Cyclization and Rearrangement Strategies of Ynamide/ Yne-Dienone

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in
CHEMISTRY

By

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September, 2019

To

My Parents

&

Well-Wishers

DECLARATION

I hereby declare that the matter embodied in the thesis entitled **"Cyclization and Rearrangement Strategies of Ynamide/ Yne-Dienone"** 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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List of Abbreviations

AcOH	acetic acid
Ac	acetyl
acac	acetylacetone
Alk	alkyl
α	alpha
Å	angstrom
Ar	aryl
AIBN	azobisisobutyronitrile
Bn	benzyl
β	beta
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
^{t}Bu	^{t}butyl
calcd	calculated
Cat.	catalyst
cm^{-1}	centimetre inverse
cod	1,5-cyclooctadiene
Cp*	pentamethylcyclopentadiene
^{o}C	degree celsius
*m*CPBA	*m*-chloroperbenzoic acid
δ	delta
DFT	density functional theory
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide
d	doublet

dd	doublet of doublet
dt	doublet of triplet
ESI	electron-spray ionization
EWG	electron-withdrawing group
E^+	electrophile
E1	elimination unimolecular
equiv	equivalent
Et	ethyl
e.g.	exempli gratia
Et_3N	triethylamine
FT-IR	fourier transform infrared spectroscopy
γ	gamma
GP	general procedure
g	gram
Hz	hertz
HOMO	highest occupied molecular orbital
HRMS	high-resolution mass spectrometry
h	hour
HAT	hydrogen atom transfer
J	coupling constant in hertz
K	kelvin
LA	Lewis acid
L	ligand
LUMO	lowest unoccupied molecular orbital
MHz	mega-hertz
mp	melting point
m	meta
Ms	methanesulfonyl

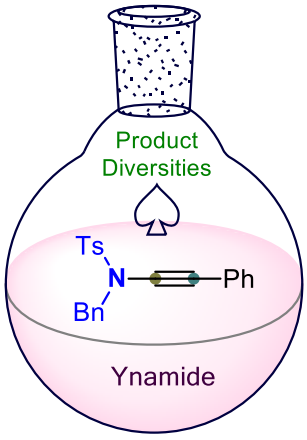
Me	methyl
μL	microliter
MW	microwave
mg	milligram
mL	milliliter
mmol	millimole
M	molar
MS	molecular sieves
Nu^-	nucleophile
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NHPI	*N*-hydroxypthalimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance spectroscopy
o	ortho
π	pi
PIDA	phenyliodine(III) diacetate
*p*TSA	*p*-toluenesulfonic acid
p	para
ppm	parts per million
^{n}Pent	*n*-pentyl
Ph	phenyl
Piv	pivalyl
^{i}Pr	*i*-propyl
^{n}Pr	*n*-propyl
PG	protecting group
Ph_3P	triphenylphosphine
R_f	retention factor

rt	room temperature
σ	sigma
S_N2	substitution nucleophilic bimolecular
T	temperature
tert	tertiary
THF	tetrahydrofuran
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TLC	thin-layer chromatography
TOF	time-of-flight analyzer
Ts	*p*-toluenesulfonyl
TM	transition metal
TFE	trifluoroethanol
TfOH	trifluoromethanesulfonic acid
Tf_2NH	bis(trifluoromethanesulfonyl)amine
UV	ultra-violet
VBT	valency-bond theory
1^o	primary
2^o	secondary
3^o	tertiary

Chapter-1

Ynamide: A Versatile Building Block in Organic Synthesis

Abstract



Ynamides represent one of the foremost and versatile building blocks in organic synthesis, as these motifs are extensively used for the synthesis of structurally diverse nitrogen containing heterocycles. The emergence and synthetic utility of nitrogen protected ynamides are discussed for the development of novel organic transformations and the building of synthetically demanding carbo- and heterocycles. Moreover, the synthetic diversities of various arene-tethered ynamides is enumerated via BrØnsted acid mediated cationic polycyclization, metal-catalyzed carbene generation followed by C–H insertion, radical difunctionalization, and so on.

1.1. Introduction

Alkyne is one of the most important and versatile building block in organic synthesis.[1] On the basis of valence bond theory (VBT), the carbon atoms in an alkyne are *sp*-hybridized; hence they possess more s-character and exhibit higher electronegativity. Thus, the acetylenic hydrogen of terminal alkynes is acidic; accordingly, they are applicable for various organic transformations (**I**; **Figure 1.1**).[2] Moreover, the symmetrically di-substituted internal alkynes experience a balanced electron distribution in the triple bond and are amenable for diverse range of novel organic transformations (annulation, cycloaddition, difunctionalization, and etc.); importantly, these transformations do not suffer the major issues of regioselectivity (**II**; **Figure 1.1**).[3] However, the uneven electron distribution and the change in the dipole moment of unsymmetrical alkynes result the product with lack of regioselectivity (**III**; **Figure 1.1**).[4] Because of their low pKa value, short bond length, small HOMO-LUMO gap and increased electron density, the alkynes are more reactive over the olefin counterparts.

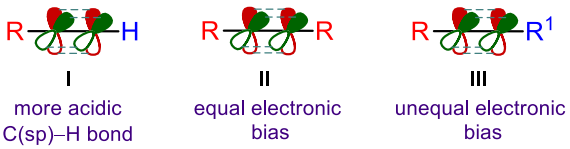


Figure 1.1. Electron bias of alkynes

1.1.1. Heteroatom (nitrogen) substituted alkynes

The nitrogen substituted alkynes (ynamines) represent a very useful functional groups in synthetic organic chemistry.[5] The strong electron donation of nitrogen lone pair towards the triple bond of ynamine forms a highly reactive keteniminium species (which is **Figure 1.2**). Hence, simultaneous attack of electrophile and nucleophile to the α- and β-position of keteniminium ion would furnish new products with high regioselectivity (**Figure 1.2**). As a result, ynamines are highly reactive possessing poor stability; this nature in turn hampers broad synthetic potential of ynamines.

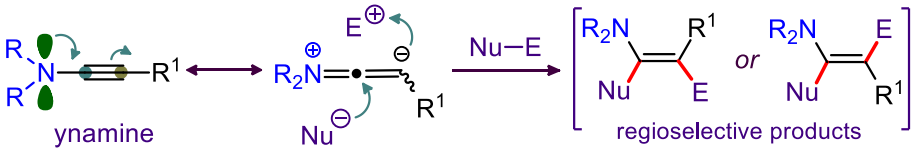


Figure 1.2. Polarization of electron density in ynamines

Moreover, ynamines are thermally as well as hydrolytically unstable. In presences of proton source, ynamines rapidly form keteniminium ion, which is then trapped by water to produce simple amide in a rather expensive manner (**Figure 1.3**).

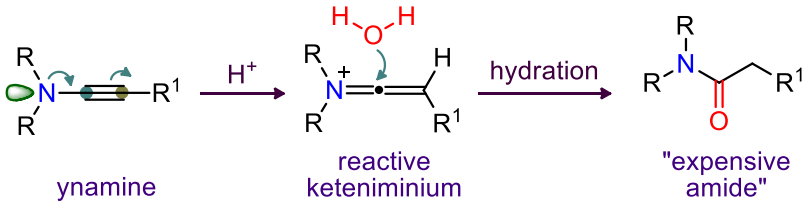


Figure 1.3. Hydrolytic instability of ynamines

1.1.2. Relative reactivity of ynol-ether and enamine with ynamine

In general, ynamines are comparatively less stable over the ynol-ether[6] and enamine[7] counterparts. Unlike ynamine, the stability of ynol-ethers can be explained in terms of electronegativity of oxygen atom. As oxygen is more electronegative than nitrogen, the electron donation of oxygen lone pair to the triple bond in ynol-ether is less; as a result, reactivity of ynol-ethers can be controlled over ynamine (**Figure 1.4**). Similarly, in case of enamine, the electron delocalization of nitrogen atom towards the double bond is diminished due to the weak overlap of nitrogen lone pair towards olefin double bond as it possesses bent structure (**Figure 1.4**).

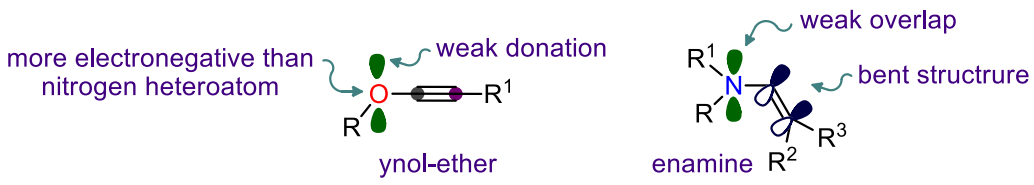


Figure 1.4. Reactivity of ynol-ether and enamines

1.1.3. Emergence of ynamide

In order to control the stability and reactivity of ynamine, synthetic chemists aimed to prepare electron deficient version of the ynamine (called ynamide; **Figure 1.5**).[5,8] The electron withdrawing group protection of nitrogen atom makes the ynamine relatively more stable. The electron withdrawing group attached to nitrogen atom diminishes the extent of polarization of nitrogen lone pair towards the triple bond (**Figure 1.5**). These characteristics attribute to better stability and controlled reactivity of ynamides.

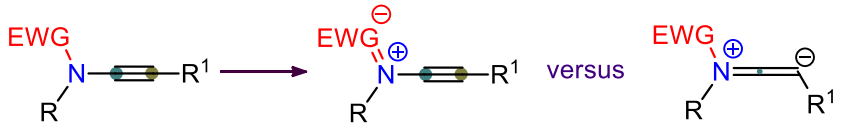


Figure 1.5. Resonance stability of ynamide

Interestingly, the electron withdrawing group (EWG) in ynamide is responsible for enhancing stability as well programming the reactivity of the compound; moreover, they act as directing group and chiral auxiliary for asymmetric induction (**Figure 1.6**). Moreover, it is also responsible for umpolung nucleophilic addition via the possible chelation with metal salts (**Figure 1.6**).

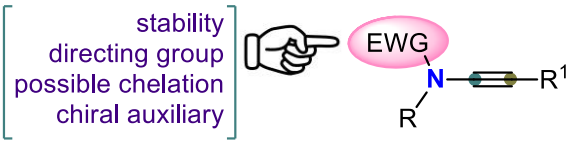


Figure 1.6. Electron withdrawing group protected ynamide

1.1.4. Analogues of ynamide

In the last few decades, various structurally different ynamides have been synthesized.[8a,8b] These species have been utilized in the development of many novel organic transformations. A diverse range of stable ynamide precursors with various N-protecting groups, such as, carbamate, amide, carbonyl, sulfonyl, phosphonate, sulfoximine, cyclic carbamate, and diamides have been synthesized (**Figure 1.7**).[8d] Most of the ynamides can be accessed by using standard synthetic transformations and some of them are also commercially available.

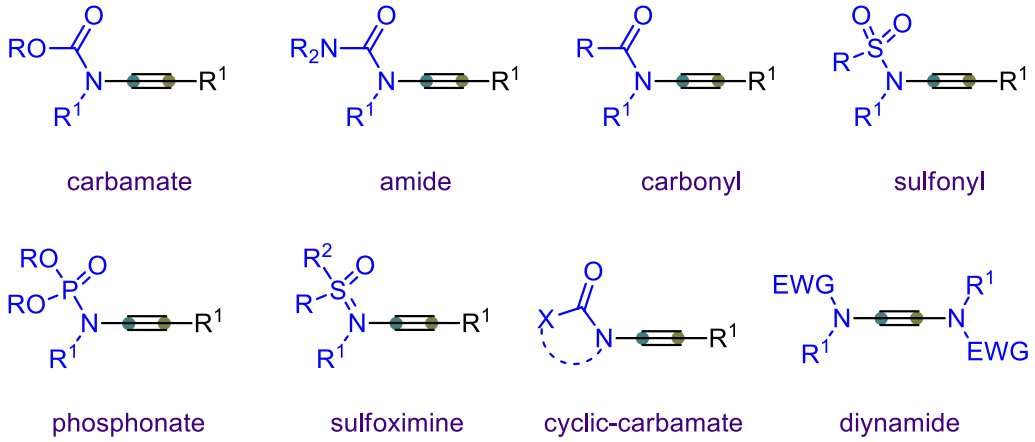
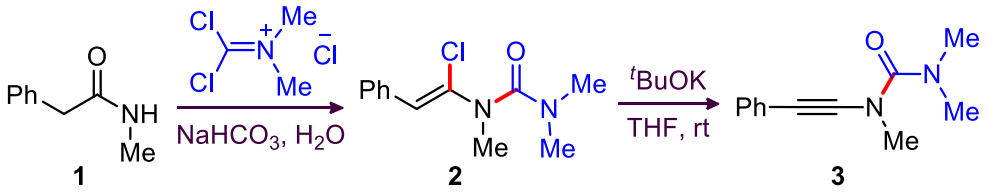


Figure 1.7. Various analogue of ynamides

1.2. Synthesis of Ynamide

1.2.1. Viehe's approach

In 1972, the very first ynamide synthesis was reported by Viehe.[9] The treatment of benzylamide **1** with phosgeneimonium chloride followed by hydrolysis can generate *α*-halo enamide **2**. Finally, removal of HCl from **2** in presence of potassium *tert*-butoxide forms ynamide **3** (**Scheme 1.1**).



Scheme 1.1. The first ynamide synthesis

1.2.2. General methods for the preparation of ynamides

Apart from Viehe's protocol, many groups later developed various methods for the synthesis of ynamide derivatives. In general, the ynamides derivatives cab be accessed through: (I) the base mediated elimination of hydrogen halide from haloenamide, (II) the base mediated isomerization of allenylamide, (III) the cross-coupling of nucleophilic amide with hypervalent-alkynyliodonium complex, (IV) the copper catalyzed oxidative amination of sulphonamide, oxygen, and terminal alkynes, (V) the copper catalyzed cross-coupling of bromo-alkynes with sulphonamides, and so on (**Figure 1.8**).[8a,8b,10]

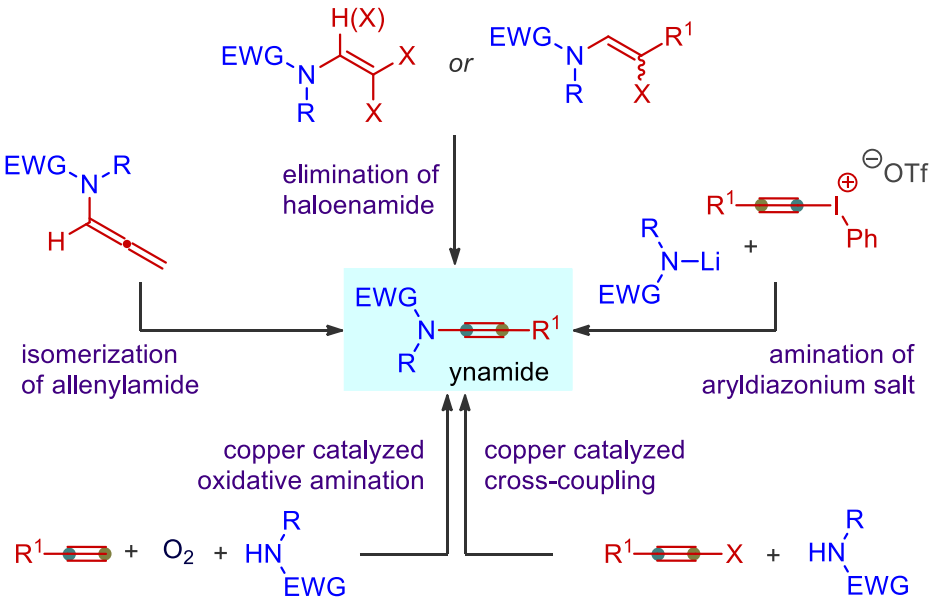
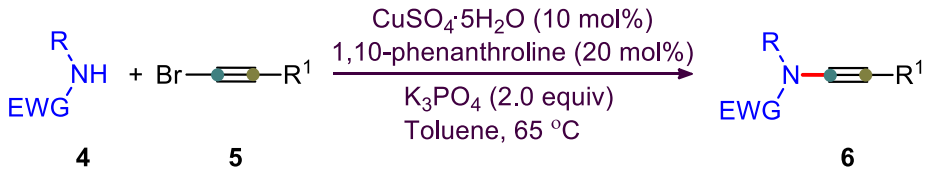


Figure 1.8. Various approaches towards ynamide synthesis

1.2.3. Hsung protocol for ynamide synthesis

In addition, Hsung and co-workers developed an elegant method for the synthesis of ynamide **6** from sulfonyl-protected amide **4** and bromoalkyne **5** in presence of copper catalyst to provide wide range ynamide derivatives. This protocol is found viable and general (**Scheme 1.2**).[11]



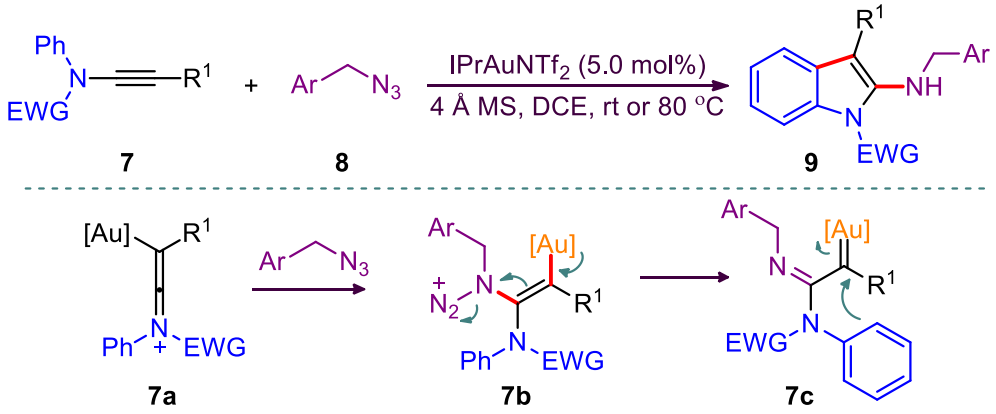
Scheme 1.2. Hsung protocol for ynamide synthesis

1.3. Synthetic Utility of Ynamide

Since last two decades, ynamide chemistry has been extensively used in the frontier area of research due to its unique reactivity and high regioselectivity. In this context, many conceptual developments have been made in this area to showcase its utility in synthetic organic chemistry. Some notable reactions include: cyclization, cycloaddition, umpolung addition, total synthesis of natural and non-natural complex molecular entities, and etc.

1.3.1. Reactions of α-imino gold carbene species

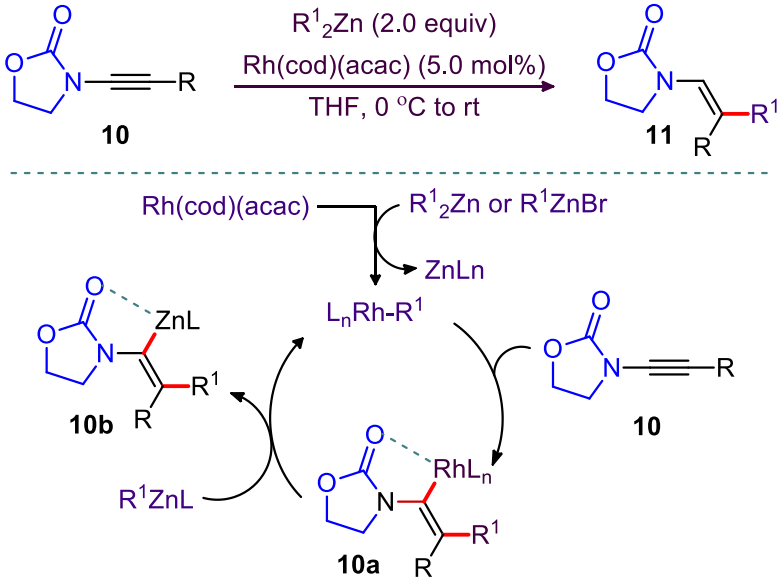
Ye and co-workers demonstrated a process for the *α*-imino-gold carbene generation from the reaction of benzyl azide **8** with ynamide **7** in presence of gold catalyst (**Scheme 1.3**).[12] The reaction involves the attack of azide moiety (**8**) to the *α*-position of gold activated keteniminium ion **7a** followed by the removal of nitrogen gas from **7b**; this process leads to *α*-imino gold carbene intermediate **7c**. Finally, trapping of gold-cabene **7c** by a tethered arene moiety gives the desired indole derivatives **9**.



Scheme 1.3. Gold catalyzed generation of *α*-imino gold carbene

1.3.2. Rhodium catalyzed carbozincation of ynamide

Lam and co-workers developed an elegant protocol for the synthesis of *β*-substituted

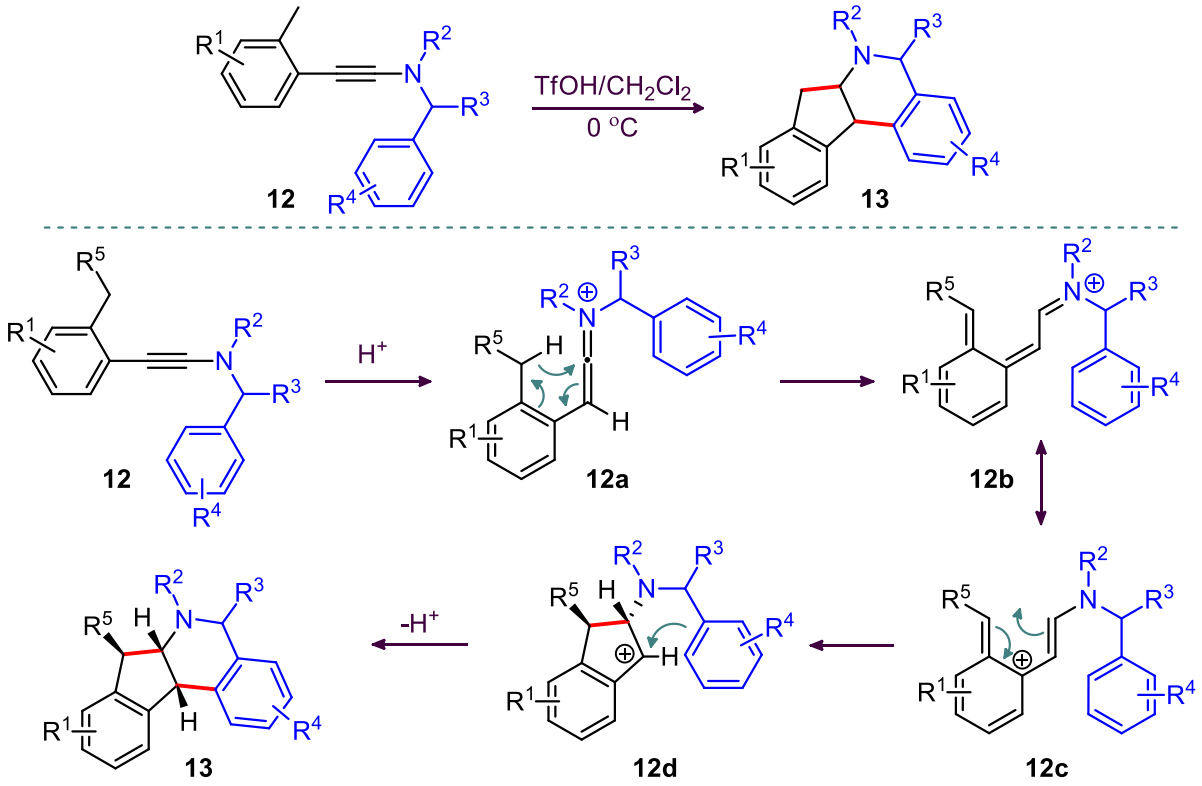


Scheme 1.4. Synthesis of *β*-substituted enamide

enamide **11** via a rhodium catalyzed carbozincation of ynamide **10** (**Scheme 1.4**).[13] The first step involves the ligand exchange with organozinc compound followed by umpolung-carbometallation with oxazolidinone ynamide **10** to generate chelated vinylic rhodium intermediate **10a**. Finally, transmetalation of **10a** with the respective zinc-motifs deliver **10b**.

1.3.3. Bronsted acid catalyzed polycyclization of ynamide

In 2014, Evano and co-workers reported an interesting demonstration of triflic acid (TfOH) or bistriflimide (Tf_2NH) mediated multiple cyclization of ynamide **12** to construct complex *N*-heterocycles **13** having three contiguous stereocentres (**Scheme 1.5**).[14] The reaction is initiated by the formation of reactive keteniminium ion **12a**. The key step of this transformation involves a 1,5-hydride shift.

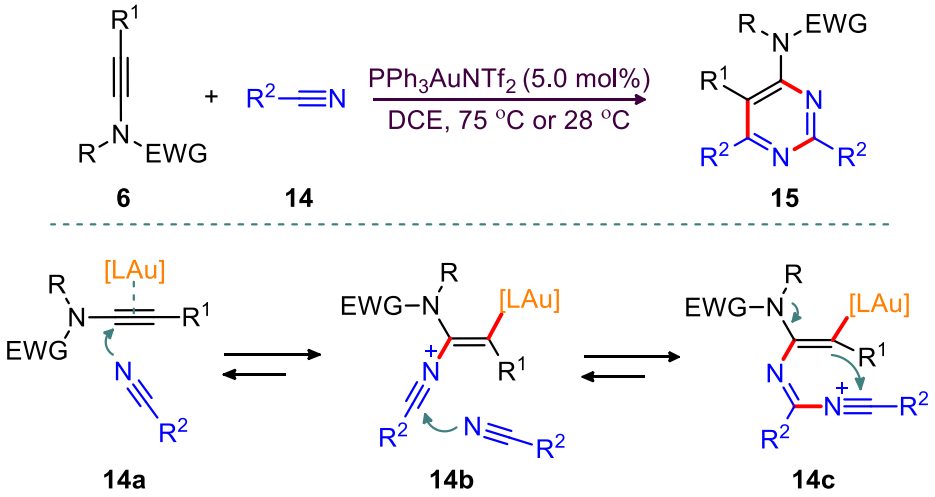


Scheme 1.5. Keteniminium ion induced multiple cyclization

1.3.4. Synthesis of 4-aminopyrimidine by [2+2+2] cycloaddition

Liu group shown an intermolecular [2+2+2] cycloaddition strategies of ynamide **6** with two discrete nitriles **14** to furnish 4-amino pyrimidine derivatives **15** (**Scheme 1.6**).[15] The

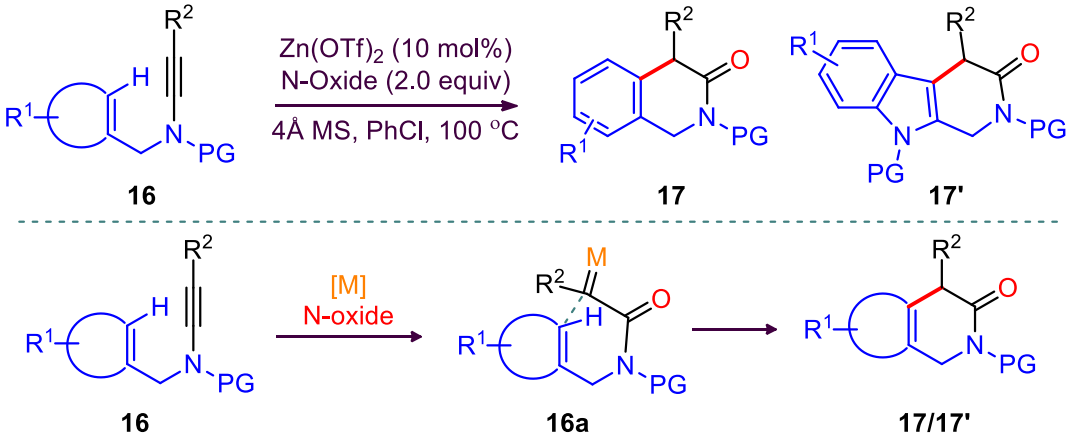
mechanism involves, the attack of nitrile to the gold-activated ynamide (**14a**) to generate nitrilium intermediate **14b**. Next, the attack of other nitrile species to the nitrilium intermediate **14b** generates **14c.** Finally, intermediate **14c** undergoes cyclization/aromatization sequence to provide the desired product **15**.



Scheme 1.6. [2+2+2]-cycloaddition of ynamide with two nitriles

1.3.5. Zinc-catalyzed alkyne oxidation/C–H functionalization

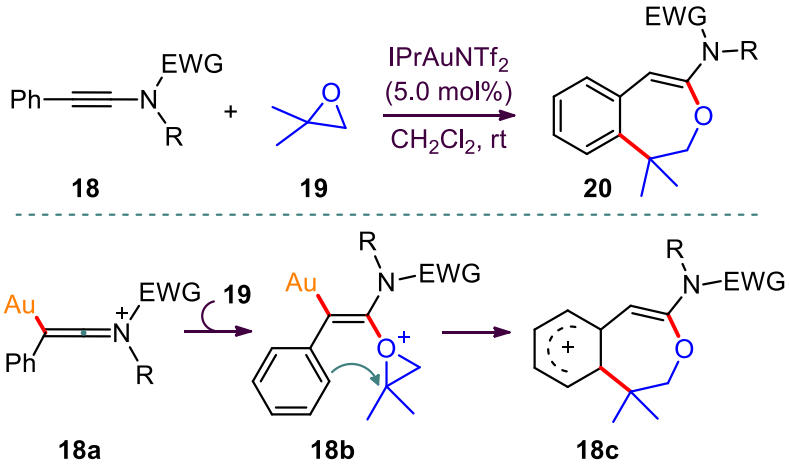
Ye et al demonstrated a non-noble metal catalyzed oxidation of ynamide **16** in presence of pyridine *N*-oxide to access *α*-oxo metal carbene intermediate **16a** (**Scheme 1.7**).[16] Final trapping of zinc-carbene intermediate **16a** by intramolecular C(sp²)–H bond of arene or heteroarenes delivers diverse range of isoquinolone and *β*-carboline derivatives **17/17′**.



Scheme 1.7. Zinc-catalyzed C–H functionalization of ynamide

1.3.6. [4+3] cycloaddition of epoxides with arene-ynamides

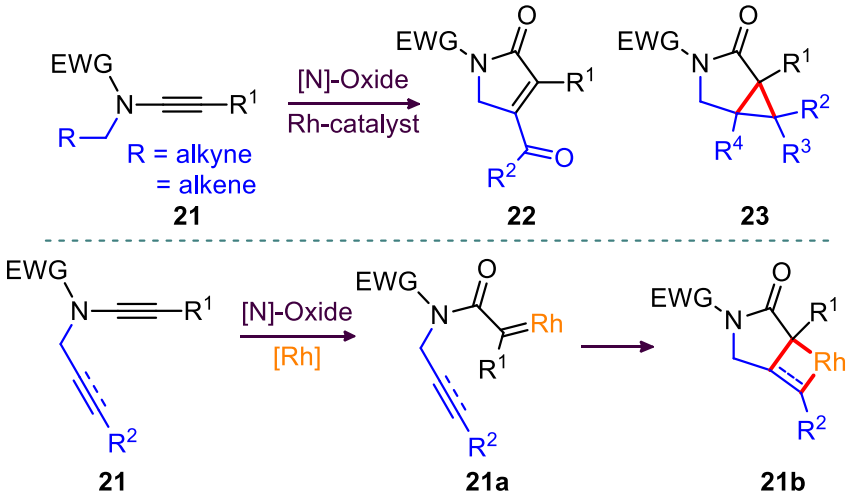
Liu and co-workers showcased a gold catalyzed [4+3] cycloaddition of epoxide **19** with arene-ynamides **18** to provide dihydrobenzoxepine derivatives **20** (**Scheme 1.8**).[17] The reaction proceeds through the attack of epoxide **19** to the *α*-position of gold activated keteniminium ion **18a** followed by electrophilic cyclization of arene moiety with the epoxide ring. Finally, aromatization of arenium ion intermediate **18c** gives the desired product **20**.



Scheme 1.8. Cycloaddition strategy of epoxide and ynamide

1.3.7. Generation and reaction of rhodium(I) carbenes from ynamides

Tang group reported a rhodium catalyzed synthesis of 2-oxopyrrolidines **22** and 3-azabicyclo [3.1.0] hexane **23** from the corresponding alkyne/alkene tethered ynamide

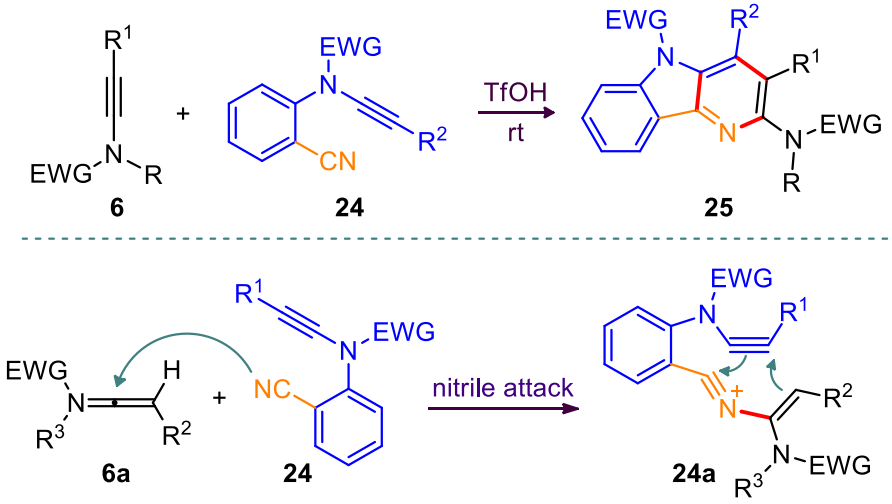


Scheme 1.9. Generation of rhodium(I) carbenes from ynamides

precursor **21** (**Scheme 1.9**).[18] At the beginning, ynamide **21** forms α-oxo metal carbene **21a** by reacting with pyridine *N*-oxide in presence of rhodium catalysts. The generated rhodium carbene intermediate **21a** undergoes metathesis with the pendant alkyne or alkene via **Int-21b** to yield the desired products **22** or **23**.

1.3.8. Synthesis of δ-carboline via metal-free cycloaddition strategy

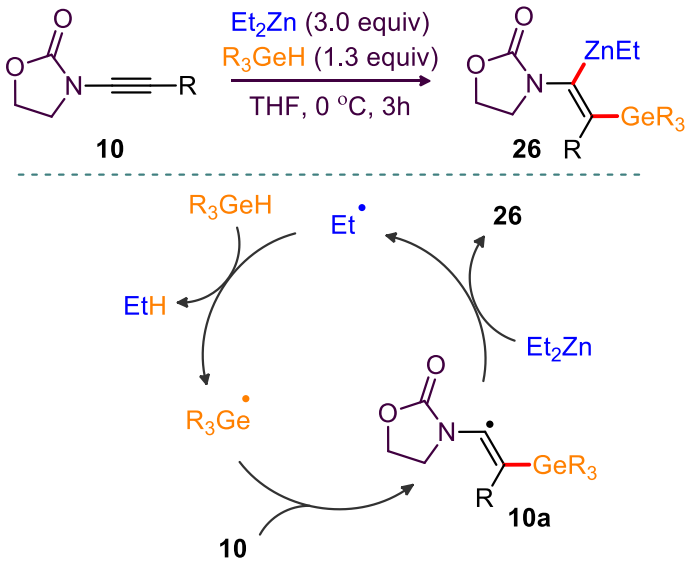
In 2018, Tang group established a [2+2+2] cycloaddition of ynamide-nitrile **24** with ynamide **6** in the presence of BrØnsted acid (TfOH) for the synthesis of polycyclic δ-carboline derivatives **25** (**Scheme 1.10**).[19] The electron withdrawing nitrile group in **24** hinders the formation of keteniminium ion. Thus, attack of nitrile **24** to keteniminium ion **6a** (produced from the ynamide **6** in presence of triflic acid) generates a nitrilium intermediate **24a**. Finally, cyclization and aromatization sequence of **24a** gives the desired product **25**.



Scheme 1.10. Cycloaddition approach of ynamide-nitrile with ynamide

1.3.9. Radical germylzincation of ynamide

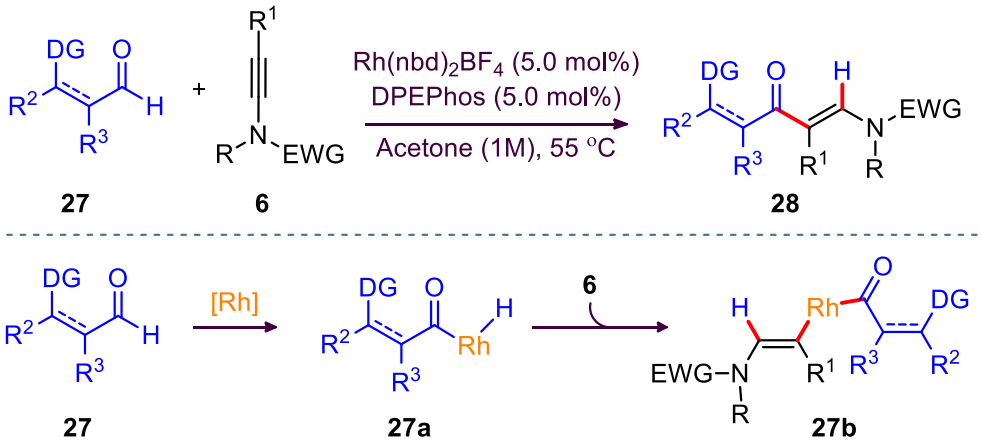
Luna and co-workers developed a germylzincation of heteroalkynes **10** to provide **26** (**Scheme 1.11**).[20] The transformation involves the attack of germyl-radical (generated from hydrogermane and diethylzinc) to the β-position of hetero-alkyne **10** to afford heteroatom stabilized vinyl radical **10a**. Finally, trapping of vinyl-radical **10a** with diethylzinc produces the germylzincation product **26**. Further functionalization of vinylated zinc with electrophile leads to various coupled products.



Scheme 1.11. Germyl-zincation of heteroalkynes

1.3.10. Rhodium-catalyzed hydroacylation of ynamide

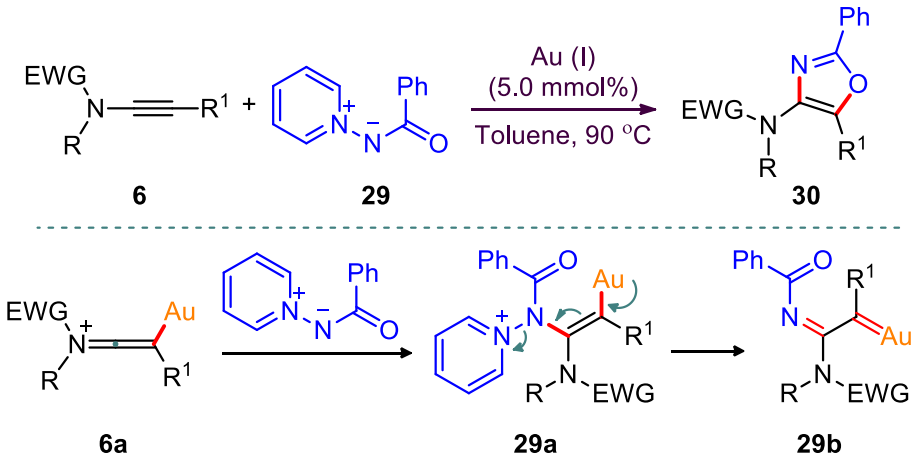
Wills and co-workers reported a novel and interesting protocol for rhodium catalyzed hydroacylation of ynamide **6** with aldehyde **27** (**Scheme 1.12**).[21] This is the first example of ynamide hydroacylation. The transformation involves the oxidative addition of rhodium with acyl-hydrogen bond in aldehydes **27** to generate metal hydride complex **27a**. Next, the hydride transfer of **27a** to the α-position of ynamide generates vinylic rhodium intermediate **27b**. Finally, reductive elimination of acyl and vinyl group of **27b** leads to hydroacylation product **28**.



Scheme 1.12. Rhodium catalyzed hydroacylation reaction

1.3.11. Synthesis of highly substituted oxazole from ynamide

Davis group utilized α-imino gold carbene species for the synthesis of highly substituted oxazole **30** from ynamide **6** (**Scheme 1.13**).[22] In this regard, *N*-aminide **29** has been used as a nitrene transfer reagent. The reaction involves the attack of *N*-aminide **29** to the α-position of gold activated keteniminium ion **6a** to give **Int-29a**. Next, gold back-donation followed by elimination of pyridine moiety leads to reactive α-imino gold-carbene intermediate **29b**. Finally, trapping of gold carbene by pendant carbonyl oxygen of **29b** furnishs the desired highly substituted oxazole derivatives **30**.



Scheme 1.13. Gold catalyzed synthesis of 4-amino-oxazole

1.4. Conclusion

In summary, a brief overview for the development of novel synthetic transformations through metallo-carbene generation, cationic poly-cyclization, radical addition, cycloaddition, metal-hydride insertion, cyclization, and cycloisomerization of ynamide derivatives and their synthetic potential is discussed in this chapter. The synthetic manifestation in the frontiers of ynamide scaffolds ensure its further development in the near future. With respect to the broad opportunities realized in discovering novel transformations in ynamide, the synthetic benefits gained though the cyclization and cycloisomerization sequence are highly inspiring. Hence, ynamide chemistry has been emerged as a powerful tool for the construction of complex nitrogen containing heterocycles. In this regard, further investigation strengthening the synthetic utility in this field is highly desirable.

1.5. References

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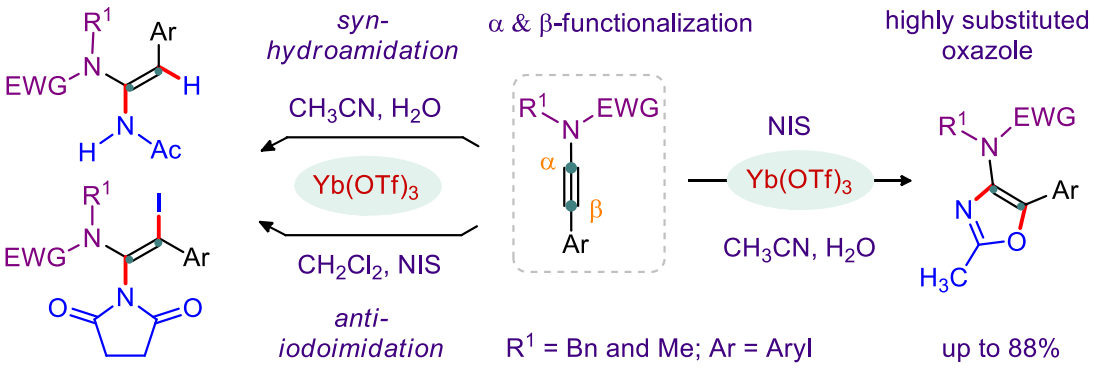
Chapter-2

Regioselective Synthesis of 2, 4, 5-Trisubstituted-Oxazoles and Ketene Aminals via Hydroamidation, and Iodo-imidation of Ynamides

Abstract



A novel and straightforward synthesis of highly substituted oxazoles from readily accessible ynamides in the presence of ytterbium(III) trifluoromethanesulfonate [$Yb(OTf)_3$], *N*-iodosuccinimide (NIS), and acetonitrile is demonstrated. Multiple oxazole skeletons in the arene-periphery are constructed in a single operation for the first time. The hydroamidation and iodo-imidation of ynamides to tri- and tetra-substituted ketene aminals is illustrated. To detect the oxygen source in this study, a set of isotope labeling experiments are conducted. The reactions are tested in the gram scale, affirming the robustness of the transformations.

Reference:

Rajendra K. Mallick, B. Prabagar, and Akhila K. Sahoo* *J. Org. Chem.* **2017**, *82*, 10583−10594.

2.1. Introduction

The oxazole motifs are important building blocks that are widely present in various natural products and bioactive molecules (**Figure 2.1**),[1] and are useful in many synthetic organic transformations.[2] In this regard, a modular paradigm to synthesize a highly substituted oxazole skeleton is extremely desirable.[3,4]

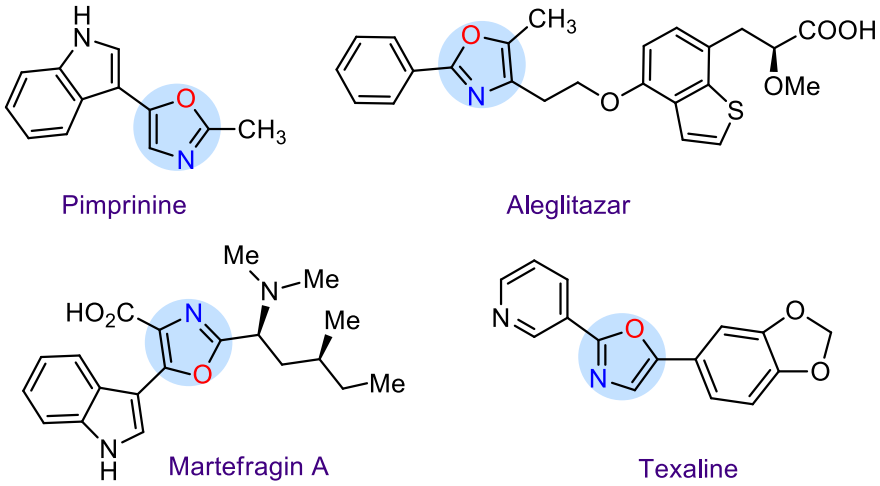


Figure 2.1. Oxazole containing bioactive molecules

Ynamides, the nitrogen atom substituted alkynes, have been broadly used in the conceptual development of various novel organic transformations.[5] The polarized triple bond in ynamide under the treatment of Brønsted/Lewis acid catalysis coherently allows *in situ* formation of reactive keteniminium species (**1**). Virtually trapping of reactive keteniminium species **1** with nucleophiles offers novel pathways for the construction of complex *N*-heterocycles.[6] The regioselective attack of *O*- and *N*-bearing nucleophiles to the α-position of activated keteniminium species **1** directly accesses ketene *N*,*O*-/*N*,*N*-acetal (**2**/**3**; **Figure 2.2**).[7] Thus, a diverse range of complex molecular scaffolds can be fabricated by intramolecular cyclization and cycloisomerization strategy of π-tethered acetals.[7b] Recently, we have explored the concept of ketene *N*,*O*- and *N*,*N*-acetal, attained from yne-ynamides by the attack of *p*-toluenesulfonic acid (*p*TSA), dimethyl sulfoxide (DMSO), or amide moieties to construct dihydropyridine, benzo[*f*]dihydroisoquinolone, pyrrolidone, and cyclobutene-fused-azepine derivatives.[8]

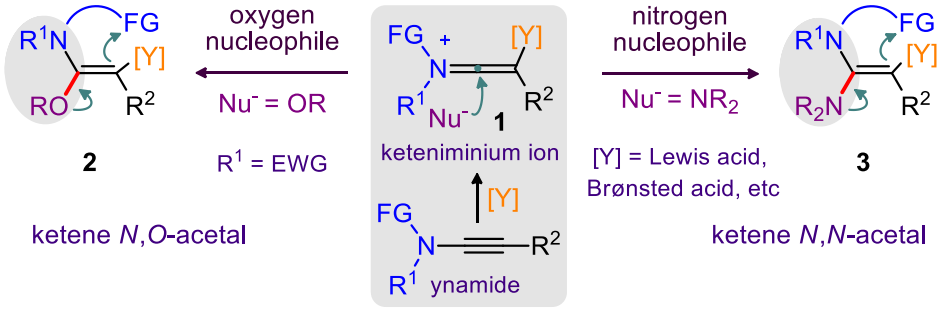


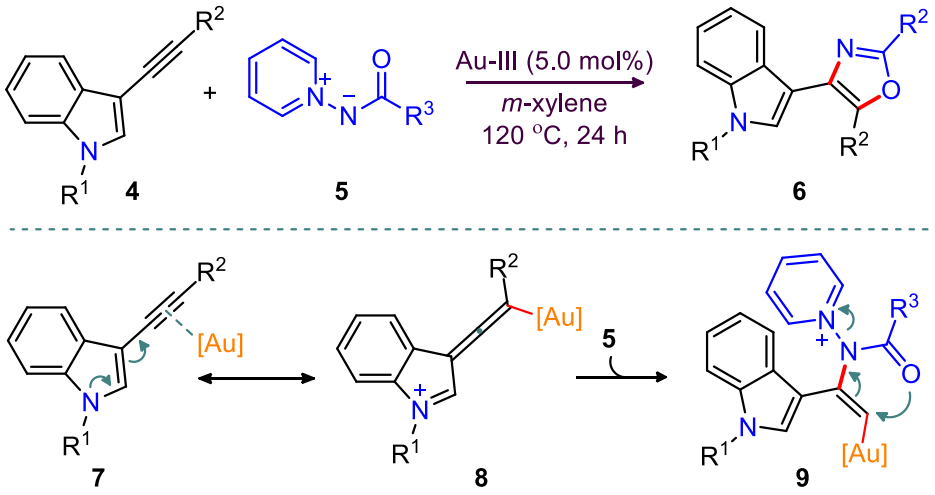
Figure 2.2. Generation of ketene *N*, *O*-acetal/*N*, *N*-acetal

2.2. Precedents

Keeping the synthetic potential and biological activity of oxazole skeleton in mind, efforts have therefore been directed to the synthesis of highly substituted oxazole from various starting precursors like alkyne, ynamide, etc. under different catalytic conditions. Some of the selected examples are discussed below (**Scheme 2.1**–**2.12**).

2.2.1. Synthesis of highly substituted oxazoles from alkyne precursor

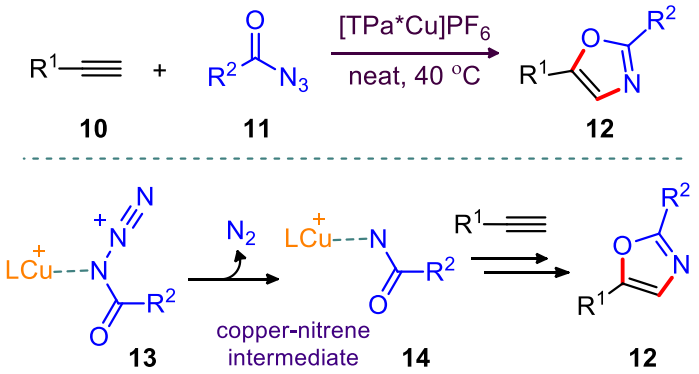
Davis group in 2013 developed a method for the synthesis of substituted oxazole **6** from heteroaryl tethered internal alkynes **4** and pyridine-N-aminide **5** in presence of gold catalysts (**Scheme 2.1**).[9] The N-aminide **5** is used as a nitrene transfer reagent. The transformation involves a reactive iminium species **8**, obtained in situ with the delocalization of nitrogen lone pair to the Au-activated triple bond of 3-alkynylindole (**7**).



Scheme 2.1. Regioselective synthesis of 2,4,5-(hetero)aryl substituted oxazoles

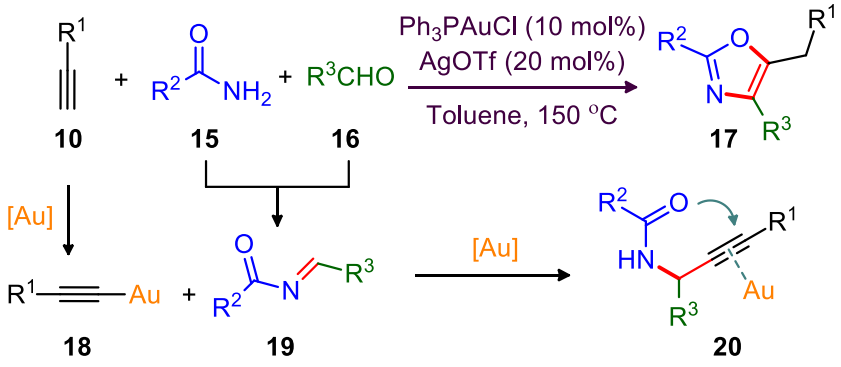
Next, a regioselective attack of aminide **5** to **Int-8** generates **Int-9**. Finally, removal of pyridine from **9** followed by cyclization leads to the desired oxazole product **6** with high regioselectivity. Moreover, the same group previously reported an identical strategy to oxazole synthesis from ynamide and N-aminide in presence of gold catalyst (discussed in Chapter-1, **Scheme 1.13**).

Perez et al in 2014 reported an interesting demonstration of oxazole synthesis from alkyne **10** and acyl azide **11** in presences of copper catalyst (**Scheme 2.2**).[10] DFT study supports the reaction mechanism. Acyl azide **11** in presence of copper catalyst at first forms **Int-13**. Next, the removal of N_2 gas from **Int-13** provides a reactive copper-nitrene intermediate **14**. Finally, cyclization of acyl nitrene **14** with alkyne **10** affords the oxazole skeleton **12**.



Scheme 2.2. Cu-catalyzed cycloaddition of alkynes and acyl-azides to oxazole synthesis

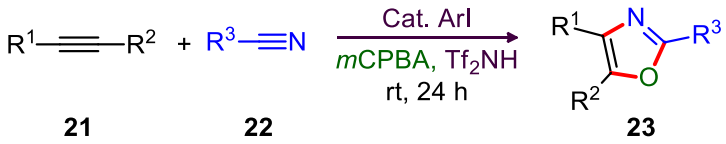
In 2015, Li and co-workers showcased a gold catalyzed multicomponent coupling of alkyne **10**, amide **15**, and aldehyde **16** to access highly substituted oxazole **17** (**Scheme**



Scheme 2.3. Gold catalyzed coupling of amide, aldehyde, and alkyne

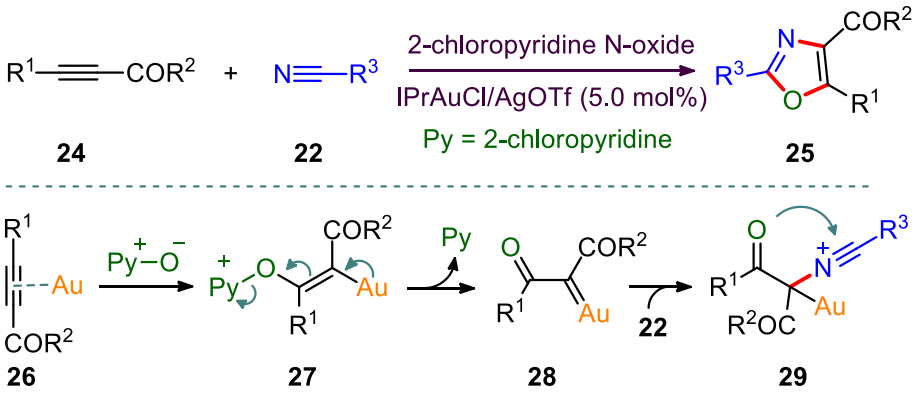
2.3).[11] The terminal alkyne **10** in presence of gold(I)-catalyst at first forms gold acetylide **18**, which then attacks to the in-situ generated acyl-imine intermediate **19** to provide **Int-20**. Finally, cycloisomerization of **Int-20** leads to **17**. This transformation uses a single cationic gold(I)-species and water is the only by-product.

Saito and co-workers developed a metal-free [2+2+1] cycloaddition of alkyne **21**, nitrile **22** and oxygen (from *m*CPBA) in presence of catalytic amount of aryl iodide for the synthesize di- and tri-substituted oxazole derivatives **23** (**Scheme 2.4**).[12] The reaction proceeds at room temperature, however, with moderate scope.



Scheme 2.4. Iodine(III)-catalyzed formal [2 + 2 + 1] cycloaddition

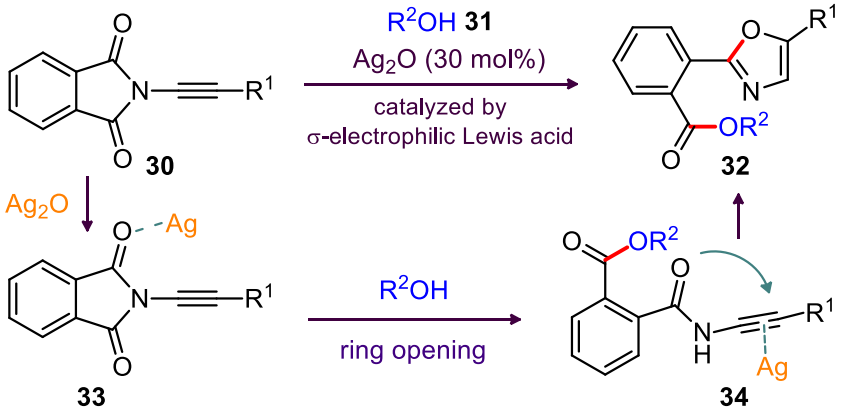
In 2019, Kukushkin group revealed a gold catalyzed three components [2 + 2 + 1] cycloaddition of electron deficient alkyne **24**, nitrile **22,** and 2-chloropyridine N-oxide to access highly substituted oxazole **25** (**Scheme 2.5**).[13] The reaction initiates by the attack of 2-chloropyridine N-oxide to the gold activated alkyne **26** to provide **27**. Next, removal of 2-chloropyridine moiety from **Int-27** via back-donation of gold leads to α-oxo gold carbene intermediate **28**. Intermolecular trapping of gold carbene intermediate **28** by nitrile **22** to give **29**. Finally, cyclization of nitrilium intermediate **29** yield highly substituted oxazole **25**.



Scheme 2.5. Gold catalyzed oxidative cyclization of activated alkyne with nitrile

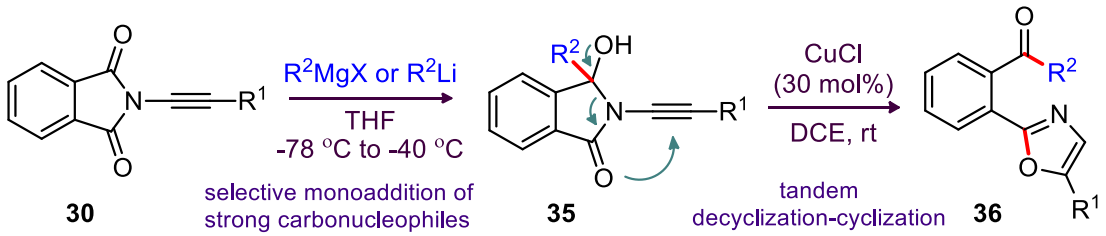
2.2.2. Synthesis of highly substituted oxazoles from ynamide

Sueda in 2013 reported a silver catalyzed synthesis of oxazole **32** from ynimide **30** and alcohol **31** (**Scheme 2.6**).[14a] At first, the activation of carbonyl group of **30** by Ag-catalyst forms **33**. Next, the attack of alcohol **31** to the carbonyl carbon of **33** followed by ring opening generates **Int-34**. Finally, cyclization of **Int-34** provides **32**.



Scheme 2.6. Silver catalyzed ring-opening and cyclization sequence of ynimide

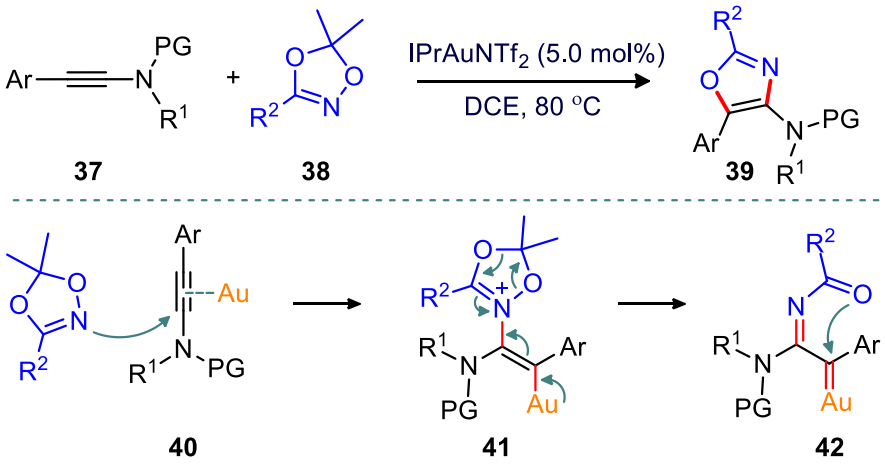
Later in 2016, an alternate method for the construction of di-substituted oxazole **36** from ynimide **30** has been shown by the same group (**Scheme 2.7**).[14b] The reaction proceeds in a similar manner as shown in **Scheme 2.6**. Initially, the organometallic reagents attack to the carbonyl group of **30** to generate *α*-hydroxy ynamide **35**. Finally, a copper catalyzed 5-*endo*-dig cyclization of **35** leads to the desired product **36**.



Scheme 2.7. Copper catalyzed synthesis of di-substituted oxazole from ynimide

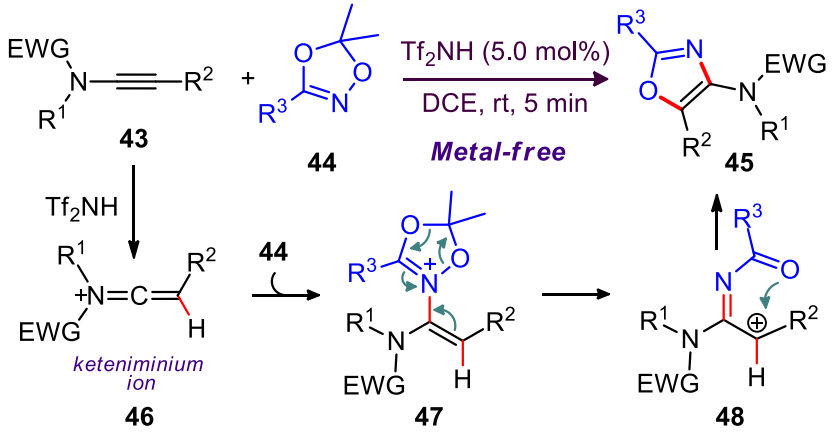
In 2016, Liu and co-workers developed an efficient method for the generation of *α*-imino gold carbene **42** by the attack of dioxazoles **38** to the α-position of gold activated ynamide **40** via intermediate **41**. The dioxazoles **38** has been used as a nitrene transfer reagent.

Finally, intramolecular trapping of gold carbene intermediate (**42**) by pendant carbonyl moiety leads to the desired product **39** (**Scheme 2.8**).[15]



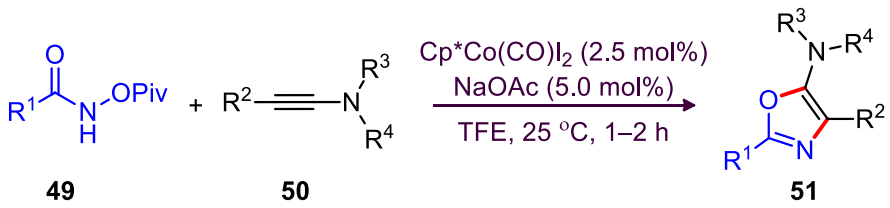
Scheme 2.8. Gold catalyzed [3+2] cycloaddition of ynamide and dioxazoles

Later, Wan group developed a similar stratergy for the synthesis of oxazole **45** from ynamide **43** and dioxazole **44** under metal free condition (**Scheme 2.9**).[16] The reaction proceeds in a similar manner mentioned in **Scheme 2.8**; moreover, the current process involves a carbocation intermediate **48**.



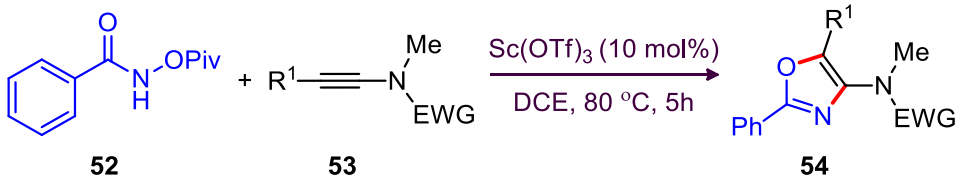
Scheme 2.9. Metal-free formal [3+2] cycloaddition of ynamide and dioxazoles

In 2017, Li and co-workers revealed a cobalt catalyzed formal [3+2] cycloaddition of N-(pivaloyloxy)amides **49** with ynamides **50** for the synthesis of highly regioselective 5-aminooxazole derivatives **51** (**Scheme 2.10**).[17] The catalyst plays an important role for the high regioselectivity.



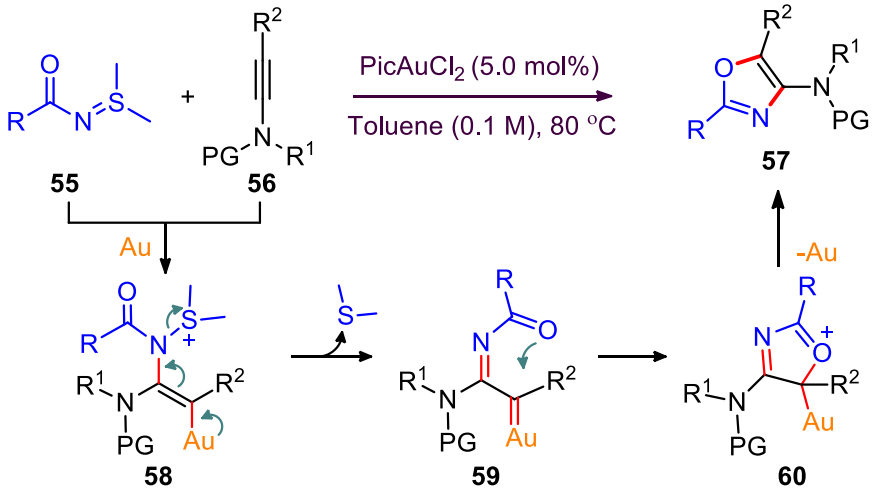
Scheme 2.10. Co-catalyzed cycloaddition of N-(pivaloyloxy)amides with ynamides

Later in 2018, Shi group demonstrated a similar kind of work for the synthesis of 4-aminooxazole **54** from N-(pivaloyloxy)amides **52** and ynamide **53** in the presence of $Sc(OTf)_3$ (**Scheme 2.11**).[18] The nucleophilic attack is completely opposite with respect to the process shown in **Scheme 2.10** providing oxazole with different regioselectivity.



Scheme 2.11. $Sc(OTf)_3$-catalyzed cycloaddition of N-(pivaloyloxy)amide with ynamides

Recently, Hashmi and co-workers developed a protocol for the synthesis of highly substituted oxazole **57** from ynamide **56** and sulfilimines **55** in the presence of gold



Scheme 2.12. Formal [3 + 2] annulations of N-acyl sulfilimines with ynamides

catalysts (**Scheme 2.12**).[19] The reaction involves the attack of sulfilimine nitrogen (**55**) to the α-position of Au-activated ynamide **56** to generate **Int-58**. Next, removal of dimethyl

sulfide (DMS) via electron-back donation of gold (**58)** to generate α-imino gold carbene intermediate **59**. Finally, cyclization of gold carbene intermediate **59** via cyclic oxonium intermediate **60** produces the highly substituted oxazole **57**.

2.3. Motivation and Scheme Design

We envisioned a Lewis acid mediated regioselective attack of nitrile at the α-position of keteniminium ion **Int-A** to form a reactive nitrilium intermediate (**Int-B**), which subsequently undergoes hydration to provide ketene-aminal **63** (**Figure 2.3**). Next, the intramolecular cyclization of ketene-aminal **63** (formed *in situ*) in the presence of NIS possibly constructs a peripherally decorated and highly regioselective 4-amino-2,5-disubstituted oxazole (**62**) (**Figure 2.3**). This is possible when the nucleophilic β-position of ketene-aminal becomes electrophilic (i.e., "*β-umpolung*"), which remains challenging. Thus, NIS is considered crucial assisting the ketene aminal (**Int-C**/**63**) for intramolecular 5-*endo*-cyclization to deliver a highly peripherally decorated oxazole **62** (**Figure 2.3**).

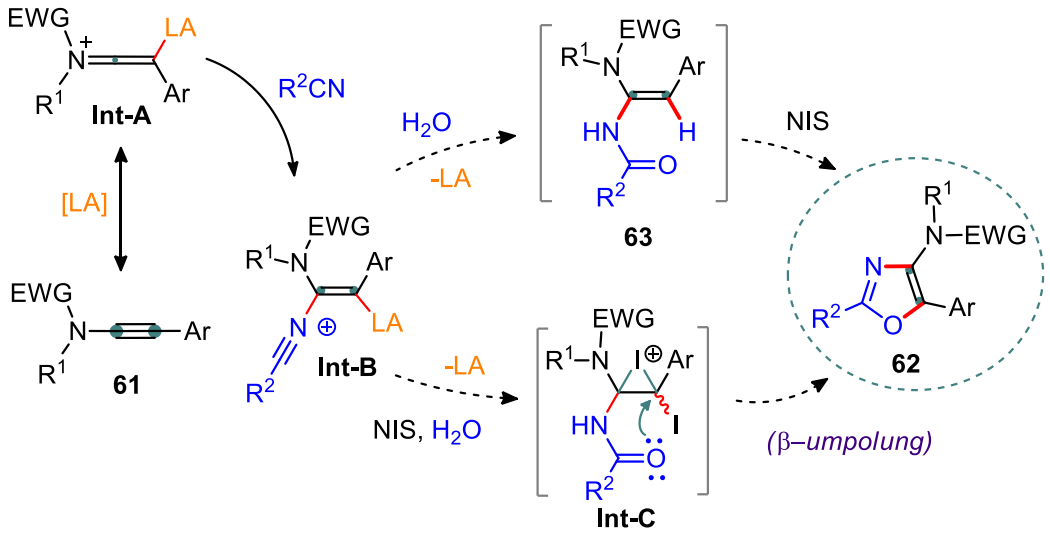


Figure 2.3. Hypothesis for the synthesis of 4-aminooxazoles from ynamides

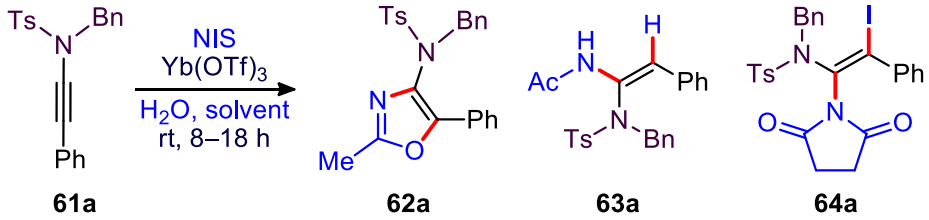
2.4. Result and Discussion

2.4.1. Reaction optimization

As envisaged in **Figure 2.3**, the investigation was initiated for the synthesis of highly substituted oxazole **62** from ynamide **61** (**Table 2.1**). To start with, ynamide **61a** was subjected to NIS (2.2 equiv), $Cu(OTf)_2$ (20 mol %), H_2O (2.0 equiv) in CH_3CN for 8 h at rt. To our delight, the desired oxazole product **62a** was isolated in 38% yield (entry 1) and the structure **62a** was elucidated by X-ray crystallographic analysis. The reaction in the presence of $Yb(OTf)_3$ was found effective producing **62a** (88%; entry 3); while other Lewis acids $Sc(OTf)_3$, $Fe(OTf)_3$ were found inferior (entries 2–4). Disappointingly, the reaction under triflic acid (TfOH) turned complex (entry 5). The use of molecular iodine (I_2) instead of NIS did not produce **62a** (entry 6); preferably NIS is better electrophilic iodinating agent over iodine.[20] Formation of **62a** was hampered in the absence of $Yb(OTf)_3$ (entry 7), demonstrating the importance of Lewis acid in this transformation. The additives NBS and NCS were not beneficial (entries 8–9). The decrease of catalyst loading and/or NIS impacted the reaction outcome (entries 10 and 11). Predictably, the reaction in the absence of H_2O led to **62a** (<10%, entry 12). To our surprise, the *syn*-hydroamidation of ynamide occurred when the reaction conducted in the absence of NIS, explicitly delivering tri-substituted aminal **63a** in 57% yield (entry 13); X-ray crystallographic studies confirmed the structure **63a**. The co-ordination of nitrogen lone pair CH_3CN to Yb-activated keteniminium species preferably builds the product **63a** with *Z*–olefin selectivity. Pleasingly, enhanced yield of **63a** (70%) was observed, when the reaction continued for 18 h (entry 14). A trace of **63a** was formed when the reaction was conducted in presence of molecular sieves (4Å) (entry 15); thus, H_2O is essential in this transformation. Not surprisingly, the reaction failed in the absence of $Yb(OTf)_3$ and NIS (entry 16). The reaction with CH_3CN (2.0 equiv) in $ClCH_2CH_2Cl$/toluene turned complex (entries 17 and 18); in contrast, the identical reaction in CH_2Cl_2 yielded 67% of *anti*-iodo-imidation product **64a** and a trace of **62a** (entry 19); structure **64a** was further characterized by X-ray crystallographic analysis. The reaction in the absence of CH_3CN

and H_2O was equally effective (entry 20). The use of either less amount of NIS or without $Yb(OTf)_3$ affected the reaction (entries 21 and 22). From these studies, it appears that ynamides undergo several transformations under the influence of $Yb(OTf)_3$ delivering oxazole (**62a**), and tri-/tetra-sustituted ketene aminals (**63a** and **64a**) in a single operation.

Table 2.1. Optimization of reaction conditions[a]



61a **62a** **63a** **64a**

entry	catalyst (20 mol%)	additive (equiv)	solvent (1.5 mL)	time (h)	yield (%) **62a/63a/64a**
1	$Cu(OTf)_2$	NIS (2.2)	CH_3CN	8	38 (**62a**)
2[c]	$Sc(OTf)_3$	NIS (2.2)	CH_3CN	8	65 (**62a**)
3	**$Yb(OTf)_3$**	**NIS (2.2)**	**CH_3CN**	**8**	**88** (**62a**)
4[c]	$Fe(OTf)_3$	NIS (2.2)	CH_3CN	8	10 (**62a**)
5[d]	HOTf	NIS (2.2)	CH_3CN	8	complex
6[e]	$Yb(OTf)_3$	I_2 (2.2)	CH_3CN	8	–
7	–	NIS (2.2)	CH_3CN	8	31 (**62a**)
8	$Yb(OTf)_3$	NBS (2.2)	CH_3CN	8	complex
9	$Yb(OTf)_3$	NCS (2.2)	CH_3CN	8	complex
10[f]	$Yb(OTf)_3$	NIS (2.2)	CH_3CN	8	62 (**62a**)
11[f]	$Yb(OTf)_3$	NIS (1.2)	CH_3CN	8	<20 (**62a**)
12[g]	$Yb(OTf)_3$	NIS (2.2)	CH_3CN	8	<10 (**62a**)
13[c]	$Yb(OTf)_3$	–	CH_3CN	8	57 (**63a**)
14	**$Yb(OTf)_3$**	**–**	**CH_3CN**	**18**	**70** (**63a**)
15	$Yb(OTf)_3$	4Å MS	CH_3CN	18	<5 (**63a**)
16	–	–	CH_3CN	18	NR

17[h]	$Yb(OTf)_3$	NIS (2.2)	$ClCH_2CH_2Cl$	8	complex
18[h]	$Yb(OTf)_3$	NIS (2.2)	toluene	8	complex
19[c,h]	$Yb(OTf)_3$	NIS (2.2)	CH_2Cl_2	8	67 (**64a**)
20[g]	**$Yb(OTf)_3$**	**NIS (2.2)**	**CH_2Cl_2**	**8**	**69** (**64a**)
21[g]	$Yb(OTf)_3$	NIS (1.2)	CH_2Cl_2	8	56 (**64a**)
22[g]	–	NIS (1.2)	CH_2Cl_2	8	40 (**64a**)

[a]Reactions were carried out using **61a** (0.2 mmol), catalyst (20 mol%), H_2O (2.0 equiv.) in solvent at rt; [b]Yield; [c]Crude NMR yield; [d]HOTf (1.2 equiv.) was used; [e]**62a** was not formed; [f]$Yb(OTf)_3$ (10 mol %) was used; [g]without H_2O; [h]CH_3CN (2.0 equiv) was used.

2.4.2. Synthesis of starting materials

Following the known Cu-catalyzed C–N bond forming procedure, ynamides **61a**–**ae** are synthesized from the reaction of N-protected amides with 1-bromoalkynes (**Table 2.2** and **Table 2.3**).[21-23]

Table 2.2. Starting materials chart-1; synthesis of ynamide derivatives

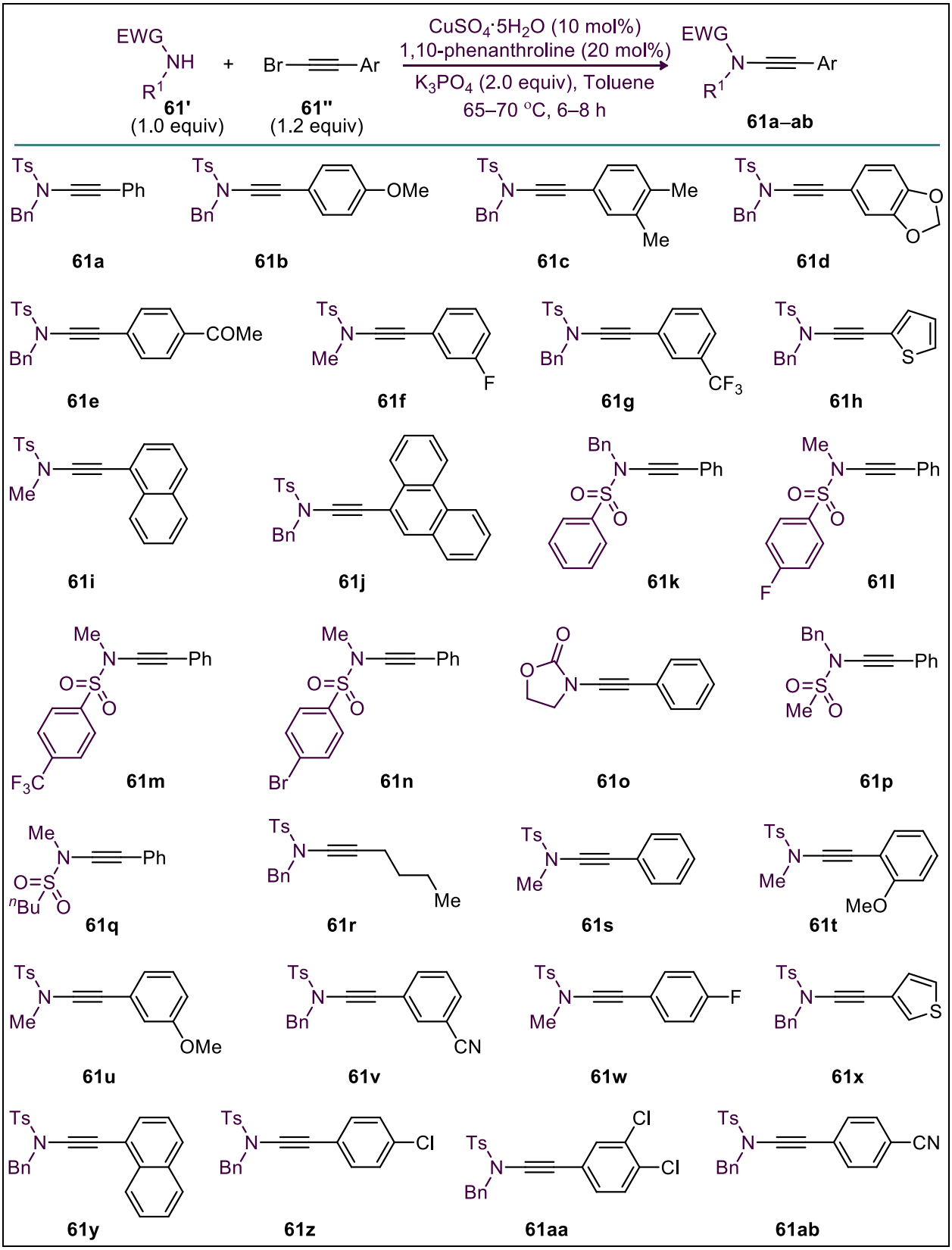
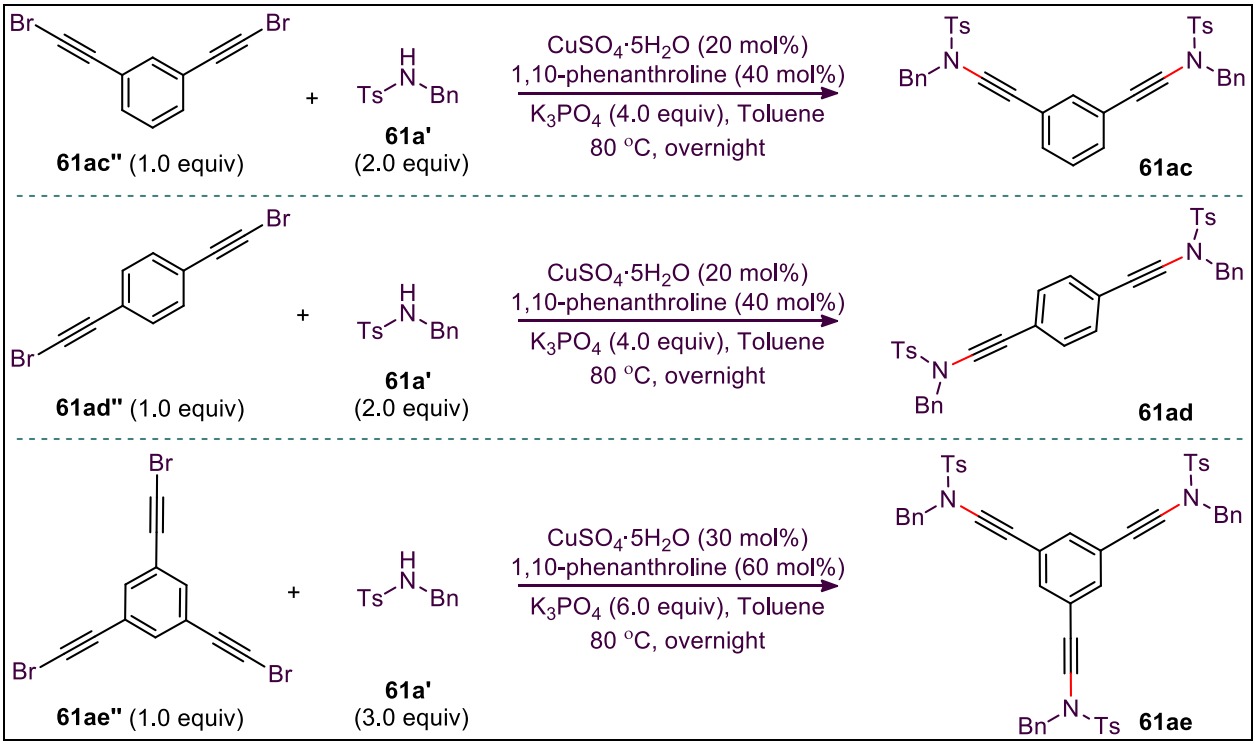


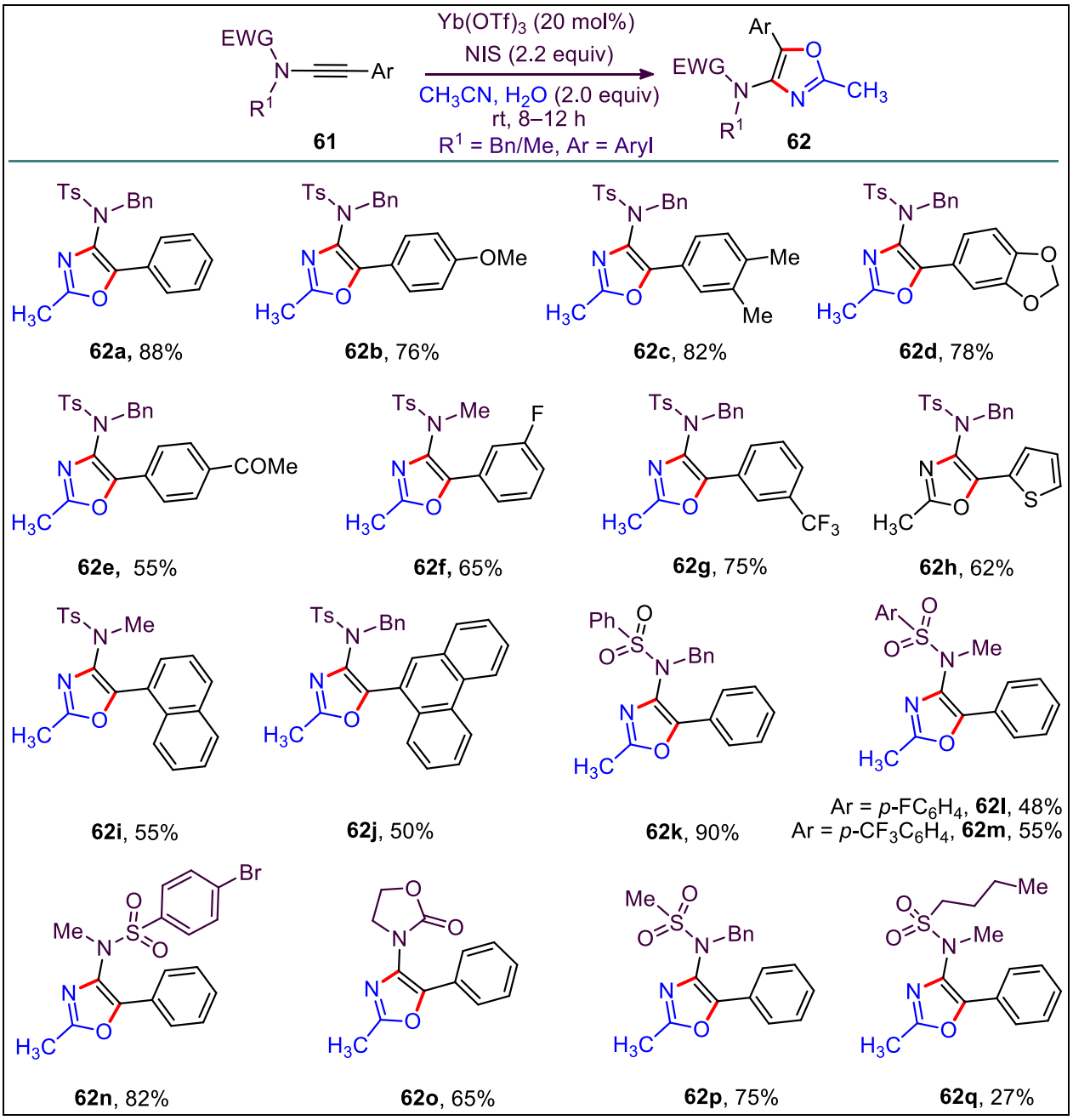
Table 2.3. Starting materials chart-2; synthesis of bis/tris-ynamides



2.4.3. Substrate scope-I; synthesis of 4-amino oxazole derivatives

The reaction generality for the synthesis of highly substituted 4-amino oxazoles under the optimized conditions outlined in entry 3, **Table 2.1** was next investigated (**Table 2.4**). The ynamide **61a** was effectively reacted with acetonitrile providing oxazole **62a** in 88% yield. Similarly, the ynamides **61b–d** with electron rich arenes in the alkyne-terminus successfully delivered the corresponding oxazoles derivatives **62b–d** [76–82%]. The electron-deficient arene bearing ynamides provided **62e–g** [*p*-COMe-**62e** (55%), *m*–F-**62f** (65%), and *m*–CF_3-**62g** (75%)]. Pleasingly, the heteroaryl substituted ynamide **61h** was not exception, yielding **62h** in 62% yield. The sterically encumbered napthyl and phenanthryl enabled oxazoles **62i** and **62j** were accessed albeit in moderate yield. Instead of N-Ts protection, the neutral N-benzenesulfonyl protected ynamide **61k** furnished the desired oxazole product **62k** in excellent yield (90%). Likewise, various *N*-arenesulfonyl protected ynamides [*p*–F-C_6H_4 (**61l**), *p*–CF_3-C_6H_4 (**61m**), & *p*–Br-C_6H_4 (**61n**)] were

Table 2.4. Scope of highly substituted oxazole[a]



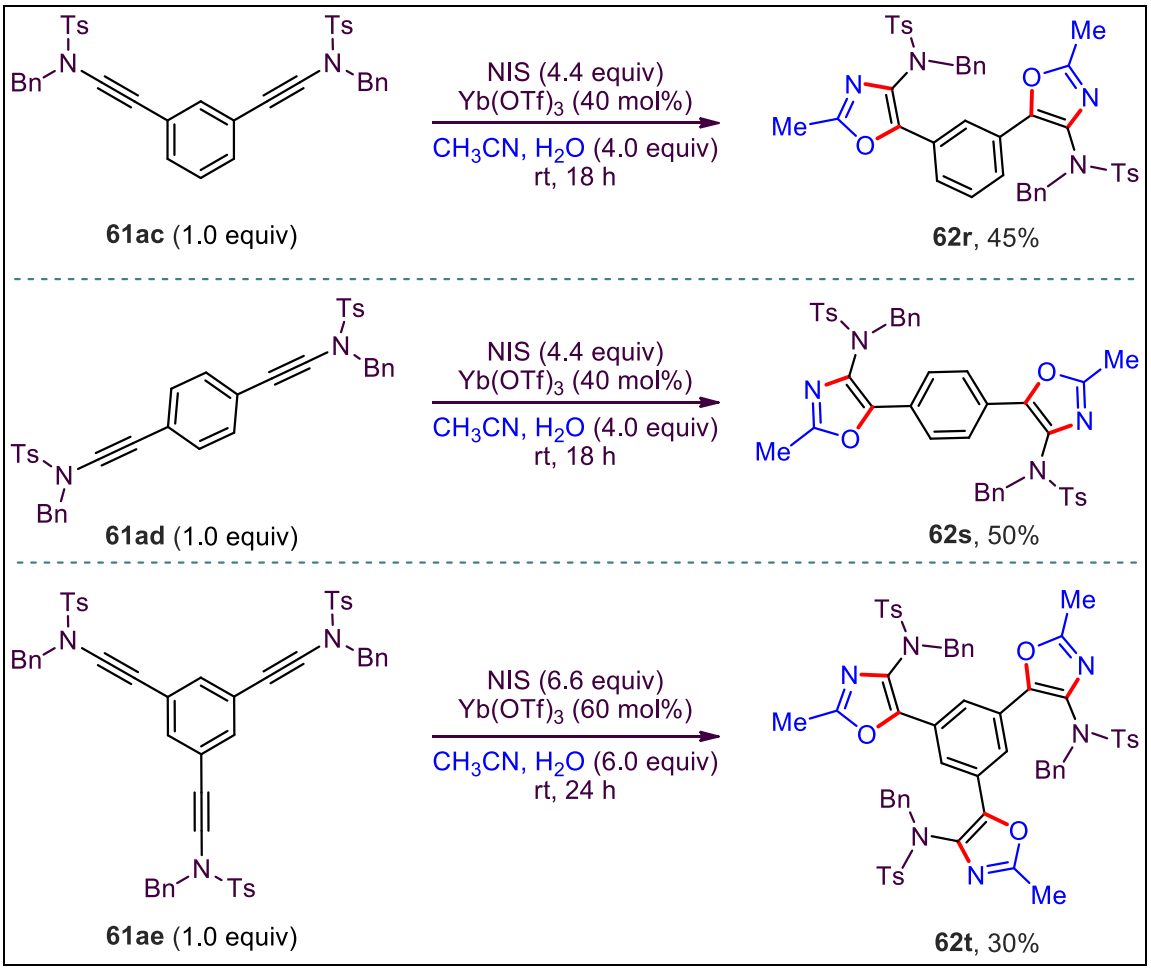
[a]Reactions were carried out using **61** (0.5 mmol), NIS (1.1 mmol), $Yb(OTf)_3$ (0.1 mmol), H_2O (1.0 mmol) in CH_3CN (3.0 mL) at rt for 8–12 h.

effectively tolerated under the optimized conditions, yielding the corresponding highly substituted 4-amino-oxazoles **62l**–**n** in good yields. To our delight, the modifiable oxazolidinone protected ynamide delivered **62o** (65%). Gratifyingly, the alkyl-enabled *N*-

sulfonyl protected oxazoles were reliably constructed (**62p**; 75% and **62q**; 27%). However, the ynamide (having alkyl moiety in the alkyne terminus) provided complex mixture, without forming the desired product. Disappointingly, repeated attempts to condense other nitriles (benzonitriles, butyronitrile, valeronitrile) with ynamide were failed; probably the absence of acidic α–H and the steric bulkiness of nitriles obstruct the cyclization pathways (see **Int-68** and **69** in **Scheme 2.16**).

A programmed synthetic manifestation for the $Yb(OTf)_3$ and NIS mediated amidation and cyclization sequence of multiple ynamides within a molecule would directly construct many oxazole skeletons in a single operation. Gratifyingly, this complexity driven notion eventually allowed the construction of 1,3- and 1,4-bis-oxazoles **62r** (45%)

Table 2.5. Construction of poly-oxazoles on arene

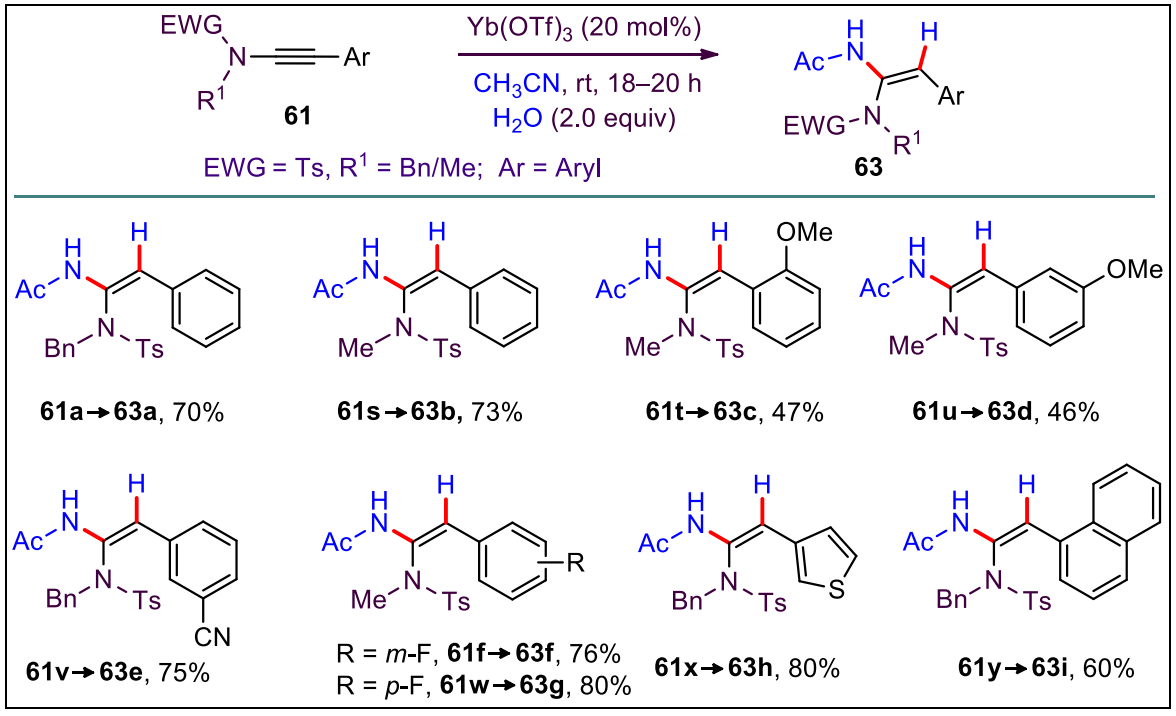


and **62s** (50%), forming six bonds (two C–N and four C–O) in a single operation, from easily accessible precursors **61ac** and **61ad**. Pleasingly, a complex tri-substituted 4-amino-oxazole **62t** was successfully obtained from triynamide precursor **61ae** (**Table 2.5**).

2.4.4. Substrate scope-II; synthesis of ketene-aminals

The scope of $Yb(OTf)_3$ mediated hydroamidation of ynamide with acetonitrile in presence of H_2O was then surveyed (entry 14, **Table 2.1**) for the synthesis of ketene aminals **63** (**Table 2.6**). The N-benzyl and N-methyl protected ketene aminals **63a** and **63b** were obtained in 70% and 73% yield, respectively. The ynamides bearing electron donating group on arene terminus successfully delivered the ketene aminals **63c–d** [*o*-OMe-**63c** (47%) and *m*-OMe-**63d** (46%)] in moderate yield. Whereas the desired products **63e**–**g** [*m*-CN-**63e** (75%), *m*–F-**63f** (76%), and *p*–F-**63g** (80%)] were accessed from the electron-poor arene bearing ynamides. Moreover, 3-thienyl and 1-naphthyl enabled products **63h** (80%) and **63i** (60%) were reliably accessed.

Table 2.6: Scope of hydroamidation of ynamides[a]

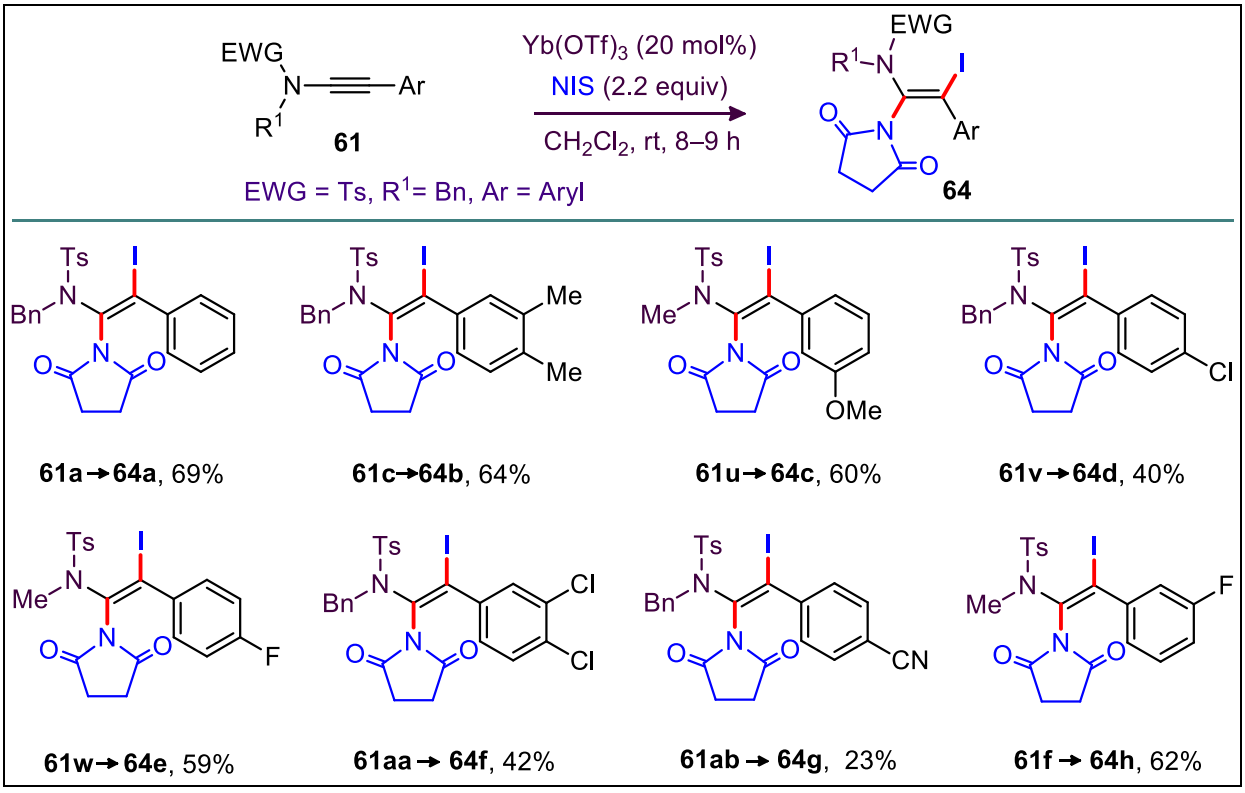


[a]Reactions were carried out using **61** (0.5 mmol), $Yb(OTf)_3$ (0.1 mmol), H_2O (1.0 mmol) in CH_3CN (3.0 mL) at rt for 18–20 h.

2.4.5. Substrate scope-III; synthesis of *β*-iodo ketene aminals

The synthetic importance of *β*-halo ketene aminals motivated us scrutinizing the scope of *anti*-iodoimidation **64a** under the optimized conditions outlined in entry 20, **Table 2.1** (**Table 2.7**). The ynamide **61a** afforded *Z*-*β*-iodo ketene aminal **64a** in 69% yield. The iodo-imidation was fruitfully exhibited for *N*-Bn/Me-protected ynamides having electron-rich/-poor arenes in the alkyne-terminus to yield the products **64b**–**h** [*m,p-di*Me-**64b** (64%), *m*-OMe-**64c** (60%), *p*-Cl-**64d** (40%), *p*-F-**64e** (59%), *m,p-di*Cl-**64f** (42%), *p*-CN-**64g** (23%), and *m*-F-**64h** (62%)] (**Table 2.7**).

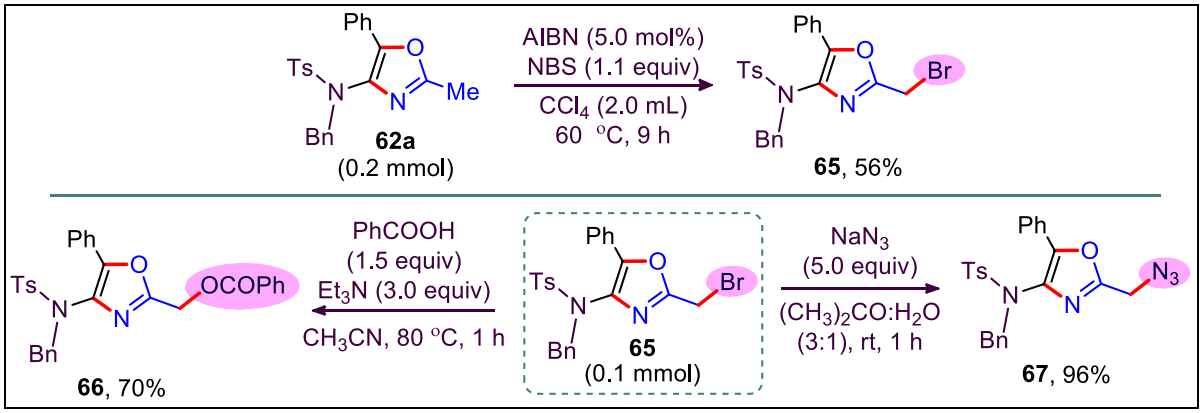
Table 2.7: Scope of iodoimidation of ynamides[a]



[a]Reactions were carried out using **61** (0.5 mmol), NIS (1.1 mmol), $Yb(OTf)_3$ (0.1 mmol) in CH_2Cl_2 (3.0 mL) at rt for 8–9 h.

2.4.6. Synthetic application of 2-methyl oxazole

As discussed in **Table 2.4**, the reaction of large varieties of ynamides with CH_3CN in the presence of $Yb(OTf)_3$, NIS, and H_2O has reliably been demonstrated for the construction of 2-methyl-bearing peripheral decorated oxazoles **62**. The exclusive participation of CH_3CN significantly undermines broad synthetic potential of this demonstration. As the methyl group in the 2-position of oxazole core is acidic, further functionalization of the active-methyl moiety is therefore possible. As anticipated, bromination of methyl-group of **62a** with NBS in presence of AIBN smoothly provided the desired bromination product **65** in 56% yield (**Scheme 2.13**). Next, the nucleophilic displacement of the bromo group in **65** with carboxylate and azide moieties constructed C–O (**66**, 70%) and C–N (**67**, 96%) bonds (**Scheme 2.13**). Therefore, we believe the 2-methyl oxazole motifs fabricated from ynamides and CH_3CN, would be capable of showing broad synthetic potential.

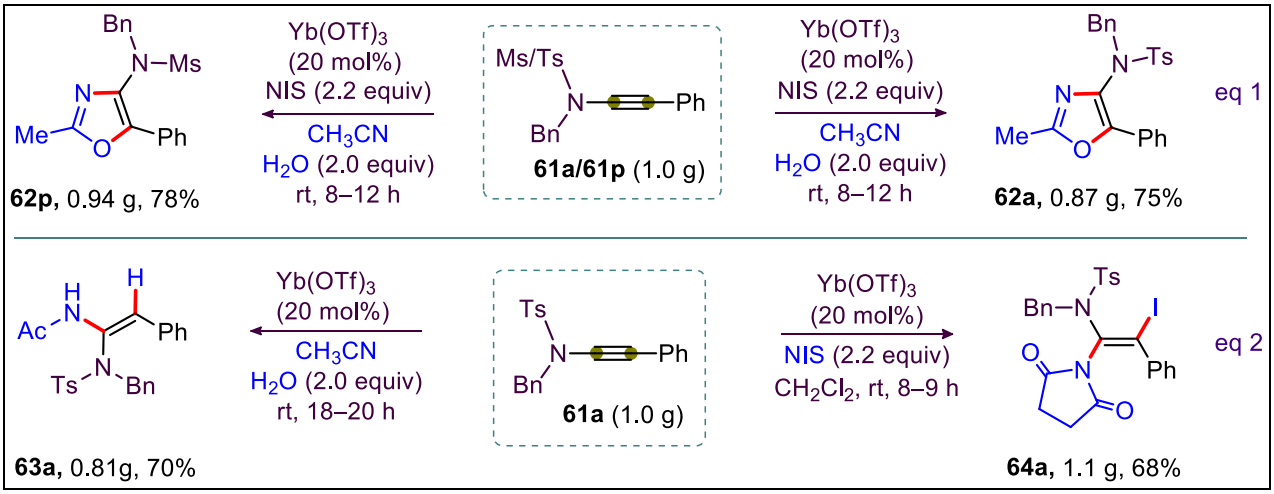


Scheme 2.13: Functionalization of methyl group

2.4.7. Gram scale synthesis

The robustness of the reaction was tested for gram scale (**Scheme 2.14**). Exposing **61a** and **61p** (1.0 g) to the mixture of NIS, $Yb(OTf)_3$, and CH_3CN furnished **62a** (0.87 g, 75%), and **62p** (0.94 g, 78%), respectively (eq 1; **Scheme 2.14**). Similarly,

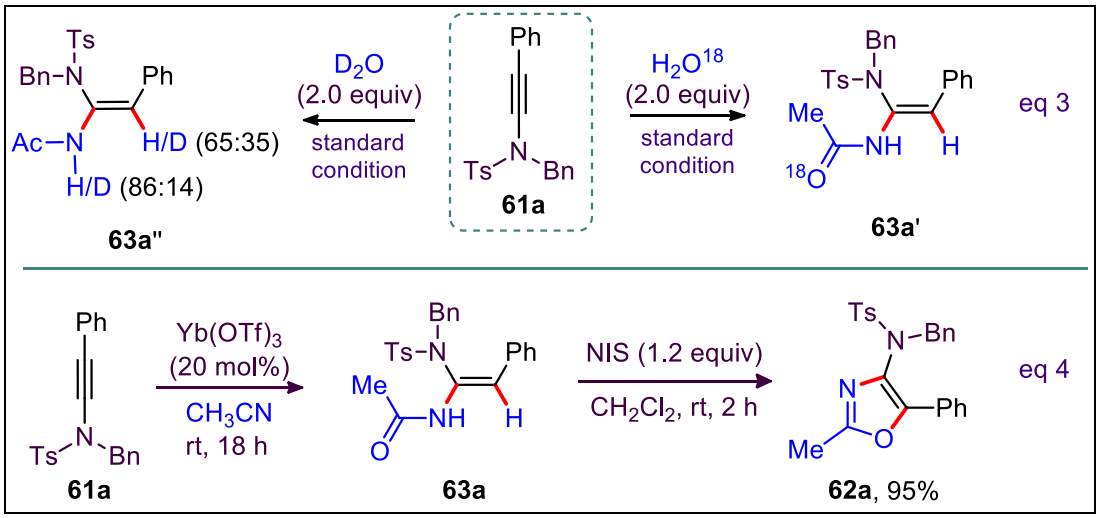
compounds **63a** (0.81 g, 70%) and **64a** (1.1 g, 68%) were achieved from **61a** (1.0 g) under the respective optimized conditions of hydroamidation and iodo-amidation of ynamides (eq 2; **Scheme 2.14**). These results corroborate the scalability of the transformations.



Scheme 2.14: Reaction scalability

2.4.8. Mechanistic insights

To understand the source of water in this transformation, a set of isotope labeling experiments were carried out independently between **61a** and ^{18}O-labelled H_2O or D_2O (eq 3; **Scheme 2.15**). The incorporation of ^{18}O in the amide and D-insertion in the vinyl position in the hydroamidation product (**63a′** and **63a″**; observed by HRMS and ^1H NMR analysis) clearly shows the critical role of H_2O in this study (eq 3; **Scheme 2.15**). To acquire preliminary insight into the mechanism and the necessity of NIS in these transformations, a stepwise conversion of **61a** to **62a** was planned via $Yb(OTf)_3$ mediated hydroamidation and NIS-assisted cyclization sequence. As envisioned, **63a** (obtained from **61a**) was efficiently converted to **62a** (95%), when subjected to NIS in CH_2Cl_2 at rt (eq 4; **Scheme 2.15**). Hence, we conclude that the hydroamidation product **63a** is one of the intermediate in this transformation. Moreover, NIS acts as a promoter by activating the enamide **63a** for intramolecular cyclization.

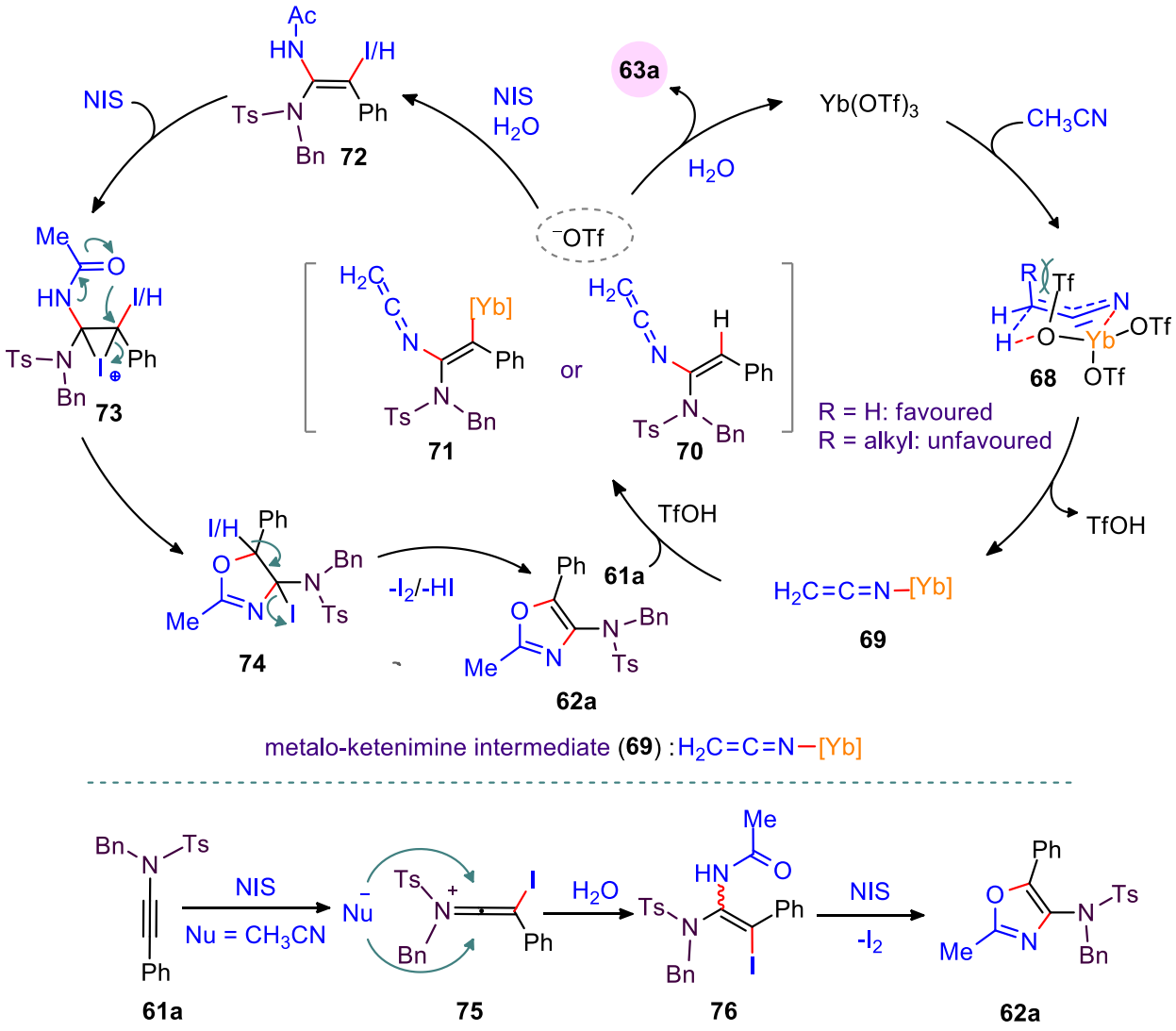


Scheme 2.15: Control experiments

2.4.9. Mechanism

Although the mechanistic details are yet to be established, a plausible mechanism is depicted in **Scheme 2.16**. The transient metalo-ketenininium intermediate **69** is generated in situ from acetonitrile with $Yb(OTf)_3$, possibly via intermediate **68** along with the release of triflic acid.[24] The direct attack of the metalo-ketenininium species **69** to the *α*-position of ynamide (**61a**) results in the formation of intermediate **71**. Alternatively, the TfOH-mediated protonation of ynamide forms the keteniminum species in situ, which rapidly reacts with metalo-ketenininium species **69** to generate intermediate **70.** Next, the hydration of intermediate **70** provides hydroamidation product **63a** with syn-selectivity, justifying the participation of the intermediate **70** in this transformation.[25] In the presence of NIS and H_2O, intermediate **71** undergoes Yb-iodo exchange/ protodemetalation and hydration to give intermediate **72**.[26] Simultaneously, the activation of the olefin moiety in ketene aminal **72** with NIS produces **73**. Next, the S_N2-type 5-*endo*-cyclization of **73** provides **Int-74**. Finally, elimination of I_2/HI from **Int-74** leads to the highly substituted 4-amino-oxazole **62a**, authenticating the requirements of 2.0 equiv of NIS for reaction productivity. Alternatively, the reaction of ynamide **61a** with NIS initially forms an active *β*-iodoketeneiminium intermediate **75**, which subsequently undergoes the nitrile attack followed by hydration to form intermediate **76** (**Scheme 2.16**). Finally, the NIS-promoted

activation of the olefin moiety of **76** followed by the intramolecular cyclization and elimination of I_2 affords **62a**, albeit in poor yield (entry 7, **Table 2.1**). These results reveal that $Yb(OTf)_3$ facilitates enhancing the reaction outcome.



Scheme 2.16: Plausible mechanism

2.5. Conclusion

In summary, a convenient and reliable protocol for the synthesis of highly peripheral decorated 4-amino-2,5-disubstituted oxazoles from ynamides in the presence of $Yb(OTf)_3$, NIS, and H_2O in CH_3CN at rt is revealed. Multiple oxazole skeletons on the arene periphery are constructed to build the molecular complexity. Regio and stereoselective hydroamidation and iodo-imidation of ynamides reliably provides highly substituted ketene aminals. The robustness of the catalytic conditions is tested in gram scale synthesis. The H_2O^{18} labelling experiments and sequential reaction studies shed light on the underlying plausible mechanistic cycle that is involved.

2.6. Experimental Section

2.6.1. General information

All the reactions were performed in an oven-dried reaction vial. Commercial grade solvents were distilled prior to use. Column chromatography was performed using silica gel (100–200 Mesh) and neutral alumina eluting with hexanes and ethyl acetate mixture. 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 and carbon nuclear magnetic resonance spectra (^1H NMR, ^{13}C NMR and ^{19}F NMR) were recorded on a 400 MHz (^1H NMR, 400 MHz; ^{13}C NMR, 101 MHz; ^{19}F NMR, 376 MHz) spectrometer and 500 MHz (^1H NMR, 500 MHz; ^{13}C NMR, 126 MHz; ^{19}F NMR, 470 MHz) spectrometer having solvent resonance as internal standard (^1H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.0 ppm). Data for ^1H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet; br s = broad singlet; d = doublet; br d = broad doublet, t = triplet; br t = broad triplet; q = quartet; m = multiplet), coupling constants *J*, in (Hz). IR spectra were recorded on FT/IR spectrometer and are reported in cm^{-1}. High resolution mass spectra (HRMS) are obtained by using TOF analyzer in ESI mode. Melting points are determined by electro-thermal heating and are uncorrected.

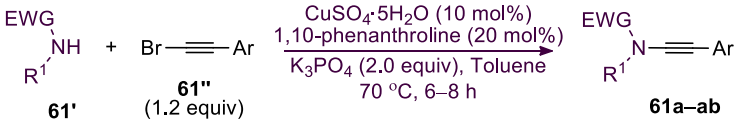
X–ray data are collected at 298K on a Bruker D8 Quest CCD diffractometer using Mo-Kα radiation (0.71073 Å).

2.6.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Acetone, dichloromethane (CH_2Cl_2), toluene, acetonitrile, ethyl acetate, and hexane were distilled over CaH_2. THF was freshly distilled over sodium/benzophenone ketyl under dry nitrogen. $Yb(OTf)_3$, CuI, K_3PO_4, $PdCl_2(PPh_3)_2$, $CuSO_4 \cdot 5H_2O$, trimethylsilane, 1,10–phenanthroline, and aryl iodides were purchased and used as received.

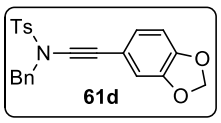
2.6.3. General procedure and spectral/analytical data

2.6.3.1. General procedure for the synthesis of ynamide 61 (GP–1)[22,23]



Mixture of sulfonamide **61′** (1.0 mmol), $CuSO_4 \cdot 5H_2O$ (0.10 mmol, 25 mg), 1,10-phenanthroline (0.20 mmol, 36 mg), and K_3PO_4 (2.0 mmol, 425 mg) in dry toluene (5.0 mL) was taken in a schlenk tube. Subsequently, 1-bromo-2-arylacetylene **61″** was introduced and the resulting mixture was heated up to 70 °C under the nitrogen atmosphere for 6–8 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature and diluted with dichloromethane (10 mL). The crude mixture was filtered through a small pad of Celite and concentrated under reduced pressure. The crude residue was purified using column chromatography on silica gel to provide **61a–ab**.

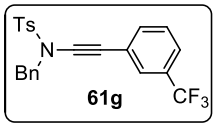
N-(Benzo[d][1,3]dioxol-5-ylethynyl)-N-benzyl-4-methylbenzenesulfonamide (61d):



Following the general procedure GP–1, compound **61d** (316 mg) was obtained in 78% yield as yellow solid; mp = 120–122 °C; R_f = 0.64 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.4 Hz, 2H), 7.36–7.30 (m, 7H), 6.78 (dd, J = 8.4, 1.6 Hz, 1H), 6.72–6.65 (m, 2H), 5.93 (s, 2H), 4.56 (s, 2H),

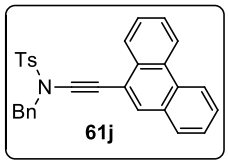
2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.6, 147.2, 144.6, 134.6, 134.4, 129.6, 128.8, 128.4, 128.2, 127.7, 126.1, 115.8, 111.6, 108.3, 101.2, 80.9, 71.0, 55.6, 21.6; IR (Neat)ν_{max} 3034, 2899, 2237, 1598, 1493, 1446, 1364, 1249 cm^{-1}; HRMS (ESI) for $C_{23}H_{19}NNaO_4S$ $(M+Na)^+$: calcd 428.0932, found 428.0931.

N-benzyl-4-methyl-N-((3-(trifluoromethyl)phenyl)ethynyl)benzenesulfonamide



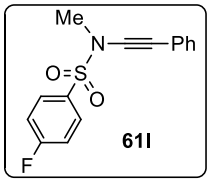
(61g): Following the general procedure GP–1, compound **61g** (279 mg) was obtained in 65% yield as pale brown semi solid; R_f = 0.45 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 8.4 Hz, 2H), 7.50–7.45 (m, 1H), 7.43 (br s, 1H), 7.40–7.32 (m, 9H), 4.60 (s, 2H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.9, 134.6, 134.2, 133.9, 129.9, 128.9, 128.7, 128.6, 128.5, 128.2 (q, J = 242 Hz 1C), 127.8, 127.6 (q, J = 15 Hz, 1C), 124.1 (q, J = 15 Hz, 1C), 123.8, 84.3, 70.5, 55.6, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.7; IR (Neat)ν_{max} 3034, 2936, 2238, 1702, 1597, 1494, 1365, 1330 cm^{-1}; HRMS (ESI) for $C_{23}H_{19}F_3NO_2S$ $(M+H)^+$: calcd 430.1089, found 430.1089.

N-Benzyl-4-methyl-N-(phenanthren-9-ylethynyl)benzenesulfonamide (61j):



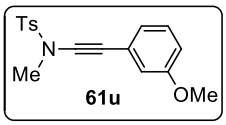
Following the general procedure GP–1, compound **61j** (323 mg) was obtained in 70% yield as pale yellow semi solid; R_f = 0.52 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 8.62 (t, J = 9.2 Hz, 2H), 7.92 (d, J = 8.4 Hz, 3H), 7.83–7.75 (m, 2H), 7.68–7.50 (m, 4H), 7.48–7.37 (m, 5H), 7.35 (d, J = 8.0 Hz, 2H), 4.72 (s, 2H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.9, 134.7, 134.5, 131.2, 131.0, 130.5, 130.0, 129.9, 129.1, 128.7, 128.5, 128.3, 127.9, 127.2, 126.9, 122.64, 122.59, 119.3, 86.8, 70.3, 55.7, 21.7; IR (Neat)ν_{max} 3064, 2925, 2231, 1596, 1493, 1365 cm^{-1}; HRMS (ESI) for $C_{30}H_{24}NO_2S$ $(M+H)^+$: calcd 462.1528, found 462.1528.

4-Fluoro-N-methyl-N-(phenylethynyl)benzenesulfonamide (61l): Following the general procedure GP–1, compound **61l** (249 mg) was obtained in 86% yield as yellow solid; mp = 93–95 °C; R_f = 0.72 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08–7.95 (m, 2H), 7.43–7.36 (m, 2H), 7.35–7.25 (m, 5H), 3.19 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.8



(d, J = 258 Hz, 1C), 132.1, 131.4, 130.5 (d, J = 9.1 Hz, 1C), 128.3, 128.0, 122.3, 116.5 (d, J = 23.2 Hz, 1C), 83.4, 69.2, 39.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –103.1; IR (Neat)ν_{max} 3106, 3075, 2936, 2234, 1696, 1593, 1495, 1454 cm^{-1}; HRMS (ESI) for $C_{15}H_{12}FNNaO_2S$ $(M+Na)^+$: calcd 312.0470, found 312.0470.

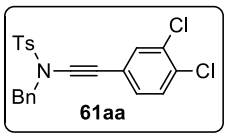
N-((3-Methoxyphenyl)ethynyl)-N,4-dimethylbenzenesulfonamide (61u): Following



61u

the general procedure GP–1, compound **61u** (282 mg) was obtained in 72% yield as yellow semi solid; R_f = 0.67 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 7.8 Hz, 1H), 6.97–6.93 (m, 1H), 6.91–6.88 (m, 1H), 6.86–6.82 (m, 1H), 3.79 (s, 3H), 3.15 (s, 3H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.2, 144.8, 133.1, 129.8, 129.3, 127.8, 123.8, 123.6, 116.2, 114.2, 83.7, 68.9, 55.2, 39.2, 21.6; IR (Neat)ν_{max} 2939, 2838, 2238, 1699, 1599, 1490, 1460, 1364 cm^{-1}; HRMS (ESI) for $C_{17}H_{18}NO_3S$ $(M+H)^+$: calcd 316.1007, found 316.1007.

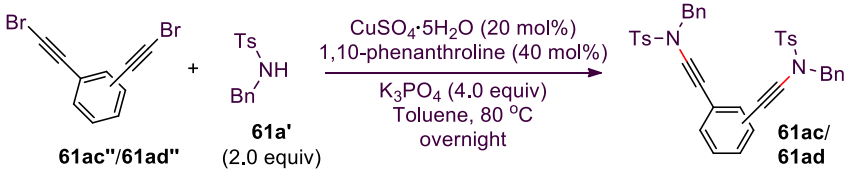
N-Benzyl-N-((3,4-dichlorophenyl)ethynyl)-4-methylbenzenesulfonamide (61aa):



61aa

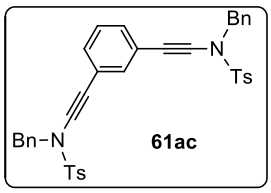
Following the general procedure GP–1, compound **61aa** (357 mg) was obtained in 83% yield as yellow solid; mp = 117–119 °C; R_f = 0.75 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.0 Hz, 2H), 7.37–7.27 (m, 9H), 7.03 (dd, J = 8.4, 2.0 Hz, 1H), 4.58 (s, 2H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.9, 134.5, 134.1, 132.4, 132.3, 131.7, 130.14, 130.02, 129.8, 128.8, 128.6, 128.5, 127.6, 122.8, 84.5, 69.6, 55.5, 21.6; IR (Neat)ν_{max} 3061, 3034, 2924, 2868, 2247, 1925, 1593, 1451 cm^{-1}; HRMS (ESI) for $C_{22}H_{17}Cl_2NNaO_2S$ $(M+Na)^+$: calcd 452.0255, found 452.0256.

2.6.3.2. General procedure for the preparation of 61ac and 61ad (GP–1A)[23f]



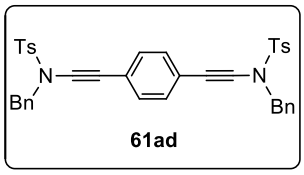
A solution of bis(bromoethynyl)benzene **61ac''/61ad''** (1.0 mmol), sulfonamide **61a'** (2.0 mmol), $CuSO_4 \cdot 5H_2O$ (0.2 mmol, 50 mg), 1,10-phenanthroline (0.4 mmol, 72 mg), and K_3PO_4 (4.0 mmol, 849 mg) in dry toluene (5.0 mL) was stirred independently in a Schlenk tube at 80 °C for overnight under the nitrogen atmosphere. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature and diluted with dichloromethane (10 mL). The reaction mixture was filtered through a small pad of Celite and concentrated under reduced pressure. The crude residue was purified by using column chromatography on silica gel to provide arene tethered bis ynamides (**61ac** and **61ad**) in good yields.

N,N'-(1,3-phenylenebis(ethyne-2,1-diyl))bis(N-benzyl-4-methylbenzenesulfonamide)



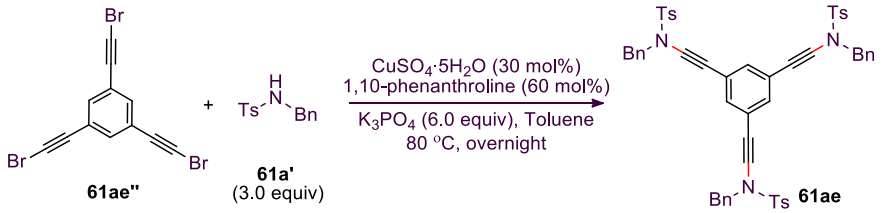
(61ac): Following the general procedure GP–1A, compound **61ac** (574 mg) was obtained in 89% yield as yellow semi solid; R_f = 0.43 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.0 Hz, 4H), 7.39–7.32 (m, 14H), 7.17–7.08 (m, 4H), 4.60 (s, 4H), 2.47 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.7, 134.5, 134.3, 133.3, 130.0, 129.7, 128.8, 128.5, 128.3, 128.1, 127.6, 122.9, 83.1, 70.7, 55.6, 21.6; IR (KBr)ν_{max} 3065, 3034, 2925, 2362, 2236, 1596, 1495, 1302 cm^{-1}; HRMS (ESI) for $C_{38}H_{32}N_2NaO_4S_2$ $(M+Na)^+$: calcd 667.1701, found 667.1706.

N,N'-(1,4-phenylenebis(ethyne-2,1-diyl))bis(N-benzyl-4-methylbenzenesulfonamide)



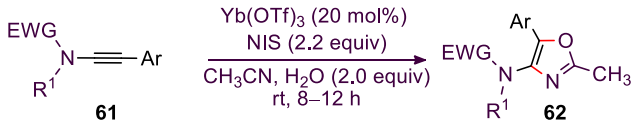
(61ad): Following the general procedure GP–1A, compound **61ad** (516 mg) was obtained in 80% yield as yellow solid; mp = 160–162 °C; R_f = 0.45 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.0 Hz, 4H), 7.38–7.31 (m, 14H), 7.10 (s, 4H), 4.58 (s, 4H), 2.45 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.7, 134.5, 134.2, 130.7, 129.7, 128.8, 128.5, 128.3, 127.7, 121.9, 84.2, 71.3, 55.6, 21.6; IR (Neat)ν_{max} 3032, 2977, 2926, 2225, 1593, 1493, 1452, 1172 cm^{-1}; HRMS (ESI) for $C_{38}H_{32}N_2NaO_4S_2$ $(M+Na)^+$: calcd 667.1701, found 667.1700.

2.6.3.3. Synthesis of 1,3,5-tris-ynamide precursor 61ae[23f]



A solution of tris(bromoethynyl)benzene **61ae''** (1.0 mmol), sulfonamide **61a'** (3.0 mmol), $CuSO_4 \cdot 5H_2O$ (0.3 mmol, 75 mg), 1,10-phenanthroline (0.6 mmol, 108 mg), and K_3PO_4 (6.0 mmol, 1.27 gm) in dry toluene (5.0 mL) was stirred in a Schlenk tube at 80 °C for overnight under the nitrogen atmosphere. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature and diluted with dichloromethane (10 mL). The reaction mixture was filtered through a small pad of Celite and concentrated under reduced pressure. The crude residue was purified by using column chromatography on silica gel to provide **61ae** in 94% yield (872 mg) as yellow solid; mp = 156–158 °C; R_f = 0.26 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 6.0 Hz, 6H), 7.36–7.28 (m, 21H), 6.93 (s, 3H), 4.56 (s, 6H), 2.45 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.8, 134.5, 134.2, 132.0, 129.8, 128.7, 128.5, 128.4, 127.6, 123.1, 83.6, 70.1, 55.5, 21.6; IR (Neat)ν_{max} 3065, 3034, 2926, 2235, 1583, 1495, 1454, 1366 cm^{-1}; HRMS (ESI) for $C_{54}H_{45}N_3NaO_6S_3$ $(M+Na)^+$: calcd 950.2368, found 950.2368.

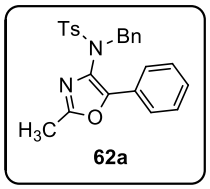
2.6.3.4. General procedure for the synthesis of 2,4,5-trisubstituted oxazoles 62 (GP–2)



A mixture of ynamide **61** (0.5 mmol), N-iodosuccinimide (NIS; 1.1 mmol, 247 mg), $Yb(OTf)_3$ (0.1 mmol, 62 mg), and H_2O (1.0 mmol, 18 µL) in freshly distilled acetonitrile (3.0 mL) was stirred at room temperature for 8–12 h. The progress of the reaction was monitered by TLC. After completion, the reaction mixture was quenched with saturated aqueous sodium thiosulfate. The organic layer was separated and the aqeous layer was extracted with ethylacetate (2 × 15 mL). The combined organic layers were dried over

anhydrous sodium sulfate and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to give the product **62**.

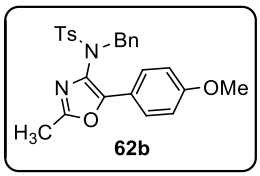
4-(N-Benzyl-N-tosyl)-2-methyl-5-phenyloxazole (62a): Following the general procedure



62a

GP–2, compound **62a** (184 mg) was obtained in 88% yield as colorless solid; mp = 196–198 °C; R_f = 0.48 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 7.2 Hz, 2H), 7.39–7.28 (m, 5H), 7.21 (dd, J = 5.6, 2.0 Hz, 2H), 7.12 (dd, J = 5.2, 1.6 Hz, 3H), 4.60 (s, 2H), 2.48 (s, 3H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.2, 147.4, 144.0, 135.4, 134.7, 130.9, 129.5, 129.0, 128.4, 128.2, 128.1, 127.8, 126.8, 125.3, 53.7, 21.6, 14.2; IR (Neat)ν_{max} 3063, 2926, 2361, 1594, 1446, 1347, 1210 cm^{-1}; HRMS (ESI) for $C_{24}H_{23}N_2O_3S$ $(M+H)^+$: calcd 419.1429, found 419.1429.

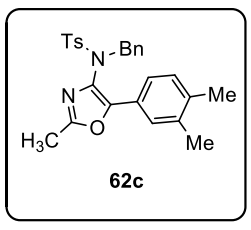
4-(N-Benzyl-N-tosyl)-2-methyl-5-(4-methoxyphenyl)oxazole (62b): Following the



62b

general procedure GP–2, compound **62b** (170 mg) was obtained in 76% yield as pale yellow solid; mp = 189–191 °C; R_f = 0.48 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.18 (dd, J = 5.6, 2.0 Hz, 2H) 7.13–7.07 (m, 3H), 6.85 (d, J = 8.8 Hz, 2H)) 4.55 (s, 2H), 3.81 (s, 3H), 2.45 (s, 3H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.8, 157.5, 147.6, 144.0, 135.5, 135.0, 129.60, 129.57, 129.1, 128.5, 128.1, 127.8, 126.9, 119.7, 113.8, 55.3, 53.8, 21.7, 14.2; IR (Neat)ν_{max} 2931, 2838, 1589, 1642, 1243, 1150, 1035 cm^{-1}; HRMS (ESI) for $C_{25}H_{25}N_2O_4S$ $(M+H)^+$: calcd 449.1535, found 449.1537.

4-(N-Benzyl-N-tosyl)-2-methyl-5-(3,4-dimethylphenyl)oxazole (62c): Following the

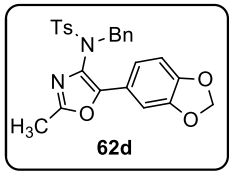


62c

general procedure GP–2, compound **62c** (183 mg) was obtained in 82% yield as pale yellow solid; mp = 144–147 °C; R_f = 0.42 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.4 Hz, 2H), 7.44 (dd, J = 8.0, 1.2 Hz, 1H), 7.37 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.24–7.18 (m, 2H), 7.16–7.10 (m, 3H), 7.07 (d, J = 8.0 Hz, 1H), 4.58 (s, 2H);

2.45 (s, 3H), 2.41 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.8, 147.6, 143.8, 137.2, 136.3, 135.63, 135.60, 135.0, 130.2, 129.5, 129.1, 128.4, 128.1, 127.7, 126.3, 124.4, 122.8, 53.6, 21.6, 19.7, 19.6, 14.2; IR (Neat)ν_{max} 2920, 1589, 1495, 1446, 1265, 1090, 821 cm^{-1}; HRMS (ESI) for $C_{26}H_{27}N_2O_3S$ $(M+H)^+$: calcd 447.1742, found 447.1745.

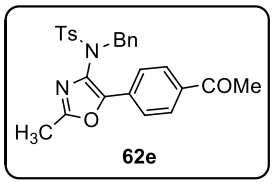
4-(N-Benzyl-N-tosyl)-2-methyl-5-(benzo[d][1,3]dioxol-5-yl)oxazole (62d): Following



62d

the general procedure GP–2, compound **62d** (180 mg) was obtained in 78% yield as pale yellow solid; mp = 203–205 °C; R_f = 0.52 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.22 (dd, J = 8.0, 1.6 Hz, 1H), 7.20–7.16 (m, 2H), 7.15–7.10 (m, 4H), 6.75 (d, J = 8.4 Hz, 1H), 5.95 (s, 2H), 4.55 (s, 2H), 2.45 (s, 3H), 2.39 (s, 3H), $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.6, 147.8, 147.5, 147.4, 144.0, 135.5, 134.9, 129.9, 129.6, 129.2, 128.5, 128.2, 127.9, 121.0, 119.9, 108.3, 106.0, 101.2, 53.8, 21.7, 14.2; IR (Neat)ν_{max} 3068, 2904, 2361, 1594, 1490, 1238, 1046, 882 cm^{-1}; HRMS (ESI) for $C_{25}H_{22}N_2NaO_5S$ $(M+Na)^+$: calcd 485.1147, found 485.1147.

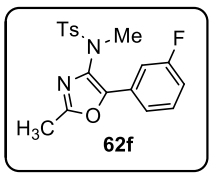
4-(N-Benzyl-N-tosyl)-2-methyl-5-(4-acetylphenyl)oxazole (62e): Following the general



62e

procedure GP–2, compound **62e** (127 mg) was obtained in 55% yield as pale yellow solid; mp = 182–184 °C; R_f = 0.35 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92–7.87 (m, 2H), 7.84–7.76 (m, 4H), 7.35 (d, J = 8.0 Hz, 2H), 7.19 (dd, J = 5.6, 2.4 Hz, 2H), 7.12–7.07 (m, 3H), 4.57 (br s, 2H), 2.59 (s, 3H), 2.45 (s, 3H), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.5, 159.3, 146.4, 144.3, 136.3, 135.2, 134.7, 133.0, 131.0, 129.7, 129.1, 128.5, 128.4, 128.3, 128.0, 125.1, 53.8, 26.6, 21.7, 14.3; IR (Neat)ν_{max} 3024, 1682, 1605, 1578, 1358, 1260, 1156 cm^{-1}; HRMS (ESI) for $C_{26}H_{24}N_2NaO_4S$ $(M+Na)^+$: calcd 483.1354, found 483.1349.

4-(N-Methyl-N-tosyl)-2-methyl-5-(3-Fluorophenyl)-oxazole (62f): Following the

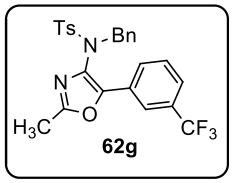


62f

general procedure GP–2, compound **62f** (114 mg) was obtained in 65% yield as colorless solid; mp = 178–180 °C; R_f = 0.42 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.78–7.72 (m, 3H),

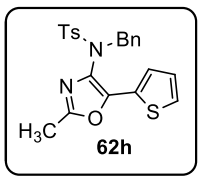
7.62–7.57 (m, 1H), 7.44–7.37 (m, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.08–7.0 (m, 1H), 3.10 (s, 3H), 2.45 (s, 3H), 2.44 (s, 3H), $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.9 (d, J = 246 Hz, 1C), 158.8, 144.4 (d, J = 3.0 Hz, 1C), 144.1, 134.2 (d, J = 8.0 Hz, 1C), 130.4 (d, J = 9.1 Hz, 1C), 129.6, 129.1 (d, J = 9.1 Hz, 1C), 128.6, 120.89, 120.86, 115.5 (d, J = 21.2 Hz, 1C), 112.1 (d, J = 24.2 Hz, 1C), 37.1, 21.6, 14.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ –112.1; IR (Neat)ν_{max} 1578, 1484, 1347, 1265, 1024, 882 cm^{-1}; HRMS (ESI) for $C_{18}H_{18}FN_2O_3S$ $(M+H)^+$: calcd 361.1022, found 361.1020.

4-(N-Benzyl-N-tosyl)-2-methyl-5-(3-(trifluoromethyl)phenyl)oxazole (62g): Following the general procedure GP–2, compound **62g** (182 mg) was obtained in 75% yield as colorless solid; mp = 152–155 °C; R_f = 0.46 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.0 Hz, 1H), 7.85 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.17 (dd, J = 5.6, 2.0 Hz, 2H), 7.12 – 6.07 (m, 3H), 4.57 (s, 2H), 2.46 (s, 3H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.0, 146.1, 144.2, 135.3, 134.6, 132.1, 130.7 (q, J = 33.3 Hz, 1C), 129.7, 129.2, 128.8, 128.5, 128.4, 128.3, 128.0, 127.6, 126.5 (q, J = 253 Hz, 1C), 124.9 (q, J = 4.0 Hz, 1C), 122.0 (q, J = 3.0 Hz, 1C), 53.7, 21.7, 14.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.8; IR (Neat)ν_{max} 3073, 1638, 1583, 1452, 1254, 1167, 904 cm^{-1}; HRMS (ESI) for $C_{25}H_{22}F_3N_2O_3S$ $(M+H)^+$: calcd 487.1303, found 487.1302.



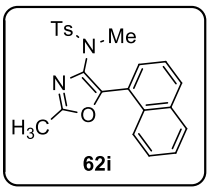
62g

4-(N-Benzyl-N-tosyl)-2-methyl-5-(thiophen-2-yl)oxazole (62h): Following the general procedure GP–2, compound **62h** (132 mg) was obtained in 62% yield as brown color solid; mp = 152–155 °C; R_f = 0.51 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.0 Hz, 2H), 7.42 (dd, J = 3.6, 1.2 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.28 (dd, J = 5.2, 1.2 Hz, 1H), 7.21 (dd, J = 6.0, 2.0 Hz, 2H), 7.14–7.09 (m, 3H), 7.0 (dd, J = 5.2, 4.0 Hz, 1H), 4.54 (s, 2H), 2.46 (s, 3H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.9, 144.3, 144.1, 135.4, 134.8, 129.9, 129.7, 129.0, 128.4, 128.1, 127.8, 127.2, 126.3, 125.9, 53.6, 21.7, 14.2; IR (Neat)ν_{max} 3073, 1583, 1495, 1435, 1353, 1172, 1084, 1052 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}N_2NaO_3S_2$ $(M+Na)^+$: calcd 447.0813, found 447.0818.

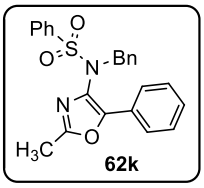


62h

4-(N-Methyl-N-tosyl)-2-methyl-5-(naphthalen-1-yl)oxazole (62i): Following the general procedure GP–2, compound **62i** (108 mg) was obtained in 55% yield as light brown solid; mp = 195–197 °C; R_f = 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94–7.87 (m, 3H), 7.79 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.55–7.49 (m, 3H), 7.14 (d, J = 8.0 Hz, 2H), 3.10 (s, 3H); 2.54 (s, 3H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.4, 145.4, 143.6, 135.5, 134.8, 133.6, 131.1, 130.1, 129.2, 128.6, 128.4, 128.2, 126.7, 126.1, 125.23, 125.19, 124.2, 37.3, 21.5, 14.4; IR (Neat)ν_{max} 3046, 1715, 1589, 1506, 1364, 1156, 1084, cm^{-1}; HRMS (ESI) for $C_{22}H_{20}N_2NaO_3S$ $(M+Na)^+$: calcd 415.1092, found 415.1094.



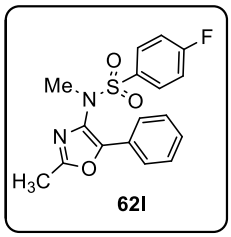
4-(N-Benzyl-N-tosyl)-2-methyl-5-(phenanthren-9-yl)oxazole (62j): Following the general procedure GP–2, compound **62j** (130 mg) was obtained in 50% yield as pale brown solid; mp = 200–202 °C; R_f = 0.45 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 8.0 Hz, 2H), 7.81–7.67 (m, 4H), 7.65–7.58 (m, 2H), 7.48 (s, 1H), 7.44–7.34 (m, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.04 (br t, J = 7.2 Hz, 3H), 6.98–6.92 (m, 2H), 4.60 (s, 2H), 2.54 (s, 3H), 2.31 (s, 3H), ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.5, 147.9, 143.7, 135.8, 135.2, 133.5, 130.88, 130.85, 130.6, 130.2, 130.1, 129.5, 129.4, 129.3, 128.3, 128.2, 127.8, 127.7, 126.8, 126.6, 126.5, 126.2, 122.7, 122.5, 122.4, 53.4, 21.6, 14.6; IR (Neat)ν_{max} 3073, 1589, 1446, 1353, 1161, 1046, 816 cm^{-1}; HRMS (ESI) for $C_{32}H_{27}N_2O_3S$ $(M+H)^+$: calcd 519.1742, found 519.1748.



N-Benzyl-N-(2-methyl-5-phenyloxazol-4-yl)benzenesulfonamide (62k): Following the general procedure GP–2, compound **62k** (182 mg) was obtained in 90% yield as colorless solid; mp = 189–190 °C; R_f = 0.51 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 8.0 Hz, 2H), 7.72 (dd, J = 7.2, 1.6 Hz, 2H), 7.69–7.63 (m, 1H), 7.61–7.54 (m, 2H), 7.36–7.28 (m, 3H), 7.20 (dd, J = 6.0, 2.0 Hz, 2H), 7.15–7.08 (m, 3H), 4.61 (s, 2H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.2, 147.4, 138.4, 134.6, 133.1, 130.8, 129.1, 128.9, 128.5 128.4, 128.2, 128.1,

127.8, 126.7, 125.3, 53.8, 14.2; IR (Neat)ν_{max} 2926, 2853, 1583, 1495, 1448, 1350, 1268, 1159 cm^{-1}; HRMS (ESI) for $C_{23}H_{20}N_2NaO_3S$ $(M+Na)^+$: calcd 427.1092, found 427.1092.

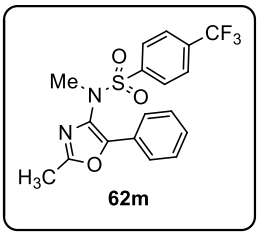
4-Fluoro-N-methyl-N-(2-methyl-5-phenyloxazol-4-yl)benzenesulfonamide (62l):



62l

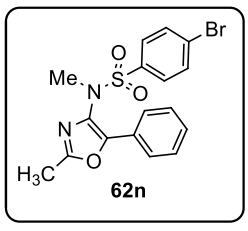
Following the general procedure GP–2, compound **62l** (83 mg) was obtained in 48% yield as colorless thick liquid; R_f = 0.57 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.95–7.89 (m, 4H), 7.44 (t, J = 7.2 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.24–7.17 (m, 2H), 3.11 (s, 3H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.4 (d, J = 257 Hz, 1C), 158.4, 145.5, 133.5, 133.4, 132.9, 131.3 (d, J = 9.1 Hz, 1C), 128.7, 126.9, 125.0, 116.1 (d, J = 22.2 Hz, 1C), 27.2, 14.2; ^{19}F NMR (376.4 MHz) δ -104.7; IR (Neat)ν_{max} 3060, 2926, 2848, 1629, 1588, 1495, 1366, 1159 cm^{-1}; HRMS (ESI) for $C_{17}H_{15}FN_2NaO_3S$ $(M+Na)^+$: calcd 369.0685, found 369.0687.

N-Methyl-N-(2-methyl-5-phenyloxazol-4-yl)-4-(trifluoromethyl)benzenesulfonamide (62m): Following the general procedure GP–2, compound **62m** (109 mg) was obtained in 55% as pale yellow solid; mp = 180–182 °C; R_f= 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.0, 2H), 7.94–7.88 (m, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.49–7.42 (m, 2H), 7.41–7.33 (m, 1H), 3.15 (s, 3H), 2.46 (s, 3H), $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.6, 145.8, 141.2, 134.7 (q, J = 33 Hz, 1C), 132.7, 126.8 (q, J = 263 Hz, 1C), 129.1, 128.9, 128.8, 126.9, 126.2–125.9 (m, 1C), 125.1, 124.7, 122.0, 37.4, 14.3; ^{19}F NMR (471 MHz) δ -63.1; IR (Neat)ν_{max} 2920, 1593, 1448, 1365, 1319, 1128, 1061, 622 cm^{-1}; HRMS (ESI) for $C_{18}H_{16}F_3N_2O_3S$ $(M+H)^+$: calcd 397.0834, found 397.0839.



62m

4-Bromo-N-methyl-N-(2-methyl-5-phenyloxazol-4-yl)benzenesulfonamide (62n):

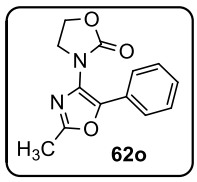


62n

Following the general procedure GP–2, compound **62n** (166 mg) was obtained in 82% as pale brown solid; mp = 172–174 °C; R_f= 0.35 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93–7.89 (m, 2H), 7.78–7.74 (m, 2H), 7.68–7.64 (m, 2H), 7.47–7.41 (m,

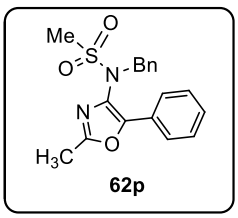
2H), 7.38–7.33 (m, 1H), 3.11 (s, 3H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.5, 145.7, 136.6, 132.9, 132.2, 130.1, 128.8, 128.4, 126.9, 125.1, 37.3, 14.3; IR (Neat)ν_{max} 3090, 1634, 1572, 1386, 1267, 1071, 859 cm^{-1}; HRMS (ESI) for $C_{17}H_{16}BrN_2O_3S$ $(M+H)^+$: calcd 407.0065, found 407.0068.

3-(2-Methyl-5-phenyloxazol-4-yl)oxazolidin-2-one (62o): Following the general procedure GP–2, compound **62o** (79 mg) was obtained in 65% yield as yellow color gummy liquid; R_f = 0.41 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64–7.59 (m, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.36–7.32 (m, 1H), 4.59–4.51 (m, 2H), 4.04–3.98 (m, 2H), 2.50 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.1, 156.4, 143.5, 129.7, 128.8, 128.5, 127.1, 125.0, 62.8, 46.0, 14.2; IR (Neat)ν_{max} 2921, 1758, 1634, 1583, 1418, 1257, 1211 cm^{-1}; HRMS (ESI) for $C_{13}H_{12}N_2NaO_3$ $(M+Na)^+$: calcd 267.0746, found 267.0746.



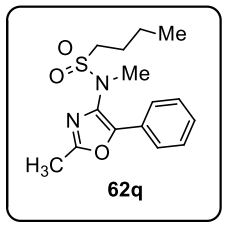
62o

4-(N-Benzyl-N-mesyl)-2-methyl-5-phenyloxazole (62p): Following the general procedure GP–2, compound **62p** (128 mg) was obtained in 75% yield as yellow solid; mp = 190–192 °C; R_f = 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68–7.64 (m, 2H), 7.33–7.27 (m, 3H), 7.24 (dd, J = 4.8, 2.0 Hz, 2H), 7.16–7.13 (m, 3H), 4.76 (s, 2H), 3.15 (s, 3H), 2.50 (s, 3H), $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.7, 147.2, 134.7, 131.1, 129.3, 128.7, 128.31, 128.26, 128.1, 126.6, 125.3, 54.6, 38.5, 14.3; IR (Neat)ν_{max} 2910, 1329, 1593, 1494, 1448, 1340, 1267, 1169 cm^{-1}; HRMS (ESI) for $C_{18}H_{18}N_2NaO_3S$ $(M+Na)^+$: calcd 365.0936, found 365.0930.



62p

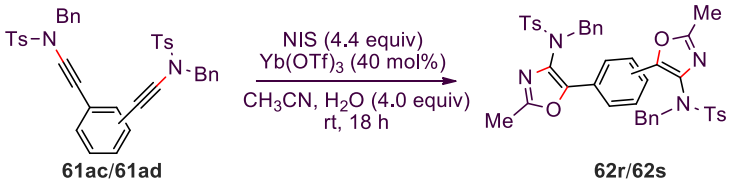
N-Methyl-N-(2-methyl-5-phenyloxazol-4-yl)butane-1-sulfonamide (62q): Following the general procedure GP–2, compound **62q** (52 mg) was obtained in 27% yield as colorless gummy liquid; R_f = 0.64 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.91–7.87 (m, 2H), 7.44–7.39 (m, 2H), 7.36–7.30 (m, 1H), 3.31–3.27 (m, 2H), 3.26 (s, 3H), 2.49 (s, 3H), 1.94–1.85 (m, 2H), 1.53–1.44 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101



62q

MHz, $CDCl_3$) δ 158.6, 145.3, 133.0, 128.7, 126.9, 125.0, 50.2, 37.8, 24.7, 21.7, 14.3, 13.6; IR (Neat)ν_{max} 3060, 2962, 2931, 2874, 2853, 1588, 1443, 1263 cm^{-1}; HRMS (ESI) for $C_{15}H_{20}N_2NaO_3S$ $(M+Na)^+$: calcd 331.1092, found 331.1092.

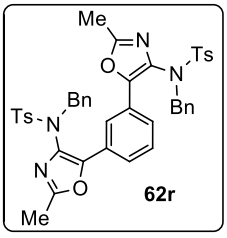
2.6.3.5. General procedure for the synthesis of bis–oxazoles 62r and 62s (GP–3)



61ac/61ad **62r/62s**

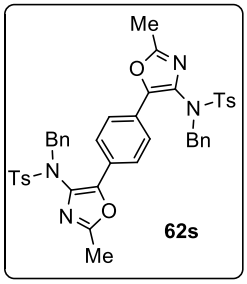
A mixture of arene tethered bis-ynamide **61ac/61ad** (0.3 mmol), N-iodosuccinimide (1.32 mmol, 297 mg), $Yb(OTf)_3$ (0.12 mmol, 74 mg), and H_2O (1.2 mmol, 22 µ) in freshly distilled acetonitrile (3.0 mL) was stirred at room temperature for 18 h. The progress of the reaction was monitered by TLC. Upon complete consumption of precursor, the reaction mixture was quenched with saturated sodium thiosulfate. The organic layer was separated and the aqeous layer was extracted with ethylacetate (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to give bis-oxazole **62r/62s**.

N,N'-(5,5'-(1,3-Phenylene)bis(2-methyloxazole-5,4-diyl))bis(N-benzyl-4-methyl benzenesulfonamide) (62r): Following the general procedure GP–3, compound **62r** (102 mg) was obtained in 45% yield as colorless thick liquid; R_f = 0.48 (1.5:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (br s, 1H), 7.81 (d, J = 8.4 Hz, 4H), 7.72 (dd, J = 8.0, 2.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 4H), 7.30–7.24 (m, 2H), 7.21–7.16 (m, 4H), 7.09–7.04 (m, 5H), 4.58 (br s, 4H), 2.47 (s, 6H), 2.46 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 158.4, 146.9, 144.0, 135.4, 134.7, 131.3, 129.6, 129.0, 128.4, 128.3, 128.1, 127.9, 126.7, 125.3, 121.8, 53.7, 21.6, 14.2; IR (Neat) ν_{max} 2921, 1712, 1629, 1593, 1490, 1350, 1263, 1159 cm^{-1}; HRMS (ESI) for $C_{42}H_{39}N_4O_6S_2$ $(M+H)^+$: calcd 759.2311, found 759.2313.

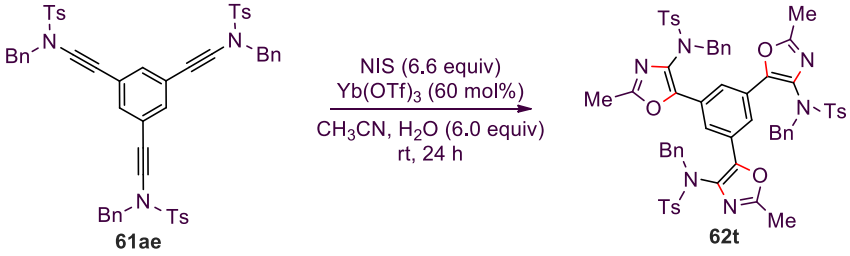


62r

N,N'-(5,5'-(1,4-Phenylene)bis(2-methyloxazole-5,4-diyl))bis(N-benzyl-4-methyl benzenesulfonamide) (62s): Following the general procedure GP–3, compound **62s** (114 mg) was obtained in 50% yield as light brown solid; mp = 222–224 °C; R_f = 0.30 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.4 Hz, 4H), 7.64 (s, 4H), 7.35 (d, J = 8.0 Hz, 4H), 7.17 (dd, J = 6.4, 2.0 Hz, 4H), 7.12–6.07 (m, 6H), 4.57 (s, 4H), 2.46 (s, 6H), 2.42 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.5, 147.0, 144.1, 135.5, 134.7, 131.5, 129.6, 129.1, 128.5, 128.2, 128.0, 126.6, 125.1, 53.8, 21.6, 14.3; IR (Neat) ν_{max} 2910, 2848, 1583, 1350, 1257, 1170 cm^{-1}; HRMS (ESI) for $C_{42}H_{39}N_4O_6S_2$ $(M+H)^+$: calcd 759.2311, found 759.2304.

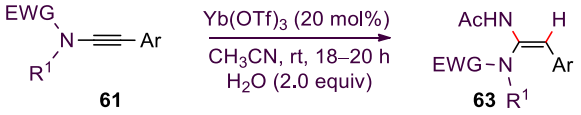


2.6.3.6. Synthesis of 1,3,5-tris-oxazole 62t on arene



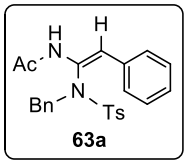
A mixture of **61ae** (187 mg), N-iodosuccinimide (297 mg), $Yb(OTf)_3$ (74 mg), and H_2O (22 µL) in dry acetonitrile (3.0 mL) was stirred at room temperature for 24 h. The progress of the reaction was monitered by TLC. After completion, the reaction mixture was quenched with saturated sodium thiosulfate. The organic layer was separated and the aqeous layer was extracted with ethylacetate (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to give **62t** (99 mg) in 30% yield as yellow gummy liquid; R_f = 0.33 (1.5:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (s, 3H), 7.81 (d, J = 8.0 Hz, 6H), 7.30 (d, J = 8.0 Hz, 6H), 7.18 (dd, J = 7.5, 1.5 Hz, 6H), 7.02–6.07 (m, 9H), 4.59 (s, 6H), 2.54 (s, 9H), 2.43 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 158.7, 146.4, 143.9, 135.7, 134.8, 131.7, 129.5, 129.1, 128.5, 128.1, 127.9, 126.8, 121.6, 53.9, 21.6, 14.3; IR (Neat) ν_{max} 2926, 1707, 1624, 1578, 1490, 1454, 1350, 1263, cm^{-1}; HRMS (ESI) for $C_{60}H_{58}N_7O_9S_3$ $(M+NH_4)^+$: calcd 1116.3458, found 1116.3446.

2.6.3.7. General procedure for the hydroamidation of ynamides with CH_3CN (GP–4)



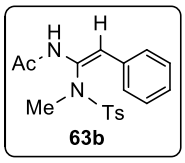
A mixture of ynamide **61** (0.5 mmol), $Yb(OTf)_3$ (0.1 mmol, 62 mg), and H_2O (1.0 mmol, 18 µL) in freshly distilled acetonitrile (3.0 mL) was stirred at room temperature for 18–20 h. The progress of the reaction was monitered by TLC. After completion, the reaction mixture was filtered through a small pad of Celite and concentrated under reduced pressure. The crude mixture was purified by neutral alumina column chromatography eluting with 25% EtOAc and hexane mixture to give the desired product **63**.

(*Z*)-N-(1-(N-Benzyl-4-methylphenylsulfonamido)-2-phenylvinyl)acetamide (63a):



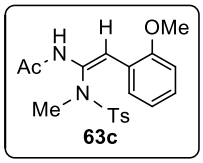
Following the general procedure GP–4, compound **63a** (147 mg) was obtained in 70% yield as colorless solid; mp = 158–159 °C; R_f = 0.40 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, DMSO-D_6): δ 8.82 (s, 1H, NH), 7.72 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.22–7.08 (m, 10H), 6.63 (s, 1H), 4.53 (s, 2H), 2.46 (s, 3H), 1.89 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-D_6): δ 169.2, 144.1, 136.7, 135.1, 134.4, 130.1, 130.0, 128.6, 128.3, 128.13, 128.09, 127.5, 127.4, 122.8, 52.0, 23.8, 21.5; IR (KBr) ν_{max} 3275, 3025, 2359, 2338, 1672, 1592, 1448, 1352 cm^{-1}; HRMS (ESI) for $C_{24}H_{24}N_2NaO_3S$ $(M+Na)^+$: calcd 443.1405, found 443.1402.

(*Z*)-N-(1-(N,4-Dimethylphenylsulfonamido)-2-phenylvinyl)acetamide (63b):



Following the general procedure GP–4, compound **63b** (126 mg) was obtained in 73% yield as colorless solid; mp = 165–166 °C; R_f = 0.37 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.34 (s, 1H, NH), 7.19–7.11 (m, 7H), 6.59 (s, 1H), 3.10 (s, 3H), 2.35 (s, 3H), 1.95 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 169.3, 144.0, 135.5, 133.2, 129.6, 129.4, 128.3, 128.2, 127.6, 127.5, 122.0, 36.4, 23.7, 21.5; IR (KBr) ν_{max} 3266, 3052, 1688, 1594, 1523, 1342, 1255, 1162 cm^{-1}; HRMS (ESI) for $C_{18}H_{20}N_2NaO_3S$ $(M+Na)^+$: calcd 367.1092, found 367.1097.

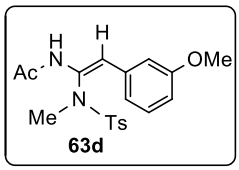
(*Z*)-N-(1-(N,4-Dimethylphenylsulfonamido)-2-(2-methoxyphenyl)vinyl)acetamide



63c

(63c): Following the general procedure GP–4, compound **63c** (88 mg) was obtained in 47% yield as pale yellow solid; mp = 178–179 °C; R_f = 0.26 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, DMSO-D_6): δ 9.55 (s, 1H, NH), 7.65 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.50 (s, 1H), 3.82 (s, 3H), 2.97 (s, 3H), 2.44 (s, 3H), 1.74 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-D_6): δ 169.4, 156.8, 143.6, 136.9, 132.0, 130.1, 129.9, 129.4, 127.9, 127.5, 122.4, 120.8, 114.0, 111.3, 55.8, 37.0, 23.1, 21.5; IR (KBr) ν_{max} 3649, 2986, 2362, 1655, 1523, 1479, 1342, 1293 cm^{-1}; HRMS (ESI) for $C_{19}H_{23}N_2O_4S$ $(M+H)^+$: calcd 375.1379, found 375.1374.

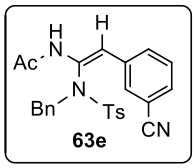
(*Z*)-N-(1-(N,4-Dimethylphenylsulfonamido)-2-(3-methoxyphenyl)vinyl)acetamide



63d

(63d): Following the general procedure GP–4, compound **63d** (86 mg) was obtained in 46% yield as colorless solid; mp = 149–150 °C; R_f = 0.26 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, DMSO-D_6): δ 9.56 (s, 1H, NH), 7.68 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.41 (s, 1H), 3.79 (s, 3H), 3.05 (s, 3H), 2.44 (s, 3H), 1.74 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-D_6): δ 169.4, 159.7, 143.7, 136.8. 135.4, 132.1, 130.1, 130.0, 129.9, 127.6, 127.2, 121.3, 119.6, 113.9, 113.2, 55.4, 37.0, 23.1, 21.5; IR (Neat) ν_{max} 3030, 2920, 1682, 1594, 1490, 1347, 1161 cm^{-1}; HRMS (ESI) for $C_{19}H_{22}N_2NaO_4S$ $(M+Na)^+$: calcd 397.1198, found 397.1202.

(*Z*)-N-(1-(N-Benzyl-4-methylphenylsulfonamido)-2-(3-cyanophenyl)vinyl)acetamide

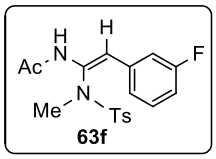


63e

(63e): Following the general procedure GP–4, compound **63e** (167 mg) was obtained in 75% yield as colorless gummy liquid; R_f = 0.52 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, DMSO-D_6): δ 9.07 (s, 1H, NH), 7.70 (d, *J* = 6.8 Hz, 2H), 7.49 (d, *J* = 6.8 Hz, 1H), 7.41–7.32 (m, 3H), 7.26 (br t, *J* = 7.2 Hz, 1H), 7.22–7.14 (m, 6H), 6.75 (s, 1H), 4.65 (br s, 2H), 2.43 (s, 3H), 1.95 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-D_6): δ 169.5, 144.2, 136.7, 135.8, 134.9, 133.3, 131.1, 130.4, 130.20, 130.16, 129.2, 128.5, 128.4, 128.0, 120.3, 119.0, 111.3, 52.1, 23.9, 21.5; IR (Neat)

ν_{max} 3260, 3030, 2926, 2230, 1693, 1589, 1348, 1156 cm^{-1}; HRMS (ESI) for $C_{25}H_{24}N_3O_3S$ $(M+H)^+$: calcd 446.1538, found 446.1539.

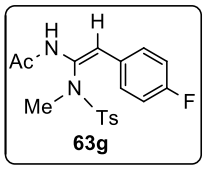
(*Z*)-N-(1-(N,4-Dimethylphenylsulfonamido)-2-(3-fluorophenyl)vinyl)acetamide (63f):



63f

Following the general procedure GP–4, compound **63f** (138 mg) was obtained in 76% yield as colorless solid; mp = 179–180 °C; R_f = 0.38 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, DMSO-D_6): δ 9.54 (s, 1H, NH), 7.67 (d, *J* = 8.0 Hz, 2H), 7.45–7.38 (m, 3H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.16–7.08 (m, 1H), 6.53 (s, 1H), 3.06 (s, 3H), 2.55 (s, 3H), 1.78 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-D_6): δ 169.4, 162.7 (d, *J* = 242 Hz), 143.9, 136.64 (d, *J* = 8.1 Hz), 136.63, 133.0, 130.7 (d, *J* = 8.1 Hz), 130.1, 130.0, 127.6, 127.2, 124.9 (d, *J* = 3.0 Hz), 118.0, 114.54 (d, *J* = 21.2 Hz), 114.48 (d, *J* = 23.2 Hz), 36.9, 23.3, 21.5; 19F NMR (376.4 MHz) δ –113.24; IR (KBr) ν_{max} 3304, 2920, 1687, 1583, 1490, 1441, 1326, 1260 cm^{-1}; HRMS (ESI) for $C_{18}H_{19}FN_2NaO_3S$ $(M+Na)^+$: calcd 385.0998, found 385.0998.

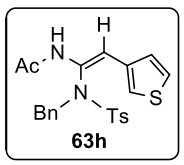
(*Z*)-N-(1-(N,4-Dimethylphenylsulfonamido)-2-(4-fluorophenyl)vinyl)acetamide (63g):



63g

Following the general procedure GP–4, compound **63g** (145 mg) was obtained in 80% yield as colorless solid; mp = 168–170 °C; R_f = 0.31 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, DMSO-D_6): δ 9.51 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.57–7.49 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 8.4 Hz, 2H), 6.47 (s, 1H), 3.04 (s, 3H), 2.43 (s, 3H), 1.74 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-D_6): δ 169.4, 161.8 (d, *J* = 246.4 Hz), 143.7, 136.8, 131.7, 130.6 (d, *J* = 3.0 Hz), 130.4 (d, *J* = 8.1 Hz), 129.9, 127.6, 118.6, 115.8 (d, *J* = 21.2 Hz), 36.9, 23.2, 21.5; ^{19}F NMR (376.4 MHz) δ -114.04; IR (KBr) ν_{max} 3331, 1693, 1600, 1512, 1342, 1227, 1156, 1084 cm^{-1}; HRMS (ESI) for $C_{18}H_{19}FN_2NaO_3S$ $(M+Na)^+$: calcd 385.0998, found 385.1005.

(*Z*)-N-(1-(N-Benzyl-4-methylphenylsulfonamido)-2-(thiophen-3-yl)vinyl)acetamide

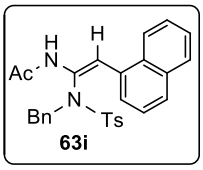


63h

(63h): Following the general procedure GP–4, compound **63h** (171 mg) was obtained in 80% yield as colorless solid; mp = 137–138 °C; R_f = 0.46 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, DMSO-D_6): δ

8.7 (s, 1H, NH), 7.76 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.31–7.21 (m, 4H), 7.20–7.13 (m, 3H), 7.08 (d, *J* = 4.8 Hz, 1H), 6.76 (s, 1H), 4.55 (br s, 2H), 2.46 (s, 3H), 1.86 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-D_6): δ 169.0, 144.1, 136.7, 135.6, 135.2, 130.1, 128.7, 128.3, 128.22, 128.17, 128.0, 127.0, 126.2, 125.2, 124.7, 118.7, 51.7, 23.8, 21.5; IR (KBr) ν_{max} 3222, 1737, 1666, 1595, 1458, 1403, 1332, 1167 cm^{-1}; HRMS (ESI) for $C_{22}H_{23}N_2O_3S_2$ $(M+H)^+$: calcd 427.1150, found 427.1157.

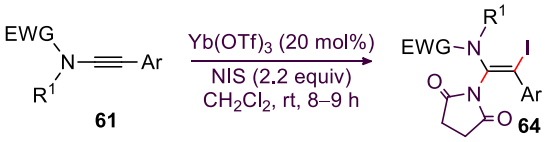
(*Z*)-N-(1-(N-Benzyl-4-methylphenylsulfonamido)-2-(naphthalen-1-yl)vinyl)acetamide



63i

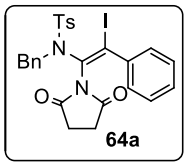
(63i): Following the general procedure GP–4, compound **63i** (141 mg) was obtained in 60% yield as colorless semi-solid; R_f = 0.67 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, DMSO-D_6): δ 9.16 (s, 1H, NH), 7.84 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.63–7.54 (m, 3H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.23–7.15 (m, 3H), 7.03 (d, *J* = 7.2 Hz, 1H), 7.01–6.92 (m, 5H), 4.44 (s, 2H), 2.37 (s, 3H), 1.99 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-D_6): δ 169.5, 143.8, 136.7, 135.2, 133.3, 131.5, 131.4, 129.8, 129.7, 129.6, 128.5, 128.1, 127.9, 127.8, 127.7, 126.1, 126.0, 125.9, 125.4, 124.8, 119.5, 52.4, 23.9, 21.5; IR (Neat) ν_{max} 3057, 2931, 2350, 1687, 1594, 1501, 1452, 1342, 1265 cm^{-1}; HRMS (ESI) for $C_{28}H_{27}N_2O_3S$ $(M+H)^+$: calcd 471.1742, found 471.1743.

2.6.3.8. General procedure for the iodo-imidation of ynamide (GP–5)



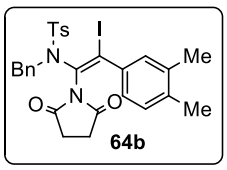
A mixture of ynamide **61** (0.5 mmol), N-iodosuccinimide (1.1 mmol, 247 mg), and $Yb(OTf)_3$ (0.1 mmol, 62 mg) in dry dichloromethane (3.0 mL) was stirred at room temperature for 8–9 h. The progress of the reaction was monitered by TLC. After completion, the reaction mixture was quenched with saturated sodium thiosulfate. The organic layer was separated and the aqeous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude mixture was purified by silica gel

column chromatography eluting with mixture of hexane/EtOAc to give the desired product **64**.

(*Z*)-N-Benzyl-N-(1-(2,5-dioxopyrrolidin-1-yl)-2-iodo-2-phenylvinyl)-4-methyl benzenesulfonamide (64a): 

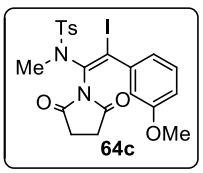
64a

Following the general procedure GP–5, compound **64a** (191 mg) was obtained in 69% yield as yellow solid; mp = 215–216 °C; R_f = 0.55 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.5 Hz, 2H), 7.51 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.36–7.29 (m, 5H), 7.24–7.19 (m, 3H), 7.18–7.15 (m, 2H), 4.94 (s, 2H), 2.46 (s, 3H), 2.41 (d, *J* = 13.5 Hz, 2H), 2.13 (d, *J* = 14 Hz, 2H); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ 144.1, 141.3, 136.5, 136.2, 129.9, 129.7, 129.3, 129.1, 128.5, 128.1, 128.0, 127.8, 127.3, 107.4, 55.7, 27.8, 21.6; IR (KBR) ν_{max} 1720, 1589, 1490, 1353, 1156, 1090 cm^{-1}; HRMS (ESI) for $C_{26}H_{23}IN_2NaO_4S$(M+Na): calcd 609.0321, found 609.0321.

(*Z*)-N-Benzyl-N-(2-(3,4-dimethylphenyl)-1-(2,5-dioxopyrrolidin-1-yl)-2-iodovinyl)-4-methylbenzenesulfonamide (64b): 

64b

Following the general procedure GP–5, compound **64b** (197 mg) was obtained in 64% yield as yellow solid; mp = 168–170 °C; R_f = 0.68 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.53–7.47 (m, 2H), 7.37–7.27 (m, 5H), 6.94 (d, *J* = 10 Hz, 2H), 6.87 (d, *J* = 7.6 Hz, 1H), 4.93 (s, 2H), 2.45 (s, 3H), 2.41 (d, *J* = 14 Hz, 2H), 2.21–2.14 (m, 8 H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.0, 138.8, 137.9, 136.5, 136.4, 136.2, 129.8, 129.6, 129.2, 128.6, 128.4, 127.9, 127.7, 124.4, 108.4, 55.7, 27.8, 21.6, 19.6, 19.5; IR (Neat) ν_{max} 3075, 2920, 1789, 1727, 1598, 1453, 1252 cm^{-1}; HRMS (ESI) for $C_{28}H_{28}IN_2O_4S$ $(M+H)^+$: calcd 615.0814, found 615.0815.

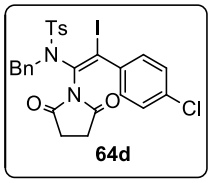
(*Z*)-N-(1-(2,5-Dioxopyrrolidin-1-yl)-2-iodo-2-(3-methoxyphenyl)vinyl)-N,4-dimethylbenzenesulfonamide (64c): 

64c

Following the general procedure GP–5, compound **64c** (185 mg) was obtained in 60% yield as red solid; mp = 193–195 °C; R_f = 0.54 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 8.4

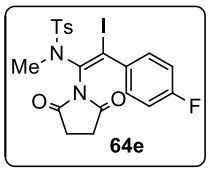
Hz, 1H), 6.77–6.71 (m, 3H), 3.75 (s, 3H), 3.46 (s, 3H), 2.58 (d, *J* = 14.0 Hz, 2H), 2.46 (s, 3H), 2.34 (d, *J* = 13.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.1, 144.1, 141.6, 136.2, 130.8, 129.8, 129.2, 127.8, 119.6, 115.1, 113.1, 103.1, 55.3, 39.7, 28.0, 21.6; IR (Neat) ν_{max} 3057, 2936, 1720, 1600, 1484, 1347, 1287 cm^{-1}; HRMS (ESI) for $C_{21}H_{21}N_2NaO_5S$ $(M+Na)^+$: calcd 563.0114, found 563.0117.

(*Z*)-N-Benzyl-N-(2-(4-chlorophenyl)-1-(2,5-dioxopyrrolidin-1-yl)-2-iodovinyl)-4-methylbenzenesulfonamide (64d): Following the general procedure GP–5, compound **64d** (124 mg) was obtained in 40% yield as yellow solid; mp = 240–242 °C; R_f = 0.74 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.51–7.45 (m, 2H), 7.37–7.28 (m, 5H), 7.19 (d, *J* =8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.92 (s, 2H), 2.46 (s, 3H) 2,44 (d, *J* = 14 Hz, 2H), 2.20 (d, *J* = 14 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.3, 139.8, 136.4, 135.9, 135.0, 129.9, 129.8, 129.7, 128.9, 128.5, 128.4, 128.1, 127.9, 105.4, 55.5, 27.9, 21.7; IR (Neat) ν_{max} 1726, 1342, 1161, 1084, 1013, 882 cm^{-1}; HRMS (ESI) for $C_{26}H_{23}ClIN_2O_4S$ $(M+H)^+$: calcd 621.0112, found 621.0114.



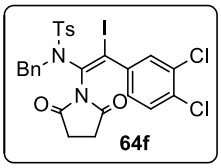
64d

(*Z*)-N-(1-(2,5-Dioxopyrrolidin-1-yl)-2-(4-fluorophenyl)-2-iodovinyl)-N,4-dimethyl benzenesulfonamide (64e): Following the general procedure GP–5, compound **64e** (156 mg) was obtained in 59% yield as colorless solid; mp = 187–189 °C; R_f = 0.70 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.19–7.12 (m, 2H), 6.92 (t, *J* = 8.4 Hz, 2H), 3.45 (s, 3H), 2.60 (d, *J* = 14.0 Hz, 2H), 2.45 (s, 3H), 2.35 (d, *J* = 14.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.7 (d, *J* = 250.5 Hz), 144.2, 136.6 (d, *J* = 4.0 Hz), 136.1, 131.2, 129.9, 129.6 (d, *J* = 8.1 Hz), 127.7, 115.4 (d, *J* = 22.2 Hz), 101.7, 39.7, 28.0, 21.6; 19F NMR (470.6 MHz) δ -111.1; IR (Neat) ν_{max} 3064, 2501, 1902, 1732, 1597, 1422, 1344 cm^{-1}; HRMS (ESI) for $C_{20}H_{19}FIN_2O_4S$ $(M+H)^+$: calcd 529.0094, found 529.0092.



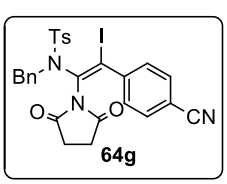
64e

(*Z*)-N-Benzyl-N-(2-(3,4-dichlorophenyl)-1-(2,5-dioxopyrrolidin-1-yl)-2-iodovinyl)-4-methylbenzenesulfonamide (64f): Following the general procedure GP–5, compound **64f** (138 mg) was obtained in 42% yield as yellow solid; mp = 238–240 °C; R_f = 0.76 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.46 (dd, *J* = 7.6, 4.0 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.33–7.29 (m, 3H), 7.28 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.90 (s, 2H), 2.46 (s, 3H), 2.44 (d, *J* = 14 Hz, 2H), 2.25 (d, *J* = 14 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.4, 141.1, 136.3, 135.7, 133.3, 132.3, 130.3, 130.2, 129.9, 129.8, 129.5, 128.4, 128.1, 128.0, 126.9, 103.1, 55.5, 27.9, 21.7; IR (Neat) ν_{max} 1720, 1336, 1216, 1156, 1079, 1030, cm^{-1}; HRMS (ESI) for $C_{26}H_{21}Cl_2IN_2NaO_4S$ (M+Na)$^+$: calcd 676.9541, found 676.9542.



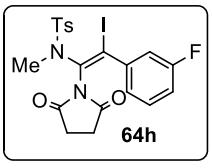
64f

(*Z*)-N-Benzyl-N-(2-(4-cyanophenyl)-1-(2,5-dioxopyrrolidin-1-yl)-2-iodovinyl)-4-methylbenzenesulfonamide (64g): Following the general procedure GP–5, compound **64g** (70 mg) was obtained in 23% yield as light yellow solid; mp = 270–271 °C; R_f = 0.58 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.50–7.46 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.36–7.33 (m, 3H), 7.30 (s, 1H), 7.28 (d, *J* = 2.8 Hz, 1H), 4.93 (s, 2H), 2.49 (s, 3H), 2.46 (d, *J* = 13.6 Hz, 2H), 2.21 (d, *J* = 13.6 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.8, 145.8, 144.5, 136.2, 135.6, 132.0, 130.6, 130.0, 129.9, 128.5, 128.14, 128.06, 118.0, 112.7, 103.2, 55.4, 27.8, 21.7; IR (Neat) ν_{max} 3065, 2228, 1727, 1598, 1458, 1427, 1402 cm^{-1}; HRMS (ESI) for $C_{27}H_{23}IN_3O_4S$ (M+H)$^+$: calcd 612.0454, found 612.0450.



64g

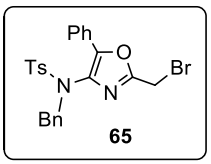
(*Z*)-N-(1-(2,5-Dioxopyrrolidin-1-yl)-2-(3-fluorophenyl)-2-iodovinyl)-N,4-dimethyl benzenesulfonamide (64h): Following the general procedure GP–5, compound **64h** (164 mg) was obtained in 62% yield as yellow solid; mp = 199–200 °C; R_f = 0.65 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.24–7.17 (m, 1H), 6.96–6.88 (m, 3H), 3.45 (s, 3H), 2.62 (d, *J* = 13.6 Hz, 2H), 2.46 (s, 3H), 2.37 (d, *J* = 14 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.0 (d, *J* = 248.5 Hz), 144.2, 142.4 (d, *J* = 8.1 Hz), 136.1, 131.6, 129.9, 129.8 (d, *J* = 8.1 Hz), 127.7, 123.2 (d, *J* = 3.0 Hz), 116.1 (d, *J* = 21.2 Hz),



64h

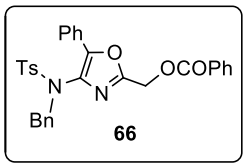
115.1 (d, J = 23.2 Hz), 100.1, 39.7, 28.0, 21.6; 19F NMR (470.6 MHz) δ –111.83; IR (Neat) ν_{max} 2931, 1731, 1610, 1583, 1430, 1342, 1271, 1079 cm^{-1}; HRMS (ESI) for $C_{20}H_{18}FIN_2NaO_4S$ $(M+Na)^+$: calcd 550.9914, found 550.9921.

2.6.3.9. Synthesis of N-benzyl-N-(2-(bromomethyl)-5-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (65) (Scheme 2.13): A mixture of **62a** (0.2 mmol, 84 mg), N-bromosuccinimide (0.22 mmol, 39 mg), AIBN (0.01 mmol, 1.7 mg) in tetrachloromethane (2.0 mL) was stirred at 60 °C for 9 h. The reaction was cooled to room temperature and the crude mixture was purified by silica gel column chromatography to give **65** (56 mg) in 56% yield as colorless solid; mp = 180–181 °C; R_f = 0.47 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79–7.73 (m, 4H), 7.37–7.30 (m, 5H), 7.19–7.16 (m, 2H), 7.11–7.07 (m, 3H), 4.58 (s, 2H), 4.37 (s, 2H), 2.47 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 155.6, 149.0, 144.2, 134.7, 134.3, 131.8, 129.7, 129.2, 128.5, 128.3, 128.2, 127.9, 126.1, 125.6, 53.9, 21.7, 20.4; IR (Neat) ν_{max} 2926, 1598, 1495, 1450, 1355, 1266 cm^{-1}; HRMS (ESI) for $C_{24}H_{21}BrN_2NaO_3S$ $(M+Na)^+$: calcd 519.0354, found 519.0354.



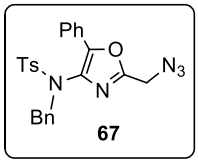
65

2.6.3.10. Synthesis of (4-(N-benzyl-4-methylphenylsulfonamido)-5-phenyloxazol-2-yl)methyl benzoate (66) (Scheme 2.13): A mixture of **65** (0.1 mmol, 50 mg), benzoic acid (0.15 mmol, 18 mg), triethylamine (0.3 mmol, 42 µL) in acetonitrile (2.0 mL) was stirred at 80 °C for 1 h. After completion, the reaction mixture was cooled to room temperature and purified by silica gel column chromatography to give **66** (38 mg) in 70% yield as colorless solid; mp = 149–150 °C; R_f = 0.45 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 7.2 Hz, 2H), 7.83–7.75 (m, 4H), 7.65 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.2 Hz, 2H), 7.40–7.32 (m, 3H), 7.28 (d, J = 8.0 Hz, 2H), 7.22–7.18 (m, 2H), 7.14–7.07 (m, 3H), 5.35 (s, 2H), 4.61 (s, 2H), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 165.6, 155.2, 148.8, 144.1, 134.9, 134.5, 133.5, 131.5, 130.0, 129.8, 129.5, 129.2, 129.13, 129.06, 128.6, 128.5, 128.3, 126.3, 125.7, 125.6, 58.2, 21.61, 21.59; IR (Neat) ν_{max} 2926, 1727, 1598, 1495, 1450, 1354, 1265 cm^{-1}; HRMS (ESI) for $C_{31}H_{26}N_2NaO_5S$ $(M+Na)^+$: calcd 561.1460, found 561.1460.



66

2.6.3.11. Synthesis of N-(2-(azidomethyl)-5-phenyloxazol-4-yl)-N-benzyl-4-methylbenzenesulfonamide (67) (Scheme 2.13): A mixture of **65** (0.1 mmol, 50 mg), sodium azide (0.5 mmol, 33 mg) in $(CH_3)_2CO$:H_2O (3:1; 2.0 mL) was stirred at rt for 1 h. After completion, the reaction mixture was purified by silica gel column chromatography to give **67** (38 mg) in 96% yield as colorless solid; mp = 139–140 °C; R_f = 0.46 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.4 Hz, 2H), 7.75 (dd, J = 8.0, 1.6 Hz, 2H), 7.37–7.31 (m, 5H), 7.18–7.14 (m, 2H), 7.11–7.05 (m, 3H), 4.58 (s, 2H), 4.32 (s, 2H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.1, 149.0, 144.2, 135.0, 134.4, 131.4, 129.7, 129.2, 129.1, 128.5, 128.4, 128.2, 127.9, 126.1, 125.7, 46.5, 21.7, 21.6; IR (Neat) ν_{max} 2956, 2101, 1597, 1449, 1352, 1165, 1090, 692 cm^{-1}; HRMS (ESI) for $C_{24}H_{21}N_5NaO_3S$ $(M+Na)^+$: calcd 482.1263, found 482.1262.



67

2.6.3.12. Gram scale synthesis of 62a and 62p (Scheme 2.14)

A mixture of ynamide **61a/61p** (1.0 g, 1.0 equiv), N-iodosuccinimide (NIS; 2.2 equiv), $Yb(OTf)_3$ (20 mol%), and H_2O (2.0 equiv) in freshly distilled acetonitrile (10 mL) was stirred independently at room temperature for 8–9 h. The progress of the reaction was monitered by TLC. After completion, the reaction mixture was quenched with saturated aqueous sodium thiosulfate. The organic layer was separated and the aqeous layer was extracted with ethylacetate (2 × 40 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to give the products **62a** and **62p** in 75% (0.87 g) and 78% (0.94 g), respectively.

2.6.3.13. Gram scale synthesis of 63a (Scheme 2.14)

A mixture of ynamide **61a** (2.77 mmol, 1.0 g), $Yb(OTf)_3$ (0.55 mmol, 344 mg), and H_2O (5.54 mmol, 100 µL) in freshly distilled acetonitrile (10 mL) was stirred at room temperature for 18 h. After completion, the reaction mixture was filtered through a small pad of Celite and concentrated under reduced pressure. The crude mixture was purified by neutral alumina column chromatography eluting with 25% EtOAc and hexane mixture to give the desired product **63a** in 70% (0.81 g) yield as colorless solid.

2.6.3.14. Gram scale synthesis of 64a (Scheme 2.14)

A mixture of ynamide **61a** (2.77 mmol, 1.0 g), N-iodosuccinimide (6.09 mmol, 1.37 g), and $Yb(OTf)_3$ (0.55 mmol, 344 mg) in dry dichloromethane (10 mL) was stirred at room temperature for 9 h. After completion, the reaction mixture was quenched with saturated sodium thiosulfate. The organic layer was separated and the aqeous layer was extracted with dichloromethane (2 × 40 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography eluting with mixture of hexane/EtOAc to give the desired product **64a** in 68% (1.1 g) yield as yellow solid.

2.6.3.15. Procedure for ^{18}O-incorporation (Scheme 2.15)

A mixture of ynamide **61a** (0.5 mmol, 181 mg), $Yb(OTf)_3$ (0.1 mmol, 62 mg) and H_2O^{18} (1.0 mmol, 18 µL) in freshly distilled acetonitrile (3.0 mL) was stirred at room temperature for 18 h. After completion, the reaction mixture was filtered through a small pad of Celite and concentrated under reduced pressure. The crude mixture was purified by neutral alumina column chromatography to give the ^{18}O-incorporated product **63a'** as colorless solid.

2.6.3.16. Procedure for D-incorporation (Scheme 2.15)

A mixture of ynamide **61a** (0.5 mmol, 181 mg), $Yb(OTf)_3$ (0.1 mmol, 62 mg), and D_2O (1.0 mmol, 18 µL) in freshly distilled acetonitrile (3.0 mL) was stirred at room temperature for 18 h. After completion, the reaction mixture was filtered through a small pad of Celite and concentrated under reduced pressure. The crude mixture was purified by neutral alumina column chromatography to give the D-incorporated products **63a''** as colorless semisolid.

2.7. X-ray Crystallography

X-ray reflections for **62a**, **63a,** and **64a** were collected on Bruker D8 Quest CCD diffractometer using Mo-Kα, radiation. Data reduction was performed using CrysAlisPro (version 1.171.33.55).[27] Apex 2 and SHELX-TL 97 and Diamomd program were used to solve and refine the data.[28] All non-hydrogen atoms were refined anisotropically and C−H hydrogens were fixed.

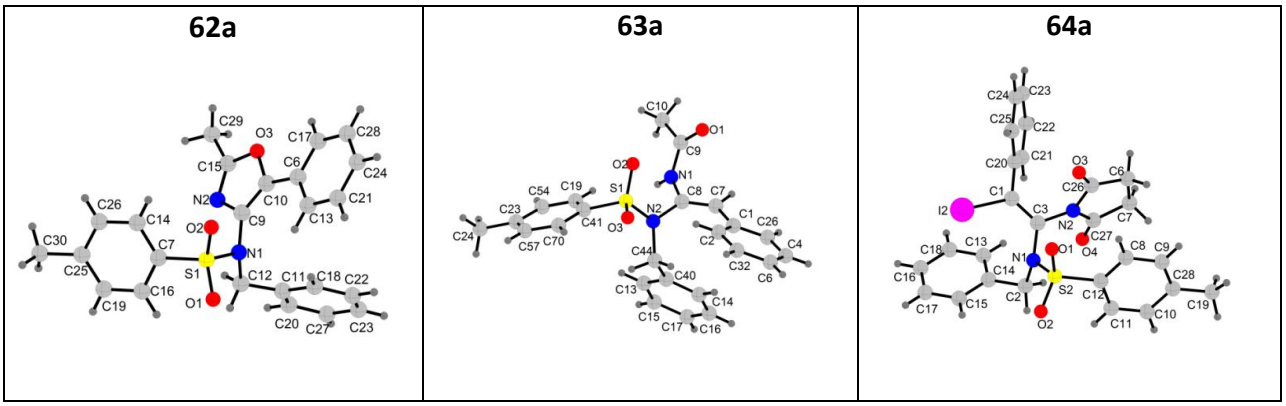


Figure 2.4. Molecular structures of compounds **62a**, **63a,** and **64a**; thermal ellipsoids are set at 30% probability. Carbon (light gray), Hydrogen (gray), Oxygen (red), Nitrogen (blue), Sulphur (yellow) and Iodine (pink).

Table 2.8. Crystallographic data for compound **62a, 63a,** and **64a**

Compound	**62a**	**63a**	**64a**
formula	$C_{24}H_{22}N_2O_3S$	$C_{24}H_{24}N_2O_3S$	$C_{26}H_{23}IN_2O_4S$
Mw	418.50	420.51	586.42
crystal system	monoclinic	monoclinic	monoclinic
space group	P 21/c	P 21/n	C 2/c
T [K]	298 K	295 K	296 K
a [Å]	20.188 (2)	9.2350(4)	32.959 (4)
b [Å]	9.8499 (8)	10.6767(4)	8.5274 (8)
c [Å]	10.9975 (10)	44.894(2)	18.548 (2)
α [°]	90	90	90
β [°]	102.392 (3)	92.065(1)	109.063 (4)
γ [°]	90	90	90
V [Å^3]	2135.9 (3)	4423.6(3)	4927.1 (9)
Z	4	8	8
ρ_{calcd} [g cm^{-3}]	1.301	1.263	1.576
μ [mm^{-1}]	0.179	0.174	1.420
total reflns	4936	7842	6207
unique reflns	4647	7741	6182
observed	3672	5521	4535
R_1[I>2σ(I)]	0.0448	0.0625	0.0370
wR2 [all]	0.1218 (4647)	0.1397	0.0942
GOF	1.055	1.156	1.097
Diffractometer	Bruker D8 Quest CCD	Bruker D8 Quest CCD	Bruker D8 Quest CCD
CCDC No	1546059	1546061	1546060

2.8. References

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25. Alternatively, the possibility of *anti*-addition of nitrile to Yb-keteneiminium species followed by a sequence of hydration, demetalation, and complete isomerization of the olefin to obtain the *Z*-hydroamidation product although difficult but could not completely be rule out.

26. At present, we have no clear evidence to authenticate the mode of attack of nitrile to the *β*-iodo-keteneiminium ion (**Int-75**; **Scheme 2.16**). Looking in to the formation of thermodynamically stable *trans*-iodo-imidation product **64**, we believe the nitrile can undergo *trans*-attack to *β*-iodo-keteniminium species and hydration to provide **Int-76**.

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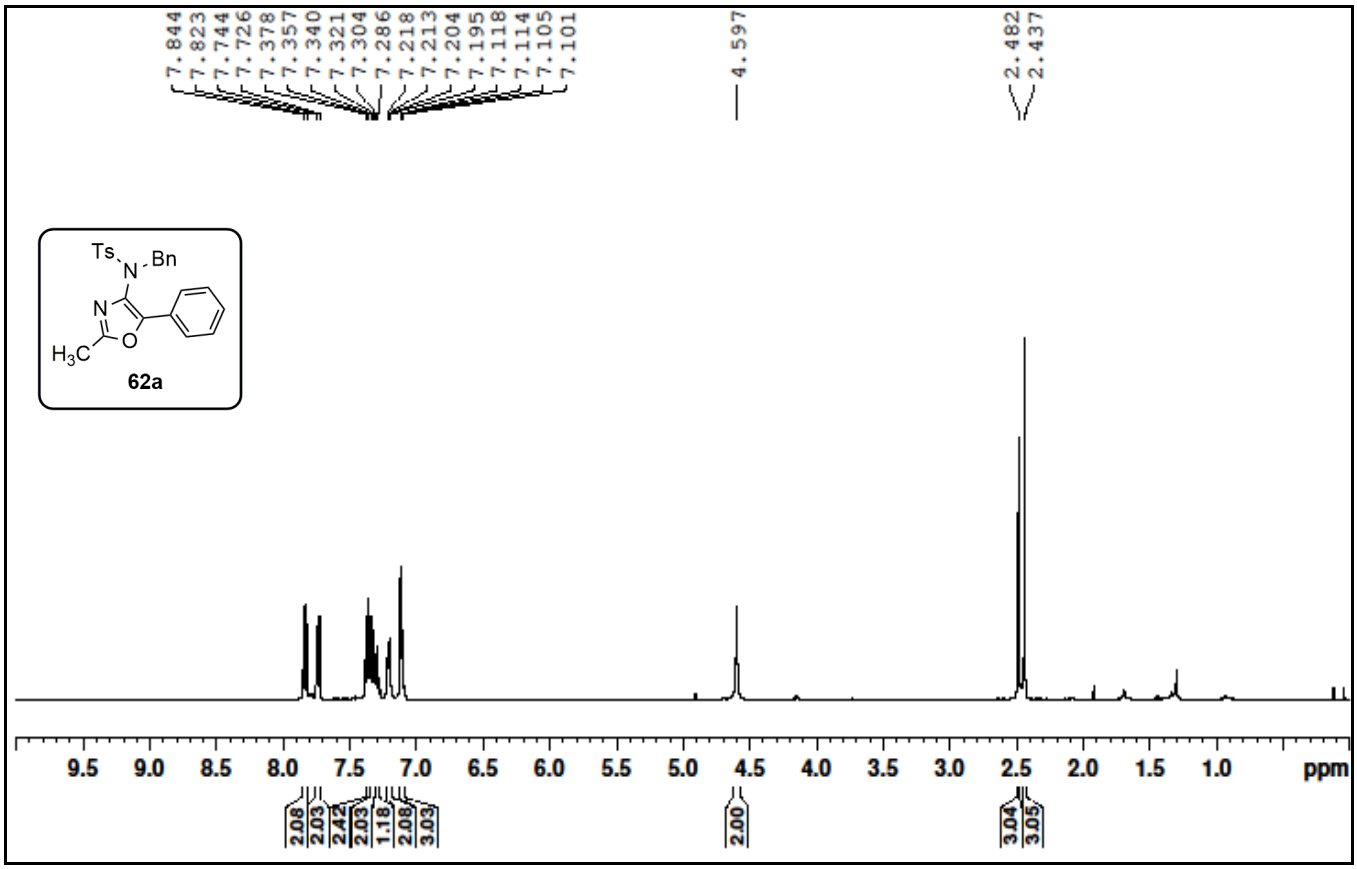
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Bn
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O
H3C
62a
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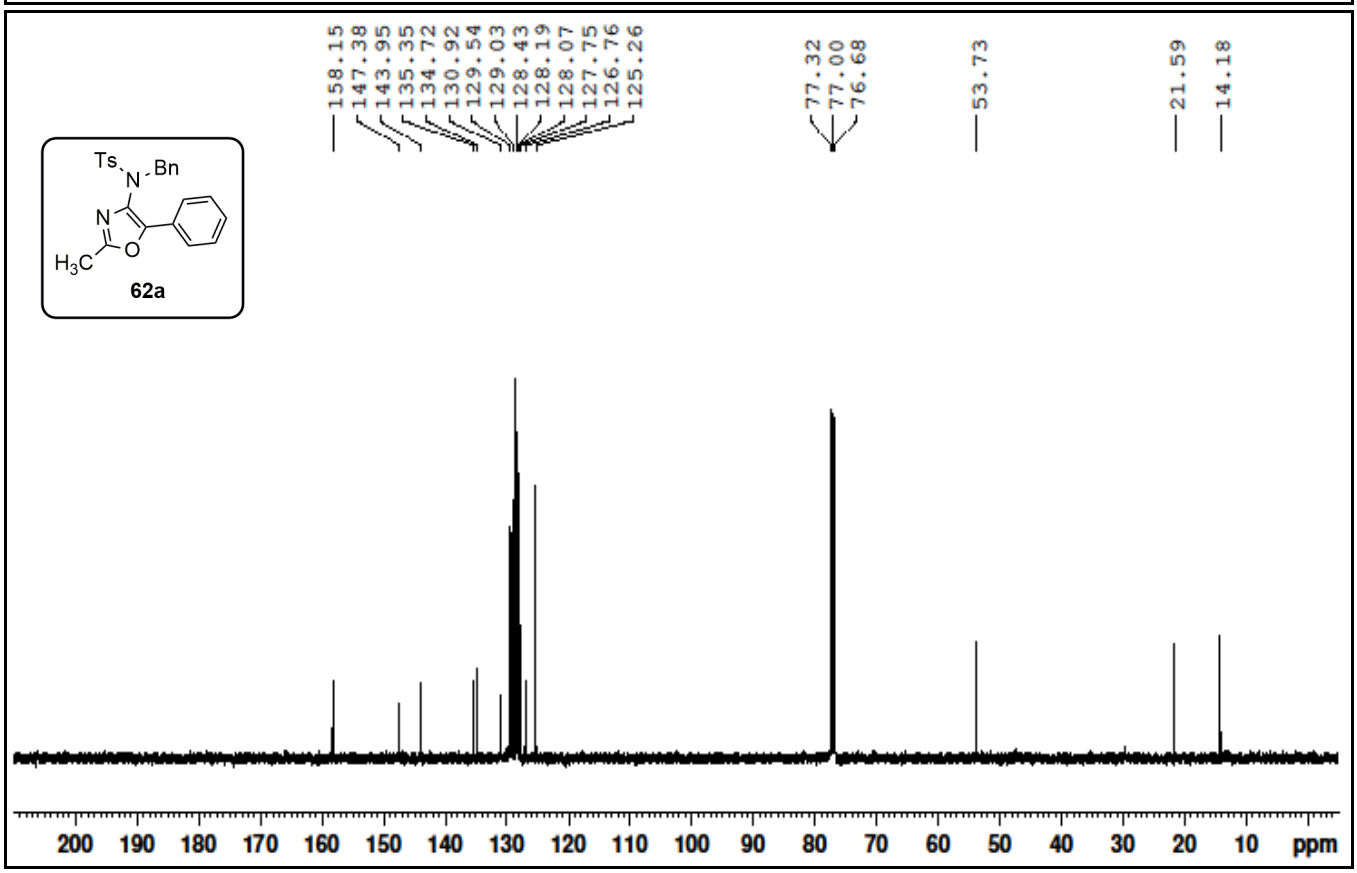
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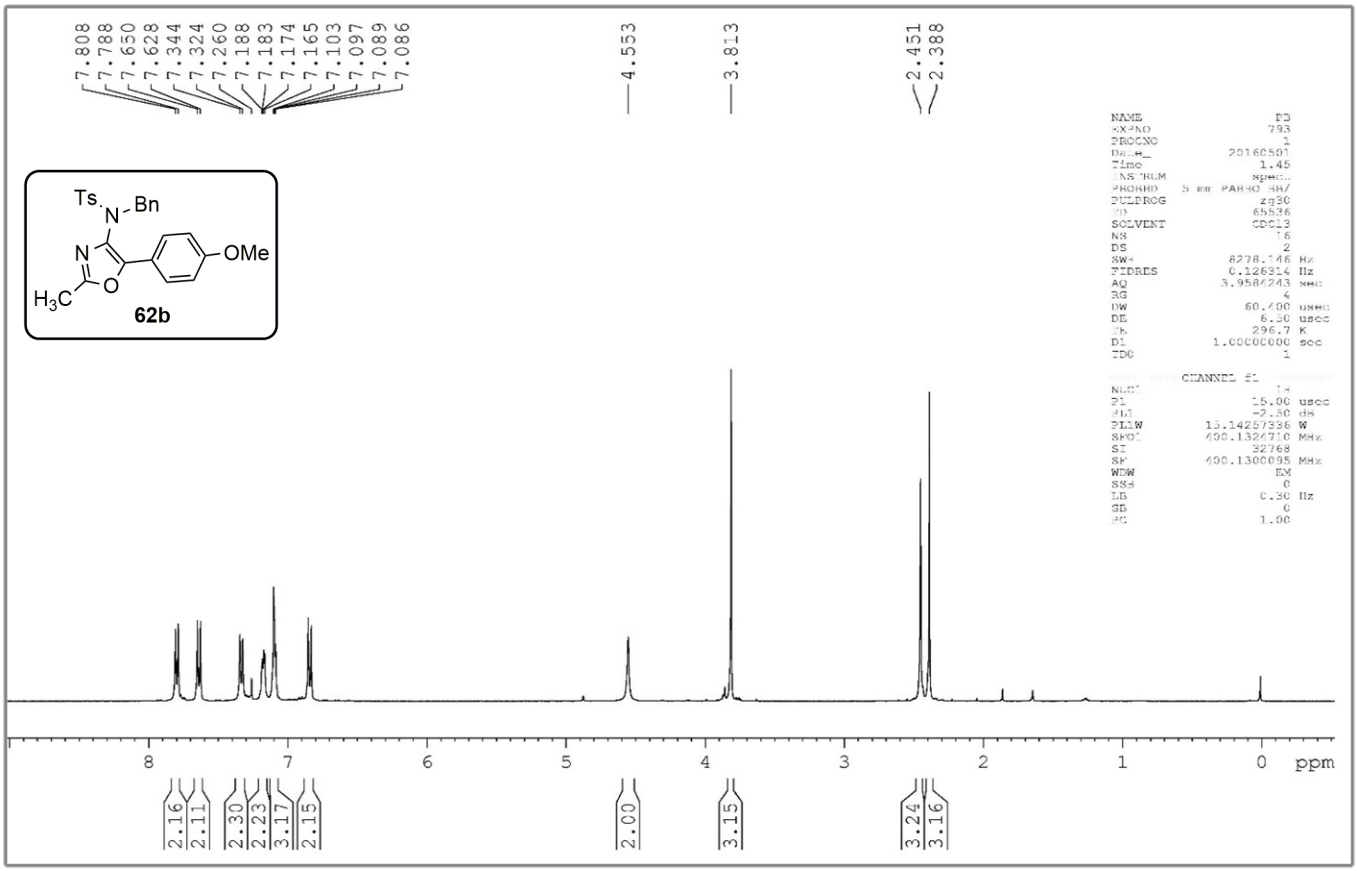
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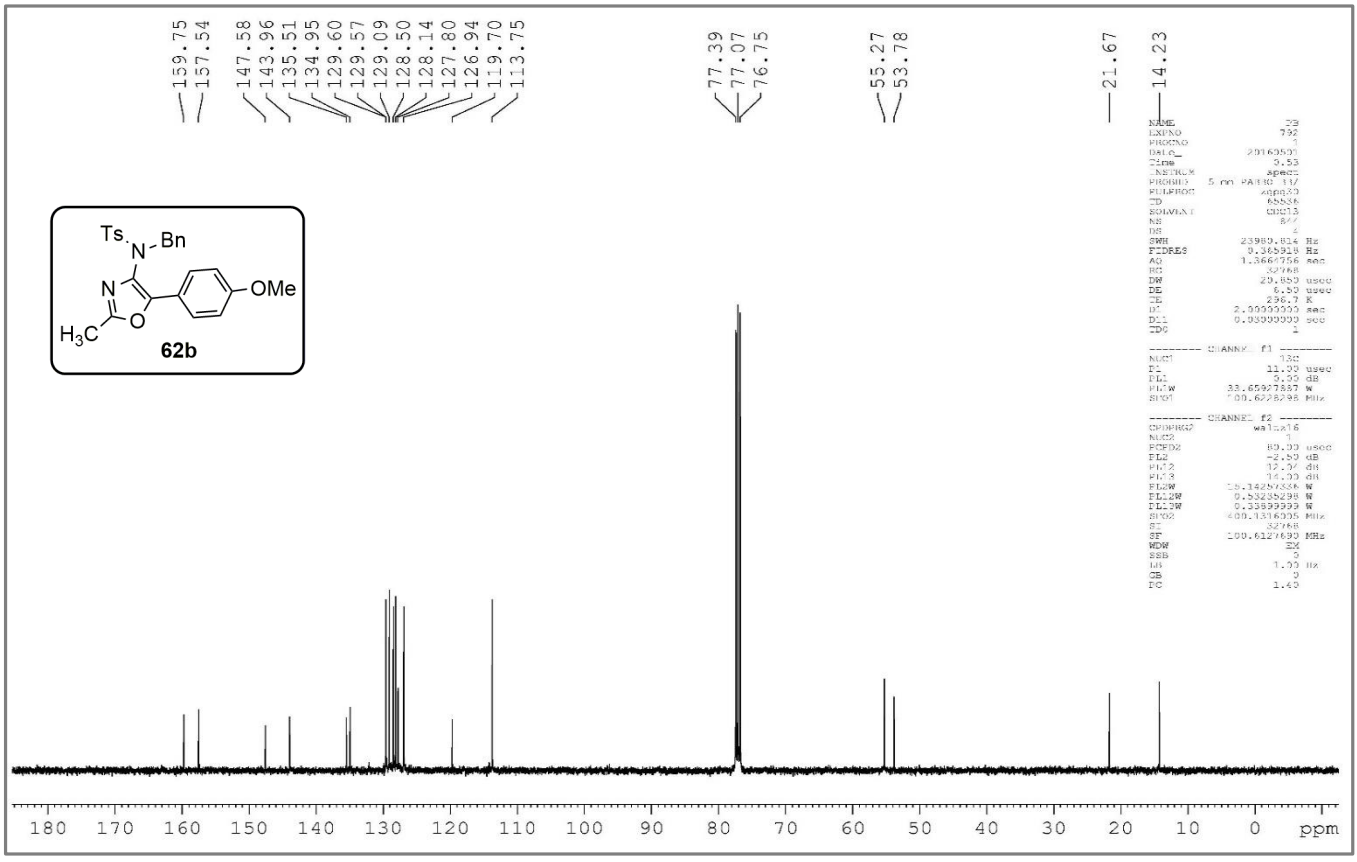
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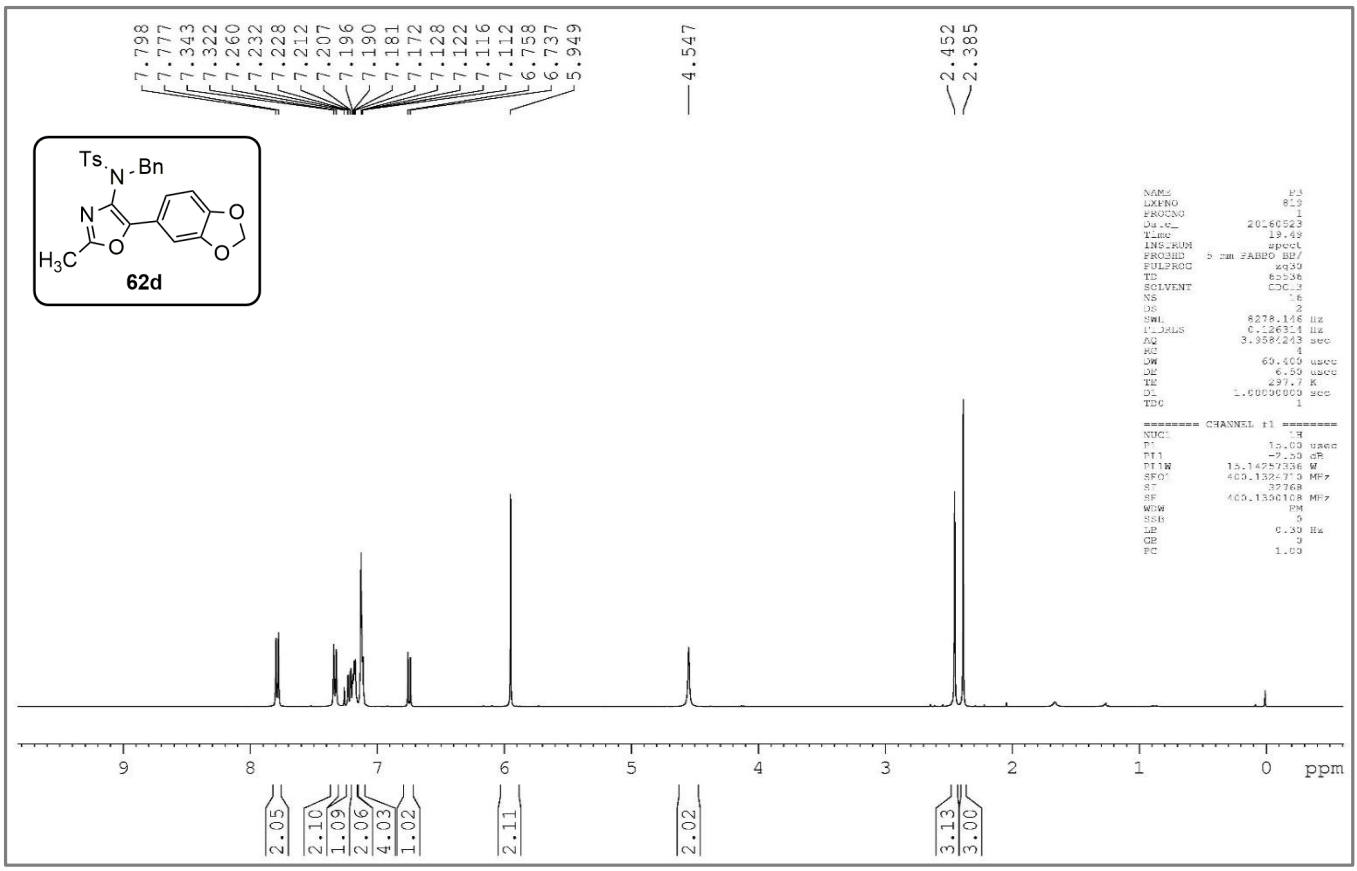
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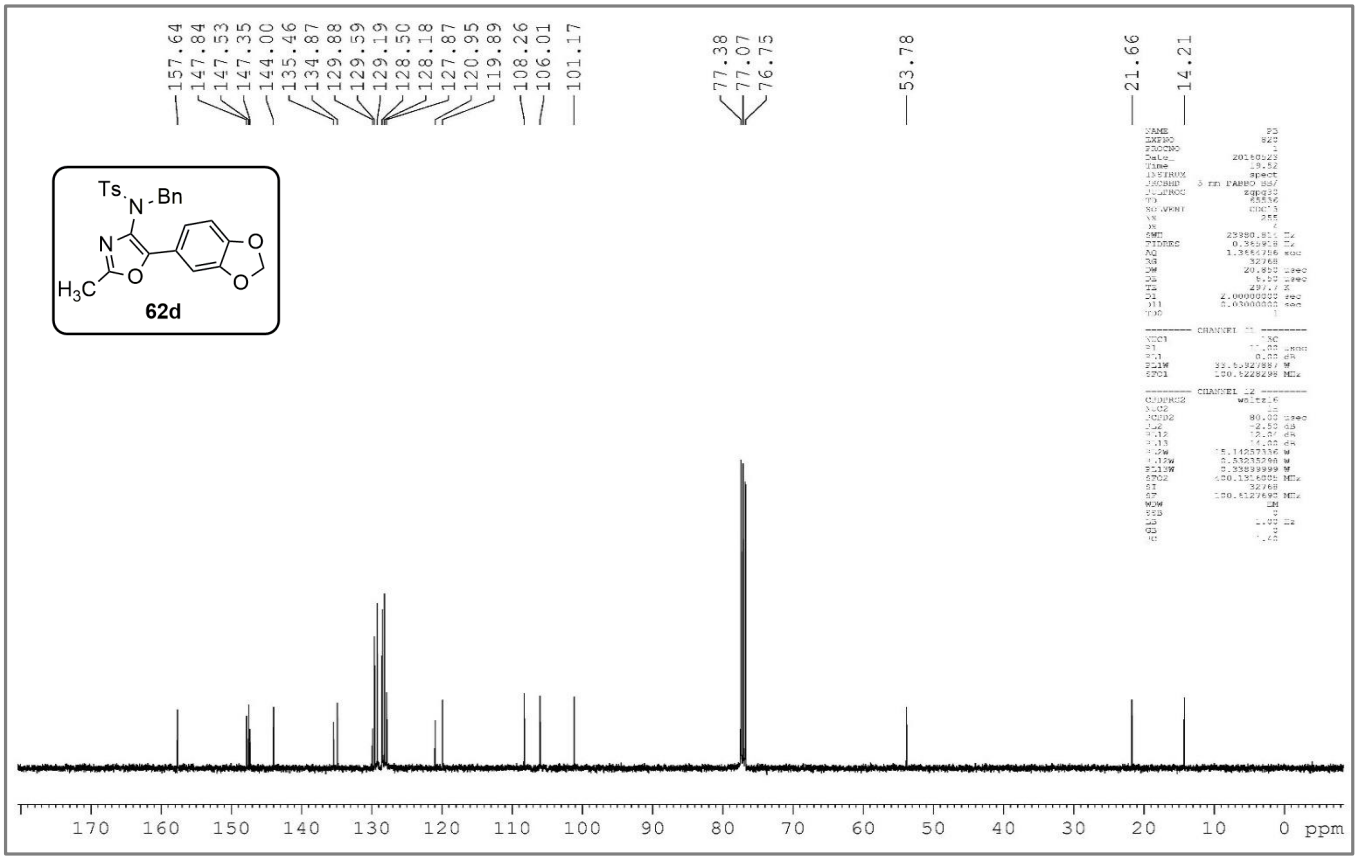
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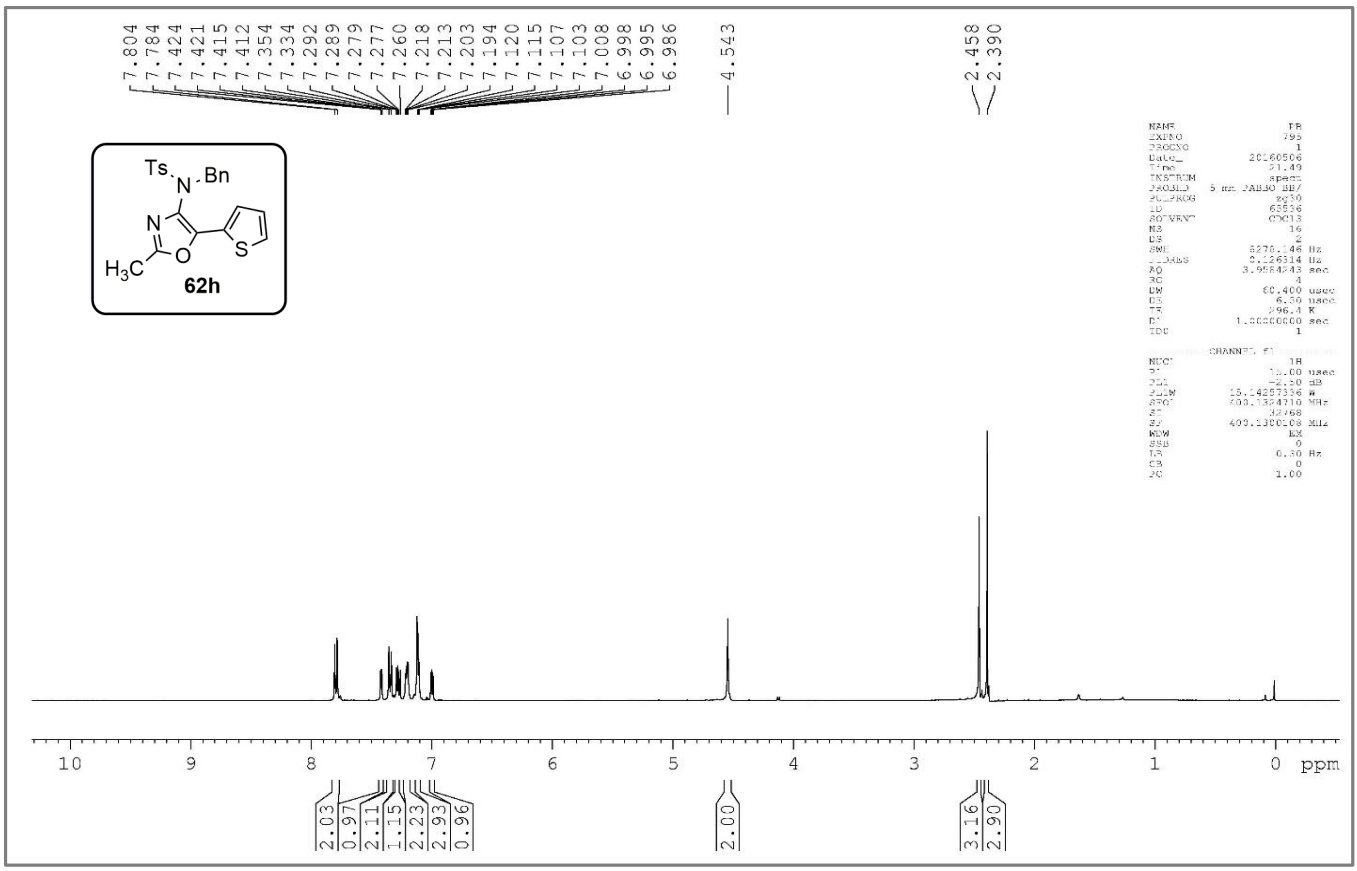
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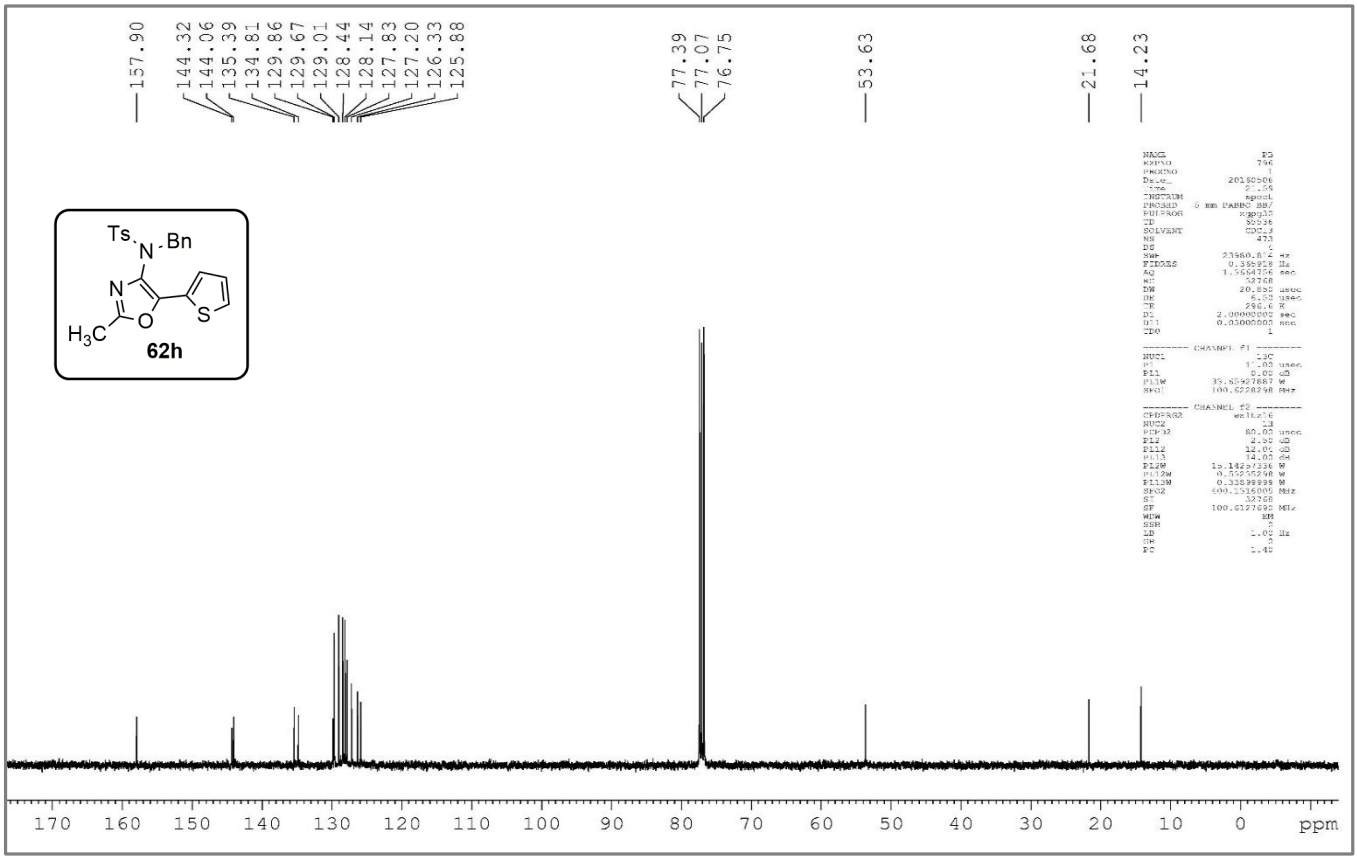
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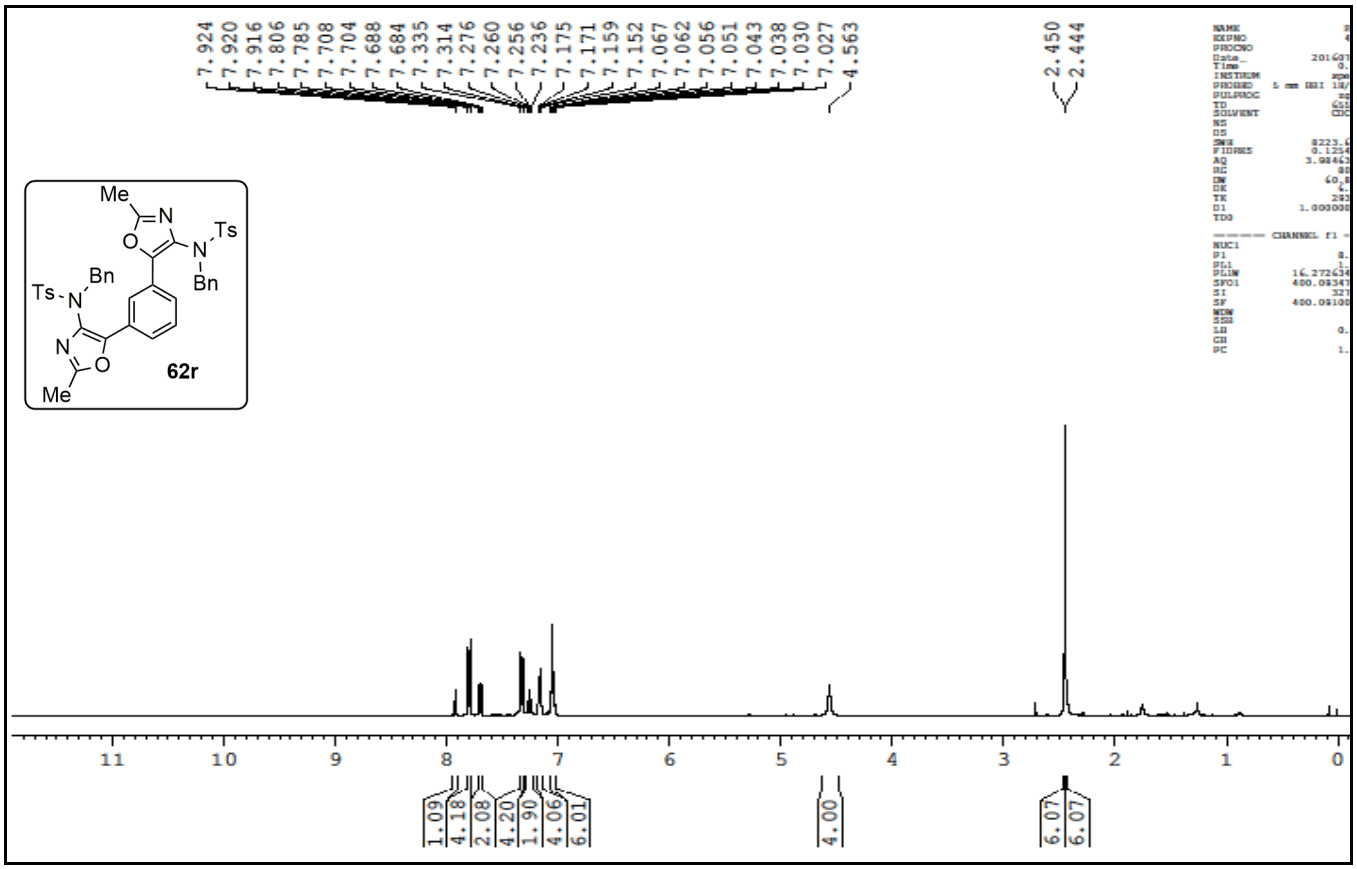
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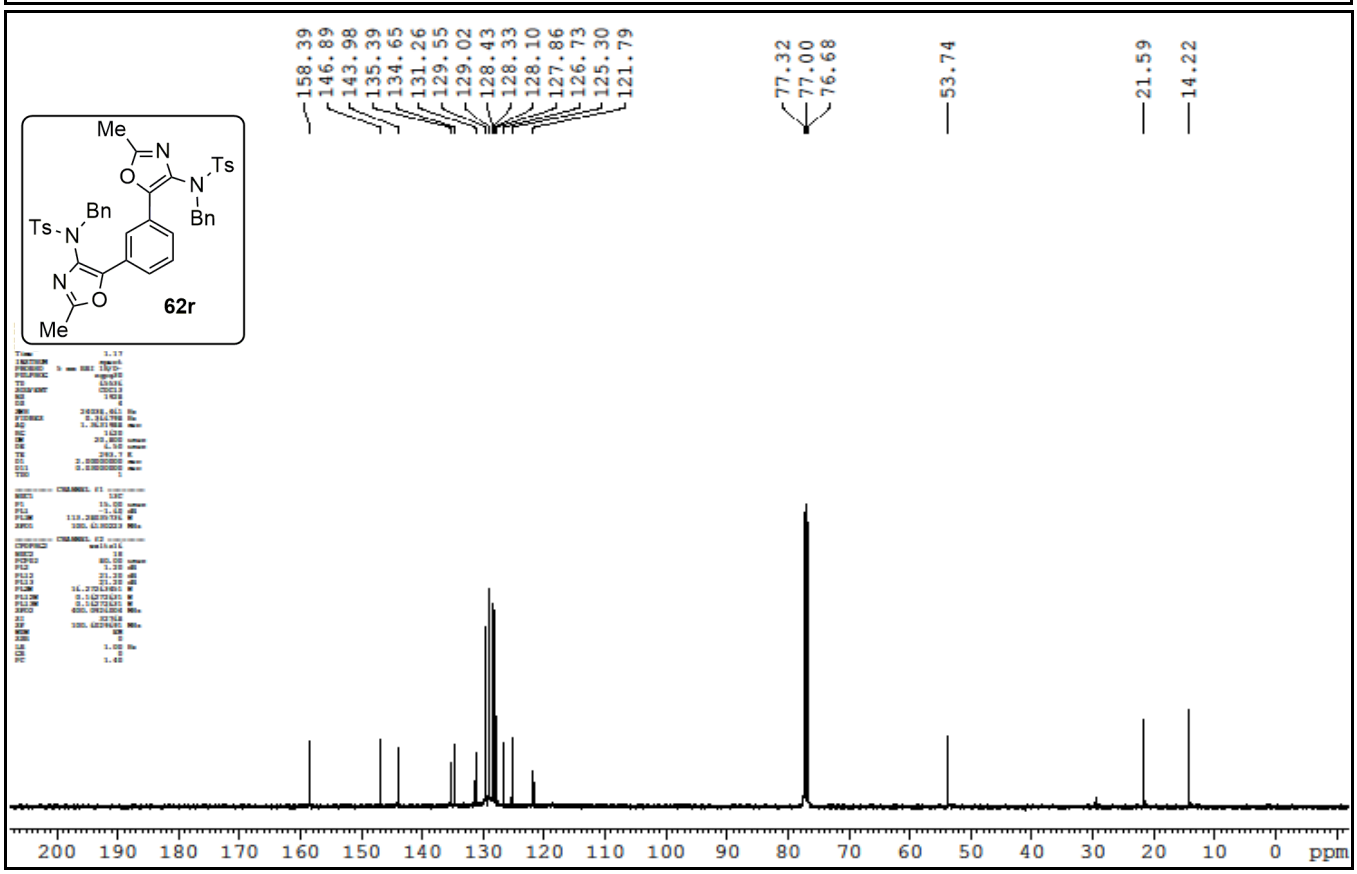
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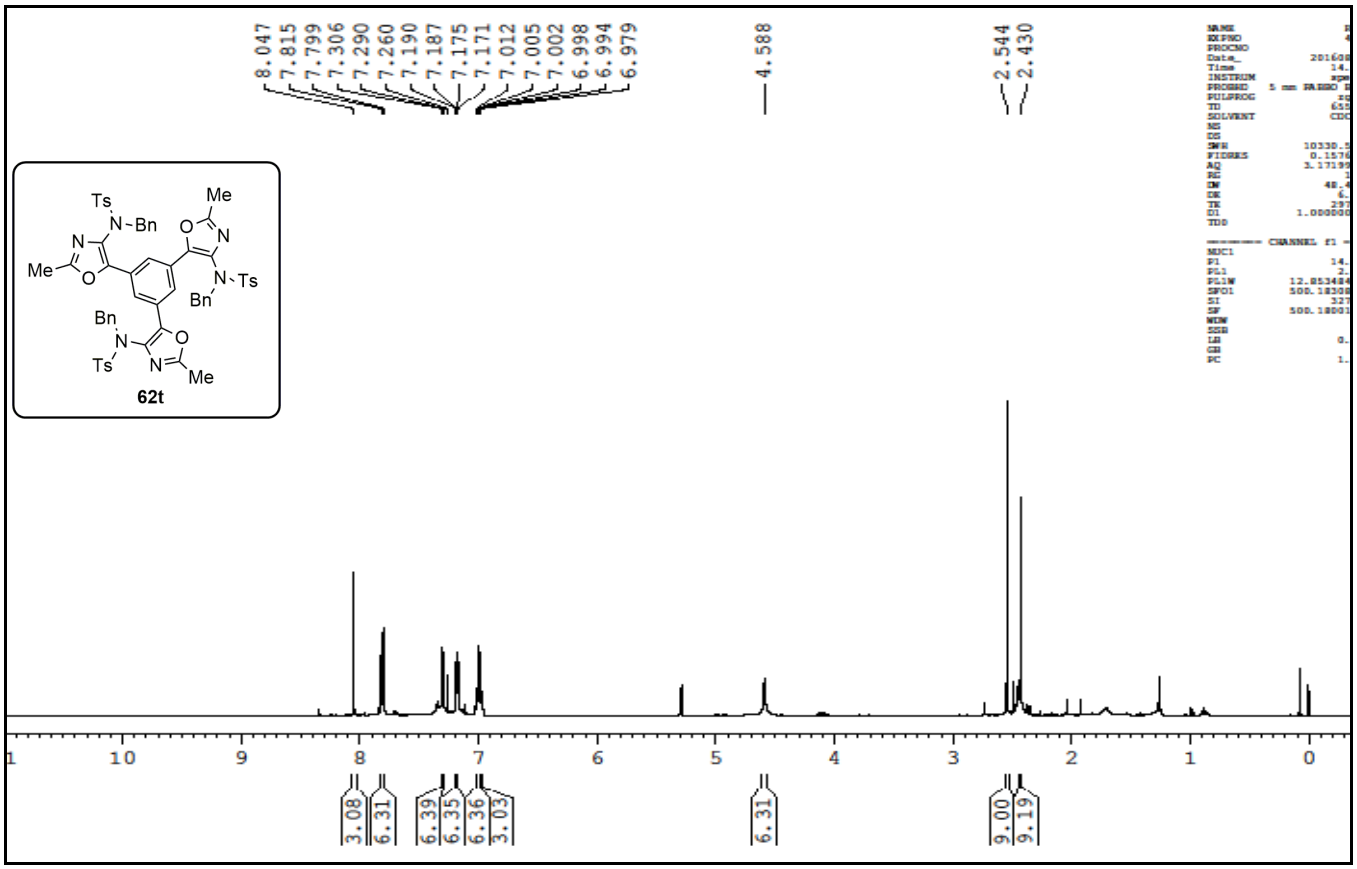
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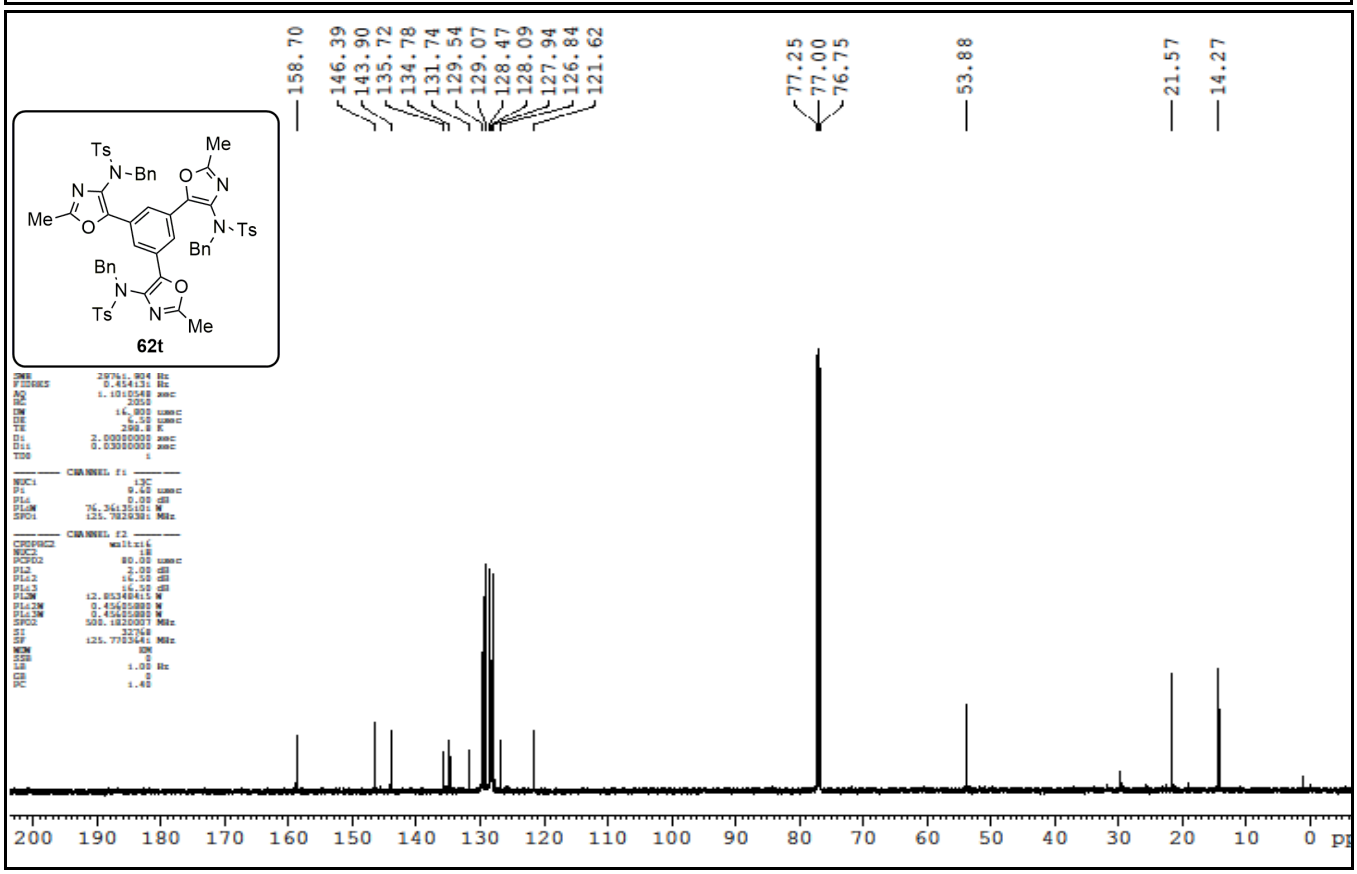
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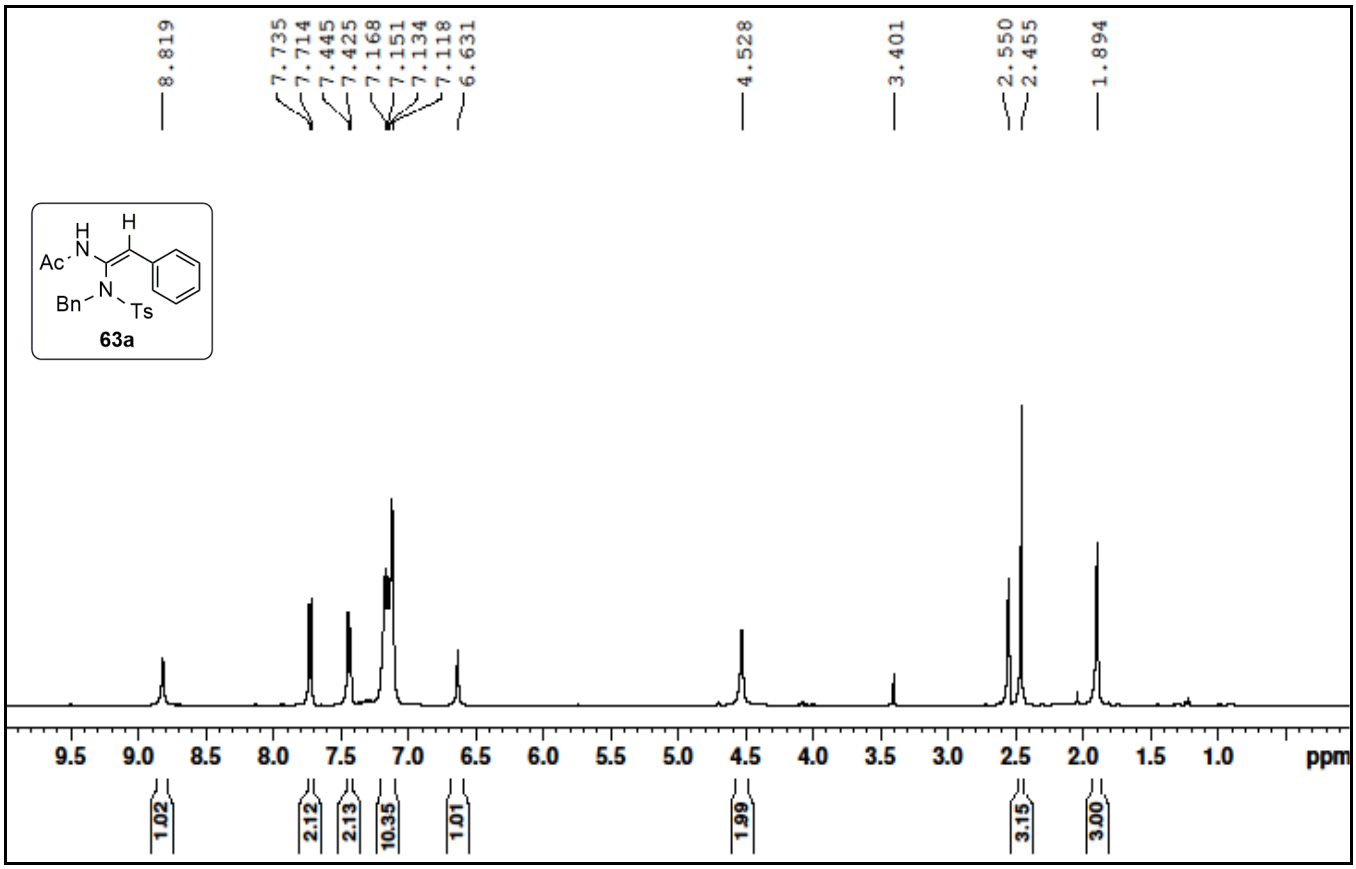
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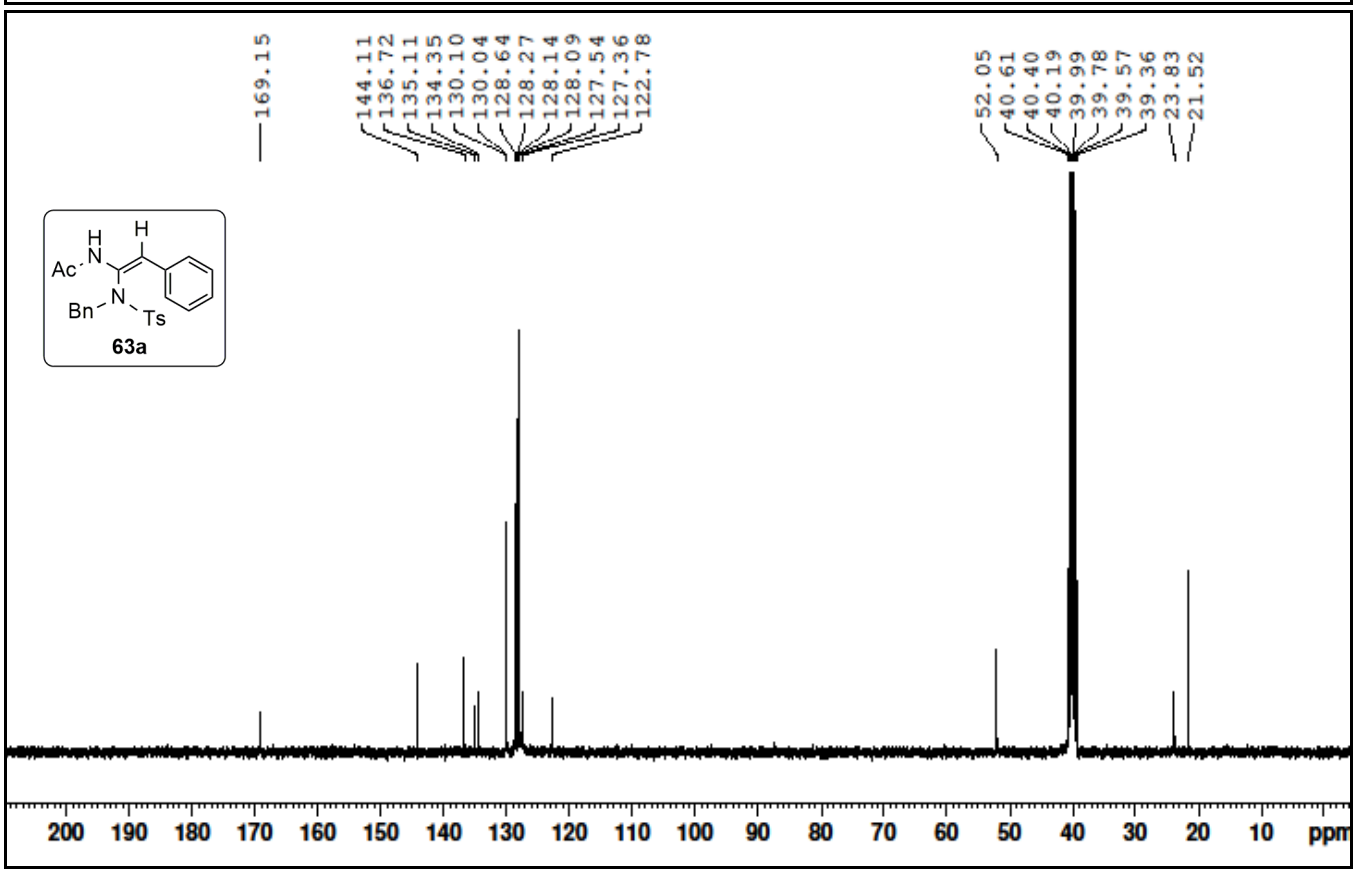
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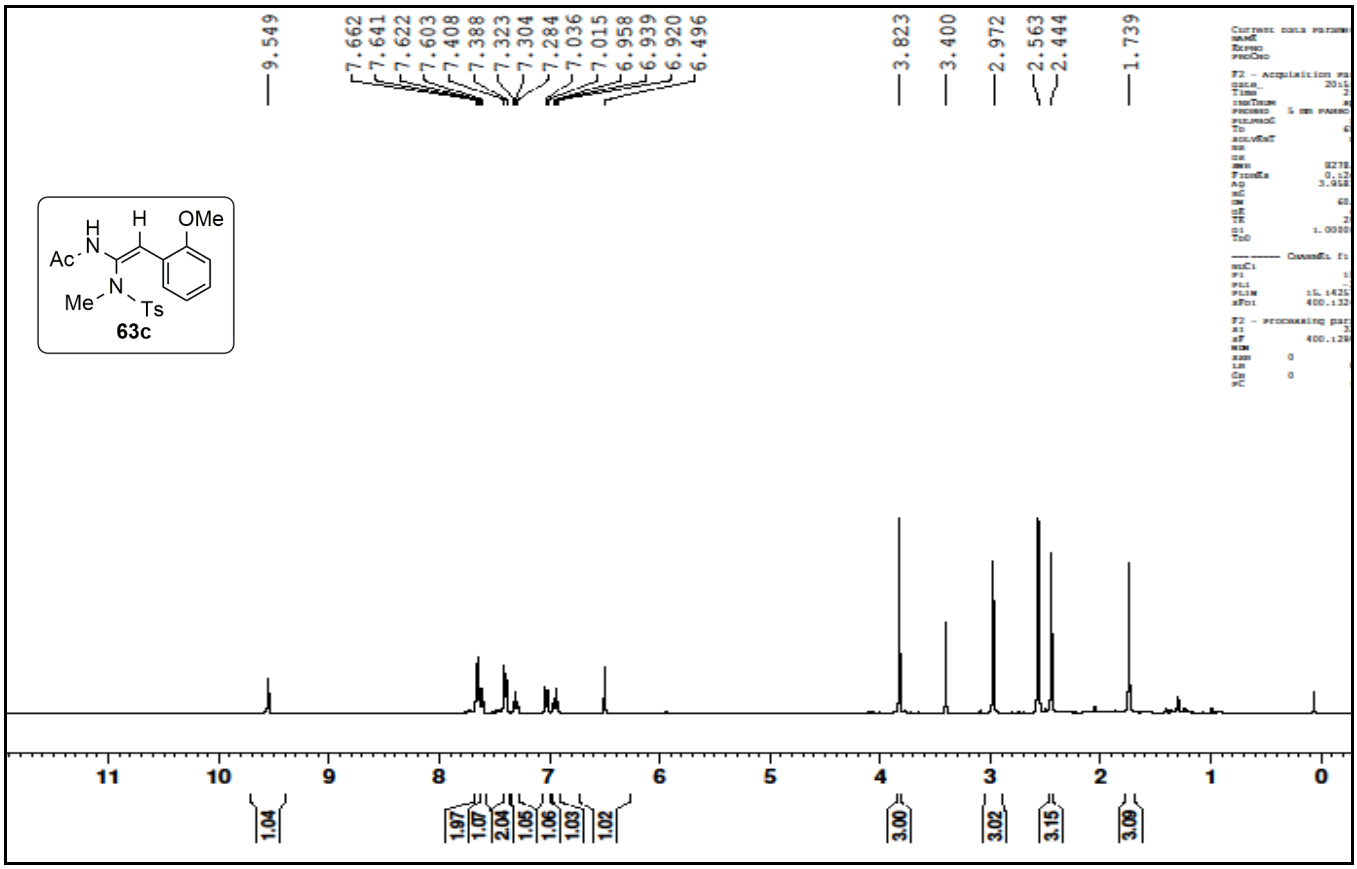
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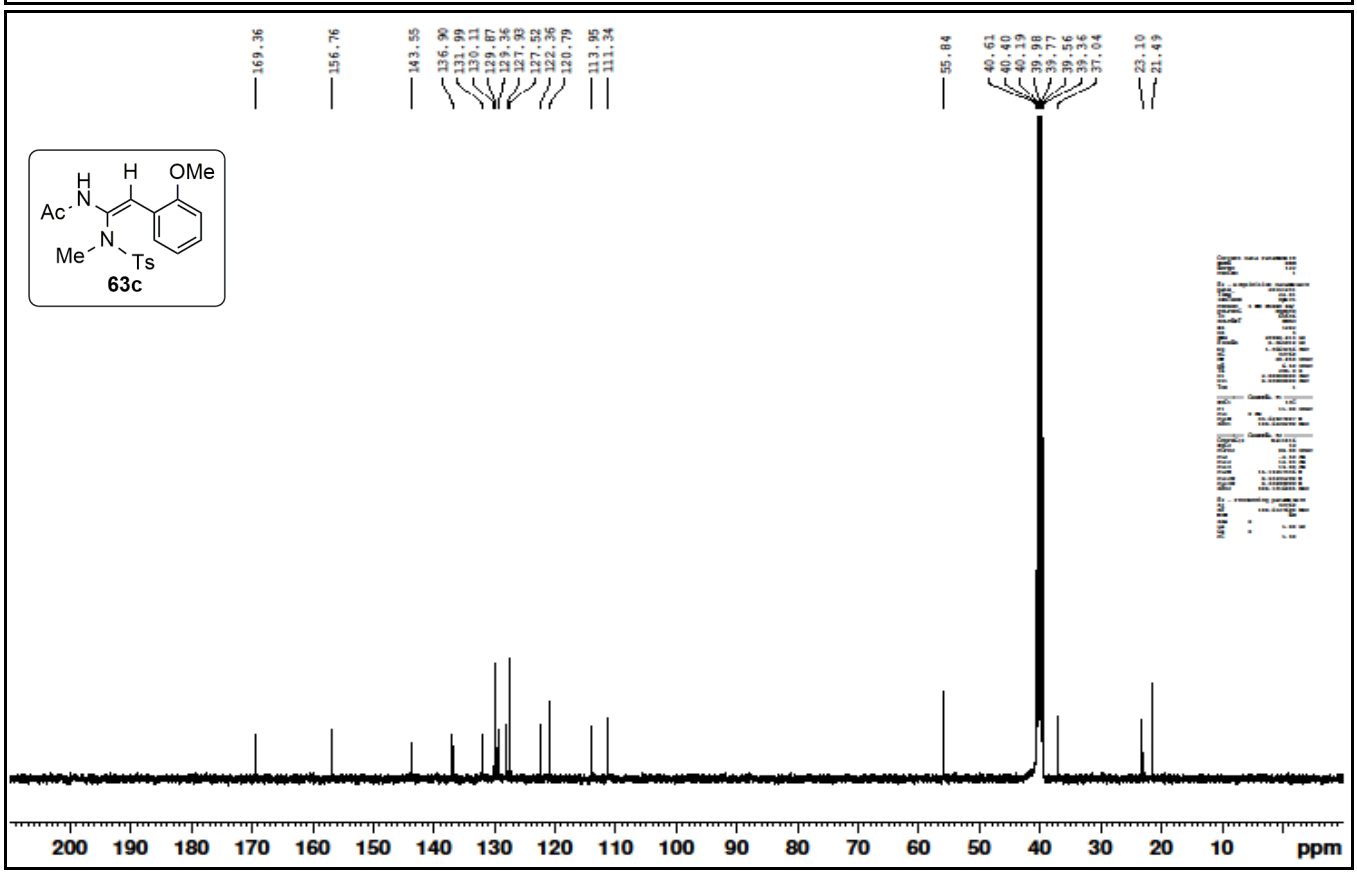
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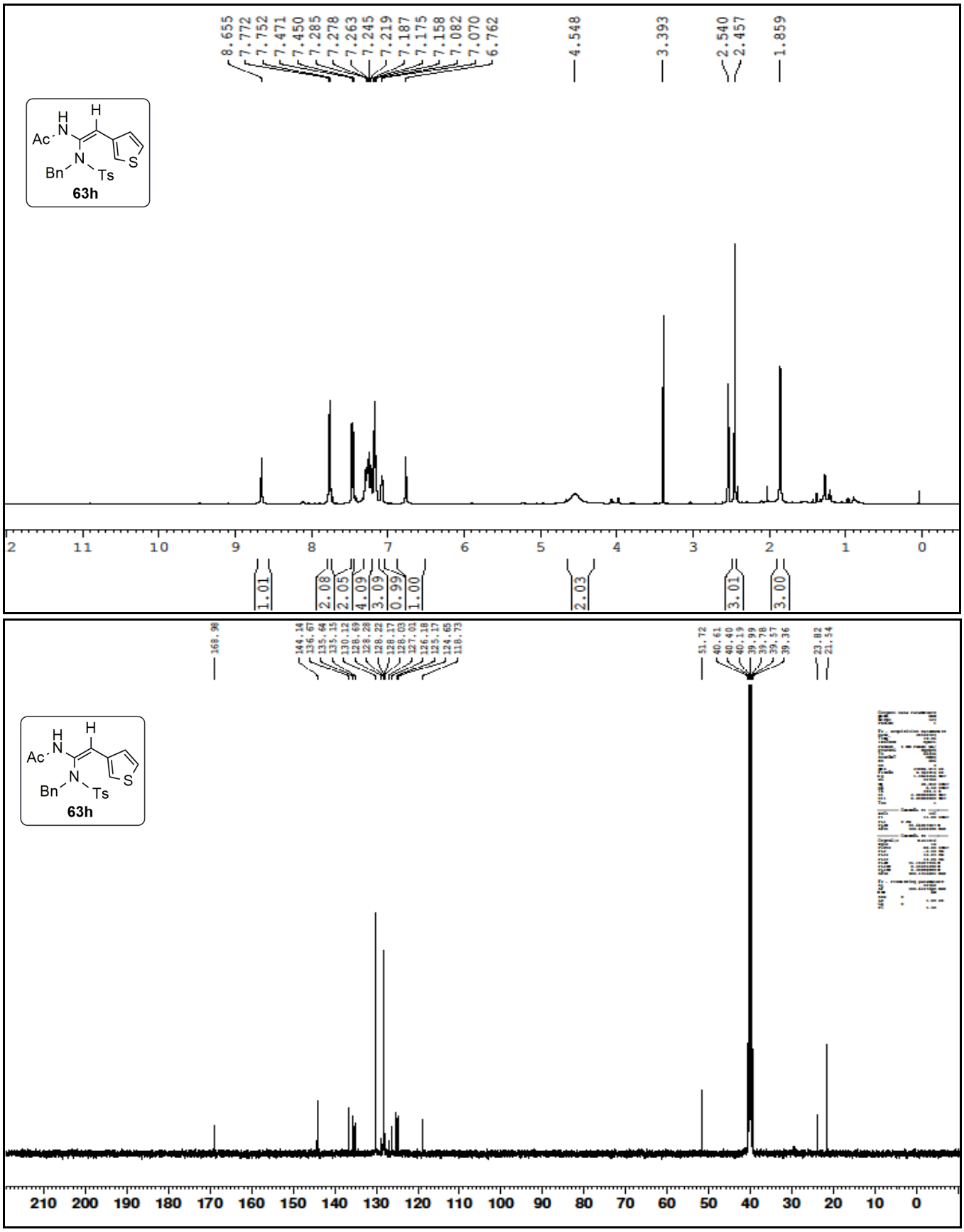
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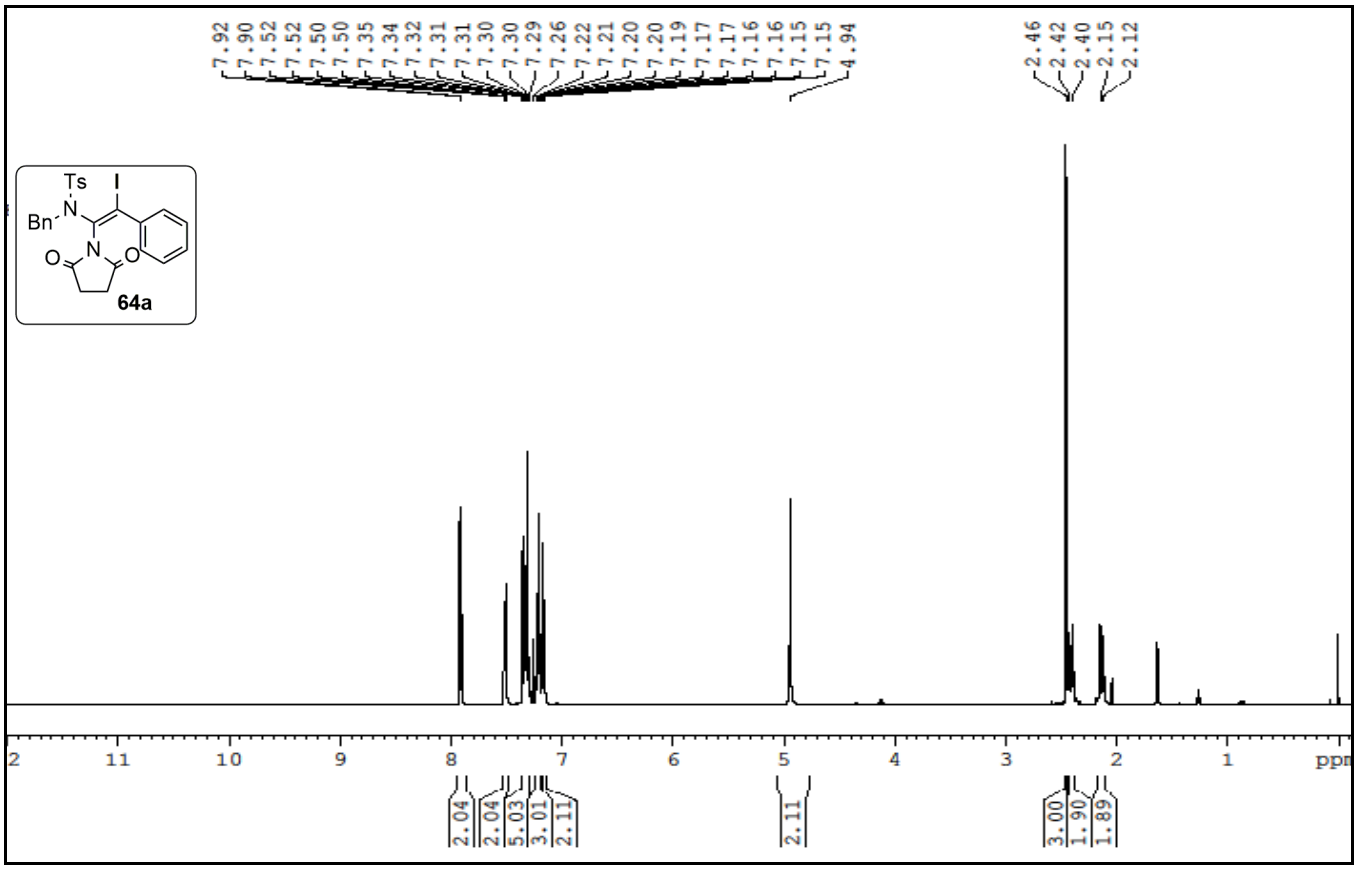
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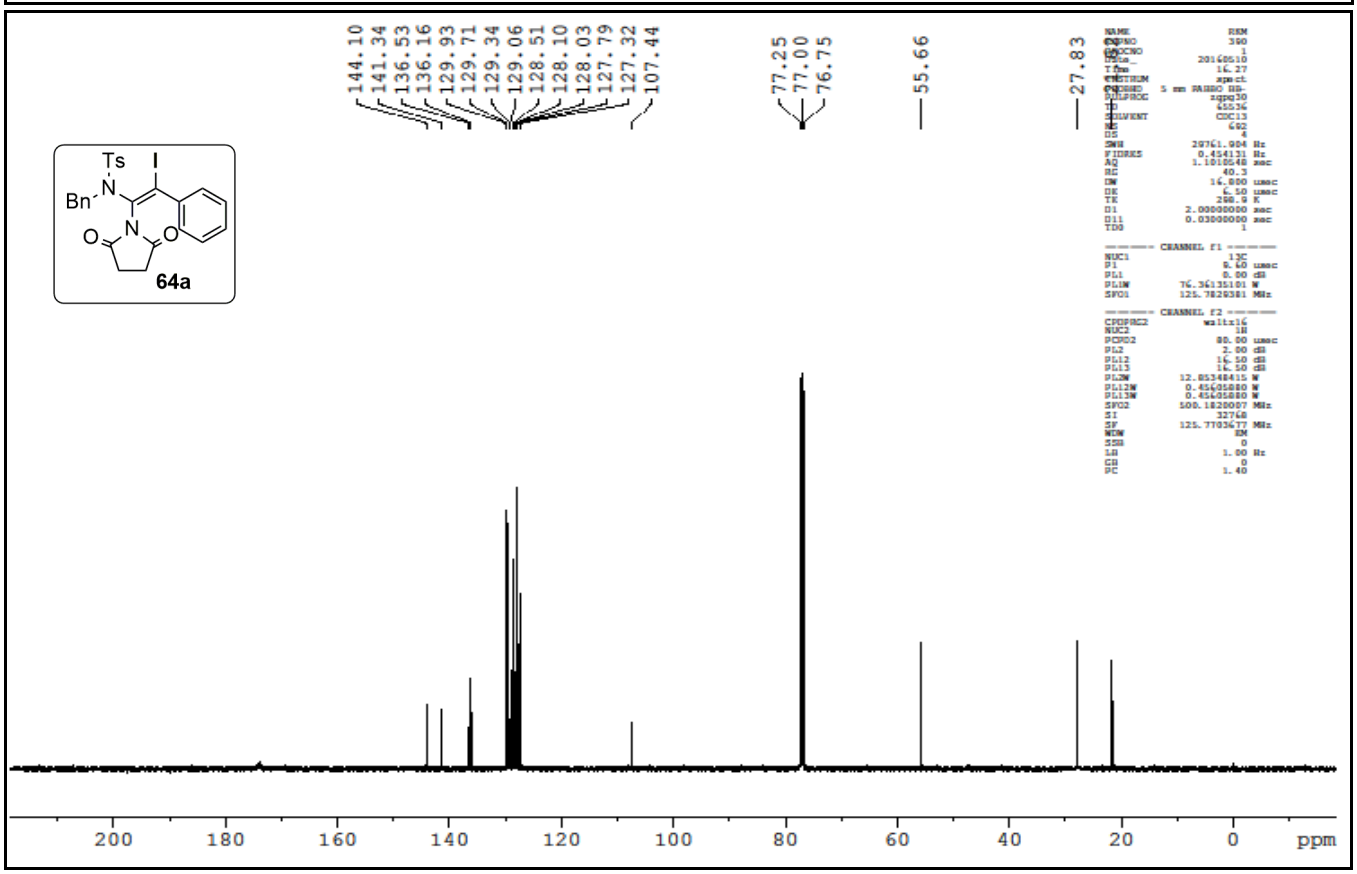
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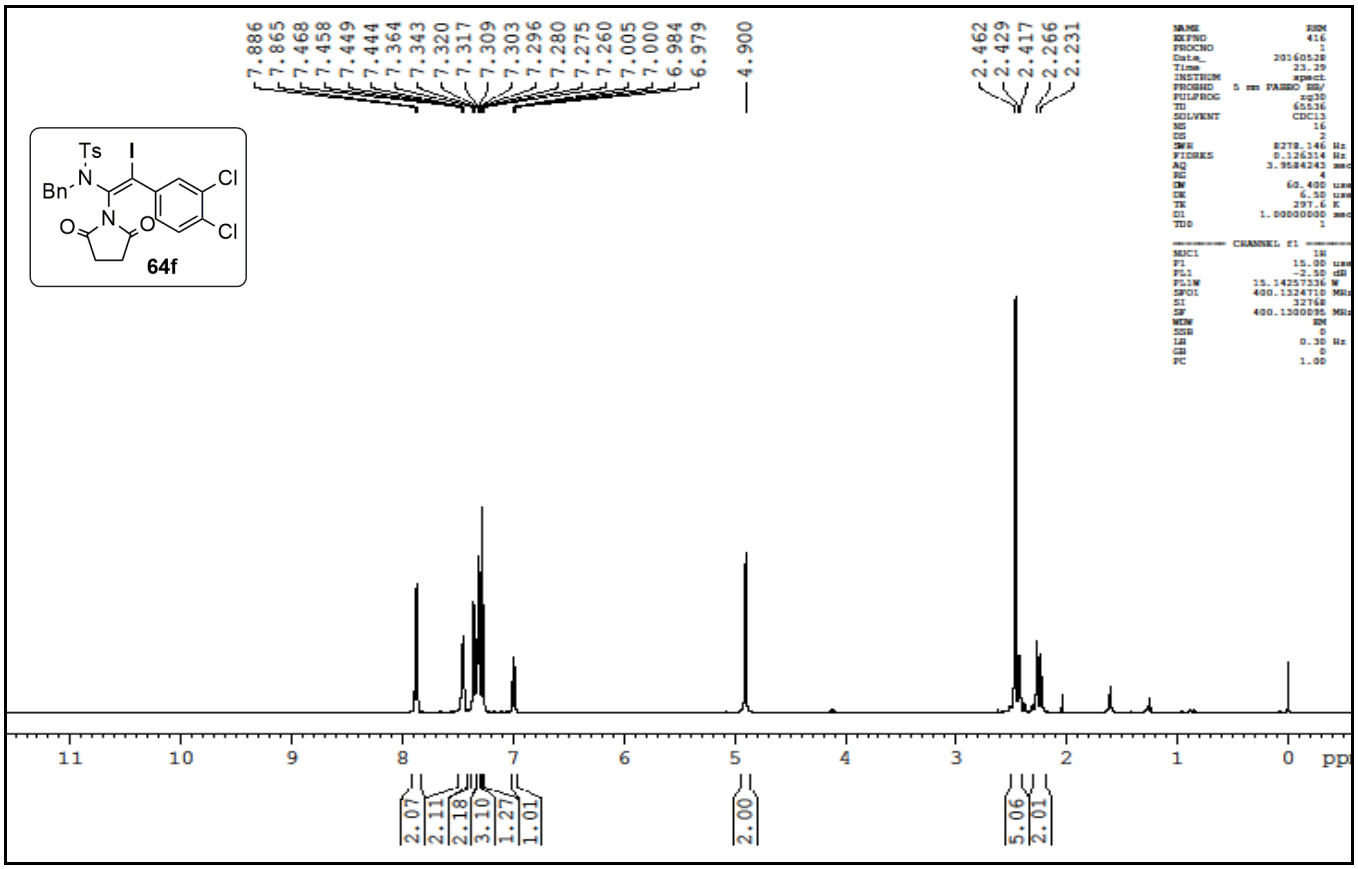
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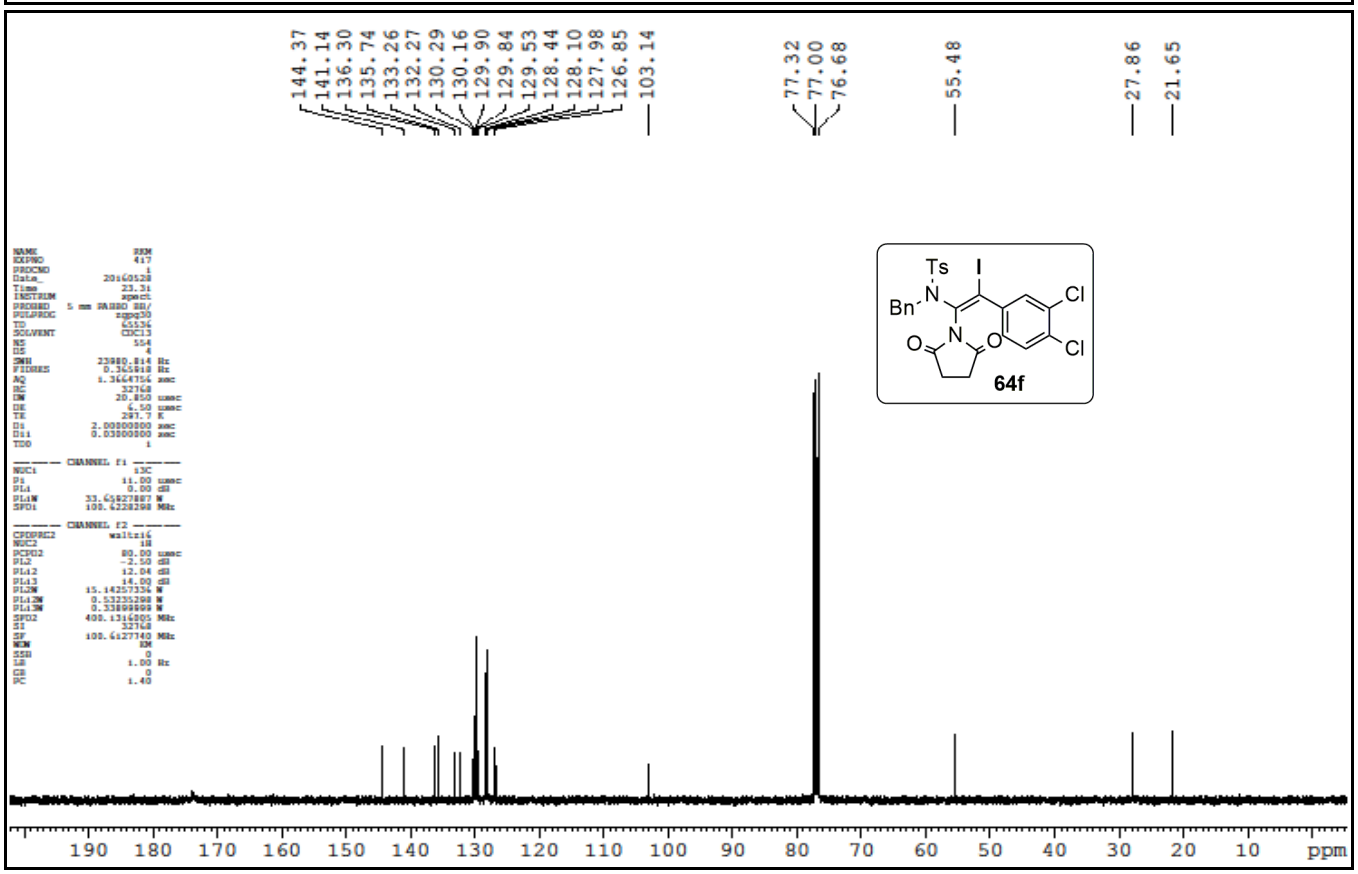
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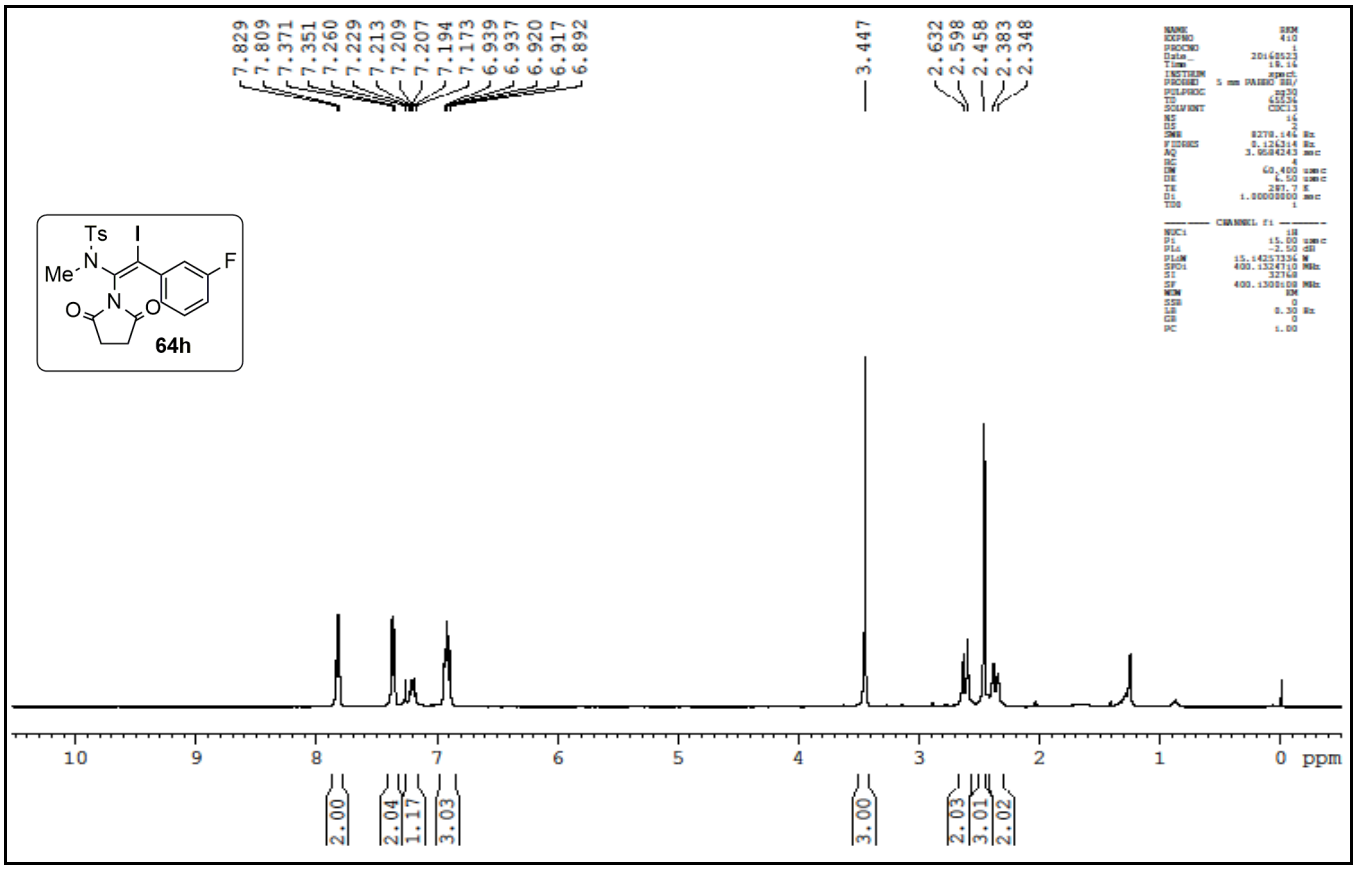
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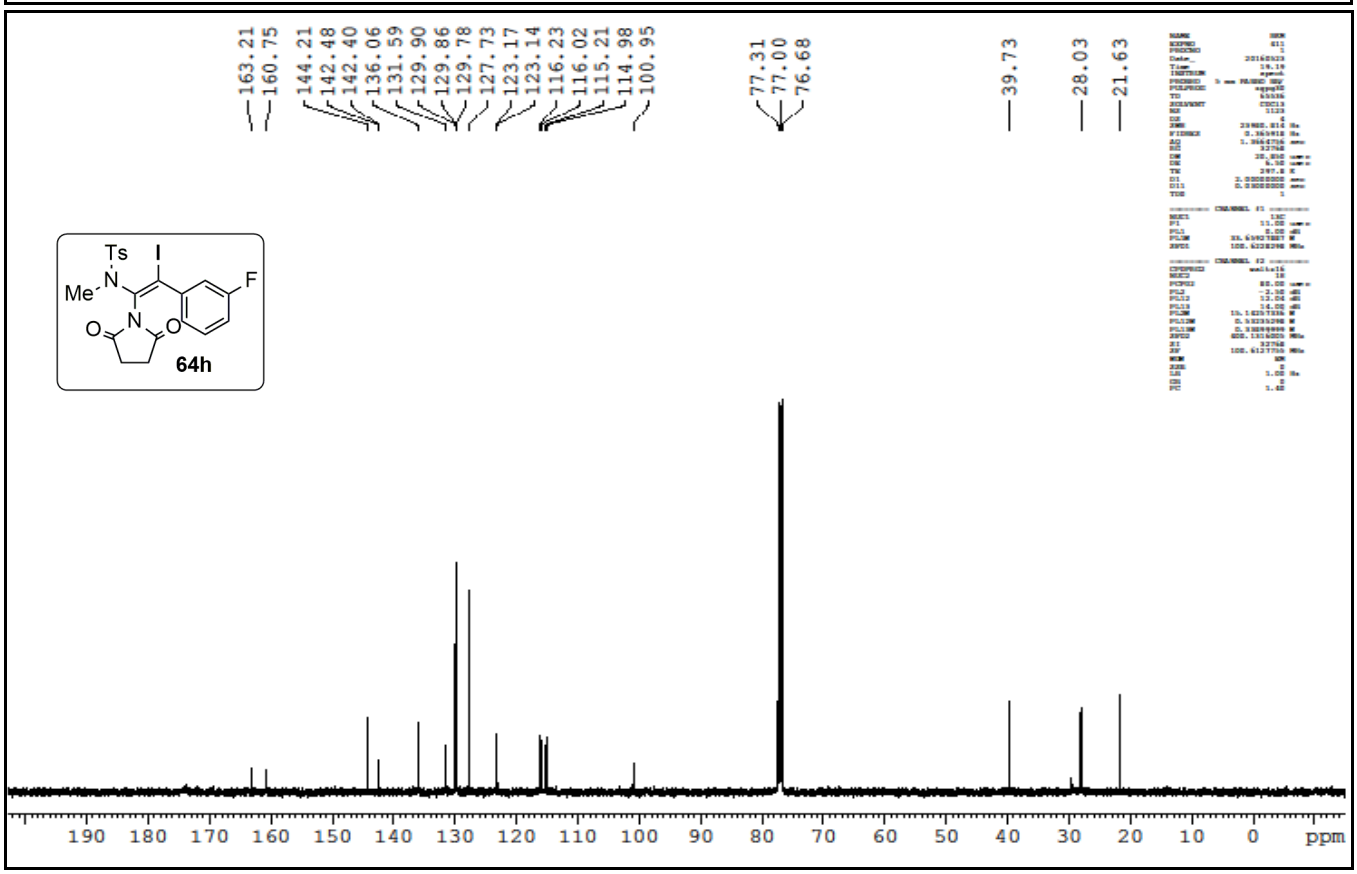
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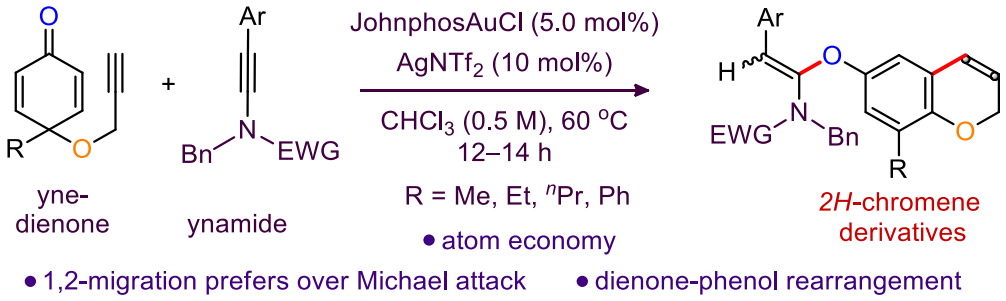
Chapter-3

Access to 2*H*-Chromenes via Gold-Catalyzed and Keteniminium Induced Dienone-Phenol Rearrangement of Yne-Dienone

Abstract



A gold catalyzed keteniminium induced 1,2–migration/aromatization/pseudo-umpolung cyclization sequence of *O*–propargyl tethered 2,5-cyclohexadienone with ynamides for the synthesis of *2H*-chromene analogue is demonstrated. Deuterium scrambling study enables the intramolecular proton transfer to the vinylic gold species. The π–activation of alkyne by gold catalyst is further confirmed by D-labelling experiment and ^{1}H NMR analysis.

Reference:

Rajendra K. Mallick, Shubham Dutta, Manash P. Gogoi, and Akhila K. Sahoo* *(Manuscript to be Communicated)*

3.1. Introduction

The *2H*-chromene is an important structural entity that are widely present in various natural products,[1] medicines, and materials displaying unique photophysical properties. Moreover, it exhibits a broad spectrum of biological activities like; antioxidant, anti-inflammatory, anticancer, antitubercular, antitumor, antiviral, antibacterial/ antimicrobial, anticoagulant, antidiabetic, diuretic, fungicidal, and anti-HIV activity, etc (**Figure 3.1**). In addition, other *2H*-chromene derivatives act as sex-pheromones, potassium channel activators, or inhibitor for the enzyme's phosphodiesterase IV and dihydrofolate reductase.[2] The diverse array of biological activities of *2H*-chromene derivatives and the structural importance of benzopyran moiety has provoked a great deal of interest in the field of organic synthesis and chemical biology to develop new and improved synthesis of these molecular skeletons.

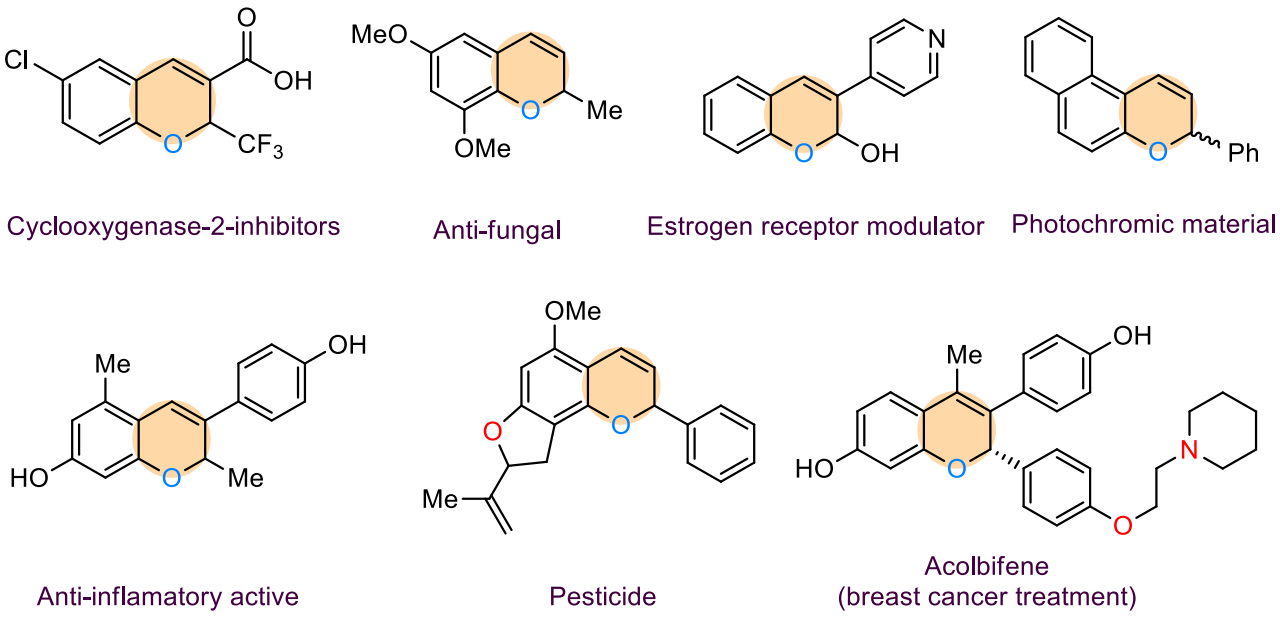


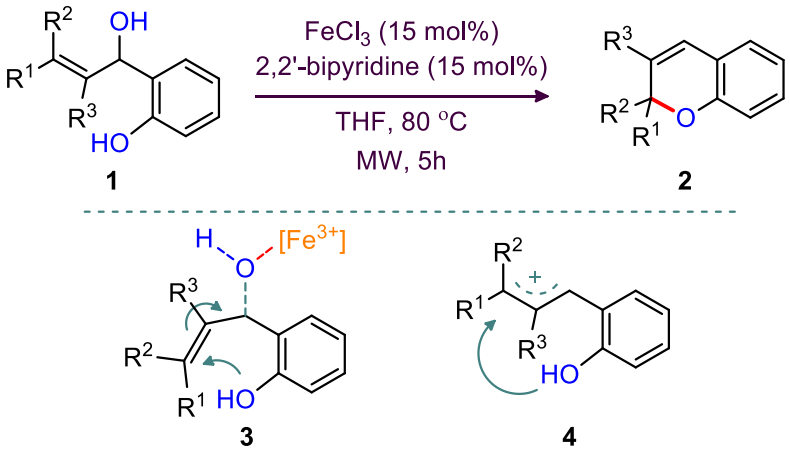
Figure 3.1. *2H*-Chromene containing bioactive molecules

3.2. Precedents

Keeping the importance and biological activity of *2H*-chromene skeleton in mind, many novel methods for the synthesis of benzopyran analogues have been developed. Enumerated herein some of the specific contributions for the synthesis of benzopyran analogues (**Scheme 3.1**–**3.9**).

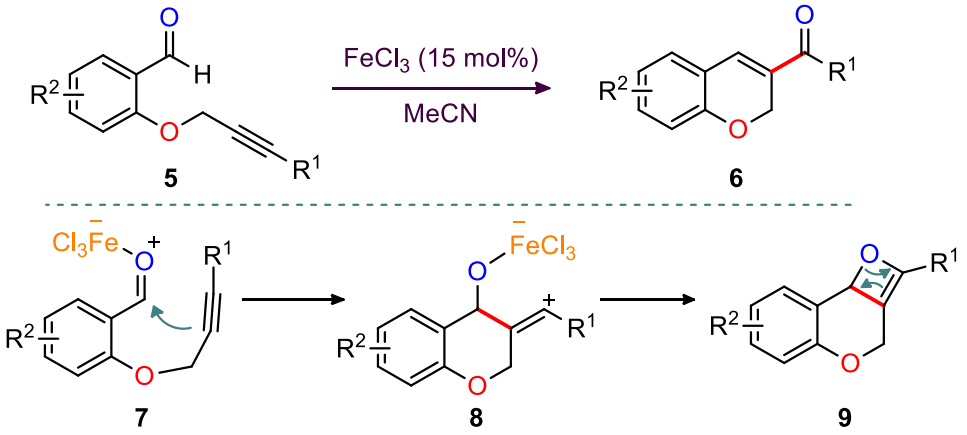
3.2.1. Lewis acid mediated synthesis of *2H*-chromenes

Cossy and co-workers developed a 2,2′ bipyridine ligated Fe^{III}-catalyzed cyclization of allylic alcohol tethered phenol **1** to construct *2H*-chromene derivatives **2**; the reaction was facile under microwave (**Scheme 3.1**).[3] The electron rich phenol derivatives reacted smoothly at room temperature. This method is successfully applied for the synthesis of tephrowatsin B analogue. The Lewis acid ($FeCl_3$) promotes the elimination of –OH group from **3** to form **4**. Finally, a nucleophilic attack of –OH group at the allylic cation of **Int-4** provides the desired product **2**.



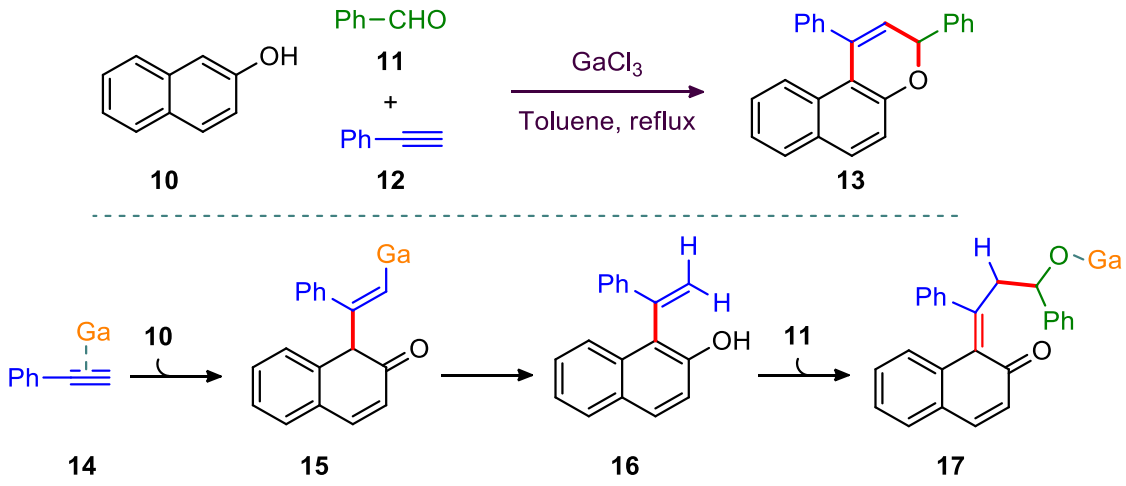
Scheme 3.1. Fe^{III}-catalyzed allylic cyclization

Jana et al. shown a mild method for the construction of *2H*-chromene **6** via $FeCl_3$ catalyzed alkyne-carbonyl metathesis of alkynyl ether of salicylaldehyde **5** (**Scheme 3.2**).[4] The reaction involves intramolecular [2+2] cycloaddition of carbonyl and alkyne of **5** in presence of Lewis acid ($FeCl_3$) to produce 4-membered cyclobutene intermediate **9**. Finally, electrocyclic ring opening of intermediate **9** gives the desired product **6**.



Scheme 3.2. Fe-catalyzed intramolecular aldehyde-alkyne metathesis

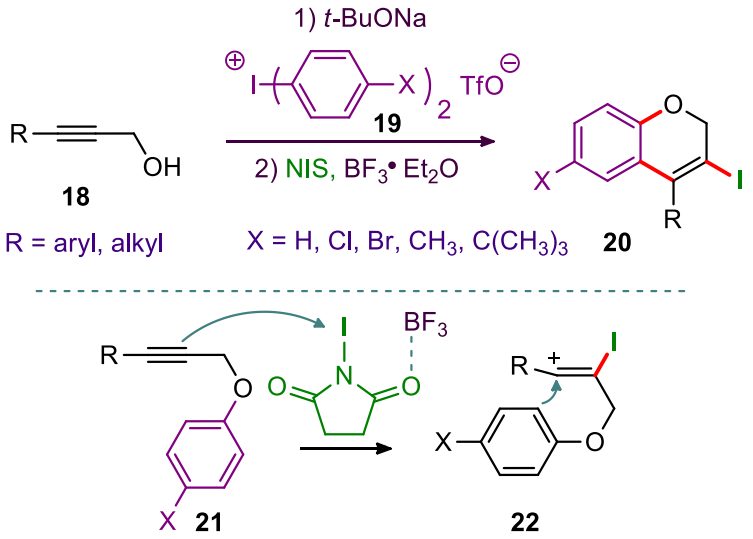
Yadav group reported a Ga(III)-catalyzed multicomponent coupling of napthol **10**, aldehyde **11** and alkyne **12** to deliver 1,3-disubstituted-*3H*-benzo[*f*] chromene derivatives **13** (**Scheme 3.3**).[5] The reaction begins with the attack of C-nucleophile of napthol **10** to the activated alkyne **14** to generate vinylic metal intermediate **15**. Next, aromatization/protodemetallation sequence of **15** leads to **16**. Finally, attack of **16** to aldehyde **11** gives **17**; finally, intramolecular cyclization of **17** provides the desired product **13**.



Scheme 3.3. Gallium(III) chloride-catalyzed three-component coupling reaction

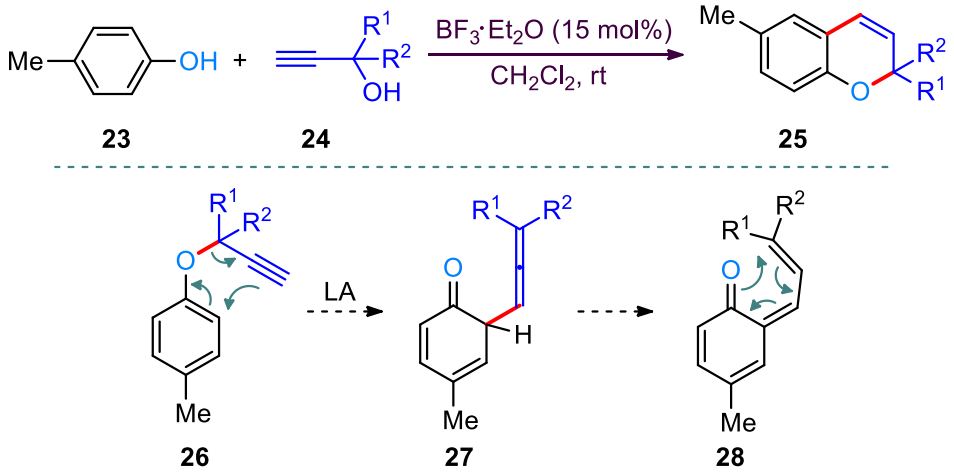
Togo and co-workers developed a one pot transformation of 3-aryl-2-propyn-1-ols/3-alkyl-2-propyn-1-ols **18** to 3-iodo-*2H*-benzopyrans **20** in presence of diaryliodonium

triflate **19** (**Scheme 3.4**).[6] The transformation initiates with the formation of O-aryl propargyl alcohol **21** from diaryliodonium triflate **19** and propargyl alcohol derivatives **18.** Next, alkyne activation of **21** by NIS produces the intermediate **22**, which subsequently undergoes *endo*-cyclization to deliver the desired iodoarylation product **20**.



Scheme 3.4. Lewis acid promoted iodocyclization reaction

In 2012, Madabhusi et al. reported a Lewis acid mediated synthesis of 2,2-disubstituted *2H*-chromene **25** from phenol **23** and 1,1-disubstituted propargyl alcohol **24** at room

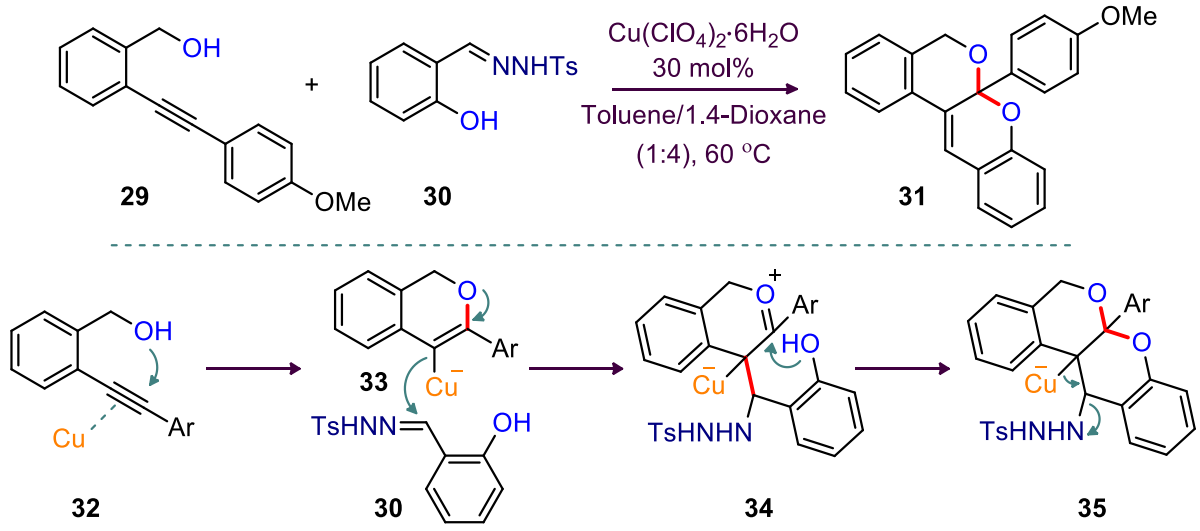


Scheme 3.5. Lewis acid mediated synthesis of 2,2-disubstituted *2H*-chromene

temperature (**Scheme 3.5**).[7] The reaction begins with the formation aryl-propargyl ether **26** from **23** and **24**. Next, Lewis acid mediated dearomative rearrangement to allene intermediate **27** followed by aromatization and 1,5-hydride shift sequence to give intermediate **28**. Finally, cyclization of **28** delivers the respective product **25**.

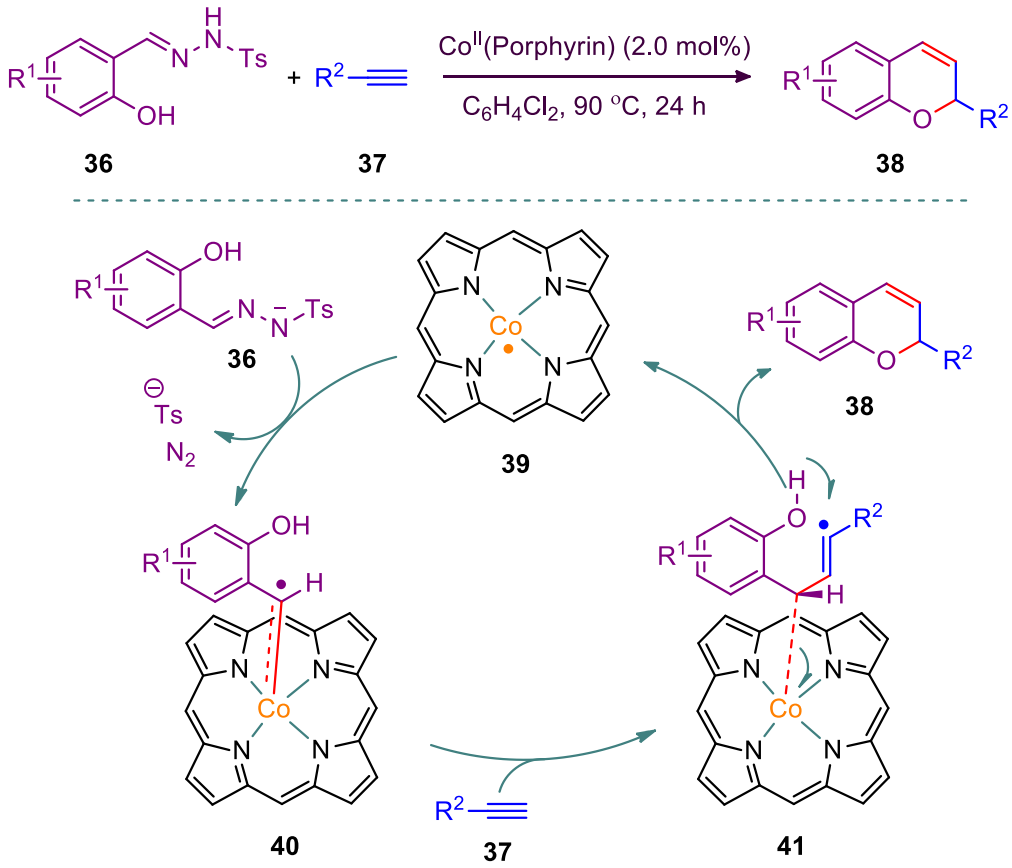
3.2.2. Metal/π-acid catalyzed synthesis of 2*H*-chromenes

Liu and co-workers showcased a novel method for the construction of isochromeno[3,4-b]chromene **31** from the reaction of internal alkynol **29** and salicyl N-tosylhydrazone **30** in presence of copper catalyst (**Scheme 3.6**).[8] The reaction involves cycloisomerization of alkynol **32** followed by formal [4+2] cycloaddition with N-tosylhydrazone **30** and finally elimination of copper catalyst and tosyl-hydrazine from **35** provides **31**.



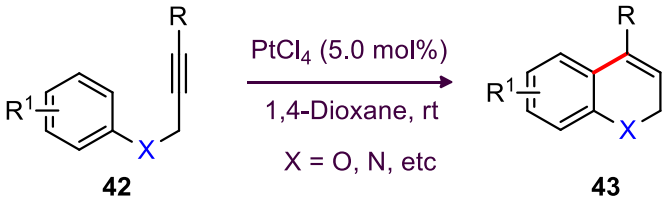
Scheme 3.6. Tandem reaction of internal alkynol and salicyl N-tosylhydrazone

Bruin and co-workers demonstrated a novel protocol for the construction of 2*H*-chromene **38** via Co^{II}(porphyrin) catalyzed metalloradical approach (**Scheme 3.7**).[9] Cobalt(III)-carbene radicals **40**, generated via metalloradical activation of **36** by cobalt(II) porphyrin complex **39**, readily undergo radical addition to alkyne **37** and provides salicyl vinyl radical intermediate **41**. Successively, the hydrogen atom transfer (HAT) from the salicyl moiety **41** to the vinyl radical leads to the desired product **38**.



Scheme 3.7. Metalloradical approach to *2H*-chromene

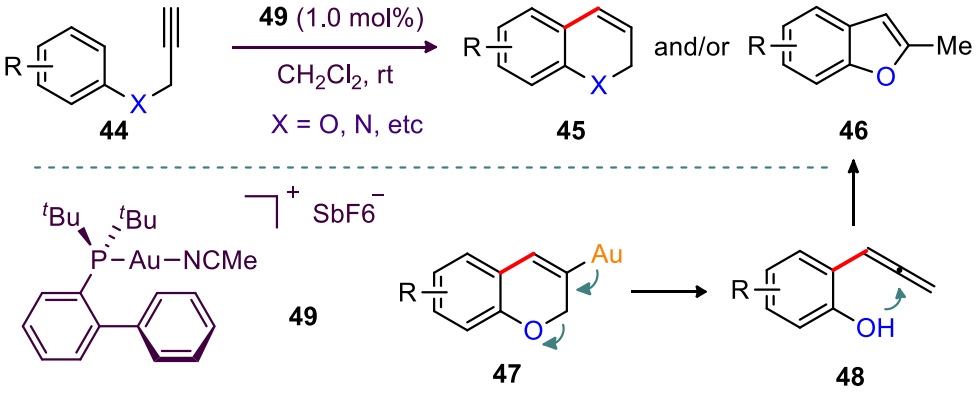
In 2003, Sames et. al. reported a platinum (IV) catalyzed hydroarylation of arene-yne species **42** comprising propargyl ethers, propargylamines, and alkynoate esters to provide 6-6-fused carbo(hetero)cycles **43** (example: chromenes, dihydroquinolines, and coumarins) in good to excellent yields (**Scheme 3.8**).[10] The reaction proceeds with the 6-*endo*-dig intramolecular attack of arene moiety to the platinum activated triple bond.



Scheme 3.8. Pt^{IV}-catalyzed intramolecular hydroarylation

Later in 2009, Banwell and co-workers demonstrated a mild and efficient method for gold(I)-catalyzed intramolecular hydroarylation of terminal alkyne **44** to construct

desired *2H*-chromenes, coumarins, benzofurans, and dihydroquinolines **45**/**46** (**Scheme 3.9**).[11] The formation of benzofuran **46** involves the cyclization of allenyl phenol **48**, which is generated in situ from vinylic gold species **47**.



Scheme 3.9. Au(I)-catalyzed intramolecular hydroarylation of terminal alkyne

3.3. Motivation and Scheme Design

The alkynyl-cyclohexadienone **50** is an important and versatile precursor in organic synthesis as these motifs are amenable for diverse reactions and applicable for the construction of novel structural entities.[12] Some significant transformations involve the nucleophile triggered and transition metal (TM)-catalyzed borylative/ silylative/ arylative/reductive/sulfonylative, and acetate triggered cyclization of yne-dienones **50** to construct [5,6]-fused (**51**) and/or [6,6]-fused (**52**) heterocycles (**Figure 3.2a**).[13,14] However, all these modes of cyclization (5-*exo*/6-*exo*) primarily involve the Michael attack of nucleophilic alkynes to the cyclohexadienone core; mostly, the products are non-aromatic (**Figure 3.2a**). In contrast, altering the reactivity of cyclohexadienone core of yne-dienone **50** towards pseudo-umpolung cyclization with pendant alkyne has remained poorly explored and remains challenging (**Figure 3.2b**).

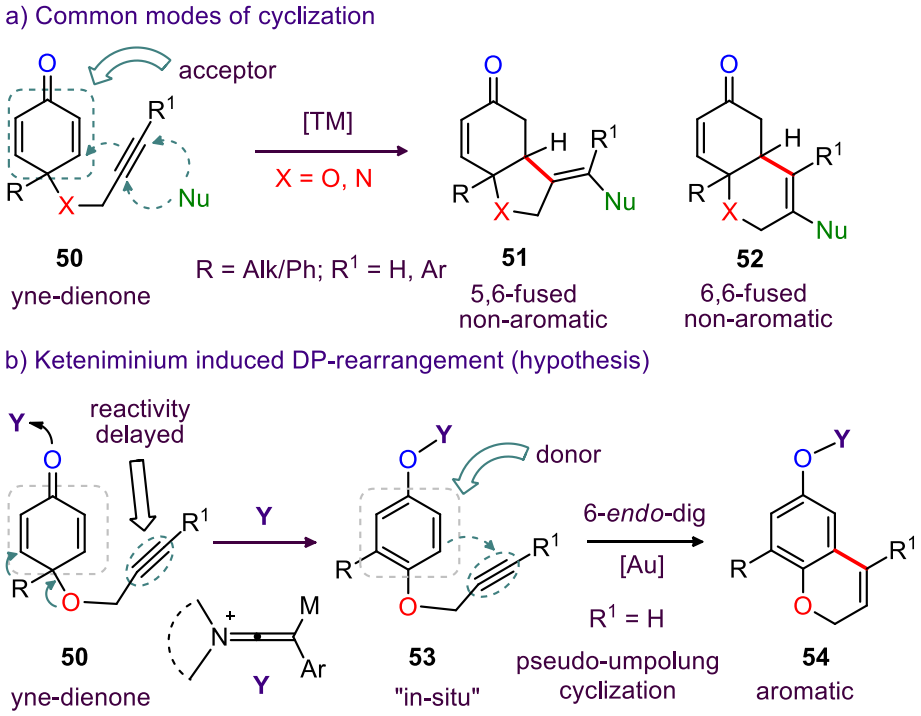


Figure 3.2. Hypothesis for keteniminium induced dienone-phenol rearrangement

Thus, looking into the importance and molecular diversities of cyclohexadienone backbone and our ongoing research in ynamide chemistry, we envisaged for a keteniminium (**Y**) induced dienone-phenol rearrangements of alkynyl cyclohexadienones **50**. This process could indeed generate a reactive alkynyl-phenol intermediate **53**. Finally, the gold-catayzed intramolecular 6-*endo*-dig cyclization of **53** led to *2H*-chromene derivatives **54** (**Figure 3.2b**). This can be viable provided the cyclohexadienone moiety being more reactive over the alkyne core. Consequently, electrophilic cyclization of arene to alkyne (pseudo-umpolung) is being realized (**Figure 3.2b**). To the best of our knowledge, such type of reverse mode of cyclization for the synthesis of *2H*-chromene from alkynyl cyclohexadienone **50** remians elusive.

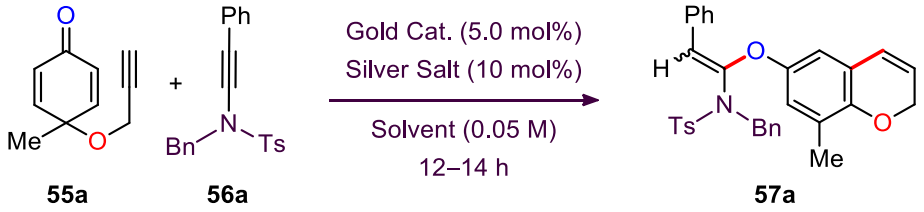
3.4. Result and Discussion

3.4.1. Reaction optimization

Inspired by the above mentioned plan in **Figure 3.2b**, the optimization study is initiated by reacting 4-methyl-4-(prop-2-yn-1- yloxy)cyclohexa-2,5-dienone **55a**

with N-tosyl/benzyl protected ynamide **56a** (**Table 3.1**). At the outset, alkynyl cyclohexadienone **55a** was reacted with ynamide **56a** in presence of XPhosAuNTf$_2$ catalyst in $CHCl_3$ at 60 ^oC for 12 hours; disappointingly the desired *2H*-chromene **57a** was obtained in <5% yield (entry 1, **Table 3.1**). Next, the catalytic potential of different precatalyst like IPrAuNTf$_2$ and JohnPhosAuNTf$_2$ were tested. Likewise, the product **57a** was observed in poor yield (<5%-13%; entries 2 & 3). The use of Echavarren catalyst was not beneficial (entry 4, **Table 3.1**). Next, the reaction in combination of PPh_3AuCl (5.0 mol%) or JohnPhosAuCl (5.0 mol%) with halide scavenger AgNTf$_2$ (10 mol%) was probed. Surprisingly, the catalyst combination of JohnPhosAuCl (5.0 mol%) and AgNTf$_2$ (10 mol%) in $CHCl_3$ (0.05 M) at 60 ^oC for 12 hours delivered the product **57a** in 74% yield (entry 6, **Table 3.1**); whereas PPh_3AuCl was not effective (entry 5). To examine the counter anion effect of silver salts, various $AgSbF_6$, $AgBF_4$, and AgOTf were employed (entries 7-9). Disappointingly, a trace amount of product was detected (^1H NMR analysis of crude mixture). As expected, the reaction in absence of AgNTf$_2$ couldn't furnish the desired product **57a** (entry 10, **Table 3.1**). Similarly, no product was formed in the absence of gold catalyst (entry 11). Trace amount of product was detected when the reaction was conducted at room temperature instead of 60 ^oC (entry 12). The reaction at the elevated temperature 80 ^oC or 100 ^oC did not show any significant change (entry 13 & 14). As expected, treating the alkynyl cyclohexadienone **55a** without ynamide **56a** in presences of JohnPhosAuCl and AgNTf$_2$ didn't provide any cyclization product (entry 15). Other solvents like dichloromethane, 1,2-dichloroethane, and 1,4-dioxane were not suitable (entries 16–18, **Table 3.1**). From the above screening, the reaction of alkynyl cyclohexadienone **55a** (1.0 equiv), ynamide **56a** (1.2 equiv), JohnPhosAuCl (5.0 mol%), AgNTf$_2$ (10 mol%) in $CHCl_3$ (0.05 M) at 60 ^oC for 12 hours was found optimum (entry 6).

Table 3.1. Optimization of reaction conditions[a,b]



55a **56a** **57a**

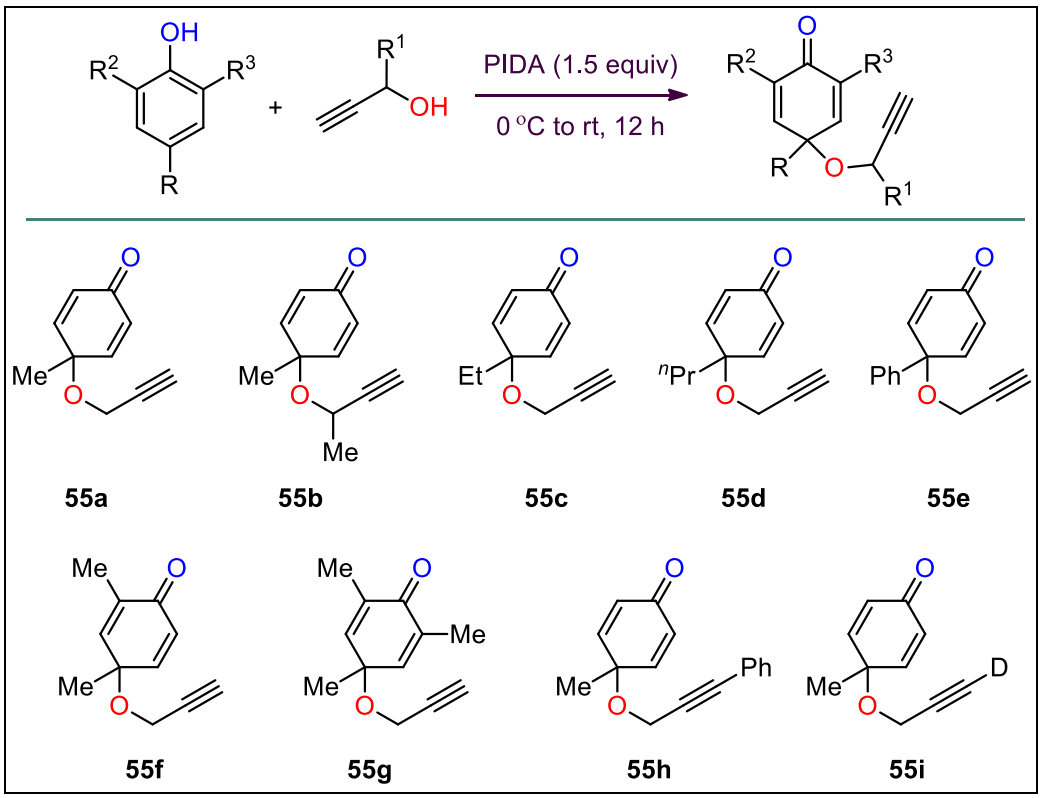
entry	catalyst (5.0 mol%)	additive (10 mol%)	temp(° C)	yield (%)
1	$XphosAuNTf_2$	-	60	<5
2	$IPrAuNTf_2$	-	60	<5
3	$JohnPhosAuNTf_2$	-	60	13
4	Echavarren Cat.	-	60	<5
5	Ph_3PAuCl	$AgNTf_2$	60	20
6[c]	JohnPhosAuCl	$AgNTf_2$	60	74
7	JohnPhosAuCl	$AgSbF_6$	60	trace
8	JohnPhosAuCl	$AgBF_4$	60	trace
9	JohnPhosAuCl	AgOTf	60	trace
10	JohnPhosAuCl	–	60	nr
11	–	$AgNTf_2$	60	nr
12	JohnPhosAuCl	$AgNTf_2$	RT	trace
13	JohnPhosAuCl	$AgNTf_2$	80	46
14	JohnPhosAuCl	$AgNTf_2$	100	trace
15[d]	JohnPhosAuCl	$AgNTf_2$	60	nr
16[e]	JohnPhosAuCl	$AgNTf_2$	60	15
17[f]	JohnPhosAuCl	$AgNTf_2$	60	18
18[g]	JohnPhosAuCl	$AgNTf_2$	60	10

[a]reaction condition: **55a** (0.1 mmol), **56a** (0.12 mmol), gold catalyst (5.0 mol%), silver additives (10 mol%), $CHCl_3$ (0.05 M) at 60 °C for 12 h; [b]crude NMR yield; [c]isolated yield; [d]without ynamide; [e]solvent $ClCH_2CH_2Cl$; [f]solvent CH_2Cl_2; [g]solvent 1,4-Dioxane [nr = no reaction].

3.4.2. Synthesis of precursors-I

Following the known hypervalent iodine mediated oxidative dearomatization procedure, alkynyl cyclohexadienones **55a**–**i** were synthesized from 4-substituted phenol and propargyl alcohol derivatives (**Table 3.2**). [15]

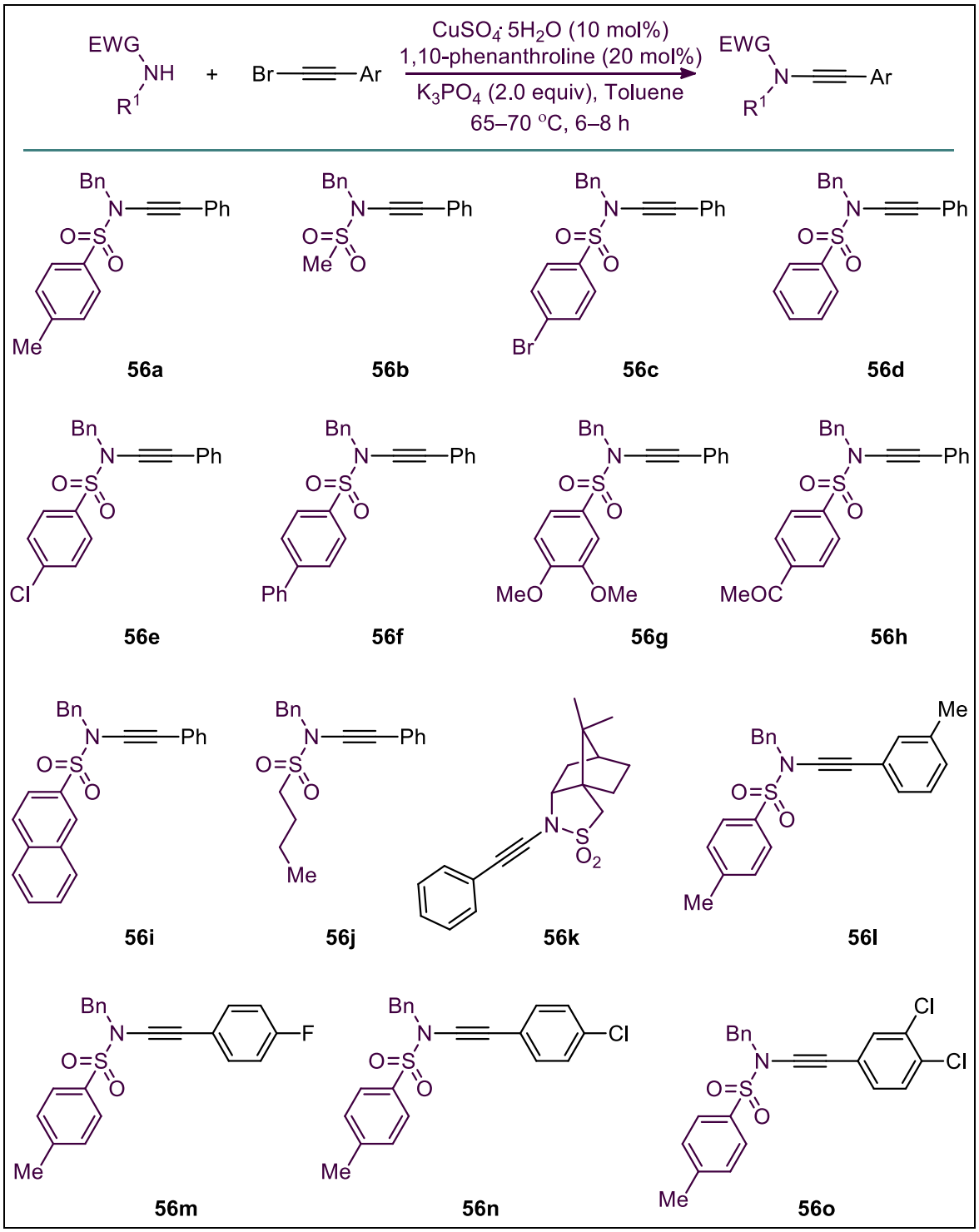
Table 3.2. Alkynyl cyclohexadienones: Chart-I



3.4.3. Synthesis of precursors-II

Following the known Cu-catalyzed C–N bond forming procedure, ynamides **56a**–**o** were synthesized from *N*-sulfonyl protected amides and 1-bromoalkynes (**Table 3.3**).[16,17]

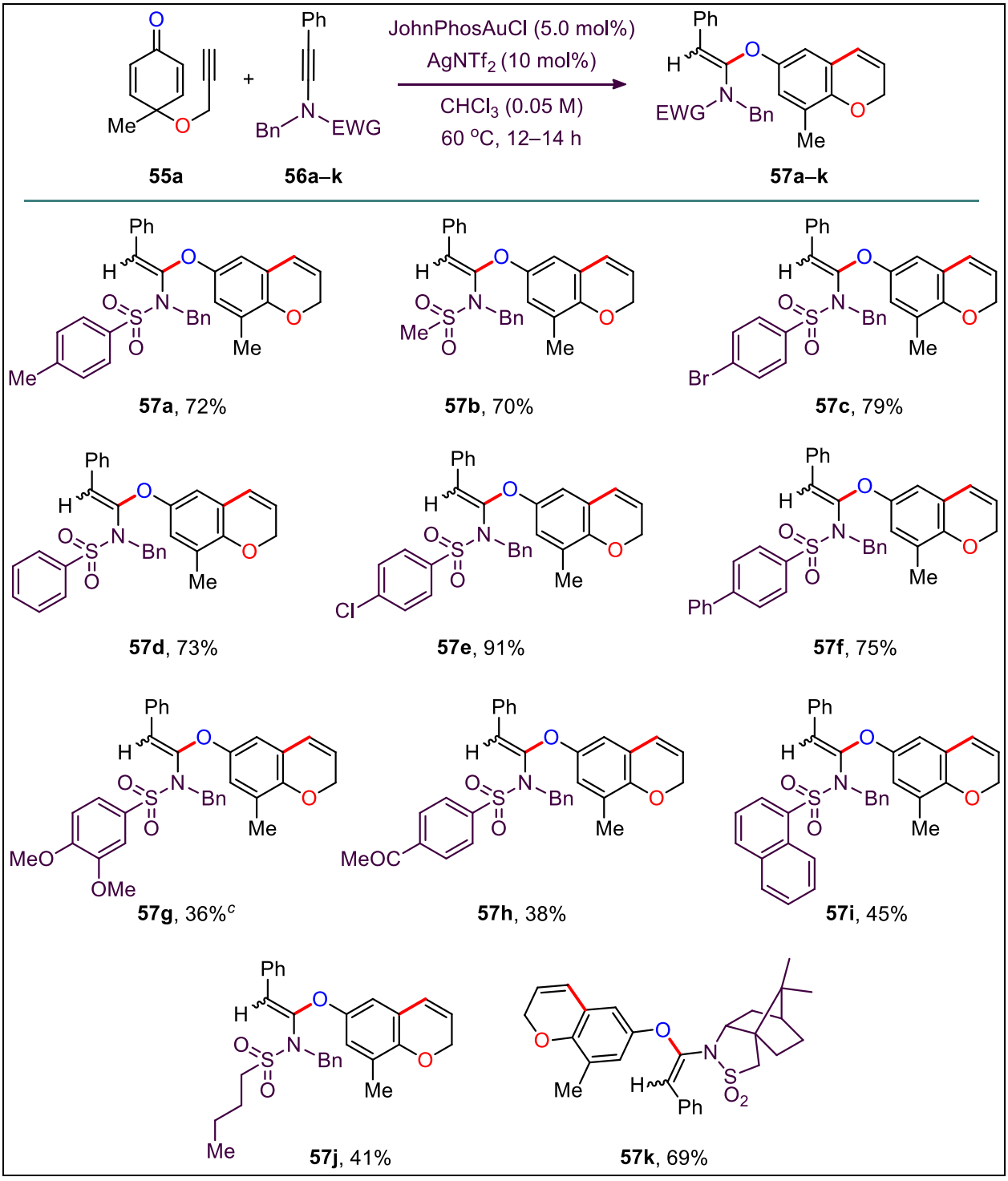
Table 3.3. Starting materials chart-II



3.4.4. Substrate scope-I

Next, the scope of *2H*-chromene derivatives was investigated by subjecting O-propargyl tethered cyclohexadienone **55a** with various ynamides **56** (having different electron withdrawing groups) under standard optimized conditions (**Table 3.4**). The most common *p*-toluenesulfonyl (Ts) protected ynamide **56a** delivered the desired product **57a** in 72% yield. The aliphatic methanesulfonyl (Ms) protected ynamide **56b** underwent migration/aromatization/cyclization cascade to form the product **57b** in 70% yield. Similarly, *p*-bromobenzenesulfonyl protected ynamide **56c** was successfully utilized for the cyclization reaction with the alkynyl cyclohexadienone **55a** to form **57c** in good yield. To our delight, electron neutral benzenesulfonyl ynamide **56d** also delivered the *2H*-chromene **57d** in 73% yield. Then *p*-chlorobenzenesulfonyl protected precursor **56e** successfully furnished the desired product **57e** in excellent yield. Pleasingly, the π-bond elongated biphenylsulfonyl protected ynamide **56f** under the optimized reaction conditions provided the chromene **57f** in 75% yield. Moreover, 3,4-dimethoxybenzenesulfonyl **56g** and 4-acetyl benzenesulfonyl **56h** protected ynamides delivered the desired product **57g** and **57h** albeit in poor yield. Polyaryl such as 2-napthalenesulfonyl protected ynamide **56i** also reacted with O-propargyl tethered cyclohexadienone **55a** to furnish the product **57i** (45%). Long chain aliphatic ^{n}butanesulfonyl protected ynamide **56j** successfully utilized for the cyclization reaction to deliver the desired product **57j** in 41% yield. The bicyclic camphorsultam ptotected ynamides **56k** provided the respective product **57k** in 69% yield.

Table 3.4. Variation of electron withdrawing groups[a,b]

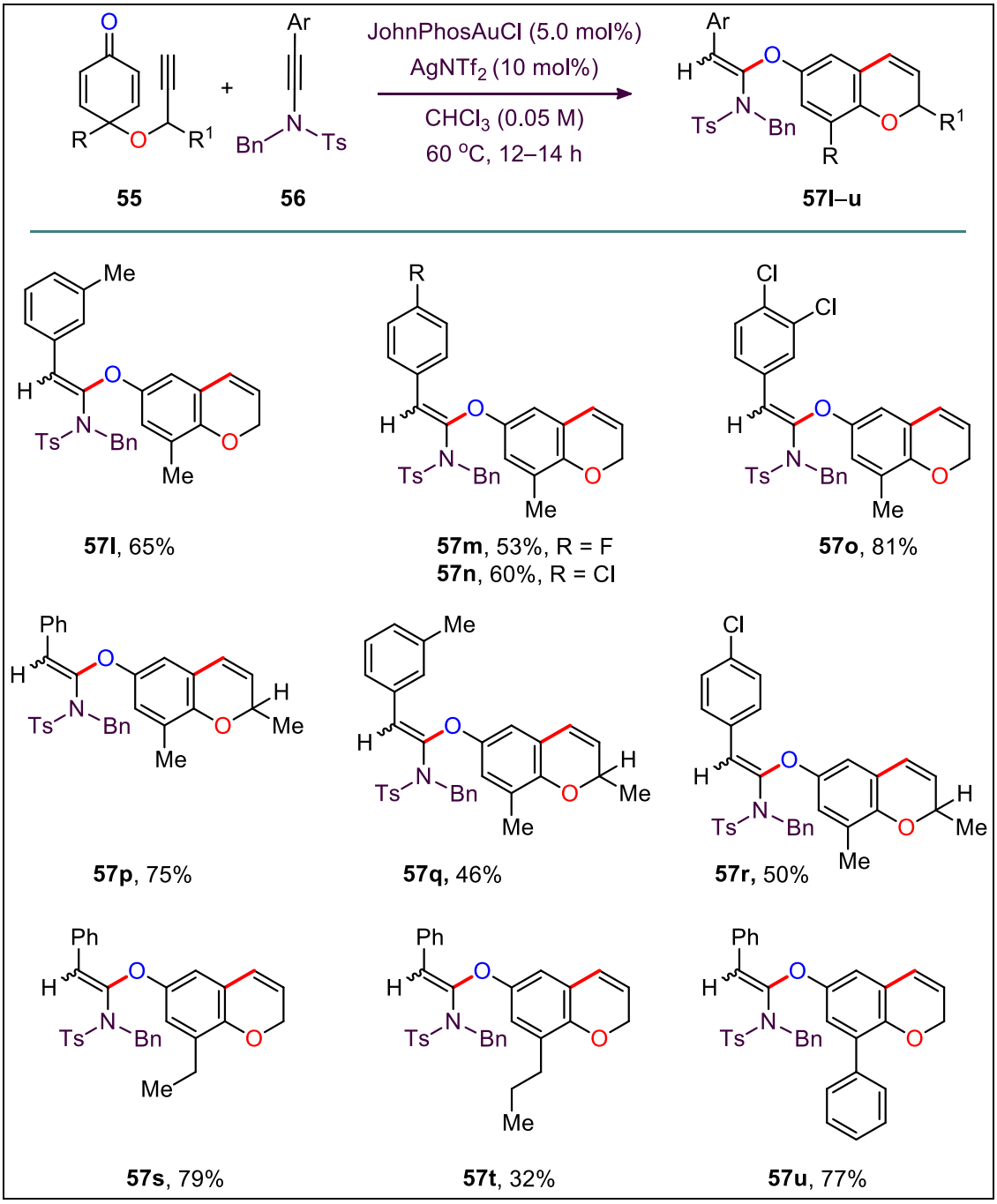


[a]**55a** (0.3 mmol), **56** (0.36 mmol), JohnphosAuCl (5.0 mol%), $AgNTf_2$ (10 mol%), $CHCl_3$ (6.0 mL) at 60 °C for 12–14 h; [b]Isolated yield; [c]Reaction was stirred for 36 hours.

3.4.5. Substrate scope-II

The electronic effect of different substituents on the alkyne terminus of ynamide was next tested (**Table 3.5**). The electron donating methyl group on the *meta*-position of arene ring in ynamide terminus underwent migration/aromatization/cyclization cascade to deliver the desired *2H*-chromene products **57l** in 65% yield. The *p*-F, *p*-Cl and *m*,*p*-diCl substituted ynamides (**56m**–**o**) successfully underwent the reactions under the standard reaction condition providing desired products **57m**–**o**; the labile halo groups are survived. Next, the cyclization of 4-(but-3-yn-2-yloxy)-4-methylcyclohexa-2,5-dienone **55b** with ynamides was probed; formation of a cyclization product with stereogenic cetre would provide opportunity in uncovering the stereoselective cyclization processes (**Table 3.5**). To our delight, simple tosyl-benzyl ynamides **56a** reacted successfully with alkynyl cyclohexadienone **55b** to deliver the desired product **57p** in 75% yield. Moreover, the *m*-Me and *p*-Cl containing ynamides (**56l** and **56n**) provided the desired product in moderate yield. Furthermore, the migrating aptitude of different groups (alkyl/phenyl) of the cyclohexadienone core was examined under the standard reaction condition (**Table 3.5**). Pleasingly, ethyl group on angular position of **55c** was successfully migrated and the product **57s** was accessed in 79% yield. Long chain aliphatic (^{n}Pr) group was also migrated furnishing **57t** albeit in poor yield. Migration of bulky phenyl group was fruitful to provide the desired product **57u** in 77% yield.

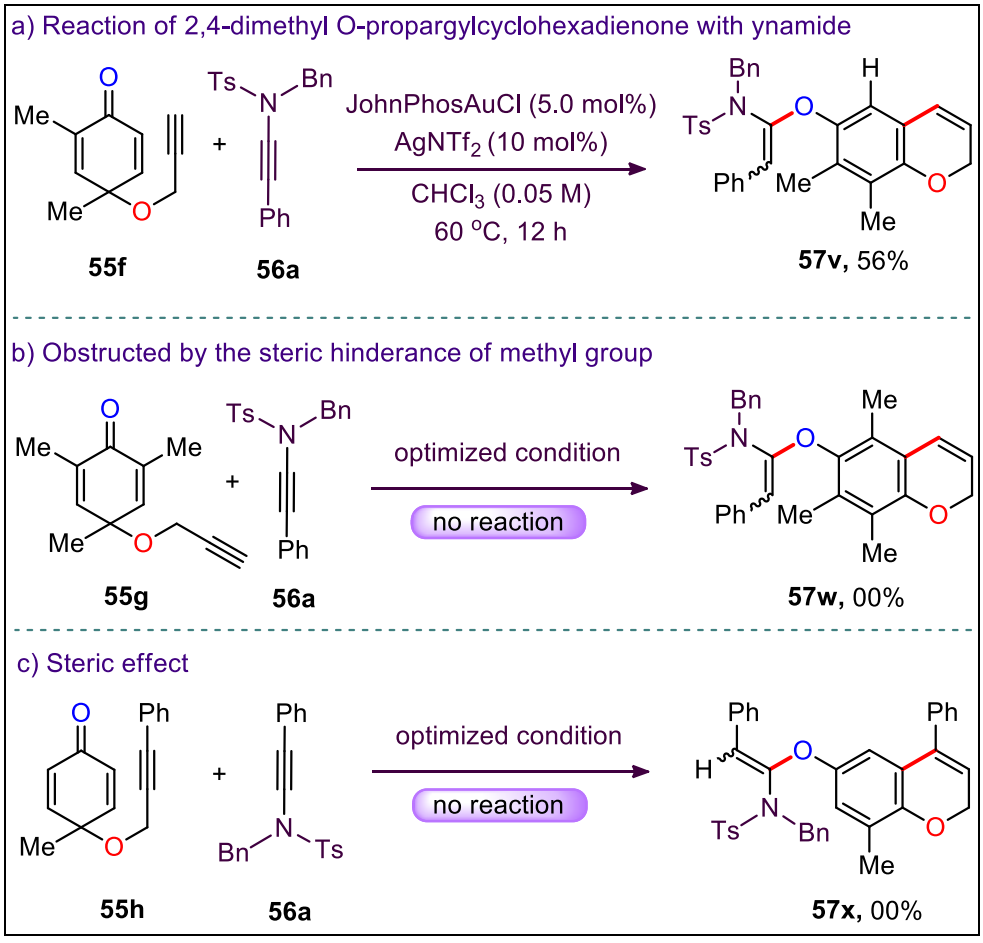
Table 3.5: Variation of both alkynyl-cyclohexadienone and ynamide[a,b]



[a]**55** (0.3 mmol), **56** (0.36 mmol), JohnphosAuCl (5.0 mol%), $AgNTf_2$ (10 mol%), $CHCl_3$ (6.0 mL) at 60 °C for 12–14h; [b]Isolated yield.

3.4.6. Control experiments

To gain insight into the mechanistic details of the current method, a series of reactions were planned under the standard optimized conditions (**Scheme 3.10**). When 2,4-dimethyl-4-(prop-2-yn-1-yloxy)cyclohexa-2,5-dienone (**55f)** and 2,4,6-trimethyl-4-(prop-2-yn-1-yloxy)cyclohexa-2,5-dienone (**55g)** were independently subjected with ynamide **56a** under the optimized conditions (**Scheme 3.10a** & **3.10b**); only 2,4-dimethyl substituted *2H*-chromene **57v** was formed in 56% yield whereas the reaction of 2,4,6-trimethyl substituted cyclohexadienone **55g** is failed; a consequence of steric hinderance of methyl group to the gold activated alkyne.

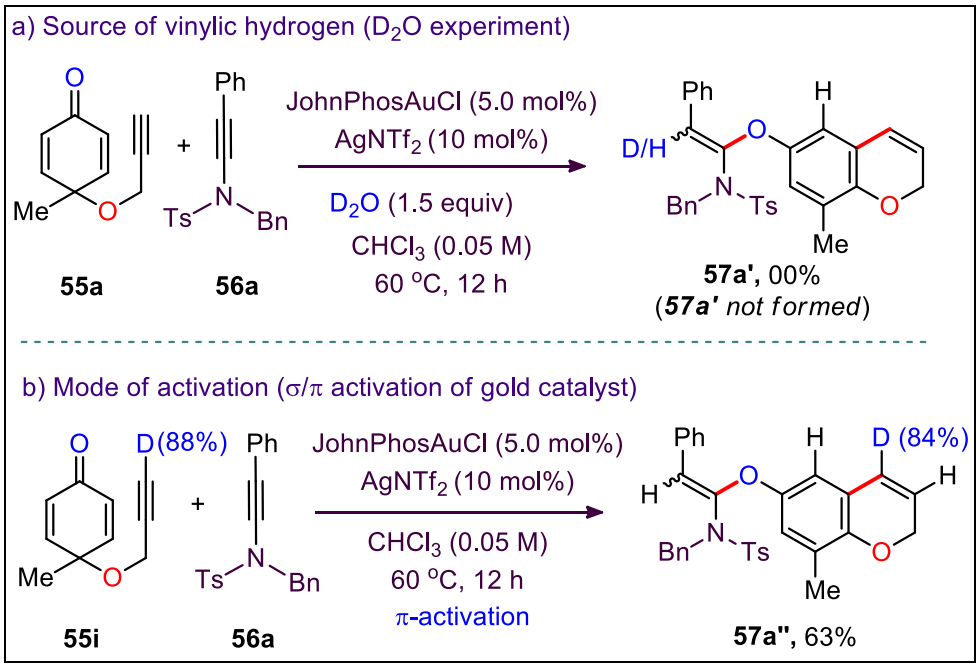


Scheme 3.10: Control experiments

No product **57x** was formed when the reaction was conducted in presence of internal alkyne **55h** instead of terminal alkyne **55a** (**Scheme 3.10c**); steric factor plays a vital role inhibiting the reaction outcome.

3.4.7. Isotope labelling experiments

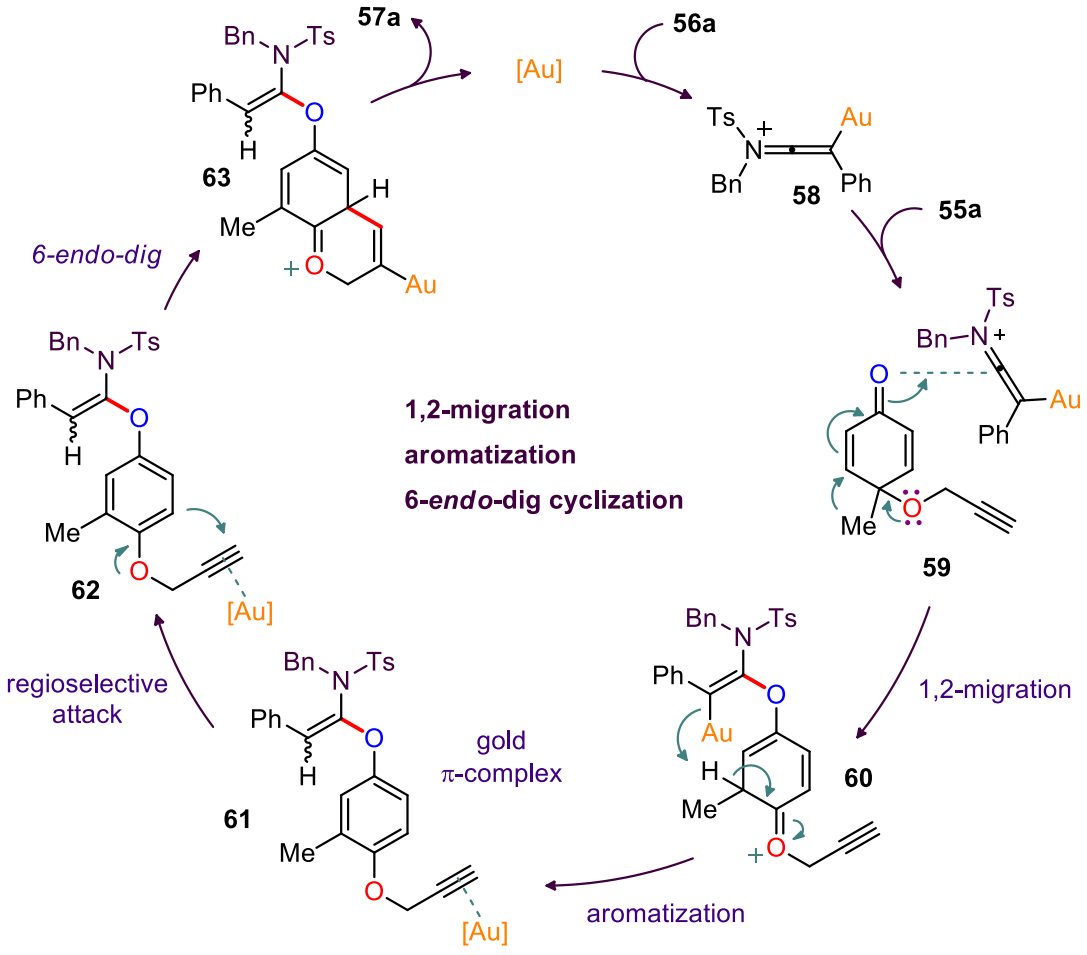
To further understand the mechanistic rationale, a set of isotopic labelling experiments has been carried out (**Scheme 3.11**). No formation of product **57a'** was observed, when the reaction was conducted between **55a** and ynamide **56a** under optimized condition in presence of 1.5 equivalents of D_2O; instead precursor **56a** was decomposed. This finding reveals that the presence of external H_2O in the reaction medium affects the reactivity of ynamides and hence the proton transfer is intramolecular (See **Int-60**; **Scheme 3.12**). In order to understand the mode of alkyne activation (σ or π) by gold catalyst**,** the reaction was performed between deuterated alkyne **55i** and **56a** (**Scheme 3.11b**). No change of the deuterium position in the product **57a''** (observed by ^1H NMR) validates the π-activation of **55i** by gold catalyst.



Scheme 3.11: Isotope labelling experiments

3.4.8. Mechanism

Based on the above experimental fact and control experiments, the plausible mechanism is depicted in **Scheme 3.12**. To start with, the ynamide **56a** in presence of gold catalyst forms the keteniminium species **58**. Next, the in-situ generated keteniminium ion **58** triggers the 1,2-migration of **59** to obtain the intermediate **60** (**Scheme 3.12**). Aromatization followed by protodeauration of **Int-60** generates the gold π-complex **61**. Next, a regioselective intramolecular *6-endo-dig* cyclization of **Int-62** forms the intermediate **63**. Finally protodeauration followed by rearomatization of the intermediate **63** builts the desired product **57a**.



Scheme 3.12: Plausible mechanism

3.5. Conclusion

In summary, a gold catalyzed pseudo-umpolung cyclization of alkynyl 2,5-cyclohexadienones with ynamides for the synthesis of *2H*-chromene analogues has been demonstrated; the transformation involves a migration/aromatization/cyclization cascade. Various ynamides and different migrating group (alkyl/phenyl) containing alkynyl 2,5-cyclohexadienones was successfully tested. A set of control experiments and isotope labelling study shed lights to the proposed mechanism.

3.6. Experimental Section

3.6.1. General information

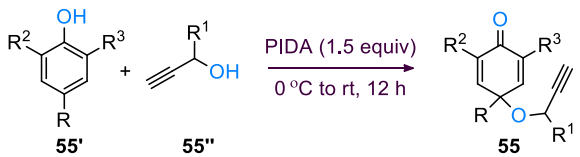
The identical procedure is shown in page no: 42, in Chapter 2.

3.6.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Chloroform ($CHCl_3$), acetone, dichloromethane (CH_2Cl_2), toluene, acetonitrile, ethyl acetate, and hexane were distilled over CaH_2. THF was freshly distilled over sodium/benzophenone ketyl under dry nitrogen. JohnPhosAuCl, $AgNTf_2$, CuI, K_3PO_4, and $PdCl_2(PPh_3)_2$ were purchased and used as received. $CuSO_4 \cdot 5H_2O$, trimethylsilane, and 1,10–phenanthroline were purchased from Avra and Merck chemicals. Aryl iodides were purchased from Aldrich and used. Analytical and spectral data of all those known compounds are exactly matching with the reported values.

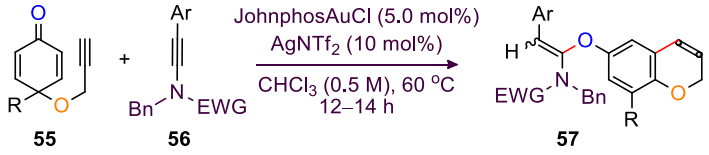
3.6.3. General procedure and spectral/analytical data

3.6.3.1. General procedure for the synthesis of terminal alkyne 55



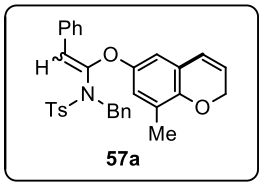
To a stirred solution of 4-substituted phenol **55′** (10 mmol) in 10 mL of propargyl alcohol (**55''**) was added phenyliodo(III)diacetate (15 mmol) in several portions at 0 °C. The resulting reaction mixture was stirred at room temperature overnight. Then the reaction mixture was quenched with saturated aqueous sodium bicarbonate (30 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude reaction mixture was purified by using silica gel (100–200 mesh) column chromatography (EtOAc/hexane) to give the the terminal cyclohexadienones **55**.

3.6.3.2. General procedure for the synthesis of *2H*-chromene derivatives 57



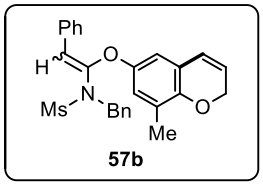
A mixture of alkynyl cyclohexadienone **55** (0.3 mmol), ynamide **56** (0.36 mmol) was taken in a screw cap sealed tube. To the above mixture, JohnPhosAuCl (0.015 mmol, 5.0 mol%) and $AgNTf_2$ (0.03 mmol, 10 mol%) were added in a glove box. Finally, chloroform (0.05 M, 6 mL) was added under nitrogen atmosphere and the reaction mixture allowed to stir at 60 °C for 12–14 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with dichloromethane (10 mL). The crude residue was purified using column chromatography on basic alumina to provide **57**.

N-benzyl-4-methyl-N-(1-((8-methyl-2H-chromen-6-yl)oxy)-2-phenylvinyl)benzene Sulfonamide (57a): Following the general procedure, compound **57a** (116 mg) was obtained in 74% yield: yellow liquid; R_f = 0.51 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, DMSO–d_6): δ 7.68 (d, J = 8.0 Hz, 2H), 7.42–7.37 (m, 4H), 7.29–7.22 (m, 7H), 7.18 (tt, J = 7.0, 1.5 Hz, 1H), 6.34 (d, J = 2.5 Hz, 1H), 6.26 (d, J = 2.5 Hz, 1H), 6.22 (dt, J = 10, 2.0 Hz, 1H), 5.93 (s, 1H), 5.88 (dt, J = 9.5, 4.0 Hz, 1H), 4.75 (dd, J = 3.5, 1.5 Hz, 2H), 4.55 (s, 2H), 2.41 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 151.8, 148.2, 147.1, 144.4, 142.0, 135.9, 135.8, 133.8,



130.1, 129.1, 128.97, 128.7, 128.5, 128.2, 128.1, 127.9, 125.6, 124.4, 123.9, 122.6, 120.1, 114.0, 65.6, 52.0, 21.5, 15.8; IR (Neat)ν_{max} 3407, 2255, 1731, 1654 cm^{-1}; HRMS (ESI) for $C_{32}H_{30}NO_4S$ $(M+H)^+$: calcd 524.1896, found 524.1898.

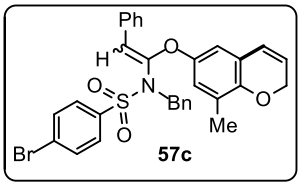
N-benzyl-N-(1-((8-methyl-2H-chromen-6-yl)oxy)-2-phenylvinyl)methanesulfonamide



57b

(57b): Following the general procedure, compound **57b** (94 mg) was obtained in 70% yield: colorless liquid; R_f = 0.34 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, DMSO–d_6): δ 7.47 (d, J = 7.5 Hz, 2H), 7.37–7.29 (m, 5H), 7.26 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.5 Hz, 2H), 6.68 (d, J = 2.5 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 6.36 (dt, J = 10, 2.0 Hz, 1H), 6.04 (s, 1H), 5.90 (dt, J = 10, 3.5 Hz, 1H), 4.77 (dd, J = 3.0, 1.5 Hz, 2H), 4.54 (s, 2H), 3.0 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 148.3, 147.3, 141.8, 136.1, 134.0, 129.1, 128.9, 128.8, 128.5, 128.2, 127.8, 125.9, 124.3, 124.2, 122.9, 120.2, 114.3, 114.0, 65.6, 51.3, 15.8; IR (Neat)ν_{max} 3431, 1731, 1655, 1473, 1340 cm^{-1}; HRMS (ESI) for $C_{26}H_{26}NO_4S$ $(M+H)^+$: calcd 448.1583, found 448.1585.

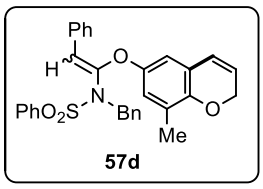
N-benzyl-4-bromo-N-(1-((8-methyl-2H-chromen-6-yl)oxy)-2-phenylvinyl)benzene



57c

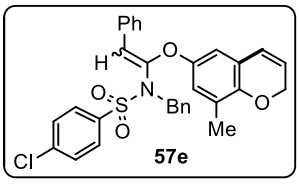
sulfonamide (57c): Following the general procedure, compound **57c** (139 mg) was obtained in 79% yield: colorless gummy liquid; R_f = 0.45 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.54 (m, 4H), 7.42 (d, J = 8.0 Hz, 2H), 7.30–7.26 (m, 5H), 7.22 (d, J = 7.6 Hz, 1H), 6.39 (d, J = 2.8 Hz, 1H), 6.21 (d, J = 2.8 Hz, 1H), 6.15 (dt, J = 9.6, 1.2 Hz, 1H), 5.87 (s, 1H), 5.77 (dt, J = 9.6, 3.2 Hz, 1H), 4.80 (dd, J = 3.2, 1.2 Hz, 2H), 4.56 (s, 2H), 2.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 147.2, 141.3, 138.4, 135.1, 133.3, 132.0, 129.3, 128.9, 128.6, 128.41, 128.39, 128.0, 127.8, 127.6, 126.1, 124.5, 122.6, 122.3, 120.3, 116.0, 113.8, 65.5, 52.4, 15.5; IR (Neat)ν_{max} 3061, 1708, 1654, 1573, 1207 cm^{-1}; HRMS (ESI) for $C_{31}H_{27}BrNO_4S$ $(M+H)^+$: calcd 588.0844, found 588.0838.

N-benzyl-N-(1-((8-methyl-2H-chromen-6-yl)oxy)-2-phenylvinyl)benzenesulfonamide



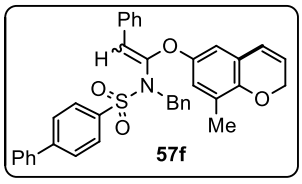
(57d): Following the general procedure, compound **57d** (112 mg) was obtained in 73% yield: colorless gummy liquid; R_f = 0.59 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 7.2 Hz, 2H), 7.61 (tt, J = 7.6, 1.2 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.30–7.23 (m, 8H), 6.43 (d, J = 2.8 Hz, 1H), 6.28 (d, J = 3.2 Hz, 1H), 6.20 (dt, J = 10, 1.6 Hz, 1H), 5.86 (s, 1H), 5.79 (dt, J = 9.6, 3.6 Hz, 1H), 4.81 (dd, J = 3.2, 1.6 Hz, 2H), 4.55 (s, 2H), 2.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 147.2, 141.7, 139.0, 135.2, 133.5, 132.9, 128.9, 128.7, 128.5, 128.34, 128.26, 127.9, 127.8, 127.4, 125.9, 124.7, 122.3, 120.4, 115.2, 113.9, 65.4, 52.3, 15.5; IR (Neat)ν_{max} 3487, 3061, 1729, 1652, 1589, 1473, 1288 cm^{-1}; HRMS (ESI) for $C_{31}H_{27}NNaO_4S$ $(M+Na)^+$: calcd 532.1558, found 532.1559.

N-benzyl-4-chloro-N-(1-((8-methyl-2H-chromen-6-yl)oxy)-2-phenylvinyl)benzene



sulfonamide (57e): Following the general procedure, compound **57e** (149 mg) was obtained in 91% yield: colorless gummy liquid; R_f = 0.41 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, DMSO–d_6): δ 7.79 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 7.31–7.28 (m, 5H), 7.26–7.24 (m, 2H), 7.20 (d, J = 7.2 Hz, 1H), 6.36 (d, J = 2.0 Hz, 1H), 6.29 (d, J = 2.4 Hz, 1H), 6.23 (d, J = 10 Hz, 1H), 5.99 (s, 1H), 5.88 (dt, J = 10, 3.2 Hz, 1H), 4.77 (s, 2H), 4.64 (s, 2H), 1.93 (s, 3H); ^{13}C NMR (101 MHz, DMSO–d_6) δ 148.3, 147.1, 141.7, 138.8, 137.7, 135.8, 133.7, 129.8, 129.1, 129.0, 128.72, 128.65, 128.3, 125.7, 124.3, 124.0, 122.6, 120.2, 114.8, 114.0, 65.6, 52.3, 15.8; IR (Neat)ν_{max} 3399, 2958, 1706, 1650, 1455, 1362 cm^{-1}; HRMS (ESI) for $C_{31}H_{26}ClNNaO_4S$ $(M+H)^+$: calcd 566.1169, found 566.1177.

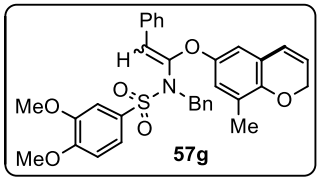
N-benzyl-N-(1-((8-methyl-2H-chromen-6-yl)oxy)-2-phenylvinyl)-[1,1'-biphenyl]-4-



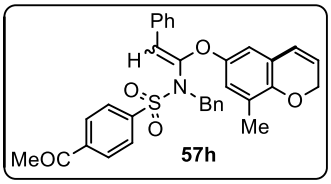
sulfonamide (57f): Following the general procedure, compound **57f** (132 mg) was obtained in 75% yield: colorless gummy liquid; R_f = 0.48 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, DMSO–d_6): δ 7.88–7.85 (m, 4H), 7.77 (d, J = 8.0 Hz, 2H), 7.57–7.42 (m, 5H), 7.33–7.24 (m, 8H), 6.38 (s, 1H), 6.31 (s, 1H), 6.21 (dd, J = 9.6, 1.2 Hz, 1H), 6.01 (s, 1H), 5.81 (dt, J =

9.6, 3.2 Hz, 1H), 4.68 (dd, J = 3.2, 1.6 Hz, 2H), 4.64 (s, 2H), 1.90 (s, 3H); ^{13}C NMR (101 MHz, DMSO–d_6) δ 148.2, 147.1, 145.2, 141.9, 138.7, 137.5, 135.9, 133.8, 129.6, 129.2, 128.7, 128.2, 127.8, 127.6, 125.7, 124.3, 123.9, 122.6, 120.0, 114.5, 114.0, 113.9, 65.5, 52.1, 15.8; IR (Neat)ν_{max} 3408, 3060, 1709, 1654, 1474, 1350 cm^{-1}; HRMS (ESI) for $C_{37}H_{32}NO_4S$ $(M+H)^+$: calcd 586.2052, found 586.2054.

N-benzyl-2,4-dimethoxy-N-(1-((8-methyl-2H-chromen-6-yl)oxy)-2-phenylvinyl) Benzenesulfonamide (57g): Following the general procedure, compound **57g** (62 mg) was obtained in 36% yield: colorless gummy liquid; R_f = 0.25 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, DMSO–d_6): δ 7.43–7.39 (m, 4H), 7.27–7.29 (m, 3H), 7.26–7.23 (m, 4H), 7.12–7.10 (m, 2H), 6.31 (d, J = 3.0 Hz, 1H), 6.24 (d, J = 3.0 Hz, 1H), 6.20 (dt, J = 9.5, 2.0 Hz, 1H), 5.97 (s, 1H), 5.87 (dt, J = 10, 3.5 Hz, 1H), 4.74 (dd, J = 3.5, 2.0 Hz, 2H), 4.60 (s, 2H), 3.86 (s, 3H), 3.68 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (126 MHz, DMSO–d_6) δ 153.2, 149.1, 148.1, 147.2, 142.4, 136.2, 133.9, 129.9, 129.2, 129.0, 128.7, 128.5, 128.1, 127.8, 125.6, 124.3, 123.9, 122.6, 122.3, 120.0, 113.9, 113.4, 111.5, 110.3, 65.5, 56.3, 56.1, 52.2, 15.8; IR (Neat)ν_{max} 3408, 1653, 1588, 1508, 1351 cm^{-1}; HRMS (ESI) for $C_{33}H_{31}NNaO_6S$ $(M+Na)^+$: calcd 592.1770, found 592.1769.

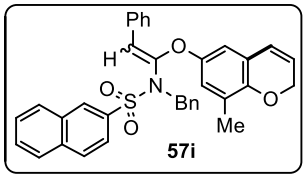


4-acetyl-N-benzyl-N-(1-((8-methyl-2H-chromen-6-yl)oxy)-2-phenylvinyl) Benzene sulfonamide (57h): Following the general procedure, compound **57h** (63 mg) was obtained in 38% yield: colorless gummy liquid; R_f = 0.38 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, DMSO–d_6): δ 8.06 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 7.2 Hz, 2H), 7.32–7.29 (m, 5H), 7.25 (d, J = 7.6 Hz, 2H), 7.22–7.19 (m, 1H), 6.37 (d, J = 2.8 Hz, 1H), 6.26 (d, J = 2.8 Hz, 1H), 6.20 (dt, J = 10, 1.6 Hz, 1H), 5.99 (s, 1H), 5.85 (dt, J = 10, 3.6 Hz, 1H), 4.71 (dd, J = 3.2, 1.6 Hz, 2H), 4.69 (s, 2H), 2.65 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (101 MHz, DMSO–d_6) δ 148.3, 147.0, 142.6, 141.5, 140.2, 135.7, 133.6, 129.3, 129.1, 129.0, 128.8, 128.7, 128.3, 128.1, 125.7, 124.3, 123.9, 122.6, 120.2, 115.2, 114.0, 65.5, 52.2, 27.5,



15.8; IR (Neat)ν_{max} 3381, 2969, 1737, 1650, 1365, 1228 cm^{-1}; HRMS (ESI) for $C_{33}H_{30}NO_5S$ $(M+H)^+$: calcd 552.1845, found 552.1849.

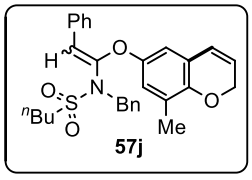
N-benzyl-N-(1-((8-methyl-2H-chromen-6-yl)oxy)-2-phenylvinyl)naphthalene-2-



57i

sulfonamide (57i): Following the general procedure, compound **57i** (76 mg) was obtained in 45% yield: colorless gummy liquid; R_f = 0.40 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, J = 1.5 Hz, 1H), 7.92–7.86 (m, 3H), 7.71 (dd, J = 9.0, 2.0 Hz, 1H), 7.66 (td, J = 8.0, 1.0 Hz, 1H), 7.60 (td, J = 9.0, 1.5 Hz, 1H), 7.44 (d, J = 7.5 Hz, 2H), 7.30–7.26 (m, 5H), 7.23 (t, J = 5.5 Hz, 2H), 7.20–7.16 (m, 1H), 6.40 (d, J = 2.5 Hz, 1H), 6.25 (d, J = 3.0 Hz, 1H), 6.20 (dt, J = 10, 2.0 Hz, 1H), 5.93 (s, 1H), 5.68 (dt, J = 9.5, 4.0 Hz, 1H), 4.73 (dd, J = 3.5, 2.0 Hz, 2H), 4.62 (s, 2H), 1.92 (s, 3H); ^{13}C NMR (126 MHz, DMSO–d_6) δ 148.2, 147.2, 141.6, 136.3, 135.4, 134.9, 133.5, 132.0, 129.3, 129.0, 128.8, 128.6, 128.34, 128.30, 127.9, 127.8, 127.4, 125.9, 124.5, 123.0, 122.21, 122.17, 120.3, 115.5, 113.9, 65.4, 52.5, 15.5; IR (Neat)ν_{max} 3480, 3024, 1653, 1589, 1473, 1345 cm^{-1}; HRMS (ESI) for $C_{35}H_{29}NNaO_4S$ $(M+Na)^+$: calcd 582.1715, found 582.1715.

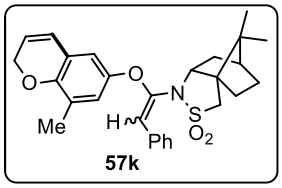
N-benzyl-N-(1-((8-methyl-2H-chromen-6-yl)oxy)-2-phenylvinyl)butane-1-



57j

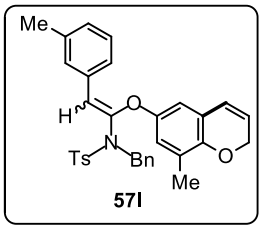
sulfonamide (57j): Following the general procedure, compound **57j** (119 mg) was obtained in 81% yield: pale yellow gummy liquid; R_f = 0.49 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (500 MHz, DMSO–d_6): δ 7.44 (d, J = 7.5 Hz, 2H), 7.39–7.34 (m, 4H), 7.30 (d, J = 7.0 Hz, 1H), 7.26 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.5 Hz, 1H), 6.70 (d, J = 2.5 Hz, 1H), 6.61 (d, J = 3.0 Hz, 1H), 6.37 (dt, J = 10, 2.0 Hz, 1H), 6.02 (s, 1H), 5.91 (dt, J = 9.5, 3.5 Hz, 1H), 4.76 (dd, J = 3.5, 2.0 Hz, 2H), 4.58 (s, 2H), 3.02 (t, J = 8.0 Hz, 2H), 2.03 (s, 3H), 1.50–1.55 (m, 2H), 1.26 (sext, J = 7.5 Hz, 2H), 0.80 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, DMSO–d_6) δ 148.4, 147.3, 141.6, 136.3, 133.9, 129.1, 129.0, 128.8, 128.5, 128.2, 127.8, 126.0, 124.3, 124.2, 122.9, 120.1, 114.8, 114.0, 65.6, 52.4, 51.4, 25.3, 21.3, 15.8, 13.8; IR (Neat)ν_{max} 3061, 2960, 1658, 1474, 1340 cm^{-1}; HRMS (ESI) for $C_{29}H_{32}NO_4S$ $(M+H)^+$: calcd 490.2052, found 490.2056.

8,8-dimethyl-1-((E)-1-((8-methyl-2H-chromen-6-yl)oxy)-2-phenylvinyl)hexahydro-1H-3a,6-methanobenzo[c]isothiazole 2,2-dioxide (57k): Following the general procedure, compound **57k** (99 mg) was obtained in 69% yield: colorless gummy liquid; R_f= 0.48 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, DMSO–d_6): δ 7.47 (d, J = 8.0 Hz, 2H), 7.27 (t, J = 7.5 Hz, 2H), 7.16 (t, J = 7.0 Hz, 1H), 6.67 (s, 1H), 6.58 (s, 1H), 6.42 (d, J = 9.0, 1H), 5.90–5.85(s, 2H), 4.73 (s, 2H), 3.58 (t, J = 7.0 Hz, 1H), 3.43 (s, 2H), 2.04 (s, 3H), 1.95–1.88 (m, 2H), 1.82–1.78 (m, 2H), 0.85 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (101 MHz, DMSO–d_6) δ 148.5, 147.7, 141.2, 134.3, 129.0, 128.2, 127.2, 125.5, 124.5, 124.0, 122.8, 118.6, 112.5, 106.5, 65.6, 64.8, 51.1, 49.4, 47.9, 44.4, 35.4, 32.3, 26.8, 20.1, 19.8, 15.8; IR (Neat)ν_{max} 3383, 2259, 1650, 1474, 1205 cm^{-1}; HRMS (ESI) for $C_{28}H_{32}NO_4S$ (M+H)$^+$: calcd 478.2052, found 478.2054.

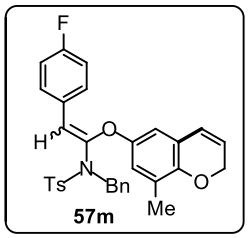


57k

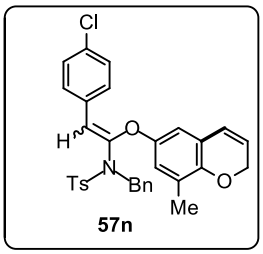
N-benzyl-4-methyl-N-(1-((8-methyl-2H-chromen-6-yl)oxy)-2-(m-tolyl)vinyl)benzene sulfonamide (57l): Following the general procedure, compound **57l** (105 mg) was obtained in 65% yield: yellow liquid; R_f = 0.45 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, DMSO–d_6): δ 7.66 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.29–7.25 (m, 3H), 7.23–7.18 (m, 4H), 7.11 (t, J = 7.5, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.32 (d, J = 2.5 Hz, 1H), 6.24 (d, J = 3.0 Hz, 1H), 6.21 (dt, J = 10, 2.0 Hz, 1H), 5.90–5.84 (m, 2H), 4.74 (dd, J = 3.5, 2.0 Hz, 2H), 4.51 (s, 2H), 2.40 (s, 3H), 2.19 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 148.2, 147.2, 144.4, 141.9, 137.9, 135.9, 135.8, 133.7, 130.2, 129.5, 129.1, 128.9, 128.7, 128.6, 128.2, 128.0, 127.1, 125.6, 125.5, 124.4, 123.9, 122.6, 120.1, 114.0, 65.6, 51.9, 21.54, 21.46, 158; IR (Neat)ν_{max} 3410, 2255, 1655, 1473, 1346, 1206, 1161 cm^{-1}; HRMS (ESI) for $C_{33}H_{31}NNaO_4S$ (M+Na)$^+$: calcd 560.1871, found 560.1871.



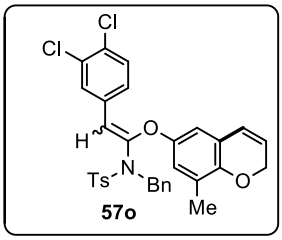
57l

N-benzyl-N-(2-(4-fluorophenyl)-1-((8-methyl-2H-chromen-6-yl)oxy)vinyl)-4-methylbenzenesulfonamide (57m): 

Following the general procedure, compound **57m** (86 mg) was obtained in 53% yield: colorless liquid; R_f = 0.43 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, DMSO–d_6): δ 7.67 (d, J = 8.5 Hz, 2H), 7.48–7.43 (m, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.29–7.25 (m, 3H), 7.23–7.19 (m, 2H), 7.09 (t, J = 8.5, 2H), 6.32 (d, J = 3.0 Hz, 1H), 6.24 (d, J = 3.0 Hz, 1H), 6.21 (dt, J = 10, 1.5 Hz, 1H), 5.96 (s, 1H), 5.87 (dt, J = 9.5, 3.5 Hz, 1H), 4.74 (dd, J = 3.5, 2.0 Hz, 2H), 4.52 (s, 2H), 2.40 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.6 (d, J = 246 Hz, 1C), 148.3, 147.0, 144.4, 141.8, 135.9, 135.8, 130.5 (d, J = 7.6 Hz, 1C), 130.3 (d, J = 3.8 Hz, 1C), 130.1, 129.1, 128.6, 128.2, 128.0, 125.7, 125.3, 124.3, 123.9, 122.6, 120.1, 115.9 (d, J = 21.4 Hz, 1C), 113.8, 112.9, 65.6, 52.0, 21.5, 15.8; ^{19}F NMR (471 MHz, DMSO–d_6) δ –113.8; IR (Neat)ν_{max} 3412, 2359, 1658, 1507, 1346, 1206, 1151 cm^{-1}; HRMS (ESI) for $C_{32}H_{28}FNNaO_4S$ $(M+Na)^+$: calcd 564.1621, found 564.1616.

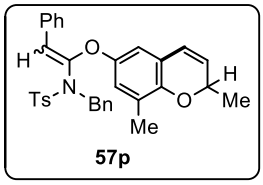
N-benzyl-N-(2-(4-chlorophenyl)-1-((8-methyl-2H-chromen-6-yl)oxy)vinyl)-4-methylbenzenesulfonamide (57n): 

Following the general procedure, compound **57n** (101 mg) was obtained in 60% yield: colorless liquid; R_f = 0.33 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, DMSO–d_6): δ 7.67 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.29–7.25 (m, 3H), 7.23–7.19 (m, 2H), 6.32 (d, J = 3.0 Hz, 1H), 6.32 (d, J = 3.0 Hz, 1H), 6.24 (d, J = 3.0 Hz, 1H), 6.22 (dt, J = 10, 2.0 Hz, 1H), 5.95 (s, 1H), 5.88 (dt, J = 10, 3.5 Hz, 1H), 4.75 (dd, J = 3.5, 2.0 Hz, 2H), 4.53 (s, 2H), 2.40 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 148.3, 146.9, 144.5, 142.7, 135.8, 135.7, 132.8, 132.2, 130.2, 129.1, 129.0, 128.7, 128.2, 128.1, 125.7, 124.3, 123.9, 122.7, 120.2, 114.1, 112.5, 65.6, 52.0, 21.5, 15.8; IR (Neat)ν_{max} 3436, 2250, 1654, 1349, 1208, 1157 cm^{-1}; HRMS (ESI) for $C_{32}H_{28}ClNNaO_4S$ $(M+Na)^+$: calcd 580.1325, found 580.1331.

N-benzyl-N-(2-(3,4-dichlorophenyl)-1-((8-methyl-2H-chromen-6-yl)oxy)vinyl)-4-methylbenzenesulfonamide (57o): 

57o

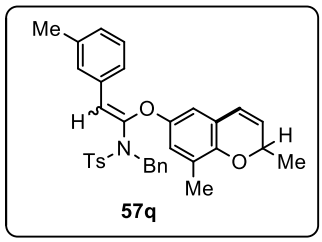
Following the general procedure, compound **57o** (144 mg) was obtained in 81% yield: colorless liquid; R_f = 0.43 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.4 Hz, 2H), 7.47 (s, 1H), 7.26–7.19 (m, 9H), 6.36 (d, J = 2.8 Hz, 1H), 6.19 (d, J = 2.8 Hz, 1H), 6.16 (dt, J = 10, 2.0 Hz, 1H), 5.77 (dt, J = 10, 3.2 Hz, 1H), 5.74 (s, 1H), 4.79 (dd, J = 2.8, 1.6 Hz, 2H), 4.50 (s, 2H), 2.44 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 146.8, 144.0, 143.3, 135.8, 135.1, 133.7, 132.3, 130.7, 130.2, 130.1, 129.5, 128.9, 128.4, 127.9, 127.5, 126.1, 124.6, 122.5, 122.3, 120.4, 113.9, 111.7, 65.5, 52.1, 21.6, 15.5; IR (Neat)ν_{max} 3428, 3064, 2920, 1654, 1549, 1386, 1208 cm^{-1}; HRMS (ESI) for $C_{32}H_{28}Cl_2NO_4S$ (M+H)$^+$: calcd 592.1116, found 592.1119.

N-benzyl-N-(1-((2,8-dimethyl-2H-chromen-6-yl)oxy)-2-phenylvinyl)-4-methylbenzenesulfonamide (57p): 

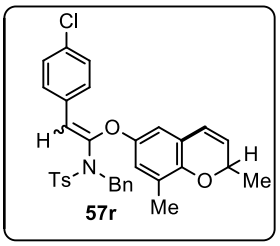
57p

Following the general procedure, compound **57p** (121 mg) was obtained in 75% yield: colorless liquid; R_f = 0.48 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, DMSO–d_6): δ 7.69 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.29–7.22 (m, 7H), 7.20–7.15 (m, 1H), 6.37 (d, J = 2.8 Hz, 1H), 6.29 (d, J = 3.2 Hz, 1H), 6.19 (dd, J = 10, 1.6 Hz, 1H), 5.95 (s, 1H), 5.78 (dd, J = 9.6, 3.2 Hz, 1H), 4.98–4.90 (m, 1H), 4.55 (s, 2H), 2.40 (s, 3H), 1.94 (s, 3H), 1.34 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO–d_6) δ 147.4, 146.9, 144.4, 142.0, 135.9, 135.8, 133.9, 130.1, 129.1, 129.0, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8, 125.9, 123.6, 121.9, 120.1, 113.9, 113.8, 71.3, 52.0, 21.6, 21.4, 15.8; IR (Neat)ν_{max} 3029, 2918, 1735, 1654, 1595, 1495, 1348, 1208 cm^{-1}; HRMS (ESI) for $C_{33}H_{32}NO_4S$ (M+H)$^+$: calcd 538.2052, found 538.2054.

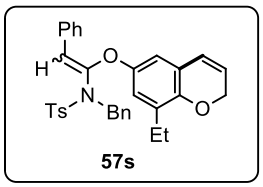
N-benzyl-N-(1-((2,8-dimethyl-2H-chromen-6-yl)oxy)-2-(m-tolyl)vinyl)-4-methyl benzenesulfonamide (57q): Following the general procedure, compound **57q** (76 mg) was obtained in 46% yield: colorless liquid; R_f = 0.59 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, DMSO–d_6): δ 7.66 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.28–7.25 (m, 3H), 7.24–7.18 (m, 4H), 7.12 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.34 (d, J = 3.0 Hz, 1H), 6.26 (d, J = 2.5 Hz, 1H), 6.18 (dd, J = 9.5, 1.5 Hz, 1H), 5.87 (s, 1H), 5.78 (dd, J = 9.5, 3.0 Hz, 1H), 4.97–4.90 (m, 1H), 4.52 (s, 2H), 2.40 (s, 3H), 2.19 (s, 3H), 1.92 (s, 3H), 1.34 (d, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, DMSO–d_6) δ 147.4, 147.0, 144.4, 142.0, 137.9, 136.0, 135.9, 133.7, 130.1, 129.5, 129.1, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 125.8, 125.5, 123.6, 121.9, 120.1, 114.0, 113.9, 71.3, 52.0, 21.5, 21.43, 21.36, 15.7; IR (Neat)ν_{max} 3426, 2253, 1655, 1469, 1347, 1025 cm^{-1}; HRMS (ESI) for $C_{34}H_{34}NO_4S$ $(M+H)^+$: calcd 552.2209, found 552.2208.



N-benzyl-N-(2-(4-chlorophenyl)-1-((2,8-dimethyl-2H-chromen-6-yl)oxy)vinyl)-4-methylbenzenesulfonamide (57r): Following the general procedure, compound **57r** (86 mg) was obtained in 50% yield: colorless liquid; R_f = 0.49 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, DMSO–d_6): δ 7.66 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.32–7.29 (m, 2H), 7.28–7.25 (m, 3H), 7.20 (dd, J = 7.0, 3.0 Hz, 2H), 6.32 (d, J = 3.0 Hz, 1H), 6.24 (d, J = 3.0 Hz, 1H), 6.18 (dd, J = 10, 1.5 Hz, 1H), 5.94 (s, 1H), 5.78 (dd, J = 10, 3.5 Hz, 1H), 4.97–4.89 (m, 1H), 4.52 (s, 2H), 2.39 (s, 3H), 1.92 (s, 3H), 1.33 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, DMSO–d_6) δ 147.5, 146.7, 144.5, 142.7, 135.8, 135.6, 132.8, 132.1, 130.2, 129.1, 129.0, 128.7, 128.5, 128.2, 128.1, 125.9, 123.5, 121.9, 120.2, 113.9, 112.4, 71.3, 52.0, 21.5, 21.3, 15.8; IR (Neat)ν_{max} 3400, 2254, 1653, 1349, 1152, 1023 cm^{-1}; HRMS (ESI) for $C_{33}H_{30}ClNNaO_4S$ $(M+Na)^+$: calcd 594.1482, found 594.1483.



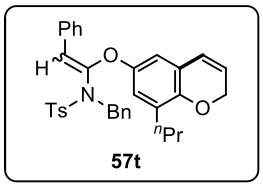
N-benzyl-N-(1-((8-ethyl-2H-chromen-6-yl)oxy)-2-phenylvinyl)-4-methylbenzene



57s

Sulfonamide (57s): Following the general procedure, compound **57s** (127 mg) was obtained in 79% yield: colorless liquid; R_f = 0.52 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, DMSO–d_6): δ 7.68 (d, J = 8.4 Hz, 2H), 7.43–7.36 (m, 4H), 7.29–7.18 (m, 8H), 6.49 (d, J = 2.8 Hz, 1H), 6.26 (d, J = 2.8 Hz, 1H), 6.25–6.20 (m, 1H), 5.93 (s, 1H), 5.89 (dt, J = 9.6, 3.6 Hz, 1H), 4.74 (dd, J = 3.2, 1.6 Hz, 2H), 4.53 (s, 2H), 2.41 (s, 3H), 2.36 (q, J = 7.2 Hz, 2H), 1.0 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 147.7, 147.4, 144.4, 142.0, 135.94, 135.91, 133.8, 131.9, 130.2, 129.02, 128.95, 128.64, 128.56, 128.1, 128.0, 127.9, 124.5, 124.0, 123.0, 118.6, 114.2, 114.0, 65.5, 52.0, 22.7, 21.5, 14.4; IR (Neat)ν_{max} 3384, 2968, 1653, 1448, 1348 cm^{-1}; HRMS (ESI) for $C_{33}H_{32}NO_4S$ $(M+H)^+$: calcd 538.2052, found 538.2051.

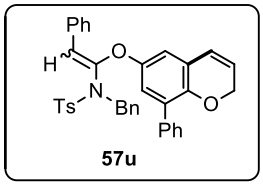
N-benzyl-4-methyl-N-(2-phenyl-1-((8-propyl-2H-chromen-6-yl)oxy)vinyl)benzene



57t

sulfonamide (57t): Following the general procedure, compound **57t** (53 mg) was obtained in 32% yield: colorless liquid; R_f = 0.57 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, DMSO–d_6): δ 7.67 (d, J = 8.0 Hz, 2H), 7.42–7.34 (m, 5H), 7.28–7.23 (m, 6H), 7.21–7.18 (m, 3H), 6.45 (d, J = 2.8 Hz, 1H), 6.26–6.20 (m, 2H), 5.92 (s, 1H), 5.89 (dt, J = 10, 3.6 Hz, 1H), 4.72 (dd, J = 3.6, 2.0 Hz, 2H), 4.52 (s, 2H), 2.41 (s, 3H), 2.30 (q, J = 7.2 Hz, 2H), 1.44–1.35 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 147.9, 147.3, 144.4, 142.0, 135.9, 135.88, 133.8, 130.3, 130.2, 129.0, 128.96, 128.7, 128.6, 128.1, 128.0, 127.9, 124.5, 124.1, 123.1, 119.4, 114.2, 114.0, 65.5, 51.9, 31.5, 22.9, 21.6, 14.2; IR (Neat)ν_{max} 3438, 2252, 1732, 1373, 1242, 1024 cm^{-1}; HRMS (ESI) for $C_{34}H_{34}NO_4S$ $(M+H)^+$: calcd 552.2209, found 552.2207.

N-benzyl-4-methyl-N-(2-phenyl-1-((8-phenyl-2H-chromen-6-yl)oxy)vinyl)benzene

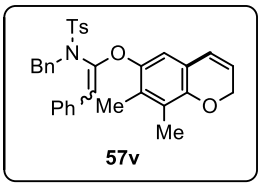


57u

sulfonamide (57u): Following the general procedure, compound **57u** (135 mg) was obtained in 77% yield: colorless jelly compound; R_f = 0.44 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, DMSO–d_6): δ 7.69 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.40–7.36 (m, 6H), 7.34–7.30 (m, 1H), 7.29–7.25 (m, 2H), 7.24–7.18 (m, 6H), 6.69 (d, J = 2.8 Hz, 1H), 6.44 (d, J = 3.2 Hz,

1H), 6.32 (dt, J = 10, 1.6 Hz, 1H), 5.99–5.96 (m, 1H), 5.95 (s, 1H), 4.74 (dd, J = 3.2, 1.6 Hz, 2H), 4.55 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 147.7, 147.1, 144.5, 141.9, 137.1, 135.9, 133.7, 130.2, 129.6, 129.5, 129.0, 128.6, 128.5, 128.14, 128.06, 128.0, 127.7, 124.6, 124.4, 124.3, 119.6, 116.0, 114.5, 65.6, 52.0, 21.5; IR (Neat)ν_{max} 3406, 3057, 2256, 1725, 1653, 1595, 1347, 1151, 1024 cm^{-1}; HRMS (ESI) for $C_{37}H_{31}NNaO_4S$ $(M+Na)^+$: calcd 608.1871, found 608.1876.

N-benzyl-N-(1-((7,8-dimethyl-2H-chromen-6-yl)oxy)-2-phenylvinyl)-4methylbenzene sulfonamide (57v): Following the general procedure, compound **57v** (90 mg) was obtained in 56% yield: colorless liquid; R_f = 0.46 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, DMSO–d_6): δ 7.73 (d, J = 6.5 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 7.5 Hz, 2H), 7.26–7.22 (m, 5H), 7.19–7.16 (m, 3H), 6.61 (dt, J = 10, 1.5 Hz, 1H), 6.17 (s, 1H), 5.99–5.95 (m, 2H), 4.66 (dd, J = 3.5, 1.5 Hz, 2H), 4.49 (s, 2H), 2.42 (s, 3H), 2.0 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 148.1, 145.4, 144.5, 142.0, 135.9, 135.6, 133.8, 130.2, 128.9, 128.7, 128.6, 128.1, 128.05, 127.9, 123.6, 122.2, 122.1, 122.0, 121.3, 118.2, 114.6, 64.6, 52.1, 21.5, 15.7, 11.0; IR (Neat)ν_{max} 3415, 3026, 2254, 1651, 1448, 1151, 1025 cm^{-1}; HRMS (ESI) for $C_{33}H_{31}NNaO_4S$ $(M+Na)^+$: calcd 560.1871, found 560.1873.



57v

3.7. X-ray Crystallography

Single crystal X-ray data for the compound **57a** was collected using the Bruker D8 Quest CMOS detector system [λ(Mo-Kα) = 0.71073 Å] at 298K, graphite monochromator with a ω scan width of 0.3o, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software was used for the intensity data acquisition and the SAINTPLUS Software was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program, an empirical absorption correction using equivalent reflections was performed with the program. The structure was solved using SHELXS-97, and full-matrix least-squares refinement against F2 was carried out using SHELXL-97. All non-hydrogen atoms were refined anisotropically. Aromatic and methyl hydrogens were introduced on calculated positions and included in the refinement riding on their respective parent atoms.[18,19]

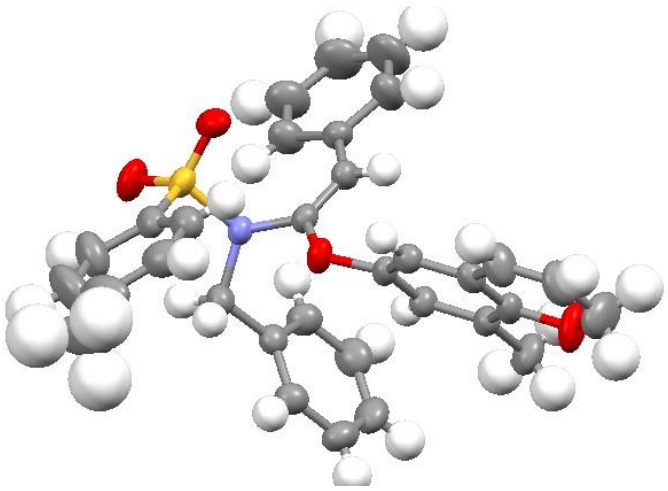


Figure 3.3. Thermal ellipsoid plot of compound **57a.** Ellipsoid counter set at 50% probability level. Carbon (gray), Hydrogen (light gray), Oxygen (red), Nitrogen (light blue), and Sulphur (yellow).

Table 3.6. Crystallographic data for compound **57a.**

Compound	**57a**
formula	$C_{32}H_{29}NO_4S$
Mw	523.62
crystal system	monoclinic
space group	P2(1)/c
T [K]	301 K
a [Å]	11.6967(8)
b [Å]	11.8203(7)
c [Å]	19.7737(14)
α [°]	90
β [°]	101.098(2
γ [°]	90
V [Å^3]	2682.8(3)
Z	4
ρ_{calcd} [g cm^{-3}]	1.296
μ [mm^{-1}]	0.159
total reflns	4773
unique reflns	4742
observed	4019
R_1[I>2σ(I)]	0.0400
wR2 [all]	0.1142(4742)
GOF	1.033
Diffractometer	Bruker D8 Quest CCD
CCDC Number	1883663

3.8. References

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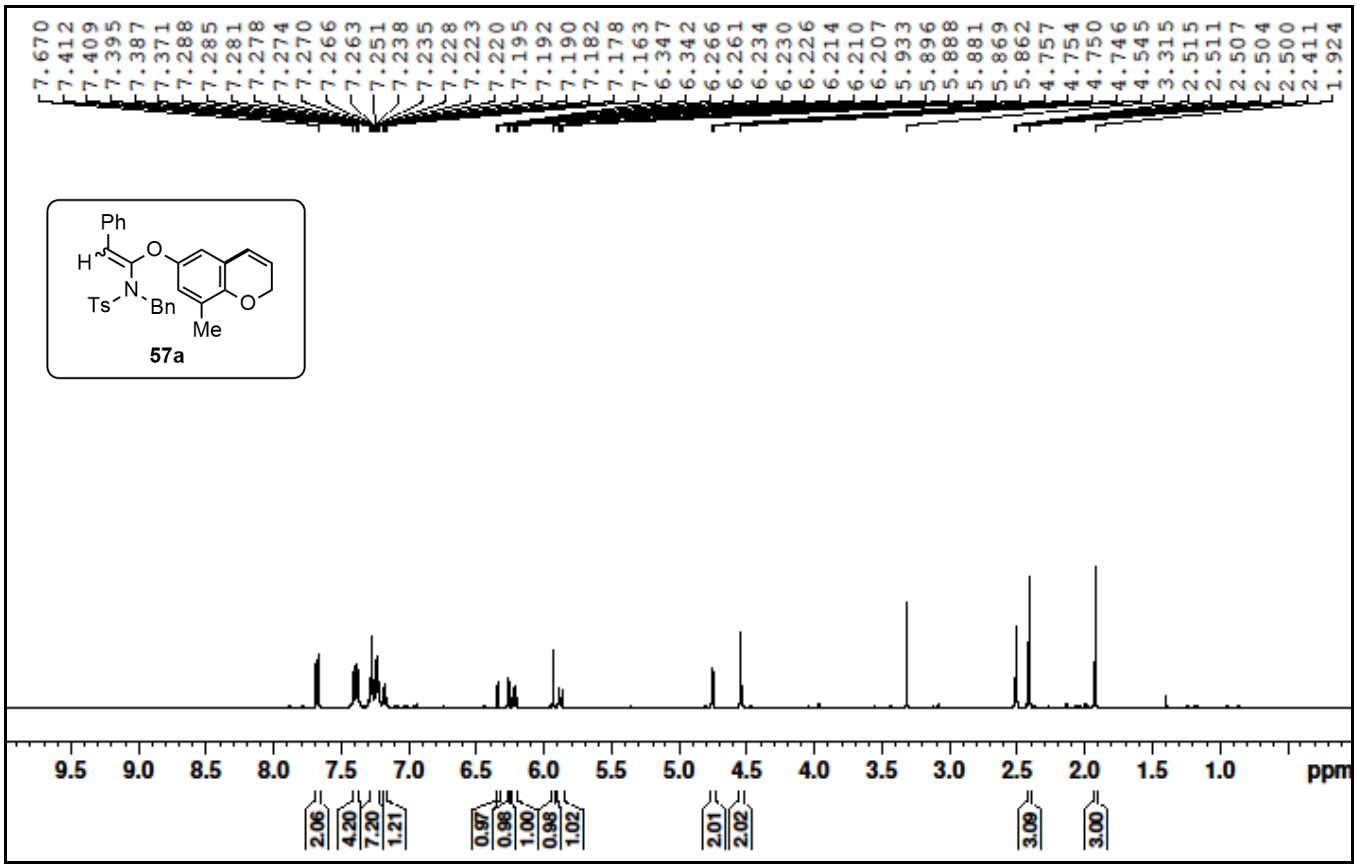
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Bn
Me
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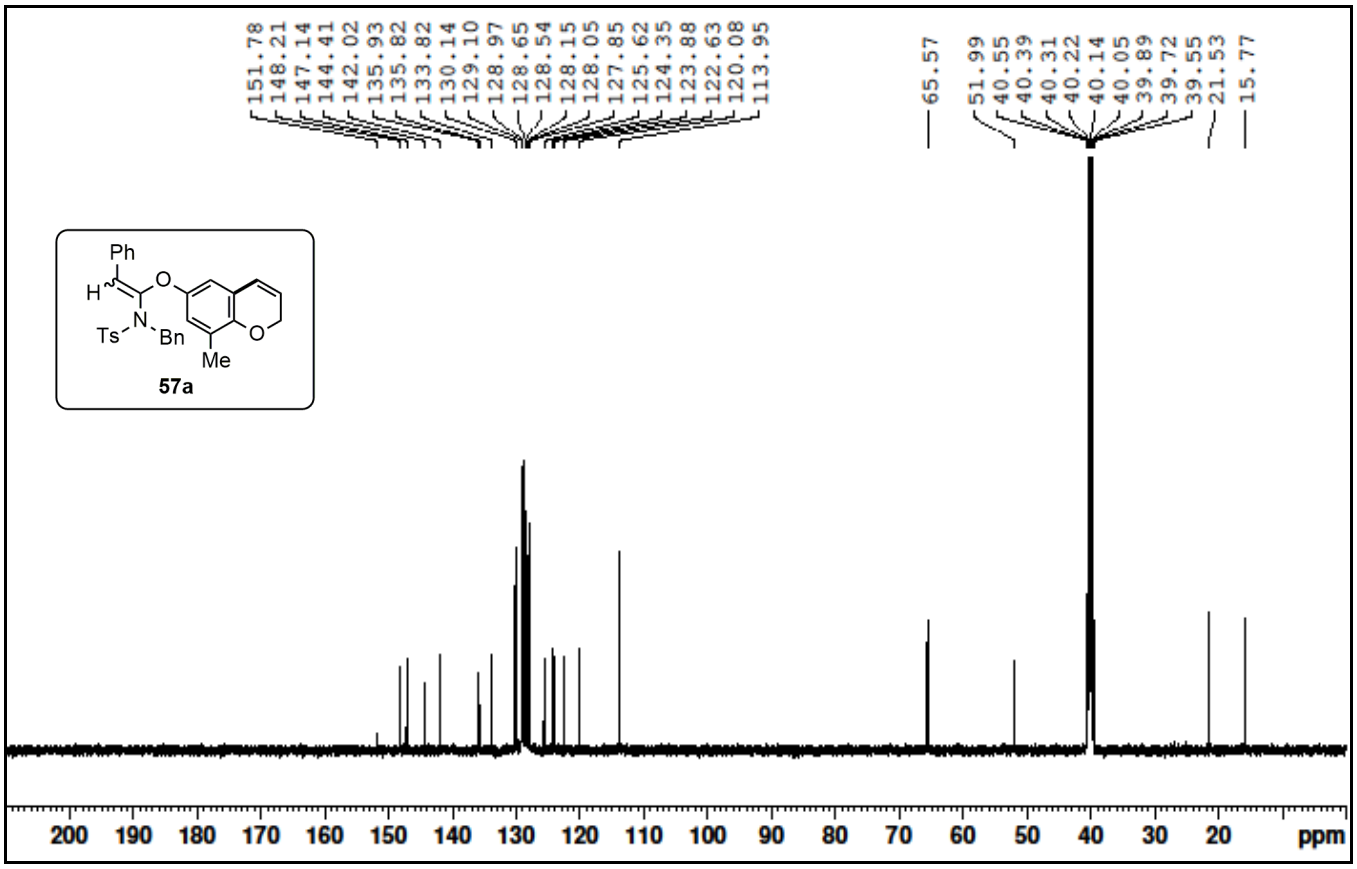
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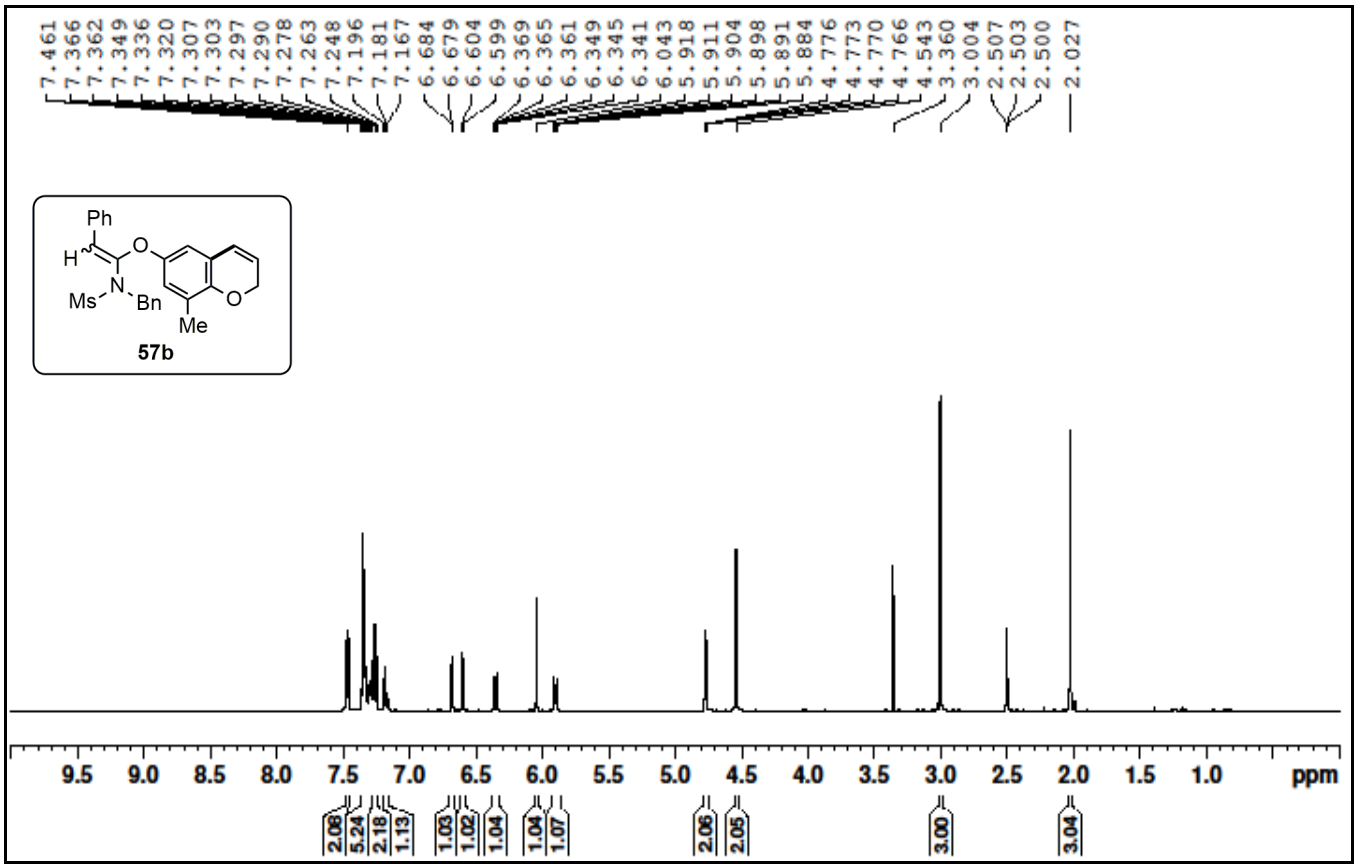
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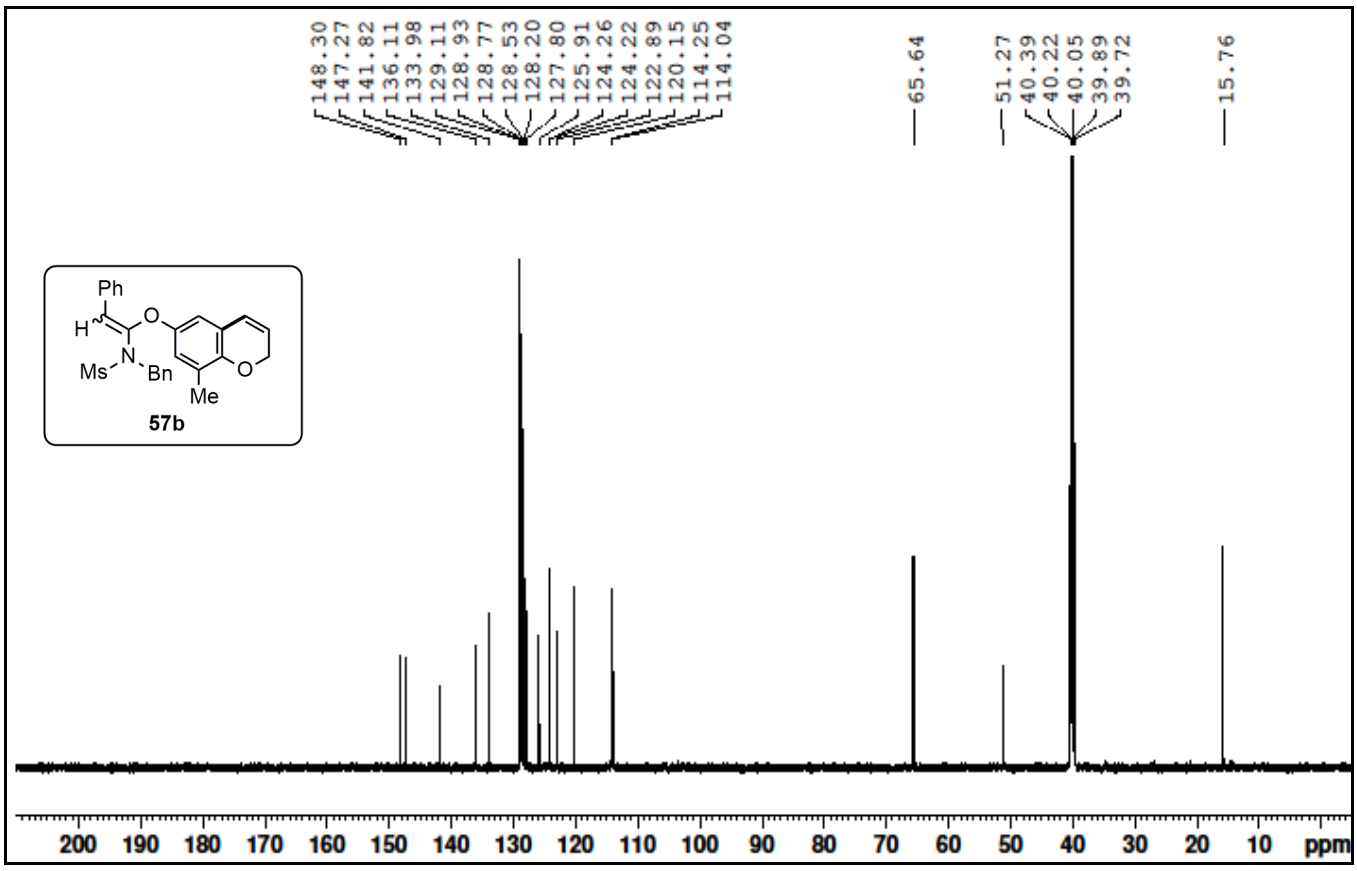
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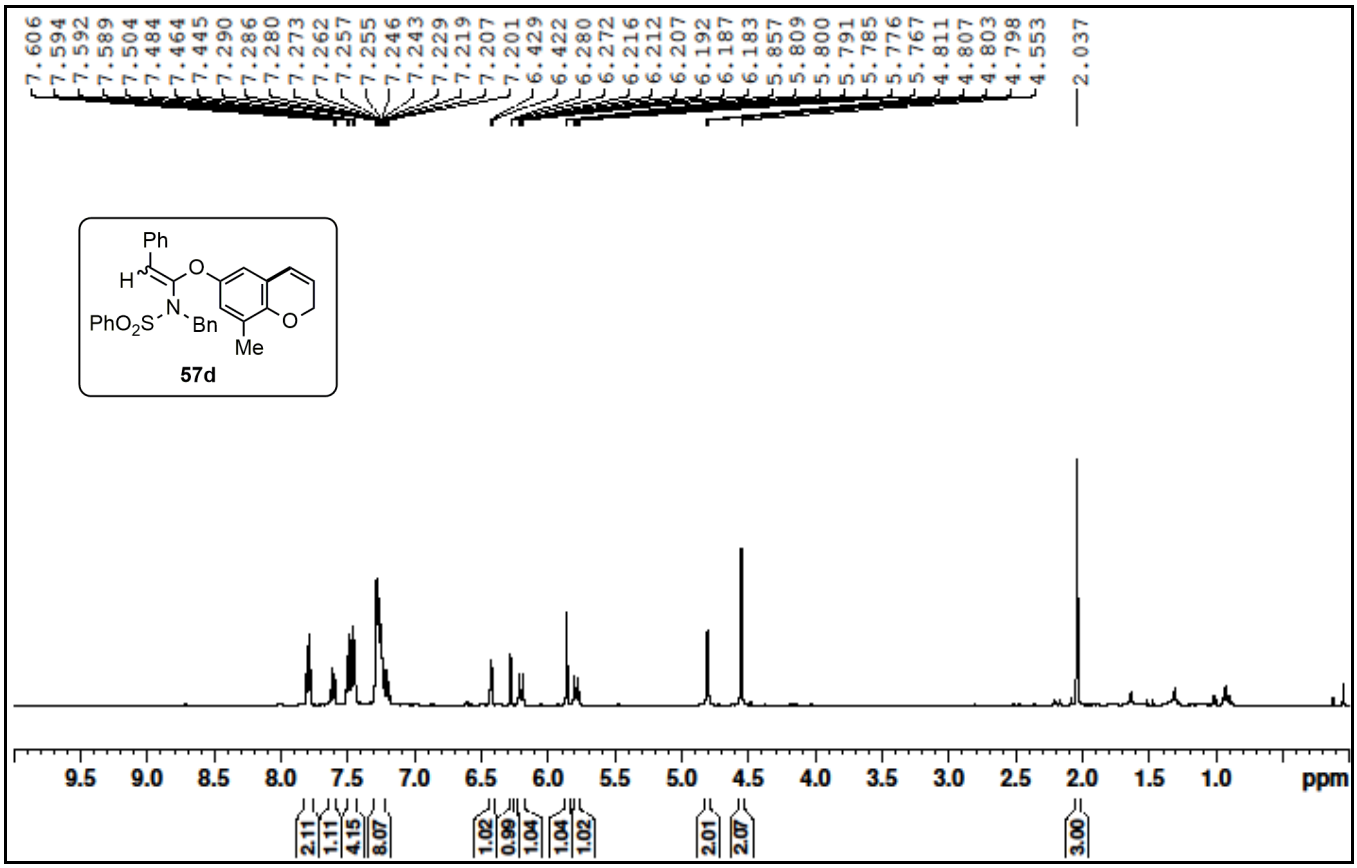
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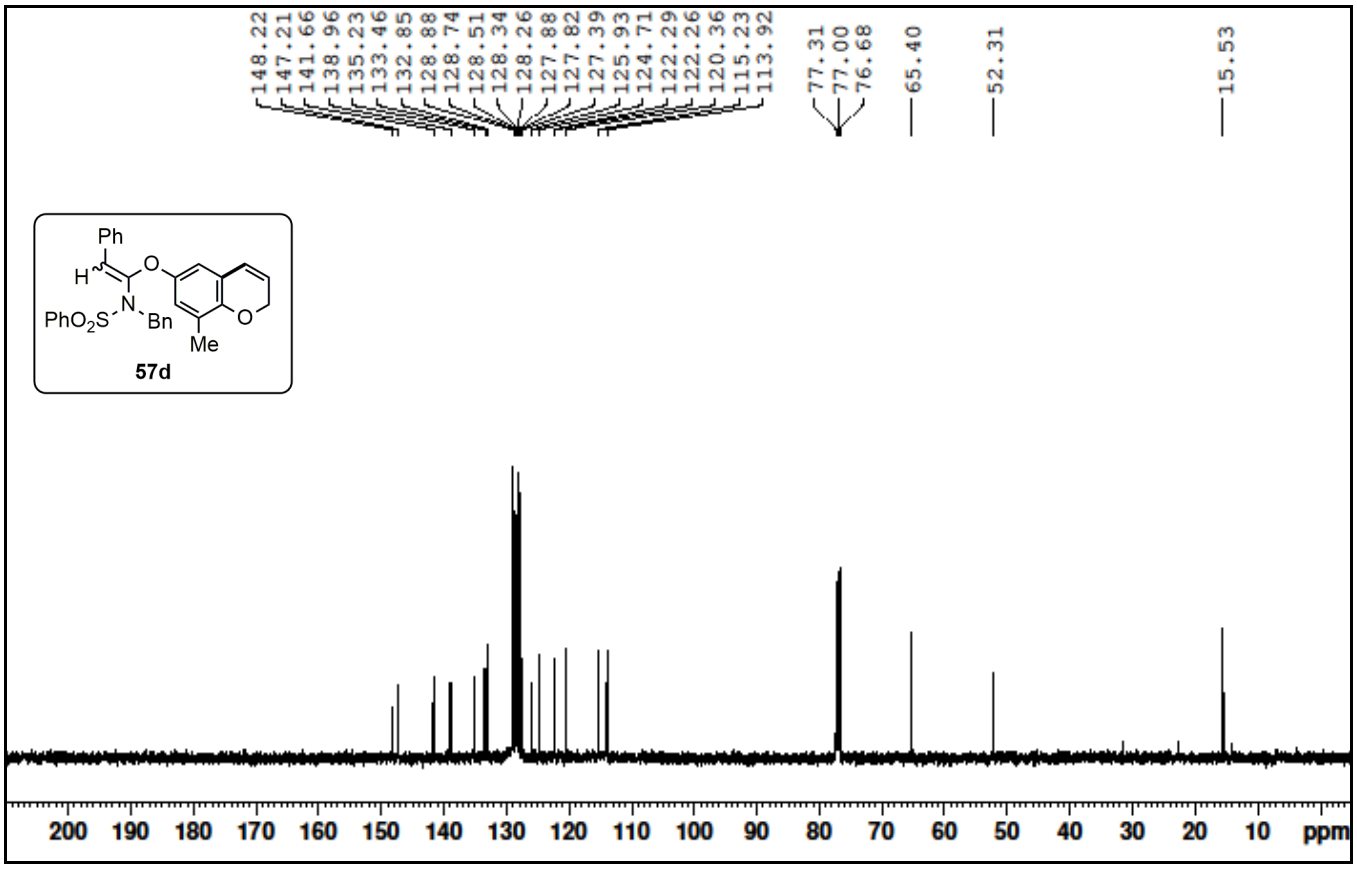
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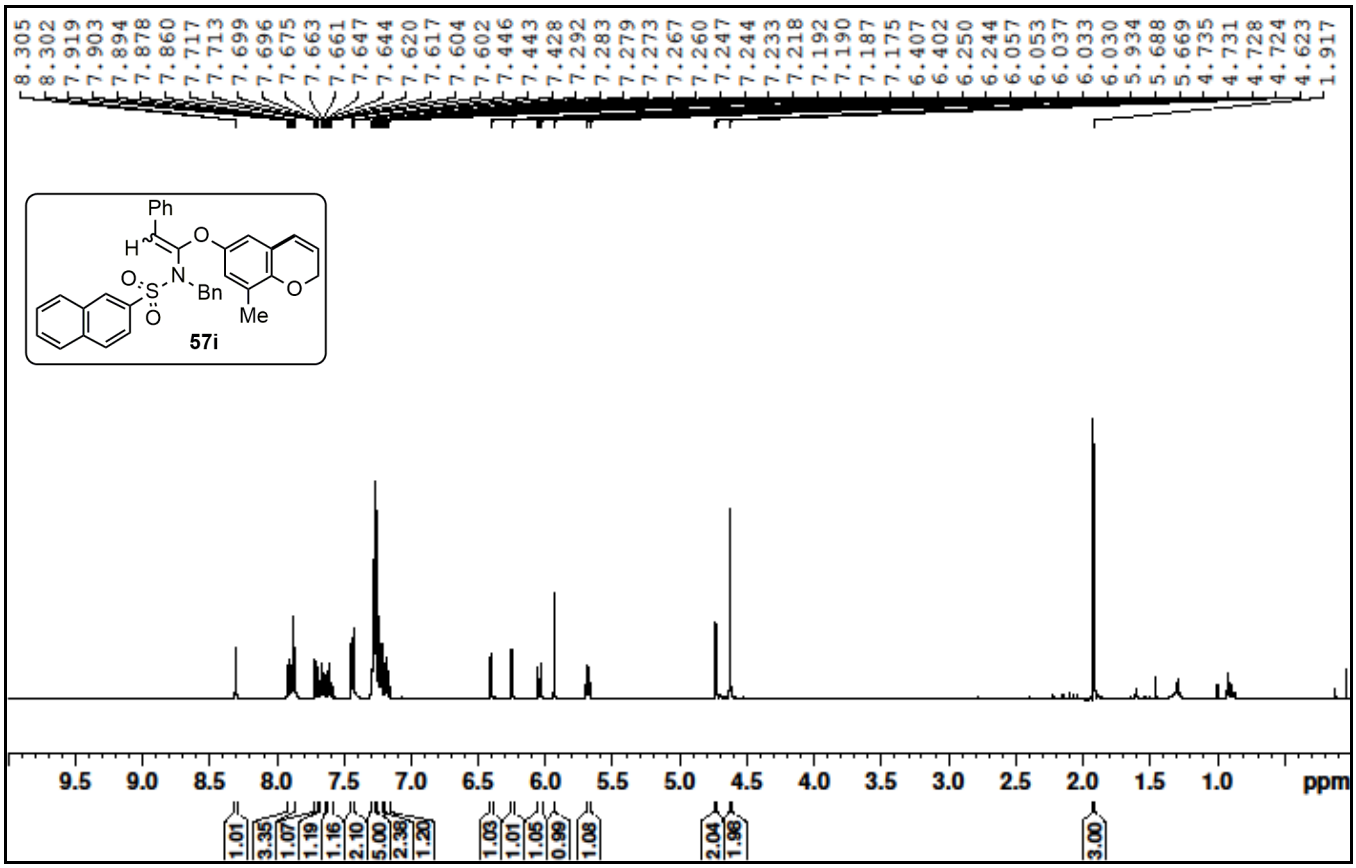
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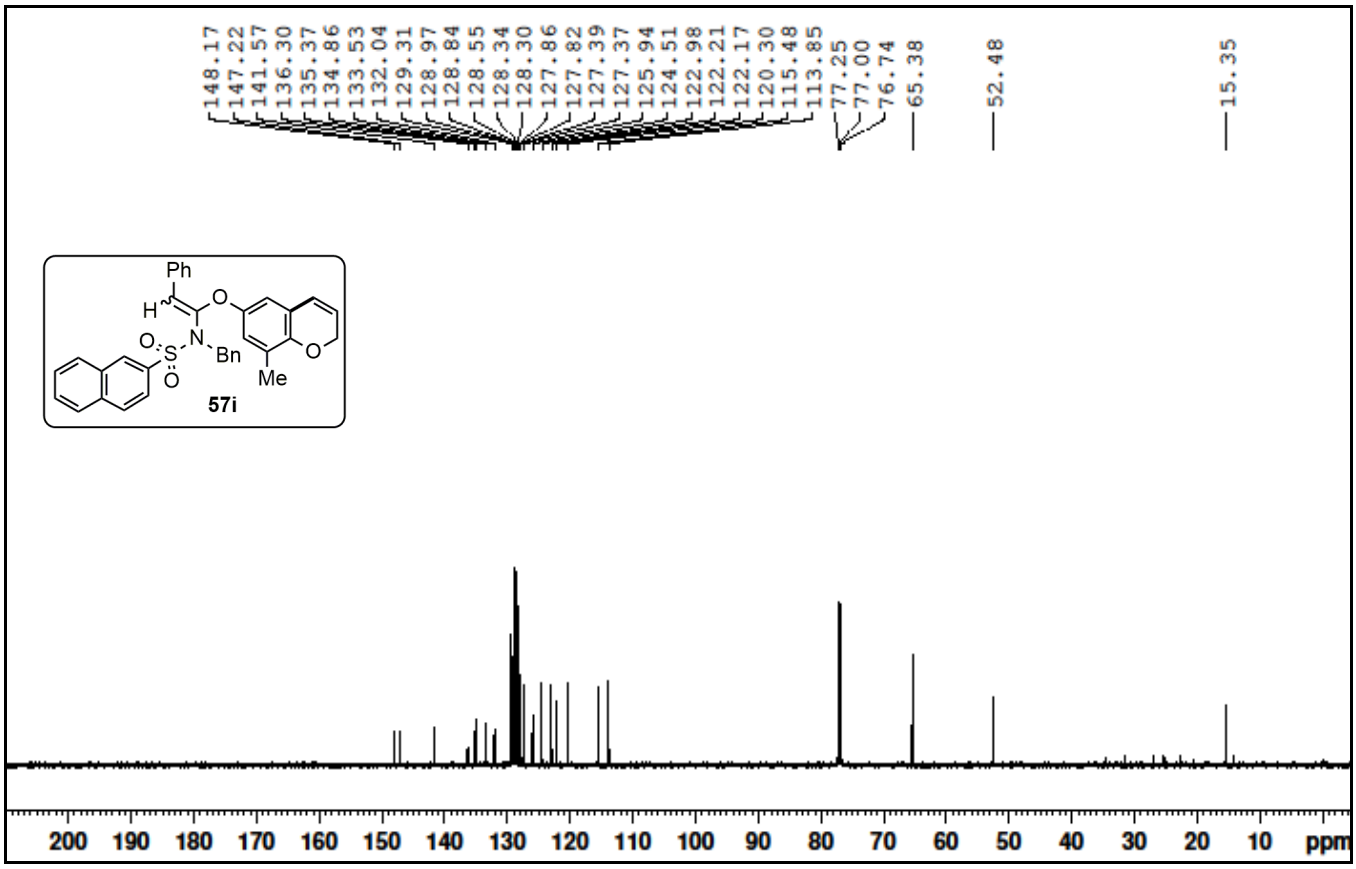
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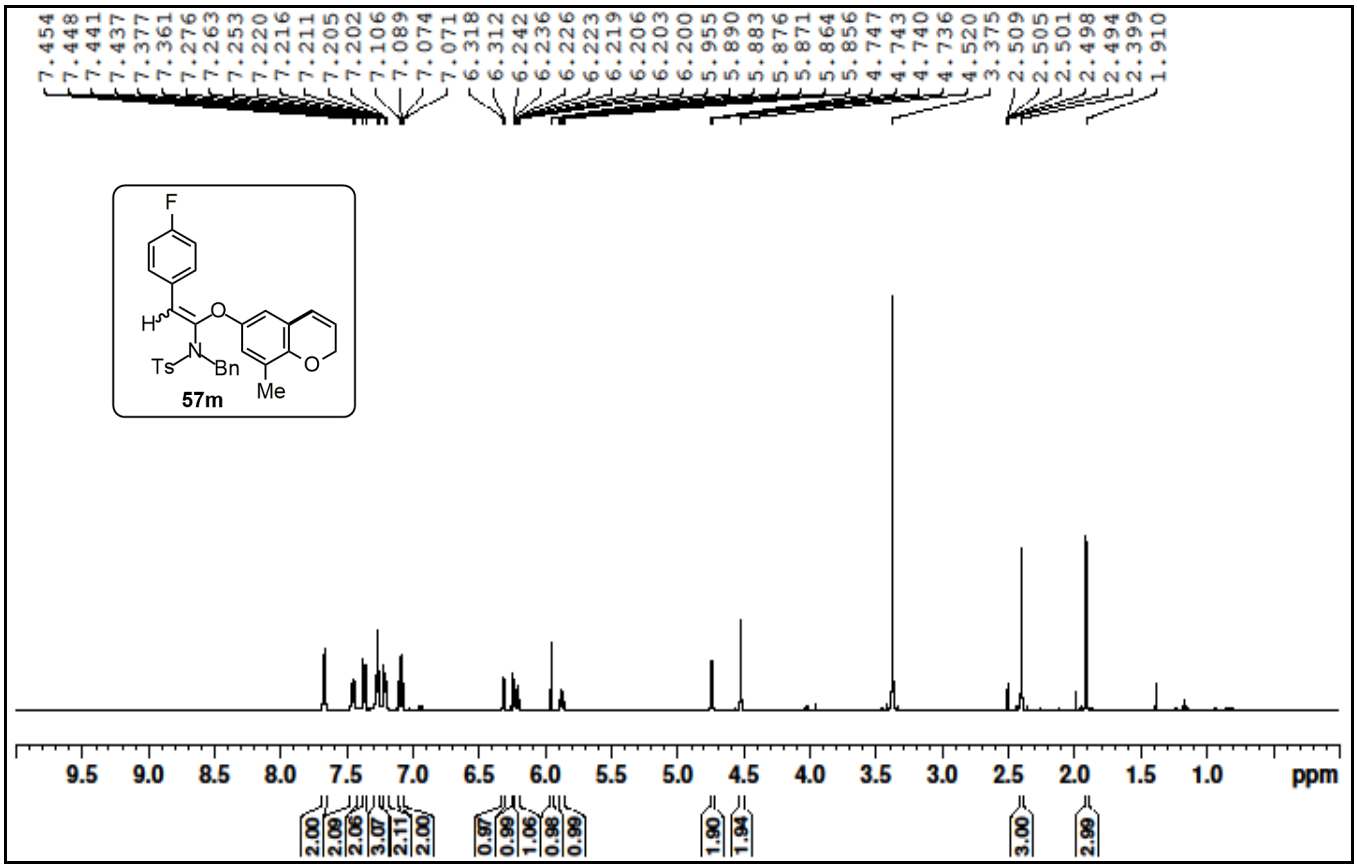
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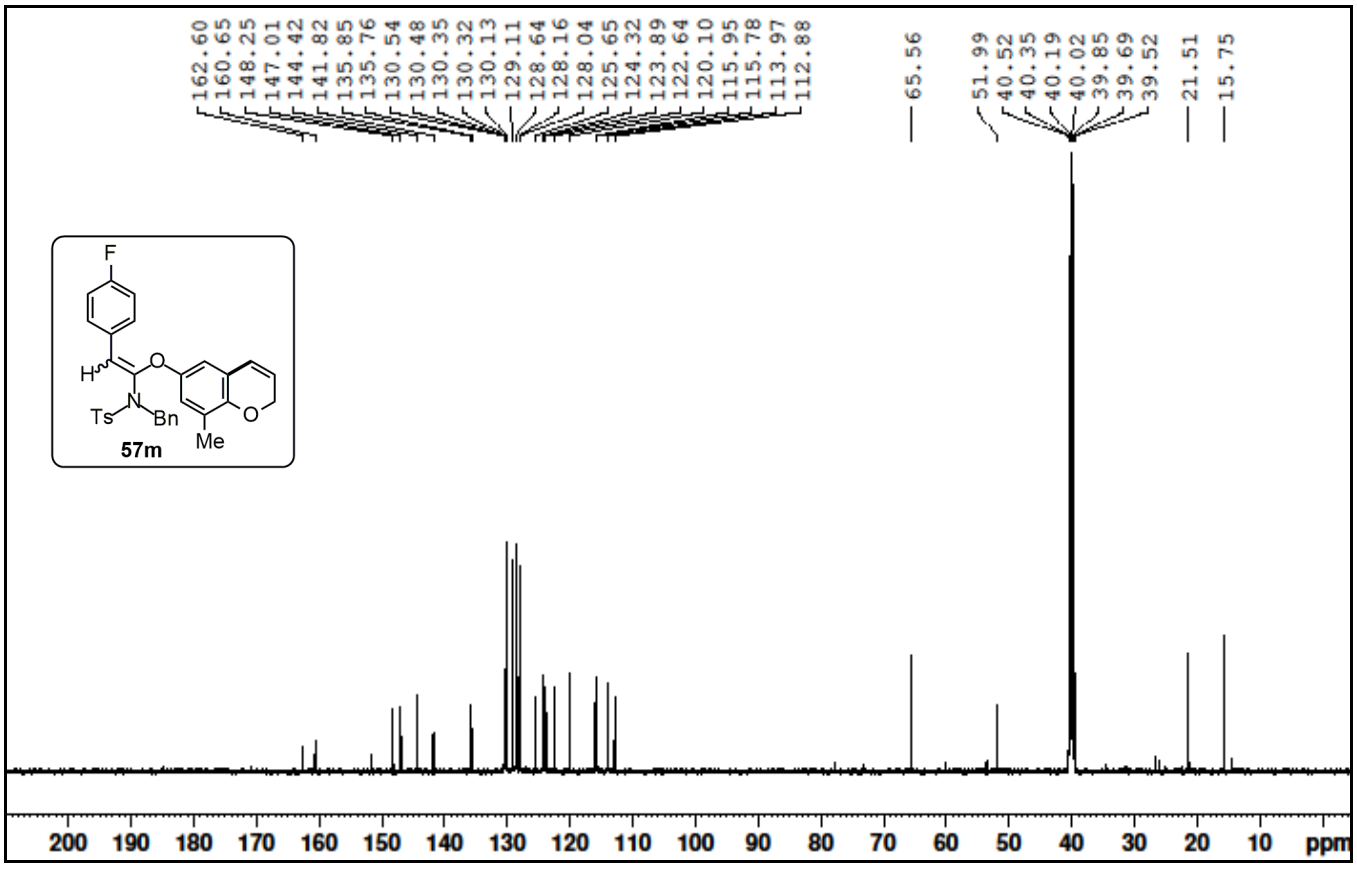
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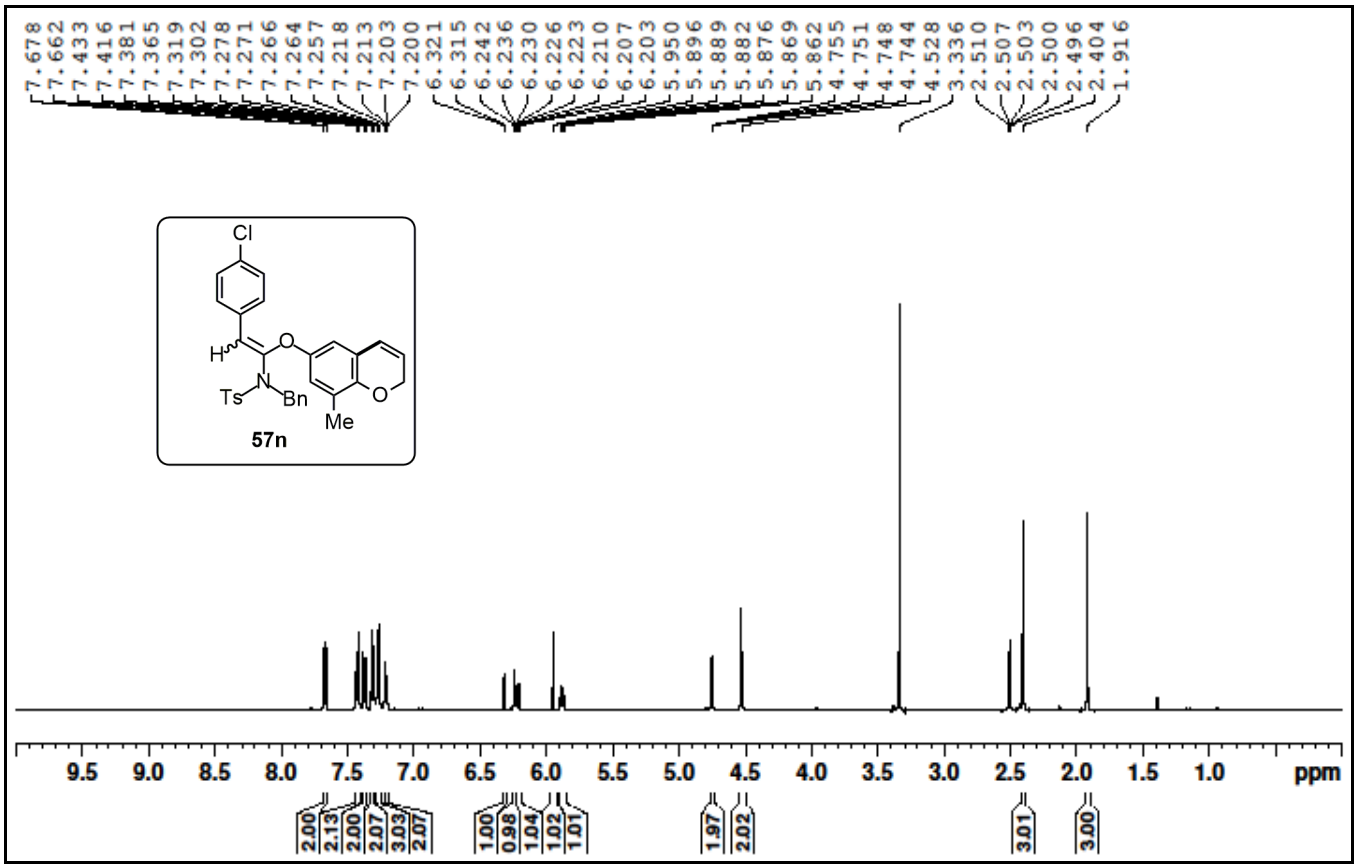
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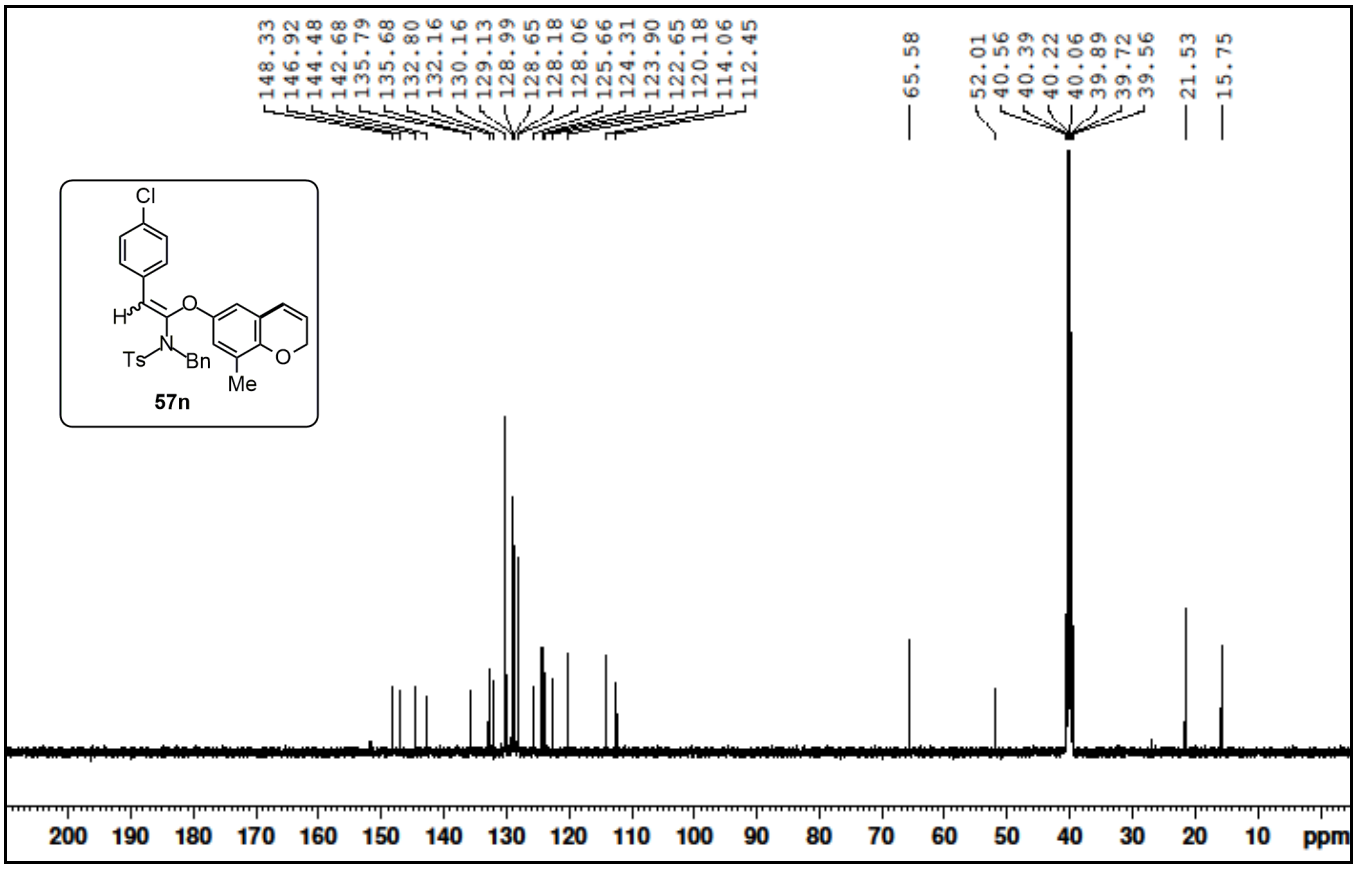
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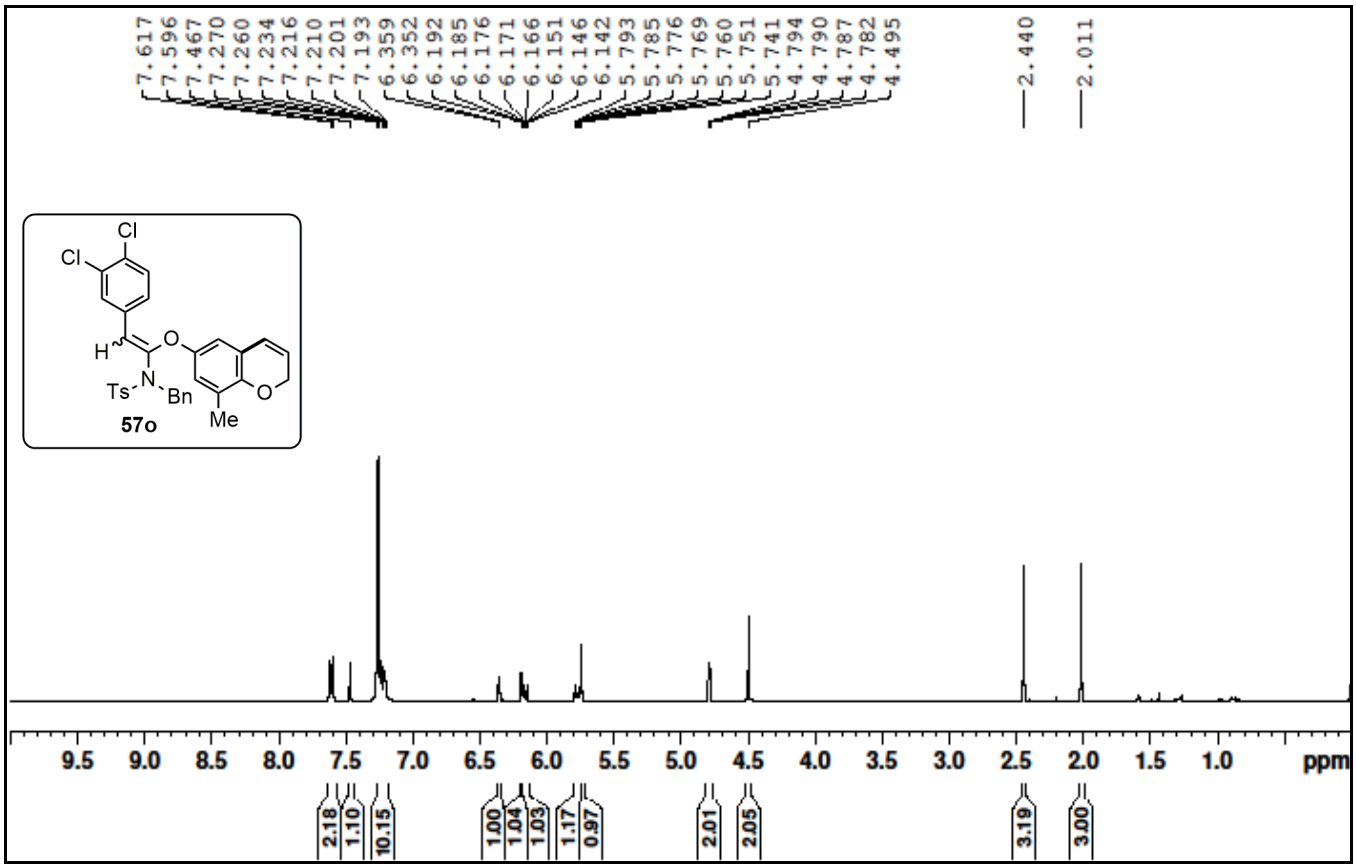
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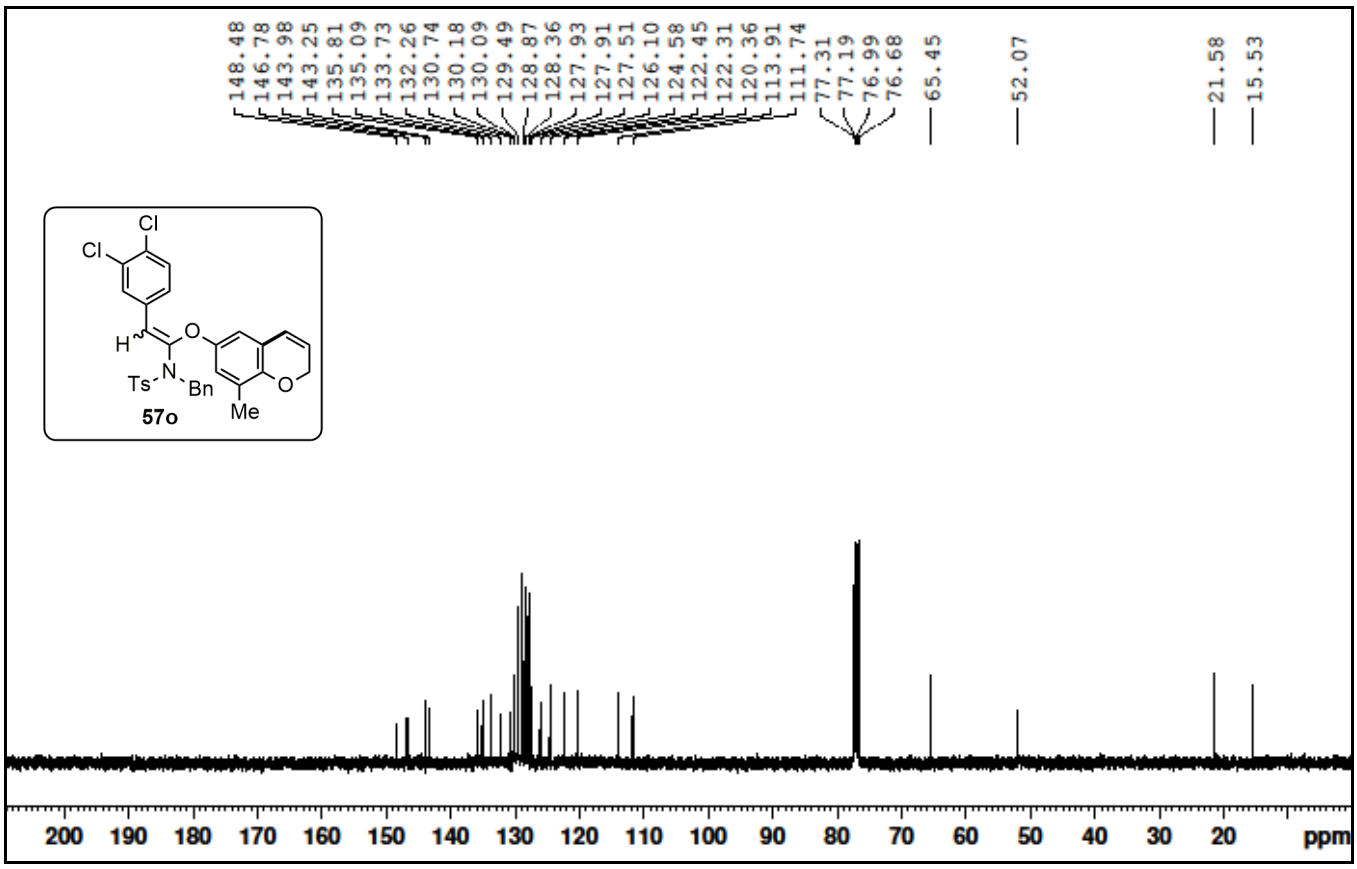
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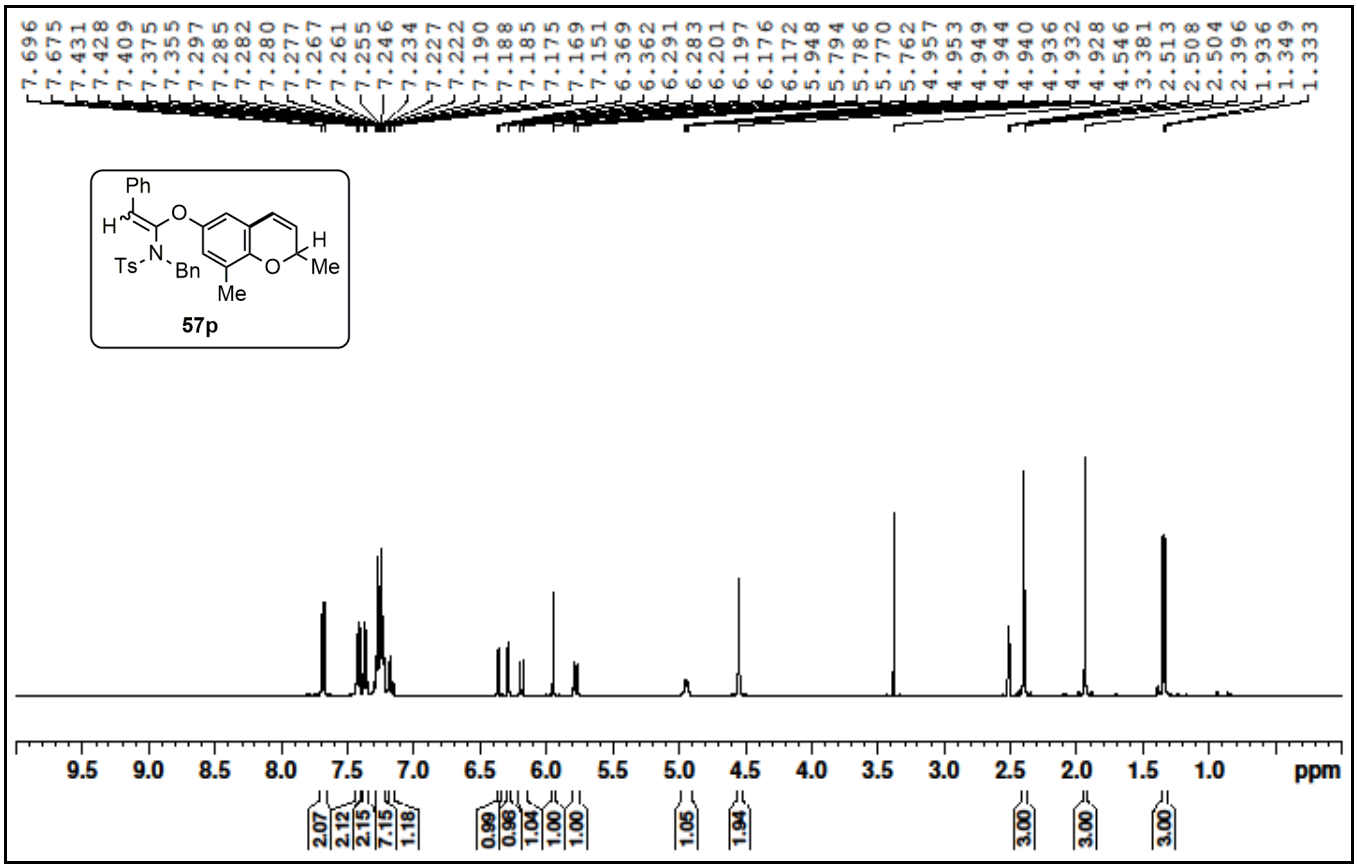
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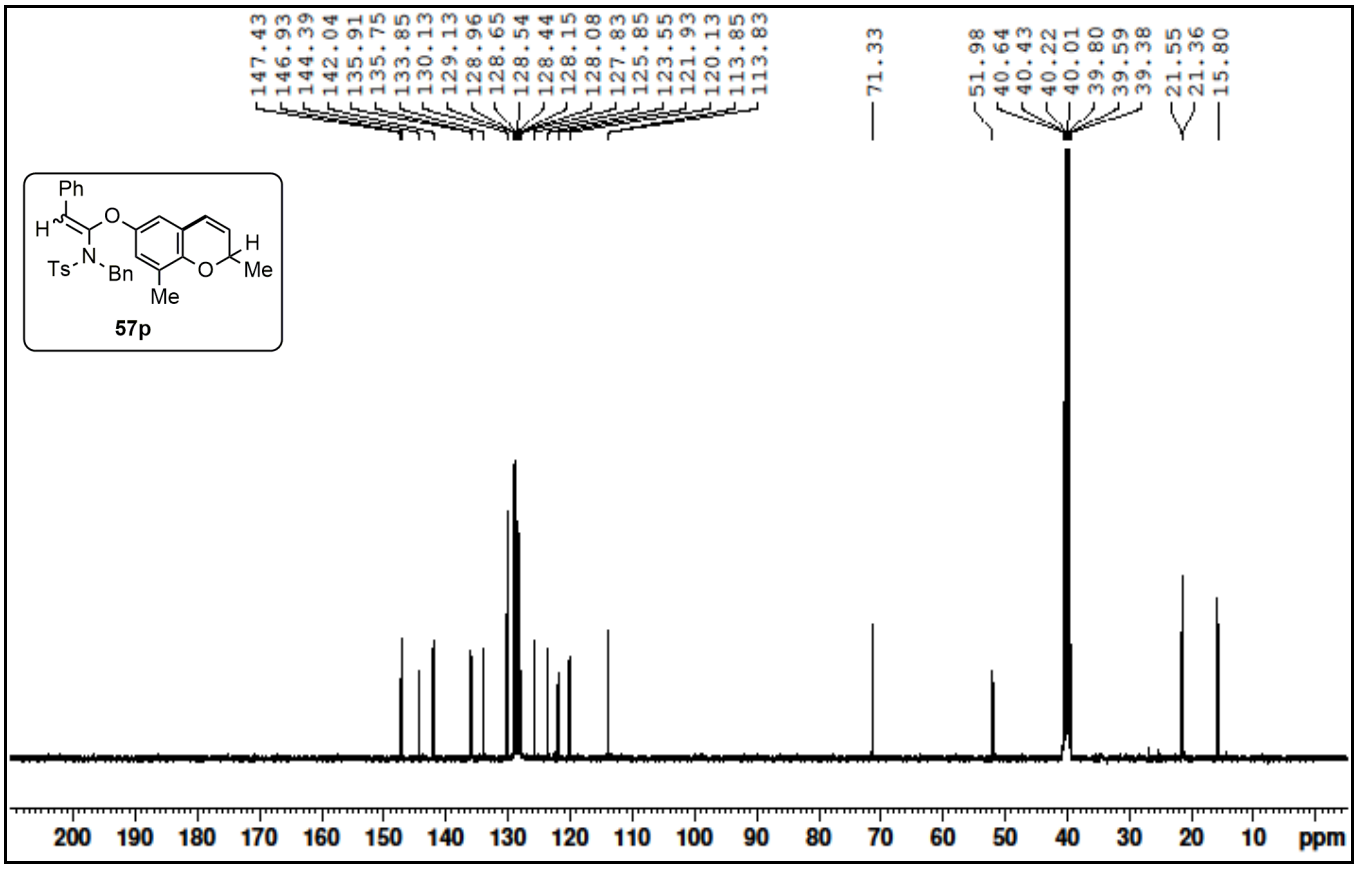
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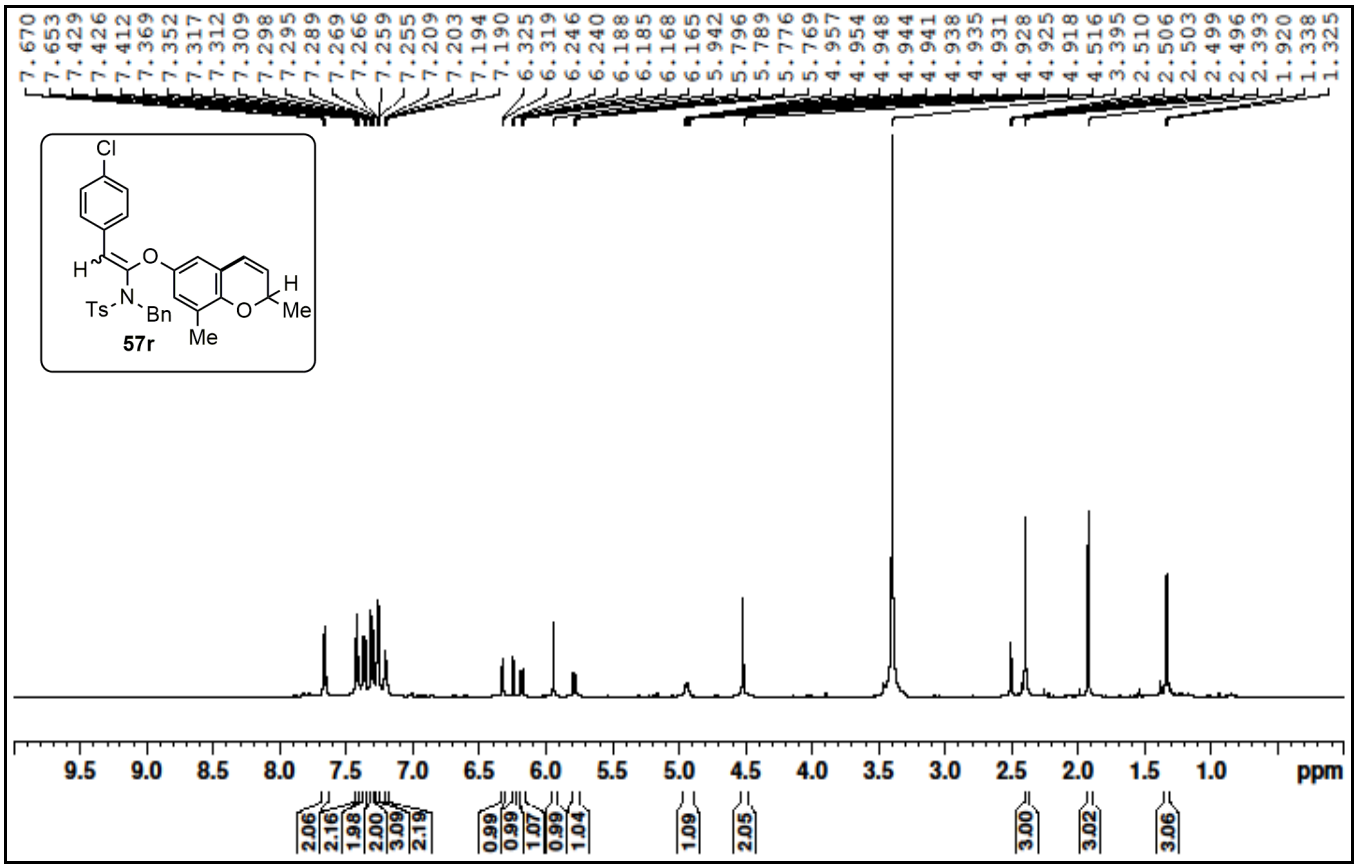
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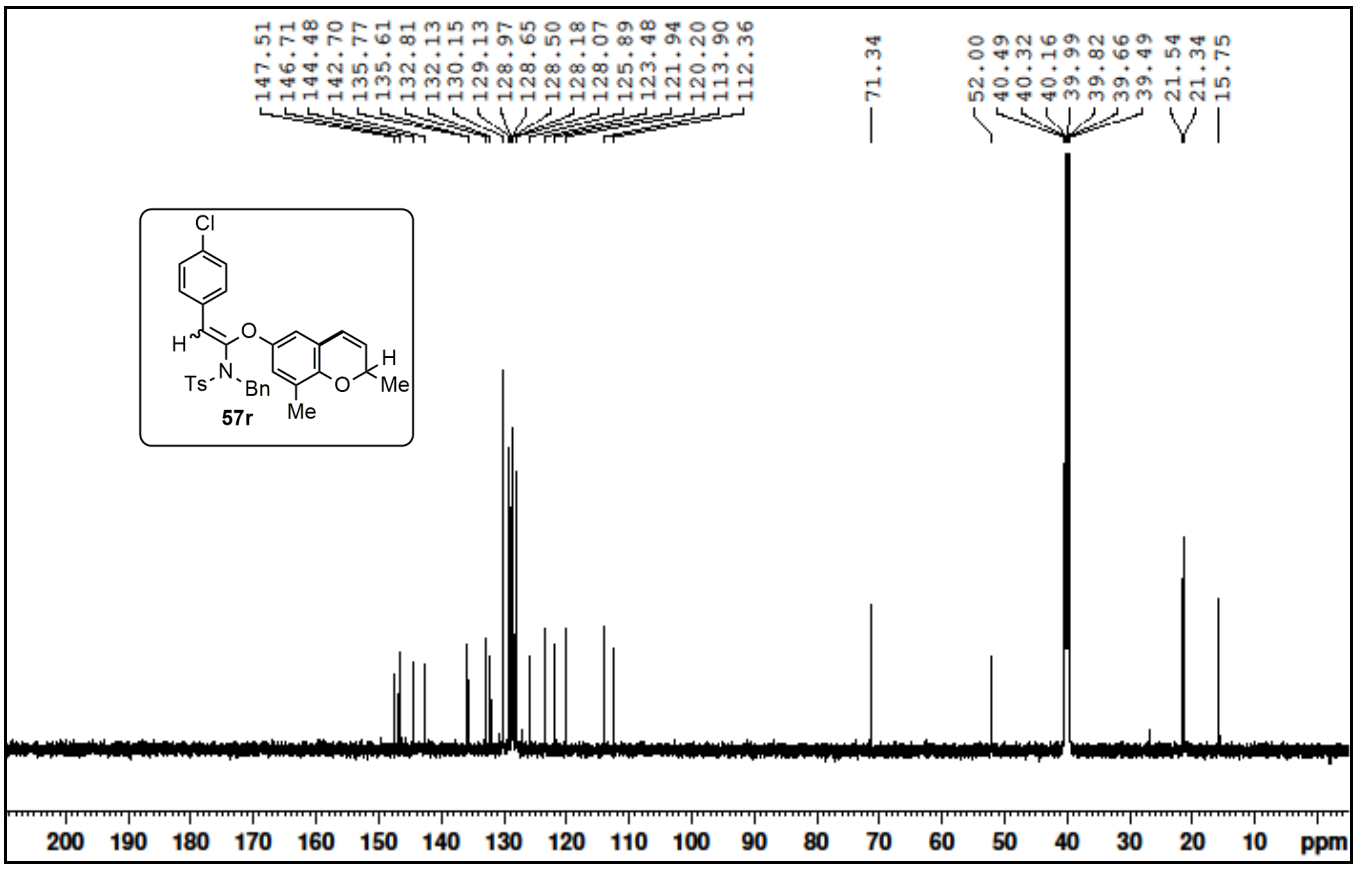
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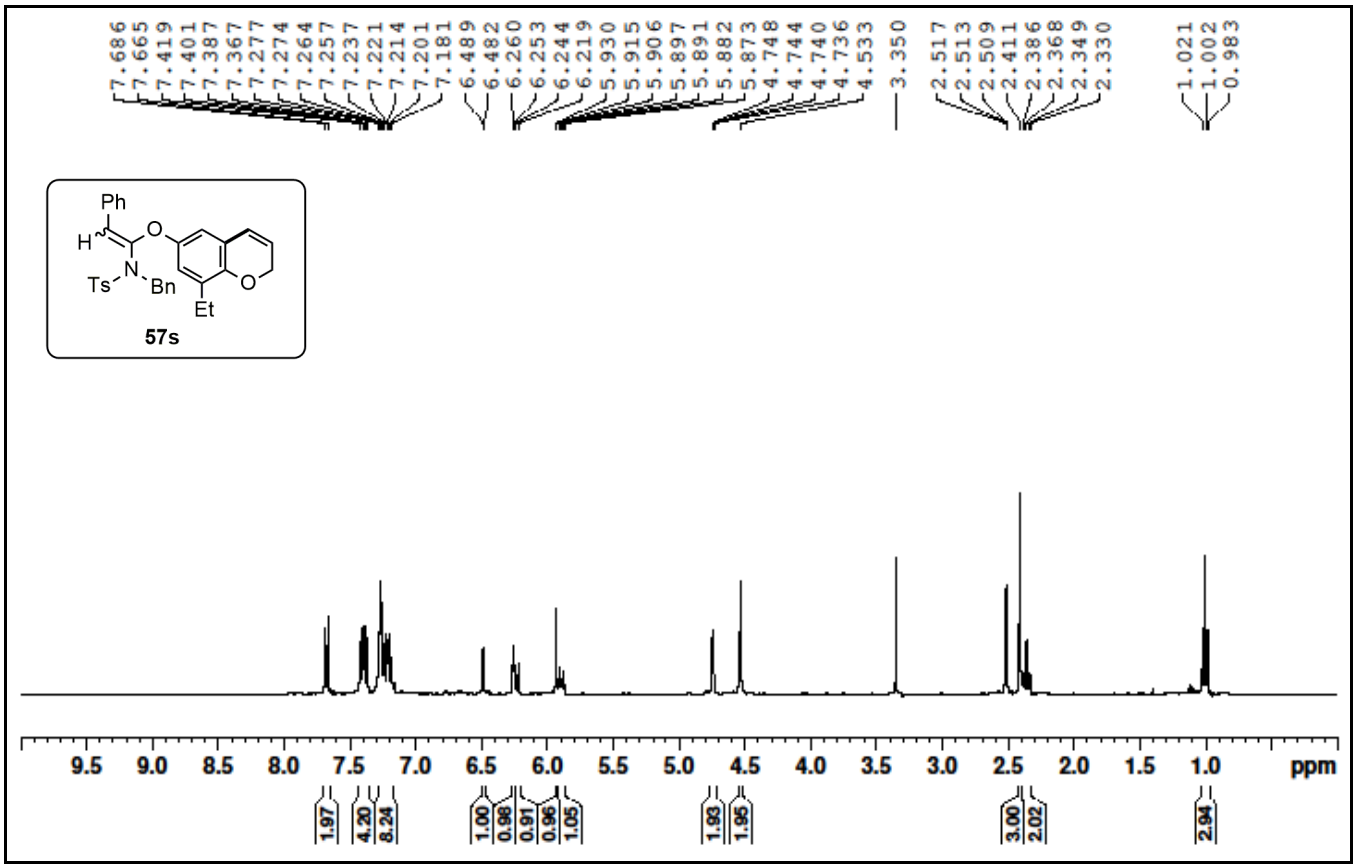
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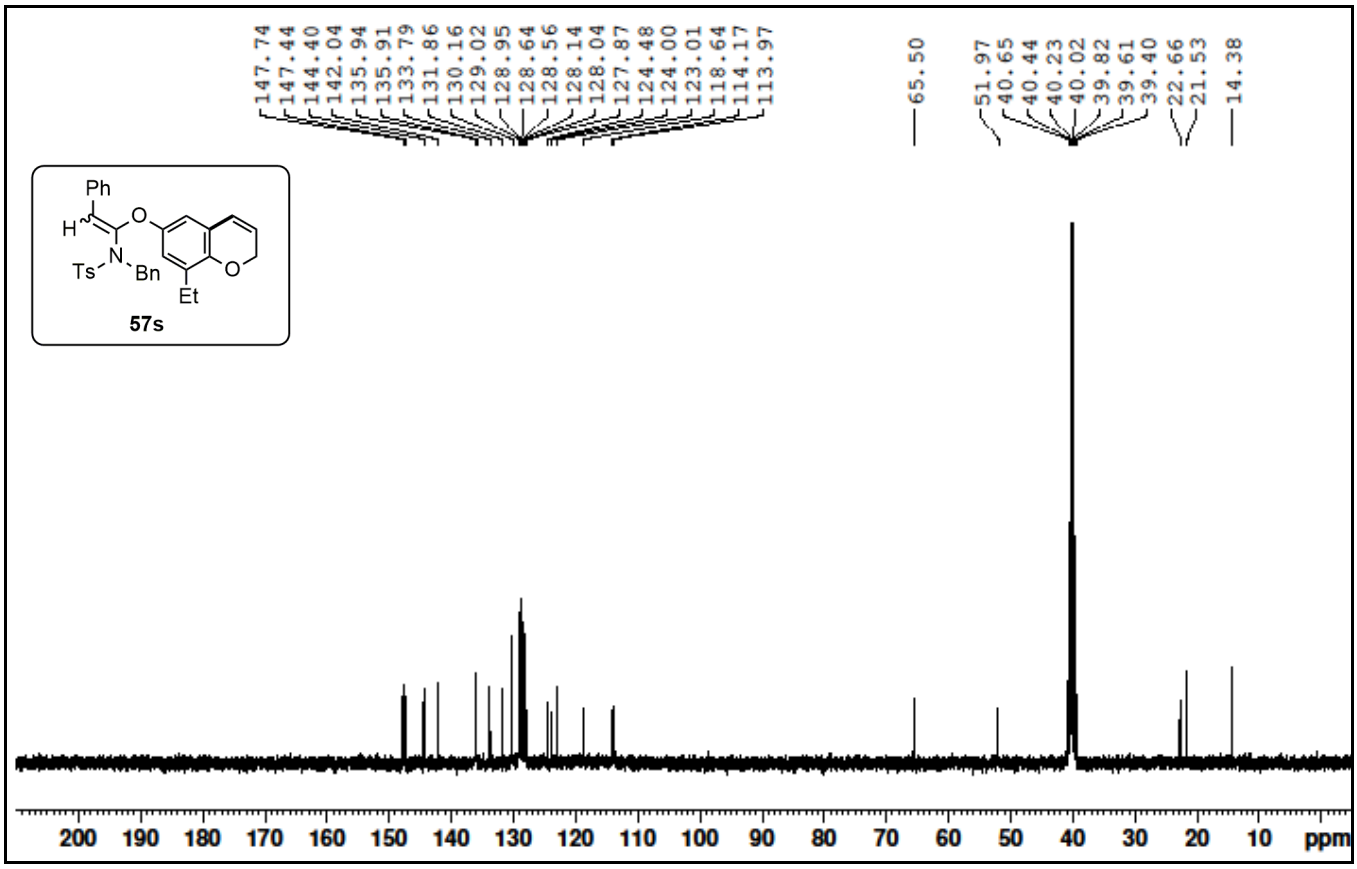
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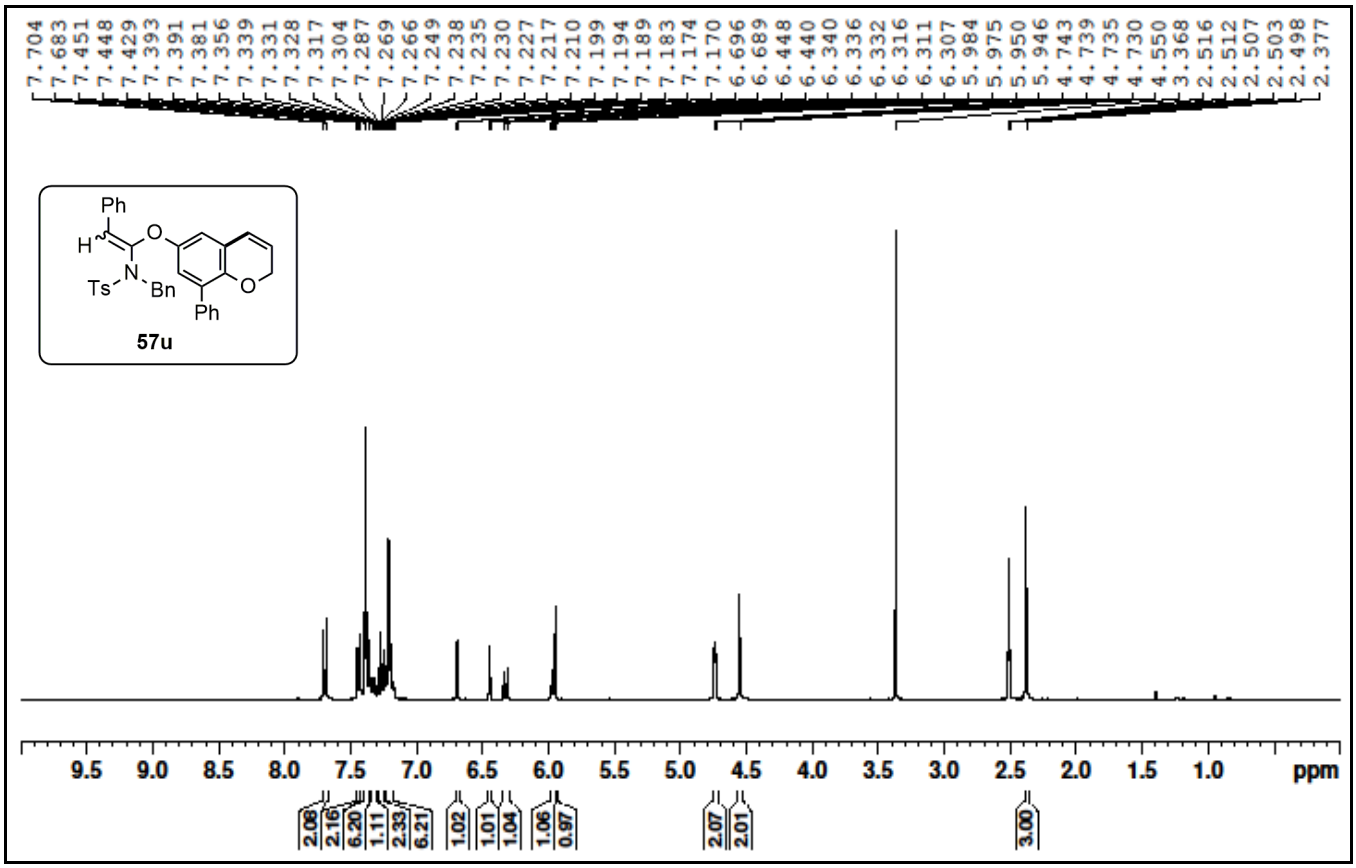
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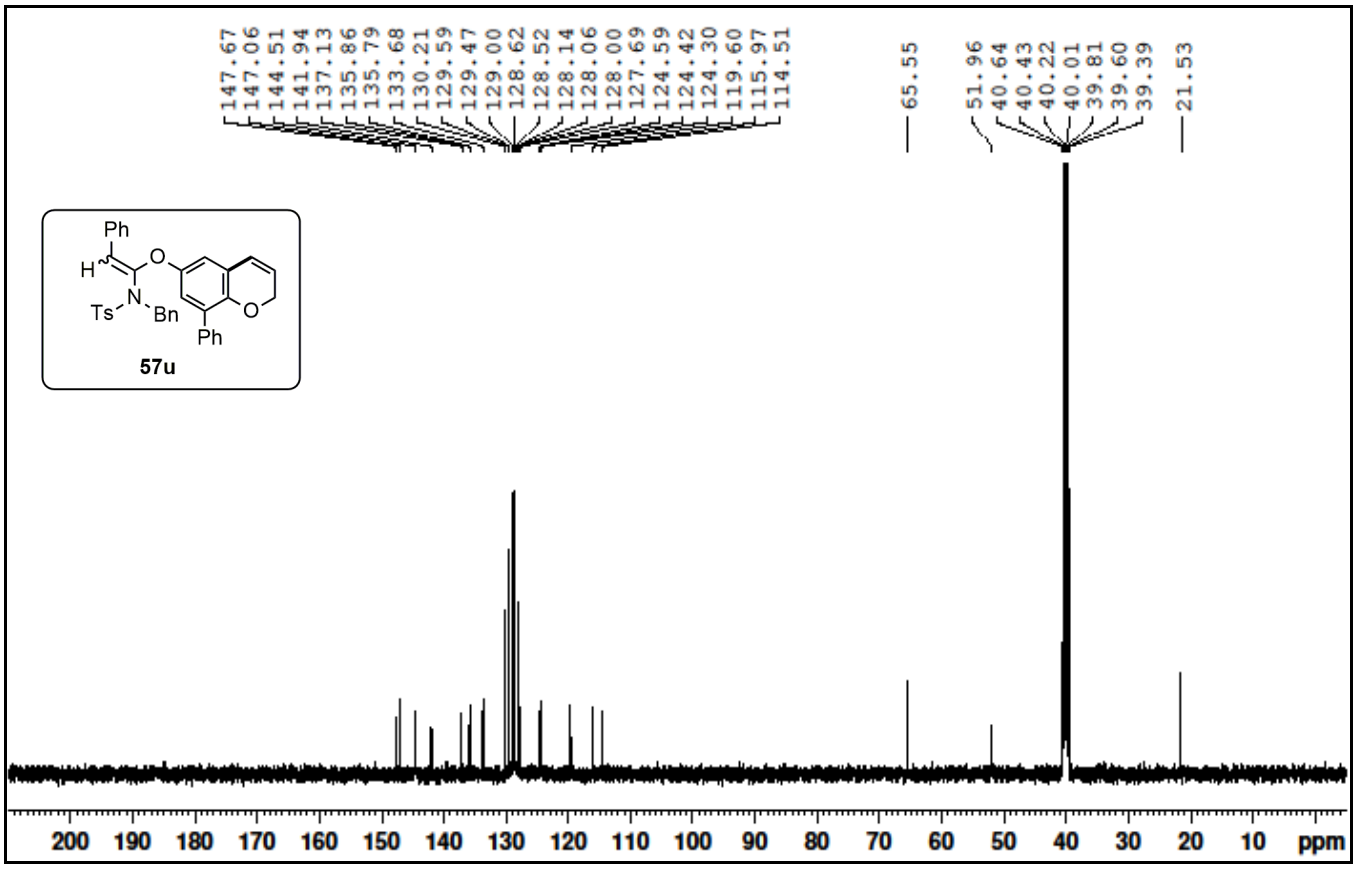
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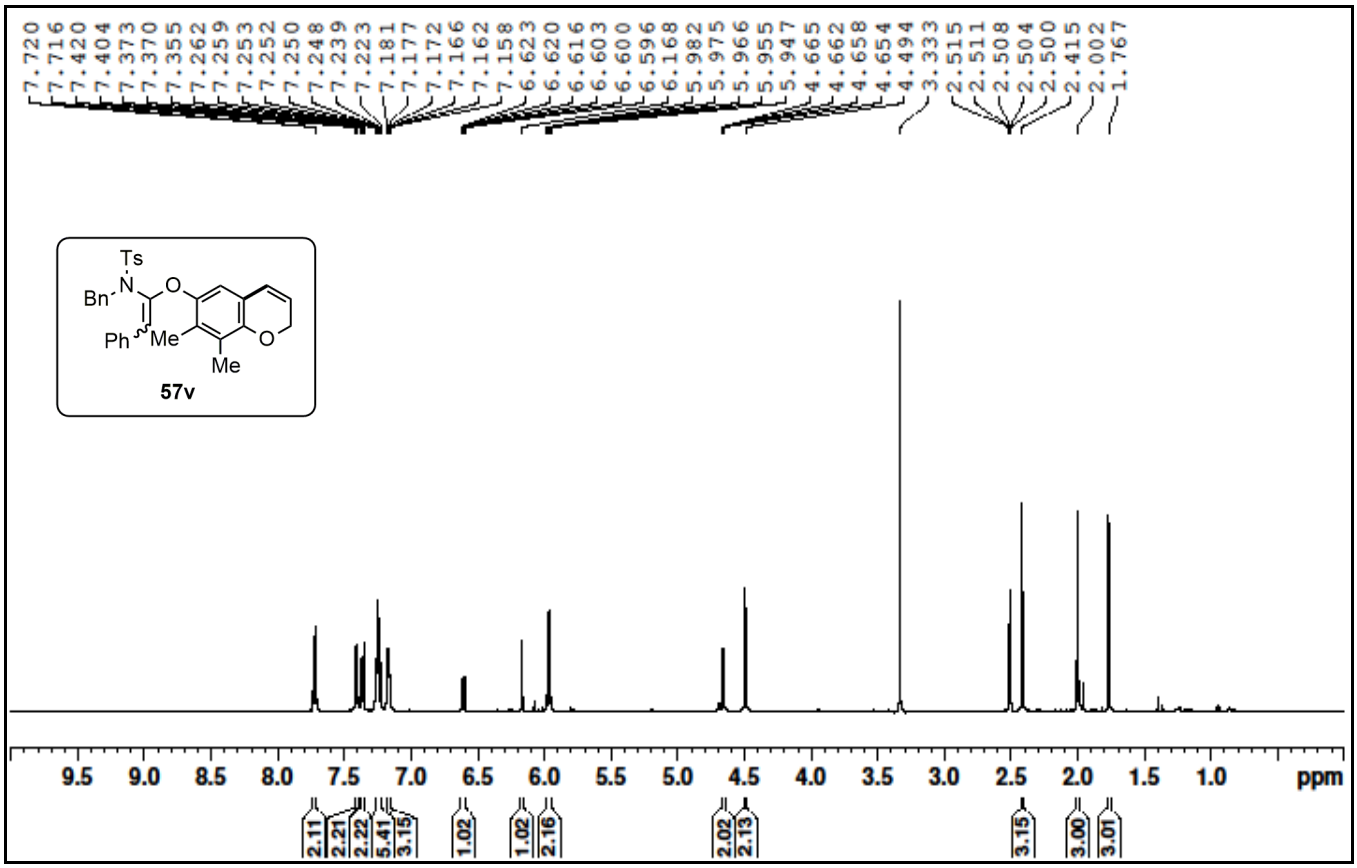
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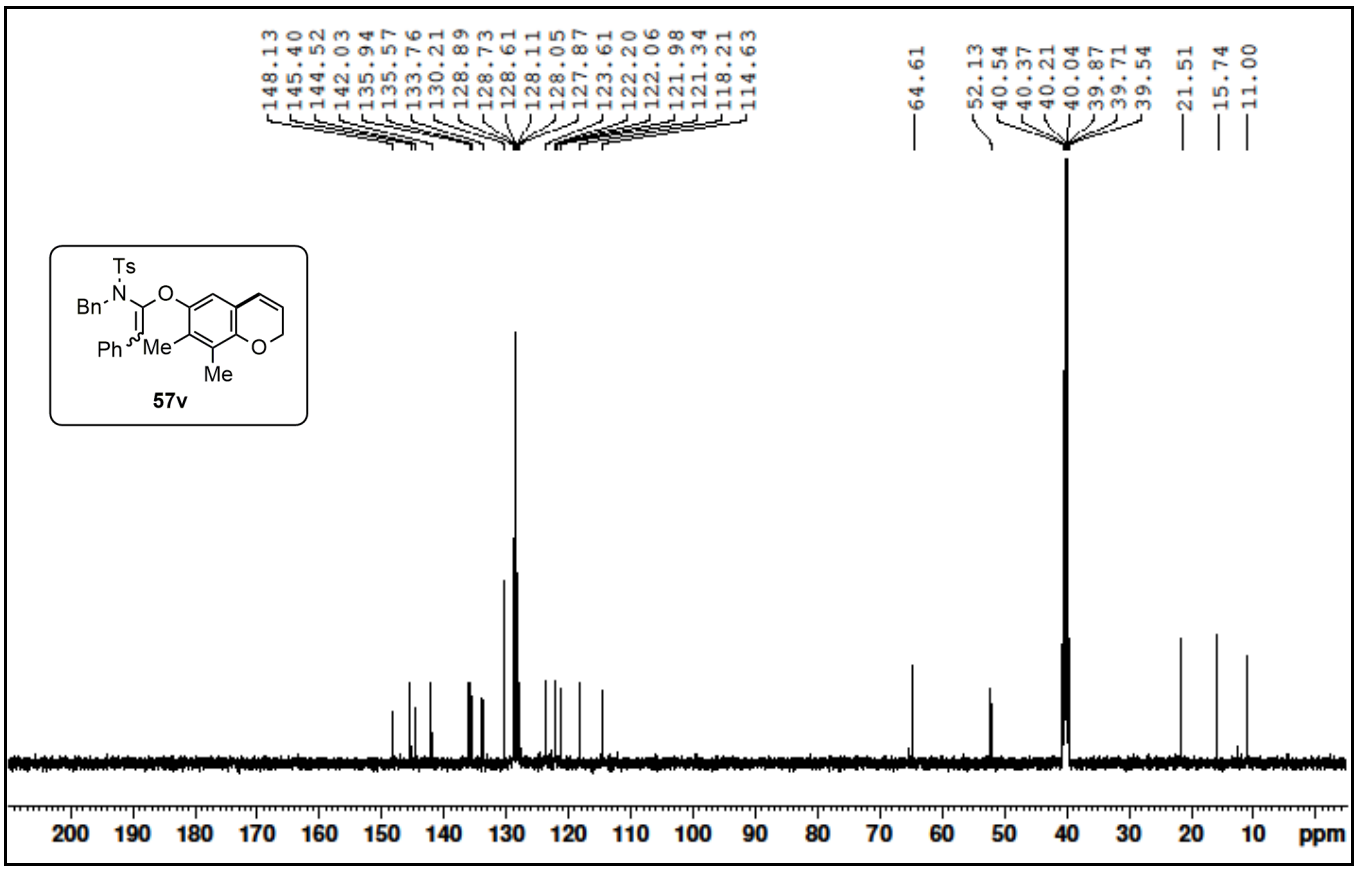
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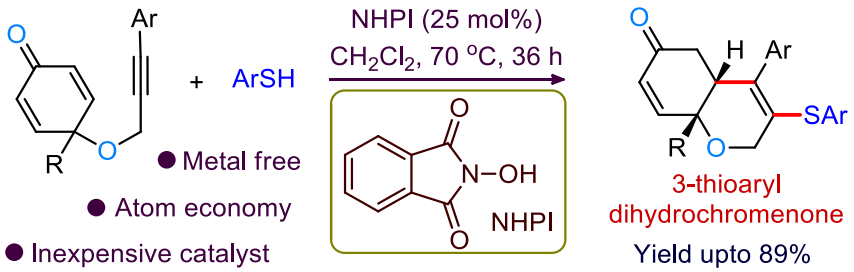
Chapter-4

This chapter is divided in two sections. The Section-A discusses "Thioarylative Radical Cyclization of Yne-Dienone". The Section-B describes "Access to α-aryl-α,β-Unsaturated Ketones via Lewis Acid Mediated Meyer-Schuster Rearrangement of Yne-Dienone".

Section-A: Thioarylative Radical Cyclization of Yne-Dienone

Abstract



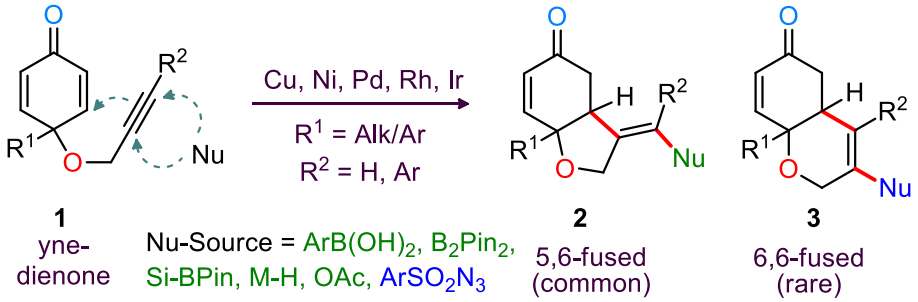
Demonstrated herein a N-hydroxypthalimide (NHPI) mediated chemo- and regioselective radical cyclization of alkynyl-cyclohexadienone with aryl-thiols to construct 3-thioaryl bearing [6,6]-fused dihydrochromenone derivatives. This transformation tolerates common functional groups and has broad scope. The reaction proceeds via the attack of a thioaryl radical to alkyne over the activated Michael acceptor. The involvement of radical intermediate is confirmed by TEMPO quenching experiment. Synthetic versatility of 3-thioaryl bearing dihydrochromenones is also showcased.

Reference:

Rajendra K. Mallick, Shubham Dutta, Rajeshwer Vanjari, Arnaud Voituriez, and Akhila K. Sahoo* *J. Org. Chem.* **2019**, *84*, 10509−10517.

4A.1. Introduction

Radical cascade transformations are synthetically valuable as these strategies have been largely used for the construction of complex molecular frameworks from readily accessible precursors.[1] Especially, mild reaction conditions of the radical processes are compatible to many common functional groups and hence synthetically viable. In general, the intramolecular radical cascades are feasible over the intermolecular processes.[1b] Particularly, the cascade annulations via intermolecular radical addition to the double bond [i.e. C=C, C=N, and/or C=O] are well exhibited;[2] indeed further investigations is required to examine the identical transformation with triple bonds [C≡C or C≡N].[3]



Scheme 4A.1. TM- catalyzed nucleophile triggered cyclization

The alkynylcyclohexadienone **1** demonstrate an unequivocal importance in chemistry as these motifs are amenable to diverse annulations and synthesis of novel structural entities.[4] Some noteworthy transformations involve the transition-metal (TM)-catalyzed borylative/ silylative/ arylative/reductive/sulfonylative, and acetate triggered cyclization of yne-dienones (**Scheme 4A.1**). Most of these transformations primarily happen via nucleophile assisted 5-*exo*-trig cyclization providing [5,6]-fused heterocycles **2** (**Scheme 4A.1**).[5,6] Whereas a similar 6-*exo*-trig cyclization for the construction of [6,6] fused skeletons **3** are less explored.[7] Thus, harsh reaction conditions and use of expensive TM-catalysts are essential for the cyclization of alkynyl-cyclohexadienones, which limits wide synthetic applications. Despite these challenges, the development of metal-free

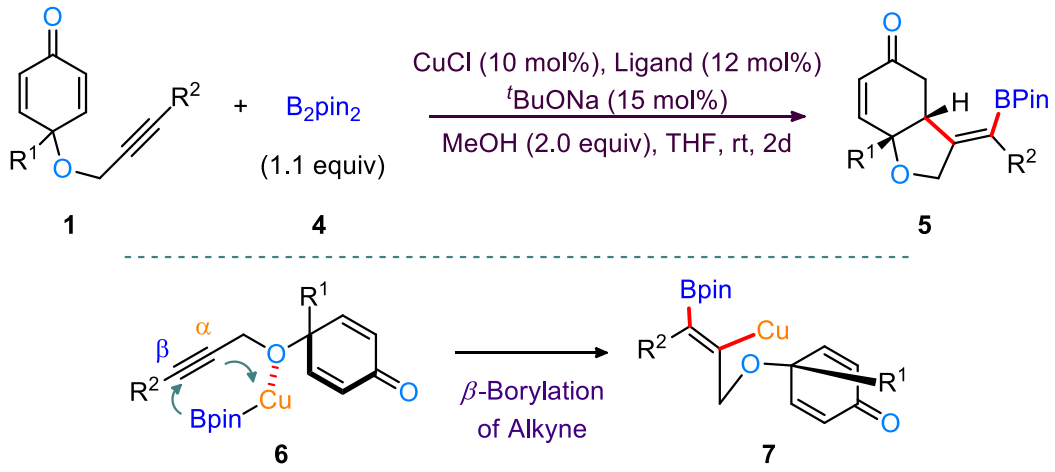
intermolecular radical cyclization of alkynyl cyclohexadienone **1** to [6,6]-fused dihydrochromenone is a worthwhile endeavor.

4A.2. Precedents

Alkynyl cyclohexadienone has been largely used for various transition-metal catalyzed cyclization reactions. Some selected examples for the synthesis of 5,6-fused and 6,6-fused bicyclic systems from alkynyl cyclohexadienones are discussed below (**Scheme 4A.2–4A.12**).

4A.2.1. Transition metal catalyzed 5-*exo*-trig nucleophilic cyclization

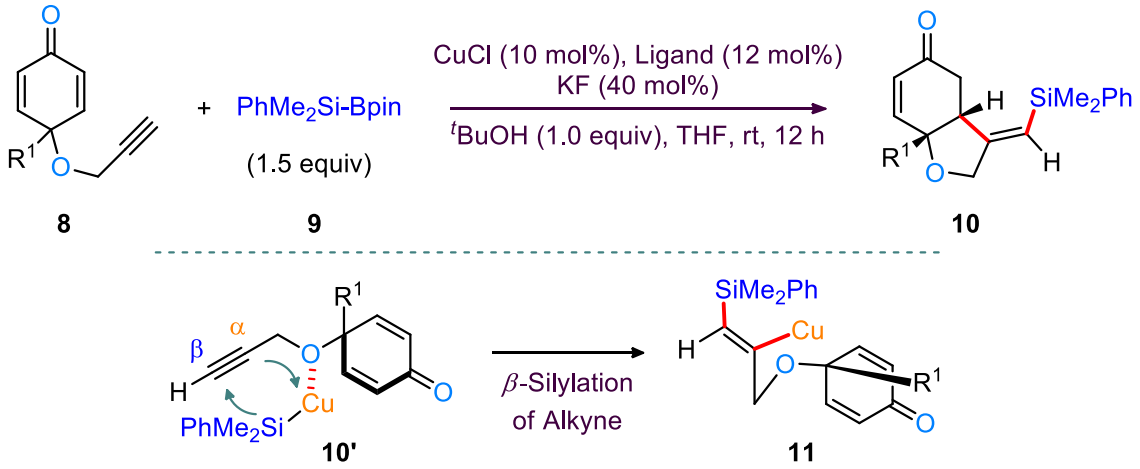
Lin and co-workers developed a protocol for copper catalyzed borylative cyclization of alkynyl cyclohexadienone **1** to furnish an enantiopure *cis*-hydrobenzofuran core **5** containing alkenylboronate and enone functionalities (**Scheme 4A.2**).[5c] The reaction proceeds with the regioselective attack of copper boronate species to the *β*-position of alkynyl ether **6** to generate vinyl copper intermediate **7**. Next, intramolecular asymmetric 5-*exo*-trig cyclization of **Int-7** leads to the desired product **5**.



Scheme 4A.2. Copper catalyzed borylative cyclization

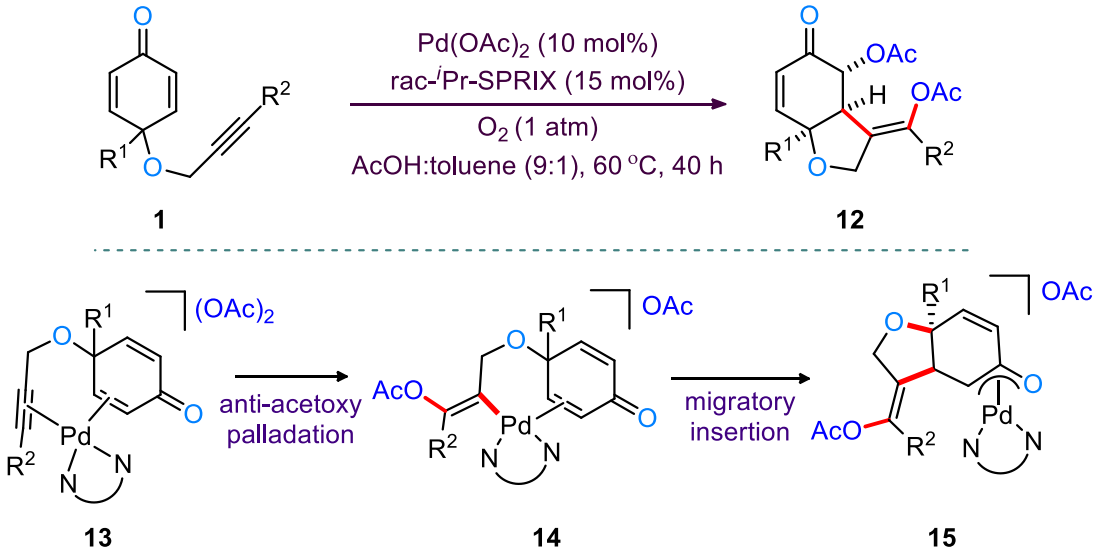
Later in 2019, the same group reported a regioselective silylcupration of terminal unactivated alkyne **8** followed by 5-*exo*-trig cyclization to yield the desired product **10** (**Scheme 4A.3**).[6f] This is the first example of asymmetric copper catalyzed silylative

cyclization on 1,6-enyne systems. The mechanism is similar to the previous borylative cyclization pathway (**Scheme 4A.2**).



Scheme 4A.3. Copper catalyzed silylative cyclization

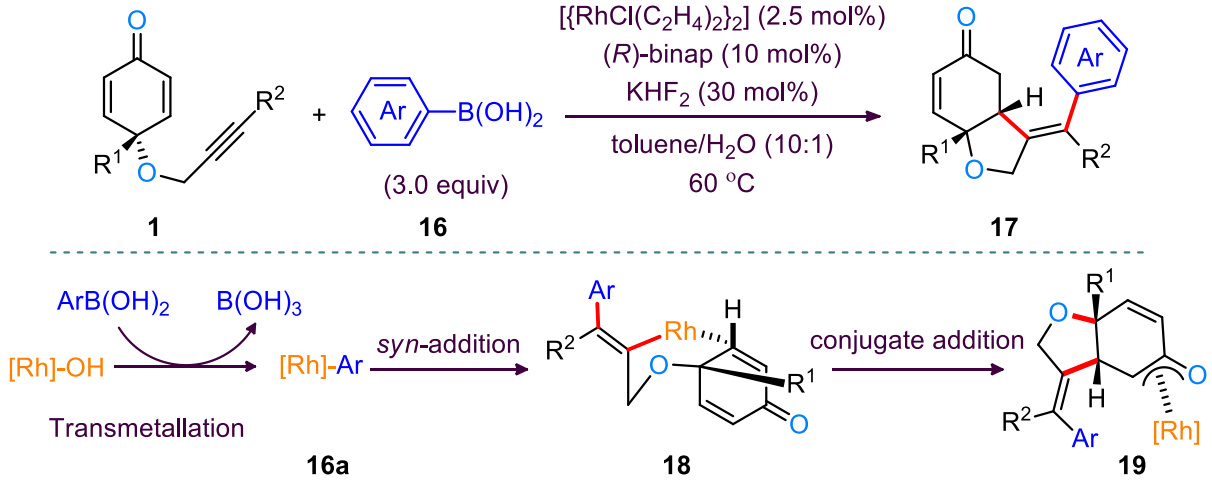
In 2014, Sasai and co-workers showcased an interesting demonstration of asymmetric cyclative diacetoxylation of alkynyl cyclohexadienone **1** with acetic acid in presence of palladium catalyst (**Scheme 4A.4**).[6b] An optically pure SPRIX ligand plays vital in the enantioselective cyclative diacetoxylation process. The mechanism involves the *anti*-acetoxypalladation of the activated carbon–carbon triple bond of complex **13** to give vinyl palladium intermediate **14**. Next, intramolecular migratory insertion of olefin followed



Scheme 4A.4. Palladium catalyzed acetate anion triggered cyclization

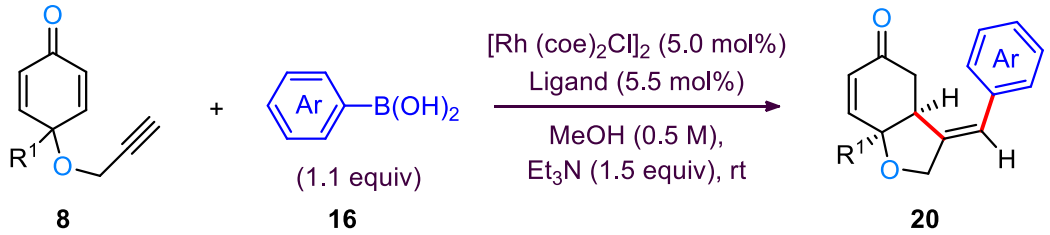
by the nucleophilic displacement of acetate anion delivers the diacetoxylated product **12**.

In 2013, Lin group demonstrated a rhodium catalyzed arylative cyclization of boronic acid with internal alkyne of alkynyl cyclohexadienone **1** to furnish 5,6-fused heterocycles **17** (**Scheme 4A.5**).[5b] The transformation initiates with the transmetallation of rhodium catalyst with aryl boronic acid **16** to form aryl rhodium **16a**. Next, *syn*-addition of **16a** to alkyne **1** generates vinylic rhodium intermediate **18**. Finally, migratory insertion of **Int-18** and protonation gives the desired product **17**.



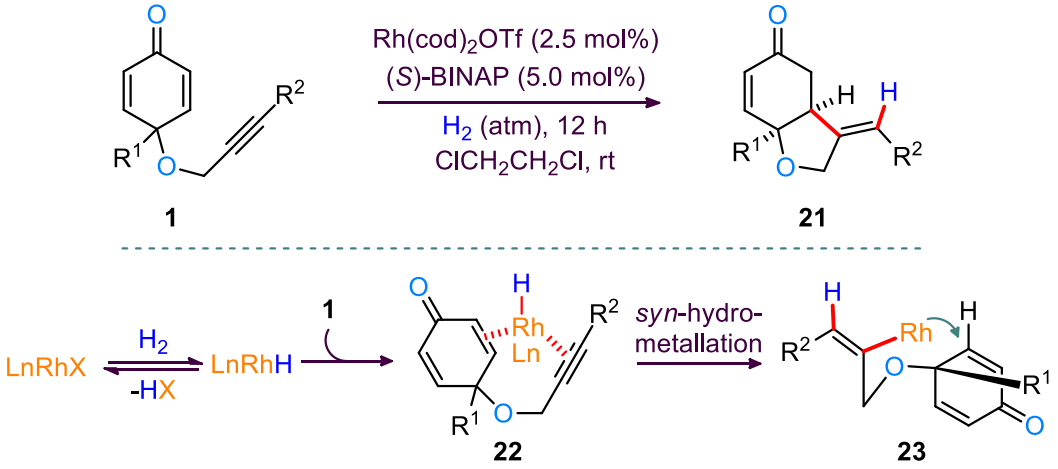
Scheme 4A.5. Rhodium catalyzed arylative cyclization of internal alkynes

In the same year, Lautens and co-workers reported a similar rhodium catalyzed arylative cyclization strategy of aryl boronic acid **16** and alkynyl cyclohexadienone **8**; the catalytic system is quite identical to the previous reaction condition (**Scheme 4A.6**).[5d] Moreover, this transformation explicitely works with the terminal alkynes.



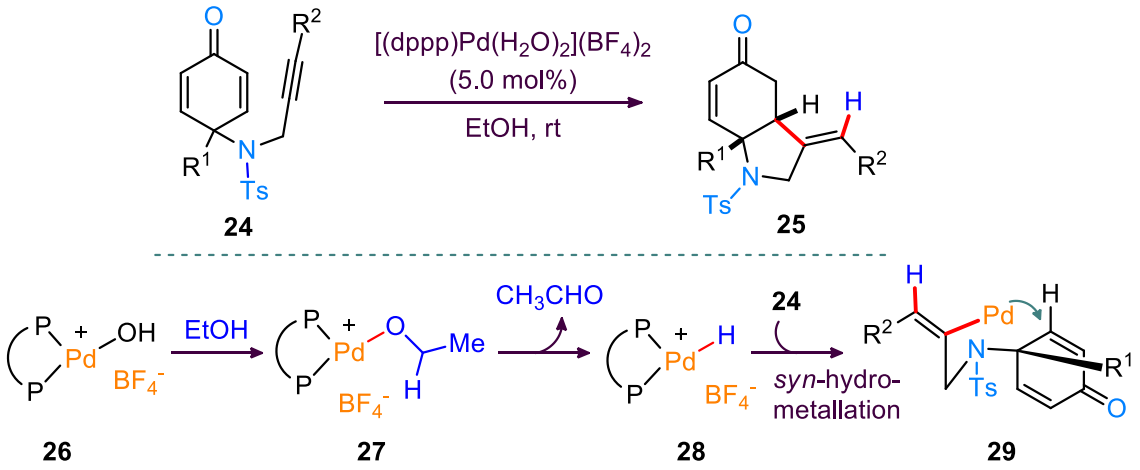
Scheme 4A.6. Rhodium catalyzed arylative cyclization of terminal alkynes

In 2018, Chegondi et. al. disclosed a rhodium catalyzed reductive cyclization of alkynyl cyclohexadienone **1** to the synthesis of cis-hydrobenzofuran derivatives (**Scheme 4A.7**).[6c] Rhodium hydride generated in-situ from hydrogen gas and rhodium catalyst undergoes *syn*-hydrometallation with alkyne of complex **22** to form vinylic rhodium intermediate **23**. Next, 5-*exo*-trig cyclization of vinyl rhodium with activated enone affords the desired product **21**.



Scheme 4A.7. Rhodium catalyzed reductive cyclization of yne-dienone

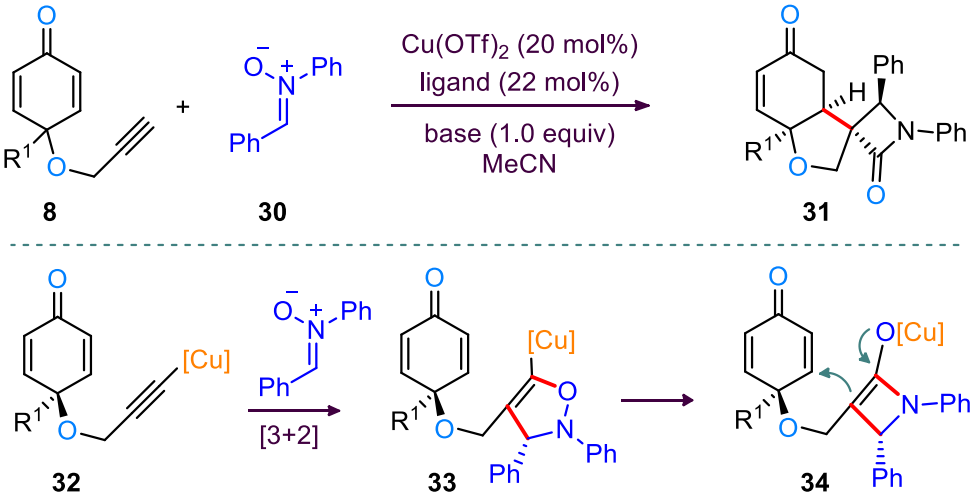
Han and co-workers shown a similar method for the palladium catalyzed reductive cyclization of aza-1,6-enyne to furnish 5,6-fused bicyclic frameworks (**Scheme 4A.8**). In this study, ethanol is being used as proton source as well as solvent.[6d] A palladium



Scheme 4A.8. Ethanol as a hydrogen doner for reductive cyclization

hydride complex **28**, obtained from ethanol and palladium hydroxide complex **26** via **27**, is responsible in this transformation. The hydropalladation of **28** to alkyne gives intermediate **29**, which undergoes cyclization with the pendant Michael acceptor to afford **25**.

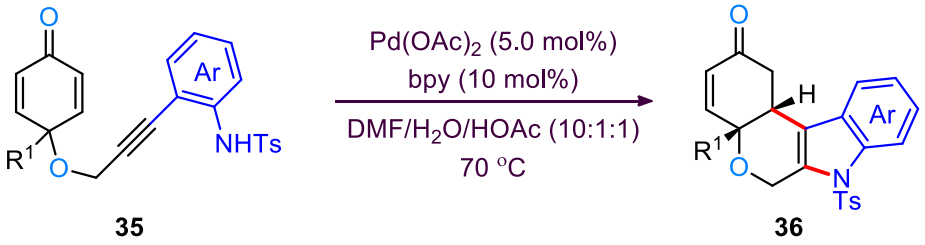
Enders and co-workers developed an elegant protocol for copper catalyzed chemo-, regio-, diastereo- and enantioselective Kinugasa/Michael domino reaction for the desymmetrization of prochiral cyclohexadienones **8**; this method provides access for the synthesis of chiral spirocyclic lactam **31** (**Scheme 4A.9**).[6e] The copper acetylide **32**, generated from alkyne **8**, undergoes [3+2] dipolar cycloaddition with nitrone **30** to give five-membered intermediate **33**. Next, rearrangement of **33** generates **34**, which subsequently undergoes desymmetric Michael addition to provide the desired spirocyclic product **31**.



Scheme 4A.9. Copper catalyzed spirocyclization of yne-dienone with nitrones

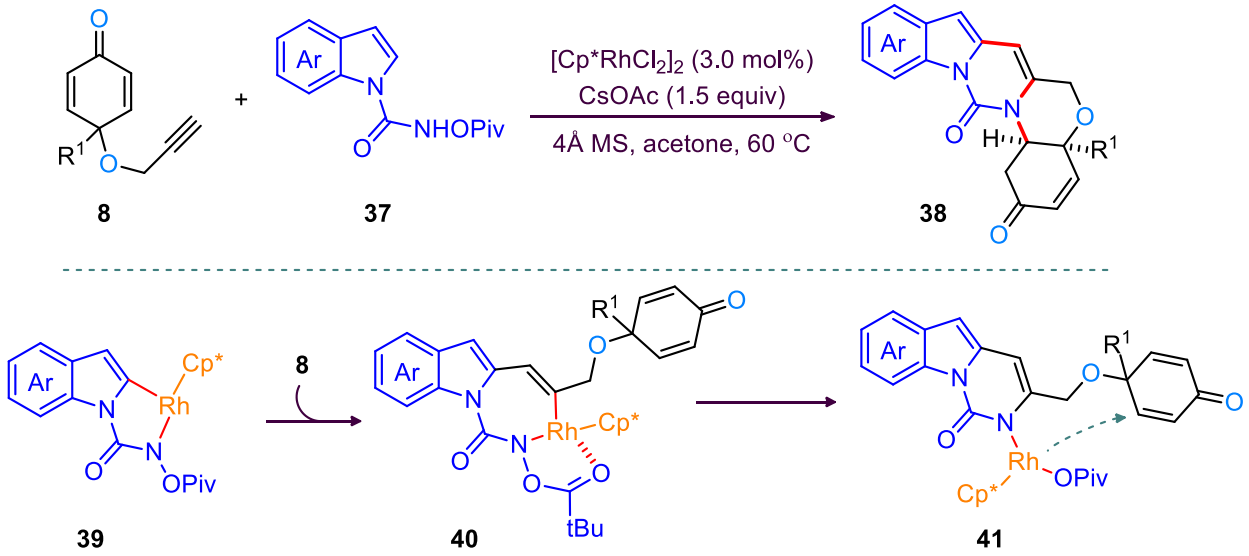
4A.2.2. Access to 6,6-fused bicycles via 6-*exo*-trig cyclization of yne-dienones

Lu group reported a palladium catalyzed cyclization sequence of aniline-tethered alkynyl cyclohexadienones **35** to yield various cyclohexenone-fused tetrahydropyrano[3,4-b]indole derivatives **36** (**Scheme 4A.10**).[7b] This is the first example of TM-catalyzed asymmetric intramolecular aminopalladation followed by 1,4 addition sequence.



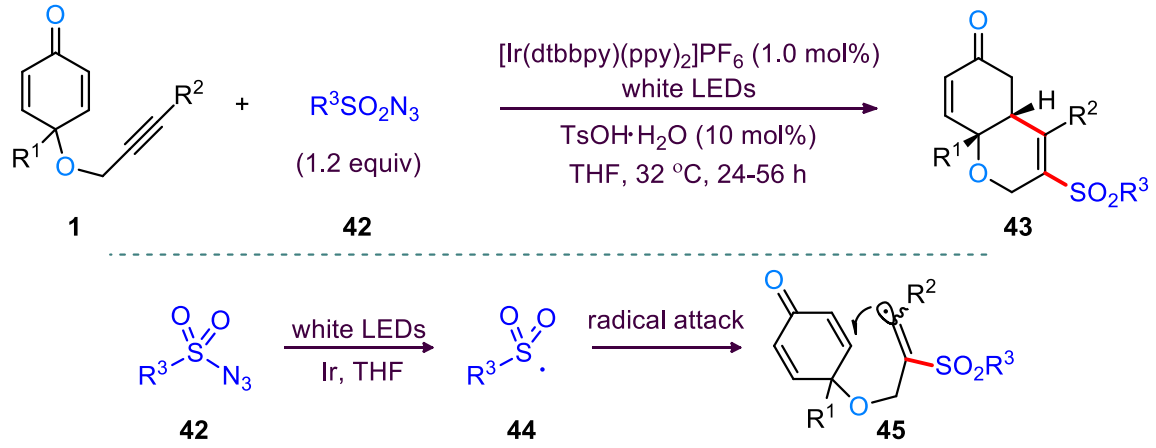
Scheme 4A.10. Palladium catalyzed amino triggered cyclization

Reddy and co-workers discussed a palladium catalyzed tandem cyclization of indole **37** with alkyne-tethered cyclohexadienone **8** to construct polycyclic indole frameworks **38** (**Scheme 4A.11**).[7c] The reaction initiates with a formation of five membered rhodacycle of indole motif **39** followed by carbopalladation of alkyne to give **40** and subsequent Michael attack leads to product **38**.



Scheme 4A.11. Palladium catalyzed tandem cyclization of indole and yne-dienone

In 2017, Lam group demonstrated an interesting protocol for the sulfonylative radical cyclization of alkynyl cyclohexadienone **1** with sulfonyl azide **42** to provide 3-sulfonylative 6,6-fused bicycles **43** under iridium photocatalyst (**Scheme 4A.12**).[7a] The reaction involves the attack of a sulfonyl radical **44** to alkyne and generates a reactive vinyl radical **45**. Finally, intramolecular 5-*exo*-trig vinyl radical cyclization of **45** with activated olefin delivers the desired product **43**.



Scheme 4A.12. Photoredox catalyzed sulfonylative cyclization

4A.3. Motivation and Scheme Design

Inspired by the heteroatom radical mediated cyclization of unsaturated system,[8] a thioaryl radical promoted cyclization diversity of alkynyl-cyclohexadienone **1** is therefore envisioned. We hypothesized that a N-hydroxy phthalimide (NHPI) mediated regioselective attack of thioaryl radical to alkyne followed by intramolecular radical cyclization with the cyclohexadienone would result [5,6]-fused thioaryl tetrahydrobenzofuranone (**47**) and/or [6,6]-fused thioaryl dihydrochromenone (**49**) derivatives (**Figure 4A.1**). The radical attack to alkyne would presumably be regioselective, preferably forming **Int-48** (aryl-stabilized vinyl-radical) over **Int-46** (alkyl-

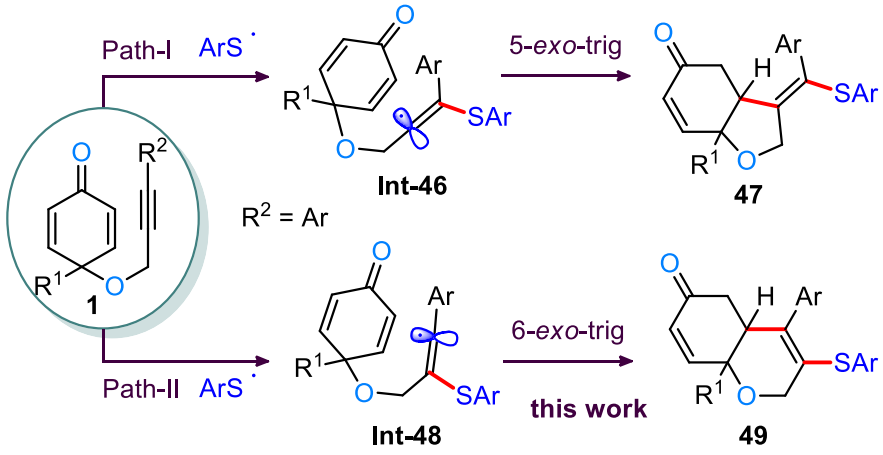


Figure 4A.1. Hypothesis for metal-free thiyl radical cyclization

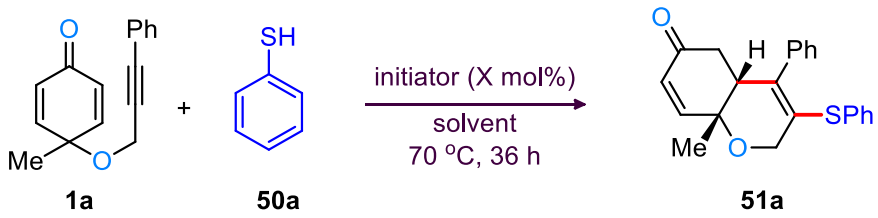
bearing vinyl-radical). Next, the 6-*exo*-trig vinyl-radical cyclization of **Int-48** with the enone would result [6,6]-fused 3-thioaryl dihydrochromenone (**49**); to the best of our knowledge, *the addition of arylthiols with alkynyl-cyclohexadienones is poorly explored.*

4A.4. Result and Discussion

4A.4.1. Reaction optimization

To start with, a reaction between 4-methyl-4-((3-phenylprop-2-yn-1-yl)oxy)cyclohexa-2,5-dienone (**1a**) and coupling partner thiophenol (**50a**) was envisaged in the presence of radical initiator (**Table 4A.1**). To our delight, the reaction in the presence of AIBN in dichloromethane (DCM) at 85 °C produced the desired 3-phenylthio dihydrochromenone (**51a**) in 58% yield (entry 1). Whereas the use of $K_2S_2O_8$ and $Na_2S_2O_8$ led to complex mixture (entries 2 and 3). Interestingly, 61% dihydrochromenone **51a** was isolated, when the reaction was conducted in the presence of N-hydroxy phthalimide (NHPI; entry 4). Whereas the reaction without radical initiator (air) furnished poor amount **51a** (entry 5). Pleasingly, the reaction at 70 °C produced enhanced yield of **51a** (74%) (entry 6). Under the identical conditions, the reaction in other solvents ($ClCH_2CH_2Cl$, 1,4-dioxane, toluene, and acetonitrile) was found moderate (entries 7–10). The reaction at 90/60 °C affected the product outcome (entries 11 and 12). The use of NHPI (10/15 mol%) yielded moderate amount **51a** (entries 13 & 14). Product **51a** (55%) was noticed when **50a** (1.5 equiv) was used (entry 15). Reaction in 12 h and 24 h delivered the product in less yield (entry 16 and 17).

Table 4A.1. Optimization of reaction conditions[a,c]



1a **50a** **51a**

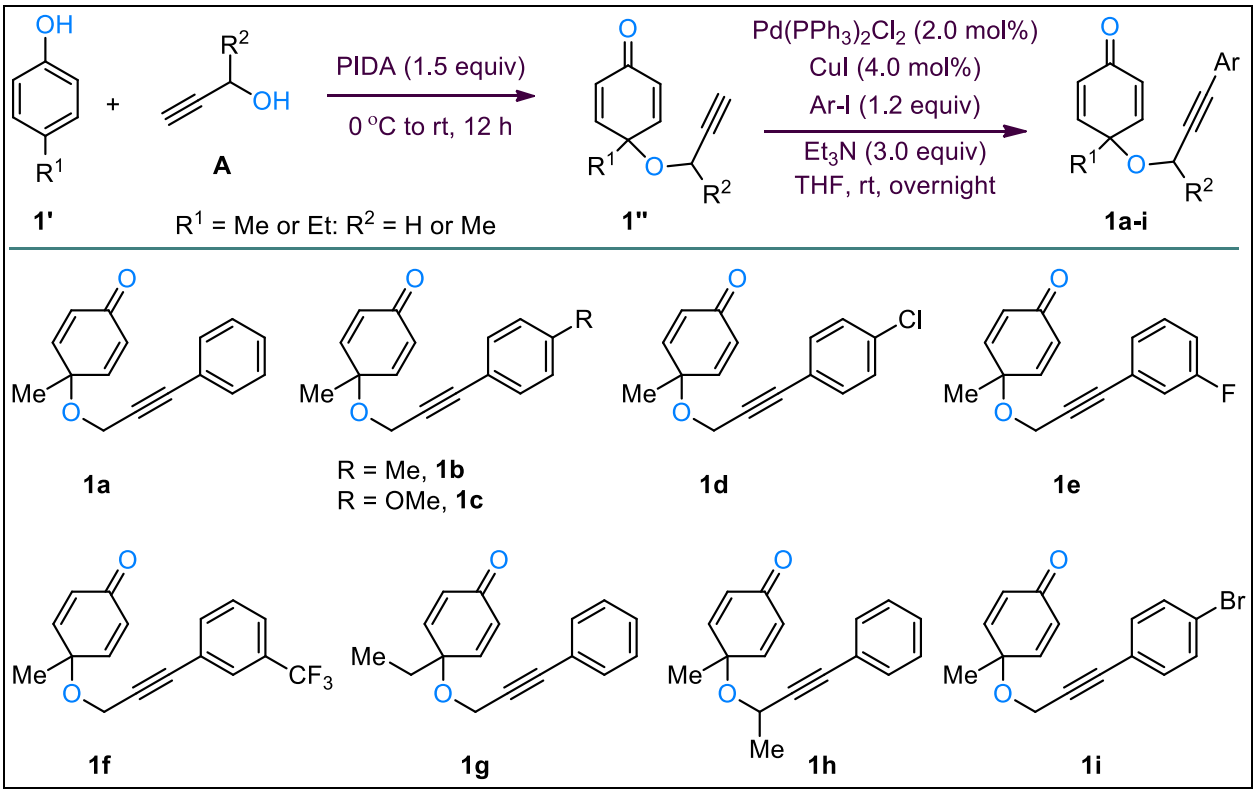
entry	initiator (mol%)	solvent	temp (°C)	yield (%)
1	AIBN (25)	CH_2Cl_2	85	58
2[d]	$K_2S_2O_8$ (25)	CH_2Cl_2	85	complex
3[d]	$Na_2S_2O_8$ (25)	CH_2Cl_2	85	complex
4[b]	NHPI (25)	CH_2Cl_2	85	61
5	Air	CH_2Cl_2	85	18
6[b]	**NHPI (25)**	**CH_2Cl_2**	**70**	**74**
7	NHPI (25)	$ClCH_2CH_2Cl$	70	41
8	NHPI (25)	1,4-dioxane	70	40
9	NHPI (25)	toluene	70	45
10	NHPI (25)	CH_3CN	70	44
11	NHPI (25)	CH_2Cl_2	90	45
12	NHPI (25)	CH_2Cl_2	60	66
13	NHPI (10)	CH_2Cl_2	70	47
14	NHPI (15)	CH_2Cl_2	70	52
15[e]	NHPI (25)	CH_2Cl_2	70	55
16[f]	NHPI (25)	CH_2Cl_2	70	33
17[g]	NHPI (25)	CH_2Cl_2	70	48

[a]Reactions were carried out using **1a** (0.1 mmol), **50a** (0.25 mmol), initiator (25 mol%) in solvent (0.5 M); [b]Isolated yield; [c]Crude NMR yield; [d]Observed by TLC; [e]**50a** (1.5 equiv) was used; [f]Stirred for 12 h; [g]Stirred for 24 h. [AIBN = Azobisisobutyronitrile].

4A.4.2. Synthesis of starting materials

Following the known hypervalent iodine mediated oxidative dearomatization procedure, alkynyl cyclohexadienones **1a**–**i** were synthesized from 4-substituted phenol **1′** and propargyl alcohol (**A**) derivatives (**Table 4A.2**).[6c,14,15]

Table 4A.2. Starting materials chart

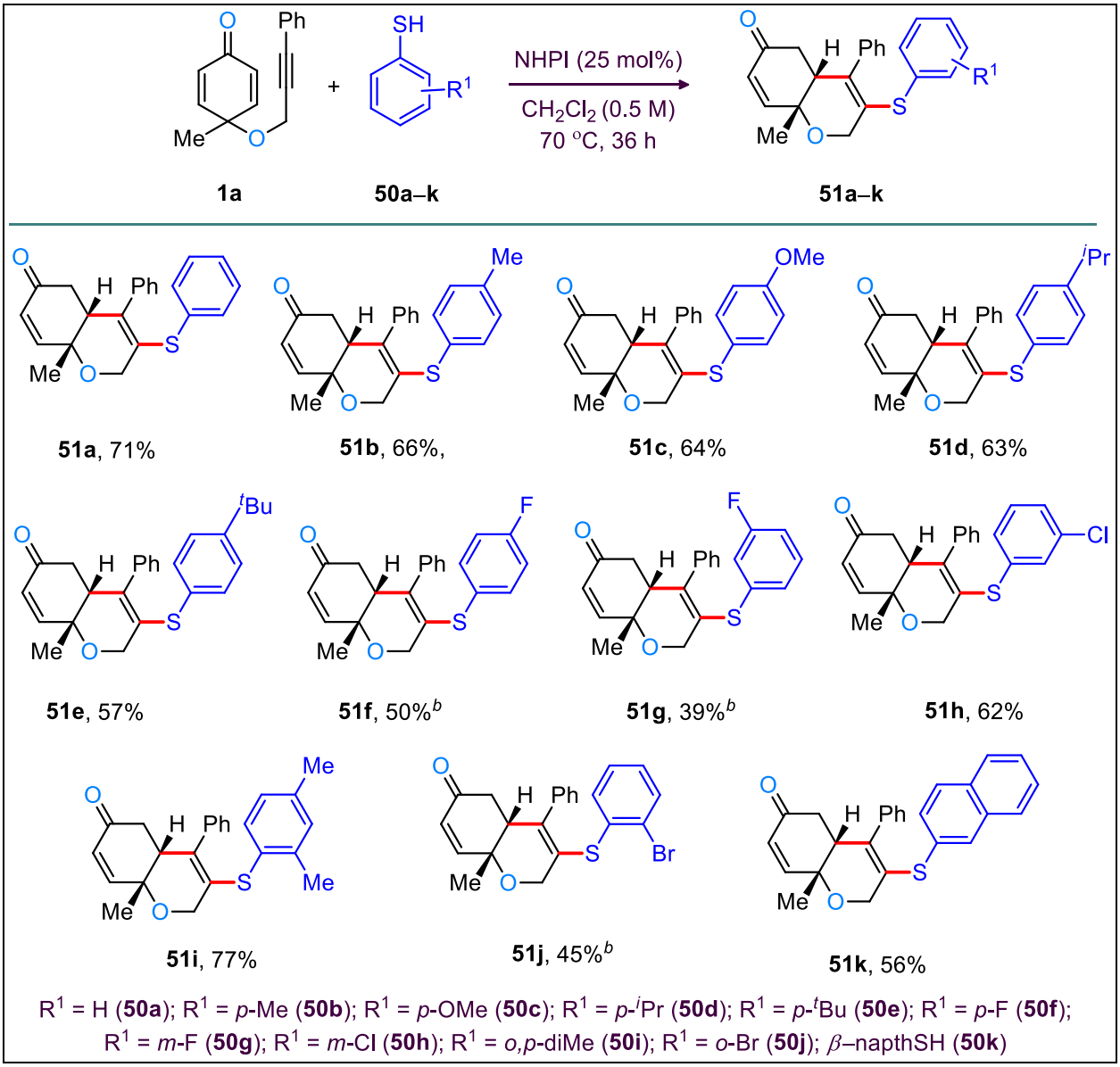


4A.4.3. Substrate scope-I; variation of thiophenols

With the optimized conditions outlined in entry 6 (**Table 4A.1**), the scope of the current transformation was explored by independently screening arylthiols (**Table 4A.3.**) and alkynyl-cyclohexadienones (**Table 4A.4.**). The reaction between **1a** (0.3 mmol) and **50a** (0.75 mmol) in the presence of NHPI (25 mol%) in CH_2Cl_2 at 70 °C for 36 h furnished **51a** in 71% yield. The electron-rich thiophenol (having a substituent –Me/ –OMe/ –^{i}Pr/ –^{t}Bu on the *para*-position; **50b**–**e**) successfully underwent the radical cyclization with **1a** to deliver the respective products **51b**–**e** (57–66%). Similarly, electron-deficient *p*-F-

thiophenol (**50f**) reacted with **1a** providing 50% 3-thioaryl-dihydrochromenone **51f**. The desired dihydrochromenone products **51g** and **51h** were achieved from the *meta*-substituted arylthiols [*m*-F (**50g**) and *m*-Cl (**50h**)]. The product **51i** (77%) was obtained from the reaction of *o,p*-dimethylbenzenethiol (**50i**) with **1a**.

Table 4A.3. Scope of thiophenols[a]



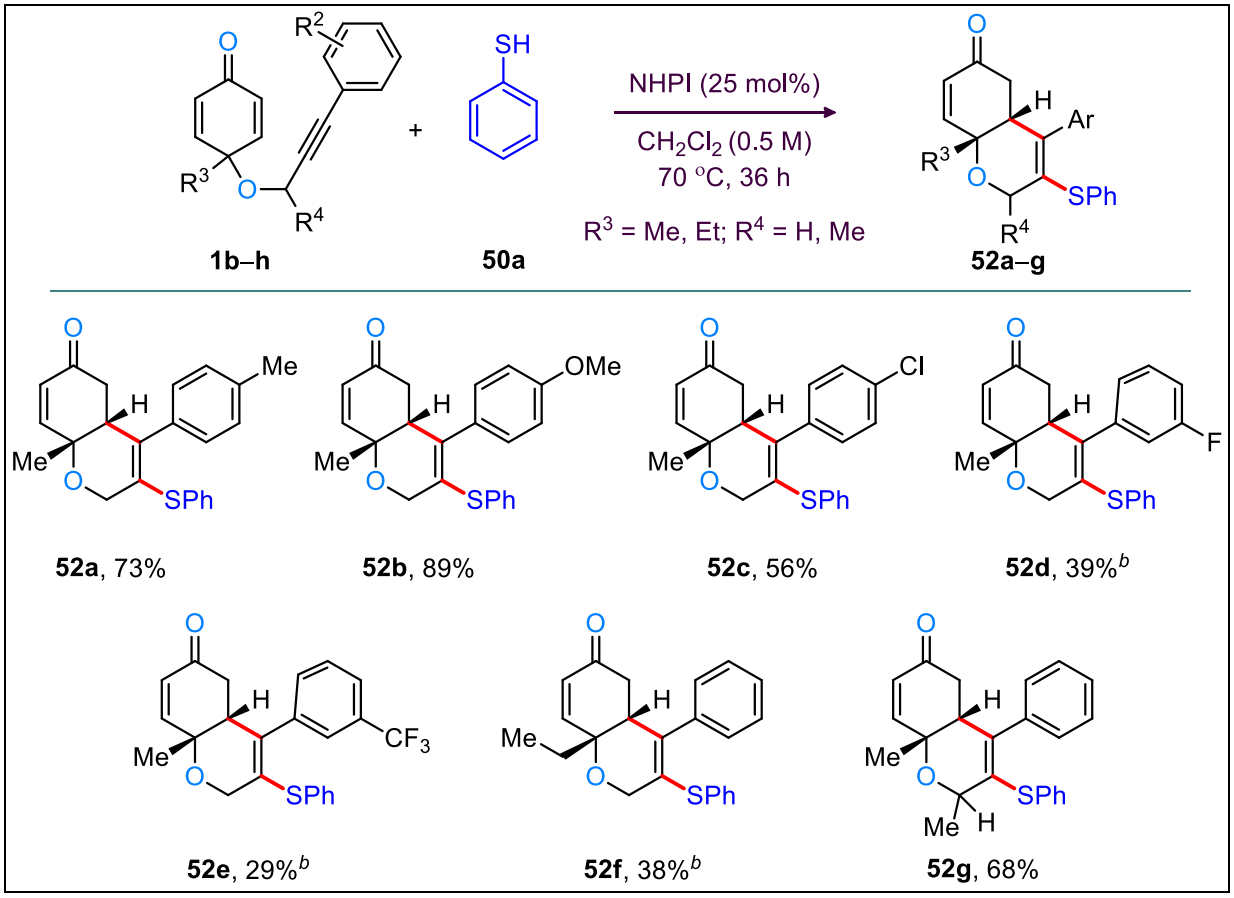
[a]Reactions were carried out using **1** (0.3 mmol), **50** (0.75 mmol), NHPI (25 mol%), in CH_2Cl_2 (0.5 M) at 70 °C for 36 h. [b]Unreacted precursors recovered.

The sterically encumbered *o*-Br (**50j**) bearing thiophenol did not obstruct the reaction providing 45% **51j**. Finally, π–extended *β*–napthalene thiol (**50k**) was also involved the radical cyclization with **1a** leading to **51k** (56%). By contrast, the reaction of **1a** with aliphatic dodecanethiol failed even under the harsh conditions; presumably the unstable aliphatic thiol radical is incompetent to undergo the cyclization.

4A.4.4. Substrate scope-II; variation of alkynyl-cyclohexadienone

We next explored the scope of alkynyl-cyclohexadienones (**1b**–**h**) for the reaction with **50a** (**Table 4A.4**). The cyclohexadienones (**1b** and **1c**; having electron-rich *p*-Me and *p*-OMe substituted arene in alkyne-terminus) effectively reacted with **50a** to provide **52a** and **52b** in excellent yields. Similarly, the dihydrochromenone skeleton **52c** (56%) was accessed from the electron-deficient *p*-Cl (**1d**) aryl substituted cyclohexadienone. The radical cyclization of **50a** with the *m*-F (**1e**)/*m*-CF_3 (**1f**) aryl-enabled alkynyl-cyclohexadienone delivered **52d** and **52e**, respectively, albeit in low yield (a consequence of ineffective cyclization of less stable electron-deficient vinyl radical with enones). The radical cyclization was also viable for the cyclohexadienone having ethyl (**1j**) moiety in the angular position, furnishing dihydrochromenone motif **52f** (38%). Highly decorated 2-methyl substituted dihydrochromenone product **52g** was synthesized from the respective precursor **1h** in 68% yield.

Table 4A.4: Scope of cyclohexadienones[a]

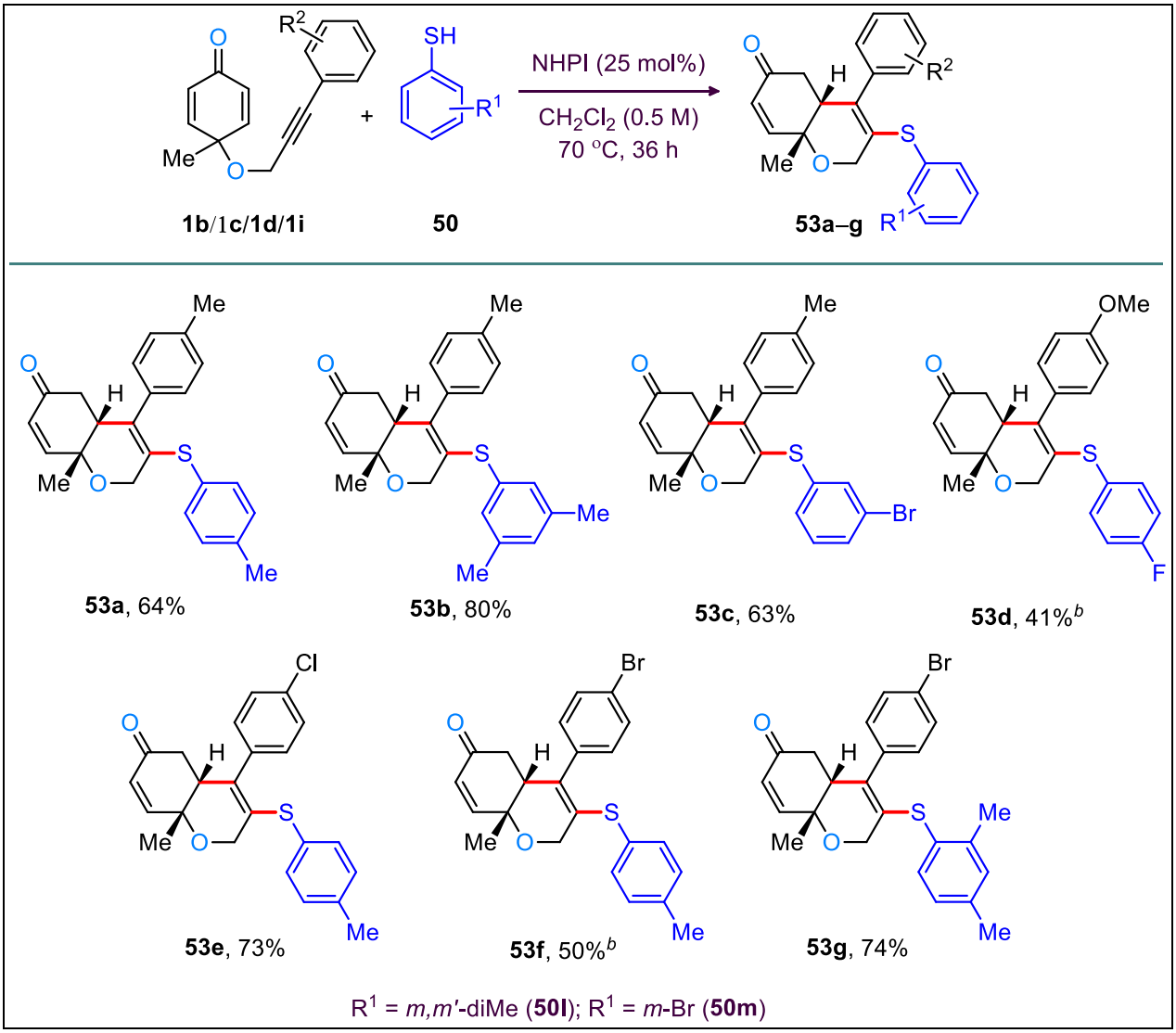


[a]Reactions were carried out using **1** (0.3 mmol), **50a** (0.75 mmol), NHPI (25 mol%), in CH_2Cl_2 (0.5 M) at 70 °C for 36 h. [b]Unreacted precursors recovered.

4A.4.5. Substrate scope-III; variation of both thiophenols and cyclohexadienones

To further understand the transformation generality and the reactivity profile, reaction among various thiophenols and alkynyl-cyclohexadienones was next scrutinized (**Table 4A.5**). In this regard, reactions between **1b** and **50b**, **1b** and **50l**, **1b** and **50m**, **1c** and **50f**, **1d** and **50b**, **1i** and **50b**, and **1i** and **50i** independently delivered **53a**–**g** in 41%–80% yield, respectively. The steric and electronic variation of both thiophenols and cyclohexadienones does not significantly affect the reaction outcome; consequently, this transformation is general.

Table 4A.5: Variation of thiophenols and cyclohexadienones[a]



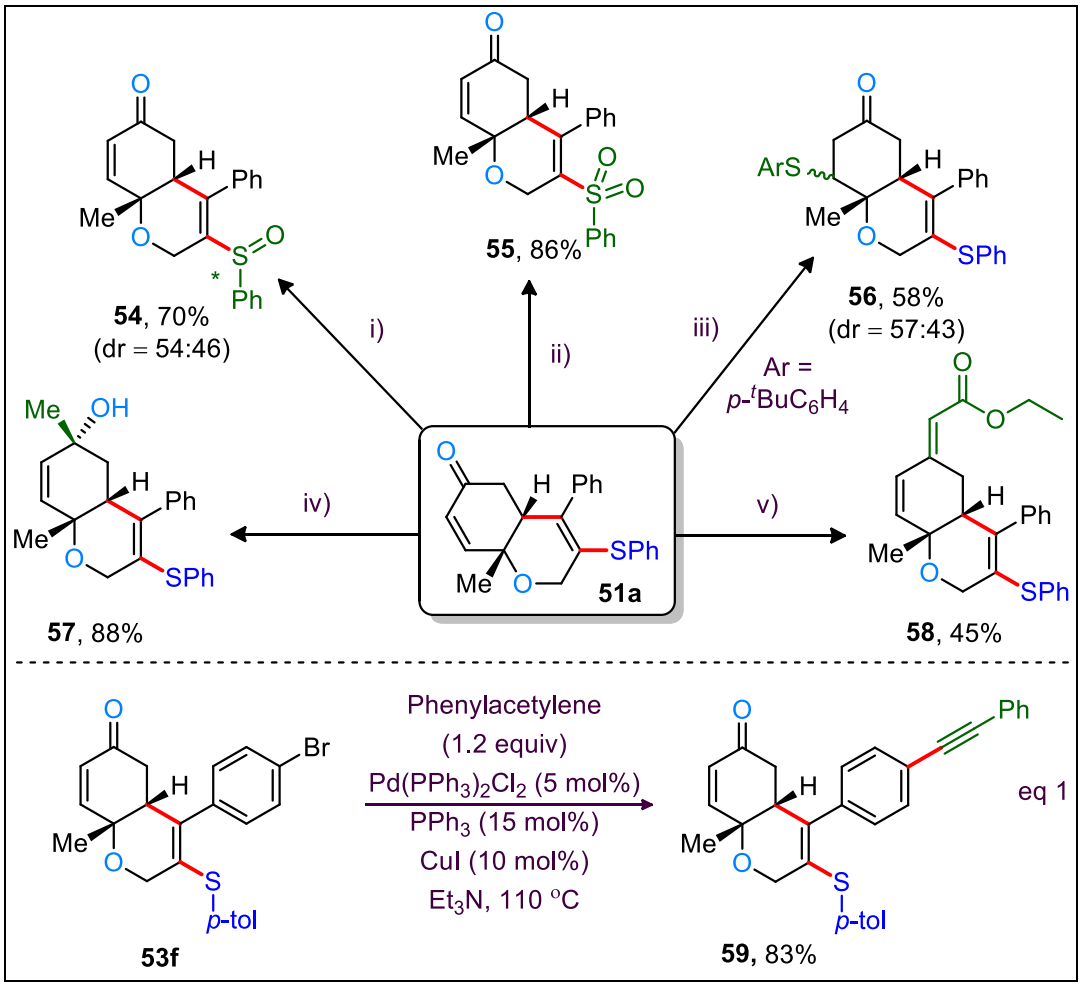
[a]Reactions were carried out using **1** (0.3 mmol), **50** (0.75 mmol), NHPI (25 mol%), in CH_2Cl_2 (0.5 M) at 70 °C for 36 h. [b]Unreacted precursors recovered.

4A.4.6. Synthetic application of 3-thioaryldihydrochromenone

To test the synthetic versatility of 3-thioaryl dihydrochromenones, various common organic transformations were executed with **51a** (**Table 4A.6**). For instance, *m*CPBA (1.0 / 4.0 equiv) mediated oxidation of **51a** independently delivered sulfoxide **54** (an inseparable mixture of diastereomers) and sulfone **55** in 70% and 86% yield, respectively (**Table 4A.6**).[8g] Moreover, base promoted 1,4-

Michael addition of *p*-^{t}Bu-benzenethiol to **51a** afforded **56** (an inseparable mixture of diastereomers, with three consecutive stereogenic centers) in 58% yield (**Table 4A.6**).[9] The corresponding 3°–alcohol product **57** (88%) was achieved via 1,2-addition of MeMgBr to the carbonyl moiety of **51a** (**Table 4A.6**).[10] The base mediated Wittig olefination of activated ketone of **51a** delivered 45% **58** (**Table 4A.6**).[11] Sonogashira cross-coupling of labile Br-group on the arene moiety of **53f** with phenylacetylene provided the alkynylation product **59** (83%) (eq 1, **Table 4A.6**).[12] Thus, 3-thioarylated dihydrochromenone is synthetically versatile.

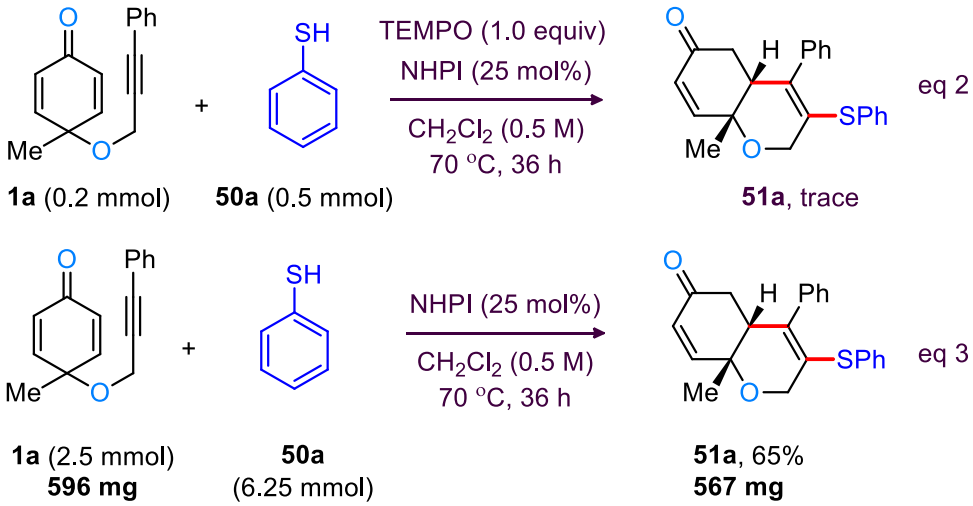
Table 4A.6: Synthetic versatility



Reaction conditions: (i) **51a** (0.2 mmol, 70 mg), *m*CPBA (0.2 mmol, 35 mg), CH_2Cl_2 (2.0 mL), rt, overnight; (ii) **51a** (0.2 mmol, 70 mg), *m*CPBA (0.8 mmol, 138 mg), CH_2Cl_2 (2.0 mL), rt, overnight; (iii) **51a** (0.2 mmol, 70 mg), Et_3N (42 µL), *p*-^{t}Bu-benzenethiol (0.3 mmol, 52 µL), $CHCl_3$ (2.0 mL), rt, 48 h; (iv) **51a** (0.2 mmol), MeMgBr (1.6 M, 0.6 mmol), THF (4.0 mL), rt, overnight; (v) **51a** (0.2 mmol, 70 mg), triethyl phosphonoacetate (0.4 mmol, 89 µL), NaH (0.8 mmol, 19 mg), THF (2.0 mL), 0 °C, 1 h. [*m*CPBA = *meta*-chloroperbenzoic acid]

4A.4.7. Radical trapping reaction and scalability

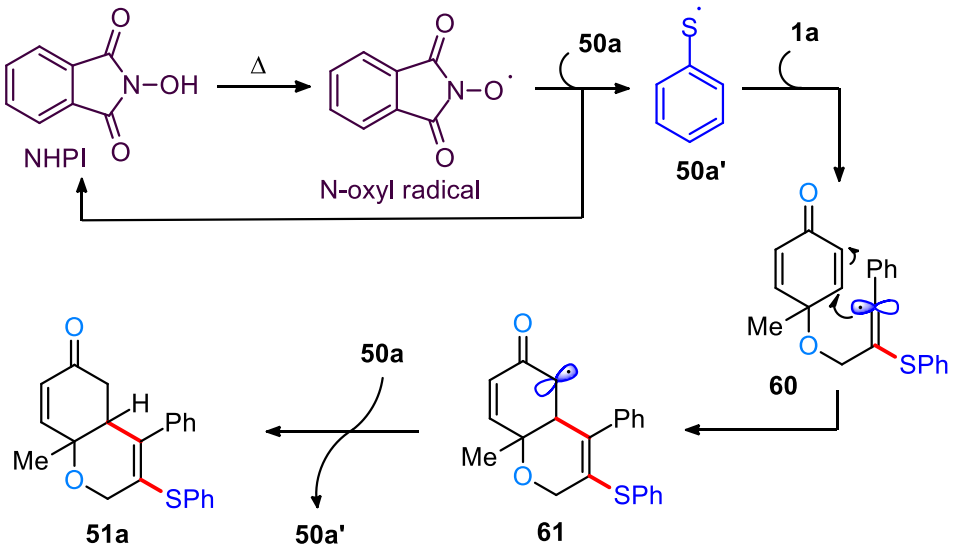
To ensure the involvement of radical in this cyclization strategy, the reaction was conducted in the presence of radical scavenger TEMPO (1.0 equiv) under optimized conditions (eq 2, **Scheme 4A.13**). A trace amount 3–thioaryldihydrochromenone product **51a** was formed (eq 2, **Scheme 4A.13**). This result suggests that the current cascade cyclization primarily requires a thioaryl-radical. The robustness of this transformation was tested by performing the reaction **1a** (596 mg, 2.5 mmol) under the optimized conditions (eq 3, **Scheme 4A.13**). The desired **3a** (567 mg) was isolated in 65% yield.



Scheme 4A.13: TEMPO experiment and reaction scalability

4A.4.8. Mechanism

A plausible mechanism for this transformation is depicted in **Scheme 4A.14**. The reaction begins with the attack of a thioaryl radical **50a'**, generated in-situ from thiophenol in the presence of NHPI,[8g,13] to the alkyne-moiety over the Michael acceptor cyclohexadienone of **1a** to provide a vinyl radical intermediate **60**. Next, the 6-*exo*-trig cyclization of the vinyl-radical with the cyclohexadienone core generates intermediate-**61** {a [6,6]-fused bicyclic system}. Finally, hydrogen radical abstraction of **Int-61** from thiophenol **50a** leads to the desired product **51a**.



Scheme 4A.14: Plausible mechanism

4A.5. Conclusion

In summary, a metal-free chemo- and regioselective thiyl radical attack to alkyne followed by 6-*exo*-trig radical cyclization of aryl-stabilized vinyl radical with enone to result novel 3-thioaryl-dihydrochromenone derivatives has been developed. The transformation is general exhibiting broad scope. The radical-quenching experiment (TEMPO) validates the involvement of thioaryl radical intermediate. Synthetic value of unusual 3-thioaryl dihydrochromenones have also been demonstrated.

4A.6. Experimental Section

4A.6.1. General information

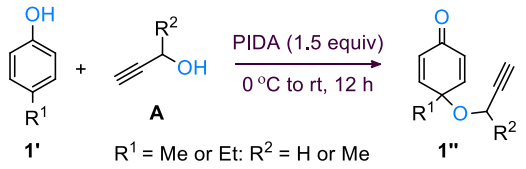
The identical procedure is shown in page no: 42, in Chapter 2.

4A.6.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Chloroform ($CHCl_3$), acetone, dichloromethane (CH_2Cl_2), toluene, acetonitrile, ethyl acetate, and hexane were distilled over CaH_2. THF was freshly distilled over sodium/benzophenone ketyl under dry nitrogen. N-Hydroxypthalimide (NHPI), AIBN, $K_2S_2O_8$, $Na_2S_2O_8$, CuI, and $PdCl_2(PPh_3)_2$ were commercially available and used as received. Aryl iodides were purchased and used as such. Following the known procedure,[6c,14,15] compounds **1a**–**i** have been synthesized. Analytical and spectral data of all those known compounds are exactly matching with the reported values.

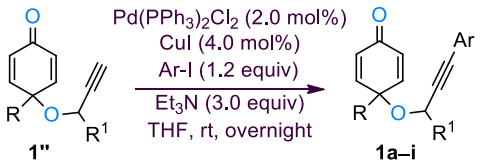
4A.6.3. General procedure and spectral/analytical data

4A.6.3.1. General procedure for the synthesis of 1″



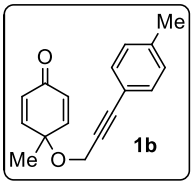
To a stirred solution of 4-substituted phenol **1′** (10 mmol) in 10 mL of propargyl alcohol (**A**) was added phenyliodo(III)diacetate (15 mmol) in several portions at 0 °C. The resulting reaction mixture was stirred at room temperature overnight. Then the reaction mixture was quenched with saturated aqueous sodium bicarbonate (30 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude reaction mixture was purified by using silica gel (100–200 mesh) column chromatography (EtOAc/hexane) to give terminal cyclohexadienones **1″**.

4A.6.3.2. General procedure for the synthesis of 1a–i (GP–1)



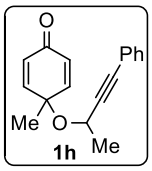
To a solution of **1″** (1.0 mmol), $Pd(PPh_3)_2Cl_2$ (2.0 mol%, 14 mg), and CuI (4.0 mol%, 7.6 mg) in THF (2.0 mL) was added aryliodide (1.2 mmol) under nitrogen atmosphere. Finally, triethylamine (3.0 mmol, 0.42 mL) was added to the above mixture and the resulting mixture was stirred at room temperature overnight. After completion, the reaction mixture was filtered, concentrated in vacuo and purified by silica gel (100–200 mesh) column chromatography to give the desired alkynyl cyclohexadienones **1a**–**i**.

4-Methyl-4-((3-(*p*-tolyl)prop-2-yn-1-yl)oxy)cyclohexa-2,5-dienone (1b): Compound **1b**



(159 mg) was obtained in 63% yield. Yellow solid; mp = 140–142 °C; R_f = 0.43 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 10 Hz, 2H), 6.32 (d, J = 10.5 Hz, 2H), 4.21 (s, 2H), 2.33 (s, 3H), 1.49 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 185.1, 151.1, 138.7, 131.6, 130.3, 129.0, 119.2, 86.9, 85.0, 73.1, 54.6, 26.3, 21.4; IR (Neat)ν_{max} 2978, 2923, 2221, 1706, 1666, 1628, 1604, 1508, 1448, 1376, 1300, 1181, 1075 cm^{-1}; HRMS (ESI) for $C_{17}H_{17}O_2$ $(M+H)^+$: calcd 253.1223, found 253.1230.

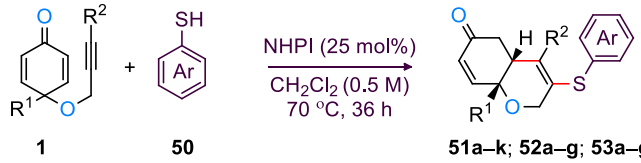
4-Methyl-4-((4-phenylbut-3-yn-2-yl)oxy)cyclohexa-2,5-dienone (1h): Compound **1h**



(106 mg) was obtained in 42% yield. Yellow thick liquid; R_f = 0.61 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.35 (m, 2H), 7.34–7.28 (m, 2H), 7.17 (dd, J = 10, 3.2 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.82–6.74 (m, 1H), 6.35 (dd, J = 10.4, 2.0 Hz, 1H), 6.27 (dd, J = 10, 2.0 Hz, 1H), 4.28 (q, J = 6.8 Hz, 1H), 1.50 (s, 3H), 1.48 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 185.6, 153.1, 150.9, 131.5, 130.5, 129.9, 128.5, 128.4, 128.3, 122.5, 115.1, 90.9, 85.7, 73.4, 62.2, 26.6, 23.7; IR

(Neat)ν_{max} 2982, 1665, 1626, 1514, 1489, 1441, 1337, 1302, 1183, 1068, 1038 cm^{-1}; HRMS (ESI) for $C_{17}H_{16}NaO_2$ $(M+Na)^+$: calcd 275.1043, found 275.1051.

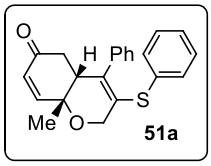
4A.6.3.3. General procedure for the synthesis of dihydrochromenones (GP-2)



1 **50** **51a–k; 52a–g; 53a–g**

A mixture of alkynyl cyclohexadienone **1** (0.3 mmol) and N-hydroxypthalimide (NHPI) (0.075 mmol, 12.2 mg) in CH_2Cl_2 (0.5M) was taken in a screw cap sealed tube. To the above mixture, arylthiols **50** (0.75 mmol) was added. Finally, the reaction mixture was stirred at 70 °C for 36 hours in a heating block. Upon completion, the reaction mixture was cooled to room temperature and diluted with dichloromethane (3.0 mL). The crude residue was purified using column chromatography on silica gel (100–200 mesh) to provide 3-thioaryl dihydrochromenone **51a–51k; 52a–52g; 53a–53g**.

8a-Methyl-4-phenyl-3-(phenylthio)-4a,5-dihydro-2H-chromen-6(8aH)-one (51a):



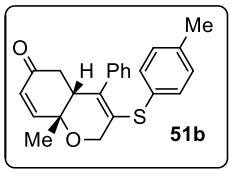
51a

Following the general procedure GP-2, compound **51a** (74 mg) was obtained in 71% yield. Colorless solid; mp = 145–147 °C; R_f = 0.28 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.33 (m, 2H), 7.31 (tt, J = 7.5, 1.0 Hz, 1H), 7.28–7.22 (m, 4H), 7.21–7.17 (m, 1H), 7.16–7.12 (m, 2H), 6.74 (d, J = 10 Hz, 1H), 6.07 (d, J = 10.5 Hz, 1H), 4.26 (dd, J = 16.5, 2.0 Hz, 1H), 4.15 (dd, J = 16.5, 2.0 Hz, 1H), 3.06–3.01 (m, 1H), 2.53–2.42 (m, 2H), 1.58 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.6, 151.1, 142.6, 138.4, 134.0, 130.2, 129.9, 129.1, 128.3, 128.2, 127.8, 126.69, 126.65, 71.0, 64.6, 45.3, 39.3, 24.0; IR (Neat)ν_{max} 3054, 1684, 1581, 1490, 1418, 1149, 1109 cm^{-1}; HRMS (ESI) for $C_{22}H_{21}O_2S$ $(M+H)^+$: calcd 349.1257, found 349.1262.

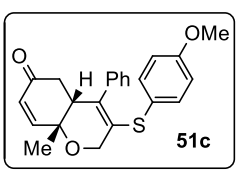
8a-Methyl-4-phenyl-3-(*p*-tolylthio)-4a,5-dihydro-2H-chromen-6(8aH)-one (51b):

Following the general procedure GP-2, compound **51b** (72 mg) was obtained in 66% yield. Colorless semisolid; R_f = 0.46 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz,

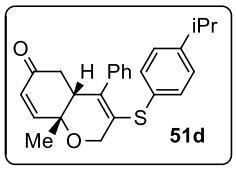
$CDCl_3$): δ 7.39–7.34 (m, 2H), 7.31 (tt, J = 7.5, 1.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 4H), 7.07 (d, J = 8.0 Hz, 2H), 6.72 (d, J = 10.5 Hz, 1H), 6.06 (d, J = 10.0 Hz, 1H), 4.22 (dd, J = 17.0, 2.0 Hz, 1H), 4.11 (dd, J = 16.5, 2.0 Hz, 1H), 3.03–2.98 (m, 1H), 2.52–2.41 (m, 2H), 2.30 (s, 3H), 1.56 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 197.9, 151.2, 141.2, 138.6, 137.1, 130.7, 130.3, 130.0, 129.9, 128.42, 128.37, 127.8, 127.2, 71.1, 64.6, 45.2, 39.4, 24.0, 21.1; IR (Neat)ν_{max} 2973, 2923, 1682, 1490, 1360, 1219, 1148 cm^{-1}; HRMS (ESI) for $C_{23}H_{22}NaO_2S$ $(M+Na)^+$: calcd 385.1233, found 385.1239.



3-((4-Methoxyphenyl)thio)-8a-methyl-4-phenyl-4a,5-dihydro-2H-chromen-6(8aH)-one (51c): Following the general procedure GP-2, compound **51c** (73 mg) was obtained in 64% yield. Yellow liquid; R_f = 0.26 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40–7.35 (m, 2H), 7.31 (tt, J = 7.5, 1.5 Hz, 1H), 7.23–7.19 (m, 2H), 7.16–7.13 (m, 2H), 6.81–6.78 (m, 2H), 6.70 (d, J = 10.5 Hz, 1H), 6.04 (d, J = 10.0 Hz, 1H), 4.16 (dd, J = 17.0, 2.0 Hz, 1H), 4.06 (dd, J = 16.5, 2.0 Hz, 1H), 3.77 (s, 3H), 3.00–2.94 (m, 1H), 2.49–2.39 (m, 2H), 1.54 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 197.8, 159.4, 151.1, 138.9, 138.6, 133.8, 133.6, 130.2, 128.5, 128.4, 128.1, 127.7, 123.2, 114.7, 71.0, 64.4, 55.3, 45.1, 39.3, 23.9; IR (Neat)ν_{max} 2930, 2836, 1682, 1570, 1491, 1243, 1171 cm^{-1}; HRMS (ESI) for $C_{23}H_{22}NaO_3S$ $(M+Na)^+$: calcd 401.1182, found 401.1187.

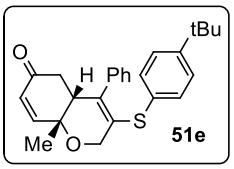


3-((4-*iso*-Propylphenyl)thio)-8a-methyl-4-phenyl-4a,5-dihydro-2H-chromen-6(8aH)-one (51d): Following the general procedure GP-2, compound **51d** (74 mg) was obtained in 63% yield. Colorless gummy liquid; R_f = 0.44 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.28 (m, 3H), 7.20–7.10 (m, 6H), 6.73 (d, J = 10.4 Hz, 1H), 6.07 (d, J = 10.0 Hz, 1H), 4.23 (dd, J = 16.8, 2.0 Hz, 1H), 4.12 (dd, J = 16.8, 2.0 Hz, 1H), 3.05–2.99 (m, 1H), 2.91–2.80 (m, 1H), 2.54–2.41 (m, 2H), 1.57 (s, 3H), 1.22 (d, J = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.7, 151.1, 147.9, 141.2, 138.5, 130.5, 130.24, 130.19, 128.31, 128.27, 127.7, 127.2,

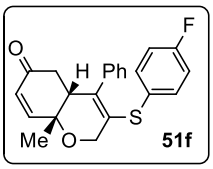


127.1, 71.0, 64.5, 45.1, 39.3, 33.6, 24.0, 23.8; IR (Neat)ν_{max} 2959, 1683, 1490, 1406, 1381, 1278, 1148 cm^{-1}; HRMS (ESI) for $C_{25}H_{27}O_2S$ $(M+H)^+$: calcd 391.1726, found 391.1731.

3-((4-(*tert*-Butyl)phenyl)thio)-8a-methyl-4-phenyl-4a,5-dihydro-2H-chromen-6(8aH)-one (51e): Following the general procedure GP-2, compound **51e** (69 mg) was obtained in 57% yield. Colorless gummy liquid; R_f = 0.46 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.33 (m, 2H), 7.33–7.27 (m, 3H), 7.19–7.13 (m, 4H), 6.74 (d, J = 10.0 Hz, 1H), 6.07 (d, J = 10.0 Hz, 1H), 4.23 (dd, J = 16.5, 2.0 Hz, 1H), 4.13 (dd, J = 17.0, 2.0 Hz, 1H), 3.05–3.00 (m, 1H), 2.53–2.42 (m, 2H), 1.58 (s, 3H), 1.29 (s, 9H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 197.7, 151.1, 150.2, 141.4, 138.5, 130.3, 130.2, 130.14, 130.09, 128.32, 128.28, 127.7, 126.1, 71.0, 64.6, 45.2, 39.3, 34.4, 31.2, 24.0; IR (Neat)ν_{max} 2962, 1685, 1489, 1360, 1267, 1219, 1149 cm^{-1}; HRMS (ESI) for $C_{26}H_{28}NaO_2S$ $(M+Na)^+$: calcd 427.1702, found 427.1708.

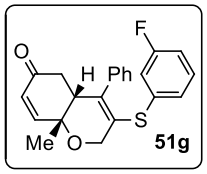


3-((4-Fluorophenyl)thio)-8a-methyl-4-phenyl-4a,5-dihydro-2H-chromen-6(8aH)-one (51f): Following the general procedure GP-2, compound **51f** (55 mg) was obtained in 50% yield along with the unreacted **1a** (35%). Colorless solid; mp = 140–142 °C; R_f = 0.37 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.29 (m, 3H), 7.25–7.18 (m, 2H), 7.15–7.10 (m, 2H), 7.00–6.92 (m, 2H), 6.72 (d, J = 10.4 Hz, 1H), 6.06 (d, J = 10.4 Hz, 1H), 4.20 (dd, J = 16.8, 2.0 Hz, 1H), 4.08 (dd, J = 16.8, 2.0 Hz, 1H), 3.06–2.98 (m, 1H), 2.54–2.38 (m, 2H), 1.56 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.6, 162.1 (d, J = 248 Hz, 1C), 151.1, 141.6, 138.3, 132.7 (d, J = 8.1 Hz, 1C), 130.3, 128.6 (d, J = 3.0 Hz, 1C), 128.4, 128.3, 127.9, 127.1, 116.2 (d, J = 22 Hz, 1C), 71.1, 64.4, 45.2, 39.2, 24.0; ^{19}F NMR (471 MHz, $CDCl_3$): δ –114.3; IR (Neat)ν_{max} 2924, 2158, 1674, 1585, 1487, 1384, 1217, 1148 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}FO_2S$ $(M+H)^+$: calcd 367.1163, found 367.1168.



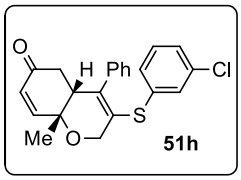
3-((3-Fluorophenyl)thio)-8a-methyl-4-phenyl-4a,5-dihydro-2H-chromen-6(8aH)-one (51g): Following the general procedure GP-2, compound **51g** (43 mg) was obtained in 39% yield along with the unreacted **1a** (42%). Yellow semisolid; R_f = 0.38 (9:1 hexane/EtOAc);

[Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.28 (m, 3H), 7.25–7.18 (m, 1H),



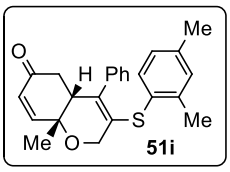
7.14–7.08 (m, 2H), 7.00–6.95 (m, 1H), 6.93–6.84 (m, 2H), 6.76 (d, J = 10.4 Hz, 1H), 6.09 (d, J = 10.4 Hz, 1H), 4.28 (dd, J = 16.8, 2.0 Hz, 1H), 4.16 (dd, J = 16.8, 2.4 Hz, 1H), 3.11–3.03 (m, 1H), 2.56–2.40 (m, 2H), 1.59 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.4, 162.8 (d, J = 250 Hz, 1C), 151.1, 144.7, 138.1, 136.8 (d, J = 8.1 Hz, 1C), 130.4 (d, J = 8.1 Hz, 1C), 130.3, 128.4, 128.0, 127.98, 125.8, 124.6 (d, J = 3.0 Hz, 1C), 115.9 (d, J = 23.2 Hz, 1C), 113.5 (d, J = 22.2 Hz, 1C), 71.2, 64.6, 45.4, 39.2, 24.0; ^{19}F NMR (471 MHz, $CDCl_3$): δ –111.7; IR (Neat)ν_{max} 2973, 1683, 1596, 1490, 1472, 1214, 1171 cm^{-1}; HRMS (ESI) for $C_{22}H_{19}FNaO_2S$ (M+Na)$^+$: calcd 389.0982, found 389.0988.

3-((3-Chlorophenyl)thio)-8a-methyl-4-phenyl-4a,5-dihydro-2H-chromen-6(8aH)-one



(51h): Following the general procedure GP-2, compound **51h** (71 mg) was obtained in 62% yield. Yellow liquid; R_f = 0.38 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.29 (m, 3H), 7.19–7.13 (m, 3H), 7.12–7.06 (m, 3H), 6.75 (d, J = 10.0 Hz, 1H), 6.09 (d, J = 10.5 Hz, 1H), 4.27 (dd, J = 16.5, 2.0 Hz, 1H), 4.16 (dd, J = 17.0, 2.5 Hz, 1H), 3.09–3.03 (m, 1H), 2.54–2.41 (m, 2H), 1.59 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.3, 151.1, 144.5, 138.1, 136.5, 134.8, 130.4, 130.1, 128.9, 128.4, 128.01, 127.97, 127.2, 126.7, 125.9, 71.2, 64.6, 45.4, 39.2, 24.0; IR (Neat)ν_{max} 2973, 1684, 1574, 1490, 1459, 1278, 1148, 1109 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}ClO_2S$ (M+H)$^+$: calcd 383.0867, found 383.0876.

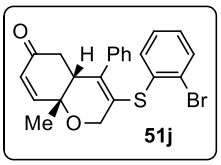
3-((2,4-Dimethylphenyl)thio)-8a-methyl-4-phenyl-4a,5-dihydro-2H-chromen-6(8aH)-



one (51i): Following the general procedure GP-2, compound **51i** (87 mg) was obtained in 77% yield. Colorless solid; mp = 143–145 °C; R_f = 0.33 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.28 (m, 3H), 7.21–7.13 (m, 3H), 6.97 (s, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.71 (d, J = 10.4 Hz, 1H), 6.06 (d, J = 10.4 Hz, 1H), 4.11 (dd, J = 16.8, 2.0 Hz, 1H), 3.99 (dd, J = 16.8, 2.0 Hz, 1H), 3.05–2.97 (m, 1H), 2.54–2.40 (m, 2H), 2.28 (s, 3H), 2.24 (s, 3H), 1.56 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.7, 151.2, 139.4, 138.5, 137.5, 131.7, 131.2, 130.2,

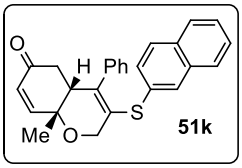
128.4, 128.3, 128.2, 127.7, 127.3, 127.2, 71.1, 64.3, 45.0, 39.3, 24.0, 20.9, 20.4; IR (Neat)ν_{max} 2973, 2831, 1675, 1598, 1475, 1439, 1386, 1282, 1150 cm^{-1}; HRMS (ESI) for $C_{24}H_{24}NaO_2S$ $(M+Na)^+$: calcd 399.1389, found 399.1399.

3-((2-Bromophenyl)thio)-8a-methyl-4-phenyl-4a,5-dihydro-2H-chromen-6(8aH)-one



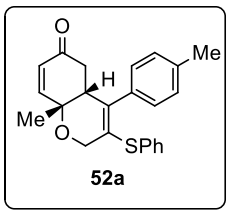
(51j): Following the general procedure GP-2, compound **51j** (58 mg) was obtained in 45% yield along with the unreacted **1a** (30%). Yellow gummy liquid; R_f = 0.26 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J = 8.5 Hz, 1H), 7.36–7.28 (m, 3H), 7.25–7.21 (m, 2H), 7.14–7.10 (m, 2H), 7.06–7.01 (m, 1H), 6.75 (d, J = 10.5 Hz, 1H), 6.08 (d, J = 10.0 Hz, 1H), 4.25 (dd, J = 17.0, 2.0 Hz, 1H), 4.13 (dd, J = 17.0, 2.0 Hz, 1H), 3.08–3.02 (m, 1H), 2.54–2.43 (m, 2H), 1.60 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.6, 151.1, 144.6, 138.2, 135.8, 133.3, 130.3, 129.6, 128.5, 128.1, 128.0, 127.9, 127.7, 125.8, 124.2, 71.2, 64.5, 45.4, 39.4, 24.1; IR (Neat)ν_{max} 2927, 1684, 1597, 1490, 1444, 1219, 1148, 1105 cm^{-1}; HRMS (ESI) for $C_{22}H_{19}BrNaO_2S$ $(M+Na)^+$: calcd 449.0181, found 449.0189.

8a-Methyl-3-(naphthalen-2-ylthio)-4-phenyl-4a,5-dihydro-2H-chromen-6(8aH)-one



(51k): Following the general procedure GP-2, compound **51k** (67 mg) was obtained in 56% yield. Colorless gummy liquid; R_f = 0.34 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81–7.68 (m, 4H), 7.51–7.43 (m, 2H), 7.41–7.29 (m, 4H), 7.21–7.16 (m, 2H), 6.75 (d, J = 10.0 Hz, 1H), 6.11 (d, J = 10.4 Hz, 1H), 4.31 (dd, J = 16.8, 2.0 Hz, 1H), 4.20 (dd, J = 16.8, 2.0 Hz, 1H), 3.12–3.05 (m, 1H), 2.59–2.51 (m, 2H), 1.60 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.6, 151.2, 142.9, 138.4, 133.6, 132.0, 131.4, 130.3, 128.7, 128.4, 128.2, 128.1, 127.9, 127.7, 127.4, 127.2, 126.7, 126.5, 126.0, 71.1, 64.8, 45.3, 39.3, 24.0; IR (Neat)ν_{max} 3053, 2927, 1682, 1589, 1491, 1420, 1148, 1108 cm^{-1}; HRMS (ESI) for $C_{26}H_{22}NaO_2S$ $(M+Na)^+$: calcd 421.1233, found 421.1238.

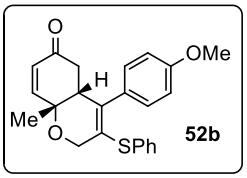
8a-Methyl-3-(phenylthio)-4-(*p*-tolyl)-4a,5-dihydro-2H-chromen-6(8aH)-one (52a):



52a

Following the general procedure GP-2, compound **52a** (79 mg) was obtained in 73% yield. Pale yellow gummy liquid; R_f = 0.34 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.25 (m, 4H), 7.22–7.17 (m, 3H), 7.06 (d, J = 8.0 Hz, 2H), 6.75 (d, J = 10.0 Hz, 1H), 6.09 (d, J = 10.0 Hz, 1H), 4.27 (dd, J = 16.8, 2.0 Hz, 1H), 4.16 (dd, J = 16.4, 1.6 Hz, 1H), 3.10–3.02 (m, 1H), 2.57–2.54 (m, 2H), 2.37 (s, 3H), 1.59 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.6, 151.1, 142.7, 137.5, 135.3, 134.1, 130.1, 129.6, 129.0, 127.9, 126.5, 126.1, 71.0, 64.5, 45.1, 39.3, 23.9, 21.1; IR (Neat)ν_{max} 2973, 2920, 1674, 1579, 1473, 1333, 1280, 1178 cm^{-1}; HRMS (ESI) for $C_{23}H_{22}NaO_2S$ (M+Na)$^+$: calcd 385.1233, found 385.1237.

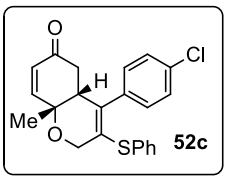
4-(4-Methoxyphenyl)-8a-methyl-3-(phenylthio)-4a,5-dihydro-2H-chromen-6(8aH)-one



52b

(52b): Following the general procedure GP-2, compound **52b** (101 mg) was obtained in 89% yield. Pale yellow gummy liquid; R_f = 0.26 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.18 (m, 5H), 7.07 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 10.0 Hz, 1H), 6.06 (d, J = 10.0 Hz, 1H), 4.24 (dd, J = 16.8, 2.0 Hz, 1H), 4.13 (dd, J = 16.8, 1.6 Hz, 1H), 3.80 (s, 3H), 3.05–2.99 (m, 1H), 2.54–2.42 (m, 2H), 1.57 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.8, 159.1, 151.2, 142.4, 134.2, 130.6, 130.2, 129.6, 129.3, 129.1, 126.6, 126.2, 113.7, 71.1, 64.6, 55.1, 45.3, 39.4, 24.0; IR (Neat)ν_{max} 2929, 2833, 1677, 1605, 1574, 1507, 1473, 1371, 1240, 1147 cm^{-1}; HRMS (ESI) for $C_{23}H_{22}NaO_3S$ (M+Na)$^+$: calcd 401.1182, found 401.1186.

4-(4-Chlorophenyl)-8a-methyl-3-(phenylthio)-4a,5-dihydro-2H-chromen-6(8aH)-one

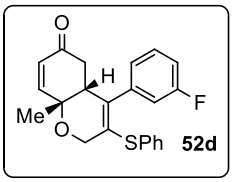


52c

(52c): Following the general procedure GP-2, compound **52c** (64 mg) was obtained in 56% yield. Pale yellow gummy liquid; R_f = 0.43 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.33 (m, 2H), 7.30–7.25 (m, 2H), 7.24–7.20 (m, 3H), 7.11–7.07 (m, 2H), 6.75 (d, J = 10.5 Hz, 1H), 6.09 (d, J = 10.5 Hz, 1H), 4.25 (dd, J = 17.0, 2.0 Hz, 1H), 4.14 (dd, J = 17.0, 2.0 Hz, 1H), 3.07–3.01 (m, 1H), 2.54–2.41 (m, 2H), 1.58 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ

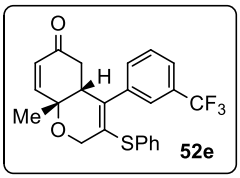
197.3, 151.1, 141.1, 136.7, 133.7, 133.5, 130.3, 129.9, 129.6, 129.1, 128.6, 127.7, 126.9, 71.2, 64.5, 45.1, 39.3, 24.0; IR (Neat)ν_{max} 3054, 2972, 1680, 1581, 1487, 1438, 1369, 1279, 1148 cm^{-1}; HRMS (ESI) for $C_{22}H_{19}ClNaO_2S$ $(M+Na)^+$: calcd 405.0686, found 405.0691.

4-(3-Fluorophenyl)-8a-methyl-3-(phenylthio)-4a,5-dihydro-2H-chromen-6(8aH)-one



(52d): Following the general procedure GP-2, compound **52d** (43 mg) was obtained in 39% yield along with the unreacted **1a** (35%). Pale yellow gummy liquid; R_f = 0.30 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.20 (m, 6H), 7.07–7.01 (m, 1H), 6.95 (dt, J = 7.6, 1.2 Hz, 1H), 6.92–6.86 (m, 1H), 6.76 (d, J = 10.0 Hz, 1H), 6.10 (d, J = 10.0 Hz, 1H), 4.26 (dd, J = 16.8, 2.0 Hz, 1H), 4.15 (dd, J = 16.8, 2.0 Hz, 1H), 3.07–3.01 (m, 1H), 2.57–2.42 (m, 2H), 1.60 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.4, 162.6 (d, J = 248 Hz, 1C), 151.0, 140.81, 140.79, 140.5 (d, J = 8.1 Hz, 1C), 133.4, 130.2, 130.1, 129.9 (d, J = 9.1 Hz, 1C), 129.1, 127.8, 127.0, 124.2 (d, J = 3.0 Hz, 1C), 115.2 (d, J = 22 Hz, 1C), 114.8 (d, J = 21 Hz, 1C), 71.0, 64.5, 45.0, 39.2, 24.0; ^{19}F NMR (471 MHz, $CDCl_3$): δ –112.5; IR (Neat)ν_{max} 3053, 2971, 1679, 1579, 1476, 1428, 1264, 1148 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}FO_2S$ $(M+H)^+$: calcd 367.1163, found 367.1168.

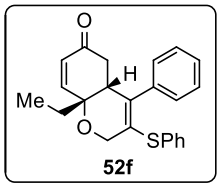
8a-Methyl-3-(phenylthio)-4-(3-(trifluoromethyl)phenyl)-4a,5-dihydro-2H-chromen-



6(8aH)-one (52e): Following the general procedure GP-2, compound **52e** (36 mg) was obtained in 29% yield along with the unreacted **1a** (50%). Pale yellow gummy liquid; R_f = 0.27 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.37 (s, 1H), 7.35–7.27 (m, 3H), 7.23–7.19 (m, 3H), 6.74 (d, J = 10.0 Hz, 1H), 6.08 (d, J = 10.0 Hz, 1H), 4.25 (dd, J = 17.0, 2.0 Hz, 1H), 4.15 (dd, J = 17.0, 2.0 Hz, 1H), 3.06–3.01 (m, 1H), 2.52–2.38 (m, 2H), 1.59 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 197.3, 150.9, 140.4, 139.2, 133.2, 132.2, 131.9, 130.9 (q, J = 252 Hz, 1C), 130.4, 130.3, 129.2, 128.92, 128.88, 128.8, 127.2, 124.8 (q, J = 3.8 Hz, 1C), 124.6 (q, J = 5.0 Hz, 1C), 71.1, 64.6, 45.1, 39.3, 23.9; ^{19}F

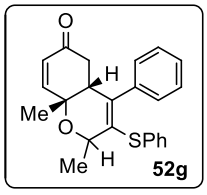
NMR (471 MHz, $CDCl_3$): δ –62.6; IR (Neat)ν_{max} 2930, 1684, 1581, 1475, 1438, 1370, 1328, 1277, 1163 cm^{-1}; HRMS (ESI) for $C_{23}H_{19}F_3NaO_2S$ $(M+Na)^+$: calcd 439.0950, found 439.0957.

8a-Ethyl-4-phenyl-3-(phenylthio)-4a,5-dihydro-2H-chromen-6(8aH)-one (52f):



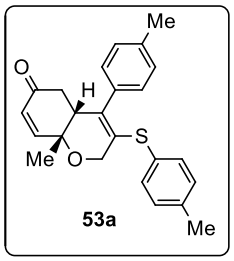
Following the general procedure GP-2, compound **52f** (41 mg) was obtained in 38% yield along with the unreacted **1a** (35%). Colorless solid; mp = 118–120 °C; R_f = 0.43 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.33 (m, 2H), 7.33–7.28 (m, 1H), 7.28–7.21 (m, 4H), 7.21–7.16 (m, 1H), 7.15–7.11 (m, 2H), 6.82 (d, J = 10.0 Hz, 1H), 6.13 (d, J = 10.0 Hz, 1H), 4.23 (dd, J = 17.0, 2.0 Hz, 1H), 4.14 (dd, J = 17.0, 2.0 Hz, 1H), 3.13–3.06 (m, 1H), 2.53–2.41 (m, 2H), 2.02–1.88 (m, 2H), 1.07 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 197.7, 150.3, 142.6, 138.6, 134.1, 131.1, 129.9, 129.1, 128.4, 128.2, 127.8, 126.7, 73.3, 64.6, 43.2, 39.2, 29.6, 7.8; IR (Neat)ν_{max} 3055, 2919, 2836, 1678, 1579, 1471, 1438, 1383, 1261 cm^{-1}; HRMS (ESI) for $C_{23}H_{22}NaO_2S$ $(M+Na)^+$: calcd 385.1233, found 385.1241.

2,8a-Dimethyl-4-phenyl-3-(phenylthio)-4a,5-dihydro-2H-chromen-6(8aH)-one (52g):



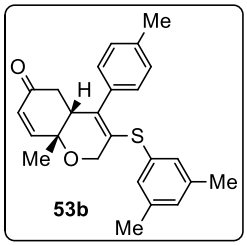
Following the general procedure GP-2, compound **52g** (74 mg) was obtained in 68% yield. Yellow liquid; R_f = 0.31 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.27 (m, 3H), 7.23–7.17 (m, 2H), 7.15–7.09 (m, 3H), 7.04–7.00 (m, 2H), 6.90 (dd, J = 10.4, 1.6 Hz, 1H), 6.17 (dd, J = 10.4, 1.2 Hz, 1H), 4.41–4.33 (m, 1H), 3.25–3.19 (m, 1H), 2.57 (dd, J = 16.8, 5.6 Hz, 1H), 2.36–2.29 (m, 1H), 1.59 (s, 3H), 1.42 (d, J = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 196.9, 153.8, 146.1, 138.8, 135.9, 131.7, 130.3, 128.9, 128.3, 128.2, 127.9, 127.5, 125.8, 72.6, 69.6, 46.5, 39.1, 25.5, 21.0; IR (Neat)ν_{max} 2978, 1684, 1580, 1476, 1439, 1380, 1263 cm^{-1}; HRMS (ESI) for $C_{23}H_{22}NaO_2S$ $(M+Na)^+$: calcd 385.1233, found 385.1239.

8a-Methyl-4-(*p*-tolyl)-3-(*p*-tolylthio)-4a,5-dihydro-2H-chromen-6(8aH)-one (53a):



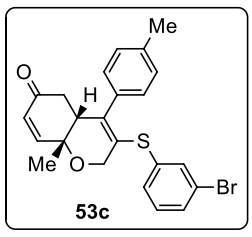
Following the general procedure GP-2, compound **53a** (72 mg) was obtained in 64% yield. Yellow gummy liquid; R_f = 0.43 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.13 (m, 4H), 7.09–7.01 (m, 4H), 6.71 (d, J = 10 Hz, 1H), 6.05 (d, J = 10.4 Hz, 1H), 4.21 (dd, J = 16.4, 2.0 Hz, 1H), 4.10 (dd, J = 16.8, 2.0 Hz, 1H), 3.02–2.96 (m, 1H), 2.52–2.40 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), 1.55 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.8, 151.2, 141.2, 137.5, 136.9, 135.5, 130.6, 130.2, 130.0, 129.8, 129.1, 128.1, 126.8, 71.0, 64.5, 45.2, 39.3, 24.0, 21.2, 21.0; IR (Neat)ν_{max} 3020, 2972, 1684, 1509, 1490, 1444, 1369, 1266, 1181, 1148, 1108 cm^{-1}; HRMS (ESI) for $C_{24}H_{25}O_2S$ $(M+H)^+$: calcd 377.1570, found 377.1579.

3-((3,5-Dimethylphenyl)thio)-8a-methyl-4-(*p*-tolyl)-4a,5-dihydro-2H-chromen-6(8aH)-one (53b):



Following the general procedure GP-2, compound **53b** (94 mg) was obtained in 80% yield. Yellow gummy liquid; R_f = 0.43 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 6.85 (s, 2H), 6.82 (s, 1H), 6.73 (d, J = 10.4 Hz, 1H), 6.06 (d, J = 10.0 Hz, 1H), 4.25 (dd, J = 16.8, 2.0 Hz, 1H), 4.15 (dd, J = 16.8, 2.0 Hz, 1H), 3.05–2.98 (m, 1H), 2.53–2.42 (m, 2H), 2.35 (s, 3H), 2.59 (s, 6H), 1.57 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.7, 151.2, 141.9, 138.6, 137.4, 135.5, 133.4, 130.2, 129.0, 128.5, 128.0, 127.5, 126.4, 71.0, 64.7, 45.2, 39.3, 23.9, 21.2, 21.1; IR (Neat)ν_{max} 2972, 2917, 1684, 1598, 1578, 1509, 1444, 1369, 1265, 1148, 1108 cm^{-1}; HRMS (ESI) for $C_{25}H_{26}NaO_2S$ $(M+Na)^+$: calcd 413.1546, found 413.1552.

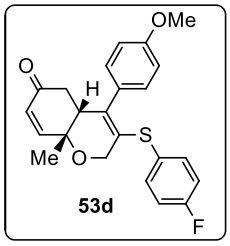
3-((3-Bromophenyl)thio)-8a-methyl-4-(*p*-tolyl)-4a,5-dihydro-2H-chromen-6(8aH)-one (53c):



Following the general procedure GP-2, compound **53c** (83 mg) was obtained in 63% yield. Yellow thick liquid; R_f = 0.35 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.27 (m, 2H), 7.19–7.10 (m, 4H), 6.99 (d, J = 8.0 Hz, 2H), 6.75 (d,

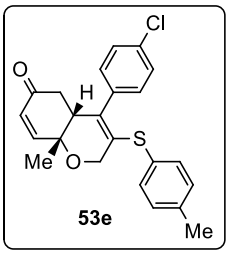
J = 10.4 Hz, 1H), 6.09 (d, *J* = 10.4 Hz, 1H), 4.26 (dd, *J* = 16.8, 2.0 Hz, 1H), 4.15 (dd, *J* = 16.8, 2.0 Hz, 1H), 3.08–3.01 (m, 1H), 2.55–2.40 (m, 2H), 2.35 (s, 3H), 1.58 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.4, 151.1, 144.6, 137.8, 137.0, 135.1, 131.7, 130.4, 130.3, 129.5, 129.1, 127.9, 127.6, 125.5, 122.9, 71.2, 64.7, 45.4, 39.3, 24.1, 21.2; IR (Neat)ν_{max} 3047, 2973, 1684, 1571, 1557, 1509, 1456, 1369, 1265, 1108 cm^{-1}; HRMS (ESI) for $C_{23}H_{21}BrNaO_2S$ $(M+Na)^+$: calcd 463.0338, found 463.0346.

3-((4-Fluorophenyl)thio)-4-(4-methoxyphenyl)-8a-methyl-4a,5-dihydro-2H-chromen-6(8aH)-one (53d): Following the general procedure GP-2, compound **53d** (49 mg) was obtained in 41% yield along with the unreacted **1a** (40%). Yellow gummy liquid; R_f = 0.18 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24–7.19 (m, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.96 (t, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 10.0 Hz, 1H), 6.05 (d, *J* = 10.0 Hz, 1H), 4.19 (dd, *J* = 16.8, 1.6 Hz, 1H), 4.07 (dd, *J* = 16.8, 1.6 Hz, 1H), 3.81 (s, 3H), 3.03–2.96 (m, 1H), 2.52–2.39 (m, 2H), 1.55 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.6, 162.2 (d, *J* = 248 Hz, 1C), 159.2, 151.1, 141.3, 132.7 (d, *J* = 8.1 Hz, 1C), 130.6, 130.4, 129.5, 128.8 (d, *J* = 4.0 Hz, 1C), 126.9, 116.2 (d, *J* = 22.2 Hz, 1C), 113.9, 71.3, 64.6, 55.2, 45.4, 39.4, 24.1; ^{19}F NMR (471 MHz, $CDCl_3$): δ –114.5; IR (Neat)ν_{max} 2970, 2835, 1681, 1605, 1587, 1508, 1486, 1370, 1245, 1221, 1176 cm^{-1}; HRMS (ESI) for $C_{23}H_{21}FNaO_3S$ $(M+Na)^+$: calcd 419.1088, found 419.1094.



53d

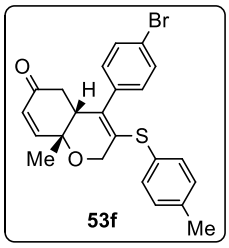
4-(4-Chlorophenyl)-8a-methyl-3-(*p*-tolylthio)-4a,5-dihydro-2H-chromen-6(8aH)-one (53e): Following the general procedure GP-2, compound **53e** (87 mg) was obtained in 73% yield. Yellow gummy liquid; R_f = 0.26 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.10–7.03 (m, 4H), 6.71 (d, *J* = 10.4 Hz, 1H), 6.06 (d, *J* = 10.4 Hz, 1H), 4.19 (dd, *J* = 16.8, 2.0 Hz, 1H), 4.09 (dd, *J* = 16.8, 1.6 Hz, 1H), 3.01–2.94 (m, 1H), 2.51–2.37 (m, 2H), 2.31 (s, 3H), 1.55 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.4, 151.1, 139.5, 137.3, 136.8, 133.6, 130.7, 130.2, 129.9, 129.7, 129.3,



53e

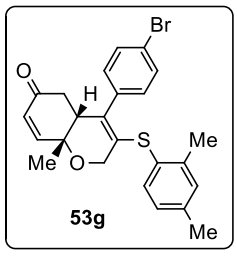
128.6, 128.2, 71.1, 64.4, 45.0, 39.3, 24.0, 21.0; IR (Neat)ν_{max} 3023, 2973, 1683, 1592, 1488, 1443, 1369, 1279, 1149, 1088 cm^{-1}; HRMS (ESI) for $C_{23}H_{21}ClNaO_2S$ $(M+Na)^+$: calcd 419.0843, found 419.0847.

4-(4-Bromophenyl)-8a-methyl-3-(*p*-tolylthio)-4a,5-dihydro-2H-chromen-6(8aH)-one



(53f): Following the general procedure GP-2, compound **53f** (66 mg) was obtained in 50% yield along with the unreacted **1a** (30%). Yellow thick liquid; R_f = 0.31 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 8.4 Hz, 2H), 7.15–7.05 (m, 4H), 7.01 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 10.0 Hz, 1H), 6.06 (d, J = 10.0 Hz, 1H), 4.18 (dd, J = 16.8, 2.0 Hz, 1H), 4.08 (dd, J = 16.8, 2.0 Hz, 1H), 3.02–2.95 (m, 1H), 2.52–2.36 (m, 2H), 2.30 (s, 3H), 1.55 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.5, 151.1, 139.5, 137.3, 131.6, 130.8, 130.3, 130.1, 129.9, 129.3, 128.3, 121.9, 71.2, 64.5, 45.0, 39.3, 24.0, 21.0; IR (Neat)ν_{max} 3021, 2971, 1683, 1585, 1486, 1369, 1264, 1178, 1068 cm^{-1}; HRMS (ESI) for $C_{23}H_{21}BrNaO_2S$ $(M+Na)^+$: calcd 463.0338, found 463.0345.

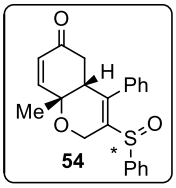
4-(4-Bromophenyl)-3-((2,4-dimethylphenyl)thio)-8a-methyl-4a,5-dihydro-2H



chromen-6(8aH)-one (53g): Following the general procedure GP-2, compound **53g** (101 mg) was obtained in 74% yield. Yellow gummy liquid; R_f = 0.35 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 1H), 7.05–7.00 (m, 2H), 6.97 (s, 1H), 6.92 (br d, J = 7.6 Hz, 1H), 6.69 (d, J = 10.0 Hz, 1H), 6.05 (d, J = 10.0 Hz, 1H), 4.07 (dd, J = 16.8, 2.0 Hz, 1H), 3.95 (dd, J = 16.8, 2.0 Hz, 1H), 3.01–2.94(m, 1H), 2.51–2.35 (m, 2H), 2.28 (s, 3H), 2.23 (s, 3H), 1.54 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.4, 151.2, 139.5, 137.81, 137.79, 137.4, 131.9, 131.6, 131.3, 130.3, 129.9, 128.4, 127.9, 127.3, 121.8, 71.3, 64.3, 44.9, 39.3, 24.1, 20.9, 20.5; IR (Neat)ν_{max} 2972, 1683, 1481, 1442, 1370, 1265, 1148, 1106, 1068 cm^{-1}; HRMS (ESI) for $C_{24}H_{24}BrO_2S$ $(M+H)^+$: calcd 455.0675, found 455.0686.

4A.6.3.4. Large scale synthesis of 3-thiophenyl dihydrochromenone 51a

A mixture of alkynyl cyclohexadienone **1a** (2.5 mmol, 596 mg) and N-hydroxypthalimide (NHPI) (0.625 mmol, 102 mg) in CH_2Cl_2 (0.5 M, 4 mL) was taken in a screw cap sealed tube. To the above mixture, thiophenol **50a** (6.25 mmol, 0.6 mL) was added. Finally, the reaction mixture was stirred at 70 °C for 36 hours in a heating block. Upon completion, the reaction mixture was cooled to room temperature and diluted with dichloromethane (20 mL). The crude residue was purified using column chromatography on silica gel (100–200 mesh) to provide 3-thioaryl dihydrochromenone **51a** (596 mg) in 65% yield.



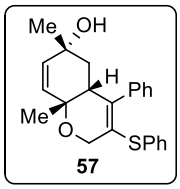
4A.6.3.5. Synthesis of 8a-methyl-4-phenyl-3-(phenylsulfinyl)-4a,5-dihydro-2H-chromen-6(8aH)-one (54): To a solution of **51a** (70 mg, 0.2 mmol) in CH_2Cl_2 (2.0 mL) was added *m*CPBA (35 mg, 0.2 mmol) portion wise. The resulting mixture was stirred at room temperature overnight. Upon completion, the crude reaction mixture was diluted with CH_2Cl_2 (5.0 mL) and washed with aquous sodium bicarbonate solution (10 mL, 2 M). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified using column chromatography (2% THF/chloroform) on silica gel to afford **54** (51 mg) as inseparable mixture of diastereomers in 70% yield as colorless solid; mp = 168–170 °C; R_f = 0.25 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.34 (m, 15H), 7.29 (d, J = 7.2 Hz, 1.58H), 7.19–7.14 (m, 2H), 6.63 (t, J = 9.6 Hz, 1.86H), 6.02 (d, J = 10.4 Hz, 0.75H), 5.98 (d, J = 10.0 Hz, 1H), 4.68 (dd, J = 16.4, 0.8 Hz, 1.81H), 3.97 (dd, J = 16.8, 1.6 Hz, 0.79H), 3.77 (dd, J = 16.8, 2.4 Hz, 1H), 3.12–3.06 (m, 1H), 2.88–2.82 (m, 0.77H), 2.62–2.35 (m, 3.73H), 1.56 (s, 3H), 1.32 (s, 2.6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.0, 196.7, 151.8, 150.0, 146.4, 145.2, 142.1, 141.6, 138.6, 138.2, 135.9, 135.5, 130.7, 130.5, 130.46, 130.1, 129.2, 129.1, 129.0, 128.81, 128.75, 128.6, 128.5, 128.2, 124.3, 123.7, 72.0, 70.3, 57.3, 56.4, 45.5, 44.5, 38.5, 38.0, 24.3, 23.3; IR (Neat)ν_{max} 3055, 2921, 2850, 1684, 1578, 1474, 1442, 1372, 1142, 1079 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}NaO_3S$ $(M+Na)^+$: calcd 387.1025, found 387.1030.

4A.6.3.6. Synthesis of 8a-methyl-4-phenyl-3-(phenylsulfonyl)-4a,5-dihydro-2H-chromen-6(8aH)-one (55): To a solution of **51a** (70 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was added *m*CPBA (140 mg, 0.8 mmol) portion wise. The resulting mixture was stirred at room temperature overnight. Upon completion, the crude reaction mixture was diluted with CH_2Cl_2 (5.0 mL) and washed with aquous sodium bicarbonate solution (10 mL, 2 M). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified using column chromatography on silica gel to afford **55** (66 mg) in 86% yield as pale yellow gummy liquid; R_f = 0.43 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.44 (m, 1H), 7.35–7.19 (m, 9H), 6.73 (d, J = 10.4 Hz, 1H), 6.06 (d, J = 10.0 Hz, 1H), 4.76 (dd, J = 17.6, 2.0 Hz, 1H), 4.70 (dd, J = 17.6, 2.4 Hz, 1H), 2.72–2.63 (m, 1H), 2.44–2.30 (m, 2H), 1.51 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 196.6, 150.1, 148.6, 140.9, 137.0, 135.2, 133.1, 130.4, 128.7, 128.4, 128.0, 127.4, 70.6, 61.3, 46.1, 38.1, 23.7; IR (Neat)ν_{max} 3058, 2974, 2359, 1684, 1490, 1445, 1372, 1306, 1148, 1084 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}NaO_4S$ $(M+Na)^+$: calcd 403.0975, found 403.0980.

4A.6.3.7. Synthesis of 8-((4-(*tert*-butyl)phenyl)thio)-8a-methyl-4-phenyl-3-(phenylthio)-4a,5,8,8a-tetrahydro-2H-chromen-6(7H)-one (56): To a solution of **51a** (70 mg, 0.2 mmol) in $CHCl_3$ (2 mL) was added 4-*tert*-butylbenzenethiol (0.3 mmol, 52µL) and trimethylamine (0.3 mmol, 42µL) subsequently. The resulting mixture was stirred at room temperature for 48 hours. Upon completion, the crude reaction mixture was purified using column chromatography (ethylacetate/hexane) on silica gel to afford **56** (60 mg) as inseparable mixture of diastereomers in 58% yield as pale yellow gummy liquid; R_f = 0.30 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.27 (m, 21.3H), 7.25–7.19 (m, 6.33H), 4.44–4.18 (m, 4.26H), 3.73–3.59 (m, 1.34H), 3.41–3.22 (m, 0.90H), 3.08–3.00 (m, 1.45H), 3.00–2.88 (m, 1.27H), 2.69–2.28 (m, 7.30H), 1.77 (s, 1.58H), 1.70 (s, 3H), 1.32 (s, 6.91H), 1.31 (s, 9.15H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 207.7, 207.4, 151.4, 151.1, 144.7, 144.0, 139.14, 139.09, 134.2, 133.4, 132.9, 130.7, 130.3, 129.9, 129.6, 129.14,

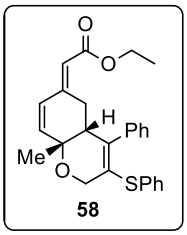
129.07, 128.4, 128.1, 128.0, 127.93, 127.89, 127.0, 126.8, 126.4, 126.2, 126.1, 124.9, 124.5, 73.5, 73.2, 65.0, 64.9, 57.5, 55.0, 48.6, 44.93, 44.87, 43.4, 43.0, 41.6, 34.59, 34.55, 31.2, 21.5, 20.5; IR (Neat)ν_{max} 2959, 2865, 1715, 1580, 1474, 1363, 1264, 1146, 1058 cm^{-1}; HRMS (ESI) for $C_{32}H_{34}NaO_2S_2$ $(M+Na)^+$: calcd 537.1892, found 537.1897.

4A.6.3.8. Synthesis of 6,8a-dimethyl-4-phenyl-3-(phenylthio)-4a,5,6,8a-tetrahydro-2H-chromen-6-ol (57): In an oven dried 50 mL two-neck RB flask, a solution of compound **51a** (70 mg, 0.2 mmol) in THF (4.0 mL) was taken under the inert atmosphere. Methylmagnesium bromide (1.6 M, 0.6 mmol) in THF was added dropwise at 0 °C. After 30 minutes, the resulting reaction mixture was warmed to room temperature and allowed to stir overnight. Upon completion, the reaction mixture was quenched with saturated aqueous ammonium chloride (30 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic solvents were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude reaction mixture was purified by using silica gel column chromatography (EtOAc/hexane) to give **57** (64 mg) in 88% yield as pale yellow gummy liquid; R_f = 0.55 (1:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.27 (m, 4H), 7.26–7.22 (m, 5H), 7.20–7.15 (m, 1H), 5.76 (dd, J = 10.0, 1.0 Hz, 1H), 5.57 (d, J = 10.0 Hz, 1H), 4.23 (d, J = 17.0 Hz, 1H), 4.13 (dd, J = 16.5, 2.0 Hz, 1H), 2.45–2.37 (m, 1H), 1.93 (br s, 1H), 1.85–1.79 (m, 2H), 1.43 (s, 3H), 1.13 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 145.2, 139.7, 137.2, 135.0, 130.8, 129.0, 128.8, 128.2, 128.1, 127.6, 126.2, 124.7, 69.9, 69.3, 64.2, 44.8, 40.1, 26.4, 23.0; IR (Neat)ν_{max} 3448, 3019, 2964, 2360, 1579, 1476, 1439, 1393, 1259, 1174 cm^{-1}; HRMS (ESI) for $C_{23}H_{24}NaO_2S$ $(M+Na)^+$: calcd 387.1389, found 387.1392.



57

4A.6.3.9. Synthesis of (*E*)-ethyl-2-8a-methyl-4-phenyl-3-(phenylthio)-4a,5-dihydro-2H-chromen-6(8aH)- ylidene)acetate (58): A mixture of NaH (0.8 mmol; 4.0 equiv., 19 mg) in THF (1.0 mL) was taken in an oven dried two-neck round bottom flask under nitrogen atmosphere and cooled to 0 °C. Next, triethyl phosphonoacetate (0.4 mmol; 2.0 equiv, 101 mg) was added to the resulting solution at 0 °C and stirred for 30 minutes at same temperature. Subsequently,



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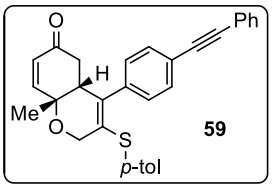
a solution of **51a** (0.2 mmol, 70 mg) in THF (1.0 mL) was added dropwise to the above reaction mixture at 0 °C. The resulting reaction mixture was stirred for one hour at 0 °C. Finally, the reaction was quenched with saturated aqueous NH_4Cl (5.0 mL) followed by work-up with ethyl acetate (3 × 5.0 mL). The organic layers were combined and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixure was purified by using silica gel column chromatography (EtOAc/hexane) to provide the desired olefin product **58** (38 mg) in 45% yield as colorless gummy compound; R_f = 0.43 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (dd, J = 10.0, 1.0 Hz, 1H), 7.37–7.28 (m, 3H), 7.24 (d, J = 7.5 Hz, 2H), 7.22–7.13 (m, 5H), 5.99 (dd, J = 10.5, 1.5 Hz, 1H), 5.34 (s, 1H), 4.23 (dd, J = 17.0, 2.5 Hz, 1H), 4.20–4.12 (m, 2H), 4.07 (dd, J = 17.0, 2.0 Hz, 1H), 2.84–2.78 (m, 1H), 2.46–2.40 (m, 1H), 2.33–2.27 (m, 1H), 1.49 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.9, 148.7, 144.1, 139.3, 139.0, 135.0, 129.03, 129.0, 128.4, 128.2, 128.1, 127.6, 127.0, 126.2, 116.1, 71.6, 64.5, 59.9, 45.2, 34.3, 24.6, 14.3; IR (Neat)ν_{max} 2975, 1708, 1636, 1597, 1476, 1365, 1235, 1157 cm^{-1}; HRMS (ESI) for $C_{26}H_{26}NaO_3S$ $(M+Na)^+$: calcd 441.1495, found 441.1502.

4A.6.3.10. Synthesis of 8a-methyl-4-(4-(phenylethynyl)phenyl)-3-(*p*-tolylthio)-4a,5-dihydro-2H-chromen-6(8aH)-one (59): A solution of **53f** (0.2 mmol; 88 mg), $Pd(Ph_3P)_2Cl_2$ (0.01 mmol; 7 mg), CuI (0.02 mmol; 3.8 mg), and Ph_3P (0.03 mmol; 7.9 mg) in Et_3N (2.0 mL) was taken in a screw cap sealed tube. Subsequently, phenylacetylene (0.24 mmol; 26 μL) was added to the above reaction mixture and stirred at 110 °C for 24 h in a heating block. Upon completion, the reaction was cooled to room temperature, filtered through Celite and concentrated under reduced pressure. Finally, the crude residue was purified by using silica gel column chromatography (EtOAc/hexane) to provide the desired alkynylated product **59** (77 mg) in 83% yield as yellow liquid; R_f = 0.29 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56–7.51 (m, 4H), 7.37–7.33 (m, 3H), 7.14 (d, J = 7.2 Hz, 4H), 7.08 (d, J = 8.0 Hz, 2H), 6.72 (d, J = 10.4 Hz, 1H), 6.07 (d, J = 10.0 Hz, 1H), 4.22 (dd, J = 16.8, 2.0 Hz, 1H), 4.11 (dd, J = 16.8, 2.0 Hz, 1H), 3.05–2.98 (m, 1H), 2.53–2.40 (m, 2H), 2.31 (s,



3H), 1.56 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 197.6, 151.1, 140.3, 138.5, 137.2, 134.3, 131.6, 130.8, 130.3, 129.9, 129.6, 128.5, 128.31, 128.28, 127.9, 123.2, 122.8, 89.9, 89.1, 71.1, 64.5, 45.0, 39.4, 24.0, 21.0; IR (Neat)ν_{max} 2922, 2851, 1685, 1507, 1490, 1370, 1278, 1107 cm^{-1}; HRMS (ESI) for $C_{31}H_{27}O_2S$ $(M+H)^+$: calcd 463.1726, found 463.1737.

4A.7. X-ray Crystallography

Single crystal X-ray data for the compound **51a** was collected using the Bruker D8 Quest CMOS detector system [λ(Mo-Kα) = 0.71073 Å] at 298K, graphite monochromator with a ω scan width of 0.3o, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software was used for the intensity data acquisition and the SAINTPLUS Software was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program, an empirical absorption correction using equivalent reflections was performed with the program. The structure was solved using SHELXS-97, OLEX, and full-matrix least-squares refinement against F2 was carried out using SHELXL-97. All non-hydrogen atoms were refined anisotropically. Aromatic and methyl hydrogens were introduced on calculated positions and included in the refinement riding on their respective parent atoms.[16,17]

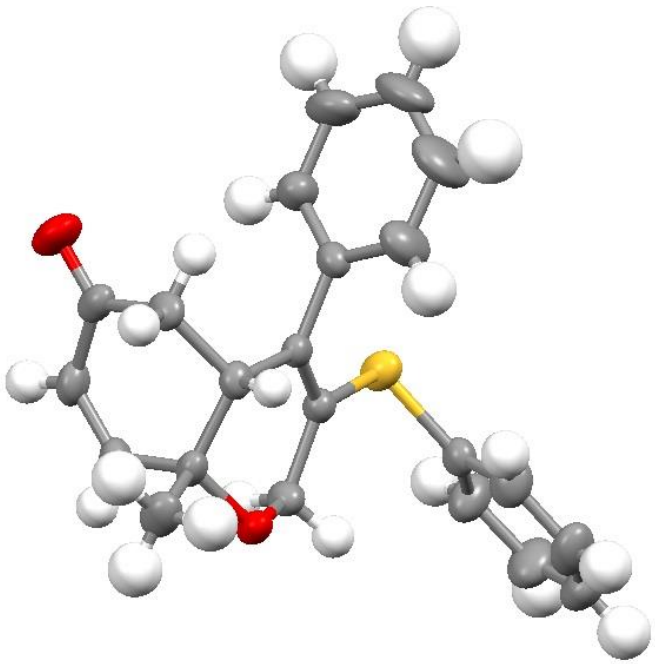


Figure 4A.2. Thermal ellipsoid plot of compound **51a** and it shows ellipsoid contour at the 50% probability level. Single crystal was grown by the slow evaporation of the solution of compound **51a** in chloroform and *n*-hexane (1:1) mixture. Carbon (gray), Hydrogen (light gray), Oxygen (red), and Sulphur (yellow).

Table 4A.7. Crystallographic data for compound **51a.**

Compound	**51a**
formula	$C_{22}H_{20}O_2S$
MW	348.44
crystal system	triclinic
space group	P -1
T [K]	297 K
a [Å]	11.189(3)
b [Å]	11.474(2)
c [Å]	14.860(3)
α [°]	84.479(9)
β [°]	87.969(10)
γ [°]	77.882(9)
V [Å^3]	1856.3(7)
Z	4
ρ_{calcd} [g cm^{-3}]	1.247
μ [mm^{-1}]	0.186
total reflns	8731
unique reflns	8632
observed	4762
$R_1[I>2\sigma(I)]$	0.0609
wR2 [all]	0.1335(8632)
GOF	1.063
Diffractometer	Bruker D8 Quest CCD
CCDC Number	1897537

4A.8. References

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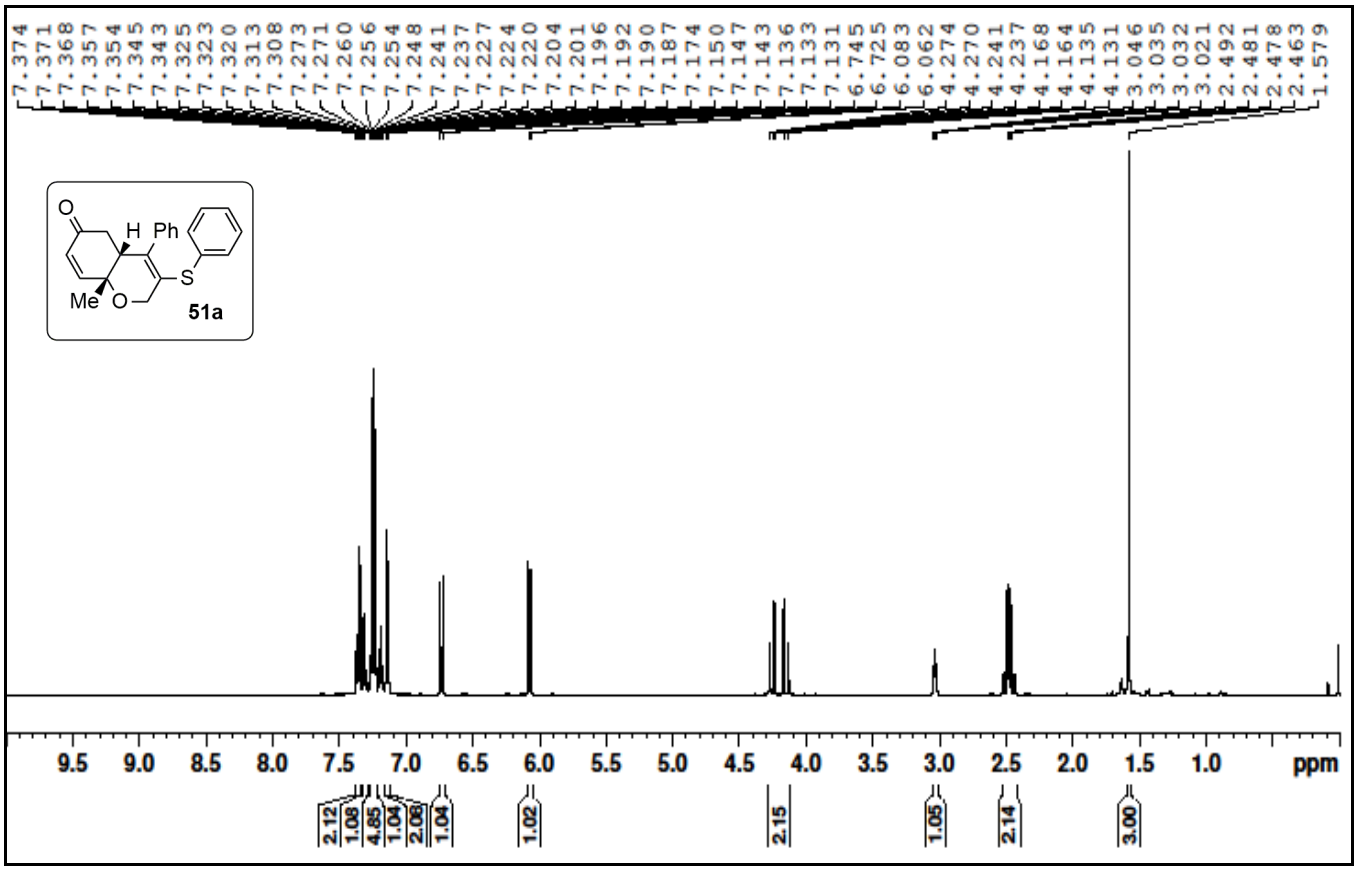
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2.0
1.5
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2.08
1.04
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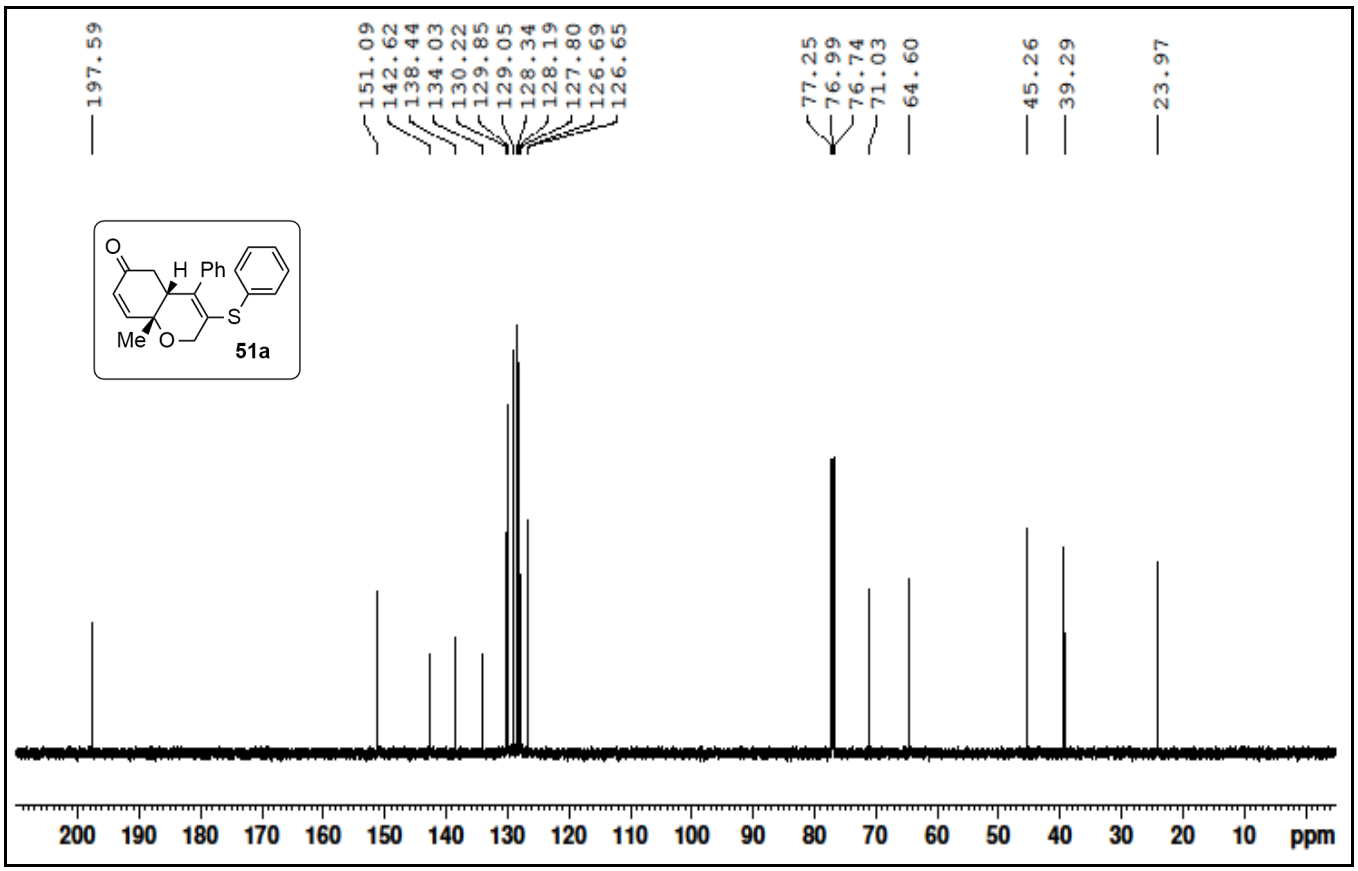
3.00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76.74
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23.97
O
H
Ph
S
Me
O
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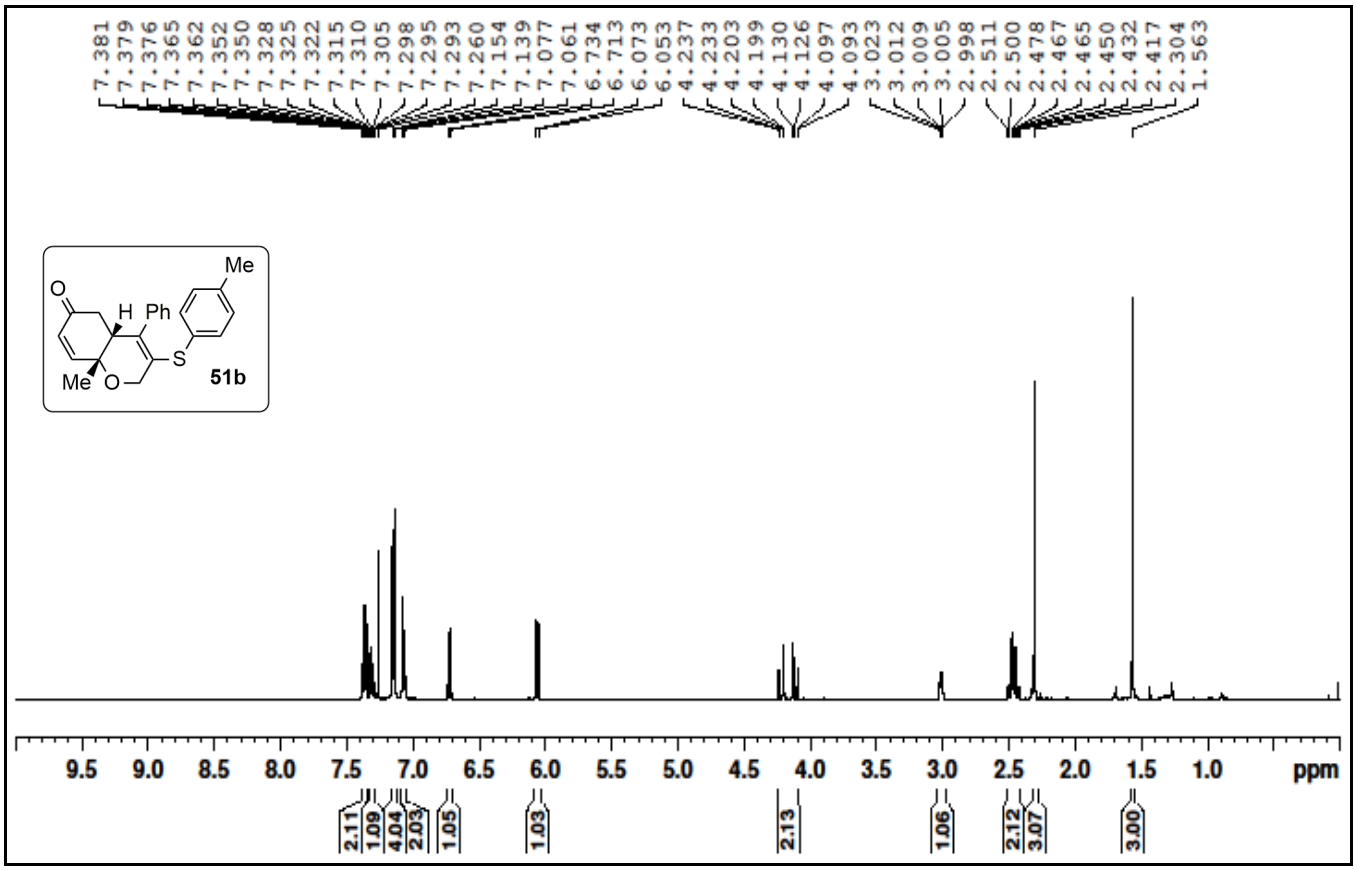
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1.563
Me
O
H
Ph
S
Me
O
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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2.0
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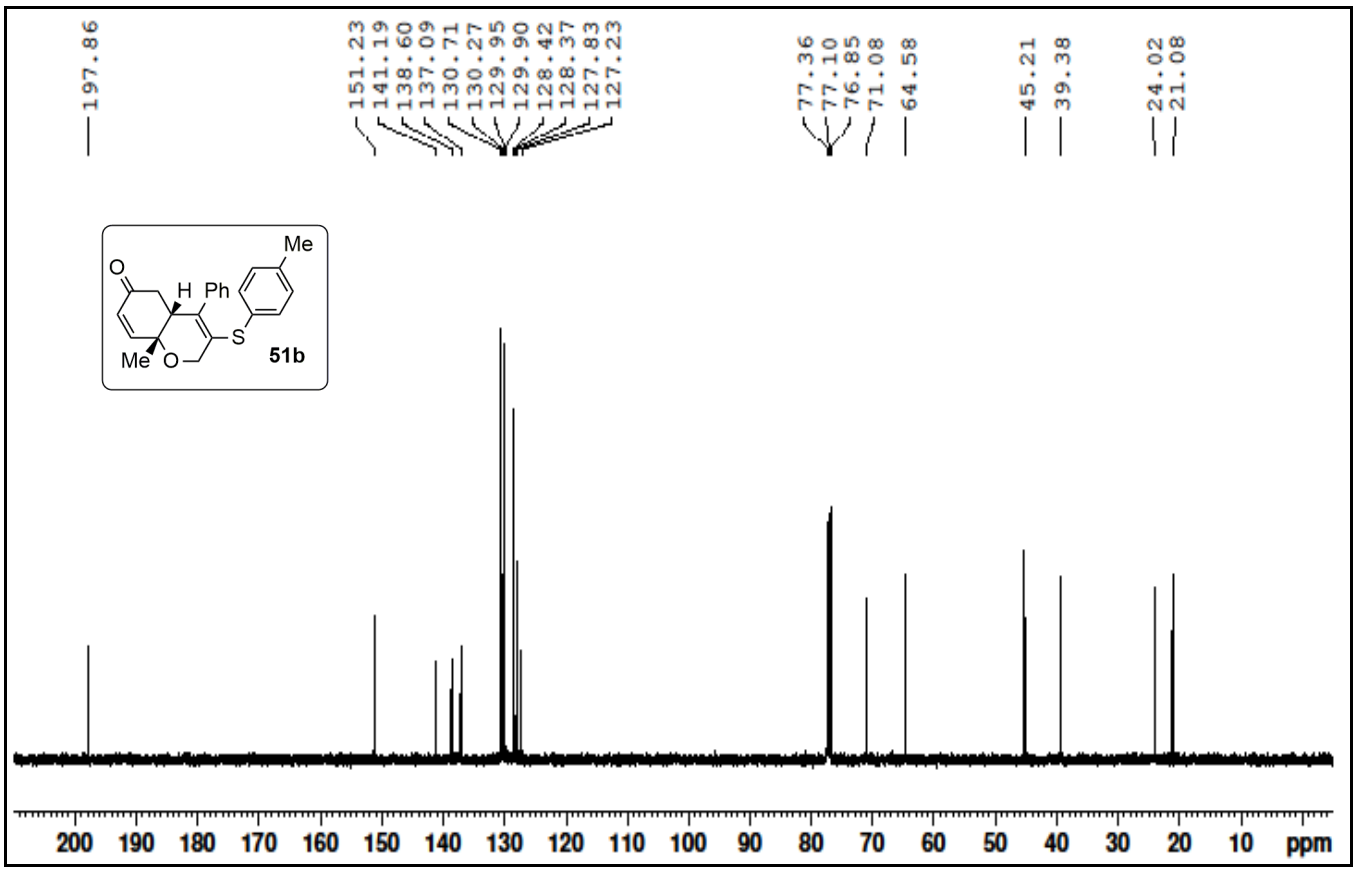
3.00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24.02
21.08
Me
O
H
Ph
S
Me
O
51b
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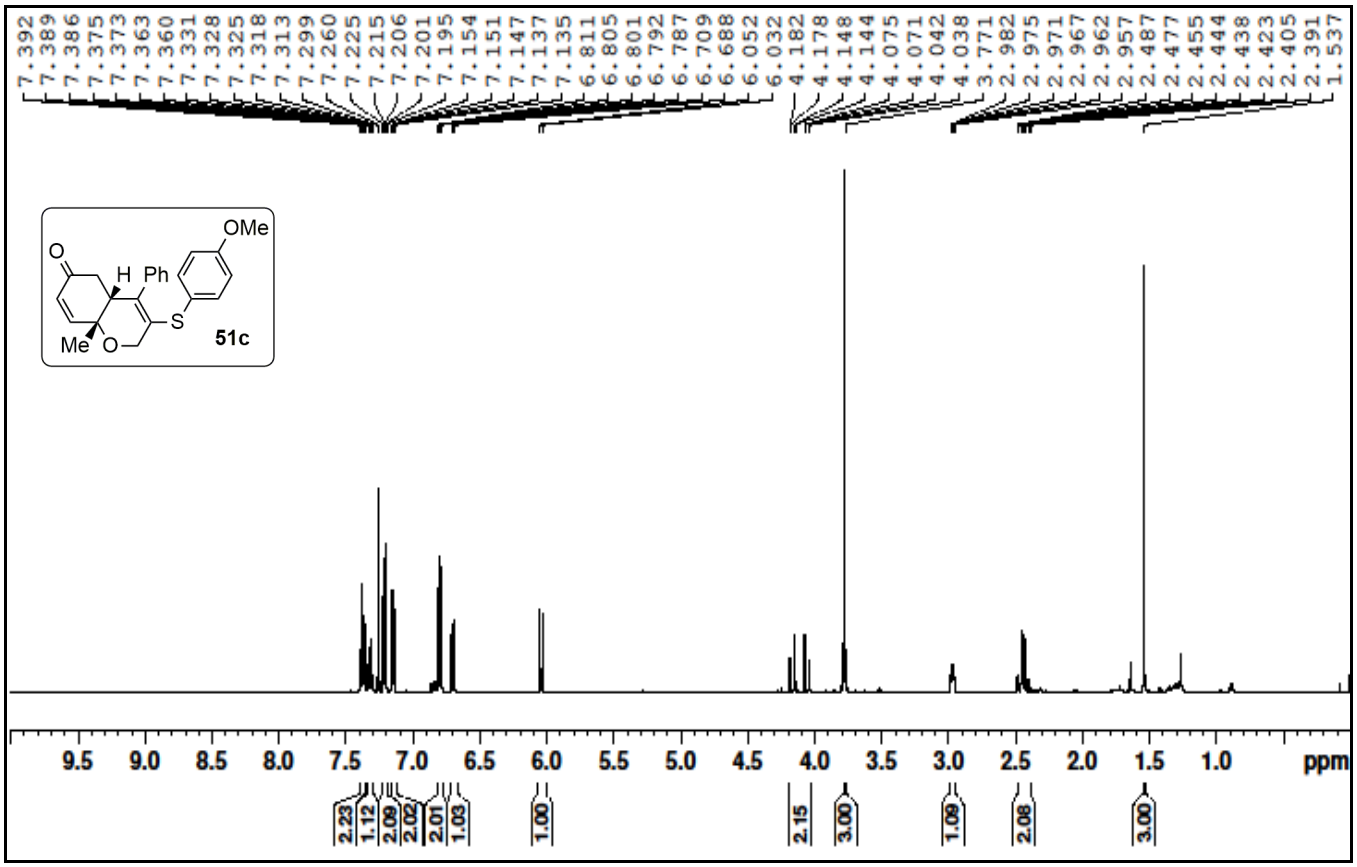
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OMe
O
H Ph
S
Me O
51c
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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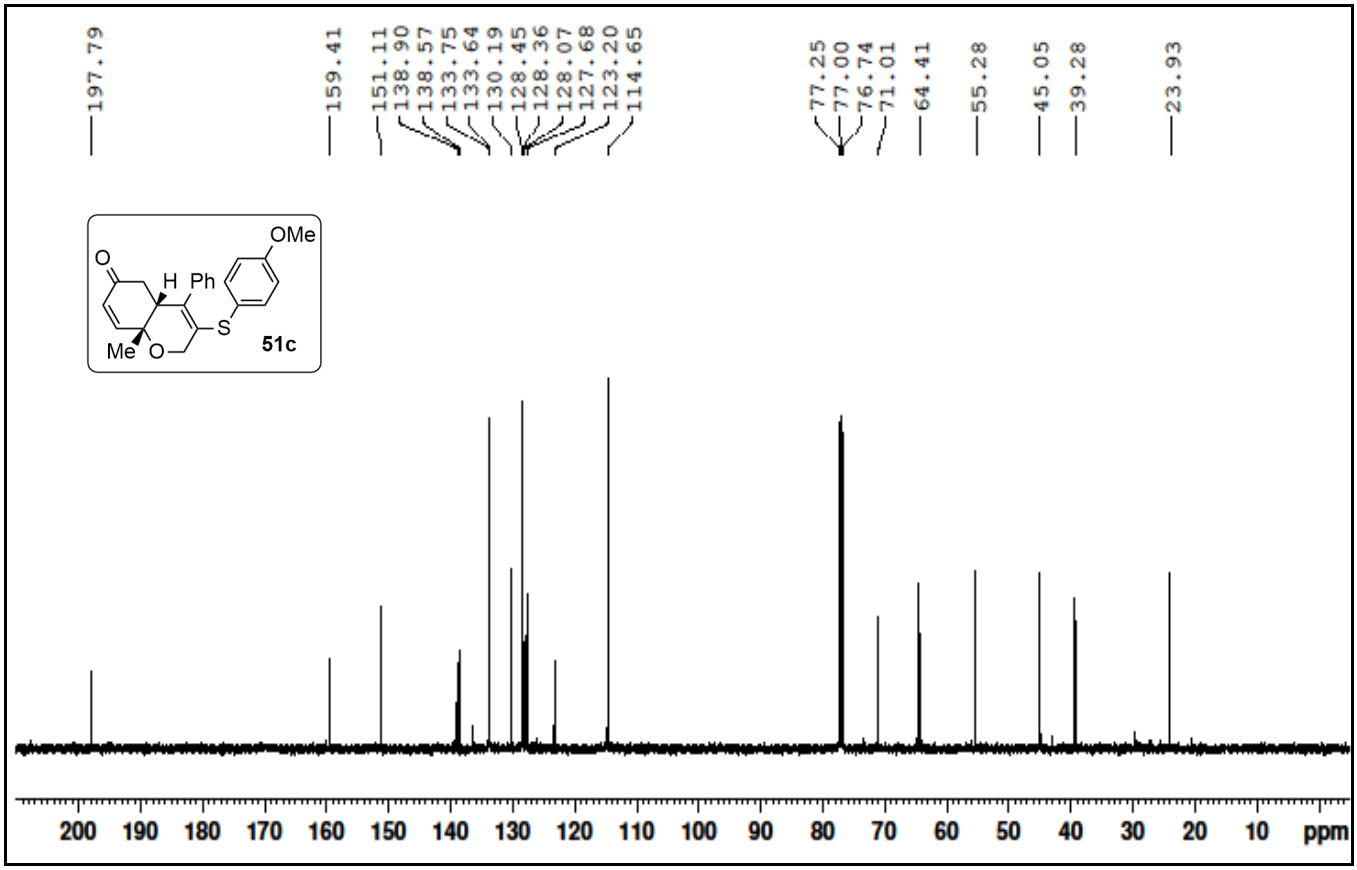
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77.25 77.00 76.74 71.01
64.41
55.28
45.05
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OMe
O
H Ph
S
Me O
51c
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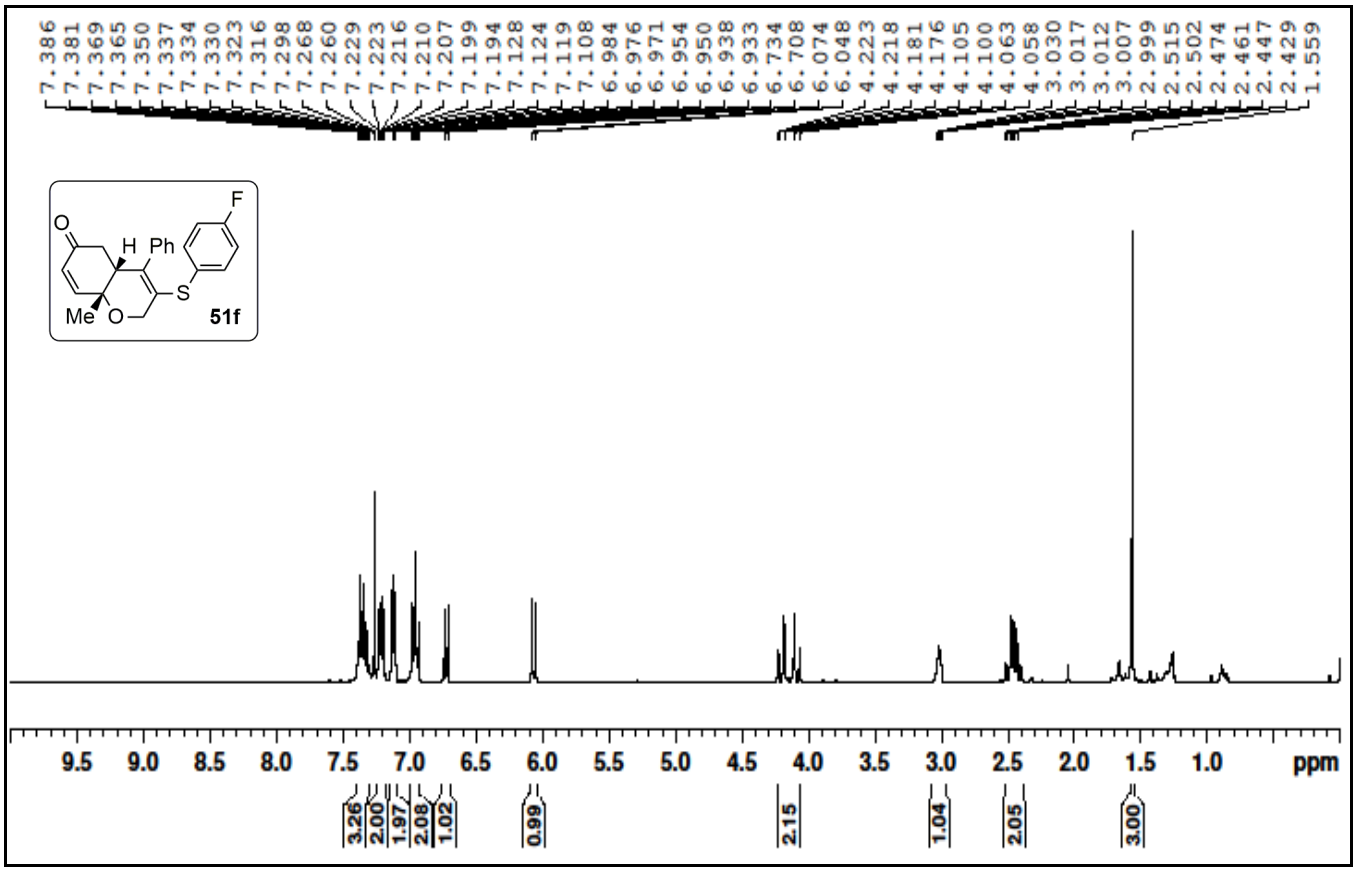
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7.194
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7.124
7.119
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6.976
6.971
6.954
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6.933
6.734
6.708
6.074
6.048
4.223
4.218
4.181
4.176
4.105
4.100
4.063
4.058
3.030
3.017
3.012
3.007
2.999
2.515
2.502
2.474
2.461
2.447
2.429
1.559
F
O
H
Ph
S
Me
O
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3.5
3.0
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2.0
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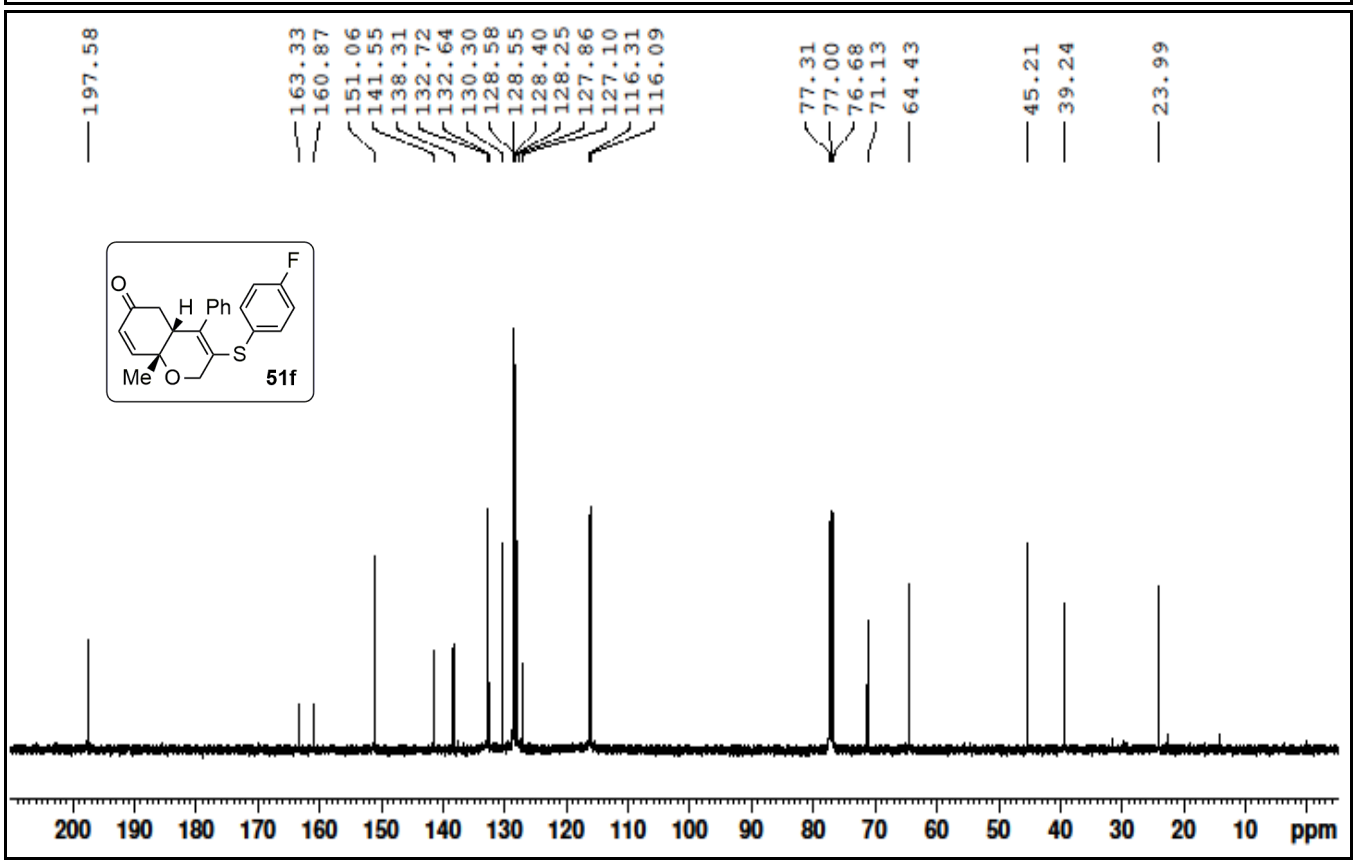
3.00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127.86
127.10
116.31
116.09
77.31
77.00
76.68
71.13
64.43
45.21
39.24
23.99
F
O
H
Ph
S
Me
O
51f
200
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150
140
130
120
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90
80
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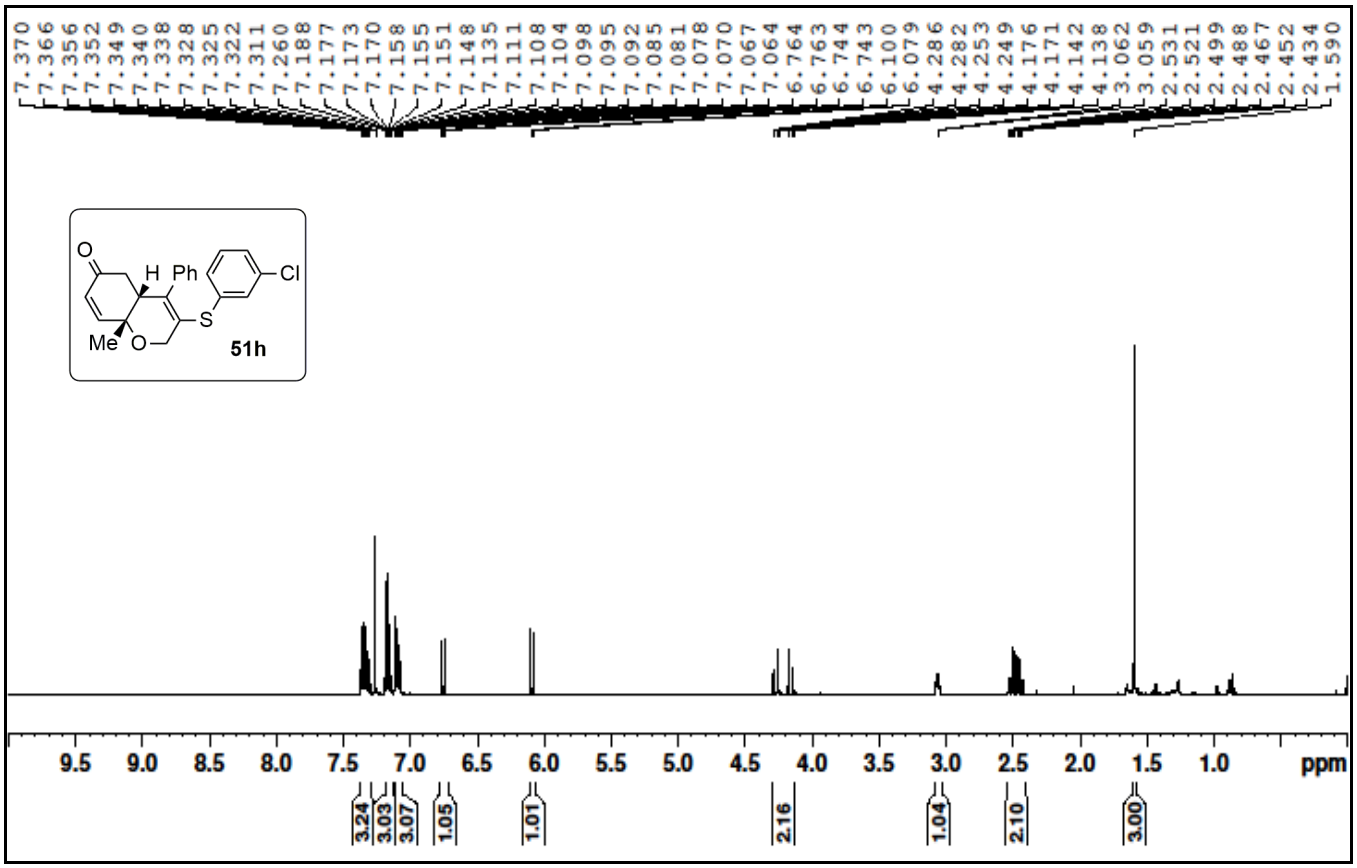
30
20
10
ppm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7.151
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7.135
7.111
7.108
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7.098
7.095
7.092
7.085
7.081
7.078
7.070
7.067
7.064
6.764
6.763
6.744
6.743
6.100
6.079
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4.282
4.253
4.249
4.176
4.171
4.142
4.138
3.062
3.059
2.531
2.521
2.499
2.488
2.467
2.452
2.434
1.590
O
H
Ph
Cl
S
Me
O
51h
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
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ppm
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1.01
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1.04
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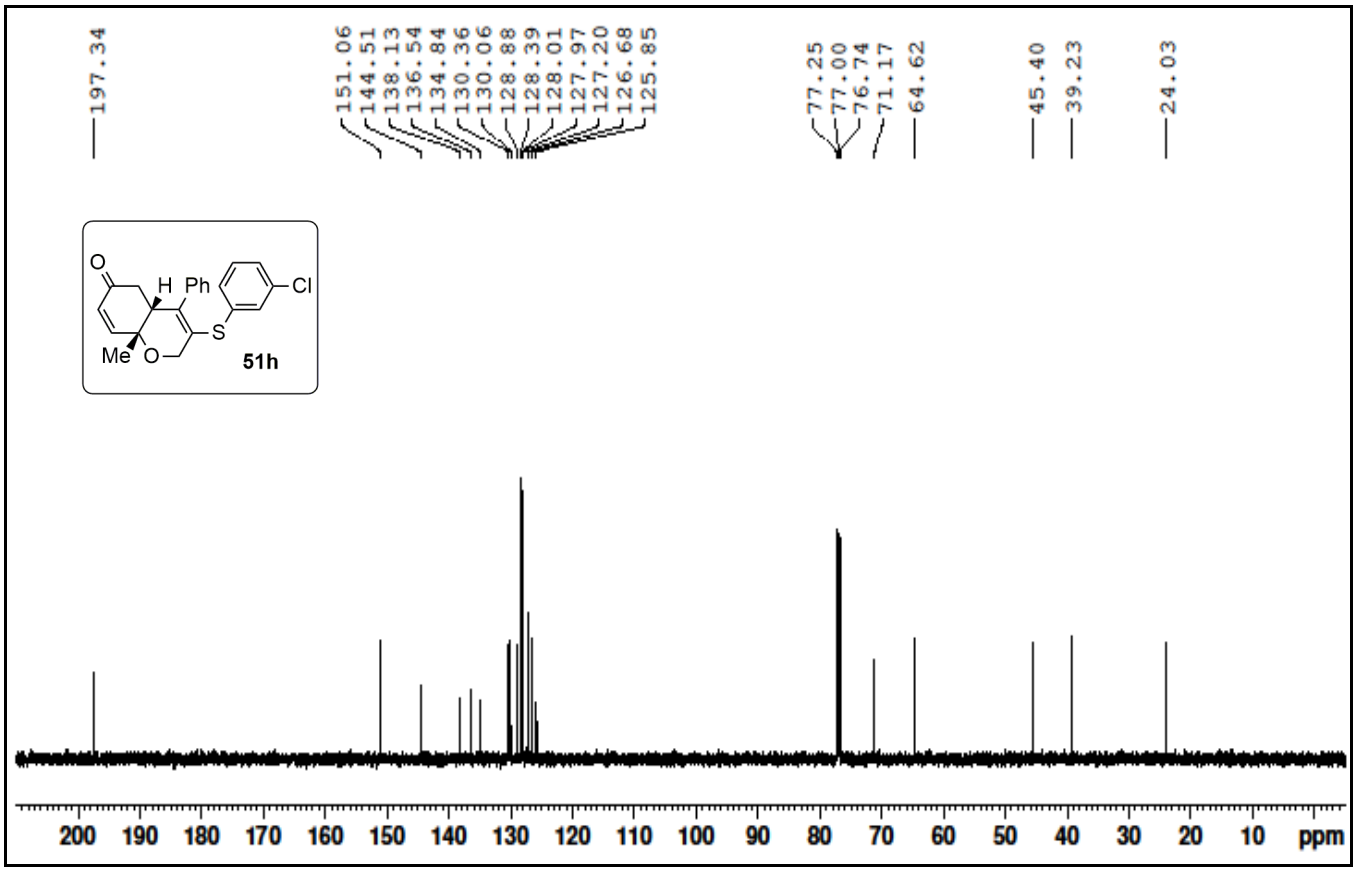
3.00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126.68
125.85
77.25
77.00
76.74
71.17
64.62
45.40
39.23
24.03
O
H
Ph
Cl
S
Me
O
51h
200
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150
140
130
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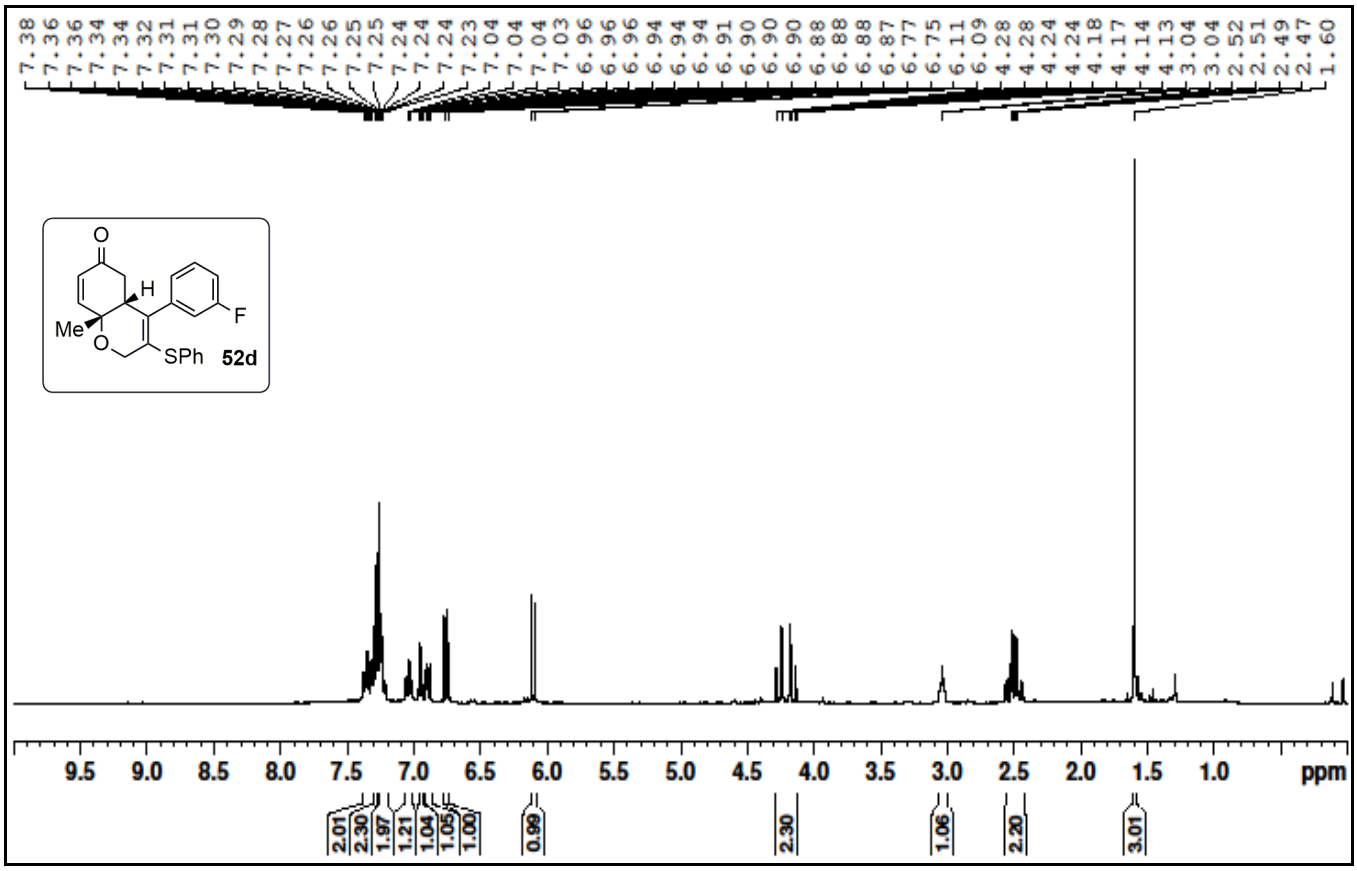
10
ppm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O
H
F
Me
O
SPh
52d
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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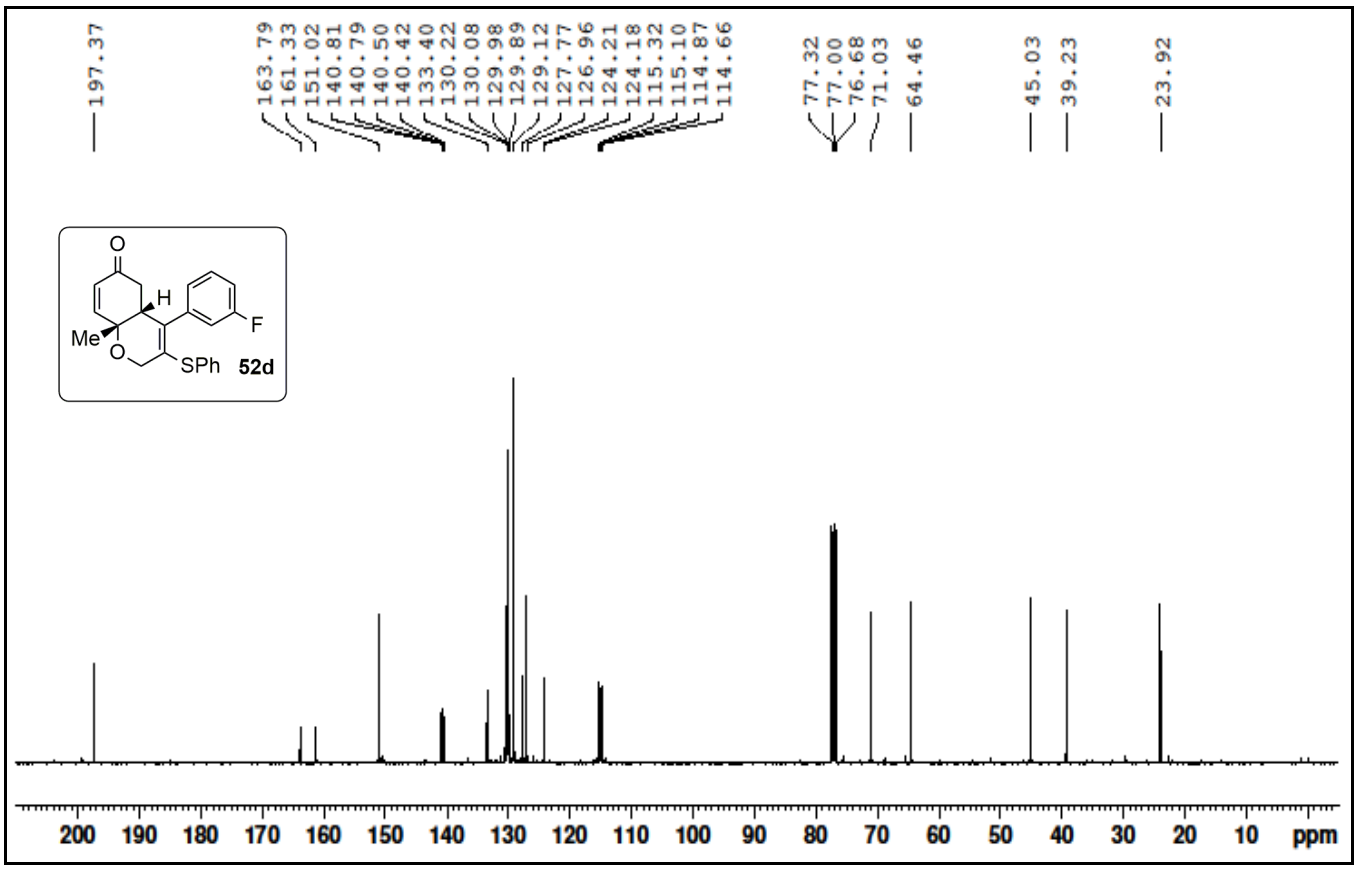
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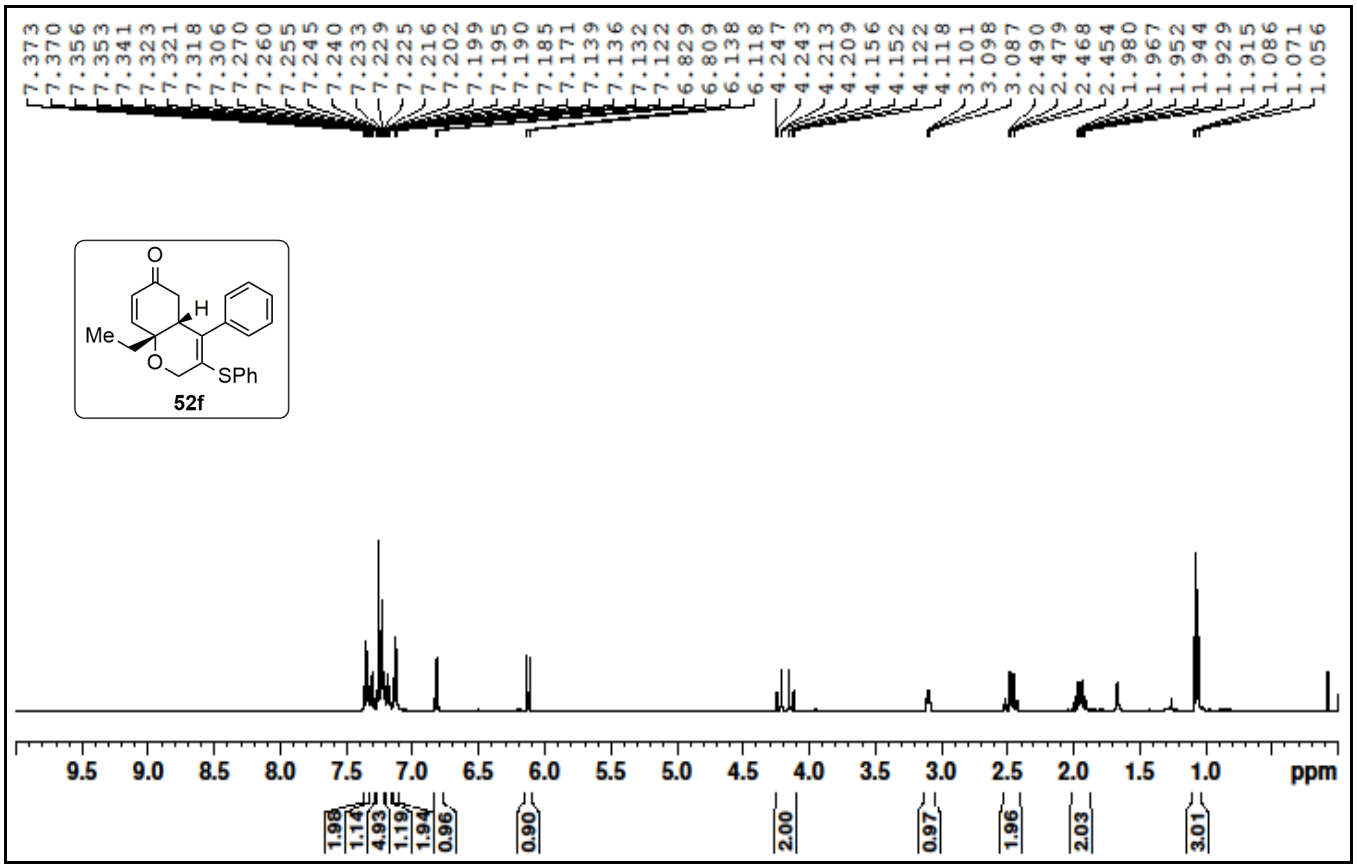
77.32 77.00 76.68 71.03 64.46
45.03 39.23 23.92
O
H
F
Me
O
SPh
52d
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.132
7.122
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6.809
6.138
6.118
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4.243
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4.209
4.156
4.152
4.122
4.118
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2.454
1.980
1.967
1.952
1.944
1.929
1.915
1.086
1.071
1.056
O
H
Me
O
SPh
52f
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.0
2.5
2.0
1.5
1.0
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2.00
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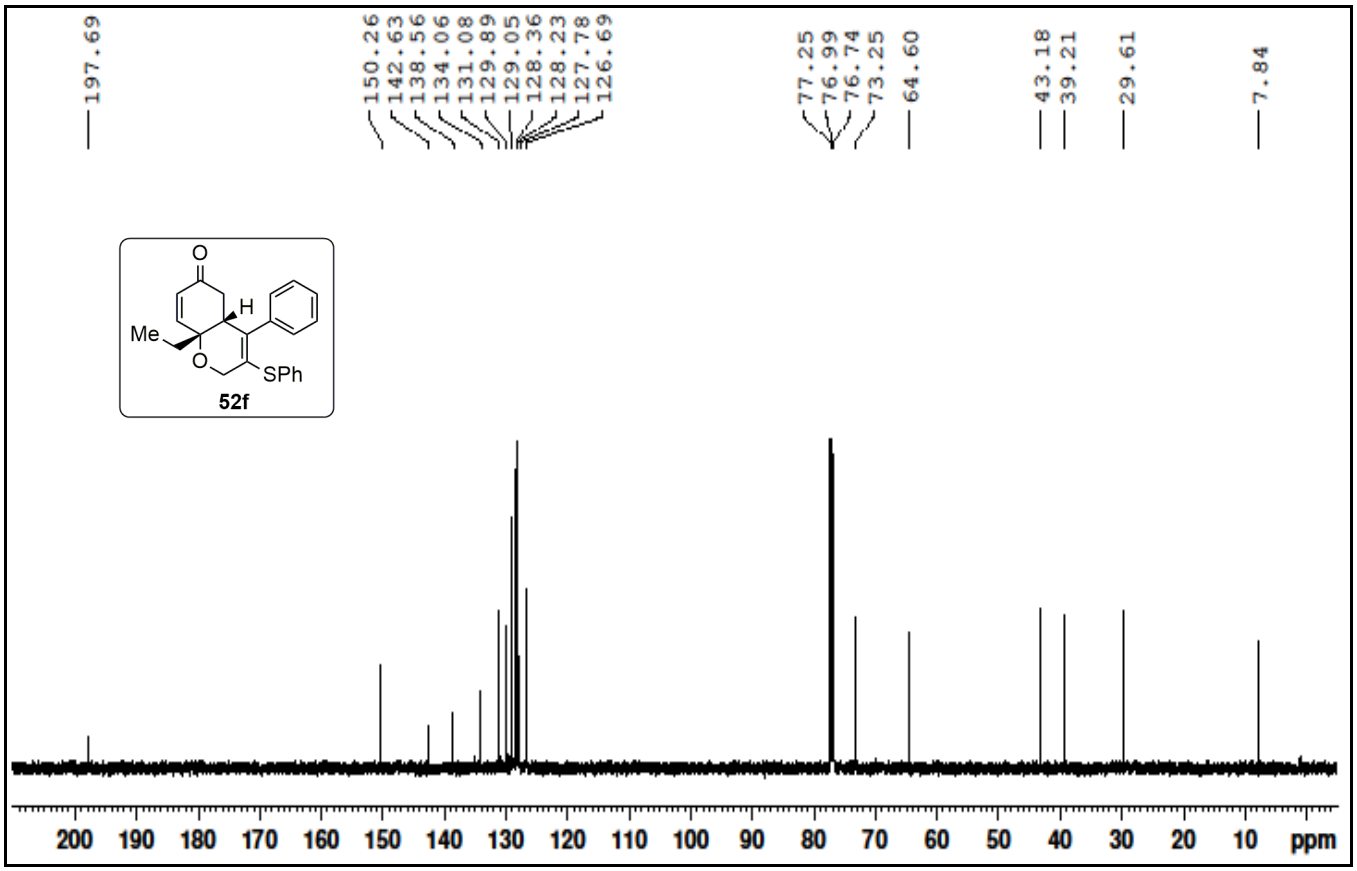
3.01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76.99
76.74
73.25
64.60
43.18
39.21
29.61
7.84
O
H
Me
O
SPh
52f
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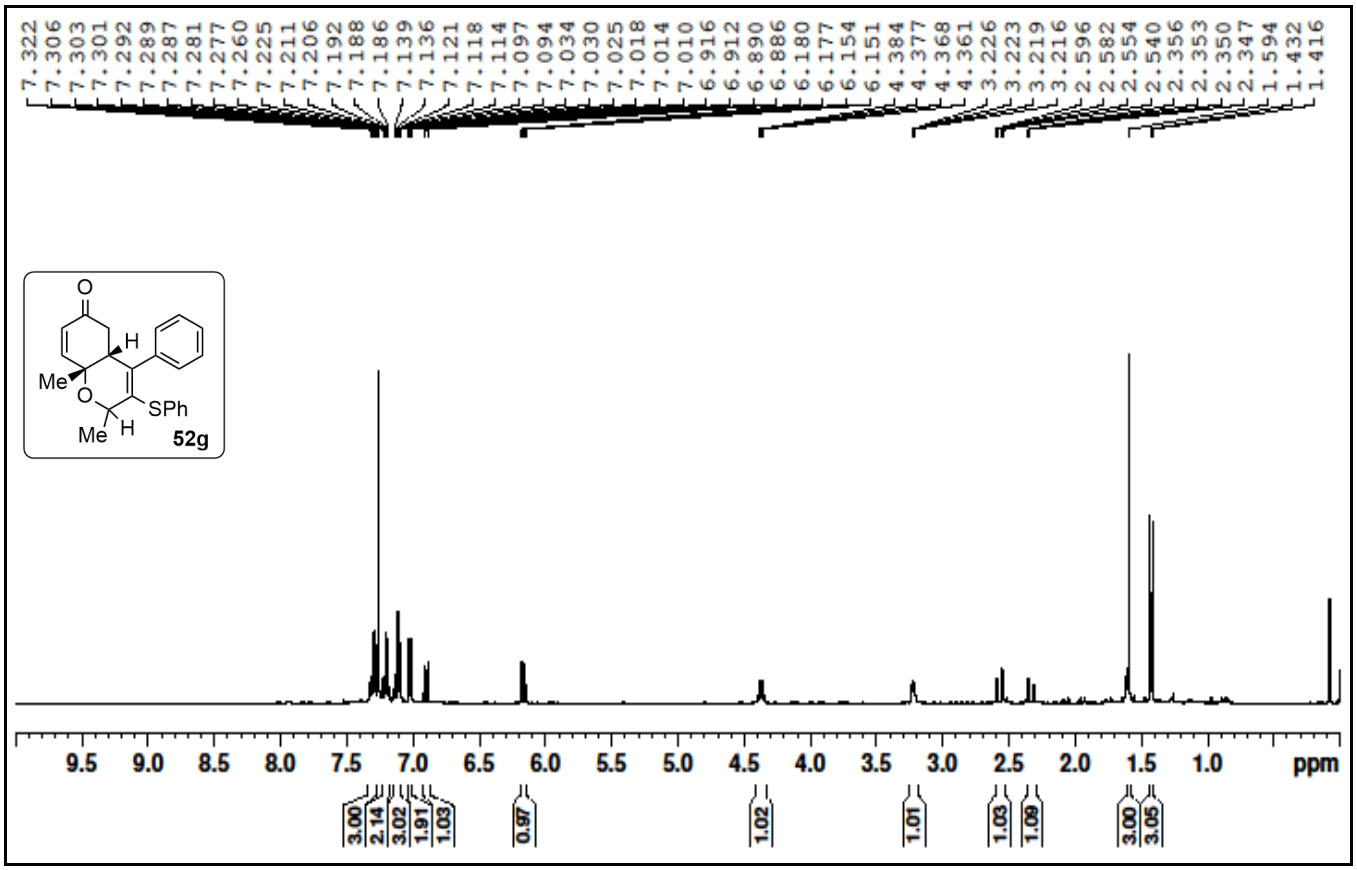
10
ppm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7.188
7.186
7.139
7.136
7.121
7.118
7.114
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7.094
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7.025
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7.014
7.010
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6.912
6.890
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6.180
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6.151
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3.223
3.219
3.216
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2.582
2.554
2.540
2.356
2.353
2.350
2.347
1.594
1.432
1.416
O
H
Me
O
SPh
Me
H
52g
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8.5
8.0
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7.0
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6.0
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3.5
3.0
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1.01
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1.09
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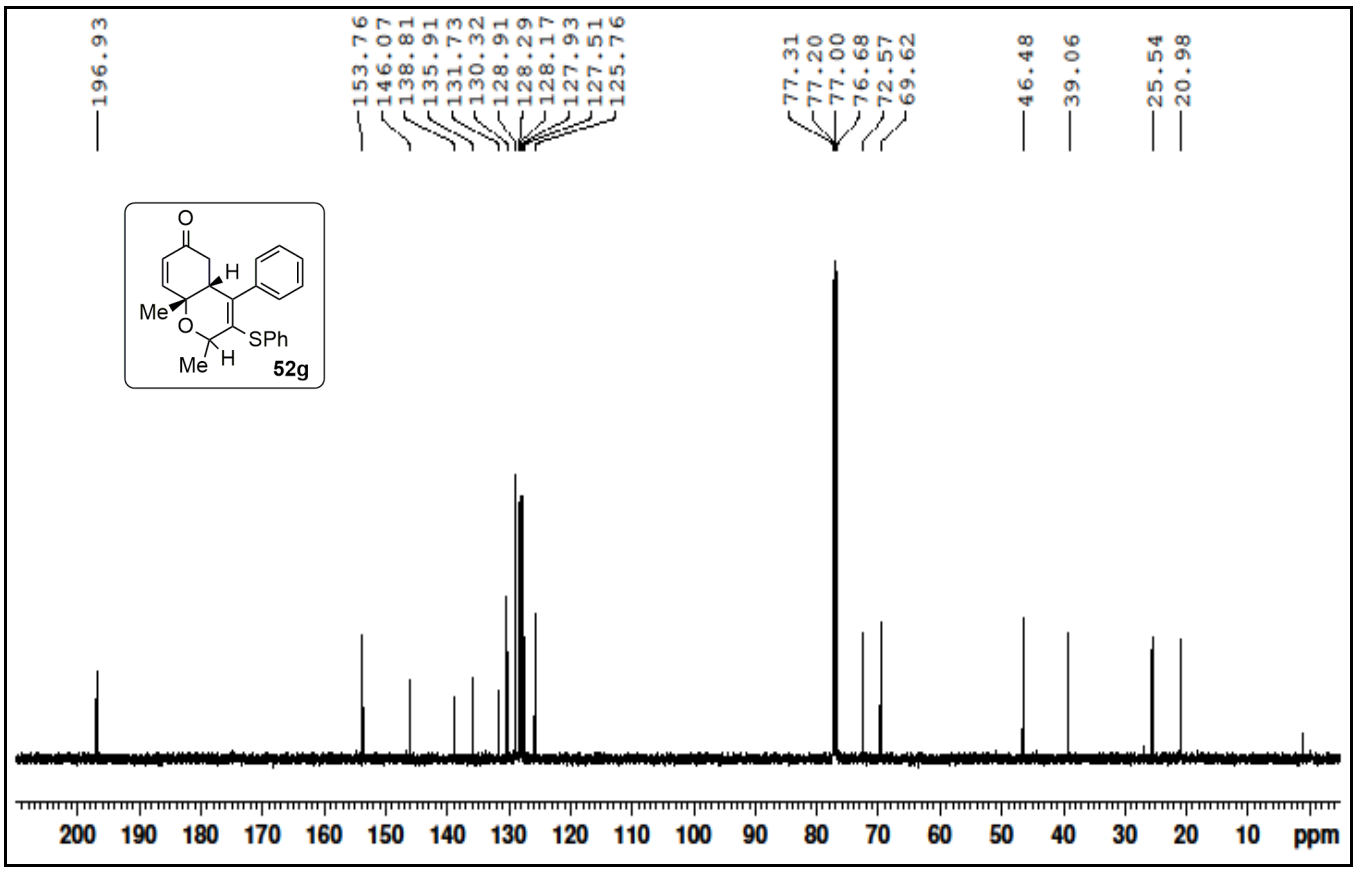
3.05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77.20
77.00
76.68
72.57
69.62
46.48
39.06
25.54
20.98
O
H
Me
O
SPh
Me
H
52g
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150
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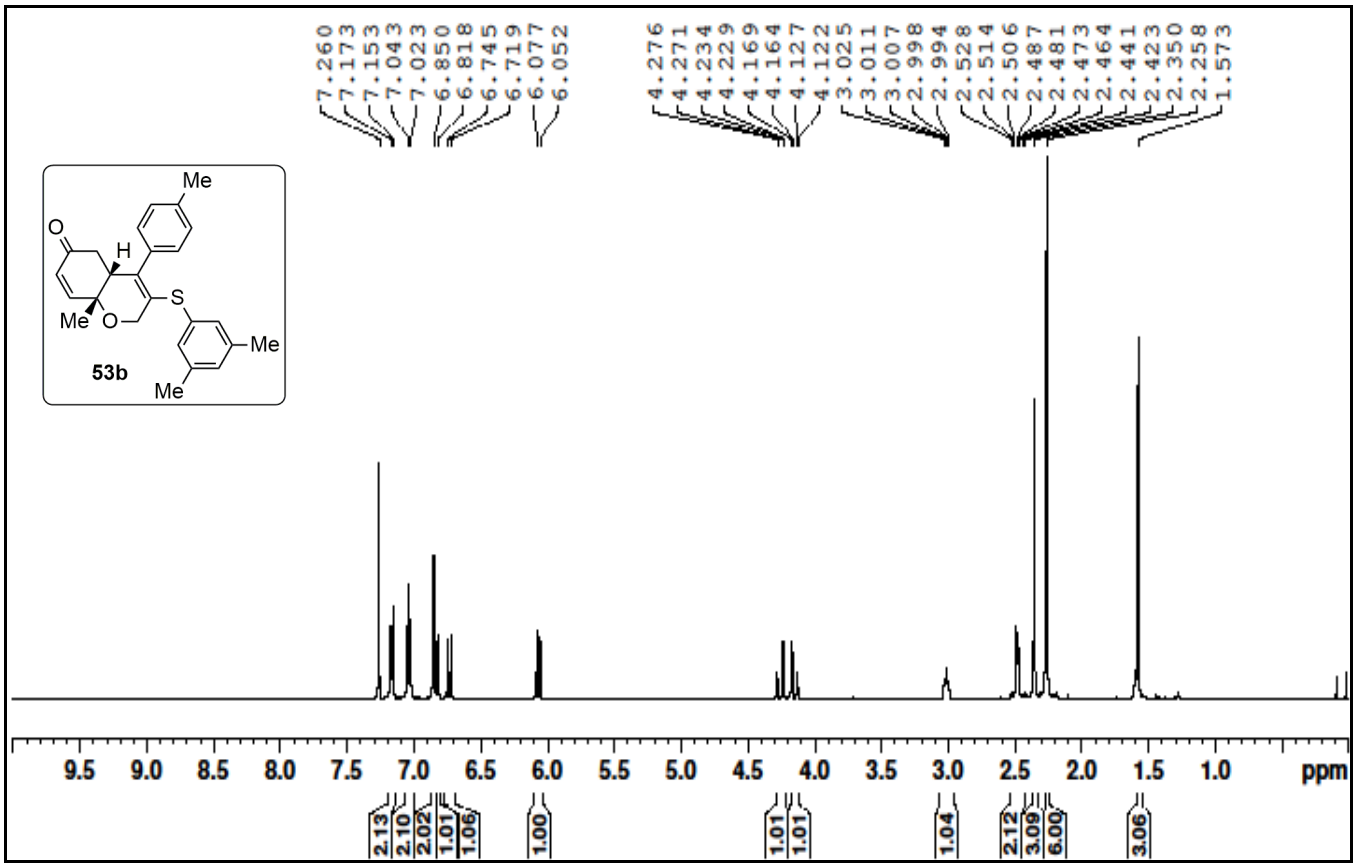
10
ppm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4.271
4.234
4.229
4.169
4.164
4.127
4.122
3.025
3.011
3.007
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2.994
2.528
2.514
2.506
2.487
2.481
2.473
2.464
2.441
2.423
2.350
2.258
1.573
Me
O
H
S
Me
O
Me
Me
53b
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.13
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1.06
1.00
1.01
1.01
1.04
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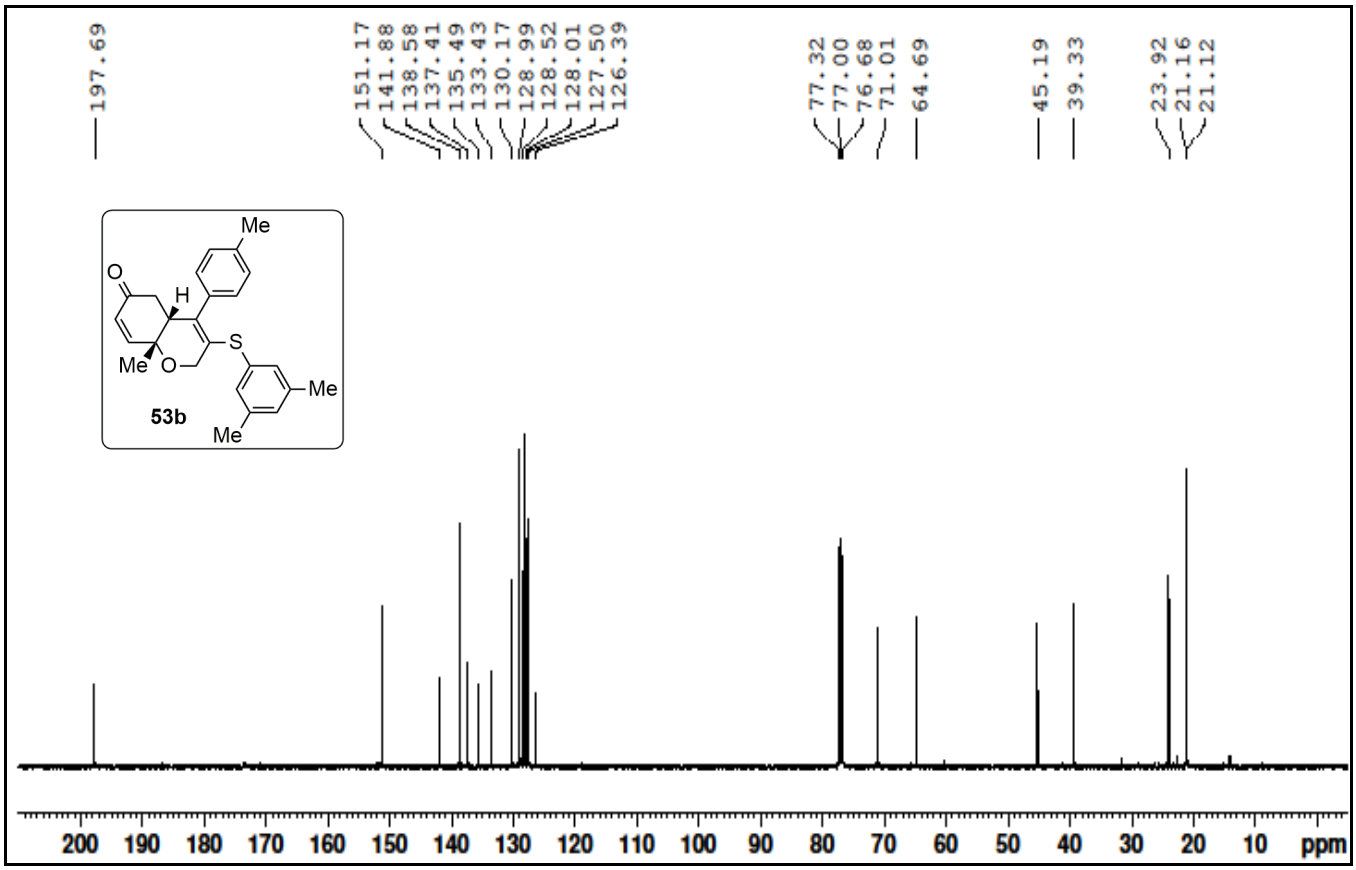
6.00
3.06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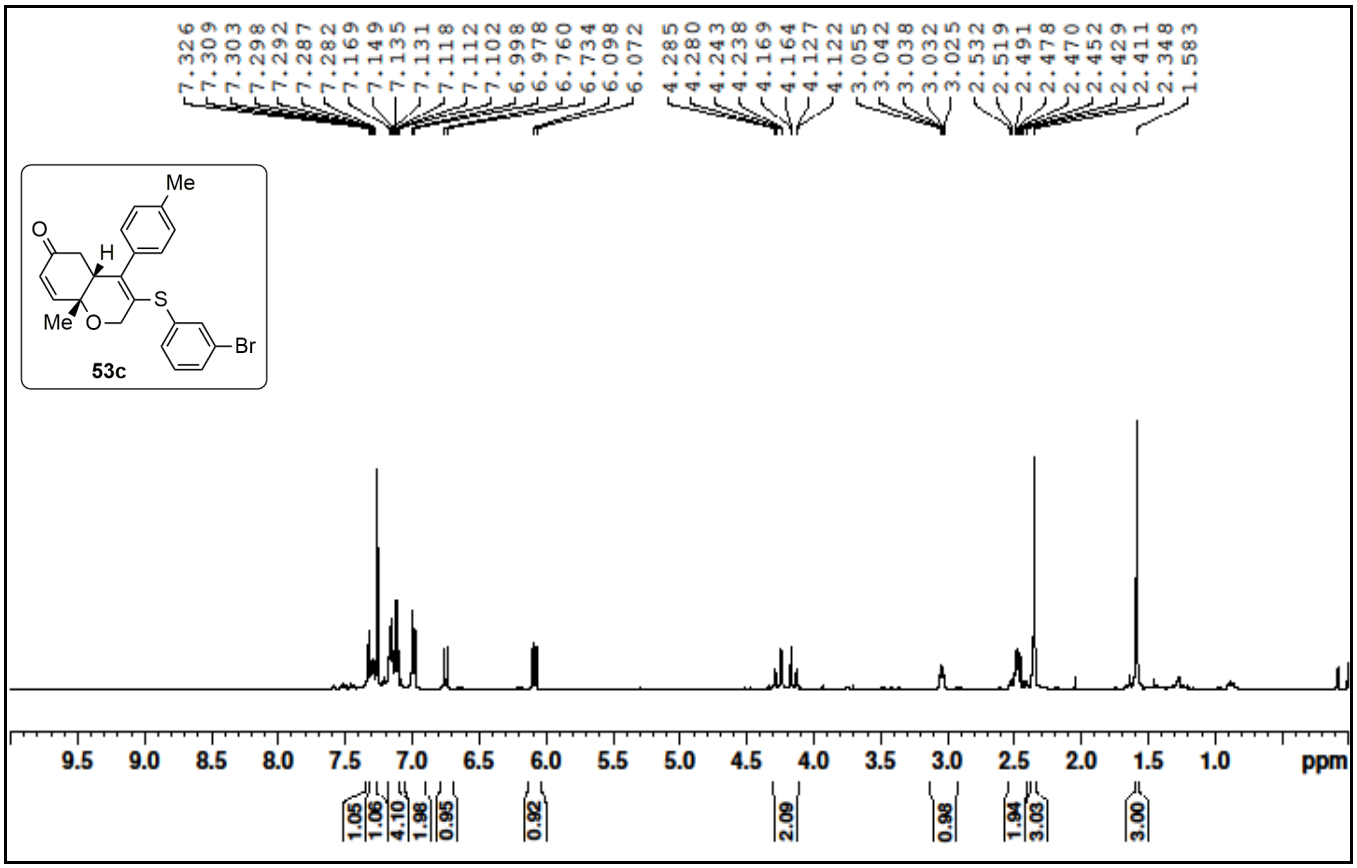
77.00
76.68
71.01
64.69
45.19
39.33
23.92
21.16
21.12
Me
O
H
S
Me
O
Me
Me
53b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.102
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6.760
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4.127
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3.038
3.032
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Me
O
H
S
Me
O
Br
53c
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8.5
8.0
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6.0
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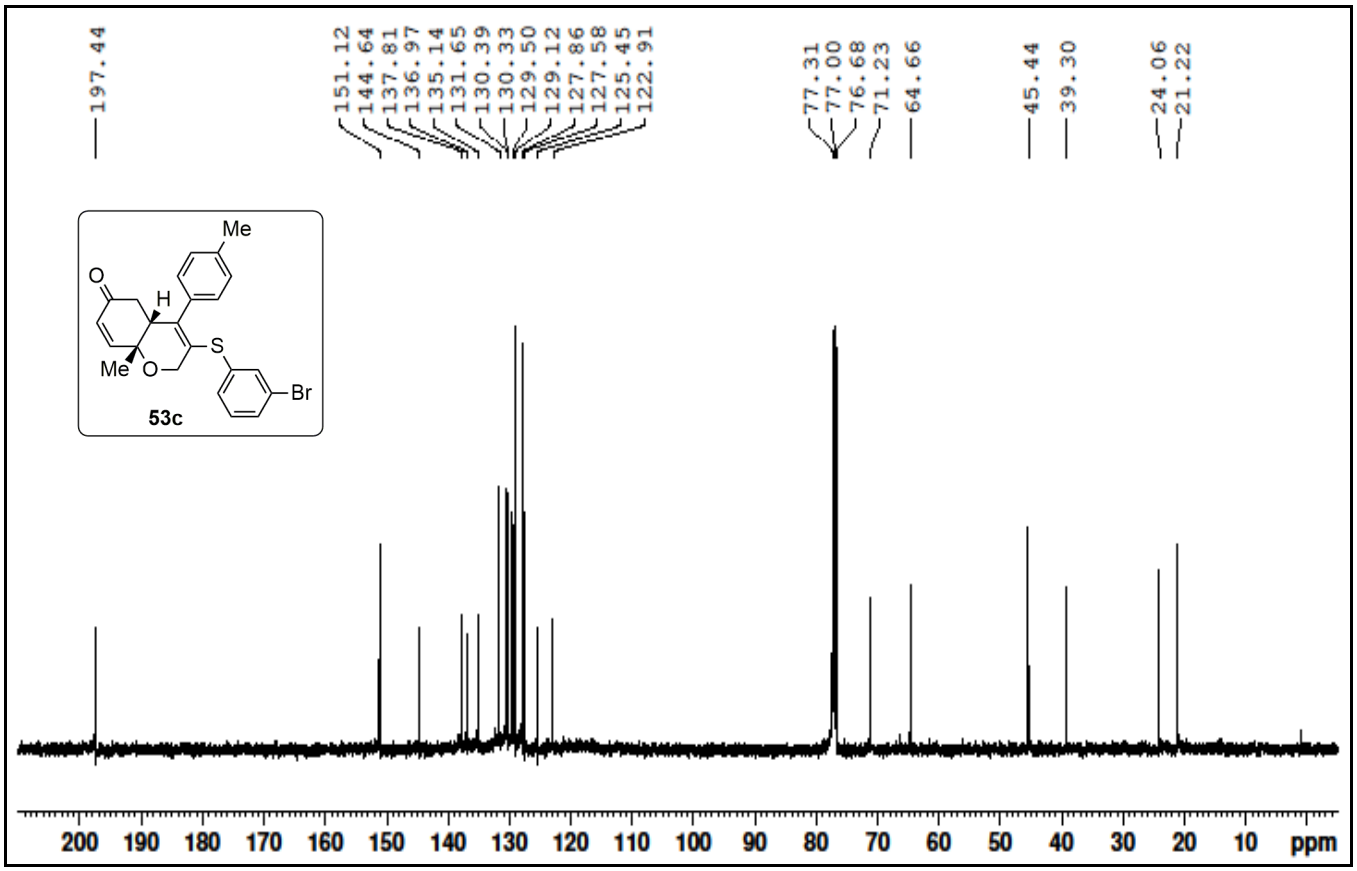
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77.31
77.00
76.68
71.23
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45.44
39.30
24.06
21.22
Me
O
H
S
Me
O
Br
53c
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70
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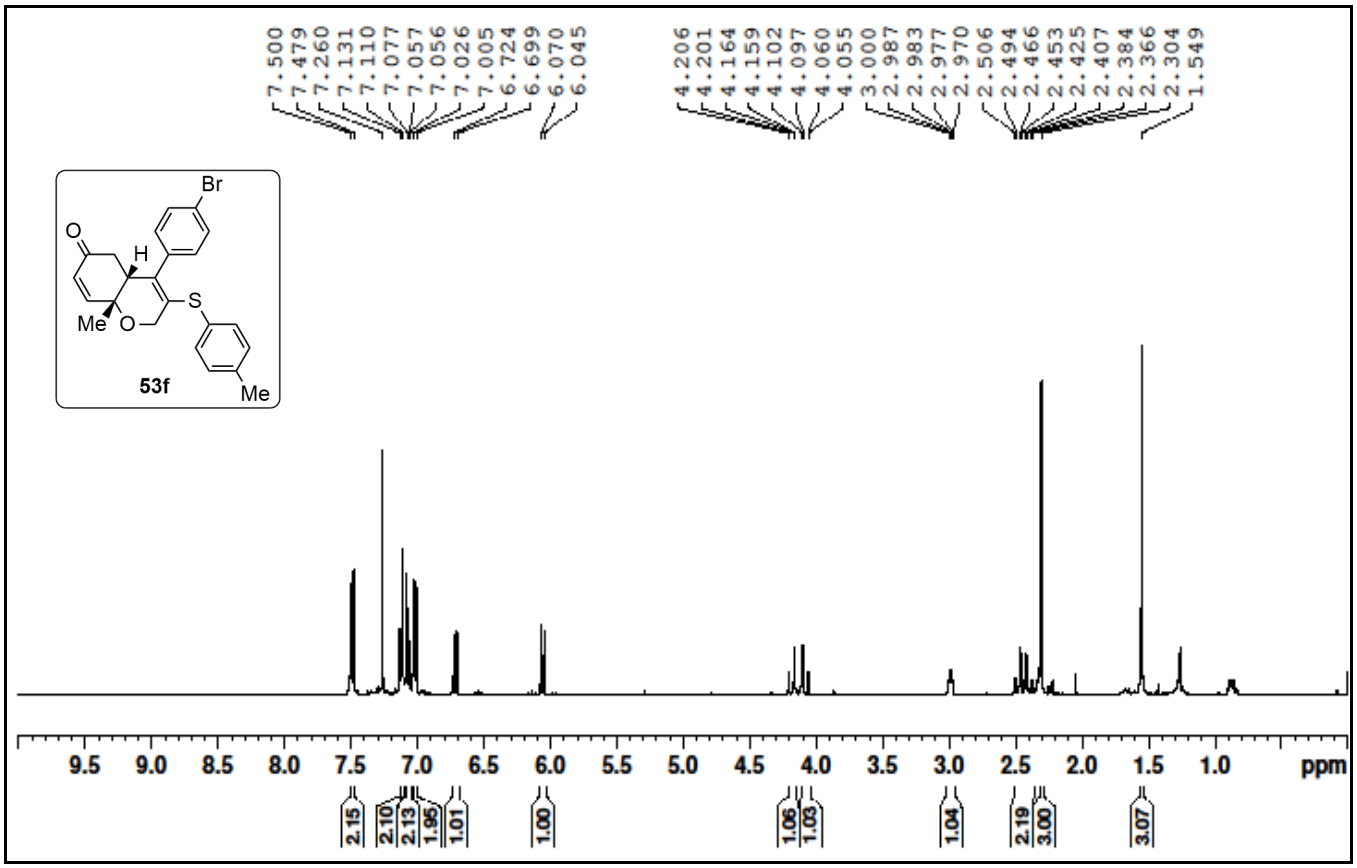
10
ppm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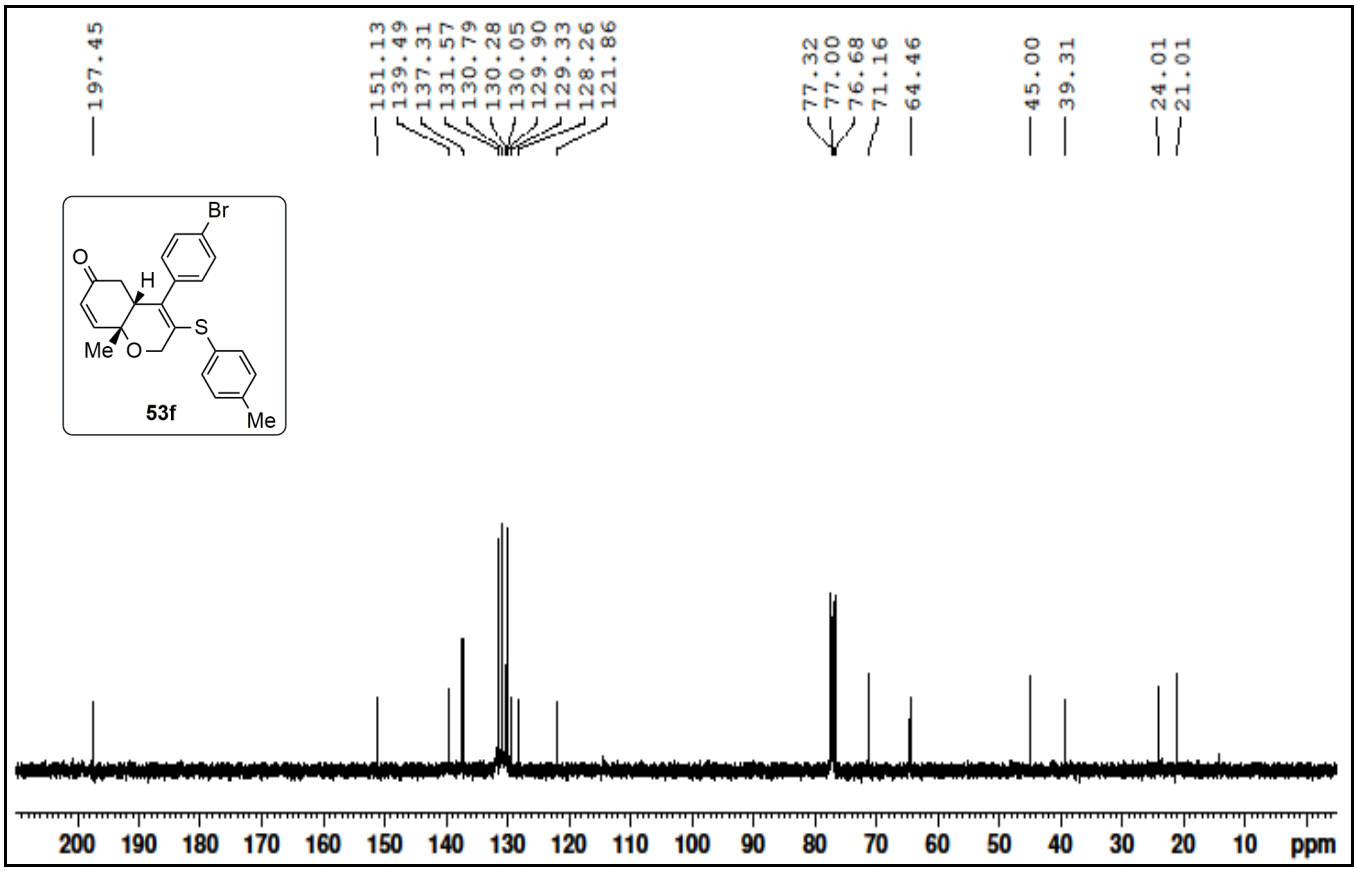
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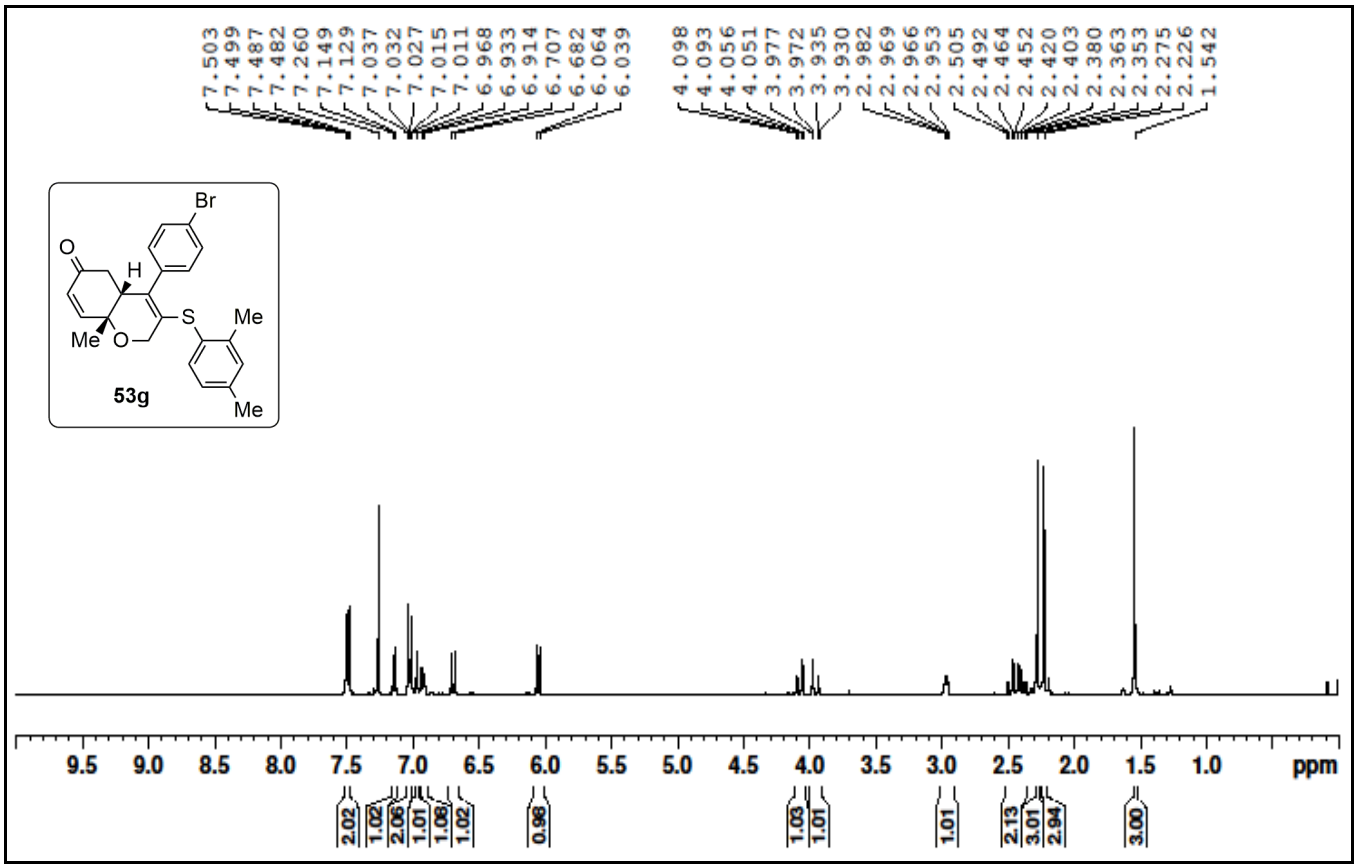
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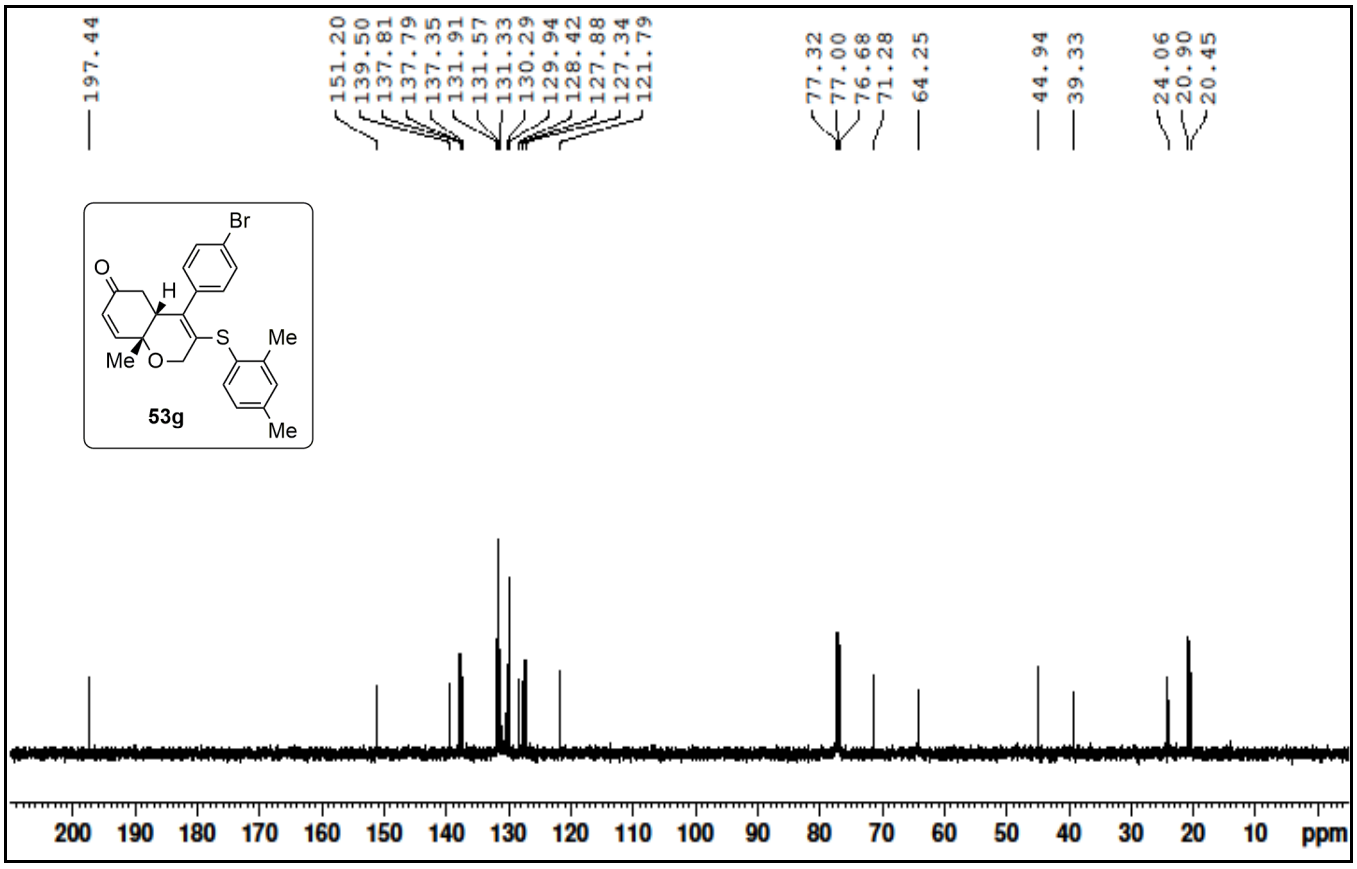
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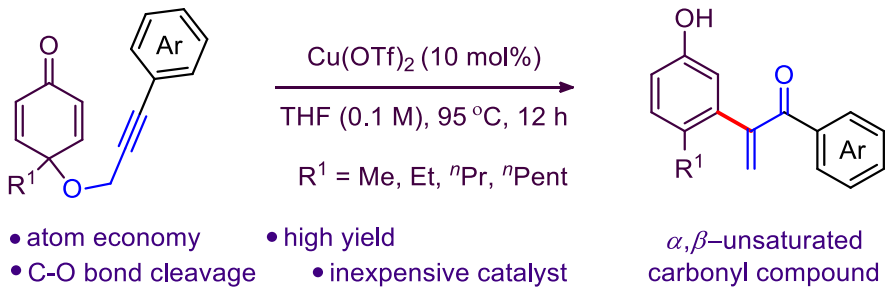
Section-B: Access to α-Aryl-α, β-Unsaturated Ketones via Lewis Acid Mediated Meyer-Schuster Rearrangement of Yne-Dienone

Abstract



Discussed herein a Lewis acid mediated Meyer-Schuster rearrangement of alkynyl cyclohexadienone for the construction of α-aryl-α, β-unsaturated ketones. The transformation involves the cleavage of C–O bond and a vinylic carbocation intermediate. The transformation is atom-efficient without producing any substantial waste.

Reference:

Rajendra K. Mallick, Tirumaleswararao Guntreddi, and Akhila K. Sahoo* *(Manuscript Under Preparation)*

4B.1. Introduction

The easily accessible propargyl alcohols are important bi-functional motifs largely used in the development of novel synthetic transformations and fabrication of complex molecular scaffolds.[1,2] The Meyer–Schuster (M-S) rearrangement converts propargyl alcohol to α,β-unsaturated carbonyl compounds and is one of the most valuable demonstration in the large domain of synthetic community. The transformation mainly involves a formal 1,3-hydroxyl shift and tautomerization sequence (**Figure 4B.1**).[3,4] Interestingly, the M-S rearrangement is truly an atom-efficient synthetic manifestation.

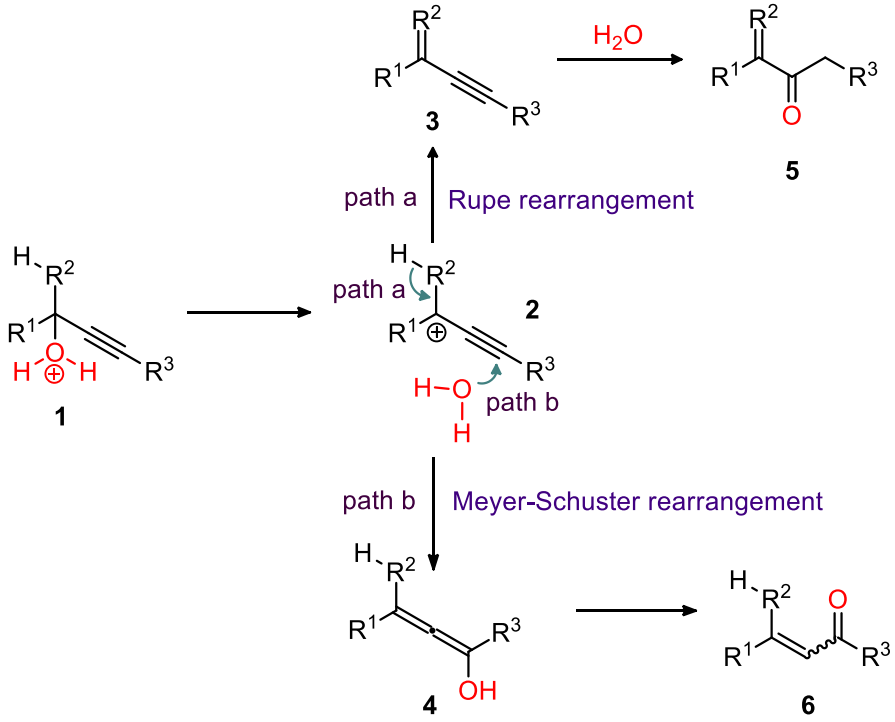


Figure 4B.1. Competing Rupe and Meyer–Schuster pathways

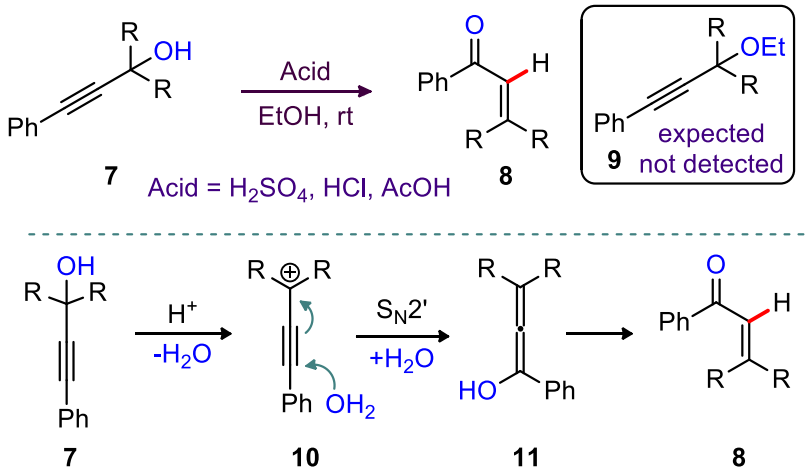
The propargyl alcohols generally amenable to Rupe and Meyer–Schuster rearrangements. The Rupe rearrangement involves an enyne **3** (obtained in-situ via *β*-hydrogen elimination from carbocation **Int-2**); next, hydrolysis of alkyne motif of **3** gives Rupe-arranged product **5** (**Figure 4B.1**).[5] Whereas M-S rearrangement involves the γ-hydroxy substitution of carbocation **Int-2** to generate allenol **4**; next, the tautomerization of allenol leads to M-S rearranged α,β-unsaturated carbonyl compound **6** (**Figure 4B.1**).[6]

4B.2. Precedents

Some selected reports of the Meyer–Schuster rearrangement for the synthesis of α,β-unsaturated carbonyl compounds from propargyl alcohol are herein enumerated (**Scheme 4B.1**–**4B.9**).

4B.2.1. The classical Meyer-Schuster (M-S) rearrangement

In 1922, Meyer and Schuster aimed to prepare the ethyl ether **9** from propargyl alcohol **7** in the presence of concentrated sulfuric acid. But surprisingly, the α,β-unsaturated carbonyl compound **8** has been formed (**Scheme 4B.1**).[6] Moreover, use of HCl and AcOH also delivered the same product **8**. The mechanism involves an E1 elimination of water molecule from **7** to give carbocation intermediate **10**. Next, S_N2' attack of H_2O at the γ-position of alkyne **10** to generate allenol **11**. Finally, **11** undergoes tautomerization in presence of proton source to deliver the enone **8**.



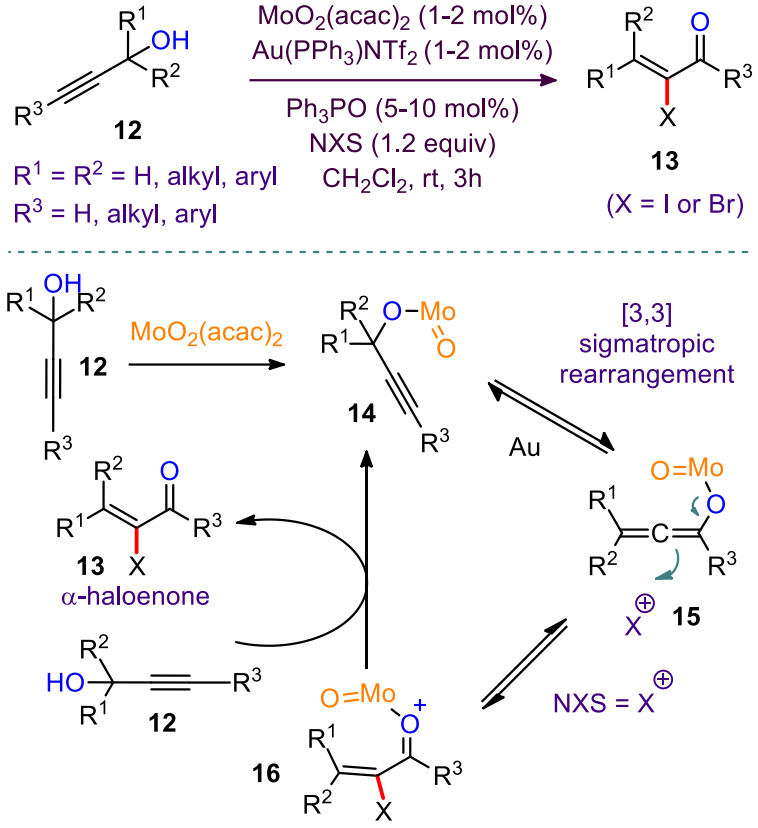
Scheme 4B.1. The classical Meyer-Schuster (M-S) rearrangement

This is the first example for the formation of unsaturated ketone **8** from propargyl alcohol **7**. This serendipitous discovery is named as Meyer-Schuster (M-S) rearrangement.

4B.2.2. Halo-intercepted Meyer-Schuster rearrangements

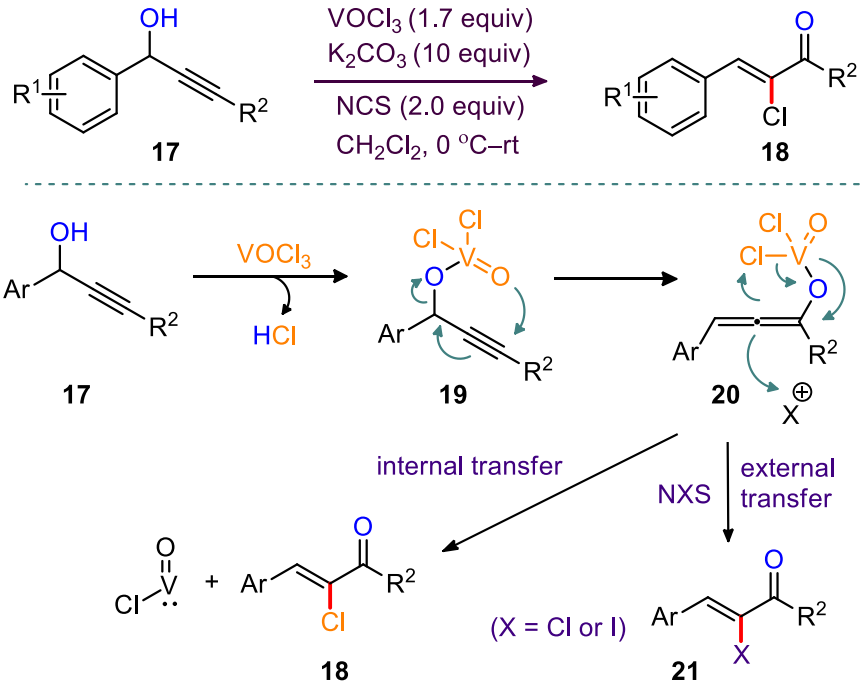
Zhang and co-workers reported a co-operative molybdenum (Mo) and gold (Au) catalyzed halo- intercepted Meyer-Schuster rearrangement of propargyl alcohol **12** to *α*-halo enone **13** (**Scheme 4B.2**).[7] The use of triphenylphosphine oxide (Ph_3PO) as an

additive suppresses the formation of undesired enal or enone. The reaction begins with the formation of molybdenum propargyl alkoxide **14** from the propargyl alcohol **12** in presence of Mo-catalyst. Next, a gold catalyzed [3,3] sigmatropic rearrangement of **Int-14** generates an allenyl-ether **15**. Finally, trapping of **Int-15** with halo electrophile gives oxonium intermediate **16** and subsequent demetallation provides the desired product **13**.



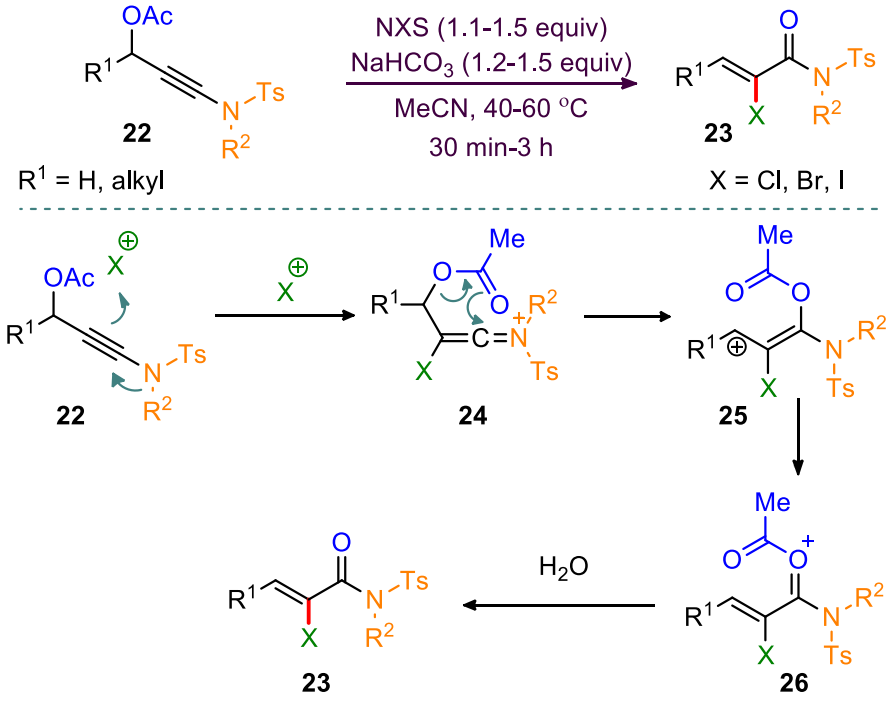
Scheme 4B.2. Mo and Au based cooperative catalysis for the M-S rearrangement

In 2017, Mohr group has shown a vanadium catalyzed similar kind of halo intercepted M-S rearrangement to access *α*-chloro enone **18** from corresponding propargyl alcohol **17** (**Scheme 4B.3**).[8] The $VOCl_3$ acts as a promotor as well as chloronium ion (Cl^+) source. Moreover, the addition of external NCS accelerates the reaction. The reaction in presence of external electrophile (NIS) provides a mixture of products (**21**). The transformation involves the formation of **19** from **17** in presence of $VOCl_3$. Next, 1,3-shift of vanadate ester of **Int-19** provides allenyl-ether **20**. Finally, tautomerization of **Int-20** via intramolecular Cl^+ trapping leads to the desired product **18**.



Scheme 4B.3. Chloro-intercepted Meyer-Schuster rearrangement by $VOCl_3$

Skrydstrup et al. reported the synthesis of (*Z*)-α-halo (Cl, Br and I) acrylamide **23** via a halonium ion promoted M-S rearrangement of 3-acetoxy ynamide **22** (**Scheme 4B.4**).[9] The

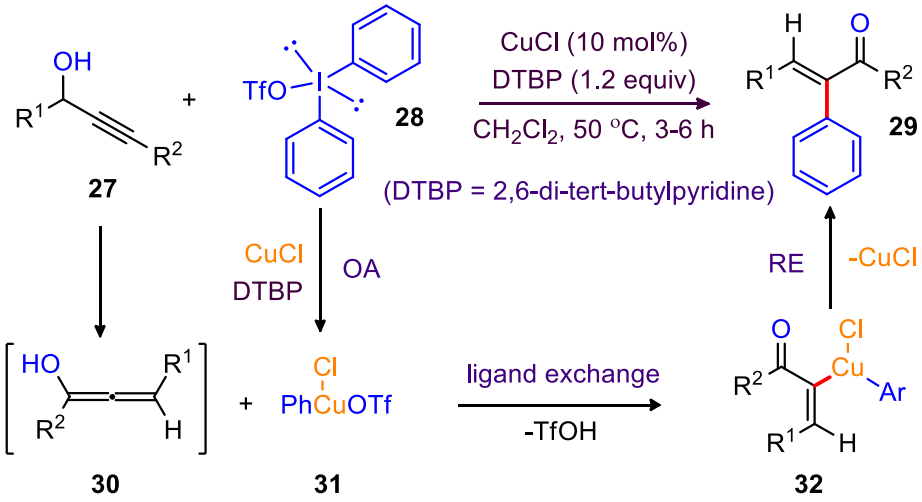


Scheme 4B.4. M-S rearrangement of 3-acetoxy-ynamides to (*Z*)–α-haloacrylimides

transformation initiates with the formation of keteniminium ion **24** from ynamide **22**. Next, 1,3-acetate shift of **Int-24** to give **Int-25**. Finally, double bond isomerization of **Int-25** leads to **26**, which subsequently undergoes hydrolysis to give the desired product **23**.

4B.2.3. Aryl-intercepted Meyer-Schuster rearrangements

In 2013, Gaunt and co-workers demonstrated a copper catalyzed M-S rearrangement of propargyl alcohol **27** to α-aryl enabled enone **29** in presence of hypervalent iodine reagent **28** (**Scheme 4B.5**).[10] This method tolerates a wide range of 1°, 2°, and 3° propargyl alcohol derivatives.

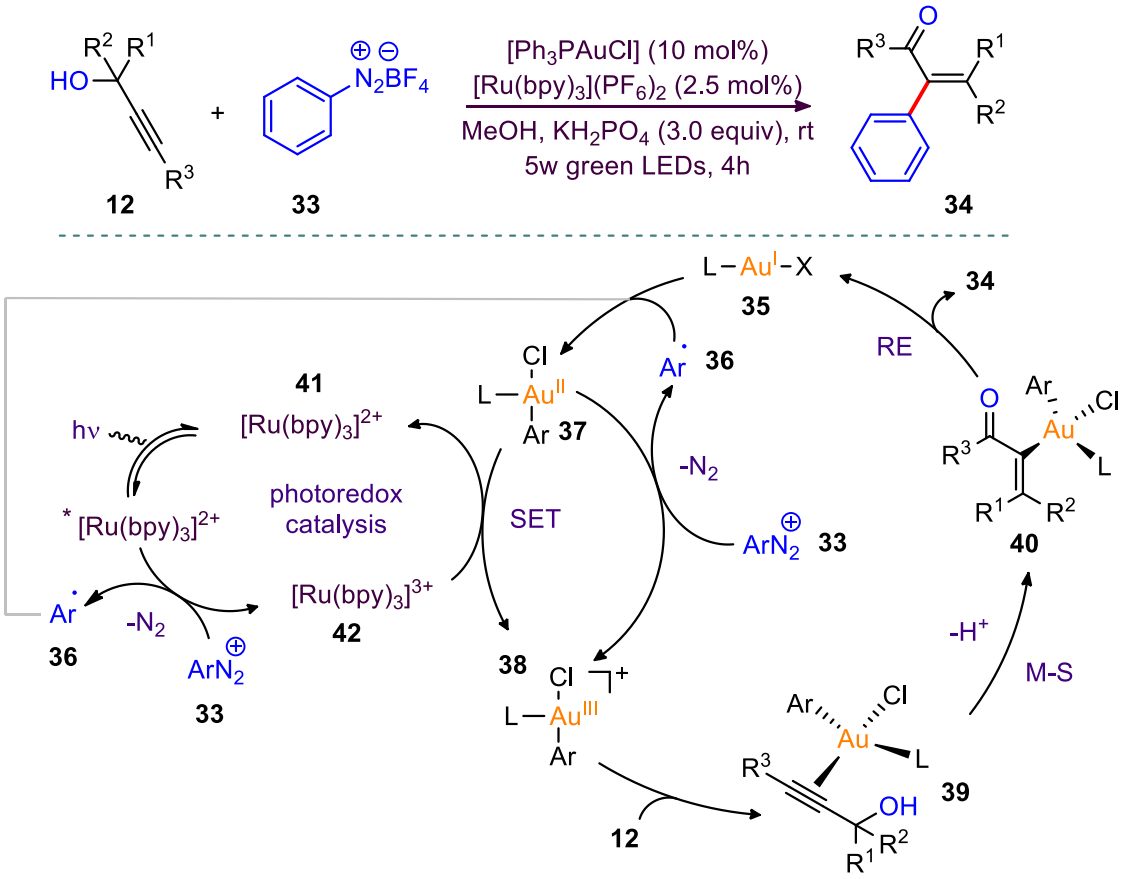


Scheme 4B.5. Cu(I)-promoted first arylative intercepted M-S rearrangement

The reaction involves the formation of allenol **30** from propargyl alcohol **27**. Simultaneously, oxidative addition of diphenyl iodonium triflate **28** to Cu(I)-salt generates Cu(III)-complex **31**. Next, tautomerization of **30** followed by ligand exchange with **31** gives vinylic Cu(III)-complex **32**. Finally, reductive elimination of **Int-32** delivers the desired product **29**.

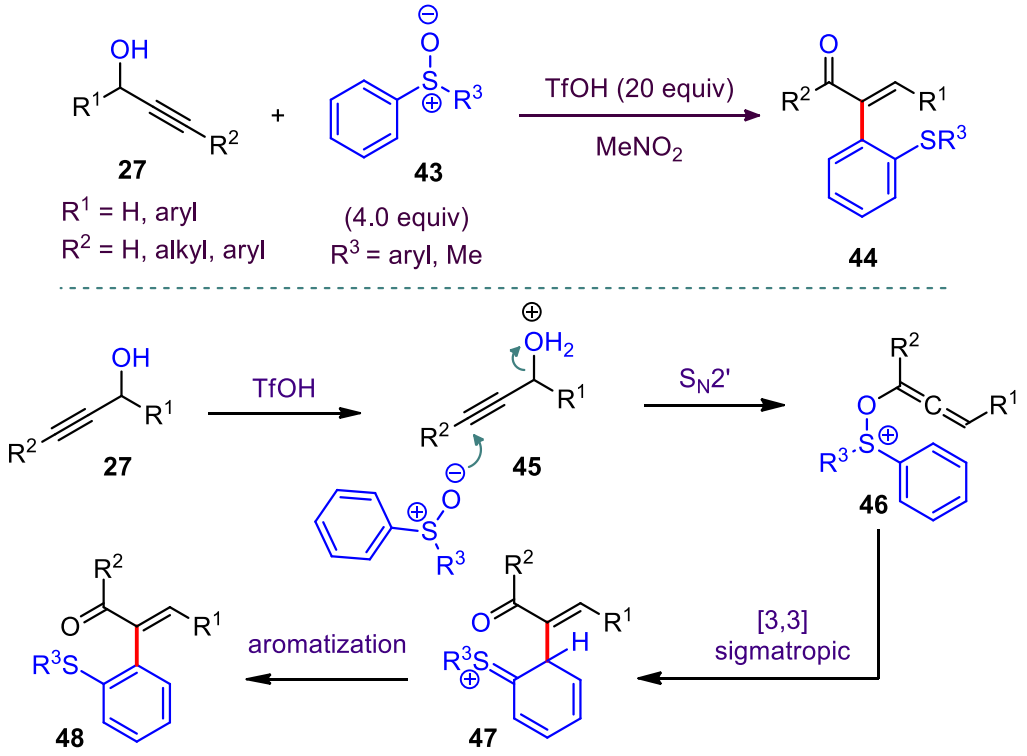
Later, Glorious group developed a gold-photoredox dual catalyzed visible light mediated arylative M-S rearrangement of propargyl alcohol **12** with aryl diazonium salt **33** to furnish α-aryl enone **34** (**Scheme 4B.6**).[11] Mechanistically, the oxidative radical addition of gold(I)-catalyst (**35**) with aryl radical **36** (generated in-situ from **33**) to form gold(II)-aryl species **37**. Next, single electron oxidation of **Int-37** in presence of photocatalyst **42**

provides Au(III)-intermediate **38**. Subsequently, Au(III) assisted alkyne activation of **12** produces **Int-39**; next, the C–O cleavage and carbo-auration leads to **40**. Finally, reductive elimination of **40** delivers **34**.



Scheme 4B.6. Gold-photoredox dual-catalysis for an arylative M-S rearrangement

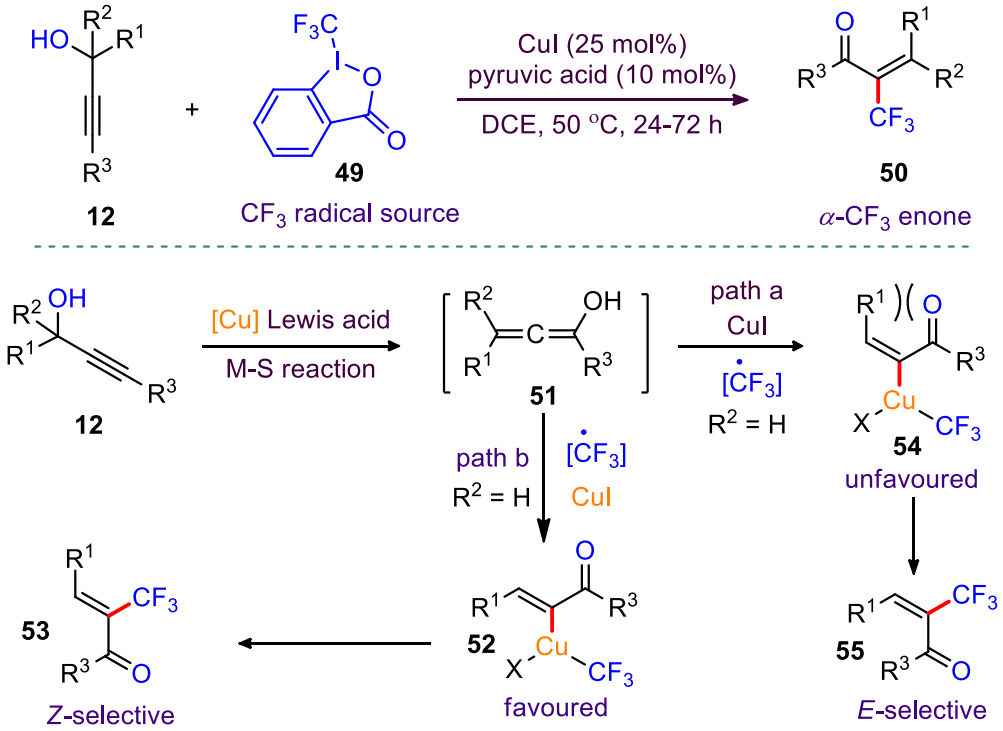
Maulide and co-workers have shown a triflic acid (TfOH) promoted nucleophile-intercepted M-S rearrangement of propargyl alcohol **27** and sulfoxide **43** to access α-thioaryl enabled enone **44** (**Scheme 4B.7**).[12] The reaction begins with the protonation of **27** by TfOH to give **Int-45**. Next, S_N2' attack of sulfoxide **43** to the protonated propargyl alcohol **45** provides **46**. Next, a [3,3]-sigmatropic rearrangement of **46** leads to **47**. Finally, aromatization of **Int-47** delivers the desired product **48**.



Scheme 4B.7. Arylsulfoxide intercepted M-S rearrangement for α-thioarylenones

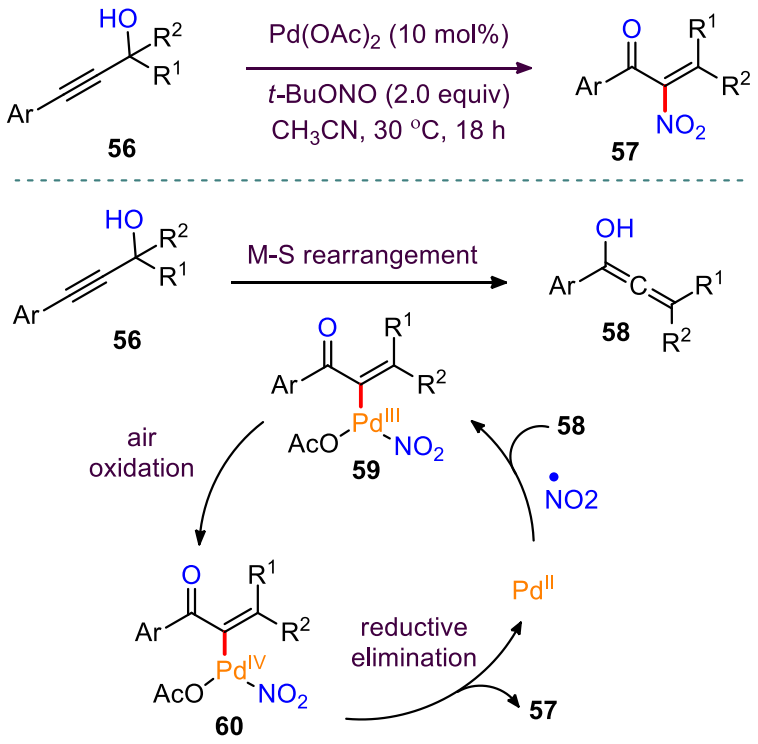
4B.2.4. Trifluoromethyl/nitro-intercepted Meyer-Schuster rearrangements

In 2014, Liu et al. reported a copper catalyzed trifluoromethyl-intercepted M-S rearrangement of **12** to provide α-CF_3 enabled unsaturated enone **50** in presence of Togni's reagent **49** (**Scheme 4B.8**).[13] Control experiments suggest the involvement of trifluoromethyl radical. Moreover, this method is applicable for both 2° and 3° propargyl alcohols. The transformation initiates a copper catalyzed allenol formation **51** from **12**. Next, Cu-mediated tautomerization of allenol **51** followed by oxidative CF_3 radical addition to generate high valent copper complex **52** (path-b). Finally, the reductive elimination of **52** affords the major product **53**. By contrast, the alternate path-a is less viable due to steric hindrance intercepted in **Int-55**. This selectivity is applicable only in case of 2° propargyl alcohols.



Scheme 4B.8. Trifluoromethyl-intercepted M-S rearrangement

Song and co-workers demonstrated a palladium catalyzed nitro-intercepted Meyer-Schuster (M-S) rearrangement of propargyl alcohol **56** to deliver the α-nitro substituted enone **57** (**Scheme 4B.9**).[14] Control experiment confirms that *t*-BuONO is the NO_2 source. The reaction involves a classical M-S rearrangement to generate allenol **58**. Next, palladium mediated tautomerization of **58** followed by oxidative nitro radical addition to generate Pd(III)-intermediate (**59**). Air oxidation of **59** leads to Pd(IV)-complex (**60**). Finally, reductive elimination of Pd(IV)-complex (**60**) furnishes the desired α-nitro enone product (**57**).



Scheme 4B.9. Pd(II)-catalyzed nitro-intercepted M-S rearrangement

4B.3. Motivation and Scheme Design

Inspired by the electrophile/nucleophile intercepted Meyer-Schuster rearrangement for the synthesis of α-functionalized α,β-unsaturated ketones[3,4,6-14] and our ongoing work on substituted-alkyne analogues, we aimed a Lewis acid mediated Meyer-Schuster rearrangement of easily accessible yne-dienone **61** to α-arylenone **62** (**Figure 4B.2**). The extended conjugations of α-arylenones is synthetically important and valuable building block for the synthesis of organic materials, an essential requirement for electrical conductance and color properties. In this context, a Lewis acid mediated M-S rearrangement of **61** is envisioned (path a & b; **Figure 4B.2**). In path a, the propargyl ether **61** undergoes 1,3-alkoxy shift in presences of Lewis acid to form allenyl ether **63**. Next, intramolecular Michael attack of the tethered allene in **63** generates the cyclic oxonium intermediate **64**. Finally, aromatization of **64** via C–O bond cleavage probably delivers the desired product **62** (**Figure 4B.2**). Whereas in path b, the Lewis acid initially activates the carbonyl moiety of propargyl ether **61**; next, the Michael attack of pendant alkyne

generates the vinylic carbocation intermediate **65**. Next, aromatization followed by C–O bond cleavage of **Int-65** leads to oxy-cyclobutene intermediate **66**. Finally, 4π-electrocyclic ring opening of **Int-66** provides α,β-unsaturated carbonyl compound **62** (**Figure 4B.2**). To the best of our knowledge, the use of yne-dienone **61** for aryl-intercepted M-S rearrangement for the synthesis of α-aryl α,β-unsaturated ketone is so far unknown.

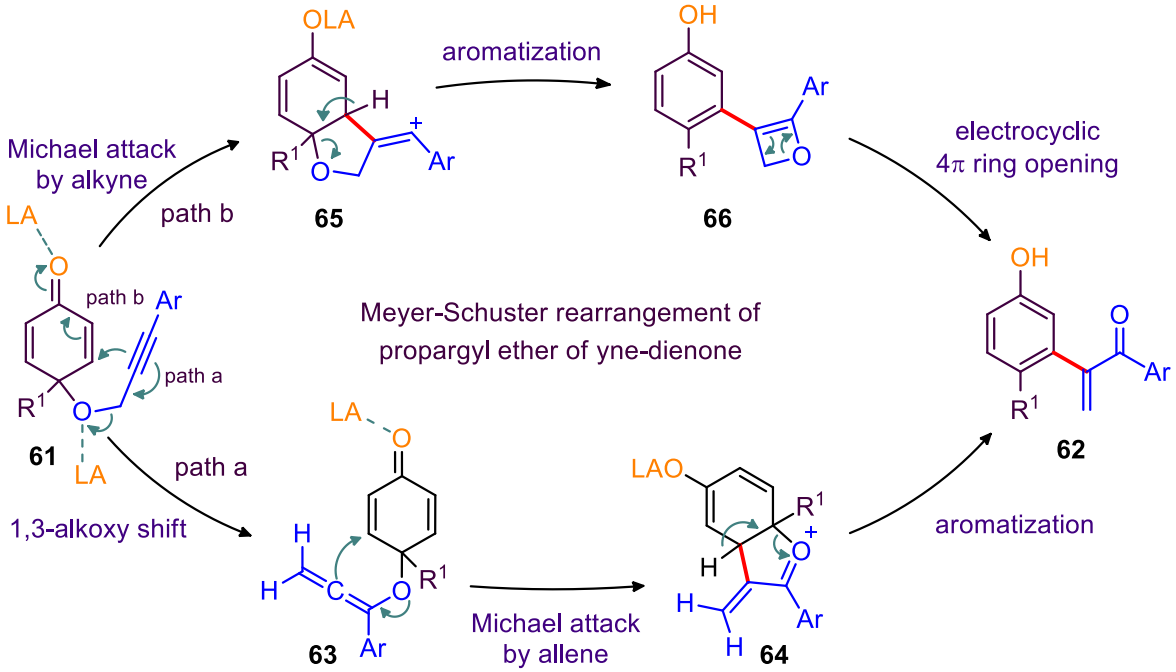


Figure 4B.2. Scheme design and the working hypothesis

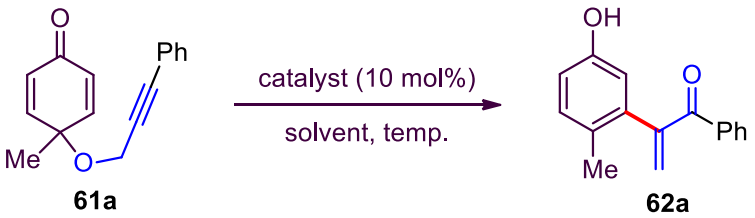
4B.4. Result and Discussion

4B.4.1. Reaction optimization

To begin with, a reaction of 4-methyl-4-((3-phenylprop-2-yn-1-yl)oxy)cyclohexa-2,5-dienone (**61a**) was envisioned in the presence of Lewis acid (**Table 4B.1**). To our delight, the reaction in the presence of $Sc(OTf)_3$ (10 mol%) in tetrahydrofuran (THF) at 85 °C produced the desired α,β-unsaturated enone (**62a**) in 63% yield (entry 1). Interestingly, the use of $Yb(OTf)_3$ was found superior giving the desired product **62a** in 73% yield (entries 2). Whereas other Lewis acids such as, $Fe(OTf)_3$ and $In(OTf)_3$ provided **62a** in 54% and 66%, respectively (entry 3 & 4). Pleasingly an enhanced yield of **62a** (75%) was observed when the reaction conducted in

presences of $Cu(OTf)_2$ (10 mol%) (entry 5). As expected, the reaction in absence of catalyst couldn't deliver the desired product **62a** (entry 6). Next, we screened the reaction in different solvents. The use of $ClCH_2CH_2Cl$, 1,4-dioxane, toluene, and $CHCl_3$ was not beneficial (entries 7–10). Disappointingly, **62a** (30%) was obtained when the reaction was stopped in 5 h (entry 11). The reaction in low temperature couldn't provide **62a** (entry 12 & 13). Surprisingly, the reaction at 95 °C provided

Table 4B.1. Optimization of reaction conditions[a,b]



61a **62a**

entry	catalyst	solvent	temp. (°C)	time (h)	yield
1	$Sc(OTf)_3$	THF	85	12	63
2	$Yb(OTf)_3$	THF	85	12	73
3	$Fe(OTf)_3$	THF	85	12	54
4	$In(OTf)_3$	THF	85	12	66
5	$Cu(OTf)_2$	THF	85	12	75
6[c]	-	THF	85	12	no reaction
7[c]	$Cu(OTf)_2$	$ClCH_2CH_2Cl$	85	12	trace
8	$Cu(OTf)_2$	1,4-Dioxane	85	12	42
9[c]	$Cu(OTf)_2$	Toluene	85	12	no reaction
10[c]	$Cu(OTf)_2$	$CHCl_3$	85	12	trace
11	$Cu(OTf)_2$	THF	85	5	30
12[c]	$Cu(OTf)_2$	THF	rt	12	no reaction
13[c]	$Cu(OTf)_2$	THF	60	12	trace
14	$Cu(OTf)_2$	THF	95	12	98

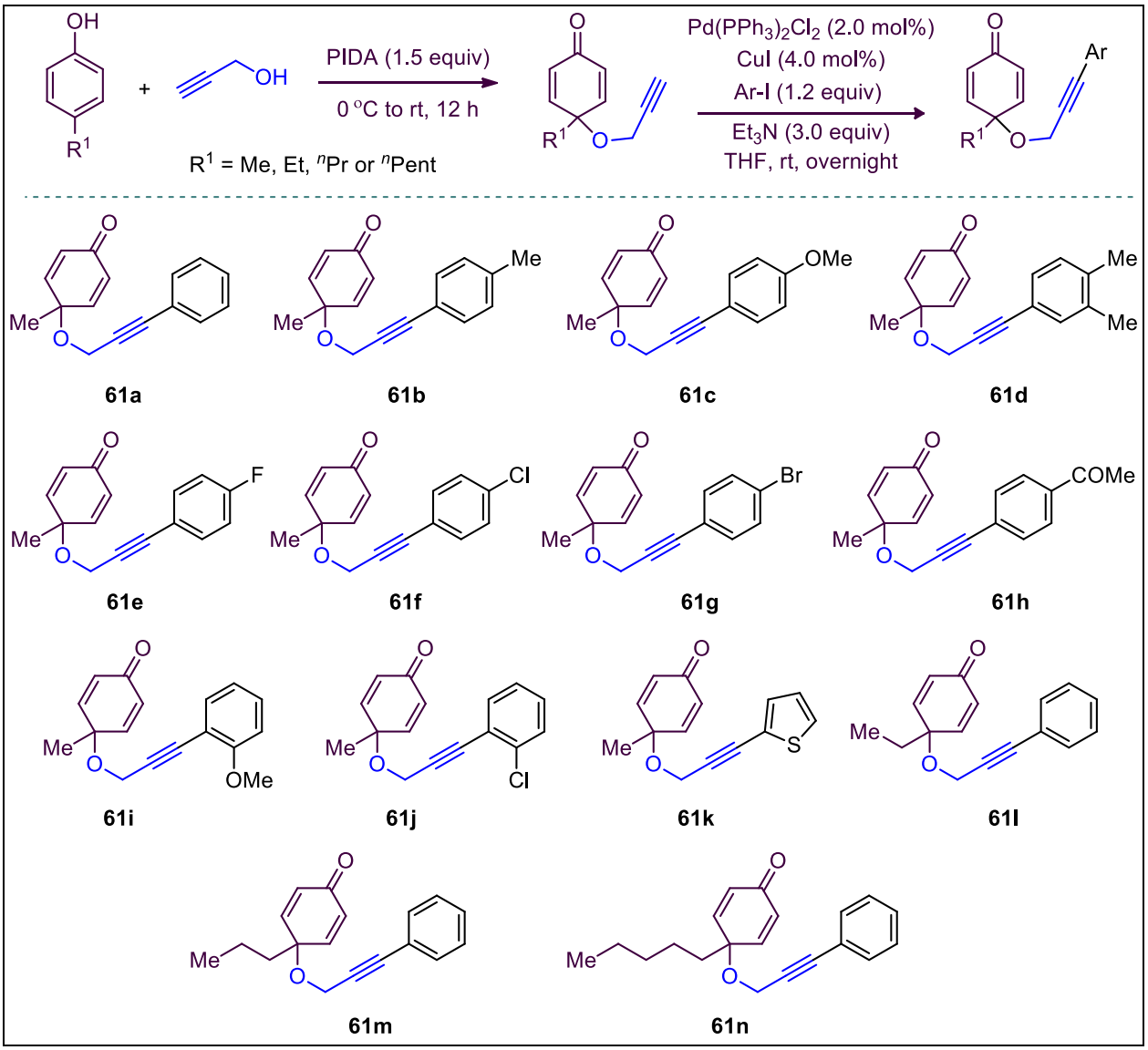
[a]Reactions were carried out using **61a** (0.06 mmol), Lewis acid (10 mol%) in solvent (0.1 M); [b]Crude NMR yield; [c]Observed by TLC.

excellent yield of **62a** (98%) (entry 14). Thus, combination of yne-dienone **61a** (1.0 equiv) and $Cu(OTf)_2$ (10 mol%) in THF at 95 °C for 12 h was considered optimum for the synthesis of **62a**.

4B.4.2. Synthesis of starting materials

Following the known hypervalent iodine mediated oxidative dearomatization procedure, alkynyl cyclohexadienones **61a**–**n** are synthesized from 4-substituted phenol and propargyl alcohol derivatives (**Table 4B.2**).[15,16]

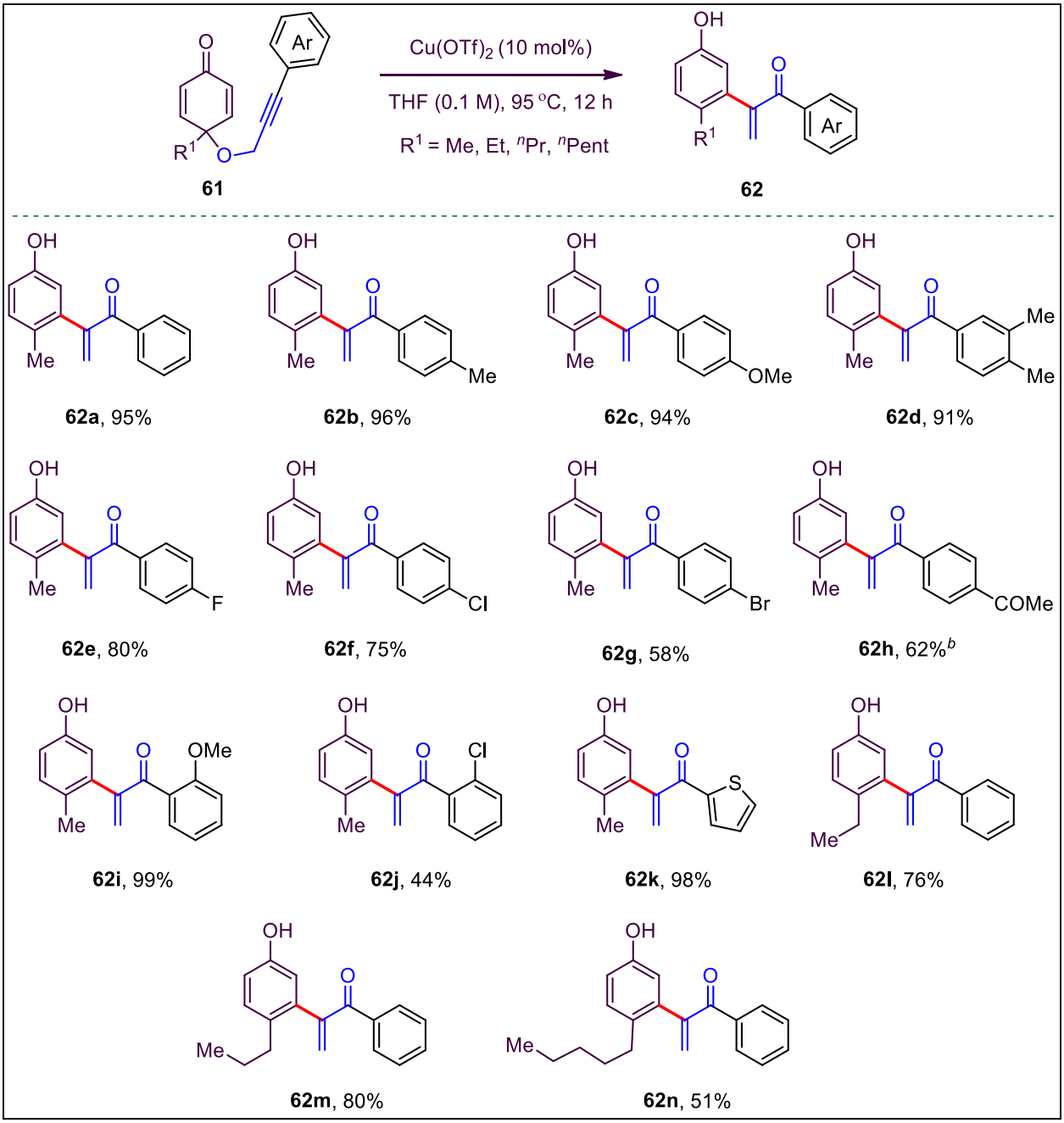
Table 4B.2. Starting materials chart



4B.4.3. Substrate scope for α-aryl-α,β-unsaturated ketones

With the optimized conditions outlined in entry 14, **Table 4B.1**, the scope of the current transformation was examined by reacting alkynyl-cyclohexadienones **61** in presence of $Cu(OTf)_2$ (**Table 4B.3**). The reaction of **61a** (0.3 mmol) in the presence of $Cu(OTf)_2$ (10 mol%) in THF at 95 °C for 12 h furnished the desired product **62a** in excellent yield (95%). The electron-rich arenes (having a substituent *p*–Me/ *p*–OMe/ m,*p*–diMe; (**61b**–**d**) successfully underwent the cationic rearrangement to deliver the respective products **62b**–**d** in excellent yields (91–96%). The halo-substituted arene (having a substituent –F/ –Cl/ –Br on the *para*-position; **61e**–**g**) fruitfully utilized under the standard reaction condition to provide **62e**–**g** in 58–80% yield; the labile halo groups survived under the catalytic system. The electron-deficient *p*-COMe substituted alkynyl cyclohexadienone (**61h**) delivered the desired rearranged product **62h** (62%) in moderate yield. The sterically encumbered *ortho*-substituted alkynyl-cyclohexadienone [*o*-OMe (**61i**) and *o*-Cl (**61j**)] did not obstruct the reaction providing **62i** and **62j** in 99% and 44% yield, respectively. The heteroaryl-tethered **61k** also found effective providing **62k** in quantitative yield (98%). Finally, alkynyl cyclohexadienone with various alkyl [–Et (**61l**)/ –^{n}Pr (**61m**)/ –^{n}Pent (**61n**)] groups in the angular position successfully participated in the reaction to furnish **62l**–**n** in 51%-80% yield.

Table 4B.3. Scope of α-aryl-α,β-unsaturated ketones[a]



[a]Reactions were carried out using **61** (0.3 mmol), $Cu(OTf)_2$ (10 mol%), in THF (0.1 M, 3 mL) at 95 °C for 12 h. [b]Stirred for 24 h.

4B.5. Conclusion

In summary, a copper-catalyzed Meyer-Schuster rearrangement of yne-dienone to access α-aryl-α,β-unsaturated carbonyl compounds have been developed. The overall process is atom economic and forms a wide range of novel Baylis–Hillman adducts. The reaction tolerates labile halo groups, heteroaryl systems, and the aliphatic chains; consequently, the transformation exhibits broad scope and is synthetically viable.

4B.6. Experimental Section

4B.6.1. General information

The identical procedure is shown in page no: 42, in Chapter 2.

4B.6.2. Materials

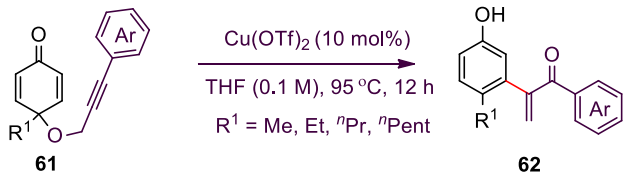
Unless otherwise noted, all the reagents and intermediates are obtained commercially and used without purification. Dichloroethane ($ClCH_2CH_2Cl$), chloroform ($CHCl_3$), toluene, and 1,4-dioxane are distilled over CaH_2. Ethyl acetate and hexane are distilled over anhydrous P_2O_5. THF is freshly distilled over sodium/benzophenone ketyl under dry nitrogen. $Cu(OTf)_2$, $Sc(OTf)_3$, $Fe(OTf)_3$, $Yb(OTf)_3$, $In(OTf)_3$, PIDA, CuI, and $PdCl_2(PPh_3)_2$ are commercially available and used as received. 4-Alkyl phenols, aryl iodides are purchased and used as such. Following the known procedure,[15,16] compounds **61a**–**n** are synthesized. Analytical and spectral data of the known compounds are exactly matching with the reported values.

4B.6.3. General procedure and spectral/analytical data

4B.6.3.1. General procedure for the synthesis of starting materials 61a-n

The general procedure for the synthesis of alkynyl-cyclohexadienone (**61**) is shown in page no: 153 and 154, in Chapter 4A (**4A.6.3.1** and **4A.6.3.2**).

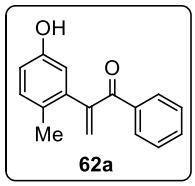
4B.6.3.2. General procedure for the synthesis of α-aryl-α,β-unsaturated ketones 62



A mixture of alkynyl-cyclohexadienone **61** (0.3 mmol) and $Cu(OTf)_2$ (0.03 mmol) in THF (3.0 mL) was taken in a screw-cap sealed tube. The reaction mixture was heated to 95 °C and stirred for overnight. The progress of the reaction was monitered by thin layer

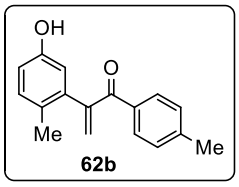
chromatography (TLC) analysis. Upon completion, the reaction mixture was cooled to room temperature and diluted with dichloromethane (3.0 mL). The crude residue was purified using column chromatography on silica gel (100–200 mesh) to provide desired α-aryl-α,β-unsaturated ketones **62** in quantitative yield.

2-(5-hydroxy-2-methylphenyl)-1-phenylprop-2-en-1-one (62a): Following the general procedure, compound **62a** (68 mg) was obtained in 95% yield; yellow gummy liquid; R_f = 0.54 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90–7.87 (m, 2H), 7.58–7.54 (m, 1H), 7.46–7.42 (m, 2H), 6.98 (d, J = 8.5 Hz, 1H), 6.74 (d, J = 2.5 Hz, 1H), 6.70 (dd, J = 8.0, 2.5 Hz, 1H), 5.97 (dd, J = 21, 1.0 Hz, 2H), 2.10 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.3, 154.1, 148.8, 138.8, 136.9, 132.8, 131.2, 129.8, 128.4, 128.3, 127.0, 116.8, 115.5, 19.4; IR (Neat)ν_{max} 3368, 3058, 2922, 1649, 1596, 1576, 1495, 1446, 1281, 1253, 1228 cm^{-1}; HRMS (ESI) for $C_{16}H_{15}O_2$ $(M+H)^+$: calcd 239.1067, found 239.1073.



62a

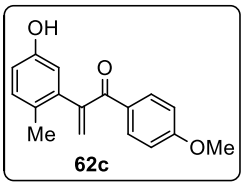
2-(5-hydroxy-2-methylphenyl)-1-(p-tolyl)prop-2-en-1-one (62b): Following the general procedure, compound **62b** (73 mg) was obtained in 96% yield; colorless solid; R_f = 0.46 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 10 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.68 (dd, J = 8.4, 2.8 Hz, 1H), 6.40 (br s, 1H), 5.93 (d, J = 10 Hz, 2H), 2.41 (s, 3H), 2.09 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.1, 154.1, 148.9, 143.8, 139.0, 134.4, 131.2, 130.1, 129.0, 127.7, 127.0, 116.9, 115.5, 21.6, 19.5; IR (Neat)ν_{max} 3331, 3031, 2920, 1631, 1597, 1563, 1498, 1437, 1408, 1286, 1218 cm^{-1}; HRMS (ESI) for $C_{17}H_{17}O_2$ $(M+H)^+$: calcd 253.1223, found 253.1228.



62b

2-(5-hydroxy-2-methylphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (62c): Following the general procedure, compound **62c** (76 mg) was obtained in 94% yield; colorless solid; R_f = 0.35 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.29 (s, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.69–6.64 (m,

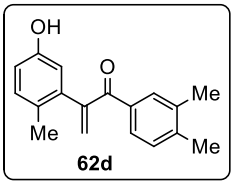
2H), 5.91 (s, 1H), 5.79 (s, 1H), 3.83 (s, 3H), 1.99 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ



62c

194.9, 163.5, 155.8, 149.1, 139.6, 132.2, 131.5, 129.6, 126.2, 125.4, 116.7, 115.5, 114.3, 56.0, 19.5; IR (Neat)ν_{max} 3282, 3022, 2918, 1624, 1591, 1563, 1313, 1291, 1255, 1217 cm^{-1}; HRMS (ESI) for $C_{17}H_{16}NaO_3$ $(M+Na)^+$: calcd 291.0992, found 291.0998.

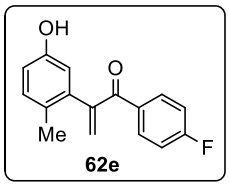
1-(3,4-dimethylphenyl)-2-(5-hydroxy-2-methylphenyl)prop-2-en-1-one (62d):



62d

Following the general procedure, compound **62d** (73 mg) was obtained in 91% yield; pale yellow solid; R_f = 0.44 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.64 (dd, J = 7.6, 1.6 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.67 (dd, J = 8.4, 2.8 Hz, 1H), 6.33 (br s, 1H), 5.93 (dd, J = 18.8, 1.2 Hz, 2H), 2.32 (s, 3H), 2.30 (s, 3H), 2.09 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.3, 154.1, 149.0, 142.6, 139.0, 136.8, 134.6, 131.2, 131.0, 129.5, 127.9, 127.6, 127.0, 116.9, 115.5, 20.0, 19.7, 19.5; IR (Neat)ν_{max} 3337, 2921, 2854, 1626, 1600, 1563, 1498, 1437, 1356, 1291, 1224 cm^{-1}; HRMS (ESI) for $C_{18}H_{19}O_2$ $(M+H)^+$: calcd 267.1380, found 267.1385.

1-(4-fluorophenyl)-2-(5-hydroxy-2-methylphenyl)prop-2-en-1-one (62e): Following the

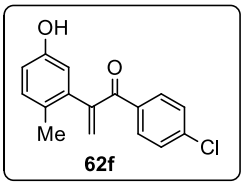


62e

general procedure, compound **62e** (62 mg) was obtained in 80% yield; colorless liquid; R_f = 0.64 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (500 MHz, $CDCl_3$): δ 7.95–7.89 (m, 2H), 7.13–7.07 (m, 2H), 6.96 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 2.5 Hz, 1H), 6.69 (dd, J = 8.0, 2.5 Hz, 1H), 6.33 (s, 1H), 5.95 (dd, J = 15, 0.5 Hz, 1H), 2.07 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 195.7, 165.6 (d, J = 156 Hz, 1C), 154.1, 148.7, 138.7, 133.1 (d, J = 2.5 Hz, 1C), 132.5 (d, J = 10 Hz, 1C), 131.3, 128.0, 127.1, 116.8, 115.6, 115.4, 19.4; ^{19}F NMR (471 MHz, $CDCl_3$): δ –104.9; IR (Neat)ν_{max} 3368, 2923, 1643, 1596, 1502, 1282, 1228, 1154 cm^{-1}; HRMS (ESI) for $C_{16}H_{14}FO_2$ $(M+H)^+$: calcd 257.0972, found 257.0977.

1-(4-chlorophenyl)-2-(5-hydroxy-2-methylphenyl)prop-2-en-1-one (62f): Following the general procedure, compound **62f** (61 mg) was obtained in 75% yield; pale yellow solid;

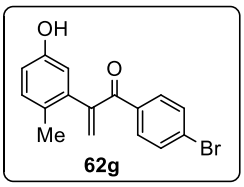
R_f = 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.79



62f

(m, 2H), 7.42–7.38 (m, 2H), 6.96 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 2.8 Hz, 1H), 6.68 (dd, J = 8.4, 2.4 Hz, 1H), 6.33 (s, 1H), 5.96 (d, J = 10.8 Hz, 2H), 2.07 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 195.9, 154.0, 146.6, 139.3, 138.6, 135.1, 131.3, 131.2, 128.7, 128.4, 127.1, 116.7, 115.6, 19.4; IR (Neat)ν_{max} 3361, 2922, 1630, 1602, 1583, 1562, 1498, 1432, 1400, 1346, 1284, 1207 cm^{-1}; HRMS (ESI) for $C_{16}H_{14}ClO_2$ $(M+H)^+$: calcd 273.0677, found 273.0683.

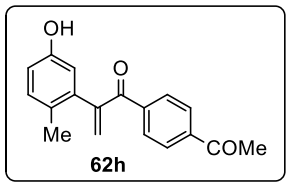
1-(4-bromophenyl)-2-(5-hydroxy-2-methylphenyl)prop-2-en-1-one (62g): Following the



62g

general procedure, compound **62g** (55 mg) was obtained in 58% yield; yellow solid; R_f = 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 2.8 Hz, 1H), 6.69 (dd, J = 8.0, 2.8 Hz, 1H), 5.96 (d, J = 10.8 Hz, 2H), 2.07 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 195.9, 154.0, 148.6, 138.7, 135.6, 131.7, 131.4, 131.3, 128.4, 128.0, 127.2, 116.7, 115.6, 19.4; IR (Neat)ν_{max} 3359, 2922, 1628, 1603, 1580, 1497, 1451, 1398, 1283, 1254 cm^{-1}; HRMS (ESI) for $C_{16}H_{13}BrNaO_2$ $(M+Na)^+$: calcd 338.9991, found 339.0008.

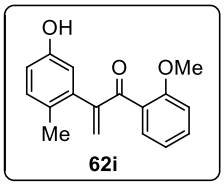
1-(4-acetylphenyl)-2-(5-hydroxy-2-methylphenyl)prop-2-en-1-one (62h): Following the



62h

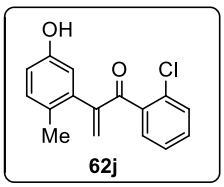
general procedure, compound **62h** (52 mg) was obtained in 62% yield; yellow solid; R_f = 0.21 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, DMSO-D_6): δ 9.05 (s, 1H), 8.00 (s, 1H), 7.99 (d, J = 3,6 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.8 Hz, 1H), 6.70-6.63 (m, 2H), 6.01 (s, 1H), 5.91 (s, 1H), 2.60 (s, 3H), 2.01 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-D_6): δ 195.4, 193.7, 153.9, 147.0, 138.9, 138.0, 136.8, 129.3, 127.9, 126.9, 126.5, 123.6, 114.9, 113.8, 25.3, 17.6; IR (Neat)ν_{max} 3310, 2919, 1683, 1637, 1604, 1560, 1494, 1451, 1354, 1286, 1253 cm^{-1}; HRMS (ESI) for $C_{18}H_{17}O_3$ $(M+H)^+$: calcd 281.1172, found 281.1179.

2-(5-hydroxy-2-methylphenyl)-1-(2-methoxyphenyl)prop-2-en-1-one (62i): Following the general procedure, compound **62i** (80 mg) was obtained in 99% yield; yellow liquid; R_f = 0.36 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.39 (m, 2H), 7.00 (d, J = 7.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 1H), 6.68 (dd, J = 8.0, 3.0 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 5.97 (dd, J = 11.5, 1.0 Hz, 2H), 5.83 (br s, 1H), 3.78 (s, 3H), 2.16 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.2, 157.3, 153.6, 150.1, 138.2, 132.0, 130.9, 130.4, 129.7, 128.7, 127.8, 120.3, 116.9, 115.1, 111.4, 55.4, 19.2; IR (Neat)ν_{max} 3379, 2924, 1651, 1597, 1487, 1460, 1285, 1248 cm^{-1}; HRMS (ESI) for $C_{17}H_{17}O_3$ (M+H)$^+$: calcd 269.1172, found 269.1179.



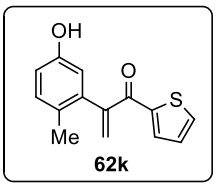
62i

1-(2-chlorophenyl)-2-(5-hydroxy-2-methylphenyl)prop-2-en-1-one (62j): Following the general procedure, compound **62j** (36 mg) was obtained in 44% yield; yellow semisolid; R_f = 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.43 (m, 1H), 7.41–7.38 (m, 2H), 7.35–7.32 (m, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.72 (dd, J = 8.0, 2.5 Hz, 1H), 6.67 (d, J = 2.5 Hz, 1H), 6.67 (d, J = 2.5 Hz, 1H),6.16 (s, 1H), 6.02 (s, 1H), 5.50 (br s, 1H), 2.20 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 195.5, 153.5, 149.0, 138.4, 137.3, 133.7, 131.2, 131.1, 131.0, 130.1, 129.0, 128.1, 126.5, 116.8, 115.4, 19.2; IR (Neat)ν_{max} 3349, 3056, 2922, 1641, 1604, 1587, 1496, 1346, 1286, 1205 cm^{-1}; HRMS (ESI) for $C_{16}H_{14}ClO_2$ (M+H)$^+$: calcd 273.0677, found 273.0686.



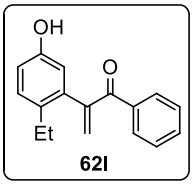
62j

2-(5-hydroxy-2-methylphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (62k): Following the general procedure, compound **62k** (72 mg) was obtained in 98% yield; yellow liquid; R_f = 0.55 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (dd, J = 5.0, 1.0 Hz, 1H), 7.53 (dd, J = 4.0, 1.0 Hz, 1H), 7.05–7.02 (m, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 3.0 Hz, 1H), 6.74 (dd, J = 8.5, 2.5 Hz, 1H), 6.13 (s, 1H), 5.81 (s, 1H), 2.07 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 188.2, 154.2, 148.7, 143.1, 138.7, 134.8, 134.6, 131.3, 128.1, 127.4, 126.5, 116.9, 115.8, 19.4; IR (Neat)ν_{max} 3365, 2920, 1605, 1577, 1495, 1407, 1353, 1233, 1052 cm^{-1}; HRMS (ESI) for $C_{14}H_{13}O_2S$ (M+H)$^+$: calcd 245.0631, found 245.0637.



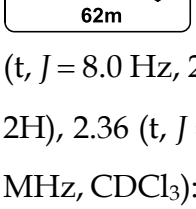
62k

2-(2-ethyl-5-hydroxyphenyl)-1-phenylprop-2-en-1-one (62l): Following the general procedure, compound **62l** (58 mg) was obtained in 76% yield; yellow liquid; R_f = 0.64 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (dd, J = 8.0, 1.5 Hz, 2H), 7.59–7.54 (m, 1H), 7.45 (t, J = 8.0 Hz, 2H), 7.02 (d, J = 8.0 Hz, 1H), 6.74 (dd, J = 8.5, 3.0 Hz, 1H), 6.72 (d, J = 2.5 Hz, 1H), 6.31 (br s, 1H), 5.98 (dd, J = 25, 1.0 Hz, 2H), 2.43 (q, J = 7.5 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.3, 153.9, 148.7, 138.4, 137.0, 133.3, 132.8, 129.8, 129.4, 128.8, 128.3, 117.1, 115.8, 25.8, 15.3; IR (Neat)ν_{max} 3367, 2964, 2871, 1648, 1597, 1576, 1495, 1446, 1260, 1226 cm^{-1}; HRMS (ESI) for $C_{17}H_{17}O_2$ $(M+H)^+$: calcd 253.1223, found 253.1233.



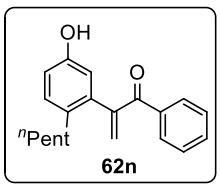
62l

2-(5-hydroxy-2-propylphenyl)-1-phenylprop-2-en-1-one (62m): Following general the procedure, compound **62m** (64 mg) was obtained in 80% yield; pale yellow solid; R_f = 0.56 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, J = 8.8, 1.6 Hz, 2H), 7.60–7.55 (m, 1H), 7.45 (t, J = 8.0 Hz, 2H), 7.02–6.97 (m, 1H), 6.75–6.70 (m, 2H), 6.48 (br s, 1H), 5.97 (d, J = 20.8 Hz, 2H), 2.36 (t, J = 7.6 Hz, 2H), 1.55–1.45 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.4, 153.9, 148.8, 138.6, 136.9, 132.8, 131.8, 130.2, 129.8, 128.8, 128.3, 117.3, 115.6, 35.1, 24.4, 13.9; IR (Neat)ν_{max} 3367, 2956, 2867, 1629, 1595, 1493, 1441, 1345, 1318, 1253 cm^{-1}; HRMS (ESI) for $C_{18}H_{19}O_2$ $(M+H)^+$: calcd 267.1380, found 267.1386.



62m

2-(5-hydroxy-2-pentylphenyl)-1-phenylprop-2-en-1-one (62n): Following the general procedure, compound **62n** (45 mg) was obtained in 51% yield; colorless gummy liquid; R_f = 0.70 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (dd, J = 8.5, 1.5 Hz, 2H), 7.59–7.55 (m, 1H), 7.45 (t, J = 8.0 Hz, 2H), 7.00 (dd, J = 7.0, 1.5 Hz, 1H), 6.75–6.71 (m, 2H), 6.12 (br s, 1H), 5.97 (d, J = 24.5, 1.5 Hz, 2H), 2.37 (t, J = 8.0 Hz, 2H), 1.50–1.43 (m, 2H), 1.27–1.15 (m, 4H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.2, 153.8, 148.8, 138.6, 137.0, 132.8, 132.2, 130.2, 129.9, 128.7, 128.3, 117.2, 115.6, 33.0, 31.6, 30.9, 22.4, 14.0; IR (Neat)ν_{max}



62n

3381, 2954, 2926, 2857, 1648, 1597, 1576, 1494, 1445, 1260, 1228 cm^{-1}; HRMS (ESI) for $C_{20}H_{23}O_2$ $(M+H)^+$: calcd 295.1693, found 295.1695.

4B.7. X-ray Crystallography

Single crystal X-ray data for the compound **62a** was collected using the Bruker D8 Quest CMOS detector system [λ(Mo-Kα) = 0.71073 Å] at 298K, graphite monochromator with a ω scan width of 0.3o, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software was used for the intensity data acquisition and the SAINTPLUS Software was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program, an empirical absorption correction using equivalent reflections was performed with the program. The structure was solved using SHELXS-97, and full-matrix least-squares refinement against F2 was carried out using SHELXL-97. All non-hydrogen atoms were refined anisotropically. Aromatic and methyl hydrogens were introduced on calculated positions and included in the refinement riding on their respective parent atoms.[17,18]

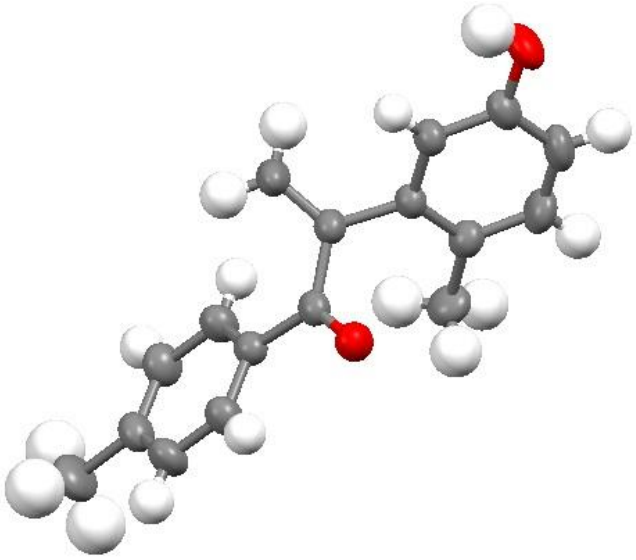


Figure 4B.3. Thermal ellipsoid plot of compound **62a**; ellipsoid contour at the 50% probability level. Single crystal was grown by the slow evaporation of the solution of compound **62a** in $CDCl_3$. Carbon (gray), Hydrogen (light gray), and Oxygen (red).

Table 4B.4. Crystallographic data for compound **62a.**

Compound	**62a**
formula	C_{17} H_{16} O_2
MW	252.30
crystal system	orthorhombic
space group	P 21 21 21
T [K]	298 K
a [Å]	7.9003(19)
b [Å]	12.169(3)
c [Å]	14.402(4)
α [°]	90
β [°]	90
γ [°]	90
V [Å^3]	1384.6(6)
Z	4
ρ_{calcd} [g cm^{-3}]	1.210
μ [mm^{-1}]	0.078
total reflns	1820
unique reflns	1809
observed	1537
$R_1[I>2\sigma(I)]$	0.0429
wR2 [all]	0.1142(1809)
GOF	1.083
Diffractometer	Bruker D8 Quest CCD
CCDC Number	1947873

4B.8. References

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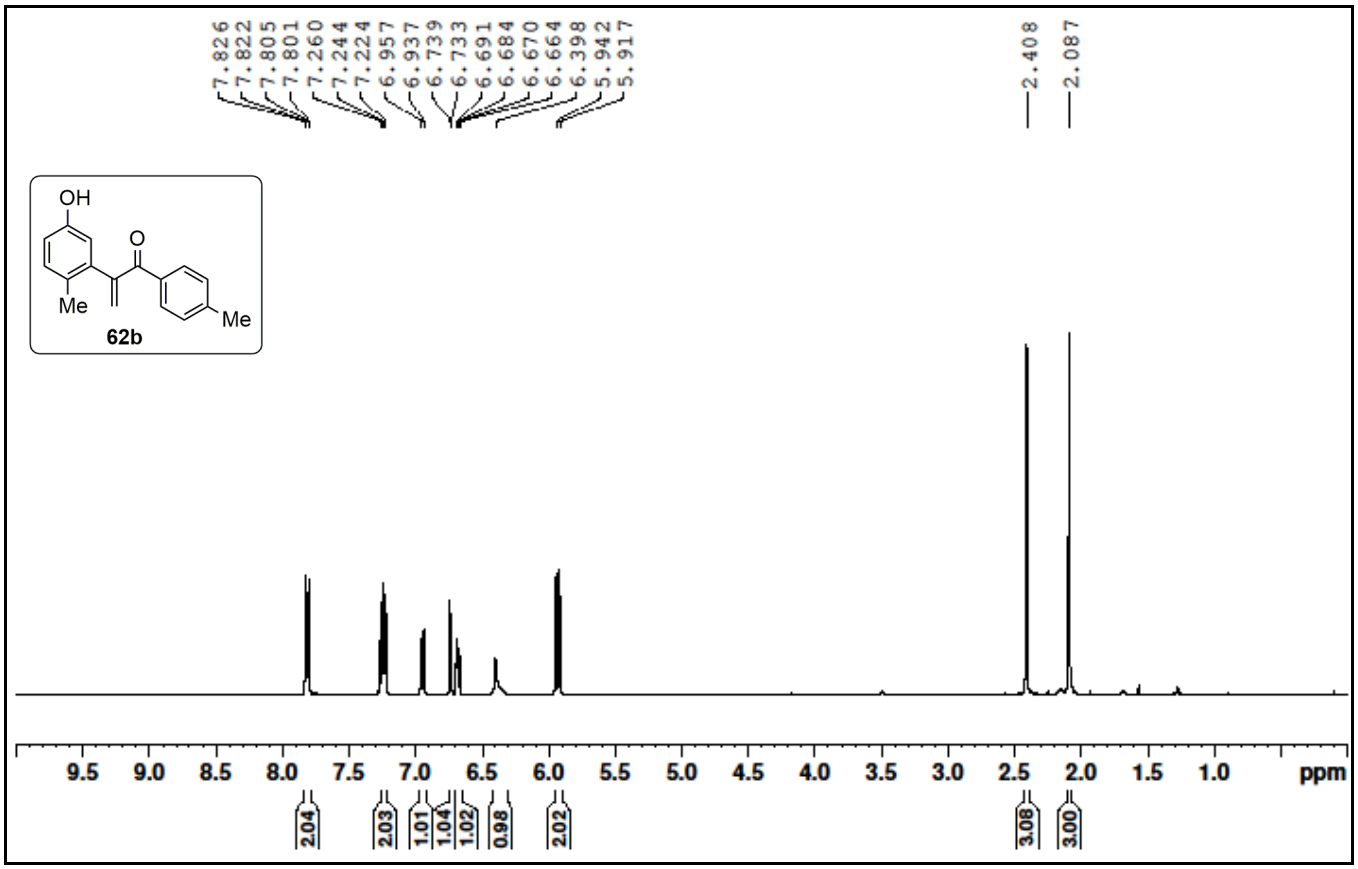
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6.670
6.664
6.398
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2.087
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62b
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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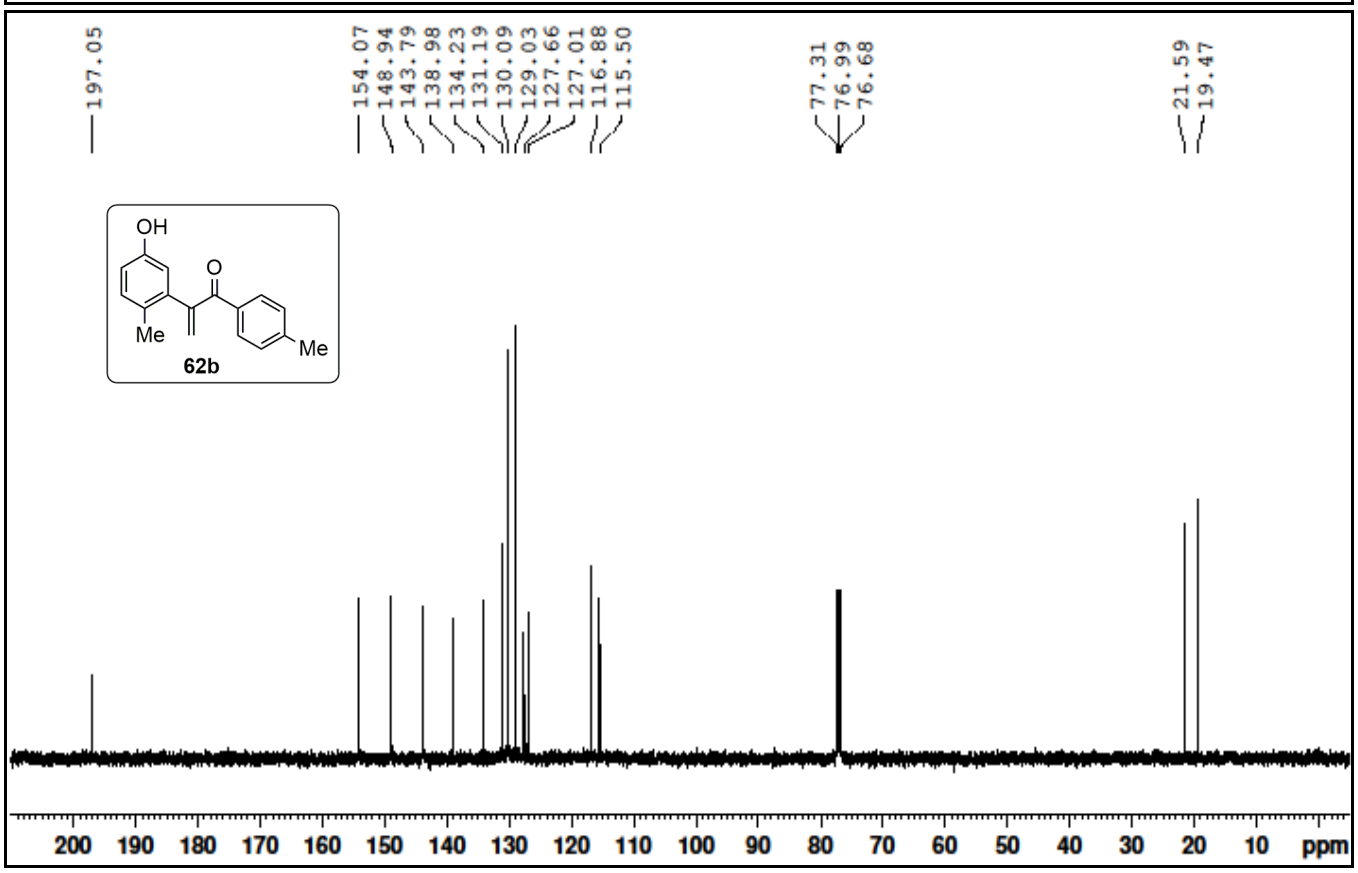
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19.47
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Me
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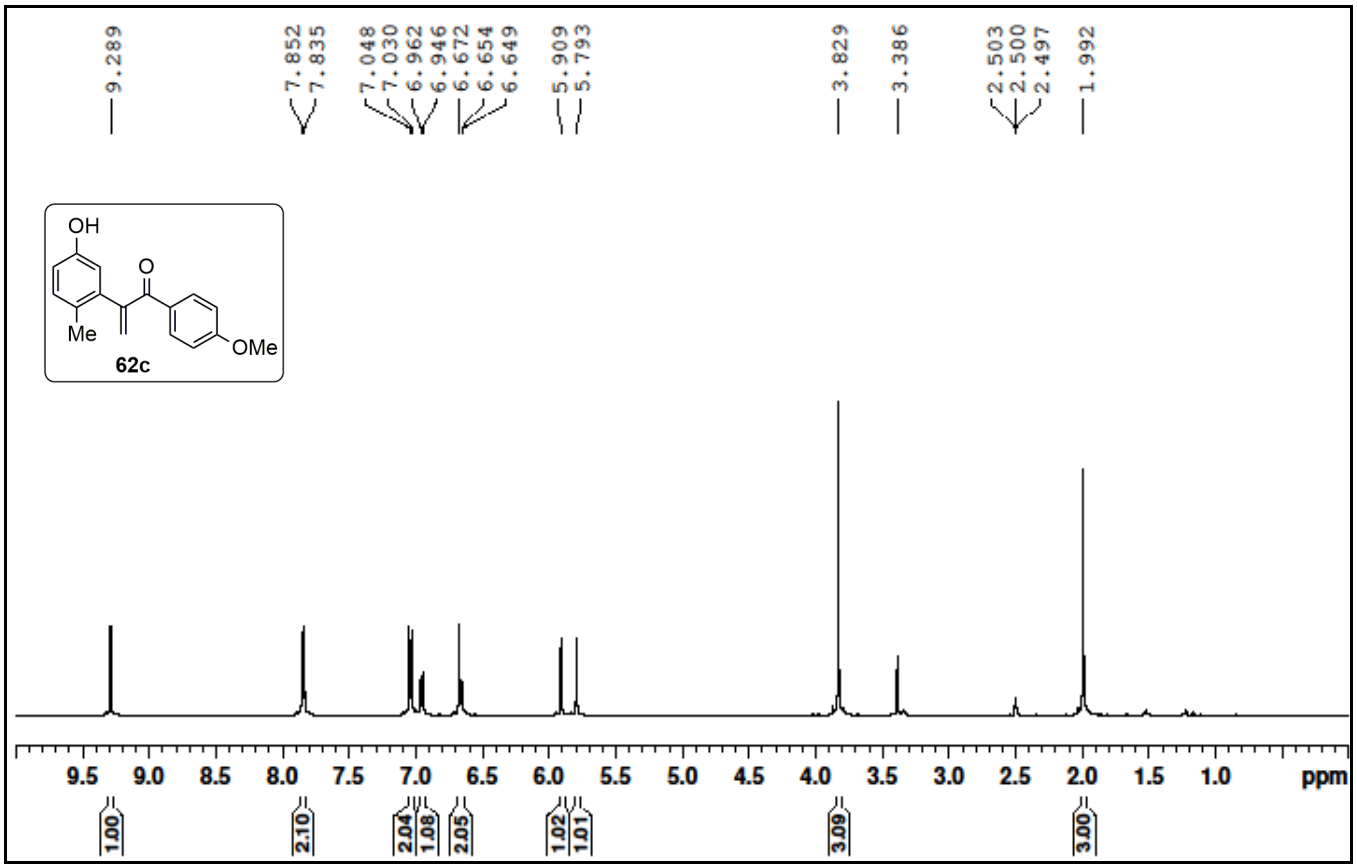
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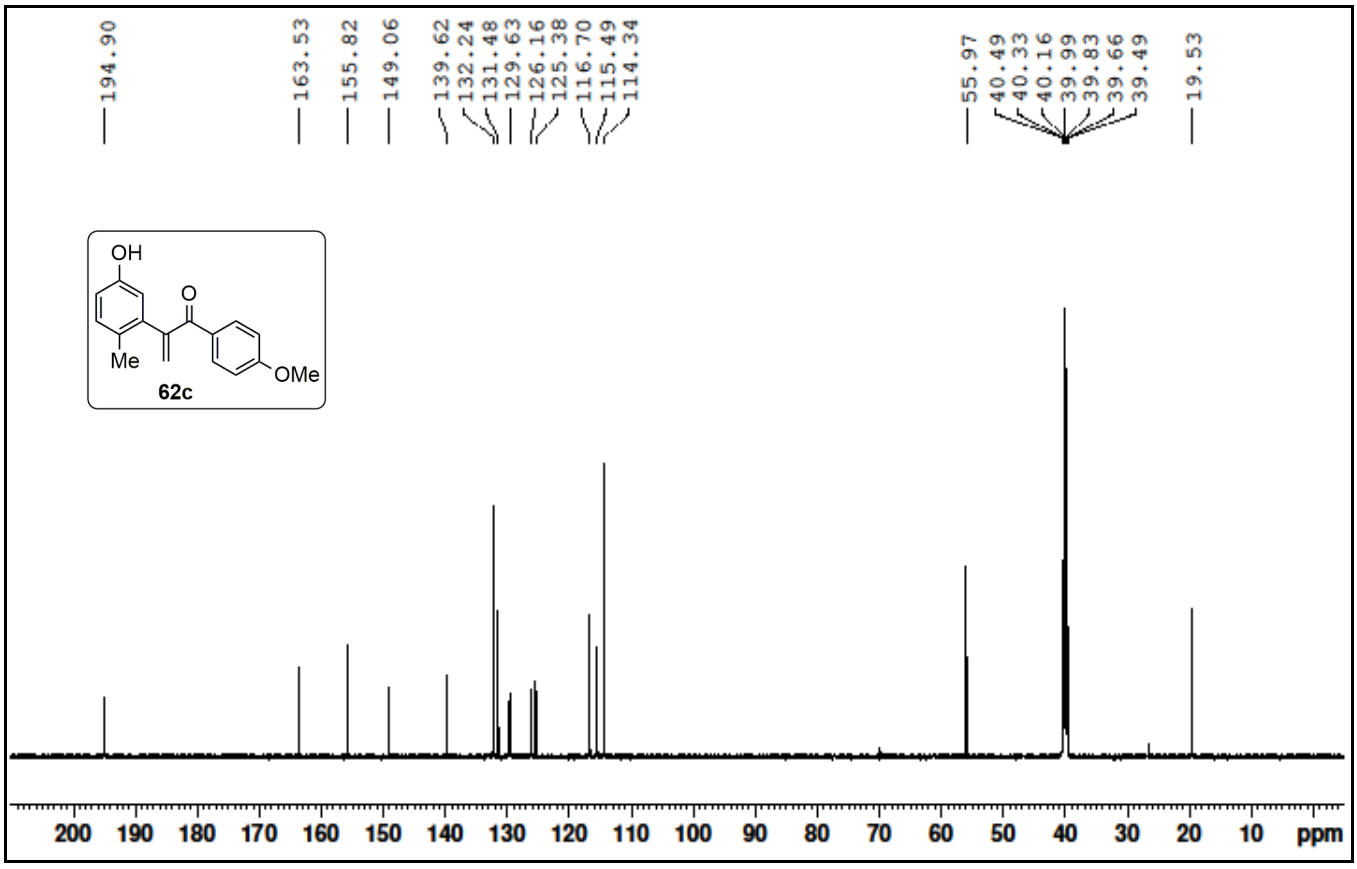
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40.33
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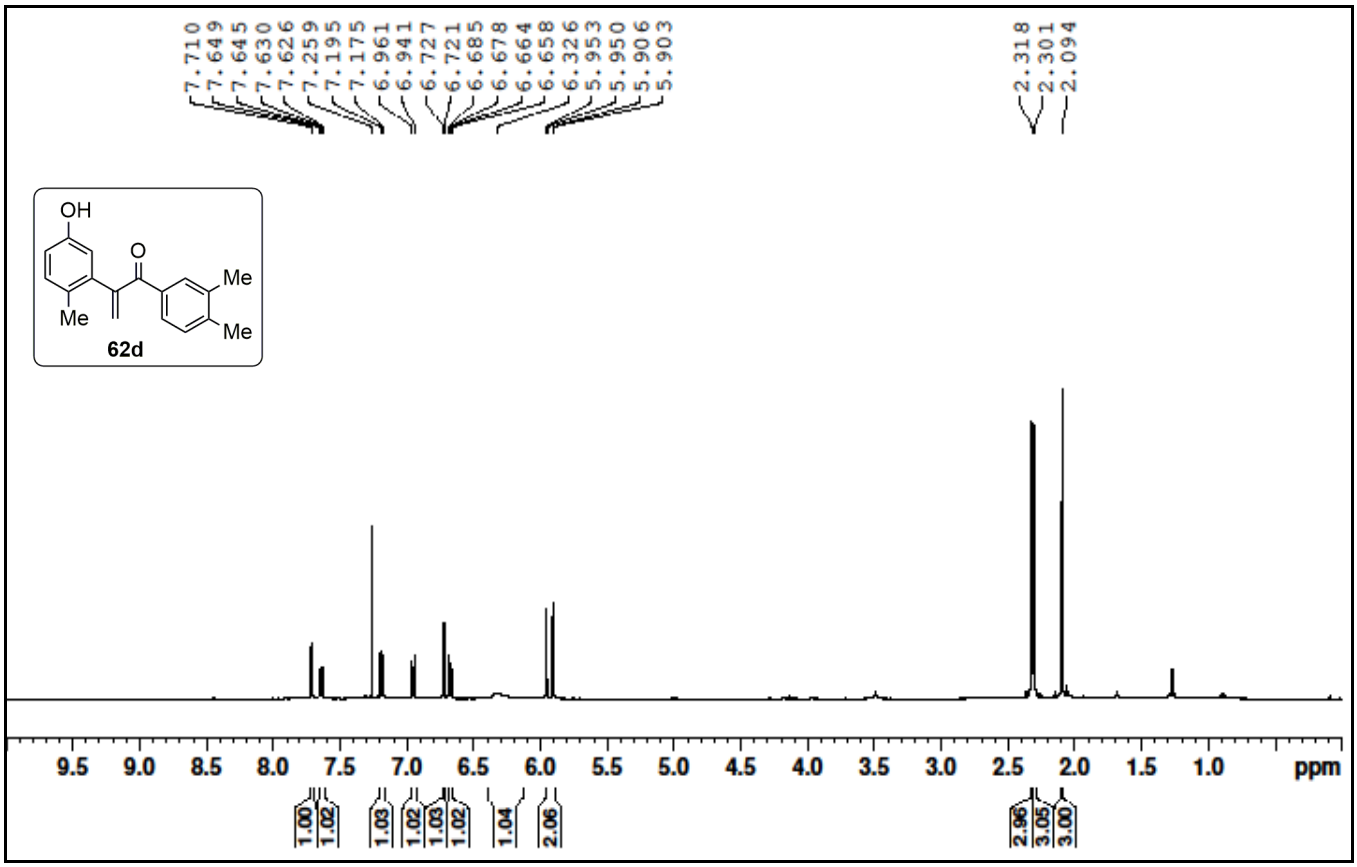
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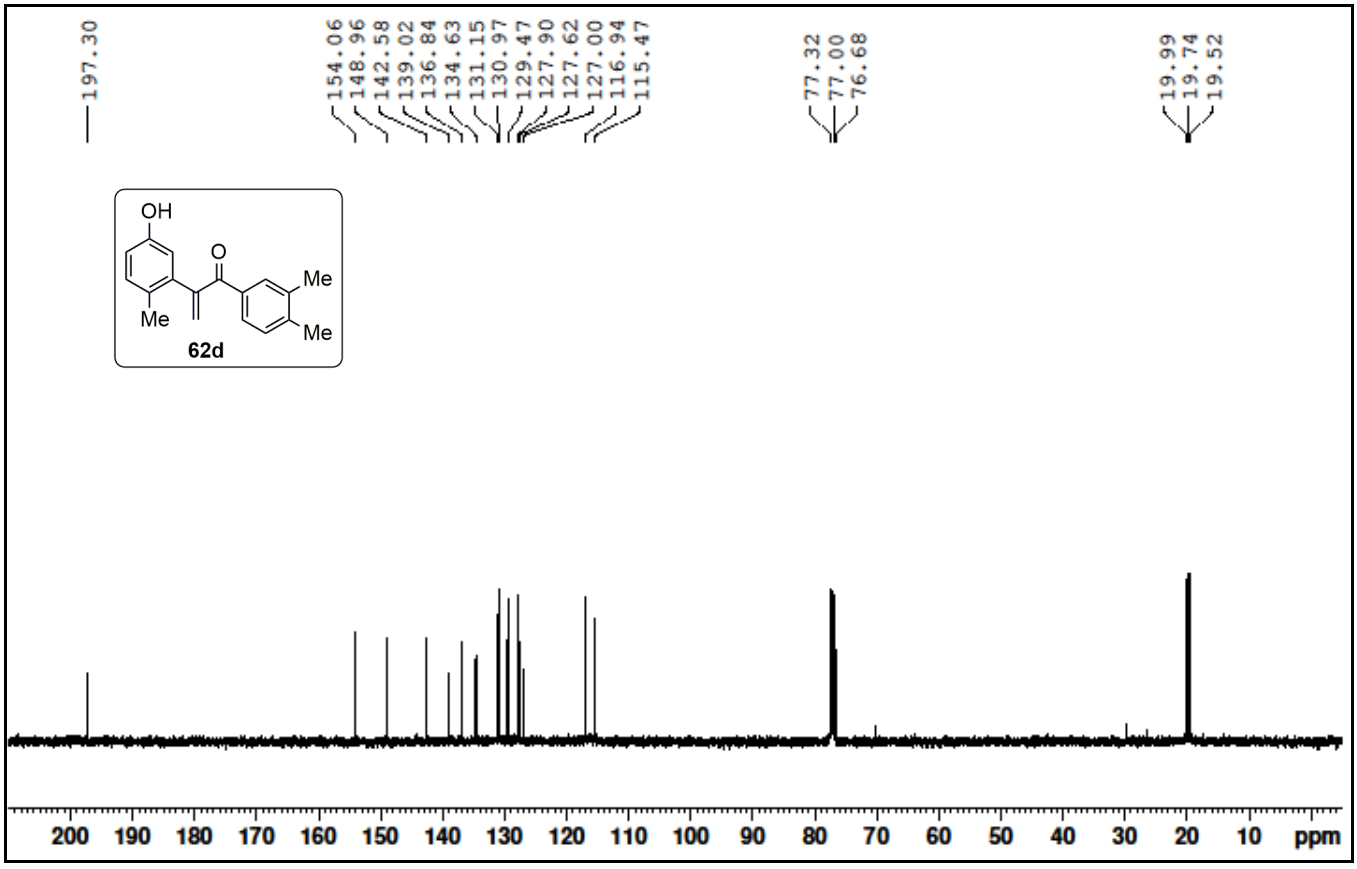
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Me
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Me
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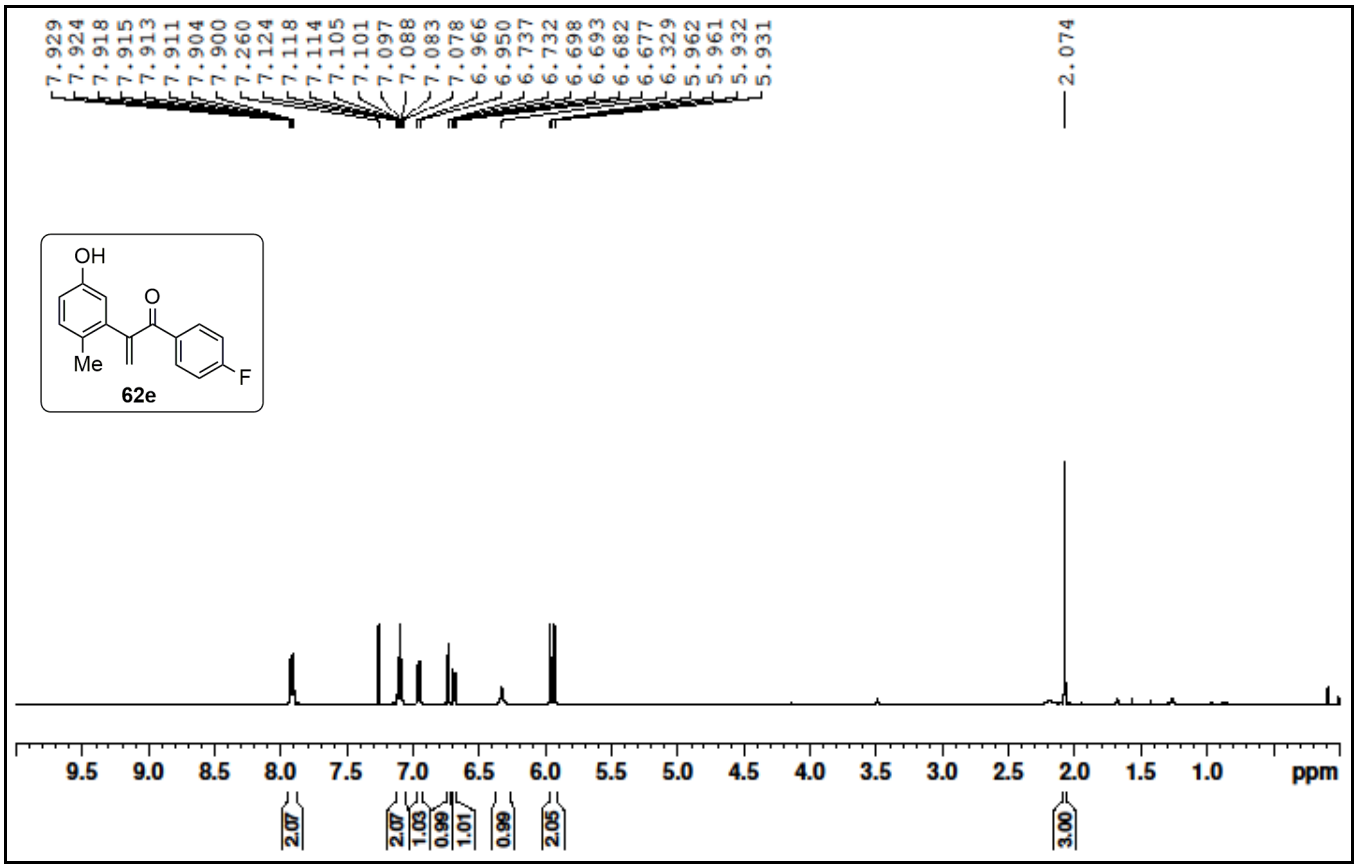
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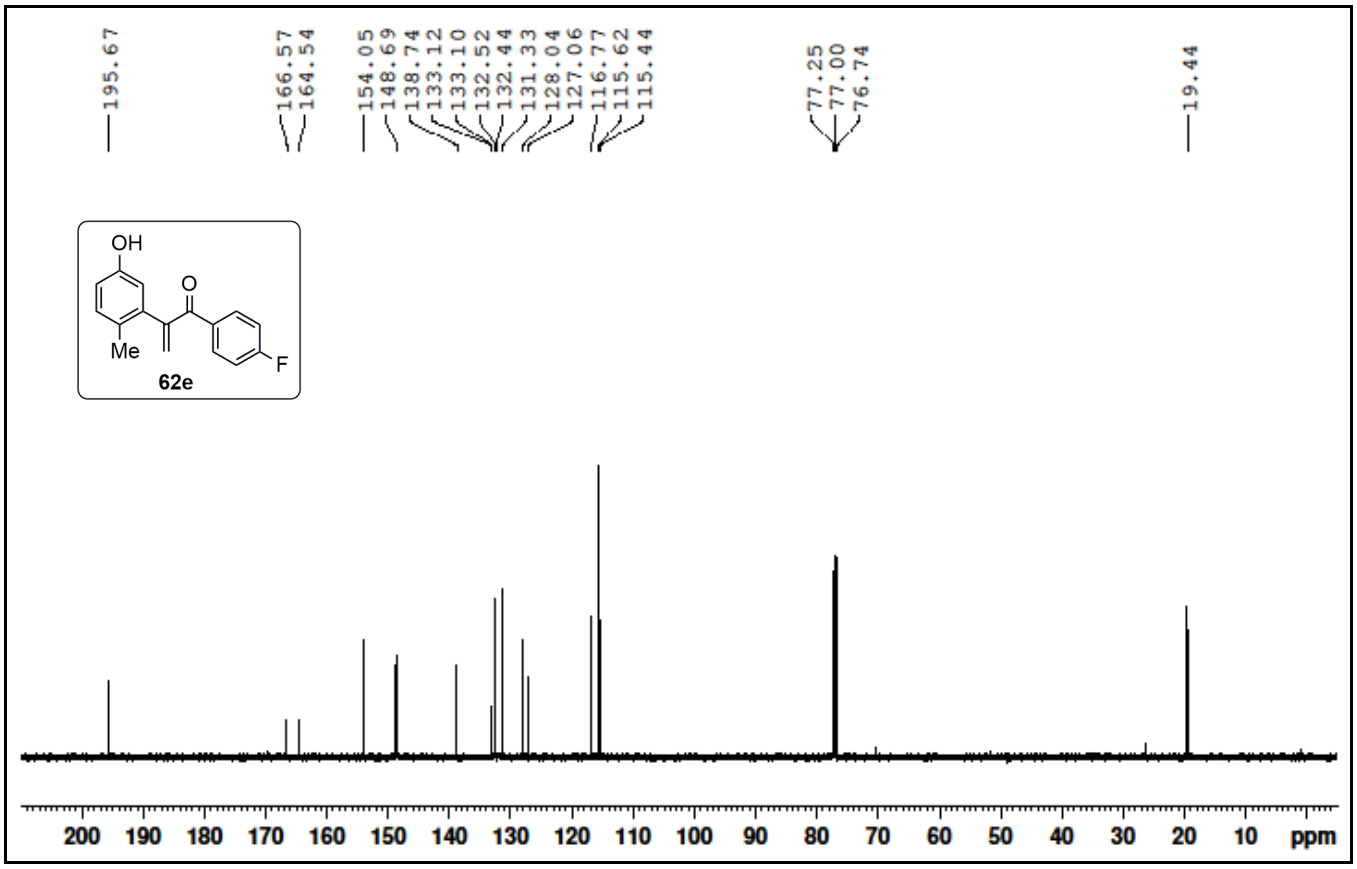
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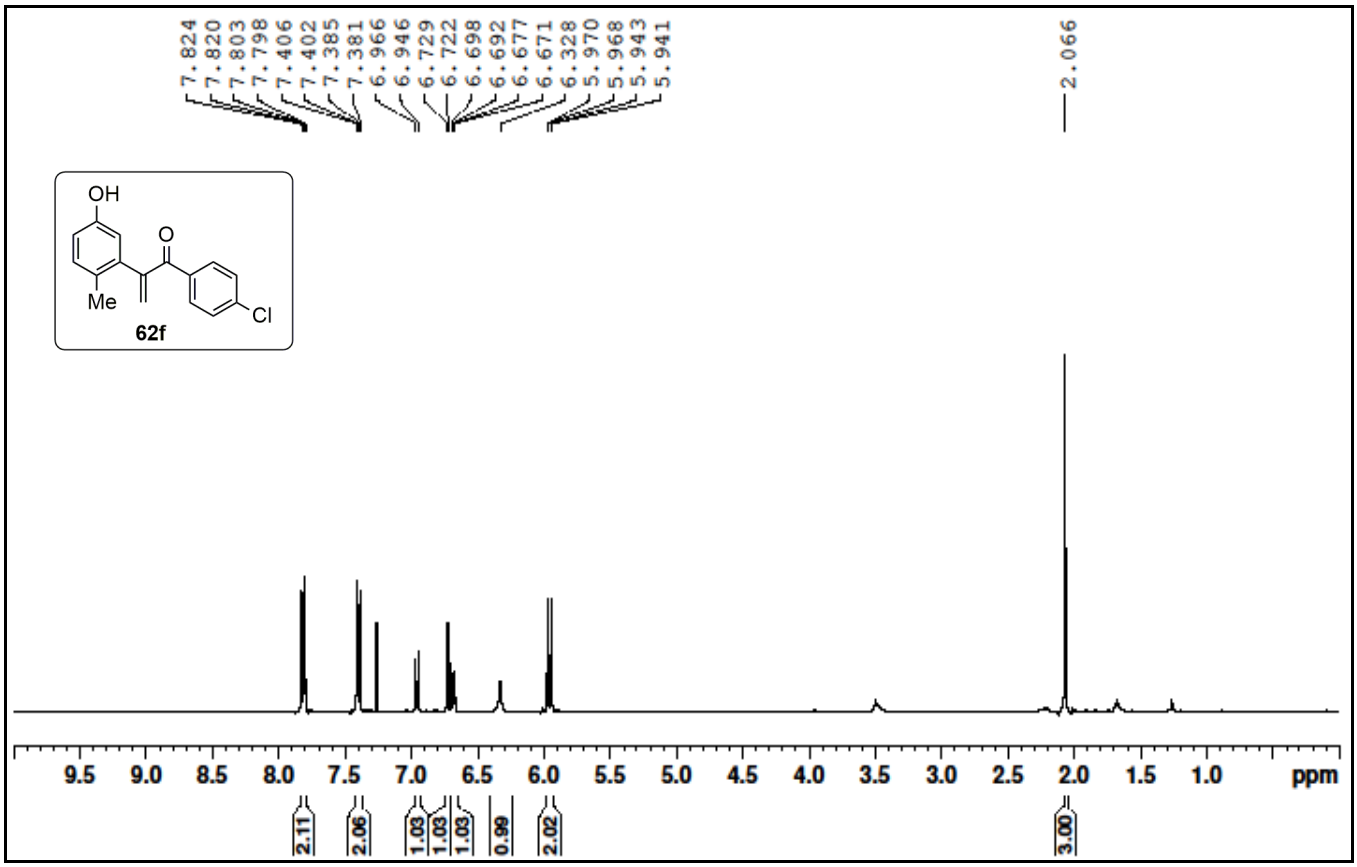
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Me
Cl
62f
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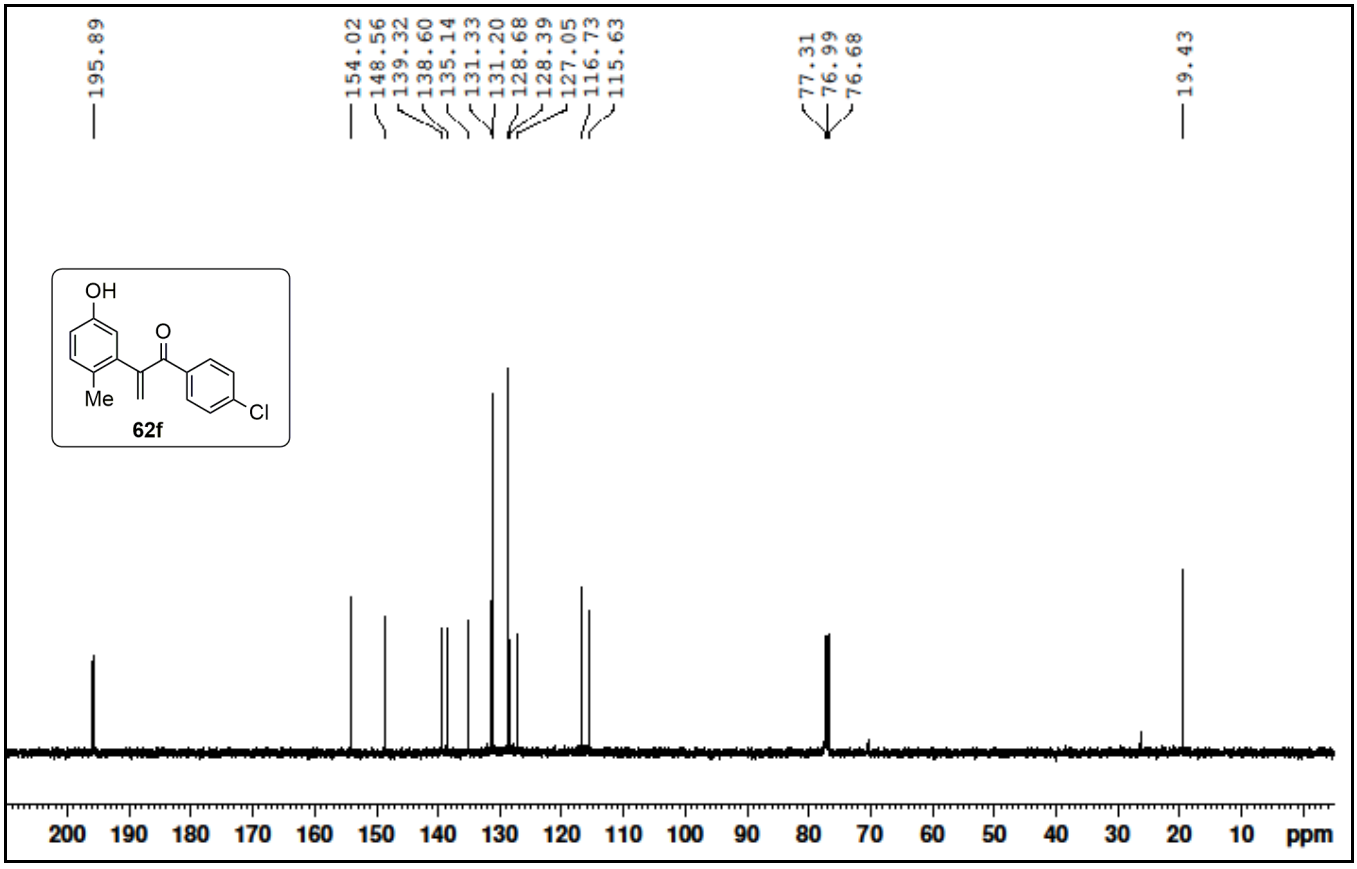
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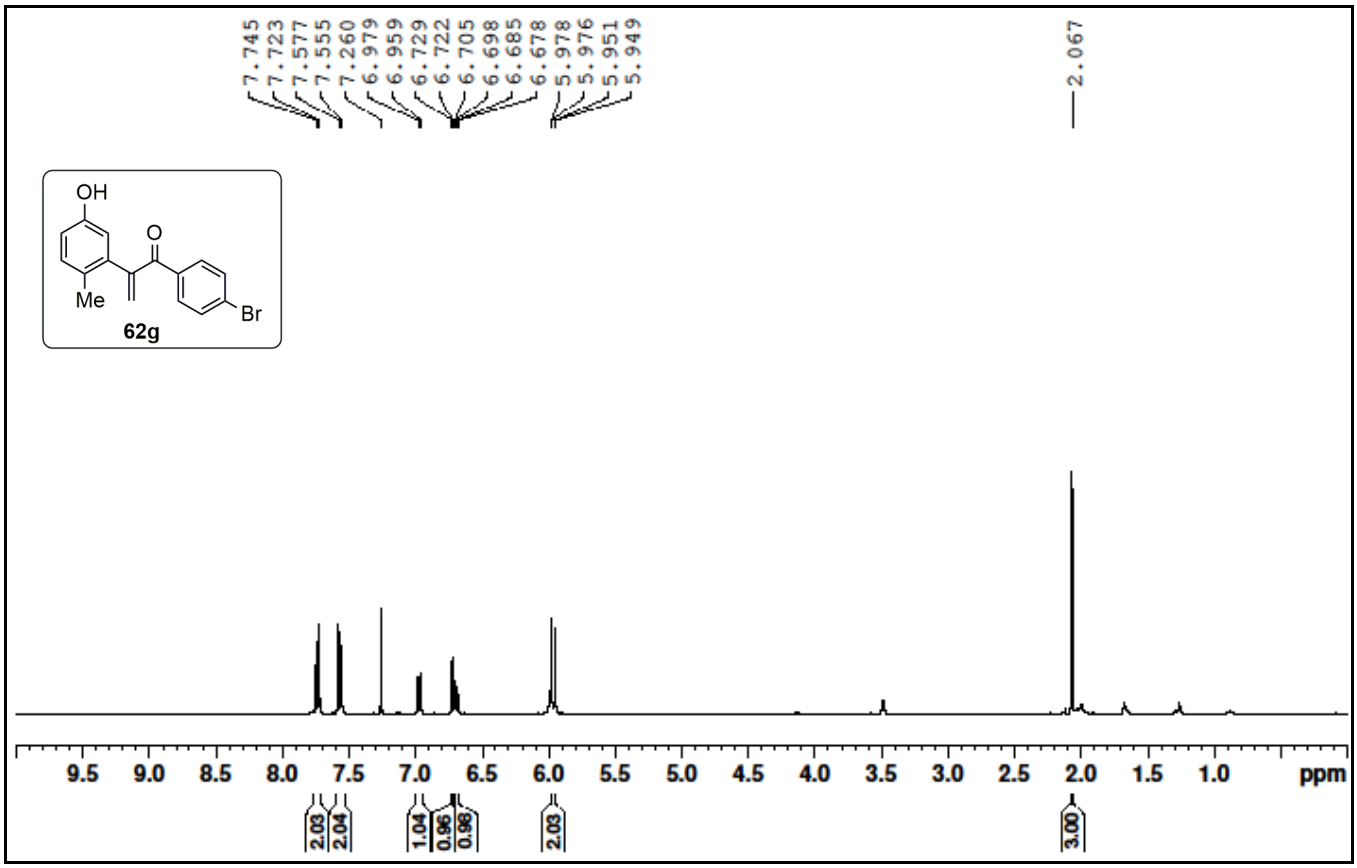
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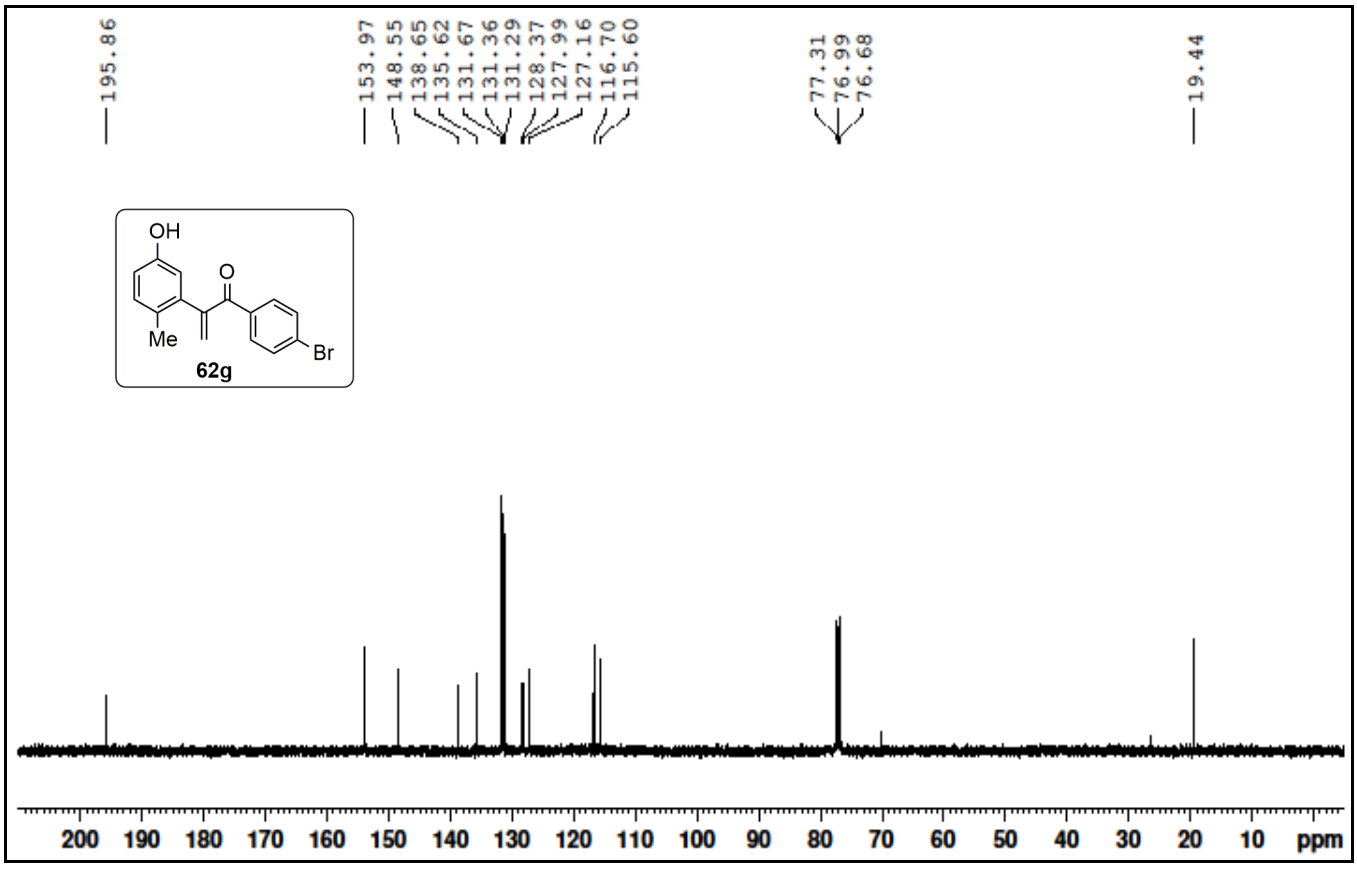
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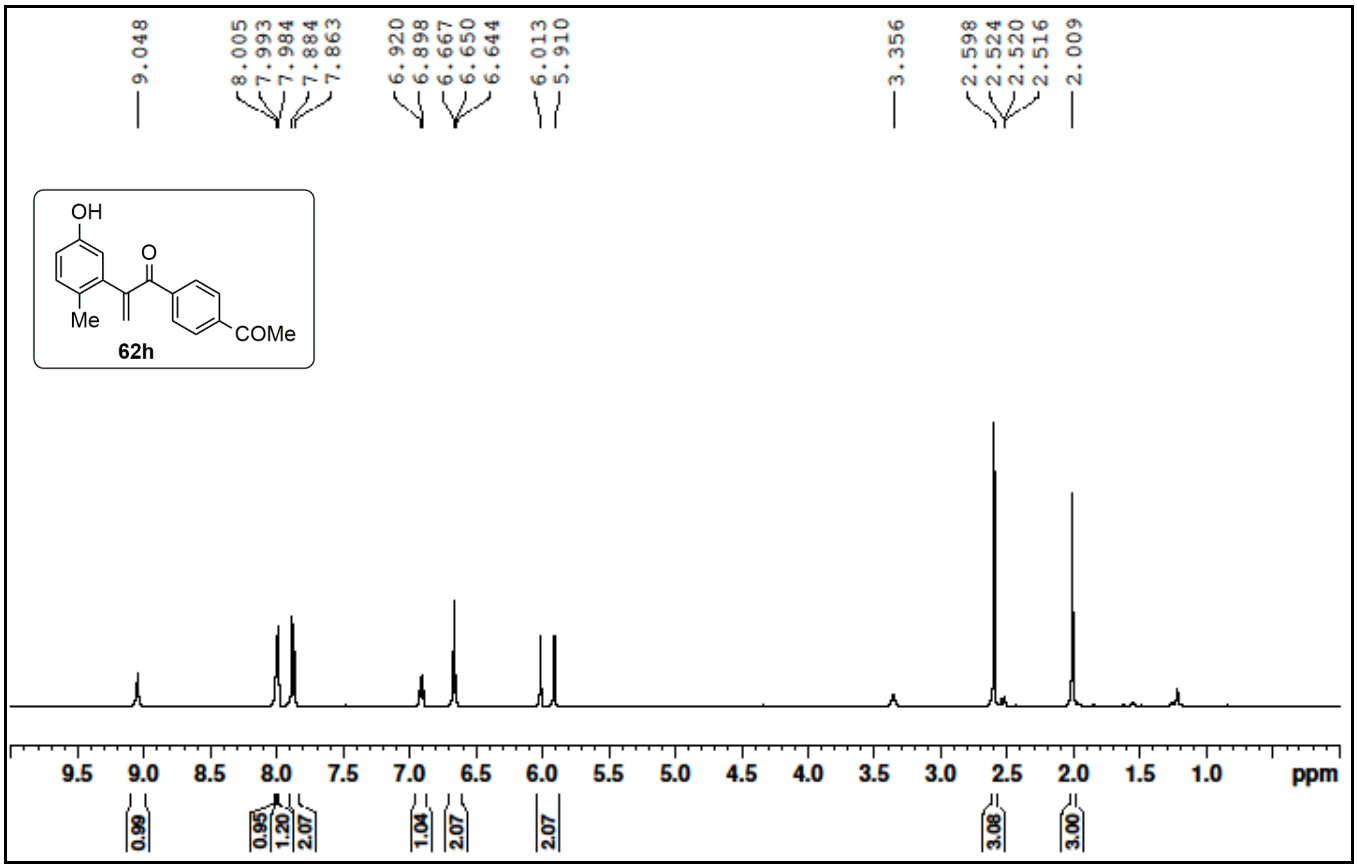
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6.0
5.5
5.0
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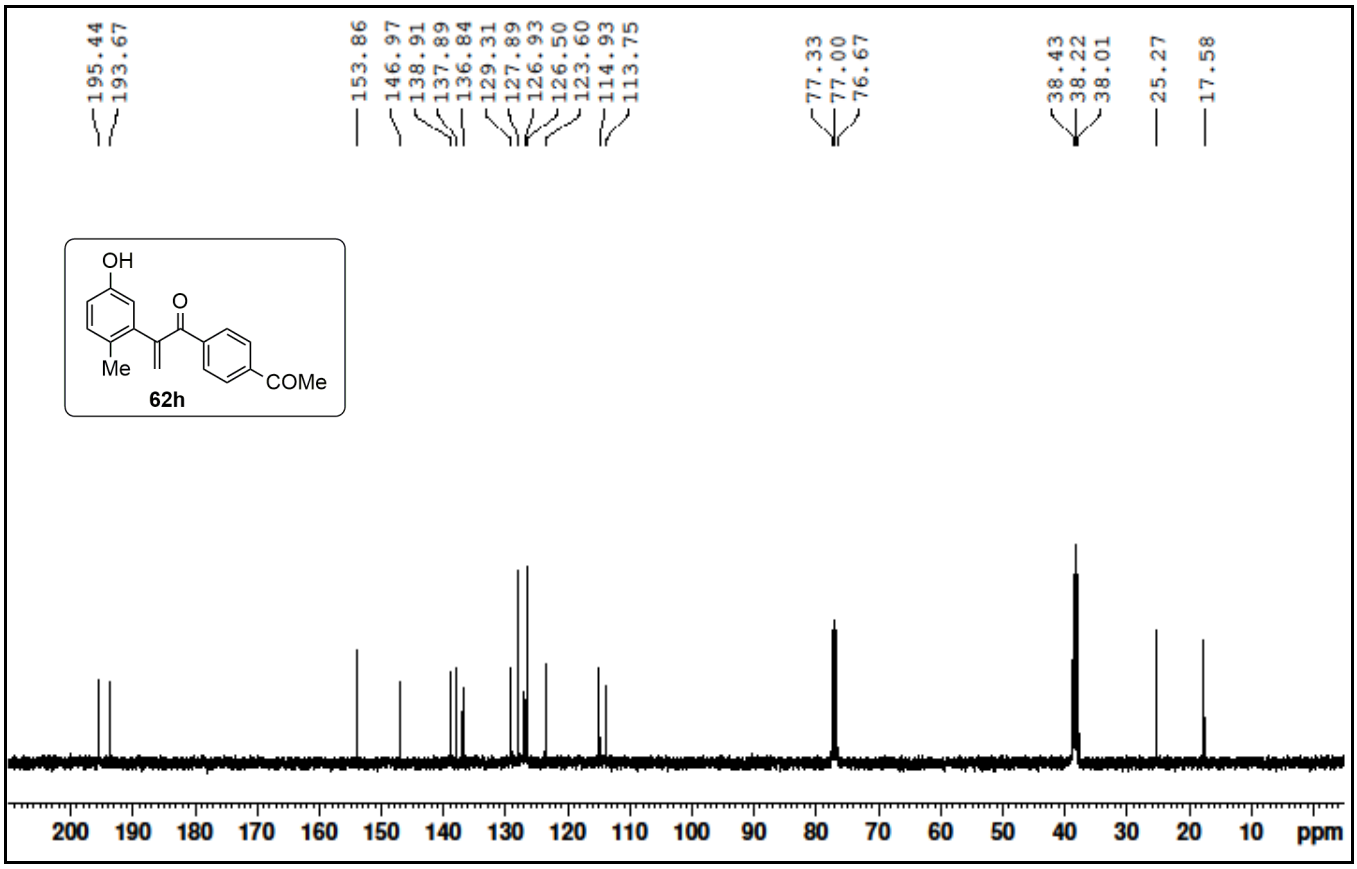
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OH
O
Me
COMe
62h
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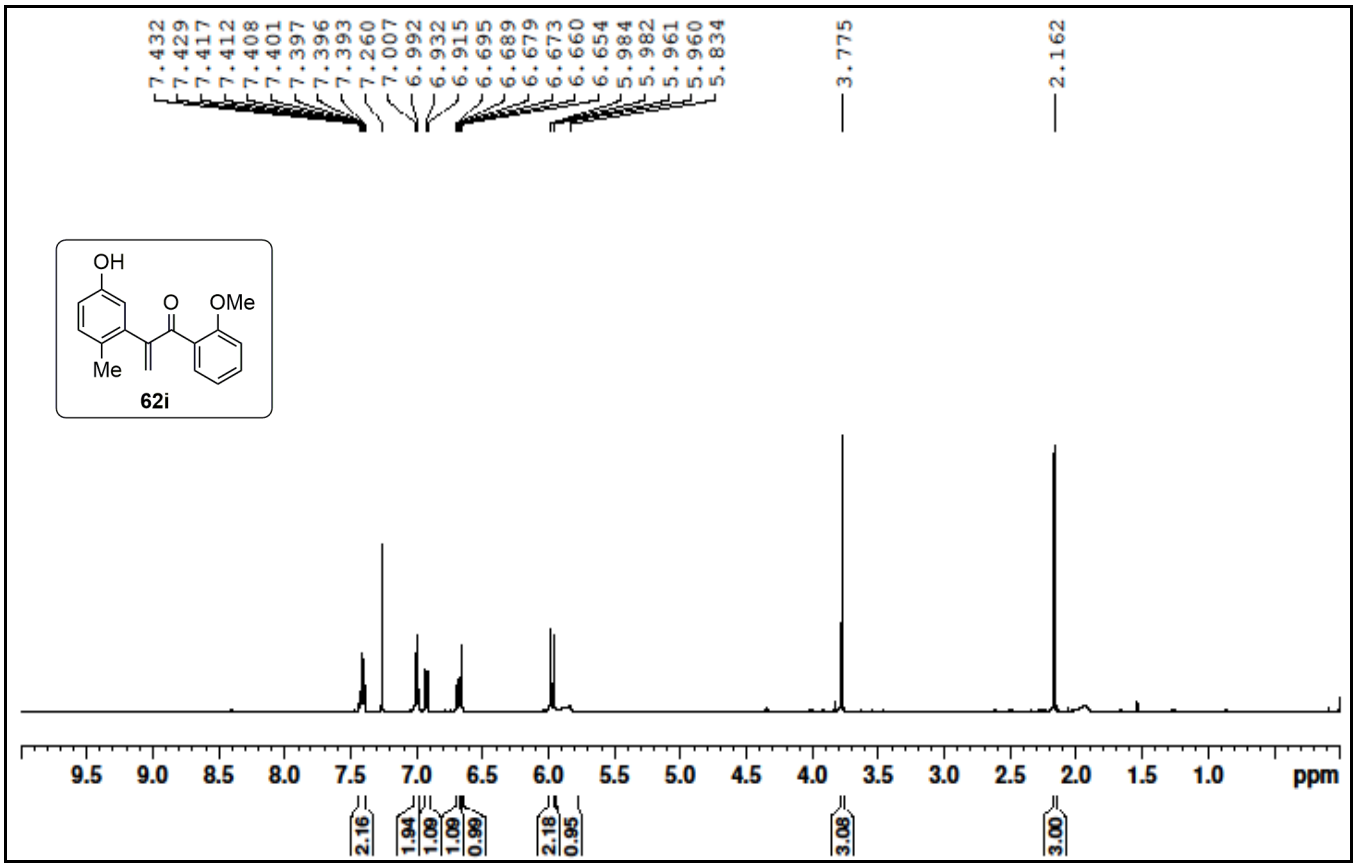
ppm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5.961
5.960
5.834
3.775
2.162
OH
O
OMe
Me
62i
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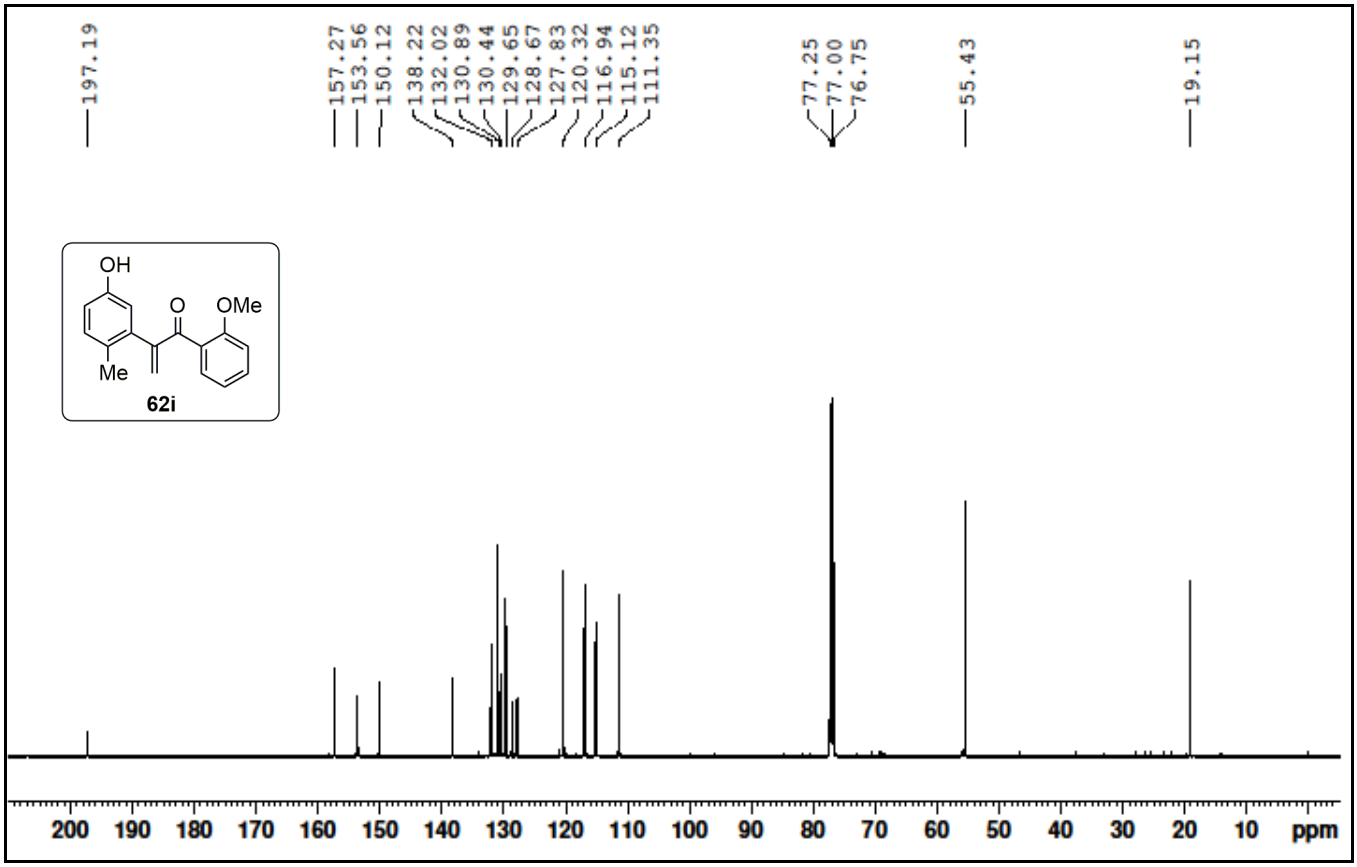
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115.12
111.35
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77.00
76.75
55.43
19.15
OH
O
OMe
Me
62i
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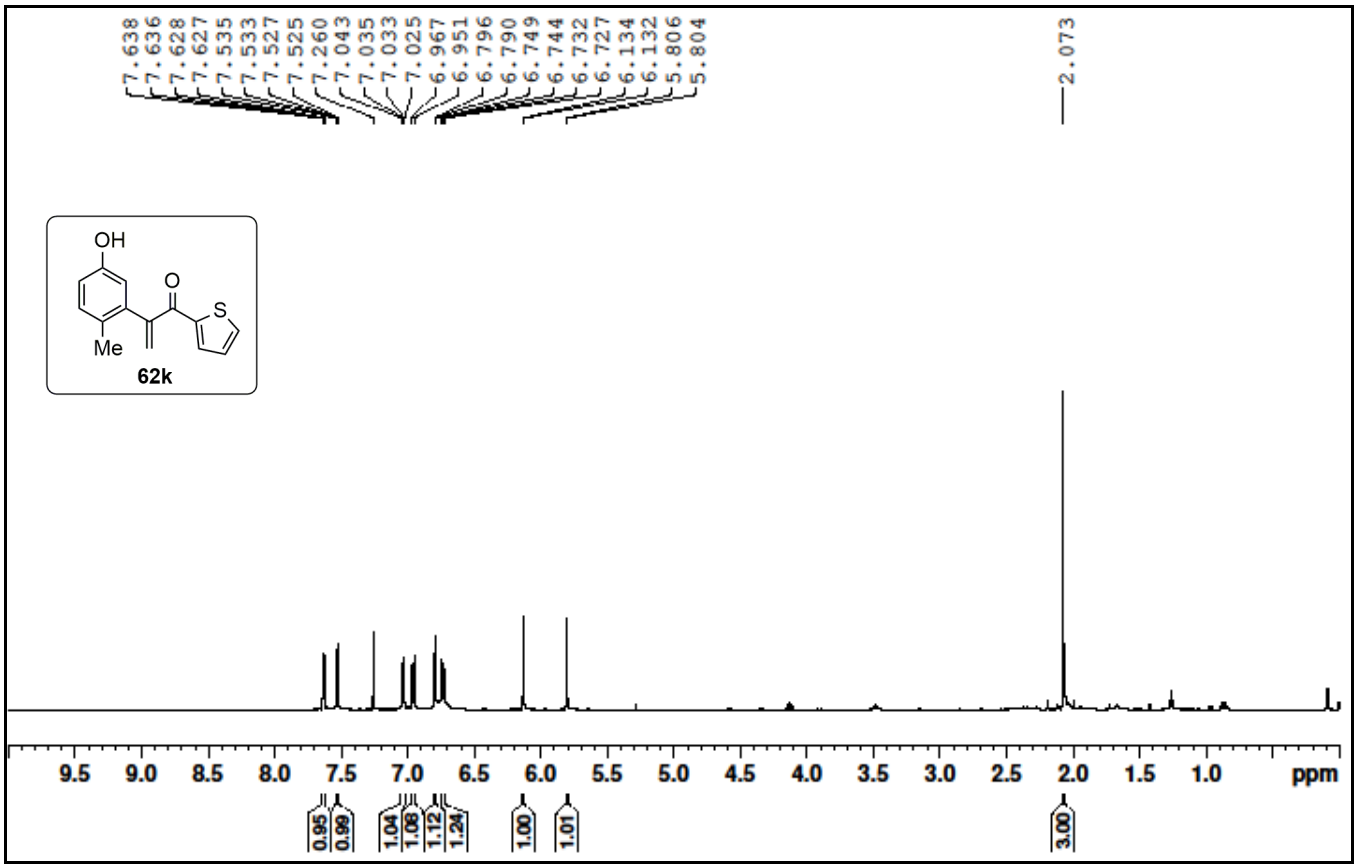
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7.627
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7.533
7.527
7.525
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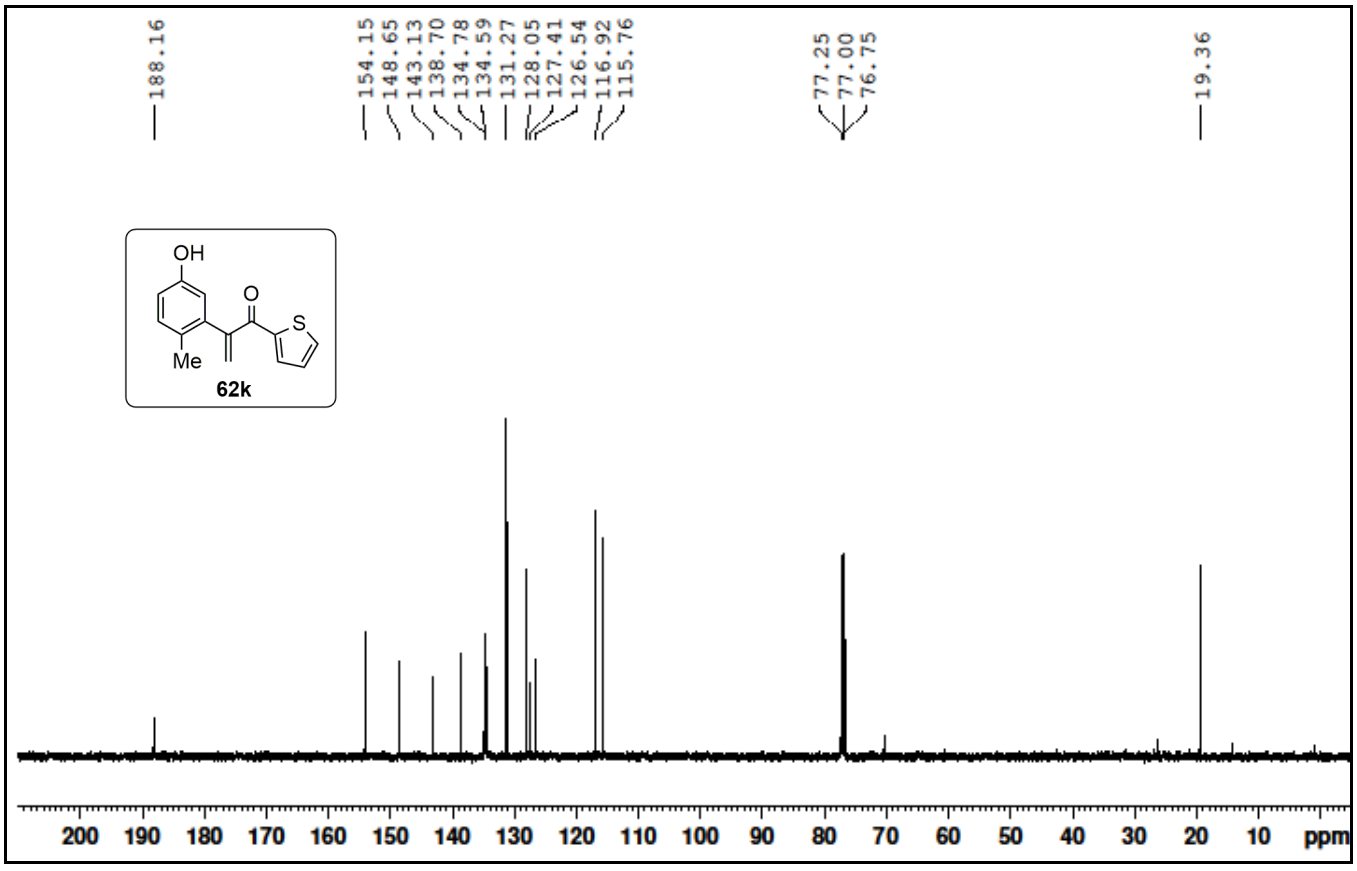
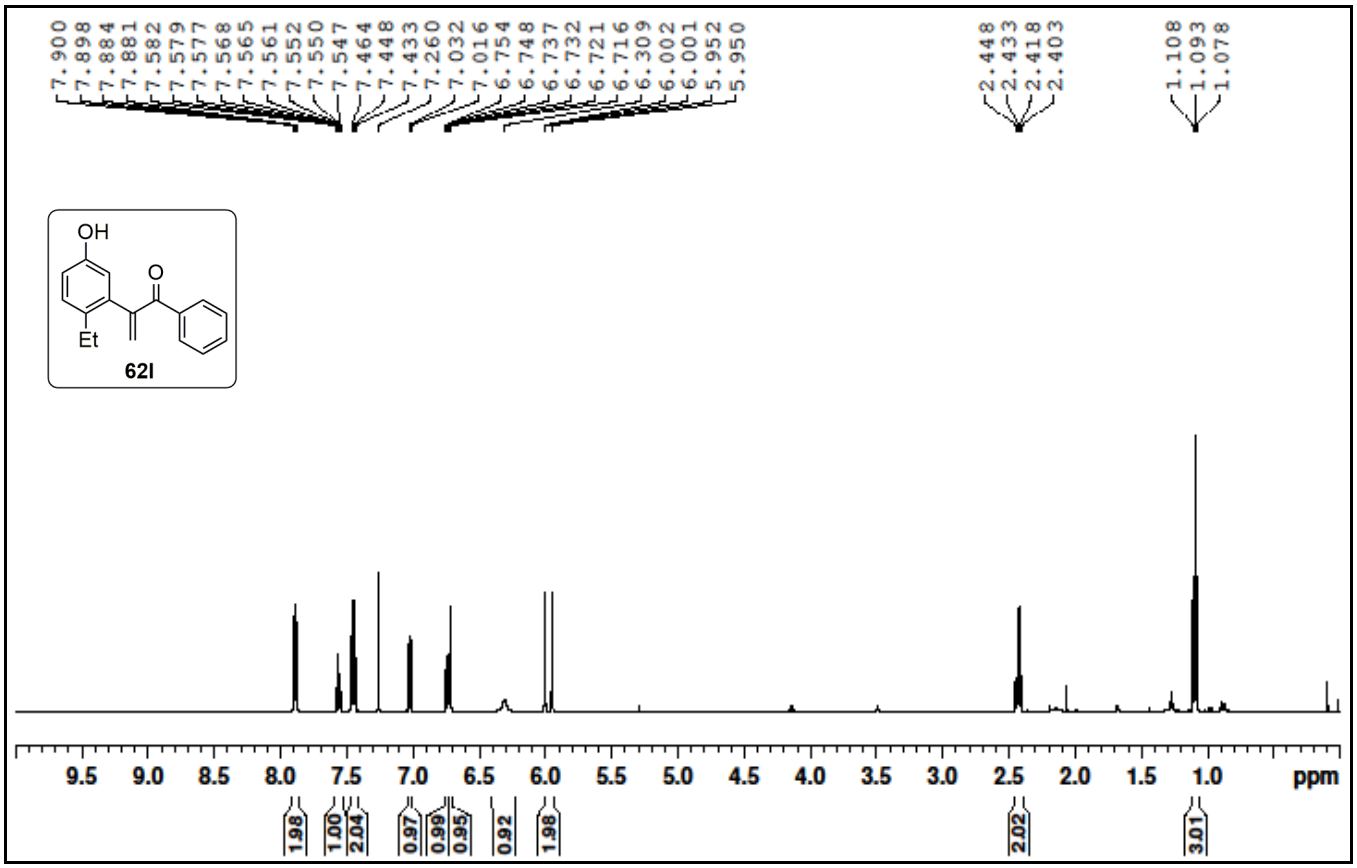
7.035
7.033
7.025
6.967
6.951
6.796
6.790
6.749
6.744
6.732
6.727
6.134
6.132
5.806
5.804
2.073
OH
O
S
Me
62k
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.95
0.99
1.04
1.08
1.12
1.24
1.00
1.01
3.00


188.16
154.15
148.65
143.13
138.70
134.78
134.59
131.27
128.05
127.41
126.54
116.92
115.76
77.25
77.00
76.75
19.36
OH
O
S
Me
62k
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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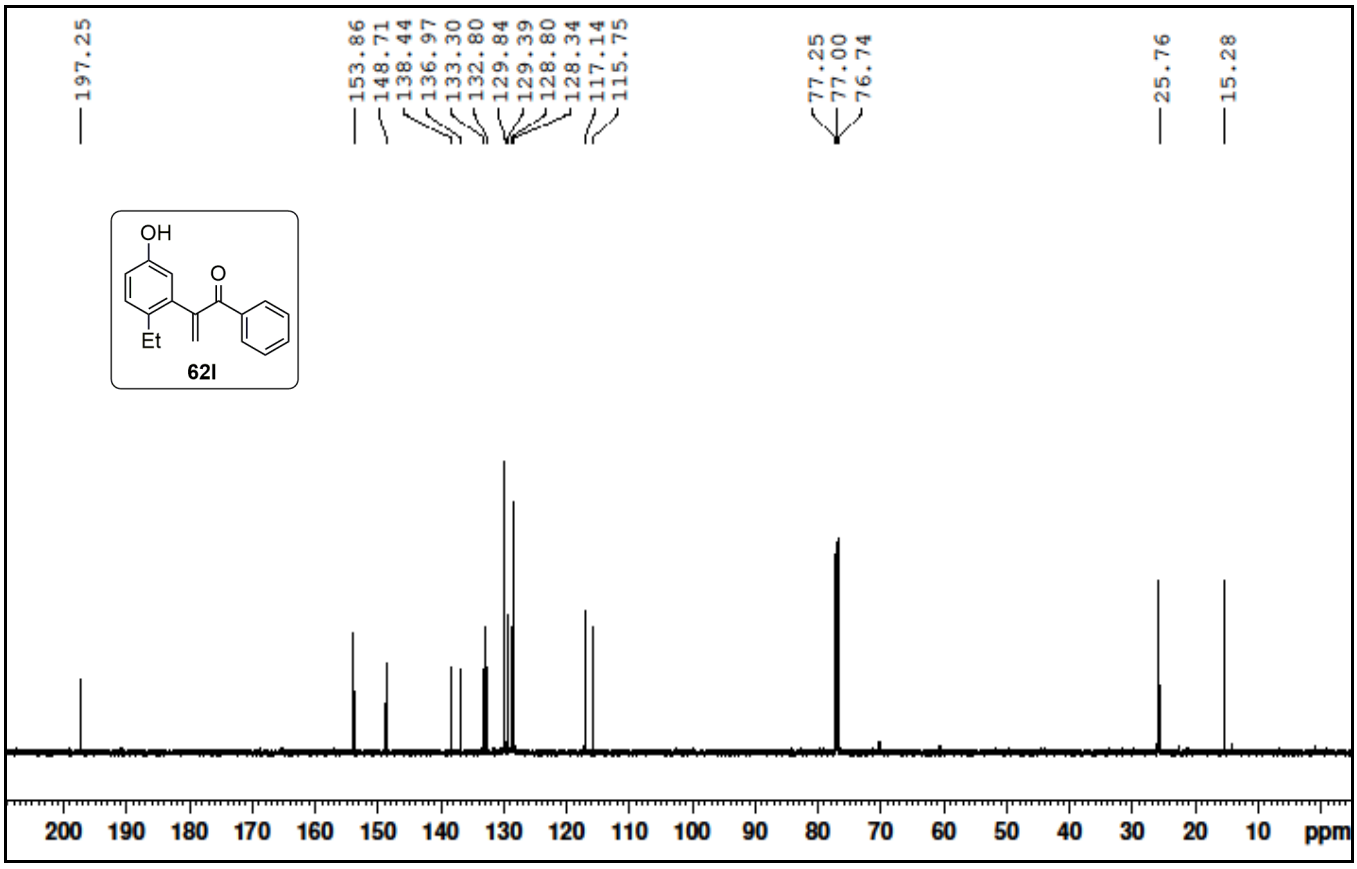
7.884
7.881
7.582
7.579
7.577
7.568
7.565
7.561
7.552
7.550
7.547
7.464
7.448
7.433
7.260
7.032
7.016
6.754
6.748
6.737
6.732
6.721
6.716
6.309
6.002
6.001
5.952
5.950
2.448
2.433
2.418
2.403
1.108
1.093
1.078
OH
O
Et
62l
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.98
1.00
2.04
0.97
0.99
0.95
0.92
1.98
2.02
3.01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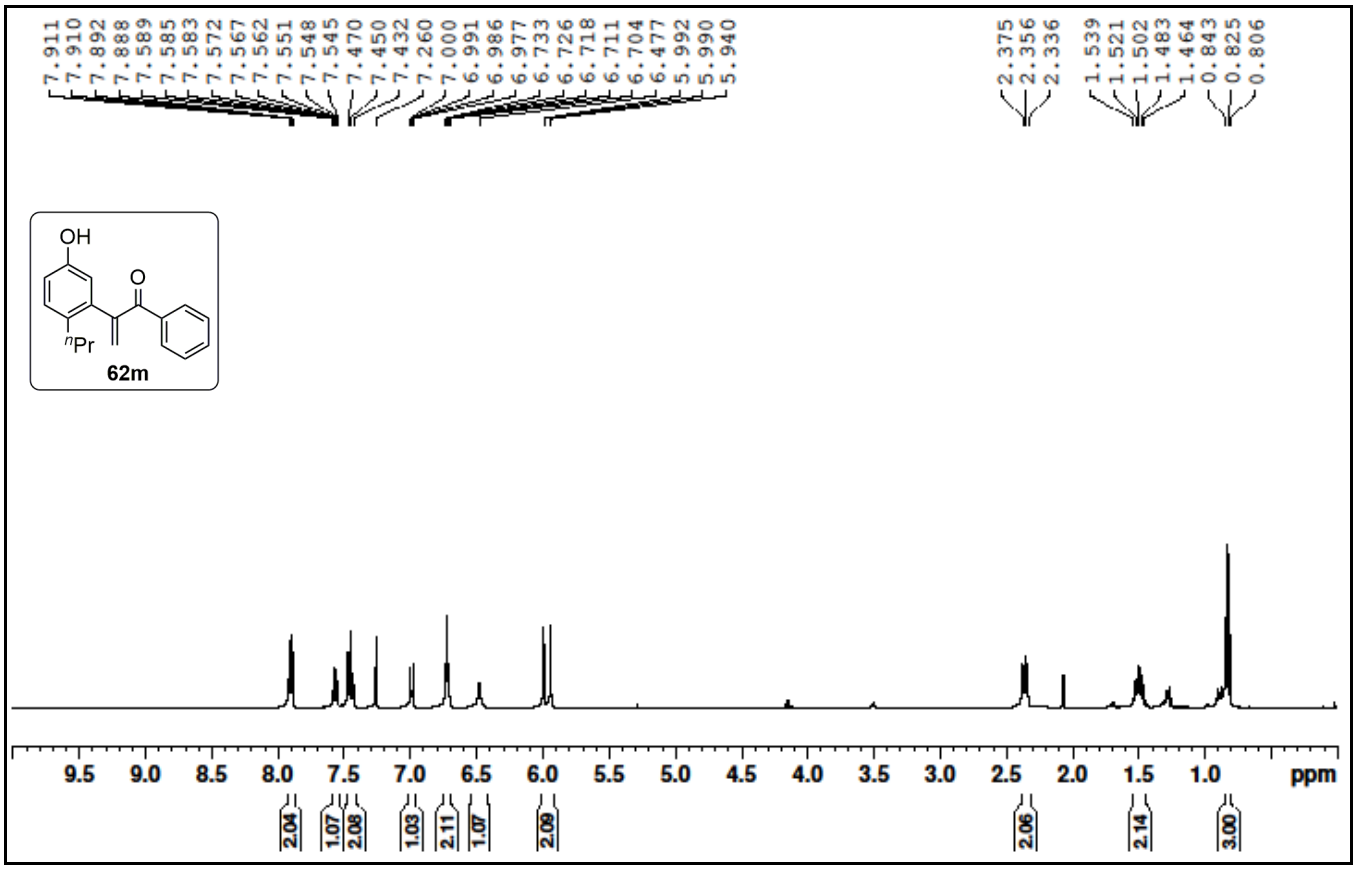
153.86
148.71
138.44
136.97
133.30
132.80
129.84
129.39
128.80
128.34
117.14
115.75
77.25
77.00
76.74
25.76
15.28
OH
O
Et
62l
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.892
7.888
7.589
7.585
7.583
7.572
7.567
7.562
7.551
7.548
7.545
7.470
7.450
7.432
7.260
7.000
6.991
6.986
6.977
6.733
6.726
6.718
6.711
6.704
6.477
5.992
5.990
5.940
2.375
2.356
2.336
1.539
1.521
1.502
1.483
1.464
0.843
0.825
0.806
OH
O
nPr
62m
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
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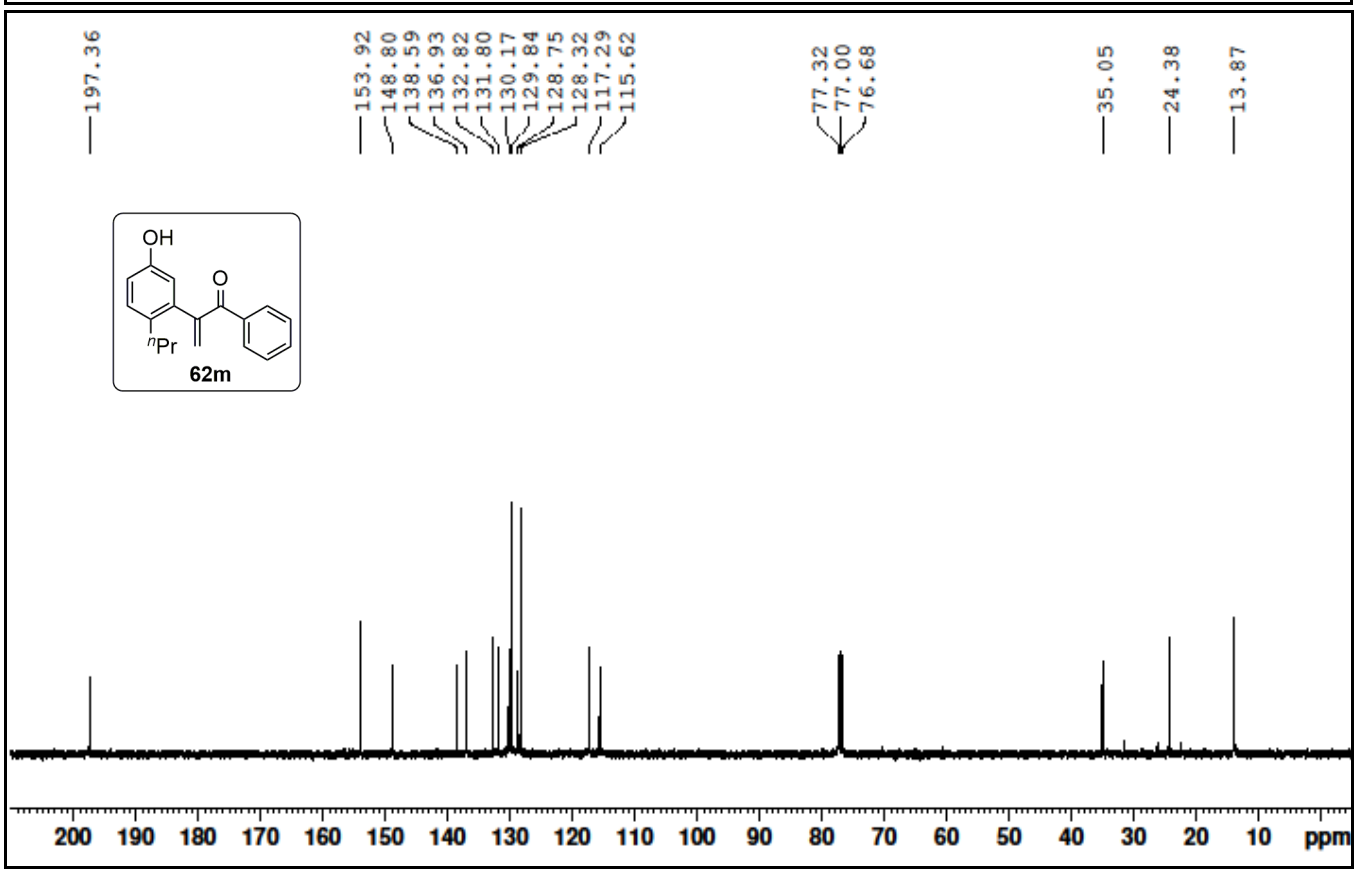
1.07
2.08
1.03
2.11
1.07
2.09
2.06
2.14
3.00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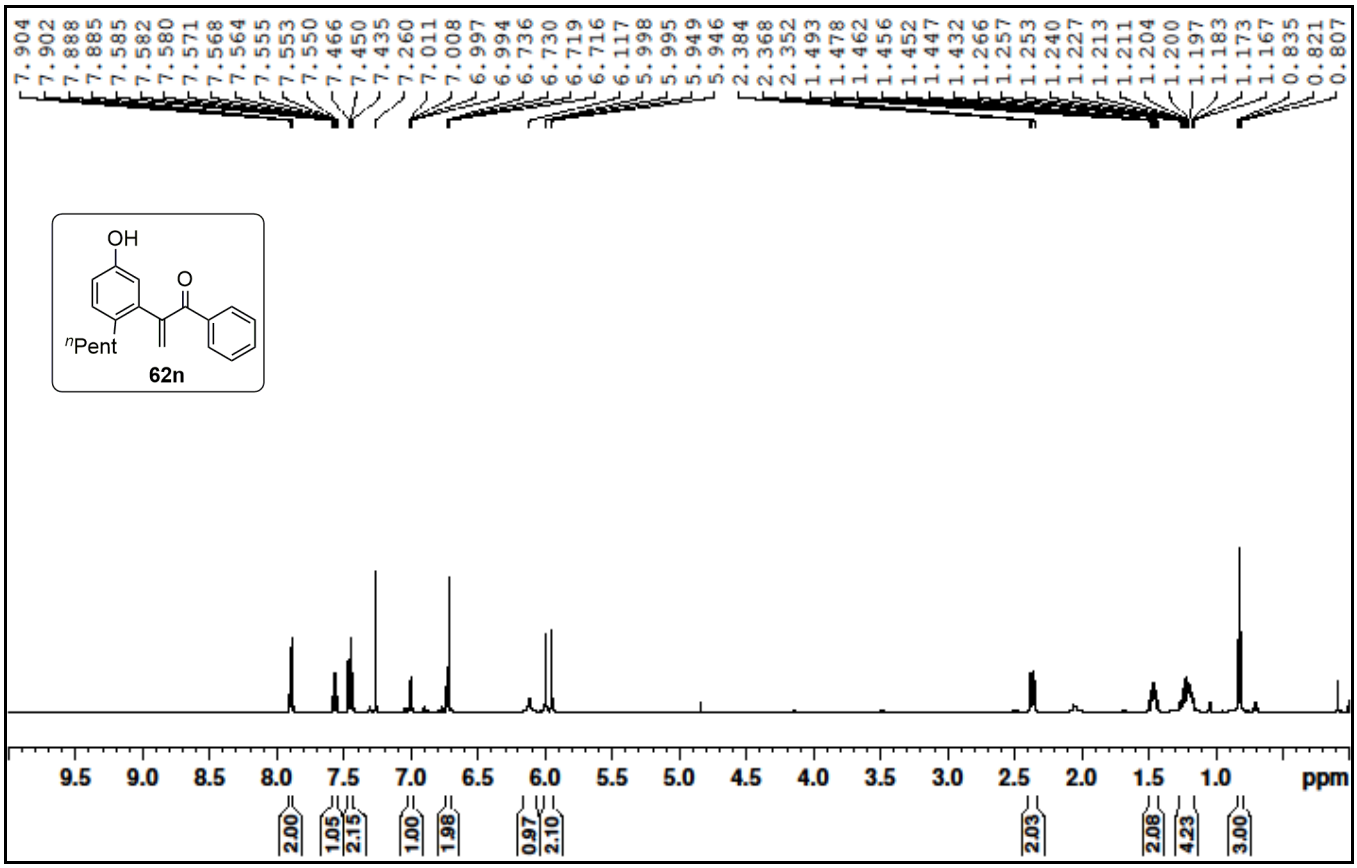
148.80
138.59
136.93
132.82
131.80
130.17
129.84
128.75
128.32
117.29
115.62
77.32
77.00
76.68
35.05
24.38
13.87
OH
O
nPr
62m
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.553
7.550
7.466
7.450
7.435
7.260
7.011
7.008
6.997
6.994
6.736
6.730
6.719
6.716
6.117
5.998
5.995
5.949
5.946
2.384
2.368
2.352
1.493
1.478
1.462
1.456
1.452
1.447
1.432
1.266
1.257
1.253
1.240
1.227
1.213
1.211
1.204
1.200
1.197
1.183
1.173
1.167
0.835
0.821
0.807
OH
O
nPent
62n
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
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0.97
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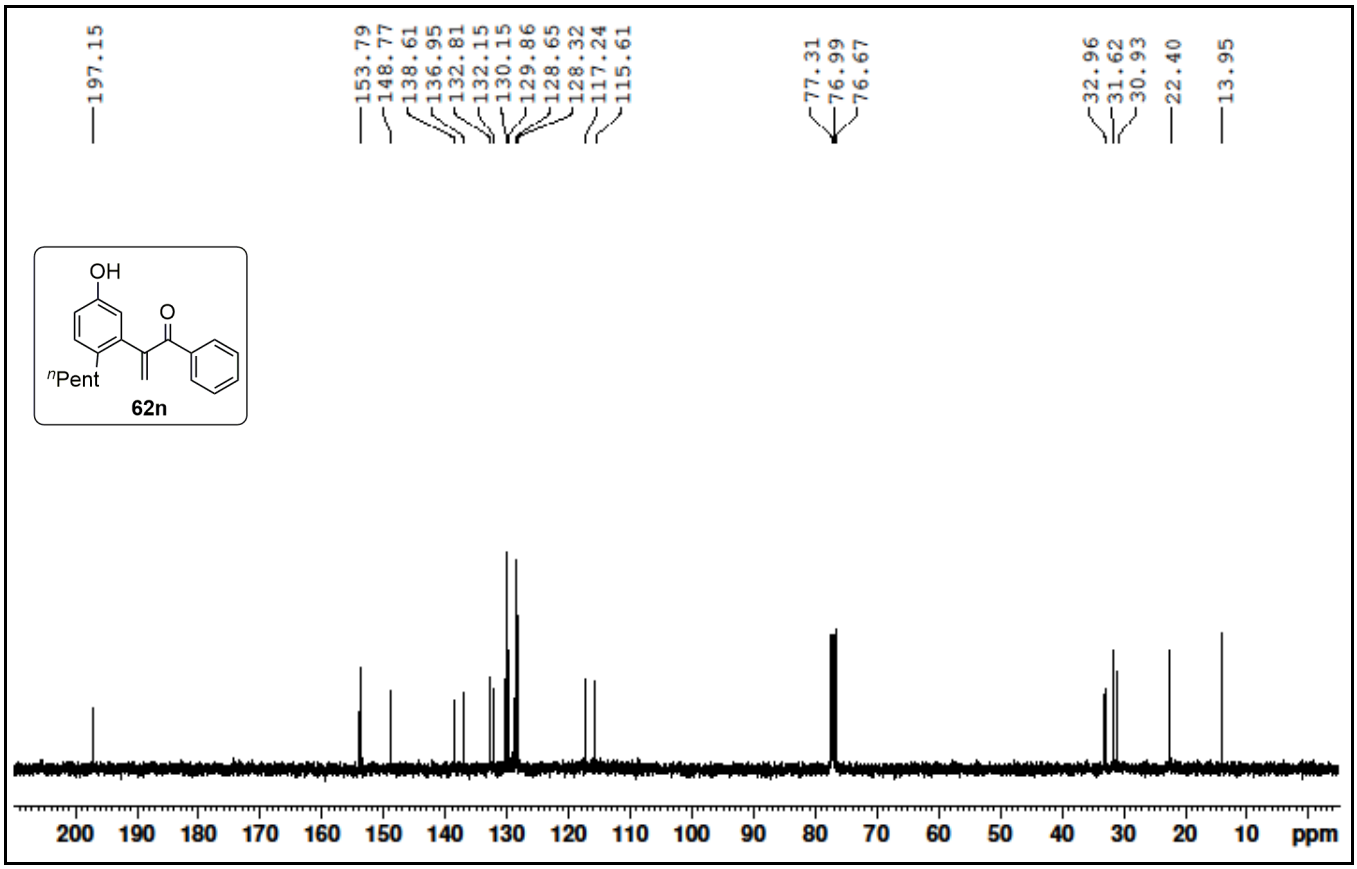
2.08
4.23
3.00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128.32
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115.61
77.31
76.99
76.67
32.96
31.62
30.93
22.40
13.95
OH
O
nPent
62n
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

List of Publications

1. Triphenylphosphine promoted regio- and stereoselective α-halogenation of ynamides: B. Prabagar, Sanatan Nayak, **Rajendra K. Mallick**, R. Prasad and Akhila K. Sahoo, *Org. Chem. Front.* **2016**, *3*, 110-115.

2. Regioselective Synthesis of 2,4,5-Trisubstituted Oxazoles and Ketene Aminals via Hydroamidation and Iodo-Imidation of Ynamides: **Rajendra K. Mallick**, B. Prabagar, and Akhila K. Sahoo* *J. Org. Chem.* **2017**, *82*, 10583−10594.

3. Ag(I)-Catalyzed Cycloisomerization and Cyclization of Ketene Aminals: Construction of Azepine and 1,2-Dihydropyridine Derivatives: Sanatan Nayak, B. Prabagar, Nayan Ghosh, **Rajendra K. Mallick** and Akhila K. Sahoo (*all authors contributed equally*) *Synthesis*, **2017**, *49*, 4261-4271.

4. Umpolung Reactivity of Ynamides: An Unconventional [1,3]-Sulfonyl and [1,5]-Sulfinyl Migration Cascade: B. Prabagar, **Rajendra K. Mallick**, Rangu Prasad, Vincent Gandon,* and Akhila K. Sahoo* *Angew. Chem. Int. Ed.* **2019**, *58*, 2365 –2370.

5. Alkyne Versus Ynamide Reactivity: Regioselective Radical Cyclization of Yne-Ynamides: Shubham Dutta, **Rajendra K. Mallick**, Rangu Prasad, Vincent Gandon,* and Akhila K. Sahoo* *Angew. Chem. Int. Ed.* **2019**, *58*, 2289 –2294.

6. Thioarylative Radical Cyclization of Yne-Dienone: **Rajendra K. Mallick,** Shubham Dutta, Rajeshwer Vanjari, Arnaud Voituriez, and Akhila K. Sahoo* *J. Org. Chem.* **2019**, *84*, 10509−10517.

7. Access to *2H*-Chromenes via Gold-Catalyzed and Keteniminium Induced Dienone-Phenol Rearrangement of Yne-Dienone: **Rajendra K. Mallick**, Shubham Dutta, Manash P. Gogoi and Akhila K. Sahoo (*Manuscript to be Communicated*).

8. Access to α–aryl–α,β–Unsaturated Ketones via Lewis Acid Mediated Meyer-Schuster Rearrangement of Yne-Dienone: **Rajendra K. Mallick**, Tirumaleswararao Guntreddi, and Akhila K. Sahoo* (*Manuscript Under Preparation*).

9. Regioselective Cascade Double Arylation of Ynamide: Shubham Dutta, Rajeshwer Vanjari, **Rajendra K. Mallick**, Vincent Gandon, * and Akhila K. Sahoo* (*Manuscript to be Communicated*).

10. Carbothiolation of Ynamides: Manash Protim Gogoi, B. Prabagar, V. Rajeshwar, **Rajendra K. Mallick** and Akhila K. Sahoo* (*Manuscript Under Preparation*).

Conference Attended

1. A Convenient Protocol for Regio- and Stereoselective α-Halogenation, α-Amidation, and α-Imidation of Ynamides

   Rajendra K. Mallick and Akhila K. Sahoo*

   Poster Presentation at *21st International conference on Organic Synthesis* **(ICOS-21)** held at IIT Bombay, Mumbai, India on **December 11-16, 2016**.

2. Regioselective Synthesis of 2,4,5-Trisubstituted Oxazoles and Ketene Aminals via Hydroamidation, and Iodo-Imidation of Ynamides

   Rajendra K. Mallick and Akhila K. Sahoo*

   Poster Presentation at **National Meeting on Synthetic and Theoretical Chemistry (NMSTC)** held at School of Chemistry, University of Hyderabad, Hyderabad, India on **October 13-14, 2017**.

3. Regioselective Synthesis of 2,4,5-Trisubstituted Oxazoles and Ketene Aminals via Hydroamidation, and Iodo-Imidation of Ynamides

   Rajendra K. Mallick and Akhila K. Sahoo*

   Poster Presentation at **13th Junior National Organic Symposium Trust** (**XIII J-NOST**) held at Department of Chemistry, Banaras Hindu University, India on **November 09-12, 2017**.

4. Regioselective Synthesis of 2,4,5-Trisubstituted-Oxazoles, Ketene Aminals and 2H-Chromenes via Keteniminium Ion Induced Functionalization of Ynamides

   Rajendra K. Mallick and Akhila K. Sahoo*

   Oral Presentation at **14th Junior National Organic Symposium Trust** (**XIV J-NOST**) held at CSIR-Indian Institute of Chemical Technology, India on **28th Nov-1st Dec, 2018.**

5. Diverse Reactivities of Ynamide and Alkynyl Cyclohexadienone: Access to Novel Heterocycles

   Rajendra K. Mallick and Akhila K. Sahoo*

   Oral Presentation at **16th Annual In-House Symposium (CHEMFEST-2019)** held at School of Chemistry, University of Hyderabad, India on **February 22-23, 2019.**

6. National Symposium on Transcending Frontiers in Organic Chemistry-2014 (TFOC-2014) held at CSIR-NIIST, Trivandrum, India on **October 09-11, 2014** (**Attended**).
7. Winter School on Computational Chemistry held at School of Chemistry, University of Hyderabad, India on **29th Dec 2014-10th Jan 2015** (**Attended**).
8. ACS on Campus held at School of Chemistry, University of Hyderabad, India on **January 29, 2016** (**Attended**).

Biographical Sketch

Rajendra Kumar Mallick was born in Paripada Village, Jajpur (dist), Odisha, India in 1991. He did primary schooling at Kansaldiha Srima High School (10th standard), Chasakhand in 2006. He finished Intermediate in Science at J. B. College, Bitana in 2008. Then he received BSc degree (Chemistry honors) from N. C. Autonomous College, Jajpur, Odisha in 2011 where he gained some interest in chemistry. He obtained Master's degree in Chemical Sciences (Organic Chemistry) in 2013 from Ravenshaw University, Cuttack. In June-2013 he cleared UGC-JRF (93 Rank) and subsequently qualified GATE in February 2014. In March-2014, he started doctoral research at the School of Chemistry, University of Hyderabad under the guidance of Prof. Akhila Kumar Sahoo, where he works on ***Cyclization and Rearrangement Strategies of Ynamide/Yne-Dienone***.

Cyclization and Rearrangement Strategies of Ynamide/ Yne-Dienone

by Rajendra Kumar Mallick

Submission date: 25-Sep-2019 03:37PM (UTC+0530)
Submission ID: 1179700922
File name: Thesis for plagiarism.pdf (8.27M)
Word count: 13047
Character count: 72849

Cyclization and Rearrangement Strategies of Ynamide/ Yne-Dienone

ORIGINALITY REPORT

32%	1%	32%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Rajendra K. Mallick, B. Prabagar, Akhila K. Sahoo. "Regioselective Synthesis of 2,4,5-Trisubstituted Oxazoles and Ketene Aminals via Hydroamidation and Iodo-Imidation of Ynamides", The Journal of Organic Chemistry, 2017 Publication	15%
2	Rajendra K. Mallick, Shubham Dutta, Rajeshwer Vanjari, Arnaud Voituriez, Akhila K. Sahoo. "Thioarylative Radical Cyclization of Yne-Dienone", The Journal of Organic Chemistry, 2019 Publication	12%
3	Majumdar, Nilanjana, Nanda Dulal Paul, Sutanuva Mandal, Bas de Bruin, and William D. Wulff. "Catalytic Synthesis of 2H-Chromenes", ACS Catalysis Publication	1%
4	Debayan Roy, Prabhakararao Tharra, Beeraiah Baire. "Intercepted Meyer-Schuster	1%

Rearrangements in Organic Synthesis", Asian Journal of Organic Chemistry, 2018
Publication

5	Submitted to University of Hyderabad, Hyderabad Student Paper	<1%
6	Imtiaz Khan, Aliya Ibrar, Syeda Aaliya Shehzadi. "Building molecular complexity through transition-metal-catalyzed oxidative annulations/cyclizations: Harnessing the utility of phenols, naphthols and 1,3-dicarbonyl compounds", Coordination Chemistry Reviews, 2019 Publication	<1%
7	Rajeshwer Vanjari, Shubham Dutta, Manash P. Gogoi, Vincent Gandon, Akhila K. Sahoo. " Gold-Catalyzed -1,2-Difunctionalization of Ynamides via Nitrile Activation ", Organic Letters, 2018 Publication	<1%
8	Vadim P. Boyarskiy, Dmitry S. Ryabukhin, Nadezhda A. Bokach, Aleksander V. Vasilyev. "Alkenylation of Arenes and Heteroarenes with Alkynes", Chemical Reviews, 2016 Publication	<1%
9	Xian-Rong Song, Bo Song, Yi-Feng Qiu, Ya-Ping Han, Zi-Hang Qiu, Xin-Hua Hao, Xue-Yuan	<1%