

Harnessing Pyridyl-Sulfoximine Enabled Functionalization of Multiple C–H Bonds with Bifunctional Reagents

A Thesis Submitted for

the Degree of

DOCTOR OF PHILOSOPHY

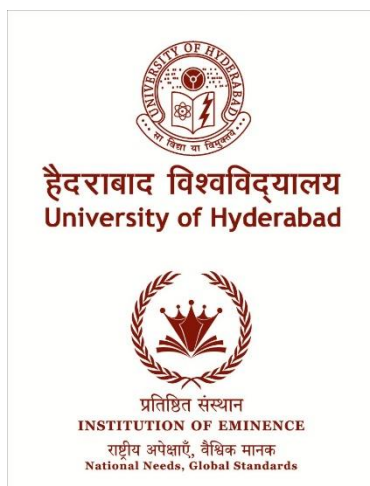
in

CHEMISTRY

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To

My Family

&

Well-wishers

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DECLARATION

I hereby declare that the matter embodied in the thesis entitled "Harnessing Pyridyl-Sulfoximine Enabled Functionalization of Multiple C-H Bonds with Bifunctional Reagents" is the result of an investigation carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India, under the supervision of Prof. **Akhila Kumar Sahoo**.

In keeping in mind, the general practice of reporting scientific observations, due acknowledgements have been made on the basis of the findings of other investigations. Any omission, that might have occurred by oversight or error, is regretted. This research work is free from plagiarism. I hereby agree that my thesis can be deposited in Shodhganga/INFLIBNET. A report of plagiarism from the University Librarian is enclosed.

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April, 2024



CERTIFICATE

This is to certify that the thesis entitled **“Harnessing Pyridyl-Sulfoximine Enabled Functionalization of Multiple C-H Bonds with Bifunctional Reagents”** submitted by **Arghadip Ghosh** holding registration number **17CHPH46** in partial fulfilment of the requirements for award of Doctor of Philosophy in the School of Chemistry is a bonafide work carried out by him under my supervision and guidance.

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

Parts of the thesis have been:

A. Published in the following publication

- i) Ghosh, A.; Grimblat, N.; Sau, S.; Saha, A.; Gandon, V.; Sahoo, A. K. Palladium (II)-Catalyzed Annulative Difunctionalization of Two Inert C(Sp³)-H Bonds by a Bifunctional Reagent. *ACS Catal.* **2023**, *13*, 7627-7636.
- ii) Ghosh, A.; Kondalarao, K.; Saha, A.; Gandon, V.; Sahoo, A. K. A Three-Component Arene Difunctionalization: Merger of C(Sp³)/(Sp²)-H Bond Addition. *Angew Chem Int Ed* **2023**, *62*, e202314395.
- iii) Ghosh, A.; Kondalarao, K.; Sahoo, A. K. δ -Annulative 1,1-Difunctionalization of Unactivated Alkenes: Synthesis of α -Substituted Isoindolinones [manuscript under preparation]
- iv) Ghosh, A.; Sahoo, A. K. Double Functionalization of Two Distinct Inert C-H Bonds. [manuscript under preparation]
- v) Ghosh, A.; Sahoo, A. K. Chelation Assisted C-H Activation/Annulation: Construction of Seven-Membered Heterocycles [manuscript under preparation]

B. Presented in the following conferences

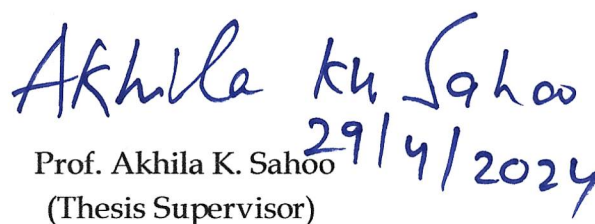
1. ChemFest-2022; 2. FCASI-2023; 3. J-NOST Conference-2023.

Further, the student has passed the following courses towards fulfilment of course work requirements for Ph.D.

Course code	Name	Credits	Pass/Fail
CY-801	Research Proposal	4	Pass
CY-805	Instrumental Methods A	4	Pass
CY-806	Instrumental Methods B	4	Pass


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Arghadip Ghosh

List of Abbreviations

AcOH	acetic acid
Ac	acetyl
Ar	aryl
ABFR	ambiphilic bifunctional reagent
AMLA	ambiphilic metal-ligand activation
Ag	silver
α	alpha
aq	aqueous
β	beta
BFR	bifunctional reagent
BQ	1,4-benzoquinone
Br ₂	bromine
br	broad
BCBs	bicyclobutanes
BCl ₃	boron trichloride
<i>n</i> Bu	<i>n</i> -butyl
<i>t</i> Bu	<i>tert</i> -butyl
Bz	benzoyl
°C	degree celsius
cat.	catalyst
calcd	calculated
¹³ C NMR	carbon-13 nuclear magnetic resonance spectroscopy
CH ₃ CN	acetonitrile
CHCl ₃	chloroform
CMD	concerted metalation–deprotonation
CD ₃ I	iodomethane d ³

CuI	copper iodide
<i>m</i> -CPBA	<i>m</i> -chloroperbenzoic acid
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
dd	doublet of doublet
ddd	doublet of doublet of doublet
dt	doublet of triplet
bd	broad doublet
DG	directing group
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DMPU	<i>N,N'</i> dimethylpropyleneurea
DIPA	diisopropylamine
DEA	diethanolamine
DFT	density functional theory
dt	doublet of triplet
δ	delta
EDC.HCl	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
equiv	equivalent
Et	ethyl
e.g.	exempli gratia
ESI	electron spray ionization
EWG	electron-withdrawing group
E	trans

FT-IR	fourier transform infrared spectroscopy
Eq	equation
g	gram
γ	gamma
h	hour
^1H NMR	proton nuclear magnetic resonance spectroscopy
HRMS	high-resolution mass spectroscopy
Hz	hertz
HCl	Hydrochloric acid
IPA	isopropyl alcohol
J	coupling constant in hertz
$\text{K}_2\text{S}_2\text{O}_8$	potassium persulfate
KI	potassium iodide
KIE	kinetic isotope effect
K_3PO_4	tripotassium phosphate
MeOH	methanol
MPAA	Mono protected amino acid
MPyS	methyl-2-pyridyl sulfoximine
mg	milligram
m.p.	melting point
mmol	millimole
mL	milliliter
m	meta
NHC	N-heterocyclic carbene
N_2	nitrogen
Nu	nucleophile
NaHSO_3	sodium hydrogen sulfite

Na ₂ SO ₄	sodium sulfate
NaBrO ₃	sodium bromate
NaCl	sodium chloride
Na ₂ S ₂ O ₃	sodium thiosulfate
Pd	palladium
PhI(OAc) ₂	phenyl iodo diacetate
Uv	ultra violet
UAA	unnatural amino acid
Piv	pivaloyl
<i>n</i> Pr	n-propyl
rt	room temperature
Ru	ruthenium
Rh	rhodium
R _f	retention factor
TBHP	<i>tert</i> -butyl hydroperoxide
td	triplet of doublets
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxy
THF	tetrahydrofuran
TLC	thin-layer Chromatography
TM	transition metals
TMS	trimethylsilyl
Ts	tosyl
μm	micromolar
μl	microliter

Chapter 1

Introduction to C–H Activation, and the Merging of Bifunctional Reagent-Enabled Transformations

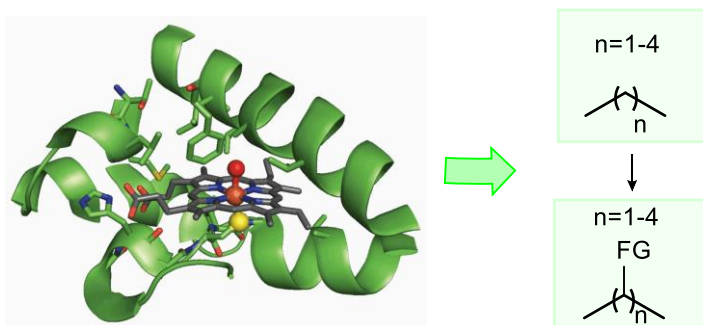
Abstract

C–H bonds are ubiquitous; therefore, development of expedient transformations by activating C–H bonds are valuable. However, selective activation and functionalization of C–H bonds using transition metal catalysts pose formidable challenges due to low reactivity, and selectivity; especially in the case of aliphatic C–H bonds, and the activation of remote C(sp²)–H bonds. Moreover, these challenges are compounded by distance and geometry concerns. Over the past two decades, directing groups have been largely used for C–H bond activation. Nevertheless, in recent times, not only the directing group but also the ligand plays significant role in making proximal and distal C–H activation feasible. Finally, the importance, challenges, and developments associated with C(sp³)–H activation, as well as remote C(alkenyl)–H activation, are briefed. In addition, the use of bifunctional reagents in the C–H activation domain is narrated.

1.1. Introduction

A curious mind is often inspired by nature and its functioning. Monitoring natural processes has consistently provided new understanding, and applying these insights to the scientific world has ultimately benefited mankind. In this vein, monitoring the reactivity of metalloenzymes like Cytochrome P450 in biological systems has given us an understanding that it can functionalize alkane chains with high selectivity, both in terms of regio- as well as enantioselectivity. Therefore, continuous efforts have been and continue to be applied to mimic that reactivity synthetically.

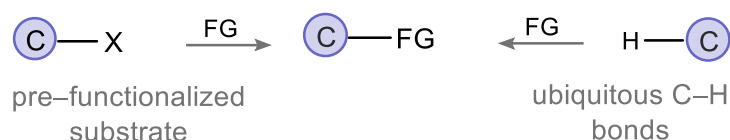
However, in this paradigm, the catalytic C–H activation strategy stands as one of the pioneering fields. In 1968, Jack Halpern, an inorganic chemist, stated: “To develop a successful approach



for activation of C–H bonds, particularly saturated hydrocarbons, is one of the most important and challenging in the entire field of homogeneous catalysis.”¹ Later, in 1995, a special issue in *‘Accounts of Chemical Research’* depicted 8 Holy Grails of chemistry. Among them, one of the Holy Grails was a homogeneous metal complex guided selective intermolecular C–H bond activation written by Robert G. Bergman. According to him “one Holy Grail is not simply to find new C–H activation reactions, but to obtain an understanding of them that will allow the development of selective transformations of C–H bonds.”

In this context, the direct functionalization of unactivated C–H bonds presents a powerful avenue in synthetic chemistry, offering wide potential for constructing new molecules in step and atom efficiently.¹ Conventionally, introducing functional groups into molecules necessitates the use of pre-functionalized substrates (Scheme 1.1, left), leading to additional synthetic steps and the generation of byproducts such as inorganic salts or acids in transition–metal–catalyzed cross-coupling reactions.^{2,3}

In stark contrast, the direct functionalization of inert C–H bonds bypasses the need for pre-functionalized compounds, exemplifying a



Scheme 1.1. fundamental in making new bond

streamlined and environmentally favorable approach to chemical transformations.¹ Given the ubiquitous nature of C–H bonds in organic molecules, the development of innovative strategies for their direct functionalization (Scheme 1.1, right) is highly sought-after. Such advancements promise to significantly enhance the efficiency and sustainability of synthetic methods in organic chemistry^{1,4}

Meanwhile, the direct functionalization of C–H bonds hinges on their activation, yet several fundamental challenges impede the activation of inert C–H bonds. Foremost among these challenges is selectivity, as organic molecules encompass a myriad of 1°, 2°, 3°-alkyl/*o*-, *m*-, *p*-aryl C–H bonds (Table 1.1). Moreover, the presence of aromatic and/or alkyl C–H bonds with closely matched bond dissociation energies

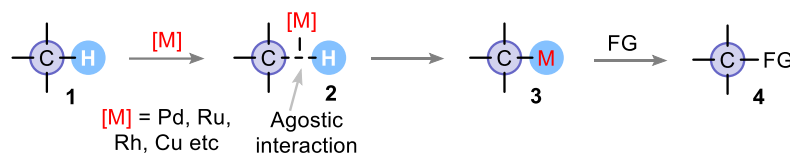
Type of C-H	C(sp ³) _{allylic}	C(sp ³) _{3°}	C(sp ³) _{2°}	C(sp ³) _{1°}	C(sp ²) _{vinyl}	C(sp ²) _{arene}	C(sp)
structure							
BDE	361.1	389.9	397.9	410.8	460.2	473.0	552.2
pK _a	43	50	50	50	44	43	25

Table 1.1. Various C-H bonds dissociation energy

and pK_a's poses hurdles for achieving regio- and chemoselective C–H activations.¹ The second challenge lies in the low reactivity substantial kinetic barrier associated with homo- or heterolytic cleavage of C–H bonds. These bonds are inert, owing to factors such as high bond dissociation energies (typically in the range of 90–110 kcal/mol), low energy HOMOs, high energy LUMOs, and weak polarization (Table 1.1). Intriguingly, the use of transition-metal catalysts effectively activates C–H bonds by tackling these crucial issues.^{1,5}

Merging C–H Bond Activation with bifunctional reagent...

Thus, the C–H activation can be conceptualized as the insertion of a transition-metal into



Scheme 1.2. Metal insertion to C–H bond

unreactive C–H bonds of arenes, alkanes, or alkyl chains, forming a more reactive metal-carbon bond-bearing species. It typically initiates with the interaction of a transition-metal with the C–H bond, yielding a transient σ -complex. This metal-to-C–H interaction weakens the C–H bond by agostic interaction. This agostic interaction facilitates the formation of a M–C bond with concurrent cleavage of the C–H bond. Furthermore, functionalization of the intermediate with electrophiles or nucleophiles leads to the formation of diverse C–C and C–X (X = heteroatom) bonds (Scheme 1.2).^{1,5}

1.2. Mechanism of C–H Activation

The development of a new carbon-metal bond via C–H activation hinges on the bond environment, transition-metal catalyst, and the ligands used in the reaction. It has been categorized in two segments, firstly, initial C–H insertion happens into the ligand of a transition-metal complex, often termed as outer sphere mechanism. Secondly, the inner sphere mechanism occurs through the coordination of the C–H bond with the metal center, resulting in the formation of an organometallic complex where the hydrocarbyl unit becomes integrated within the inner sphere of the metal upon C–H bond cleavage. There is ongoing discussion regarding the terminology "C–H functionalization" and "C–H activation" often used interchangeably. However, there is a growing agreement to reserve the latter term specifically for describing the inner sphere mechanism.

1.2.1. Outer sphere mechanism

In the process of alkane oxidation, bio-inspired or enzymatic metal-oxo species, often referred to as rebound mechanisms, facilitate C–H activation via a metalloradical pathway.^{5,6} Initially, hydrogen radical abstraction is catalyzed by the metal-oxo species precursor, followed by a rapid rebound to form a metal-hydroxo

intermediate (Scheme 1.3). Similarly, in Scheme 1.4, the N-atom of metal-nitrenes or the C-atom of metal-carbenes directly interacts with a C–H bond, leading to the simultaneous formation of H–N and C–N bonds or H–C and C–C bonds via metal dissociation. This interaction pathway is illustrated in Scheme 1.4.

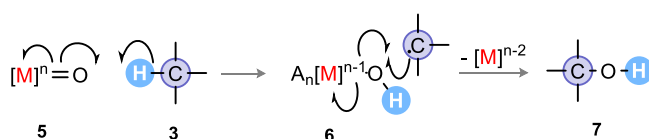
Key features of outer sphere mechanisms:

- i) No direct involvement of metal with C–H bond.
- ii) Ligands associated with metal are probably the important factor for the outer sphere mechanism.

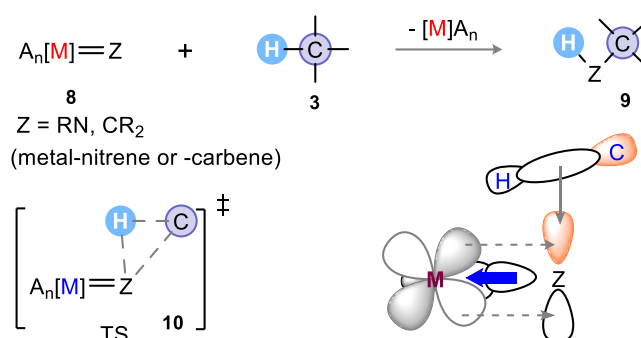
1.2.2. Inner sphere mechanisms

Inner sphere mechanism has been classified into three modes of transition metal-mediated C–H activation; a) oxidative addition,^{5,7} b) σ -bond metathesis,^{5,8} and c) electrophilic substitution^{5,9}. However, these distinctions can sometime be ambiguous. Logically the approach involves through the charge transfer interactions between the metal centre and the C–H bond. Charge transfer can occur in two ways: (i) reverse CT,

where electron transfer happens from the metal-based filled $d\pi$ orbital to the σ^* orbital of the coordinated C–H bond, and (ii) forward CT, where electron transfer occurs from the occupied σ orbital of the C–H bond to an empty metal-based $d\sigma$ orbital. These interactions weaken the C–H bond and eventually cleavage the bond. Based on the electronic nature of the resulting transition state, C–H activation can be categorized as either electrophilic or nucleophilic. This distinction depends on whether the transition state is electrophilic or nucleophilic nature. A qualitative molecular orbital (M.O.) diagram is depicted in Figure 1.1.



Scheme 1.3. Radical rebound mechanism



Scheme 1.4. Metal- nitrene and metal-carbene insertions

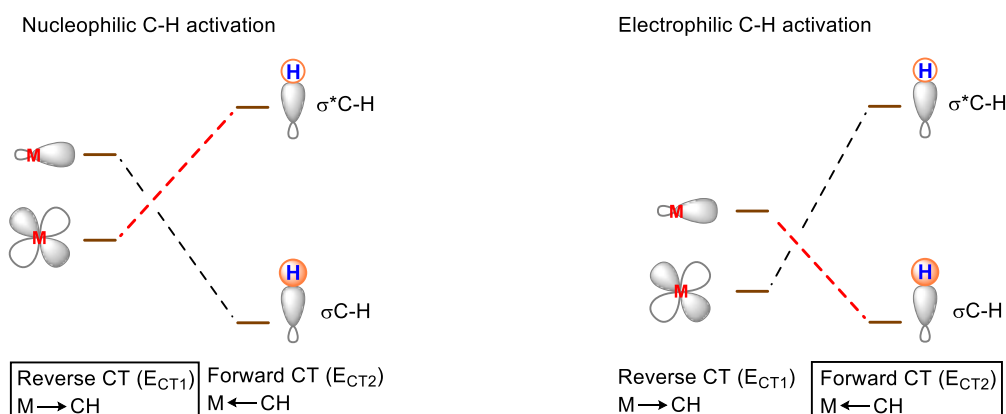


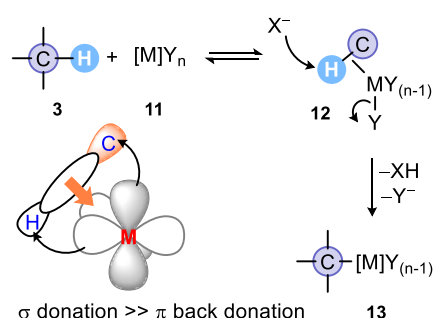
Figure 1.1. Frontier orbital interaction for nucleophilic (left side) and electrophilic (right side) mechanism

Key features for inner sphere mechanism:

- Cleavage of a carbon–hydrogen bond to afford a transition metal alkyl/aryl species. Therefore, the direct involvement of metal is obvious.
- This mechanism is often formed of a discrete organometallic intermediate and the structural and electronic requirements of this intermediate dictate the regio- and stereoselectivity of functionalization. These transformations often proceed with high selectivity for the less sterically hindered C–H bonds of a molecule; however, other factors, including the ligand environment at the metal center and the mechanism of the C–H bond cleavage step, can also influence selectivity in these systems.

1.2.2.1. Electrophilic and nucleophilic C–H activation (Oxidative addition) ^{5,7}

Late transition-metals with high oxidation states, such as Ru(II), Pd(II), Pt(II), Rh(III), and Ir(III), typically exhibit electron-deficient characteristics due to their low-lying



Scheme 1.5. Mechanism of Electrophilic substitution

$d\sigma$ and $d\pi$ orbitals. Consequently, when interacting with C–H bonds, these metals predominantly engage in forward charge transfer (CT). This forward CT arises from the donation of electrons from the occupied σ orbital of the C–H bond to the vacant $d\sigma$ orbital of the metal center, resulting in an electrophilic metal complex.

Conversely, the transition-metal complexes with high electron density, characterized by high-energy $d\sigma$ and $d\pi$ orbitals, favor reverse charge transfer. In this scenario, electrons are transferred from the metal-based filled $d\pi$ orbital to the σ^* orbital of the coordinated C–H bond, leading to a nucleophilic metal complex.

The nature and oxidation state of the metal complex dictate whether the C–H activation process is electrophilic or nucleophilic under the inner sphere mechanism. For electron-poor late transition metals, electrophilic activation predominates. Here, initial coordination of the C–H bond to the metal center facilitates strong σ -donation, while weak π back

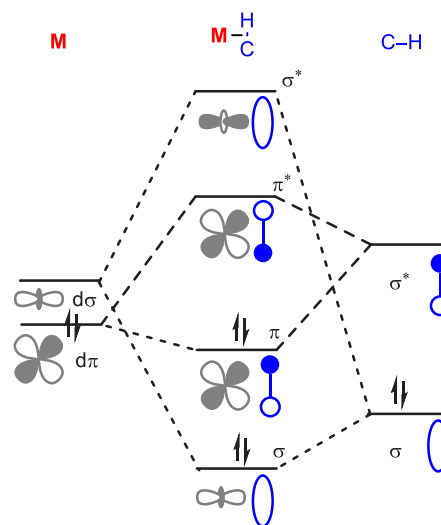
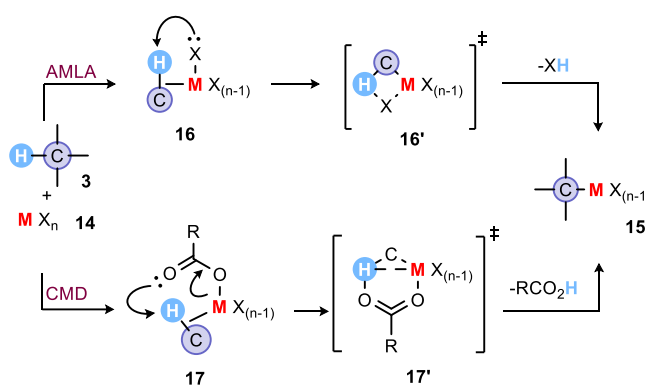
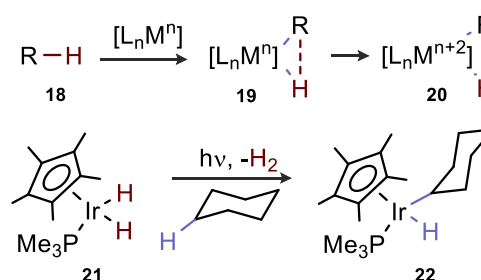


Figure 1.2. MO diagram of oxidative addition



Scheme 1.6. Ambiphilic concerted mechanism



Scheme 1.7. C–H Activation *via* oxidative

donation from the metal promotes heterolytic cleavage of the C–H bond, which is often assisted by an external anion (see Scheme 1.5).

1.2.2.2. Ambiphilic concerted C–H activation

The inner sphere mechanism involves intramolecular deprotonation, facilitated by a cyclic and concerted process with the assistance of heteroatom-based ligands. These ligands, which can include bridging species such as carbonate anions (CO_3^{2-}), acyloxy groups (RCO_2^-), halides (X^-), or alkoxy anions (RO^-), play a crucial role in guiding the reaction through various pathways. These pathways are known by different names such as concerted metalation deprotonation (CMD),

ambiphilic metal-ligand activation (AMLA), internal electrophilic substitution (IES), or 1,2-addition pathways (see Scheme 1.6). The process is often influenced by hydrogen bonding interactions between the H–C proton and lone pairs on the ligand, typically oxygen-based. This interaction biases proton abstraction, sometimes through agostic interactions, where the electron density of the C–H bond distorts towards the metal center. This distortion is facilitated by electronic interactions between the σ orbital of the C–H bond and the d_{π} orbital of the metal, often resulting in the formation of three-centered two-electron bonds. A qualitative molecular orbital (MO) interaction diagram for C–H bond activation via oxidative addition is depicted in Figure 1.2.

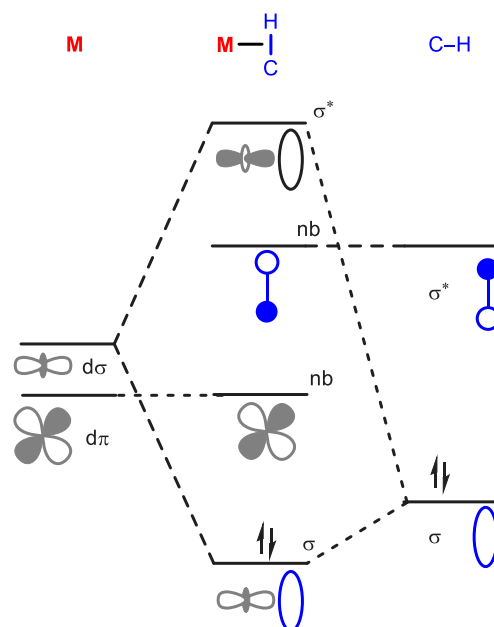
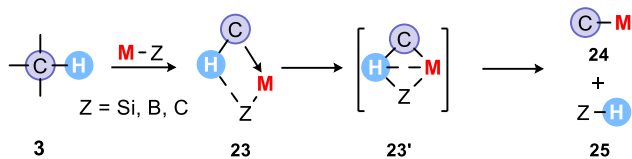


Figure 1.3. MO diagram of sigma bond metathesis

1.2.2.3. Sigma-bond metathesis^{5,8}

Transition metals in high oxidation states, particularly those with early d^0 configurations, lack d electrons and can undergo oxidative addition (OA). Consequently, they exhibit a tendency for σ -bond metathesis with

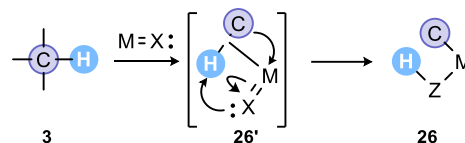


Scheme 1.8. Metathesis by the assistance of σ -complex

C–H bonds. This process involves a concerted four-electron transition state resembling a kite, wherein the metal's oxidation state remains unchanged (Scheme 1.8). Additionally, transition metal with d^4 to d^8 configurations can participate in σ -bond metathesis. These fragments possess vacant sites, allowing them to form stable σ -adducts before and after metathesis, a mechanism termed σ -complex-assisted metathesis (σ -CAM) (Figure 1.3).

1.2.2.4. 1,2-Addition mechanism^{5,9}

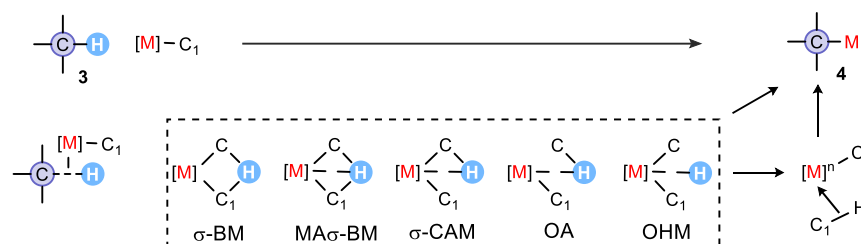
The final step of C–H activation, is termed 1,2-addition. This process involves the addition of C–H bond from compound **3** across the M–X bond, yielding compound **26'** via a



Scheme 1.9. 1,2-addition mechanism

four-centered species. While bearing similarities to σ -BM, this process differs in that the newly generated X–H moiety remains bound to the metal center, utilizing π or lone pair electrons to activate the C–H bond rather than σ -bonds. Early and middle transition-metal complexes containing alkoxy, amido, or alkylidene ligands undergo this mode of C–H activation (Scheme 1.9).

In summary, the C–H activation step is dictated by the nature of the metal and the ligands present. It can proceed via a two-step oxidative addition-reductive elimination pathway with discrete oxidative addition intermediates or through a σ -bond metathesis pathway in a single transition state. The possible paths associated in the C–H bond activation are summarized in Scheme 1.10.



Scheme 1.10 : Possible involving paths for the activation of C–H bonds

1.3. General challenges for transition-metal catalyzed C–H bond functionalization¹⁰

In catalytic oxidative functionalization of complex organic molecules of C–H bonds poses five major challenges (a) reactivity, (b) chemoselectivity, (c) regioselectivity, (d) stereoselectivity, and (e) sustainability. A short description of each challenge is detailed below.

1.3.1. Reactivity

The strength of typical carbon–hydrogen bonds (with bond dissociation energies between 90–110 kcal/mol) presents a first and very significant challenge in this area. While most oxidation reactions are thermodynamically downhill, there is generally a large kinetic barrier associated with the C–H bond cleavage event required before/during functionalization. Transition metal catalysts serve to increase the rate of reaction of C–H bonds by many orders of magnitude.

1.3.2. Chemoselectivity

Achieving precise functionalization at the desired oxidation state poses a significant hurdle, given the tendency for over-oxidation, which is often energetically favorable. Various approaches have been employed to tackle this critical challenge, such as: (i) limiting reactions to partial conversion, (ii) employing substantial excess of substrate compared to oxidant, (iii) favoring intramolecular over intermolecular functionalization reactions, (iv) employing functional groups that kinetically impede over-oxidation, and (v) a meticulous design and selection of catalysts.

1.3.3. Regioselectivity

Achieving selective functionalization of a single carbon-hydrogen (C–H) bond within the intricate framework of organic molecules presents a formidable challenge in this domain. Several strategies have been devised to overcome this hurdle, including: (i) targeting substrates with inherently weaker or activated C–H bonds, such as benzylic or allylic systems, (ii) employing coordinating ligands integrated into the substrate as directing agents, (iii) favoring intramolecular functionalization via thermodynamically favored five- or six-membered transition states, (iv) leveraging supramolecular chemistry to position a specific C–H bond proximal to the active site of the catalyst, and (v) utilizing transition metal catalysts and ligands to govern selectivity.

1.3.4. Stereoselectivity

Establishing new stereogenic centers through the functionalization of carbon-hydrogen (C–H) bonds with high diastereoselectivity and/or enantioselectivity poses a significant challenge in this realm. While this aspect remains relatively underexplored, two primary avenues have emerged: substrate-driven strategies involving substrates with inherent stereocenters or chiral auxiliaries, and catalyst-driven approaches employing chiral transition metal complexes to direct enantioselective functionalization. Additionally, the stereospecific oxidative functionalization of C–H bonds at pre-existing stereocenters presents a promising avenue for chiral molecule synthesis with numerous practical applications.

1.3.5. Sustainability

In 1998, Anastas and Warner introduced the "12 Principles of Green Chemistry" as guidelines aimed at enhancing the sustainability of chemical processes. These principles encompass various design considerations, including prevention, real-time analysis, inherently safer chemistry, design for degradation, use of renewable feedstock, less hazardous chemical synthesis, design of safer chemicals, energy efficiency, sustainable metal catalysis, avoidance of derivatives, use of safer solvents and auxiliaries, and consideration of atom economy. Comparatively, C–H activation reactions hold significant promise in advancing sustainability, particularly as they align with several of these principles. For instance, C–H activation reactions often

adhere to the principles of sustainable metal catalysis, avoidance of derivatives, use of safer solvents and auxiliaries, and consideration of atom economy, thus contributing to greener and more sustainable chemical processes. However, it's important to note that while C–H activation reactions offer substantial potential, their continuous development should be viewed as an ongoing advancement toward sustainability rather than a static green objective. This evolution underscores the dynamic nature of sustainable chemistry and the need for ongoing innovation and improvement in chemical processes.

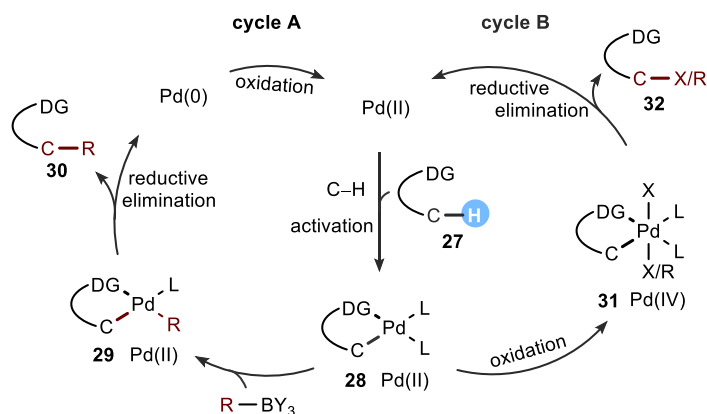
1.4 C(sp³)–H / C(alkenyl)–H activation

The transition-metal (mainly palladium) catalyzed directing group assisted C–H activation has been emerged as the straightforward and powerful strategy for the functionalization of organic molecules from commercially available chemicals. Among several different kinds of C–H bonds, past two decades has witnessed several advancements for the functionalization of proximal C(sp³)–H or C(alkenyl)–H bonds. This realm has produced myriad strategical disconnection that has never been possible in conventional way.

1.4.1. Mechanism of proximal C(sp³)–H / C(alkenyl)–H activation

Two different catalytic pathways are possibly involved in the DG assisted Pd-catalyzed functionalization of C(sp³)–H bonds (Scheme 1.11).^{1,11} The reaction begins with the coordination of Pd(II) catalyst to DG followed by the activation of proximal C–H bond to give the palladacycle **28**. The species **28** is a crucial reactive intermediate, as it reacts differently with the reagents used. One of the possible pathway involves the trans-metalation of **28** with the nucleophilic reagents,^{2,3} such as boronic acid; which on successive reductive elimination produces the desired product **30** with the release of Pd(0) catalyst (cycle A). The oxidation of Pd(0) catalyst concomitantly occurs in presence of oxidant, commonly known as terminal oxidant, and keeps the catalytic cycle active. The alternate method involves the oxidation of activated complex **28** in presence of oxidant to form high-valent Pd(IV) intermediate **31**, which on facile reductive elimination produces the desired functionalized product **32** with the direct regeneration of Pd(II) catalyst (cycle B). *Thus the catalytic cycle-A revolves utilizing the Pd(II)/Pd(0) systems, while the catalytic cycle-B works with*

the Pd(II)/Pd(IV) systems. The third type of mechanism is oxidative addition-induced activation; this process is realized with the participation of Pd(0)/Pd(II) catalysts.



Scheme 1.11. General mechanism of C(sp³)-H functionalization

A brief discussion on the ligand scaffolds, intermediates, and the plausible independent steps involved for the C(sp³)-H activation will shed light on understanding the broad-based mechanism shown in Scheme 1.11.

Identification of ligand scaffolds for Pd(II)-catalyzed C-H functionalization:¹²

Keeping in mind several interrelated challenges, designing ligand scaffolds for Pd(II)-catalyzed C-H functionalization reaction is impotent. These correlated challenges are listed below.

i) Assembling a 1:1 ligand/substrate coordination structure:

The ligand could outcompete the substrate binding to the Pd(II) centre or vice-versa. In directed C-H activation, traditional directing groups like pyridines, oxazolines, oximes, etc., could inhibit ligand coordination prior to C-H cleavage. In addition, the ligand would not play a dominant role in influencing reactivity and/or selectivity as it makes the C-H cleavage step so facile.

ii) Promoting the C-H cleavage step:

The requirement of supporting ligands are completely depends on the electronic behaviour of the Pd(II) centre, under different mechanistic realm of C-H cleavage (for instance; for electrophilic palladation mechanism, metal centre should be electrophilic in nature. Whereas, for CMD metal requirement is nucleophilic in nature.), and thus the supporting ligands are different. A combination of factors,

including the substrate, the reaction conditions, and also the ligand are necessary for the operative mechanism for C–H cleavage.

iii) Compatibility with the other steps in the catalytic cycle and the reaction conditions:

ligand engineering is necessary because of different Pd(II)-mediated C–H functionalization reactions proceed via different elementary steps. For instance, certain steps might necessitate ligand dissociation to create a vacant coordination site, whereas others demand ligands resistant to reductive elimination from high-valent intermediates. Furthermore, during the reaction, ligands may interact with the substrate, coupling partner, or Pd(II) catalyst along multiple potential degradation pathways.

iv) Modifiability and modularity:

Screening multiple distinct ligand scaffolds are necessary because it is inconvenient that a single ligand will be sufficient for each combination of substrate and reaction partner. In addition, utilizing modifiable and modular ligand scaffolds is not only superior for fine-tuning but also for developing multiple complementary ligand scaffolds for the specific combination of substrate and reaction type is impotent.

These ideas provide a roadmap for making better ligands in a specific type of chemical reaction in Pd(II)-catalyzed C–H functionalization reaction. Since it is hard to predict which ligand will work best, researchers often rely on trial and error. *They need to be thoughtful and open to trying new things, whether it's improving existing ligands or creating brand-new ones.*

Transmetalation: The transmetalation process is defined as a transfer of ligands from one metal to another. Therefore, a range of carbon or heteroatom ligands transfer is possible in this step. For example, in presence of base aryl or alkyl group transfer can be feasible from boron to the palladium center.¹³

Oxidative addition: In the case of cycle A oxidant regenerates the active catalyst in the last step of the reaction, whereas the same is used to get the high-valent metal complex in cycle B. A range of one electron and two-electron oxidants have been used to keep the catalytic cycle active. Therefore, the oxidation of metal catalyst is crucial in both the cycles presented in Scheme 1.11. In all oxidation processes the formal charge of the metal increases by two units.

Reductive elimination: Reductive elimination (RE) is a fundamental step in C-H functionalization reactions, involving the formation of a new bond between two anionic ligands bound to the Pd-metal and reducing the metal's oxidation state by two units. Therefore, it encompasses the formation of new C-C and C-heteroatom bonds. The rate of reductive elimination depends on several factors, such as orbital symmetry, bite angle/cone angle, coordination number, and oxidation state. For cycle A, reductive elimination could be facile due to the steric bulkiness of the ancillary ligands, allowing the ready formation of the product. In the case of strong bonding of M-X (X = heteroatom) and higher electronegativity of the heteroatom, C-X reductive elimination is a difficult task. For cycle B, the oxidation of the metal with an increased oxidation number would enhance the orbital overlap between M-C and M-X bonds, thus facilitating the RE. Therefore, catalytic cycle B is operative for Pd-catalyzed C-X bond formation^{1,14}

1.5. Bifunctional reagent (BFR)

In 1988, "Edward Piers" introduced the concept of bifunctional reagents (BFR),¹⁵ defining them as organic compounds possessing two reactive sites, typically nucleophilic and/or electrophilic. Intriguingly, these reactive centers of the species can be clipped into a substrate molecule either sequentially or through "simultaneous" activation. These "bifunctional conjunctive reagents" have gained increasing importance in organic synthesis, particularly for the synthesis of carbocycles or heterocycles through annulation sequences. Their utility lies in enabling relatively short synthetic routes, transforming structurally simple substrates into significantly more complex and functionalized products.

As organic chemistry progressed, the scope of reactive sites expanded with advancements in radical chemistry, cross-coupling reactions, and C-H functionalization. Therefore, the restriction of organic reactive sites to nucleophiles and electrophiles is mitigated. Moreover, both reactive sites need not necessarily be retained in the final product. Consequently, achieving a perfect atom economy can diminish the substrate and reagent relationship. Hence, attention is directed towards selected bifunctional substrates believed to inspire future conceptual developments.

Therefore, the classification of bifunctional reagent is portrayed based on the identities of the reactive sites (Fig – 1.4).¹⁶

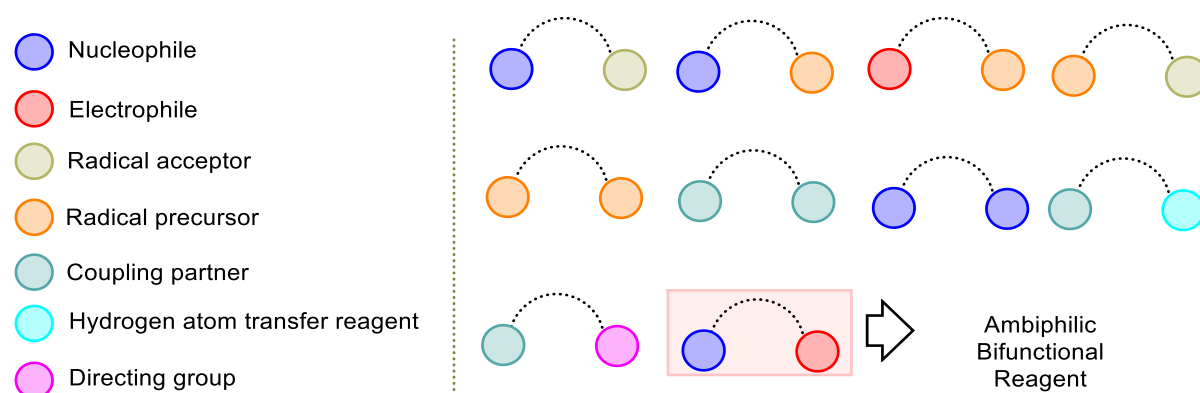


Figure 1.4. Classification of bifunctional reagent

1.5.1 Ambiphilic bifunctional reagent (ABFR)

Among the several aforementioned combinations of bifunctional reagents, the ambiphilic bifunctional reagent stands out as the most common, possessing both a nucleophilic and an electrophilic reactive center. Consequently, it has found heavy utilization in conventional cascade reactions, effectively embedding two organic molecules in a step and atom-economical manner.¹⁷ Additionally, the conjunctive nature of these ambiphilic bifunctional reagents, for instance, their easily removable functionality, can serve as a masking reactive site. Nevertheless, the potential for unveiling new reactivity of ABFR is yet to be fully understood. Moreover, ambiphilic bifunctional reagents not only facilitate the transfer of two functionalities to design a core molecule but also enable the assembly of acyclic molecules in a multicomponent fashion. This process works within the realm of the basic principles of step economy, and enables transforming simple substrates into significantly more complex and functionalized products. Thus far, the use of bifunctional reagents in catalytic transformations has been showing promise for the possibility of discovering new reactions that are often difficult or impossible to achieve using conventional methods.

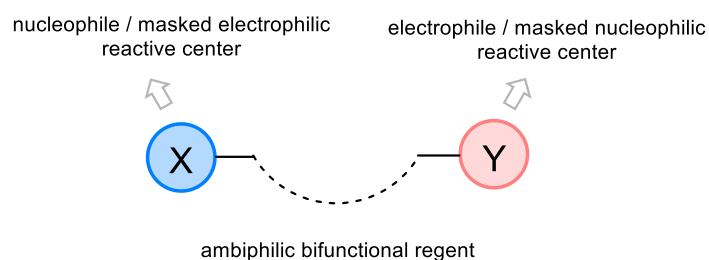
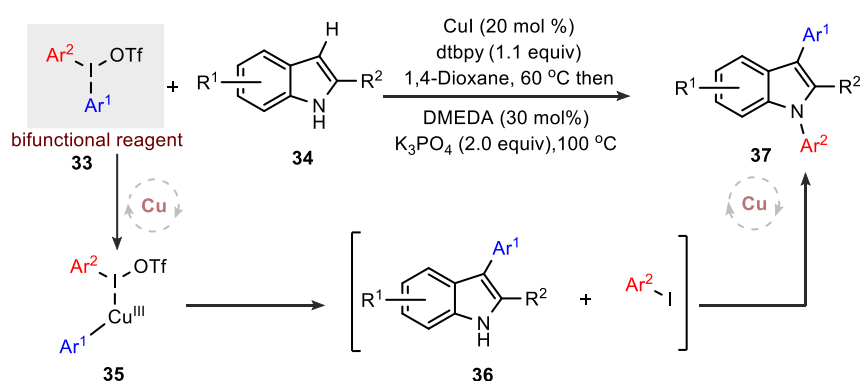


Figure 1.5. Ambiphilic bifunctional reagent

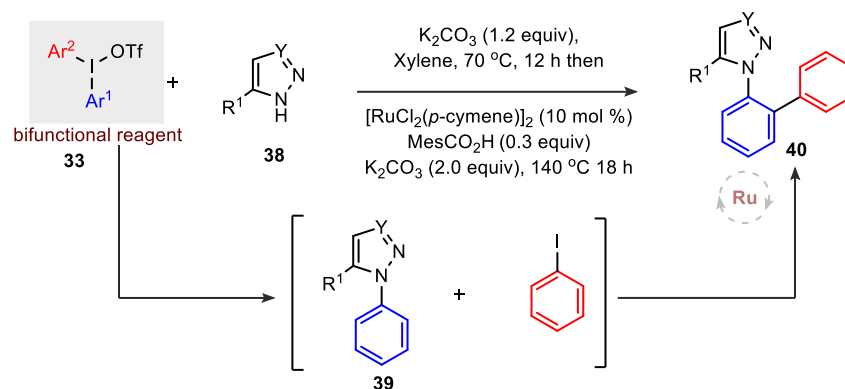
1.5.2 Example of bifunctional reagent in metal-catalyzed C–H functionalization reaction

In 2015, Greaney and Modha made a pioneering use of diaryliodonium salts as bifunctional reagents, marking a significant milestone in the field. Their approach enabled the tandem C–H/N–H arylation of indoles, a breakthrough achieved by employing a copper iodide catalyst. This method facilitated the direct formation of indole motifs through tandem C–H/N–H diarylation, incorporating both aryl groups from a single reagent (Scheme 1.13). Based on the mechanism, diaryliodonium salts first undergo oxidative addition with Cu^{I} salt to deliver Cu^{III} reactive species **35**. This reactive species first transfers one aryl group to the indole 3 position via C–C coupling. The next attachment happened with the indole N atom via N–C coupling. Later, the same reagent has been used for a Ru-catalyzed N-/C-arylation N-heterocycles (Scheme 1.14).^{18,19}



Scheme 1.13. Diaryliodonium salts as a bifunctional reagent

Merging C–H Bond Activation with bifunctional reagent...



Scheme 1.14. Diaryliodonium salts as a bifunctional reagent

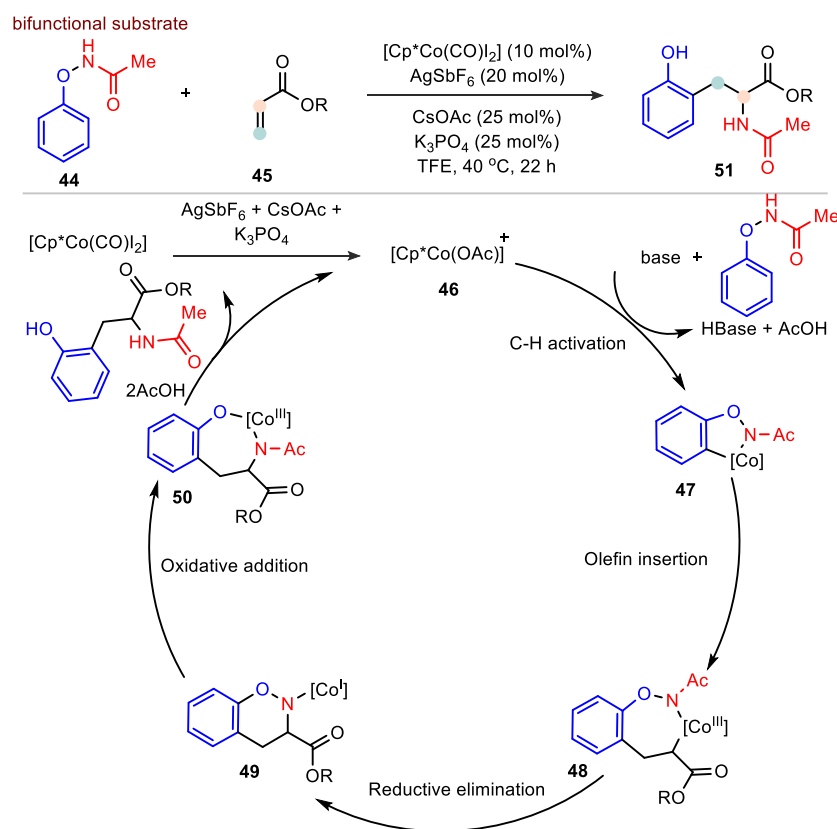
In 2019, Kong, Li, and colleagues demonstrated a noteworthy instance of Cu-mediated domino N-/C-arylation or N-/N-/C-arylation of imidazoles. This transformation possesses good to excellent yield (Scheme 1.15).²⁰ Moreover, diarylation shows high atom economy and excellent selectivity with unsymmetrical iodonium salts. Nevertheless, the reaction was performed in stoichiometric Cu-salt, which is a potential pitfall.



Scheme 1.15. Diaryliodonium salts as a bifunctional reagent

In 2016, Glorius and coworkers showcased an interesting reactivity of phenoxyacetamide derivatives **44** as a bifunctional substrate in Co(III)-catalyzed, intermolecular carboamination reaction (Scheme 1.16).²¹ In this transformation, synthesizing unnatural amino acid derivatives under redox-neutral conditions has been a noteworthy approach. According to their experimental findings, a catalytically active Co(III) species **46** interacts with phenoxyacetamide derivatives **44** to form intermediate **47** via C–H activation. Next, olefin insertion delivered a seven-membered ring intermediate **48**, which can undergo reductive elimination to release the six-membered ring intermediate **49**. Then, low valent Co(I) species subsequently

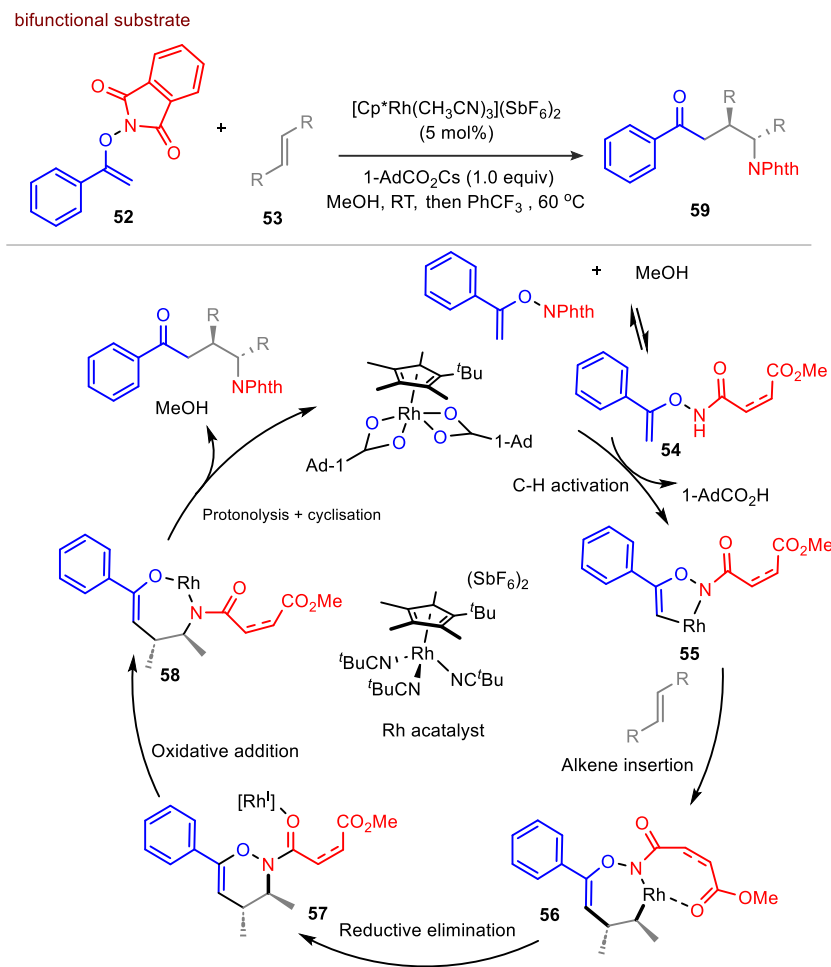
undergo oxidative addition with N-O bond to form the seven-membered Co(III) intermediate **50**. Finally, protodemetalation of **50** yields the desired product **51**.



Scheme 1.16. Phenoxyacetamide as a bifunctional reagent

In 2015, Rovis and Piou demonstrated a Rh-catalyzed carboamination of alkenes using enoxyphthalimides. However, the author did not highlight enoxyphthalimides as a bifunctional reagent, but its reactivity was sought after (Scheme 1.17).²² Based on their experimental findings, the C-H activated, and Rh-metalated species **55** was constructed via ring-opening of the phthalimido system. Next, insertion of alkene to **55** forms **56**. Further, reductive elimination of **56** delivers intermediate **57**. Subsequently, N-O bond of **57** undergoes oxidative addition to provide seven-membered Rh(III) complex **58**. Finally, protonolysis and cyclization delivers acyclic products containing two contiguous stereocenters **59**.

Merging C–H Bond Activation with bifunctional reagent...

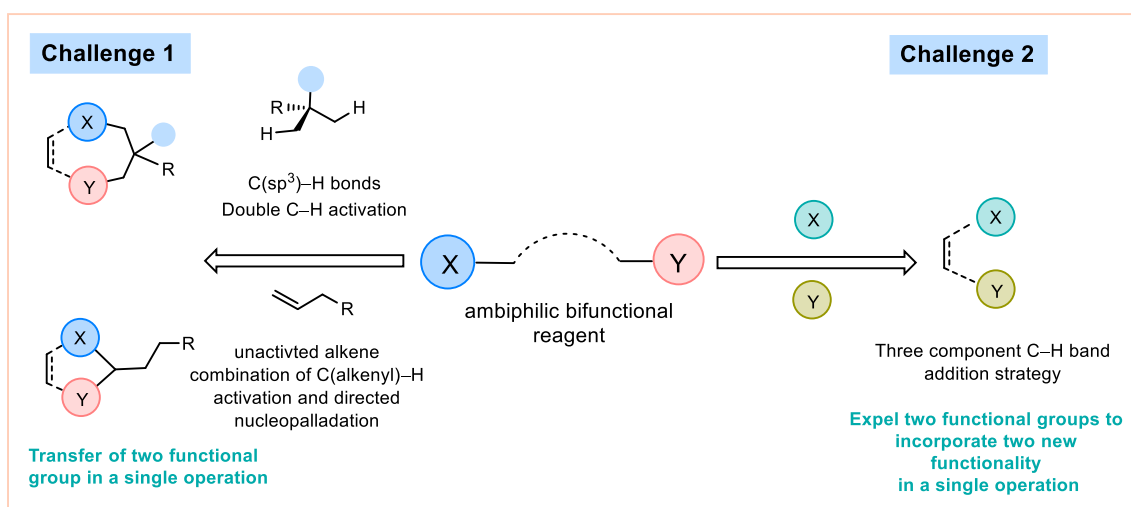


Scheme 1.17. Enoxyphthalimides as a bifunctional reagent

1.6. Motivation, Hypothesis, and Planning

The use of bifunctional reagents in C–H functionalization reactions is indeed rare. Despite their potential to drive atom and step-economical transformations, as well as to facilitate the conversion of straightforward substrates into complex and functionalized products, the full extent of their utility in intricate C–H activation process remains unexplored. Therefore, merging bifunctional reagents into C–H activation chemistry holds promise for unlocking new avenues in synthetic chemistry. By harnessing the reactivity of these reagents, researchers aim to access chemical space that has traditionally been challenging or even inaccessible through conventional means. By addressing the limitations of conventional methods and leveraging the unique reactivity of bifunctional reagents, this approach promises to open doors to novel chemical transformations and unlock opportunities for the synthesis of previously elusive molecular structures.

To elucidate the utility of these ambiphilic bifunctional reagents, we have portrayed two types of challenges. Whereas, challenge 1 showcases a quest of transferring two functionalities via dual C(sp³)-H activation as well as remote C(alkenyl)-H activation in a one-step operation (Scheme 1.18, left side). On the other hand, challenges 2 involves expelling two functionalities, while introducing two new functionalities in a one-step operation (Scheme 1.18, right side). Each process underscores the molecular editing ability through insertion as well as the combination of deletion and insertion methodology.

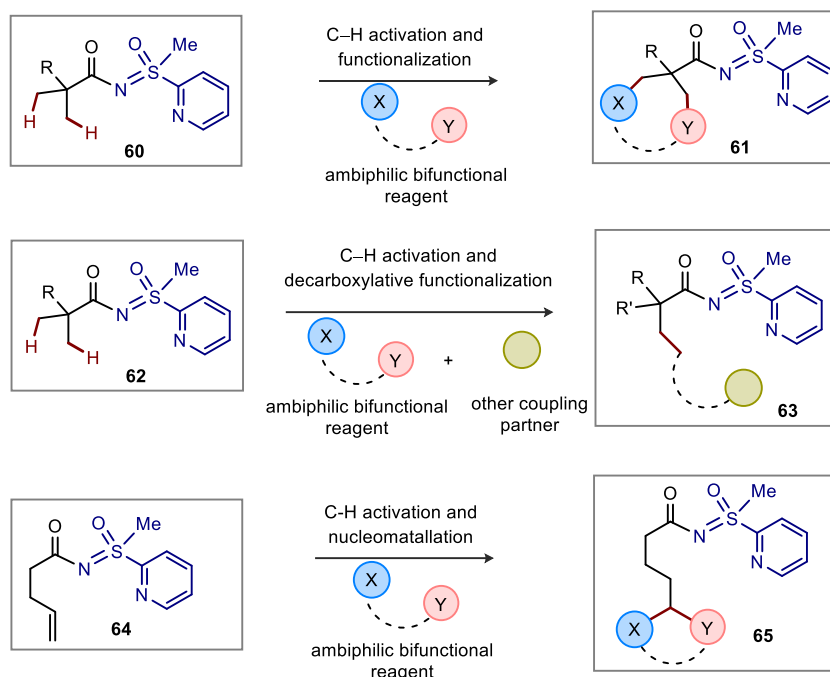


Scheme 1.18. Merging bifunctional reagent with C-H activation

Thus, we hypothesized that merging the reactivity of a bifunctional reagent with C-H activation could be achievable using a neutral chelating directing group, methyl-2-pyridylsulfoximine (MPyS). This bidentate directing group overcomes the fundamental challenges associated with C(sp³)-H / remote C(alkenyl)-H bond activation (Scheme 1.19). Furthermore, its neutral chelating ability could not only facilitate C(sp³)-H / remote C(alkenyl)-H bond activation but also promote dual C(sp³)-H bond activation, integrating various catalytic systems such as decarboxylative functionalization and nucleometallation.

Additionally, leveraging the ligand effect with bidentate methyl-2-pyridylsulfoximine is necessary to achieve this catalytic hypothesis. This approach could provide a new opportunity to identify ligands that enhance reaction kinetics in C-H activation reactions.

Merging C–H Bond Activation with bifunctional reagent...



Scheme 1.19. MPyS-DG and bifunctional reagent enabled transformation

This thesis aims to develop new chemical transformations and unlock opportunities for the synthesis of new molecular structures that are remained elusive. Consequently, the use of a direct C–H activation strategy extends the potential of retrosynthetic disconnection to synthesize novel scaffolds. In addition, employing the MPyS directing group with readily available starting materials, mainly aliphatic acid derivatives, to carry out multiple functionalization reactions is indeed a value addition (Scheme 1.19). However, after completion of the reaction, reusing the directing group through a simple hydrolysis procedure showcases practicality. Finally, combining the MPyS-DG with 2-iodobenzamide and 2-iodobenzoic acid as an ambiphilic bifunctional reagent is deployed for the formation of cyclic benzofused lactone and lactam formation, as well as the acyclic assembly of 1,2-difunctionalized arene scaffolds (Scheme 1.19).

1.7. Reference

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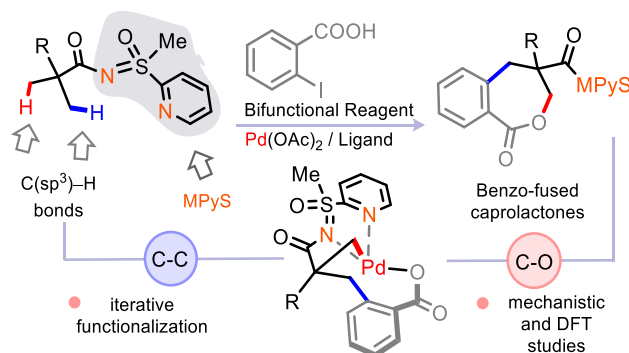
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Chapter 2

Palladium (II)-Catalyzed Annulative Difunctionalization of Two Inert C(sp³)–H Bonds by a Bifunctional Reagent

Abstract



Illustrated herein is a Pd (II)-catalyzed direct difunctionalization of two C(sp³)–H bonds of aliphatic carboxylic acid derivatives by bifunctional reagents (BFRs) of the 2-iodobenzoic acid series. The methyl 2-pyridyl sulfoximine (MPyS) bidentate directing group (DG), 2-chloro-5-trifluoromethylpyridine ligand, AgOAc as base and NaBrO₃ as co-oxidant, help the concerted metalation deprotonation (CMD) of inert C(sp³)–H bonds, as well as the reductive elimination; density functional theory (DFT) studies shed light on these crucial steps. This process makes two bonds [C–C and C–O] at *gem*- α,α' -di-Me groups in a single operation, offering access to unusual benzo-fused peripheral substituted caprolactones. The transformation tolerates labile functional groups and allows the construction of a wide range of caprolactones with structural diversity. Mechanistic studies reveal the participation of monomeric Pd-species in the catalytic cycle. The synthetic versatility of the complex molecular entities is also presented.

Reference:

Arghadip Ghosh, Nicolas Grimblat, Somratan Sau, Arijit Saha, Vincent Gandon, and Akhila K. Sahoo *ACS Catalysis*. **2023**, *13*, 7627-7636.

2.1. Introduction

Cyclic structural motifs are ubiquitous in natural and non-natural molecules of pharmaceutical, agrochemical, and material relevance.¹ While cycloaddition reactions are the common pathway to build complex cyclic molecules,² an emerging strategy is the directing group (DG) assisted transition-metal (TM) catalyzed annulative multiple C-H functionalization.^{3,4} The coupling of the two substrates is achieved by C-H/C-H, C-H/C-I, or C-H/insertion strategies, all leading to the formation of C-C bonds. However, this methodology is so far limited to the construction of carbocycles. Building up heterocycles could be envisaged, for instance, by C-H/C-I and C-H/O-H coupling [i.e., simultaneous C-C and C-O bond formation]. This implies the use of a bifunctional transfer reagent (BFR) exhibiting reactive C-I and O-H bonds to make this synthetic paradigm feasible.⁵ This process encapsulates an efficient transfer of diverse functionalities in a single step, building complex cyclic structural units that are difficult to access by conventional means (Figure 2.1).⁶ TM-catalyzed activation and functionalization of inert $C(sp^3)$ -H bond reactions represent a sustainable toolkit for making unusual molecules of great structural diversity. In this regard, the Pd-catalyzed $C(sp^3)$ -H bond activation has been mainly used in mono-functionalization processes (Figure 2.1, left).⁷ Double functionalization of $C(sp^3)$ -H bonds is, on the other hand, more challenging to execute (Figure 2.1, right).³

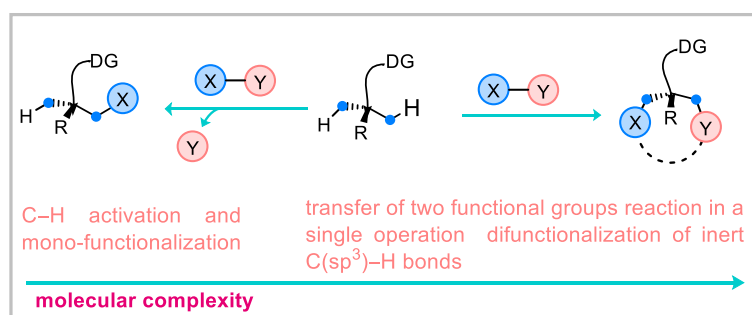


Figure 2.1. C-H activation and use of bifunctional reagents (BFRs) for complexity-driven transformations.

The TM-catalyzed annulation of unsaturated species such as alkenes, alkynes, allenes, and dienes, with ambiphilic BFRs, offers a potent means to construct cyclic motifs

(Dieck and Larock; Figure 2.2, left), yet with limited chemical space.⁸ Surprisingly, annulation by clipping an ambiphilic BFR at two $C(sp^3)$ -H bonds of a substrate has not been described (Figure 2.2, right). Nevertheless, given the potential of one-pot unsymmetrical multiple functionalizations of C-H bonds, the development of such a synthetic paradigm allowing the simultaneous functionalization of two geminal methyl groups with a BFR appears to be a worthwhile endeavor.

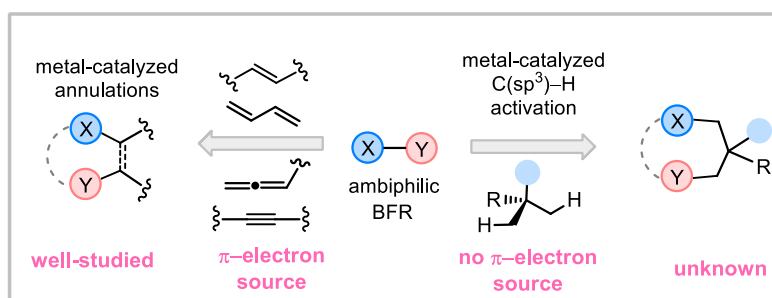
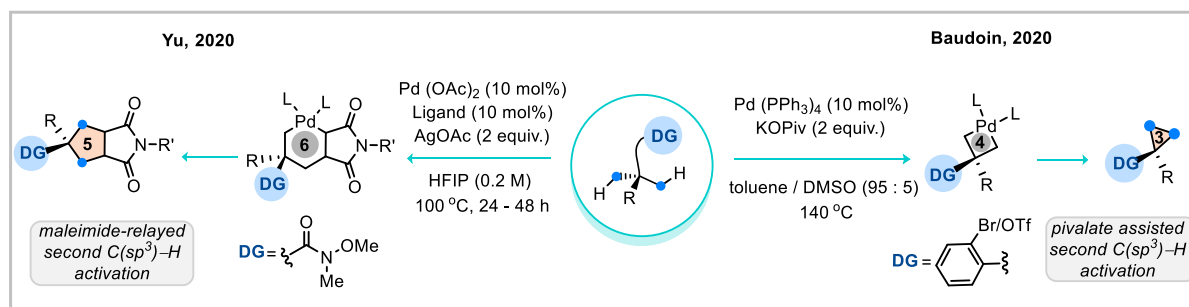


Figure 2.2. Ambiphilic BFRs for annulations

2.1.1. Precedents and Strategies for Double $C(sp^3)$ -H Bond activation

Yu's pioneering work on Pd-catalyzed amide-directed twofold α, α' -di-Me- $C(sp^3)$ -H bond activation via maleimide relay offers a direct entry to 5-membered carbocycles (Scheme 2.1, left).¹⁰ Moreover, the annulative difunctionalization of *gem*- α, α' -di-Me groups has been reflected independently by oxazoline-promoted $C(sp^3)$ -H di-iodination followed by radical cyclization [Yu] and by pivalate-assisted intramolecular coupling of in-situ generated σ -alkyl-Pd species via a 1,4-Pd shift of aryl-Pd-halide [Baudoin]; these methods could build functionalized cyclopropanes (Scheme 2.1, right).¹¹

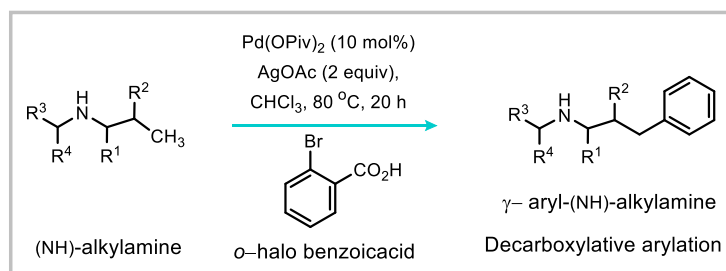


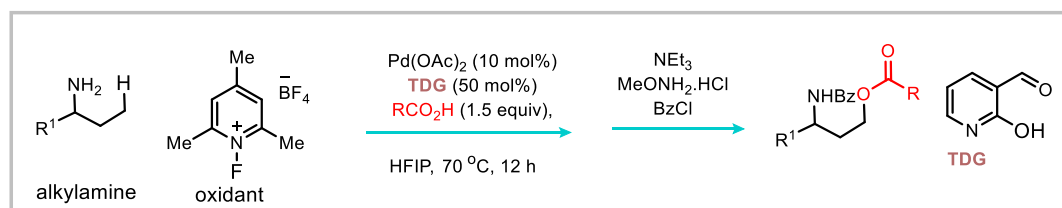
Scheme 2.1. Prior art for double C-H activation

2.2. Motivation, Hypothesis, and Design

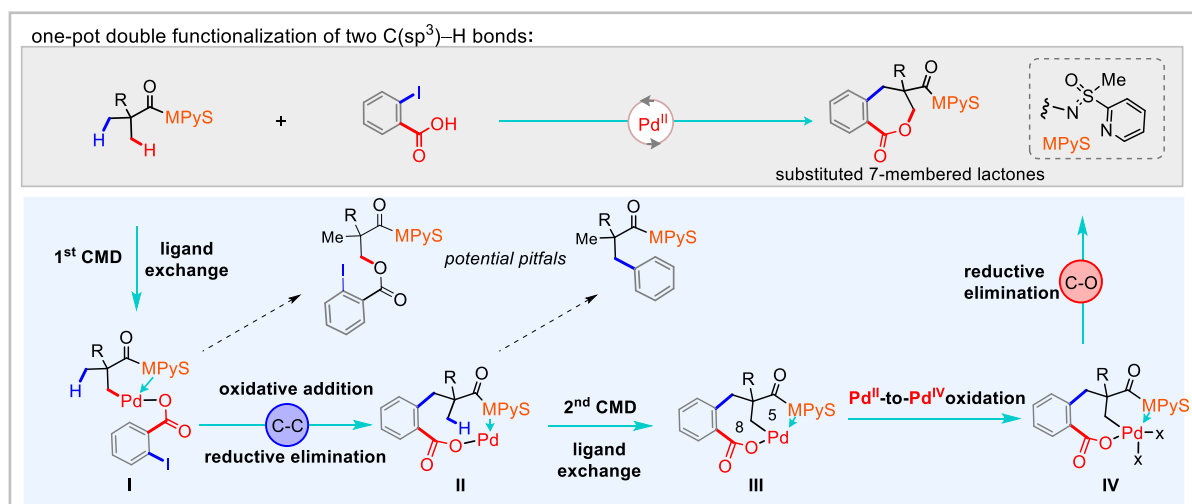
The above-mentioned approaches rely on two consecutive C–C bonds formation for the construction of 3/5-membered carbocycles (Figure 2.3). However, this strategy does not provide access to seven-membered carbo/heterocycles, which is perhaps due to the involvement of a hard-to-get 8-membered palladacycle in the second C–H activation.^{4b} We reasoned that a DG-enabled independent double functionalization of inert C–H bonds could be useful for the construction of large-membered cyclic motifs (Figure 2.3). Based on our recent work on methyl pyridyl sulfoximine (MPyS) aided sequential functionalization of two β -C(sp³)-H bonds,¹² we intended to trap both *gem*-di-Me groups with a BFR (for instance, 2-iodobenzoic acid) to form uncommon benzo-fused caprolactones (Figure 2.3). Our plan was to use an MPyS-DG bearing aliphatic carboxylic acid derivative exhibiting α,α' -di-Me groups, a 2-iodobenzoic acid, Pd(OAc)₂ as a catalyst along with a base and an oxidant. We can anticipate that the transformation relies on the coordination of a Pd(II) species to the MPyS-DG to trigger an acetate-assisted CMD of an α -Me-C(sp³)-H bond, followed by AcO[−]/benzoic acid ligand exchange resulting in intermediate **I**. Next, oxidative addition of the iodoaryl moiety of **I**, followed by reductive elimination, would deliver **II**. Acetate-aided second CMD of another α' -Me-C(sp³)-H bond of **II** could then provide **III**. Finally, oxidant-promoted reductive elimination of **IV** could build benzo-fused peripheral substituted caprolactones (Figure 2.3). Generally, intermediates of type **I** and **II** are prone to C-benzoylation and decarboxylative arylation, respectively (Figure 2.3).¹³ As evident by Gaunt's decarboxylative arylation of (NH)-alkylamine, using 2-bromobenzoic acid as an aryl transfer reagent (Scheme 2.2) and Yu's γ -alkoxylation of free amine by 2-hydroxynicotinaldehyde as a transient directing group (Scheme 2.3).

Scheme 2.2. Gaunt's decarboxylative arylation via C(sp³)-H activation



Scheme 2.3. Yu's oxidative alkoxylation via C(sp³)-H activation

We envisioned addressing the challenges depicted in Figure 2.3 by considering the following parameters: *i*) a suitable ligand to facilitate the CMD processes for the two C(sp³)-H activation through Pd-arene interaction, *ii*) a solvent mixture and an oxidant for preventing the decarboxylative arylation and make the C-O reductive elimination smooth. We describe herein the successful uncovering of a Pd(II)-catalyzed two-fold functionalization of *gem*- α,α' -di-Me groups with 2-iodobenzoic acid derivatives (Figure 2.3). This process makes it possible to build a wide range of benzo-fused caprolactones, which are difficult to access in a conventional manner (Figure 2.3).¹⁴

**Figure 2.3.** Concept for one-pot double functionalization of two C(sp³)-H bonds

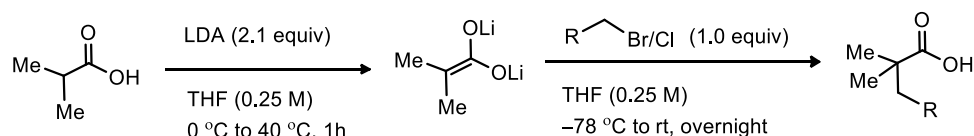
2.3. Results and Discussion

2.3.1. Synthesis of Precursors

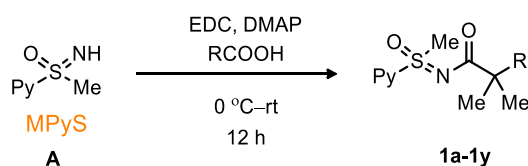
A wide range of *N*-carboxyl sulfoximine derivatives were synthesized involving the procedure mentioned herein.

2.3.1.1. Preparation of carboxylic acids **2g'–2j'**: General Procedure (GP-1):¹⁵

Scheme 2.4. Preparation of carboxylic acids



To a stirred solution of diisopropylamine (3.0 mL, 21 mmol) in THF (40 mL) was added *n*-BuLi solution (8.4 mL, 21 mmol, 2.5 M in hexane) dropwise at 0 °C. The resulting solution was stirred at 0 °C for 30 min. Isobutyric acid (910 μ L, 10 mmol) was added dropwise at the same temperature and the reaction mixture was heated to 40 °C and stirred for 1 h. The resulting mixture was then cooled to –78 °C; next, the respective alkyl bromide (10 mmol) was added dropwise. The reaction mixture was slowly warmed to room temperature (rt) overnight. The reaction mixture was quenched with water and diluted with EtOAc (30 mL). The layers were separated and the organic layer was extracted with water. The aqueous layer was combined and acidified to pH<4 with aqueous 3 M HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo. The crude carboxylic acid was subsequently used without further purification.

2.3.1.2 Preparation of N-protected S-methyl-S-(2-pyridyl) sulfoximines: General Procedure (GP-2):¹⁶

A solution of *N'*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, hydrochloride salt (EDC $\cdot$ HCl) (1.1 equiv), 4-*N,N*-dimethylaminopyridine (DMAP) (2.2 equiv), and carboxylic acid (1.1 equiv) in CH_2Cl_2 (5.0 mL for 1.0 mmol of sulfoximine) was stirred under an argon atmosphere. Sulfoximine (**A**; 1.0 equiv) was introduced dropwise at 0 °C. The resulting reaction mixture was stirred for about 1 h at 0 °C and warmed to ambient temperature and stirred overnight. Upon complete consumption of the

sulfoximine, the reaction mixture was acidified with hydrochloric acid (HCl, 1N). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3 times). The combined extracts were washed with 10% aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 . Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography eluting with (EA/hexane mixture) on silica gel. Thus, a series of compounds **1** was made (Figure 2.4). This procedure has been successfully adopted for the synthesis of **1c**, **1d**, **1f**, **1g**, **1n**, **1q**, **1r**, **1s**, **1t**, **1v**, **1x**, **1y** (Figure 2.5).

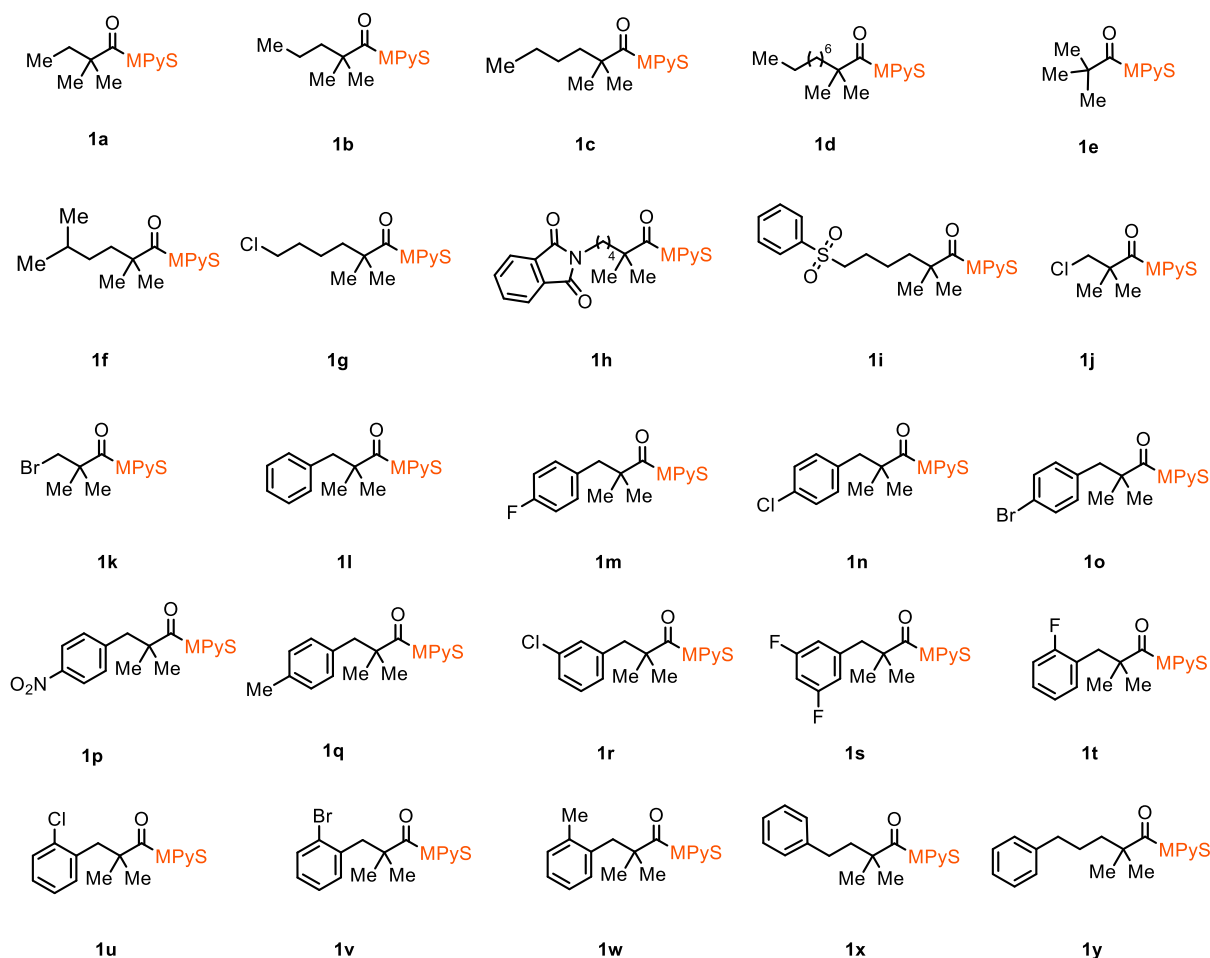
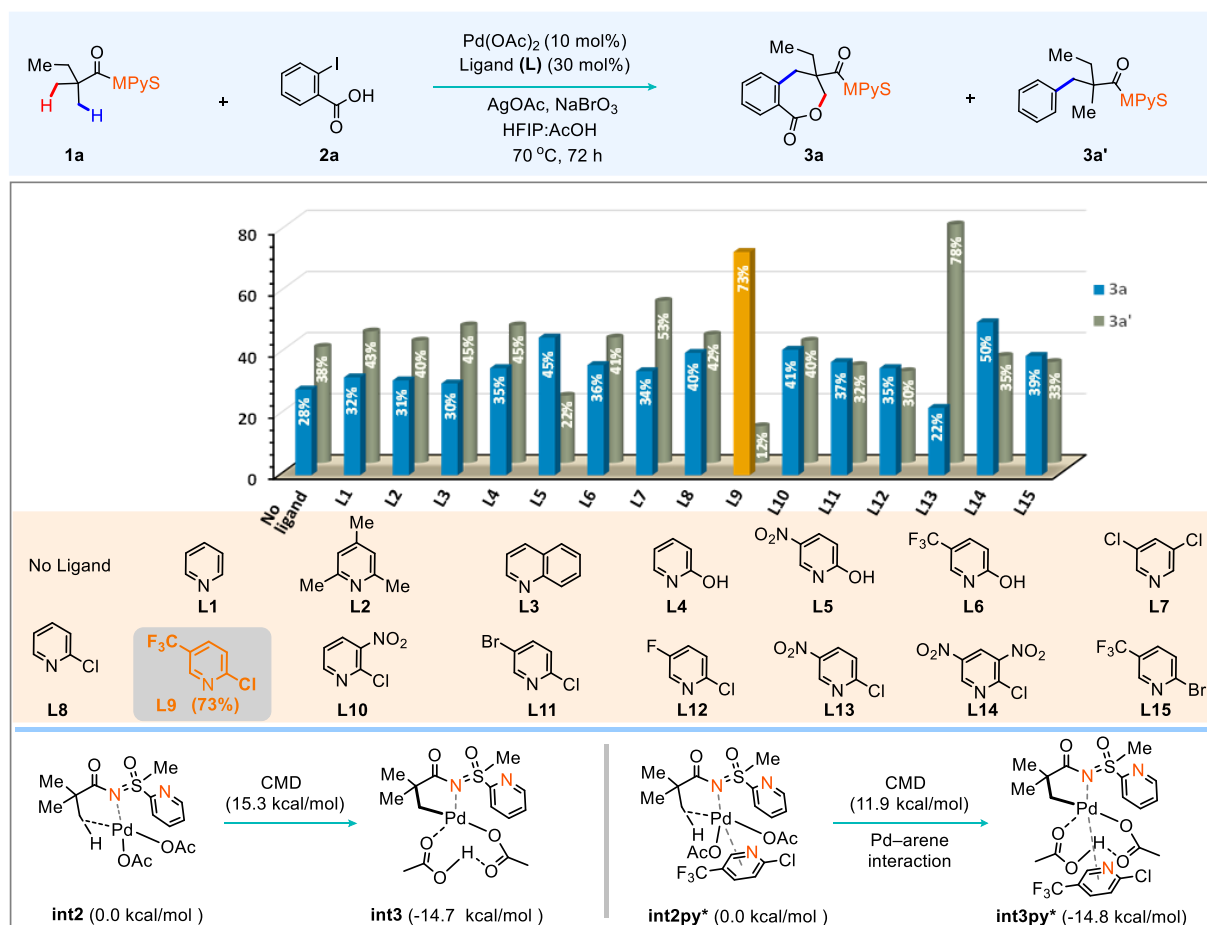


Figure 2.4. Substrate list

2.3.2. Reaction Optimization

To examine the unsymmetrical difunctionalization of inert $C(sp^3)$ -H bonds, the reaction of amide **1a**, bearing a 2-pyridyl-methyl sulfoximine (MPyS) and α,α' -dimethyl groups, with 2-iodobenzoic acid **2a** in the presence of a Pd-catalyst was studied (Scheme 2.5). Unlike the projected scenario in Figure 2.4, the desired caprolactone

product **3a** was not even detected as a trace when the reaction was conducted in the absence of ligands, bases, or oxidants, while the decarboxylated mono-C(sp³)-H arylation product **3a'** was formed in substantial amount. A thorough screening of additives (see Tables 2.1–2.4) pointed out that Pd(OAc)₂, along with AgOAc, and NaBrO₃ in combination with a mixture of HFIP and AcOH is highly relevant. These conditions provided **3a** and **3a'** in 28% and 38% yield, respectively, in the absence of external ligands (see Table 2.1). To circumvent the mono-C-H arylation product formation and enhance the reactivity, we studied the effect of a range of pyridine-based ligands (see Table 2.1). Pyridine ligand coordination to Pd-species generally helps in stabilizing the high-valent Pd motif. Electron-rich pyridines (**L1**–**L3**) proved to be less efficient, delivering **3a'** as the major product. The 2-hydroxy pyridine (pyridone) ligand **L4** was found moderately efficient. To our surprise, the electron-deficient pyridine ligand **L5** slightly enhanced the yield of **3a** (45% vs 22% for **3a'**). This observation encouraged us to screen electron-deficient pyridine ligands; **L6**, **L7** was, however, ineffective. Interestingly, the conversion of **1a** towards **3a** (40%) and **3a'** (42%) increased when 2-chloropyridine **L8** was used. In this line, the electron-deficient 2-chloro-5-trifluoromethyl pyridine ligand **L9** afforded **3a** in a gratifying 73% yield. Of note, the racemic MPyS-DG produces **3a** as a 1:1 mixture of diastereomers, as reflected by ¹H NMR and ¹³C NMR, which is not an issue since the DG is removable (vide infra). Other ligands **L10**–**L15** were found to be less efficient. Besides, when the identical reactions were carried out with *N*-(quinolin-8-yl)pivalamide, *N*-(pyridin-2-ylmethyl)pivalamide or 5-methyl-2-pyridyl sulfonyl protected pivalamide derivatives, the desired benzo-fused caprolactone did not form (Table 2.1). The role of the 2-chloro-5-trifluoromethyl pyridine ligand **L9** in this transformation could be able to facilitate the CMD process. Indeed, DFT computations suggest that a Pd-arene-like interaction lowers the energy barriers [11.9 kcal/mol towards **Int3py***, vs 15.3 kcal/mol towards **Int3**] (Scheme 2.2, additional calculations; Figures 2.7–2.8).

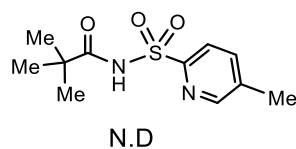
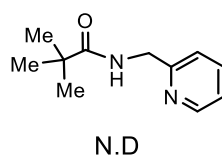
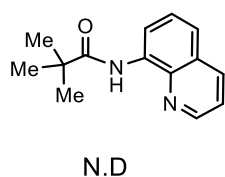
Scheme 2.5. Ligand investigation for twofold C-H activation^a

Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), $AgOAc$ (0.2 mmol), $NaBrO_3$ (0.2 mmol), HFIP (46 equiv), AcOH (40 equiv) at 70 °C, under air, 72 h. ^aThe yield was determined by 1H NMR analysis of the crude product using CH_2Br_2 as an internal standard.

Table 2.1: Ligand optimization and directing group effect. ^a

No Ligand				
3a 28%, 3a' 38%	3a 32%, 3a' 43%	3a 31%, 3a' 40%	3a 30%, 3a' 45%	3a 35%, 3a' 45%
3a 45%, 3a' 22%	3a 36%, 3a' 41%	3a 34%, 3a' 53%	3a 40%, 3a' 42%	3a 73%, 3a' 12%
3a 41%, 3a' 40%	3a 37%, 3a' 32%	3a 35%, 3a' 30%	3a 22%, 3a' 78%	3a 50%, 3a' 35%
3a 39%, 3a' 33%	3a 37%, 3a' 50%	3a 45%, 3a' 41%	3a 34%, 3a' 52%	3a 00%, 3a' 00%

Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Pd(OAc)₂ (10 mol%), AgOAc (0.2 mmol), NaBrO₃ (0.2 mmol), HFIP (46 equiv), AcOH (40 equiv) at 70 °C, under air, 72 h. ^bThe yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard.

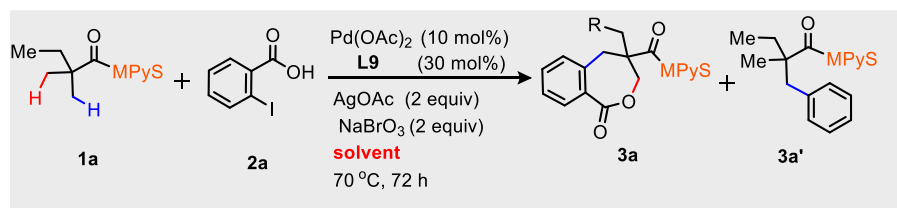
Directing group screening.^a

^aN.D = Not determine

Table 2.2: Oxidant optimization ^a

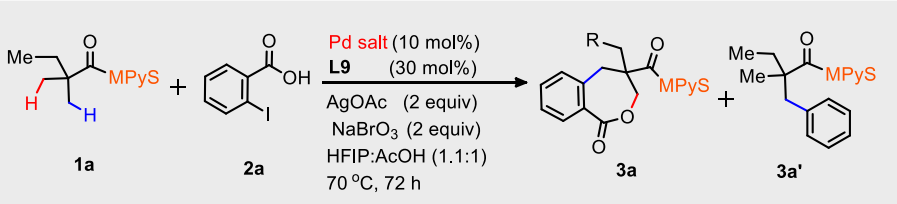
Entry	Oxidant	Yield 3a (%)	Yield 3a' (%)
1	Ag ₂ SO ₄	0	0
2	Ag ₂ CO ₃	43	41
3	AgOAc	55	22
4	Ag ₂ O	57	34
5	AgTFA	0	0
6	AgF	45	38
7	AgOAc + Ag ₂ CO ₃	60	29
8	AgOAc + Ag ₂ O	63	27
9	Cu(OAc) ₂ ·H ₂ O	0	0
10	PhI(OAc) ₂	0	0
11	K ₂ S ₂ O ₈	0	0
12	TBHP	0	0
13	NaBrO ₃	0	0
14	KBrO ₃	0	0
15	AgOAc + NaBrO ₃	73	12
16	AgOAc + KBrO ₃	21	34

Conditions: ^a**1a** (0.1 mmol), **2a** (0.2 mmol), Pd(OAc)₂ (10 mol%), AgOAc (0.2 mmol), NaBrO₃ (0.2 mmol), HFIP (46 equiv), AcOH (40 equiv) at 70 °C, under air, 72 h. ^bThe yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard

Table 2.3: Solvent optimization ^a

Entry	Solvent	Yield 3a (%)	Yield 3a' (%)
1	HFIP	31	60
2	AcOH	20	47
3	HFIP : AcOH (5 : 1)	51	40
4	HFIP : AcOH (2.5 : 1)	42	37
5	HFIP : AcOH (1.6 : 1)	45	38
6	HFIP : AcOH (1.1 : 1)	73	12
7	HFIP : AcOH (1 : 1.1)	51	32
8	DCM	0	0
9	CHCl ₃	0	0
10	1,2-DCE	0	0
11	1,4-dioxane	0	0
12	TFE	0	0
13	t-amylOH	0	0
14	Ac ₂ O	0	0

Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Pd(OAc)₂ (10 mol%), AgOAc (0.2 mmol), NaBrO₃ (0.2 mmol), HFIP (46 equiv), AcOH (40 equiv) at 70 °C, under air, 72 h. ^bThe yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard

Table 2.4: Palladium salt optimization ^a


Entry	Pd salt	Yield 3a (%)	Yield 3a' (%)
1	PdCl ₂ (dppf) ₂	0	0
2	PdCl ₂ (MeCN) ₂	47	40
3	PdCl ₂	54	30
4	Pd(acac) ₂	34	44
5	Pd(OTf) ₂	0	0
6	Pd(COD)Cl ₂	23	48
7	Pd(OAc)₂	73	12
8	Pd(PPh) ₂ Cl ₂	32	43
9	Pd(OH) ₂	0	0

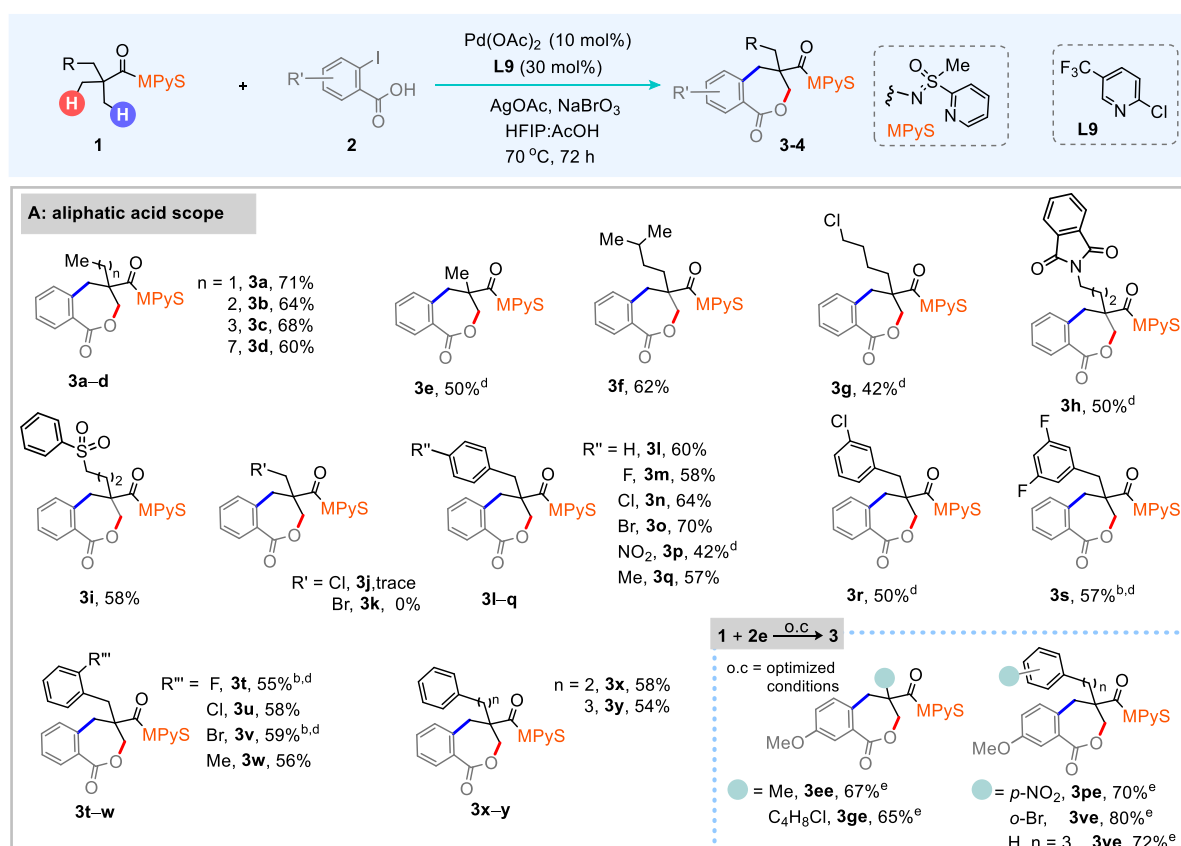
Conditions: ^a**1a** (0.1 mmol), **2a** (0.2 mmol), Pd(OAc)₂ (10 mol%), AgOAc (0.2 mmol), NaBrO₃ (0.2 mmol), HFIP (46 equiv), AcOH (40 equiv) at 70 °C, under air, 72 h. ^bThe yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard

2.3.3. Reaction Scope

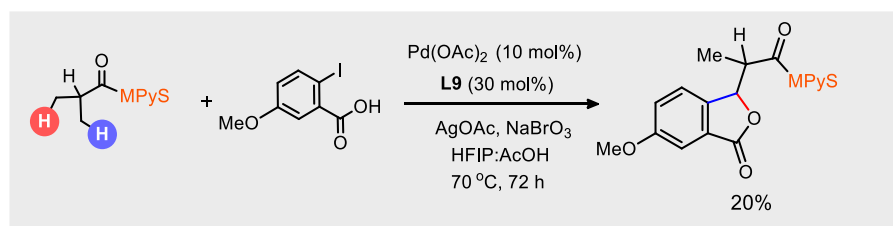
With the optimized conditions in hand, we set out to examine the reaction scope. Various MPyS-protected aliphatic acids having α,α' -gem-di-Me groups were reacted successfully with **2a**, providing the desired lactones **3a–y** (Scheme 2.6). Irrespective of the alkyl groups (different chain lengths and bulkiness) at the α -position of the aliphatic acid derivative, the product yield was good (**3a–f**; 50–71%). Common functional groups like chloro, amide, and sulfone were compatible with the Pd-catalytic system making **3g–3i** in good yields. On the other hand, the reaction of **1j** (β -chloro) and **1k** (β -bromo) exhibiting substituted MPyS with **2a** failed, probably because of the reactivity of the C–X bond which inhibits the directed C–H activation process. Despite a possible concurrent activation of the tethered *ortho*-C(arene)–H bonds, a wide range of α -gem-diMe- β -arylated MPyS enabled aliphatic acids could be reacted with **2a** to deliver the respective caprolactones **3l–w** (Scheme 2.6). Importantly, steric, and electronic variation in the aryl motif had no detrimental effect in the reaction outcome. In

addition, modifiable halo and nitro groups were tolerated under the developed reaction conditions, which paves the way for potential post-functionalization of the peripheral decorated caprolactones. Next, **3x** (58%) and **3y** (54%) were obtained from simple phenyl-bearing MPyS-enabled aliphatic acids. Furthermore, **2e** reacted with (**1e**, **1g**, **1p**, **1v**, **1y**) to deliver the respective caprolactones (**3ee**, **3ge**, **3pe**, **3ve**, **3ye**) with good yields. Occasionally, complex mixtures due to incomplete conversion and side reactions are responsible for a moderate yield. However, some of these yields could be improved by adding an additional portion of catalyst (~10% yield increase for **3s**, **3t**, and **3v**). In any case, access to such caprolactones is expedient compared to known multi-step processes. While the identical reaction of α -tertiary carboxylic acid derivatives provided 5-membered benzo-fused lactone, albeit in low yield, instead the desired caprolactone (Scheme 2.7).

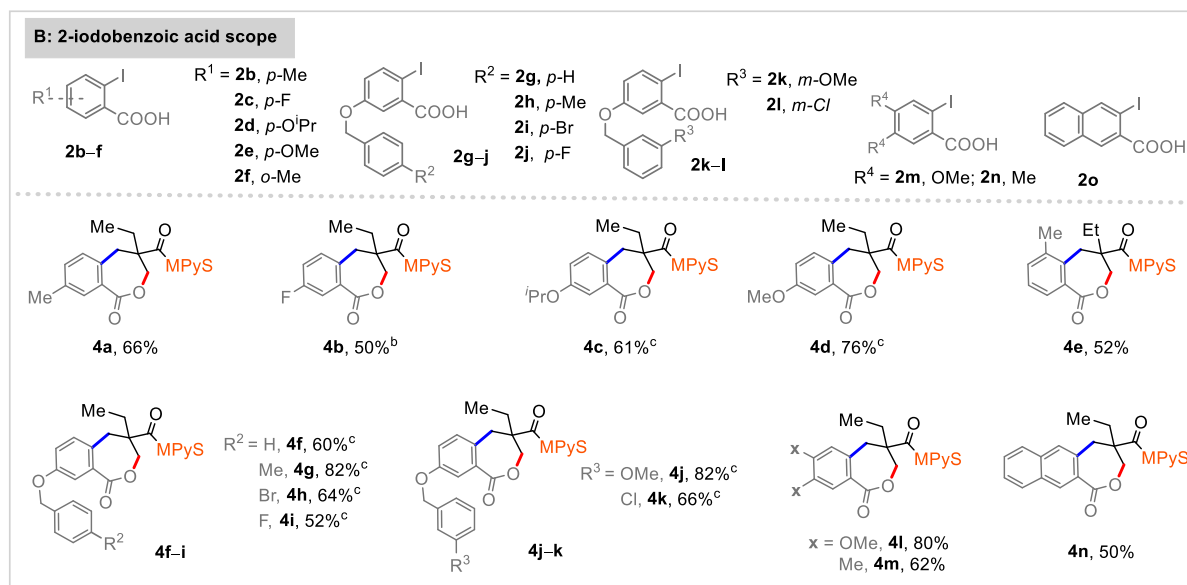
Scheme 2.6. Reaction scope of aliphatic acid and bifunctional 2-iodobenzoic acid^a



^aConditions: **1** (0.2 mmol), **2** (0.4 mmol), Pd(OAc)₂ (10 mol%), **L9** (30 mol%), AgOAc (0.4 mmol), NaBrO₃ (0.4 mmol), HFIP (46 equiv), AcOH (40 equiv) at 70 °C, under air, 72 h; isolated yield. All compound formed in a 1:1 diastereomeric ratio. ^bA second portion of Pd(OAc)₂ (10 mol%) was added after 12 h.

Scheme 2.7. α -Tertiary carboxylic acid derivative with a bifunctional 2-iodobenzoic acid reagent

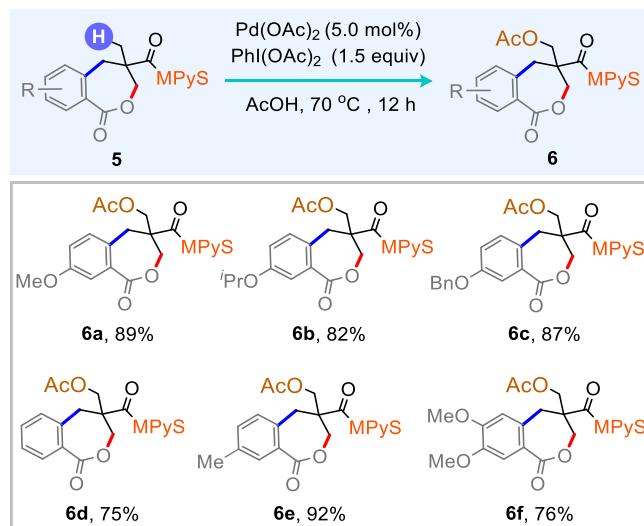
We next scrutinized the scope of 2-iodobenzoic acid derivatives under the optimized conditions (Scheme 2.8). The reaction of such BFRs having electron-donating and -withdrawing substituents at position *ortho*-, *meta*-, and *para*-with **1b** afforded the respective *ortho*-, *meta*-, and *para*-substituted benzo-fused caprolactones. Thus, **4a–d** (50–76%) were constructed from the respective reaction of **1b** with **2b–e**. Even the presence of an *o*-Me group (proximity to the DG) did not obstruct the reaction; the corresponding product **4e** was isolated in 52% yield. Various benzyl- protecting groups irrespective of electronic variation in the arene moiety were unaffected under the strong oxidative conditions, giving access to a wide array of

Scheme 2.8. Reaction scope bifunctional 2-iodobenzoic acid^a

^aConditions: **1** (0.2 mmol), **2** (0.4 mmol), Pd(OAc)₂ (10 mol%), **L9** (30 mol%), AgOAc (0.4 mmol), NaBrO₃ (0.4 mmol), HFIP (46 equiv), AcOH (40 equiv) at 70 °C, under air, 72 h; isolated yield. All compound formed in a 1:1 diastereomeric ratio. ^cReaction carried out for 36 h. ^dFormation of non-cyclized products **3'** (<5%) and recovery of unreacted precursor **1** (15–20%) justify the moderate product yields. ^e**2e** used as a coupling partner.

caprolactones **4f–k** (52–82%) from the reaction of **1b** when performed independently with **2g–l**. Likewise, **4l** (80%) and **4m** (62%) were constructed from the difunctionalization of **1b** with 4,5-dimethoxy-2-iodobenzoic acid **2m** and 4,5-methyl-2-iodobenzoic acid **2n**, respectively. Even 2-iodo-3-naphthanoic acid **2o** participated in the reaction, despite the facile reactivity of the *peri*-C–H bond, constructing **4n** in 50% yield.

Scheme 2.9: Iterative acetoxylation^a



^aConditions: **5** (0.1 mmol), $\text{PhI}(\text{OAc})_2$ (0.15 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol%), AcOH (0.1 mL) at 70 °C, under air, 12 h. All compound formed in a 1:1 diastereomeric ratio.

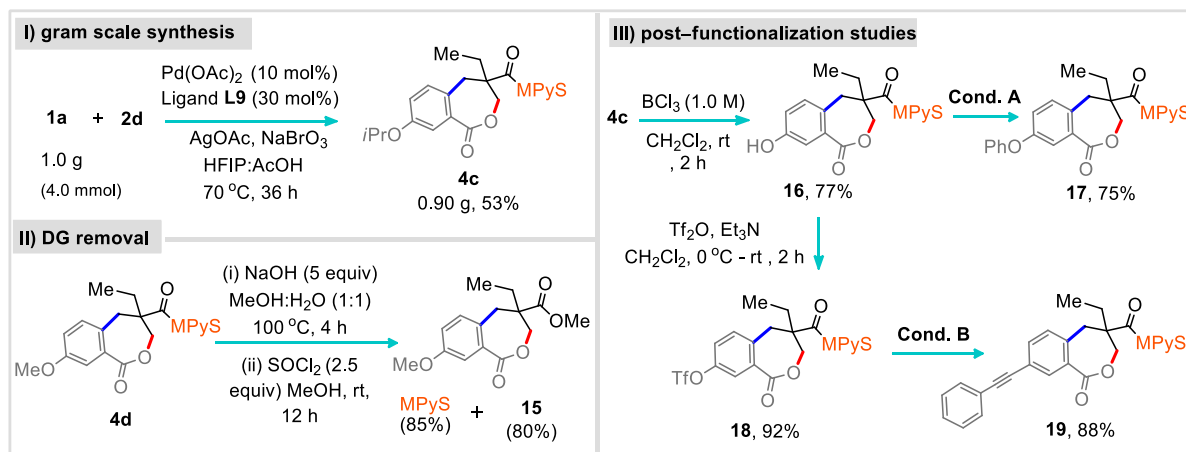
The functionalization of three $C(sp^3)$ -H bonds with two heteroatoms was achieved to build complex molecular entities which would be difficult to access through conventional routes. We indeed performed a Pd-catalyzed MPyS-aided oxidative β - $C(sp^3)$ -H acetoxylation of benzo-fused caprolactones (**5**) in presence of $\text{PhI}(\text{OAc})_2$ at 70 °C (Scheme 2.9).¹² Thus, a range of functionalized products **6a–f** deriving from the sequential functionalization of three C–H bonds of substrates **1** was made with excellent yields.

2.3.4. Application

A few additional reactions were performed to show the robustness of the developed methodology and some post-functionalizations (Scheme 2.10). The reaction was still successful when conducted on the gram scale. Indeed, starting from 1.0 g of **1d** and **2d** as coupling partners under the optimized conditions for 36 h led to **4c** (0.9 g) in 53%

yield (Scheme 2.10-I). Base hydrolysis of the benzo-fused caprolactone **4d**, followed by esterification provided the ester-bearing lactone **15** (Scheme 2.10-II) with the recovery of MPyS-DG (85%). Next, BCl_3 -mediated de-alkylation of **4c** afforded the respective phenol derivative **16** in 73% yield (Scheme 2.10-III). Next, copper-catalyzed arylation of the phenolic OH group of **16** with iodobenzene led to **17** in 75% yield (Scheme 2.10-III). The respective triflate derivative **18**, obtained from **16**, was amenable to Pd-catalyzed Sonogashira cross-coupling to give **19** in 88% yield (Scheme 2.10-III). Thus, the caprolactone moiety was unaffected either by a strong base, Lewis's acid, and even transition-metal catalysts.

Scheme 2.10.: Gram scale synthesis, DG removal, and post synthetic modification.



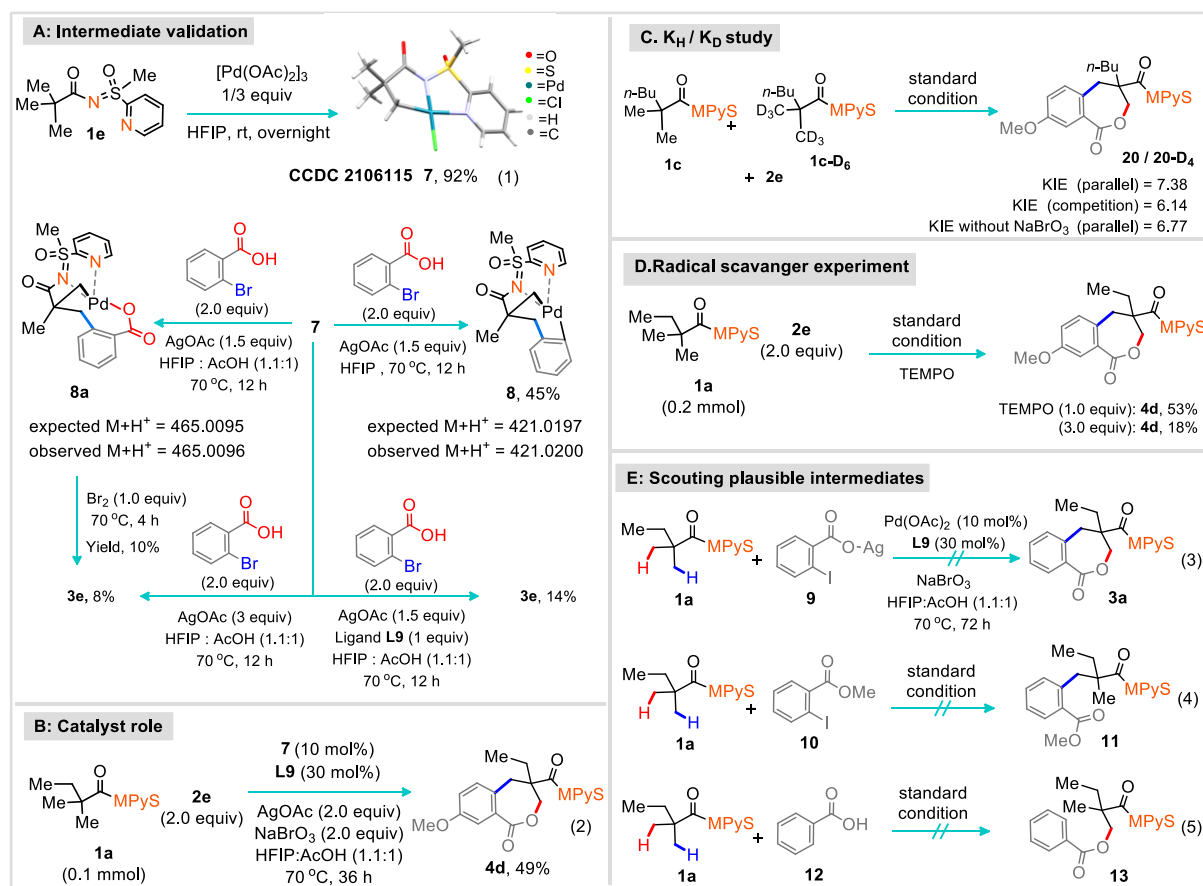
Conditions A: CuI (5.0 mol%), picolinic acid (10 mol%), K_3PO_4 (2.0 equiv), iodobenzene (1.0 equiv), 80 $^\circ\text{C}$, DMSO, 36 h. Conditions B: $Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (5.0 mol%), DIPA (3.0 equiv), phenylacetylene (1.5 equiv), 80 $^\circ\text{C}$, DMF, 24 h.

2.4. Mechanistic study

To get an insight into the reaction mechanism, the reaction of **1e** with $[Pd(OAc)_2]_3$ in HFIP was studied. It successfully delivered the monomeric Pd-complex **7** in 92% yield. X-ray diffraction analysis confirmed its molecular topology (Scheme 2.11, eq 1, Table 2.5); the Cl-insertion is perhaps due to the presence of the residual amount of HCl in HFIP. The reaction of the Pd-complex **7** with 2-bromobenzoic acid (2-iodobenzoic acid proved too reactive) in presence of AgOAc gave the $C(Me)$ -H activated decarboxylated (6,5,5-fused) pincer type Pd-complex **8** (confirmed by 1H NMR and HRMS). The carboxylate ligated $C(Me)$ -H activated-[8,5,5]-fused pincer type Pd-complex **8a** (confirmed by HRMS) was formed when **7** was exposed to 2-

bromobenzoic acid in HFIP and AcOH. These studies validate the sequential functionalization of the two β -C(sp³)-H bonds as well the importance of AcOH to obtain intermediate **8a**. Furthermore, the reaction of complex **7** with 2-bromo benzoic acid with an excess amount of silver oxidant (3.0 equiv) or ligand **L9** (1.0 equiv) could deliver the desired product **3e** in 8% and 14% yield, respectively (Scheme 2.11); we assume that both the oxidant and the ligand are vital in the reductive elimination step. It is also worthy of note that the addition of Br₂ to the **8a** (generated in situ) could deliver the desired product **3e** in 10% yield; probably Br₂ facilitates the oxidation of complex **8a** (Scheme 2.11). Moreover, the reaction of **1a** and **2e** in presence of catalyst **7** under the optimized conditions delivered **4d**, albeit in moderate yield (Scheme 2.11, eq 2); a monomeric Pd-species such as **7** is presumably the active catalyst involved in the transformation. To get further insights, the kinetic isotope effect (KIE) was studied when **1c** and **1c-D₆**, and **2e** were exposed to the optimized conditions (Scheme 2.11). The k_H/k_D value indicates that at least one of the two C-H activation steps is rate-determining. The transformation involves two distinct C-H bond. The average k_H/k_D value is calculated by taking into consideration the overall conversion of the reaction. We observed the k_H/k_D values for KIE (parallel) and KIE (competition) as 7.38 and 6.14, respectively. The value is on the higher side and warrants further investigations.¹⁷ Besides, the same reaction in the absence of NaBrO₃ shows a high k_H/k_D value, an observation whose rationale is unclear at present (Scheme 2.11). Besides, the reaction is feasible in the presence of TEMPO; **4d** being formed in noticeable amount (Scheme 2.11). Next, the reaction of 2-iodobenzoic acid silver salt **9** and **1a** did not give **3a** (Scheme 2.11, eq 3); presumably, AgOAc helps the iodide scavenging (vide infra for a DFT study, Figure 2.9). No formation of C-arylation product **11** and C-O bond formation product **13** was detected from the reaction of 2-iodobenzoic acid methyl ester (**10**) or benzoic acid (**12**) with **1a** when independently carried out under the optimized conditions (Scheme 2.11, eq 4 and 5). The reaction may rely on carboxylic acid-assisted oxidative addition (DFT study, Figure 2.10). Thus, we suggest that a cooperative effect of iodo and carboxylic acid groups is essential to stitch the two C(sp³)-H bonds. While 2-iodobenzoic acid does not directly participate in the CMD (see Table 2.5 for the X-ray crystallographic data of **21** and its use in the reaction).

Scheme 2.11: Mechanistic chart.



2.4.1. DFT study

To further understand the mechanism of this double functionalization, DFT computations related to the reaction of **1e** with **2a** were performed (Figure 2.5). We used the Gaussian 09¹⁸ software package, the ω B97X-D functional¹⁹ and the basis sets LANL2DZ²⁰ for Pd and I and 6-31+G(d,p)²¹ for the C, H, O, S, and N atoms. The solvent effect of HFIP: AcOH (1.1:1) was included using the SMD²² model with the same functional but with the Karlsruhe def2-QZVPP basis set.²³ The mechanistic rationale includes two concerted metalation-deprotonation (CMD) steps, an intramolecular oxidative addition and a reductive elimination. While the CMDs should allow the functionalization of the two $C(sp^3)$ centers, oxidative addition and reductive elimination seem needed to incorporate benzoic acid into the final product. At first, coordination of **1e** with $Pd(OAc)_2$ converged as the chelate complex **int1**, chosen as reference of the free energy profile. Substitution of the pyridine group by a t butyl-C-H bond is achieved through **TS-1-2**, lying at 16.8 kcal/mol on the free energy surface, leading to

the agostic complex **int2**. The latter is less stable than **int1** by 8.8 kcal/mol. An acetate group from this intermediate is responsible for the first CMD (**TS-2-3**), which requires 15.3 kcal/mol free energy of activation (24.1 kcal/mol from **int1**) to give **int3** in an exergonic way (−5.9 kcal/mol). The positive effect of the external pyridine ligand used on the CMD is reported in the additional calculations (Figures 2.7–2.8). Substitution of AcOH by the pyridine fragment then provides **int4** (−0.9 kcal/mol) through **TS-3-4** (−0.1 kcal/mol). The remaining acetate group of **int4** is then exchanged by 2-iodobenzoic acid **2a**, lowering the free energy by 3.6 kcal/mol (**int5**, −4.5 kcal/mol) and making it available for an intramolecular oxidative addition, which has an activation barrier of 28 kcal/mol (**TS-5-6**, 23.5 kcal/mol). The resulting Pd(IV) species **int6** (−1.8 kcal/mol) is slightly higher energy than **int5** by 2.7 kcal/mol; however, iodine scavenger by AgOAc provides **int7** (−13.5 kcal/mol), which is almost 12 kcal/mol more stable than **int6**. The first carbon center functionalization is achieved through a reductive elimination, which might form either a C(sp³)-C(Ar) bond (**int8**) or C(sp³)-O bond (**int8-CO**, not shown). The formation of C(sp³)-O bond actually demands 20.5 kcal/mol more than that of the C(sp³)-C(Ar) bond and was thus ruled out (additional calculations, Figure 2.9). This in turn means that the second functionalization will be the formation of the C(sp³)-O bond. The C(sp³)-C(Ar) bond formation has an overall barrier of 17.0 kcal/mol (**TS-7-8**; 3.5 kcal/mol) and yields **int8** (−31.8 kcal/mol) in a highly exergonic manner. Complex **int8** still has an acetate group in its coordination sphere (incorporated from AgOAc), which is able to perform the second CMD step towards the last C(sp³)-H functionalization (Figure 2.6). This process requires 19.8 kcal/mol to reach **TS-8-9** (−12.0 kcal/mol) and provides **int9** (−31.4 kcal/mol). Starting from **int9**, three pathways were studied to rationalize the C-O bond formation: *i*) Pd(II)-to-Pd(0); *ii*) Pd(II)-to-Pd(IV)-to-Pd(II) with bromine groups, and *iii*) Pd(II)-to-Pd(IV)-to-Pd(II) with acetate groups (additional calculations, Figure 2.9.A). Hypothesis-*i* is the one that demands the highest energy, i.e., almost 50 kcal/mol (additional calculations, Figure 2.9.A). In both Pd(IV) species **int10-Br₂** and **int10-(OAc)₂**, the *cis* conformation is more stable than its *trans* counterpart. For the bromide system (hypothesis-*ii*), Br₂ was used as model oxidant (likely obtained from NaBrO₃).²⁴ The

formation of **int10-Br₂** (−44.8 kcal/mol) is detailed in the additional data (additional calculations, Figure 2.9.A). The corresponding reductive elimination step (**TS-10-11-Br₂**; −25.7 kcal/mol) requires almost 20 kcal/mol to give **int11-Br₂** (−68.4 kcal/mol), which is 36.9 kcal/mol more stable than **int9**. Oxidation by just AgOAc was also studied (hypothesis-*iii*, additional calculations, Figure 2.9.A), but it generates silver(0), which cannot be easily dealt with computationally as it may form nanoparticles and/or stay bound to donor atoms. Comparing the energy of [AgOAc and **int9**] with [**int10**-(OAc)₂ and Ag] gave a positive difference of several hundreds of kcal/mol.

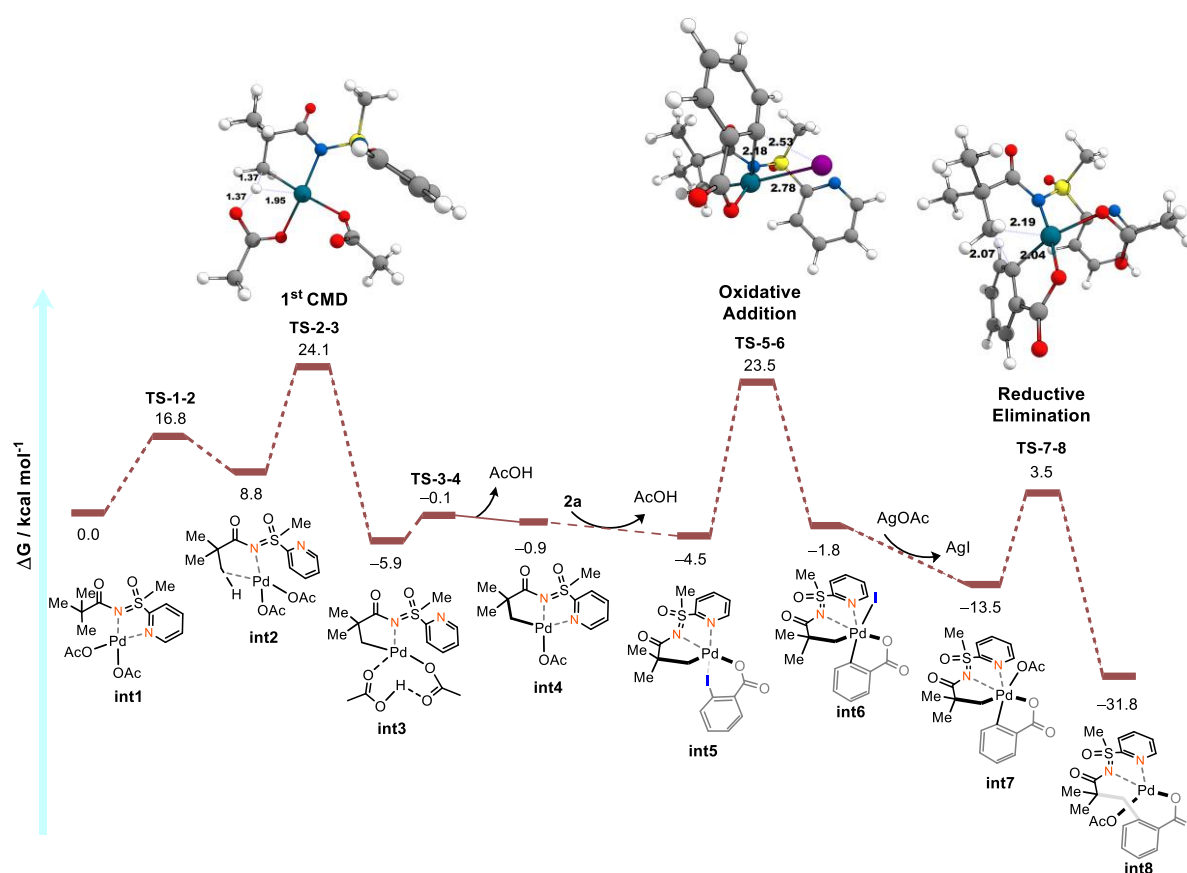


Figure 2.5. Free energy profile ($\Delta G_{343.15}$ in kcal/mol) of the 1st C-H functionalization. Selected distances (in Å) are shown in the transition structures.

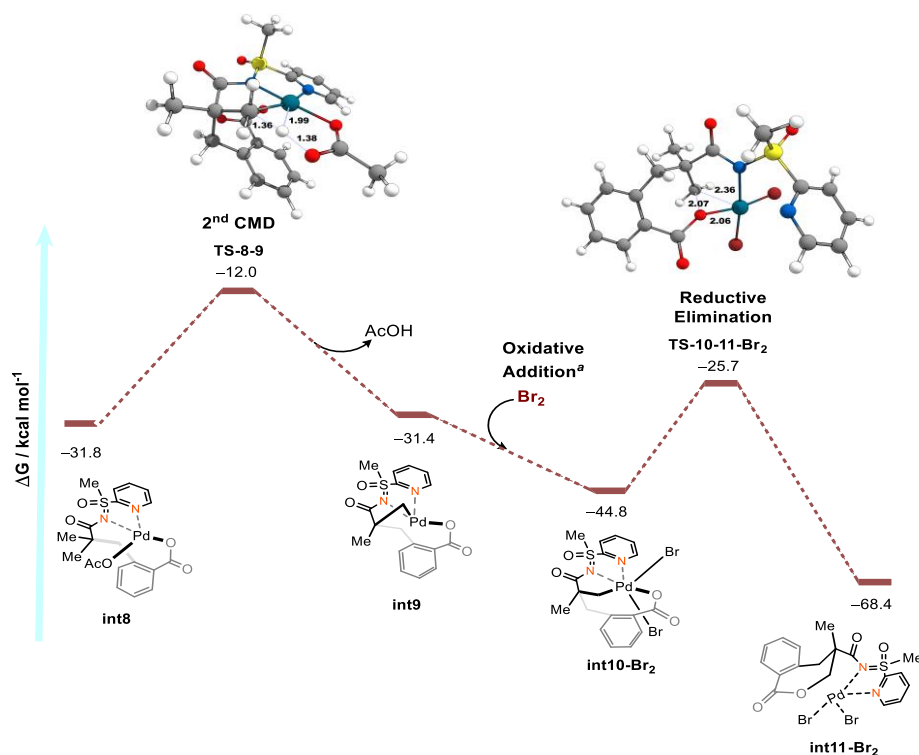


Figure 2.6. Free energy profile ($\Delta G_{343.15}$ in kcal/mol) of the 2nd C-H functionalization. Selected distances (in Å) are shown in the transition structures.

Since AgOAc is a dimer, we then used $Ag_2(OAc)^{25a}$ and Ag_2^{25b} as model silver (0) cluster, but again the difference was ~60–70 kcal/mol (additional calculations, Figure 2.9.A). If this point is reached, then the reductive elimination can occur at reasonable free energy of activation cost: 23.9 kcal/mol. Thus, the computations cannot support one external oxidant other another, but they clearly show that a Pd (II)-to-Pd(IV)-to-Pd(II) pathway is preferable over Pd(II)-to-Pd(0).

2.4.2 Additional calculations:

Considering Yu's and Hong's work,²⁶ we studied the possibility of the first CMD being assisted by the external pyridine (2-chloro-5-(trifluoromethyl) pyridine), referred to as **py*** in Figure 2.7. As discussed in the manuscript, from the agostic complex **int2**, the CMD barrier is 15.34 kcal/mol. From the corresponding cationic complex **int2_py***⁺, the barrier is significantly lowered to 11.89 kcal/mol. Interestingly, the pyridine ring is also able to form the neutral adduct **int2_py*** with **int2**. Despite the entropic penalty, the formation of this adduct is endergonic by 0.46 kcal/mol only. The corresponding

CMD barrier is 11.87 kcal/mol, which is also markedly lower than the ligand-free neutral CMD. Thus, although the external pyridine may interfere with the intermediates at various steps, these calculations suggest that the interaction between the aromatic ring of the ligand and the metal can facilitate the CMD.

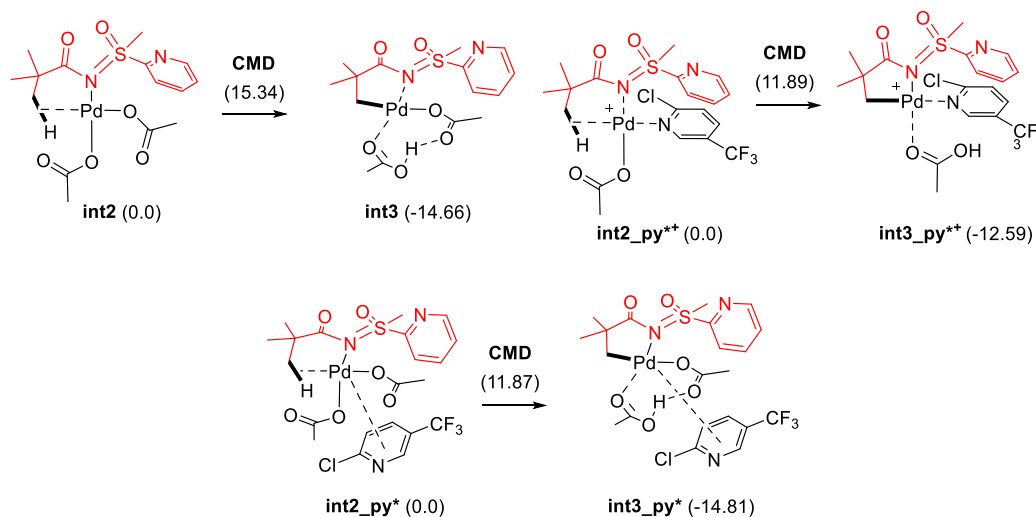


Figure 2.7. Free energy profile ($\Delta G_{343.15}$ in kcal/mol) of the different approaches for the first $C(sp^3)$ -H activation of **1e**. Selected distances (in Å) are shown in the transition structure.

Orbital overlap between Pd and the π -system of the pyridine can be found in the HOMO and the HOMO-1 of **int2_py*** (Figure 2.8).

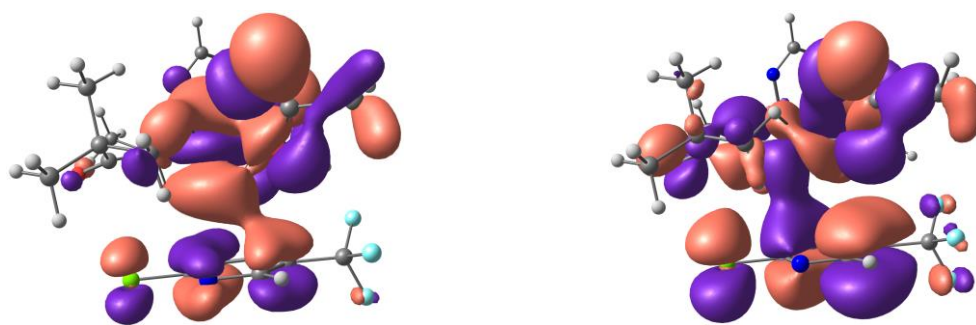


Figure 2.8. HOMO (left) and HOMO-1 (right) of complex **int2_py*** (contour value 0.01447).

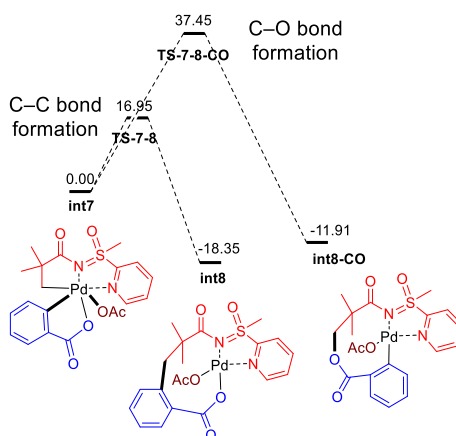


Figure 2.9. Free energy profile ($\Delta G_{343.15}$ in kcal/mol) for the different possible products for the first $C(sp^3)$ -H functionalization of **1e**.

Figure 2.10. shows hypothesis *i*) Pd(II)-to-Pd(0); hypothesis *ii*) Pd(II)-to-Pd(IV)-to-Pd(II) with bromine groups and hypothesis *iii*) Pd(II)-to-Pd(IV)-to-Pd(II) with acetate groups, corresponding to the 2nd reductive elimination forming the C-O bond.

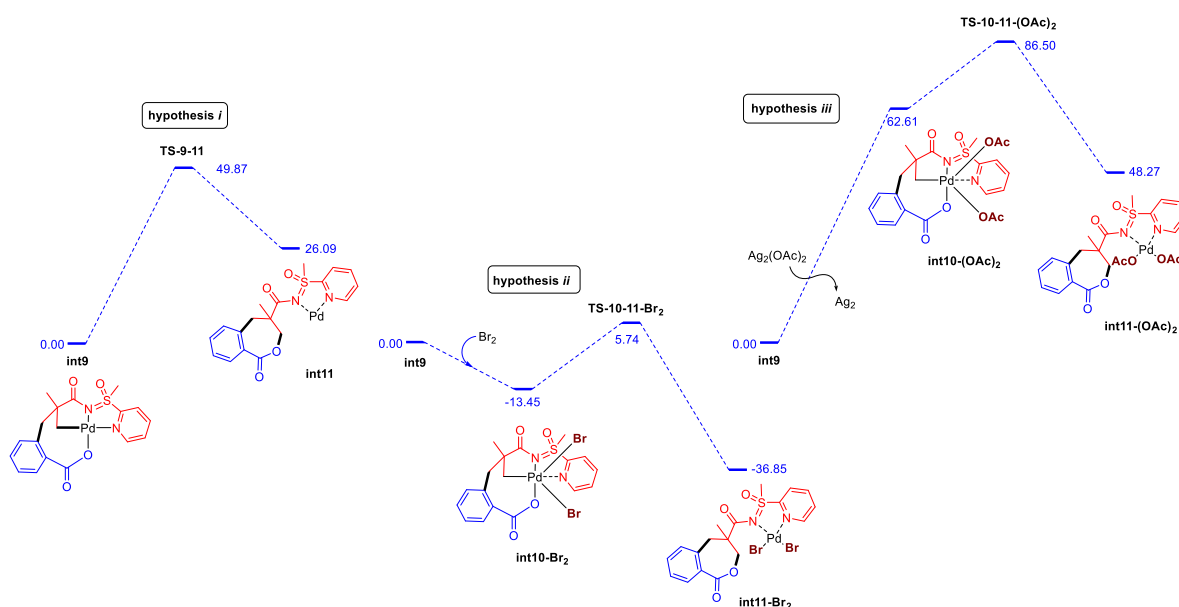


Figure 2.10. Free energy profile ($\Delta G_{343.15}$ in kcal/mol) for the different possible products for the second $C(sp^3)$ -H functionalization of **1e**.

Finally, the transformation of **int9** into **int10-Br₂** was studied in detail. As a preliminary note, complex **int9** is positively charged at the metal center (Pd NBO charge for **int9-S²⁷**: 0.702) and strongly negatively charged at the oxygen atom bond to palladium

(O NBO charge for **int9-S**²⁷: -0.576). Thus, the formation of an adduct between **int9** and Br_2 gives two isomers, one involving the bromine lone pair ($Br \rightarrow Pd$ coordination, **int12-Br₂**, not shown), but one involving the σ -hole²⁸ of Br_2 ($O \cdots Br-Br$ interaction, **int13-Br₂**). The latter is actually more stable by 0.7 kcal/mol but more importantly, it can be connected via a transition state to the hypervalent bromine(III) species **int14-Br₂**. This step requires 9.2 kcal/mol of free energy of activation. While the resulting complex **int14-Br₂** is less stable than **int9** by 4.0 kcal/mol, it can be connected to the oxidative addition product **int10-Br₂** via **TS-14-10** at the expense of 17.7 kcal/mol. This step is appreciably exergonic by 24.7 kcal/mol (Figure 2.11).

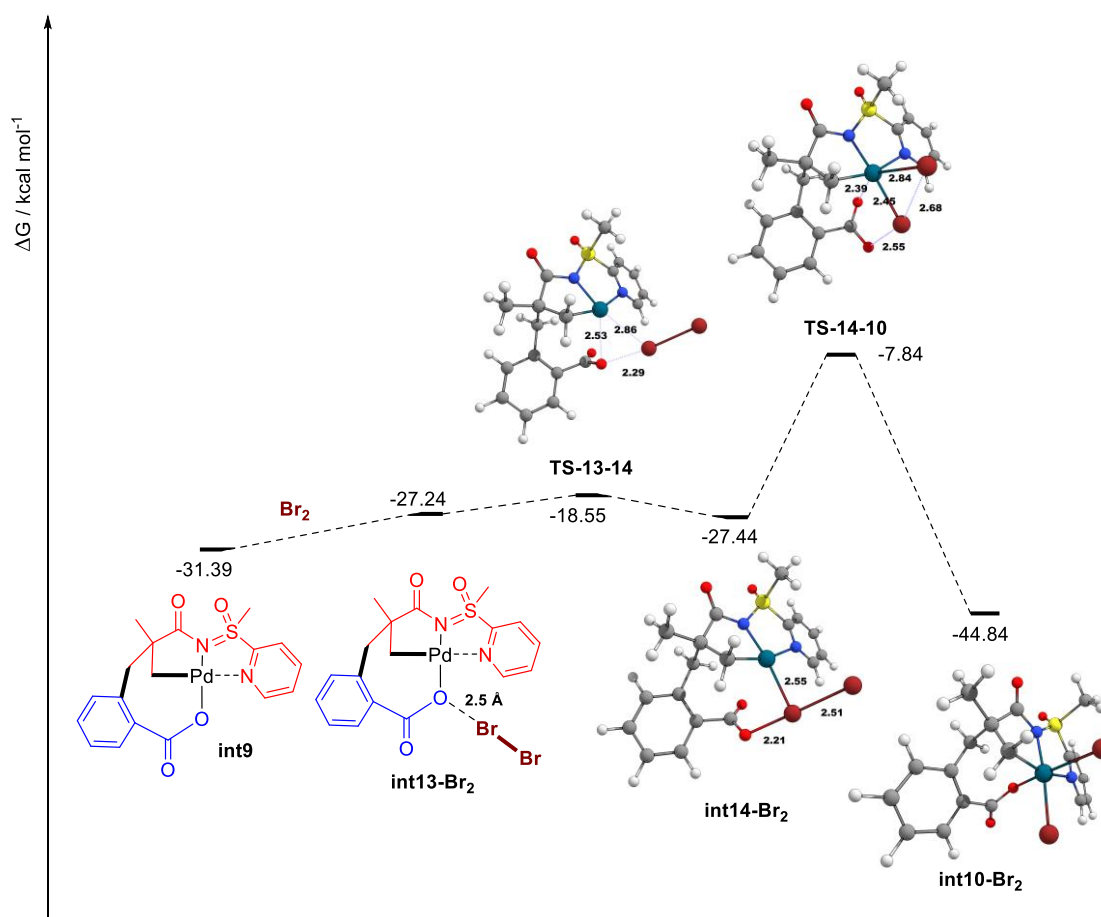


Figure 2.11. Free energy profile ($\Delta G_{343.15}$ in kcal/mol) of the bromination of **int9** to give **int10-Br₂**. Selected distances (in Å) are shown in the transition structures.

2.5. Conclusion

In summary, this work describes the difunctionalization of two distinct inert C(sp³)-H bonds with a bifunctional reagent (2-iodobenzoic acid) to obtain unusual benzo-fused caprolactones. The combination of a bidentate MPyS directing group, 2-chloro-5-trifluoromethyl pyridine as ligand, AgOAc as base and oxidant, NaBrO₃ as co-oxidant, in presence of a Pd (II) catalyst proved successful in making C(sp³)-C(arene) and C(sp³)-O bond smoothly in a single operation. In-depth DFT calculations validate the role of the ligand and oxidant, as well as the key intermediates involved in the sequential functionalization of the two C(sp³)-H bonds [*gem*- α,α' -di-Me groups bearing aliphatic carboxylic acid] for the construction of caprolactones. A monomeric Pd-complex is involved in the catalytic cycle, a stoichiometric experiment justifies this observation. The transformation tolerates common functional groups, providing access to a large range of functionalized caprolactones that can be used for further synthetic elaborations. Overall, this work underscores a few key features: 1) Pd-arene interaction from the pyridine ligand accelerates the CMD of the C(sp³)-H bonds; 2) oxidation of Pd (II) to Pd (IV) species by an external oxidant makes the C-O reductive elimination facile; 3) a mixture of solvents prevent the decarboxylative arylation, which is highly likely. The current findings on the double functionalization of two C(sp³)-H bonds to access cyclic molecular scaffolds pave the way for the development of new reactions in this emerging area.

2.6. Experimental

2.6.1. General Experimental Information

All the reactions were performed in an oven-dried 5 mL screw capped pressure tube. Commercial grade solvents were distilled prior to use. Column chromatography was performed using either 100–200 Mesh or 230–400 Mesh silica gel. Thin layer chromatography (TLC) was performed on silica gel GF254 plates. Visualization of spots on TLC plates was accomplished with UV light (254 nm) and staining over molecular iodine. Proton and carbon nuclear magnetic resonance spectra (¹H and ¹³C NMR) were

recorded based on the resonating frequencies as follows: (^1H NMR, 400 MHz; ^{13}C NMR, 101 MHz) and (^1H NMR, 500 MHz; ^{13}C NMR, 126 MHz) having the solvent resonance as internal standard (^1H NMR, CHCl_3 at 7.26 ppm; ^{13}C NMR, CDCl_3 at 77.0 ppm). In few cases, tetramethylsilane (TMS) was used as reference standard at 0.00 ppm. Data for ^1H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet; bs = broad singlet; d = doublet; bd = broad doublet, t = triplet; bt = broad triplet; q = quartet; dd = doublet of doublet; td = triplet of doublet, dt = doublet of triplet, ddd; doublet of doublet of doublet; m = multiplet), coupling constants, J , in Hz, and integration. Data for ^{13}C NMR are reported as chemical shifts (ppm). IR spectra were reported in cm^{-1} . High resolution mass spectra were obtained in ESI mode in the Maxis-TOF analyser. X-ray data was collected at 298 K using graphite monochromated Mo- $K\alpha$ radiation (0.71073 Å). Melting points were determined by electro-thermal heating and are uncorrected.

2.6.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Dichloromethane (DCM) and chloroform were distilled over CaH_2 . Acetic acid was distilled over KMnO_4 . Tetrahydrofuran (THF) was freshly distilled over sodium/benzophenone ketyl under nitrogen. $\text{Pd}(\text{OAc})_2$, PdCl_2 , $\text{Pd}(\text{OTFA})_2$, $\text{Pd}(\text{acac})_2$, $\text{Pd}(\text{CH}_3\text{CN})_2(\text{Cl})_2$, NaBrO_3 were purchased from Sigma Aldrich Ltd, and used as received. All pyridine ligands were purchased from Sigma Aldrich Ltd and ChemScene. All sodium and potassium salts were purchased from Sigma Aldrich Ltd and used as received. Oxidants such as $\text{Na}_2\text{S}_2\text{O}_8$, $\text{PhI}(\text{OAc})_2$, BQ, TBHP, oxone, and various silver salts were purchased from Aldrich Ltd and $\text{K}_2\text{S}_2\text{O}_8$ was purchased from Merck Ltd. Analytical and spectral data of all those known compounds are exactly matching with the reported values.

2.6.3. Experimental Procedures and Analytical Data

2.6.3.1. Preparation of *S*-methyl-*S*-2-pyridylsulfoximine (MPyS):²⁹

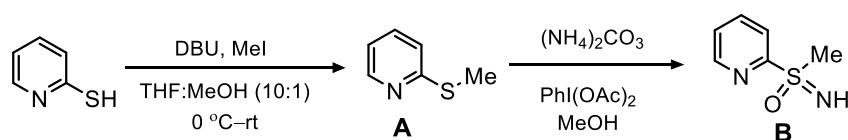
Part- I ^{29a}

To a solution of 2-mercaptopyridine (100 mmol, 11.11 g) in dry THF (200 mL) and CH_3CN (20 mL), cooled to 0 °C, was added DBU (110 mmol, 16.75 g). The resulting mixture was stirred at 0 °C for 5 min before MeI (110 mmol, 15.61 g) was slowly added. The ice bath was removed and the mixture was stirred overnight. The reaction mixture

was washed with water (100 mL) and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (n-hexane-EtOAc 2:1) to afford the methyl 2-pyridyl sulfide (A) as a colorless oil.

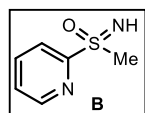
Part- II ^{29b}

To a stirred solution of sulfide (1 mmol) in MeOH (10 ml) was added the $(NH_4)_2CO_3$ (1.5 equiv.). Subsequently, $PhI(OAc)_2$ (2.3 equiv) was added and the solution was stirred at rt. After the disappearance of the sulfide (checked by TLC), the solvent was removed under reduced pressure. The crude product was purified by column chromatography (DCM-MeOH 10:1) to afford the S-Methyl-S-2-pyridylsulfoximine (B) as a colorless oil.



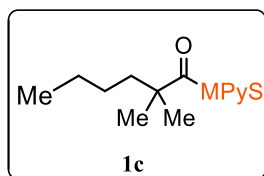
Scheme 2.13 Preparation of MPyS

S-Methyl-S-2-pyridylsulfoximine (MPyS) (B):

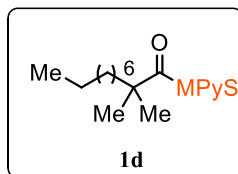


¹H NMR (400 MHz, $CDCl_3$) δ 8.73 (bd, $J = 4.0$ Hz, 1H), 8.13 (bd, $J = 7.6$ Hz, 1H), 7.95 (td, $J = 7.7, 1.3$ Hz, 1H), 7.51 (dd, $J = 6.8, 4.8$ Hz, 1H), 3.26 (s, 3H), 2.89 (bs, 1H, NH). ¹³C NMR (101 MHz, $CDCl_3$) δ 160.4, 150.0, 138.2, 126.7, 121.1, 42.3.

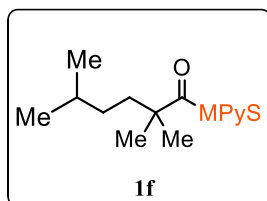
N-[2,2-Dimethylpropanoyl]-S-methyl-S-(2-pyridyl) sulfoximine (1c):



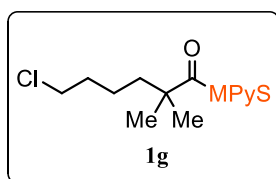
Compound **1c** (1.55 g, 72%) was prepared following the general procedure GP-2; colorless solid. **mp** = 107–109 °C. R_f = 0.19 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ¹H NMR (500 MHz, $CDCl_3$) δ 8.69–8.63 (m, 1H), 8.24 (dt, $J = 8.0, 1.0$ Hz, 1H), 7.98–7.92 (m, 1H), 7.56–7.50 (m, 1H), 3.38 (s, 3H), 1.55–1.43 (m, 2H), 1.28–1.17 (m, 2H), 1.17–1.07 (m, 8H), 0.87–0.82 (m, 3H). ¹³C[¹H] NMR (126 MHz, $CDCl_3$) δ 188.0, 157.3, 149.6, 138.0, 127.0, 123.3, 44.3, 40.9, 39.5, 27.0, 25.6, 25.2, 23.3, 14.0. IR (Neat) ν_{max} 2922, 1617, 1577, 1423, 1317, 1208, 1168, 977, 961, 854, 752 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{14}H_{23}N_2O_2S^+$ [M+H], 283.1475; found 283.1477.

N-[2,2-Dimethylbutyroyl]-S-methyl-S-(2-pyridyl) sulfoximine (1d):

compound **1d** (1.76 g, 74%) was prepared following the general procedure GP-2; colorless solid. **mp** = 81–83 °C. R_f = 0.35 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.64 (m, 1H), 8.26 (dt, J = 8.0, 1.0 Hz, 1H), 7.99–7.93 (m, 1H), 7.56–7.51 (m, 1H), 3.39 (s, 3H), 1.55–1.43 (m, 2H), 1.31–1.15 (m, 12H), 1.13 (s, 3H), 1.10 (s, 3H), 0.89–0.84 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 188.1, 157.4, 149.6, 138.0, 127.0, 123.3, 44.4, 41.2, 39.5, 31.9, 30.3, 29.5, 29.3, 25.6, 25.2, 24.8, 22.7, 14.1. IR (Neat) ν_{max} 2921, 2852, 1618, 1448, 1215, 1182, 977, 962, 752 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{18}\text{H}_{31}\text{N}_2\text{O}_2\text{S}^+$ [$\text{M} + \text{H}$], 339.2101; found 339.2101.

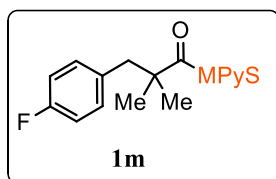
N-[2,2,5-Trimethylhexanoyl]-S-methyl-S-(2-pyridyl) sulfoximine (1f):

compound **1f** (1.35 g, 65%) was prepared following the general procedure GP-2; colorless solid. **mp** = 115–117 °C. R_f = 0.26 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.68–8.62 (m, 1H), 8.27–8.21 (m, 1H), 7.99–7.92 (m, 1H), 7.54–7.48 (m, 1H), 3.36 (s, 3H), 1.55–1.37 (m, 3H), 1.10 (s, 3H), 1.07 (s, 3H), 1.05–0.98 (m, 2H), 0.85–0.78 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 188.0, 157.4, 149.7, 138.0, 127.1, 123.4, 44.4, 39.5, 39.0, 33.8, 28.6, 25.7, 25.2, 25.1, 22.6. IR (KBr) ν_{max} 2951, 1618, 1423, 1317, 1280, 1208, 1175, 1084, 978, 858, 752 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{NaO}_2\text{S}^+$ [$\text{M} + \text{Na}$], 319.1451; found 319.1451.

N-[6-Chloro-2,2-dimethylhexanoyl]-S-methyl-S-(2-pyridyl) sulfoximine (1g):

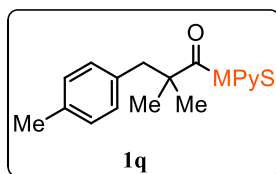
compound **1g** (936 mg, 42%) was prepared following the general procedure GP-2; colorless solid. **mp** = 139–141 °C. R_f = 0.30 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.65 (bs, 1H), 8.26–8.19 (m, 1H), 7.99–7.93 (m, 1H), 7.55–7.48 (m, 1H), 3.52–3.44 (m, 2H), 3.36 (s, 3H), 1.77–1.66 (m, 2H), 1.59–1.45 (s, 2H), 1.37–1.27 (m, 2H), 1.12 (bs, 3H), 1.09 (bs, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 187.5, 157.2, 149.6, 138.0, 127.0, 123.2, 44.9, 44.3, 40.2, 39.5, 33.1, 25.5, 25.2, 22.3. IR (KBr) ν_{max} 2934, 1623, 1453, 1307, 1254, 1208, 1179, 988, 975, 856, 819, 759 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{14}\text{H}_{22}\text{ClN}_2\text{O}_2\text{S}^+$ [$\text{M} + \text{H}$], 317.1085; found 317.1088.

N-[3-(4-Fluorophenyl)-2,2-dimethylpropanoyl]-S-methyl-S-(2-pyridyl) sulfoximine (1m):



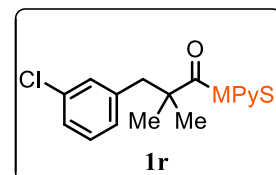
compound **1m** (1.62 g, 69%) was prepared following the general procedure GP-2; colorless solid. **mp** = 160–162 °C. R_f = 0.30 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.72–8.66 (m, 1H), 8.22 (dd, J = 8.0, 1.0 Hz, 1H), 7.95 (td, J = 7.5, 1.5 Hz, 1H), 7.58–7.51 (m, 1H), 7.14–7.05 (m, 2H), 6.90–6.81 (m, 2H), 3.39 (s, 3H), 2.90–2.78 (m, 2H), 1.13 (s, 3H), 1.08 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.9, 161.5 (d, J = 232 Hz), 157.3, 149.6, 138.1, 134.4, 131.6 (d, J = 7.2 Hz, 1C), 127.1, 123.4, 114.6 (d, J = 19 Hz, 1C), 114.4 (d, J = 20 Hz, 1C), 45.56 & 45.52 (1C), 39.5, 25.6, 25.0, 24.7; ^{19}F NMR (376 MHz, CDCl_3) δ -116.70 & -117.56 (1F); IR (Neat) ν_{max} 2972, 2922, 1626, 1507, 1466, 1448, 1279, 1214, 1192, 1126, 989, 956, 844, 772 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{17}\text{H}_{20}\text{FN}_2\text{O}_2\text{S}^+$ $[M+H]$, 335.1224; found 335.1229.

N-[2,2-Dimethyl-3-(*p*-tolyl)propanoyl]-S-methyl-S-(2-pyridyl) sulfoximine (1q):



compound **1q** (1.74 g, 75%) was prepared following the general procedure GP-2; colorless solid. **mp** = 167–169 °C. R_f = 0.32 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.71 (bd, J = 4.5 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.96 (td, J = 8.0, 1.5 Hz, 1H), 7.55 (dd, J = 7.25, 4.75 Hz, 1H), 7.10–6.97 (m, 4H), 3.43 (s, 3H), 2.90–2.78 (m, 2H), 2.28 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 187.3, 157.3, 149.6, 138.0, 135.6, 135.3, 130.2, 128.4, 127.1, 123.3, 45.9, 45.6, 39.5, 25.4, 25.0, 21.0. IR (Neat) ν_{max} 2965, 2923, 1627, 1576, 1446, 1421, 1216, 1194, 1128, 987, 956 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_2\text{S}^+$ $[M+H]$, 331.1475; found 331.1475.

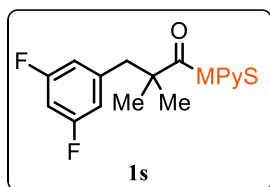
N-[3-(3-Chlorophenyl)-2,2-dimethylpropanoyl]-S-methyl-S-(2-pyridyl)-sulfoximine (1r):



compound **1r** (1.68 g, 68%) was prepared following the general procedure GP-2; colorless solid. **mp** = 152–155 °C. R_f = 0.34 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.70 (bd, J = 4.0 Hz, 1H), 8.20 (d, J = 6.5 Hz, 1H), 8.01–7.91 (m, 1H), 7.57–7.50 (m, 1H), 7.15 (s, 1H), 7.14–6.98 (m, 3H), 3.40 (s, 3H), 2.92–2.78 (m, 2H), 1.15 (s, 3H), 1.10 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (121 MHz, CDCl_3) δ 186.6, 157.0, 149.7, 140.8, 138.1, 133.3, 130.1, 128.8, 128.5, 127.1, 126.1, 123.1, 45.8, 45.4, 39.4, 25.6, 25.0. IR (Neat)

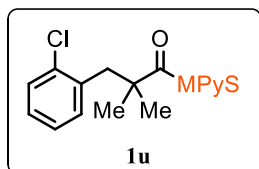
$\nu_{\max}$ 2923, 1625, 1576, 1446, 1421, 1197, 1130, 990, 958, 844, 755 cm^{-1} . HRMS (ESI-TOF) m/z calcd. for $\text{C}_{17}\text{H}_{20}\text{ClN}_2\text{O}_2\text{S}^+$ [M+H], 351.0929; found 351.0929.

N-[3-(3,5-Difluorophenyl)-2,2-dimethylpropanoyl]-S-methyl-S-(2-pyridyl) sulfoximine (1s):



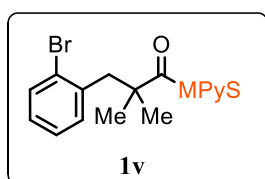
compound **1s** (1.56 g, 63%) was prepared following the general procedure GP-2; colorless solid. **mp** = 162–164 °C. R_f = 0.40 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (400 MHz, CDCl_3) δ 8.69 (bs, 1H), 8.26–8.20 (m, 1H), 8.01–7.91 (m, 1H), 7.57–7.49 (m, 1H), 6.65 (bd, J = 7.6 Hz, 2H), 6.61–6.53 (m, 1H), 3.38 (s, 3H), 2.93 (d, J = 13.2 Hz, 1H), 2.76 (d, J = 13.2 Hz, 1H), 1.18 (s, 3H), 1.06 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 186.2, 163.36 (dd, J = 248.5, 13.13 Hz, 1C), 157.1, 149.8, 142.8 (t, J = 9.1 Hz, 1C), 138.0, 127.1, 123.3, 112.8 (dd, J = 18.2, 6.1 Hz, 1C), 101.3 (t, J = 25.3 Hz, 1C), 46.1, 45.5, 39.6, 26.1, 24.9; ^{19}F NMR (376 MHz, CDCl_3) δ -111.33, -111.34; IR (Neat) $\nu_{\max}$ 2968, 1624, 1591, 1449, 1318, 1217, 1195, 1113, 998, 979, 959, 870, 840 cm^{-1} . HRMS (ESI) m/z : [M+H] $^+$ calcd. for $\text{C}_{17}\text{H}_{19}\text{F}_2\text{N}_2\text{O}_2\text{S}$, 353.1130; found 353.1130.

N-[3-(2-Chlorophenyl)-2,2-dimethylpropanoyl]-S-methyl-S-(2-pyridyl) sulfoximine (1u):



compound **1u** (1.38 g, 56%) was prepared following the general procedure GP-2; colorless solid. **mp** = 153–155 °C. R_f = 0.25 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (400 MHz, CDCl_3) δ 8.70 (bs, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.98–7.91 (m, 1H), 7.57–7.48 (m, 1H), 7.15 (s, 1H), 7.14–6.88 (m, 3H), 3.40 (s, 3H), 2.89 (d, J = 13.6 Hz, 1H), 2.81 (d, J = 13.2 Hz, 1H), 1.15 (s, 3H), 1.10 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 186.5, 157.1, 149.7, 140.9, 138.0, 133.3, 130.1, 128.9, 127.1, 126.1, 123.1, 45.9, 45.5, 39.4, 25.6, 25.1. IR (Neat) $\nu_{\max}$ 2922, 1624, 1421, 1274, 1196, 1129, 1080, 980, 958, 755 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{17}\text{H}_{20}\text{ClN}_2\text{O}_2\text{S}^+$ [M+H], 351.0929; found 351.0932.

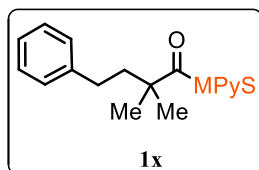
N-[3-(2-Bromophenyl)-2,2-dimethylpropanoyl]-S-methyl-S-(2-pyridyl) sulfoximine (1v):



compound **1v** (1.61 g, 58%) was prepared following the general procedure GP-2; colorless solid. **mp** = 155–157 °C. R_f = 0.25 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.68 (bs, 1H), 8.28–8.21 (m, 1H), 7.98–7.92 (m, 1H), 7.58–7.50 (m,

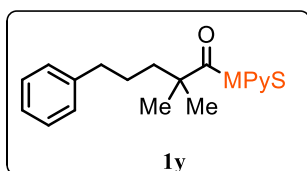
1H), 7.47 (bd, $J = 7.0$ Hz, 1H), 7.23 (d, $J = 7.5$ Hz, 1H), 7.08 (t, $J = 7.5$ Hz, 1H), 6.97 (bt, $J = 7.5$ Hz, 1H), 3.40 (s, 3H), 3.16 (d, $J = 13.5$ Hz, 1H), 3.13 (d, $J = 13.5$ Hz, 1H), 1.19 (s, 3H), 1.15 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.9, 157.09 & 157.04 (1C), 149.6, 138.6, 138.03 & 138.02 (1C), 132.6, 131.5, 127.5, 127.10 & 127.07 (1C), 126.8, 125.9, 123.3, 46.2, 44.0, 39.5, 25.5, 24.9. IR (Neat) ν_{max} 29266, 1627, 1422, 1278, 1214, 1136, 991, 958, 844, 749 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{17}\text{H}_{20}\text{BrN}_2\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]$, 395.0423; found 395.0423.

N-[2,2-Dimethyl-4-phenylbutanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (1x):

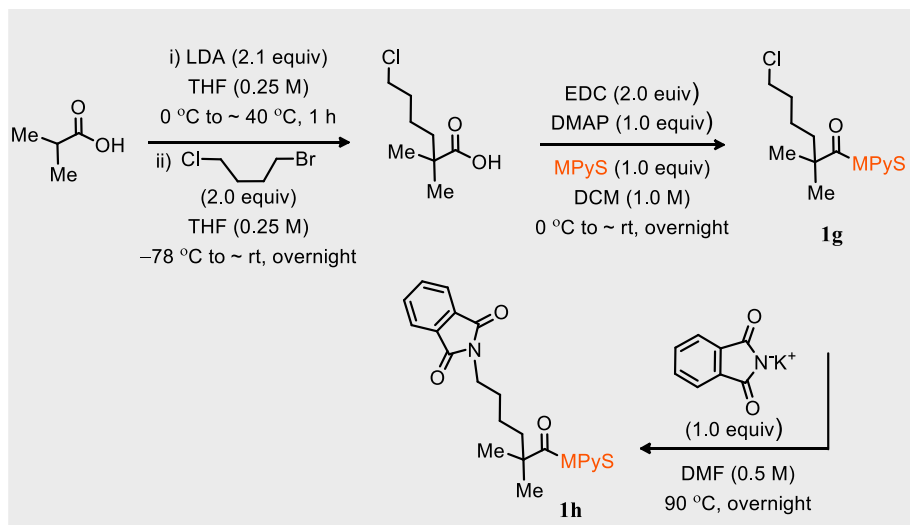


compound **1x** (1.65 g, 71%) was prepared following the general procedure GP-2; colorless solid. **mp** = 154–156 °C. R_f = 0.25 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.66 (d, $J = 4.0$ Hz, 1H), 8.29 (d, $J = 8.0$, 1H), 7.98 (td, $J = 7.8, 1.3$ Hz, 1H), 7.56–7.51 (m, 1H), 7.30–7.24 (m, 2H), 7.22–7.14 (m, 3H), 3.41 (s, 3H), 2.55–2.45 (m, 2H), 1.92–1.76 (m, 2H), 1.23 (s, 3H), 1.18 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (121 MHz, CDCl_3) δ 187.4, 157.3, 149.7, 143.1, 138.0, 128.3, 128.2, 127.0, 125.5, 123.4, 44.5, 43.5, 39.6, 31.4, 25.7, 25.0. IR (Neat) ν_{max} 2921, 1607, 1578, 1424, 1320, 1260, 1221, 1185, 979, 959, 752 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]$, 331.1475; found 331.1476.

N-[2,2-Dimethyl-5-phenylpentanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (1y):



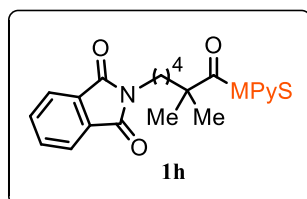
compound **1y** (1.45 g, 60%) was prepared following the general procedure GP-2; colorless solid. **mp** = 147–149 °C. R_f = 0.28 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (400 MHz, CDCl_3) δ 8.59 (bd, $J = 4.4$, Hz, 1H), 8.22 (d, $J = 8.0$ Hz, 1H), 7.93 (t, $J = 7.8$ Hz, 1H), 7.53–7.47 (m, 1H), 7.30–7.22 (m, 2H), 7.20–7.13 (m, 3H), 3.35 (s, 3H), 2.60–2.52 (m, 2H), 1.66–1.48 (m, 4H), 1.14, (s, 3H), 1.10, (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 187.6, 157.3, 149.6, 142.6, 137.9, 128.4, 128.1, 127.0, 125.4, 123.3, 44.3, 40.8, 39.5, 36.4, 26.5, 25.6, 25.2. IR (Neat) ν_{max} 2916, 1614, 1560, 1449, 1217, 1180, 1122, 984, 749 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]$, 345.1631; found 345.1632.

2.6.3.2 Preparation of **1h**:

The compound **1g** was at first prepared following the general procedures (**GP-1** and **2**) narrated above from isobutyric acid and 1-bromo-4-chlorobutane.

Next, a suspension of **1g** (300 mg, 0.946 mmol) and potassium phthalimide (210 mg, 1.13 mmol) in DMF (3.0 mL) was stirred overnight at 90 °C. The reaction mixture was cooled to room temperature and diluted with EtOAc. The organic layer was washed with water and brine. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo. The crude residue was purified by column chromatography eluting with (EA/hexane 1:1) to afford **1h** (254 mg, 63%).

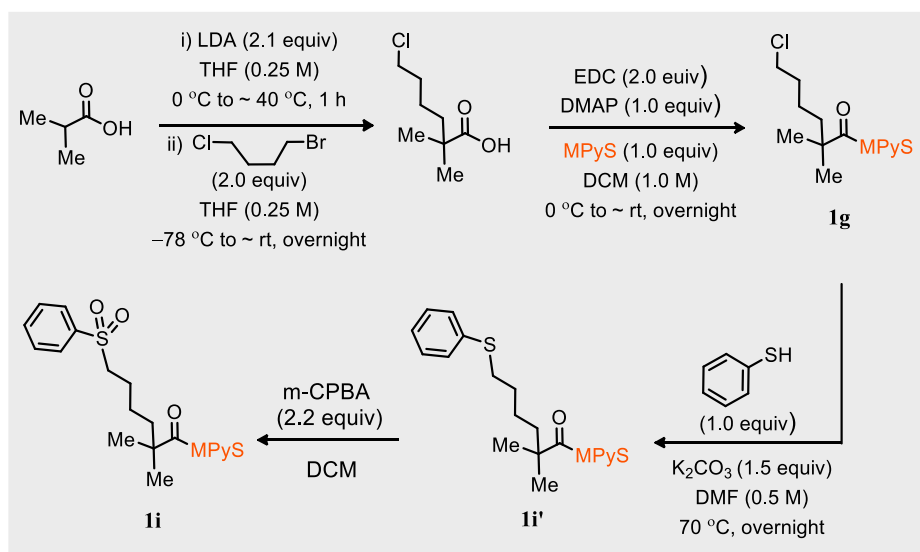
N-[6-(1,3-Dioxoisindolin-2-yl)-2,2-dimethylhexanoyl]-S-methyl-S-(2-pyridyl) sulfoximine (1h):



compound **1h** (254 mg, 63%) was prepared as colorless solid.

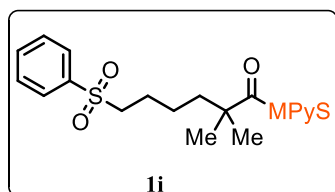
mp = 244–248 °C. R_f = 0.33 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (400 MHz, CDCl_3) δ 8.69 (bd, J = 4.8 Hz 1H), 8.23 (d, J = 7.6 Hz, 1H), 7.97 (td, J = 8.4, 1.6 Hz, 1H), 7.80 (dd, J = 5.2, 2.8 Hz, 2H), 7.68 (dd, J = 5.6, 3.2 Hz, 2H), 7.52 (ddd, J = 7.8, 4.6, 1.1 Hz, 1H), 3.61 (t, J = 7.2 Hz, 2H), 3.35 (s, 3H), 1.64–1.48 (m, 4H), 1.26–1.17 (m, 2H), 1.12 (s, 3H), 1.07 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 187.5, 168.3, 157.3, 149.7, 138.0, 133.8, 132.1, 127.0, 123.3, 123.0, 44.3, 40.6, 39.5, 37.9, 29.1, 25.7, 25.0, 22.2. IR (Neat) ν_{max} 2929, 1700, 1606, 1396, 1273, 1214, 1185, 1080, 1034, 970, 870, 762 cm^{-1} . HRMS (ESI-TOF) m/z :

calcd. for $\text{C}_{22}\text{H}_{26}\text{N}_3\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 428.1639; found 428.1641.

2.6.3.3 Preparation of **1i**:

The compound **1g** was prepared following the general procedures (**GP-1** and **2**) narrated above from isobutyric acid and 1-bromo-4-chlorobutane. A solution of **1g** (300 mg, 0.946 mmol) and thiophenol (210 mg, 0.946 mmol) in DMF (3.0 mL) was stirred overnight at 70 °C. The reaction mixture was cooled to room temperature and diluted with EtOAc. The organic layer was washed with water and brine. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography to afford **1i'**. Next, a solution of **1i'** (100 mg, 0.258 mmol) and *m*-CPBA (98 mg, 0.567 mmol) in DCM (3.0 mL) was stirred at rt for 2 h. Upon completion, the reaction mixture was diluted with EtOAc. The organic layer was washed with water and NaHCO₃. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography eluting with (EtOAc/hexane 7:1) to afford **1i**.

N-[2,2-Dimethyl-6-(phenylsulfonyl)hexanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (1i):



compound **1i** (100 mg, 94%) was prepared as colorless liquid. R_f = 0.15 (7:3 hexane/EtOAc); [Silica, UV and I₂]. ¹H NMR (400 MHz, CDCl₃) δ 8.63–8.62 (m, 1H), 8.19 (d, J = 6.4 Hz, 1H), 7.94 (td, J = 6.2, 1.5 Hz, 1H), 7.85 (d, J = 5.6 Hz, 2H), 7.63–7.60 (m, 1H), 7.55–7.48 (m, 3H), 3.32 (s, 3H), 3.10–2.99 (m, 2H), 1.65–1.58 (m, 2H), 1.49–1.37 (m, 2H), 1.26–1.16 (m, 2H), 1.05 (s, 3H), 1.02 (s, 3H). ¹³C{¹H} NMR (101 MHz,

$CDCl_3$) δ 187.2, 157.1, 149.6, 139.0, 138.0, 133.5, 129.1, 127.9, 127.1, 123.2, 56.0, 44.1, 40.1, 39.5, 25.5, 25.0, 23.6, 23.0. **IR (Neat)** ν_{max} 2930, 1629, 1446, 1426, 1302, 1217, 1177, 1143, 1085, 988, 751 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $C_{20}H_{26}N_2NaO_4S^+$ $[M+Na]$, 445.1226; found 445.1226.

2.6.3.4. Preparation of (1c-D₆):

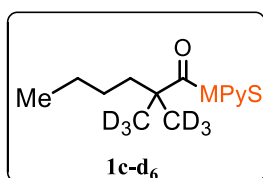
n-BuLi (4.01 mL, 10.5 mmol, 2.5M solution in hexane, 2.1 equiv) was added to a solution of *i*-Pr₂NH (2.18 mL, 15.6 mmol, 3 equiv) in THF (4 mL) at $-40^\circ C$. The reaction mixture was stirred at $-40^\circ C$ for 10 min and then warmed to $-20^\circ C$. A solution of hexanoic acid (754 μ L, 6.03 mmol, 1.2 equiv) in DMPU (1.02 mL) was added dropwise to the LDA (prepared in-situ) and the reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was cooled to $0^\circ C$ and CD_3I (312 μ L, 5.02 mmol, 1.0 equiv) in THF (2.0 mL) was subsequently added. The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (2×10 mL). The aqueous phase was acidified to pH 2 by addition of HCl (6 M). The aqueous phase was extracted with Et_2O (2×10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was used without further purification.

The same reaction was repeated using the crude 2-(methyl-d³)hexanoic acid as starting material, yielding 2,2-bis(methyl-d₃) hexanoic acid as a colourless oil.

The spectroscopic properties of this compound are consistent with the data reported in the literature.³⁰

Next, the crude material 2-bis(methyl-d₃) hexanoic acid was further used for the coupling reaction with MPyS. The general procedure 2 has been used for this step.

N-[2,2-bis(methyl-d₃)propanoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (1c-D₆):



Compound **d₆-1c** (0.4 g, 34%) was prepared following the general procedure GP-2; colorless solid. **mp** = 107–109 $^\circ C$. R_f = 0.19 (7:3 hexane/ $EtOAc$); [Silica, UV and I_2]. **1H NMR (500 MHz, $CDCl_3$)** δ 8.67 (ddd, J = 4.7, 1.7, 0.8 Hz, 1H), 8.26 (dt, J = 7.9, 1.0 Hz, 1H), 7.97 (td, J = 7.8, 1.7 Hz, 1H), 7.52 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 3.39 (s, 3H), 1.53–1.43 (m, 2H), 1.25 (dd, J = 14.3, 7.0 Hz, 2H), 1.19–1.10 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H). **$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$)** δ 188.1, 157.5, 149.7, 138.1, 127.0, 123.4, 44.0, 40.8,

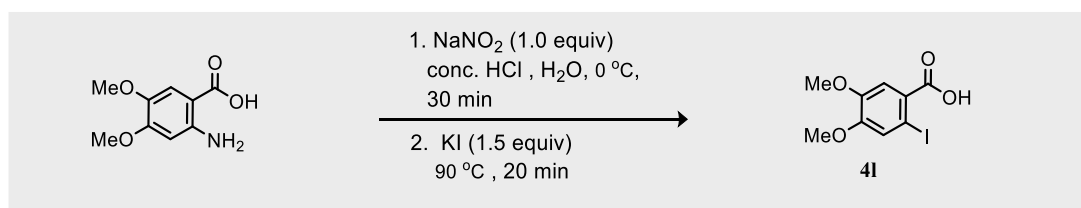
39.5, 27.0, 24.6, 24.3, 23.4, 14.1. **IR (Neat)** $\nu_{\max}$ 2922, 1617, 1577, 1423, 1317, 1208, 1168, 977, 961, 854, 752 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{14}\text{H}_{17}\text{D}_6\text{N}_2\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]$, 289.1851; found 289.1859.

2.6.3.5. Preparation of ligands:

All ligands (see Table 2.1) were obtained from commercial sources.

2.6.3.6. Preparation of 2-iodobenzoic acid derivatives:

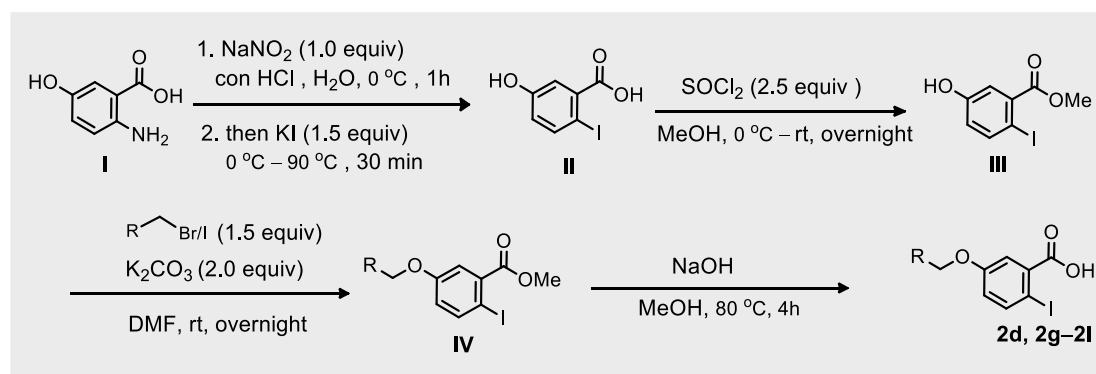
2-Iodo-4,5-dimethoxybenzoic acid (**4l**):³¹



A solution of NaNO_2 (450 mg, 6.5 mmol) in water (2.0 mL) was added slowly to a cold stirred solution of 2-amino-4,5-dimethoxybenzoic acid (1.18 g, 6.0 mmol), concentrated HCl (8.0 mL), and crushed ice (5.0 g) in water (10 mL) at $0\text{ }^\circ\text{C}$. After the addition was complete, the solution was stirred for an additional 30 min below $5\text{ }^\circ\text{C}$. A solution of KI (1.66 g, 10 mmol) in water (4.0 mL) was added slowly. The resulting mixture was stirred for 20 min at $0\text{ }^\circ\text{C}$ and then heated to $90\text{ }^\circ\text{C}$ for 20 minutes to ensure the evaporation of N_2 gas. The mixture was cooled to room temperature and extracted with EtOAc ($5 \times 10\text{ mL}$). The combined organic layer was washed with saturated aqueous NaHSO_3 (several times) and water, and then dried over anhydrous Na_2SO_4 . The solvents were removed in vacuo to give crude product as reddish yellow solid. The residue was chromatographed on silica gel (eluent: hexane / diethyl ether = 1:1) to give **4l** (1.29 g, 4.2 mmol, 70% yield) as a brown solid.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.43 (s, 1H), 7.38 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), spectral data matching with reported ones.

2.6.3.7. Preparation of 2-iodo-5-substituted benzoic acid (2d, 2g–2l): General Procedure (GP3):



Preparation of II. A solution of NaNO_2 (1.1 g, 15.67 mmol) in water (28 mL) was added slowly to a cold stirred solution of 5-hydroxyanthranilic acid (2.0 g, 13.06 mmol), concentrated HCl (10 mL) at 0°C . After addition was complete, the solution was stirred for additional 30 min at 0°C . A solution of KI (3.25 g, 19.59 mmol) in water (5.0 mL) was added slowly. The resulting mixture was stirred for 20 min at 0°C and then heated 90°C for 30 min. The mixture was cooled to room temperature, extracted with EtOAc , and washed with $\text{Na}_2\text{S}_2\text{O}_3$. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The desired 5-hydroxy-2-iodobenzoic acid **II** was obtained as brown solid and used further without purification (3.48 g, 13.18 mmol, quantitative).

Preparation of III. 5-Hydroxy-2-iodobenzoic acid **II** (3.48 g, 13.18 mmol) was dissolved in MeOH (10 mL) at 0°C . Next, SOCl_2 (2.5 equiv) was added dropwise to the solution. The resulting mixture was stirred for 14 h at room temperature. The reaction was quenched by the addition of H_2O (30 mL) and the aqueous phase was extracted with EtOAc (4×40 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated. The desired methyl 5-hydroxy-2-iodobenzoate **III** was obtained as brown solid and the compound was used further without purification.

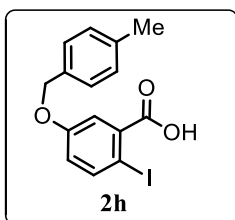
Preparation of IV. To a suspension of methyl 5-hydroxy-2-iodobenzoate **III** and K_2CO_3 (2.0 equiv) in anhydrous DMF (25 mL) was added benzyl bromide / 2-iodopropane (1.5 equiv). The resulting mixture was stirred at rt for 14 h. The reaction was quenched by the addition of H_2O (30 mL); the aqueous phase extracted with EtOAc (4×20 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated. The product

was purified through chromatography eluting hexanes: EtOAc (8:1) to afford **IV** as light-yellow oil.

Preparation of (2d, 2g–2l). To a solution of **IV** in MeOH was added NaOH (20% aq.). The resulting mixture was refluxed for 4 h. The solvents were removed under vacuo and the residue was dissolved in water and extracted with EtOAc (2×20 mL). The aqueous layer was acidified with 2N HCl and extracted with EtOAc (3×10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. A short column chromatography of the crude material on silica gel [eluent: hexane–EtOAc (8:2)] produced compound **2d, 2g–2l** as colorless solid.

Full characterization of new compounds:

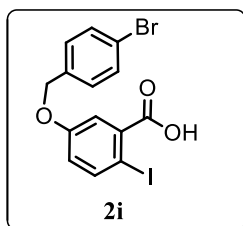
2-Iodo-5-(4-methylbenzyloxy)benzoic acid (2h):



compound **2h** (750 mg, 75%) was prepared following the general procedure GP-3; colorless solid. **mp** = 243–245 °C. R_f = 0.43 (1:5 hexane/EtOAc). ^1H NMR (500 MHz, CDCl_3) δ 7.89 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 3.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 7.5 Hz, 2H), 6.86 (dd, J = 9.0, 3.0 Hz, 1H), 5.05 (s, 2H), 2.37 (s, 3H).

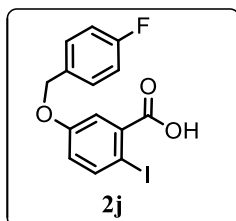
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 170.9, 158.7, 142.5, 138.1, 133.8, 132.9, 129.4, 127.7, 121.2, 118.3, 83.4, 70.3, 21.2; IR (Neat) ν_{max} 2920, 2556, 1679, 1585, 1451, 1275, 996, 755 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{15}\text{H}_{14}\text{IO}_3^+$ [$\text{M}+\text{H}$], 368.9982; found 368.9986. The desired peak for carboxylic acid group is not detected by ^1H NMR.

5-(4-Bromobenzyloxy)-2-iodobenzoic acid (2i):



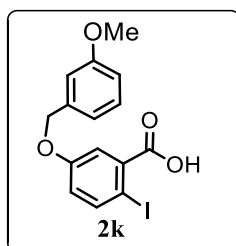
compound **2i** (800 mg, 82%) was prepared following the general procedure GP-3; colorless solid. **mp** = 221–224 °C. R_f = 0.21 (1:5 hexane/EtOAc). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.83 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 3.0 Hz, 1H), 6.93 (dd, J = 8.75, 2.75 Hz, 1H), 5.12 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$

NMR (126 MHz, $\text{DMSO}-d_6$) δ 167.8, 158.0, 141.3, 138.0, 136.0, 131.4, 129.8, 121.1, 119.6, 116.6, 82.8, 68.8; IR (Neat) ν_{max} 2878, 1679, 1586, 1277, 1232, 1001, 833, 757 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{14}\text{H}_{10}\text{INO}_3^+$ [$\text{M}+\text{Na}$], 454.8750; found 454.8759. The desired peak for carboxylic acid group is not detected by ^1H NMR.

5-(4-Fluorobenzoyloxy)-2-iodobenzoic acid (2j):

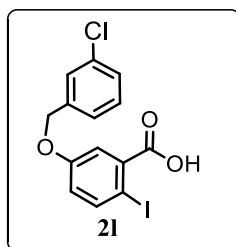
compound **2j** (600 mg, 62%), was prepared following the general procedure GP-3; colorless solid. **mp** = 213–216 °C. R_f = 0.43 (1:5 hexane/EtOAc). ^1H NMR (400 MHz, DMSO- d_6) δ 7.81 (d, J = 8.5 Hz, 1H), 7.50–7.45 (m, 2H), 7.34 (d, J = 3.0 Hz, 1H), 7.22–7.15 (m, 2H), 6.92 (dd, J = 9.0, 3.0 Hz, 1H), 5.10 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126

MHz, DMSO- d_6) δ 167.8, 161.9 (d, J = 293 Hz), 158.1, 141.3, 137.9, 132.7, 130.0 (d, J = 9.7 Hz), 119.6, 116.6, 115.3 (d, J = 26.6 Hz), 82.7, 79.0 (t, J = 39.9 Hz), 68.9. ^{19}F NMR (376 MHz, DMSO- d_6) δ -114.14; IR (Neat) ν_{max} 2920, 1680, 1583, 1259, 1230, 1002, 801, 752 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{14}\text{H}_{10}\text{INaO}_3^+$ [$\text{M}+\text{Na}$], 394.9551; found 394.9550. The desired peak for carboxylic acid group is not detected by ^1H NMR.

5-(3-Chlorobenzoyloxy)-2-iodobenzoic acid (2k):

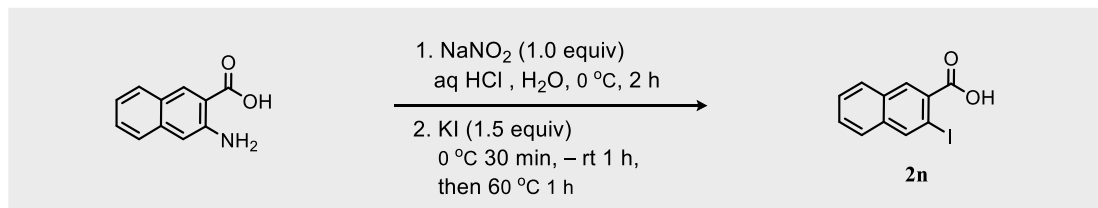
compound **2k** (650 mg, 67%), was prepared following the general procedure GP-3; colorless solid. **mp** = 201–203 °C. R_f = 0.26 (3:7 hexane/EtOAc). ^1H NMR (500 MHz, DMSO- d_6) δ 7.82 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 3.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 6.99 (bs, 2H), 6.95–6.87 (m, 2H), 5.10 (s, 2H), 3.74 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126

MHz, DMSO- d_6) δ 168.3, 159.8, 158.6, 141.7, 138.5, 138.4, 130.1, 120.2, 120.0, 117.1, 113.8, 113.6, 83.1, 69.8, 55.5; IR (Neat) ν_{max} 2922, 2614, 1695, 1582, 1488, 1408, 1253, 1221, 1037, 1005, 930 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{15}\text{H}_{14}\text{IO}_4^+$ [$\text{M}+\text{H}$], 384.9931; found 384.9932. The desired peak for carboxylic acid group is not detected by ^1H NMR.

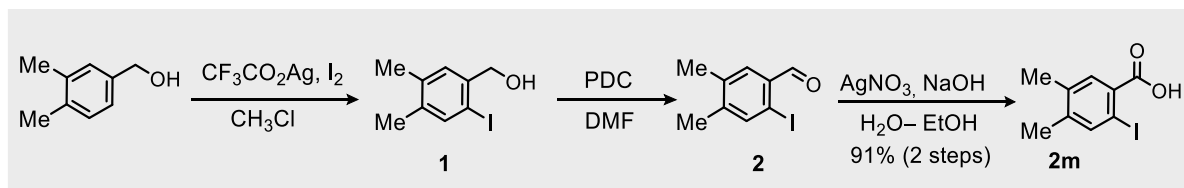
5-((3-Chlorobenzyl) oxy)-2-iodobenzoic acid (2l):

compound **2l** (600 mg, 62%), was prepared following the general procedure GP-3; colorless solid. **mp** = 206–208 °C. R_f = 0.21 (3:7 hexane/EtOAc). ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 4.0 Hz, 1H), 7.43 (s, 1H), 7.33–7.28 (m, 3H), 6.85 (dd, J = 8.0, 4.0 Hz, 1H), 5.05 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

δ 171.1, 158.3, 142.7, 138.0, 134.6, 133.8, 130.0, 128.4, 127.4, 125.3, 121.1, 118.3, 83.9, 69.4; IR (Neat) ν_{max} 2876, 2556, 2361, 1699, 1582, 1472, 1261, 1228, 1007, 781 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{14}\text{H}_{11}\text{ClIO}_3^+$ [$\text{M}+\text{H}$], 388.9436; found 388.9436. The desired peak for carboxylic acid group is not detected by ^1H NMR.

2.6.3.8. Preparation of 3-iodo-2-naphthoic acid (4n):³²

To an ice-cold stirred suspension of commercially available 3-amino-2-naphthoic acid (1.0 g, 5.34 mmol) in a 1:1 mixture of 37% aqueous HCl (20 mL) and H_2O (20 mL) was slowly added an aqueous solution of NaNO_2 (737 mg, 10.68 mmol, in 10 mL distilled water). The resulting orange solution was stirred at 0°C for 2 h. Next, an aqueous solution of KI (5.3 g, 32.0 mmol, in 10 mL distilled water) was added dropwise. The mixture was stirred at 0°C for 30 min, then at room temperature for 1 h, and finally heated at 60°C for 1 h. EtOAc (20 mL) was then poured into the mixture and heating was maintained for an additional 30 min. Powdered $\text{Na}_2\text{S}_2\text{O}_3$ was added until the complete discoloration of the solution; the reaction mixture was then extracted with EtOAc (4×30 mL). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4 , filtered and evaporated to dryness. The resulting brown oily residue was purified by column chromatography, eluting with hexane / diethyl ether (10:1) to yield 3-iodo-2-naphthoic acid (**2n**; 1.41 g, 89%) as beige solid.

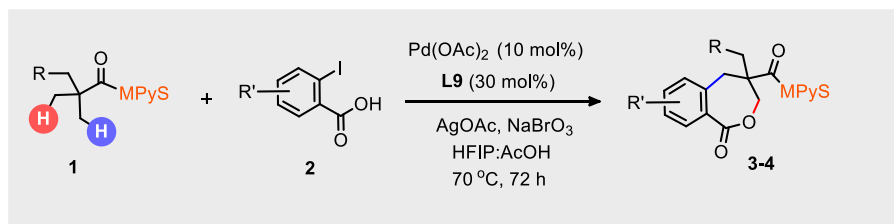
2.6.3.9. Preparation of 2-iodo-4,5-dimethylbenzoic acid (4m).³³**2-Iodo-4,5-dimethylbenzoic acid (4m):**

To a solution of (3,4-dimethylphenyl) methanol (1.0 g, 7.34 mmol) in CHCl_3 (20 mL) were successively added $\text{CF}_3\text{CO}_2\text{Ag}$ (1.78 g, 8.07 mmol) and I_2 (2.03 g, 8.0 mmol) at -5°C . After stirring for 30 min., the resulting heterogeneous mixture was filtered through a small pad Celite plug. The filtrate was then washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$, dried over anhydrous MgSO_4 and concentrated in vacuo. The crude mixture was chromatographed on silica gel (eluent: hexane-EtOAc= 10:1) to give **1** (1.27 g, 4.84 mmol, 66% yield) as colorless solid.

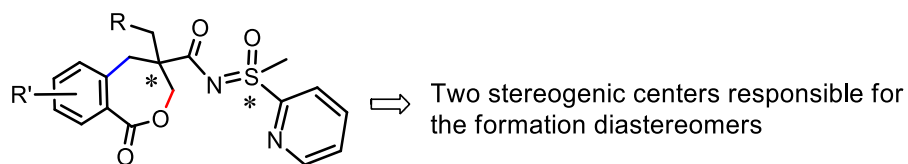
To a solution of **1** (1.27 g, 4.84 mmol) in DMF (10 mL) was added pyridinium dichromate (4.88 g, 12.96 mmol) at 0 °C. After stirring for 12 h at room temperature, the reaction was quenched with water, and extracted with Et₂O (3 times), dried over anhydrous MgSO₄, and concentrated in vacuo to give **2** which was used for next step without further purification.

To a solution of AgNO₃ (1.51 g, 8.86 mmol) in H₂O (18 mL) was added powdered NaOH (726 mg, 18.1 mmol), and the resulting mixture was stirred at room temperature for 1 h. Then, compound **2** in EtOH (7 mL) was added and stirred for 2 h at room temperature. The resulting mixture was filtered through a small Celite pad. The aqueous layer was acidified using 4N HCl; the resulting precipitates was then dissolved in Et₂O, dried over anhydrous Na₂SO₄ and concentrated in vacuo to give pure **2m** as colorless solid (1.09 g, 3.93 mmol, 91% yield for 2 steps).

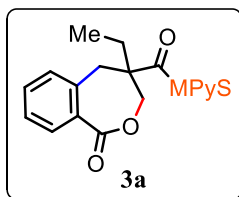
2.6.3.10. General Procedure for double C(sp³)-H functionalization reaction (GP-4):



A 5 mL sealed tube equipped with a magnetic stir bar was charged with Pd(OAc)₂ (10 mol%, 4.5 mg), substrate **1** (0.2 mmol), AgOAc (0.4 mmol, 66.0 mg), NaBrO₃ (0.4 mmol, 60.0 mg), 2-iodobenzoic acid **2** (0.4 mmol, 99.0 mg), and **L9** (30 mol%, 10.8 mg) in air. Then, a solvent combination of HFIP (0.97 mL) and AcOH (0.46 mL) was added. The reaction mixture was stirred at 70 °C for 72 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with CH₂Cl₂ (DCM), filtered through a small Celite pad, and concentrated in vacuo. The crude reaction mixture was purified on silica gel using hexane/EtOAc (30 – 80%) eluent to afford the desired products. Most of the compounds possess minor amount of impurity that are difficult to isolated by column chromatography. These compounds are purified by reverse-phase liquid chromatography (HPLC system) in C18 column eluting with acetonitrile and water (7:3) mixture.

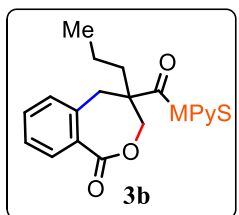


***N*-[4-Ethyl-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3a):**



compound **3a** (53 mg, 71%) was prepared from **1a** and **2a** following the general procedure GP-4 as colorless thick liquid, R_f = 0.24 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.71–8.61 (m, 1H), 8.25–8.19 (m, 1H), 8.01–7.95 (m, 1H), 7.71–7.65 (m, 1H), 7.58–7.53 (m, 1H), 7.40 (tt, J = 7.5, 3.5 Hz, 1H), 7.35–7.29 (m, 1H), 7.22–7.14 (m, 1H), 4.39 (dd, J = 12.3, 3.3 Hz, 1H), 3.97 (t, J = 13.0 Hz, 1H), 3.40 (s, 3H), 3.31 (d, J = 14.0 Hz, 1H), 2.72 (dd, J = 14.0, 4.0 Hz, 1H), 1.75–1.55 (m, 2H), 0.88–0.83 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.29 & 182.13 (1C), 172.02 & 172.00 (1C), 156.6, 149.84 & 149.81 (1C), 138.20 & 138.15 (1C), 136.93 & 136.88 (1C), 132.31 & 132.26 (1C), 131.12 & 131.08 (1C), 130.02 & 130.0 (1C), 129.9, 129.8, 127.42 & 127.33 (1C), 123.39 & 123.34 (1C), 71.50 & 71.48 (1C), 54.44 & 54.42 (1C), 39.67 & 39.65 (1C), 37.8, 28.75 & 28.66 (1C), 8.52 & 8.48 (1C). IR (Neat) ν_{max} 2924, 1718, 1629, 1452, 1215, 1078, 987, 753 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{NaO}_4\text{S}^+$ [$\text{M}+\text{Na}$], 395.1036; found 395.1046

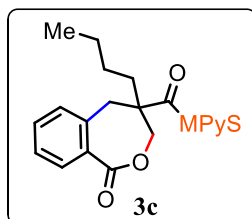
***N*-[1-Oxo-4-propyl-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3b):**



compound **3b** (50 mg, 64%) was prepared from **1b** and **2a** following the general procedure GP-4 as colorless thick liquid ; R_f = 0.22 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.59 (m, 1H), 8.22 (t, J = 8.0, 1H), 7.98 (td, J = 7.5, 1.6 Hz, 1H), 7.71–7.66 (m, 1H), 7.58–7.53 (m, 1H), 7.43–7.37 (m, 1H), 7.35–7.29 (m, 1H), 7.23–7.13 (m, 1H), 4.40 (dd, J = 12.5, 8.5 Hz, 1H), 3.97 (t, J = 12.0 Hz, 1H), 3.39 (bd, J = 2.0 Hz, 3H), 3.30 (d, J = 13.5 Hz, 1H), 2.73 (dd, J = 14.0, 3.0 Hz, 1H), 1.70–1.55 (m, 2H), 1.34–1.22 (m, 2H), 0.92–0.83 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.35 & 182.22 (1C), 172.0, 156.6, 149.79 & 149.75 (1C), 138.17 & 138.12 (1C), 136.94 & 136.88 (1C), 132.27 & 132.24 (1C), 131.16 & 131.11 (1C), 130.0 & 129.98 (1C), 129.8, 127.4, 127.32 & 127.30 (1C), 123.36 & 123.29 (1C), 71.77 &

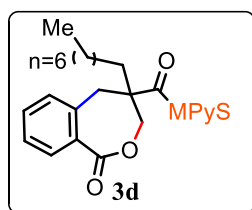
71.74 (1C), 54.18 & 54.15 (1C), 39.66 & 39.64 (1C), 38.3, 38.22 & 38.17 (1C), 17.37 & 17.34 (1C), 14.48 & 14.47 (1C). **IR (Neat)** $\nu_{\max}$ 2928, 1722, 1633, 1453, 1225, 1084, 982, 734 cm^{-1} . **HRMS (ESI)** m/z : $[M+H]^+$ calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4\text{S}$, 387.1373; found 387.1377.

N-[4-Butyl-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (3c):



compound **3c** (54 mg, 68%) was prepared from **1c** and **2a** following the general procedure GP-4 as colorless thick liquid $R_f = 0.30$ (1:1 hexane/EtOAc); ^1H NMR (500 MHz, DMSO-d_6) δ 8.79–8.68 (m, 1H), 8.23–8.13 (m, 2H), 7.81–7.72 (m, 1H), 7.63–7.55 (m, 1H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.45–7.35 (m, 1H), 7.30–7.29 (m, 1H), 4.28 (d, $J = 10.0$ Hz, 1H), 3.85–3.77 (m, 1H), 3.49 & 3.48 (two s, 3H), 3.13 (dd, $J = 20.0, 15.0$ Hz, 1H), 2.75–2.65 (m, 1H), 1.50–1.47 (m, 2H), 1.20–1.08 (m, 4H), 0.84 (q, $J = 5.0$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO-d_6) δ 181.70 & 181.52 (1C), 171.35 & 171.32 (1C), 156.5, 150.5, 139.26 & 139.22 (1C), 136.9, 132.86 & 132.79 (1C), 131.44 & 131.40 (1C), 130.48 & 130.35 (1C), 130.15 & 130.11 (1C), 128.3, 127.9, 123.87 & 123.78 (1C), 72.02 & 71.86 (1C), 53.70 & 53.64 (1C), 37.97 & 37.64 (1C), 35.4, 26.0, 23.1, 14.3. **IR (Neat)** $\nu_{\max}$ 2929, 1721, 1630, 1453, 1213, 1082, 980, 755 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_4\text{S}^+ [M+H]$, 401.1530; found 401.1533.

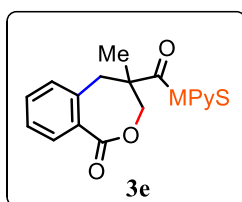
N-[4-Octyl-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (3d):



compound **3d** (55 mg, 60%), was prepared from **1d** and **2a** following the general procedure GP-4 as colorless thick liquid; $R_f = 0.32$ (1:1 hexane/EtOAc); ^1H NMR (500 MHz, DMSO-d_6) δ 8.78–8.70 (m, 1H), 8.22–8.16 (m, 2H), 7.78–7.75 (m, 1H), 7.63–7.58 (m, 1H), 7.52 (t, $J = 5.0$ Hz, 1H), 7.45–7.38 (m, 1H), 7.27 (d, $J = 5.0$ Hz, 1H), 4.27 (t, $J = 15.0$ Hz, 1H), 3.85–3.77 (m, 1H), 3.49 & 3.48 (two s, 3H), 3.16–3.09 (m, 1H), 2.75–2.65 (m, 1H), 1.51–1.42 (m, 2H), 1.30–1.19 (m, 12H), 0.89–0.85 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.43 & 182.25 (1C), 172.01 & 171.99 (1C), 156.7, 149.78 & 149.75 (1C), 138.17

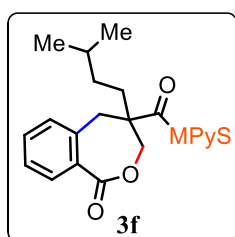
& 138.11 (1C), 136.98 & 136.95 (1C), 132.30 & 132.26 (1C), 131.19 & 131.14 (1C), 130.04 & 130.02 (1C), 130.0, 129.8, 127.37 & 127.32 (1C), 123.41 & 123.36 (1C), 71.82 & 71.76 (1C), 54.15 & 54.12 (1C), 39.66 & 39.64 (1C), 38.23 & 38.19 (1C), 36.06 & 35.95 (1C), 31.8, 30.0, 29.4, 29.2, 23.97 & 23.94 (1C), 22.6, 14.1; **IR (Neat)** $\nu_{\max}$ 2924, 1721, 1634, 1453, 1220, 1077, 980, 755 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 457.2156; found 457.2158.

***N*-[4-Methyl-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3e):**



compound **3e** (36 mg, 50%) was prepared from **1e** and **2a** following the general procedure GP-4 as colorless thick liquid; R_f = 0.20 (1:1 hexane/EtOAc); **^1H NMR (500 MHz, CDCl_3)** δ 8.71–8.63 (m, 1H), 8.21 (t, J = 8.0, 1H), 7.98 (td, J = 7.5, 1.6 Hz, 1H), 7.75–7.67 (m, 1H), 7.58–7.53 (m, 1H), 7.44–7.38 (m, 1H), 7.37–7.31 (m, 1H), 7.18 (m, 1H), 4.46 (dd, J = 12.5, 8.5 Hz, 1H), 3.85 (dd, J = 12.5, 5.0 Hz, 1H), 3.41 & 3.40 (two s, 3H), 3.34 (d, J = 14.0 Hz, 1H), 2.70 (dd, J = 14.0, 9.0 Hz, 1H), 1.27 (bs, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)** δ 183.12 & 183.08 (1C), 172.0, 156.44 & 156.42 (1C), 149.94 & 149.93 (1C), 138.26 & 138.21 (1C), 136.85 & 136.77 (1C), 132.3, 131.14 & 131.12 (1C), 130.1, 129.91 & 129.85 (1C), 127.47 & 127.41 (1C), 127.4, 123.31 & 123.25 (1C), 73.01 & 72.88 (1C), 50.39 & 50.37 (1C), 39.65 & 39.62 (1C), 39.6, 22.28 & 22.18 (1C). **IR (Neat)** $\nu_{\max}$ 2926, 1721, 1633, 1453, 1223, 1152, 1081, 987 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{NaO}_4\text{S}^+$ $[\text{M}+\text{Na}]$, 381.0879; found 381.0883.

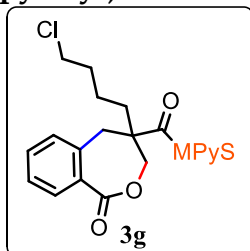
***N*-[4-Isopentyl-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-2-(pyridyl) sulfoximine (3f):**



compound **3f** (51 mg, 62%) was prepared from **1f** and **2a** following the general procedure GP-4 as colorless thick liquid; R_f = 0.36 (1:1 hexane/EtOAc); **^1H NMR (500 MHz, CDCl_3)** δ 8.70–8.59 (m, 1H), 8.26–8.20 (m, 1H), 8.20–7.95 (m, 1H), 7.71–7.66 (m, 1H), 7.58–7.52 (m, 1H), 7.43–7.37 (m, 1H), 7.35–7.29 (m, 1H), 7.22–7.15 (m, 1H), 4.39

(dd, $J = 12.5, 6.0$ Hz, 1H), 4.02–3.92 (m, 1H), 3.39 (bs, 3H), 3.31 (dd, $J = 13.5, 11.0$ Hz, 1H), 2.73 (dd, $J = 15.5, 14.0$ Hz, 1H), 1.69–1.60 (m, 2H), 1.50–1.41 (m, 1H), 1.17–1.07 (m, 2H) 0.88–0.78 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 182.4, 172.0, 156.6, 149.8, 138.16 & 138.09 (1C), 137.0, 132.3, 131.16, 130.0, 129.8, 127.3, 123.44, 123.38, 71.90 & 71.74 (1C), 54.0, 39.7, 38.19 & 38.02 (1C), 33.81, 33.69, 32.8, 28.4, 22.53 & 22.39 (1C). IR (Neat) ν_{max} 2953, 1721, 1631, 1452, 1213, 1072, 981 cm^{-1} . HRMS (ESI-TOF) m/z : calcd for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_4\text{S}^+$ [M+H], 415.1686; found 415.1686.

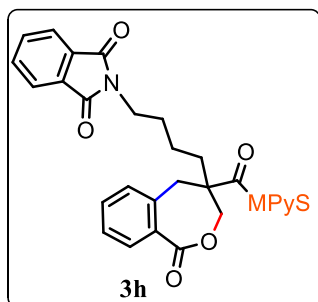
***N*-[4-(4-Chlorobutyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3g):**



compound **3g** (37 mg, 42%) was prepared from **1g** and **2a** following the general procedure GP-4 as colorless thick liquid; $R_f = 0.47$ (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.59 (m, 1H), 8.26–8.18 (m, 1H), 8.02–7.97 (m, 1H), 7.71–7.66 (m, 1H), 7.58–7.53 (m, 1H), 7.45–7.39 (m, 1H), 7.37–7.31 (m, 1H), 7.24–7.14 (m, 1H), 4.40 (d, $J = 12.5$, 1H), 3.99 (dd, $J = 20.0, 12.5$ Hz, 1H), 3.58–3.46 (m, 2H), 3.39 (d, $J = 4.5$ Hz, 3H), 3.32 (dd, $J = 13.5, 9.5$ Hz, 1H), 2.72 (t, $J = 13.5$ Hz, 1H), 1.77–1.65 (m, 4H), 1.49–1.36 (m, 2H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.09 & 181.85 (1C), 171.91 & 171.90 (1C), 156.4, 149.88 & 149.86 (1C), 138.25 & 138.19 (1C), 136.66 & 136.64 (1C), 132.40 & 132.37 (1C), 131.02 & 130.96 (1C), 130.05 & 130.03 (1C), 130.0, 129.8, 127.4, 123.44 & 123.37 (1C), 71.61 & 71.51 (1C), 53.96 & 53.92 (1C), 44.62 & 44.60 (1C), 39.69 & 39.66 (1C), 38.18 & 38.06 (1C), 35.21 & 35.06 (1C), 32.78 & 32.76 (1C), 21.43 & 21.40 (1C). IR (Neat) ν_{max} 2963, 1719, 1630, 1452, 1218, 1079, 980 cm^{-1} . HRMS (ESI-TOF) m/z : calcd for $\text{C}_{21}\text{H}_{24}\text{ClN}_2\text{O}_4\text{S}^+$ [M+H], 435.1140; found 435.1141.

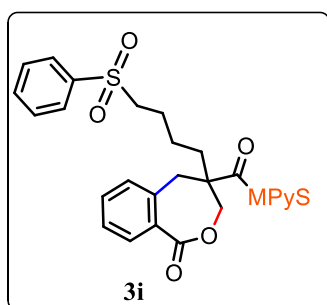
***N*-[4-(4-(1,3-Dioxoisindolin-2-yl)butyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3h):**



compound **3h** (55 mg, 50%) was prepared from **1h** and **2a** following the general procedure GP-4 as colorless thick liquid; R_f = 0.23 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, DMSO- d_6) δ 8.75–8.67 (m, 1H), 8.19–8.14 (m, 2H), 7.89–7.83 (m, 4H), 7.75–7.72 (m, 1H), 7.63–7.59 (m, 1H), 7.55–7.51 (m, 1H),

7.45–7.39 (m, 1H), 7.32–7.26 (m, 1H), 4.26 (t, J = 12.5 Hz, 1H), 3.88–3.78 (m, 1H), 3.52 (dd, J = 15.0, 5.0 Hz, 2H), 3.46 & 3.45 (two s, 3H), 3.18–3.07 (m, 1H), 2.78–2.63 (m, 1H), 1.55–1.52 (m, 4H), 1.18–1.06 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.07 & 181.72 (1C), 171.8, 168.3, 156.47 & 156.44 (1C), 149.95 & 149.91 (1C), 138.16 & 138.12 (1C), 136.72 & 136.68 (1C), 133.8, 132.34 & 132.31 (1C), 132.8, 131.08 & 130.01 (1C), 130.0, 129.8, 127.39 & 127.36 (1C), 123.45 & 123.37 (1C), 123.1, 71.75 & 71.41 (1C), 54.00 & 53.91 (1C), 39.68 & 39.64 (1C), 38.3, 37.76 & 37.64 (1C), 35.51 & 35.36 (1C), 35.21 & 35.06 (1C), 28.9, 21.40 & 21.36 (1C). IR (Neat) ν_{max} 2964, 1703, 1631, 1395, 1219, 1078, 983 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{29}\text{H}_{28}\text{N}_3\text{NaO}_6\text{S}^+$ $[\text{M}+\text{H}]$, 546.1693; found 546.1693.

***N*-[1-Oxo-4-(4-(phenylsulfonyl)butyl)-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3i):**

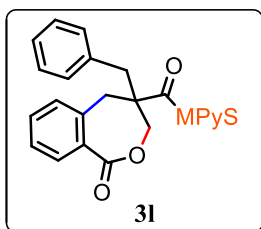


compound **3i** (63 mg, 58%), was prepared from **1i** and **2a** following the general procedure GP-4 as colorless liquid; R_f = 0.19 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.71–8.62 (m, 1H), 8.25–8.17 (m, 1H), 8.02–7.97 (m, 1H), 7.92–7.88 (m, 2H), 7.71–7.63 (m, 2H), 7.60–7.54 (m, 3H), 7.44–7.38 (m, 1H), 7.35–7.29 (m, 1H), 7.20–7.12 (m, 1H), 4.33

(dd, J = 12.5, 6.5 Hz, 1H), 3.98–3.87 (m, 1H), 3.37 (bs, 3H), 3.28 (dd, J = 14.0, 7.0 Hz, 1H), 3.10–3.00 (m, 2H), 2.66 (t, J = 14.0 Hz, 1H), 1.75–1.60 (m, 4H), 1.41–1.30 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 181.87 & 181.61 (1C), 171.7, 156.4, 150.0, 139.0, 138.30 & 138.24 (1C), 136.5, 133.7, 132.42 & 132.39 (1C), 131.03 & 130.96 (1C), 130.10 & 130.07

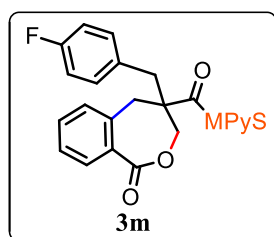
(1C), 130.0, 129.8, 129.3, 128.0, 127.55, 127.50, 123.53 & 123.46 (1C), 71.43 & 71.30 (1C), 56.00, 53.93 & 53.87 (1C), 39.8, 38.24 & 38.04 (1C), 35.42 & 35.23 (1C), 22.99 & 22.97 (1C), 22.92 & 22.89 (1C). **IR (Neat)** $\nu_{\max}$ 2926, 1724, 1625, 1446, 1292, 1212, 1141, 1083, 980 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_6\text{S}_2^+$ $[\text{M}+\text{H}]$, 541.1462; found 541.1469.

***N*-[4-Benzyl-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3l):**



compound **3l** (52 mg, 60%) was prepared from **1l** and **2a** following the general procedure GP-4 as colorless thick liquid R_f = 0.28 (1:1 hexane/EtOAc); **^1H NMR (500 MHz, CDCl_3)** δ 8.74–8.66 (m, 1H), 8.20–8.11 (m, 1H), 8.00–7.95 (m, 1H), 7.75–7.70 (m, 1H), 7.61–7.55 (m, 1H), 7.42–7.40 (m, 1H), 7.34 (q, J = 7.5 Hz, 1H), 7.25–7.15 (m, 6H), 4.27 (d, J = 15.0 Hz, 1H), 4.12 (dd, J = 15.0, 5.0 Hz, 1H), 3.41 & 3.40 (two s, 3H), 3.35–3.25 (m, 1H), 3.15 (d, J = 10.0 Hz, 1H), 3.03 (dd, J = 15.0, 5.0 Hz, 1H), 2.83 (dd, J = 14.5, 4.5 Hz, 1H), **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)** δ 181.24 & 181.09 (1C), 172.01 & 171.98 (1C), 156.66 & 156.61 (1C), 149.7, 138.20 & 138.15 (1C), 136.7, 136.42 & 136.37 (1C), 132.40 & 132.32 (1C), 131.22 & 131.18 (1C), 130.24 & 131.17 (1C), 130.12 & 130.03 (1C), 129.8, 128.14 & 128.11 (1C), 127.48 & 127.46 (1C), 127.43 & 127.35 (1C), 126.75 & 126.74 (1C), 123.40 & 123.34 (1C), 71.04 & 70.74 (1C), 55.4, 41.98 & 41.95 (1C), 39.5, 39.20 & 38.90 (1C); **IR (Neat)** $\nu_{\max}$ 2929, 1720, 1630, 1452, 1272, 1212, 1152, 1082, 979 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd for $\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 435.1373; found 435.1375.

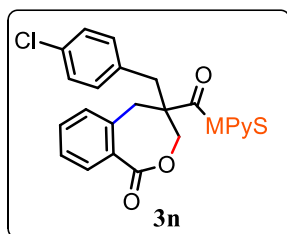
***N*-[4-(4-Fluorobenzyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3m):**



compound **3m** (52 mg, 58%) was prepared from **1m** and **2a** following the general procedure GP-4 as colorless thick liquid: R_f = 0.30 (1:1 hexane/EtOAc); **^1H NMR (500 MHz, CDCl_3)** δ 8.71–8.60 (m, 1H), 8.22–8.13 (m, 1H), 8.00–7.94 (m, 1H), 7.71 (bt, J = 7.25 Hz 1H), 7.60–7.51 (m, 1H), 7.40 (t, J = 7.0 Hz 1H),

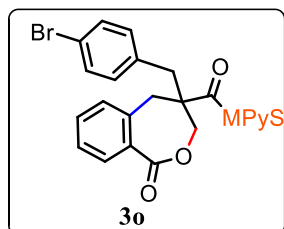
7.35 (t, $J = 7.5$ Hz 1H), 7.18–7.08 (m, 3H), 6.88 (bt, $J = 8.25$ Hz 2H), 4.28–4.20 (m, 1H), 4.13–4.02 (m, 1H), 3.39 & 3.38 (two s, 3H), 3.34–3.24 (m, 1H), 3.13 (bd, $J = 13.5$ Hz, 1H), 3.03–2.96 (m, 1H), 2.80 (bd, $J = 14.0$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 181.11 & 180.93 (1C), 171.9, 161.9 (d, $J = 245$ Hz, 1C), 156.6, 149.7, 138.23 & 138.18 (1C), 136.5, 132.41 & 132.35 (1C), 132.13 & 132.11 (1C), 131.7 (d, $J = 7.5$ Hz, 1C), 131.6, 131.21 & 131.16 (1C), 130.0, 129.9 (d, $J = 52$ Hz, 1C), 127.5, 127.4, 123.4, 114.9 (dd, $J = 21.0, 3.2$ Hz, 1C), 70.79 & 70.54 (1C), 55.4, 41.2, 39.6, 39.21 & 38.96 (1C). ^{19}F NMR (376 MHz, CDCl_3) δ -116.16, -116.17; IR (Neat) ν_{max} 2922, 1717, 1633, 1507, 1451, 1215, 1073, 978, 837, 757 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{24}\text{H}_{22}\text{FN}_2\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 453.1279; found 453.1283.

***N*-[4-(4-Chlorobenzyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3n):**



compound **3n** (60 mg, 64%), was prepared from **1n** and **2a** following the general procedure GP-4 as colorless thick liquid; $R_f = 0.31$ (7:3 hexane/EtOAc); ^1H NMR (500 MHz, DMSO) δ 8.90–8.82 (m, 1H), 8.19–8.13 (m, 2H), 7.79 (t, $J = 5.0$ Hz, 1H), 7.65–7.60 (m, 1H), 7.55–7.52 (m, 1H), 7.45–7.40 (m, 1H), 7.30–7.15 (m, 5H), 4.11 (t, $J = 15.0$ Hz, 1H), 4.00–3.90 (m, 1H), 3.56 (s, 3H), 3.18–3.01 (m, 2H), 2.96–2.75 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 180.98 & 180.76 (1C), 171.9, 156.4, 149.7, 138.22 & 138.18 (1C), 136.4, 134.85 & 134.82 (1C), 132.6, 132.44 & 132.38 (1C), 131.54 & 131.46 (1C), 131.07 & 131.01 (1C), 130.11 & 129.97 (1C), 129.7, 128.2, 127.5, 127.4, 123.51 & 123.42 (1C), 70.70 & 70.40 (1C), 55.2, 41.2, 39.6, 39.22 & 38.90 (1C); IR (Neat) ν_{max} 2926, 1719, 1630, 1451, 1215, 1073, 979, 743. cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{24}\text{H}_{22}\text{ClN}_2\text{O}_4\text{S}^+$ $[\text{M} + \text{H}]$, 469.0983; found 469.0984.

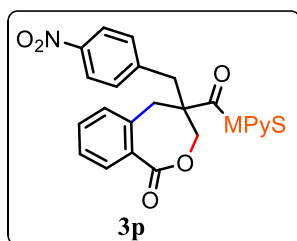
N-[4-(4-Bromobenzyl)-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinonyl]-S-methyl-S-(2-pyridyl) sulfoximine (3o):



compound **3o** (72 mg, 70%) was prepared from **1o** and **2a** following the general procedure GP-4 as colorless thick liquid R_f = 0.32 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.72–8.64 (m, 1H), 8.18–8.11 (m, 1H), 8.01–7.97 (m, 1H), 7.74–7.68 (m, 1H), 7.60–7.55 (m, 1H), 7.43–7.38 (m, 1H),

7.36–7.29 (m, 3H), 7.24–7.12 (m, 1H), 7.08–7.00 (m, 2H), 4.23 (dd, J = 15.0, 5.0 Hz, 1H), 4.07 (t, J = 14.5 Hz, 1H), 3.38 (s, 3H), 3.32–3.23 (m, 1H), 3.11 (d, J = 15.0 Hz, 1H), 2.98 (dd, J = 15.0, 5.0 Hz, 1H), 2.79 (dd, J = 15.0, 10.0 Hz, 1H), $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 180.97 & 180.75 (1C), 171.90 & 171.88 (1C), 156.49 & 156.47 (1C), 149.7, 138.25 & 138.21 (1C), 136.41 & 136.39 (1C), 135.40 & 135.37 (1C), 132.47 & 132.40 (1C), 131.96 & 131.87 (1C), 131.21 & 130.20 (1C), 131.10 & 131.04 (1C), 130.15 & 130.13 (1C), 130.00 & 129.71 (1C), 127.57 & 127.55 (1C), 127.50 & 127.43 (1C), 123.54 & 123.45 (1C), 120.8, 70.71 & 70.43 (1C), 55.2, 41.3, 39.66 & 39.64 (1C), 39.26 & 38.95 (1C) IR (Neat) ν_{max} 2925, 1721, 1631, 1486, 1215, 1073, 1010, 980 cm^{-1} . HRMS (ESI-TOF) m/z : calcd for $\text{C}_{24}\text{H}_{22}\text{BrN}_2\text{O}_4\text{S}^+$ [M+H], 513.0478; found 513.0486.

N-[4-(4-Nitrobenzyl)-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinonyl]-S-methyl-S-(2-pyridyl) sulfoximine (3p):

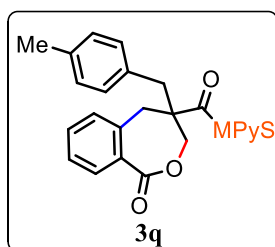


compound **3p** (30 mg, 42%) was prepared from **1p** and **2a** following the general procedure GP-4 as colorless thick liquid; R_f = 0.22 (7:3 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.75–8.64 (m, 1H), 8.24–8.16 (m, 1H), 8.10–7.96 (m, 3H), 7.72 (t, J = 7.5 Hz 1H), 7.66–7.57 (m, 1H), 7.47–7.28 (m, 4H),

7.25–7.12 (m, 1H), 4.28–4.20 (m, 1H), 4.12–4.04 (m, 1H), 3.39 (s, 3H), 3.35–3.24 (m, 2H), 3.18–3.04 (m, 1H), 2.98–2.78 (m, 1H), $^{13}\text{C}\{^1\text{H}\}$ NMR (121 MHz, CDCl_3) δ 180.46 & 180.20 (1C), 171.6, 156.3, 149.7, 146.9, 144.2, 138.29 & 138.24 (1C), 136.0, 132.51 & 132.47 (1C), 131.1, 131.0, 130.16 & 130.14 (1C), 130.0, 129.7, 127.68 & 127.61 (1C), 127.5, 123.6, 123.5, 123.2, 70.43 & 70.18 (1C), 55.20 & 55.18 (1C), 41.6, 39.76 & 39.72 (1C), 39.3 IR

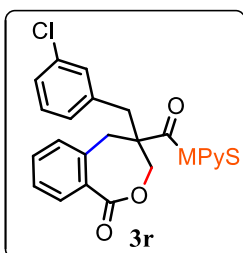
(Neat) $\nu_{\max}$ 2922, 1736, 1514, 1343, 1196, 1108, 978 cm^{-1} . HRMS (ESI-TOF) m/z : calcd for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{NaO}_6\text{S}^+$ $[\text{M} + \text{Na}]$, 502.1043; found 502.1052.

***N*-[4-(4-Methylbenzyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3q):**



compound **3q** (51 mg, 57%), was prepared from **1q** and **2a** following the general procedure GP-4 as colorless thick liquid; R_f = 0.30 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, DMSO-d_6) δ 8.89–8.81 (m, 1H), 8.19–8.13 (m, 2H), 7.81–7.78 (m, 1H), 7.65–7.60 (m, 1H), 7.55–7.52 (m, 1H), 7.45–7.40 (m, 1H), 7.30–7.27 (m, 1H), 7.02–6.99 (m, 4H), 4.09 (dd, J = 15.0, 7.5 Hz, 1H), 3.97–3.88 (m, 1H), 3.54 & 3.53 (two s, 3H), 3.18–2.97 (m, 2H), 2.90–2.73 (m, 2H), 2.25 & 2.23 (two s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 181.33 & 181.20 (1C), 172.0, 156.60 & 156.55 (1C), 149.7, 138.17 & 138.11 (1C), 136.7, 136.2, 133.23 & 133.17 (1C), 132.38 & 132.29 (1C), 131.18 & 131.14 (1C), 130.05 & 129.97 (1C), 129.8, 128.83 & 128.80 (1C), 127.4, 127.3, 123.39 & 123.31 (1C), 71.00 & 70.77 (1C), 55.4, 41.5, 39.5, 39.10 & 38.84 (1C), 21.0. IR (Neat) $\nu_{\max}$ 2921, 1720, 1632, 1452, 1216, 1075, 980, 753. cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_4\text{S}^+$ $[\text{M} + \text{H}]$, 449.1530; found 449.1539.

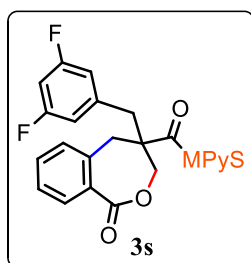
***N*-[4-(3-Chlorobenzyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3r):**



compound **3r** (47 mg, 50%), was prepared from **1r** and **2a** following the general procedure GP-4 as colorless thick liquid; R_f = 0.26 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, DMSO-d_6) δ 8.87–8.78 (m, 1H), 8.20–8.14 (m, 2H), 7.78 (t, J = 5.0 Hz, 1H), 7.61 (dd, J = 12.5, 7.5 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.42 (dd, J = 15.0, 10.0 Hz, 1H), 7.29–7.21 (m, 4H), 7.11 (dd, J = 15.0, 10.0 Hz, 1H), 4.09 (t, J = 10.0 Hz, 1H), 4.01–3.92 (m, 1H), 3.53 & 3.52 (two s, 3H), 3.16–3.04 (m, 2H), 2.99–2.78 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 180.83 & 180.63 (1C), 171.88 & 171.87 (1C), 156.43 & 156.41 (1C), 149.9, 138.48 & 138.44 (1C), 138.27 & 138.20 (1C), 136.35 & 136.33 (1C), 133.9, 132.50 &

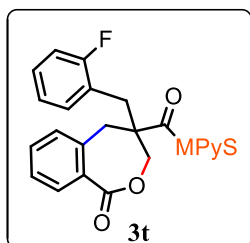
132.42 (1C), 131.05 & 130.99 (1C), 130.16 & 130.11 (1C), 130.0, 129.8, 129.37 & 129.35 (1C), 128.53 & 128.46 (1C), 127.58 & 127.53 (1C), 127.4, 127.00 & 126.98 (1C), 123.24 & 123.16 (1C), 70.71 & 70.44 (1C), 55.2, 41.53 & 41.48 (1C), 39.59 & 39.58 (1C), 39.31 & 38.92 (1C). **IR (Neat)** $\nu_{\max}$ 2964, 1721, 1623, 1593, 1453, 1214, 1114, 1077, 980, 839 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{24}\text{H}_{21}\text{ClN}_2\text{NaO}_4\text{S}^+$ $[\text{M}+\text{Na}]$, 491.0803; found 491.0813.

***N*-[4-(3,5-Difluorobenzyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3s):**



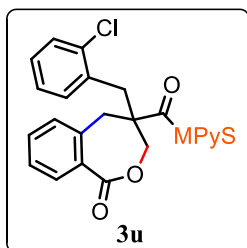
compound **3s** (53 mg, 57%), was prepared from **1s** and **2a** following the general procedure GP-4 as colorless thick liquid $R_f = 0.29$ (1:1 hexane/EtOAc); **^1H NMR (500 MHz, CDCl_3)** δ 8.75–8.68 (m, 1H), 8.22–8.16 (m, 1H), 8.04–7.95 (m, 1H), 7.74–7.71 (m, 1H), 7.60–7.55 (m, 1H), 7.45–7.42 (m, 1H), 7.39–7.32 (m, 1H), 7.21 (d, $J = 5.0$ Hz, 1H), 6.78–6.7 (m, 3H), 4.30–4.21 (m, 1H), 4.15–3.99 (m, 1H), 3.40 & 3.35 (two s, 3H), 3.21–3.11 (m, 2H), 3.09–2.97 (m, 1H), 2.87–2.73 (m, 1H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)** δ 180.72 & 180.16 (1C), 171.7, 162.6 (dd, $J = 248.2, 1.26$ Hz, 1C), 156.43 & 156.41 (1C), 150.0, 140.3 (td, $J = 9.5, 2.9$ Hz, 1C), 138.24 & 138.17 (1C), 136.28 & 136.11 (1C), 132.58 & 132.51 (1C), 131.07 & 130.91 (1C), 130.2, 130.14 & 130.10 (1C), 129.7, 127.70 & 127.59 (1C), 127.55 & 127.45 (1C), 123.47 & 123.36 (1C), 113.0 (dd, $J = 25.2, 8.8$ Hz, 1C), 102.3 (t, $J = 25.2$ Hz, 1C), 70.87 & 70.02 (1C), 55.21 & 55.13 (1C), 41.65 & 41.56 (1C), 39.75 & 39.73 (1C), 38.6. **^{19}F NMR (376 MHz, CDCl_3)** δ -110.20, -110.22; **IR (Neat)** $\nu_{\max}$ 1621, 1592, 1455, 1239, 1114, 1079, 988, 837 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{24}\text{H}_{21}\text{F}_2\text{N}_2\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 471.1185; found 471.1192.

***N*-[4-(2-Fluorobenzyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3t):**



compound **3t** (50 mg, 55%) was prepared from **1t** and **2a** following the general procedure GP-4 as colorless thick liquid; R_f = 0.30 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.87–8.77 (m, 1H), 8.21–8.11 (m, 2H), 7.80–7.76 (m, 1H), 7.65–7.60 (m, 1H), 7.55–7.49 (m, 1H), 7.46–7.40 (m, 1H), 7.30–7.18 (m, 3H), 7.15–7.09 (m, 1H), 7.05–6.97 (m, 1H), 4.11 (dd, J = 15.0, 5.0 Hz, 1H), 3.99–3.92 (m, 1H), 3.53 & 3.52 (two s, 3H), 3.22–2.99 (m, 3H), 2.87–2.77 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 180.90 & 180.84 (1C), 171.9, 161.3 (dd, J = 245, 5.0 Hz), 156.48 & 156.41 (1C), 149.7, 138.20 & 138.13 (1C), 136.58 & 136.52 (1C), 132.57 & 132.53 (1C), 132.48 & 132.45 (1C), 132.3, 130.6 (d, J = 125 Hz, 1C), 130.06 & 130.04 (1C), 128.63 & 128.56 (1C), 127.45 & 127.41 (1C), 127.37 & 127.25 (1C), 123.80 & 123.78 (1C), 123.4 (q, J = 8.8 Hz), 123.1 (d, J = 13 Hz), 115.2 (d, J = 23 Hz), 71.3, 55.2, 39.4, 38.2, 34.69 & 34.57 (1C). ^{19}F NMR (376 MHz, DMSO) δ -116.30 & -116.38 (1F); IR (Neat) ν_{max} 2924, 1721, 1632, 1452, 1215, 1178, 1073, 980, 755 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{24}\text{H}_{22}\text{FN}_2\text{O}_4\text{S}^+$ [$\text{M}+\text{H}$], 453.1279; found 453.1281.

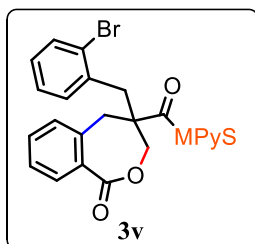
***N*-[4-(2-Chlorobenzyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3u):**



compound **3u** (54 mg, 58%) was prepared from **1u** and **2a** following the general procedure GP-4 as colorless thick liquid; R_f = 0.31 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.74–8.67 (m, 1H), 8.18–8.09 (m, 1H), 8.02–7.94 (m, 1H), 7.74–7.70 (m, 1H), 7.60–7.54 (m, 1H), 7.44–7.40 (m, 1H), 7.37–7.32 (m, 1H), 7.24–7.05 (m, 5H), 4.25 (dd, J = 15.0, 5.0 Hz, 1H), 4.13–4.06 (m, 1H), 3.41 & 3.40 (two s, 3H), 3.34–3.24 (m, 1H), 3.14 (dd, J = 10.0, 7.5 Hz, 1H), 3.01 (t, J = 10.0 Hz, 1H), 2.81 (t, J = 15.0 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 180.82 & 180.64 (1C), 171.86 & 171.84 (1C), 156.58 & 156.56 (1C), 149.9, 138.55 & 138.51 (1C), 138.27 & 138.21 (1C), 136.42 & 136.40 (1C), 133.9, 132.49 & 132.42 (1C), 131.14 & 131.08 (1C), 130.22 & 130.17 (1C), 130.0,

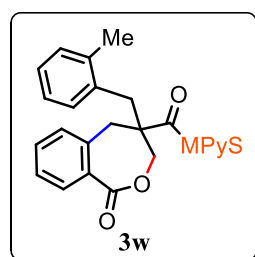
129.8, 129.39 & 129.37 (1C), 128.58 & 128.51 (1C), 127.60 & 127.58 (1C), 127.52 & 127.41 (1C), 127.03 & 127.02 (1C), 123.24 & 123.17 (1C), 70.75 & 70.50 (1C), 55.3, 41.59 & 41.54 (1C), 39.61 & 39.60 (1), 39.34 & 38.98 (1C); **IR (Neat)** $\nu_{\max}$ 2926, 1720, 1630, 1452, 1211, 1120, 1074, 980, 732 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{24}\text{H}_{22}\text{ClN}_2\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 469.0983; found 469.0989.

***N*-[4-(2-Bromobenzyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3v):**



compound **3v** (60 mg, 59%) was prepared from **1v** and **2a** following the general procedure GP-4 as colorless thick liquid; R_f = 0.28 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.60 (m, 1H), 8.22–8.11 (m, 1H), 8.00–7.94 (m, 1H), 7.72–7.68 (m, 1H), 7.60–7.53 (m, 1H), 7.48 (d, J = 10.0 Hz, 1H), 7.42–7.33 (m, 2H), 7.27–7.19 (m, 2H), 7.15–7.08 (m, 1H), 7.05–7.01 (m, 1H), 4.23 (d, J = 5.0 Hz, 2H), 3.47–3.42 (m, 4H), 3.37–3.22 (m, 2H), 2.99–2.92 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 181.2, 171.97 & 171.95 (1C), 156.49 & 156.45 (1C), 149.8, 138.26 & 138.17 (1C), 136.47 & 136.43 (1C), 136.25 & 136.18 (1C), 132.30 & 132.27 (1C), 131.93 & 131.75 (1C), 131.17 & 131.11 (1C), 130.3, 130.1, 130.04 & 130.02 (1C), 128.3, 127.49 & 127.45 (1C), 127.41 & 127.35 (1C), 127.19 & 127.16 (1C), 125.66 & 125.62 (1C), 123.51 & 123.40 (1C), 70.89 & 70.68 (1C), 55.6, 40.51 & 40.46 (1C), 39.6, 38.51 & 38.37 (1C); **IR (Neat)** $\nu_{\max}$ 2927, 1719, 1630, 1452, 1214, 1128, 1074, 980, 730 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{24}\text{H}_{21}\text{BrN}_2\text{NaO}_4\text{S}^+$ $[\text{M}+\text{Na}]$, 535.0298; found 535.0309.

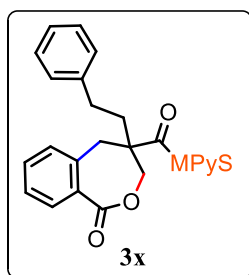
***N*-[4-(2-Methylbenzyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3w):**



compound **3w** (50 mg, 56%), was prepared from **1w** and **2a** following the general procedure GP-4 as colorless thick liquid; R_f = 0.30 (1:1 hexane/EtOAc); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.90–8.83 (m, 1H), 8.22–8.13 (m, 2H), 7.82–7.79 (m, 1H), 7.65–7.61 (m, 1H), 7.46–7.40 (m, 1H), 7.30–7.23 (m, 3H), 7.20–7.14

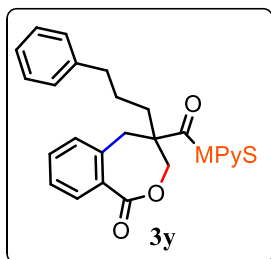
(m, 2H), 4.10 (t, $J = 15.0$ Hz, 1H), 4.00–3.89 (m, 1H), 3.53 (s, 3H), 3.17–3.01 (m, 2H), 2.97–2.75 (m, 2H), 2.5 (s, 3H peak merge with DMSO); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 181.5, 172.0, 156.40, 149.64 & 149.61 (1C), 138.11 & 138.08 (1C), 137.22 & 137.14 (1C), 136.55 & 136.51 (1C), 135.0, 132.29 & 132.20 (1C), 131.13 & 131.11 (1C), 130.6, 130.4, 129.94 & 129.92 (1C), 129.7, 127.39 & 127.28 (1C), 126.6, 125.56 & 125.45 (1C), 123.28 & 123.23 (1C), 70.59 & 70.36 (1C), 55.39 & 55.35 (1C), 39.67 & 39.61 (1C), 39.44 & 39.38 (1C), 38.20 & 38.05 (1C), 19.95 & 19.93 (1C); IR (Neat) ν_{max} 2926, 1720, 1631, 1452, 1215, 1075, 980 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 449.1530; found 449.1530.

N-[1-Oxo-4-phenethyl-1,3,4,5-tetrahydrobenzo[c]oxepinonyl]-S-methyl-S-(2-pyridyl) sulfoximine (3x):



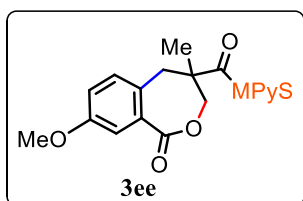
compound **3x** (52 mg, 58%) was prepared from **1x** and **2a** following the general procedure GP-4 as colorless thick liquid: $R_f = 0.40$ (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.68–8.62 (m, 1H), 8.28 (dd, $J = 12.0, 8.0$ Hz, 1H), 8.04–7.97 (m, 1H), 7.73–7.70 (m, 1H), 7.58–7.53 (m, 1H), 7.45–7.40 (m, 1H), 7.37–7.32 (m, 1H), 7.30–7.27 (m, 1H), 7.24–7.14 (m, 5H), 4.46 (dd, $J = 12.5, 9.0$ Hz, 1H), 4.09–4.0 (m, 1H), 3.43 & 3.41 (two s, 3H), 3.38–3.26 (m, 1H), 2.81 (dd, $J = 19.0, 14.0$ Hz, 1H), 2.62–2.45 (m, 2H), 2.01–1.94 (m, 2H), $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.13 & 181.78 (1C), 171.93 & 171.91 (1C), 156.5, 149.90 & 149.88 (1C), 141.8, 138.28 & 138.21 (1C), 136.67 & 136.62 (1C), 132.46 & 132.41 (1C), 131.07 & 131.01 (1C), 130.11 & 130.09 (1C), 130.0, 129.8, 128.4, 128.32 & 128.29 (1C), 127.47 & 127.44 (1C), 125.9, 123.60 & 123.54 (1C), 71.71 & 71.35 (1C), 54.23 & 54.15 (1C), 39.85 & 39.83 (1C), 38.36 & 38.06 (1C), 37.94 & 37.90 (1C), 30.53 & 30.46 (1C); IR (Neat) ν_{max} 2922, 1719, 1630, 1452, 1217, 1110, 1080, 979, 750. cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 449.1530; found 449.1530.

***N*-[1-Oxo-4-(3-phenylpropyl)-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3y):**



compound **3y** (50 mg, 54%) was prepared from **1y** and **2a** following the general procedure GP-4 as colorless thick liquid; R_f = 0.44 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, DMSO- d_6) δ 8.73–8.66 (m, 1H), 8.21–8.15 (m, 2H), 7.74 (t, J = 5.0 Hz, 1H), 7.63–7.58 (m, 1H), 7.51–7.48 (m, 1H), 7.43–7.38 (m, 1H), 7.31–7.28 (m, 2H), 7.22–7.14 (m, 4H), 4.27 (dd, J = 12.5, 7.5 Hz 1H), 3.83–3.75 (m, 1H), 3.48 & 3.47 (two s, 3H), 3.14–3.07 (m, 1H), 2.72–2.64 (m, 1H), 2.49–2.52 (m, 1H peak merge with DMSO), 1.57–1.44 (m, 5H), $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.0, 171.9, 156.5, 149.81 & 149.77 (1C), 141.9, 138.16 & 138.09 (1C), 136.8, 132.33 & 132.29 (1C), 131.3, 131.09 & 131.05 (1C), 129.99 & 129.95 (1C), 129.8, 128.44 & 128.42 (1C), 128.3, 127.37 & 127.33 (1C), 125.8, 123.41 & 123.37 (1C), 71.8, 54.05 & 54.00 (1C), 39.7, 38.0, 36.19 & 35.97 (1C), 35.32 & 35.17 (1C) 25.66 & 25.57 (1C); IR (Neat) ν_{max} 2927, 1720, 1632, 1452, 1218, 1119, 1078, 980, 750 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_4\text{S}^+$ $[M+H]$, 463.1686; found 463.1687.

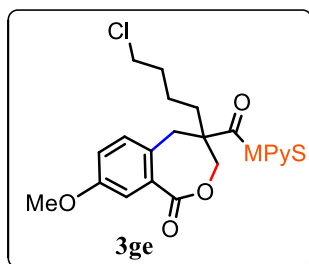
***N*-[8-methoxy-4-methyl-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3ee):**



Compound **3ee** (52 mg, 67%) was prepared from **1e** and **2e** following the general procedure GP-4 as colorless thick liquid; R_f = 0.16 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.65 (m, 1H), 8.21 (t, J = 5.0, 1H), 8.02–7.95 (m, 1H), 7.60–7.55 (m, 1H), 7.24–7.21 (m, 1H), 7.12–7.07 (m, 1H), 6.97–6.94 (m, 1H), 4.47 (dd, J = 12.0, 10.0 Hz, 1H), 3.85 (dd, J = 10.0, 5.0 Hz, 1H), 3.80 & 3.79 (two s, 3H), 3.40 & 3.39 (two s, 3H), 3.26 (d, J = 15.0, 1.5 Hz, 1H), 2.64 (dd, J = 15.0, 10.0 Hz, 1H), 1.25 & 1.24 (two s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 183.22 & 183.19 (1C), 171.9, 158.8, 156.52 & 156.50 (1C), 149.9, 138.24 & 138.21 (1C), 132.0, 131.10 & 131.05 (1C), 129.00 & 128.92 (1C), 127.44 & 127.38 (1C), 123.28 & 123.21 (1C), 118.80 & 118.78 (1C), 114.23 & 114.22 (1C), 73.17 & 73.05 (1C), 55.48 & 55.47 (1C), 50.50 & 50.49 (1C), 39.65 & 39.62 (1C), 38.84

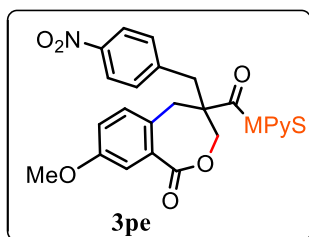
& 38.74 (1C), 22.18 & 22.07 (1C). **IR (Neat)** $\nu_{\max}$ 2924, 1718, 1631, 1454, 1257, 1219, 1146, 1024, 987, 845 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{S}^+$ $[\text{M}+\text{H}]$, 389.1166; found 389.1168.

***N*-[4-(4-chlorobutyl)-8-methoxy-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3ge):**



compound **3ge** (60 mg, 65%) was prepared from **1g** and **2e** following the general procedure GP-4 as colorless thick liquid; R_f = 0.24 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.63 (m, 1H), 8.26–8.22 (m, 1H), 8.02–7.98 (m, 1H), 7.60–7.57 (m, 1H), 7.21 (dd, J = 5, 2.5 Hz, 1H), 7.14–7.08 (m, 1H), 6.94 (dd, J = 8.5, 3 Hz, 1H), 4.40 (d, J = 12.5, 1H), 3.98 (dd, J = 21.5, 12.5 Hz, 1H), 3.81 & 3.80 (two s, 3H) 3.53–3.50 (m, 2H), 3.39 & 3.38 (two s, 3H), 3.25 (dd, J = 14.0, 10.0 Hz, 1H), 2.66 (t, J = 15 Hz, 1H), 1.80–1.64 (m, 4H), 1.44–1.40 (m, 2H). $^{13}\text{C}[^1\text{H}]$ NMR (126 MHz, CDCl_3) δ 182.21 & 181.97 (1C), 171.8, 158.8, 156.5, 149.86 & 149.85 (1C), 138.23 & 138.17 (1C), 131.86 & 131.80 (1C), 131.16 & 130.97 (1C), 128.8, 127.45 & 127.38 (1C), 123.42 & 123.35 (1C), 118.92 & 118.89 (1C), 114.20 & 114.15 (1C), 71.73 & 71.64 (1C), 55.48 & 55.47 (1C), 54.10 & 54.07 (1C), 44.60 & 44.58 (1C), 39.69 & 39.66 (1C), 37.40 & 37.30 (1C), 35.16 & 35.02 (1C), 32.81 & 32.80 (1C), 21.45 & 21.42 (1C). **IR (Neat)** $\nu_{\max}$ 2927, 1721, 1630, 1494, 1453, 1217, 1068, 981, 830, 757 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd for $\text{C}_{22}\text{H}_{26}\text{ClN}_2\text{O}_5\text{S}^+$ $[\text{M}+\text{H}]$, 465.1245; found 465.1241.

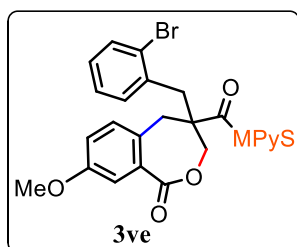
***N*-[8-methoxy-4-(4-nitrobenzyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinonyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (3pe):**



compound **3pe** (71 mg, 70%) was prepared from **1p** and **2e** following the general procedure GP-4 as colorless thick liquid; R_f = 0.20 (7:3 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.73–8.68 (m, 1H), 8.28–8.18 (m, 1H), 8.05–8.00 (m, 3H), 7.64–7.58 (m, 1H), 7.38–7.36 (m, 2H), 7.24–7.05 (m, 2H), 6.96–6.94 (m, 1H), 4.26–4.22 (m, 1H), 4.11–4.02 (m, 1H), 3.81 & 3.80 (two s, 3H), 3.37(s,

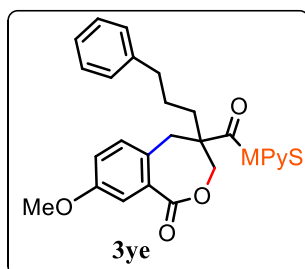
3H), 3.27–3.22 (m, 2H), 3.14–3.09 (m, 1H), 2.79–2.73 (m, 1H), $^{13}\text{C}\{^1\text{H}\}$ NMR (121 MHz, CDCl_3) δ 180.70 & 180.41 (1C), 171.6, 158.99 & 158.96 (1C), 156.4, 149.8, 146.9, 144.3, 138.31 & 138.27 (1C), 131.83 & 132.75 (1C), 131.20 & 131.10 (1C), 131.01 & 130.89 (1C), 128.13 & 128.10 (1C), 127.62 & 127.54 (1C), 123.69 & 123.60 (1C), 123.27 & 123.26 (1C), 119.04 & 119.01 (1C), 114.39 & 114.31 (1C), 70.55 & 70.29 (1C), 55.50 & 55.34 (1C), 41.65 & 41.59 (1C), 39.78 & 39.74 (1C), 38.58 & 38.29 (1C), 36.6; IR (Neat) ν_{max} 2924, 1723, 1632, 1516, 1343, 1196, 1217, 1075, 981, 843, 731 cm^{-1} . HRMS (ESI-TOF) m/z : calcd for $\text{C}_{25}\text{H}_{24}\text{N}_3\text{O}_7\text{S}^+$ [$\text{M} + \text{H}$], 510.1329; found 510.1325.

N-[4-(2-bromobenzyl)-8-methoxy-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (3ve):



compound **3ve** (87 mg, 80%) was prepared from **1v** and **2e** following the general procedure GP-4 as colorless thick liquid; R_f = 0.22 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.74–8.63 (m, 1H), 8.24–8.12 (m, 1H), 8.04–7.96 (m, 1H), 7.63–7.58 (m, 1H), 7.52–7.46 (m, 1H), 7.29–7.23 (m, 2H), 7.18–7.05 (m, 3H), 6.99–6.94 (m, 1H), 4.29–4.22 (m, 2H), 3.83 & 3.82 (two s, 3H), 3.50–3.40 (m, 4H), 3.35–3.22 (m, 2H), 2.96–2.87 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 181.3, 171.91 & 171.88 (1C), 158.77 & 158.76 (1C), 156.49 & 156.47 (1C), 149.8, 138.26 & 138.19 (1C), 136.30 & 136.24 (1C), 132.9, 131.97 & 131.91 (1C), 131.72 & 131.49 (1C), 131.3, 128.57 & 128.55 (1C), 128.3, 127.49 & 127.37 (1C), 127.18 & 127.13 (1C), 125.63 & 125.60 (1C), 123.48 & 123.39 (1C), 118.93 & 118.91 (1C), 114.05 & 114.03 (1C), 70.97 & 70.74 (1C), 55.69 & 55.48 (1C), 40.42 & 40.39 (1C), 39.6, 37.8, 37.7; IR (Neat) ν_{max} 2929, 1722, 1631, 1424, 1217, 1128, 1022, 981, 753 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{25}\text{H}_{24}\text{BrN}_2\text{O}_5\text{S}^+$ [$\text{M} + \text{H}$], 543.0584; found 543.0585.

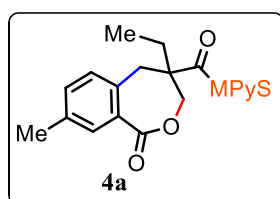
N-[8-methoxy-1-oxo-4-(3-phenylpropyl)-1,3,4,5-tetrahydrobenzo[c]oxepinonyl]-S-methyl-S-(2-pyridyl) sulfoximine (3ye):



compound **3ye** (71 mg, 72%) was prepared from **1y** and **2a** following the general procedure GP-4 as colorless thick liquid; R_f = 0.33 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.60–8.54 (m, 1H), 8.23–8.19 (m, 1H), 8.01–7.95 (m, 1H), 7.30–7.27 (m, 2H), 7.22–7.15 (m, 5H), 7.02–6.87 (m, 2H), 4.40

(dd, J = 12.0, 7.5 Hz, 1H), 4.00–3.92 (m, 1H), 3.80 & 3.79 (two s, 3H), 3.36 & 3.35 (two s, 3H), 3.23 (dd, J = 14.0, 10.0 Hz, 1H), 2.68–2.57 (m, 3H), 1.68–1.55 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.40 & 182.18 (1C), 171.9, 158.7, 156.5, 149.80 & 149.77 (1C), 141.91 & 141.87 (1C), 138.15 & 138.10 (1C), 131.86 & 131.81 (1C), 131.15 & 130.95 (1C), 128.9, 128.4, 128.2, 127.37 & 127.31 (1C), 125.7, 123.42 & 123.38 (1C), 118.90 & 118.87 (1C), 114.13 & 114.07 (1C), 71.91 & 71.80 (1C), 55.5, 54.14 & 54.11 (1C), 39.7, 37.23 & 37.16 (1C), 36.0, 35.25 & 35.09 (1C), 25.67 & 25.59 (1C); IR (Neat) ν_{max} 2924, 1722, 1632, 1493, 1453, 1425, 1218, 1071, 981, 752 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_5\text{S}^+$ [M+H], 493.1792; found 493.1792.

N-[4-Ethyl-8-methyl-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (4a):

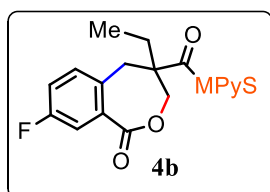


compound **4a** (51 mg, 66%) was prepared from **1a** and **2b** following the general procedure GP-4 as colorless thick liquid; R_f = 0.30 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, $\text{DMSO}-d_6$)

δ 8.80–8.73 (m, 1H), 8.22–8.17 (m, 2H), 7.79–7.76 (m, 1H), 7.41 (d, J = 10.0 Hz, 1H), 7.33 (d, J = 10.0 Hz, 1H), 7.16 (dd, J = 10.0, 5.0 Hz, 1H), 4.26 (d, J = 10.0, 5.0 Hz, 1H), 3.86–3.76 (m, 1H), 3.49 & 3.48 (two s, 3H), 3.09 (dd, J = 17.5, 12.5 Hz, 1H), 2.68–2.61 (m, 1H), 2.34 & 2.32 (two s, 3H), 1.57–1.49 (m, 2H), 0.79–0.75 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.49 & 182.28 (1C), 172.31 & 172.28 (1C), 156.62 & 156.60 (1C), 149.8, 138.20 & 138.15 (1C), 137.2, 133.87 & 133.85 (1C), 133.07 & 133.00 (1C), 130.89 & 130.84 (1C), 130.5, 129.85 & 129.66 (1C), 127.41 & 127.34 (1C), 123.37 & 123.32 (1C), 71.57 & 71.49 (1C), 54.45 & 54.42 (1C), 39.65 & 39.63 (1C), 37.42 & 37.37 (1C), 28.69 & 28.57 (1C), 20.8,

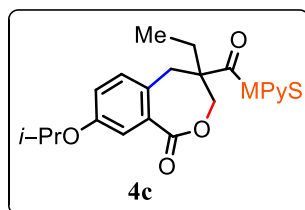
8.52 & 8.49 (1C). IR (Neat) $\nu_{\max}$ 1760, 1622, 1212, 1132, 1073, 977, 757 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 387.1373; found 387.1375.

N-[4-Ethyl-8-fluoro-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (4b):



compound **4b** (39 mg, 50%) was prepared from **1a** and **2c** following the general procedure GP-4 as colorless thick liquid; R_f = 0.32 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.80–8.74 (m, J = 12.5 Hz, 1H), 8.20–8.17 (m, 2H), 7.78–7.75 (m, 1H), 7.43–7.33 (m, 3H), 4.28 (t, 1H), 3.87 (dd, J = 20.0, 15.0 Hz, 1H), 3.39 (s, 3H), 3.11 (dd, J = 15.0, 10.0 Hz, 1H), 2.74–2.64 (m, 1H), 1.57–1.51 (m, 2H) 0.79–0.70 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.00 & 182.85 (1C), 170.6, 161.7 (d, J = 296 Hz), 156.5, 149.8, 138.22 & 138.16 (1C), 132.7, 131.78 & 138.71 (1C), 131.59 & 131.52 (1C), 127.47 & 127.38 (1C), 123.47 & 123.42 (1C), 119.1 (d, J = 24 Hz), 116.3 (d, J = 27 Hz), 71.5, 54.4, 39.7, 37.1, 28.84 & 28.73 (1C), 8.51 & 8.47 (1C). ^{19}F NMR (376 MHz, DMSO) δ -114.96 & -114.99 (1F); IR (Neat) $\nu_{\max}$ 2927, 1722, 1629, 1424, 1217, 1069, 979, 756. cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{19}\text{H}_{20}\text{FN}_2\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 391.1122; found 391.1125.

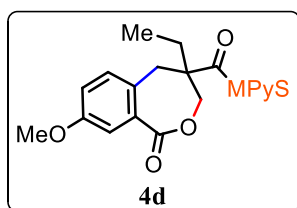
N-[4-Ethyl-8-isopropoxy-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (4c):



compound **4c** (52 mg, 61%) was prepared from **1a** and **2d** following the general procedure GP-4 as colorless thick liquid; R_f = 0.23 (1:1 hexane/EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 8.69–8.63 (m, 1H), 8.25–8.21 (m, 1H), 8.01–7.96 (m, 1H), 7.56–7.53 (m, 1H), 7.20 (dd, J = 6.0, 2.5 Hz, 1H), 7.06 (dd, J = 20.0, 10.0 Hz, 1H), 6.90 (dd, J = 8.5, 2.5 Hz, 1H), 4.58–4.51 (m, J = 1H), 4.40 (dd, J = 15.0, 10.0 Hz, 1H), 3.98 (t, J = 15.0 Hz, 1H), 3.340 (s, 3H), 3.23 (dd, J = 12.5, 5.0 Hz, 1H), 2.64 (dd, J = 12.5, 7.5 Hz, 1H), 1.75–1.66 (m, 2H), 1.34–1.31 (m, 6H), 0.88–0.84 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.50 & 182.33 (1C), 171.96 & 171.95 (1C), 157.1, 156.73 & 156.71 (1C), 149.83 & 149.81 (1C), 138.19 & 138.13 (1C), 131.95 & 133.91 (1C), 131.2, 131.0, 128.81 & 128.77

(1C), 127.39 & 127.33 (1C), 123.38 & 123.31 (1C), 120.52 & 120.46 (1C), 116.14 & 116.07 (1C), 71.6, 70.26 & 70.25 (1C), 54.59 & 54.58 (1C), 39.67 & 39.64 (1C), 37.08 & 37.04 (1C), 28.72 & 28.63 (1C), 21.98 & 21.97 (1C), 8.55 & 8.52 (1C). **IR (Neat)** $\nu_{\max}$ 2967, 2359, 1760, 1720, 1631, 1454, 1223, 1218, 1109, 960 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_5\text{S}^+$ $[\text{M}+\text{H}]$, 431.1635; found 431.1641.

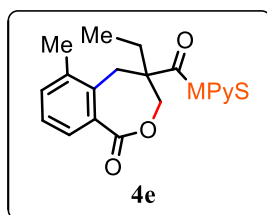
N-[4-Ethyl-8-methoxy-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (4d)



compound **4d** (61 mg, 76%) was prepared from **1a** and **2e** following the general procedure GP-4 as colorless thick liquid. R_f = 0.21 (1:1 hexane/EtOAc); **^1H NMR (400 MHz, CDCl_3)**

δ 8.69–8.61 (m, 1H), 8.25–8.18 (m, 1H), 7.99 (td, J = 7.8, 1.6 Hz, 1H), 7.58–7.52 (m, 1H), 7.22–7.18 (m, 1H), 7.12–7.04 (m, 1H), 6.95–6.91 (m, 1H), 4.39 (dd, J = 12.4, 2.4 Hz, 1H), 3.97 (t, J = 12.0 Hz, 1H), 3.79 & 3.78 (two s, 3H), 3.39 (s, 3H), 3.23 (dd, J = 14.0, 3.6 Hz, 1H), 2.65 (dd, J = 14.0, 5.6 Hz, 1H), 1.73–1.65 (m, 2H) 0.88–0.83 (m, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)** δ 182.36 & 182.20 (1C), 171.9, 158.7, 156.6, 149.79 & 149.77 (1C), 138.16 & 138.11 (1C), 131.93 & 133.88 (1C), 131.1, 130.9, 129.04 & 129.01 (1C), 127.37 & 127.31 (1C), 123.32 & 123.26 (1C), 118.81 & 118.77 (1C), 114.17 & 114.11 (1C), 71.6, 55.4, 54.55 & 54.54 (1C), 39.64 & 39.62 (1C), 37.0, 28.67 & 28.59 (1C), 8.49 & 8.46 (1C). **IR (Neat)** $\nu_{\max}$ 2920, 1718, 1628, 1494, 1424, 1215, 1070, 1026, 980, 755 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_5\text{S}^+$ $[\text{M}+\text{H}]$, 403.1322; found 403.1322.

N-[4-Ethyl-6-methyl-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (4e):

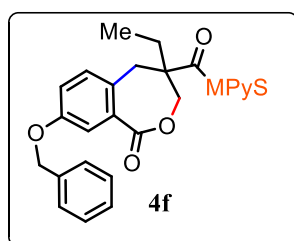


compound **4e** (40 mg, 52%) was prepared from **1a** and **2f** following the general procedure GP-4 as colorless thick liquid; R_f = 0.30 (1:1 hexane/EtOAc); **^1H NMR (500 MHz, $\text{DMSO}-d_6$)**

δ 8.80–8.76 (m, 1H), 8.24–8.18 (m, 2H), 7.79–7.76 (m, 1H), 7.67–7.40 (m, 2H), 7.28 (t, J = 7.5 Hz, 1H), 4.32 (d, J = 10.0 Hz, 1H), 3.87 (d, J = 10.0 Hz, 1H), 3.49 (s, 3H), 3.08 (d, J = 7.5 Hz, 1H), 2.67 (d, J = 7.5 Hz, 1H), 2.34 (s, 3H), 1.51 (q,

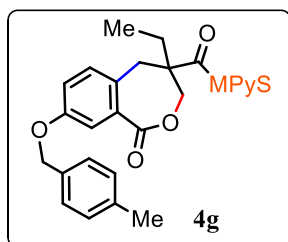
$J = 5.0$ Hz, 2H), 0.77 (t, $J = 7.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.43 & 182.35 (1C), 172.46 & 172.41 (1C), 156.73 & 156.65 (1C), 149.8, 138.22 & 138.08 (1C), 136.70 & 136.57 (1C), 134.76 & 134.67 (1C), 134.18 & 134.14 (1C), 132.1, 127.87 & 127.82 (1C), 127.42 & 127.31 (1C), 126.9, 123.50 & 123.23 (1C), 70.94 & 70.57 (1C), 54.64 & 54.54 (1C), 39.73 & 39.54 (1C), 33.64 & 33.30 (1C), 28.43 & 28.26 (1C), 19.82 & 19.70 (1C), 8.56 & 8.52 (1C); IR (Neat) ν_{max} 2928, 1716, 1628, 1453, 1216, 1147, 1079, 978, 754 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 387.1373; found 387.1377.

***N*-[8-(Benzyloxy)-4-ethyl-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (4f):**



compound **4f** (57 mg, 60%) was prepared from **1a** and **2g** following the general procedure GP-4 as colorless thick liquid; $R_f = 0.20$ (1:1 hexane/EtOAc); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.80–8.72 (m, 1H), 8.20–8.16 (m, 2H), 7.77–7.74 (m, 1H), 7.48–7.45 (m, 2H), 7.43–7.39 (m, 2H), 7.36–7.33 (m, 1H), 7.22–7.16 (m, 3H), 5.13 (d, $J = 5.0$ Hz, 2H), 4.27 (t, $J = 15.0$ Hz, 1H), 3.87–3.80 (m, 1H), 3.49 (s, 3H), 3.06 (t, $J = 15.0$ Hz, 1H), 2.67–2.60 (m, 1H), 1.57–1.50 (m, 2H), 0.78–0.74 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.40 & 182.25 (1C), 171.8, 157.9, 156.55 & 156.53 (1C), 149.81 & 149.78 (1C), 138.16 & 138.12 (1C), 136.42 & 136.39 (1C), 131.93 & 131.89 (1C), 131.17 & 130.98 (1C), 129.31 & 129.27 (1C), 128.6, 128.1, 127.5, 127.40 & 127.32 (1C), 123.36 & 123.31 (1C), 119.48 & 119.44 (1C), 115.22 & 115.14 (1C), 71.5, 70.2, 54.52 & 54.50 (1C), 39.64 & 39.62 (1C), 37.05 & 37.01 (1C), 28.69 & 28.60 (1C), 8.52 & 8.49 (1C). IR (Neat) ν_{max} 2925, 1718, 1628, 1453, 1217, 1145, 1070, 981, 731 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_5\text{S}$, 479.1635; found 479.1640.

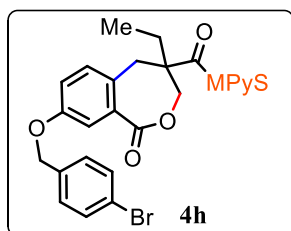
***N*-[4-Ethyl-8-((4-methylbenzyl)oxy)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (4g):**



compound **4g** (81 mg, 82%) was prepared from **1a** and **2h** following the general procedure GP-4 as colorless thick liquid; $R_f = 0.22$ (1:1 hexane/EtOAc); ^1H NMR (500 MHz, $\text{DMSO}-d_6$)

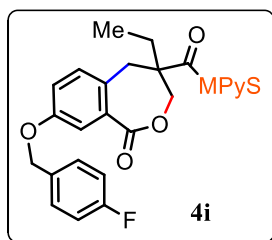
d₆) δ 8.79–8.72 (m, 1H), 8.20–8.17 (m, 2H), 7.75 (t, J = 5.0 Hz, 1H), 7.34 (t, J = 5.0 Hz, 2H), 7.22–7.15 (m, 5H), 5.08 (d, J = 10.0 Hz, 2H), 4.27 (t, J = 12.5 Hz, 1H), 3.82 (dd, J = 20.0, 12.5 Hz, 1H), 3.49 (s, 3H), 3.06 (t, J = 15.0 Hz, 1H), 2.66–2.57 (m, 1H), 2.31 (s, 3H), 1.56–1.45 (m, 2H), 0.79–0.74 (m, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)** δ 182.34 & 182.20 (1C), 171.8, 157.9, 156.5, 149.78 & 149.75 (1C), 138.30 & 138.14 (1C), 138.09 & 137.82 (1C), 133.36 & 133.33 (1C), 131.88 & 131.84 (1C), 131.10 & 130.93 (1C), 129.27 & 129.22 (1C), 129.1, 127.61 & 127.58 (1C), 127.36 & 127.29 (1C), 123.28 & 123.24 (1C), 119.44 & 119.40 (1C), 115.26 & 115.19 (1C), 71.6, 70.1, 54.50 & 54.48 (1C), 39.61 & 39.60 (1C), 37.01 & 36.96 (1C), 28.62 & 28.56 (1C), 21.1, 8.47 & 8.44 (1C). **IR (Neat)** ν_{max} 2921, 1720, 1630, 1454, 1218, 1069, 980, 756 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_5\text{S}^+$ $[\text{M}+\text{H}]$, 493.1792; found 493.1799.

***N*-[8-((4-Bromobenzyl)oxy)-4-ethyl-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (**4h**):**



compound **4h** (71 mg, 64%) was prepared from **1a** and **2i** following the general procedure GP-4 colorless thick liquid; **^1H NMR (500 MHz, CDCl_3)** δ 8.68–8.60 (m, 1H), 8.26–8.20 (m, 1H), 8.01 (tt, J = 8.0, 1.5 Hz, 1H), 7.58–7.48 (m, 3H), 7.32–7.25 (m, 3H), 7.15–7.11 (m, 1H), 7.00–6.96 (m, 1H), 5.02 (d, J = 5.0 Hz, 2H), 4.40 (dd, J = 12.5, 7.5 Hz, 1H), 3.99 (dd, J = 17.5, 12.5 Hz, 1H), 3.40 & 3.39 (two s, 3H), 3.26 (dd, J = 15.0, 5.0 Hz, 1H), 2.67 (dd, J = 15.0, 10.0 Hz, 1H), 1.74–1.65 (m, 2H), 0.88–0.80 (m, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)** δ 182.41 & 182.21 (1C), 171.8, 157.68 & 157.67 (1C), 156.70 & 156.68 (1C), 149.84 & 149.81 (1C), 138.20 & 138.15 (1C), 135.5, 132.09 & 131.05 (1C), 131.8, 131.3, 131.1, 129.1, 127.41 & 127.34 (1C), 123.43 & 123.36 (1C), 119.57 & 119.49 (1C), 115.26 & 115.20 (1C), 71.6, 69.5, 54.59 & 54.58 (1C), 39.71 & 39.67 (1C), 37.1, 28.80 & 28.68 (1C), 8.56 & 8.53 (1C). **IR (Neat)** ν_{max} 2927, 1722, 1632, 1491, 1221, 1070, 984, 734 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{26}\text{H}_{26}\text{BrN}_2\text{O}_5\text{S}^+$ $[\text{M}+\text{H}]$, 557.0740; found

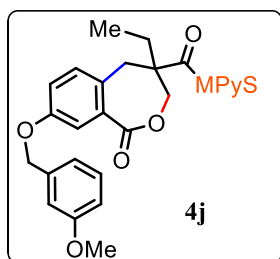
N-[4-Ethyl-8-((4-fluorobenzyl)oxy)-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinpyl]-S-methyl-S-(2-pyridyl) sulfoximine (4i):



compound **4i** (52 mg, 52%) was prepared from **1a** and **2j** following the general procedure GP-4 colorless thick liquid; ^1H NMR (500 MHz, CDCl_3) δ 8.68–8.61 (m, 1H), 8.25–8.22 (m, 1H), 7.99 (tt, J = 8.0, 1.5 Hz, 1H), 7.58–7.52 (m, 1H), 7.43–7.35 (m, 2H), 7.99

(tt, J = 7.8, 1.5 Hz, 1H), 7.29 (dd, J = 6.0, 2.5 Hz, 1H), 7.15–7.02 (m, 3H), 6.99 (dt, J = 8.5, 2.5 Hz, 1H), 5.02 (d, J = 5.0 Hz, 2H), 4.40 (dd, J = 10.0, 5.0 Hz, 1H), 3.99 (dd, J = 17.5, 12.5 Hz, 1H), 3.40 & 3.39 (two s, 3H), 3.26 (dd, J = 15.0, 10.0 Hz, 1H), 2.67 (dd, J = 15.0, 10.0 Hz, 1H), 1.74–1.70 (m, 2H), 0.88–0.82 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.43 & 182.23 (1C), 171.8, 163.5 (d, J = 247.0 Hz), 157.7, 156.66 & 156.63 (1C), 149.84 & 149.81 (1C), 138.20 & 138.15 (1C), 132.2, 132.03 & 131.99 (1C), 131.4 (d, J = 24.0 Hz), 129.54 & 129.51, 129.42 & 129.36 (1C), 127.41 & 127.35 (1C), 123.42 & 123.36 (1C), 119.62 & 119.56 (1C), 115.5 (d, J = 21.0 Hz), 115.1 (d, J = 8.8 Hz), 71.60 & 71.57 (1C), 69.6, 54.58 & 54.56 (1C), 39.70 & 39.65 (1C), 37.1, 28.78 & 28.65 (1C), 8.55 & 8.52 (1C). ^{19}F NMR (376 MHz, CDCl_3) δ -113.9; IR (Neat) ν_{max} 2925, 1719, 1630, 1510, 1217, 1070, 981, 825 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{26}\text{H}_{26}\text{FN}_2\text{O}_5\text{S}^+$ [$\text{M}+\text{H}$], 497.1541; found 497.1541.

N-[4-Ethyl-8-((3-methoxybenzyl)oxy)-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (4j):

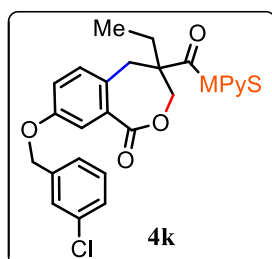


compound **4j** (84 mg, 82%) was prepared from **1a** and **2k** following the general procedure GP-4 as colorless thick liquid; R_f = 0.17 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.81–8.72 (m, 1H), 8.22–8.16 (m, 2H), 7.77–7.75 (m, 1H),

7.57 (d, J = 10.0 Hz, 1H), 7.25–7.18 (m, 4H), 6.92 (dd, J = 10.0, 5.0 Hz, 1H), 5.10 (d, J = 10.0 Hz, 2H), 4.28 (t, J = 10.0 Hz, 1H), 3.87–3.81 (m, 1H), 3.77 & 3.76 (two s, 3H), 3.50 & 3.49 (two s, 3H), 3.07 (t, J = 15.0, 1H), 2.67–2.59 (m, 1H), 1.57–1.51 (m, 2H), 0.79–0.74 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.41 & 182.25 (1C), 171.8, 159.2, 157.6, 156.6, 149.85 & 149.81 (1C), 138.20 & 138.14 (1C), 136.8, 133.3, 132.12 & 132.08 (1C),

131.27 & 131.09 (1C), 129.70 & 129.65 (1C), 127.41 & 127.34 (1C), 123.42 & 123.38 (1C), 119.27 & 119.22 (1C), 115.7, 115.1, 114.5, 112.4, 71.6, 69.6, 55.5, 54.6, 39.7, 37.11 & 37.05 (1C), 28.77 & 28.67 (1C), 8.55 & 8.53 (1C). **IR (Neat)** $\nu_{\max}$ 2928, 1719, 1630, 1424, 1217, 1071, 980, 756 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_6\text{S}^+$ $[\text{M}+\text{H}]$, 509.1741; found 509.1748.

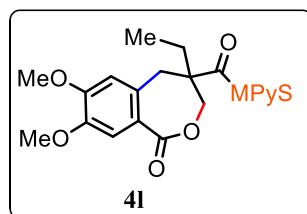
N-[8-((4-Chlorobenzyl)oxy)-4-ethyl-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (4k):



compound **4k** (68 mg, 66%) was prepared from **1a** and **2l** following the general procedure GP-4 as colorless thick liquid; R_f = 0.24 (1:1 hexane/EtOAc); **^1H NMR (500 MHz, DMSO- d_6)** δ 8.80–8.72 (m, 1H), 8.21–8.16 (m, 2H), 7.78–7.74 (m, 1H), 7.55–7.53 (m, 1H),

7.46–7.40 (m, 3H), 7.24–7.16 (m, 3H), 5.15 (d, J = 10.0 Hz, 2H), 4.27 (t, J = 12.5 Hz, 1H), 3.82 (dd, J = 20.0, 12.5 Hz, 1H), 3.49 (s, 3H), 3.07 (t, J = 15.0 Hz, 1H), 2.67–2.58 (m, 1H), 1.57–1.49 (m, 2H), 0.79–0.75 (m, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)** δ 182.39 & 182.22 (1C), 171.7, 157.6, 156.6, 149.8, 138.5, 138.19 & 138.15 (1C), 134.5, 132.05 & 132.01 (1C), 131.3, 131.1, 129.9, 129.6, 128.2, 127.4, 125.4, 123.40 & 123.34 (1C), 119.5, 115.20 & 115.13 (1C), 71.6, 69.3, 54.5, 39.7, 37.1, 28.74 & 28.63 (1C), 8.51. **IR (Neat)** $\nu_{\max}$ 2928, 1719, 1630, 1453, 1218, 1071, 980, 729 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{26}\text{H}_{26}\text{N}_2\text{ClO}_5\text{S}^+$ $[\text{M}+\text{H}]$, 513.1245; found 513.1243.

N-[4-Ethyl-7,8-dimethoxy-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (4l):

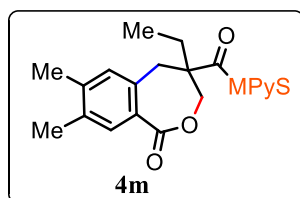


compound **4l** (69 mg, 80%), was prepared from **1a** and **2m** following the general procedure GP-4 as colorless thick liquid; R_f = 0.1 (3:7 hexane/EtOAc); **^1H NMR (500 MHz, CDCl_3)**

δ 8.69–8.52 (m, 1H), 8.20 (dd, J = 16.0, 8.0 Hz, 1H), 8.01–7.94 (m, 1H), 7.58–7.52 (m, 1H), 7.20 (s, 1H), 6.70–6.60 (m, 1H), 4.38 (dd, J = 12.5, 8.5 Hz, 1H), 4.02 (dd, J = 12.5, 6.0 Hz, 1H), 3.90 (d, J = 21.5 Hz, 3H), 3.85 (d, J = 19.0 Hz, 3H), 3.37 (d, J = 15.0 Hz, 3H), 3.25–3.18 (m, 1H), 2.66 (dd, J = 13.8, 2.8 Hz, 1H), 1.79–1.70 (m, 2H) 0.90–0.82 (m, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.30 & 182.23 (1C), 172.17 & 172.11 (1C), 156.6, 151.95 & 151.86 (1C), 149.79 & 149.75 (1C), 147.90 & 147.83 (1C), 138.19 & 138.02 (1C), 131.33 & 131.27 (1C), 127.42 & 127.24 (1C), 123.37 & 129.29 (1C), 122.6, 112.76 & 112.69 (1C), 112.57 & 112.50 (1C), 71.75 & 71.72 (1C), 56.08 & 56.04 (1C), 56.02 & 55.95 (1C), 54.79 & 54.75 (1C), 39.74 & 39.67 (1C), 37.86 & 37.77 (1C), 29.09 & 29.01 (1C), 8.56 & 8.48 (1C). IR (Neat) ν_{max} 2924, 1715, 1633, 1513, 1264, 1070, 985, 734 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_6\text{S}^+$ [M+H], 433.1428; found 433.1427.

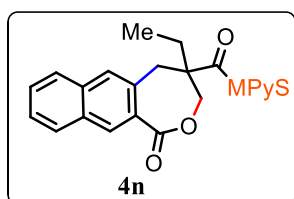
***N*-[4-Ethyl-7,8-dimethyl-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (4m):**



compound **4m** (40 mg, 50%), was prepared from **1a** and **2n** following the general procedure GP-4 as colorless thick liquid; R_f = 0.32 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.69–8.61 (m, 1H), 8.25–8.20 (m, 1H), 8.01–7.95 (m, 1H), 7.57–7.53 (m, 1H), 7.44 (d, J = 1.5 Hz, 1H), 6.92 (d, J = 10.0 Hz, 1H), 4.41 (d, J = 15.0 Hz, 1H), 3.97–3.90 (m, 1H), 3.39 & 3.38 (two s, 3H), 3.20 (dd, J = 15.0, 5.0 Hz, 1H), 2.64 (dd, J = 15.0, 10.0 Hz, 1H), 2.23 & 2.22 (two s, 6H) 1.70–1.65 (m, 2H) 0.87–0.81 (m, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 182.62 & 182.38 (1C), 172.4, 156.7, 149.8, 141.5, 138.22 & 138.15 (1C), 135.8, 134.46 & 134.43 (1C), 131.21 & 131.19 (1C), 131.1, 128.42 & 128.36 (1C), 127.39 & 127.30 (1C), 123.39 & 123.31 (1C), 71.73 & 71.66 (1C), 54.5, 39.68 & 39.62 (1C), 37.4, 28.76 & 28.61 (1C), 19.9, 19.1, 8.55 & 8.50 (1C); IR (Neat) ν_{max} 2924, 1720, 1634, 1453, 1223, 983, 735 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_4\text{S}^+$ [M+H], 401.1530; found 401.1533.

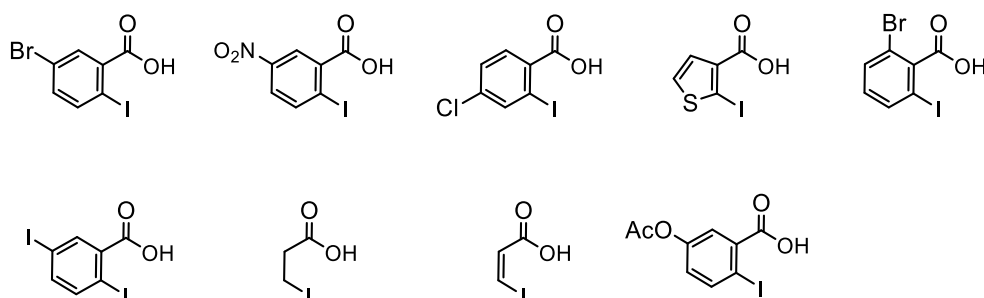
***N*-[4-Ethyl-1-oxo-1,3,4,5-tetrahydronaphtho[2,3-*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (4n):**



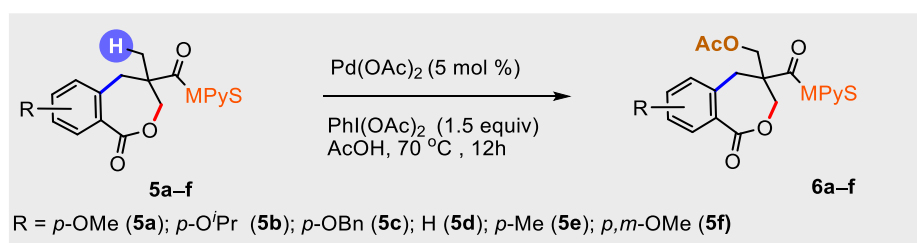
compound **4n** (52 mg, 62%), was prepared from **1a** and **2o** following the general procedure GP-4 as colorless thick liquid; R_f = 0.30 (1:1 hexane/EtOAc); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.78–8.63 (m, 1H), 8.28 (d, J = 10.0 Hz, 1H), 8.19–8.15 (m, 2H),

8.08 (t, $J = 7.5$ Hz, 1H), 7.94 (dd, $J = 20.0, 10.0$ Hz, 1H), 7.78–7.72 (m, 2H), 7.66 (t, $J = 7.5$ Hz, 1H), 7.58 (dd, $J = 15.0, 5.0$ Hz, 1H), 4.31 (t, $J = 10.0$ Hz, 1H), 3.88 (t, $J = 15.0$ Hz, 1H), 3.51 & 3.50 (two s, 3H), 3.28 (t, $J = 12.5$ Hz, 1H), 2.89–2.81 (m, 1H), 1.60–1.54 (m, 2H), 0.80 (t, $J = 7.5$ Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 182.14, 171.89 & 171.85 (1C), 156.68 & 156.61 (1C), 149.79 & 149.74 (1C), 138.16 & 138.02 (1C), 135.03, 132.60 & 132.50 (1C), 131.8, 131.34 & 131.27 (1C), 129.62 & 129.57 (1C), 128.75 & 128.73 (1C), 128.41 & 128.33 (1C), 128.16 & 128.12 (1C), 127.45 & 127.39 (1C), 127.36 & 127.24 (1C), 126.4, 123.3, 71.54 & 71.37 (1C), 60.3, 54.18 & 54.16 (1C), 39.7, 38.09 & 37.81 (1C), 28.6, 8.54 & 8.49 (1C). IR (Neat) $\nu_{\max}$ 2925, 1721, 1629, 1452, 1217, 1165, 1061, 980 cm⁻¹. HRMS (ESI-TOF) m/z : calcd. for C₂₃H₂₃N₂O₄S⁺ [M+H], 423.1373; found 423.1375.

The difunctionalization transformation developed herein failed with the following 2-iodobenzoic acid derivatives, probably due to their lesser solubility under the reaction conditions.



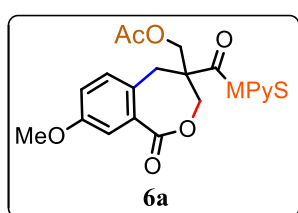
2.6.3.11. General procedure for iterative C(sp³)-H acetoxylation of benzolactones (GP-5):



A screw-capped tube (5.0 mL) equipped with a magnetic stir bar was charged with benzolactone (**5a–f**; 0.1 mmol), Pd(OAc)₂ (1.12 mg, 5.0 mol%), PhI(OAc)₂ (48.3 mg, 1.5 mmol), AcOH (1.0 mL) in open air. The resulting mixture was stirred at 70 °C for 12

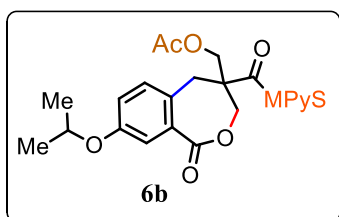
h. Solvent was evaporated under the reduced pressure and the crude material was purified using column chromatography on silica gel. Most of the compounds possess minor amount of impurity that are difficult to isolated by column chromatography. These compounds are purified by reverse-phase liquid chromatography (HPLC system) in C18 column eluting with acetonitrile and water (7:3) mixture.

N-[4-(Acetoxymethyl)-8-methoxy-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (6a):



compound **6a** (40 mg, 89%) was prepared following the general procedure GP-5 as colorless thick liquid; R_f = 0.15 (3:7 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.71–8.63 (m, 1H), 8.25–8.18 (m, 1H), 7.99 (td, J = 8.0, 2.0 Hz, 1H), 7.61–7.56 (m, 1H), 7.24–7.20 (m, 1H), 7.12–7.05 (m, 1H), 6.98–6.88 (m, 1H), 4.50–4.37 (m, 2H), 4.22–4.13 (m, 2H), 3.80 (d, J = 8.5 Hz, 3H), 3.40 (s, 3H), 3.21 (dd, J = 14.0, 8.0 Hz, 1H), 2.74 (d, J = 14.0 Hz, 1H), 2.01 (d, J = 13.0 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 179.66 & 179.61 (1C), 171.43 & 171.42 (1C), 170.59 & 170.52 (1C), 159.01 & 158.98 (1C), 156.31 & 156.29 (1C), 149.8, 138.27 & 138.22 (1C), 131.6, 131.10 & 131.06 (1C), 127.53 & 127.48 (1C), 127.34 & 127.25 (1C), 123.40 & 123.36 (1C), 119.11 & 119.05 (1C), 114.49 & 114.29 (1C), 68.90 & 68.82 (1C), 66.14 & 66.00 (1C), 55.50 & 55.48 (1C), 54.30 & 54.27 (1C), 39.55 & 39.51 (1C), 35.11 & 35.00 (1C), 20.8; IR (Neat) ν_{max} 1727, 1637, 1425, 1262, 1219, 1035, 985, 732 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_7\text{S}^+$ $[\text{M}+\text{H}]$, 447.1220; found 447.1225.

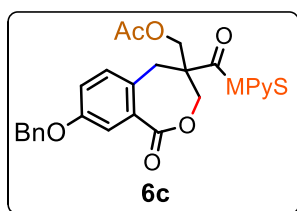
N-[4-(Acetoxymethyl)-8-isopropoxy-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (6b):



compound **6b** (39 mg, 82%) was prepared following the general procedure GP-5 as colorless thick liquid; R_f = 0.17 (3:7 hexane/EtOAc); ^1H NMR (500 MHz, DMSO) δ 8.85–8.75 (m, 1H), 8.22–8.13 (m, 2H), 7.79–7.76 (m, 1H), 7.19–7.14 (m, 1H), 7.10–7.06 (m, 2H), 4.68–4.62 (m, 1H), 4.30–4.22 (m, 2H), 4.14–4.03 (m, 2H), 3.50 &

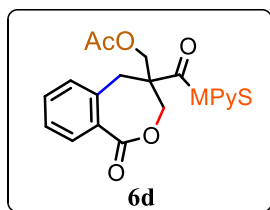
3.49 (two s, 3H), 3.05 (dd, $J = 15.0, 10.0$ Hz, 1H), 2.73 (t, $J = 12.5$ Hz, 1H), 1.98 & 1.95 (two s, 3H), 1.29–1.26 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 179.72 & 179.67 (1C), 171.5, 170.58 & 170.52 (1C), 157.46 & 157.42 (1C), 156.5, 149.83 & 149.82 (1C), 138.27 & 138.22 (1C), 131.7, 131.16 & 131.14 (1C), 127.51 & 127.46 (1C), 127.11 & 127.01 (1C), 123.38 & 123.34 (1C), 120.73 & 120.64 (1C), 116.47 & 116.26 (1C), 70.34 & 70.31 (1C), 68.98 & 68.89 (1C), 66.21 & 66.09 (1C), 54.37 & 56.34 (1C), 39.57 & 39.52 (1C), 35.18 & 35.06 (1C), 21.98 & 21.94 (1C), 20.8; IR (Neat) ν_{max} 2975, 2926, 1723, 1635, 1577, 1492, 1454, 1424, 1214, 1109, 1037, 984, 759 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_7\text{S}^+$ [M+H], 475.1533; found 475.1536.

***N*-[4-(Acetoxymethyl)-8-(benzyloxy)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (6c):**



compound **6c** (45 mg, 87%) was prepared following the general procedure GP-5 as colorless thick liquid; $R_f = 0.2$ (3:7 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.62 (m, 1H), 8.28–8.15 (m, 1H), 8.03–7.94 (m, 1H), 7.59–7.53 (m, 1H), 7.46–7.37 (m, 4H), 7.36–7.30 (m, 2H), 7.13–6.96 (m, 2H), 5.12–5.04 (m, 2H), 4.53–4.37 (m, 2H), 4.33–4.16 (m, 2H), 3.40 (s, 3H), 3.22 (dd, $J = 14.0, 8.0$ Hz, 1H), 2.75 (d, $J = 14.0$ Hz, 1H), 2.02 (d, $J = 11.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 179.6, 171.3, 170.57 & 170.51 (1C), 158.2, 156.4, 149.8, 138.26 & 138.21 (1C), 136.39 & 136.35 (1C), 131.8, 131.2, 128.6, 128.1, 127.52 & 127.50 (1C), 127.5, 123.4, 119.80 & 119.70 (1C), 115.6, 115.5, 70.3, 69.0, 66.18 & 66.05 (1C), 54.36 & 54.33 (1C), 39.57 & 39.52 (1C), 35.19 & 35.06 (1C), 20.8; IR (Neat) ν_{max} 2924, 1735, 1639, 1426, 1226, 1038, 843, 736 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_7\text{S}^+$ [M+H], 523.1533; found 523.1541.

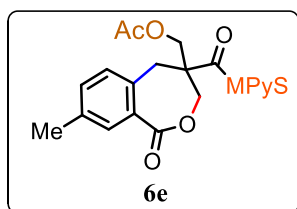
***N*-[4-(Acetoxymethyl)-1-oxo-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (6d):**



compound **6d** (31 mg, 75%) was prepared following the general procedure GP-5 as colorless thick liquid; $R_f = 0.20$ (3:7 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.77–8.61 (m, 1H), 8.24–8.18 (m, 1H), 7.99 (td, $J = 7.5, 1.0$ Hz, 1H), 7.71 (t, $J = 9.0$, 1H),

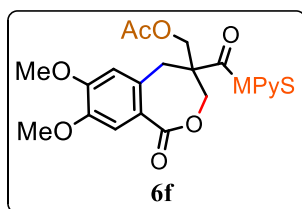
7.63–7.54 (m, 1H), 7.52–7.33 (m, 2H), 7.19 (dd, $J = 13.3, 7.8$ Hz, 1H), 4.50–4.37 (m, 2H), 4.31–4.15 (m, 2H), 3.41 (s, 3H), 3.29 (dd, $J = 14.0, 7.5$ Hz, 1H), 2.81 (d, $J = 14.0$ Hz, 1H), 2.01 (d, $J = 10.0$ Hz, 3H), $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 179.49 & 179.44 (1C), 171.47 & 171.44 (1C), 170.55 & 171.50 (1C), 156.4, 149.8, 138.28 & 138.23 (1C), 135.43 & 135.33 (1C), 132.65 & 132.46 (1C), 130.9, 130.33 & 130.31 (1C), 129.94 & 129.92 (1C), 127.8, 127.53 & 127.48 (1C), 123.38 & 123.35 (1C), 68.84 & 68.77 (1C), 66.22 & 66.08 (1C), 54.26 & 54.23 (1C), 39.57 & 39.53 (1C), 35.98 & 35.87 (1C), 20.8; IR (Neat) ν_{max} 1732, 1639, 1225, 1088, 1039, 987, 735 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_6\text{S}^+$ [M+H], 417.1115; found 417.1118.

N-[4-(Acetoxymethyl)-8-methyl-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (6e):



compound **6e** (40 mg, 92%) was prepared following the general procedure GP-5 as colorless thick liquid; $R_f = 0.22$ (3:7 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.71–8.63 (m, 1H), 8.24–8.20 (m, 1H), 7.99 (t, $J = 7.25$ Hz, 1H), 7.61–7.56 (m, 1H), 7.52 (d, $J = 10.0$ Hz, 1H), 7.25–7.17 (m, 1H), 7.09–7.01 (m, 1H), 4.50–4.36 (m, 2H), 4.32–4.12 (m, 2H), 3.41 (s, 3H), 3.24 (dd, $J = 14.0, 10.5$ Hz, 1H), 2.77 (dd, $J = 14.0, 3.0$ Hz, 1H), 2.34 (d, $J = 10.5$ Hz, 3H), 2.01 (d, $J = 12.0$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 179.6, 171.8, 170.57 & 170.51 (1C), 156.4, 149.83 & 149.81 (1C), 138.28 & 138.22 (1C), 137.71 & 137.69 (1C), 133.4, 133.2, 132.29 & 132.21 (1C), 130.8, 130.6, 129.81 & 129.78 (1C), 127.52 & 127.47 (1C), 123.37 & 123.34 (1C), 68.84 & 68.78 (1C), 66.20 & 66.05 (1C), 54.23 & 54.21 (1C), 39.56 & 39.51 (1C), 35.55 & 35.46 (1C), 20.85 & 20.75 (1C). IR (Neat) ν_{max} 2923, 1728, 1618, 1579, 1453, 1221, 1175, 1032, 981, 756 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_6\text{S}^+$ [M+H], 431.1271; found 431.1276.

N-[4-(Acetoxymethyl)-7,8-dimethoxy-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (6f):

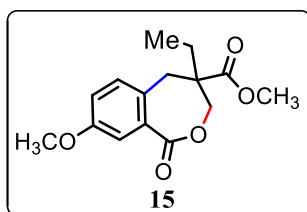


compound **6f** (36 mg, 76%) was prepared following the general procedure GP-5 as colorless thick liquid; R_f = 0.15 (100% EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.69–8.58 (m, 1H), 8.24–8.18 (m, 1H), 8.02–7.95 (m, 1H), 7.60–7.53 (m, 1H), 7.22 (d, J = 10.0 Hz, 1H), 6.68 (d, J = 10.0 Hz, 1H), 4.50–4.37 (m, 2H), 4.23–4.15 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.39 (d, J = 10.5 Hz, 3H), 3.21 (dd, J = 13.8, 3.3 Hz, 1H), 2.77 (d, J = 14.0 Hz, 1H), 2.01 (bd, J = 2.0 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 179.64 & 179.52 (1C), 171.69 & 171.63 (1C), 170.5, 156.4, 152.2, 149.84 & 149.77 (1C), 148.22 & 148.16 (1C), 138.31 & 138.17 (1C), 129.71 & 129.61 (1C), 127.57 & 127.43 (1C), 123.40 & 123.26 (1C), 122.38 & 122.30 (1C), 112.8, 112.6, 69.1, 66.33 & 66.18 (1C), 56.2, 56.08 & 56.04 (1C), 54.62 & 54.59 (1C), 39.63 & 39.58 (1C), 35.81 & 35.73 (1C), 20.8; IR (Neat) ν_{max} 2928, 1718, 1635, 1511, 1454, 1212, 1063, 1035, 983, 758 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_8\text{S}^+$ $[\text{M}+\text{H}]$, 477.1326; found 477.1326.

2.6.3.12. General Procedure for the Cleavage of MPyS:

To a solution of **4d** (0.25 mmol) in MeOH : H_2O (1:1 mL) was added NaOH (5.0 equiv). The resulting mixture was refluxed for 4 h. After reaction completion, MeOH was evaporated and the reaction mixture was neutralized with 2N HCl. The crude mixture was then extracted with EtOAc, dried over Na_2SO_4 , and concentrated under vacuum to give the corresponding carboxylic acid. Next, the crude mixture was dissolved in MeOH and SOCl_2 (2.5 equiv) was added dropwise at 0 $^\circ\text{C}$. The resulting mixture was stirred at rt for 12 h. The reaction mixture was extracted with EtOAc and washed with water 2 times, dried over Na_2SO_4 . Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography eluting with EA/hexane (1/20) on silica gel.

Methyl 4-ethyl-8-methoxy-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepine-4-carboxylate(15):



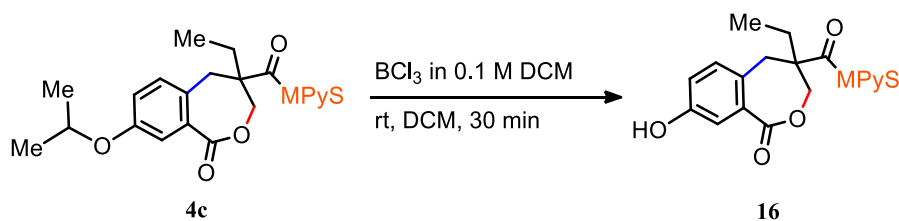
compound **15** (35 mg, 80%) was prepared as colorless liquid; R_f = 0.44 (9:1 hexane/EtOAc); ^1H NMR (500 MHz, CDCl_3) 7.25 (d, J = 3.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.12 (dd, J = 8.3, 2.8 Hz, 1H), 4.39 (d, J = 12.5 Hz, 1H), 3.97 (d, J = 12.5 Hz, 1H),

3.82 (s, 3H), 3.72 (s, 3H), 3.24 (d, J = 14.0 Hz, 1H), 2.75 (d, J = 14.5 Hz, 1H), 1.70–1.65 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 173.9, 171.3, 159.1, 131.9, 131.0, 128.0, 119.1, 114.6, 71.0, 55.5, 52.9, 52.2, 36.4, 28.2, 8.7; IR (Neat) ν_{max} 2927, 1728, 1610, 1498, 1288, 1263, 1239, 1076, 1030, 736 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{15}\text{H}_{19}\text{O}_5^+$ $[M+H]$, 279.1227; found 279.1226.

2.6.3.13. Gram Scale Synthesis of 4c:

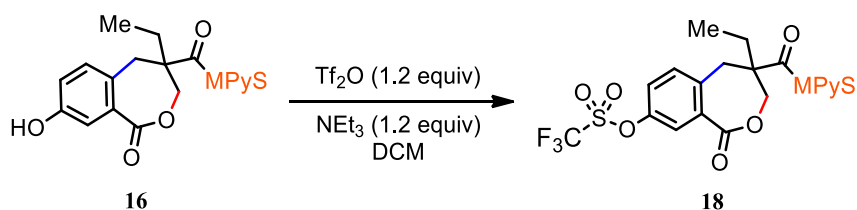
A 100 mL sealed tube equipped with magnetic stir bar was charged with $\text{Pd}(\text{OAc})_2$ (88 mg, 0.39 mmol), **1a** (1.0 g, 3.93 mmol), AgOAc (1.312 g, 7.86 mmol), NaBrO_3 (1.185 g, 7.86 mmol), 2-iodo-5-isopropoxybenzoic acid **2d** (2.41 g, 7.86 mmol), and **L9** (214.0 mg, 1.51 mL, 1.18 mmol) in open air. Then HFIP (19 mL) and AcOH (9.0 mL) was added. The resulting reaction mixture was stirred at 70 °C for 36 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with DCM, filtered through Celite plug. The filtrate was washed with saturated NaHCO_3 solution and concentrated in vacuo. The crude reaction mixture was purified on silica gel using hexane/EtOAc (4/6) as eluent to afford the desired product **4c** (0.9 g) in 53% yield.

2.6.3.14. Preparation of N-[4-ethyl-8-hydroxy-1-oxo-1,3,4,5-tetrahydrobenzo[c]oxepinoyl]-S-methyl-S-(2-pyridyl) sulfoximine (16):



A round bottom flask (50 mL) equipped with magnetic stir bar was charged with **4c** (1.69 mmol, 0.730 g) and excess amount of BCl_3 (in 0.1M THF) in DCM. The reaction mixture was stirred at rt for 30 minutes. Upon completion, the crude reaction mixture was purified on silica gel using hexanes/EtOAc as eluent to afford the desired product **16** (511 mg, 77%); $R_f = 0.17$ (3:7 hexane/EtOAc); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.69–8.64 (m, 1H), 8.26–8.22 (m, 1H), 8.01–7.7.96 (m, 1H), 7.58–7.54 (m, 1H), 7.17 (dd, $J = 7.3, 2.8$ Hz, 1H), 7.06–6.97 (m, 1H), 6.85–6.81 (m, 1H), 6.40 (bs, 1H), 4.44–4.39 (m, 1H), 4.01 (dd, $J = 14.3, 12.8$ Hz, 1H), 3.40 (s, 3H), 3.22 (d, $J = 14.0$ Hz, 1H), 2.65 (dd, $J = 14.0, 5.0$ Hz, 1H), 1.74–1.70 (m, 2H), 0.88–0.82 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.97 & 182.86 (1C), 172.1, 172.7, 155.7, 150.0, 138.3, 131.4, 131.19 & 131.03 (1C), 127.95 & 127.90 (1C), 127.6, 123.4, 119.78 & 119.68 (1C), 116.6, 71.8, 54.6, 39.8, 36.9, 28.6, 8.5; IR (Neat) ν_{max} 1721, 1624, 1454, 1302, 1224, 1152, 1074, 983, 747 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_5\text{S}^+$ $[M+H]$, 389.1166; found 389.1164.

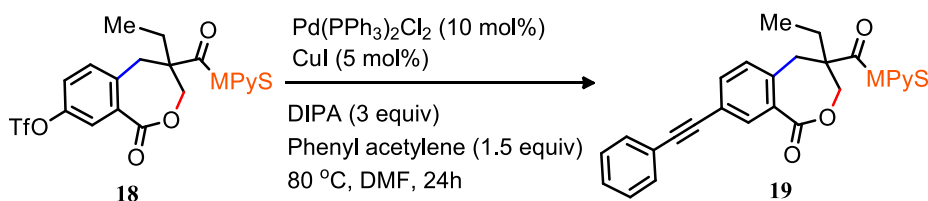
2.6.3.15. Preparation of *N*-[4-Ethyl-1-oxo-8-(((trifluoromethyl)sulfonyl)oxy)-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (**18**):



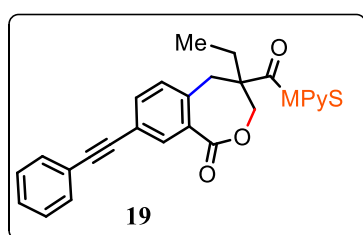
A round bottom flask (50 mL) equipped with magnetic stir bar was charged **16** (0.5 mmol, 0.200 g) in DCM solvent and cooled to 0 °C. Triethylamine (1.2 equiv) was added dropwise followed by the addition of Tf_2O (1.2 equiv). After 5 min, the ice bath was removed, and the reaction was stirred at rt. The reaction progress was monitored by TLC. Upon completion, the crude reaction mixture was purified on silica gel using hexanes/EtOAc as eluent to afford the desired product **18** (246 mg, 92%) as colorless thick liquid; $R_f = 0.16$ (1:1 hexane/EtOAc). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.69–8.54 (m, 1H), 8.27–8.20 (dd, $J = 13.8, 7.8$ Hz, 1H), 8.06–7.96 (m, 1H), 7.64–7.54 (m, 2H), 7.38–7.31 (m, 1H), 7.30–7.24 (m, 1H), 4.35 (dd, $J = 12.5, 10.5$ Hz, 1H), 4.08 (d, $J = 12.5$ Hz, 1H), 3.40–3.31 (m, 4H), 2.71 (dd, $J = 14.0, 7.0$ Hz, 1H), 1.80–1.72 (m, 2H), 0.94–0.84

(m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 181.39 & 181.36 (1C), 169.60 & 169.57 (1C), 156.39 & 156.35 (1C), 149.91 & 149.88 (1C), 148.37 & 148.27 (1C), 138.24 & 138.15 (1C), 137.67 & 137.54 (1C), 133.29 & 133.26 (1C), 132.0, 127.51 & 127.41 (1C), 124.92 & 124.89 (1C), 123.49 & 123.47 (1C), 122.5, 118.6 (q, $J = 308.0$ Hz), 71.73 & 71.58 (1C), 54.3, 39.8, 37.20 & 36.99 (1C), 29.08 & 29.03 (1C), 8.50 & 8.44 (1C); ^{19}F NMR (376 MHz, CDCl_3) δ -72.77 & -72.82 (3F); IR (Neat) ν_{max} 1728, 1634, 1423, 1215, 1139, 1080, 982, 904, 735 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_7\text{S}_2^+$ $[\text{M}+\text{H}]$, 521.0659; found 521.0659.

2.6.3.16. Synthesis of *N*-[4-ethyl-1-oxo-8-(phenylethynyl)-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (**19**); Procedure for Sonogashira coupling:



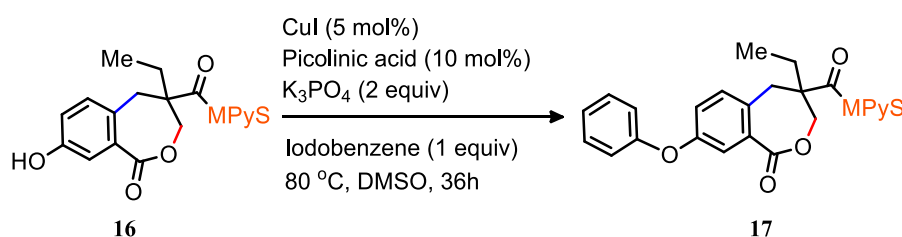
A 5 mL screw-capped tube equipped with magnetic stir bar was charged with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (10 mol%, 7 mg), **18** (0.1 mmol, 52.0 mg), CuI (5.0 mol%, 0.95 mg), diisopropyl amine (DIPA, 0.3 mmol, 0.042 mL), and phenyl acetylene (0.15 mmol, 0.016 mL) in N_2 atmosphere. DMF was then added. The reaction mixture was stirred at 80 $^\circ\text{C}$ for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with DCM, filtered through a Celite plug, and concentrated in vacuo. The crude reaction mixture was purified on silica gel using hexanes/ EtOAc as eluent to afford the desired product **19** (41 mg, 88%) as colorless thick liquid; $R_f = 0.31$ (1:1 hexane/ EtOAc).



^1H NMR (500 MHz, CDCl_3) δ 8.70–8.61 (m, 1H), 8.23 (t, $J = 8.25$ Hz, 1H), 8.02–7.98 (m, 1H), 7.86 (dd, $J = 5.3, 1.8$ Hz, 1H), 7.58–7.50 (m, 4H), 7.37–7.33 (m, 3H), 7.24–7.15 (m, 1H), 4.40 (dd, $J = 12.5, 7.5$ Hz, 1H), 4.02 (dd, $J = 12.75, 6.75$ Hz, 1H), 3.40 (d, $J = 6.0$ Hz, 3H), 3.32 (dd, $J = 14.0, 4.5$ Hz, 1H), 2.73 (d, $J = 14.0$ Hz, 1H),

1.78–1.70 (m, 2H), 0.92–0.85 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.00, 171.1, 156.5, 149.9, 138.2, 136.9, 134.9, 133.0, 131.6, 131.5, 130.2, 130.0, 128.5, 128.3, 127.48 & 127.38 (1C), 123.4, 122.8, 90.5, 87.9, 71.58 & 71.47 (1C), 54.4, 39.7, 37.8, 28.9, 8.6; IR (Neat) ν_{max} 1725, 1634, 1496, 1227, 1079, 982, 754 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 473.1530; found 473.1531.

2.6.3.17. Synthesis of *N*-[4-ethyl-1-oxo-8-phenoxy-1,3,4,5-tetrahydrobenzo[*c*]oxepinoyl]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (17):

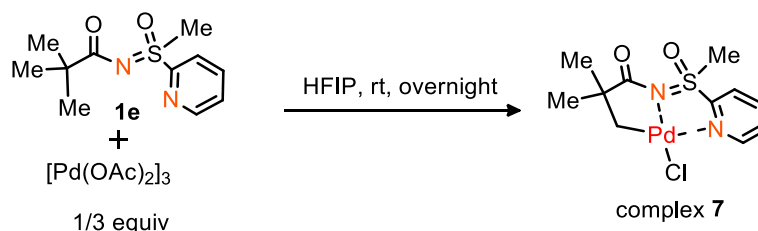


A 5 mL screw-capped tube equipped with magnetic stir bar was charged with CuI (5.0 mol%, 1.0 mg), **16** (0.1 mmol, 39 mg), picolinic acid (10 mol%, 1.23 mg), K_3PO_4 (0.2 mmol, 42.5 mg), iodobenzene (0.1 mmol, 20.4 mg) in N_2 atmosphere. DMSO was then added. The reaction mixture was stirred at 80 °C for 36 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with DCM, filtered through a Celite plug, and concentrated in vacuum. The crude reaction mixture was purified on silica gel using hexanes/EtOAc as eluent to afford the desired product **17** (35 mg, 75%) as colorless thick liquid; R_f = 0.25 (1:1 hexane/EtOAc).

^1H NMR (500 MHz, CDCl_3) δ 8.68–8.62 (m, 1H), 8.23 (t, J = 8.3 Hz, 1H), 8.02–7.96 (m, 1H), 7.58–7.52 (m, 1H), 7.37–7.32 (m, 2H), 7.30–7.27 (m, 1H), 7.19–7.10 (m, 2H), 7.06–6.98 (m, 3H), 4.40 (dd, J = 12.3, 4.8 Hz, 1H), 4.01 (dd, J = 14.8, 12.8 Hz, 1H), 3.40 (d, J = 0.5 Hz, 3H), 3.28 (dd, J = 14.0, 5.0 Hz, 1H), 2.68 (dd, J = 14.0, 8.5 Hz, 1H), 1.76–1.68 (m, 2H), 0.90–0.83 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.24 & 182.06 (1C), 171.2, 156.8, 156.6, 156.3, 149.83 & 149.80 (1C), 138.19 & 138.14 (1C), 132.43 & 132.38 (1C), 131.43, 131.37 & 131.34 (1C), 131.2, 129.9, 127.3, 123.95 & 123.94 (1C), 123.41 & 123.35 (1C), 122.17 & 122.13 (1C), 119.37 & 119.34 (1C), 71.57 & 71.53 (1C), 54.51 & 54.48 (1C), 39.72 & 39.68 (1C), 37.1, 28.83 & 28.73 (1C), 8.53 & 8.49 (1C); IR (Neat) ν_{max} 1723,

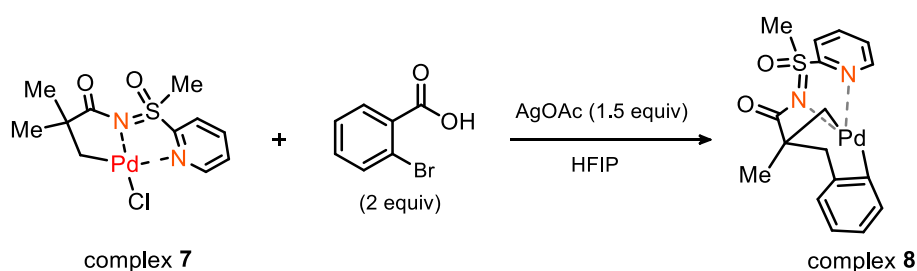
1634, 1485, 1424, 1224, 1072, 983, 735 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_5\text{S}^+ [\text{M}+\text{H}]$, 465.1479; found 465.1480.

2.6.3.18. Procedure for the synthesis of organo-palladium complex 7:



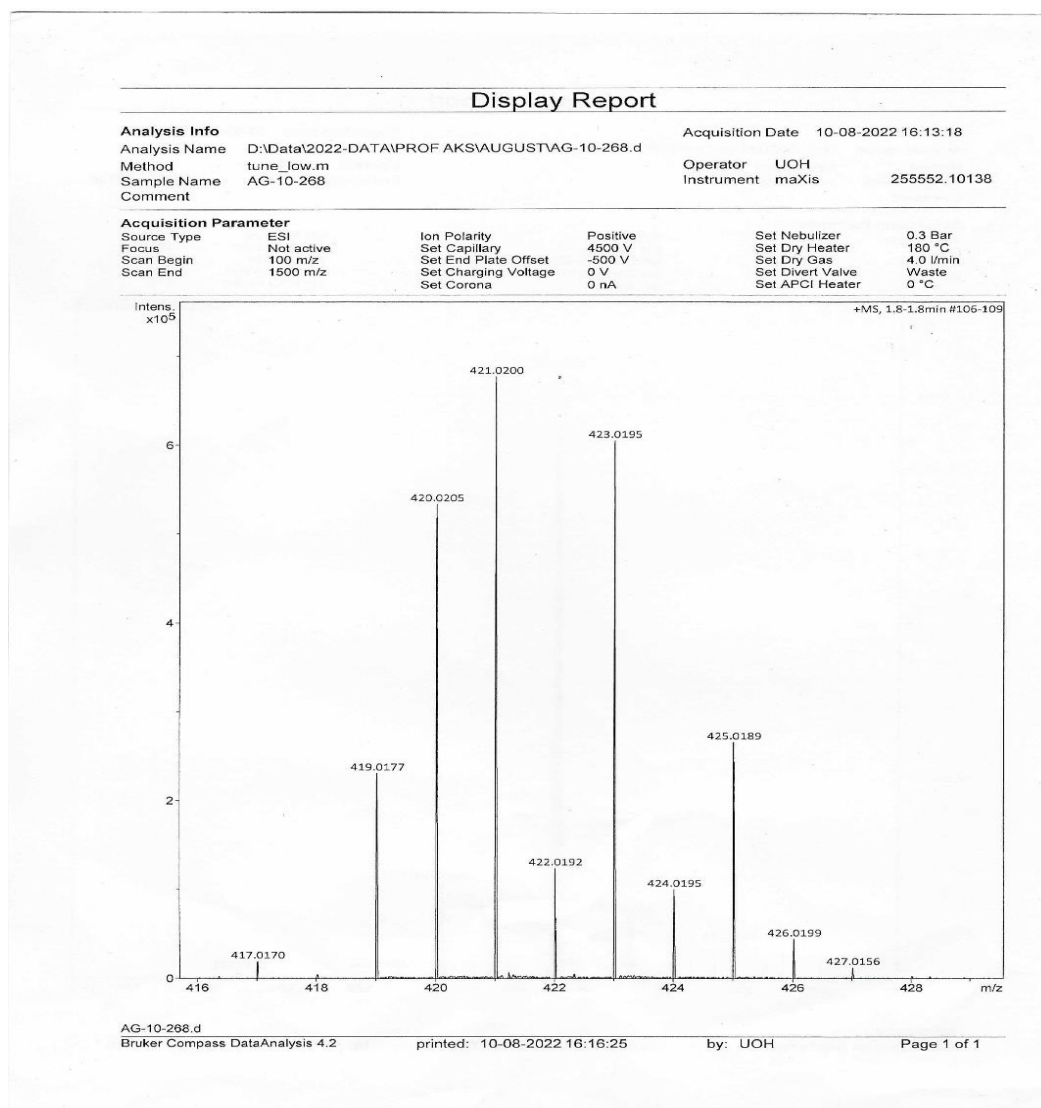
A solution of methylphenylsulfoximine derived from pivalic acid (**1e**; 0.133 mmol, 31 mg) and $\text{Pd}(\text{OAc})_2$ (0.133 mmol, 30 mg) in HFIP (0.5 mL) was stirred at room temperature overnight. The reaction mixture was filtered. The solvent was evaporated and the resulting solid was washed with diethyl ether (3 times), and then dried under vacuum to produce a yellow powder (47 mg, 92% yield). The complex was recrystallized via vapor diffusion of MeOH. The structure of **7** was unambiguously established by X-ray diffraction studies. ^1H NMR (500 MHz, $\text{MeOH}-d_6$) δ 8.50–8.48 (m, 3H), 8.03–7.99 (m, 1H), 2.06 (bs, 3H), 1.77 (d, $J = 10.0$ Hz, 1H), 1.72 (d, $J = 10.0$ Hz, 1H), 1.30 (s, 3H), 1.20 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, $\text{MeOH}-d_6$) δ 188.0, 156.6, 149.8, 141.7, 131.0, 126.0, 48.9, 27.8, 26.1, 22.0, 20.6.

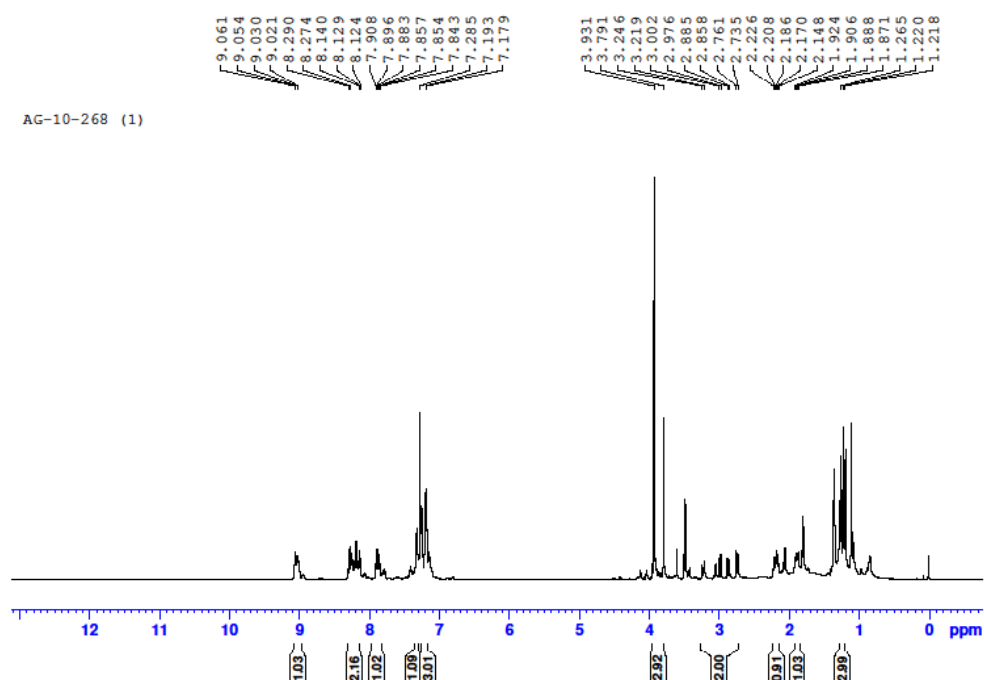
2.6.3.19. Procedure for the synthesis of organo-palladium complex 8:



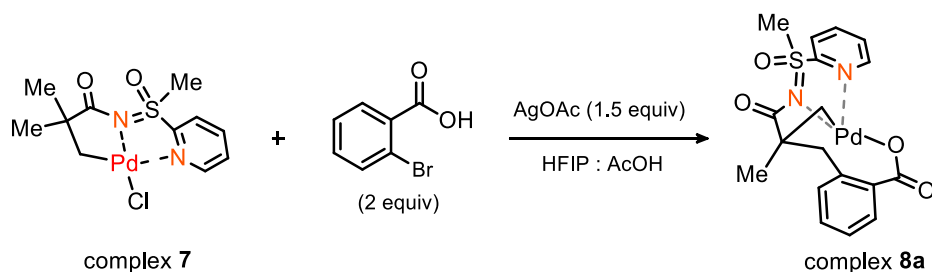
A solution of methylphenylsulfoximine derived from pivalic acid (**1e**; 0.45 mmol, 108 mg) and $\text{Pd}(\text{OAc})_2$ (0.45 mmol, 100 mg) in HFIP (5 mL) was stirred at room temperature overnight. Then 2-bromo benzoic acid (0.90 mmol, 180 mg) and AgOAc (0.68 mmol, 112 mg) were added into the reaction mixture, which was stirred at 70 $^\circ\text{C}$ for

24 h. The crude reaction mixture was purified on neutral alumina using hexanes/EtOAc as eluent to afford product **8** (79 mg, 45%) as a yellow solid. **HRMS (ESI-TOF)** m/z : calcd. for $C_{17}H_{19}N_2O_2PdS^+$ [(M-CO₂)+H], 421.0197; found 421.0200.

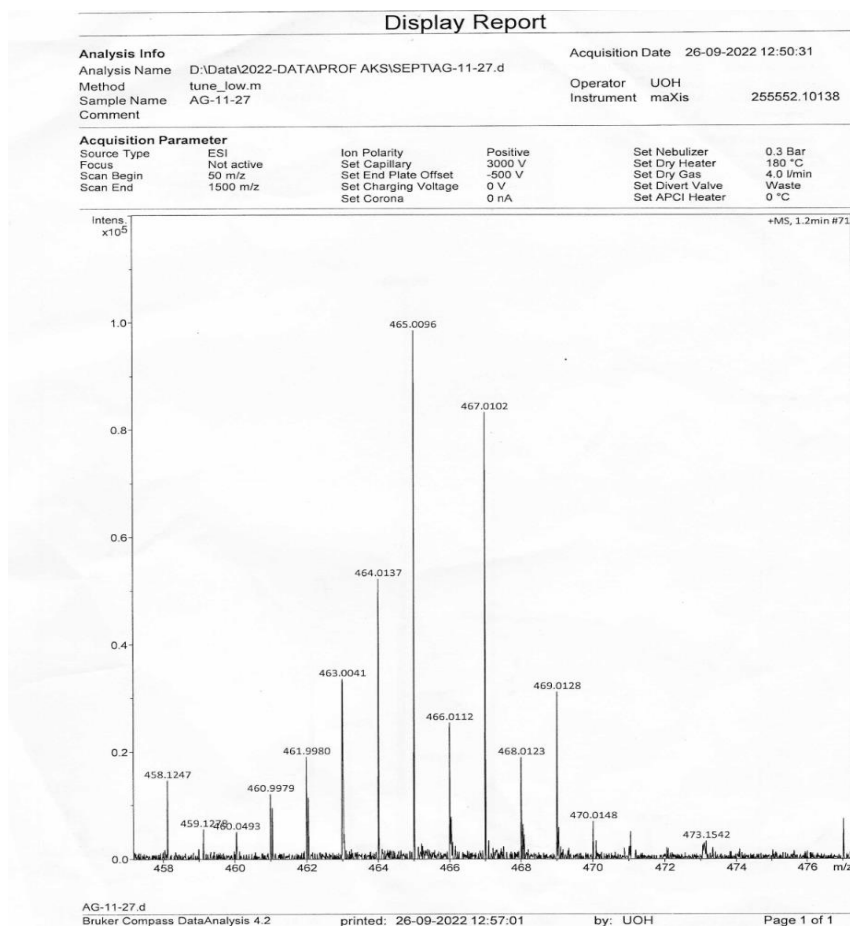




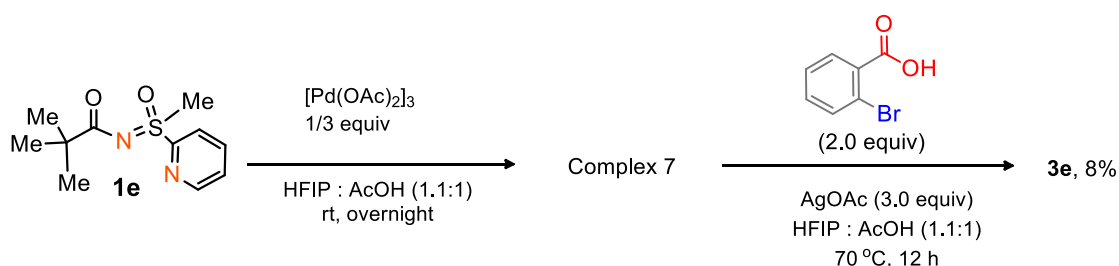
2.6.3.20. Procedure for the synthesis of organo-palladium complex **8a**:



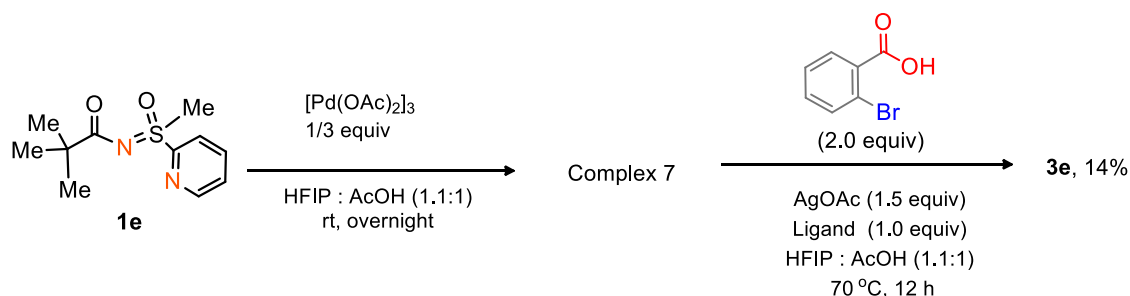
A solution of methylphenylsulfoximine derived from pivalic acid **1e** (0.45 mmol, 108 mg) and $\text{Pd}(\text{OAc})_2$ (0.45 mmol, 100 mg) in HFIP : AcOH (5 mL 1:1) was stirred at room temperature overnight. Then 2-bromo benzoic acid (0.90 mmol, 180 mg) and AgOAc (0.68 mmol, 112 mg) were added into the reaction mixture, which was stirred at 70 °C for 24 h. The crude reaction mixture was filtered through neutral alumina using hexanes/EtOAc eluent. The crude compound **8a** was isolated as yellow solid. **HRMS** (ESI-TOF) m/z : calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4\text{PdS}^+$ $[\text{M}+\text{H}]$, 465.0095; found 465.0096.



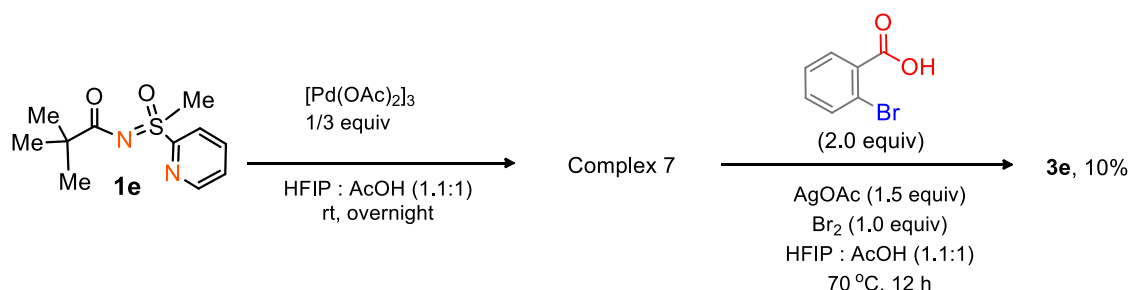
2.6.3.21. Reaction of complex 7 with excess amount of silver acetate:



A solution of methylphenylsulfoximine derived from pivalic acid **1e** (0.133 mmol, 32 mg) and Pd(OAc)_2 (0.133 mmol, 30 mg) in HFIP (0.485 mL) : AcOH (0.230 mL) was stirred at room temperature overnight. Then 2-bromo benzoic acid (0.27 mmol, 45 mg) and AgOAc (3 equiv, 0.40 mmol, 67 mg) were added into the reaction mixture, which was stirred at 70 °C for 12 h. The crude reaction mixture was purified on silica gel using hexane/EtOAc eluent to afford the desired products **3e** in 8% yield.

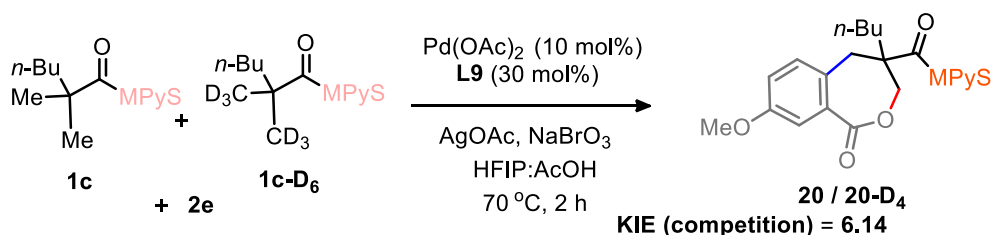
2.6.3.22. Reaction of complex 7 with excess amount of ligand 9:

A solution of methylphenylsulfoximine derived from pivalic acid **1e** (0.133 mmol, 32 mg) and $Pd(OAc)_2$ (0.133 mmol, 30 mg) in HFIP (0.485 mL) : AcOH (0.230 mL) was stirred at room temperature overnight. Then 2-bromo benzoic acid (0.27 mmol, 45 mg) and AgOAc (1.5 equiv, 0.20 mmol, 33 mg) and ligand **L9** (1.0 equiv, 0.133 mmol, 24 mg) were added into the reaction mixture, which was stirred at 70 °C for 12 h. The crude reaction mixture was purified on silica gel using hexane/EtOAc eluent to afford the desired products **3e** in 14% yield.

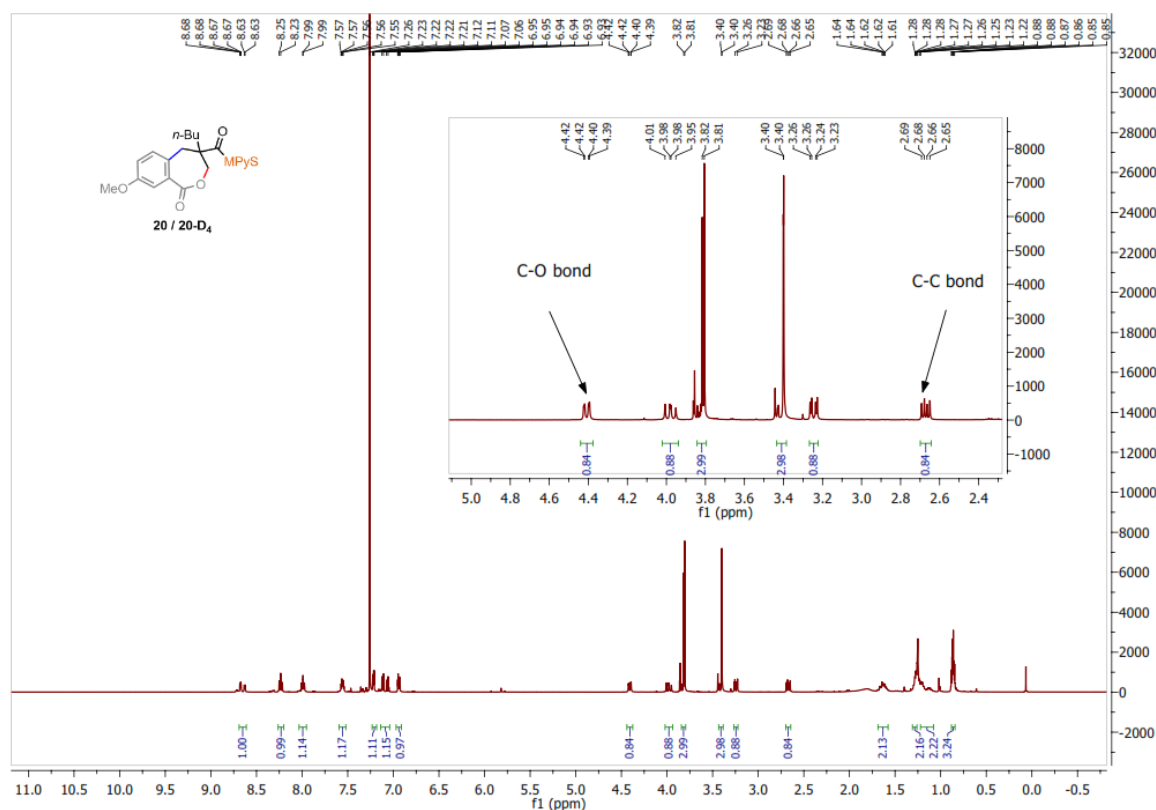
2.6.3.23. Reaction of complex 7 with Br_2 :

A solution of methylphenylsulfoximine derived from pivalic acid **1e** (0.133 mmol, 32 mg) and $Pd(OAc)_2$ (0.133 mmol, 30 mg) in HFIP (0.485 mL) : AcOH (0.230 mL) was stirred at room temperature overnight. Then 2-bromo benzoic acid (0.27 mmol, 45 mg) and AgOAc (1.5 equiv, 0.20 mmol, 33 mg) were added into the reaction mixture, which was stirred at 70 °C for 12 h. Then Br_2 (1.0 equiv, 0.20 mmol, 21 mg) was added into the reaction mixture, which was stirred at 70 °C for 4 h. The crude reaction mixture was purified on silica gel using hexane/EtOAc eluent to afford the desired products **3e** in 10% yield.

2.6.3.24. Procedure for the competitive KIE study:



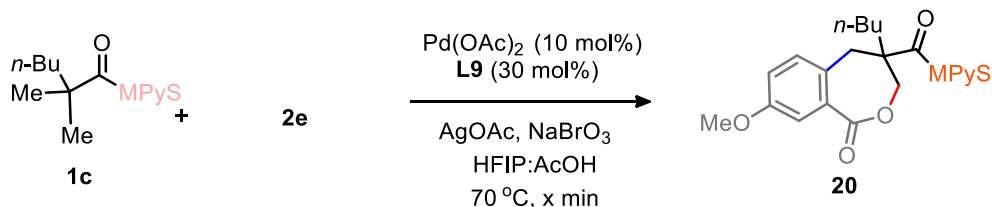
A 5 mL sealed tube equipped with a magnetic stir bar was charged with Pd(OAc)₂ (10 mol%, 4.5 mg), substrate **1c** (0.1 mmol) and **1c-D₆** (0.1 mmol), AgOAc (0.4 mmol, 66.0 mg), NaBrO₃ (0.4 mmol, 60.0 mg), 5- methoxy-2-iodobenzoic acid **2e** (0.4 mmol, 99.0 mg), and **L9** (30 mol%, 10.8 mg) in air. Then, a solvent combination of HFIP (0.97 mL) and AcOH (0.46 mL) was added. The reaction mixture was stirred at 70 °C for 2 h. Then, the reaction mixture was cooled to 0 °C, diluted with CH₂Cl₂ (DCM), filtered through a small Celite pad, and concentrated in vacuo. The crude reaction mixture was purified on silica gel using (1:1) hexane/EtOAc eluent. The competitive KIE was determined by ¹H-NMR analysis.



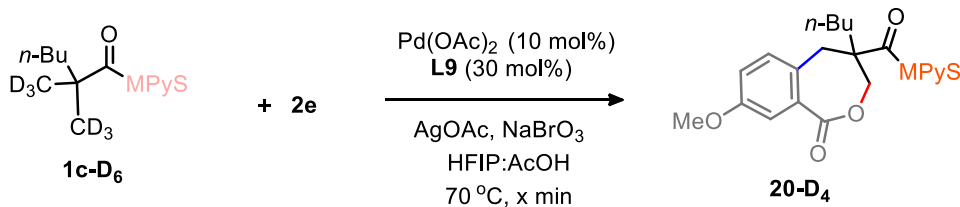
$$\text{KIE} = k_{\text{H}}/k_{\text{D}} = 1.72 / 0.28 = 6.14$$

2.6.3.25. Procedure for the parallel KIE study:

A 5 mL sealed tube equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (10 mol%, 4.5 mg), substrate **1c** (0.2 mmol), $AgOAc$ (0.4 mmol, 66.0 mg), $NaBrO_3$ (0.4 mmol, 60.0 mg), 5-methoxy-2-iodobenzoic acid **2e** (0.4 mmol, 99.0 mg), and **L9** (30 mol%, 10.8 mg) in air. Then, a solvent combination of HFIP (0.97 mL) and AcOH (0.46 mL) was added. The reaction mixture was stirred at 70 °C. Then, the aliquot was removed from the reaction mixture in different time interval shown below. The crude material was diluted with CH_2Cl_2 (DCM), filtered through a small Celite pad, and concentrated in vacuo. The conversion was determined by 1H -NMR analysis.

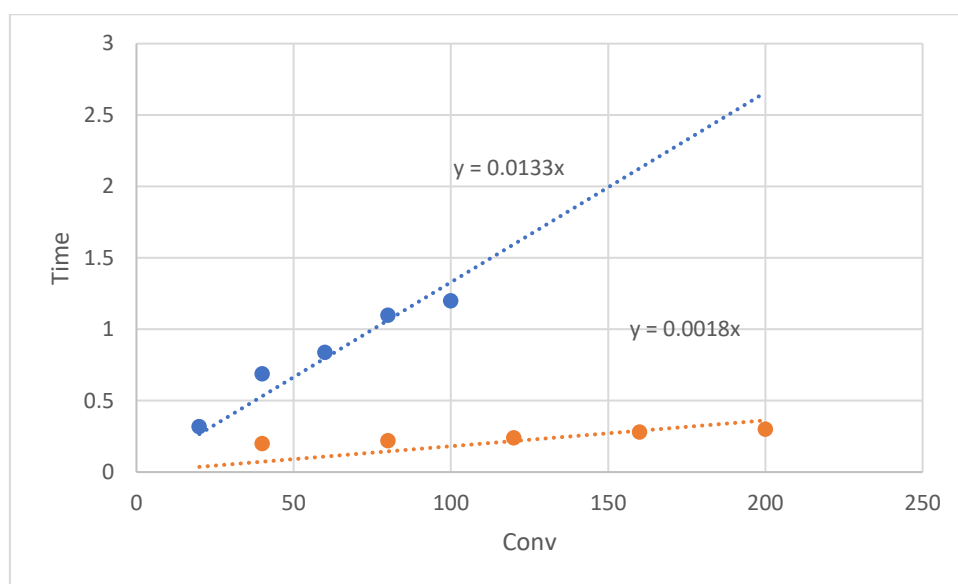


Time (min)	Conversion
20	0.32
40	0.69
60	0.84
80	1.1
100	1.2



Time (min)	Conversion
------------	------------

40	0.2
80	0.22
120	0.24
160	0.28
200	0.30

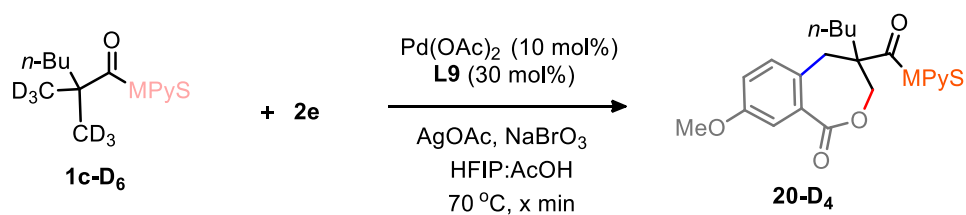
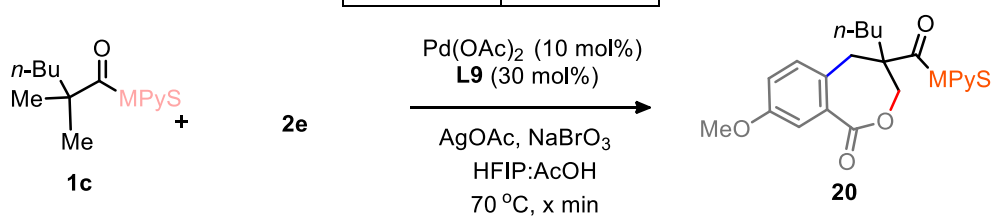


$$\text{KIE} = k_H/k_D = 0.0133 / 0.0018 = 7.38$$

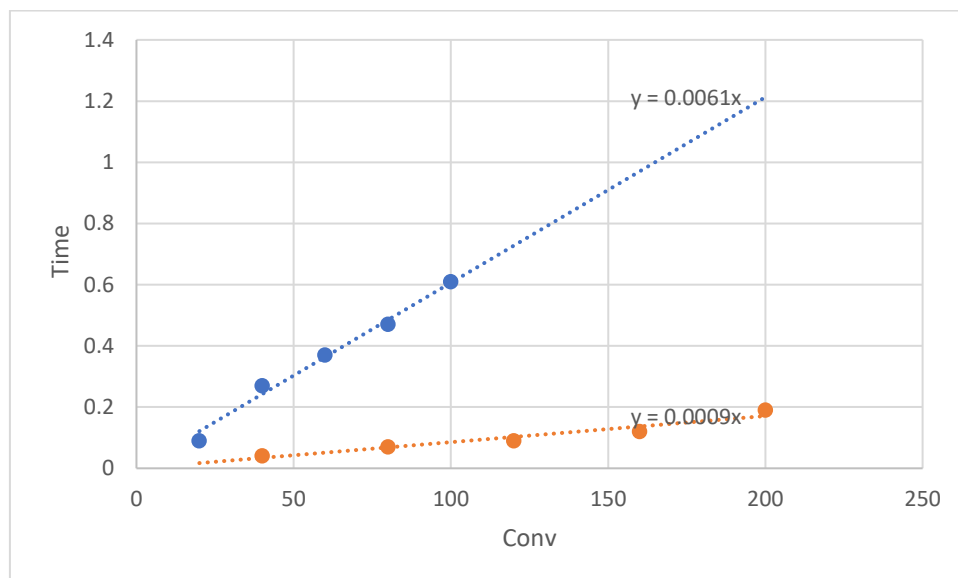
2.6.3.26. Procedure for the parallel KIE study without NaBrO_3 :

A 5 mL sealed tube equipped with a magnetic stir bar was charged with $\text{Pd}(\text{OAc})_2$ (10 mol%, 4.5 mg), substrate **1c** (0.2 mmol), AgOAc (0.4 mmol, 66.0 mg), 5-methoxy-2-iodobenzoic acid **2e** (0.4 mmol, 99.0 mg), and **L9** (30 mol%, 10.8 mg) in air. Then, a solvent combination of HFIP (0.97 mL) and AcOH (0.46 mL) was added. The reaction mixture was stirred at 70 °C. Then, the aliquot was removed from the reaction mixture in different time interval shown below. The crude material was diluted with CH_2Cl_2 (DCM), filtered through a small Celite pad, and concentrated in vacuo. The conversion was determined by ^1H -NMR analysis.

Time (min)	Conversion
20	0.09
40	0.27
60	0.37
80	0.47
100	0.61



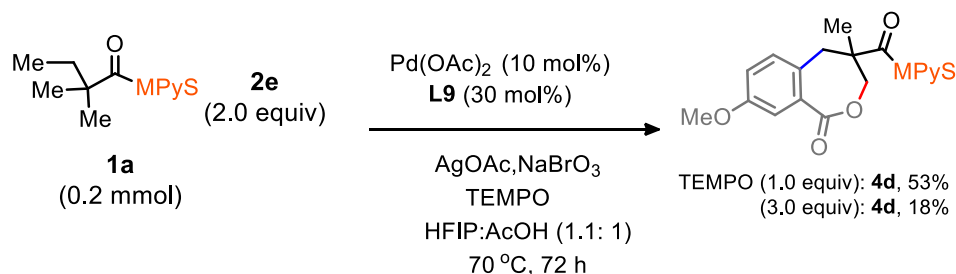
Time (min)	Conversion
40	0.04
80	0.07
120	0.09
160	0.12
200	0.19

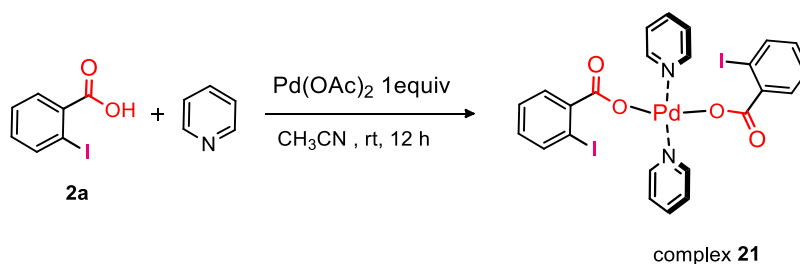


$$\text{KIE} = k_{\text{H}}/k_{\text{D}} = 0.0061 / 0.0009 = 6.7$$

2.6.3.27. Procedure for the radical scavenger experiment:

A 5 mL sealed tube equipped with a magnetic stir bar was charged with Pd(OAc)₂ (10 mol%, 4.5 mg), substrate **1** (0.2 mmol), AgOAc (0.4 mmol, 66.0 mg), NaBrO₃ (0.4 mmol, 60.0 mg), 2-iodobenzoic acid **2e** (0.4 mmol, 99.0 mg), TEMPO (1.0 equiv / 3.0 equiv) and **L9** (30 mol%, 10.8 mg) in air. Then, a solvent combination of HFIP (0.97 mL) and AcOH (0.46 mL) we added. The reaction mixture was stirred at 70 °C for 36 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with CH₂Cl₂ (DCM), filtered through a small Celite pad, and concentrated in vacuo. The crude reaction mixture was purified on silica gel using hexane/EtOAc eluent to afford the desired products in 53% and 18% respectively.



2.6.3.28 Procedure for the synthesis of organo-palladium complex **21**:

A solution of 2-iodobenzoic acid (**2a**; 1.33 mmol, 329 mg), Pd(OAc)_2 (1.33 mmol, 300 mg) and pyridine (2.66 mmol, 210 mg) in CH_3CN (1M) was stirred at room temperature overnight. The reaction mixture was filtered. The solvent was evaporated and the resulting solid was washed with diethyl ether (3 times), and then dried under vacuum to producing soft pale green powder (428 mg, 42% yield). The complex was recrystallized via vapor diffusion of CDCl_3 . The structure of complex **21** was unambiguously established by X-ray diffraction studies. ^1H NMR (500 MHz, CDCl_3) δ 8.93 (dd, J = 10.0, 1.5 Hz, 2H), 7.81–7.73 (m, 2H), 7.41–7.34 (m, 3H), 7.25–7.18 (m, 2H), 6.98–6.95 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 174.1, 152.8, 152.2, 141.4, 139.9, 138.7, 138.6, 130.2, 129.2, 127.5, 124.9, 93.0.

2.6.3.29. X-ray crystallography:

Single crystal X-ray data for the compound **7** were collected using the detector system [$\lambda(\text{Mo-K}\alpha) = 0.71073 \text{ \AA}$] at 293K, graphite monochromator with a ω scan width of 0.3o, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software³⁴ was used for the intensity data acquisition and the SAINTPLUS Software³⁴ was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program,³⁴ an empirical absorption correction using equivalent reflections was performed with the program. The structure was solved using SHELXS-97, and full-matrix least-squares refinement against F^2 was carried out using SHELXL-97,³⁵ 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.

X-ray crystal structure and data for 7: The compound **7** was recrystallized via vapor diffusion of MeOH.

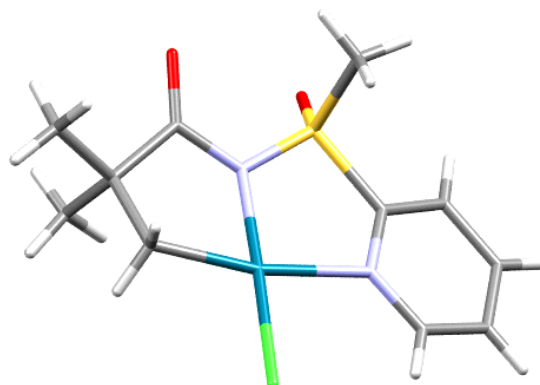


Figure 2.12. Molecular structures of compound **7**; thermal ellipsoids are set at 30% probability.

X-ray crystal structure and data for 21: The compound **21** was recrystallized via vapor diffusion of $CDCl_3$.

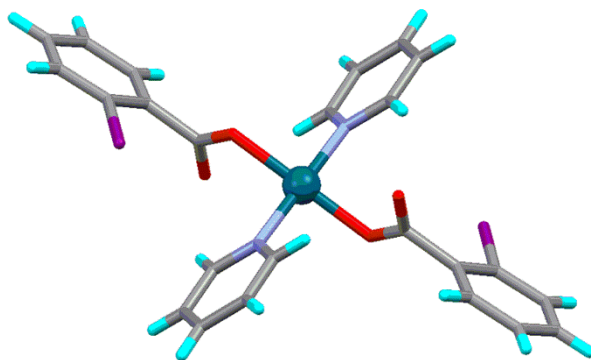


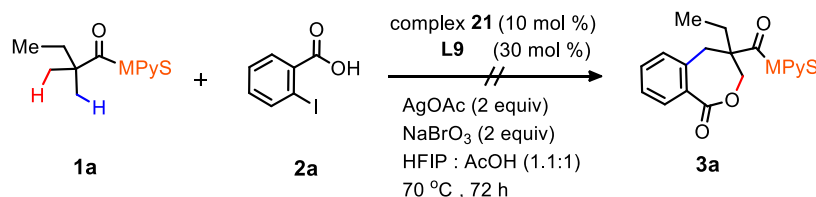
Figure 2.13. Molecular structures of compound **21**; thermal ellipsoids are set at 30% probability.

Table 2.5. Crystal data for **7** and **21**

Identification code	7	21
Formula	$C_{11}H_{15}ClN_2O_2Pd$ S	$C_{24}H_{18}I_2N_2O_4Pd$
F_w	381.16	758.60

T (K)	297 K	293 K
λ (Å)	0.71073	0.71073
Crystal system	monoclinic	monoclinic
Space group	$P 1 2 1 1$	$P 2_1 / C$
a (Å)	5.5115 (8)	11.3120 (19)
b (Å)	18.033 (2)	8.4850 (14)
c (Å)	7.1387 (10)	13.892 (2)
α (°)	90	90
β (°)	93.937 (5)	112.081 (6)
γ (°)	90	90
V (Å ³)	707.82 (17)	1235.6 (3)
Z	2	2
ρ_{calcd} (Mg m ⁻³)	1.788	2.039
μ [mm ⁻¹]	1.642	3.282
total reflns	40949	21054
unique reflns	3291	2844
observed reflns	2818	1738
$R_1[I > 2\sigma(I)]$	0.0333	0.0501
wR_2 [all]	0.0725	0.0873
GOF	1.055	1.018
Diffractionmeter	SMART APEX CCD	SMART APEX CCD
CCDC Number	2106115	2078781

Scheme 2.14. Reaction carried out in presence of complex 21



This study indicates that 2-iodobenzoic acid is not involved in the concerted metalation-deprotonation (CMD) process.

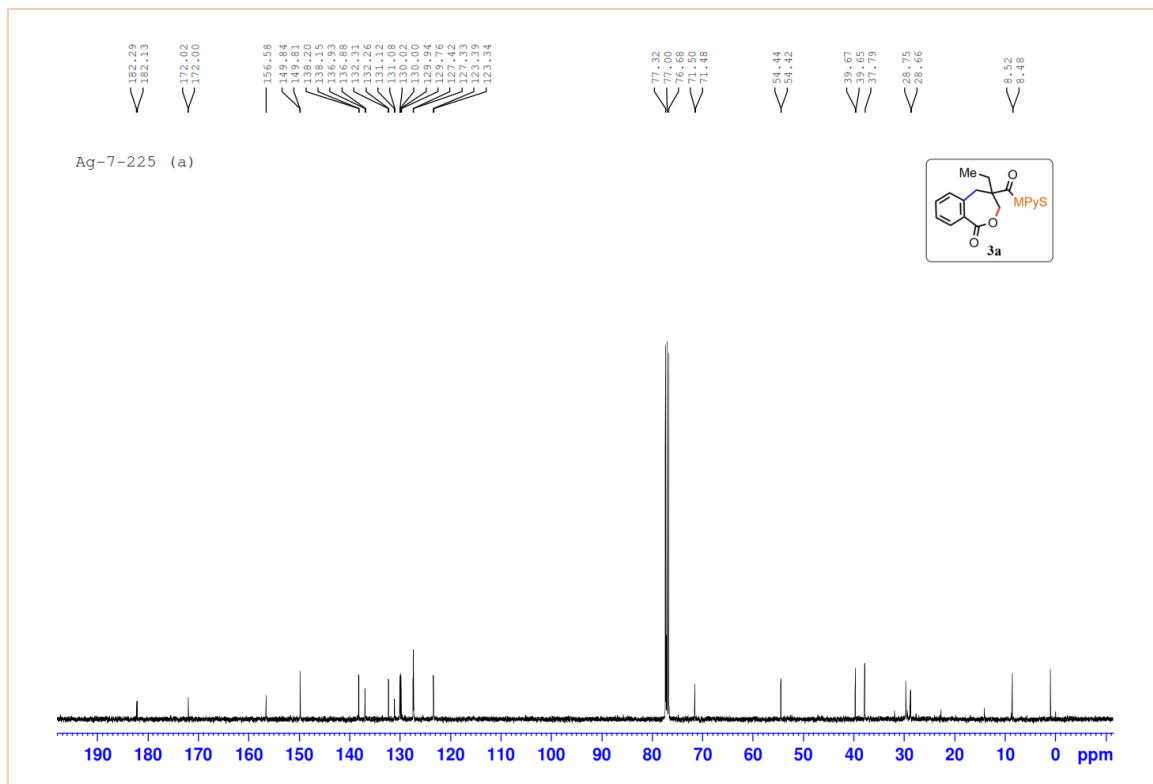
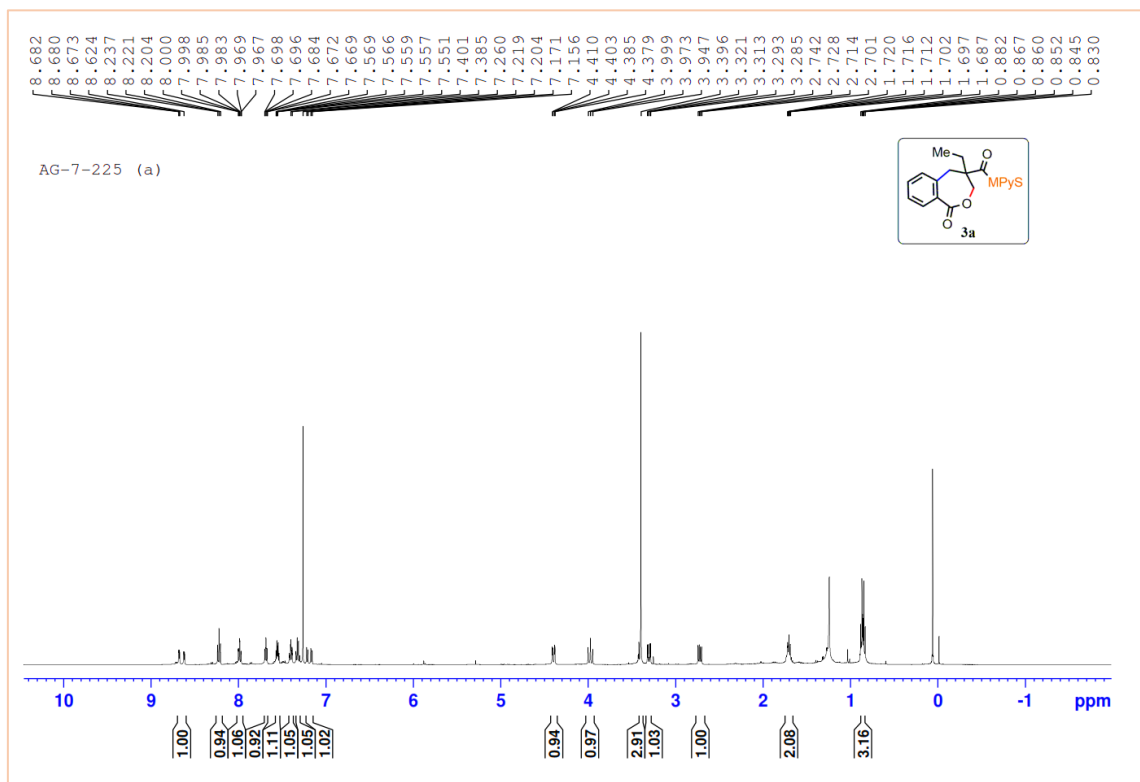
2.7. Reference

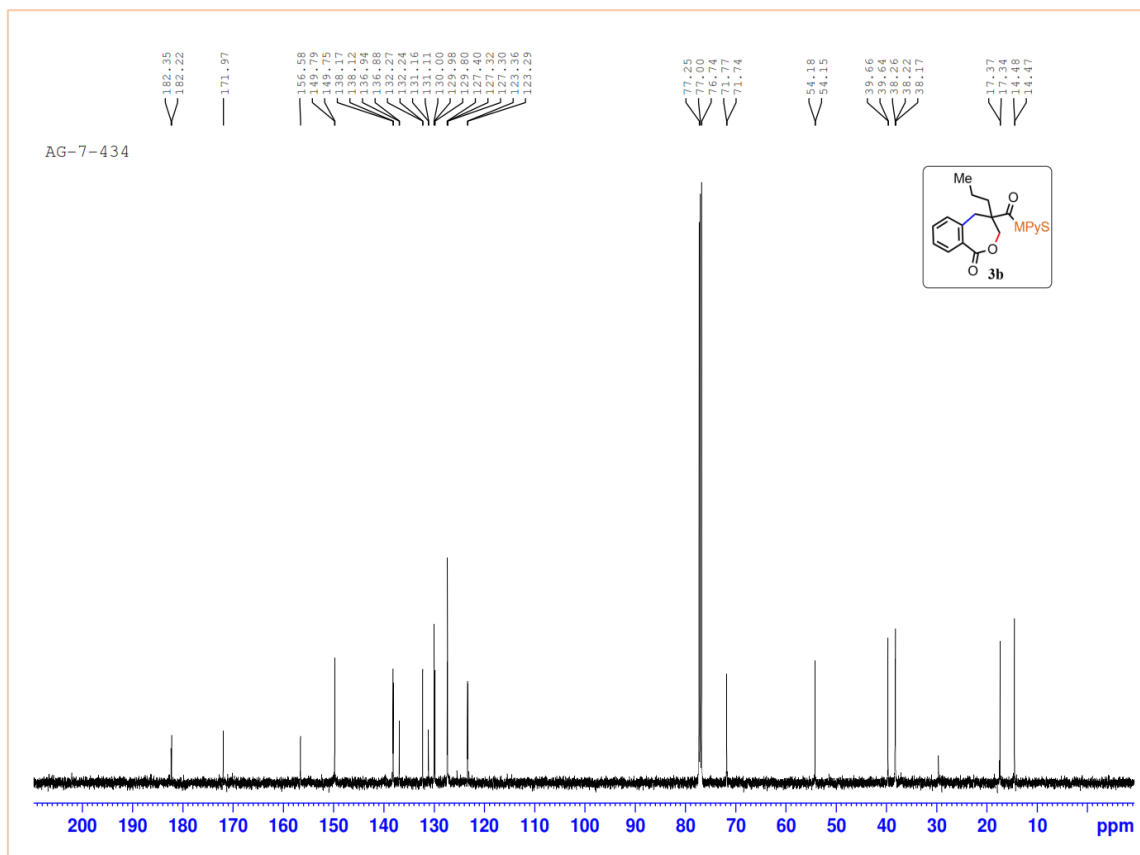
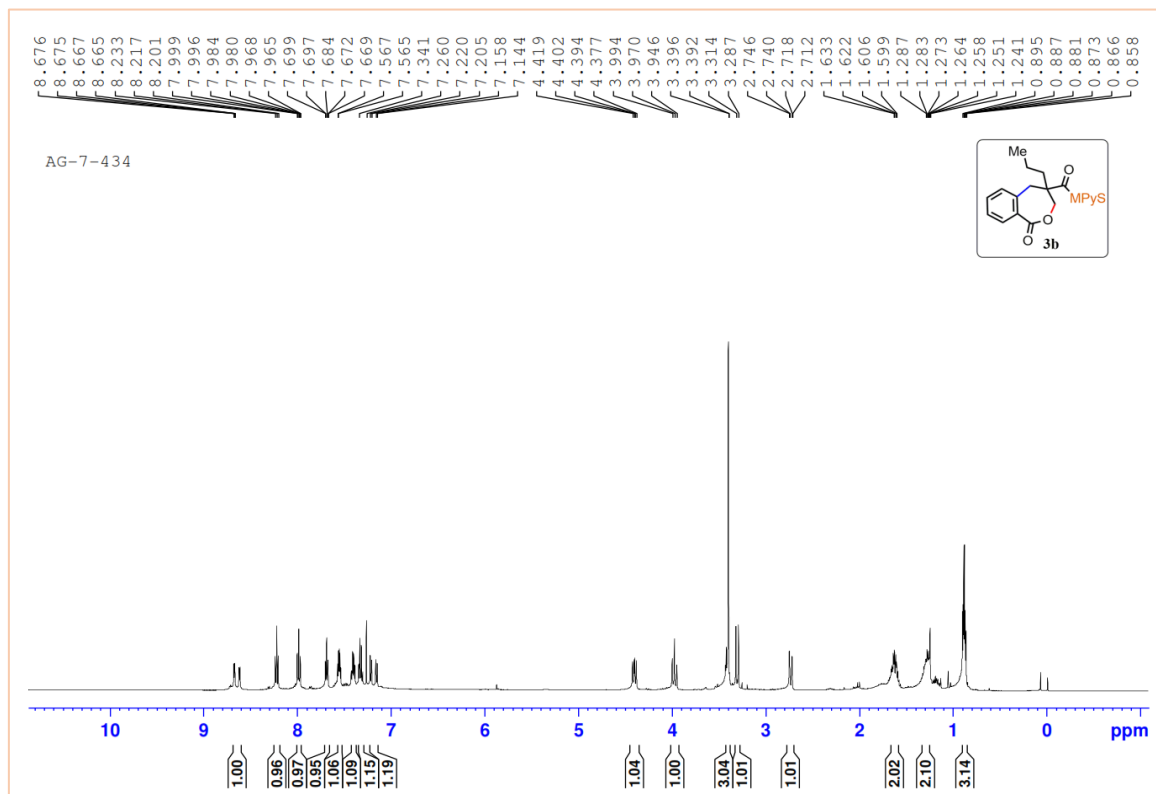
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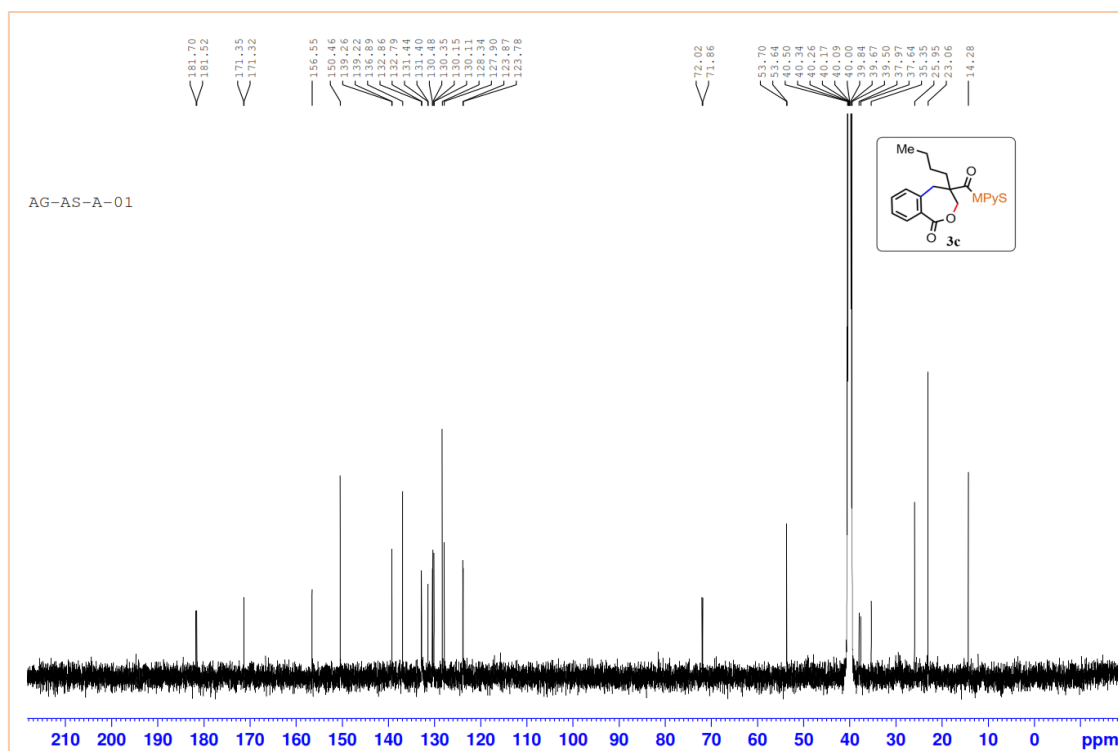
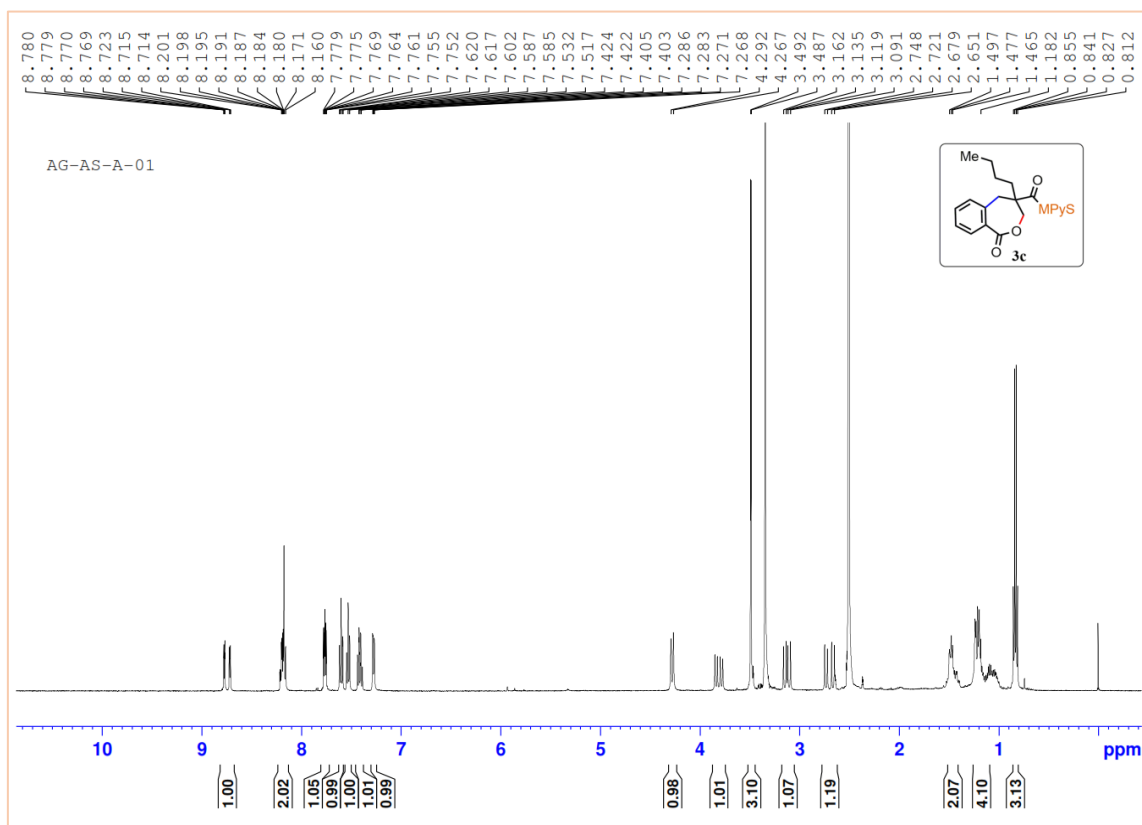
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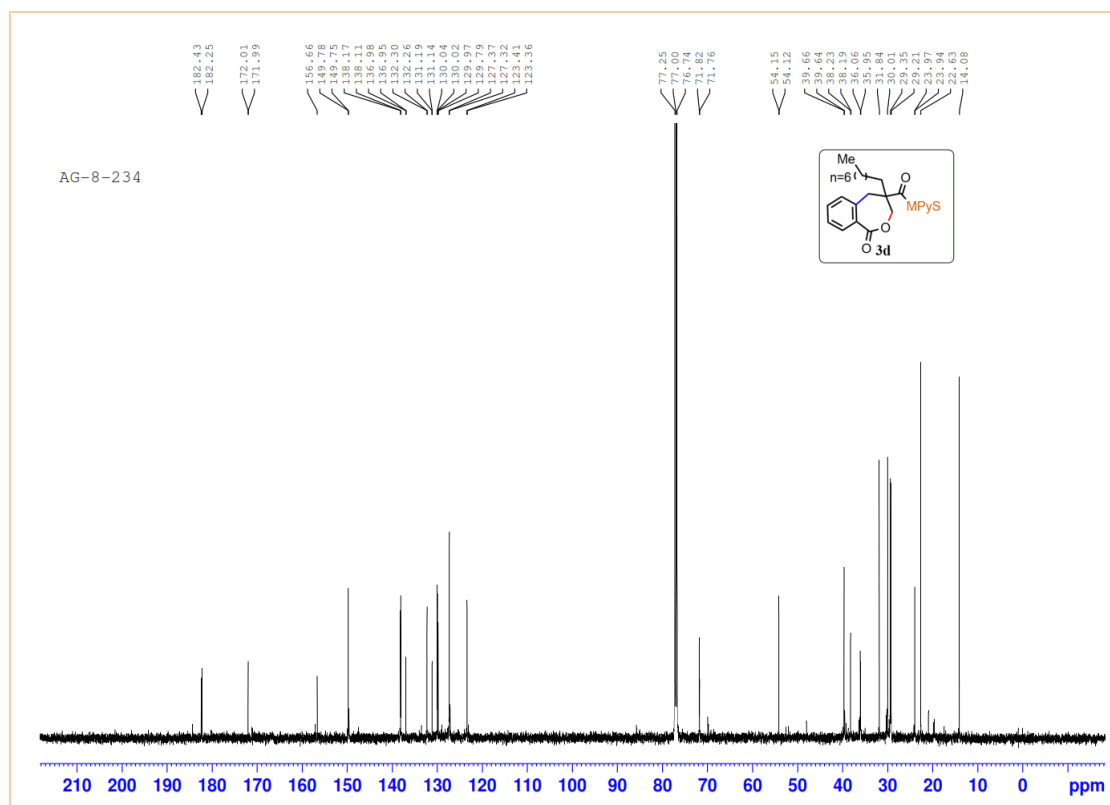
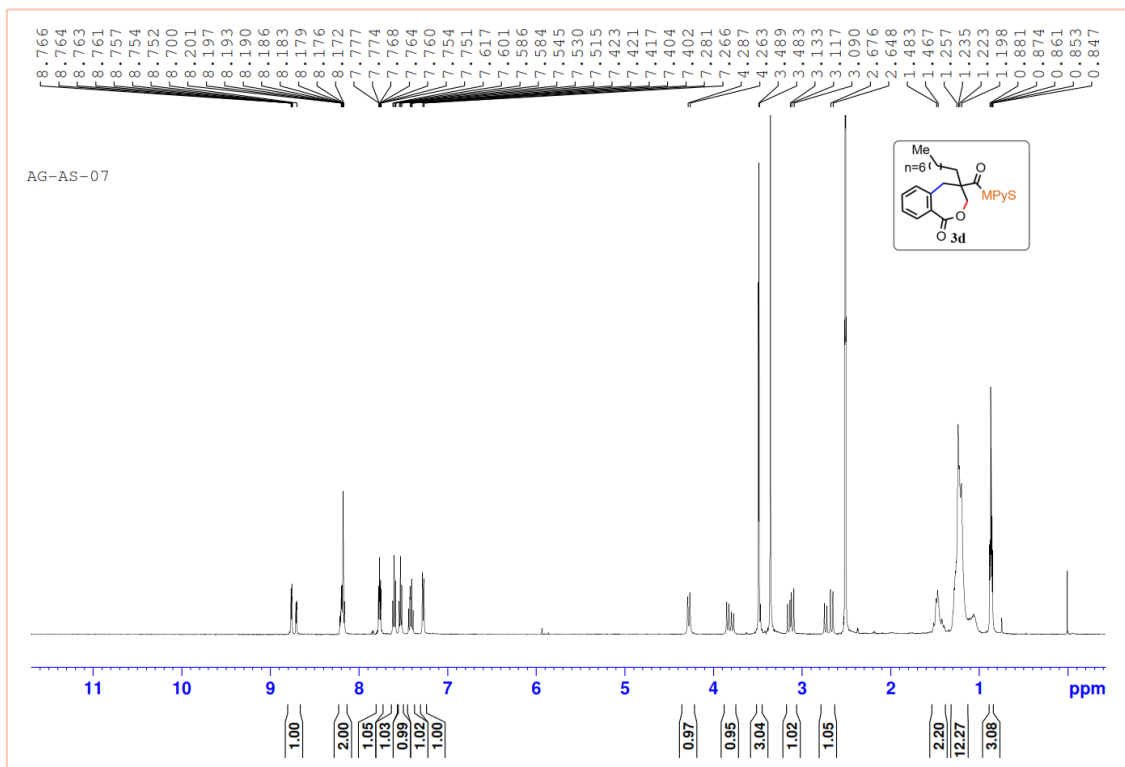
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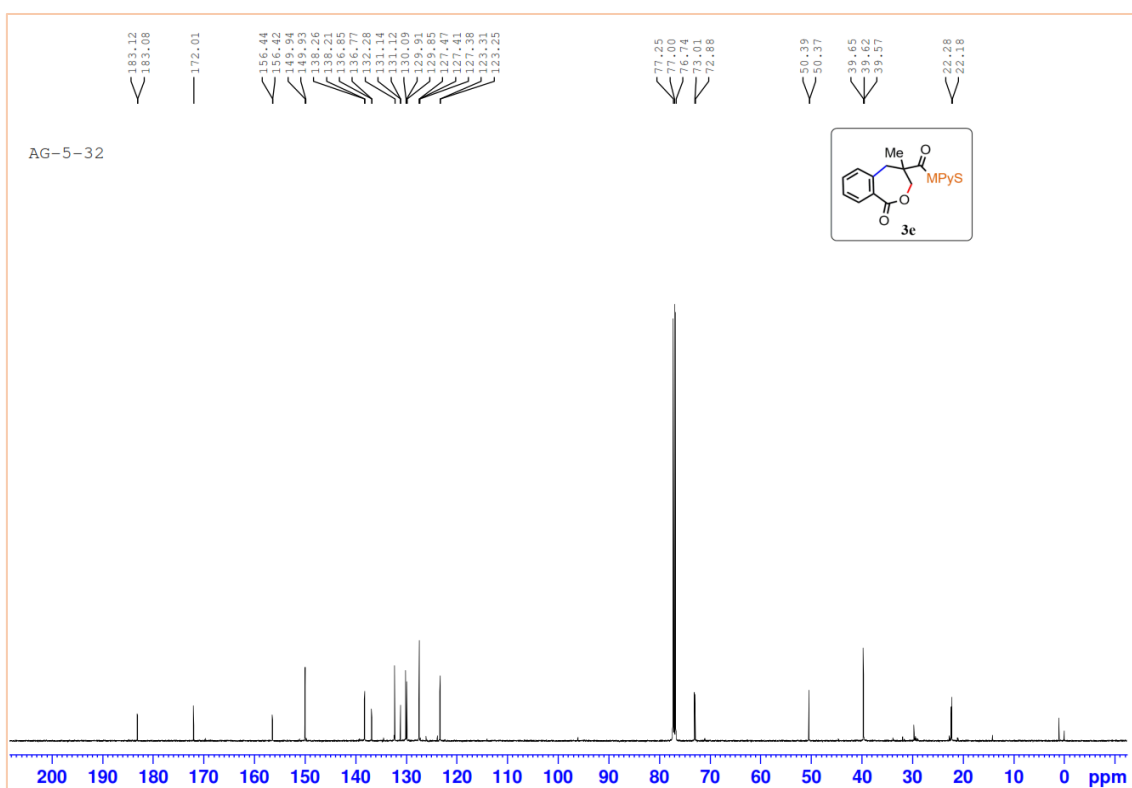
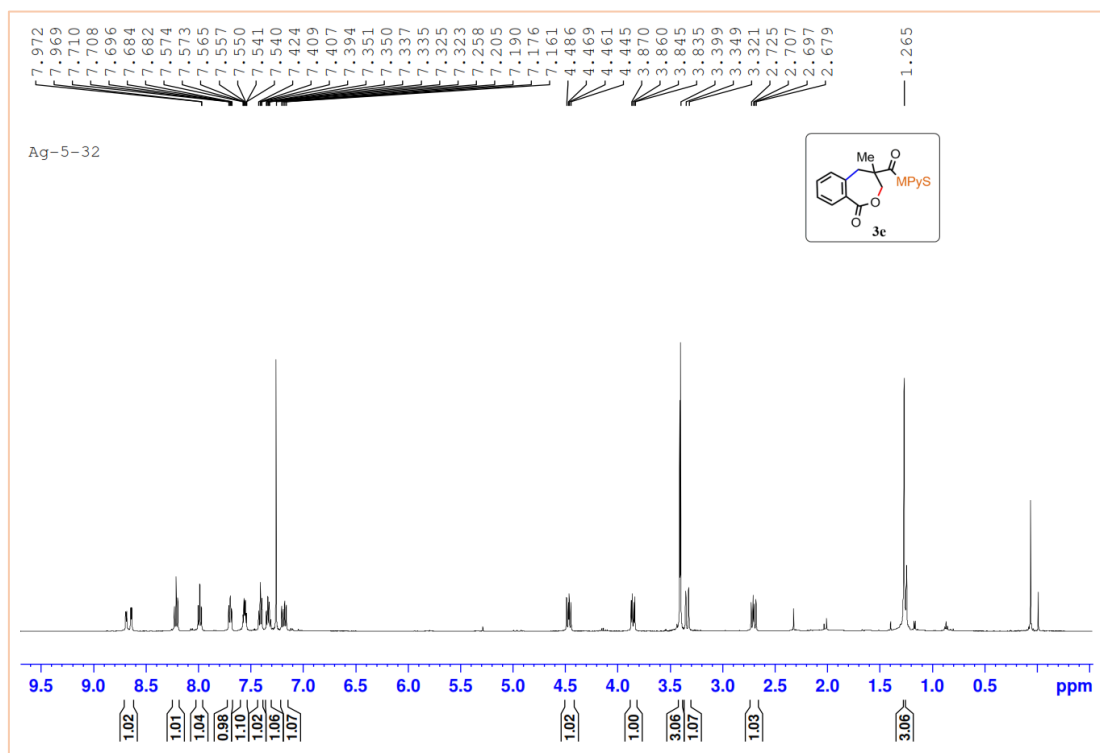
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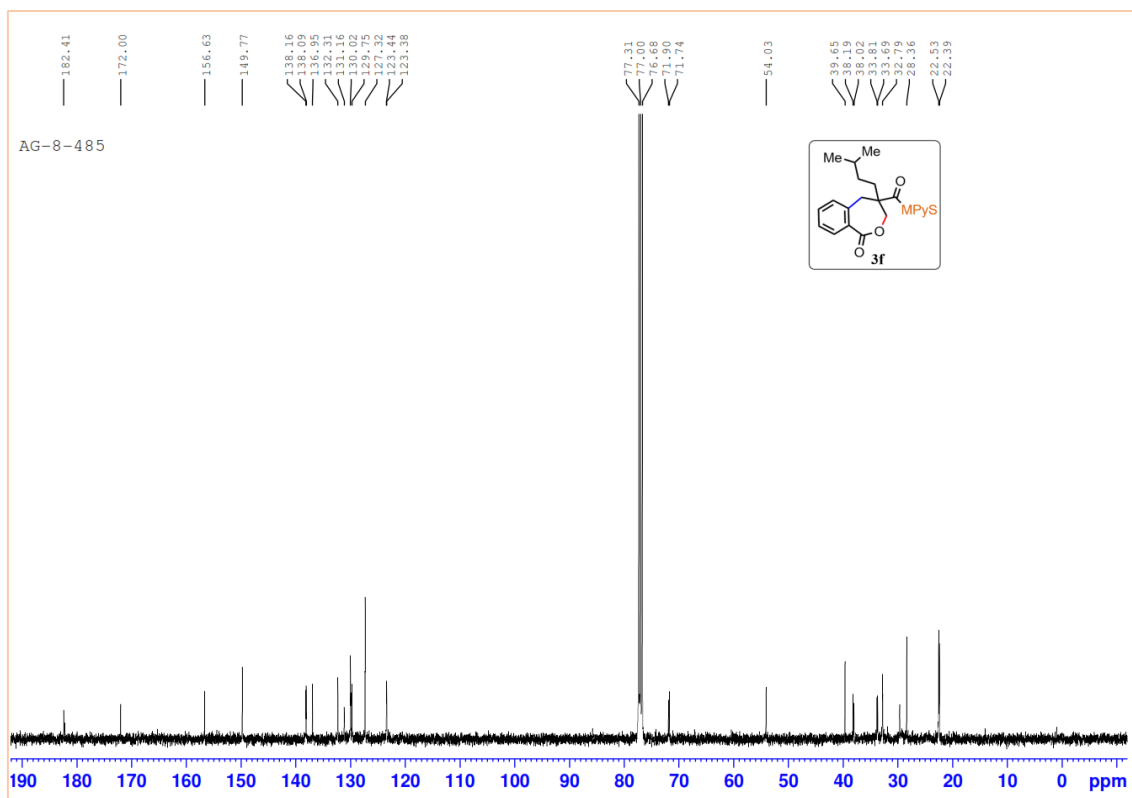
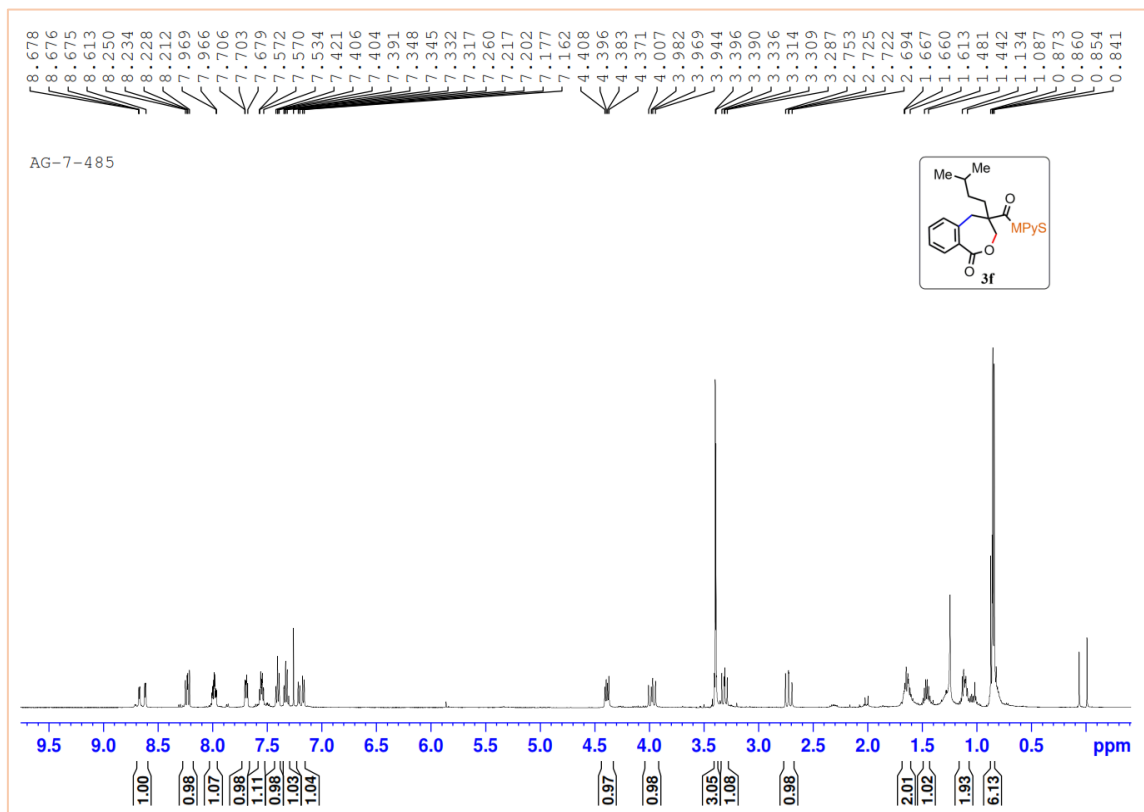


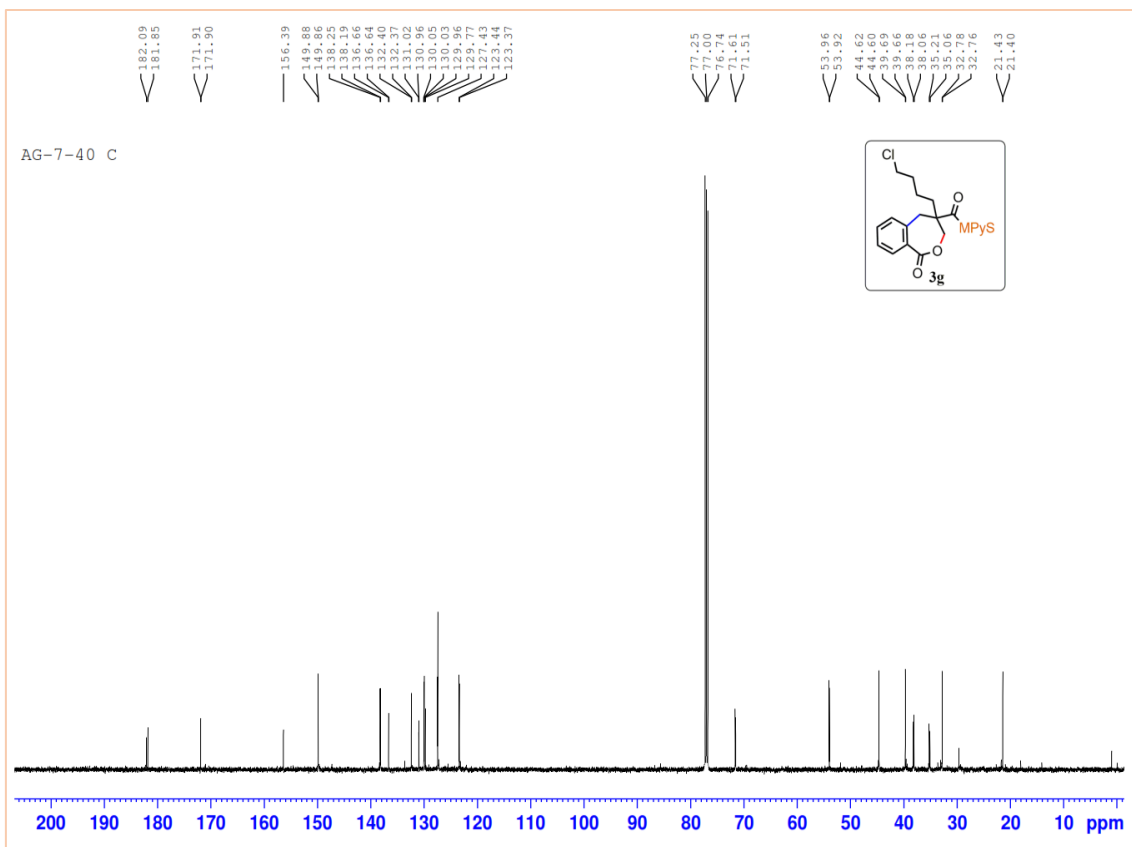
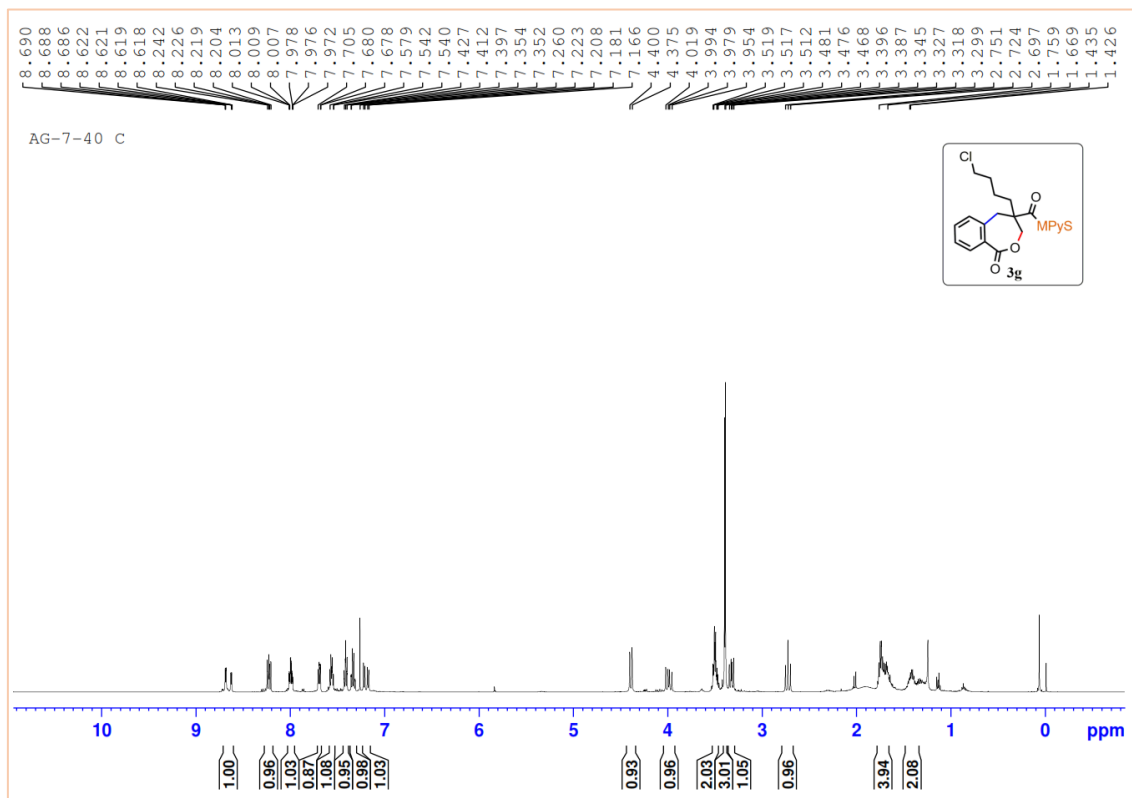


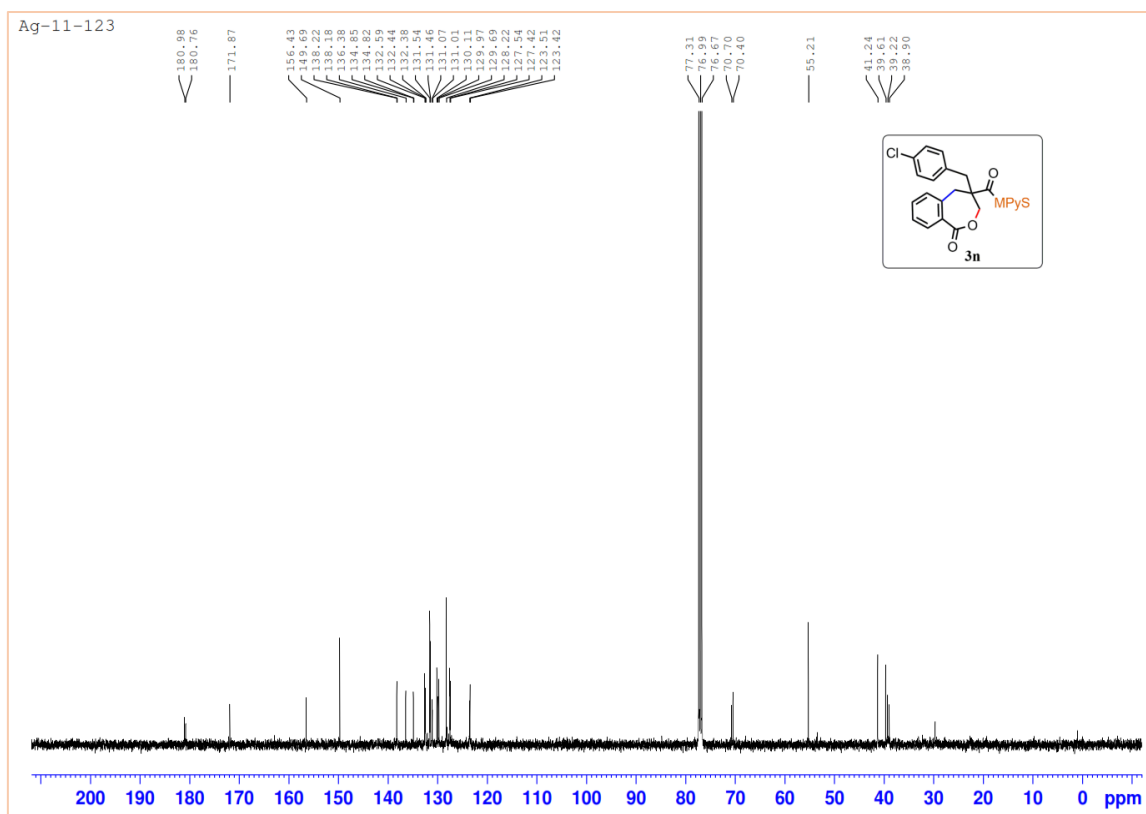
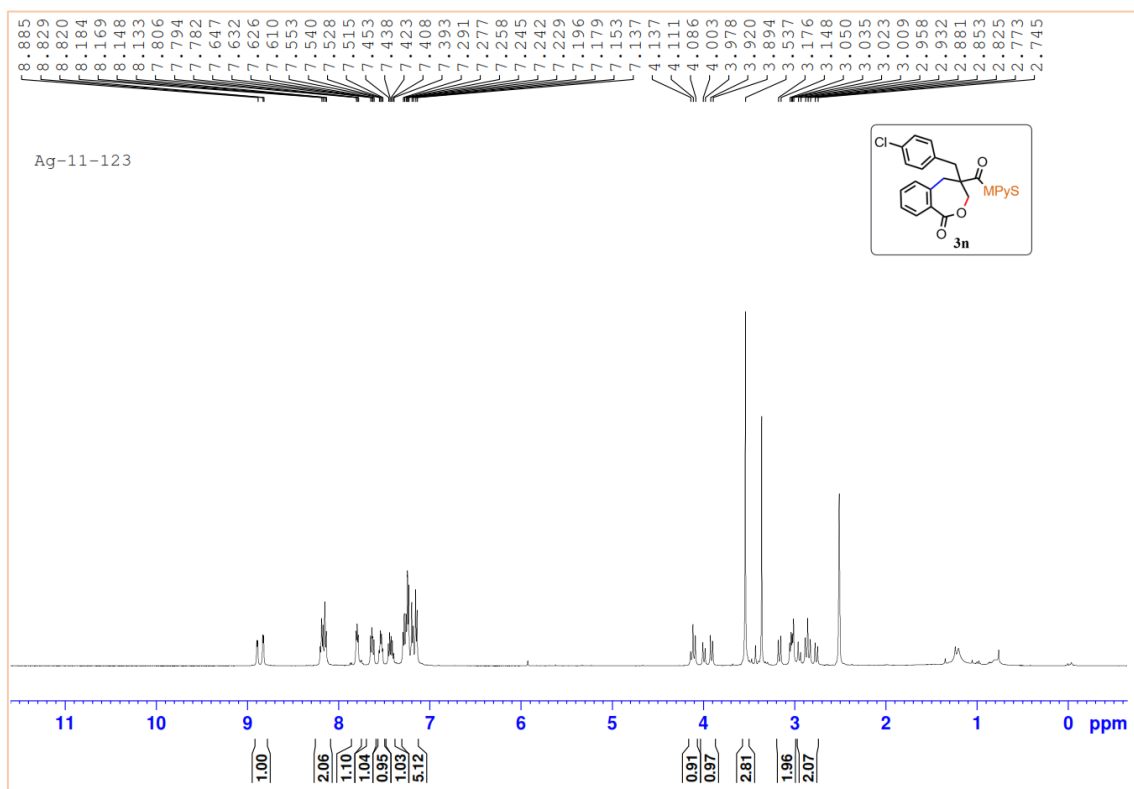


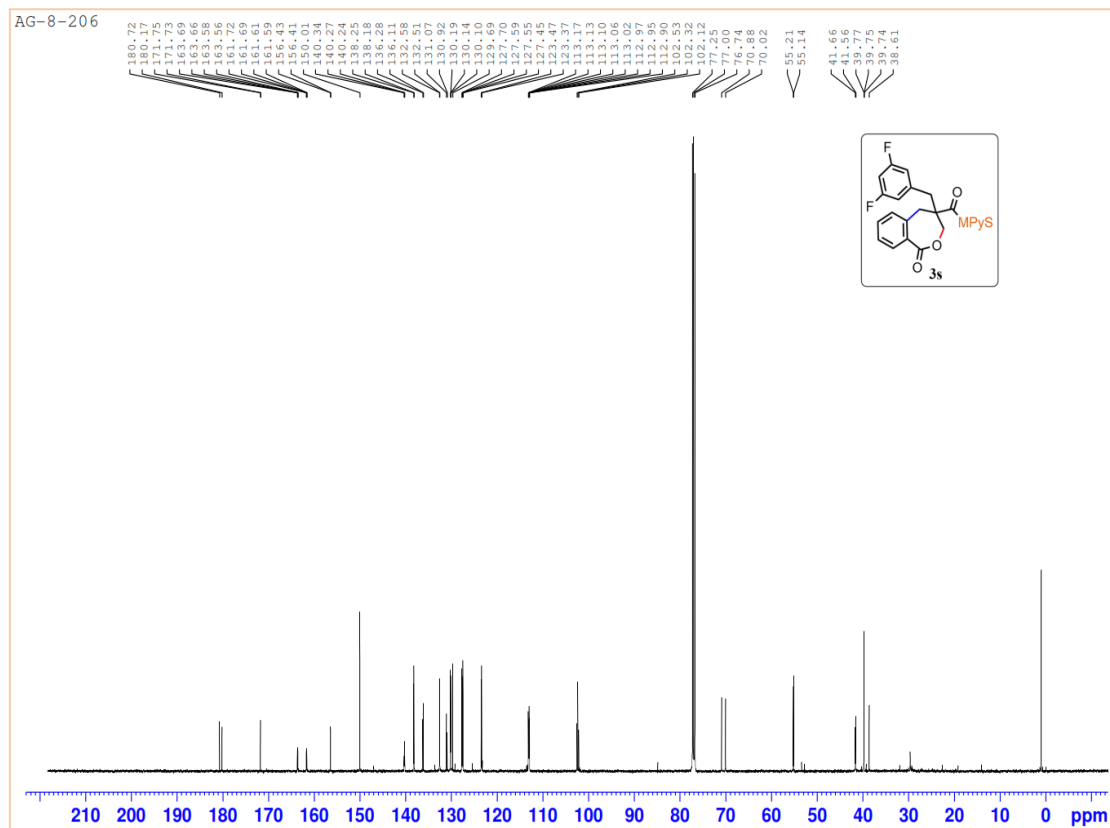
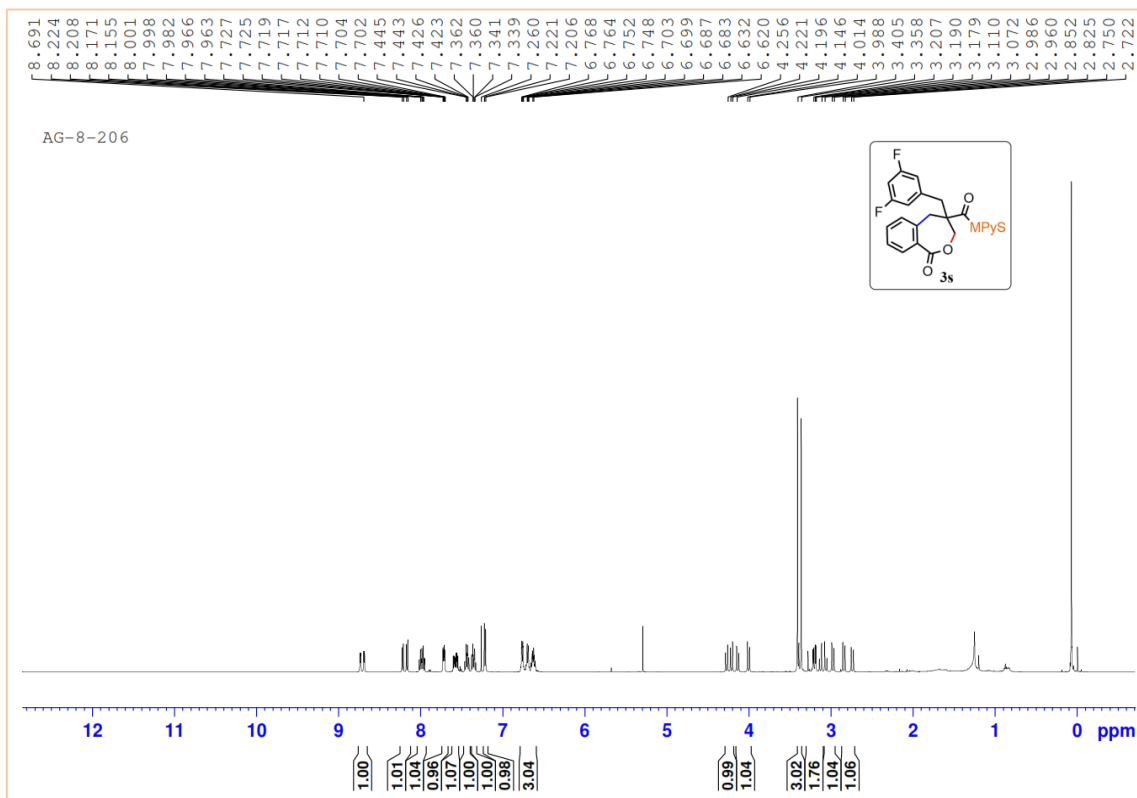


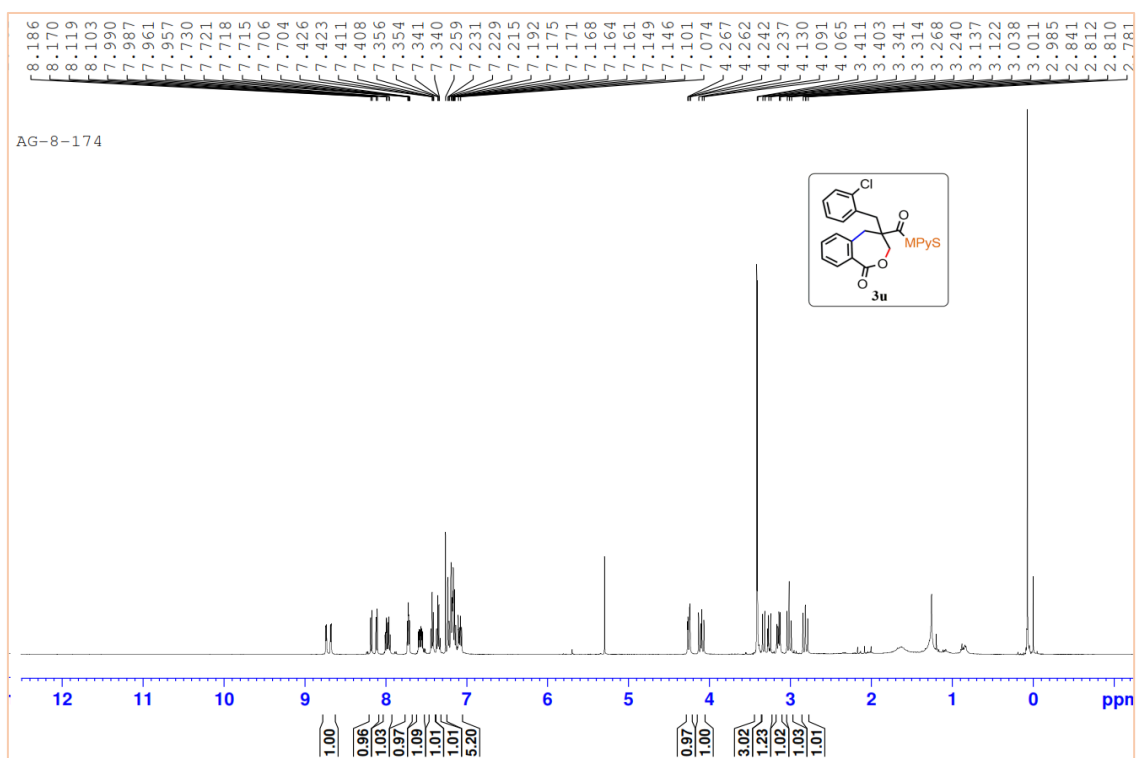
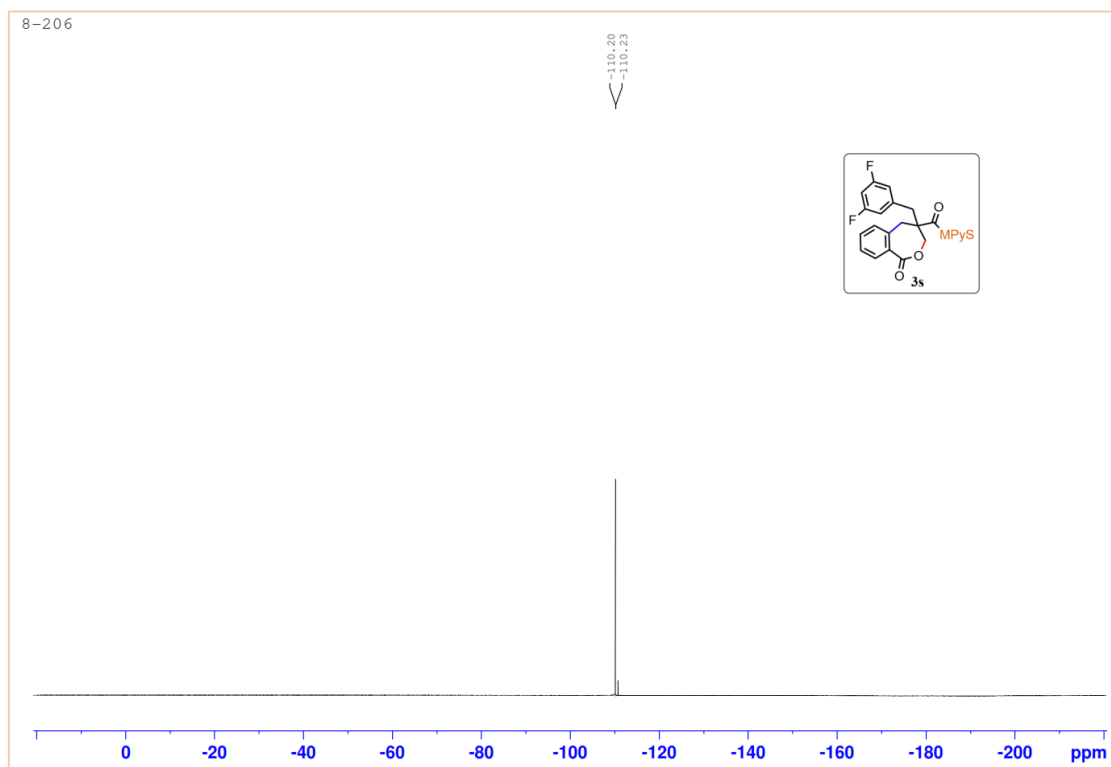


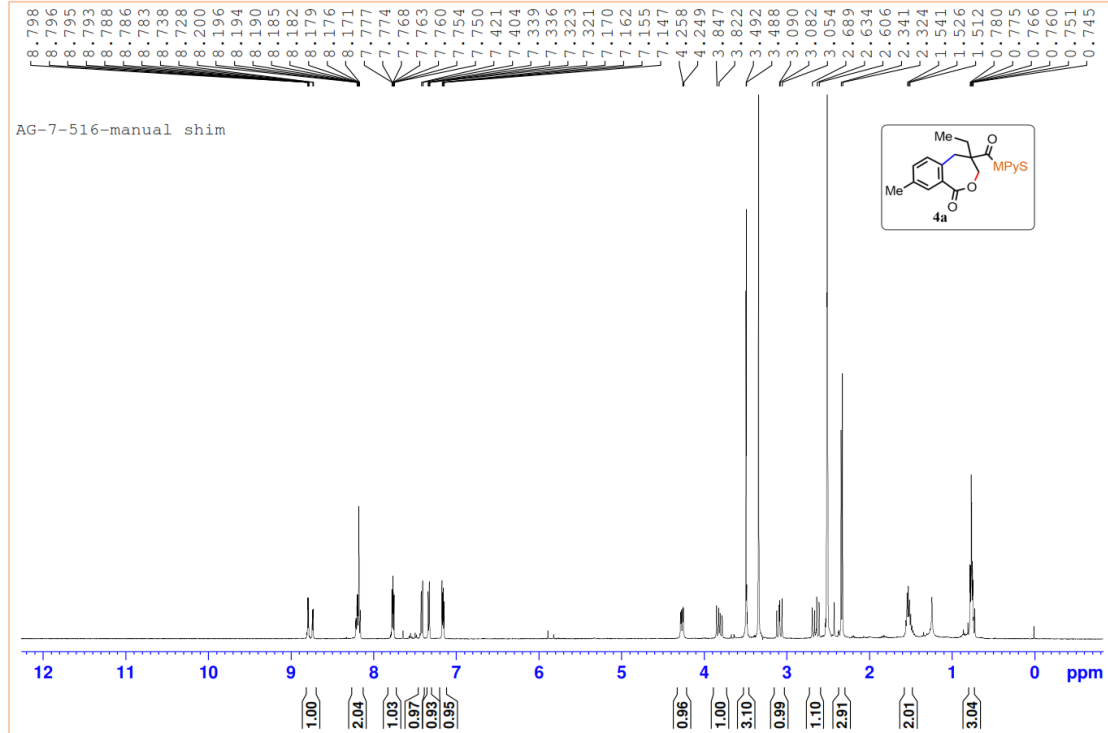
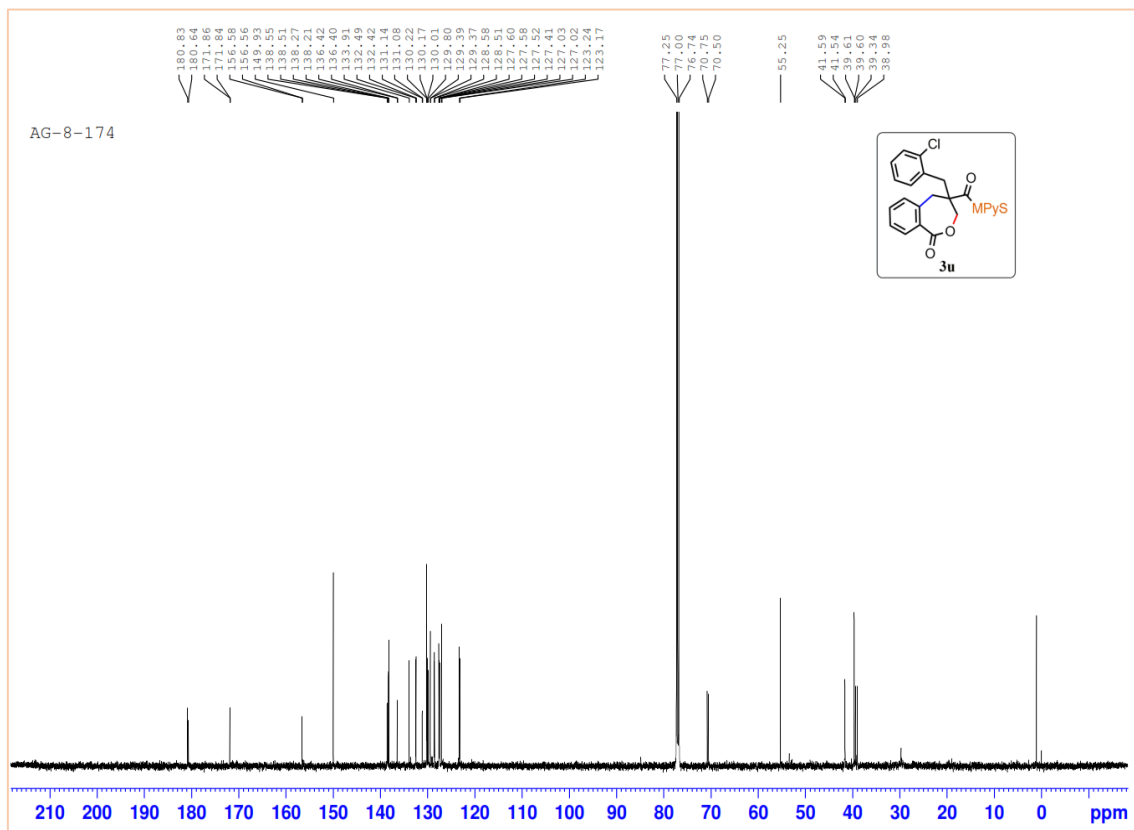


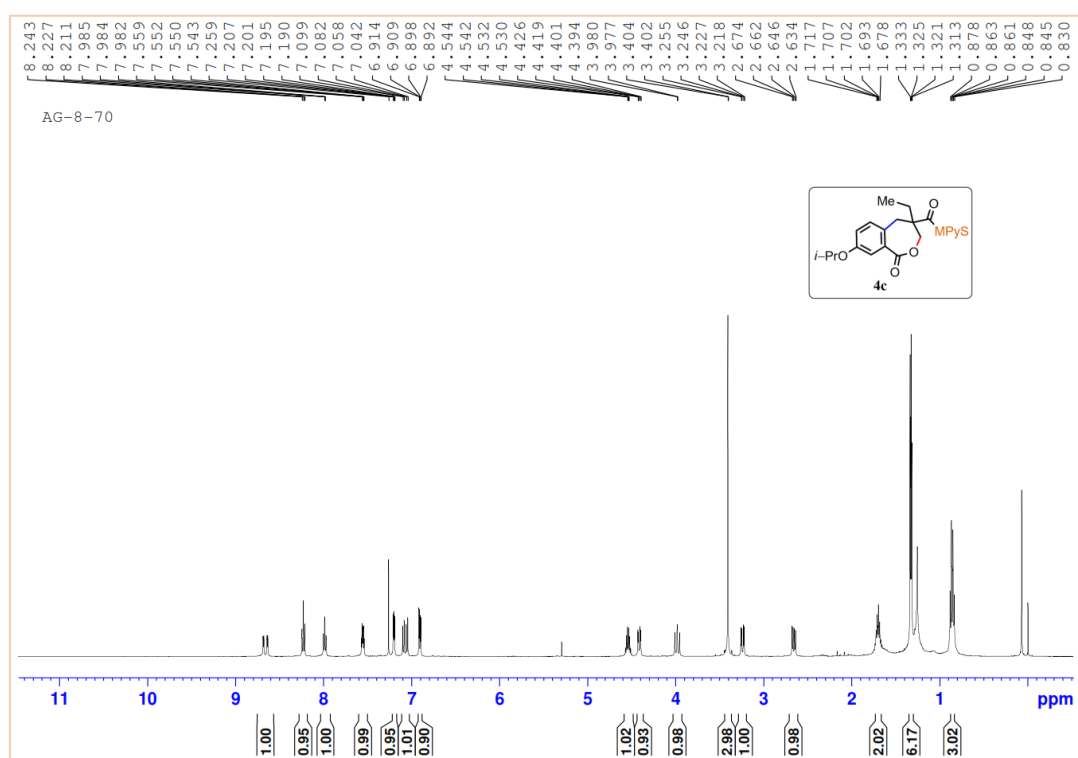
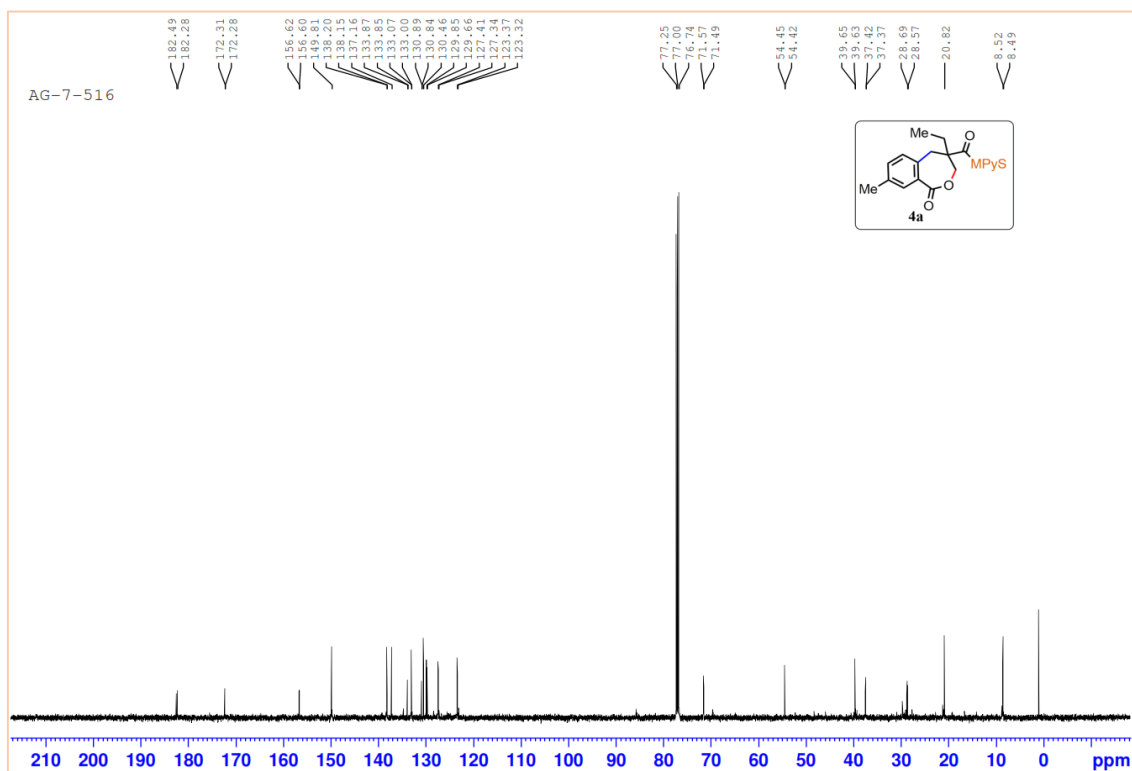


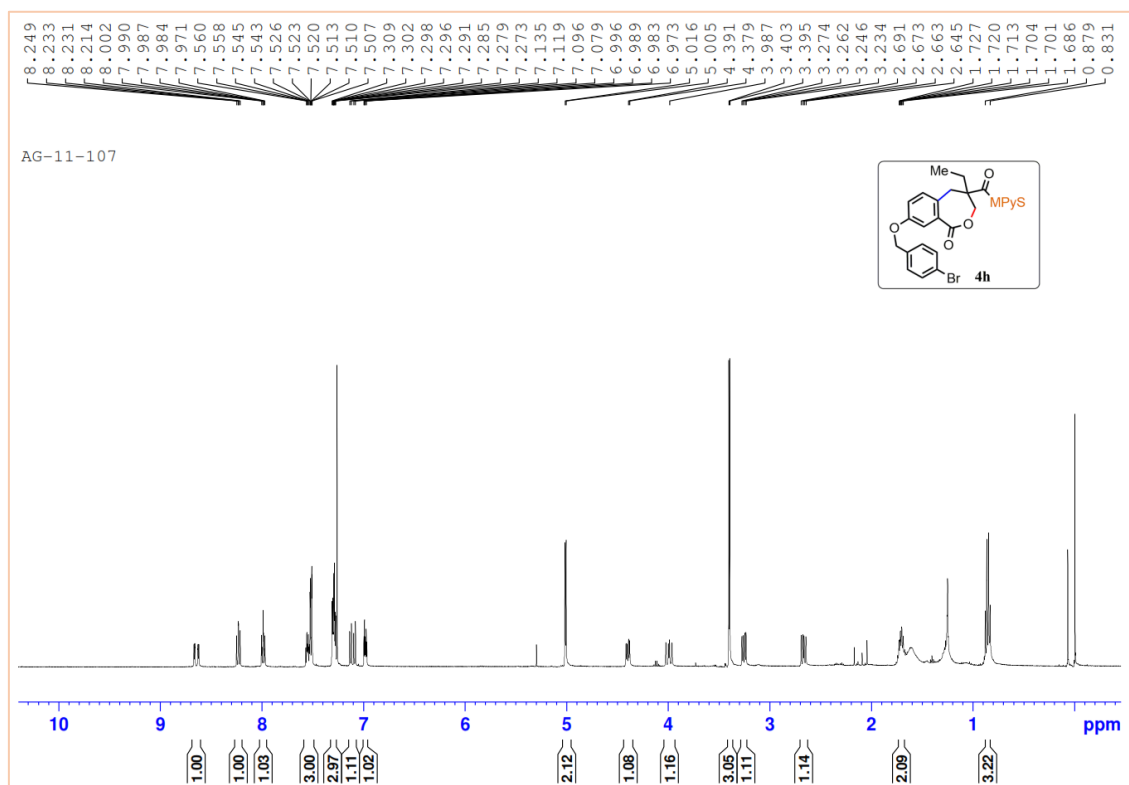
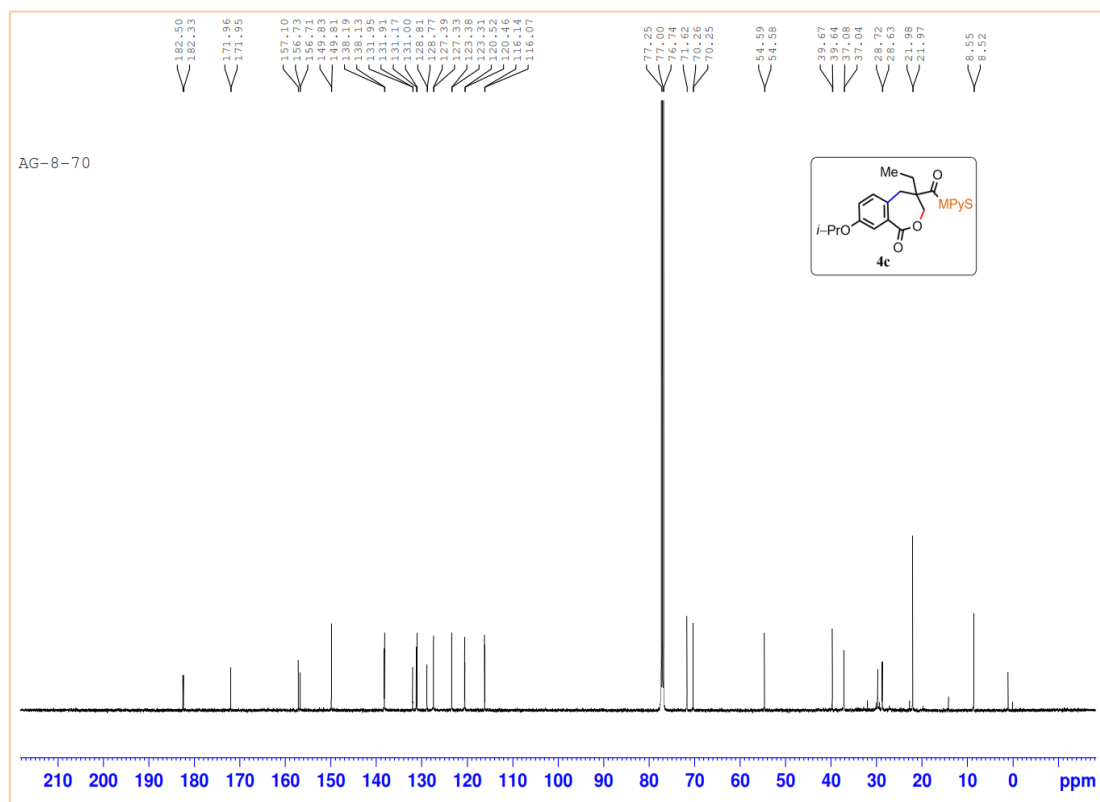


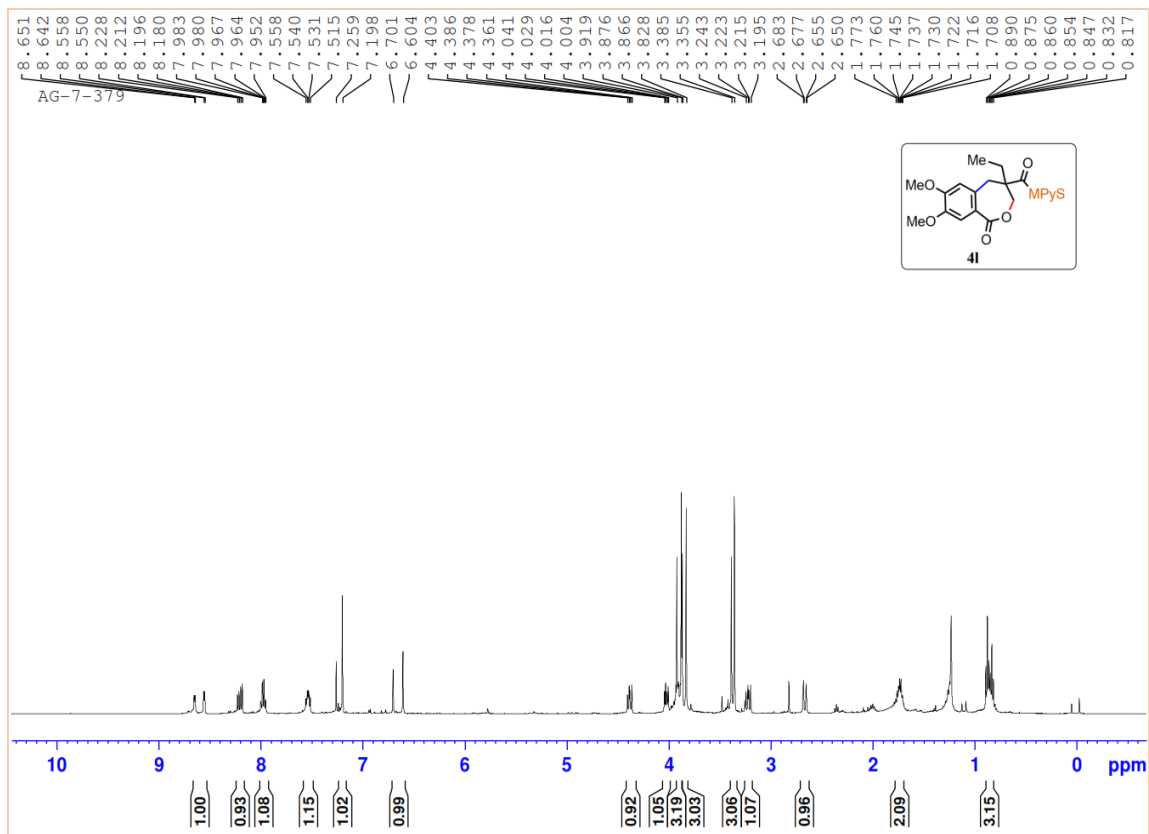
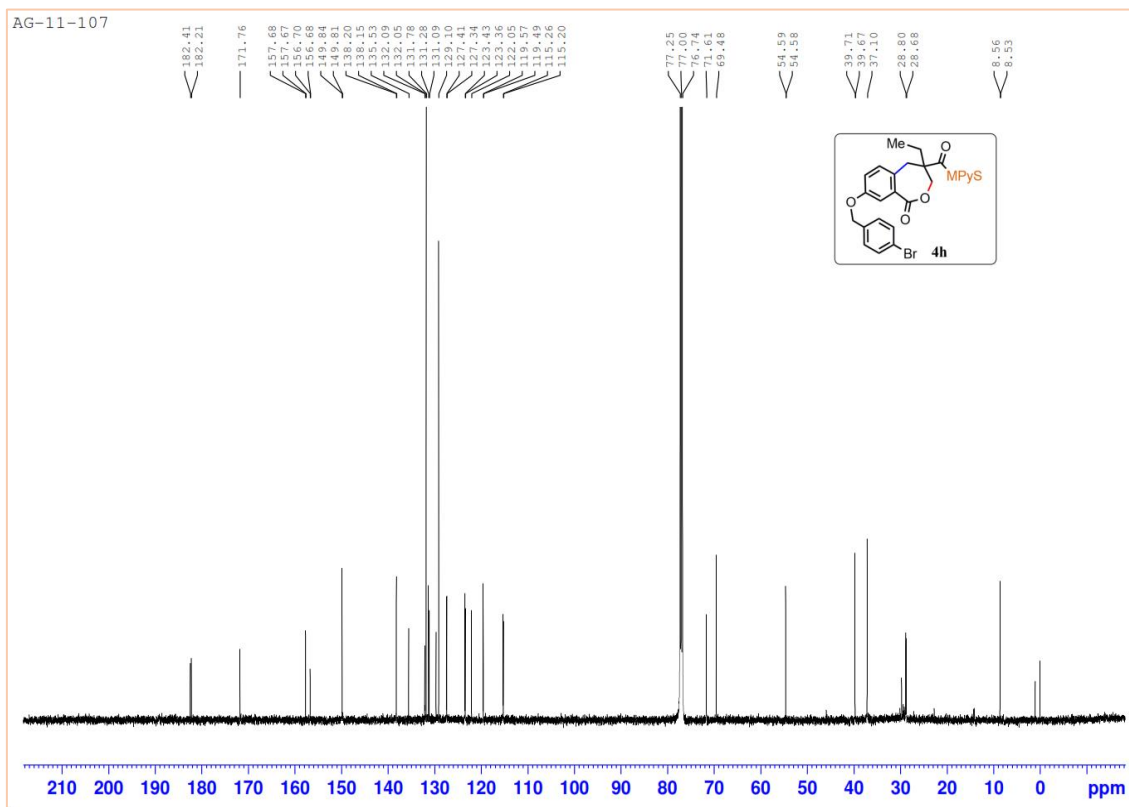


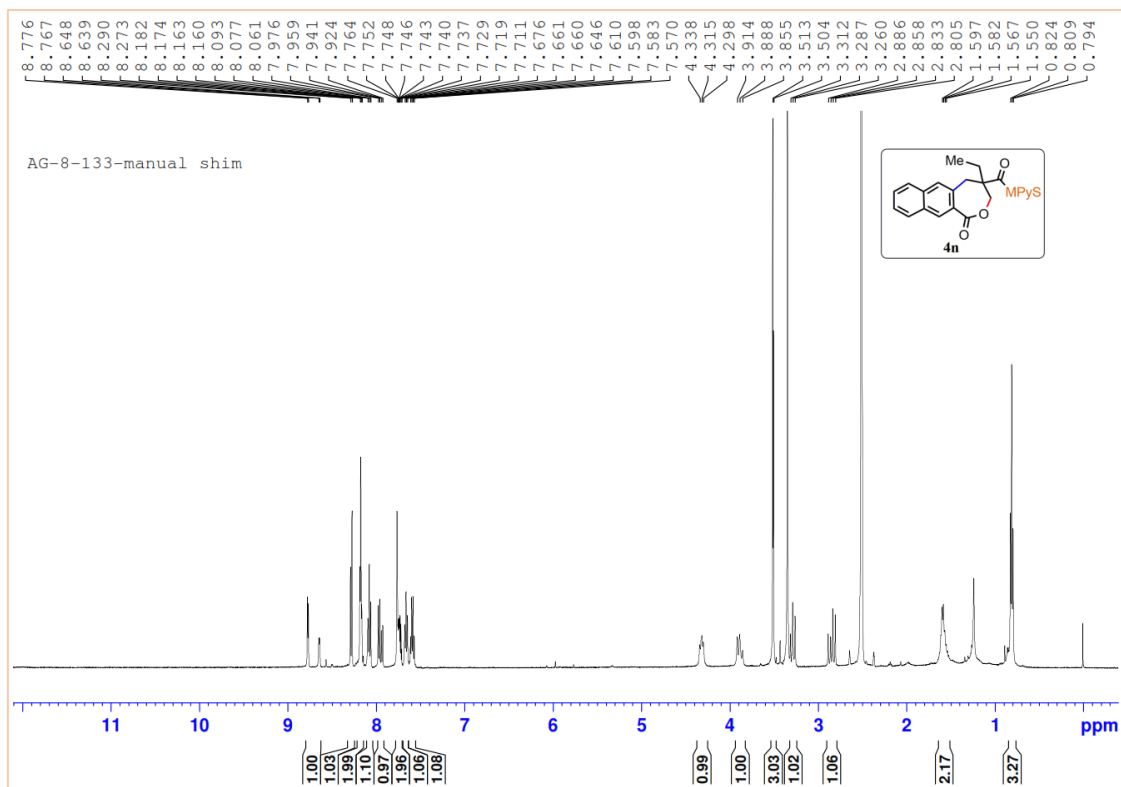
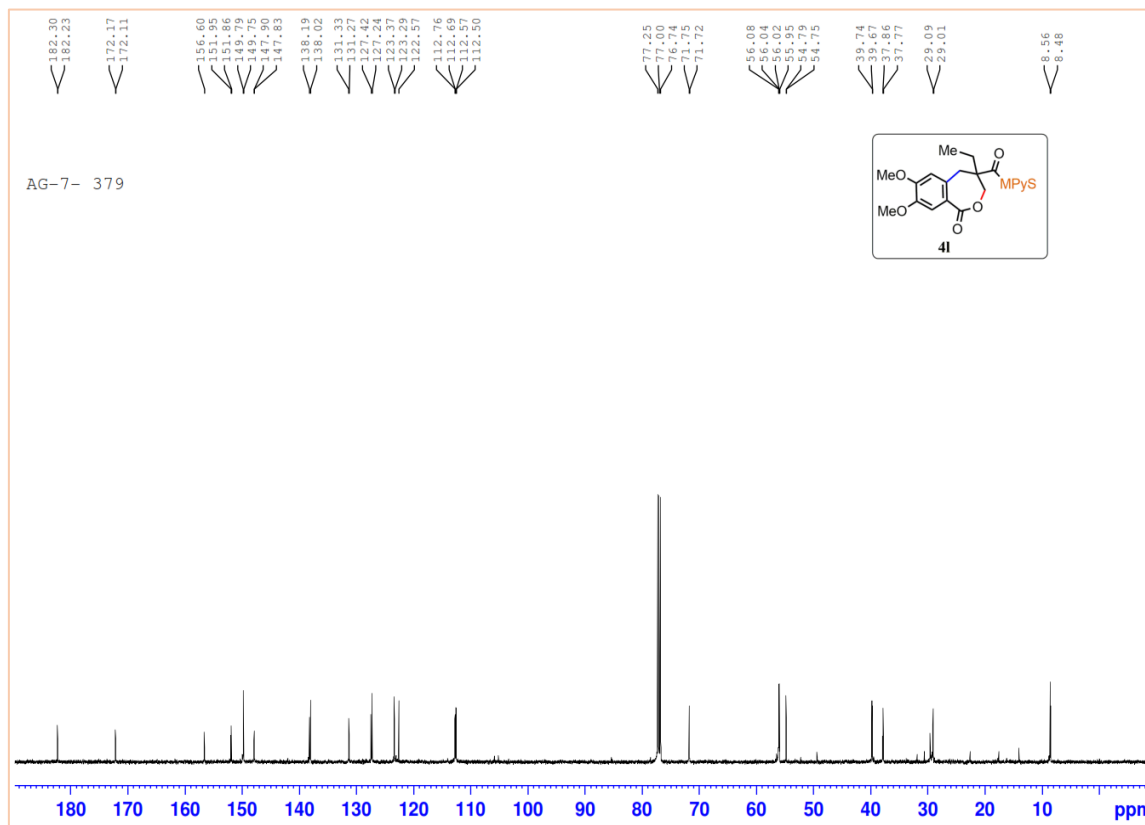


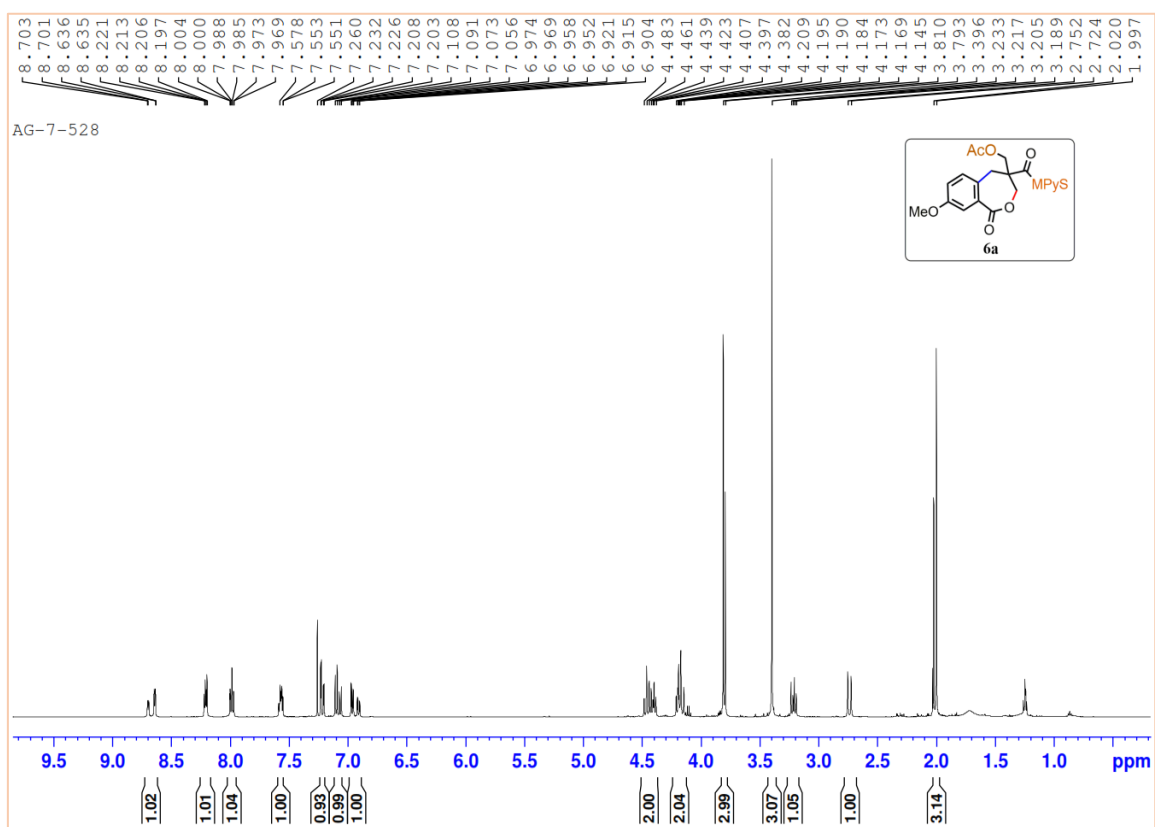
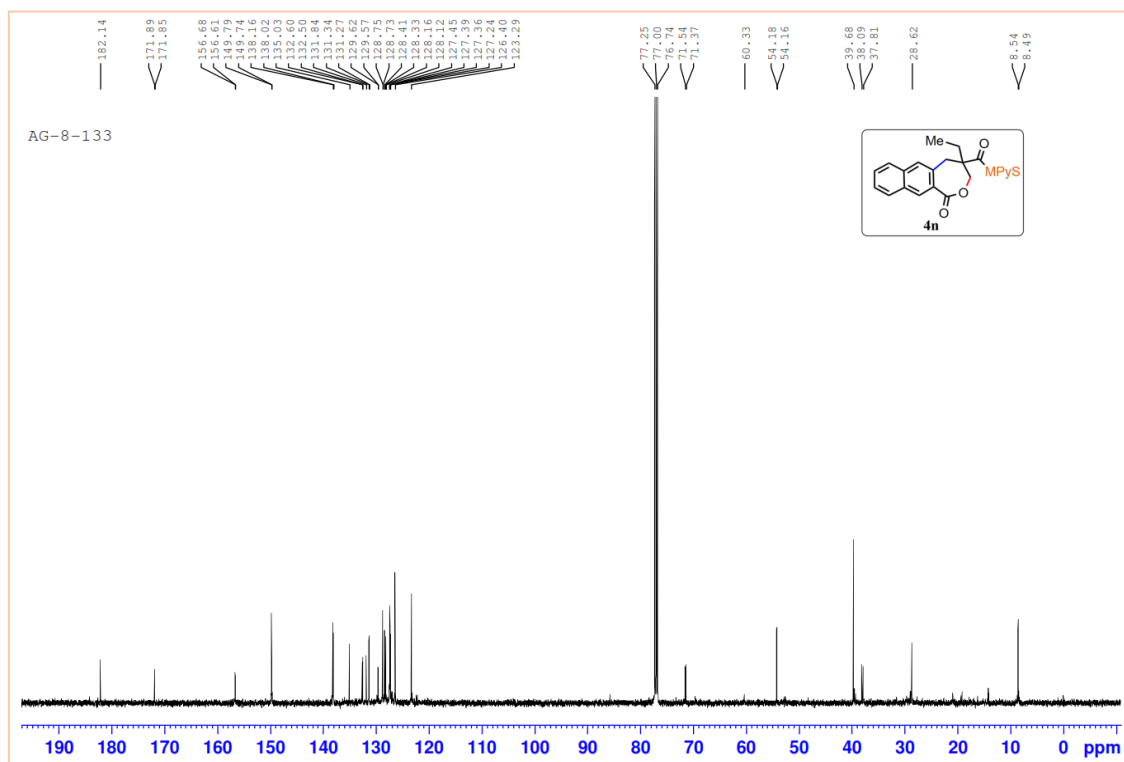


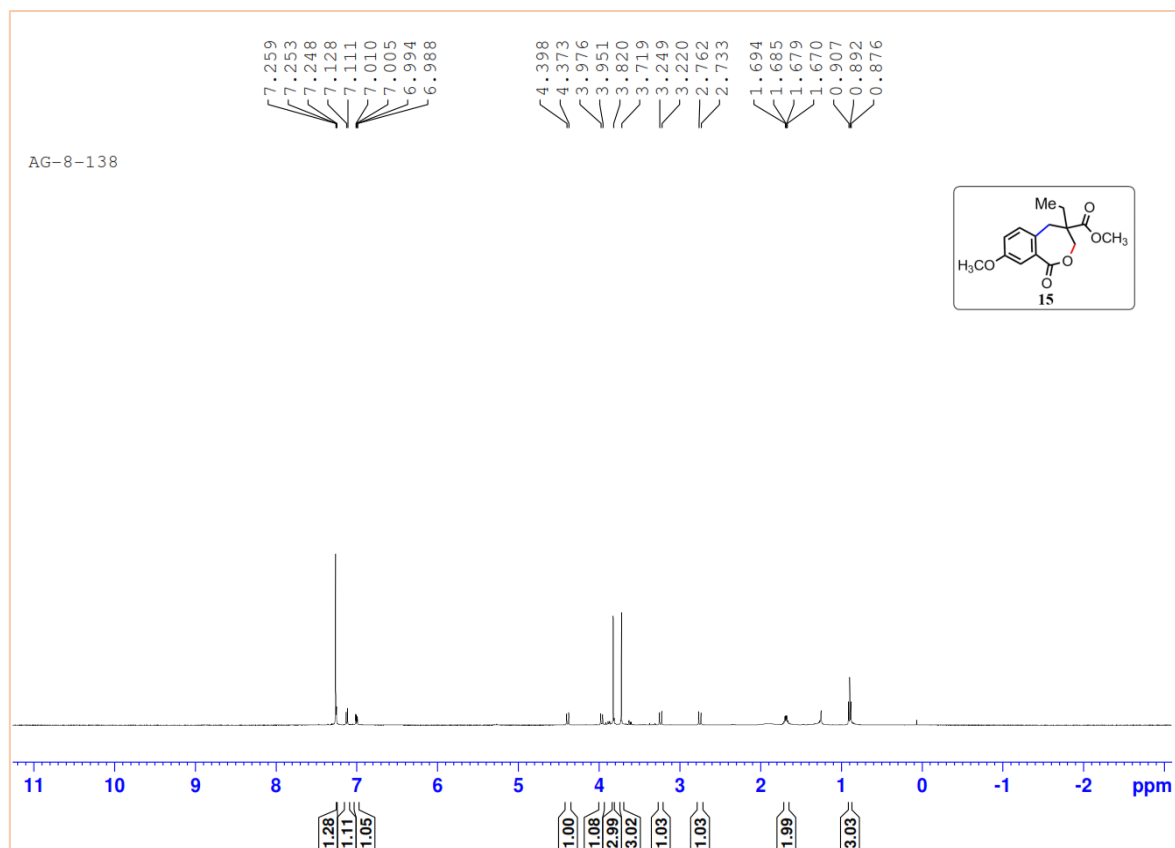
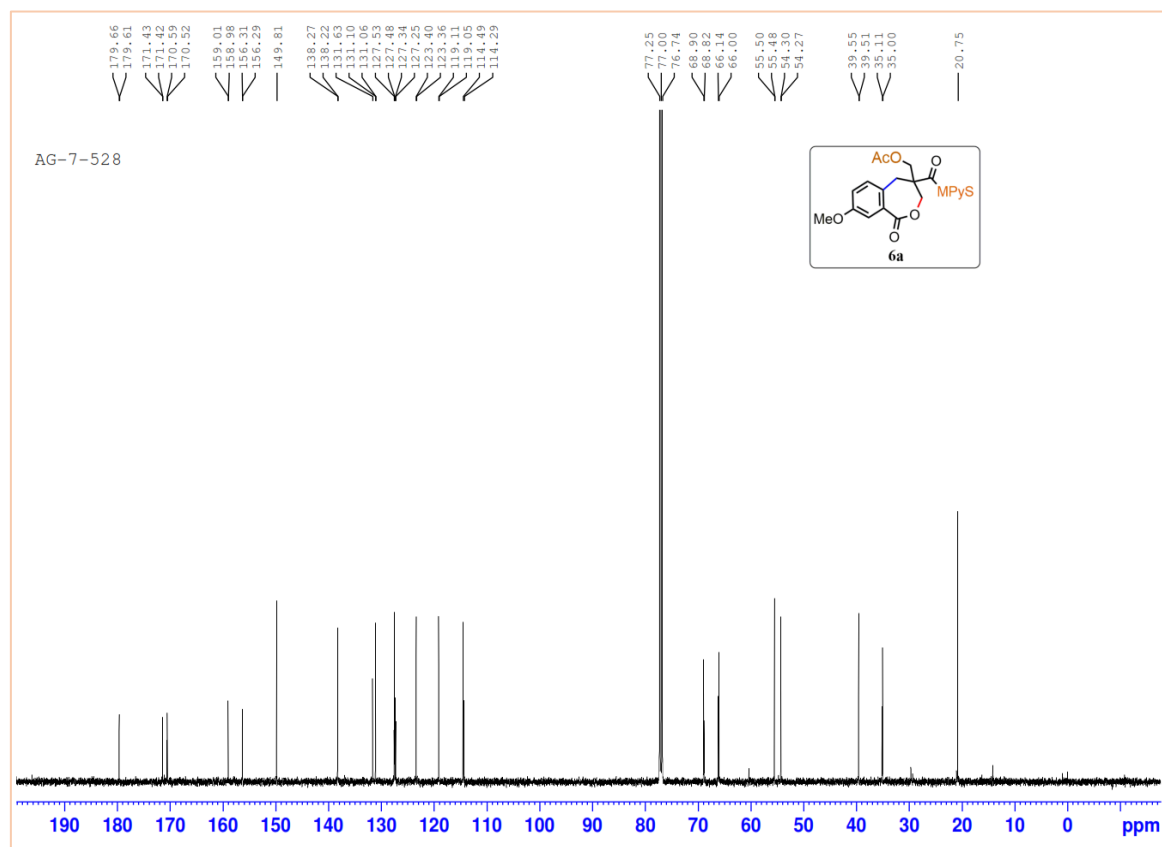


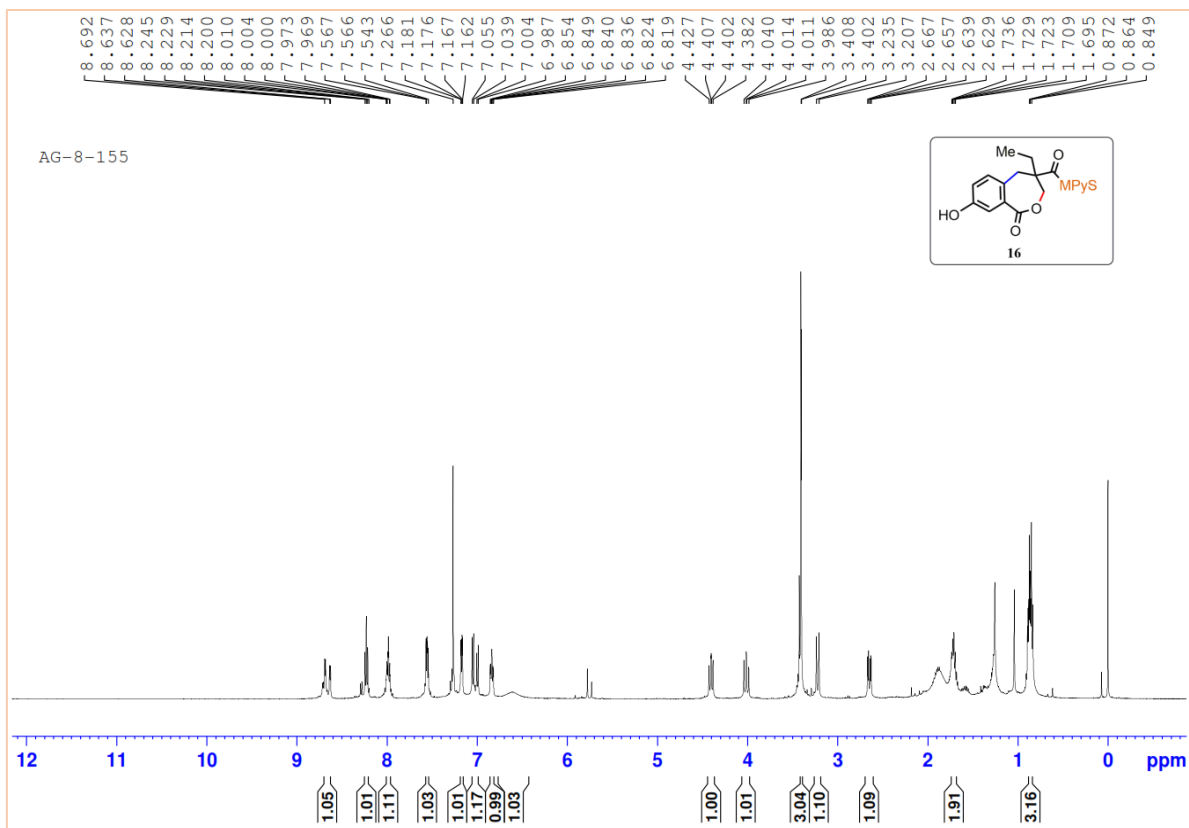
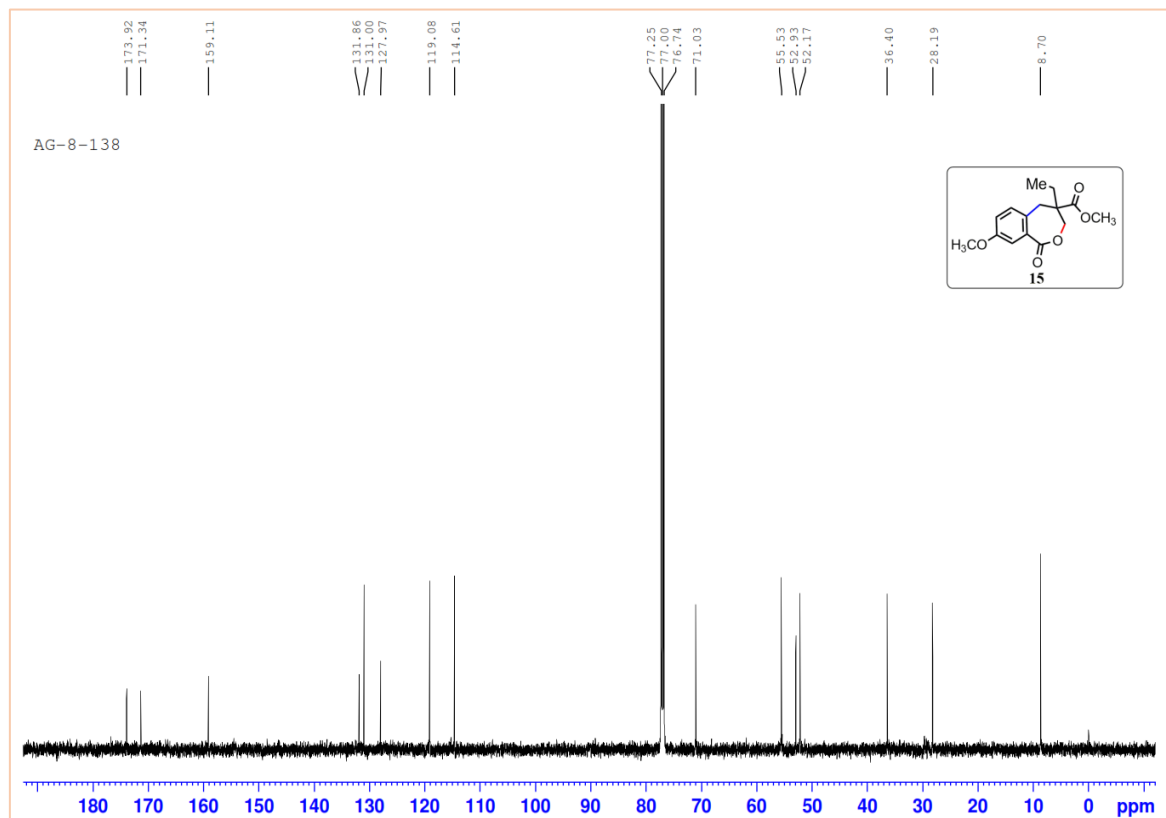


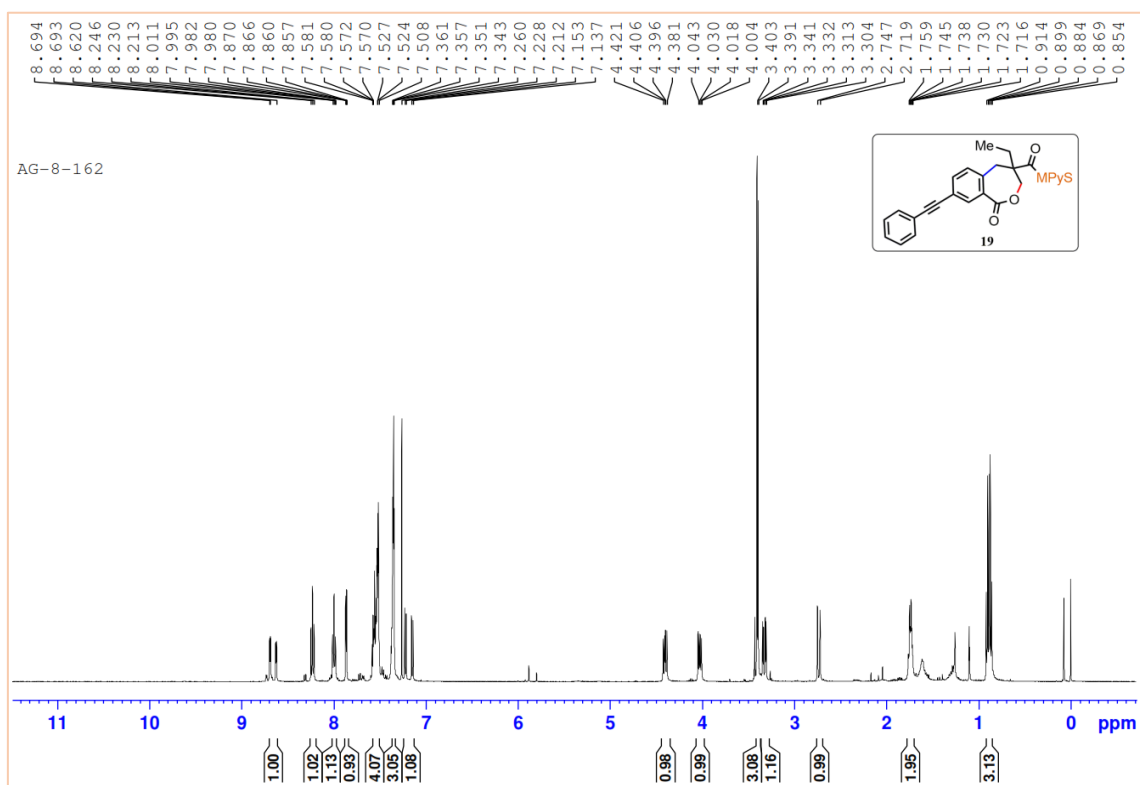
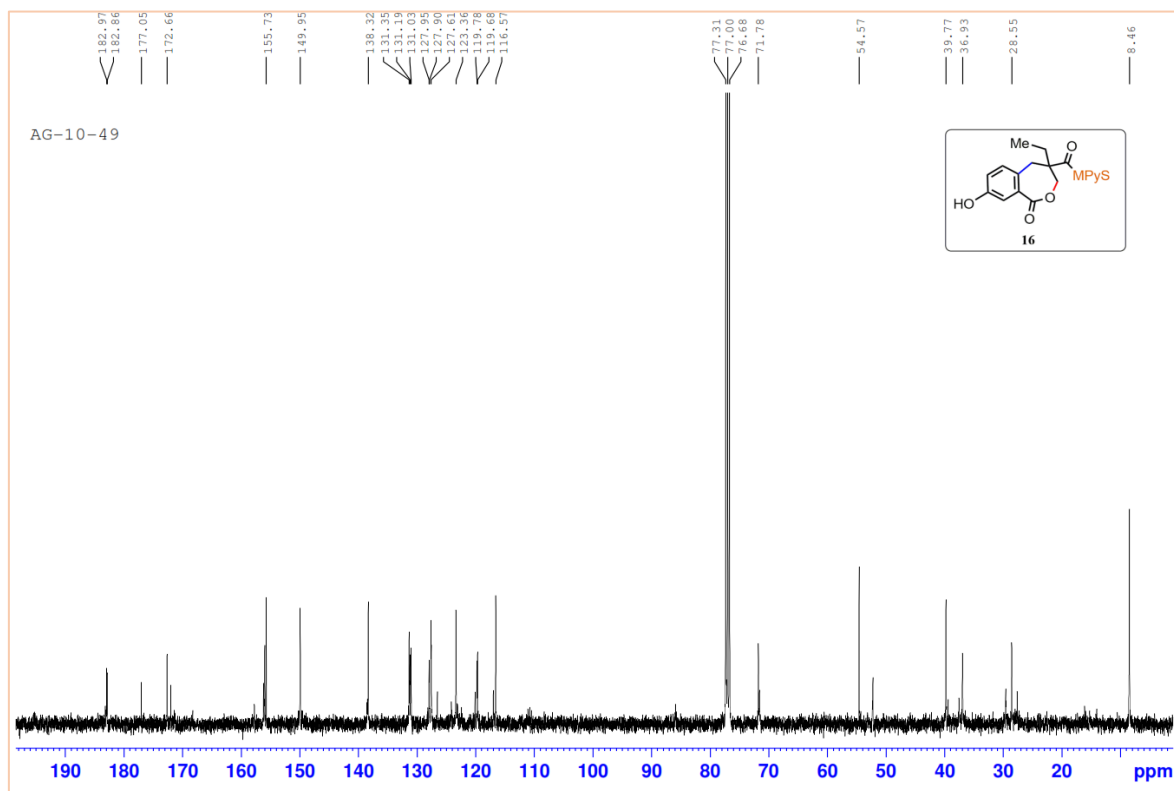


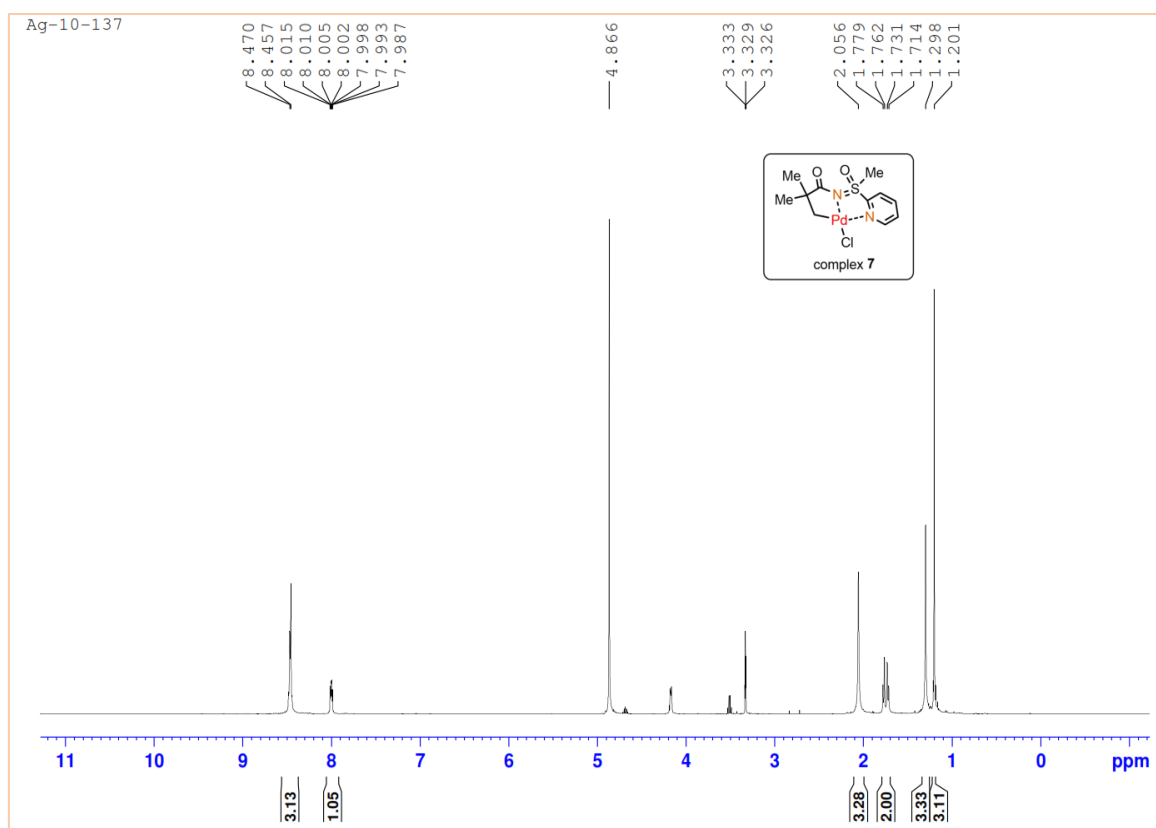
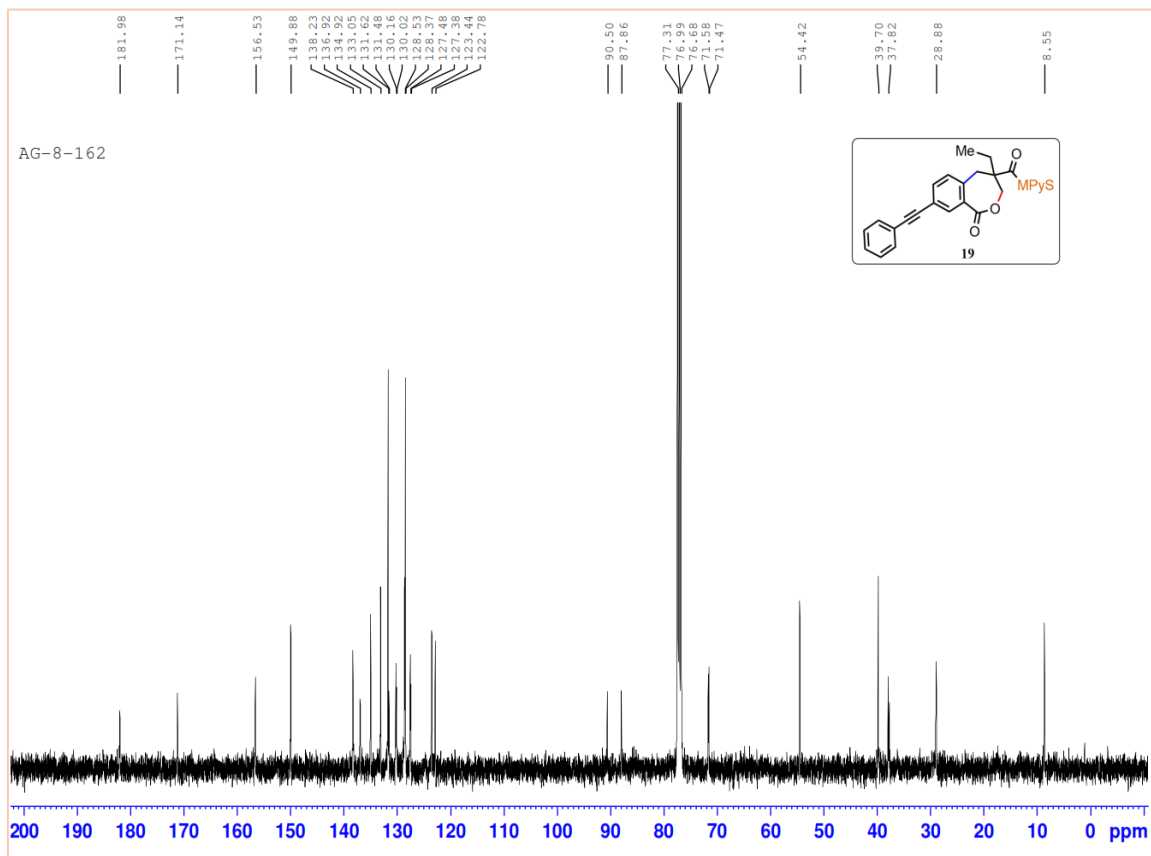


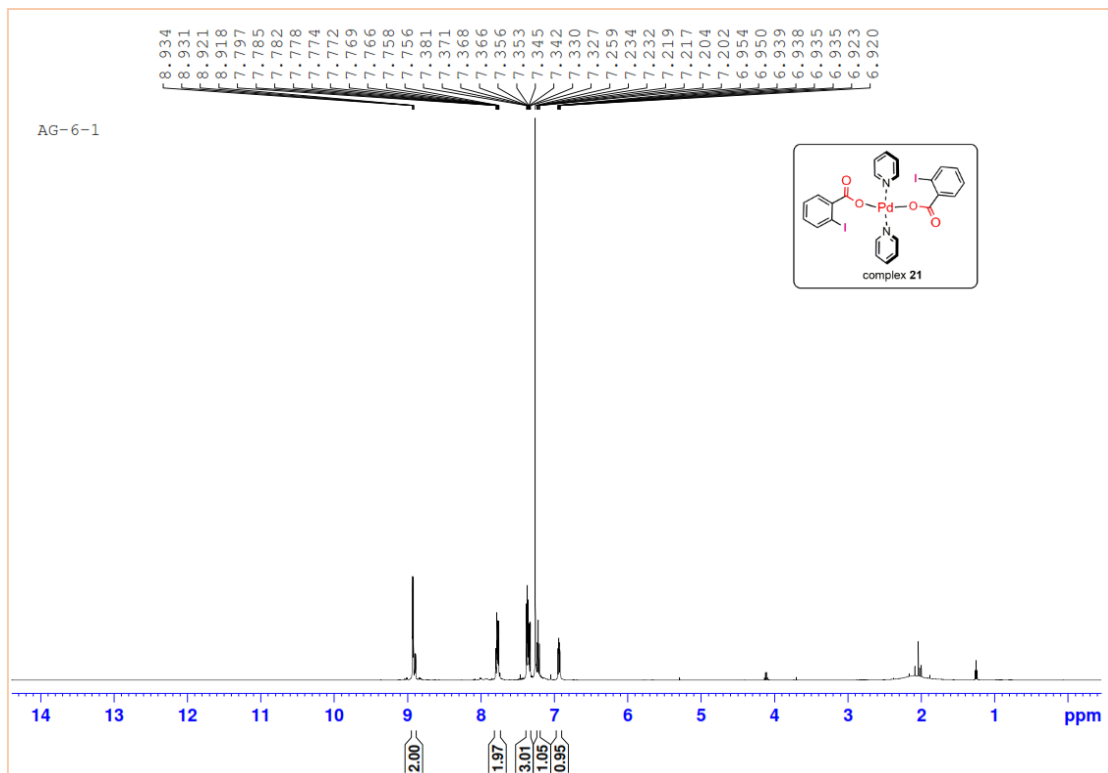
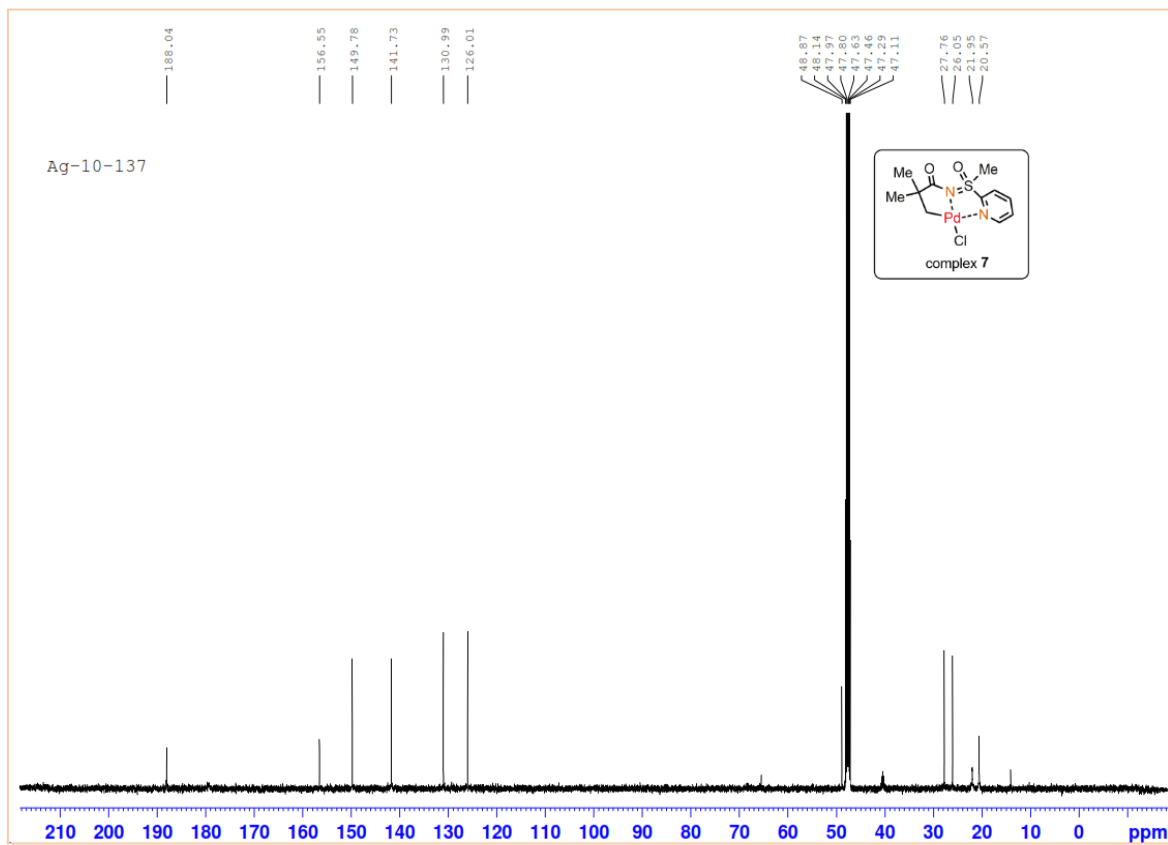


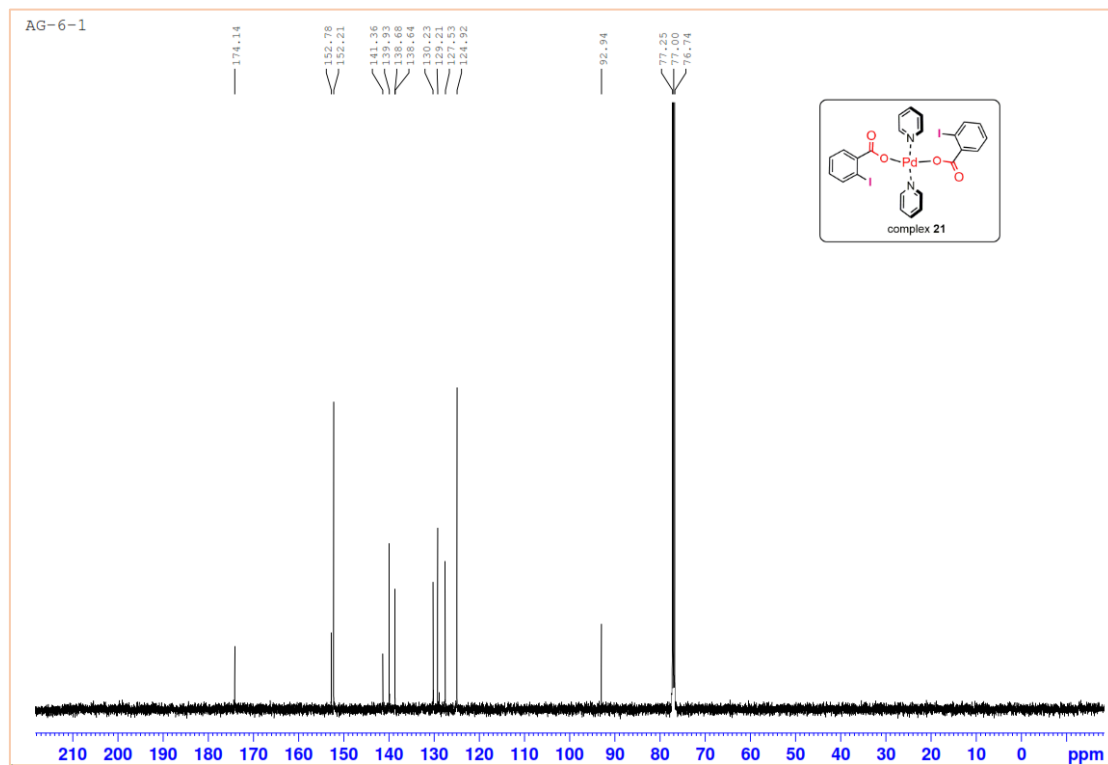








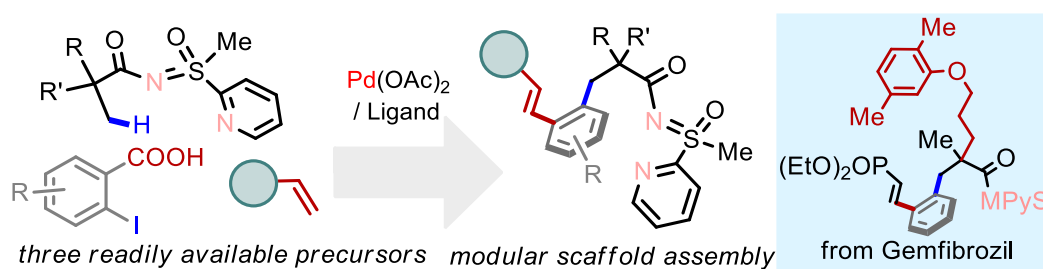




Chapter 3

A Three-Component Arene Difunctionalization: Merger of C(sp³)/(sp²)-H Bond Addition

Abstract



A tandem three-component C–H bond addition involving the activation of an inert C(sp³)–H bond is reported. The process enables the direct regioselective synthesis of 1,2-difunctionalized arenes with the formation of C(sp³)– and C(sp²)–C(arene) bonds. 2-Iodobenzoic acid derivatives behave as masked bifunctional reagent (BFR) and react with 2-pyridyl-methyl sulfoximine (MPyS) protected aliphatic acids bearing α,α -disubstituted groups, and alkenes to produce β -aryl- δ -alkenyl amide derivatives in a single operation. The transformation involves Pd(II)/Pd(IV) and Pd(II)/Pd(0) catalytic systems. Detailed mechanistic studies, including density functional theory (DFT) calculations, reveal the formation of large T-shaped palladacycles and the onset of a 1,2-palladium migration via decarboxylation.

Reference:

Arghadip Ghosh, Koneti Kondalarao, Arijit Saha, Vincent Gandon, and Akhila K. Sahoo *Angew. Chem. Int. Ed.* **2023**, 62, e2023143.

3.1. Introduction

Harnessing the reactivity of non-functionalized simple molecular scaffolds is an effective approach to access the intricate structures of naturally occurring compounds.¹ In this regard, multicomponent reactions (MCRs) that involve functionalizations of ubiquitous C–H bonds can prove very effective.² However, careful design is required to modulate the reactivity of the different coupling partners according to specific functional groups.² Despite the recent introduction of transition metal (TM)-catalyzed C–H functionalization strategies in MCRs,² site-selectivity remains a formidable challenge. Therefore, we present a new method using a Pd-catalyst and methyl pyridyl sulfoximine (MPyS) as directing group (DG) to activate inert C–H bonds in aliphatic acid derivatives. An ambiphilic BFR³ of the 2-iodo benzoic acid family and an alkene are used as other two coupling partners, reacting sequentially (Figure 3.1). This process paves the way for the selective functionalization of distant arene moiety of α,α -disubstituted hydrocinnamic acid derivatives (Figure 3.1).

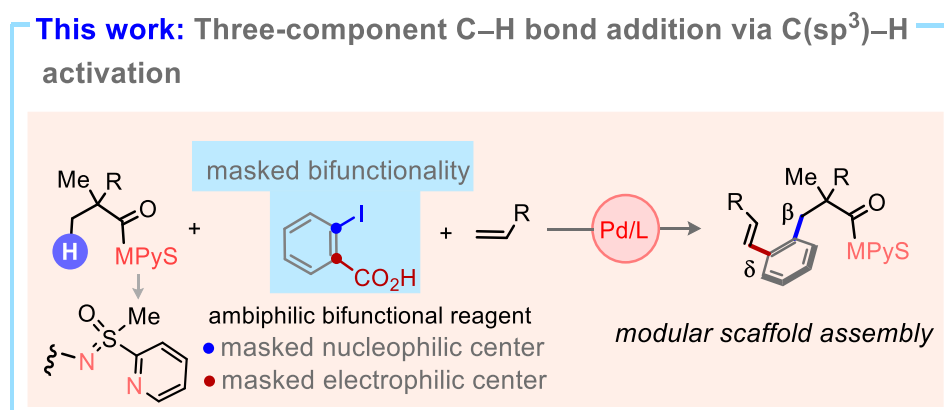
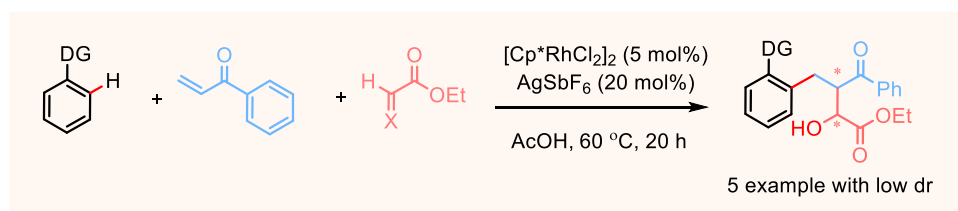


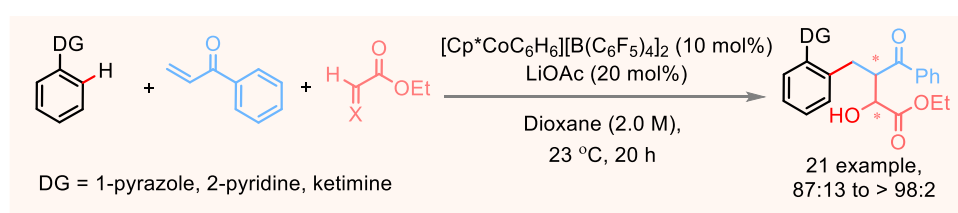
Figure 3.1. Strategy for three-component C–H bond addition reaction

3.1.1. Precedents and Strategies for three-component C–H bond addition

In 2016, the first example of three-component C–H bond addition using C(sp²)–H bond activation was achieved by Ellman and coworkers.⁴ The initial Rh-catalysed cascade conjugation across three different coupling partners led to the formation of intricate structure of aliphatic alcohol with two stereogenic centers. However, this initial study has showcased low diastereoselectivity (Scheme 3.1). Later on, the same group provided high diastereoselective transformation using a specific design cobalt catalyst (Scheme 3.2).

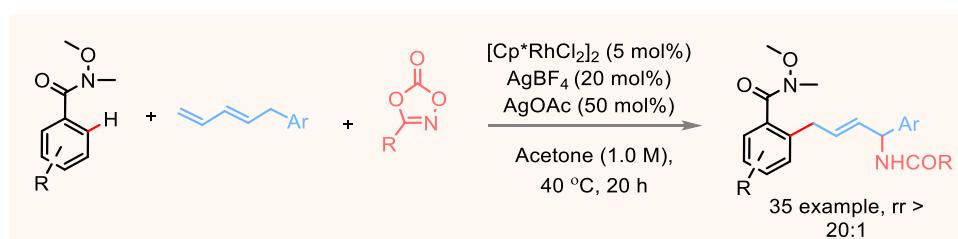


Scheme 3.1. Ellman's three-component coupling strategy via $C(sp^2)$ -H bond activation

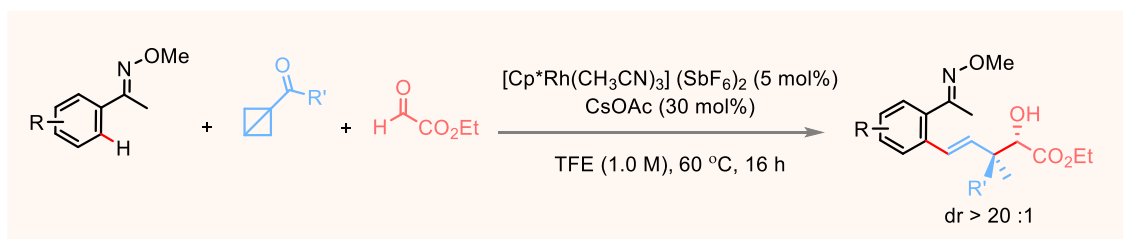


Scheme 3.2. Ellman's three-component coupling strategy via $C(sp^2)$ -H bond activation

In 2019 and 2021, Glorius group reported an elegant method for three-component C-H bond addition using $C(sp^2)$ -H bond activation.⁵ This innovative approach utilized 1,3-dienes and strained bicyclobutanes (BCBs) as bridging elements. Owing to their importance in organic synthesis, employing them in Rh-catalyzed three-component C-H addition reactions not only adds value but also yields uncommon intricate molecules. These molecules are difficult to synthesize conventionally, especially with high diastereoselectivity (Scheme 3.3 and 3.4).

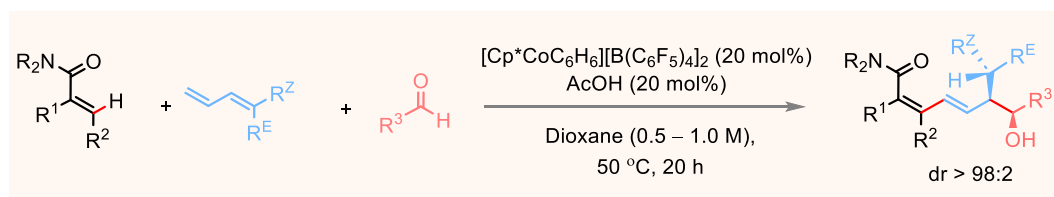


Scheme 3.3. Glorius's three-component coupling strategy via $C(sp^2)$ -H bond activation



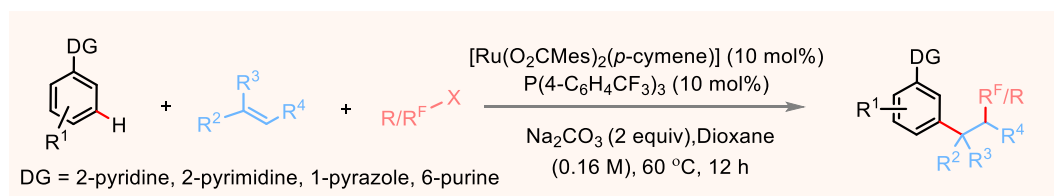
Scheme 3.4. Glorius's three-component coupling strategy via $C(sp^2)$ -H bond activation

In 2018, Ellman and coworkers encompassed the $C(\text{alkenyl})$ -H bond as an anchoring substrate in a three-component C-H bond addition reaction.⁵ Despite being good Michael acceptors, vinylic substrates participated effectively with excellent diastereoselectivity (Scheme 3.5).



Scheme 3.5. Ellman's three-component coupling strategy via $C(\text{alkenyl})$ -H bond activation

In 2019, employing *meta*- $C(\text{arene})$ -H bond, Liang and coworkers reported a three-component C-H bond addition reaction.⁶ This reaction exhibits a large substrate scope, encompassing several activated and unactivated alkenes, and a range of different nitrogen-based static directing groups. Furthermore, the addition of a fluorine-containing alkyl group enhances the applicability of this synthetic method (Scheme 3.6).



Scheme 3.6. Liang's three-component coupling strategy via *meta*- $C(\text{arene})$ -H bond activation.

3.2. Motivation, Hypothesis, and Design

Nevertheless, a conceptual void still exists in this area, specifically pertaining to the three-component couplings involving inert $C(sp^3)$ -H bond activation. Such an approach, however, holds great promise for expanding the chemical space of $C(sp^3)$ -enriched compounds that are difficult to obtain by conventional means (Figure 3.2).⁷

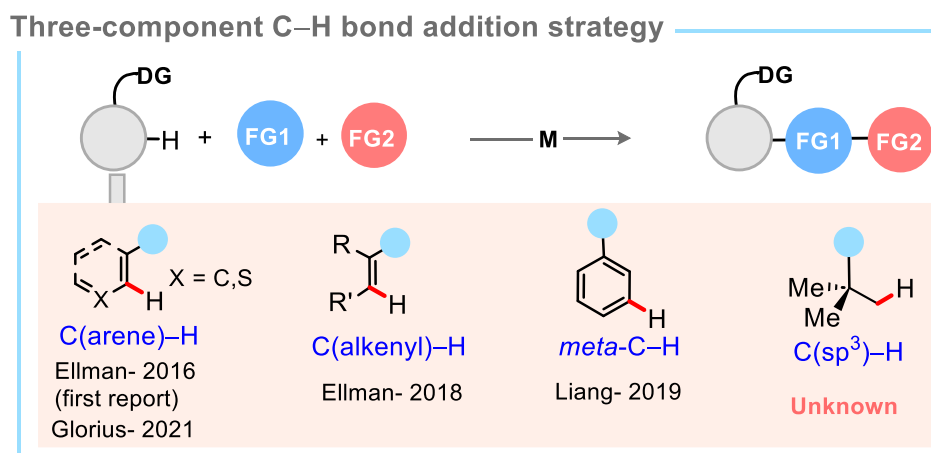


Figure 3.2. Concept and existing challenge in the three-component C–H bond addition workspace

In line with our hypothesis, our objective was to achieve a highly regioselective, atom and step-economical construction, leading to a $C(sp^3)$ -enriched 1,2-difunctionalized product within the arene framework. This process results in δ -arene substituted derivatives of hydrocinnamic acid. To accomplish this, a complementary synthetic approach has recently been successfully demonstrated through the functionalization of inert δ -arene C–H bonds in hydrocinnamic acids (Figure 3.3-I). However, despite this success, achieving complete site-selective bond formations by readily accessible bifunctional arene derivatives via catalytic C–H bond addition remains a great challenge (Figure 3.3-II).⁸ As shown herein, this relies on the formation of rare 9,5-fused palladium complexes (Figure 3.3-II-a) and the involvement of an uncommon 1,2-Pd-migration through decarboxylation (Figure 3.3-II-b).⁹ Moreover, it is crucial to avoid the facile protodemetalation (Figure 3.3-II-c)¹⁰ and to control the selective functionalization of δ -arene position, even in the presence of competing β - $C(sp^3)$ -H bonds (Figure 3.3-II-d).⁸

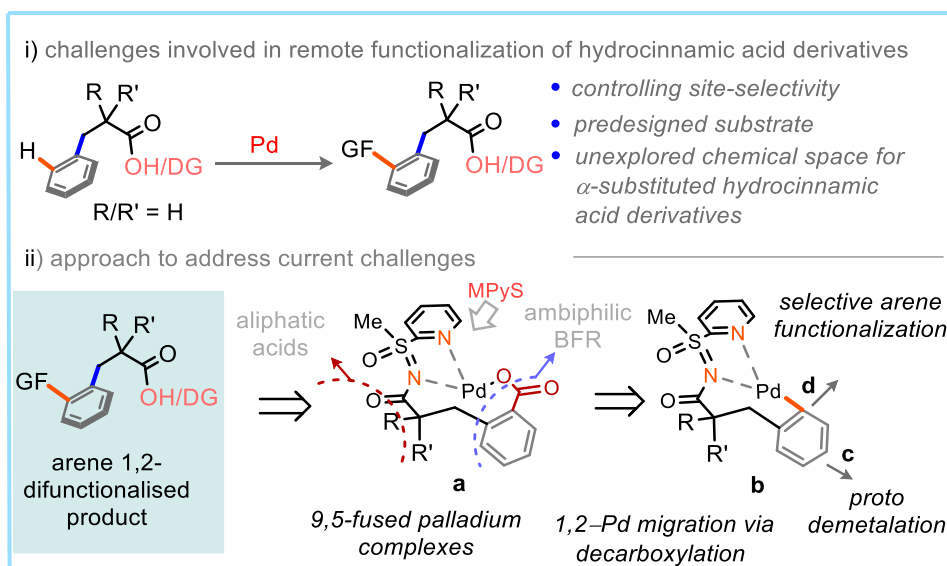


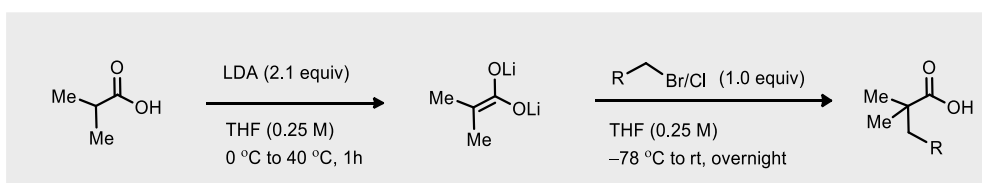
Figure 3.3. Challenges associate with remote functionalization of hydrocinnamic acid.

3.3. Results and Discussion

3.3.1. Synthesis of Precursors

A wide range of *N*-carboxyl sulfoximine derivatives were synthesized involving the procedure mentioned herein.

3.3.1.1. Preparation of carboxylic acids: General Procedure (GP-1):¹¹

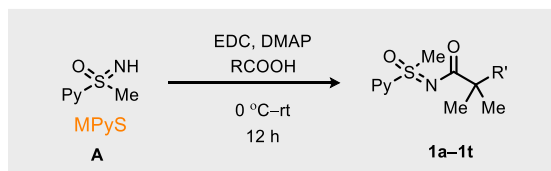


Scheme 3.7. Preparation of carboxylic acids

To a stirred solution of diisopropylamine (3.0 mL, 21 mmol) in THF (40 mL) was added *n*-BuLi solution (8.4 mL, 21 mmol, 2.5 M in hexane) dropwise at 0 °C. The resulting solution was stirred at 0 °C for 30 min. Isobutyric acid (910 μ L, 10 mmol) was added dropwise at the same temperature and the reaction mixture was heated to 40 °C and stirred for 1 h. The resulting mixture was then cooled to -78 °C; next the respective alkyl bromide (10 mmol) was added dropwise. The reaction mixture was slowly warmed to room temperature (rt) overnight. The reaction mixture was

quenched with water and diluted with EtOAc (30 mL). The organic layer was separated, and then washed with water. The aqueous layers were combined and acidified to $pH < 4$ with aqueous 3M HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo. The crude carboxylic acid was subsequently used without further purification.

3.3.3.2 Preparation of N-protected S-methyl-S-(2-pyridyl) sulfoximines: General Procedure (GP-2):¹²

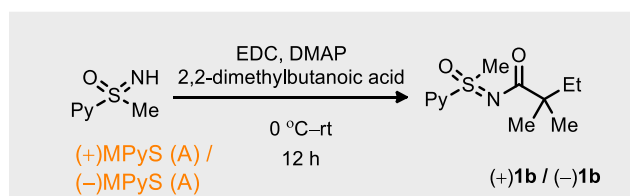


A solution of N' -(3-dimethylaminopropyl)- N -ethylcarbodiimide, hydrochloride salt (EDC $\cdot$ HCl) (1.1 equiv), 4- N , N -dimethylaminopyridine (DMAP) (2.2 equiv), and carboxylic acid (1.1 equiv) in CH_2Cl_2 (5.0 mL for 1.0 mmol of sulfoximine) was stirred under an argon atmosphere. Sulfoximine (**1**; 1.0 equiv) was introduced dropwise at 0 °C. The resulting reaction mixture was stirred for about 1 h at 0 °C, and warmed to ambient temperature and stirred overnight. Upon complete consumption of sulfoximine, the reaction mixture was acidified with hydrochloric acid (HCl, 1N). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined extracts were washed with 10% aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 . Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography eluting with (EtOAc/hexane mixture) on silica gel. The spectral data of the following compounds are matching with the data reported in the literature.

3.3.3.3 Preparation of 2,2-dimethylbutanoic acid coupled to optically active (*R* or *S*) S-methyl-S-(2-pyridyl) sulfoximines:¹²

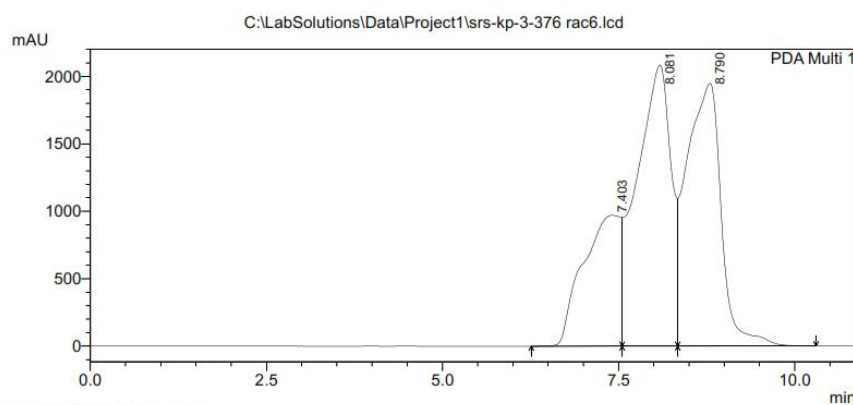
A solution of N' -(3-dimethylaminopropyl)- N -ethylcarbodiimide, hydrochloride salt (EDC $\cdot$ HCl) (1.1 equiv), 4- N , N -dimethylaminopyridine (DMAP) (2.2 equiv), and 2,2-

dimethylbutanoic acid (1.1 equiv) in CH_2Cl_2 (5.0 mL for 1.0 mmol of sulfoximine) was stirred under an argon atmosphere. Sulfoximine (**1-R/S**; 1.0 equiv) was introduced dropwise at 0 °C. The resulting reaction mixture was stirred for 1 h at 0 °C, warmed to ambient temperature and stirred overnight. Upon complete consumption of the sulfoximine, the reaction mixture was acidified with hydrochloric acid (HCl, 1N). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined extracts were washed with 10% aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 . Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography eluting with (EtOAc/hexane mixture) on silica gel. The spectral data of the following compounds are matching with the data reported in the literature.



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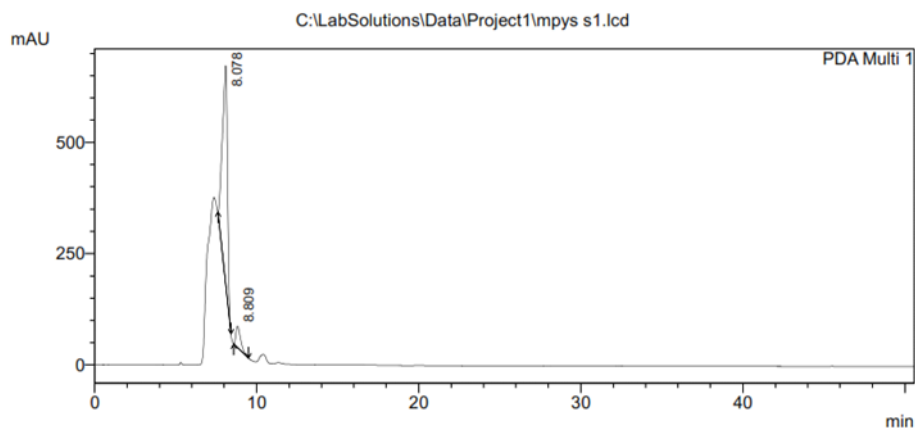


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3	8.790	65947897	1947627	38.266	38.936
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Sample Name : mpys s C:\LabSolutions\Data\Project1\mpys s1.lcd

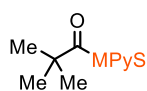
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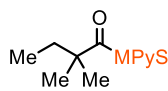
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Total		11346096	539356	100.000	100.000

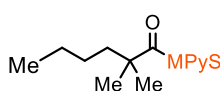
Substrate list:



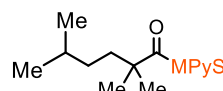
1a



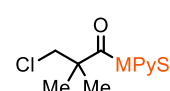
1b



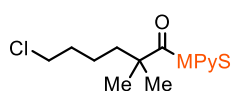
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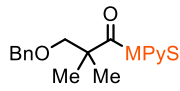
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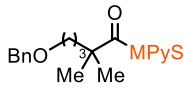
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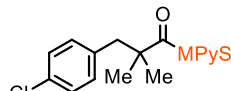
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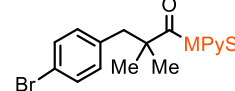
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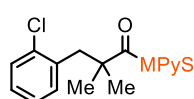
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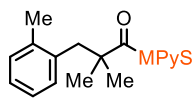
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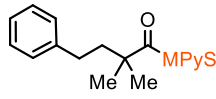
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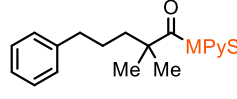
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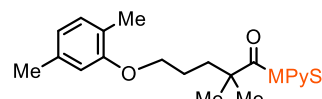
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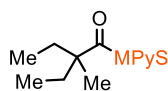
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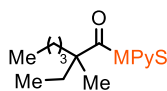
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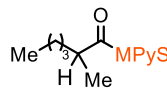
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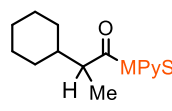
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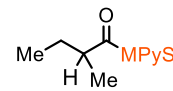
1q



1r

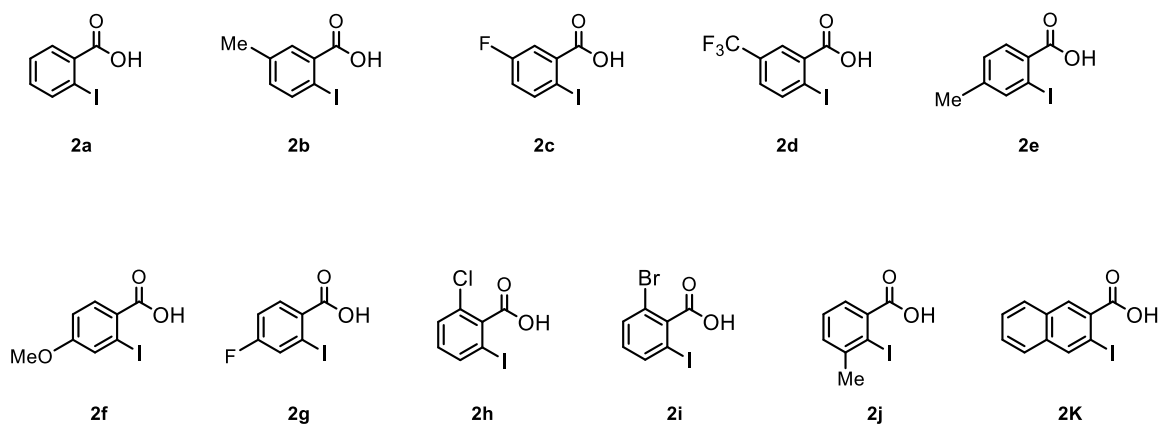


1s

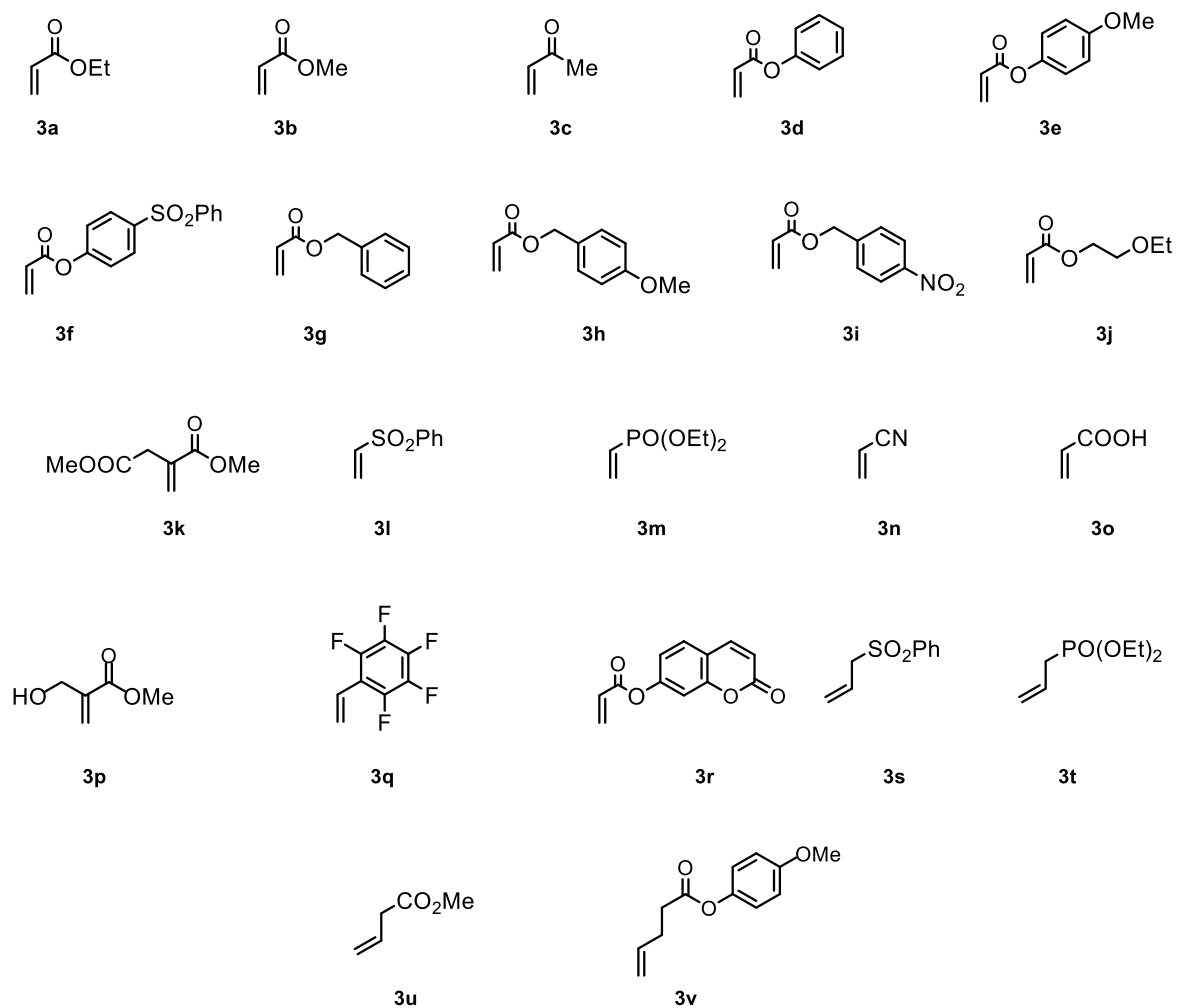


1t

List of 2-iodobenzoic acids (2): The respective compounds were purchased and used.



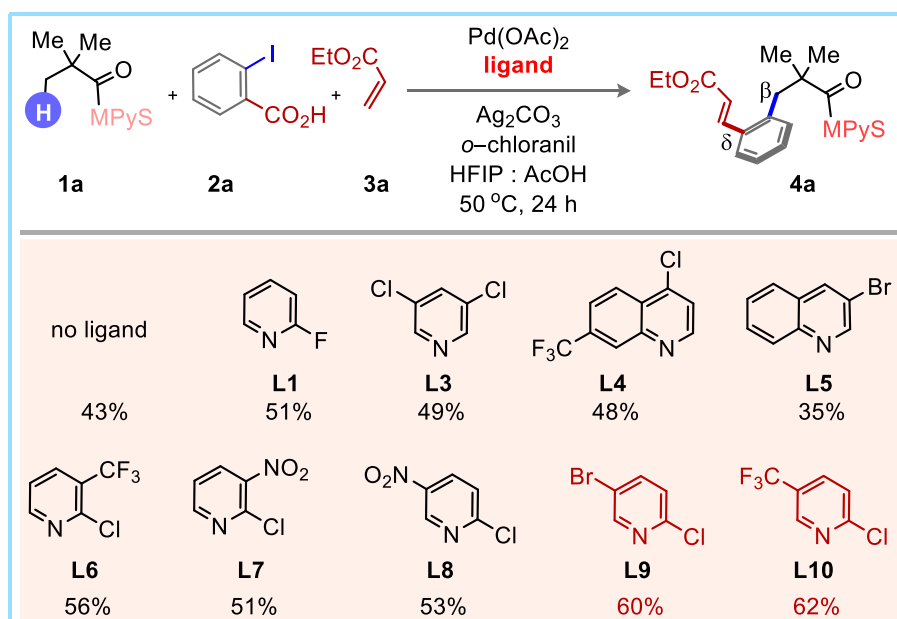
List of olefins (3): The respective olefins were purchased and used.



3.3.2. Reaction Optimization

To explore the projected three-component C–H addition reaction through the activation of an inert C(sp³)-H bond, the reaction between amide **1a** (which displays 2-pyridyl-methyl sulfoximine (MPyS) and α,α -dimethyl groups), 2-iodo benzoic acid **2a**, and ethyl acrylate **3a**, in the presence of a Pd catalyst was studied (Scheme 3.8). We were able to obtain the desired 1,2-functionalized arene product **4a** in 43% yield when the reaction was carried out in the presence of an oxidant mixture of silver carbonate and *o*-chloranil in the absence of ligands (Table 3.1).¹³ Building on our previous understanding of the ligand-activated concerted metalation deprotonation (CMD) process, where an electron-deficient pyridine develops a Pd-arene interaction,¹⁴ we hypothesized that similar ligands might improve the yield of the desired product in this reaction. We thus screened a range of electron-deficient pyridines. Interestingly, both 2-chloro-5-bromopyridine (**L9**) and 2-chloro-5-trifluoromethylpyridine (**L10**) provided 60% and 62% of the desired product **4a**, respectively, in presence of Pd(OAc)₂ (10 mol%), Ag₂CO₃ (0.2 mmol), *o*-chloranil (0.1 mmol), HFIP (0.485 mL), AcOH (0.170 mL) at 50 °C, for more details see Table 3.2. In agreement with our previous observation,¹⁴ increasing the ligand loading from 15 to 50 mol% led to a decreased yield. Other electron-deficient pyridine ligands were found less efficient (Table 3.2), as well as other solvents and palladium salts (Tables 3.3 and 3.4).

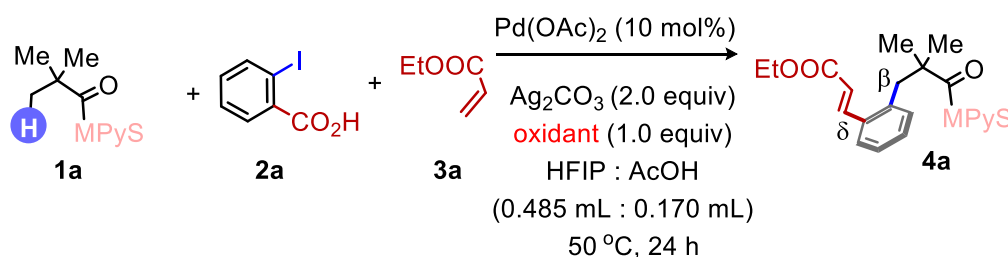
Scheme 3.8. Ligands screening ^a



1a (0.1 mmol), **2a** (0.2 mmol), **3a** (0.2 mmol), Pd(OAc)₂ (10 mol%), Ligand (**L**; 15 mol%), Ag₂CO₃ (0.2 mmol), *o*-chloranil (0.1 mmol), HFIP (0.485 mL), AcOH (0.170 mL) at 50 °C, under air, 24 h. ^bThe yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard. [HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; AcOH = acetic acid].

Detail optimization of the reaction conditions:

Table 3.1: Oxidant optimization



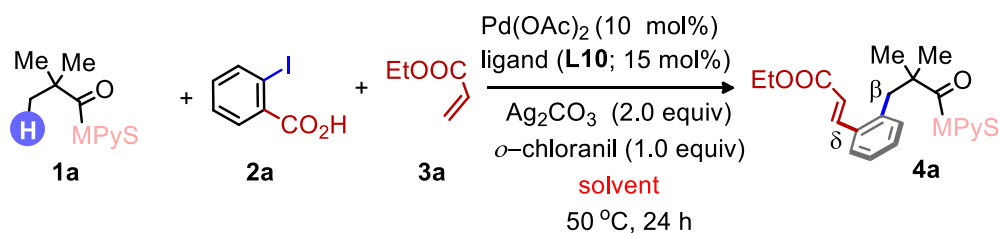
Entry	Oxidant	Yield 4a (%)	Yield 1a (%)
1	CuCl ₂	0	90
2	Cu(OAc) ₂ · H ₂ O	27	72
3	Cu ₂ O	28	72
4	CuSO ₄ · 5H ₂ O	0	92
5	Cu(NO ₃) ₂ · 3H ₂ O	0	85
6	CuF ₂	22	76
7	2,3-dichloro-1,4-naphthoquinone	31	68
8	methyl- <i>p</i> -benzoquinone	17	82
9	2-chloro-1,4-benzoquinone	23	77
10	2,5-di- ^t butyl-1,4-benzoquinone	21	78
11	chloranil	33	66
12	<i>o</i>-chloranil	43	57

Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), **3a** (0.2 mmol), Pd(OAc)₂ (10 mol%), ligand (15 mol%), Ag₂CO₃ (0.2 mmol), *o*-chloranil (0.1 mmol), HFIP (0.485 mL), AcOH (0.170 mL) at 50 °C, under air, 24 h. The yield was determined by ¹H NMR analysis of the crude product, using CH₂Br₂ as an internal standard. HFIP = hexafluoroisopropanol, AcOH = acetic acid

Table 3.2: Ligand optimization

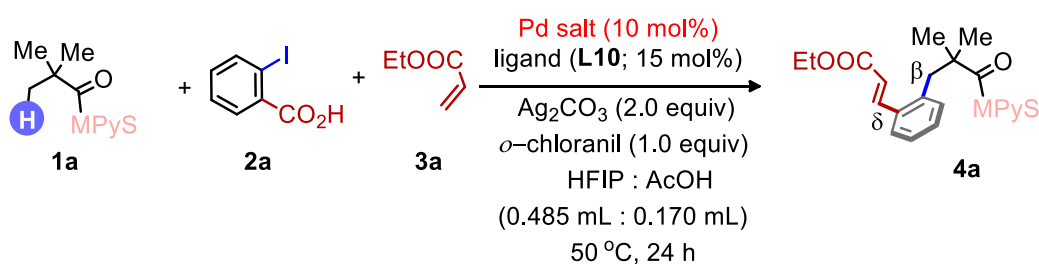
 L1 51%	 L2 52%	 L3 46%	 L4 53%	 L5 60%
 L6 49%	 L7 46%	 L8 43%	 L9 51%	 L10 62%
 L11 48%	 L12 35%	 L13 41%	 L14 56%	 L15 46%
 L16 37%	 L17 00%	 L18 00%		

Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), **3a** (0.2 mmol), Pd(OAc)₂ (10 mol%), ligand (15 mol%), Ag₂CO₃ (0.2 mmol), *o*-chloranil (0.1 mmol), HFIP (0.485 mL), AcOH (0.170 mL) at 50 °C, under air, 24 h. The yield was determined by ¹H NMR analysis of the crude product, using CH₂Br₂ as an internal standard. HFIP = hexafluoroisopropanol, AcOH = acetic acid

Table 3.3: Solvent optimization

Entry	Solvent	Yield 4a (%)	Yield 1a (%)
1	HFIP	0	90
2	AcOH	0	90
3	HFIP : AcOH (46 equiv : 10 equiv)	48	52
4	HFIP : AcOH (46 equiv : 20 equiv)	57	43
5	HFIP : AcOH (46 equiv : 30 equiv)	62	35
6	HFIP : AcOH (46 equiv : 40 equiv)	58	42
7	HFIP : AcOH (46 equiv : 50 equiv)	44	56
8	DCM	0	94
9	CHCl_3	0	88
10	1,2-DCE	0	93
11	1,4-dioxane	0	97
12	TFE	0	82
13	<i>t</i> -amylOH	0	98
14	Ac_2O	0	90

Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), **3a** (0.2 mmol), $\text{Pd}(\text{OAc})_2$ (10 mol%), ligand (15 mol%), Ag_2CO_3 (0.2 mmol), *o*-chloranil (0.1 mmol), HFIP (0.485 mL), AcOH (0.170 mL) at 50 °C, under air, 24 h. The yield was determined by ^1H NMR analysis of the crude product, using CH_2Br_2 as an internal standard. HFIP = hexafluoroisopropanol, AcOH = acetic acid, DCM = dichloromethane, 1,2-DCE = 1,2-dichloroethene, TFE = tetrafluoroethylene, Ac_2O = acetic anhydride

Table 3.4: Palladium salt optimization

Entry	Pd salt	Yield 4a (%)	Yield 1a (%)
1	$PdCl_2(dppf)_2$	0	0
2	$PdCl_2(MeCN)_2$	57	43
3	$PdCl_2$	29	71
4	$Pd(acac)_2$	42	57
5	$Pd(OTf)_2$	0	0
6	$Pd(cod)Cl_2$	52	48
7	$Pd(OAc)_2$	62	35
8	$Pd(PPh)_2Cl_2$	46	54
9	$Pd(OH)_2$	0	0

Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), **3a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), ligand (15 mol%), Ag_2CO_3 (0.2 mmol), *o*-chloranil (0.1 mmol), HFIP (0.485 mL), AcOH (0.170 mL) at 50 °C, under air, 24 h. The yield was determined by 1H NMR analysis of the crude product, using CH_2Br_2 as an internal standard. HFIP = hexafluoroisopropanol, AcOH = acetic acid

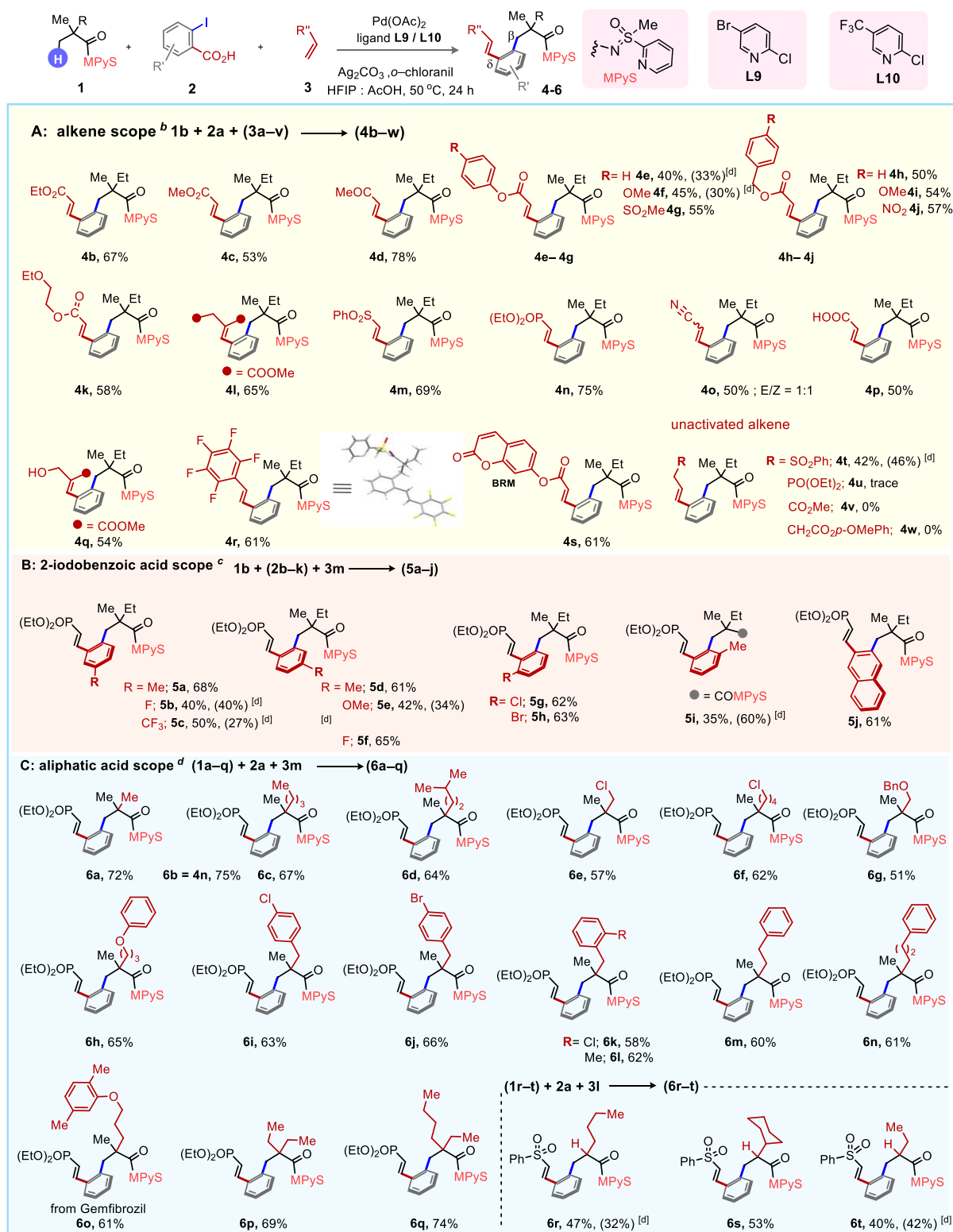
3.3.3. Reaction Scope

We next explored the reaction scope of the 1,2-difunctionlization of arenes under the optimized conditions (Scheme 3.9). To begin with, the compatibility of various olefin coupling partners (**3a–r**) was assessed (Scheme 3.9A). The three-component couplings of **1a** and **2a** with a range of olefins [including alkyl acrylates (**3a–c**), aryl acrylates (**3d–f**), benzyl acrylates (**3g–i**), 2-ethoxyethyl acrylate (**3j**), and sterically congested dimethyl itaconate (**3k**)] led to the desired products (**4b–l**) in moderate to good yields. Even functionalized olefins such as phenyl vinyl sulfone (**3l**), diethyl vinyl phosphonate (**3m**) and acrylonitrile (**3n**) provided the coupling products **4m–n** in good yields. The presence of the strongly binding acrylic acid (**3o**) and alcohol functionality [methyl 2-(hydroxymethyl) acrylate (**3p**)] did not hamper the outcome, products **4p** (50%)

and **4q** (54%) being successfully isolated. In spite of the strong Michael-acceptor nature of pentafluorostyrene (**3q**), it delivered the fluorine-rich product **4r** in 61% yield. X-ray crystallographic analysis established molecular topology of **4r**¹⁵. The biologically relevant umbelliferone-coupled acrylate **3r** yielded the C-H addition product **4s** in 61% yield, highlighting the broad applicability of the synthetic method. Having demonstrated the broad reactivity of activated alkenes, we were also curious to study the reactivity of unactivated ones. Therefore, the simple alkenes **3s–3v** were subjected to the optimized conditions, but only **3s** led to the formation of product **4t** in 42% isolated yield (Scheme 3.9A). Of note, compounds **4b–4t** were obtained in a 1:1 diastereomeric ratio. We then examined the compatibility of 2-iodobenzoic acid derivatives **2** in the three-component reaction of **1a** and diethyl vinyl phosphonate (**3m**) (Scheme 3.3B). Irrespective of the electron-variation of the 2-iodobenzoic acids [i.e. 5-Me (**2b**), 5-F (**2c**), 5-CF₃ (**2d**), 4-Me (**2e**), 4-OMe (**2f**) and 4-F (**2g**)], the reaction successfully furnished products **5a–f** in moderate to good yields. Even the sterically demanding *o*-substituted substrates, i.e. 6-Cl (**2h**) and 6-Br (**2i**) afforded **5g** (62%) and **5h** (63%) worked well. In addition, the methyl substituent at the *ortho*-position to the C-I bond [i.e. 3-Me (**2j**)] provided **5i** (35%); the moderate yield is possibly due to the steric hindrance hampering the oxidative addition. Lastly, the naphthyl derivative **5j** was made from the coupling with 2-iodonaphthanoic acid (**2k**) (Scheme 3.9B; of note, compound **5e** was obtained in a 1.7:1 diastereomeric ratio while all other products were obtained in a 1:1 diastereomeric ratio).

Next, the compatibility of the MPyS-enabled aliphatic acid derivatives **1** was investigated, using olefin **3m** and the aryl transfer agent **2a** (Scheme 3.9C). The reaction of compounds **1** exhibiting an α -gem-methyl-alkyl group (with different chain length of the alkyl moiety) delivered the desired products [**1a**→**6a** (72%); **1b**→**6b** = **4n** (75%); **1c**→**6c** (67%); **1d**→**6d** (64%); **1e**→**6e** (57%); **1f**→**6f** (62%)]. The alkyl-chloro group sensitive to Pd-catalytic systems was well tolerated (see **6e** and **6f**). Despite the coordination possibility of electron lone pair, the β -benzyloxy (**1g**) and δ -phenoxy (**1h**) substituted acid derivatives smoothly reacted to build **6g** (51%) and **6h** (65%),

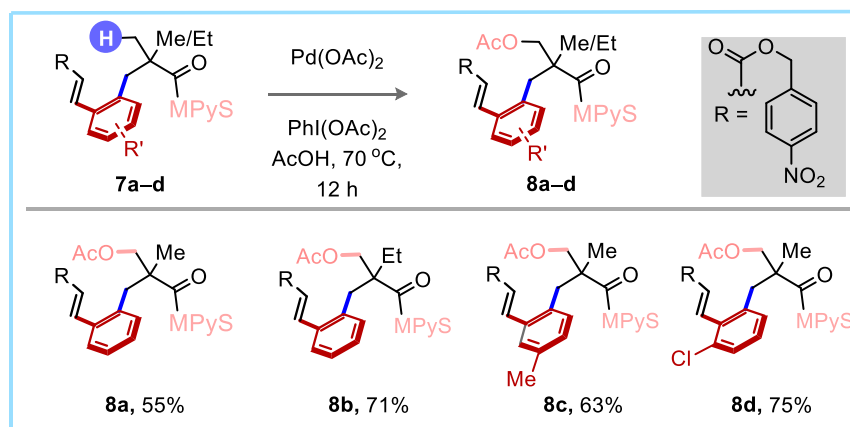
respectively. A range of β -arylated MPyS-enabled aliphatic acids (**1i–l**) participated well in the reaction, making the desired difunctionalized products **6i–l**. The easily oxidizable 4-halo (Cl/Br) groups and sterically demanding *o*-substituents were also tolerated. The MPyS-enabled acids having alkyl chains with a phenyl group at the γ - or δ -position (**1m** and **1n**) also turned out to be relevant substrates, affording the coupling products **6m** (60%) and **6n** (61%). The derivatization of Gemfibrozil (**1o**), an oral drug for lowering lipid levels,¹⁶ could deliver the product **6o** (61%). Likewise, the difunctionalized arenes **6p** and **6q** were accessed from the reaction of α -*gem*-dialkyl group containing MPyS-acid derivatives **1p** and **1q** with **2a** and **3m**. The MPyS-enabled tertiary aliphatic acids having an α -hydrogen (**1r–t**) are potentially challenging substrates since the absence of *gem*-disubstituent effect (Thorpe-Ingold or active rotamer effect)¹⁷ might hinder the desired reactivity and encourage a β -hydride elimination route. Nevertheless, the coupled products **6r–t** was obtained from **2a** and phenyl vinyl sulfone (**3l**) (Scheme 3.9C), albeit in moderate yields (Scheme 3.9C; compounds **6e**, **6g**, **6i**, and **6j** were obtained in diastereomeric ratios of 1.7:1, 2.0:1, 3.3:1, 2.6:1, and 1.4:1 respectively, while all other compounds were obtained in a 1:1 diastereomeric ratio).

Scheme 3.9. Scope of alkenes, 2-iodobenzoic acids and α,α -disubstituted aliphatic acid derivatives in the three-component C-H addition reaction.^a


^a Conditions: 1a-s (0.2 mmol), 2a-i (0.4 mmol), 3a-q (0.4 mmol), Pd(OAc)₂ (10 mol%), ligand L9/L10 (15 mol%), Ag₂CO₃ (0.4 mmol), *o*-chloranil (0.2 mmol), HFIP (0.970 mL), AcOH (0.340 mL) at 50 °C, under air, 24 h. ^b 1b and

2a fixed, Ligand **L10** used. ^c **1b** ad **3m** fixed, Ligand **L10** used. ^d **2a** and **3m** fixed, Ligand **L9** used. All compounds formed in a 1:1 diastereomeric ratio, while **5e**, **6e**, **6g**, **6i**, **6j** were obtained in a 1.7:1, 2.0:1, 3.3:1, 2.6:1 and 1.4:1 diastereomeric ratio respectively. ^e The yield in parenthesis is the isolated amount of the unreacted respective starting material.

Scheme 3.10: Iterative acetoxylation^a



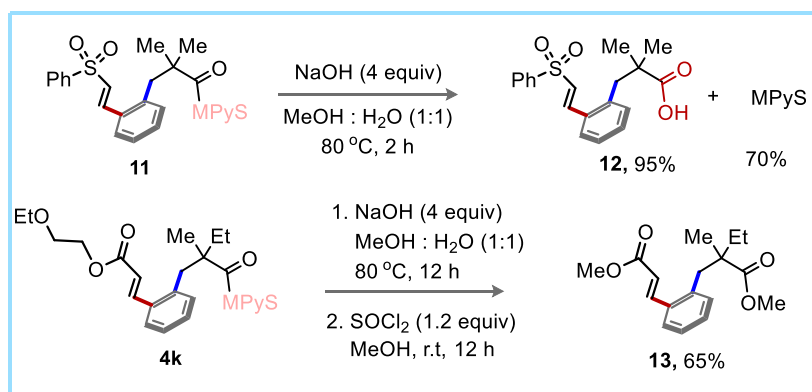
^a Subsequent acetoxylation reaction Conditions: **7** (0.1 mmol), $\text{PhI}(\text{OAc})_2$ (0.15 mmol), $\text{Pd}(\text{OAc})_2$ (10 mol%), AcOH (0.1 mL) at 70 °C, under air, 12 h. **8a**, **8b**, **8c**, **8d** were obtained in 2.7:1, 1:1, 2.4:1, 2.3:1 diastereomeric ratio, respectively.

We then focused on the Pd-catalyzed oxidative $C(sp^3)$ -H acetoxylation of these functionalized arenes using $\text{PhI}(\text{OAc})_2$ (Scheme 3.10).¹⁸ This process emphasizes the diverse role of MPyS in the oxidation of inert $C(sp^3)$ -H bonds, while tolerating the presence of the alkene functionality. Besides, it enables the construction of more complex molecular entities that are not easily accessible by conventional methods. Thus, the Pd-catalyzed MPyS-aided oxidative $C(sp^3)$ -H acetoxylation of the difunctionalized arenes (**7a-d**) in the presence of $\text{PhI}(\text{OAc})_2$ at 70 °C delivered the desired functionalized products **8a-d** in excellent yields (Scheme 3.10, of note, **8a**, **8b**, **8c**, and **8d** are obtained in 2.7:1, 1:1, 2.4:1, and 2.3:1 dr, respectively).

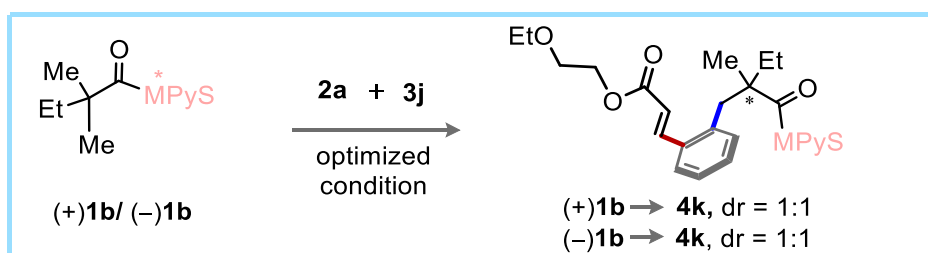
3.3.4. Application

To probe the synthetic utility of the difunctionalized products, a base-mediated hydrolysis of **11** to cleave MPyS was performed (Scheme 3.12). The desired MPyS-free product **12** (95%) was isolated along with 70% recovery of the MPyS pre-DG. Importantly, through base-mediated hydrolysis followed by methylation of the 1:1 diastereomeric mixture **4k**, compound **13** could be produced as a sole compound (Scheme

3.11). Lastly, the title reaction has been conducted with the optically pure MPyS coupled substrates (+)**1b** and (–)**1b** independently with **2a** and **3j**, which also delivered product **4k** in a 1:1 diastereomeric ratio (Scheme 3.12).



Scheme 3.11 Removal of the MPS-DG.

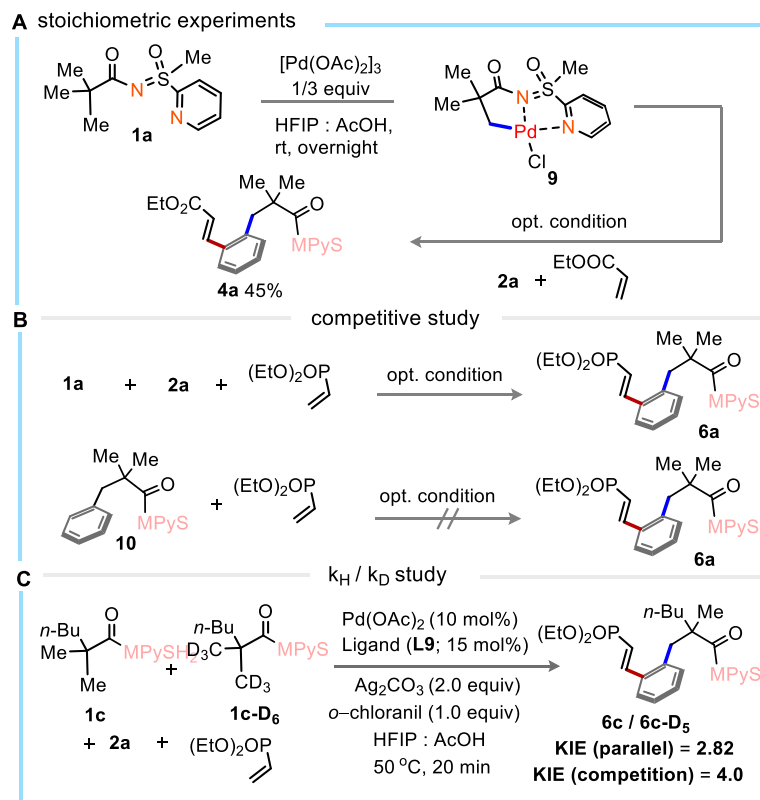


Scheme 3.12 Optically pure sulfoximine enabled transformations.

3.4. Mechanistic study

A series of mechanistic studies were then carried out (Scheme 3.11). The use of a stoichiometric amount of **1a** and $Pd(OAc)_2$ in a solvent mixture of HFIP and AcOH afforded the C–H activated palladium complex **9** in 80% yield (Scheme 3.13). Complex **9** could deliver the desired product **4a** when treated with 2-iodobenzoic acid and ethyl acrylate (Scheme 3.13). It is clearly indicating that monomeric C–H activated pallado-complex present in the reaction mixture. Besides, a competitive experiment involving **1a**, **2a** and diethyl vinyl phosphonate led to the desired product **6a** in 72% yield; this establishes a decarboxylative 1,2-Pd migration pathway (Scheme 3.13). On the other hand, the reaction of **10** with diethyl vinyl phosphonate did not deliver **6a**; thus,

alkenylation occurs via a decarboxylative pathway rather than C–H activation (Scheme 3.13)



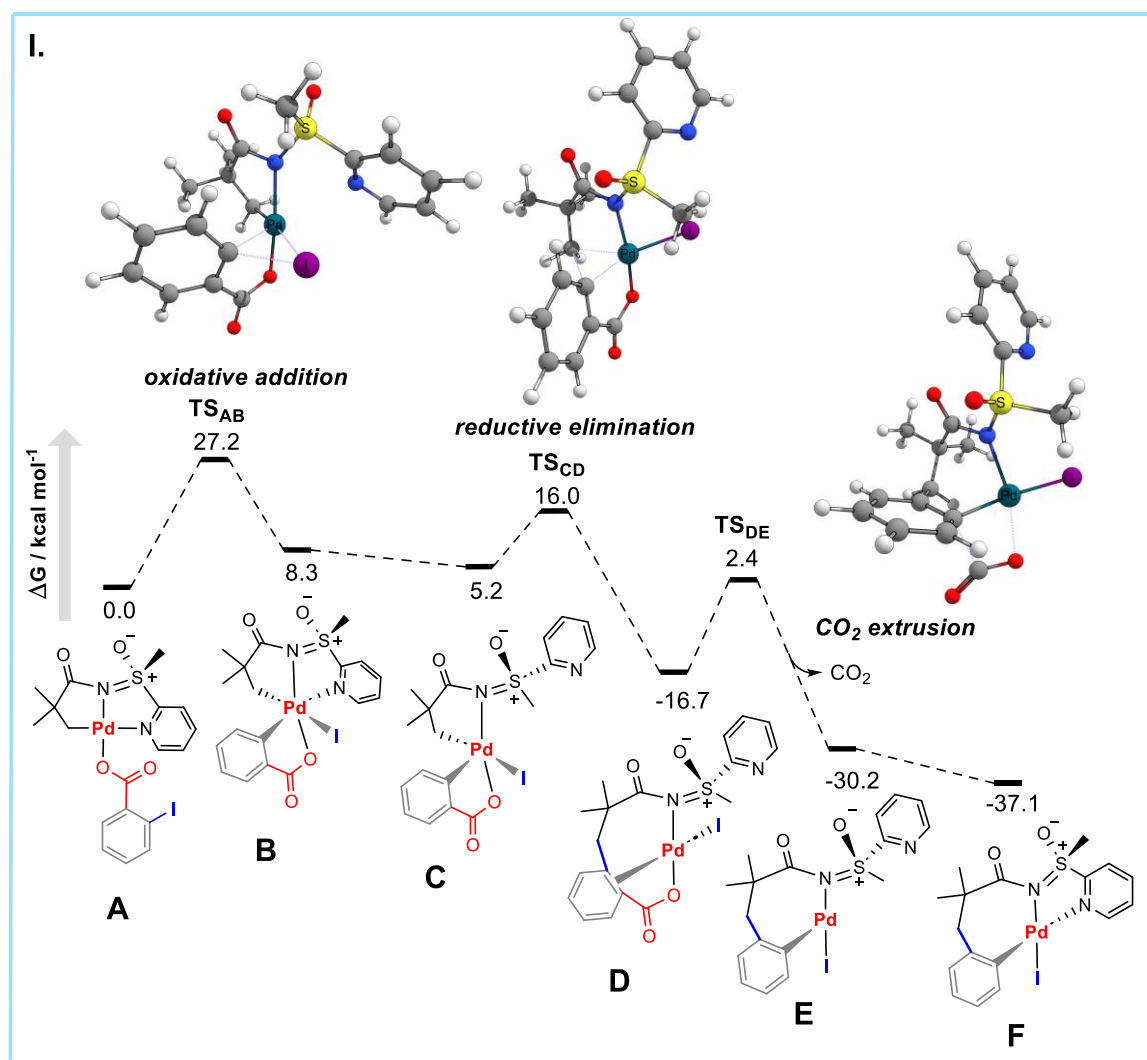
Scheme 3.13 Mechanistic studies.

The k_H/k_D [2.82 (parallel) and 4.0 (competition)] value indicated that C–H activation is the rate-determining step;^{14, 25} Accordingly, the reaction at first undergoes a $C(sp^3)$ – $C(sp^2)$ coupling (Scheme 3.13).

3.4.1. DFT study

To understand the reaction mechanism, density functional theory (DFT) calculations were performed. Based on our previous study on the Pd(II)-catalyzed annulative difunctionalization of two inert $C(sp^3)$ –H bonds by a BFR,¹⁴ minima and transition states were optimized at 343.15 K using the Gaussian 16¹⁹ software package, the ω B97X-D functional²⁰ and the basis sets LANL2DZ²¹ for Pd and I and 6-31+G(d,p)²² for the other elements (C, H, O, S, and N). The solvent effect of the acidic mixture HFIP:AcOH (1.1:1) was included using the SMD²³ model with the same functional but

with the Karlsruhe def2-QZVPP basis set.²⁴ The values discussed are Gibbs free energies (ΔG_{343} , kcal/mol). The formation of complex **A** (Figure 3.4, Part-I) was already discussed in our previous study (CMD process, rate-determining step).^{14, 25} The oxidative addition into the C(aryl)-I bond gives the octahedral Pd(IV) complex **B**. This step requires a high free energy of activation of 27.2 kcal/mol and is endergonic by 8.3 kcal/mol. Of note, the pyridine ligand is dissociated from the metal center in **TS_{AB}** but comes back moving along on the reaction coordinates. The dissociation of the pyridine moiety from **B** releases 3.1 kcal/mol to provide the square pyramidal complex **C**. The reductive elimination could only be modelled from **C** to form the



square planar Pd(II) complex **D** (-16.7 kcal/mol); this exergonic step passes through the **TS_{CD}**, located at 16.0 kcal/mol on the free energy surface. Next, elimination of CO₂ was modelled through **TS_{DE}** (2.4 kcal/mol). This step is also markedly exergonic,

providing the T-shaped complex **E** located at -30 kcal/mol. This time, ligation of the pyridine moiety of **E** produces the square planar complex **F**; the process is favorable (-37.1 kcal/mol). Of note, replacing the iodine ligand in **D** by CO_3^{2-} increases the decarboxylation barrier by about 10 kcal/mol, which means that this substitution is

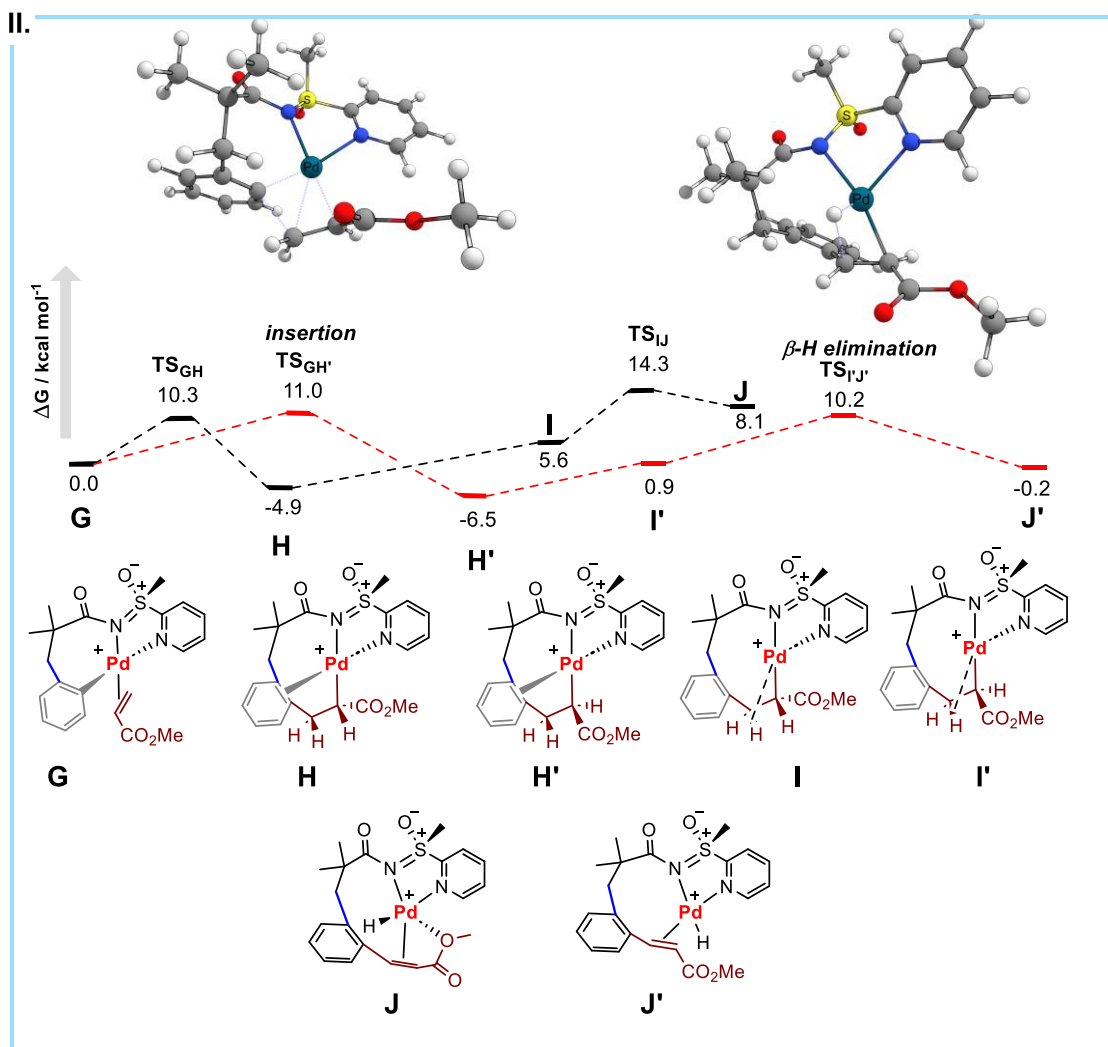


Figure 3.4. Free energy profile (ΔG_{343} , kcal/mol), neutral part and cationic part. Selected distances (in Å) are shown in the transition structures.

unlikely. This is in line with the fact that, in contrast with our previous study in which AgOAc was used,¹⁴ we do not observe products arising from a second CMD with Ag_2CO_3 . Then, we envisaged the substitution of the iodine ligand of the Pd(II) species **F** by methyl acrylate to give the cationic complex **G** (Figure 3.4, Part-II). The mode of alkene insertion into the Pd–C bond forms the two diastereomeric complexes **H** and **H'**, via **TS_{GH}** (10.3 kcal/mol) and **TS_{GH'}** (11.0 kcal/mol), respectively, followed by the

two agostic complexes **I** (marked in black) and **I'** (marked in red) in Figure 3.4, Part-II. The β -H elimination step leads to the respective palladium hydride species **J** and **J'**. The kinetically favored of these two pathways is the one marked in red, furnishing the *E*-isomer. The highest-lying transition state corresponds to the insertion at 11.0 kcal/mol (**TS_{GH}**). The *Z* pathway is hampered by the β -elimination step, requiring 14.3 kcal/mol (**TS_{IJ}**) of free energy of activation. The red *E*-pathway is virtually thermoneutral, but **J'** (−0.2 kcal/mol) corresponds to the experimentally observed stereoisomer and is much more stable than the *Z*-complex **J** (8.1 kcal/mol).

3.5. Conclusion

In summary, a three-component coupling protocol was developed for the regioselective synthesis of 1,2-difunctionalized arenes. The successful formation of β - $C(sp^3)$ - C (arene) and σ - $C(sp^2)$ - C (arene) bonds in a unified process was achieved by employing a combination of a Pd(II) catalyst, a bidentate MPyS-DG, a ligand (specifically 2-chloro-5-trifluoromethyl or 2-chloro-5-bromo pyridine ligands) along with Ag_2CO_3 and *o*-chloranil oxidants. The transformation tolerates common functional groups, providing access to a large range of modular 1,2-difunctionalized arenes, which can undergo further functionalization. DFT and mechanistic investigations offer valuable insights regarding the occurrence of 1,2-Pd migration through decarboxylation, which is rare outside the realm of norbornene-assisted Catellani processes.²⁶

3.6. Experimental

3.6.1. General Experimental Information

All the reactions were performed in an oven-dried 5 mL screw capped pressure tube. Commercial grade solvents were distilled prior to use. Column chromatography was performed using either 100–200 Mesh or 230–400 Mesh silica gel. Thin layer chromatography (TLC) was performed on silica gel GF254 plates. The spots on TLC plates were detected with UV light (254 nm) and staining over molecular iodine. Proton and carbon nuclear magnetic resonance spectra (1H and ^{13}C NMR) were recorded based on the resonating frequencies as follows: (1H NMR, 400 MHz; ^{13}C NMR, 101 MHz) and (1H NMR, 500 MHz; ^{13}C NMR, 126 MHz) having the solvent resonance as internal

standard (^1H NMR, CHCl_3 at 7.26 ppm; ^{13}C NMR, CDCl_3 at 77.0 ppm). In few cases, tetramethylsilane (TMS) was used as reference standard at 0.00 ppm. Data for ^1H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet; bs = broad singlet; d = doublet; bd = broad doublet, t = triplet; bt = broad triplet; q = quartet; dd = doublet of doublet; td = triplet of doublet, dt = doublet of triplet, ddd; doublet of doublet of doublet; m = multiplet), coupling constants, J , in Hz, and integration. Data for ^{13}C NMR are reported as chemical shifts (ppm). IR spectra were reported in cm^{-1} . High resolution mass spectra were obtained in ESI mode in the Maxis-TOF analyzer. X-ray data was collected at 298 K using graphite monochromated Mo- $K\alpha$ radiation (0.71073 Å). Melting points were determined by electro-thermal heating and are uncorrected.

3.6.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Dichloromethane (DCM) and chloroform were distilled over CaH_2 . Acetic acid was distilled over KMnO_4 . Tetrahydrofuran (THF) was freshly distilled over sodium/benzophenone ketyl under nitrogen. $\text{Pd}(\text{OAc})_2$, PdCl_2 , $\text{Pd}(\text{OTFA})_2$, $\text{Pd}(\text{acac})_2$, $\text{Pd}(\text{CH}_3\text{CN})_2(\text{Cl})_2$, NaBrO_3 were purchased from commercially available sources and used as received. All pyridine ligands, sodium and potassium salts, oxidants such as $\text{Na}_2\text{S}_2\text{O}_8$, $\text{PhI}(\text{OAc})_2$, BQ, TBHP, oxone, $\text{K}_2\text{S}_2\text{O}_8$, and various silver salts and benzoquinones were purchased from commercially available sources and used as received. Analytical and spectral data of all known compounds exactly match the reported values.

3.6.3. Experimental Procedures and Analytical Data

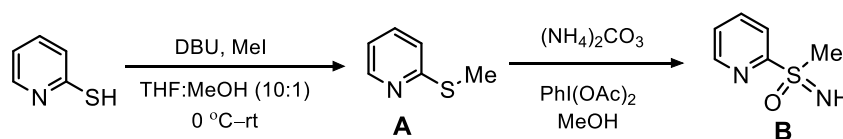
3.6.3.1. Preparation of *S*-methyl-*S*-2-pyridylsulfoximine (MPyS) (40):²⁷

Part- I ^{27a}

To a solution of 2-mercaptopyridine (100 mmol, 11.11 g) in dry THF (200 mL) and CH_3CN (20 mL), cooled to 0 °C, was added DBU (110 mmol, 16.75 g). The resulting mixture was stirred at 0 °C for 5 min before MeI (110 mmol, 15.61 g) was slowly added. The ice bath was removed and the mixture was stirred overnight. The reaction mixture was washed with water (100 mL) and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated. The residue was purified by column chromatography (n-hexane-EtOAc 2:1) to afford the methyl 2-pyridyl sulfide (A) as a colorless oil.

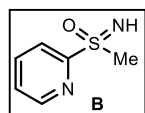
Part- II ^{27b}

To a stirred solution of sulfide (1 mmol) in MeOH (10 ml) was added the $(NH_4)_2CO_3$ (1.5 equiv.). Subsequently, $PhI(OAc)_2$ (2.3 equiv) was added and the solution was stirred at rt. After the disappearance of the sulfide (checked by TLC), the solvent was removed under reduced pressure. The crude product was purified by column chromatography (DCM-MeOH 10:1) to afford the *S*-Methyl-*S*-2-pyridylsulfoximine (**B**) as a colorless oil.



Scheme 3.14. Preparation of MPyS

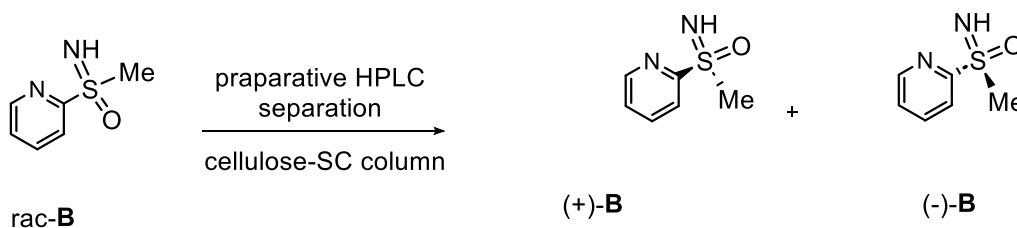
***S*-Methyl-*S*-2-pyridylsulfoximine (MPyS) (**B**):**



¹H NMR (400 MHz, $CDCl_3$) δ 8.73 (bd, $J = 4.0$ Hz, 1H), 8.13 (bd, $J = 7.6$ Hz, 1H), 7.95 (td, $J = 7.7, 1.3$ Hz, 1H), 7.51 (dd, $J = 6.8, 4.8$ Hz, 1H), 3.26 (s, 3H), 2.89 (bs, 1H, NH). ¹³C NMR (101 MHz, $CDCl_3$) δ 160.4, 150.0, 138.2, 126.7, 121.1, 42.3.

3.6.3.2. Separation of enantiopure sulfoximines by preparative chiral HPLC

The enantiomers of sulfoximine **B** were separated using LC/Forte YMC-make preparative HPLC (Column: CHIRAL ART Cellulose-SC, mobile phase: *n*-hexane:EtOH:DEA = (80:20:0.1), flow rate: 15 mL/min, uv-230 nm, pressure: 5.7 mPA). This resolution has been successfully performed on a 2.0 g batch. The two fractions were isolated within 10–30 min retention time. The solvents were removed to yield the enantiopure sulfoximines which were used for the next step. DEA = diethylamine.

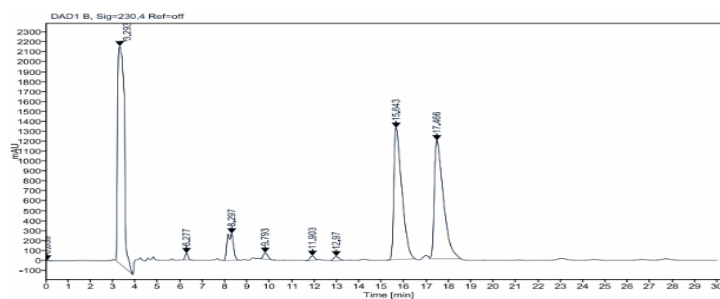


Scheme 3.15. Procedure for racemic MPyS separation

YMC INDIA PVT LTD.

YMC

Sample name: YMC-PP-08-23-238-Crude
 Sample type: Sample
 Injection date: 8/28/2023 12:51:43 PM
 Acq. operator: Gurunaidu
 Instrument ID: YMC-ARD-AI-001
 Location: P2-A2
 Injection volume: 10,000



Signal: DAD1 B, Sig=230,4 Ref=off

RT [min]	Area	Area%	RRT
0.04	5.07	0.00	
3.29	44165.47	37.24	
6.28	577.96	0.49	
8.30	5172.98	4.36	
9.79	869.86	0.73	
11.90	667.71	0.56	
12.97	736.09	0.62	
15.64	32629.51	27.68	
17.47	33586.41	28.32	
Sum	118611.0506		

HPLC Report New.rdl [Rev. 7]

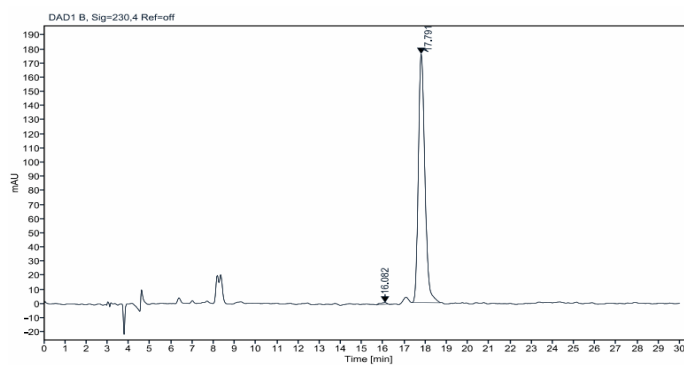
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YMC INDIA PVT LTD.

YMC

Sample name: YMC-PP-08-23-238-Peak-2
 Sample type: Sample
 Injection date: 8/28/2023 12:20:35 PM
 Acq. operator: Gurunaidu
 Instrument ID: YMC-ARD-AI-001
 Location: P2-A4
 Injection volume: 20,000



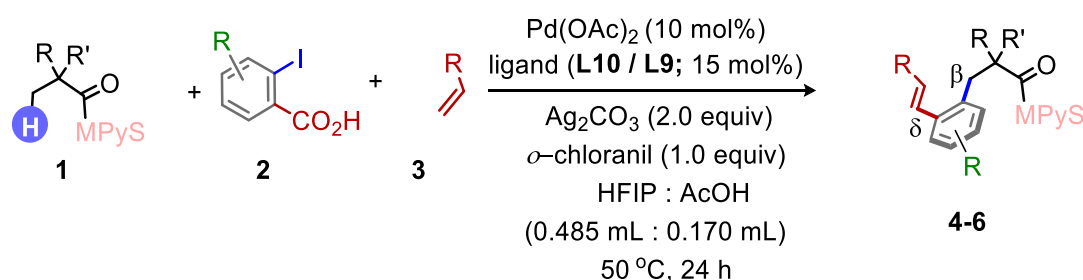
Signal: DAD1 B, Sig=230,4 Ref=off

RT [min]	Area	Area%	RRT
16.08	28.96	0.76	
17.79	3761.63	99.24	
Sum	3790.5866		

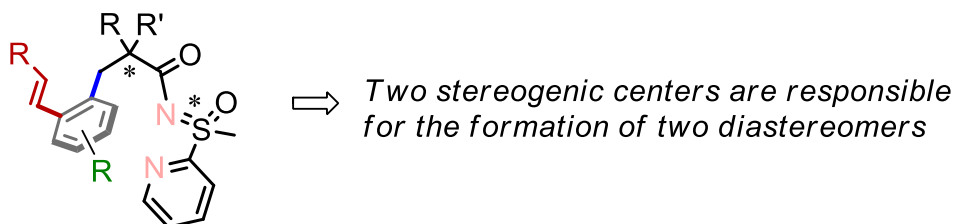
3.6.3.3. Preparation of ligands:

All ligands (see Table 3.2) were obtained from commercial sources.

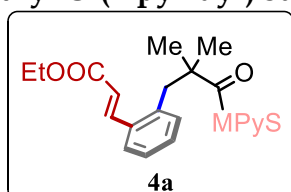
3.6.3.4. General Procedure for Three Component C–H Bond Addition Reaction (GP–3):



A 5 mL screw capped tube equipped with a magnetic stir bar was charged with Pd(OAc)_2 (10 mol%, 4.5 mg), substrate **1** (0.2 mmol), Ag_2CO_3 (0.4 mmol, 110 mg), *o*-chloranil (0.2 mmol, 49 mg), 2-iodobenzoic acid derivative **2** (0.4 mmol), alkene surrogate **3** (0.4 mmol), and **L10** (15 mol%, 5.44 mg) / **L9** (15 mol%, 5.77 mg) in air. Then, a solvent combination of HFIP (0.97 mL) and AcOH (0.34 mL) was added via syringe. The reaction mixture was stirred at 50 °C for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (DCM), filtered through a small Celite pad, and concentrated in vacuo. The crude reaction mixture was extracted with DCM and washed with saturated NaHCO_3 solution, and concentrated in vacuo. Finally, the reaction mixture was purified on silica gel using hexane/EtOAc eluent to afford the desired products.



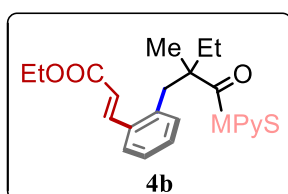
N-[(*E*)-2-(2-(3-Methoxy-3-oxoprop-1-en-1-yl) benzyl)-2-methyl butanoic acid]-*S*-methyl-*S*-(2-pyridyl) sulfoximine (**4a**):



Following the general procedure GP–3, the compound **4a** (50 mg, 60%, colorless thick liquid) was prepared from the reaction of **1a**, **2a**, and **3a**. ^1H NMR (500 MHz, CDCl_3) δ 8.69 (d, J = 4.0

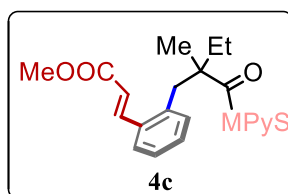
Hz, 1H), 8.26 (d, $J = 7.9$ Hz, 1H), 8.12 (d, $J = 15.8$ Hz, 1H), 8.03–7.93 (m, 1H), 7.54 (dd, $J = 11.3, 8.5$ Hz, 2H), 7.24–7.11 (m, 3H), 6.31 (d, $J = 15.8$ Hz, 1H), 4.25 (dd, $J = 14.2, 7.1$ Hz, 2H), 3.44 (s, 3H), 3.13–3.05 (m, 2H), 1.32 (t, $J = 7.1$ Hz, 3H), 1.12 (s, 3H), 1.09 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 186.5, 166.9, 158.2, 149.6, 143.6, 139.0, 138.0, 134.8, 132.0, 129.2, 126.9, 126.6, 126.5, 123.2, 119.6, 60.2, 46.5, 41.7, 39.6, 25.7, 25.5, 14.3. IR (Neat) ν_{max} 2967, 2928, 1425, 1216, 1166, 1040, 982, 758 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{22}H_{27}N_2O_4S^+$ $[M+H]$, 415.17; found 415.16.

N-[(E)-2-(2-(3-Ethoxy-3-oxoprop-1-en-1-yl) benzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4b):



Following the general procedure GP-3, the compound **4b** (57 mg, 67%, colorless thick liquid) was prepared from the reaction of **1b**, **2a**, and **3a**. 1H NMR (500 MHz, $CDCl_3$) δ 8.68 (ddd, $J = 13.5, 3.9, 0.7$ Hz, 1H), 8.27 (d, $J = 7.9$ Hz, 1H), 8.13 (dd, $J = 18.8, 15.8$ Hz, 1H), 7.97 (td, $J = 7.9, 1.6$ Hz, 1H), 7.57–7.48 (m, 2H), 7.24–7.11 (m, 3H), 6.31 (dd, $J = 15.8, 6.8$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 3.43 & 3.42 (two s, 3H), 3.19 (t, $J = 14.0$ Hz, 1H), 3.00 (dd, $J = 13.9, 3.3$ Hz, 1H), 1.92–1.83 (m, 1H), 1.45–1.41 (m, 1H), 1.33 (t, $J = 7.2$ Hz, 3H), 0.94 & 0.93 (two s, 3H), 0.84 & 0.79 (two t, $J = 7.5$ Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 186.2, 167.1, 157.38 & 157.30 (1C), 149.6, 143.5, 138.7, 138.10 & 138.04 (1C), 134.3, 131.7, 129.44 & 129.35 (1C), 127.1, 126.53 & 126.46 (1C), 126.37 & 126.30 (1C), 123.6, 119.0, 60.4, 50.31 & 50.16 (1C), 40.87 & 40.69 (1C), 39.6, 33.08 & 32.92 (1C), 19.98 & 19.85 (1C), 14.3, 9.01 & 8.96 (1C). IR (Neat) ν_{max} 2967, 2928, 1708, 1629, 1425, 1216, 1166, 1040, 982, 758 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{23}H_{29}N_2O_4S^+$ $[M+H]$, 429.1843; found 429.1845.

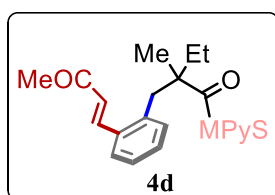
N-[(E)-2-(2-(3-Methoxy-3-oxoprop-1-en-1-yl) benzyl)-2-methylbutanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4c):



Following the general procedure GP-3, the compound **4c** (44 mg, 53%, colorless thick liquid) was prepared from the reaction of **1b**, **2a**, and **3b**. 1H NMR (500 MHz, $CDCl_3$) δ 8.68 (ddd, $J = 13.7, 4.7, 0.8$ Hz, 1H), 8.26 (d, $J = 7.9$ Hz, 1H), 8.13 (dd, $J = 20.0,$

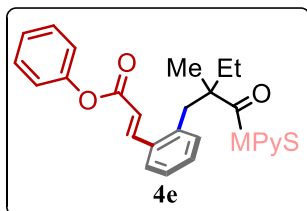
15.8 Hz, 1H), 7.97 (td, $J = 7.7, 1.3$ Hz, 1H), 7.56–7.52 (m, 2H), 7.29–7.12 (m, 3H), 6.31 (dd, $J = 15.8, 6.8$ Hz, 1H), 3.79 (s, 3H), 3.42 & 3.41 (two s, 3H), 3.22–3.15 (m, 1H), 2.99 (dd, $J = 13.9, 2.6$ Hz, 1H), 1.93–1.85 (m, 1H), 1.45–1.34 (m, 1H), 0.93 & 0.91 (two s, 3H), 0.83 & 0.78 (two t, $J = 7.5$ Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 186.16 & 186.13 (1C), 167.53 & 167.48 (1C), 157.39 & 157.31 (1C), 149.55 & 149.53 (1C), 143.78 & 143.74 (1C), 138.71 & 138.69 (1C), 138.08 & 138.02 (1C), 134.27 & 134.24 (1C), 131.74 & 131.70 (1C), 129.48 & 129.40 (1C), 127.05 & 127.04 (1C), 126.53 & 126.47 (1C), 126.38 & 126.32 (1C), 123.59 & 123.56 (1C), 118.58 & 118.54 (1C), 51.6, 50.29 & 50.15 (1C), 40.91 & 40.71 (1C), 39.5, 33.04 & 32.90 (1C), 20.00 & 19.91 (1C), 8.99 & 8.94 (1C). IR (Neat) ν_{max} 2925, 1704, 1623, 1424, 1197, 977, 758 cm^{-1} . HRMS (ESI) m/z : $[M+H]$ calcd. for $C_{22}H_{27}N_2O_4S$, 415.1686; found 415.1689.

N-[(*E*)-2-Methyl-2-(2-(3-oxobut-1-en-1-yl) benzyl) butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4d):



Following the general procedure GP-3, the compound **4d** (62 mg, 78%, colorless thick liquid) was prepared from the reaction of **1b**, **2a**, and **3c**. 1H NMR (500 MHz, $CDCl_3$) δ 8.67 (ddd, $J = 19.2, 4.7, 0.7$ Hz, 1H), 8.23 (d, $J = 8.0$ Hz, 1H), 8.01–7.90 (m, 2H), 7.57–7.50 (m, 2H), 7.28–7.15 (m, 3H), 6.57 (dd, $J = 16.0, 2.2$ Hz, 1H), 3.39 (s, 3H), 3.20 (dd, $J = 13.8, 11.7$ Hz, 1H), 2.96 (d, $J = 13.9$ Hz, 1H), 2.37 & 2.35 (two s, 3H), 1.88–1.82 (m, 1H), 1.43–1.35 (m, 1H), 0.96 (s, 3H), 0.83 & 0.79 (two t, $J = 7.5$ Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 198.6, 186.14 & 186.11 (1C), 157.29 & 157.20 (1C), 149.58 & 149.57 (1C), 142.35 & 142.32 (1C), 138.9, 138.09 & 138.01 (1C), 134.22 & 134.15 (1C), 131.97 & 131.95 (1C), 129.63 & 129.56 (1C), 128.03 & 127.82 (1C), 127.10 & 127.08 (1C), 126.63 & 126.59 (1C), 126.33 & 126.31 (1C), 123.52 & 123.50 (1C), 50.14 & 50.03 (1C), 41.00 & 40.90 (1C), 39.56 & 39.51 (1C), 33.08 & 32.97 (1C), 27.62 & 27.50 (1C), 20.19 & 20.15 (1C), 9.01 & 8.98 (1C). IR (Neat) ν_{max} 2930, 1717, 1629, 1424, 1216, 975, 754 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{22}H_{27}N_2O_3S^+$ $[M+H]$, 399.1737; found 399.1735.

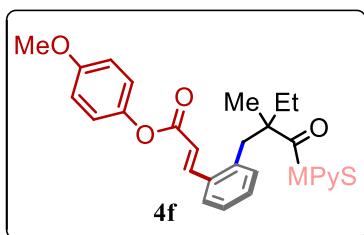
N-[(*E*)-2-Methyl-2-(2-(3-oxo-3-phenoxyprop-1-en-1-yl) benzyl) butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4e):



Following the general procedure GP-3, the compound **4e** (38 mg, 40%, colorless thick liquid) was prepared from the reaction of **1b**, **2a**, and **3d**. The unreacted starting material **1b** (17 mg, 33%) was recovered. ^1H NMR (500 MHz, CDCl_3) δ 8.70–

8.64 (m, 1H), 8.40–8.30 (m, 1H), 8.29–8.24 (m, 1H), 7.98–7.89 (m, 1H), 7.66–7.61 (m, 1H), 7.57–7.48 (m, 1H), 7.44–7.36 (m, 2H), 7.30–7.12 (m, 7H), 6.53 (dd, $J = 15, 10$ Hz, 1H), 3.41 (s, 3H), 3.23 (dd, $J = 21.6, 13.9$ Hz, 1H), 3.03 (dd, $J = 13.8, 11.0$ Hz, 1H), 1.90 (dtd, $J = 14.9, 7.5, 5.8$ Hz, 1H), 1.48–1.36 (m, 1H), 0.97 (bs, 3H), 0.85 & 0.79 (two t, $J = 7.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.10 & 186.05 (1C), 165.56 & 165.49 (1C), 157.39 & 157.30 (1C), 150.9, 149.5, 145.49 & 145.44 (1C), 139.03 & 139.01 (1C), 138.09 & 138.01 (1C), 134.00 & 133.96 (1C), 131.9, 129.89 & 129.82 (1C), 129.3, 127.06 & 127.03 (1C), 126.66 & 126.60 (1C), 126.51 & 126.44 (1C), 125.7, 123.63 & 123.58 (1C), 121.67 & 121.65 (1C), 117.91 & 117.86 (1C), 50.30 & 50.15 (1C), 40.96 & 40.79 (1C), 39.6, 33.03 & 32.94 (1C), 20.05 & 19.96 (1C), 9.02 & 8.96 (1C); IR (Neat) ν_{max} 2930, 1723, 1623, 1453, 1162, 1132, 976, 758 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{27}\text{H}_{28}\text{N}_2\text{NaO}_4\text{S}^+$ [$\text{M}+\text{Na}$], 499.1662; found 499.1665.

N-[(*E*)-2-(2-(3-(4-methoxyphenoxy)-3-oxoprop-1-en-1-yl) benzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4f):

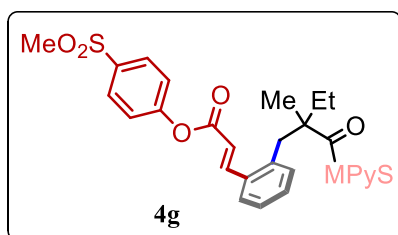


Following the general procedure GP-3, the compound **4f** (45 mg, 45%, colorless thick liquid) was prepared from the reaction of **1b**, **2a**, and **3e**. The unreacted starting material **1b** (15 mg, 30%) was recovered. ^1H NMR (500 MHz,

CDCl_3) δ 8.70–8.61 (m, 1H), 8.36–8.22 (m, 2H), 7.92 (tt, $J = 9.4, 4.7$ Hz, 1H), 7.64–7.56 (m, 1H), 7.52–7.46 (m, 1H), 7.29–7.15 (m, 3H), 7.11–7.04 (m, 2H), 6.93–6.86 (m, 2H), 6.48 (dt, $J = 12.7, 6.4$ Hz, 1H), 3.78 (s, 3H), 3.39 & 3.38 (two s, 3H), 3.21 (dd, $J = 20.7, 13.9$ Hz, 1H), 3.01 (dd, $J = 13.8, 10.9$ Hz, 1H), 1.93–1.81 (m, 1H), 1.46–1.35 (m, 1H), 0.96 (s, 3H), 0.85 & 0.78 (two t, $J = 7.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.10 &

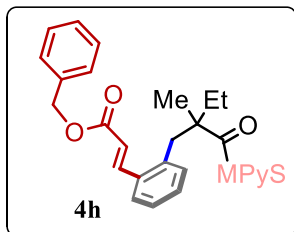
186.06 (1C), 165.92 & 165.85 (1C), 157.37 & 157.28 (1C), 157.2, 149.5, 145.30 & 145.25 (1C), 144.37 & 144.35 (1C), 138.98 & 138.97 (1C), 138.09 & 138.01 (1C), 134.04 & 134.00 (1C), 131.9, 129.83 & 129.76 (1C), 127.06 & 127.03 (1C), 126.64 & 126.58 (1C), 126.49 & 126.42 (1C), 123.62 & 123.56 (1C), 122.39 & 122.37 (1C), 117.98 & 117.93 (1C), 114.4, 55.6, 50.28 & 50.14 (1C), 40.94 & 40.77 (1C), 39.6, 33.01 & 32.92 (1C), 20.05 & 19.96 (1C), 9.00 & 8.95 (1C). **IR (Neat)** $\nu_{\max}$ 2967, 2360, 1722, 1628, 1503, 1190, 1132, 1029, 842, 759 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_5\text{S}^+$ $[\text{M}+\text{H}]$, 507. 1948; found 507. 1947.

N-[(E)-2-methyl-2-(2-(3-(4-(methylsulfonyl) phenoxy)-3-oxoprop-1-en-1-yl) benzyl) butanoic acid]-S-methyl-S-2-(pyridyl) sulfoximine (4g):



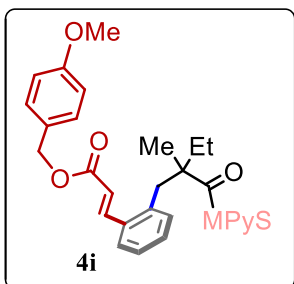
Following the general procedure GP-3, the compound **4g** (61 mg, 55% colorless thick liquid) was prepared from the reaction of **1b**, **2a**, and **3f**. ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.64 (m, 1H), 8.43–8.31 (m, 1H), 8.25 (d, $J = 7.9$ Hz, 1H), 8.02–7.92 (m, 2H), 7.74–7.50 (m, 3H), 7.43–7.38 (m, 2H), 7.33–7.21 (m, 3H), 6.51 (dd, $J = 15.7, 9.1$ Hz, 1H), 3.40 (s, 3H), 3.29–3.21 (m, 1H), 3.07 (s, 3H), 3.04–2.97 (m, 1H), 1.95–1.84 (m, 1H), 1.44–1.37 (m, 1H), 0.96 & 0.95 (two s, 3H), 0.84 & 0.78 (two t, $J = 7.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.02 & 185.96 (1C), 164.73 & 164.63 (1C), 157.29 & 157.19 (1C), 155.00 & 154.97 (1C), 149.6, 146.71 & 146.64 (1C), 139.22 & 139.20 (1C), 138.08 & 138.01 (1C), 137.6, 133.61 & 133.56 (1C), 132.1, 130.24 & 130.19 (1C), 129.5, 129.1, 127.12 & 127.09 (1C), 126.74 & 126.69 (1C), 126.53 & 126.47 (1C), 123.61 & 123.53 (1C), 122.75 & 122.73 (1C), 116.84 & 116.77 (1C), 116.0, 50.22 & 50.10 (1C), 44.6, 41.03 & 40.80 (1C), 39.60 & 39.59 (1C), 33.0, 20.11 & 20.08 (1C), 9.00 & 8.94 (1C). **IR (Neat)** $\nu_{\max}$ 2924, 1729, 1626, 1310, 1291, 1199, 1124, 957, 854, 760 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd for $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_6\text{S}_2^+$ $[\text{M}+\text{H}]$, 555.1618; found 555.1618.

N-[(E)-2-(2-(3-(benzyloxy)-3-oxoprop-1-en-1-yl) benzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4h):



Following the general procedure GP-3, the compound **4h** (49 mg, 50% colorless thick liquid) was prepared from the reaction of **1b**, **2a**, and **3g**. ^1H NMR (500 MHz, CDCl_3) δ 8.67 (ddd, J = 12.2, 6.1, 5.3 Hz, 1H), 8.26 (d, J = 7.9 Hz, 1H), 8.24–8.16 (m, 1H), 7.99–7.93 (m, 1H), 7.53 (dt, J = 7.7, 5.6 Hz, 2H), 7.44–7.30 (m, 5H), 7.27–7.13 (m, 3H), 6.37 (dd, J = 15.8, 7.2 Hz, 1H), 5.25 (d, J = 3.6 Hz, 2H), 3.40 (s, 3H), 3.20 (dd, J = 16.3, 14.0 Hz, 1H), 3.00 (dd, J = 13.8, 4.9 Hz, 1H), 1.93–1.85 (m, 1H), 1.45–1.36 (m, 1H), 0.95 & 0.94 (two s, 3H), 0.84 & 0.79 (two t, J = 7.5 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.12 & 186.09 (1C), 166.89 & 166.84 (1C), 157.40 & 157.32 (1C), 149.54 & 149.51 (1C), 144.13 & 144.09 (1C), 138.8, 138.07 & 138.01 (1C), 136.2, 134.19 & 134.16 (1C), 131.76 & 131.72 (1C), 129.57 & 129.49 (1C), 128.5, 128.12, 128.1, 127.0, 126.54 & 126.48 (1C), 126.37 & 126.30 (1C), 123.59 & 123.57 (1C), 118.54 & 118.50 (1C), 66.2, 50.29 & 50.15 (1C), 40.92 & 40.75 (1C), 39.5, 33.09 & 32.95 (1C), 20.01 & 19.87 (1C), 8.99 & 8.95 (1C). IR (Neat) ν_{max} 2930, 1708, 1629, 1453, 1215, 1157, 978, 756 cm^{-1} . HRMS (ESI-TOF) m/z : calcd for $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_4\text{S}^+$ $[M+H]^+$, 491.1999; found 491.1997.

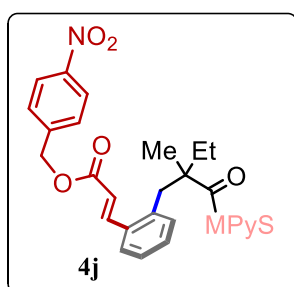
N-[(E)-2-(2-(3-((4-methoxybenzyl) oxy)-3-oxoprop-1-en-1-yl) benzyl)-2-methylbutanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4i):



Following the general procedure GP-3, the compound **4i** (56 mg, 54% colorless thick liquid) was prepared from the reaction of **1b**, **2a**, and **3h**. ^1H NMR (500 MHz, CDCl_3) δ 8.72–8.65 (m, 1H), 8.27 (dd, J = 7.9, 0.8 Hz, 1H), 8.21 – 8.13 (m, 1H), 7.96 (dd, J = 11.4, 4.2 Hz, 1H), 7.56–7.48 (m, 2H), 7.35 (d, J = 7.7 Hz, 2H), 7.25–7.12 (m, 3H), 6.90 (d, J = 7.9 Hz, 2H), 6.34 (dd, J = 15.8, 7.0 Hz, 1H), 5.18 (d, J = 3.0 Hz, 2H), 3.81 (s, 3H), 3.41 (s, 3H), 3.23–3.17 (m, 1H), 2.99 (dd, J = 13.8, 3.1 Hz, 1H), 1.94–1.82 (m, 1H), 1.46–1.33 (m, 1H), 0.94 & 0.92 (two s, 3H), 0.84 & 0.78 (two t, J = 7.5 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.2, 167.00 & 166.96 (1C), 159.6, 157.43 & 157.35 (1C), 149.57 & 149.54 (1C), 143.98 & 143.94 (1C), 138.8, 138.09 & 138.03 (1C),

134.2, 131.76 & 131.71 (1C), 130.0, 129.54 & 129.45 (1C), 128.3, 127.0, 126.55 & 126.49 (1C), 126.38 & 126.31 (1C), 123.63 & 123.61 (1C), 118.71 & 118.68 (1C), 114.0, 66.0, 55.3, 50.32 & 50.17 (1C), 40.92 & 40.75 (1C), 39.5, 33.12 & 32.95 (1C), 20.01 & 19.87 (1C), 9.02 & 8.97 (1C). **IR (Neat)** $\nu_{\max}$ 2930, 1707, 1630, 1216, 1157, 980, 761 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{29}\text{H}_{33}\text{N}_2\text{O}_5\text{S}^+$ $[\text{M}+\text{H}]$, 521.2105; found 521.2106.

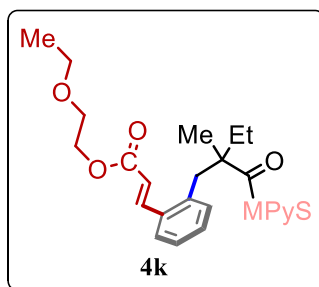
N-[(E)-2-methyl-2-(2-(3-((4-nitrobenzyl) oxy)-3-oxoprop-1-en-1-yl) benzyl) butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4j):



Following the general procedure GP-3, the compound **4j** (61 mg, 57% colorless thick liquid), was prepared from the reaction of **1b**, **2a**, and **3i**. **^1H NMR (500 MHz, CDCl_3)** δ 8.70–8.65 (m, 1H), 8.30–8.17 (m, 4H), 7.97 (td, J = 7.8, 1.4 Hz, 1H), 7.61–7.51 (m, 4H), 7.24–7.15 (m, 2H), 6.43–6.34 (m, 1H), 5.37–5.30 (m, 2H),

3.41 & 3.40 (two s, 3H), 3.20 (dd, J = 17.8, 13.9 Hz, 1H), 2.99 (dd, J = 13.9, 2.3 Hz, 1H), 1.90–1.84 (m, 1H), 1.45–1.36 (m, 1H), 0.94 & 0.93 (two s, 3H), 0.83 & 0.78 (two t, J = 7.5 Hz, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)** δ 186.09 & 186.03 (1C), 166.54 & 166.47 (1C), 157.37 & 157.28 (1C), 149.59 & 149.56 (1C), 147.6, 144.92 & 144.86 (1C), 143.55 & 143.52 (1C), 138.94 & 138.90 (1C), 138.11 & 138.05 (1C), 133.93 & 133.88 (1C), 131.9, 129.85 & 129.78 (1C), 128.22 & 128.20 (1C), 127.09 & 127.08 (1C), 126.65 & 126.58 (1C), 126.39 & 126.33 (1C), 123.8, 123.66 & 123.62 (1C), 117.72 & 117.66 (1C), 64.67 & 64.65 (1C), 50.24 & 50.12 (1C), 40.97 & 40.61 (1C), 39.6, 32.98 & 32.93 (1C), 20.05 & 19.96 (1C), 9.02 & 8.96 (1C). **IR (Neat)** $\nu_{\max}$ 3015, 2968, 1738, 1627, 1518, 1452, 1346, 1312, 1215, 1151, 980 766 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd for $\text{C}_{28}\text{H}_{30}\text{N}_3\text{O}_6\text{S}^+$ $[\text{M}+\text{H}]$, 536.1850; found 536.1850.

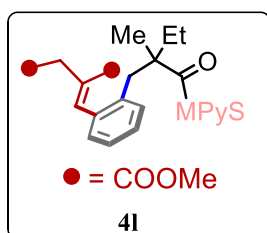
N-[(E)-2-(2-(3-(2-ethoxyethoxy)-3-oxoprop-1-en-1-yl) benzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4k):



Following the general procedure GP-3, the compound **4k** (55 mg, 58% colorless thick liquid) was prepared from the reaction of **1b**, **2a**, and **3j**. **^1H NMR (500 MHz, CDCl_3)** δ 8.72–8.63 (m, 1H), 8.26 (dd, J = 7.9, 0.8 Hz, 1H), 8.15 (dd, J = 18.4, 15.8 Hz, 1H), 7.97 (td, J = 7.7, 1.2 Hz, 1H), 7.55–7.49 (m, 2H), 7.27–7.11 (m, 3H), 6.36 (dd, J

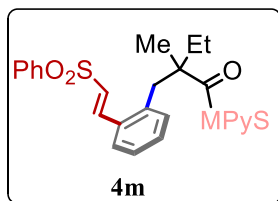
= 15.8, 7.0 Hz, 1H), 4.35–4.31 (m, 2H), 3.70 (t, J = 3.8 Hz, 2H), 3.56 (qd, J = 7.0, 0.8 Hz, 2H), 3.42 (s, 3H), 3.19 (t, J = 13.3 Hz, 1H), 2.99 (dd, J = 13.8, 1.7 Hz, 1H), 1.93–1.82 (m, 1H), 1.45–1.34 (m, 1H), 1.22 (t, J = 7.0 Hz, 3H), 0.93 & 0.92 (two s, 3H), 0.84 & 0.78 (two t, J = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 186.12 & 186.09 (1C), 167.06 & 167.02 (1C), 157.36 & 157.27 (1C), 149.55 & 149.52 (1C), 143.90 & 143.87 (1C), 138.7, 138.08 & 138.02 (1C), 134.21 & 134.18 (1C), 131.71 & 131.65 (1C), 129.52 & 129.43 (1C), 127.0, 126.53 & 126.46 (1C), 126.37 & 126.30 (1C), 123.60 & 123.59 (1C), 118.60 & 118.56 (1C), 68.4, 66.6, 63.7, 50.30 & 50.14 (1C), 40.91 & 40.74 (1C), 39.5, 33.16 & 32.96 (1C), 19.95 & 19.78 (1C), 15.1, 8.99 & 8.94 (1C). IR (Neat) ν_{max} 2969, 2929, 2873, 1708, 1630, 1311, 1216, 1170, 1123, 1043, 980, 842, 762 cm^{-1} . HRMS (ESI-TOF) m/z : calcd for $C_{25}H_{33}N_2O_5S^+$ [M+H], 473.2105; found 473.2100.

N-[(*E*)-2-(2-(4-methoxy-2-(methoxycarbonyl)-4-oxobut-1-en-1-yl) benzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4l):



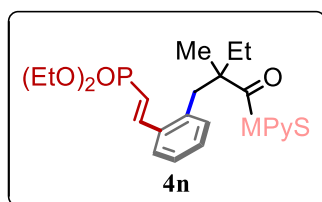
Following the general procedure GP-3, the compound **4l** (63 mg, 65% colorless thick liquid) was prepared from the reaction of **1b**, **2a**, and **3k**. 1H NMR (500 MHz, $CDCl_3$) δ 8.72–8.64 (m, 1H), 8.26 (dd, J = 11.2, 4.0 Hz, 1H), 8.04 (dd, J = 9.5, 3.1 Hz, 1H), 7.97 (tt, J = 7.7, 2.8 Hz, 1H), 7.55–7.50 (m, 1H), 7.24 (dd, J = 6.5, 1.9 Hz, 1H), 7.21–7.07 (m, 3H), 3.80 (s, 3H), 3.68 (two s, 3H), 3.40 (s, 3H), 3.33 & 3.32 (two s, 2H), 3.08 (dd, J = 13.8, 5.0 Hz, 1H), 2.76 (dd, J = 16.5, 13.8 Hz, 1H), 1.87–1.75 (m, 1H), 1.41–1.30 (m, 1H), 0.88 & 0.86 (two s, 3H), 0.80 & 0.77 (two t, J = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 186.30 & 186.29 (1C), 171.6, 167.55 & 167.54 (1C), 157.33 & 157.24 (1C), 149.58 & 149.53 (1C), 143.08 & 143.05 (1C), 138.10 & 138.04 (1C), 137.92 & 137.90 (1C), 135.1, 130.89 & 130.79 (1C), 128.46 & 128.44 (1C), 128.40 & 128.35 (1C), 127.1, 126.6, 126.12 & 126.06 (1C), 123.63 & 123.60 (1C), 52.15 & 51.97 (1C), 50.21 & 50.06 (1C), 41.65 & 41.52 (1C), 39.57 & 39.55 (1C), 33.5, 33.21 & 32.92 (1C), 25.05 & 24.73 (1C), 19.78 & 19.59 (1C), 8.92 & 8.89 (1C). IR (Neat) ν_{max} 2928, 1712, 1632, 1431, 1197, 1170, 1097, 982, 757 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{25}H_{30}N_2NaO_6S^+$ [M+Na], 509.1717; found 509.1715.

N-[(E)-2-methyl-2-(2-(2-(phenylsulfonyl) vinyl) benzyl) butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4m):



Following the general procedure GP-3, the compound **4m** (69 mg, 69% colorless thick liquid), was prepared from the reaction of **1b**, **2a**, and **3l**. ^1H NMR (500 MHz, CDCl_3) δ 8.74–8.60 (m, 1H), 8.28 (d, $J = 7.9$ Hz, 1H), 8.15 (dd, $J = 22.0, 15.2$ Hz, 1H), 8.02–7.90 (m, 3H), 7.65–7.48 (m, 4H), 7.48–7.35 (m, 2H), 7.25–7.06 (m, 2H), 6.76–6.66 (m, 1H), 3.45 & 3.44 (two s, 3H), 3.20–3.12 (m, 1H), 3.09–3.01 (m, 1H), 1.92–1.82 (m, 1H), 1.37–1.28 (m, 1H), 0.93 & 0.91 (two s, 3H), 0.83 & 0.77 (two t, $J = 7.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 185.9, 157.23 & 157.16 (1C), 149.6, 141.52 & 141.46 (1C), 140.76 & 140.74 (1C), 139.17 & 139.15 (1C), 138.16 & 138.09 (1C), 133.24 & 133.23 (1C), 132.2, 132.05 & 131.99 (1C), 130.33 & 130.28 (1C), 129.3, 127.82 & 127.81 (1C), 127.57 & 127.54 (1C), 127.12 & 127.10 (1C), 126.7, 126.64 & 126.62 (1C), 123.60 & 123.55 (1C), 50.21 & 50.09 (1C), 41.12 & 41.00 (1C), 39.64 & 39.61 (1C), 32.79 & 32.64 (1C), 19.97 & 19.83 (1C), 8.97 & 8.90 (1C); IR (Neat) ν_{max} 2929, 1718, 1632, 1303, 1215, 1141, 1082, 973, 848, 750. cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_4\text{S}_2^+$ [$M + H$], 497.1563; found 497.1563.

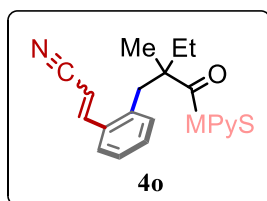
N-[(E)-2-(2-(2-(diethoxy phosphoryl) vinyl)benzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4n):



Following the general procedure GP-3, the compound **4n** (74 mg, 75% colorless thick liquid) was prepared from the reaction of **1b**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.72–8.62 (m, 1H), 8.24 (d, $J = 9.6$ Hz, 1H), 8.01–7.82 (m, 2H), 7.57–7.43 (m, 2H), 7.25–7.10 (m, 3H), 6.12 (ddd, $J = 19.0, 17.3, 5.2$ Hz, 1H), 4.17–4.04 (m, 4H), 3.43 & 3.42 (two s, 3H), 3.20–3.11 (m, 1H), 2.98 (dd, $J = 13.9, 4.5$ Hz, 1H), 1.93–1.82 (m, 1H), 1.45–1.27 (m, 7H), 0.94 & 0.92 (two s, 3H), 0.83 & 0.76 (two t, $J = 7.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.09 & 186.06 (1C), 157.34 & 157.27 (1C), 149.55 & 149.53 (1C), 147.6 (dd, $J_{C-P} = 10, 7.0$ Hz; 1C), 138.17 & 138.15 (1C), 138.09 & 138.02 (1C), 134.9 (dd, $J_{C-P} = 19, 4.0$ Hz), 131.65 & 131.60 (1C), 129.40 & 129.32 (1C), 127.05 &

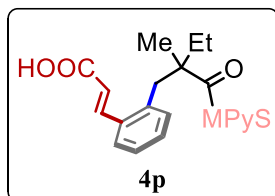
127.03 (1C), 126.51 & 126.44 (1C), 126.12 & 126.06 (1C), 123.60 & 123.58 (1C), 115.0 (dd, $J_{C-P} = 190, 8.0$ Hz), 61.72 & 61.70 (1C), 50.35 & 50.20 (1C), 40.87 & 40.73 (1C), 39.6, 33.11 & 32.92 (1C), 19.90 & 19.72 (1C), 16.40 & 16.34 (1C), 8.9; ^{31}P NMR (202 MHz, CDCl_3) δ 19.60, 19.51 (1P); IR (Neat) ν_{max} 2970, 2927, 1632, 1452, 1218, 1020, 957, 751 cm^{-1} . HRMS (ESI-TOF) m/z : calcd for $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_5\text{PS}^+$ [M+H], 493.1921; found 493.1923.

N-[(E)-2-(2-(2-cyanovinyl) benzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4o):



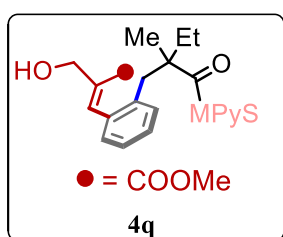
Following the general procedure GP-3, the compound **4o** [38 mg, 50% colorless thick with a mixture of cis : trans ratio (1: 1)] was prepared from the reaction of **1b**, **2a**, and **3n**. ^1H NMR (500 MHz, CDCl_3) δ 8.72–8.64 (m, 1H), 8.31–8.19 (m, 1H), 7.98 (tdd, $J = 7.7, 5.9, 1.7$ Hz, 1H), 7.85 (ddd, $J = 14.5, 12.5, 8.6$ Hz, 1H), 7.56–7.41 (m, 2H), 7.29–7.20 (m, 3H), 5.77–5.72 (m, 0.5H), 5.47 (dd, $J = 11.9, 8.7$ Hz, 0.5H), 3.41 (two s, 1.5H), 3.38 (two s, 1.5H), 3.13 (ddd, $J = 17.6, 14.0, 7.1$ Hz, 1H), 2.89–2.75 (m, 1H), 1.90–1.80 (m, 1H), 1.44–1.35 (m, 1H), 0.96 & 0.94 (two s, 3H), 0.86–0.78 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.14, 185.87 (1C), [157.32 & 157.28, 157.20 (1C)], [149.79 & 149.77, 149.63 & 149.59 (1C)], 149.28 & 149.26 (1C), [138.33 & 138.17, 138.14 & 138.08 (1C)], [133.72, 133.50 & 133.41 (1C)], [132.05 & 132.00, 131.59 & 131.55 (1C)], [130.39 & 130.29, 129.94 & 129.87 (1C)], 128.0, 127.1, [126.81 & 126.76, 126.62 & 126.60 (1C)], 125.58 & 125.55 (1C), [123.63 & 123.60, 123.52 (1C)], [118.60 & 118.55, 117.19 & 117.17 (1C)], [97.17 & 97.07, 96.94 & 96.83 (1C)], [50.10 & 50.09, 49.99 & 49.94 (1C)], [41.26 & 41.16, 40.93 & 40.85 (1C)], [39.68 & 39.61, 39.58 & 39.54 (1C)], [33.13 & 33.07, 33.01 & 32.87 (1C)], [20.28 & 20.20, 20.11 & 20.04 (1C)], [8.99 & 8.98, 8.95 (1C)]; IR (Neat) ν_{max} 2965, 2925, 2214, 1628, 1425, 1215, 1108, 980, 754 cm^{-1} . HRMS (ESI-TOF) m/z : calcd for $\text{C}_{21}\text{H}_{24}\text{N}_3\text{O}_2\text{S}^+$ [M + H], 382.1584; found 382.1588.

N-[(E)-2-(2-(2-carboxyvinyl) benzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4p):



Following the general procedure GP-3, the compound **4p** (40 mg, 50% colorless thick liquid), was prepared from the reaction of **1b**, **2a**, and **3o**. ^1H NMR (500 MHz, CDCl_3) δ 8.69 (dd, $J = 13.7$, 4.4 Hz, 1H), 8.25 (dd, $J = 20.4$, 12.8 Hz, 2H), 7.98 (t, $J = 7.7$ Hz, 1H), 7.61 – 7.50 (m, 2H), 7.28–7.17 (m, 3H), 6.33 (dd, $J = 15.7$, 4.3 Hz, 1H), 3.43 (s, 3H), 3.21 (t, $J = 13.4$ Hz, 1H), 3.01 (d, $J = 13.9$ Hz, 1H), 1.95–1.86 (m, 1H), 1.44–1.36 (m, 1H), 0.96 (bs, 3H), 0.89–0.77 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.2, 172.0, 157.37 & 157.28 (1C), 149.6, 145.83 & 145.76 (1C), 139.0, 138.13 & 138.07 (1C), 133.9, 131.93 & 131.89 (1C), 129.92 & 129.84 (1C), 127.1, 126.7, 126.58 & 126.52 (1C), 123.61 & 123.58 (1C), 118.00 & 117.92 (1C), 50.29 & 50.17 (1C), 40.99 & 40.86 (1C), 39.6, 33.03 & 32.90 (1C), 29.7, 20.09 & 20.00 (1C), 9.04 & 8.99 (1C). IR (Neat) ν_{max} 2920, 1703, 1625, 1452, 1212, 1191, 1081, 975, 758. cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{NaO}_4\text{S}^+$ $[\text{M}+\text{Na}]$, 423.1349; found 423.1346.

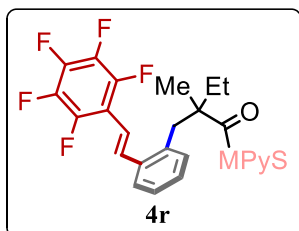
N-[(E)-2-(2-(2-(hydroxymethyl)-3-methoxy-3-oxoprop-1-en-1-yl)benzyl)-2-methylbutanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4q):



Following the general procedure GP-3, the compound **4q** (48 mg, 54% colorless thick liquid) was prepared from the reaction of **1b**, **2a**, and **3p**. ^1H NMR (500 MHz, CDCl_3) δ 8.72–8.64 (m, 1H), 8.30–8.22 (m, 1H), 8.01–7.94 (m, 2H), 7.57–7.50 (m, 1H), 7.25–7.10 (m, 4H), 4.31 (dd, $J = 8.3$, 4.2 Hz, 2H), 3.85 (s, 3H), 3.41 & 3.40 (two s, 3H), 3.10 (d, $J = 13.8$ Hz, 1H), 2.79 (dd, $J = 16.3$, 13.8 Hz, 1H), 2.15 (bs, $-\text{OH}$, 1H), 1.85–1.80 (m, 1H), 1.42–1.34 (m, 1H), 0.89 & 0.88 (two s, 3H), 0.85–0.75 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 186.3, 168.3, 157.4, 149.6, 143.0, 138.1, 134.8, 131.3, 130.98 & 130.92 (1C), 129.49 & 129.44 (1C), 128.72 & 128.63 (1C), 127.1, 126.16 & 126.10 (1C), 123.67 & 123.64 (1C), 58.3, 52.1, 50.31 & 50.17 (1C), 41.77 & 41.61 (1C), 39.6, 33.24 & 33.00 (1C), 20.03 & 19.93

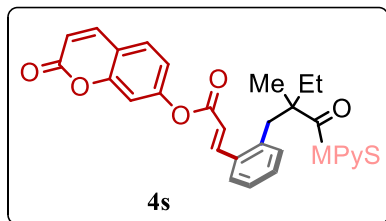
(1C), 8.97. **IR (Neat)** $\nu_{\max}$ 3405, 2928, 1703 1629, 1427, 1211, 982, 759 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_5\text{S}^+$ $[\text{M}+\text{H}]$, 445.1792; found 445.1790.

N-[(E)-2-methyl-2-(2-(2-(perfluorophenyl) vinyl)benzyl) butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4r):



Following the general procedure GP-3, the compound **4r** (64 mg, 61% white solid), was prepared from the reaction of **1b**, **2a**, and **3q**. **^1H NMR (500 MHz, CDCl_3)** δ 8.70 (dd, $J = 18.0, 4.0$ Hz, 1H), 8.26 (ddd, $J = 15.4, 8.2, 7.2$ Hz, 1H), 7.97 (tt, $J = 7.8, 1.7$ Hz, 1H), 7.87–7.78 (m, 1H), 7.62–7.52 (m, 2H), 7.25–7.10 (m, 3H), 6.83–6.78 (m, 1H), 3.42 (s, 3H), 3.15 (d, $J = 13.4$ Hz, 1H), 2.99 (dd, $J = 13.8, 11.2$ Hz, 1H), 1.90 (td, $J = 14.0, 7.1$ Hz, 1H), 1.41 (ddq, $J = 18.6, 14.8, 7.5$ Hz, 1H), 0.97 & 0.96 (two s, 3H), 0.85 & 0.81 (two t, $J = 7.5$ Hz, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)** δ 186.3, 157.42 & 157.34 (1C), 149.58 & 149.57 (1C), 144.73 (d, $J_{\text{C-F}} = 254$ Hz), 139.59 (d, $J_{\text{C-F}} = 242$ Hz), 138.05 & 137.99 (1C), 137.6, 136.6, 136.41 (t, $J_{\text{C-F}} = 8.3$ Hz), 131.60 & 131.54 (1C), 128.36 & 128.26 (1C), 127.07 & 127.05 (1C), 126.59 & 126.55 (1C), 125.53 & 125.51 (1C), 123.5, 113.6, 112.76 (td, $J_{\text{C-F}} = 14, 3.8$ Hz), 50.36 & 50.23 (1C), 40.87 & 40.81 (1C), 39.54 & 39.51 (1C), 33.0, 32.7, 19.92 & 19.77 (1C), 9.01 & 8.97 (1C). **^{19}F NMR (376 MHz, CDCl_3)** δ -142.93, & -142.95 (1F), -156.92, -162.99 & -163.04 (1F). **IR (Neat)** $\nu_{\max}$ 2917, 2849, 1631, 1521, 1493, 1199, 1026, 963, 754 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{26}\text{H}_{24}\text{F}_5\text{N}_2\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]$, 523.1473; found 523.1470.

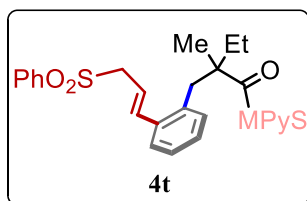
N-[(E)-2-methyl-2-(2-(3-oxo-3-((2-oxo-2H-chromen-7-yl) oxy) prop-1-en-1-yl) benzyl) butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (4s):



Following the general procedure GP-3, the compound **4s** (66 mg, 61% as colorless thick liquid), was prepared from the reaction of **1b**, **2a**, and **3r**. **^1H NMR (500 MHz, CDCl_3)** δ 8.68 (dd, $J = 17.4, 4.0$ Hz, 1H), 8.42 – 8.33 (m, 1H), 8.26 (d, $J = 7.9$ Hz, 1H), 8.00–7.92 (m, 1H), 7.70 (d, $J = 9.6$ Hz, 1H), 7.62 (dt, $J = 7.0, 6.2$ Hz, 1H), 7.55–7.48 (m, 2H), 7.31–7.19 (m, 4H), 7.16–7.12 (m, 1H), 6.51 (dd, $J = 15.7, 10.9$ Hz, 1H), 6.39 (dd, $J = 9.5, 0.9$ Hz, 1H), 3.41 (s, 3H), 3.29–3.20 (m, 1H), 3.00 (t, $J =$

14.0 Hz, 1H), 1.95–1.84 (m, 1H), 1.46–1.36 (m, 1H), 0.97 & 0.95 (two s, 3H), 0.84 & 0.79 (two t, $J = 7.5$ Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 186.01 & 185.93 (1C), 164.87 & 164.73 (1C), 160.4, 157.27 & 157.17 (1C), 154.6, 153.5, 149.6, 146.57 & 146.49 (1C), 142.9, 139.2, 138.10 & 138.01 (1C), 133.65 & 133.59 (1C), 132.1, 130.17 & 130.12 (1C), 128.5, 127.1, 126.72 & 126.66 (1C), 126.53 & 126.45 (1C), 123.67 & 123.57 (1C), 118.5, 116.94 & 116.87 (1C), 116.5, 115.9, 110.47 & 110.43 (1C), 50.20 & 50.08 (1C), 41.07 & 40.81 (1C), 39.6, 33.1, 20.0, 9.01 & 8.95 (1C). IR (Neat) ν_{max} 2925, 2805, 1728, 1614, 1452, 1210, 1116, 988, 842, 757. cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{30}H_{29}N_2O_6S^+$ [M+H], 545.1741; found 545.1740.

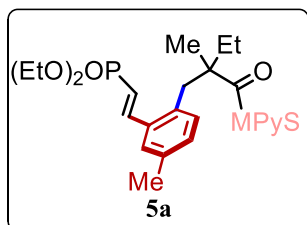
N[(E)-2-methyl-2-(2-(3-(phenylsulfonyl)prop-1-en-1-yl)benzyl)butanoic acidS-methyl-S-(2-pyridyl) sulfoximine (4t):



Following the general procedure GP-3, the compound **4t** (26 mg, 25% colorless thick liquid), was prepared from the reaction of **1b**, **2a**, and **3s**. The unreacted starting material **1b** (18 mg, 37%) was recovered. 1H NMR (500 MHz, DMSO) δ 8.88–

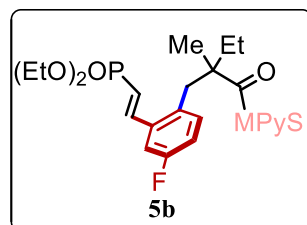
8.73 (m, 1H), 8.21–8.13 (m, 2H), 7.92–7.80 (m, 2H), 7.79–7.69 (m, 2H), 7.67 – 7.59 (m, 2H), 7.36 – 7.31 (m, 1H), 7.16 – 6.99 (m, 3H), 6.79 (dd, $J = 15.6, 6.7$ Hz, 1H), 5.91–5.80 (m, 1H), 4.31 (d, $J = 7.5$ Hz, 2H), 3.45 (s, 3H), 2.88 (dd, $J = 13.7, 2.8$ Hz, 1H), 2.57 (dd, $J = 13.7, 9.1$ Hz, 1H), 1.71 (td, $J = 12.8, 7.1$ Hz, 1H), 1.31 – 1.25 (m, 1H), 0.73–0.69 (m, 3H), 0.63 – 0.57 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 186.3, 157.36 & 157.28 (1C), 149.61 & 49.57 (1C), 138.4, 138.21 & 138.16 (1C), 138.09 & 138.05 (1C), 136.8, 135.86 & 135.84 (1C), 133.7, 131.28 & 131.22 (1C), 129.1, 128.4, 127.89 & 127.80 (1C), 127.1, 126.39 & 126.35 (1C), 126.09 & 126.06 (1C), 123.50 & 123.47 (1C), 116.3, 60.62 & 60.59 (1C), 50.01 & 49.87 (1C), 40.66 & 40.47 (1C), 39.58 & 39.53 (1C), 33.03 & 32.85 (1C), 19.94 & 19.89 (1C), 8.99 & 8.97 (1C). IR (Neat) ν_{max} 2929, 1718, 1632, 1303, 1215, 1141, 1082, 973, 848, 750. cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{27}H_{31}N_2O_4S_2^+$ [M + H], 511.1720; found 511.1726.

N-[(E)-2-(2-(2-(diethoxyphosphoryl) vinyl)-4-methylbenzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (5a):



Following the general procedure GP-3, the compound **5a** (69 mg, 68% colorless thick liquid) was prepared from the reaction of **1b**, **2b**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.73–8.62 (m, 1H), 8.25 (d, $J = 7.9$ Hz, 1H), 7.99–7.81 (m, 2H), 7.56–7.48 (m, 1H), 7.30 (d, $J = 11.6$ Hz, 1H), 7.12 (dt, $J = 16.1, 8.1$ Hz, 1H), 7.05–6.94 (m, 1H), 6.11 (ddd, $J = 19.1, 17.3, 4.8$ Hz, 1H), 4.15–4.05 (m, 4H), 3.43 & 3.42 (two s, 3H), 3.11 (dd, $J = 19.8, 13.9$ Hz, 1H), 2.94 (dd, $J = 13.9, 7.6$ Hz, 1H), 2.29 & 2.27 (two s, 3H), 1.90–1.82 (m, 1H), 1.41–1.30 (m, 7H), 0.92 & 0.91 (two s, 3H), 0.81 & 0.75 (two t, $J = 7.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.17 & 186.12 (1C), 157.42 & 157.35 (1C), 149.5, 147.8 (dd, $J_{C-P} = 12.8, 7.2$ Hz), 138.07 & 138.00 (1C), 135.91 & 135.84 (1C), 135.20 & 135.17 (1C), 134.7 (dd, $J_{C-P} = 23, 5$ Hz, 1C), 131.58 & 131.56 (1C), 130.36 & 130.27 (1C), 127.02 & 126.99 (1C), 126.59 & 126.54 (1C), 123.57 & 123.52 (1C), 114.6 (dd, $J_{C-P} = 190, 11$ Hz, 1C), 61.68 & 61.66 (1C), 50.35 & 50.24 (1C), 40.55 & 40.37 (1C), 39.6, 32.96 & 32.85 (1C), 20.9, 19.88 & 19.77 (1C), 16.39 & 16.34 (1C), 8.98 & 8.91 (1C). ^{31}P NMR (162 MHz, CDCl_3) δ 19.74, 19.64. IR (Neat) ν_{max} 2969, 2922, 1620, 1451, 1219, 1192, 1046, 940, 754 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{25}\text{H}_{36}\text{N}_2\text{O}_5\text{PS}^+$ $[\text{M}+\text{H}]$, 507.2077; found 507.2078.

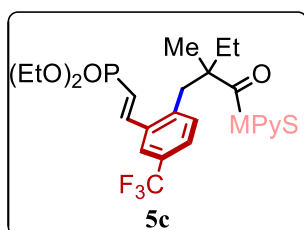
N-[(E)-2-(2-(2-(diethoxyphosphoryl) vinyl)-4-fluorobenzyl)-2-methylbutanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (5b):



Following the general procedure GP-3, the compound **5b** (41 mg, 40% colorless thick liquid) was prepared from the reaction of **1b**, **2c**, and **3m**. The unreacted starting material **1b** (18 mg, 35%) was recovered. ^1H NMR (500 MHz, CDCl_3) δ 8.71–8.63 (m, 1H), 8.25 (dt, $J = 9.1, 5.0$ Hz, 1H), 7.97 (tt, $J = 7.9, 1.9$ Hz, 1H), 7.91–7.75 (m, 1H), 7.56–7.50 (m, 1H), 7.25–7.11 (m, 2H), 6.93–6.81 (m, 1H), 6.10 (td, $J = 17.8, 4.3$ Hz, 1H), 4.18–4.04 (m, 4H), 3.42 & 3.41 (d, $J = 6.7$ Hz, 3H), 3.13 (t, $J = 13.7$ Hz, 1H), 2.90 (dd, $J = 14.0, 6.3$ Hz, 1H), 1.92–1.80 (m, 1H), 1.45–1.30 (m, 7H), 0.92 & 0.91 (two s, 3H), 0.83 &

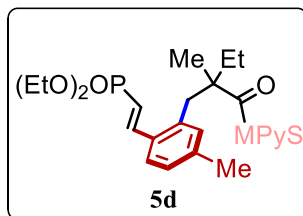
0.77 (two t, $J = 7.5$ Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 185.9, 161.3 (d, $J_{C-F} = 246$ Hz), 157.32 & 157.22 (1C), 149.5, 146.5, 138.12 & 138.03 (1C), 136.6 (d, $J_{C-P} = 29$ Hz), 133.9, 133.3, 127.11 & 127.06 (1C), 123.7, 116.35 (dd, $J_{C-F} = 20.5, 10.7$ Hz), 116.3, (dd, $J_{C-P} = 191, 9$ Hz), 112.31 (dd, $J_{C-F} = 21.2, 5.8$ Hz), 61.8, 50.39 & 50.21 (1C), 40.34 & 40.21 (1C), 39.6, 33.27 & 33.06 (1C), 19.80 & 19.57 (1C), 16.40 & 16.34 (1C), 8.94. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.3; ^{31}P NMR (202 MHz, $CDCl_3$) δ 18.77 & 18.67 (1P). IR (Neat) ν_{max} 2970, 2925, 1720, 1630, 1620, 1577, 1219, 1194, 1167, 1021, 956, 878, 754 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{24}H_{33}FN_2O_5PS^+$ $[M+H]$, 511.1826; found 511.1832.

N-[(E)-2-(2-(2-(diethoxyphosphoryl) vinyl)-4-(trifluoromethyl)benzyl)-2-methylbutanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (5c):



Following the general procedure GP-3, the compound **5c** (56 mg, 50% colorless thick liquid) was prepared from the reaction of **1b**, **2d**, and **3m**. The unreacted starting material **1b** (14 mg, 27%) was recovered. 1H NMR (500 MHz, $CDCl_3$) δ 8.70–8.66 (m, 1H), 8.29–8.23 (m, 1H), 8.01–7.83 (m, 2H), 7.70 (d, $J = 12.1$ Hz, 1H), 7.55 (td, $J = 7.6, 4.7, 1.1$ Hz, 1H), 7.44–7.34 (m, 2H), 6.19 (td, $J = 17.6, 4.7$ Hz, 1H), 4.17–4.08 (m, 4H), 3.42 & 3.41 (two s, 3H), 3.27–3.19 (m, 1H), 2.98 (dd, $J = 13.8, 8.3$ Hz, 1H), 1.92–1.87 (m, 1H), 1.47–1.39 (m, 1H), 1.37–1.31 (m, 6H), 0.94 & 0.92 (two s, 3H), 0.85 & 0.79 (two t, $J = 7.5$ Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 185.6, 157.37 & 157.27 (1C), 149.60 & 149.56 (1C), 146.2, 142.1, 138.21 & 138.10 (1C), 135.64 (d, $J_{C-P} = 22.4$ Hz), 132.16 & 132.11 (1C), 128.85 (qd, $J_{C-F} = 32.6, 6.1$ Hz), 127.18 & 127.13 (1C), 125.6, 125.1, 123.77 & 123.74 (1C), 123.1, 117.4 (d, $J_{C-P} = 193$ Hz), 62.0, 50.39 & 50.24 (1C), 40.89 & 40.80 (1C), 39.7, 33.49 & 33.28 (1C), 20.04 & 19.81 (1C), 16.44 & 16.39 (1C), 8.94 & 8.90 (1C); ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.60 & -62.6 (3F); ^{31}P NMR (202 MHz, $CDCl_3$) δ 18.38 & 18.29 (1P); IR (Neat) ν_{max} 2931, 1628, 1329, 1240, 1217, 1215, 1162, 1077, 1023, 962, 840 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{25}H_{33}F_3N_2O_5PS^+$ $[M+H]$, 561.1794; found 561.1795.

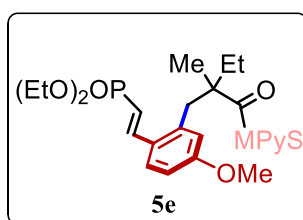
N-[(*E*)-2-(2-(2-(diethoxyphosphoryl) vinyl)-5-methylbenzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (**5d**):



Following the general procedure GP-3, the compound **5d** (62 mg, 61% colorless thick liquid), was prepared from **1b**, **2e**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.61 (m, 1H), 8.25 (t, J = 6.9 Hz, 1H), 8.01–7.79 (m, 2H), 7.52 (dt, J = 6.4, 4.7 Hz, 1H),

7.46–7.37 (m, 1H), 7.14–7.07 (m, 1H), 6.99 (t, J = 7.2 Hz, 1H), 6.13–6.03 (m, 1H), 4.15–4.04 (m, 4H), 3.45 & 3.43 (two s, 3H), 3.12 (dd, J = 18.2, 13.9 Hz, 1H), 2.97 (dd, J = 13.8, 8.4 Hz, 1H), 2.29 & 2.27 (two s, 3H), 1.88 (tq, J = 14.4, 7.3 Hz, 1H), 1.41–1.29 (m, 7H), 0.95 & 0.92 (two s, 3H), 0.81 & 0.77 (two t, J = 7.5 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.14 & 186.00 (1C), 157.50 & 157.42 (1C), 149.64 & 149.58 (1C), 147.6, 139.56 & 139.53 (1C), 138.12 & 138.09 (1C), 138.0, 132.4, 132.1 (dd, $J_{\text{C-P}}$ = 22.5, 7.6 Hz), 127.48 & 127.42 (1C), 127.04 & 127.01 (1C), 126.0, 123.47 & 123.40 (1C), 113.5 (dd, $J_{\text{C-P}}$ = 190.8, 13.3 Hz), 61.68 & 61.66 (1C), 50.31 & 50.28 (1C), 40.86 & 40.67 (1C), 39.61 & 39.59 (1C), 32.9, 21.27 & 21.25 (1C), 19.90 & 19.80 (1C), 16.40 & 16.35 (1C), 8.99 & 8.94 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 20.12 & 20.04 (1P). IR (Neat) ν_{max} 3001, 2968, 1738, 1598, 1367, 1215, 1032, 960, 868, 803 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{25}\text{H}_{36}\text{FN}_2\text{O}_5\text{PS}^+$ [M+H], 507.2077; found 507.2080.

N-[(*E*)-2-(2-(2-(diethoxyphosphoryl) vinyl)-5-methoxybenzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (**5e**):



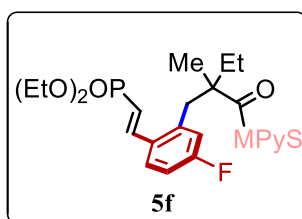
following the general procedure GP-3, the compound **5e** (44 mg, 42% and d.r 1.7:1 colorless thick liquid colorless thick liquid) was prepared from the reaction of **1b**, **2f**, and **3m**. The unreacted starting material **1b** (17 mg, 34%) was recovered. ^1H

NMR (500 MHz, CDCl_3) δ 8.72–8.61 (m, 1H), 8.25 (d, J = 7.9 Hz, 1H), 8.00–7.76 (m, 2H), 7.56–7.45 (m, 2H), 6.85–6.70 (m, 2H), 6.01 (dd, J = 18.9, 17.3 Hz, 1H), 4.15–4.05 (m, 4H), 3.79 & 3.78 (two s, 3H), 3.44 & 3.43 (two s, 3H), 3.23–3.11 (m, 1H), 3.02–2.94 (m, 1H), 1.95–1.87 (m, 1H), 1.41 (dt, J = 14.6, 7.3 Hz, 1H), 1.35–1.31 (m, 6H), 0.97 & 0.92 (two s, 3H), 0.82 & 0.77 (two t, J = 7.5 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 186.02

& 184.80 (1C), 160.6, 157.3, 149.78 & 149.64 (1C), 147.0, 140.3, 138.0, 127.5, 127.0, 123.60 & 123.33 (1C), 115.9, 113.2, 111.7 (d, $J_{C-P} = 191$ Hz, 1C), 63.45, 61.64, 55.29 & 55.22 (1C), 50.33, 41.1, 39.67 & 39.57 (1C), 33.3, 19.86 & 19.66 (1C), 16.43 & 16.37 (1C), 8.9. ^{31}P NMR (202 MHz, CDCl_3) δ 20.57. IR (Neat) ν_{max} 2965, 2919, 1617, 1598, 1251, 1190, 1032, 960, 868. cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{25}\text{H}_{36}\text{N}_2\text{O}_6\text{PS}^+$ $[\text{M}+\text{H}]$, 523.2026; found 523.2023.

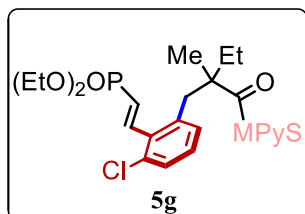
Some representative peaks for the minor isomer: $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 184.80, 149.64, 123.33, 55.22, 39.57, 19.66, 16.37.

N-[(E)-2-(2-(2-(diethoxyphosphoryl) vinyl)-5-fluorobenzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (5f):



Following the general procedure GP-3, the compound **5f** (66 mg, 65% colorless thick liquid) was prepared from the reaction of **1b**, **2g**, and **3m**. ^1H NMR (500MHz, CDCl_3) δ 8.71–8.64 (m, 1H), 8.26 (dd, $J = 7.9, 3.1$ Hz, 1H), 8.02–7.94 (m, 1H), 7.91–7.77 (m, 1H), 7.57–7.52 (m, 1H), 7.25–7.14 (m, 2H), 6.93–6.82 (m, 1H), 6.11 (td, $J = 17.7, 4.2$ Hz, 1H), 4.16–4.05 (m, 4H), 3.42 & 3.41 (two s, 3H), 3.14 (t, $J = 13.7$ Hz, 1H), 2.91 (dd, $J = 14.0, 6.2$ Hz, 1H), 1.91–1.81 (m, 1H), 1.43–1.30 (m, 7H), 0.92 & 0.91 (two s, 3H), 0.83 & 0.77 (two t, $J = 7.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 185.8, 161.33 (dd, $J = 245.0, 4.6$ Hz), 157.41 & 157.31 (1C), 149.55 & 149.53 (1C), 146.56 & 146.40 (1C), 138.13 & 138.03 (1C), 136.6 (d, $J = 29$ Hz), 133.96 (t, $J = 3.2$ Hz), 133.29 (t, $J = 6.9$ Hz), 127.10 & 127.05 (1C), 123.69 & 123.66 (1C), 116.4 (dd, $J = 191, 13$ Hz, 1C), 116.4 (dd, $J = 20.9, 12.8$ Hz), 112.3 (dd, $J = 21.9, 6.8$ Hz), 61.88 & 61.81 (1C), 50.40 & 50.23 (1C), 40.34 & 40.21 (1C), 39.6, 33.26 & 33.05 (1C), 19.88 & 19.66 (1C), 16.41 & 16.36 (1C), 8.95 & 8.90 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 18.74 & 18.65 (1P). ^{19}F NMR (471 MHz, CDCl_3) δ -116.32 & -116.39 (1F). IR (Neat) ν_{max} 2968, 1738, 1604, 1435, 1366, 1228, 1215, 1093, 876, 805 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{24}\text{H}_{33}\text{FN}_2\text{O}_5\text{PS}^+$ $[\text{M}+\text{H}]$, 511.1826; found 511.1828.

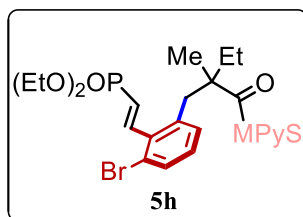
N-[(E)-2-(3-chloro-2-(2-(diethoxyphosphoryl) vinyl)benzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (5g):



Following the general procedure GP-3, the compound **5g** (65 mg, 62% colorless thick liquid) was prepared from **1b**, **2h**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.67 (dd, $J = 15.8, 4.6$ Hz, 1H), 8.25 (d, $J = 7.9$ Hz, 1H), 7.97 (td, $J = 7.8, 1.6$ Hz, 1H), 7.63–

7.49 (m, 2H), 7.18 (tt, $J = 19.9, 10.0$ Hz, 2H), 7.11–6.96 (m, 1H), 6.02–5.91 (m, 1H), 4.19–4.10 (m, 4H), 3.40 (s, 3H), 3.17 (dd, $J = 14.0, 5.7$ Hz, 1H), 2.88 (t, $J = 13.9$ Hz, 1H), 1.88–1.76 (m, 1H), 1.43–1.30 (m, 7H), 0.92 & 0.91 (two s, 3H), 0.81 & 0.75 (two t, $J = 7.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 185.8, 157.51 & 157.42 (1C), 149.55 & 149.53 (1C), 146.3, 139.2, 138.08 & 138.01 (1C), 135.5 (dd, $J_{C-P} = 23, 3$ Hz, 1C), 132.42 & 132.36 (1C), 129.29 & 129.14 (1C), 128.55 & 128.44 (1C), 127.53 & 127.48 (1C), 127.0, 123.6, 123.3 (d, $J_{C-P} = 183$ Hz, 1C), 61.93 & 61.88 (1C), 50.34 & 50.19 (1C), 41.4, 41.35, 39.64 & 39.62 (1C), 33.58 & 33.23 (1C), 20.02 & 19.75 (1C), 16.41 & 16.36 (1C), 8.82 & 8.79 (1C). ^{31}P NMR (203 MHz, CDCl_3) δ 17.13. IR (Neat) ν_{max} 2973, 1629, 1425, 1217, 1020, 961, 755. cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{24}\text{H}_{33}\text{ClN}_2\text{O}_5\text{PS}^+$ $[\text{M}+\text{H}]$, 527.1531; found 527.1531.

N-[(E)-2-(3-bromo-2-(2-(diethoxyphosphoryl) vinyl)benzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (5h):

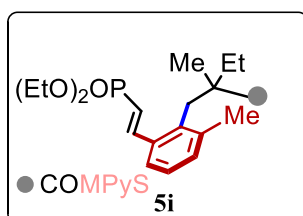


Following the general procedure GP-3, the compound **5h** (72 mg, 63% colorless thick liquid) was prepared from the reaction of **1b**, **2i**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.73–8.63 (m, 1H), 8.25 (dd, $J = 7.9, 0.7$ Hz, 1H), 8.01–7.93 (m, 1H), 7.59–7.46

(m, 2H), 7.40 (dd, $J = 15.1, 7.6$ Hz, 1H), 7.21 (d, $J = 7.8$ Hz, 1H), 6.96 (dt, $J = 37.7, 7.9$ Hz, 1H), 5.96–5.81 (m, 1H), 4.21–4.11 (m, 4H), 3.40 (s, 3H), 3.18 (dd, $J = 14.0, 6.4$ Hz, 1H), 2.90 (t, $J = 14.1$ Hz, 1H), 1.87–1.76 (m, 1H), 1.43–1.31 (m, 7H), 0.92 & 0.91 (two s, 3H), 0.81 & 0.76 (two t, $J = 7.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 186.0, 157.35 & 157.25 (1C), 149.6, 148.6, 138.9, 138.1, 137.4 (d, $J_{C-P} = 27.3$ Hz), 130.1, 129.8, 129.7, 128.9, 128.8, 127.1, 123.0 (dd, $J_{C-P} = 160.4, 22.9$ Hz), 62.0, 50.37 & 50.21 (1C), 41.7, 39.6, 33.68 & 33.28 (1C), 19.87 & 19.57 (1C), 16.46 & 16.39 (1C), 8.84. ^{31}P NMR (202 MHz, CDCl_3)

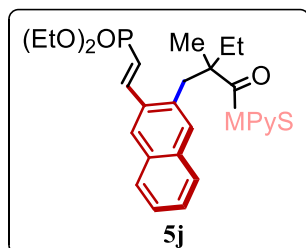
δ 16.97; **IR (Neat)** $\nu_{\max}$ 2974, 2931, 1630, 1216, 1019, 960, 823, 756 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{24}\text{H}_{33}\text{BrN}_2\text{O}_5\text{PS}^+$ $[\text{M}+\text{H}]$, 571.1026; found 571.1027.

N-[(E)-2-(2-(2-(diethoxyphosphoryl) vinyl)-6-methylbenzyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (5i):



Following the general procedure GP-3, the compound **5i** (35 mg, 35% colorless thick liquid), was prepared from **1b**, **2j**, and **3m**. The unreacted starting material **1b** (20 mg, 39%) was recovered. ^1H NMR (500 MHz, CDCl_3) δ 8.66 (dd, $J = 9.0, 4.2$ Hz, 1H), 8.24 (d, $J = 7.7$ Hz, 1H), 8.05–7.87 (m, 2H), 7.53 (dd, $J = 11.9, 6.4$ Hz, 1H), 7.38 (d, $J = 5.0$ Hz, 1H), 7.20–7.04 (m, 2H), 6.12 (t, $J = 18.2$ Hz, 1H), 4.24–4.00 (m, 4H), 3.42 & 3.41 (two s, 3H), 3.29–3.08 (m, 2H), 2.31 & 2.29 (two s, 3H), 2.03–1.89 (m, 1H), 1.41–1.26 (m, 8H), 0.94 & 0.90 (two s, 3H), 0.74 & 0.71 (two t, $J = 7.5, 7.2$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 186.72 & 186.68 (1C), 157.29 & 157.25 (1C), 149.64 & 149.58 (1C), 149.27 & 149.24 (1C), 139.1, 138.14 & 138.08 (1C), 137.3, 136.00 (d, $J = 22.2$ Hz), 132.1, 127.09 & 127.07 (1C), 126.2, 124.3, 123.62 & 123.58 (1C), 114.58 (d, $J = 190.4$ Hz), 61.76 & 61.72 (1C), 50.45 & 50.42 (1C), 39.57 & 39.53 (1C), 37.47 & 37.27 (1C), 33.0, 21.43 & 21.38 (1C), 20.35 & 20.10 (1C), 16.46 & 16.41 (1C), 9.23 & 9.15 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 19.71. **IR (Neat)** $\nu_{\max}$ 3001, 2968, 1738, 1598, 1367, 1215, 1032, 960, 868, 803 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{25}\text{H}_{36}\text{FN}_2\text{O}_5\text{PS}^+$ $[\text{M}+\text{H}]$, 507.2077; found 507.2080.

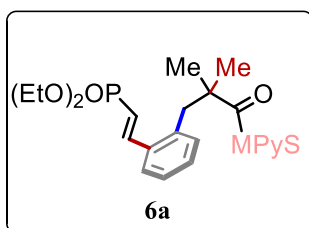
N-[(E)-2-((3-(2-(diethoxyphosphoryl) vinyl) naphthalen-2-yl) methyl)-2-methyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (5j)



Following the general procedure GP-3, the compound **5j** (66 mg, 61% colorless thick liquid) was prepared from the reaction of **1b**, **2k**, and **3m**. ^1H NMR (400 MHz, CDCl_3) δ 8.66–8.57 (m, 1H), 8.20 (dt, $J = 11.6, 5.8$ Hz, 1H), 8.10–7.95 (m, 2H), 7.94–7.86 (m, 1H), 7.82–7.69 (m, 3H), 7.52–7.36 (m, 3H), 6.33–6.23 (m, 1H), 4.20–4.10 (m, 4H), 3.45 & 3.42 (d, $J = 10.2$ Hz, 3H), 3.38–3.31 (m, 1H), 3.10 (d, $J = 14.1$ Hz, 1H), 1.94 (dt, $J = 20.6, 6.8$ Hz, 1H), 1.51–1.41 (m, 1H), 1.37 (tdd, $J = 6.8, 4.1, 2.3$ Hz, 6H), 1.01 & 1.00 (two s,

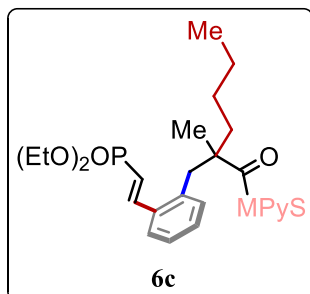
3H), 0.85 & 0.81 (two t, $J = 7.5$ Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 186.09 & 186.02 (1C), 157.51 & 157.45 (1C), 149.67 & 149.65 (1C), 148.2, 138.09 & 138.07 (1C), 135.11 & 135.08 (1C), 134.2 (dd, $J_{C-P} = 23, 9$ Hz, 1C), 133.87 & 133.84 (1C), 131.89 & 131.87 (1C), 130.12 & 130.08 (1C), 127.9, 127.59 & 127.54 (1C), 127.1, 126.70 & 126.62 (1C), 125.95 & 125.92 (1C), 125.89 & 125.86 (1C), 123.43 & 123.39 (1C), 116.0 (dd, $J_{C-P} = 190, 9$ Hz, 1C), 61.86 & 61.82 (1C), 50.55 & 50.51 (1C), 41.08 & 40.97 (1C), 39.67 & 39.63 (1C), 33.25 & 33.11 (1C), 20.1, 16.50 & 16.45 (1C), 9.03 & 9.00 (1C). ^{31}P NMR (202 MHz, $CDCl_3$) δ 19.14, 19.08 (1P). IR (Neat) ν_{max} 2971, 2930, 1631, 1453, 1217, 1019, 956, 750 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{28}H_{36}N_2O_5PS^+$ [M+H], 543.2077; found 543.2076.

N-[(E)-3-(2-(2-(diethoxy phosphoryl) vinyl) phenyl)-2,2-dimethyl propanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6a):



Following the general procedure GP-3, the compound **6a** (69 mg, 72% colorless thick liquids) was prepared from the reaction of **1a**, **2a**, and **3m**. 1H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, $J = 3.4$ Hz, 1H), 8.24 (d, $J = 7.8$ Hz, 1H), 7.99–7.85 (m, 2H), 7.55–7.48 (m, 2H), 7.23–7.15 (m, 3H), 6.13 (t, $J = 18.1$ Hz, 1H), 4.14–4.05 (m, 4H), 3.43 (s, 3H), 3.11–3.03 (m, 2H), 1.32 (t, $J = 6.8$ Hz, 6H), 1.11 (s, 3H), 1.07 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 186.9, 157.1, 149.7, 147.6, 147.5, 138.1, 134.8 (d, $J_{C-P} = 22$ Hz, 1C), 131.8, 129.3, 127.1, 126.5, 126.1, 123.4, 114.9 (d, $J_{C-P} = 191$ Hz), 61.7, 46.3, 41.2, 39.5, 25.5, 25.1, 16.38 & 16.32 (1C). ^{31}P NMR (202 MHz, $CDCl_3$) δ 19.51. IR (Neat) ν_{max} 2924, 1624, 1218, 1192, 1021, 961, 845, 750 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{23}H_{32}N_2O_5PS^+$ [M+H], 479.1764; found 479.1767.

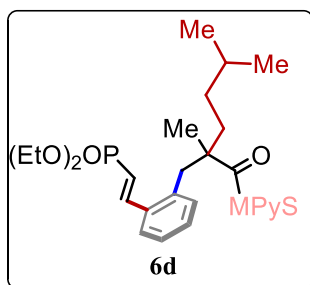
N-[(E)-2-(2-(2-(diethoxy phosphoryl) vinyl) benzyl)-2-methyl hexanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6c):



Following the general procedure GP-3, the compound **6c** (70 mg, 67% colorless thick liquid) was prepared from the reaction of **1c**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.63 (m, 1H), 8.30–8.21 (m, 1H), 8.00–7.82 (m, 2H), 7.57–7.45 (m, 2H), 7.24–7.11 (m, 3H), 6.16–6.06 (m, 1H), 4.14–4.07 (m, 4H),

3.42 & 3.41 (two s, 3H), 3.21–3.13 (m, 1H), 2.96 (dd, $J = 13.8, 4.0$ Hz, 1H), 1.83–1.78 (m, 1H), 1.36–1.28 (m, 6H), 1.27–1.20 (m, 3H), 1.18–1.00 (m, 2H), 0.93 (s, 3H), 0.85–0.81 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 186.18 & 186.13 (1C), 157.35 & 157.24 (1C), 149.5, 147.73 & 147.65 (1C), 138.2, 138.07 & 137.98 (1C), 134.9 (dd, $J_{C-P} = 22, 3$ Hz, 1C), 131.62 & 131.58 (1C), 129.40 & 129.32 (1C), 127.03 & 127.00 (1C), 126.49 & 126.42 (1C), 126.11 & 126.04 (1C), 123.60 & 123.54 (1C), 114.9 (dd, $J_{C-P} = 191, 6$ Hz, 1C), 61.78 & 61.72 (1C), 50.01 & 49.88 (1C), 41.13 & 40.98 (1C), 40.39 & 40.20 (1C), 39.5, 26.62 & 26.60 (1C), 23.24 & 23.22 (1C), 20.40 & 20.28 (1C), 16.38 & 16.32 (1C), 14.0. ^{31}P NMR (202 MHz, CDCl_3) δ 19.59. IR (Neat) ν_{max} 2930, 1632, 1211, 1162, 1020, 958, 853, 753 cm^{-1} . HRMS (ESI) m/z : calcd. for $\text{C}_{26}\text{H}_{38}\text{N}_2\text{O}_5\text{PS}^+$ $[M+H]$, 521.2234; found 521.2239.

N-[(E)-2-(2-(2-(diethoxy phosphoryl) vinyl) benzyl)-2,5-dimethyl hexanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6d):

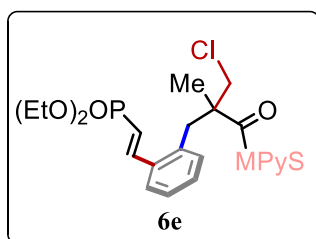


Following the general procedure GP-3, the compound **6d** (68 mg, 64% colorless thick liquid) was prepared from the reaction of **1d**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.73–8.62 (m, 1H), 8.24 (t, $J = 10.7$ Hz, 1H), 8.04–7.81 (m, 2H), 7.57–7.44 (m, 2H), 7.24–7.08 (m, 3H), 6.17–6.09 (m, 1H), 4.13–4.06 (m,

4H), 3.42 & 3.41 (two s, 3H), 3.23–3.14 (m, 1H), 2.96 (d, $J = 13.8$ Hz, 1H), 1.84 (td, $J = 12.6, 4.1$ Hz, 1H), 1.46–1.41 (m, 1H), 1.37–1.28 (m, 7H), 1.14–1.00 (m, 2H), 0.91 (s, 3H), 0.86–0.81 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 186.17 & 186.06 (1C), 157.39 & 157.29 (1C), 149.48 & 149.46 (1C), 147.72 & 147.66 (1C), 147.60 & 147.54 (1C), 138.19 & 138.17 (1C), 138.06 & 137.96 (1C), 135.0 (dd, $J_{C-P} = 23, 6$ Hz, 1C), 131.62 & 131.58 (1C),

129.43 & 129.32 (1C), 127.02 & 126.98 (1C), 126.51 & 126.44 (1C), 126.11 & 126.05 (1C), 123.65 & 123.55 (1C), 115.0 (dd, $J_{C-P} = 190, 13$ Hz, 1C), 61.77 & 61.73 (1C), 50.04 & 49.90 (1C), 41.33 & 41.10 (1C), 39.55 & 39.53 (1C), 38.53 & 38.41 (1C), 33.40 & 33.31 (1C), 28.5, 22.5, 20.24 & 20.20 (1C), 16.39 & 16.33 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 19.62. IR (Neat) ν_{max} 2950, 1633, 1209, 1021, 957, 752 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{27}\text{H}_{40}\text{N}_2\text{O}_5\text{PS}^+$ $[\text{M}+\text{H}]$, 535.2390; found 535.2394.

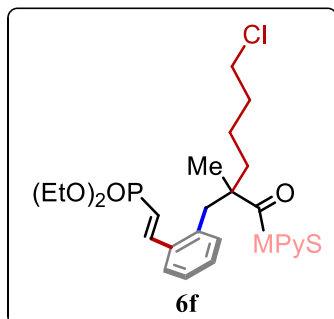
N-[(E)-3-chloro-2-(2-(2-(diethoxyphosphoryl) vinyl) benzyl)-2-methyl propanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6e):



Following the general procedure GP-3, the compound **6e** (58 mg, 57% and **d.r** 2.0:1 colorless thick liquid) was prepared from the reaction of **1e**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.69 (dd, $J = 9.5, 4.0$ Hz, 1H), 8.24 (dd, $J = 15.7, 7.9$ Hz, 1H), 8.00–7.87 (m, 2H), 7.57–7.50 (m, 2H), 7.30–7.27 (m, 1H), 7.25–7.20 (m, 2H), 6.18–6.10 (m, 1H), 4.15–4.08 (m, 4H), 3.79–3.68 (m, 1H), 3.60 (dd, $J = 10.7, 1.7$ Hz, 1H), 3.48 (s, 3H), 3.23–3.14 (m, 2H), 1.38–1.31 (m, 6H), 1.14 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.9, 156.80 & 156.73 (1C), 149.7, 147.14 & 147.08 (1C), 138.24 & 138.14 (1C), 136.6, 135.1 (d, $J = 23$ Hz, 1C), 131.6, 129.6, 127.3, 127.0, 126.4, 123.3, 115.7 (d, $J = 192$ Hz, 1C), 61.89 & 61.85 (1C), 51.4, 39.36 & 39.31 (1C), 37.24 & 37.06 (1C), 24.7, 20.66 & 20.39 (1C), 16.42 & 16.37 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 19.22; IR (Neat) ν_{max} 2925, 1631, 1317, 1196, 1107, 1016, 942, 846, 751 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{23}\text{H}_{31}\text{ClN}_2\text{O}_5\text{PS}^+$ $[\text{M}+\text{H}]$, 513.1374; found 513.1373.

Some representative peaks for the minor isomer: $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 156.73, 147.08, 138.14, 61.85, 39.31, 37.06, 20.39, 16.37.

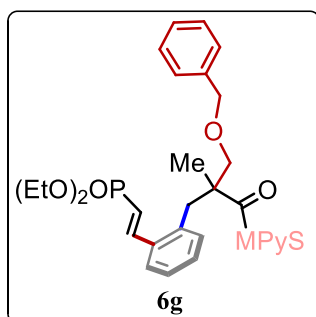
N-[(E)-6-chloro-2-(2-(2-(diethoxyphosphoryl) vinyl) benzyl)-2-methyl hexanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6f):



Following the general procedure GP-3, the compound **6f** (69 mg, 62% colorless thick liquid) was prepared from the reaction of **1f**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.75–8.64 (m, 1H), 8.26 (d, $J = 7.9$ Hz, 1H), 8.02–7.87 (m, 2H), 7.57–7.45 (m, 2H), 7.25–7.14 (m, 3H), 6.13 (ddd, $J = 18.9, 17.3, 4.8$ Hz, 1H), 4.17–4.06 (m, 4H), 3.52–3.46 (m, 2H), 3.44 & 3.43

(two s, 3H), 3.23–3.14 (m, 1H), 3.03–2.94 (m, 1H), 1.88–1.81 (m, 1H), 1.75–1.68 (m, 2H), 1.39–1.28 (m, 9H), 0.96 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 185.86 & 185.77 (1C), 157.2, 149.6, 147.6 (dd, $J = 14, 8$ Hz, 1C), 147.53, 138.14 & 138.07 (1C), 137.89 & 137.86 (1C), 131.70 & 131.65 (1C), 129.47 & 129.39 (1C), 127.1, 126.64 & 126.57 (1C), 126.17 & 126.11 (1C), 123.65 & 123.57 (1C), 115.0 (dd, $J = 190, 10$ Hz, 1C), 61.8, 49.94 & 49.84 (1C), 44.88 & 44.80 (1C), 41.23 & 41.05 (1C), 39.63 & 39.57 (1C), 39.42, 33.23 & 33.15 (1C), 22.06 & 21.99 (1C), 20.45 & 20.40 (1C), 16.42 & 16.37 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 19.60 & 19.51 (1P); IR (Neat) ν_{max} 2933, 1633, 1218, 1020, 957, 854, 753 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{26}\text{H}_{37}\text{ClN}_2\text{O}_5\text{PS}^+$ [$\text{M}+\text{H}$], 555.1844; found 555.1845.

N-[(E)-3-(benzyloxy)-2-(2-(2-(diethoxyphosphoryl) vinyl) benzyl)-2-methyl propionic acid S-methyl-S-(2-pyridyl) sulfoximine (6g):



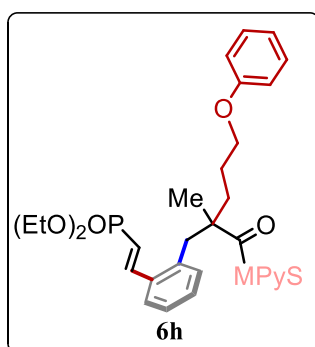
Following the general procedure GP-3, the inseparable mixture of compounds **6g** and **6g'** (60 mg, 51% and d.r 3.3:1 colorless thick liquid) was prepared from the reaction of **1g**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.65–8.57 (m, 1H), 8.17 (dd, $J = 18.6, 7.9$ Hz, 1H), 7.98–7.89 (m, 1H), 7.82–7.73 (m, 1H), 7.56–7.44 (m, 2H), 7.34–7.28 (m, 4H), 7.24–7.15 (m, 4H), 6.20–

6.08 (m, 1H), 4.56–4.47 (m, 2H), 4.15–4.06 (m, 4H), 3.60–3.48 (m, 2H), 3.44 & 3.43 (two s, 3H), 3.18–3.11 (m, 2H), 1.33 (t, $J = 7.1$ Hz, 6H), 1.12 & 1.10 (two s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 184.6, 157.0, 149.6, 147.4, 147.41 & 138.63 (1C), 138.1, 137.7, 135.1 (d, $J = 22$ Hz, 1C), 131.9, 129.4, 128.2, 127.5, 127.3, 127.1, 126.6, 126.2, 123.2, 115.2 (d, $J =$

190 Hz, 1C), 75.50, 73.10, 61.81, 50.88, 39.23, 36.27, 19.99, 16.44 & 16.39 (1C). IR (Neat) $\nu_{\max}$ 2968, 2920, 1738, 1436, 1366, 1228, 1215, 1092, 901, cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_6\text{PS}^+$ [M+H], 585.2183; found 585.2186.

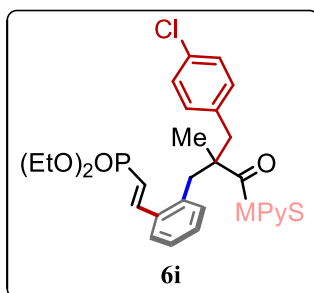
Some representative peaks for the minor isomer: $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 138.07, 137.71, 131.94, 129.44, 127.49, 123.13, 75.34, 73.05, 50.78, 36.10, 20.17.

N-[(E)-2-(2-(2-(diethoxyphosphoryl) vinyl) benzyl)-2-methyl-5-phenoxy pentanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6h):



Following the general procedure GP-3, the compound **6h** (78 mg, 65% colorless thick liquid) was prepared from **1h**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.68–8.59 (m, 1H), 8.26 (t, J = 8.3 Hz, 1H), 8.04–7.83 (m, 2H), 7.56–7.46 (m, 2H), 7.30–7.11 (m, 5H), 6.96–6.78 (m, 3H), 6.14 (ddd, J = 18.9, 17.4, 4.7 Hz, 1H), 4.16–4.05 (m, 4H), 3.96–3.86 (m, 2H), 3.43 & 3.40 (two s, 3H), 3.23 (dd, J = 20.4, 13.9 Hz, 1H), 3.00 (dd, J = 13.9, 7.6 Hz, 1H), 2.06–1.92 (m, 2H), 1.75–1.67 (m, 1H), 1.61–1.50 (m, 1H), 1.36–1.30 (m, 6H), 1.00 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 185.79 & 185.70 (1C), 159.02 & 158.96 (1C), 157.20 & 157.12 (1C), 149.6, 147.5 (dd, J = 12, 7 Hz), 138.13 & 138.02 (1C), 137.9, 135.0 (d, J = 18 Hz, 1C), 131.7, 129.47 & 129.39 (1C), 129.3, 127.1, 126.64 & 126.58 (1C), 126.20 & 126.14 (1C), 123.60 & 123.56 (1C), 120.4, 115.2 (dd, J = 191, 9 Hz, 1C), 114.4, 68.17 & 68.03 (1C), 61.7, 49.82 & 49.69 (1C), 41.02 & 40.92 (1C), 39.59 & 39.51 (1C), 36.72 & 36.50 (1C), 24.5, 20.53 & 20.41 (1C), 16.43 & 16.36 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 19.50 & 19.39 (1P). IR (Neat) $\nu_{\max}$ 3014, 2968, 2920, 1738, 1436, 1366, 1228, 1215, 1092, 901 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{31}\text{H}_{40}\text{N}_2\text{O}_6\text{PS}^+$ [M+H], 599.2339; found 599.2345.

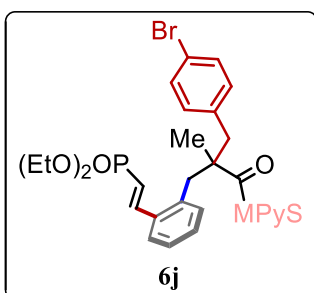
N-[(E)-2-(4-chlorobenzyl)-3-(2-(2-(diethoxyphosphoryl) vinyl) phenyl)-2-methyl propanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6i):



Following the general procedure GP-3, the compound **6i** (74 mg, 63% and **d.r** 3.3:1 colorless thick liquid), was prepared from the reaction of **1i**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.73–8.67 (m, 1H), 8.25–8.16 (m, 1H), 8.0–7.83 (m, 2H), 7.61–7.47 (m, 2H), 7.32–7.18 (m, 3H), 7.14–7.01 (m, 4H), 6.14 (ddd, J = 18.9, 17.3, 6.5 Hz, 1H), 4.16–4.04 (m, 4H), 3.47 & 3.41 (two s, 3H), 3.34–3.21 (m, 2H), 3.08 (d, J = 13.8 Hz, 1H), 2.57 (dd, J = 13.1, 9.4 Hz, 1H), 1.37–1.29 (m, 6H), 0.89 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 184.84 & 184.77 (1C), 157.3, 149.55 & 149.48 (1C), 147.5 (dd, J = 20, 9 Hz), 138.13 & 138.08 (1C), 137.49 & 137.45 (1C), 136.6, 135.1 (d, J = 21 Hz), 131.80 & 131.71 (1C), 129.53 & 129.45 (1C), 127.9, 127.8, 127.16 & 127.12 (1C), 126.83 & 126.75 (1C), 126.35 & 126.26 (1C), 123.6, 116.2, 114.7 (d, J = 190 Hz), 61.8, 51.10, 45.3, 41.8, 39.5, 20.3, 16.44 & 16.39 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 19.50. IR (Neat) ν_{max} 2926, 1632, 1199, 1018, 959, 839, 751 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{29}\text{H}_{35}\text{ClN}_2\text{O}_5\text{PS}^+$ $[\text{M}+\text{H}]$, 589.1687; found 589.1688.

Some representative peaks for the minor isomer: $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 184.77, 149.48, 138.08, 137.45, 131.71, 129.45, 127.12, 126.75, 126.26, 16.39.

N-[(E)-2-(4-bromobenzyl)-3-(2-(2-(diethoxyphosphoryl) vinyl) phenyl)-2-methyl propanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6j):

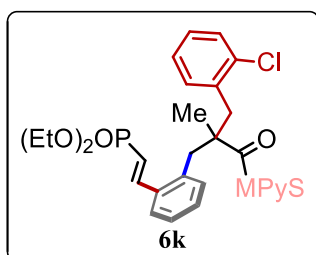


Following the general procedure GP-3, the compound **6j** (83 mg, 66% and **d.r** 1.4:1 colorless thick liquid) was prepared from the reaction of **1j**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.77–8.63 (m, 1H), 8.27–8.14 (m, 1H), 8.01–7.84 (m, 2H), 7.63–7.49 (m, 2H), 7.31–7.17 (m, 5H), 7.06 – 6.94 (m, 2H), 6.14 (td, J = 18.3, 5.7 Hz, 1H), 4.18–4.03 (m, 4H), 3.46 & 3.41 (two s, 3H), 3.34–3.23 (m, 2H), 3.08 (d, J = 13.8 Hz, 1H), 2.61–2.50 (m, 1H), 1.38–1.28 (m, 6H), 0.90 & 0.89 (two s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 184.8, 157.10 & 157.06 (1C), 149.56 & 149.49 (1C), 147.73 & 147.67 (1C), 147.58 & 147.52 (1C), 138.18 & 138.13 (1C), 137.43 & 137.40 (1C), 137.0, 135.0 (d, J = 22.6 Hz), 132.18 & 132.09 (1C), 130.83 & 130.73 (1C), 129.58 &

129.50 (1C), 127.21 & 127.17 (1C), 126.85 & 126.76 (1C), 126.32 & 126.24 (1C), 123.7, 120.13 & 120.04 (1C), 115.1 (d, $J = 190.3$ Hz), 61.9, 51.0, 45.35 & 45.32 (1C), 41.83 & 41.72 (1C), 39.63 & 39.51 (1C), 20.24 & 20.17 (1C), 16.42 & 16.39 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 19.60, 19.51 (1P). IR (Neat) ν_{max} 2931, 1631, 1453, 1218, 1020, 958, 750 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{29}\text{H}_{35}\text{BrN}_2\text{NaO}_5\text{PS}^+$ $[\text{M}+\text{Na}]$, 655.1002; found 655.1001.

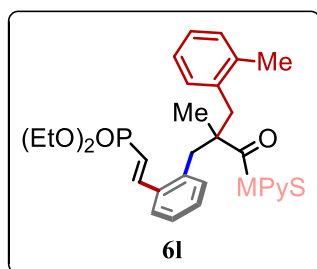
Some representative peaks for the minor isomer: $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 157.06, 149.49, 147.67, 147.52, 138.13, 137.40, 132.09, 130.73, 129.50, 127.17, 126.76, 126.24, 120.04, 45.32, 41.72, 39.51, 20.17, 16.39.

N-[(E)-2-(2-chlorobenzyl)-3-(2-(2-(diethoxyphosphoryl) vinyl) phenyl)-2-methyl propanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6k):



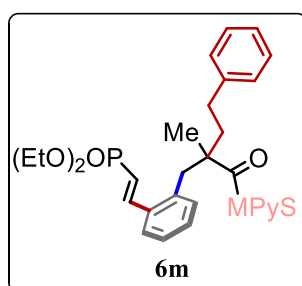
Following the general procedure GP-3, the compound **6k** (68 mg, 58% colorless thick liquid), was prepared from the reaction of **1k**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.71 (t, $J = 4.6$ Hz, 1H), 8.25–8.14 (m, 1H), 8.01–7.83 (m, 2H), 7.59–7.49 (m, 2H), 7.31–7.28 (m, 1H), 7.25–7.19 (m, 2H), 7.15–6.98 (m, 4H), 6.19–6.10 (m, 1H), 4.16–4.04 (m, 4H), 3.47 & 3.44 (two s, 3H), 3.38–3.20 (m, 2H), 3.10 (d, $J = 13.8$ Hz, 1H), 2.58 (dd, $J = 13.1, 6.7$ Hz, 1H), 1.35–1.30 (m, 6H), 0.93 & 0.91 (two s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 184.7, 157.15 & 157.10 (1C), 149.70 & 149.67 (1C), 147.67 & 147.61 (1C), 147.54 & 147.49 (1C), 140.20 & 140.18 (1C), 138.17 & 138.11 (1C), 137.37 & 137.34 (1C), 135.0 (d, $J = 23$ Hz), 133.45 & 133.42 (1C), 131.8, 130.4, 129.56 & 129.50 (1C), 129.03 & 128.91 (1C), 128.75 & 128.61 (1C), 127.20 & 127.11 (1C), 126.86 & 126.79 (1C), 126.35 & 126.29 (1C), 123.42 & 123.37 (1C), 115.3 (d, $J = 181$ Hz), 61.84 & 61.81 (1C), 51.14 & 51.03 (1C), 45.48 & 45.45 (1C), 41.93 & 41.78 (1C), 39.5, 20.34 & 20.30 (1C), 16.40 & 16.35 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 19.48 & 19.39 (1P). IR (Neat) ν_{max} 2977, 2924, 1738, 1625, 1218, 1198, 1019, 958, 851, 751 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{29}\text{H}_{34}\text{ClN}_2\text{NaO}_5\text{PS}^+$ $[\text{M}+\text{Na}]$, 611.1507; found 611.1514.

N-[(E)-2-(2-(2-(diethoxyphosphoryl) vinyl)benzyl)-2-methyl-3-(o-tolyl) propanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6l):



Following the general procedure GP-3, the compound **6l** (71 mg, 62% colorless thick liquid), was prepared from the reaction of **1l**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.70 (d, J = 4.6 Hz, 1H), 8.18 (dt, J = 13.4, 6.7 Hz, 1H), 7.99–7.79 (m, 2H), 7.56–7.47 (m, 2H), 7.29–7.11 (m, 4H), 7.09–6.91 (m, 3H), 6.13 (ddd, J = 19.1, 17.3, 7.0 Hz, 1H), 4.14–4.01 (m, 4H), 3.45 & 3.42 (two s, 3H), 3.34 (dd, J = 19.8, 13.8 Hz, 1H), 3.23 (d, J = 13.9 Hz, 1H), 3.09 (dd, J = 13.8, 4.1 Hz, 1H), 2.92–2.85 (m, 1H), 2.22 & 2.21 (two s, 3H), 1.34–1.28 (m, 6H), 0.92 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 185.7, 157.2, 149.51 & 149.48 (1C), 147.5 (dd, J = 19.9, 7.0 Hz), 138.09 & 138.07 (1C), 137.7, 137.02 & 137.00 (1C), 136.7, 135.2 (dd, J = 23, 4 Hz, 1C), 131.77 & 131.71 (1C), 130.5, 130.4, 130.17 & 130.11 (1C), 129.44 & 129.36 (1C), 127.10 & 127.07 (1C), 126.69 & 126.64 (1C), 126.26 & 126.21 (1C), 126.04 & 125.98 (1C), 125.48 & 125.34 (1C), 123.59 & 123.51 (1C), 115.3 (dd, J = 190, 11 Hz, 1C), 61.8 & 61.77 (1C), 51.6, 41.50 & 41.43 (1C), 39.4, 36.6, 20.32 & 20.29 (1C), 20.11, 16.39 & 16.36 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 19.43; IR (Neat) ν_{max} 2978, 2925, 1633, 1452, 1217, 1020, 958, 850, 743 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_5\text{PS}^+$ [$\text{M}+\text{H}$], 569.2234; found 569.2236.

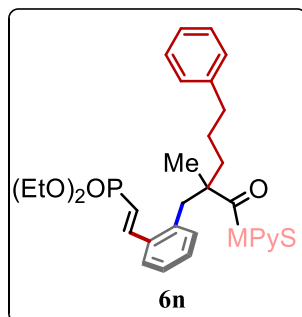
N-[(E)-2-(2-(2-(diethoxyphosphoryl) vinyl)benzyl)-2-methyl-4-phenyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6m):



Following the general procedure GP-3, the compound **6m** (52 mg, 60% colorless thick liquid), was prepared from the reaction of **1m**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.73–8.66 (m, 1H), 8.32 (d, J = 7.9 Hz, 1H), 8.07–7.86 (m, 2H), 7.61–7.49 (m, 2H), 7.36–7.15 (m, 8H), 6.21–6.10 (m, 1H), 4.19–4.02 (m, 4H), 3.51 & 3.48 (two s, 3H), 3.34–3.20 (m, 1H), 3.05 (d, J = 14.0 Hz, 1H), 2.64–2.39 (m, 2H), 2.20 (qd, J = 13.0, 4.4 Hz, 1H), 1.69 (dtd, J = 18.4, 12.7, 5.5 Hz, 1H), 1.39–1.31 (m, 6H), 1.06 (d, J = 9.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 185.75 & 185.64 (1C), 157.32 & 157.21 (1C), 149.61 & 149.59 (1C), 147.5 (dd, J = 19.8, 7.2 Hz), 142.94 & 142.72 (1C), 138.13 & 138.06 (1C), 137.86 & 137.80 (1C), 134.9 (dd, J = 22, 9 Hz, 1C), 131.68 & 131.64 (1C), 129.52 & 129.39 (1C), 128.37 & 128.34 (1C), 128.2, 127.1, 126.67 & 126.57

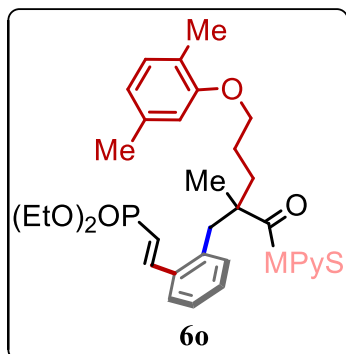
(1C), 126.20 & 126.13 (1C), 125.55 & 125.52 (1C), 123.78 & 123.65 (1C), 115.1 (dd, J = 190, 16 Hz, 1C), 61.70, 50.22 & 50.11 (1C), 42.74 & 42.55 (1C), 41.37 & 40.99 (1C), 39.76 & 39.67 (1C), 31.08 & 30.99 (1C), 20.32 & 20.14 (1C), 16.41 & 16.36 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 19.55 & 19.41 (1P). IR (Neat) ν_{max} 2927, 1633, 1452, 1219, 1020, 958, 855, 748 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_5\text{PS}^+$ $[\text{M}+\text{H}]$, 569.2234; found 569.2236.

N-[(*E*)-2-(2-(2-(diethoxyphosphoryl) vinyl)benzyl)-2-methyl-4-phenyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6n):



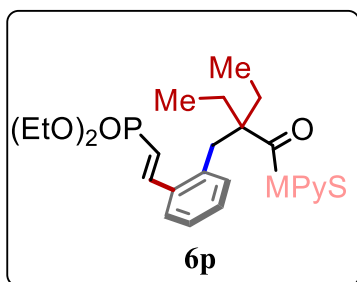
Following the general procedure GP-3, the compound **6n** (52 mg, 61% colorless thick liquid), was prepared from **1n**, **2a** and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.64–8.53 (m, 1H), 8.23 (dd, J = 7.9, 3.1 Hz, 1H), 8.01–7.83 (m, 2H), 7.55–7.45 (m, 2H), 7.29–7.10 (m, 8H), 6.14 (ddd, J = 19.0, 17.4, 7.1 Hz, 1H), 4.16–4.07 (m, 4H), 3.42 & 3.38 (two s, 3H), 3.26–3.11 (m, 1H), 2.96 (dd, J = 13.8, 6.1 Hz, 1H), 2.62–2.52 (m, 2H), 1.95–1.87 (m, 1H), 1.65–1.40 (m, 3H), 1.37–1.29 (m, 6H), 0.94 (bs, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 185.96 & 185.82 (1C), 157.29 & 157.22 (1C), 149.5, 147.6 (dd, J = 18, 7 Hz, 1C), 142.53 & 142.41 (1C), 138.05 & 138.02 (1C), 137.99 & 137.93 (1C), 134.9 (d, J = 23 Hz, 1C), 131.60 & 131.58 (1C), 129.4, 128.45 & 128.40 (1C), 128.11 & 128.08 (1C), 127.00 & 126.96 (1C), 126.56 & 126.47 (1C), 126.13 & 126.05 (1C), 125.52 & 125.50 (1C), 123.62 & 123.54 (1C), 115.0 (dd, J = 190, 13 Hz, 1C), 61.77 & 61.73 (1C), 50.00 & 49.88 (1C), 41.21 & 40.96 (1C), 40.26 & 40.22 (1C), 39.57 & 39.50 (1C), 36.38 & 36.27 (1C), 26.26 & 26.22 (1C), 20.36 & 20.34 (1C), 16.40 & 16.35 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 19.58, 19.44 (1P). IR (Neat) ν_{max} 2929, 1632, 1452, 1218, 1020, 957, 854, 748 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{31}\text{H}_{40}\text{N}_2\text{O}_5\text{PS}^+$ $[\text{M}+\text{H}]$, 583.2390; found 583.2395.

N-[(E)-2-(2-(2-(diethoxyphosphoryl) vinyl) benzyl)-5-(2,5-dimethylphenoxy)-2-methylpentanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6o):



Following the general procedure GP-3, the compound **6o** (76 mg, 61% colorless thick liquid), was prepared from the reaction of **1o**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.56 (m, 1H), 8.31–8.23 (m, 1H), 8.03–7.84 (m, 2H), 7.58–7.45 (m, 2H), 7.31–7.12 (m, 3H), 6.99 (dd, $J = 7.3, 4.6$ Hz, 1H), 6.63 (dd, $J = 16.0, 6.2$ Hz, 2H), 6.19–6.12 (m, 1H), 4.17–4.05 (m, 4H), 3.94–3.84 (m, 2H), 3.43 & 3.41 (two s, 3H), 3.29–3.19 (m, 1H), 3.01 (dd, $J = 13.9, 1.6$ Hz, 1H), 2.30 (s, 3H), 2.14 (s, 3H), 2.07–1.97 (m, 1H), 1.78–1.51 (m, 3H), 1.37–1.30 (m, 6H), 1.00 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 185.86 & 185.76 (1C), 157.35 & 157.25 (1C), 157.04 & 157.00 (1C), 149.63 & 149.58 (1C), 147.7 (dd, $J = 17, 8$ Hz, 1C), 138.10 & 138.01 (1C), 137.94 & 137.91 (1C), 136.40, 135.1 (dd, $J = 23, 5$ Hz, 1C), 131.7, 130.2, 129.48 & 129.38 (1C), 127.08 & 127.05 (1C), 126.66 & 126.58 (1C), 126.24 & 126.17 (1C), 123.62 & 123.57 (1C), 123.53 & 123.51 (1C), 120.54 & 120.52 (1C), 115.3 (dd, $J_{C-P} = 191, 13$ Hz, 1C), 112.00 & 111.97 (1C), 68.25 & 68.15 (1C), 61.79 & 61.75 (1C), 49.83 & 49.73 (1C), 41.08 & 40.90 (1C), 39.64 & 39.55 (1C), 36.87 & 36.69 (1C), 24.77 & 24.72 (1C), 21.4, 20.55 & 20.52 (1C), 16.43 & 16.38 (1C), 15.79 & 15.77 (1C). ^{31}P NMR (202 MHz, CDCl_3) δ 19.61, 19.50. IR (Neat) ν_{max} 2924, 1738, 1633, 1451, 1219, 1157, 1021, 957, 800, 751 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{33}\text{H}_{44}\text{N}_2\text{O}_6\text{PS}^+$ $[\text{M}+\text{H}]$, 627.2652; found 627.2648.

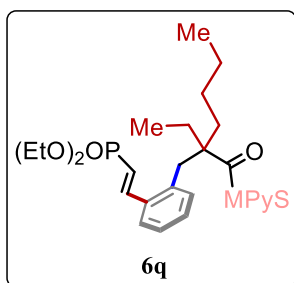
N-[(E)-2-(2-(2-(diethoxyphosphoryl) vinyl) benzyl)-2-ethyl butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6p):



Following the general procedure GP-3, the compound **6p** (70 mg, 69% as colorless thick liquid), was prepared from **1p**, **2a**, and **3m**. ^1H NMR (500 MHz, CDCl_3) δ 8.65 (d, $J = 4.1$ Hz, 1H), 8.21 (d, $J = 7.9$ Hz, 1H), 8.03–7.92 (m, 2H), 7.53–7.43 (m, 2H), 7.21–7.12 (m, 3H), 6.10 (dd, $J = 19.0, 17.4$ Hz, 1H), 4.16–4.07 (m, 4H), 3.40 (s, 3H), 3.08–3.01 (m, 2H), 1.64 (dt, $J = 14.9, 7.2$ Hz, 2H),

1.56–1.45 (m, 2H), 1.34 (td, $J = 7.1, 1.4$ Hz, 6H), 0.81–0.73 (m, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 186.0, 157.4, 149.5, 147.73, 147.66, 138.2, 138.0, 135.0 (d, $J = 23$ Hz), 131.0, 129.3, 127.0, 126.3, 123.6, 115.2 (d, $J_{C-P} = 191$ Hz), 61.7, 52.6, 39.5, 36.6, 26.4, 26.3, 16.4, 16.4, 8.5. ^{31}P NMR (202 MHz, $CDCl_3$) δ 19.48. IR (Neat) ν_{max} 2964, 2930, 1630, 1452, 1217, 1021, 957, 752 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{25}H_{36}N_2O_5PS^+$ [M+H], 507.2077; found 507.2079.

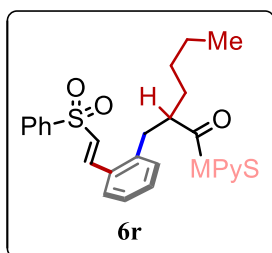
N-[(E)-2-(2-(2-(diethoxyphosphoryl) vinyl) benzyl)-2-ethyl hexanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6q):



Following the general procedure GP-3, the compound **6q** (79 mg, 74% colorless thick liquid), was prepared from the reaction of **1q**, **2a**, and **3m**. 1H NMR (500 MHz, $CDCl_3$) δ 8.67–8.62 (m, 1H), 8.20 (dt, $J = 16.4, 8.2$ Hz, 1H), 8.05–7.92 (m, 2H), 7.54–7.43 (m, 2H), 7.20–7.11 (m, 3H), 6.14–6.06 (m, 1H), 4.16–4.08 (m, 4H),

3.40 (bs, 3H), 3.10–3.00 (m, 2H), 1.71–1.40 (m, 5H), 1.34 (t, $J = 7.1$ Hz, 6H), 1.26–1.18 (m, 3H), 0.85–0.72 (m, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 186.1, 157.41 & 157.39 (1C), 149.43 & 149.41 (1C), 147.67 & 147.65 (1C), 147.62 & 147.59 (1C), 138.2, 137.98 & 137.96 (1C), 135.0 (dd, $J = 22, 1$ Hz, 1C), 130.9, 129.29 & 129.27 (1C), 127.0, 126.31 & 126.23 (1C), 123.65 & 123.62 (1C), 115.2 (dd, $J_{C-P} = 191, 5$ Hz, 1C), 61.70 & 61.66 (1C), 52.4, 39.5, 37.12 & 37.03 (1C), 33.87 & 33.72 (1C), 26.66 & 26.45 (1C), 26.0, 23.3, 16.42 & 16.37 (1C), 13.98 & 13.95 (1C), 8.60 & 8.57 (1C). ^{31}P NMR (202 MHz, $CDCl_3$) δ 19.42 (1P). IR (Neat) ν_{max} 2974, 1630, 1200, 1117, 1020, 958, 837, 779, 751 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{27}H_{40}N_2O_5PS^+$ [M+H], 535.2390; found 535.2396.

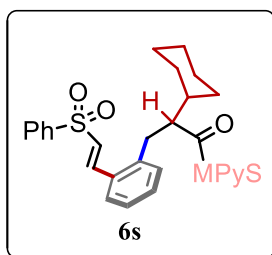
N-[(E)-2-(2-(2-(phenylsulfonyl) vinyl)benzyl) hexanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6r):



Following the general procedure GP-3, the compound **6r** (48 mg, 47% colorless thick liquid), was prepared from the reaction of **1r**, **2a**, and **3l**. The unreacted starting material **1r** (17 mg, 32%) was recovered. 1H NMR (500 MHz, $CDCl_3$) δ 8.68–8.60 (m, 1H), 8.27–8.12 (m, 2H), 8.06–7.89 (m, 3H), 7.65–7.48 (m, 5H), 7.41 (d, J

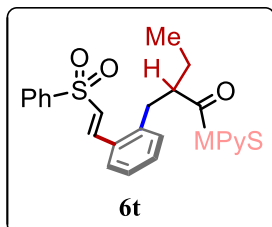
= 7.6 Hz, 1H), 7.25–7.12 (m, 2H), 6.75 (d, J = 15.2 Hz, 1H), 3.42 & 3.41 (two s, 3H), 3.24–3.16 (m, 1H), 2.80–2.66 (m, 1H), 2.58–2.49 (m, 1H), 1.71–1.60 (m, 1H), 1.40–1.34 (m, 1H), 1.28–1.18 (m, 4H), 0.81 (t, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 184.1, 156.8, 149.7, 140.8, 140.7, 140.6, 138.1, 133.3, 131.3, 131.1, 130.6, 129.3, 128.4, 127.7, 127.1, 127.0, 126.7, 123.57 & 123.40 (1C), 51.2, 39.61 & 39.51 (1C), 36.2, 31.84 & 31.63 (1C), 29.54 & 29.42 (1C), 22.7, 13.9. IR (Neat) ν_{max} 2927, 1633, 1452, 1303, 1217, 1142, 1083, 976, 839, 751 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{27}H_{31}N_2O_4S_2^+$ [M+H], 511.1720; found 511.1720.

N-[(E)-2-cyclohexyl-3-(2-(2-(phenylsulfonyl) vinyl) phenyl) propanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (6s):



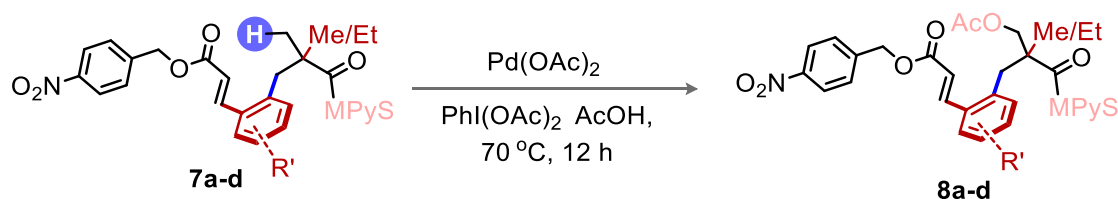
Following the general procedure GP-3, the compound **6s** (56 mg, 53% colorless thick liquid), was prepared from the reaction of **1s**, **2a**, and **3l**. 1H NMR (500 MHz, $CDCl_3$) δ 8.60–8.55 (m, 1H), 8.14–8.01 (m, 2H), 7.99–7.93 (m, 2H), 7.88 (dtd, J = 9.5, 7.8, 1.7 Hz, 1H), 7.64–7.58 (m, 1H), 7.58–7.51 (m, 2H), 7.51–7.44 (m, 1H), 7.36 (dd, J = 7.3, 5.3 Hz, 1H), 7.27–7.09 (m, 3H), 6.73 (dd, J = 15.2, 11.4 Hz, 1H), 3.31 & 3.30 (two s, 3H), 3.02–2.94 (m, 2H), 2.39 (dt, J = 14.8, 6.5 Hz, 1H), 1.93–1.65 (m, 8H), 1.19–1.09 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 183.3, 157.0, 149.51 & 149.45 (1C), 141.0, 140.8, 137.9, 133.3, 131.26 & 131.19 (1C), 131.1, 130.9, 130.59 & 130.55 (1C), 129.3, 128.1, 127.69 & 127.65 (1C), 127.02 & 126.99 (1C), 126.86 & 126.80 (1C), 126.4, 123.31 & 123.16 (1C), 57.41 & 57.30 (1C), 41.01 & 40.95 (1C), 39.29 & 39.25 (1C), 32.58 & 32.41 (1C), 30.97 & 30.94 (1C), 30.51 & 30.49 (1C), 26.48 & 26.41 (1C). IR (Neat) ν_{max} 2923, 1631, 1445, 1304, 1209, 1143, 1082, 1024, 970, 839, 753 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $C_{29}H_{33}N_2O_4S_2^+$ [M+H], 537.1876; found 537.1875.

N-[(*E*)-2-(2-(2-(phenylsulfonyl) vinyl) benzyl) butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (**6t**):



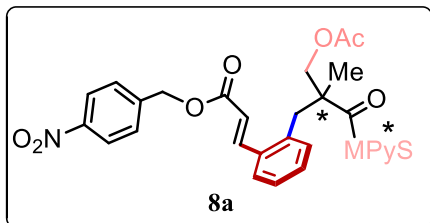
Following the general procedure GP-3, the compound **6t** (39 mg, 40% colorless thick liquid), was prepared from the reaction of **1t**, **2a**, and **3l**. The unreacted starting material **1t** (17 mg, 35%) was recovered. ^1H NMR (500 MHz, CDCl_3) δ 8.68–8.64 (m, 1H), 8.28–8.13 (m, 2H), 8.03–7.93 (m, 3H), 7.63–7.58 (m, 1H), 7.57–7.49 (m, 3H), 7.43–7.40 (m, 1H), 7.25–7.15 (m, 3H), 6.76 (dd, J = 15.2, 2.6 Hz, 1H), 3.43 & 3.42 (two s, 3H), 3.20 (ddd, J = 14.0, 7.4, 2.1 Hz, 1H), 2.82–2.70 (m, 1H), 2.51–2.42 (m, 1H), 1.72–1.61 (m, 1H), 1.50–1.40 (m, 1H), 0.89–0.83 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 183.9, 156.9, 149.69 & 149.60 (1C), 140.9, 140.7, 140.6, 138.12 & 138.10 (1C), 133.3, 131.36 & 131.30 (1C), 131.11 & 131.03 (1C), 130.6, 129.3, 128.55 & 128.48 (1C), 127.73 & 127.72 (1C), 127.2, 127.01 & 126.96 (1C), 126.7, 123.51 & 123.37 (1C), 52.83 & 52.75 (1C), 39.60 & 39.55 (1C), 35.7, 25.13 & 25.05 (1C), 11.86 & 11.79 (1C). IR (Neat) ν_{max} 2926, 1633, 1446, 1303, 1207, 1142, 1083, 975, 840, 750 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}_4\text{S}_2^+$ [$\text{M}+\text{H}$], 483.1407; found 483.1408.

3.6.3.5. General procedure for iterative $C(sp^3)-H$ acetoxylation of 1,2- difunctionalized products (GP-4):



A screw-capped tube (5.0 mL) equipped with a magnetic stir bar was charged with difunctionalized arenes (**7a–d**; 0.1 mmol), $\text{Pd}(\text{OAc})_2$ (2.24 mg, 10.0 mol%), $\text{PhI}(\text{OAc})_2$ (48.3 mg, 1.5 mmol), AcOH (1.0 mL) in open air. The resulting mixture was stirred at 70 °C for 12 h. Solvent was evaporated under the reduced pressure and the crude material was purified using column chromatography on silica gel eluting with ethyl acetate and hexane mixture.

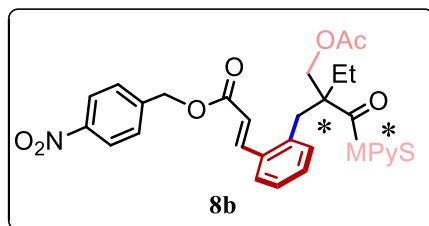
N-[(*E*)-3-acetoxy-2-methyl-2-(2-(3-((4-nitrobenzyl)oxy)-3-oxoprop-1-en-1-yl)benzyl)propanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (**8a** and **8a'**):



Following the general procedure GP-4, the inseparable mixture of compounds **8a** and **8a'** (32 mg, 55%, and **d.r** 2.7:1) are obtained as colorless thick liquid. ^1H NMR (500 MHz, CDCl_3) δ 8.72–8.66 (m, 1H), 8.29–8.16 (m, 4H), 8.01–7.97 (m, 1H), 7.60–7.53 (m, 4H), 7.24–7.15 (m, 3H), 6.40 (dd, J = 15.8, 8.7 Hz, 1H), 5.32 (s, 2H), 4.16–4.04 (m, 2H), 3.40 & 3.39 (two s, 3H, **2:1**), 3.18–3.13 (m, 2H), 2.03 & 2.02 (two s, 3H, **2:1**), 1.08 & 1.07 (two s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 183.3, 170.9, 166.4, 156.9, 149.6, 147.6, 144.3, 143.5, 138.2, 137.6, 134.0, 132.0, 129.9, 128.2, 127.3, 126.9, 126.6, 123.8, 123.6, 118.1, 68.3, 64.6, 49.4, 39.5, 36.3, 20.9, 20.1; IR (Neat) ν_{max} 2923, 2850, 2360, 1712, 1628, 1519, 1345, 1312, 1216, 1154, 1036, 978, 854, 762 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{29}\text{H}_{30}\text{N}_3\text{O}_8\text{S}^+$ [$\text{M}+\text{H}$], 580.1748; found 580.1744.

Some representative peaks for the minor isomer: $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 68.48, 36.68.

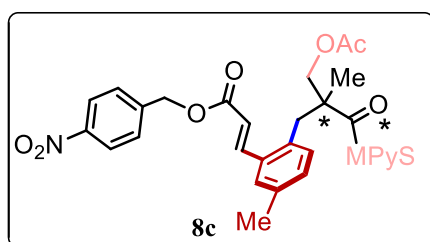
N-[(*E*)-2-(acetoxymethyl)-2-(2-(3-((4-nitrobenzyl)oxy)-3-oxoprop-1-en-1-yl)benzyl)butanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (**8b**):



Following the general procedure GP-4, the inseparable mixture of compounds **8b** and **8b'** (42 mg, 71%, and **d.r** 1:1) are obtained as colorless thick liquid. ^1H NMR (500 MHz, CDCl_3) δ 8.72–8.64 (m, 1H), 8.32–8.20 (m, 4H), 8.01–7.95 (m, 1H), 7.62–7.52 (m, 4H), 7.26–7.15 (m, 3H), 6.38 (dd, J = 15.7, 2.5 Hz, 1H), 5.32 (s, 2H), 4.18–4.04 (m, 1H), 3.97–3.92 (m, 1H), 3.38 & 3.36 (two s, 3H), 3.24–3.19 (m, 1H), 3.07 (dd, J = 14.2, 2.3 Hz, 1H), 2.02 & 2.01 (two s, 3H), 1.76–1.68 (m, 1H), 1.62–1.58 (m, 1H), 0.85–0.74 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.74 & 182.67 (1C), 170.99 & 170.94 (1C), 166.52 & 166.46 (1C), 156.9, 149.62 & 149.55 (1C), 147.6, 144.64 & 144.56 (1C), 143.5, 138.15 & 138.09 (1C), 137.9, 133.9, 131.78 & 131.66

(1C), 130.0, 128.3, 127.3, 126.9, 126.6, 123.8, 123.69 & 123.58 (1C), 117.97 & 117.87 (1C), 64.6, 63.93 & 63.82 (1C), 52.86 & 52.80 (1C), 39.59 & 39.56 (1C), 35.59 & 35.47(1C), 27.67 & 27.51(1C), 20.9, 8.57 & 8.51(1C); **IR (Neat)** $\nu_{\max}$ 2924, 2851, 1714, 1628, 1519, 1345, 1313, 1217, 1155, 1084, 978, 843, 760, 736 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{30}\text{H}_{32}\text{N}_3\text{O}_8\text{S}^+$ $[\text{M}+\text{H}]$, 594.1905; found 594.1907.

N-[(E)-3-acetoxy-2-methyl-2-(4-methyl-2-(3-((4-nitrobenzyl) oxy)-3-oxoprop-1-en-1-yl) benzyl) propanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (8c):

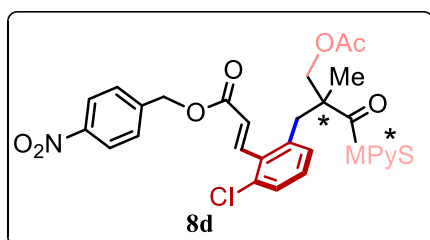


Following the general procedure GP-4, the inseparable mixture of compounds **8c** and **8c'** (37 mg, 63%, and **d.r** 2.4:1) are obtained in as colorless thick liquid

^1H NMR (500 MHz, CDCl_3) δ 8.71–8.65 (m, 1H), 8.29–8.15 (m, 4H), 8.02–7.95 (m, 1H), 7.61–7.53 (m, 3H), 7.42–7.34 (m, 1H), 7.15–7.01 (m, 2H), 6.43–6.36 (m, 1H), 5.32 (s, 2H), 4.16–4.03 (m, 2H), 3.40 (s, 3H), 3.15–3.09 (m, 2H), 2.30 (s, 3H), 2.03 (s, 3H), 1.07 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 183.4, 170.9, 166.4, 157.0, 149.66 & 149.62 (1C), 147.6, 144.5, 143.5, 138.1, 136.5, 134.6, 133.8, 131.9, 130.9, 128.2, 127.2, 127.0, 123.9, 123.5, 117.8, 68.4, 64.6, 49.4, 39.53 & 39.52 (1C), 36.0, 20.94, 20.88, 20.1; **IR (Neat)** $\nu_{\max}$ 2924, 2852, 2359, 1713, 1630, 1519, 1345, 1218, 1157, 1036, 979, 835, 736 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{30}\text{H}_{32}\text{N}_3\text{O}_8\text{S}^+$ $[\text{M}+\text{H}]$, 594.1905; found 594.1909.

Some representative peaks for the minor isomer: $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 68.56, 49.46, 39.53, 36.36, 20.03.

N- [(E)-3-acetoxy-2-(3-chloro-2-(3-((4-nitrobenzyl) oxy)-3-oxoprop-1-en-1-yl) benzyl)-2-methylpropanoic acid]-S-methyl-S-(2-pyridyl) sulfoximine (8d):



Following the general procedure GP-4, the inseparable mixture of compounds **8d** and **8d'** (46 mg, 75%, and **d.r** 2.3:1) are obtained as colorless thick liquid. ^1H NMR (500 MHz, CDCl_3) δ 8.74–8.61 (m, 1H),

8.30–8.17 (m, 3H), 8.03–7.93 (m, 1H), 7.92–7.81 (m, 1H), 7.63–7.49 (m, 3H), 7.25–7.05 (m, 3H), 6.33–6.20 (m, 1H), 5.34 (s, 2H), 4.21–3.97 (m, 2H), 3.42–3.38 (s, 3H), 3.16–3.00 (m, 2H), 2.0 (s, 3H), 1.06 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 183.0, 170.83 & 170.80 (1C), 165.60 & 165.58 (1C), 156.8, 149.69 & 149.66 (1C), 147.7, 143.2, 143.0, 138.25 & 138.19 (1C), 134.1, 133.1, 129.6, 128.9, 128.3, 128.2, 127.3, 125.0, 123.8, 123.6, 68.7, 64.8, 49.6, 39.57 & 39.55 (1C), 37.51 & 37.17 (1C), 20.8, 20.04 & 19.9 (1C); IR (Neat) ν_{max} 2850, 1718, 1638, 1519, 1345, 1303, 1262, 1157, 981, 842, 733 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{29}\text{H}_{29}\text{ClN}_3\text{O}_8\text{S}^+$ $[M+H]$, 614.1358; found 614.1356.

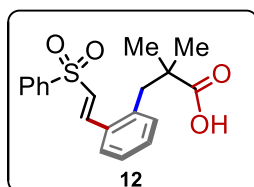
Some representative peaks for the minor isomer: $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 68.64, 49.57, 39.57, 37.51, 20.04.

3.6.3.6. Procedure for the Cleavage of MPyS:

To a solution of **11** (1.25 mmol) in MeOH: H_2O (1:1 mL) was added NaOH (5.0 equiv). The resulting mixture was refluxed overnight. After reaction completion, MeOH was evaporated, and the reaction mixture was neutralized with 2N HCl. The crude mixture was then extracted with EtOAc, dried over Na_2SO_4 , and concentrated under vacuum to give the corresponding carboxylic acid.

Next, the water layer was neutralized with 2N NaOH to strictly maintain pH = 7. The water layer was extracted by EtOAc, dried over Na_2SO_4 , and concentrated under vacuum to give the corresponding S-methyl-S-(2-pyridyl) sulfoximine in 70% yield.

(E)-2,2-dimethyl-3-(2-(2-(phenylsulfonyl)vinyl)phenyl)propanoic acid (**12**):



Compound **12** (0.435 gm, 95%) was prepared as reddish liquid; ^1H NMR (500 MHz, CDCl_3) δ 8.03 (d, J = 15.2 Hz, 1H), 7.95 (dd, J = 8.4, 1.2 Hz, 2H), 7.68–7.45 (m, 6H), 7.34–7.30 (m, 1H), 7.23 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 15.2 Hz, 1H), 3.08 (d, J = 19.6 Hz, 2H), 1.17 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.3, 140.7, 140.5, 138.0, 133.4, 132.2, 132.1, 130.6, 129.3, 128.4, 127.7, 127.3, 127.0, 44.0, 41.5, 24.9; IR (Neat) ν_{max} 3219, 2932,

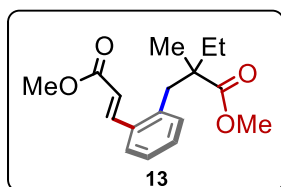
1729, 1597, 1444, 1275, 1078, 972, 847, 750 cm⁻¹; **HRMS (ESI)** *m/z*: calcd. for C₁₉H₂₀NaO₄S⁺ [M+Na], 367.0975; found 367.0979.

3.6.3.7. Procedure for the Cleavage of MPyS:

To a solution of **4k** (0.1 mmol) in MeOH: H₂O (1:1 mL) was added NaOH (5.0 equiv). The resulting mixture was refluxed overnight. After reaction completion, MeOH was evaporated, and the reaction mixture was neutralized with 2N HCl. The crude mixture was then extracted with EtOAc, dried over Na₂SO₄, and concentrated under vacuum to give the corresponding carboxylic acid.

Next, the crude mixture was dissolved in MeOH and SOCl₂ (2.5 equiv) was added dropwise at 0 °C. The resulting mixture was stirred at rt for 12 h. The reaction mixture was extracted with EtOAc and washed with water 2 times, dried over Na₂SO₄. Solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography eluting with EA/hexane (3:97) on silica gel.

(E)-methyl 2-(2-(3-methoxy-3-oxoprop-1-en-1-yl)benzyl)-2-methylbutanoate (**13**):

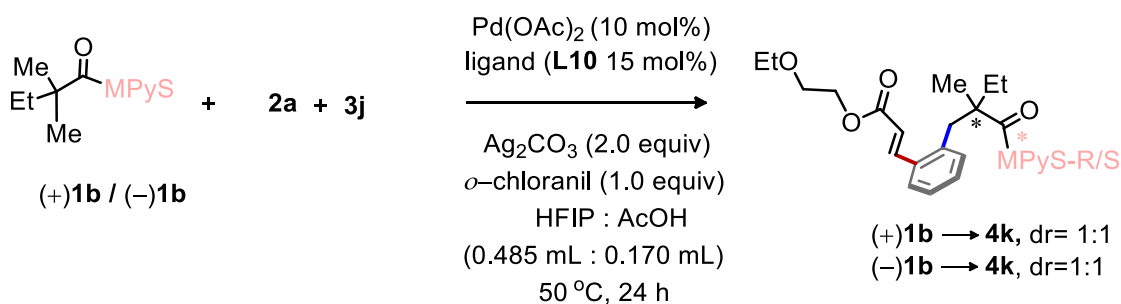


Compound **13** (0.038 gm, 65%) was prepared as colorless liquid; ¹H NMR (500 MHz, CDCl₃) δ 8.04 (d, *J* = 15.8 Hz, 1H), 7.57 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.31–7.20 (m, 3H), 7.12 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.35 (d, *J* = 15.8 Hz, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 3.15 (d, *J* = 13.9 Hz, 1H), 2.94 (d, *J* = 13.9 Hz, 1H), 1.88 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.46 (td, *J* = 14.9, 7.5 Hz, 1H), 1.03 (s, 3H), 0.86 (t, *J* = 7.4 Hz, 4H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 176.8, 167.4, 143.1, 137.8, 134.2, 131.5, 129.6, 127.0, 126.6, 118.9, 51.7, 51.6, 48.6, 41.3, 32.7, 20.1, 9.2. **IR (Neat)** ν_{max} 2927, 1728, 1729, 1597, 1444, 1275, 1078, 972, 847, 750 cm⁻¹; **HRMS (ESI)** *m/z*: calcd. for C₁₇H₂₂NaO₄⁺ [M+Na], 313.1415; found 313.1412.

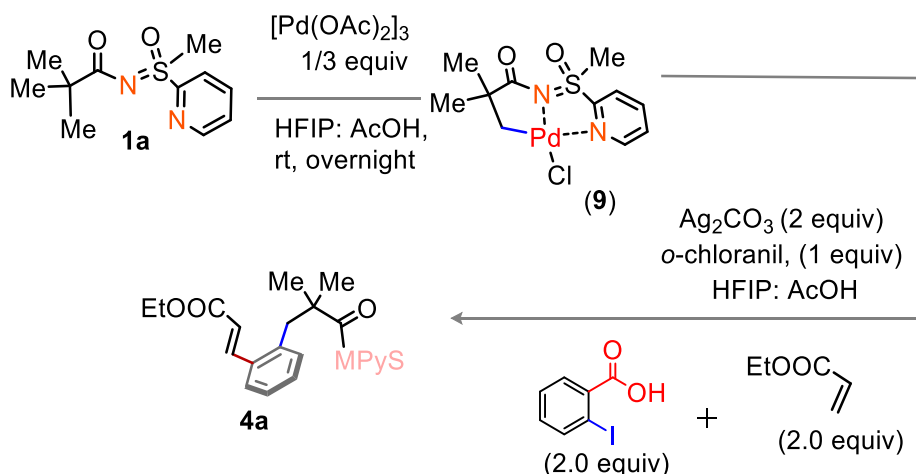
3.6.3.8. Procedure for the Three Component C–H Bond Addition Reaction using Chiral MPyS coupled **1b** :

To a 5 mL screw capped tube equipped with a magnetic stir bar, was independently charged with Pd(OAc)₂ (10 mol%, 4.5 mg), substrate (+)**1b** / (–)**1b** (0.2 mmol), Ag₂CO₃

(0.4 mmol, 110 mg), *o*-chloranil (0.2 mmol, 49 mg), 2-iodobenzoic acid derivative **2** (0.4 mmol), alkene surrogate **3** (0.4 mmol), and **L10** (15 mol%, 5.44 mg) in air. Then, a solvent combination of HFIP (0.97 mL) and AcOH (0.34 mL) was added via syringe. The reaction mixture was stirred at 50 °C for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (DCM), filtered through a small Celite pad, and concentrated in vacuo. The crude reaction mixture was extracted with DCM and washed with saturated $NaHCO_3$ solution and concentrated in vacuo. Finally, the reaction mixture was purified on silica gel using hexane/EtOAc eluent to afford the desired product in 1:1 diastereomeric ratio.



3.6.3.9. Stoichiometric experiment:

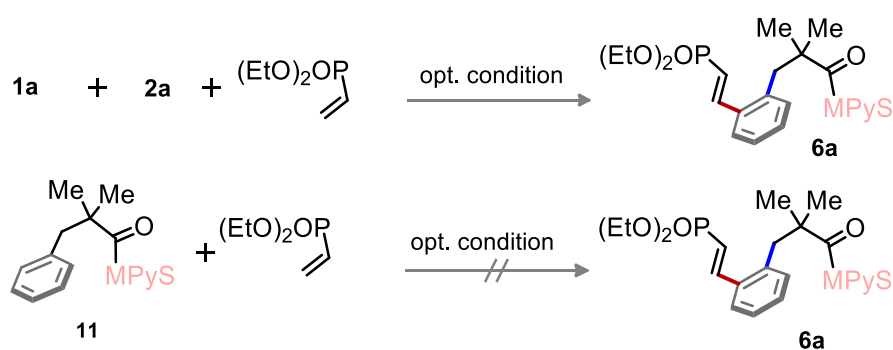


A solution of methylphenyl sulfoximine derived from pivalic acid **1a** (0.133 mmol, 32 mg) and $Pd(OAc)_2$ (0.133 mmol, 30 mg) in HFIP (0.485 mL) : AcOH (0.170 mL) was stirred at room temperature overnight. Then 2-iodobenzoic acid (0.27 mmol, 45 mg) and Ag_2CO_3 (2.0 equiv, 0.27 mmol, 74 mg), *o*-chloranil (1.0 equiv, 0.133 mmol, 33mg),

and ethyl acrylate (2.0 equiv, 0.27 mmol, 27 mg) were added to the crude reaction mixture. Then the reaction mixture was stirred at 50 °C for 12 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (DCM), filtered through a small Celite pad, and concentrated in vacuo. The crude reaction mixture was extracted with DCM and washed with saturated $NaHCO_3$ solution and concentrated in vacuo. The desired compound **4a** was isolated in 45% yield.

The intermediate **9** was obtained and the structure was exactly matched with the structure reported in literature. [14]

3.6.3.10 Competitive study:

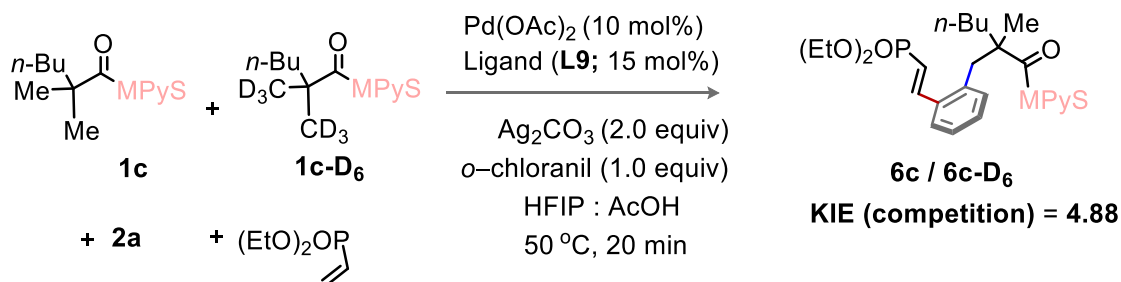


A 5 mL screw capped tube equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (10 mol%, 2.24 mg), **1a** (0.1 mmol), Ag_2CO_3 (0.2 mmol, 55 mg), *o*-chloranil (0.1 mmol, 28 mg), 2-iodobenzoic acid **2a** (0.2 mmol), **3n** (0.2 mmol), and **L9** (15 mol%, 2.88 mg) in air. A combination of HFIP (0.485 mL) and AcOH (0.17 mL) solvent was added. The reaction mixture was stirred at 50 °C for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (DCM), filtered through a small Celite pad, and concentrated in vacuo. The crude reaction mixture was extracted with DCM and washed with saturated $NaHCO_3$ solution and concentrated in vacuo. The compound **6a** was isolated in 72 % yield.

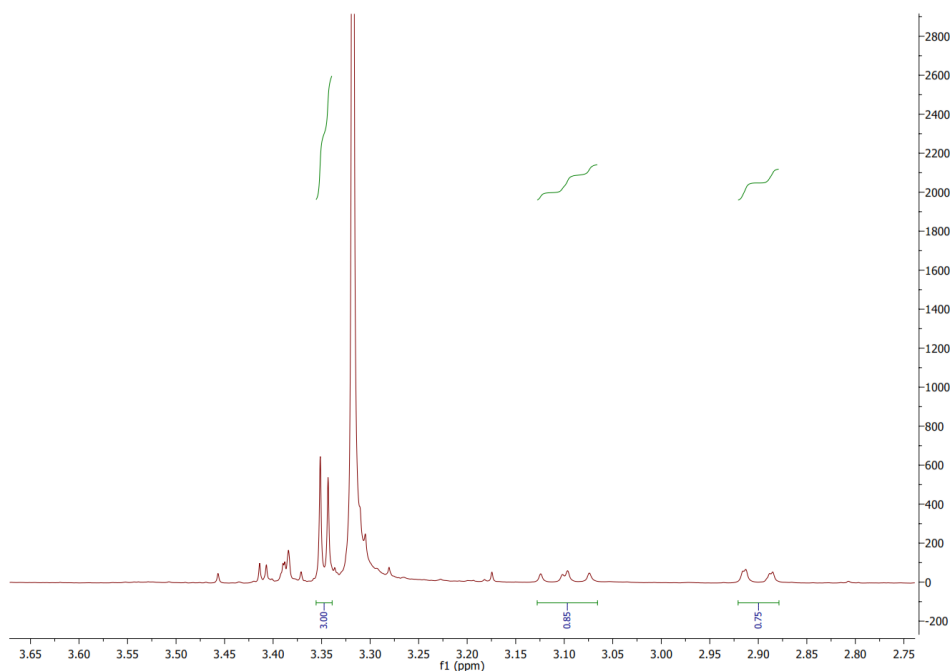
A 5 mL screw capped tube equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (10 mol%, 2.24 mg), substrate **11** (0.1 mmol), Ag_2CO_3 (0.2 mmol, 55 mg), *o*-chloranil (0.1 mmol, 28 mg), **3n** (0.2 mmol), and **L9** (15 mol%, 2.88 mg) in air. Then,

a combination of HFIP (0.485 mL) and AcOH (0.17 mL) solvent was added. The reaction mixture was stirred at 50 °C for 24 h. No desired product **6a** was isolated.

3.6.3.11. Procedure for the competitive KIE study:



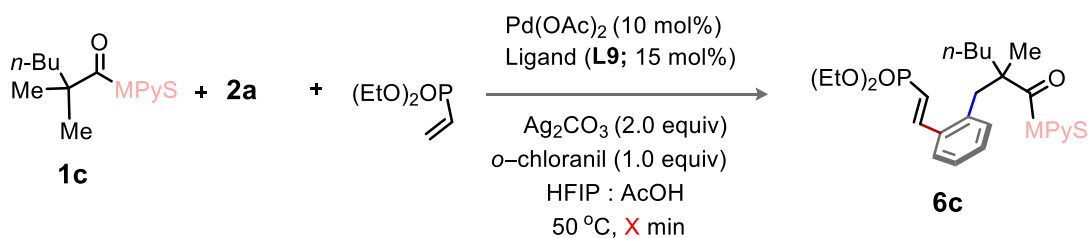
A 5 mL sealed tube equipped with a magnetic stir bar was charged with Pd(OAc)_2 (10 mol%, 4.5 mg), **1b** (0.1 mmol) and **1b-D₆** (0.1 mmol), Ag_2CO_3 (0.4 mmol, 110 mg), *o*-chloranil (0.2 mmol, 49 mg), 2-iodobenzoic acid **2a** (0.4 mmol), diethyl vinyl phosphonate **4m** (0.4 mmol), and **L9** (15 mol%, 5.77 mg) in air. Then, a combination of HFIP (0.97 mL) and AcOH (0.340 mL) solvent was added. The reaction mixture was stirred at 50 °C for 20 min. Then, the reaction mixture was cooled to 0 °C, diluted with CH_2Cl_2 (DCM), filtered through a small Celite pad, and concentrated in vacuo. The competitive KIE was determined by crude $^1\text{H-NMR}$ analysis.



$$KIE = k_H/k_D = 1.6 / 0.4 = 4$$

3.6.3.12. Procedure for the parallel KIE study:

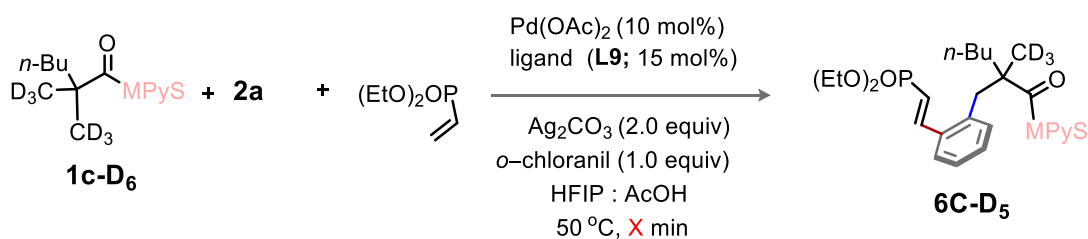
A 5 mL sealed tube equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (10 mol%, 4.5 mg), substrate **1b** (0.2 mmol, 54 mg), Ag_2CO_3 (0.4 mmol, 110 mg), *o*-chloranil (0.2 mmol, 49 mg), 2-iodobenzoic acid **2a** (0.4 mmol, 99 mg), diethyl vinyl phosphonate **4m** (0.4 mmol, 0.061 mL), and **L9** (15 mol%, 5.77 mg) in air. Then, a solvent combination of HFIP (0.97 mL) and AcOH (0.340 mL) was added. The reaction mixture was stirred at 50 °C. The aliquot was removed from the reaction mixture in different time interval shown below. The crude material was diluted with CH_2Cl_2 (DCM), filtered through a small Celite pad, and concentrated in vacuo. The conversion was determined by 1H -NMR analysis.



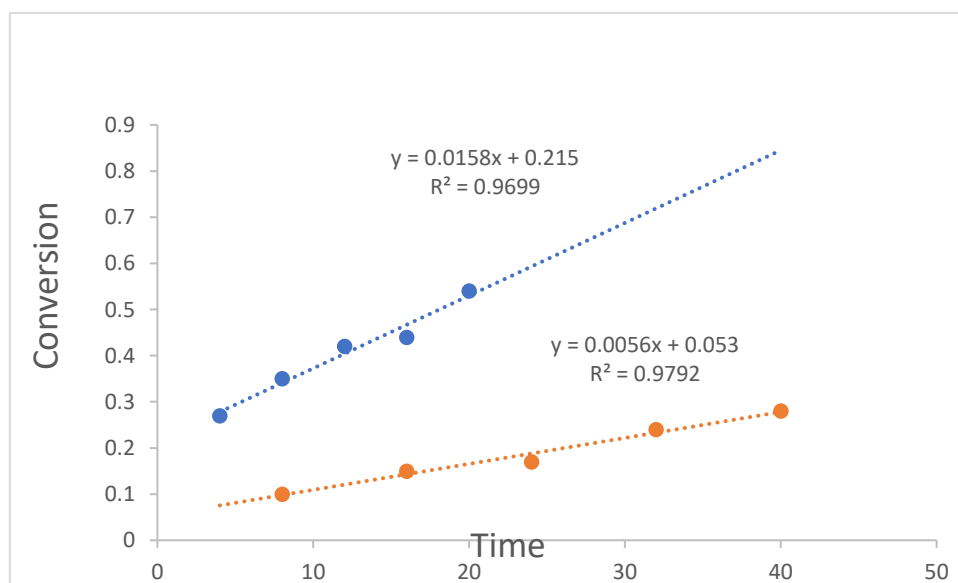
Time (min)	Conversion
4	0.27
8	0.35
12	0.42
16	0.44
20	0.54

A 5 mL sealed tube equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (10 mol%, 4.5 mg), substrate **1b-D₆** (0.2 mmol, 54 mg), Ag_2CO_3 (0.4 mmol, 110 mg), *o*-chloranil (0.2 mmol, 49 mg), 2-iodobenzoic acid **2a** (0.4 mmol, 99 mg), diethyl vinyl phosphonate **4m** (0.4 mmol, 0.061ml), and **L9** (15 mol%, 5.77 mg) in air. Then, a solvent

combination of HFIP (0.97 mL) and AcOH (0.340 mL) was added. The reaction mixture was stirred at 50 °C. The aliquot was removed from the reaction mixture in different time interval shown below. The crude material was diluted with CH₂Cl₂ (DCM), filtered through a small Celite pad, and concentrated in vacuo. The conversion was determined by ¹H-NMR analysis.



Time (min)	Conversion
8	0.1
16	0.15
24	0.17
32	0.24
40	0.28



$$\text{KIE} = k_{\text{H}}/k_{\text{D}} = 0.0158 / 0.0056 = 2.82$$

3.6.3.13. X-ray crystallography:

Single crystal X-ray data for the compound **4p** were collected using the detector system [$\lambda(\text{Mo-K}\alpha) = 0.71073 \text{ \AA}$] at 293K, graphite monochromator with a ω scan width of 0.30, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software²⁸ was used for the intensity data acquisition and the SAINTPLUS Software²⁸ was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program,²⁸ 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-97,²⁹ 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.

X-ray crystal structure and data for 4p: The compound was recrystallized via vapor diffusion of DCM and Hexane at -4 °C.



Figure 3.5. Molecular structures of compound **4p**; thermal ellipsoids are set at 30% probability.

Table 3.5. Crystal data for **4p**

Identification code	4p
Formula	C ₂₆ H ₂₃ F ₅ N ₂ O ₂ S

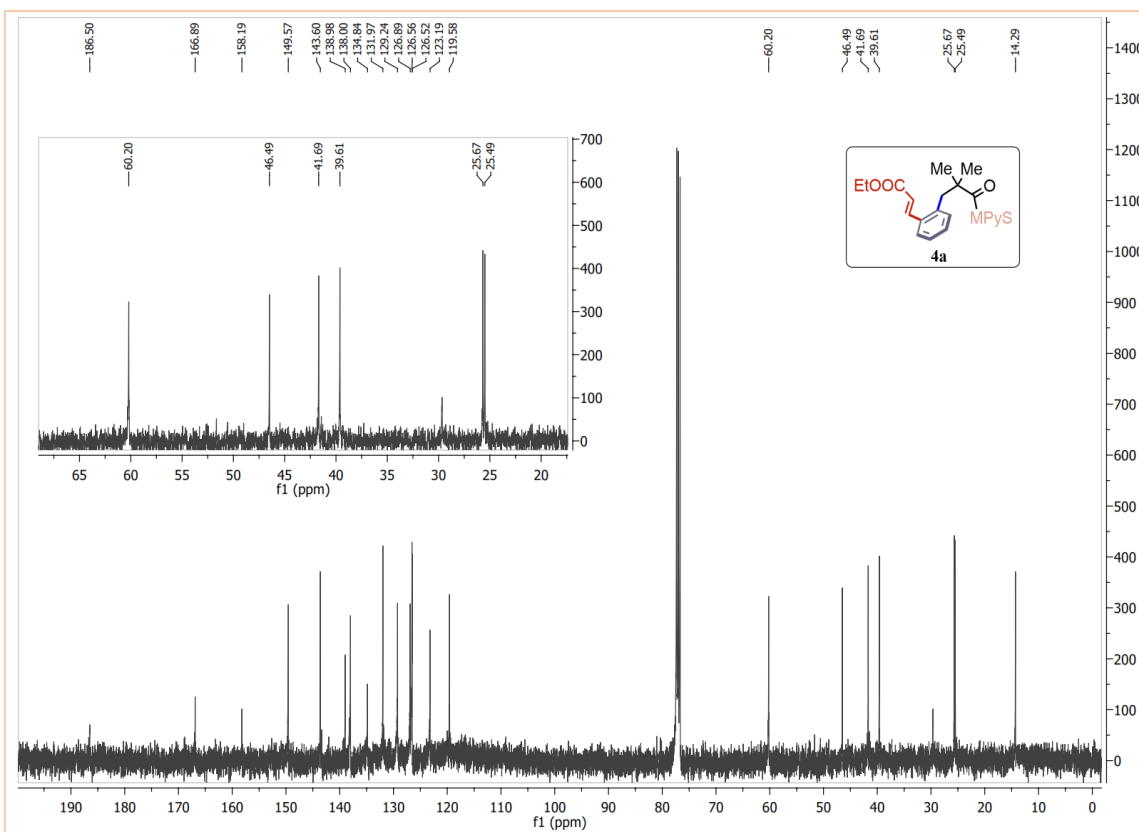
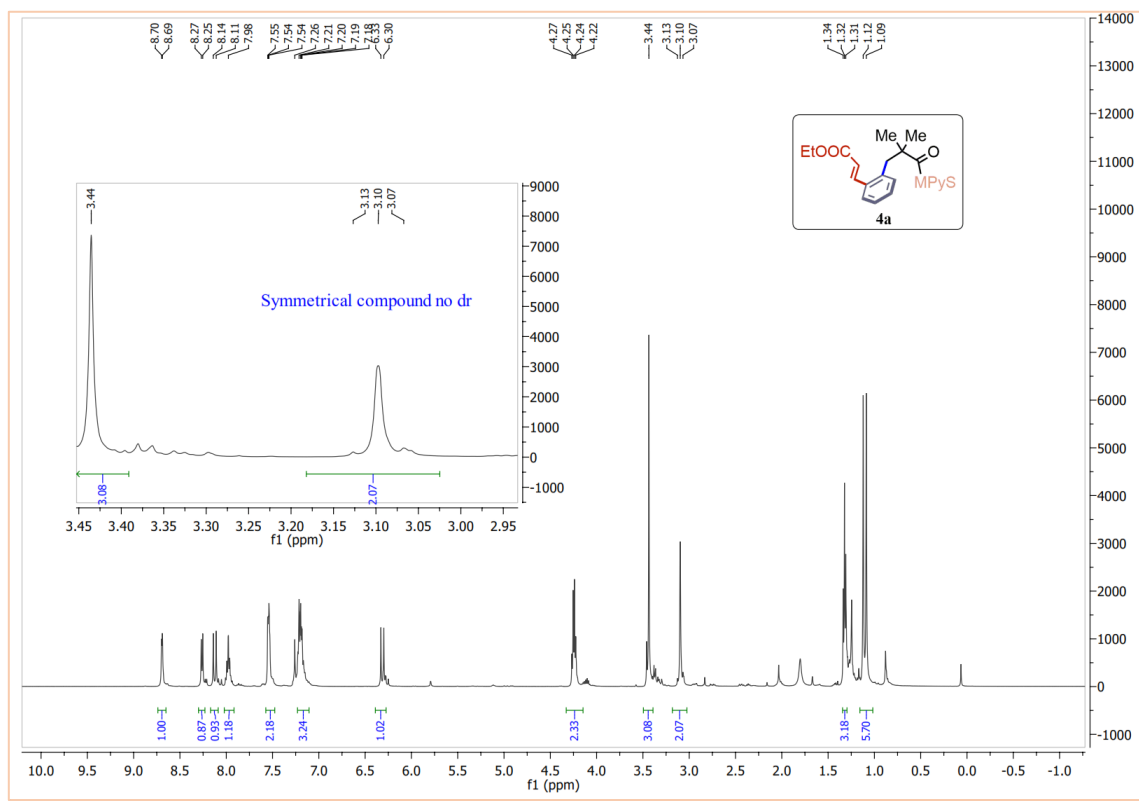
F_w	522.52
T (K)	299 K
λ (Å)	0.71073
Crystal system	triclinic
Space group	$P -1$
a (Å)	7.5092(2)
b (Å)	8.5617(3)
c (Å)	20.9205(6)
α (°)	82.245(3)
β (°)	80.917(2)
γ (°)	68.802(3)
V (Å ³)	1233.84(7)
Z	2
ρ_{calcd} (Mg m ⁻³)	1.406
μ [mm ⁻¹]	0.196
total reflns	26154
unique reflns	4334
observed reflns	1954
$R_1[I > 2\sigma(I)]$	0.0688
wR_2 [all]	0.2429
GOF	1.044
Diffractometer	SMART APEX CCD
CCDC Number	2267982

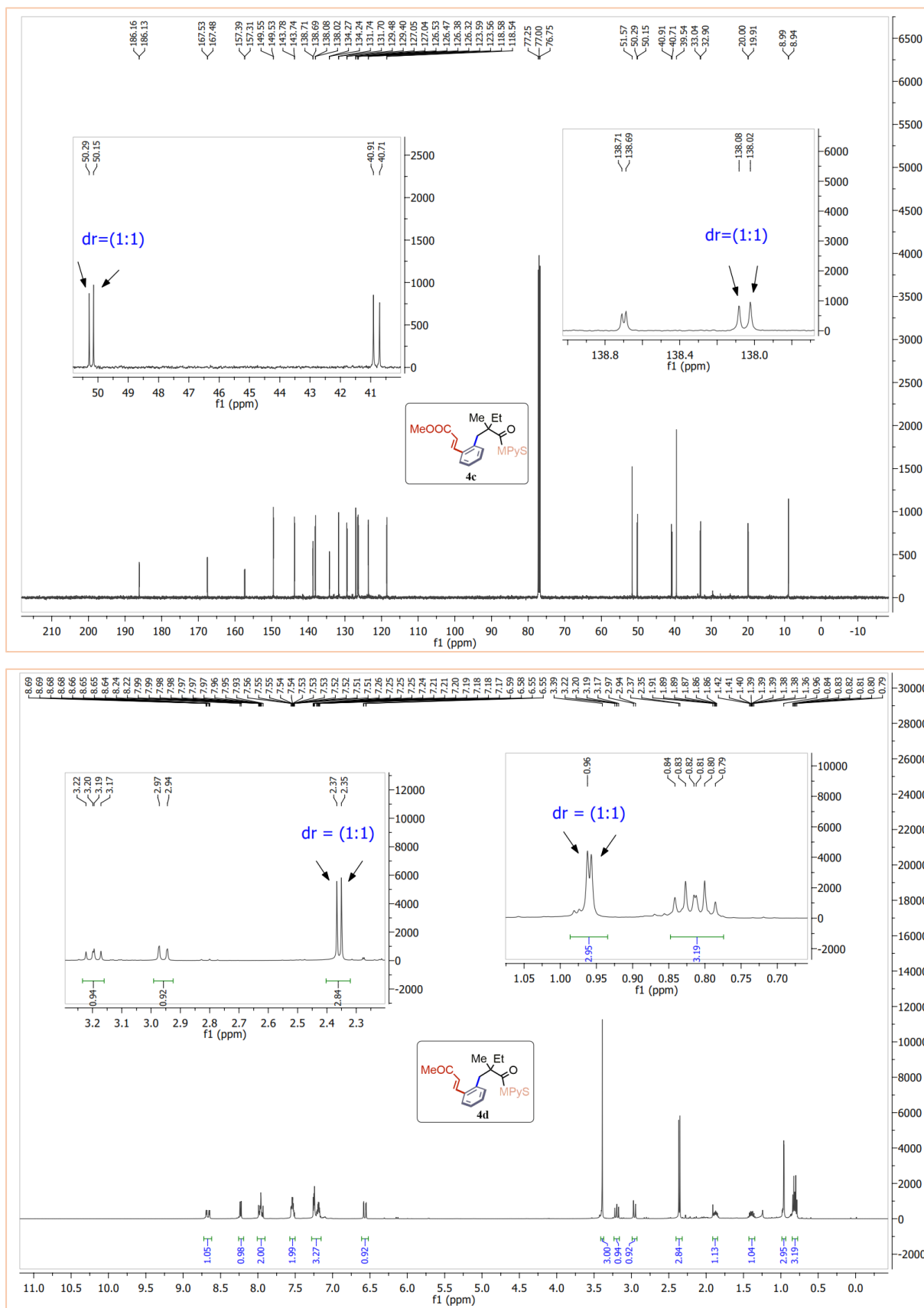
3.7. Reference

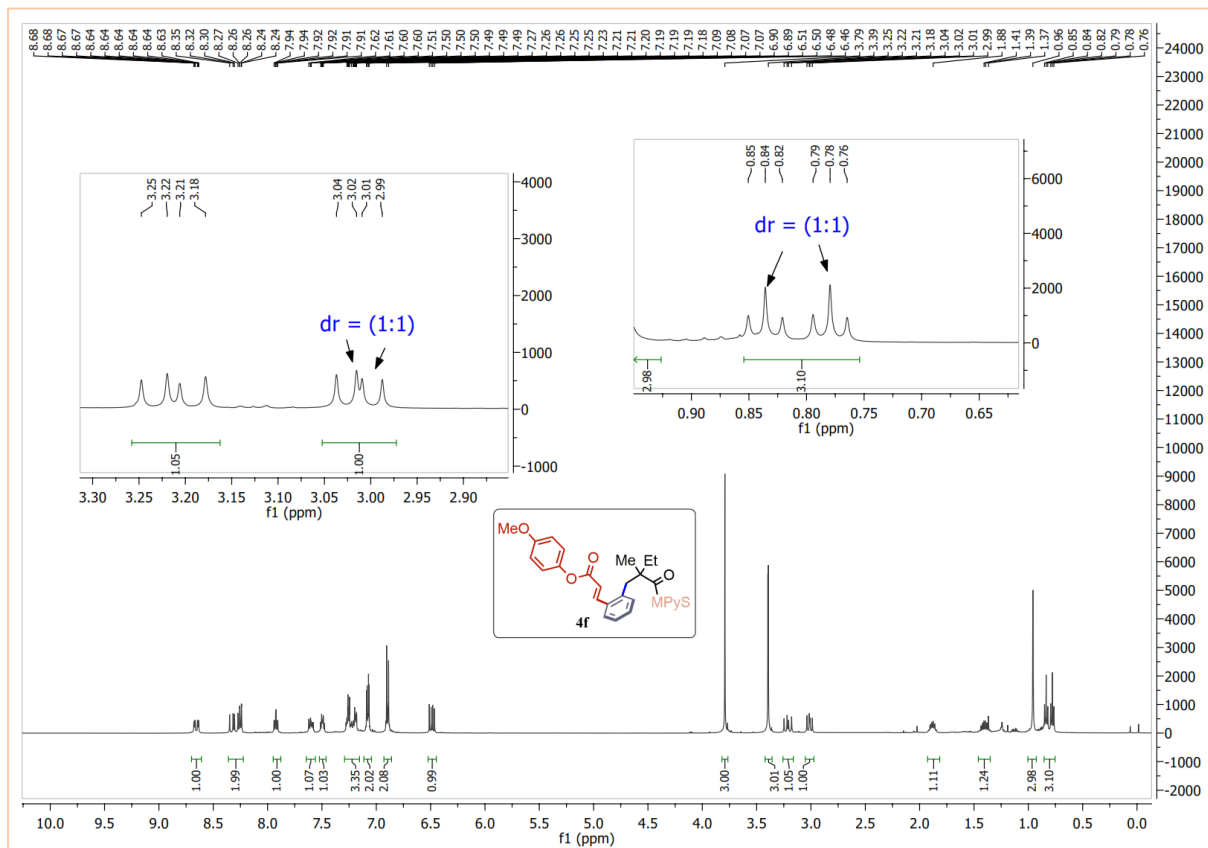
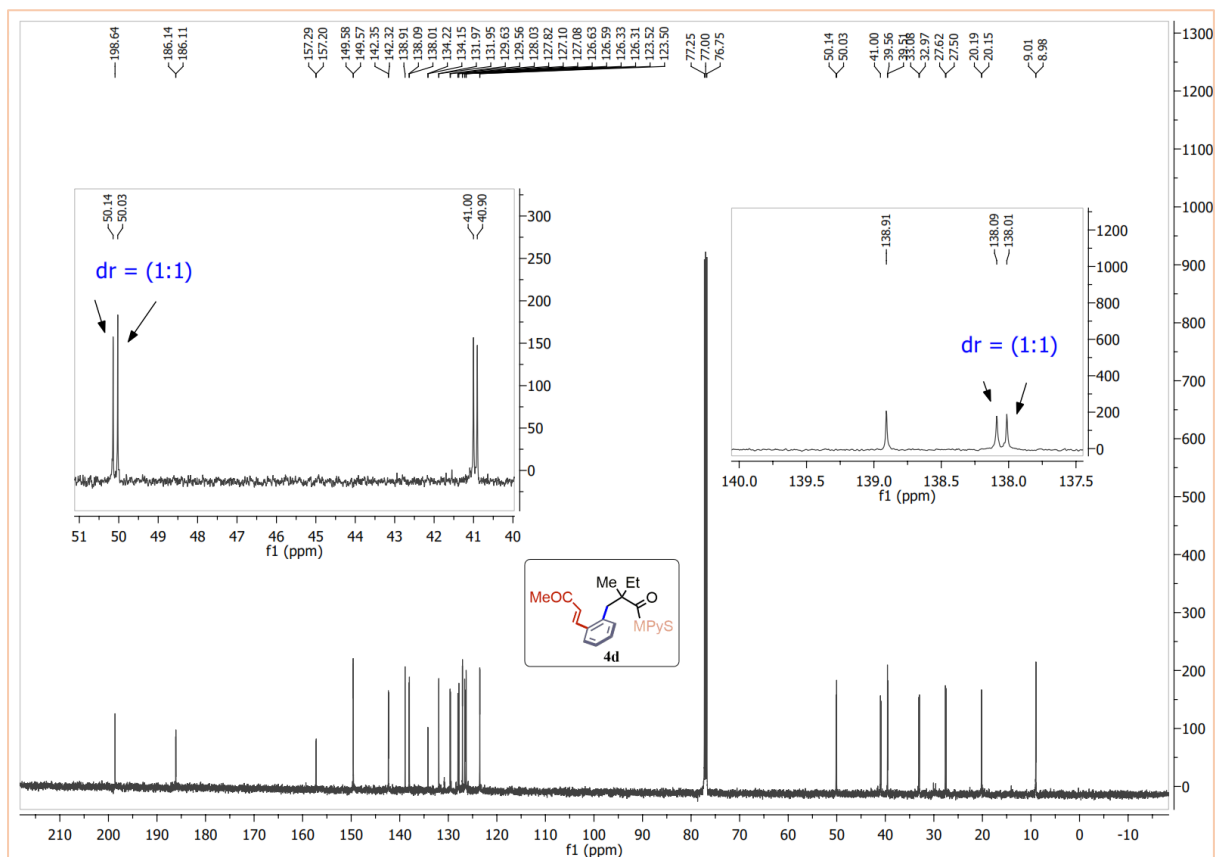
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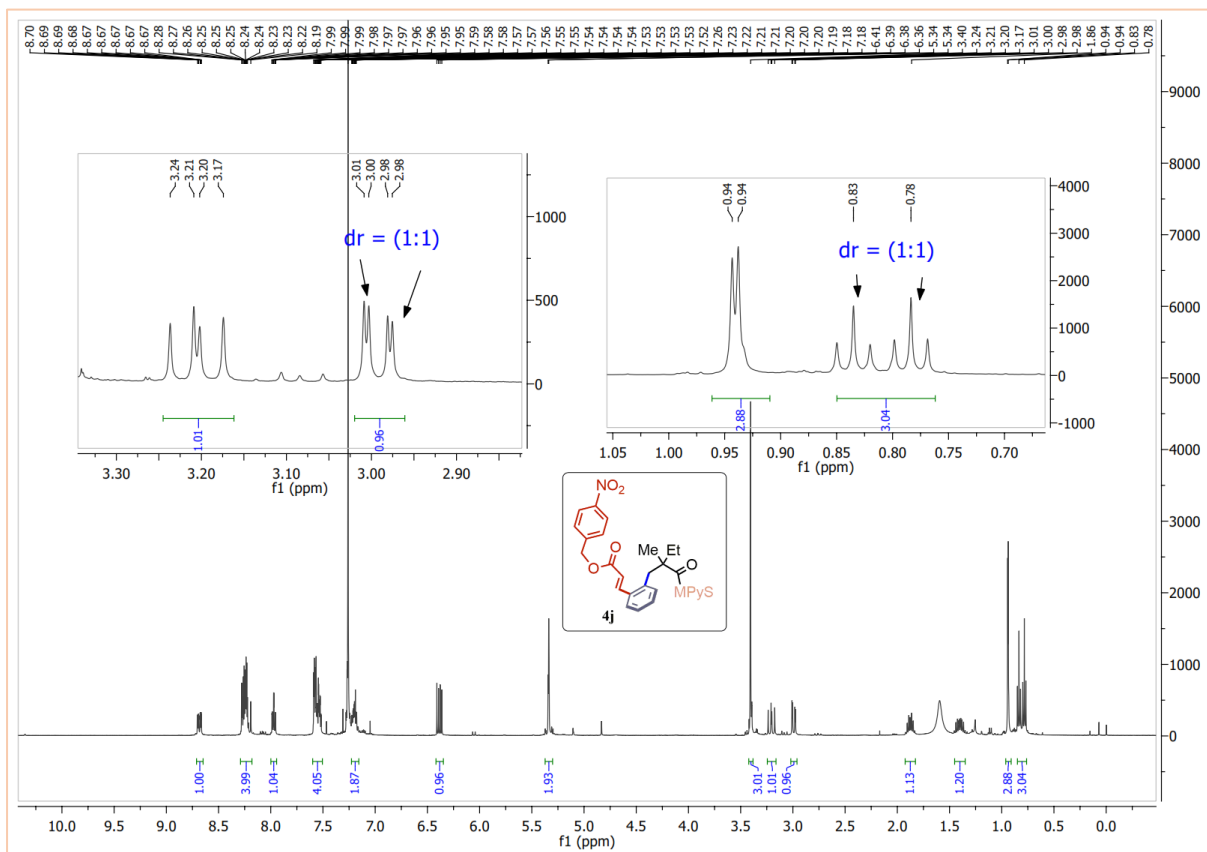
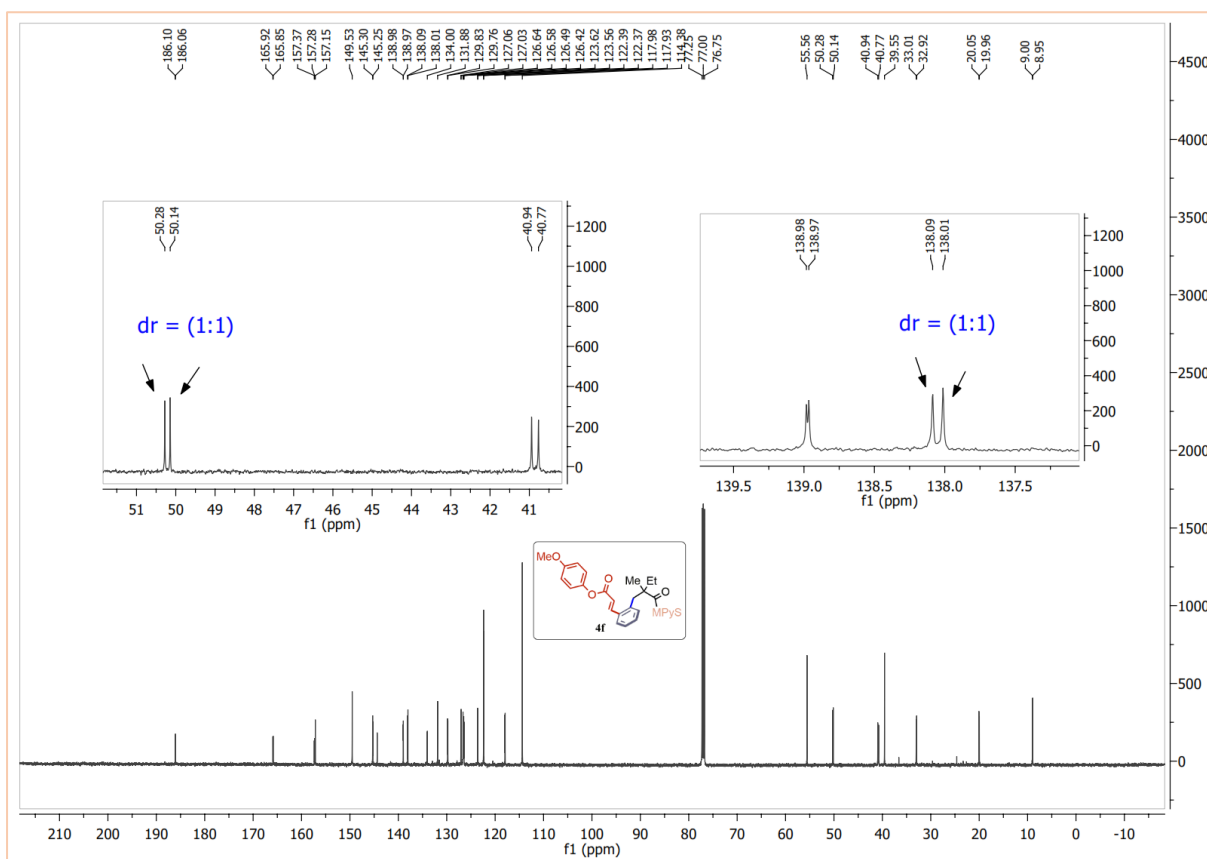
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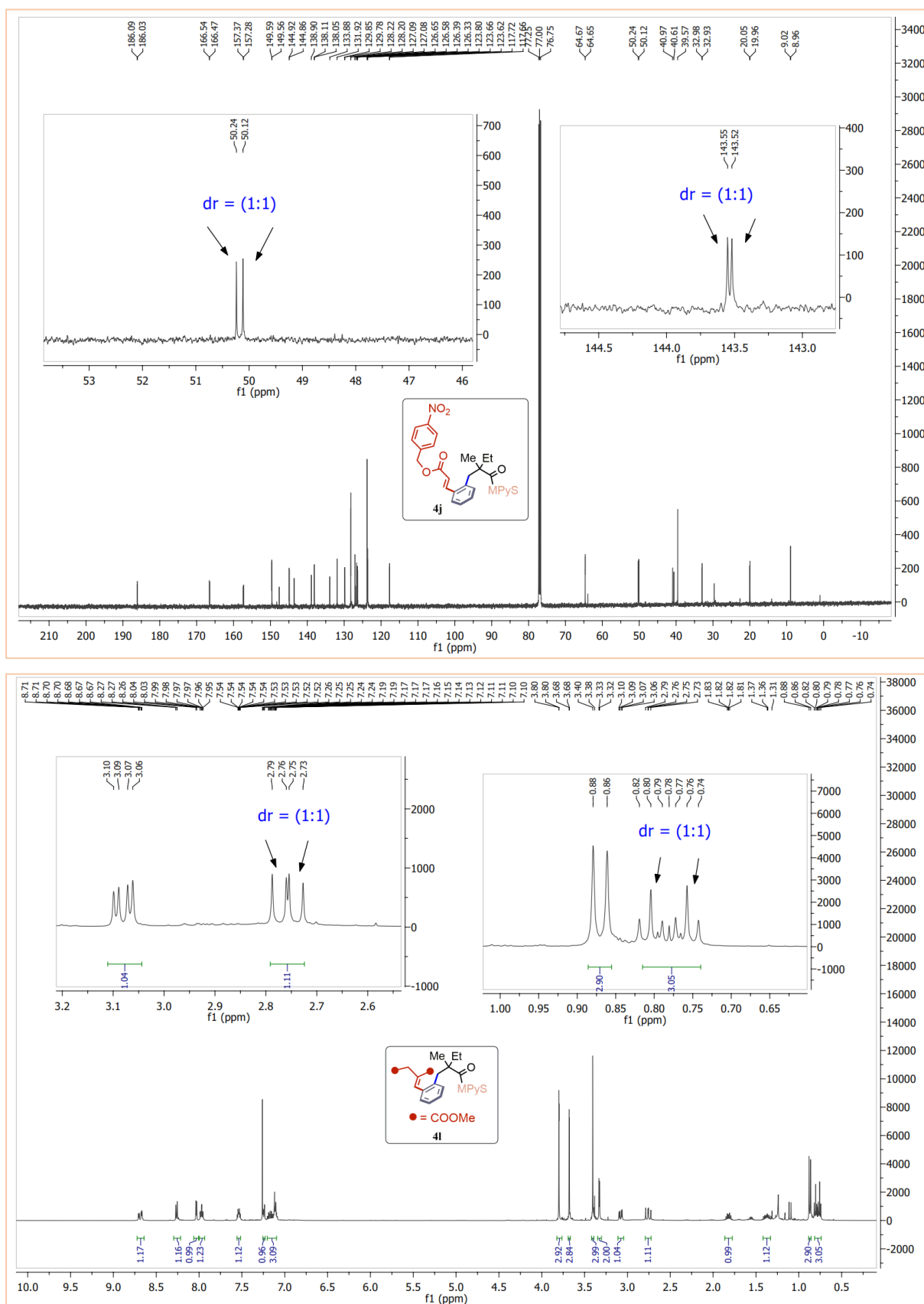
3.8. Spectra

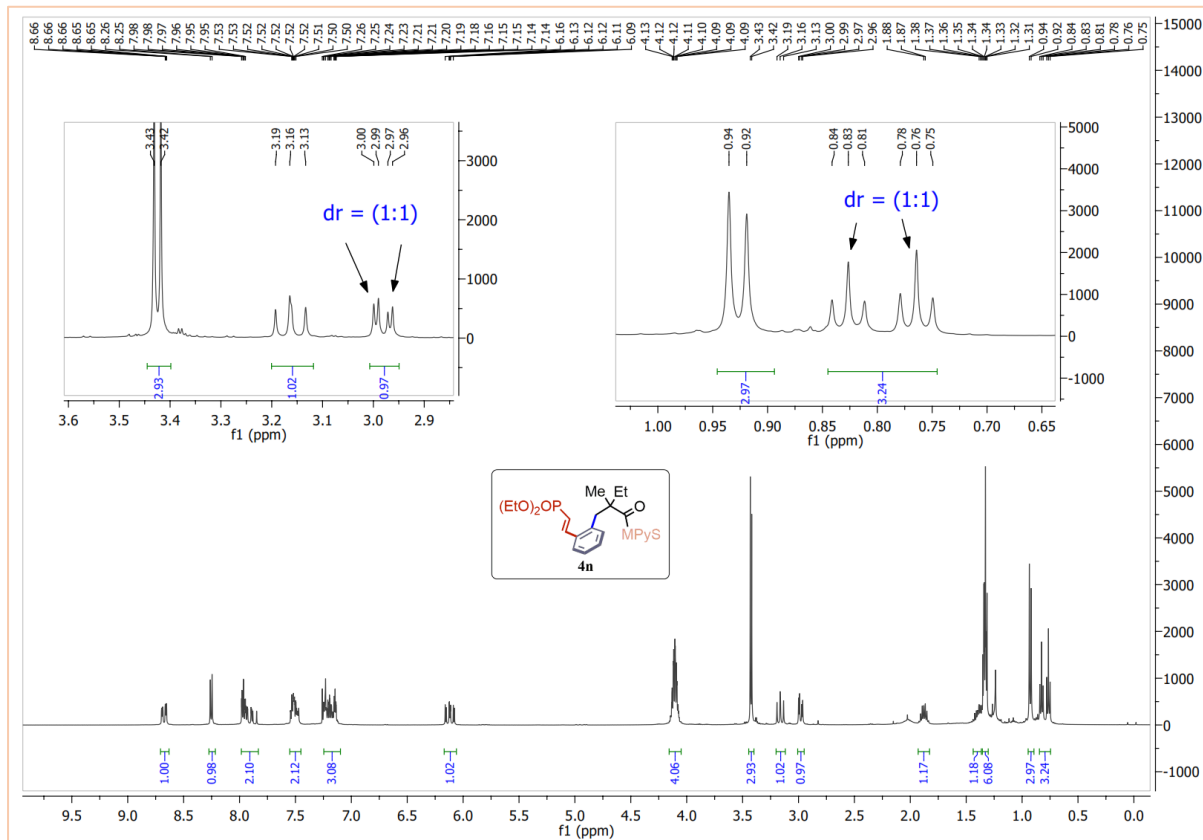


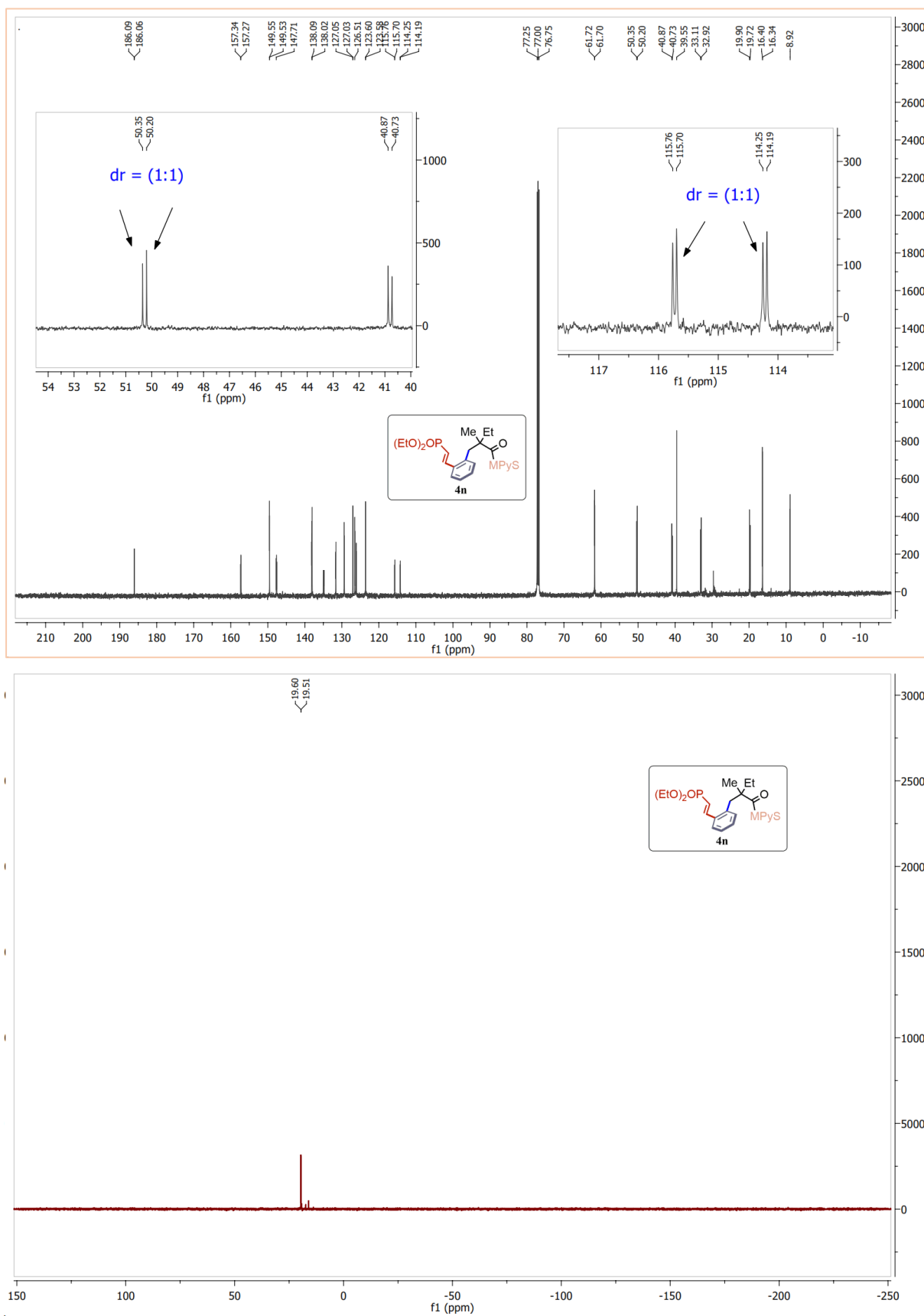


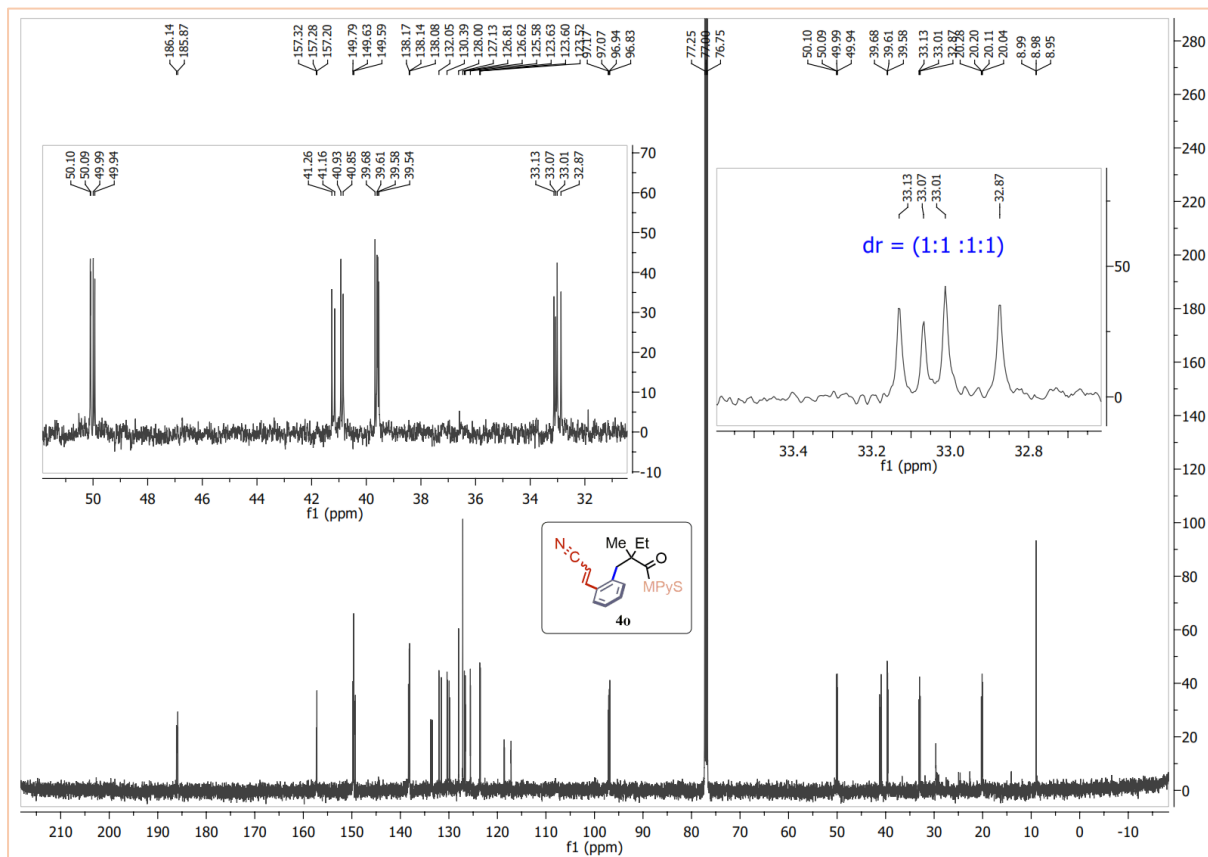
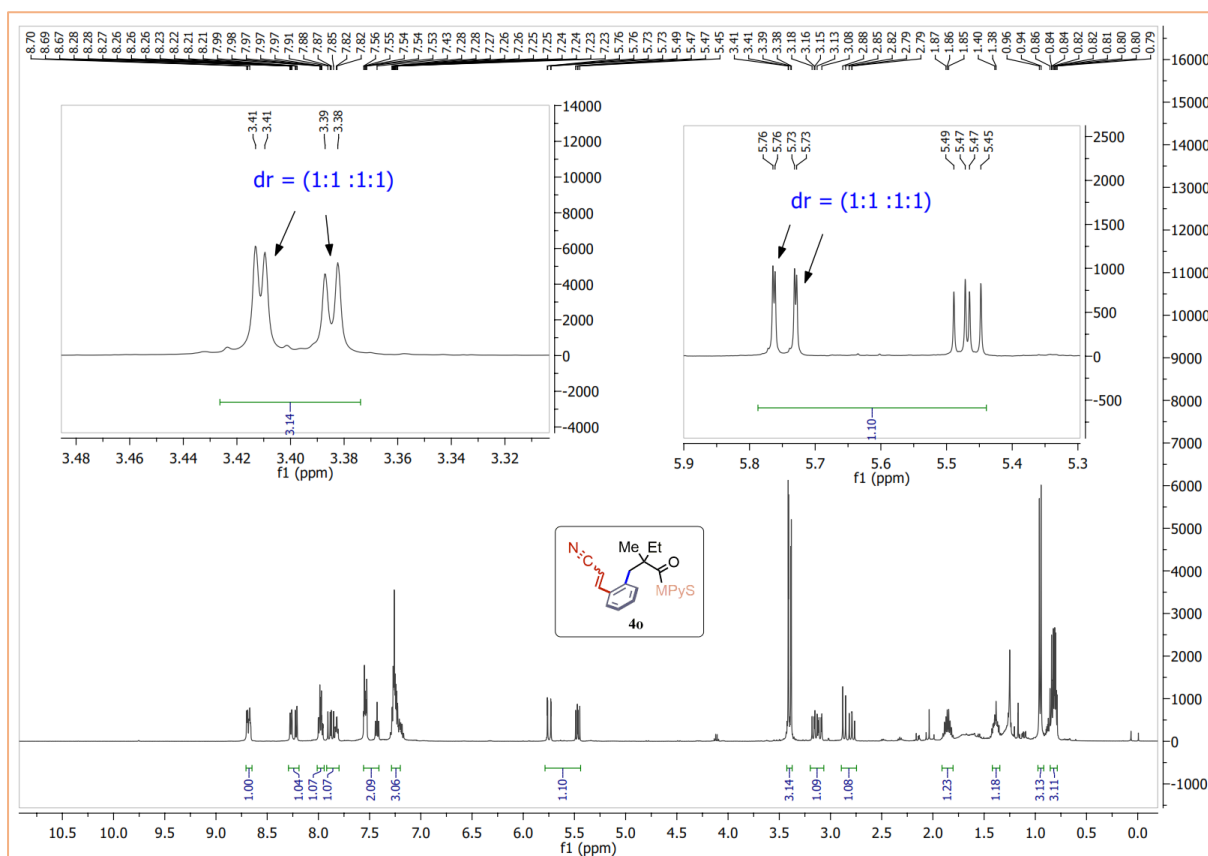


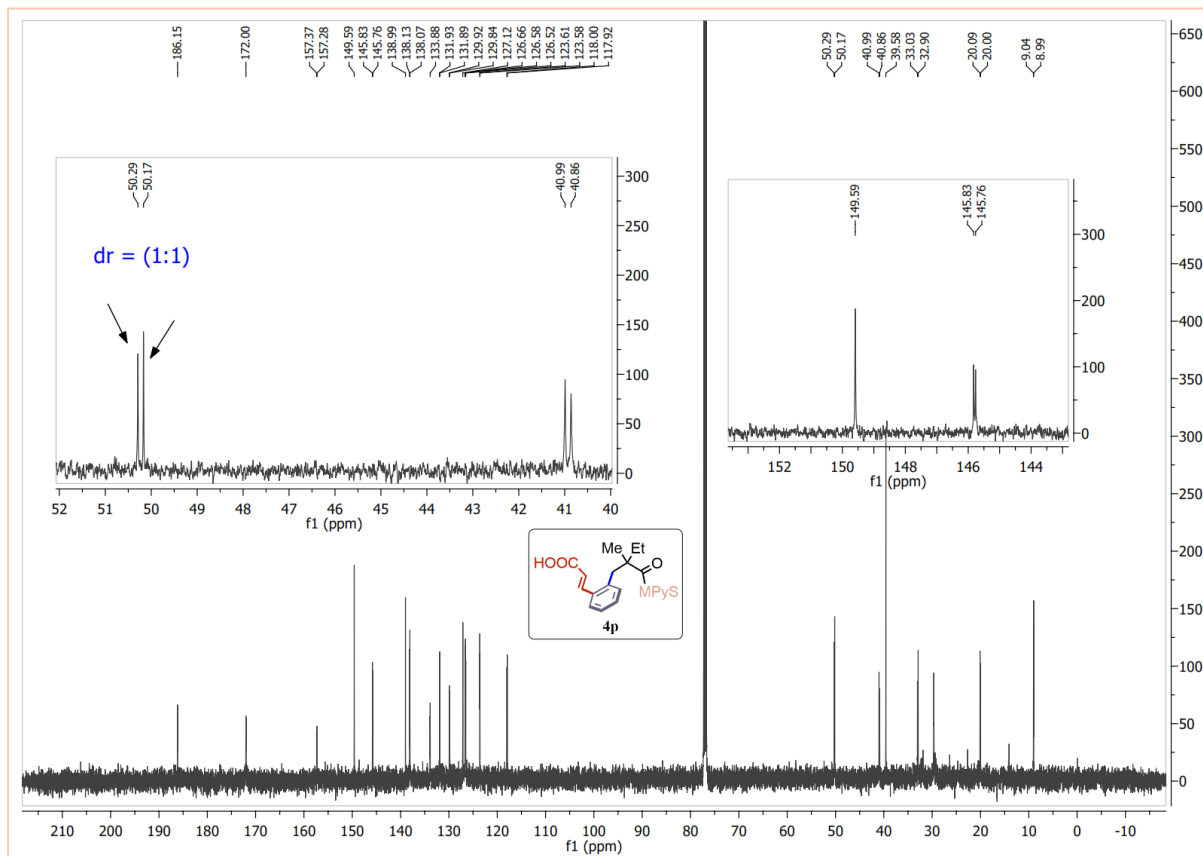


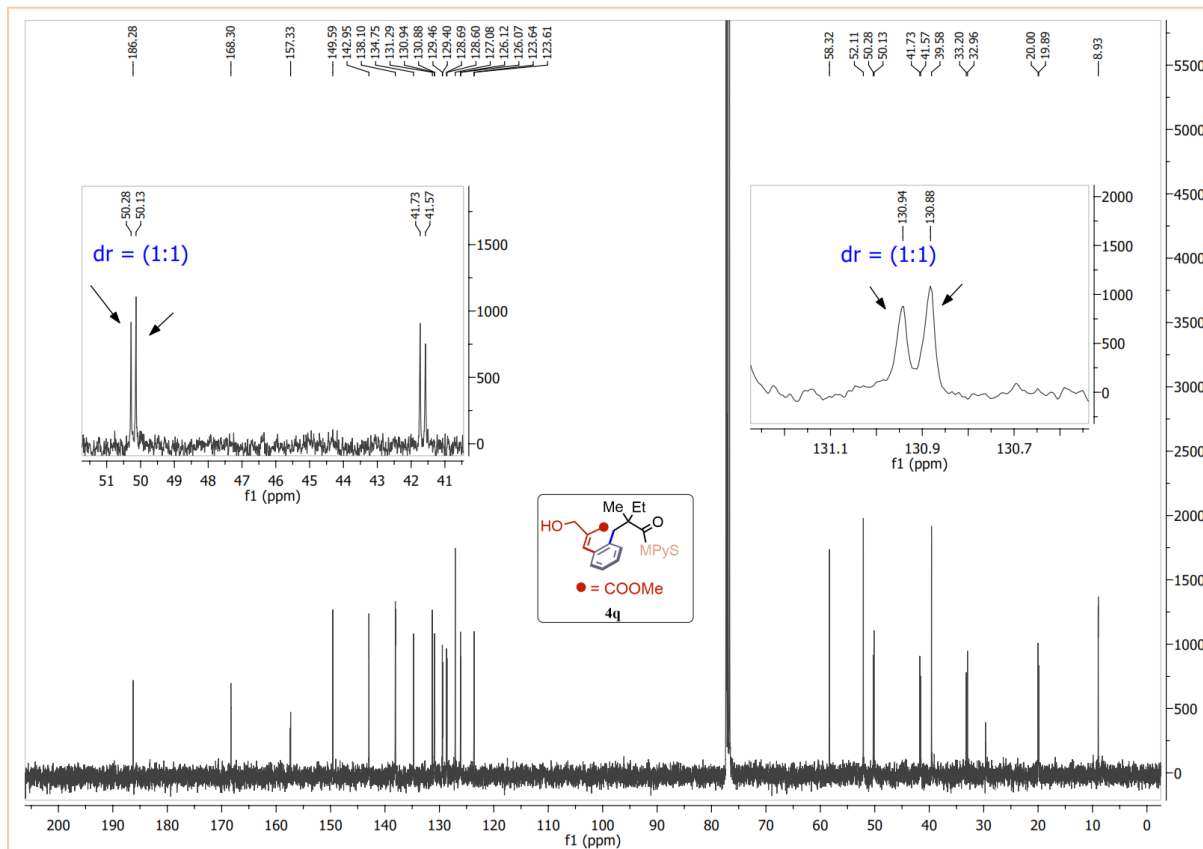
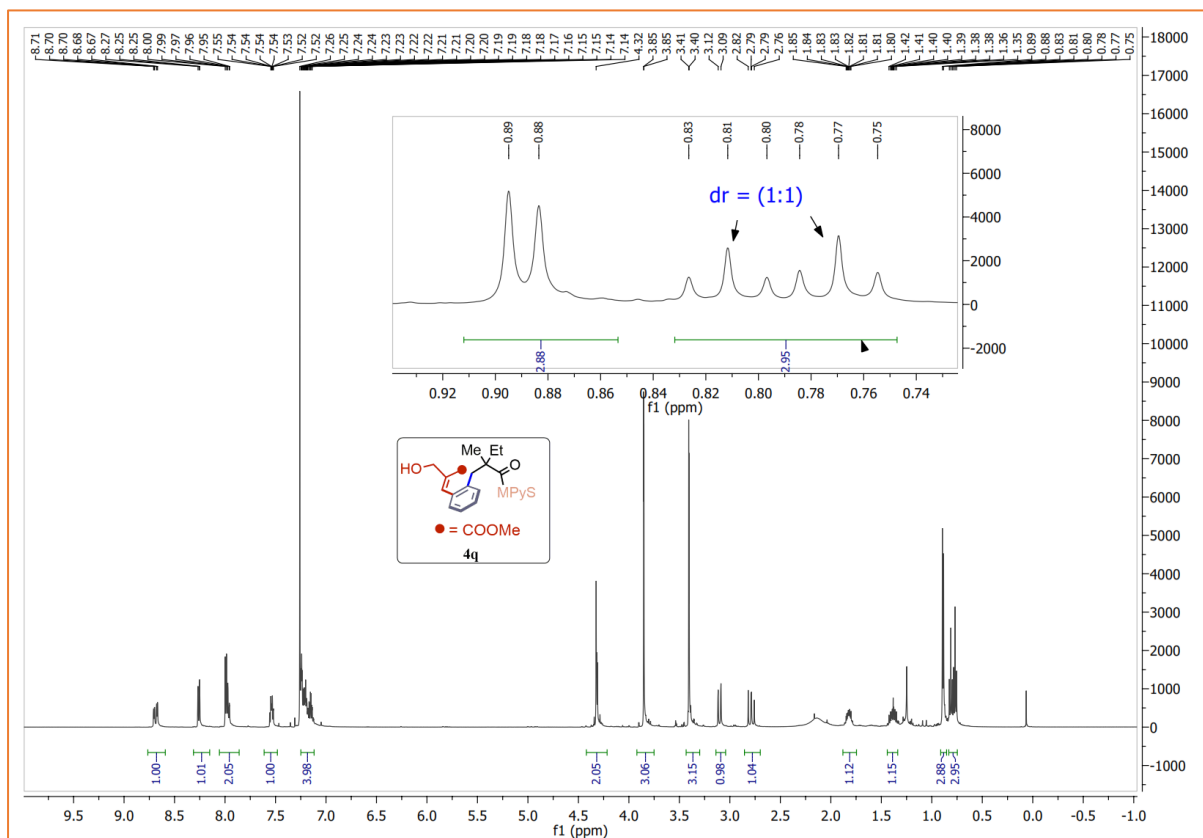


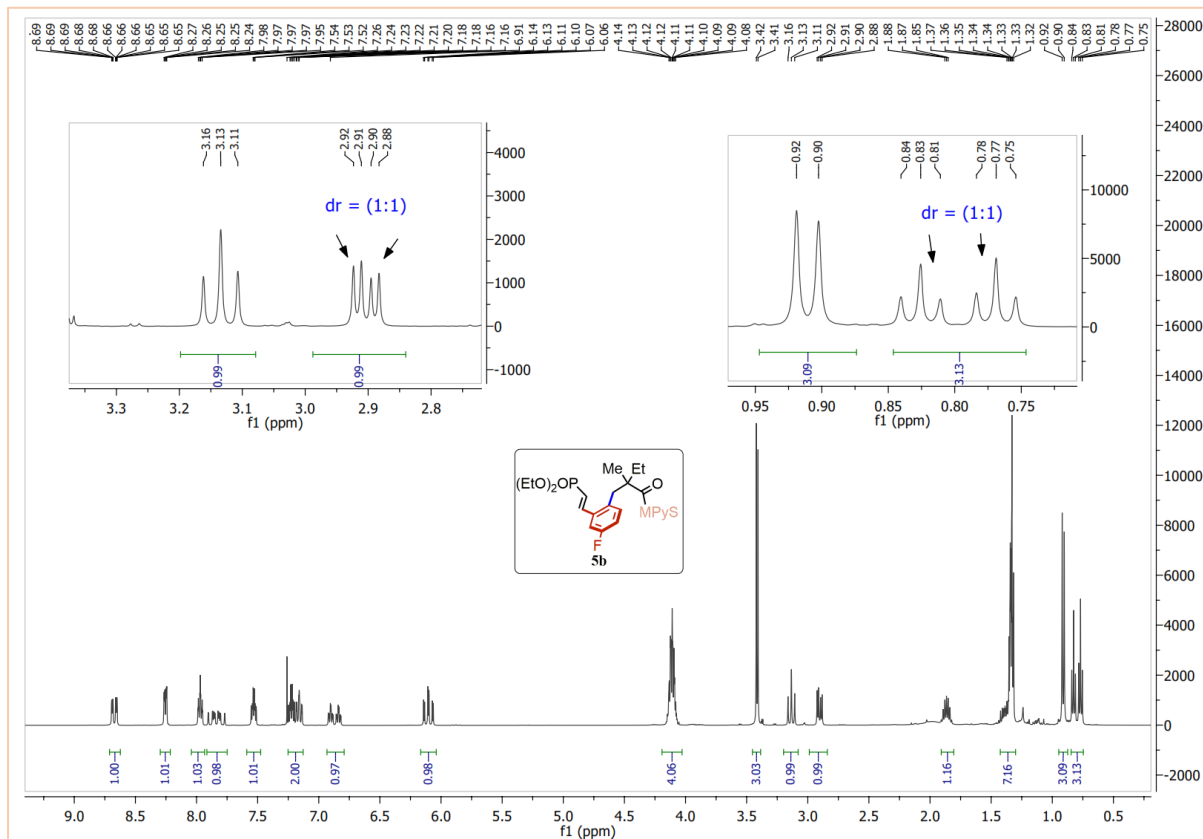
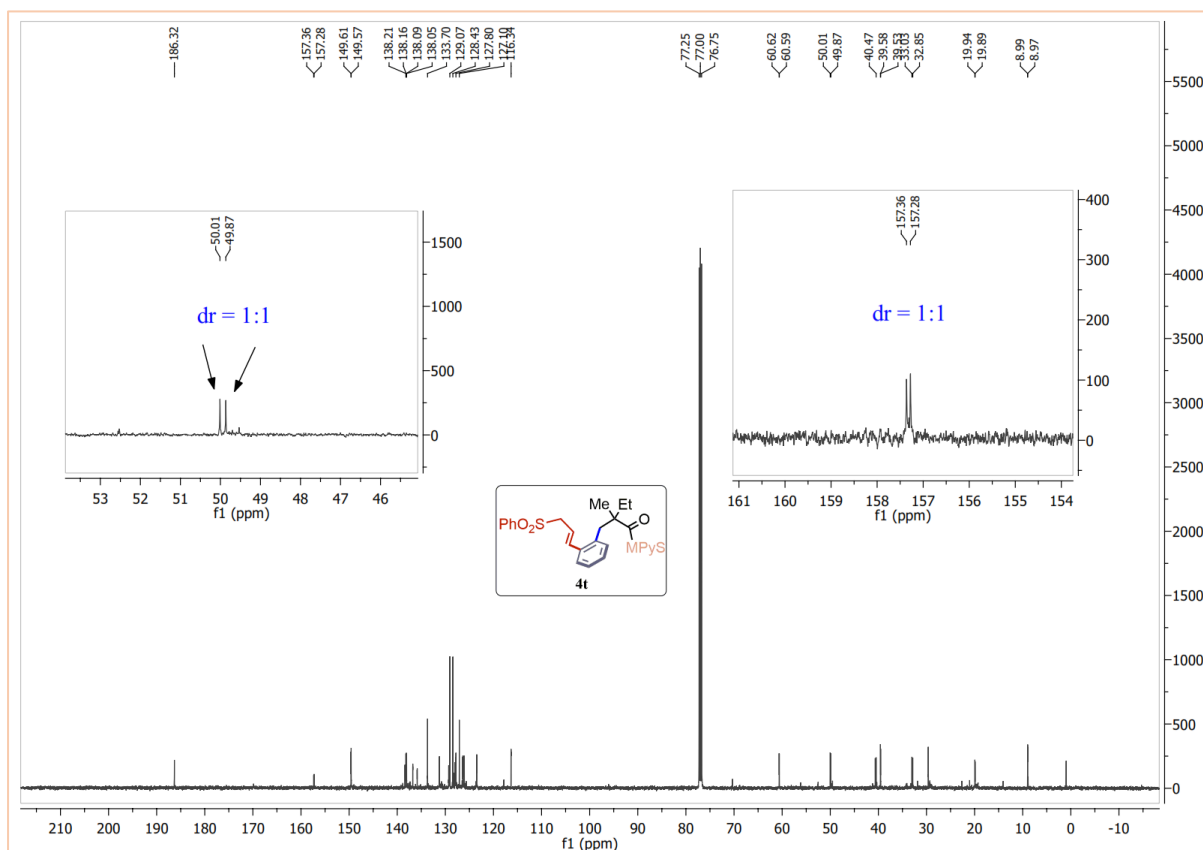


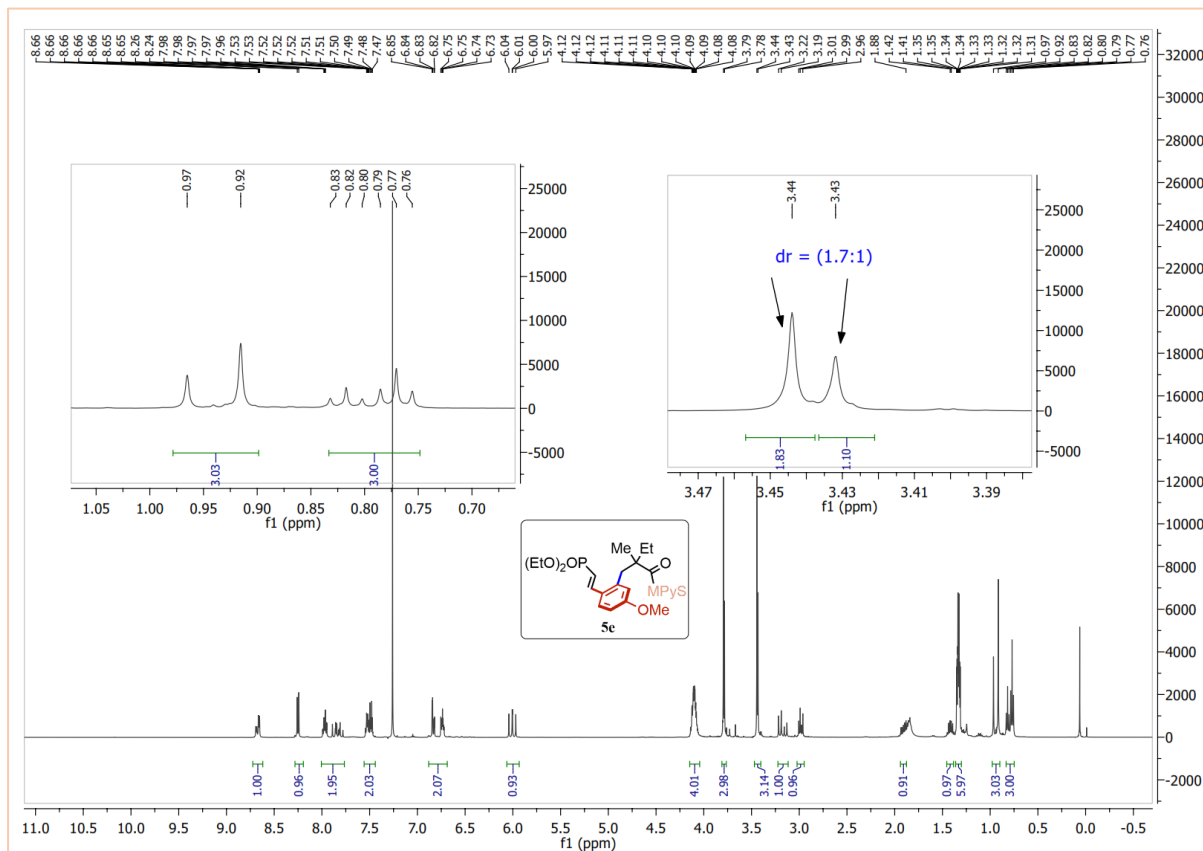
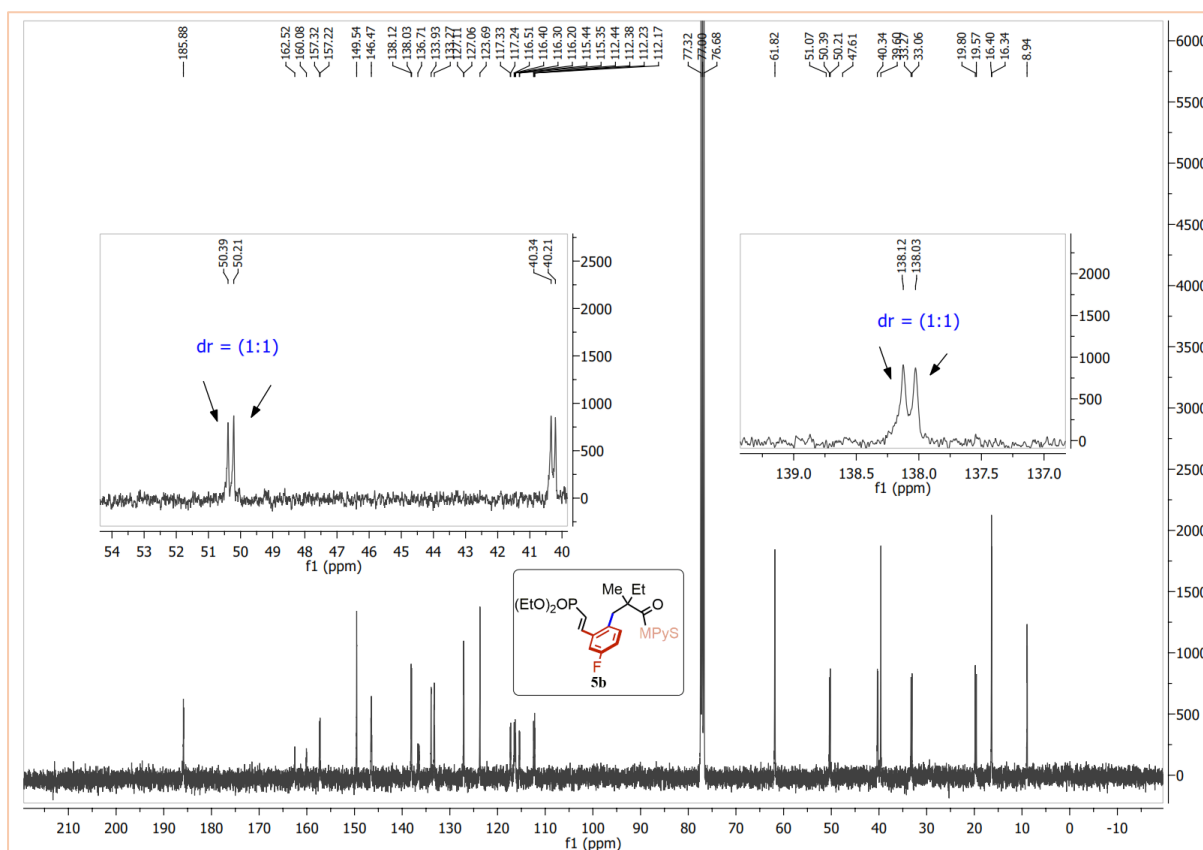


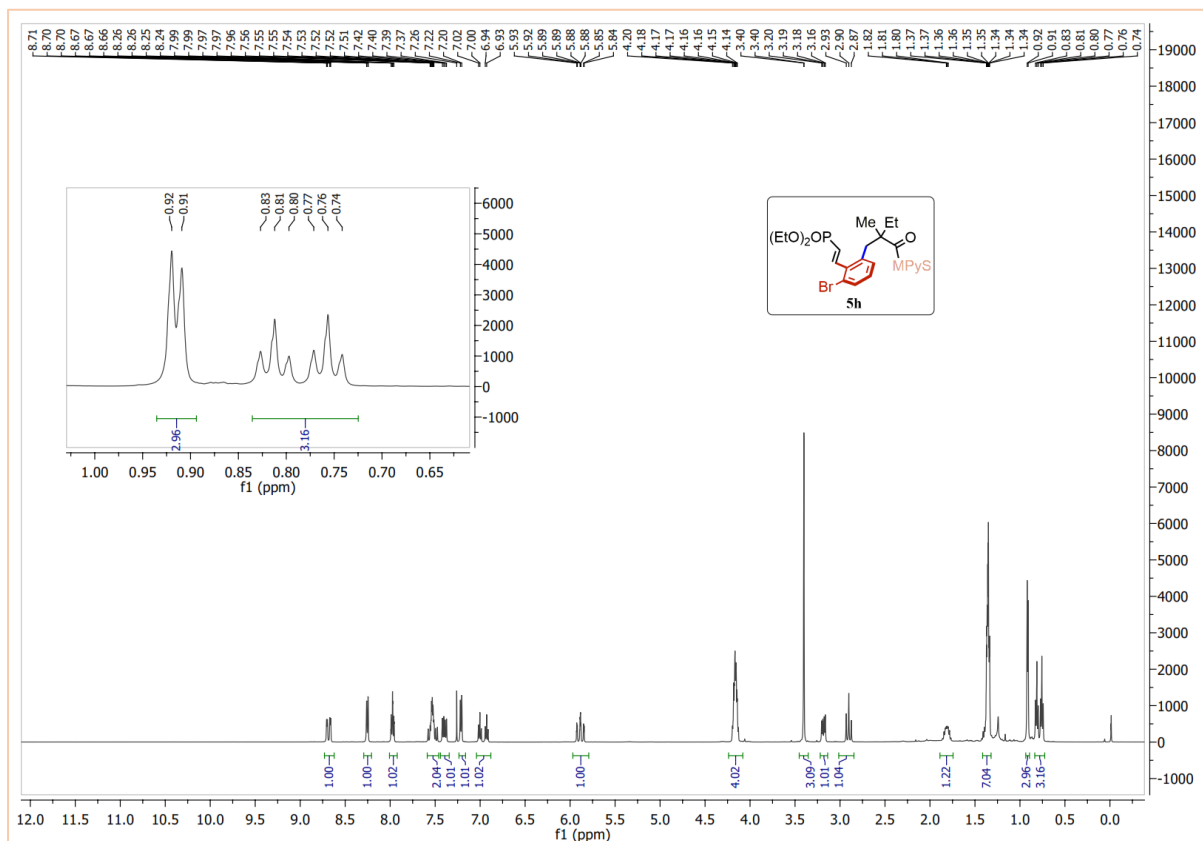
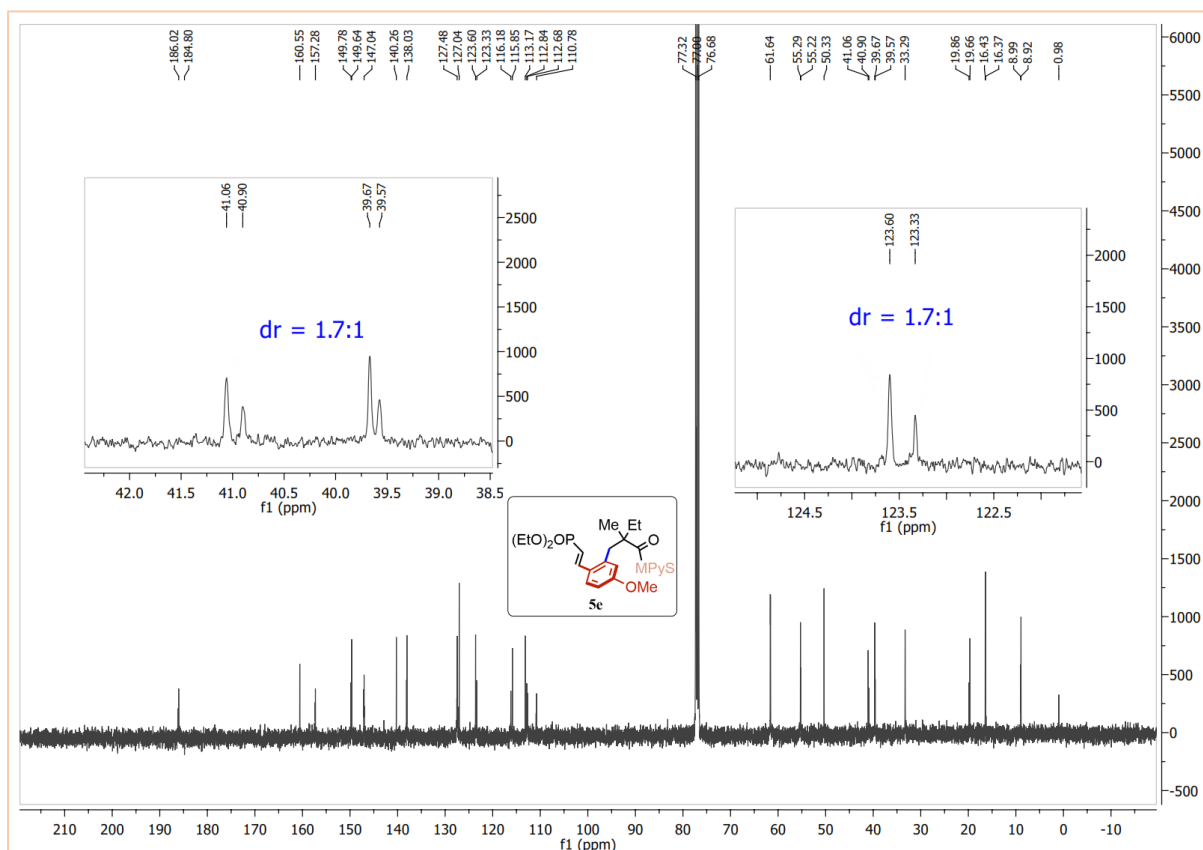


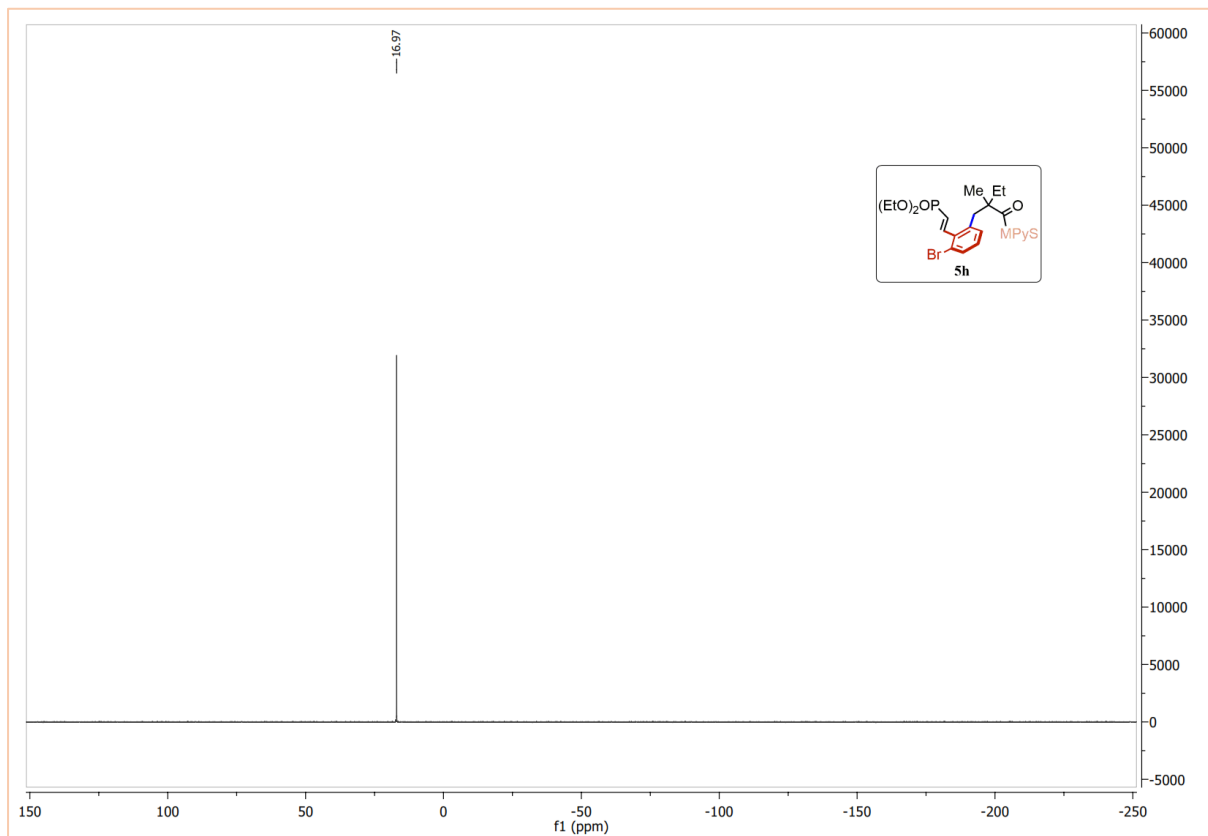


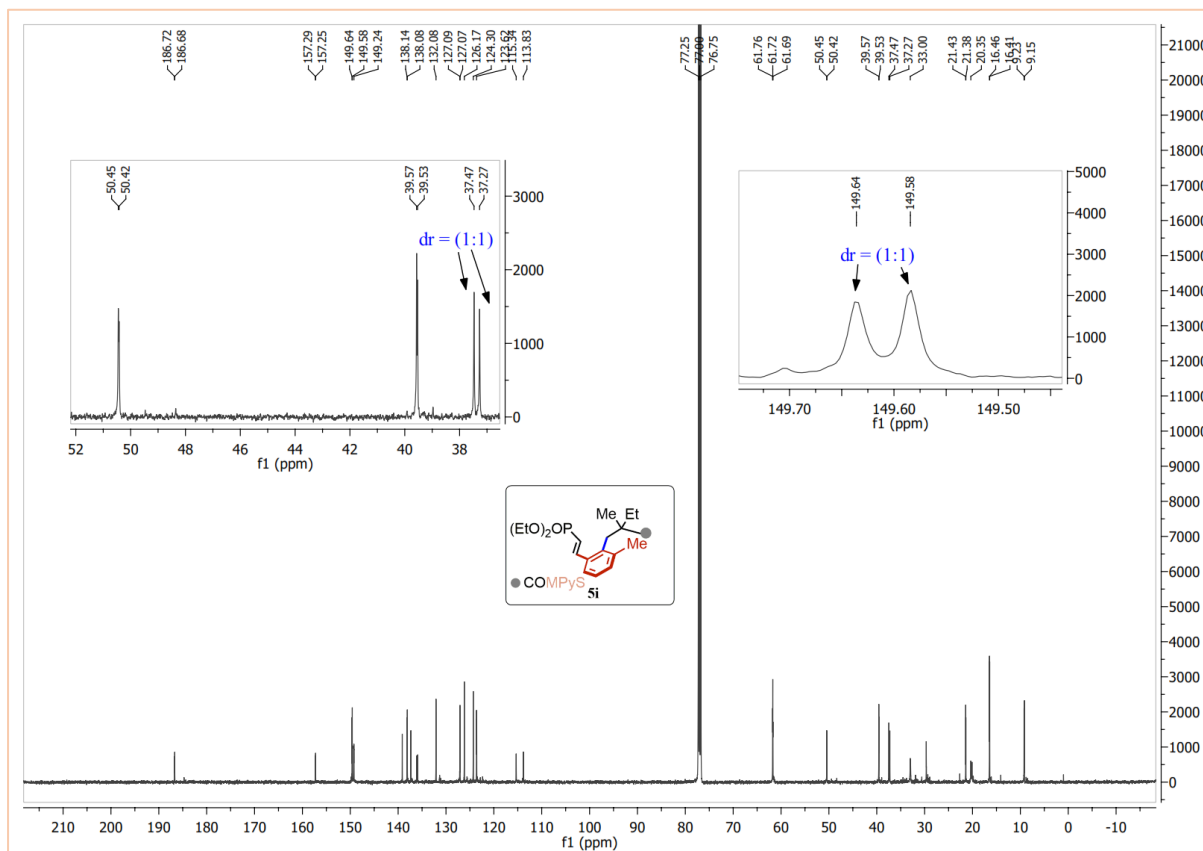
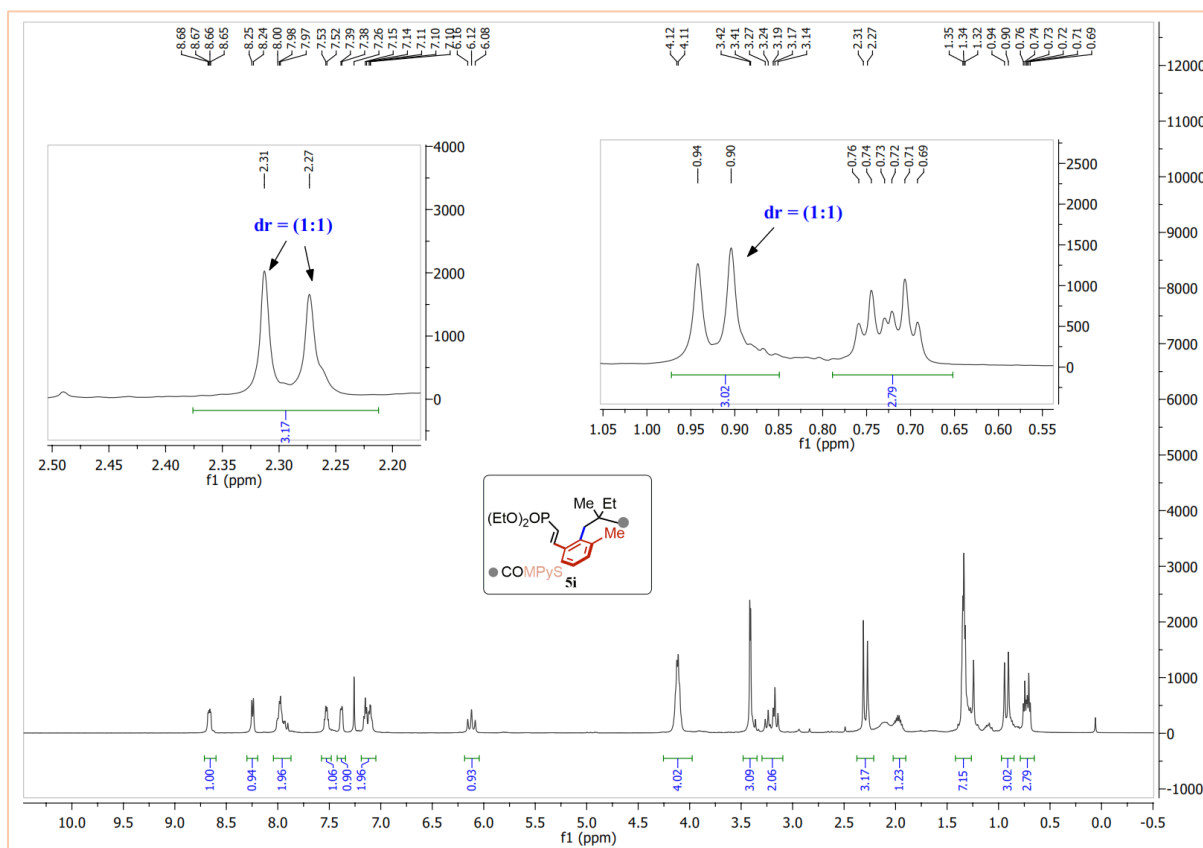


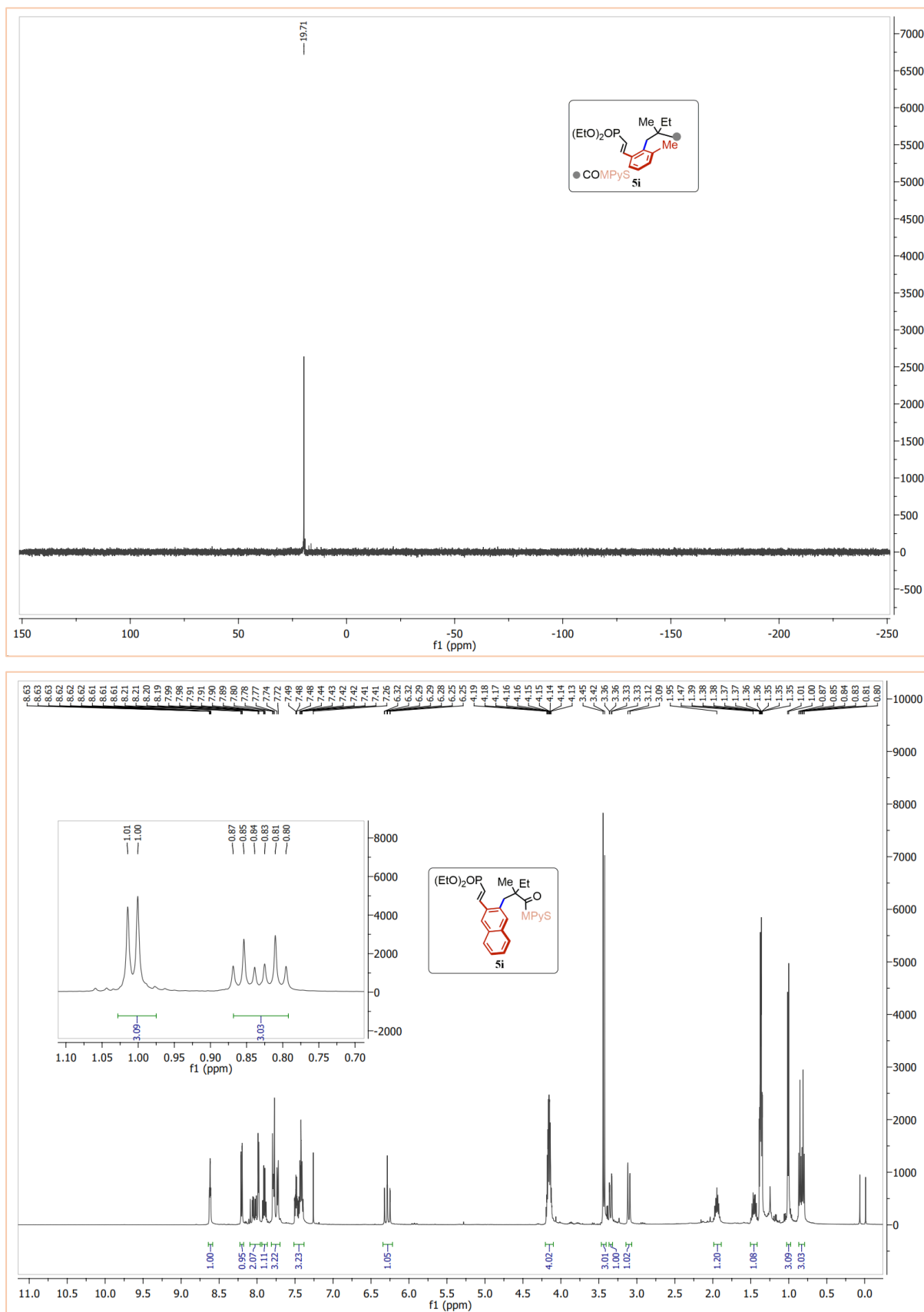


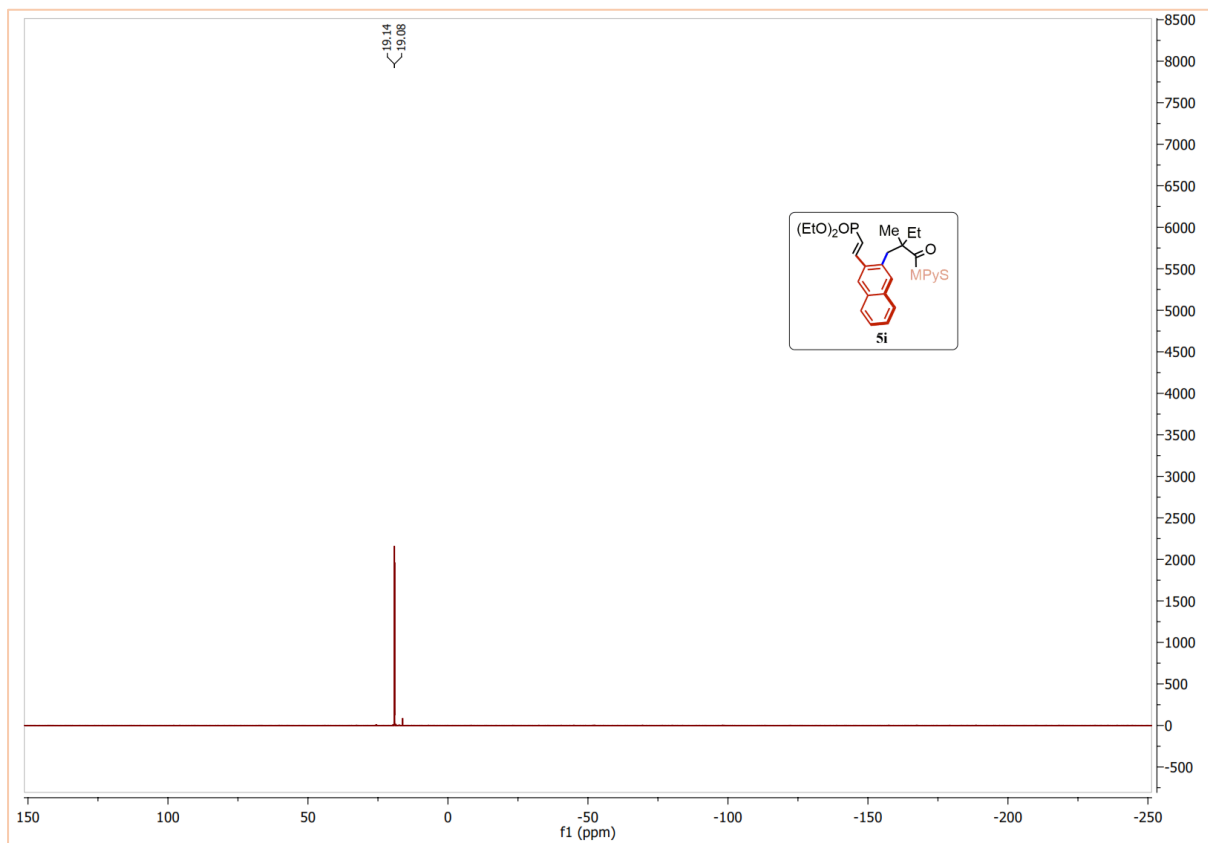
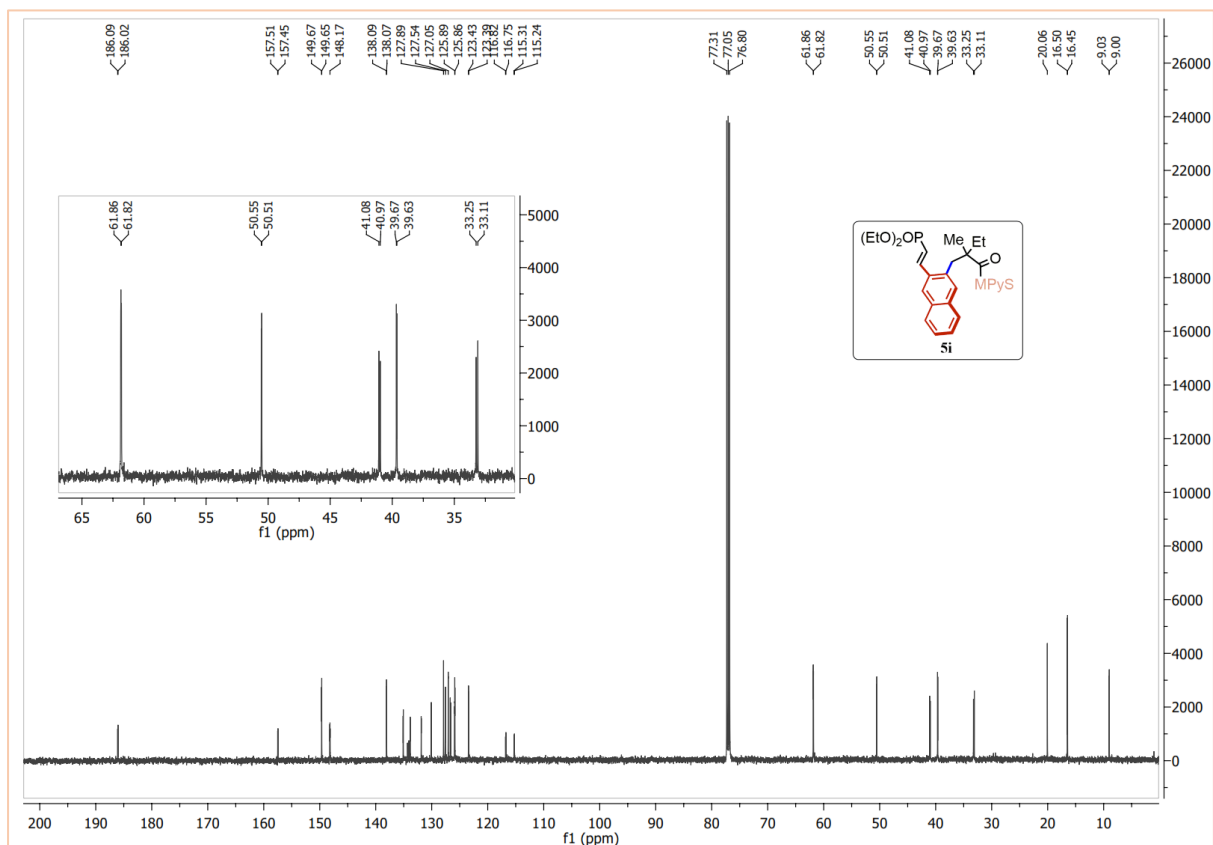


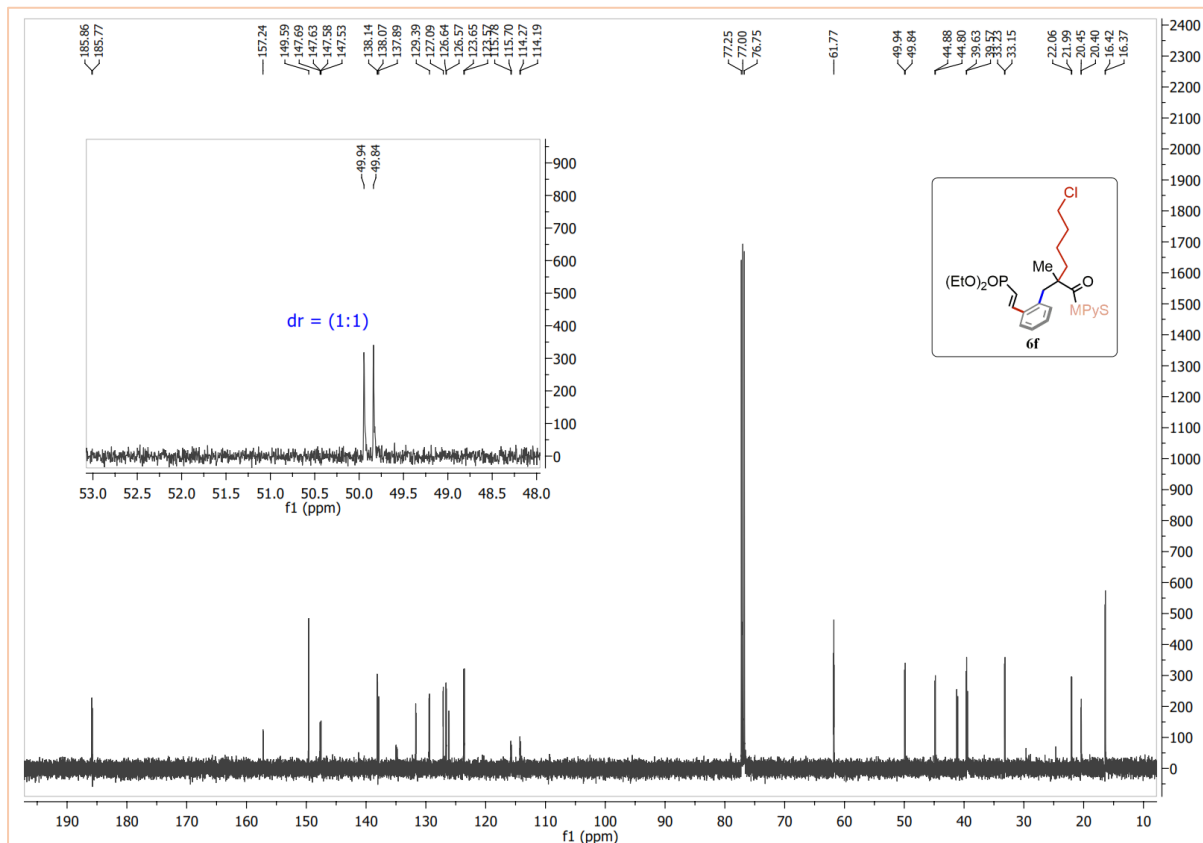
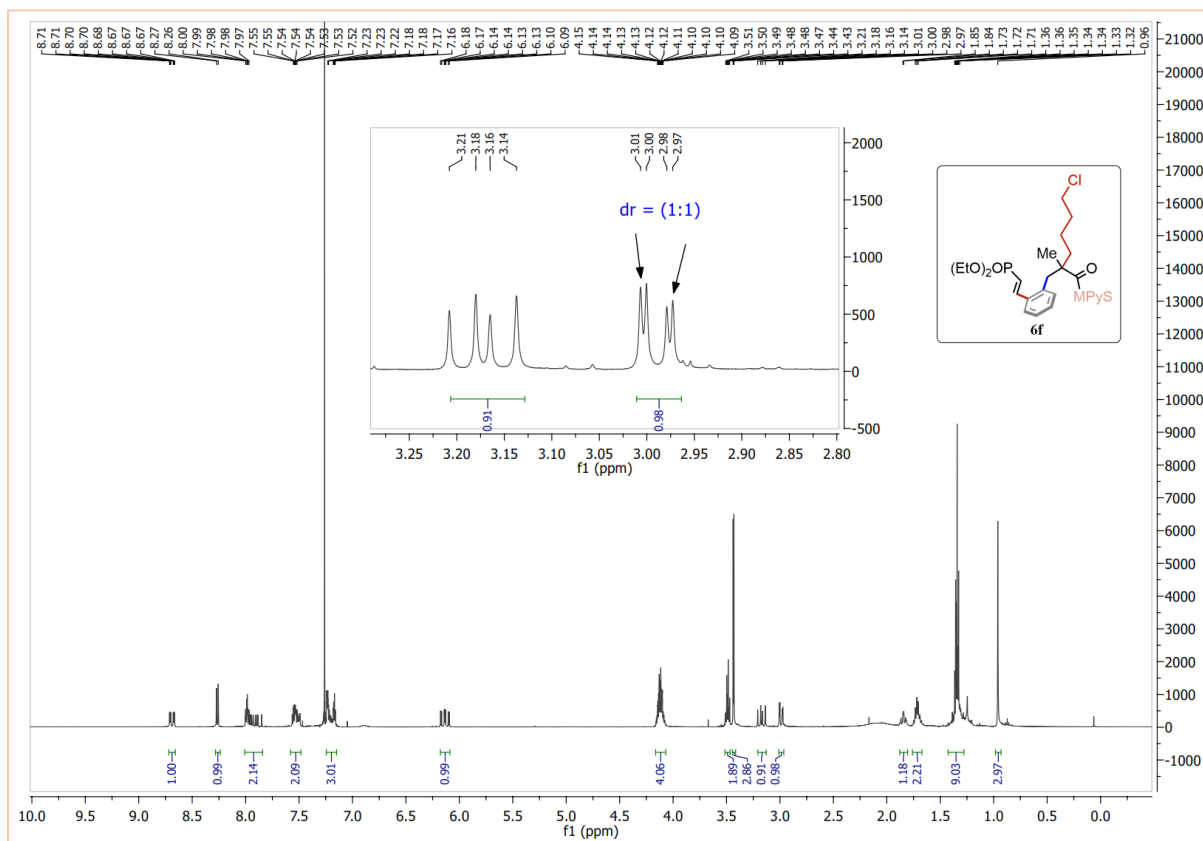


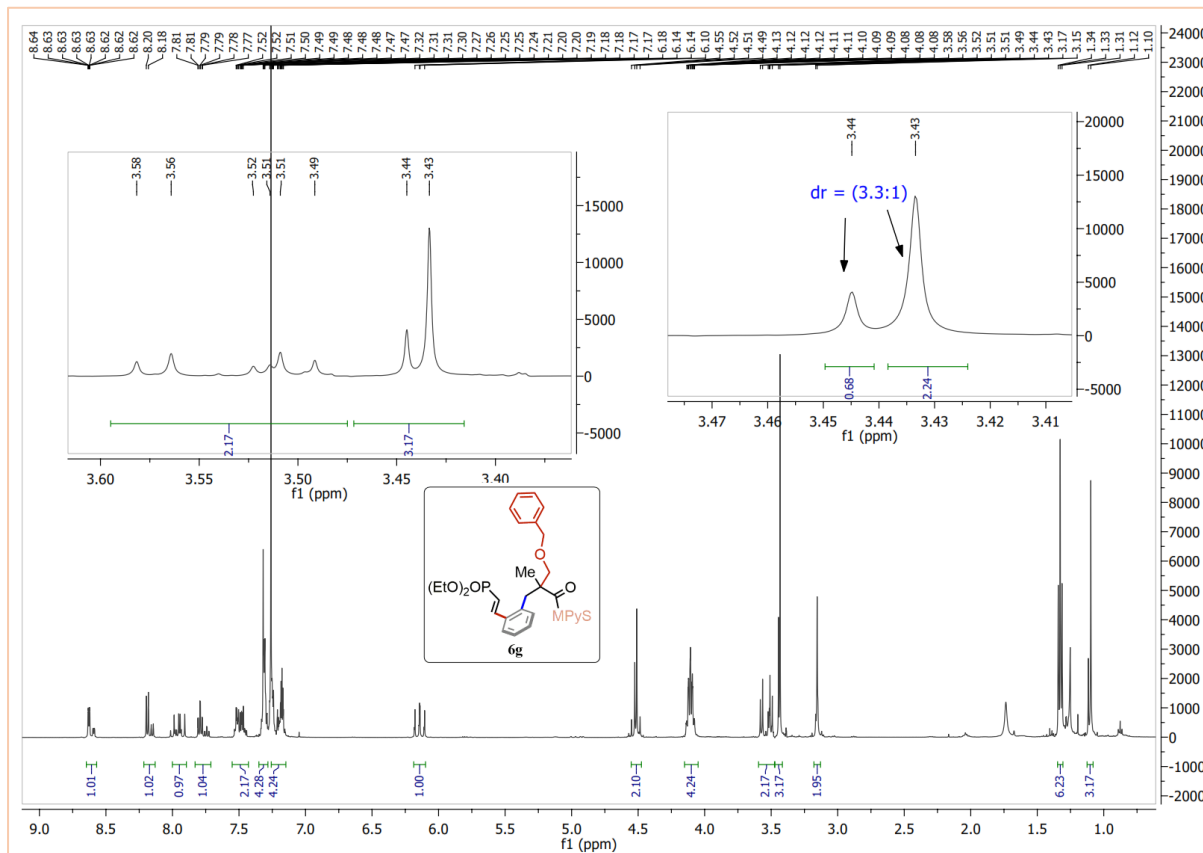
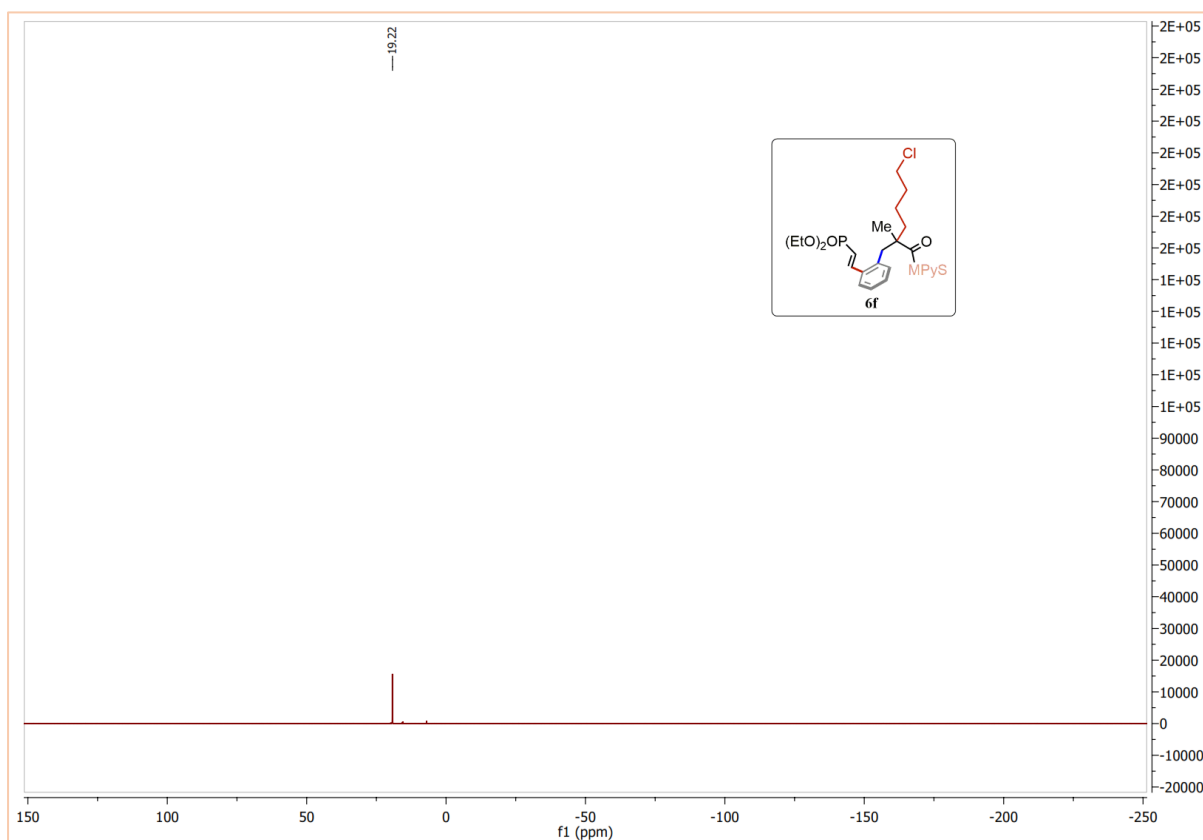


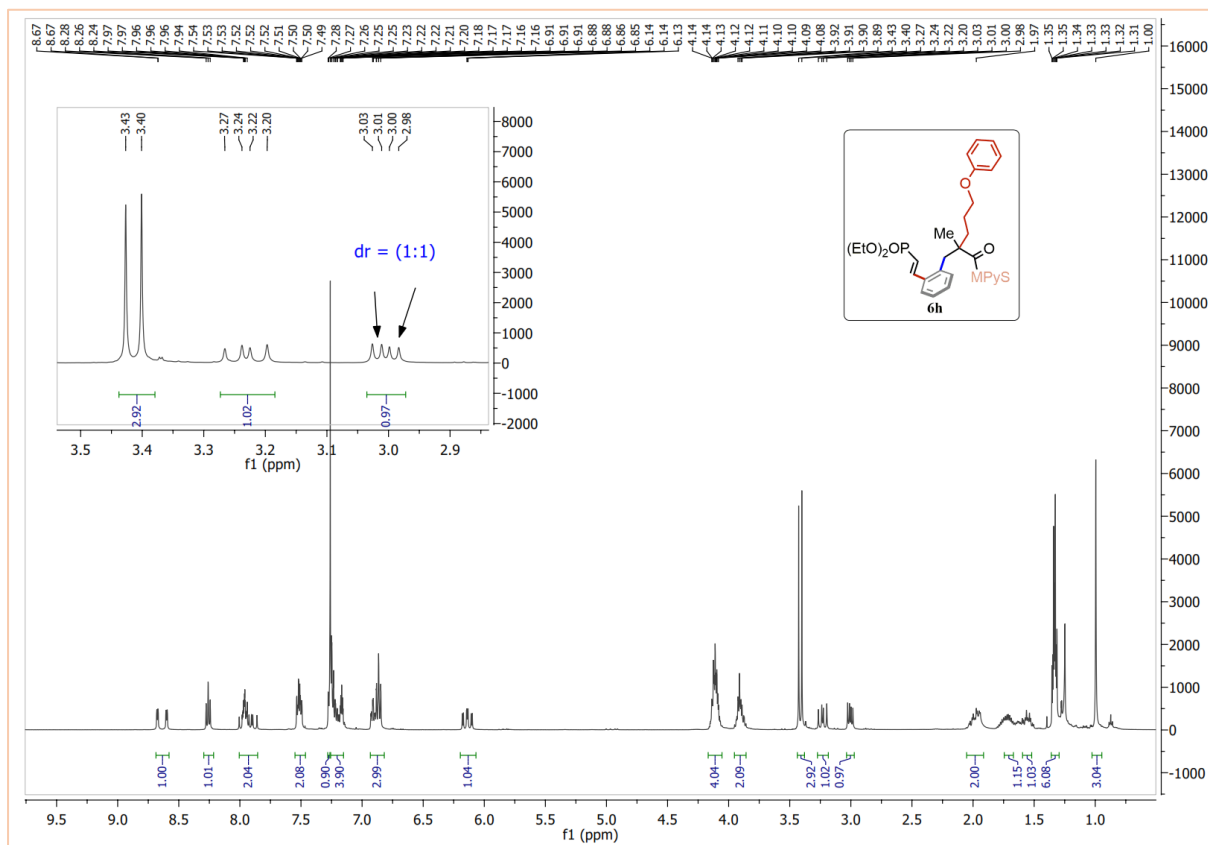
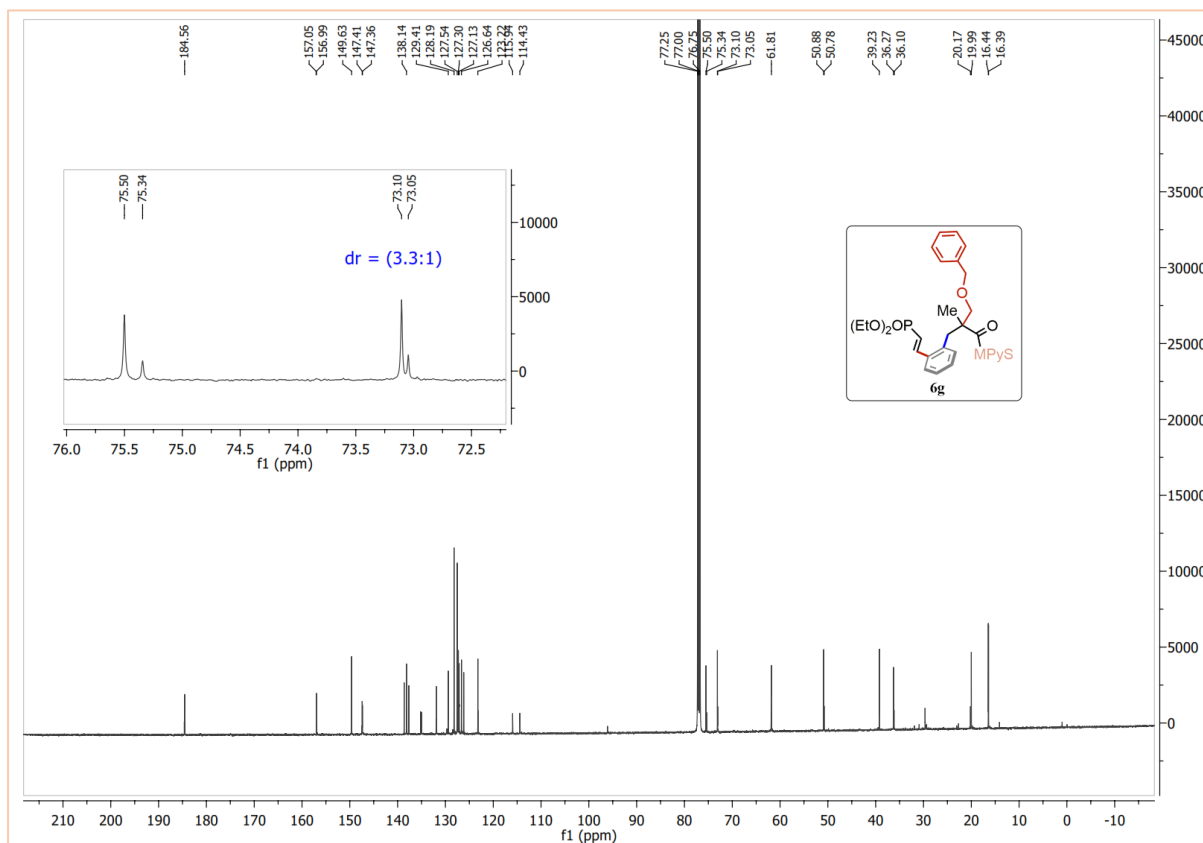


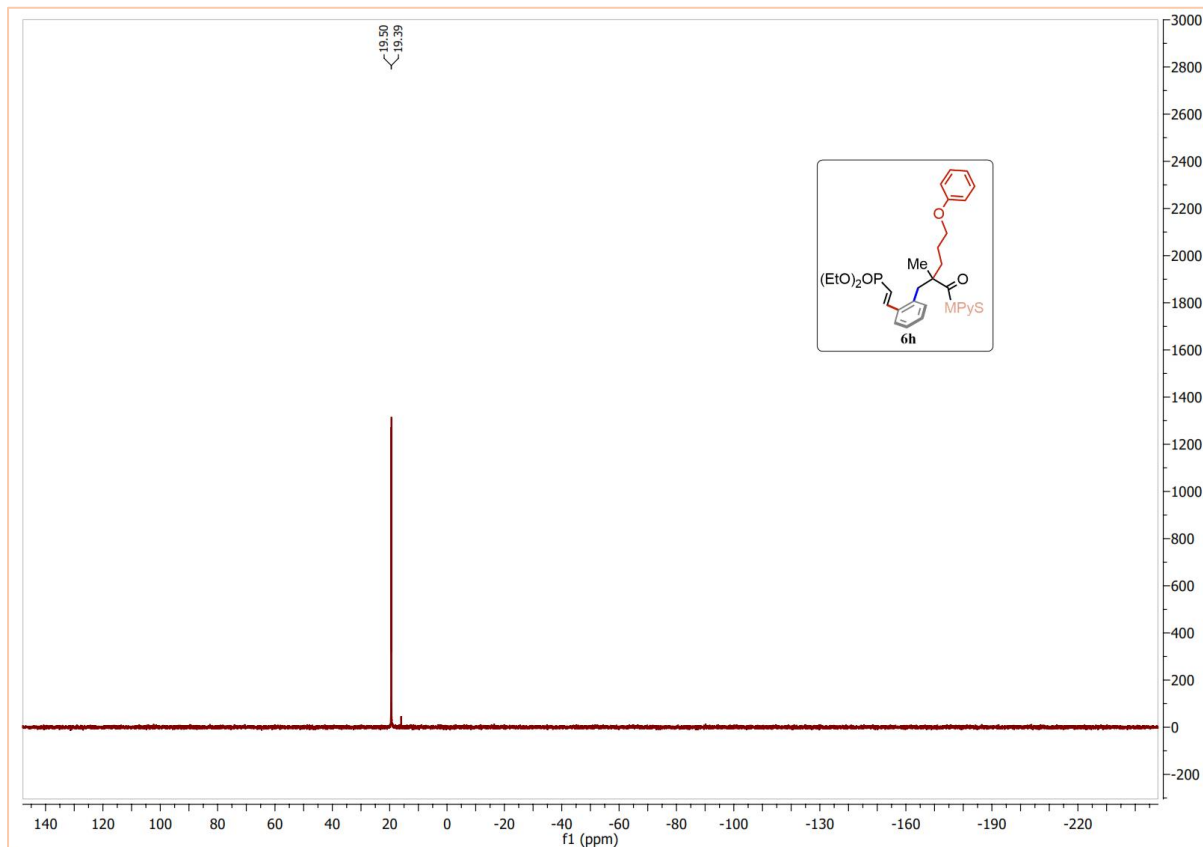


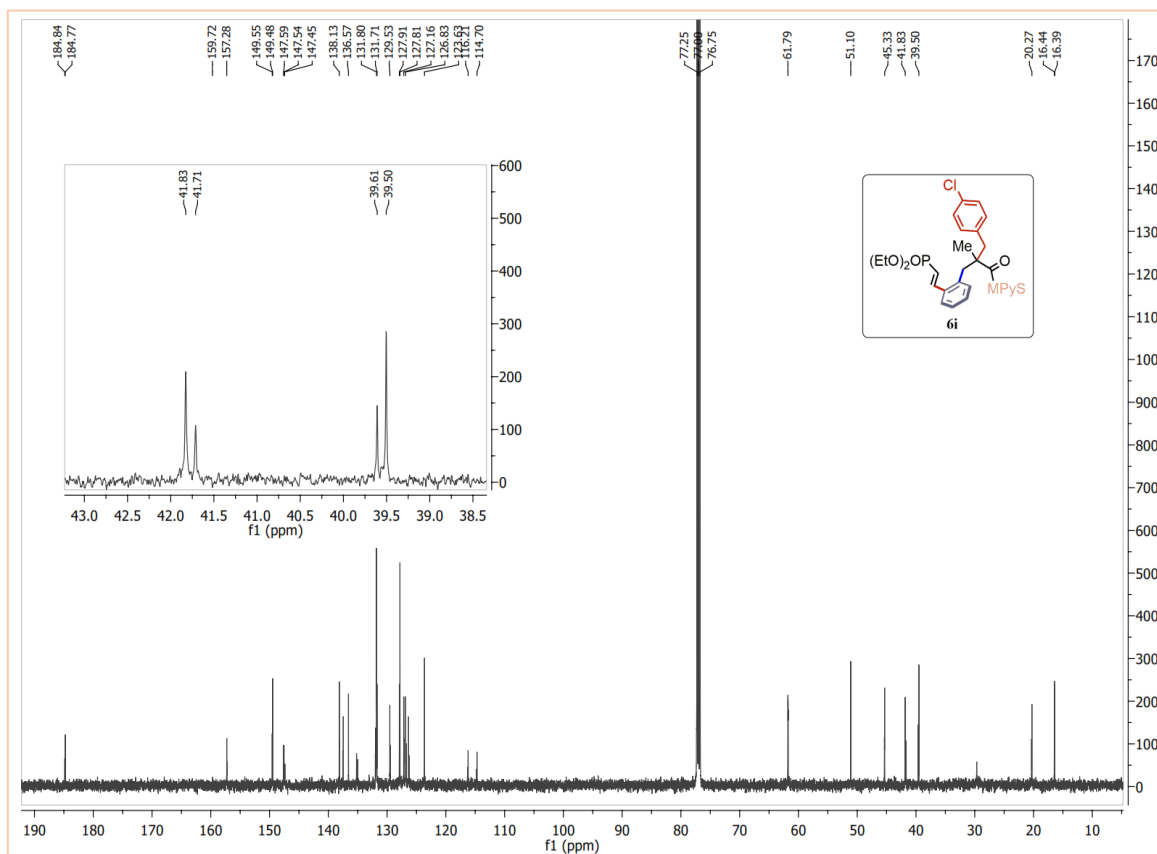
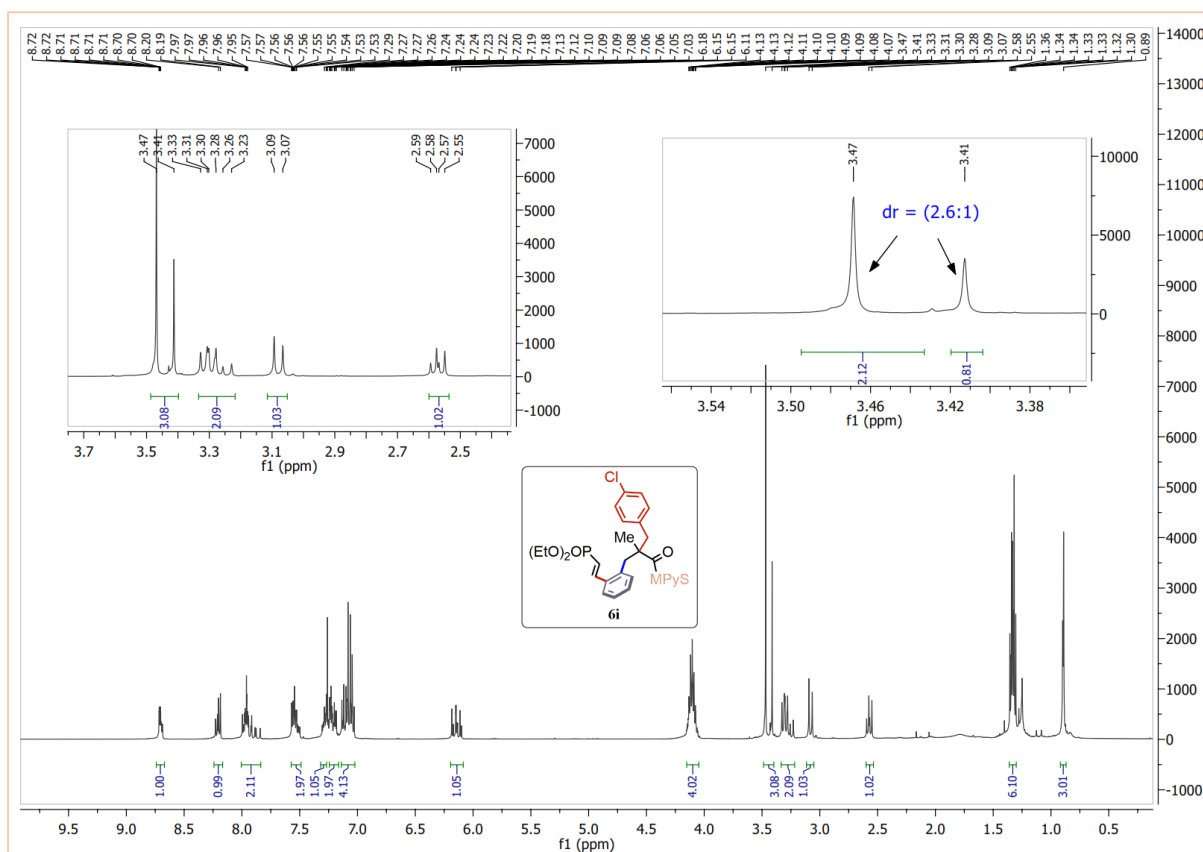


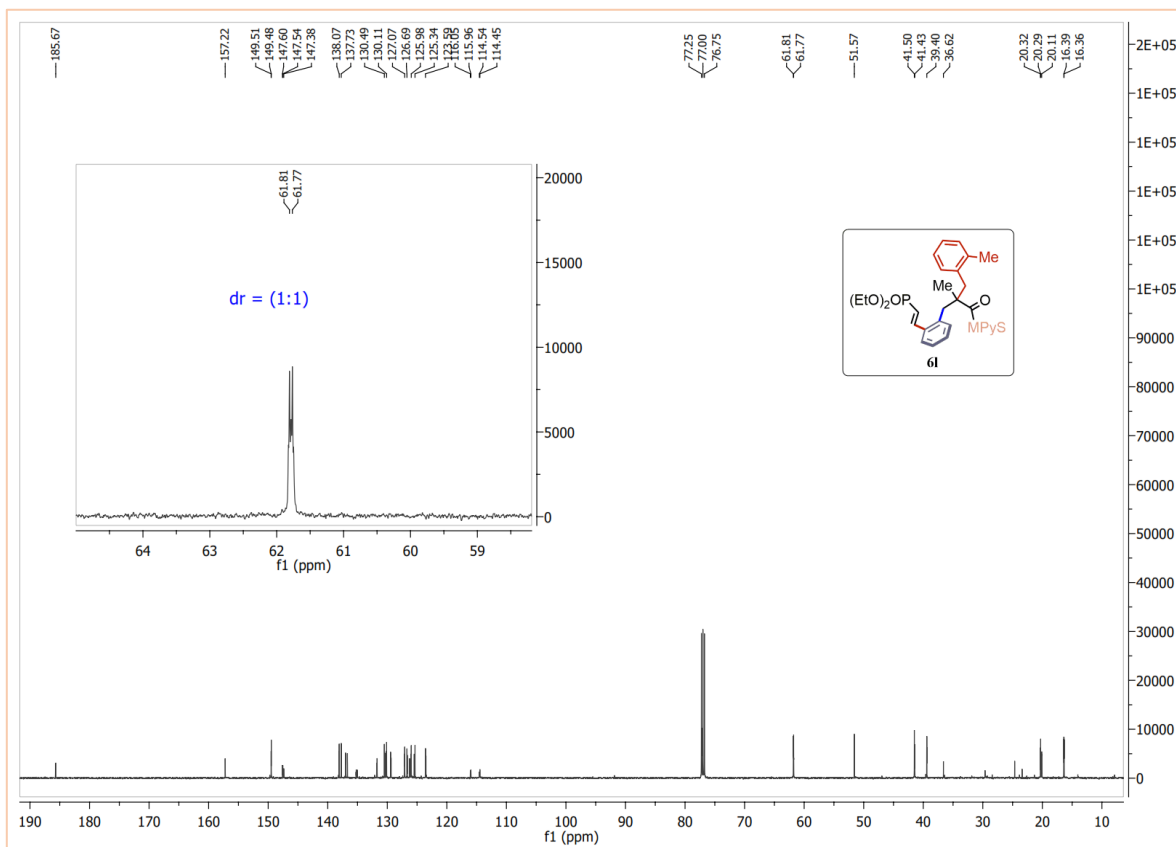


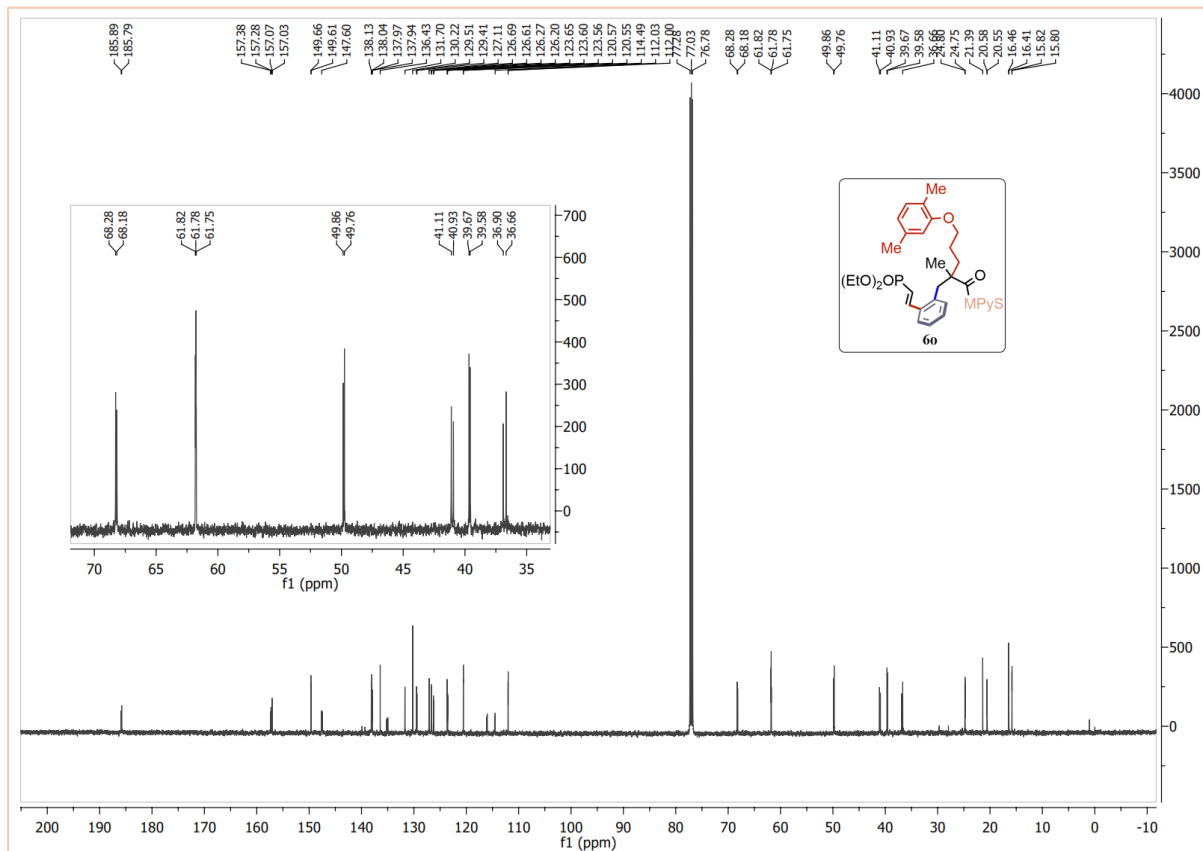


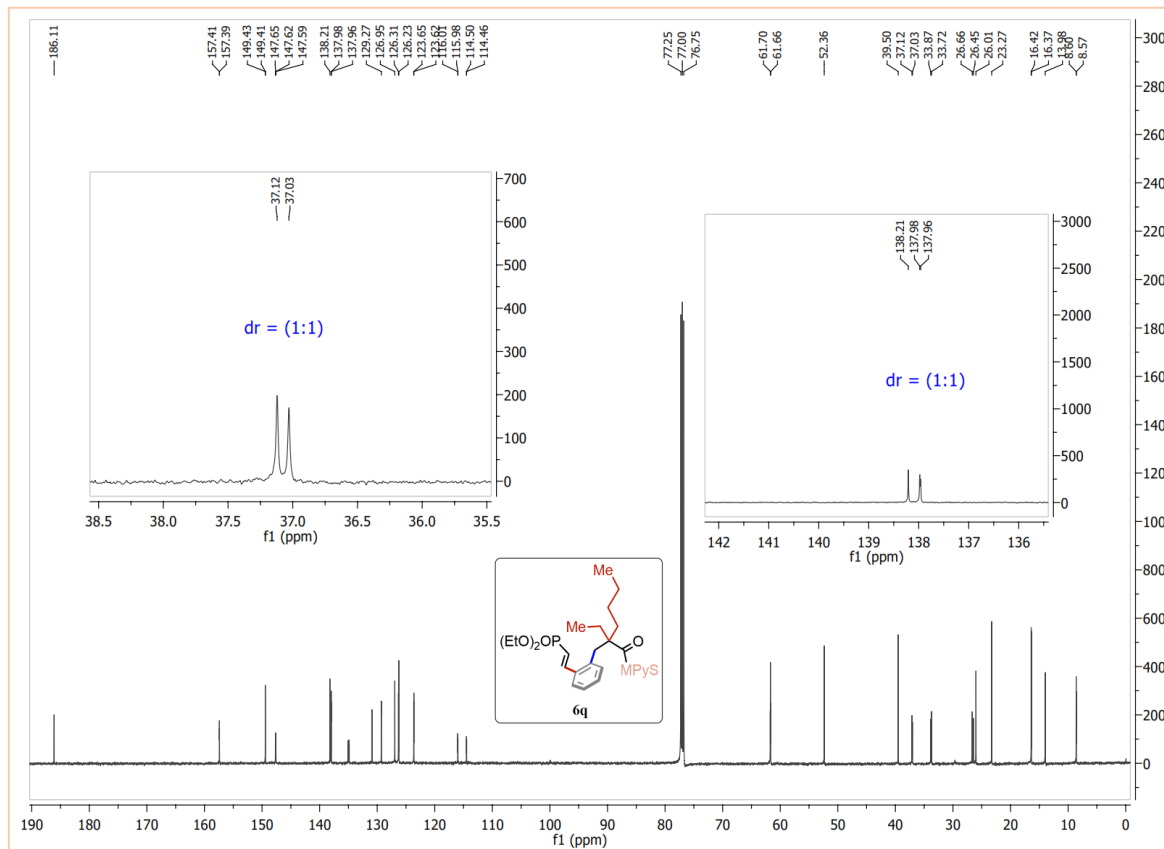
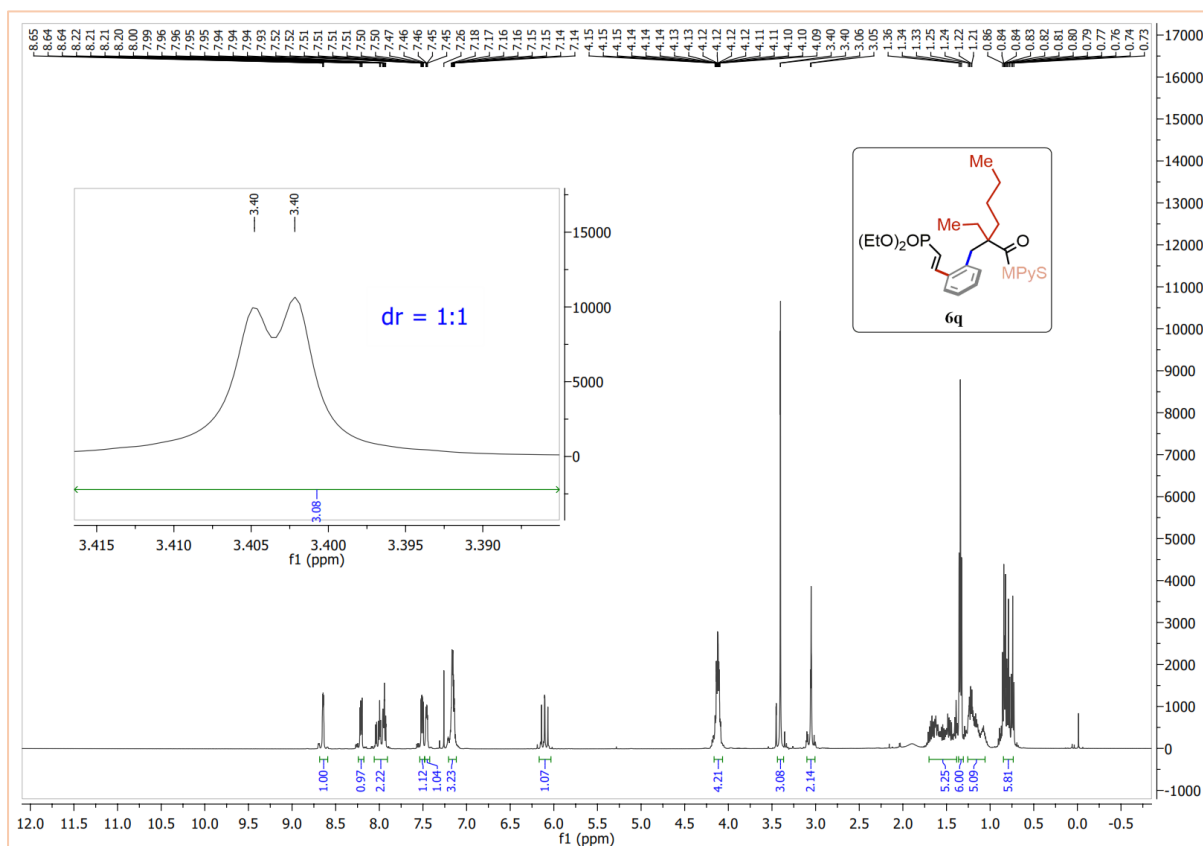


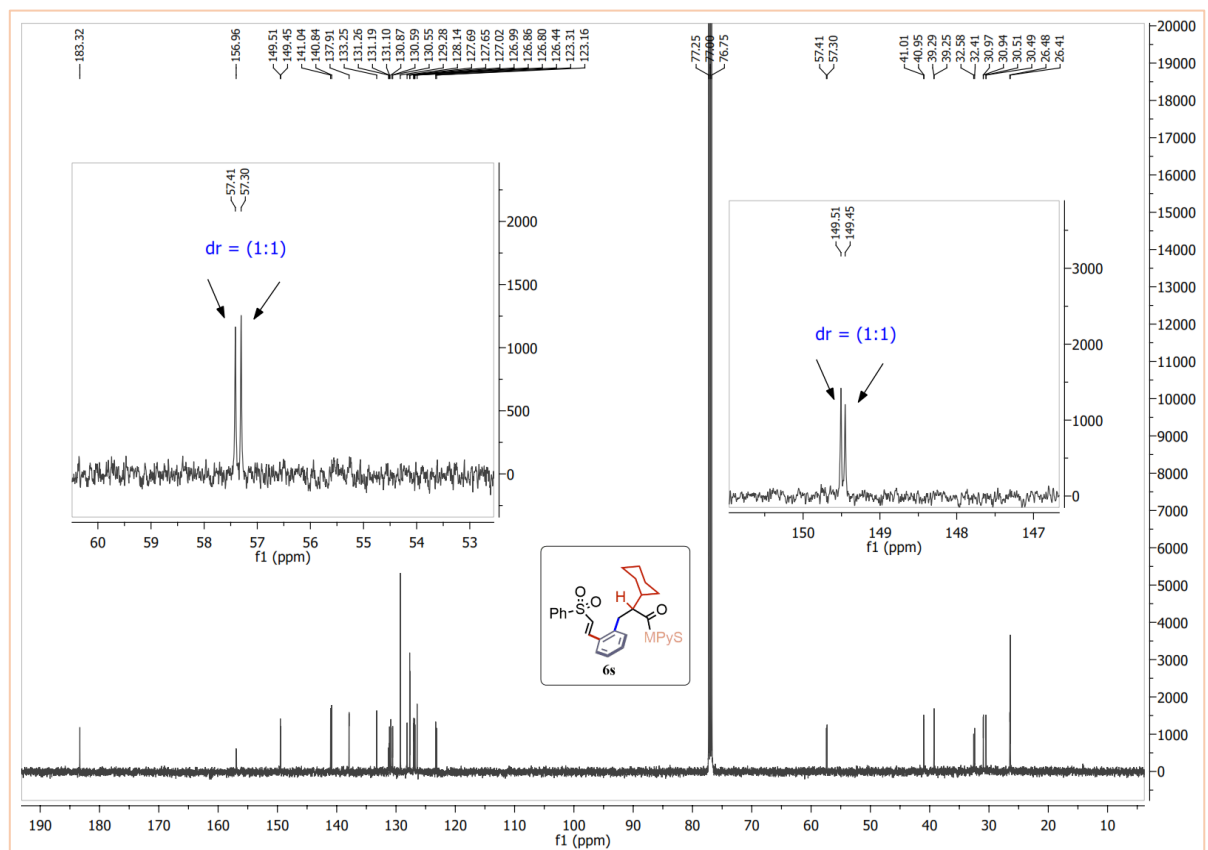
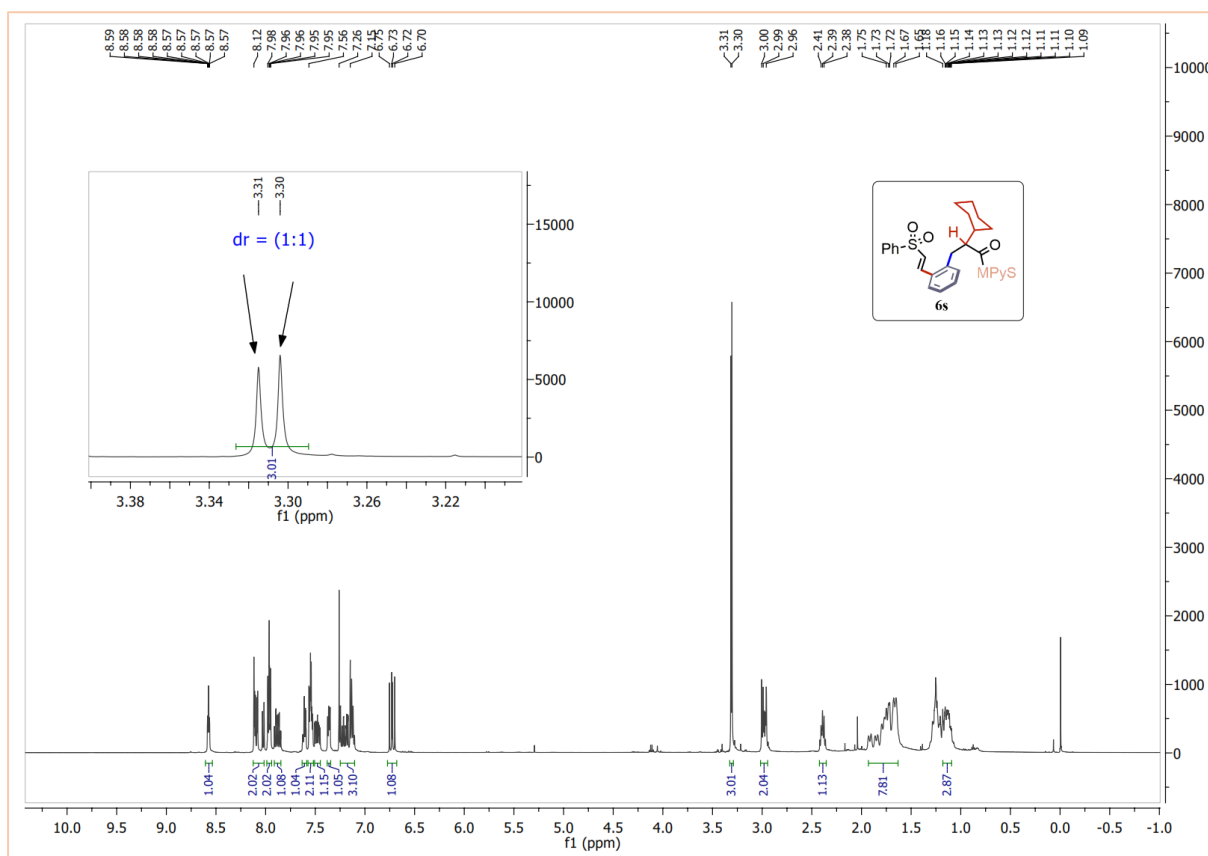


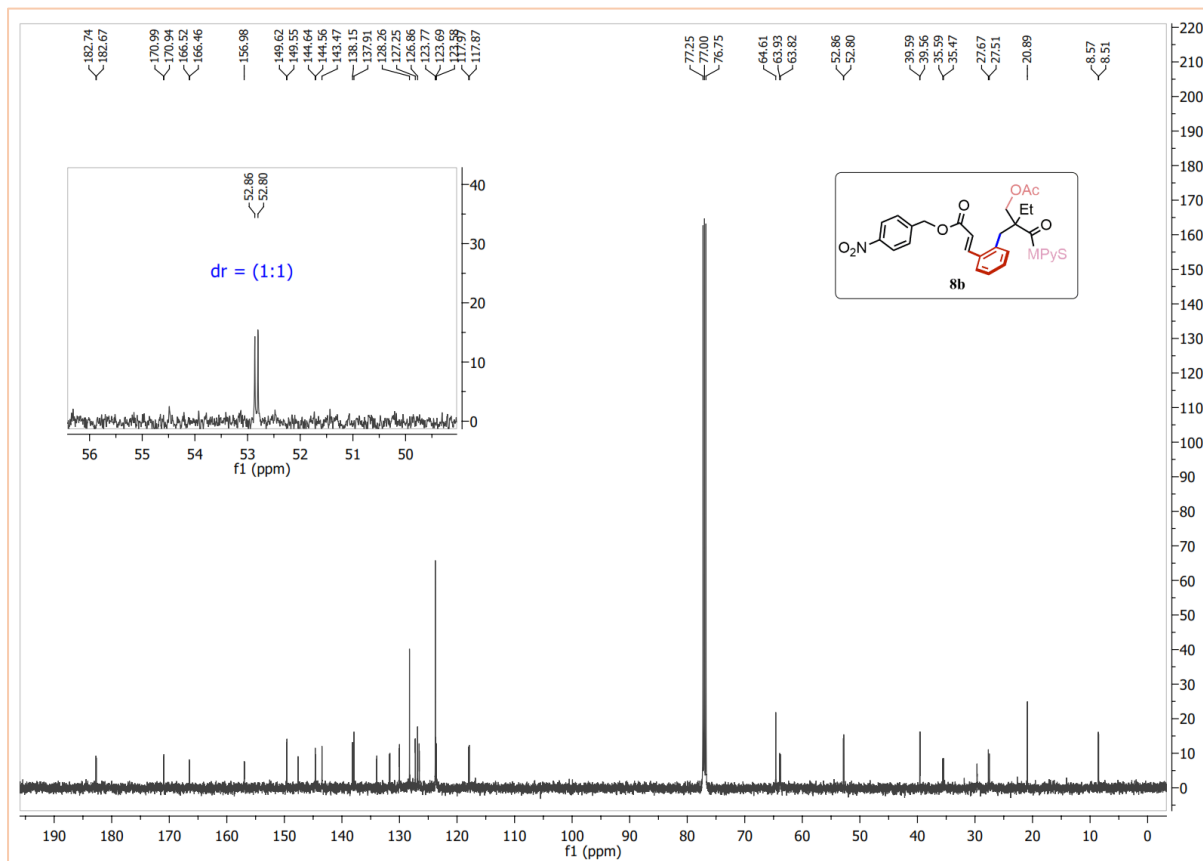


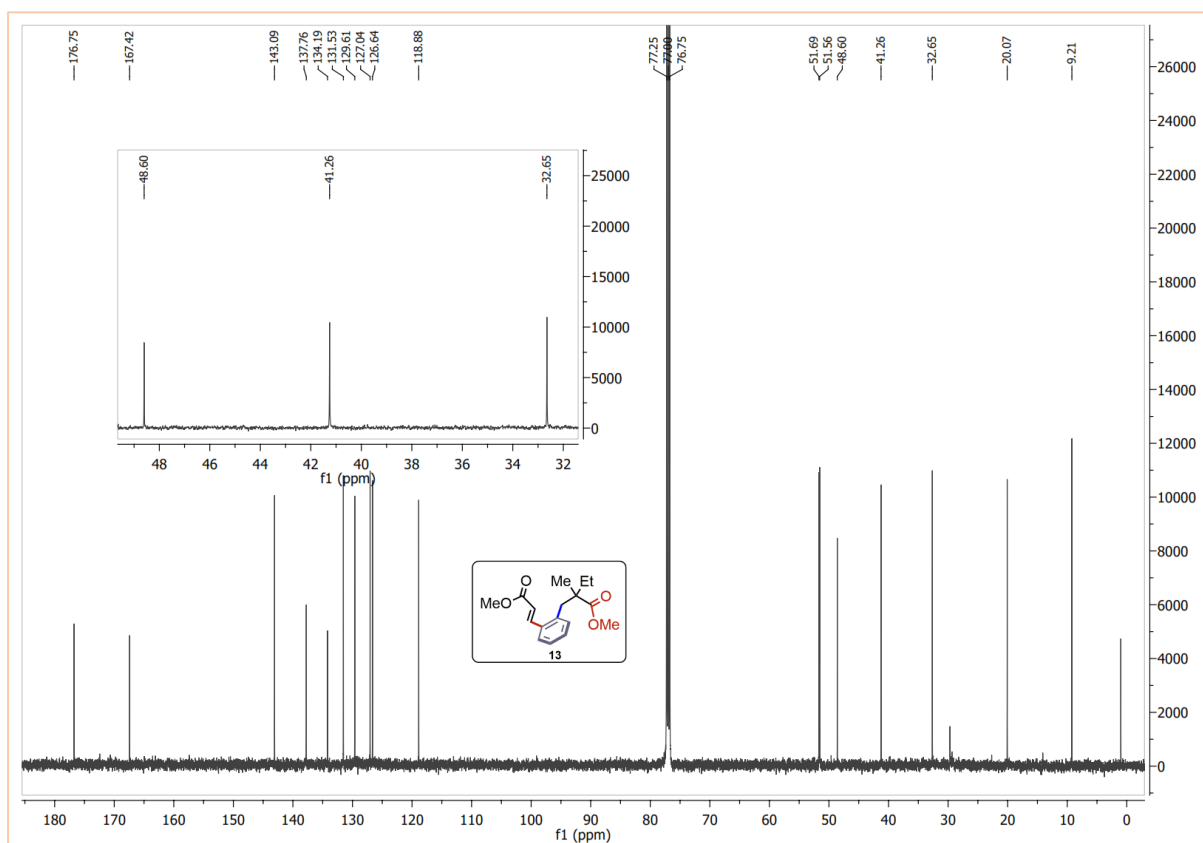
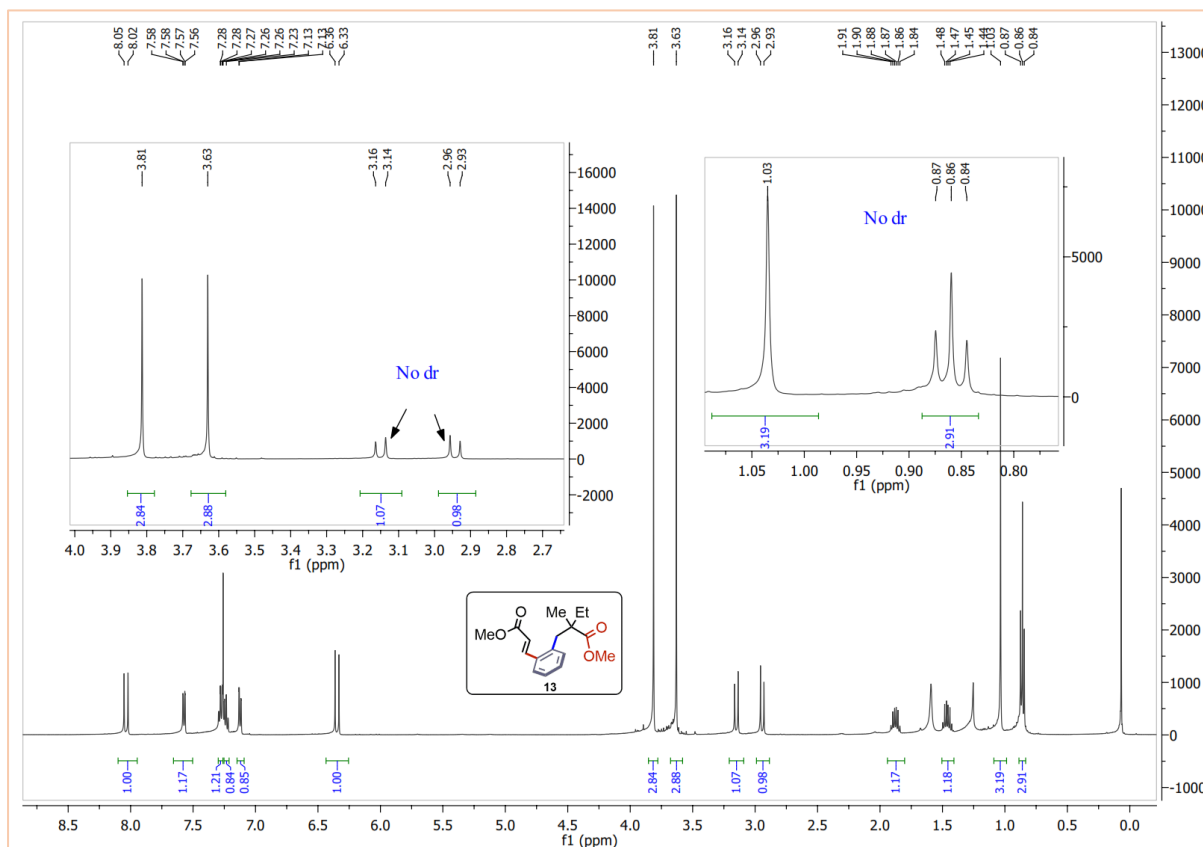








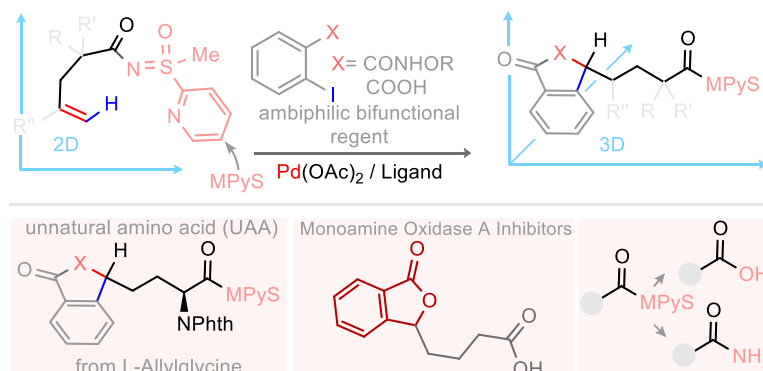




Chapter 4

δ -Annulative 1,1-Difunctionalization of Unactivated Alkenes: Synthesis of α -Substituted Isoindolinones.

Abstract



A palladium-catalyzed δ -annulative 1,1-difunctionalization of unactivated alkene was achieved through the merging of C(alkenyl)–H activation and Wacker-type nucleometallation. The 2-pyridyl methyl sulfoximine (MPyS) bidentate directing group in combination with 2-hydroxy-5-methylpyridine ligand plays significant in making the transformation viable under mild conditions. The process enables the cascade formation of C–C/C–N & C–C/C–O bonds in a single operation, as evidenced by bifunctional reagents (BFRs) from the 2-iodobenzamide, and 2-iodobenzoic acid series. Notably, the de-novo synthesis of α -branched isoindolinones/phthalides motifs highlights its practicality. Mechanistic studies uncover the intricacies of the catalytic cycle. Moreover, the ‘N’ to ‘O’ atom swap showcases the skeletal editing of these complex molecular entities; this process provides direct access to the synthesis of monoamine oxidase A inhibitor.

Reference:

Arghadip Ghosh, Koneti Kondalarao, and Akhila K. Sahoo* [Manuscript under Preparation]

4.1. Introduction

Forging multiple functionalities in an unactivated two-dimensional alkene motif to access a fused ring,^{1a} creates three-dimensionally intricate heterocycles. This signifies a conceptual advancement in the strategy of "escape from flatland"^{1b, c, d} within the realm of "drug-like chemical space".¹ In this regard, an amenable catalytic strategy is the 1,2-annulative difunctionalization of unactivated alkene using ambiphilic bifunctional reagent (BFR) (Fig 4.1.1, left side).² Despite these recent trends, conversely, access to expedient chemical space via 1,1-annulative difunctionalization of unactivated alkene in the presence of an ambiphilic bifunctional reagent (BFR) remains a significant challenge (Fig 4.1.1, right side).^{3,4} In addition, these expeditious 1,1-clipping strategies of unactivated alkene could lead to α -branched isoindolinones or α -branched phthalides. These α -branched isoindolinones are not only found in natural products, such as stachybotrin C and lennoxamine but also in the synthetic entities of paramount pharmacological significance, including pagocloner, indoprofen, pazinaclone, or (S)-PD172938; they routinely serve as anti-inflammatory, anxiolytic, and sedative agents (Fig 4.1.2).⁵ Moreover, a recent study suggests that 3-*n*-butylphthalide-11-oic acid has a potential drug-likeness for antidepressant activity (Fig 4.1.2).⁶ Given their ubiquity in biological activity, developing de-novo catalytic versions for embedding isoindolinones / phthalides motifs in the molecular core is synthetically challenging.⁷

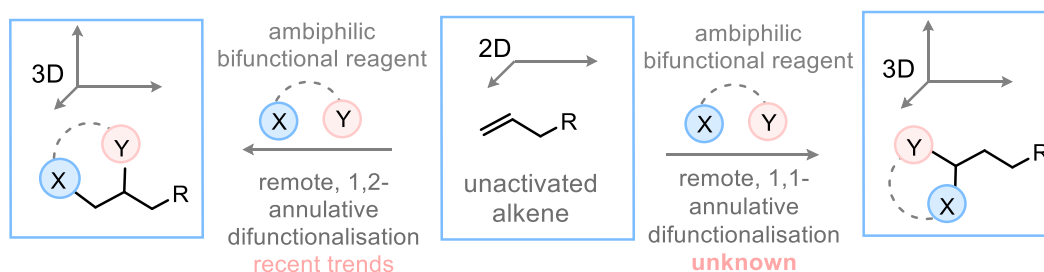


Figure 4.1.1 Concepts 1,1-annulative difunctionalization and molecule design

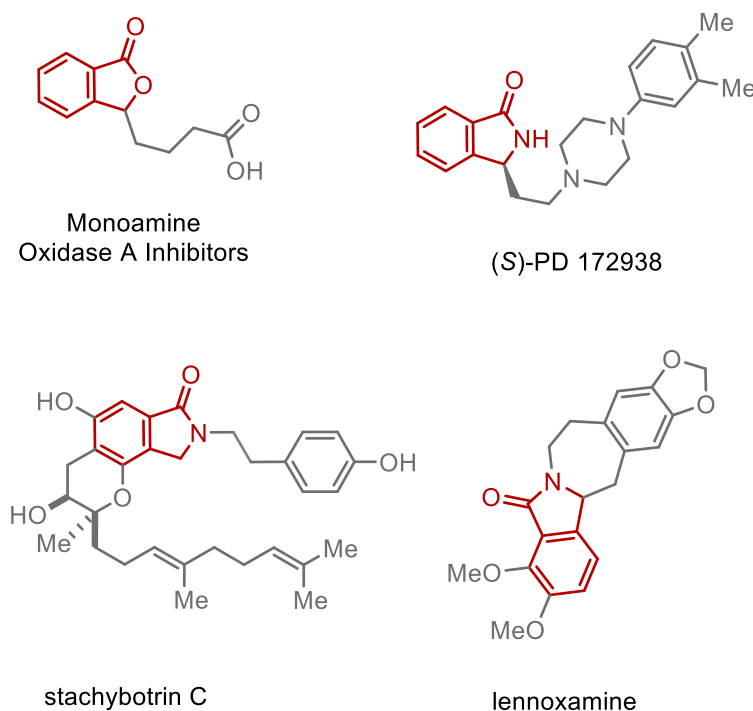
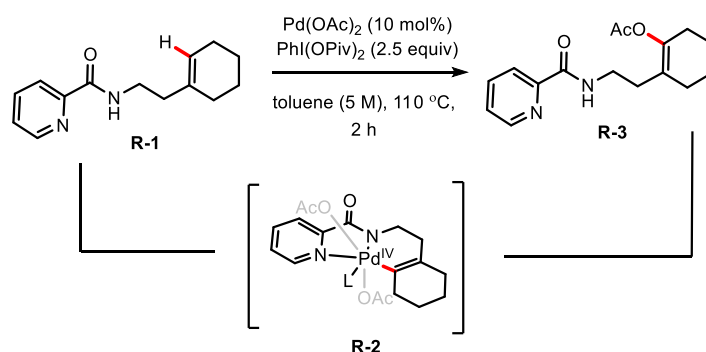


Figure 4.1.2. Phthalides and isoindolinone core in bioactive molecules

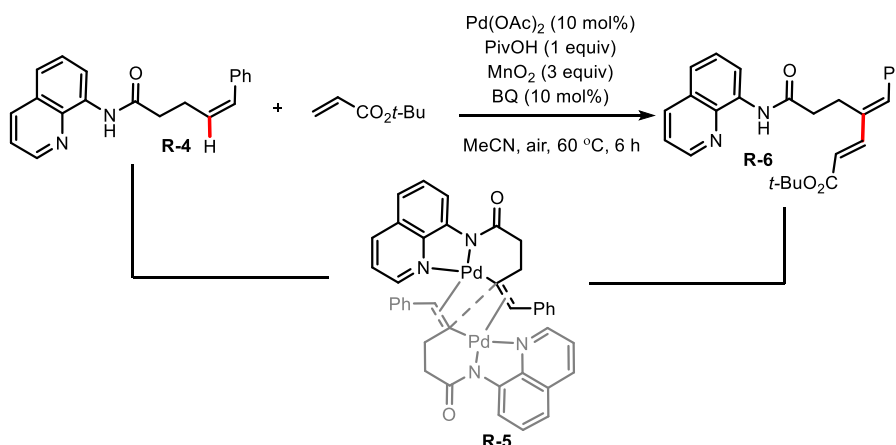
4.1.1. Precedents and Strategies for C(alkenyl)–H Bond Activation and Nucleometallation

To delve into this notion, merging different catalytic systems in a cascade reaction is a worthwhile endeavour,⁸ by enforcing C(alkenyl)–H activation as a crucial foundation. However, despite the advancement of proximal C(alkenyl)–H bond activation (e.g, styrene, acrylates/acrylamides, enamide, and enol esters/ethers),⁹ the activation of C(alkenyl)–H bonds in distal non-conjugated alkenes has been challenging due to the inherent allylic oxidation,¹⁰ nucleometallation,¹¹ and directed Heck¹² side reactions. Consequently, addressing the issues of chemo- and regioselectivity remains a significant challenge. At this juncture, involvement of a directing group (DG) could help making the reaction viable. The synthetic methods developed along this line is herein discussed.

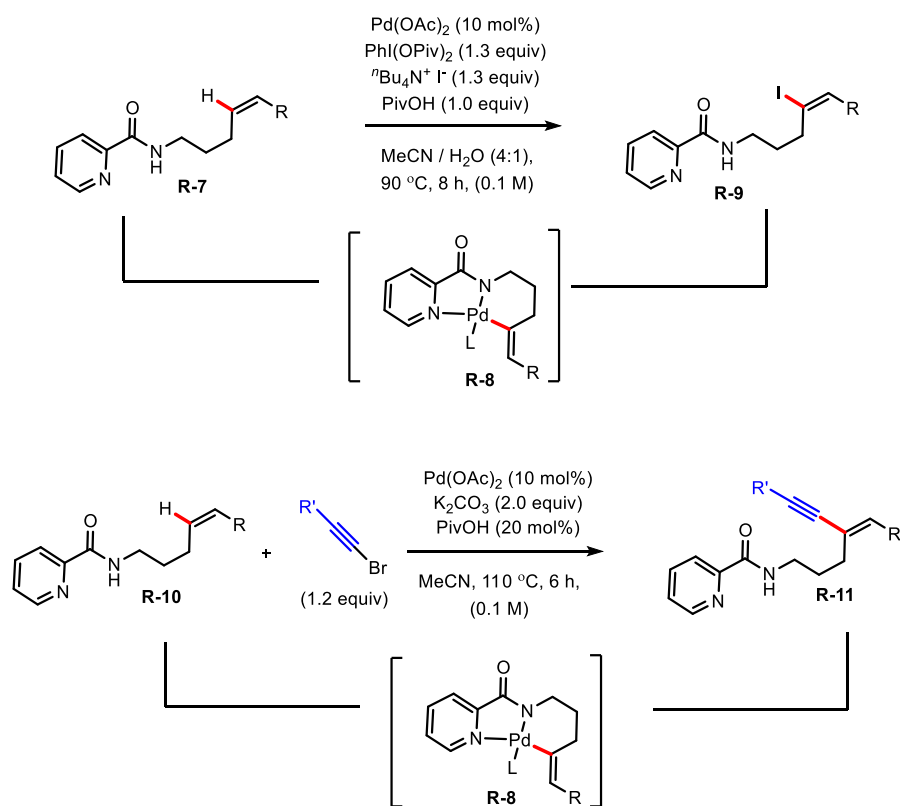
In 2016, He and coworkers reported picolinamide-directed acetoxylation of amine-containing unactivated alkenes.¹³ A wide variety of substrates readily acetoxylation under mild condition. Mechanistic study suggests that Pd (IV) intermediate (**R-2**) has been involved in making the acetoxylation feasible (Scheme 4.1).

Scheme 4.1: γ -Acetoxylation via C(alkenyl)-H activation

In 2018, the Engle group demonstrated an expedient way for the synthesis of 1,3-diene compounds, using C(alkenyl)-H activation strategy of 8-aminoquinoline protected aliphatic carboxylic acid derivative (Scheme 4.2).¹⁴ A wide range of internal and terminal alkenes has been used in this process. The mechanistic study revealed that the C(alkenyl)-H activation pathways predominate over other possible paths; the formation of alkenylpalladium(II) dimer **R-5** supports this proposal.

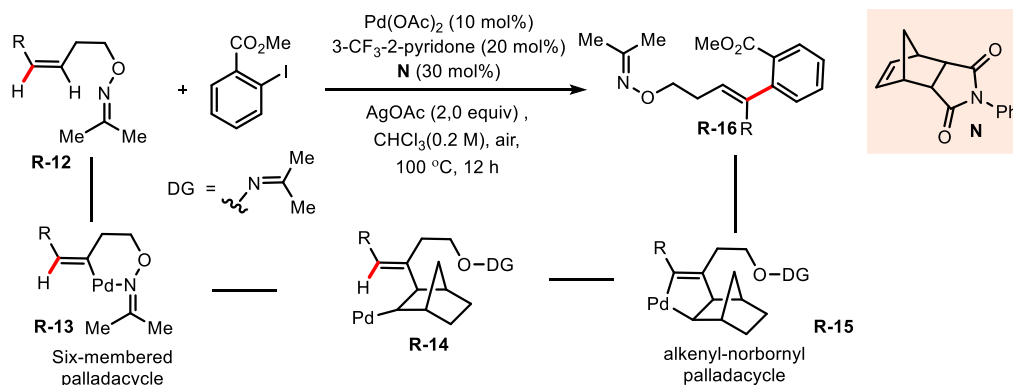
Scheme 4.2: γ -Alkenylation via C(alkenyl)-H activation

The Carreira group reported regio and stereoselective δ -C(alkenyl)-H activation followed by iodination and alkynylation of picolinamide-protected unactivated alkenes (Scheme 4.3).¹⁵ In both cases, δ -C(alkenyl)-H activated intermediate **R-8** was highly evident. Despite the possibility of internal alkenes undergoing side reactions like cross-coupling, allylic C-H activation etc, a wide range of internal alkenes have been participated in this transformation.

Scheme 4.3: δ -Iodination and alkynylation via C(alkenyl)-H activation

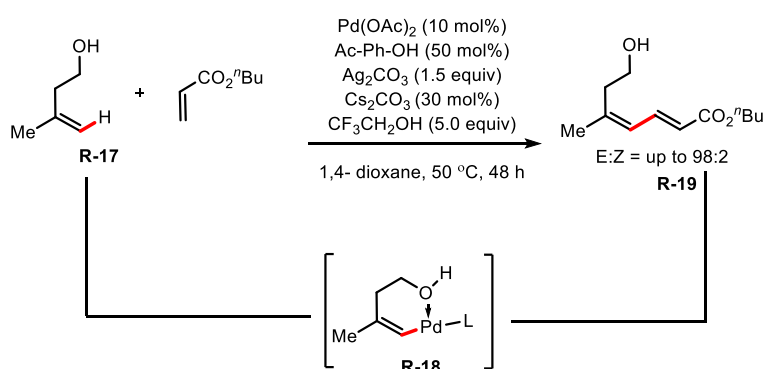
In 2020, Dong group showcased a distal C(alkenyl)-H arylation of oxygen protected unactivated alkene substrates (Scheme 4.4).¹⁶ In order to achieve this reactivity, an orchestrated γ -C(alkenyl)-H activation intermediate **R-13** and proximal to distal palladium migration using norbornene derivative (**N**) intermediate **R-15** are proposed. Finally, oxidative arylation of **R-15** delivered the δ -C(alkenyl)-H product **R-16**. This method showed broad scope; a wide range of oxygen-bearing unactivated internal alkenes are well participated. However, arylation has been restricted only with protected 2-iodobenzoic acid derivatives. Moreover, the mechanistic study completely disputes the possibility of a directed Heck reaction.

Scheme 4.4: δ -Arylation via γ -C(alkenyl)-H activation and norbornene-assisted palladium migration.



In 2017, Loh and coworkers revealed a native hydroxy group directed δ -C(alkenyl)-H activation followed by alkenylation of a terminal position of unactivated alkenes (Scheme 4.5).¹⁷ The products are formed with good to excellent E/Z ratio when the reaction was conducted with various unactivated alkenes. The kinetic isotopic effect (KIE) value is 2.02 and the reaction shows first-order dependence with respect to $\text{Pd}(\text{OAc})_2$; thus, C-H activation is possibly a rate-determining step of this reaction.

Scheme 4.5: δ -Alkenylation via hydroxy group assisted δ -C(alkenyl)-H activation.



In recent years, the directing group-enabled nucleometallation techniques have paved the way for synthesizing regioselective heteroatom bearing sp^3 enrich chemical space.

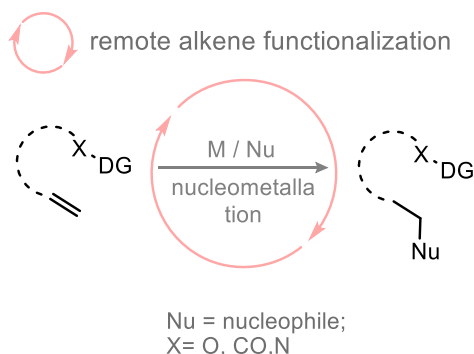
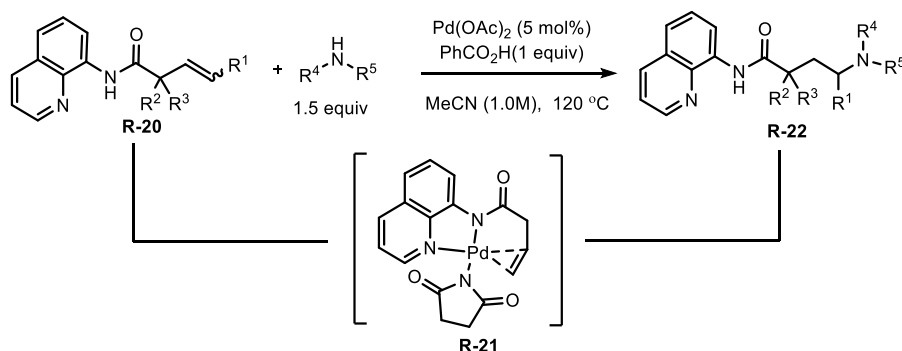


Figure 4.2 Nucleometallation technique for remote alkene functionalization

In 2016, Engle and coworkers showed a directing group enabled highly regio-controlled hydroamination of 8-aminoquinoline-protected acid containing unactivated alkenes (Scheme 4.6).¹⁸ This directed nucleopalladation technique has paved the way for realizing the incorporation of nitrogen-containing nucleophiles in remote positions of alkene. To support this observation, a π -activated palladium(II) complex **R-21** has been isolated and characterized through X-ray diffraction study. This mechanistic insight allows the successful demonstration of several nucleometallation techniques to the remote installation of heteroatom as well as difunctionalization of unactivated alkenes.

Scheme 4.6 : Engle's nucleopalladation of unactivated alkene.



4.2. Motivation, Hypothesis, and Design

Owing to the difficulties and advantages for functionalization of unactivated alkenes (Fig-4.2.1), we wondered whether we could merge the δ -C(alkenyl)-H activation and regioselective hydroamination processes to circumvent for the de-novo synthesis of α -branched isoindolinones / α -branched isobenzofuran-1(3H)-one. This realization

possesses mechanistically distinct catalytic cycle and is synthetically important. To our knowledge, such demonstration has not been reported so far. In pursuit of this goal, a suitable bifunctional reagent could be a warhead.¹⁹ In addition, this catalytic blueprint could deliver unnatural amino acid (UAA)²⁰ that are rather difficult to access in the conventional methods (Fig-4.2.2).

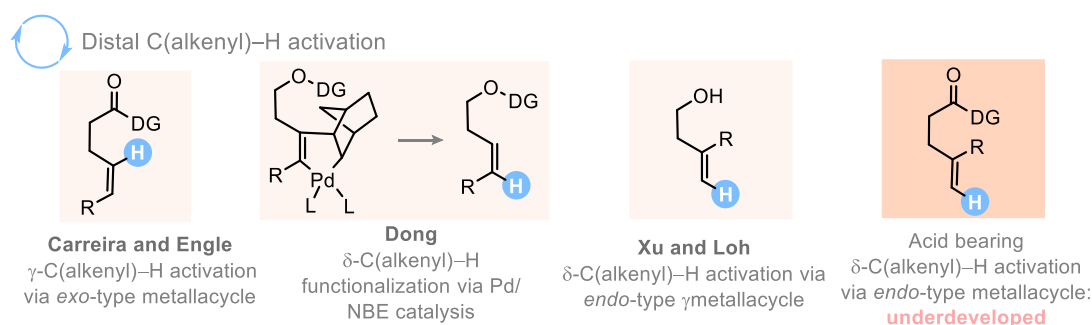


Figure 4.2.1 Motivation for remote annulative difunctionalization.

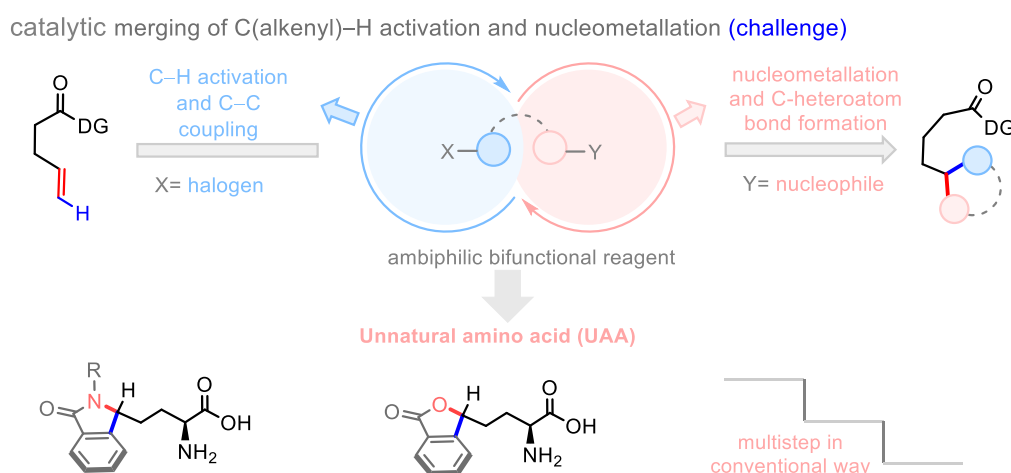


Figure 4.2.2 Merging alkenyl C-H arylation and annulative hydroamidation of unactivated alkenes

Herein, 2-iodo-N-alkoxybenzamide / 2-iodo-benzoic acid derivatives could transfer two functionalities (C/N) / (C/O) to access α -branched isoindolinones / α -branched isobenzofuran-1(3H)-one in a single operation. We planned to use a MPyS-DG bearing pentenoic acid derivative, a 2-iodo-N-alkoxybenzamide / 2-iodo-benzoic acid, Pd(OAc)₂ catalyst along with a ligand, oxidant. We can anticipate that the transformation relies on the coordination of a Pd(II) species to the MPyS-DG to trigger a ligand-assisted CMD of an δ -C(alkenyl)-H bond, followed by N-alkoxybenzamide/ 2-iodo-benzoic acid ligand exchange to result the intermediate **I**. Next, oxidative addition of iodoaryl moiety of **I**, followed by reductive elimination, would deliver **II**.

Intermediate **II** could then undergo aminopalladation to provide intermediate **III**. Finally, protodemetalation could build isoindolinone / isobenzofuran-1(3H)-one derivatives (Fig-4.2.3)

This work

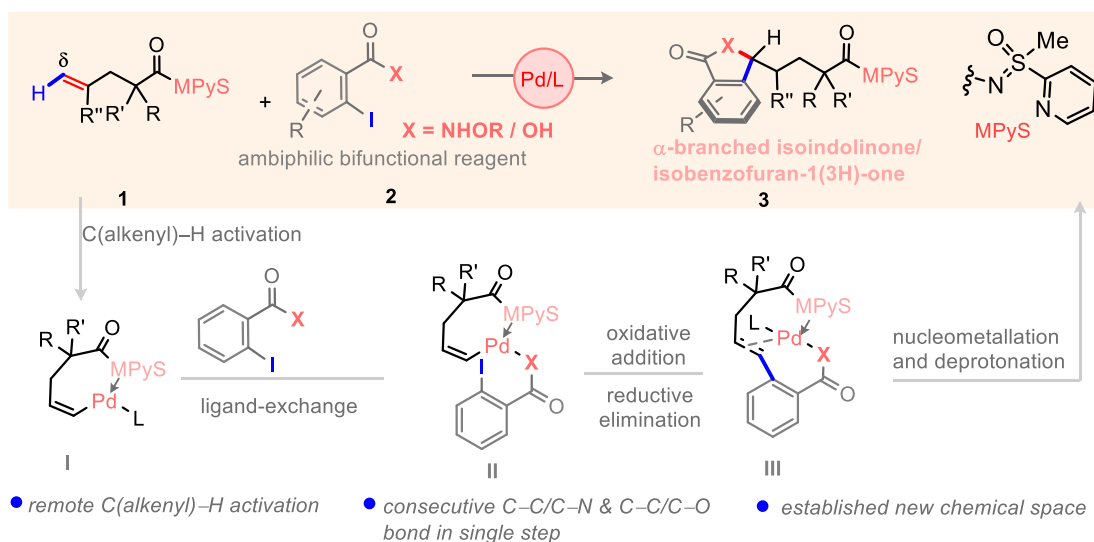


Figure 4.2.3 working hypothesis.

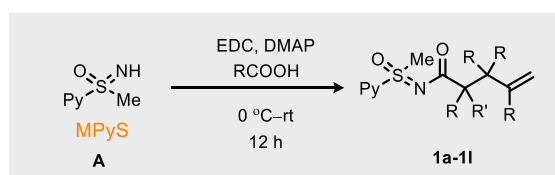
4.3. Results and Discussion

4.3.1. Synthesis of Precursors

A wide range of *N*-carboxyl sulfoximine derivatives were synthesized involving the procedure mentioned herein.

4.3.1.1. Preparation of *N*-protected *S*-methyl-*S*-(2-pyridyl) sulfoximines: General Procedure (GP-1):²¹

Scheme 4.7. Preparation of carboxylic acids

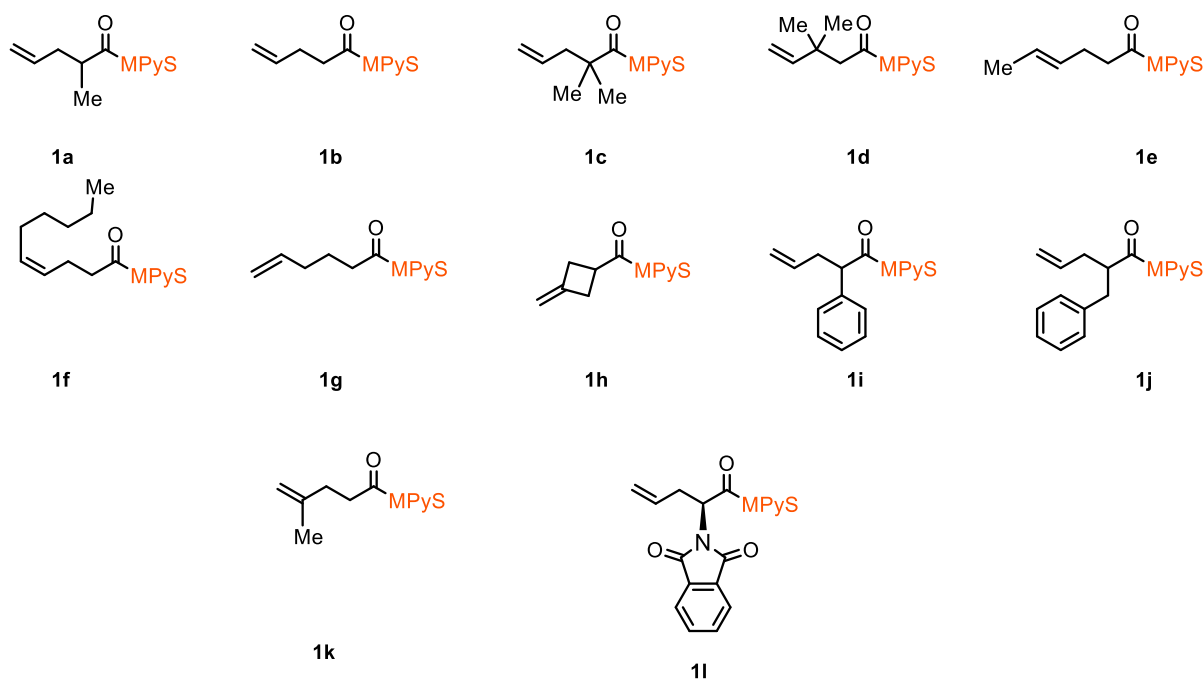


A solution of *N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, hydrochloride salt (EDC · HCl) (1.1 equiv), 4-*N*, *N*-dimethylaminopyridine (DMAP) (2.2 equiv), and carboxylic acid (1.1 equiv) in CH_2Cl_2 (5.0 mL for 1.0 mmol of sulfoximine) was stirred under an argon atmosphere. Sulfoximine (**1**; 1.0 equiv) was introduced dropwise at 0

°C. The resulting reaction mixture was stirred for about 1 h at 0 °C, and warmed to ambient temperature and stirred overnight. Upon complete consumption of sulfoximine, the reaction mixture was acidified with hydrochloric acid (HCl, 1N). The organic layer was separated; the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined extracts were washed with 10% aqueous NaHCO₃ and brine. The organic layer was dried over Na₂SO₄. The solvent was filtered and evaporated under reduced pressure. The crude residue was purified using column chromatography eluting with (EtOAc/hexane mixture) on silica gel.

The compounds **1a**, **1b**, **1c**, **1d**, **1g**, **1h**, and **1k** are prepared, using above mentioned procedure. However, **1e**, **1f**, **1i**, **1j**, and **1l** compounds are made after 1 step of acid synthesis, which is mentioned below.

Substrates list:



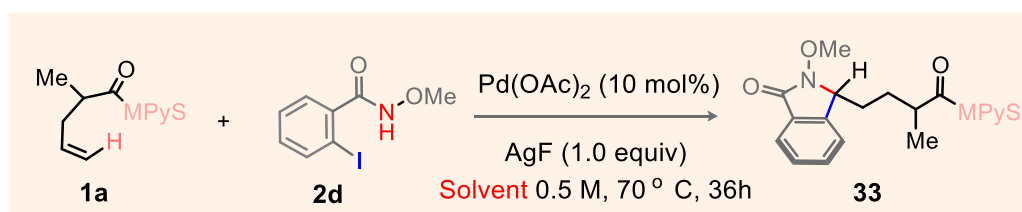
4.3.2. Reaction Optimization

To explore the projected model reaction in Figure 4.2.3, we have chosen amide **1a** bearing a 2-pyridyl-methyl sulfoximine (MPyS) as a substrate, 2-iodo-N-methoxybenzamide **2d** as a coupling partner. The desired isoindolinone compound (**33**) was obtained in 35% yield when the reaction was carried out in the presence of AgF oxidant

in HFIP solvent (Table 4.1). Instead of AgF, only AgOAc was able to deliver the desired isoindolinone (**33**) in 23% yield, whereas other silver salts were ineffective (Table 4.2).²⁶ Despite the mechanistic conflict (for instance; C–H activation/ nucleometallation/ directed Heck), we extended our investigation from our recent success with external ligand 2-pyridyl-methyl sulfoximine-directed C–H activation²⁷ in the context of δ -alkenyl C–H activation. With this realization, we screened various pyridine-based ligands. Initially, electron-rich pyridine ligands showed a complete shutdown of the reaction. However, electron-deficient pyridine ligands remained inferior (Table 4.3). Next, we moved to pyridone-based ligands. Interestingly, 2-hydroxy pyridine (**L3**) was able to deliver the desired isoindolinone compound (**33**) in 63% yield (¹H NMR), with dr= (1:1) ratio. This observation encouraged us to screen various pyridone ligands; the electron-rich 5-methylpyridin-2-ol ligand (**L4**) was found effective to provide the desired isoindolinone compound in 84% yield (¹H NMR) with 76% isolated yield and with dr = (1:1) ratio, when the reaction was performed in presence of Pd(OAc)₂ (10 mol %), AgF (0.1 mmol), HFIP (1 mL) at 70 °C under air. Moreover, increasing the ligand loading from 15 to 50 mol% led to a decreased yield, and other solvents, palladium salts, and other combinations of oxidant and coupling partner ratios remained inferior (Tables 4.4, 4.5, and 4.6). In addition, it is interesting to observe that only 2-iodo-N-methoxy benzamide **2d** was able to deliver the desired product. While other protecting groups bearing compounds **2a–2c** gave only non-cyclized arylation products rather than desired cyclized products (Figure-4.3).

The reaction optimization details:

Table 4.1: Solvent optimization

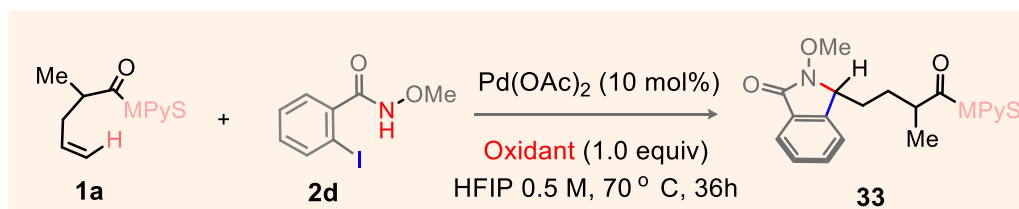


Entry	Solvent	Yield 33%
1	HFIP	35
2	AcOH	0

3	1,2-DCE	0
4	1,4-dioxane	0
5	DCM	0
6	TFE	0
7	<i>t</i> -amylOH	0
8	Ac ₂ O	0
9	CH ₃ CN	0

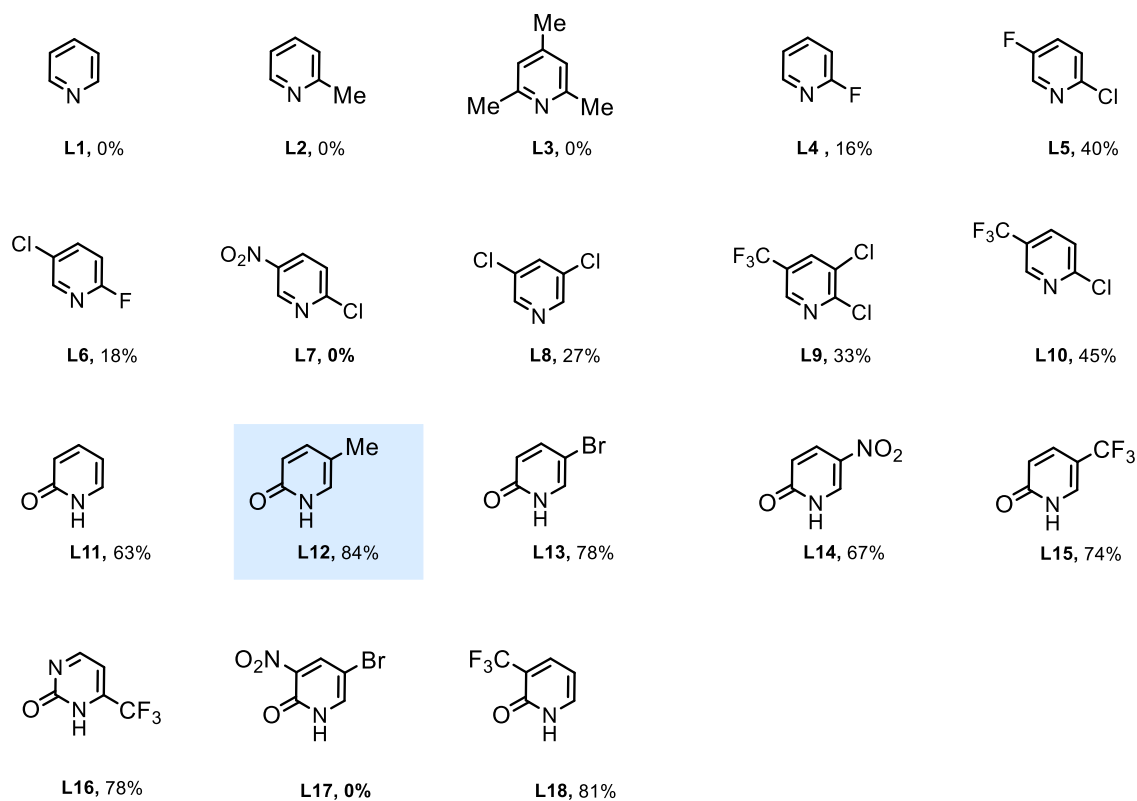
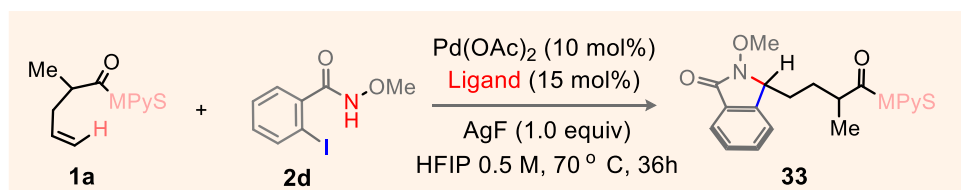
Reaction conditions: **1a** (0.1 mmol), **2d** (0.15 mmol), Pd(OAc)₂ (10 mol %), AgF (0.1 mmol), solvent (1.0 mL), at 70 °C, under air, 36 h. The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard.

Table 4.2: Oxidant optimization

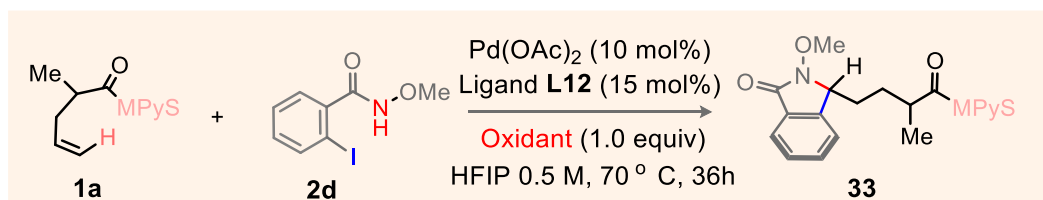


Entry	Oxidant	Yield 33%
1	AgOAc	23
2	Ag ₂ CO ₃	0
3	Ag ₂ O	0
4	AgF	35
5	AgBF ₄	0
6	AgSbF ₆	0

Reaction conditions: **1a** (0.1 mmol), **2d** (0.15 mmol), Pd(OAc)₂ (10 mol %), AgX (0.1 mmol), HFIP (1.0 mL), at 70 °C, under air, 36 h. The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard.

Table 4.3: Ligand optimization

Reaction conditions: **1a** (0.1 mmol), **2d** (0.15 mmol), $\text{Pd}(\text{OAc})_2$ (10 mol %), Ligand (15 mol %), AgF (0.1 mmol), HFIP (1.0 mL), at 70 °C under air, 36 h. The yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard.

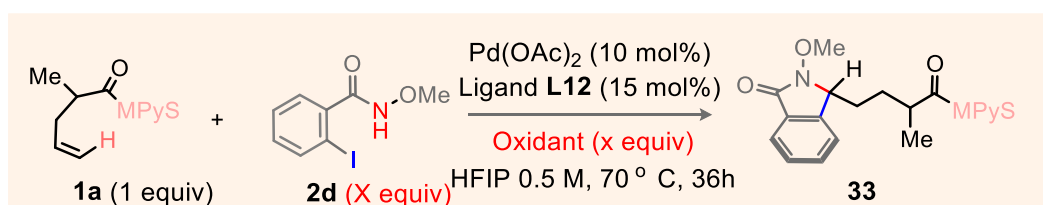
Table 4.4: Oxidant optimization in the presence of ligand

Entry	Oxidant	Yield 33%
1	AgOAc	41

2	Ag ₂ CO ₃	0
3	Ag ₂ O	0
4	AgCl	0
5	AgBr	0
6	AgSCF ₃	0

Reaction conditions: **1a** (0.1 mmol), **2d** (0.15 mmol), Pd(OAc)₂ (10 mol %), Ligand (15 mol %), AgX (0.1 mmol), HFIP (1.0 mL), at 70 °C, under air, 36 h. The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard.

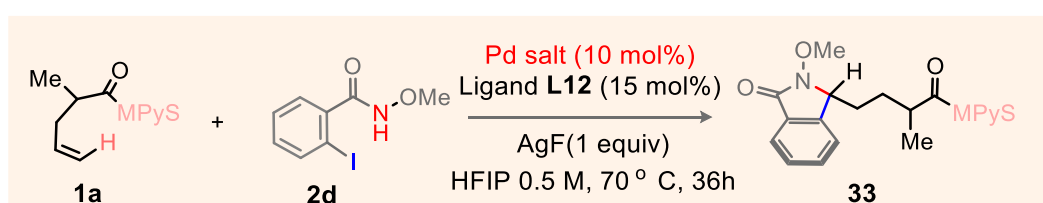
Table 4.5: Variation amount of oxidant and coupling partner.



Entry	Oxidant	coupling partner(2)	Yield 33%
1	AgOAc (2 equiv)	2 (1.5 equiv)	22
2	AgOAc (0.5 equiv)	2 (1.5 equiv)	53
3	AgOAc (2 equiv)	2 (1 equiv)	14

Reaction conditions: **1a** (0.1 mmol), **2d** (0.X mmol), Pd(OAc)₂ (10 mol %), Ligand (15 mol %), Oxidant (0.1 mmol), HFIP (1.0 mL), at 70 °C under air, 36 h. The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard.

Table 4.6: Palladium salt optimization

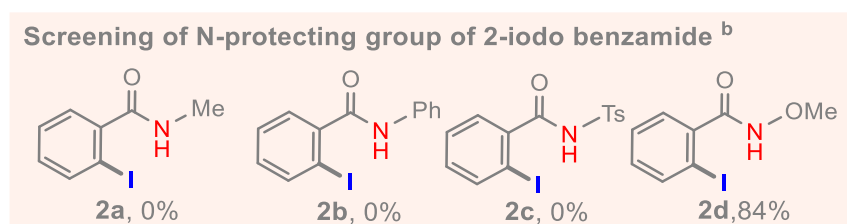


Entry	Palladium salt	Yield 33%
1	PdCl ₂	0

2	$\text{PdCl}_2(\text{CH}_3\text{CN})_2$	68
3	$\text{Pd}(\text{acac})_2$	73
4	$\text{PdCl}_2(o\text{-tolylphosphine})_2$	67
5	$\text{Pd}(\text{OAc})_2$	84
6	$\text{Pd}(\text{OTf})_2$	0
7	$\text{Pd}(\text{OH})_2$	0

Reaction conditions: **1a** (0.1 mmol), **2d** (0.15 mmol), Pd salt (10 mol %), Ligand (15 mol %), AgF (0.1 mmol), HFIP (1.0 mL) at 70 °C under air, 36 h. The yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard.

Figure 4.3: Screening of different 2-iodobenzoic acid^a



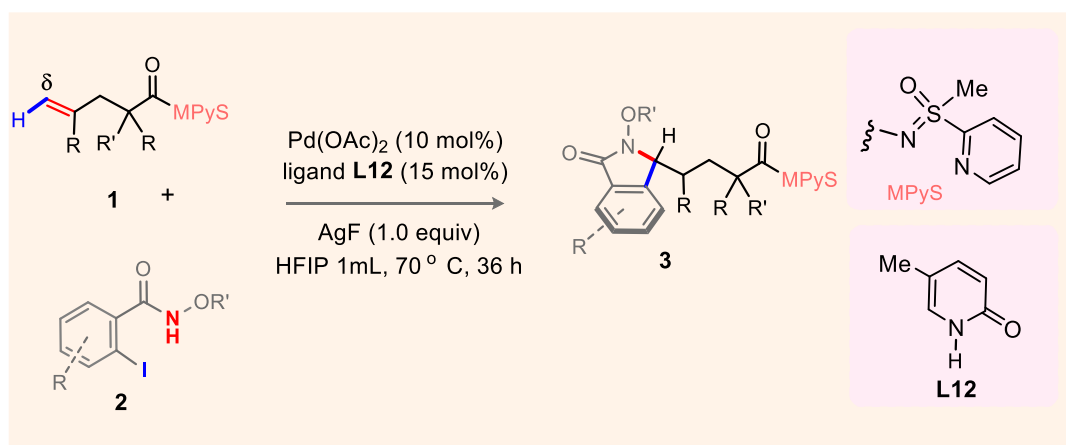
^a Reaction conditions: **1a** (0.1 mmol), **2d** (0.15 mmol), $\text{Pd}(\text{OAc})_2$ (10 mol %), Ligand **L12** (15 mol%), AgF (0.1 mmol), HFIP (1.0 mL) at 70 °C under air, 36 h. ^b The yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard. ^c Isolated yield.

4.3.3. Reaction Scope

With these optimized conditions in hand, we next explored the reaction scope of this δ -1,1-difunctionalization for the formation of C–C/C–N & C–C/C–O bonds. To begin with, we investigated the nature of the N-alkoxy-protecting group in 2-iodo-N-alkoxybenzamide. However, due to its redox-active nature, it could potentially limit the generality of this reaction. The coupling of **1b** with 2-iodo-N-methoxybenzamide **2d**, 2-iodo-N-benzyloxybenzamide **2e** delivered the corresponding products **3** and **4** in yields of 55%, and 78%, respectively. This observation indicated that the benzyloxy group could withstand oxidative conditions (Scheme 4.8–i). Based on this observation, we investigated the electronic behaviour of coupling partners **2f–2s** with **1b**. Intriguingly, 5-substituted electron donating groups like Me (**2f**) exhibited a descending

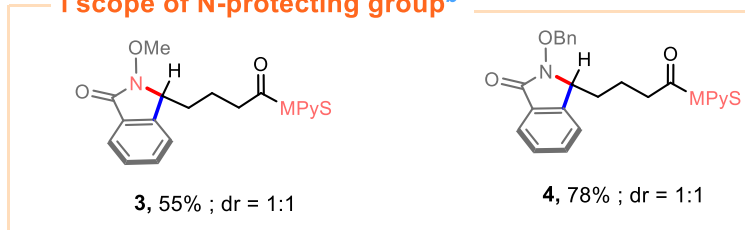
reactivity trend (**5**, 63%). In contrast, 5-substituted electron-withdrawing groups F (**2g**), Cl (**2h**), Br (**2i**), and CF₃ (**2j**) in 2-iodo-N-benzyloxybenzamide derivatives followed an ascending trend reaction outcome (**6**, 73%, **7**, 67%, **8**, 65%, **9**, 52%). This highlights that electron-withdrawing groups react more readily in oxidative addition. Conversely, 4-substituted electron-donating groups Me (**2k**), OMe (**2l**) in 2-iodo-N-benzyloxybenzamide derivatives displayed an ascending trend of reaction outcome (**10**, 77%, **11**, 85%). While electron-withdrawing groups F (**2m**), Cl (**2n**), Br (**2o**) in 2-iodo-N-benzyloxybenzamide derivatives showed a descending reaction outcome trend (**12**, 62%, **13**, 65%, **14**, 63%). It is indicated that electron-donating groups enhance the N-atom's nucleophilic character. In a similar trend, 6-substituted electron-withdrawing group F (**2p**) in 2-iodo-N-benzyloxybenzamide derivatives provided the desired isoindoline **15** in 52 % yield.

Scheme 4.8: Reaction scope of N-protecting group, bifunctional 2-iodo-N-benzyloxybenzamide, and branched aliphatic alkene. ^a

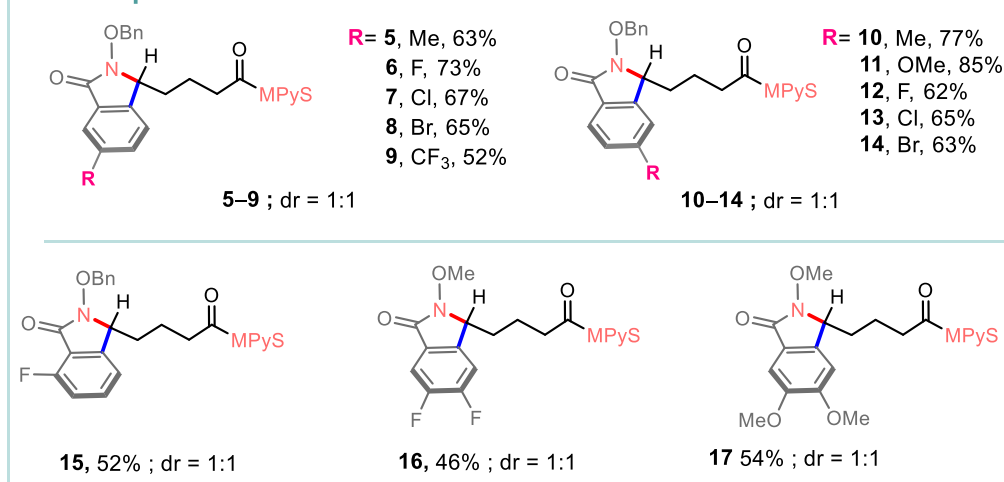


C–C / C–N bond

i scope of N-protecting group^b

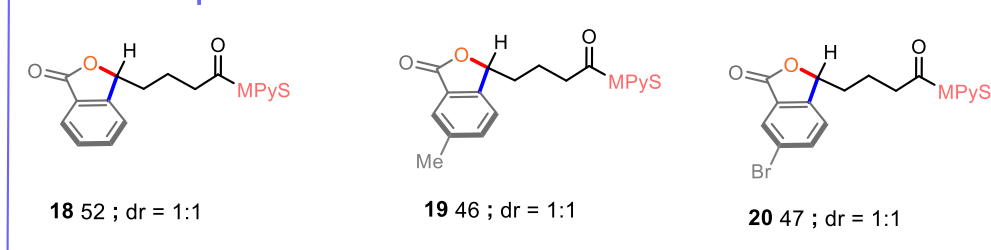


^a Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), Pd(OAc)₂ (10 mol %), Ligand **L12** (15 mol%), AgF (0.1 mmol), HFIP (1.0 mL) at 70 °C under air, 36 h. ^b The reactions were performed for 24 h.

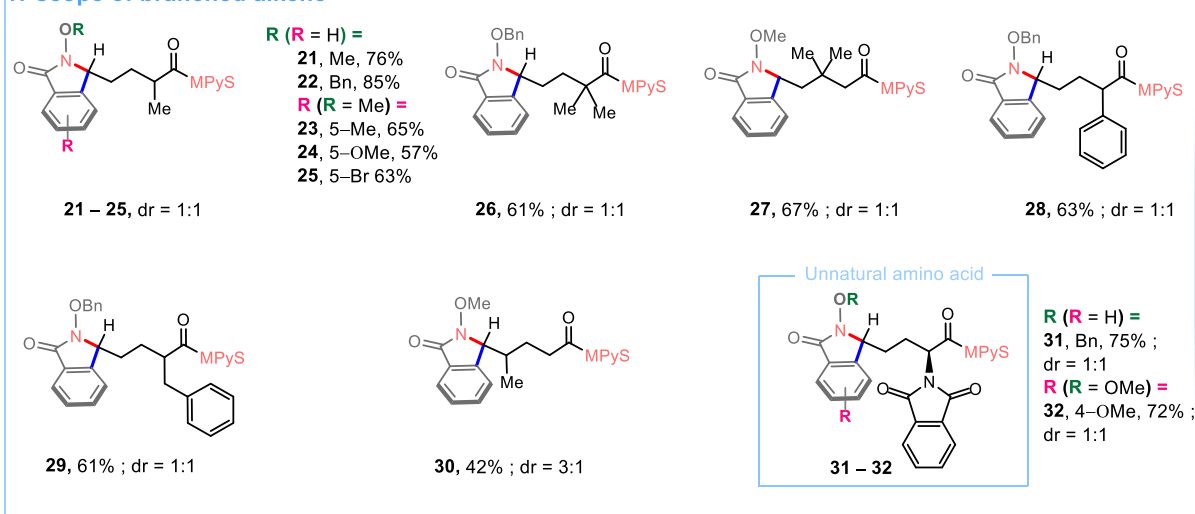
ii scope of 2-iodo benzamide derivatives^b

^a Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), Pd(OAc)₂ (10 mol %), Lignad **L12** (15 mol%), AgF (0.1 mmol), HFIP (1.0 mL) at 70 °C under air, 36 h. ^b The reactions were performed for 24 h.

C-C / C-O bond

iii scope of 2-iodobenzoic acid derivatives^b

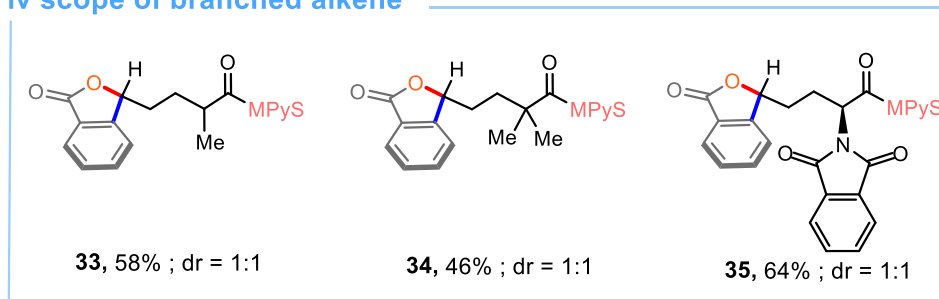
^a Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), Pd(OAc)₂ (10 mol %), Lignad **L12** (15 mol%), AgF (0.1 mmol), HFIP (1.0 mL) at 70 °C under air, 36 h. ^b The reactions were performed for 24 h.

iv scope of branched alkene^a

^a Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), Pd(OAc)₂ (10 mol %), Lignad **L12** (15 mol%), AgF (0.1 mmol), HFIP (1.0 mL) at 70 °C under air, 36 h.

C–C / C–O bond

iv scope of branched alkene^a



^a Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), Pd(OAc)₂ (10 mol %), Lignad **L12** (15 mol%), AgF (0.1 mmol), HFIP (1.0 mL) at 70 °C under air, 36 h.

However, 4,5-disubstituted electron-donating and withdrawing groups OMe (**2q**) and F (**2r**) in 2-iodo-N-benzyloxybenzamide derivatives provided the desired isoindoline **16** and **17** in moderate yields (Scheme 4.8–ii). On this front, reaction of various 2-iodo benzoic acid derivatives **2w–2y** delivered α -branched isobenzofuran-1(3H)-one **19–21** in moderate yield under similar catalytic conditions. This showcases the broad applicability of the optimized conditions (of note; compounds **3–20** were obtained in 1:1 diastereomeric ratio, Scheme 4.8–iii).

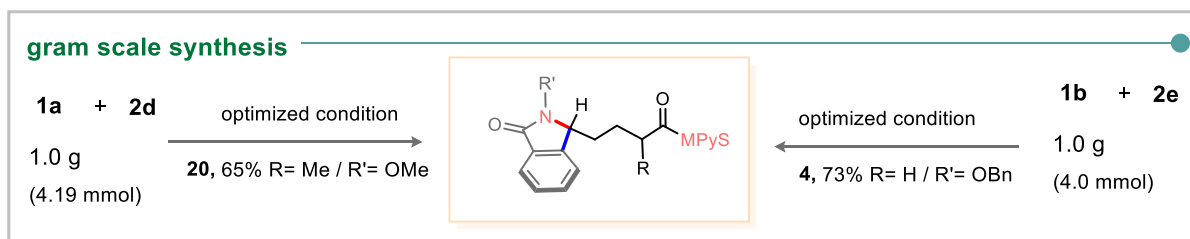
Next, we moved to the alkene scope, even in the presence of potential β -C(sp³)–H bond. The MPyS coupled a methyl substituted 4-pentenoic acids (**1a**) delivered the desired isoindolinone derivatives **22** in excellent yields with dr 1:1 ratio. Despite different electronic environment of 2-iodo-N-alkoxybenzamide derivatives (**2d**, **2e**, **2t**, **2u**, **2v**), the reaction with **1a** could provide the desired isoindolinones **22–26** in good to excellent yield with dr 1:1 ratio. In similar line, α,α' -di-methyl substituted 4-pentenoic acids (**1c**) reacted with **2e** and afforded isoindolinone derivative **26** in 61% yield, with dr = 1:1 ratio. Despite the presence of reactive C(arene)–H bonds, α/β -arylated MPyS-enabled 4-pentenoic acid derivative (**1i**, **1j**) participated well in the reaction, yielding desired isoindolinone products (**27**, **28**) in good yields. Interestingly, sterically congested alkene **1k** reacted with **2d**, and delivered isoindolinone in moderate yield with dr = 3:1 ratio. Next, MPyS coupled optically

pure L-allylglycine (**1l**), reacted smoothly with electron donating 2-iodo-N-benzyloxybenzamide (**2e**, **2t**), under the optimized conditions to build various unnatural amino acid derivatives (**30**, **31**) in dr = 1:1 ratio, which could be difficult to access with conventional methods. Moreover, MPyS-enabled internal alkenes **1e**, **1f**, **1g**, and conformationally restricted alkene **1h** remained unsuccessful under the developed condition. The current effort is directed to address the concerns of the substrates failed for this transformation (Scheme 4.8–iv).

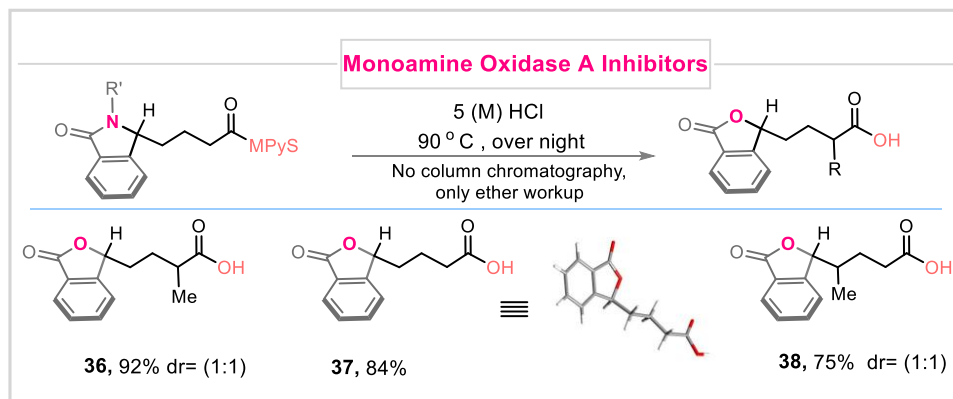
Next, we extended this condition to C–C/C–O bond formations with various branched alkenes. Thus, the reaction of MPyS coupled α -methyl, and $\alpha,\alpha'/\beta,\beta'$ -dimethyl substituted 4-pentenoic acids (**1a**, **1c**, **1d**) and MPyS coupled optically pure L-allylglycine (**1l**) with 2-iodobenzoic acid (**2w**) were independently performed under the optimized conditions to result in the formation of the respective isobenzofuran-1(3H)-one derivatives **32–35** in moderate to good yields. Besides, **1d** did not adversely affect the reaction outcome for formation of compound **34**, ruling out the possibility of π -allyl intermediate involvement (Scheme 4.8–v).

4.3.4. Application

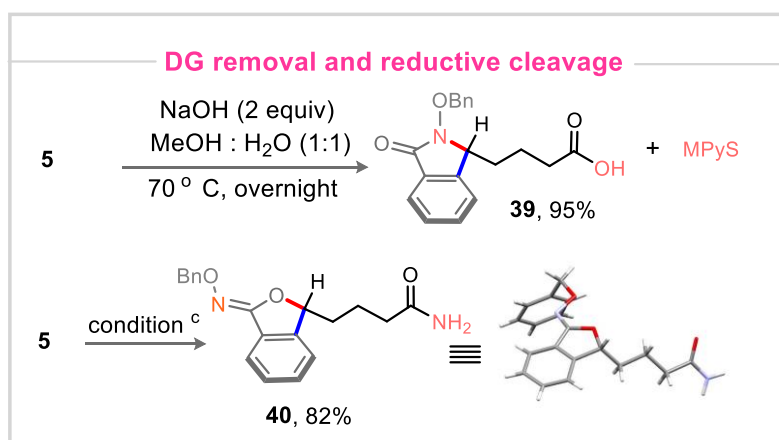
Scheme 4.9: Gram scale synthesis and post-modification study.



To evaluate the scalability of our established method, gram-scale reactions were performed. Starting with 1.0 g of **1a/1b** and **2d/2e** as coupling partners under the optimized conditions for 36 h, we obtained **20/4** in yields of 65% and 73%, respectively

Scheme 4.10: Derivatives of Monoamine Oxidase an Inhibitors.

Acid hydrolysis of the isoindolinone derivatives (**21**, **4**, **31**) yielded the hydrolyzed product along with the N-O atom swap products (**37**, **38**, **39**) in excellent yield. Notably, compound **38** exhibited activity against the monoamine oxidase A (MAO-A) isoform, with an inhibitory constant (K_i) < 0.001 $\mu\text{mol/L}$ (Scheme 4.10).⁶

Scheme 4.11: Directing group removal and reductive cleavage ^a

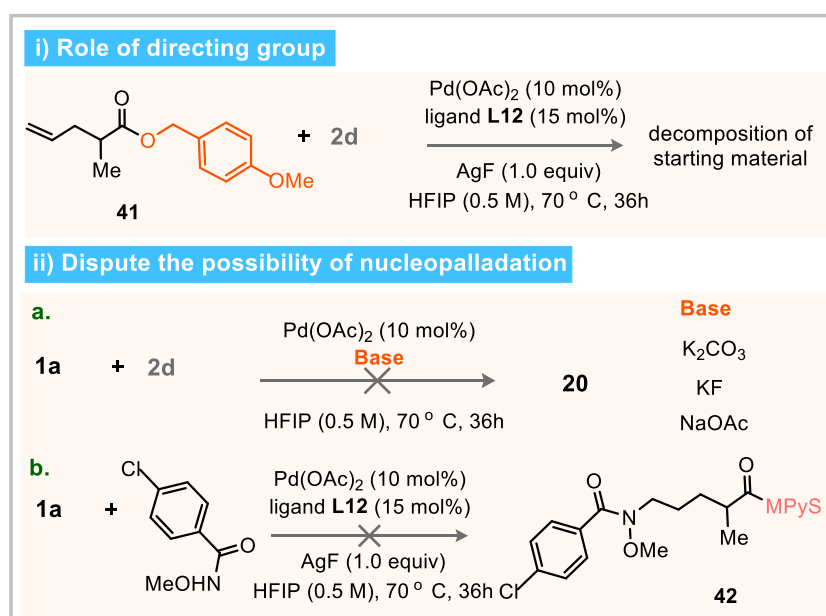
^a SmI₂ in 0.1M THF (4.0 equiv.), MeOH (35.0 equiv.), THF (2M), rt, 4 h

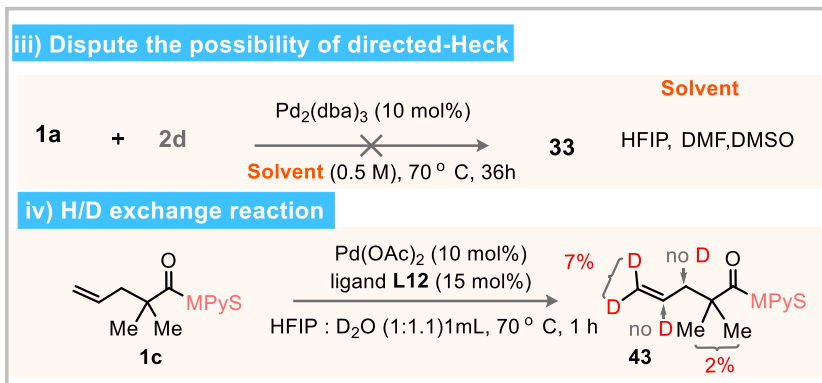
Furthermore, base hydrolysis selectively removed the MPyS moiety of **5** to make **39** in 95% isolated yield. While reductive cleavage in the presence of SmI₂ in 0.1M THF afforded amide derivative **40** in 82% yield. This process emphasizes the diverse role of MPyS in synthetic applications, where it serves as a masking reagent for acid substrate and a nitrogen transfer reagent.

4.4. Mechanistic study

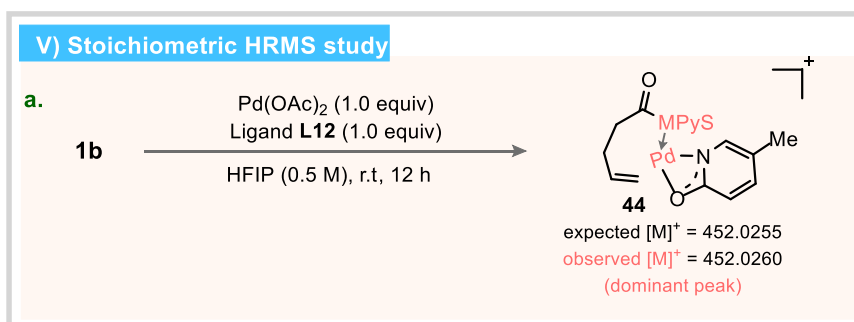
To unravel the catalytic cycle of the reaction, a series of mechanistic studies were conducted. Despite attempts to remove MPyS directing group, isoindolinone formation failed, and instead, we observed the decomposition of the starting material. This underscores the significant role of the directing group in catalysis (Scheme 4.12-i). In exploring the potential nucleometallation pathway as an initial step, the reaction with various bases surprisingly did not yield the desired product **20** (Scheme 4.12-ii-a). Additionally, when 4-chloro-N-methoxy benzamide was used as a nucleophile, **1a** could not deliver the δ -adduct product **42**; this challenges the possibility of catalytic nucleometallation (Scheme 4.12-ii-b). Moreover, transitioning from a polar protic to a polar aprotic solvent, the reaction of **1a** and **2d** with Pd₂(dba)₃ catalyst remained unresponsive, disputing the likelihood of directed Heck (Scheme 4.12-iii). Next, H/D exchange in HFIP : D₂O (1 : 1.1) revealed 7%-D incorporation at the δ -position, suggesting C–H activation over π -allylic activation (Scheme 4.12-iv).

Scheme 4.12: Mechanistic study.

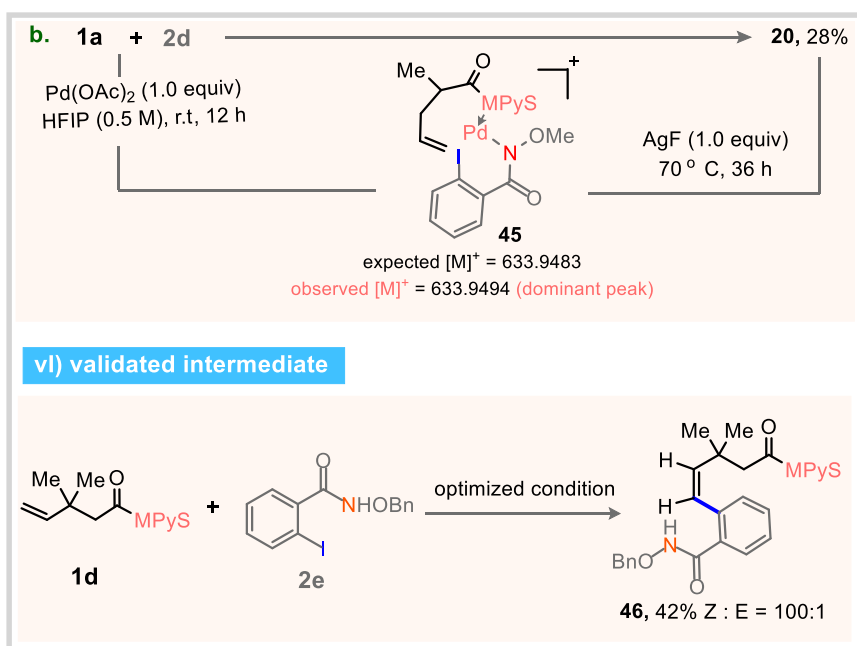




The stoichiometric reaction of **1b**, Pd(OAc)₂, and ligand **L12** in HFIP solvent at room temperature unveiled a dominant peak of the MPyS-directed, ligand-coordinated cationic palladium complex (**44**) [m/z [M]⁺calcd for C₁₇H₂₀N₃O₃PdS⁺ 452.0255; found 452.0260] in HRMS; ESI positive mode (Scheme 4.12-V-a).²⁸ It is indicated that the ligand did not outcompete the substrate; therefore, a substrate ligand assembly promotes C–H activation.



Similarly, **1a** and Pd(OAc)₂ in HFIP solvent exhibited a dominant peak of palladium complex **45** [m/z [M]⁺calcd for C₂₀H₂₃IN₃O₄PdS⁺ 633.9483; found 633.9494] in HRMS; ESI positive mode, which upon treatment with AgF, yielded isoindolinone compound **20** in 28% yield (Scheme 4.12-V-b), affirming a δ -C(alkenyl)–H activation pathway. Finally, steric hindrance from the N-benzyloxy protecting group of **2e** and the β / β' -dimethyl group of **1d** resulted in a 100% Z-selective δ -arylated product **46**. This observation emphasizes that the catalytic cycle probably begins with C–C bond formation (Scheme 4.12-VI).



4.5. Conclusion

In summary, we have developed an efficient method for transferring C–C/C–N and C–C/C–O bonds to the remote positions of unactivated alkenes. Essentially, this process enables the one-step synthesis of α -branched isoindolinones and α -branched isobenzofuran-1(3H)-ones. This synthetic method involves the use of a Pd(II)-catalyst, a bidentate MPyS directing group, and a specific ligand (5-methylpyridin-2-ol), in conjunction with an AgF oxidant. The transformation tolerates common functional groups providing access to a diverse range of modular α -branched isoindolinones and α -branched isobenzofuran-1(3H)-one derivative. An interesting observation includes an unusual 'N' to 'O' atom swap for α -branched isoindolinones derivatives and the versatile role of MPyS in masking acid derivatives, as well as transferring N-atom via reductive cleavage. Furthermore, mechanistic studies revealed the occurrence of δ -C(alkenyl)–H activation, highlighting the sequence of C–C bond formation preceding C–heteroatom bond formation.

4.6. Experimental

4.6.1. General Experimental Information

All the reactions were performed in an oven-dried 5 mL screw capped pressure tube. The commercial grade solvents were distilled prior to use. Column chromatography was performed using either 100–200 Mesh or 230–400 Mesh silica gel. Thin layer chromatography (TLC) was performed on silica gel GF254 plates. The spots on TLC plates were detected with UV light (254 nm) and staining over molecular iodine. Proton and carbon nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded based on the resonating frequencies as follows: (^1H NMR, 400 MHz; ^{13}C NMR, 101 MHz) and (^1H NMR, 500 MHz; ^{13}C NMR, 126 MHz) having the solvent resonance as internal standard (^1H NMR, CHCl_3 at 7.26 ppm; ^{13}C NMR, CDCl_3 at 77.0 ppm). In few cases, tetramethylsilane (TMS) was used as reference standard at 0.00 ppm. Data for ^1H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet; bs = broad singlet; d = doublet; bd = broad doublet, t = triplet; bt = broad triplet; q = quartet; dd = doublet of doublet; td = triplet of doublet, dt = doublet of triplet, ddd; doublet of doublet of doublet; m = multiplet), coupling constants, J , in Hz, and integration. Data for ^{13}C NMR are reported as chemical shifts (ppm). IR spectra were reported in cm^{-1} . High resolution mass spectra were obtained in ESI mode in the Maxis-TOF analyzer. X-ray data was collected at 298 K using graphite monochromated Mo- $\text{K}\alpha$ radiation (0.71073 Å). Melting points were determined by electro-thermal heating and are uncorrected.

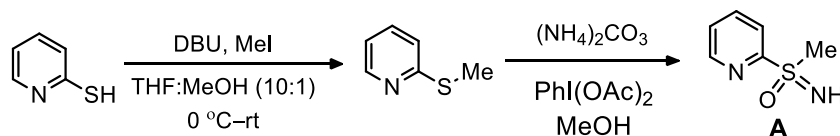
4.6.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Dichloromethane (DCM) and chloroform were distilled over CaH_2 . Acetic acid was distilled over KMnO_4 . Tetrahydrofuran (THF) was freshly distilled over sodium/benzophenone ketyl under nitrogen. $\text{Pd}(\text{OAc})_2$, PdCl_2 , $\text{Pd}(\text{OTFA})_2$, $\text{Pd}(\text{acac})_2$, $\text{Pd}(\text{CH}_3\text{CN})_2(\text{Cl})_2$, NaBrO_3 were purchased from commercially available sources, and used as received. All pyridine ligands were purchased from commercially available sources. All sodium and potassium salts were purchased from commercially available sources and used as received. Oxidants such as $\text{Na}_2\text{S}_2\text{O}_8$, $\text{PhI}(\text{OAc})_2$, BQ, TBHP, oxone, $\text{K}_2\text{S}_2\text{O}_8$, and various silver salts were purchased from commercially available sources. Analytical and spectral data of all those known compounds are exactly matching with the reported values.

4.6.3. Experimental Procedures and Analytical Data

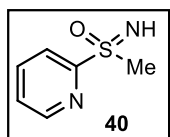
4.6.3.1. Preparation of *S*-methyl-*S*-2-pyridylsulfoximine (MPyS) (40):²⁹

Scheme 4.13. Preparation of MPyS.



Following the known procedure,^{29 a, b} sulfoximine (**A**) was prepared from commercially available reagents in excellent yield over two steps.

S-Methyl-*S*-2-pyridylsulfoximine (MPyS) (40):

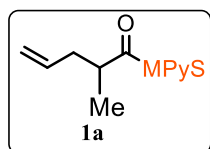


¹H NMR (400 MHz, CDCl₃) δ 8.73 (bd, J = 4.0 Hz, 1H), 8.13 (bd, J = 7.6 Hz, 1H), 7.95 (td, J = 7.7, 1.3 Hz, 1H), 7.51 (dd, J = 6.8, 4.8 Hz, 1H), 3.26 (s, 3H), 2.89 (bs, 1H, NH). ¹³C NMR (101 MHz, CDCl₃) δ 160.4, 150.0, 138.2, 126.7, 121.1, 42.3.

4.6.3.2. Preparation of ligands:

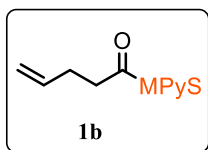
All ligands (see Table 4.3) were obtained from commercial sources.

2-Methyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)pent-4-enamide (**1a**):

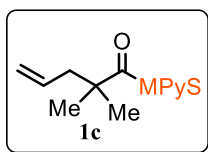


compound **1a** (1.25 g, 78%) was prepared following the general procedure GP-1; colorless liquid. R_f = 0.30 (1:1 hexane/EtOAc); [Silica, UV and I₂]. ¹H NMR (500 MHz, CDCl₃) δ 8.68 (ddd, J = 4.5, 2.1, 0.9

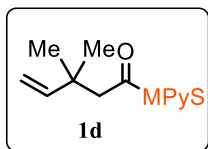
Hz, 1H), 8.26 (dt, J = 8.0, 0.9 Hz, 1H), 7.98 (td, J = 7.8, 1.7 Hz, 1H), 7.56 – 7.49 (m, 1H), 5.82–5.65 (m, 1H), 5.06–4.89 (m, 2H), 3.42 & 3.41 (two s, 3H), 2.52 (dtd, J = 13.9, 7.0, 1.1 Hz, 1H), 2.47–2.37 (m, 1H), 2.18–2.06 (m, 1H), 1.11 & 1.08 (two d, J = 10.0 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 185.4, 157.0, 149.85 & 149.82 (1C), 138.18 & 138.16 (1C), 136.39 & 136.32 (1C), 127.3, 123.37 & 123.32 (1C), 116.19 & 116.13 (1C), 42.97 & 42.90 (1C), 39.6, 38.31 & 38.24 (1C), 16.8. IR (KBr) $\nu_{\max}$ 2969, 1629, 1738, 1371, 1214, 907, 838, 768 cm⁻¹. HRMS (ESI-TOF) m/z : calcd. for C₁₂H₁₇N₂O₂S⁺ [M+H], 253.1005; found 253.1004.

N-(Methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)pent-4-enamide (1b):

compound **1b** (1.14 g, 75%) was prepared following the general procedure GP-1; colorless liquid. R_f = 0.27 (1:1 hexane/EtOAc); [Silica, UV and I₂]. ^1H NMR (500 MHz, CDCl₃) δ 8.69 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.26 (dt, J = 7.9, 1.0 Hz, 1H), 7.98 (td, J = 7.8, 1.8 Hz, 1H), 7.54 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 5.80 (ddt, J = 16.7, 10.2, 6.4 Hz, 1H), 5.00 (dq, J = 17.2, 1.7 Hz, 1H), 4.92 (dq, J = 10.2, 1.4 Hz, 1H), 3.41 (s, 3H), 2.49–2.39 (m, 2H), 2.43–2.26 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl₃) δ 182.0, 157.0, 149.9, 138.2, 137.4, 127.3, 123.3, 114.8, 39.6, 38.3, 29.4. IR (KBr) ν_{max} 2969, 1738, 1630, 1368, 1213, 978, 908, 843, 765 cm⁻¹. HRMS (ESI-TOF) m/z : calcd. for C₁₁H₁₅N₂O₂S⁺ [M+H], 239.0849; found 239.0853.

3,3-Dimethyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)pent-4-enamide (1c):

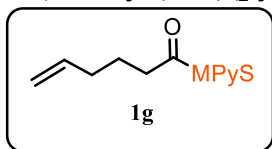
compound **1c** (1.40 g, 82%) was prepared following the general procedure GP-1; colorless liquid. R_f = 0.34 (1:1 hexane/EtOAc); [Silica, UV and I₂]. ^1H NMR (500 MHz, CDCl₃) δ 8.70–8.64 (m, 1H), 8.24 (dt, J = 8.0, 1.0 Hz, 1H), 7.96 (tt, J = 6.9, 1.9 Hz, 1H), 7.52 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 5.79–5.64 (m, 1H), 5.02–4.95 (m, 1H), 4.98–4.92 (m, 1H), 3.39 (s, 3H), 2.34–2.22 (m, 2H), 1.13 (s, 3H), 1.11 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl₃) δ 187.3, 157.3, 149.7, 138.1, 135.2, 127.1, 123.2, 117.1, 45.2, 44.4, 39.5, 25.2, 25.0. IR (KBr) ν_{max} 2968, 1738, 1618, 1375, 1212, 1170, 978, 961, 851, 753 cm⁻¹. HRMS (ESI-TOF) m/z : calcd. for C₁₃H₁₉N₂O₂S⁺ [M+H], 267.1162; found 267.1162.

3,3-Dimethyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)pent-4-enamide (1d):

compound **1d** (1.1 g, 65%) was prepared following the general procedure GP-1; colorless liquid. R_f = 0.32 (1:1 hexane/EtOAc); [Silica, UV and I₂]. ^1H NMR (500 MHz, CDCl₃) δ 8.67 (ddd, J = 4.7, 1.7, 0.8 Hz, 1H), 8.24 (dt, J = 7.9, 0.9 Hz, 1H), 7.96 (td, J = 7.8, 1.7 Hz, 1H), 7.53 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 5.90 (dd, J = 17.4, 10.7 Hz, 1H), 4.94–4.79 (m, 2H), 3.38 (s, 3H), 2.39–2.25 (m, 2H), 1.09 (s, 3H), 1.08 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl₃) δ 180.9, 156.9, 149.7, 147.7, 138.1, 127.1, 123.3, 110.0, 51.1, 39.5, 36.5, 26.9, 26.8. IR (KBr) ν_{max} 2968, 1738, 1628,

1372, 1213, 1124, 1017, 976, 908, 844, 766 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_2\text{S}^+$ [M+H], 267.1162; found 267.1166.

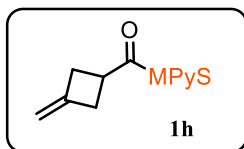
N-(Methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)hex-5-enamide (1g):



compound **1g** (1.2 g, 76%) was prepared following the general procedure GP-1; colorless liquid. R_f = 0.30 (1:1 hexane/EtOAc); [Silica, UV and I_2].

^1H NMR (500 MHz, CDCl_3) δ 8.68 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.25 (dt, J = 7.9, 1.0 Hz, 1H), 7.98 (td, J = 7.8, 1.7 Hz, 1H), 7.53 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 5.74 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 4.96 (dq, J = 17.2, 1.7 Hz, 1H), 4.91 (ddt, J = 10.2, 2.2, 1.2 Hz, 1H), 3.39 (s, 3H), 2.39–2.28 (m, 2H), 2.02 (qt, J = 6.8, 1.3 Hz, 2H), 1.73–1.58 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.6, 157.0, 149.9, 138.3, 138.2, 127.3, 123.4, 114.9, 39.6, 38.4, 33.1, 24.6. IR (KBr) ν_{max} 2969, 1738, 1630, 1369, 1214, 977, 908, 846, 767 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_2\text{S}^+$ [M+H], 253.1005; found 253.1007.

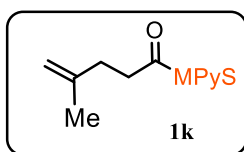
N-(Methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)-3-methylenecyclobutane-1-carboxamide (1h):



compound **1h** (993 mg, 62%) was prepared following the general procedure GP-1; colorless liquid. R_f = 0.25 (1:1 hexane/EtOAc); [Silica, UV and I_2].

^1H NMR (500 MHz, CDCl_3) δ 8.63 (dd, J = 4.4, 1.9 Hz, 1H), 8.20 (dt, J = 7.9, 1.2 Hz, 1H), 7.94 (tt, J = 7.9, 1.9 Hz, 1H), 7.50 (ddt, J = 7.5, 4.7, 1.3 Hz, 1H), 4.69–4.65 (m, J = 2.4 Hz, 2H), 3.36 (s, 3H), 3.09 (ttt, J = 9.3, 7.3, 1.9 Hz, 1H), 2.96–2.69 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 183.5, 156.7, 149.7, 144.9, 138.1, 127.2, 123.1, 105.9, 39.5, 37.0, 35.5, 35.3. IR (KBr) ν_{max} 3018, 2969, 1737, 1633, 1371, 1215, 1160, 977, 843, 819, 766 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_2\text{S}^+$ [M+H], 251.0849; found 251.0853.

4-Methyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)pent-4-enamide (1k):



compound **1k** (1.2 mg, 73%) was prepared following the general procedure GP-1; colorless liquid. R_f = 0.30 (1:1 hexane/EtOAc); [Silica, UV and I_2].

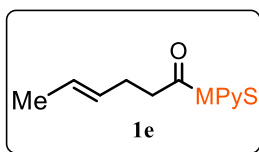
^1H NMR (500 MHz, CDCl_3) δ 8.67 (ddd, J = 4.7,

1.7, 0.9 Hz, 1H), 8.23 (dt, $J = 7.9, 1.0$ Hz, 1H), 7.97 (td, $J = 7.8, 1.7$ Hz, 1H), 7.53 (ddd, $J = 7.6, 4.7, 1.1$ Hz, 1H), 4.67–4.59 (m, 2H), 3.39 (s, 3H), 2.47 (td, $J = 7.5, 3.1$ Hz, 2H), 2.72–2.21 (m, 2H), 1.67 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.1, 156.8, 149.8, 144.7, 138.1, 127.2, 123.2, 109.8, 39.5, 37.3, 32.9, 22.5. IR (KBr) ν_{max} 3018, 2969, 1738, 1628, 1351, 1200, 1057, 976, 866, 745 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_2\text{S}^+ [\text{M}+\text{H}]$, 253.1005; found 253.1008.

4.6.3.3 Procedure for the synthesis (*E*)-*N*-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) hex-4-enamide (**1e**):²²

Following the literature procedure, ‘Jones oxidation’ has been used for the preparation of (*E*)-hex-4-enoic acid from (*E*)-hex-en-1-ol. Jones reagent was prepared by dissolving chromium(VI) oxide (2.73 g, 27 mmol) in distilled water (4 mL). It was cooled to 0 °C, and concentrated sulfuric acid (2.3 mL) was added dropwise. The solution of the Jones reagent was then diluted to a total volume of 10 mL with distilled water. (*E*)-4-Hexen-1-ol (1.35 g, 13.5 mmol) was dissolved in acetone (30 mL) and cooled to 0 °C. Jones reagent was added slowly into the reaction mixture over a 30-min period. The reaction was maintained at 0 °C for an additional 2 h. After this time, the reaction mixture was quenched with EtOH (20 mL) while cooling. The reaction mixture was poured carefully into a separatory funnel containing water (30 mL) and extracted with CH_2Cl_2 (2 $\times$ 30 mL). The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude carboxylic acid product was subsequently used for the next step without further purification. The title compound was prepared from (*E*)-hex4-enoic acid (1.0 g) following the general procedure GP-1 and compound **1e** was isolated as thick liquid.

(*E*)-*N*-(Methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)hex-4-enamide (**1e**):



compound **1e** (872 mg, 54%) was prepared following the general procedure GP-1; colorless liquid. R_f = 0.25 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.69 (ddd, $J = 4.7,$

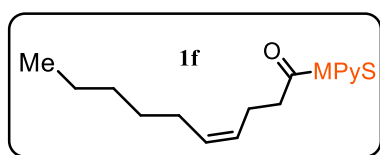
1.7, 0.9 Hz, 1H), 8.29–8.23 (m, 1H), 7.98 (td, $J = 7.8, 1.7$ Hz, 1H), 7.54 (ddd, $J = 7.6, 4.7,$

1.1 Hz, 1H), 5.47–5.35 (m, 2H), 3.40 (s, 3H), 2.44–2.36 (m, 2H), 2.28–2.21 (m, 2H), 1.63–1.57 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.3, 157.1, 149.9, 138.2, 129.9, 127.3, 125.4, 123.4, 39.6, 39.0, 28.4, 17.9. IR (KBr) ν_{max} 1767, 1715, 1628, 1266, 1211, 1166, 1012, 960, 848, 759 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]$, 253.1005; found 253.0999.

4.6.3.4 Procedure for the synthesis of (Z)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) dec-4-enamide (1f): ²²

Following the known procedure, Jones oxidation has been used for the preparation of (Z)-dec-4-enoic acid from (Z)-dec-en-1-ol. Jones reagent was prepared by dissolving chromium(VI) oxide (2.73 g, 27 mmol) in distilled water (4.0 mL). Then it was cooled to 0 °C, and concentrated sulfuric acid (2.3 mL) was added dropwise. The solution of the Jones reagent was then diluted to a total volume of 10 mL with distilled water. (Z)-Dec-en-1-ol (1.35 g, 13.5 mmol) was dissolved in acetone (30 mL) and cooled to 0 °C. Jones reagent was added slowly into the reaction mixture over a 30-min period. The reaction was maintained at 0 °C for an additional 2 h. After this time, the reaction mixture was quenched with EtOH (20 mL) while cooling. The reaction mixture was poured carefully into a separatory funnel containing water (30 mL) and extracted with CH_2Cl_2 (2 $\times$ 30 mL). The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude carboxylic acid product was then carried on to the next step without further purification. The title compound was prepared from (Z)-dec-4-enoic acid (1.0 g) following the general procedure GP-1; compound 1f was isolated as thick liquid.

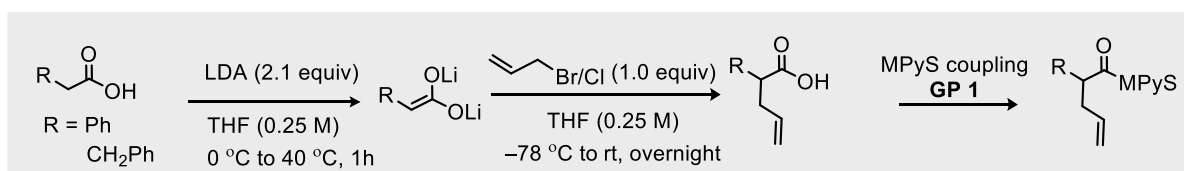
(Z)-N-(Methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) dec-4-enamide (1f):



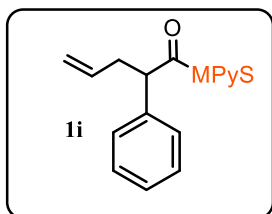
compound 1f (1.14 g, 58%) was prepared following the general procedure GP-1; colorless liquid. R_f = 0.25 (7:3 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.70 (dt, J = 4.8, 2.3 Hz, 1H), 8.30–8.24 (m, 1H), 7.99 (tq, J = 6.6, 2.0 Hz, 1H), 7.55 (qd, J = 4.4, 2.2 Hz, 1H), 5.41–5.27 (m, 2H), 3.42 (dd, J = 3.3, 1.7 Hz, 3H), 2.44–2.37

(m, 2H), 2.37–2.27 (m, 2H) 2.06–1.95 (m, 2H), 1.36–1.22 (m, 6H), 0.93–0.83 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.2, 157.0, 149.9, 138.2, 130.9, 128.1, 127.3, 123.3, 39.6, 39.2, 31.5, 29.3, 27.2, 23.3, 22.6, 14.1. IR (KBr) ν_{max} 2932, 1737, 1371, 1214, 1013, 957, 846, 733 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]$, 309.1631; found 309.1634.

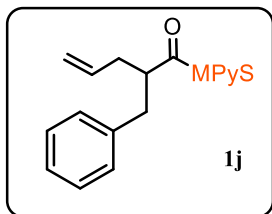
4.6.3.5 Procedure for the synthesis of N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)-2-phenylpent-4-enamide (**1i**) and 2-benzyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) pent-4-enamide (**1j**)



To a stirred solution of diisopropylamine (3.0 mL, 21 mmol) in THF (40 mL) was added *n*-BuLi solution (8.4 mL, 21 mmol, 2.5 M in hexane) dropwise at 0 °C. The resulting solution was stirred at 0 °C for 30 min. Phenylacetic acid / hydrocinamic acid (10 mmol) was added dropwise independently at the same temperature and the reaction mixture was heated to 40 °C and stirred for 1 h. The resulting mixture was then cooled to -78 °C; next, the respective allyl bromide/chloride (10 mmol) was added dropwise. The reaction mixture was slowly warmed to room temperature (rt) overnight. The reaction mixture was quenched with water and diluted with EtOAc (30 mL). The organic layer was separated and then washed with water. The aqueous layers were combined and acidified to pH < 4 with aqueous 3M HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo.²³ The crude carboxylic acid was subsequently used without further purification. The title compound was prepared from 2-phenylpent-4-enoic acid / 2-benzylpent-4-enoic acid (1.0 g) following the general procedure **GP-1**; the respective products **1i** and **1j** are obtained as thick liquid.

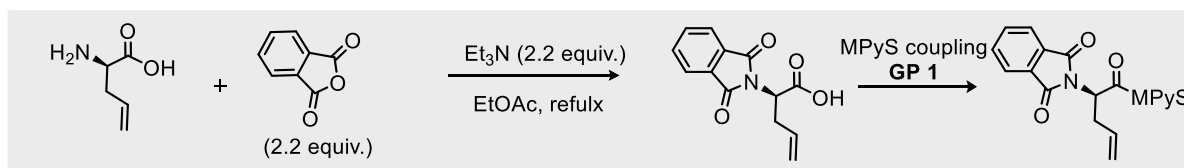
N-(Methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)-2-phenylpent-4-enamide (1i):

compound **1i** (1.35 g, 67% and **d.r** 1:1) was prepared following the general procedure GP-1; colorless liquid. R_f = 0.40 (1:1 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.69–8.58 (m, 1H), 8.07–8.00 (m, 1H), 7.88–7.83 (m, 1H), 7.55–7.47 (m, 1H), 7.36–7.17 (m, 5H), 5.78–5.63 (m, 1H), 5.07–4.86 (m, 2H), 3.74–3.64 (m, 1H), 3.39 & 3.38 (two s, 3H), 2.86–2.75 (m, 1H), 2.50–2.42 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 182.1, 156.7, 149.77 & 149.68 (1C), 139.8, 138.12 & 138.04 (1C), 136.13 & 136.07 (1C), 128.35 & 128.23 (1C), 128.19 & 128.17 (1C), 127.24 & 127.19 (1C), 126.77 & 126.69 (1C), 123.0, 116.27 & 116.13 (1C), 55.28 & 55.04 (1C), 39.36 & 39.31 (1C), 37.79 & 37.70 (1C). IR (KBr) ν_{max} 2931, 2857, 1737, 1628, 1372, 1214, 1165, 1012, 957, 846, 768 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_2\text{S}^+$ [M+H], 315.1162; found 315.1166.

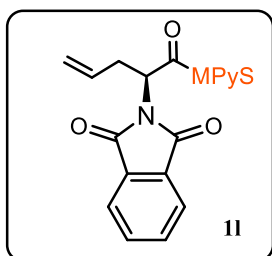
2-Benzyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)pent-4-enamide (1j):

compound **1j** (1.32 g, 63% and **d.r** 1:1) was prepared following the general procedure GP-1; colorless liquid. R_f = 0.47 (1:1 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.69–8.60 (m, 1H), 8.12–7.87 (m, 2H), 7.56–7.46 (m, 1H), 7.25–7.10 (m, 5H), 5.92–5.62 (m, 1H), 5.08–4.92 (m, 2H), 3.38 & 3.37 (two s, 3H), 3.00–2.91 (m, 1H), 2.86–2.65 (m, 2H), 2.44–2.31 (m, 1H), 2.29–2.17 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 183.91 & 183.89 (1C), 156.86 & 156.77 (1C), 149.7, 140.00 & 139.91 (1C), 138.04 & 138.02 (1C), 135.96 & 135.87 (1C), 129.12 & 129.08 (1C), 128.13 & 128.09 (1C), 127.17 & 127.15 (1C), 125.89 & 125.85 (1C), 122.99 & 122.96 (1C), 116.42 & 116.38 (1C), 50.43 & 50.31 (1C), 39.2, 37.87 & 37.74 (1C), 36.40 & 36.28 (1C). IR (KBr) ν_{max} 3024, 2969, 1738, 1630, 1369, 1214, 1167, 957, 907, 840, 742, 699 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_2\text{S}^+$ [M+H], 329.1318; found 329.1318.

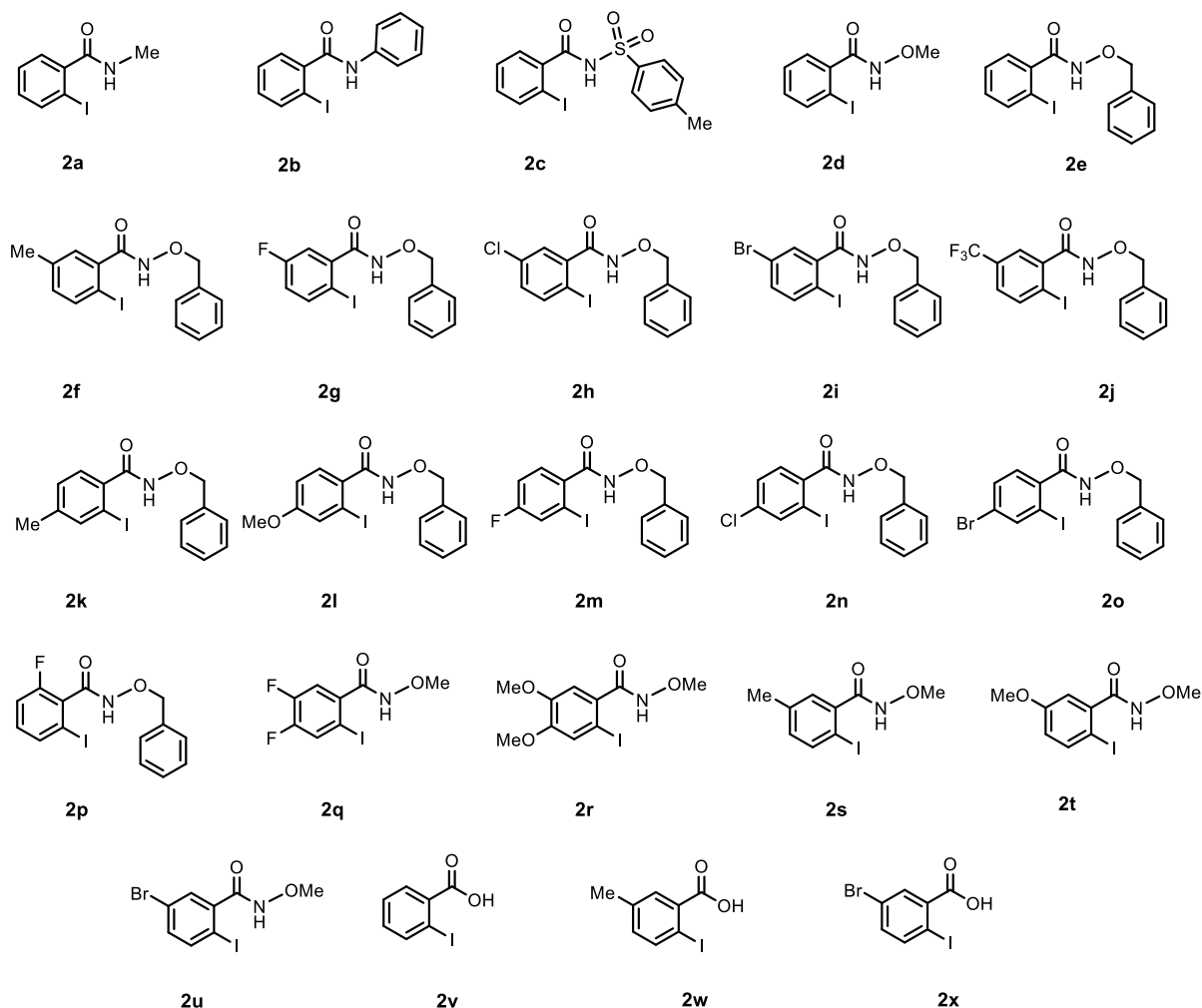
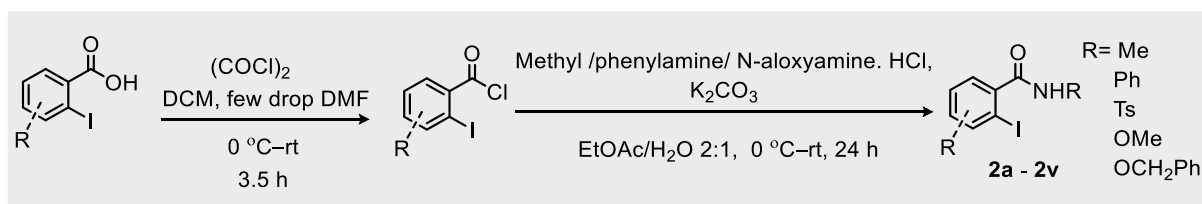
4.6.3.6 Procedure for the synthesis of (2S)-2-(1,3-dioxoisindolin-2-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) pent-4-enamide (**11**):



Compound L-allylglycine was refluxed with 2.2 equivalents of phthalic anhydride in the presence of 2.2 equivalents triethylamine in ethyl acetate until the reaction was complete. The solvent was removed under pressure. The residual was dissolved in water and the pH was maintained to 4. The resulting reaction mass was then extracted with ethyl acetate. The combined organic layers were washed twice with water maintaining pH of the medium 4. The organic phase was dried over sodium sulphate. The solvent was removed, providing (R)-2-(1,3-dioxoisindolin-2-yl) pent-4-enoic acid as colorless solid.²⁴ The title compound **11** was prepared from 2-(1,3-dioxoisindolin-2-yl) pent-4-enoic acid (1.0 g) following the general procedure GP-1. The product was obtained as a thick liquid.



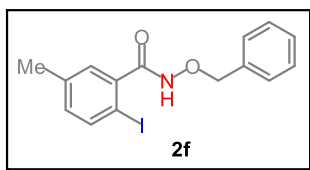
compound **11** (1.96 g, 80% and **d.r** 4.3:1) was prepared following the general procedure GP-1; colorless thick liquid. R_f = 0.2 (1:1 hexane/EtOAc); [Silica, UV and I_2]. ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.65 (m, 1H), 8.22–8.14 (m, 1H), 7.98–7.93 (m, 1H), 7.84–7.75 (m, 2H), 7.73–7.63 (m, 2H), 7.57–7.48 (m, 1H), 5.78–5.66 (m, 1H), 5.03 (dq, J = 17.0, 1.5 Hz, 1H), 4.97–4.84 (m, 2H), 3.45 & 3.43 (two s, 3H, major and minor), 3.13–2.96 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 176.82 & 176.55 (major and minor 1C), 167.88 & 167.86 (major and minor 1C), 156.2, 149.92 & 149.88 (major and minor 1C), 138.26 & 138.24 (major and minor 1C), 134.3, 133.79 & 133.77 (major and minor 1C), 131.9, 127.52 & 127.49 (major and minor 1C), 123.23 & 123.21 (major and minor 1C), 122.86 & 122.62 (major and minor 1C), 117.8, 55.25 & 55.17 (major and minor 1C), 39.26 & 38.91 (major and minor 1C), 33.47 & 33.26 (major and minor 1C). IR (KBr) ν_{max} 3022, 2969, 1738, 1707, 1637, 1384, 1264, 1214, 887, 720 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_3\text{O}_4\text{S}^+$ $[M+H]$, 384.1011; found 384.1013.

4.6.3.7. List of 2-iodobenzamide / 2-iodobenzoic acid derivatives:**4.6.3.8. Preparation of N-protected 2-iodobenzamide: General Procedure (GP-2):**²⁵

A dried two-necked round-bottom flask was charged with 2-iodobenzoic acid derivatives (1.0 g), CH₂Cl₂ (20 mL), and 6-7 drops of DMF. Then, oxalyl chloride (2 equiv.) was added dropwise in an argon atmosphere within 5 min at 0 °C. The resulting mixture was stirred at rt for 3.5 h and concentrated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and K₂CO₃ (2 equiv.), MeNH₂ / PhNH₂ / MeONH₂. HCl / BnONH₂. HCl (1.2 equiv.) and water (10 mL) was added sequentially. The

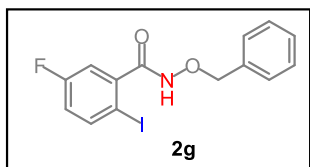
resulting mixture was stirred for 24 h at rt and extracted with EtOAc (50 mL × 2). The organic layer was washed with saturated brine (15 mL × 2), and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude products **2a**, **2b**, **2c**, **2d**, **2q**, **2r**, **2s**, **2t**, **2u**, and **2v** was purified by silica gel column chromatography, using EtOAc/hexane eluent. The compounds **2e**-to-**2p** were recrystallized in ethyl acetate to afford the pure product. The data of unknown compounds are depicted below.

N-(Benzyloxy)-2-iodo-5-methylbenzamide (2f):



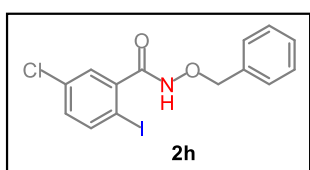
Following the general procedure GP-2, the compound **2f** (1.21 g, 87%, colorless solid) ¹H NMR (500 MHz, CDCl₃) δ 8.67 (s, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 7.1 Hz, 2H), 7.35 (q, *J* = 6.7 Hz, 3H), 7.05 (s, 1H), 6.91–6.85 (m, 1H), 5.05 (s, 2H), 2.24 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 166.9, 139.5, 138.4, 138.2, 135.1, 132.6, 129.5, 129.3, 128.7, 128.5, 88.8, 78.2, 20.7. HRMS (ESI-TOF) *m/z*: calcd. for C₁₅H₁₅INO₂⁺ [M+H], 368.0147; found 368.0147.

N-(Benzyloxy)-5-fluoro-2-iodobenzamide (2g):



Following the general procedure GP-2, the compound **2g** (1.04 g, 75%, colorless solid). ¹H NMR (500 MHz, DMSO) δ 11.71 (s, 1H), 7.91 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 2H), 7.45–7.35 (m, 3H), 7.27 (dd, *J* = 8.8, 3.1 Hz, 1H), 7.13 (td, *J* = 8.7, 3.1 Hz, 1H), 4.99 (s, 2H). ¹³C{¹H} NMR (126 MHz, DMSO) δ 165.0, 162.19 (d, *J* = 246.9 Hz), 142.05 (d, *J* = 6.5 Hz), 141.52 (d, *J* = 7.7 Hz), 136.2, 129.5, 128.90, 128.84, 119.15 (d, *J* = 21.6 Hz), 116.58 (d, *J* = 23.5 Hz), 88.7, 77.6. ¹⁹F NMR (471 MHz, DMSO) δ -112.34. HRMS (ESI-TOF) *m/z*: calcd. for C₁₄H₁₂FINO₂⁺ [M+H], 371.9891; found 371.9895.

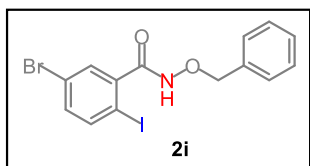
N-(Benzyloxy)-5-chloro-2-iodobenzamide (2h):



Following the general procedure GP-2, the compound **2h** (0.919 g, 67%, colorless solid). ¹H NMR (500 MHz, DMSO) δ 11.71 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 6.5 Hz, 2H), 7.42 (dd, *J* = 8.8, 4.7 Hz, 3H), 7.38 (dd, *J* = 8.3, 5.6 Hz, 1H), 7.29 (dd, *J* = 8.4, 2.6 Hz, 1H),

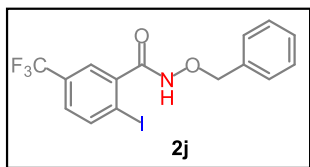
4.98 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 164.9, 142.0, 141.4, 136.2, 133.5, 131.7, 129.5, 128.9, 128.8, 128.8, 93.0, 77.6. HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{14}\text{H}_{12}\text{ClINO}_2^+$ [M+H], 387.9596; found 387.9591.

N-(Benzyloxy)-5-bromo-2-iodobenzamide (2i):



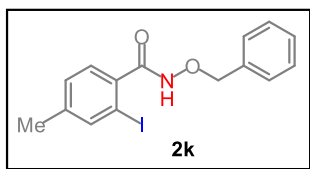
Following the general procedure GP-2, the compound **2i** (0.911 g, 69%, colorless solid). ^1H NMR (500 MHz, DMSO) δ 11.70 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.53–7.46 (m, 3H), 7.41 (ddt, J = 12.3, 9.5, 4.3 Hz, 4H), 4.97 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 164.8, 142.2, 141.6, 136.2, 134.6, 131.6, 129.5, 128.9, 128.8, 121.8, 93.7, 77.6. HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{14}\text{H}_{12}\text{BrINO}_2^+$ [M+H], 431.9091; found 431.9094.

N-(Benzyloxy)-2-iodo-5-(trifluoromethyl)benzamide (2j):

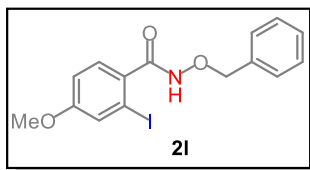


Following the general procedure GP-2, the compound **2j** (0.811 g, 61%, colorless solid). ^1H NMR (500 MHz, DMSO) δ 11.69 (s, 1H), 8.15 (d, J = 8.3 Hz, 1H), 7.65 (s, 1H), 7.55 (dd, J = 8.3, 2.3 Hz, 1H), 7.50 (d, J = 7.1 Hz, 2H), 7.48–7.30 (m, 3H), 5.03–4.99 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 165.0, 141.3, 140.9, 136.2, 129.5, 128.9, 128.8, 128.0, 125.4, 123.12, 100.7, 77.6. ^{19}F NMR (471 MHz, DMSO) δ -61.48. HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{15}\text{H}_{12}\text{F}_3\text{INO}_2^+$ [M+H], 421.9859; found 421.9859.

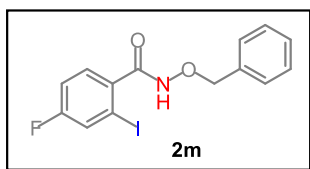
N-(Benzyloxy)-2-iodo-4-Methylbenzamide (2k):



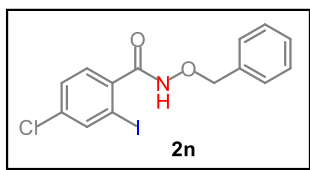
Following the general procedure GP-2, the compound **2k** (1.22 g, 87%, colorless solid). ^1H NMR (500 MHz, DMSO) δ 11.62–11.54 (m, 1H), 7.75 (s, 1H), 7.51 (q, J = 5.6 Hz, 2H), 7.45–7.38 (m, 3H), 7.31–7.17 (m, 2H), 5.04–4.95 (m, 2H), 2.29 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 166.3, 149.7, 141.9, 140.0, 137.4, 136.3, 132.4, 129.5, 129.0, 128.8, 94.7, 77.5, 20.7. HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{15}\text{H}_{15}\text{INO}_2^+$ [M+H], 368.0142; found 368.0146.

N-(Benzyloxy)-2-iodo-4-Methoxybenzamide (2l):

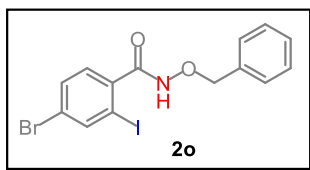
Following the general procedure GP-2, the compound **2l** (1.25 g, 91%, colorless solid). ^1H NMR (500 MHz, DMSO) δ 11.51 (s, 1H), 7.48 (d, J = 6.6 Hz, 2H), 7.46–7.34 (m, 4H), 7.24 (d, J = 8.5 Hz, 1H), 7.01 (dd, J = 8.5, 2.5 Hz, 1H), 4.96 (s, 2H), 3.79 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 166.1, 160.8, 136.3, 132.5, 130.0, 129.4, 128.8, 125.0, 114.1, 95.4, 77.4, 56.1. HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{15}\text{H}_{15}\text{INO}_3^+$ $[\text{M}+\text{H}]$, 384.0091; found 384.0096.

N-(Benzyloxy)-4-fluoro-2-iodo-benzamide (2m):

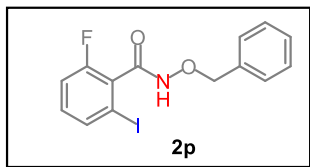
Following the general procedure GP-2, the compound **2m** (0.906 g, 65%, colorless solid). ^1H NMR (500 MHz, DMSO) δ 11.62 (s, 1H), 7.81 (dd, J = 8.5, 2.4 Hz, 1H), 7.49 (dt, J = 8.6, 3.0 Hz, 2H), 7.45–7.26 (m, 5H), 4.98 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 165.7, 162.3 (d, J = 251.8 Hz), 137.0 (d, J = 2.8 Hz), 136.3, 130.6 (d, J = 8.6 Hz), 129.5, 128.88, 128.84, 126.5 (d, J = 23.5 Hz), 115.6 (d, J = 21.3 Hz), 95.4 (d, J = 7.9 Hz), 77.5. ^{19}F NMR (471 MHz, DMSO) δ -109.86. HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{14}\text{H}_{12}\text{FINO}_2^+$ $[\text{M}+\text{H}]$, 371.9891; found 371.9895.

N-(Benzyloxy)-4-chloro-2-iodobenzamide (2n):

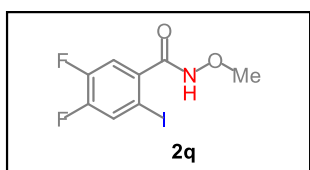
Following the general procedure GP-2, the compound **2n** (0.864 g, 63%, colorless solid). ^1H NMR (500 MHz, DMSO) δ 11.50 (s, 1H), 7.99 (d, J = 2.1 Hz, 1H), 7.62–7.23 (m, 7H), 4.98 (d, J = 2.3 Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 165.4, 139.2, 138.6, 136.2, 135.3, 130.2, 129.4, 129.3, 128.9, 128.8, 128.5, 95.8, 77.5. HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{14}\text{H}_{12}\text{ClINO}_2^+$ $[\text{M}+\text{H}]$, 387.9596; found 387.9591.

N-(Benzyloxy)-4-bromo-2-iodobenzamide (2o):

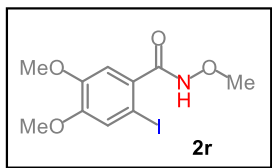
Following the general procedure GP-2, the compound **2o** (0.898 g, 68%, colorless solid). ^1H NMR (500 MHz, DMSO) δ 11.65 (bs, 1H), 8.11 (d, J = 1.9 Hz, 1H), 7.78–7.11 (m, 7H), 4.98 (t, J = 3.5 Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 165.5, 141.2, 139.65, 136.2, 131.5, 130.5, 129.5, 128.9, 128.8, 123.9, 96.1, 77.6. HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{14}\text{H}_{12}\text{BrINO}_2^+$ [$\text{M}+\text{H}$], 431.9091; found 431.9094.

N-(Benzyloxy)-6-fluoro-2-iodobenzamide (2p):

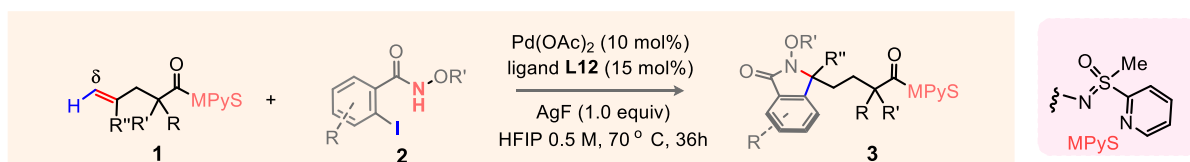
Following the general procedure GP-2, the compound **2p** (1.03 g, 73%, colorless solid). ^1H NMR (500 MHz, CDCl_3) δ 11.71 (s, 1H), 7.91 (dd, J = 8.7, 5.3 Hz, 1H), 7.50 (d, J = 6.9 Hz, 2H), 7.42 (t, J = 7.0 Hz, 2H), 7.41–7.35 (m, 1H), 7.27 (dd, J = 8.8, 3.0 Hz, 1H), 7.13 (td, J = 8.7, 3.1 Hz, 1H), 4.99 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 165.0, 162.2 (d, J = 246.9 Hz), 142.1 (d, J = 6.8 Hz), 141.5 (d, J = 7.7 Hz), 136.2, 129.5, 128.89, 128.84, 119.2 (d, J = 21.5 Hz), 116.6 (d, J = 23.4 Hz). 88.7, 77.6. ^{19}F NMR (471 MHz, DMSO) δ -114.02. HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{14}\text{H}_{12}\text{FINO}_2^+$ [$\text{M}+\text{H}$], 371.9891; found 371.9895.

4,5-Difluoro-2-iodo-N-methoxybenzamide (2q):

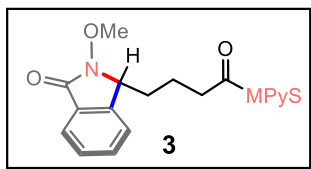
Following the general procedure GP-2, the compound **2q** (1.05 g, 77%, colorless solid). ^1H NMR (500 MHz, DMSO) δ 11.62 (s, 1H), 8.05 (dd, J = 10.0, 7.6 Hz, 1H), 7.62 (dd, J = 10.6, 8.1 Hz, 1H), 3.74 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 164.1, 150.2 (d, J = 254.5 Hz), 149.6 (d, J = 249.5 Hz), 137.5, 128.44 (d, J = 19.1 Hz), 118.31 (d, J = 19.0 Hz), 88.7, 63.7. ^{19}F NMR (471 MHz, DMSO) δ -134.83 (d, J = 22.4 Hz), -138.57 (d, J = 21.8 Hz). HRMS (ESI-TOF) m/z : calcd. for $\text{C}_8\text{H}_7\text{F}_2\text{INO}_2^+$ [$\text{M}+\text{H}$], 313.9486; found 313.9484.

2-Iodo-N,4,5-trimethoxybenzamide (2r):

Following the general procedure GP-2, the compound **2r** (1.16 g, 87%, colorless solid). ^1H NMR (500 MHz, DMSO) δ 11.41 (s, 1H), 7.33 (s, 1H), 6.96 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 165.7, 150.7, 149.0, 132.3, 122.3, 112.7, 83.3, 63.6, 56.5, 56.3. HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{10}\text{H}_{13}\text{INO}_4$ $[\text{M}+\text{H}]$, 337.9884; found 337.9880.

4.6.3.9. General Procedure for δ -annulative 1,1-difunctionalization of unactivated alkenes (GP-3):

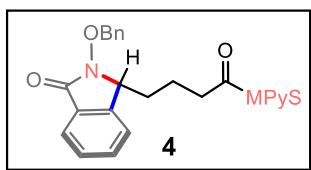
A 5 mL screw capped tube equipped with a magnetic stir bar was charged with $\text{Pd}(\text{OAc})_2$ (10 mol%, 4.5 mg), the substrate **1** (0.2 mmol), AgF (0.2 mmol, 24 mg), 2-iodo benzamide derivatives **2** (0.3 mmol), and **L12** (15 mol%, 3.26 mg) under air. Then, a solvent HFIP was added. The reaction mixture was stirred at 70 °C for 36 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (DCM), filtered through a small Celite pad, and concentrated in vacuo. The crude reaction mixture was extracted with CH_2Cl_2 and washed with saturated NaOH (0.05 M) solution and concentrated in vacuo. Finally, the reaction mixture was purified on neutral alumina using hexane/ EtOAc eluent to afford the desired products.

4-(2-Methoxy-3-oxoisindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (3):

Following the general procedure GP-3, the compound **3** was isolated (43 mg, 55% yield as colorless thick liquid; **dr** = 1:1) from the reaction of **1b** and **2d**. ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.64 (m, 1H), 8.27–8.20 (m, 1H), 8.01–7.93 (m, 1H), 7.66 (dd, J = 7.1, 3.3 Hz, 1H), 7.55–7.51 (m, 1H), 7.46–7.31 (m, 2H), 7.27 (s, 1H), 5.59 (dd, J = 11.7, 7.0 Hz, 1H), 3.92 & 3.91 (two s, 3H), 3.38 & 3.37 (two s, 3H), 2.43–2.35 (m, 2H), 2.08–1.97 (m, 1H), 1.89–1.64 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 181.9, 156.96 & 156.94 (1C), 156.6, 149.9,

144.4, 138.2, 130.9, 128.7, 128.3, 127.3, 123.4, 121.8, 121.42 & 121.41 (1C), 86.2, 62.7, 39.7, 38.53 & 38.49 (1C), 34.53 & 34.42 (1C), 20.37 & 20.25 (1C). **IR (Neat)** $\nu_{\max}$ 2925, 1738, 1635, 1364, 1216, 1084, 987, 732 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_3\text{O}_4\text{S}^+$ [M+H], 388.1326; found 388.1327.

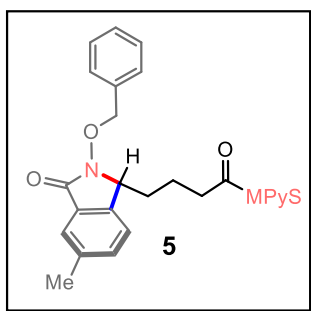
4-(2-(Benzyloxy)-3-oxoisindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (4):



Following the general procedure GP-3, the compound **4** (72 mg, 78%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2e**. **^1H NMR (500 MHz, DMSO)** δ 8.72

(d, J = 4.5 Hz, 1H), 8.19–8.12 (m, 2H), 7.72 (ddd, J = 9.0, 4.5, 2.3 Hz, 1H), 7.54 (dd, J = 13.6, 5.1 Hz, 2H), 7.47–7.28 (m, 7H), 5.73–5.67 (m, 1H), 5.03 (d, J = 1.7 Hz, 2H), 3.41 (s, 3H), 2.32–2.22 (m, 2H), 2.04–1.91 (m, 1H), 1.76–1.62 (m, 1H), 1.58–1.40 (m, 2H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 181.0, 156.9, 156.42 & 156.41 (1C), 150.5, 145.0, 139.2, 138.5, 131.5, 129.3, 128.7, 128.6, 128.3, 128.1, 123.6, 122.4, 121.5, 86.0, 75.9, 38.44 & 38.40 (1C), 34.36 & 34.32 (1C), 20.67 & 20.64 (1C). **IR (Neat)** $\nu_{\max}$ 2929, 1738, 1636, 1363, 1216, 1018, 980, 731 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_4\text{S}^+$ [M+H], 464.1639; found 464.1636.

4-(2-(Benzyloxy)-5-methyl-3-oxoisindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (5):

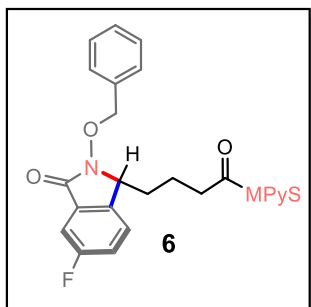


Following the general procedure GP-3, the compound **5** (60 mg, 63%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2f**. **^1H NMR (500 MHz, DMSO)** δ 8.76–8.69 (m, 1H), 8.20–8.11 (m, 2H), 7.75–7.69 (m, 1H), 7.45–7.26 (m, 8H), 5.65 (bs, 1H), 5.07–4.99 (m, 2H), 3.41 (s, 3H), 2.35 (s, 3H), 2.24 (dt, J = 8.1, 5.1 Hz, 2H), 2.00–1.87 (m, 1H), 1.72–1.59

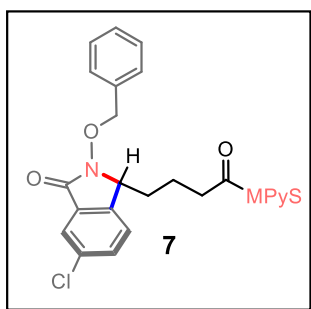
(m, 1H), 1.57–1.38 (m, 2H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)** δ 181.0, 156.9, 156.4, 150.5, 142.3, 139.3, 139.0, 138.6, 138.5, 132.5, 128.7, 128.5, 128.4, 128.14 & 128.10 (1C), 123.6, 122.1, 121.5, 85.9, 75.9, 38.45 & 38.41 (1C), 34.42 & 34.38 (1C), 21.2, 20.61 & 20.58 (1C).

IR (Neat) $\nu_{\max}$ 2912, 1709, 1636, 1217, 1186, 1019, 986, 746 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 478. 1795; found 478. 1791.

4-(2-(Benzyloxy)-5-fluoro-3-oxoisindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (6):

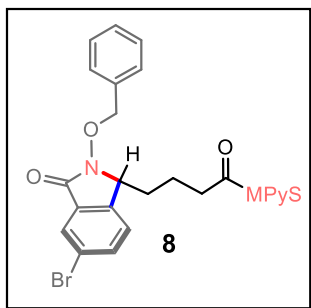


Following the general procedure GP-3, the compound **6** (70 mg, 73%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2g**. **^1H NMR (500 MHz, DMSO)** δ 8.70 (dd, J = 25.8, 6.6 Hz, 1H), 8.23–8.04 (m, 2H), 7.78–7.63 (m, 1H), 7.60–7.25 (m, 8H), 5.75–5.64 (m, 1H), 5.10–4.97 (m, 2H), 2.35–2.17 (m, 2H), 2.03–1.89 (m, 1H), 1.76–1.60 (m, 1H), 1.57–1.38 (m, 2H) [3H of Methyl group of sulfoximine merging with DMSO]. **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 180.9, 162.9 (d, J = 244.6 Hz), 156.9, 155.6, 150.5, 140.9, 139.3, 138.2, 130.32 (d, J = 7.7 Hz), 128.8, 128.7, 128.6, 128.18 (d, J = 7.0 Hz), 124.57 (d, J = 9.1 Hz), 123.6, 119.13 (d, J = 23.6 Hz), 108.01 (d, J = 24.5 Hz), 85.9, 76.1, 38.4, 34.3, 20.59 & 20.56 (1C). **^{19}F NMR (376 MHz, CDCl_3)** δ -113.11, -113.12 (1F). **IR (Neat)** $\nu_{\max}$ 3434, 1707, 1621, 1483, 1451, 1359, 1218, 1019, 982, 872, 735 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{25}\text{H}_{25}\text{FN}_3\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 482.1544; found 482. 1545. **4-(2-(Benzyloxy)-5-chloro-3-oxoisindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (7):**



Following the general procedure GP-3, the compound **7** (67 mg, 67%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2h**. **^1H NMR (500 MHz, DMSO)** δ 8.74–8.72 (m, 1H), 8.22–8.11 (m, 2H), 7.76–7.72 (m, 1H), 7.62–7.46 (m, 3H), 7.44–7.26 (m, 5H), 5.71 (dd, J = 6.8, 3.5 Hz, 1H), 5.03 (d, J = 2.6 Hz, 2H), 3.41 (s, 3H), 2.31–2.18 (m, 2H), 2.03–1.89 (m, 1H), 1.74–1.63 (m, 1H), 1.57–1.38 (m, 2H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 180.9, 156.9, 155.2, 150.5, 143.7, 139.3, 138.2, 134.1, 131.6, 128.8, 128.74, 128.69, 128.22, 128.15, 124.4, 123.6, 121.1, 86.0, 76.1, 38.4, 34.1, 20.59 & 20.55 (1C). **IR (Neat)** $\nu_{\max}$ 2924, 1762, 1639, 1425, 1219, 1086, 981, 840, 759 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{25}\text{H}_{25}\text{ClN}_3\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 498. 1249; found 498. 1244.

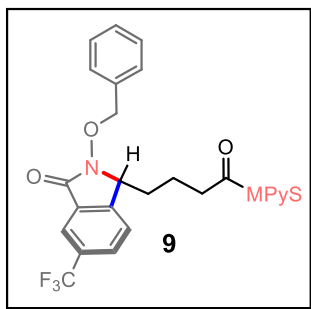
4-(2-(Benzyloxy)-5-bromo-3-oxoisindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)-λ⁶-sulfaneylidene) butanamide (8):



Following the general procedure GP-3, the compound **8** (71 mg, 65%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2i**. ¹H NMR (500 MHz, DMSO) δ 8.73 (d, J = 4.6 Hz, 1H), 8.16 (dt, J = 13.3, 7.9 Hz, 2H), 7.78–7.70 (m, 2H), 7.67 (s, 1H), 7.45–7.28 (m, 6H), 5.70 (dd, J = 6.8, 3.5 Hz, 1H), 5.07–4.99 (m, 2H), 3.41 (s, 3H), 2.30–2.20 (m, 2H), 2.01–

1.91 (m, 1H), 1.70–1.66 (m, 1H), 1.55–1.38 (m, 2H). ¹³C{¹H} NMR (126 MHz, DMSO) δ 180.9, 156.9, 155.1, 150.5, 144.2, 139.3, 138.2, 134.3, 130.7, 128.8, 128.7, 128.22, 128.15, 124.7, 124.0, 123.6, 122.3, 86.0, 76.1, 38.4, 34.03, 20.59 & 20.55 (1C). IR (Neat) ν_{max} 2924, 1762, 1639, 1425, 1219, 1086, 981, 840, 759 cm⁻¹. HRMS (ESI-TOF) m/z : calcd. for C₂₅H₂₅BrN₃O₄S⁺ [M+H], 542.0744; found 542.0745.

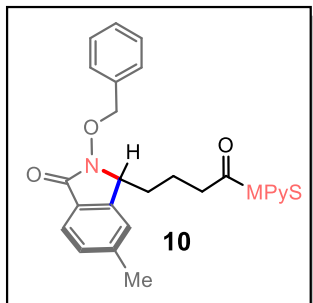
4-(2-(Benzyloxy)-3-oxo-5-(trifluoromethyl) isoindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)-λ⁶-sulfaneylidene) butanamide (9)



Following the general procedure GP-3, the compound **9** (55 mg, 52%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2j**. ¹H NMR (500 MHz, DMSO) δ 8.75–8.67 (m, 1H), 8.21–8.12 (m, 2H), 7.92 (dt, J = 8.4, 2.2 Hz, 1H), 7.85–7.66 (m, 3H), 7.44–7.20 (m, 5H), 5.83 (dd, J = 7.5, 3.9 Hz, 1H), 5.12–4.98 (m, 2H), 3.41 (s, 3H), 2.27 (q, J = 7.6 Hz, 2H),

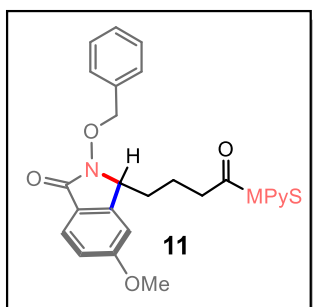
2.01 (td, J = 10.7, 5.1 Hz, 1H), 1.76 (dt, J = 17.5, 6.6 Hz, 1H), 1.54–1.43 (m, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 181.9, 156.9, 155.2, 150.0, 147.5, 138.3, 137.7, 131.48 (d, J = 32.6 Hz), 129.8, 128.39, 128.37, 127.9, 127.6, 127.3, 123.5, 122.2, 119.2, 85.9, 39.8, 38.4, 34.26 & 34.12 (1C), 20.15 & 20.01 (1C). ¹⁹F NMR (376 MHz, CDCl₃) δ -62.39. IR (Neat) ν_{max} 2921, 1755, 1639, 1218, 1018, 1132, 986, 758 cm⁻¹. HRMS (ESI-TOF) m/z : calcd. for C₂₆H₂₅F₃N₃O₄S⁺ [M+H], 532.1512; found 532.1514.

4-(2-(Benzyloxy)-3-oxo-4-(methyl) isoindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (10)



Following the general procedure GP-3, the compound **10** (74 mg, 77%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2k**. ¹H NMR (500 MHz, CDCl₃) δ 8.71–8.64 (m, 1H), 8.27 (t, *J* = 8.1 Hz, 1H), 7.98 (td, *J* = 7.8, 4.5, 1.7 Hz, 1H), 7.67–7.43 (m, 4H), 7.35 (td, *J* = 7.5, 3.1 Hz, 2H), 7.31–7.28 (m, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 7.08 (s, 1H), 5.57 (dq, *J* = 10.3, 5.1 Hz, 1H), 5.13 (d, *J* = 2.4 Hz, 2H), 3.41 & 3.40 (two s, 3H), 2.48–2.30 (m, 5H), 2.08–2.03 (m, 1H), 1.91–1.65 (m, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 182.1, 156.95 & 156.93 (1C), 156.8, 149.9, 144.79 & 144.75 (1C), 141.2, 138.2, 138.1, 129.7, 128.4, 128.3, 127.6, 127.3, 126.04 & 126.01 (1C), 123.41 & 123.39 (1C), 121.74 & 121.73 (1C), 121.5, 85.79 & 85.72 (1C), 76.5, 39.7, 38.66 & 38.61 (1C), 34.55 & 34.42 (1C), 21.8, 20.33 & 20.19 (1C). IR (Neat) ν_{max} 2921, 1755, 1639, 1218, 1019, 802, 758 cm⁻¹. HRMS (ESI-TOF) *m/z*: calcd. for C₂₆H₂₈N₃O₄S⁺ [M+H], 478. 1795; found 478. 1793.

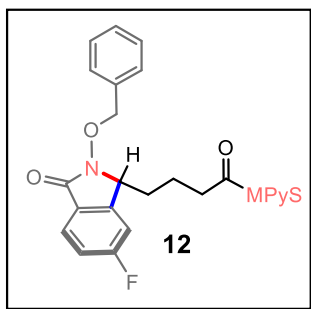
4-(2-(Benzyloxy)-3-oxo-4-(methoxy) isoindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (11)



Following the general procedure GP-3, the compound **11** (84 mg, 85%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2l**. ¹H NMR (500 MHz, DMSO) δ 8.74–8.71 (m, 1H), 8.20–8.10 (m, 2H), 7.72 (ddt, *J* = 6.7, 4.3, 2.1 Hz, 1H), 7.42–7.28 (m, 6H), 7.04–6.95 (m, 2H), 5.63 (dt, *J* = 6.8, 3.4 Hz, 1H), 4.99 (d, *J* = 2.4 Hz, 2H), 3.81 (two s, 3H), 3.41 (s, 3H), 2.26 (q, *J* = 8.3 Hz, 2H), 1.99 (dtd, *J* = 14.4, 9.7, 4.5 Hz, 1H), 1.74–1.61 (m, 1H), 1.57–1.39 (m, 2H). ¹³C{¹H} NMR (126 MHz, DMSO) δ 181.0, 162.3, 156.9, 156.4, 150.5, 147.2, 139.3, 138.59 & 138.53 (1C), 130.3, 128.7, 128.5, 128.15 & 128.07 (1C), 123.6, 122.8, 120.42 & 120.41 (1C), 116.44 & 116.41 (1C), 106.85 & 106.80 (1C), 85.5, 75.8, 56.17 & 56.13 (1C), 38.49 & 38.43 (1C), 34.23 & 34.19 (1C), 20.61 & 20.59 (1C). IR (Neat) ν_{max} 2928, 1635,

1490, 1257, 1209, 1018, 981, 824, 753 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_5\text{S}^+$ $[\text{M}+\text{H}]$, 494.1746; found 494.1744.

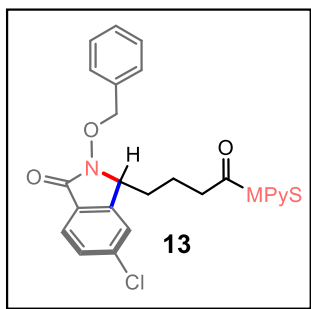
4-(2-(Benzyloxy)-3-oxo-4-(fluoro)isoindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (12)



Following the general procedure GP-3, the compound **12** (60 mg, 62%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2m**. ^1H NMR (500 MHz, DMSO) δ 8.75–8.69 (m, 1H), 8.20–8.12 (m, 2H), 7.72 (ddt, J = 7.4, 5.2, 2.7 Hz, 1H), 7.58 (dd, J = 8.7, 4.8 Hz, 1H), 7.47–7.23 (m, 7H), 5.70 (dq, J = 8.0, 3.1 Hz, 1H), 5.02 (d, J = 2.5 Hz, 2H), 2.33–2.14 (m,

2H), 2.06–1.94 (m, 1H), 1.75–1.63 (m, 1H), 1.56–1.35 (m, 2H) [3H of Methyl group of sulfoximine merging with DMSO]. $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 180.9, 164.35 (d, J = 248.1 Hz), 156.9, 155.58 & 155.56 (1C), 150.5, 147.60 (d, J = 9.6 Hz), 139.3, 138.4, 130.3, 128.7, 128.6, 128.2, 124.6, 123.76 (d, J = 9.6 Hz), 123.61 & 123.60 (1C), 117.11 (d, J = 24.1 Hz), 109.86 (d, J = 24.8 Hz), 85.5, 76.0, 38.41 & 38.37 (1C), 34.0, 20.52 & 20.48 (1C). **IR (Neat)** ν_{max} 2924, 1636, 1483, 1362, 1252, 1218, 1021, 985, 830, 754 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{25}\text{H}_{25}\text{FN}_3\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 482.1544; found 482.1541.

4-(2-(Benzyloxy)-3-oxo-4-(chloro)isoindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (13)

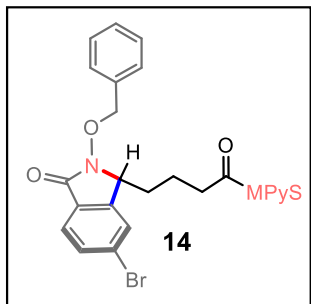


Following the general procedure GP-3, the compound **13** (65 mg, 65%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2n**. ^1H NMR (500 MHz, DMSO) δ 8.75–8.72 (m, 1H), 8.21–8.11 (m, 2H), 7.76–7.71 (m, 1H), 7.64–7.52 (m, 2H), 7.49 (dt, J = 8.3, 2.0 Hz, 1H), 7.43–7.24 (m, 5H), 5.71 (dt, J = 7.8, 4.0 Hz, 1H), 5.02 (d, J = 2.6 Hz, 2H), 3.41 (s,

3H), 2.29–2.22 (m, 2H), 2.24–1.96 (m, 1H), 1.77–1.64 (m, 1H), 1.54–1.35 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 180.9, 157.0, 155.6, 150.5, 147.2, 139.3, 138.3, 132.5, 128.7, 128.66 & 128.63 (1C), 128.5, 128.19 & 128.15 (1C), 127.7, 125.7, 124.8, 123.6, 123.4, 85.6,

76.1, 38.5, 34.0, 20.59 & 20.55 (1C). **IR (Neat)** $\nu_{\max}$ 2923, 1710, 1637, 1424, 1359, 1217, 1017, 980, 842, 759 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{25}\text{H}_{25}\text{ClN}_3\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 498.1249; found 498.1247.

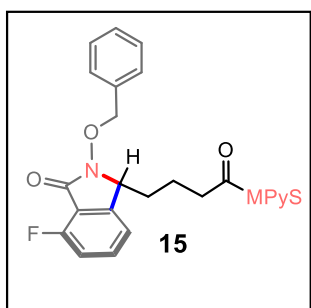
4-(2-(Benzyloxy)-3-oxo-4-(bromo)isoindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (14)



Following the general procedure GP-3, the compound **14** (68 mg, 63%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2o**. **^1H NMR (500 MHz, DMSO)** δ 8.74–8.71 (m, 1H), 8.22–8.09 (m, 2H), 7.73 (ddd, J = 6.5, 4.5, 1.9 Hz, 2H), 7.65–7.58 (m, 1H), 7.48 (dd, J = 8.3, 1.4 Hz, 1H), 7.45–7.27 (m, 5H), 5.71 (dq, J = 7.5, 4.3 Hz, 1H), 5.03 (d, J = 2.6 Hz,

2H), 2.25 (td, J = 9.1, 6.5 Hz, 2H), 2.03–1.92 (m, 1H), 1.78–1.64 (m, 1H), 1.60–1.36 (m, 2H), [3H of Methyl group of sulfoximine merging with DMSO]. **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 180.9, 157.0, 155.6, 150.5, 147.2, 139.3, 138.3, 132.5, 128.7, 128.66 & 128.63 (1C), 128.5, 128.19 & 128.15 (1C), 127.7, 125.7, 124.8, 123.6, 123.4, 85.6, 76.1, 38.5, 34.0, 20.59 & 20.55 (1C). **IR (Neat)** $\nu_{\max}$ 2924, 1636, 1425, 1359, 1217, 1021, 985, 828, 757 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{25}\text{H}_{25}\text{BrN}_3\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 542.0744; found 542.0741.

4-(2-(Benzyloxy)-3-oxo-6-(fluoro)isoindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (15)

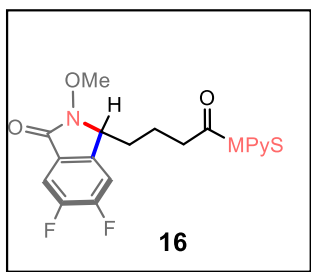


Following the general procedure GP-3, the compound **15** (59 mg, 52%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2p**. **^1H NMR (500 MHz, DMSO)** δ 8.75–8.70 (m, 1H), 8.22–8.10 (m, 2H), 7.73 (ddd, J = 6.8, 3.6, 1.8 Hz, 1H), 7.57 (tdd, J = 7.8, 4.7, 2.9 Hz, 1H), 7.44–7.17 (m, 7H), 5.75 (dd, J = 7.0, 3.6 Hz, 1H), 5.03 (d, J = 2.1 Hz, 2H), 2.26 (q, J

= 8.3 Hz, 2H), 2.03–1.93 (m, 1H), 1.77–1.64 (m, 1H), 1.58–1.37 (m, 2H), [3H of Methyl group of sulfoximine merging with DMSO]. **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 180.9,

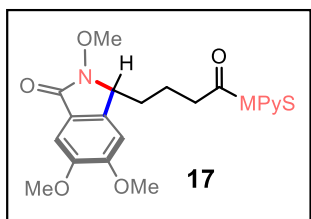
157.7, 156.9 155.6, 154.6 (d, $J = 6.2$ Hz), 150.5, 148.2, 139.3, 138.3, 133.87 (d, $J = 7.1$ Hz), 129.68 (d, $J = 172.3$ Hz), 128.73 & 128.67 (1C), 128.21 & 128.16 (1C), 123.6, 118.66 & 118.63 (1C), 116.2 (d, $J = 18.9$ Hz), 115.7 (d, $J = 15.0$ Hz), 86.0, 76.1, 38.37 & 38.34 (1C), 34.23 & 34.19 (1C), 20.56 & 20.52 (1C). ^{19}F NMR (471 MHz, DMSO) δ -113.53, -113.54 (1F). IR (Neat) ν_{max} 2927, 1710, 1631, 1484, 1362, 1254, 1217, 1018, 979, 731 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{25}\text{H}_{25}\text{FN}_3\text{O}_4\text{S}^+$ [$\text{M}+\text{H}$], 482.1544; found 482.1541.

4-(5,6-Difluoro-2-methoxy-3-oxoisindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (16)



Following the general procedure GP-3, the compound **16** (46 mg, 46%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2q**. ^1H NMR (500 MHz, DMSO) δ 8.74 (tdd, $J = 3.5, 2.1, 1.0$ Hz, 1H), 8.23–8.07 (m, 2H), 7.75 (ddd, $J = 9.0, 4.4, 1.8$ Hz, 1H), 7.63 (dq, $J = 9.7, 7.0$ Hz, 2H), 5.73–5.55 (m, 1H), 3.77 (s, 3H), 3.42 (s, 3H), 2.29–2.15 (m, 2H), 2.06–1.89 (m, 1H), 1.73–1.61 (m, 1H), 1.57–1.41 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 180.9, 156.9, 154.7, 152.4 (dd, $J = 171.3, 14.0$ Hz), 150.5 (dd, $J = 168.8, 14.3$ Hz), 150.50 & 150.48 (1C), 141.72 (d, $J = 10.4$ Hz), 139.3, 128.2, 124.81 (d, $J = 7.5$ Hz), 123.6, 112.07 (d, $J = 20.3$ Hz), 110.42 (d, $J = 20.2$ Hz), 85.6, 62.3, 38.38 & 38.35 (1C), 34.11 & 34.06 (1C), 20.61 & 20.58 (1C). ^{19}F NMR (471 MHz, DMSO) δ -132.84 & -132.88 (1F), -136.48 & -1136.53 (F). IR (Neat) ν_{max} 2939, 1738, 1635, 1492, 1363, 1217, 1046, 1024, 1003, 892, 761 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{19}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_5\text{S}^+$ [$\text{M}+\text{H}$], 424.1127; found 424.1134.

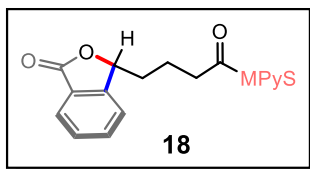
N-(Methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)-4-(2,5,6-trimethoxy-3-oxoisindolin-1-yl) butanamide (17)



Following the general procedure GP-3, the compound **17** (57 mg, 54%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2r**. ^1H NMR (500 MHz, DMSO) δ 8.76–8.72 (m, 1H), 8.23–8.08 (m, 2H), 7.83–7.69 (m, 1H), 7.02 (d, $J = 7.6$ Hz, 1H), 6.97 (s, 1H), 5.55 (ddd, $J = 7.6, 3.5, 1.9$ Hz, 1H), 3.82–3.79 (m, 6H), 3.74 (s,

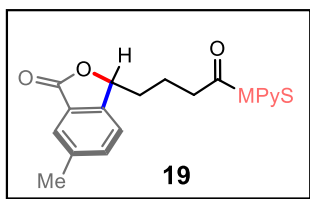
3H), 3.42 (s, 3H), 2.32–2.20 (m, 2H), 2.04–1.93 (m, 1H), 1.67–1.59 (m, 1H), 1.57–1.41 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 181.0, 157.0, 156.4, 152.4, 150.5, 150.2, 140.3, 139.3, 138.1, 128.2, 123.6, 119.72 & 119.70 (1C), 104.8, 103.1, 95.9, 85.6, 62.0, 56.32 & 56.20 (1C), 38.51 & 38.45 (1C), 34.44 & 34.40 (1C), 20.8. IR (Neat) ν_{max} 2934, 1738, 1637, 1500, 1361, 1216, 1047, 987, 763 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_6\text{S}^+$ [M+H], 448.1537; found 448.1534.

N-(Methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl) butanamide (18):



Following the general procedure GP-3, the compound **18** (37 mg, 52%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2v**. ^1H NMR (500 MHz, DMSO) δ 8.75–8.68 (m, 1H), 8.20–8.12 (m, 2H), 7.87–7.70 (m, 3H), 7.61 (dd, J = 16.5, 7.8 Hz, 2H), 5.63 (dd, J = 7.5, 3.7 Hz, 1H), 3.41 (s, 3H), 2.33–2.23 (m, 2H), 2.08–2.00 (m, 1H), 1.72–1.62 (m, 1H), 1.61–1.42 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 180.9, 170.4, 156.9, 150.5, 139.3, 134.8, 129.7, 128.2, 125.7, 125.4, 123.6, 123.0, 81.4, 38.4, 33.70 & 33.66 (1C), 20.98 & 20.95 (1C). IR (Neat) ν_{max} 2924, 1753, 1634, 1425, 1363, 1215, 1083, 984, 755 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_4\text{S}^+$ [M+H], 359.1060; found 359.1056.

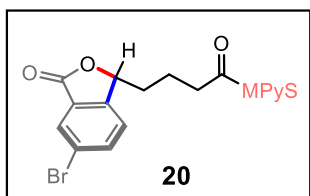
N-(Methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)-4-(5-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl) butanamide (19):



Following the general procedure GP-3, the compound **19** (34 mg, 46%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2v**. ^1H NMR (500 MHz, DMSO) δ 8.73 (dddd, J = 4.6, 2.6, 1.7, 0.9 Hz, 1H), 8.25–8.08 (m, 2H), 7.74 (ddt, J = 8.0, 4.7, 1.7 Hz, 1H), 7.68–7.54 (m, 2H), 7.50 (d, J = 7.8 Hz, 1H), 5.58 (dd, J = 7.6, 3.9 Hz, 1H), 3.42 (s, 3H), 2.42 (s, 3H), 2.29–2.25 (m, 2H), 2.06–1.94 (m, 1H), 1.71–1.39 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 180.9, 170.4, 156.9, 150.5, 147.9, 139.5, 139.3, 135.8, 128.2, 125.9, 125.2, 123.6, 122.7, 81.22 & 81.21 (1C), 38.36 & 38.34 (1C), 33.77 & 33.73 (1C), 21.1, 20.91 & 20.88 (1C). IR (Neat) ν_{max} 2927, 1752, 1635, 1217, 1154, 980,

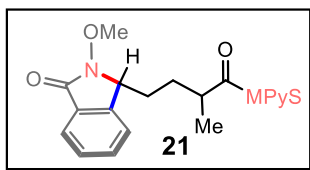
730 cm⁻¹. HRMS (ESI-TOF) *m/z*: calcd. for C₁₉H₂₁N₂O₄S⁺ [M+H], 373.1217; found 373.1214.

4-(5-Bromo-3-oxo-1,3-dihydroisobenzofuran-1-yl)-N-(methyl(oxo)(pyridin-2-yl)-λ⁶-sulfaneylidene) butanamide (20):



Following the general procedure GP-3, the compound **20** (41 mg, 47%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1b** and **2v**. ¹H NMR (500 MHz, DMSO) δ 8.74–8.70 (m, 1H), 8.22–8.11 (m, 2H), 8.04–7.93 (m, 2H), 7.78–7.71 (m, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 5.62 (dd, *J* = 7.8, 3.8 Hz, 1H), 3.42 (s, 3H), 2.34–2.18 (m, 2H), 2.07–1.98 (m, 1H), 1.74–1.39 (m, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 180.82, 168.9, 156.90 & 156.68 (1C), 150.64 & 150.49 (1C), 149.6, 139.37 & 139.28 (1C), 137.6, 128.18 & 128.11 (1C), 128.0, 125.3, 123.6, 122.6, 121.5, 120.6, 81.5, 38.31 & 38.28 (1C), 33.38 & 33.34 (1C), 20.94 & 20.90 (1C). IR (Neat) ν_{max} 3406, 1760, 1634, 1216, 1024, 989, 761 cm⁻¹. HRMS (ESI-TOF) *m/z*: calcd. for C₁₈H₁₈BrN₂O₄S⁺ [M+H], 437.0165; found 437.0163.

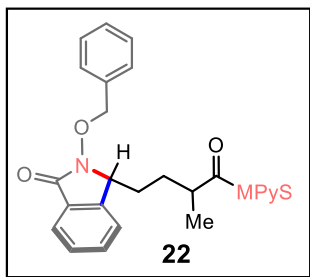
4-(2-Methoxy-3-oxoisindolin-1-yl)-2-methyl-N-(methyl(oxo)(pyridin-2-yl)-λ⁶-sulfaneylidene) butanamide (21):



Following the general procedure GP-3, the compound **21** (61 mg, 76%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1a** and **2d**. ¹H NMR (500 MHz, CDCl₃) δ 8.67–8.51 (m, 1H), 8.28–8.11 (m, 1H), 8.04–7.92 (m, 1H), 7.64 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.54–7.48 (m, 1H), 7.48–7.33 (m, 2H), 7.33–7.27 (m, 1H), 5.70–5.47 (m, 1H), 4.11–3.81 (m, 3H), 3.39–3.35 (m, 3H), 2.56–2.37 (m, 1H), 2.11–1.90 (m, 2H), 1.71–1.49 (m, 2H), 1.17–1.01 (m, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 185.5, 157.1, 156.3, 149.81 & 149.79 (1C), 144.49 & 144.47 (1C), 138.16 & 138.14 (1C), [130.71 & 130.70 & 130.68 (1C)], 128.64 & 128.60 (1C), 128.55 & 128.50 (1C), 127.2, 123.45 & 123.43 (1C), 121.63 & 121.59 (1C), [121.51 & 121.44 & 121.39 (1C)], [86.51 & 86.44 & 86.03 & 86.01 (1C)], 62.61 & 62.59 (1C), [43.17, & 43.09 & 43.02 & 42.82 (1C)], [39.75 & 39.70 & 39.68 (1C)], [33.09 & 32.90 & 32.68 & 32.63 (1C)], [29.14 & 29.10 & 28.60 & 28.46 (1C)], [17.70 & 17.65 & 17.55 & 17.36

(1C)]. **IR (Neat)** $\nu_{\max}$ 2929, 1757, 1635, 1266, 1215, 1046, 982, 730, cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{20}\text{H}_{24}\text{N}_3\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 402.1482; found 402.1482.

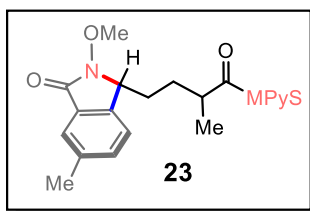
4-(2-(Benzyloxy)-3-oxoisindolin-1-yl)-2-methyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (22):



Following the general procedure GP-3, the compound **22** (81 mg, 85%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1a** and **2e**. **^1H NMR (500 MHz, DMSO)** δ 8.75–8.62 (m, 1H), 8.21–8.03 (m, 2H), 7.70 (dtdd, J = 9.6, 4.6, 2.5, 1.2 Hz, 1H), 7.60–7.25 (m, 9H), 5.69 (ddd, J = 11.5, 7.2, 3.9 Hz, 1H),

5.03 (s, 2H), 3.41 (s, 3H), 2.42–2.28 (m, 1H), 2.04–1.98 (m, 1H), 1.74–1.31 (m, 3H), 1.01–0.96 (m, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 184.19 & 184.16 (1C), 156.9, 156.4, [150.46 & 150.41 & 150.37 (1C)], 145.0, 139.2, 138.5, 131.5, 130.3, 129.3, 129.0, 128.7, [128.60 & 128.58 & 128.56 (1C)], 128.13 & 128.11 (1C), 123.64 & 123.57 (1C), 122.44 & 122.38 (1C), 121.5, 86.12 & 86.08 (1C), 75.9, [42.89 & 42.73 & 42.48 (1C)], [32.76 & 32.65 & 32.47 (1C)], 29.00 & 28.82 (1C), [18.01 & 17.91 & 17.73 & 17.58 (1C)]. **IR (Neat)** $\nu_{\max}$ 2925, 1635, 1452, 1361, 1213, 1021, 981, 733 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 478.1790; found 478.1795.

4-(2-Methoxy-5-methyl-3-oxoisindolin-1-yl)-2-methyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (23):

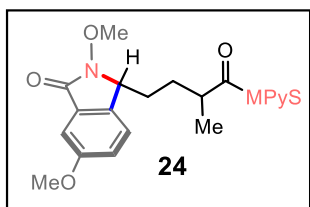


Following the general procedure GP-3, the compound **23** (54 mg, 65%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1a** and **2s**. **^1H NMR (500 MHz, DMSO)** δ 8.76–8.65 (m, 1H), 8.21–8.10 (m, 2H), 7.77–7.71 (m, 1H), 7.54–7.24

(m, 3H), 5.65–5.52 (m, 1H), 3.76 (s, 3H), 3.42 (s, 3H), 2.45–2.19 (m, 4H), 1.97–1.82 (m, 1H), 1.71–1.29 (m, 3H), 1.04–0.94 (m, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 184.2, [156.99 & 156.96 & 156.94 (1C)], [155.95 & 155.92 & 155.90 (1C)], 150.4, 142.27 & 142.22 (1C), 139.2, 139.0, 132.4, 128.5, 128.1, 123.6, 122.11 & 122.05 (1C), 121.5, 85.93 & 85.88 (1C), 62.1, [42.84 & 42.72 & 42.51 (1C)], [32.88 & 32.77 & 32.61 (1C)], [29.14 & 29.04 & 28.87, & 28.84 (1C)], 21.2, [17.98 & 17.70 & 17.61 (1C)]. **IR (Neat)** $\nu_{\max}$ 2967, 2928, 1708,

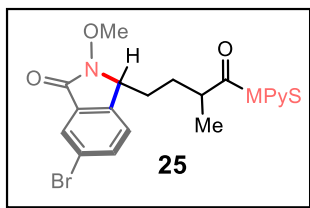
1629, 1425, 1216, 1166, 1040, 982, 758 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 416.1639; found 416.1639.

4-(2,5-Dimethoxy-3-oxoisindolin-1-yl)-2-methyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (24):



Following the general procedure GP-3, the compound **24** (49 mg, 57%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1a** and **2t**. **^1H NMR (500 MHz, DMSO)** δ 8.77–8.65 (m, 1H), 8.24–8.08 (m, 2H), 7.78–7.68 (m, 1H), 7.44–7.28 (m, 1H), 7.11 (dq, J = 8.5, 2.9 Hz, 1H), 7.01 (t, J = 2.0 Hz, 1H), 5.63–5.51 (m, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.44–3.40 (m, 3H), 2.40–2.26 (m, 1H), 2.03–1.78 (m, 1H), 1.68–1.41 (m, 2H), 1.40–1.25 (m, 1H), 1.02–0.93 (m, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 184.2, 160.4, 157.0, 156.0, [150.48 & 150.45 & 150.40 (1C)], 139.2, 137.2, 129.7, 128.2, 123.66 & 123.59 (1C), 123.4, 119.52, 104.4, 85.81 & 85.77 (1C), 62.2, 56.0, [42.85 & 42.73 & 42.51 (1C)], [32.98 & 32.87 & 32.69 (1C)], [29.16 & 29.05 & 28.87 (1C)], [18.00 & 17.95 & 17.72 & 17.62 (1C)]. **IR (Neat)** ν_{max} 2925, 1716, 1635, 1426, 1219, 1017, 799, 733 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_5\text{S}^+$ $[\text{M}+\text{H}]$, 432.1588; found 432.1592.

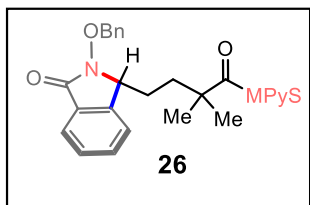
4-(5-Bromo-2-methoxy-3-oxoisindolin-1-yl)-2-methyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (25):



Following the general procedure GP-3, the compound **25** (61 mg, 63%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1a** and **2u**. **^1H NMR (500 MHz, DMSO)** δ 8.77–8.58 (m, 1H), 8.22–8.11 (m, 2H), 7.77–7.67 (m, 3H), 7.51–7.37 (m, 1H), 5.70–5.60 (m, 1H), 3.78 (s, 3H), 3.42 (dd, J = 3.0, 1.4 Hz, 3H), 2.41–2.24 (m, 1H), 2.03–1.85 (m, 1H), 1.73–1.42 (m, 2H), 1.40–1.25 (m, 1H), 1.03–0.93 (m, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ [184.20 & 184.17 & 184.15 (1C)], 156.96 & 156.94 (1C), [154.69 & 154.67 & 154.63 (1C)], [150.47 & 150.43 & 150.39 (1C)], 144.1, 139.2, 134.3, 130.7, 128.2, 124.70 & 124.68 (1C), 123.9, 123.63 & 123.56 (1C), 122.3, [86.10 & 86.08 & 86.06 & 86.04 (1C)], 62.34, [42.82 & 42.68 & 42.45 (1C)], [32.57 & 32.44 & 32.26 (1C)],

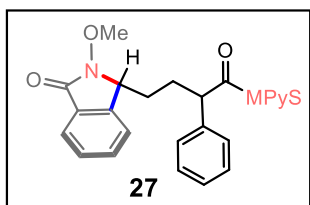
[29.11 & 28.99 & 28.82 & 28.78 (1C)], [17.99 & 17.91 & 17.70 & 17.57]. **IR (Neat)** $\nu_{\max}$ 2924, 1636, 1425, 1359, 1217, 1021, 985, 828, 757 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{20}\text{H}_{23}\text{BrN}_3\text{O}_4\text{S}^+$ [M+H], 480.0587; found 480.0552.

4-(2-(Benzyloxy)-3-oxoisindolin-1-yl)-2,2-dimethyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (26):



Following the general procedure GP-3, the compound **26** (60 mg, 61%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1c** and **2e**. **^1H NMR (500 MHz, DMSO)** δ 8.71–8.53 (m, 1H), 8.19–8.08 (m, 2H), 7.82–7.10 (m, 10H), 5.69 (dt, J = 7.1, 3.7 Hz, 1H), 5.07–5.01 (m, 2H), 3.38 (two s, 3H), 1.98–1.81 (m, 1H), 1.68–1.33 (m, 3H), 1.05 (s, 3H), 0.99 (two s, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 185.76 & 185.74 (1C), 157.09 & 157.04 (1C), 156.53 & 156.48 (1C), 150.38 & 150.29 (1C), 144.97 & 144.90 (1C), 139.18 & 139.16 (1C), 138.52 & 138.48 (1C), 131.5, 129.3, 128.7, 128.56 & 128.53 (1C), 128.38 & 128.35 (1C), 128.1, 128.08 & 128.03 (1C), 123.69 & 123.59 (1C), 122.48 & 122.44 (1C), 121.52 & 121.50 (1C), 86.4, 75.9, 43.70 & 43.66 (1C), 35.36 & 35.33 (1C), 30.45 & 30.40 (1C), 26.4, 25.78 & 25.71 (1C), 25.1. **IR (Neat)** $\nu_{\max}$ 2923, 1633, 1469, 1452, 1217, 1190, 1017, 986, 732 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{27}\text{H}_{30}\text{N}_3\text{O}_4\text{S}^+$ [M+H], 492.1952; found 492.1961.

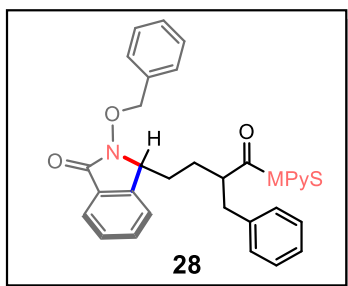
4-(2-Methoxy-3-oxoisindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)-2-phenyl butanamide (27):



Following the general procedure GP-3, the compound **27** (58 mg, 63%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1i** and **2e**. **^1H NMR (500 MHz, DMSO)** δ 8.75–8.58 (m, 1H), 8.21–8.05 (m, 2H), 7.79–7.68 (m, 1H), 7.63–7.01 (m, 9H), 5.75–5.63 (m, 1H), 3.77 (s, 3H), 3.62–3.48 (m, 1H), 3.44–3.39 (m, 3H), 2.02–1.80 (m, 2H), 1.75–1.43 (m, 2H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 181.29 & 181.22 (1C), 156.81 & 156.67 (1C), 155.9, [150.50 & 150.42 & 150.37 (1C)], 144.86 & 144.77 (1C), 140.78 & 140.73 (1C), 139.2, 131.5, 129.4, 128.83 & 128.76 (1C), [128.33 & 128.27 & 128.22 (1C)],

127.20 & 127.13 (1C), [123.70 & 123.56 & 123.48 (1C)], 122.43 & 122.34 (1C), 121.5, [85.95 & 85.86 & 85.79 (1C)], 62.2, [54.77 & 54.64 & 54.35 (1C)], 33.24 & 33.13 (1C), [29.49 & 29.32 & 29.11 (1C)]. **IR (Neat)** $\nu_{\max}$ 1636, 1264, 1220, 1045, 980, 730 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_4\text{S}^+$ [M+H], 464.1639; found 464.1645.

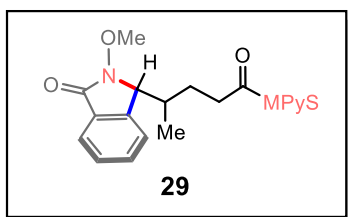
2-Benzyl-4-(2-(benzyloxy)-3-oxoisindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (28):



Following the general procedure GP-3, the compound **28** (68 mg, 61%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **1j** and **2e**. **^1H NMR (500 MHz, DMSO)** δ 8.74–8.54 (m, 1H), 8.30–7.90 (m, 2H), 7.76–7.64 (m, 1H), 7.58–7.28 (m, 9H), 7.24–7.02 (m, 5H), 5.72–5.64 (m, 1H),

5.06–5.01 (m, 2H), 3.40–3.38 (m, 3H), 2.87–2.77 (m, 1H), 2.67–2.51 (m, 2H), 2.05–1.87 (m, 1H), 1.74–1.32 (m, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 182.9, 156.85 & 156.81(1C), 156.4, [150.42 & 150.38 & 150.34 & 150.33 (1C)], 144.9 & 144.86 (1C), 140.26 & 140.16 (1C), 139.16 & 139.13 (1C), 138.5, 131.5, [129.37 & 129.33 & 129.30 (1C)], 128.82 & 128.79 (1C), 128.7, 128.63 & 128.62 (1C), 128.59 & 128.57 (1C), 128.55 & 128.53 (1C), 128.3, 128.15 & 128.11 (1C), 126.3, [123.61 & 123.57 & 123.53 (1C)], 122.4, 121.5, [86.10 & 86.08 & 86.03 & 86.01 (1C)], 75.9, [50.53 & 50.32 & 50.26 (1C)], 38.42 & 38.11 (1C), [32.71 & 32.66 & 32.54 (1C)], [27.43 & 27.32 & 27.14 (1C)]. **IR (Neat)** $\nu_{\max}$ 2924, 1635, 1363, 1264, 1218, 1020, 980, 732 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{32}\text{H}_{31}\text{N}_3\text{NaO}_4\text{S}^+$ [M+Na], 576.1927; found 576.1928.

4-(2-Methoxy-3-oxoisindolin-1-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) pentanamide (29):

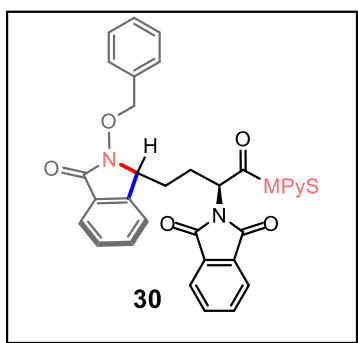


Following the general procedure GP-3, the compound **29** (40 mg, 42%, colorless thick liquid; **dr** = 3:1) was prepared from the reaction of **1k** and **2e**. **^1H NMR (500 MHz, DMSO)** δ 8.75–8.63 (m, 1H), 8.33–8.21 (m, 1H), 8.06–7.97

(m, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.60–7.52 (m, 1H), 7.49–7.31 (m, 3H), 5.65–5.53 (m,

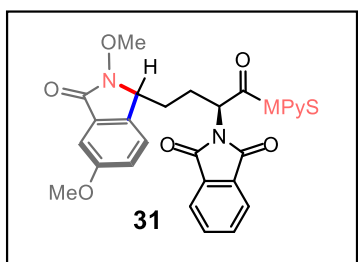
1H), 3.99–3.87 (m, 3H), 3.46–3.37 (m, 3H), 2.58–2.44 (m, 1H), 2.43–2.19 (m, 1H), 2.16–1.94 (m, 1H), 1.80–1.68 (m, 2H), 0.91 & 0.71 (two dd, $J = 6.7, 2.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 182.24 & 182.02 (1C), 156.96 & 156.90 (1C), 156.54 & 156.42 (1C), [149.90 & 149.88 & 149.85 (1C)], [143.55 & 143.52 & 142.58 & 142.53 (1C)], [138.20 & 138.18, & 138.14 (1C)], [130.63 & 130.52 & 130.50 (1C)], 129.36 & 129.12 (1C), 128.62 & 128.60 (1C), 127.27 & 127.25 (1C), 123.42 & 123.37 (1C), 122.08 & 122.00 (1C), [121.59 & 121.54 & 121.46 & 121.44 (1C)], [89.75 & 89.66 & 89.15 & 88.96 (1C)], 62.60 & 62.50 (1C), [39.70 & 39.66 & 39.64 (1C)], [37.21 & 37.17 & 37.12 & 37.09 (1C)], [36.86 & 36.69 & 36.63 (1C)], [28.68 & 28.61 & 26.36 & 26.19 (1C)], [14.52 & 14.47 & 12.49 & 12.31 (1C)]. IR (Neat) ν_{max} 2927, 1637, 1218, 1044, 980, 730 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{20}\text{H}_{24}\text{N}_3\text{O}_4\text{S}^+$ [M+H], 402.1484; found 402.1484.

4-(2-(Benzyloxy)-3-oxoisindolin-1-yl)-2-(1,3-dioxoisindolin-2-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene) butanamide (30):



Following the general procedure GP-3, the compound **30** (91 mg, 75%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **11** and **2e**. ^1H NMR (500 MHz, DMSO) δ 8.82–8.64 (m, 1H), 8.17–7.96 (m, 2H), 7.92–7.84 (m, 4H), 7.79–7.67 (m, 1H), 7.64–7.10 (m, 9H), 5.82–5.63 (m, 1H), 5.03 (q, $J = 5.7$ Hz, 2H), 4.80–4.59 (m, 1H), 3.50–3.42 (m, 3H), 2.41–1.94 (m, 3H), 1.85–1.70 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 176.83 & 176.55 (1C), 168.01 & 167.93 (1C), 156.40 & 156.31 (1C), 149.95 & 149.92 (1C), 144.0, 138.34 & 138.29 (1C), 138.1, 134.0, 132.1, 130.77 & 130.74 (1C), 128.7, 128.4, 128.28 & 128.26 (1C), 127.7, 127.54 & 127.50 (1C), 123.4, 122.9, 122.7, 121.9, 121.5, 121.3, 85.58 & 85.40 (1C), 76.61 & 76.59 (1C), [55.74 & 55.64 & 55.44 (1C)], [39.31 & 39.28 & 38.99 (1C)], [32.77 & 32.64 & 32.46 (1C)], [24.57 & 24.34 & 24.30 & 24.17 (1C)]. IR (Neat) ν_{max} 2932, 1713, 1653, 1387, 1263, 1226, 1047, 884, 730 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{33}\text{H}_{28}\text{N}_4\text{NaO}_6\text{S}^+$ [M+Na], 631.1622; found 631.1622.

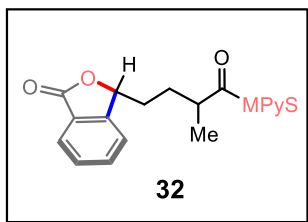
4-(2,5-Dimethoxy-3-oxoisindolin-1-yl)-2-(1,3-dioxoisindolin-2-yl)-N-(methyl(oxo)(pyridin-2-yl)-λ⁶-sulfaneylidene) butanamide (31):



Following the general procedure GP-3, the compound **31** (81 mg, 72%, colorless thick liquid; **dr** = **1:1**) was prepared from the reaction of **1b** and **2e**. ¹H NMR (500 MHz, CDCl₃) δ 8.77–8.60 (m, 1H), 8.27–8.08 (m, 1H), 8.06–7.89 (m, 1H), 7.89–7.75 (m, 2H), 7.76–7.65 (m, 2H), 7.62–7.49 (m,

2H), 6.94–6.90 (m, 1H), 6.80–6.66 (m, 1H), 5.62–5.52 (m, 1H), 4.91–4.78 (m, 1H), 3.94–3.85 (m, 3H), 3.86–3.79 (m, 3H), 3.49–3.41 (m, 3H), 2.61–2.41 (m, 1H), 2.38–2.08 (m, 1H), 2.01–1.95 (m, 1H), 1.89–1.79 (m, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 176.85 & 176.59 (1C), [168.02 & 168.00 & 167.94 & 167.91(1C)], 162.21 & 162.19 (1C), 156.3, 156.1, 150.00 & 149.95 (1C), 146.1, 138.35 & 138.30 (1C), 134.0, [132.06 & 132.04 & 132.02 (1C)], 127.57 & 127.53 (1C), 123.41 & 123.39 (1C), 122.96 & 122.91(1C), 122.7, 120.7, [115.96 & 115.88 & 115.85 (1C)], 106.03 & 105.85 (1C), 85.14 & 84.98 (1C), 62.5, 55.71 & 55.64 (1C), 55.42 & 55.32 (1C), 39.35 & 39.31 & 39.02 & 38.96 (1C), [32.70 & 32.54 & 32.36 & 32.29 (1C)], [24.59 & 24.34 & 24.30 & 24.18 (1C)]. IR (Neat) ν_{max} 2932, 1713, 1653, 1387, 1263, 1226, 1047, 884, 730 cm⁻¹. HRMS (ESI-TOF) *m/z*: calcd. for C₂₈H₂₇N₄O₇S⁺ [M+H], 563.1595; found 563.1595.

2-Methyl-N-(methyl(oxo)(pyridin-2-yl)-λ⁶-sulfaneylidene)-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl) butanamide (32):

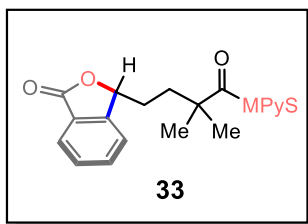


Following the general procedure GP-3, the compound **32** (43 mg, 58%, colorless thick liquid; **dr** = **1:1**) was prepared from the reaction of **1a** and **2v**. ¹H NMR (500 MHz, DMSO) δ 8.75–8.61 (m, 1H), 8.21–8.12 (m, 2H), 7.88–7.57 (m, 5H), 5.68–5.59

(m, 1H), 3.43–3.41 (m, 3H), 2.41–2.28 (m, 1H), 2.10–1.93 (m, 1H), 1.80–1.26 (m, 3H), 1.07–0.88 (m, 3H). ¹³C{¹H} NMR (126 MHz, DMSO) δ [184.17 & 184.12 & 184.10 (1C)], [170.36 & 170.34 & 170.30 (1C)], 156.97 & 156.93 (1C), [150.49 & 150.46 & 150.44 (1C)], [150.39 & 150.37 & 150.35 (1C)], 139.2, 134.8, 129.7, 128.16 & 128.14 (1C), 125.77 & 125.72 (1C), 125.4, [123.68 & 123.66 & 123.60 (1C)], [123.01 & 122.99 & 122.94 (1C)], [81.45 &

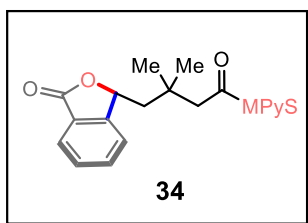
81.41 & 81.38 (1C)], [42.84 & 42.65 & 42.42, 42.37 (1C)], [32.13 & 31.98 & 31.79 (1C)], [29.43 & 29.32 & 29.12 (1C)], [17.99 & 17.90 & 17.69 & 17.52 (1C)]. **IR (Neat)** $\nu_{\max}$ 2928, 1753, 1633, 1283, 1213, 1062, 987, 756 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_4\text{S}^+$ [M+H], 373.1217; found 373.1220.

2,2-Dimethyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)-4-(3-oxo-1,3 dihydroisobenzofuran-1-yl) butanamide (33):



Following the general procedure GP-3, the compound **33** (36 mg, 46%, colorless thick liquid; **dr** = **1:1**) was prepared from the reaction of **1c** and **2v**. **^1H NMR (500 MHz, DMSO)** δ 8.70–8.45 (m, 1H), 8.27–8.05 (m, 2H), 7.83 (two t, J = 7.3 Hz, 2H), 7.70–7.57 (m, 3H), 5.66–5.59 (m, 1H), 3.41 & 3.40 (two s, 3H), 2.04–1.92 (m, 1H), 1.67–1.37 (m, 3H), 1.06 & 1.05 (two s, 3H), 1.00 & 0.98 (two s, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 185.71 & 185.68 (1C), 170.42 & 170.35 (1C), 157.09 & 157.05 (1C), 150.50 & 150.44 (1C), 150.36 & 150.19 (1C), 139.22 & 139.20 (1C), 134.8, 129.7, 128.11 & 128.07 (1C), 125.87 & 125.83 (1C), 125.37 & 125.34 (1C), 123.77 & 123.66 (1C), 123.05 & 123.01 (1C), 81.68 & 81.64 (1C), 43.71 & 43.66 (1C), 35.67 & 35.64 (1C), 29.86 & 29.81 (1C), 26.4, 25.7, 25.0. **IR (Neat)** $\nu_{\max}$ 1758, 1631, 1265, 1216, 1072, 987, 731 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4\text{S}^+$ [M+H], 373.1373; found 373.1376.

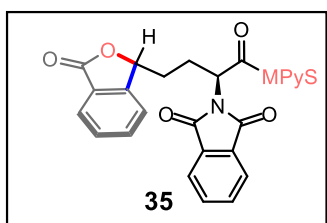
3,3-Dimethyl-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl) butanamide (34):



Following the general procedure GP-3, the compound **34** (39 mg, 50%, colorless thick liquid; **dr** = **1:1**) was prepared from the reaction of **1c** and **2v**. **^1H NMR (500 MHz, CDCl_3)** δ 8.71–8.56 (m, 1H), 8.29 (dd, J = 8.0, 3.2 Hz, 1H), 7.99 (dtd, J = 9.7, 7.7, 1.7 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.61 (dt, J = 7.5, 3.7 Hz, 2H), 7.49–7.37 (m, 2H), 5.70–5.60 (m, 1H), 3.41 & 3.38 (two s, 3H), 2.57–2.38 (m, 2H), 2.30–2.15 (m, 1H), 1.66–1.56 (m, 1H), 1.21 & 1.19 (two s, 3H), 1.18 & 1.16 (two s, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)** δ 180.7, 151.4, 149.6, 137.95 & 137.92 (1C), 133.6, 130.6, 128.6, 126.9, 126.0, 125.3,

123.18 & 123.07 (1C), 122.0, 79.28 & 79.25 (1C), 50.5, 46.8, 39.77 & 39.71 (1C), 33.60 & 33.51 (1C), 28.75 & 28.62 (1C), 28.39 & 28.36 (1C). **IR (Neat)** $\nu_{\max}$ 1758, 1631, 1265, 1216, 1072, 987, 731 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]$, 373.1373; found 373.1376.

2-(1,3-Dioxoisindolin-2-yl)-N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl) butanamide (35):

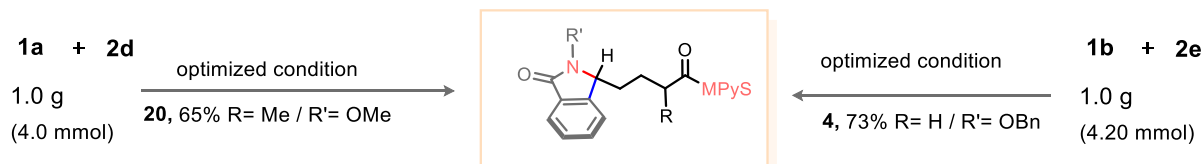


Following the general procedure GP-3, the compound **35** (64 mg, 64%, colorless thick liquid; **dr** = 1:1) was prepared from the reaction of **11** and **2v**. **^1H NMR (500 MHz, DMSO)** δ 8.72–8.62 (m, 1H), 8.24–8.07 (m, 1H), 8.0–7.89 (m, 1H), 7.88–7.82 (m, 3H), 7.71 (td, J = 5.6, 2.7 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.57–7.46 (m, 2H), 7.44–7.33 (m, 1H), 5.55–5.43 (m, 1H), 4.93–4.79 (m, 1H), 3.51–3.41 (m, 3H), 2.67–2.25 (m, 2H), 2.21–1.99 (m, 1H), 1.83 (s, 1H). **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO)** δ 176.73 & 176.44 (1C), 170.4, [168.07 & 168.04, 167.98 & 167.95 1C], 156.2, 150.0, 149.52 & 149.49 (1C), 138.42 & 138.35 (1C), 134.0, 132.02 & 132.00 (1C), 129.2, 127.63 & 127.58 (1C), 126.1, 125.7, 123.46 & 123.44 (1C), [122.97 & 122.73 & 122.70 (1C)], 121.94 & 121.84 (1C), [80.88 & 80.45 & 80.40 (1C)], [55.70 & 55.61 & 55.24 & 55.18 (1C)], [39.42 & 39.35 & 39.08 & 39.01 (1C)], [32.54 & 32.35 & 32.06 (1C)], [25.36 & 25.05 & 24.88 & 24.81(1C)]. **IR (Neat)** $\nu_{\max}$ 2924, 1757, 1710, 1644, 1387, 1223, 1027, 1040, 889, 722 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_6\text{S}^+$ $[\text{M}+\text{H}]$, 504.1224; found 504.1228.

4.6.3.10. Gram Scale Synthesis of 20 / 4:

A 100 mL sealed tube equipped with magnetic stir bar was charged with $\text{Pd}(\text{OAc})_2$ (10 mol%, 89 / 94 mg, 0.4 / 0.42 mmol), the substrate **1a** / **1b** (1.0 g, 4.0 / 4.20 mmol), AgF (0.507 / 0.532 g, 4.0 / 4.20 mmol), 2-iodo benzamide derivatives **2d** / **2e** (1.6 / 2.22 g, 6.0 / 6.3 mmol), and **L12** (15 mol%, 65 / 68 mg, 0.6 / 0.63 mmol) in air. Then, HFIP (0.05 M) was added. The reaction mixture was stirred at 70 $^\circ\text{C}$ for 36 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (DCM), filtered through a small Celite pad, and concentrated in vacuo. The crude reaction mixture was extracted with CH_2Cl_2 and washed with saturated NaOH (0.05 M)

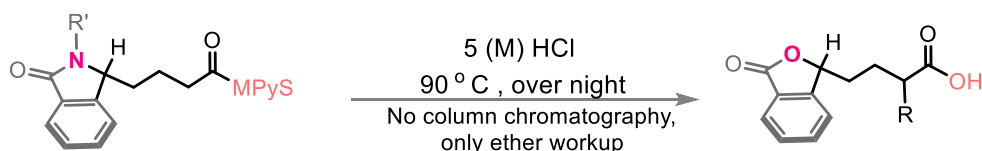
solution and concentrated in vacuo. Finally, the reaction mixture was purified on neutral alumina using hexane/EtOAc eluent to afford the desired products **20** / **4** in 65 / 73 % yield, respectively.



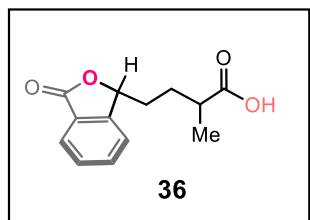
4.6.3.11. General Procedure for N–O atom exchange reaction (GP–4):

A 5 mL screw capped tube equipped with a magnetic stir bar was charged with substrate **20** / **4** / **31** (0.1 mmol), then, 0.5 M HCl was added. The reaction mixture was stirred at 70 °C for 8 h. Upon completion, the reaction mixture was cooled to room temperature, washed with water and extracted with Et₂O and the solvent was evaporated in vacuo. The crude carboxylic acids were obtained without column chromatography.

Next, the water layer was neutralized with 2N NaOH to maintain pH = 7. The water layer was extracted by EtOAc, dried over Na₂SO₄, and concentrated under vacuum to give the corresponding S-methyl-S-(2-pyridyl) sulfoximine in 55-60% yield.



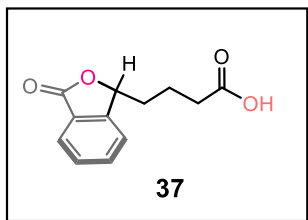
2-Methyl-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl) butanoic acid (**36**):



Following the general procedure GP–4, the compound **36** (22 mg, 92%, colorless thick liquid; **dr** = **1:1**) was prepared from the **21**. ¹H NMR (500 MHz, CDCl₃) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.68 (tt, *J* = 7.6, 1.3 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 5.49 (ddd, *J* = 19.4, 7.9, 3.8 Hz, 1H), 2.54–2.35 (m, 1H), 2.15–2.02 (m, 1H), 1.87–1.53 (m, 3H), 1.21 (t, *J* = 7.2 Hz, 3H) The desired peak for carboxylic acid group is not detected by ¹H NMR. ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 182.04 & 181.93 (1C),

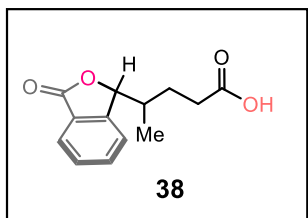
170.6, 149.6, 134.2, 129.3, 126.1, 125.9, 121.8, 81.16 & 80.85 (1C), 39.08 & 38.81 (1C), 32.51 & 32.01 (1C), 28.77 & 28.30 (1C), 17.08 & 16.99 (1C). **IR (Neat)** $\nu_{\max}$ 2920, 1743, 1464, 1286, 1214, 1060, 927, 742 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{13}\text{H}_{15}\text{O}_4^+$ [M+H], 235.0965; found 235.0971.

2-Methyl-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl) butanoic acid (**37**):



Following the general procedure GP-4, the compound **37** (20 mg, 84%, yellow solid) was prepared from the **4**. **^1H NMR (500 MHz, CDCl_3)** δ 7.93 (d, J = 7.6 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 5.56–5.44 (m, 1H), 2.57–2.36 (m, 2H), 2.27–2.10 (m, 1H), 1.85 (qd, J = 15.4, 8.1 Hz, 3H). The desired peak for carboxylic acid group is not detected by ^1H NMR. **$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3)** δ 178.48, 170.48, 149.53, 134.14, 129.27, 126.08, 125.84, 121.75, 80.88, 33.87, 33.28, 20.08. **IR (Neat)** $\nu_{\max}$ 2916, 1745, 1287, 1214, 1053, 945, 751 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{12}\text{H}_{13}\text{O}_4^+$ [M+H], 221.0808; found 221.0809.

4-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)pentanoic acid (**38**):

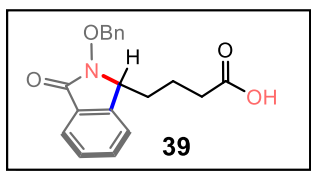


Following the general procedure GP-4, the compound **38** (18 mg, 75%, colorless thick liquid; **dr** = 1:1) was prepared from the **30**. **^1H NMR (500 MHz, CDCl_3)** δ 7.91 (d, J = 7.6 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.45 (dd, J = 17.1, 7.6 Hz, 1H), 5.62–5.30 (m, 1H), 2.67–2.05 (m, 3H), 2.10–1.74 (m, 1H), 1.66–1.45 (m, 1H), 1.09 & 0.67 (two d, J = 6.8 Hz, 3H). The desired peak for carboxylic acid group is not detected by ^1H NMR. **$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)** δ 178.72 & 178.56 (1C), 170.72 & 170.55 (1C), 148.68 & 148.13 (1C), 134.12 & 134.01 (1C), 129.32 & 129.23 (1C), 126.82 & 126.64 (1C), 125.85 & 125.80 (1C), 122.31 & 121.85 (1C), 85.00 & 83.82 (1C), 36.38 & 36.20 (1C), 31.92 & 31.43 (1C), 28.35 & 25.19 (1C), 15.42 & 12.07 (1C). **IR (Neat)** $\nu_{\max}$ 2921, 1706, 1285, 1264, 1061, 984, 734 cm^{-1} . **HRMS (ESI-TOF)** m/z : calcd. for $\text{C}_{13}\text{H}_{14}\text{O}_4^+$ [M+Na], 257.0785; found 257.0784.

4.6.3.12. Procedure for the cleavage of MPyS:

To a solution of **4** (0.1 mmol) in MeOH: H₂O (1:1 mL) was added NaOH (2.0 equiv). The resulting mixture was refluxed overnight. After reaction completion, MeOH was evaporated and the reaction mixture was neutralized with 2N HCl. The crude mixture was then extracted with EtOAc, dried over Na₂SO₄, and concentrated under vacuum to give the corresponding carboxylic acid.

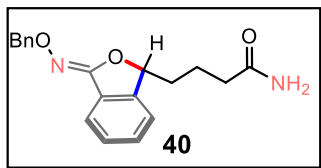
Next, the water layer was neutralized with 2N NaOH to strictly maintain pH = 7. The water layer was extracted by EtOAc, dried over Na₂SO₄, and concentrated under vacuum to give the corresponding S-methyl-S-(2-pyridyl) sulfoximine in 63% yield.

4-(2-(Benzyloxy)-3-oxoisindolin-1-yl) butanoic acid (39**):**

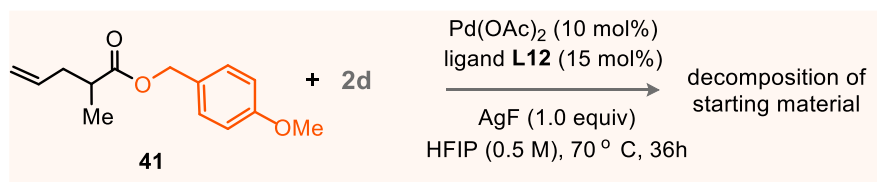
The compound **39** (31 mg, 95%, colorless thick liquid) was prepared from the hydrolysis of **4**. ¹H NMR (500 MHz, CDCl₃) δ 7.69–7.27 (m, 9H), 5.66 (s, 1H), 5.17 (s, 2H), 2.42 (bs, 2H), 2.14 (bs, 1H), 1.98–1.72 (m, *J* = 46.0 Hz, 3H). The desired peak for carboxylic acid group is not detected by ¹H NMR. ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 178.8, 156.6, 144.0, 138.0, 130.9, 129.0, 128.4, 128.3, 127.8, 125.8, 122.0, 121.2, 85.7, 76.7, 34.2, 33.5, 19.4. IR (Neat) ν_{max} 2923, 1705, 1655, 1362, 1209, 1017, 926, 736 cm⁻¹. HRMS (ESI-TOF) *m/z*: calcd. for C₁₉H₂₀NO₄⁺ [*M*+H], 326.1387; found 326.1391.

4.6.3.13. Procedure for the reductive cleavage of MPyS:

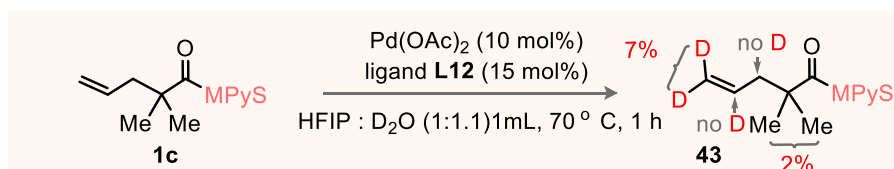
To a solution of **4** (47 mg, 0.1 mmol) in anhydrous THF (2.0 mL) were added successively CH₃OH (0.04 mL, 3.5 mmol) and a solution of SmI₂ (0.1 M, 4.0 mL, 1.40 mmol) in THF under nitrogen atmosphere. After stirring at room temperature for 3 h, the reaction was quenched with saturated aqueous NH₄Cl solution and the mixture was extracted with EtOAc. The combined extracts were washed with aqueous Na₂S₂O₃ solution, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (DCM / MeOH = 10:1) to afford the desired product **40**.

4-(2-(Benzyloxy)-3-oxoisindolin-1-yl) butanamide (40):

The compound **40** (27 mg, 82%, colorless solid) was prepared from **4**. ^1H NMR (500 MHz, CDCl_3) δ 7.67 (dt, $J = 7.7, 1.0$ Hz, 1H), 7.47 (tdd, $J = 5.8, 3.2, 1.4$ Hz, 3H), 7.42–7.35 (m, 3H), 7.34–7.29 (m, 2H), 5.83 (bd, 1H), 5.65 (dd, $J = 6.6, 3.7$ Hz, 1H), 5.46 (bs, 1H), 5.15 (s, 2H), 2.35–2.21 (m, 2H), 2.17–2.11 (m, 1H), 1.86–1.75 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 175.0, 156.5, 144.1, 137.7, 130.9, 128.8, 128.5, 128.4, 128.0, 121.9, 121.3, 86.4, 76.8, 35.0, 33.8, 21.0. IR (Neat) ν_{max} 3337, 3204, 2923, 1656, 1362, 1019, 926, 739 cm^{-1} . HRMS (ESI-TOF) m/z : calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_3^+$ $[\text{M}+\text{H}]$, 325.1547; found 325.1544.

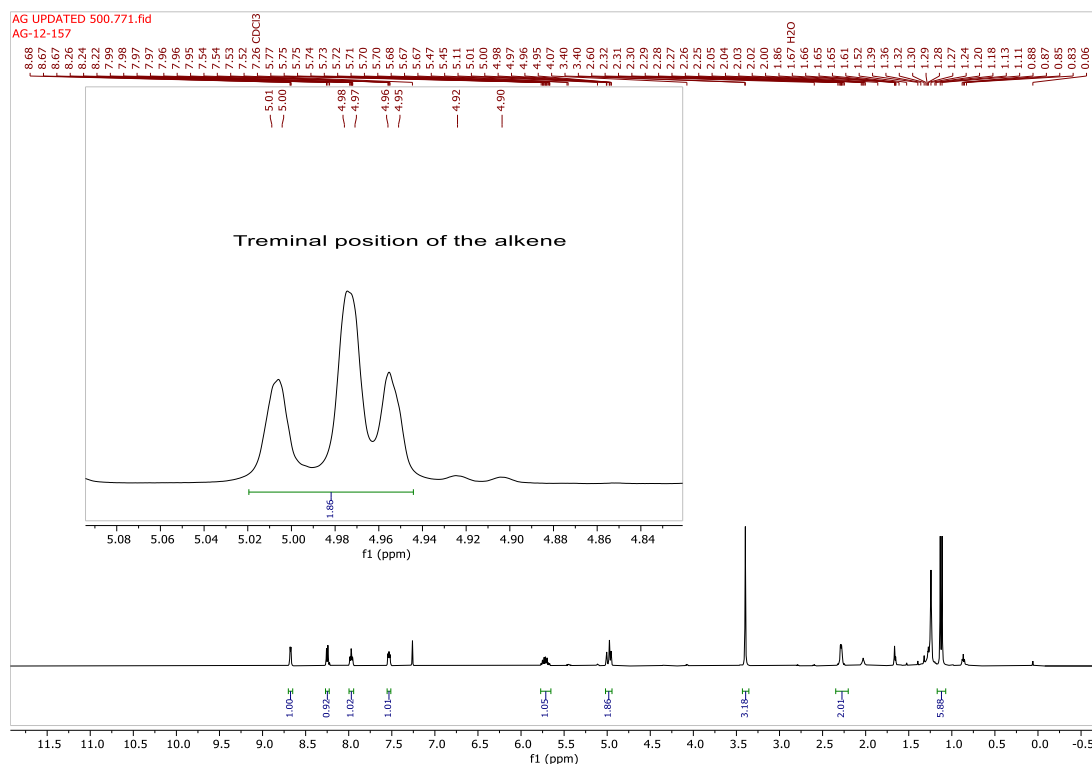
4.6.3.14. Procedure for the reaction proceeded in the absence of MPyS directing group

A 5 mL screw capped tube equipped with a magnetic stir bar was charged with $\text{Pd}(\text{OAc})_2$ (10 mol%, 4.5 mg), the 4-methoxybenzyl-2-methylpent-4-enoate (**41**; 0.2 mmol), AgF (0.2 mmol, 24 mg), 2-iodo-benzamide (**2d**; 0.3 mmol), and **L12** (15 mol%, 3.26 mg) in air. Then, a solvent HFIP was added. The reaction mixture was stirred at 70 °C for 36 h. Finally, we could observe decomposition of starting material with multiple spots in TLC.

4.6.3.15. Procedure for the H/D exchange reaction

A 5 mL screw capped tube equipped with a magnetic stir bar was charged with $\text{Pd}(\text{OAc})_2$ (10 mol%, 2.24 mg), and 3,3-dimethyl-N-(methyl(oxo)(pyridin-2-yl))- λ^6 -

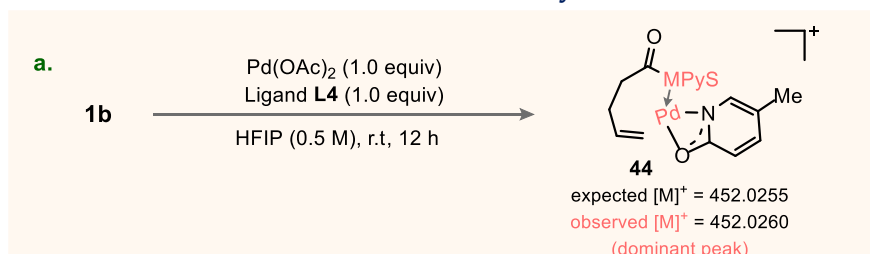
sulfaneylidene)pent-4-enamide (**1c**; 0.1 mmol). Then, HFIP and D₂O (1:1.1) ratio solvent was added. The reaction mixture was stirred at 70 °C for 1 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with CH₂Cl₂ (DCM), and purified through column chromatography. Finally, 7% H/D exchange was observed at terminal position of the alkene (detected by ¹H NMR analysis).



% Deuteration at terminal position of the alkene: $[(2.00-1.86)/2.000] \times 100\% = 7\%$

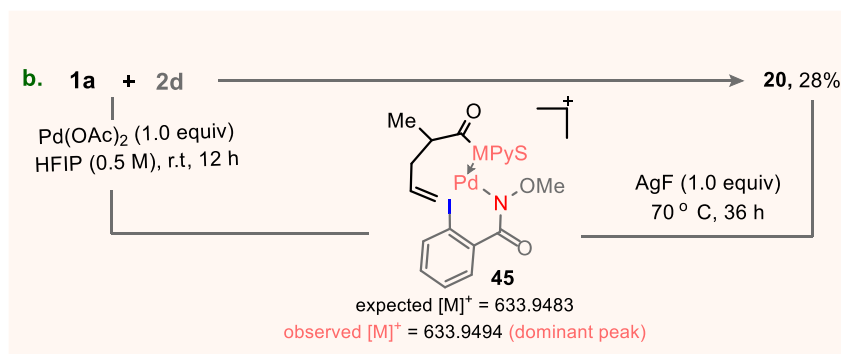
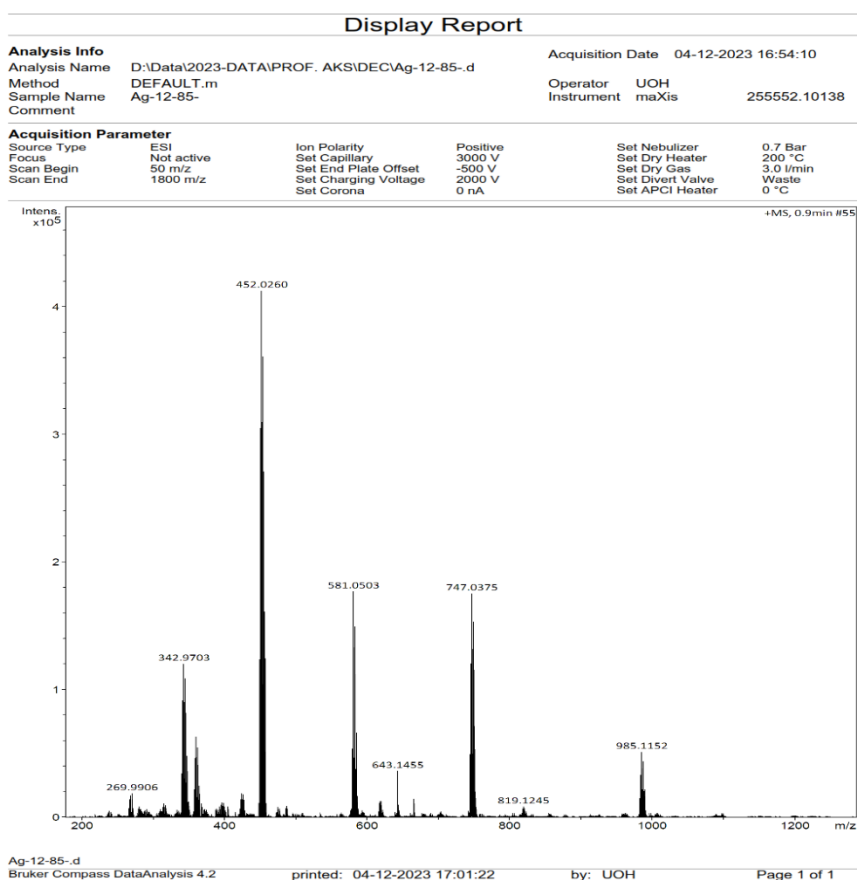
% Deuteration at two α -methyl group: $[(6.00-5.88)/6.00] \times 100\% = 2\%$

4.6.3.16. Procedure for the stoichiometric HRMS study

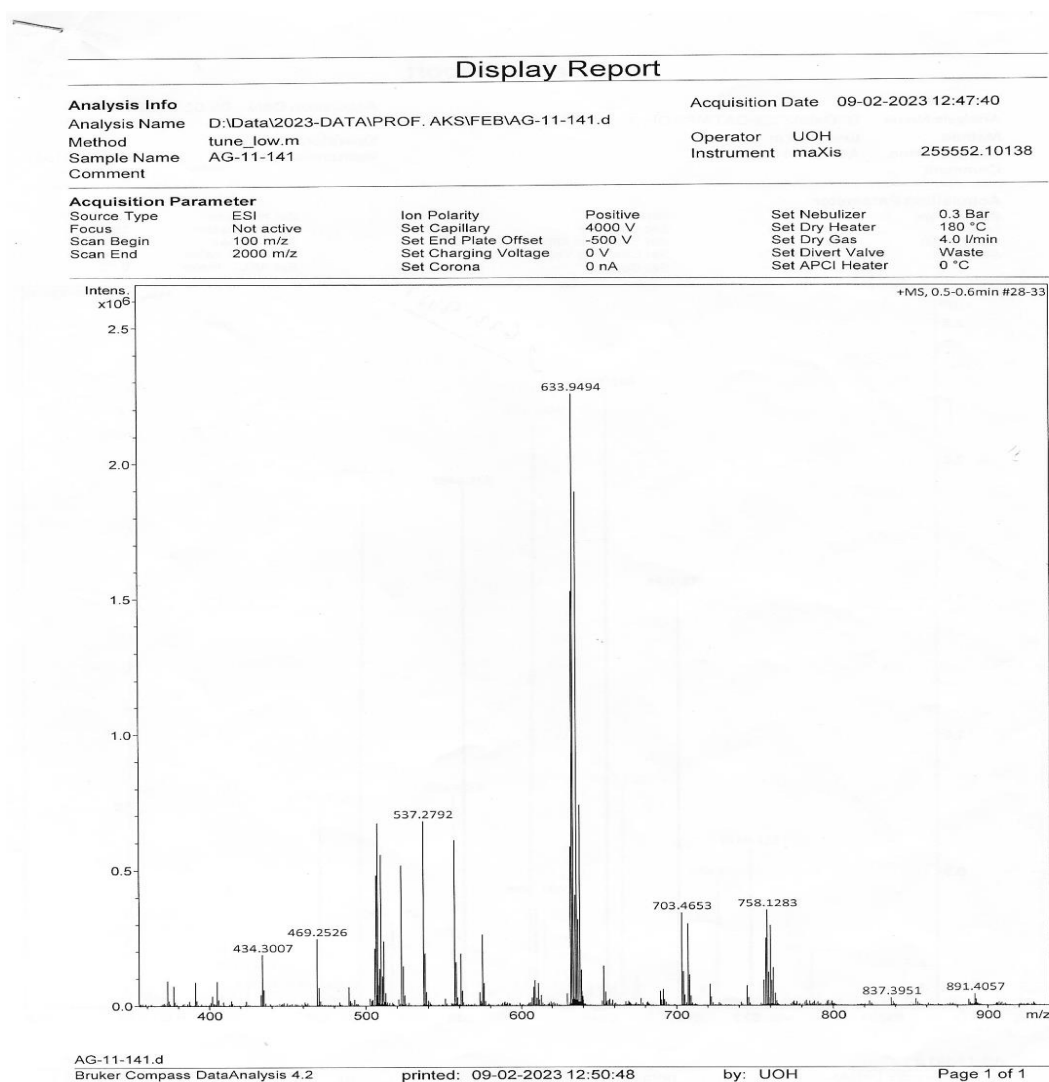


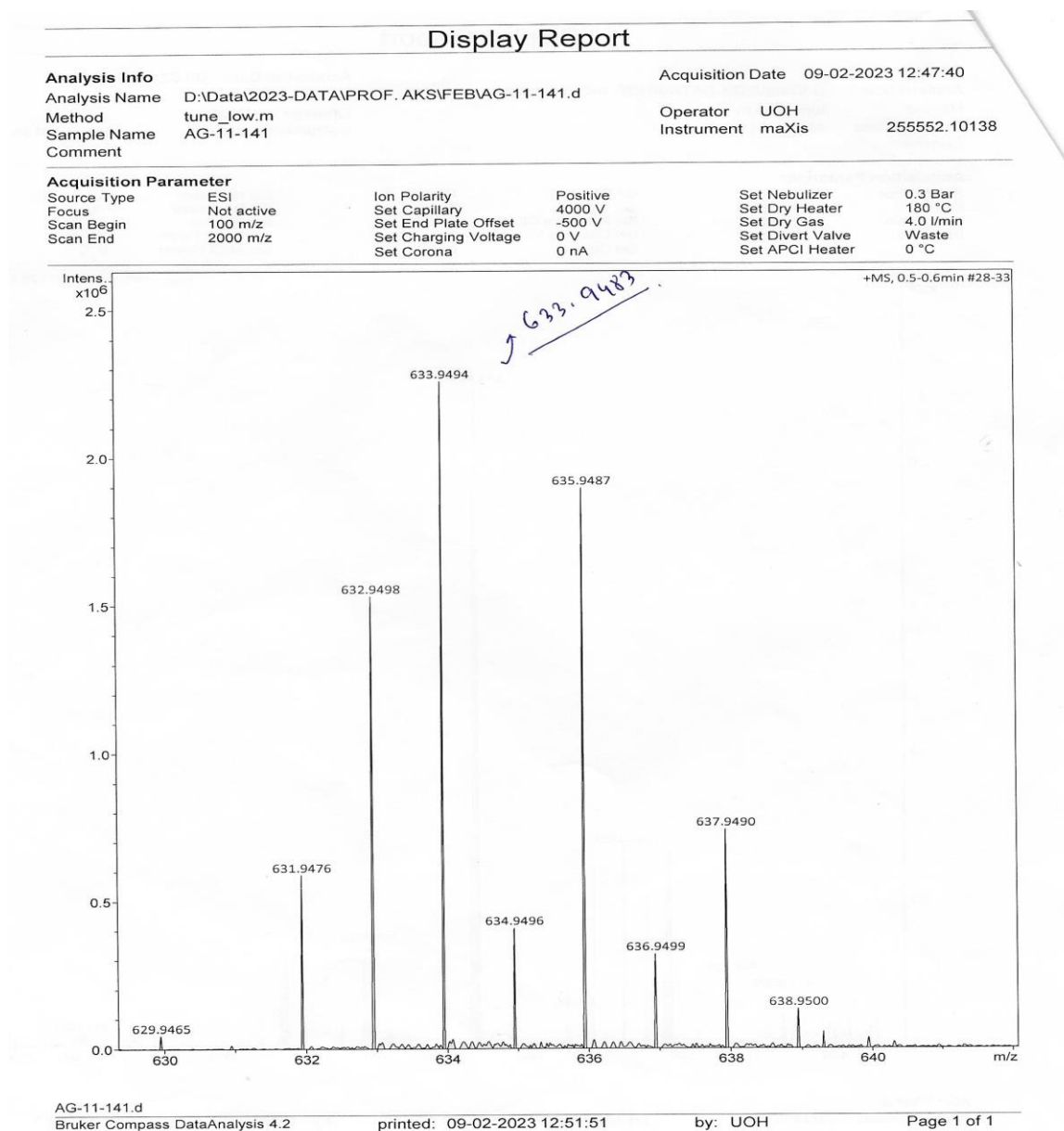
4.6.4..a A 5 mL screw capped tube equipped with a magnetic stir bar was charged with Pd(OAc)₂ (0.1 mmol), ligand **L12** (0.1 mmol), and N-(methyl(oxo)(pyridin-2-yl)- λ^6 -sulfaneylidene)pent-4-enamide (**1b**; 0.1 mmol). Then HFIP solvent was added. The

reaction mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was diluted with CH₂Cl₂ (DCM), filtered through a small Celite pad, and concentrated in vacuo. Finally, a small aliquot was taken for ESI-MS analysis. The aforementioned pallado-complex **44** has been observed as a dominant peak. **HRMS (ESI-TOF) m/z**: calcd. for C₁₇H₂₀N₃O₃PdS+ [M+H], 452.0255; found 452.0260. Despite our repeated trial, we failed to obtain single crystal of this intermediate.

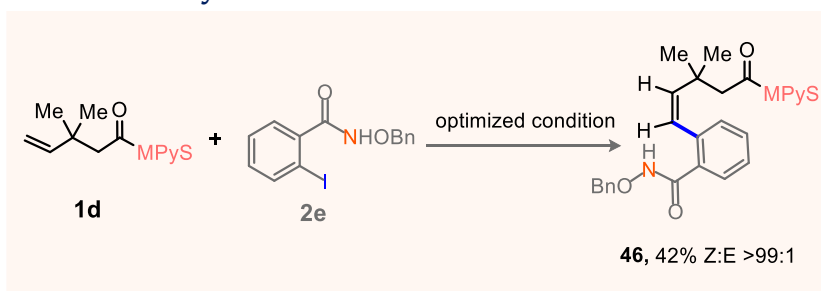


4.6.4.0.b A 5 mL screw capped tube equipped with a magnetic stir bar was charged with Pd(OAc)₂ (0.1 mmol), 2-methyl-N-(methyl(oxo)(pyridin-2-yl)-λ⁶-sulfaneylidene)pent-4-enamide (**1a**; 0.1 mmol), and 2-iodo-N-methoxybenzamide (**2d**). Then HFIP solvent was added. The reaction mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was diluted with MeOH, filtered through a small Celite pad, and concentrated in vacuo. Finally, a small aliquot was taken for ESI-MS analysis. The aforementioned pallado-complex **45** has been observed as a dominant peak. **HRMS (ESI-TOF)** m/z: calcd. for C₂₀H₂₃IN₃O₄PdS⁺ [M+H]⁺, 633.9483; found 633.9494. Next, Silver fluoride (0.1 mmol), and HFIP solvent were added to the reaction mixture, which eventually delivered isoindolinone derivative **20** in 28% isolated yield.



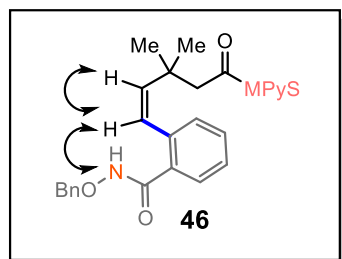


4.6.3.17. Procedure for δ -arylation of 1d with 3e



A 5 mL screw capped tube equipped with a magnetic stir bar was charged with Pd(OAc)₂ (10 mol%, 4.5 mg), the substrate **1d** (0.2 mmol), AgF (0.2 mmol, 24 mg), N-(benzyloxy)-2-iodo-benzamide **2e** (0.3 mmol), and **L12** (15 mol%, 3.26 mg) in air. Then, a solvent HFIP was added. The reaction mixture was stirred at 70 °C for 36 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with CH₂Cl₂ (DCM), filtered through a small Celite pad, and concentrated in vacuo. Finally, the reaction mixture was purified on neutral alumina using hexane/EtOAc eluent to afford the non-cyclized product **46**.

(Z)-N-(Benzyloxy)-2-(3,3-dimethyl-5-((methyl(oxo)(pyridin-2-yl)-λ⁶-sulfaneylidene) amino)-5-oxopent-1-en-1-yl) benzamide (46)



The compound **46** (41 mg, 42%, colorless thick liquid) was prepared from the reaction of **1d** and **2e**; the structure was confirmed by NOESY. ¹H NMR (500 MHz, CDCl₃) δ 9.36 (s, 1H), 8.38–8.34 (m, 1H), 8.15 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.79 (td, *J* = 7.8, 1.7 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 2H), 7.43–7.30 (m, 6H), 7.33–7.23 (m, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.07 (d, *J* = 16.1 Hz, 1H), 5.09 (q, *J* = 10.6 Hz, 2H), 3.30 (s, 3H), 2.43 (d, *J* = 2.1 Hz, 2H), 1.20 & 1.19 (two s, 6H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 181.0, 166.8, 156.7, 149.6, 143.3, 138.2, 136.7, 135.6, 131.6, 130.7, 129.4, 128.9, 128.6, 128.5, 127.1, 127.1, 127.0, 124.4, 123.6, 78.2, 51.4, 39.6, 36.6, 27.8, 27.5. IR (Neat) ν_{max} 2957, 1737, 1629, 1425, 1214, 1023, 976, 732 cm⁻¹. HRMS (ESI-TOF) *m/z*: calcd. For C₂₇H₃₀N₃O₄S⁺ [M+H], 492.1952; found 482.1949.

4.6.3.18. X-ray crystallography:

Single crystal X-ray data for the compound **37** and **40** were collected using the detector system [λ (Mo-K α) = 0.71073 Å] at 293K, graphite monochromator with a ω scan width of 0.3°, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software³⁰ was used for the intensity data acquisition and the SAINTPLUS Software³⁰ was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program,³⁰ 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-97,³¹ 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.

X-ray crystal structure and data for 37 and 40: The compound was recrystallized via vapor diffusion of DCM and Hexane.

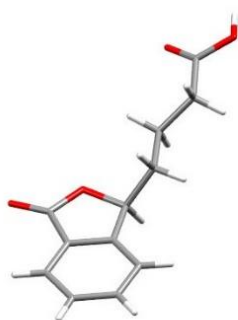


Figure 4.3. Molecular structures of compound **37**; thermal ellipsoids are set at 30% probability.

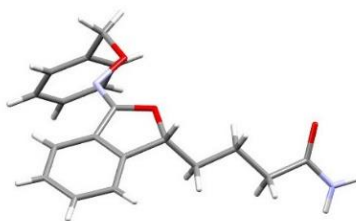


Figure 4.4. Molecular structures of compound **40**; thermal ellipsoids are set at 30% probability.

Table 4.7. Crystal data for **37** and **40**

Identification code	37	40
Formula	C ₁₂ H ₁₂ O ₄	C ₁₉ H ₂₀ N ₂ O ₃
<i>F_w</i>	220.22	344.0

<i>T</i> (K)	100 K	299K
λ (Å)	0.71073	0.71073
Crystal system	monoclinic	monoclinic
Space group	<i>P</i> 1 21 / <i>c</i> 1	<i>P</i> 1 21 1
<i>a</i> (Å)	4.6946 (10)	11.795(4)
<i>b</i> (Å)	21.106 (5)	4.7426(15)
<i>c</i> (Å)	10.785 (2)	17.542(6)
<i>a</i> (°)	90	90
<i>β</i> (°)	91.483 (9)	99.992(11)
<i>γ</i> (°)	90	90
<i>V</i> (Å ³)	707.82 (17)	966.4(6)
<i>Z</i>	4	2
ρ_{calcd} (Mg m ⁻³)	1.369	1.115
μ [mm ⁻¹]	0.103	0.076
total reflns	17827	30044
unique reflns	2447	3538
observed reflns	1744	2543
<i>R</i> ₁ [<i>I</i> > 2σ(<i>I</i>)]	0.0500	0.1551
<i>W</i> <i>r</i> ₂ [all]	0.1355	0.4085
GOF	1.076	1.516
Diffractionmeter	SMART APEX CCD	SMART APEX CCD
CCDC Number	2332477	2334996

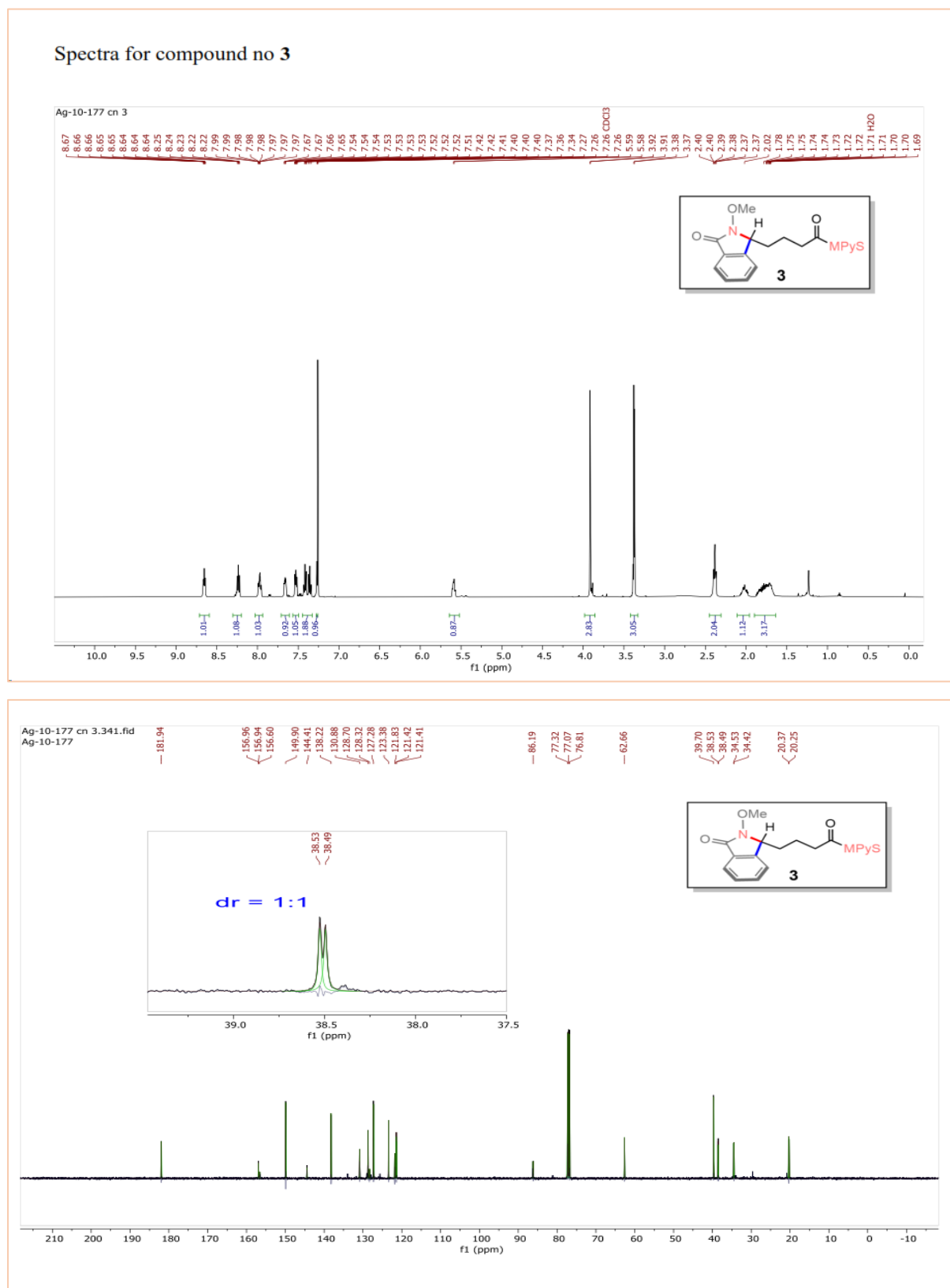
4.7. Reference

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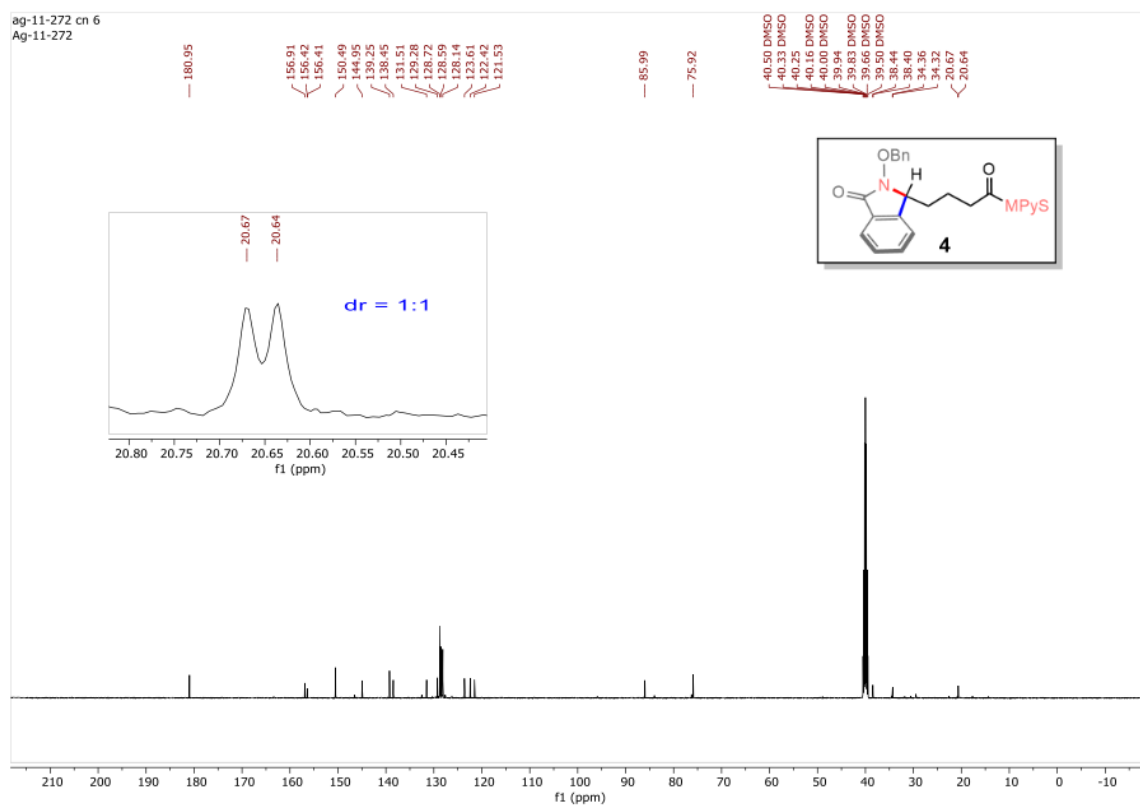
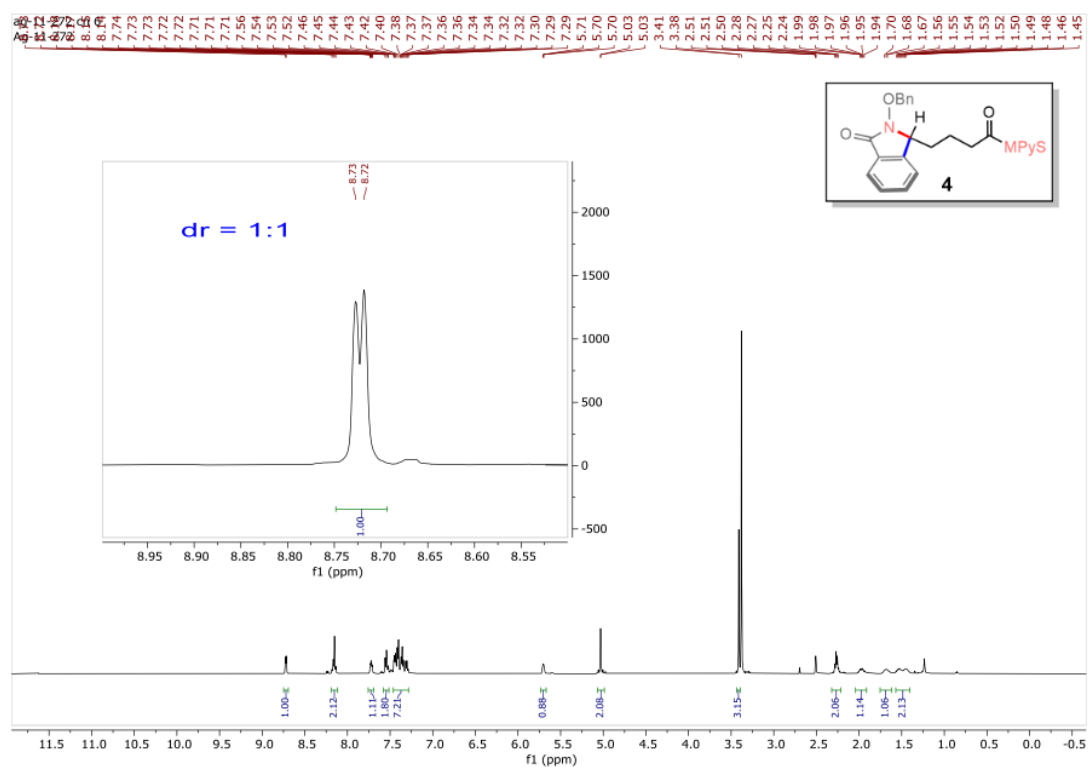
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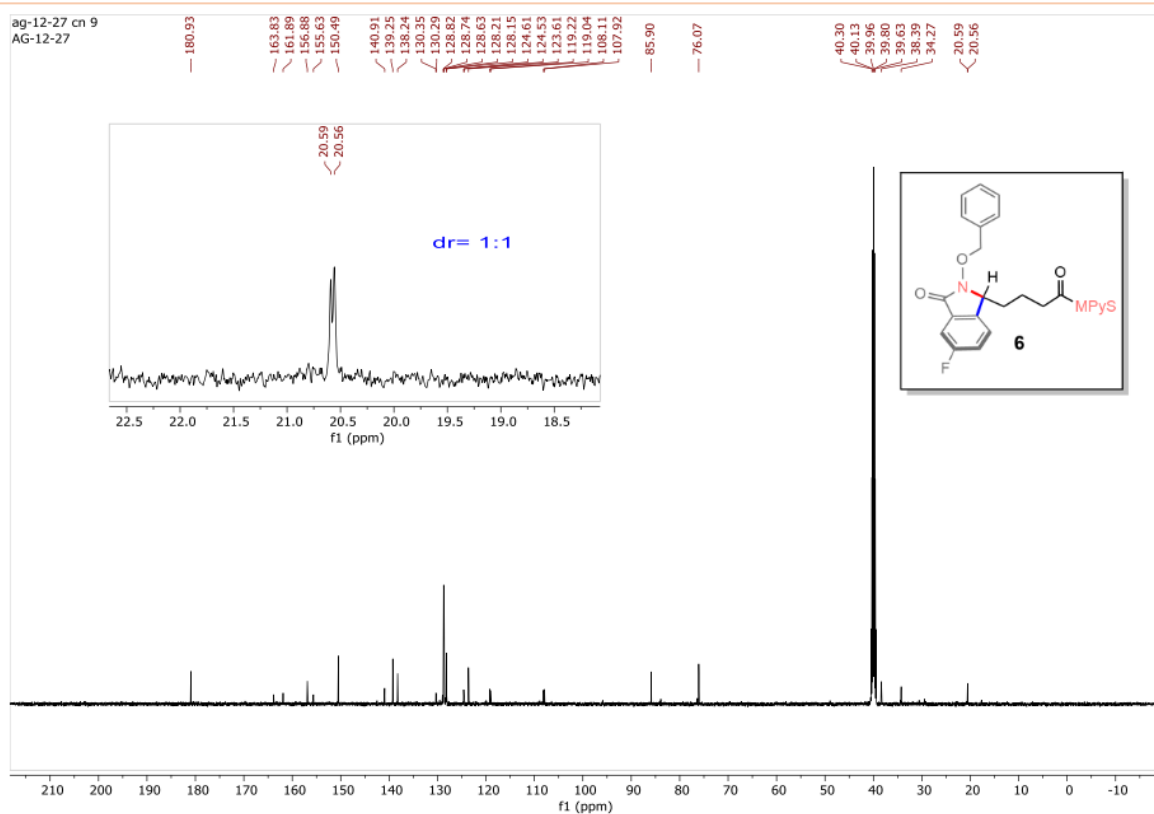
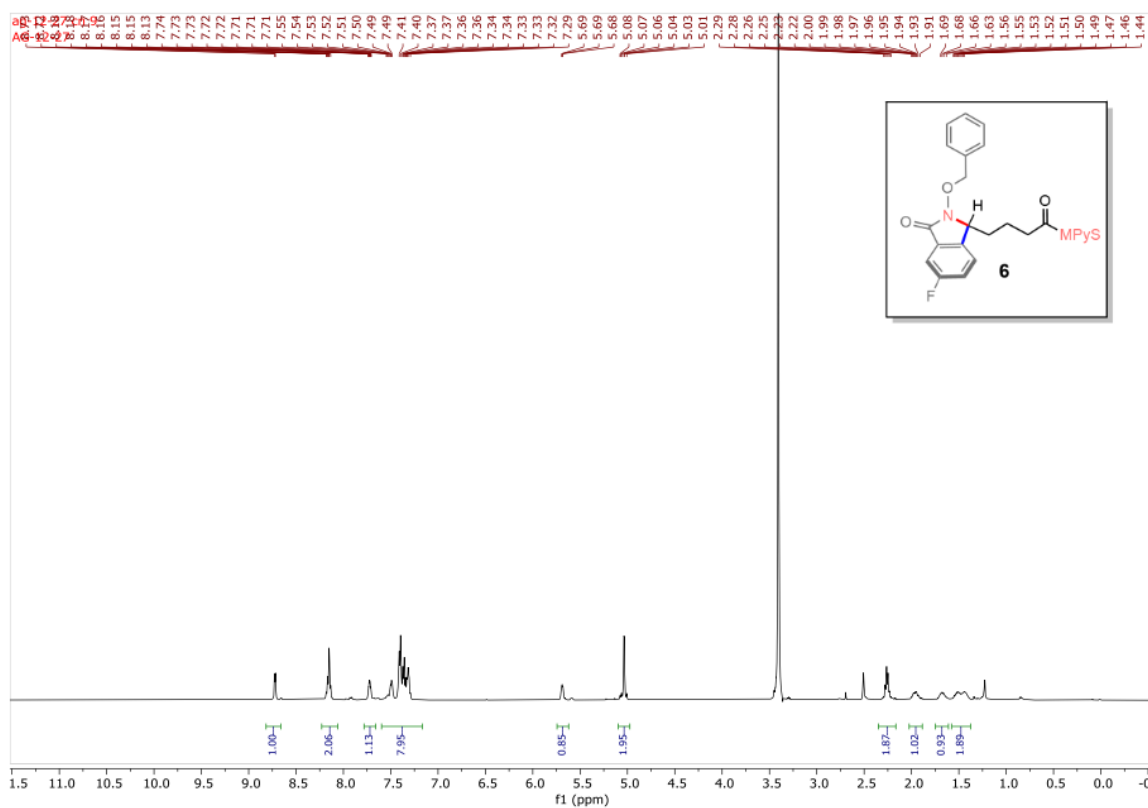
4.8. Spectra

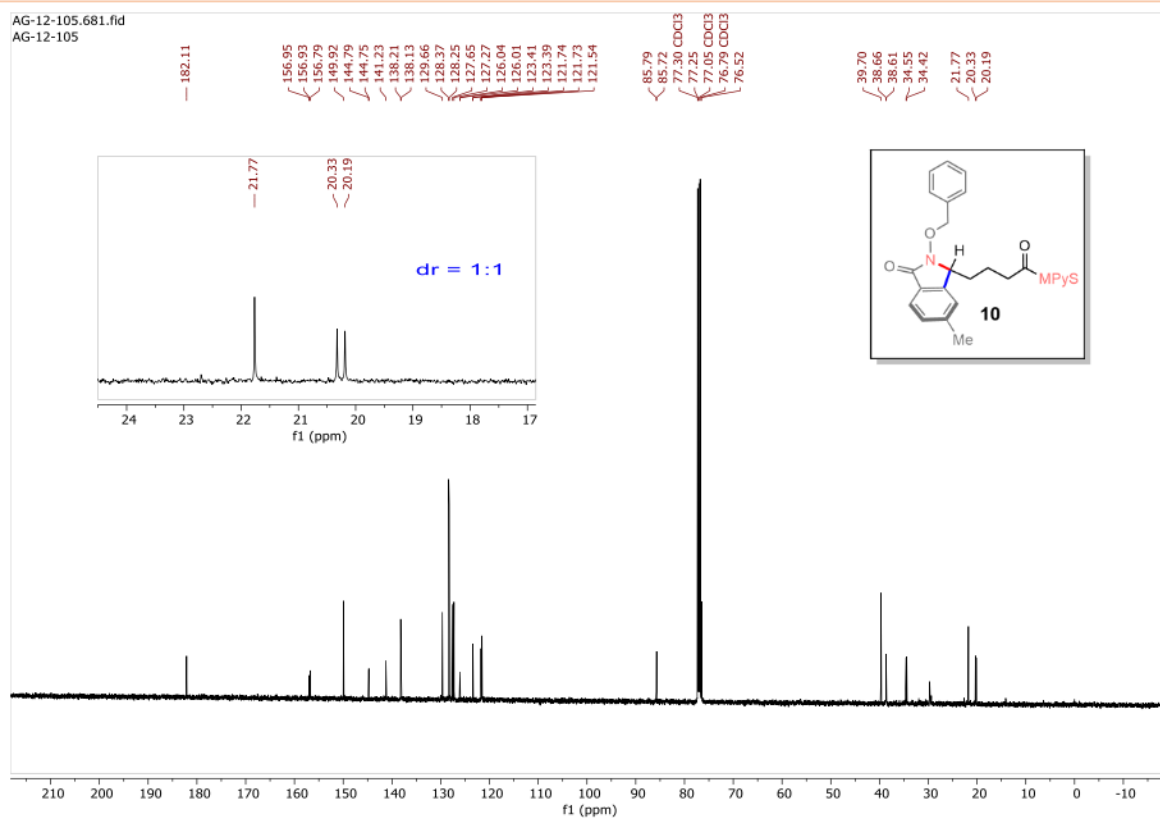
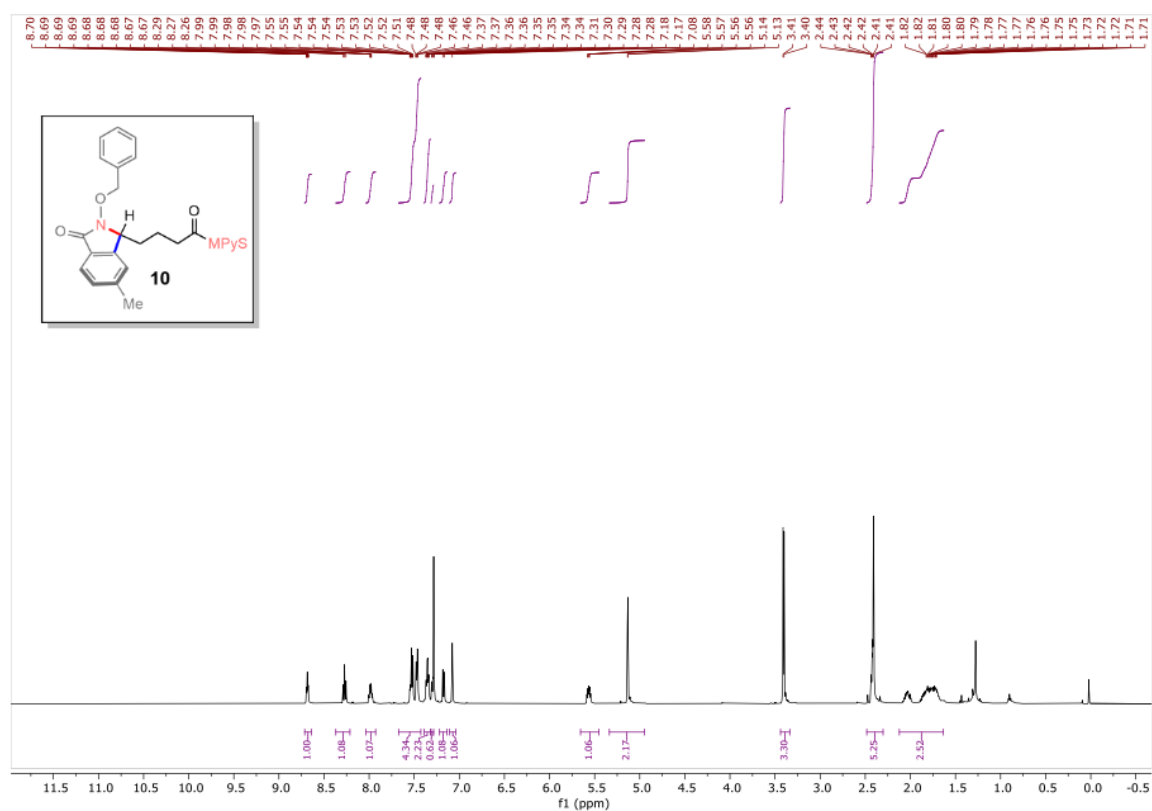


Spectra for compound no 4

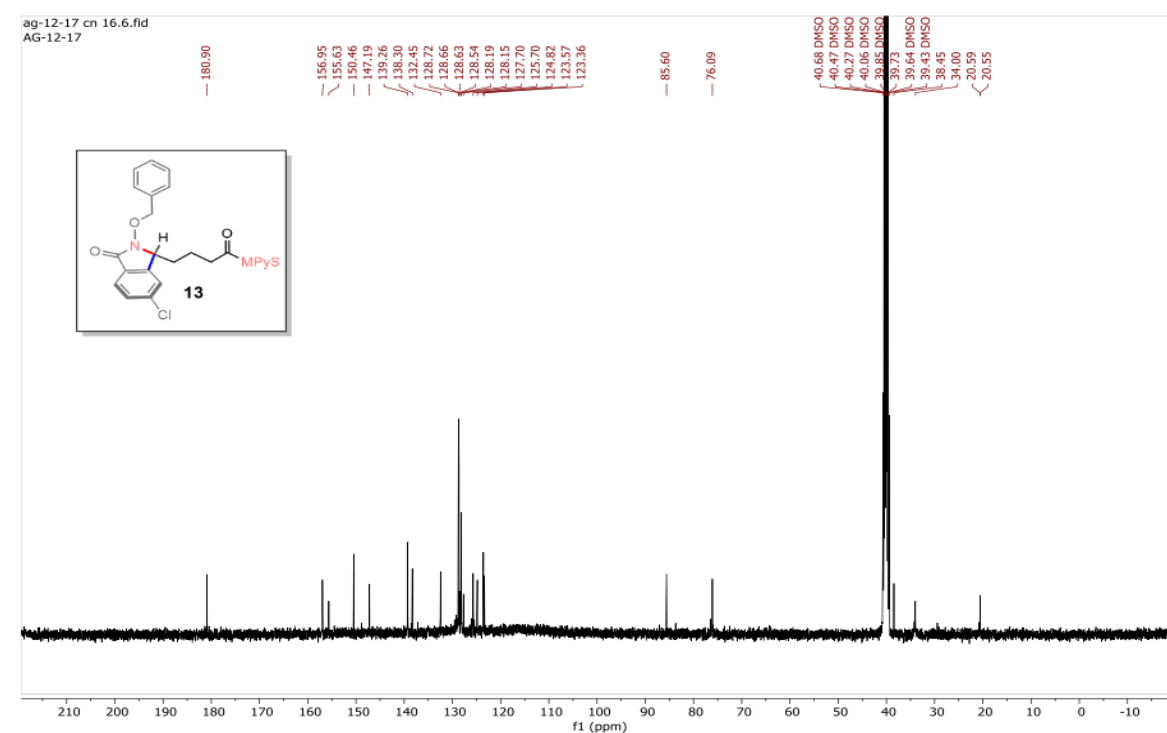
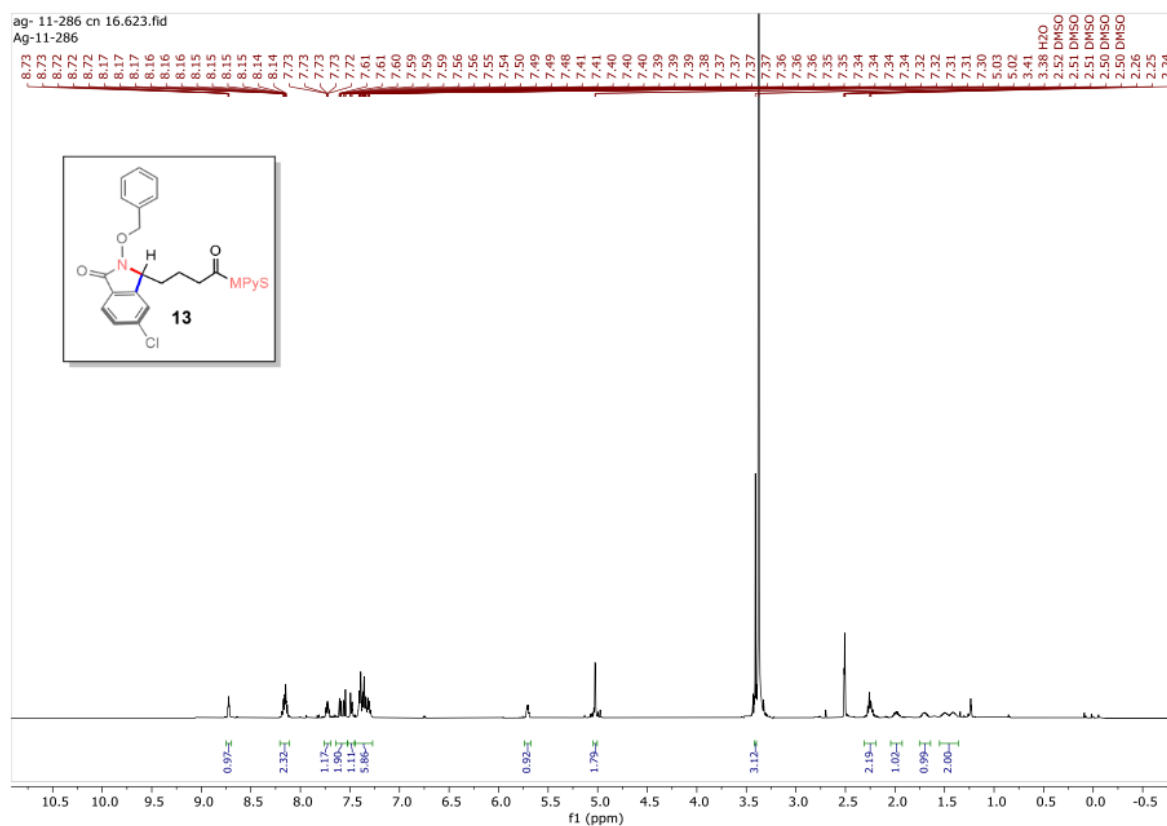


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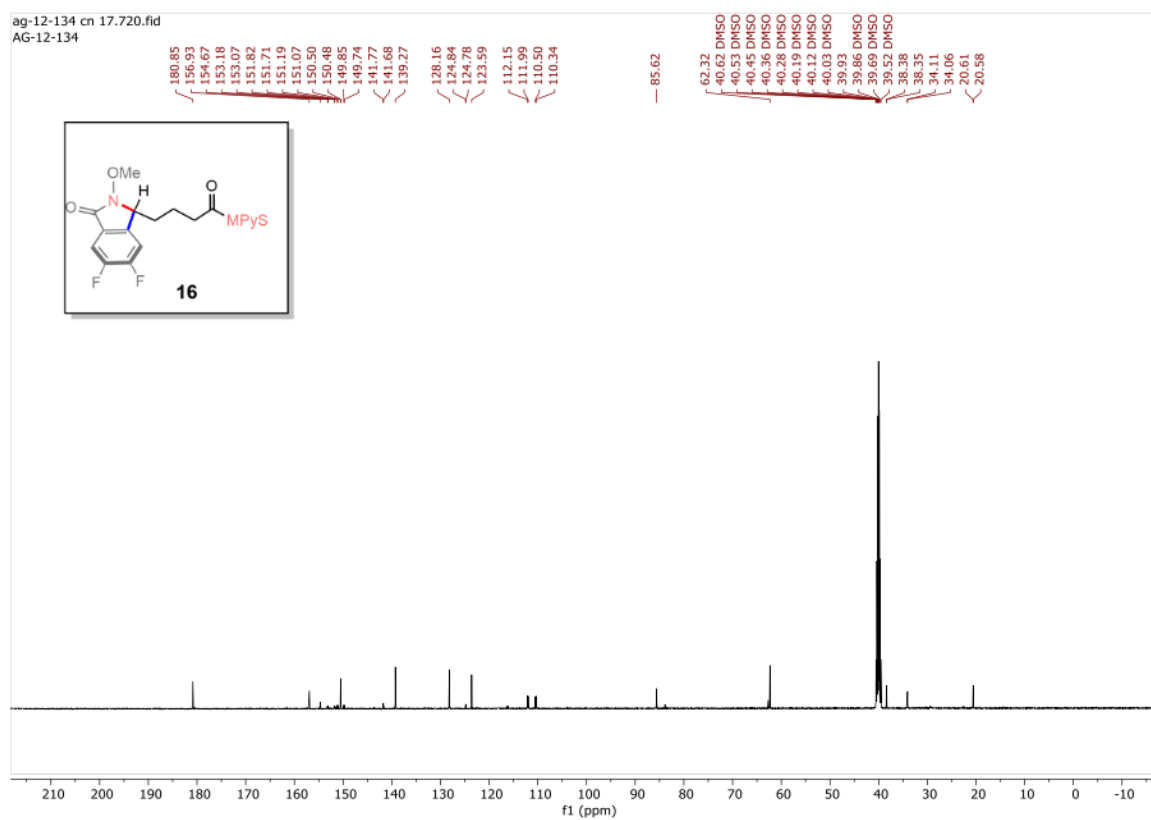
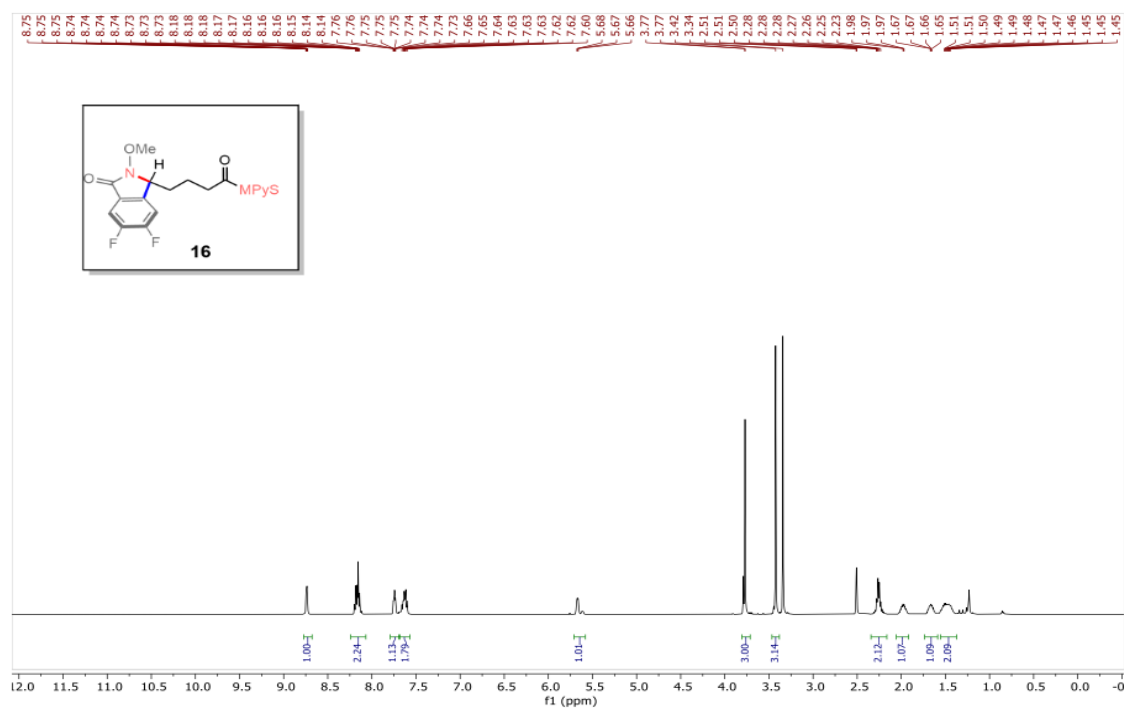


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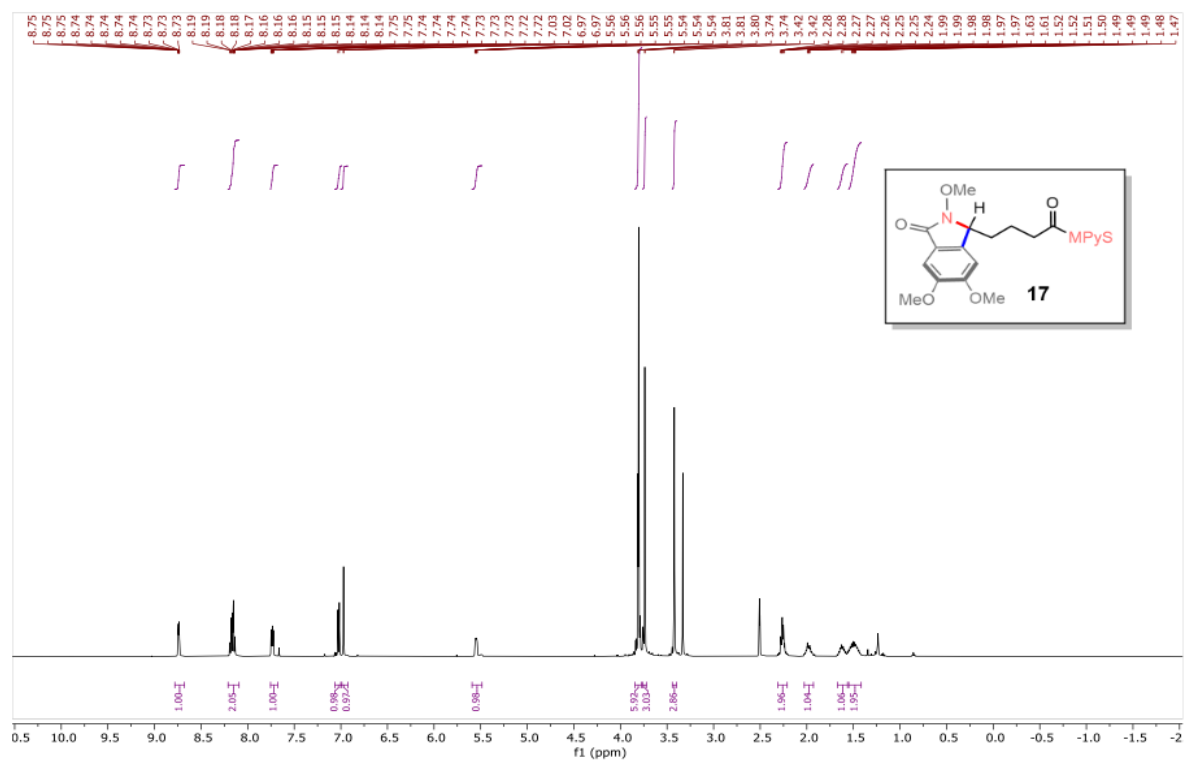
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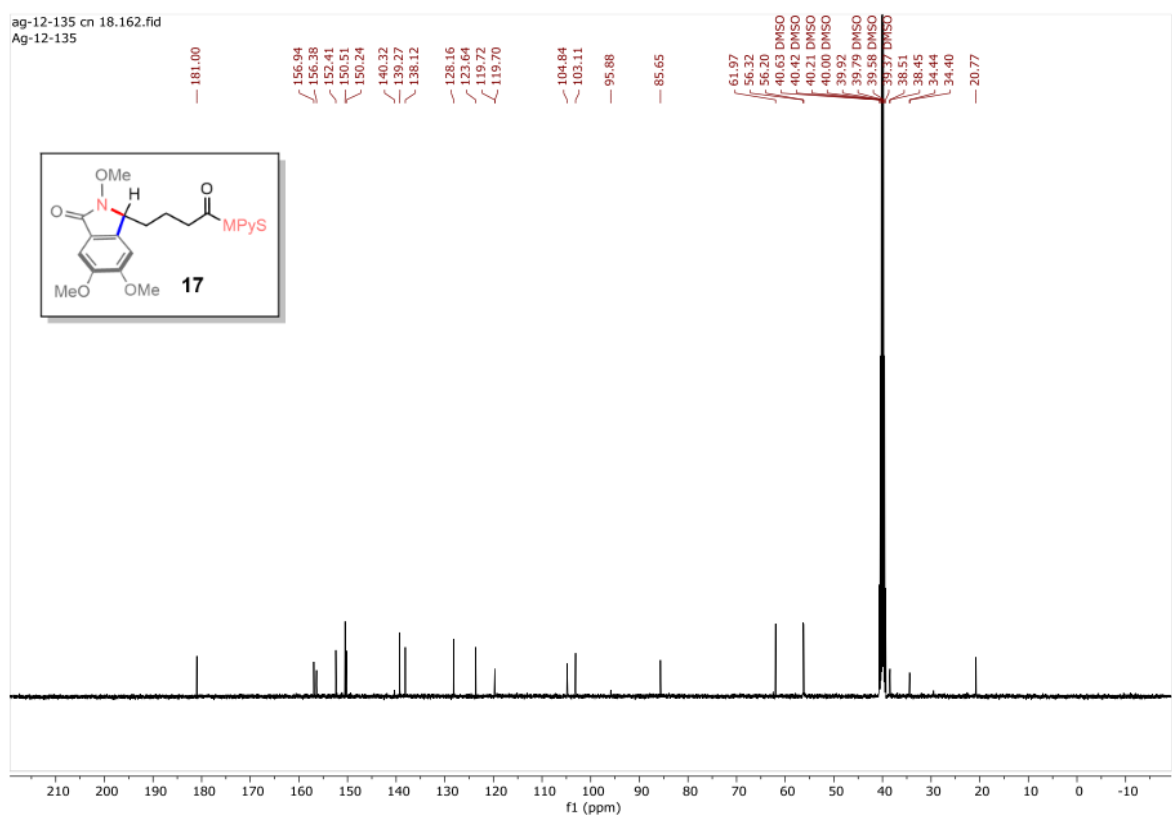
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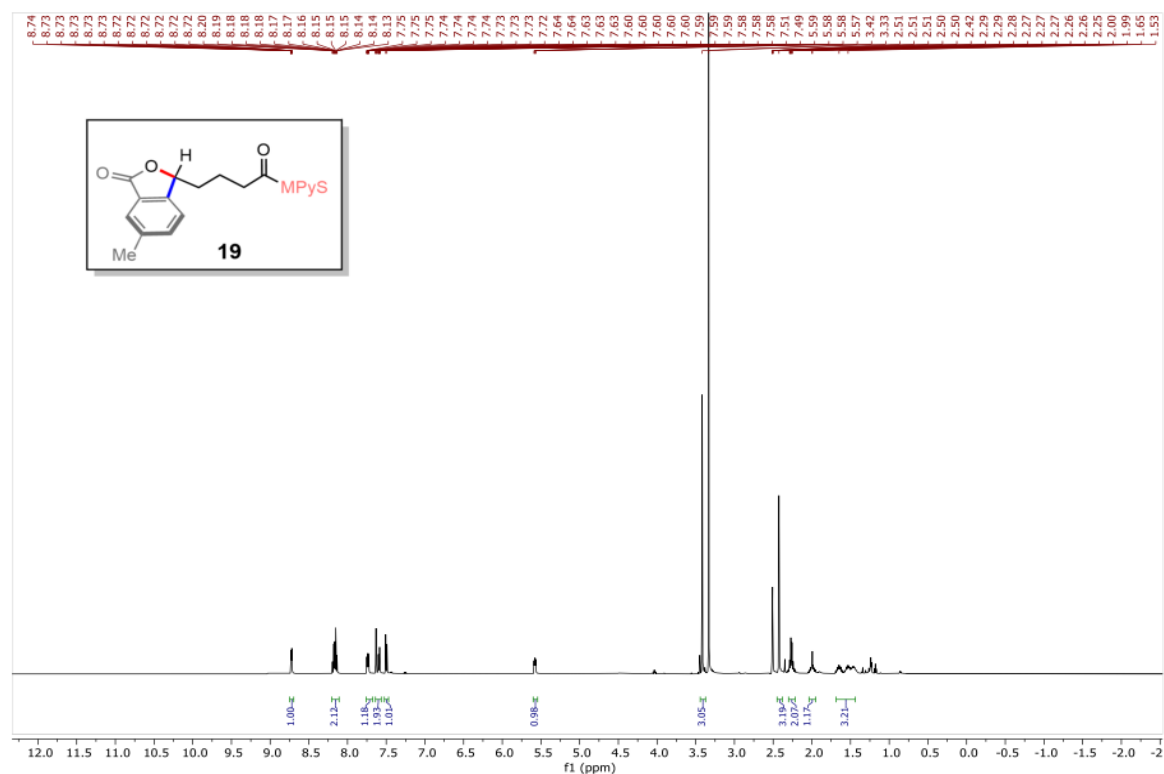
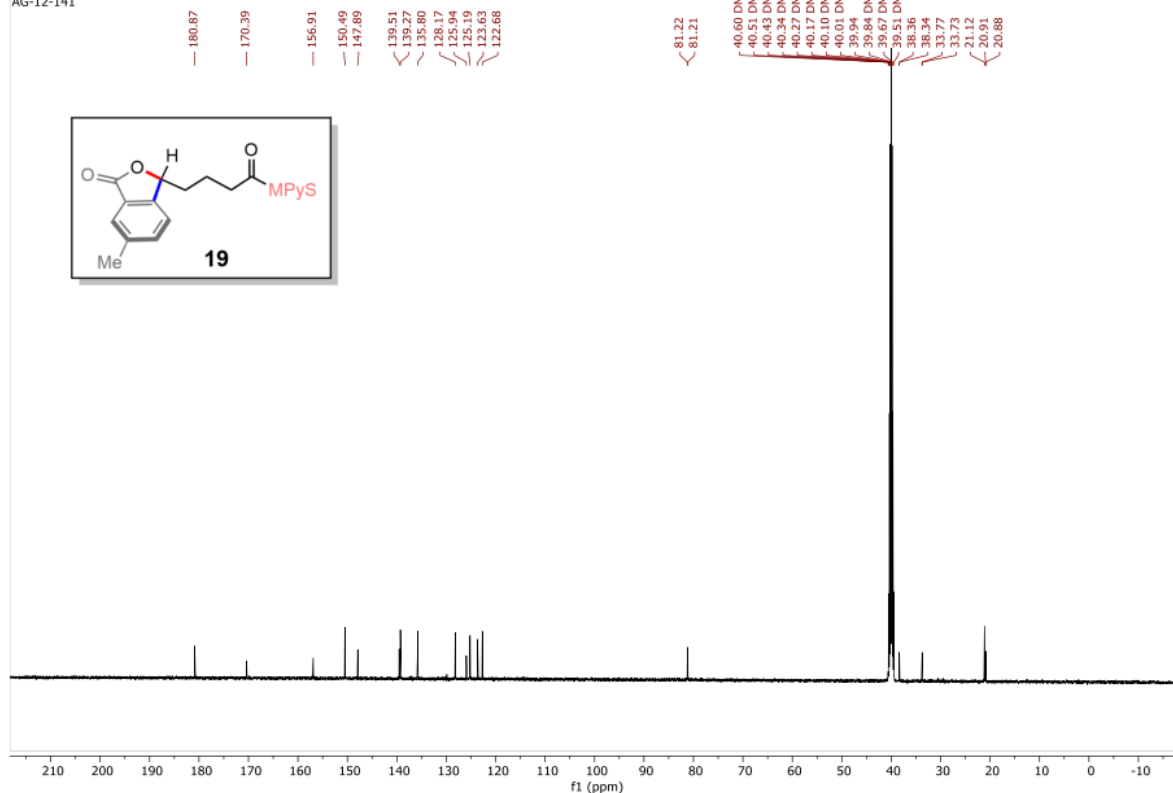


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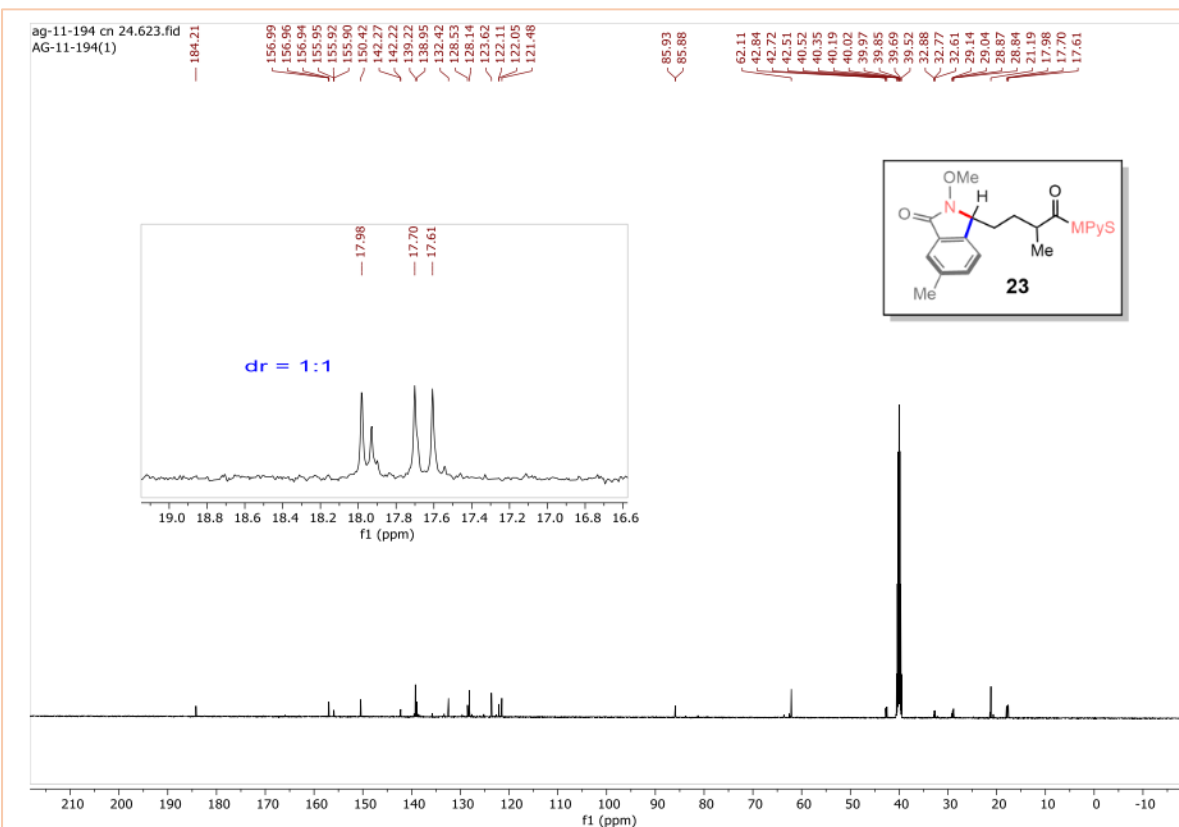
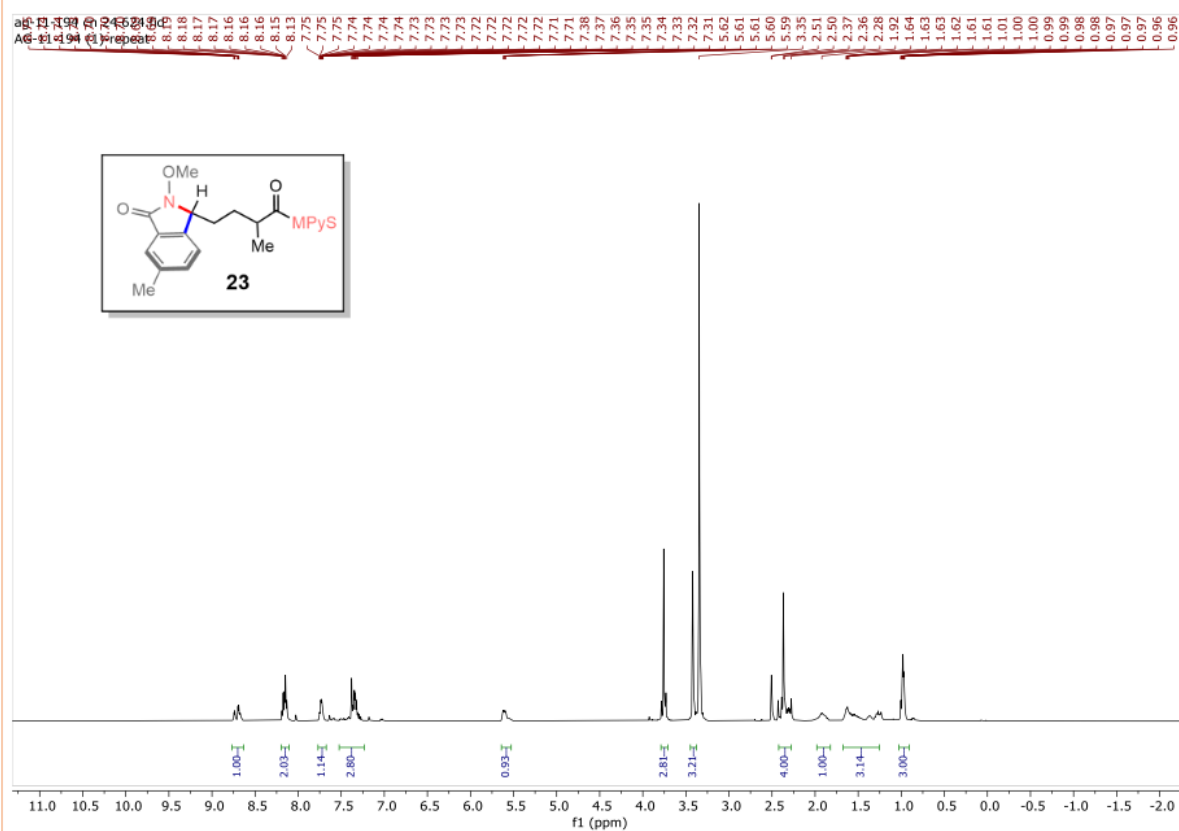


ag-12-135 cn 18.162.fid
Ag-12-135

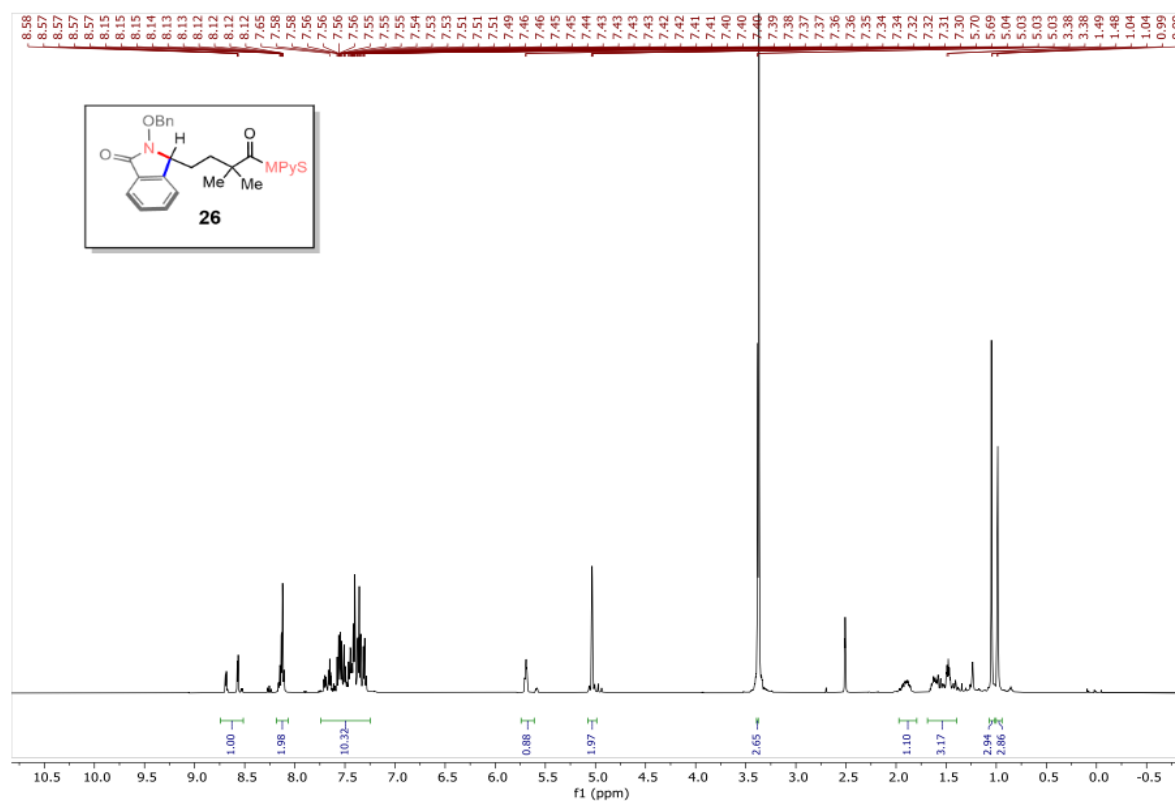


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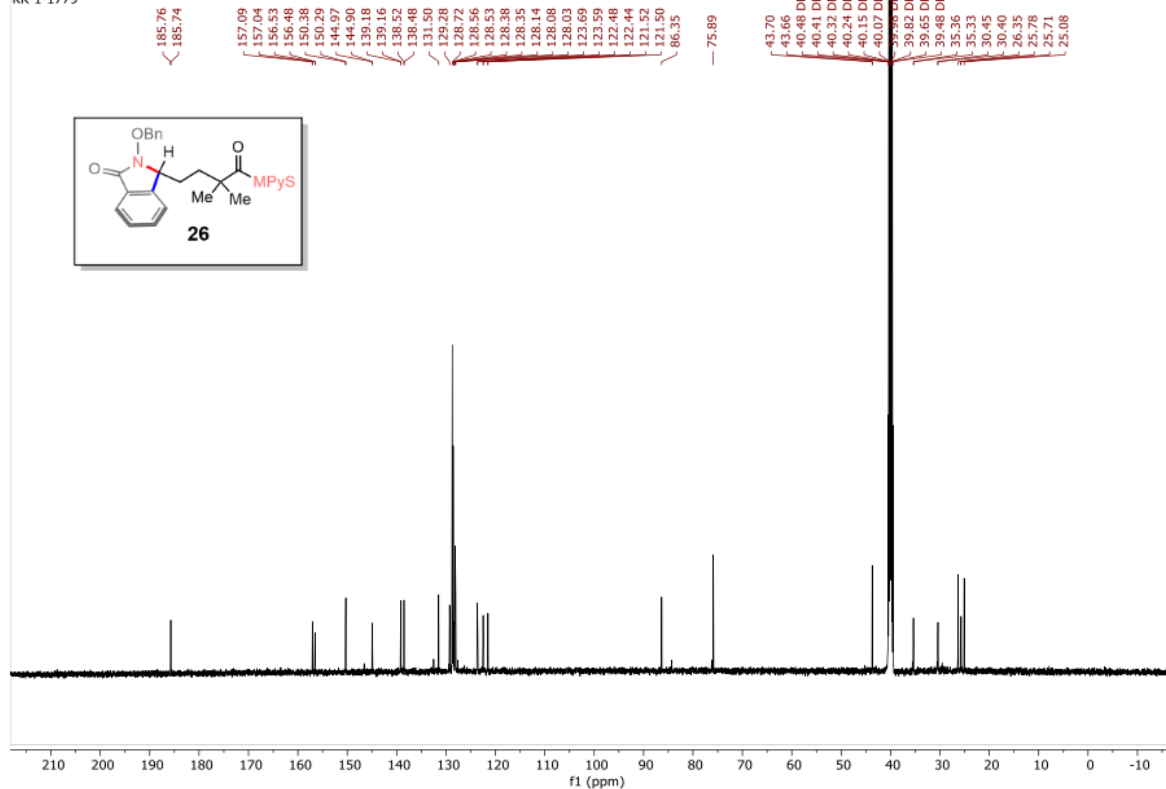
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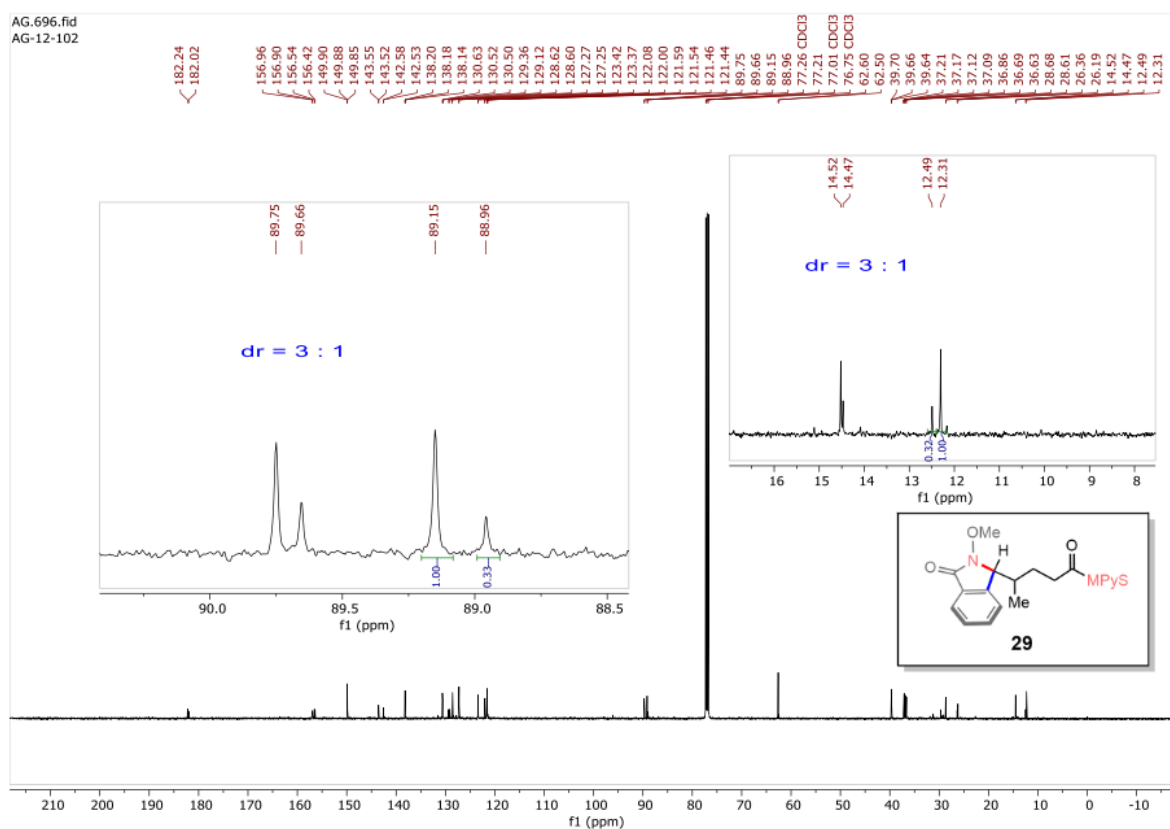
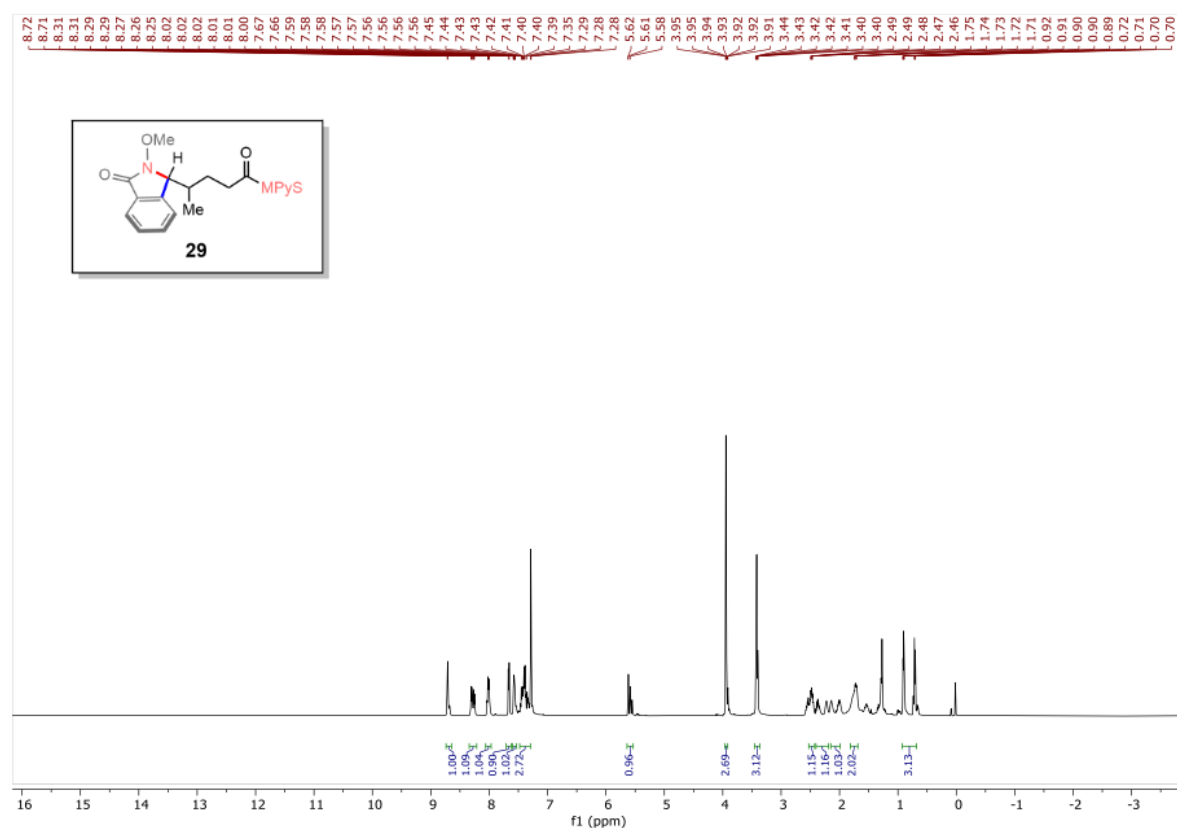


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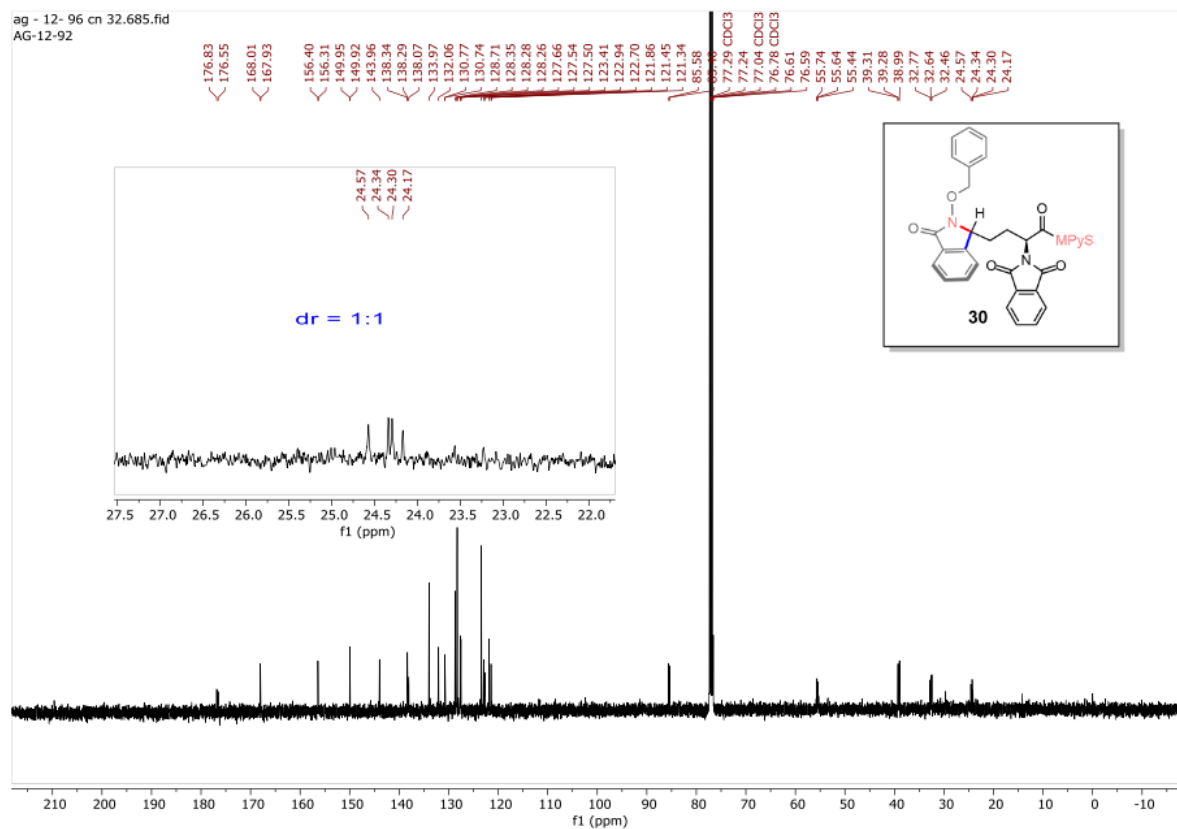
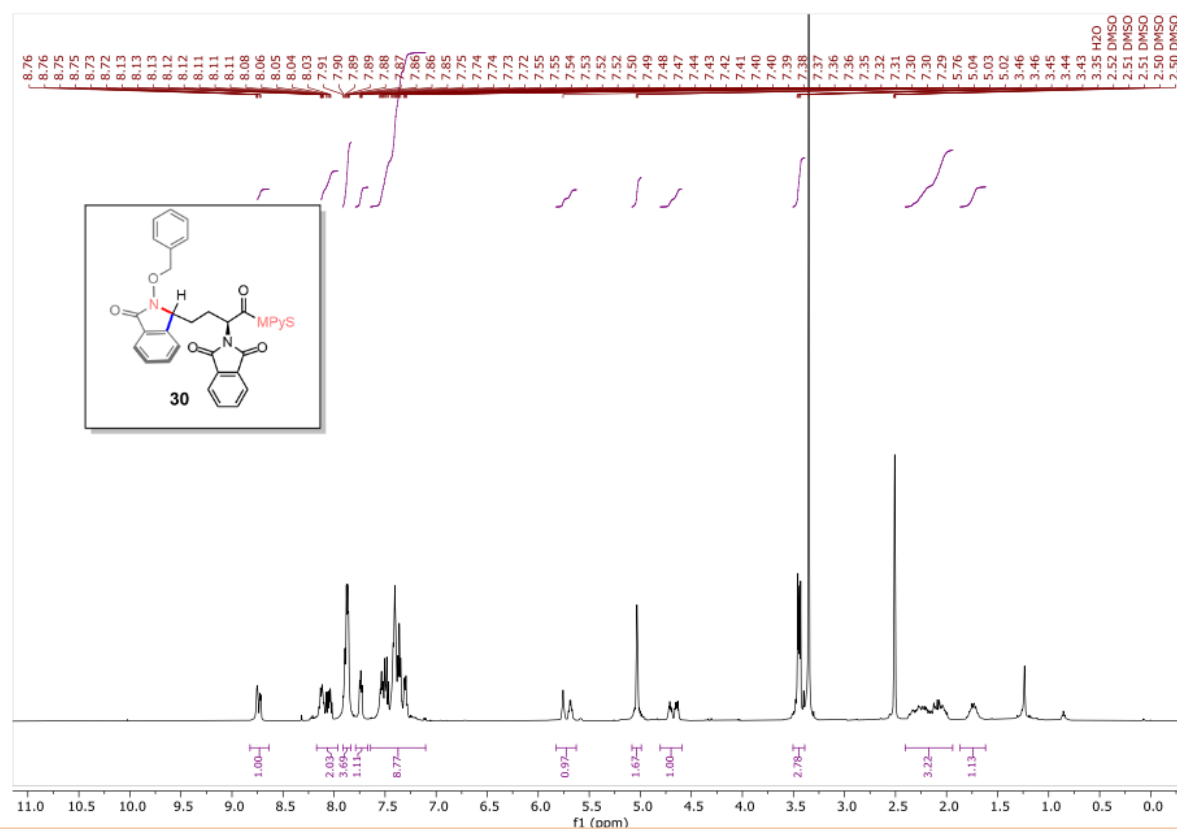


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KK-1-1779

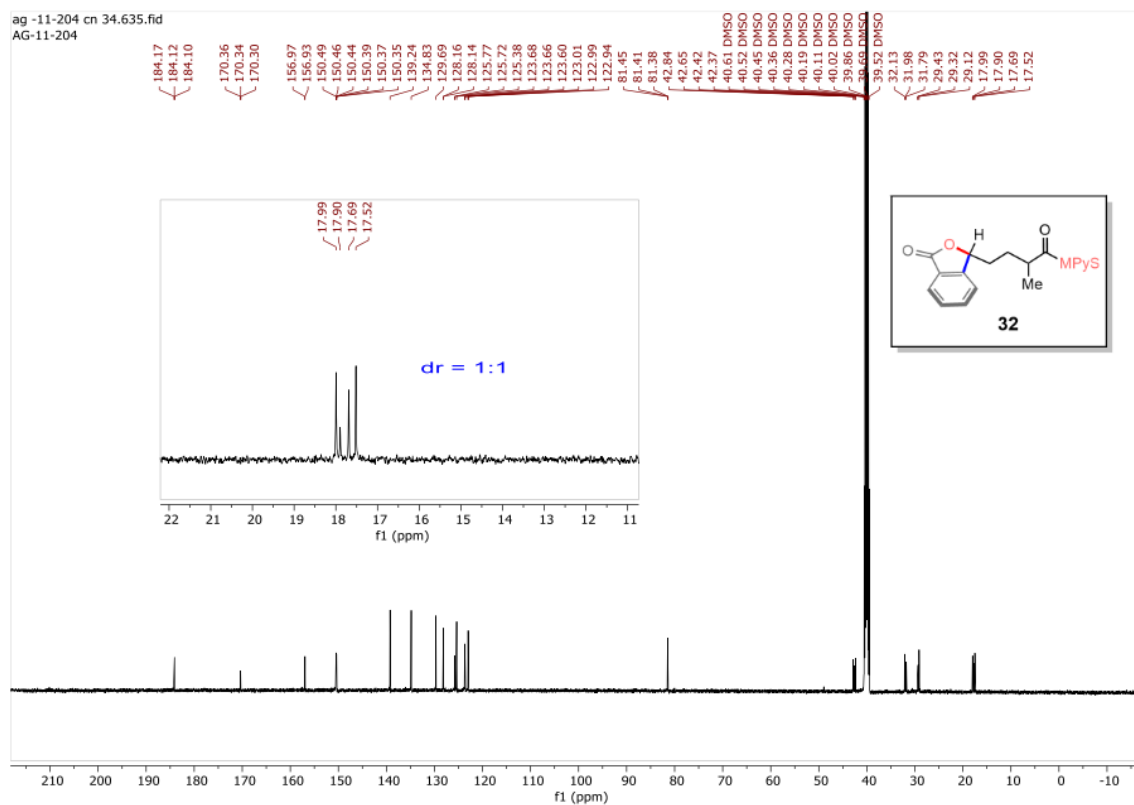
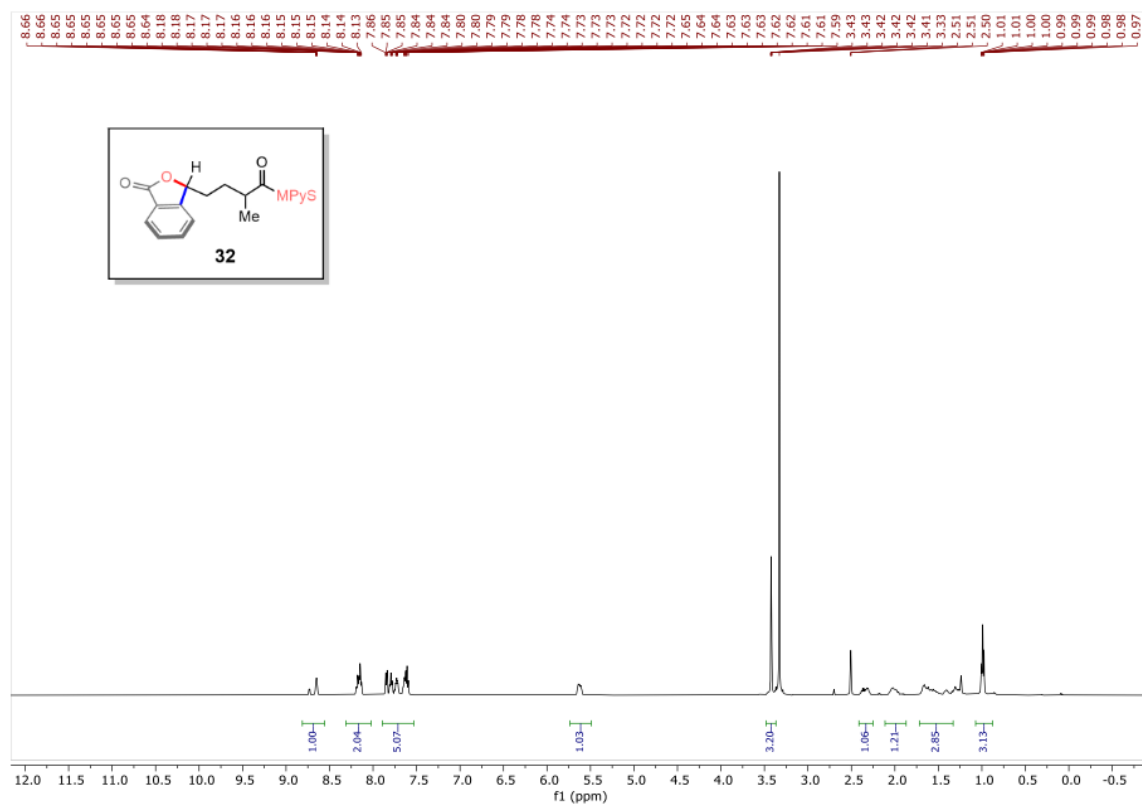


Spectra for compound no **29**

Spectra for compound no 30



Spectra for compound no 32



List of Publications

1. Sulfoximine-Assisted Unsymmetrical Twofold C–H Functionalization of Arenes
K. Ghosh†, A. Ghosh†, K. Mukherjee, R. K. Rit, A. K. Sahoo* (†K.G and A.G contributed equally)
J. Org. Chem. **2020**, *83*, 8618.
2. Harnessing sulfur and nitrogen in the cobalt (III)-catalyzed unsymmetrical double annulation of thioamides: probing the origin of chemo-and regio-selectivity
M. Shankar, A. Saha, S. Sau, **A. Ghosh**, V. Gandon*, A. K. Sahoo*
Chem. Sci. **2021**, *12*, 6393.
3. Sulfur and Nitrogen Modulated One-Pot Double Annulation of Arenes
M. Shankar, A. Saha, **A. Ghosh**, S. Sau, A. K. Sahoo*
J. Org. Chem. **2021**, *86*, 14942.
4. Cobalt-Catalyzed Thioamide Directed C (arene)–H Annulation with Ynamide: Regioselective Access to 2-Amidoindenones
S. Sau, **A. Ghosh**, M. Shankar, M. P. Gogoi, A. K. Sahoo*
Org. Lett. **2022**, *24*, 9508.
5. Palladium (II)-Catalyzed Annulative Difunctionalization of Two Inert C(sp³)–H Bonds by a Bifunctional Reagent
A. Ghosh, N. Grimblat, S. Sau, A. Saha, V. Gandon*, A. K. Sahoo*
ACS Catal. **2023**, *13*, 7627.
6. A Three-Component Arene Difunctionalization: Merger of C (sp³)/(sp²)–H Bond Addition
A. Ghosh, K. Kondalarao, S. Sau, A. Saha, V. Gandon *, A. K. Sahoo*
Angew. Chem. Int. Ed. **2023**, e202314395.
7. δ-Annulative 1,1- Difunctionalization of Unactivated Alkenes: Synthesis of α-substituted Isoindolinones
A. Ghosh, K. Kondalarao, A. K. Sahoo* [*Communicated*]

Conference Attended

1. Palladium (II)-Catalyzed Annulative Difunctionalization of Two Inert C(sp³)-H Bonds by a Bifunctional Reagent

Arghadip Ghosh, Akhila K. Sahoo*

Poster and Oral presentation at “**Chem Fest-2022**” held at School of Chemistry, University of Hyderabad, India on April, 2022. (*selected for best oral presentation*)

2. Palladium (II)-Catalyzed Annulative Difunctionalization of Two Inert C(sp³)-H Bonds by a Bifunctional Reagent

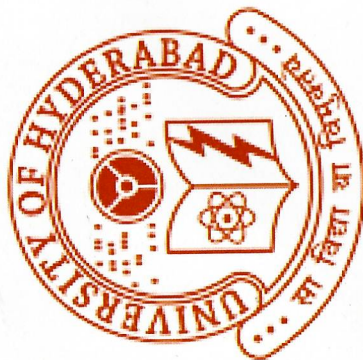
Arghadip Ghosh, Akhila K. Sahoo*

Oral presentation at “**FCASI-2023**” held at University of Rajasthan, Jaipur, India on April, 2023. (*selected for best oral presentation*)

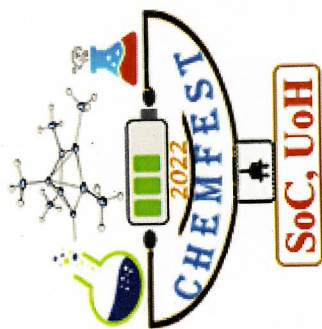
3. Sulfoximine Aided Double Functionalizations of Inert C-H Bonds: Synthesis of New Chemical Space and Mechanistic Study

Arghadip Ghosh, Akhila K. Sahoo*

Oral presentation at “**XVIII J-NOST Conference-2023**” held at IISER Pune, Pune, India on October, 2023.



CERTIFICATE OF PARTICIPATION



This is to certified that

Arghadip Ghosh

_____ has presented

an *Oral/Poster presentation* in CHEMFEST-2022, organized by the School of Chemistry, University Of Hyderabad.

Ashwini Nangia

Prof. Ashwini Nangia

Dean

K. M. S.

Prof. K. Muralidharan

Co-ordinator

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CHEMFEST-2022

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RECOGNIZES

ARGHADIP GHOSH (ORAL PRESENTATION)

School of Chemistry, University of Hyderabad, Telangana, India

FOR BEST POSTER

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Department of Chemistry
University of Rajasthan
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FCASI – 2023: International Conference on

“Frontiers at the Chemistry – Allied Sciences Interface”

University of Rajasthan, Jaipur, India



Rajasthan Chapter



International Conference on Frontiers at the Chemistry-Allied Sciences Interface (FCASI-2023)

20-21 April, 2023

CERTIFICATE

This is to certify that Prof./Dr./Mr./Ms. ✓

Arghadip Ghosh

.....of

School of Chemistry, University of Hyderabad, Hyderabad has actively participated/ presented paper (Oral/Poster) entitled

Palladium (II)-Catalyzed Annulative Difunctionalization of Two Inert C(sp³)-H Bonds by a Bifunctional Reagent

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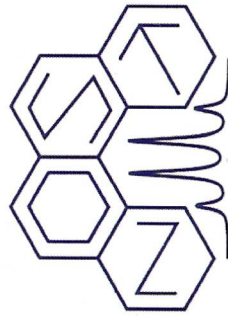
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XVIII J-NOST Conference 2023

For Young Researchers



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Arghadip Ghosh

**Sulfoximine Aided Double Functionalizations of Inert C-H Bonds: Synthesis of
New Chemical Space and Mechanistic Study**

Presented an Oral Presentation in XVIII J-NOST 2023 Conference for
Young Researchers at IISER Pune during October 10-12, 2023.

Krishna P. Kaliappan, IIT Bombay
Chairperson, NOST Council

Harinath Chakrapani, IISER Pune
Convener, JNOST-2023

Biographical Sketch



Arghadip Ghosh was born in Dantan (village), Paschim Medinipur (dist), West Bengal, India on 1st Feb, 1995. He completed his primary schooling and intermediate education from Danton H. S. Multipurpose School (10th & 12th standard). Then he received B. Sc degree from Calcutta University (St. Paul's Cathedral Mission College), West Bengal in 2015. Then, he qualified JAM-2015 exam and obtained Master's degree in Chemistry (Organic chemistry) in 2017 from NIT Durgapur, West Bengal. In December 2016, he cleared CSIR-UGC-NET JRF and GATE (2017) Examination. In Jan-2018, he started the research work at the School of Chemistry, University of Hyderabad under the guidance of Prof. Akhila Kumar Sahoo. His research interest deals with the new reaction development of “sp³/sp² C–H activation using transition metal catalyst”.

Harnessing Pyridyl-Sulfoximine Enabled Functionalization of Multiple C-H Bonds with Bifunctional Reagents

by ARGHADIP GHOSH

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Arghadip Ghosh, Koneti Kondalarao, Arijit Saha, Vincent Gandon, Akhila Kumar Sahoo. "A Three-Component Arene Difunctionalization: Merger of C(sp³)/(sp²)-H Bond Addition", Angewandte Chemie, 2023

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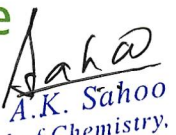
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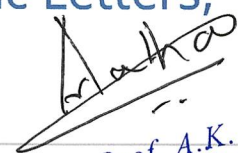

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