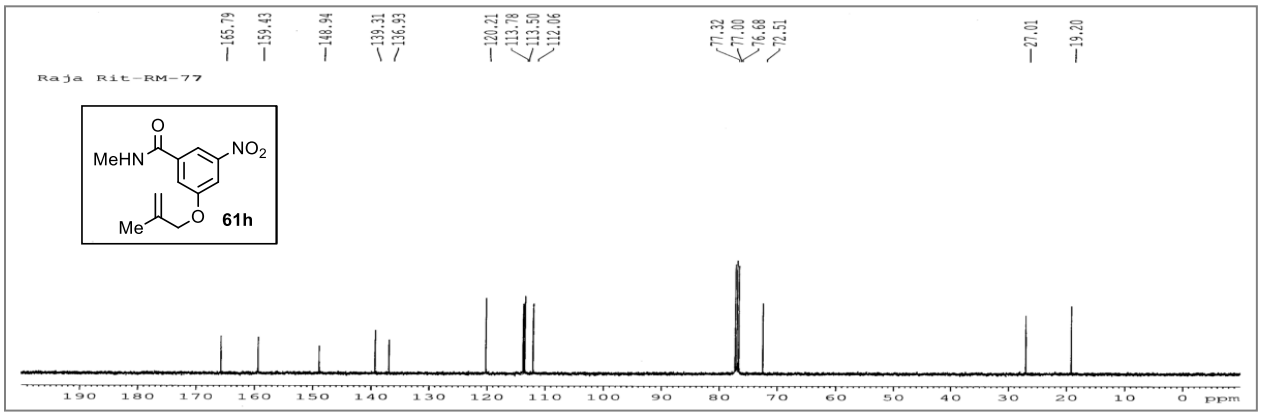

Rm-197
MeHN
OTBDMS
Me
61f

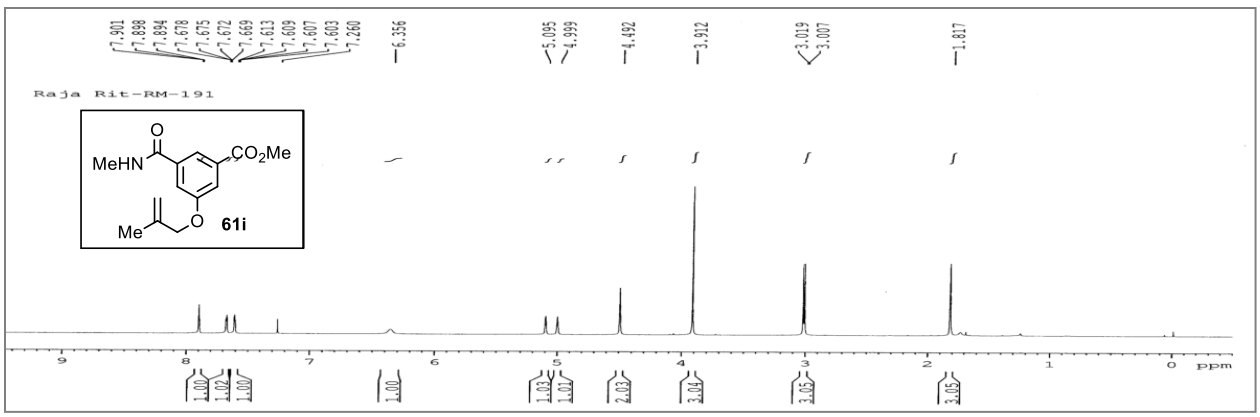

Rm-197
MeHN
OTBDMS
Me
61f

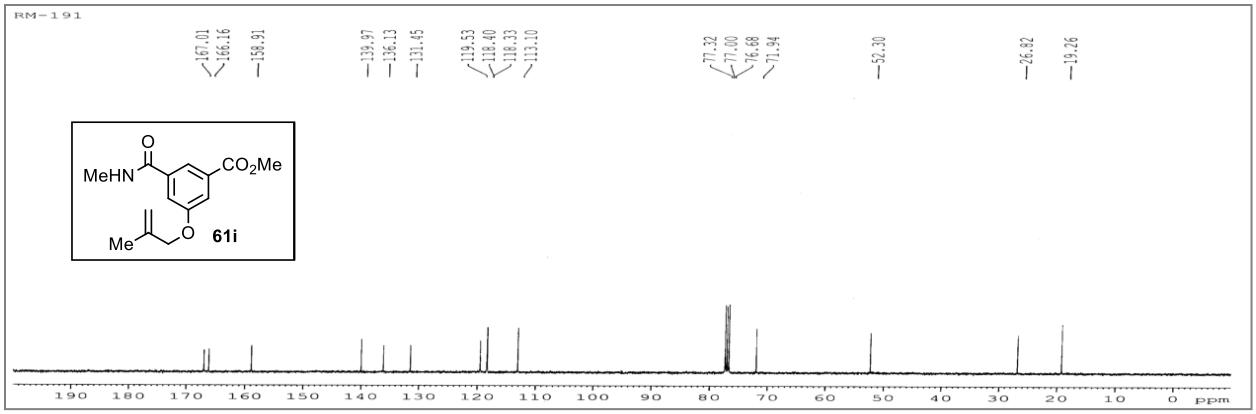

RM-200
MeHN
Cl
Me
61g

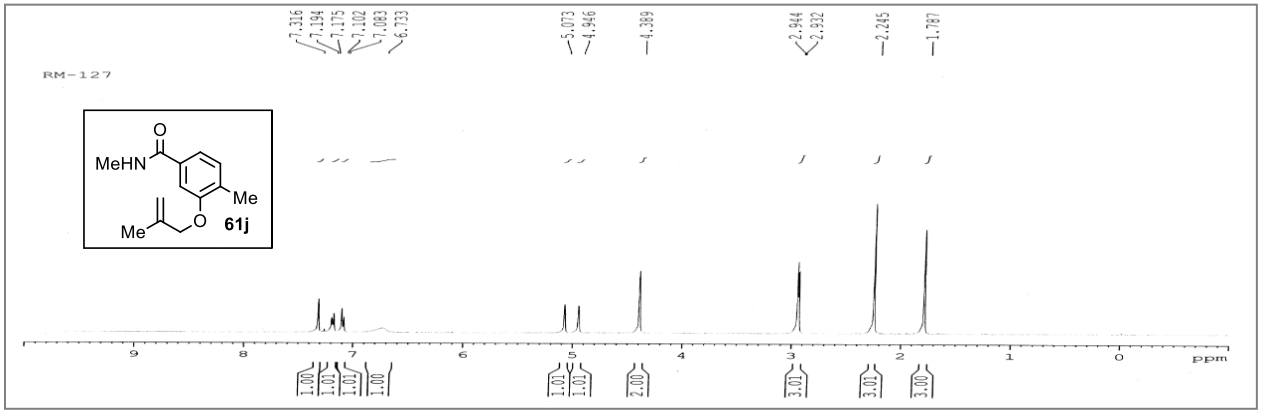

RM-200
MeHN
O
Cl
Me
O
61g
166.88
159.46
139.89
137.06
134.99
119.14
118.03
113.22
111.95
77.32
77.00
76.68
72.03
26.89
19.27
ppm

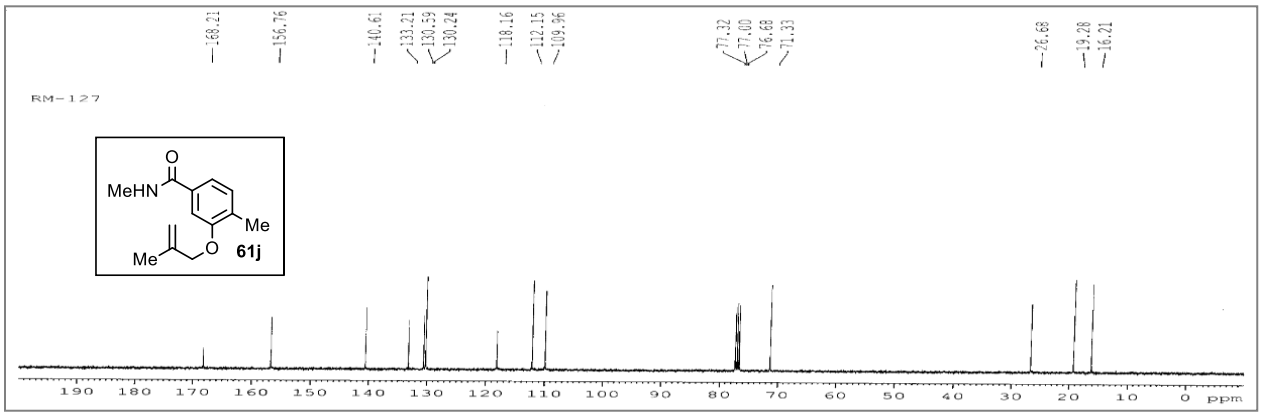

Raja Rit-RM-77
MeHN
O
NO2
Me
O
61h
8.130
8.126
8.122
7.816
7.810
7.805
7.719
7.716
7.713
7.710
7.260
6.814
5.087
5.019
4.514
3.027
3.015
1.808
1.00
1.00
0.99
1.02
1.04
1.03
2.07
2.98
3.08
ppm

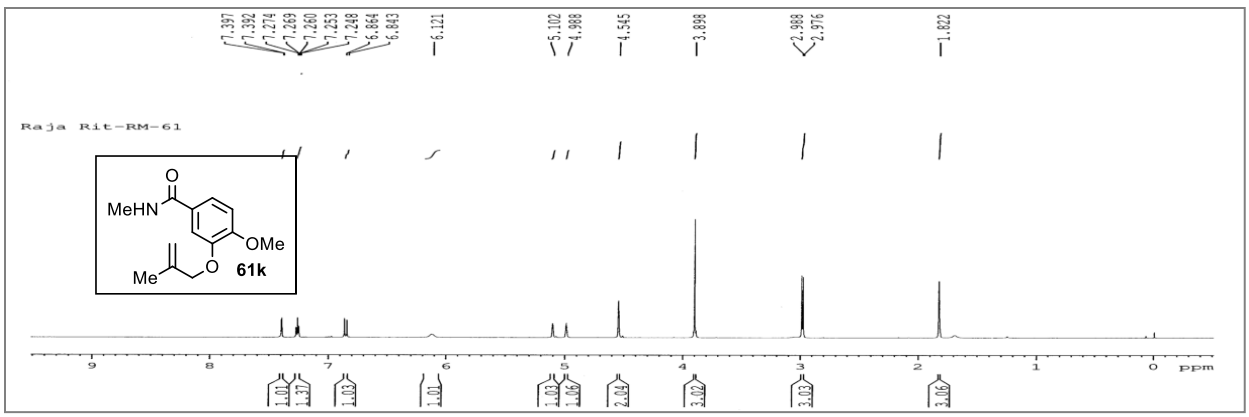

Raja Rit-RM-77
MeHN
O
NO2
Me
O
61h
165.79
159.43
148.94
139.31
136.93
120.21
113.78
113.50
112.06
77.32
77.00
76.68
72.51
27.01
19.20
ppm

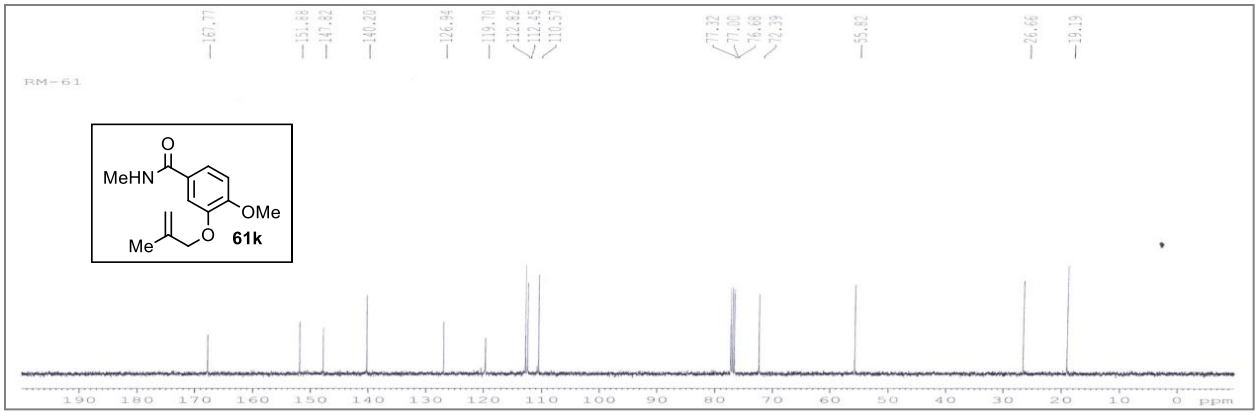

Raja Rit-RM-191
MeHN
O
CO2Me
Me
O
61i
7.901
7.898
7.894
7.678
7.675
7.672
7.669
7.613
7.609
7.607
7.603
7.260
6.356
5.095
4.999
4.492
3.912
3.019
3.007
1.817
1.00
1.02
1.00
1.00
1.03
1.07
2.03
3.04
3.05
3.05
ppm

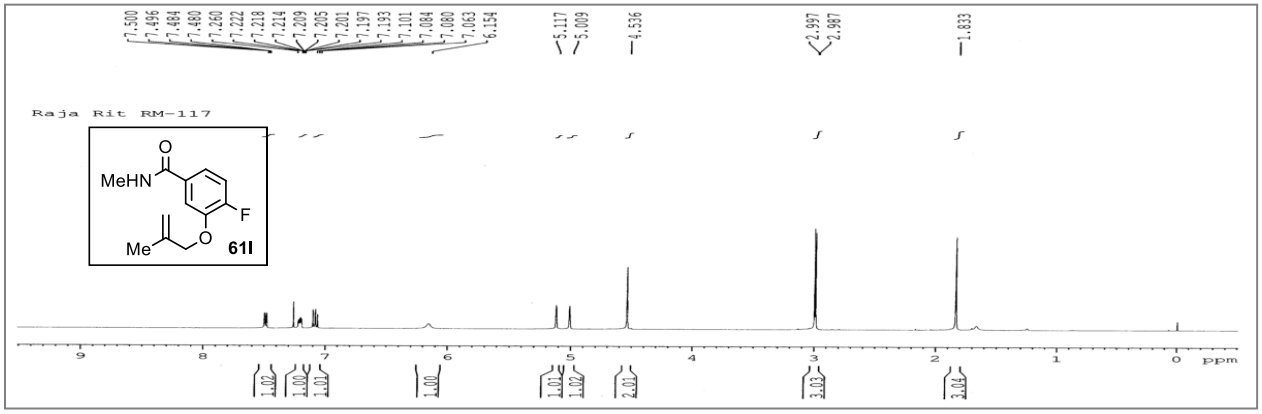

RM-191
167.01
166.16
158.91
139.97
136.13
131.45
119.53
118.40
118.33
113.10
77.32
77.00
76.68
71.94
52.30
26.82
19.26
MeHN
O
CO2Me
Me
O
61i
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

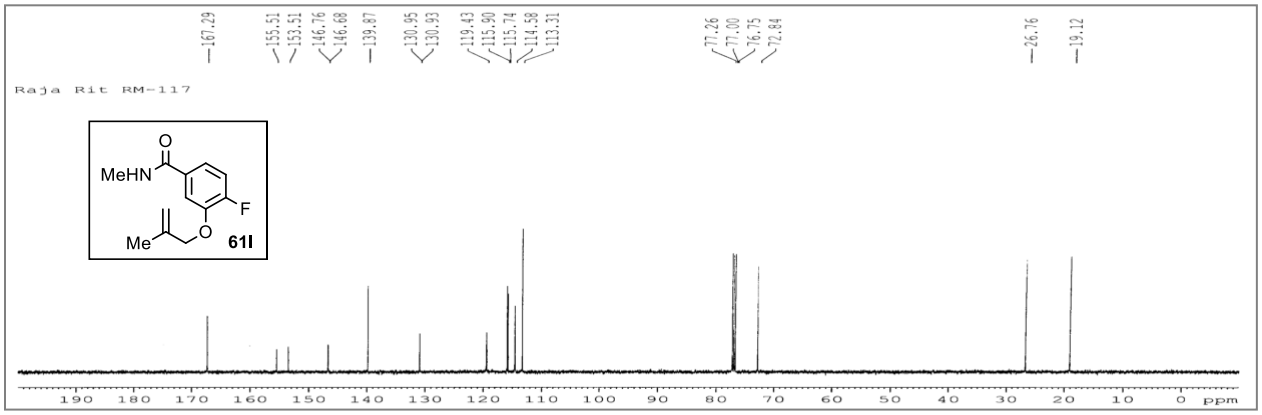

RM-127
7.316
7.194
7.175
7.102
7.083
6.733
5.073
4.946
4.389
2.944
2.932
2.245
1.787
MeHN
O
Me
Me
O
61j
9 8 7 6 5 4 3 2 1 0 ppm
1.00
1.01
1.01
1.00
1.01
1.01
2.00
3.01
3.01
3.00

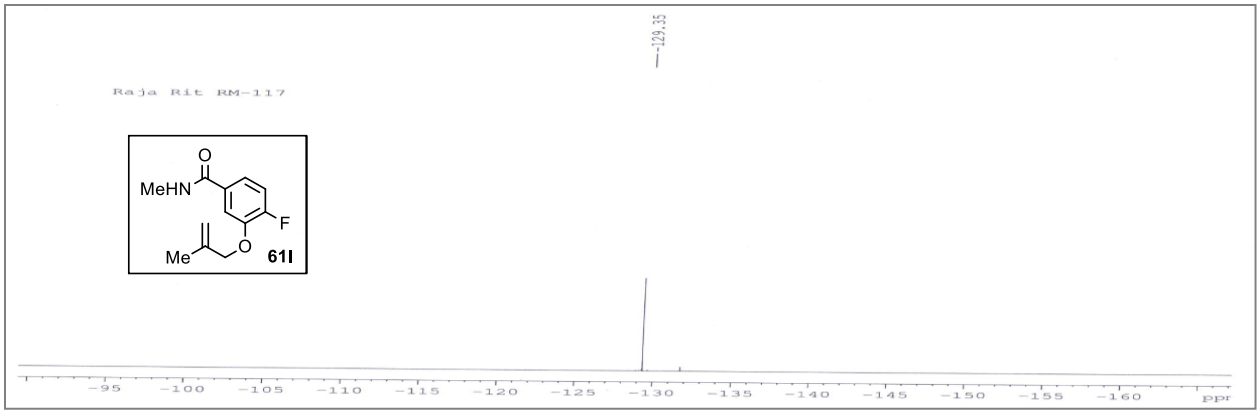

RM-127
168.21
156.76
140.61
133.21
130.59
130.24
118.16
112.15
109.96
77.32
77.00
76.68
71.33
26.68
19.28
16.21
MeHN
O
Me
Me
O
61j
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

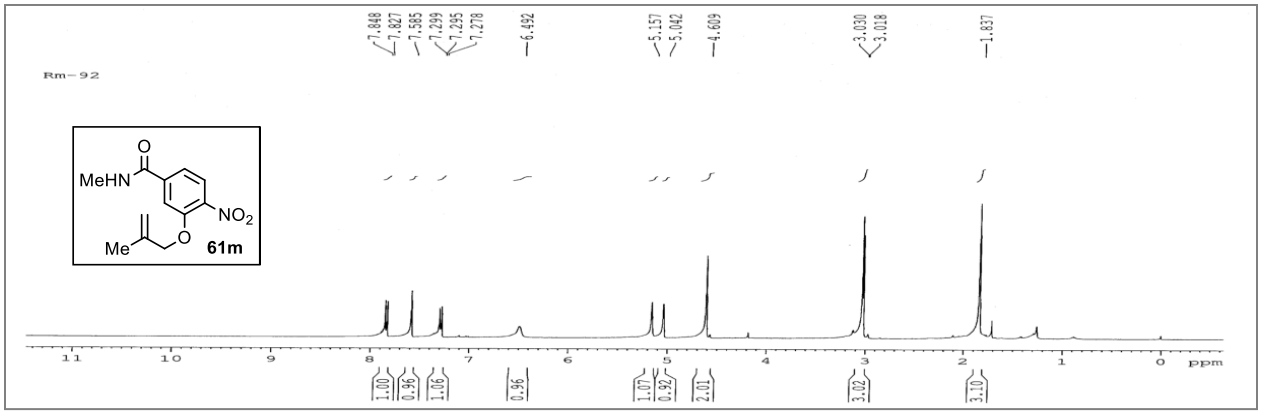

Raja Rit-RM-61
7.397
7.392
7.274
7.269
7.260
7.253
7.248
6.864
6.843
6.121
5.102
4.988
4.545
3.898
2.988
2.976
1.822
MeHN
O
OMe
Me
O
61k
9 8 7 6 5 4 3 2 1 0 ppm
1.01
1.37
1.03
1.01
1.03
1.06
2.04
3.02
3.03
3.06

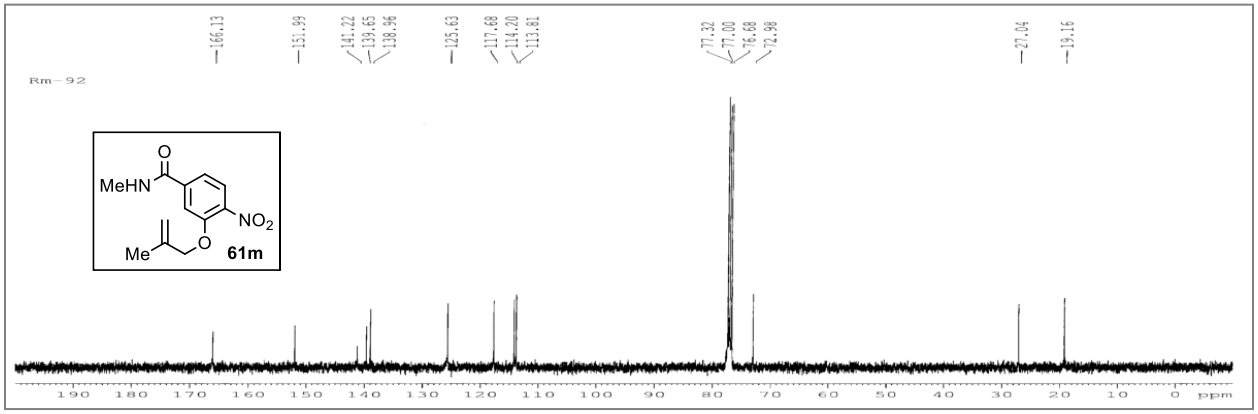

RM-61
MeHN
OMe
Me
61k

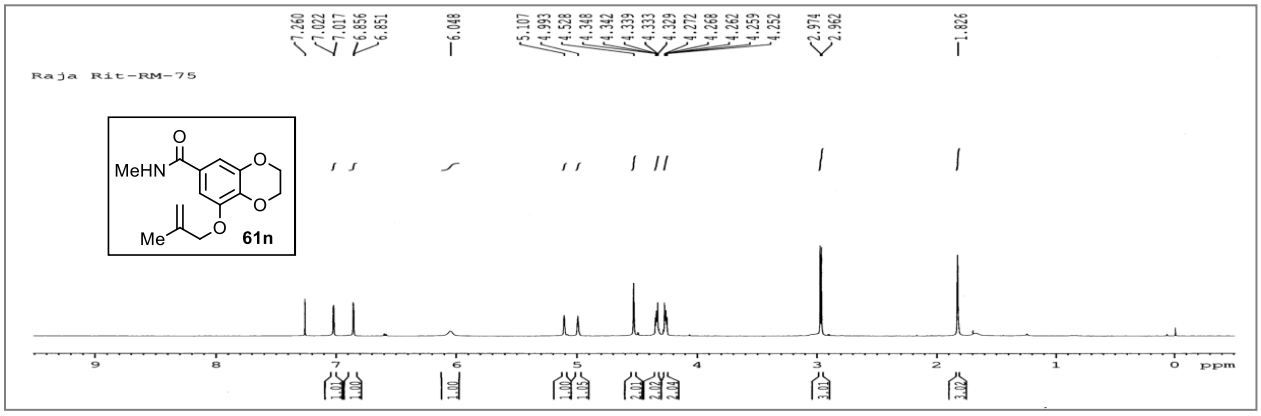

Raja Rit RM-117
MeHN
F
Me
61l

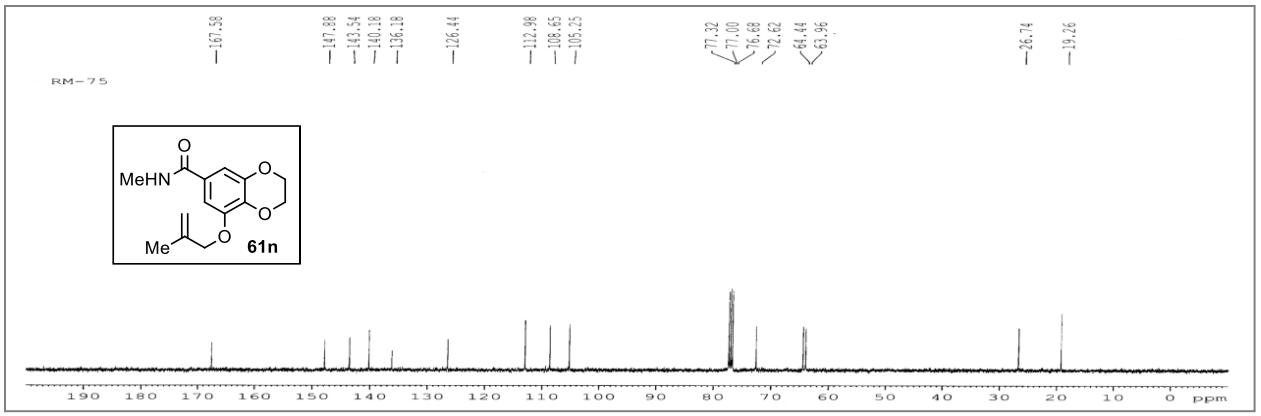

Raja Rit RM-117
MeHN
F
Me
61l

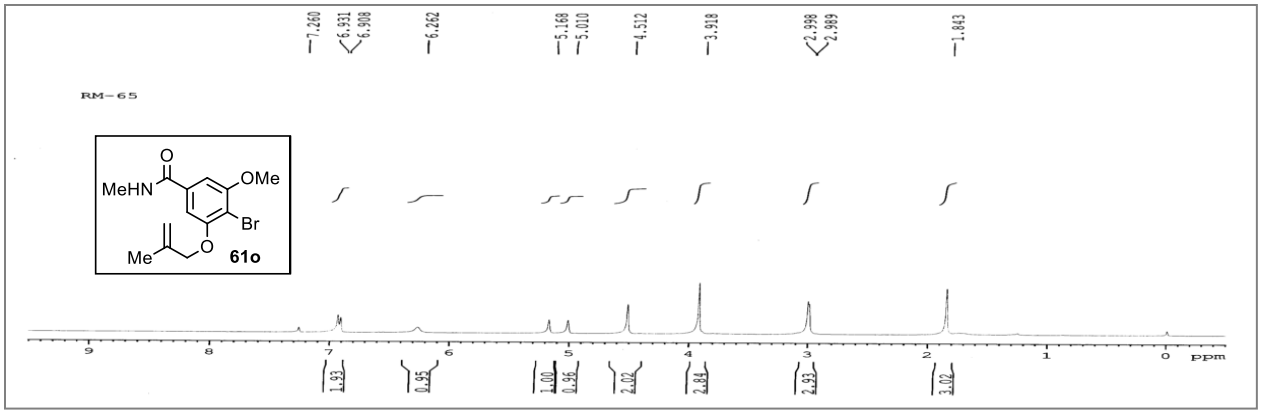

Raja Rit RM-117
MeHN
F
Me
61l

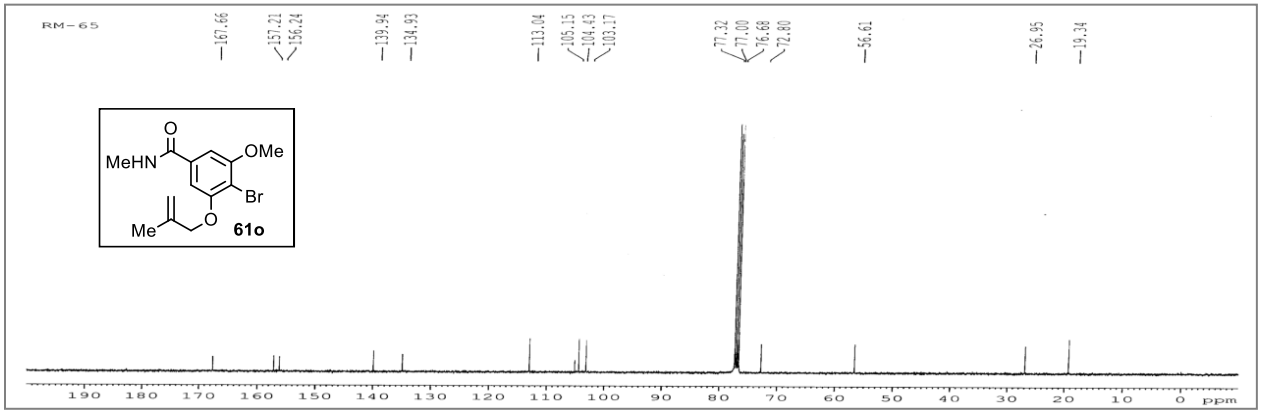

Rm-92
MeHN
NO2
Me
61m

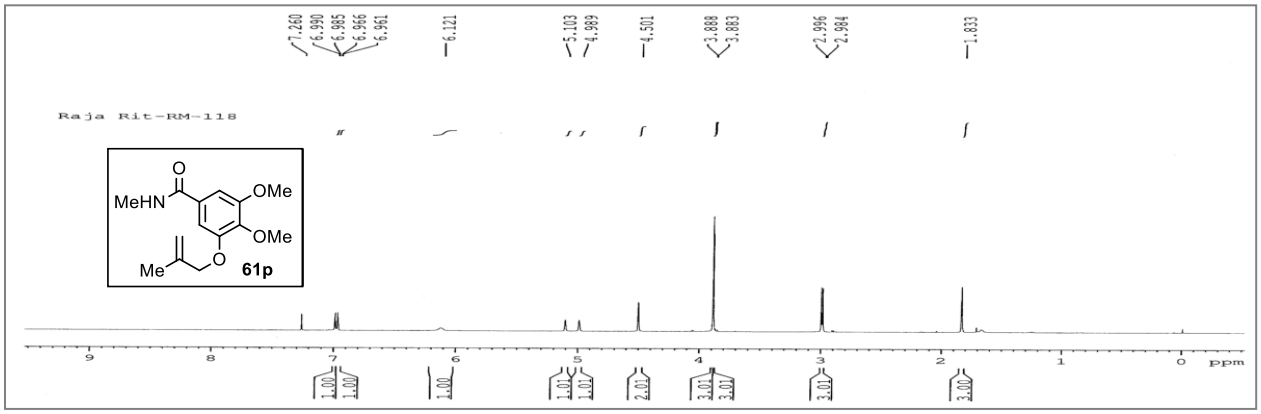

Rm-92
MeHN
NO2
Me
61m

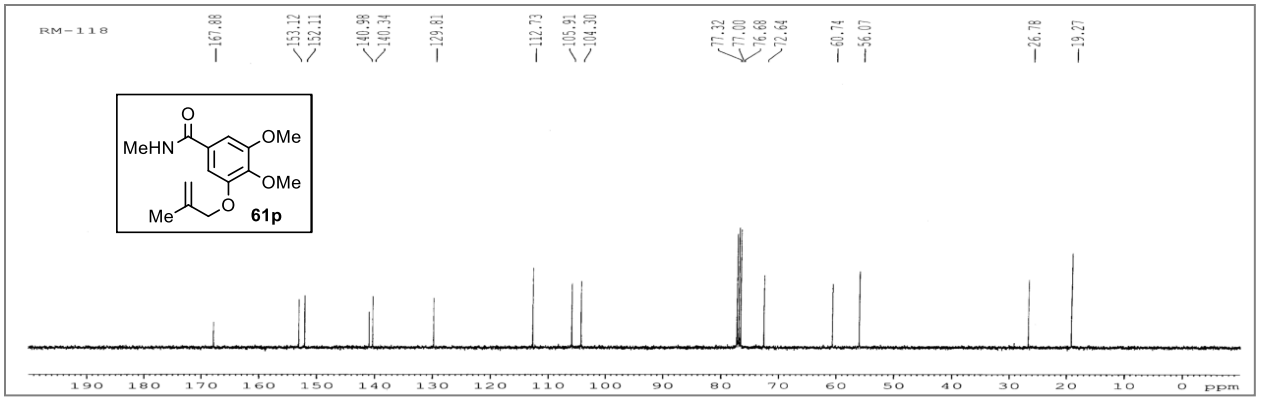

Raja Rit-RM-75
MeHN
Me
61n

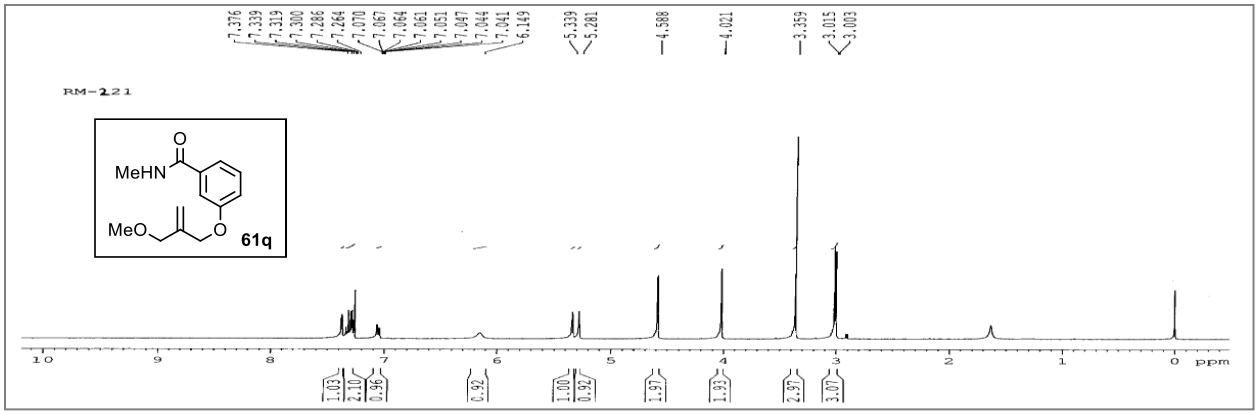

RM-75
MeHN
Me
61n

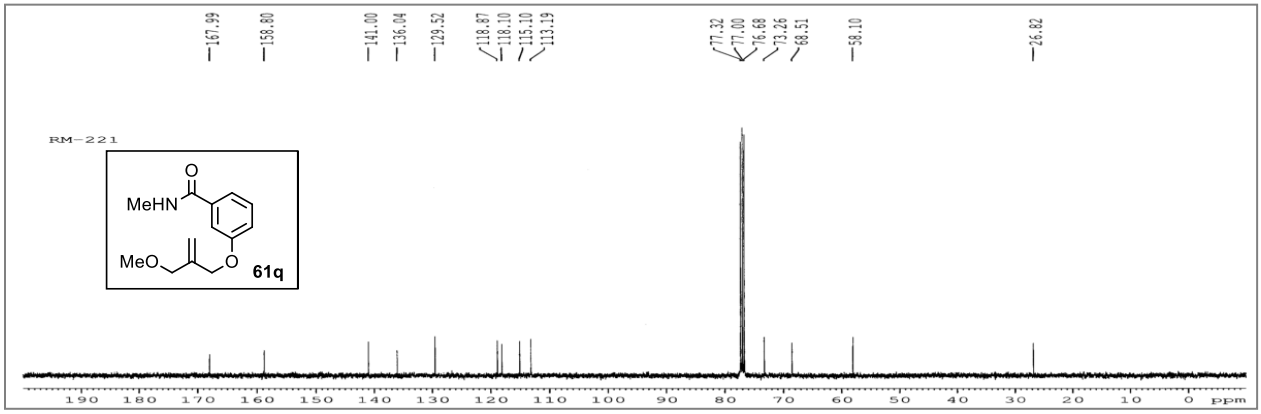

RM-65
MeHN
OMe
Br
Me
61o

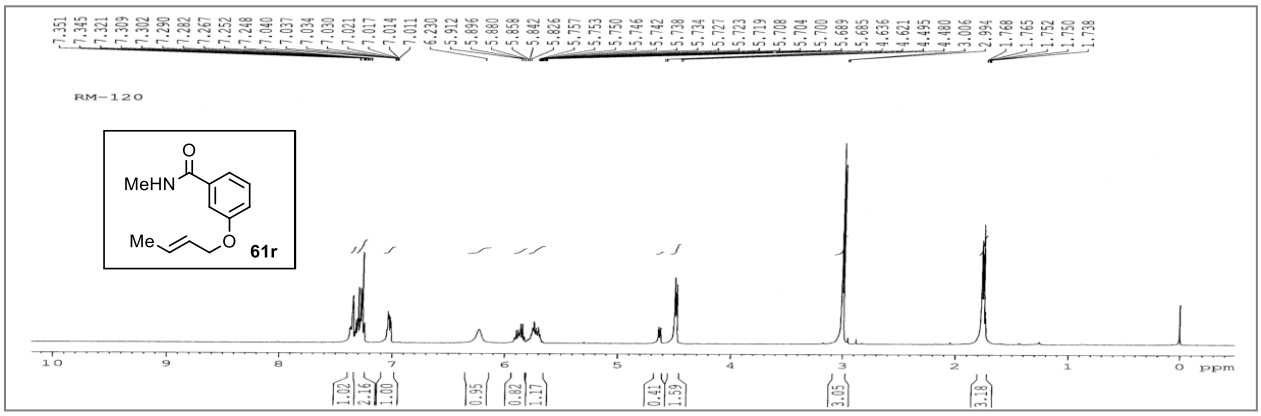

RM-65
MeHN
OMe
Br
Me
61o

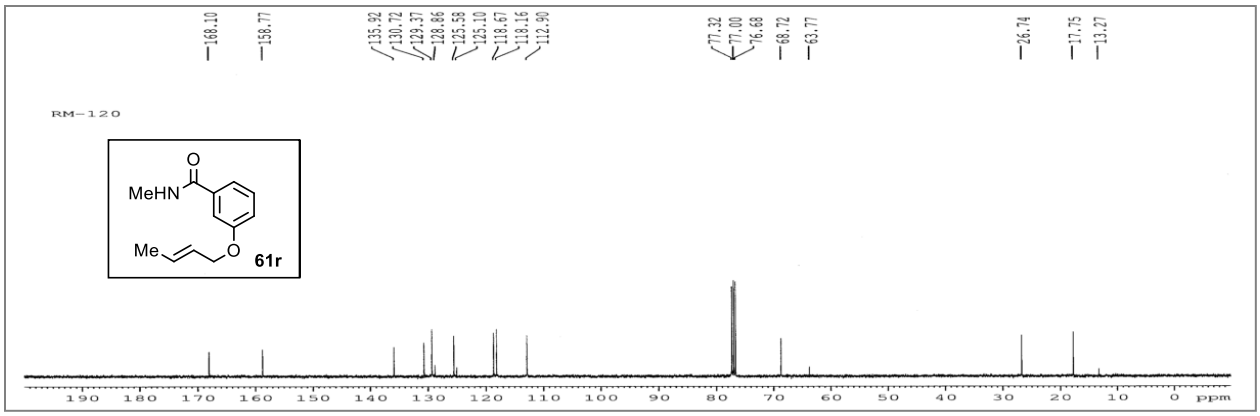

Raja Rit-RM-118
MeHN
OMe
OMe
Me
61p

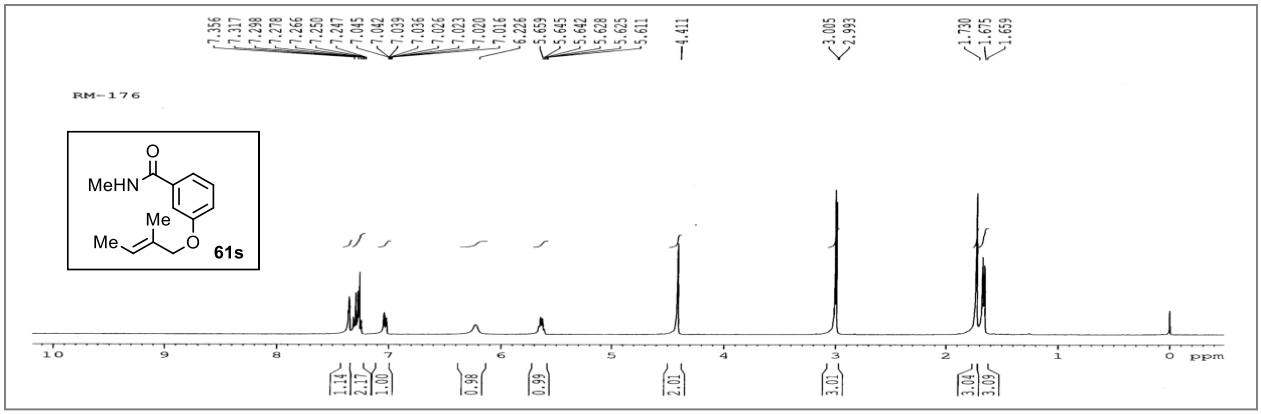

RM-118
MeHN
OMe
OMe
Me
61p

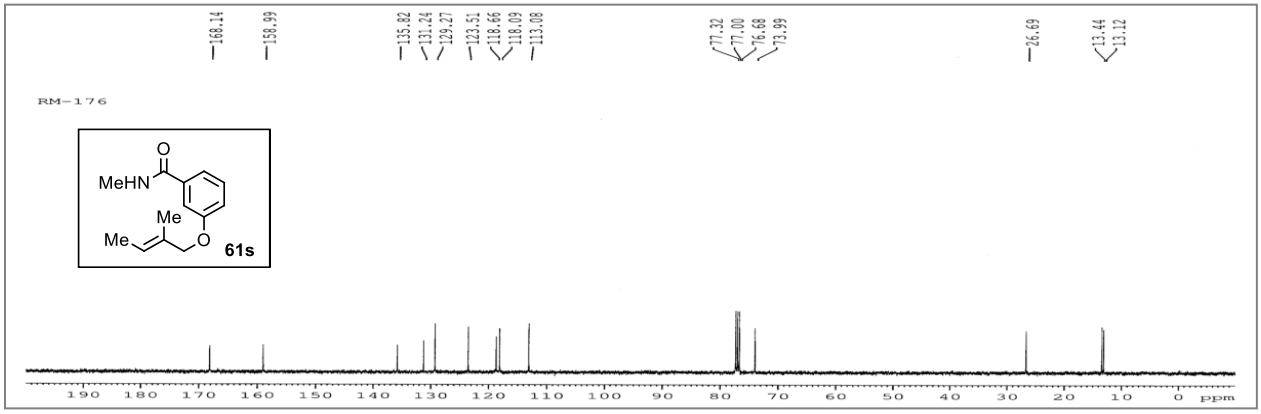

RM-221
MeHN
MeO
61q

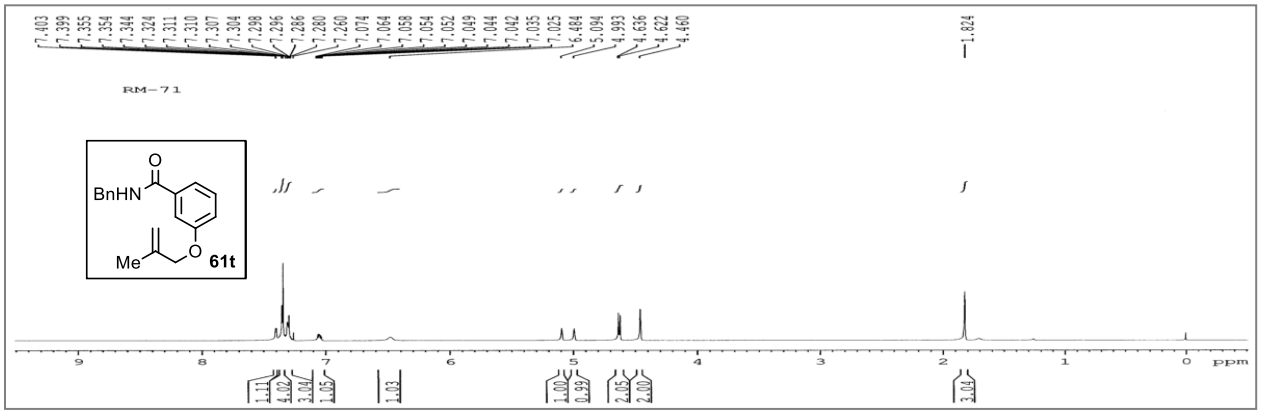

RM-221
MeHN
MeO
61q

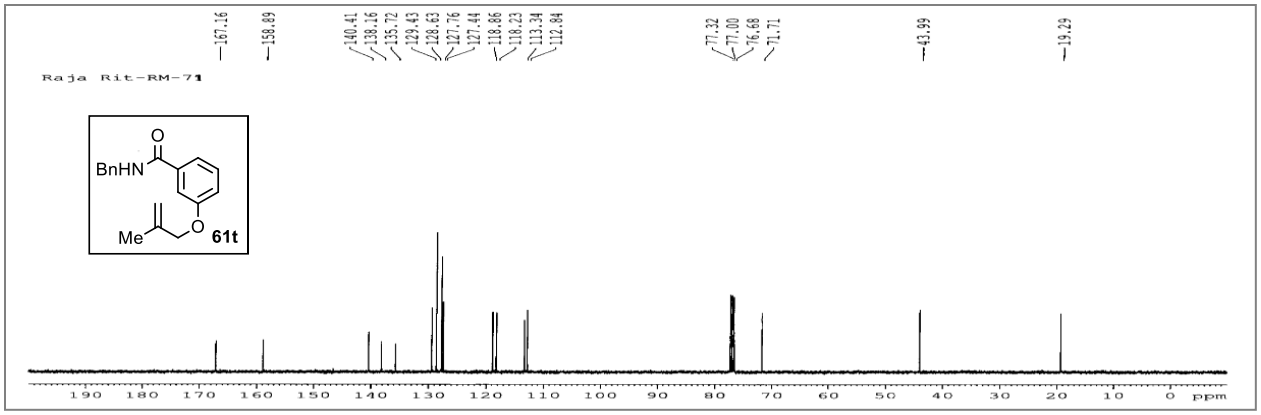

RM-120
MeHN
Me
61r

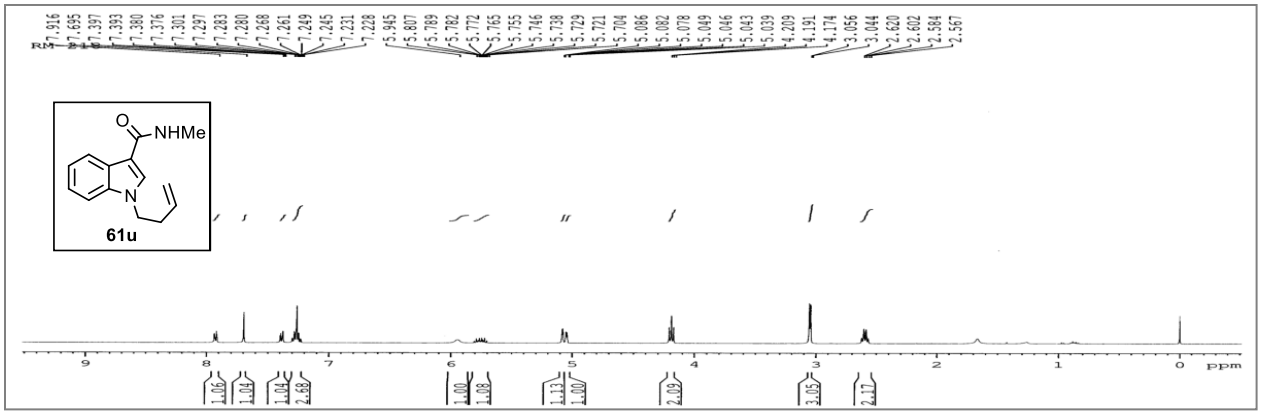

RM-120
MeHN
Me
61r

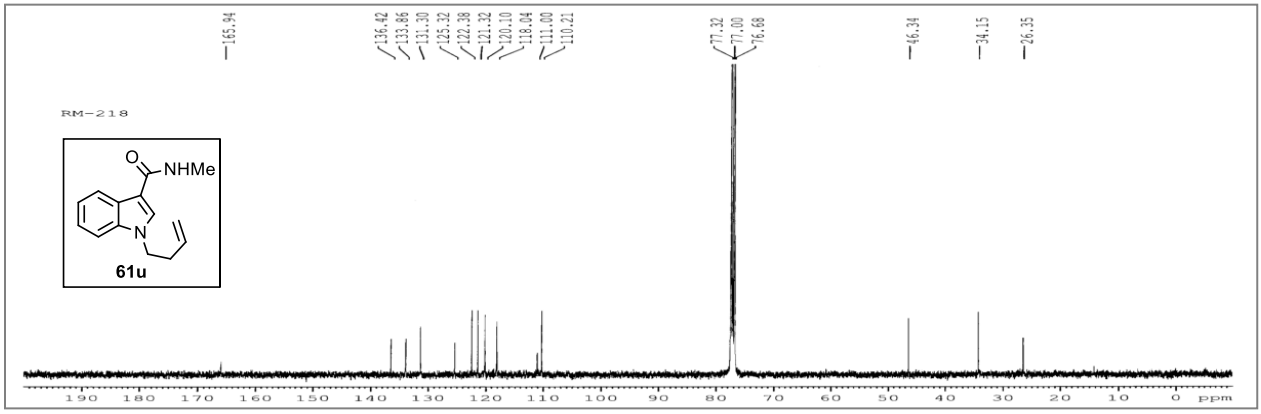

RM-176
MeHN
Me
Me
O
61s

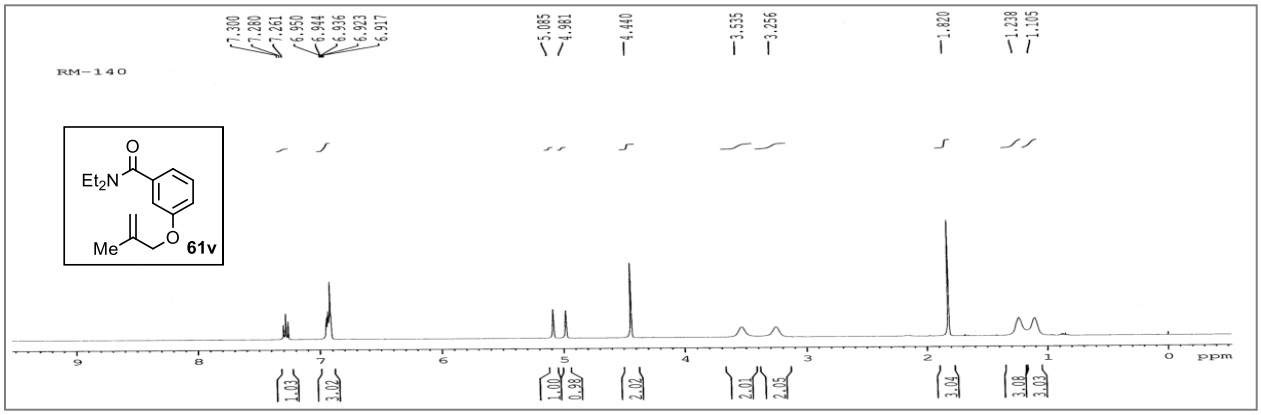

RM-176
MeHN
Me
Me
O
61s

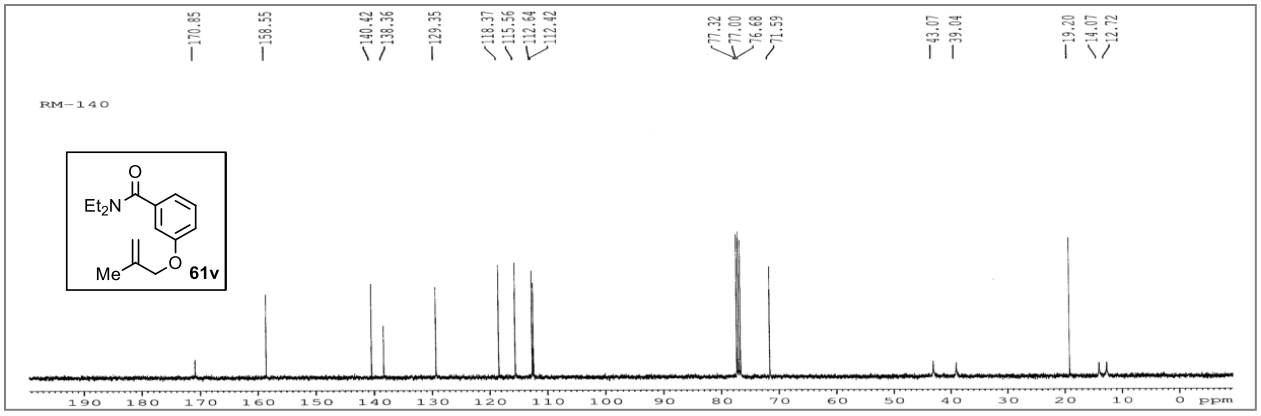

RM-71
BnHN
Me
O
61t

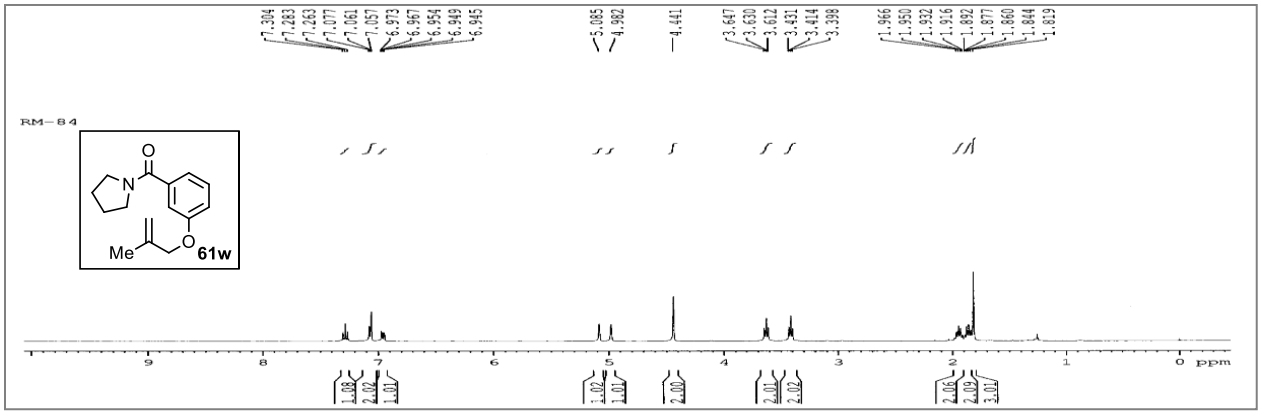

Raja Rit-RM-71
BnHN
Me
O
61t

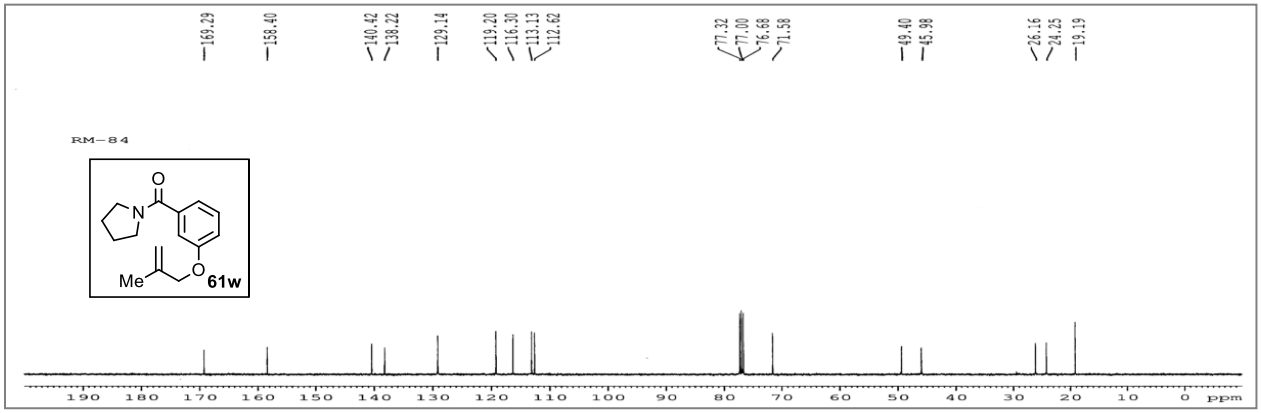

NHMe
61u

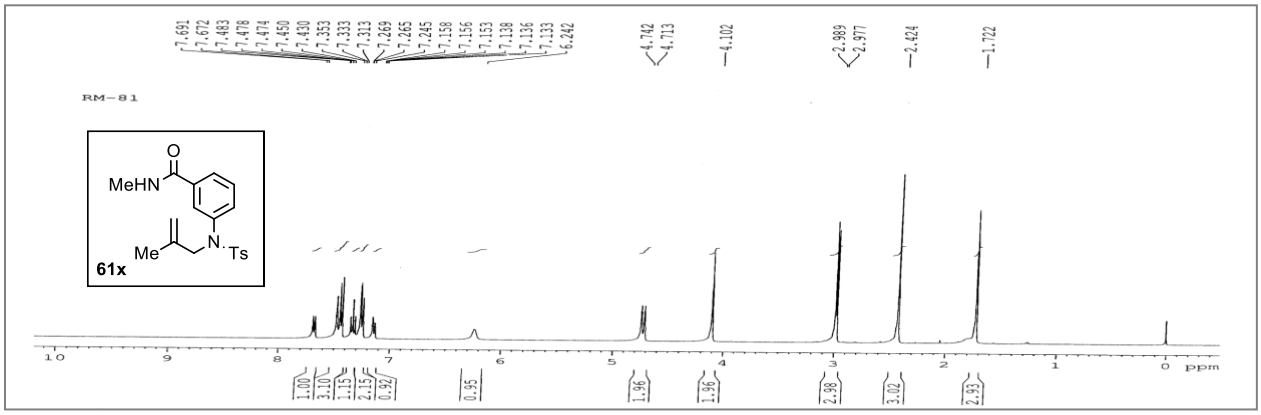

RM-218
NHMe
61u

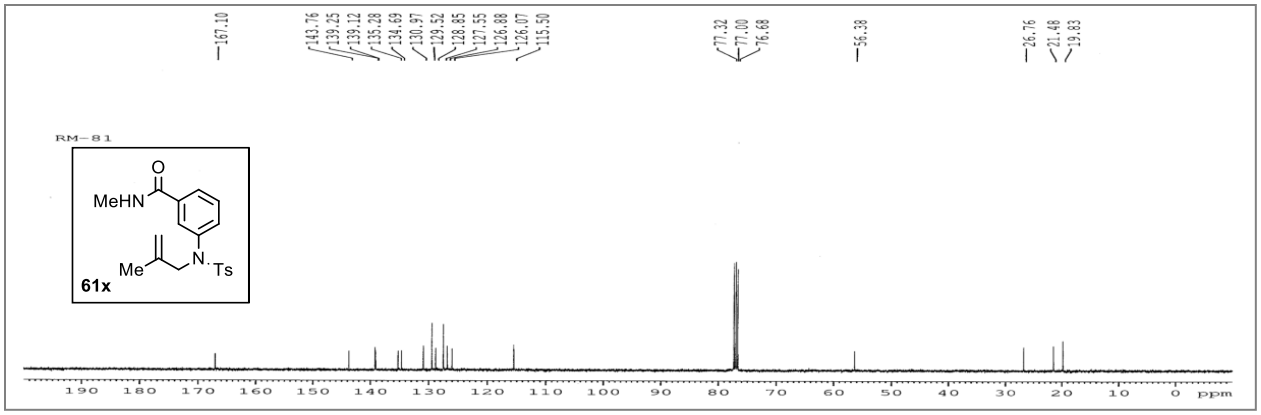

RM-140
Et2N
Me
61v

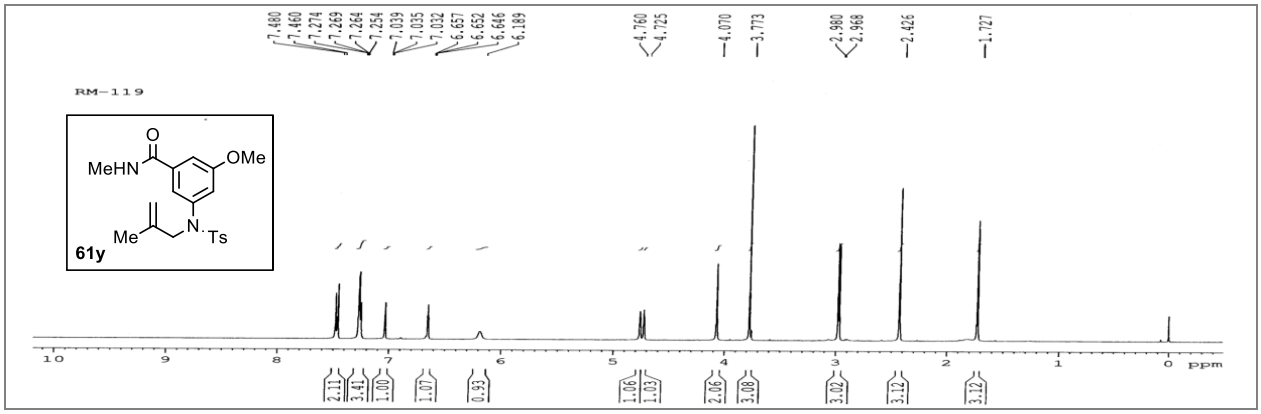

RM-140
Et2N
Me
61v

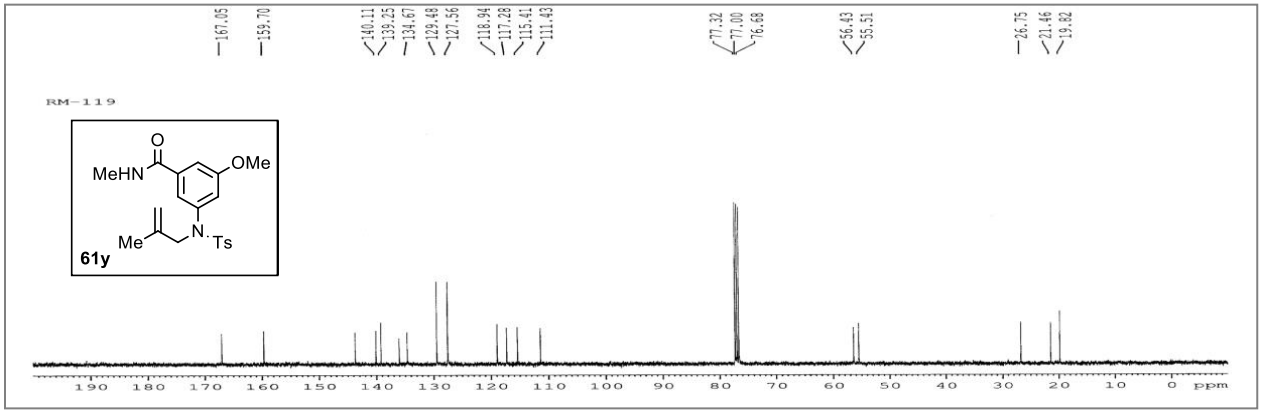

RM-84
Me
61w

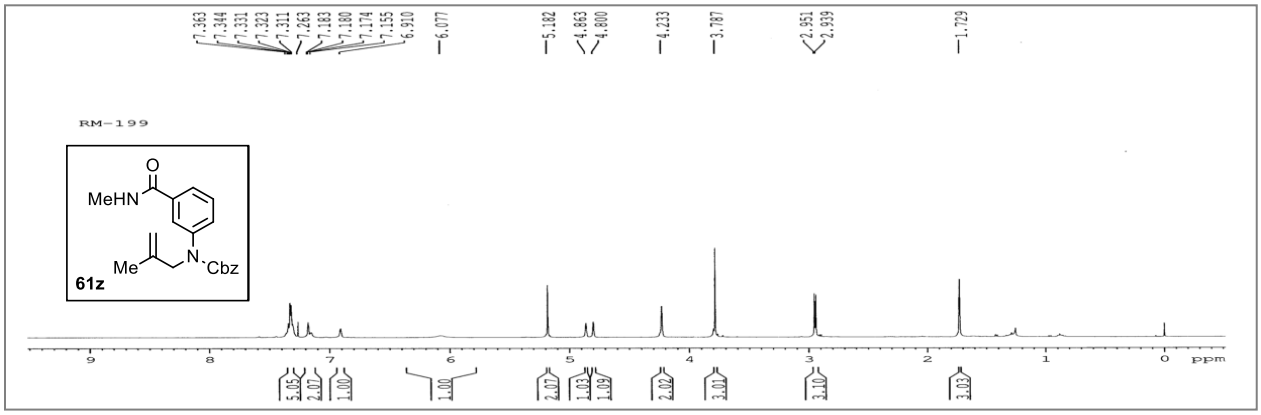

RM-84
Me
61w

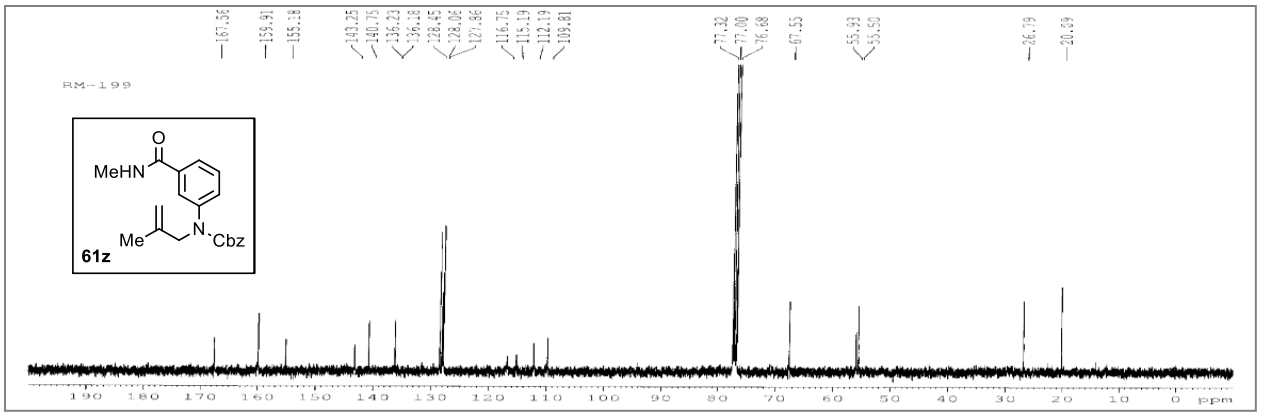

RM-81
MeHN
Me
Ts
61x

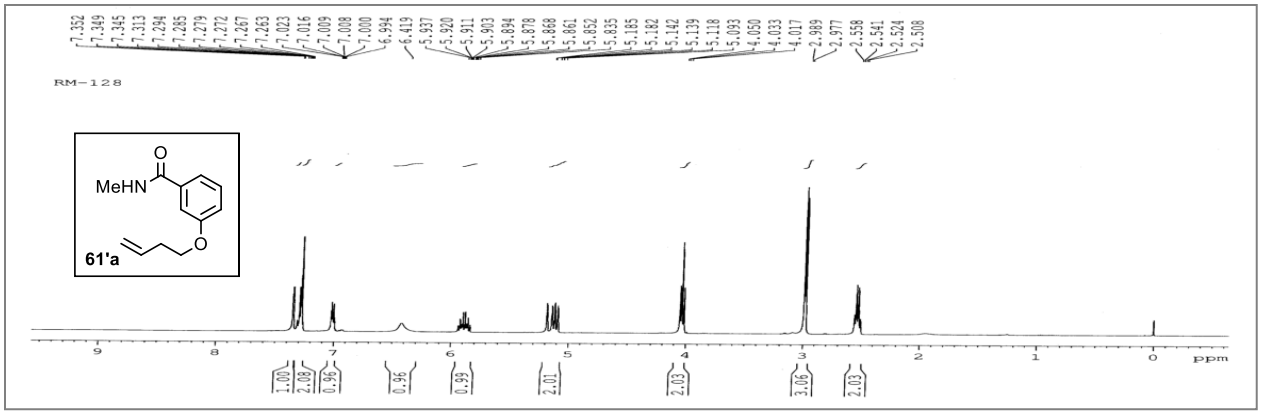

RM-81
MeHN
Me
Ts
61x

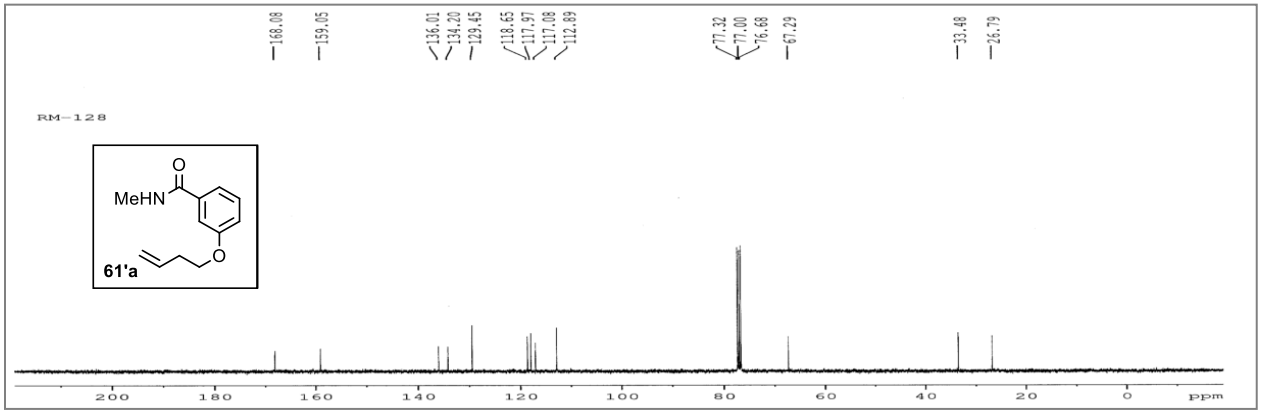

RM-119
MeHN
OMe
Me
N
Ts
61y

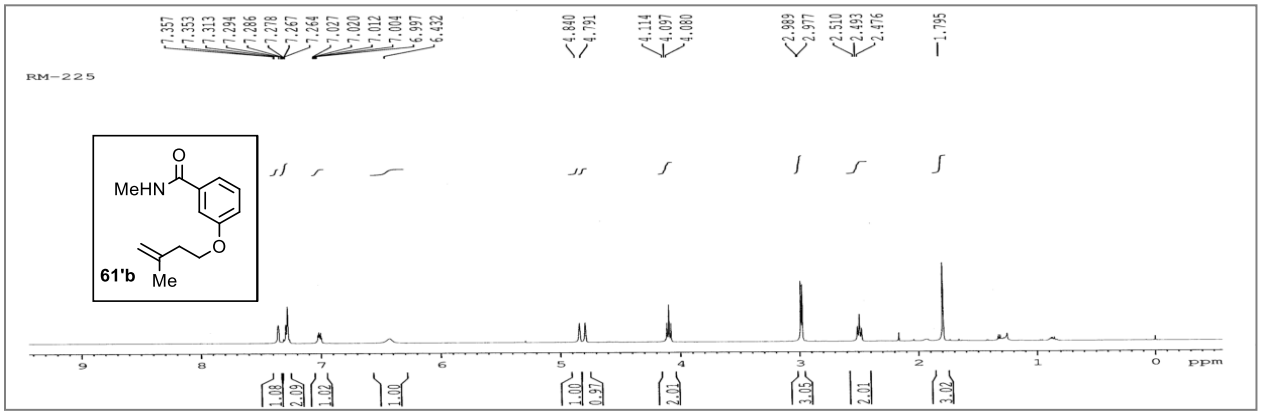

RM-119
MeHN
OMe
Me
N
Ts
61y

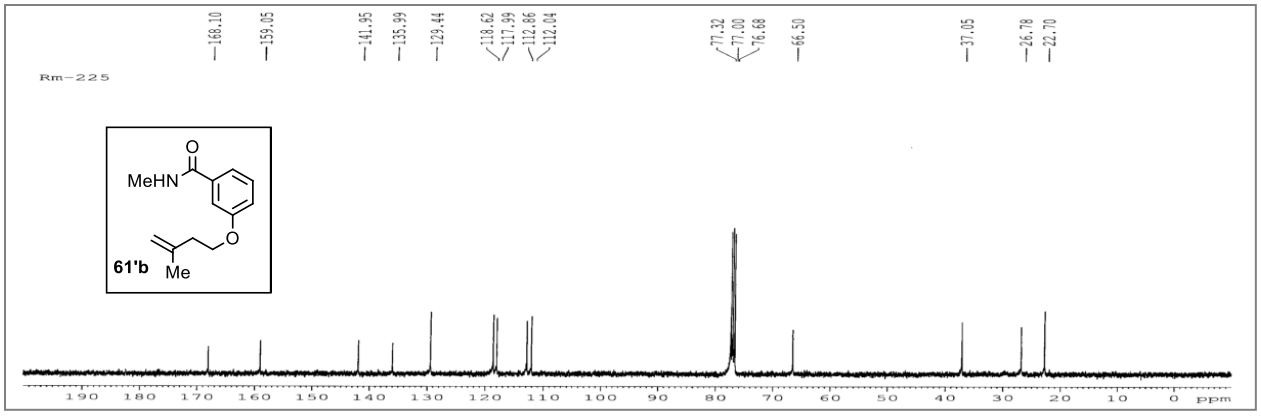

RM-199
MeHN
Me
N
Cbz
61z

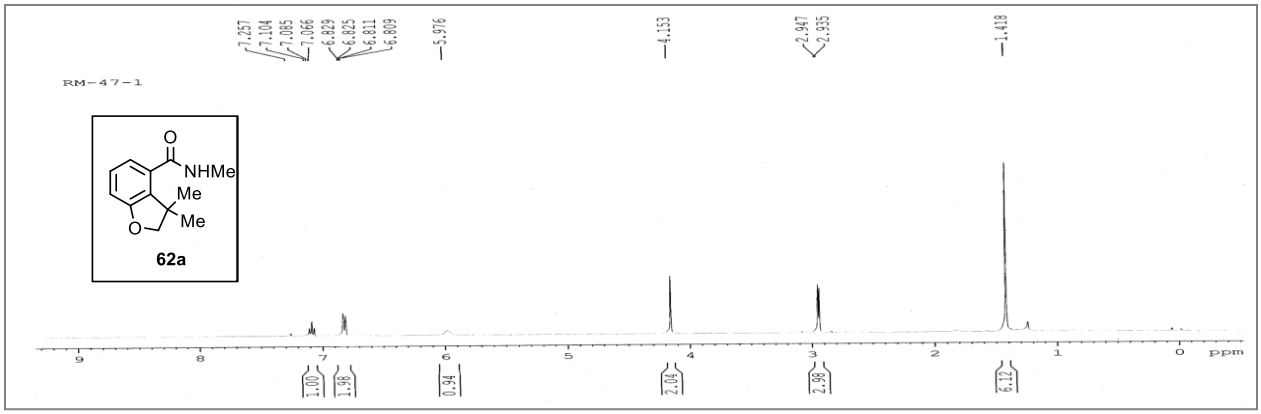

RM-199
MeHN
Me
N
Cbz
61z

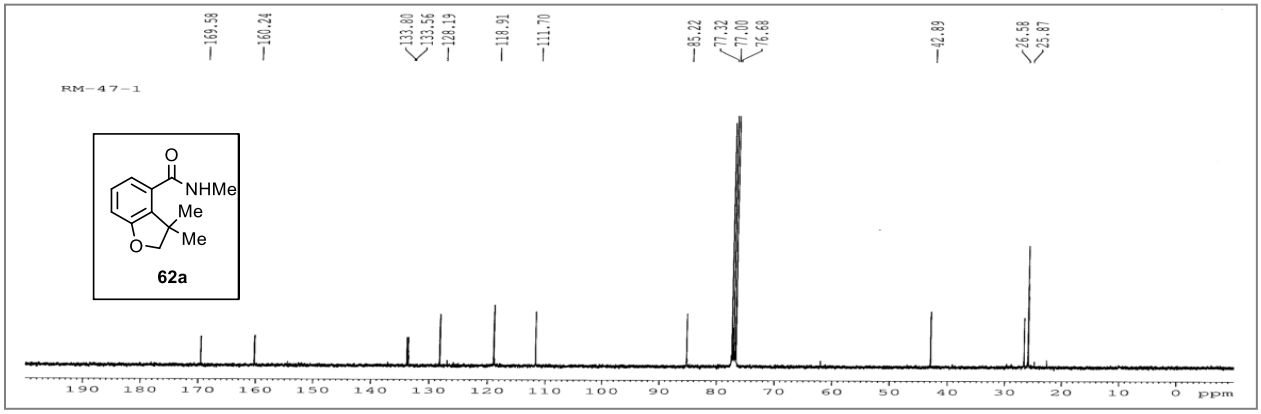

RM-128
MeHN
61'a

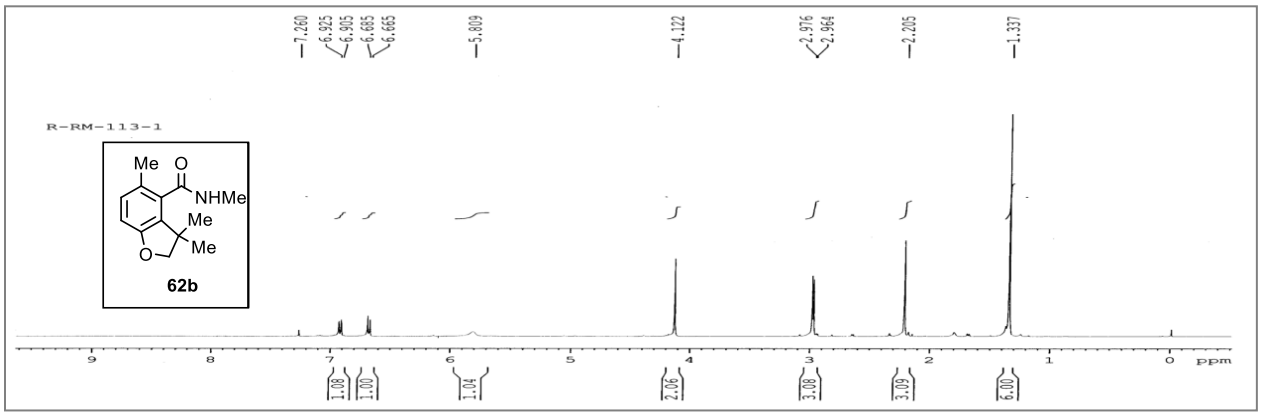

RM-128
MeHN
61'a

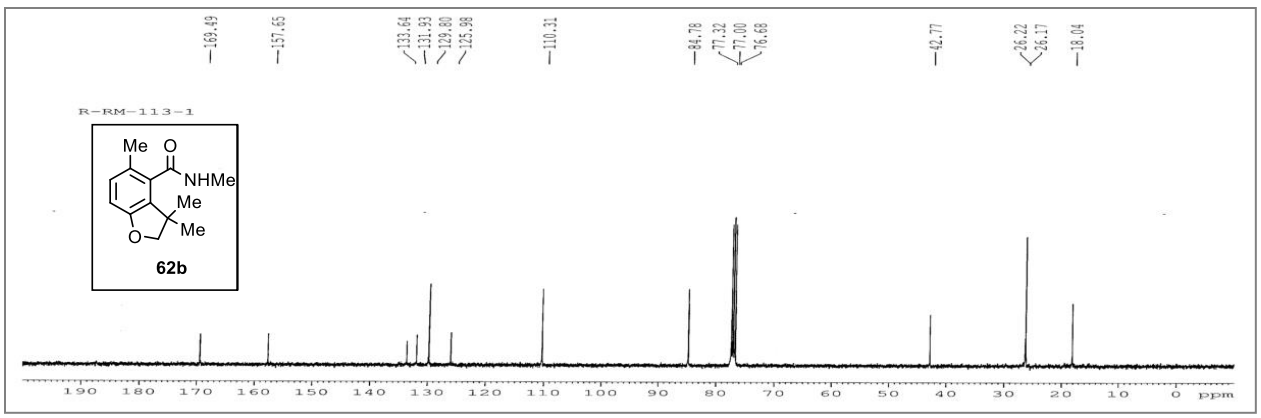

RM-225
MeHN
61'b
Me

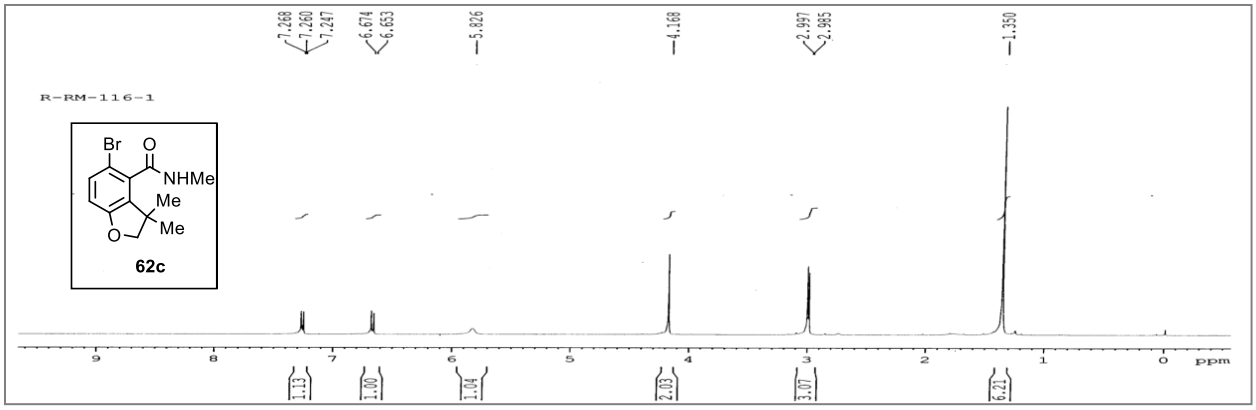

Rm-225
MeHN
61'b
Me

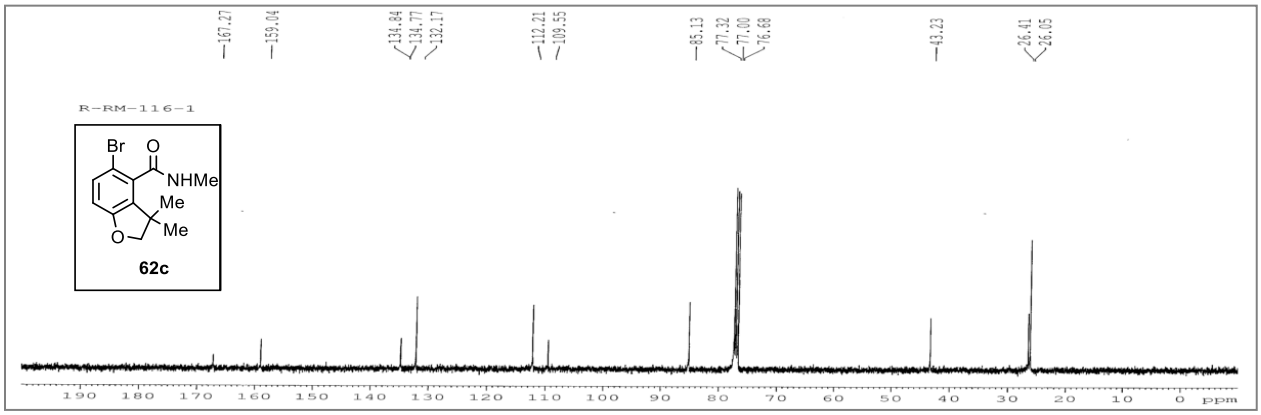

RM-47-1
NHMe
Me
Me
O
62a
7.257
7.104
7.085
7.066
6.829
6.825
6.811
6.809
5.976
4.153
2.947
2.935
1.418
ppm

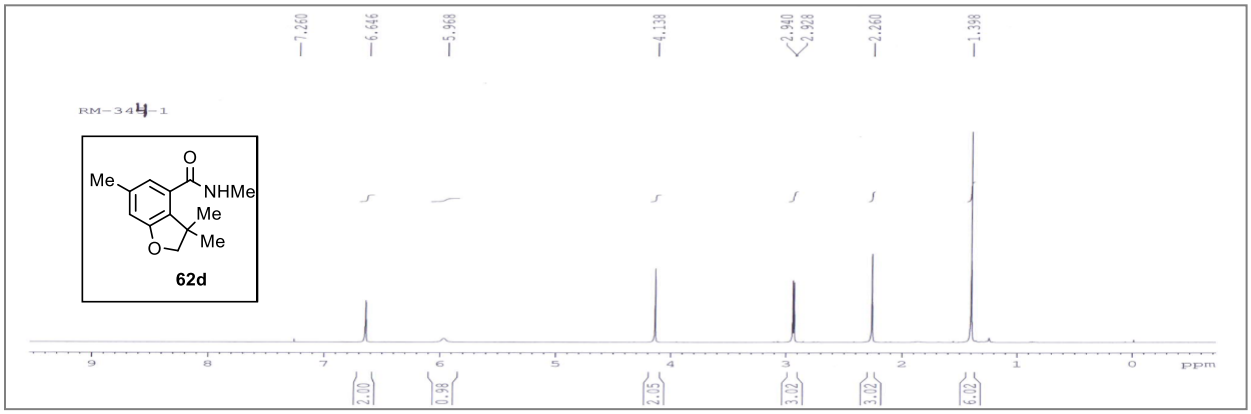

RM-47-1
NHMe
Me
Me
O
62a
169.58
160.24
133.80
133.56
128.19
118.91
111.70
85.22
77.32
77.00
76.68
42.89
26.58
25.87
ppm

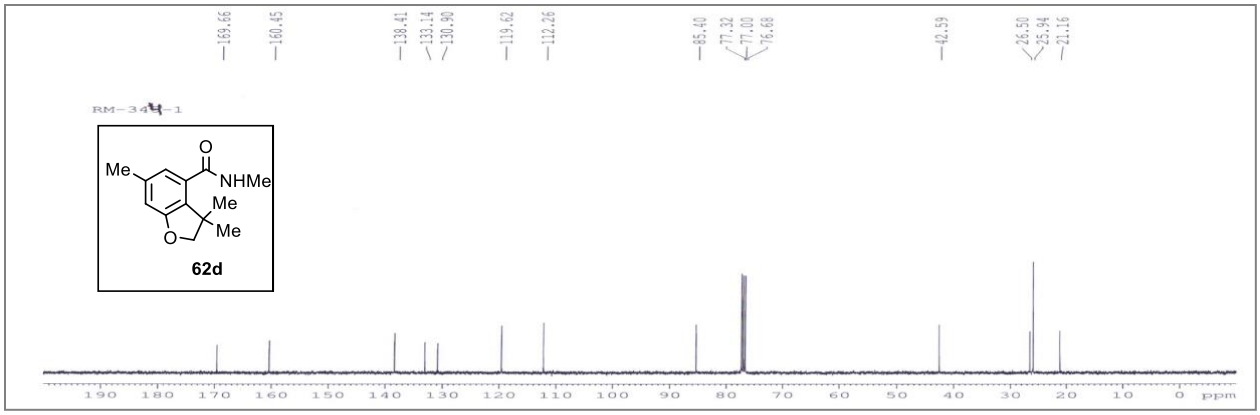

R-RM-113-1
Me
O
NHMe
Me
Me
O
62b
7.260
6.925
6.905
6.685
6.665
5.809
4.122
2.976
2.964
2.205
1.337
ppm

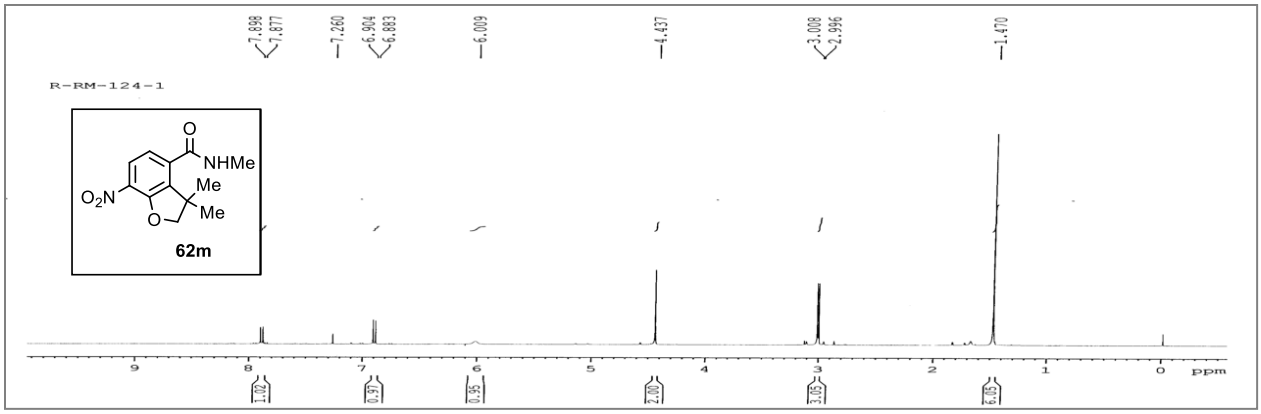

R-RM-113-1
Me
O
NHMe
Me
Me
O
62b
169.49
157.65
133.64
131.93
129.80
125.98
110.31
84.78
77.32
77.00
76.68
42.77
26.22
26.17
18.04
ppm

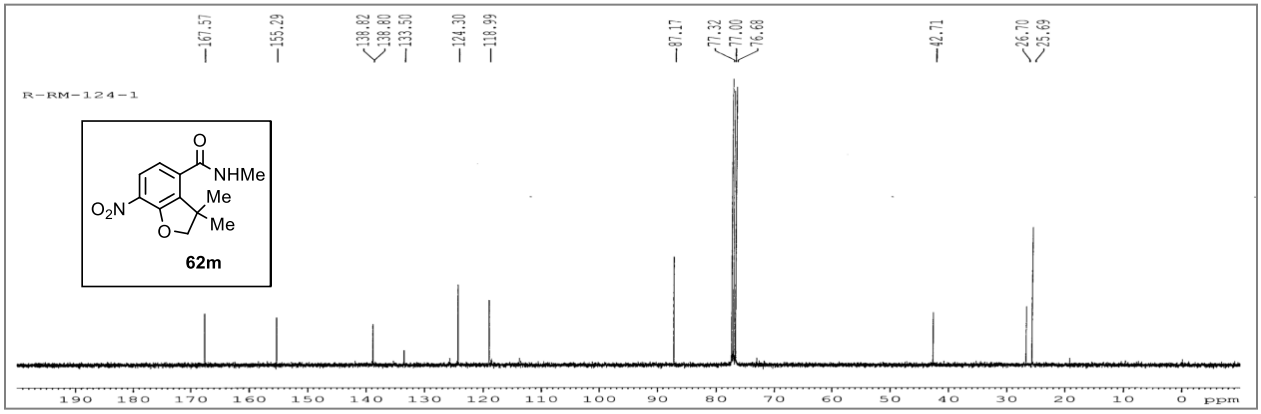

R-RM-116-1
Br
O
NHMe
Me
Me
O
62c
7.268
7.260
7.247
6.674
6.653
5.826
4.168
2.997
2.985
1.350
ppm

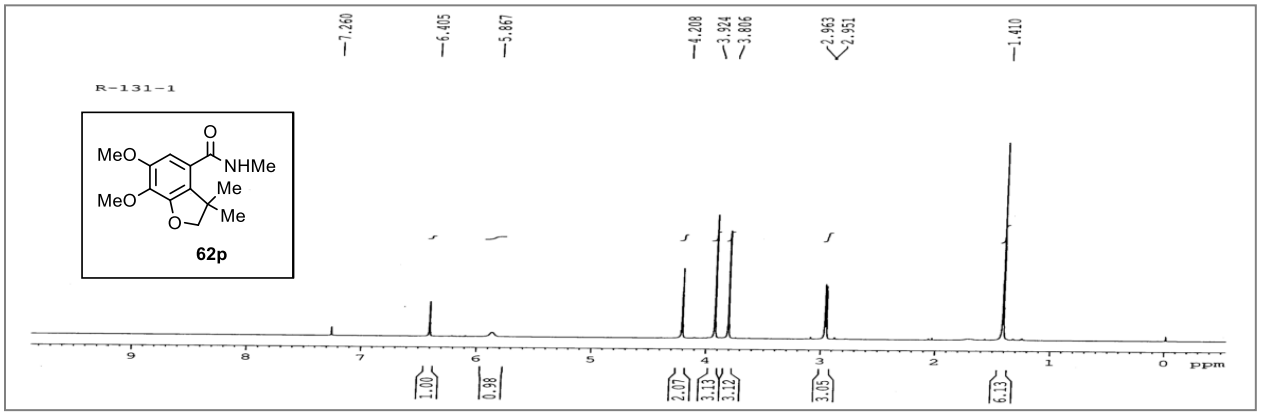

R-RM-116-1
Br
O
NHMe
Me
Me
O
62c
167.27
159.04
134.84
134.77
132.17
112.21
109.55
85.13
77.32
77.00
76.68
43.23
26.41
26.05
ppm

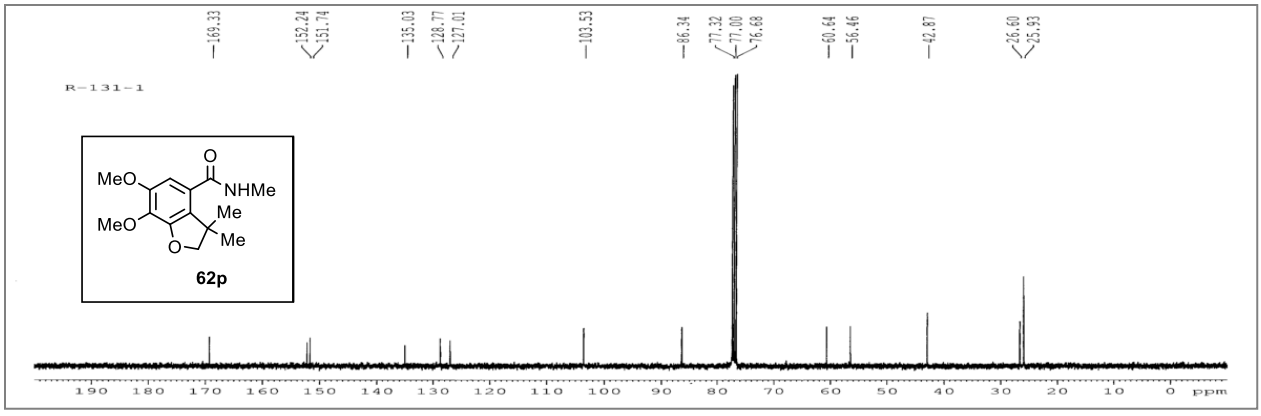

RM-344-1
Me
O
NHMe
Me
Me
O
62d
7.260
6.646
5.968
4.138
2.940
2.928
2.260
1.398
ppm

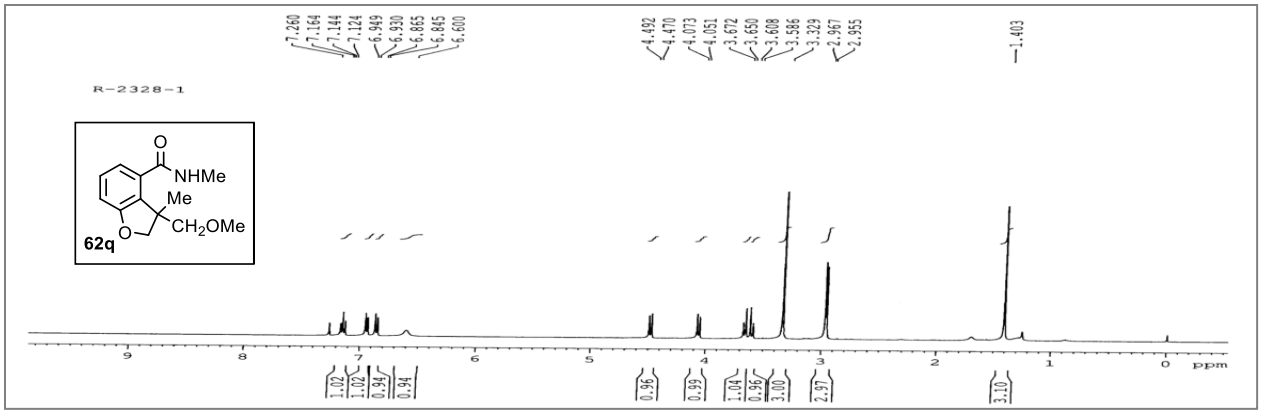

RM-344-1
Me
O
NHMe
Me
Me
O
62d
169.66
160.45
138.41
133.14
130.90
119.62
112.26
85.40
77.32
77.00
76.68
42.59
26.50
25.94
21.16
ppm

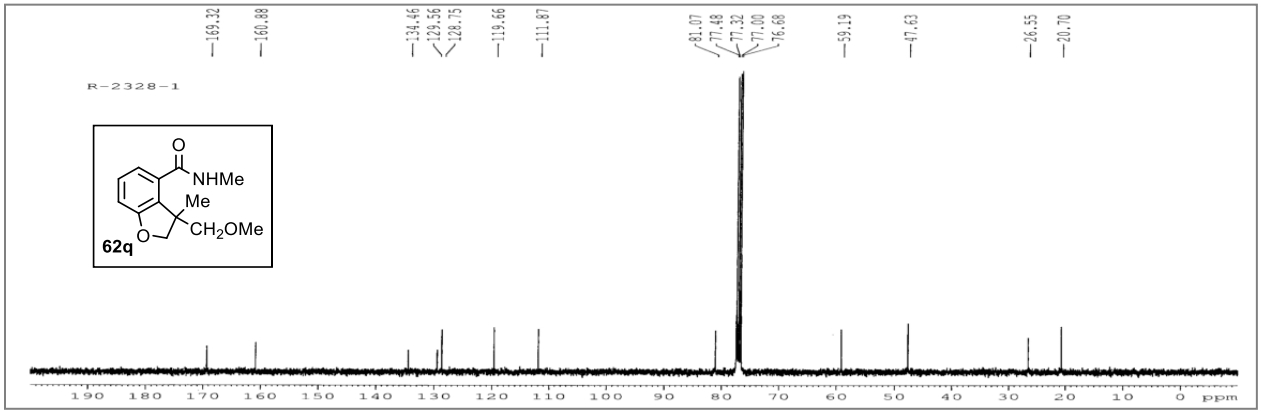

R-RM-124-1
62m
ppm

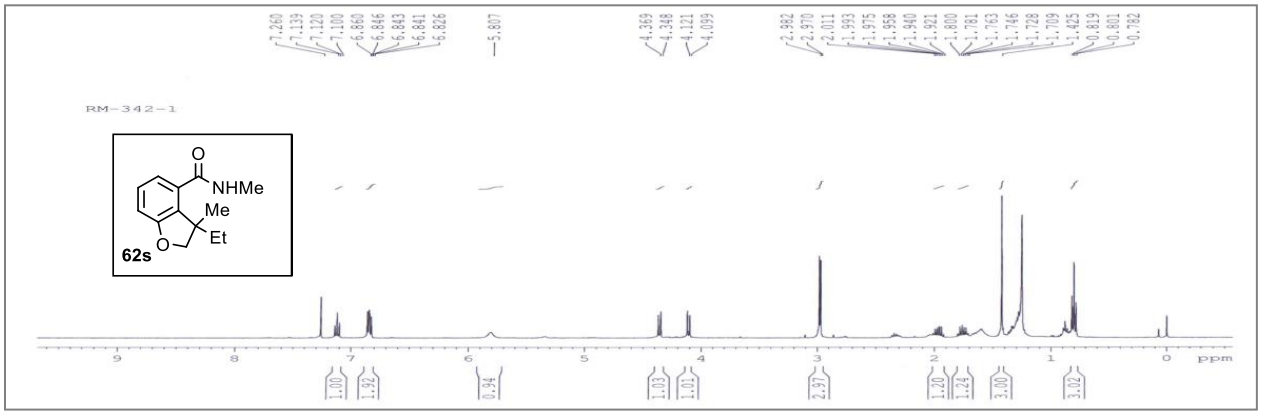

R-RM-124-1
62m
ppm

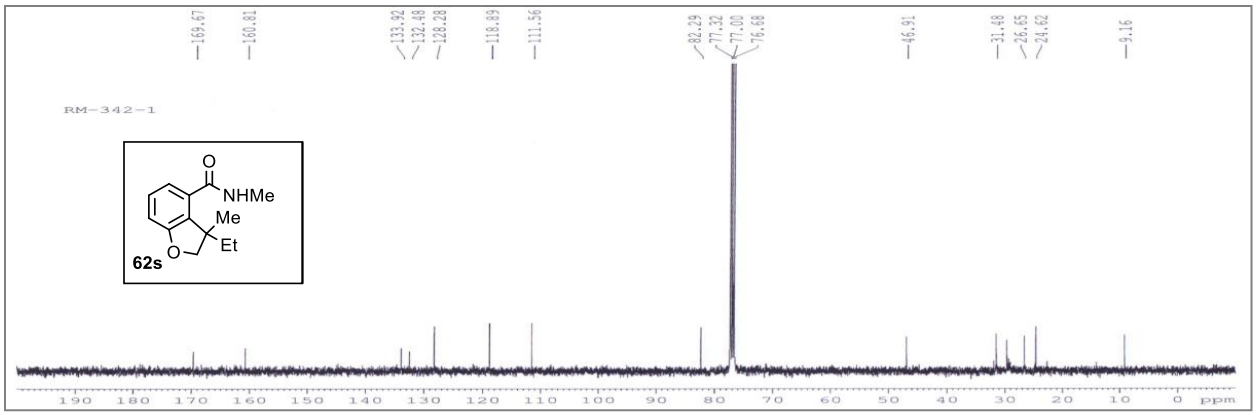

R-131-1
62p
ppm

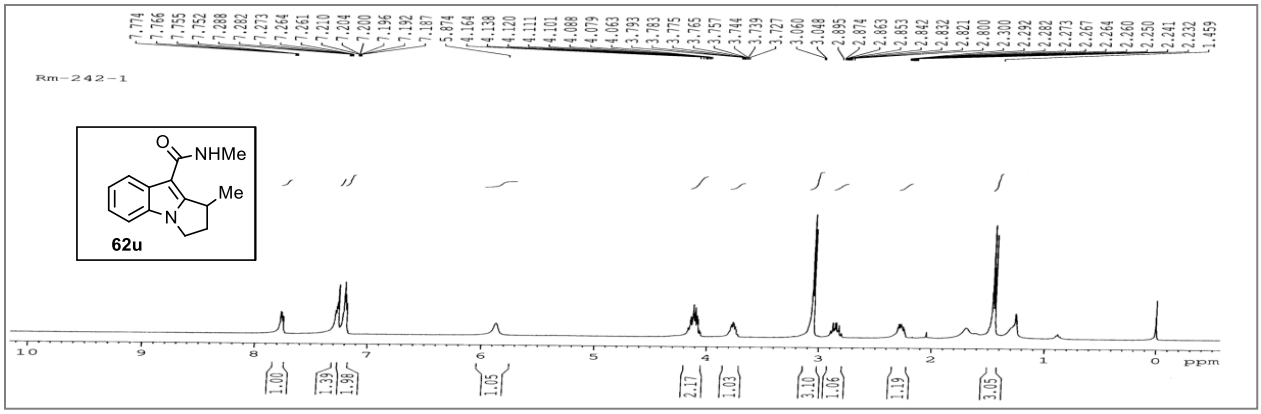

R-131-1
62p
ppm

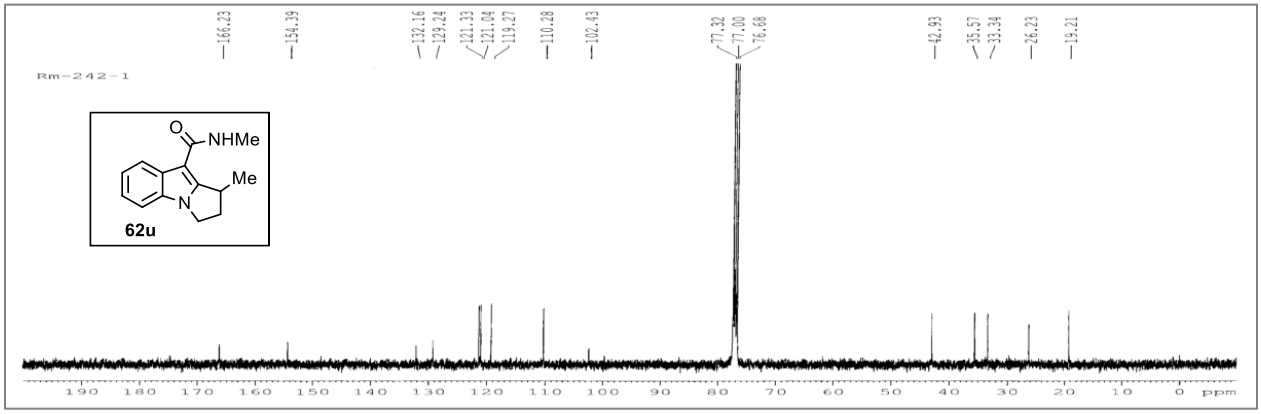

R-2328-1
NHMe
Me
CH2OMe
62q

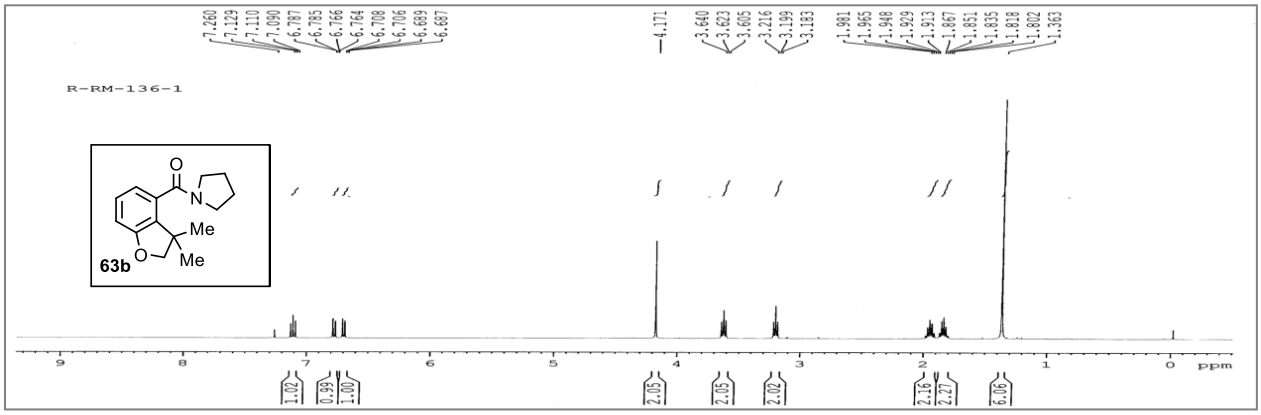

R-2328-1
NHMe
Me
CH2OMe
62q

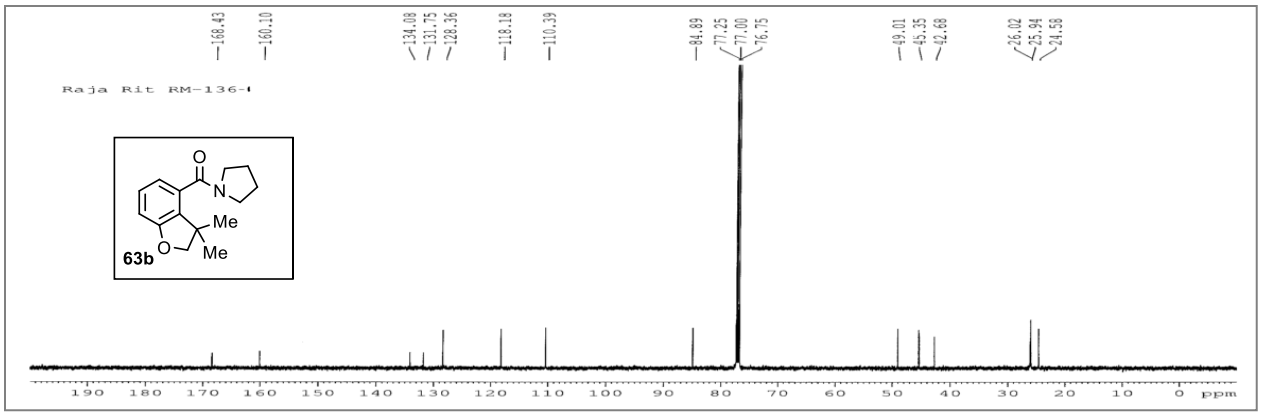

RM-342-1
NHMe
Me
Et
62s

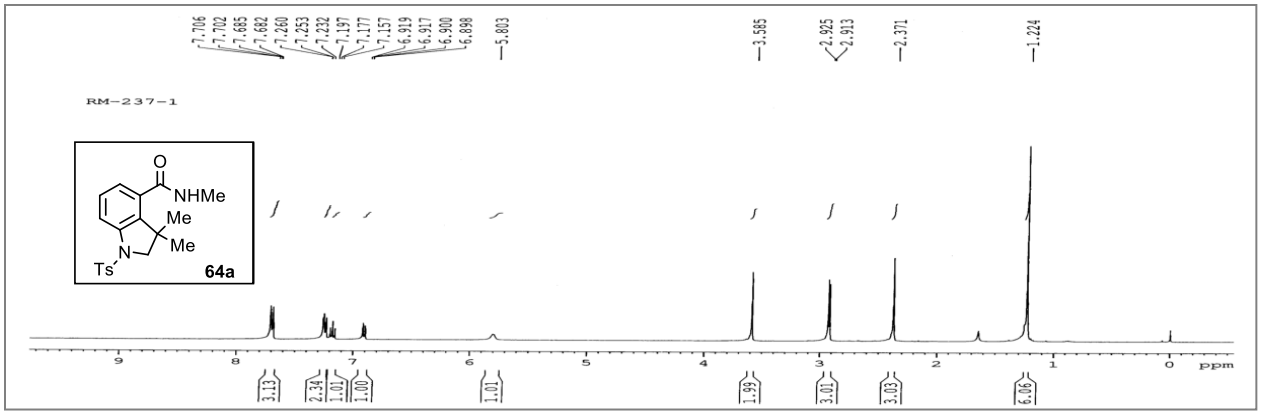

RM-342-1
NHMe
Me
Et
62s

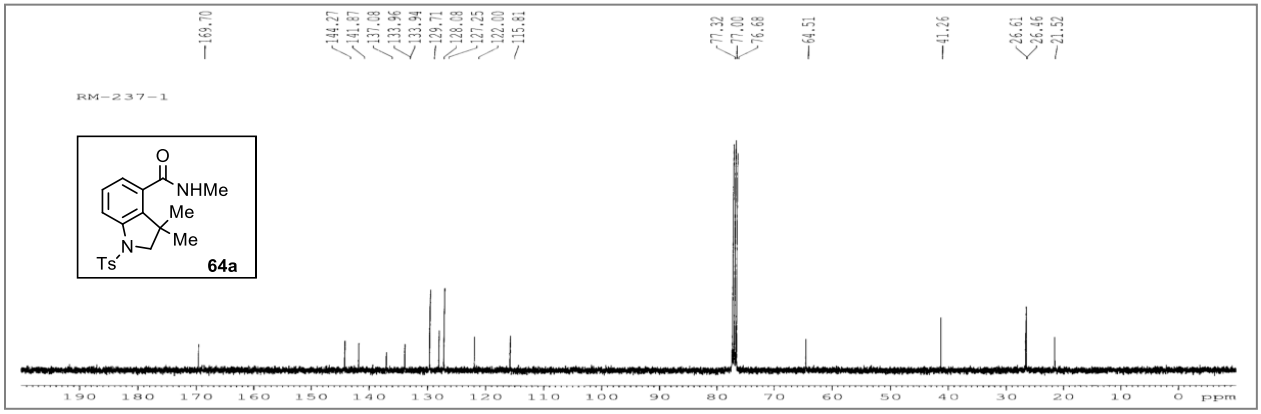

Rm-242-1
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Me
62u
ppm

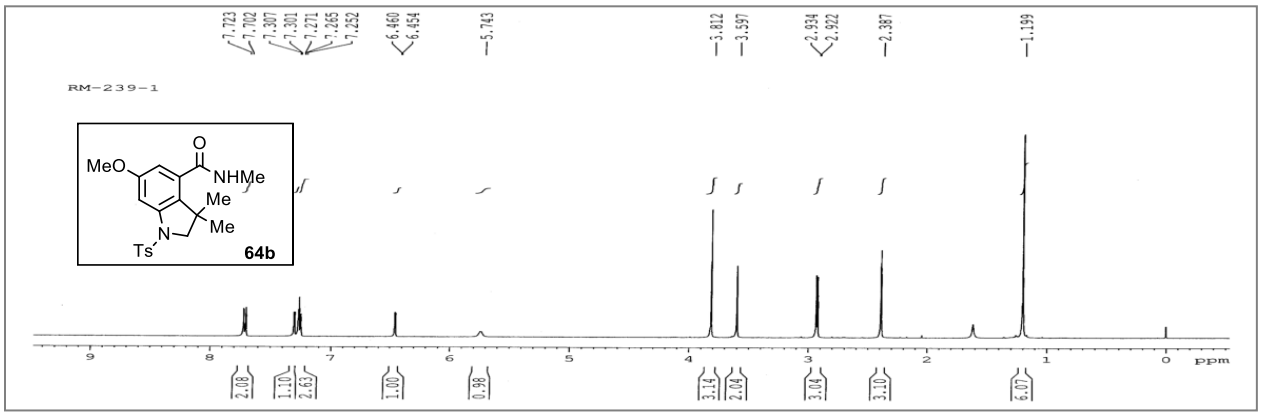

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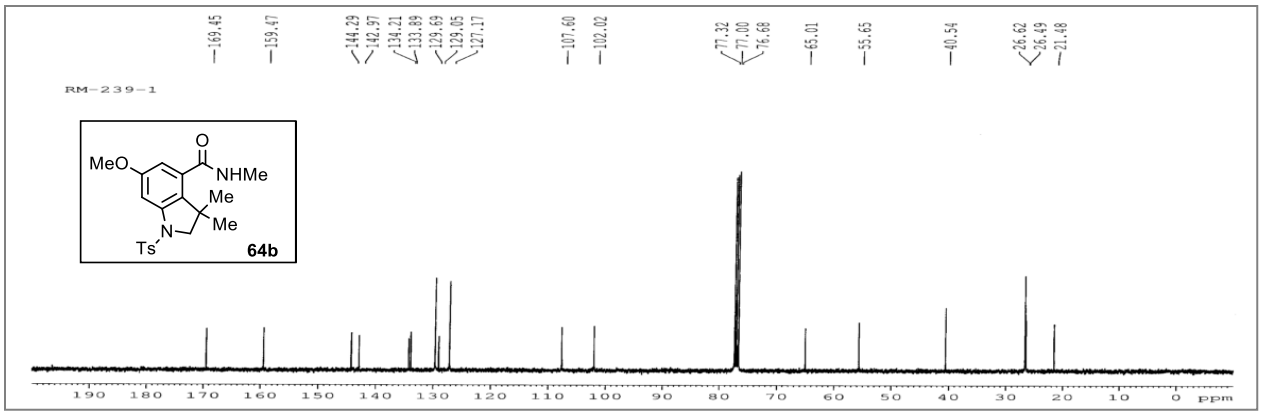

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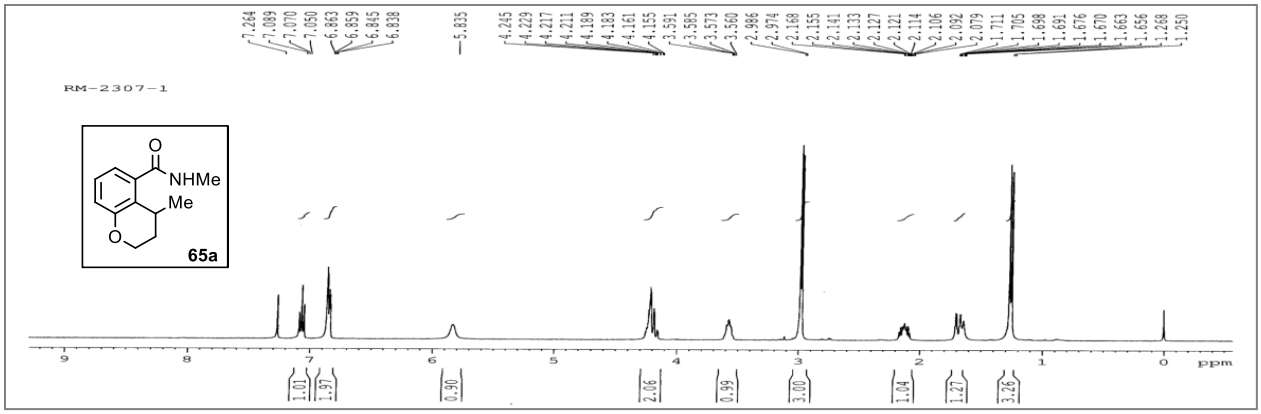

Raja Rit RM-136-
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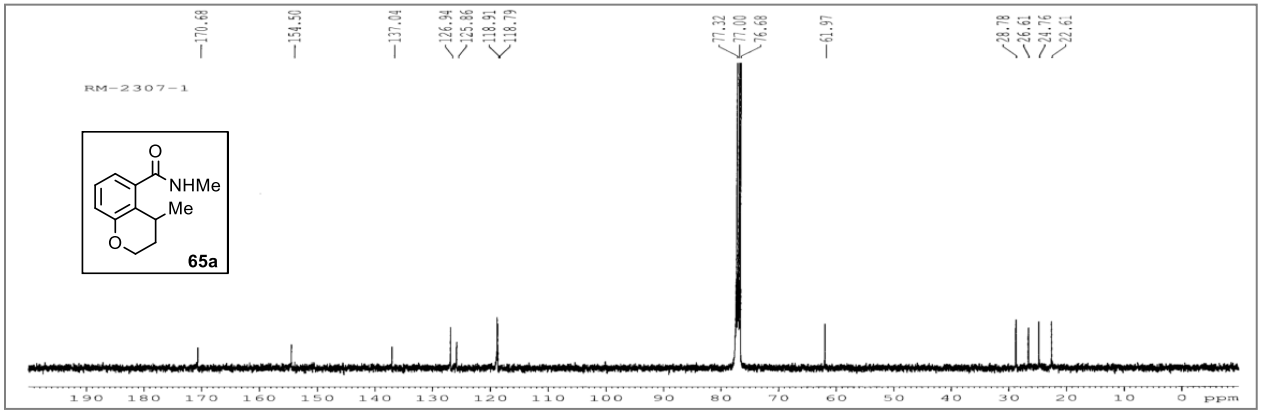

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Me
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64a
ppm

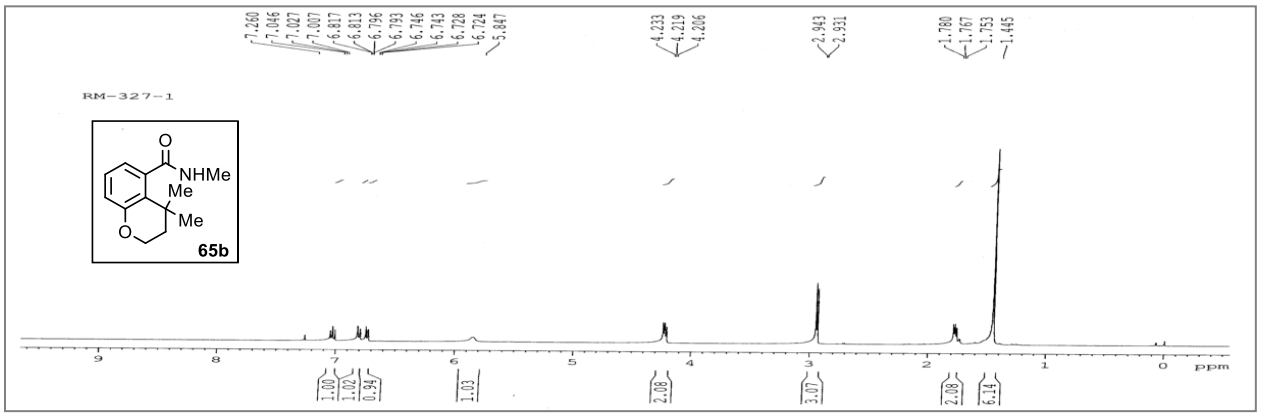

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Me
Ts
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ppm

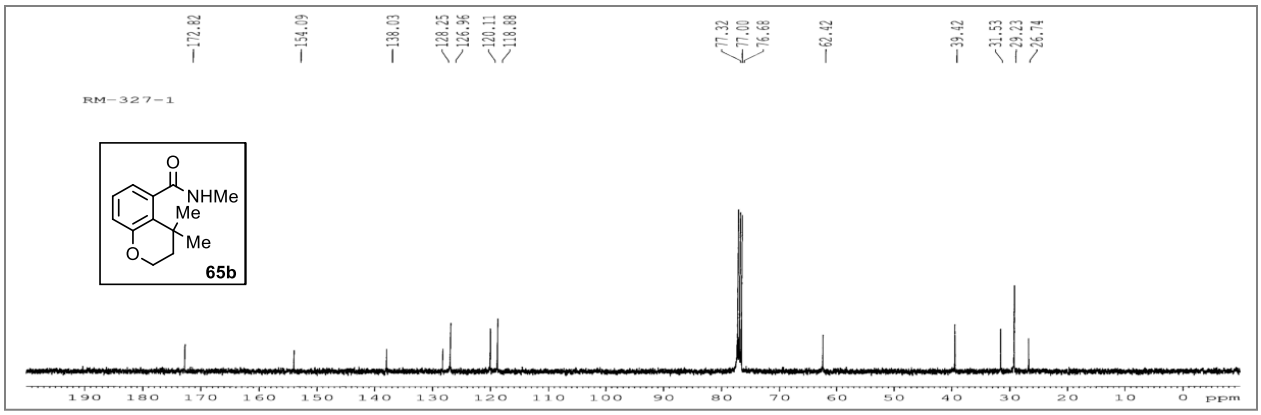

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Me
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64b
ppm

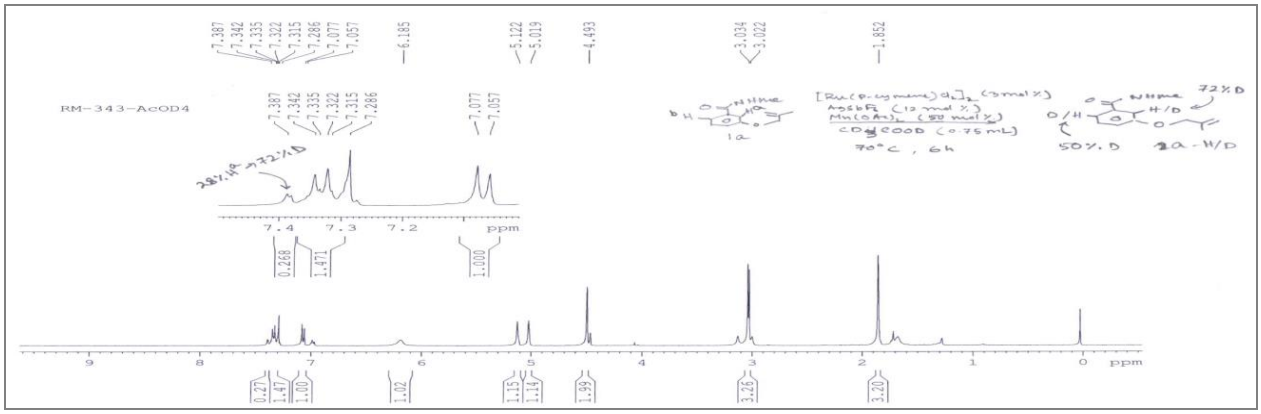

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Me
Me
Ts
64b
ppm

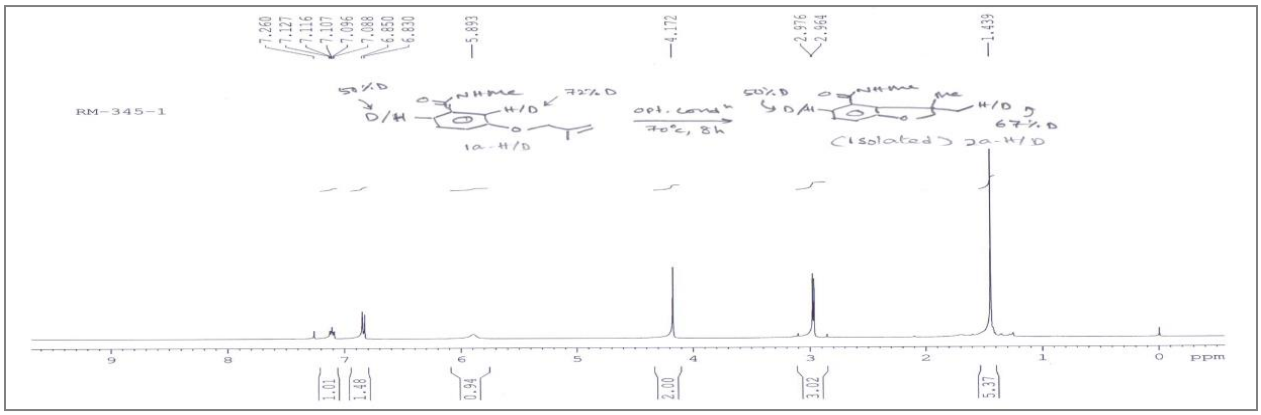

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65a
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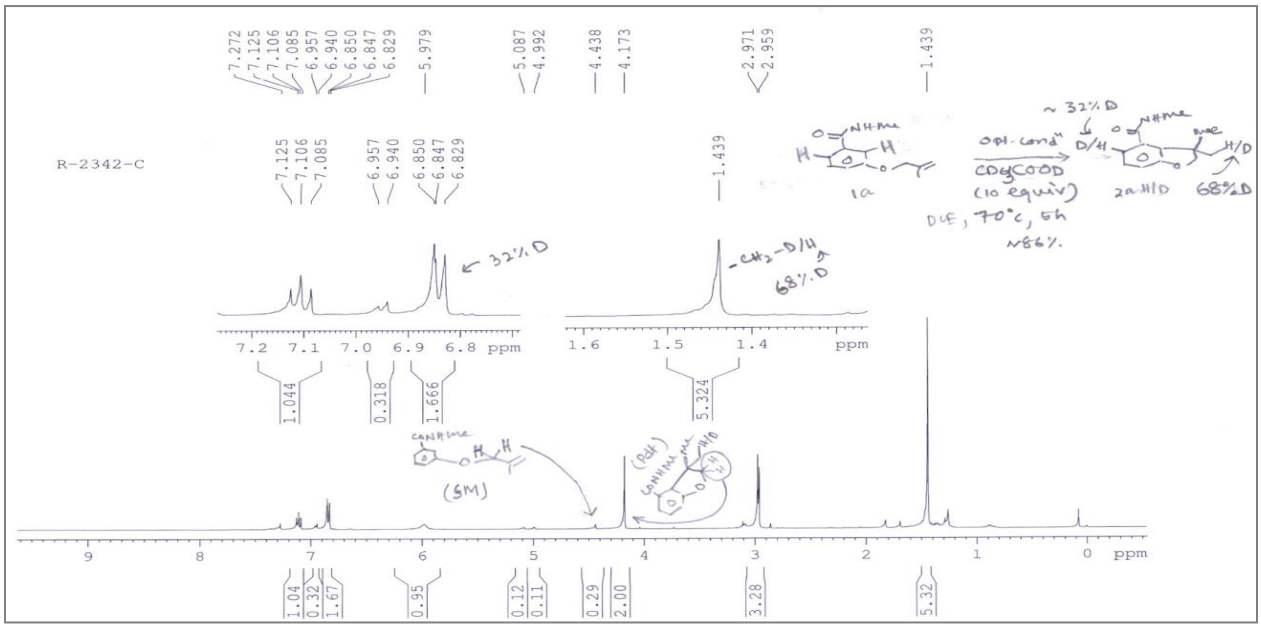

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65a
ppm


RM-327-1
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Me
65b
ppm

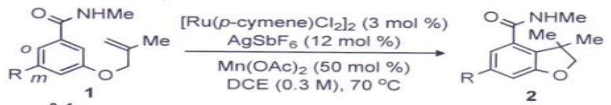

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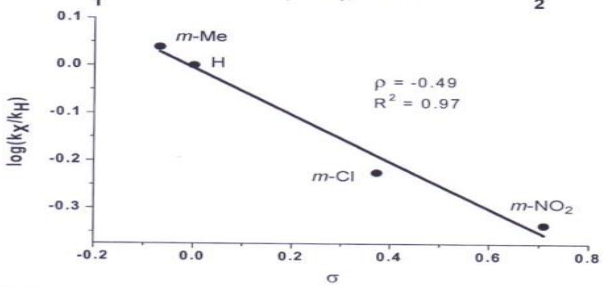

RM-343-AcOD4


RM-345-1


R-2342-C

C. Hammett analysis





Entry	R	k_x
1	Me	0.040 /min
2	H	0.0366/min
3	Cl	0.0207/min
4	NO_2	0.0169/min

$\log \frac{k_{Me}}{k_H} = \log \frac{0.040}{0.0366} = 0.0385$

$\log \frac{k_{Cl}}{k_H} = \log \frac{0.0207}{0.0366} = -0.2475$

$\log \frac{k_{NO_2}}{k_H} = \log \frac{0.0169}{0.0366} = -0.3356$

$\sigma_{m\text{-}Me} = -0.069$

$\sigma_{m\text{-}Cl} = +0.373$

$\sigma_{m\text{-}NO_2} = +0.710$

* Hammett equation:

$\log \frac{k_x}{k_H} = \sigma \cdot \rho$ — (1)

σ	vs	$\log k_x/k_H$	
−0.069		0.0385	→ point-1
0		0	→ point-2
+0.373		−0.2475	→ point-3
+0.710		−0.3356	→ point-4

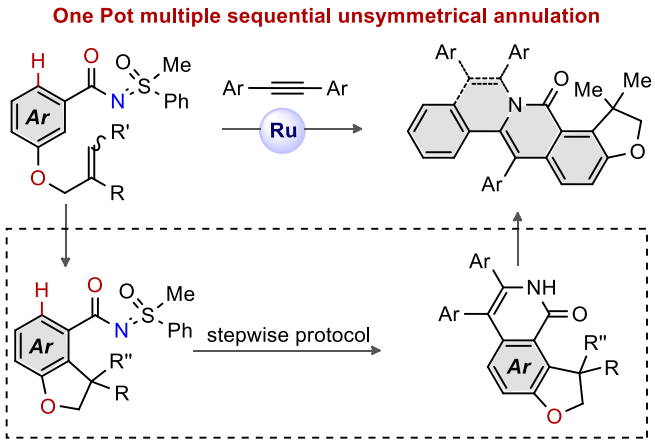
Chapter 3

One pot Unsymmetrical Functionalization of Multiple C–H Bonds of Arenes

Abstract

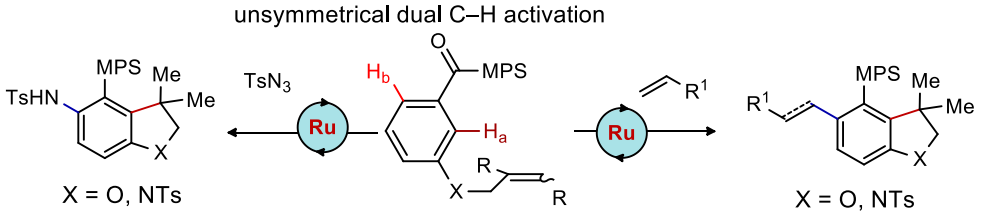
Section A: Transformable Sulfoximine Directed Multiple Functionalization of Arene C–H Bonds via Hydroarylation and Annulation

An unprecedented two-fold unsymmetrical C–H functionalization of arenes comprising intramolecular hydroarylation with olefins and intermolecular annulation with alkynes is developed and successfully adopted for the construction of unusual dihydrofuran-fused-isoquinolone heterocycles. The transformation readily occurs under the assistance of methyl phenyl sulfoximine (MPS) directing group (DG) in the presence of Ru-catalysis forming 2-C–C and 1-C–N bonds in a single operation. The overall process is atom economical and step-efficient. Further annulation of NH and the proximal *o*-C–H-arene of isoquinolone scaffold with alkynes build highly conjugated novel polycyclic compounds. Overall, three independent modes of annulations in arene motifs have been executed in the fabrication of novel structural entities by fusing 5 rings and erecting 3-C–C and 2-C–N bonds.



Section B: Sulfoximine Directed One-pot Two-fold Unsymmetrical C–H Functionalization of Arenes

Unsymmetrical functionalization of multiple C–H bonds proficiently constructs densely-functionalized scaffolds with the induction of diverse substituents in to a molecular backbone. Introduction of non-identical functionalities in a molecule through the assistance of suitable MPS-DG under one catalytic system (Ru-catalysis) is developed herein. Broadly *o,o'*-hydroarylation–amidation and *o,o'*-hydroarylation–olefination of benzoic acid derivatives is demonstrated.



Reference:

Koushik Ghosh, Majji Shankar, Raja K. Rit and Akhila K. Sahoo (Manuscript communicated)

Koushik Ghosh, Raja K. Rit, E. Ramesh and Akhila K. Sahoo *Angew. Chem., Int. Ed.* **2016**, *55*, 7821.

3.1. Introduction

Nature has enormous potential creating complex molecular entities. As these scaffolds have found broad applications, the scientific community consequently draws inspiration in the fabrication of identical skeletons. Accordingly, design and construction of complex molecular framework from readily accessible simple precursors revives interest among synthetic chemists. Considerable attention has therefore gone in the development of new synthetic methods and subsequently applied them for building novel framework.[1,2]

Introduction of assorted functionalities in a molecular template builds complexity, fulfilling the requirement of being a potential candidate to pharmaceutical drug, agrochemical, and material.[3] Conventionally, complexities are introduced in a molecule via multistep synthetic modification of pre-functionalized substrate, which often suffers with tedious reactions, separation, and poor yields. In this regard, transition-metal (TM) catalyzed direct functionalization of ubiquitous C–H bond allows rapid installation of diverse functionality in a molecule, overcoming the use of classical synthetic approaches.[4] Of note, the designed domino C–H functionalization sequences of readily available precursor would subtle fabricating complex molecular architecture.[5]

Heterocycles, such as dihydrobenzofurans and isoquinolones are privileged molecular entities in organic synthesis due to their widespread presence in bioactive molecules and natural products. Obviously, integration of both the representative heterocycle core (dihydrobenzofuran and isoquinolone) in a single compound would build a unique molecule with distinct feature.[6,7] Realization of such novel heterocyclic scaffold, therefore, entices considerable attention (Figure 3.1).

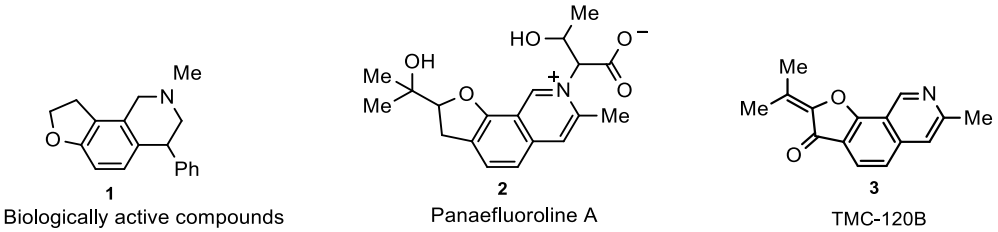
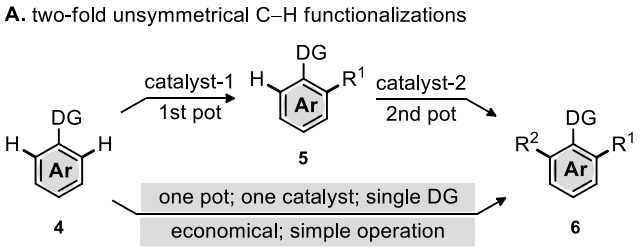


Figure 3.1 Furan-fused-isoquinolone core containing biologically significant compounds

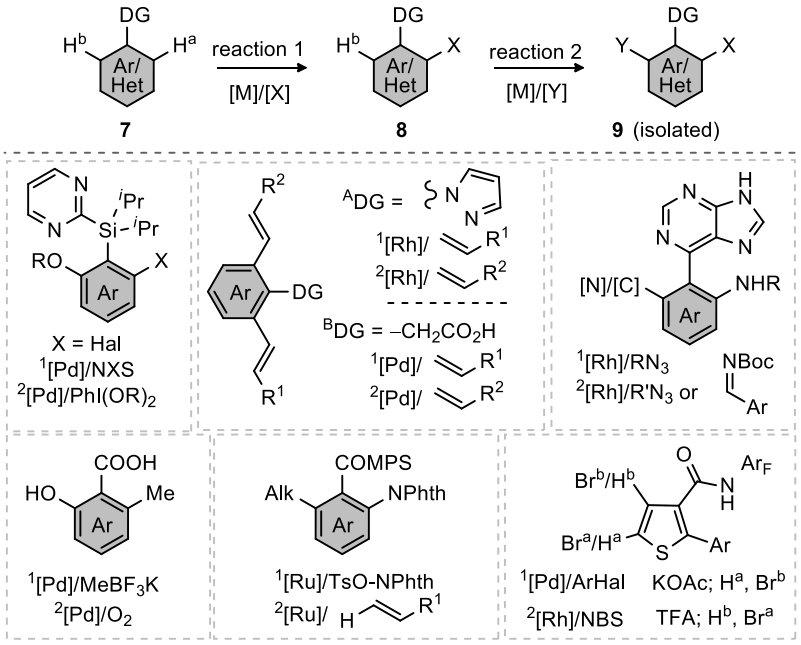
Of note, the directing group (DG) triggered uninterrupted functionalizations and annulations of ubiquitous C–H bonds proficiently manufacture large number of bonds, rapidly fabricating complex molecular scaffolds.[7] Despite the noticeable advancement perceived in the arena of annulations, a one pot domino or sequential functionalization of multiple C–H bonds for the synthesis of unsymmetrically fused heterocycle is scarcely explored. The accumulation of by-products, incomplete reaction profile, and lack of selectivity in each step of the transformation makes the overall one-pot domino process unproductive. Moreover, the unique selectivity of each catalytic system and DG for a particular functionalization possesses significant challenge (discussed in chapter 1).[8] Nevertheless, a two-step protocol under two different catalytic systems has recently been implemented demonstrating the synthesis of such a novel heterocycle which consists of different functional groups (FGs) (discussed in chapter 1). Therefore, attention to surge the development of a challenging one-pot domino/sequential two-fold C–H functionalization process for the fabrication of novel heterocycles is always interesting; furthermore, understanding the mechanistic insights of the reaction proficiently add values to the realm of C–H activation (Scheme 3.1).



Scheme 3.1 Strategies for multiple functionalization of C–H bonds

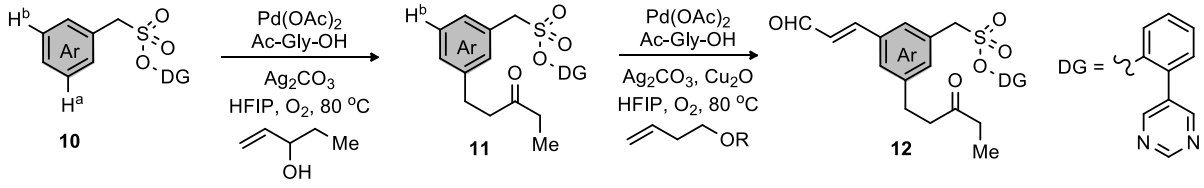
3.1.1. Precedents of Transition-Metal-Catalyzed Unsymmetrical Functionalization

The unsymmetrical multiple functionalization of ubiquitous C–H bonds successfully occurs in two-step synthetic methods, obviously requiring different catalytic conditions. The multiple functionalization of C–H bonds is briefly outlined in scheme 3.2 (also discussed in chapter 1).[9]



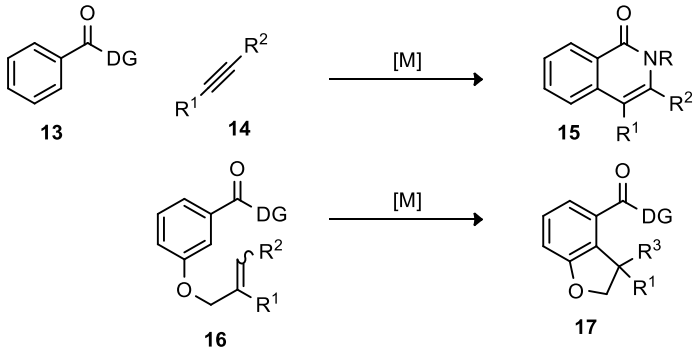
Scheme 3.2. Multiple functionalization of (hetero)arene C–H bonds

The unsymmetrical two-fold C–H functionalization has mostly been perceived in *ortho*-C–H bonds of arenes in a step wise manner. Recently, an extended DG enable *m,m'*-difunctionalization of arene has successfully been implemented in a two-step procedure (Scheme 3.3).[10]



Scheme 3.3. Stepwise *m,m'*-difunctionalization of multiple C–H bonds of arenes

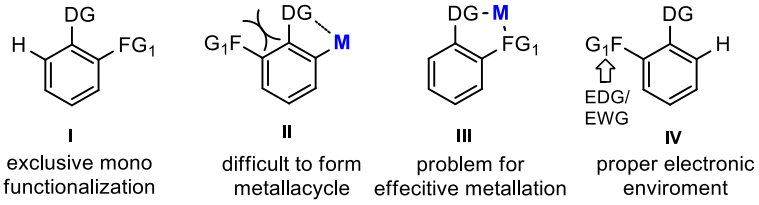
Detailed scrutiny of results clearly reveals that a one-pot synthetic method for unsymmetrical multiple functionalization of various C–H bonds remains elusive, to the best of our knowledge.[8] At this juncture, we envisaged in the development of a synthetic technique integrating isoquinolone and dihydrofuran scaffolds in arene motif through MPS-DG assisted intramolecular hydroarylation of olefins and intermolecular annulation with alkyne under one-catalytic condition in a single operation. Although isoquinolone and dihydrobenzofuran cores are successfully constructed with the aid of various DG under different transition-metal catalyst (Scheme 3.4).[11,12,13]



Scheme 3.4. Synthesis of isoquinolone and dihydrobenzofuran core via C–H activation

3.1.2. Problems associated with one pot multiple functionalization with different FGs:

The presence of more number of proximal C–H bonds adjacent to DG would offer wider opportunity for the multiple C–H bonds functionalization. Although two *o*-C–H bonds of arene are open for functionalization, however, selective mono-functionalization of one *o*-C–H bond of arene-motif leaving the other ineffectual is challenging. Moreover symmetrical di-functionalization of *o,o'*-C–H bonds of arene is facile. The transient-blocking of one *o*-C–H bond, carrying the reaction at low temperature, controlling the time to suboptimal stage, or employing reduced amount of reactant would help addressing these perennial problems.[9b] The presence of non-interfering reacting species could somehow address the problem, although extremely challenging. For example, installation of a bulky functional group (FG) in the arene-scaffold affect further metallation of other free *o*-C–H bonds, affecting the overall unsymmetrical di-functionalization of the molecule.[14] Otherwise, induction of electron withdrawing FG (e.g. carboxylate, halogen, nitro, or olefin) diminishes overall electron density of aryl ring and consequently hampers second *o*-C–H bond activation. In some cases, bis-coordination of catalyst to both FG and the pre-installed DG prevents activation of other *o*-C–H bond (discussed in chapter 1).

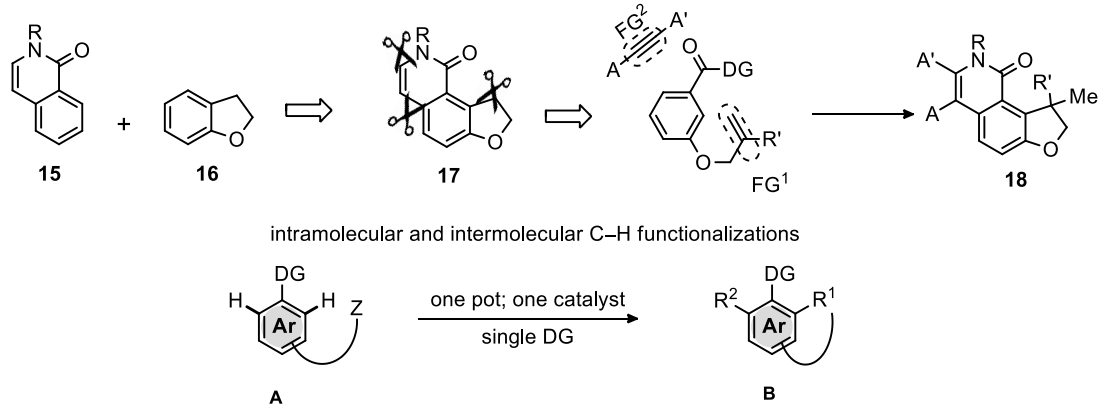


Scheme 3.5. Challenges for unsymmetrical multiple functionalization of C–H bonds

Therefore, stepwise protocols have been adopted for unsymmetrical di-functionalization of arene.[9]

3.2. Motivation and Design Plan

As discussed in Chapter 2, the MPS-DG assisted intramolecular hydroarylation of arene manufactures dihydrobenzofuran skeleton through selective activation of *o*-C–H bond leaving the other proximal *o'*-C–H untouched.[15] The EWG bearing arene affects C–H metallation and functionalization, as ionic character of M–C bond influences metal elimination from the system.[16] Whereas the presence of bulkier group in the close proximity to DG affects metallation due to steric strain, consequently further functionalization is hampered.[14] We believe dihydrofuran ring would neither hinder geometry anchored crowding nor electronic bias to the dihydrobenzofuran scaffold; thus metallation of the proximal *o'*-C–H bond is possible. Furthermore, formation of C–C bond in the hydroarylation step opting out the possibility of bis-co-ordination of metal. As a result, DG promoted TM catalyzed activation of *o*-C–H bond of dihydrobenzofuran motif is realizable, which would eventually lead to further functionalization. Thus, unsymmetrical difunctionalization of arene moiety through intramolecular hydroarylation and intermolecular functionalization of proximal C–H bond to DG is envisaged in a single pot (Scheme 3.6).



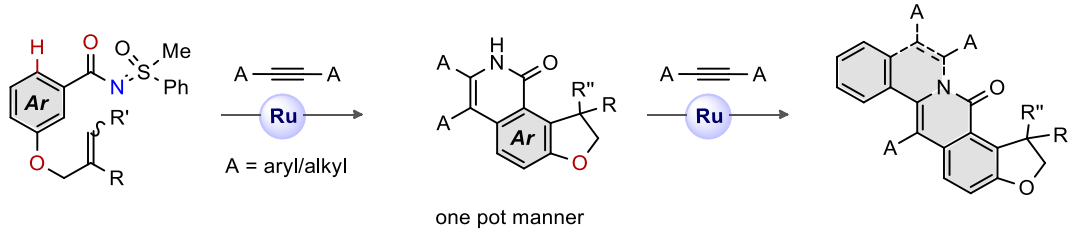
Scheme 3.6. Strategy for one pot multiple functionalization of C–H bonds

Accordingly, two successive annulations of C–H bonds [intramolecular hydroarylation with olefin and intermolecular annulation with alkyne] would

directly build the unusual dihydrofuran-fused-isoquinolone **18**; both the transformations can be performed under the assistance of MPS-DG under one catalytic condition.

Section A: Transformable Sulfoximine Directed Multiple Functionalization of Arene C–H Bonds via Hydroarylation and Annulation

First step involves the Ru-catalyzed hydroarylation of O-allyl-tethered *N*-aroyl sulfoximine derivative to produce dihydrobenzofuran ring. Further activation of proximal *ortho'*-C–H and alkyne insertion followed by modification of MPS-DG constructs pyridinone ring. The use of intramolecular hydroarylation and intermolecular annulation therefore offers one pot unsymmetrical functionalization to achieve furano-isoqunoline moiety. Further C–H activation would be possible with the aid of -NH moiety to deliver dihyrofuran fused polycyclic amide.

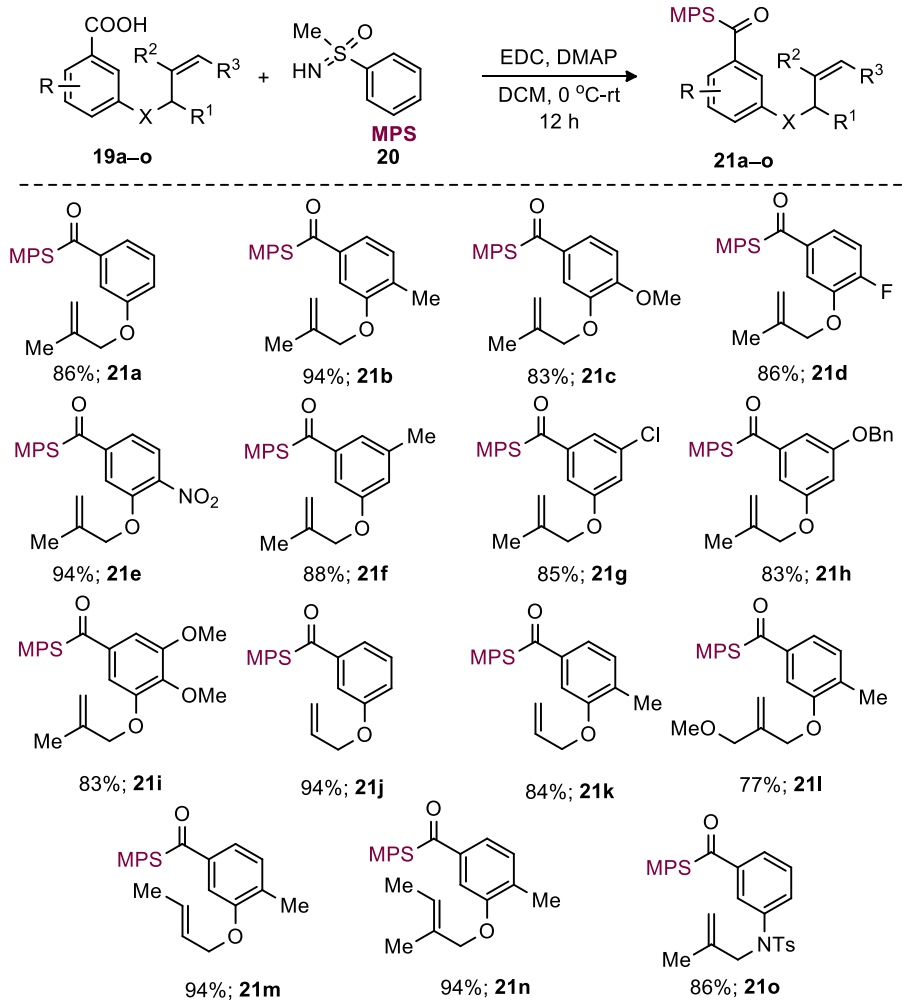


3.3. Results and Discussion

3.3.1. Synthesis of Precursors:

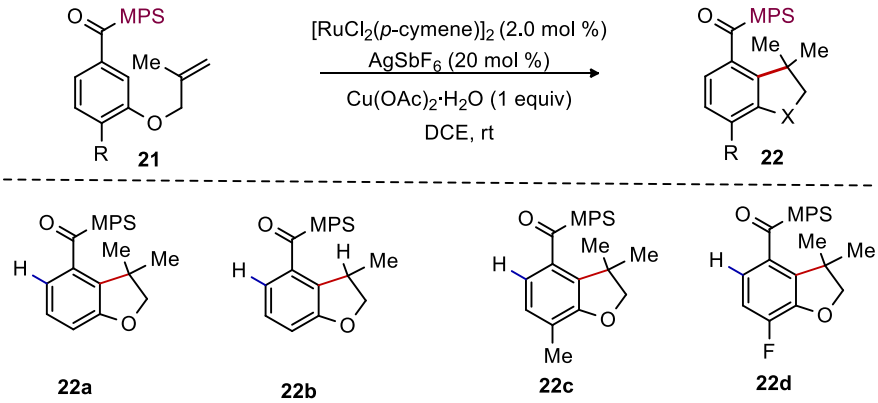
Following the known synthetic procedures, various *N*-aroyl sulfoximines derivatives were prepared (Table 3.1). The EDC.HCl coupling protocol has been adopted for the coupling of O-allyl tether benzoic acid derivatives (**19**) with the MPS-moiety (**20**) (procedure is detailed in experimental section). The synthetic procedure and the analytical data pertaining to compounds **21** are detailed in Chapter 2 (see the identical compounds in the series of **50**); the relevant data for the compounds **21f**, **21g**, **21k**, and **21l** are discussed in Chapter 3.

Table 3.1. Preparation of *N*-aroyl sulfoximine derivatives



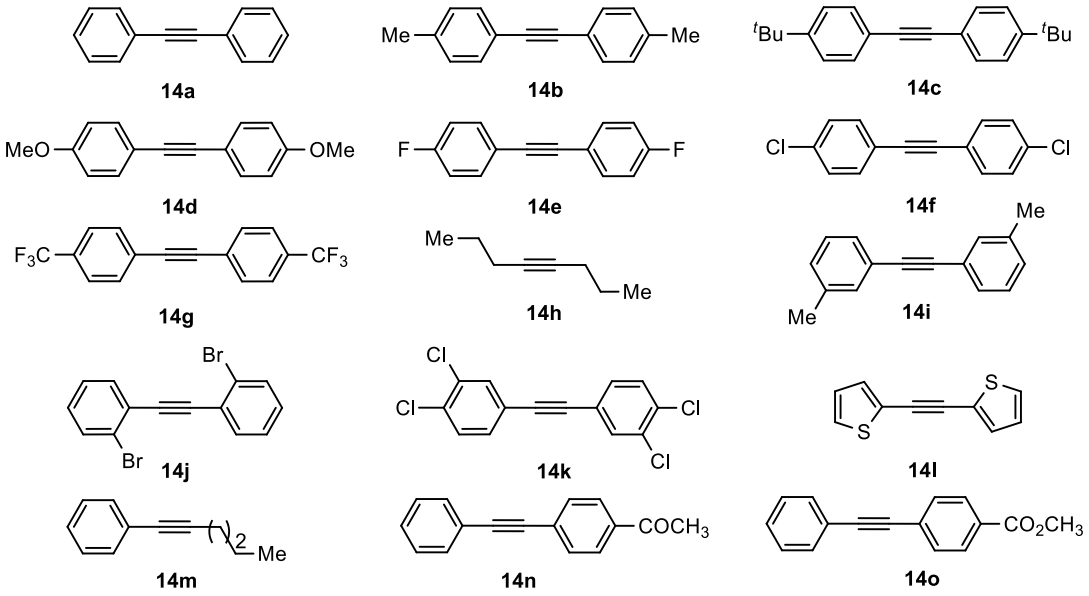
The optimized synthetic procedure (detailed in Chapter 2) has successfully been implemented for the preparation of hydroarylation products **22a**–**d** from the corresponding precursors **21** (as shown in Table 3.2).

Table 3.2. Preparation of dihydrobenzofuran derivatives:



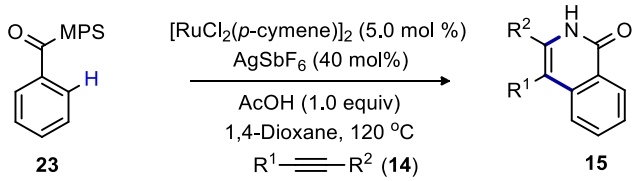
The 1,2-disubstituted acetylenes used in the annulation studies are listed in Table 3.3.

Table 3.3. Alkynes used in various transformations



3.3.2. Step-wise Hydroarylation and Annulation of Multiple C–H bonds:

We recently demonstrated Ru-catalyzed MPS directed annulation of arenes **23** with alkynes **14** for the synthesis of quinolones **15** (Scheme 3.7).[17]

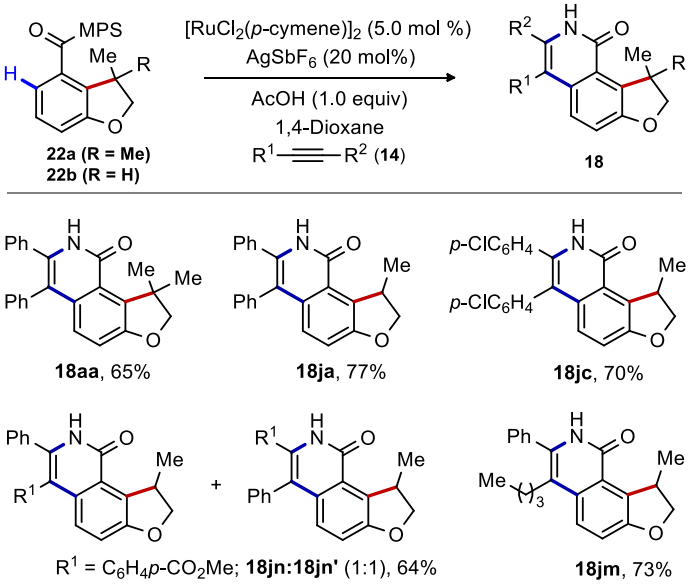


Scheme 3.7. MPS assisted annulation of benzoic acid derivatives

The *o*-C-H bond in dihydrobenzofuran derivative (**22**), synthesized through intramolecular hydroarylation of arene with olefin under the assistance of MPS-DG, could be useful for further annulation with alkyne. As envisaged, this process enables constructing furan-fused-isoquinolone skeleton. To fulfil this campaign, compound **22a** (R=Me) was reacted with diphenylacetylene (**14a**) under the catalytic conditions comprising with Ru-cat, Ag-salt, AcOH in 1,4-Dioxane; pleasingly the expected **18aa** was obtained in 65% yield (Table 3.4). Similarly, annulation of 3-methyl dihydrobenzofuran (R=H, **22b**) with diphenylacetylene (**14a**) and bis(*p*-chlorophenyl)acetylene (**14f**) delivers the desired furano-isoquinolone product in

18ja (77%) and **18jc** (70%) (Table 3.4). The discrimination of yield among **18aa** and **18ja/18jc** is possibly due to the steric inhibition imposed with the additional methyl

Table 3.4. Annulation of Hydroarylation Derivatives[a,b]

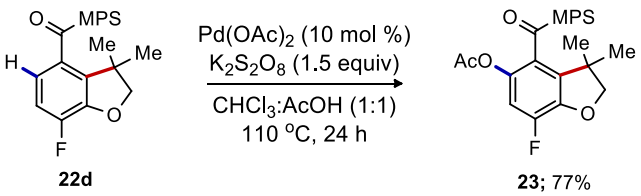


[a]Reactions were carried out using **22** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %), AcOH (0.5 mmol) in 1,4-dioxane (4.0 mL) at 120 °C for 24 h. [b]Isolated yields.

moiety. A regioisomeric mixture of **18jn** and **18jn'** (1:1; 64%) was obtained when **22b** reacted with unsymmetrical alkyne [methyl 4-(phenylethynyl)benzoate (**14n**)]. Whereas reaction of unsymmetrical 1-phenyl-1-hexyne (**14m**) with **22b** exclusively provided **18jm** in 73% yield (Table 3.4); structure of **18jm** was established by NOESY studies suggesting the presence of aryl moiety adjacent to NH-isoquinolone (see the Experimental section 3.7.3.3, page no 202). Thus, unsymmetrical two-fold functionalization of inert C–H bonds (hydroarylation and annulation) is synthetically viable, although these reactions are carried out in a step-wise manner.

3.3.3. Unsymmetrical Functionalization of Multiple C–H Bonds through Hydroarylation and Acetoxylation Sequence:

We next explored scrutinizing unsymmetrical functionalization of *o*-C–H bonds through sequential hydroarylation and acetoxylation of arenes. Pleasingly, *o*-C–H of dihydrobenzofuran **22d**, obtained through hydroarylation, under the catalytic conditions [$Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (1.5 equiv) in $CHCl_3$:AcOH at 110 °C] successfully provided the *o*-acetoxylation product 23 in 77% yield (Scheme 3.8).[18]

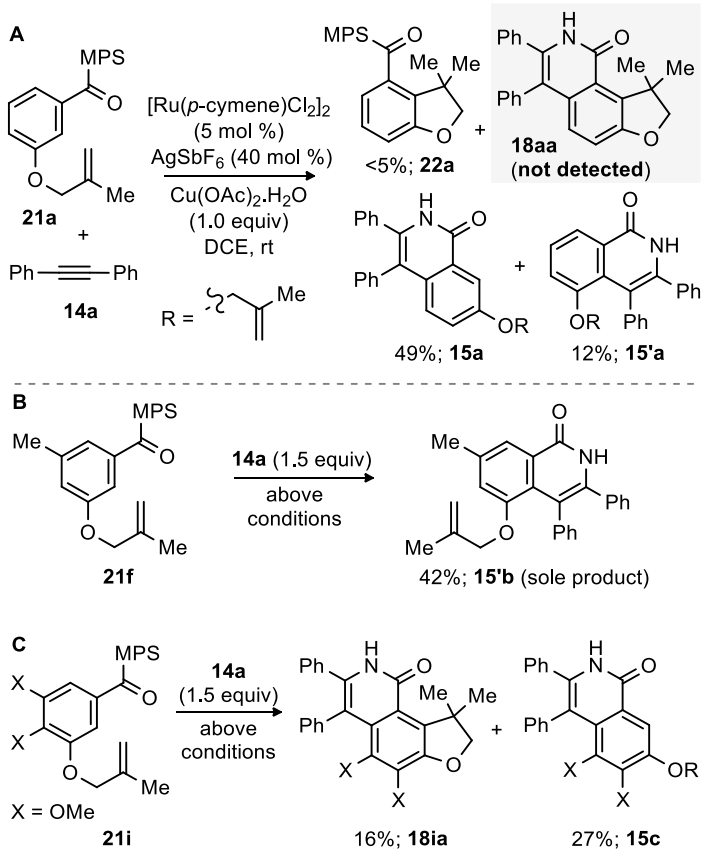


Scheme 3.8. Acetoxylation of hydroarylated derivative

3.3.4. One-pot Unsymmetrical Functionalization of Multiple C–H Bonds:

Inspired from independent *o*-C–H annulation and acetoxylation of dihydrobenzofuran scaffold [Table 3.4 and Scheme 3.8], a one pot two-fold unsymmetrical functionalization of arene derivative is thus envisaged. As observed, hydroarylation involves protodemetallation whereas annulation requires C–N reductive elimination; consequently, oxidant is indispensable in this catalytic cycle. The acetate source $Cu(OAc)_2$ not only assists CMD process in the hydroarylation but also acts as oxidizing agent. As hydroarylation involves protodemetallation, acetate moiety promotes oxidation of reduced Ru-species. In the annulation step, the oxidizable MPS-DG keeps the Ru-oxidation state unchanged. We thus believe that the oxidative catalytic system would be useful or the successful occurrence of hydroarylation and annulation of arenes under the assistance of an oxidizable DG.[19] As intramolecular hydroarylation occurs at room temperature and annulation requires high temperature, we envisaged a one-pot synthetic procedure where both the transformations can strategically be performed at various temperature. In addition, this overall one-pot process avoids more catalyst load, extra purification of hydroarylation product. Moreover, the intramolecular reaction is thermodynamically favourable than the intermolecular reaction. Obviously, our intention is to explore a one-pot two-fold unsymmetrical C–H functionalization of arenes involving hydroarylation-annulation transformation under the assistance of a single DG.

3.3.4.1. One-pot Unsymmetrical Functionalization of Multiple C–H Bonds: Preliminary Observation:



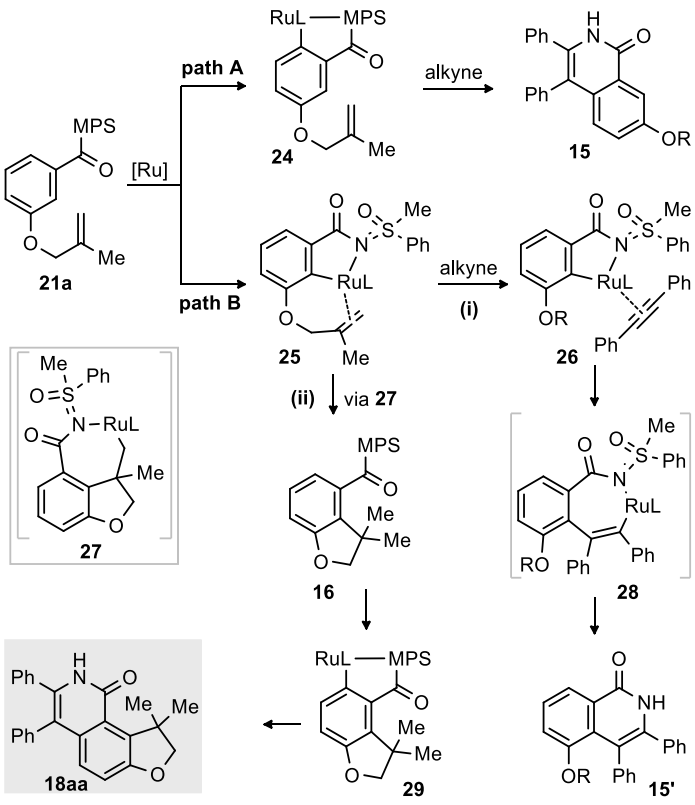
Scheme 3.9. Initial studies of one pot hydroarylation-annulation reaction

To check the hypothesis, the reaction between [3-(2-methylallyloxy)-benzoyl]methyl phenyl sulfoximine (**21a**) and diphenyl acetylene (**14a**) under the catalytic condition comprising {[$RuCl_2$(*p*-cymene)]$_2$ (5 mol %), $AgSbF_6$ (40 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv) in 1,2-DCE} at 25 ^oC is investigated. Unfortunately, we did not detect the desired product **18aa** (hydroarylation-annulation); instead annulation products **15a** (alkyne cyclization from sterically free *o*-site) and **15'a** (alkyne cyclization from sterically hindered *o*-site) were formed along with minor amount of hydroarylation product **22a** (<5%) (Scheme3.9-A). While reaction of diphenyl acetylene and **21f** (both *o,o'*-positions sterically encumbered) under the identical condition led exclusively to **15'b** (cyclization occurred between *ortho*-C–H bond flanked between tethered O-allyl moiety and the MPS-DG) (Scheme 3.9-B). To understand steric and electronic factor in this cascade hydroarylation-annulation sequence, the reaction between **14a** (diphenyl acetylene) and 4,5-dimethoxy bearing electron rich **21i**

(having similar secondary directing influence of '*m*-O' and sterically encumbered *o*-sides) was executed under the Ru-catalysis. Fortunately, this reaction delivers the desired dihydrofuran-fused-isoquinolone **18ia** (16%) as well as **15c** (27%) (Scheme 3.9-C).

3.3.4.2. Probable Reason:

These observations led us to consider the probable three competitive reaction paths (Scheme 3.10). As shown in Scheme 3.9-A, Ru catalyzed activation of sterically less hindered *o*-C–H bond of arene **21a** produced ruthenacycle **24** and finally produces isoquinolone product **15** through migratory insertion of alkyne followed by C–N bond formation (Scheme 3.10, path A). On the other hand, ruthenacycle **25** can be generated via the activation of sterically encumbered *o*-C–H bond; an additional interaction of Ru and ethereal oxygen promotes this process (Scheme 3.10, path B). Then alkyne insertion to complex **25** finally leads to annulation product **15′** [path B(i)]. Otherwise intramolecular hydroarylation with O-tethered alkene followed by second *o*′-C–H activation and alkyne annulations could deliver desired product **18aa** [path B(ii)]. It thus appears that the complex **25** (formed via the coordination of olefin in competitive pathways A and B) is easily replaced with alkyne well before hydroarylation [path B(ii)] and forms **27**. Now, **27** undergoes a parallel protodemetallation (fast) followed by C–H activation of second *o*′-C–H and migratory insertion of alkyne (slow) to generate the desired product **18aa**, concurrently fulfilling the results shown in Scheme 3.10. The Raybov's study matches this outcome.[20] Thus, attack of nucleophilic '*O*-ruthenated' HOMO to the LUMO of alkyne possibly forms stable C(sp^2)–M bonded intermediate **28**, which is responsible for final reaction outcome. On the other hand, the transfer of electron density from '*O*-ruthenated' HOMO of C–M bond to LUMO of alkene forms intermediate **27** C(sp^3)–M, which is relatively less stable than **28** (Scheme 3.10).[20] This analogy supports the intermolecular annulation, which is facile over intramolecular one.



Scheme 3.10. Analysis of one pot domino reaction

3.3.4.3. DFT Calculation to Understand the Reaction Outcome:

On the basis of DFT calculations [performed using Becke's three parameter hybrid density functional method (B3LYP) with LANL2DZ triple zeta pseudo potential for Ru and 6-31+G(d,p) basis set for all other atoms], the desired dihydrofuran-fused isoquinolone **18aa** is more stable over **15** and **15′** by 7.4 and 20.6 kcal/mol, respectively. The formation of **15** and **15′** requires overall barrier of 19.8 and 32.9 kcal/mol, respectively. Although energy barrier among path A and path B is small, the one pot single step double C–H functionalization possibly favors path A (Scheme 3.10), surfacing major amount of annulation with alkyne. Energy barrier for path B(ii) leading to **18aa** requires overall barrier of 26.9 kcal/mol. Seemingly, the energy barrier required for intramolecular insertion of alkene in path B(ii) (Scheme 3.10) is 1.5 kcal/mol larger than the energy barrier for migratory alkyne insertion in path B(i). These insightful theoretical data indicated that both intermolecular hydroarylation and intermolecular annulations are energetically favorable; this would eventually result complex outcome when conducted in a single step.

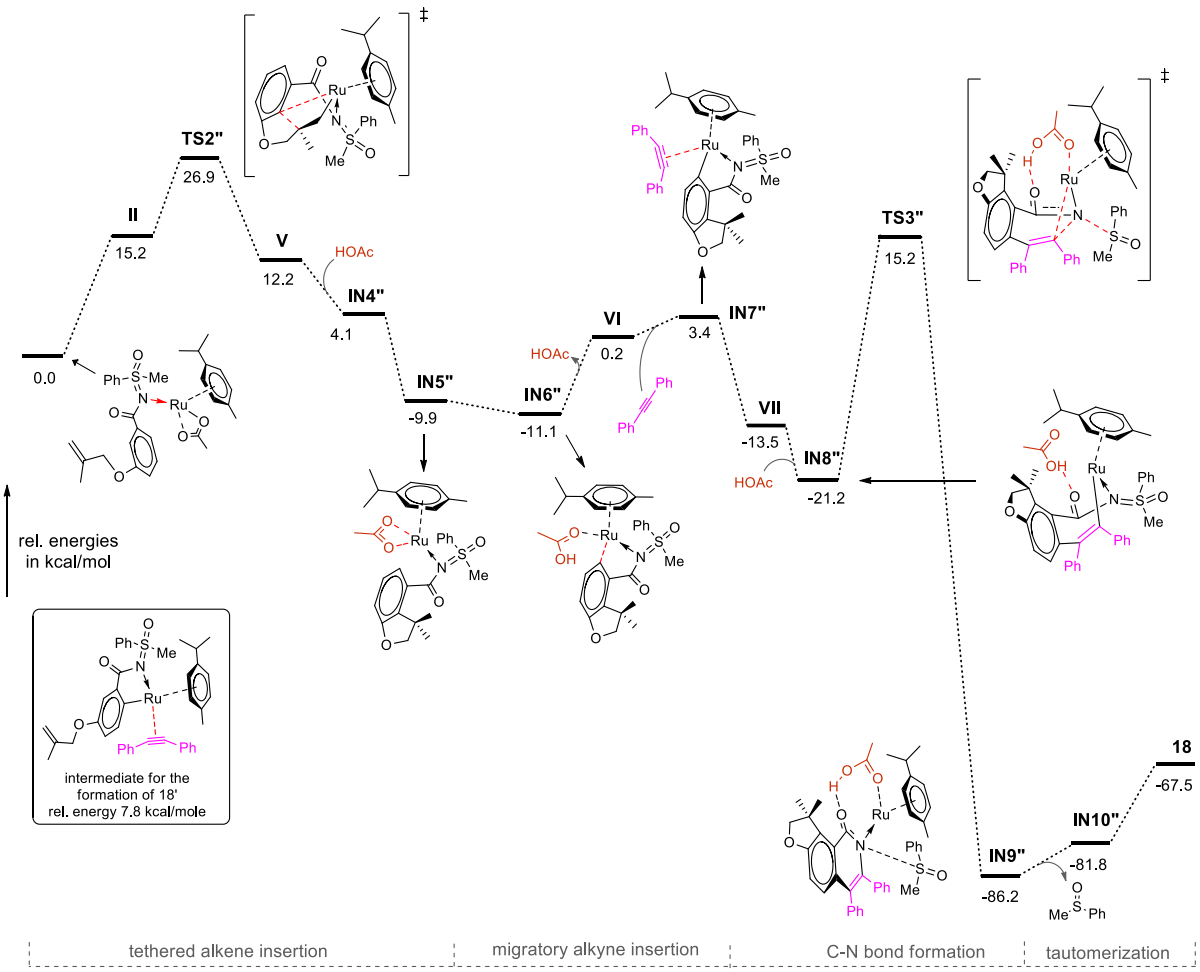
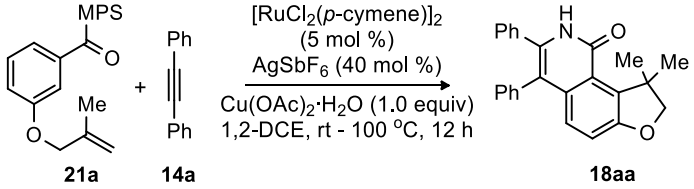


Figure 3.2. DFT Analysis for one pot domino reaction

3.3.5. Reaction Optimization:

To avoid the perennial challenges in the one-pot multiple functionalization of C–H bonds (from the preliminary-experimental results and theoretical calculations; Scheme 3.10 and Figure 3.2), sequential introduction of alkyne to the reaction mixture set for the intramolecular hydroarylation under the single catalytic conditions is envisaged. Thus, the entire transformation is conducted as follows: the intramolecular hydroarylation **21a** under Ru-catalysis for 2 h, addition of alkyne **14a** and finally heating the resulting mixture at 120 °C for 10 h; this process led to the desired product **18aa** in 59% yield (Table 3.5, entry 1).The initial result in entry 1, Table 3.5, encouraged us to get the optimized catalytic conditions for the efficient synthesis of **18aa** from **21a** and **14a**; the results are discussed in Table 3.5. The use of other acetate bases/oxidants except Cu-salt was inferior (entries 2–5).

Table 3.5: Optimization of the Reaction Conditions[a]



Entry	Additive (40 mol %)	Base/Oxidant (1.0 equiv)	Solvent	yield (%) of **18aa**[b]
1	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	DCE	59
2	$AgSbF_6$	$Cu(OAc)_2$	DCE	54
3	$AgSbF_6$	NaOAc	DCE	11
4	$AgSbF_6$	KOAc	DCE	~10
5	$AgSbF_6$	$Mn(OAc)_2$	DCE	37
6	$AgBF_4$	$Cu(OAc)_2 \cdot H_2O$	DCE	21
7	$AgPF_6$	$Cu(OAc)_2 \cdot H_2O$	DCE	36
8	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	Dioxane	49
9	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	HFIP	29
10[c]	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	DCE	69
11[d]	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	DCE	71
12[e]	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	DCE	67
13[f]	**$AgSbF_6$**	**$Cu(OAc)_2.H_2O$**	**DCE**	**74**

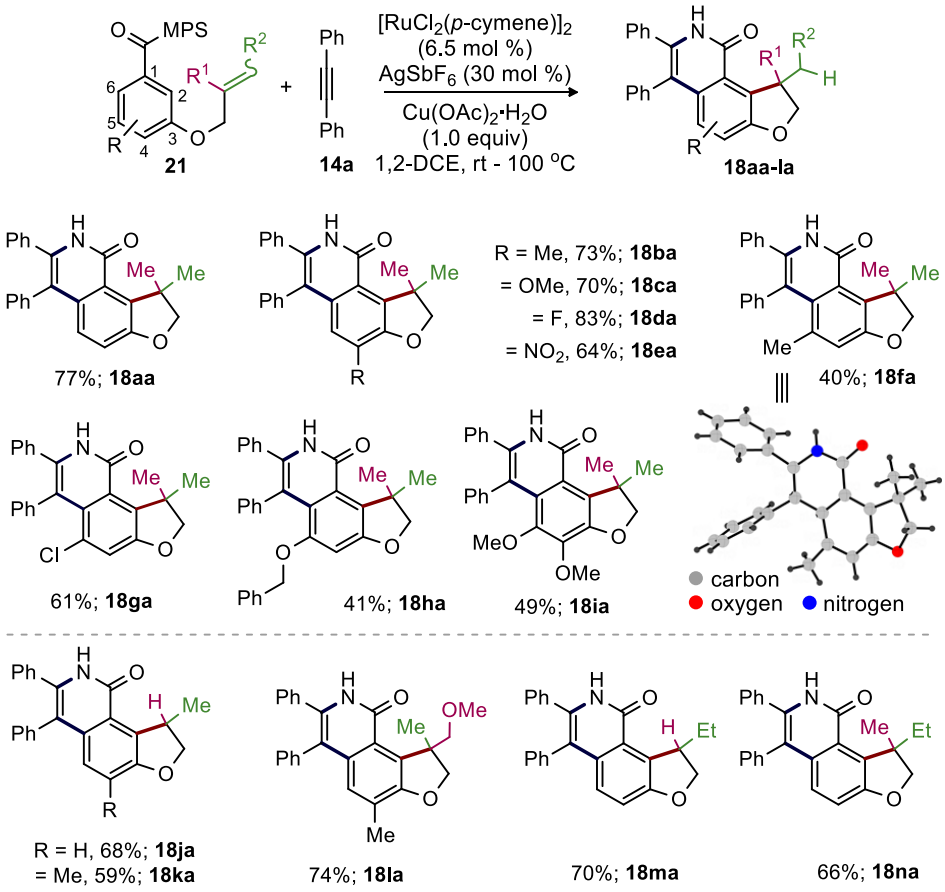
[a]Reaction conditions: **21a** (0.1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), Ag-salt (40 mol %), base/oxidant (1.0 equiv), solvent (1.0 mL) at rt for 2 h; then **14a** (0.11 mmol) was introduced and heated at 120 °C for 10 h. [b]Conversion based on crude ^1H NMR and number in the parenthesis indicates the isolated yield. [c]Ru-cat. (6.5 mol %). [d]Ru-cat.(7.5 mol %). [e]Ru-cat. (6.5 mol %), $AgSbF_6$ (30 mol %). [f]Reaction was stirred at rt for 2 h then **14a** was added and heated at 100°C for 10 h under the identical condition of (e).

Screening of various Ag-additives (such as, $AgPF_6$, $AgBF_4$) and solvents (1,4-dioxane, HFIP) were turned less productive (entry 6–9). The increased catalyst loading (6.5 mol %) led to improved product yield (69%, entry 10), while 7.5% catalyst load did not substantially affect the reaction outcome (entry 11). The less load of Ag-additive (up to 30 mol %) was equally effective (entry 12). Finally, the reaction of **21a** under the catalyst {$[RuCl_2(p\text{-cymene})]_2$ (6.5 mol %), $AgSbF_6$ (30 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv) in 1,2-DCE} at rt for 2 h followed by the addition of **14a** and heating at 100 °C for 10 h led the desired **18aa** (*fused heteroaryl scaffold*) in 74% yield (entry 13).

3.3.6. Scope of the Reaction

The scope of one pot sequential two-fold unsymmetrical functionalization of O-allyl-tethered arenes with alkynes furnishing dihydrofuran-fused-isoquinolone is next explored (Table 3.6). Arenes with electron donating and withdrawing substituent at 4-position (**21b**–**e**) smoothly reacted with **14a** to produce **18ba**–**ea** in good to excellent yield. Substitution at 5-position, which makes '*o*' sterically congested for second annulation, did not hamper the reactivity and offers moderate to good yield of the desired products (**18fa**–**ha**). Of note, the labile O-benzyl group was survived under catalytic conditions.

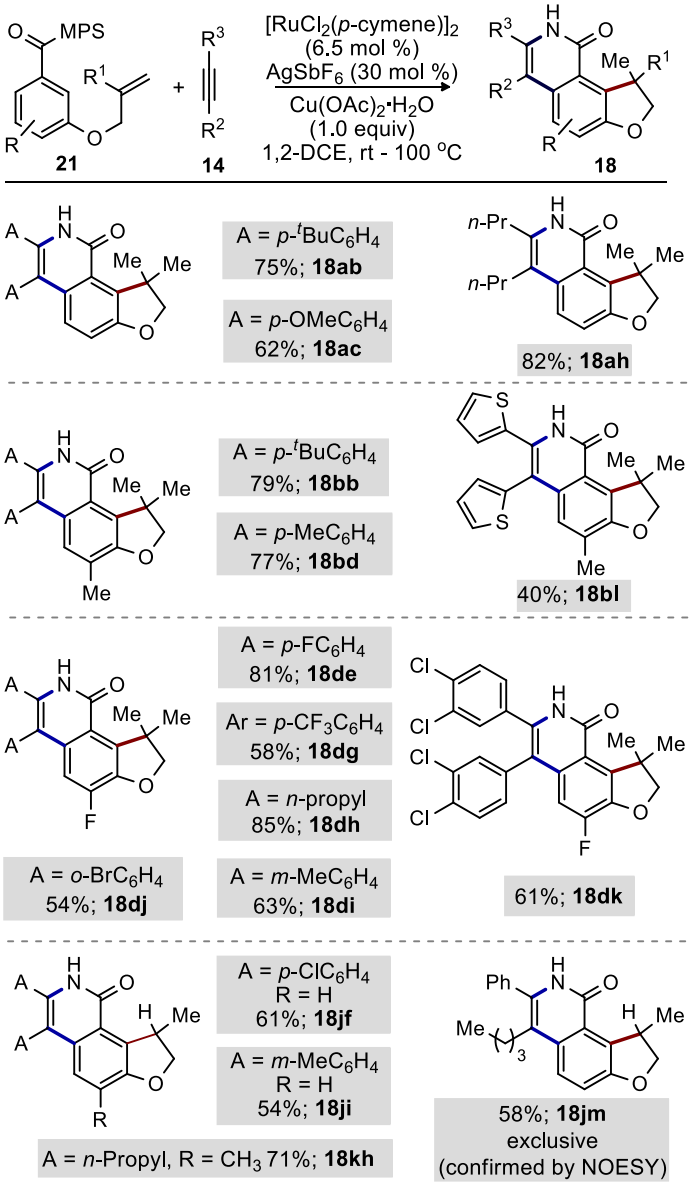
Table3.6. One Pot Domino Reaction of Arenes with 1,2-Diphenylacetylene[a,b]



[a]Reaction conditions: **21** (0.25 mmol), Ru-catalyst (6.5 mol %), $AgSbF_6$ (30 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.25 mmol), 1,2-DCE (2.0 mL) at room temperature for 2–3 h followed by addition of **14a** (0.28 mmol) and heating at 100 °C for 10–12 h. [b]Isolated yields.

The 4,5-dimethoxy substituted **18ia** (49%) was isolated from **21i**. The modified tethered alkenes were reacted effectively; several 1,1 and 1,2-disubstuted alkene bearing arenes were converted to the desired product (**18ja**–**na**).

Table 3.7. One Pot Domino Reaction of Arenes with 1,2-Disubstituted Alkynes[a,b]

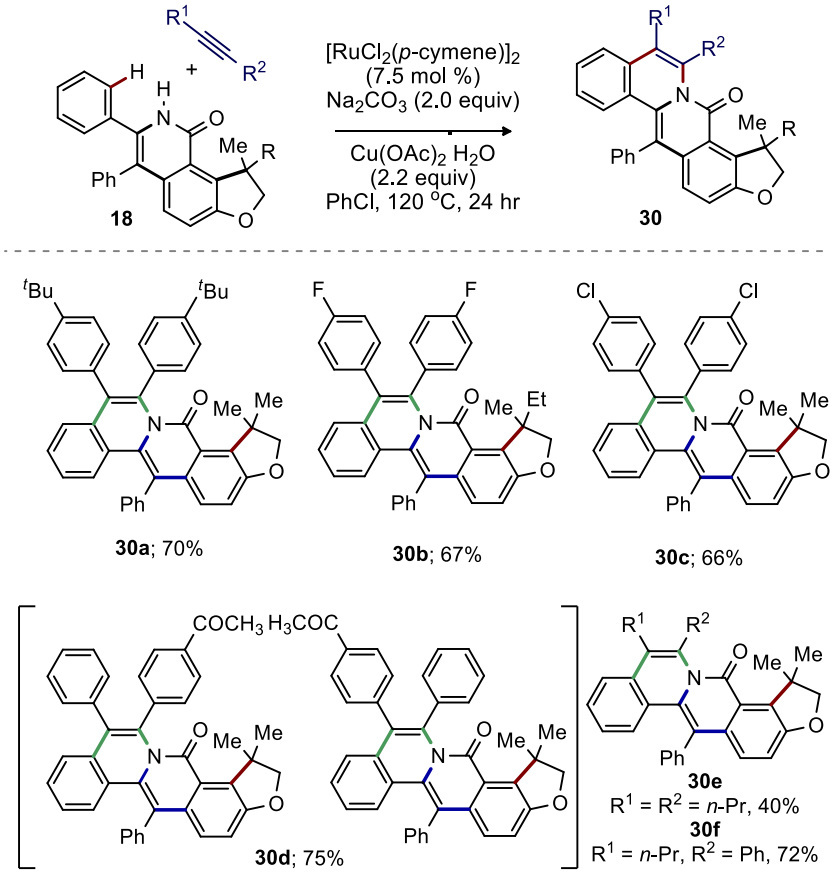


[a]Reaction conditions: **21** (0.25 mmol), Ru-catalyst (6.5 mol %), $AgSbF_6$ (30 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.25 mmol), 1,2-DCE (2.0 mL) at room temperature for 2–3 h followed by addition of **14** (0.28 mmol) and heating at 100 °C for 8–10 h. [b]Isolated yields.

Next, the reactivity of diverse range of 1,2-disubstituted alkynes (**14b**–**n**) in this direct double annulation was checked and the outcome is summarized in Table 3.7. The electron-rich/poor alkynes **14b**–**g**, by means of having substitution (Me, ^{t}Bu, OMe, F, Cl, CF_3) at the *p*-position of aryl ring, reacted proficiently with **21a**, **21b**, **21d**, **21j,** and/or **21k** to deliver the corresponding products [**18ab** (75%), **18ac** (62%), **18bb** (79%), **18bd** (77%), **18de** (81%), **18dg** (58%), **18jf** (61%)]. Gratifyingly, *meta, para*-Cl (**14k**) or *meta-Me* (**14i**) substituted arene containing alkynes smoothly annulated

producing **18dk** (61%) and **18di** (63%). Even sterically crowded 1,2-bis(2-bromophenyl)ethyne (**14j**) worked well under the optimized conditions affording 54% of **18dj**. The diheteroaryl alkyne **14l** was not exception, allowing **18bl** albeit in moderate yield. The corresponding annulation product **18ah** (82%) was isolated when 4-octyne **14h** reacted with **21a**. The reaction of **21j** with alkyl-aryl alkyne **14m** exclusively produced **18jm**; the structure was unambiguously confirmed by NOESY studies.

Table 3.8. Annulaion of Dihydrofurano-fused-isoquinolone with 1,2-Diarylacetylenes[a,b]

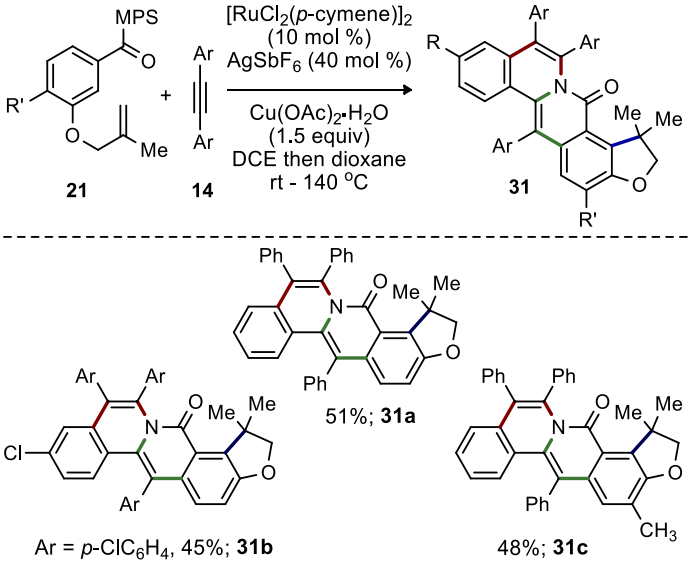


[a]Reaction conditions: **18** (0.20 mmol), **14** (0.30 mmol), Ru-catalyst (7.5 mol %), Na_2CO_3 (0.40 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.44 mmol), in PhCl (2.0 mL) at 120 °C for 24 h. [b]Isolated yields.

Polycyclic amides are often found in the molecules of material and biological importance.[12] Thus, development of a strategy for the synthesis of novel polycyclic amide always attracts attention to the synthetic chemists.[21-22] The presence of NH and the proximal arene C–H bond of the dihydrofuran-fused-quinolinone **18** triggered our interest to further execute the annulation of **18** with alkynes under Ru-

catalysis. Thus, annulation between a range of compounds **18** and alkynes (**14b**, **14e**, **14f**, **14n**, **14h**, **14m**) were conducted under the catalytic condition using Ru, Na_2CO_3, $Cu(OAc)_2$. Gratifyingly, dihydrofuran-fused novel π-extended five-ring-fused polycyclic amides **30a**–**f** were prepared (Table 3.8). This unique multi-fold unsymmetrical annulation allowed us orchestrating the electronics on the periphery of the polycyclic amide through the employment of different alkynes.

Table 3.9. Synthesis of Dihydrofuran fused Polycyclic Amide via Three C–H Bond Activation [a,b]



[a]Reaction conditions: **21** (0.2 mmol), Ru-catalyst (10 mol %), $AgSbF_6$ (40 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.3 mmol), 1,2-DCE (1.0 mL) at room temperature for 2–3 h followed by addition of 1,4-dioxane (2.0 mL) and **14** (0.6 mmol) and heated at 140 °C for 24 h. [b]Isolated yield.

Having established the synthesis of polycyclic amides from **18** and **14** (Table 3.8), the hydroarylation-diannulation reaction sequences among **21** and **14** is then investigated; this process would eventually construct 3-C–C and 2-C–N bonds in a single operation directly erecting five-ring fused heteroaryl amides **31**.[23] Pleasingly, a range of five-ring fused unusual heteroaryl amides **31** (in overall ~50% yield) were prepared through the hydroarylation-diannulation sequence of easily accessible **21** and **14** under 10 mol % Ru, 40 mol % Ag salt, 1.5 equiv. Cu-salt. The distinct feature of this transformation is: three distinct C–H bonds (resides under different chemical

environment) are activated and functionalized under a single catalytic system (Table 3.9).

3.3.7. Mechanism:

On the basis of observed facts (Scheme 3.10) and DFT calculations, the probable mechanistic cycle is deduced (Figure 3.3). The reaction initiates with the coordination of active catalyst [Ru(*p*-cymene)(OAc)]$^+$, obtained in-situ from [Ru(*p*-cymene)Cl_2]$_2$ in presence of $AgSbF_6$ & $Cu(OAc)_2$, with MPS. Acetate assisted proton removal of proximal *o*-C–H bond of arene then generates five membered metallacycle **25**, which is possibly stabilized by the tethered alkene. The C–C bond formation through alkene insertion and migration of Ru- species gives intermediate **27**. Next, AcOH mediated protodemetallation delivers dihydrobezofuran skeleton; the simultaneous acetate incorporation to the Ru generates active catalyst and coordinates to the N-of sulfoximine.

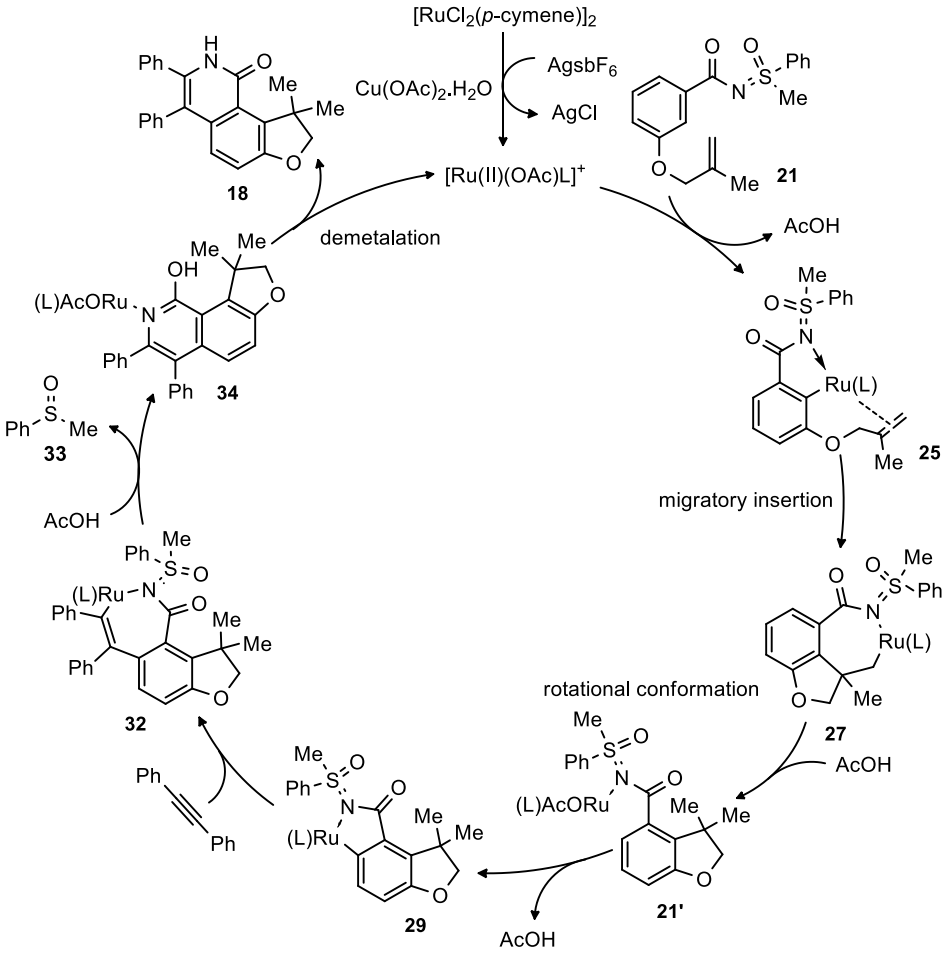


Figure 3.3. Catalytic cycle of the one pot diannulation

Then, C–C (arene and carbonyl) bond rotation and activation of *o'*-C–H bond of arene with the removal of AcOH affords cyclometalation complex **29**. Alkyne insertion to **29** and carboruthanation to alkyne produces seven-membered Ru-species **32**. The acetic acid promoted expulsion of phenyl methyl sulfoxide **33** finally provides metal coordinated iminol intermediate **34**, which further undergo amide-iminol tautomerization to deliver the desired furano-isoquinolone **18** with the generation of active catalyst (Figure 3.3).

3.4. Conclusions

A conceptual synthetic manifestation for the two-fold unsymmetrical C–H functionalization of arenes involving intramolecular hydroarylation with olefins and intermolecular annulation with alkynes is developed. Unusual dihydrofuran-fused-isoquinolone heterocycles are constructed. The methyl phenyl sulfoximine (MPS) directing group (DG) plays vital, activating multiple C–H bonds with the formation of 2-C–C and 1-C–N bonds in a single operation. The overall process is atom economical and step-efficient. Highly conjugated novel polycyclic compounds by fusing 7 rings with the creation of 3-C–C and 2-C–N bonds have successfully been implemented under single catalytic conditions, which is unprecedented.

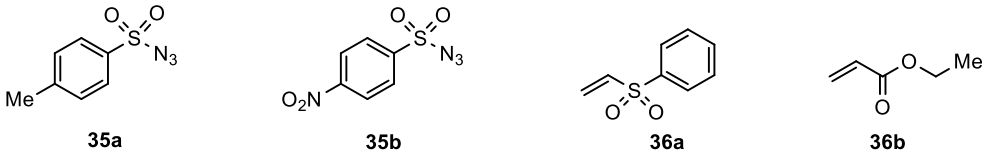
Section B: Ru-Catalyzed One Pot Twofold Unsymmetrical C–H Functionalization of Arenes

3.5. Result and Discussion

3.5.1. Scope of the Reaction

The following azides and alkenes (listed in Table 3.10) were prepared and used in the one pot two fold unsymmetrical C–H functionalization of arenes.

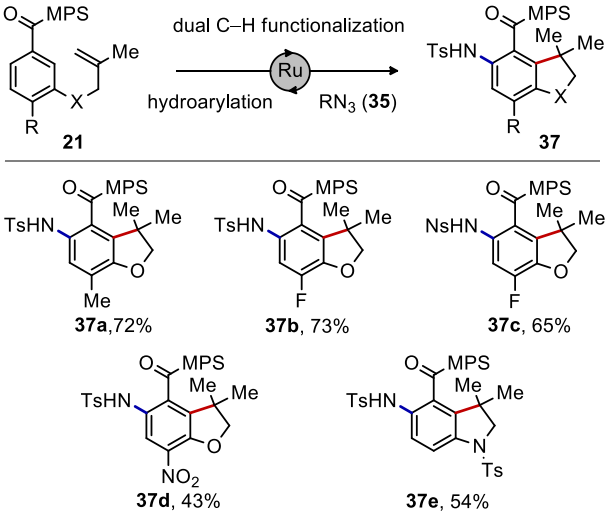
Table 3.10. List of Azides and Alkenes



35a **35b** **36a** **36b**

Motivated from the sequential one-pot twofold unsymmetrical functionalization of arenes for the construction of benzofuro-isoquinolone skeleton (Section 3.3), introduction of different functional groups in the molecular scaffold is next studied. To achieve this challenging task, the entire transformation has been conducted under different temperature. Thus, the hydroarylation reaction proceeds at room-temperature providing the desired bezofuran ring and later alkenylation and amination occurs at higher temperature.

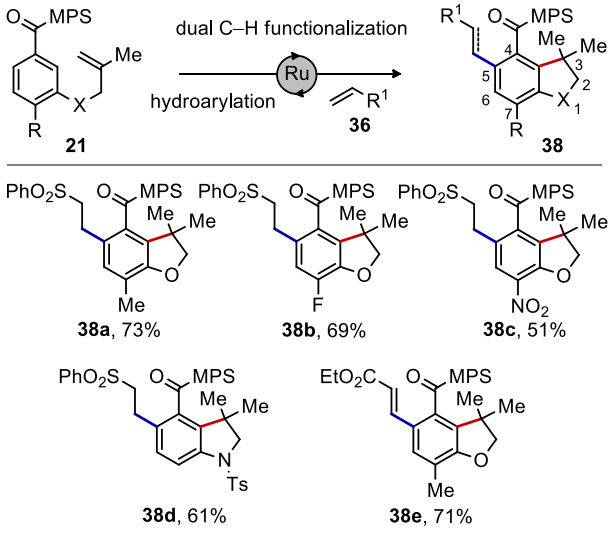
Table 3.11. One Pot Hydroarylation and Amidation of MPS-DG Enabled Benzoic Acid Derivatives[a,b]



[a]Reactions were carried out using **21** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.5 mmol), sulfonyl azide (**35**) (1.0 mmol) in DCE (4.0 mL) at room temperature for 12–16 h and then heated up to 120 °C for 24 h. [b]Isolated yields. Ns = *p*-nitrosulfonyl.

The feasibility of hydroarylation-amidation of aryl *o*-C–H bonds (a hypothesis shown in Scheme 3.6) was inspected by performing *o*-C–H amidation of dihydrobenzofuran **22c** under the catalytic conditions $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv) in $ClCH_2CH_2Cl$ (DCE)] in the presence of TsN_3 at 120 °C. To our delight, the desired product **37a** was formed in 82% yield, showing the sequential C–C and C–N bond formation under one catalytic condition. To attain the productive one pot unsymmetrical twofold C–H functionalizations, the intramolecular hydroarylation followed by intermolecular amidation under the one-catalytic condition is envisioned. Gratifyingly, an appreciable yield of compound **37a** (72%) was isolated (Table 3.11), when **21b** was exposed to the Ru-catalyzed conditions in the presence of TsN_3 and the reaction was performed at rt for 12 h followed by heating at 120 °C for 24 h.[24] Likewise, reaction of **21d** with TsN_3 (**35a**)/ NsN_3 (**35b**) under the Ru-catalysis were successfully conducted to deliver the corresponding **37b** and **37c** in good yields (Table 3.11). Similarly, various functional groups (nitro, amido, and amide) bearing dihydrobenzofuran **37d** was constructed; the electron withdrawing nitro group on arene impart moderate reactivity. *N*-tethered indoline derivative **37e** produced 54% yield under the same reaction condition (Table 3.11).

Table 3.12. One Pot Hydroarylation and Alkylation/Alkenylation of Benzoic Acid Derivatives[a,b]



[a]Reactions were carried out using **21** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), alkene (**36**; 1.0 mmol), $AgSbF_6$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol) in DCE (4.0 mL) at room temperature for 12–16 h and then heated up to 120 °C for 24 h. [b]Isolated yields.

The success of one pot unsymmetrical hydroarylation-amidation reaction indulged us to explore twofold unsymmetrical *o,o'*-C–C bond forming reactions of benzoic acid derivatives (Table 3.12). Pleasingly, the reaction of **21b** with phenyl vinyl sulfone (**36a**) under the optimized conditions $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv) in $ClCH_2CH_2Cl$ (DCE)] at rt (12 h) followed by heating at 120 °C (24 h) directly led to 5-alkyl substituted dihydrobenzofuran **38a** in 73% yield in a single operation.[25,17] Among the possibilities of different C–C bond forming processes, the intramolecular hydroarylation was found facile over the intermolecular C–C bond formations. The reaction of 4-F/NO_2 groups bearing arene (**21d** and **21e**) smoothly participated the hydroarylation/C-C bond forming process, delivering the desired dihydrobenzofurans product **38b** (69%) and **38c** (51%). Presumably, newly generated quaternary centre at 3-position of dihydrobenzofuran ring provide sufficient steric strain in the transition state as well as the acidity of sufonyl group suppresses the β-hydride elimination over protodemetallation; alkylation product instead of alkenylation product is therefore obtained.[21] The one-pot twofold C–C bond formations were not only confined to O-bearing olefins; the N-tethered **21o** was also effectively participated to produce the corresponding indoline derivative **38d** in 61% yield. On the other hand, the reaction of ethyl acrylate (**38b**) with **21b** led to the alkenylation (**38e)** in 71% isolated yield. We believe, the results in Table 3.11 and Table 3.12 displaying a one-pot single DG enabled unsymmetrical functionalization of *o,o'*-arenes [hydroarylation/amidation, hydroarylation/olefination] under one catalytic condition is the first report.

3.6. Conclusions

In summary, a novel and efficient MPS DG-promoted Ru-catalyzed unprecedented one-pot twofold unsymmetrical C–H functionalization of arene derivatives through hydroarylation–amidation and hydroarylation–alkylation/alkenylation is discussed. The scope of the reaction is broad and reliable.

3.7. Experimental

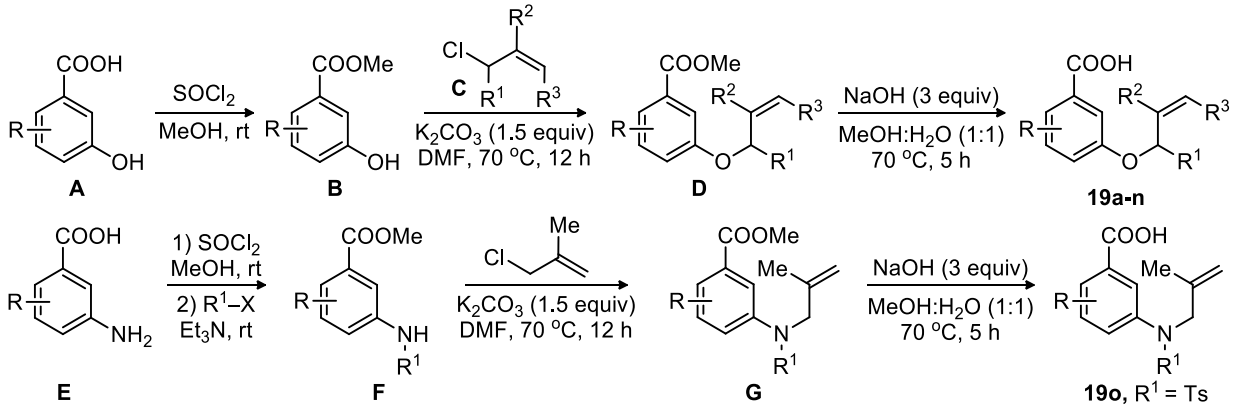
3.7.1. General Experimental Information is shown in section 2.7.1, page 67, Chapter 2.

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.

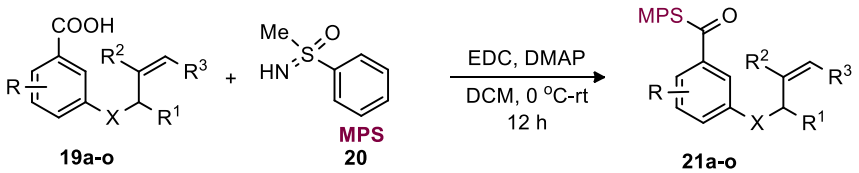
3.7.3. Experimental Procedures and Analytical Data

3.7.3.1. Preparation of carboxylic acid 19a–o: General procedure (GP-1):



Following the above Schemes, corresponding benzoic acid derivatives were prepared and used for the next step. The analytical data of the benzoic acid derivatives are exactly matching with the reported values.

3.7.3.2. Preparation of *N*-Aroyl Sulfoximines (21); General Procedure (GP-2); EDC-coupling:

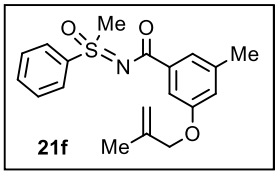


A solution of *N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodimide, hydrochloride salt (EDC.HCl) (1.1 equiv), 4-*N,N*-dimethylaminopyridine (DMAP) (2.2 equiv) and carboxylic acid (1.1 equiv) in CH_2Cl_2 (5.0 mL, for 1.0 mmol of sulfoximine) was

stirred under an argon atmosphere. Sulfoximine (**20**) (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.

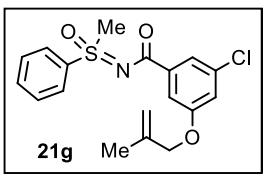
In this chapter we have shown four starting materials (**21f**, **21g**, **21k**, **21l**). The data of other starting materials are available in chapter 2.

***N*-[3-Methyl-5-((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (21f):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**20**, 0.5 g, 3.22 mmol), EDC.HCl (1.23 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-methyl-5-((2-methylallyl)oxy)benzoic acid (0.73 g, 3.54 mmol) afforded **21f** (0.97 g) in 88% yield as colorless solid. m.p. = 128–130 °C; R_f = 0.34 (7:3 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ8.03 (d, J = 8.0 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.63–7.57 (m, 3H), 7.50 (bs, 1H), 6.90 (bs, 1H), 5.09 (s, 1H), 4.98 (s, 1H), 4.44 (s, 2H), 3.44 (s, 3H), 2.35 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ174.1, 158.5, 140.7, 139.0, 136.7, 133.7, 129.6, 127.0, 122.8, 120.1, 112.6, 111.9, 71.7, 44.2, 21.3, 19.3; IR (Neat) ν_{max} 3054, 2923, 1628, 1591, 1449, 1327, 1228, 1157, 1119, 1051 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{22}NO_3S$ $(M+H)^+$: calcd. 344.1320, found 344.1318.

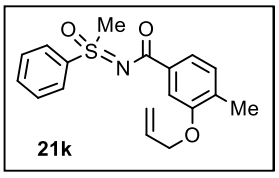
***N*-[3-Chloro-5-((2-methylallyl)oxy)benzoyl]-*S*-methyl-*S*-phenylsulfoximine (21g):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**20**, 0.5 g, 3.22 mmol), EDC.HCl (1.23 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-chloro-5-((2-methylallyl)oxy)benzoic acid (0.802 g, 3.54 mmol) afforded **21g** (1.0 g) in 85% yield as colorless solid. m.p. = 134–137 °C; R_f = 0.35 (7:3 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ8.02 (d, J = 7.0 Hz, 2H), 7.74 (bs, 1H), 7.68 (bt, J = 8.2 Hz, 1H), 7.61 (bt, J = 7.2

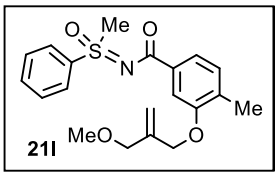
Hz, 2H), 7.57 (bs, 1H), 7.05 (bs, 1H), 5.07 (s, 1H), 4.98 (s, 1H), 4.43 (s, 2H), 3.44 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ172.6, 159.1, 140.1, 138.5, 138.0, 134.4, 133.9, 129.7, 127.0, 122.0, 119.1, 113.5, 113.1, 72.0, 44.3, 19.3; IR (Neat) ν_{max} 3065, 2925, 1627, 1591, 1449, 1327, 1305, 1229, 1120, 1052 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{19}ClNO_3S$ $(M+H)^+$: calcd. 364.0774, found 364.0773.

***N*-[3-(Allyloxy)-4-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoximine (21k):**



Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**20**, 0.5 g, 3.22 mmol), EDC.HCl (1.23 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-(allyloxy)-4-methylbenzoic acid (0.68 g, 3.54 mmol) afforded **21k** (0.90 g) in 84% yield as colorless solid. m.p. = 85–88^{o}C; R_f = 0.43 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.05 (d, J = 7.6 Hz, 2H), 7.73 (dd, J = 7.6, 1.6 Hz, 1H), 7.68 (bt, J = 7.4 Hz, 1H), 7.64–7.57 (m, 3H), 7.17 (d, J = 7.6 Hz, 1H), 6.14–6.01 (m, 1H), 5.43 (dd, J = 17.2, 1.6 Hz, 1H), 5.27 (dd, J = 10.6, 1.4 Hz, 1H), 4.59 (dt, J = 4.8, 1.6 Hz, 2H), 3.46 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.2, 156.4, 139.2, 134.4, 133.7, 133.4, 131.9, 130.1, 129.6, 127.1, 122.1, 117.0, 111.6, 68.7, 44.3, 16.5; IR (Neat) ν_{max} 3065, 3018, 2920, 1625, 1576, 1501, 1448, 1410, 1266, 1224, 1121, 1021 cm^{-1}; **HRMS (ESI)** for $C_{18}H_{20}NO_3S$ $(M+H)^+$: calcd. 330.1164, found 330.1158.

***N*-[3-((2-(Methoxymethyl)allyl)oxy)-4-methylbenzoyl]-*S*-methyl-*S*-phenylsulfoxim-ine (21l):**



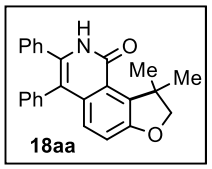
Following the general procedure (GP-2); reaction of *S*-methyl-*S*-phenylsulfoximine (**20**, 0.5 g, 3.22 mmol), EDC.HCl (1.23 g, 6.44 mmol), DMAP (0.863 g, 7.08 mmol) and 3-((2-(methoxymethyl)allyl)oxy)-4-methylbenzoic acid (0.84 g, 3.54 mmol) afforded **21l** (0.93 g) in 77% yield as colorless viscous liquid; R_f = 0.23 (7:3 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ8.06–8.01 (m, 2H), 7.72 (dd, J = 8.0, 1.5 Hz, 1H), 7.67 (tt, J = 7.5, 1.8 Hz, 1H), 7.63–7.57 (m, 3H), 7.17 (d, J = 7.5 Hz, 1H), 5.36 (s, 1H), 5.26 (s, 1H), 4.58 (s, 2H), 4.03 (s, 2H), 3.45 (s, 3H), 3.34 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.1, 156.4, 141.5, 139.2, 134.5, 133.7, 131.8, 130.1, 129.6, 127.1, 122.1, 114.3, 111.5, 73.3, 68.5, 58.0, 44.3, 16.5; IR (Neat) ν_{max} 3065, 2925, 1717, 1626, 1576, 1502,

1449, 1409, 1289, 1223, 1115 cm^{-1}; **HRMS (ESI)** for $C_{20}H_{24}NO_4S$ $(M+H)^+$: calcd. 374.1426, found 374.1424.

3.7.3.3. General Procedure for the Annulation of Dihydrobenzofurans (22) with Unactivated Alkynes (GP-3).

The annulation reactions were conducted in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with **22** (0.5 mmol), alkyne (**14**, 1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.0 mg, 5.0 mol %), and AcOH (30 µL, 0.5 mmol). Subsequently, the additive $AgSbF_6$ (35 mg, 0.1 mmol) was introduced to the flask in a glove box. 1,4-Dioxane (2.0 mL) was added to the mixture and the resulting mixture was stirred at 120 °C for 24 h. The reaction mixture was 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 purified using column chromatography on silica gel (20–30% *n*-hexane/EtOAc eluent) to give the desired product.

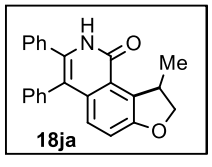
9,9-Dimethyl-3,4-diphenyl-8,9-dihydrofuro[2,3-*h*]isoquinolin-1(2H)-one (18aa):



18aa

18aa (119 mg, 65%) as colorless crystalline solid. m.p. = >350 °C; R_f = 0.50 (7:3 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (bs, 1H), 7.31–7.11 (m, 11H), 7.06 (d, J = 8.8 Hz, 1H), 4.32 (s, 2H), 1.57 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 159.5, 136.7, 135.3, 134.5, 134.4, 134.3, 131.9 (2C), 129.2 (2C), 128.32 (3C), 128.29 (2C), 128.2, 127.5, 127.1, 117.6, 116.2, 86.4, 44.6, 26.7 (2C); IR (Neat) ν_{max} 3117, 3090, 1638, 1594, 1561, 1468, 1336, 1183 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{22}NO_2$ $(M+H)^+$: calcd. 368.1651, found 368.1651.

9-Methyl-3,4-diphenyl-8,9-dihydrofuro[2,3-*h*]isoquinolin-1(2H)-one (18ja):

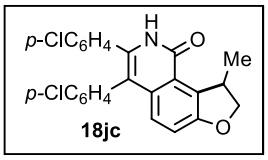


18ja

18ja (136 mg, 77%) as colorless crystalline solid. m.p. = 320–321 °C; R_f = 0.80 (7:3 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 10.03 (bs, 1H), 7.37–7.23 (m, 8H), 7.22–7.15 (m, 3H), 7.09 (d, J = 8.8 Hz, 1H), 4.64 (t, J = 8.4 Hz, 1H), 4.43 (dd, J = 8.6, 2.0 Hz, 1H), 4.26–4.14 (m, 1H), 1.36 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 158.7, 136.5, 135.3, 134.6, 133.6, 132.1, 131.9, 131.8, 129.4 (2C), 128.3, 128.2, 128.1 (3C), 127.1, 126.8, 122.1, 117.6, 115.6,

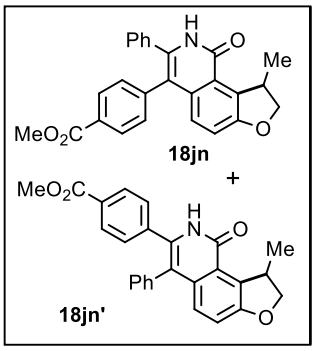
79.7, 37.6, 21.3; IR (Neat) ν_{max} 2914, 2882, 1643, 1572, 1457, 1254, 1084 cm^{-1}; **HRMS (ESI)** for $C_{24}H_{20}NO_2$ $(M+H)^+$: calcd. 354.1494, found 354.1493.

3,4-Bis(4-chlorophenyl)-9-methyl-8,9-dihydrofuro[2,3-*h*]isoquinolin-1(2H)-one (18jc):



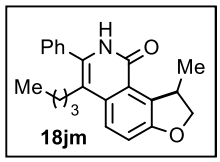
18jc (148 mg, 70%) as yellow solid. m.p. =>300 °C; R_f = 0.50 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, DMSO-D_6) δ 11.42 (bs, 1H), 7.37 (bd, J = 9.6 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.21–7.13 (m, 3H), 6.92 (d, J = 8.8 Hz, 1H), 4.60 (t, J = 8.4 Hz, 1H), 4.39 (dd, J = 8.6, 2.2 Hz, 1H), 4.19 (bt, J = 6.6 Hz, 1H) 1.32 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 158.7, 135.7, 135.3, 134.0 (2C), 133.9, 133.3, 133.0, 132.4, 132.3, 132.2 (2C), 128.9 (2C), 128.3 (2C), 126.5, 122.7, 115.9, 115.4, 79.4, 37.4, 21.7; IR (KBr) ν_{max} 3671, 2914, 1643, 1484, 1397, 1353, 1249, 1150, 1084 cm^{-1}; **MS(EI)** m/z (%) 422 (M^+, 100); 391 (11); Anal. Calcd for $C_{24}H_{17}Cl_2NO_2$: C, 68.26; H, 4.06; N, 3.32. Found: C, 68.15; H, 4.10; N, 3.38.

Methyl 4-(9-methyl-1-oxo-3-phenyl-1,2,8,9-tetrahydrofuro[2,3-*h*]isoquinolin-4-yl) -benzoate [18jn and 13jn′ (1:1)]:



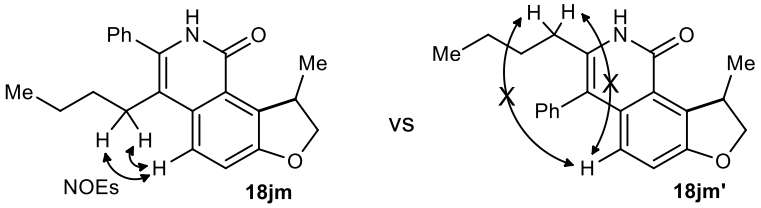
[18jn and 18jn′ (1:1)] (132 mg, 64%) as colorless solid. m.p. = 258–262 °C; R_f = 0.48 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, DMSO-D_6) δ11.48 (bs, 1H), 11.44 (bs, 1H), 7.89–7.82 (m, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.37–7.10 (m, 17H), 6.98 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 4.61 (t, J = 8.4 Hz, 2H), 4.40 (d, J= 8.8 Hz, 2H), 4.21 (bt, J = 7.0 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 1.33 (d, J= 6.8 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-D_6) δ166.5, 166.3, 161.53, 161.50, 158.8, 158.6, 142.5, 139.9, 136.6, 136.5, 135.1, 134.9, 133.2, 132.8, 132.7, 132.31, 132.26, 132.15, 132.13, 130.8, 130.4, 129.5, 129.3, 128.8, 128.6, 128.2, 127.7, 126.8, 126.3, 122.9, 122.7, 117.0, 115.90, 115.86, 115.4, 79.4, 52.7, 52.6, 37.5, 37.4, 21.7; IR (Neat) ν_{max} 2936, 2860, 1720, 1643, 1402, 1271 cm^{-1}; **HRMS (ESI)** for $C_{26}H_{21}NNaO_4$ $(M+Na)^+$: calcd. 434.1368, found 434.1365.

4-Butyl-9-methyl-3-phenyl-8,9-dihydrofuro[2,3-*h*]isoquinolin-1(2H)-one (18jm):



18jm (122 mg, 73%) as colorless viscous liquid. m.p. = 221–225 °C; R_f = 0.80 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (bs, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.53–7.43 (m, 5H), 7.26 (d, J = 8.8 Hz, 1H), 4.64 (t, J = 8.2 Hz, 1H), 4.42 (dd, J = 8.4, 1.6 Hz, 1H), 4.24–4.11 (m, 1H), 2.67–2.57 (m, 2H), 1.63–1.51 (m, 2H), 1.35 (d, J = 6.8 Hz, 3H), 1.33–1.26 (m, 2H), 0.85 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 158.4, 135.8, 134.3, 132.7, 132.6, 129.1 (2C), 128.7, 128.6 (2C), 124.6, 115.6, 114.6, 79.7, 37.7, 32.8, 27.5, 22.7, 21.3, 13.7; IR (KBr) ν_{max} 2957, 2930, 2849, 1664, 1482, 1352, 1244 cm^{-1}; **HRMS (ESI)** for $C_{22}H_{23}NNaO_2$ $(M+Na)^+$: calcd. 334.1087, found 334.1086.

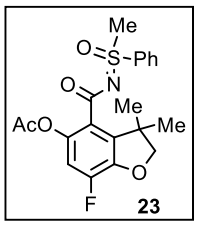
The structure of **18jm** is established with NOESY studies; intramolecular NOEs between alkyl CH_2 (δ = 2.67–2.57 ppm) and the aryl CH (δ = 7.62 ppm) was observed.



3.7.3.4. General Procedure for the C–H Oxidation Reaction (GP-4):

The C(sp^2)–H oxidation was carried out in a 20 mL Schlenk tube with high pressure value and side arm. The tube was charged with dihydrobenzofuran (**22d,** 70 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 10 mol %), $K_2S_2O_8$ (108 mg, 0.4 mmol), AcOH (0.5 mL), and $CHCl_3$ (1.0 mL) in air. The reaction was stirred at 110 °C for 24 h. The reaction mixture was cooled to ambient temperature and the solvents are evaporated under reduced pressure. The crude material was purified using column chromatography on silica gel.

_N_-[5-Acetoxy-7-fluoro-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxyl]-_S_-methyl-_S_-phenylsulfoximine (23):



23 (156 mg, 77%) as yellow viscous liquid; R_f = 0.23 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 2H), 7.71 (bt, J = 7.2 Hz, 1H), 7.63 (t, J = 7.6 Hz, 2H), 6.73 (d, J = 10.4

Hz, 1H), 4.26 (s, 2H), 3.43 (s, 3H), 2.12 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 169.4, 146.6 (d, *J* = 251 Hz), 144.2 (d, *J* = 10 Hz), 141.0 (d, *J* = 8.1 Hz), 138.0, 136.8, 134.1, 129.6 (2C), 127.1 (2C), 124.7 (d, *J* = 3.0 Hz), 110.5 (d, *J* = 20 Hz), 86.4, 44.1 (2C), 25.4, 25.2, 20.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –134.7; IR (Neat) ν_{max} 3062, 2931, 1769, 1632, 1430, 1369, 1287 cm^{-1}; **HRMS (ESI)** for $C_{20}H_{21}FNO_5S$ $(M+H)^+$: calcd. 406.1124, found 406.1121.

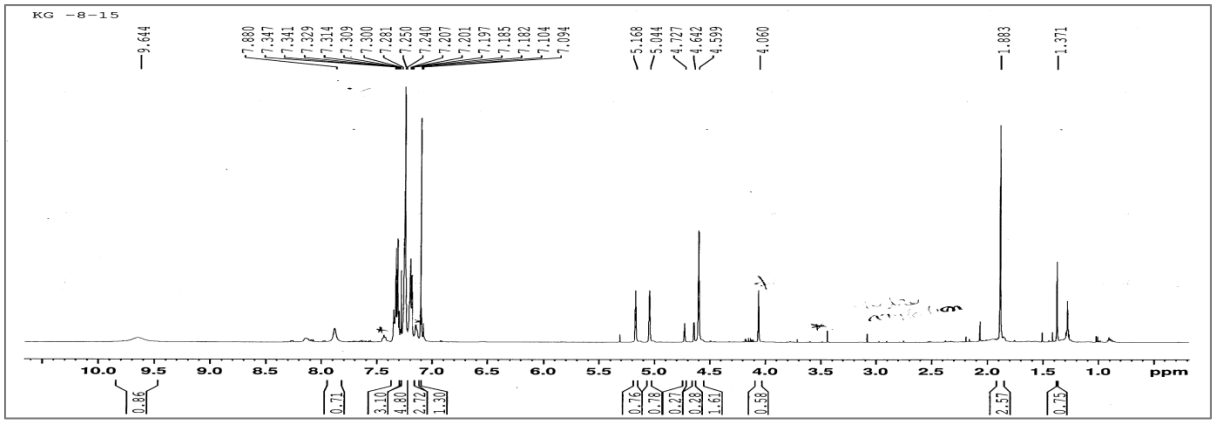
3.7.3.5. Preliminary Study Adopted for the Unsymmetrical Two-fold C–H Functionalization (*Intramolecular Hydroarylation & Intermolecular annulation*) Reaction in Scheme 3.9 (GP-5):

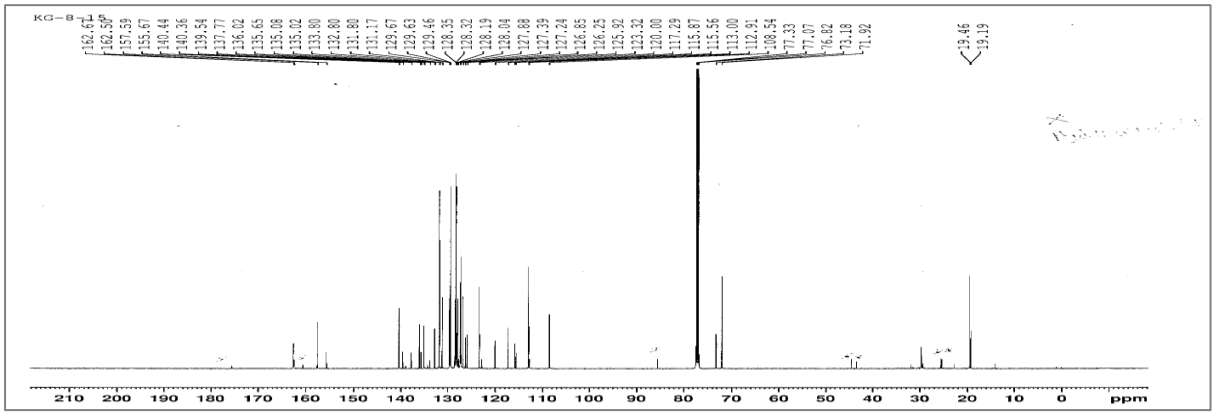
The two fold C–H functionalization reactions were conducted in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with (**21**, 0.25 mmol), alkyne (**14**, 0.30 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (10.0 mg, 6.5 mol %), and $Cu(OAc)_2 \cdot H_2O$ (50.0 mg, 0.25 mmol). Subsequently, the additive $AgSbF_6$ (26.0 mg, 0.075 mmol) was introduced to the flask in a glove box. 1,2-Dichloroethene (DCE; 2.0 mL) was added to the mixture and the resulting mixture was stirred at room temparature for 12–16 h followed by heating the resulting mixture at 100˚C for 10-12 h. The reaction mixture was 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 purified using column chromatography on silica gel (10–30% *n*-hexane/EtOAc eluent) to give the desired product.

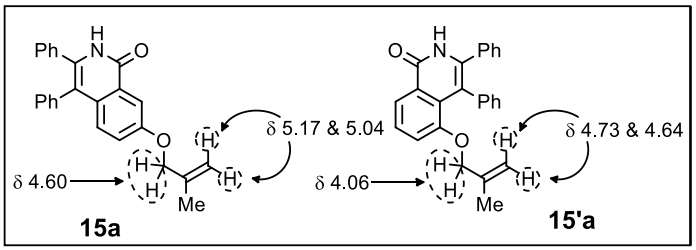
Reactioon between 21a and 14a:

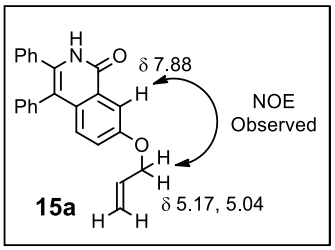
Following the GP-5, the reaction between **21a** and **14a** was conducted. The formation of the corresponding annulation products **15a** (49%) and **15′a** (12%) along with the trace amount of hydroarylation product **22a** (<5%) was detected in the crude NMR.

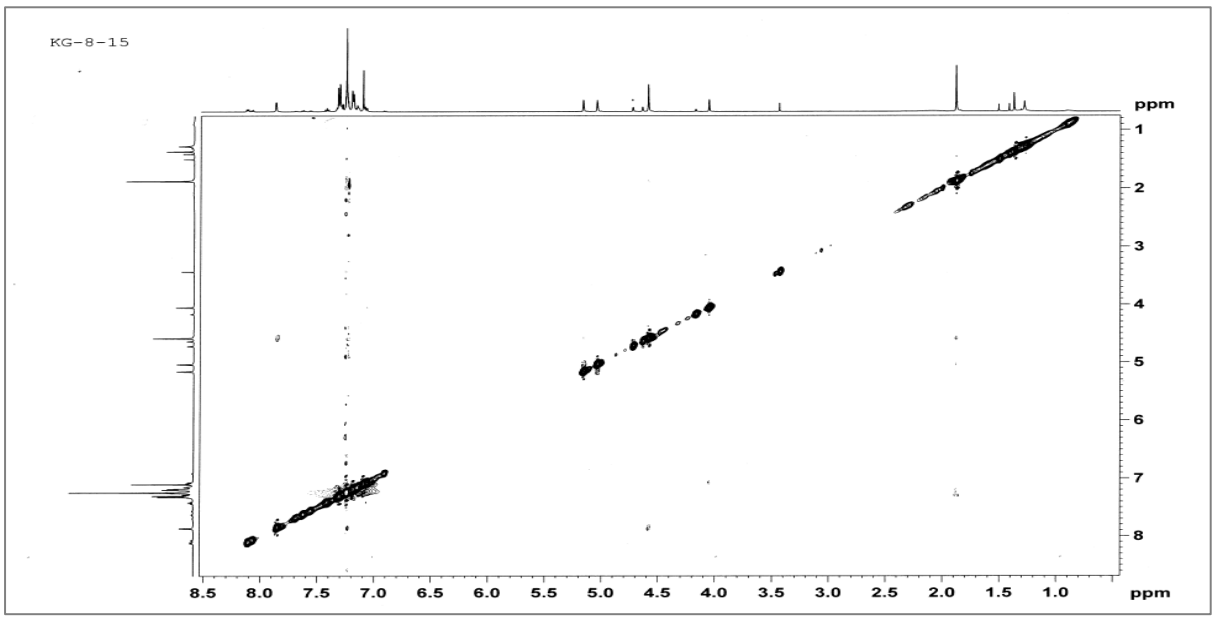
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.88 (s, 1H), 7.20-7.09 (m, 10H), 5.19 (s, 1H), 5.04 (s, 1H), 4.63 (s, 2H), 3.92 (s, 3H), 3.13 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 162.5, 157.6, 155.7, 140.44, 140.36, 139.5, 137.8, 136.0, 135.1, 135.0, 133.8, 132.8, 131.8, 13.2, 29.7, 129.67, 129.63, 129.5, 128.35, 128.32, 128.2, 128.0, 127.9, 127.4, 127.2, 126.8, 126.2, 125.9, 23.3, 120.0, 117.3, 115.9, 115.6, 113.0, 112.9, 108.5, 73.2, 71.9, 19.5, 19.2.


KG -8-15
9.644
7.880
7.347
7.341
7.329
7.314
7.309
7.300
7.281
7.250
7.240
7.207
7.201
7.197
7.185
7.182
7.104
7.094
5.168
5.044
4.727
4.642
4.599
4.060
1.883
1.371
ppm


KG-8-15
ppm


Ph
Ph
O
δ 5.17 & 5.04
δ 4.60
Me
15a
δ 4.73 & 4.64
δ 4.06
15'a


δ 7.88
NOE
Observed
15a
δ 5.17, 5.04

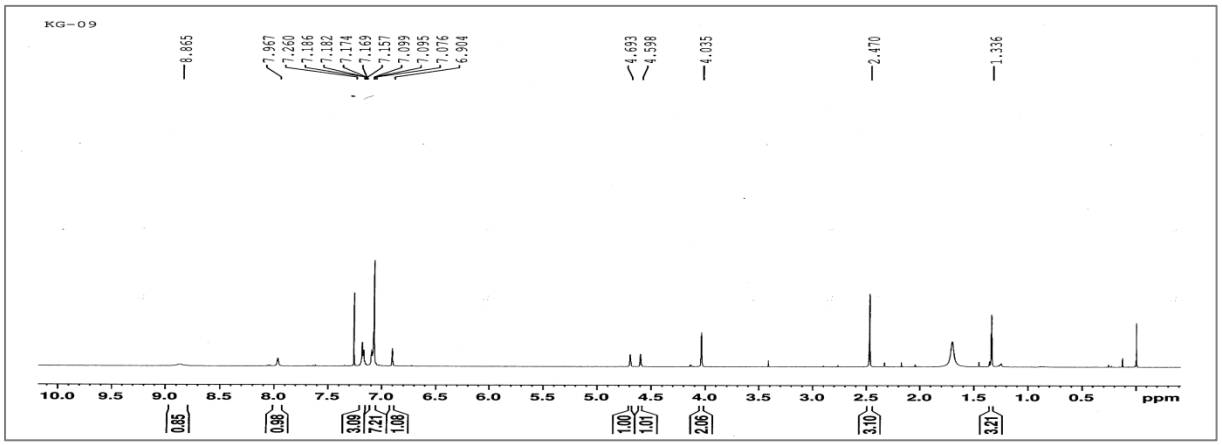

KG-8-15
ppm

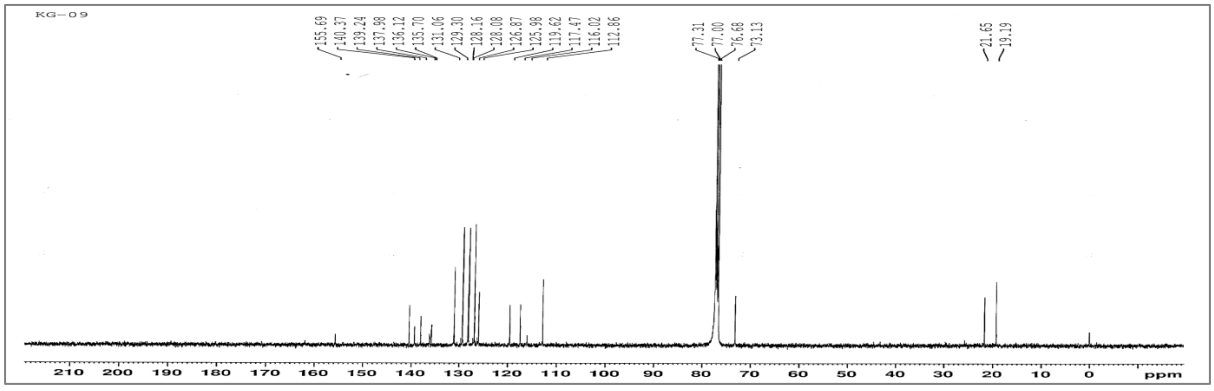
Reaction between 21f and 14a:

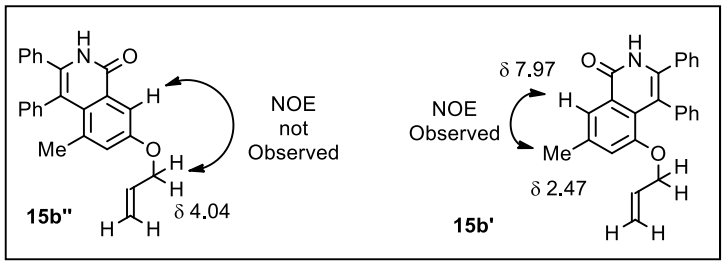
Following the GP-5, the reaction between **21f** and **14a** provided the corresponding annulation product **15′b** (42%).

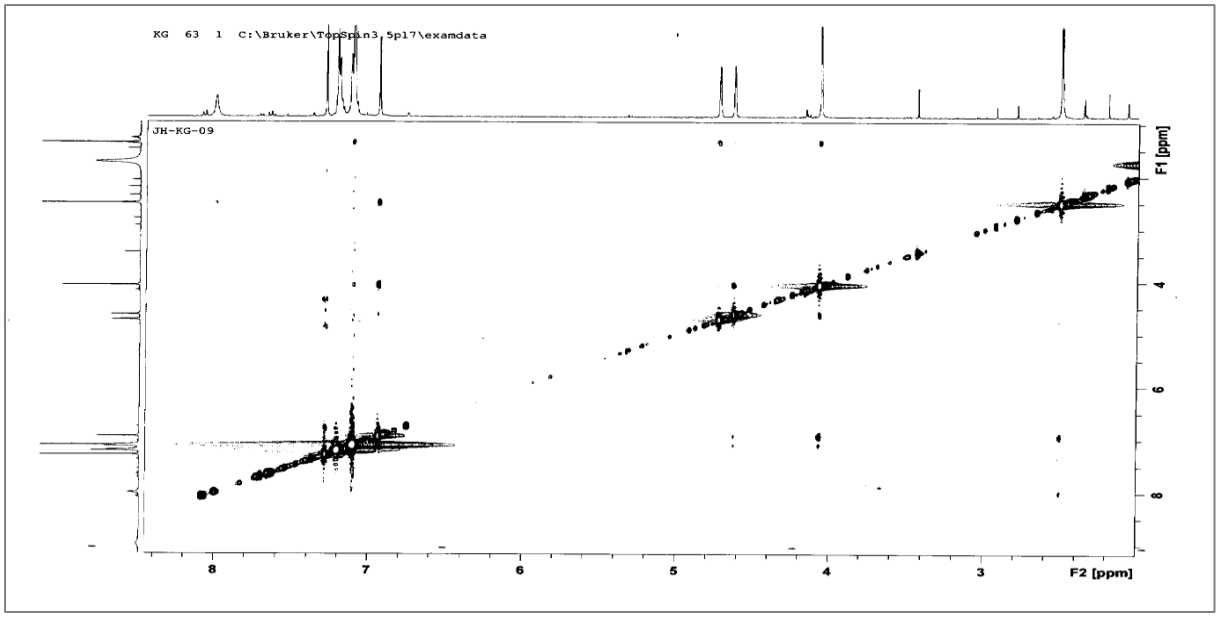
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (bs, 1H), 7.97 (bs, 1H), 7.21–7.14 (m, 3H), 7.12–7.06 (m, 7H), 6.90 (s, 1H), 4.69 (s, 1H), 4.60 (s, 1H), 4.04 (s, 2H), 2.47 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 140.4, 139.2, 138.0, 136.1, 135.7, 131.1, 129.3, 128.2, 128.1, 126.9, 126.0, 119.6, 117.5, 116.0, 112.9, 73.1, 21.7, 19.2.



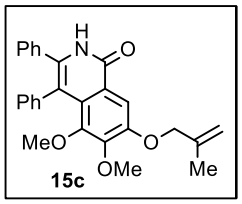




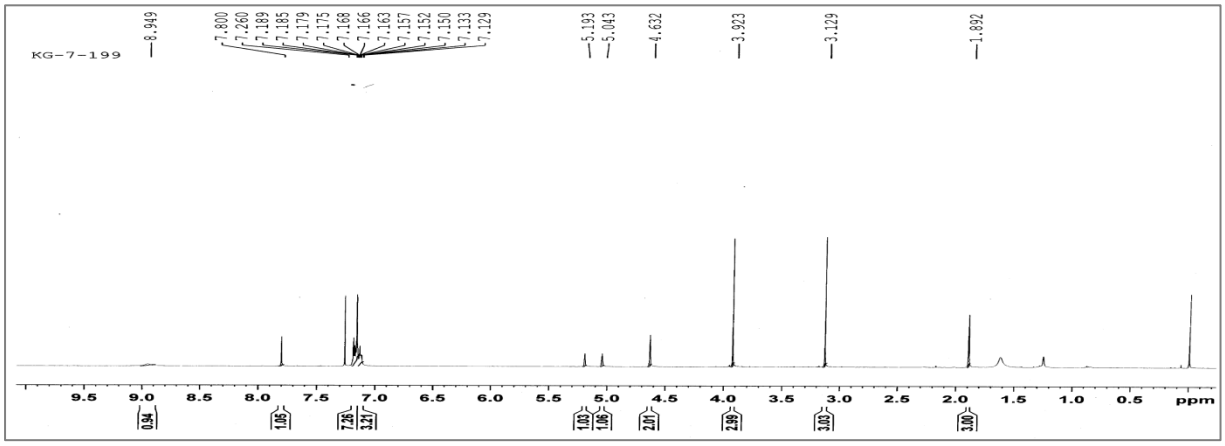


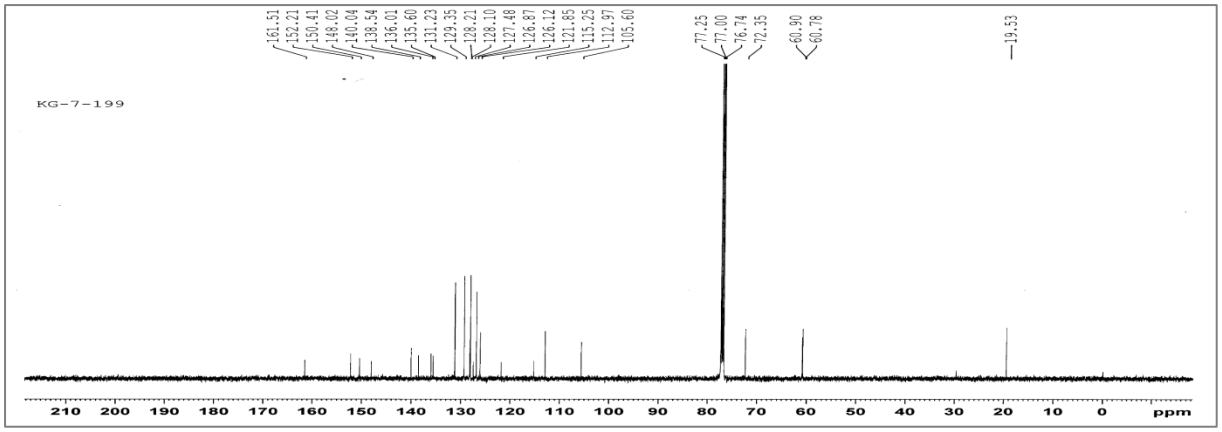
Reaction between 21i and 14a:

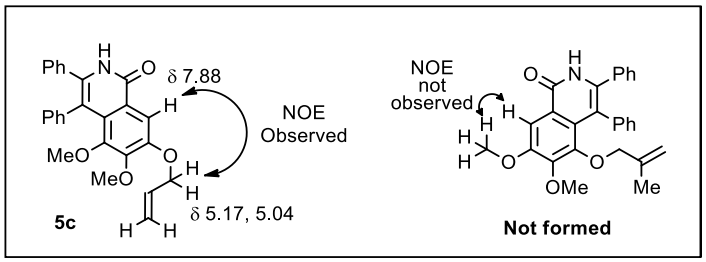
Following the GP-5, the reaction between **21i** and **14a** provided the corresponding di-annulation products **18ia** (16%) and **15c** (27%). Both the compounds were purified by column chromatography eluting with 15% EtOAc:hexane mixture.

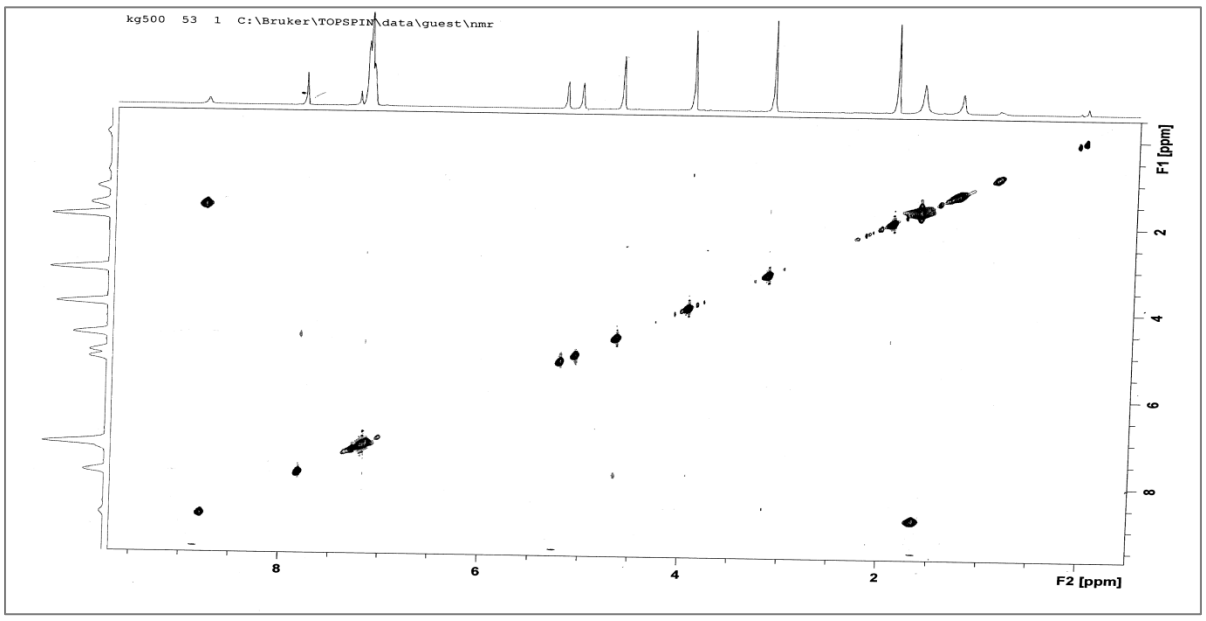


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.80 (s, 1H), 7.20–7.09 (m, 10H), 5.19 (s, 1H), 5.04 (s, 1H), 4.63 (s, 2H), 3.92 (s, 3H), 3.13 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ161.5, 152.2, 150.4, 148.0, 138.5, 136.0, 135.6, 131.2, 129.3, 128.2, 128.1, 127.5, 126.9, 126.1, 121.8, 115.2, 113.0, 105.6, 72.3, 60.9, 60.8, 19.5.







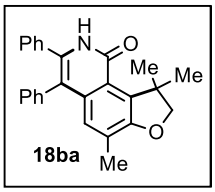


3.7.3.6. General Procedure for the Unsymmetrical Two-fold C–H Functionalization (*Intramolecular Hydroarylation & Intermolecular Annulation*) Reaction (GP-6):

The two fold C–H functionalization reactions were conducted in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with (**21**, 0.25 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (10.0 mg, 6.5 mol %), and Cu(OAc)$_2$·H_2O (50.0 mg, 0.25 mmol). Subsequently, the additive $AgSbF_6$ (26.0 mg, 0.075 mmol) was introduced to the flask in a glove box. 1,2-Dichloroethene (DCE; 2.0 mL) was added to the mixture

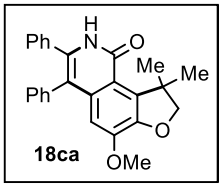
and the resulting mixture was stirred at room temperature for 2–4 h followed by addition of alkyne (**14**, 0.30 mmol); the resulting mixture was then heated at 100°C for 10-12 h. The reaction mixture was filtered through a plug of Celite and washed with dichloromethane (3 × 5.0 mL). The solvents were evaporated under the reduced pressure and the crude material was purified using column chromatography on silica gel (10–30% *n*-hexane/EtOAc eluent) to give the desired product.

6,9,9-Trimethyl-3,4-diphenyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18ba):



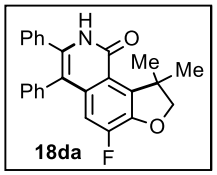
18ba (0.069 gm) 73% yield as colorless solid. m.p. = >360 °C; R_f = 0.48 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ11.21 (bs, 1H), 7.32–7.22 (m, 3H), 7.19 (bs, 5H), 7.11 (d, J = 6.4 Hz, 2H), 6.79 (bs, 1H), 4.32 (bs, 2H), 2.11 (s, 3H), 1.60 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ160.9, 157.8, 137.3, 136.1, 135.2, 134.5, 133.3, 132.3, 130.2, 128.7, 128.3, 128.1, 127.4, 127.1, 126.4, 121.7, 116.1, 85.7, 44.9, 27.1, 16.4; IR (KBr) ν_{max} 2863, 1634, 1469, 1433, 1381, 1340, 1081, 1035 cm^{-1}; **HRMS (ESI)** for $C_{26}H_{24}NO_2$ $(M+H)^+$: calcd. 382.1807, found 382.1803.

6-Methoxy-9,9-dimethyl-3,4-diphenyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18ca):



18ca (0.07 g) in 70% yield as colorless solid. m.p. = >351–354 °C; R_f = 0.33 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ11.02 (bs, 1H), 7.34–7.24 (m, 3H), 7.21 (bs, 5H), 7.16 (d, J = 6.8 Hz, 2H), 6.51 (s, 1H), 4.33 (s, 2H), 3.56 (s, 3H), 1.62 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ160.5, 148.6, 148.5, 137.3, 137.0, 136.3, 135.3, 135.2, 132.2, 130.2, 128.7, 128.3, 128.1, 127.5, 117.0, 116.1,107.1, 86.2, 55.5, 45.2, 27.0; IR (Neat) ν_{max} 2920, 1634, 1593, 1453, 1417, 1293, 1216, 1174, 1097 cm^{-1}; **HRMS (ESI)** for $C_{26}H_{24}NO_3$: $(M+H)^+$: calcd. 398.1756, found 398.1754.

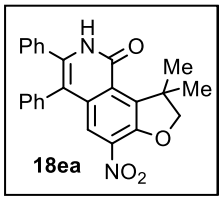
6-Fluoro-9,9-dimethyl-3,4-diphenyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18da):



18da (0.080 g) in 83% yield as colorless solid.m.p. => 365 °C; R_f = 0.54 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ9.86 (bs, 1H), 7.33–7.27 (m, 3H), 7.25–7.18 (m, 5H), 7.14–7.09 (m, 2H), 6.91 (d, J = 9.6 Hz, 1H), 4.41 (s, 2H), 1.54 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ161.0, 151.1

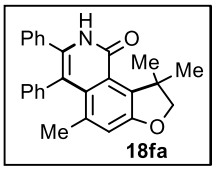
(d, J = 254 Hz), 147.1 (d, J = 12 Hz), 138.7 (d, J = 4.0 Hz), 136.3, 136.2, 136.0, 134.9, 131.7, 129.3, 129.2, 128.4, 128.3, 127.4, 119.3 (d, J = 3.0 Hz), 117.1 (d, J = 3.0 Hz), 112.4 (d, J = 18 Hz), 87.6, 45.5, 26.5; ^{19}F NMR (376 Hz): –129.1; IR (KBr) ν_{max} 2915, 2848, 1737, 1639, 1603, 1489, 1417, 1334, 1257 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{21}FNO_2$ $(M+H)^+$: calcd. 386.1556, found 386.1554.

9,9-Dimethyl-6-nitro-3,4-diphenyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18ea):



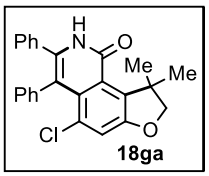
18ea (0.066 g) in 64% yield as brown solid. m.p. =>365 ^{o}C; R_f = 0.30 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, DMSO-d$_6$ + CDCl$_3$) δ 11.68 (bs, 1H), 7.67 (s, 1H), 7.37–7.27 (m, 3H), 7.23 (bs, 5H), 7.20–7.15 (m, 2H), 4.54 (s, 2H), 1.65 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ160.0, 152.4, 140.9, 138.2, 136.1, 136.0, 134.5, 134.0, 132.2, 130.2, 129.0, 128.8, 128.2, 128.0, 127.1, 122.1, 115.7, 87.6, 44.8, 26.4; IR (Neat) ν_{max} 3168, 2915, 1644, 1520, 1438, 1329, 1236, 1035 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{20}N_2NaO_4$: $(M+Na)^+$: calcd. 435.1321, found 435.1314.

5,9,9-Trimethyl-3,4-diphenyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18fa):



18fa (0.038 g) in 40% yield as colorless crystalline solid. m.p. => 354–357 ^{o}C; R_f = 0.67 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, THF-d$_8$) δ 10.50 (bs, 1H), 7.16–7.11 (m, 5H), 7.11–7.07 (m, 3H), 7.07–7.03 (m, 2H), 6.87 (s, 1H), 4.23 (s, 2H), 1.70 (s, 3H), 1.62 (s, 6H); ^{13}C NMR (101 MHz, CDCl$_3$) δ160.7, 159.2, 146.5, 140.4, 136.6, 136.5, 132.24, 132.18, 132.1, 129.8, 127.4, 127.24, 127.22, 126.2, 125.4, 119.4, 115.7, 85.9, 45.1, 25.9, 24.8; IR (Neat) ν_{max} 2941, 1643, 1587, 1448, 1364, 1092, 1024 cm^{-1}; **HRMS (ESI)** for $C_{26}H_{24}NO_2$ $(M+H)^+$: calcd. 382.1807, found 382.1807.

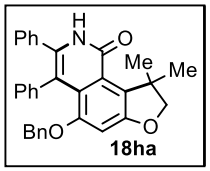
5-Chloro-9,9-dimethyl-3,4-diphenyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18ga):



18ga (0.061 g) in 61% yield as colorless solid. m.p.=> 350–352^{o}C; R_f = 0.58 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ10.59 (bs, 1H), 7.22–7.17 (m, 3H), 7.16 (s, 1H), 7.15–7.07 (m, 5H), 7.05–6.98 (m, 2H), 4.24 (s, 2H), 1.37 (s, 6H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 161.1, 159.2, 138.2, 137.1, 137.0, 135.3, 134.4, 132.1, 131.6, 130.1, 129.5, 128.0, 127.2, 126.5, 125.4, 119.8, 115.8,

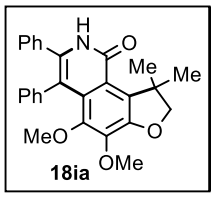
86.6, 45.1, 26.2; IR (KBr) ν_{max} 3044, 2951, 2920, 1639, 1577, 1437, 1370, 1241, 1122 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{21}NO_2$ $(M+H)^+$: calcd. 402.1261, found 402.1255.

5-(Benzyloxy)-9,9-dimethyl-3,4-diphenyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18ha):



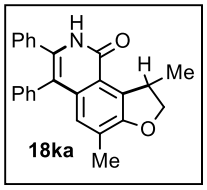
18ha (0.048 g) in 41% yield as colorless solid. m.p. => 349–352 °C; R_f = 0.46 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ11.18 (bs, 1H), 7.22–7.10 (m, 6H), 7.10–7.03 (m, 2H), 7.00–6.94 (m, 2H), 6.93–6.79 (m, 6H), 4.64 (s, 2H), 4.25 (s, 2H), 1.57 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ160.5, 159.8, 156.4, 140.6, 136.5, 136.4, 135.8, 131.2, 130.4, 128.4, 127.9, 127.83, 127.79, 127.7, 126.8, 125.7, 125.5, 125.1, 123.6, 114.4, 100.9, 86.0, 70.6, 44.8, 27.3; IR (KBr) ν_{max} 2920, 2848, 1644, 1593, 1448, 1329, 1293, 1076 cm^{-1}; **HRMS (ESI)** for $C_{32}H_{28}NO_3$ $(M+H)^+$: calcd. 474.2069, found 474.2067.

5,6-Dimethoxy-9,9-dimethyl-3,4-diphenyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18ia):



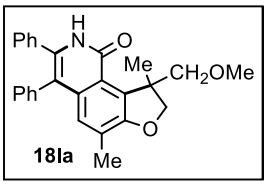
18ia (0.052 g) in 49% yield as colorless solid. m.p. = 194–197 °C; R_f = 0.32 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (bs, 1H), 7.16–7.12 (m, 3H), 7.12–7.01 (m, 7H), 4.33 (s, 2H), 3.97 (s, 3H), 3.75 (s, 3H), 1.59 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 148.8, 149.0, 139.5, 139.3, 135.8, 135.7, 131.9, 131.0, 129.4, 127.97, 127.95, 126.7, 125.7, 115.3, 114.1, 86.9, 60.7, 60.4, 45.3, 26.6; IR (KBr) ν_{max} 2923, 1637, 1584, 1432, 1102, 1071 cm^{-1}; **HRMS (ESI)** for $C_{27}H_{25}NNaO_4$ $(M+Na)^+$: calcd. 428.1862, found 428.1865.

6,9-Dimethyl-3,4-diphenyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18ka):



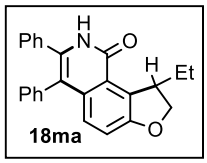
18ka (0.054 g) in 59% yield as colorless solid. m.p. => 204–208 °C; R_f = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ9.97 (bs, 1H), 7.20–7.04 (m, 10H), 6.84 (bs, 1H), 4.52 (bt, J = 8.4 Hz, 1H), 4.35–4.29 (m, 1H), 4.13–4.06 (m, 1H), 2.12 (s, 3H), 1.25 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$ + DMSO-d_6) 161.9, 157.2, 136.5, 135.2, 134.5, 133.4, 131.7, 131.6, 130.8, 129.2, 128.0, 127.8, 126.8, 126.6, 126.4, 120.0, 117.0, 79.3, 37.6, 21.1, 15.8; IR (Neat) ν_{max} 2928, 1638, 1443, 1355, 1293, 1152 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{22}NO_2$ $(M+H)^+$: calcd. 368.1651, found 368.1650.

9-(Methoxymethyl)-6,9-dimethyl-3,4-diphenyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18la):



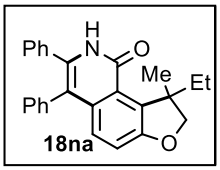
18la (0.076 g) in 74% yield as colorless solid; m.p. => 285–288 °C; R_f = 0.37 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (bs, 1H), 7.31–7.27 (m, 3H), 7.24–7.17 (m, 5H), 7.15–7.11 (m, 2H), 6.99 (d, J = 0.4 Hz, 1H), 4.74 (d, J = 6.8 Hz, 1H), 4.27 (d, J = 6.8 Hz, 1H), 4.05 (bd, J = 6.8 Hz, 1H), 3.67 (d, J = 6.8 Hz, 1H), 3.30 (s, 3H), 2.19 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 159.3, 136.8, 135.4, 134.4, 134.3, 131.9, 129.3, 129.2, 128.3, 128.2, 128.14, 128.12, 127.3, 127.1, 121.4, 117.5, 82.3, 77.7, 59.3, 49.6, 23.2, 16.2; IR (KBr) ν_{max} 3158, 2920, 1629, 1433, 1329, 1293, 1190, 1107, 1076 cm^{-1}; **HRMS (ESI)** for $C_{27}H_{26}NO_3$ $(M+H)^+$: calcd. 412.1913, found 412.1911.

9-Ethyl-3,4-diphenyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18ma):



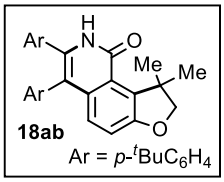
18ma (0.064 g) in 70% yield as colorless solid. m.p. => 290–293 °C; R_f = 0.42 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.27 (bs, 1H), 7.32–7.22 (m, 3H), 7.20 (bs, 5H), 7.17–7.09 (m, 3H), 6.94 (d, J = 8.4 Hz, 1H), 4.57–4.51 (m, 2H), 4.13–4.05 (m, 1H), 1.92–1.82 (m, 1H), 1.62–1.51 (m, 1H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.5, 158.8, 137.0, 136.1, 135.3, 133.5, 132.19, 132.16, 130.4, 130.3, 128.7, 128.6, 128.3, 128.1, 127.4, 126.6, 122.8, 116.3, 115.5, 76.5, 43.9, 27.6, 11.4; IR (KBr) ν_{max} 3018, 2920, 2858, 1639, 1593, 1484, 1345, 1247, 1148 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{22}NO_2$ $(M+H)^+$: calcd. 368.1651, found 368.1656.

9-Ethyl-9-methyl-3,4-diphenyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18na):



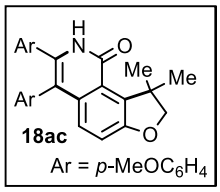
18na (0.063 g) in 66% yield as colorless solid. m.p. => 330–333 °C; R_f = 0.51; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (bs, 1H), 7.33–7.27 (m, 3H), 7.24 (bs, 5H), 7.23–7.13 (m, 3H), 7.06 (d, J = 8.8 Hz, 1H), 4.49 (d, J = 8.4 Hz, 1H), 4.25 (d, J = 8.8 Hz, 1H), 2.39–2.29 (m, 1H), 1.64–1.56 (m, 1H), 1.54 (s, 3H), 0.74 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 136.8, 135.2, 134.4, 132.2, 131.9, 129.2, 129.1, 128.33, 128.27, 128.25, 128.16, 127.5, 127.1, 117.6, 116.0, 115.9, 83.5, 48.7, 31.3, 26.2, 9.6; IR (KBr) ν_{max} 3158, 2920, 1649, 1598, 1463, 1329, 1272, 1247 cm^{-1}; **HRMS (ESI)** for $C_{26}H_{24}NO_2$ $(M+H)^+$: calcd. 382.1807, found 382.1807.

3,4-Bis(4-(*tert*-butyl)phenyl)-9,9-dimethyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18ab):



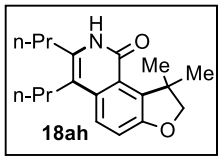
18ab (0.090 g) in 75% yield as colorless solid. R_f = 0.57 (8:2 hexane/EtOAc); m.p => 331–334 °C; ^{1}H NMR (500 MHz, THF-d_8) δ10.48 (bs, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 8.5 Hz, 3H), 7.08 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 9.0 Hz, 1H), 4.31 (s, 2H), 1.67 (s, 6H), 1.33 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, THF-d_8) δ159.3, 150.4, 149.4, 135.5, 134.7, 134.55, 134.47, 133.8, 133.0, 132.5, 131.6, 129.2, 127.0, 124.7, 124.3, 115.9, 115.1, 86.0, 44.5, 34.14, 34.12, 30.7, 30.5, 26.2; IR (KBr) ν_{max} 2961, 1638, 1465, 1263, 1100, 1084 cm^{-1}; **HRMS (ESI)** for $C_{33}H_{38}NO_2$ $(M+H)^+$: calcd. 480.2903, found 480.2907.

3,4-Bis(4-methoxyphenyl)-9,9-dimethyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18ac):



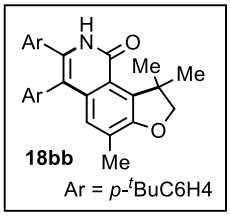
18ac (0.066 g) in 62% yield as colorless solid. m.p. => 358–361 °C; R_f = 0.35 (8:2 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ9.81 (bs, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.16–7.11 (m, 2H), 7.07–7.02 (m, 3H), 6.86–6.81 (m, 2H), 6.77–6.73 (m, 2H), 4.30 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ161.6, 159.22, 159.16, 158.5, 135.0, 134.4, 134.1, 132.9, 130.4, 129.0, 127.7, 127.3, 122.9, 116.8, 116.1, 113.8, 113.7, 86.4, 55.2, 44.6, 26.7; IR (KBr) ν_{max} 3059, 2951, 2920, 1634, 1505, 1458, 1329, 1241, 1179, 1004 cm^{-1}; **HRMS (ESI)** for $C_{27}H_{26}NO_4$ $(M+H)^+$: calcd. 428.1862, found 428.1861.

9,9-Dimethyl-3,4-dipropyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18ah):



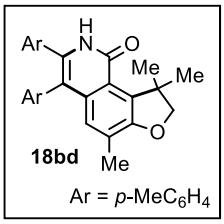
18ah (0.061 g) in 82% yield as colorless solid. m. p. => 212–214 °C; R_f = 0.68 (8:2 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ11.95 (bs, 1H), 7.57 (d, J = 9.2 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 4.33 (s, 2H), 2.69 (q, J = 8.0 Hz, 4H), 1.83–1.72 (m, 2H), 1.71 (s, 6H), 1.68–1.53 (m, 2H), 1.04 (t, J = 7.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ162.8, 158.4, 135.5, 134.3, 134.0, 124.4, 123.2, 116.1, 113.0, 86.2, 44.8, 32.4, 29.3, 26.9, 23.5, 23.0, 14.3, 13.9; IR (Neat) ν_{max} 2951, 2868, 1644, 1463, 1355, 1267, 1128, 1004 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{26}NO_2$ $(M+H)^+$: calcd. 300.1964, found 300.1966.

3,4-Bis(4-(*tert*-butyl)phenyl)-6,9,9-trimethyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18bb):



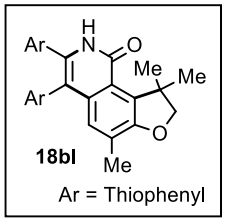
18bb (0.097 g) in 79% yield as colorless solid.m.p. => 360 ˚C; R_f = 0.68 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.91 (s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.08–7.02 (m, 5H), 4.34 (s, 2H), 2.22 (s, 3H), 1.63 (s, 6H), 1.32 (s, 9H), 1.25 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ161.2, 158.2, 151.0, 149.9, 134.8, 134.3, 133.9, 133.3, 132.6, 131.5, 128.6, 127.7, 127.1, 125.0, 121.1, 117.1, 86.3, 44.9, 34.53, 34.51, 31.3, 31.1, 26.9, 16.1; IR (Neat) ν_{max} 2951, 1634, 1453, 1324, 1200, 1107, 885 cm^{-1}; **HRMS (ESI)** for $C_{34}H_{40}NO_2$ $(M+H)^+$: calcd. 494.3059, found 494.3059.

6,9,9-Trimethyl-3,4-di-*p*-tolyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18bd):



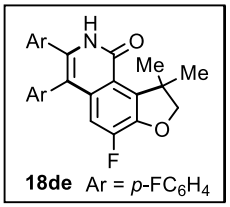
18bd (0.079 g) in 77% yield as colorless solid. m.p. => 318-321 °C; R_f = 0.58 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (bs, 1H), 7.13–7.05 (m,4H), 7.05–6.99 (m, 4H), 6.98 (s, 1H), 4.32 (s, 2H), 2.35 (s, 3H), 2.29 (s, 3H), 2.20 (s, 3H), 1.56 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 161.5, 158.1, 137.7, 136.5, 134.9, 134.5, 133.9, 133.2, 132.7, 131.7, 129.0, 127.5, 127.0, 121.0, 117.0, 86.2, 44.8, 26.8, 21.3, 21.2, 16.1; IR (KBr) ν_{max} 3287, 3152, 2920, 1644, 1515, 1543, 1257 cm^{-1}; **HRMS (ESI)** for $C_{28}H_{28}NO_2$ $(M+H)^+$: calcd. 410.2120, found 410.2124.

6,9,9-trimethyl-3,4-di(thiophen-2-yl)-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18bl):



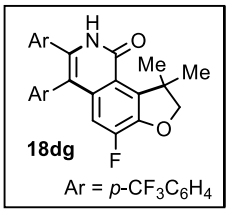
18bl (0.039 g) in 40% yield as colorless solid. High melting; R_f = 0.42 (3:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ9.76 (bs, 1H), 7.50 (dd, J = 4.4, 0.8 Hz, 1H), 7.32–7.26 (m, 2H), 7.17 (dd, J = 4.4, 2.8 Hz, 1H), 7.05 (s, 1H), 7.04 (dd, J = 2.8, 0.8 Hz, 1H), 7.02–6.97 (m, 1H), 4.35 (s, 2H), 2.25 (s, 3H), 1.61 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 158.7, 137.3, 136.3, 135.1, 133.4, 130.8, 130.4, 128.2, 127.74, 127.70, 127.5, 127.4, 127.1, 126.7, 120.9, 109.2, 86.3, 44.8, 26.7, 16.2; IR (Neat) ν_{max} 3152, 2961, 1639, 1433, 1252, 1061, 694 cm^{-1}; **HRMS (ESI)** for $C_{22}H_{20}NO_2S_2$ $(M+H)^+$: calcd. 394.0935, found 394.0932.

6-Fluoro-3,4-bis(4-fluorophenyl)-9,9-dimethyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18de):



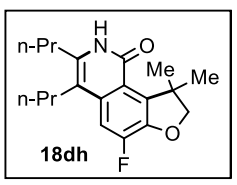
18de (0.086 g) in 81% yield as colorless solid; R_f = 0.44 (8:2 hexane/EtOAc); m. p. => 350 °C; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ11.50 (bs, 1H), 7.29–7.22 (m, 2H), 7.21–7.12 (m, 4H), 7.12–7.04 (m, 2H), 6.70 (d, J = 15.5 Hz, 1H), 4.44 (s, 2H), 1.62 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ162.1 (J = 247 Hz), 161.7 (J = 245 Hz), 160.3, 150.4 (J = 252 Hz), 146.5 (J = 12.1 Hz), 139.2 (J = 4.0 Hz), 137.1, 135.9 (J = 7.1 Hz), 134.1 (J = 8.1 Hz), 132.8 (J = 4.0 Hz), 132.5 (J = 9.1 Hz), 131.2 (J = 3.0 Hz), 120.1, 115.8 (J = 21 Hz), 115.2 (J = 22 Hz), 114.9 (J = 2.0 Hz), 111.7 (J = 18 Hz), 87.1, 45.6, 26.6; F^{19} NMR (126 MHz, CDCl3) δ –129.89, –114.65, –113.13; IR (Neat) ν_{max} 3152, 2956, 2920, 1634, 1505, 1448, 1334, 1216, 1154, 1086 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{19}F_3NO_2$ $(M+H)^+$: calcd. 422.1368, found 422.1369.

6-Fluoro-9,9-dimethyl-3,4-bis(4-(trifluoromethyl)phenyl)-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18dg):



18dg (0.075 g) in 58% yield as colorless solid. m.p. => 350°C R_f = 0.68 (8:2 hexane/EtOAc); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 11.66 (bs, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.45 (m, J = 8.0 Hz, 2H), 7.41 (d, J = 7.5 Hz, 2H), 6.67 (d, J = 12 Hz, 1H), 4.46 (s, 2H), 1.63 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 157.8, 149.1, 147.1, 144.5, 144.4, 138.4, 137.02, 137.00, 136.2, 134.3, 132.7, 132.6, 130.7, 128.8, 127.1, 126.8, 126.6, 126.5, 126.2, 126.0, 125.7, 123.39, 123.36, 123.25, 123.1, 122.70, 122.68, 121.1, 120.9, 117.9, 112.6, 109.4, 109.3, 84.8, 43.2, 24.2; ^{19}F NMR (376 MHz, CdCl$_3$): –61.02, –61.21, –129.57; IR (Neat) ν_{max} 2920, 1639, 1613, 1453, 1319, 1164 cm^{-1}; **HRMS (ESI)** for $C_{27}H_{19}F_7NO_2$ $(M+H)^+$: calcd. 522.1304, found 522.1303.

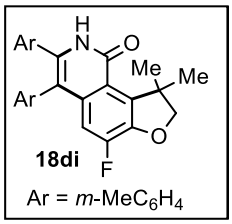
6-Fluoro-9,9-dimethyl-3,4-dipropyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18dh):



18dh (0.067 g) in 85% yield as colorless solid. m.p. => 257 °C; R_f = 0.60 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ12.00 (s, 1H), 7.29 (s, 1H), 4.43 (s, 2H), 2.68 (t, J = 7.8 Hz, 2H), 2.62 (t, J = 8.0 Hz, 2H), 1.82–1.72 (m, 2H), 1.71 (bs, 6H), 1.65–1.52 (m, 2H), 1.08–0.99 (m, 6H); ^{13}C

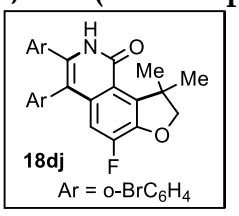
NMR (101 MHz, $CDCl_3$) δ162.2, 151.3 (d, J = 253.3 Hz), 146.1 (d, J = 12.1 Hz), 138.4 (d, J = 4 Hz), 137.0, 136.1 (d, J = 8.1 Hz), 119.3, 112.6 (d, J = 4.0 Hz), 109.5 (d, J = 17.2 Hz), 87.4, 45.8, 32.4, 29.4, 26.7, 23.3, 23.0, 14.3, 13.9; IR (KBr) ν_{max} 3168, 2956, 2930, 1644, 1500, 1453, 1340, 1272, 1164, 1045 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{25}FNO_2$ $(M+H)^+$: calcd. 318.1869, found 318.1866.

6-Fluoro-9,9-dimethyl-3,4-di-*m*-tolyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18di):



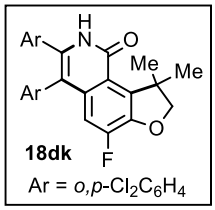
18di (0.065 g) in 63% yield as colorless viscous liquid. m.p. => 288–291 °C. R_f = 0.59 (8:2 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.14 (bs, 1H), 7.16 (t, J = 7.7 Hz, 1H), 7.12–6.98 (m, 5H), 6.95–6.87 (m, 3H), 4.36 (s, 2H), 2.28 (s, 3H), 2.24 (s, 3H), 1.38 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ161.4, 151.0 (d, J = 253.3 Hz), 146.9 (d, J = 11.3 Hz), 138.4 (d, J = 3.8 Hz), 137.8, 137.6, 136.4 (d, J = 7.6 Hz), 136.2, 134.7, 132.3, 130.0, 129.0, 128.7, 128.2, 127.99, 127.96, 126.5, 119.1, 117.3 (d, J =2.5 Hz), 112.3 (d, J =17.6 Hz), 87.5, 45.4, 26.4, 21.3; ^{19}F NMR (376 MHz, $CdCl_3$): –129.24; IR (Neat) ν_{max} 3158, 2920, 1644, 1598, 1453, 1334, 1169, 1086 cm^{-1}; **HRMS (ESI)** for $C_{27}H_{25}FNO_2$ $(M+H)^+$: calcd. 414.1869, found 414.1875.

3,4-Bis(2-bromophenyl)-6-fluoro-9,9-dimethyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18dj):



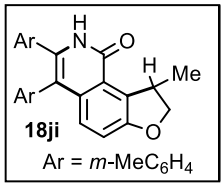
18dj (0.073 g) in 54% yield as yellow solid; R_f = 0.48 (8:2 hexane/EtOAc); m. p. => 347–350 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ11.65 (bs, 1H), 7.69–7.58 (m, 2H), 7.34–7.17 (m, 6H), 6.44 (d, J = 11.6 Hz, 1H), 4.46 (s, 2H), 1.64 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ160.1, 150.6 (J = 252.5 Hz), 146.9 (J = 12.1 Hz), 139.4 (J = 4.0 Hz), 137.0, 136.8, 135.7, 134.6 (J = 7.1 Hz), 133.0, 132.7, 132.3, 131.3, 130.6, 130.5, 128.5, 127.8, 126.1, 123.8, 120.3, 115.5 (J = 2.0 Hz), 111.3 (J = 18.2 Hz), 87.1, 45.7, 26.7, 26.6; ^{19}F NMR (126 MHz, CDCl3) δ –130.05; IR (KBr) ν_{max} 2956, 2919, 1653, 1506, 1453, 1339, 1192, 1024 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{19}Br_2FNO_2$ $(M+H)^+$: calcd. 541.9767, found 541.9766.

3,4-Bis(2,4-dichlorophenyl)-6-fluoro-9,9-dimethyl-8,9-dihydrofuro[2,3-h]isoquinoli-n-1(2H)-one (18dk):



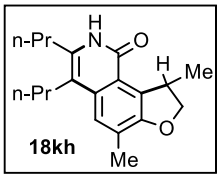
18dk (0.080 g) in 61% yield as colorless solid; R_f = 0.53 (8:2 hexane/EtOAc); m. p. => 360 ^{o}C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ11.63 (s, 1H), 7.64–7.57 (m, 2H), 7.57–7.50 (m, 2H), 7.22–7.15 (m, 2H), 6.75 (d, J = 9.6 Hz, 1H), 4.45 (s, 2H), 1.62 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 150.5 (d, J = 252.0 Hz), 146.9 (d, J = 11.3 Hz), 139.4, 137.0, 135.8, 135.1 (d, J = 7.6 Hz), 134.9, 134.0, 132.55, 132.46, 131.7, 131.6, 131.2, 131.0, 130.9, 130.6, 130.5, 120.3 (d, J= 1.3 Hz), 114.1 (d, J= 2.5 Hz), 111.9 (d, J= 17.6 Hz), 87.2, 45.6, 26.7, 26.6; ^{19}F NMR (126 MHz, $CDCl_3$) δ –129.43; IR (Neat) ν_{max} 2879, 1639, 1608, 1448, 1329, 1293, 1128, 1092 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{16}Cl_4FNNaO_2$ $(M+Na)^+$: calcd. 543.9817, found 543.9817.

9-Methyl-3,4-di-*m*-tolyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18ji):



18ji (0.053 g) in 54% yield as colorless solid. m.p. => 241–244 ^{o}C. R_f = 0.34 (8:2 hexane/EtOAc); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.24 (bs, 1H), 7.17 (td, J = 7.5, 3.0 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 7.11–7.00 (m, 4H), 7.00–6.87 (m, 4H), 4.59 (t, J = 8.5 Hz, 1H), 4.38 (dd, J = 8.7, 2.2 Hz, 1H), 4.24–4.15 (m, 1H), 2.22 (s, 3H), 2.19 (s, 3H), 1.32 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.5, 158.3, 137.6, 137.1, 137.0, 136.0, 135.1, 133.6, 132.7, 132.0, 130.9, 129.9, 129.2, 128.9, 128.5, 128.0, 127.9, 127.4, 126.7, 122.6, 116.3, 79.3, 37.4, 21.7, 21.42, 21.36; IR (Neat) ν_{max} 2922, 2879, 1642, 1593, 1480, 1351, 1077 cm^{-1}; **HRMS (ESI)** for $C_{26}H_{24}NO_2$ $(M+H)^+$: calcd. 382.1807, found 382.1810.

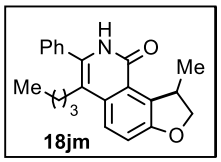
6,9-Dimethyl-3,4-dipropyl-8,9-dihydrofuro[2,3-h]isoquinolin-1(2H)-one (18kh):



18kh (0.053 g) in 71% yield as colorless solid. R_f = 0.63 (8:2 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ10.90 (bs, 1H), 7.29 (s, 1H), 4.60 (t, J = 8.4 Hz, 1H), 4.41 (dd, J = 8.4, 2.0 Hz, 1H), 4.31–4.23 (m, 1H), 2.69–2.57 (m, 4H), 2.37 (s, 3H), 1.79–1.69 (m, 2H), 1.64–1.54 (m, 2H), 1.40 (d, J = 6.8 Hz, 3H), 1.07–0.90 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ162.9, 156.5, 135.0, 133.5, 131.0, 126.5, 124.1, 120.2, 113.0, 79.4, 38.2, 32.8, 29.1, 23.5, 22.7, 21.3,

16.4, 14.3, 13.9; IR (KBr) ν_{max} 3158, 2956, 2863, 1649, 1458, 1351, 1272, 1179, 1071 cm^{-1}; **HRMS (ESI)** for $C_{19}H_{26}NO_2$ $(M+H)^+$: calcd. 300.1964, found 300.1967.

4-Butyl-9-methyl-3-phenyl-8,9-dihydrofuro[2,3-*h*]isoquinolin-1(2H)-one (18jm):

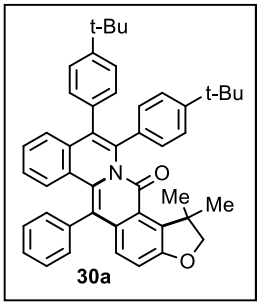


18jm (0.048 g, 58%) as colorless solid. m.p. => 221–225 °C; R_f = 0.80 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ9.46 (bs, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.53–7.43 (m, 5H), 7.26 (d, J = 8.8 Hz, 1H), 4.64 (t, J = 8.2 Hz, 1H), 4.42 (dd, J = 8.4, 1.6 Hz, 1H), 4.24–4.11 (m, 1H), 2.67–2.57 (m, 2H), 1.63–1.51 (m, 2H), 1.35 (d, J = 6.8 Hz, 3H), 1.33–1.26 (m, 2H), 0.85 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ161.7, 158.4, 135.8, 134.3, 132.7, 132.6, 129.1 (2C), 128.7, 128.6 (2C), 124.6, 115.6, 114.6, 79.7, 37.7, 32.8, 27.5, 22.7, 21.3, 13.7; IR (KBr) ν_{max} 2957, 2930, 2849, 1664, 1482, 1352, 1244 cm^{-1}; **HRMS (ESI)** for $C_{22}H_{23}NNaO_2$ $(M+Na)^+$: calcd. 334.1087, found 334.1086.

3.7.3.7. General Procedure for Annulation of Benzofurano-isoquinoline (18) with 1,2-Diarylalkynes (GP-7):

The annulation reactions were conducted in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with furano-isoquinolone (**18**, 0.20 mmol, 1.0 equiv), alkyne (**14**) (0.40 mmol, 2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (10.0 mg, 0.015 mmol, 0.075 equiv), and Na_2CO_3 (43.0 mg, 0.40 mmol, 2.0 equiv) $Cu(OAc)_2 \cdot H_2O$ (110 mg, 0.44 mmol, 2.2 equiv). 1,2-Chlorobenzene (PhCl) (2.0 mL) was added to the mixture and the resulting mixture was stirred at 120 ˚C for 24 h. The reaction mixture was filtered through a plug of Celite and washed with dichloromethane (3 × 5.0 mL). The solvents were evaporated under the reduced pressure and the crude material was purified using column chromatography on silica gel (10–20% *n*-hexane/EtOAc eluent) to give the desired product.

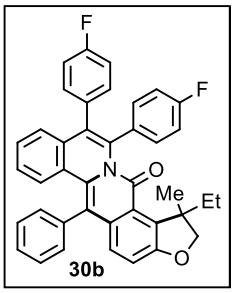
11,12-Bis(4-(tert-butyl)phenyl)-1,1-dimethyl-6-phenyl-1H-furo[2,3-h]isoquinolino[
-2,1-b]isoquinolin-14(2H)-one (30a):



30a (91 mg, 70%) as colourless solid. m.p. => 299–300 °C; R_f = 0.58 (9:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.60–7.50 (m, 5H), 7.29 (d, J = 8.4 Hz, 2H), 7.24–6.97 (m, 11H), 6.90–6.83 (m, 1H), 4.27 (s, 2H), 1.33 (s, 9H), 1.27 (s, 6H), 1.23 (s, 9H); ^{13}C

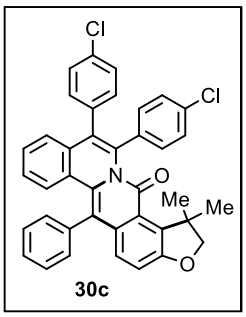
NMR (101 MHz, $CDCl_3$) δ162.2, 159.2, 149.5, 149.1, 139.4, 136.5, 134.5, 133.23, 133.16, 133.1, 133.0, 132.1, 131.1, 130.9, 129.6, 128.7, 128.3, 127.9, 127.7, 127.3, 126.0, 125.8, 125.6, 124.5, 124.1, 123.9, 116.3, 115.5, 86.4, 44.2, 34.4, 34.2, 31.3, 31.1, 26.1; IR (Neat) ν_{max} 2961, 1753, 1680, 1593, 1479, 1453, 1267 cm^{-1}; **HRMS (ESI)** for $C_{47}H_{46}NO_2$ $(M+H)^+$: calcd. 656.3529, found 656.3527.

1-Ethyl-11,12-bis(4-fluorophenyl)-1-methyl-6-phenyl-1H-furo[2,3-h]isoquinolino[2-,1-b]isoquinolin-14(2H)-one (30b):



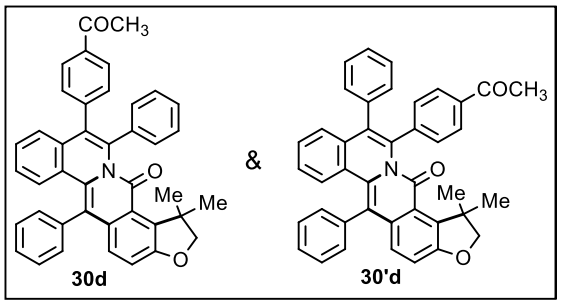
30b (79 mg) 67% as yellow colour solid.^{1}H NMR (400 MHz, $CDCl_3$)δ 7.56–7.44 (m, 5H), 7.18–7.09 (m, 4H), 7.09–6.94 (m, 7H), 6.90–6.83 (m, 1H), 6.77 (t, J = 7.0 Hz, 2H), 4.42 (d, J = 7.2 Hz, 1H), 4.18 (d, J = 6.8 Hz, 1H), 2.00–1.89 (m, 1H), 1.47–1.36 (m, 1H), 1.24 (s, 3H), 0.59 (t, J = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ162.8, 162.3, 161.7, 160.8, 160.3, 139.2, 135.8, 133.42, 133.39, 133.03, 132.97, 132.6, 132.15, 132.09, 131.5, 130.9, 130.8, 130.5, 129.69, 129.66, 128.5, 128.1, 128.0, 127.9, 127.8, 126.5, 125.7, 125.4, 124.4, 117.3, 115.6, 115.2, 115.0, 114.3, 114.2, 83.6, 48.5, 31.0, 25.4, 9.5 (due presence of F atom more peak observed); F^{19} NMR (126 MHz, CDCl3) δ –114.74, –115.02; IR (Neat) ν_{max} 2961, 2915, 1752, 1670, 1598, 1505, 1453, 1226, 1004 cm^{-1}; **HRMS (ESI)** for $C_{40}H_{30}F_2NO_2$ $(M+H)^+$: calcd. 594.2245, found 594.2245.

11,12-bis(4-chlorophenyl)-1,1-dimethyl-6-phenyl-1H-furo[2,3-h]isoquinolino[2,1-b]isoquinolin-14(2H)-one (30c):



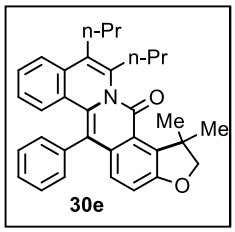
30c (80 mg, 66%) as yellow colour solid. m.p. => 244–246 ^{o}C; R_f= 0.50 (9:1 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$)δ7.58–7.44 (m, 5H), 7.30–7.26 (m, 2H), 7.18–6.94 (m, 11H), 6.90–6.83 (m, 1H), 4.26 (s, 2H), 1.27 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ161.8, 159.7, 139.1, 135.8, 135.5, 134.6, 133.5, 133.3, 133.0, 132.8, 132.6, 132.3, 132.1, 130.5, 129.7, 128.53, 128.48, 128.1, 128.0, 127.69, 127.67, 126.7, 125.5, 125.4, 124.0, 117.2, 115.9, 86.5, 44.3, 26.1; IR (Neat) ν_{max} 2951, 2930, 1675, 1593, 1479, 1458, 1350, 1319, 1272, 1086 cm^{-1}; **HRMS (ESI)** for $C_{40}H_{31}Cl_2NO_2$ $(M)^+$: calcd. 611.1419, found 611.1419.

11-(4-acetylphenyl)-1,1-dimethyl-6,12-diphenyl-1H-furo[2,3-h]isoquinolino[2,1-b]isoquinolin-14(2H)-one & 12-(4-acetylphenyl)-1,1-dimethyl-6,11-diphenyl-1H-furo[2,3-h]isoquinolino[2,1-b]isoquinolin-14(2H)-one (30d & 30′d) :



30d & **30′d** (87 mg, 75%) as yellow colour solid. m.p. => 145–147 °C; R_f = 0.60 (7:3 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ7.89 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.59–7.48 (m, 8H), 7.35–6.97 (m, 15H), 6.93–6.85 (m, 2H), 4.26 (s, 3.16H), 2.61 (s, 1.63H), 2.52 (s, 3.10H), 1.25 (s, 3.17H) 1.24 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ197.7, 197.6, 161.9, 161.7, 159.6, 159.5, 142.7, 141.8, 139.1, 137.0, 136.5, 135.8, 135.6, 135.0, 133.5, 133.03, 132.98, 132.5, 132.2, 132.0, 131.8, 131.3, 130.53, 130.49, 129.69, 129.67, 129.15, 129.07, 128.5, 128.4, 128.1, 128.0, 127.95, 127.93, 127.89, 127.7, 127.5, 127.4, 127.2, 126.93, 126.89, 126.7, 126.5, 125.8, 125.2, 125.1, 124.1, 123.9, 117.2, 117.0, 115.9, 115.7, 86.44, 86.40, 44.3, 44.2, 26.52, 26.46, 26.2, 26.1; IR (Neat) ν_{max} 3054, 2946, 2915, 1665, 1593, 1474, 1453, 1319, 1272, 1009 cm^{-1}; **HRMS (ESI)** for $C_{41}H_{33}NO_3$ $(M+H)^+$: calcd. 586.2382, found 586.2381.

1,1-dimethyl-6-phenyl-11,12-dipropyl-1H-furo[2,3-h]isoquinolino[2,1-b]isoquinoli-n-14(2H)-one (30e):

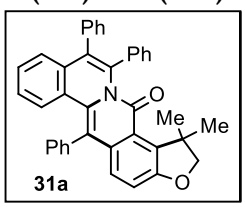


30e (33 mg, 40%) as pale yellow colour solid. m.p. => 166–167 °C; R_f = 0.58 (9:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.50–7.42 (m, 4H), 7.40–7.34 (m, 2H), 7.25–7.17 (m, 1H), 7.15 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.88 (dd, J = 8.2 & 1.0 Hz, 1H), 6.83–6.75 (m, 1H), 4.38 (s, 2H), 3.06 (t, J= 7.6 Hz, 2H), 2.77–2.69 (m, 2H), 1.70 (s, 6H), 1.69–1.61 (m, 2H), 1.46–1.37 (m, 2H), 1.08 (t, J = 7.2 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ161.6, 159.4, 139.3, 136.4, 133.1, 132.7, 132.3, 130.8, 129.4, 128.5, 127.8, 127.4, 125.3, 123.8, 122.7, 122.2, 117.1, 115.5, 86.4, 44.6, 30.2, 30.0, 26.5, 23.1, 21.5, 14.4, 13.8; IR (Neat) ν_{max} 3059, 2956, 2874, 1660, 1593, 1453, 1324, 1272, 1190 cm^{-1}; **HRMS (ESI)** for $C_{33}H_{34}NO_2$ $(M+H)^+$: calcd. 476.2590, found 476.2590.

3.7.3.8. General Procedure for the Unsymmetrical Two-fold C–H Functionalization (*Intramolecular Hydroarylation & Intermolecular Annulation*) Reaction (GP-8):

The three fold C–H functionalization reactions were conducted in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with (**15**,0.20 mmol), alkyne (**17**, 0.60 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (13.0 mg, 10.0 mol %), and $Cu(OAc)_2 \cdot H_2O$ (120 mg, 0.3 mmol). Subsequently, the additive $AgSbF_6$ (27.0 mg, 0.08 mmol) was introduced to the flask in a glove box. 1,2-Dichloroethene (DCE) (1.0 mL) was added to the mixture and the resulting mixture was stirred at room temperature for 2 h then 1,4-Dioxane (2 mL) was added to the reaction mixture followed by heating the resulting mixture at 130 ^oC for 24 h. The reaction mixture was filtered through a plug of Celite and washed with dichloromethane (3 × 5.0 mL). The solvents were evaporated under the reduced pressure and the crude material was purified using column chromatography on silica gel (10–20% *n*-hexane/EtOAc eluent) to give the desired product.

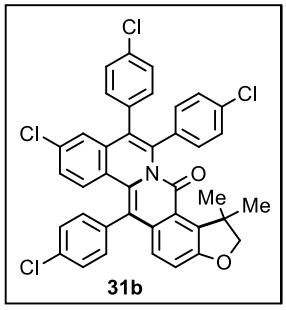
1,1-dimethyl-6,11,12-triphenyl-1H-furo[2,3-h]isoquinolino[2,1-b]isoquinolin-14(2H)-one(31a)



31a

31a (0.055 gm) 51% as Yellow colour solid. m.p. High melting; R_f = 0.73 (8:2 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ7.60–7.48 (m, 5H), 7.33-7.21 (m, 3H), 7.21–7.14 (m, 3H), 7.14-7.01 (m, 8H), 7.00 (d, J = 8.5 Hz, 1H), 6.90–6.83 (m, 1H), 4.26 (s, 2H), 1.26 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ162.0, 159.4, 139.3, 137.5, 136.4, 136.3, 133.4, 133.0, 132.9, 132.1, 131.5, 130.8, 129.6, 129.2, 129.1, 128.4, 127.95, 127.88, 127.82, 127.5, 127.2, 126.9, 126.5, 126.25, 126.20, 125.6, 124.1, 116.7, 115.6, 86.5, 44.3, 26.1; IR (Neat) ν_{max} 2925, 2848, 1768, 1673, 1479, 1457, 1269, 1071 cm^{-1}; **HRMS (ESI)** for $C_{39}H_{30}NO_2$ $(M+H)^+$: calcd. 544.2277, found 544.2277.

9-Chloro-6,11,12-tris(4-chlorophenyl)-1,1-dimethyl-1H-furo[2,3-h]isoquinolino[2,1 b]isoquinolin-14(2H)-one (31b)

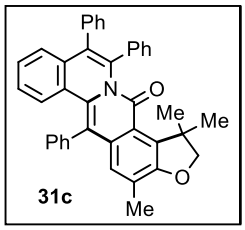


31b

31b (0.061 gm) 45% as yellow colour solid. m.p. High melting (mass loss observed at 300^oC); R_f = 0.74 (8:2 hexane/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ7.53 (d, J = 10.0 Hz, 2H), 7.39 (d, J = 10.5 Hz, 2H), 7.29 (d, J = 10.5 Hz, 2H), 7.11–7.04 (m, 6H),

7.03–6.94 (m, 3H), 6.89 (bs, 2H), 4.26 (s, 2H), 1.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ161.6, 159.9, 137.1, 136.7, 135.2, 134.4, 134.3, 134.1, 133.9, 133.63, 133.59, 133.3, 132.8, 132.6, 132.4, 130.3, 130.2, 129.8, 129.7, 128.7, 127.7, 127.3, 126.9, 126.0, 124.9, 124.2, 124.1, 116.2, 116.1, 86.4, 44.3, 26.0; IR (Neat) ν_{max} 2951, 2915, 2889, 1675, 1593, 1469, 1319, 1272 cm^{-1}; **HRMS (ESI)** for $C_{39}H_{26}Cl_4NO_2$ $(M+H)^+$: calcd. 680.0718, found 680.0714.

1,1,4-Trimethyl-6,11,12-triphenyl-1H-furo[2,3-h]isoquinolino[2,1-b]isoquinolin-14(2H)-one (31c):

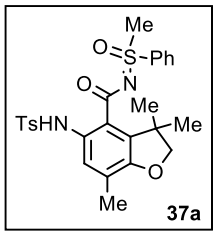


31c (0.053 gm) 48% as yellow color solid. m.p. High melting; R_f = 0.75 (8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$)δ7.58–7.45 (m, 6H), 7.25–7.19 (m, 2H), 7.19–7.14 (m, 2H), 7.12–7.07 (m, 4H), 7.06–6.99 (m, 3H), 6.99–6.90 (m, 2H), 6.87–6.79 (m, 1H), 4.24 (s, 2H), 2.23 (s, 3H), 1.23 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ162.0, 158.3, 139.4, 137.6, 136.4, 136.3, 133.1, 132.9, 132.5, 132.2, 131.5, 130.9, 129.6, 129.0, 128.4, 128.0, 127.91, 127.88, 127.7, 127.6, 127.2, 126.8, 126.6, 126.5, 126.2, 126.0, 125.5, 122.3, 116.6, 86.3, 44.5, 26.2, 16.2; IR (Neat) ν_{max} 3054, 3018, 2956, 1732, 1670, 1598, 1474, 1438, 1288 cm^{-1}; **HRMS (ESI)** for $C_{40}H_{32}NO_2$ $(M+H)^+$: calcd. 558.2433, found 558.2433.

3.7.3.9. General Procedure for the Unsymmetrical Two-fold C–H Functionalization (*Intramolecular Hydroarylation & Intermolecular Amidation*) Reaction (GP-9):

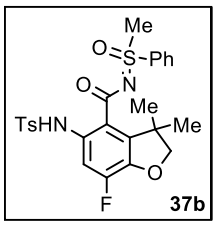
The twofold C–H functionalization reactions were conducted in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with **21**(0.5 mmol), sulfonyl azide (**35**, 0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.0 mg, 5.0 mol %), and $Cu(OAc)_2 \cdot H_2O$ (100 mg, 0.5 mmol). Subsequently, the additive $AgSbF_6$ (35 mg, 0.1 mmol) was introduced to the flask in a glove box. 1,2-Dichloroethene (DCE) (2.0 mL) was added to the mixture and the resulting mixture was stirred at room temparature for 12–16 h followed by heating the resulting mixture at 120 ^{o}C for 24 h. The reaction mixture was filtered through a plug of Celite and washed with dichloromethane (3 × 5.0 mL). The solvents were evaporated under the reduced pressure and the crude material was purified using column chromatography on silica gel (35–50% *n*-hexane/EtOAc eluent) to give the desired product.

***N*-[3,3,7-Trimethyl-5-(4-methylphenylsulfonamido)-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (37a):**



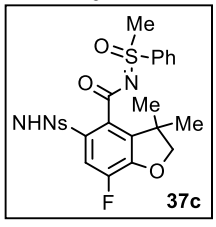
37a (185 mg, 72%) as colourless viscous liquid.m.p. = 110–115 °C; R_f = 0.35 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ9.01 (s, 1H), 8.00 (d, J = 7.2 Hz, 2H), 7.72 (t, J = 7.4 Hz, 1H), 7.63 (t, J = 7.6 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.11 (s, 1H), 4.06 (d, J = 8.0 Hz, 1H), 4.03 (d, J = 8.4 Hz, 1H), 3.42 (s, 3H), 2.33 (s, 3H), 2.16 (s, 3H), 1.28 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 156.2, 143.4, 137.7, 136.0, 135.0, 134.2, 129.8 (2C), 129.4 (2C), 128.2, 127.3 (2C), 127.1 (2C), 125.6, 125.5, 123.2, 85.4, 44.4, 43.8, 25.2, 24.7, 21.5, 15.4; IR (KBr) ν_{max} 2958, 2925, 1715, 1638, 1621, 1452, 1402, 1320, 1145 cm^{-1}; **HRMS (ESI)** for $C_{26}H_{28}N_2NaO_5S_2$ $(M+Na)^+$: calcd. 535.1338, found 535.1340.

***N*-[7-Fluoro-3,3-dimethyl-5-(4-methylphenylsulfonamido)-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (37b):**



37b (189 mg, 73%) as colourless viscous liquid. m.p. = 68–71 °C; R_f= 0.32 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ9.31 (s, 1H), 8.00 (d, J = 7.6 Hz, 2H), 7.73 (t, J = 7.4 Hz, 1H), 7.64 (t, J = 7.6 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.17 (d, J= 8.0 Hz, 2H), 7.11 (d, J = 11.6 Hz, 1H), 4.13 (d, J = 8.4 Hz, 1H), 4.11 (d, J = 8.4 Hz, 1H), 3.44 (s, 3H), 2.33 (s, 3H), 1.30 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ172.2, 148.1 (d, J = 252 Hz), 144.4 (d, J = 11 Hz), 143.8, 139.6 (d, J = 4.0 Hz), 137.4, 135.7, 134.3, 129.9 (2C), 129.6 (2C), 127.2 (2C), 127.0 (2C), 123.0 (d, J = 3.0 Hz), 111.2 (d, J= 21 Hz), 86.6, 44.5, 44.3, 25.0, 24.3, 21.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –132.3; IR (Neat) ν_{max} 2925, 2860, 1720, 1649, 1616, 1490, 1430, 1331, 1221, 1156, 1090 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{25}FN_2NaO_5S_2$ $(M+Na)^+$: calcd. 539.1087, found 539.1089.

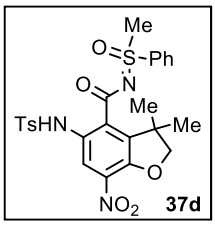
***N*-[7-Fluoro-3,3-dimethyl-5-((4-nitrophenyl)sulfonyl)-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (37c):**



37c (178 mg, 65%) as colorless solid.m.p. = 248–252 °C; R_f = 0.24 (3:7 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-D_6) δ9.51 (s, 1H), 8.08 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.62 (bt, J = 6.8 Hz, 1H), 7.53 (bt, J = 7.8 Hz, 2H), 6.69 (d,

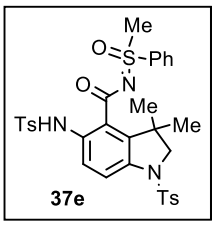
J=11.2 Hz, 1H), 4.06 (d, *J*= 8.4 Hz, 1H), 4.03 (d, *J*= 8.8 Hz, 1H), 3.42 (s, 3H), 1.17 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ171.1, 148.6, 145.5 (d, *J* = 250 Hz), 144.0 (d, *J* = 10 Hz), 143.8, 136.7, 136.6, 132.9, 128.4 (2C), 127.3 (2C), 127.1, 126.0 (2C), 125.0 (d, *J* = 7.1 Hz), 122.9 (2C), 112.7 (d, *J* = 20 Hz), 85.1, 42.8, 42.5, 24.1, 23.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –131.7; IR (KBr) ν_{max} 3747, 3117, 2964, 2827, 1621, 1534, 1331, 1210, 1172 cm^{-1}; **HRMS (ESI)** for $C_{24}H_{22}FN_3NaO_7S_2$ $(M+Na)^+$: calcd. 570.0781, found 570.0782

N-[3,3-Dimethyl-5-(4-methylphenylsulfonamido)-7-nitro-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (37d):



31d (117 mg, 43%) as dark yellow viscous liquid; R_f = 0.20 (4:6 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.14 (s, 1H), 8.08 (d, *J* = 7.6 Hz, 2H), 7.81 (s, 1H), 7.76 (bt, *J* = 7.4 Hz, 1H), 7.72–7.61 (m, 4H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.34 (d, *J* = 8.4 Hz, 1H), 4.31 (d, *J* = 8.4 Hz, 1H), 3.53 (s, 3H), 2.38 (s, 3H), 1.41 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ171.9, 152.8, 144.2, 139.9, 137.2, 135.8, 134.9, 132.5, 130.0 (2C), 129.8 (2C), 127.4 (2C), 127.3, 127.1 (2C), 126.9, 119.2, 87.2, 44.2, 43.2, 25.1, 24.8, 21.5; IR (Neat) ν_{max} 3276, 2964, 2926, 1715, 1649, 1605, 1441, 1156 cm^{-1}; **HRMS (ESI)** for $C_{25}H_{25}N_3NaO_7S_2$ $(M+Na)^+$: calcd. 566.1032, found 566.1034.

N-[3,3-Dimethyl-5-(4-methylphenylsulfonamido)-1-tosylindoline-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (37e):

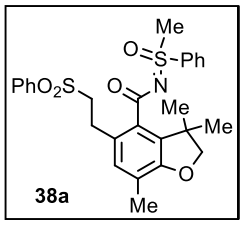


37e (176 mg, 54%) as brown solid.m.p. = 75–79 ^{o}C; R_f = 0.16 (7:3 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ8.21 (s, 1H), 8.04 (d, *J* = 7.5 Hz, 2H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.72–7.63 (m, 4H), 7.61–7.54 (m, 3H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 8.2 Hz, 3H), 3.52–3.44 (m, 5H), 2.40 (s, 3H), 2.38 (s, 3H), 1.23 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 144.3, 143.8, 139.4, 138.6, 137.5, 136.2, 134.3, 133.5, 129.95 (2C), 129.88, 129.7 (2C), 129.6 (2C), 129.1, 127.4 (2C), 127.3 (2C), 127.1 (2C), 123.3, 115.5, 64.9, 44.2, 41.6, 25.7, 25.5, 21.54, 21.52; IR (KBr) ν_{max} 3479, 2920, 2849, 1736, 1627, 1588, 1462, 1353, 1227, 1156 cm^{-1}; **HRMS (ESI)** for $C_{32}H_{33}N_3NaO_6S_3$ $(M+Na)^+$: calcd. 674.1429, found 674.1429.

3.7.3.10. General Procedure for the Unsymmetrical Two-fold C–H Functionalization (*Intramolecular Hydroarylation & Intermolecular Alkylation/Alkenylation*) Reaction (GP-10):

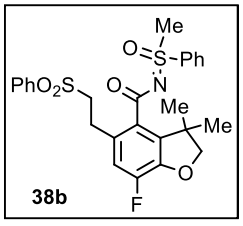
The twofold C–H functionalization reactions were conducted in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with (**21**,0.5 mmol), olefin (**36**, 1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.0 mg, 5.0 mol %), and $Cu(OAc)_2 \cdot H_2O$ (100 mg, 0.5 mmol). Subsequently, the additive $AgSbF_6$ (35 mg, 0.1 mmol) was introduced to the flask in a glove box. 1,2-Dichloroethene (DCE) solvent (2.0 mL) was added to the mixture and the resulting mixture was stirred at room temparature for 12–16 h and at 120 °C for 24 h. The reaction mixture was 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 purified using column chromatography on silica gel (35–50% *n*-hexane/EtOAc eluent) to give the desired product.

***N*-[3,3,7-Trimethyl-5-(2-(phenylsulfonyl)ethyl)-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (38a):**



38a (187 mg, 73%) as colourless solid.m.p. = 68–72 °C; R_f = 0.30 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H), 7.70–7.62 (m, 4H), 7.55 (bt, J = 7.6 Hz, 2H), 6.67 (s, 1H), 4.11 (s, 2H), 3.62 (s, 3H), 3.52 (td, J = 13.0, 3.6 Hz, 1H), 3.36 (td, J = 12.8, 4.4 Hz, 1H), 3.24 (td, J = 12.6, 3.2 Hz, 1H), 3.14–2.95 (m, 1H), 2.11 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 157.1, 139.4, 138.5, 133.9, 133.6, 133.4, 132.1, 130.5, 129.7 (2C), 129.3 (2C), 127.8 (2C), 127.1 (2C), 124.9, 120.7, 85.0, 58.1, 43.7, 43.3, 25.8, 25.7, 14.9; IR (Neat) ν_{max} 2964, 2925, 1621, 1506, 1446, 1413, 1221 cm^{-1}; **HRMS (ESI)** for $C_{27}H_{30}NO_5S_2$ $(M+H)^+$: calcd. 512.1565, found 512.1568.

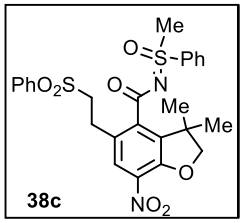
***N*-[7-Fluoro-3,3-dimethyl-5-(2-(phenylsulfonyl)ethyl)-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (38b):**



38b (178 mg, 69%) as colourless solid.m.p. => 144–148 °C; R_f = 0.29 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.6 Hz, 2H), 7.89 (d, J = 7.6 Hz, 2H), 7.77–7.62 (m, 4H), 7.56 (t, J

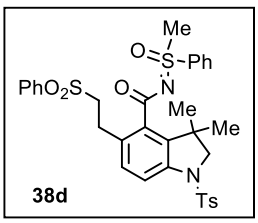
= 7.6 Hz, 2H), 6.66 (d, *J* = 10.8 Hz, 1H), 4.21 (s, 2H), 3.64 (s, 3H), 3.51 (td, *J* = 12.8, 3.6 Hz, 1H), 3.35 (td, *J* = 12.8, 4.1 Hz, 1H), 3.26 (td, *J* = 12.6, 3.7 Hz, 1H), 3.08 (td, *J* = 12.8, 4.0 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ176.3, 147.1 (d, *J* = 248 Hz), 145.3 (d, *J* = 11 Hz), 139.1, 138.2, 136.8 (d, *J* = 2.0 Hz), 134.1, 133.8, 131.7 (d, *J* = 4.0 Hz), 129.8 (2C), 129.4 (2C), 127.8 (2C), 127.0 (2C), 126.5 (d, *J* = 5.0 Hz), 116.2 (d, *J* = 17 Hz), 86.4, 57.7, 43.9, 43.7, 26.0, 25.6, 25.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –137.5; IR (Neat) ν_{max} 2964, 2925, 1621, 1506, 1446, 1287, 1216 cm^{-1}; **HRMS (ESI)** for $C_{26}H_{26}FNNaO_5S_2$(M+Na)$^+$: calcd. 538.1134, found 538.1135.

***N*-[3,3-dimethyl-7-nitro-5-(2-(phenylsulfonyl)ethyl)-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (38c):**



38c (138 mg, 51%) as pale yellow solid. m.p. = 155–158 °C; R_f = 0.33 (6:4 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.17 (d, *J* = 7.6 Hz, 2H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.79–7.64 (m, 5H), 7.58 (bt, *J* = 7.8 Hz, 2H), 4.38 (s, 2H), 3.72 (s, 3H), 3.52 (td, *J*= 12.8, 4.1 Hz, 1H), 3.39 (td, *J* = 12.8, 4.8, 1H), 3.26 (td, *J* = 12.8, 4.4 Hz, 1H), 3.14 (td, *J* = 13.0, 4.8 Hz, 1H), 1.46 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.8, 154.3, 141.6, 138.9, 137.8, 137.6, 134.4, 134.0, 132.1, 129.9 (2C), 129.5 (2C), 127.9 (2C), 126.9 (2C), 125.9, 124.7, 87.1, 57.3, 43.8, 42.9, 25.8, 25.6, 25.5; IR (Neat) ν_{max} 3057, 2953, 2926, 1632, 1512, 1293, 1183 cm^{-1}; **HRMS (ESI)** for $C_{26}H_{26}N_2NaO_7S_2$ (M+Na)$^+$: calcd. 565.1079, found 565.1076.

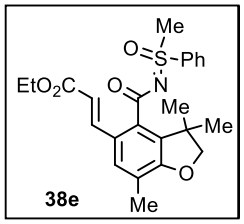
***N*-[3,3-Dimethyl-5-(2-(phenylsulfonyl)ethyl)-1-tosylindoline-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (38d):**



38d (198 mg, 61%) as yellow solid. m.p. = 213–219 °C; R_f = 0.16 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.12 (d, *J* = 7.6 Hz, 2H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.77–7.63 (m, 6H), 7.61–7.48 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 3.67 (s, 3H), 3.53 (s, 2H), 3.51–3.40 (m, 1H), 3.32 (td, *J* = 12.8, 4.0 Hz, 1H), 3.23 (td, *J* = 12.8, 3.8 Hz, 1H), 3.08 (td, *J* = 12.9, 4.0 Hz, 1H), 2.35 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ177.0, 144.2, 140.6, 139.1, 138.1, 136.2, 136.1, 134.1, 133.8, 133.6, 129.8 (2C), 129.7 (2C), 129.4 (2C), 129.1, 127.8 (2C), 127.3 (2C), 127.0 (2C), 114.4, 64.5, 57.7, 43.6, 41.4, 26.3, 26.2, 25.8, 21.5; IR (Neat) ν_{max} 2925, 2854, 1616, 1594, 1441, 1347, 1276,

1156 cm^{-1}; **HRMS (ESI)** for $C_{33}H_{34}N_2NaO_6S_3$ $(M+Na)^+$: calcd. 673.1477, found 673.1477.

***N*-[(E)-5-(3-Ethoxy-3-oxoprop-1-enyl)-3,3,7-trimethyl-2,3-dihydrobenzofuran-4-carboxyl]-*S*-methyl-*S*-phenylsulfoximine (38e):**



38e (157 mg, 71%) as colourless solid. m.p. = 161–166 °C; R_f = 0.40 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.12 (d, J = 7.6 Hz, 2H), 8.01 (d, J = 15.6 Hz, 1H), 7.73–7.55 (m,3H), 7.31 (s, 1H), 6.28 (d, J = 15.6 Hz, 1H), 4.28–4.14 (m, 4H), 3.55 (s, 3H), 2.20 (s, 3H), 1.50 (s, 3H), 1.41 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ176.6, 167.6, 160.2, 142.8, 138.1, 134.8, 134.0, 132.0, 129.8 (2C), 127.9, 127.3 (2C), 123.6, 121.1, 116.1, 85.5, 60.2, 44.1, 43.1, 26.3, 25.6, 15.1, 14.4; IR (Neat) ν_{max} 2986, 2920, 1715, 1627, 1578, 1446, 1408, 1287, 1150 cm^{-1}; **HRMS (ESI)** for $C_{24}H_{27}NNaO_5S$ $(M+Na)^+$: calcd. 464.1508, found 464.1509.

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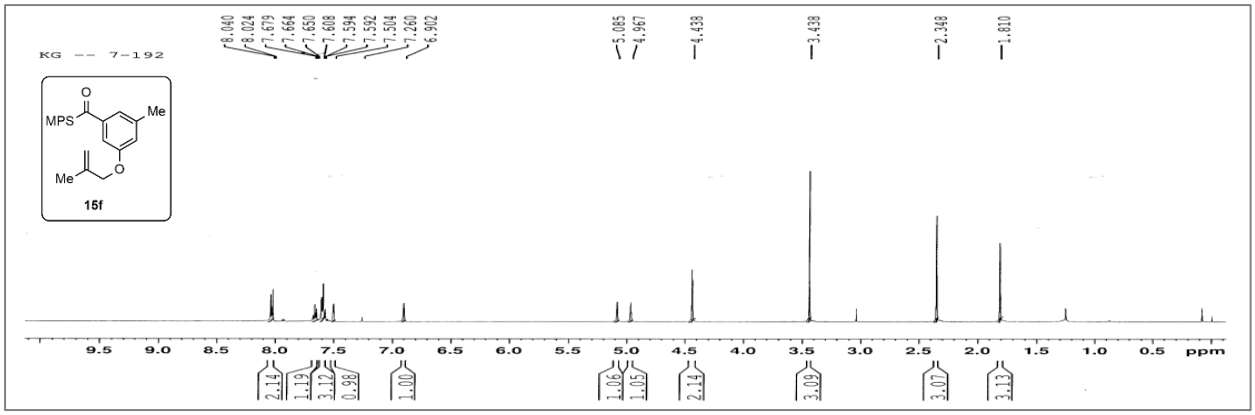
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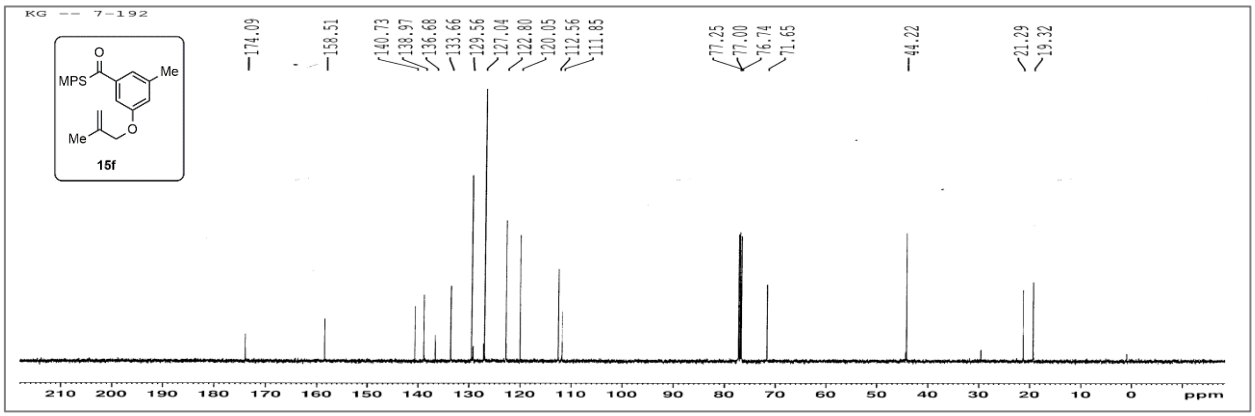
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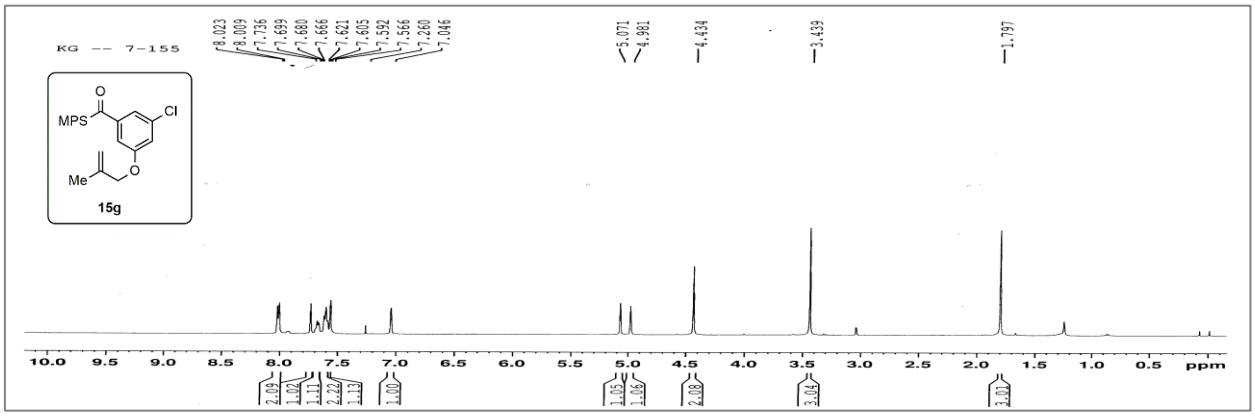
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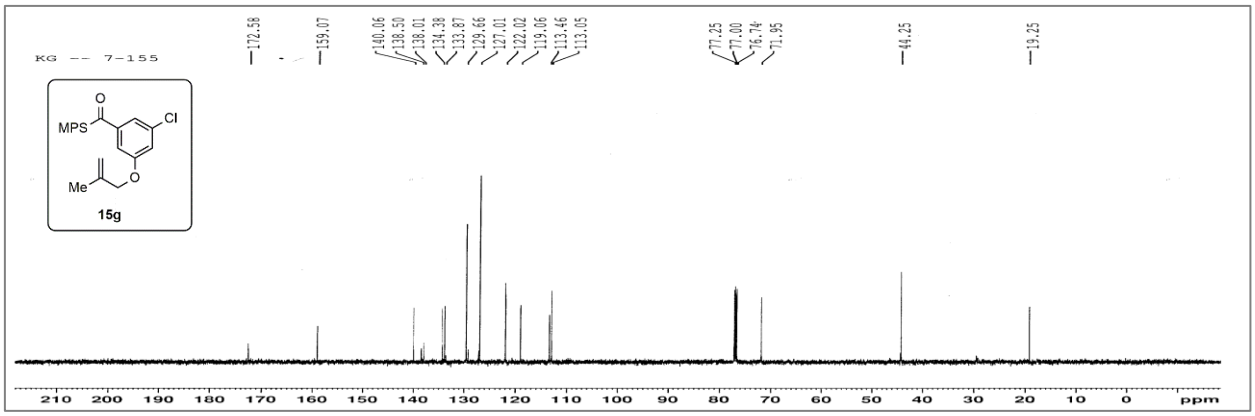
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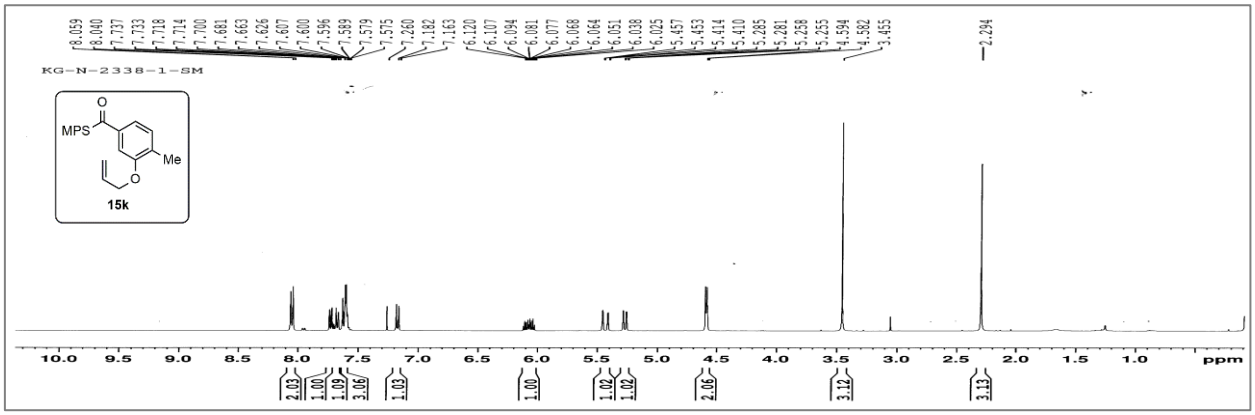
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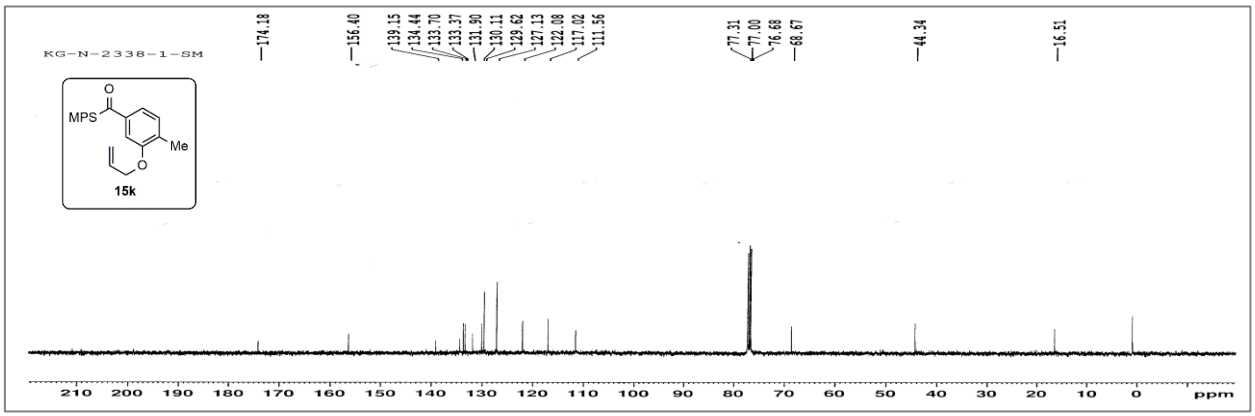

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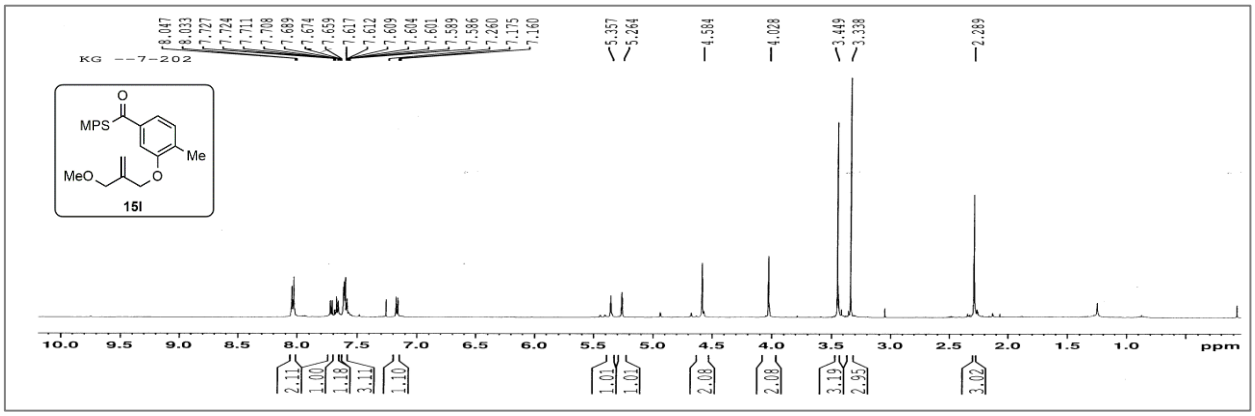

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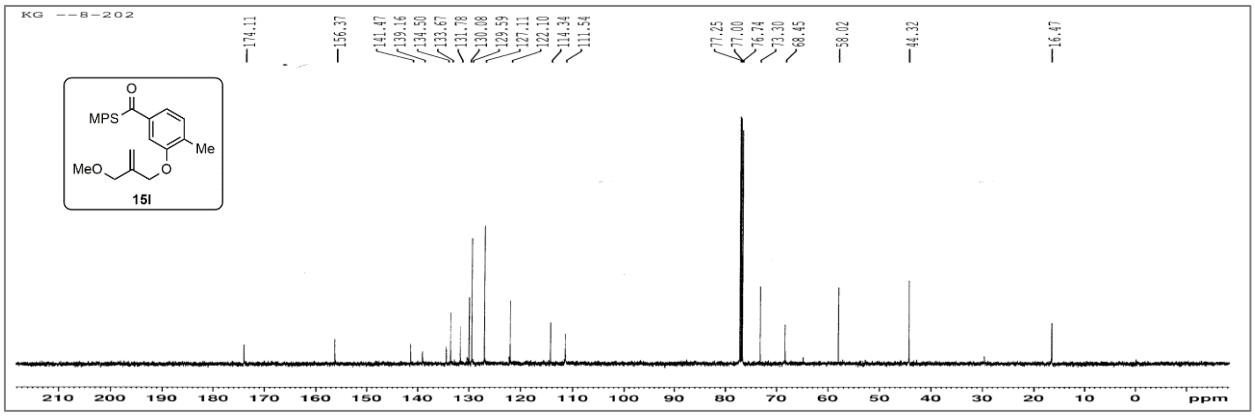

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7.566
7.260
7.046
5.071
4.981
4.434
3.439
1.797
MPS
Cl
Me
O
15g
2.19
1.02
1.11
2.22
1.13
1.00
1.05
1.06
2.08
3.04
3.00
ppm

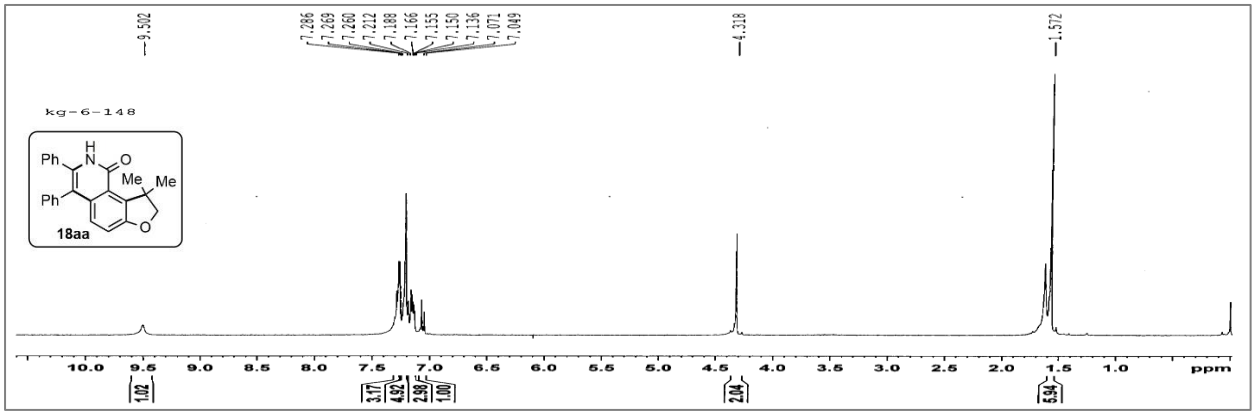

KG -- 7-155
172.58
159.07
140.06
138.50
138.01
134.38
133.87
129.66
127.01
122.02
119.06
113.46
113.05
77.25
77.00
76.74
71.95
44.25
19.25
MPS
Cl
Me
O
15g
ppm

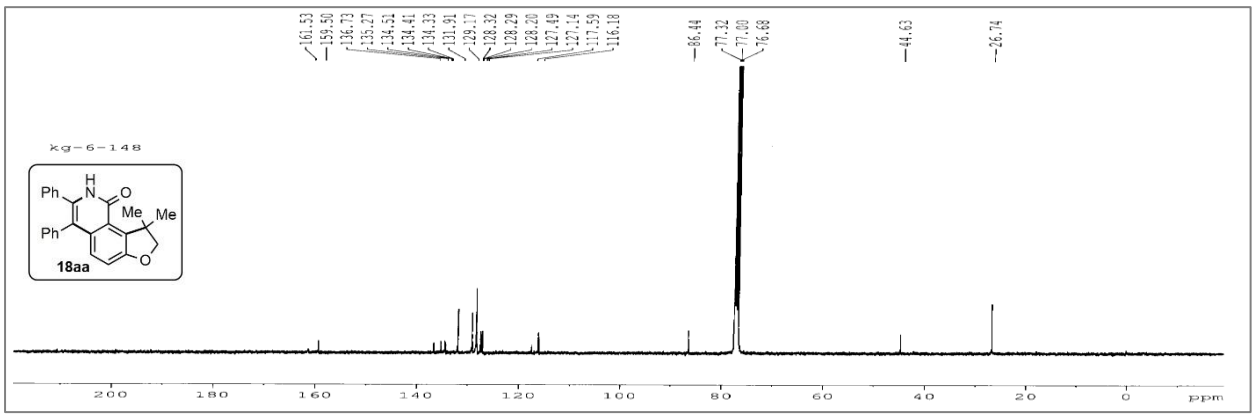

KG-N-2338-1-SM
MPS
Me
O
15k
ppm

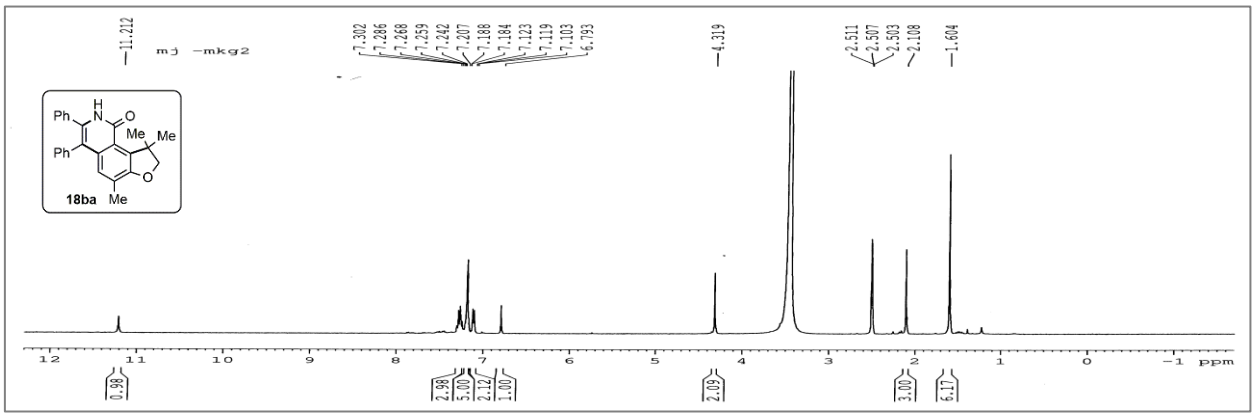

KG-N-2338-1-SM
MPS
Me
O
15k
ppm

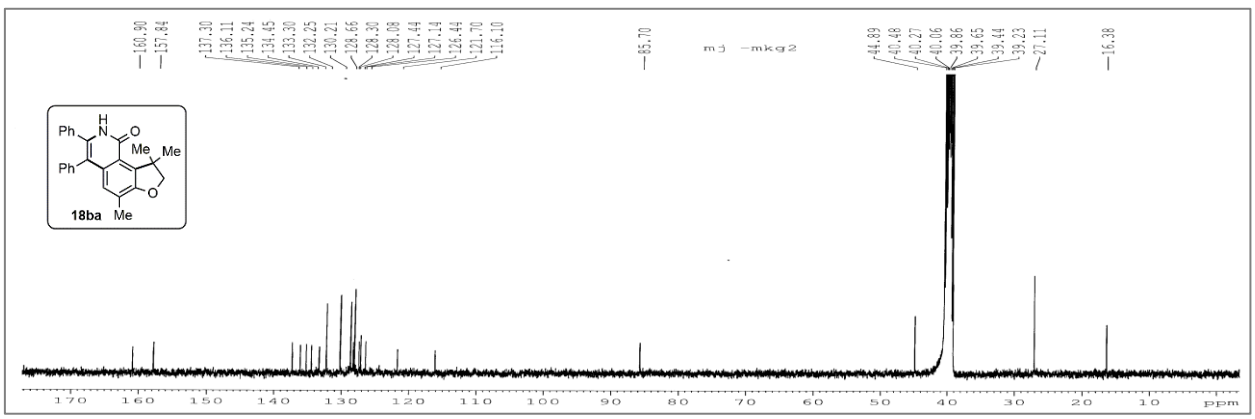

KG --7-202
MPS
Me
MeO
O
15l
ppm

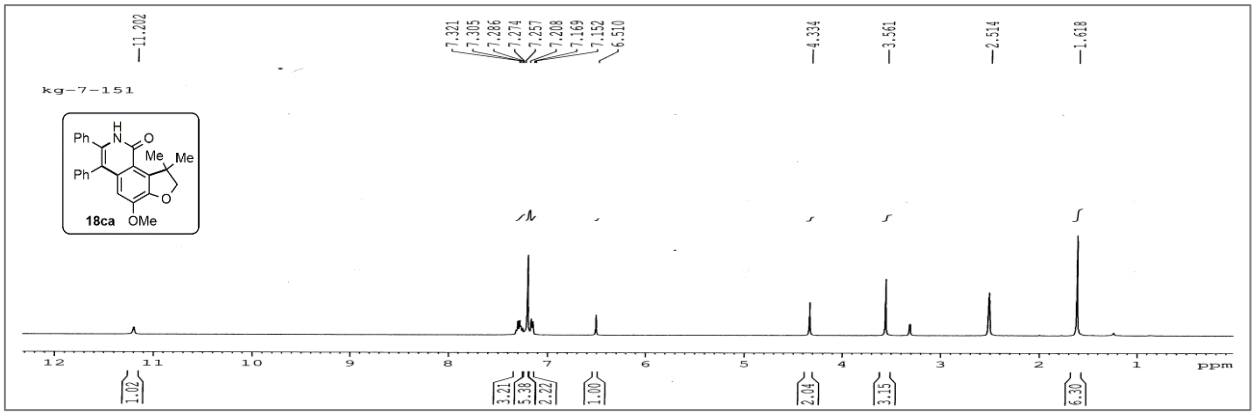

KG --8-202
MPS
Me
MeO
O
15l
ppm

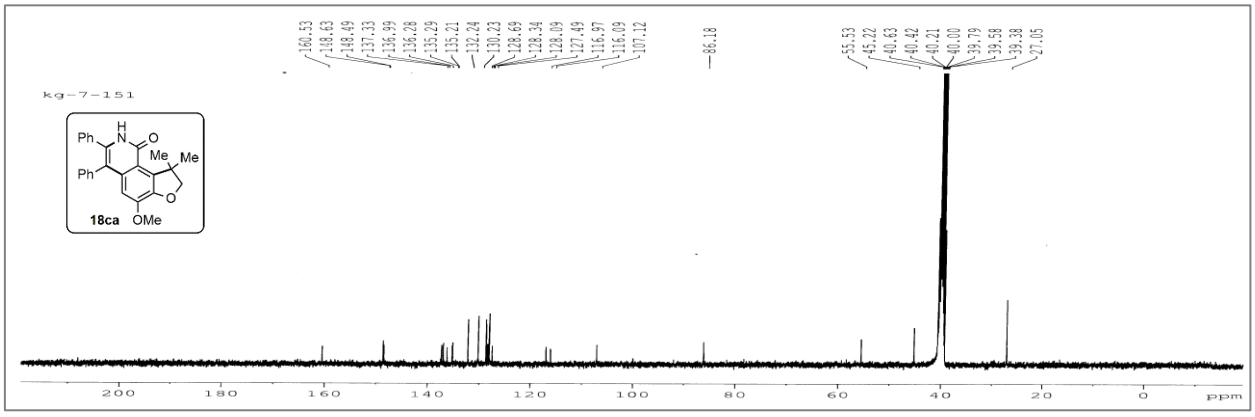

kg-6-148
18aa
9.502
7.286
7.269
7.260
7.212
7.188
7.166
7.155
7.150
7.136
7.071
7.049
4.318
1.572
ppm

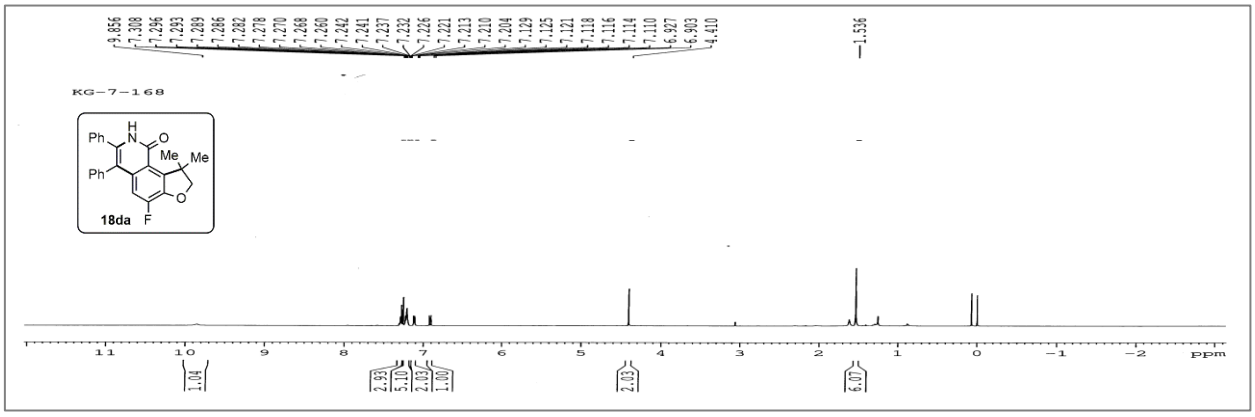

kg-6-148
18aa
161.53
159.50
136.73
135.27
134.51
134.41
134.33
131.91
129.17
128.32
128.29
128.20
127.49
127.14
117.59
116.18
86.44
77.32
77.00
76.68
44.63
26.74
ppm

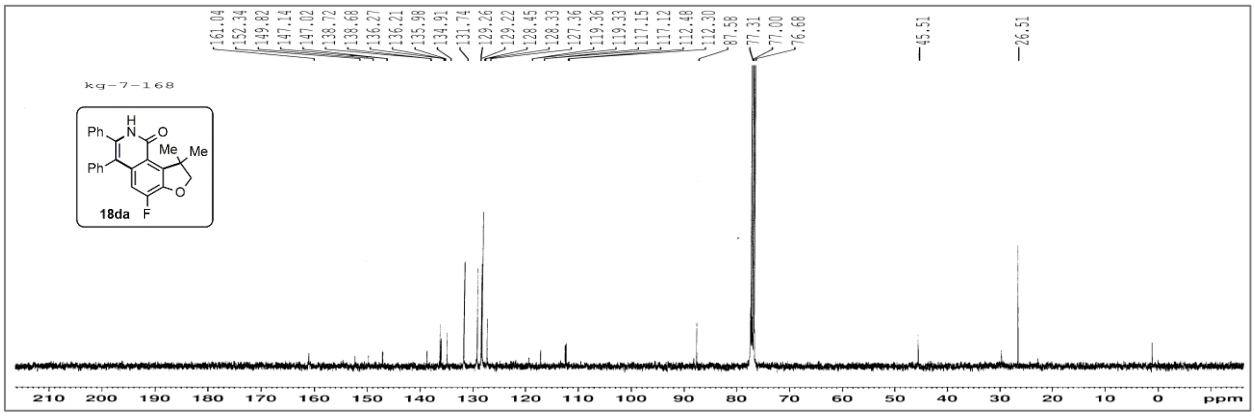

mj -mkg2
18ba Me
11.212
7.302
7.286
7.268
7.259
7.242
7.207
7.188
7.184
7.123
7.119
7.103
6.793
4.319
2.511
2.507
2.503
2.108
1.604
ppm

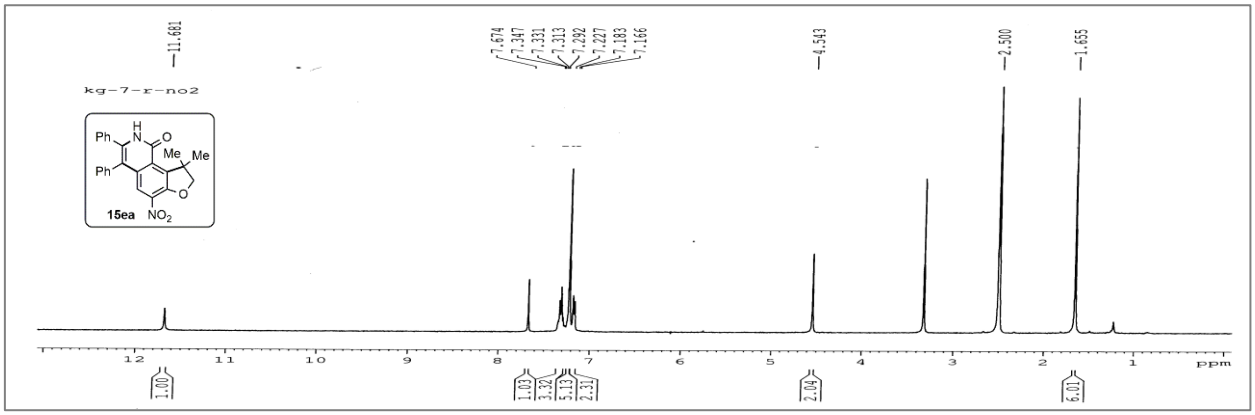

mj -mkg2
18ba Me
160.90
157.84
137.30
136.11
135.24
134.45
133.30
132.25
130.21
128.66
128.30
128.08
127.44
127.14
126.44
121.70
116.10
85.70
44.89
40.48
40.27
40.06
39.86
39.65
39.44
39.23
27.11
16.38
ppm

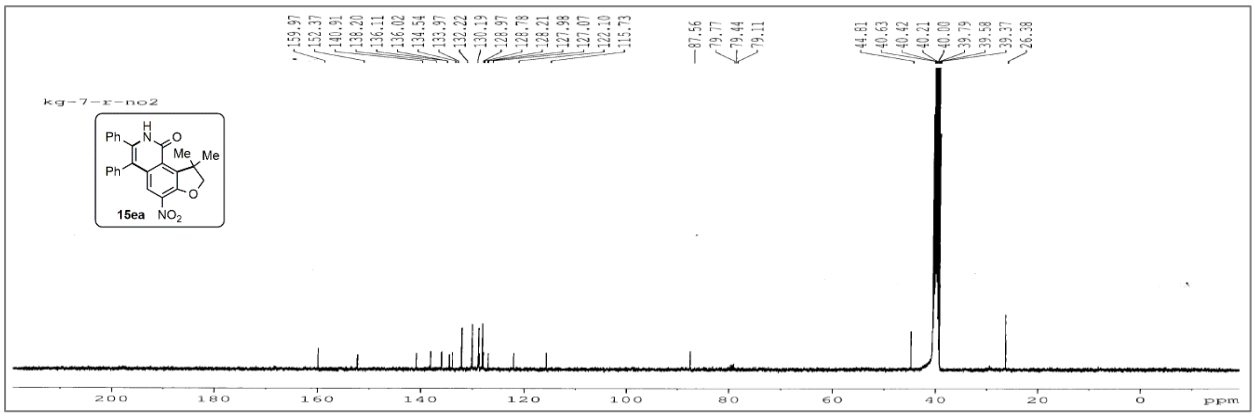

kg-7-151
18ca OMe

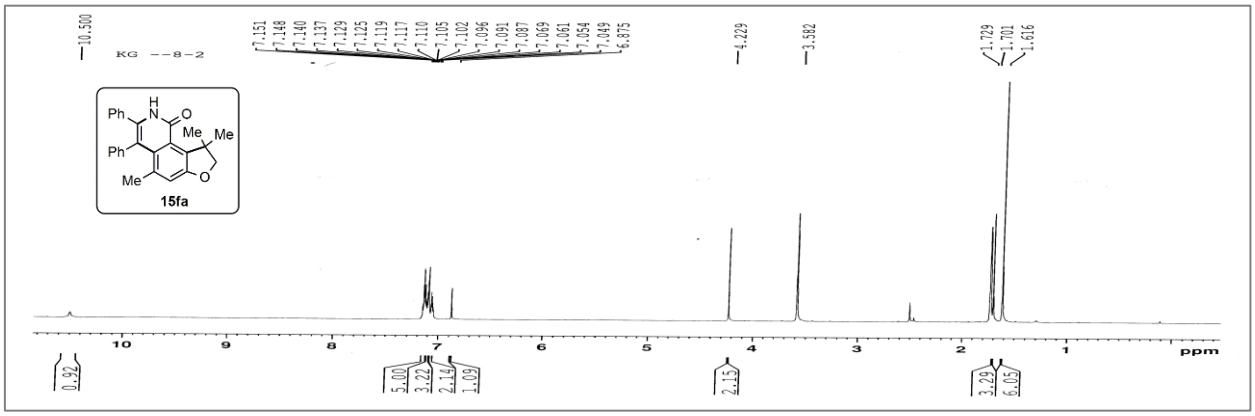

kg-7-151
18ca OMe

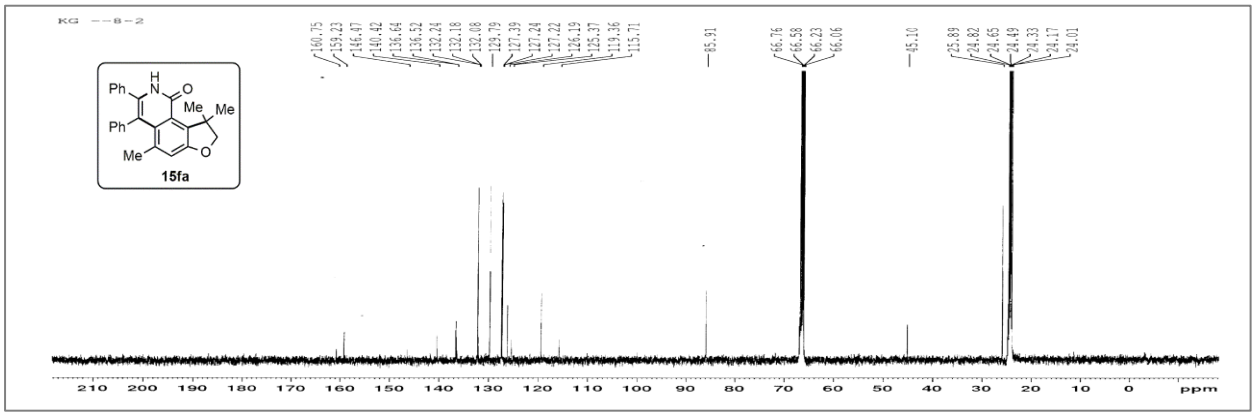

KG-7-168
18da F

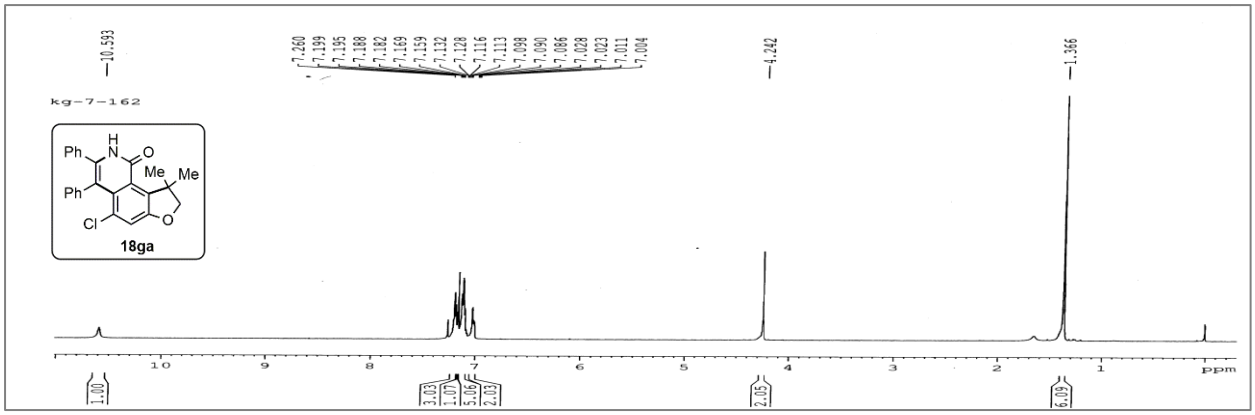

kg-7-168
18da F

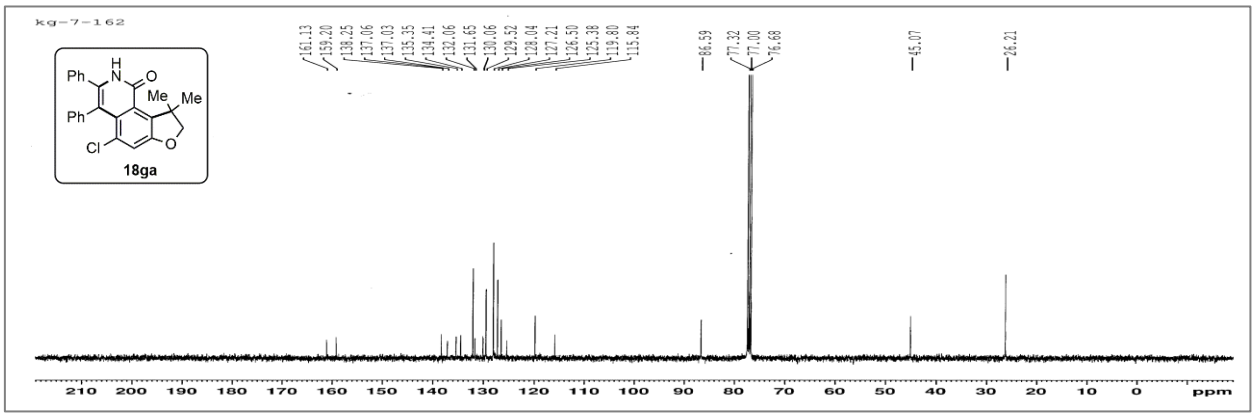

kg-7-r-no2
15ea NO2
11.681
7.674
7.347
7.331
7.313
7.292
7.227
7.183
7.166
4.543
2.500
1.655
ppm

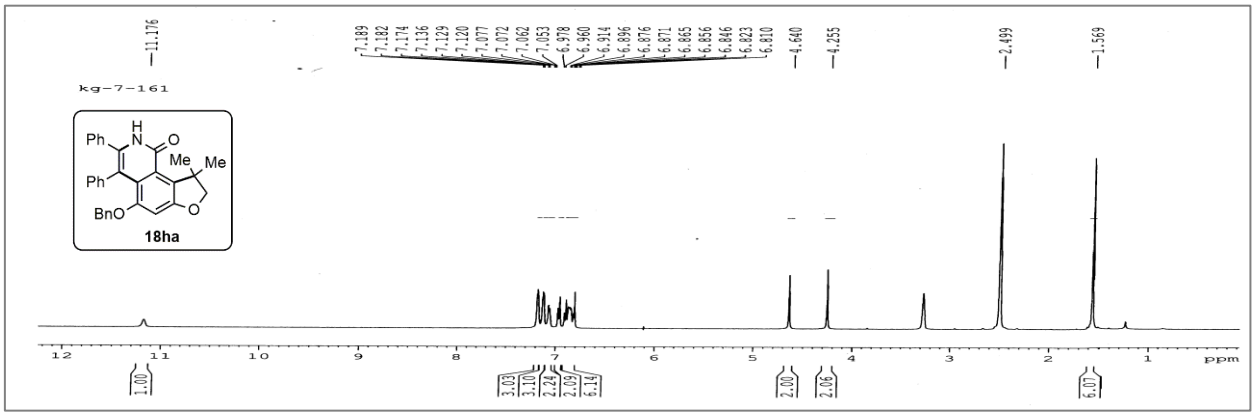

kg-7-r-no2
15ea NO2
159.97
152.37
140.91
138.20
136.11
136.02
134.54
133.97
132.22
130.19
128.97
128.78
128.21
127.98
127.07
122.10
115.73
87.56
79.77
79.44
79.11
44.81
40.63
40.42
40.21
40.00
39.79
39.58
39.37
26.38
ppm

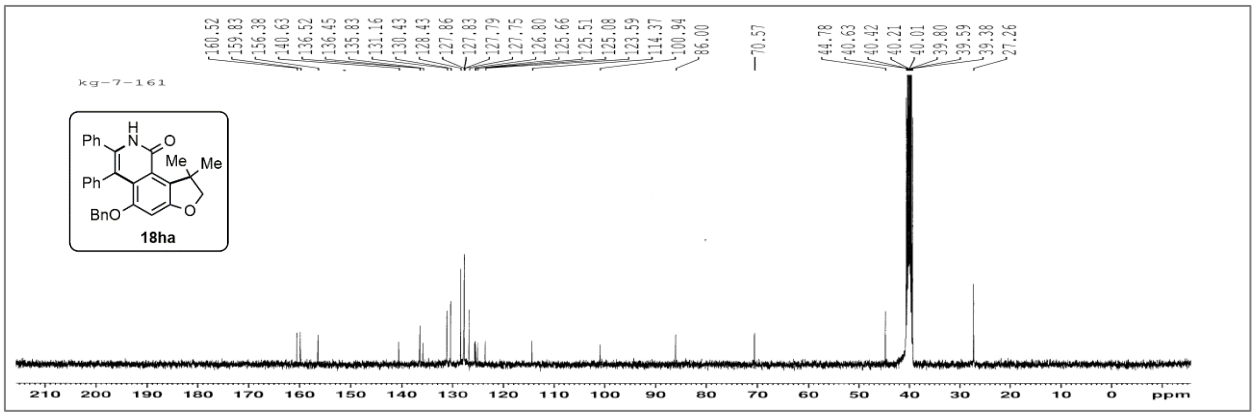

10.500
KG --8-2
15fa
7.151
7.148
7.140
7.137
7.129
7.125
7.119
7.117
7.110
7.105
7.102
7.096
7.091
7.087
7.069
7.061
7.054
7.049
6.875
4.229
3.582
1.729
1.701
1.616
ppm

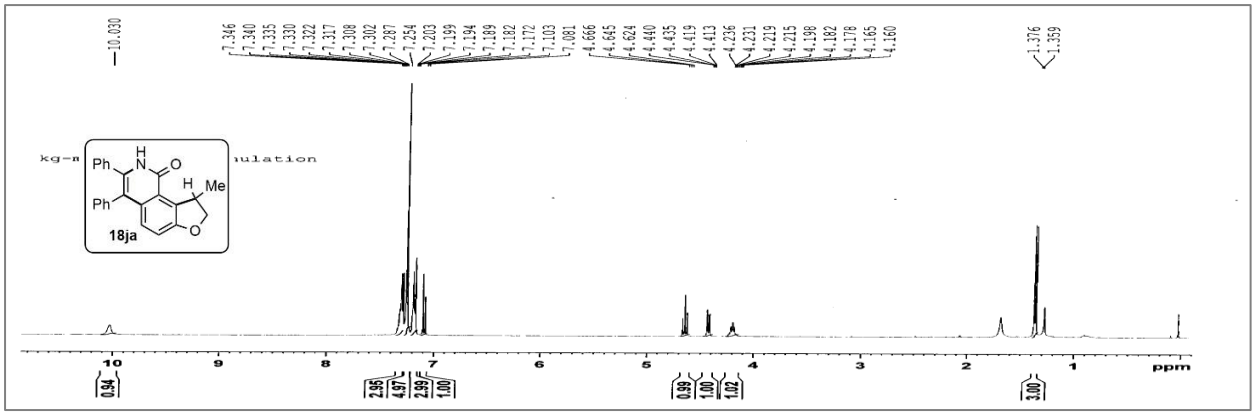

KG --8-2
15fa
160.75
159.23
146.97
140.42
136.64
136.52
132.24
132.18
132.08
129.79
127.39
127.24
127.22
126.19
125.37
119.36
115.71
85.91
66.76
66.58
66.23
66.06
45.10
25.89
24.82
24.65
24.49
24.33
24.17
24.01
ppm

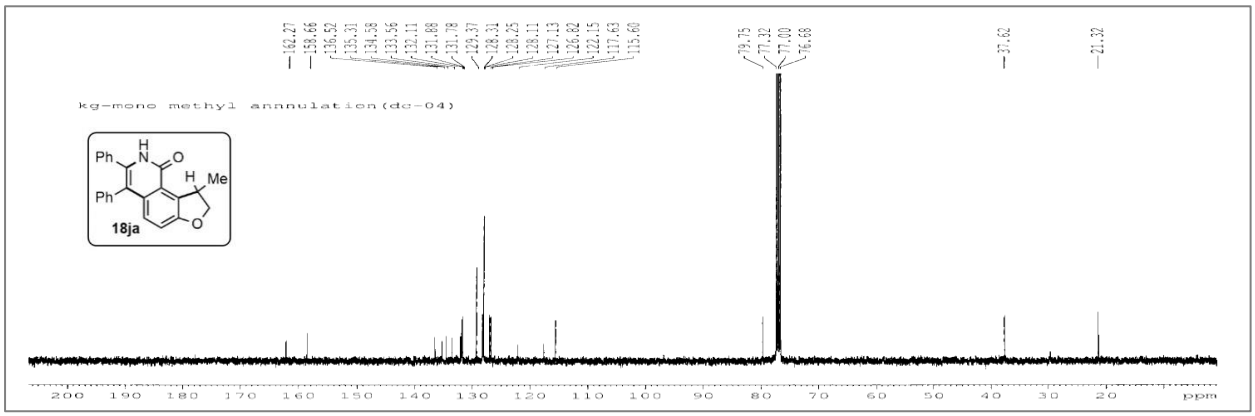

kg-7-162
18ga
ppm

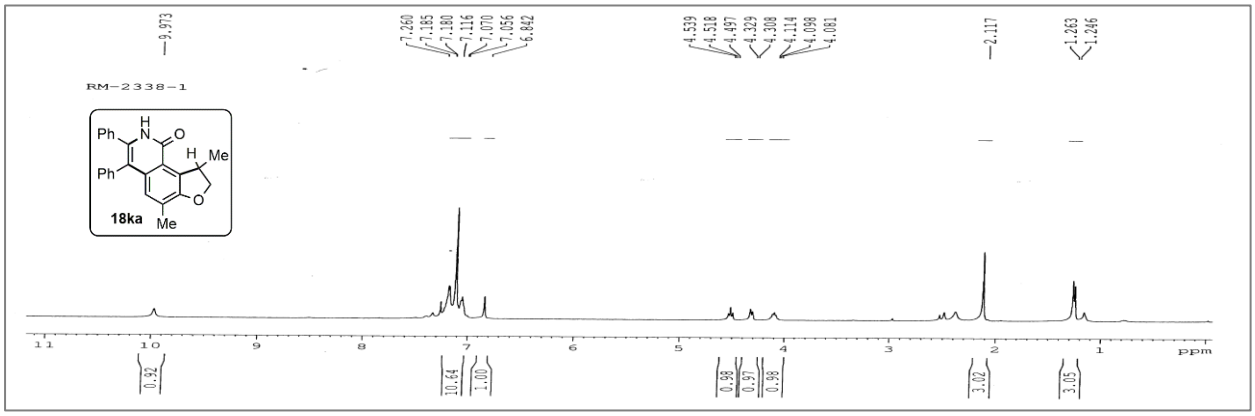

kg-7-162
18ga
ppm

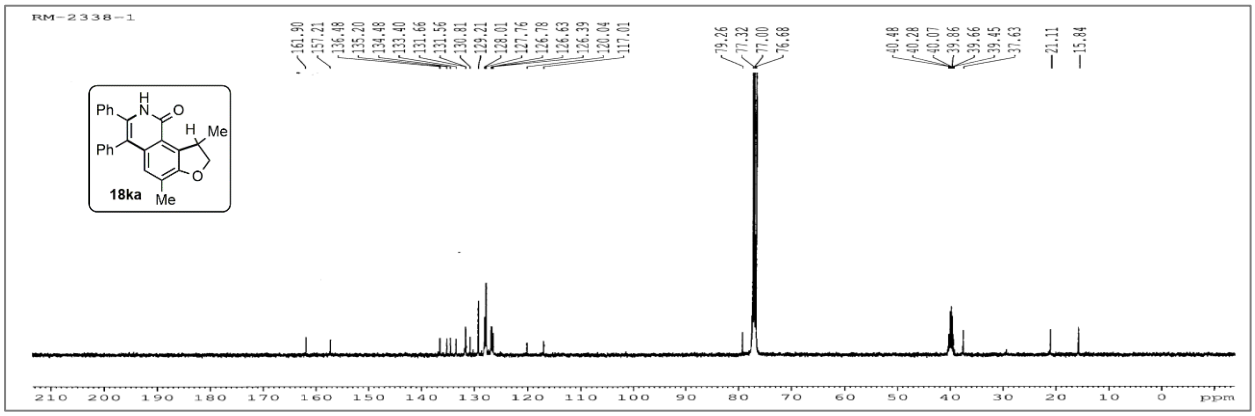

kg-7-161
18ha
ppm

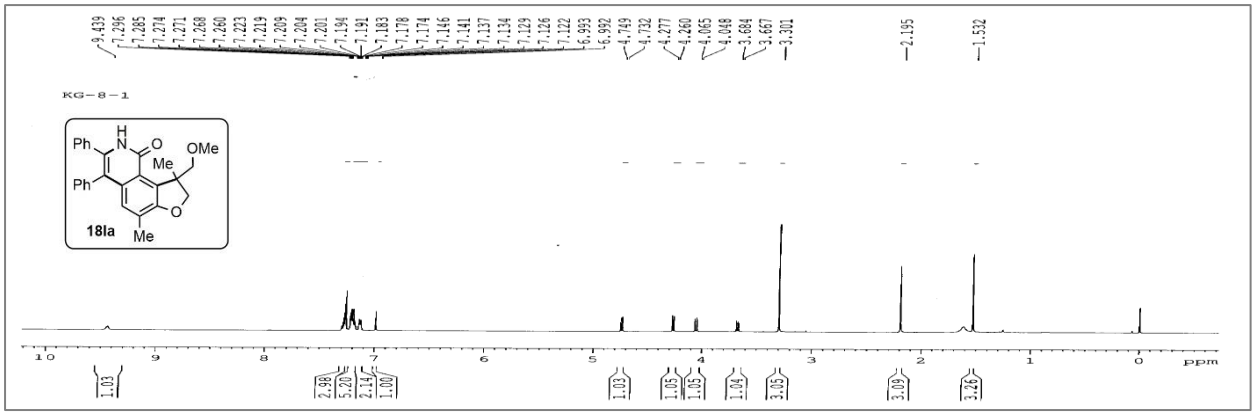

kg-7-161
18ha
ppm

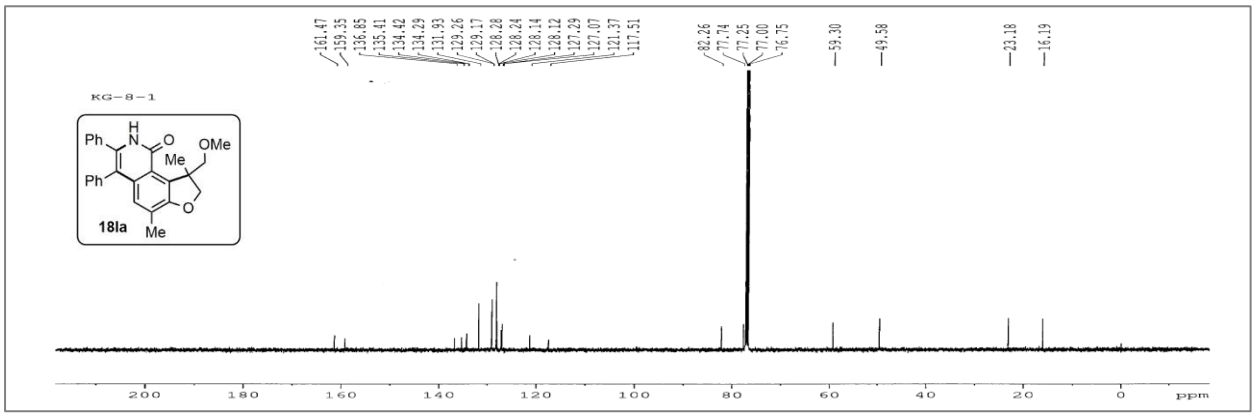

18ja

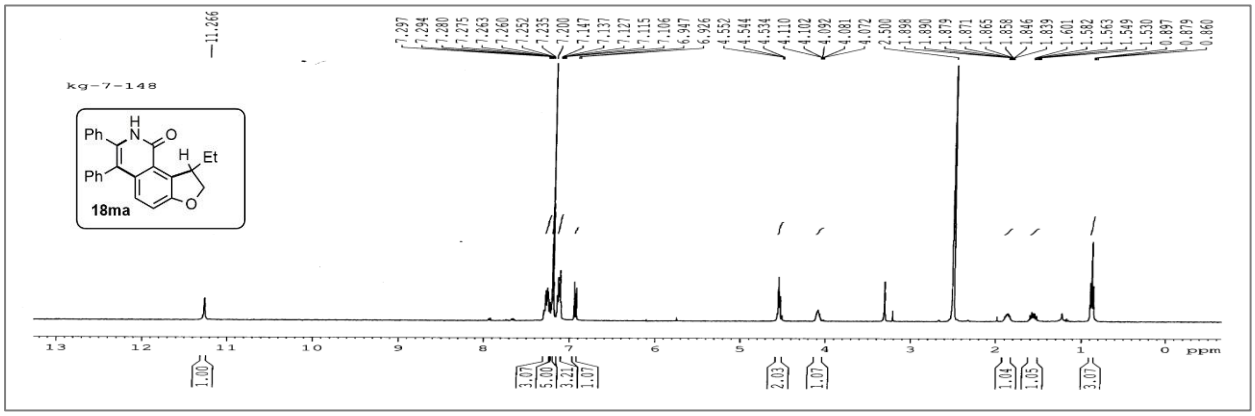

kg-mono methyl annnulation(dc-04)
18ja

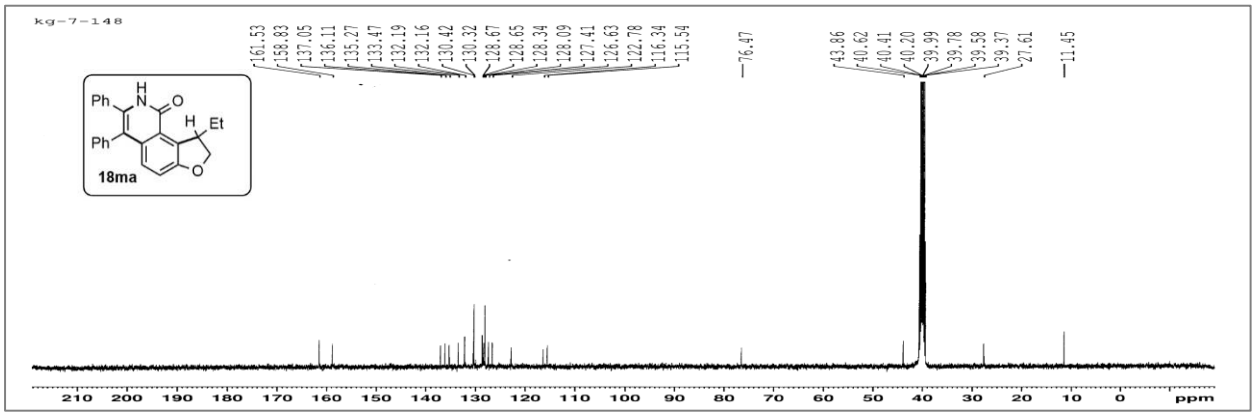

RM-2338-1
18ka

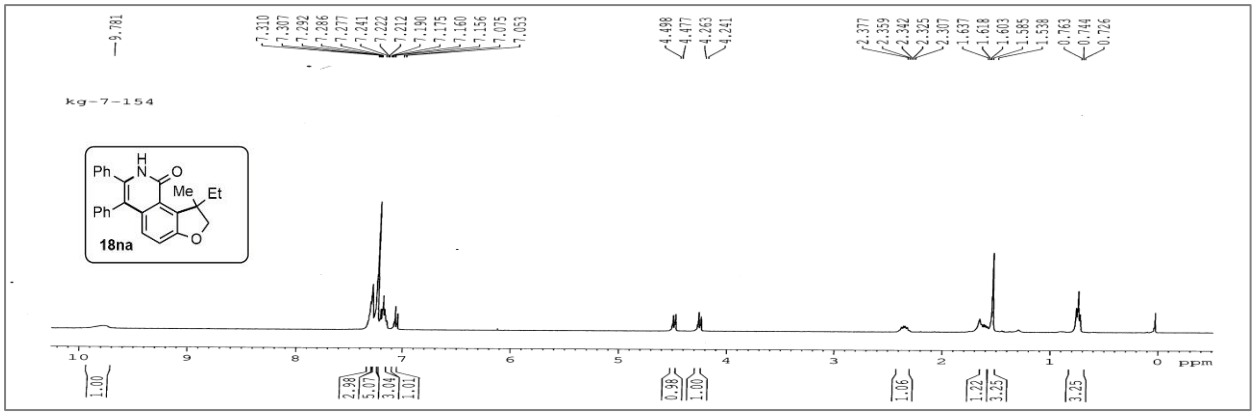

RM-2338-1
18ka

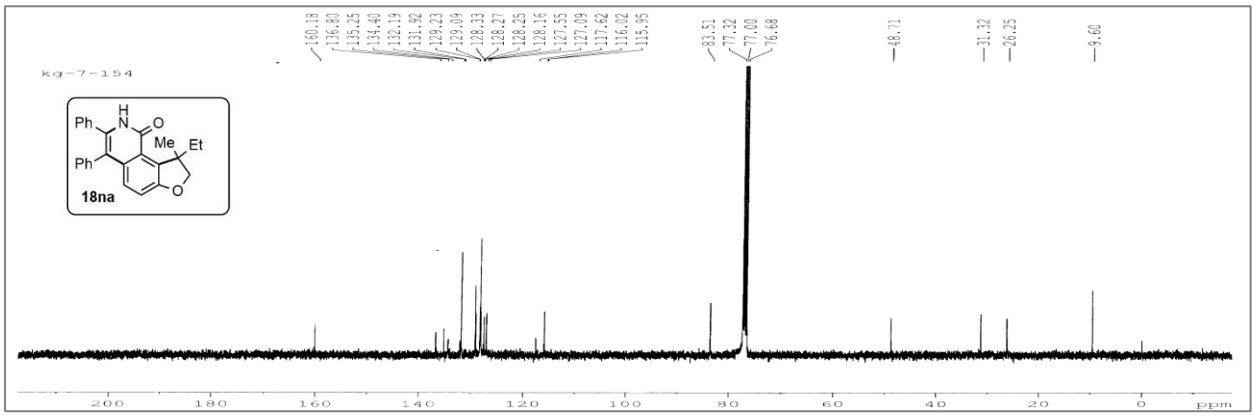

KG-8-1
18la

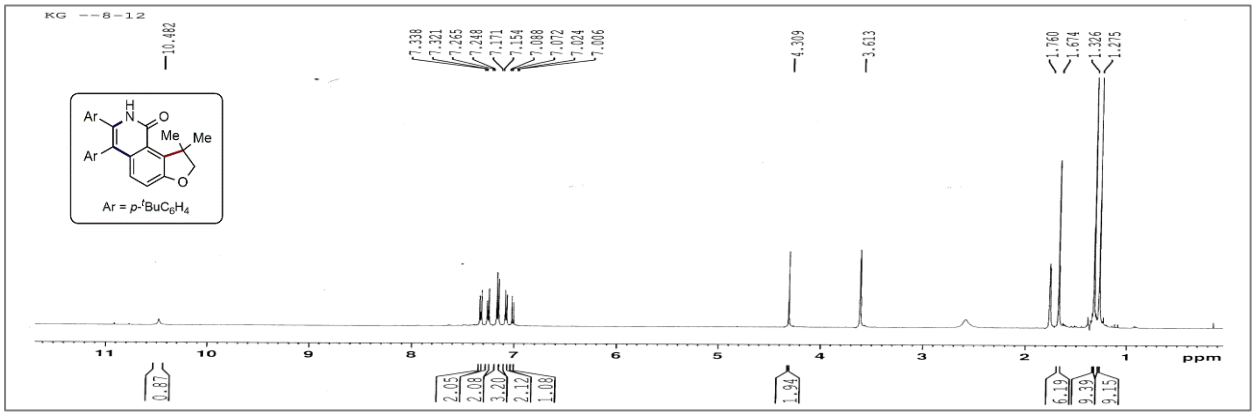

KG-8-1
18la

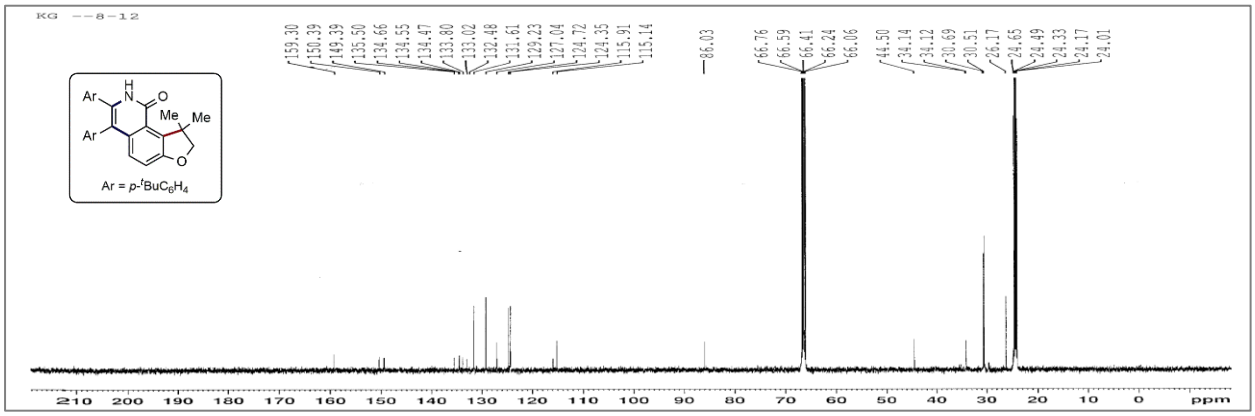

kg-7-148
18ma

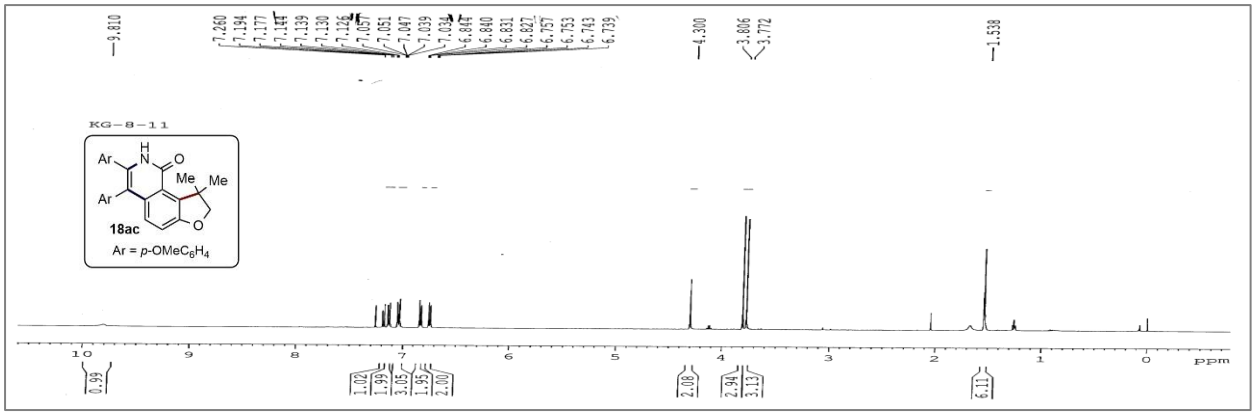

kg-7-148
18ma

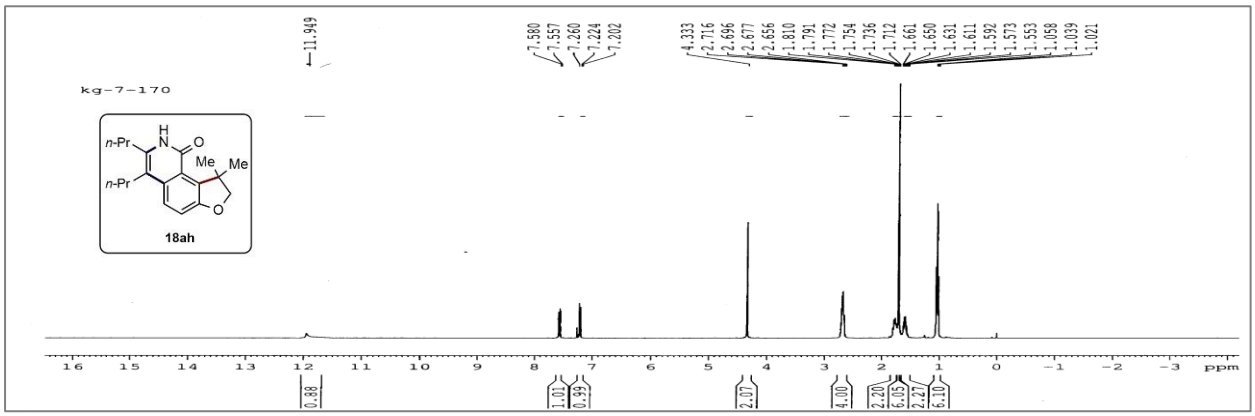

kg-7-154
18na

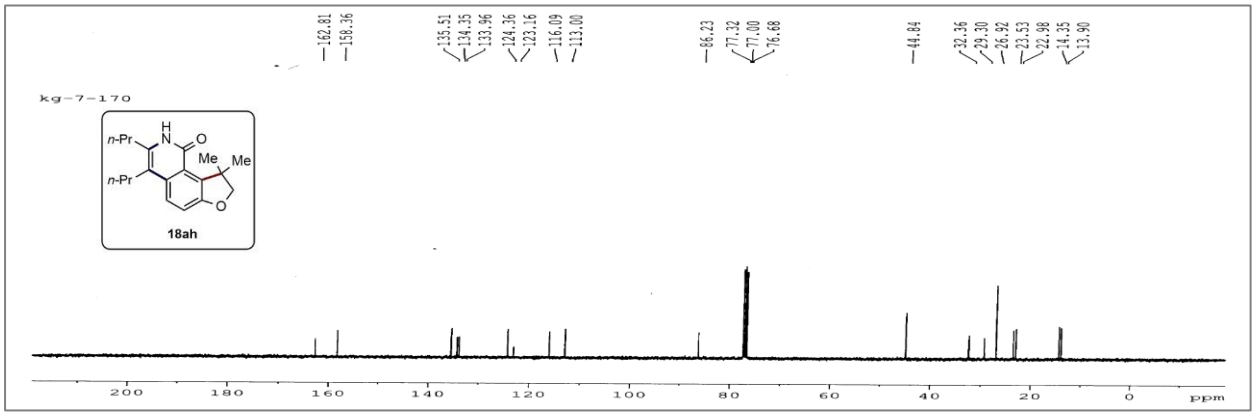

kg-7-154
18na

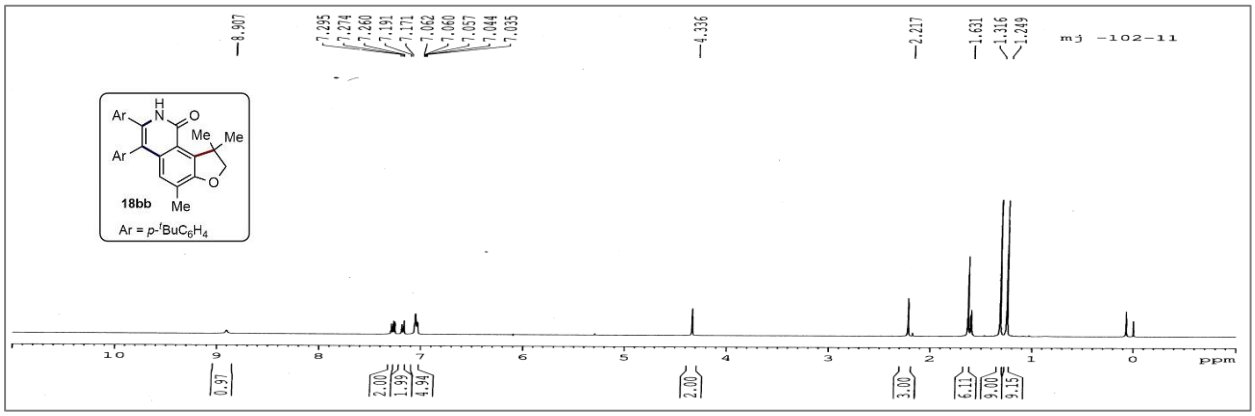

KG --8-12
Ar = p-tBuC6H4

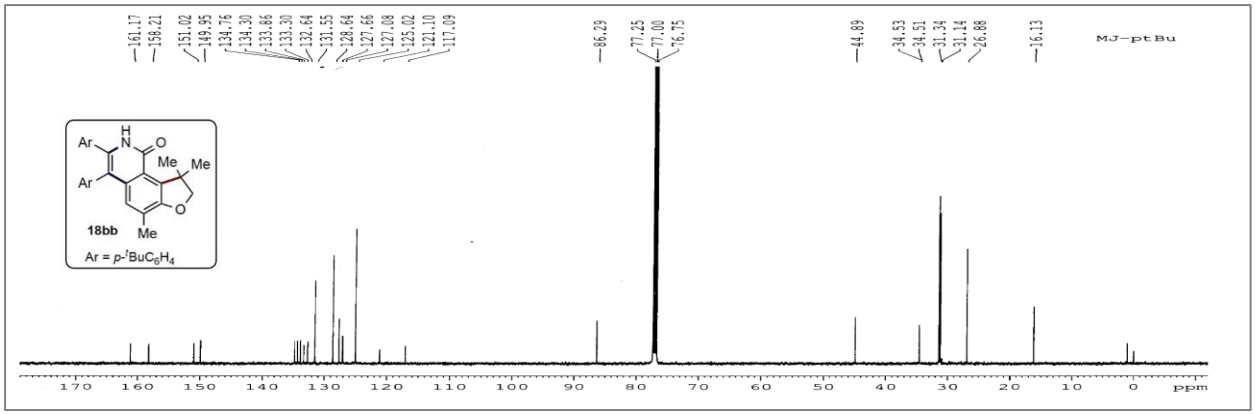

KG --8-12
Ar = p-tBuC6H4

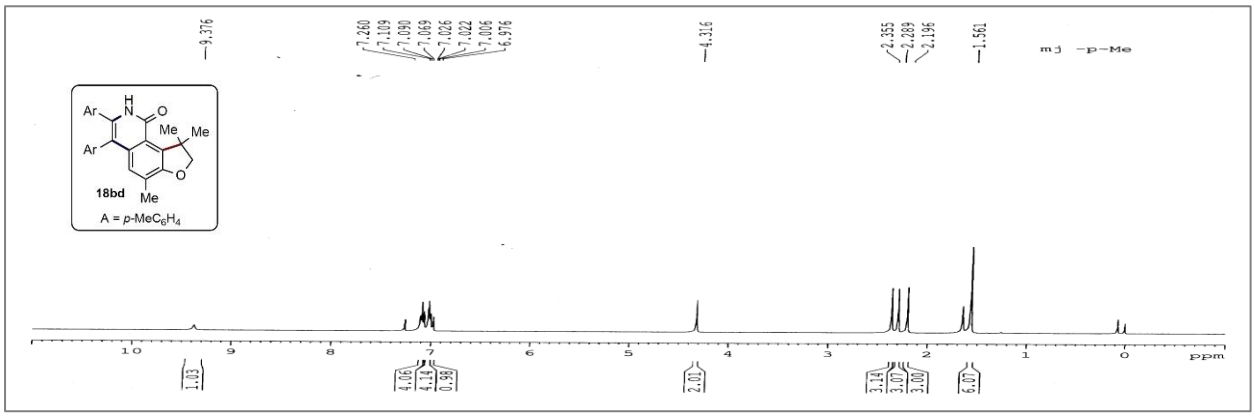

KG-8-11
18ac
Ar = p-OMeC6H4

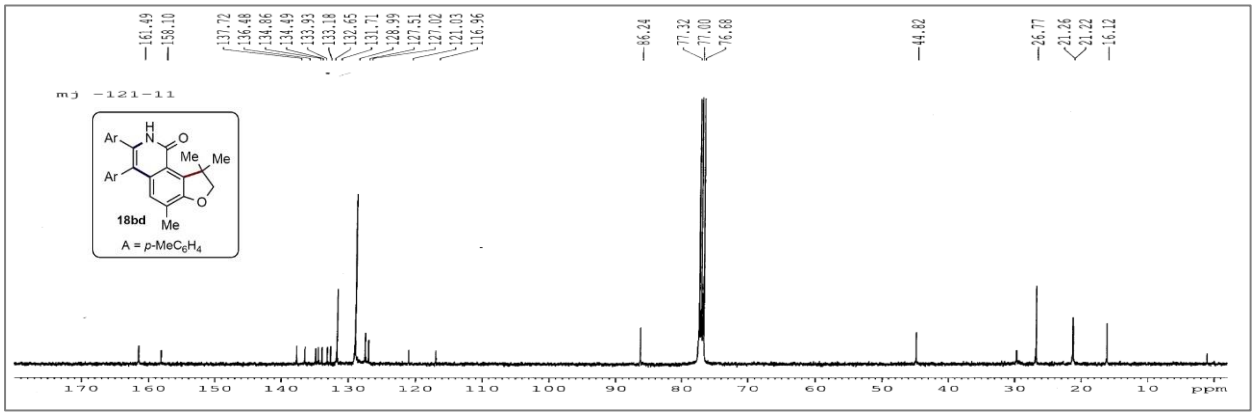

kg-7-170
18ah


kg-7-170
18ah

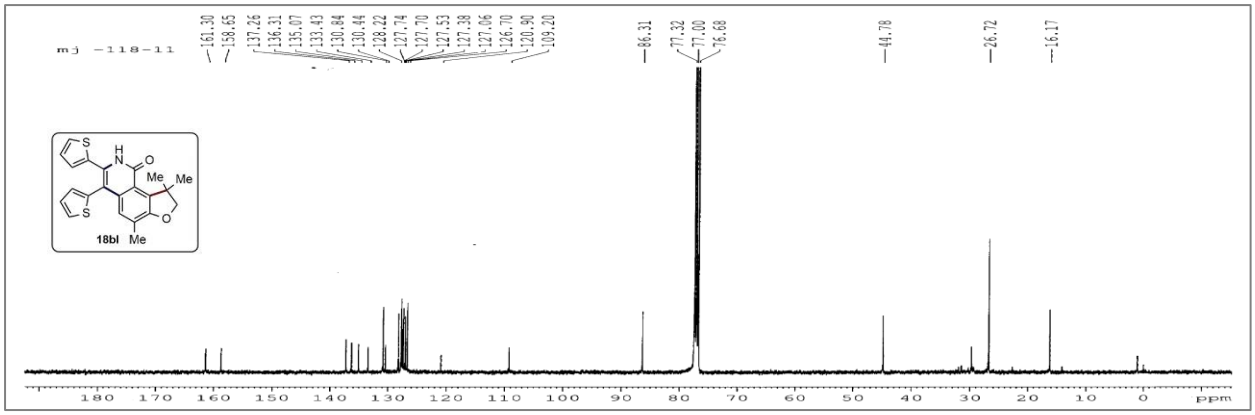

mj -102-11
18bb
Ar = p-tBuC6H4

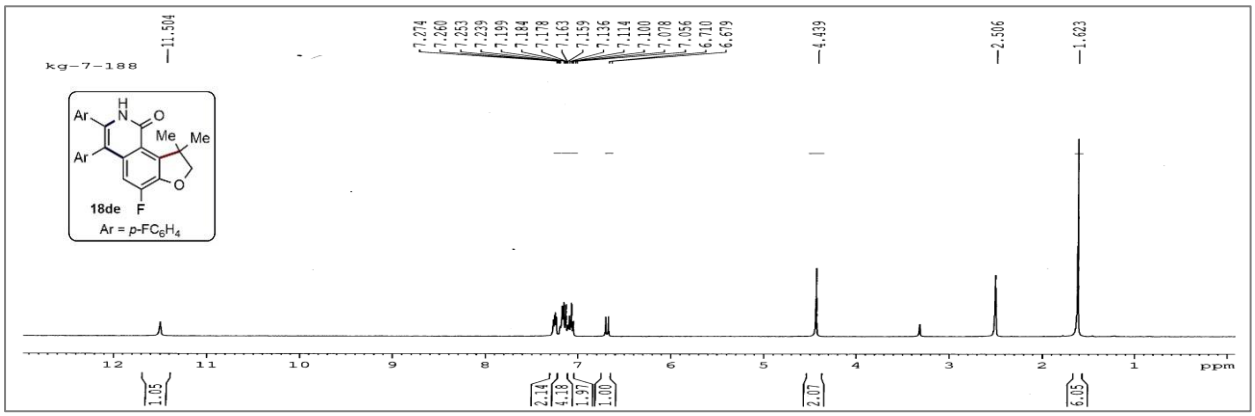

MJ-ptBu
18bb
Ar = p-tBuC6H4

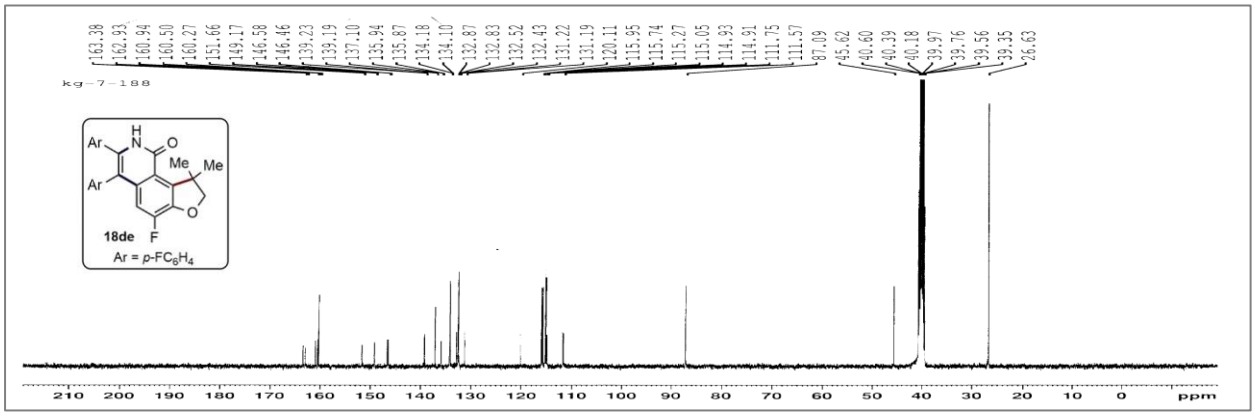

mj -p-Me
18bd
A = p-MeC6H4

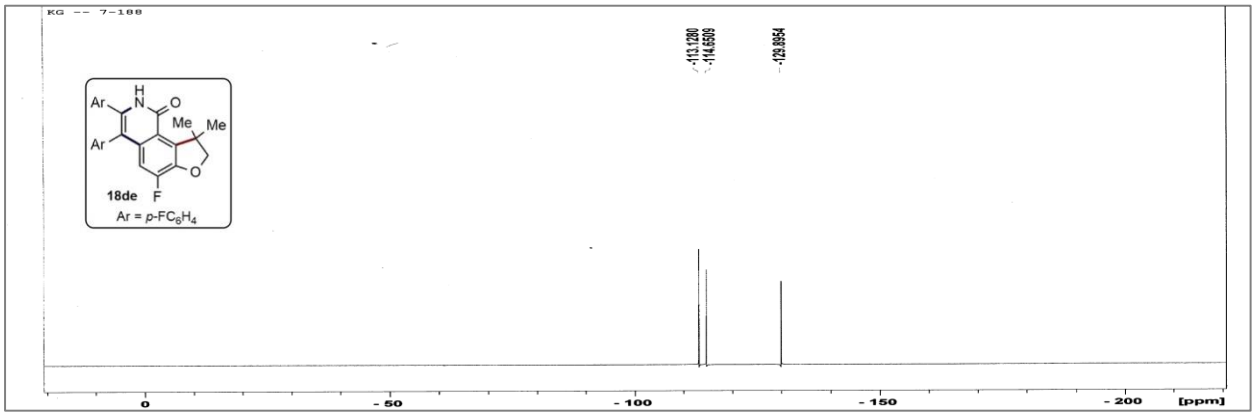

mj -121-11
18bd
A = p-MeC6H4

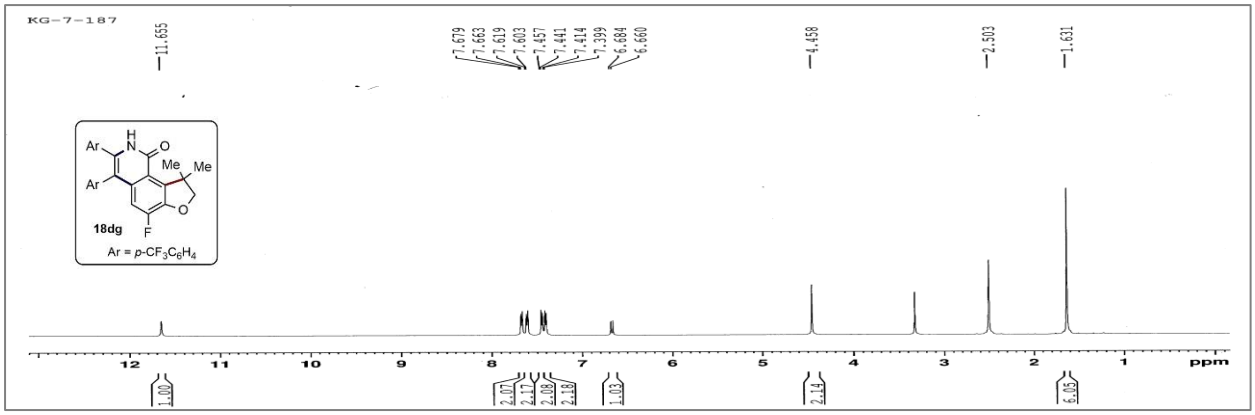

MJ-118-11
18bl

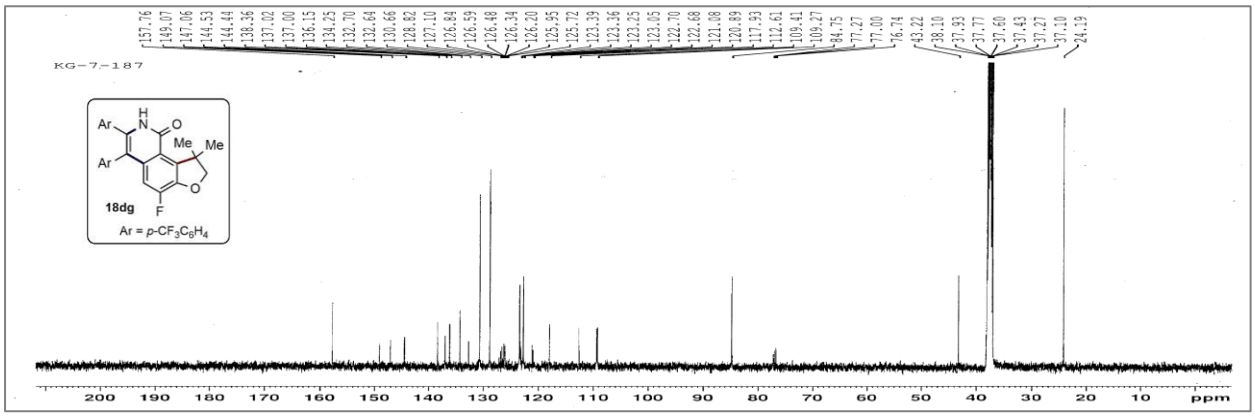

mj -118-11
18bl Me

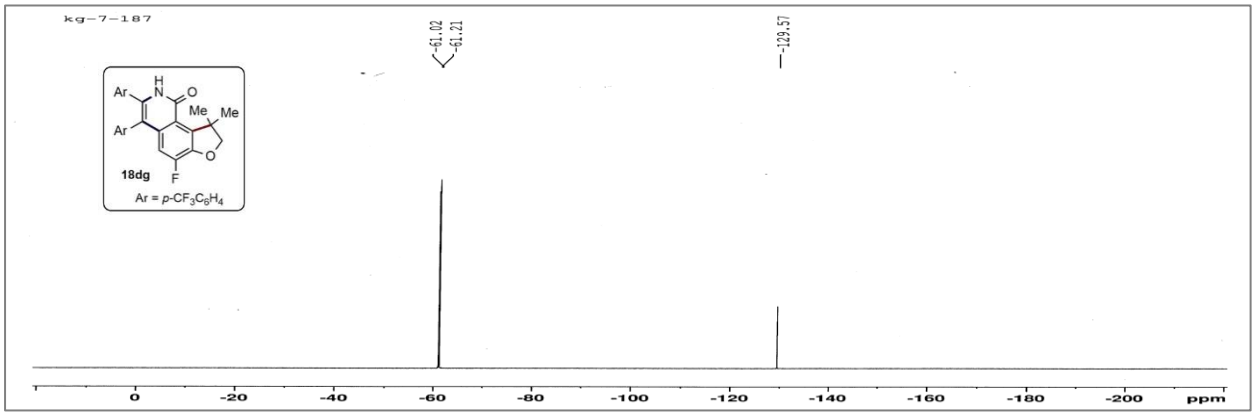

kg-7-188
18de F
Ar = p-FC6H4

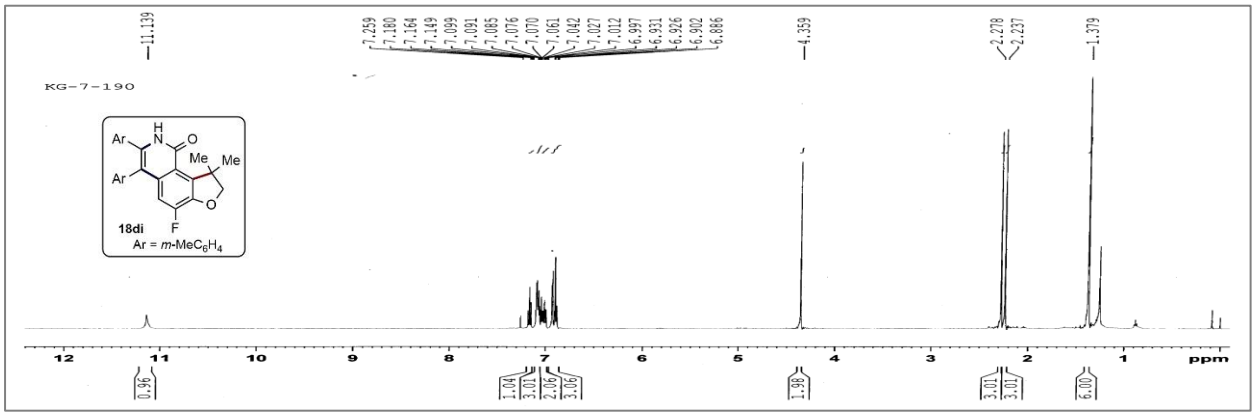

kg-7-188
18de F
Ar = p-FC6H4

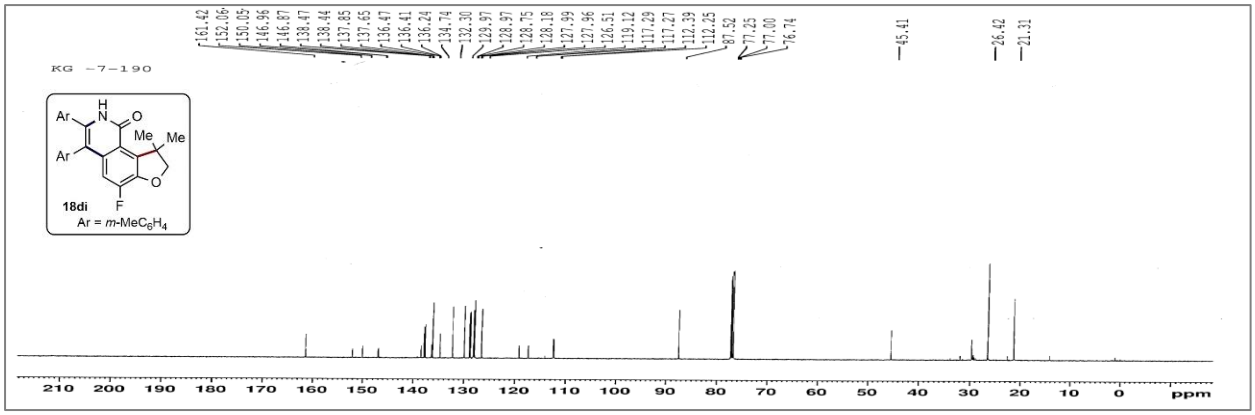

KG -- 7-188
18de F
Ar = p-FC6H4

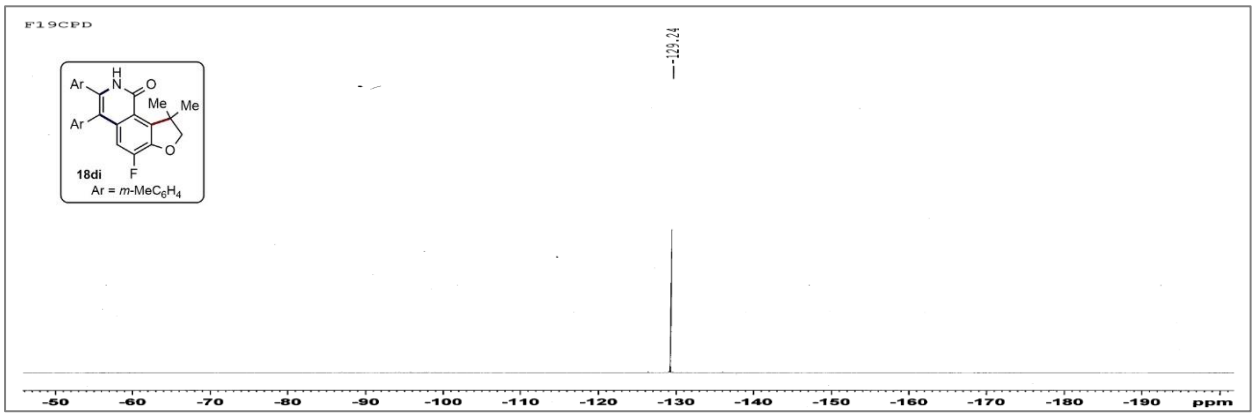

KG-7-187
11.655
7.679
7.663
7.619
7.603
7.457
7.441
7.414
7.399
6.684
6.660
4.458
2.503
1.631
18dg
Ar = p-CF3C6H4
ppm

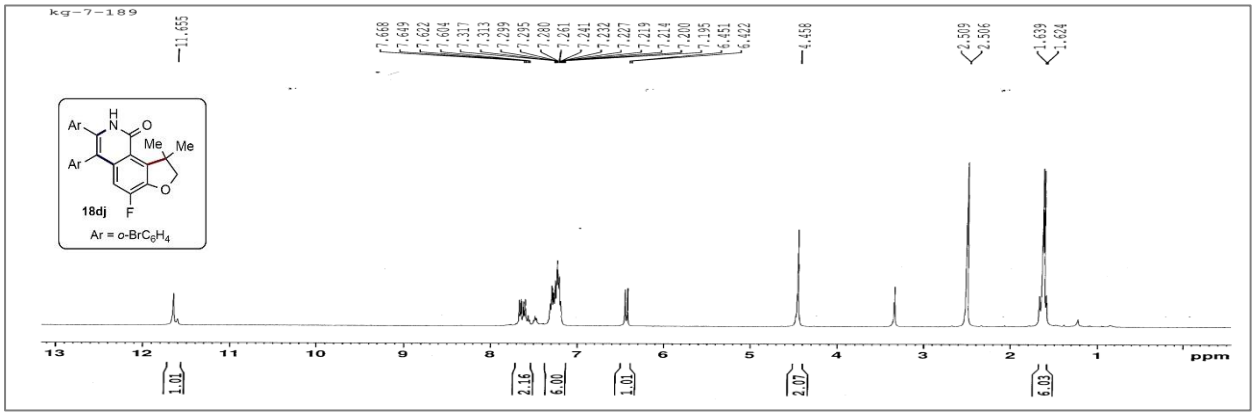

KG-7-187
18dg
Ar = p-CF3C6H4
ppm

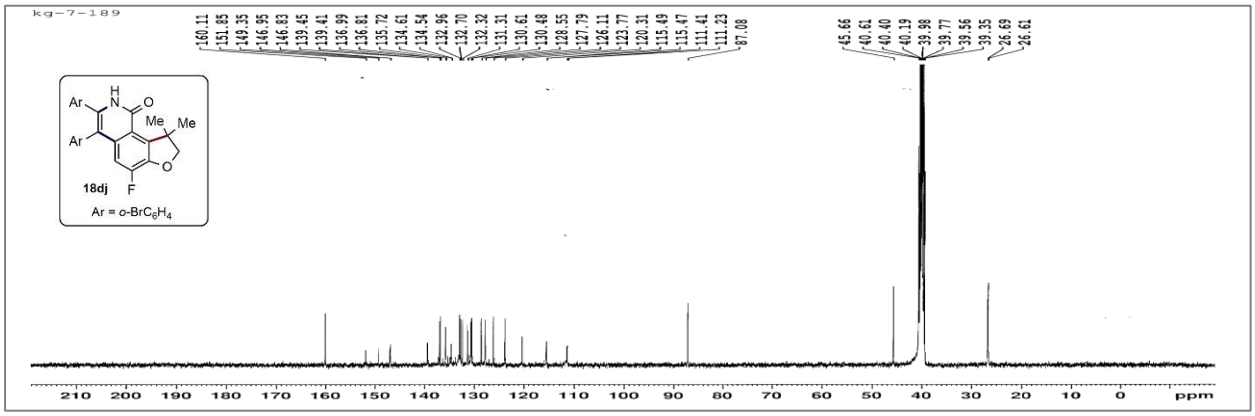

kg-7-187
-61.02
-61.21
-129.57
18dg
Ar = p-CF3C6H4
ppm

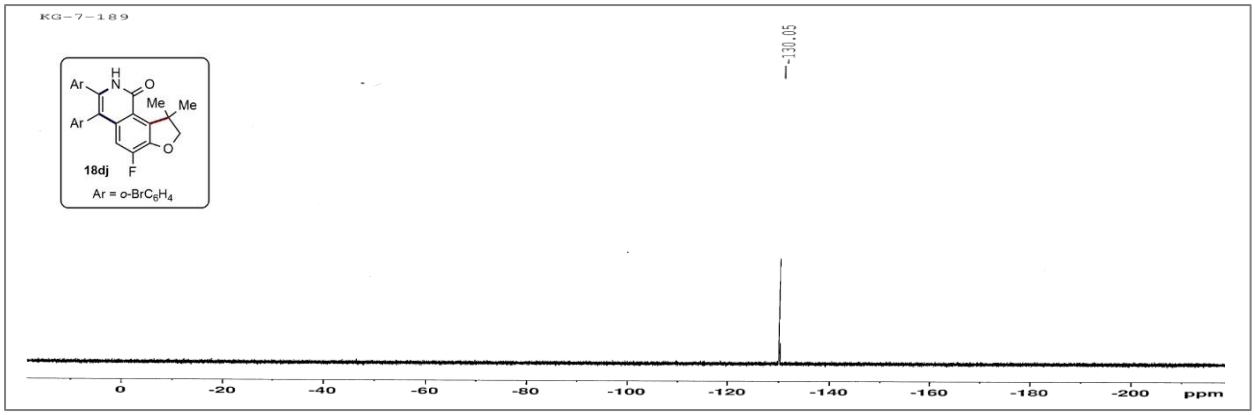

KG-7-190
11.139
7.259
7.180
7.164
7.149
7.099
7.091
7.085
7.076
7.070
7.061
7.042
7.027
7.012
6.997
6.931
6.926
6.902
6.886
4.359
2.278
2.237
1.379
18di
Ar = m-MeC6H4
ppm

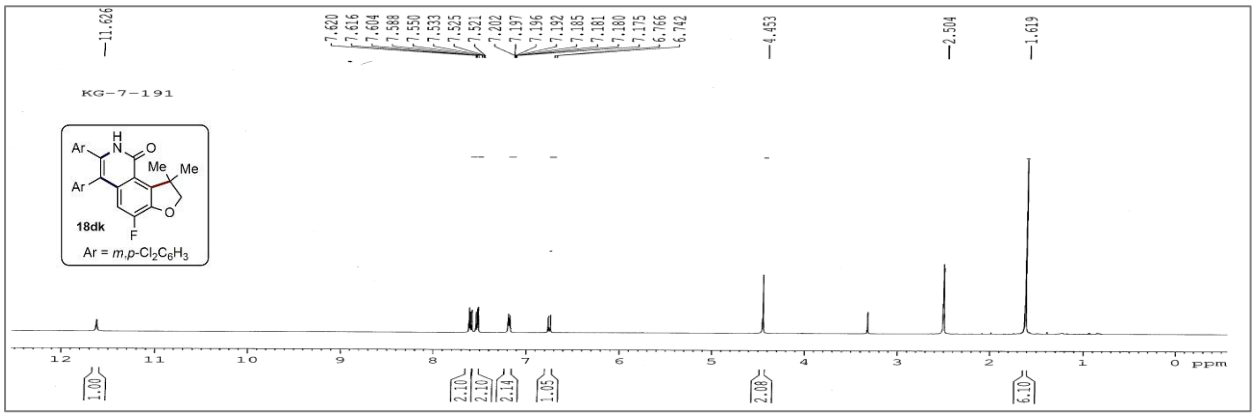

KG -7-190
18di
Ar = m-MeC6H4

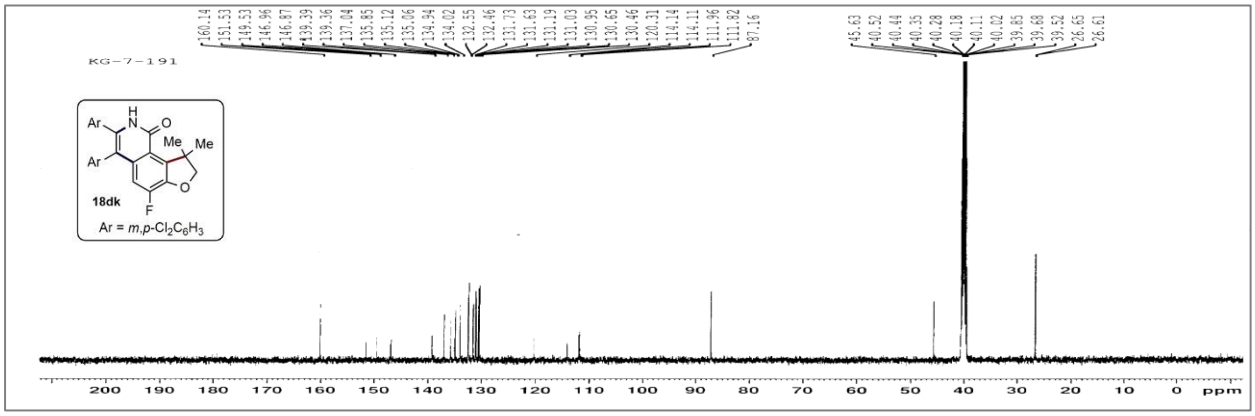

F19CPD
18di
Ar = m-MeC6H4

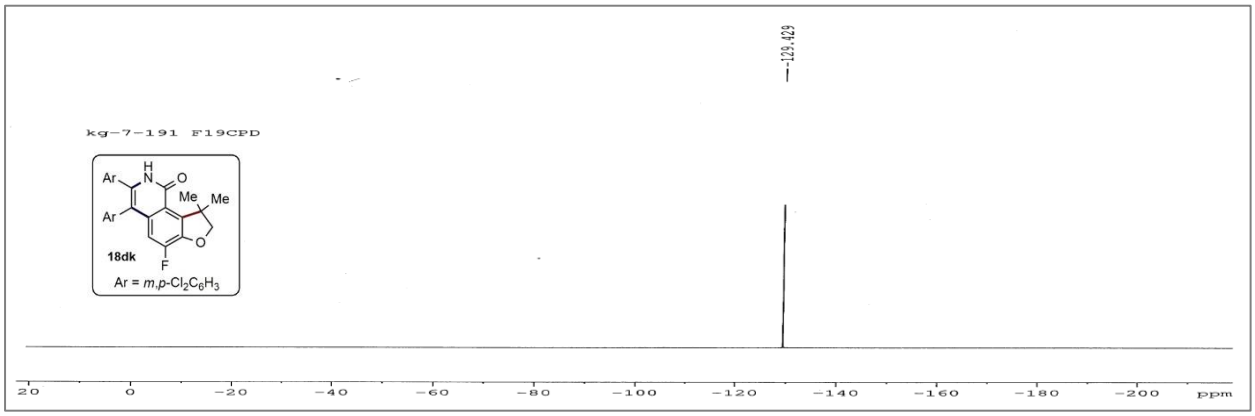

kg-7-189
18dj
Ar = o-BrC6H4

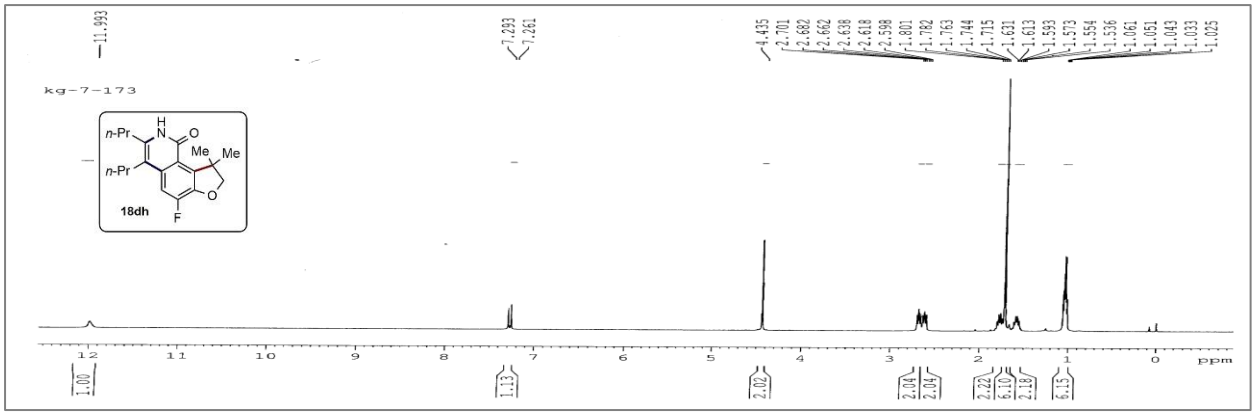

kg-7-189
18dj
Ar = o-BrC6H4

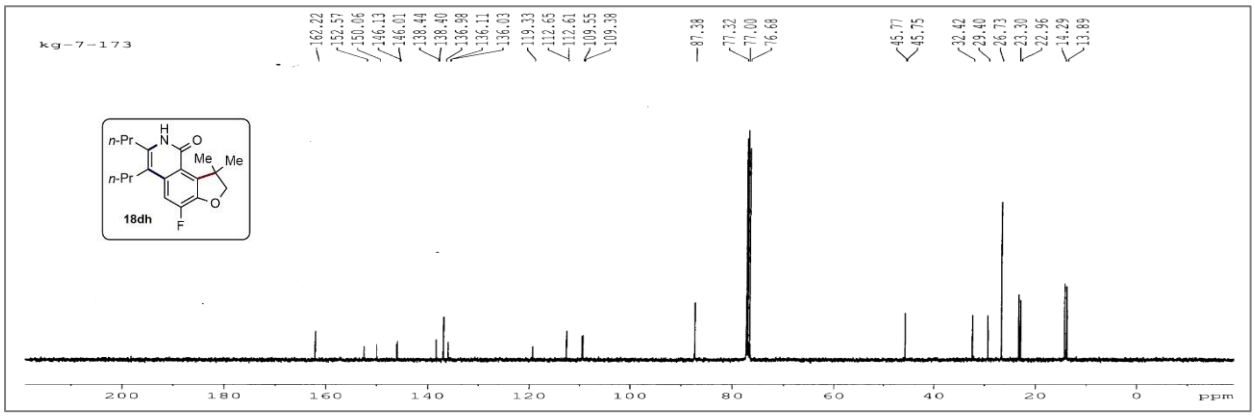

KG-7-189
-130.05
18dj
Ar = o-BrC6H4
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

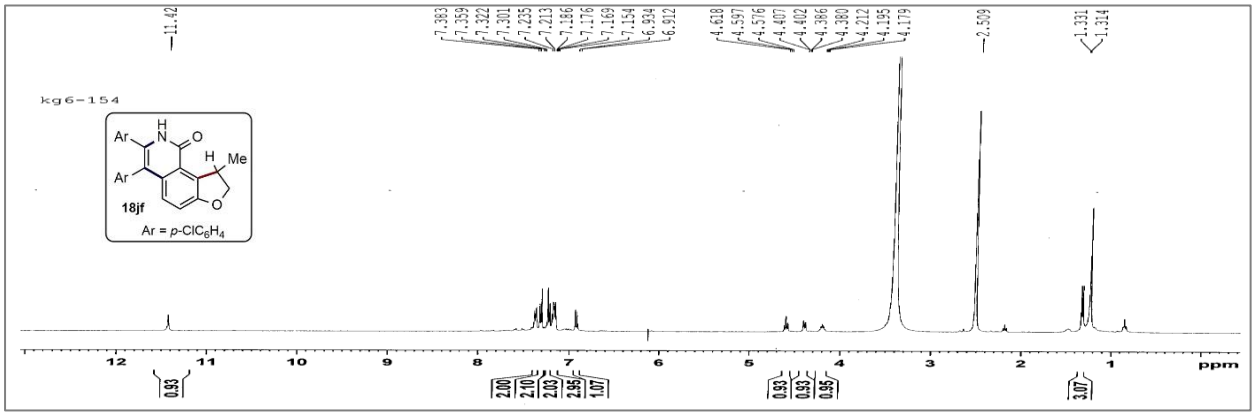

11.626
7.620 7.616 7.604 7.588 7.550 7.533 7.525 7.521 7.202 7.197 7.196 7.192 7.185 7.181 7.180 7.175 6.766 6.742
4.453
2.504
1.619
KG-7-191
18dk
Ar = m,p-Cl2C6H3
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 2.10 2.10 2.14 1.05 2.08 6.10

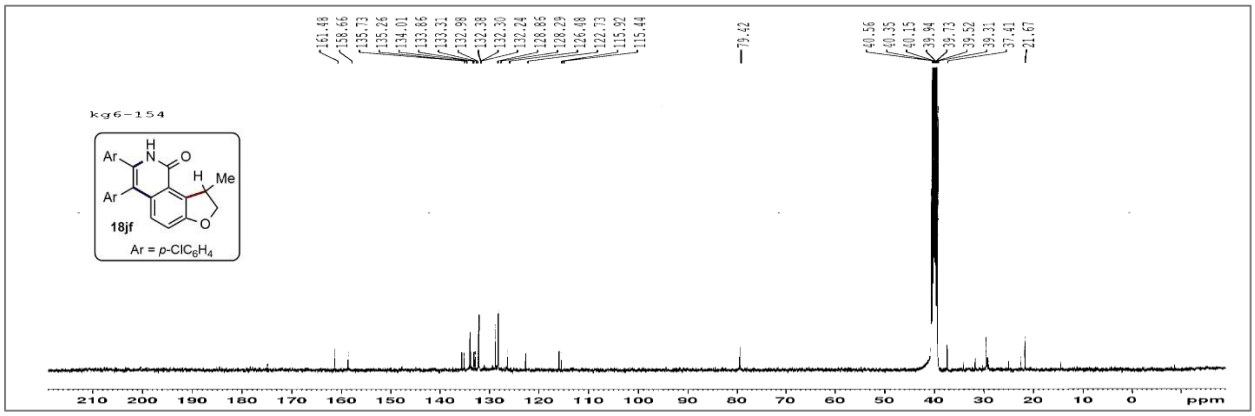

160.14 151.53 149.53 146.96 146.67 139.39 139.36 137.04 135.85 135.12 135.06 134.94 134.02 132.55 132.46 131.73 131.63 131.19 131.03 130.95 130.65 130.46 120.31 114.14 114.11 111.96 111.82 87.16
45.63 40.52 40.44 40.35 40.28 40.18 40.11 40.02 39.85 39.68 39.52 26.65 26.61
KG-7-191
18dk
Ar = m,p-Cl2C6H3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

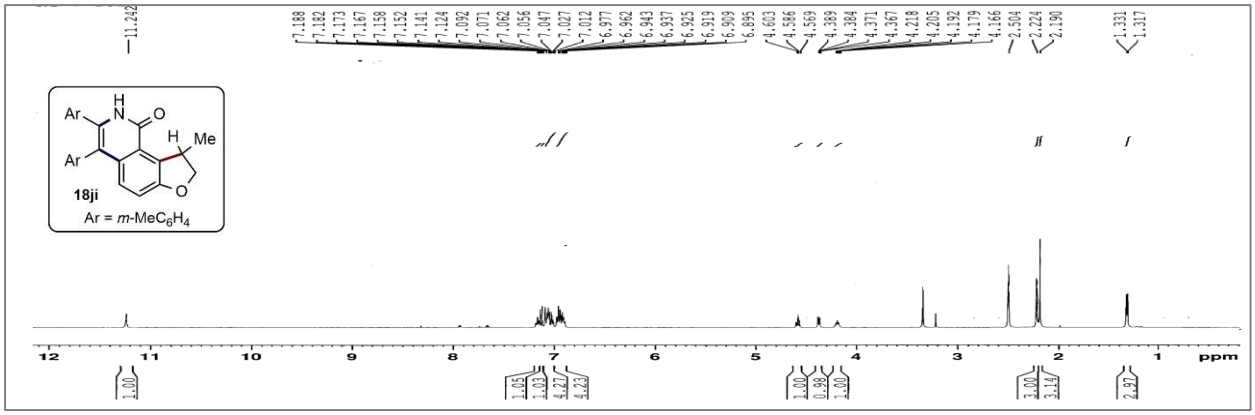

-129.429
kg-7-191 F19CPD
18dk
Ar = m,p-Cl2C6H3
20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

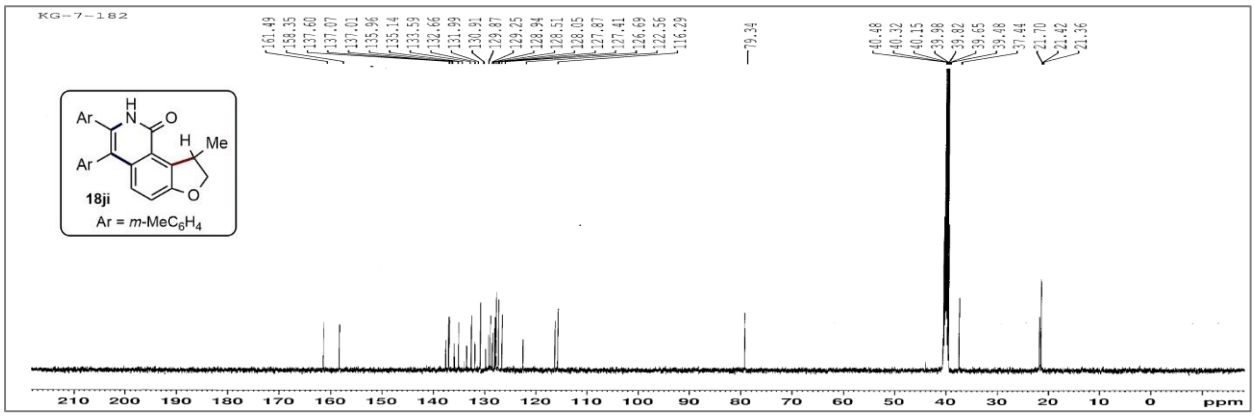

kg-7-173
18dh


kg-7-173
18dh

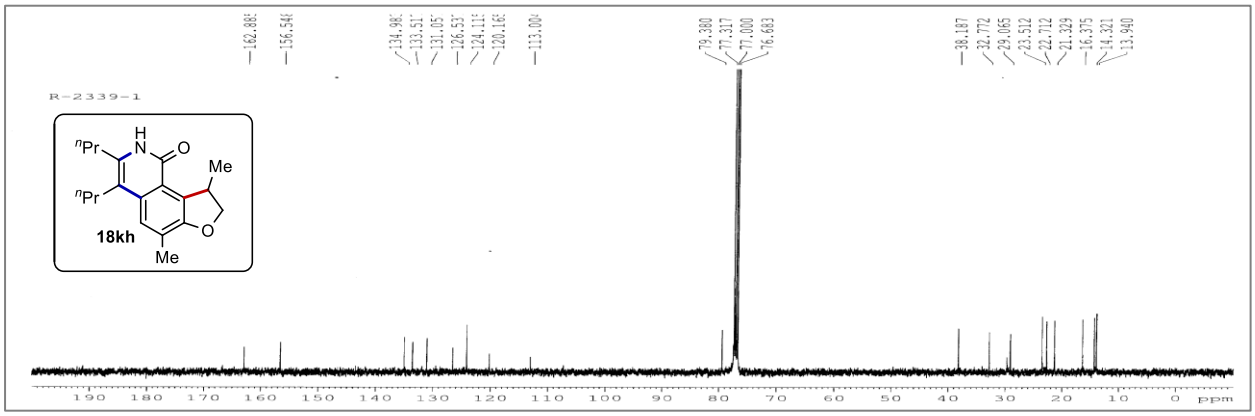

kg6-154
18jf
Ar = p-ClC6H4

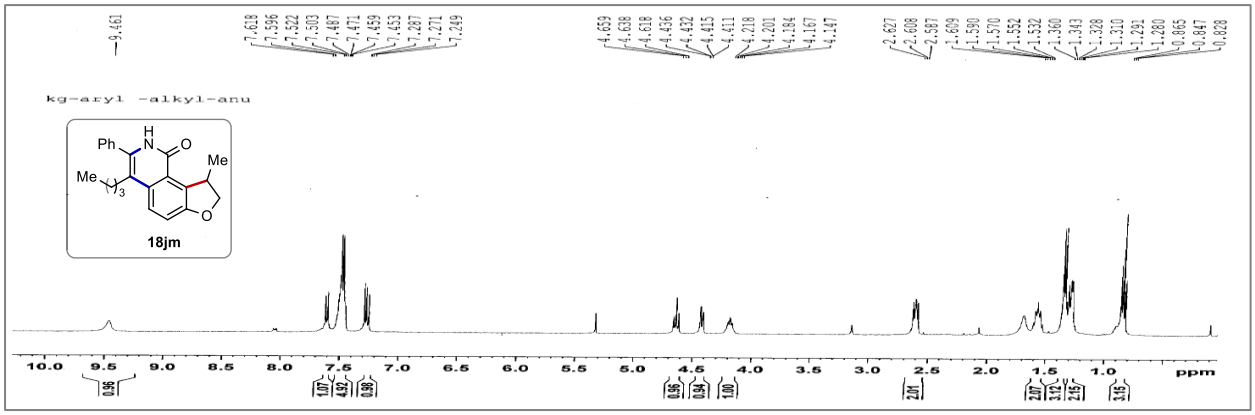

kg6-154
18jf
Ar = p-ClC6H4

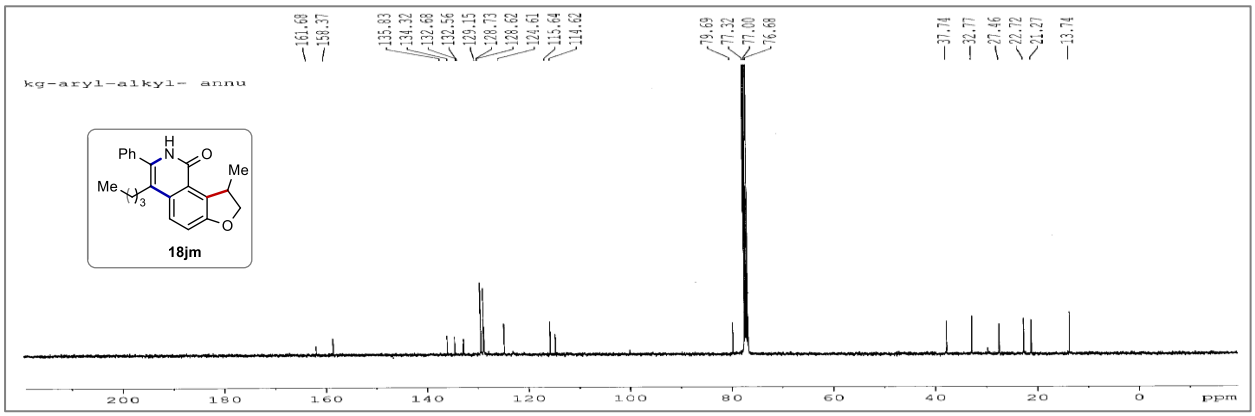

18ji
Ar = m-MeC6H4

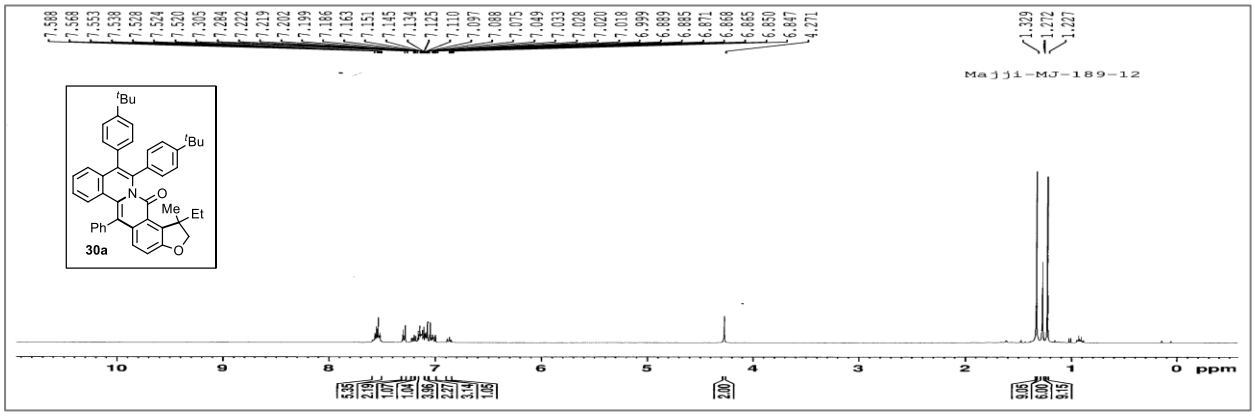

KG-7-182
18ji
Ar = m-MeC6H4

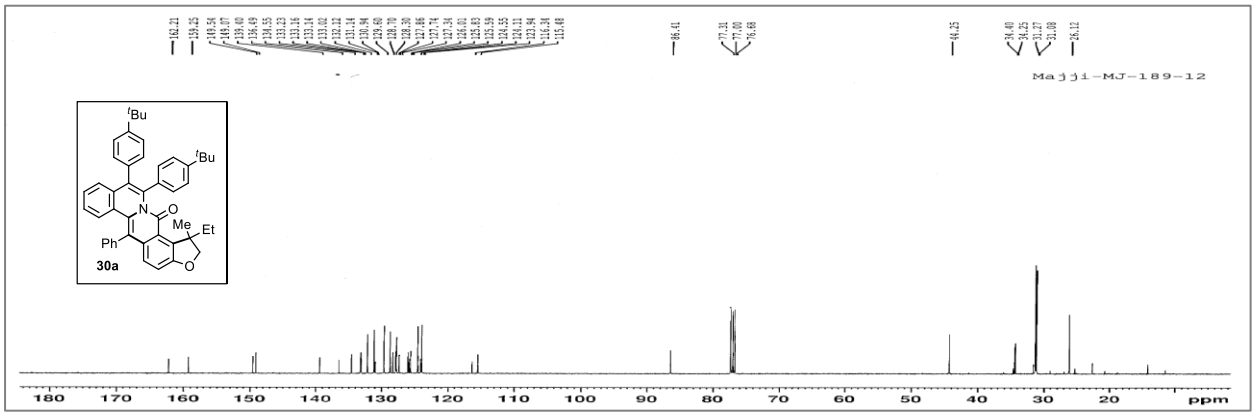

R-2339-1
18kh

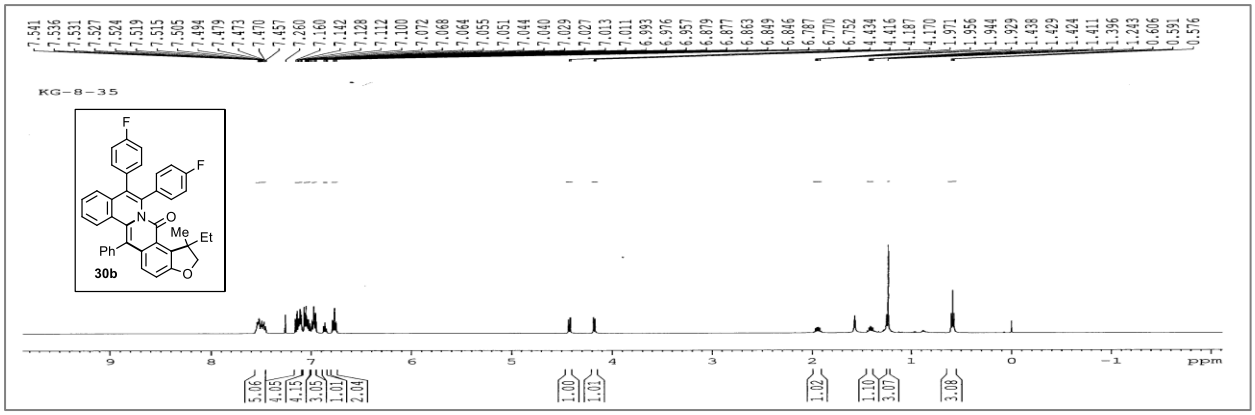

R-2339-1
18kh

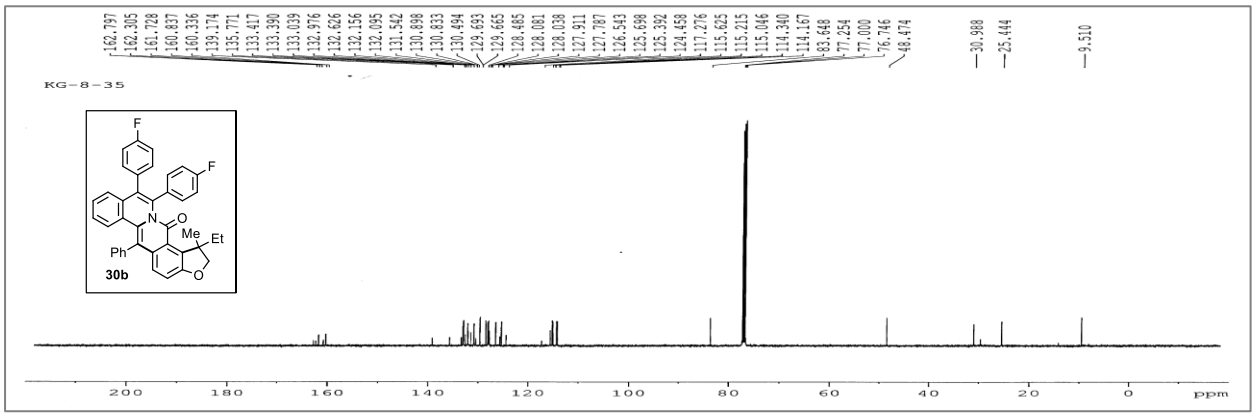

kg-aryl -alkyl-anu
18jm

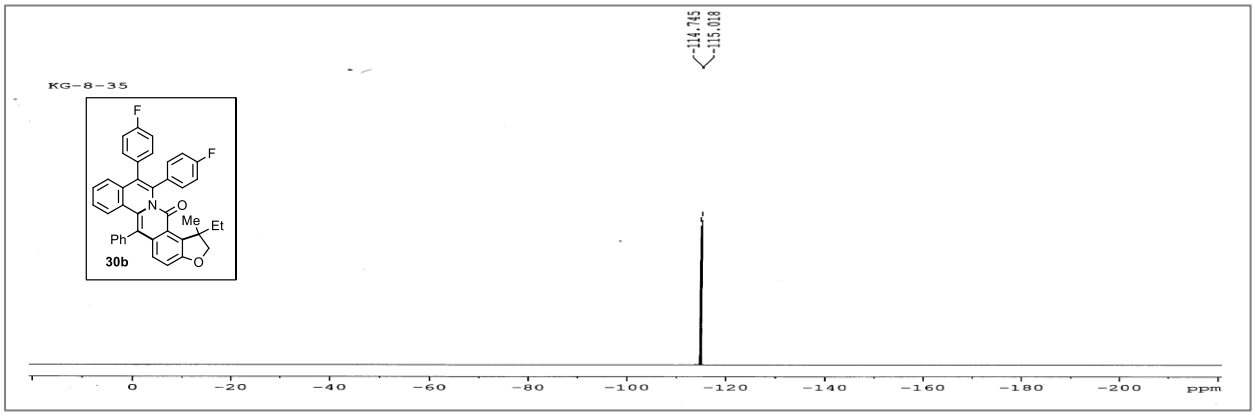

kg-aryl-alkyl- annu
18jm

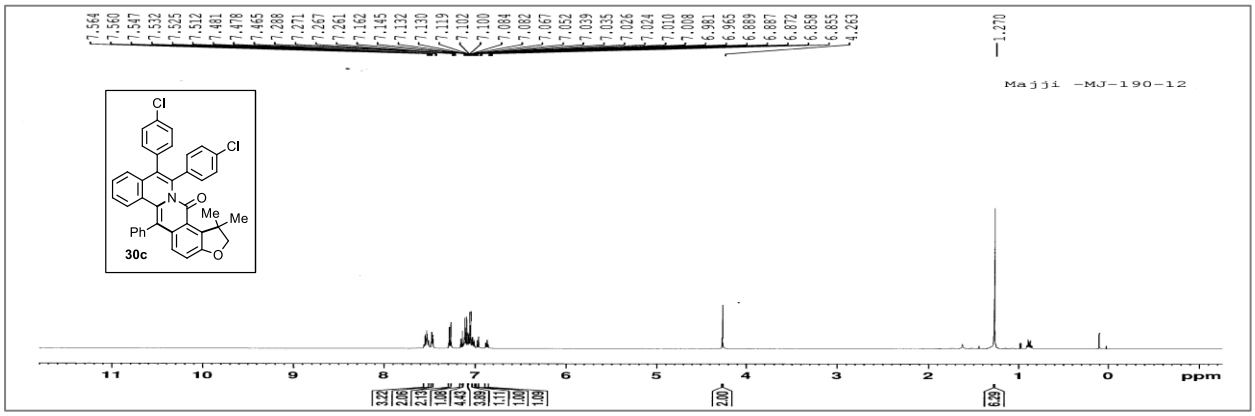

Majji-MJ-189-12
30a

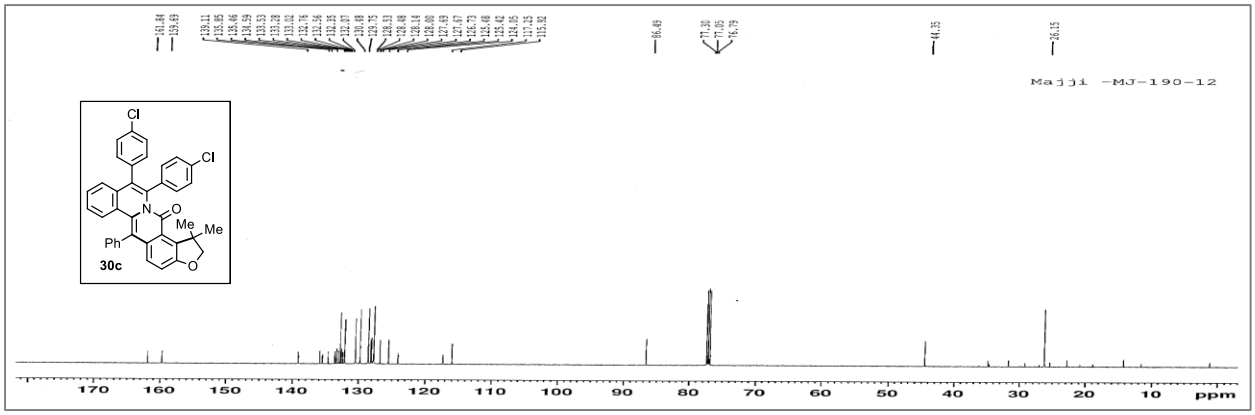

Majji-MJ-189-12
30a

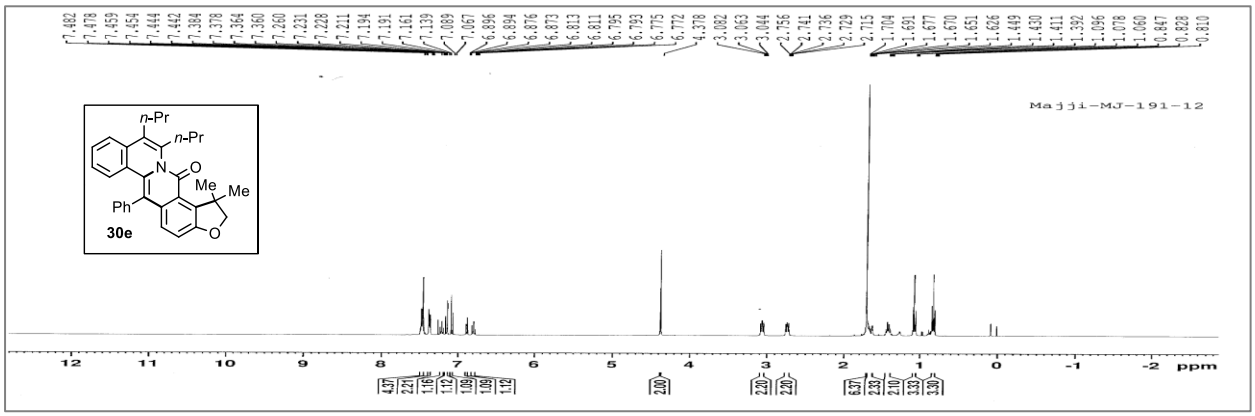

KG-8-35
30b

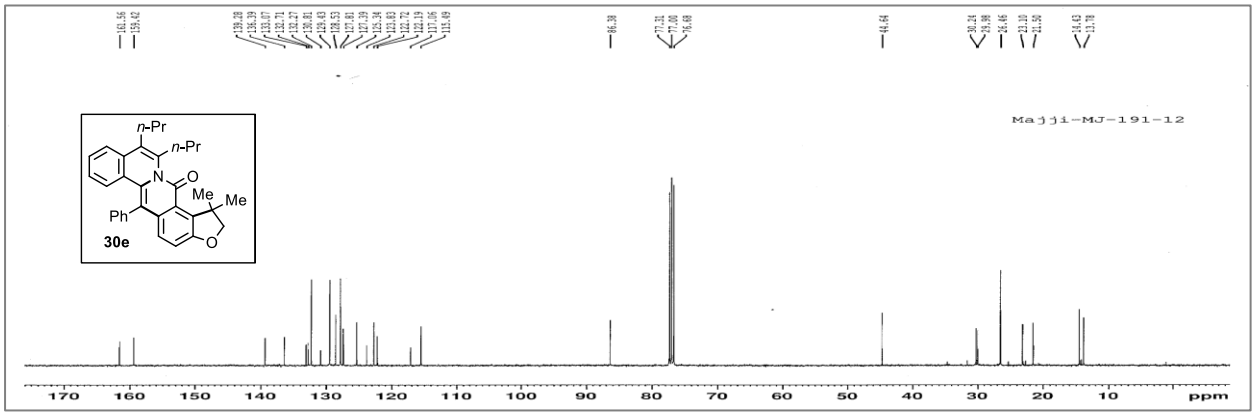

KG-8-35
30b

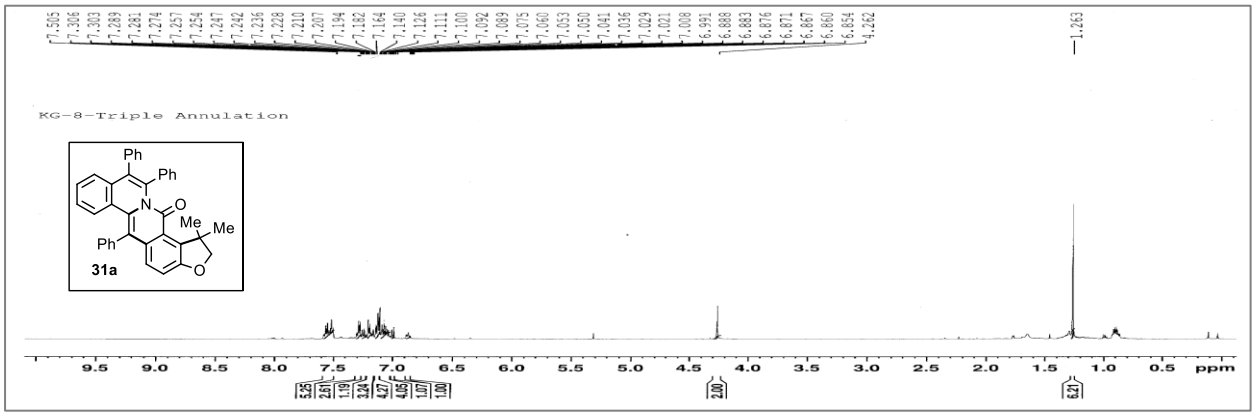

KG-8-35
30b

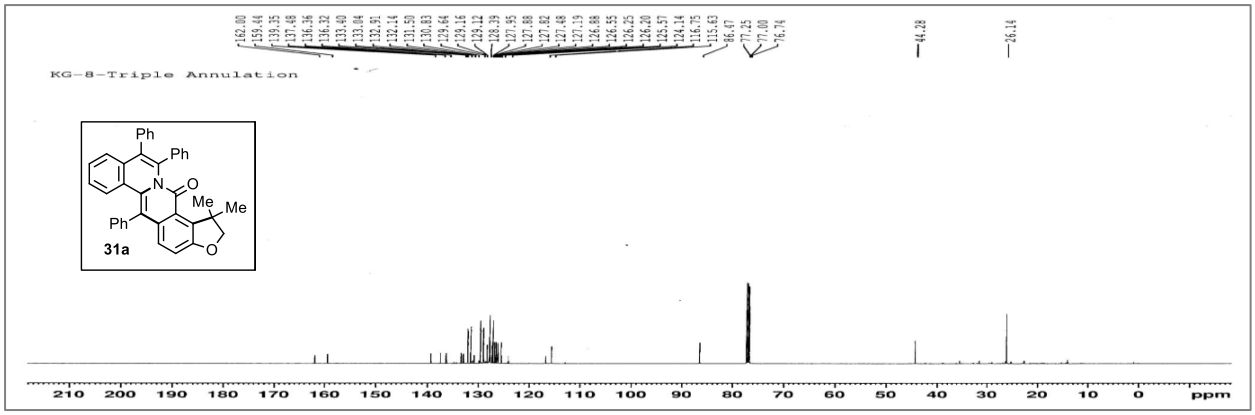

Majji -MJ-190-12
30c

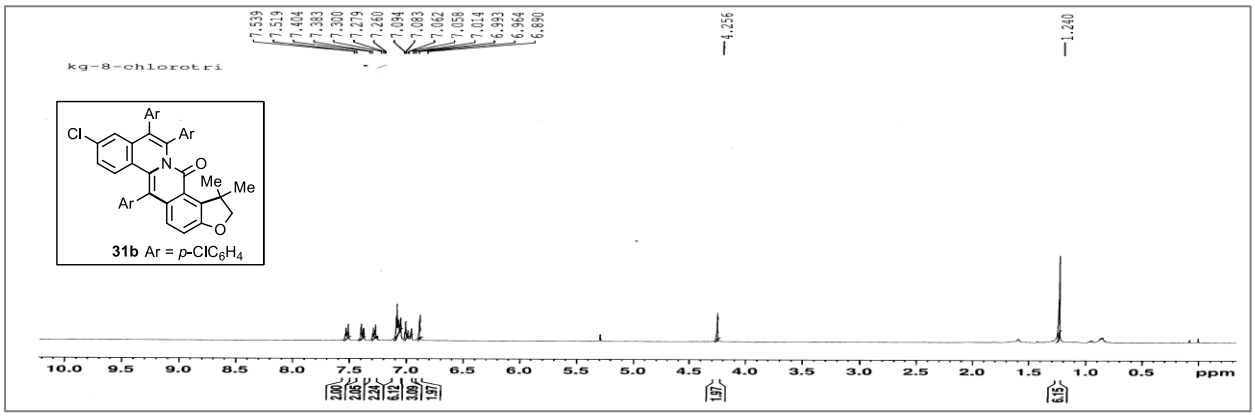

Majji -MJ-190-12
Cl
Cl
N
O
Me
Me
Ph
O
30c

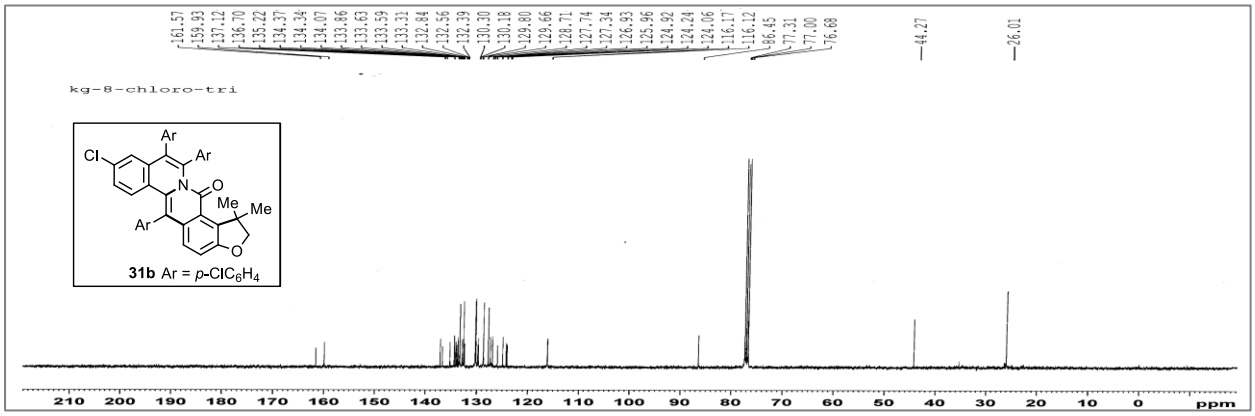

Majji-MJ-191-12
n-Pr
n-Pr
N
O
Me
Me
Ph
O
30e

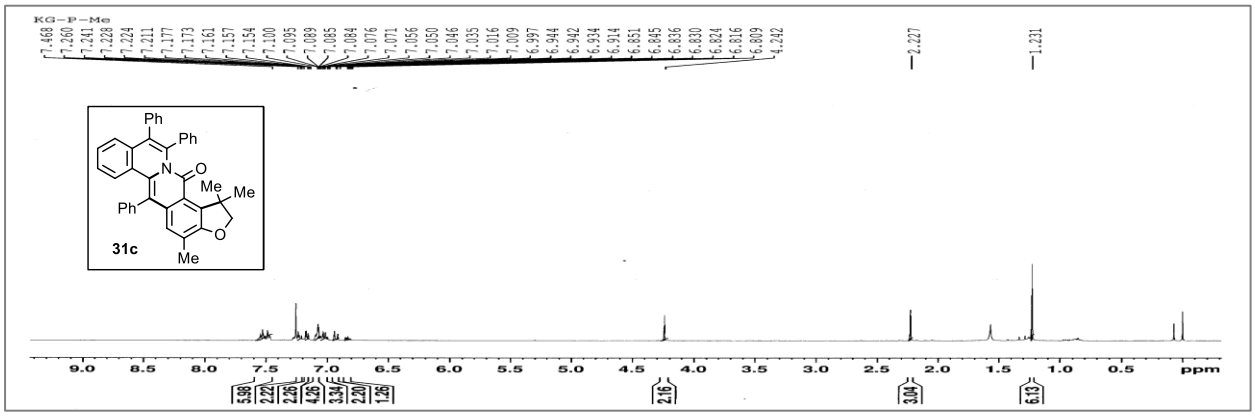

Majji-MJ-191-12
n-Pr
n-Pr
N
O
Me
Me
Ph
O
30e

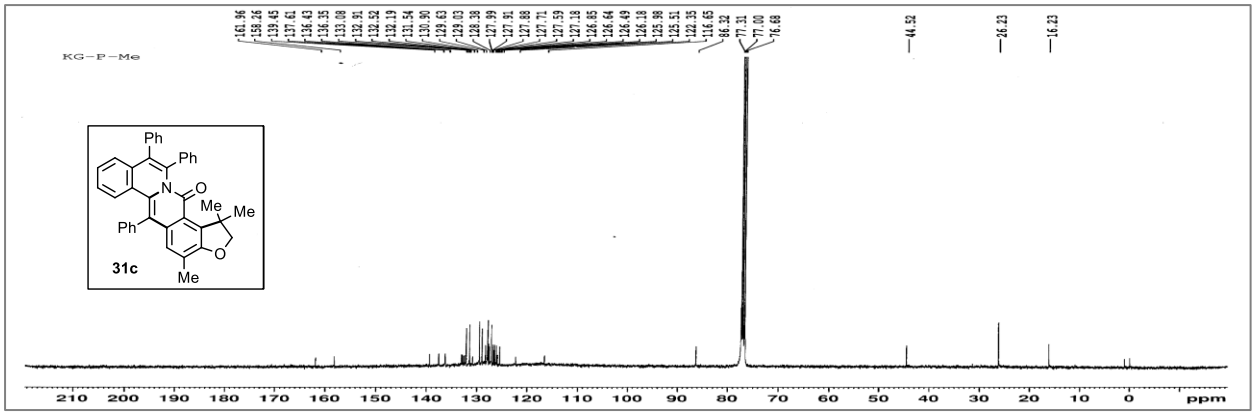

KG-8-Triple Annulation
Ph
Ph
N
O
Me
Me
Ph
O
31a

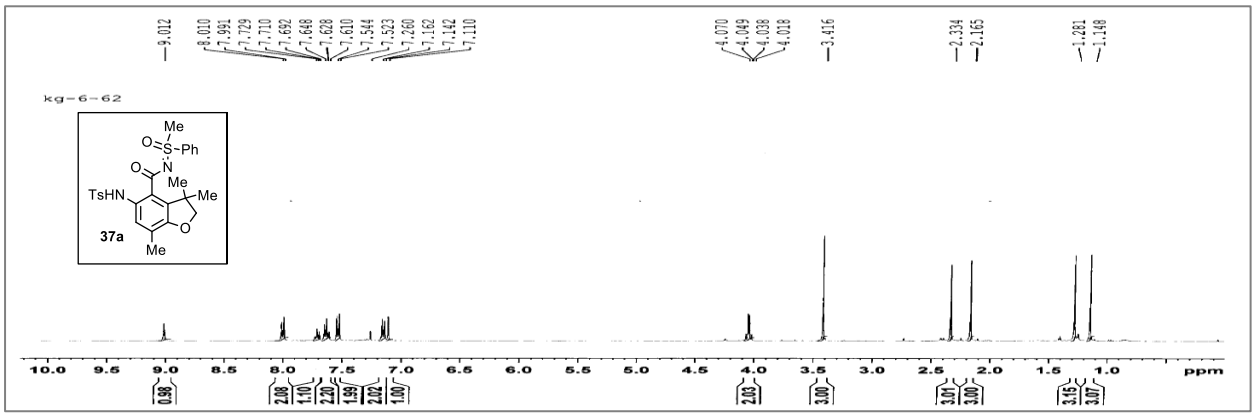

KG-8-Triple Annulation
31a

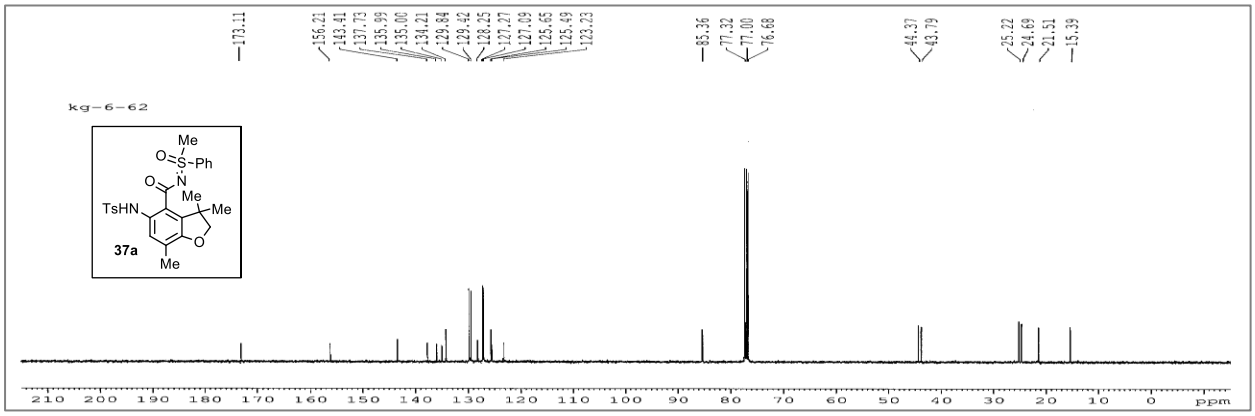

kg-8-chlorotri
31b Ar = p-ClC6H4

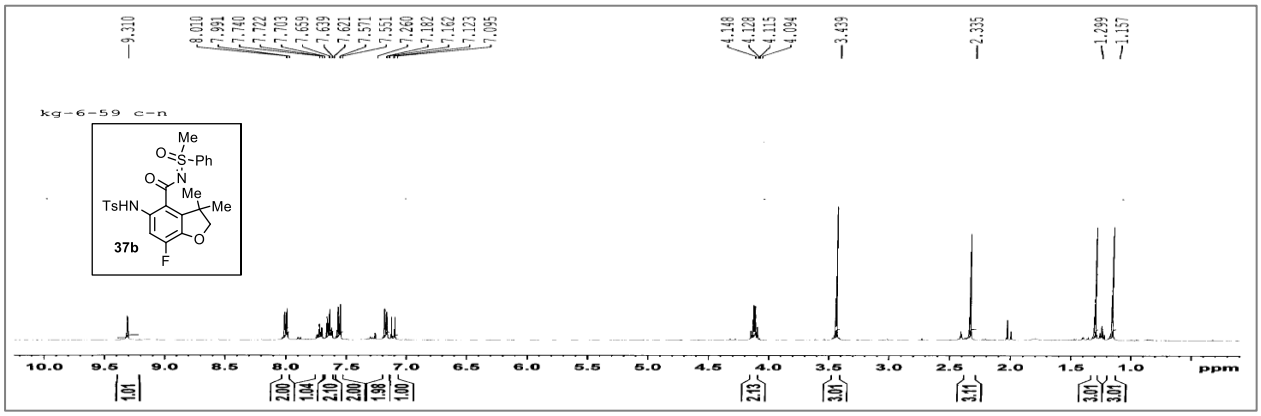

kg-8-chloro-tri
31b Ar = p-ClC6H4

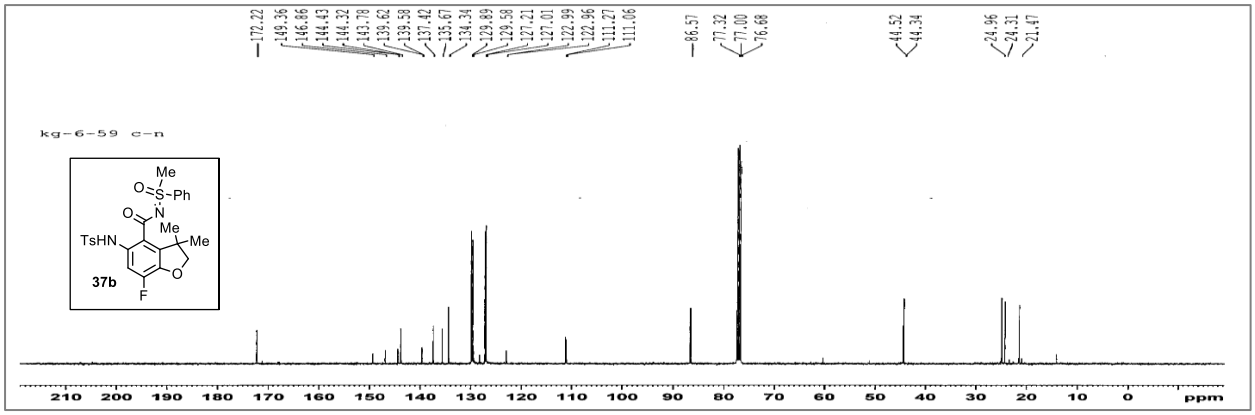

KG-P-Me
31c

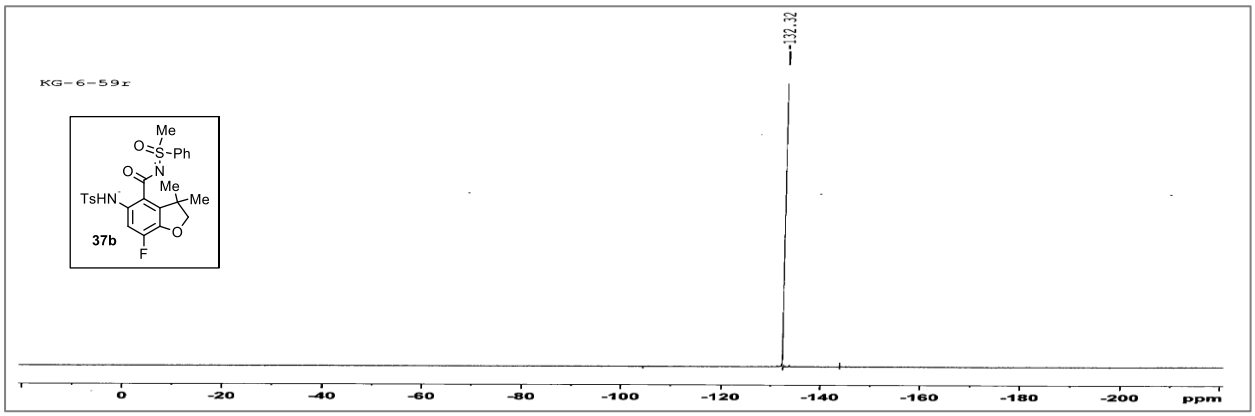

KG-P-Me
Ph
Ph
N
O
Me
Me
Ph
O
Me
31c
161.96
158.26
139.45
137.61
136.43
136.35
133.08
132.91
132.52
132.19
131.54
130.90
129.63
129.03
128.38
127.99
127.91
127.88
127.71
127.59
127.18
126.85
126.64
126.49
126.18
125.98
125.51
122.35
116.65
86.32
77.31
77.00
76.68
44.52
26.23
16.23
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

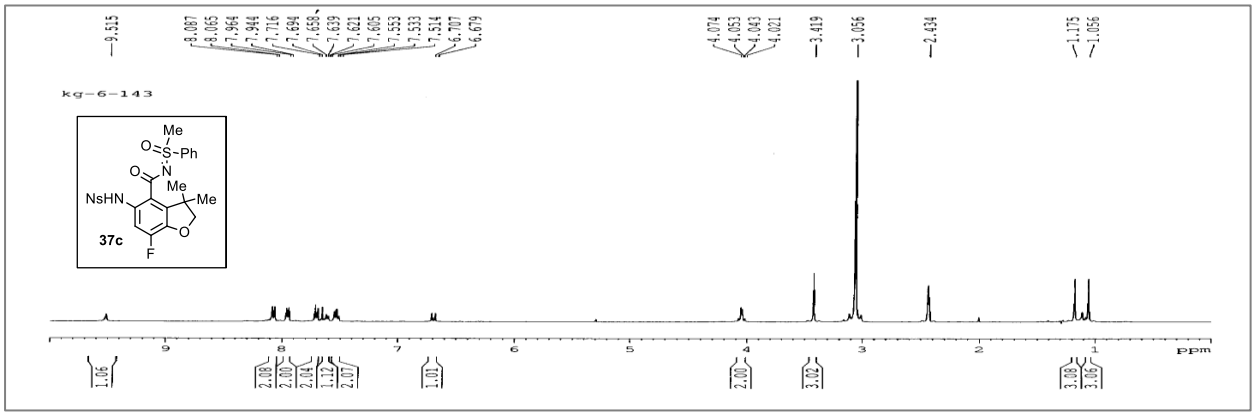

kg-6-62
Me
O
S-Ph
O
N
Me
TsHN
Me
Me
O
37a
Me
9.012
8.010
7.991
7.729
7.710
7.692
7.648
7.628
7.610
7.544
7.523
7.260
7.162
7.142
7.110
4.070
4.049
4.038
4.018
3.416
2.334
2.165
1.261
1.148
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.98
2.06
1.10
2.20
1.98
2.02
1.00
2.03
3.00
3.01
3.00
3.15
3.07

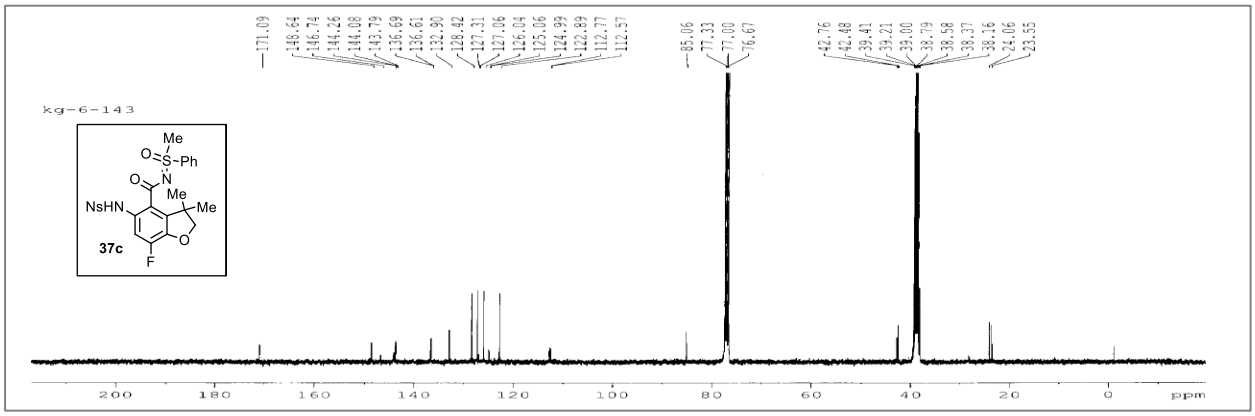

kg-6-62
Me
O
S-Ph
O
N
Me
TsHN
Me
Me
O
37a
Me
173.11
156.21
143.41
137.73
135.99
135.00
134.21
129.84
129.42
128.25
127.27
127.09
125.65
125.49
123.23
85.36
77.32
77.00
76.68
44.37
43.79
25.22
24.69
21.51
15.39
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

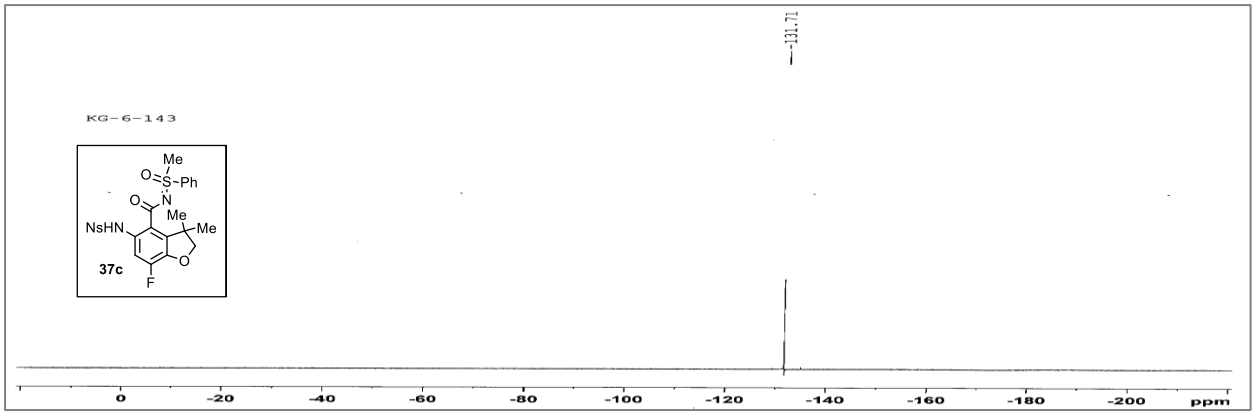

kg-6-59 c-n
Me
O
S-Ph
O
N
Me
TsHN
Me
Me
O
37b
F
9.310
8.010
7.991
7.740
7.722
7.703
7.639
7.639
7.621
7.571
7.551
7.260
7.182
7.162
7.123
7.095
4.148
4.128
4.115
4.094
3.439
2.335
1.299
1.157
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.01
2.00
1.04
2.10
2.00
1.98
1.00
2.13
3.01
3.11
3.01
3.01

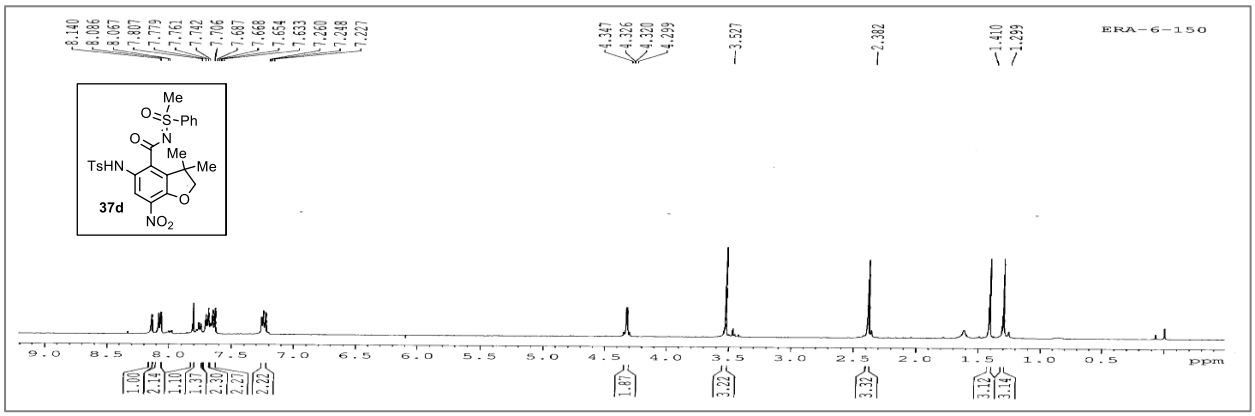

kg-6-59 c-n
37b

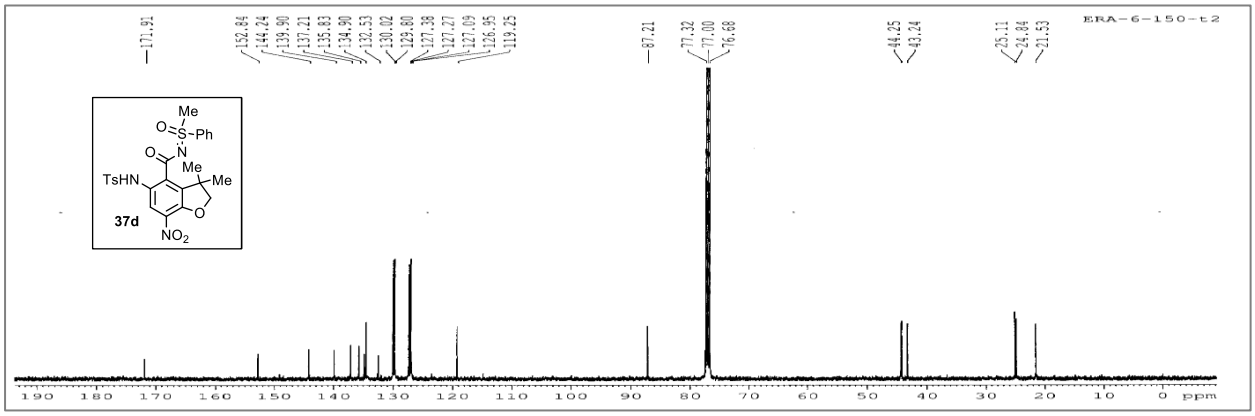

KG-6-59r
37b

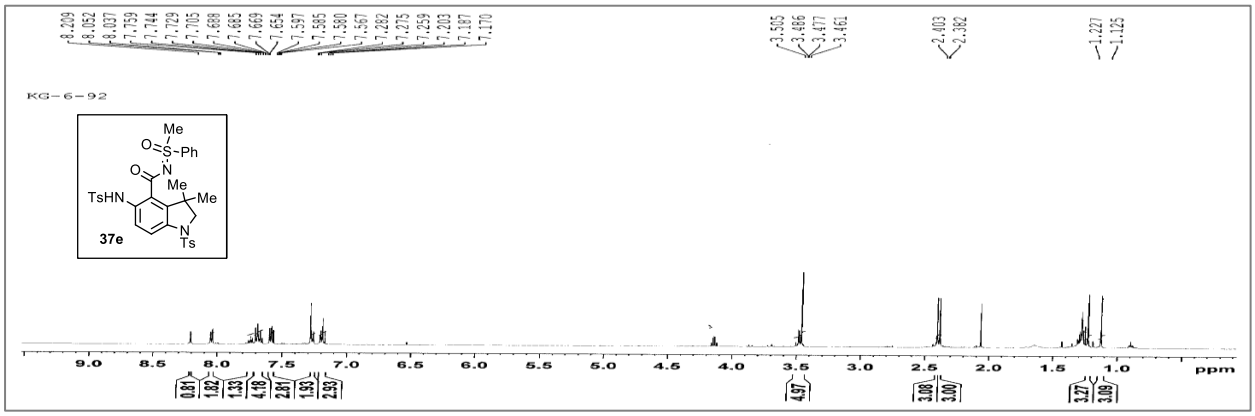

kg-6-143
37c

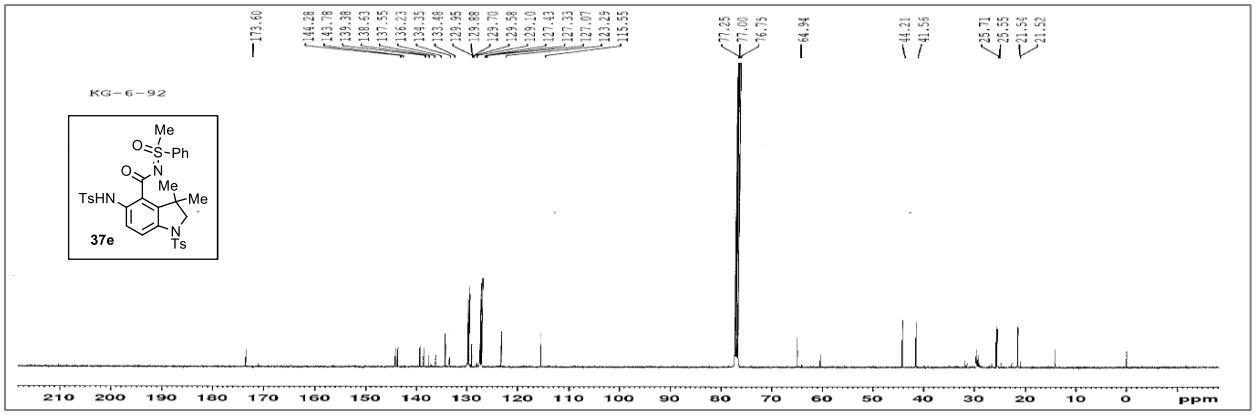

kg-6-143
37c

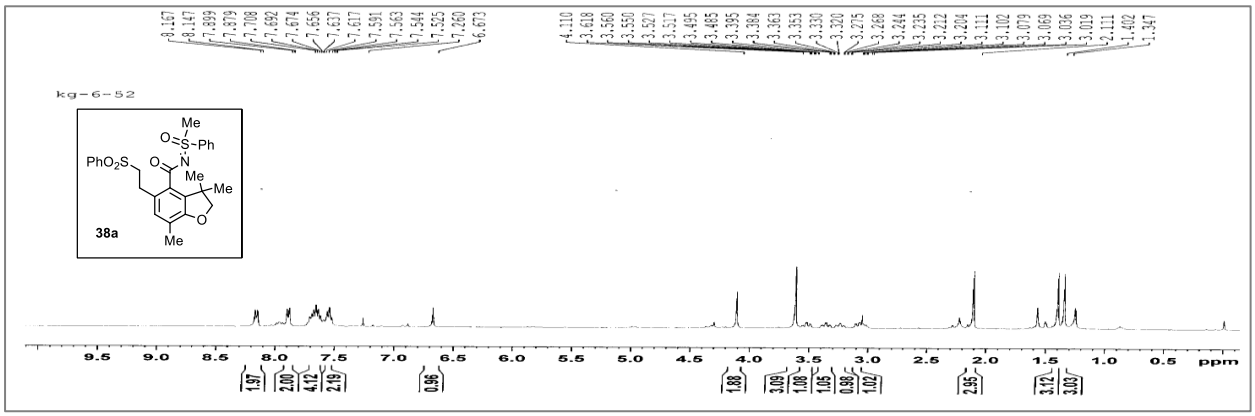

KG-6-143
-131.71
37c
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

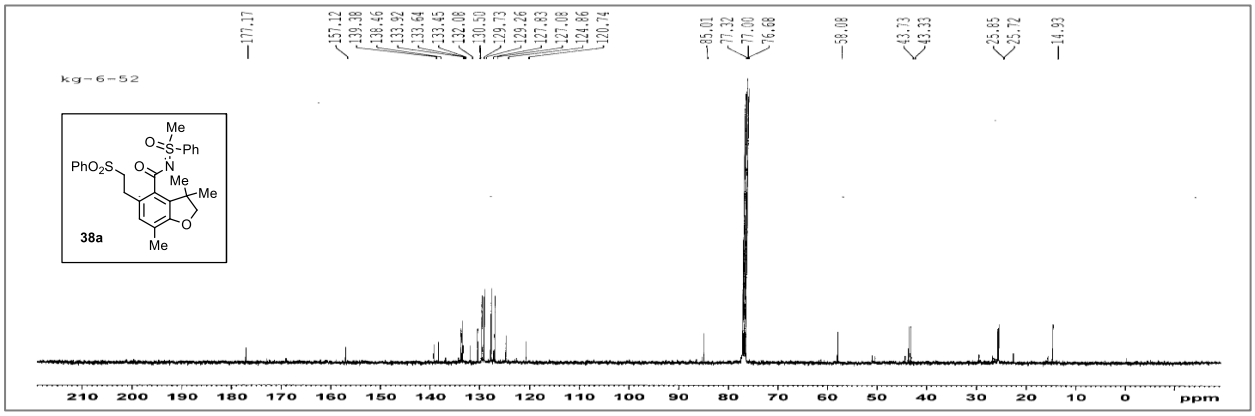

ERA-6-150
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

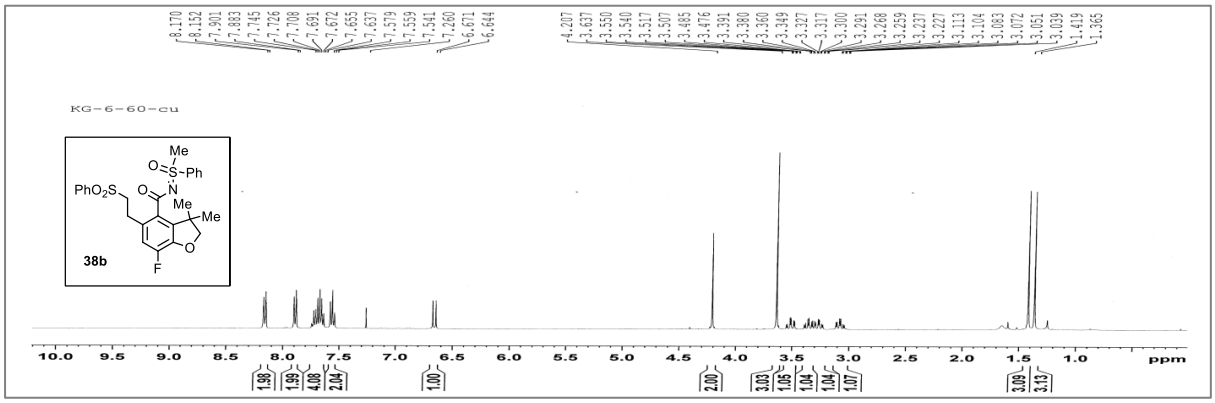

ERA-6-150-t2
37d
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160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

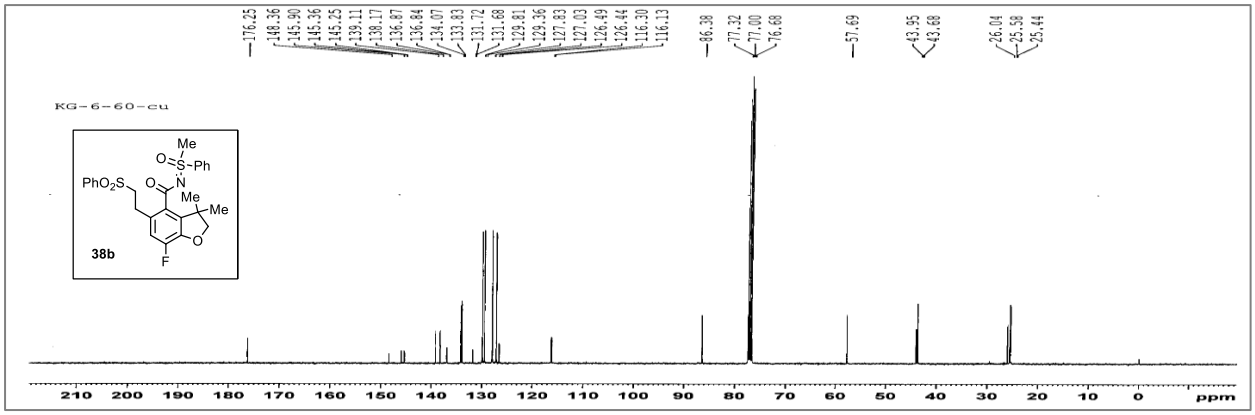

KG-6-92
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7.0
6.5
6.0
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

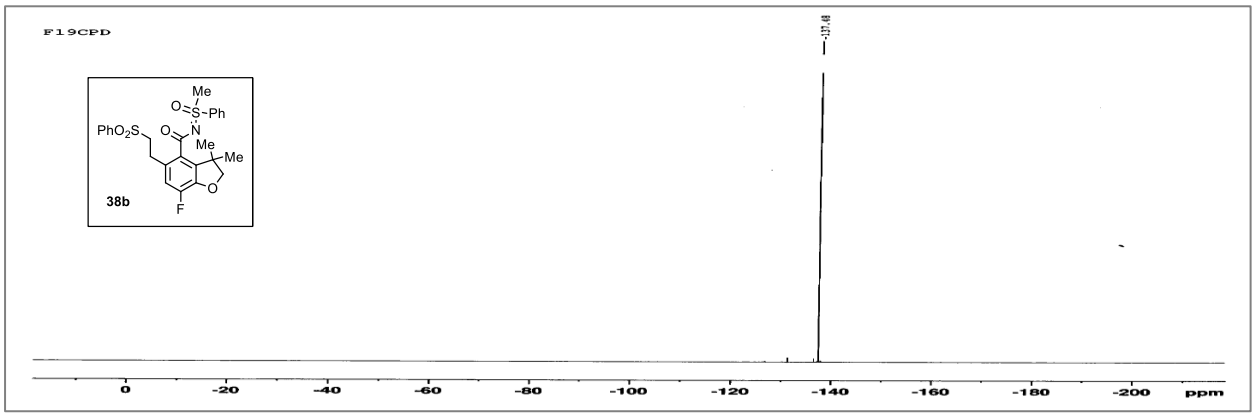

KG-6-92
37e

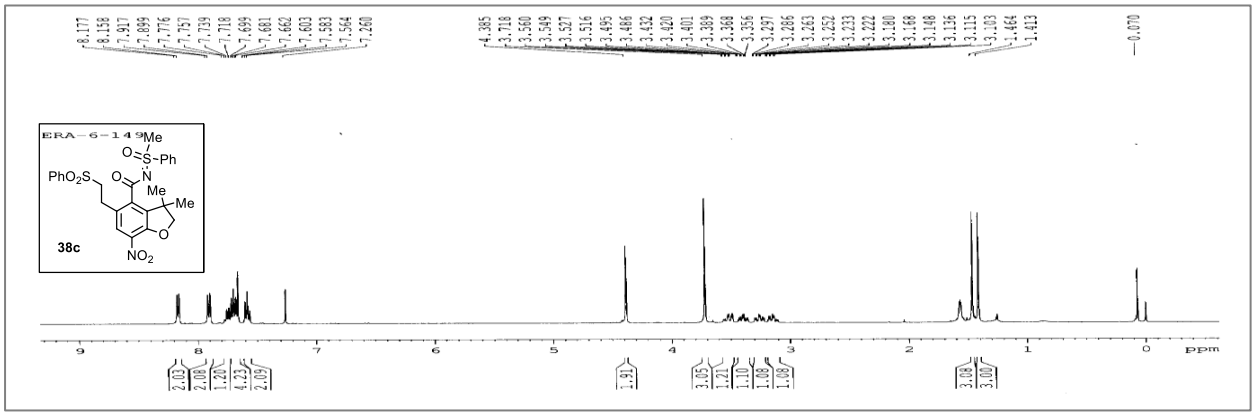

kg-6-52
38a

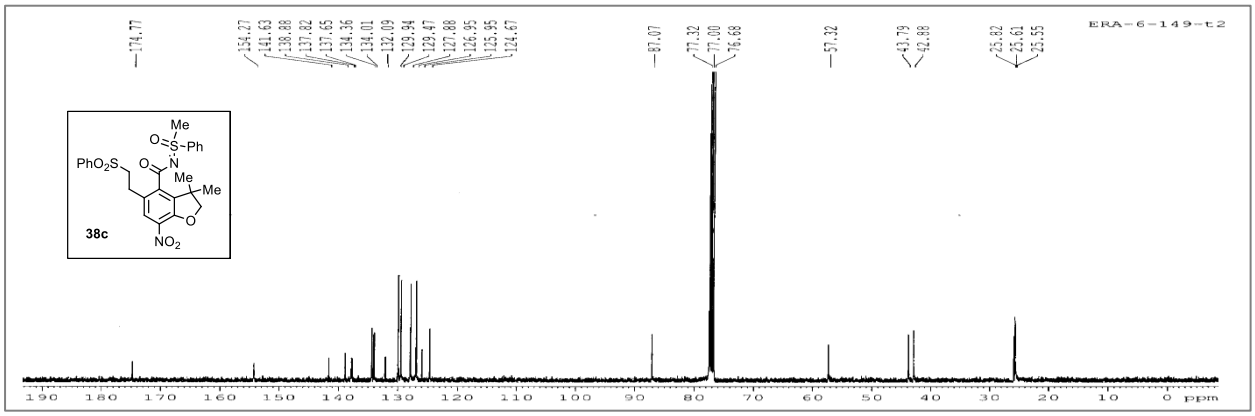

kg-6-52
38a

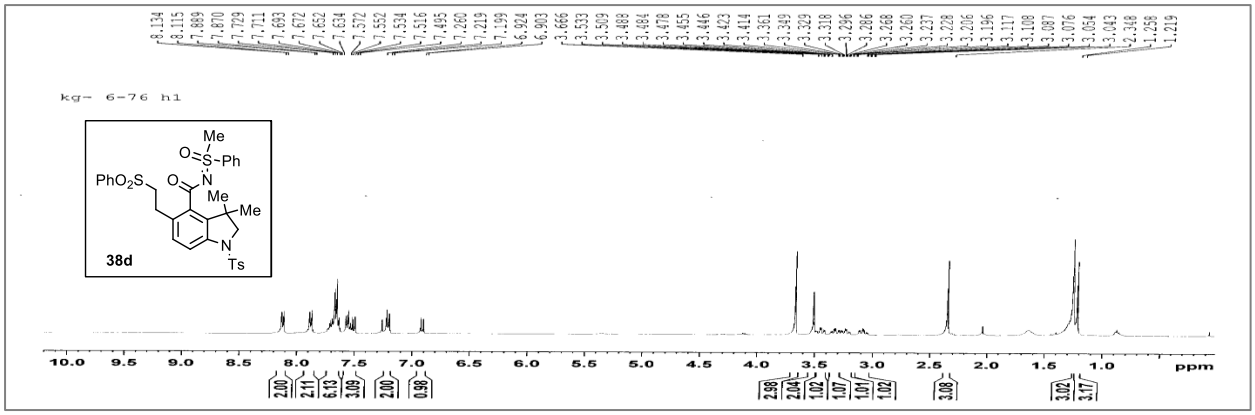

KG-6-60-cu
38b

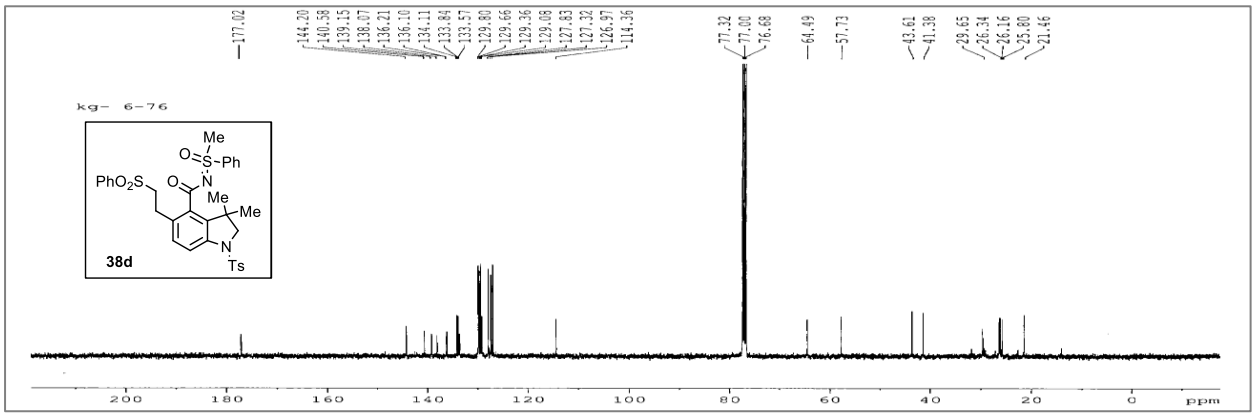

KG-6-60-cu
38b

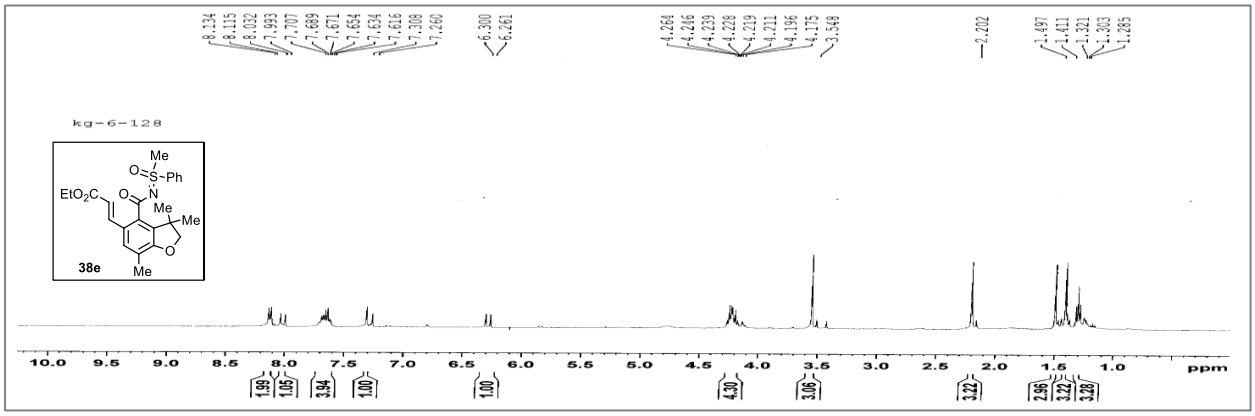

F19CPD
38b

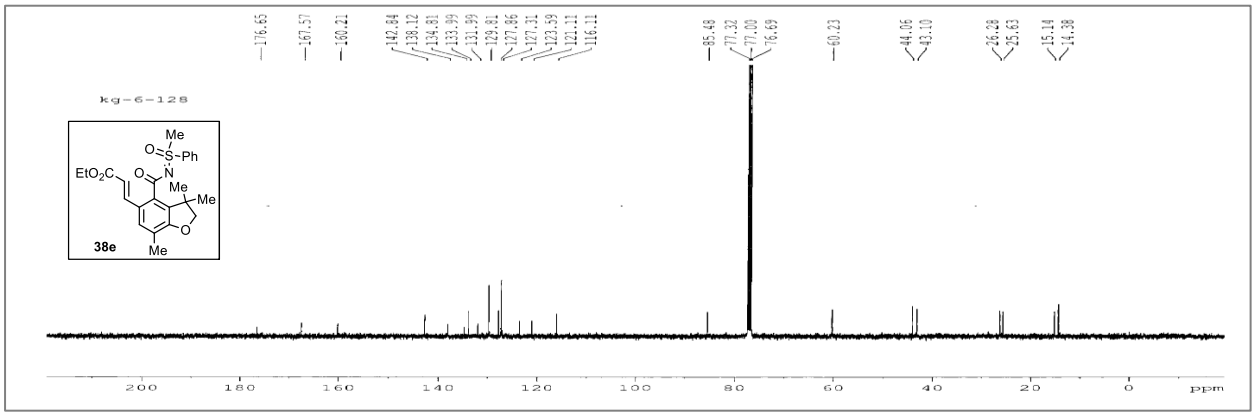

ERA-6-149
38c


ERA-6-149-t2
38c


kg- 6-76 h1
38d
Ts


kg- 6-76
38d
Ts

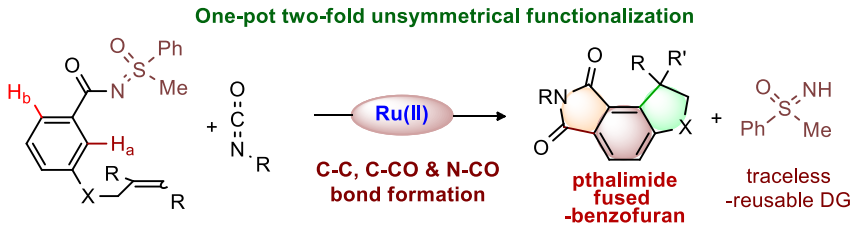

kg-6-128
38e


kg-6-128
38e

Chapter 4

Traceless-Reusable Sulfoximine DG Assisted Unsymmetrical Two-fold Functionalization of Arenes

An unprecedented one-pot two-fold unsymmetrical functionalization of C–H bonds of arene (demonstrating intramolecular hydroarylation with olefin and intermolecular aminocarbonylation with isocyanate) has been revealed with the aid of traceless-recoverable sulfoximine-DG. The methyl phenyl sulfoximine (MPS) plays important, successfully promoting hydroarylation-aminocarbonylation of arene. The removal of MPS-DG delivers phthalimide fused dihydro(benzofuran/ indoline) derivative erecting C–C/C–CO/N–CO bonds under one reaction sequence. The MPS group is easily removed from the substrate after cyclization, successfully recovered and reused, validating traceless nature of the DG. The reaction exhibits broad scope, tolerating common functional groups, labile protecting units, and heteroaryl motifs.



Reference:

Koushik Ghosh, Kallol Mukherjee, Arghadip Ghosh and Akhila K. Sahoo (Manuscript under preparation)

4.1. Introduction

The strategy of C–H bond functionalization is synthetically viable, largely employed building complex molecular scaffolds from readily accessible precursors with ease.[1] In this regard, the functionalization of particular C–H bond with greater level of selectivity is found essential although challenging; the presence of directing group (DG), however, regulates the regioselective activation of C–H bonds. Thus, DG aided site-selective C–H functionalization exhibits wider acceptance in the realm of C–H bond activation. Consequently, extensive work has then gone to understand the role and impact of DG in organic synthesis.[2] Despite the efficiency of directed C–H activation, the use of removable DG enriches synthetic potential of the strategy. The selective C–H functionalization under the traceless DG efficiently promotes synthetic adaptability of the method, thereby considered ideal.[3]

Phthalimide skeletons are widely found in the molecules of pharmaceutical importance and agrochemicals (Figure 4.1).[4] Among the known strategies, the transition-metal catalyzed amidative-cyclization in the presence of CO holds important; although CO is toxic.[5,6] Moreover, harsh reaction conditions are mostly needed for the insertion of CO in the amidation process. Thus, use of alternate carbonyl source instead of hazardous CO for C–H amidation always attract considerable attention.

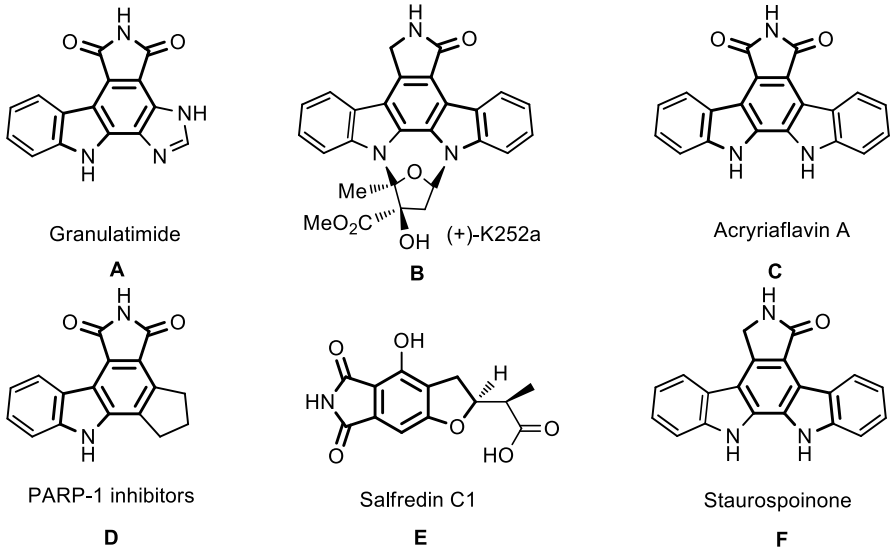


Figure 4.1: Biologically active molecules containing phthalimide skeletons

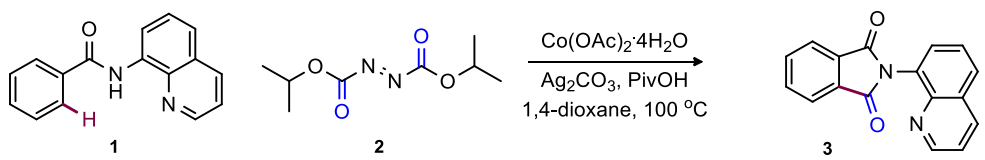
Recently, the relatively stable isocyanate species have successfully been used for the amidation of C–H bonds. Importantly, the non-removal/non-modifiable DG's have been implemented for C–H amidation of arenes in presence of isocyanate; consequently phthalimide motifs are constructed using this method. Despite the growth, the removable/traceless DG assisted amidative-cyclization of C–H bonds with isocyanate for the fabrication of phthalimide skeleton is so far remain elusive. The use of removable/traceless/modifiable/transformable DG in the arena of C–H activation has seen profound impact; as this process eventually broadens synthetic utility of the strategy.

Inspired from the previous studies of removable methyl phenyl sulfoximine (MPS) directed functionalization of C-H bonds, herein a traceless MPS directed amidation and cyclization cascade of arene carboxylic acid derivatives under the Ru-catalysis is envisioned. Owing to the importance of one-pot multiple functionalization of C-H bonds, the MPS directed intramolecular hydroarylation and intermolecular amidative-cyclization to phthalimide is planned and executed.

4.1.1. Precedents of C(sp^2)C–CO in Arenes via C–H Activation (using isocyanate, DMF, CH_3NO_2, DIAD as carbonyl source):

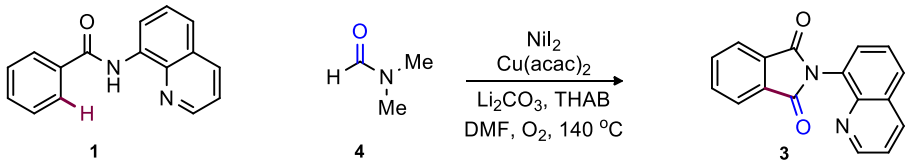
Installation of phthalimide motif in the presence of carbonylating agents other than CO is the focus of this work. Thus, the use of carbonylating agents such as, azodicarboxylate, isocyanate, DMF, and nitromethane for the construction of phthalimide skeleton is briefly discussed herein.

Zhang group reported the cobalt-catalyzed C(sp^2)–H bond carbonylation of arenes under the assistance of 8-amino quinoline in the presence of azodicarboxylates **2** for the synthesis of phthalimide skeleton **3**. However, the non-removal nature of the DG affects broad synthetic utility of this method (Scheme 4.1).[7]



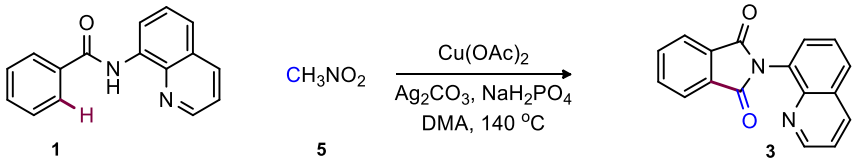
Scheme 4.1: Co(II)-catalyzed amino-carbonylative cyclization using DIAD

In 2012, Ge group revealed carbonylation of C(sp²)−H bond using nickel/copper catalysis and the assistance of 8AQ-DG. DMF is used as carbonyl surrogate; the reaction was exhibited in presence of Cu salt and atmospheric O_2 to give **3** (Scheme 4.2). Mechanistic studies suggested the involvement of synergistic catalysis nickel/copper system in this transformation.[8]



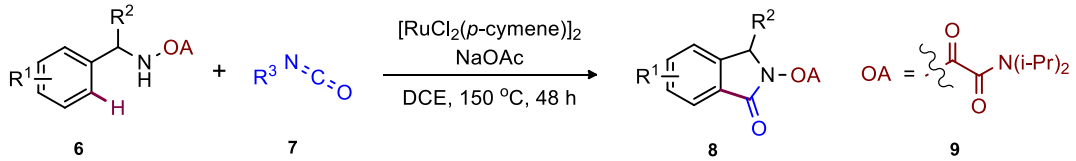
Scheme 4.2: Ni/Cu-Catalyzed amino-carbonylative cyclization using DMF

The Cu-catalyzed and 8-AQ directed carbonylation of C(sp³)–H and C(sp²)–H bond in the presence of nitromethane **5** carbonyl source was developed by Ge group. On the basis of mechanistic studies, dehydrogenative coupling between **1** and **5**, followed by Nef type carbonylation provided the desired phthalimide skeleton **3**.[9]



Scheme 4.3: Cu(II)-Catalyzed amino-carbonylative cyclization using nitromethane

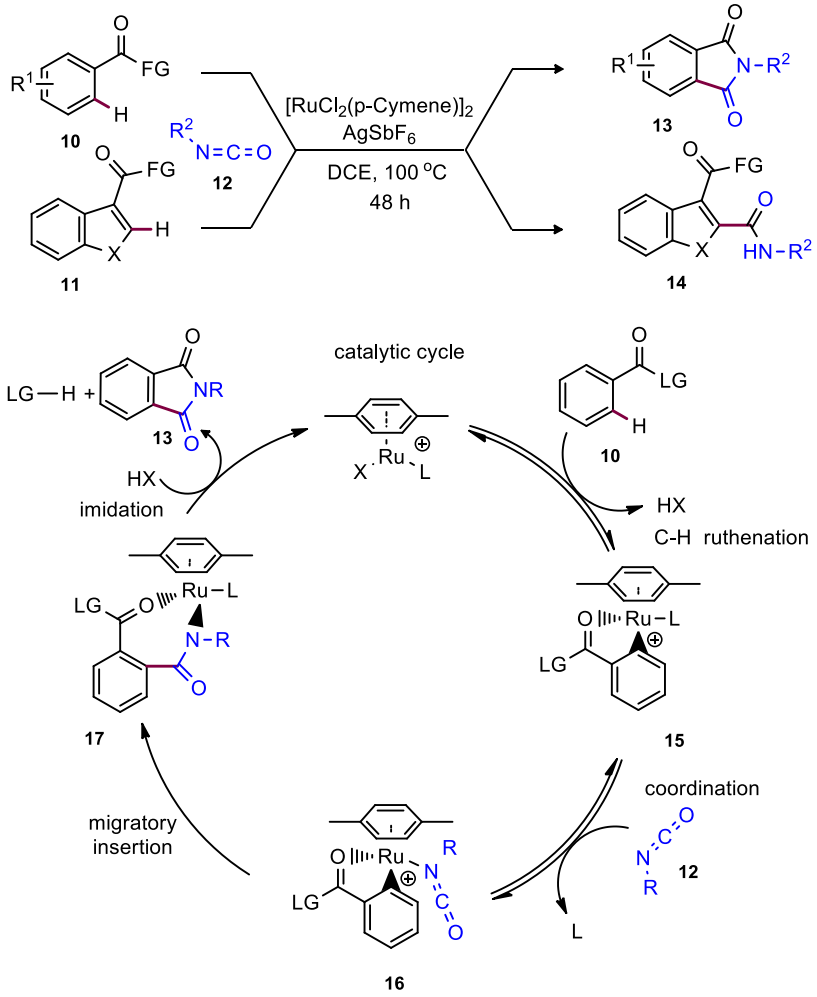
The Ru-catalyzed oxalyl amide directed carbonylation of benzyl amines offered a straightforward synthesis of isoindolinones scaffold **8**. Further removal of the DG effectively delivered isoindolinones in moderate to good yield. The transformation involves C–H activation followed by amino carbonylative cyclization of **6** in presence of Ru(II) and NaOAc at higher temperature to give **8** (Scheme 4.4).[10]



Scheme 4.4: Ru(II)-Catalyzed amino-carbonylative cyclization using isocyanate

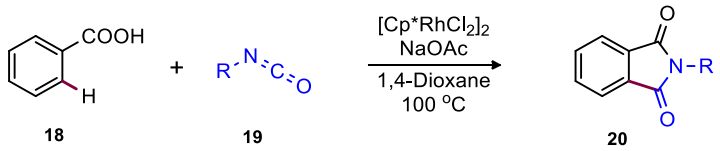
The pyrrolidine coupled benzoic acid derivative **10** successfully underwent amino-carbonylative cyclization with isocyanate **12** in presence of Ru catalysis. This method has been used for the synthesis of COX-2 enzyme inhibitor. The reaction begins with the formation of active cationic Ru-species, generated in-situ in presence of $AgSbF_6$,

which then activates the proximal arene C–H bond to deliver active metal complex **15**. Next, coordination of isocyanate to **15** produces five membered metallacycle intermediate **16**. The migratory insertion then forms the intermediate **17** creating a C–C bond. Direct imidation of **17** finally provided the cyclization product **13**, while protodemetallation of **17** gave diamide **14** with the concurrent production of cationic ruthenium species for the next catalytic cycle (Scheme 4.5).[11]



Scheme 4.5: Ru(II)-Catalyzed amino carbonylative cyclization using isocyanate

An efficient synthetic method developed by C. J. Li group demonstrates the Rh(III)-catalyzed amidation of carboxylic acid derivatives **18** and isocyanates **19** followed by intramolecular cyclization to deliver phthalimide skeleton **20**.[12]

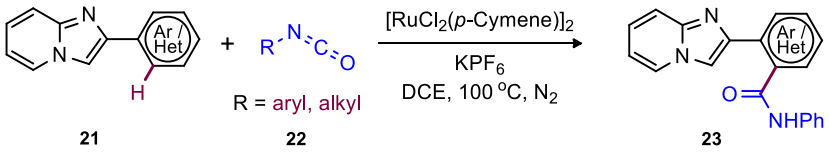


Scheme 4.6: Rh(III)-Catalyzed amino-carbonylative cyclization of carboxylic acid

Disappointingly, the EWG group bearing arene did not yield the final product exhibiting narrow scope of the strategy (Scheme 4.6).

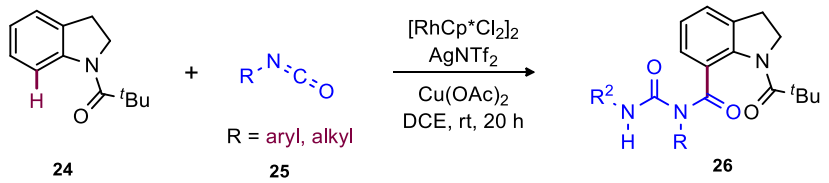
Isocyanate species not only used for the installation of phthalimide scaffold but also employed for the amidation process (*vide infra*).

The Ru-catalyzed imidazopyridines directed amidation of arene motif **21** with aryl isocyanate **22** afforded the desired *ortho*-amidation product **23** (Scheme 4.7). The non-modifiable/removable DG eventually hampers synthetic utility of this method (Scheme 4.7).[13]



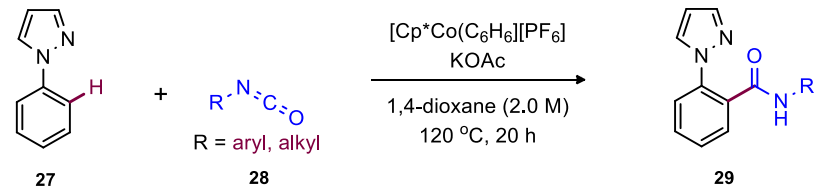
Scheme 4.7: Ru(II)-Catalyzed imidazopyridines directed amidation of (hetero)arenes

Kim group described Rh-catalyzed isocyanate insertion in the C-7 position of indoline **24** under redox-neutral strategy for the synthesis *N*-aroylureas (**26**). The ^{t}Bu bearing amide DG plays vital, as other alkyl containing amides failed assisting C-7 amidation of indolines. Interestingly, this transformation successfully occurs at room temperature (Scheme 4.8).[14]



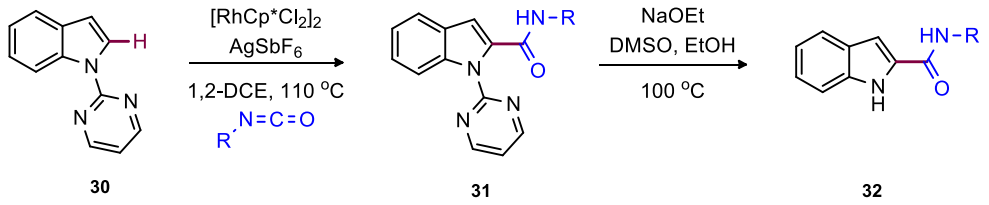
Scheme 4.8: Ru(II)-Catalyzed ketone directed amidation of indolines

Ellman group for the first time revealed cobalt(III)-catalyzed amidation of arenes **27**; this reaction occurs under the assistance of non-removal/non-modifiable pyrazole DG. In spite of drawback, the gram scale synthesis and the use of air stable cationic Co catalyst makes this process synthetically viable (Scheme 4.9).[15]



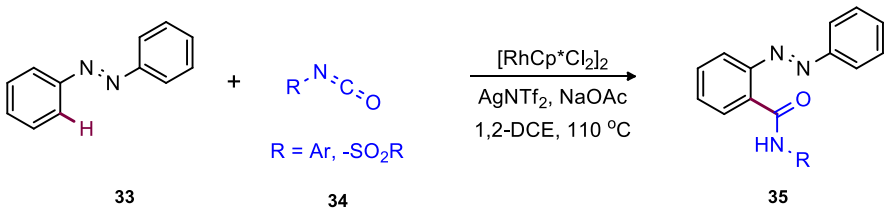
Scheme 4.9: Co(II)-Catalyzed amidation of arenes

Kim group reported Rh(III)-catalyzed pyrimidine directed C-2 amidation of indole **30**. The scope of the reaction is broad; various alkyl and aryl isocyanates are successfully employed. The base triggered removal of DG delivers substituted indole scaffolds **32**, albeit in poor yields (Scheme 4.10).[16]



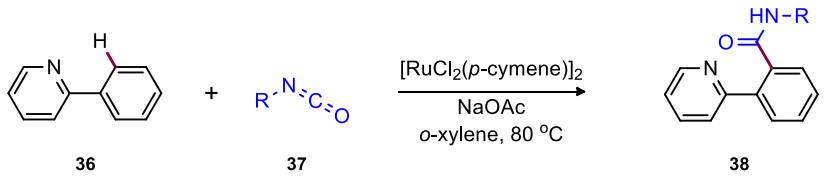
Scheme 4.10: Rh(III)-Catalyzed pyrimidine directed amidation of indoles

Likewise azo-group assisted C−H amidation of arenes **33** under Rh(III)-catalysis in presence of arylsulfonyl and aryl/alkyl isocyanates **34** are successfully presented (Scheme 4.11). Naturally, electron-rich arene preferably underwent amidation when unsymmetrical azobenzene exposed to the reaction conditions. The azo group finally cleaved under the reductive conditions.[17]



Scheme 4.11: Rh(III) catalyzed amidation of azobenzene

In 2012, the first report for the Ru-catalyzed amidation of 2-aryl pyridines **36** in presence of isocyanate was emanated from Cheng group. The reaction occurred under mild reaction condition showing broad substrate scope; although non-modifiable/removable Py-DG has primarily been used (Scheme 4.12).[18]

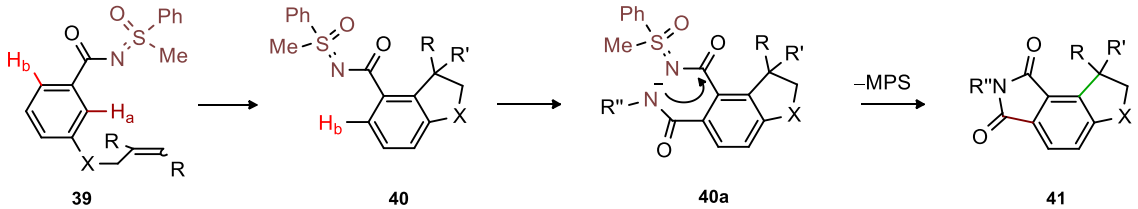


Scheme 4.12: Ru(II)-Catalyzed pyridine directed amidation of arenes

4.2. Motivation, Hypothesis, and Design

Isocyanate is an alternate source of CO. Isocyanate can be handled easily unlike CO; thus, fabrication of phthalimide scaffold using isocyanate motif is advisable, although less explored.[11,12] Mostly the DG-enabled amide analogues undergoes cyclization to provide the desired phthalimide; however, the non-modifiable or non-removal DG inhibits such transformation. To address these perennial problems, a removal DG enabled *o*-C–H carbonylative-amidation and cyclization cascade manufacturing pthalimide scaffold is visualized; the recovery of DG from the reaction mixture would supplement traceless DG in this study.

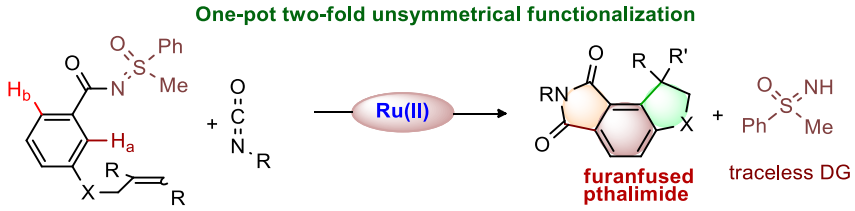
As discussed in chapter 1 and 3, the one-pot multiple functionalization of C–H bonds inherited with possible challenges: the incomplete conversion of precursor under the first set of reaction, formation of mixture of side products in every step of the reactions, and the issue of steric and electronic environment upon the introduction of new FG. Our current interest in the one pot unsymmetrical multiple functionalizations of inert C–H bonds inspires us to investigate Ru-catalyzed methyl phenyl sulfoximine (MPS) directed intramolecular hydroarylation of arenes with olefins of **39** followed by intermolecular carbonylative amidation of the o'-C–H bonds of **40** with readily accessible isocyanate to yield **40a** (Scheme 4.13); these two transformations can be implemented in a single pot by conducting the reactions at different temperature. Finally, intramolecular nucleophilic replacement of MPS motif of **40a** constructs phthalimide scaffold. The recovery of MPS-DG from reaction mixture showcases traceless DG in this study; the entire transformation not only is step efficient but atom-economy (Scheme 4.13). This process finally builds a novel structural manifold **41** integrating two heterocyclic analogues dihydrofuran and phthalimide on arene in a single molecule.



Scheme 4.13: Working hypothesis

4.3. Results and Discussions:

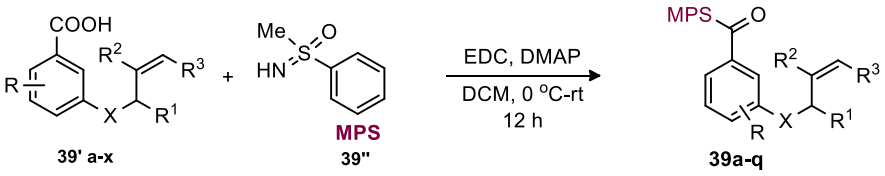
The known synthetic methods adopted for the formation of phthalimide through DG-assisted amino-carbonylation of arene motivated demonstrating a one-pot method of intramolecular hydroarylation and intermolecular amino-carbonylation to construct unusual furan-fused-phthalimide, which is unprecedented. Herein, methyl phenyl sufoximine (MPS) directed intramolecular hydroarylation of olefin followed by amino-carbonylation with isocyanate in the presence of air stable Ru-catalysis is presented. The DG is traceless, as MPS-moiety instantaneously cleaves from the reaction mixture and finally recovered.

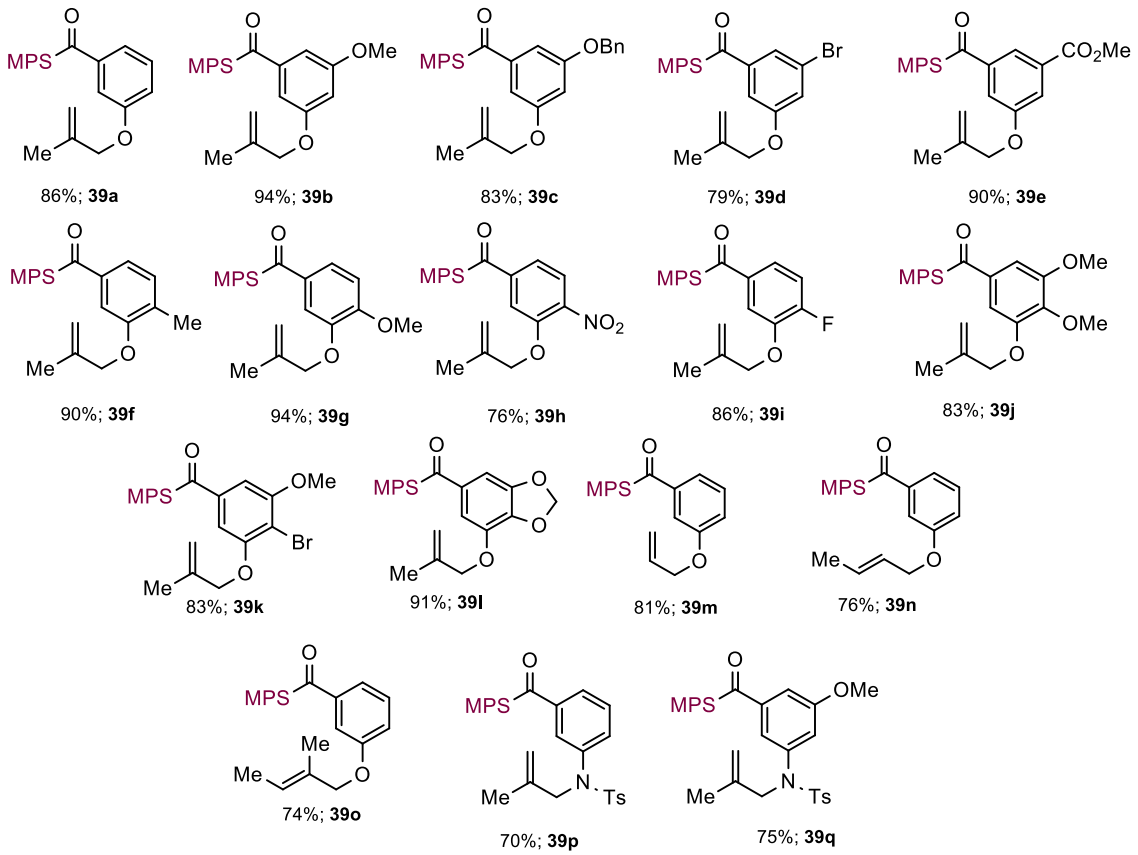


4.3.1. Synthesis of Precursors

Wide range of *N*-aroyl sulfoximine derivatives **39** were readily prepared by coupling methylphenyl sulfoximine (**39''**) and benzoic acid in presence of EDC·HCl and catalytic DMAP in CH_2Cl_2 at 0 °C. Following the known procedures, library of *N*-aroyl sulfoximines **39** were reliably prepared. The compounds are listed in Table 4.1 (the working procedure is detailed in the Experimental Section).

Table 4.1. Preparation of *N*-aroyl sulfoximine derivatives

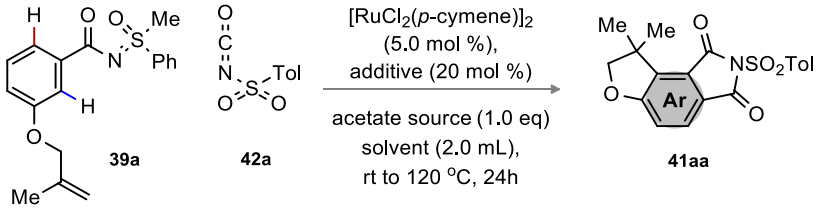




4.3.2. Reaction Condition Optimization

With the library of *N*-aroyl sulfoximine precursor **39** in hand, the feasibility of reaction hypothesis (discussed in Scheme 4.13) was thus assessed under the catalytic conditions comprising of Ru-catalysis (Table 4.2). Interestingly, the reaction between [3-(2-methylallyloxy)-benzoyl]methyl phenyl sulfoximine (**39a**; 0.3 mmol) and 4-methylbenzenesulfonyl isocyanate (**42a**) under the catalytic conditions comprising of Ru-Ag-Cu delivered **41aa** in 59% yield (entry 1). Formation of **41aa** (through intramolecular hydroarylation and intermolecular amino-carbonylative cyclization in one pot) indicated that the transformation involves redox neutral process maintaining oxidation state Ru(II) in the entire catalytic cycle. Screening of various acetate sources [$Mn(OAc)_2$, $Zn(OAc)_2$ NaOAc, KOAc (entries 2–5) did not improve the product yield. Pleasingly, $Cu(OAc)_2 \cdot H_2O$ found superior affording **41aa** in 54% yield (entry 6).

Table 4.2: Optimization of Reaction Conditions[a]



entry	additive (20 mol %)	acetate source (1.0 equiv)	solvent	yield of **41aa** (%)[b]
1	$AgSbF_6$	–	$ClCH_2CH_2Cl$	59
2	$AgSbF_6$	$Mn(OAc)_2$	$ClCH_2CH_2Cl$	32
3	$AgSbF_6$	$Zn(OAc)_2 \cdot 2H_2O$	$ClCH_2CH_2Cl$	29
4	$AgSbF_6$	NaOAc	$ClCH_2CH_2Cl$	Nr
5	$AgSbF_6$	KOAc	$ClCH_2CH_2Cl$	45
6	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	$ClCH_2CH_2Cl$	54
7	$AgBF_4$	$Cu(OAc)_2 \cdot H_2O$	$ClCH_2CH_2Cl$	32
8	KPF_6	$Cu(OAc)_2 \cdot H_2O$	$ClCH_2CH_2Cl$	19
9	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	58
10	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	Toluene	46
11[c,d,e]	**$AgSbF_6$**	**$Cu(OAc)_2 \cdot H_2O$**	**$ClCH_2CH_2Cl$**	**81**[f]
12[c,d,e]	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	$ClCH_2CH_2Cl$	77

Conditions: [a]Ru-cat (5.0 mol%), additive (20 mol%), acetate source (1.0 equiv), isocyanate **42a** (1.5 equiv.) solvent. [b]NMR yield. [c]**42a** (2.0 equiv) instead of 1.5 equiv was used. [d]isolated yield. [e]heating the mixture at 130 ˚C. [f]addition of **42a** to the reaction mixture after 2h.

Use of other additive such as $AgBF_4$, KPF_6 provided the desired product in 32 and 19% yield, respectively (entries 7 and 8); while $AgSbF_6$ worked better (entry 6). Presumably, the counter anion SbF_6^- in the outer sphere of the active catalyst [RuII(*p*-cymene)OAc]$^+$ plays crucial over BF_4^-/PF_6^-. The reaction in 1,4-dioxane or toluene was moderate (entries 9 and 10). As isocyanate is unstable in the reaction medium, the use of excess amount of isocyanate enhances reaction productivity. Consequently, the reaction of **39a** with **42a** (2.0 equiv) led to **41aa** in 81% yield (entry 11). Finally, the optimized reaction condition comprising {$[RuCl_2(p\text{-cymene})_2]_2$ (5.0 mol%), $AgSbF_6$ (20 mol%) in presence of $Cu(OAc)_2 \cdot H_2O$ at 130 ^{0}C} delivered the

desired product in 81% yield (entry 11). Moreover the step wise addition of isocyanate has little effect (entry 12).

The feasibility of this unprecedented one pot two-fold unsymmetrical functionalization was then checked with the aid of other DG. To our delight, MPS-coupled aroyl derivative delivers 81% isolated yield (entry 12, Table 1), whereas other DG failed to produce the desired **41aa** (Figure 2.3). Although the reason is not known, however, presumably the steric and electronic factor of MPS-DG helps this unprecedented one pot two-fold unsymmetrical C–H functionalization to occur.

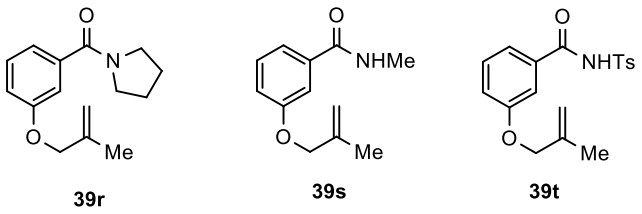


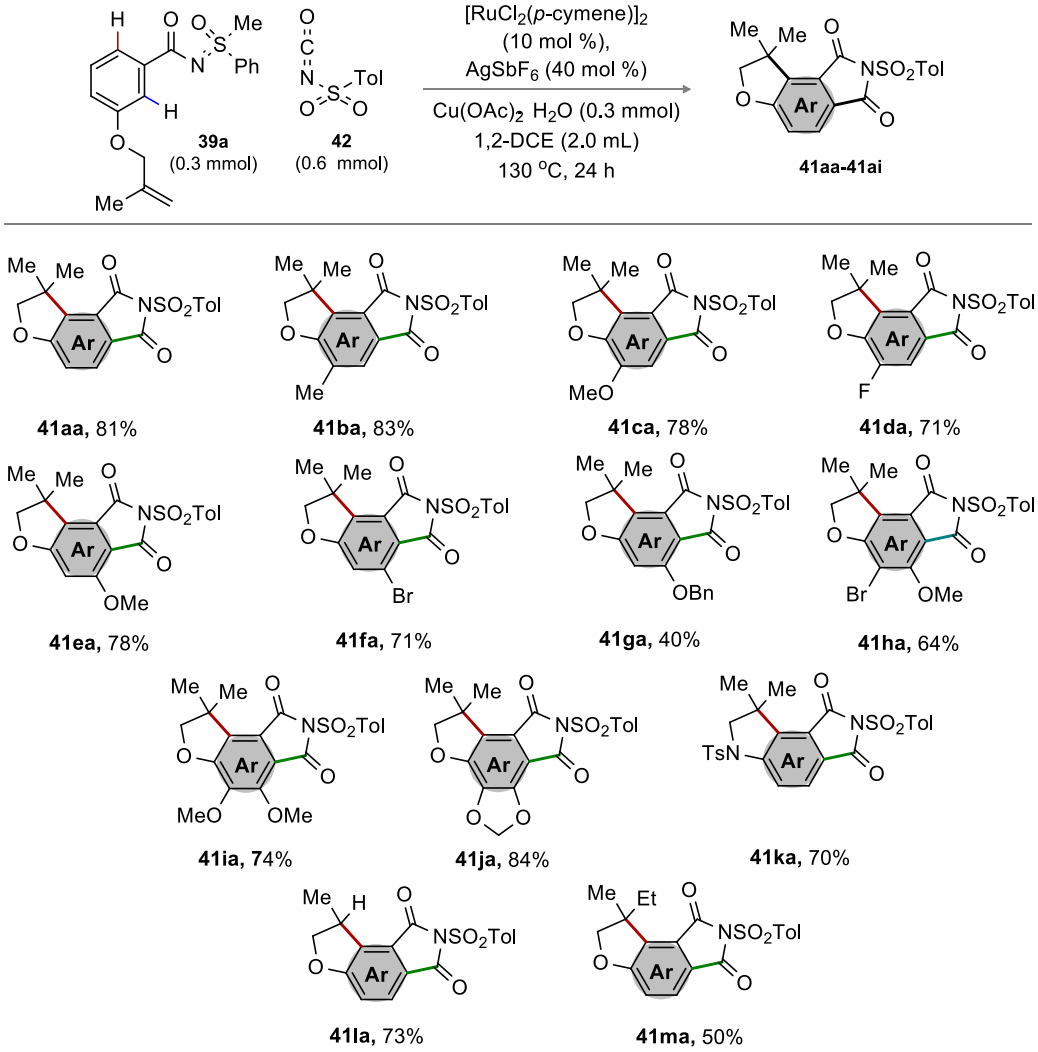
Figure 2.3. Screening of various DGs

4.3.3. Scope of One Pot Twofold Unsymmetrical Functionalization of C–H bonds

The successful coupling between **39a** and **42a** for the construction of novel scaffold **41aa** was next assessed examining the scope of the transformation by subjecting MPS coupled aroyl derivatives under the optimized condition shown in entry 11, Table 1. The substrates having electron-donating substituent at *para*-position of arene ring (**39f** and **39g**) reacted well with **42a** to deliver **41ba** (83%) and **41ca** (78%). The F-substituted desired product **41da** was successfully constructed. The electron perturbation in terms of donating, and halo groups at the meta-position of arene moiety bearing substrates for this double unsymmetrical functionalizations has further been checked. Gratifyingly, the corresponding compounds **39b**–**39d** are constructed in good yields (79-40%); the steric bulkiness in the second functionalization did not hamper the reaction productivity. This method successfully delivered the furan-fused-phthalimide skeleton having all carbon functionalized arene back bone **41ha**–**41ja**; which are difficult to synthesize in traditional method. The methodology is further extended for the synthesis of pyrrole-fused-

phthalimide derivatives (**41ka**) using N-tethered olefin bearing benzoic acid derivative **39p**. Not only terminal alkene, tri-substituted internal alkenes were also successfully participated in the hydroarylation-aminocarbonylation-cyclization sequence to afford the desired furano-phthalimido architecture **41ma**.

Table 4.4: Two-fold unsymmetrical C-H functionalization[a,b]

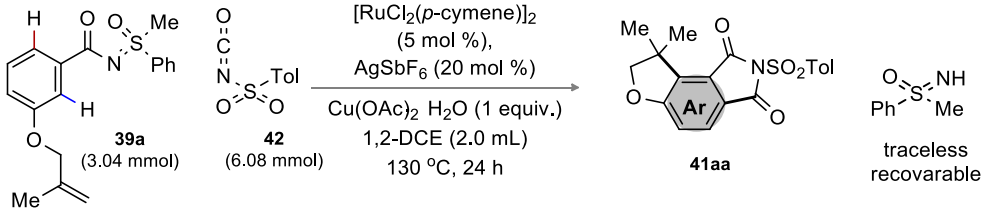


[a]Reaction conditions: **39** (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.3 mmol), DCE (2.0 mL) at rt for 2-5 hrs then addition of **42** (0.6 mmol) and followed by heating the reaction mixture at 130 °C for 24 h. [b]Isolated yields.

4.3.4. Gram Scale Synthesis

The scalability of hydroarylation-aminocarbonylation-cyclization reaction was executed through a gram scale experiment. The reaction of **39a** (1.0 g) under Ru-catalyzed conditions furnished **41aa** (0.95 g) with the isolation of MPS (41%). The

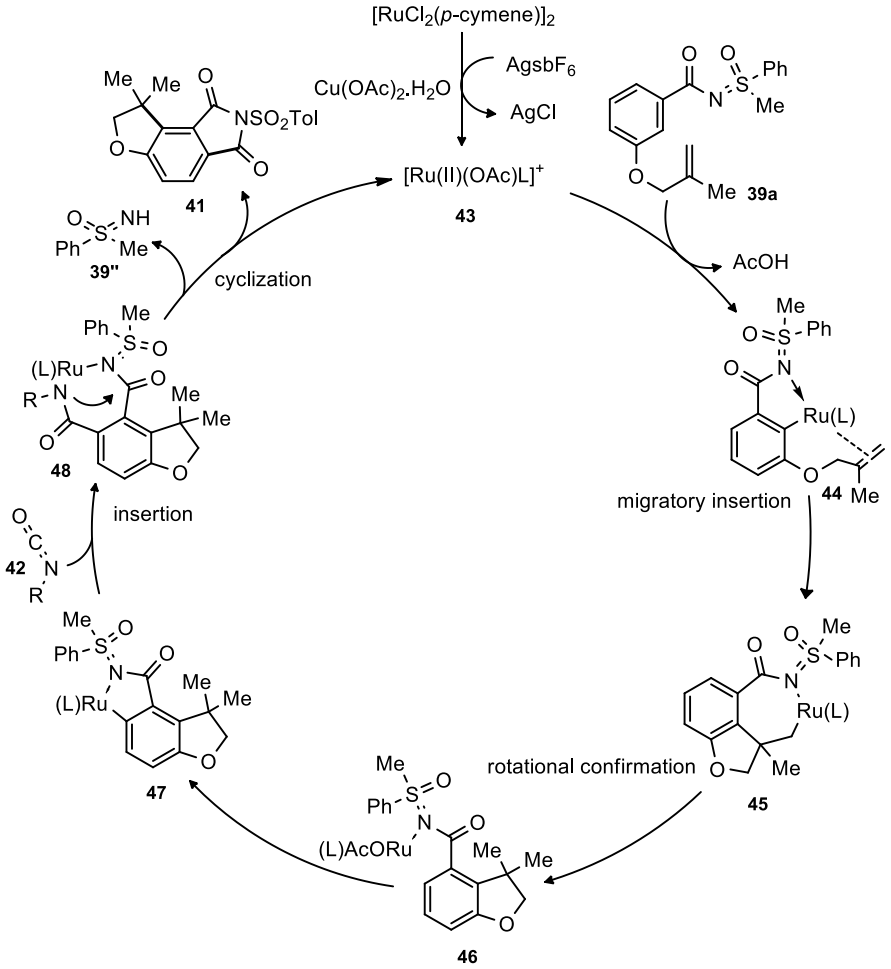
recovery of traceless MPS-DG makes this process atom-efficient and synthetically useful.



Scheme 2.14. Gram scale synthesis

4.3.5. Probable Mechanism

Based on previous findings and recent kinetic studies, the probable mechanistic cycle of this transformation is sketched in scheme 2.15. Extrusion of AgCl from $[RuCl_2(p\text{-cymene})]_2$ provided active cationic ruthenium complex **43** in presence of $AgSbF_6$ and $Cu(OAc)_2$. Acetate assisted proton removal from **39a** generates



Scheme 2.15. Proposed catalytic cycle

metalacycle **44**. Subsequent insertion of double bond to the carbon metal bond proficiently forms five membered dihydrobenzofuran skeleton with MPS coordinated metal embedded seven membered ring **45**. Subsequently proto demetalation followed by C–C bond rotation between arene and carbonyl moiety gave intermediate **46**. Next, the activation of proximal C–H bond in presence of acetate base forms five membered metal containing species **47**. Coordination of isocyanate to **47** and concurrent insertion leads to cabonylative amide containing seven membered complex **48**. Finally, cyclization of 48 via the nucleophilic attack of amide moiety to MPS attached carbonyl affords the desired cyclized product **41** with the removal of MPS-moiety from the molecule; truly attributing traceless nature of MPS-DG.

4.4. Conclusion:

In summary, a one-pot synthetic strategy through multiple unsymmetrical functionalization of arene *ortho*-C–H bonds involving intramolecular hydroarylation of olefin and intermolecular amino-carbonylation with isocyanate has been developed. The transformation occurs in presence of Ru-catalysis and sulfoximine DG plays vital. Wide array of novel benzofuran-fused-phthalimide scaffolds are readily constructed. Cyclization occurs with the concurrent expulsion of MPS group. The recovery of traceless MPS-DG validates the synthetic viability of the current demonstration.

4.5. Experimental

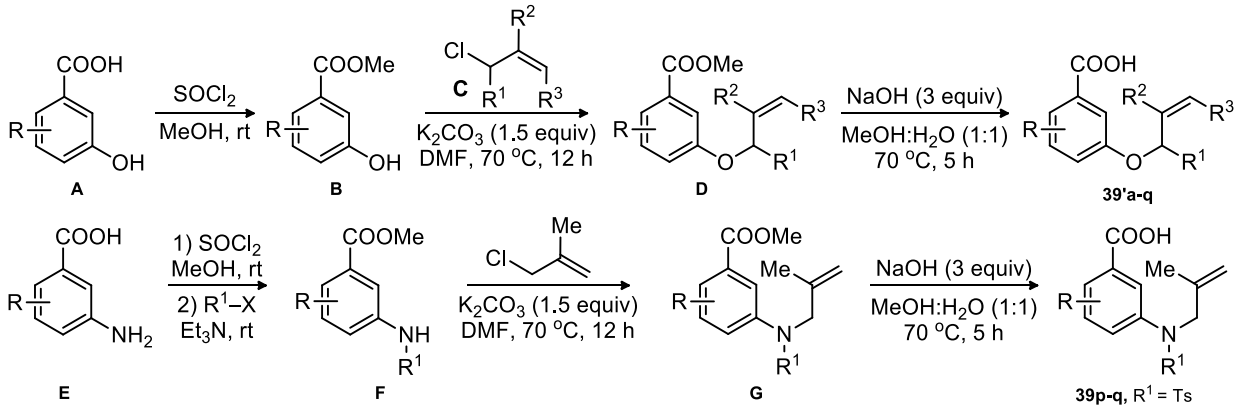
4.5.1. General Experimental Information is shown in Chapter 2 page no 67

4.5.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Dichloromethane (DCM), 1,2-dichloroethane (DCE), and chloroform were distilled over CaH_2. THF was freshly distilled over sodium/benzophenone ketyl under dry nitrogen. $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$, $AgBF_4$, KPF_6 were purchased from Sigma Aldrich Ltd, and used as received. Bases such as $Cu(OAc)_2{\cdot}H_2O$, KOAc, NaOAc, AgOAc were purchased from Aldrich Ltd. and used as received. Analytical and spectral data of all those known compounds are exactly matching with the reported values.

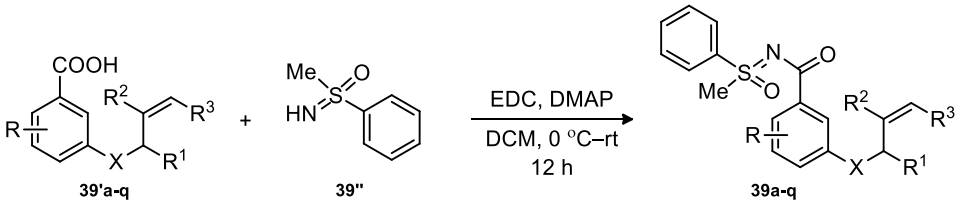
4.5.3. Experimental Procedures and Analytical Data

4.5.3.1. Preparation of Carboxylic Acid 39a–t: General Procedure (GP-1):



As depicted in the above scheme, corresponding benzoic acid derivatives (**39a–t**) were prepared and used for the next step. The analytical data of the benzoic acid derivatives are exactly matching with the reported values.

4.5.3.2. Preparation of *N*-Aroyl Sulfoximines (39); General Procedure (GP-2); EDC-Coupling:



A solution of *N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodimide, hydrochloride salt (EDC.HCl) (2.0 equiv), 4-*N*,*N*-dimethylaminopyridine (DMAP) (2.2 equiv) and carboxylic acid (**39'a–x**) (1.1 equiv) in CH_2Cl_2 (5.0 mL, for 1 mmol of sulfoximine) was stirred under an argon atmosphere. Methyl phenyl sulfoximine (**39''**) (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 the reduced pressure. The crude residue was purified using column chromatography on silica gel.

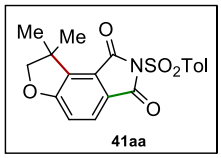
The other precursors (**39r–t**) are prepared using known synthetic procedure.

All the starting materials data are available in chapter 2 and chapter 3.

4.5.3.3. General Procedure for the Unsymmetrical Two-fold C–H Functionalization (*Intramolecular Hydroarylation & Intermolecular Amino-carbonylative Cyclization*) Reaction (GP-3):

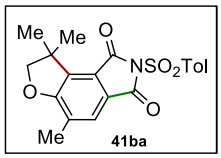
The two fold C–H functionalization reactions were conducted in a 50 mL Schlenk tube having high pressure valve and side arm. The tube was charged with (**39**, 0.30 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.0 mg, 5 mol %), and $Cu(OAc)_2 \cdot H_2O$ (60.0 mg, 0.30 mmol). Subsequently, the additive $AgSbF_6$ (21.0 mg, 0.06 mmol) was introduced to the flask in a glove box. 1,2-Dichloroethene (DCE; 2.0 mL) was added to the mixture and the resulting mixture was stirred at room temperature for 2–5 hrs. followed by addition of isocyanate (**42**, 0.60 mmol); the resulting mixture was then heated at 130 ^oC for 24 h. The reaction mixture was filtered through a plug of Celite and washed with dichloromethane (3 × 5.0 mL). The solvents were evaporated under the reduced pressure and the crude material was purified using column chromatography on silica gel (10–30% *n*-hexane/EtOAc eluent) to give the desired product.

8,8-Dimethyl-2-tosyl-7,8-dihydro-1H-furo[3,2-e]isoindole-1,3(2H)-dione (41aa):



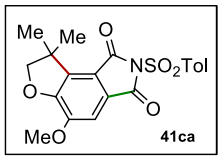
41aa (91 mg, 81%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 4.40 (s, 2H), 2.43 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 162.8, 162.3, 145.8, 136.7, 135.7, 129.9, 128.4, 127.4, 126.2, 123.4, 115.8, 86.4, 42.4, 26.1, 21.7.

5,8,8-Trimethyl-2-tosyl-7,8-dihydro-1H-furo[3,2-e]isoindole-1,3(2H)-dione (41ba):



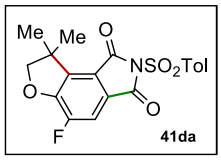
41ba (96 mg, 83%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.52 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 4.40 (s, 2H), 2.43 (s, 3H), 2.27 (s, 3H), 1.52 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164. 9, 163.1, 162.4, 145.7, 135.8, 135.5, 129.8, 128.3, 127.9, 126.6, 125.1, 123.6, 86.1, 42.7, 26.2, 21.7, 15.9.

5-Methoxy-8,8-dimethyl-2-tosyl-7,8-dihydro-1H-furo[3,2-e]isoindole-1,3(2H)-dione (41ca):



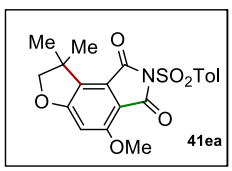
41ca (89 mg, 78%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.23 (s, 1H), 4.46 (s, 2H), 3.96 (s, 3H), 2.43 (s, 3H), 1.53 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 162.1, 154.6, 150.1, 145.7, 136.6, 135.8, 129.9, 128.3, 126.0, 119.6, 106.8, 86.9, 56.6, 43.2, 26.2, 21.7.

5-Fluoro-8,8-dimethyl-2-tosyl-7,8-dihydro-1H-furo[3,2-e]isoindole-1,3(2H)-dione (41da):



41da (79 mg, 71%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 4.52 (s, 2H), 2.44 (s, 3H), 1.56 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 161.5, 153.6 (J = 11.1 Hz), 151.3 (J = 260.6 Hz), 146.0, 140.2 (J = 4.0 Hz), 135.4, 129.9, 128.4, 125.1 (J = 6.0 Hz), 122.9, 112.8 (J = 20.2 Hz), 87.6, 43.4, 26.0, 21.7.

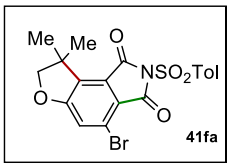
4-Methoxy-8,8-dimethyl-2-tosyl-7,8-dihydro-1H-furo[3,2-e]isoindole-1,3(2H)-dione (41ea):



41ea (89 mg, 78%) as colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 6.56 (s, 1H), 4.39 (s, 2H), 3.92 (s, 3H), 2.42 (s, 3H), 1.52 (s, 6H); ^{13}C NMR (101 MHz,

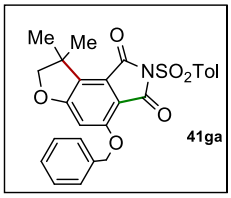
$CDCl_3$) δ 168.9, 162.0, 161.2, 160.0, 145.6, 135.9, 129.8, 129.7, 129.0, 128.5, 126.5, 99.3, 87.2, 56.5, 42.0, 26.2, 21.7.

4-Bromo-8,8-dimethyl-2-tosyl-7,8-dihydro-1H-furo[3,2-e]isoindole-1,3(2H)-dione (41fa):



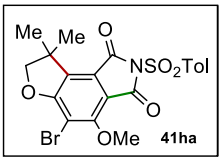
41fa (95 mg, 71%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.20 (s, 1H), 4.42 (s, 2H), 2.44 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 161.0, 160.9, 146.0, 136.6, 135.3, 130.0, 128.9, 128.5, 120.7, 120.5, 120.4, 87.0, 42.4, 25.9, 21.8.

4-(Benzyloxy)-8,8-dimethyl-2-tosyl-7,8-dihydro-1H-furo[3,2-e]isoindole-1,3(2H)-dione (41ga):



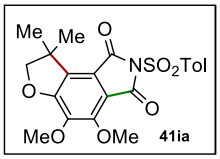
41ga (58 mg, 40%) as colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.5 Hz, 2H), 7.48-7.43 (m, 2H), 7.42-7.28 (m, 5H), 6.58 (s, 1H), 5.21 (s, 2H), 4.37 (s, 2H), 2.43 (s, 3H), 1.51 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 162.1, 160.8, 158.9, 145.6, 135.8, 135.2, 129.8, 129.2, 128.8, 128.4, 128.3, 128.2, 126.7, 109.5, 100.8, 87.1, 70.8, 42.0, 26.1, 21.7.

5-Bromo-4-methoxy-8,8-dimethyl-2-tosyl-7,8-dihydro-1H-furo[3,2-e]isoindole-1,3(2H)-dione (41ha):



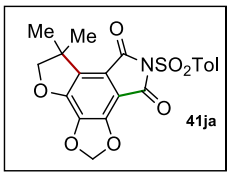
41ha (91 mg, 64%) as colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 4.50 (s, 2H), 4.06 (s, 3H), 2.44 (s, 3H), 1.55 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 161.5, 160.4, 157.2, 146.0, 135.4, 132.5, 129.9, 128.4, 126.2, 114.0, 106.3, 87.2, 62.9, 43.6, 26.1, 21.7.

4,5-Dimethoxy-8,8-dimethyl-2-tosyl-7,8-dihydro-1H-furo[3,2-e]isoindole-1,3(2H)-dione (41ia):



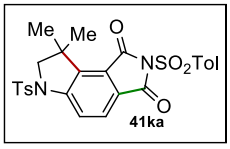
41ia (90 mg, 74%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.42 (s, 2H), 4.02 (s, 3H), 3.99 (s, 3H), 2.42 (s, 3H), 1.52 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 161.0, 158.6, 151.9, 145.7, 142.6, 135.7, 133.9, 129.8, 128.3, 120.7, 114.8, 87.2, 62.4, 61.0, 42.7, 25.9, 21.7.

6,6-Dimethyl-8-tosyl-5H-[1,3]dioxolo[4,5-e]furo[2,3-g]isoindole-7,9(6H,8H)-dione (41ja):



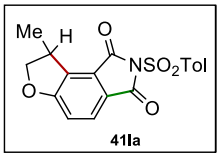
41ja (105 mg, 84%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 6.21 (s, 2H), 4.45 (s, 2H), 2.43 (s, 3H), 1.53 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 160.3, 147.8, 146.9, 145.8, 136.4, 136.0, 135.7, 129.9, 128.4, 118.7, 105.0, 87.9, 42.9, 25.8, 21.7.

8,8-Dimethyl-2,6-ditosyl-7,8-dihydropyrrolo[3,4-e]indole-1,3(2H,6H)-dione (41ka):



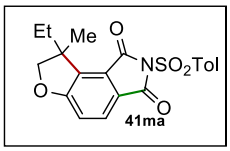
41ka (109 mg, 70%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 3.78 (s, 2H), 2.42 (s, 3H), 2.38 (s, 3H), 1.36 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 162.0, 148.6, 146.0, 145.2, 140.6, 135.4, 133.5, 130.1, 129.9, 28.4, 127.1, 127.0, 125.9, 125.6, 119.3, 64.6, 40.9, 26.6, 21.7, 21.6.

8-Methyl-2-tosyl-7,8-dihydro-1H-furo[3,2-e]isoindole-1,3(2H)-dione (41la):



41la (78 mg, 73%) as colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 8.5 Hz, 1H), 4.82 (t, J = 9.0 Hz, 1H), 4.40-4.34 (m, 1H), 2.43 (s, 3H), 1.46 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 162.7, 162.6, 145.8, 135.7, 132.4, 129.9, 128.4, 126.2, 123.0, 115.5, 80.6, 35.2, 21.7, 19.3.

8-Ethyl-8-methyl-2-tosyl-7,8-dihydro-1H-furo[3,2-e]isoindole-1,3(2H)-dione (41ma):



41ma (58 mg, 50%) as colourless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 1H), 4.56 (d, J = 9.0 Hz, 1H), 4.31 (d, J = 9.0 Hz, 1H), 2.44 (s, 3H), 2.52-1.96 (m, 1H), 1.86-1.77 (m, 1H), 1.54 (s, 3H), 0.77 (t, J = 7.5Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 162.8, 162.3, 149.8, 135.6, 129.9, 128.4, 127.7, 127.1, 126.2, 123.5, 115.6, 83.6, 48.5, 31.3, 24.5, 21.7, 9.1.

4.8. Reference

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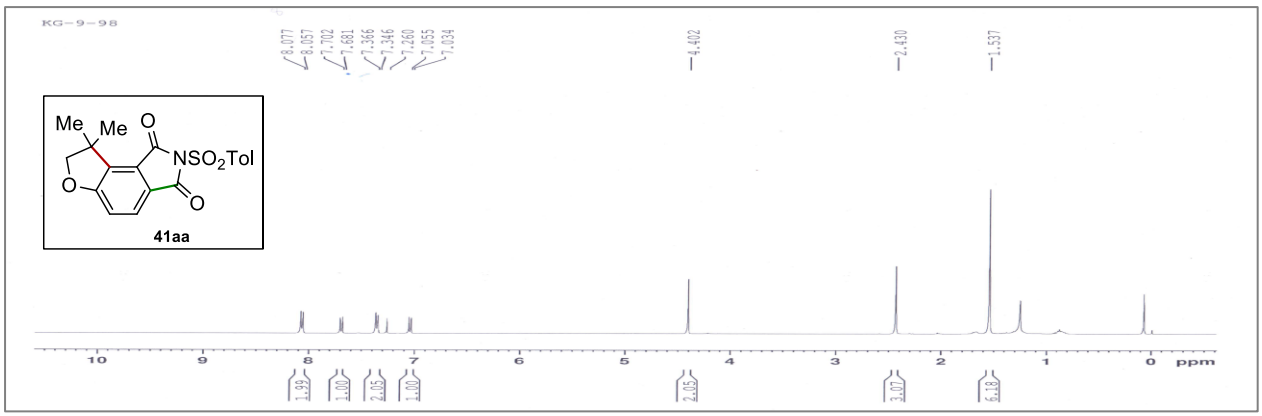
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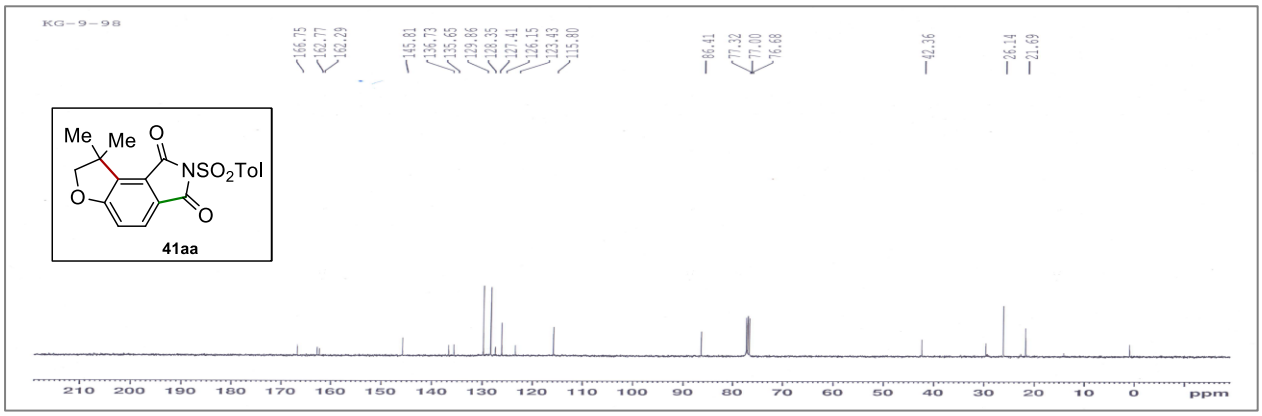
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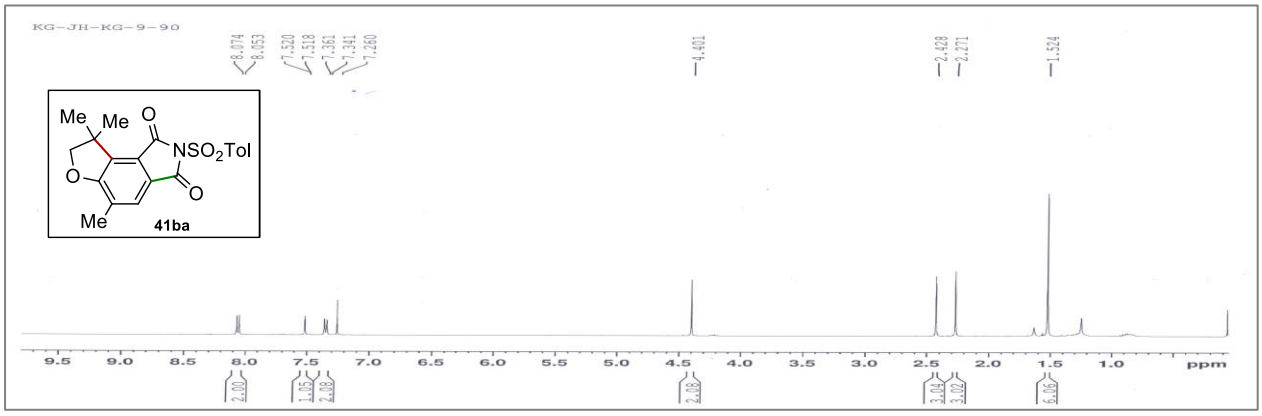
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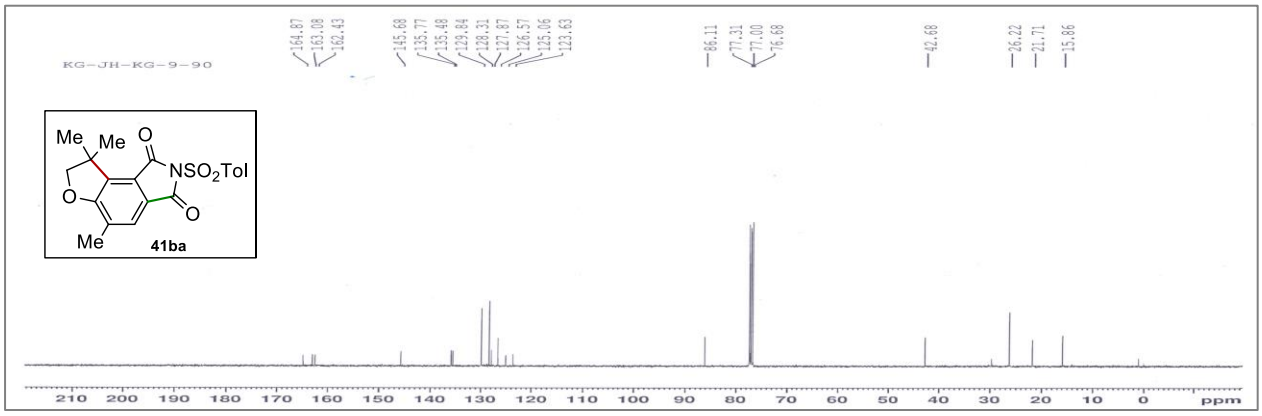
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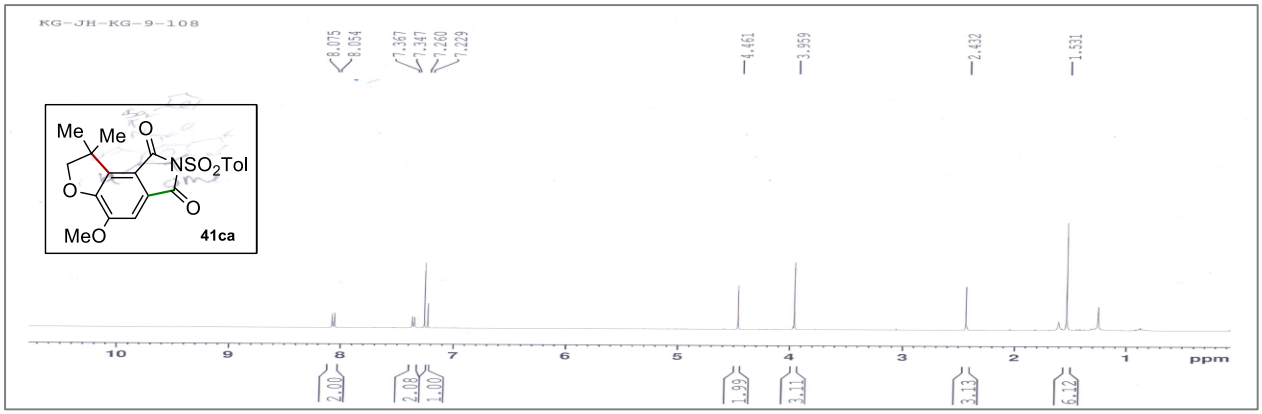
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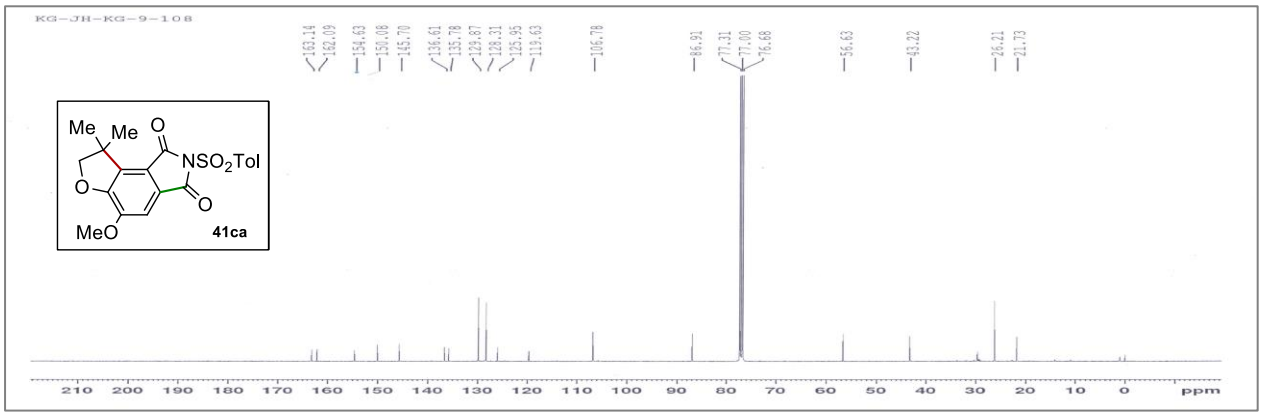

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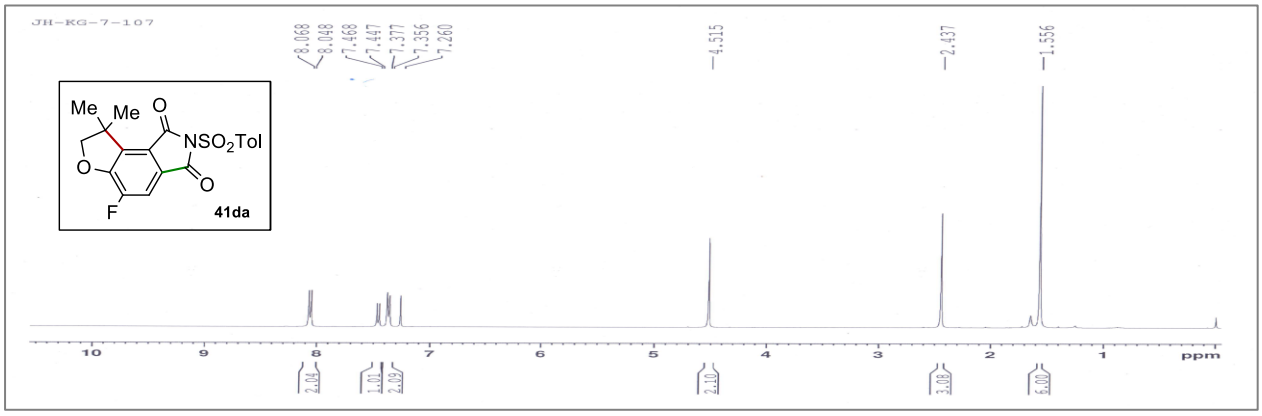

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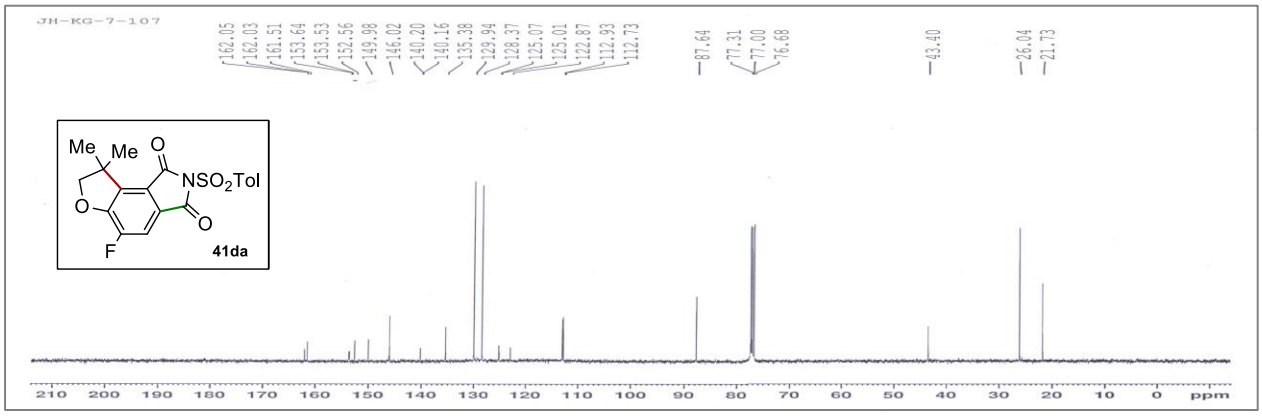

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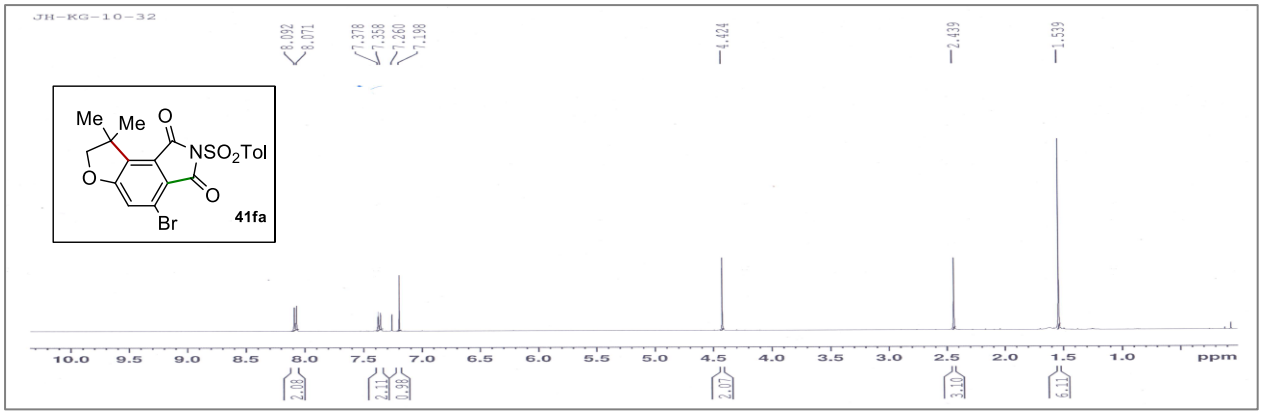

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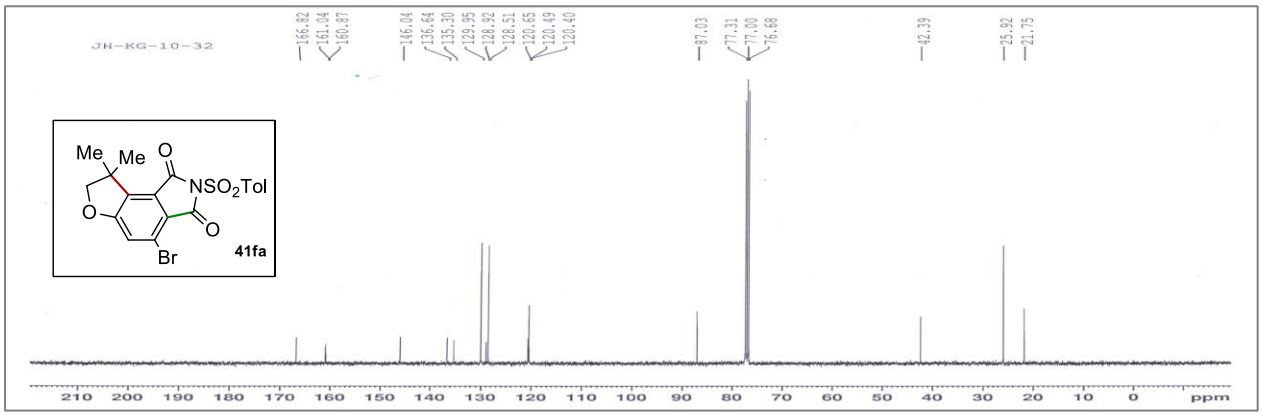

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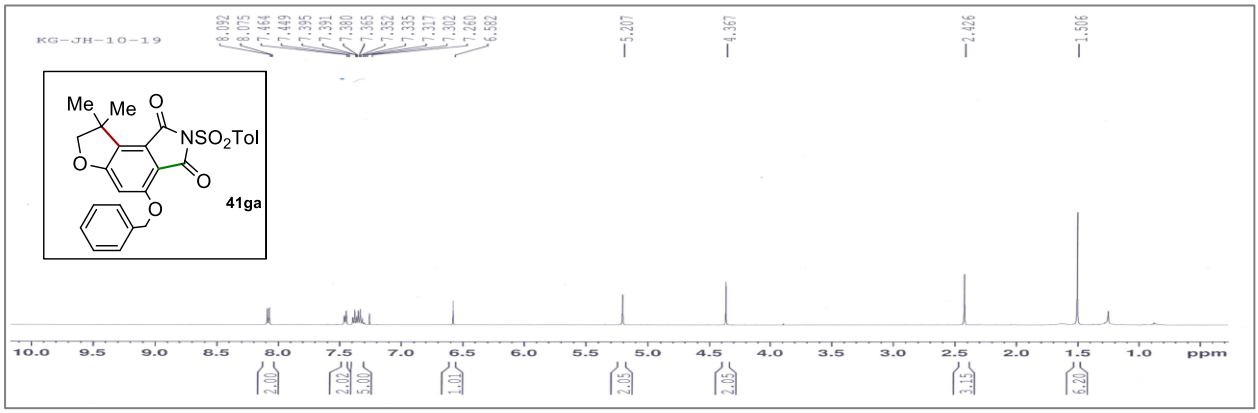

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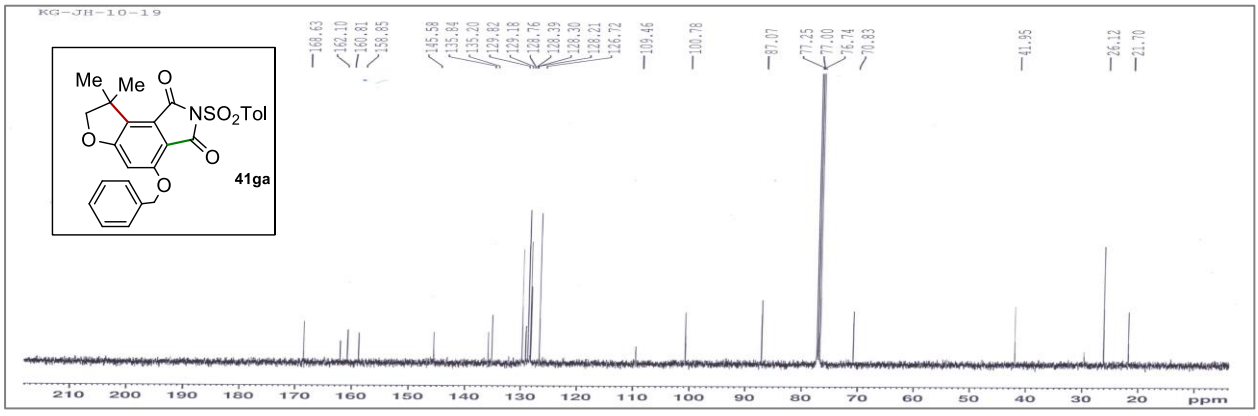

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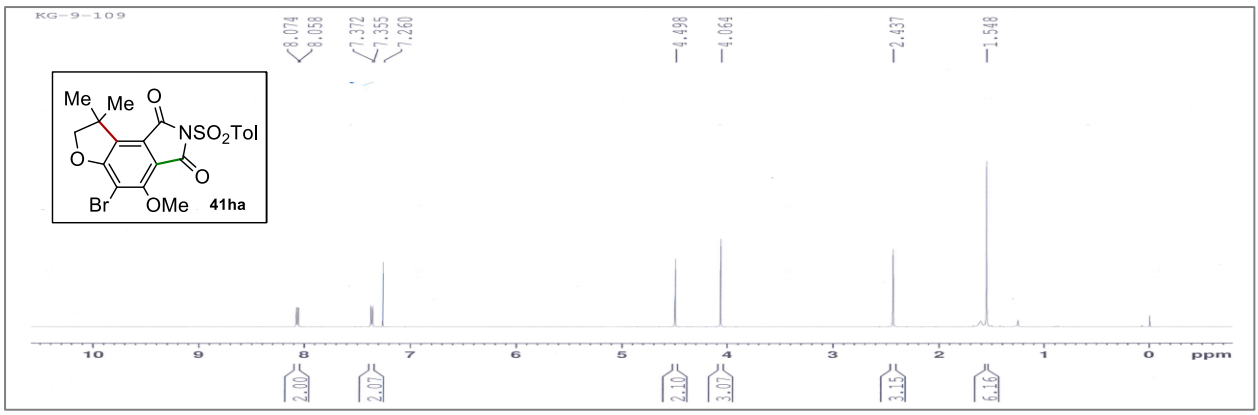

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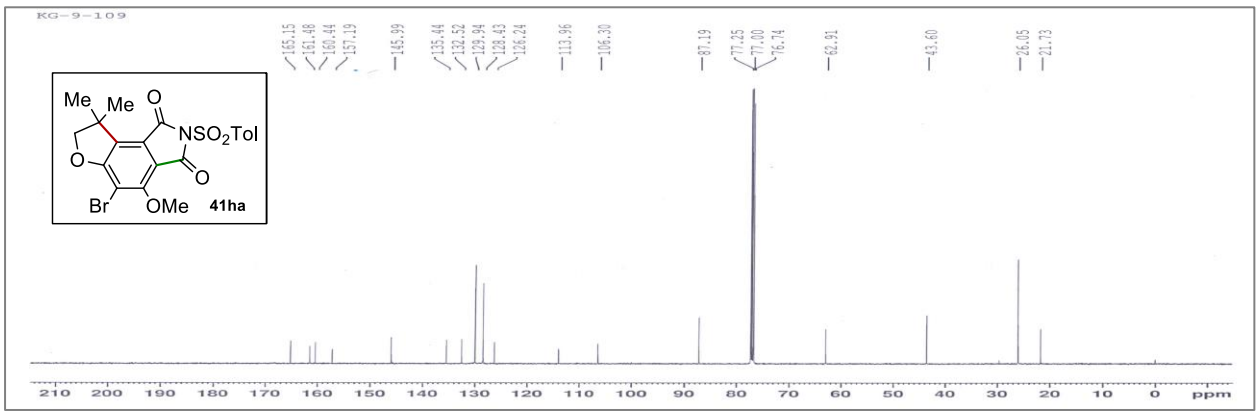

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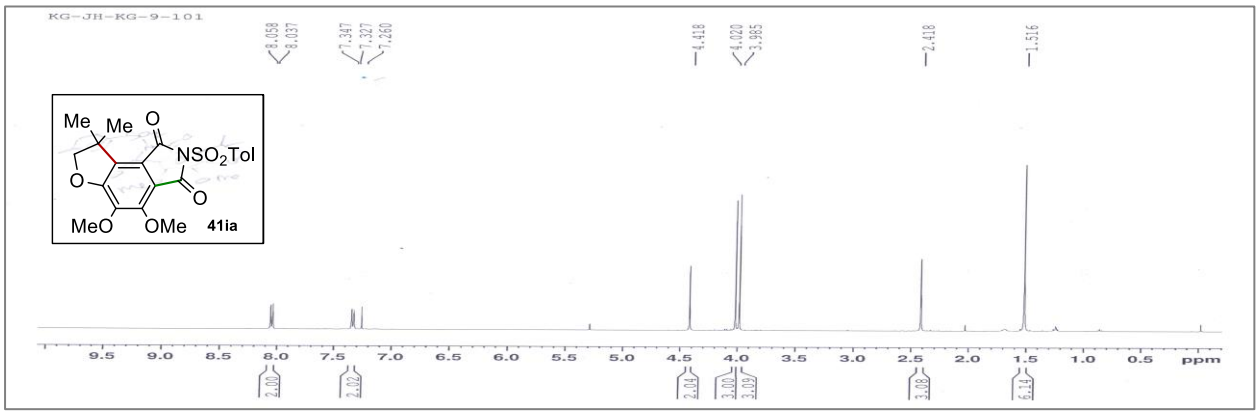

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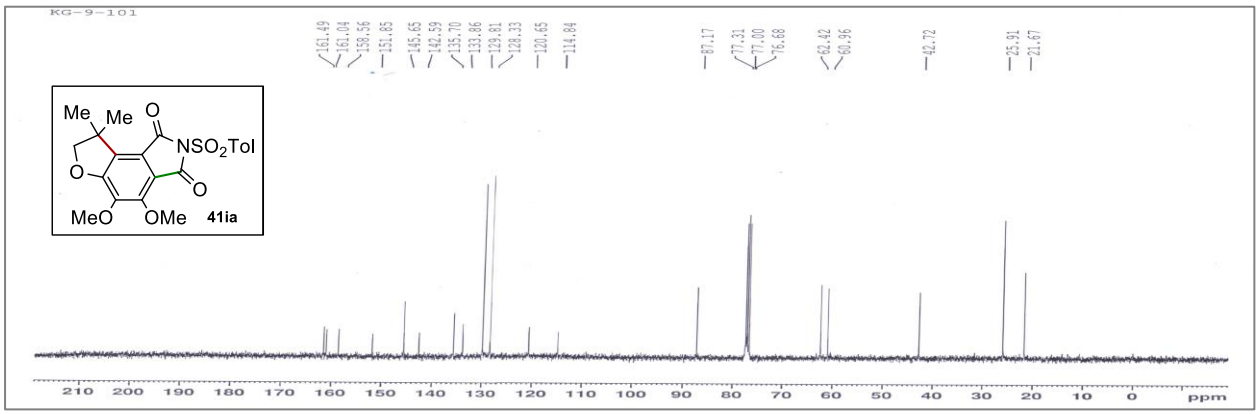

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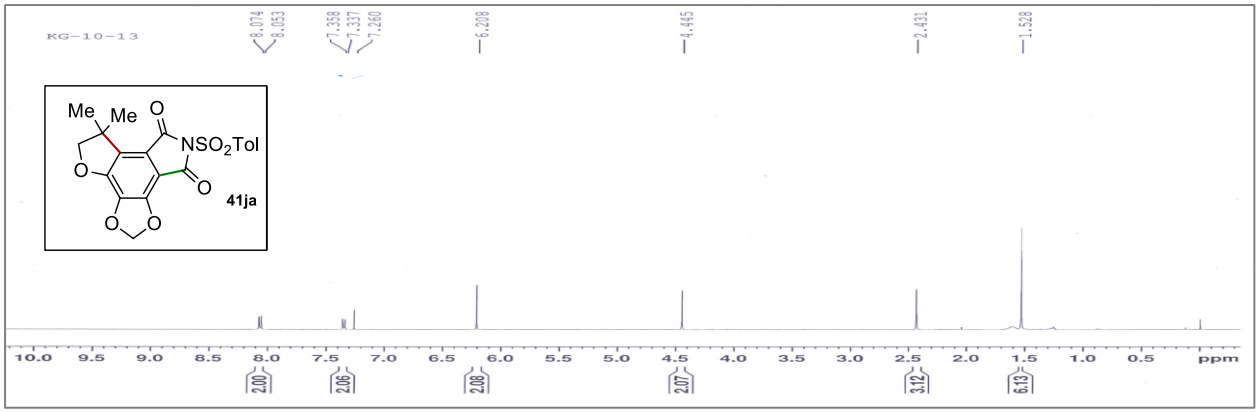

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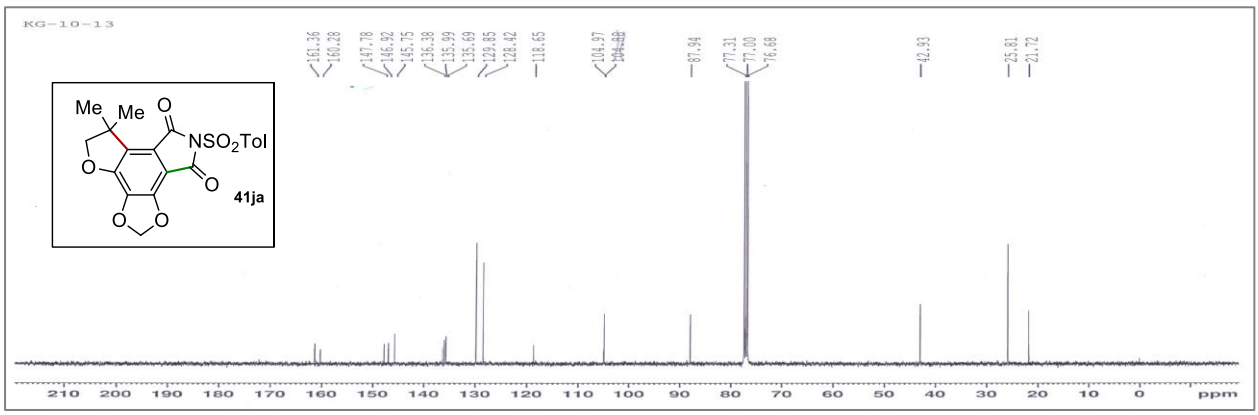

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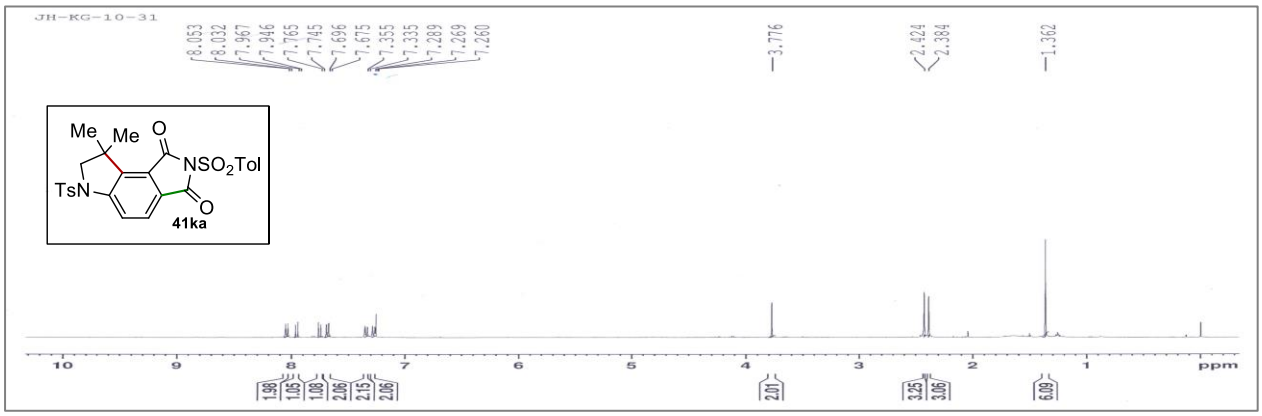

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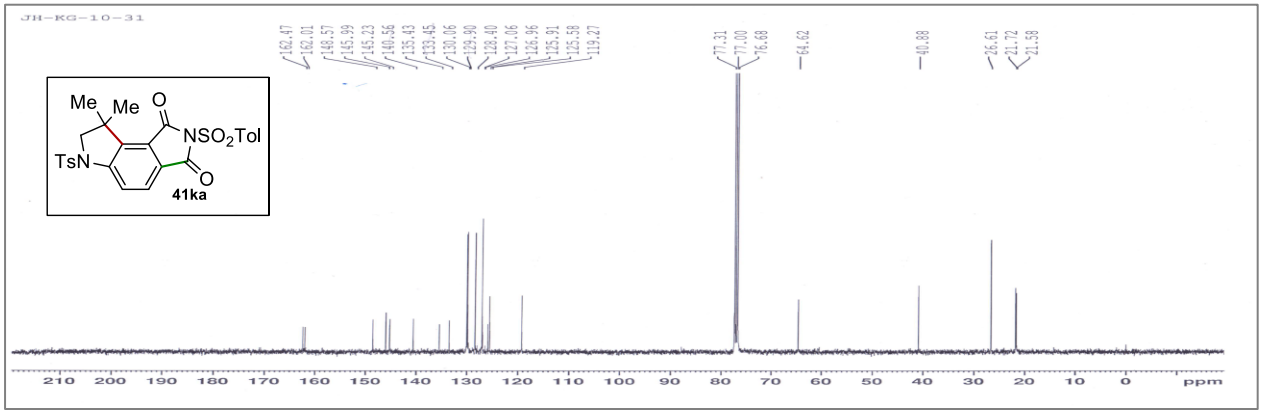

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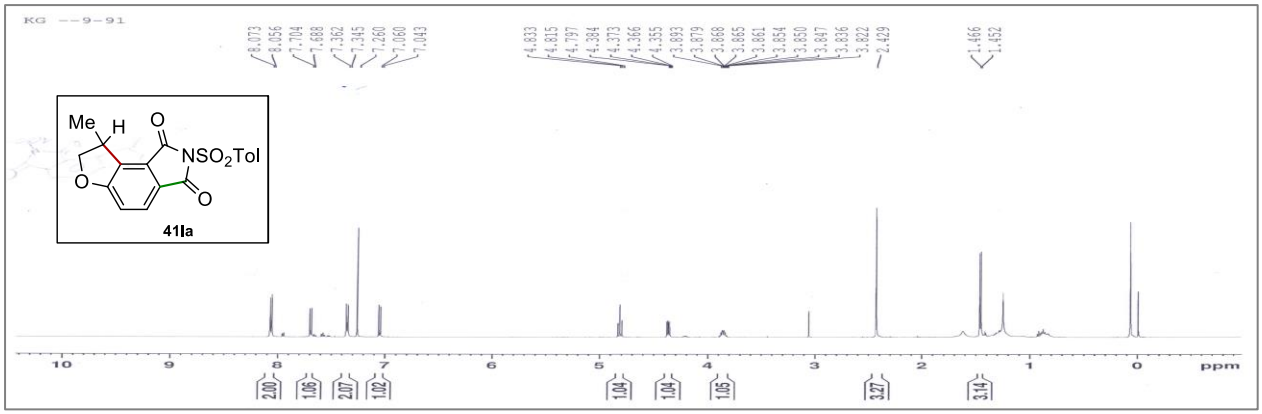

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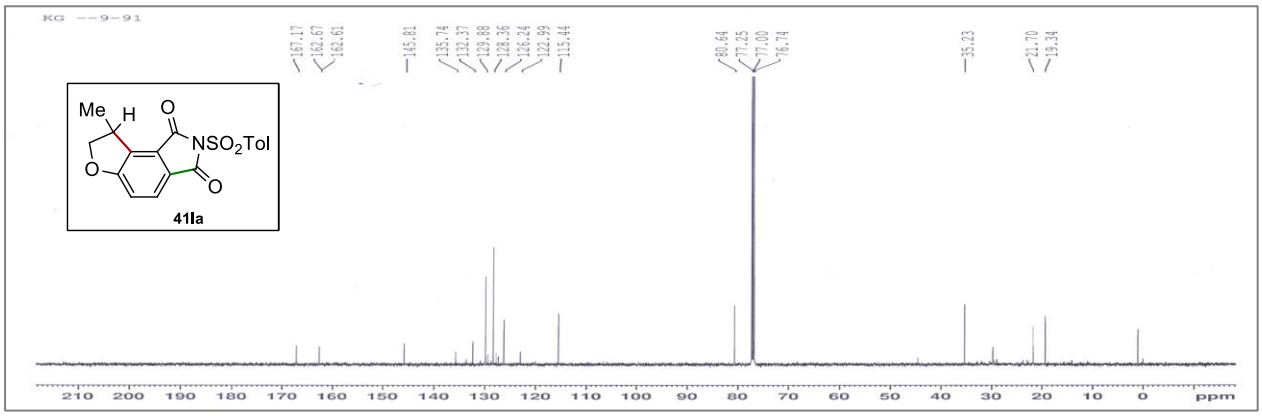

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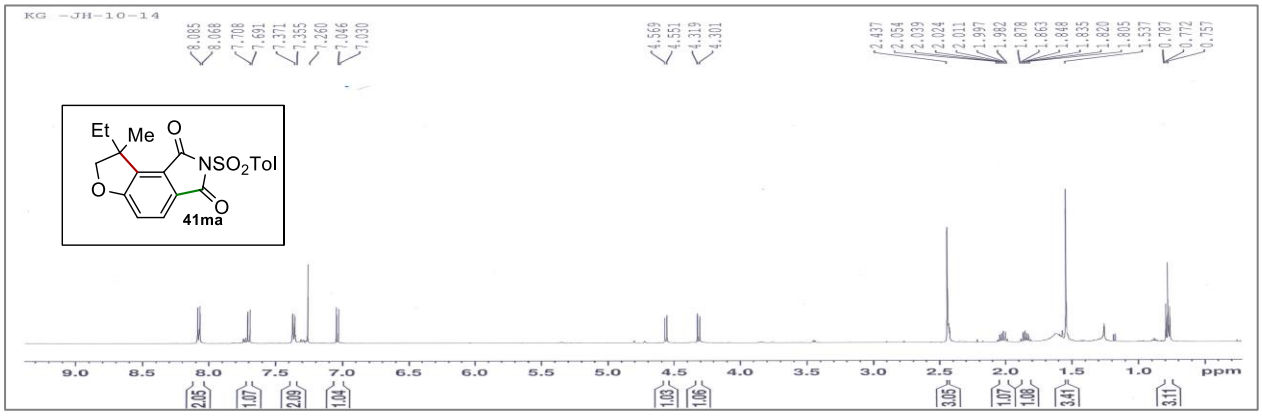

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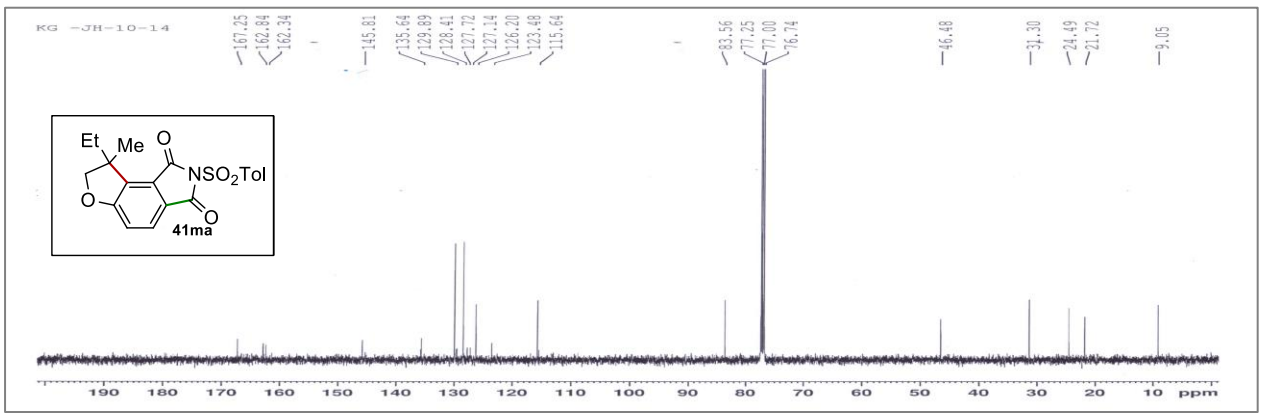

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TsN
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41ka


JH-KG-10-31
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KG --9-91
Me
H
O
NSO2Tol
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41la
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KG --9-91
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KG -JH-10-14
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O
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KG -JH-10-14
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Me
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NSO2Tol
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List of Publication

1. "Sulfoximine Assisted Pd(II)-Catalyzed Bromination and Chlorination of Primary-C(sp^3)–H Bond" Raja K. Rit, M. Ramu Yadav, **Koushik Ghosh**, Majji Shankar and Akhila K. Sahoo. *Org. Lett.* **2014**, *16*, 5258.
2. "Ruthenium-Catalyzed ortho-C–H Mono-and Di-imidation of Arenes with N-Tosyloxyphthalimide" M. Ramu Yadav, Majji Shankar, E. Ramesh, **Koushik Ghosh**, Akhila K Sahoo *Org. Lett.* **2015**, *17*, 1886.
3. "Reusable Directing Groups [8-Aminoquinoline, Picolinamide, Sulfoximine] in C(sp^3)−H Bond Activation: Present and Future" Raja K. Rit, Ramu M. Yadav, Koushik Ghosh, Akhila K. Sahoo *Tetrahedron*. **2016**, *71*, 4450.
4. "Ruthenium-Catalyzed Hydroarylation and One–Pot Twofold Unsymmetrical C− H Functionalization of Arenes" **Koushik Ghosh**, R. K. Rit, E Ramesh, Akhila K. Sahoo *Angew. Chem., Int. Ed.* **2016**, *55*, 7821.
5. "Ruthenium Catalyzed Intramolecular Hydroarylation of Arenes and Mechanistic Study: Synthesis of Dihydrobenzofurans, Indolines, and Chromans" Raja K. Rit, **Koushik Ghosh**, Rajib Mandal, and Akhila K. Sahoo *J. Org. Chem.*, **2016**, *81*, 8552.
6. "Ru-Catalyzed One-Pot Di-Annulation of Heteroaryls: Direct Access to π-Conjugated Polycyclic Amides" Majji Shankar, **Koushik Ghosh**, Kallol Mukherjee, Raja K. Rit, and Akhila K. Sahoo *Org. Lett.* **2017**, *17*, 1886.
7. "Ruthenium catalyzed one-pot two fold unsymmetrical C–H activation: Synthesis of Benzofurano-isoquinolone" **Koushik Ghosh**, Majji Shankar, R. K. Rit, and Akhila K. Sahoo* (Manuscript submitted)
8. "An Orchestrated Cyclization Episode of C(sp^2)–H Bonds with Alkynes and Quinones: Access to Spiro-Quinolinones" Kallol Mukherjee, Majji Shankar, **Koushik Ghosh**, and Akhila K. Sahoo (Manuscript prepared)
9. "Traceless-reusable Sulfoximine DG Assisted Unsymmetrical Two-fold Functionalization of Arenes" **Koushik Ghosh**, Kallol Mukherjee, Arghadip Ghosh and Akhila K. Sahoo (Manuscript under preparation)
10. "A One-Pot Consecutive two-[4+2] and {[4+2] & [5+2]} Annulations of Hetero(arenes): Access to Unusual Fused Pyrano-Isoquinolines and Oxepino-isoquinoline" Majji Shankar, **Koushik Ghosh**, Kallol Mukherjee, Raja K. Rit, and Akhila K. Sahoo (Manuscript under preparation)

Conference Attended

1. Sulfoximine Assisted Halogenation of Primary C(sp^3)–H Bond

   Raja K. Rit, M. Ramu Yadav, Koushik Ghosh, Majji Shankar, and Akhila K. Sahoo

   Poster Presentation at "**Chem Fest-2014**" held at School of Chemistry, University of Hyderabad, Hyderabad, India on **February, 2014**.

2. Ru-Catalyzed Hydroarylation and One Pot Twofold Unsymmetrical C−H Functionalizations of Arenes

   Koushik Ghosh, Raja K. Rit, E. Ramesh, and Akhila K. Sahoo

   (i) Oral Presentation at "**Chem Fest-2016**" held at School of Chemistry, University of Hyderabad, Hyderabad, India on **February, 2013**.

   (ii) Oral Presentation at "**XII-J-NOST**", held at Central Drug Research Institute, Lucknow, India on **November, 2016**.

3. Functionalization of Multiple C-H Bonds: A Sustainable Paradigm for Building Complex Molecular Framework

   Koushik Ghosh, Majji Shankar, Raja K. Rit, E. Ramesh, and Akhila K. Sahoo

   Poster Presentation at the International Conference "**ICCCS8**" held at School of Chemistry, University of Hyderabad, Hyderabad, India on **December, 2017**.