

Synthesis of Substituted Alkenes and Annulated Heterocycles via A Ruthenium-Catalyzed C-H Bond Activation

A Thesis

**Submitted in Partial Fulfillment of the Requirements
of the Degree of
Doctor of Philosophy**

By

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August- 2017

Dedicated to My parents, Brother,

And

Teachers of all the levels (primary standard

to Ph. D.) who have given their wonderful

knowledge which assisted me to reach

today's position (including my Ph. D.

mentor)



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CERTIFICATE

Certified that the work described in this thesis entitled “*Synthesis of Substituted Alkenes and Annulated Heterocycles via A Ruthenium-Catalyzed C-H Bond Activation*” submitted by *Mr. Mallu Chenna Reddy* was carried out by the candidate, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other university or institution.

Date: 16th August 2017

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Date: 16th August 2017

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Acknowledgements

My first debt of gratitude must go to my advisor, Dr. Masilamani Jeganmohan for providing a wonderful opportunity me to work with him. And I am very thankful to my mentor Dr. Masilamani Jeganmohan for his excellent guidance, constant encouragement, continuous strong support, indispensable suggestions throughout my doctoral program. I earned the knowledge (designing projects, bench skills, writing and communicating of journals, lab arrangements) under the guidance of Dr. Masilamani Jeganmohan will be undoubtedly a base for my scientific career. It would not be possible to reach the end of Ph.D. without his great efforts and hard work on each individual event in the Ph.D. program. It is difficult to compose an appropriate sentence to express my gratefulness to him for his guidance and keen interest which made this work possible.

It gives me an immense pleasure to express my deep sense of gratitude towards Dr. Sandanaraj Britto who took all the care, responsibilities and especially for spending his valuable time at the end time of my Doctoral program.

I sincerely thank Director Prof K. N. Ganesh for providing such excellent infrastructure and research facility here at IISER Pune. His enthusiasm about science was always a source of inspiration.

I am deeply grateful to the entire Department of Chemistry at IISER Pune, all the faculty members and staff for being extremely helpful.

I am really lucky to have wonderful lab mates who have played a very crucial role in my day to day life during my research tenure. My special thanks to all the members in MJM group Kishor Padala, Ravi Kiran, Sandeep Pimparkar, Nagesh More, Manikandan R, Manoharan, G.Shivakumar for their help, encouragements, and discussions during this study.

I am grateful to Deepali Jadhav and Pooja Lunawat for taking NMR spectra. I deeply thank Swati Dixit, Swati Hegde and Archana Jogdand for recording MALDI, HRMS, X-ray crystal data, and Mayuresh for administrative and official support.

No words can ever convey my sense of gratitude felt for my parents (my father: Mr. M. Sesha Reddy and mother: Mrs. Anjamma) and brother (Mr. M. Kesava Reddy).

Finally, I am thankful to Council of Scientific and Industrial Research (CSIR) for Research Fellowship.

Mallu Chenna Reddy

Synopsis

The thesis entitled “***Synthesis of Substituted Alkenes and Annulated Heterocycles via A Ruthenium-Catalyzed C-H Bond Activation***” consists of four chapters followed by Experimental details, References and Spectra.

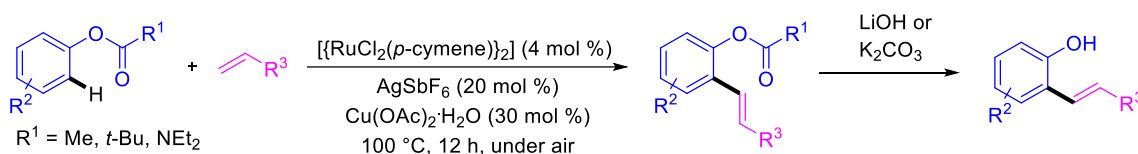
The research area in my doctoral study is focused on the transition-metal-catalyzed chelation assisted C-H bond functionalization or functionalization followed by cyclization of aromatic and heteroaromatic compounds with alkenes or alkynes. The transition metal-catalyzed chelation-assisted direct transformation of unactivated C-H bonds into C-C bonds at the *ortho* position of the aromatic rings with alkenes and alkynes is a practical method to synthesize highly substituted alkenes, heterocyclic products and natural products in organic synthesis. These reactions are environmentally friendly and highly atom-economical when compared with the other conventional methods such as carbon-halide functionalization. Various transition metal complexes such as palladium, rhodium, and ruthenium complexes have been widely used as catalysts in this type of reaction. Very recently, a less expensive ruthenium complex has gained tremendous attention in this type of heteroatom-directed reaction, due to their remarkable reactivity, compatibility, and selectivity.

Chapter 1 of this thesis describes definition and history of C-H bond activation. A brief introduction of chelation-assisted C-H bond activation via oxidative addition pathway as well as deprotonation pathway was discussed. The variation in products, intermediates, and mechanisms of chelation-assisted C-H bond activation via oxidative addition pathway as well as deprotonation pathway was discussed. The different orientations of alkenes and alkynes in both pathways were explained. The significant examples for the total synthesis of natural products by using C-H activation as a key step were shown.

Chapter 2 of this thesis describes a ruthenium-catalyzed *ortho* alkenylation of aromatic carbamates with alkenes providing *ortho* alkenylation and hydroarylation of aromatic carbamates with alkynes providing hydroarylated carbamates in a highly regio- and stereoselective fashion. It contains two subdivisions as follows:

Section 2A: Ruthenium-Catalyzed Selective Aerobic Oxidative *ortho*-Alkenylation of Substituted Phenols with Alkenes through C–H Bond Activation:

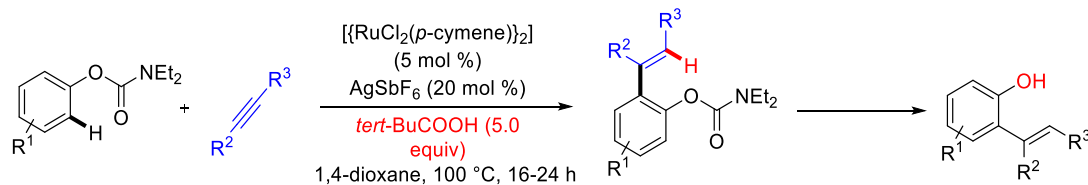
A highly regioselective ruthenium-catalyzed chelation-assisted *ortho* C-H bond olefination of aromatic carbamates with alkenes to afford substituted alkene derivatives is described (Scheme 1). The catalytic reaction was done under air to reduce the amount of Cu(OAc)₂·H₂O from 2.0 equiv to 30 mol %. The catalytic reaction was compatible with various alkenes and different substituted phenyl carbamates and acetates. Further, the substituted alkene derivatives treated with LiOH·H₂O or K₂CO₃ to provide the corresponding phenol derivatives. A possible reaction mechanism was proposed to account for the present reaction.



Scheme 1: *ortho* alkenylation of aromatic carbamates followed removal of carbamate DG

Section 2B: Ruthenium-Catalyzed Highly Regio- and Stereoselective Hydroarylation of Aryl Carbamates with Alkynes via C-H Bond Activation

In this section, a weak directing carbamate group assisted hydroarylation of aryl carbamates with alkynes in the presence of [RuCl₂(*p*-cymene)]₂, AgSbF₆ and pivalic acid, affording highly substituted alkene derivatives in good to excellent yields in a highly regio- and stereoselective manner is demonstrated (Scheme 2). The catalytic reaction is compatible with various functional groups substituted alkynes. The hydroarylated products were converted into phenol or carboxylic derivatives by the treatment with LiOH. A possible mechanism is proposed which follows concerted deprotonation metalation pathway. Deuterium studies were performed. This deuterium study clearly revealed that the present reaction proceeds via deprotonation pathway. Further, the stereo- and regioselectivity of the product was confirmed by X-ray analysis.



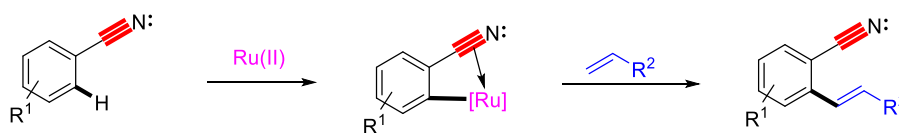
Scheme 2: Ruthenium-catalyzed hydroarylation of aryl carbamates with alkynes

Chapter 3 of this thesis demonstrates an efficient method for the synthesis of isoindolinones and isoquinolones via a ruthenium-catalyzed oxidative cyclization of aromatic and heteroaromatic nitriles with alkynes. Meanwhile, a ruthenium-catalyzed C≡N π -bond-assisted *ortho* alkenylation of aromatic and heteroaromatic nitriles with

activated alkenes providing *ortho* alkenylated products in a highly regio- and stereoselective manner is described. It contains three subdivisions as follows:

Section 3A: Ruthenium-Catalyzed C≡N π -Bond-Assisted *ortho* Alkenylation of Aromatic and Hetero Aromatic Nitriles with Activated Alkenes

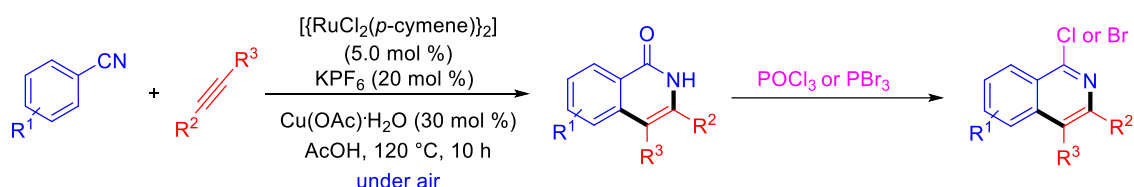
In this section, a ruthenium-catalyzed C≡N π -bond-assisted *ortho* alkenylation of aromatic and heteroaromatic nitriles with activated alkenes providing *ortho* olefinated products in a highly regio- and stereoselective manner is described (Scheme 3). For the first time, we have developed ruthenium C≡N π -bond-assisted *ortho* alkenylation of aromatic nitriles. Later, *ortho* alkenyl benzonitrile was converted into chiral phthalide in the presence of AD-mix- β . Further, *ortho* alkenylated aromatic nitriles were treated with 4-iodo nitrobenzene in the presence of Pd(OAc)₂ and Ag₂O in CF₃COOH at 110 °C for 12 h, yielding trisubstituted alkenes in a 10:1 *Z:E* ratio. A possible mechanism was proposed to account for the present reaction.



Scheme 3: C≡N π -bond-assisted *ortho* alkenylation

Section 3B: Ruthenium-Catalyzed Aerobic Oxidative Cyclization of Aromatic and Heteroaromatic Nitriles with Alkynes: a New Route to Isoquinolones

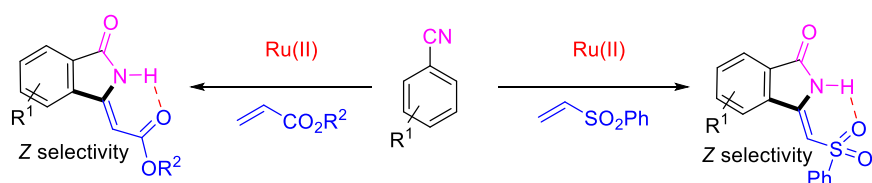
In this section, the oxidative cyclization of aromatic and heteroaromatic nitriles with alkynes in the presence of a catalytic amount of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$], Cu(OAc)₂·H₂O and KPF₆ in acetic acid under air affording isoquinolones in good to excellent yields is discussed (Scheme 4). This reaction is highly atom-economical, step-economical, and environmentally friendly. Interestingly, the present catalytic reaction was conducted under an air atmosphere and only 30 mol% of oxidant Cu(OAc)₂·H₂O was used and the remaining oxidant was regenerated under air. The observed isoquinolone derivatives were further converted into very useful heterocyclic compounds 1-chloro and 1-bromo isoquinoline derivatives in the presence of POCl₃ or PBr₃. A cooperatively ruthenium- and copper-catalyzed reaction mechanism is proposed for the present cyclization reaction. Further, experiments were performed to support the proposed mechanism.



Scheme 4: Ruthenium-catalyzed isoquinolone synthesis and further conversion of products into 1-halo quinolines

Section 3C: Ruthenium-Catalyzed Cyclization of Aromatic Nitriles with Alkenes: Stereoselective Synthesis of (Z)-3-Methyleneisoindolin-1-ones

In this section, aromatic nitriles underwent cyclization with activated alkenes in the presence of a ruthenium catalyst, AgSbF₆ and Cu(OAc)₂·H₂O providing substituted 3-methyleneisoindolin-1-ones in a highly Z-stereoselectivity is described (Scheme 5). The hydrogen bonding and stereochemistry (Z) was confirmed by X-ray analysis. By employing the present method, a key starting material was prepared to synthesize the sedative active drug molecules. The present method was applied on pyrene nitrile to study the optical behaviour. Next, 3-methyleneisoindolin-1-one was treated with di-*tert*-butyl dicarbonate in the presence 4-dimethylamino pyridine (4-DMAP) in CH₃CN and also subjected with iodobenzene in the presence of CuI and K₂CO₃ in DMF at 150 °C for 16 h led to corresponding *N*-substituted (Z)-3-Methyleneisoindolin-1-one. A possible reaction mechanism was proposed and strongly supported by experimental evidence.

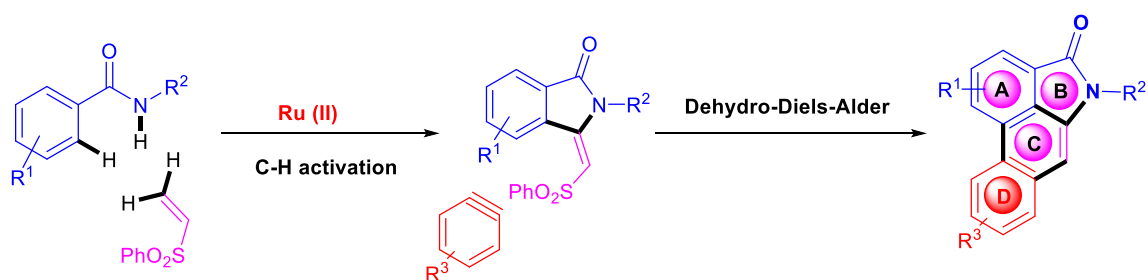


Scheme 5: Ruthenium-catalyzed Z-3-methyleneisoindolin-1-one synthesis from aromatic nitriles.

Chapter 4: Total Synthesis of Aristolactam Alkaloids via Synergistic C-H Bond Activation and Dehydro-Diels-Alder Reactions

In this chapter, an efficient two steps synthesis of aristolactam alkaloids from easily available and affordable starting materials is described. For this, two new synthetic methodologies were developed. One is ruthenium-catalyzed oxidative cyclization aromatic amides with vinyl sulphone affords 3-methyleneisoindolin-1-ones. Second one is Dehydro-Diels-Alder reaction followed by fluoride ion promoted SO₂Ph cleavage of 3-methyleneisoindolin-1-ones with benzyne (Scheme 6). By employing these methodologies, several *N*-methyl and *N*-H aristolactam alkaloids and their derivatives

were prepared in good yields. Possible reaction mechanisms were proposed to account for the present reaction.



Scheme 6: Synthesis of aristolactams

Publications:

1. **Reddy, M.C.;** Jeganmohan, M. “Ruthenium-Catalyzed Selective Aerobic Oxidative *ortho*-Alkenylation of Substituted Phenols with Alkenes through C–H Bond Activation” *Eur. J. Org. Chem.* **2013**, 1150-1157.
2. **Reddy, M.C.;** Jeganmohan, M.; “Ruthenium-catalyzed highly regio- and stereoselective hydroarylation of aryl carbamates with alkynes via C–H bond activation”. *Chem. Commun.* **2013**, 49, 481–483.
3. **Reddy, M.C.;** Manikandan, R.; Jeganmohan, M.; “Ruthenium-catalyzed aerobic oxidative cyclization of aromatic and heteroaromatic nitriles with alkynes: a new route to isoquinolones”. *Chem Commun.* **2013**, 49, 6060–6062.
4. **Reddy, M.C.;** Jeganmohan, M.; “Ruthenium-Catalyzed Cyclization of Aromatic Nitriles with Alkenes: Stereoselective Synthesis of (*Z*)-3-Methyleneisoindolin-1-ones”. *Org. Lett.* **2014**, 16, 4866–4869.
5. **Reddy, M.C.;** Jeganmohan, M.; “Ruthenium-catalyzed *ortho* alkenylation of aromatic nitriles with activated alkenes via C–H bond activation”. *Chem. Commun.* **2015**, 51, 10738–10741.
6. **Reddy, M.C.;** Jeganmohan, M.; “Total synthesis of aristolactam alkaloids via synergistic C–H bond activation and dehydro-Diels–Alder reactions”. *Chem. Sci.* **2017**, 8, 4130-4135

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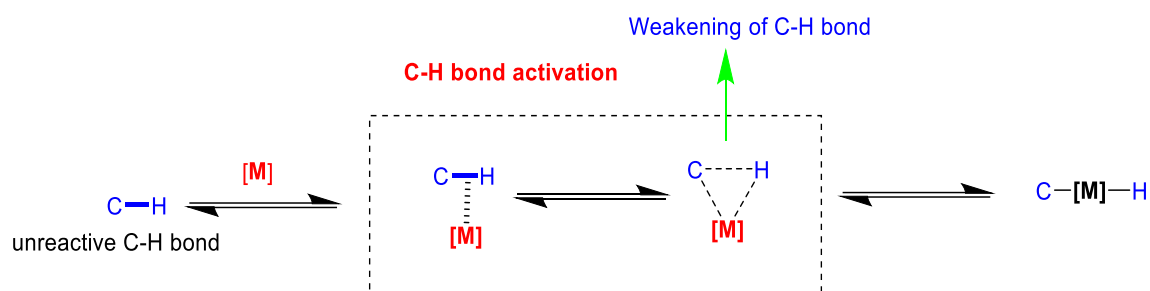
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Chapter 1

Introduction

1.1: C-H Bond Activation

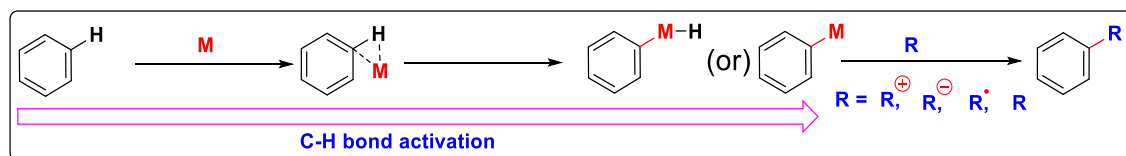
The unreactive C-H bond interacts directly with a metal catalyst and often affords a C-M intermediate. When metal approaches the C-H bond closely, it immediately interacts with the metal. The interaction causes weakening of the C-H bond which leads to cleavage of C-H bond and forms a C-M intermediate (Scheme 1.1).^{1a, b} This process is called as C-H bond activation.



Scheme 1.1: C-H bond activation

1.2: C-H Bond Functionalization via C-H Bond Activation

The C-M intermediate which is formed via the C-H bond activation further can undergo functionalization with various coupling reagents to replace C-H with C-X (where X is usually carbon, oxygen, nitrogen, halogens or sulfur)(Scheme 1.2).



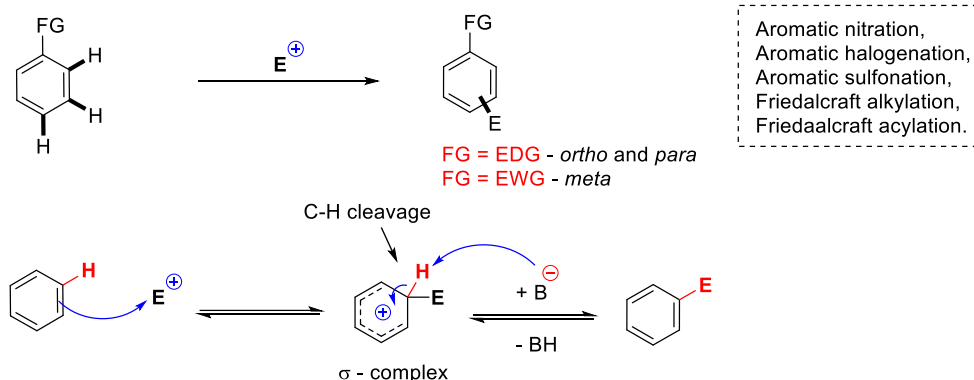
Scheme 1.2: C-H bond functionalization

C-H Bond Functionalizations via C-H Activation Vs Electrophilic Substitution Reactions, Directed *ortho* Metallation and Cross-Coupling Reactions.

1.3: Electrophilic Aromatic Substitution Reactions

In the beginning of 19th century, doing functionalization of sp^2 C-H bonds on benzene rings was a really challenging task. This problem had been resolved by developing electrophilic substitution reactions. In these reactions, initially, electrophilic attack results to form σ - complex intermediate and followed by deprotonation takes place which gives functionalization product. Aromatization is driving force for C-H cleavage of σ - complex intermediate (Scheme 1.3). In this reaction, C-H bond activation is not necessary for C-H cleavage. The regioselectivity of incoming electrophile can be influenced by an electron withdrawing group or electron donating group which is present on the aromatic ring.

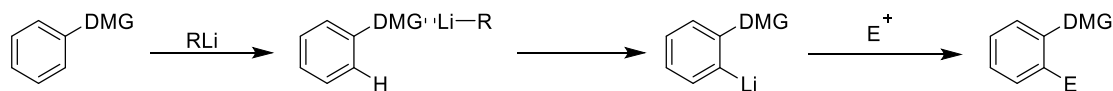
Another thing to overcome is stopping multi-functionalization on the aromatic ring. In addition, this reaction is limited to only a few electrophiles.^{1c} Later increasing the scope of electrophiles and regioselectivity was well addressed by developing directed *ortho* metalation where the directing group was introduced to get high *ortho* selectivity.



Scheme 1.3: Electrophilic Aromatic Substitution Reactions

1.4 Directed *ortho* Metalation

Henry Gilman^{1d} and Georg Wittig^{1e} independently reported directed *ortho* metalation type reaction around 1940. A hetero atom-containing direct metalation group (DMG) was used to inducing *ortho* selectivity exclusively (Scheme 1.4). In this reaction, the heteroatom of DMG coordinates to the metal of organometallic reagent followed by deprotonation leads to an *ortho*-metallated intermediate which can further undergo functionalization with an electrophile. This reaction is not limited to few electrophiles. Moreover, several electrophile sources (CO_2 , TsN_3 , O_2 , Br_2 , MeI , HCO_2Et , Bu_3SnCl , PPhCl etc) were showed to use in this reaction. Several synthetic groups worked on directed *ortho* metalation and successfully explored this reaction to more than 40 DMGs.¹⁶ These methods are limited to only electrophile reagents for functionalization.

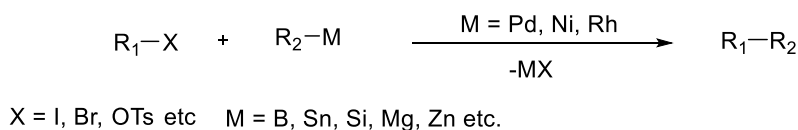


Scheme 1.4: Directed *ortho* metalation

1.5: Cross-Coupling Reactions

In this reaction, two coupling reagents (halo or pseudo-halo compounds, organometallic compounds) reacts in the presence of a metal catalyst to provide corresponding coupling product (Scheme 1.5).^{1f-m} Cross-coupling reactions have become a powerful tool for making C-C and C-hetero bonds in the last several decades and simplified complicated

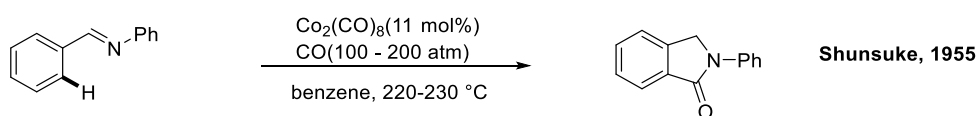
synthetic routes to make attractive, useful molecules in different applicable fields of science such as natural product synthesis, biology, materials, agrochemistry, dyes, and pharmaceuticals. A wide range of reagents such as electrophiles, nucleophiles, radicals and neutral type of reagents can be used. The significance of cross-coupling reactions was greatly honored by winning a noble prize in 2010 in chemistry. These classic transformations are mostly based on the utilization of organometallic reagents and halo compounds which are synthesized from the pre-functionalization of their corresponding hydrocarbons. Finally, halide and metal are wasted as byproducts. The development of one reaction with less wastage and minimize the number of steps by avoiding the usage of pre-functionalized reagents would be always a great interest to the chemists and highly attractive atom and step economic process in green chemistry point of view. This can be achieved by doing functionalization via C-H activation. Usage of pre-functionalized starting materials is not needed. These reactions are highly step and atom economical by avoiding more number of steps and more wastage. In other hand, several reagents electrophiles, radicals, nucleophiles and neutral reagents should be utilized to extend wide range of synthetic efficacy in organic chemistry.



Scheme 1.5: Cross-coupling reactions

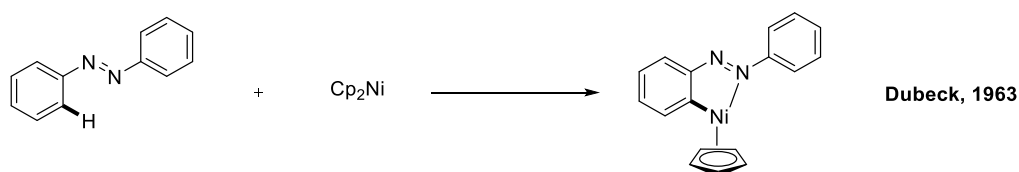
1.6 History of C-H Activation:

In 1955, Shunsuke Murahashi reported a reaction of imine with CO in presence of a cobalt catalyst which produced isoindolinone product. This is one of early example for a functionalization reaction via C-H bond activation (Scheme 1.6).^{2a}



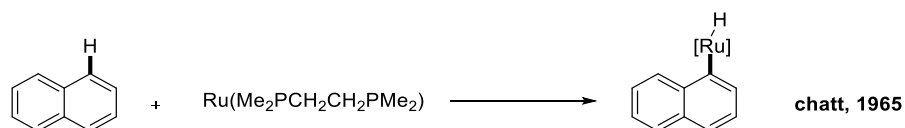
Scheme 1.6: C-H activation of imines.

Ortho metalation involving of C-H bond cleavage via C-H bond activation of diphenyl diazene with a nickel complex was achieved by Michael Dubeck in 1963 (Scheme 1.7).^{2b}



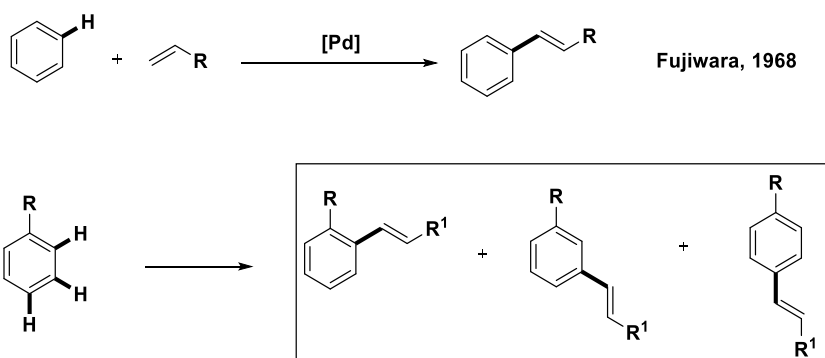
Scheme 1.7: *Ortho* metalation via C-H bond activation.

In 1965, Joseph Chatt observed the insertion of ruthenium of $\text{RuCl}_2(\text{dmpe})_2$ into the C-H bond of naphthalene (Scheme 1.8)^{2c}



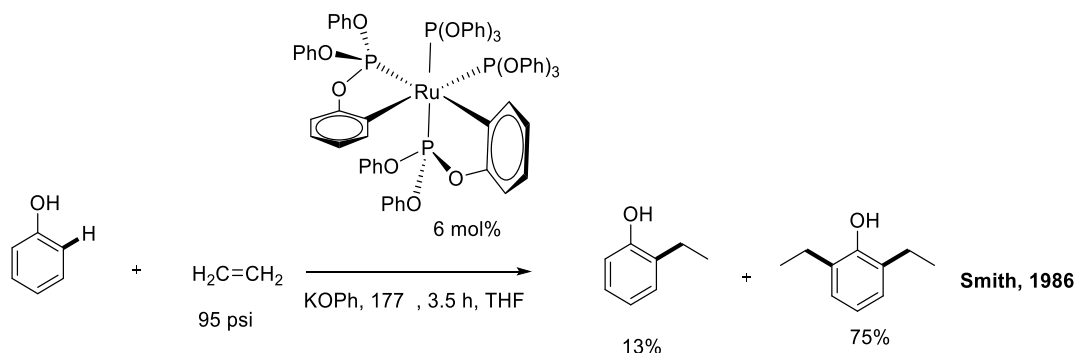
Scheme 1.8: Naphthalene Ru-H formation via C-H bond activation.

In 1968, Fujiwara's group developed coupling of styrene with benzene in the presence of a palladium catalyst providing stilbene (Scheme 1.9). It is a very beginning example to shown a cross-coupling reaction without using any pre-activated coupling partner. This reaction minimizes wastage and highly atom economical reaction. But unfortunately, metal activates each and every C-H bond on arene moiety and provides multiple products. Later, this type of reaction has been brought up by Murai by introducing directing group in C-H activation.



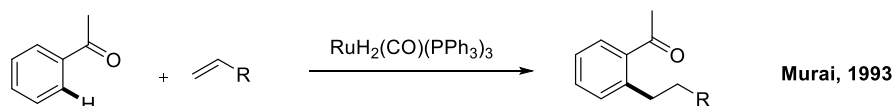
Scheme 1.9: Fujiwara-Moritani reaction

In 1986, Lewis and Smith reported *ortho*-selective C-H alkylation of phenols with ethylene using a ruthenium Catalyst(1) (Scheme 1.10).^{2d} The phosphite ligand played an important role which generates a directing group in the site from phenol to assist Ru for the success of alkylation via *ortho*-C-H bond activation.



Scheme 1.10: Ru-Catalyzed *ortho*-Selective C-H Alkylation of Phenols by in situ generated directing group.

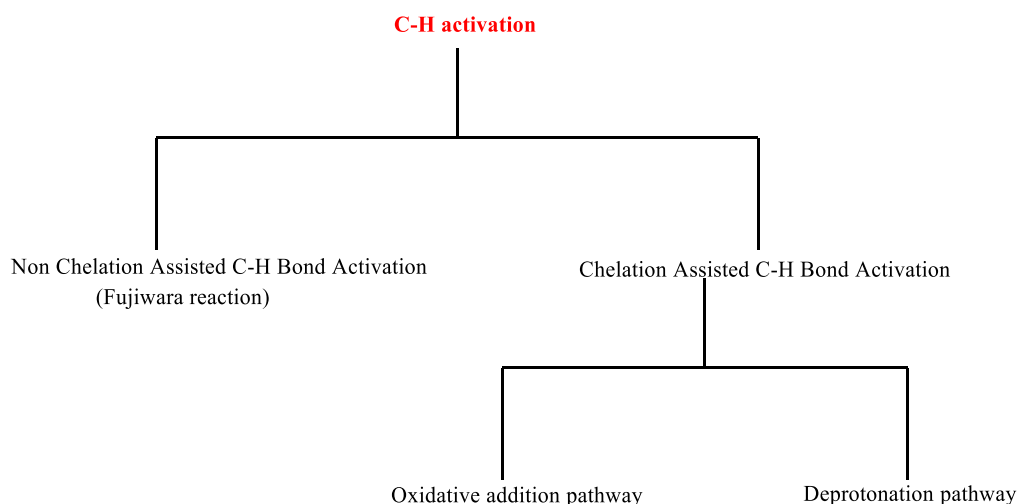
In 1993, Murai's group reported *ortho*-alkylation of aromatic ketones with alkenes via C–H bond activation (Scheme 1.11).^{2e} In this reaction, for the first time, new strategy utilization of directing group was successfully introduced in order to overcome the regioselectivity problem and to get highly *ortho* selectivity. The key step to achieving regioselectivity is chelation of metal with heteroatom of directing group. So this type of reactions is also called as chelation-assisted C-H bond activation reaction.



Scheme 1.11: Ru-Catalyzed *ortho*-Selective C-H Alkylation of Ketones.

1.7 C-H Activation/Functionalization:

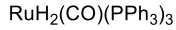
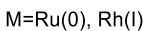
Murai initiated the pioneering work in *ortho*-directed C–H bond activation/functionalization with ruthenium(0) catalysts. Initially, there was not much clear idea about classification about C-H activation. After Murai's first report on C-H bond functionalization, several synthetic groups worked and explored into new directions which gave a new classification to C-H activation (Scheme 1.12).

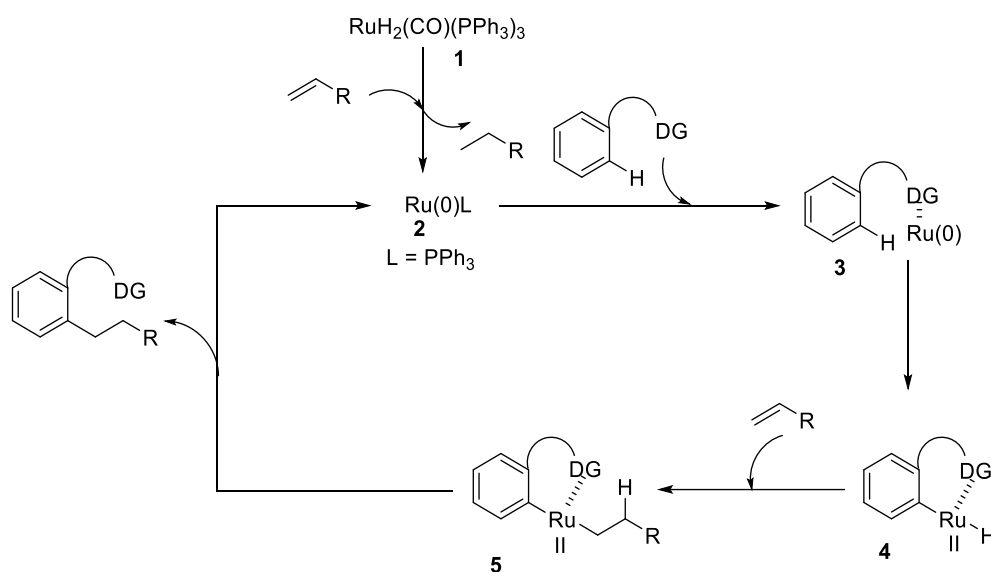


Scheme 1.12: General Classification of C-H activation.

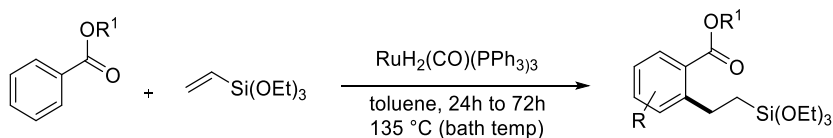
1.8: Oxidative Addition Pathway:

Murai with Chatani and Kakiuchi initiated the pioneering work in *ortho*-directed C–H bond activation/functionalization with ruthenium(0) catalysts. In this pathway, heteroatom of directing group coordinates to metal catalyst providing intermediate **1**

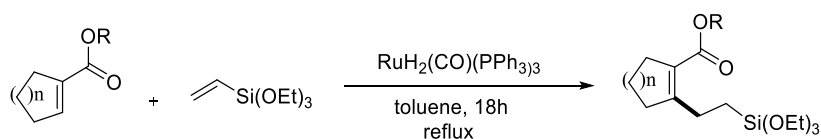


Scheme 1.15: Mechanism of *ortho*-alkylation

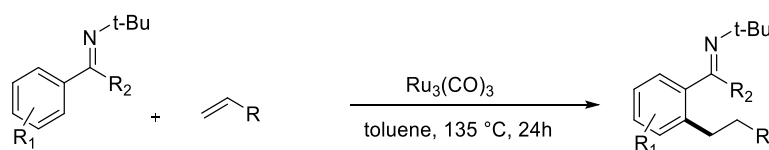
In 1993, Murai's group reported Ru(0) catalyzed *ortho*-alkylation of aromatic ketones with alkenes via C-H bond activation (Scheme 1.11). This was the first report for alkylation of chelation-assisted C-H activation via oxidative addition pathway. In 1995, B. M. Trost and co-workers successfully explored the alkylation with ester directing group by using $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ (Scheme 1.16).^{3a}

Scheme 1.16: *Ortho*-alkylation of aromatic esters.

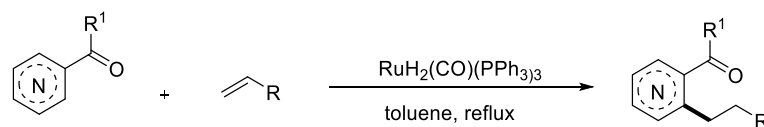
Later in 1996, Murai's group showed *ortho* alkylation reaction of aromatic esters with alkenes in the presence of $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ (Scheme 1.17).^{3b}

Scheme 1.17: *Ortho*-alkylation of alkene esters.

In the same year, the first *ortho*-alkylation of aromatic imines with simple olefins was developed by Murai and co-workers (Scheme 1.18).^{3c}

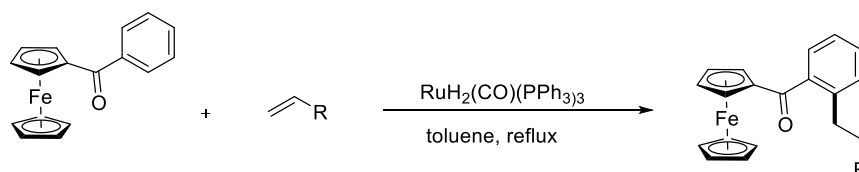
Scheme 1.18: *Ortho*-alkylation of aromatic imines.

After Murai's elegant contribution, arene scope was extended to pyridine-derived ketones by Grigg and Savic in 1997. (Scheme 1.19).^{3d}



Scheme 1.19: *Ortho*-alkylation of aromatic pyridine-derived ketones.

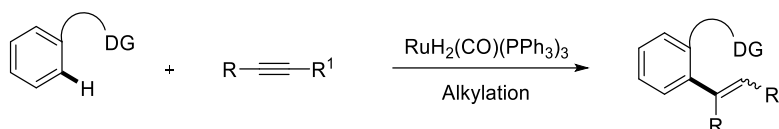
Du and co-workers succeeded the alkylation reaction of 9-ferrocenyl ketones with alkenes by using Ru(0) catalyst. (Scheme 1.20).^{3e}



Scheme 1.20: *Ortho*-alkylation of 9-ferrocenyl ketones

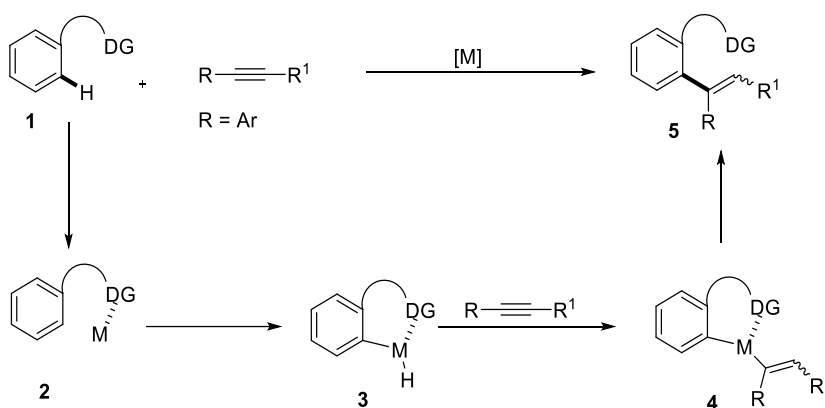
1.10: Functionalization of Alkynes in Oxidative Addition Pathway:

Alkynes undergo *ortho* alkenylation in the oxidative addition pathway. In oxidative addition pathway, heteroatom substituted aromatics reacts with an alkyne in the presence of a metal catalyst providing *ortho* alkenylated product (Scheme 1.21).



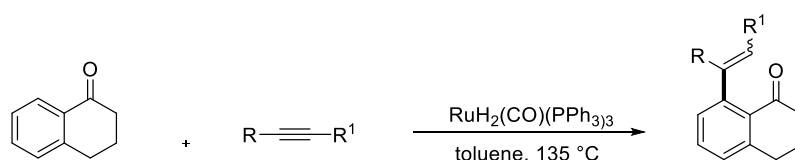
Scheme 1.21: *Ortho*-alkenylation of alkynes in oxidative addition pathway.

The *ortho* alkenylation reaction proceeds via a chelation-assisted oxidative addition of the *ortho* C-H bond of the aromatic heteroatom substituted aromatics with a metal catalyst providing a five-membered hydro metallacycle intermediate **3**. Later, an alkyne undergoes coordinative insertion into a metal-hydride bond of intermediate **3** provides intermediate **4**. Subsequent reductive elimination of intermediate **3** provides *ortho* alkenylated derivatives. This *ortho*-alkenylation reaction is not completely stereoselective and provides mixture *cis* and *trans* trisubstituted alkenes (Scheme 1.22).



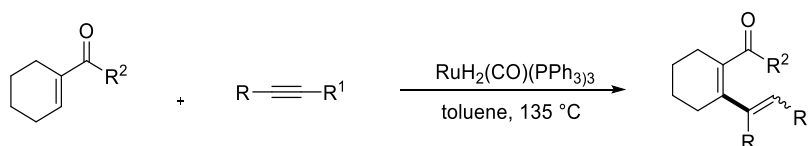
Scheme 1.22: Mechanism of *ortho*-alkenylation of alkynes in Oxidative addition pathway.

In 1995, for the first time, Murai's group showed utilization of alkynes in oxidative addition by demonstrating an *ortho* alkenylation of aromatic ketones with alkynes in the presence of a ruthenium catalyst (Scheme 1.23).^{4a}



Scheme 1.23: *Ortho*-Alkenylation of aromatic ketones

Later, the same group described an *ortho* alkenylation of alkene-derived ketones with alkynes in the presence of a ruthenium catalyst (Scheme 1.24).^{4b}



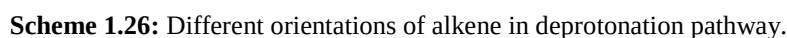
Scheme 1.24: *Ortho*-Alkenylation of alkene-derived ketones

1.11: Deprotonation Pathway:

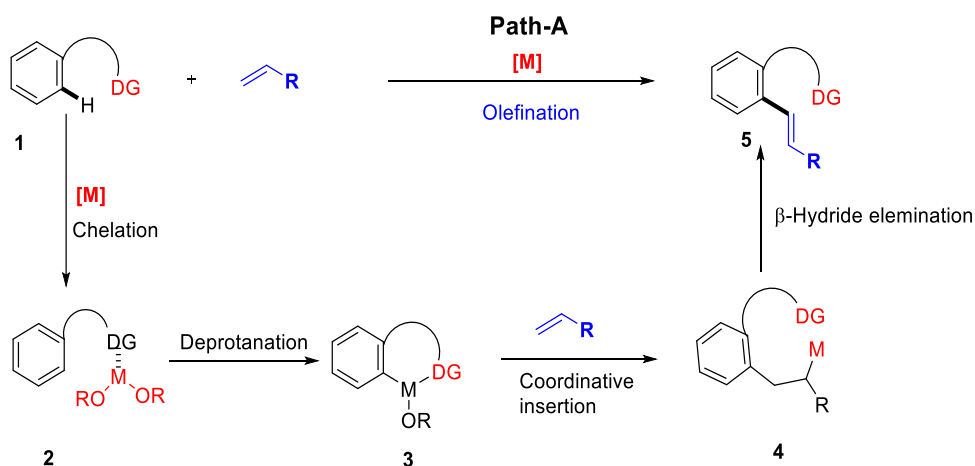
In the deprotonation pathway, the heteroatom of the directing group coordinates to a metal complex giving intermediate **1**. Intermediate **1** contains acetate or carbonate bases. Next, the base of intermediate **1** deprotonates the *ortho* C-H bond gives a five membered metallacycle intermediate **2** without having a metal hydride intermediate. Generally, the higher oxidation state M(II)(OR)₂ or M(III)(OR)₂ catalysts are more favorable for the deprotonation pathway (Scheme 1.25).



Alkenes have been showed to undergo different types of reactions in deprotonation pathway (Scheme 1.26).

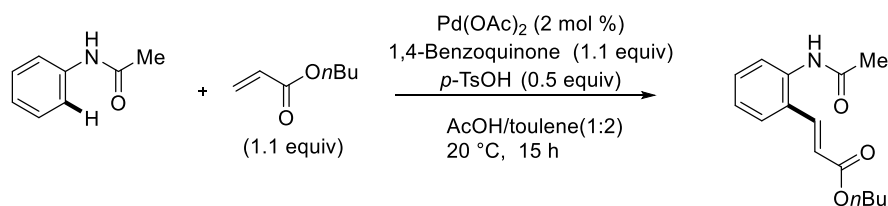


Alkenes undergo olefination in deprotonation pathway. The reaction of directing group containing organic moieties with alkenes in the presence a metal catalyst produces *ortho*-olefinated products via deprotonation pathway (Scheme 1.27). In this reaction, the heteroatom of directing group co-ordinates with a metal provides intermediate **2**. Next, intermediate **2** undergoes deprotonation to give intermediate **3**. The co-ordinative insertion of M-C bond of intermediate **3** into alkene followed by β -hydride elimination giving the *ortho* alkenylated product.



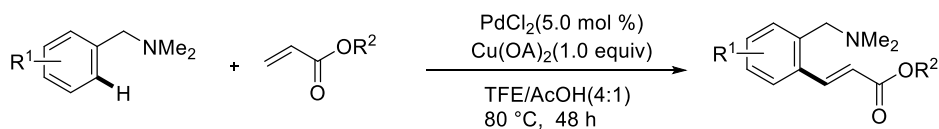
Scheme 1.27: *Ortho*- Olefination of alkenes in oxidative addition pathway.

Several synthetic groups dedicated work on metal-catalyzed olefination reaction. In 2002, de Vries and van Leeuwen reported an early example to Path-A type alkenylation of anilides with alkenes in the presence of a palladium catalyst. (Scheme 1.28).^{6a}



Scheme 1.28: *ortho*-alkenylation of anilides

Later, *Ortho*-olefination of substituted *N,N*-dimethylbenzylamines with alkenes in the presence of palladium chloride was successfully developed by Zhangjie Shi's group in 2007. In this reaction, *N,N*-dimethylbenzylamines reacted with acrylates in presence of PdCl_2 catalyst and $\text{Cu}(\text{OAc})_2$ oxidant to give the corresponding alkenylated products in good to excellent yields (Scheme 1.29).^{6b}



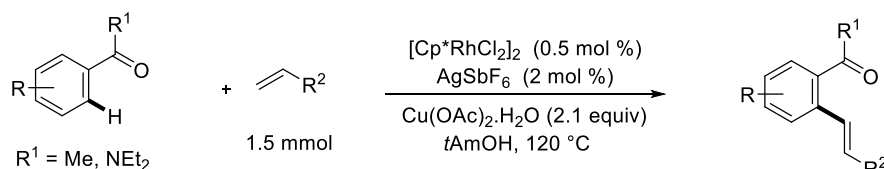
Scheme 1.29: *ortho*-alkenylation of *N,N*-dimethylbenzylamines

Carboxylate-directed Pd(II)-catalyzed C–H alkenylation reaction with phenylacetic acid and 3-phenylpropionic acid substrates was described by Yu's group (Scheme 1.30).^{6c}



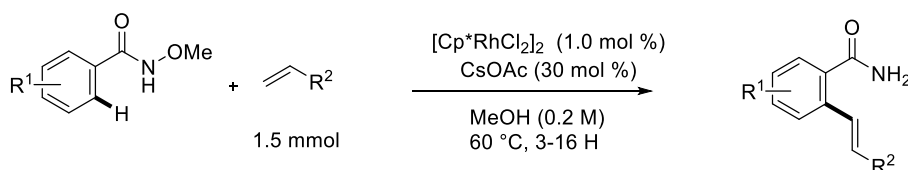
Scheme 1.30: *ortho*-alkenylation of phenylacetic acid

Rhodium(III)-catalyzed oxidative *ortho* olefination of benzamides and acetophenones was developed by Glorius's group in 2011 (Scheme 1.31).^{6d}



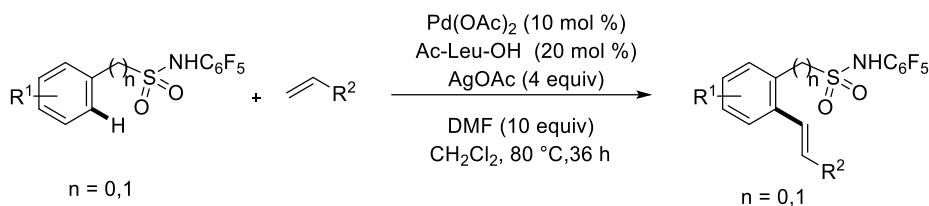
Scheme 1.31: *ortho*-alkenylation of acetophenones and benzamides

Subsequently, the same group reported the efficient Rh(III)-catalyzed C-H olefination reaction of *N*-methoxybenzamides with alkenes in 2011. In this reaction, *N*-methoxybenzamide acts as an internal oxidant. (Scheme 1.32).^{6e}



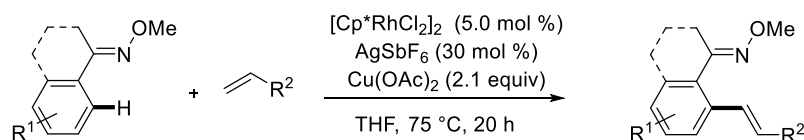
Scheme 1.32: *ortho*-alkenylation of *N*-methoxybenzamides

Pd(0)-catalyzed C-H olefination of benzylsulfonamides and benzenesulfonamides with alkenes was developed by Yu's group. (Scheme 1.33).^{6f}



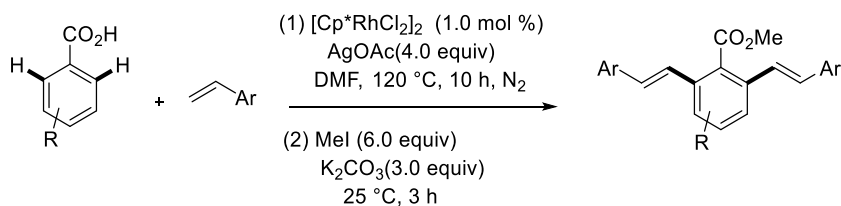
Scheme 1.33: C-H Olefination of Benzylsulfonamides

Ellman's group disclosed a Rh(III)-catalyzed *ortho* olefination reaction of oxime with alkenes. (Scheme 1.34).^{6g}



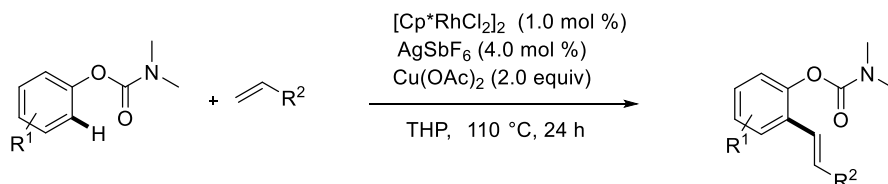
Scheme 1.34: C-H Olefination of oxime

Satoh's and Miura's groups showed carboxylic group acts as directing group for *ortho* olefination in the presence of Rh(III) catalyst. The corresponding *ortho* alkenylated acid derivatives were converted into *ortho* alkenylated esters by treatment with MeI and K_2CO_3 . (Scheme 1.35).^{6h}



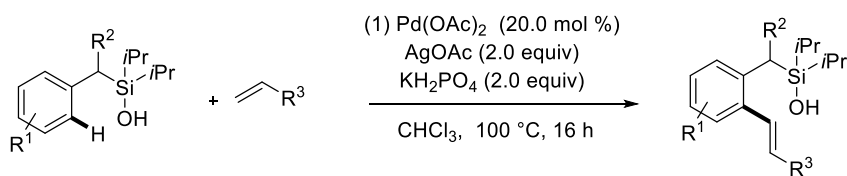
Scheme 1.35: C-H Olefination of carboxylic acids

In 2011, Liu's and Loh's groups independently reported a rhodium-catalyzed selective C-H alkenylation of phenol carbamates with alkenes (Scheme 1.35).^{6i-j}



Scheme 1.36: C-H Olefination of carbamates

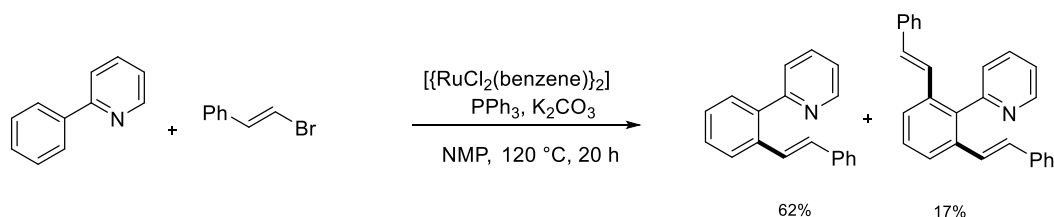
Ge's group showed the olefination of benzyldiisopropylsilanol with alkene in the presence of a palladium catalyst (Scheme 1.37).^{6k}



Scheme 1.37: C-H Olefination of benzyldiisopropylsilanol

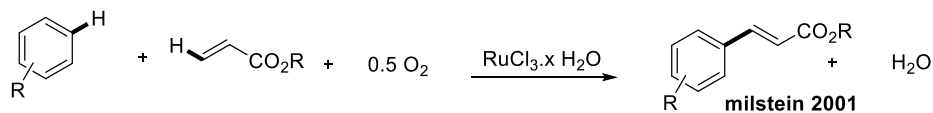
1.14: Ruthenium(II)-Catalyzed Chelation Assisted Oxidative Alkenylations of Arenes via Deprotonation Pathway.

Mostly, in the alkenylation reaction, an expensive palladium and rhodium complexes are widely used for a variety of directing groups. Exploring this useful oxidative alkenylation reaction by using cheaper ruthenium catalysts and especially the easily available and more stable Ru(II) systems could be necessary and highly attractive interesting platform in organic chemistry. Ruthenium complexes are less expensive and easily affordable compared with other rhodium and palladium complexes. Further, a ruthenium catalyzed C-H bond functionalization can be done under an air atmosphere and/or even water can be used as a solvent. Thus, an inert atmosphere is not required in the reaction. Recently, a less-expensive ruthenium catalyst has gained much attention in this type of reactions, due to its remarkable reactivity and selectivity. In 2001, for the first time, the successive usage of ruthenium(II) complexes in deprotonation pathway was achieved by Oi and Inoue. In this reaction, 2-Arylpyridines reacted with organic halides in the presence of $[\{\text{RuCl}_2(\text{benzene})\}_2]$, PPh_3 and K_2CO_3 affording correspond *ortho* C-H coupled products (Scheme 1.38).^{7a}



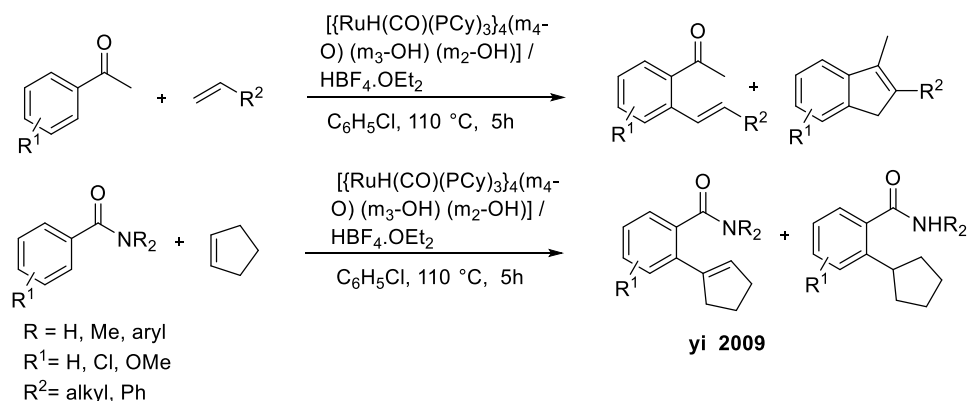
Scheme 1.38: First example of Ruthenium – complex in deprotonation.

In the same year, first example of $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ catalyzed oxidative alkenylation reaction of substituted aromatics with alkenes under CO and O_2 atmosphere without using any preactivated molecule was demonstrated Milstein's group. These two initial reports made to think about development of chelation assisted oxidative alkenylation by using such cheaper and stable ruthenium complexes. (Scheme 1.39).^{7b}



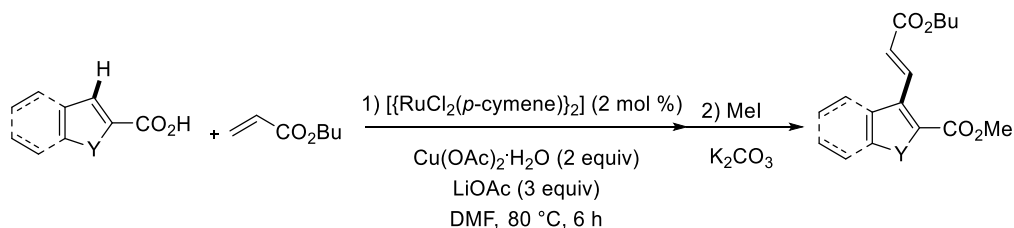
Scheme 1.39: $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ catalyzed oxidative alkenylation

In 2009, Aromatic ketone directed *ortho* alkenylation with styrenes by using ruthenium-hydride catalyst providing mixtures of *ortho* alkenylated aromatic ketones and cyclic indene derivatives was reported by Yi's group (Scheme 1.40).^{7c} Later, the similar type of reaction was extended to aromatic amides with alkenes including cyclic alkenes.^{7d}



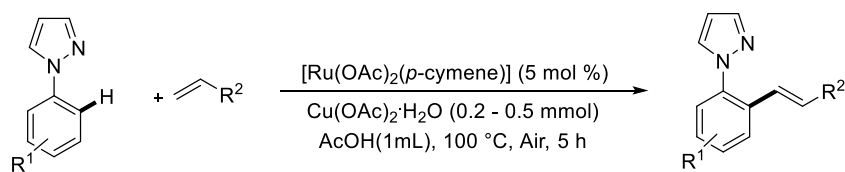
Scheme 1.40: Dehydrogenative coupling of ketone and amides

In 2011, for the first time, Miura's group disclosed C-H bond alkenylation by using a less expensive ruthenium complex. Miura's groups explored an *ortho* olefination of heteroaromatic carboxylic acids with olefins in the presence of a ruthenium(II) catalyst. (Scheme 1.41).^{7e}



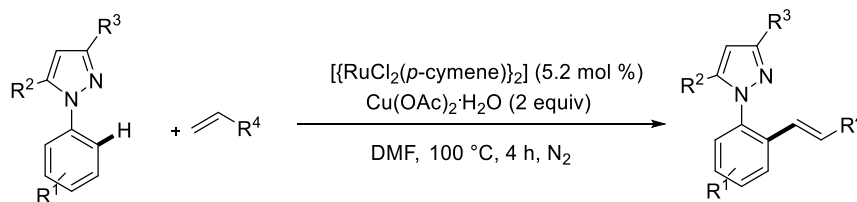
Scheme 1.41: C-H Olefination of heteroarene carboxylic acids

Dixneuf's and Bruneau's groups reported the success full oxidative alkenylation of a nitrogen-containing heterocycle such as *N*-arylpiperazines with alkenes in the presence of $\text{Ru}(\text{OAc})_2(\text{p-cymene})$ (Scheme 1.42).^{7f}



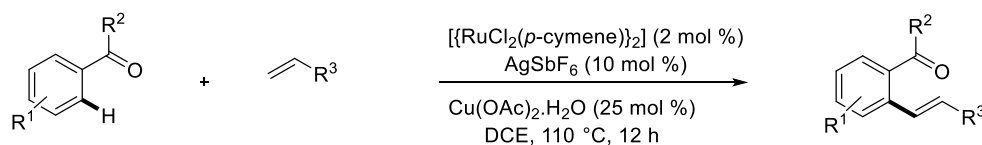
Scheme 1.42: C-H Olefination of *N*-arylpiperazines

The alkenylation of arylpiperazines in the presence of $[\text{RuCl}_2(\text{p-cymene})]_2$ catalyst with alkenes and 2 equiv of $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ in DMF under nitrogen atmosphere has been described by Satoh's and Miura's. (Scheme 1.42).^{7g}



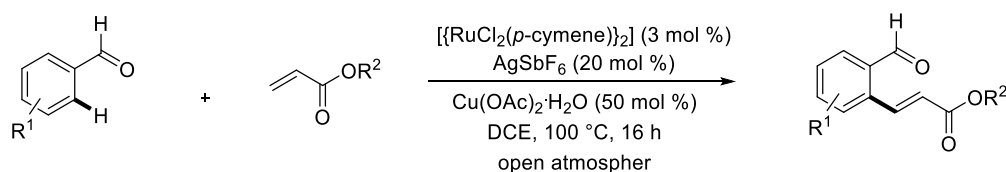
Scheme 1.43: C-H Olefination of heteroarene carboxylic acids

Our group mainly focused on the development of catalytic conditions by using $[\{\text{RuCl}_2(\text{p-cymene})\}_2]/\text{AgSbF}_6$ for *ortho* C-H bond activation of weak directing groups assisted aromatics and heteroaromatics. In 2011, our group succeeded for the first time to achieve Ru(II) catalyzed *ortho* alkenylation of aromatic ketones with alkenes providing *ortho* alkenylated aromatic ketones. (Scheme 1.44). The key step of the success is improvement of oxophilicity of Ru active catalyst for chelation with such a weak donor atom Oxygen of ketone directing group by adding an external additive AgSbF_6 . Generally stoichiometric amount of $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ (2 equiv) is required. The amount of $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ (25 mol %) was reduced by using the concept of aerobic conditions.^{7h}



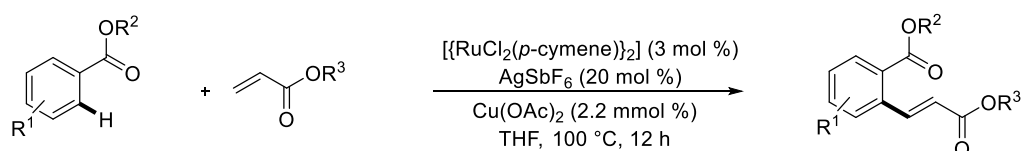
Scheme 1.44: *ortho* olefination of ketones

Later, in 2012, for the first time aldehyde was introduced as a directing for *ortho* olefination with alkene in the presence of a ruthenium by our group. (Scheme 1.45).⁷ⁱ



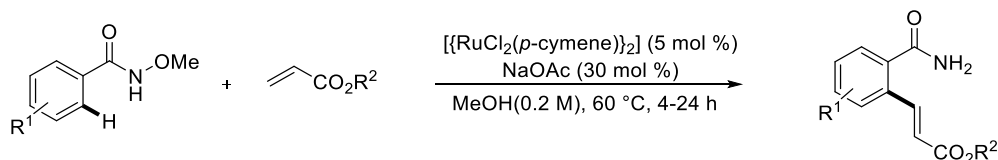
Scheme 1.45: *ortho* olefination of aldehydes

Subsequently, in the same year, another weak directing group ester was found to practice for *ortho* alkenylation with alkenes in the presence of Ru(II) catalyst by our group. (Scheme 1.46).^{7k}

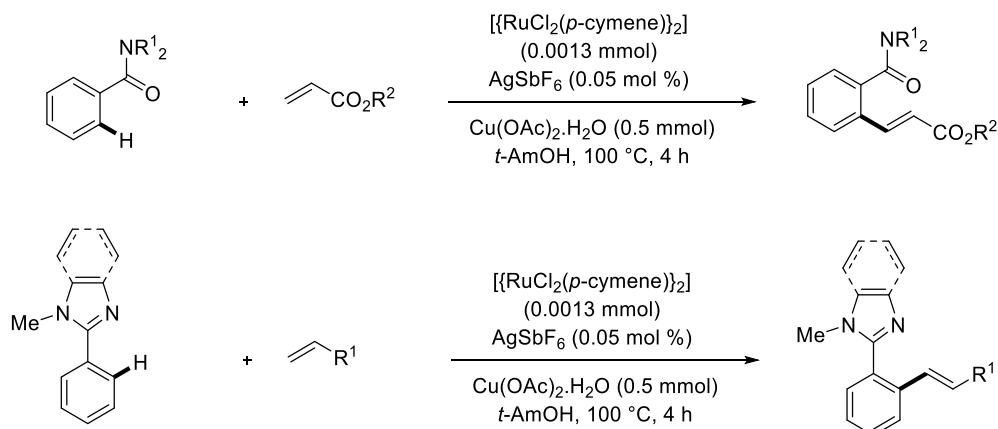


Scheme 1.46: *ortho* olefination of esters

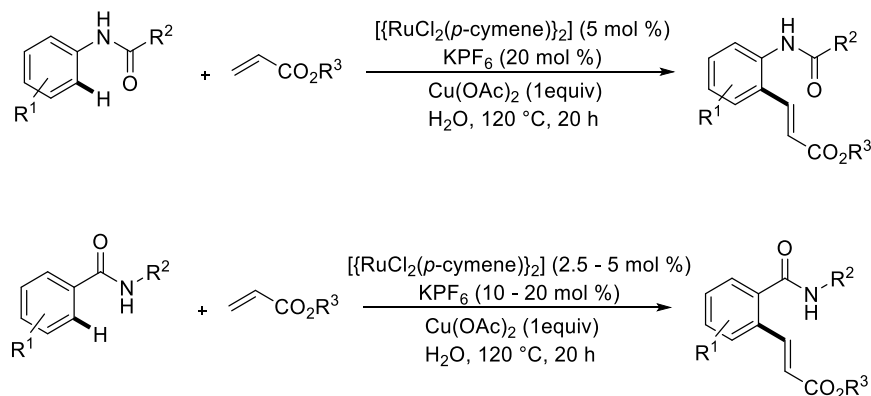
Baiquan Wang's group developed Ru(II)-catalyzed oxidative *ortho* alkenylation of *N*-methoxybenzamides using as an oxidizing directing group with alkenes. (Scheme 1.47).^{7k}

**Scheme 1.47:** *ortho* olefination of *N*-Methoxybenzamides

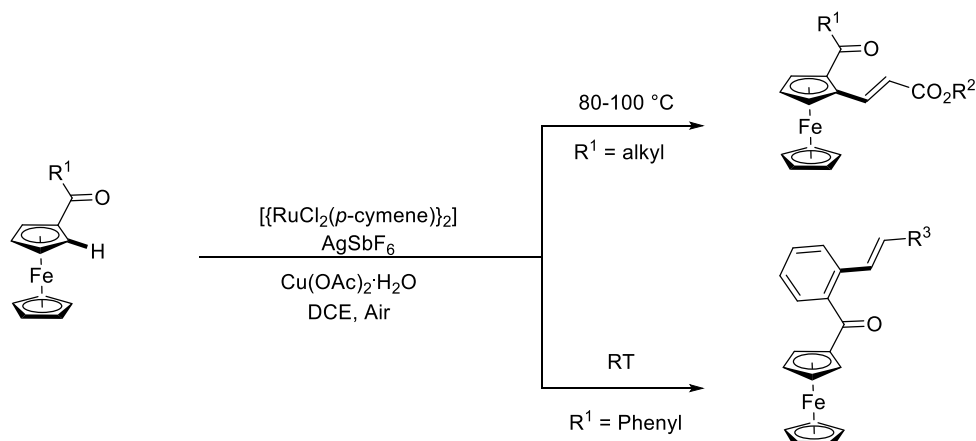
Miura's group reported Ru(II)-catalyzed oxidative *ortho* alkenylation of *N,N*-disubstituted benzamides and phenylazoles using as an oxidizing directing group with alkenes. (Scheme 1.48).^{7l}

**Scheme 1.48:** *ortho* olefination of *N, N* – dibenzamide and phenylazole

Ackermann's group showed a Ru(II)-catalyzed oxidative *ortho* alkenylation of *N*-substituted benzamides and anilides with alkenes. In this reaction, green solvent water was used as solvent (Scheme 1.49).^{7m}

**Scheme 1.49:** *ortho* olefination of *N, N* – dibenzamide and phenylazole

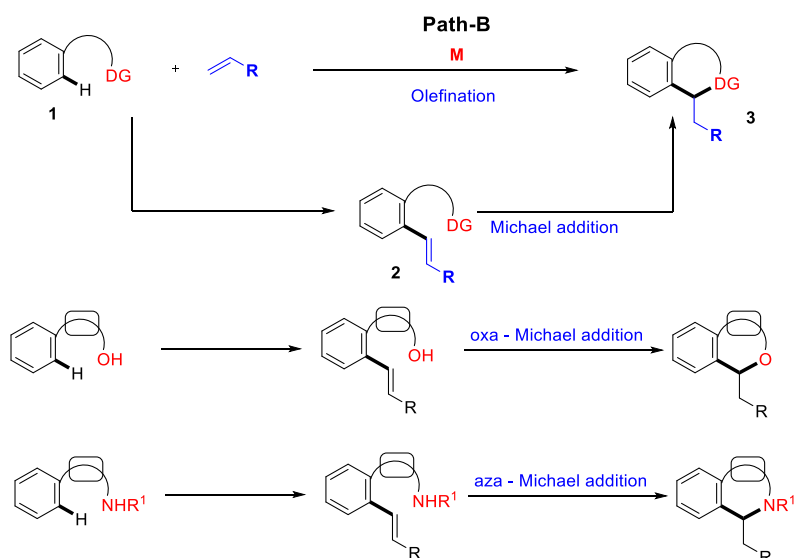
Dixneuf's group explored a ruthenium(II)-catalyzed *ortho* C-H bond alkenylation of ferrocenyl ketones with alkenes (Scheme 1.50).⁷ⁿ



Scheme 1.50: *ortho* olefination of ferrocenyl ketones

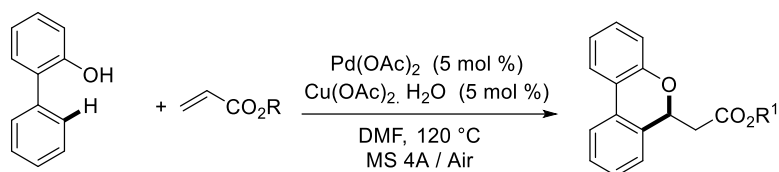
1.15: Metal Catalyzed Olefination Followed by Michael Addition with Alkenes (Path-B):

In this reaction mainly two steps are involved. In the first step, directing group containing organic moieties undergo *ortho* C-H bond olefination with alkenes via deprotonation pathway giving *ortho* olefinated products (Scheme 1.51). Subsequently, the Michael addition of *ortho* olefinated product results to provide annulated product **3**. For this type of reaction, OH or NHR containing directing groups are very crucial for Michael addition. If directing group contains OH, after olefination reaction OH involving in Michael addition type reaction with conjugated double bond of olefinated moiety providing cyclized product. The kind of Michael addition involving in this reaction is called as oxa-Michael addition. If directing group contains NHR after olefination reaction NHR involving in Michael addition type reaction with conjugated double bond of olefinated moiety providing cyclized product. The kind of Michael addition involving in this reaction is called as aza-Michael addition.



Scheme 1.51: Olefination followed by Michael addition

In 1997, for the first time, the phenol-directed olefination of sp^2 C-H bond followed by annulation was demonstrated by Miura's group (Scheme 1.52). In this reaction, 2-phenylphenols reacted with olefins in the presence of $\text{Pd}(\text{OAc})_2$, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in DMF solvent at 120°C giving 6-substituted-6*H*-dibenzo[*b,d*]pyran derivatives in good to excellent yields.^{8a}



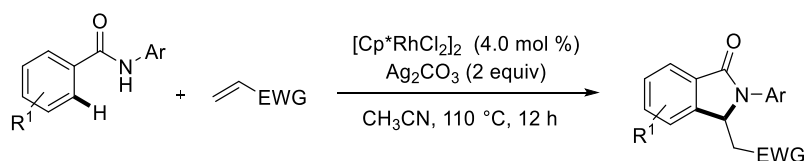
Scheme 1.52: Phenol-directed olefination followed by Michael addition.

In the later year, this type reaction was further successfully explored by the same research group by replacing OH place by NH of *N*-(arylsulfonyl)-2-phenylanilines as a directing group with alkenes (Scheme 1.53). *N*-(Arylsulfonyl)-2-phenylanilines underwent nicely oxidative coupling followed by cyclization with alkenes in the presence of $\text{Pd}(\text{OAc})_2$, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, NaOAc and molecular sieves affording corresponding cyclized products.^{8b}



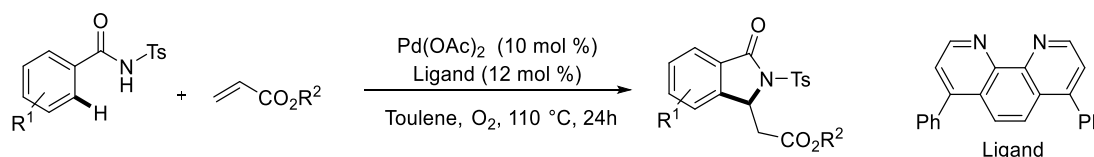
Scheme 1.53: *ortho* olefination followed by Michael addition of *N*-(arylsulfonyl)-2-phenylanilines

In 2010, Li's group showed that the *N*-aryl benzamides can undergo a Rh(III)-catalyzed oxidative *ortho* C–H bond olefination/aza-Michael addition with electron-poor alkenes, which affords the corresponding γ -lactams (Scheme 1.54).^{8c}



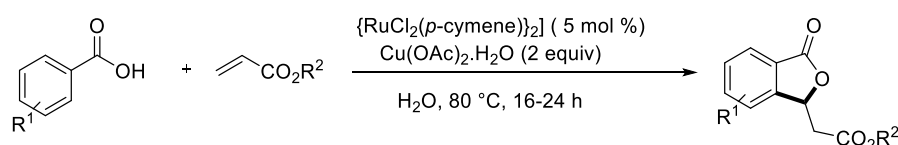
Scheme 1.54: *ortho* olefination followed by Michael addition of *N*-aryl benzamides

The Pd(II)-catalyzed *N*-acylsulfonamides directed tandem C–H olefination/annulation with alkenes for efficient synthesis of isoindolinone derivatives was successfully achieved by Zhu's group (Scheme 1.55).^{8d}



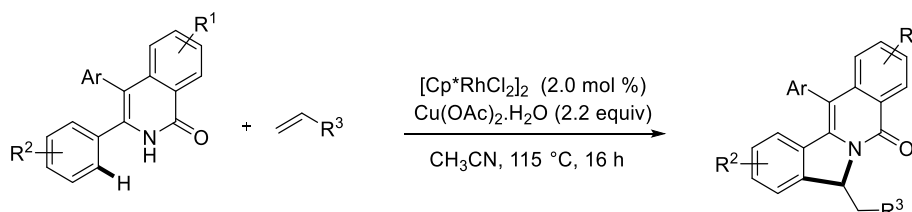
Scheme 1.55: *ortho* olefination followed by Michael addition of *N*-acylsulfonamides

In 2012, Ackermann's group described the *ortho* akenylation followed by oxa-Michael-type addition of aromatic benzoic acids with alkenes (Scheme 1.56).^{8e} The reaction of aromatic acids with alkenes in the presence of $\{\text{RuCl}_2(\text{p-cymene})\}_2$ and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ at 80 °C for 16 – 24 h afforded isocoumarin derivatives. Water used as a solvent for this catalytic system.



Scheme 1.56: *ortho* olefination followed by Michael addition of aromatic benzoic acids

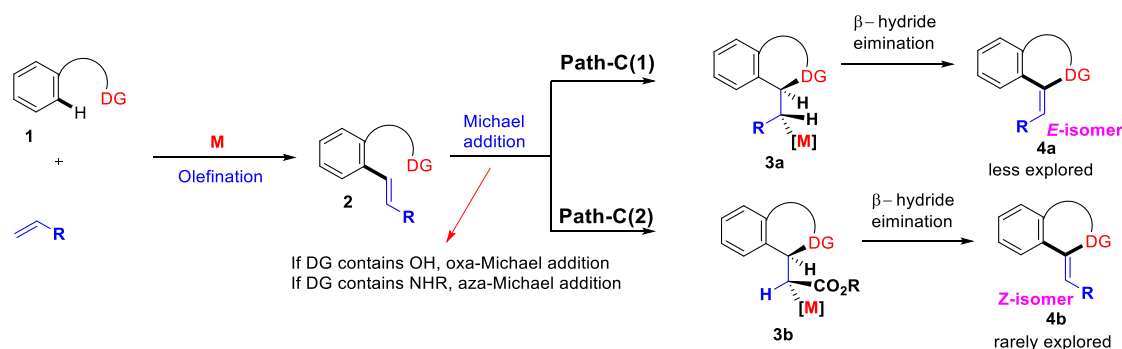
Li's group developed *ortho* C–H olefination/aza-Michael addition of NH isoquinolinones with alkenes by using $[\text{Cp}^*\text{RhCl}_2]_2$ (2.0 mol %), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.2 equiv) at 115 °C for 16 h providing tetracyclic products (Scheme 1.56).^{8f}



Scheme 1.56: *ortho* olefination followed by Michael addition of NH isoquinolinones.

1.16: Metal Catalyzed Olefination Followed by Michael Addition and β -Hydride Elimination with Alkenes (Path-C(1) and Path-C(2)):

In this type of reaction, three consecutive steps are involved. In the first step, directing group containing organic moieties undergo *ortho* C-H bond olefination with alkenes via deprotonation pathway giving *ortho* olefinated products **2**. In the second step, the Michael addition of *ortho* olefinated product providing cyclic intermediate **3**. After Michael addition, two types of intermediates **3a** and **3b** are possible to undergo β -hydride elimination. If Michael addition provides intermediate **3a**, the expected product is *E*-isomer **4a**. If Michael addition provides intermediate **3b**, the expected product is *Z*-isomer **4b** (Scheme 1.57).

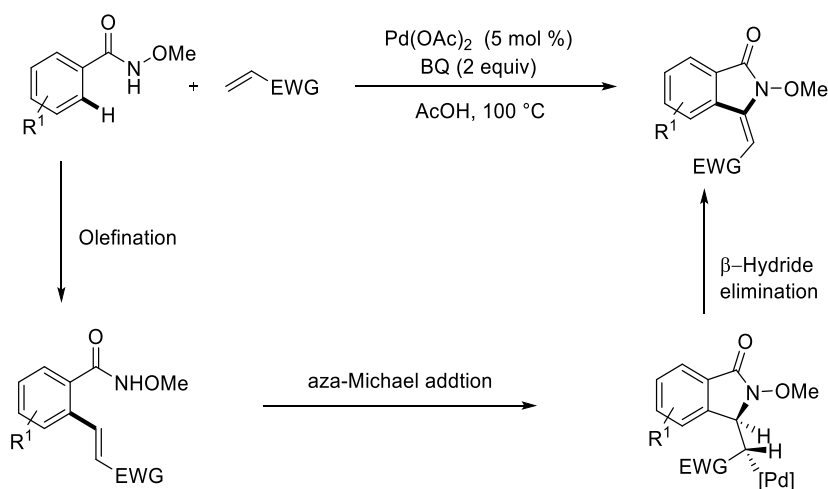


Scheme 1.57: *Ortho* olefination followed by Michael addition and β -hydride elimination

Path-C(1) Type *Ortho* C-H Olefination/Annulation:

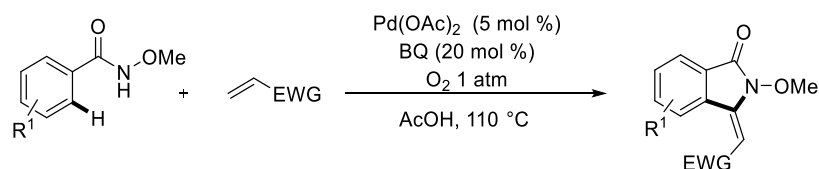
Olefination of directing group containing organic moieties following path-A type reactions to give *ortho*-olefination reactions was well explored to several directing groups by many synthetic groups since the beginning of first report in 2002. In the same time, researchers focused on C-H olefination/oxa or aza Michael which follows Path-B type reaction to provide corresponding annulated products. But *ortho* C-H olefination/annulation following path-C reaction was less explored.

Booker-Milburn's group demonstrated *N*-Alkoxybenzamides directed *ortho* C-H olefination/annulation which follows Path-C(1) type reaction with electron withdrawing containing olefins in the presence of Pd(II) catalyst affording isoindolin-1-one derivatives in *E*-selectivity. This reaction is highly stereoselective (Scheme 1.58).^{9a}



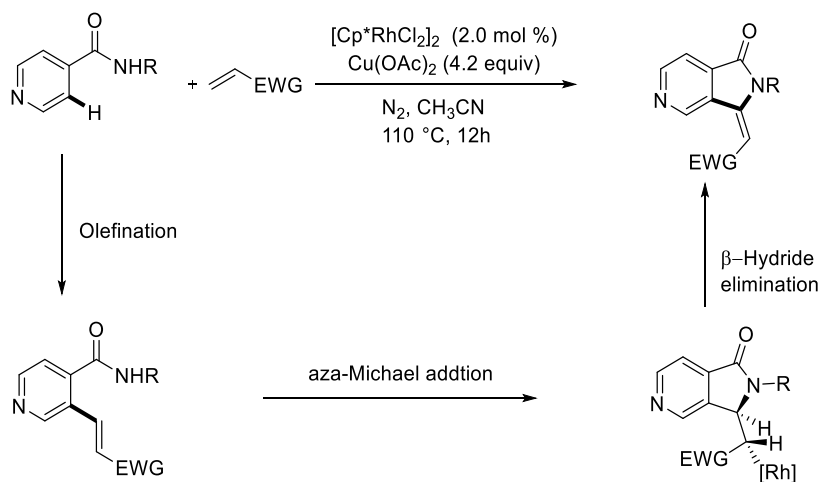
Scheme 1.58: olefination/ annulation (Path- C(1)) of *N*-Alkoxybenzamides

Simultaneously, G.-W. Wang's group reported the reaction with catalytic amount of benzoquinone. Oxygen was used for regeneration of Benzoquinone (Scheme 1.59).^{9b}



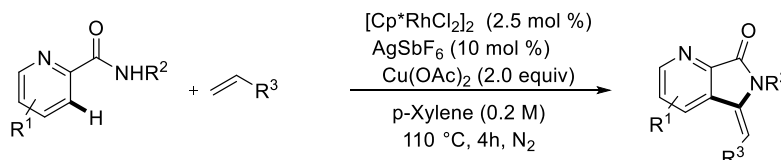
Scheme 1.59: olefination/ annulation (Path- C(1)) of isonicotinamides

Xingwei Li described isonicotinamides directed *ortho* C-H olefination/ annulation which follows Path- C(1) type reaction with electron withdrawing containing olefins in the presence of Rh(III) catalyst affording isoindolin-1-one derivatives in *E*-selectivity (Scheme 1.60). This reaction is highly stereoselective. A minor amount of *Z*-isomer was observed.^{9c}



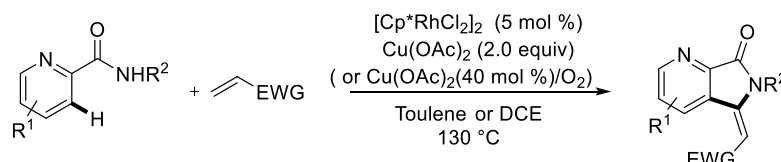
Scheme 1.60: olefination/ annulation (Path- C(1)) of isonicotinamides

In 2014, a similar type of Rh(III)-catalyzed cascade oxidative *ortho* C-H bond olefination/cyclization of picolinamides and alkenes giving pyrido pyrrolone derivatives in highly *E*-selective manner was explored by Carretero's group. A minor amount of *Z*-isomer was observed (Scheme 1.61).^{9d}



Scheme 1.61: olefination/ annulation of picolinamides

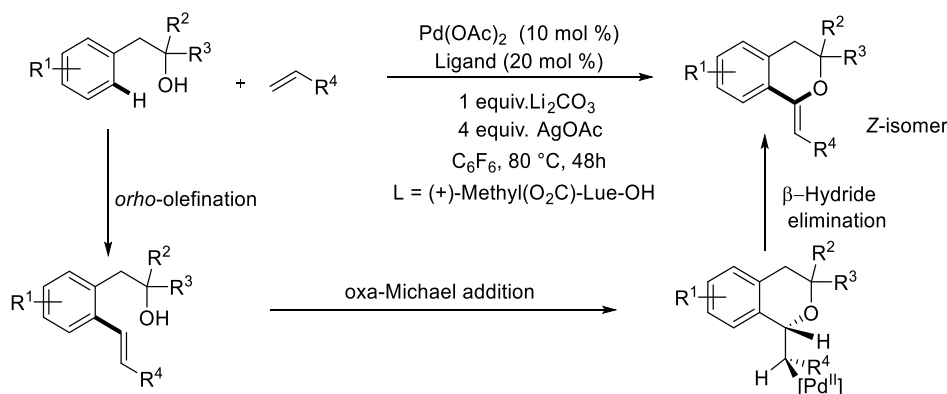
Simultaneously, Chanjuan's group reported the same reaction by using only 40 mol% of Cu(OAc)₂. In this reaction, oxygen was used for regeneration of Cu(OAc)₂. A minor amount of *Z*-isomer was observed (Scheme 1.62).^{9e}



Scheme 1.62: olefination/ annulation of picolinamides by using less Cu(OAc)₂ amount.

Path-C(2) Type *Ortho* C-H Olefination/ Annulation:

Ortho C-H olefination/annulation following Path-C type reaction was rarely explored. Path-C(1) and Path-C(2) pathways are very interesting pathways. In these two pathways common observation is Michael addition followed by β -Hydride elimination to give cyclic product with exo double bond. In Path-C(2), the expected product is *Z*-isomer. In 2010, Yu's group showed Pd(II) catalyzed *ortho* C-H olefination/ cyclization of hydroxyl group with alkenes providing corresponding pyran derivatives in highly *Z*-selective manner (Scheme 1.63).¹⁰

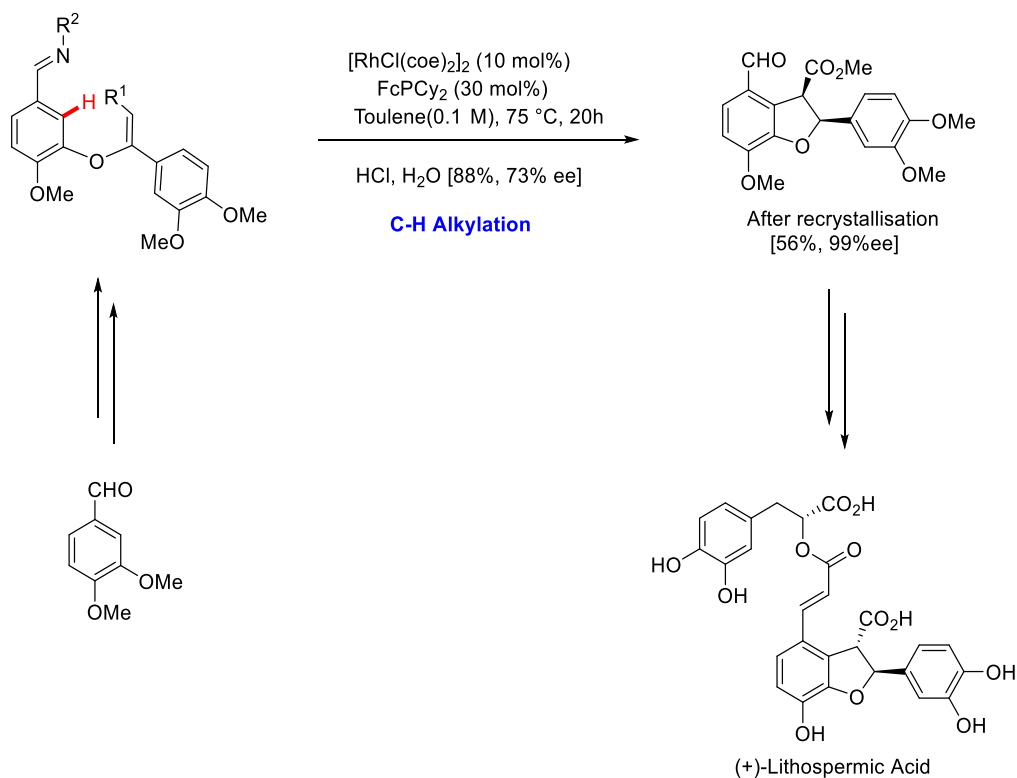


Scheme 1.63: Olefination/ annulation of hydroxyl group

Path-C(1) type ortho C-H olefination/annulation was explored with Pd and Rh metal complexes. Still, it was challenging to explore with Ru(II) metal catalyst. Path-C(2) type ortho C-H olefination/annulation to get highly Z stereo selective product with exo double with any metal was remained completely an unexplored path. In this reaction after Michael addition, two intermediates are possible to undergo β -hydride elimination to provide two stereoisomers E and Z. But only one product was formed. Because Steric, electronic and kinetic factors can greatly influence to stabilize only one intermediate. We were very interested to know, practically how Steric, electronic factors of directed group influencing on the stereochemistry of product formed in this reaction. The succeed focus of Path-C(1) type ortho C-H olefination/annulation in the beginning of fourth chapter and Path-C(2) type ortho C-H olefination/annulation in the end part of 3rd chapter will be discoursed.

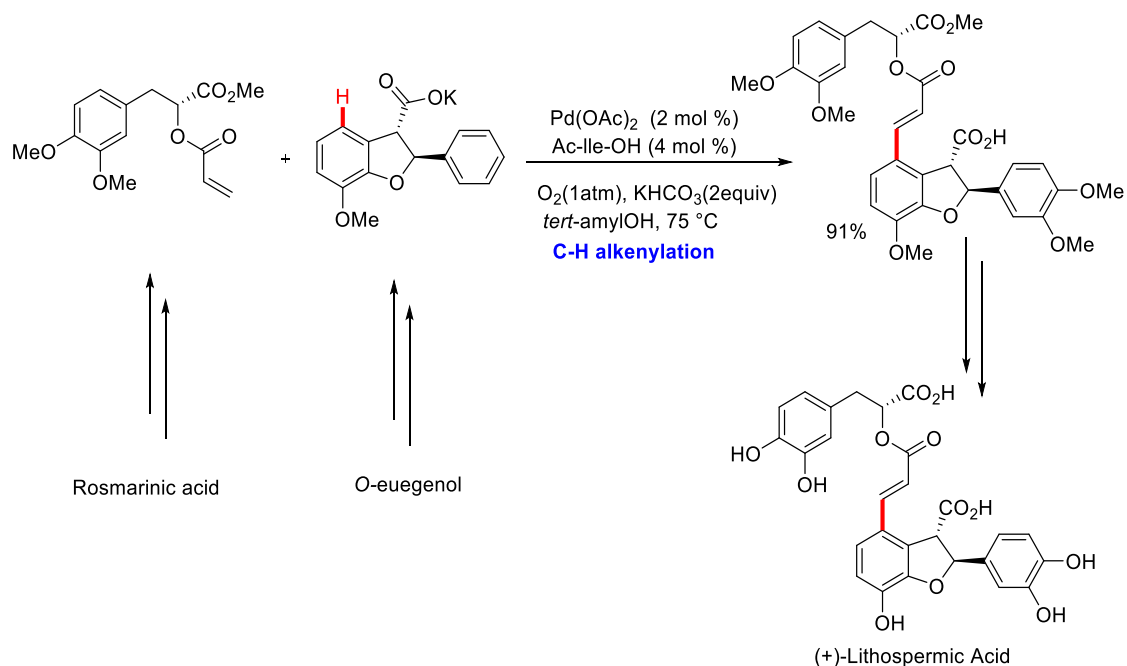
1.17: C-H Activation is A key Step in Total Synthesis.

C-H activation has emerged a powerful tool for construction of C-C and C-heteroatom bonds from the last several decades. Amongst the recent synthetic methodological advances, undoubtedly, transition-metal mediated C-H activation reactions occupy a commanding position and has revolutionized the synthetic field in an unprecedented manner. However, in spite of these advances, applications of C-H activation-based synthetic methods could largely focus on the naturally occurring biologically active building blocks. An ideal synthesis would bring similarly sized fragments together in a convergent manner by only coupling C-H bonds of two fragments to make a C-C bond in order to achieve target compound. Such a “direct” synthesis achieved through C-H functionalization can be necessarily implied a step-economical synthesis. For example, the landmark, first total synthesis of (+)-lithospermic acid was successfully achieved by Bergman’s group, using asymmetric intramolecular alkylation via rhodium-catalyzed C-H bond activation as a key step (Scheme 1.64).¹¹



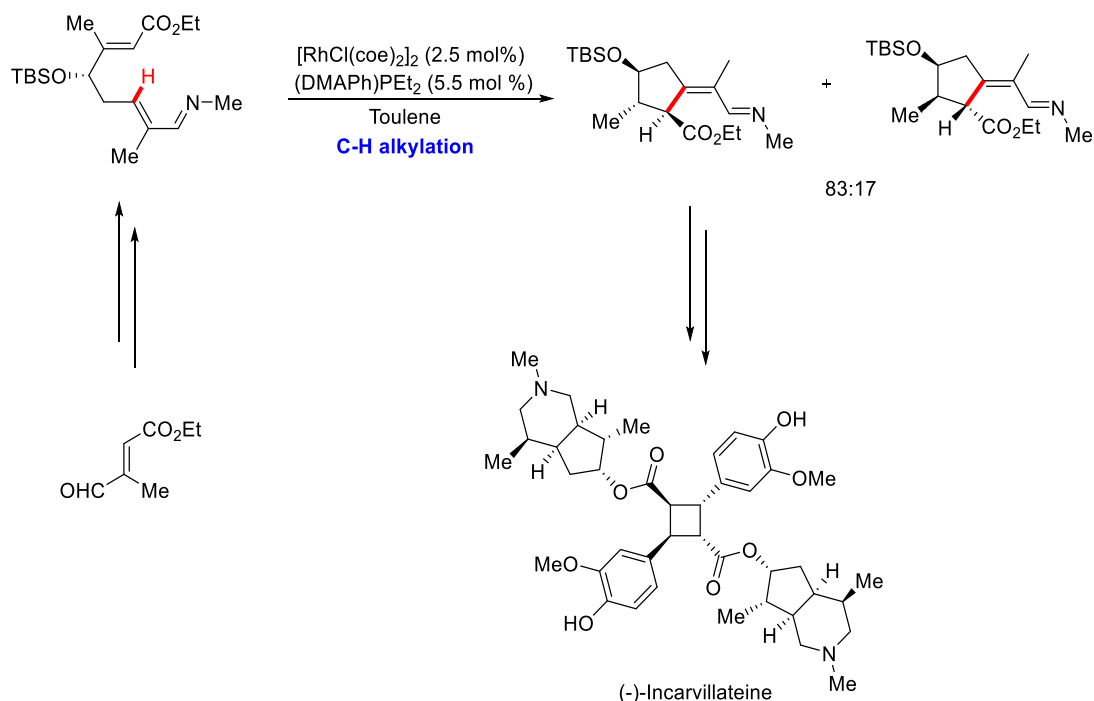
Scheme 1.64: Rhodium-catalyzed asymmetric intramolecular alkylation via C-H bond activation in the total synthesis of (+)-Lithospermic Acid

Later, in 2011, Yu's group reported an equally elegant and ingenious approach, highly convergent total synthesis of (+)-Lithospermic acid by employing carboxylic acid directed C-H activation followed by an intermolecular alkenylation in the presence of Pd(II) catalyst to construct the side chain of the targeted molecule (Scheme 1.65).¹²



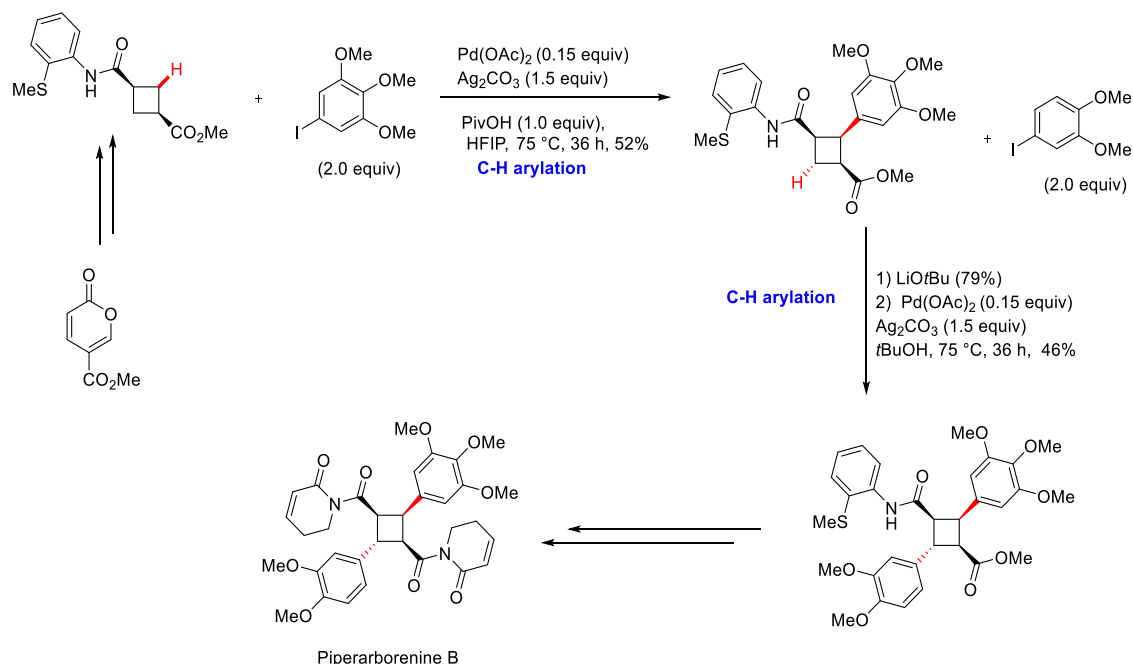
Scheme 1.65: Palladium-catalyzed C-H bond intermolecular alkenylation in the total synthesis of (+)-Lithospermic Acid

In 2008, Tsai, Bergman, and Ellman reported asymmetric synthesis of (-)-Incarvilleine employing an intramolecular alkylation via a Rh-catalyzed olefinic C-H bond activation (Scheme 1.66).¹³



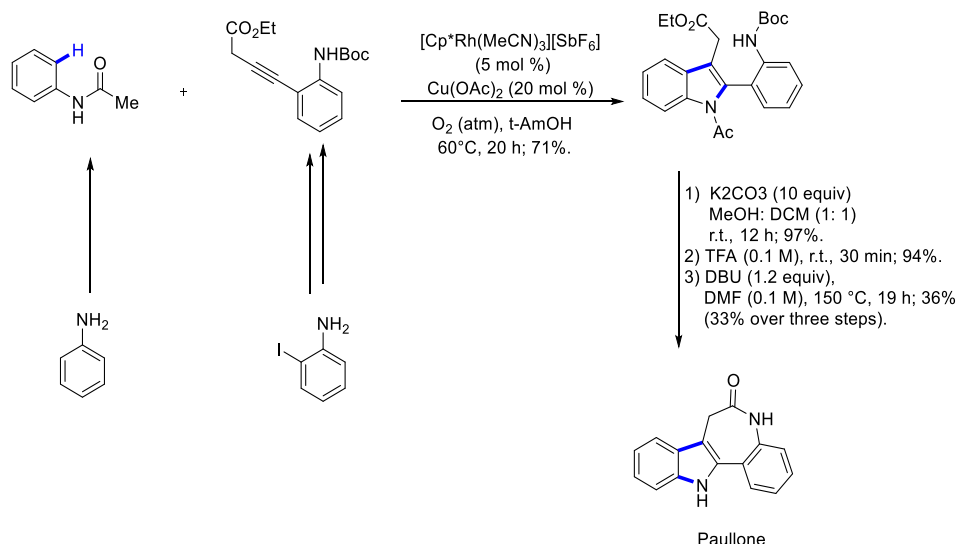
Scheme 1.66: Rhodium-catalyzed asymmetric intramolecular alkylation via olefinic C-H bond activation in the total synthesis of (-)-Incarvilleine

Logic strategy of sequential C-H bond arylations for construction of unsymmetrical cyclobutanes in the total synthesis of piperarborenine B was demonstrated by Baran and co-workers in 2011 (Scheme 1.66).¹⁵



Scheme 1.67: Pd catalyzed sequential C-H bond arylations in the total synthesis of piperarborenine B

In 2010, Fagnou's group developed a rhodium-catalyzed cyclization of anilides with alkynes affording indole derivatives and applied this synthetic method to the total synthesis of Paullone (Scheme 1.66).¹⁵



Scheme 1.66: Rhodium-catalyzed C-H bond activation is key step in the total synthesis of Paullone.

All these seminal contributions prompted us to investigate for making C-H bond activation as key step in the total synthesis. And also another side it is very important to

search of challenging synthetic problems to solve by involving construction of main or fused rings of such kind of wonderful targets with a simplified manner by using advanced synthetic methods such as less expensive, moisture insensitive and stable Ru(II) catalyzed C-H bond activation. After the first report from Oi and Inoue, tremendous contributions have been made in the ruthenium(II)-catalyzed C-H bond functionalization reaction. By employing these methodologies, chemical bonds including C-C and C-hetero bond have been constructed by several research groups in different orientations of several reagents with various arenes to construct variety of new organic core moieties. However, in the literature, it is very rare to find a solved total synthetic problem by using Ru(II) catalyzed C-H bond activation as a key step. After looking at this, we strongly decided to work on the concept of development of a challenging total synthesis by involving chelation assisted Ru(II) catalyzed C-H bond activation as a key step. We will discourse about the continuous effort and the success journey of this concept in the end chapter of thesis.

1.18: References

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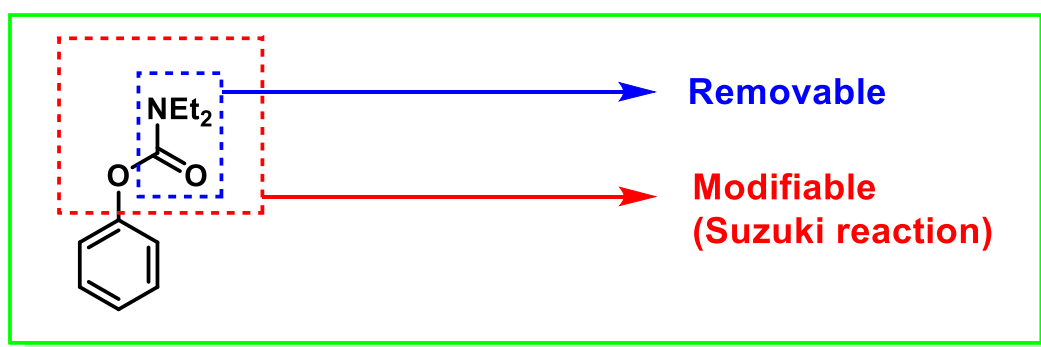
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Chapter 2

Removable and Modifiable Directing Group in Ru-Catalyzed *Ortho* C-H Bond Activation with Alkenes and Alkynes

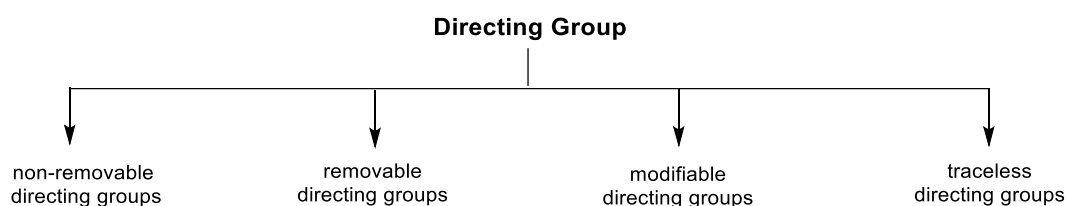


Section 2A: Ruthenium-Catalyzed Selective Aerobic Oxidative *ortho*-Alkenylation of Substituted Phenols with Alkenes through C–H Bond Activation

2A.1 Introduction:

2A.2 Classification of Directing Groups for C-H Bond Activation

In the last several decades, C-H bond functionalization via transition metal catalyzed C-H activation was explored to various directing groups.⁶⁻⁹ Based on diversity of directing group, these directing groups can be classified into four major types (Scheme 2A.1).¹³

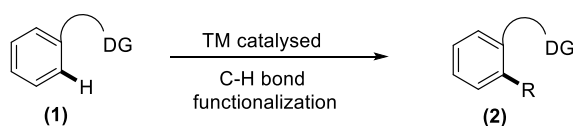


Scheme 2A.1: Classification of directing groups

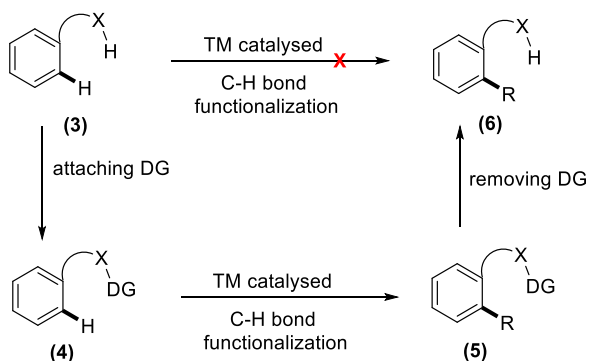
First one is non-removable directing group. This directing group will be remained as a part of the product after C-H activation (Scheme 2A.2, equation-1). These directing groups cannot undergo any modifications. And they cannot be removed. Sometimes, the lack of further versatile transformations leads to limit of the structural diversity of the products. The second one is removable directing group. Some of the organic functional groups (anilines, phenols, thiols.....) cannot undergo directly C-H bond functionalization (Scheme 2A.2, equation-2). In this, attaching one additional functional group which acts as a directing group for doing C-H bond activation is required. This directing group containing substrates undergo C-H bond functionalization. After functionalization, the directing can be easily removed by subjecting additional step. This strategy is very useful for doing C-H bond functionalization of functional groups which cannot directly perform C-H bond functionalization. The third one is modifiable directing group. Generally avoiding bis functionalization, and doing sequentially two different functionalizations is really challenging task by using conventional methods. It is only possible by doing C-H bond functionalization of the directing group which can further undergo functionalization (Scheme 2A.2, equation-3). These are called as modifiable directing groups. The fourth one is traceless directing group. The C–H bond functionalization of the substrate and directing group removal of functionalized product are carried out in one-pot (Scheme 2A.2, equation-4a). In some cases, the directing group introduction, functionalization, and

removal of functionalized product can also be done in the same pot (Scheme 2A.2, equation-4b). Such directing groups are called as traceless directing groups.

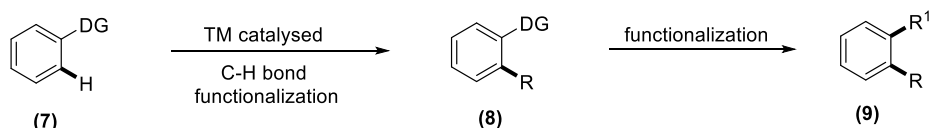
(1) Non-removal directing groups



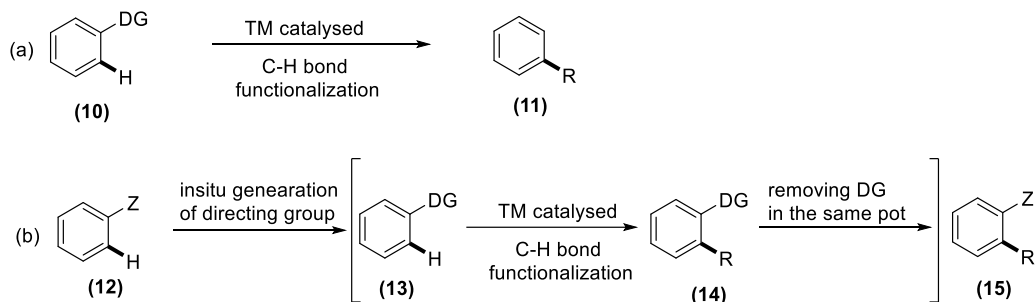
(2) Removal directing groups



(3) Modifiable directing groups



(4) Traceless directing groups

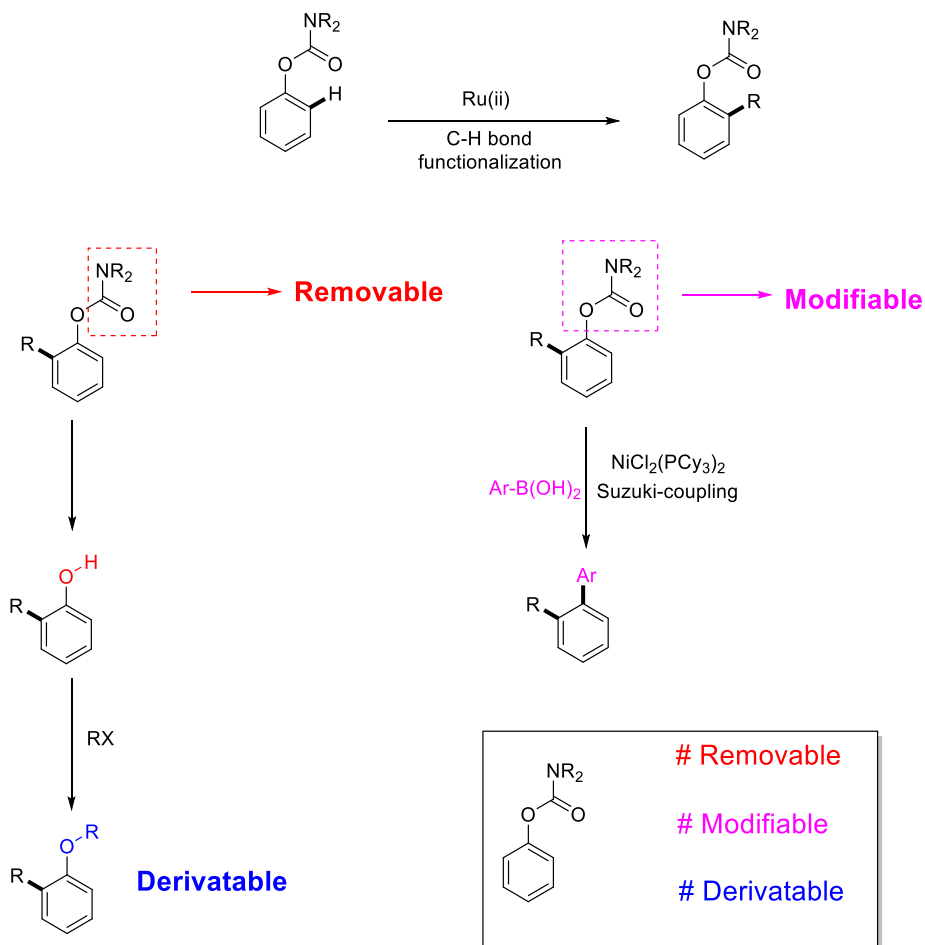


Scheme 2A.2: Classification of directing groups

2A.3 Multi Structural Diversity Features of Carbamate Group and Aim of the Present Work

Multi structural diversity features of carbamate group made us to focus on doing C-H bond functionalization of this directing by using less expensive, moisture insensitive and highly stable Ru(II) catalyst. Carbamate functional is easily removable (Scheme 2A.3). After C-H bond the *ortho* C-H bond functionalization carbamate of functionalized product can be readily removed to get *ortho* functionalized Phenol derivatives which are normally very difficult to produce from *ortho* C-H bond functionalization of phenols.

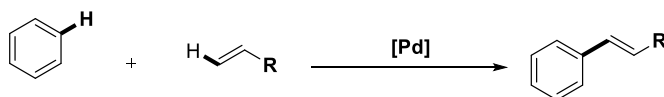
Very recent advantage of Suzuki coupling reaction is developing Suzuki reaction by using carbamate as coupling partner with aromatic boronic acids in the presence of Ni (II) catalysts. After C-H bond activation carbamate of functionalized product can be used for further functionalization. C-H bond activation of carbamate directing groups is a wonderful platform to perform two different sequential functionalizations on ortho to each other. In addition, *ortho* functionalized phenol derivatives can undergo alkylation to give *ortho* functionalized Phenol alkoxy derivatives.



Scheme 2A.3: Multi structural diversity features of carbamate group

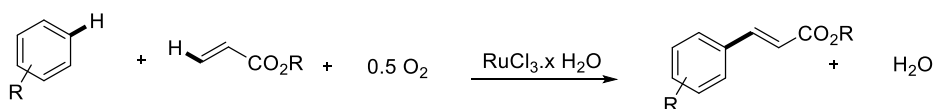
Transition-metal-catalyzed coupling of aromatic electrophiles or organometallic reagents with alkenes is a key reaction for constructing alkene derivatives in a highly stereoselective manner.¹ This type of alkenylation reaction has been widely used to synthesize various organic materials, natural products, and drug molecules.² Although this type of coupling reaction is highly useful in organic synthesis, a preactivated coupling partner such as a C–X or C–M moiety in the starting material is usually required for coupling with alkenes. Instead of using a preactivated species, a similar type of coupling reaction that is done by C–H bond activation would be even more useful in

organic synthesis.³ This type of reaction is highly atom economical and environmentally friendly. The Fujiwara group was first to describe that the alkenylation reaction of electron-rich aromatics with alkenes occurred through an electrophilic metalation pathway in the presence of a palladium catalyst (Scheme 2A.4).⁴



Scheme 2A.4: Fujiwara-Moritani reaction

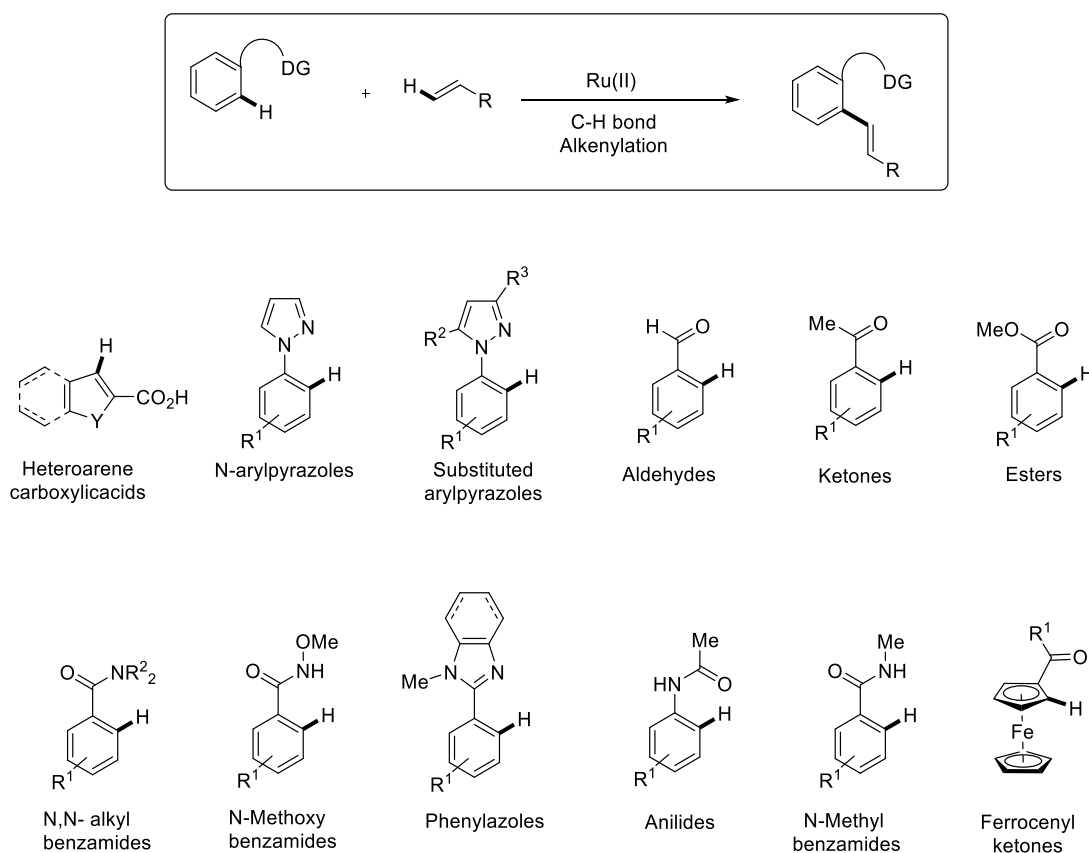
The Lewis group demonstrated that the *ortho*-C–H bond of phenol can be ethylated by ethylene in the presence of a ruthenium catalyst.⁵ Initially, the alkenylation reaction of a variety of directing groups was explored by an expensive palladium and rhodium complexes via chelation assisted C-H activation (see chapter 1).⁶ Ruthenium complexes are less expensive and easily affordable compared with other rhodium and palladium complexes. Further, a ruthenium catalyzed C-H bond functionalization can be done under an air atmosphere and/or even water can be used as a solvent.^{7a} Thus, an inert atmosphere is not required in the reaction. Recently, a less-expensive ruthenium catalysts has gained much attention in this type of reactions, due to its remarkable reactivity and selectivity. In 2001, the pioneering example of oxidative alkenylation (Fujiwara type) reaction which followed non-chelation assisted C-H bond activation pathway by using Ruthenium catalyst was reported Milstein's group (Scheme 2A.5).^{7b}



Scheme 2A.5: RuCl₃·3H₂O catalyzed oxidative alkenylation

In 2009, Yi's group showed first success full *ortho* selective C-H bond oxidative alkenylation of ketones with styrenes by using ruthenium-hydride catalyst resulting *ortho* alkenylated aromatic ketones and cyclic indene derivatives.^{7c} Later, the practice of oxidative *ortho* alkenylation by utilizing less expensive, highly stable and easy to handle Ru(II) complexes had been started by Miura's group, reporting of *ortho* olefination of heteroaromatic carboxylic acids with olefins in the presence of [{RuCl₂(p-cymene)}₂] catalyst.^{7b} Later, wonderful contributions made by exploring the Ru catalysed oxidative *ortho* Alkenylation to directing groups such as heteroarene carboxylic acids, N-aryl pyrazoles, aldehydes, ketones, esters, N, N- alkyl benzamides, N-methoxy benzamides, phenylazoles, anilides, N-methyl benzamides, ferrocenyl ketones (Scheme 2A.6).^{8,9} In

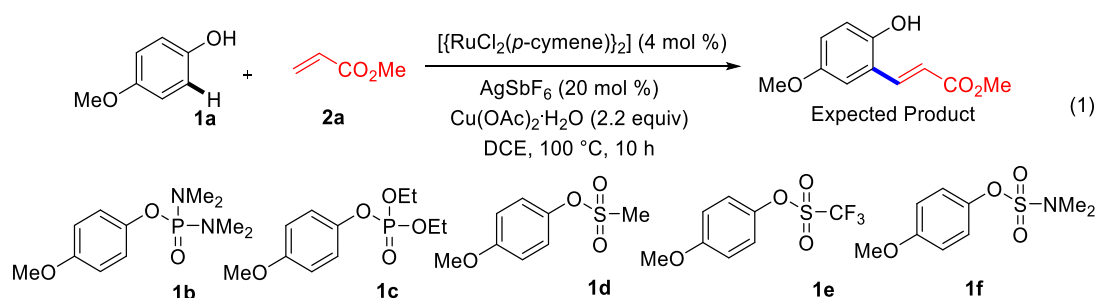
this journey, our group mainly focused on developing conditions for achieving oxidative *ortho* alkenylation of very weak directing groups.^{9a-c} Generally, It is believed that the oxygen containing functional groups would not coordinate effectively with a Ru(II) catalyst to do C-H bond activation. Because the oxophilicity of Ru(II) catalyst is not sufficient to coordinate with oxygen contacting directing groups. The oxophilicity was lifted by adding an external additive AgSbF₆ and successfully achieved the oxidative *ortho* olefination of such a weak directing groups ketones,^{9a} aldehydes^{9b} and esters.^{9c} And also Cu(OAc)₂·H₂O amount was reduced from 2 equiv to 25 mol% by using aerobic conditions. Strong directing groups and weak directing were explored to *ortho* olefination by using Ru(II) catalyst.^{8b-c} And also the oxidative *ortho* alkenylation of removal directing group anilide was reported.^{7a} At the same time, developing olefination reaction of multi-diversity directing group by using Ru(II) catalyst would be very interesting. In this investigation, we found such kind of directing group as carbamate for focusing on the development of oxidative *ortho* alkenylation reaction with alkenes in the presence of Ru(II) catalyst.



Scheme 2A.6: Ru(II) catalyzed oxidative *ortho* C-H bond olefination of various directing groups

2A.4: Results and Discussion

Initially, the coupling reaction was carried out with 4-methoxyphenol (**1a**) and methyl acrylate (**2a**) in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (4 mol %), AgSbF_6 (20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.20 mmol) in 1,2-dichloroethane (DCE) at 100 °C for 12 h (eq. 1). In the reaction, alkenylation at the *ortho* position of phenol **1a** was expected. However, no such coupling product was observed and starting material **1a** was recovered. Next, the catalytic reaction was tested with phenol derivatives such as substituted phosphorodiamidate **1b**, 4-methoxyphenyl diethyl phosphate (**1c**), 4-methoxyphenyl mesylate (**1d**), 4-methoxyphenyl triflate (**1e**) and 4-methoxyphenyl dimethylsulfamate (**1f**), whereby, an additional heteroatom such as P=O or S=O was incorporated as a directing group to assist the *ortho* C-H bond activation under similar reaction conditions. In these reactions also, no coupling products were observed.



2A.5: Optimization Studies

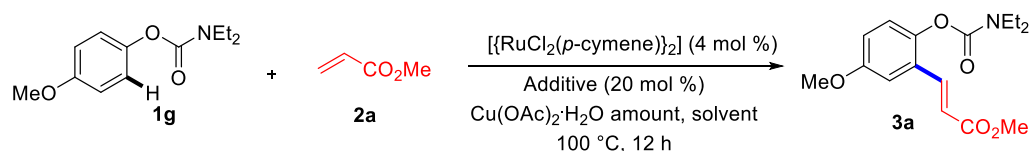


Table 2A.1: Optimization Studies ^a

entry	solvent	Cu(OAc) ₂ ·H ₂ O	additive	yield of 3a (%) ^b
1	DCE	2.20 equiv.	AgSbF ₆	65
2	THF	2.20 equiv.	AgSbF ₆	52
3	<i>t</i> -BuOH	2.20 equiv.	AgSbF ₆	15
4	DME	2.20 equiv.	AgSbF ₆	93
5	DME	2.20 equiv.	AgBF ₄	35
6	DME	2.20 equiv.	AgOTf	46
7	DME	2.20 equiv.	KPF ₆	20
8	DME	2.20 equiv.	-	15
9	DME	-	AgSbF ₆	-
10	DME	30 mol%	AgSbF₆	92^c

^aAll reactions were carried out under the following conditions: **1g** (1.0 equiv.), **2a** (3.0 equiv.), [RuCl₂(*p*-cymene)]₂ (4 mol %), additive (20 mol %), and Cu(OAc)₂·H₂O in DME at 100 °C for 12 h under N₂.

^bYields were determined by ¹H NMR integration methods with mesitylene as an internal standard. ^cUnder air, 86% isolated yield was observed.

Note: The catalytic reaction was tried without ruthenium and AgSbF₆. No product **3a** was observed.

Interestingly, in the reaction of 4-methoxyphenyl diethylcarbamate (**1g**) with methyl acrylate (**2a**), coupling product **3a** was observed in 65% yield under similar reaction conditions (Table 2A.1). In order to increase the yield of **3a**, the catalytic reaction was tested with various solvents such as THF, DMF, toluene, DMSO, *tert*-BuOH, *tert*-amyl alcohol, 1,2-dimethoxyethane (DME) and CH₃CN. Among them, DME solvent was the best for the reaction, providing coupling product **3a** in 93% yield (entry 4). The remaining solvents were less effective or totally ineffective for the coupling reaction. Next, the effect of additive (20 mol %) was examined. A variety of additives such as AgSbF₆, AgBF₄, AgOTf and KPF₆ were tested (entries 4-7). Among them, AgSbF₆ was very effective, giving **3a** in 93% yield (entry 4). AgBF₄, AgOTf and KPF₆ were less effective, giving **3a** in 35, 46, and 20% yields, respectively (entries 5-7). The catalytic reaction was also tested without AgSbF₆ (entry 8). In the reaction, coupling product **3a** was observed only in 15% yield. Similarly, the catalytic reaction was also tested without Cu(OAc)₂·H₂O (entry 9). However, in the reaction, no coupling product **3a** was observed. Then, the amount of oxidant, Cu(OAc)₂·H₂O, was reduced from 2.20 mmol to catalytic amount (30 mol %) and the reaction was conducted under air atmosphere (entry 10). The catalytic reaction underwent nicely, giving coupling product **3a** in 92% NMR yield under air

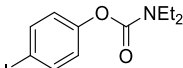
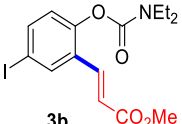
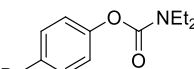
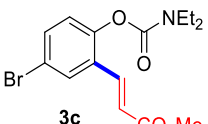
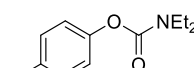
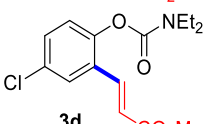
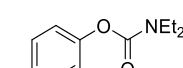
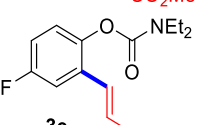
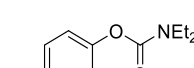
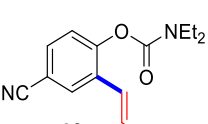
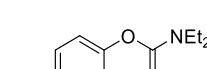
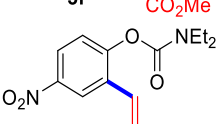
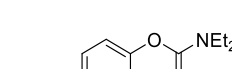
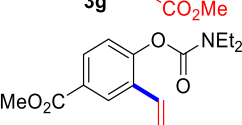
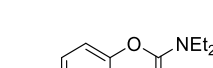
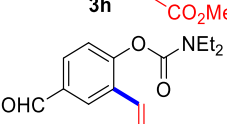
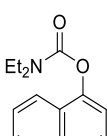
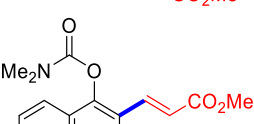
atmosphere (entry 10). Based on these optimization studies, we chose [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (4 mol %), AgSbF_6 (20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (30 mol %) in DME at 100 °C for 12 h under air atmosphere as the standard conditions for the present coupling reaction. Under the optimized reaction conditions, product **3a** was observed in 86% isolated yield. Interestingly, in the present reaction, only catalytic amount of oxidant $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (30 mol %) was used. Whereas in most of the rhodium-catalyzed chelation-assisted C-H bond activation reactions, stoichiometric amount of oxidants were required and the reaction was conducted under nitrogen atmosphere.¹⁰

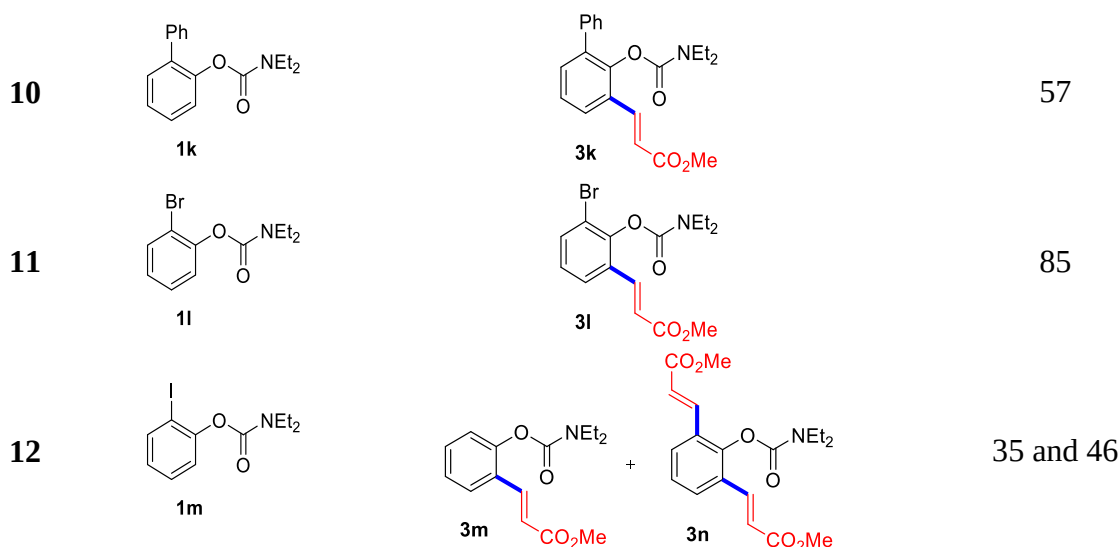
2A.6: Scope of Substituted Phenyl Carbamates.

To explore the scope of the coupling reaction, various substituted aromatic carbamates **1h-s** were examined under the optimized reaction conditions (Table 2A.2). Thus, the treatment of halogen group substituted carbamates such as 4-iodophenyl diethylcarbamate (**1h**), 4-bromophenyl diethylcarbamate (**1i**), 4-chlorophenyl diethylcarbamate (**1j**) and 4-fluorophenyl diethylcarbamate (**1k**) with methyl acrylate (**2a**) provided alkene derivatives **3b-e** in excellent to moderate 89%, 87%, 75% and 42% yields, respectively (Table 2A.2, entries 1-4). Electron-withdrawing group substituted carbamates such as 4-cyanophenyl diethylcarbamate (**1l**), 4-nitrophenyl diethylcarbamate (**1m**), methyl ester group substituted carbamate **1n** and 4-formylphenyl diethylcarbamate (**1o**) also efficiently participated in the coupling reaction with methyl acrylate (**2a**) giving coupling products **3f-i** in 27%, 23%, 52% and 66% yields, respectively (Table 2A.2, entries 5-8). In the reactions, remaining amount of starting materials were recovered. It is important to point out that the catalytic reaction is highly regioselective, alkenylation was observed only at the *ortho* C-H bond of carbamate group substituted aromatics and no alkenylation was observed at the *ortho* to CN or NO₂ or CO₂Me or CHO group substituted aromatics. It is well known that CO₂Me or CHO is also a good directing group for C-H bond activation reaction.^[11] The present results show that the carbamate group chelates with Ru better than the CO₂Me and CHO. 1-Naphthalenyl diethylcarbamate (**1j**) also reacted with **2a** affording coupling product **3j** in 61% yield (Table 2A.2, entries 9). The catalytic reaction also proceeded very well with *ortho*-substituted aromatic carbamates such as phenyl group substituted carbamate **1q** and 2-bromophenyl diethylcarbamate (**1r**), yielding coupling products **3k** and **3l** in 57% and 85% yields, respectively (Table 2A.2, entries 10-11). However, 2-iodophenyl diethylcarbamate (**1s**) reacted with methyl acrylate (**2a**) affording coupling products **3m** and **3n** in 35 and 46% yields, respectively (Table 2A.2,

entries 12)., whereby, *ortho* I group of **1s** involved in the coupling reaction via oxidative addition in addition to *ortho* C-H bond activation.¹ The exact reason for the formation of double alkenylation in the reaction of aryl iodide carbamate **1s** with alkene **2a** is not very clear to us. It might be possible that C-I bond reacts first and favours second alkenylation with respect to other substrates.

Table 2A.2: Results of the Reaction of Aromatic Carbamates **1** with Methyl Acrylate

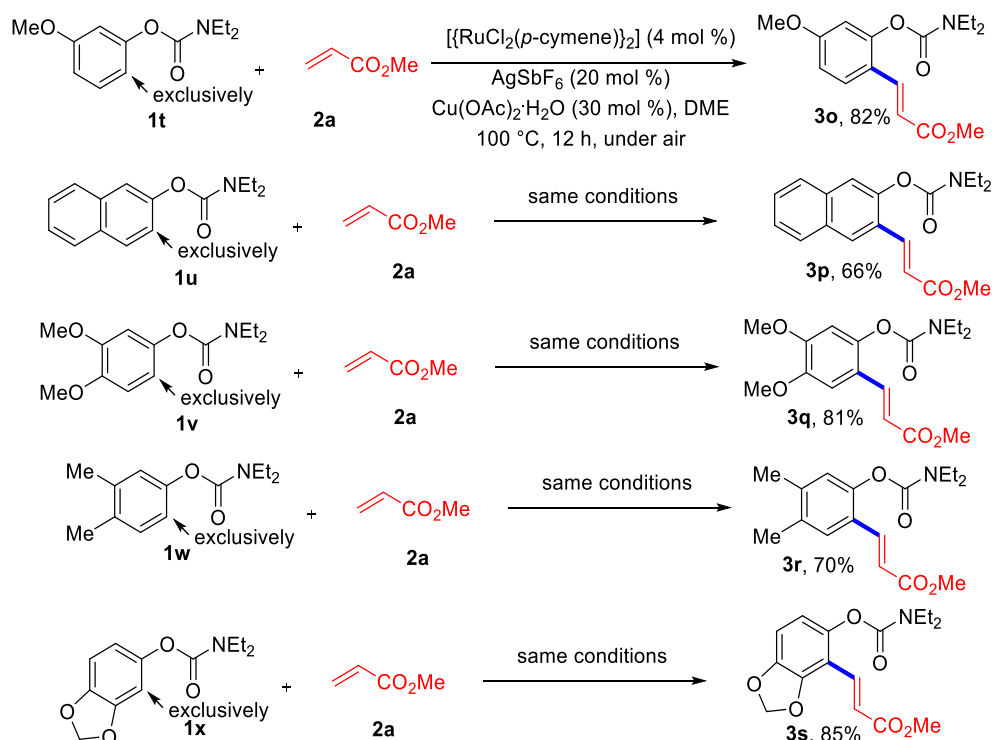
entry	1	product 3	yield (%) ^b
1	 1b	 3b	89
2	 1c	 3c	87
3	 1d	 3d	75
4	 1e	 3e	42
5	 1f	 3f	27
6	 1g	 3g	24
7	 1h	 3h	52
8	 1i	 3i	66
9	 1j	 3j	61



^aAll reactions were carried out using aromatic carbamate **1** (150 mg), methyl acrylate (**2a**) (3.0 equiv), [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (4 mol %), AgSbF_6 (20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (30 mol %) in DME (1,2-dimethoxyethane) (3.0 mL) at 100 °C for 12 h. ^bIsolated yields.

2A.7: Regioselectivity Studies

Next, the regioselectivity of substituted carbamates **1t-x** were tested under the optimized reaction conditions (Scheme 2A.7). A *meta*-substituted phenyl carbamate, 3-methoxyphenyl diethylcarbamate (**1t**), regioselectively coupled with **2a** at the less hindered C-H bond of **1t** moiety exclusively to give coupling product **3o** in 82% yield. 2-Naphthalenyl diethylcarbamate (**1u**) regioselectively reacted with **2a** at the less hindered C-H bond of **1u** moiety exclusively yielding coupling product **3p** in 66% yield. Similarly, 3,4-dimethoxyphenyl diethylcarbamate (**1v**) and 3,4-dimethylphenyl diethylcarbamate (**1w**) also reacted regioselectively with **2a** at the sterically less hindered C-H bond of **1v** and **1w** moiety exclusively providing alkene derivatives **3q** and **3r** in 81% and 70% yields, respectively. In contrast, sesamol carbamate **1x** regioselectively reacted with **2a** at the sterically highly hindered C-H bond of **1x** moiety exclusively giving coupling product **3s** in 85% yield.

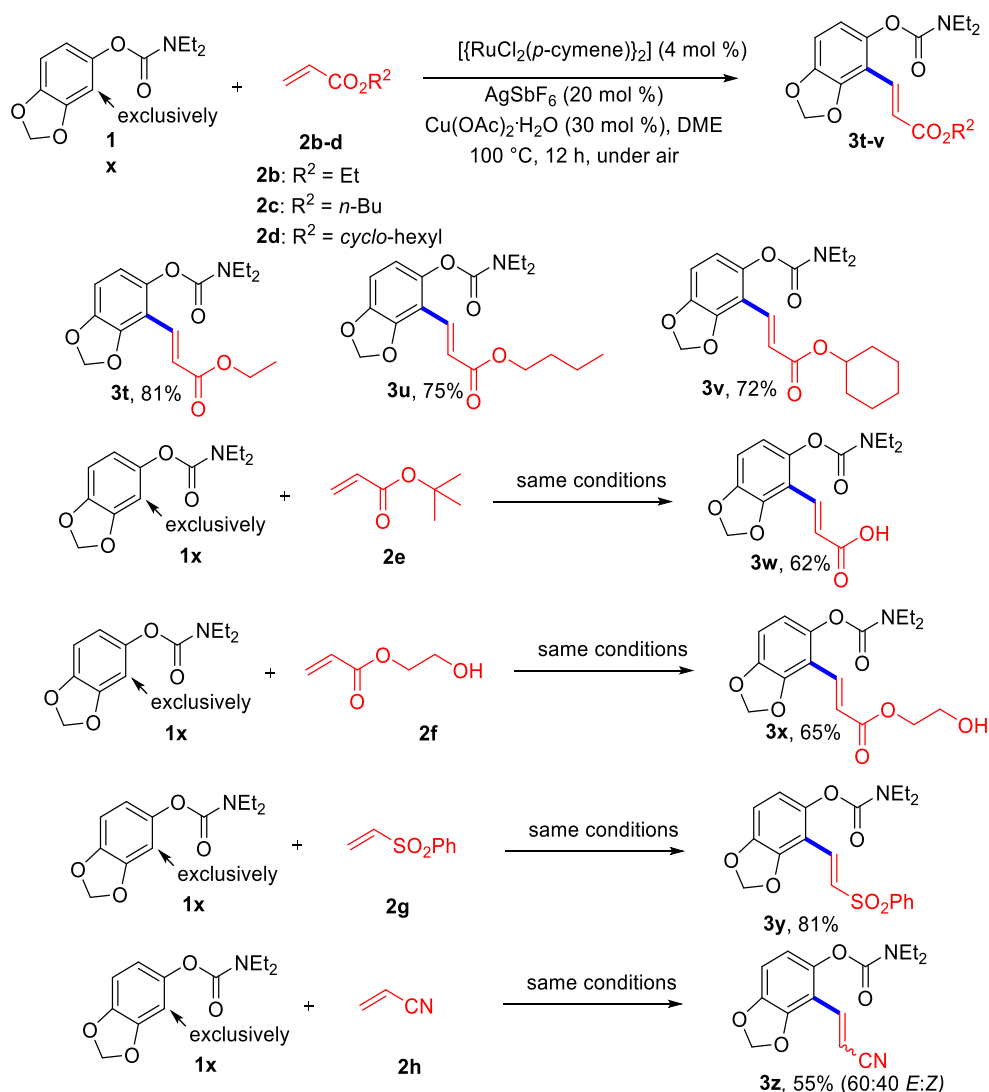


Scheme 2A.7: Regioselectivity studies of unsymmetrical phenyl carbamates.

2A.8: Scope of Alkenes

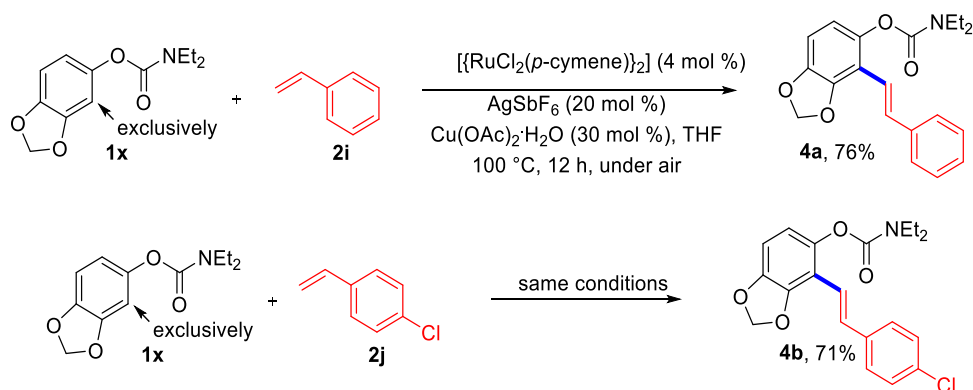
The present alkenylation reaction was extended successfully with various substituted alkenes **2b-j** under the optimized reaction conditions (Schemes 2.9 and 2.10). Ethyl acrylate (**2b**), *n*-butyl acrylate (**2c**), cyclohexyl acrylate (**2d**), *tert*-butyl acrylate (**2e**) and 2-hydroxyethyl acrylate (**2f**) reacted efficiently with sesamol carbamate **1x** giving the corresponding coupling products **3t-x** in 81%, 75%, 72%, 62% and 65% yields, respectively (Scheme 2A.8). However, in the reaction of *tert*-butyl acrylate (**2e**) with **1x**, a *tert*-butyl group on the expected alkenylated product was cleaved during the reaction and an acrylic acid derivative **3w** was observed. In meantime, the catalytic reaction was tested with acrylic acid and **1x**. However, no coupling product **3w** was observed in the reaction. It is important to note that a sensitive OH group of 2-hydroxyethyl acrylate (**2f**) does not affect the coupling reaction. Other activated alkenes such as phenyl vinyl sulfone (**2g**) and acrylonitrile (**2h**) were also compatible for the reaction. Thus, phenyl vinyl sulfone (**2g**) underwent coupling with **1x** providing an alkenylated product **3y** in excellent 81% yield. Whereas, acrylonitrile (**2h**) provided a mixture of stereoisomeric coupling products **3z** in 55% combined yields in an approximately 60:40 *E*:*Z* ratios. The catalytic

reaction was also tested with other activated alkenes such as acrolein, ethyl vinyl ketone and *N,N*-dimethylacrylamide. In these reactions, no coupling products were observed.



Scheme 2A.8: Scope of substituted alkenes.

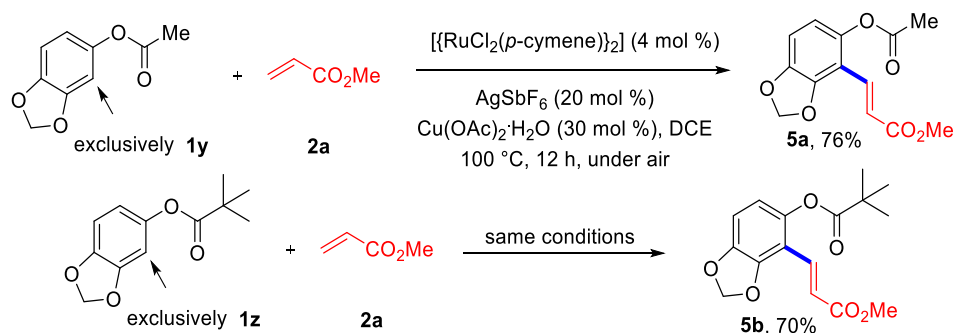
The catalytic reaction also worked very well with substituted styrenes **2i** and **2j** (Scheme 2A.9). Thus, styrene (**2i**) and 4-chlorostyrene (**2j**) reacted efficiently with **1x** giving alkene derivatives **4a** and **4b** in 76% and 71% yields, respectively. In the reaction, THF was used as a solvent. DME solvent was not suitable for the reaction. All these reactions were also highly regioselective as like product **3s** and C-H bond activation takes place exclusively at sterically highly hindered C-H bond of **1x**. It is noteworthy to say that the present catalytic reaction is compatible with electron-rich, halogen and electron-deficient group substituted phenyl carbamates.



Scheme 2A.9: Scope of substituted alkenes.

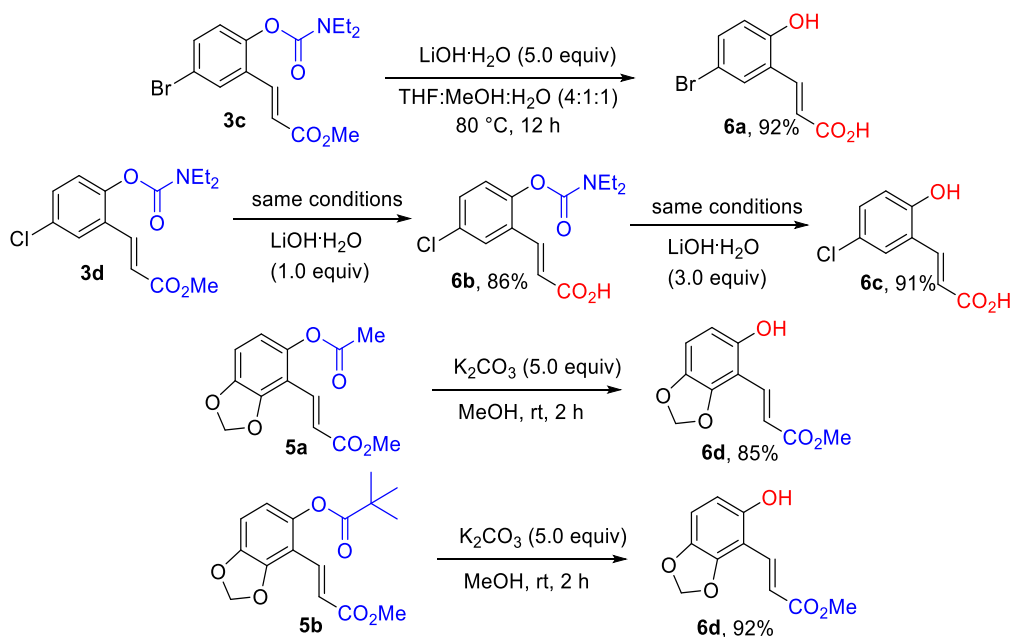
2A.9: *ortho*-Alkenylation of Substituted Phenol Acetates

To further explore the scope of the coupling reaction, *ortho*-alkenylation of substituted phenol acetates was tried (Scheme 2A.10). Treatment of sesamol acetate **1y** with methyl acrylate (**2a**) in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (4 mol %), AgSbF_6 (20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (30 mol %) in 1,2-dichloroethane at 100 °C for 12 h under air gave coupling product **5a** in 76% yield. Similarly, sesamol pivalate **1z** underwent coupling with **2a** to provide an alkenylated compound **5b** in 70% yield.

Scheme 2A.10: *ortho*-Alkenylation of phenyl acetate and phenyl pivalate with alkenes.

It is important to note that carbamate is a versatile functional group that can be utilized for various organic transformations.¹² It is well known that carbamate group is a nice directing group for metal base-mediated C-H bond activation reactions.^{12a-d} Further, carbamate group can also be used as an electrophile for cross-coupling reaction with aryl boronic acids or nucleophiles in the presence of nickel catalyst.^{12e-g} By using 5.0 equiv of $\text{LiOH} \cdot \text{H}_2\text{O}$ in $\text{THF}:\text{MeOH}:\text{H}_2\text{O}$ (4:1:1) at 80 °C for 12 h, both ester and carbamate groups of **3c** was cleaved successfully, giving a substituted phenol derivative **6a** in 92% yield (Scheme 2A.11). Interestingly, in the presence of 1.0 equiv of $\text{LiOH} \cdot \text{H}_2\text{O}$, an ester of **3d** was cleaved very selectively, providing an acrylic acid derivative **6b** in 86% yield. In the reaction, carbamate group of **6b** remained intact. Further, carbamate group of **6b** was

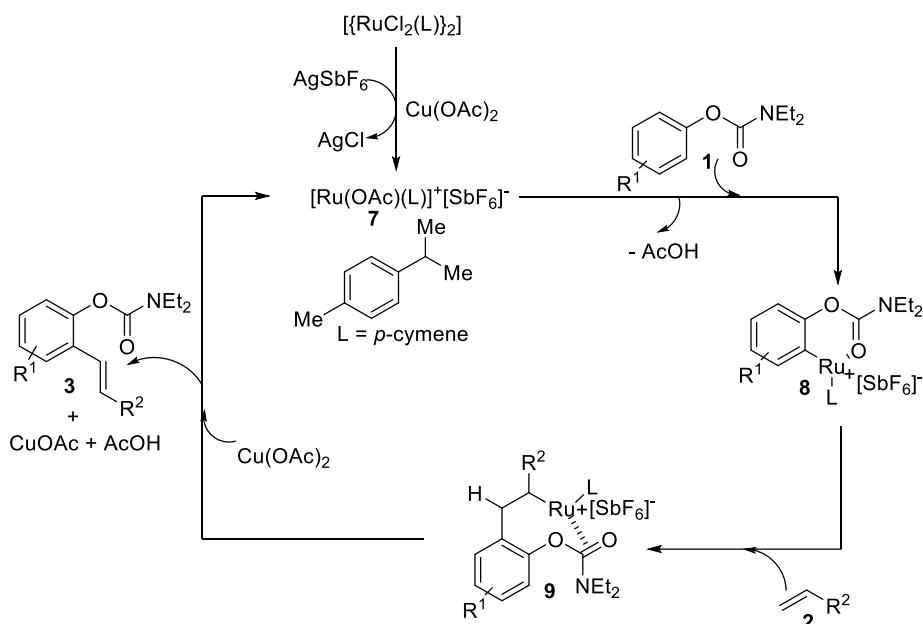
cleaved successfully in the presence of LiOH (3.0 equiv), affording substituted phenol derivative **6c** in 91% yield. Surprisingly, in the presence of K_2CO_3 in MeOH at room temperature for 2 h, acetyl (COMe) or pivaloyl (CO-*tert*Bu) groups of **5a** and **5b** were cleaved very selectively, affording corresponding phenol derivative **6d** in 85% and 92% yields, respectively. In the reaction, alkene substituted ester groups of **5a** and **5b** remained intact.



Scheme 2A.11: Synthesis of phenols.

2A.10: Mechanism

A possible reaction mechanism involving a six-membered ruthenacycle as a key intermediate is proposed to account for the present catalytic reaction (Scheme 2.12). The first step involves removal of chloride ligand by $AgSbF_6$ salt from $[RuCl_2(p\text{-cymene})_2]$ complex giving cationic ruthenium species **7**. Coordination of the carbonyl group of carbamate **1** to the ruthenium cationic species **7** followed by *ortho*-metalation affords a six-membered ruthenacycle **8**.^{3c} Coordinative insertion of alkene **2** into the Ru–carbon bond of ruthenacycle **8** provides intermediate **9**. β -Hydride elimination of intermediate **9** in the presence of $Cu(OAc)_2$ gives coupling product **3** and regenerates the active ruthenium species **7** for the next catalytic cycle. In the reaction, only 30 mol % of $Cu(OAc)_2$ is used as an internal oxidant. The remaining amount of $Cu(OAc)_2$ source is regenerated under oxygen or atmosphere from the reduced copper source.



Scheme 2.12: Proposed mechanism

2A.11: Conclusion

1. We have developed a ruthenium-catalyzed chelation-assisted aerobic oxidative *ortho*-alkenylation of phenol carbamates or acetates with alkenes to afford *ortho* alkenylated phenol carbamate or acetate derivatives in good to excellent yields in a highly regio- and stereoselective manner.
2. Further, the *ortho* alkenylated phenol carbamate or acetate derivatives were further converted into corresponding phenol derivatives quantitatively by using $LiOH \cdot H_2O$ or K_2CO_3 base.

2A.12: References

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2A.13: Experimental Section

General Procedure for the Coupling of Phenol Carbamates or Acetates with Alkenes Catalyzed by Ruthenium Complex:

[$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (0.04 mmol, 4 mol %), AgSbF_6 (0.20 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.30 mmol, 30 mol %) were taken in a 15-mL pressure tube equipped with a magnetic stirrer and septum (Note: AgSbF_6 is moisture sensitive. Thus, AgSbF_6 was taken inside the nitrogen glove box). To the tube were then added carbamate **1** (1.0 equiv), alkene **2** (3.0 equiv) and 1,2-dimethoxyethane solvent (3.0 mL) via syringes and allowed the reaction mixture to stir at room temperature for 5 min. During this time, tube was covered with septum. Then, septum was taken out and the reaction mixture was stirred under an open air for an additional 5 min (Note: During this time, nitrogen gas was in the pressure could go away and air goes inside the tube. In the reaction, only 30 mol %

of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ was used as an internal oxidant. In fact, 2.20 equiv. of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ was needed in the reaction. It is strongly believed that the remaining amount of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ source is regenerated under oxygen or atmosphere from the reduced copper source CuOAc . Thus, we have conducted the reaction under an open air). Then, the pressure tube was covered with a screw cap and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 , filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3**.

For styrenes **2i** and **2j**, THF was used as a solvent.

A similar procedure was followed for the coupling of phenol esters **1y** and **1z** with **2a**. But, the reaction was conducted in the presence of 1,2-dichloroethane solvent (3.0 mL) at 100 °C for 12 h.

General Procedure for the Preparation of Compounds **6a-c**.

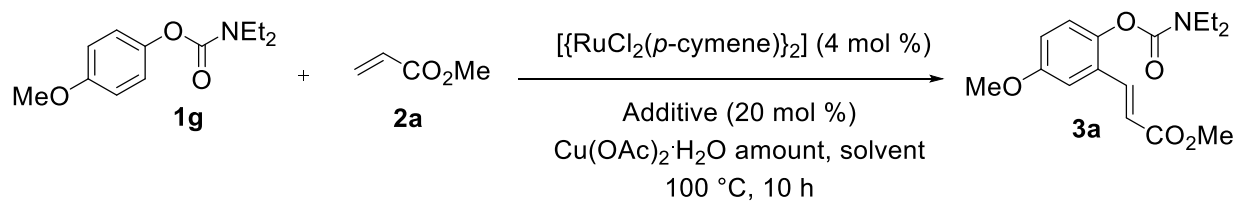
A two-neck 50 mL round bottom flask fitted with a condenser and a septum containing a mixture of **3c** (100 mg) and $\text{LiOH} \cdot \text{H}_2\text{O}$ (5.0 equiv) in 6 mL of THF/MeOH/ H_2O (4:1:1). The reaction mixture was refluxed at 80 °C for 12 h. After the reaction, reaction mixture was allowed to cool to room temperature and the reaction mixture was neutralized (pH = 6) using 1N HCl. The product was extracted with ethyl acetate, washed with water and brine. The extract was dried with anhydrous Na_2SO_4 . The solvents were evaporated under reduced pressure to give pure **6a** as a colorless solid (purification is not necessary).

A similar procedure was used for the preparation of compounds **6b** and **6c**. However, only 1.0 equiv of $\text{LiOH} \cdot \text{H}_2\text{O}$ for **6b** and 3.0 equiv of $\text{LiOH} \cdot \text{H}_2\text{O}$ for **6c** were used for the reaction.

Procedure for the Preparation of Compound **6d**.

A single-neck 25 mL round bottom flask fitted with a septum containing a mixture of **5a** or **5b** (100 mg) and K_2CO_3 (5.0 equiv) in 3 mL of MeOH. The reaction mixture was stirred at room temperature for 2 h. After the reaction, reaction mixture was neutralized (pH = 6) using 1N HCl. The product was extracted with ethyl acetate, washed with water and brine. The extract was dried with anhydrous Na_2SO_4 . The solvents were evaporated under reduced pressure to give pure **6d** as a colorless solid (purification is not necessary).

Spectral data and copies of ^1H and ^{13}C NMR spectra of all compounds **3a-z**, **4a-b**, **5a-b** and **6a-d** are listed below.

Table 1 Optimization Studies^a

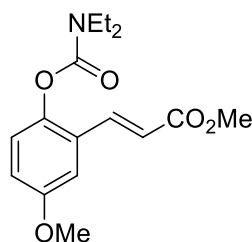
Entry	Solvent	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	Additive	Yield of 3a (%) ^b
1	DCE	2.20 equiv	AgSbF_6	65%
2	THF	2.20 equiv	AgSbF_6	52%
3	DMF	2.20 equiv	AgSbF_6	-
4	Toluene	2.20 equiv	AgSbF_6	-
5	DMSO	2.20 equiv	AgSbF_6	-
6	<i>tert</i> -BuOH	2.20 equiv	AgSbF_6	15%
7	<i>tert</i> -amyl alcohol	2.20 equiv	AgSbF_6	-
8	DME	2.20 equiv	AgSbF_6	93%
9	CH_3CN	2.20 equiv	AgSbF_6	-
10	DME	2.20 equiv	AgBF_4	35%
11	DME	2.20 equiv	AgOTf	46%
12	DME	2.20 equiv	KPF_6	20%
13	DME	2.20 equiv	-	15%
14	DME	-	AgSbF_6	-
15 ^c	DME	30 mol %	AgSbF_6	92%

^a All reactions were carried out under the following conditions: **1f** (1.0 mmol), **2a** (3.0 mmol), $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (4 mol %), additive (20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in DME at 100 °C for 12 h under N_2 atmosphere. ^b Yields were determined by the ^1H NMR integration method, using mesitylene as an internal standard. ^c Under an open atmosphere, 86% isolated was observed.

Interestingly, in the reaction of 4-methoxyphenyl diethylcarbamate (**1g**) with methyl acrylate (**2a**), coupling product **3a** was observed in 65% yield under similar reaction conditions (Table 1). In order to increase the yield of **3a**, the catalytic reaction was tested with various solvents such as THF, DMF, toluene, DMSO, *tert*-BuOH, *tert*-amyl alcohol, 1,2-dimethoxyethane (DME) and CH_3CN (entries 2-9). Among them, DME solvent was

the best for the reaction, providing coupling product **3a** in 93% yield (entry 8). The remaining solvents were less effective or totally ineffective for the coupling reaction (entries 2-7 and 9). Next, the effect of additive (20 mol %) was examined. A variety of additives such as AgSbF₆, AgBF₄, AgOTf and KPF₆ were tested (entries 8 and 10-12). Among them, AgSbF₆ was very effective, giving **3a** in 93% yield (entry 8). AgBF₄, AgOTf and KPF₆ were less effective, giving **3a** in 35, 46, and 20% yields, respectively (entries 10-12). The catalytic reaction was also tested without AgSbF₆ (entry 13). In the reaction, coupling product **3a** was observed only in 15% yield. Similarly, the catalytic reaction was also tested without Cu(OAc)₂·H₂O (entry 14). However, in the reaction no coupling product **3a** was observed. Then, the amount of oxidant, Cu(OAc)₂·H₂O, was reduced from 2.20 mmol to catalytic amount (30 mol %) and the reaction was conducted under an open atmosphere (entry 15). The catalytic reaction underwent nicely, giving coupling product **3a** in 86% isolated yield (92% NMR yield) under an open atmosphere (entry 15). Based on these optimization studies, we chose [{RuCl₂(*p*-cymene)}₂] (4 mol %), AgSbF₆ (20 mol %) and Cu(OAc)₂·H₂O (30 mol %) in DME at 100 °C for 12 h under an open atmosphere as the standard conditions for the present coupling reaction.

2A.14 Spectral Data of Compounds

(E)-Methyl 3-(2-((diethylcarbamoyl)oxy)-5-methoxyphenyl)acrylate (3a).

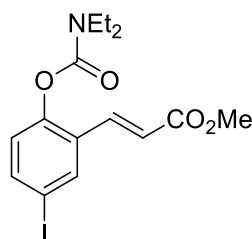
According to **general procedure**, the coupling of 4-methoxyphenyl diethylcarbamate (**1g**; 150 mg, 0.6726 mmol, 1.0 equiv) with methyl acrylate (**2a**; 173 mg, 2.017 mmol, 3.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (16.4 mg, 0.0269 mmol, 4 mol %), AgSbF_6 (45.1 mg, 0.1345 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (39.9 mg, 0.2017 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (17% ethyl acetate in hexanes) to give **3a** (178 mg, 86% yield) as a colorless semisolid. The same reaction was also performed via procedure B. The reaction worked equally to yield almost same yield (85%).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977, 1718, 1637, 1464, 1277, 1157 and 1038.

^1H NMR (CDCl_3 , 400 MHz): δ 7.75 (d, J = 16.0 Hz, 1 H), 7.04 (d, J = 4.0 Hz, 1 H), 7.02 (s, 1 H), 6.88 (dd, J = 8.0, 4.0 Hz, 1 H), 6.36 (d, J = 16.0 Hz, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.46 (q, J = 8.0 Hz, 2 H), 3.34 (q, J = 8.0 Hz, 2 H), 1.27 (t, J = 8.0 Hz, 3 H), 1.16 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.2, 156.9, 154.1, 144.1, 138.7, 127.9, 124.3, 119.4, 117.2, 111.2, 56.7, 51.8, 42.4, 41.9, 14.4, 13.4.

HRMS (ESI): calc. for $[(\text{C}_{16}\text{H}_{21}\text{NO}_5)\text{Na}]$ ($\text{M}+\text{Na}$) 330.1317, measured 330.1318.

(E)-Methyl 3-(2-((diethylcarbamoyl)oxy)-5-iodophenyl)acrylate (3b).

According to **general procedure**, the coupling of 4-iodophenyl diethylcarbamate (**1h**; 150 mg, 0.47 mmol, 1.0 equiv) with methyl acrylate (**2a**; 121 mg, 1.41 mmol, 3.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (11.5 mg, 0.0188 mmol, 4 mol

%), AgSbF₆ (31.5 mg, 0.094 mmol, 20 mol %) and Cu(OAc)₂·H₂O (27.9 mg, 0.141 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (13% ethyl acetate in hexanes) to give **3b** (169 mg, 89% yield) as a colorless semisolid.

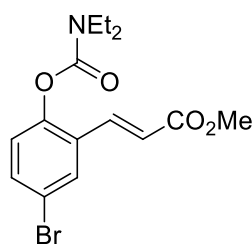
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2978, 1721, 1637, 1466, 1316, 1272, 1160 and 1105.

¹H NMR (CDCl₃, 400 MHz): δ 7.88 (s, 1 H), 7.69 (d, *J* = 16.0 Hz, 1 H), 7.63 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 6.37 (d, *J* = 16.0 Hz, 1 H), 3.76 (s, 3 H), 3.46 (q, *J* = 8.0 Hz, 2 H), 3.36 (q, *J* = 8.0 Hz, 2 H), 1.28 (t, *J* = 8.0 Hz, 3 H), 1.18 (t, *J* = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.9, 153.2, 150.0, 139.7, 137.2, 136.0, 129.8, 125.4, 120.5, 89.5, 51.9, 42.5, 42.1, 14.4, 13.4.

HRMS (ESI): calc. for [(C₁₅H₁₈INO₄)Na] (M+Na) 426.0178, measured 426.0176.

(E)-Methyl 3-(5-bromo-2-((diethylcarbamoyl)oxy)phenyl)acrylate (3c).



According to **general procedure**, the coupling of 4-bromophenyl diethylcarbamate (**1i**; 150 mg, 0.551mmol, 1.0 equiv) with methyl acrylate (**2a**; 142 mg, 1.653 mmol, 3.0 equiv) was performed in the presence of [{RuCl₂(*p*-cymene)}₂] (13.4 mg, 0.022 mmol, 4 mol %), AgSbF₆ (37 mg, 0.11 mmol, 20 mol %) and Cu(OAc)₂·H₂O (32.7mg, 0.1653 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (12% ethyl acetate in hexanes) to give **3c** (171 mg, 87% yield) as a colorless semisolid.

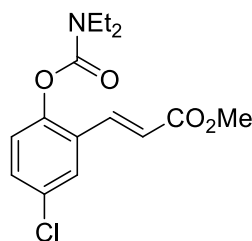
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2928, 1722, 1638, 1469, 1318, 1273, 1160, 1103 and 1035.

¹H NMR (CDCl₃, 400 MHz): δ 7.72 (d, *J* = 16.0 Hz, 1 H), 7.70 (d, *J* = 4.0 Hz, 1 H), 7.44 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.38 (d, *J* = 16.0 Hz, 1 H), 3.76 (s, 3 H), 3.46 (q, *J* = 8.0 Hz, 2 H), 3.36 (q, *J* = 8.0 Hz, 2 H), 1.28 (t, *J* = 8.0 Hz, 3 H), 1.18 (t, *J* = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.9, 153.2, 149.2, 137.2, 133.7, 129.9, 129.4, 125.2, 120.5, 118.7, 51.9, 42.5, 42.1, 14.4, 13.4.

HRMS (ESI): calc. for [(C₁₅H₁₈BrNO₄)Na] (M+Na) 378.0317, measured 378.0321.

(E)-Methyl 3-(5-chloro-2-((diethylcarbamoyl)oxy)phenyl)acrylate (3d).



According to **general procedure**, the coupling of 4-chlorophenyl diethylcarbamate (**1j**; 150 mg, 0.66 mmol, 1.0 equiv) with methyl acrylate (**2a**; 170 mg, 1.98 mmol, 3.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (16.15 mg, 0.0264 mmol, 4 mol %), AgSbF_6 (44.3 mg, 0.132 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (39.2 mg, 0.198 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (12% ethyl acetate in hexanes) to give **3d** (154 mg, 75% yield) as a pale yellow semisolid.

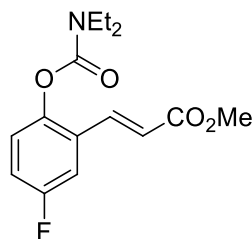
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 1722, 1639, 1469, 1271, 1181, 1105 and 1034.

^1H NMR (CDCl_3 , 400 MHz): δ 7.73 (d, J = 16.0 Hz, 1 H), 7.70 (s, 1 H), 7.30 (dd, J = 8.0, 4.0 Hz, 1 H), 7.10 (d, J = 8.0 Hz, 1 H), 6.38 (d, J = 16.0 Hz, 1 H), 3.76 (s, 3 H), 3.45 (q, J = 8.0 Hz, 2 H), 3.35 (q, J = 8.0 Hz, 2 H), 1.28 (t, J = 8.0 Hz, 3 H), 1.18 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.9, 153.3, 148.7, 137.4, 131.1, 130.8, 128.9, 126.9, 124.8, 120.5, 51.9, 42.5, 42.1, 14.4, 13.4.

HRMS (ESI): calc. for $[(\text{C}_{15}\text{H}_{18}\text{ClNO}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 334.0822, measured 334.0832.

(E)-Methyl 3-(2-((diethylcarbamoyl)oxy)-5-fluorophenyl)acrylate (3e).



According to **general procedure**, the coupling of 4-fluorophenyl diethylcarbamate (**1k**; 150 mg, 0.71 mmol, 1.0 equiv) with methyl acrylate (**2a**; 183 mg, 2.13 mmol, 3.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (17.3 mg, 0.0284 mmol, 4 mol %), AgSbF_6 (47.7 mg, 0.142 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (42.1 mg, 0.213 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (12% ethyl acetate in hexanes) to give **3e** (89 mg, 42% yield) as a colorless oil.

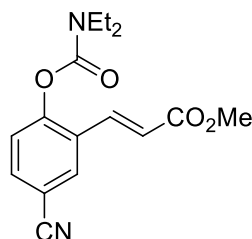
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976, 1722, 1639, 1589, 1475, 1325, 1275, 1180, 1105 and 1034.

^1H NMR (CDCl_3 , 400 MHz): δ 7.74 (d, J = 16.0 Hz, 1 H), 7.25 (dd, J = 8.0, 4.0 Hz, 1 H), 7.11 (dd, J = 8.0, 4.0 Hz, 1 H), 7.07 – 7.02 (m, 1 H), 6.37 (d, J = 16.0 Hz, 1 H), 3.76 (s, 3 H), 3.47 (q, J = 8.0 Hz, 2 H), 3.36 (q, J = 8.0 Hz, 2 H), 1.28 (t, J = 8.0 Hz, 3 H), 1.18 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.9, 161.1 and 158.7 (F coupling), 153.6, 146.2, 137.7, 128.9, 125.0 and 124.9 (F coupling), 120.4, 118.0 and 117.8 (F coupling), 113.3 and 113.0 (F coupling), 51.9, 42.5, 42.1, 14.4, 13.4.

HRMS (ESI): calc. for $[(\text{C}_{15}\text{H}_{18}\text{FNO}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 318.1118, measured 318.1122.

(E)-Methyl 3-(5-cyano-2-((diethylcarbamoyl)oxy)phenyl)acrylate (3f).



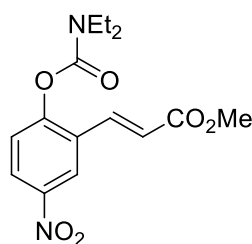
According to **general procedure**, the coupling of 4-cyanophenyl diethylcarbamate (**11**; 150 mg, 0.688 mmol, 1.0 equiv) with methyl acrylate (**2a**; 177 mg, 2.064 mmol, 3.0 equiv) was performed in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (16.8 mg, 0.0275 mmol, 4 mol %), AgSbF_6 (46.2 mg, 0.1376 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (40.8 mg, 0.206 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (15% ethyl acetate in hexanes) to give **3f** (56 mg, 27% yield) as a colorless semisolid.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2925, 2241, 1718, 1640, 1425 and 1038.

^1H NMR (CDCl_3 , 400 MHz): δ 7.86 (s, 1 H), 7.76 (d, J = 16.0, 1 H), 7.62 (dd, J = 8.0, 4.0 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 6.43 (d, J = 16.0 Hz, 1 H), 3.78 (s, 3 H), 3.47 (q, J = 8.0 Hz, 2 H), 3.37 (q, J = 8.0 Hz, 2 H), 1.29 (t, J = 8.0 Hz, 3 H), 1.20 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.6, 153.2, 152.5, 136.5, 134.1, 131.5, 128.8, 124.5, 121.8, 117.9, 109.7, 52.1, 42.7, 42.3, 14.4, 13.3.

HRMS (ESI): calc. for $[(\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 325.1164, measured 325.1161.

(E)-Methyl 3-(2-((diethylcarbamoyl)oxy)-5-nitrophenyl)acrylate (3g).

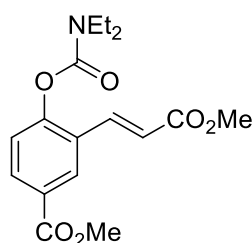
According to **general procedure**, the coupling of 4-nitrophenyl diethylcarbamate (**1m**; 150 mg, 0.630 mmol, 1.0 equiv) with methyl acrylate (**2a**; 162 mg, 1.89 mmol, 3.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (15.4 mg, 0.0252 mmol, 4 mol %), AgSbF_6 (42.3 mg, 0.126 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (37.4 mg, 0.189 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (18% ethyl acetate in hexanes) to give **3g** (49 mg, 24% yield) as a colorless semisolid.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977, 1726, 1642, 1280, 1177 and 1045.

^1H NMR (CDCl_3 , 400 MHz): δ 8.48 (s, 1 H), 8.22 (dd, $J = 8.0, 4.0$ Hz, 1 H), 7.82 (d, $J = 16.0$ Hz, 1 H), 7.40 (d, $J = 8.0$ Hz, 1 H), 6.55 (d, $J = 16.0$ Hz, 1 H), 3.81 (s, 3 H), 3.50 (q, $J = 8.0$ Hz, 2 H), 3.40 (q, $J = 8.0$ Hz, 2 H), 1.29 (t, $J = 8.0$ Hz, 3 H), 1.19 (t, $J = 8.0$ Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.6, 154.5, 152.5, 145.1, 136.5, 128.5, 125.6, 124.2, 122.7, 122.1, 52.1, 42.8, 42.3, 14.4, 13.3.

HRMS (ESI): calc. for $[(\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_6)\text{Na}]$ ($\text{M}+\text{Na}$) 345.1063, measured 345.1065.

(E)-Methyl 4-((diethylcarbamoyl)oxy)-3-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate (3h).

According to **general procedure**, the coupling of 4-methylesterphenyl diethylcarbamate (**1n**; 150 mg, 0.5976 mmol, 1.0 equiv) with methyl acrylate (**2a**; 154 mg, 1.79 mmol, 3.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (14.6 mg, 0.0239 mmol, 4 mol %), AgSbF_6 (40 mg, 0.119 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (35.49 mg, 0.179 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h.

The crude product was purified by silica gel column (18% ethyl acetate in hexanes) to give **3h** (104 mg, 52% yield) as a colorless semisolid.

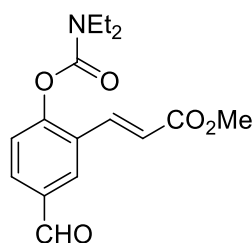
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2926, 1724, 1690, 1638, 1425, 1263 and 1121.

¹H NMR (CDCl₃, 400 MHz): δ 8.28 (s, 1 H), 8.00 (dd, J = 8.0, 4.0 Hz, 1 H), 7.80 (d, J = 8.0 Hz, 1 H), 7.24 (d, J = 8.0 Hz, 1 H), 6.49 (d, J = 16.0 Hz, 1 H), 3.88 (s, 3 H), 3.75 (s, 3 H), 3.47 (q, J = 8.0 Hz, 2 H), 3.36 (q, J = 8.0 Hz, 2 H), 1.28 (t, J = 8.0 Hz, 3 H), 1.18 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.0, 166.0, 153.6, 152.9, 137.7, 132.0, 128.9, 127.4, 123.4, 120.5, 52.4, 51.9, 42.5, 42.2, 14.4, 13.3.

HRMS (ESI): calc. for [(C₁₇H₂₁NO₆)Na] (M+Na) 358.1267, measured 358.1263.

(E)-Methyl 3-(2-((diethylcarbamoyl)oxy)-5-formylphenyl)acrylate (3i).



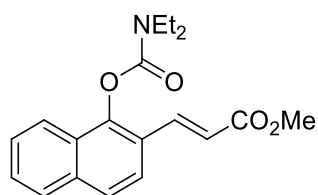
According to **general procedure**, the coupling of 4-formylphenyl diethylcarbamate (**1o**; 150 mg, 0.6787 mmol, 1.0 equiv) with methyl acrylate (**2a**; 175 mg, 2.036 mmol, 3.0 equiv) was performed in the presence of [{RuCl₂(*p*-cymene)}₂] (16.6 mg, 0.0271 mmol, 4 mol %), AgSbF₆ (45.6 mg, 0.135 mmol, 20 mol %) and Cu(OAc)₂·H₂O (40.3 mg, 0.2036 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent at 100 °C for 12 h. The crude product was purified by silica gel column (14% ethyl acetate in hexanes) to give **3i** (136 mg, 66% yield) as a pale yellow semisolid.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2978, 1735, 1723, 1641, 1423, 1320, 1221, 1154 and 1035.

¹H NMR (CDCl₃, 400 MHz): δ 9.95 (s, 1 H), 8.10 (s, 1 H), 7.86 (dd, J = 8.0, 4.0 Hz, 1 H), 7.83 (d, J = 16.0 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 1 H), 6.51 (d, J = 16.0 Hz, 1 H), 3.77 (s, 3 H), 3.48 (q, J = 8.0 Hz, 2 H), 3.38 (q, J = 8.0 Hz, 2 H), 1.29 (t, J = 8.0 Hz, 3 H), 1.19 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 190.8, 166.9, 154.6, 152.8, 137.4, 133.6, 131.8, 128.9, 128.2, 124.1, 120.9, 51.9, 42.6, 42.3, 14.4, 13.2.

HRMS (ESI): calc. for [(C₁₆H₁₉NO₅)Na] (M+Na) 328.1161, measured 328.1156.

(E)-Methyl 3-(1-((diethylcarbamoyl)oxy)naphthalen-2-yl)acrylate (3j).

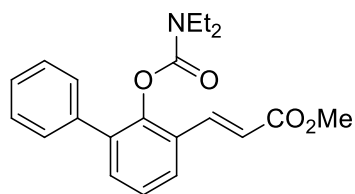
According to **general procedure**, the coupling of 1-Naphthalenyl diethylcarbamate (**1p**; 150 mg, 0.617 mmol, 1.0 equiv) with methyl acrylate (**2a**; 159 mg, 1.85 mmol, 3.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (15.1 mg, 0.0246 mmol, 4 mol %), AgSbF_6 (41.4 mg, 0.1234 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (36.6 mg, 0.185 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (12% ethyl acetate in hexanes) to give **3j** (123 mg, 61% yield) as a dark brown oil.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 1721, 1633, 1427, 1375, 1269, 1182 and 1080.

^1H NMR (CDCl_3 , 400 MHz): δ 7.98 (d, J = 16.0 Hz, 1 H), 7.86 (d, J = 8.0 Hz, 1 H), 7.80 (d, J = 8.0 Hz, 1 H), 7.67 (d, J = 8.0 Hz, 2 H), 7.51 (t, J = 8.0 Hz, 2 H), 6.52 (d, J = 16.0 Hz, 1 H), 3.79 (s, 3 H), 3.68 (q, J = 8.0 Hz, 2 H), 3.34 (q, J = 8.0 Hz, 2 H), 1.44 (t, J = 8.0 Hz, 3 H), 1.26 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.4, 153.8, 146.9, 138.5, 135.5, 128.2, 128.1, 127.6, 127.2, 126.2, 123.9, 122.9, 122.4, 119.4, 51.8, 42.5, 42.3, 14.6, 13.5.

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{21}\text{NO}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 350.1368, measured 350.1371.

(E)-Methyl 3-(2-((diethylcarbamoyl)oxy)-[1,1'-biphenyl]-3-yl)acrylate (3k).

According to **general procedure**, the coupling of biphenyl substituted diethylcarbamate (**1q**; 150 mg, 0.5576 mmol, 1.0 equiv) with methyl acrylate (**2a**; 144 mg, 1.67 mmol, 3.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (13.6 mg, 0.0223 mmol, 4 mol %), AgSbF_6 (37.47 mg, 0.1115 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (33.12 mg, 0.1672 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (12% ethyl acetate in hexanes) to give **3k** (113 mg, 57% yield) as a colorless semisolid.

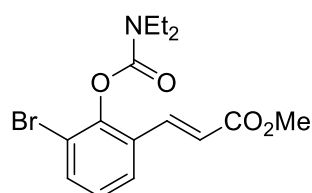
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2959, 1720, 1630, 1270 and 1194.

^1H NMR (CDCl_3 , 400 MHz): δ 7.82 (d, J = 16.0 Hz, 1 H), 7.60 (dd, J = 8.0, 4.0 Hz, 1 H), 7.39 – 7.36 (m, 4 H), 7.35 – 7.30 (m, 2 H), 7.27 (t, J = 8.0 Hz, 1 H) 6.46 (d, J = 16.0 Hz, 1 H), 3.77 (s, 3 H), 3.26 (q, J = 8.0 Hz, 2 H), 3.18 (q, J = 8.0 Hz, 2 H), 1.06 (t, J = 8.0 Hz, 3 H), 0.93 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.3, 153.2, 147.6, 139.2, 137.7, 136.2, 132.6, 129.1, 128.8, 128.2, 127.5, 126.6, 125.9, 119.7, 51.8, 42.1, 41.7, 14.0, 12.9.

HRMS (ESI): calc. for $[(\text{C}_{21}\text{H}_{23}\text{NO}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 376.1525, measured 376.1523.

(E)-Methyl 3-(3-bromo-2-((diethylcarbamoyl)oxy)phenyl)acrylate (3l).



According to **general procedure**, the coupling of 2-bromophenyl diethylcarbamate (**1r**; 150 mg, 0.551 mmol, 1.0 equiv) with methyl acrylate (**2a**; 142 mg, 1.653 mmol, 3.0 equiv) was performed in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (13.4 mg, 0.022 mmol, 4 mol %), AgSbF_6 (37 mg, 0.11 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (32.7 mg, 0.1653 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (12% ethyl acetate in hexanes) to give **3l** (167 mg, 85% yield) as a pale yellow oil.

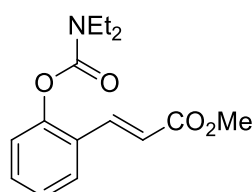
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 1712, 1635, 1457, 1311 and 1163.

^1H NMR (CDCl_3 , 400 MHz): δ 7.71 (d, J = 16.0 Hz, 1 H), 7.56 (dd, J = 8.0, 4.0 Hz, 1 H), 7.51 (dd, J = 8.0, 4.0 Hz, 1 H), 7.07 (t, J = 8.0 Hz, 1 H) 6.39 (d, J = 16.0 Hz, 1 H), 3.75 (s, 3 H), 3.52 (q, J = 8.0 Hz, 2 H), 3.37 (q, J = 8.0 Hz, 2 H), 1.33 (t, J = 8.0 Hz, 3 H), 1.19 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.9, 152.3, 147.7, 138.3, 134.6, 130.4, 127.0, 126.6, 120.7, 118.7, 51.9, 42.6, 42.3, 14.4, 13.3.

HRMS (ESI): calc. for $[(\text{C}_{15}\text{H}_{18}\text{BrNO}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 378.0317, measured 378.0320.

(E)-Methyl 3-(2-((diethylcarbamoyl)oxy)phenyl)acrylate (3m).



According to **general procedure**, the catalytic reaction was done in 1,2-dimethoxy ethane (DME) solvent.

Pale yellow oil; eluent (10% ethyl acetate in hexanes).

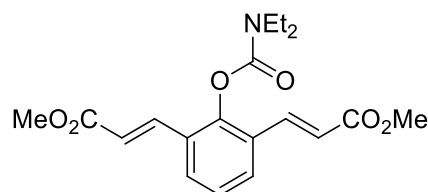
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2965, 1719, 1637 and 1155.

¹H NMR (CDCl₃, 400 MHz): δ 7.83 (d, J = 16.0 Hz, 1 H), 7.59 (dd, J = 8.0, 4.0 Hz, 1 H), 7.35 (t, J = 8.0 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 1 H), 7.15 (d, J = 8.0 Hz, 1 H) 6.41 (d, J = 16.0 Hz, 1 H), 3.75 (s, 3 H), 3.46 (q, J = 8.0 Hz, 2 H), 3.37 (q, J = 8.0 Hz, 2 H), 1.29 (t, J = 8.0 Hz, 3 H), 1.19 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.3, 153.7, 150.3, 138.8, 131.2, 127.4, 127.3, 125.7, 123.4, 119.3, 51.8, 42.4, 42.1, 14.4, 13.4.

HRMS (ESI): calc. for [(C₁₅H₁₉NO₄)Na] (M+Na) 300.1212, measured 300.1215.

(2E,2'E)-Dimethyl 3,3'-(2-((diethylcarbamoyl)oxy)-1,3-phenylene)diacrylate (3n).



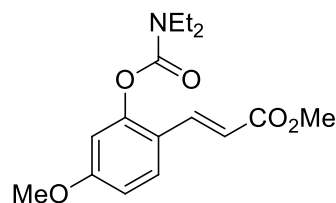
Pale yellow oil; eluent (20% ethyl acetate in hexanes).

¹H NMR (CDCl₃, 400 MHz): δ 7.72 (d, J = 16.0 Hz, 2 H), 7.59 (d, J = 8.0 Hz, 2 H), 7.22 (t, J = 8.0 Hz, 1 H) 6.39 (d, J = 16.0 Hz, 2 H), 3.74 (s, 6 H), 3.56 (q, J = 8.0 Hz, 2 H), 3.36 (q, J = 8.0 Hz, 2 H), 1.35 (t, J = 8.0 Hz, 3 H), 1.18 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.0, 153.1, 148.9, 138.2, 129.2, 128.9, 126.2, 120.3, 51.8, 42.5, 42.2, 14.4, 13.2.

HRMS (ESI): calc. for [(C₁₉H₂₃NO₆)Na] (M+Na) 384.1423, measured 384.1425.

(E)-Methyl 3-(2-((diethylcarbamoyl)oxy)-4-methoxyphenyl)acrylate (3o).



According to **general procedure**, the coupling of 3-methoxyphenyl diethylcarbamate (**1t**; 150 mg, 0.6726 mmol, 1.0 equiv) with methyl acrylate (**2a**; 173 mg, 2.017 mmol, 3.0 equiv) was performed in the presence of [{RuCl₂(*p*-cymene)}₂] (16.4 mg, 0.0269 mmol, 4 mol %), AgSbF₆ (45.1 mg, 0.1345 mmol, 20 mol %) and Cu(OAc)₂·H₂O (39.9 mg, 0.2017 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for

12 h. The crude product was purified by silica gel column (18% ethyl acetate in hexanes) to give **3o** (169 mg, 82% yield) as a pale yellow oil.

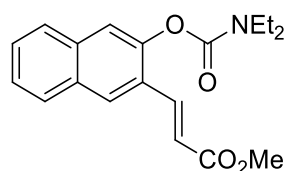
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2969, 1721, 1615, 1505, 1419, 1266, 1159 and 1033.

¹H NMR (CDCl₃, 400 MHz): δ 7.74 (d, J = 16.0 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 6.72 (dd, J = 8.0, 4.0 Hz, 1 H), 6.67 (d, J = 4.0 Hz, 1 H), 6.27 (d, J = 16.0 Hz, 1 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.46 (q, J = 8.0 Hz, 2 H), 3.34 (q, J = 8.0 Hz, 2 H), 1.27 (t, J = 8.0 Hz, 3 H), 1.17 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.7, 162.0, 153.5, 151.6, 138.5, 128.2, 119.9, 116.5, 112.5, 108.4, 55.6, 51.6, 42.4, 42.0, 14.4, 13.4.

HRMS (ESI): calc. for [(C₁₆H₂₁NO₅)Na] (M+Na) 330.1317, measured 330.1323.

(E)-Methyl 3-(3-((diethylcarbamoyl)oxy)naphthalen-2-yl)acrylate (3p).



According to **general procedure**, the coupling of 2-Naphthalenyl diethylcarbamate (**1u**; 150 mg, 0.617 mmol, 1.0 equiv) with methyl acrylate (**2a**; 159 mg, 1.85 mmol, 3.0 equiv) was performed in the presence of [{RuCl₂(*p*-cymene)}₂] (15.1 mg, 0.0246 mmol, 4 mol %), AgSbF₆ (41.4 mg, 0.1234 mmol, 20 mol %) and Cu(OAc)₂·H₂O (36.6 mg, 0.185 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (12% ethyl acetate in hexanes) to give **3p** (133 mg, 66% yield) as a dark yellow semisolid.

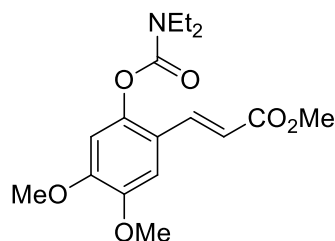
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2978, 1719, 1632, 1421, 1313, 1273, 1158 and 1094.

¹H NMR (CDCl₃, 400 MHz): δ 8.06 (s, 1 H), 7.92 (d, J = 16.0 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.72 (d, J = 8.0 Hz, 1 H), 7.59 (s, 1 H), 7.44 (t, J = 8.0 Hz, 1 H), 7.40 (t, J = 8.0 Hz, 1 H), 6.54 (d, J = 16.0 Hz, 1 H), 3.78 (s, 3 H), 3.54 (q, J = 8.0 Hz, 2 H), 3.39 (q, J = 8.0 Hz, 2 H), 1.33 (t, J = 8.0 Hz, 3 H), 1.21 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.3, 153.9, 147.5, 139.4, 134.6, 131.1, 128.3, 128.1, 127.6, 127.4, 127.2, 126.1, 120.2, 119.8, 51.8, 42.5, 42.1, 14.4, 13.4.

HRMS (ESI): calc. for [(C₁₉H₂₁NO₄)Na] (M+Na) 350.1368, measured 350.1365.

(E)-Methyl 3-(2-((diethylcarbamoyl)oxy)-4,5-dimethoxyphenyl)acrylate (3q).



According to **general procedure**, the coupling of 3,4-dimethoxyphenyl diethylcarbamate (**1v**; 150 mg, 0.5928 mmol, 1.0 equiv) with methyl acrylate (**2a**; 153 mg, 1.778 mmol, 3.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (14.5 mg, 0.0237 mmol, 4 mol %), AgSbF_6 (39.8 mg, 0.1185 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (35.2 mg, 0.1778 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (30% ethyl acetate in hexanes) to give **3q** (162 mg, 81% yield) as a pale yellow semisolid.

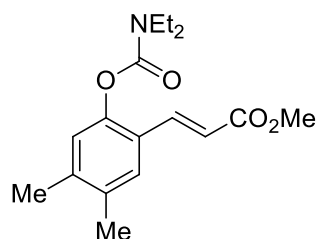
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930, 1717, 1617, 1514, 1415, 1269, 1161 and 1038.

^1H NMR (CDCl_3 , 400 MHz): δ 7.75 (d, J = 16.0 Hz, 1 H), 7.01 (s, 1 H), 6.66 (s, 1 H), 6.27 (d, J = 16.0 Hz, 1 H), 3.86 (s, 6 H), 3.75 (s, 3 H), 3.49 (q, J = 8.0 Hz, 2 H), 3.36 (q, J = 8.0 Hz, 2 H), 1.30 (t, J = 8.0 Hz, 3 H), 1.19 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.6, 153.9, 151.6, 146.8, 144.9, 138.4, 119.1, 116.6, 108.0, 106.7, 56.2, 56.1, 51.7, 42.4, 41.9, 14.4, 13.4.

HRMS (ESI): calc. for $[(\text{C}_{17}\text{H}_{23}\text{NO}_6)\text{Na}]$ ($\text{M}+\text{Na}$) 360.1423, measured 360.1417.

(E)-Methyl 3-(2-((diethylcarbamoyl)oxy)-4,5-dimethylphenyl)acrylate (3r).



According to **general procedure**, the coupling of 3,4-dimethylphenyl diethylcarbamate (**1w**; 150 mg, 0.6787 mmol, 1.0 equiv) with methyl acrylate (**2a**; 175 mg, 2.036 mmol, 3.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (16.6 mg, 0.0271 mmol, 4 mol %), AgSbF_6 (45.6 mg, 0.1357 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (40.31 mg, 0.2036 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 10 h. The crude product was purified by silica gel column (13% ethyl acetate in hexanes) to give **3r** (145 mg, 70% yield) as a colorless semisolid.

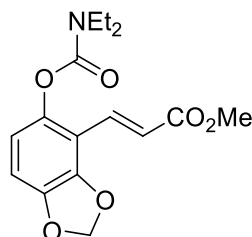
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2931, 1718, 1629, 1424, 1265, 1157 and 1082.

^1H NMR (CDCl_3 , 400 MHz): δ 7.76 (d, J = 16.0 Hz, 1 H), 7.35 (s, 1 H), 6.92 (s, 1 H), 6.36 (d, J = 16.0 Hz, 1 H), 3.76 (s, 3 H), 3.48 (q, J = 8.0 Hz, 2 H), 3.37 (q, J = 8.0 Hz, 2 H), 2.24 (s, 3 H), 2.22 (s, 3 H), 1.29 (t, J = 8.0 Hz, 3 H), 1.19 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.6, 154.0, 148.3, 140.7, 138.9, 134.1, 128.0, 124.6, 124.3, 117.9, 51.7, 42.3, 41.9, 20.0, 19.3, 14.4, 13.4.

HRMS (ESI): calc. for $[(\text{C}_{17}\text{H}_{23}\text{NO}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 328.1525, measured 328.1522.

(E)-Methyl 3-(5-((diethylcarbamoyl)oxy)benzo[d][1,3]dioxol-4-yl)acrylate (3s).



According to **general procedure**, the coupling of sesamol carbamate (**1x**; 150 mg, 0.6329 mmol, 1.0 equiv) with methyl acrylate (**2a**; 163 mg, 1.8987 mmol, 3.0 equiv) was performed in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (15.5 mg, 0.0253 mmol, 4 mol %), AgSbF_6 (42.5 mg, 0.1265 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (37.58 mg, 0.1898 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (15% ethyl acetate in hexanes) to give **3s** (173 mg, 85% yield) as a pale yellow semisolid.

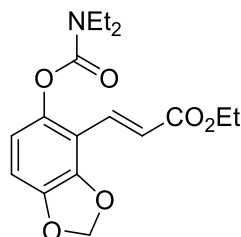
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977, 1718, 1634, 1455, 1312, 1207 and 1066.

^1H NMR (CDCl_3 , 400 MHz): δ 7.59 (d, J = 16.0 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.72 (d, J = 16.0 Hz, 1 H), 6.57 (d, J = 8.0 Hz, 1 H), 6.03 (s, 2 H), 3.74 (s, 3 H), 3.45 (q, J = 8.0 Hz, 2 H), 3.35 (q, J = 8.0 Hz, 2 H), 1.28 (t, J = 8.0 Hz, 3 H), 1.17 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.7, 154.1, 147.1, 145.2, 144.4, 133.9, 122.3, 115.4, 112.1, 109.1, 102.3, 51.7, 42.4, 41.9, 14.4, 13.4.

HRMS (ESI): calc. for $[(\text{C}_{16}\text{H}_{19}\text{NO}_6)\text{Na}]$ ($\text{M}+\text{Na}$) 344.1110, measured 344.1105.

(E)-Ethyl 3-(5-((diethylcarbamoyl)oxy)benzo[d][1,3]dioxol-4-yl)acrylate (3t).



According to **general procedure**, the coupling of sesamol carbamate (**1x**; 150 mg, 0.6329 mmol, 1.0 equiv) with ethyl acrylate (**2b**; 190 mg, 1.8987 mmol, 3.0 equiv) was

performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (15.5 mg, 0.0253 mmol, 4 mol %), AgSbF_6 (42.5 mg, 0.1265 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (37.58 mg, 0.1898 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (15% ethyl acetate in hexanes) to give **3t** (172 mg, 81% yield) as a Pale yellow semisolid.

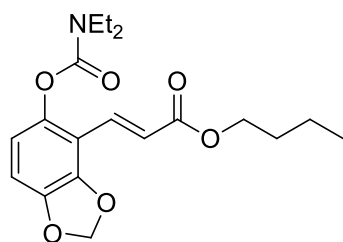
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2979, 1719, 1634, 1457, 1417, 1374, 1308, 1228, 1159 and 1067.

^1H NMR (CDCl_3 , 400 MHz): δ 7.57 (d, J = 16.0 Hz, 1 H), 6.75 (d, J = 8.0 Hz, 1 H), 6.71 (d, J = 16.0 Hz, 1 H), 6.57 (d, J = 8.0 Hz, 1 H), 6.03 (s, 2 H), 4.19 (q, J = 8.0 Hz, 2 H), 3.47 (q, J = 8.0 Hz, 2 H), 3.34 (q, J = 8.0 Hz, 2 H), 1.30 – 1.25 (m, 6 H), 1.16 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.2, 154.1, 147.1, 145.2, 144.4, 133.6, 122.8, 115.3, 112.5, 108.9, 102.3, 60.5, 42.4, 41.9, 14.4, 14.3, 13.4.

HRMS (ESI): calc. for $[(\text{C}_{17}\text{H}_{21}\text{NO}_6)\text{Na}]$ ($\text{M}+\text{Na}$) 358.1267, measured 358.1271.

(E)-Butyl 3-(5-((diethylcarbamoyl)oxy)benzo[d][1,3]dioxol-4-yl)acrylate (3u).



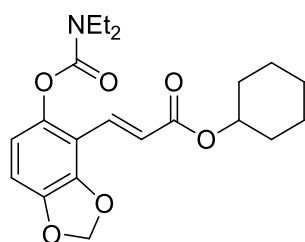
According to **general procedure**, the coupling of sesamol carbamate (**1x**; 150 mg, 0.6329 mmol, 1.0 equiv) with *n*-butyl acrylate (**2c**; 161 mg, 1.264 mmol, 2.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (15.5 mg, 0.0253 mmol, 4 mol %), AgSbF_6 (42.5 mg, 0.1265 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (37.58 mg, 0.1898 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (15% ethyl acetate in hexanes) to give **3u** (173 mg, 75% yield) as a light yellow semisolid.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2967, 1723, 1634, 1459, 1417, 1309, 1160 and 1068.

^1H NMR (CDCl_3 , 400 MHz): δ 7.57 (d, J = 16.0 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.72 (d, J = 16.0 Hz, 1 H), 6.57 (d, J = 8.0 Hz, 1 H), 6.04 (s, 2 H), 4.14 (t, J = 8.0 Hz, 2 H), 3.46 (q, J = 8.0 Hz, 2 H), 3.35 (q, J = 8.0 Hz, 2 H), 1.66 – 1.59 (m, 2 H), 1.43 – 1.34 (m, 2 H), 1.28 (t, J = 8.0 Hz, 3 H), 1.17 (t, J = 8.0 Hz, 3 H), 0.91 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.3, 154.1, 147.1, 145.2, 144.4, 133.5, 122.8, 115.4, 112.5, 108.9, 102.3, 64.4, 42.4, 41.9, 30.8, 19.3, 14.4, 13.8, 13.4.

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{25}\text{NO}_6)\text{Na}]$ ($\text{M}+\text{Na}$) 386.1580, measured 386.1583.

(E)-Cyclohexyl 3-(5-((diethylcarbamoyl)oxy)benzo[d][1,3]dioxol-4-yl)acrylate (3v).

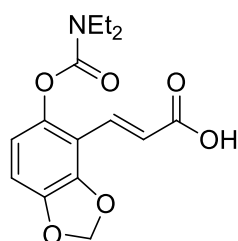
According to **general procedure**, the coupling of sesamol carbamate (**1x**; 150 mg, 0.6329 mmol, 1.0 equiv) with cyclohexyl acrylate (**2d**; 194 mg, 1.264 mmol, 2.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (15.5 mg, 0.0253 mmol, 4 mol %), AgSbF_6 (42.5 mg, 0.1265 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (37.58 mg, 0.1898 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (15% ethyl acetate in hexanes) to give **3v** (178 mg, 72% yield) as a light brown oil.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2975, 1717, 1617, 1514, 1415, 1269, 1161 and 1038.

^1H NMR (CDCl_3 , 400 MHz): δ 7.56 (d, J = 16.0 Hz, 1 H), 6.73 (d, J = 8.0 Hz, 1 H), 6.65 (d, J = 16.0 Hz, 1 H), 6.57 (d, J = 8.0 Hz, 1 H), 6.03 (s, 2 H), 4.86 – 4.79 (m, 1 H), 3.46 (q, J = 8.0 Hz, 2 H), 3.35 (q, J = 8.0 Hz, 2 H), 1.87 – 1.84 (m, 2 H), 1.73 – 1.70 (m, 2 H), 1.53 – 1.50 (m, 1 H), 1.44 – 1.32 (m, 4 H), 1.30 – 1.26 (m, 4 H), 1.17 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.7, 154.1, 147.0, 145.2, 144.3, 133.2, 123.4, 115.3, 112.6, 108.9, 102.3, 72.1, 42.4, 41.9, 31.8, 25.5, 23.9, 14.4, 13.4.

HRMS (ESI): calc. for $[(\text{C}_{21}\text{H}_{27}\text{NO}_6)\text{Na}]$ ($\text{M}+\text{Na}$) 412.1736, measured 412.1737.

(E)-3-(5-((Diethylcarbamoyl)oxy)benzo[d][1,3]dioxol-4-yl)acrylic acid (3w).

According to **general procedure**, the coupling of sesamol carbamate (**1x**; 150 mg, 0.6329 mmol, 1.0 equiv) with *tert*-butyl acrylate (**2e**; 161 mg, 1.264 mmol, 2.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (15.5 mg, 0.0253 mmol, 4 mol %), AgSbF_6 (42.5 mg, 0.1265 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (37.58 mg, 0.1898 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (35% ethyl acetate in hexanes) to give **3w** (121 mg, 62% yield) as a black color semisolid.

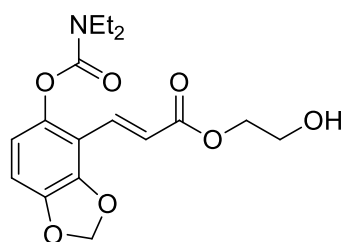
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2978, 1714, 1633, 1458, 1276, 1157 and 1067.

¹H NMR (CDCl₃, 400 MHz): δ 7.68 (d, J = 16.0 Hz, 1 H), 6.78 (d, J = 8.0 Hz, 1 H), 6.73 (d, J = 16.0 Hz, 1 H), 6.60 (d, J = 8.0 Hz, 1 H), 6.07 (s, 2 H), 3.48 (q, J = 8.0 Hz, 2 H), 3.37 (q, J = 8.0 Hz, 2 H), 1.29 (t, J = 8.0 Hz, 3 H), 1.19 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 172.5, 154.2, 147.4, 145.3, 144.5, 135.9, 115.4, 112.2, 109.4, 102.4, 42.5, 42.0, 14.3, 13.5.

HRMS (ESI): calc. for [(C₁₅H₁₇NO₆)Na] (M+Na) 330.0954, measured 330.0956.

(E)-2-Hydroxyethyl 3-(5-((diethylcarbamoyl)oxy)benzo[d][1,3]dioxol-4-yl)acrylate (3x).



According to **general procedure**, the coupling of sesamol carbamate (**1x**; 150 mg, 0.6329 mmol, 1.0 equiv) with 2-hydroxyethyl acrylate (**2f**; 126 mg, 1.264 mmol, 2.0 equiv) was performed in the presence of [{RuCl₂(*p*-cymene)}₂] (15.5 mg, 0.0253 mmol, 4 mol %), AgSbF₆ (42.5 mg, 0.1265 mmol, 20 mol %) and Cu(OAc)₂·H₂O (37.58 mg, 0.1898 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (25% ethyl acetate in hexanes) to give **3x** (145 mg, 65% yield) as a light brown semisolid.

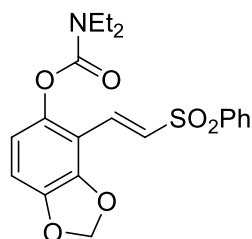
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3416, 2974, 1712, 1635, 1457, 1419, 1311 and 1163.

¹H NMR (CDCl₃, 400 MHz): δ 7.60 (d, J = 16.0 Hz, 1 H), 6.76 (d, J = 16.0 Hz, 1 H), 6.75 (d, J = 8.0 Hz, 1 H), 6.57 (d, J = 8.0 Hz, 1 H), 6.05 (s, 2 H), 4.27 (t, J = 8.0 Hz, 2 H), 3.81 (t, J = 8.0 Hz, 2 H), 3.46 (q, J = 8.0 Hz, 2 H), 3.35 (t, J = 8.0 Hz, 2 H), 2.60 (bs, 1 H), 1.28 (t, J = 8.0 Hz, 3 H), 1.17 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.6, 154.2, 147.2, 145.3, 144.4, 134.4, 122.1, 115.4, 112.2, 109.2, 102.4, 66.3, 61.2, 42.5, 42.0, 14.4, 13.4.

HRMS (ESI): calc. for [(C₁₇H₂₁NO₇)Na] (M+Na) 374.1216, measured 374.1213.

(E)-4-(2-(Phenylsulfonyl)vinyl)benzo[d][1,3]dioxol-5-yl diethylcarbamate (3y).



According to **general procedure**, the coupling of sesamol carbamate (**1x**; 150 mg, 0.6329 mmol, 1.0 equiv) with phenyl vinyl sulfone (**2g**; 212 mg, 1.2658 mmol, 2.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (15.5 mg, 0.0253 mmol, 4 mol %), AgSbF_6 (42.5 mg, 0.1265 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (37.58 mg, 0.1898 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (25% ethyl acetate in hexanes) to give **3y** (207 mg, 81% yield) as a pale yellow semisolid.

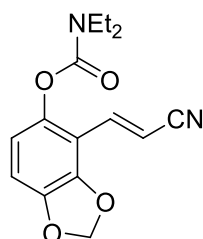
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 1719, 1627, 1456, 1308, 1226, 1150 and 1070.

^1H NMR (CDCl_3 , 400 MHz): δ 7.87 (d, J = 8.0 Hz, 2 H), 7.59 (d, J = 16.0 Hz, 1 H), 7.57 (t, J = 8.0 Hz, 1 H), 7.49 (t, J = 8.0 Hz, 2 H), 7.17 (d, J = 16.0 Hz, 1 H), 6.77 (d, J = 8.0 Hz, 1 H), 6.60 (d, J = 8.0 Hz, 1 H), 6.00 (s, 2 H), 3.48 (q, J = 8.0 Hz, 2 H), 3.36 (q, J = 8.0 Hz, 2 H), 1.31 (t, J = 8.0 Hz, 3 H), 1.20 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 153.9, 147.2, 145.2, 144.5, 140.6, 133.4, 131.6, 131.1, 129.4, 127.8, 115.5, 110.4, 109.9, 102.6, 42.6, 42.2, 14.4, 13.4.

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{21}\text{NO}_6\text{S})\text{Na}]$ ($\text{M}+\text{Na}$) 426.0987, measured 426.0983.

(E)-4-(2-Cyanovinyl)benzo[d][1,3]dioxol-5-yl diethylcarbamate (3z) (E-isomer).



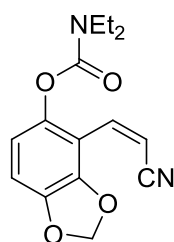
According to **general procedure**, the coupling of sesamol carbamate (**1x**; 150 mg, 0.6329 mmol, 1.0 equiv) with acrylonitrile (**2h**; 100 mg, 1.8987 mmol, 3.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (15.5 mg, 0.0253 mmol, 4 mol %), AgSbF_6 (42.5 mg, 0.1265 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (37.58 mg, 0.1898 mmol, 30 mol %) in 1,2-dimethoxy ethane (DME) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (18% ethyl acetate in hexanes) to give **3z** (101 mg, 55% yield) as a pale yellow liquid.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2945, 2225, 1720, 1634 and 1045.

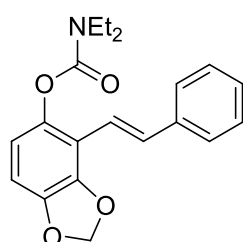
^1H NMR (CDCl_3 , 400 MHz): δ 7.24 (d, $J = 16.0$ Hz, 1 H), 6.80 (d, $J = 8.0$ Hz, 1 H), 6.58 (d, $J = 8.0$ Hz, 1 H), 6.26 (d, $J = 16.0$ Hz, 1 H), 6.08 (s, 2 H), 3.46 (q, $J = 8.0$ Hz, 2 H), 3.37 (q, $J = 8.0$ Hz, 2 H), 1.27 (t, $J = 8.0$ Hz, 3 H), 1.20 (t, $J = 8.0$ Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 153.9, 147.1, 145.4, 143.8, 139.9, 118.6, 115.5, 111.9, 109.9, 102.6, 100.9, 42.6, 42.1, 14.5, 13.4.

HRMS (ESI): calc. for $[(\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 311.1008, measured 311.1013.

(Z)-4-(2-Cyanovinyl)benzo[d][1,3]dioxol-5-yl diethylcarbamate (3z) (Z-isomer).

^1H NMR (CDCl_3 , 400 MHz): δ 7.02 (d, J = 12.0 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 6.60 (d, J = 8.0 Hz, 1 H), 6.08 (s, 2 H), 5.61 (d, J = 12.0 Hz, 1 H), 3.42 (q, J = 8.0 Hz, 2 H), 3.35 (q, J = 8.0 Hz, 2 H), 1.27 - 1.25 (m, 6 H).

(E)-4-Styrylbenzo[d][1,3]dioxol-5-yl diethylcarbamate (4a).

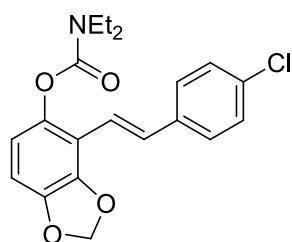
According to **general procedure**, the coupling of sesamol carbamate (**1x**; 150 mg, 0.6329 mmol, 1.0 equiv) with styrene (**2i**; 132 mg, 1.2658 mmol, 2 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (15.5 mg, 0.0253 mmol, 4 mol %), AgSbF_6 (42.5 mg, 0.1265 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (37.58 mg, 0.1898 mmol, 30 mol %) in tetrahydrofuran (THF) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (10% ethyl acetate in hexanes) to give **4a** (163 mg, 76% yield) as a pale yellow oil.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976, 1718, 1457, 1316, 1271, 1158 and 1065.

^1H NMR (CDCl_3 , 400 MHz): δ 7.45 (d, J = 16.0 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 2 H), 7.33 (t, J = 8.0 Hz, 2 H), 7.24 (t, J = 8.0 Hz, 1 H), 6.95 (d, J = 8.0 Hz, 1 H), 6.68 (d, J = 8.0 Hz, 1 H), 6.58 (d, J = 8.0 Hz, 1 H), 6.07 (s, 2 H), 3.51 (q, J = 8.0 Hz, 2 H), 3.39 (q, J = 8.0 Hz, 2 H), 1.31 (t, J = 8.0 Hz, 3 H), 1.20 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 154.5, 145.6, 145.1, 143.6, 137.9, 133.9, 128.7, 127.9, 126.6, 118.1, 115.3, 115.1, 106.6, 101.8, 42.4, 41.9, 14.6, 13.5.

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{21}\text{NO}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 362.1368, measured 362.1370.

(E)-4-(4-Chlorostyryl)benzo[d][1,3]dioxol-5-yl diethylcarbamate (4b).

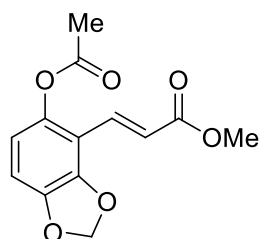
According to **general procedure**, the coupling of sesamol carbamate (**1x**; 150 mg, 0.6329 mmol, 1.0 equiv) with 4-chlorostyrene (**2j**; 174 mg, 1.2658 mmol, 2.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (15.5 mg, 0.0253 mmol, 4 mol %), AgSbF_6 (42.5 mg, 0.1265 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (37.58 mg, 0.1898 mmol, 30 mol %) in tetrahydrofuran (THF) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (10% ethyl acetate in hexanes) to give **4b** (168 mg, 71% yield) as pale yellow semisolid.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 1727, 1416, 1377, 1244 and 1051.

^1H NMR (CDCl_3 , 400 MHz): δ 7.39 (d, J = 16.0 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 6.91 (d, J = 8.0 Hz, 1 H), 6.69 (d, J = 8.0 Hz, 1 H), 6.58 (d, J = 8.0 Hz, 1 H), 6.06 (s, 2 H), 3.50 (q, J = 8.0 Hz, 2 H), 3.38 (q, J = 8.0 Hz, 2 H), 1.30 (t, J = 8.0 Hz, 3 H), 1.19 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 154.4, 145.7, 145.1, 143.6, 136.4, 133.5, 132.5, 128.9, 127.7, 118.7, 114.9, 115.3, 106.8, 101.8, 42.4, 41.9, 14.6, 13.5.

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{20}\text{ClNO}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 396.0979, measured 396.0980.

(E)-Methyl 3-(5-acetoxobenzo[d][1,3]dioxol-4-yl)acrylate (5a).

According to **general procedure**, the coupling of sesamol acetate (**1y**; 150 mg, 0.833 mmol, 1.0 equiv) with methyl acrylate (**2a**; 215 mg, 2.499 mmol, 3.0 equiv) was performed in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (20.3 mg, 0.0333 mmol, 4 mol %), AgSbF_6 (55.9 mg, 0.166 mmol, 20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (49.4 mg, 0.2499 mmol, 30 mol %) in 1,2-dichloro ethane (DCE) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (12% ethyl acetate in hexanes) to give **5a** (167 mg, 76% yield) as a colorless semisolid.

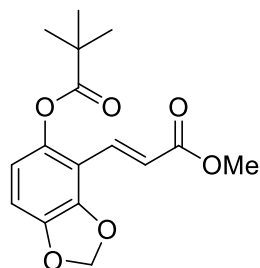
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2921, 1766, 1714, 1633, 1455 and 1192.

¹H NMR (CDCl₃, 400 MHz): δ 7.49 (d, J = 16.0 Hz, 1 H), 6.76 (d, J = 8.0 Hz, 1 H), 6.73 (d, J = 16.0 Hz, 1 H), 6.53 (d, J = 8.0 Hz, 1 H), 6.05 (s, 2 H), 3.76 (s, 3 H), 2.32 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 169.8, 167.6, 147.3, 145.7, 143.5, 133.3, 127.8, 115.1, 111.9, 109.1, 102.5, 51.8, 20.9.

HRMS (ESI): calc. for [(C₁₃H₁₂O₆)Na] (M+Na) 287.0531, measured 287.0534.

(E)-Methyl 3-(5-(pivaloyloxy)benzo[d][1,3]dioxol-4-yl)acrylate (5b).



According to **general procedure**, the coupling of sesamol acetate (**1z**; 150 mg, 0.675 mmol, 1.0 equiv) with methyl acrylate (**2a**; 174 mg, 2.027 mmol, 3.0 equiv) was performed in the presence of [{RuCl₂(*p*-cymene)}₂] (16.5 mg, 0.027 mmol, 4 mol %), AgSbF₆ (45.3 mg, 0.135 mmol, 20 mol %) and Cu(OAc)₂·H₂O (40 mg, 0.2025 mmol, 30 mol %) in 1,2-dichloro ethane (DCE) solvent (3.0 mL) at 100 °C for 12 h. The crude product was purified by silica gel column (12% ethyl acetate in hexanes) to give **5b** (145 mg, 70% yield) as a colorless semisolid.

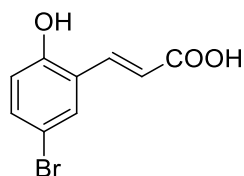
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2922, 1746, 1706, 1599, 1461 and 1202.

¹H NMR (CDCl₃, 400 MHz): δ 7.51 (d, J = 16.0 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.71 (d, J = 16.0 Hz, 1 H), 6.48 (d, J = 8.0 Hz, 1 H), 6.06 (s, 2 H), 3.75 (s, 3 H), 1.38 (s, 9 H).

¹³C NMR (CDCl₃, 100 MHz): δ 177.3, 167.6, 147.3, 145.6, 143.9, 133.4, 122.6, 114.8, 112.0, 109.8, 102.4, 51.8, 39.3, 27.3.

HRMS (ESI): calc. for [(C₁₆H₁₈O₆)Na] (M+Na) 329.1001, measured 329.1000.

(E)-3-(5-Bromo-2-hydroxyphenyl)acrylic acid (6a).



Colorless solid; eluent (55% ethyl acetate in hexanes).

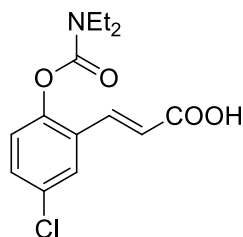
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3402, 2923, 1669, 1484, 1412, 1295, 1217 and 873.

^1H NMR (*d*-MeOH, 400 MHz): δ 7.82 (d, J = 16.0 Hz, 1 H), 7.56 (s, 1 H), 7.25 (dd, J = 8.0, 4.0 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.51 (d, J = 16.0 Hz, 1 H).

^{13}C NMR (*d*-MeOH, 100 MHz): δ 169.4, 155.9, 139.4, 133.5, 130.8, 123.4, 118.7, 117.4, 110.9.

HRMS (ESI): calc. for $[(\text{C}_9\text{H}_7\text{BrO}_3)\text{Na}]$ ($\text{M}+\text{Na}$) 264.9476, measured 264.9485.

(*E*)-3-(5-Chloro-2-((diethylcarbamoyl)oxy)phenyl)acrylic acid (6b).



Colorless solid; eluent (65% ethyl acetate in hexanes).

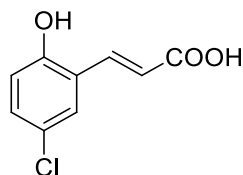
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2965, 1712, 1690, 1313, 1211 and 1075.

^1H NMR (*d*-MeOH, 400 MHz): δ 7.71 (s, 1 H), 7.64 (d, J = 16.0 Hz, 1 H), 7.38 (d, J = 8.0 Hz, 1 H), 7.12 (d, J = 8.0 Hz, 1 H), 6.46 (d, J = 16.0 Hz, 1 H), 3.52 (q, J = 8.0 Hz, 2 H), 3.36 (q, J = 8.0 Hz, 2 H), 1.29 (t, J = 8.0 Hz, 3 H), 1.17 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (*d*-MeOH, 100 MHz): δ 168.1, 153.8, 148.6, 136.8, 131.2, 130.6, 129.4, 126.8, 124.8, 121.5, 42.3, 42.0, 13.2, 12.2.

HRMS (ESI): calc. for $[(\text{C}_{14}\text{H}_{16}\text{ClINO}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 320.0666, measured 320.0665.

(*E*)-3-(5-Chloro-2-hydroxyphenyl)acrylic acid (6c).



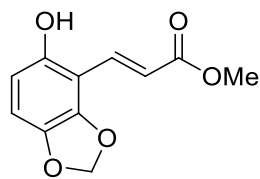
Colorless solid; eluent (55% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3409, 2933, 1657, 1286 and 1232.

^1H NMR (*d*-MeOH, 400 MHz): δ 7.84 (d, J = 16.0 Hz, 1 H), 7.44 (s, 1 H), 7.15 (dd, J = 8.0, 4.0 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 6.53 (d, J = 16.0 Hz, 1 H).

^{13}C NMR (*d*-MeOH, 100 MHz): δ 169.5, 155.5, 139.5, 130.6, 127.8, 124.1, 122.9, 118.9, 117.1.

HRMS (ESI): calc. for $[(\text{C}_9\text{H}_7\text{ClO}_3)\text{Na}]$ ($\text{M}+\text{Na}$) 220.9981, measured 220.9986.

(E)-Methyl 3-(5-hydroxybenzo[d][1,3]dioxol-4-yl)acrylate (6d).

Pale yellow solid; eluent (25% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2920, 1669, 1455, 1376 and 1241.

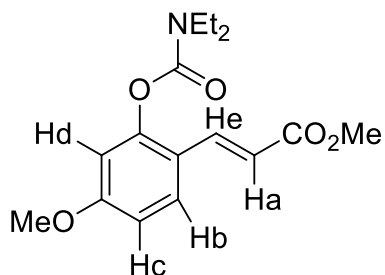
¹H NMR (*d*-MeOH, 400 MHz): δ 7.89 (d, *J* = 16.0 Hz, 1 H), 6.70 (d, *J* = 16.0 Hz, 1 H), 6.64 (d, *J* = 8.0 Hz, 1 H), 6.24 (d, *J* = 8.0 Hz, 1 H), 5.95 (s, 2 H), 3.74 (s, 3 H).

¹³C NMR (*d*-MeOH, 100 MHz): δ 168.7, 151.6, 147.3, 140.5, 135.3, 119.2, 109.6, 107.1, 105.9, 101.6, 50.7.

HRMS (ESI): calc. for [(C₁₁H₁₀O₅)H] (M+H) 223.0607, measured 223.0606.

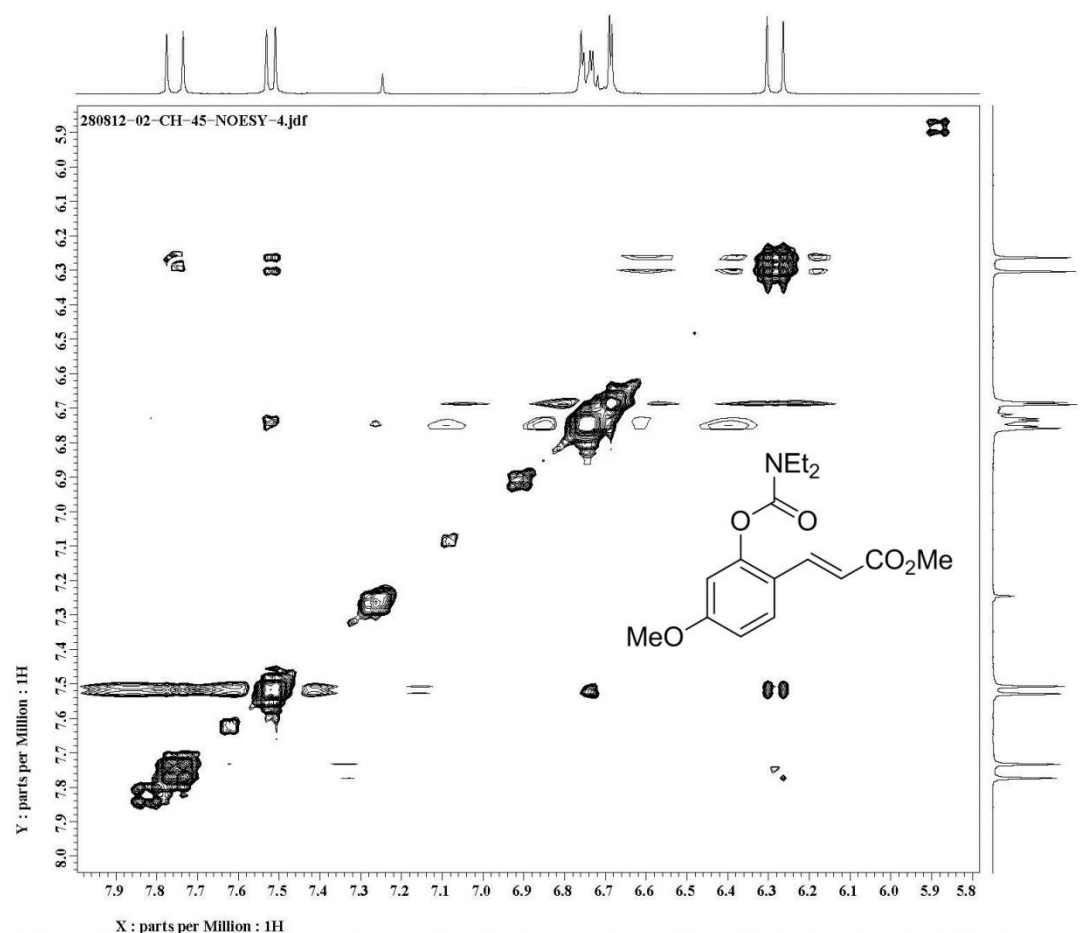
2A.15: Regioselective Studies: NOESY Experiments

Copy of NOESY Experiment of Compound **3o**.

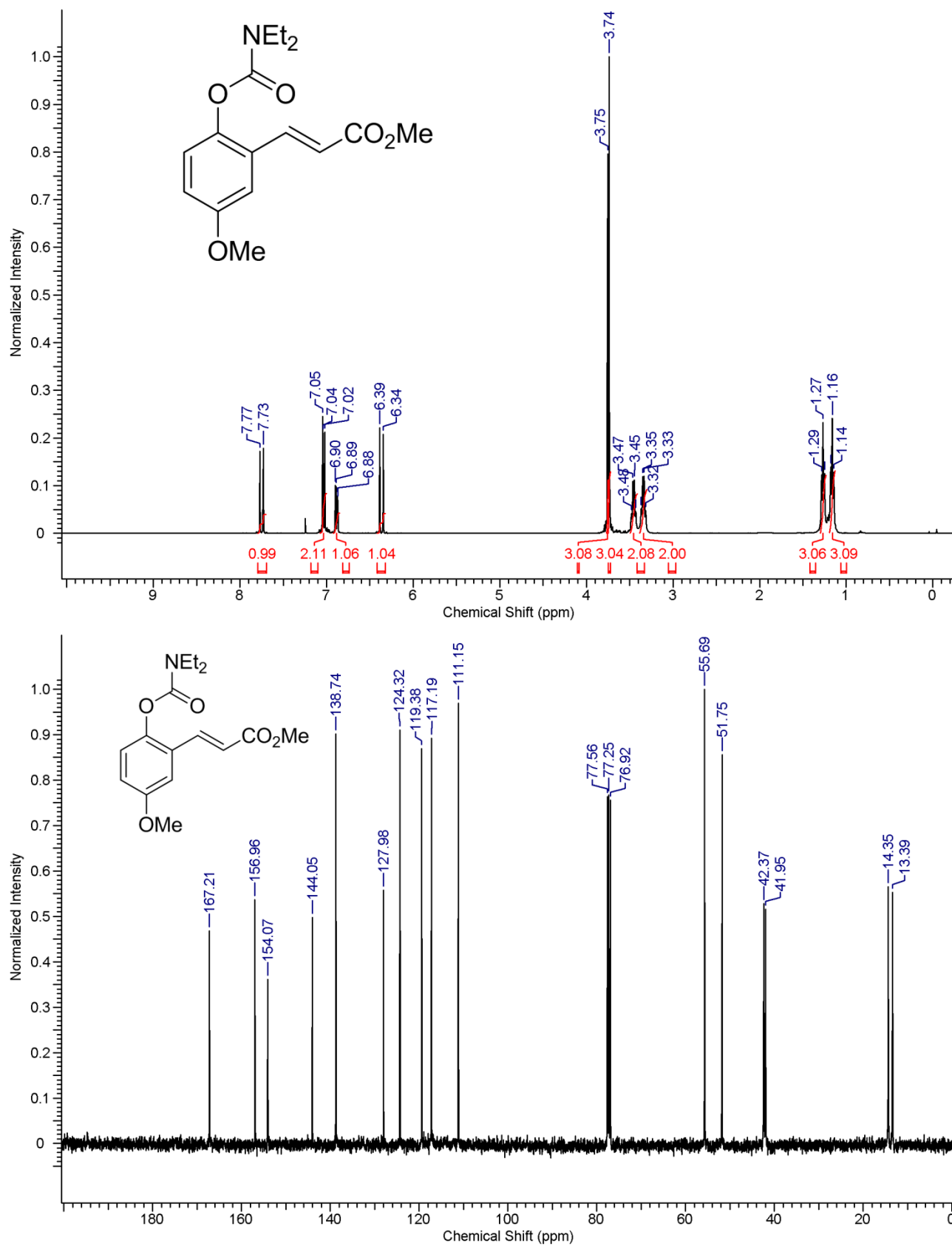


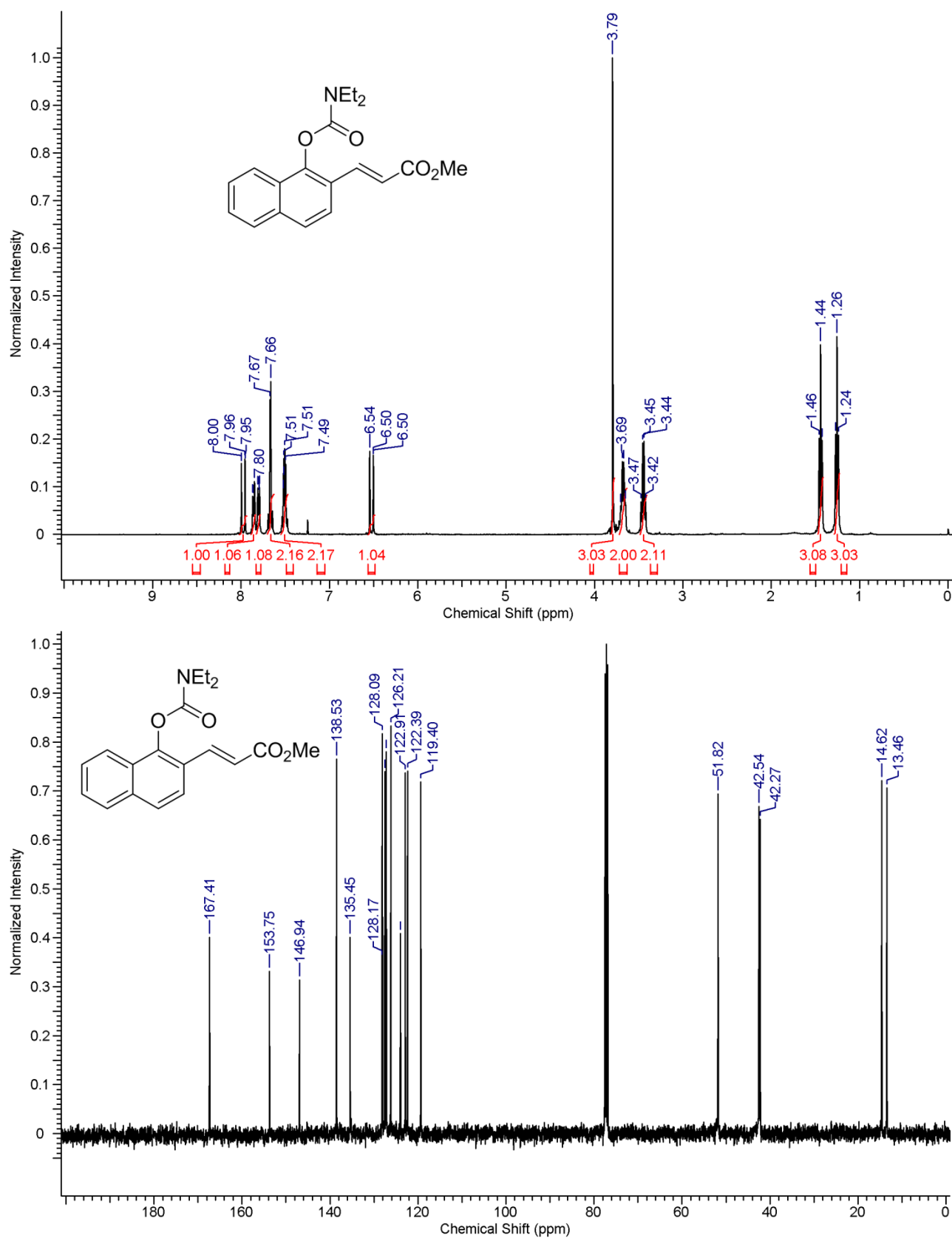
Ha δ = 6.27; Hb = 7.49; Hc = 6.72
Hd δ = 6.67; He = 7.74

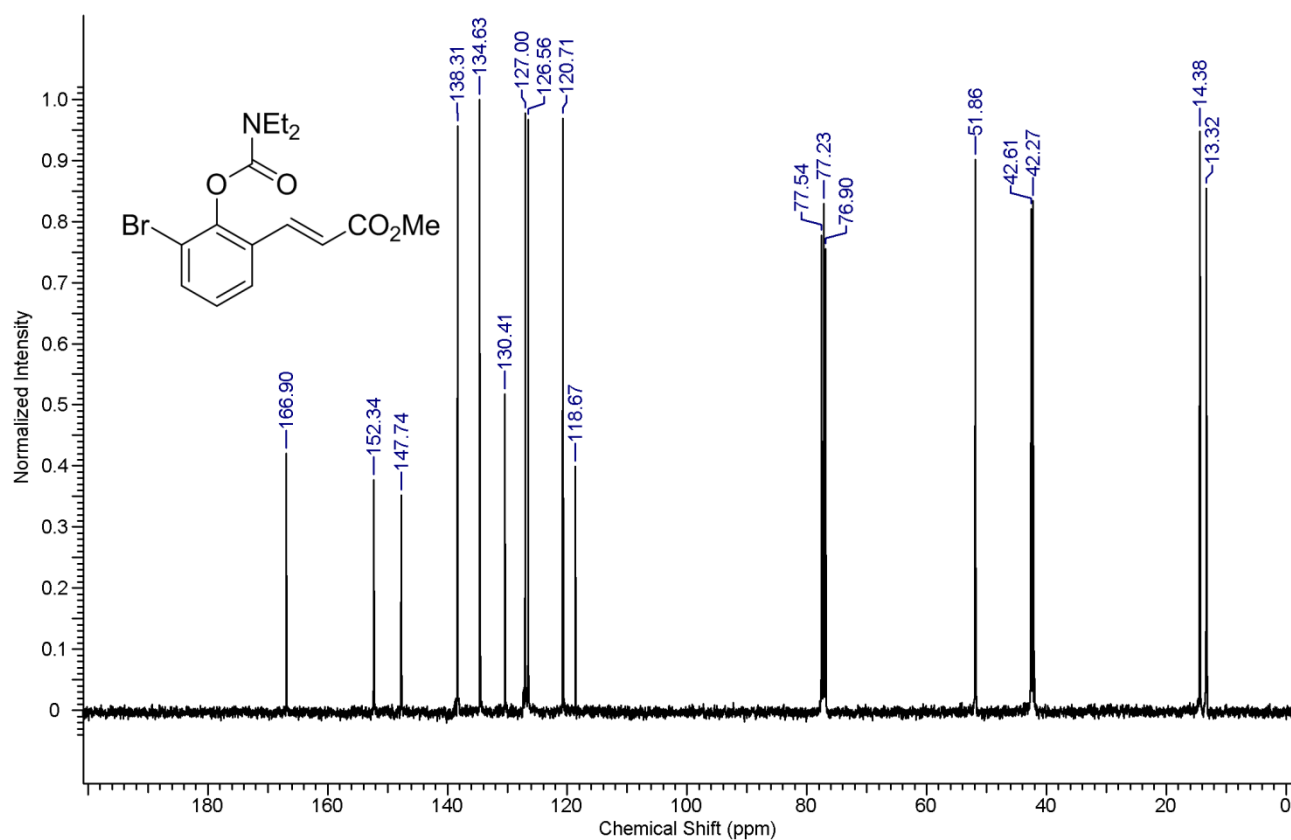
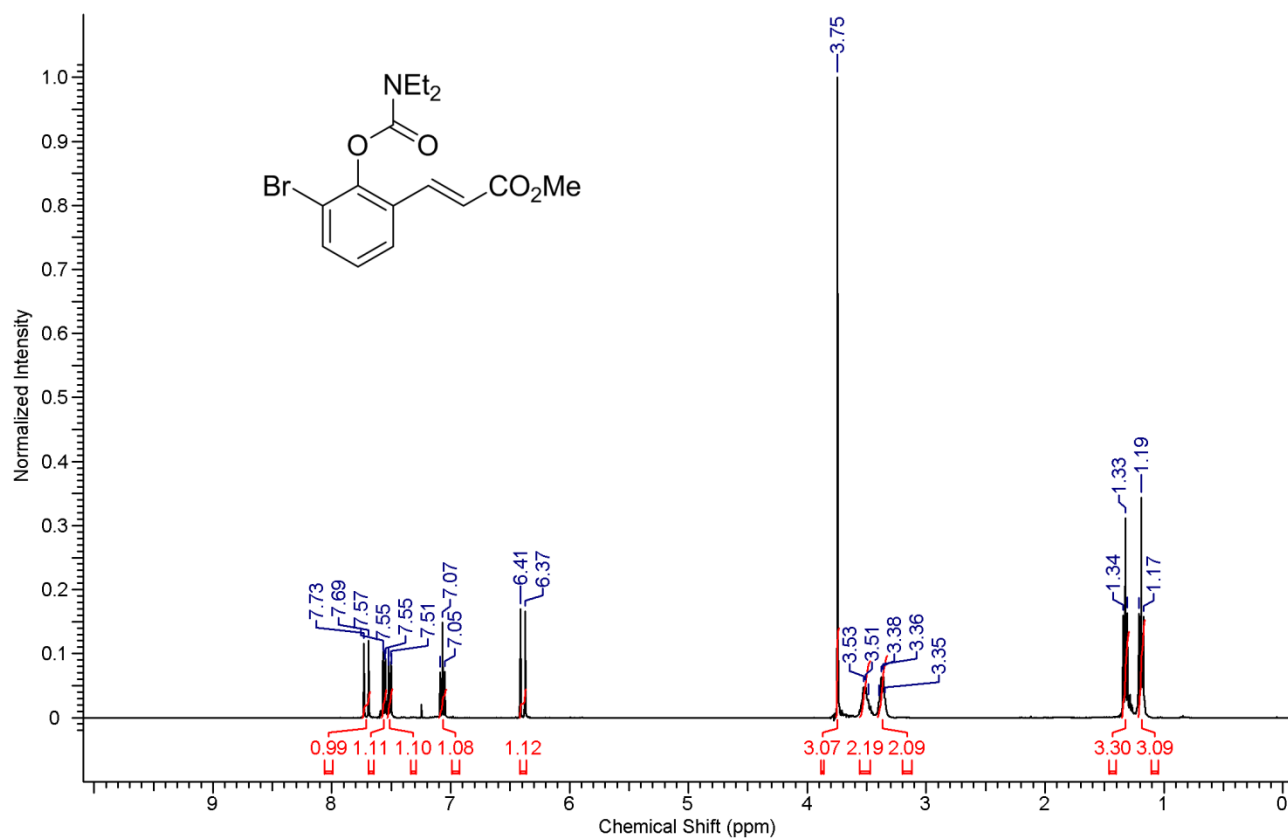
There is a NOE correlation between Ha (δ 6.27, d) and Hb (δ 7.49, d). There is a NOE correlation between Hb (δ 7.49, d) and Hc (δ 6.72, dd). However, there is no correlation between Hb (δ 7.49, d) and Hc (δ 6.72, dd). However, there is no correlation between Ha (δ 6.27, d) and Hd (δ 6.67, s). Similarly, there is no correlation between He (δ 7.74, d) and Hd (δ 6.67, s). These results clearly revealed that the regiochemistry of compound **3o** is correct.

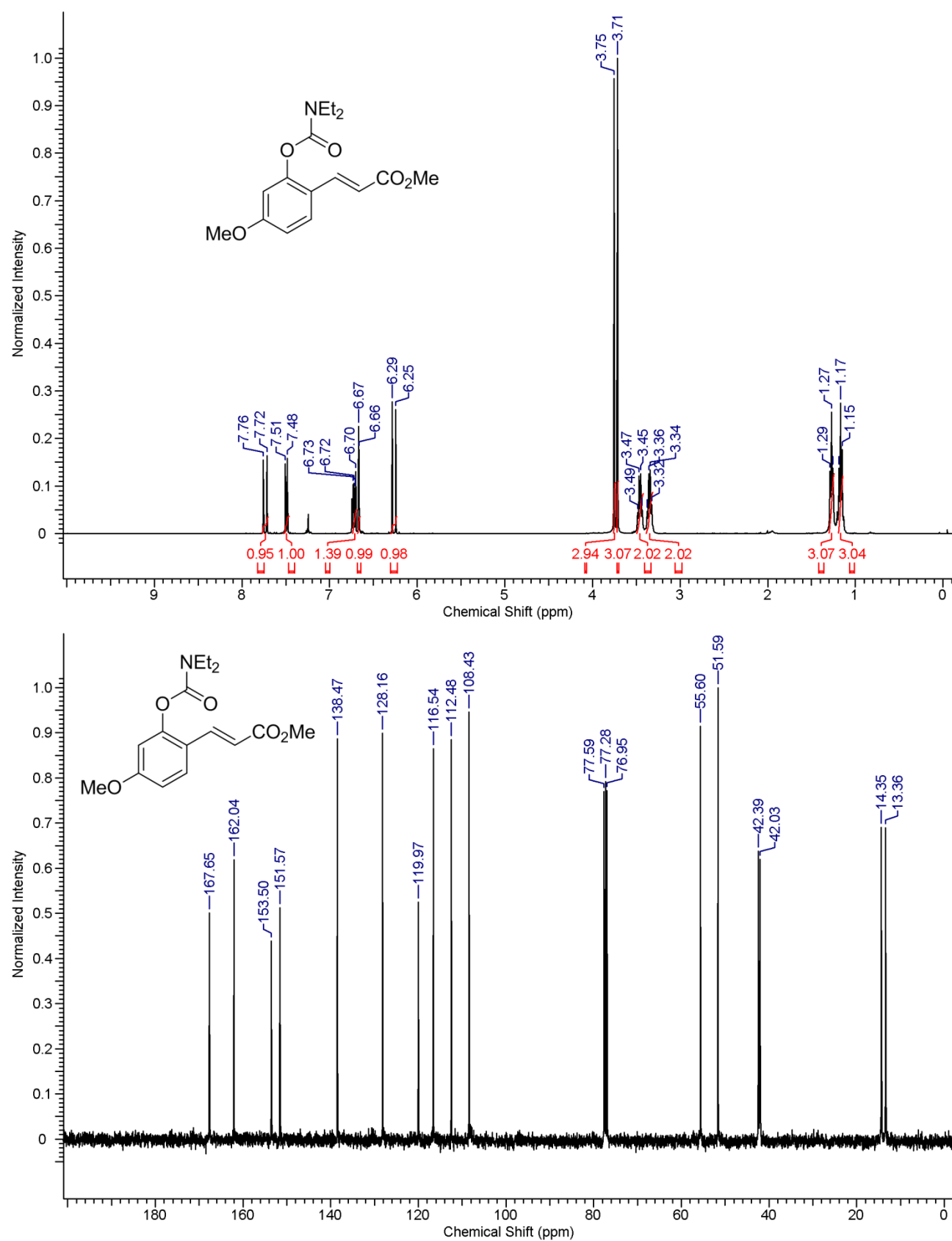


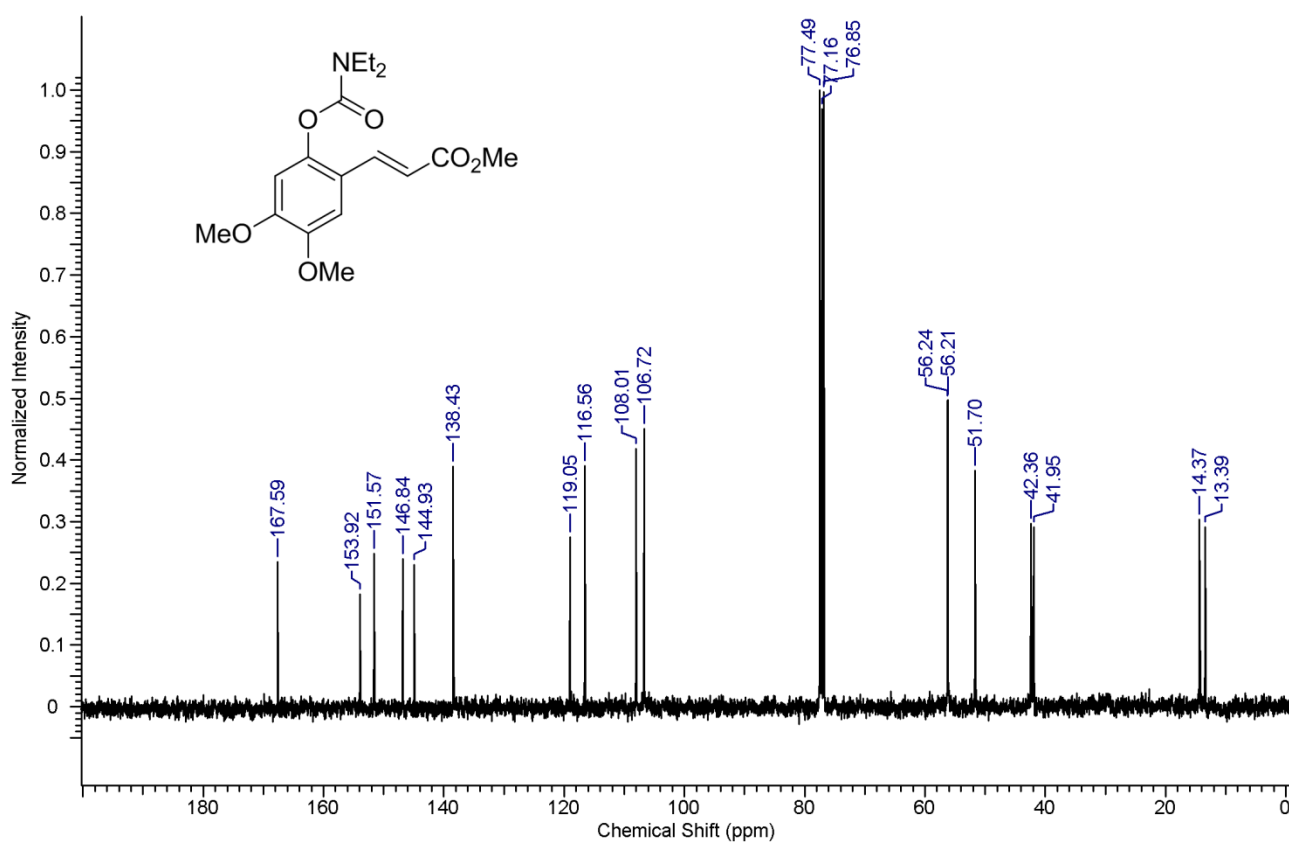
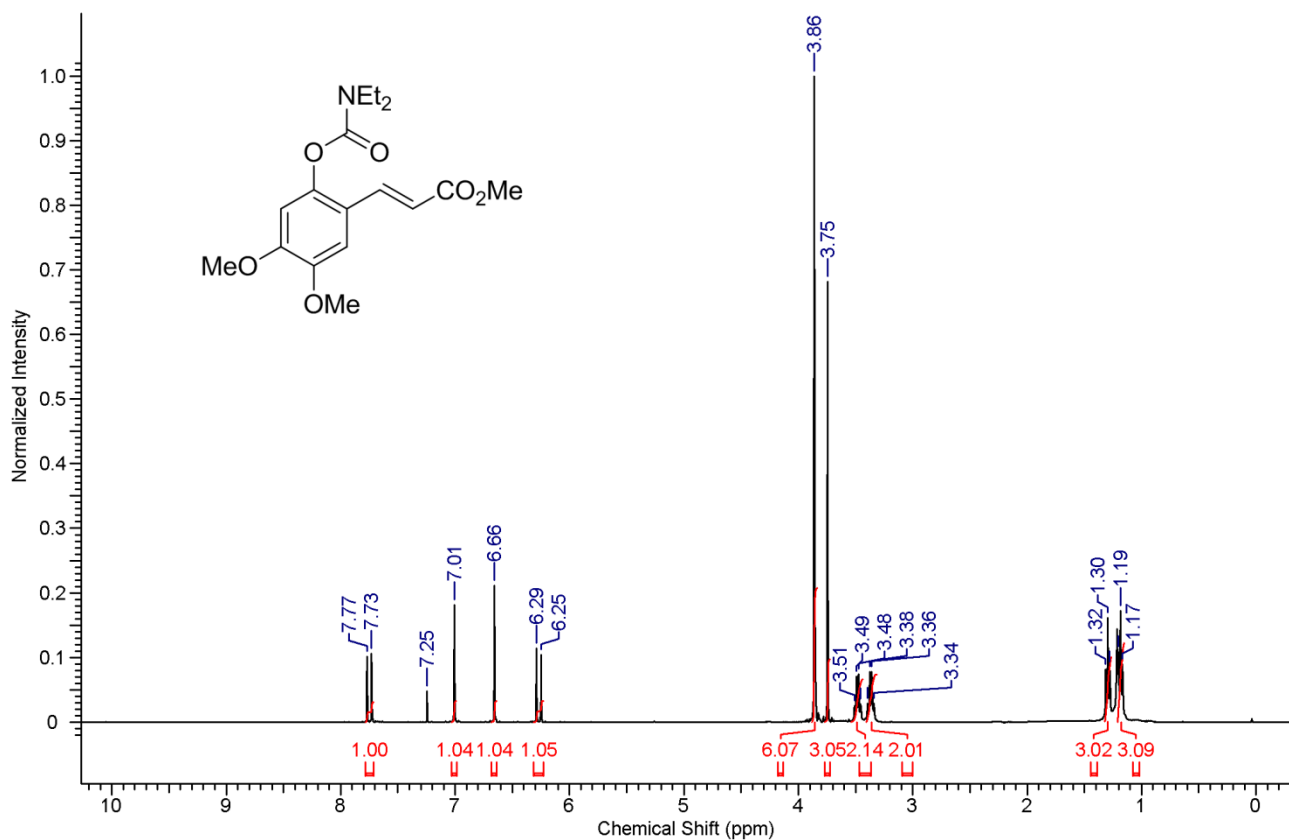
2A.16: Spectral Copies of Selected Compounds

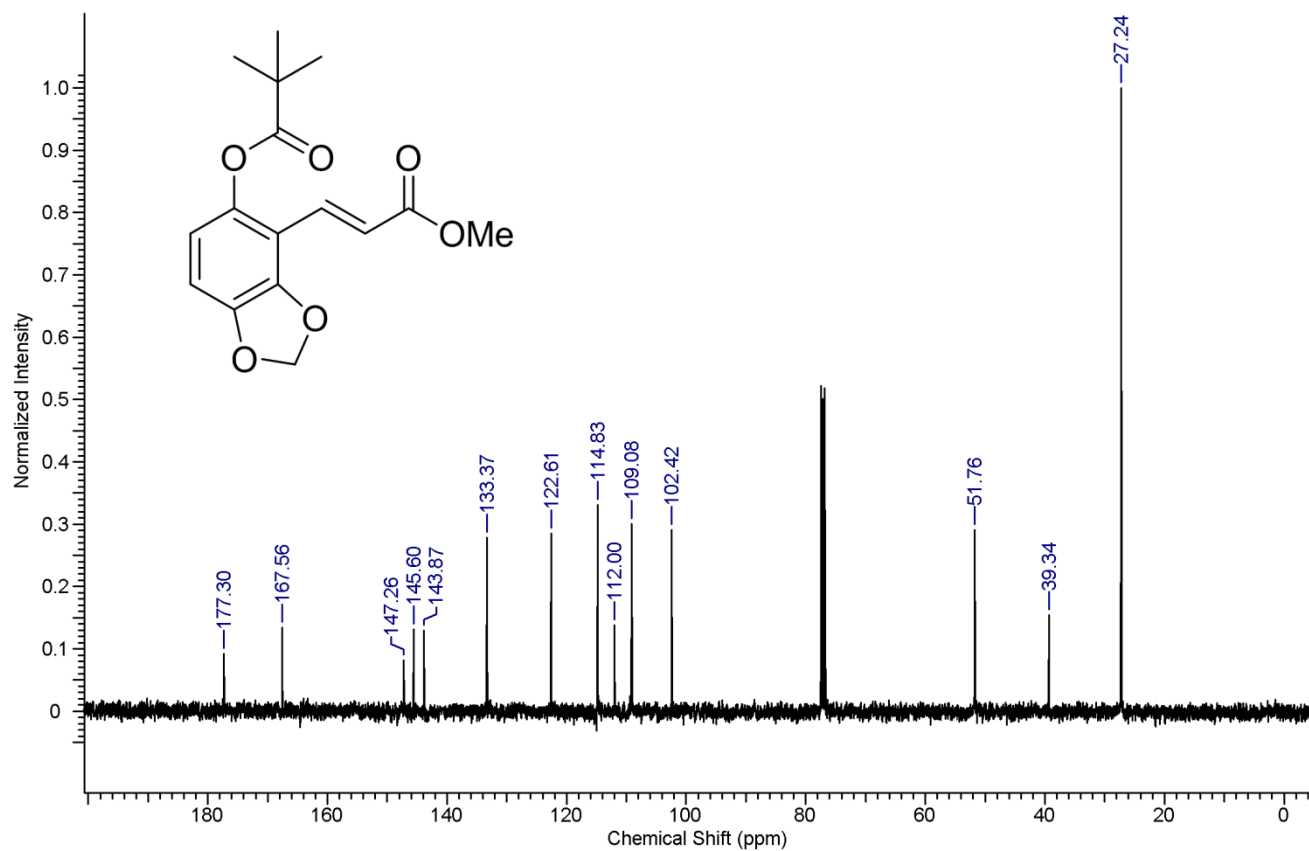
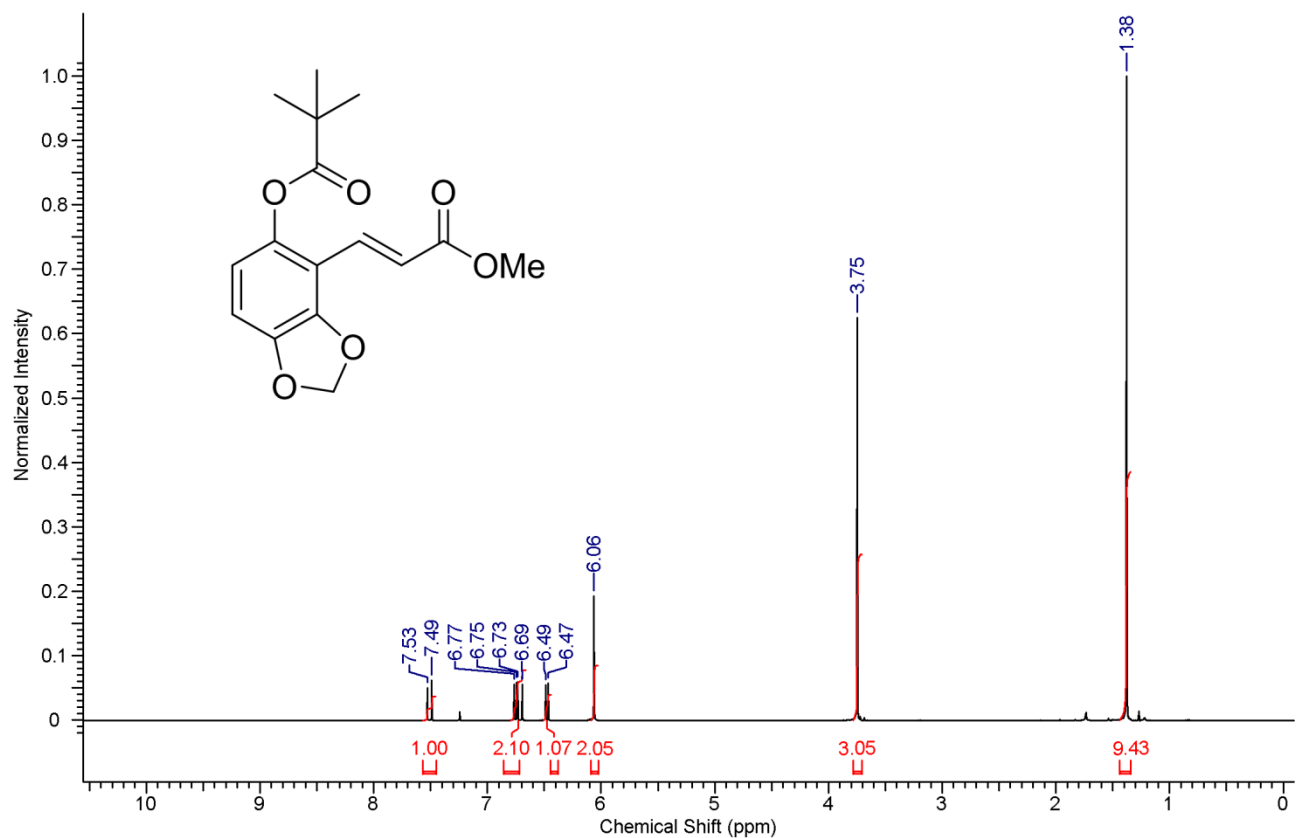
^1H and ^{13}C NMR Spectra of Compound **3a**. ^1H and ^{13}C NMR Spectra of Compound **3j**.

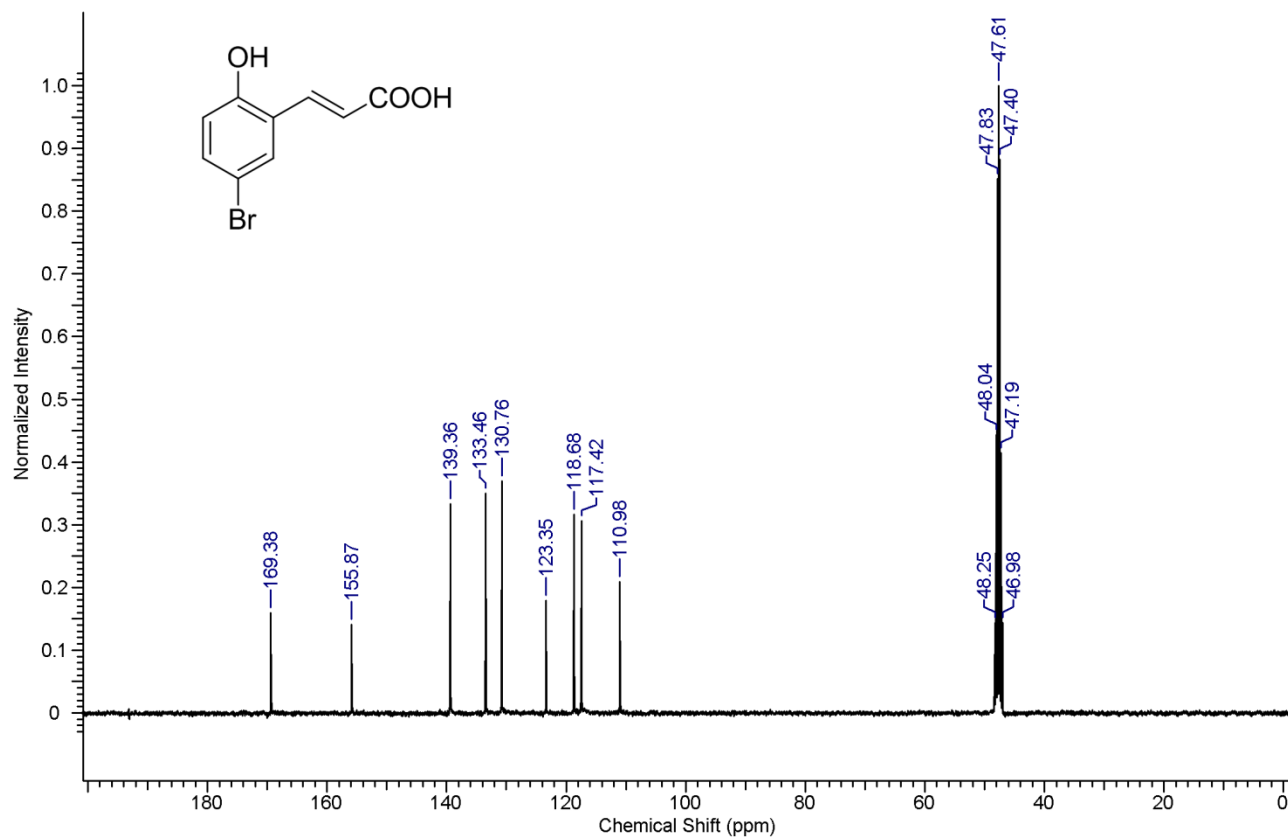
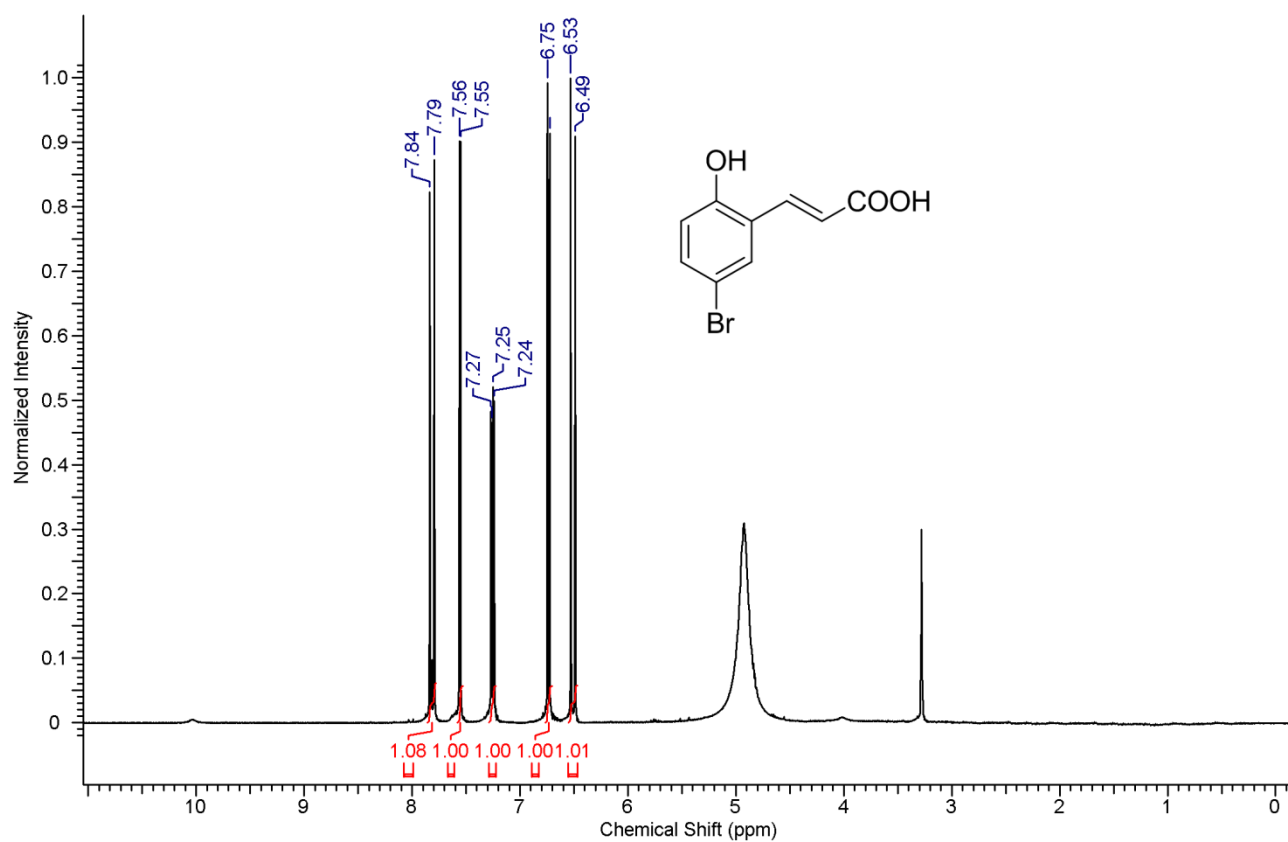
 ^1H and ^{13}C NMR Spectra of Compound **31**.



^1H and ^{13}C NMR Spectra of Compound **3o**.

^1H and ^{13}C NMR Spectra of Compound **3q**.

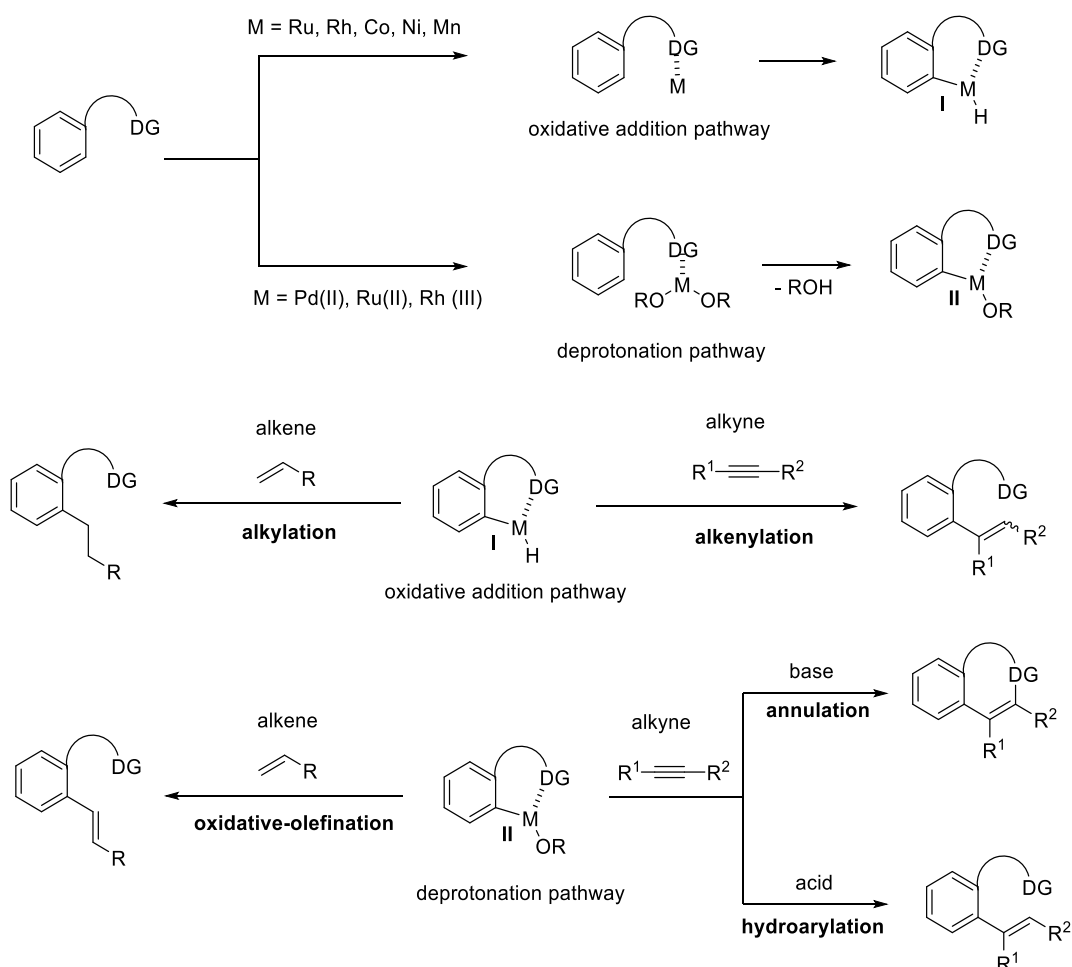
^1H and ^{13}C NMR Spectra of Compound **5b**.

^1H and ^{13}C NMR Spectra of Compound **6a** (*d*-MeOH solvent).

Section 2B: Ruthenium-Catalyzed Highly Regio- and Stereoselective Hydroarylation of Aryl Carbamates with Alkynes via C-H Bond Activation

2B.1: Introduction

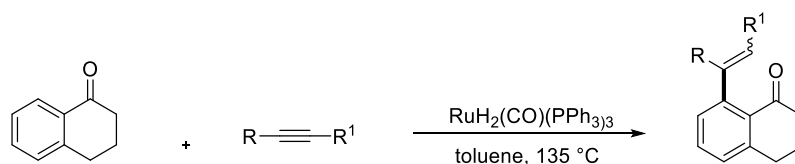
Transition metal catalyzed oxidative addition pathway and deprotonation pathway have been exploring rapidly for last few decades. It is quite interesting to look that the mechanisms, intermediates and products of these two pathways are different. These particular modes of interesting variations made significant attention to focus on the developing of deprotonation pathway, even though after having a good understanding platform on C-H activation of transition metal catalyzed oxidative addition pathway.



Scheme 2B.1: Functionalization of alkenes and alkynes via metal-catalyzed chelation assisted C-H bond activation in oxidative addition pathway and deprotonation pathway

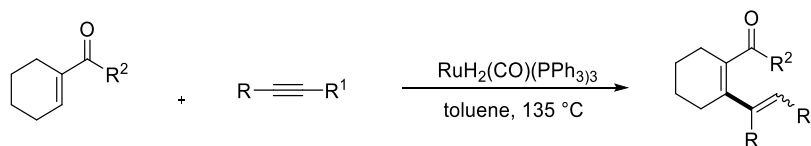
Generally, alkenes undergo alkylation in oxidative addition pathway to give alkylation product and but very interestingly same that of alkenes in deprotonation pathway involved in oxidative olefination to provide olefinated product instead of alkylation product (Scheme 2B.1). In the same way, alkynes can undergo different types of functionalization in both pathways. Alkynes undergo alkenylation reaction in oxidative addition pathway providing corresponding alkenylated products. But same alkynes undergo cyclization reaction in deprotonation pathway to provide corresponding cyclised products in the presence base. By quenching with acidic proton source, alkynes undergo hydroarylation reaction to give hydroarylated products.

Transition-metal-catalyzed chelation-assisted hydroarylation of C-H bond of hetero-atom group substituted aromatics with alkynes is one of the convenient methods to synthesise highly substituted alkene derivatives in a highly atom-economical and an environmentally friendly manner.^{1, 2} Alkene structural units are present in various organic materials, natural products and drug molecules.^{1, 2} In 1995, Murai's group reported alkenylation at C-H bond of carbonyl group substituted aromatics with alkynes in the presence of ruthenium catalyst (Scheme 2B.2).^{3a-b}



Scheme 2B.2: *Ortho*-Alkenylation of aromatic ketones

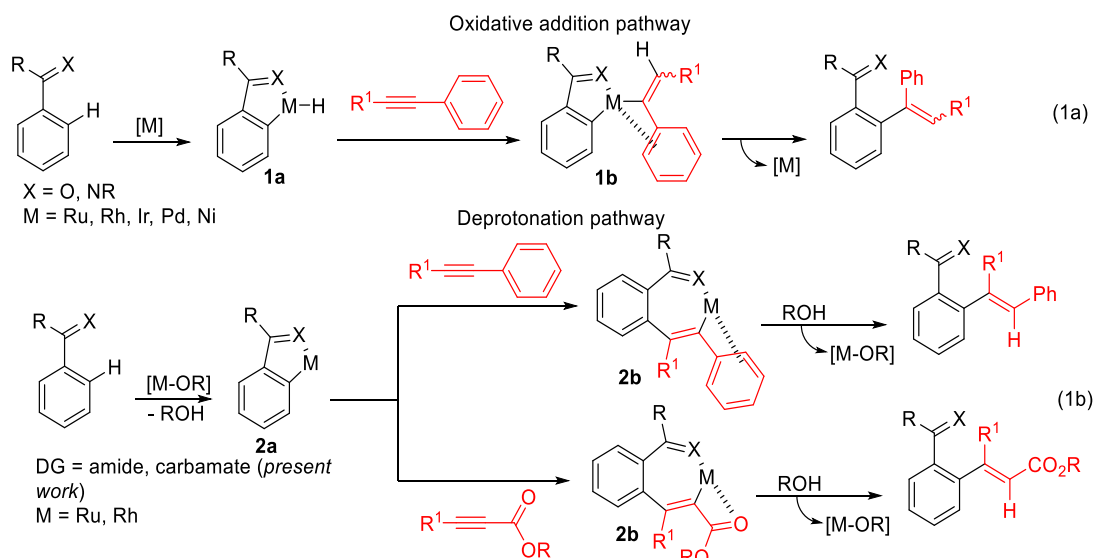
Later, the same group described an *ortho* alkenylation of alkene-derived ketones with alkynes in the presence of a ruthenium catalyst (Scheme 2B.3).^{3a-b}



Scheme 2B.3: *Ortho*-Alkenylation of alkene-derived ketones

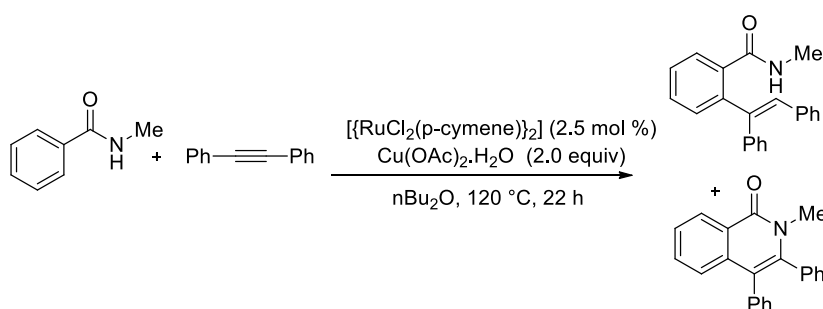
After that, various metal complexes such as rhodium, palladium, iridium and nickel complexes have been successfully used as catalysts for hydroarylation of various hetero-atom group substituted aromatics with alkynes.⁴⁻⁶ It is believed that this coupling reaction proceeds mechanistically via chelation-assisted oxidative addition of *ortho* C-H bond of hetero-atom substituted aromatics with a metal complex yielding a five-membered hydro-metallacycle intermediate **1a** (eq. 1a). Later, aromatic group substituted alkynes undergo coordinative insertion into metal-hydride species of intermediate **1a** followed by

reductive elimination providing alkene derivatives (eq. 1a). Mostly, -Ph group from the alkyne and hetero-atom substituted aromatics attach to the same carbon of alkenes, providing a mixture of *cis* and *trans* stereoisomeric addition products. This reaction is also not completely regioselective and mostly gives a mixture of regioisomers. In meantime, alkynes scope is also limited in the reaction. This kind of regio- and stereoisomeric issues can be easily overcome by doing a similar type of hydroarylation reaction via concerted deprotonation metalation pathway instead of oxidative addition pathway.⁷⁻⁹ In 2010, Fagnou's group reported strong directing amide group assisted rhodium-catalyzed hydroarylation of substituted indoles with alkynes.^{9a} Very recently, Miura's group reported strong directing amide group assisted ruthenium-catalyzed hydroarylation of benzamides with alkynes.^{9b} The catalytic reaction proceeds via chelation-assisted acetate accelerated deprotonation at *ortho* C-H bond of hetero-atom group substituted aromatics with a metal complex (Rh or Ru) providing metallacycle intermediate **2a** (eq. 1b). Coordinative insertion of aromatic group substituted alkyne into the metal-carbon bond of metallacycle **2a** provides metallacycle intermediate **2b** followed by protonation with organic acid giving alkene derivatives in a highly regio- and stereoselective manner (eq. 1b). The regiochemistry of the product of this reaction is completely reversed when compared with the regiochemistry of product observed via oxidative addition pathway (eq. 1a). A possible explanation for the reverse regiochemistry of the product is probably due to intramolecular coordination of phenyl group of alkyne to the metal species which stabilizes the corresponding intermediate (eq. 1b).



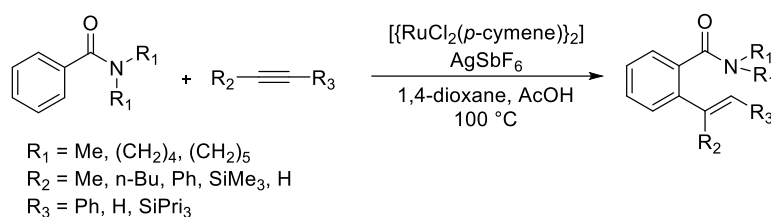
2B.2: Aim of the Present Work

In 2011, demonstrated oxidative cyclization of *N*-methyl benzamides with alkynes providing substituted isoquinolone derivatives was described by Ackermann's group (Scheme 2B.4).^{7g} In this reaction, *N*-methyl benzamide reacted with diphenylacetylene in the presence of ruthenium catalyst and $Cu(OAc)_2 \cdot H_2O$ in ether solvent, along with isoquinolone derivative a minor amount of *ortho* alkenylated benzamide was observed in 15% yield in 27% yield, respectively. This result clearly reveals that the *N*-methyl benzamides prefer cyclization reaction with alkynes rather than the hydroarylation reaction.



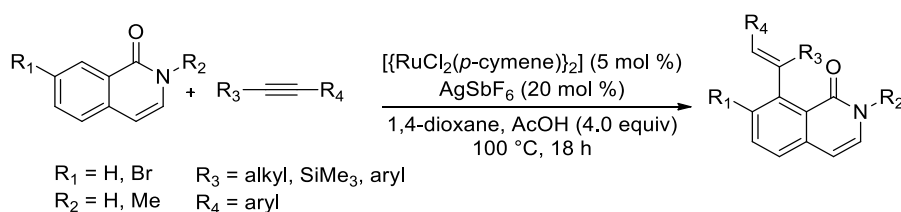
Scheme 2B.4: The hydroarylation of *N*-methyl benzamide with diphenylacetylene

In 2012, Miura's group report a highly regio- and stereoselective hydroarylation of substituted benzamides with alkynes, providing trisubstituted alkenes in a highly regio- and stereoselective manner (Scheme 2B.5).^{9b}



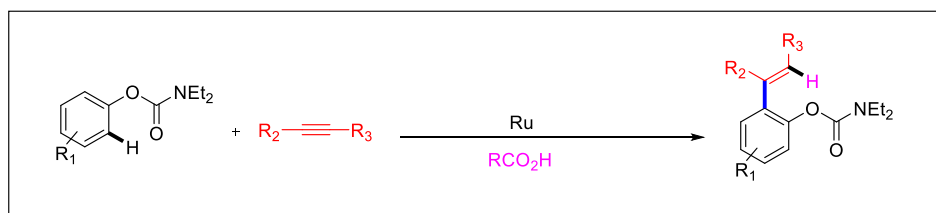
Scheme 2B.5: Ruthenium-catalyzed hydroarylation of *N,N*-dialkylbenzamides with alkynes

In the same year, Li's group reported a ruthenium-catalyzed hydroarylation of isoquinolone derivatives with alkynes in the presence of acetic acid (Scheme 2B.6).^{9c}



Scheme 2B.6: The hydroarylation of isoquinolone derivatives with alkynes

Next, we have paid out attention to explore hydroarylation of very weak directing group aromatic carbamate with alkynes. Herein, we wish to discuss about an oxidant free a regio- and stereoselective hydroarylation of aromatic carbamates with alkynes in the presence of a less expensive ruthenium catalyst (Scheme 2B.7).



Scheme 2B.7: Hydroarylation of aromatic sulfoxide in the presence of Ru catalyst

2B.3: Optimization Studies

Carbamate directing group is a very weak directing group. Usage of silver salt for this was important. Acidic source used was crucial for the success of the hydroarylation reaction. For this reaction we have chosen $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$, AgSbF_6 and AcOH for initial optimization. When 4-methoxyphenyl diethylcarbamate (**1a**) was treated with 1-phenyl-1-propyne (**2c**) in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (5 mol %), AgSbF_6 (20 mol %) and AcOH (5.0 equiv) in 1,4-dioxane at 100 °C for 24 h, a hydroarylation product **3a** was isolated in 63% yield (Table 2B.1, entry 1). In order to improve the yield, the catalytic reaction was optimized by varying different organic acid sources, solvents and additives. This reaction was examined with various organic acid sources such as

AcOH, pivalic acid, $\text{CF}_3\text{CO}_2\text{H}$, PhSO_3H , PhCO_2H . Pivalic acid was very effective for this reaction giving product **3a** in 74% yield. $\text{CF}_3\text{CO}_2\text{H}$ was less effective and afforded **3a** in 45% yield. Then, the reaction was tested with different solvents. Solvent effect is also crucial to the catalytic reaction. The best solvent for this reaction is 1,4-dioxane yielding **3a** in 92%. THF, *tert*-BuOH and MeOH were also effective for this reaction giving **3a** in 81, 75 and 79% respectively. Toluene, DMF, DMSO were totally ineffective for the catalytic reaction.

Table 2B.1: Optimization Studies.^a

entry	solvent	organic Acid	additive	yield of 3a (%) ^b
1	DME	AcOH	AgSbF_6	63
2	DME	Pivalic acid	AgSbF_6	74
3	DME	CF_3COOH	AgSbF_6	45
4	DME	$\text{CF}_3\text{SO}_3\text{H}$	AgSbF_6	trace
5	DME	PhSO_3H	AgSbF_6	trace
6	DME	PhCOOH	AgSbF_6	52
7	1,4-dioxane	Pivalic acid	AgSbF_6	92
8	DCE	Pivalic acid	AgSbF_6	45
9	CH_3CN	Pivalic acid	AgSbF_6	55
10	THF	Pivalic acid	AgSbF_6	81
11	<i>tert</i> -BuOH	Pivalic acid	AgSbF_6	75
12	Toluene	Pivalic acid	AgSbF_6	trace
13	DMF	Pivalic acid	AgSbF_6	NR
14	MeOH	Pivalic acid	AgSbF_6	79
15	DMSO	Pivalic acid	AgSbF_6	NR
16	1,4-dioxane	Pivalic acid	KPF_6	NR
17	1,4-dioxane	Pivalic acid	No	NR

^aAll reactions were carried out under the following conditions: **1e** (1.0 mmol), **2c** (1.5 mmol), $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (5 mol %), additive (20 mol %) and organic acid (5.0 mmol) in solvent (3.0 mL) at 100 °C for 16 h under N_2 atmosphere. ^b Yields were determined by the ^1H NMR integration method, using mesitylene

as an internal standard.

2B.4: Scope of Substituted Phenyl Carbamates.

Treatment of 4-methoxyphenyl diethylcarbamate (**1a**) with ethyl but-2-ynoate (**2a**) in the presence of [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (5 mol %), AgSbF_6 (20 mol %) and pivalic acid (5.0 equiv) in 1,4-dioxane at 100 °C for 24 h gave a hydroarylation product **3a** in 77% isolated yield (Table 2B.2, entry 1). The catalytic reaction is highly regioselective and *ortho* C-H bond of **1a** very selectively inserts at methyl group substituted carbon of alkyne **2a**. The catalytic reaction is also highly stereoselective giving only *E*-stereoisomer compound **3a**.

Table 2B.2 : The reaction of aryl carbamates **1a-k** with alkynes **2a-b**^a

entry	carbamate 1a-k	alkynes 2a-b	product 3	Yield (%) ^b
1				77
2				79
3				83
4				80
5				82 ^c
6				80

7				75
8				73
9				64
10				65
11				69

^aAll reactions were carried out under the following reaction conditions: **1a-k** (1.0 mmol), **2a-b** (1.5 mmol), [{RuCl₂(*p*-cymene)}₂] (5 mol %), AgSbF₆ (20 mol %) and pivalic acid (5.0 mmol) in 1,4-dioxane at 100 °C for 24 h under N₂ atmosphere. ^b Isolated yield. ^c The reaction was done at 100 °C for 16 h.

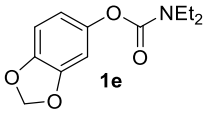
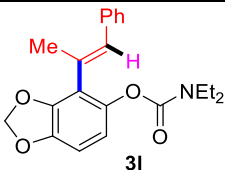
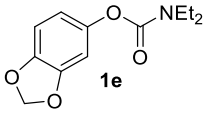
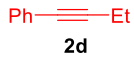
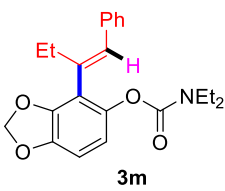
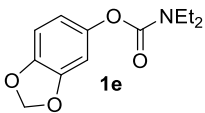
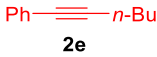
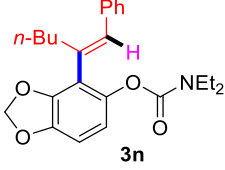
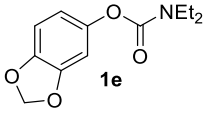
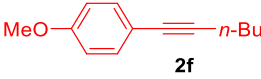
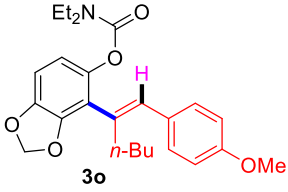
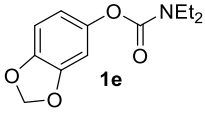
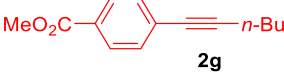
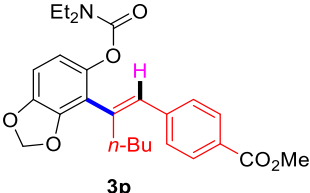
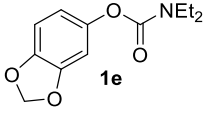
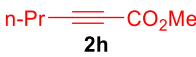
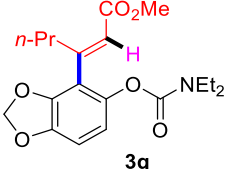
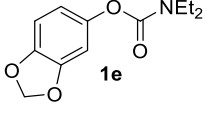
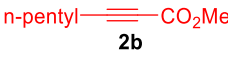
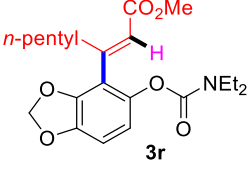
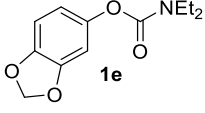
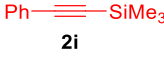
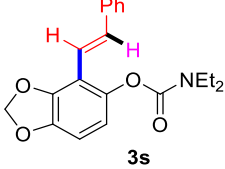
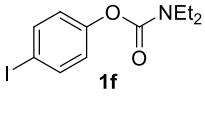
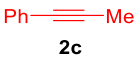
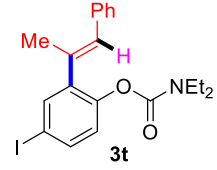
To explore the scope of the present hydroarylation reaction, the reaction of various substituted aryl carbamates **1b-k** with **2a-b** were examined (Table 1). 3-Methoxyphenyl carbamate **1b** underwent hydroarylation reaction with ethyl but-2-ynoate (**2a**) under similar reaction conditions, providing coupling product **3b** in 79% yield in a highly regio- and stereoselective manner (entry 2). In the substrate **1b**, there are two C-H bonds for stereoselective hydroarylation with **2a**. Very selectively, a less hindered C-H bond of **1b** was involved in the coupling reaction. Similarly, 3,4-dimethoxyphenyl carbamate **1c** and 3,4-dimethylphenyl carbamate **1d** afforded alkene derivatives **3c** and **3d** in 83% and 80% yields, respectively, in a highly regio- and stereoselective manner (entries 3 and 4). As like **1b**, in this reaction also alkenylation takes place selectively at less hindered C-H bond of **1c** and **1d**. In contrast, sesamol carbamate **1e** reacted with **2a** at sterically hindered C-H bond of **1e** yielding *E*-stereoselective coupling product **3e** in 82% yield in a

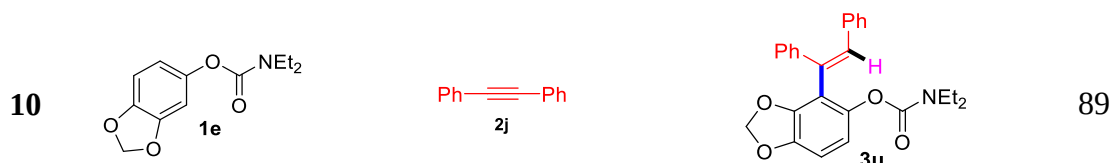
highly regioselective manner (entry 5). The exact reason for the high regioselectivity at the sterically hindered site is unclear to use. It is possible that in addition to carbamate directing group, O group of dioxole moiety of **1e** also assists the C-H bond activation. Next, the hydroarylation reaction was tested with halogen group substituted carbamates **1f-i**. Thus, 4-iodo **1f**, 4-bromo **1g**, 4-chloro **1h** and 4-fluoro **1i** phenyl carbamates efficiently reacted with methyl oct-2-ynoate (**2b**) giving *E*-stereoselective alkene derivatives **3f-i** in 80%, 75%, 73% and 64% yields, respectively (entries 6-9). Similarly, 1-naphthalenyl diethylcarbamate (**1j**) reacted with ethyl but-2-ynoate (**2a**) affording coupling product **3j** in 65% yield in a highly stereoselective manner (entry 10). Interestingly, 2-naphthalenyl diethylcarbamate (**1k**) reacted with ethyl but-2-ynoate (**2a**) at sterically less hindered C-H of **1k** moiety providing coupling product **3k** in 69% yield, in a highly regio- and stereoselective manner (entries 11). For products **3b-k** except **3e**, a similar type of regiochemistry as like **3a** was observed.

2B.5: Scope of Alkynes

The present hydroarylation reaction was extended successfully with various substituted alkynes **2b-k** (Table 2B.3). Thus, 1-phenyl-1-propyne (**2c**), 1-phenyl-1-butyne (**2d**) and 1-phenyl-1-hexyne (**2e**) reacted very selectively at sterically hindered C-H bond of sesamol carbamate **1e** providing the corresponding alkene derivatives **3l-n** in 86%, 84% and 81% yields, respectively, in a highly stereoselective manner (Table 2B.3, entries 1-3). The catalytic reaction is highly regioselective and C-H bond of **1e** added at Me or *n*-Pr or *n*-pentyl groups substituted carbon of alkynes **2c-e**. Similarly, methoxy **2f** and methylester **2g** group substituted alkynes also successfully participated in the reaction affording coupling products **3o** and **3p** in 83% and 75% yields, respectively (entries 4 and 5). Methyl hex-2-ynoate (**2h**) and methyl oct-2-ynoate (**2b**) provided the corresponding *E*-stereoselective alkene derivatives **3q** and **3r** in 79% and 76% yields, respectively (entries 6 and 7). Similarly, trimethyl(phenylethynyl)silane (**2i**) also efficiently participated in the reaction with **1e** affording alkene derivative **3s** in 72% yield (entry 8). However, in the product **3s**, TMS moiety of alkyne was cleaved under the reaction conditions. 4-Iodophenyl carbamate **1f** efficiently reacted with 1-phenyl-1-propyne (**2c**) under similar reaction conditions providing the corresponding alkene derivative **3t** in 75% yield (entry 9). Diphenylacetylene (**2j**) also reacted efficiently with **1e** yielding alkenylated product **3u** in excellent 89% yield (entry 10).

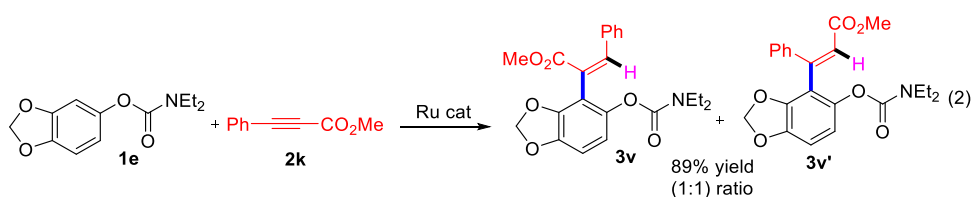
Table 2B.3: The reaction of carbamates **1e** or **1f** with alkynes **2b-j**^a

entry	carbamate 1	alkynes 2b-j	product 3l-u	Yield (%) ^b
1				86
2				84
3				81
4				83
5				75
6				79
7				76
8				72
9				75 ^c



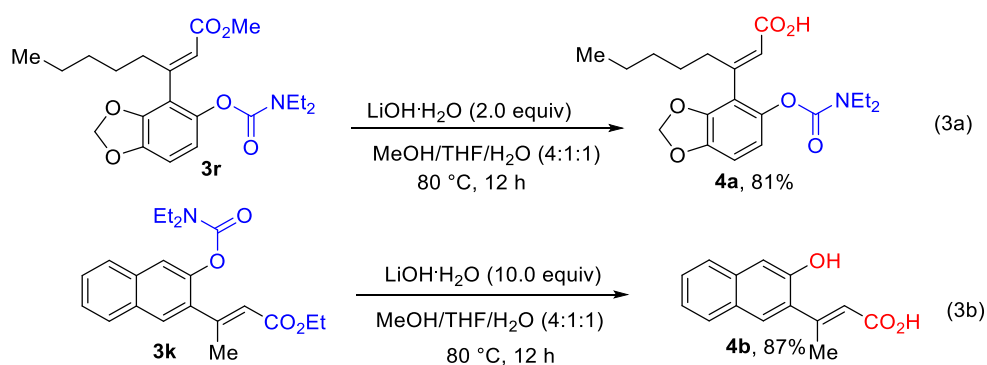
^aAll reactions were carried out under the following reaction conditions: **1e** or **1f** (1.0 mmol), **2b-j** (1.5 mmol), [$\text{RuCl}_2(p\text{-cymene})\}_2$] (5 mol %), AgSbF_6 (20 mol %) and pivalic acid (5.0 mmol) in 1,4-dioxane at 100 °C for 16 h under N_2 atmosphere. ^b Isolated yield. ^c The reaction was done at 100 °C for 24 h.

Subsequently, the reaction of **1e** with methyl 3-phenylpropiolate (**2k**) was also tested under similar reaction conditions (eq. 2). In the reaction, a mixture of regioisomeric products **3v** and **3v'** were observed in 89% yield in approx. 1:1 ratio. The observation of mixture of regioisomeric products in the reaction is most probably due to both phenyl as well as ester groups of alkyne **2k** intramolecularly coordinate with ruthenium intermediate **2b** (eq. 1b).

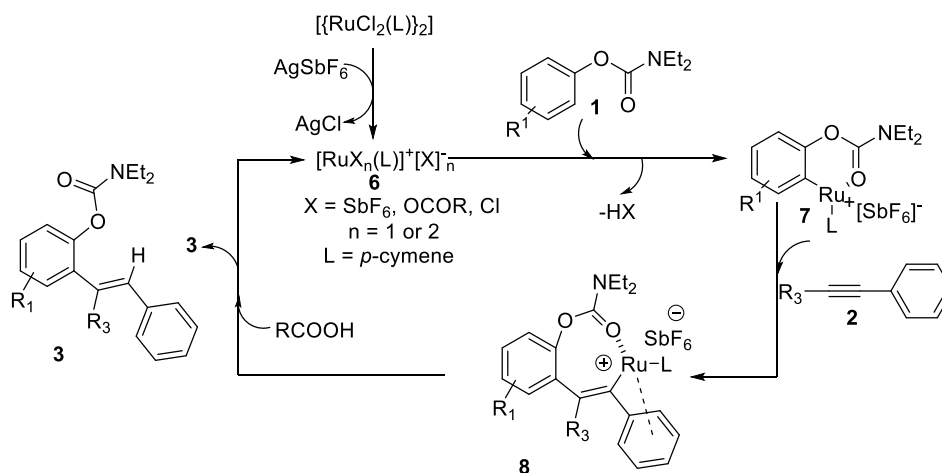


2B.6: Removal of Carbamate Group

Later, the ester group of product **3r** was converted into carboxylic acid derivative **4a** in the presence of LiOH (2.0 equiv) (eq. 3a). Whereas, 10.0 equiv of LiOH cleaved both ester and carbamate moieties of compound **3k**, giving phenol derivative **4b** in 87% yield (eq. 3b). The structure of compounds **4a** and **4b** were confirmed by single crystal X-ray diffraction (see experimental data).



2B.7: Mechanism



Scheme 2B.8: Proposed mechanism

The catalytic reaction proceeds via coordination of oxygen atom of **1** into a cationic ruthenium species **6** followed by *ortho* metalation provides intermediate **7** (Scheme 2B.8). Coordinative selective insertion of alkyne **2** into the C-Ru bond of intermediate **7** yields intermediate **8**. Protonation of C-Ru bond of intermediate **8** by pivalic acid affords *ortho* alkenylated product **3** and regenerates the active catalyst **6**. Intramolecular coordination of Ph group to the Ru metal could stabilize the intermediate **8**. Pivalic acid plays dual role in the reaction. It acts as an acetate source for the deprotonation of the *ortho* C-H bond of **1** and the proton source followed by the regeneration of the active catalyst.

2B.8: Conclusion

1. We have demonstrated Ruthenium-catalyzed highly regio- and stereoselective hydroarylation of aryl carbamates with alkynes via C-H bond activation
2. Further carbamate group of product **3** was removed to get corresponding phenol derivatives.

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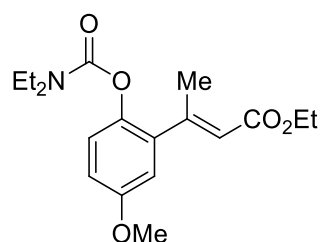
2B.8: Experimental Section

General procedure for the hydroarylation of aryl carbamates with alkynes catalyzed by ruthenium complex.

A 15-mL pressure tube equipped with a magnetic stirrer and septum containing [$\text{RuCl}_2(p\text{-cymene})\}_2$] (0.05 mmol, 5 mol %) and AgSbF_6 (0.20 mmol, 20 mol %) was evacuated and purged with nitrogen gas three times. To the tube were then added carbamate (**1**) (1.00 mmol), alkyne **2** (1.50 mmol), pivalic acid (5.00 mmol) and 1,4-dioxane solvent (3.0 mL) via syringes and again the tube was evacuated and purged with nitrogen gas three times. Then, the septum was taken out and immediately a screw cap was used to cover the tube. The reaction mixture was allowed to stir at 100 °C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 , filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3**.

2B.10: Spectral Data of Compounds

(*E*)-Ethyl 3-(2-((diethylcarbamoyl)oxy)-5-methoxyphenyl)but-2-enoate (**3a**).



Colorless semisolid; eluent (12% ethyl acetate in hexanes).

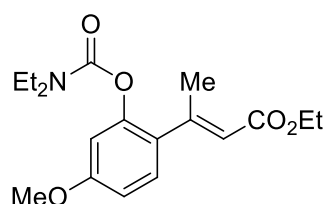
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2959, 1723, 1630, 1270 and 1194.

¹H NMR (CDCl₃, 400 MHz): δ 7.01 (d, J = 8.0 Hz, 1 H), 6.82 (dd, J = 4.0 Hz, 1 H), 6.72 (d, J = 4.0 Hz, 1 H), 5.86 (s, 1 H), 4.16 (q, J = 8.0 Hz, 2 H) 3.77 (s, 3 H), 3.39 – 3.28 (m, 4 H), 2.43 (s, 3 H), 1.26 (t, J = 8.0 Hz, 3 H), 1.18 (t, J = 8.0 Hz, 3 H), 1.12 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.5, 156.7, 154.2, 153.8, 141.4, 137.6, 124.1, 119.9, 114.1, 113.6, 59.8, 55.7, 42.2, 41.8, 19.8, 14.3, 14.2, 13.3.

HRMS (ESI): calc. for [(C₁₈H₂₅NO₅)H] (M+H) 336.1811, measured 336.1812.

(E)-Ethyl 3-(2-((diethylcarbamoyl)oxy)-4-methoxyphenyl)but-2-enoate (3b).



Pale yellow oil; eluent (12% ethyl acetate in hexanes).

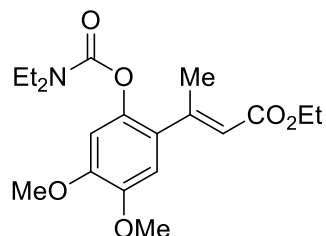
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2979, 1712, 1635, 1457, 1311 and 1163.

¹H NMR (CDCl₃, 400 MHz): δ 7.14 (d, J = 8.0 Hz, 1 H), 6.73 (dd, J = 8.0 Hz, 1 H), 6.65 (s, 1 H), 5.85 (s, 1 H) 4.17 (q, J = 8.0 Hz, 2 H), 3.79 (s, 3 H), 3.39 – 3.30 (m, 4 H), 2.42 (s, 3 H), 1.26 (t, J = 8.0 Hz, 3 H), 1.20 (t, J = 8.0 Hz, 3 H), 1.15 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.7, 160.1, 153.8, 153.6, 148.9, 129.3, 129.2, 119.3, 111.5, 108.8, 59.7, 55.5, 42.0, 41.8, 20.0, 14.4, 14.2, 13.3.

HRMS (ESI): calc. for [(C₁₈H₂₅NO₅)H] (M+H) 336.1811, measured 336.1814.

(E)-Ethyl 3-(2-((diethylcarbamoyl)oxy)-4,5-dimethoxyphenyl)but-2-enoate (3c).



Pale yellow oil; eluent (10% ethyl acetate in hexanes).

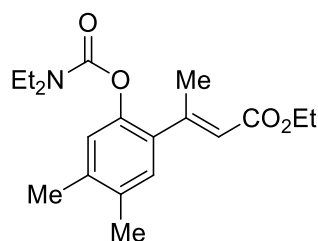
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2965, 1719, 1637 and 1155.

^1H NMR (CDCl_3 , 400 MHz): δ 6.69 (s, 1 H), 6.63 (s, 1 H), 5.87 (s, 1 H), 4.16 (q, J = 8.0 Hz, 2 H), 3.85 (s, 6 H) 3.39 – 3.28 (m, 4 H), 2.43 (s, 3 H), 1.27 (t, J = 4.0 Hz, 3 H), 1.19 (t, J = 8.0 Hz, 3 H), 1.15 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.5, 154.0, 153.7, 149.1, 146.2, 141.4, 128.2, 119.4, 110.7, 107.0, 59.6, 56.2, 56.0, 42.0, 41.6, 19.8, 14.3, 14.1, 13.2.

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{27}\text{NO}_6)\text{H}]$ (M+H) 366.1917, measured 366.1917.

(E)-Ethyl 3-(2-(((diethylcarbamoyl)oxy)-4,5-dimethylphenyl)but-2-enoate (3d).



Pale yellow oil; eluent (20% ethyl acetate in hexanes).

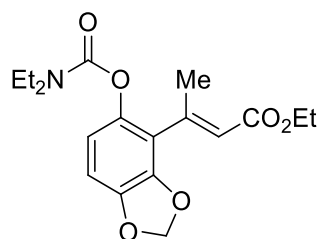
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2945, 1723, 1627, 1429 and 1155.

^1H NMR (CDCl_3 , 400 MHz): δ 6.97 (s, 1 H), 6.87 (s, 1 H), 5.85 (s, 1 H), 4.16 (q, J = 8.0 Hz, 2 H), 3.39 – 3.29 (m, 4 H), 2.42 (s, 3 H), 2.21 (s, 3 H), 2.20 (s, 3 H), 1.26 (t, J = 8.0 Hz, 3 H), 1.18 (t, J = 8.0 Hz, 3 H), 1.12 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 165.4, 153.0, 152.9, 144.4, 136.4, 132.8, 132.5, 128.3, 122.9, 118.2, 58.5, 40.9, 40.6, 18.7, 18.4, 17.9, 13.2, 12.9, 12.1.

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{27}\text{NO}_4)\text{H}]$ (M+H) 334.2018, measured 334.2014.

(E)-Ethyl 3-(5-(((diethylcarbamoyl)oxy)benzo[d][1,3]dioxol-4-yl)but-2-enoate (3e).



Pale yellow semisolid; eluent (12% ethyl acetate in hexanes).

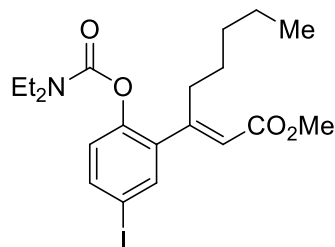
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 1722, 1639, 1469, 1271, 1181, 1105 and 1034.

^1H NMR (CDCl_3 , 400 MHz): δ 6.68 (d, J = 8.0 Hz, 1 H), 6.54 (d, J = 8.0 Hz, 1 H), 5.94 (s, 2 H), 5.88 (s, 1 H), 4.14 (q, J = 8.0 Hz, 2 H), 3.36 – 3.25 (m, 4 H), 2.41 (s, 3 H), 1.24 (t, J = 8.0 Hz, 3 H), 1.15 (t, J = 8.0 Hz, 3 H), 1.09 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.2, 154.1, 148.3, 144.98, 144.92, 142.4, 121.4, 120.2, 115.4, 107.3, 101.8, 59.8, 42.2, 41.8, 19.0, 14.3, 14.1, 13.2.

HRMS (ESI): calc. for $[(\text{C}_{18}\text{H}_{23}\text{NO}_6)\text{Na}]$ ($\text{M}+\text{Na}$) 372.1423, measured 372.1434.

(E)-Methyl 3-(2-((diethylcarbamoyl)oxy)-5-iodophenyl)oct-2-enoate (3f).



Colorless semisolid; eluent (18% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977, 1726, 1642, 1280, 1177 and 1045.

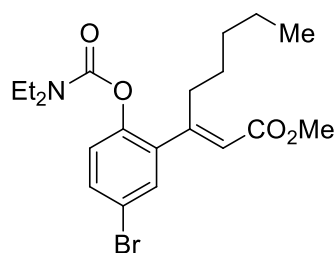
^1H NMR (CDCl_3 , 400 MHz): δ 7.59 (dd, J = 8.0, Hz, 1 H), 7.47 (s, 1 H), 6.90 (d, J = 8.0 Hz, 1 H), 5.78 (s, 1 H), 3.69 (s, 3 H), 3.36 – 3.28 (m, 4 H), 2.88 (d, J = 8.0 Hz, 2 H), 1.32 – 1.26 (m, 2 H), 1.25 – 1.23 (m, 4 H), 1.17 – 1.11 (m, 6 H), 0.81 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 165.1, 156.1, 152.2, 146.9, 136.5, 136.2, 124.3, 118.8, 87.9, 50.0, 41.1, 40.7, 31.4, 30.6, 26.7, 21.2, 12.9, 12.8, 12.0.

^{13}C NMR (CDCl_3 , 100 MHz): δ 165.1, 156.1, 152.2, 146.9, 136.5, 136.2, 131.7, 129.8, 124.3, 118.8, 50.0, 41.1, 40.7, 31.4, 30.6, 26.7, 21.2, 12.9, 12.8, 12.0.

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{28}\text{INO}_4)\text{H}]$ ($\text{M}+\text{H}$) 474.1141, measured 474.1143.

(E)-Methyl 3-(5-bromo-2-((diethylcarbamoyl)oxy)phenyl)oct-2-enoate (3g).



Colorless semisolid; eluent (18% ethyl acetate in hexanes).

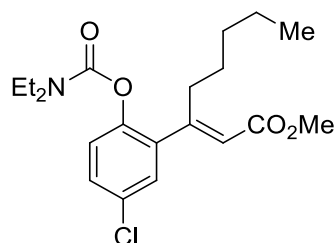
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 1724, 1638, 1425, 1263 and 1121.

^1H NMR (CDCl_3 , 400 MHz): δ 7.38 (dd, J = 8.0 Hz, 1 H), 7.28 (d, J = 4.0 Hz, 1 H), 7.02 (d, J = 8.0 Hz, 1 H), 5.78 (s, 1 H), 3.68 (s, 3 H), 3.33 – 3.29 (m, 4 H), 2.88 (t, J = 8.0 Hz, 2 H), 1.32 – 1.27 (m, 2 H), 1.25 – 1.22 (m, 4 H), 1.16 – 1.09 (m, 6 H), 0.80 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.3, 157.3, 153.4, 147.2, 137.4, 131.7, 131.5, 125.2, 120.1, 118.1, 51.1, 42.3, 41.8, 32.6, 31.8, 27.9, 22.4, 14.1, 14.0, 13.2.

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{28}\text{BrNO}_4)\text{H}]$ ($\text{M}+\text{H}$) 426.1280, measured 426.1268.

(E)-Methyl 3-(5-chloro-2-((diethylcarbamoyl)oxy)phenyl)oct-2-enoate (3h).



Pale yellow semisolid; eluent (14% ethyl acetate in hexanes).

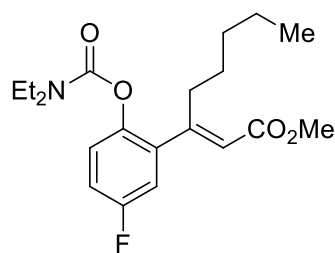
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2979, 1735, 1641, 1423, 1320, 1221, 1154 and 1035.

^1H NMR (CDCl_3 , 400 MHz): δ 7.25 (dd, $J = 8.0$, Hz, 1 H), 7.13 (s, 1 H), 7.06 (d, $J = 8.0$, Hz, 1 H), 5.78 (s, 1 H), 3.68 (s, 3 H), 3.36 – 3.27 (m, 4 H), 2.89 (t, $J = 8.0$ Hz, 2 H), 1.33 – 1.27 (m, 2 H), 1.26 – 1.22 (m, 4 H), 1.16 – 1.10 (m, 6 H), 0.80 (t, $J = 8.0$ Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.3, 157.4, 153.5, 146.7, 137.0, 130.5, 128.7, 128.6, 124.9, 120.0, 51.1, 42.3, 41.8, 32.6, 31.8, 27.9, 22.4, 14.1, 14.0, 13.2.

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{28}\text{ClNO}_4)\text{H}]$ ($\text{M}+\text{H}$) 382.1785, measured 382.1786.

(E)-Methyl 3-(2-((diethylcarbamoyl)oxy)-5-fluorophenyl)oct-2-enoateMethyl (3i).



Dark brown oil; eluent (12% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 1721, 1633, 1427, 1375, 1269, 1182 and 1080.

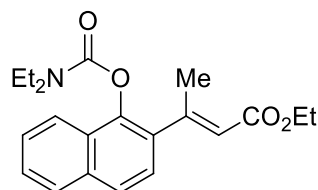
^1H NMR (CDCl_3 , 400 MHz): δ 7.09 (dd, $J = 8.0$, 4.0 Hz, 1 H), 6.99 (dd, $J = 4.0$, 4.0 Hz, 1 H, F – coupling), 6.87 (dd, $J = 8.0$, 4.0 Hz, 1 H, F – coupling), 5.80 (s, 1 H), 3.69 (s, 3 H), 3.36 – 3.28 (m, 4 H), 2.90 (t, $J = 8.0$ Hz, 2 H), 1.34 -1.32 (m, 2 H), 1.26 – 1.23 (m, 4 H), 1.17 – 1.10 (m, 6 H), 0.81 (t, $J = 8.0$ Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.4, 160.8, 158.3, 157.5, 153.8, 144.1 and 144.0 (F – coupling), 137.5 and 136.9 (F – coupling), 125.0 and 124.9 (F – coupling), 120.0, 115.57

and 115.52 (F – coupling), 115.52 and 115.3 (F – coupling)), 51.5, 42.2, 41.8, 32.6, 31.8, 27.9, 22.4, 14.1, 14.0, 13.2.

HRMS (ESI): calc. for $[(C_{20}H_{28}FNO_4)H]$ (M+H) 366.2081, measured 366.2076.

(E)-Ethyl 3-(1-((diethylcarbamoyl)oxy)naphthalen-2-yl)but-2-enoate(3j).



Pale yellow oil; eluent (18% ethyl acetate in hexanes).

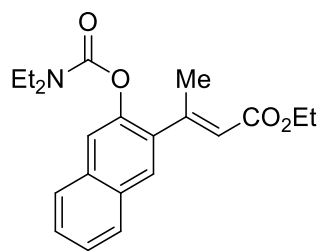
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2969, 1721, 1615, 1505, 1419, 1266, 1159 and 1033.

¹H NMR (CDCl₃, 400 MHz): δ 7.87 (d, J = 8.0 Hz, 1 H), 7.82 (d, J = 8.0 Hz, 1 H), 7.70 (d, J = 8.0 Hz, 1 H), 7.53 – 7.46 (m, 2 H), 7.32 (d, J = 8.0 Hz, 1 H), 5.98 (s, 1 H), 4.19 (q, J = 8.0 Hz, 2 H), 3.55 (q, J = 8.0 Hz, 2 H), 3.37 (q, J = 8.0 Hz, 2 H), 2.53, (s, 3 H), 1.34 (t, J = 8.0 Hz, 3 H), 1.28 (t, J = 8.0 Hz, 3 H), 1.17 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.5, 153.9, 153.6, 143.2, 134.1, 133.1, 128.1, 127.8, 126.8, 126.6, 125.6, 125.4, 122.0, 120.3, 59.8, 42.4, 42.1, 19.9, 14.4, 14.2, 13.3.

HRMS (ESI): calc. for $[(C_{21}H_{25}NO_4)H]$ (M+H) 356.1862, measured 356.1860.

(E)-Ethyl 3-(3-((diethylcarbamoyl)oxy)naphthalen-2-yl)but-2-enoate (3k).



Dark yellow semisolid; eluent (12% ethyl acetate in hexanes).

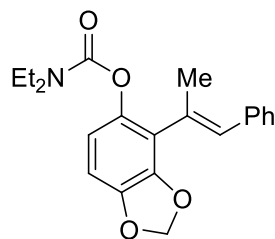
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2975, 1723, 1637, 1178 and 1054.

¹H NMR (CDCl₃, 400 MHz): δ 7.73 (d, J = 8.0 Hz, 1 H), 7.71 (d, J = 8.0 Hz, 1 H), 7.63 (s, 1 H), 7.52 (s, 1 H), 7.39 – 7.36 (m, 2 H), 5.92 (s, 1 H), 4.14 (q, J = 8.0 Hz, 2 H), 3.40 – 3.27 (m, 4 H), 2.48 (s, 3 H), 1.23 (t, J = 8.0 Hz, 3 H), 1.17 (t, J = 8.0 Hz, 3 H), 1.10 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.4, 154.0, 153.8, 145.9, 136.5, 133.3, 130.9, 127.7, 127.2, 126.7, 125.8, 120.1, 120.0, 59.7, 42.1, 41.8, 20.1, 14.2, 14.1, 13.2.

HRMS (ESI): calc. for $[(C_{21}H_{25}NO_4)H]$ (M+H) 356.1862, measured 356.1860.

(E)-4-(1-Phenylprop-1-en-2-yl)benzo[d][1,3]dioxol-5-yl diethylcarbamate (3l).



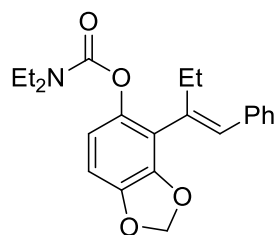
Colorless semisolid; eluent (12% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2928, 1638, 1469, 1318, 1273, 1160, 1103 and 1035.

¹H NMR (CDCl₃, 400 MHz): δ 7.33 – 7.32 (m, 4 H), 7.24 – 7.20 (m, 1 H), 6.70 (d, J = 8.0, Hz, 1 H), 6.60 (d, J = 8.0 Hz, 1 H), 6.54 (s, 1 H), 5.97 (s, 2 H), 3.31 – 3.30 (m, 4 H), 2.18 (s, 3 H), 1.12 – 1.07 (m, 6 H).

¹³C NMR (CDCl₃, 100 MHz): δ 154.5, 145.2, 144.7, 143.1, 137.4, 131.4, 129.4, 129.0, 128.1, 126.7, 122.1, 115.3, 106.3, 101.5, 42.1, 41.8, 18.1, 14.1, 13.3.

HRMS (ESI): calc. for $[(C_{21}H_{23}NO_4)H]$ (M+H) 354.1719, measured 354.1705.

(E)-4-(1-Phenylbut-1-en-2-yl)benzo[d][1,3]dioxol-5-yl diethylcarbamate (3m).

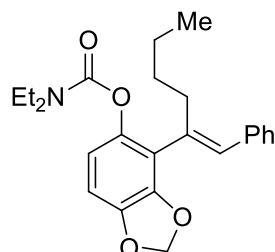
Pale yellow liquid; eluent (8% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2959, 1646, 1582, 1329, 1271, and 1175.

¹H NMR (CDCl₃, 400 MHz): δ 7.35 – 7.28 (m, 4 H), 7.22 (t, J = 8.0 Hz, 1 H), 6.72 (d, J = 8.0 Hz, 1 H), 6.70 (d, J = 8.0 Hz, 1 H), 6.52 (s, 1 H), 5.95 (s, 2 H), 3.37 – 3.29 (m, 4 H), 2.61 (q, J = 8.0 Hz, 2 H), 1.20 (q, J = 8.0 Hz, 3 H), 1.07 (q, J = 8.0 Hz, 3 H), 1.02 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 154.7, 145.6, 144.6, 143.8, 137.4, 135.6, 131.1, 128.8, 128.2, 126.8, 120.5, 115.8, 106.5, 101.5, 42.2, 41.8, 24.5, 14.2, 13.4, 13.1.

HRMS (ESI): calc. for [(C₂₂H₂₅NO₄)H] (M+H) 368.1862, measured 368.1863.

(E)-4-(1-Phenylhex-1-en-2-yl)benzo[d][1,3]dioxol-5-yl diethylcarbamate (3n).

Pale yellow liquid; eluent (8% ethyl acetate in hexanes).

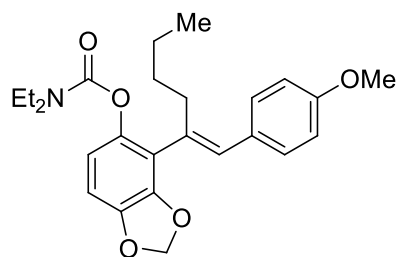
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2959, 1636 and 1229.

¹H NMR (CDCl₃, 400 MHz): δ 7.33 – 7.27 (m, 4 H), 7.21 (t, J = 8.0 Hz, 1 H), 6.71 (d, J = 8.0 Hz, 1 H), 6.62 (d, J = 8.0 Hz, 1 H), 6.53 (s, 1 H), 5.96 (s, 2 H), 3.38 – 3.30 (m, 4 H), 2.57 (t, J = 8.0 Hz, 2 H), 1.41 – 1.38 (m, 2 H), 1.31 – 1.25 (m, 2 H), 1.15 – 1.07 (m, 6 H), 0.83 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 154.7, 145.5, 144.6, 143.6, 137.5, 134.5, 131.5, 128.9, 128.2, 126.7, 120.8, 115.9, 106.5, 101.5, 42.2, 41.8, 31.1, 30.6, 22.8, 14.2, 13.9, 13.4.

HRMS (ESI): calc. for [(C₂₄H₂₉NO₄)H] (M+H) 396.2175, measured 396.2189.

(E)-4-(1-(4-Methoxyphenyl)hex-1-en-2-yl)benzo[d][1,3]dioxol-5-yl (3o).



Colorless semisolid; eluent (13% ethyl acetate in hexanes).

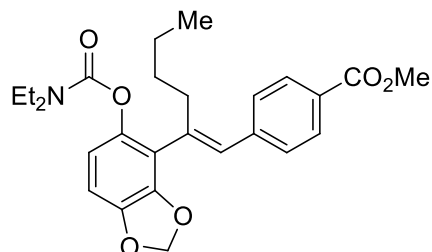
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2978, 1637, 1319, 1277, 1163 and 1107.

¹H NMR (CDCl₃, 400 MHz): δ 7.22 (d, J = 8.0 Hz, 2 H), 6.86 (d, J = 8.0 Hz, 2 H), 6.70 (d, J = 8.0, Hz, 1 H), 6.61 (d, J = 8.0, Hz, 1 H), 6.44 (s, 1 H), 5.95 (s, 2 H), 3.80 (s, 3 H), 3.32 – 3.28 (m, 4 H), 2.56 (t, J = 8.0 Hz, 2 H), 1.40 – 1.35 (m, 2 H), 1.31 – 1.28 (m, 2 H), 1.13 – 1.05 (m, 6 H), 0.83 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 158.3, 154.7, 145.4, 144.5, 143.6, 132.9, 130.9, 130.0, 121.0, 115.8, 113.6, 106.3, 101.4, 55.2, 42.1, 41.7, 31.0, 30.6, 22.8, 14.1, 13.9, 13.3.

HRMS (ESI): calc. for [(C₂₅H₃₁NO₅)H] (M+H) 426.2280, measured 426.2275.

(E)-Methyl 4-(2-(5-((diethylcarbamoyl)oxy)benzo[d][1,3]dioxol-4-yl)hex-1-en-1-yl)benzoate (3p).



Colorless semisolid; eluent (17% ethyl acetate in hexanes).

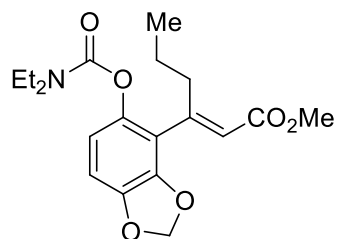
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2977, 1719, 1637, 1469, 1267, 1177 and 1068.

¹H NMR (CDCl₃, 400 MHz): δ 7.99 (d, J = 8.0 Hz, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 6.72 (d, J = 8.0 Hz, 1 H), 6.61 (d, J = 8.0 Hz, 1 H), 6.54 (s, 1 H), 5.96 (s, 2 H), 3.90 (s, 3 H), 3.32 – 3.28 (m, 4 H), 2.55 (t, J = 8.0 Hz, 2 H), 1.38 – 1.36 (m, 2 H), 1.30 – 1.26 (m, 2 H), 1.12 – 1.04 (m, 6 H), 0.81 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.0, 154.6, 145.4, 144.6, 143.4, 142.2, 136.7, 130.6, 129.5, 128.7, 128.2, 120.3, 115.8, 106.7, 101.5, 52.1, 42.1, 41.7, 31.2, 30.4, 22.7, 14.2, 13.9, 13.3.

HRMS (ESI): calc. for [(C₂₆H₃₁NO₆)H] (M+H) 454.2236, measured 454.2227.

(E)-Methyl 3-(5-((diethylcarbamoyl)oxy)benzo[d][1,3]dioxol-4-yl)hex-2-enoate (3q).



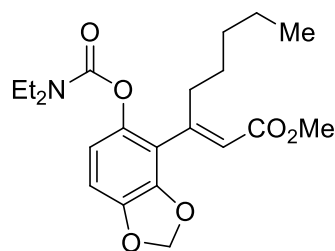
Colorless oil; eluent (12% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2967, 1631, 1639, 1279, 1177 and 1064.

¹H NMR (CDCl₃, 400 MHz): δ 6.70 (d, J = 8.0 Hz, 1 H), 6.57 (d, J = 8.0, Hz, 1 H), 5.94 (s, 2 H), 5.89 (s, 1 H), 3.68 (s, 3 H), 3.34 – 3.27 (m, 4 H), 2.90 (t, J = 8.0 Hz, 2 H), 1.43 – 1.37 (m, 2 H), 1.16 – 1.09 (m, 6 H), 0.88 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.4, 154.3, 153.0, 145.1, 144.7, 142.8, 121.1, 118.9, 115.9, 107.3, 101.7, 51.1, 42.2, 41.7, 34.0, 21.6, 14.19, 14.11, 13.2.

HRMS (ESI): calc. for [(C₁₉H₂₅NO₆)Na] (M+Na) 386.1580, measured 386.1593.

(E)-Methyl 3-(5-((diethylcarbamoyl)oxy)benzo[d][1,3]dioxol-4-yl)oct-2-enoate (3r).

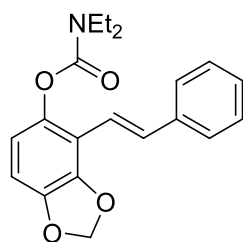
Colorless semisolid; eluent (15% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2975, 1640, 1631, 1455 and 1078.

¹H NMR (CDCl₃, 400 MHz): δ 6.68 (d, J = 8.0, 1 H), 6.55 (d, J = 8.0, 1 H), 5.90 (s, 2 H), 5.85 (s, 1 H), 3.65 (s, 3 H), 3.32 – 3.24 (m, 4 H), 2.90 (t, J = 8.0 Hz, 2 H), 1.37 – 1.33 (m, 2 H), 1.25 – 1.22 (m, 4 H), 1.13 – 1.07 (m, 6 H), 0.78 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.3, 154.2, 153.2, 145.0, 144.7, 142.7, 120.9, 118.9, 115.9, 107.3, 101.7, 51.0, 42.2, 41.7, 32.0, 31.8, 27.9, 22.4, 14.1, 14.0, 13.2.

HRMS (ESI): calc. for [(C₂₁H₂₉NO₆)H] (M+H) 392.2073, measured 392.2094.

(E)-4-Styrylbenzo[d][1,3]dioxol-5-yl diethylcarbamate (3s).

Pale yellow oil; eluent (10% ethyl acetate in hexanes).

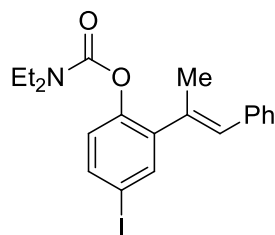
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2976, 1718, 1457, 1316, 1271, 1158 and 1065.

¹H NMR (CDCl₃, 400 MHz): δ 7.45 (d, J = 16.0 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 2 H), 7.33 (t, J = 8.0 Hz, 2 H), 7.24 (t, J = 8.0 Hz, 1 H), 6.95 (d, J = 16.0 Hz, 1 H), 6.68 (d, J = 8.0 Hz, 1 H), 6.58 (d, J = 8.0 Hz, 1 H), 6.07 (s, 2 H), 3.51 (q, J = 8.0 Hz, 2 H), 3.39 (q, J = 8.0 Hz, 2 H), 1.31 (t, J = 8.0 Hz, 3 H), 1.20 (t, J = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 154.5, 145.6, 145.1, 143.6, 137.9, 133.9, 128.7, 127.9, 126.6, 118.1, 115.3, 115.1, 106.6, 101.8, 42.4, 41.9, 14.6, 13.5.

HRMS (ESI): calc. for [(C₂₀H₂₁NO₄)Na] (M+Na) 362.1368, measured 362.1370.

(E)-4-Iodo-2-(1-phenylprop-1-en-2-yl)phenyl diethylcarbamate (3t).



Colorless semisolid; eluent (10% ethyl acetate in hexanes).

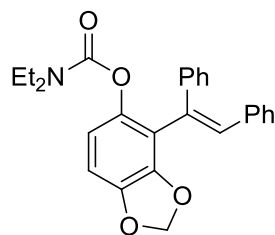
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2978, 1635, 1325, 1167 and 1049.

¹H NMR (CDCl₃, 400 MHz): δ 7.63 (s, 1 H), 7.54 (dd, J = 8.0, 4.0 Hz, 1 H), 7.36 – 7.30 (m, 4 H), 7.23 (t, J = 8.0, Hz, 1 H), 6.88 (d, J = 8.0, Hz, 1 H), 6.46 (s, 1 H), 3.36 – 3.30 (m, 4 H), 2.15 (s, 3 H), 1.14 – 1.10 (m, 6 H).

¹³C NMR (CDCl₃, 100 MHz): δ 153.8, 148.5, 141.1, 138.1, 137.5, 136.8, 133.9, 130.7, 128.9, 128.3, 126.8, 125.3, 89.4, 42.3, 41.9, 19.2, 14.2, 13.4.

HRMS (ESI): calc. for [(C₂₀H₂₂INO₂)H] (M+H) 436.0773, measured 436.0779.

(E)-4-(1,2-Diphenylvinyl)benzo[d][1,3]dioxol-5-yl diethylcarbamate (3u).



Pale yellow liquid; eluent (8% ethyl acetate in hexanes).

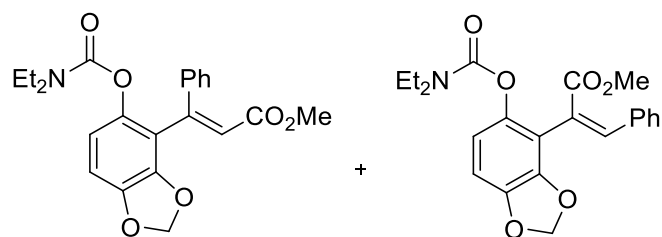
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2979, 1639, 1572 and 1227.

¹H NMR (CDCl₃, 400 MHz): δ 7.25 – 7.23 (m, 2 H), 7.19 – 7.17 (m, 3 H), 7.11 – 7.07 (m, 5 H), 6.80 (s, 1 H), 6.70 (d, J = 8.0 Hz, 1 H), 6.58 (d, J = 8.0 Hz, 1 H), 5.87 (s, 2 H), 3.17 (q, J = 8.0 Hz, 2 H), 2.98 (q, J = 8.0 Hz, 2 H), 0.99 – 0.94 (m, 6 H).

¹³C NMR (CDCl₃, 100 MHz): δ 154.3, 148.2, 146.4, 144.9, 143.9, 139.3, 136.9, 132.8, 132.6, 129.7, 129.6, 128.1, 127.9, 127.3, 127.0, 115.6, 106.9, 101.6, 41.9, 41.5, 13.9, 13.2.

HRMS (ESI): calc. for [(C₂₆H₂₅NO₄)H] (M+H) 416.1862, measured 416.1859.

Mixtures of 3v and 3v'.



Pale yellow liquid; eluent (16% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 7.29 – 7.25 (m, 5 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.54 (d, J = 8.0 Hz, 1 H), 6.22 (s, 1 H), 5.89 (s, 2 H), 3.60 (s, 3 H), 3.19 (q, J = 8.0 Hz, 2 H), 2.96 (q, J = 8.0 Hz, 2 H), 1.06 – 0.99 (m, 6 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.3, 153.9, 146.8, 146.6, 145.0, 143.4, 137.7, 128.8, 128.7, 127.6, 122.0, 118.8, 115.8, 108.3, 101.8, 51.3, 41.9, 41.4, 13.9, 13.2.

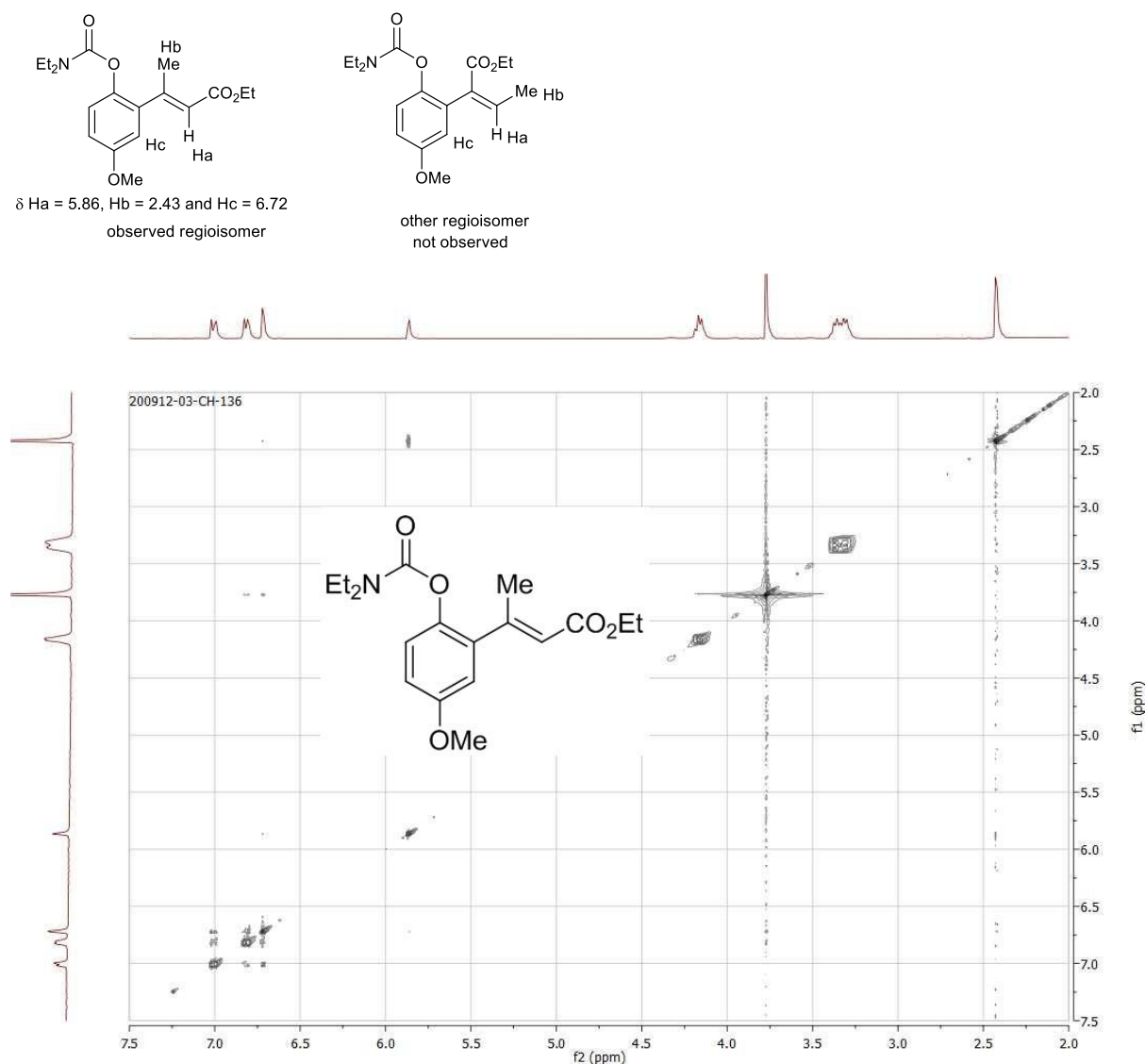
^1H NMR (CDCl_3 , 400 MHz): δ 7.36 – 7.28 (m, 5 H), 7.14 (s, 1 H), 6.74 (d, J = 8.0, Hz, 1 H), 6.59 (d, J = 8.0, Hz, 1 H), 5.97 (s, 2 H), 3.65 (s, 3 H), 3.28 (q, J = 8.0 Hz, 4 H), 1.13 – 1.05 (m, 6 H).

HRMS (ESI): calc. for $[(\text{C}_{22}\text{H}_{23}\text{NO}_6)\text{H}]$ ($\text{M}+\text{H}$) 398.1604, measured 398.1601.

2B.11: Regioselective Studies: NOESY Experiments

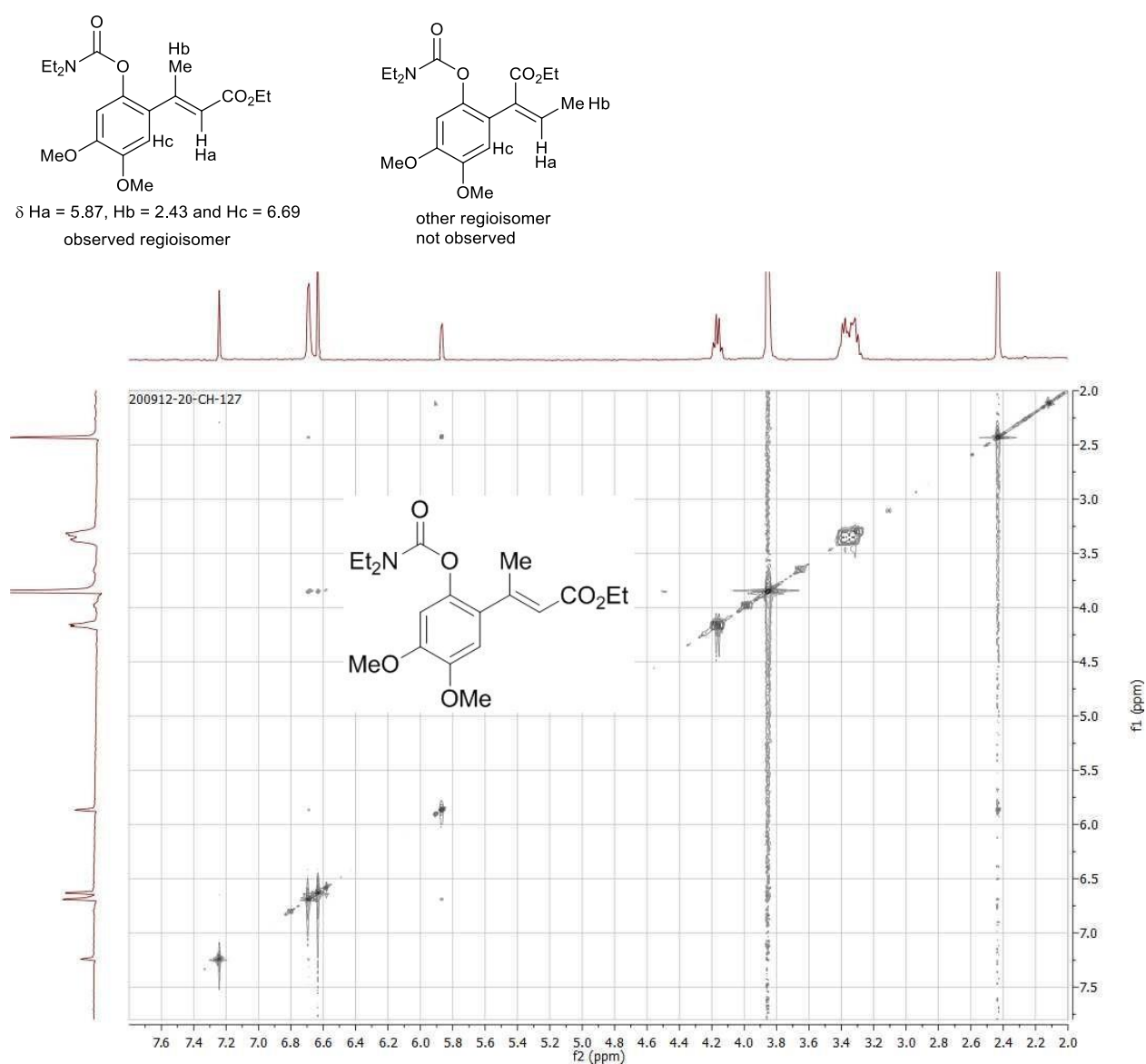
Regioselective studies of compound **3a**.

The regiochemistry of hydroarylation product **3a** was confirmed by ^1H NMR spectroscopy. Alkene Ha (δ 5.86, s) was observed as a singlet. Alkene Me (δ 2.43, s) was also observed as a singlet. Further, the regiochemistry of **3a** was confirmed by NOESY experiment. There is a NOE signal between protons Ha and Hb. There is a strong NOE signal between Hb and Hc protons. If the other regioisomer is formed, there should not be signal between Hb and Hc. Also, there is no NOE signal between ester CH_2 with Hc protons. There is a very weak NOE signal between Ha and Hc. It is clearly indicated that alkene H (Ha) and carbamate are *cis* to each other. These results clearly revealed that the regiochemistry of compound **3a** is correct.



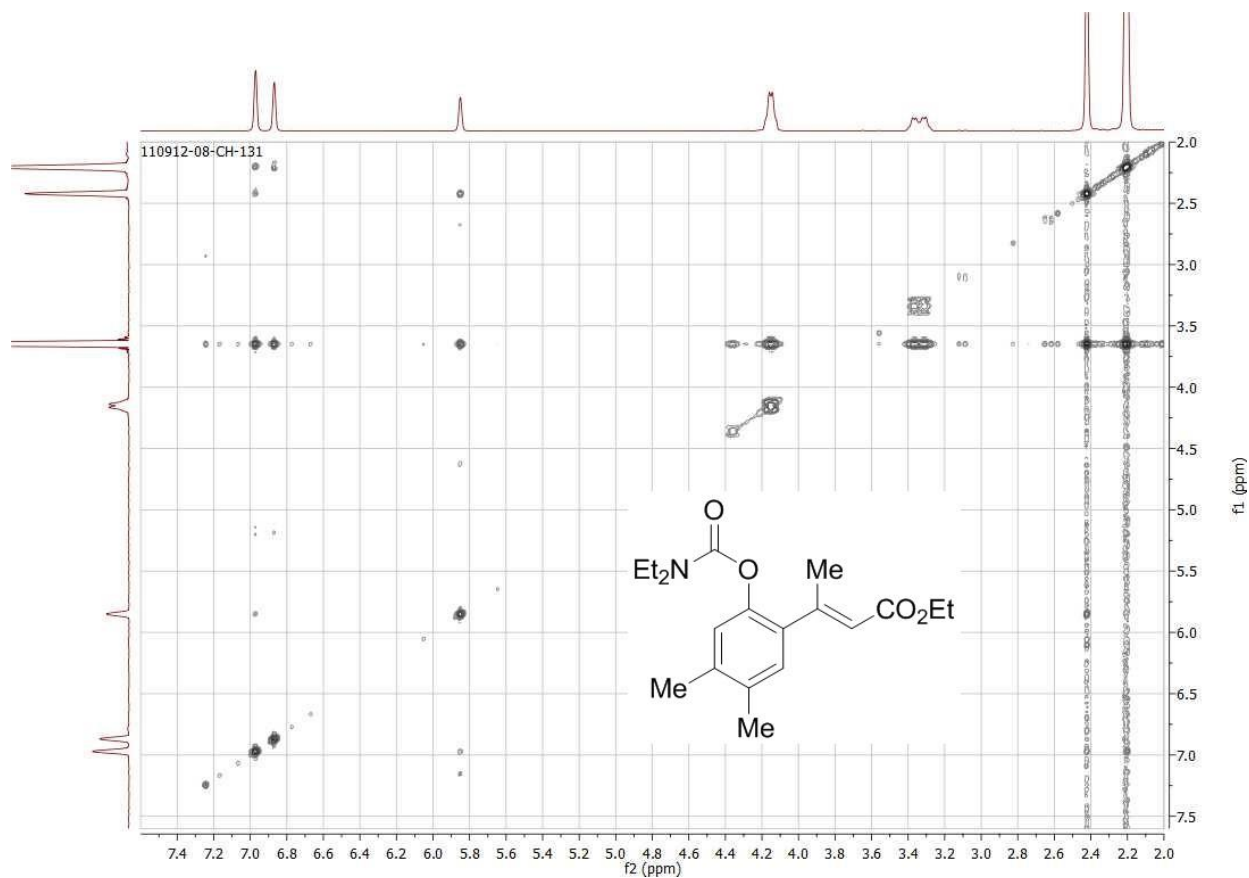
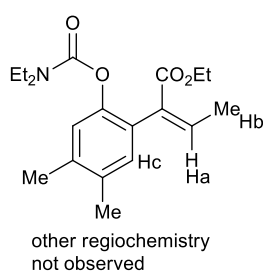
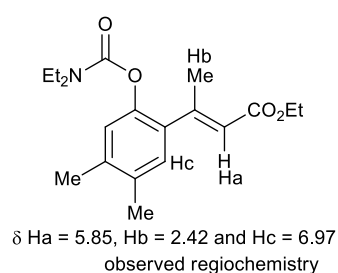
Regioselective studies of compound 3c.

The regiochemistry of hydroarylation product **3c** was confirmed by ^1H NMR spectroscopy. Alkene Ha (δ 5.87, s) was observed as a singlet. Alkene Me (δ 2.43, s) was also observed as a singlet. Further, the regiochemistry of **3c** was confirmed by NOESY experiment. There is a NOE signal between protons Ha and Hb. There is a strong NOE signal between Hb and Hc (δ 6.69, s) protons. If the other regioisomer is formed, there should not be signal between Hb and Hc. Also, there is no NOE signal between ester CH_2 with Hc protons. There is a very weak NOE signal between Ha and Hc. It is clearly indicated that alkene H (Ha) and aromatic carbamate are *cis* to each other. These results clearly revealed that the regiochemistry of compound **3c** is correct.



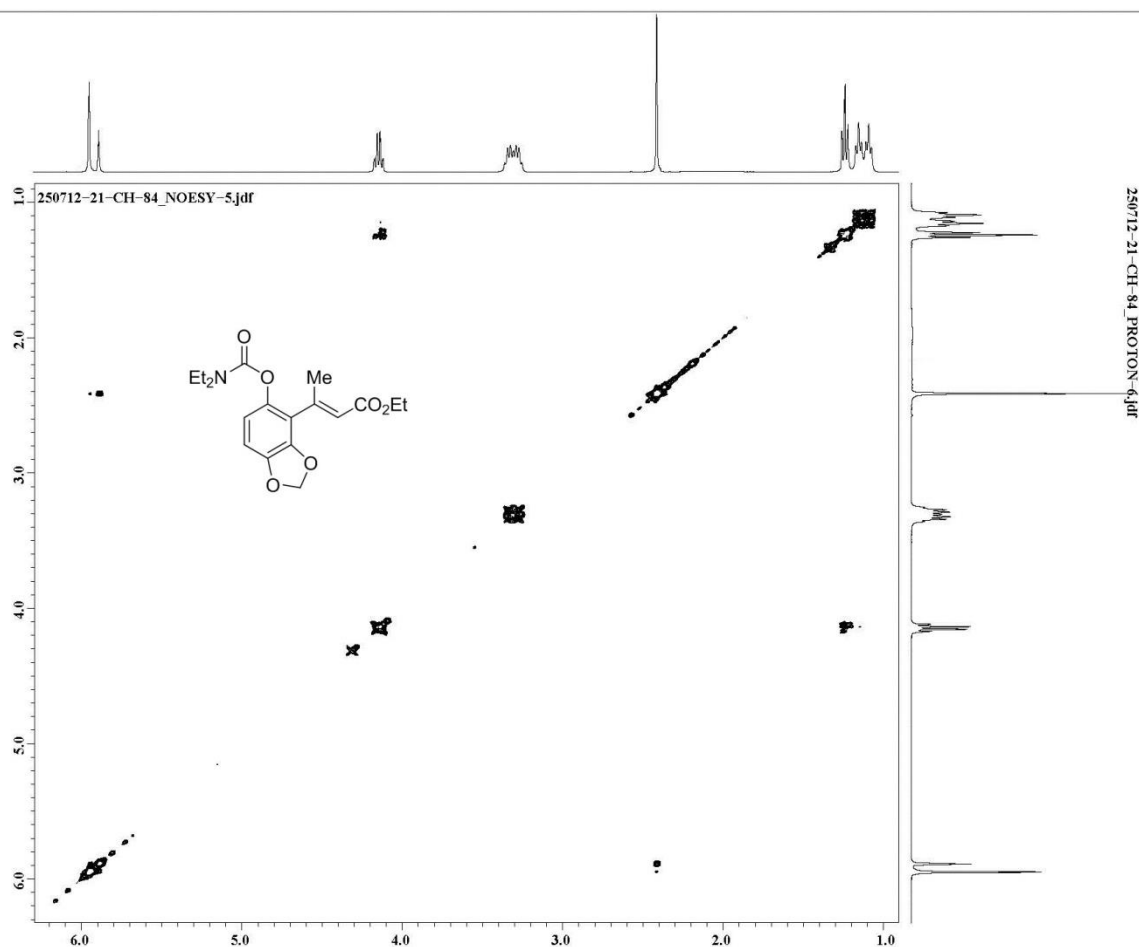
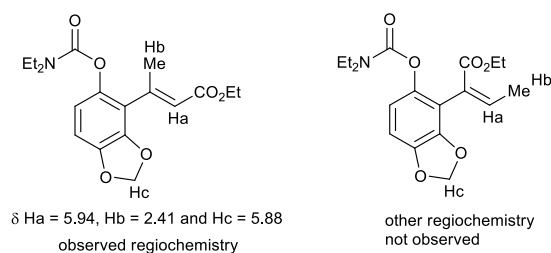
Regioselective studies of compound **3d**.

The regiochemistry of hydroarylation product **3d** was confirmed by ^1H NMR spectroscopy. Alkene Ha (δ 5.85, s) was observed as a singlet. Alkene Me (δ 2.42, s) was also observed as a singlet. Further, the regiochemistry of **3d** was confirmed by NOESY experiment. There is a NOE signal between protons Ha and Hb. There is a strong NOE signal between Hb and Hc (δ 6.97, s) protons. If the other regioisomer is formed, there should not be signal between Hb and Hc. Also, there is no NOE signal between ester CH_2 with Hc protons. There is a very weak NOE signal between Ha and Hc. It is clearly indicated that alkene H (Ha) and aromatic carbamate are *cis* to each other. These results clearly revealed that the regiochemistry of compound **3d** is correct.



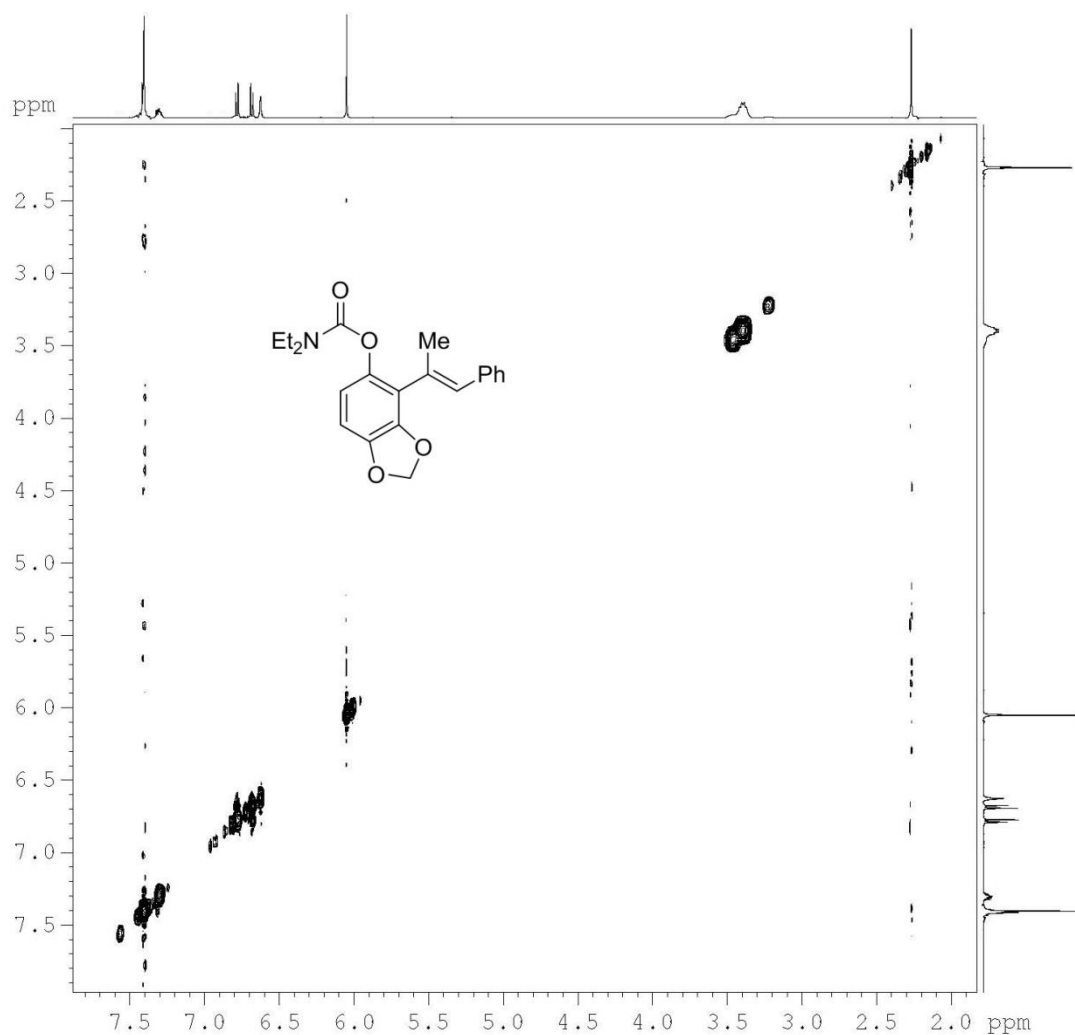
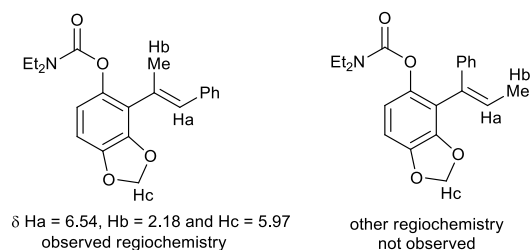
Regioselective studies of compound **3e**.

The regiochemistry of hydroarylation product **3e** was confirmed by ^1H NMR spectroscopy. Alkene Ha (δ 5.94, s) was observed as a singlet. Alkene Me (δ 2.41, s) was also observed as a singlet. Further, the regiochemistry of **3e** was confirmed by NOESY experiment. There is a NOE signal between protons Ha and Hb. There is also a NOE signal between Hb and Hc (δ 5.85, s) protons. If the other regioisomer is formed, there should not be signal between Hb and Hc. Also, there is no NOE signal between ester CH_2 with Hc protons. These results clearly revealed that the regiochemistry of compound **3e** is correct.



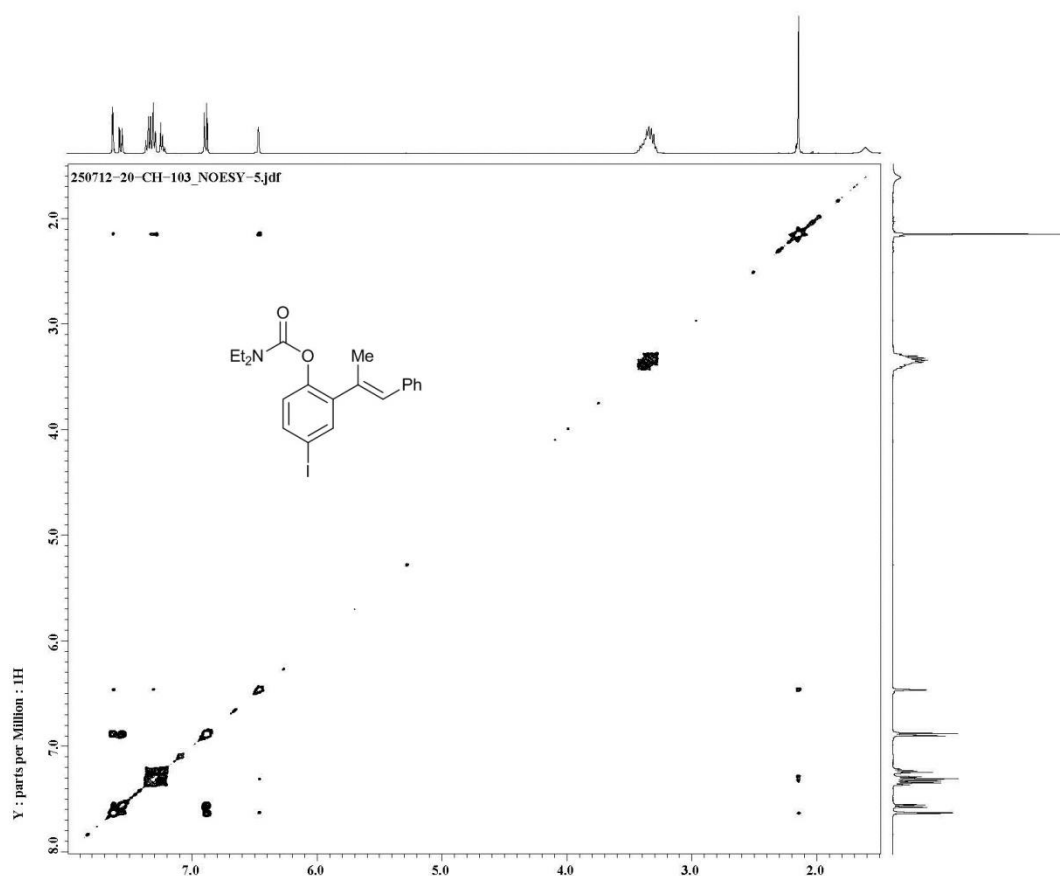
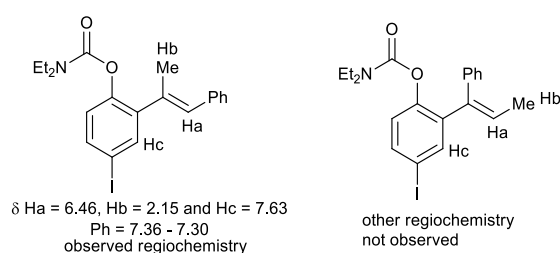
Regioselective studies of compound **3I**.

The regiochemistry of hydroarylation product **3I** was confirmed by ^1H NMR spectroscopy. Alkene Ha (δ 6.54, s) was observed as a singlet. Alkene Me (δ 2.18, s) was also observed as a singlet. Further, the regiochemistry of **3I** was confirmed by NOESY experiment. There is a NOE signal between Hb and Hc (δ 5.97, s) protons. If the other regioisomer is formed, there should not be signal between Hb and Hc. These results clearly revealed that the regiochemistry of compound **3I** is correct.



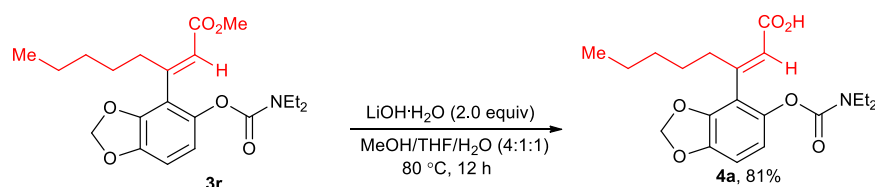
Regioselective studies of compound **3t**.

The regiochemistry of hydroarylation product **3t** was confirmed by ^1H NMR spectroscopy. Alkene Ha (δ 6.46, s) was observed as a singlet. Alkene Me (δ 2.15, s) was also observed as a singlet. Further, the regiochemistry of **3t** was confirmed by NOESY experiment. There is a NOE signal between Ha and Hb protons. There is a strong NOE signal between Hb and Hc (δ 7.63, s) protons. If the other regioisomer is formed, there should not be signal between Hb and Hc. Also, there is no NOE signal between Hc and Ph group of **3t** (δ 7.36 – 7.30). There is a weak NOE signal between Ha and Hc protons. It is clearly indicated that alkene H (Ha) and aromatic carbamate are *cis* to each other. These results clearly revealed that the regiochemistry of compound **3t** is correct.



2B.12. Regioselective studies (X-ray analysis)

The regiochemistry of coupling product **3** was further confirmed by X-ray studies. The coupling products **3** are in liquid form. In order to take X-ray diffraction, the derivative of the corresponding coupling product was used. The ester group of product **3r** was converted into the corresponding carboxylic acid derivative **4a** in the presence of LiOH base. The structure of **4a** was confirmed by single crystal X-ray diffraction.



View

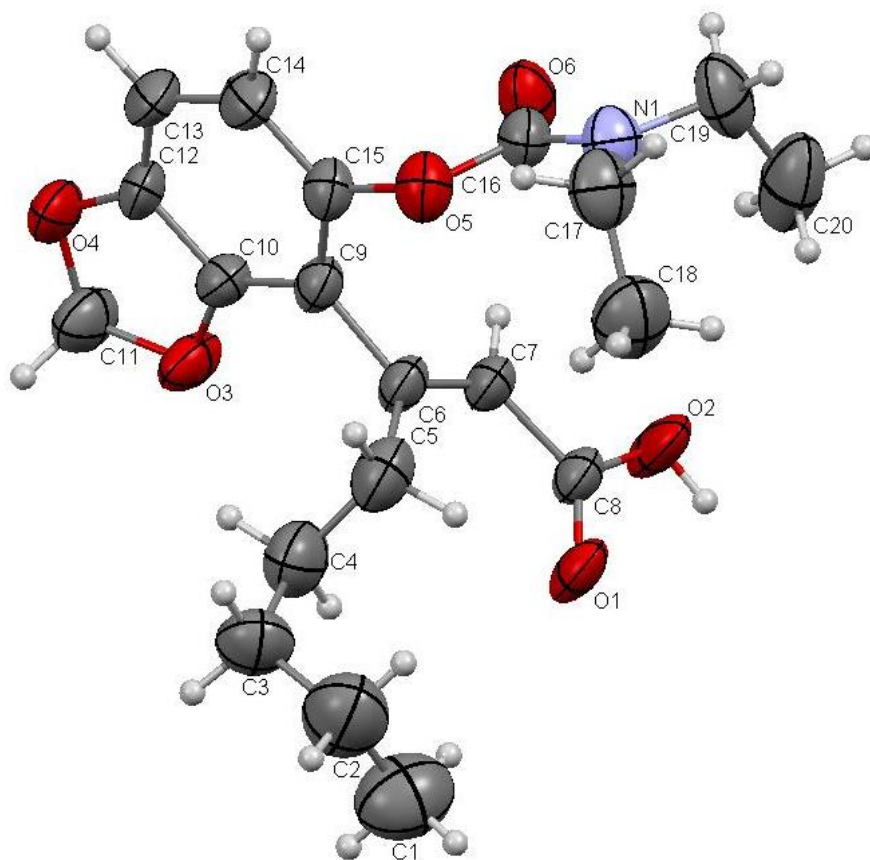
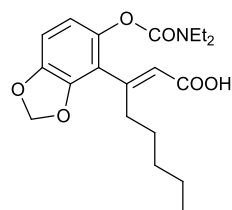


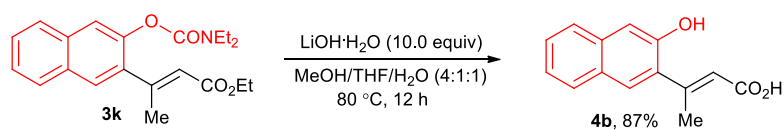
Table 1. Crystal data and structure refinement for **4a**.

Identification code

4a

Empirical formula	C ₂₀ H ₂₇ N O ₆	
Formula weight	377.43	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 12.065(2) Å	α = 92.523(4)°.
	b = 12.172(2) Å	β = 99.861(5)°.
	c = 13.880(3) Å	γ = 95.377(4)°.
Volume	1995.7(6) Å ³	
Z	4	
Density (calculated)	1.286 Mg/m ³	
Absorption coefficient	0.094 mm ⁻¹	
F(000)	820	
Crystal size	0.43 x 0.25 x 0.09 mm ³	
Theta range for data collection	1.49 to 25.00°.	
Index ranges	-14 ≤ h ≤ 14, -14 ≤ k ≤ 14, -16 ≤ l ≤ 15	
Reflections collected	28845	
Independent reflections	7050 [R(int) = 0.0478]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.992 and 0.972	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7050 / 67 / 495	
Goodness-of-fit on F ²	1.828	
Final R indices [I > 2σ(I)]	R1 = 0.0956, wR2 = 0.2683	
R indices (all data)	R1 = 0.1416, wR2 = 0.2977	
Largest diff. peak and hole	0.912 and -0.601 e.Å ⁻³	

Whereas, 10.0 equiv of LiOH cleaved both ester and carbamate moieties of compound **3k**, giving phenol derivative **4b** in 87% yield. The structure of phenol derivative **4b** was confirmed by single crystal x-ray diffraction.



View

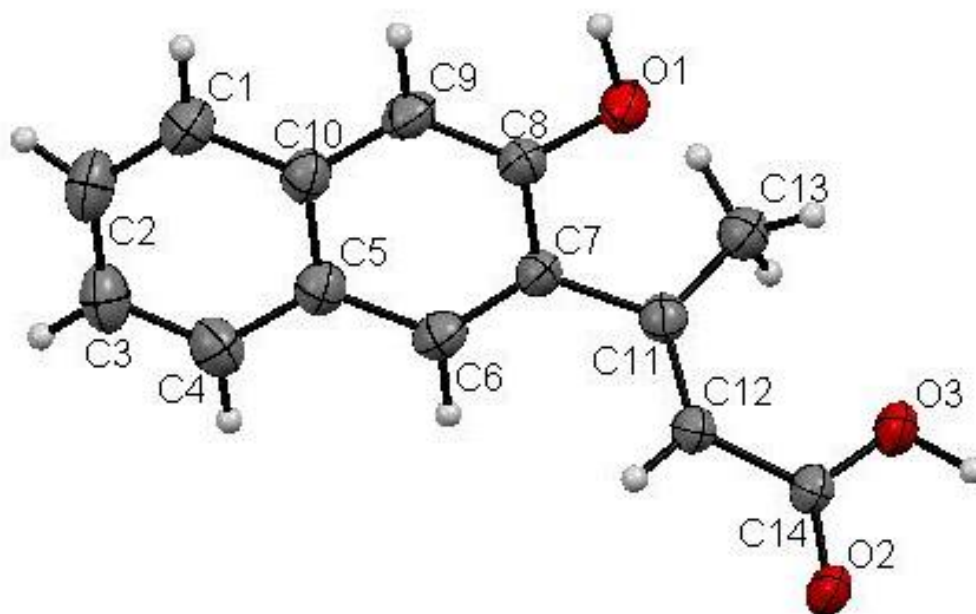
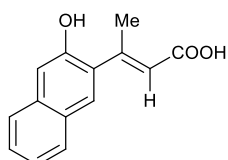


Table 1. Crystal data and structure refinement for **4b**.

Identification code	4b	
Empirical formula	C ₁₄ H ₁₂ O ₃	
Formula weight	228.24	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 23.015(7) Å	α = 90°.
	b = 5.8478(19) Å	β = 112.391(6)°.
	c = 17.370(6) Å	γ = 90°.
Volume	2161.6(12) Å ³	

Z	8
Density (calculated)	1.403 Mg/m ³
Absorption coefficient	0.098 mm ⁻¹
F(000)	960
Crystal size	0.13 x 0.08 x 0.02 mm ³
Theta range for data collection	1.91 to 28.35°.
Index ranges	-15<=h<=30, -7<=k<=7, -23<=l<=21
Reflections collected	18133
Independent reflections	2703 [R(int) = 0.1097]
Completeness to theta = 28.35°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9980 and 0.9873
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2703 / 0 / 202
Goodness-of-fit on F ²	0.869
Final R indices [I>2sigma(I)]	R1 = 0.0564, wR2 = 0.1305
R indices (all data)	R1 = 0.1649, wR2 = 0.1865
Largest diff. peak and hole	0.219 and -0.215 e.Å ⁻³

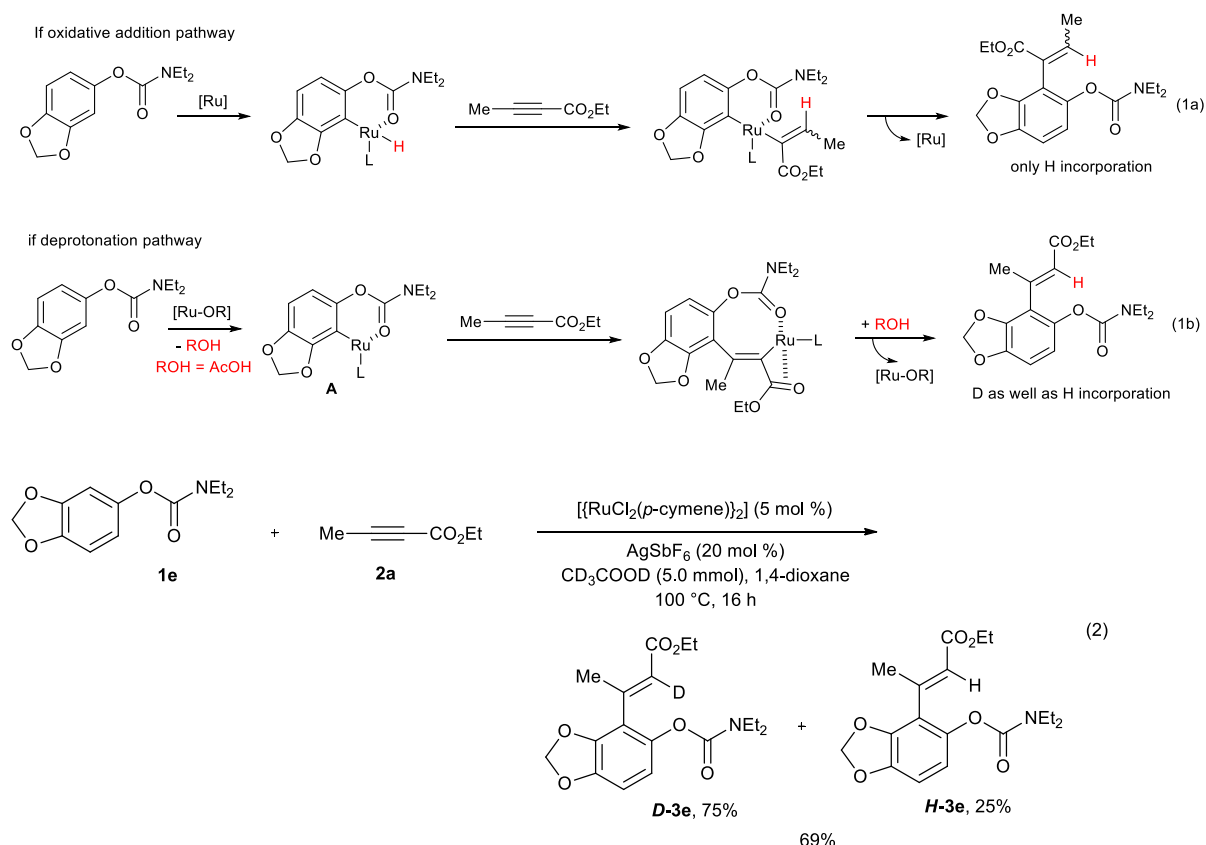
General procedure for the preparation of compounds **4a-b**.

A two-neck 50 mL round bottom flask fitted with a condenser and a septum containing a mixture of **3r** (100 mg) and LiOH·H₂O (2.0 equiv) in 6 mL of MeOH/THF/H₂O (4:1:1). The reaction mixture was refluxed at 80 °C for 12 h. After the reaction, reaction mixture was allowed to cool to room temperature and the reaction mixture was neutralized (pH = 6) using 1N HCl. The product was extracted with ethyl acetate, washed with water and brine. The extract was dried with anhydrous Na₂SO₄. The solvents were evaporated under reduced pressure to give pure **4a** as a colorless solid (purification is not necessary).

A similar procedure was used for the preparation of compounds **4b**. However, 10.0 equiv of LiOH·H₂O was used for the reaction.

Mechanistic investigation

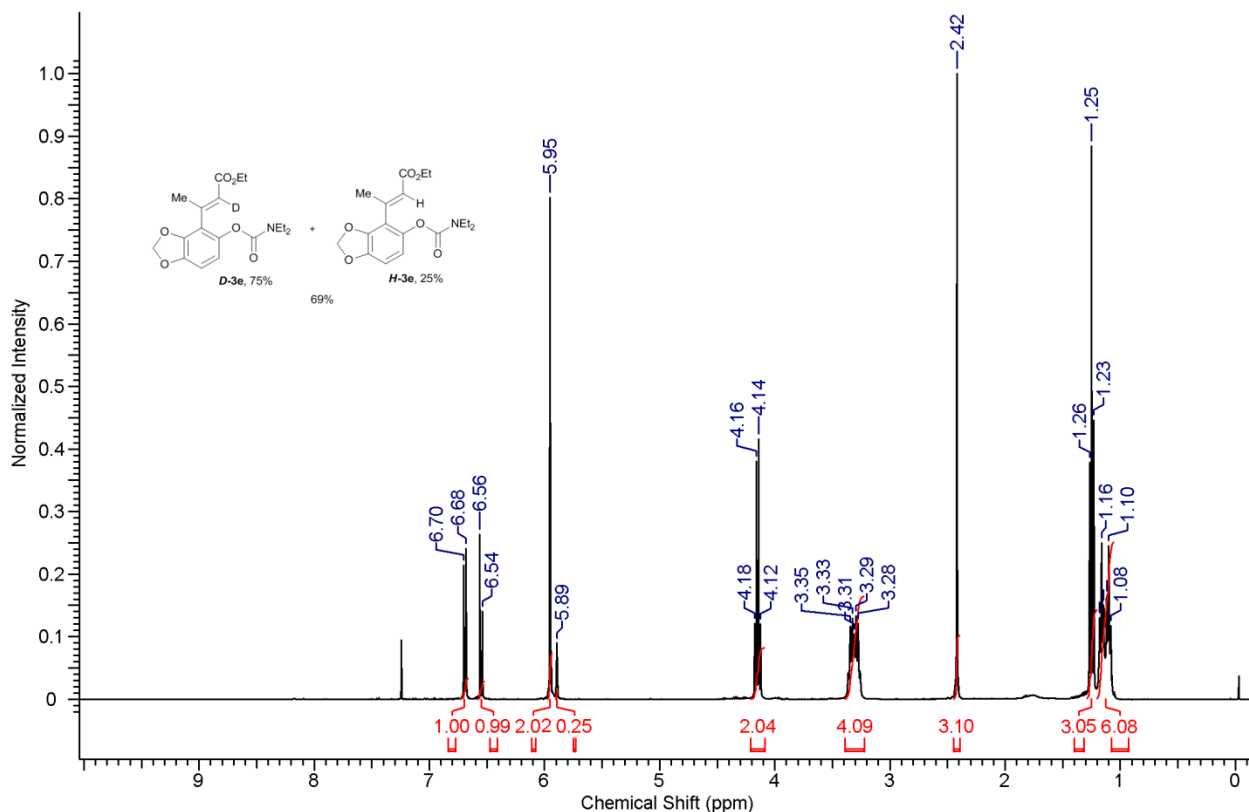
In the present reaction, a six-membered metallacycle **A** is a key intermediate (eq. 1b). The reaction proceeds through an assisted deprotonation by the ruthenium complex (eq. 1b) instead of an oxidative addition on the C-H ortho to the carbamate (eq. 1a). In order to prove the mechanism proceeds via an assisted deprotonation (eq. 2), the following mechanistic studies were done.



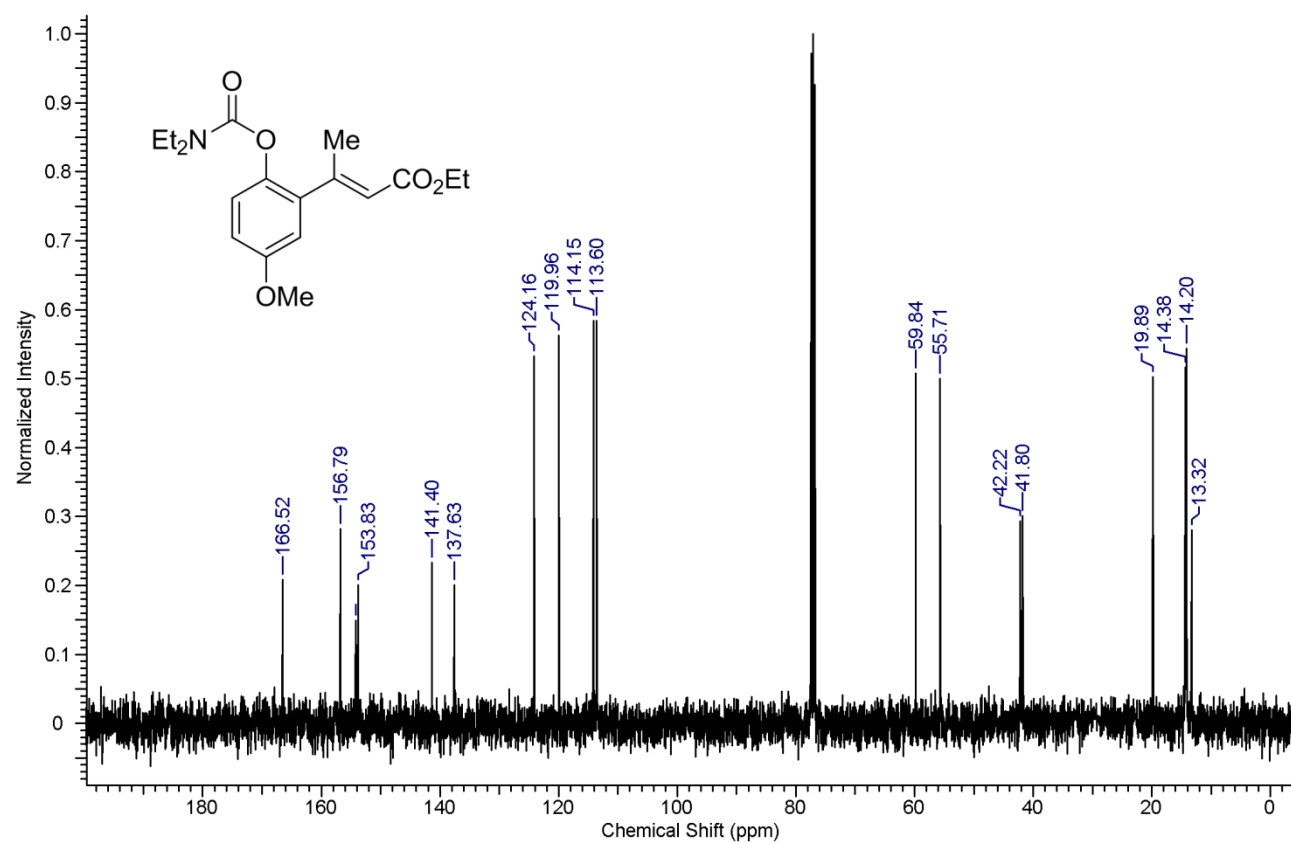
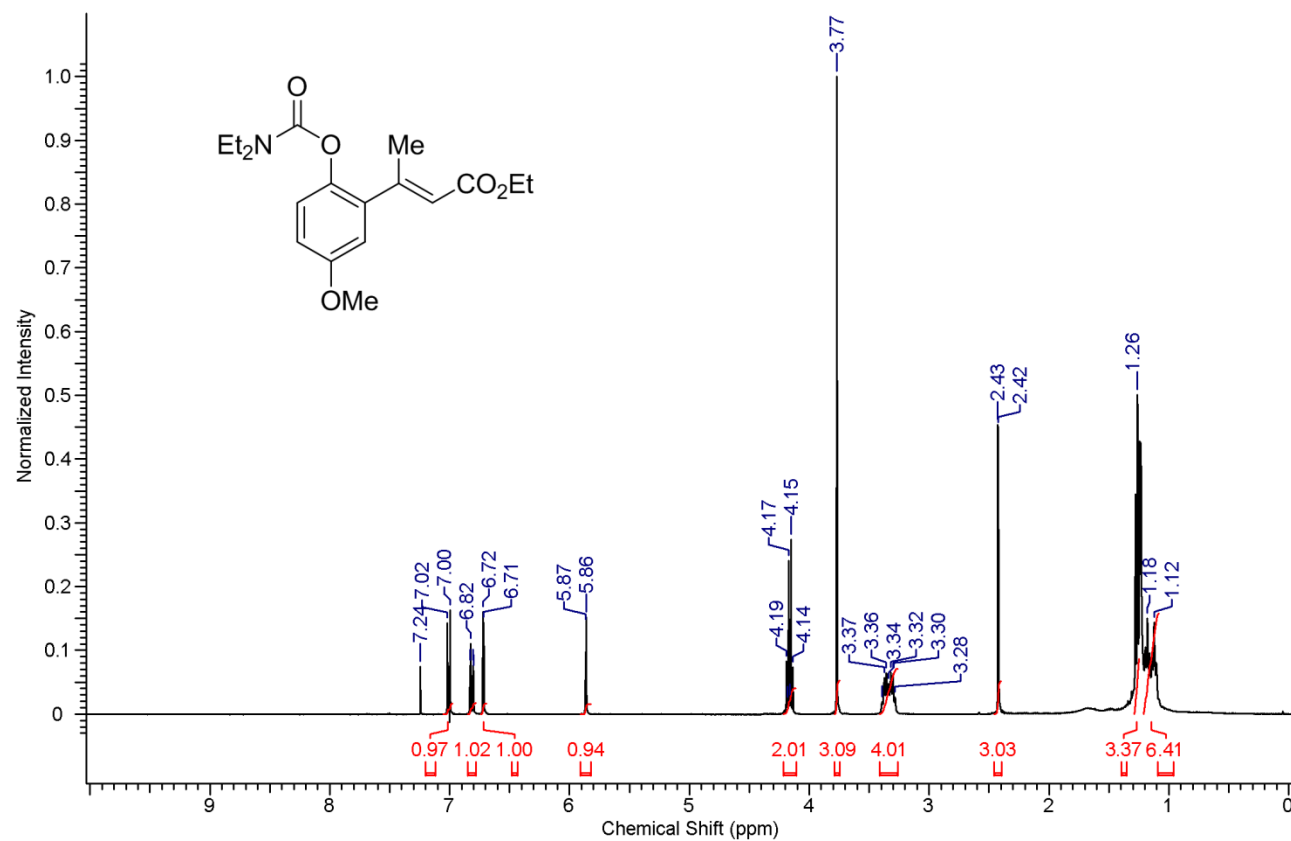
The coupling reaction of sesamol carbamate **1e** with ethyl but-2-ynoate (**2a**) in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (5 mol %), AgSbF_6 (20 mol %) and CD_3COOD (5.0 equiv) in 1,4-dioxane at 100 °C for 16 h was examined. In the reaction, instead of pivalic acid, CD_3COOD (5.0 equiv) was used. If the reaction proceeds via oxidative addition pathway (eq. 1a), in the coupling product, no deuterium incorporation would be observed in an alkene C-H bond. If the reaction proceeds via an assisted deprotonation pathway (eq. 1b), in the coupling product, deuterium incorporation should be observed in an alkene C-H bond. In the coupling product, 75% of deuterium incorporation was observed in an alkene C-H bond. In the reaction, CD_3COOH is a side product. It is well known that CD_3COOH is more reactive than CD_3COOD . Although the concentration of CD_3COOD is more in the reaction as compare to CD_3COOH , due to the less reactivity of CD_3COOD , 25% of hydrogen incorporation was found in the product. This deuterium study clearly

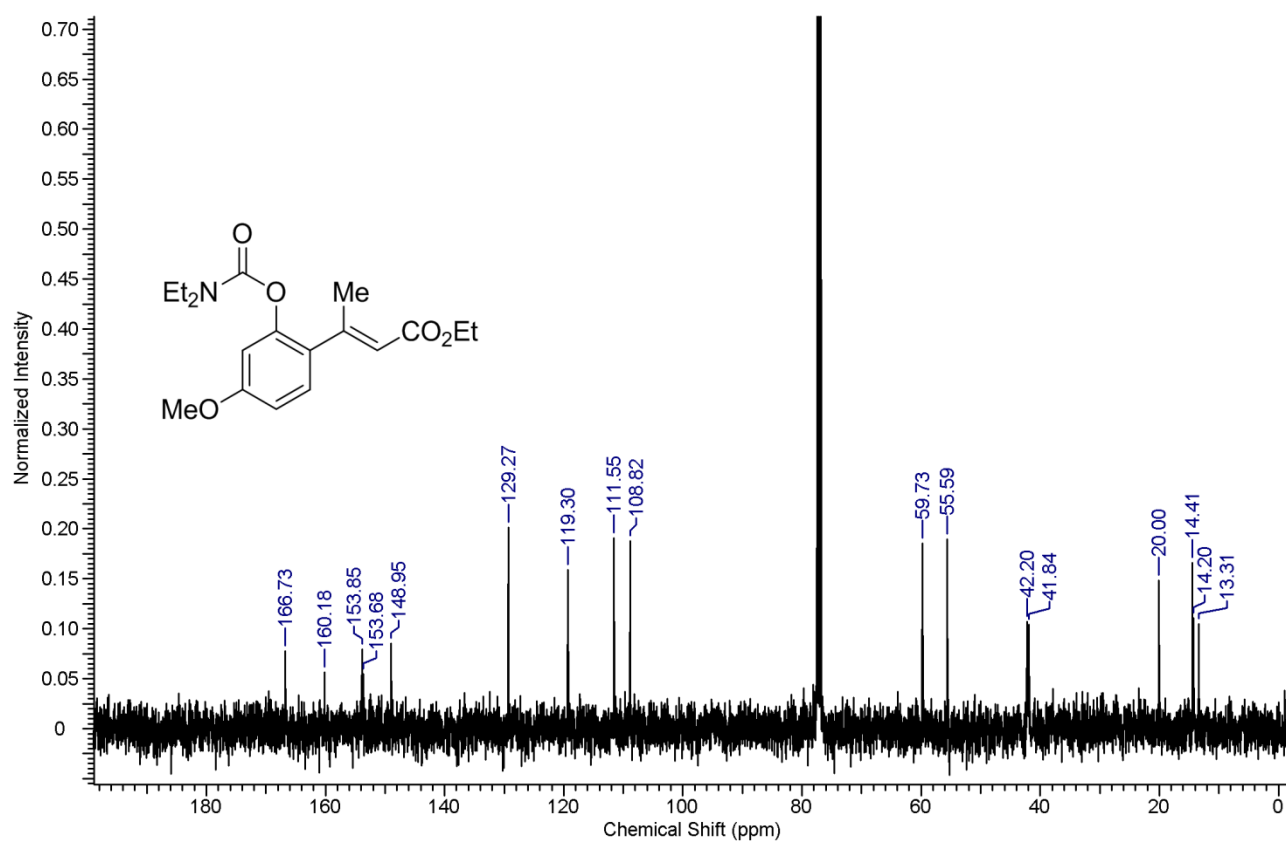
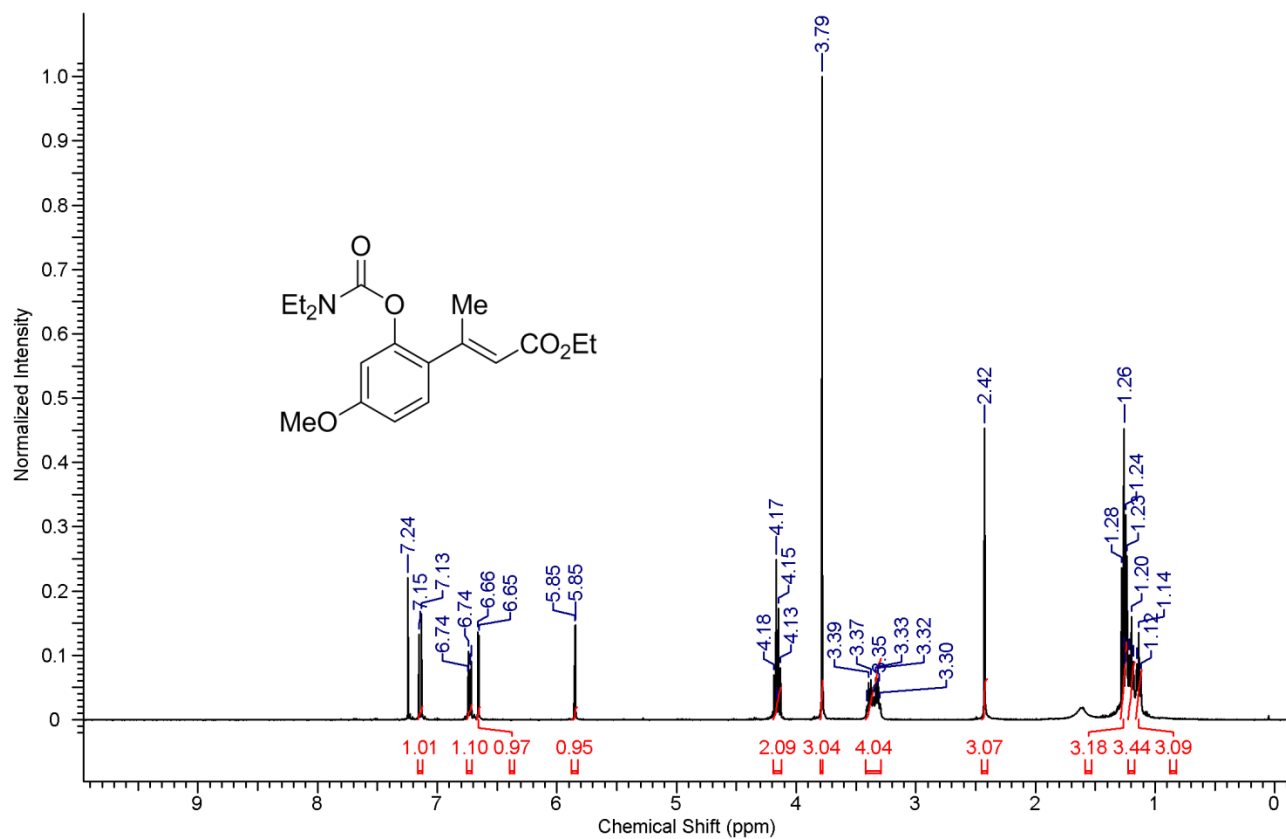
revealed that the present reaction proceeds via an assisted deprotonation pathway. In addition, if the reaction proceeds via oxidative addition pathway, a different type of regioisomeric product as explained in eq. 1a should be observed. However, in the reaction such regioisomeric product was not observed (see regioselective studies (X-ray analysis)).

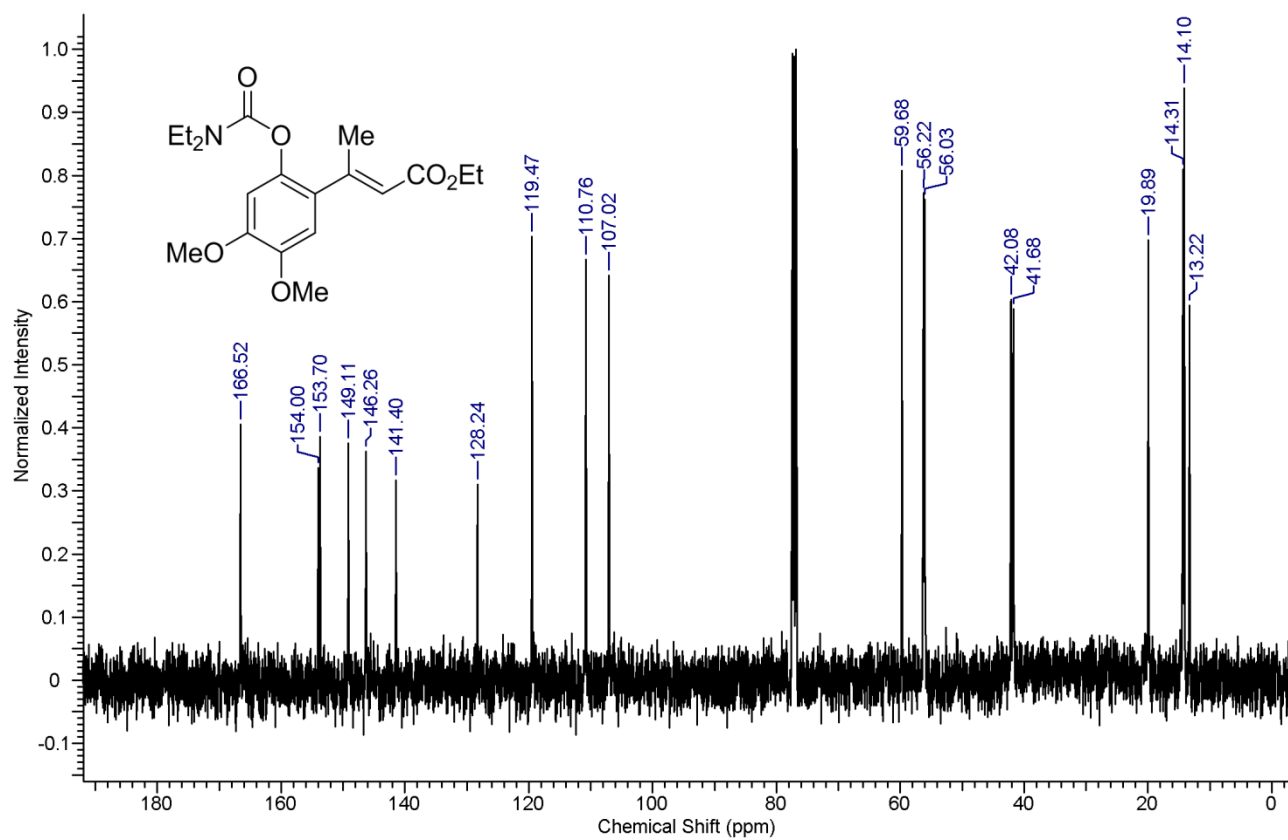
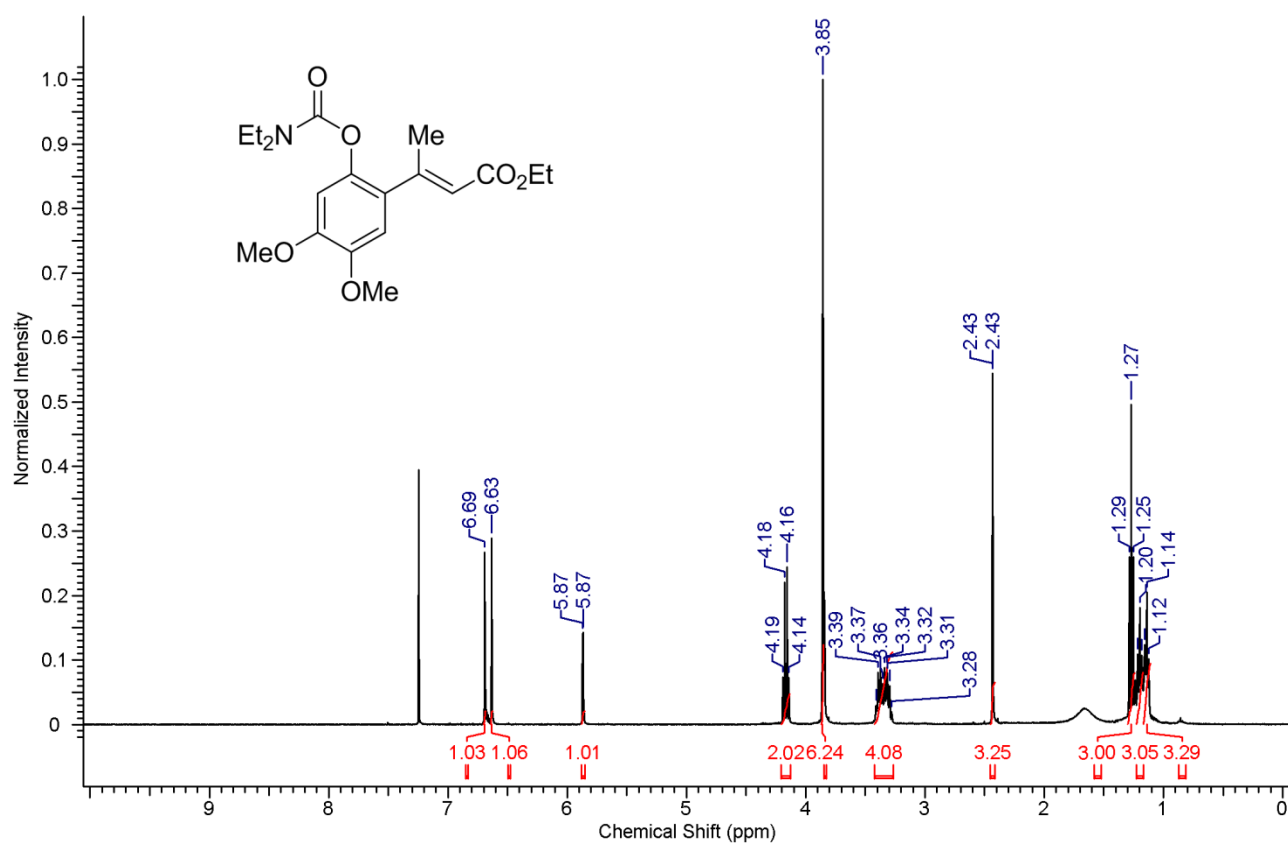
^1H and ^{13}C NMR Spectra of Compound **3e**.

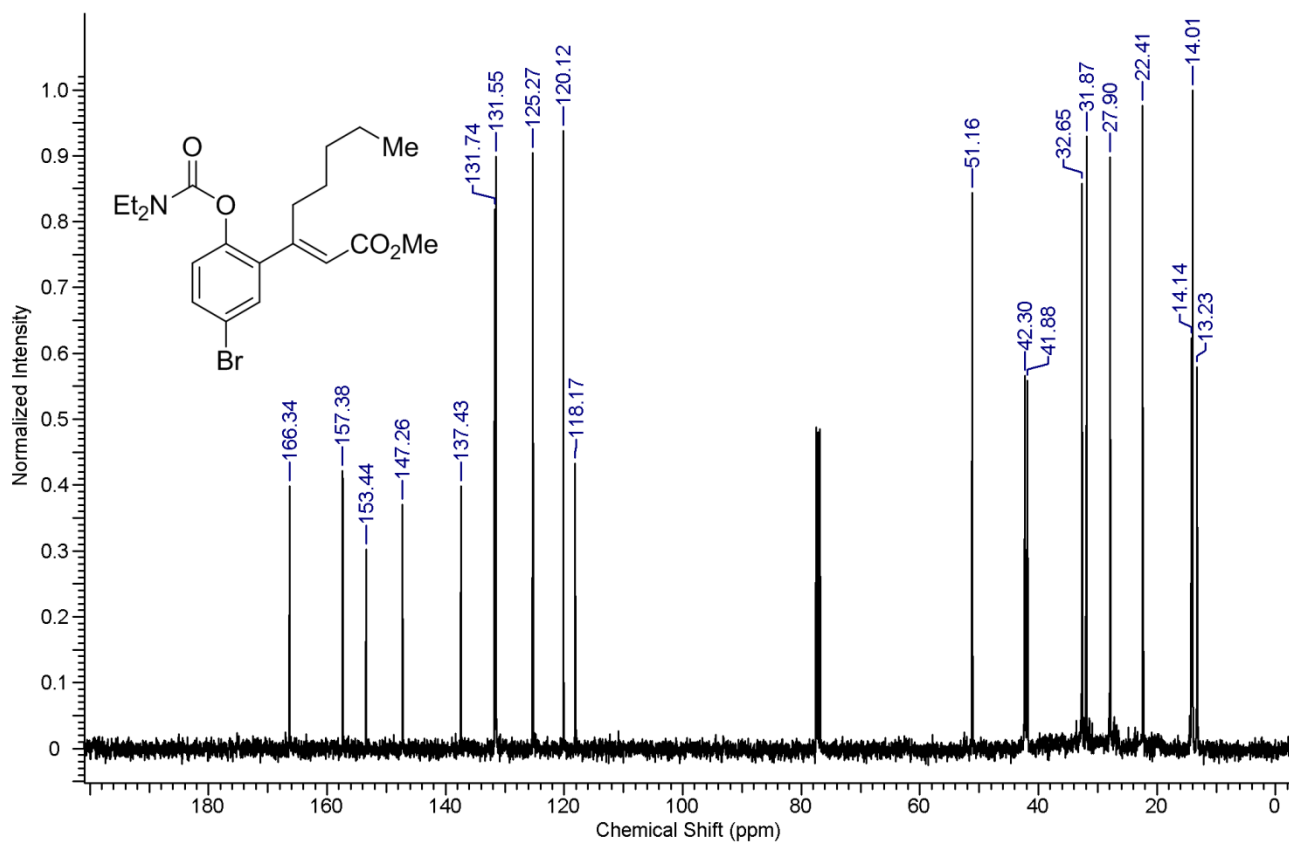
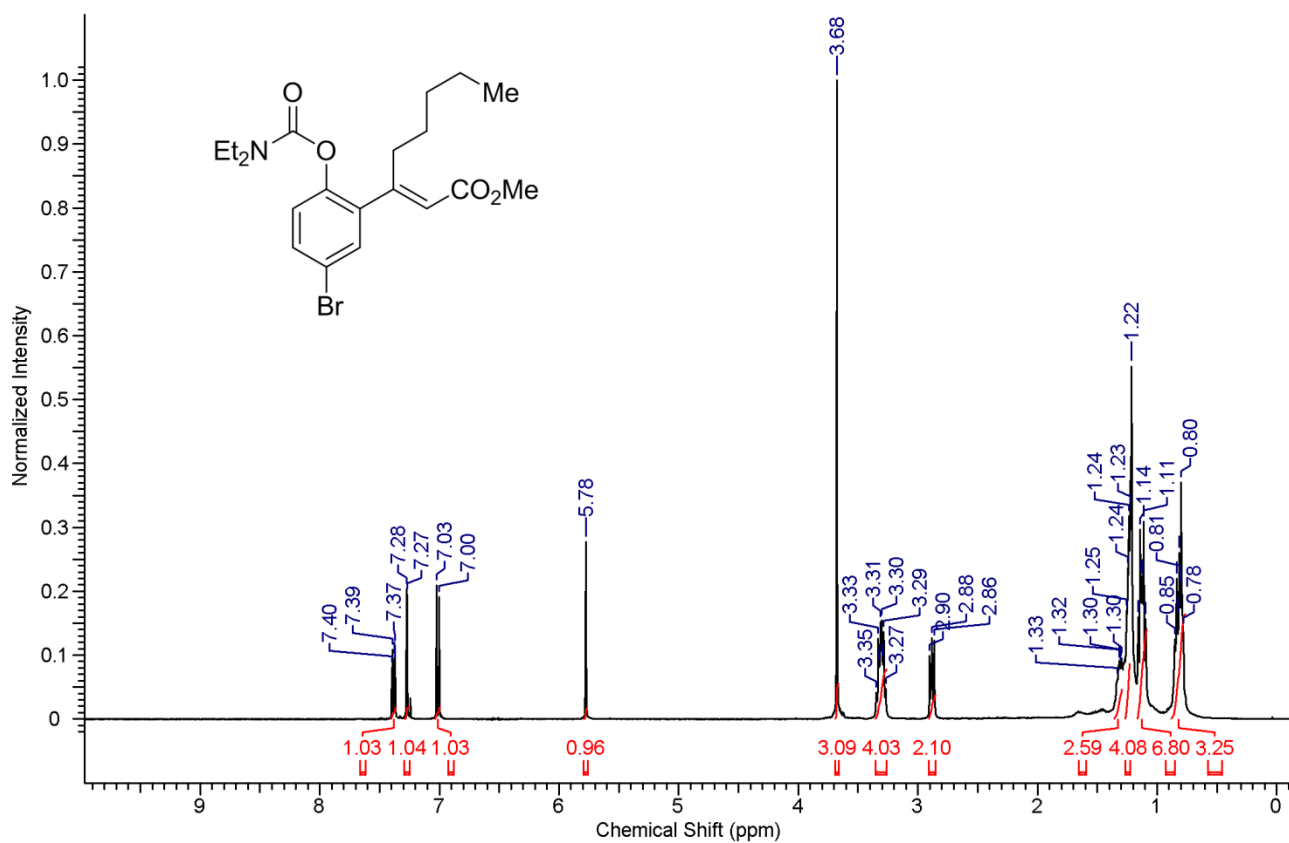


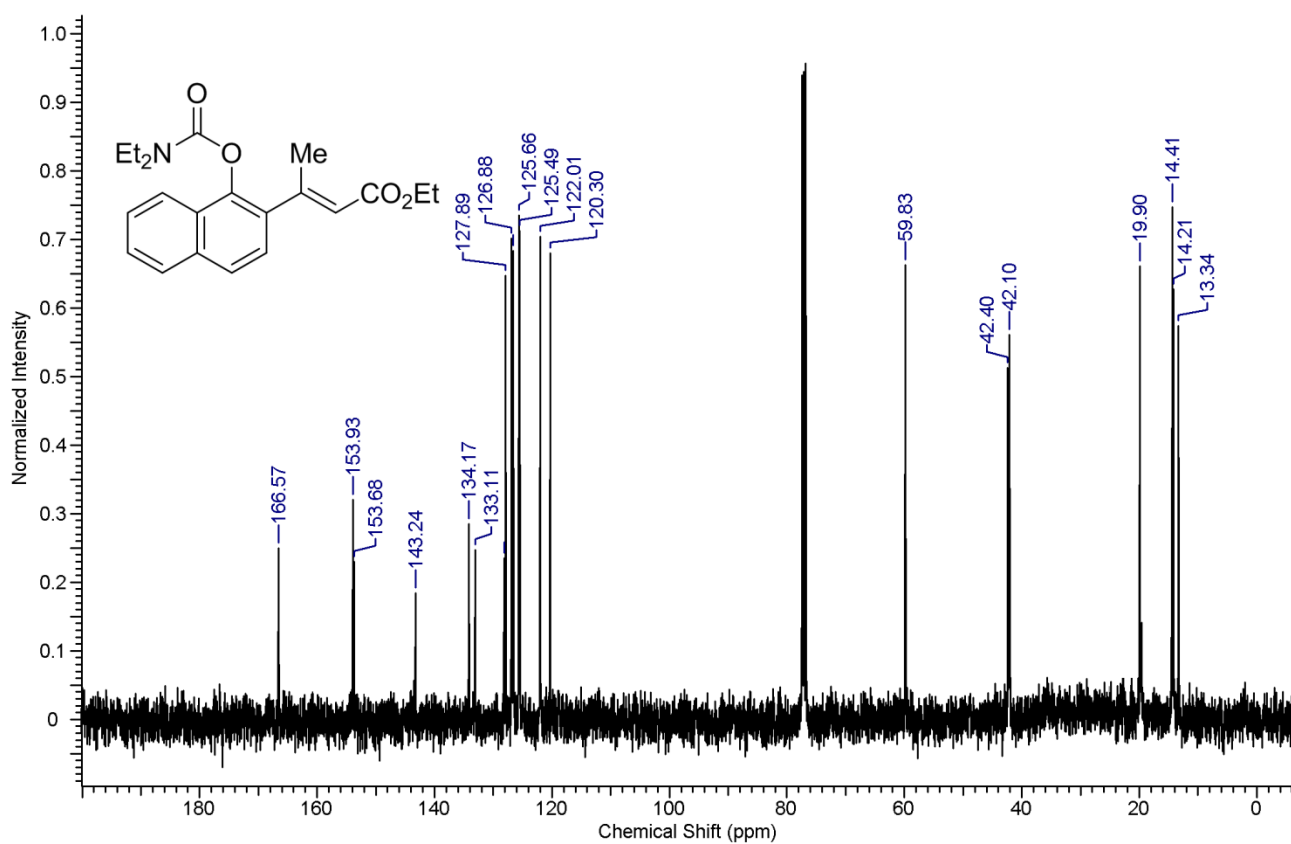
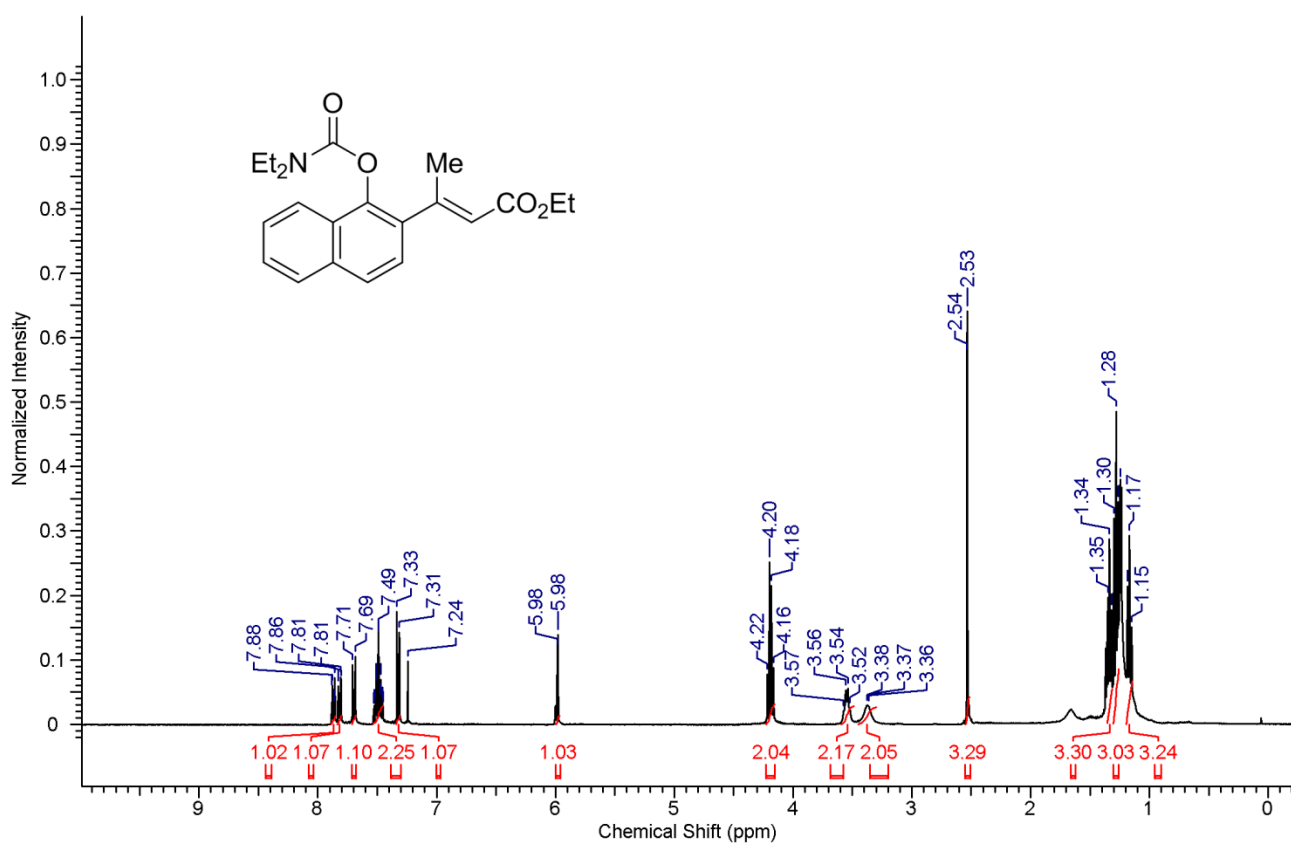
2B.13: Spectral Copies of Selected Compounds

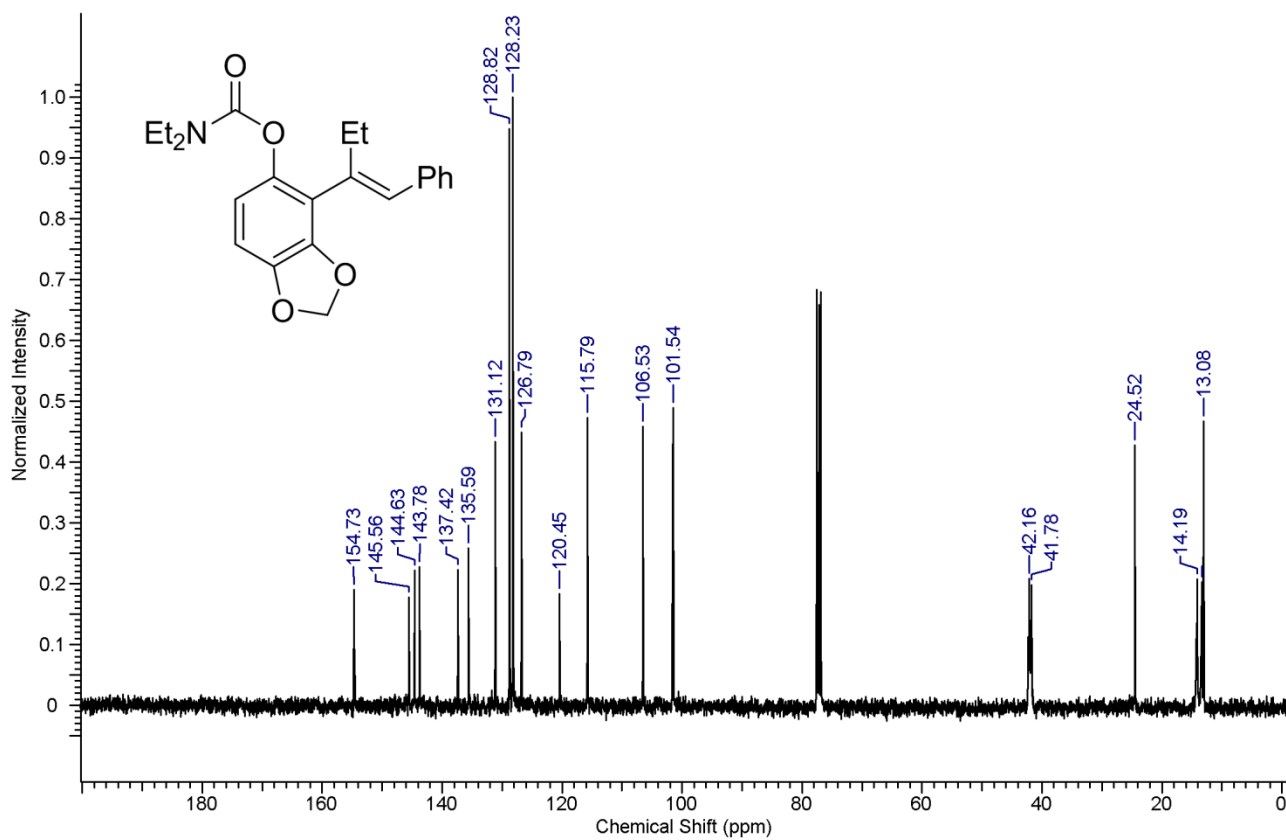
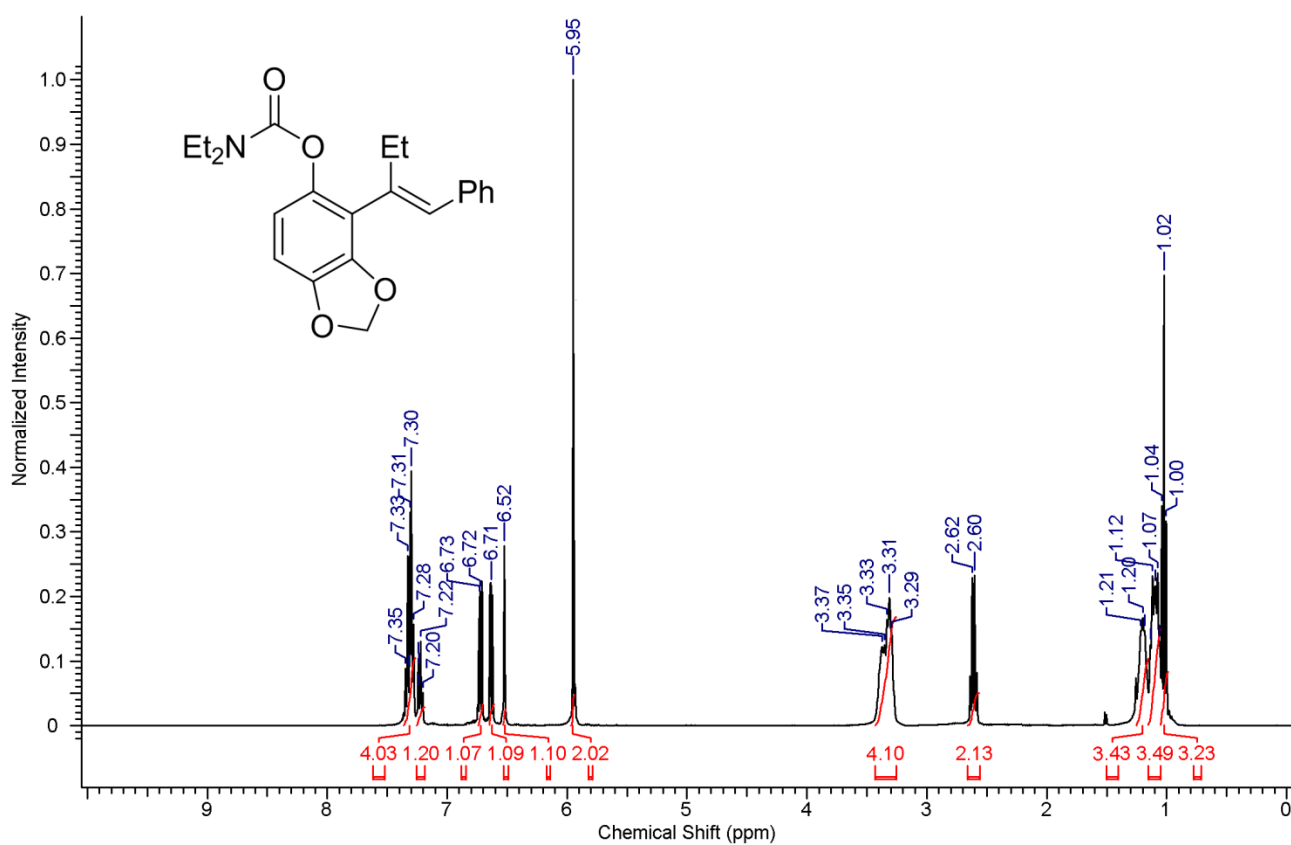
 ^1H and ^{13}C NMR Spectra of Compound 3a.

^1H and ^{13}C NMR Spectra of Compound **3b**.

^1H and ^{13}C NMR Spectra of Compound **3c**.

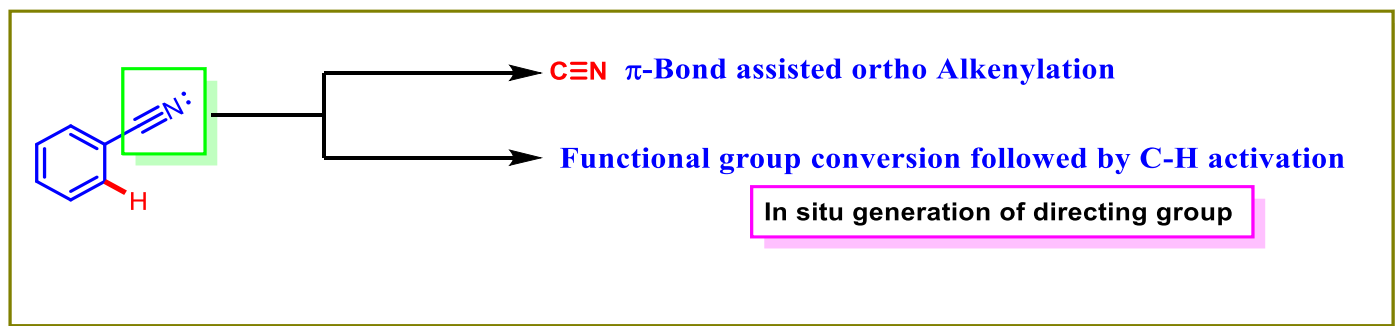
^1H and ^{13}C NMR Spectra of Compound **3g**.

^1H and ^{13}C NMR Spectra of Compound **3j**.

^1H and ^{13}C NMR Spectra of Compound **3m**.

Chapter 3

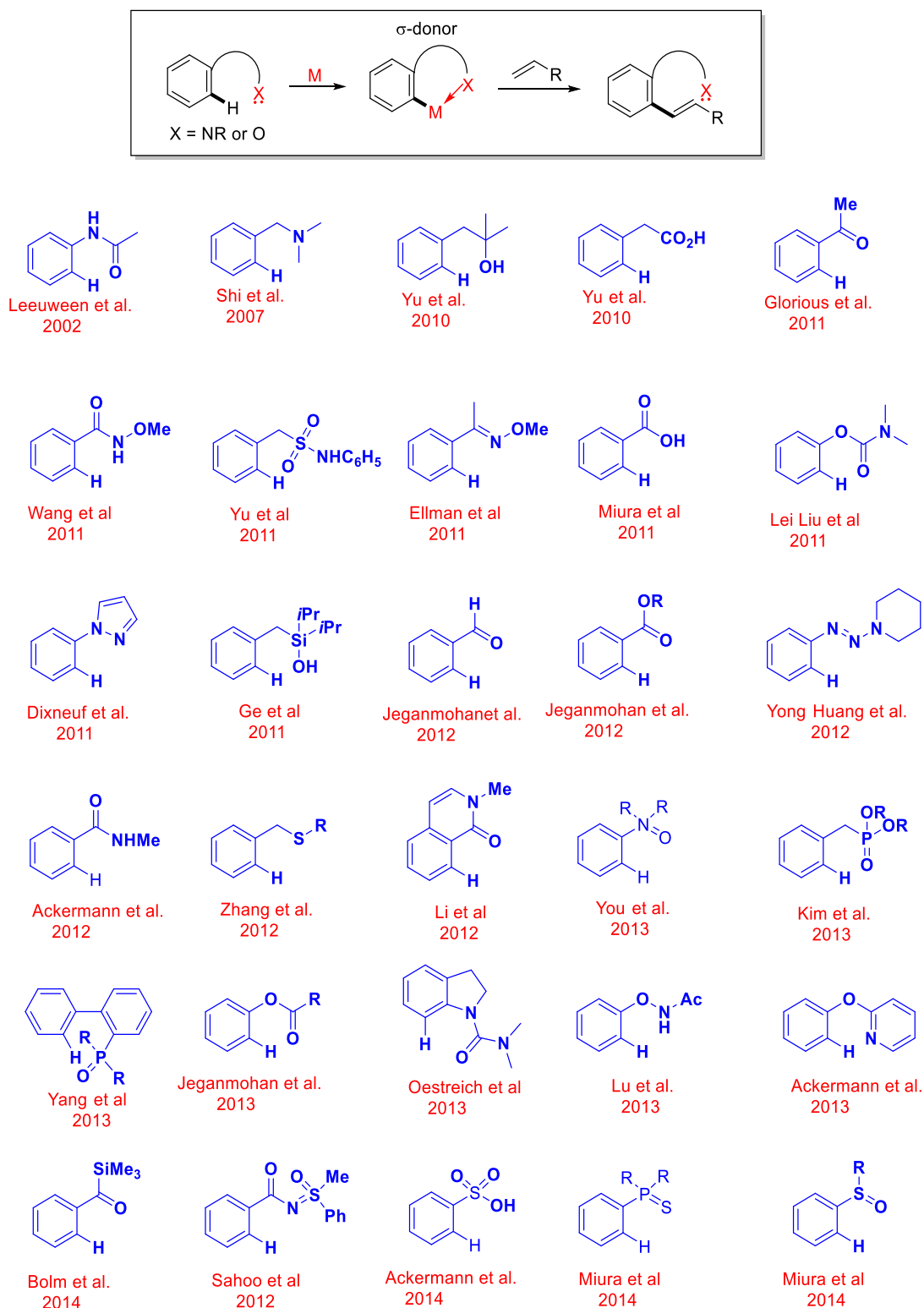
Different Orientations of Nitrile Functional group in Ru-Catalyzed C-H Bond Activation.



Section 3A: Ruthenium-Catalyzed C $\equiv$ N π -Bond-Assisted *ortho* Alkenylation of Aromatic and Hetero Aromatic Nitriles with Activated Alkenes

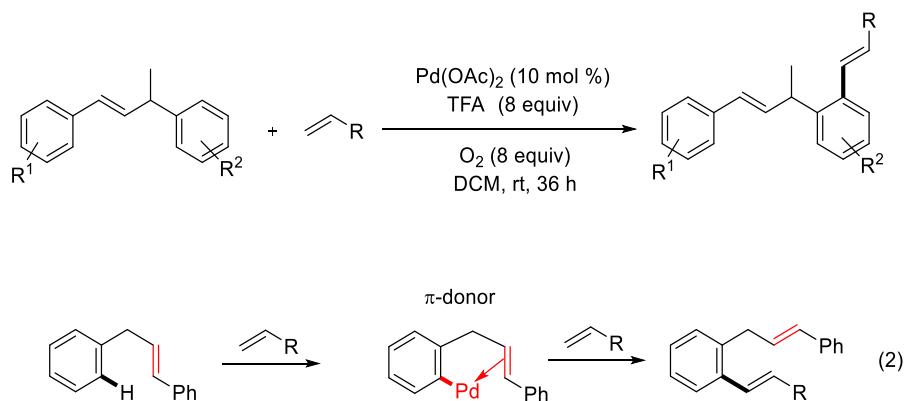
3A.1: Introduction

Selective transformation of C-H bond of organic moieties into C-C and C-heteroatom bond catalyzed by transition metal complexes via C-H bond activation is one of the most versatile and well-acknowledged methods in organic synthesis.¹ This transformation has gained tremendous attention in chemical and pharmaceutical industries, because it provides step- and atom-economical routes to synthesize useful organic molecules from the readily available starting materials.² Particularly, transition metal-catalyzed oxidative cross-coupling of heteroatom substituted aromatics with alkenes has proven to be a highly efficient route to synthesize disubstituted alkenes without having any prefunctionalized starting materials in a highly regio- and stereoselective manner.³ The selectivity of C-H bond of organic moieties can be controlled by using the suitable directing groups. Mostly, the electron lone pair of nitrogen or oxygen atom of directing groups coordinate with the metal complex through σ -coordination and activate the C-H bond of organic moieties selectively (Scheme 3A.1).⁴⁻⁵

Scheme 3A.1: σ -chelation assisted C-H alkenylation

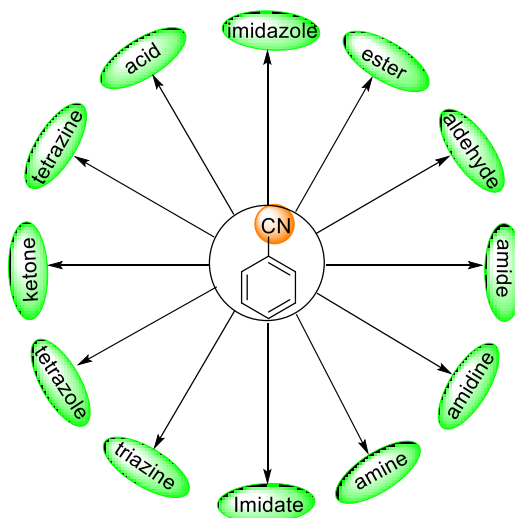
The search for new variants to activate the C-H bond of aromatics is highly important to expand the synthetic scope of the alkenylation reaction. Very recently, Cheng's group disclosed an alkene assisted alkenylation of aromatics with activated alkenes in the

presence of palladium catalyst via an unusual carbon-carbon π -bond coordination (Scheme 3A.2).⁶



Scheme 3A.2: π -chelation assisted C-H olefination

Nitrile is a versatile functional group which can be efficiently used for various organic transformations (Scheme 3A.3).⁷



Scheme 3A.3: various organic transformations of nitrile functional group

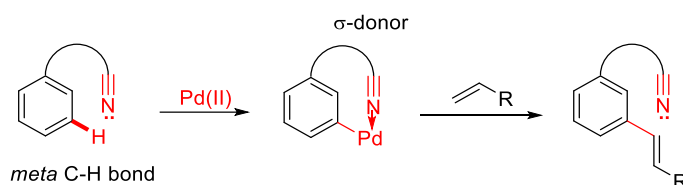
In addition, nitrile group containing organic molecules are used as pharmaceuticals, pesticides and dyes.⁸ The strong electron withdrawing nature and better hydrogen bond accepting property of nitrile group, allows it to use widely in designing drug molecules and till now around 30 nitrile-containing drugs are available in market and 20 more nitrile-containing molecules are in the clinical development.^{8b} Meanwhile, cyano group can also be used as a directing group for the C-H bond activation reaction.⁹⁻¹¹

Also, a less likely, $C\equiv N$ π -bond of benzonitrile coordinates with metal, providing the π -coordinated metal complex (Scheme 3A.4).¹⁰



Scheme 3A.4: Different modes of coordination of Nitrile with metal

Recently, by employing σ -coordination of nitrile moiety, the meta C-H bond of aromatics can be activated efficiently for the alkenylation reaction (Scheme 3A.5).¹¹

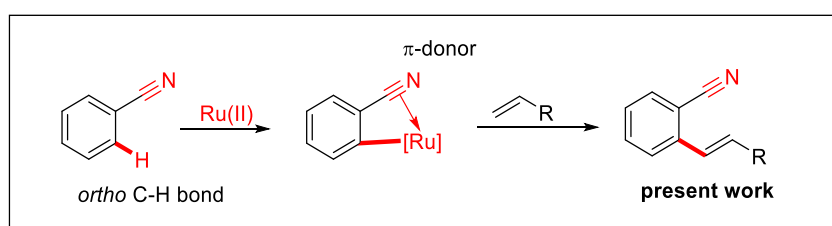


Scheme 3A.5: C≡N σ -bond-Assisted alkenylation

3A.2: Aim of The Present Work

Till that time, there was no report on the C≡N π -bond assisted alkenylation at the *ortho* position of aromatic nitriles with alkenes due to the difficult coordination of π -bond of C≡N with metal. Our ongoing interest in the finding of new C-H bond transformation reaction prompted us to explore the possibility of C≡N π -bond assisted *ortho* alkenylation of substituted aromatic nitriles with alkenes. We have reported for the first time nitrile as a π -bond coordinating group for the *ortho* alkenylation of aromatic and heteroaromatic nitriles with activated alkenes in the presence of ruthenium catalyst (Scheme 3A.6).

Our aim

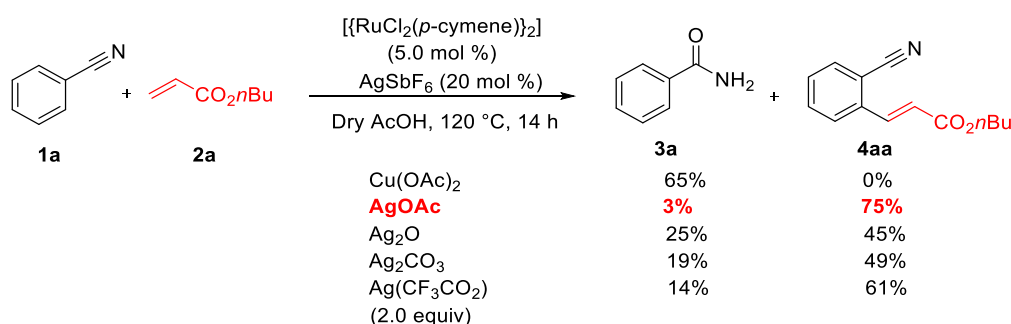


Scheme 3A.6: π bond assisted *ortho* alkenylation

3A.3: Results and Discussion

Initially, the ruthenium-catalyzed alkenylation reaction was examined with benzonitrile (**1a**) and *n*-butyl acrylate (**2a**) (Scheme 3A.7). It is expected that the nitrogen atom of **1a** prefers to coordinate with metal via lone pair electron rather than π -coordination. But, to success the *ortho* C-H bond activation, π -coordination of nitrile is crucial. Meanwhile, metal acetate base is needed for the deprotonation of C-H bond of weak coordinating group substituted aromatics. Thus, a combination of ruthenium catalyst and metal acetate having Lewis acidic nature was selected. The main idea behind the selection of Lewis

acid metal acetate is that the lone pair of nitrogen of nitrile moiety would coordinate with Lewis acid prior to the ruthenium catalyst and block the corresponding site. Therefore, a possibility is created for the π -bond coordination of nitrile moiety into ruthenium catalyst and initiates the C-H bond activation. With this idea, a combination of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (5 mol %), AgSbF_6 (20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv) was used for the reaction. As a nitrile is weak coordinating group, AgSbF_6 was used to generate a cationic ruthenium species for the C-H bond activation. As expected, nitrogen atom of nitrile moiety coordinates with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and block the site. However, before π -coordination of nitrile with ruthenium catalyst, hydration takes place at nitrile group and only benzamide (**3a**) was observed. If the same reaction is run for a long time, a cyclic isoindolin-1-one derivative was observed.¹² Later, the reaction was examined with various Lewis acids such as $\text{Co}(\text{OAc})_2$, $\text{Mn}(\text{OAc})_2$, Ag_2O , AgOAc , Ag_2CO_3 , $\text{Ag}(\text{CF}_3\text{CO}_2)$ and $\text{Fe}(\text{OAc})_2$ (2.0 equiv). Very interestingly, in AgOAc , the *ortho* C-H bond activation takes place selectively and further reacted with *n*-butyl acrylate (**2a**) providing *ortho* alkenylated benzonitrile **4aa** in 75% isolated yield. In the reaction, benzamide **3a** was observed only in very minor 3% yield. In other silver salts such as Ag_2O , Ag_2CO_3 , $\text{Ag}(\text{CF}_3\text{CO}_2)$, product **4aa** was observed in 45%, 49% and 61% yields. Benzamide **3a** was observed in 25%, 19% and 14% yields, respectively. But, in $\text{Co}(\text{OAc})_2$ and $\text{Mn}(\text{OAc})_2$, benzamide **3a** was observed in more 45% and 51% yields and product **4aa** was observed in 15% and 19% yields, respectively. Meanwhile, acidic solvent AcOH is crucial for the reaction. Other solvents such as 1,2-dichloroethane, THF, 1,4-dioxane, DMF, toluene and CF_3COOH were not suitable for the reaction. But, in *iso*-PrOH, product **4aa** was observed only in 10% yield without benzamide **3a** formation.



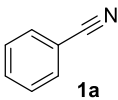
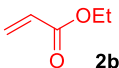
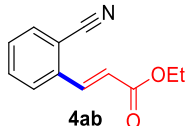
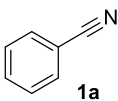
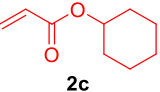
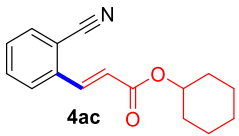
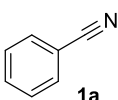
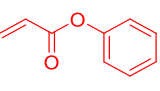
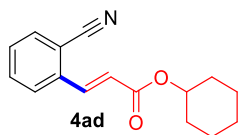
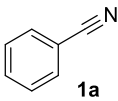
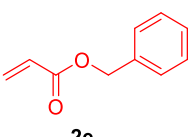
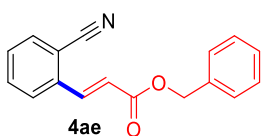
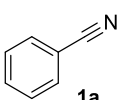
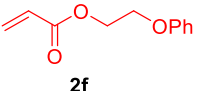
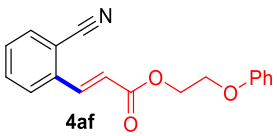
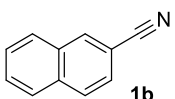
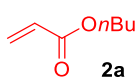
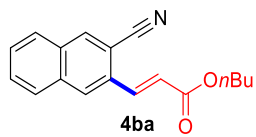
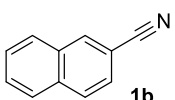
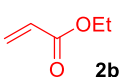
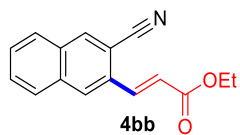
Scheme 3A.7: *ortho* Alkenylation of benzonitrile

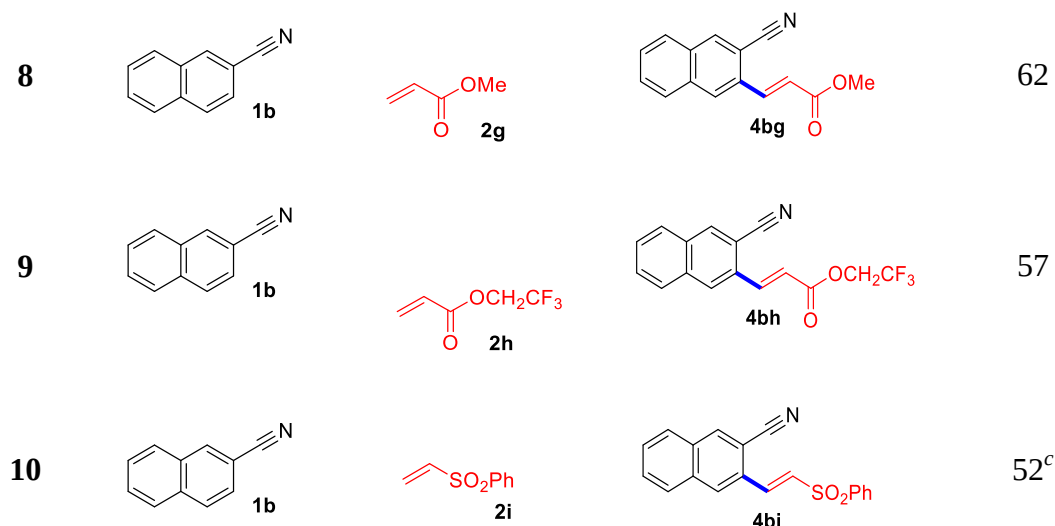
3A.4: Scope of Alkenes

The scope of alkenylation reaction was examined with various activated alkenes **2** under the optimized reaction conditions (Table 3A.1). Ethyl acrylate (**2b**), cyclohexyl acrylate

(**2c**), phenyl acrylate (**2d**), benzyl acrylate (**2e**) and 2-phenoxyethyl acrylate (**2f**) reacted efficiently with **1a**, providing the expected *ortho* alkenylated benzonitriles **4ab-ae** in 64%, 79%, 69%, 67% and 59% yields, respectively (entries 1-5). Further, *n*-butyl acrylate (**2a**), ethyl acrylate (**2b**), methyl acrylate (**2g**) and 2,2,2-trifluoroethyl acrylate (**2h**) also efficiently reacted with 2-naphthonitrile (**1b**), yielding *ortho* alkenylated 2-naphthonitriles **4ba-bh** in 75%, 65%, 62% and 57% yields, respectively (entries 6-9). In the reaction, C-H bond activation selectively takes place at the C3 position of 2-naphthonitrile (**1b**). Interestingly, phenyl vinyl sulphone (**2i**) was also efficiently involved in the reaction, providing product **4bi** in 52% yield (entry 10).

Table 3A.1 : Reaction of benzonitrile (**1a**) or 2-naphthonitrile (**1b**) with activated alkenes **2b-i**^a

entry	1	Alkenes 2	Product 4	Yield (%) ^b
1	 1a	 2b	 4ab	64
2	 1a	 2c	 4ac	79
3	 1a	 2d	 4ad	69
4	 1a	 2e	 4ae	67
5	 1a	 2f	 4af	59
6	 1b	 2a	 4ba	75
7	 1b	 2b	 4bb	65



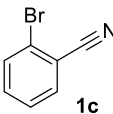
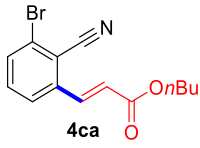
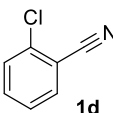
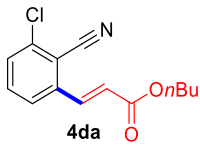
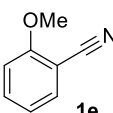
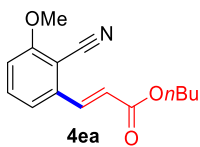
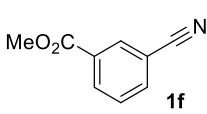
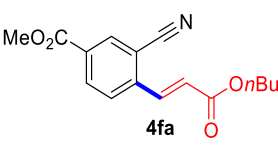
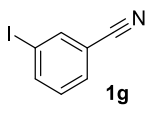
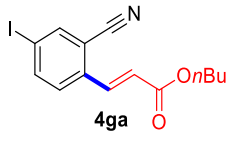
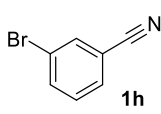
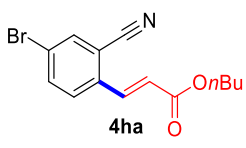
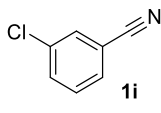
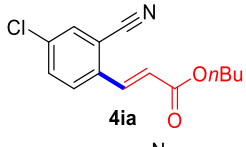
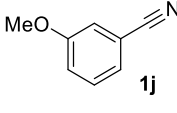
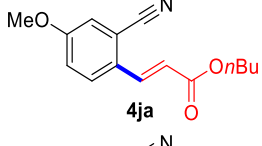
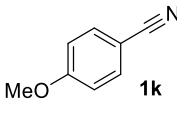
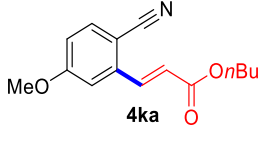
^aAll reactions were carried out using **1a** or **1b** (75 mg), alkenes **2a-h** (4.0 equiv) and **2i** (2.0 equiv), $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (5 mol %), AgSbF_6 (20 mol %) and AgOAc (2.0 equiv) in dry acetic acid (3.0 mL) at 120 °C for 14 h. ^bIsolated yield. ^cIn the reaction, DCE (3.0 mL) + pivalic acid (0.5 mL) was used instead of AcOH.

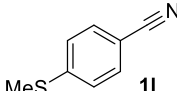
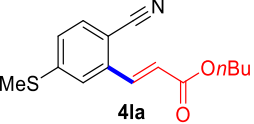
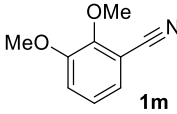
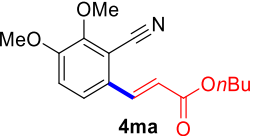
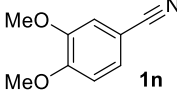
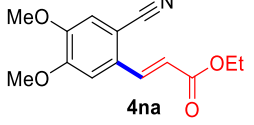
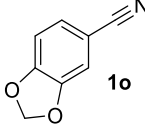
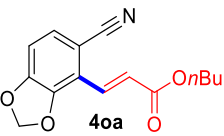
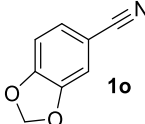
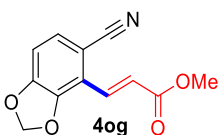
3A.5: Scope of Aromatic Nitriles

The alkenylation reaction was compatible with a variety of sensitive functional groups such as Br, Cl, I, OMe, SMe and CO_2Me substituted aromatic nitriles (Table 3A.2). *ortho* Bromo (**1c**), chloro (**1d**) and methoxy (**1e**) substituted benzonitriles reacted efficiently with *n*-butyl acrylate (**2a**), providing the corresponding *ortho* alkenylated aromatic nitriles **4ca-ea** in 51%, 50% and 47% yields, respectively (entries 1-3). Subsequently, *meta* methylester (**1f**), iodo (**1g**), bromo (**1h**), chloro (**1i**) and methoxy (**1j**) benzonitriles also efficiently participated in the reaction, providing the corresponding *ortho* alkenylated benzonitriles **4fa-ja** in 53%, 48%, 45%, 44% and 42% yields, respectively, in a highly regioselective manner (entries 4-8). In all these reactions, C-H bond activation takes place at a less hindered *ortho* C6-H bond of benzonitriles **1f-j**. 4-Methoxy (**1k**) and 4-SMe (**1l**) substituted benzonitriles provided the corresponding alkenylation products **4ka** and **4la** in 42% and 57% yields, respectively (entries 9 and 10). The alkenylation reaction was also examined with disubstituted benzonitriles **1m-o**. 2,3-Dimethoxy (**1m**) and 3,4-dimethoxy (**1n**) benzonitriles reacted with **2a** or **2b**, affording *ortho* alkenylated benzonitriles **4ma** and **4nb** in moderate 38% and 29% yields, respectively (entries 11 and 12). In the substrate **1n**, C-H bond activation takes place at a less hindered *ortho* C6-H bond. In contrast, a sterically hindered *ortho* C-H bond of piperonylnitrile (**1o**) reacted with **2a** or **2g** providing products **4oa** and **4og** in 52% and 48% yields, respectively (entries 13 and 14). The present result clearly reveals that a strong electron donating OMe group

substituent on the benzonitrile decreases the yield of the product and SMe, halogen and electron withdrawing substituent on the benzonitrile moderately increases the yield. In unsubstituted benzonitrile and 2-naphthonitrile substrates, good yields were observed.^a All reactions were carried out using **1c-o** (75 mg), alkenes **2** (4.0 equiv), [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (5 mol %), AgSbF_6 (20 mol %) and AgOAc (2.0 equiv) in dry acetic acid (3.0 mL) at 120 °C for 14 h.^b Isolated yield.^c The reaction time was 16 h.

Table 3A.2: Results of the Reaction of Aromatic nitriles **1** with *n*-Butyl Acrylate

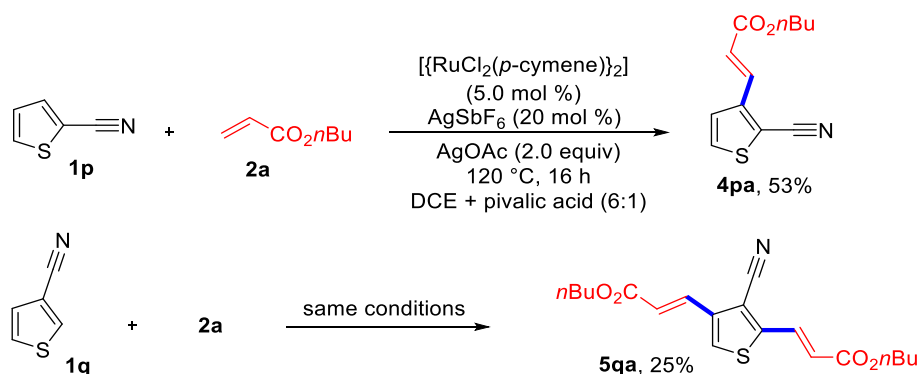
entry	1	product 4	yield (%) ^b
1	 1c	 4ca	51
2	 1d	 4da	50
3	 1e	 4ea	47
4	 1f	 4fa	53
5	 1g	 4ga	48
6	 1h	 4ha	45
7	 1i	 4ia	44
8	 1j	 4ja	42
9	 1k	 4ka	42 ^c

10			57
11			38 ^c
12			29 ^c
13			52 ^c
14			48 ^c

^aAll reactions were carried out using **1c-o** (75 mg), alkenes **2** (4.0 equiv), [{RuCl₂(*p*-cymene)}₂] (5 mol %), AgSbF₆ (20 mol %) and AgOAc (2.0 equiv) in dry acetic acid (3.0 mL) at 120 °C for 14 h. ^bIsolated yield. ^cThe reaction time was 16 h.

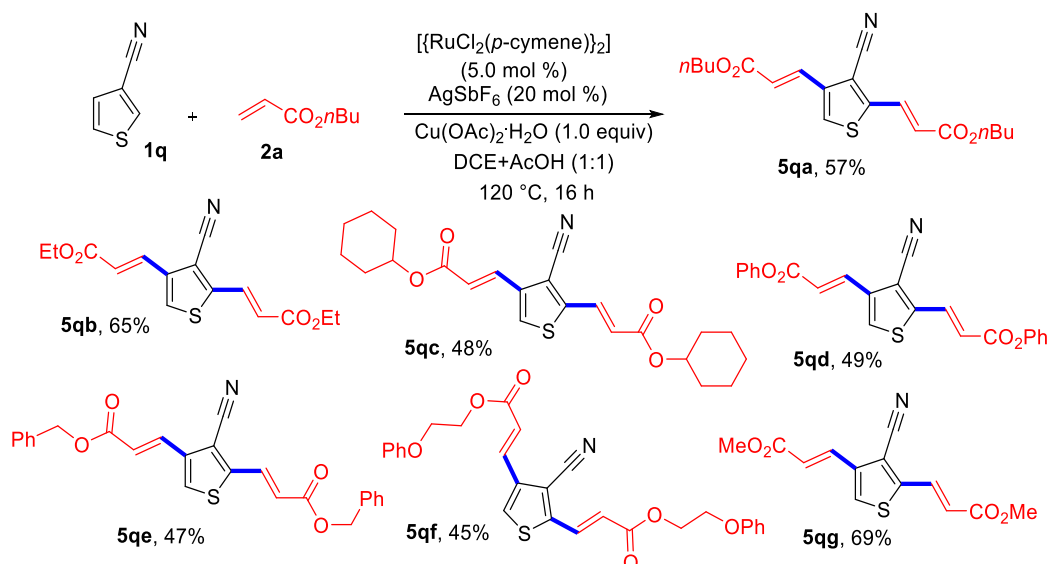
3A.6: Scope of Heteroaromatic Nitriles

The alkenylation reaction was also successfully extended with heteroaromatic nitriles (Scheme 3A.8). Treatment of 2-nitrile thiophene (**1p**) with *n*-butyl acrylate (**2a**) in the presence of [{RuCl₂(*p*-cymene)}₂] (5 mol %), AgSbF₆ (20 mol %) and AgOAc (2.0 equiv) at 120 °C for 16 h provided 2-alkenyl-3-nitrile thiophene (**4pa**) in 53% yield. 3-Nitrile thiophene (**1q**) reacted with *n*-butyl acrylate (**2a**) affording *bis* alkenylated 3-nitrile thiophene **5qa** in 25% yield.



Scheme 3A.8: Alkenylation of 2-cyano and 3-cyanothiophenes

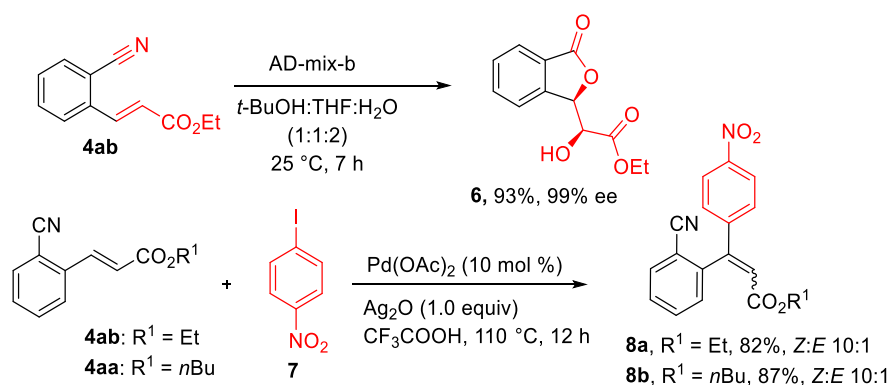
Next, the same reaction was examined with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ without AgOAc . Interestingly, in the reaction, *bis* alkenylated 3-nitrile thiophene **5qa** was observed in 57% yield (Scheme 3A.9). Similar, *n*-ethyl acrylate (**2b**), cyclohexyl acrylate (**2c**), phenyl acrylate (**2d**), benzyl acrylate (**2e**), 2-phenoxyethyl acrylate (**2f**) and methyl acrylate (**2g**) also reacted with **1q**, affording *bis* alkenylated 3-nitrile thiophenes **5qb–qg** in 65%, 48%, 49%, 47%, 45% and 69% yields, respectively (Scheme 3A.9).



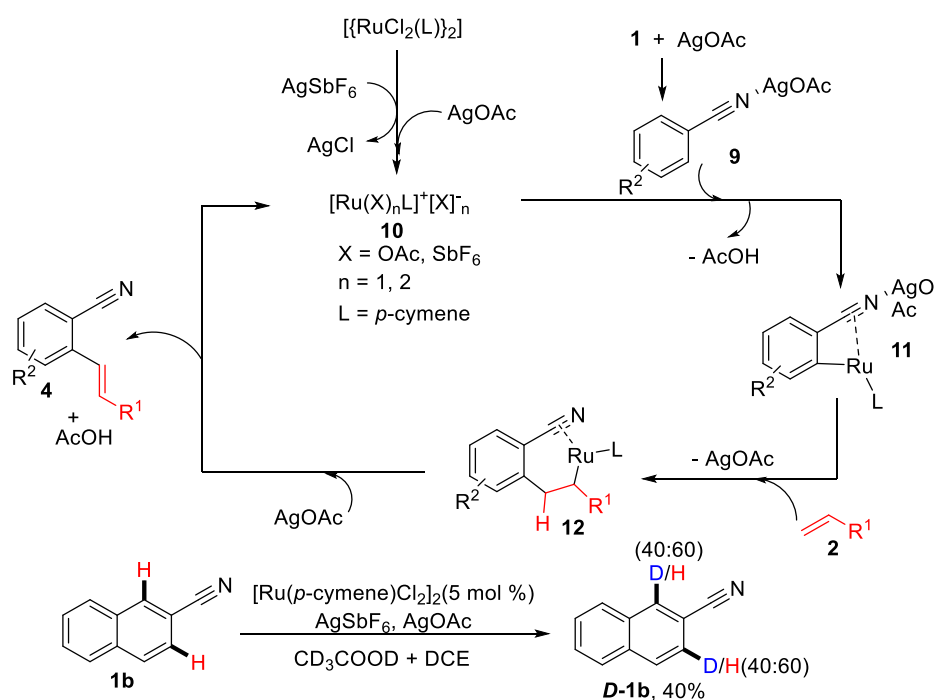
Scheme 3A.9: *bis* Alkenylation of 3-cyanothiophene

3A.7: Synthetic transformations of *ortho* alkenyl benzonitriles

Substituted *ortho* alkenyl aromatic nitrile is a versatile synthetic intermediate which can be used for synthesizing various useful organic molecules.⁷⁻⁸ *ortho* Alkenyl benzonitrile **4ab** underwent intramolecular cyclization in the presence of AD-mix- β , yielding chiral phthalide **6** in 93% yield in 99 ee% (Scheme 3A .10).¹³ By using AD-mix- α , the reverse chiral phthalide derivative can be prepared in a highly enantioselective manner.¹³ Further, by employing nitrile as a directing group, arylation was done at alkene C-H bond of **4ab** and **4aa** with 4-iodo nitrobenzene (**7**) in the presence of $\text{Pd}(\text{OAc})_2$ and Ag_2O in CF_3COOH at 110 °C for 12 h, giving trisubstituted alkenes **8a** and **8b** in 82% and 87% yields in a 10:1 *Z:E* ratio.

Scheme 3A.10: Transformation of *ortho* alkenyl benzonitriles 4

3A.8: Mechanism



Scheme 3A.11: Proposed mechanism

A possible reaction mechanism is proposed to account for the present alkenylation reaction in Scheme 3A.11. It is strongly believed that first the lone of nitrogen atom of benzonitrile **1** coordinates with Lewis acid AgOAc, providing a linear benzonitrile silver complex **9**. A similar observation is strongly supported by DFT calculation.¹⁴ Subsequently, AgSbF₆ likely removes the Cl⁻ ligand from $\{[RuCl_2(p\text{-cymene})]\}_2$ complex, providing a cationic ruthenium species **10**. Coordination of the C≡N π-bond of **9** into the ruthenium species **10** followed by *ortho*-metalation provides a five membered ruthenacycle **11**. Coordinative insertion of activated alkene **2** into the Ru–carbon bond of intermediate **11** affords intermediate **12**. Subsequent β-hydride elimination of

intermediate **12** in the presence of AgOAc gives product **4** and regenerates the active ruthenium species **10**. To support the *ortho* C-H bond cleavage of **9** is a reversible, the reaction of **1b** was done in the presence of CD₃COOD under similar reaction conditions. In the reaction, product **D-1b** was observed in 40% yield, in which 40% of deuterium incorporation was observed at both C-1 as well as C-3 carbons of **1b**.

3A.9: Conclusion

1. We have demonstrated a ruthenium-catalyzed C≡N π -bond assisted *ortho* alkenylation of substituted aromatic and heteroaromatic nitriles with activated alkenes providing *ortho* alkenylated aromatic and heteroaromatic nitriles in good to moderate yields in a highly regio- and stereoselective manner.
2. Later, *ortho* alkenylated aromatic nitrile was converted into chiral phthalide in the presence of AD-mix- β . Additional, by employing nitrile as a directing group, arylation was done at the alkene C-H bond of *ortho* alkenylated aromatic nitriles with aromatic iodides in the presence of palladium catalyst.

3A.10: References

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3A.11: Experimental Section

General Procedure for the Coupling of Aromatic Nitriles with Alkenes Catalyzed by Ruthenium Complex:

Substituted nitriles **1** (75 mg, 1.0 equiv), [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (5 mol %), AgOAc (2.0 equiv), AgSbF₆ (20 mol %) were taken in a 15-mL pressure tube equipped with a magnetic stirrer and septum. (Note: AgSbF₆ and AgOAc are moisture sensitive. Thus, AgSbF₆ and AgOAc were taken inside the nitrogen glove box). The tube was evacuated and purged with nitrogen gas three times. To the tube were then added liquid alkenes **2** (4.0 equiv), if nitrile **1** is liquid (75 mg, 1.0 equiv), dry acetic acid solvent (3.0 mL) via syringes, allowed the reaction mixture to stir at room temperature for few seconds and again the tube was evacuated and purged with nitrogen gas three times. Then, the septum was taken out and immediately a screw cap was used to cover the tube. Then, the reaction mixture was allowed to stir at 120 °C for 14 h. After cooling to ambient temperature, the reaction mixture was diluted with CH₂Cl₂, filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **4**.

Note: For the preparation of compounds **4bi** AcOH solvent (3.0 mL) was not used. Instead, 1,2-dichloroethane (3.0 mL) and pivalic acid (0.5 mL) were added. 2.0 equiv of phenyl vinyl sulfone (**2i**) was used.

Note: Dry AcOH solvent is crucial for the reaction. If AcOH is contaminated with water, the yield of alkenylation product **4** was decreased and benzamide formation **3** is increased. Thus, Dry AcOH is crucial in order to get the more yield of **4**.

Note: For the preparation of compounds **4ka**, **4ma**, **4nb**, **4oa** and **4og**, the reaction was done for 16 h.

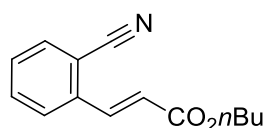
General Procedure for the Coupling of Heteroaromatic Nitriles with Alkenes Catalyzed by Ruthenium Complex:

[{RuCl₂(*p*-cymene)}₂] (5 mol %), Cu(OAc)₂·H₂O (1.0 equiv), AgSbF₆ (20 mol %) were taken in a 15-mL pressure tube equipped with a magnetic stirrer and septum. (Note: AgSbF₆ is moisture sensitive. Thus, AgSbF₆ was taken inside the nitrogen glove box). The tube was evacuated and purged with nitrogen gas three times. To the tube were then added liquid alkenes **2** (6.0 equiv), heteroaromatic nitrile **1** (75 mg, 1.0 equiv), 1,2-dichloroethane (1.5 mL) and dry acetic acid (1.5 mL) via syringes, allowed the reaction mixture to stir at room temperature for few seconds and again the tube was evacuated and purged with nitrogen gas three times. Then, the septum was taken out and immediately a screw cap was used to cover the tube. Then, the reaction mixture was allowed to stir at 120 °C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with CH₂Cl₂, filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **5**.

The same procedure was used for synthesizing compound **4pa**, but the solvent is only 1,2-dichloroethane (3.0 mL) and pivalic acid (0.5 mL) and no AcOH was added. In addition, the oxidant is AgOAc (2.0 equiv) instead of Cu(OAc)₂·H₂O.

3A.12: Spectral Data of all Compounds

Butyl (*E*)-3-(2-cyanophenyl)acrylate (4aa**).**



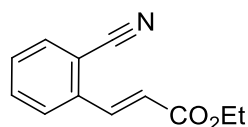
Orange oil; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 126 mg of **4aa** was isolated and yield is 75%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.94 (d, *J* = 16.0 Hz, 1 H), 7.72 (d, *J* = 7.6 Hz, 1 H), 7.68 (d, *J* = 7.6 Hz, 1 H), 7.61 (t, *J* = 7.6 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 6.59 (d, *J* = 16.0 Hz, 1 H), 4.21 (t, *J* = 6.4 Hz, 2 H), 1.71 - 1.64 (m, 2 H), 1.46 - 1.37 (m, 2 H), 0.94 (t, *J* = 7.2 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.8, 139.2, 137.2, 133.4, 132.9, 129.9, 126.9, 122.9, 116.9, 112.5, 64.7, 30.5, 19.0, 13.6.

HRMS (ESI): calc. for [(C₁₄H₁₅NO₂)Na] (M+Na) 252.1000, measured 252.0998.

Ethyl (*E*)-3-(2-cyanophenyl)acrylate (4ab).



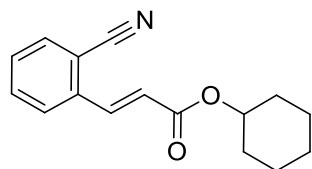
White solid; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 94mg of **4ab** was isolated and yield is 64%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.91 (d, *J* = 16.0 Hz, 1 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.66 (d, *J* = 7.8 Hz, 1 H), 7.60 (t, *J* = 7.8 Hz, 1 H), 7.45 (t, *J* = 7.8 Hz, 1 H), 6.57 (d, *J* = 16.0 Hz, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 0.94 (t, *J* = 7.2 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.6, 139.1, 137.1, 133.3, 132.9, 129.9, 126.8, 122.9, 116.9, 112.4, 60.8, 14.1.

HRMS (ESI): calc. for [(C₁₂H₁₁NO₂)Na] (M+Na) 224.0687, measured 224.0685.

Cyclohexyl (*E*)-3-(2-cyanophenyl)acrylate (4ac).

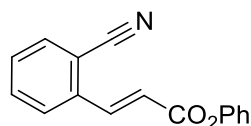


Colorless oil; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 147 mg of **4ac** was isolated and yield is 79%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.93 (d, *J* = 16.0 Hz, 1 H), 7.72 – 7.58 (m, 4 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 4.92 – 4.85 (m, 1 H), 1.92 – 1.73 (m, 4 H), 1.56 – 1.22 (m, 6 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.2, 138.9, 137.5, 133.5, 132.9, 129.9, 126.9, 123.7, 117.1, 112.6, 73.3, 31.6, 25.33, 23.7.

HRMS (ESI): calc. for [(C₁₆H₁₇NO₂)Na] (M+Na) 278.1157, measured 278.1157.

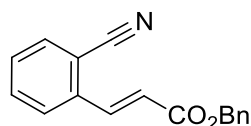
Phenyl (*E*)-3-(2-cyanophenyl)acrylate (4ad).

White solid; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 125 mg of **4ad** was isolated and yield is 69%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.16 (d, *J* = 16.0 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 7.6 Hz, 1 H), 7.66 (t, *J* = 8.0 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 1 H), 7.44 – 7.39 (m, 2 H), 7.28 – 7.17 (m, 3 H), 6.81 (d, *J* = 16.0 Hz, 1 H).

¹³C NMR (CDCl₃, 100 MHz): δ 164.2, 150.6, 141.1, 137.0, 133.6, 133.0, 130.4, 129.4, 127.3, 125.9, 122.3, 121.5, 117.0, 112.9.

HRMS (ESI): calc. for [(C₁₆H₁₁NO₂)Na] (M+Na) 272.0687, measured 272.0693.

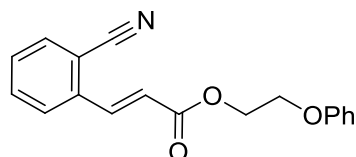
Benzyl (*E*)-3-(2-cyanophenyl)acrylate (4ae).

Colorless oil; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 129 mg of **4ae** was isolated and yield is 67%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.03 (d, *J* = 16.0 Hz, 1 H), 7.74 – 7.70 (m, 2 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 7.50 – 7.33 (m, 6 H), 6.66 (d, *J* = 16.0 Hz, 1 H), 5.29 (s, 2 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.6, 139.9, 137.3, 135.7, 133.5, 132.9, 130.1, 128.6, 128.3, 128.3, 127.0, 122.8, 117.0, 112.8, 66.7.

HRMS (ESI): calc. for [(C₁₇H₁₃NO₂)Na] (M+Na) 286.0844, measured 286.0851.

2-Phenoxyethyl (*E*)-3-(2-cyanophenyl)acrylate (4af).

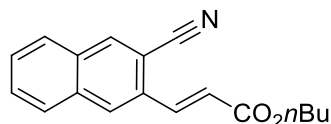
Light greenish color oil; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg, 126 mg of **4af** was isolated and yield is 59%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.02 (d, *J* = 15.6 Hz, 1 H), 7.74 – 7.70 (m, 2 H), 7.63 (t, *J* = 8.0 Hz, 1 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.33 – 7.29 (m, 2 H), 7.00 – 6.92 (m, 3 H), 6.66 (d, *J* = 15.6 Hz, 1 H), 4.60 (t, *J* = 4.8 Hz, 2 H), 4.27 (t, *J* = 4.8 Hz, 2 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 165.7, 158.4, 140.1, 137.2, 133.5, 132.9, 130.1, 129.5, 127.0, 122.5, 121.2, 116.9, 114.7, 112.8, 65.8, 63.3.

HRMS (ESI): calc. for $[(\text{C}_{18}\text{H}_{15}\text{NO}_3)\text{Na}]$ ($\text{M}+\text{Na}$) 316.0950, measured 316.0962.

Butyl (*E*)-3-(3-cyanonaphthalen-2-yl)acrylate (4ba**).**



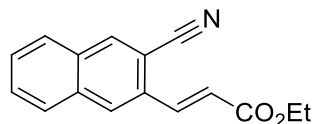
Light yellow semisolid; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 102 mg of **4ba** was isolated and yield is 75%. The reaction was done for 14 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 8.28 (s, 1 H), 8.16 (s, 1 H), 8.06 (d, J = 16.0 Hz, 1 H), 7.90 (t, J = 7.6 Hz, 2 H), 7.70 – 7.61 (m, 2 H), 6.76 (d, J = 16.0 Hz, 1 H), 4.26 (t, J = 6.8 Hz, 2 H), 1.76 - 1.69 (m, 2 H), 1.51 - 1.42 (m, 2 H), 0.98 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.1, 139.9, 135.8, 134.4, 132.4, 131.6, 129.7, 128.6, 128.6, 128.2, 127.8, 122.4, 117.6, 109.4, 64.8, 30.7, 19.2, 13.7.

HRMS (ESI): calc. for $[\text{C}_{18}\text{H}_{17}\text{NO}_2]\text{H}$ ($\text{M}+\text{H}$) 280.1338, measured 280.1337.

Ethyl (*E*)-3-(3-cyanonaphthalen-2-yl)acrylate (4bb**).**



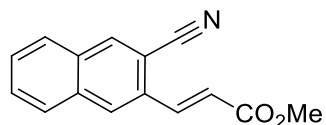
White semisolid; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 80 mg of **4bb** was isolated and yield is 65%. The reaction was done for 14 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 8.29 (s, 1 H), 8.16 (s, 1 H), 8.06 (d, J = 16.0 Hz, 1 H), 7.90 (t, J = 7.6 Hz, 2 H), 7.70 – 7.62 (m, 2 H), 6.76 (d, J = 16.0 Hz, 1 H), 4.32 (q, J = 7.2 Hz, 2 H), 1.37 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.1, 139.9, 135.9, 134.4, 132.4, 131.6, 129.7, 128.64, 128.59, 128.2, 127.8, 122.4, 117.7, 109.4, 60.9, 14.3.

HRMS (ESI): calc. for $[\text{C}_{16}\text{H}_{13}\text{NO}_2]\text{H}$ ($\text{M}+\text{H}$) 252.1025, measured 252.1025.

Methyl (*E*)-3-(3-cyanonaphthalen-2-yl)acrylate (4bg**).**



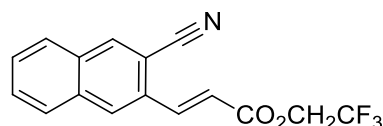
Colorless solid; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg, 72mg of **4bg** was isolated and yield is 62%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.23 (s, 1 H), 8.12 (s, 1 H), 8.04 (d, *J* = 16.0 Hz, 1 H), 7.87 (t, *J* = 8.0 Hz, 2 H), 7.68 – 7.60 (m, 2 H), 6.73 (d, *J* = 16.0 Hz, 1 H), 3.84 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.4, 140.1, 135.7, 134.2, 132.3, 131.3, 129.7, 128.62, 128.5, 128.1, 127.7, 121.8, 117.5, 109.3, 51.9.

HRMS (ESI): calc. for [(C₁₅H₁₁NO₂)Na] (M+Na) 260.0687, measured 260.0690.

2,2,2-Trifluoroethyl (*E*)-3-(3-cyanonaphthalen-2-yl)acrylate (4bh).



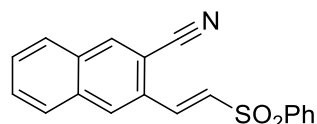
Colorless semisolid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg, 86 mg of **4bh** was isolated and yield is 57%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.28 (s, 1 H), 8.18 (s, 1 H), 8.15 (d, *J* = 16.0 Hz, 1 H), 7.91 (t, *J* = 8.4 Hz, 2 H), 7.72 – 7.64 (m, 2 H), 6.82 (d, *J* = 16.0 Hz, 1 H), 4.65 (q, *J* = 8.4 Hz, 2 H).

¹³C NMR (CDCl₃, 100 MHz): δ 164.3, 142.4, 135.9, 134.2, 132.6, 130.8, 129.9, 129.0, 128.7, 128.3, 128.2, 122.94 (q, *J* = 276 Hz, CH₂ of –O-CH₂-CF₃), 119.8, 117.4, 109.3, 60.55 (q, *J* = 36 Hz, CF₃ of –O-CH₂-CF₃).

HRMS (ESI): calc. for [(C₁₆H₁₀F₃NO₂)Na] (M+Na) 328.0561, measured 328.0570.

(*E*)-3-(2-(Phenylsulfonyl)vinyl)-2-naphthonitrile (4bi).



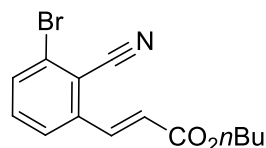
Light yellow semisolid; eluent (40% ethyl acetate in hexanes). The reaction scale is 75 mg, 81 mg of **4bi** was isolated and yield is 52%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.30 (s, 1 H), 8.10 (s, 1 H), 8.04 – 8.00 (m, 3 H), 7.91 – 7.89 (m, 2 H), 7.73 – 7.65 (m, 3 H), 7.62 – 7.56 (m, 2 H), 7.32 (d, *J* = 15.2 Hz, 1 H).

¹³C NMR (CDCl₃, 100 MHz): δ 140.1, 138.1, 136.3, 134.2, 133.7, 132.7, 131.5, 130.1, 129.7, 129.5, 129.3, 129.3, 128.7, 128.3, 127.9, 117.4, 108.9.

HRMS (ESI): calc. for [(C₁₉H₁₃NO₂S)H] (M+H) 320.0745, measured 320.0740.

Butyl (*E*)-3-(3-bromo-2-cyanophenyl)acrylate (4ca).



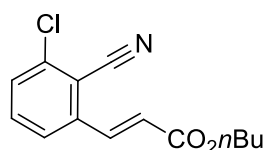
Light yellow semisolid; eluent (12% ethyl acetate in hexanes). The reaction scale is 75 mg, 65 mg of **4ca** was isolated and yield is 51%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.95 (d, *J* = 16.0 Hz, 1 H), 7.71 – 7.66 (m, 2 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 6.59 (d, *J* = 16.0 Hz, 1 H), 4.25 (t, *J* = 6.8 Hz, 2 H), 1.74 - 1.67 (m, 2 H), 1.49 - 1.40 (m, 2 H), 0.97 (t, *J* = 7.2 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.5, 140.1, 138.8, 133.8, 133.5, 126.7, 125.4, 124.4, 115.8, 115.4, 65.0, 30.6, 19.1, 13.7.

HRMS (ESI): calc. for [(C₁₄H₁₄BrNO₂)Na] (M+Na) 330.0106, measured 330.0110.

Butyl (*E*)-3-(3-chloro-2-cyanophenyl)acrylate (4da**).**



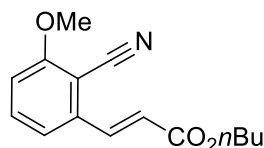
Light yellow oil; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 72 mg of **4da** was isolated and yield is 50%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.94 (d, *J* = 16.0 Hz, 1 H), 7.63 (dd, *J* = 7.6, 2.0 Hz, 1 H), 7.57 – 7.53 (m, 2 H), 6.61 (d, *J* = 16.0 Hz, 1 H), 4.25 (t, *J* = 6.8 Hz, 2 H), 1.74 - 1.67 (m, 2 H), 1.49 - 1.40 (m, 2 H), 0.97 (t, *J* = 7.2 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.6, 139.8, 138.6, 138.2, 133.4, 130.6, 124.9, 124.5, 114.2, 113.5, 65.1, 30.6, 19.1, 13.7.

HRMS (ESI): calc. for [(C₁₄H₁₄ClNO₂)Na] (M+Na) 286.0611, measured 286.0612.

Butyl (*E*)-3-(2-cyano-3-methoxyphenyl)acrylate (4ea**).**



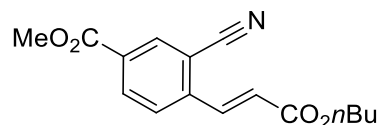
Light yellow oil; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg, 69 mg of **4ea** was isolated and yield is 47%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.91 (d, *J* = 16.0 Hz, 1 H), 7.53 (t, *J* = 8.0 Hz, 1 H), 7.27 (d, *J* = 8.8 Hz, 1 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 6.59 (d, *J* = 16.0 Hz, 1 H), 4.22 (t, *J* = 6.8 Hz, 2 H), 3.95 (s, 3 H), 1.73 - 1.65 (m, 2 H), 1.48 - 1.38 (m, 2 H), 0.96 (t, *J* = 7.2 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.92, 161.97, 139.4, 138.9, 133.9, 123.4, 118.7, 114.5, 111.9, 102.1, 64.8, 56.3, 30.6, 19.1, 13.7.

HRMS (ESI): calc. for $[(C_{15}H_{17}NO_3)Na]$ (M+Na) 282.1106, measured 282.1108.

Methyl (*E*)-4-(3-butoxy-3-oxoprop-1-en-1-yl)-3-cyanobenzoate (4fa).



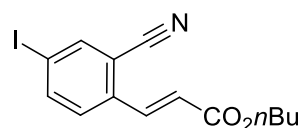
Yellow solid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg, 71 mg of **4fa** was isolated and yield is 53%. The reaction was done for 14 h at 120 °C.

1H NMR ($CDCl_3$, 400 MHz): δ 8.36 (d, J = 1.6 Hz, 1 H), 8.25 (dd, J = 8.0, 1.6 Hz, 1 H), 7.97 (d, J = 16.0 Hz, 1 H), 7.81 (d, J = 8.0 Hz, 1 H), 6.69 (d, J = 16.0 Hz, 1 H), 4.25 (t, J = 6.8 Hz, 2 H), 3.97 (s, 3 H), 1.74 - 1.67 (m, 2 H), 1.49 - 1.39 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.4, 164.6, 141.1, 138.2, 134.6, 133.6, 131.6, 127.2, 125.2, 116.2, 112.9, 65.1, 52.8, 30.6, 19.1, 13.7.

HRMS (ESI): calc. for $[(C_{16}H_{17}NO_4)Na]$ (M+Na) 310.1055, measured 310.1059.

Butyl (*E*)-3-(2-cyano-4-iodophenyl)acrylate (4ga).



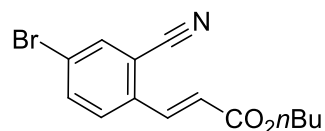
Yellow semisolid; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 56 mg of **4ga** was isolated and yield is 48%. The reaction was done for 14 h at 120 °C.

1H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, J = 1.8 Hz, 1 H), 7.94 (dd, J = 8.4, 1.8 Hz, 1 H), 7.87 (d, J = 15.6 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 6.62 (d, J = 15.6 Hz, 1 H), 4.24 (t, J = 6.8 Hz, 2 H), 1.74 - 1.67 (m, 2 H), 1.48 - 1.39 (m, 2 H), 0.97 (t, J = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.7, 142.1, 141.7, 138.3, 136.8, 128.1, 123.6, 115.5, 114.2, 94.9, 65.0, 30.6, 19.1, 13.7.

HRMS (ESI): calc. for $[(C_{14}H_{14}INO_2)Na]$ (M+Na) 377.9967, measured 377.9966.

Butyl (*E*)-3-(4-bromo-2-cyanophenyl)acrylate (4ha).



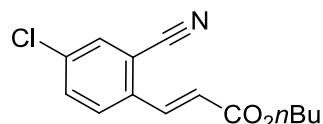
Colorless semisolid; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 57 mg of **4ha** was isolated and yield is 45%. The reaction was done for 14 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 7.89 (d, J = 16.0 Hz, 1 H), 7.84 (d, J = 2.0 Hz, 1 H), 7.75 (dd, J = 8.4, 2.0 Hz, 1 H), 7.60 (d, J = 8.4 Hz, 1 H), 6.61 (d, J = 16.0 Hz, 1 H), 4.24 (t, J = 6.8 Hz, 2 H), 1.74 - 1.66 (m, 2 H), 1.48 - 1.39 (m, 2 H), 0.97 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 165.7, 138.2, 136.3, 135.9, 128.2, 123.8, 123.7, 115.7, 114.2, 65.0, 30.6, 19.1, 13.7.

HRMS (ESI): calc. for $[(\text{C}_{14}\text{H}_{14}\text{BrNO}_2)\text{Na}]$ ($\text{M}+\text{Na}$) 330.0106, measured 330.0107.

Butyl (*E*)-3-(4-chloro-2-cyanophenyl)acrylate (4ia).



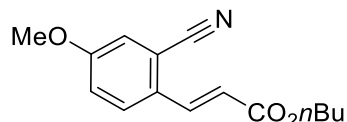
Colorless oil; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 64 mg of **4ia** was isolated and yield is 44%. The reaction was done for 14 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 7.90 (d, J = 16.0 Hz, 1 H), 7.69 – 7.67 (m, 2 H), 7.59 (dd, J = 8.8, 2.0 Hz, 1 H), 6.59 (d, J = 16.0 Hz, 1 H), 4.24 (t, J = 6.8 Hz, 2 H), 1.73 - 1.66 (m, 2 H), 1.48 - 1.39 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 165.6, 138.1, 136.1, 135.9, 133.4, 133.0, 128.2, 123.6, 115.8, 114.0, 64.9, 30.6, 19.1, 13.7.

HRMS (ESI): calc. for $[(\text{C}_{14}\text{H}_{14}\text{ClNO}_2)\text{Na}]$ ($\text{M}+\text{Na}$) 286.0611, measured 286.0616.

Butyl (*E*)-3-(2-cyano-4-methoxyphenyl)acrylate (4ja).



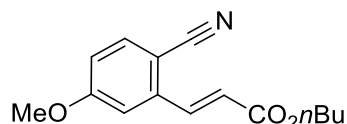
Off-white solid; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg, 61 mg of **4ja** was isolated and yield is 42%. The reaction was done for 14 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 7.87 (d, J = 16.0 Hz, 1 H), 7.64 (d, J = 8.8 Hz, 1 H), 7.13 – 7.11 (m, 2 H), 6.46 (d, J = 16.0 Hz, 1 H), 4.19 (t, J = 6.8 Hz, 2 H), 3.85 (s, 3 H), 1.70 - 1.63 (m, 2 H), 1.46 - 1.36 (m, 2 H), 0.94 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.2, 160.5, 138.9, 129.7, 128.3, 120.4, 119.7, 117.4, 116.8, 113.7, 64.6, 55.7, 30.6, 19.0, 13.6.

HRMS (ESI): calc. for $[(\text{C}_{15}\text{H}_{17}\text{NO}_3)\text{Na}]$ ($\text{M}+\text{Na}$) 282.1106, measured 282.1093.

Butyl (*E*)-3-(2-cyano-5-methoxyphenyl)acrylate (4ka).



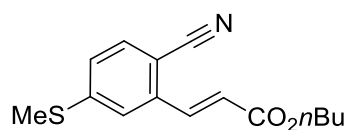
Colorless solid; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg, 61 mg of **4ka** was isolated and yield is 42%. The reaction was done for 16 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.92 (d, J = 16.0 Hz, 1 H), 7.63 (d, J = 8.4 Hz, 1 H), 7.17 (d, J = 2.4 Hz, 1 H), 6.98 (dd, J = 8.4, 2.4 Hz, 1 H), 6.58 (d, J = 16.0 Hz, 1 H), 4.24 (t, J = 6.8 Hz, 2 H), 3.89 (s, 3 H), 1.74 - 1.67 (m, 2 H), 1.49 - 1.39 (m, 2 H), 0.97 (t, J = 7.2 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.9, 162.8, 139.5, 139.3, 135.1, 123.1, 117.5, 116.1, 112.1, 104.5, 64.9, 55.7, 30.6, 19.1, 13.7.

HRMS (ESI): calc. for [(C₁₅H₁₇NO₃)Na] (M+Na) 282.1106, measured 282.1102.

Butyl (E)-3-(2-cyano-5-(methylthio)phenyl)acrylate (4la).



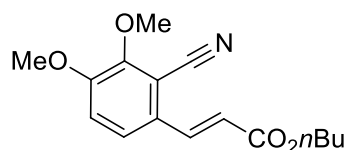
White semisolid; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 79mg of **4la** was isolated and yield is 57%. The reaction was done for 14 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.88 (d, J = 16.0 Hz, 1 H), 7.56 (d, J = 8.4 Hz, 1 H), 7.45 (d, J = 2.0 Hz, 1 H), 7.24 (dd, J = 8.4, 2.0 Hz, 1 H), 6.59 (d, J = 16.0 Hz, 1 H), 4.22 (t, J = 6.8 Hz, 2 H), 2.53 (s, 3 H), 1.72 - 1.65 (m, 2 H), 1.47 - 1.38 (m, 2 H), 0.95 (t, J = 7.2 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.7, 146.6, 139.0, 137.4, 133.3, 126.2, 123.3, 122.9, 117.3, 107.9, 64.9, 30.6, 19.1, 14.6, 13.7

HRMS (ESI): calc. for [(C₁₅H₁₇NO₂S)Na] (M+Na) 298.0878, measured 298.0880.

Butyl (E)-3-(2-cyano-3,4-dimethoxyphenyl)acrylate (4ma).



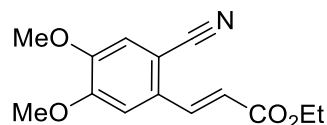
Colorless semisolid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 50 mg of **4ma** was isolated and yield is 38%. The reaction was done for 16 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.84 (d, J = 16.0 Hz, 1 H), 7.41 (d, J = 8.8 Hz, 1 H), 7.12 (d, J = 8.8 Hz, 1 H), 6.50 (d, J = 16.0 Hz, 1 H), 4.21 (t, J = 6.8 Hz, 2 H), 4.02 (s, 3 H), 3.93 (s, 3 H), 1.72 - 1.64 (m, 2 H), 1.48 - 1.38 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.3, 153.5, 152.1, 139.2, 129.7, 122.9, 120.8, 116.4, 114.3, 107.9, 64.7, 61.8, 56.2, 30.7, 19.1, 13.7.

HRMS (ESI): calc. for $[(C_{16}H_{19}NO_4)Na]$ ($M+Na$) 312.1212, measured 312.1212.

Ethyl (*E*)-3-(2-cyano-4,5-dimethoxyphenyl)acrylate (4nb**).**



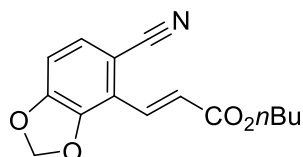
White solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 35 mg of **4nb** was isolated and yield is 29%. The reaction was done for 16 h at 120 °C.

1H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, J = 15.6 Hz, 1 H), 7.12 (s, 1 H), 7.08 (s, 1 H), 6.49 (d, J = 15.6 Hz, 1 H), 4.29 (q, J = 7.2 Hz, 2 H), 3.97 (s, 3 H), 3.94 (s, 3 H), 1.35 (t, J = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.1, 152.7, 150.5, 139.3, 131.7, 120.9, 117.4, 114.3, 108.3, 105.2, 60.9, 56.3, 56.2, 14.3.

HRMS (ESI): calc. for $[(C_{14}H_{15}NO_4)Na]$ ($M+Na$) 284.0899, measured 284.0896.

Butyl (*E*)-3-(5-cyanobenzo[*d*][1,3]dioxol-4-yl)acrylate (4oa**).**



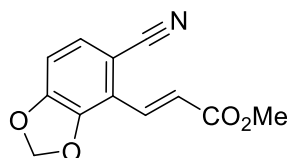
Colorless semisolid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 72 mg of **4oa** was isolated and yield is 52%. The reaction was done for 16 h at 120 °C.

1H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, J = 16.0 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 6.91 – 6.85 (m, 2 H), 6.20 (s, 2 H), 4.23 (t, J = 6.8 Hz, 2 H), 1.73 – 1.66 (m, 2 H), 1.48 – 1.39 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4, 151.5, 147.0, 134.8, 129.3, 125.7, 119.1, 117.2, 109.4, 105.8, 102.8, 64.8, 30.6, 19.1, 13.7.

HRMS (ESI): calc. for $[(C_{15}H_{15}NO_4)Na]$ ($M+Na$) 296.0899, measured 296.0900.

Methyl (*E*)-3-(5-cyanobenzo[*d*][1,3]dioxol-4-yl)acrylate (4og**).**



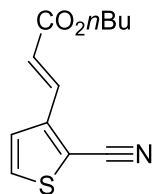
Colorless semisolid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 57 mg of **4og** was isolated and yield is 48%. The reaction was done for 16 h at 120 °C.

1H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, J = 16.0 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), 6.91 (d, J = 16.0 Hz, 1 H), 6.87 (d, J = 8.0 Hz, 1 H), 6.20 (s, 2 H), 3.83 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.7, 151.6, 147.1, 135.0, 129.3, 125.2, 118.9, 117.2, 109.5, 105.8, 102.8, 51.9.

HRMS (ESI): calc. for $[(\text{C}_{12}\text{H}_9\text{NO}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 254.0429, measured 254.0432.

Butyl (*E*)-3-(2-cyanothiophen-3-yl)acrylate (4pa).



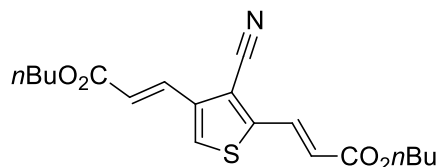
Brown oil; eluent (15% ethyl acetate in hexanes). The reaction scale is 75 mg, 86mg of **4pa** was isolated and yield is 53%. The reaction was done for 16 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 7.75 (d, J = 16.0 Hz, 1 H), 7.59 (d, J = 5.2 Hz, 1 H), 7.33 (d, J = 5.2 Hz, 1 H), 6.51 (d, J = 16.0 Hz, 1 H), 4.23 (t, J = 6.4 Hz, 2 H), 1.73 - 1.66 (m, 2 H), 1.48 - 1.39 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.1, 145.8, 133.7, 132.5, 125.7, 123.2, 113.0, 109.9, 64.9, 30.6, 19.1, 13.7.

HRMS (ESI): calc. for $[(\text{C}_{12}\text{H}_{13}\text{NO}_2\text{S})\text{Na}]$ ($\text{M}+\text{Na}$) 258.0565, measured 258.0565.

Dibutyl 3,3'-(3-cyanothiophene-2,4-diyl)(2*E*,2'*E*)-diacrylate (5qa).



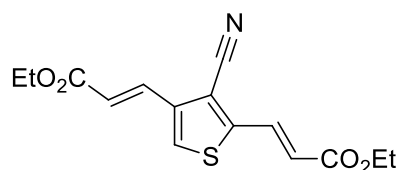
Off-white solid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg, 141 mg of **5qa** was isolated and yield is 57%. The reaction was done for 16 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 7.88 (d, J = 15.8 Hz, 1 H), 7.61 (d, J = 16.2 Hz, 1 H), 7.57 (s, 1 H), 6.66 (d, J = 16.2 Hz, 1 H), 6.50 (d, J = 15.8 Hz, 1 H), 4.25 - 4.19 (m, 4 H), 1.73 - 1.65 (m, 4 H), 1.47 - 1.38 (m, 4 H), 0.98 - 0.94 (m, 6 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.2, 165.3, 149.6, 138.2, 133.7, 132.3, 127.9, 123.1, 121.8, 113.4, 110.9, 65.1, 64.9, 30.61, 30.58, 19.1, 13.7.

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{23}\text{NO}_4\text{S})\text{H}]$ ($\text{M}+\text{H}$) 362.1426, measured 362.1429.

Dimethyl 3,3'-(3-cyanothiophene-2,4-diyl)(2*E*,2'*E*)-diacrylate (5qb).



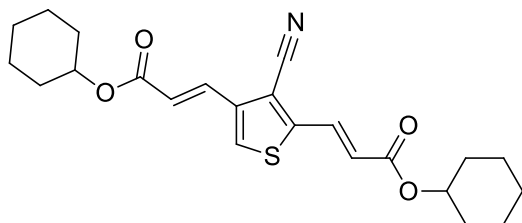
Off-white solid; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg, 136 mg of **5qb** was isolated and yield is 65%. The reaction was done for 16 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 8.43 (s, 1 H), 7.68 (d, *J* = 16.0 Hz, 1 H), 7.53 (d, *J* = 16.0 Hz, 1 H), 6.71 (d, *J* = 16.0 Hz, 1 H), 6.64 (d, *J* = 16.0 Hz, 1 H), 4.24 - 4.17 (m, 4 H), 1.28 - 1.24 (m, 6 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 165.6, 165.0, 148.8, 136.8, 134.0, 132.10, 132.07, 122.5, 120.7, 113.8, 110.2, 60.9, 60.5, 14.13, 14.10.

HRMS (ESI): calc. for [(C₁₅H₁₅NO₄S)H] (M+H) 306.0800, measured 306.0799.

Dicyclohexyl 3,3'-(3-cyanothiophene-2,4-diyl)(2*E*,2'*E*)-diacrylate (5qc**).**



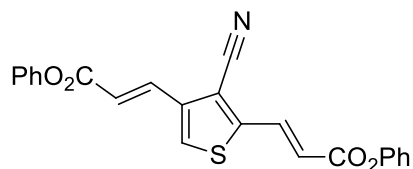
Colorless solid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg, 136 mg of **5qc** was isolated and yield is 48%. The reaction was done for 16 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.87 (d, *J* = 15.6 Hz, 1 H), 7.60 (d, *J* = 16.0 Hz, 1 H), 7.55 (s, 1 H), 6.65 (d, *J* = 16.0 Hz, 1 H), 6.50 (d, *J* = 15.6 Hz, 1 H), 4.94 - 4.84 (m, 2 H), 1.97 - 1.90 (m, 4 H), 1.78 - 1.72 (m, 4 H), 1.59 - 1.51 (m, 4 H), 1.48 - 1.41 (m, 4 H), 1.39 - 1.27 (m, 4 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.6, 164.7, 149.8, 138.3, 133.5, 132.1, 127.7, 123.7, 122.3, 113.4, 110.8, 73.8, 73.4, 31.6, 25.3, 23.8.

HRMS (ESI): calc. for [(C₂₃H₂₇NO₄S)H] (M+H) 414.1739, measured 414.1740.

Diphenyl 3,3'-(3-cyanothiophene-2,4-diyl)(2*E*,2'*E*)-diacrylate (5qd**).**



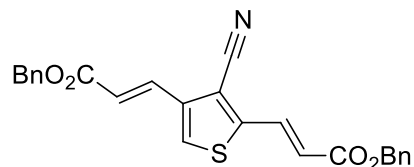
Pale yellow solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 135 mg of **5qd** was isolated and yield is 49%. The reaction was done for 16 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.09 (d, *J* = 16.0 Hz, 1 H), 7.81 (d, *J* = 16.0 Hz, 1 H), 7.69 (s, 1 H), 7.44 - 7.39 (m, 4 H), 7.29 - 7.24 (m, 2 H), 7.18 - 7.16 (m, 4 H), 6.90 (d, *J* = 16.0 Hz, 1 H), 6.73 (d, *J* = 16.0 Hz, 1 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 164.5, 163.6, 150.6, 150.4, 149.3, 138.1, 135.4, 133.9, 129.5, 129.5, 129.2, 126.1, 125.9, 122.3, 121.4, 121.4, 121.1, 113.3, 111.4.

HRMS (ESI): calc. for $[(\text{C}_{23}\text{H}_{15}\text{NO}_4\text{S})\text{Na}]$ ($\text{M}+\text{Na}$) 424.0619, measured 424.0627.

Dibenzyl 3,3'-(3-cyanothiophene-2,4-diyl)(2*E*,2'*E*)-diacrylate (5qe).



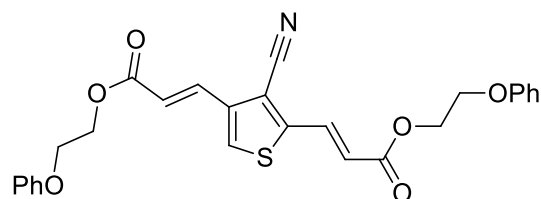
Greenish color solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 139 mg of **5qe** was isolated and yield is 47%. The reaction was done for 16 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 7.93 (d, J = 16.0 Hz, 1 H), 7.66 (d, J = 16.4 Hz, 1 H), 7.56 (s, 1 H), 7.43 – 7.34 (m, 10 H), 6.71 (d, J = 16.4 Hz, 1 H), 6.55 (d, J = 16.0 Hz, 1 H), 5.28 (s, 2 H), 5.26 (s, 2 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 165.9, 165.0, 149.5, 138.2, 135.7, 135.4, 134.3, 132.8, 128.7, 128.6, 128.5, 128.4, 128.4, 128.1, 122.8, 121.5, 113.3, 111.1, 67.0, 66.8.

HRMS (ESI): calc. for $[(\text{C}_{25}\text{H}_{19}\text{NO}_4\text{S})\text{Na}]$ ($\text{M}+\text{Na}$) 452.0932, measured 452.0942.

Bis(2-phenoxyethyl) 3,3'-(3-cyanothiophene-2,4-diyl)(2*E*,2'*E*)-diacrylate (5qf).



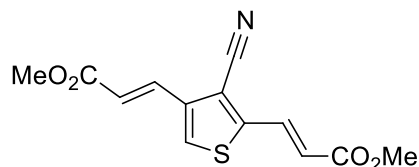
Light yellow solid; eluent (40% ethyl acetate in hexanes). The reaction scale is 75 mg, 151 mg of **5qf** was isolated and yield is 45%. The reaction was done for 16 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 7.93 (d, J = 16.0 Hz, 1 H), 7.66 (d, J = 16.4 Hz, 1 H), 7.58 (s, 1 H), 7.33 – 7.29 (m, 4 H), 7.00 – 6.93 (m, 6 H), 6.71 (d, J = 16.4 Hz, 1 H), 6.56 (d, J = 16.0 Hz, 1 H), 4.61 – 4.57 (m, 4 H), 4.27 – 4.25 (m, 4 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 165.9, 165.1, 158.4, 158.37, 149.38, 138.2, 134.4, 132.9, 129.5, 129.5, 128.3, 122.5, 121.3, 121.2, 114.7, 114.7, 113.3, 111.2, 65.8, 65.7, 63.6, 63.3.

HRMS (ESI): calc. for $[(\text{C}_{27}\text{H}_{23}\text{NO}_6\text{S})\text{Na}]$ ($\text{M}+\text{Na}$) 512.1144, measured 512.1149.

Dimethyl 3,3'-(3-cyanothiophene-2,4-diyl)(2*E*,2'*E*)-diacrylate (5qg).



Off-white solid; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg, 131 mg of **5qg** was isolated and yield is 69%. The reaction was done for 16 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 8.44 (s, 1 H), 7.69 (d, *J* = 15.6 Hz, 1 H), 7.54 (d, *J* = 16.4 Hz, 1 H), 6.75 - 6.65 (m, 2 H), 3.76 (s, 3 H), 3.74 (s, 3 H).

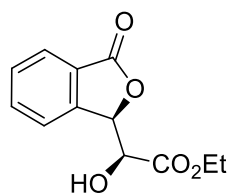
¹³C NMR (DMSO-*d*₆, 100 MHz): δ 166.1, 165.5, 148.7, 136.7, 134.2, 132.2, 122.2, 120.4, 113.8, 110.3, 52.1, 51.9.

HRMS (ESI): calc. for [(C₁₃H₁₁NO₄S)Na] (*M*+Na) 300.0306, measured 300.0305.

Procedure for the Preparation of Compound **6**.¹

A 50 mL RB flask was charged with K₃Fe(CN)₆ (0.988 g, 3 mmol), K₂CO₃ (0.414 g, 3 mmol), *tert*-BuOH (2.5 mL), THF (2.5 mL) and H₂O (5 mL) and stirred for 10 min. Subsequently, (DHQD)₂PHAL (0.008 g, 1 mol%) and K₂OsO₄·2H₂O (0.002 g, 0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, **4ab** (1 mmol) was added and allowed to stir for 7 h at 25 °C. After completion of reaction (as monitored by TLC), sodium bisulphite (1.0 g) was added slowly at 0 °C. The organic layer was separated, aqueous layer extracted with ethyl acetate (3 × 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield the crude product. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **6**.

Ethyl (S)-2-hydroxy-2-((R)-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (**6**).¹



Colorless solid; eluent (75% ethyl acetate in hexanes). The reaction scale is 201 mg, 219 mg of **6** was isolated and yield is 93%. The reaction was done for 7 h at 25 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.50 – 7.44 (m, 2 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 5.78 (d, *J* = 2.08 Hz, 1 H), 4.63 (d, *J* = 2.08 Hz, 1 H), 4.29 (d, *J* = 7.2 Hz, 2 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

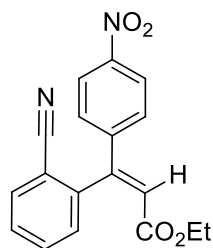
^{13}C NMR (CDCl_3 , 100 MHz): δ 171.4, 167.9, 143.2, 132.1, 129.5, 128.9, 123.9, 121.4, 83.9, 71.9, 62.0, 14.1.

HRMS (ESI): calc. for $[(\text{C}_{12}\text{H}_{12}\text{O}_5)\text{Na}]$ ($\text{M}+\text{Na}$) 259.0582, measured 259.0583.

Procedure for the Preparation of Compound 8a-b.^{2,3}

$\text{Pd}(\text{OAc})_2$ (0.0327 mmol, 10 mol%) and silver(I) oxide (0.3275 mmol, 1.0 equiv) were taken in a 15-mL pressure tube equipped with a magnetic stirrer and septum. The tube was evacuated and purged with nitrogen gas three times. To the tube were then added trifluoroacetic acid (2.0 mL), **4** (75 mg, 0.3275 mmol) and aryl iodide **7** (0.655 mmol). Again the tube was evacuated and purged with nitrogen gas three times and the reaction mixture was stirred at 110 °C for 12 h. The mixture was filtered through a short Celite pad and washed with dichloromethane several times. The filtrate was concentrated by vacuum and separated on a silica gel column using hexane/EtOAc as eluent to give the corresponding pure biphenyl-2-carbonitrile derivatives **8a-b**.

Ethyl (Z)-3-(2-cyanophenyl)-3-(4-nitrophenyl)acrylate (**8a**).



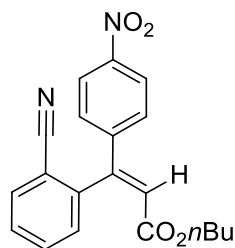
Yellow solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 98 mg of **8a** was isolated and yield is 82%. The reaction was done for 12 h at 110 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 8.20 (d, J = 8.8 Hz, 2 H), 7.77 (d, J = 7.6 Hz, 1 H), 7.69 (d, J = 7.6 Hz, 1 H), 7.55 (d, J = 7.6 Hz, 1 H), 7.46 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 7.6 Hz, 1 H), 6.69 (s, 1 H), 4.10 (q, J = 7.2 Hz, 2 H), 1.16 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 164.3, 149.9, 148.3, 144.5, 141.7, 132.8, 132.7, 129.4, 128.8, 128.5, 123.9, 123.2, 117.1, 112.3, 60.8, 13.9.

HRMS (ESI): calc. for $[(\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_4)\text{Na}]$ ($\text{M}+\text{Na}$) 345.0851, measured 345.0846.

Butyl (Z)-3-(2-cyanophenyl)-3-(4-nitrophenyl)acrylate (**8b**).



Yellow oil; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 100 mg of **8b** was isolated and yield is 87%. The reaction was done for 12 h at 110 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.21 (d, *J* = 8.8 Hz, 2 H), 7.77 (d, *J* = 7.6 Hz, 1 H), 7.69 (d, *J* = 7.6 Hz, 1 H), 7.55 (d, *J* = 7.6 Hz, 1 H), 7.46 (d, *J* = 8.8 Hz, 2 H), 7.32 (d, *J* = 7.6 Hz, 1 H), 6.69 (s, 1 H), 4.04 (t, *J* = 6.8 Hz, 2 H), 1.54 - 1.47 (m, 2 H), 1.33 - 1.24 (m, 2 H), 0.89 (t, *J* = 7.2 Hz, 3 H).

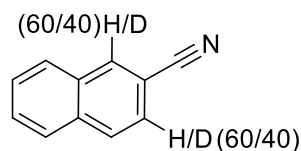
¹³C NMR (CDCl₃, 100 MHz): δ 164.5, 149.9, 148.3, 144.5, 141.7, 132.9, 132.7, 129.4, 128.8, 128.6, 123.9, 123.3, 117.2, 112.4, 64.9, 30.3, 18.9, 13.6.

HRMS (ESI): calc. for [(C₂₀H₁₈N₂O₄)Na] (M+Na) 373.1164, measured 373.1161.

Procedure for the preparation of 2-Naphthonitrile (**D-1b**).

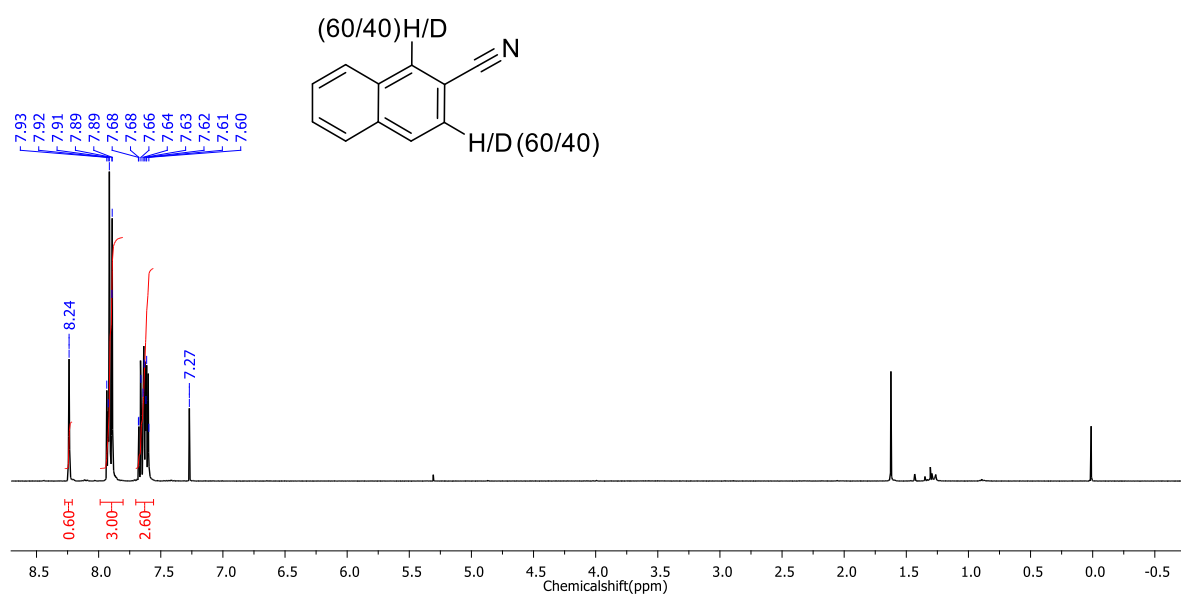
Substituted nitrile **1b** (75 mg, 1.0 equiv), [{RuCl₂(*p*-cymene)}₂] (5 mol %), AgOAc (2.0 equiv), AgSbF₆ (20 mol %) were taken in a 15-mL pressure tube equipped with a magnetic stirrer and septum. (Note: AgSbF₆ and AgOAc are moisture sensitive. Thus, AgSbF₆ and AgOAc were taken inside the nitrogen glove box). The tube was evacuated and purged with nitrogen gas three times. To the tube were then added CD₃COOD (0.4 mL) and DCE (3.0 mL) via syringes, allowed the reaction mixture to stir at room temperature for few seconds and again the tube was evacuated and purged with nitrogen gas three times. Then, the septum was taken out and immediately a screw cap was used to cover the tube. Then, the reaction mixture was allowed to stir at 120 °C for 14 h. After cooling to ambient temperature, the reaction mixture was diluted with CH₂Cl₂, filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **D-1b**.

2-Naphthonitrile (**D-1b**).



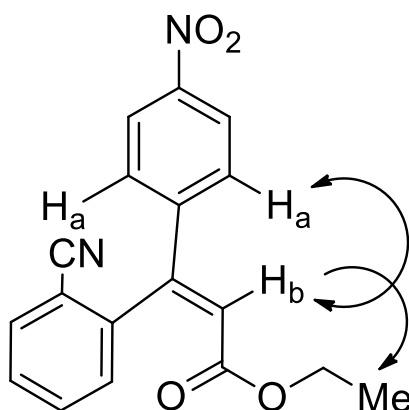
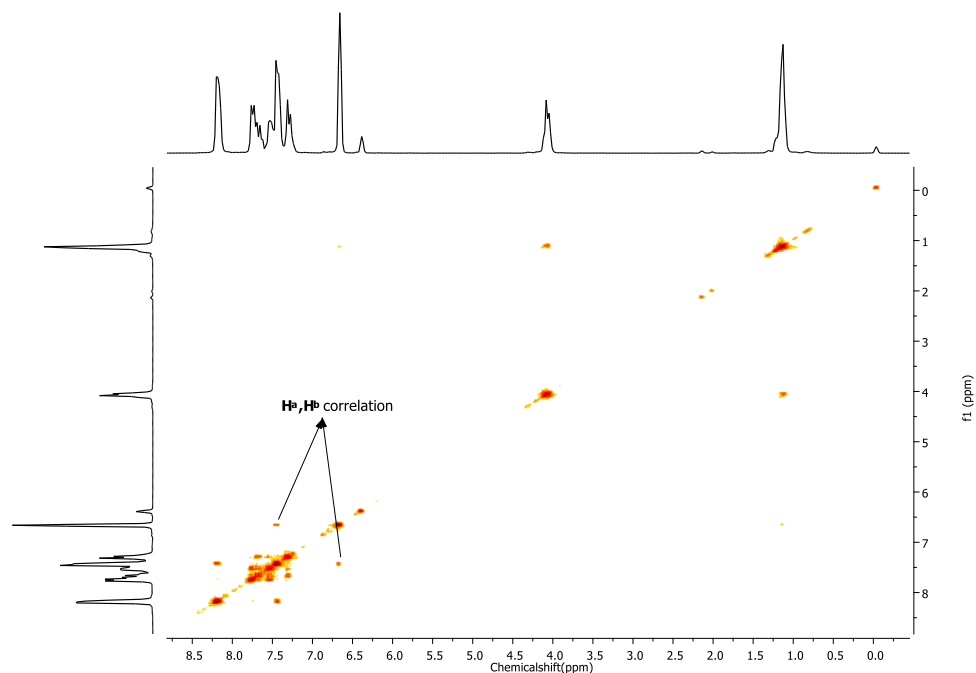
Colorless solid; eluent (10% ethyl acetate in hexanes). The reaction scale is 75 mg, 70 mg of **D-1b** was isolated. The reaction was done for 16 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.24 (s, 0.6 H), 7.93 – 7.89 (m, 3 H), 7.68 – 7.60 (m, 2.6 H).

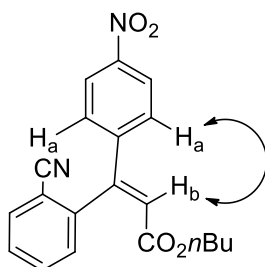
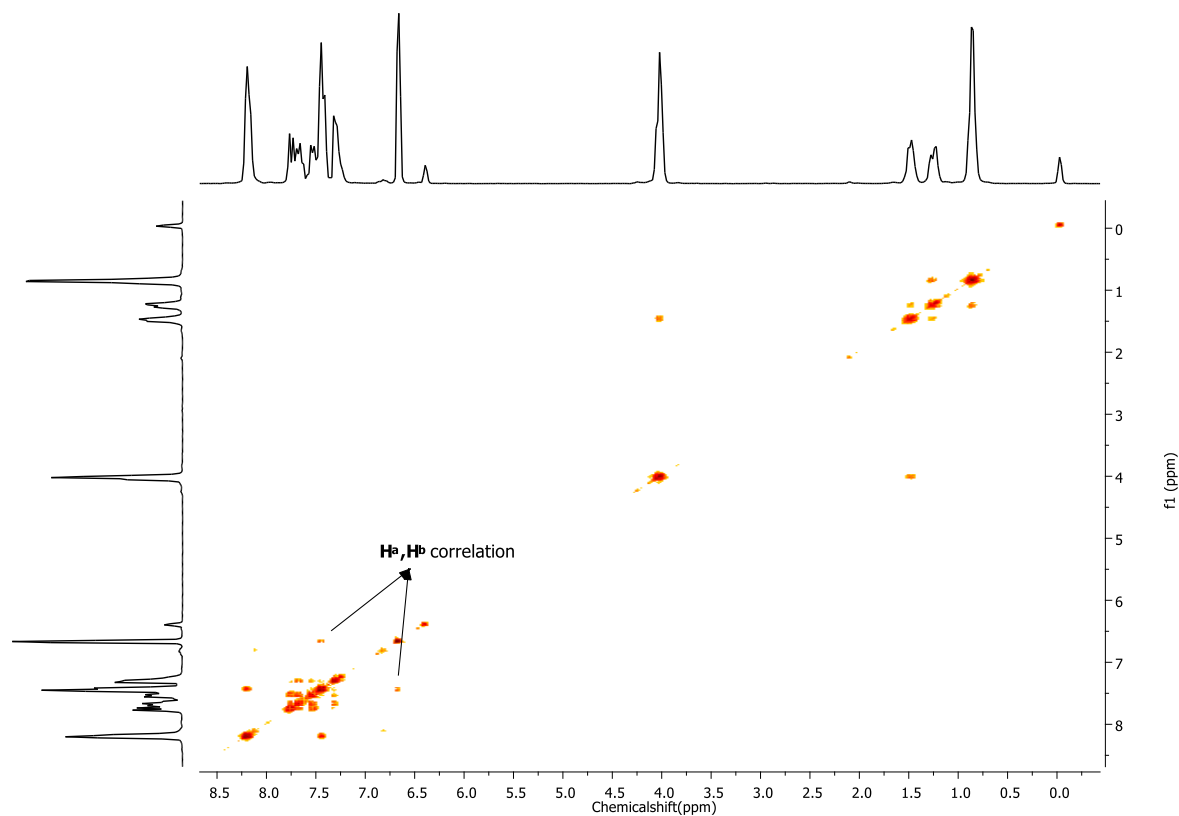


3A.13: Stereo-Selective Studies: NOESY Experiments

Copy of NOESY Experiment of Compound **8a**.



There is a NOE correlation between H_a (δ 7.46, d) and H_b (δ 6.69, s). There is also a weak signal between H_b and methyl group of ester moiety (δ 1.16, t). But, there is no signal between H_a and ethyl ester group. This clearly indicates that the stereochemistry of compound **8a** is correct.

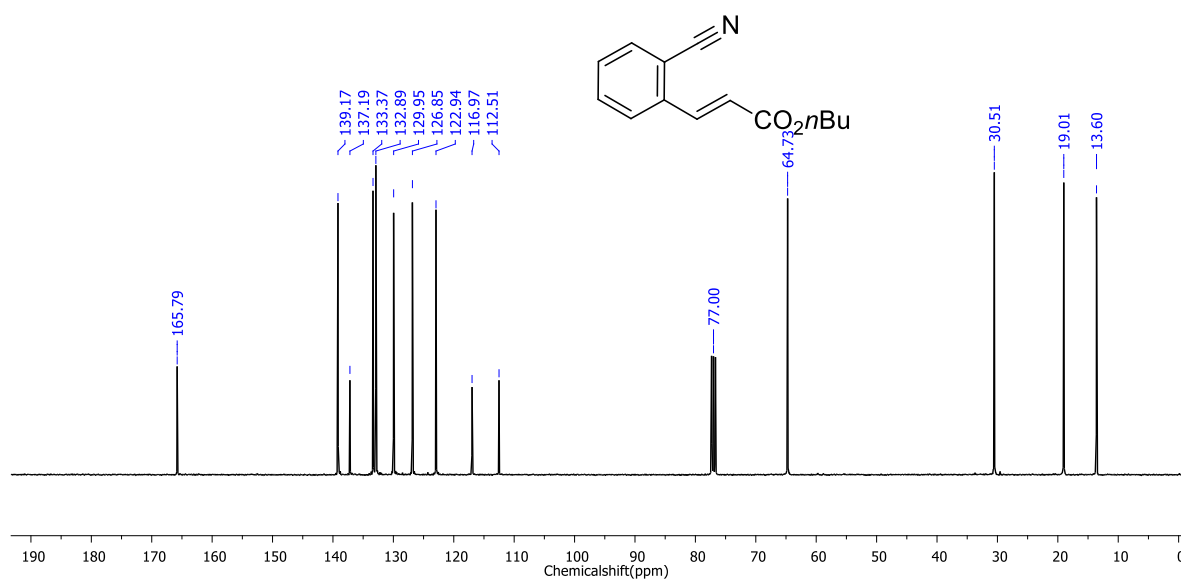
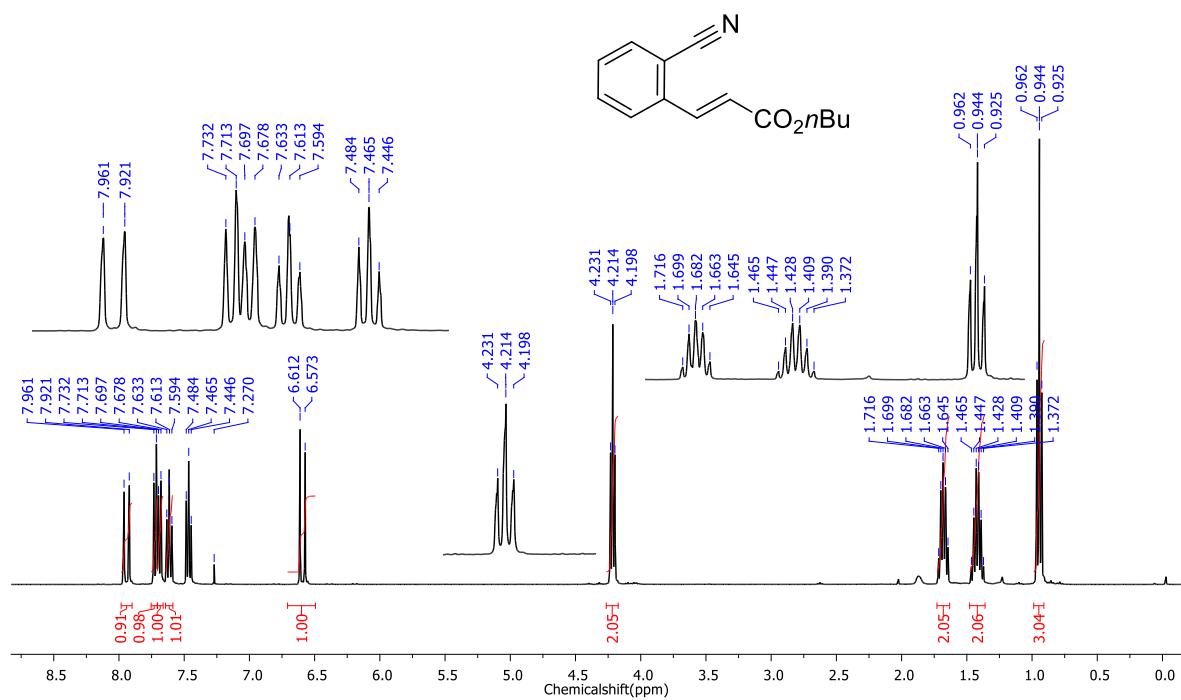
Copy of NOESY Experiment of Compound **8b**.

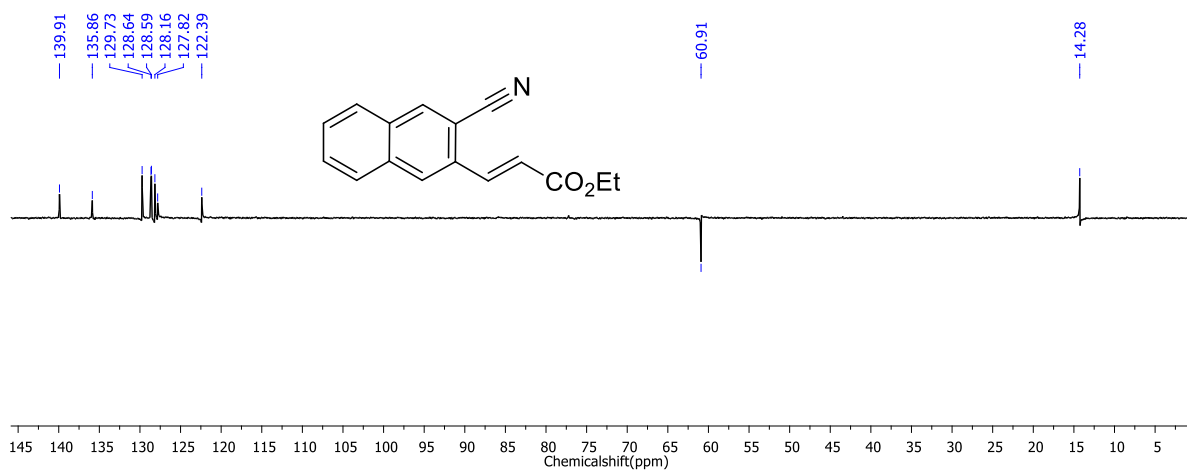
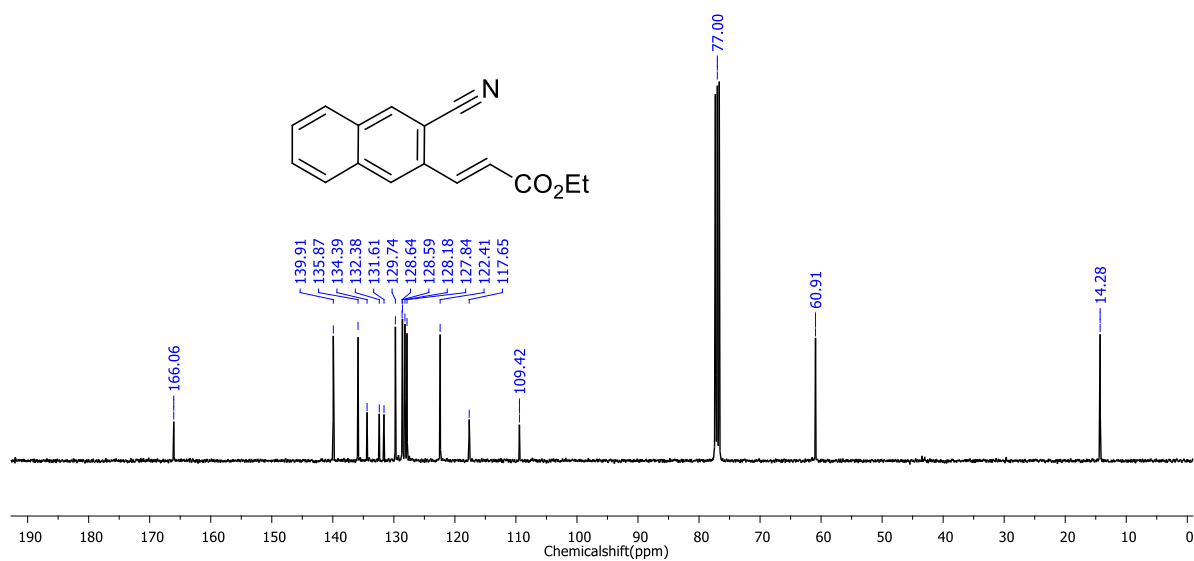
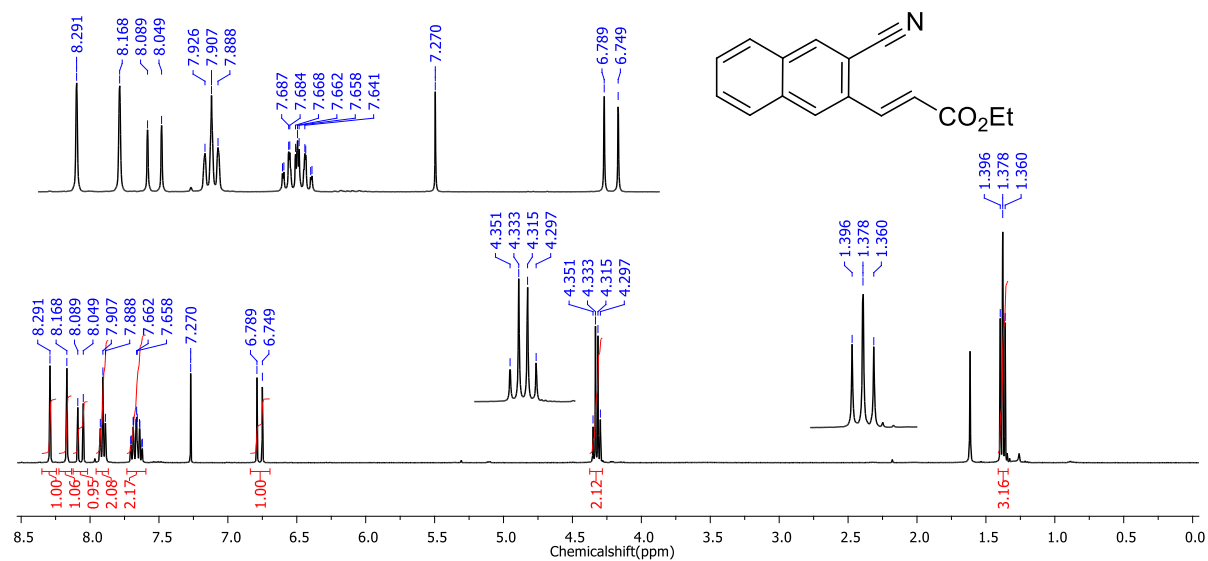
There is a NOE correlation between H_a (δ 6.69, s) and H_b (δ 7.46, d). This clearly indicates that the stereochemistry of compound **8b** is correct.

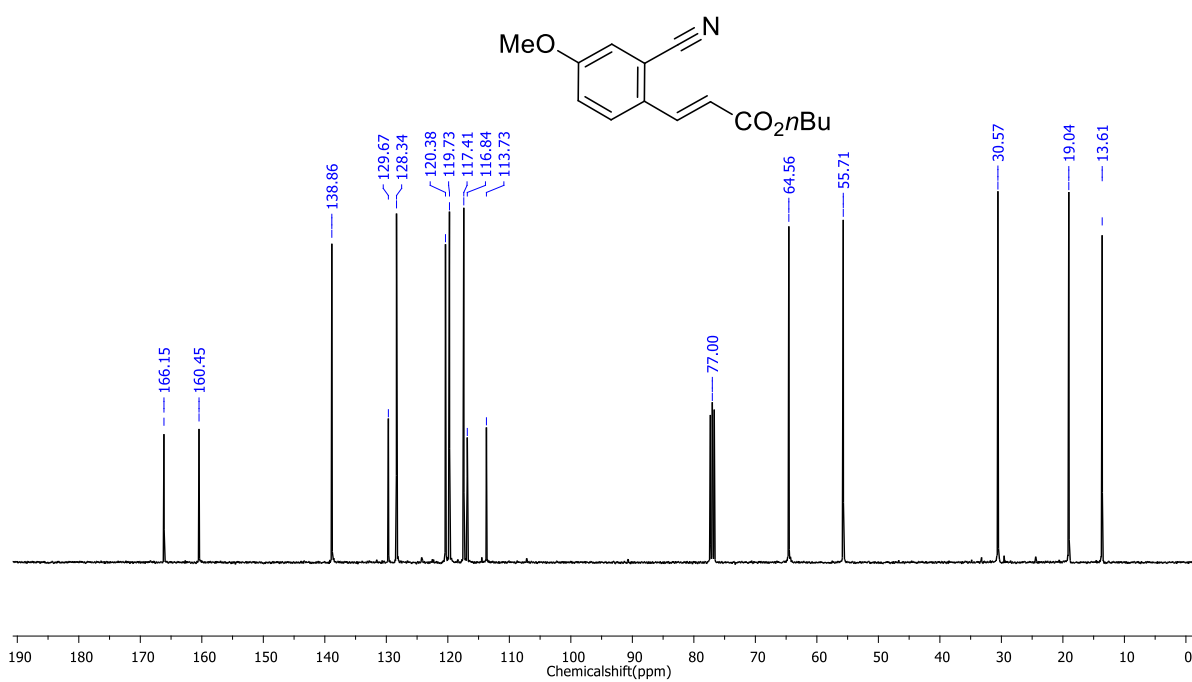
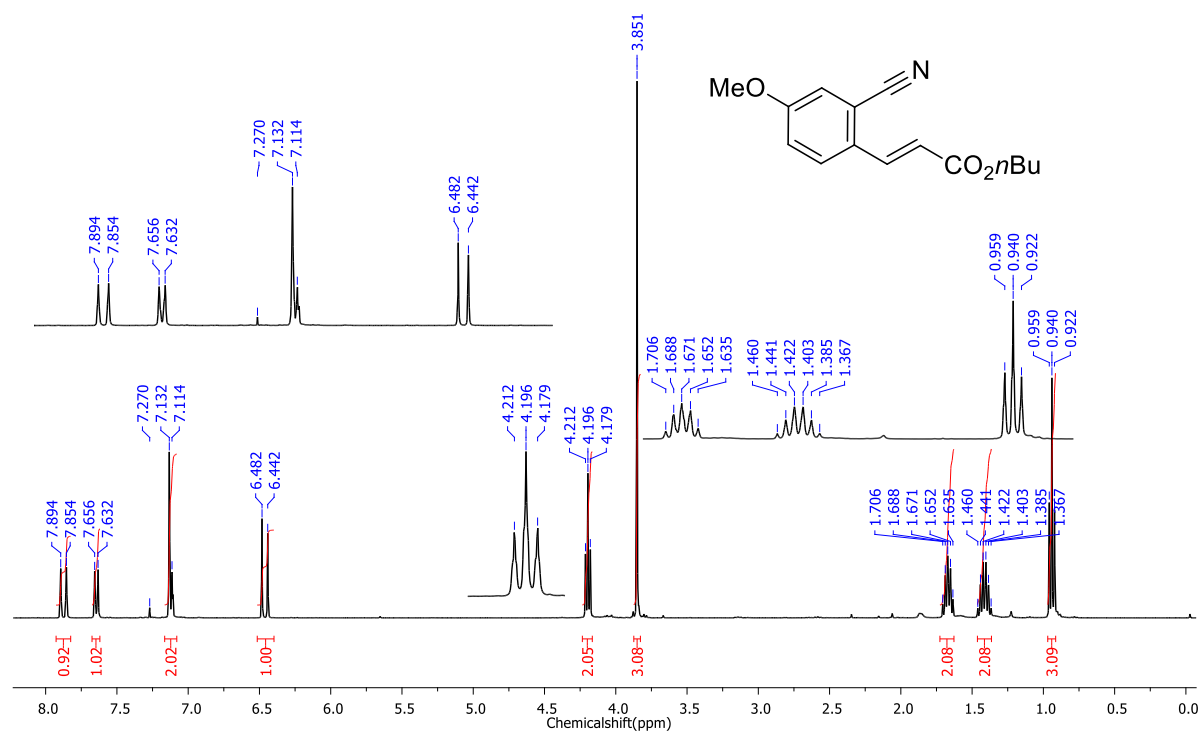
References

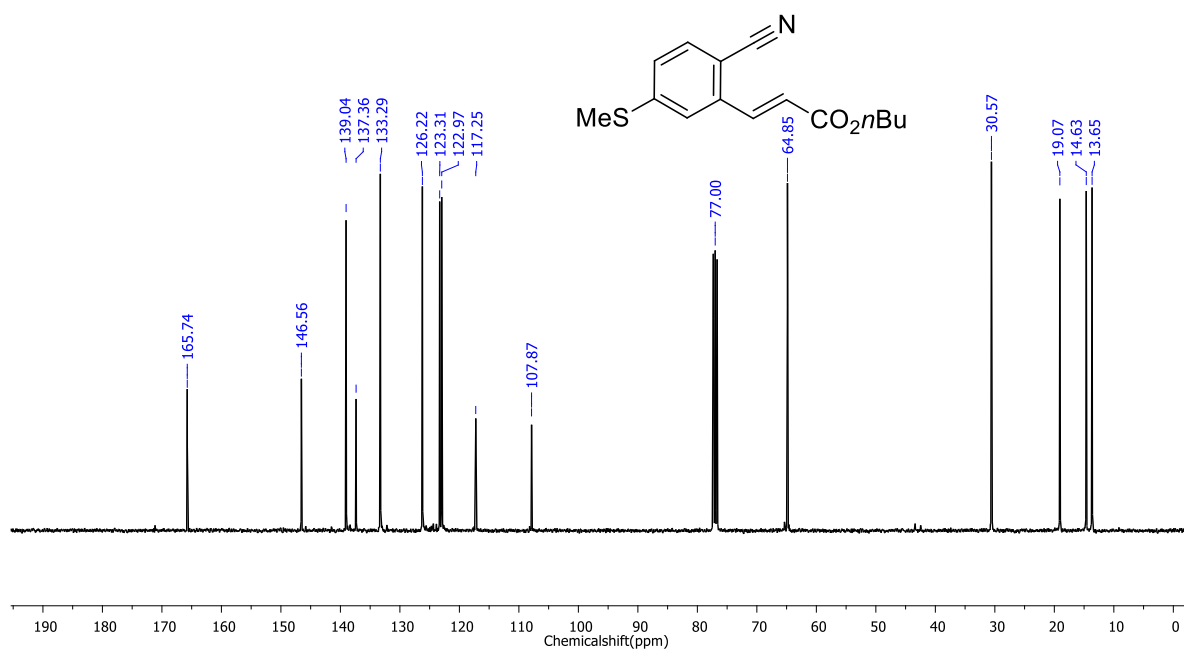
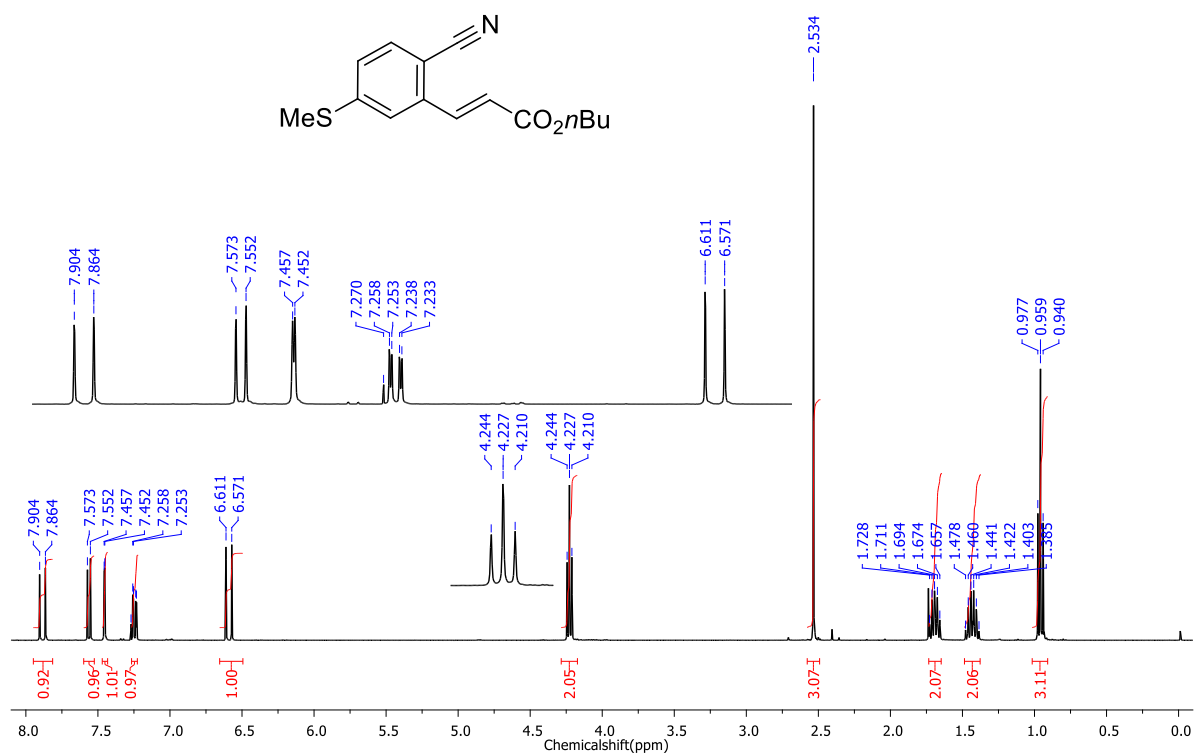
- (1) Reddy, R. S.; Kiran, I. N. C.; Sudalai, A. *Org. Biomol.Chem.* **2012**, *10*, 3655
- (2) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Synlett.* **2002**, *3*, 439.
- (3) Li, W.; Xu, Z.; Sun, P.; Jiang, X.; Fang, M. *Org. Lett.* **2011**, *13*, 1286.

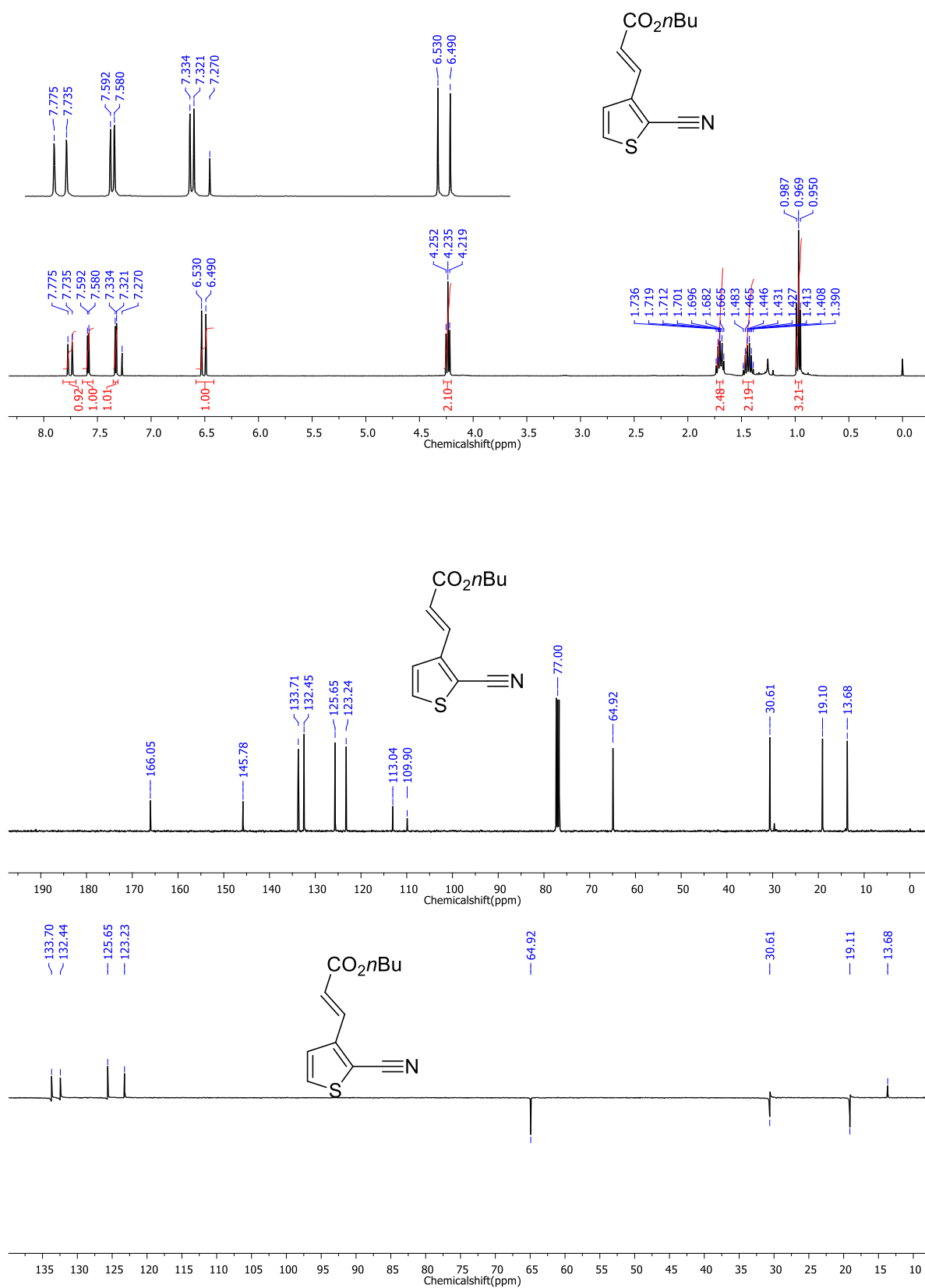
3A.14: Spectral Copies of Selected Compounds

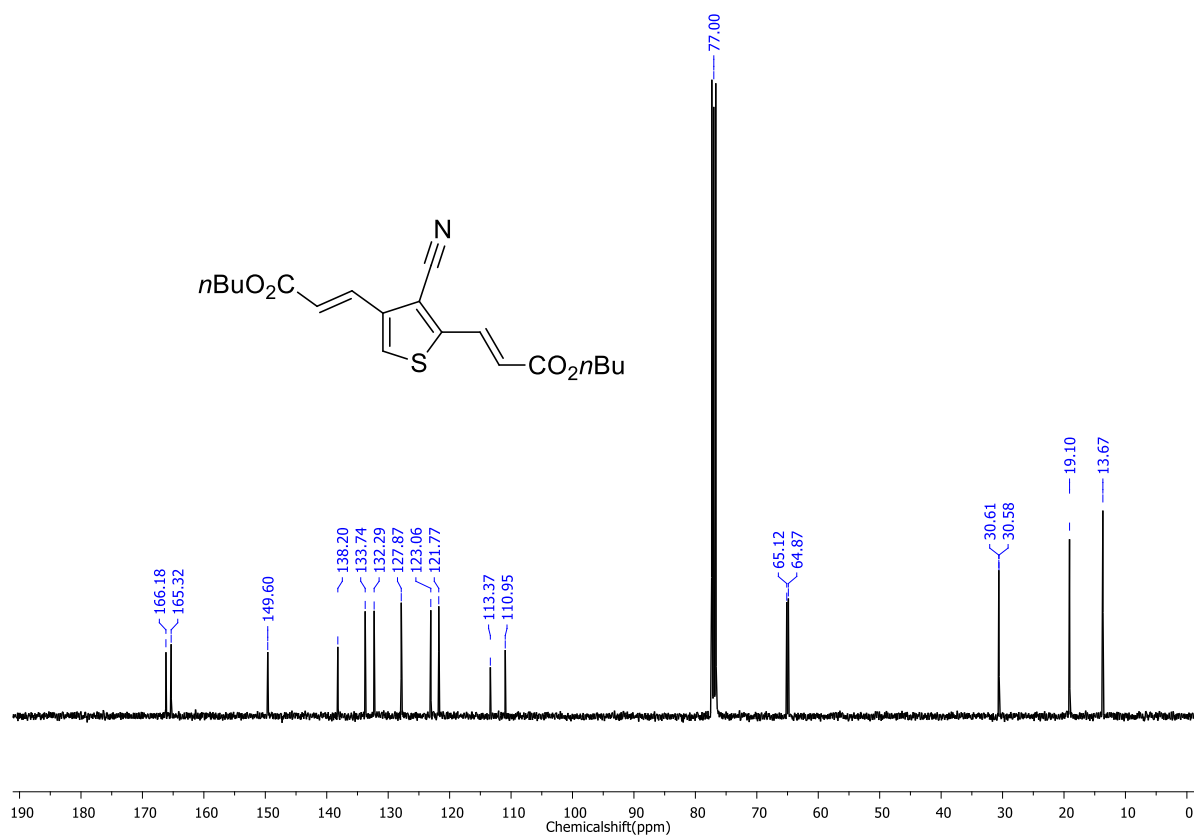
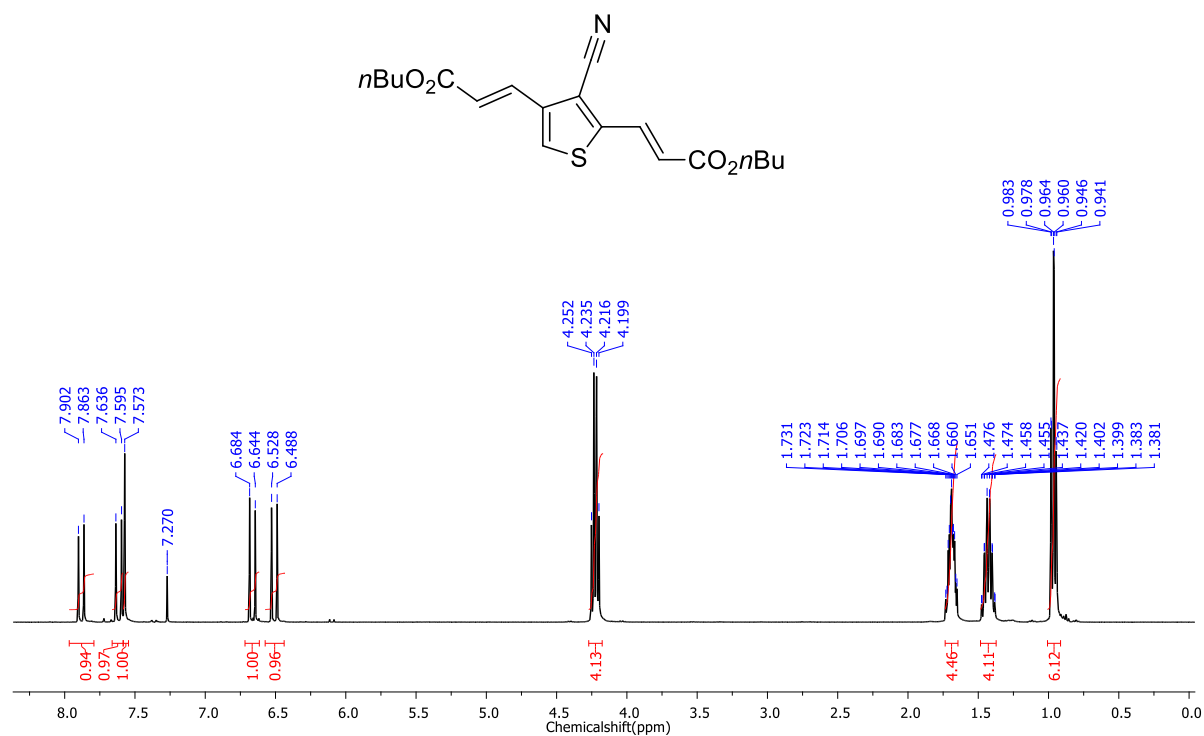
 ^1H and ^{13}C NMR Spectra of Compound 4aa.

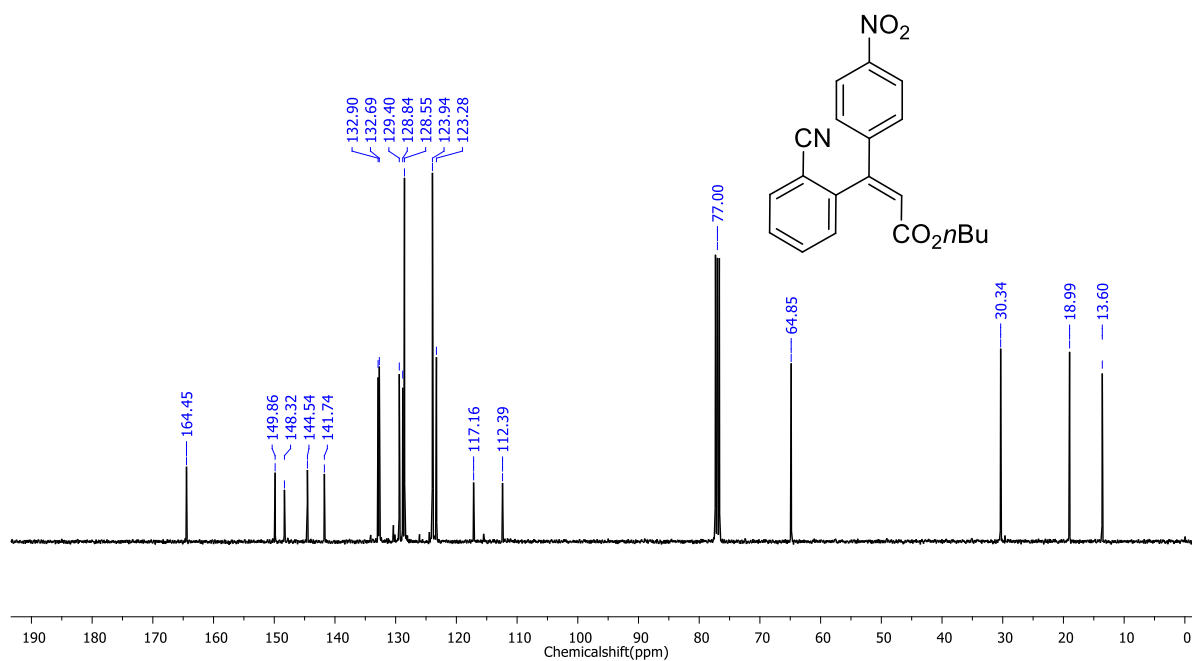
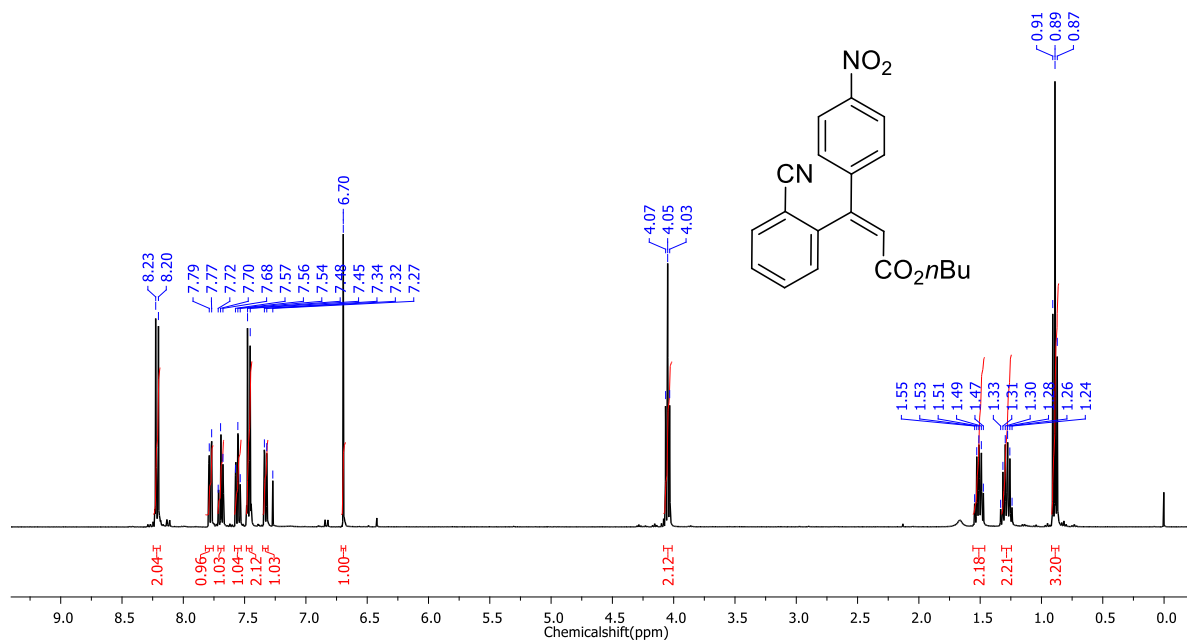
^1H and ^{13}C NMR Spectra of Compound **4bb**.

^1H and ^{13}C NMR Spectra of Compound **4ja**.

^1H and ^{13}C NMR Spectra of Compound **41a**.

^1H and ^{13}C NMR Spectra of Compound **4pa**.

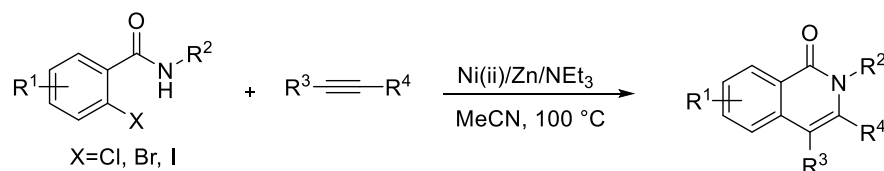
^1H and ^{13}C NMR Spectra of Compound **5qa**.

^1H and ^{13}C NMR Spectra of Compound **8b**.

Section 3B: Ruthenium-Catalyzed Aerobic Oxidative Cyclization of Aromatic and Heteroaromatic Nitriles With Alkynes: A New Route to Isoquinolones

3B.1: Introduction

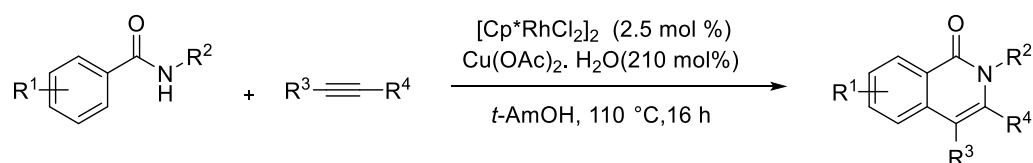
Substituted isoquinolone is one of the important classes of heterocyclic compounds. This core is present in various natural products and biologically active molecules.¹ Due to its interesting biological properties, the development of a highly efficient and easily accessible method to synthesize isoquinolone derivatives is highly important in organic synthesis. In 2010, Cheng's group reported nickel-catalyzed annulation of substituted 2-halobenzamides with alkynes providing isoquinolone derivatives (Scheme 3B.1).²



Scheme 3B.1: Ni(ii) catalyzed annulation of substituted 2-halo benzamides with alkynes

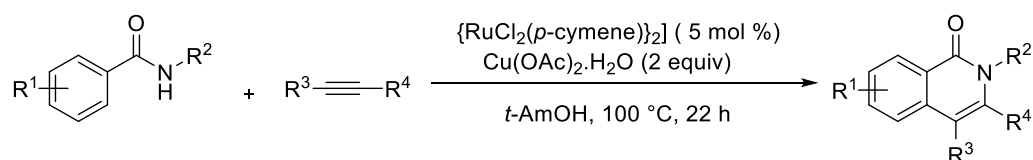
Several methods to synthesise isoquinolone derivatives are available in the literature.² Among them, metal-catalyzed oxidative cyclization of heteroatom substituted aromatics with alkynes via chelation-assisted C-H bond activation is one of the promising and practical methods.³ Rhodium and ruthenium complexes have been widely used as catalysts for this type of cyclization reaction. Oxidative cyclization of *N*-alkyl or aryl substituted benzamides (Ph-CONHR) with alkynes in the presence of rhodium- or ruthenium catalysts and a stoichiometric amount of external oxidants gave *N*-alkyl or aryl substituted isoquinolone derivatives.⁴

In 2010, Rovis and coworkers reported the oxidative cycloaddition of benzamides and alkynes in the presence of Rh(III) catalyst affording isoquinolone derivatives (Scheme 3B.2).^{4b}



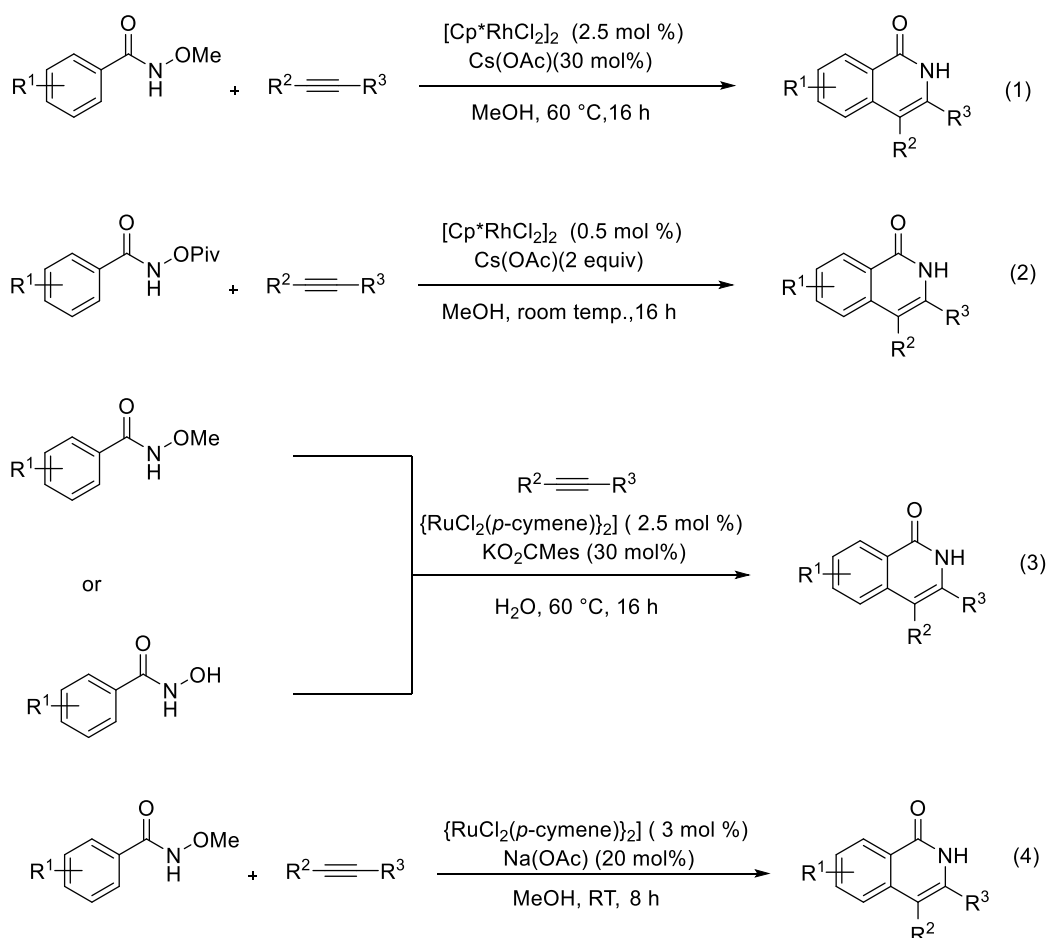
Scheme 3B.2: Rh(III) catalyzed oxidative cycloaddition of benzamides and alkynes

In 2011, Ru(II) catalyzed the oxidative cycloaddition of benzamides and alkynes affording isoquinolone derivatives was described by Ackermann's group.^{4d}



Scheme 3B.3: Ru(II) catalyzed annulation of benzamides with alkynes

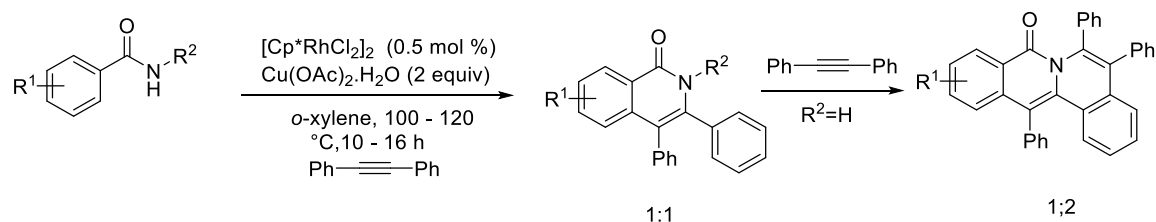
In 2010, Keith Fagnou demonstrated annulation of *N*-Methoxy benzamides (Ph-CONHOMe) with alkynes in the presence of rhodium catalyst to provide isoquinolone derivatives (eq.1).^{5a} In this reaction, the *N*-methoxy moiety acted as an internal oxidant. Later, the same group developed mild conditions for this reaction (eq.2).^{5b} In this reaction, *N*-OPiv benzamide reacted with alkyne in the presence of Rhodium catalyst affording isoquinolone derivatives at room temperature (eq.3). The reaction was explored by using less expensive Ru(II) catalyst by L.Ackermann and B.wang groups (eq.3 and eq.4). Ackermann's group showed the usage of green solvent H₂O for this reaction.^{5c} And B.wang's group developed this reaction at room temperature.^{5d}



Scheme 3B.4: Isoquinolinone synthesis from N-OR benzamides

But, in the cyclization of benzamides (Ph-CONH₂) with alkynes, only 1:2 oxidative cyclization products (one benzamide and two alkynes) were observed, and the expected

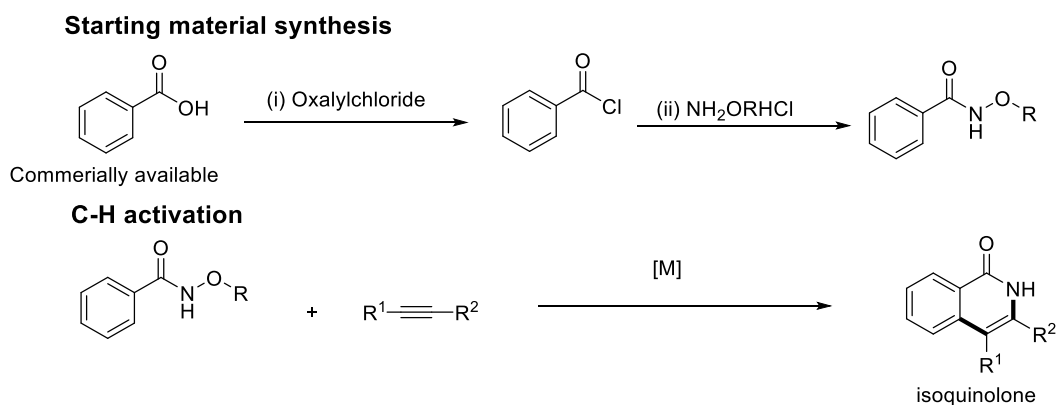
isoquinolone derivatives were not observed (Scheme 3B.5).^{4a, 6} In order to attain the isoquinolone derivatives selectively and to avoid the competitive 1:2 cyclization product, *N*-alkyl or aryl or alkoxy substituted benzamides were used.



Scheme 3B.5: Primary benzamides with alkynes

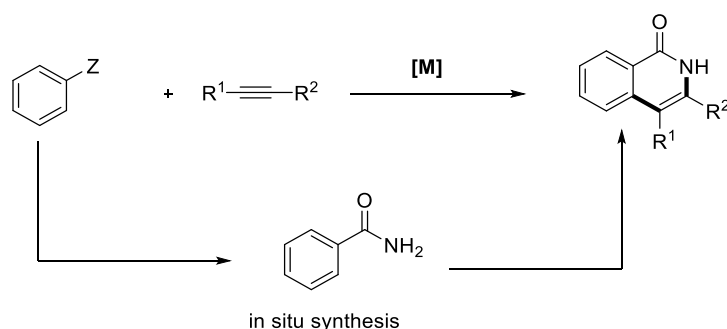
3B.2: Aim of The Present Work

N-OR substituted benzamides have been used for the synthesis of *N*-H free isoquinoline. Generally, these benzamides are not commercially available. In this reaction, directing group synthesis is required from commercially available starting material benzoic acid (Scheme 3B.6).



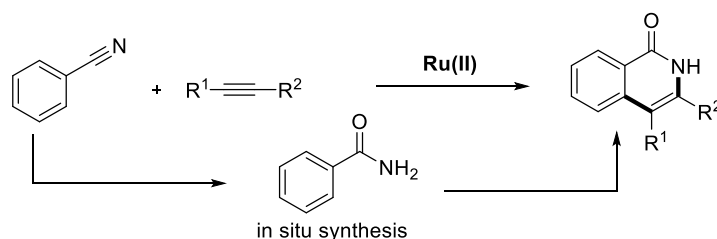
Scheme 3B.6: General methods for isoquinolone synthesis involving with starting material synthesis

In spite of these methods, the development of a method involving with in situ generation of directing group from simple and commercially available compounds would be very interesting and attractive synthetic method (Scheme 3B.7). This method can reduce the number of steps and further avoid column purification or work up.



Scheme 3B.7: Insitu synthesis of directing group

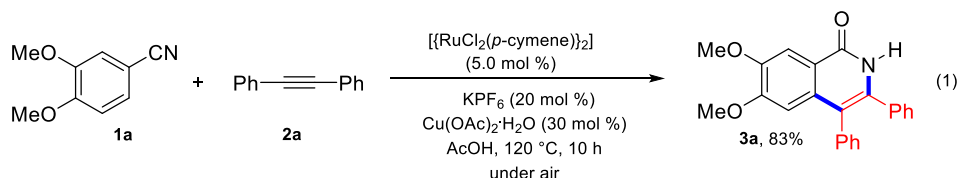
We have mainly focused on in situ generation of directing group followed by C-H activation in the same pot. Optimising solvent, temperature and other the reaction conditions to do two entirely different kind of reactions in the same pot is quite difficult and really challenging task. For this, we have chosen simple and commercially available benzonitrile as starting material. Then we have started functional group conversion of benzonitrile into benzamide followed by C-H activation in the same pot.



Scheme 3B.8: Insitu generation of directing group followed by C-H bond functionalization

3B.3: Results and Discussion

When 3,4-dimethoxybenzonitrile (**1a**) was treated with diphenylacetylene (**2a**) in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (5.0 mol %), KPF_6 (20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (30 mol %) in acetic acid at 120 °C for 10 h under an air atmosphere, isoquinolone derivative **3a** was observed in 83% isolated yield (Table 3B.1). The cyclization reaction was completely regioselective, in which a less hindered C-H bond of **1a** was involved in the cyclization reaction with **2a**.



3B.4: Optimization Studies

Table 3B.1: Optimization Studies with Various Solvents, Oxidants and Additives.^a

entry	solvent	oxidant	additive	yield of 3a (%) ^b
1	AcOH	No	No	NR
2	AcOH	Cu(OAc) ₂ ·H ₂ O (2.20 equiv)	No	65
3	AcOH	Cu(OAc) ₂ ·H ₂ O (2.20 equiv)	AgSbF ₆	83
4	AcOH	Cu(OAc) ₂ ·H ₂ O (2.20 equiv)	KPF ₆	89
5	AcOH	Cu(OAc) ₂ ·H ₂ O (2.20 equiv)	AgBF ₄	72
6	AcOH	Cu(OAc) ₂ ·H ₂ O (2.20 equiv)	AgOTf	75
7	MeOH	Cu(OAc) ₂ ·H ₂ O (2.20 equiv)	KPF ₆	10
8	<i>tert</i> -BuOH	Cu(OAc) ₂ ·H ₂ O (2.20 equiv)	KPF ₆	trace
9	DCE	Cu(OAc) ₂ ·H ₂ O (2.20 equiv)	KPF ₆	NR
10	DME	Cu(OAc) ₂ ·H ₂ O (2.20 equiv)	KPF ₆	NR
11	DMSO	Cu(OAc) ₂ ·H ₂ O (2.20 equiv)	KPF ₆	NR
12	DMF	Cu(OAc) ₂ ·H ₂ O (2.20 equiv)	KPF ₆	NR
13	AcOH	KOAc	KPF ₆	NR
14	AcOH	NaOAc	KPF ₆	NR
15	AcOH	Cu(OAc)₂·H₂O (30 mol %, open air)	KPF₆	91^c
16	AcOH	No (open air)	KPF ₆	NR ^c

^aAll reactions were carried out under the following conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), [{RuCl₂(*p*-cymene)}₂] (5 mol %), additive (20 mol %) and oxidant in solvent (3.0 mL) at 120 °C for 10 h under N₂ atmosphere. ^b Yields were determined by the ¹H NMR integration method, using mesitylene as an internal standard. ^c Under an open atmosphere.

Note: The catalytic reaction was tried without ruthenium and copper and KPF₆. No product **3a** was observed in the reaction. The catalytic reaction was also tried without ruthenium and KPF₆ only in the presence of copper catalyst. In the reaction also, no product **3a** was observed. However, in the case, 3,4-dimethoxy benzamide was observed in 91% isolated yield.

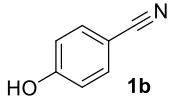
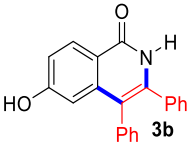
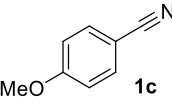
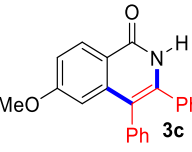
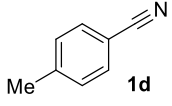
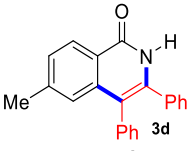
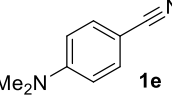
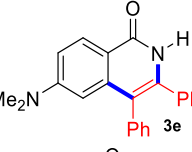
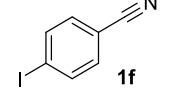
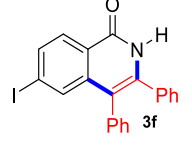
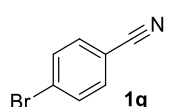
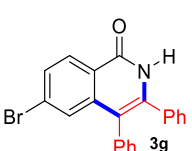
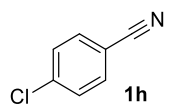
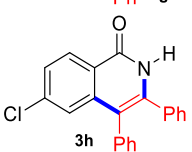
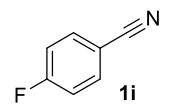
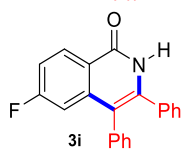
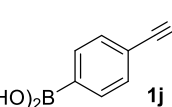
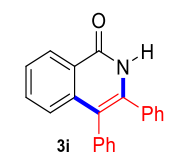
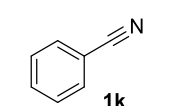
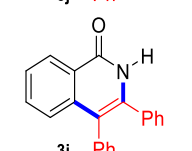
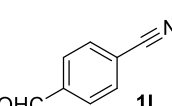
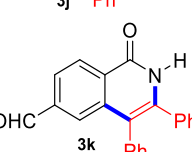
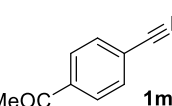
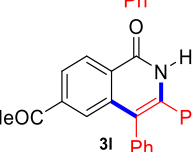
AcOH is most effective for this reaction. Other solvents such as MeOH, *tert*-BuOH, 1,2-dichloroethane, DME, THF, DMSO, DMF were totally ineffective for the reaction (entry 7-12). A variety of additives such as AgSbF₆, KPF₆, AgBF₄ and AgOTf, were tested. Among them, AgSbF₆ and KPF₆ were very effective for the reaction, giving **3a** in 83% and 89% yield respectively (entry 3 and 4). AgBF₄ and AgOTf were moderately effective giving **3a** in 72% and 75% yields, respectively (entry 5 and 6). Other oxidants such as KOAc and NaOAc were not effective for this reaction (entry 13 and 14).

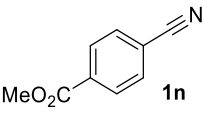
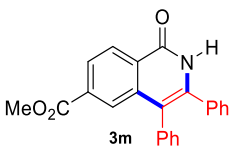
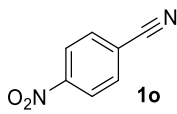
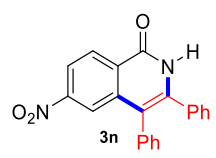
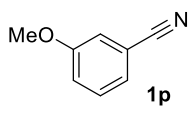
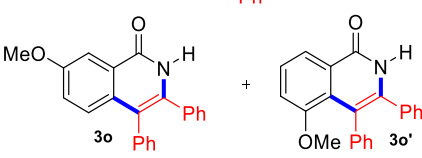
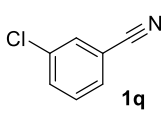
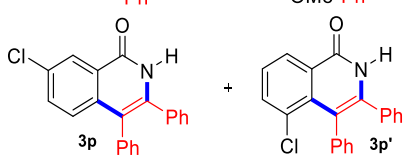
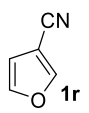
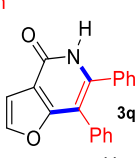
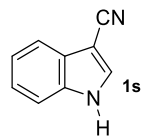
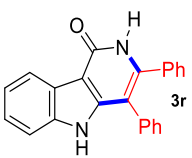
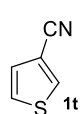
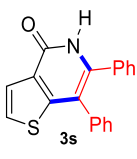
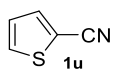
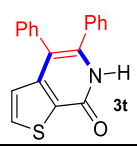
3B.5: Scope of Aromatic and Hetero Aromatic Nitriles

The present cyclization reaction was tested with various substituted aromatic nitriles and heteroaromatic nitriles (Table 3B.2). Treatment of electron-donating groups such as OH, OMe, Me and NMe₂ at the para position of the aromatic nitriles **1b-e** with **2a** gave isoquinolone derivatives **3b-e** in 76%, 78%, 72% and 82% yields, respectively (entries 1-4). A highly sensitive free OH substituent on the aromatic ring of **1b** was not affected in the reaction (entry 1). Similarly, highly sensitive halogen groups such as I, Br, Cl and F at the para position of the aromatic nitriles **1f-i** also efficiently participated in the reaction, affording isoquinolone derivatives **3f-i** in 72%, 70%, 68% and 65% yields, respectively (entries 5-8). The catalytic reaction was tested with 4-cyanophenylboronic acid (**1j**). In the reaction, the corresponding cyclization product **3j** was observed in 72% yield (entry 9). But, the boronic acid moiety was cleaved under the reaction conditions. In the meantime, benzonitrile (**1k**) reacted with **2a** yielding product **3j** in 76% yield (entry 10). Very interestingly, electron-withdrawing groups such as CHO, COMe, CO₂Me and NO₂ at the para position of the aromatic nitriles **1l-o** provided the corresponding isoquinolone derivatives **3k-n** in 73%, 75%, 63% and 74% yields, respectively (entries 11-14). It is important to mention that C-H bond activation of aromatics substituted with electron-withdrawing groups is quite difficult. Interestingly, in the present reaction, the C-H bond of aromatics substituted with electron-withdrawing groups were activated efficiently. Next, the catalytic reaction was tested with meta substituted aromatic nitriles such as 3-methoxy **1p** and 3-chlorobenzonitriles **1q** with **2a**. However, the catalytic reaction was not completely regioselective and a mixture of regioisomeric products **3o-3o'** in 41% and 30% and **3p-3p'** in 25% and 40% yields, respectively, were observed (entries 15 and 16). To demonstrate the scope of the cyclization reaction, various heteroaromatic nitriles **1r-u** were examined (entries 17-20). Thus, the treatment of 3-cyanofuran (**1r**) with diphenylacetylene (**2a**) yielded the corresponding cyclization product **3q** in excellent 93% yield (entry 17). Similarly, 3-cyanoindole (**1s**) and 3-cyanothiophene (**1t**) yielded the corresponding cyclization products **3r** and **3s** in 86% and 88% yields, respectively (entries 18 and 19). Interestingly, a less reactive 2-cyanothiophene (**1u**) also efficiently reacted with **2a**, giving cyclization product **3t** in 74% yield (entry 20). In substrate **1u**, the electron rich C3-H bond was activated efficiently.

Table 3B.2: The reaction of substituted nitriles **1** with diphenylacetylene (**2a**)^a

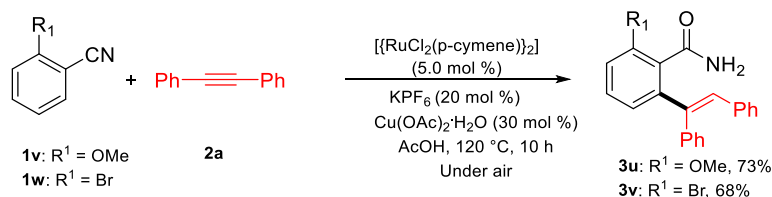
entry	nitrile 1	product 4	yield (%) ^b
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1	 1b	 3b	76
2	 1c	 3c	78
3	 1d	 3d	72
4	 1e	 3e	82
5	 1f	 3f	72
6	 1g	 3g	70
7	 1h	 3h	68
8	 1i	 3i	65
9	 1j	 3j	72
10	 1k	 3j	76
11	 1l	 3k	73
12	 1m	 3l	75

13			63
14			74
15			41+30
16			25+40
17			93
18			86
19			88
20			74

^aAll reactions were carried out using **1a-u** (1.0 mmol), diphenylacetylene (**2a**) (1.0 mmol), [{RuCl₂(*p*-cymene)}₂] (5 mol %), KPF₆ (20 mol %) and Cu(OAc)₂·H₂O (30 mol %) in acetic acid (3.0 mL) at 120 °C for 10 h under an air atmosphere. ^b Isolated yield.

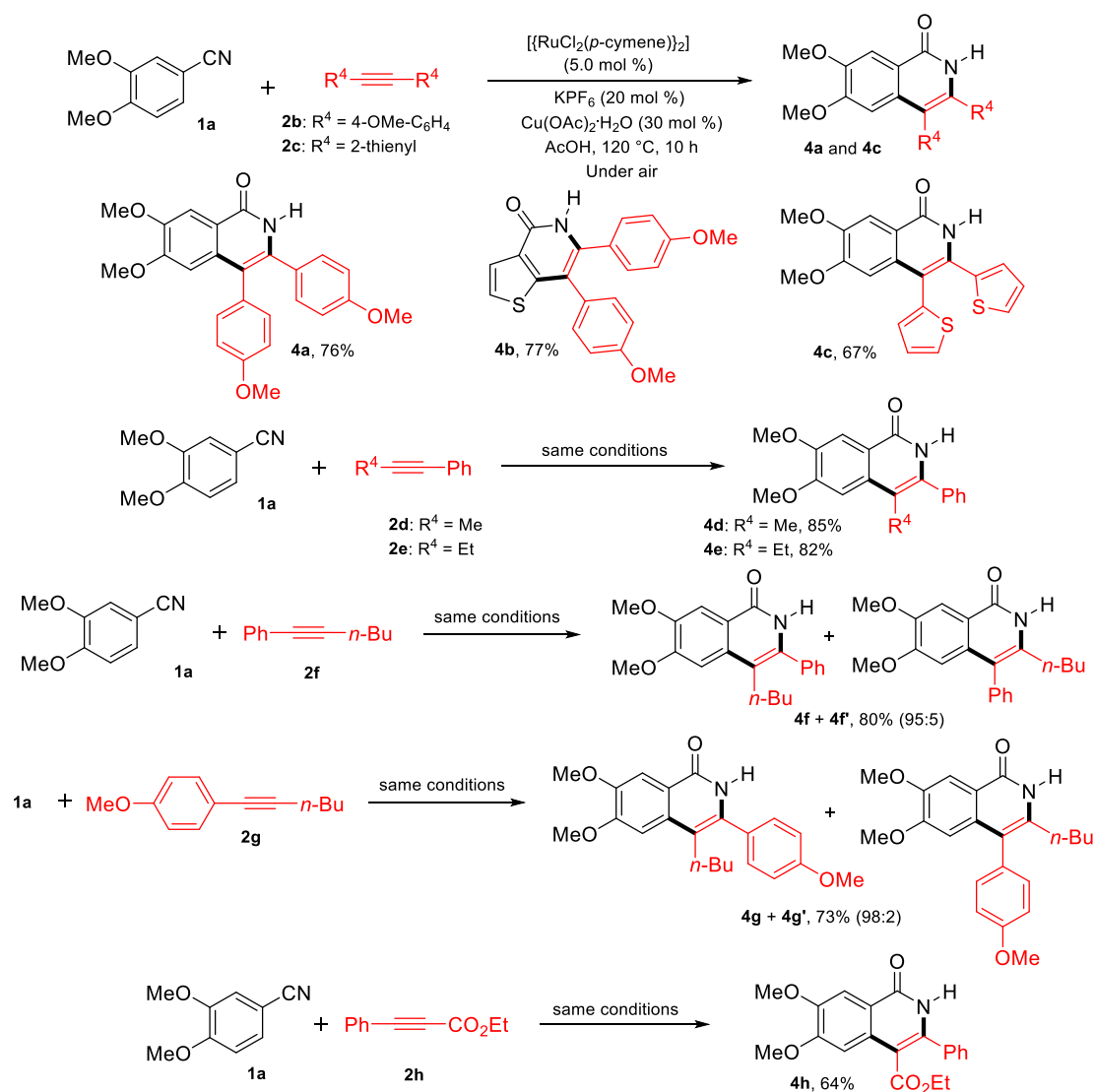
The cyclization reaction of *ortho*-substituted aromatic nitriles with diphenylacetylene (**2a**) was also tested (Scheme 3B.9). The reaction of *ortho*-methoxy (**1v**) and bromo (**1w**) benzonitriles reacted with **2a** to provide hydroarylation products **3u** and **3v** in 73% and 68% yields, respectively, instead of the expected isoquinolone derivative. The exact reason for the observation of hydroarylation product is unclear to us. This is most probably due to the steric hindrance of *ortho* substituent in the substrates **1v** and **1w**.



Scheme 3B.9: The reaction of *ortho*-substituted aromatic nitriles with diphenylacetylene

3B.6: Scope of Alkynes

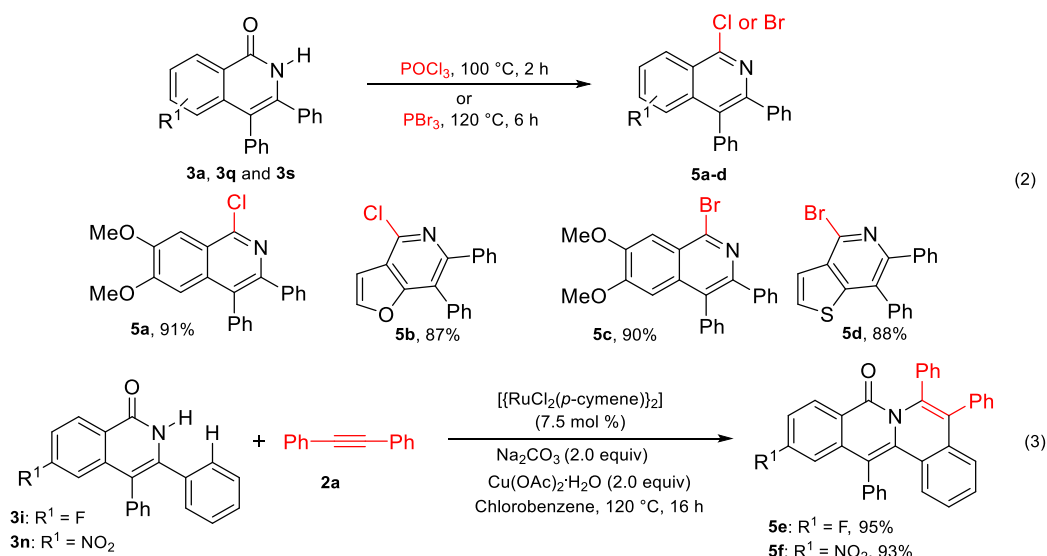
The scope of the catalytic reaction was further tested with various symmetrical and unsymmetrical alkynes (Scheme 3B.10). Thus, symmetrical alkynes such as 1,2-bis(4-methoxyphenyl)ethyne (**2b**) and 1,2-di(thiophen-2-yl)ethyne (**2c**) reacted efficiently with **1a** or **1s** to afford the corresponding cyclization products **4a-c** in 76%, 77% and 67% yields, respectively (Scheme 3B.10). Unsymmetrical alkynes such as 1-phenyl-1-propyne (**2d**) and 1-phenyl-1-butyne (**2e**) cyclized efficiently with 3,4-dimethoxybenzonitrile (**1a**), giving cyclization products **4d** and **4e** in 85% and 82% yields, respectively. The catalytic reaction is completely regioselective, in which the less hindered C-H bond of **1a** was connected to the alkyl (Me and Et) substituted carbon of alkynes **2d** and **2e**. However, 1-phenyl-1-hexyne (**2f**) reacted with **1a**, providing a mixture of regioisomeric products **4f** and **4f'** in a combined 80% yield with a 95:5 ratio of regioisomers. Whereas, methoxy substituted alkyne **2g** afforded regioisomeric products **4g** and **4g'** in a combined 73% yield (98:2 ratio). It is nice to know that the OMe substituent on the phenyl group of the alkyne **2a** increases the selectivity of the reaction. Further, the catalytic reaction was tested with ethyl 3-phenylpropiolate (**2h**) under the optimized reaction conditions. In the reaction, the corresponding cyclization product **4h** was observed in 64% yield in a highly regioselective manner, in which the less hindered C-H bond of **1a** was connected to the ester substituted carbon of alkyne **2h**.



Scheme 3B.10: Regioselective studies of substituted alkynes

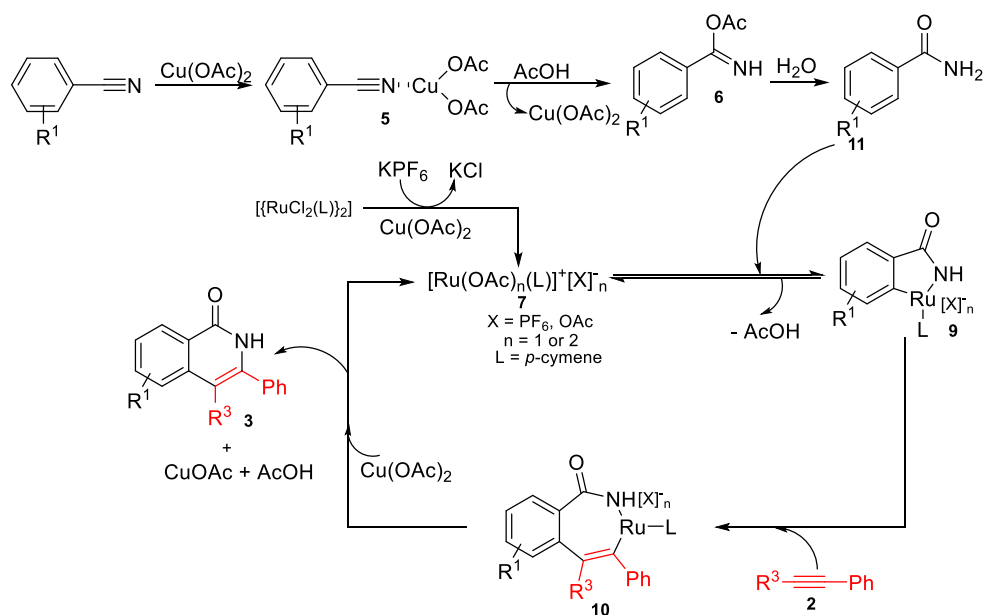
3B.7: Synthesis of 1-Chloro and 1-Bromo Isoquinoline Derivatives

The isoquinolone derivatives were further converted into highly useful 1-chloro and 1-bromo isoquinoline derivatives (eq. 2). Thus, the reaction of **3a** and **3q** with POCl_3 at 100°C for 2 h gave 1-chloroisoquinoline derivatives **5a** and **5b** in 91% and 87% yields, respectively. Similarly, **3a** and **3s** reacted with PBr_3 at 120°C for 6 h to yield 1-bromoisoquinoline derivatives **5c** and **5d** in 90% and 88% yields, respectively (eq. 2). Further, isoquinolone derivatives **3i** and **3n** reacted with diphenylacetylene (**2a**) in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$, Na_2CO_3 and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in chlorobenzene (2.0 mL) at 120°C for 12 h to yield tricyclic compounds **5e** and **5f** in 95% and 93% yields, respectively (eq. 3).^{4f} In the reaction, the *ortho* C-H bond of one of the phenyl groups and the amide N-H bond of **3i** or **3n** were involved in the cyclization reaction.



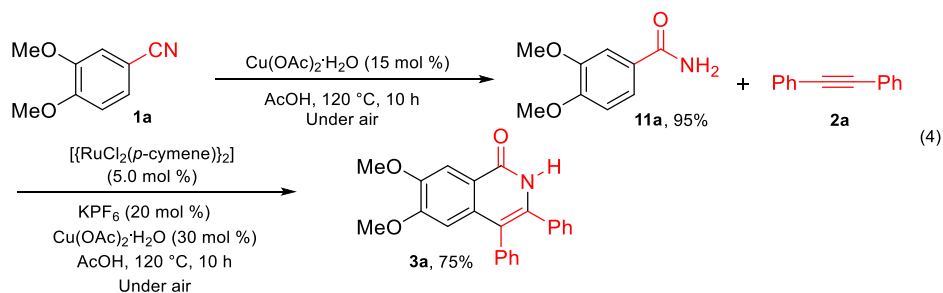
3B.8: Mechanism

A cooperatively ruthenium- and copper-catalyzed reaction mechanism is proposed for the present cyclization reaction as shown in Scheme 3B.11. In the copper-catalyzed reaction, $\text{Cu}(\text{OAc})_2$ likely acts as a Lewis acid to which the CN group of benzonitrile **1** is coordinated to give intermediate **5**. In this stage, $\text{Cu}(\text{OAc})_2$ likely reduces the electron density of nitrile group. Subsequently, nucleophilic addition of AcOH to the CN group in the intermediate **5** followed by hydrolysis affords benzamide **11** and regenerates $\text{Cu}(\text{OAc})_2$.⁸ In the ruthenium-catalyzed, KPF_6 likely removes the chloride ligand from the $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ complex followed by the ligand exchange with $\text{Cu}(\text{OAc})_2$, giving cationic ruthenium species **7**. Coordination of the nitrogen group of **6** to the ruthenium cationic species **7** followed by *ortho*-metalation in the presence of AcOH affords a five-membered ruthenacycle **9**.⁹ Coordinative insertion of alkyne **2** into the Ru–carbon bond of ruthenacycle **9** provides intermediate **10**. Reductive elimination of intermediate **10** in the presence of $\text{Cu}(\text{OAc})_2$ gives product **3** and regenerates the active ruthenium species **7** for the next catalytic cycle. In the reaction, only 30 mol % of $\text{Cu}(\text{OAc})_2$ is used as an internal oxidant. The remaining amount of $\text{Cu}(\text{OAc})_2$ source is regenerated under oxygen or air from the reduced copper source in the presence of AcOH.



Scheme 3B.11: Proposed mechanism

The proposed mechanism was strongly supported by the following mechanistic evidence (eq. 4). Treatment of **1a** (1.0 mmol) with AcOH in the presence of $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$ (15 mol %) at 120 °C under air gave 3,4-dimethoxy benzamide **11a** in 95% yield. Further, the treatment of **11a** with **2a** (1.0 equiv) in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (5.0 mol %), KPF_6 (20 mol %) and $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$ (30 mol %) in acetic acid at 120 °C for 10 h under air provided isoquinolinone **3a** in 75% isolated yield.



3B.9: Conclusion

1. We have developed the aerobic oxidative cyclization of aromatic and heteroaromatic nitriles with alkynes in the presence of ruthenium and copper catalyst giving substituted isoquinolinone derivatives in a highly stereo and region selective manner in good to excellent yields.
2. Further, the substituted isoquinolinone derivatives were converted into 1-halo quinolinone derivatives by treating with POCl_3 or POBr_3 .

3B.10: References

1. Selected references: (a) Lewis, J. R. *Nat Prod. Rep.* **1994**, *11*, 329. (b) Krane, B. D.; Fagbule, M. O.; Shamma, M. J. *Nat. Prod.* **1984**, *47*, 1. (c) Bentley, K. W. *Nat. Prod. Rep.* **1992**, 365. (d) Krane, B. D.; Shamma, M. J. *Nat. Prod.* **1982**, *45*, 377.
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3B.11: Experimental Section

General Procedure for the Cyclization of Aromatic Nitriles with Alkynes Catalyzed by Ruthenium Complex:

[{RuCl₂(*p*-cymene)}₂] (0.05 mmol, 5 mol %), KPF₆ (0.20 mmol, 20 mol %) and Cu(OAc)₂·H₂O (0.30 mmol, 30 mol %) were taken in a 25-mL round bottom flask equipped with a magnetic stirrer. To the flask were then added substituted nitriles **1** (1.0 mmol), alkyne **2** (**2a-c** and **2g** 1.00 mmol and for alkynes **2d-f** and **2h** 1.50 mmol) and acetic acid solvent (3.0 mL) via syringes. Then, condenser was fitted with water circulation in the round bottom flask and the reaction mixture was allowed to stir at 120 °C for 10 h under an open atmosphere (Note: the top of the condenser was exposed to the air and has not been covered by anything. AcOH boiling point is 118 °C. Solvent evaporation was not observed during the reaction). After cooling to ambient temperature, the reaction mixture was diluted with CH₂Cl₂, filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3** and **4**.

General Procedure for the Chlorination or Bromination Reaction.¹

In a 50 mL round-bottom flask fitted with a condenser, a suspension of isoquinolone (100 mg) in phosphorus oxychloride (POCl₃) or phosphorus tribromide (PBr₃) (2.0 mL) was heated at 100 °C for 2 h for chlorination (120 °C for 6 h for bromination). The reaction was monitored on TLC. After completion the reaction (approx. 2.0 h for chlorination and approx. 6.0 h for bromination), the reaction mixture was cooled to ambient temperature, and poured in ice and added saturated NaHCO₃, extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na₂SO₄. The solution was concentrated under reduced pressure to provide crude 1-halo isoquinolines **5a-d**. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **5a-d**.

Ref. 1: M. Tobe, Y. Isobe, H. Tomizawa, T. Nagasaki, H. Takahashi, T. Fukazawa and H. Hayashi, *Bioorg. Med. Chem.* **2003**, *11*, 383.

General Procedure for the Preparation of Compounds 5e and 5f.²

A mixture of isoquinolone (**3**) (1.0 equiv), diphenylacetylene (**2a**) (2.0 equiv), $[\text{RuCl}_2(p\text{-cymene})]_2$ (7.5 mol %), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv) and Na_2CO_3 (2.0 equiv) were taken in a 15-mL pressure tube equipped with a magnetic stirrer and a septum. Dry PhCl (2.0 mL) was added to the reaction mixture and evacuated and purged with nitrogen gas three times. Then, the reaction mixture was stirred at 120 °C for 16 h under N_2 atmosphere (During this time, septum was removed under nitrogen atmosphere and a screw cap was used to cover the tube). After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 , filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **5e** and **5f**.

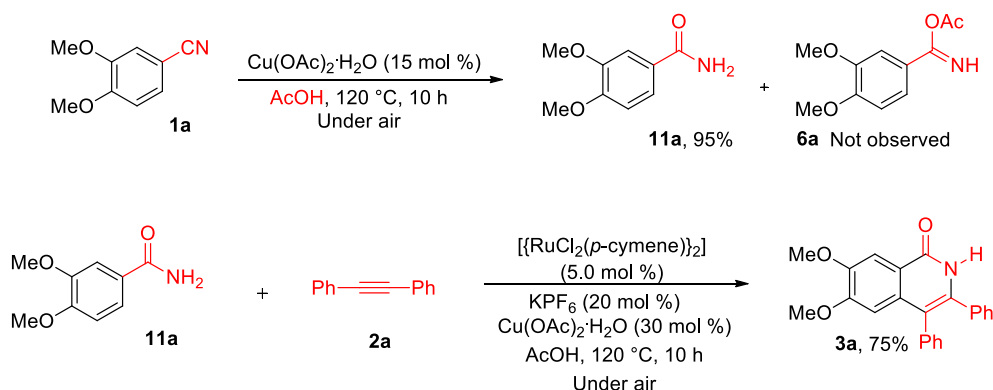
Ref 2: B. Li, H. Feng, S. Xu and B. Wang, *Chem. Eur. J.* **2012**, *18*, 12873.

Spectral data and copies of ^1H and ^{13}C NMR spectra of all compounds **3a-t**, **4a-h** and **5a-f** are listed below.

Mechanistic Investigation

The cyclization reaction of **1a** and **2a** was also tested with commercial acetic acid. However, in the reaction, product **3a** was observed only in moderate 65% isolated yield. In the aqueous acetic acid solution (2.0 mL AcOH and 1.0 mL H_2O), product **3a** was observed only in less 40% isolated yield.

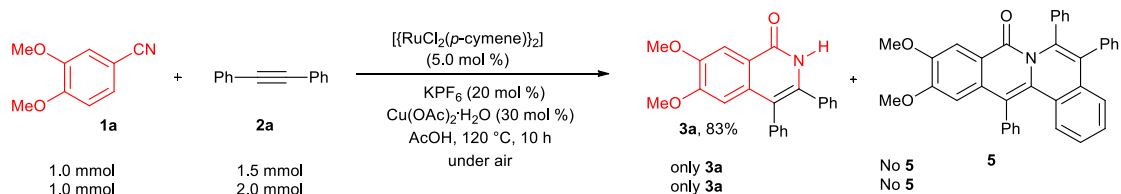
The reaction of **1a** was done without ruthenium catalyst and only in presence of copper(II) acetate. Treatment of 3,4-dimethoxy benzonitrile **1a** (1.0 mmol) with AcOH in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (15 mol %) at 120 °C under air gave 3,4-dimethoxy benzamide **11a** in 95% yield. However, in the reaction, product **6a** was not observed. We strongly believe that initially product **6a** might formed in the reaction. Later, the acidic solvent, AcOH, might hydrolyzed the product **6a** to **11a**. In the meantime, the same reaction was tested without copper catalyst and only in the presence of ruthenium catalyst. In the reaction, no product **11a** or **6a** was observed and starting material **1a** was recovered. This result clearly revealed that copper catalyst plays an important role to convert aromatic nitrile to **6a** or **11a** as well give acetate source to ruthenium catalyst to do C-H bond activation.

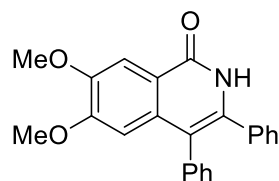


The treatment of 3,4-dimethoxy benzamide **11a** with diphenylacetylene (**2a**) (1.0 equiv) in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (5.0 mol %), KPF_6 (20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (30 mol %) in acetic acid at 120°C for 10 h under air provided isoquinolone derivative **3a** in 75% isolated yield.

At present the exact mechanism for the present reaction is not very clear. Two different types of catalytic reactions are involved. The first reaction is $\text{Cu}(\text{OAc})_2$ -catalyzed nucleophilic addition of H_2O or AcOH to benzonitrile. The second reaction is *ortho* C-H bond activation of substituted aromatics followed by cyclization with alkyne in the presence of ruthenium and copper catalysts.

We have done the reaction of **1a** (1.0 mmol) with excess amount of **2a** (1.5 mmol or 2.0 mmol) under the optimized reaction conditions. In these reactions, only first insertion product **3** was observed and no two insertion product **5** was observed. This is most likely due to the first insertion takes place under acidic conditions and the second insertion does not take place under acidic conditions.



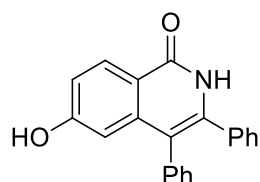
3B.12: Spectral Data of all Compounds.**6,7-Dimethoxy-3,4-diphenylisoquinolin-1(2H)-one (3a).^{3a}**

Dark brown solid; eluent (60% ethyl acetate in hexanes).

¹H NMR (DMSO-d₆, 400 MHz): δ 11.43 (bs, 1 H), 7.70 (s, 1 H), 7.31 - 7.25 (m, 3 H), 7.20 (bs, 5 H), 7.14 - 7.16 (m, 2 H), 6.56 (s, 1 H), 3.90 (s, 3 H), 3.57 (s, 3 H).

¹³C NMR (DMSO-d₆, 100 MHz): δ 161.0, 152.8, 148.5, 137.0, 136.1, 134.7, 133.2, 131.6, 129.8, 128.2, 127.9, 127.6, 127.0, 118.8, 115.1, 106.9, 105.5, 55.6, 55.1.

HRMS (ESI): calc. for [(C₂₃H₁₉NO₃)H] (M+H) 358.1443, measured 358.1434.

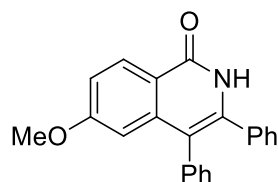
6-Hydroxy-3,4-diphenylisoquinolin-1(2H)-one (3b).

White solid; eluent (50% ethyl acetate in hexanes).

¹H NMR (DMSO-d₆, 400 MHz): δ 11.23 (bs, 1 H), 10.15 (s, 1 H), 8.15 (d, J = 8.7, 1 H), 7.31 - 7.22 (m, 3 H), 7.20 (bs, 5 H), 7.14 - 7.12 (m, 2 H), 6.94 (dd, J = 8.0, 4.0 Hz, 1 H), 6.48 (s, 1 H).

¹³C NMR (DMSO-d₆, 100 MHz): δ 161.4, 161.0, 140.3, 138.7, 136.2, 134.7, 131.7, 129.7, 129.1, 128.2, 128.0, 127.6, 126.9, 117.7, 116.0, 115.0, 108.8

HRMS (ESI): calc. for [(C₂₁H₁₅NO₂)H] (M+H) 314.1181, measured 314.1180.

6-Methoxy-3,4-diphenylisoquinolin-1(2H)-one (3c).^{3b}

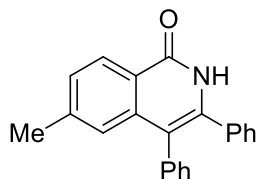
White solid; eluent (40% ethyl acetate in hexanes).

¹H NMR (DMSO-d₆, 400 MHz): δ 11.38 (bs, 1 H), 8.25 (d, J = 8.0 Hz, 1 H), 7.32 - 7.26 (m, 3 H), 7.22 (bs, 5 H), 7.16 - 7.13 (m, 3 H), 6.51 (s, 1 H), 3.67 (s, 3 H).

¹³C NMR (DMSO-d₆, 100 MHz): δ 162.3, 161.3, 140.1, 139.2, 135.9, 134.6, 131.6, 129.7, 129.1, 128.2, 128.1, 127.6, 127.0, 118.8, 115.1, 114.5, 107.13, 55.17.

HRMS (ESI): calc. for $[(C_{22}H_{17}NO_2)H]$ (M+H) 328.1338, measured 328.1333.

6-Methyl-3,4-diphenylisoquinolin-1(2H)-one (3d).^{3b}



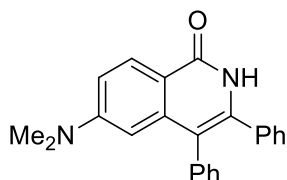
Colorless solid; eluent (30% ethyl acetate in hexanes).

1H NMR ($CDCl_3$, 400 MHz): δ 9.55 (bs, 1 H), 8.36 (d, J = 8.0, 1 H), 7.33 – 7.30 (m, 4 H), 7.27 – 7.22 (m, 5 H), 7.19 – 7.16 (m, 2 H), 7.12 (s, 1 H), 2.37 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.8, 143.3, 138.7, 137.1, 135.8, 135.0, 131.8, 129.2, 128.5, 128.3, 128.2, 127.8, 127.4, 127.2, 125.3, 122.7, 117.1, 22.0.

HRMS (ESI): calc. for $[(C_{22}H_{17}NO)H]$ (M+H) 312.1388, measured 312.1382.

6-(Dimethylamino)-3,4-diphenylisoquinolin-1(2H)-one (3e).



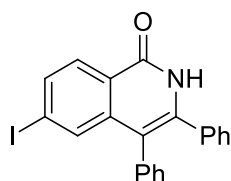
Yellow solid; eluent (40% ethyl acetate in hexanes).

1H NMR ($CDCl_3$, 400 MHz): δ 8.89 (bs, 1 H), 8.31 (d, J = 8.0 Hz, 1 H), 7.28 – 7.26 (m, 4 H), 7.21 – 7.18 (m, 6 H), 6.91 (dd, J = 8.0, 4.0 Hz, 1 H), 6.37 (s, 1 H), 2.92 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6, 153.1, 140.4, 137.1, 136.3, 135.5, 131.7, 129.1, 128.9, 128.3, 128.2, 127.0, 116.9, 114.5, 112.4, 105.2, 39.9.

HRMS (ESI): calc. for $[(C_{23}H_{20}N_2O)H]$ (M+H) 341.1654, measured 341.1661.

6-Iodo-3,4-diphenylisoquinolin-1(2H)-one (3f).^{3b}

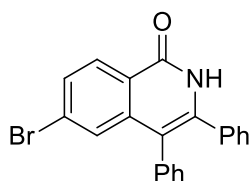


White solid; eluent (25% ethyl acetate in hexanes).

1H NMR ($DMSO-d_6$, 400 MHz): δ 11.64 (bs, 1 H), 8.00 (d, J = 8.0 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.40 (s, 1 H), 7.29 – 7.22 (m, 3 H), 7.17 (bs, 5 H), 7.10 (d, J = 8.0, 2 H).

^{13}C NMR ($DMSO-d_6$, 100 MHz): δ 161.4, 139.9, 139.7, 135.2, 134.8, 134.2, 133.2, 131.6, 129.7, 128.7, 128.4, 127.7, 127.3, 124.1, 114.2, 101.3.

HRMS (ESI): calc. for $[(C_{21}H_{14}INO)H]$ (M+H) 424.0198, measured 424.0192.

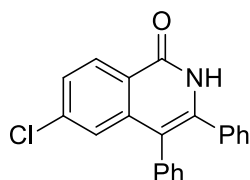
6-Bromo-3,4-diphenylisoquinolin-1(2H)-one (3g).^{3b}

White solid; eluent (30% ethyl acetate in hexanes).

¹H NMR (DMSO-d₆, 400 MHz): δ 11.73 (s, 1 H), 8.23 (d, *J* = 8.0 Hz, 1 H), 7.67 (dd, *J* = 8.0, 4 Hz, 1 H), 7.34 - 7.28 (m, 3 H), 7.25-7.21 (m, 6 H), 7.17-7.14 (m, 2 H).

¹³C NMR (DMSO-d₆, 100 MHz): δ 161.2, 140.2, 139.8, 135.1, 134.1, 131.6, 129.7, 129.3, 129.1, 128.4, 127.7, 127.4, 126.9, 126.8, 123.8, 114.4.

HRMS (ESI): calc. for [(C₂₁H₁₄BrNO)H] (M+H) 376.0337, measured 376.0343.

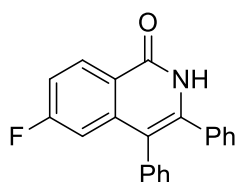
6-Chloro-3,4-diphenylisoquinolin-1(2H)-one (3h).^{3b}

Colorless solid; eluent (30% ethyl acetate in hexanes).

¹H NMR (DMSO-d₆, 400 MHz): δ 11.73 (bs, 1 H), 8.31 (d, *J* = 8.0, 1 H), 7.55 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.34-7.28 (m, 3 H), 7.23 (bs, 5 H), 7.17-7.15 (m, 2 H), 7.05 (s, 1 H).

¹³C NMR (DMSO-d₆, 100 MHz): δ 161.1, 140.3, 139.7, 137.6, 135.1, 134.1, 131.6, 129.7, 129.3, 128.4, 127.7, 127.4, 126.4, 123.8, 123.6, 114.5.

HRMS (ESI): calc. for [(C₂₁H₁₄ClNO)H] (M+H) 332.0842, measured 332.0844.

6-Fluoro-3,4-diphenylisoquinolin-1(2H)-one (3i).^{3b}

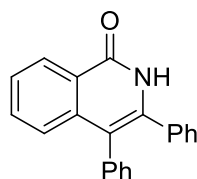
White solid; eluent (30% ethyl acetate in hexanes).

¹H NMR (CDCl₃, 400 MHz): δ 10.41 (bs, 1 H), 8.42 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.34-7.29 (m, 3 H), 7.27 - 7.22 (m, 5 H), 7.17 - 7.14 (m, 3 H), 6.98 (dd, *J* = 8.0, 4.0 Hz, 1 H)

¹³C NMR (CDCl₃, 100 MHz): δ 166.7 and 164.2 (F coupling), 162.4, 141.2 and 141.1 (F coupling), 138.7, 135.2, 134.5, 131.6, 130.6 and 130.5 (F coupling), 129.3, 128.7, 128.5, 128.1, 127.4, 121.5, 116.74 and 116.70 (F coupling), 115.2 and 114.9 (F coupling), 110.8 and 110.6 (F coupling).

HRMS (ESI): calc. for $[(C_{21}H_{14}FNO)H]$ (M+H) 316.1138, measured 316.1139.

3,4-Diphenylisoquinolin-1(2H)-one (3j).^{3b}



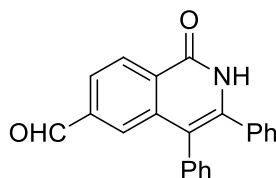
Colorless solid; eluent (30% ethyl acetate in hexanes).

1H NMR ($CDCl_3$, 400 MHz): δ 9.42 (bs, 1 H), 8.46 (dd, $J = 8.0, 4.0$ Hz, 1 H), 7.59 (t, $J = 8.0$ Hz, 1 H), 7.50 (t, $J = 8.0$ Hz, 1 H), 7.36 (d, $J = 8.0$ Hz, 1 H), 7.33 – 7.29 (m, 3 H), 7.27 – 7.23 (m, 5 H), 7.20 – 7.17 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 138.6, 137.0, 135.6, 135.0, 132.6, 131.8, 129.2, 128.6, 128.37, 128.33, 127.4, 127.3, 126.6, 125.6, 125.0, 117.2.

HRMS (ESI): calc. for $[(C_{21}H_{15}NO)H]$ (M+H) 298.1232, measured 298.1228.

1-Oxo-3,4-diphenyl-1,2-dihydroisoquinoline-6-carbaldehyde (3k).^{3b}



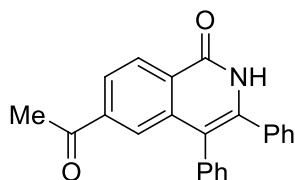
Pale yellow solid; eluent (45% ethyl acetate in hexanes).

1H NMR ($CDCl_3$, 400 MHz): δ 9.96 (s, 1 H), 9.40 (bs, 1 H), 8.55 (d, $J = 8.0$ Hz, 1 H), 7.91 (d, $J = 8.0$ Hz, 1 H), 7.79 (s, 1 H), 7.32 – 7.29 (m, 3 H), 7.25 – 7.19 (m, 7 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.1, 162.3, 139.2, 139.1, 138.4, 134.8, 134.5, 131.7, 129.5, 129.3, 129.1, 128.8, 128.7, 128.6, 127.9, 124.9, 117.5.

HRMS (ESI): calc. for $[(C_{22}H_{15}NO_2)H]$ (M+H) 326.1182, measured 326.1176.

6-Acetyl-3,4-diphenylisoquinolin-1(2H)-one (3l).



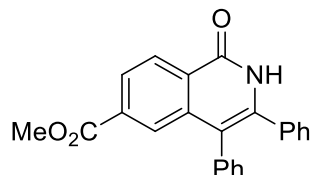
Yellow solid; eluent (40% ethyl acetate in hexanes).

1H NMR ($CDCl_3$, 400 MHz): δ 9.82 (bs, 1 H), 8.53 (d, $J = 8.0$ Hz, 1 H), 8.01 (dd, $J = 8.0, 4.0$ Hz, 1 H), 7.94 (s, 1 H), 7.36 – 7.32 (m, 3 H), 7.30 – 7.24 (m, 5 H), 7.20 – 7.18 (m, 2 H), 2.53 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 197.9, 162.3, 140.0, 138.7, 138.1, 134.9, 134.5, 131.6, 129.2, 128.8, 128.6, 128.3, 128.1, 127.7, 126.2, 125.1, 117.4, 26.8.

HRMS (ESI): calc. for $[(\text{C}_{23}\text{H}_{17}\text{NO}_2)\text{H}]$ (M+H) 340.1338, measured 340.1335.

Methyl 1-oxo-3,4-diphenyl-1,2-dihydroisoquinoline-6-carboxylate (3m).^{3b}



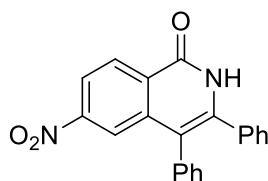
Colorless solid; eluent (40% ethyl acetate in hexanes).

^1H NMR (DMSO-d_6 , 400 MHz): δ 11.81 (s, 1 H), 8.43 (d, J = 8.0 Hz, 1 H), 8.01 (dd, J = 8.0, 4.0 Hz, 1 H), 7.80 (s, 1 H), 7.33 – 7.29 (m, 3 H), 7.23 (bs, 5 H), 7.19 -7.16 (m, 2 H), 3.80 (s, 3 H).

^{13}C NMR (DMSO-d_6 , 100 MHz): δ 165.7, 161.1, 139.7, 138.0, 135.2, 134.2, 132.8, 131.7, 129.8, 128.3, 127.7, 127.6, 127.3, 126.3, 125.7, 115.4, 54.9, 52.5.

HRMS (ESI): calc. for $[(\text{C}_{23}\text{H}_{17}\text{NO}_3)\text{H}]$ (M+H) 356.1287, measured 356.1292.

6-Nitro-3,4-diphenylisoquinolin-1(2H)-one (3n).^{3b}



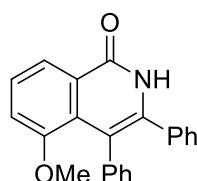
Yellow solid; eluent (35% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 10.21 (s, 1 H), 8.57 (d, 1 H), 8.23 - 8.20 (m, 2 H), 7.38 – 7.35 (m, 3 H), 7.33 – 7.31 (m, 1 H), 7.29 - 7.25 (m, 4 H), 7.19 – 7.17 (m, 2 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 161.7, 150.6, 139.7, 139.5, 134.2, 131.5, 129.5, 129.25, 129.22, 128.9, 128.6, 128.5, 128.4, 128.0, 121.1, 120.1, 117.1.

HRMS (ESI): calc. for $[(\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_3)\text{H}]$ (M+H) 343.1083, measured 343.1083.

5-Methoxy-3,4-diphenylisoquinolin-1(2H)-one (3o').^{3b}



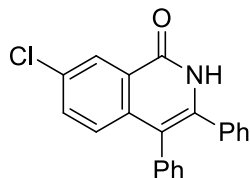
Colorless solid; eluent (40% ethyl acetate in hexanes).

^1H NMR (DMSO-d_6 , 400 MHz): δ 11.50 (bs, 1 H), 7.95 (d, J = 8.0 Hz, 1 H), 7.46 (t, J = 8.0 Hz, 1 H), 7.15 (bs, 6 H), 7.06 -7.03 (m, 5 H), 3.25 (s, 3 H),

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 161.2, 156.0, 139.7, 138.7, 135.0, 130.9, 129.9, 127.9, 127.7, 127.3, 127.1, 126.9, 126.3, 125.4, 119.0, 114.9, 113.6, 55.7.

HRMS (ESI): calc. for $[(\text{C}_{22}\text{H}_{17}\text{NO}_2)\text{H}]$ (M+H) 328.1338, measured 328.1332.

7-Chloro-3,4-diphenylisoquinolin-1(2H)-one (3p).^{3b}



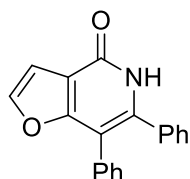
Colorless solid; eluent (30% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.77 (bs, 1 H), 8.24 (s, 1 H), 7.69 (dd, J = 8.0, 4.0, Hz, 1 H), 7.32 – 7.26 (m, 3 H), 7.23 (bs, 6 H), 7.17 - 7.14 (m, 2 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 160.6, 139.1, 136.8, 135.3, 134.2, 132.6, 131.6, 130.9, 129.8, 128.3, 127.7, 127.3, 127.2, 126.2, 125.7, 115.0.

HRMS (ESI): calc. for $[(\text{C}_{21}\text{H}_{14}\text{ClNO})\text{H}]$ (M+H) 332.0842, measured 332.0844.

6,7-Diphenylfuro[3,2-c]pyridin-4(5H)-one (3q).



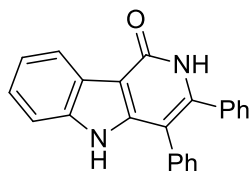
Pale yellow solid; eluent (40% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.70 (s, 1 H), 7.88 (d, J = 4.0 Hz, 1 H), 7.32-7.21 (m, 8 H), 7.14-7.17 (m, 2 H), 7.04 (d, J = 3.2 Hz, 1 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 159.1, 158.8, 144.6, 140.8, 133.3, 132.4, 130.7, 130.0, 128.7, 128.1, 127.9, 127.1, 114.4, 108.0, 107.0.

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{13}\text{NO}_2)\text{H}]$ (M+H) 288.1025, measured 288.1029.

3,4-Diphenyl-2,5-dihydro-1H-pyrido[4,3-b]indol-1-one (3r).



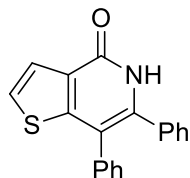
Grey solid; eluent (60% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.38 (br s, 1 H), 11.16 (s, 1 H), 8.17 (d, J = 8.0 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.37 - 7.30 (m, 3 H), 7.28 – 7.20 (m, 9 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 159.5, 144.6, 141.2, 138.1, 134.2, 134.1, 130.9, 130.0, 128.6, 128.3, 127.8, 127.2, 124.1, 123.6, 120.6, 120.4, 111.8, 107.7, 106.1.

HRMS (ESI): calc. for $[(\text{C}_{23}\text{H}_{16}\text{N}_2\text{O})\text{H}]$ (M+H) 337.1341, measured 337.1347.

6,7-Diphenylthieno[3,2-*c*]pyridin-4(5*H*)-one (3s).



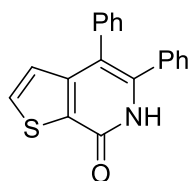
Pale yellow solid; eluent (35% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.71 (s, 1 H), 7.60 - 7.58 (d, J = 4.0 Hz, 1 H), 7.58 - 7.56 (d, J = 8.0 Hz, 1 H), 7.32-7.20 (m, 10 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 158.5, 151.2, 138.6, 136.5, 133.5, 130.1, 129.9, 129.2, 128.5, 127.8, 127.6, 125.8, 124.5, 113.6.

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{13}\text{NOS})\text{H}]$ (M+H) 304.0796, measured 304.0802.

4,5-Diphenylthieno[2,3-*c*]pyridin-7(6*H*)-one (3t).^{3b}



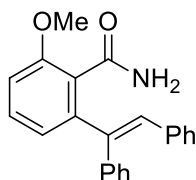
Light-yellow solid; eluent (35% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.78 (s, 1 H), 8.02 (d, J = 8.0 Hz, 1 H), 7.30 - 7.21 (m, 8 H), 7.13 - 7.15 (m, 2 H), 6.92 (d, J = 8.0 Hz, 1 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 158.0, 146.7, 139.8, 136.3, 134.1, 133.9, 130.7, 130.0, 128.3, 128.2, 128.0, 127.8, 127.0, 124.5, 114.7.

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{13}\text{NOS})\text{H}]$ (M+H) 304.0796, measured 304.0803.

(*E*)-2-(1,2-Diphenylvinyl)-6-methoxybenzamide (3u).



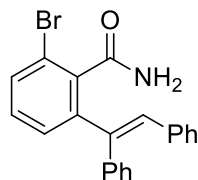
Colorless solid; eluent (50% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 7.72 (bs, 1 H), 7.36 (bs, 1 H), 7.28 -7.19 (m, 6 H), 7.14 - 7.11 (m, 3 H), 6.97 -6.95 (m, 3 H), 6.80 (s, 1 H), 6.56 (d, J = 8.0 Hz, 1 H), 3.80 (s, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 168.5, 155.7, 142.0, 140.6, 140.3, 136.8, 129.83, 129.80, 129.0, 128.5, 128.3, 127.97, 127.93, 127.2, 126.8, 121.3, 109.8, 55.6.

HRMS (ESI): calc. for $[(\text{C}_{22}\text{H}_{19}\text{NO}_2)\text{H}]$ (M+H) 330.1494, measured 330.1498.

(E)-2-Bromo-6-(1,2-diphenylvinyl)benzamide (3v).



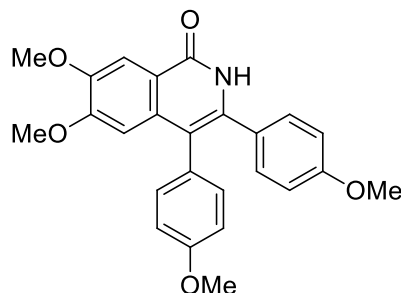
Colorless solid; eluent (40% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 8.01 (bs, 1 H), 7.64 (bs, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.31 – 7.28 (m, 5 H), 7.14 (t, J = 8.0 Hz, 1 H), 7.12 – 7.09 (m, 3 H), 6.96 – 6.90 (m, 3 H), 6.86 (s, 1 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 168.8, 142.9, 140.2, 139.6, 139.4, 136.5, 130.7, 130.9, 129.8, 129.4, 129.1, 128.6, 128.5, 128.1, 127.5, 127.1, 119.3.

HRMS (ESI): calc. for $[(\text{C}_{21}\text{H}_{16}\text{BrNO})\text{H}]$ (M+H) 378.0494, measured 378.0497.

6,7-Dimethoxy-3,4-bis(4-methoxyphenyl)isoquinolin-1(2H)-one (4a).



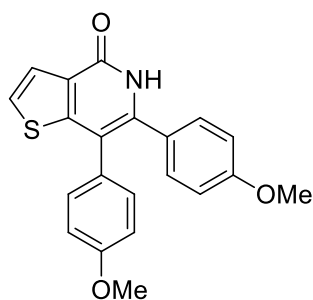
Brick-red solid; eluent (65% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.28 (bs, 1 H), 7.68 (s, 1 H), 7.10 (d, J = 8.0 Hz, 2 H), 7.05 (d, J = 8.0 Hz, 2 H), 6.86 (d, J = 8.0 Hz, 2 H), 6.76 (d, J = 8.0 Hz, 2 H), 6.58 (s, 1 H), 3.88 (s, 3 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.58 (s, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 161.1, 158.7, 157.9, 152.9, 148.4, 136.9, 134.1, 132.7, 131.1, 128.3, 127.2, 118.7, 114.5, 113.8, 113.1, 106.9, 105.6, 55.6, 55.2, 55.1, 54.9.

HRMS (ESI): calc. for $[(\text{C}_{25}\text{H}_{23}\text{NO}_5)\text{H}]$ (M+H) 418.1654, measured 418.1650.

6,7-Bis(4-methoxyphenyl)thieno[3,2-c]pyridin-4(5H)-one (4b).



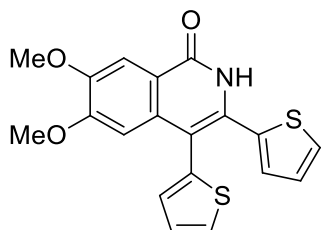
Pale yellow color semisolid; eluent (50% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.55 (s, 1 H), 7.54 (s, 2 H), 7.16 (d, J = 8.0 Hz, 2 H), 7.12 (d, J = 8.0 Hz, 2 H), 6.87 (d, J = 8.0 Hz, 2 H), 6.81 (d, J = 8.0 Hz, 2 H), 3.73 (s, 3 H), 3.72 (s, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 159.1, 158.6, 158.3, 151.9, 138.3, 131.3, 128.8, 128.7, 125.8, 125.4, 124.5, 114.0, 113.3, 112.9, 55.1, 54.9.

HRMS (ESI): calc. for $[(\text{C}_{21}\text{H}_{17}\text{NO}_3\text{S})\text{H}]$ ($\text{M}+\text{H}$) 364.1007, measured 364.1009.

6,7-Dimethoxy-3,4-di(thiophen-2-yl)isoquinolin-1(2H)-one (4c).



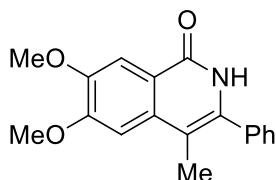
Black semisolid; eluent (55% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.46 (bs, 1 H), 7.76 (d, J = 8.0 Hz, 1 H), 7.56 (s, 1 H), 7.51 (t, J = 4.0 Hz, 2 H), 7.15 (d, J = 4.0 Hz, 1 H), 7.12 (d, J = 4.0 Hz, 1 H), 6.97 (d, J = 4.0 Hz, 1 H), 6.61 (s, 1 H), 3.90 (s, 3 H), 3.63 (s, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 161.1, 153.2, 148.9, 136.1, 135.5, 133.9, 132.9, 131.2, 129.6, 128.9, 128.8, 127.9, 126.5, 119.0, 107.0, 106.9, 105.7, 55.7, 55.3.

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{15}\text{NO}_3\text{S}_2)\text{H}]$ ($\text{M}+\text{H}$) 370.0572, measured 370.0566.

6,7-Dimethoxy-4-methyl-3-phenylisoquinolin-1(2H)-one (4d).



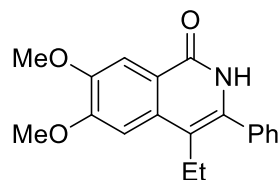
Off-white solid; eluent (60% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.11 (bs, 1 H), 7.65 (s, 1 H), 7.51 – 7.42 (m, 5 H), 7.11 (s, 1 H), 3.94 (s, 3 H), 3.88 (s, 3 H), 2.12 (s, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 160.8, 153.0, 148.3, 136.2, 134.9, 133.5, 129.7, 128.4, 128.1, 107.0, 106.9, 104.6, 55.6, 55.4, 13.8.

HRMS (ESI): calc. for $[(\text{C}_{18}\text{H}_{17}\text{NO}_3)\text{H}]$ (M+H) 296.1287, measured 296.1283.

4-Ethyl-6,7-dimethoxy-3-phenylisoquinolin-1(2H)-one (4e).



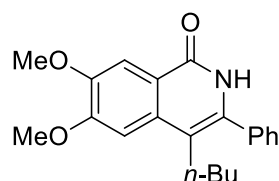
Grey solid; eluent (60% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 9.71 (bs, 1 H), 7.80 (s, 1 H), 7.47 – 7.44 (m, 5 H), 7.10 (s, 1 H), 4.03 (s, 3 H), 4.02 (s, 3 H), 2.66 (q, J = 8.0 Hz, 2 H), 1.22 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 161.8, 153.6, 148.8, 135.8, 135.6, 133.3, 129.1, 128.9, 128.7, 115.2, 107.8, 104.2, 56.2, 56.1, 20.8, 15.3.

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{19}\text{NO}_3)\text{H}]$ (M+H) 310.1443, measured 310.1439.

4-Butyl-6,7-dimethoxy-3-phenylisoquinolin-1(2H)-one (4f).



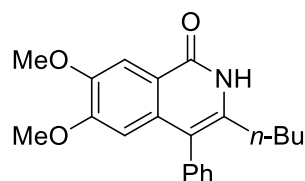
Pale yellow solid; eluent (60% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.12 (s, 1 H), 7.68 (s, 1 H), 7.53 – 7.48 (m, 3 H), 7.44 – 7.41 (m, 2 H), 7.12 (s, 1 H), 3.94 (s, 3 H), 3.91 (s, 3 H), 2.54 – 2.52 (m, 2 H), 1.53 – 1.46 (m, 2 H), 1.27 – 1.18 (m, 2 H), 0.79 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 160.6, 153.0, 148.2, 136.7, 135.1, 132.6, 129.3, 128.5, 128.2, 119.5, 111.9, 107.2, 104.4, 55.57, 55.51, 31.9, 26.2, 22.0, 13.5.

HRMS (ESI): calc. for $[(\text{C}_{21}\text{H}_{23}\text{NO}_3)\text{H}]$ (M+H) 338.1756, measured 338.1755.

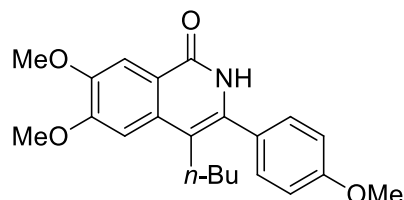
3-Butyl-6,7-dimethoxy-4-phenylisoquinolin-1(2H)-one (4f').



Brown solid; eluent (58% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.25 (s, 1 H), 7.61 (s, 1 H), 7.52 – 7.41 (m, 3 H), 7.27 (d, J = 8.0 Hz, 2 H), 6.33 (s, 1 H), 3.85 (s, 3 H), 3.53 (s, 3 H), 2.25 (t, J = 8.0 Hz, 2 H), 1.49 -1.41 (m, 2 H), 1.16 -1.07 (m, 2 H), 0.69 (t, J = 8.0 Hz, 3 H).

4-Butyl-6,7-dimethoxy-3-(4-methoxyphenyl)isoquinolin-1(2H)-one (4g).



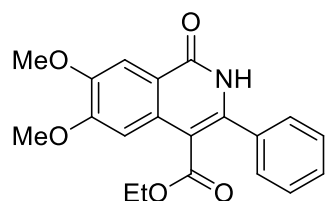
Pale yellow solid; eluent (65% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.01 (s, 1 H), 7.64 (s, 1 H), 7.32 (d, J = 8.0, 2 H), 7.08 (s, 1 H), 7.02 (d, J = 8.0 Hz, 2 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 2.53 – 2.50 (m, 2 H), 1.47 -1.46 (m, 2 H), 1.25 – 1.23 (m, 2 H), 0.79 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 160.6, 159.2, 152.9, 148.1, 136.5, 132.7, 130.6, 127.4, 119.3, 113.5, 111.9, 107.1, 104.4, 55.57, 55.51, 55.1, 32.0, 26.3, 22.0, 13.6.

HRMS (ESI): calc. for $[(\text{C}_{22}\text{H}_{25}\text{NO}_4)\text{H}]$ (M+H) 368.1862, measured 368.1860.

Ethyl 6,7-dimethoxy-1-oxo-3-phenyl-1,2-dihydroisoquinoline-4-carboxylate (4h).



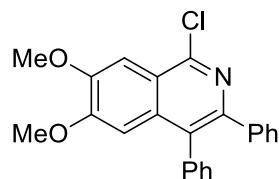
Pale yellow semisolid; eluent (65% ethyl acetate in hexanes).

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.65 (s, 1 H), 7.60 (s, 1 H), 7.44- 7.41 (m, 3 H), 7.37 (d, J = 8.0, 2 H), 7.21 (s, 1 H), 3.90 (q, J = 8.0 Hz, 2 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 0.75 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 167.3, 161.4, 153.9, 149.3, 142.3, 135.0, 130.3, 129.8, 128.9, 128.7, 118.9, 108.4, 107.4, 105.2, 61.1, 56.1 (2 OMe merged together), 13.8.

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{19}\text{NO}_5)\text{H}]$ (M+H) 354.1341, measured 354.1349.

1-Chloro-6,7-dimethoxy-3,4-diphenylisoquinoline (5a).



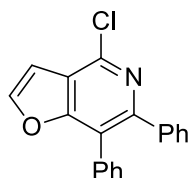
Colorless solid; eluent (18% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 7.61 (s, 1 H), 7.37 - 7.31 (m, 5 H), 7.24 - 7.22 (m, 2 H), 7.18 - 7.16 (m, 3 H), 6.90 (s, 1 H), 4.09 (s, 3 H), 3.77 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 153.2, 150.6, 148.6, 148.0, 139.5, 136.9, 134.6, 130.9, 130.1, 129.7, 128.4, 127.5, 127.1, 121.4, 104.6, 104.3, 56.2, 55.8.

HRMS (ESI): calc. for $[(\text{C}_{23}\text{H}_{18}\text{ClNO}_2)\text{H}]$ (M+H) 376.1104, measured 376.1112.

4-Chloro-6,7-diphenylfuro[3,2-c]pyridine (5b).



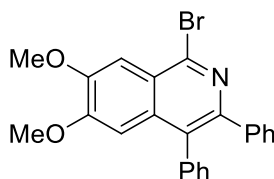
Colorless solid; eluent (5% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 7.66 (d, J = 4.0 Hz, 1 H), 7.40 – 7.37 (m, 2 H), 7.35 – 7.29 (m, 5 H), 7.23 – 7.20 (m, 3 H), 6.93 (d, J = 4.0 Hz, 1 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 159.3, 152.1, 146.6, 141.9, 138.5, 132.8, 130.5, 130.3, 128.4, 128.0, 127.9, 122.7, 119.9, 105.2.

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{12}\text{ClNO})\text{H}]$ (M+H) 306.0686, measured 306.0695.

1-Bromo-6,7-dimethoxy-3,4-diphenylisoquinoline (5c).



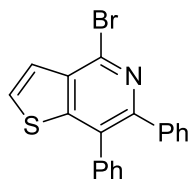
Colorless solid; eluent (18% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 7.59 (s, 1 H), 7.37 – 7.31 (m, 5 H), 7.24 – 7.22 (m, 2 H), 7.18 – 7.16 (m, 3 H), 6.89 (s, 1 H), 4.10 (s, 3 H), 3.77 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 153.2, 150.7, 149.1, 141.7, 139.4, 136.8, 134.2, 130.8, 130.1, 128.4, 127.5, 127.1, 123.5, 106.7, 104.5, 56.2, 55.8.

HRMS (ESI): calc. for $[(\text{C}_{23}\text{H}_{18}\text{BrNO}_2)\text{H}]$ (M+H) 420.0599, measured 420.0605.

4-Bromo-6,7-diphenylthieno[3,2-c]pyridine (5d).



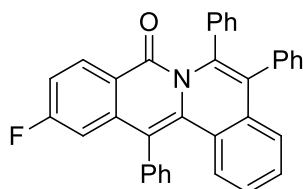
Colorless solid; eluent (5% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 7.53 (bs, 2 H), 7.39 – 7.35 (m, 5 H), 7.32 – 7.30 (m, 2 H), 7.21 – 7.18 (m, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 150.8, 150.1, 138.4, 137.2, 135.5, 135.2, 130.3, 129.5, 129.3, 129.0, 128.8, 128.2, 127.8, 124.4.

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{12}\text{BrNS})\text{H}]$ (M+H) 365.9952, measured 365.9962.

11-Fluoro-5,6,13-triphenyl-8*H*-isoquinolino[3,2-*a*]isoquinolin-8-one (5e).^{3a}



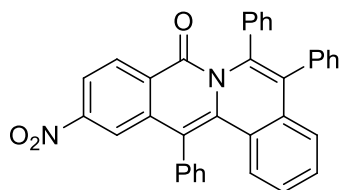
Yellow solid; eluent (13% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 8.27 – 8.23 (m, 1 H), 7.58 – 7.52 (m, 3 H), 7.51 – 7.49 (m, 2 H), 7.28 – 7.22 (m, 3 H), 7.18 – 7.10 (m, 6 H), 7.08 (bs, 5 H), 6.99 – 6.95 (m, 1 H), 6.91 – 6.87 (m, 1 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.6 and 164.1 (F coupling), 161.4, 139.6 and 139.5, 138.1, 137.0, 136.1, 135.9, 135.1, 133.1, 131.9, 131.3, 130.7 and 130.6 (F coupling), 129.8, 128.7, 128.3, 127.9, 127.1, 127.0, 128.3, 127.9, 127.1, 127.0, 126.87, 126.80, 126.3, 125.7, 122.3, 116.14 and 116.1 (F coupling), 115.1 and 114.8 (F coupling), 110.7 and 110.5 (F coupling).

HRMS (ESI): calc. for $[(\text{C}_{35}\text{H}_{22}\text{FNO})\text{H}]$ (M+H) 492.1764, measured 492.1754.

11-Nitro-5,6,13-triphenyl-8*H*-isoquinolino[3,2-*a*]isoquinolin-8-one (5f).^{3a}

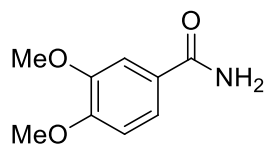


Pale yellow solid; eluent (15% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 8.37 (d, J = 8.0 Hz, 1 H), 8.22 (d, J = 2.0 Hz, 1 H), 8.15 (dd, J = 8.0, 2.0 Hz, 1 H), 7.61 – 7.58 (m, 3 H), 7.52 – 7.50 (m, 2 H), 7.28 – 7.22 (m, 4 H), 7.17 – 7.15 (m, 4 H), 7.11 – 7.06 (m, 5 H), 6.95 – 6.91 (m, 1 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 160.8, 150.3, 137.7, 137.2, 136.4, 136.0, 135.8, 135.6, 133.1, 131.8, 131.2, 130.2, 129.4, 129.3, 129.2, 128.9, 128.8, 128.4, 128.0, 127.8, 127.3, 127.2, 127.1, 126.7, 126.6, 125.9, 121.2, 119.7, 116.3.

3,4-Dimethoxybenzamide (11a).^{3c}



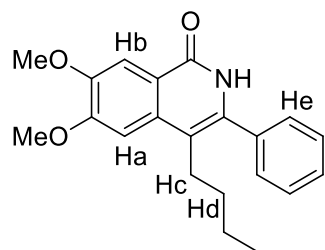
Pale yellow solid; eluent (70% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 7.46 (s, 1 H), 7.34 (d, $J = 8.0$ Hz, 1 H), 6.87 (d, $J = 8.0$ Hz, 1 H), 6.84 (bs, 2 H), 3.93 (s, 6 H).

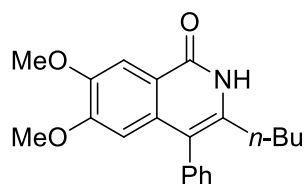
Refs:

3. (a) B. Li, H. Feng, S. Xu and B. Wang, *Chem. Eur. J.* 2012, **18**, 12873. (b). B. Li, H. Feng, S. Xu and B. Wang, *Chem. Eur. J.* 2011, **17**, 12573. (c) M. D. Ganton and M. A. Kerr, *Org. Lett.* 2005, **7**, 4777.

3B.13: Regioselective studies: NOESY Experiments

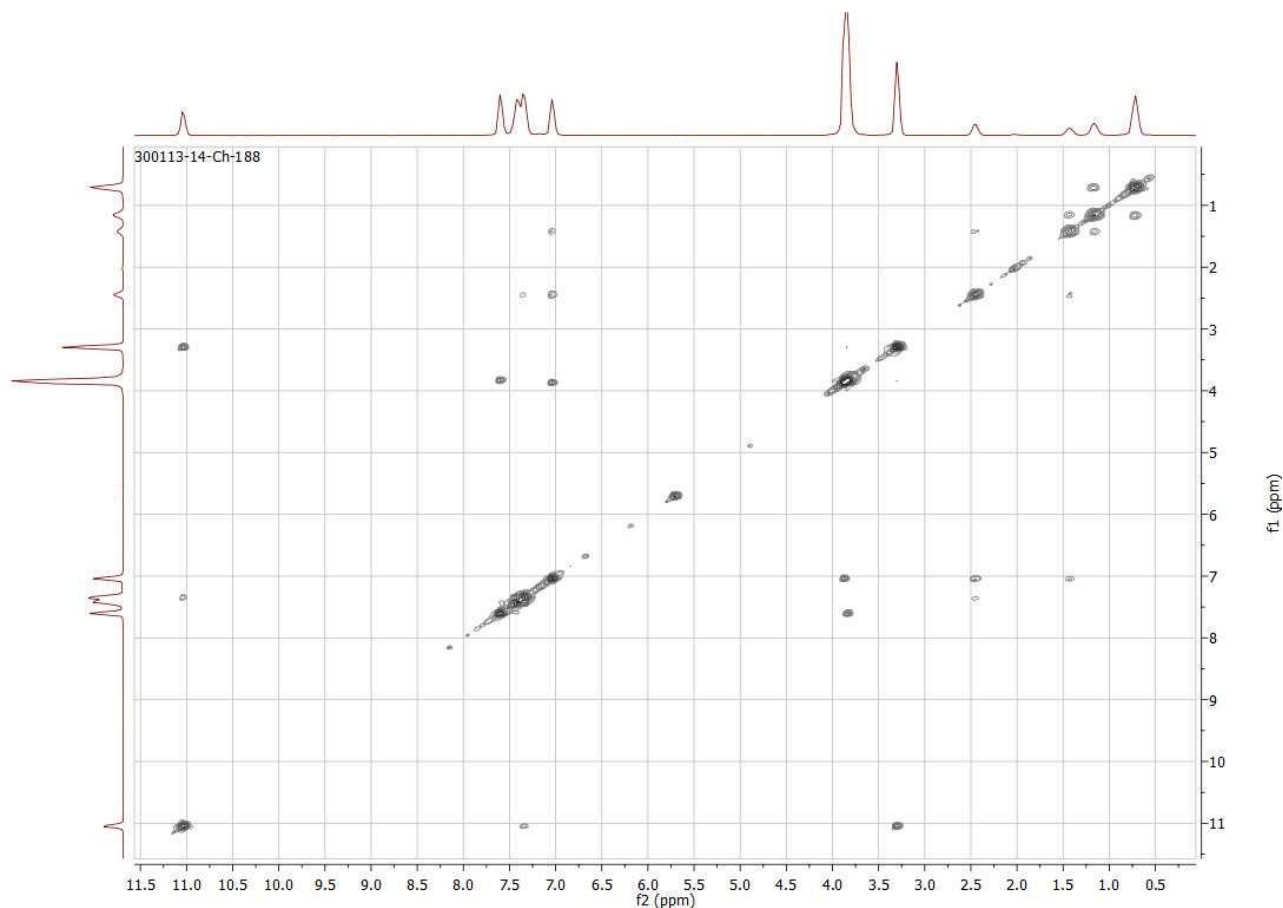
Copy of NOESY Experiment of Compound **4f**.Ha δ = 7.12; Hb = 7.68; Hc = 2.54Hd δ = 1.53, He = 7.53

Observed

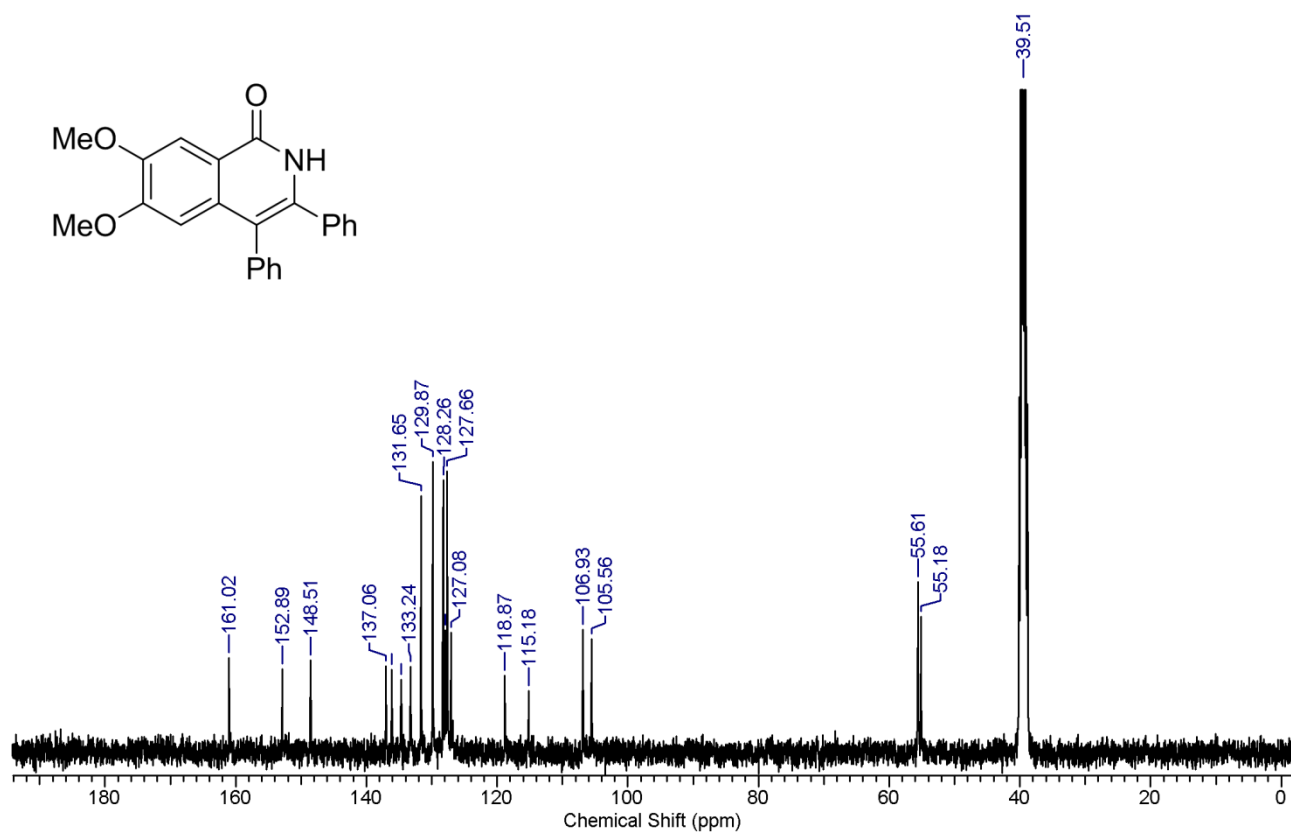
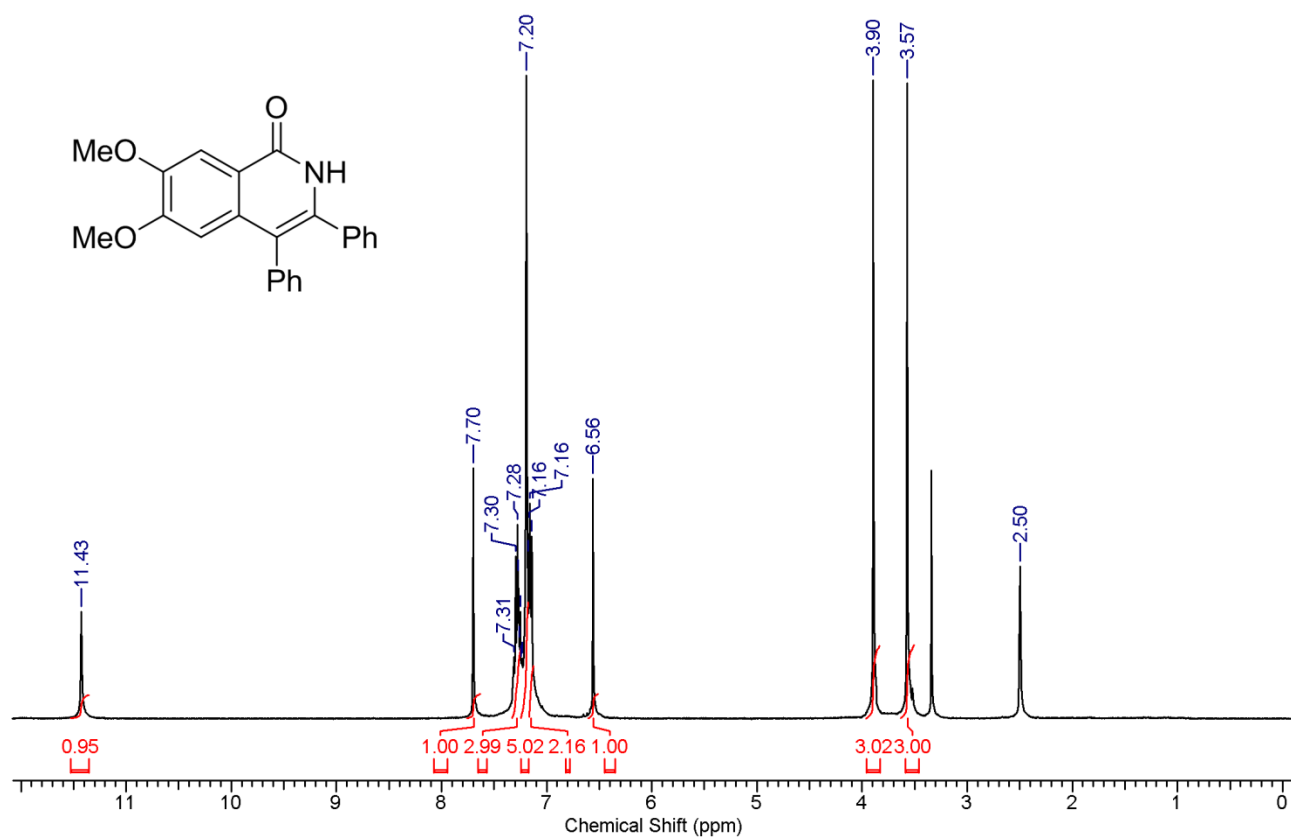


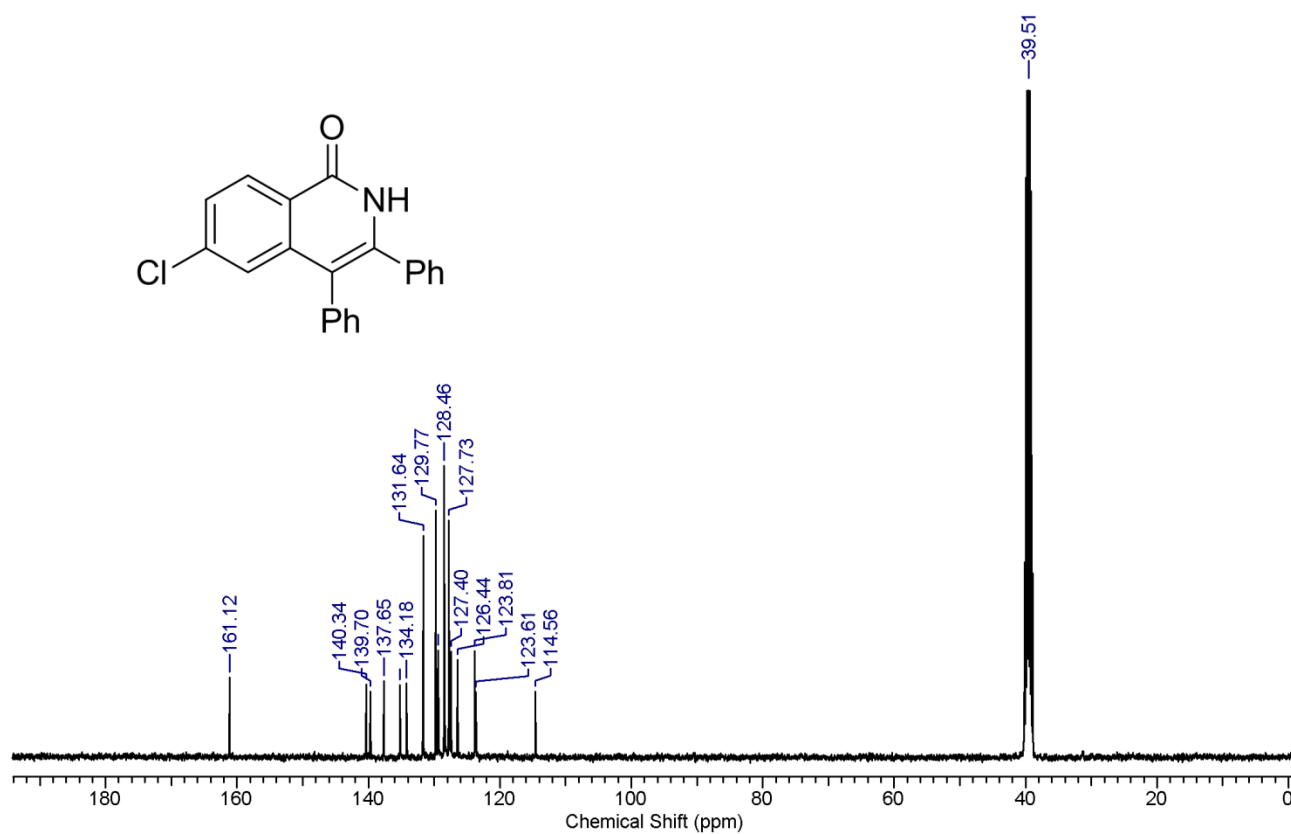
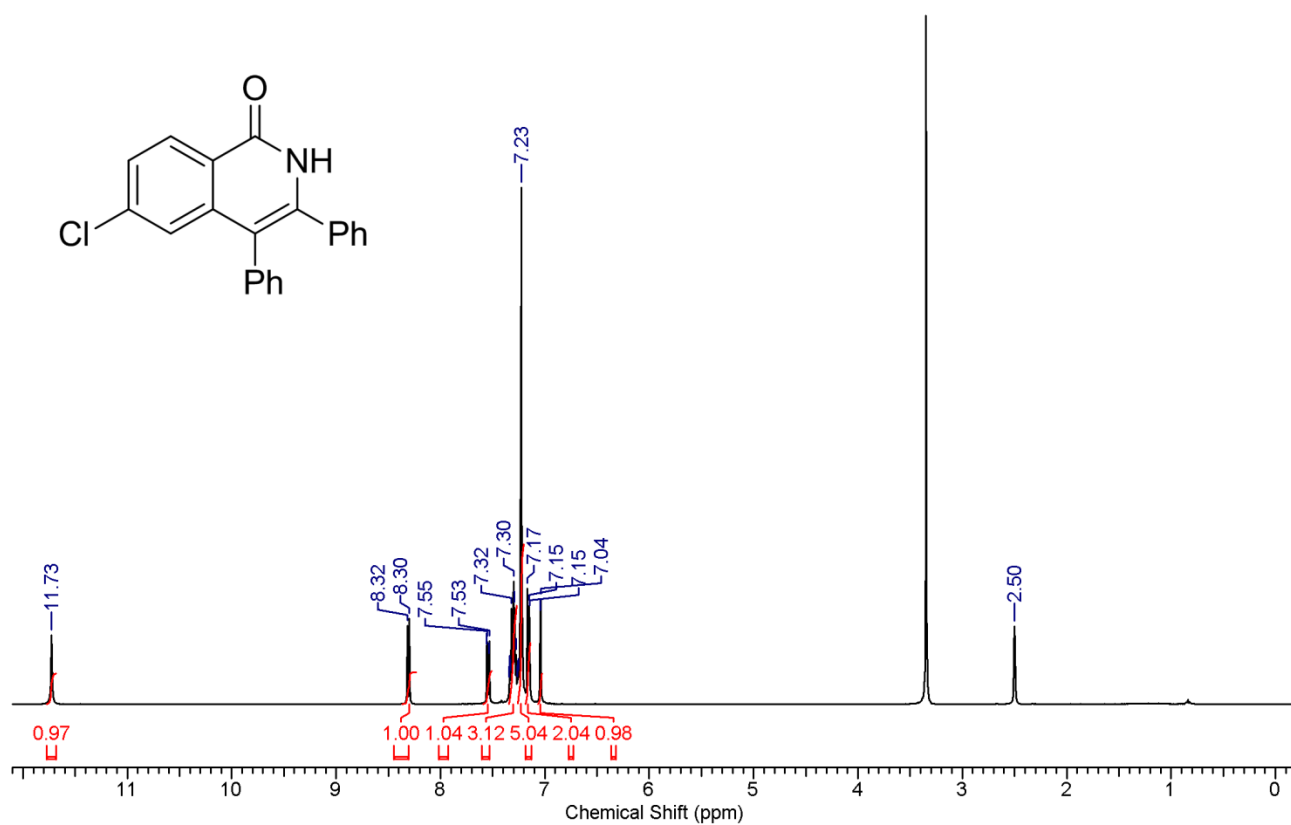
Not observed

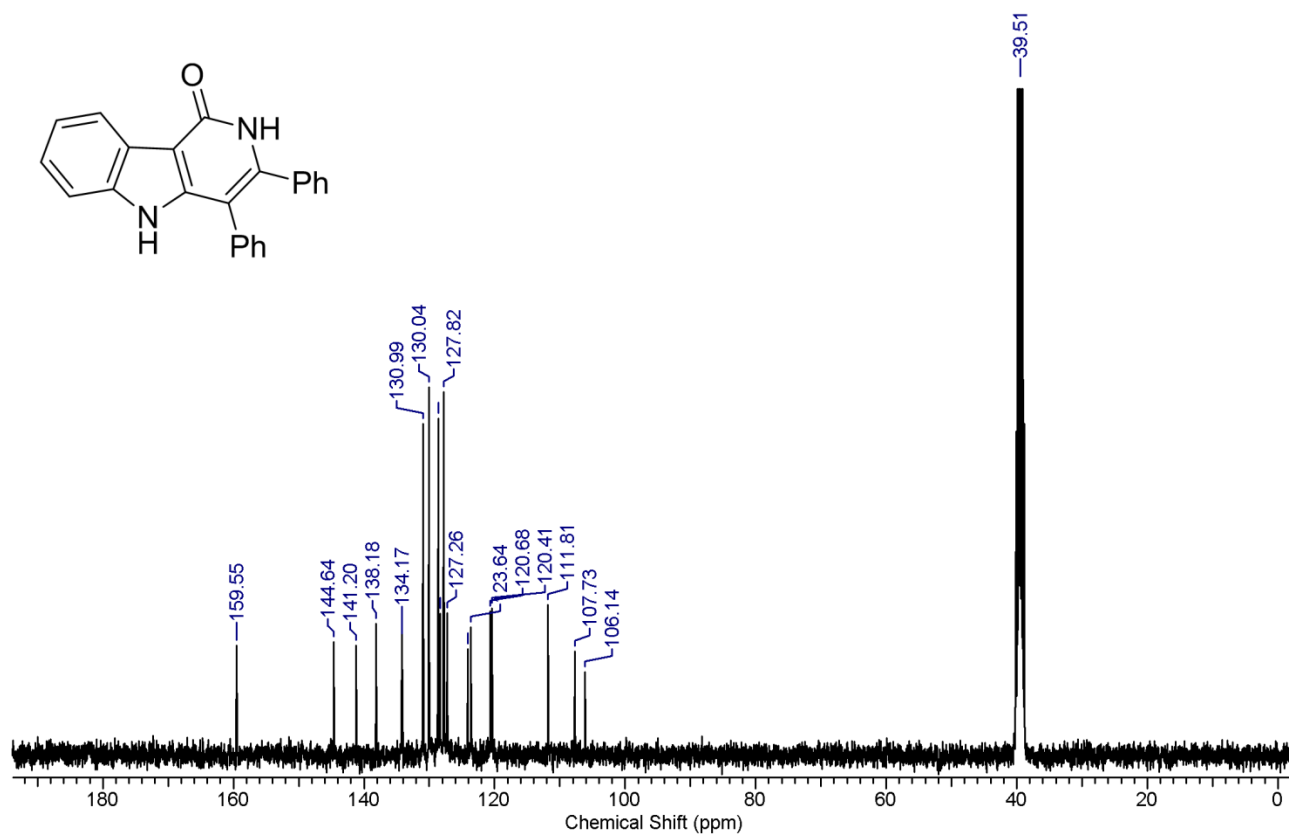
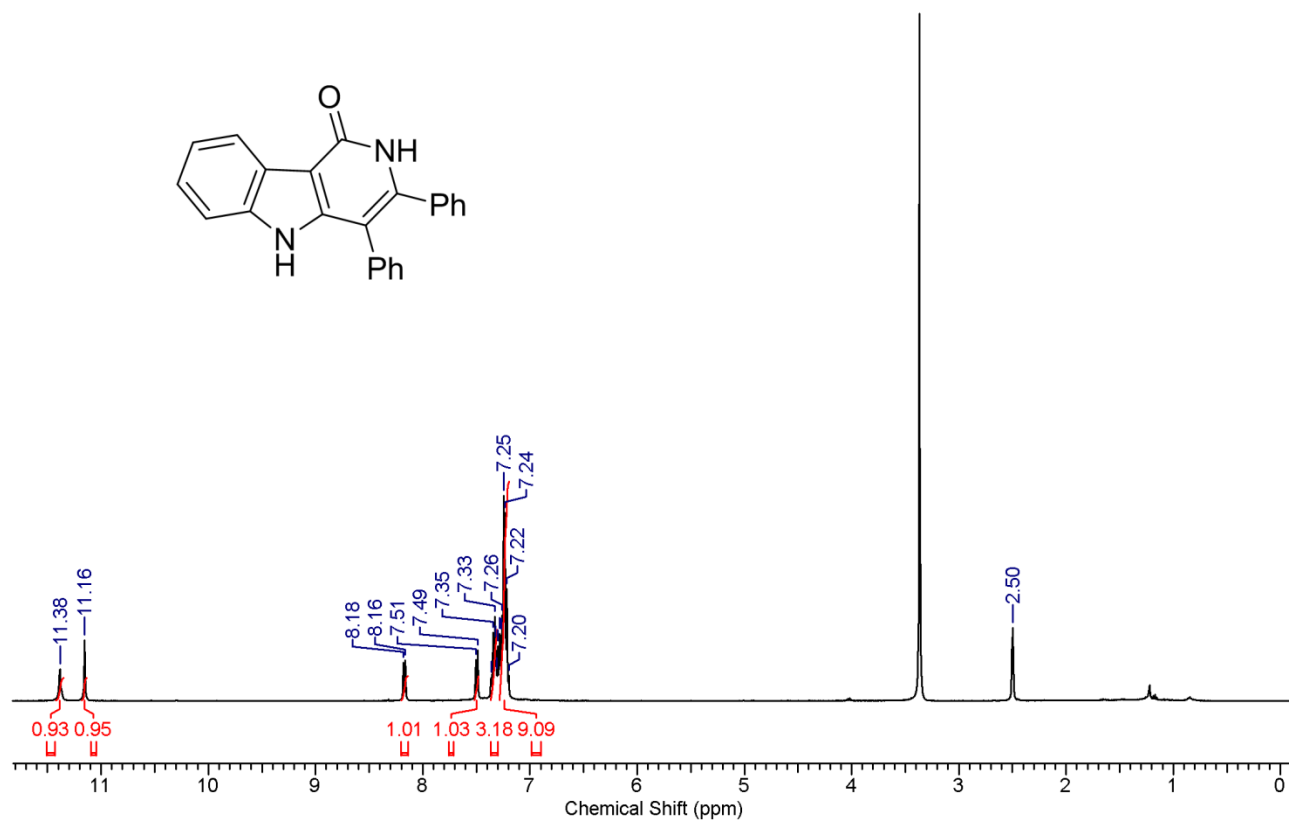
There is a NOE correlation between Ha (δ 7.12, s) and Hc (δ 2.54, m). In meantime, there is also a correlation between Hc (δ 2.54, m) and He (δ 7.53, m). These results clearly revealed that the regiochemistry of compound **4f** is correct.

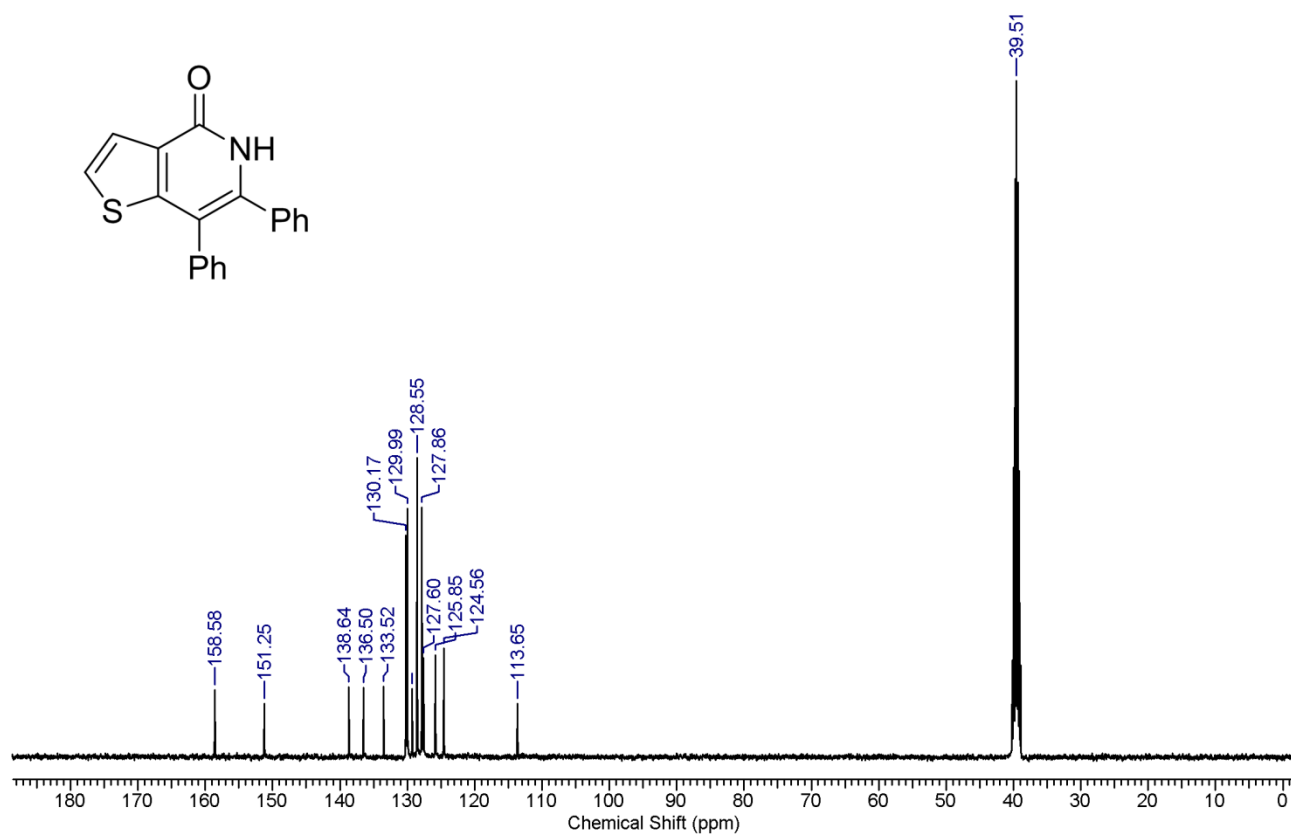
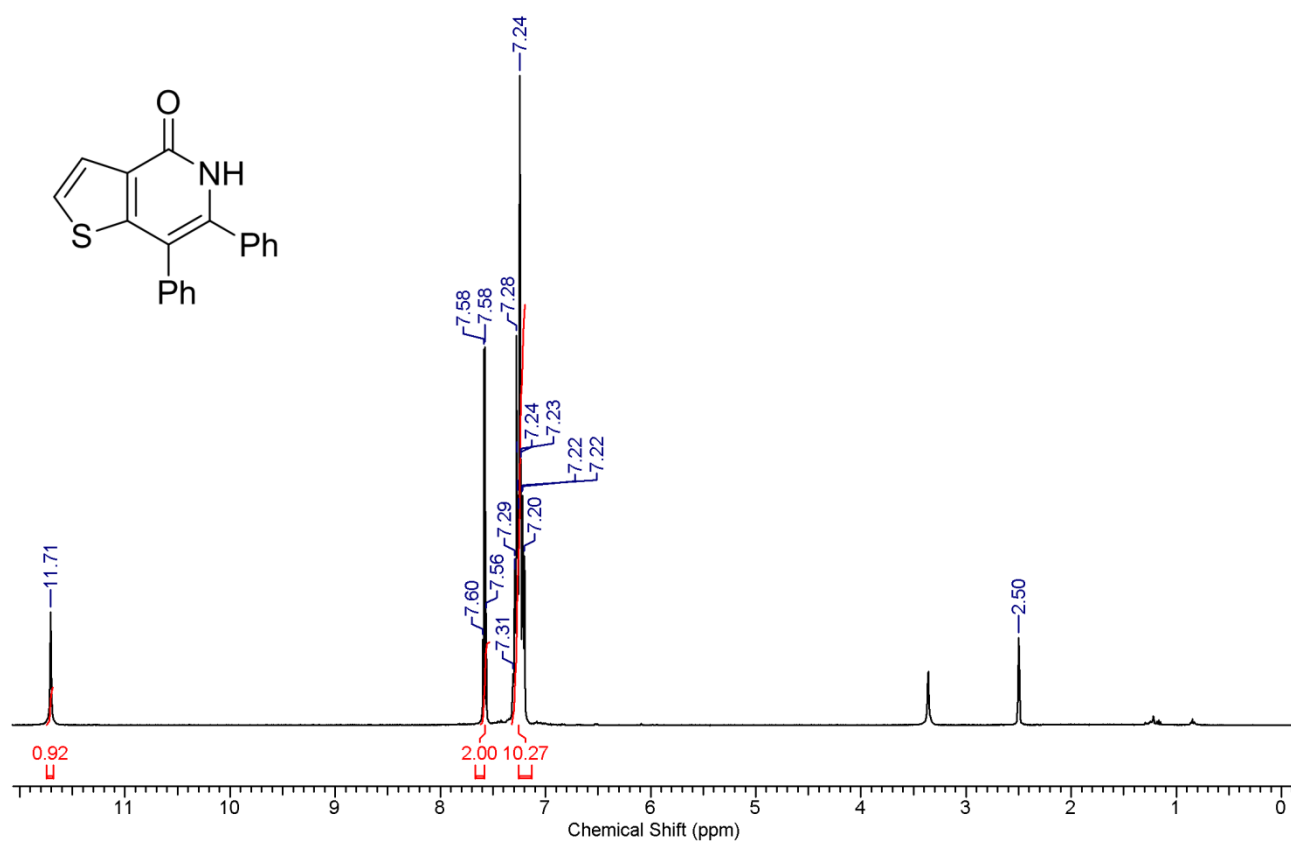


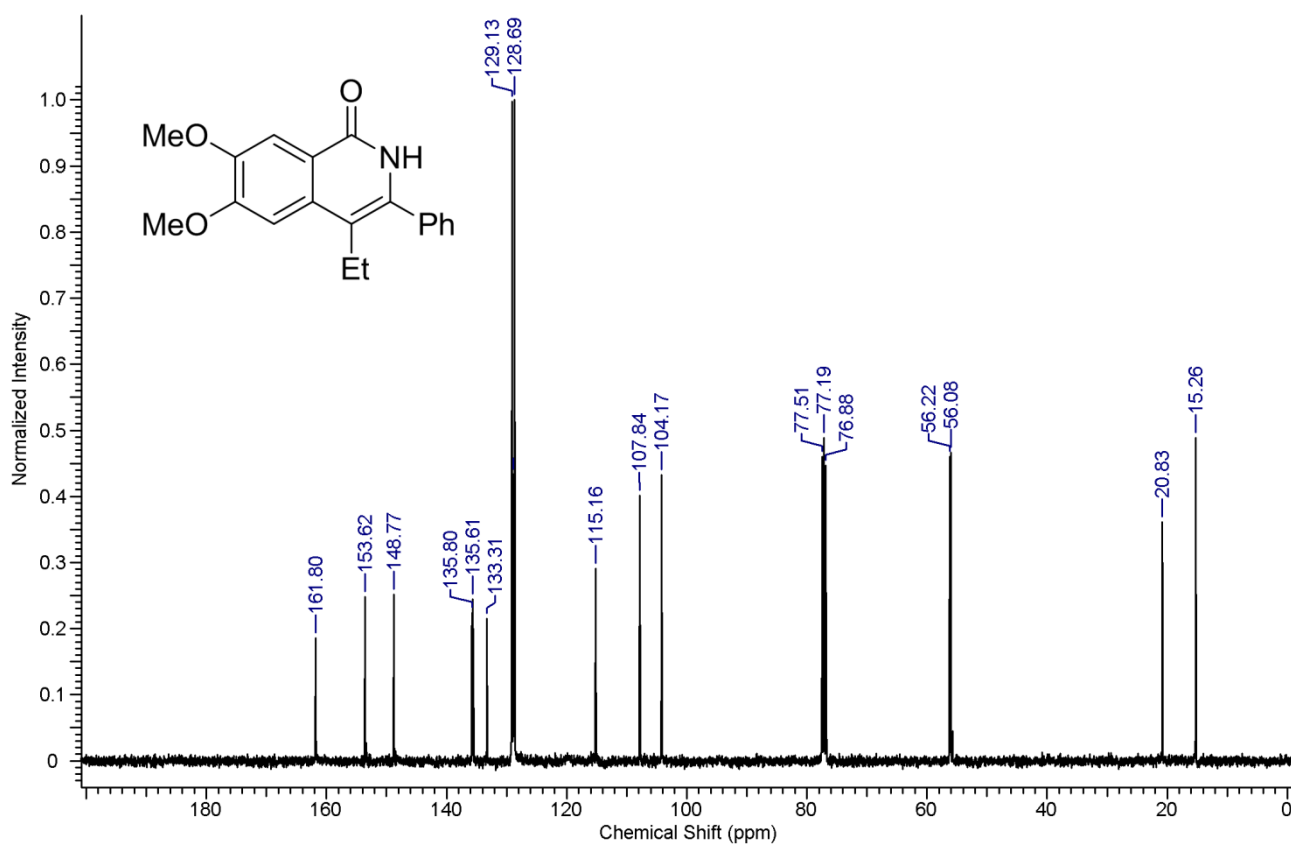
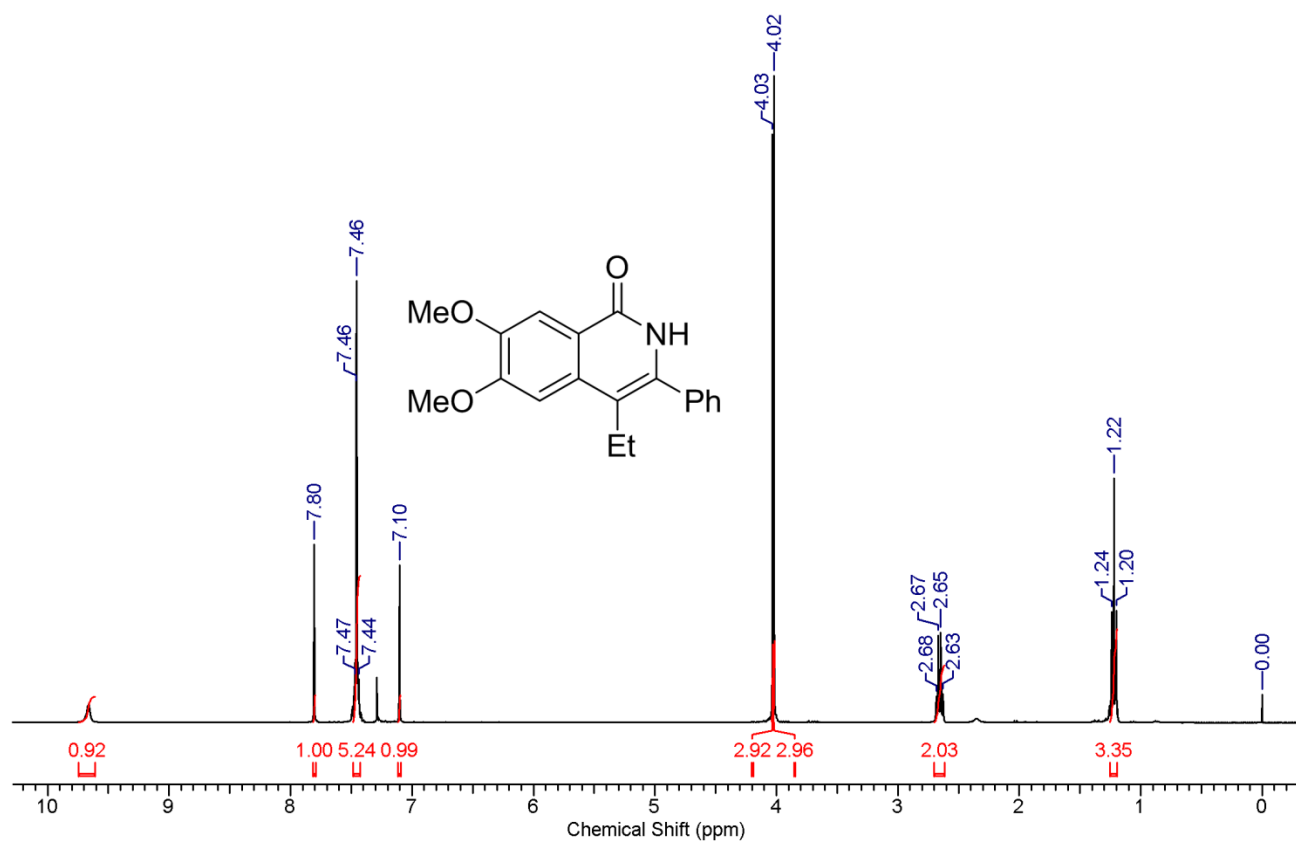
3B.14: Spectral Copies of Selected Compounds

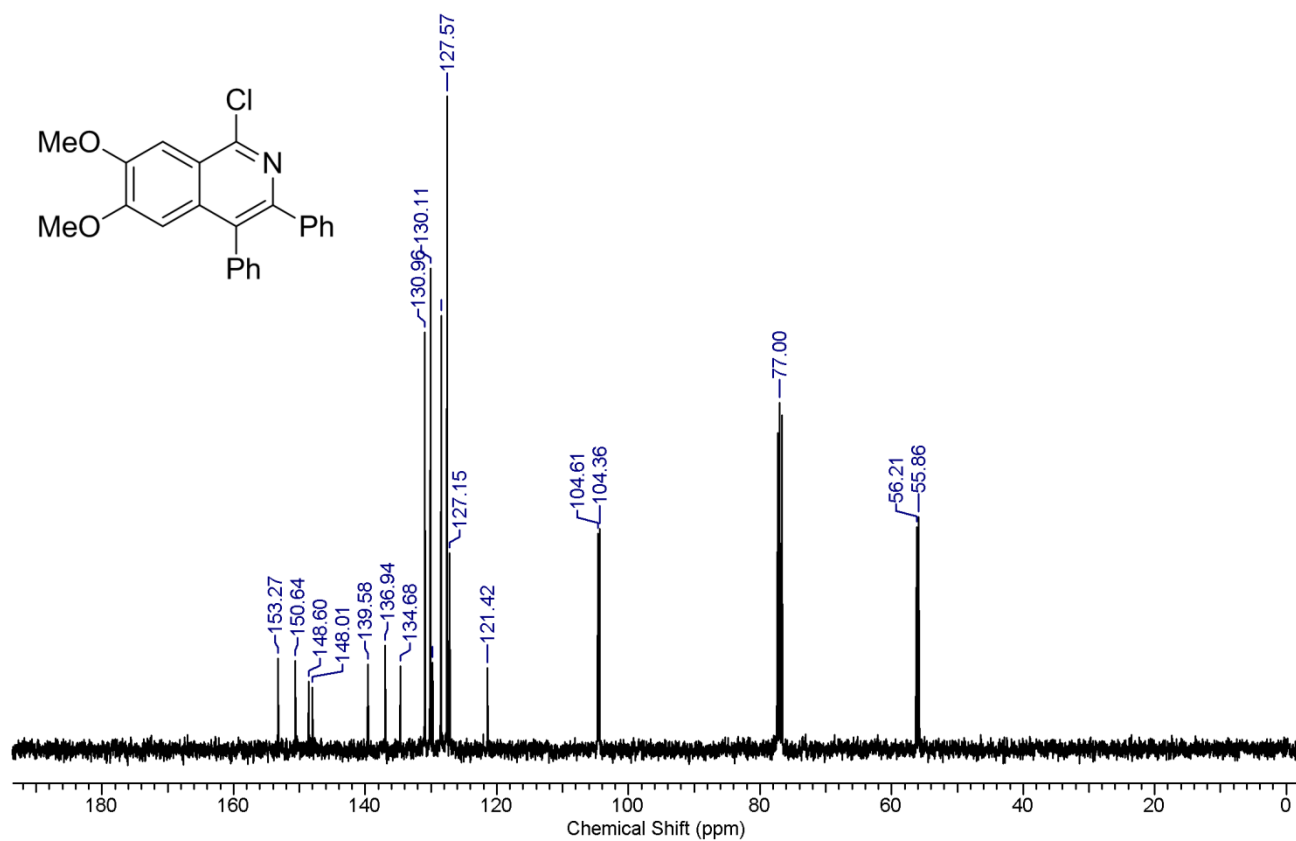
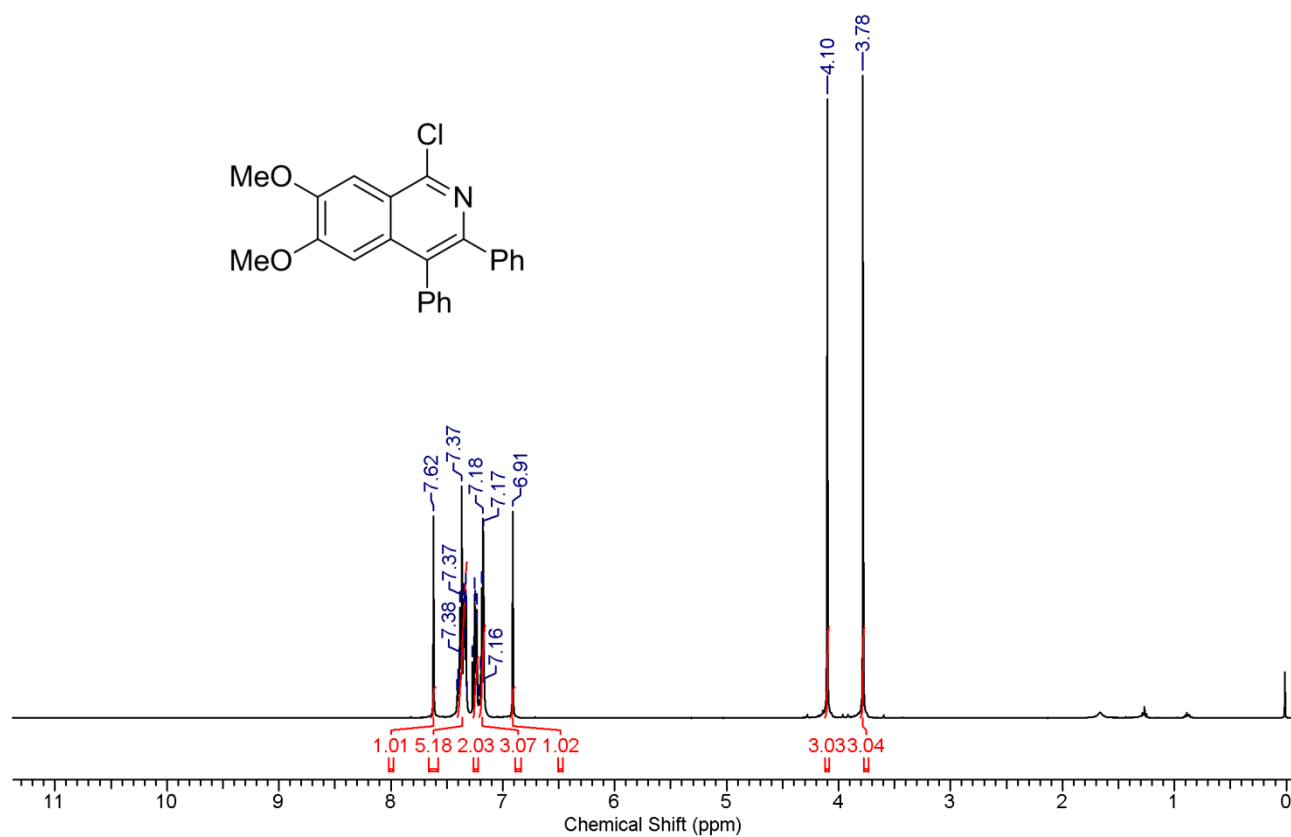
 ^1H and ^{13}C NMR Spectra of Compound 3a.

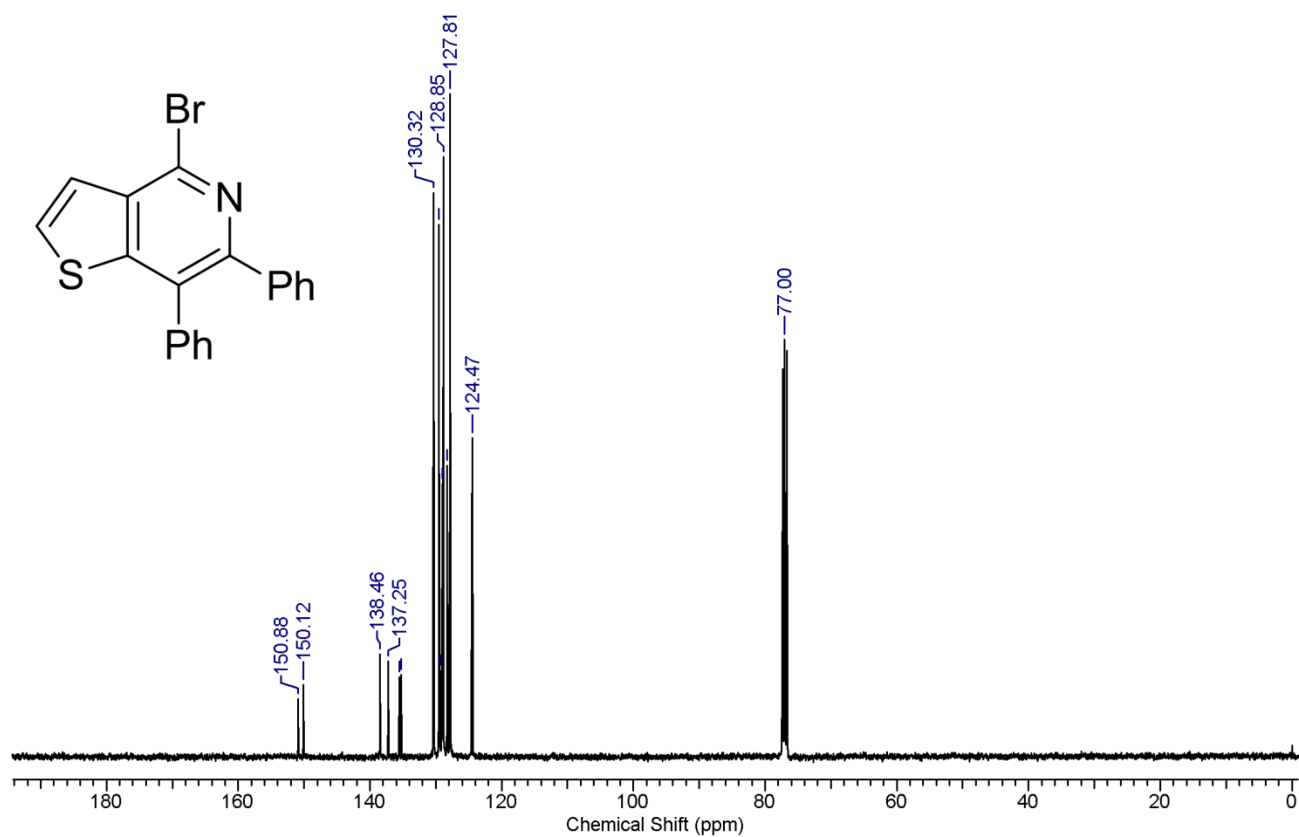
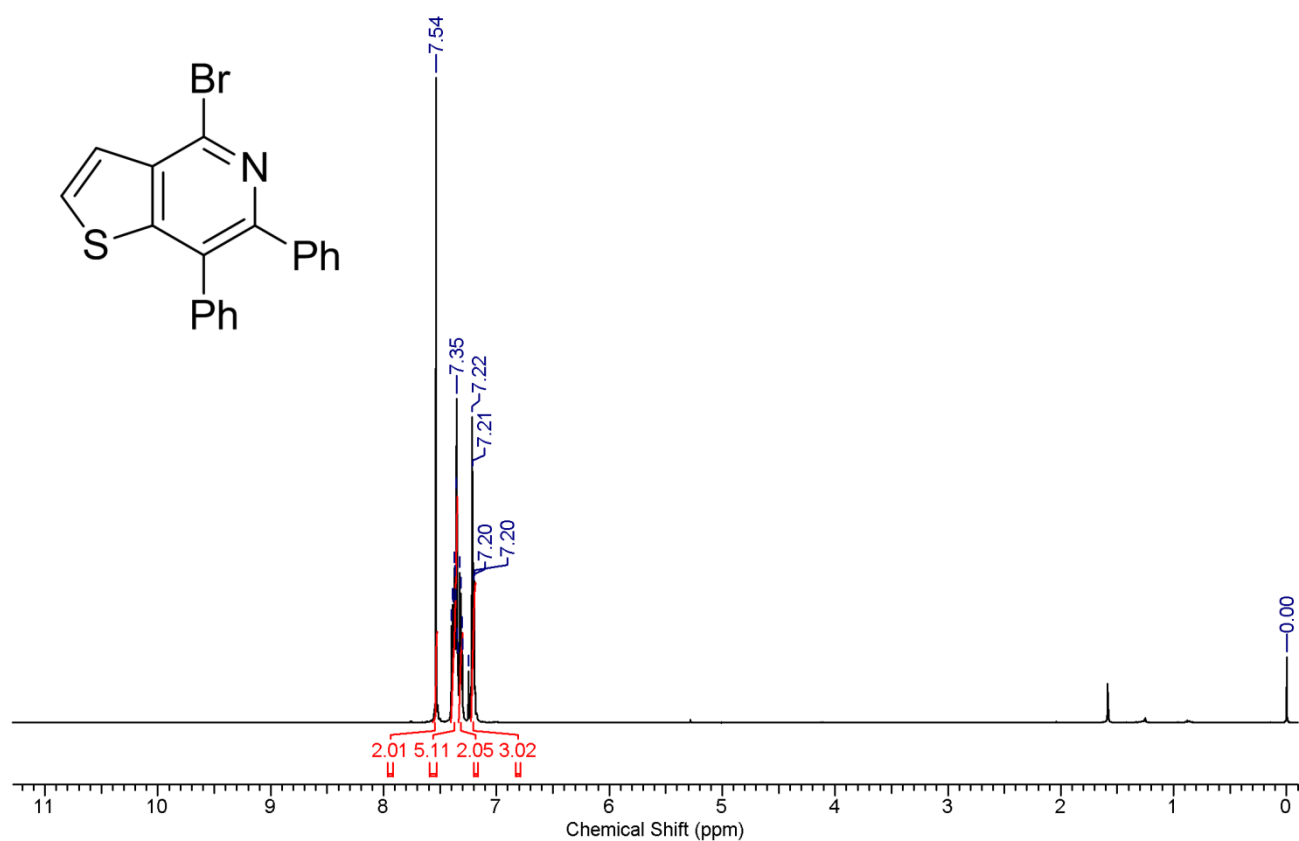
^1H and ^{13}C NMR Spectra of Compound **3h**.

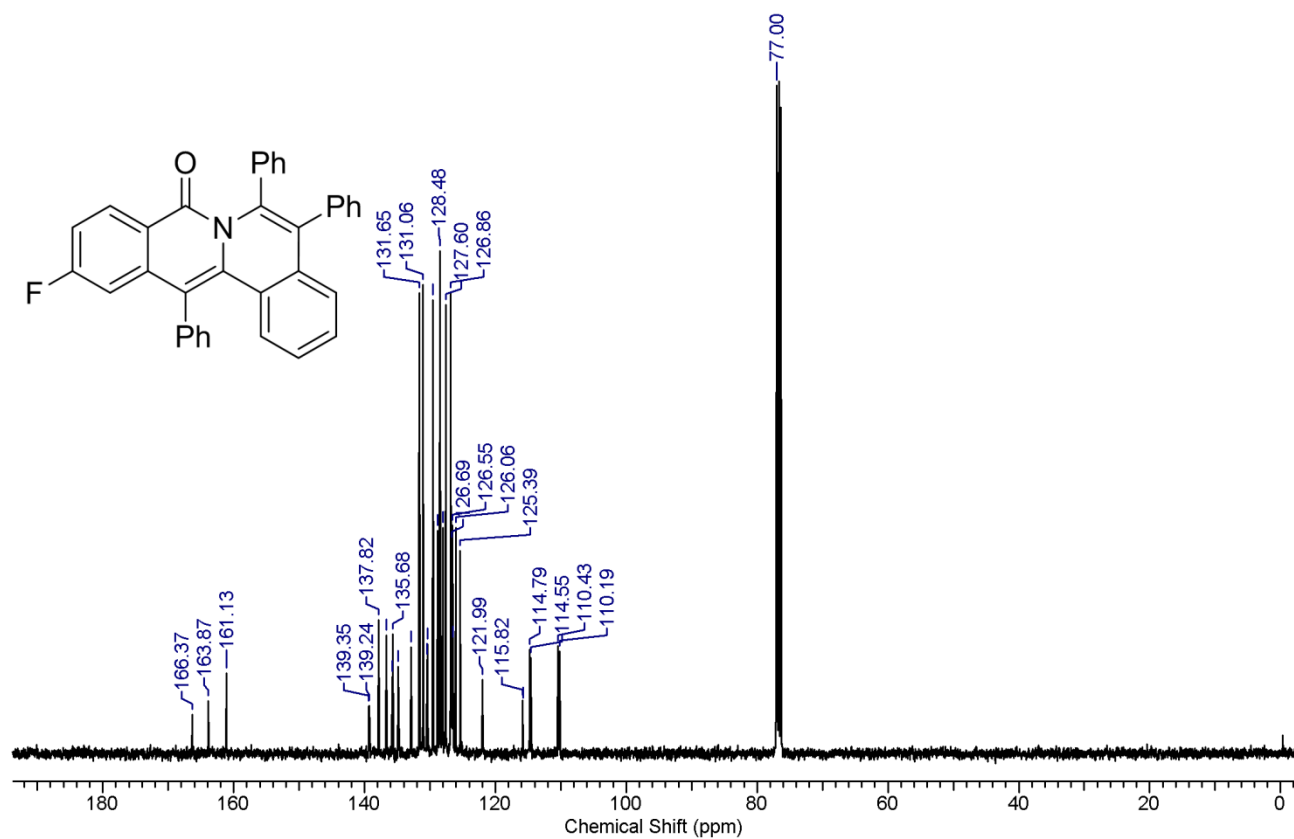
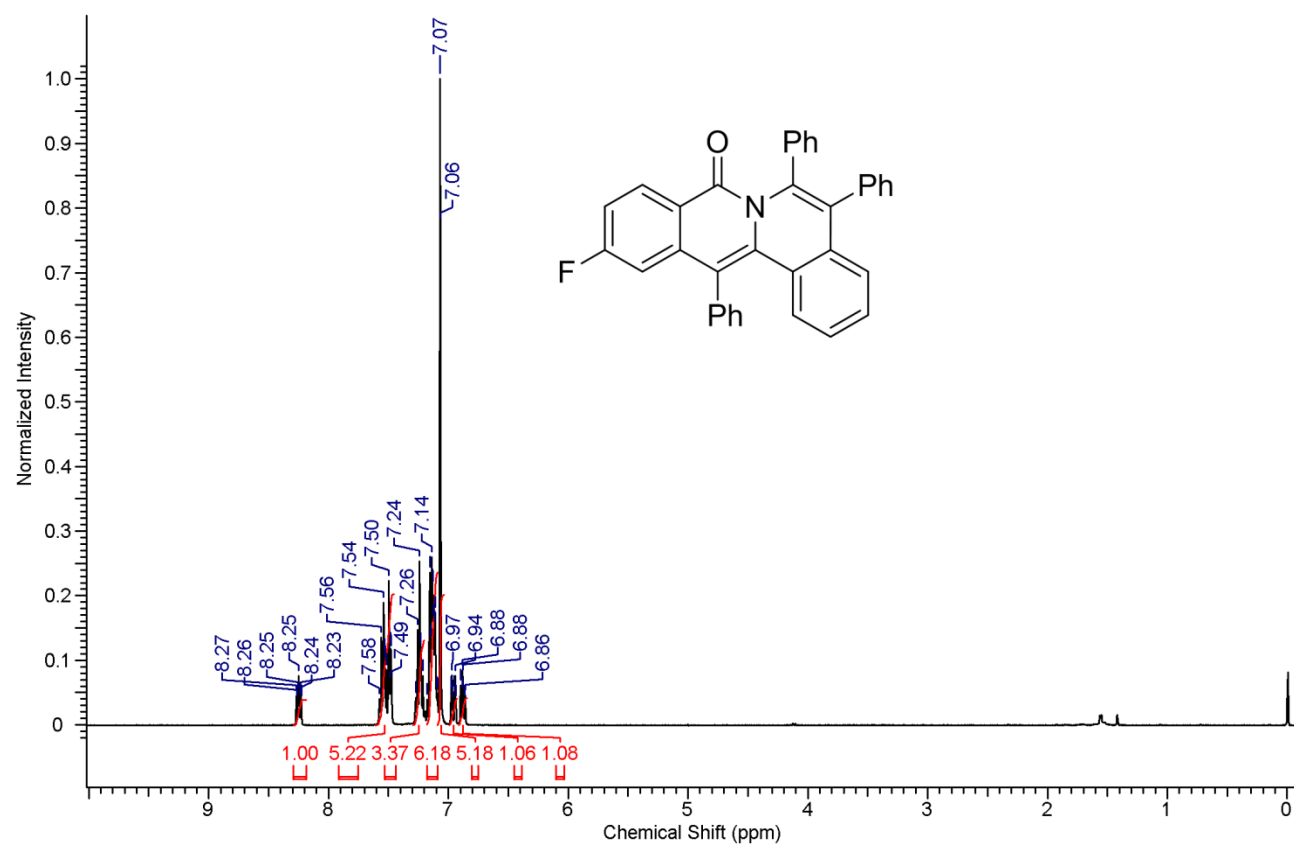
^1H and ^{13}C NMR Spectra of Compound **3r**.

^1H and ^{13}C NMR Spectra of Compound **3s**.

^1H and ^{13}C NMR Spectra of Compound **4e**.

^1H and ^{13}C NMR Spectra of Compound 5a.

^1H and ^{13}C NMR Spectra of Compound **5d**.

^1H and ^{13}C NMR Spectra of Compound 5e.

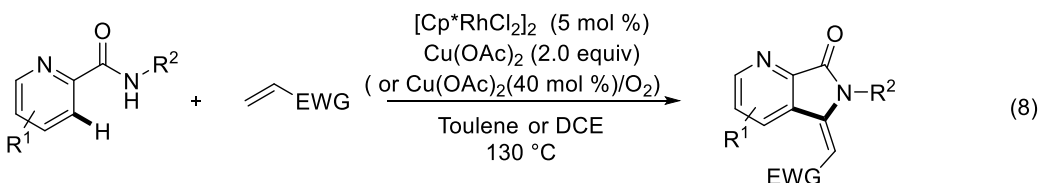
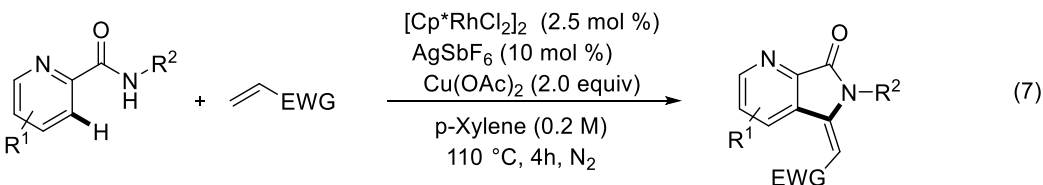
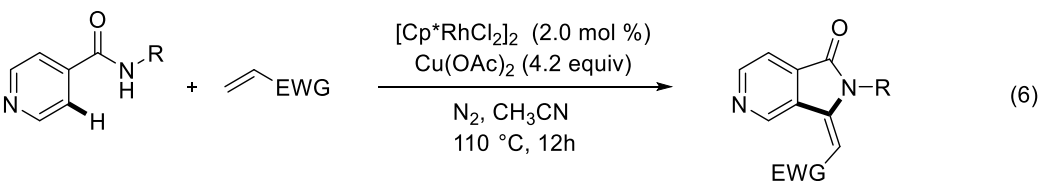
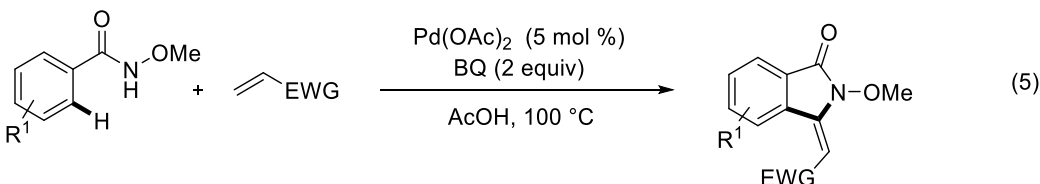
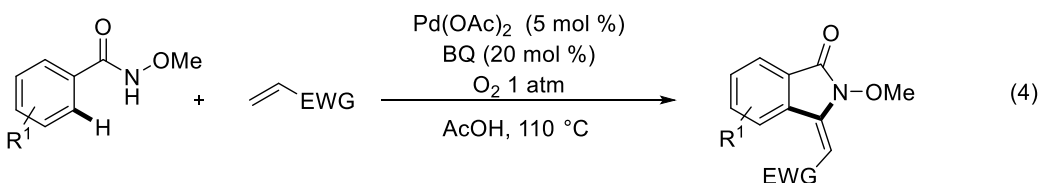
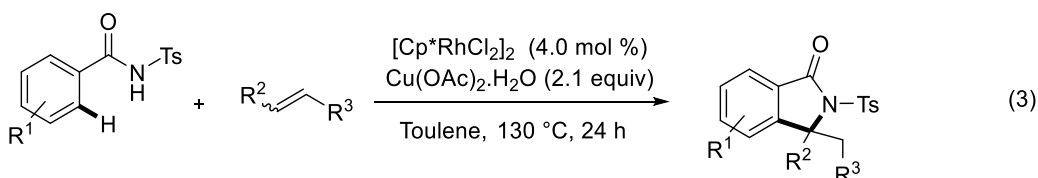
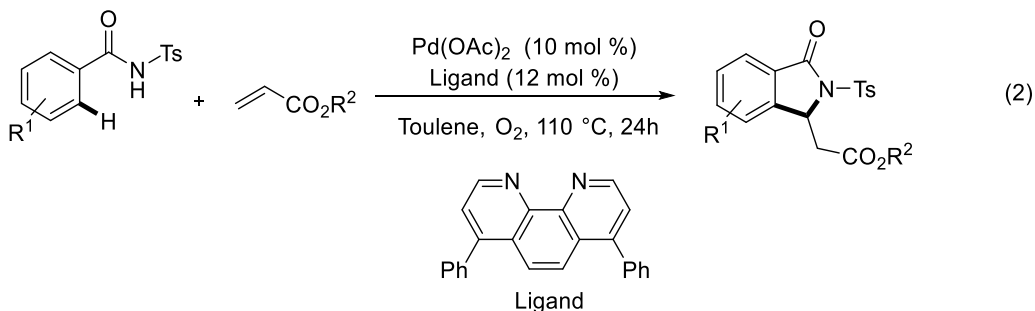
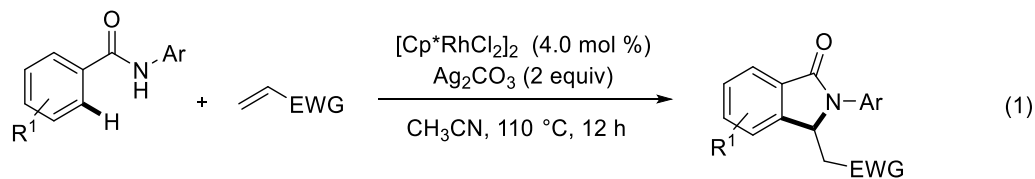
Section 3C: Ruthenium-Catalyzed Cyclization of Aromatic Nitriles with Alkenes: Stereoselective Synthesis of (Z)-3-Methyleneisoindolin-1-ones

3C.1: Introduction

Isoindolinone is a core structure unit present in various natural products and biologically active molecules.¹ Particularly, 3-methyleneisoindolin-1-one structural motif is found in several biologically active natural products and designed pharmaceutical molecules.² Traditionally, 3-methyleneisoindolin-1-ones are prepared by the reaction of phthalimides with Wittig reagents and nucleophilic addition of organometallic reagents into phthalimides followed by dehydration.³ Alternatively, it can also be prepared by metal-catalyzed intramolecular cyclization of *ortho*-alkynyl benzamides, coupling of 2-halobenzamides with terminal alkynes and intermolecular coupling of substituted ynamides or *ortho*-vinyl benzamides with aromatic boronic acids.⁴ However, the control of regio- and stereoselectivity and the observation of competitive side products are critical problems in these reactions. In addition, preactivated halo substituted aromatics are required to prepare the key starting materials.

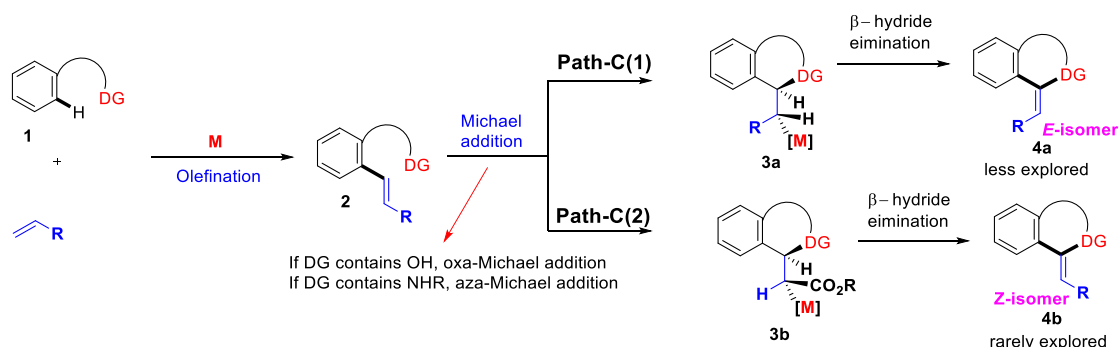
Recently, isoindolinone derivatives are efficiently prepared by metal-catalyzed oxidative cyclization of aromatic amides with alkenes without having any preactivated species on the aromatic moiety via chelation-assisted C-H bond activation.^{5,6} *N*-Aryl or tosyl benzamides reacted with alkenes in the presence of palladium or rhodium catalysts yielding five-membered isoindolinones (eq. 1 - 3).^{6a-c} *N*-Alkoxy benzamides reacted with activated alkenes in the presence of palladium catalyst yielding *E*-3-methyleneisoindolin-1-one derivatives (eq. 4 - 5).^{6d-e} In the meantime, *N*-methyl substituted benzamide or primary benzamides reacted with *n*-butyl acrylate affording 3-methyleneisoindolin-1-ones.^{6f} However, the corresponding reaction was studied with only two primary benzamides and a single 3-methoxy *N*-methyl benzamide and the observed yield was also very low. In fact, *N*-alkyl substituted benzamides and primary benzamide are not suitable substrates for the cyclization with alkenes due to the sluggish reactivity. Whereas, pyridine substituted amides underwent cyclization with alkenes efficiently in the presence of rhodium catalyst affording *cis* and *trans* stereoisomeric mixtures of 3-methyleneisoindolin-1-ones.^{6g-i} Apart from the benzamides, aromatic ketoximes reacted

with isocyanates giving a mixture of *cis* and *trans* stereoisomeric 3-methyleneisindolin-1-ones.⁷



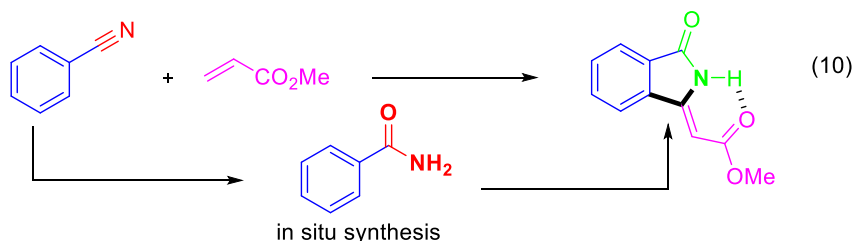
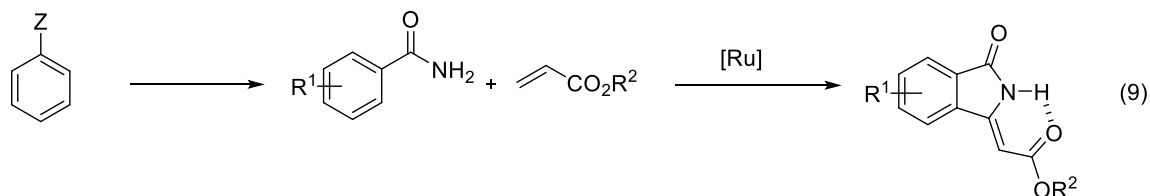
3C.2: Aim of The Present Work

We discussed about the stereoselective synthesis of *E*-isomer or *Z*-isomer via two different pathways in the first chapter. Stereoselective synthesis of *E*-isomer was shown by different synthetic groups (eq 4-8). In this work, we mainly focused very rarely explored pathway Path-C(2).



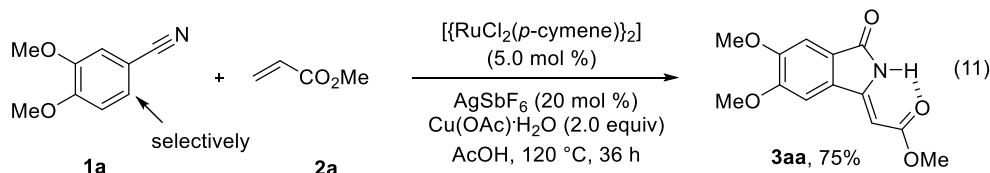
Scheme 3C.1: Stereoselective synthesis via C-H activation.

The development of a reaction by using primary benzamide with alkene in presence of metal catalyst was one of a good way to explore Path-C(2). For this reaction starting material primary benzamide synthesis is required. In this work, our first aim was to explore Path-C(2) (equ. 9) and at the same time our second aim was the in situ generation of benzamide from simple commercially available starting materials (equ. 10).



3C.3: Results and Discussion

Treatment of 3,4-dimethoxybenzonitrile (**1a**) with methyl acrylate (**2a**) in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (5.0 mol %), AgSbF_6 (20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv) in acetic acid (AcOH) at 120 °C for 36 h gave 3-methyleneisindolin-1-one **3aa** in 75% isolated yield in a high *Z*-stereoselectivity (eq 11)



3C.4: Optimization Studies

A proper selection of solvent and acetate source is crucial for the success of the reaction (Table 3C.1). The cyclization reaction of **1a** with **2a** was tested in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (5.0 mol %), additive (20 mol %) and oxidant (2.0 equiv) in various solvents at 120 °C for 36 h. Solvents such as $\text{ClCH}_2\text{CH}_2\text{Cl}$ (DCE), THF, 1,4-dioxane, $\text{OMeCH}_2\text{CH}_2\text{OMe}$ (DME), toluene, CH_3CN , DMSO, AcOH, *iso*-PrOH and DMF were tested (entries 1-10). Among them, AcOH was very effective, giving product **3aa** in 84% GC yield (entry 8). Instead of AgSbF_6 , the reaction was also tested with other additives such as AgBF_4 , AgOTf and KPF_6 . In these reactions, product **3aa** was observed only in 46%, 50%, and 27% yields, respectively (entries 11-13). Thus, AgSbF_6 was very effective additive for the reaction (entry 8). To avoid the stoichiometric amount of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, the reaction was examined with a catalytic amount of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (50 mol %) under an air atmosphere. However, cyclization product **3aa** was observed only in 32% GC yield (entry 14). Then, the reaction was tested with 1.00 equiv. amount of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (entry 15). In the reaction, product **3aa** was observed only in 49% GC yield. Thus, 2.0 equiv. amount of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ was needed for the reaction to get the better yield. Next, the reaction was tested with different acetate sources such as $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, AgOAc , $\text{Mn}(\text{OAc})_3$, NaOAc , $\text{Zn}(\text{OAc})_2$, LiOAc , $\text{PhI}(\text{OAc})_2$, NH_4OAc , $(\text{NH}_4)_2\text{S}_2\text{O}_8$, Ag_2O , Ag_2CO_3 and sodium pyruvate in AcOH solvent. Among them, only $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ was effective, affording product **3aa** in 84% GC yield (entry 8). The remaining acetate sources were not effective. No product **3aa** was observed without either $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ or AgSbF_6 in the presence of catalyst (entries 16 and 17). Based on these optimization studies, we have concluded that AcOH was the effective solvent, AgSbF_6 was the effective additive and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv) was the effective acetate source in the presence of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (5.0 mol %) at 120 °C for 36 h for the reaction.

Table 3C.1: Optimization Studies with Various Solvents, Oxidants and Additives.^a

entry	solvent	Cu(OAc) ₂ ·H ₂ O	additive	yield of 3a (%) ^b
1	DCE	2.00 equiv	AgSbF ₆	-
2	THF	2.00 equiv	AgSbF ₆	-
3	1,4-dioxane	2.00 equiv	AgSbF ₆	-
4	DME	2.00 equiv	AgSbF ₆	-
5	toluene	2.00 equiv	AgSbF ₆	-
6	CH ₃ CN	2.00 equiv	AgSbF ₆	-
7	DMSO	2.00 equiv	AgSbF ₆	-
8	AcOH	2.00 equiv	AgSbF₆	84
9	<i>iso</i> -PrOH	2.00 equiv	AgSbF ₆	-
10	DMF	2.00 equiv	AgSbF ₆	-
11	AcOH	2.00 equiv	AgBF ₄	46
12	AcOH	2.00 equiv	AgOTf	50
13	AcOH	2.00 equiv	KPF ₆	27
14	AcOH	50 mol %	AgSbF ₆	32 ^c
15	AcOH	1.00 equiv	AgSbF ₆	49 ^c
16	AcOH	-	AgSbF ₆	-
17	AcOH	2.00 equiv	-	-

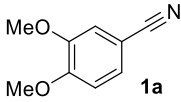
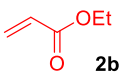
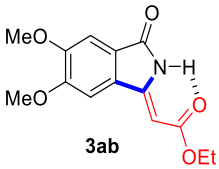
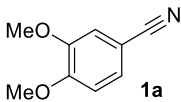
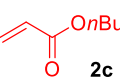
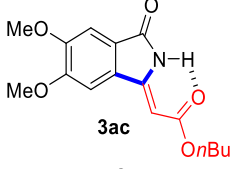
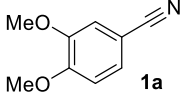
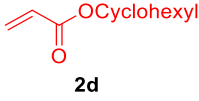
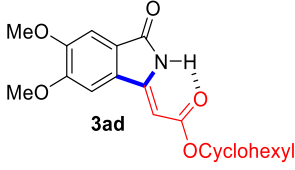
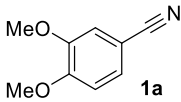
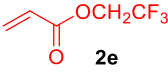
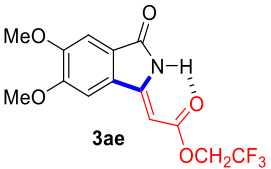
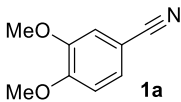
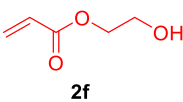
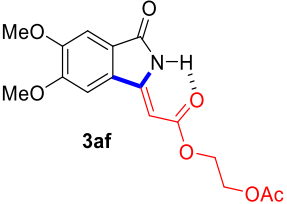
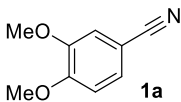
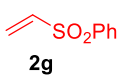
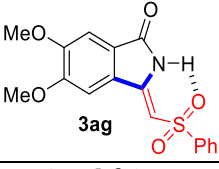
^aAll reactions were carried out under the following conditions: **1a**, **2a** (4.0 equiv), [{RuCl₂(*p*-cymene)}₂] (5 mol %), additive (20 mol %) and Cu(OAc)₂·H₂O (2.0 equiv) in AcOH at 120 °C for 36 h under the nitrogen atmosphere. ^bGC yield. ^cThe reaction was done under an air atmosphere.

3C.5: Scope of Activated Alkenes

The scope of the cyclization reaction was examined with various alkenes (Table 13C.2). Ethyl acrylate (**2b**), *n*-butyl acrylate (**2c**) and cyclohexyl acrylate (**2d**) underwent cyclization with **1a**, yielding cyclization products **3ab-ad** in 67%, 70% and 74% yields, respectively (entries 1-3). Interestingly, 2,2,2-trifluoroethyl acrylate (**2e**) and 2-

hydroxyethyl acrylate (**2f**) also efficiently reacted with **1a** giving cyclization products **3ae** and **3af** in 62% and 61% yields, respectively (entries 4 and 5). In the product **3af**, a free hydroxy group was converted into acetate group in the presence of AcOH. Surprisingly, vinyl sulphone (**2g**) also reacted efficiently with **1a** providing cyclic compound **3ag** in 65% yield, respectively (entry 6). Next, the reaction was tested with other alkenes such as methyl vinyl ketone, acrylonitrile and styrenes. However, in the reaction, no cyclization product was observed. It seems a good coordinating group such as ester and SO₂Ph substituted alkenes were suitable for the reaction.

Table 3C.2: Scope of the Activated Alkenes **2b-g**^a

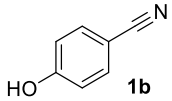
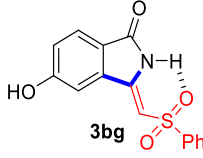
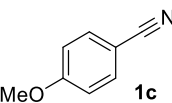
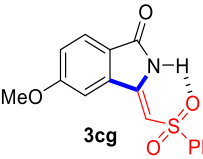
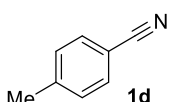
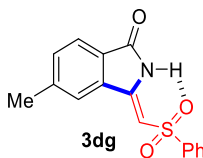
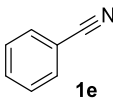
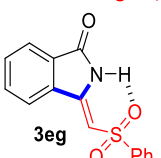
entry	1	alkenes 2	product 3	yield (%) ^b
1				67
2				70
3				74
4				62
5				61
6				61

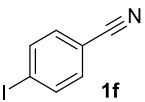
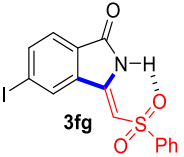
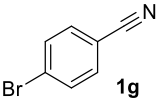
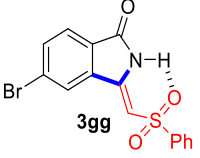
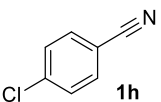
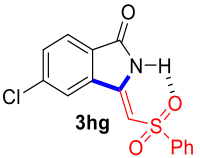
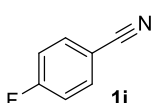
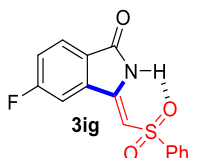
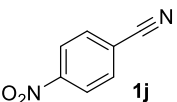
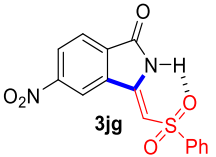
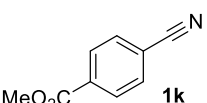
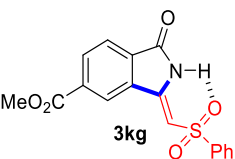
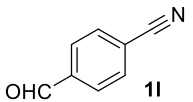
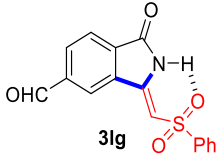
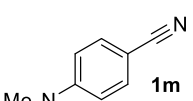
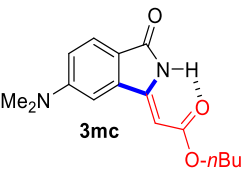
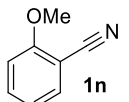
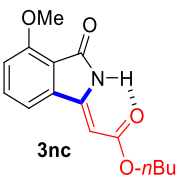
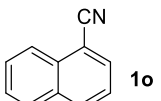
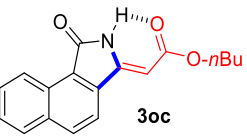
^aAll reactions were carried out using **1a**, alkenes **2b-c** (4.0 equiv), **2d-f** (3.0 equiv), and **2g** (1.2 equiv), [{RuCl₂(*p*-cymene)}₂] (5 mol %), AgSbF₆ (20 mol %) and Cu(OAc)₂·H₂O (2.0 equiv) in AcOH (3.0 mL) at 120 °C for 36 h. ^bIsolated yield.

3C.6: Scope of Aromatic Nitrile

The present catalytic reaction was also successfully extended with various substituted aromatic nitriles (Table 3C.3). Thus, electron-rich aromatic nitriles such as 4-hydroxy (**1b**), 4-methoxy (**1c**), 4-methyl (**1d**) benzonitriles and benzonitrile (**1e**) efficiently reacted with phenyl vinyl sulphone (**2g**) giving isoindolinone derivatives **3bg-eg** in good to moderate yields in a highly Z-stereoselective manner (entries 1-4). The structure of compound **3cg** was supported by a single crystal X-ray diffraction (See SI). Halogen groups such as 4-iodo (**1f**), 4-bromo (**1g**), 4-chloro (**1h**) and 4-fluoro (**1i**) benzonitriles were nicely involved in the reaction, providing cyclization products **3fg-ig** in good yields, in a highly stereoselective manner (entries 5-8). Very interestingly, electron-deficient aromatic nitriles such as 4-nitro (**1j**), 4-methylester (**1k**) and 4-formyl (**1l**) benzonitriles nicely reacted with phenyl vinyl sulphone (**2g**) affording products **3jg-lg** in 61%, 56% and 52%, respectively, in a highly regio- and stereoselective manner (entries 9-11). It is important to note that a free OH and sensitive I, Br, ester, CHO and NO₂ groups were not affected. Further, 4-dimethylamino benzonitrile (**1m**), sterically hindered *ortho*-methoxy benzonitrile (**1n**) and 1-naphthonitrile (**1o**) reacted with *n*-butyl acrylate (**2c**) providing cyclization products **3mc-oc** in 59%, 51% and 56% yields, respectively (entries 12-14).

Table 3C.3: The cyclization of Nitriles **1** with Alkenes **2c** or **2g**^a

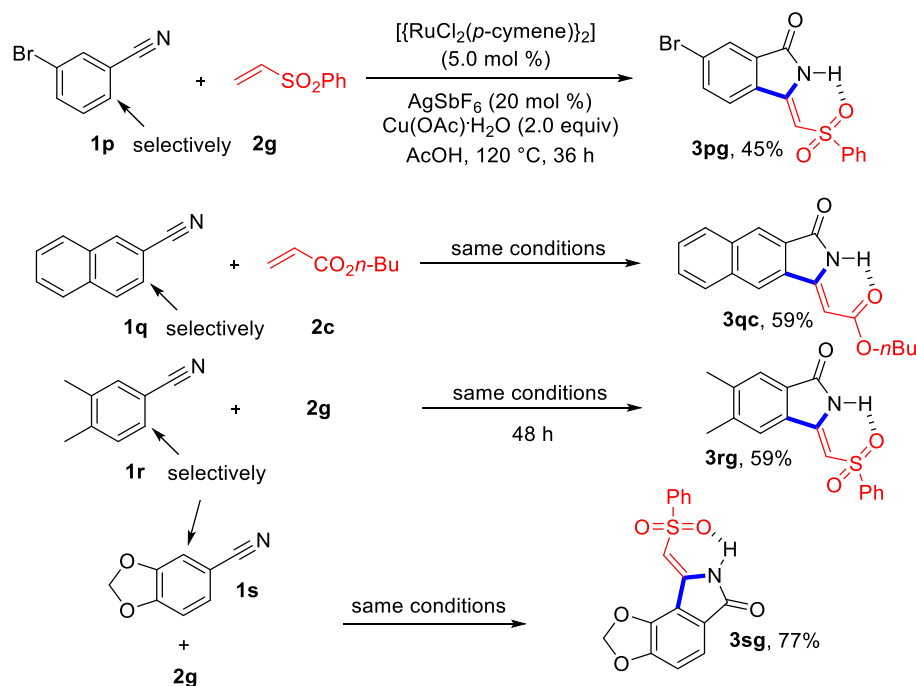
entry	nitrile 1	product 3	yield (%) ^b
1	 1b	 3bg	61
2	 1c	 3cg	75
3	 1d	 3dg	41 ^c
4	 1e	 3eg	72 ^d

5			69 ^d
6			71 ^d
7			67 ^d
8			65 ^c
9			61 ^e
10			56 ^c
11			52 ^c
12			59
13			51 ^d
14			56

^aAll reactions were carried out using **1a-o**, alkene **2g** (1.20 equiv) or **2c** (4.0 equiv), [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (5 mol %), AgSbF_6 (20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv) in acetic acid (3.0 mL) at 120 °C for 36 h. ^bIsolated yield. ^cReaction was carried out for 42 h. ^dReaction was carried out for 39 h. ^eReaction was carried out for 45 h

3C.7: Regioselective Studies

Next, the cyclization reaction was tested with unsymmetrical aromatic nitriles such as *meta* bromo benzonitrile (**1p**), 2-naphthonitrile (**1q**) and 3,4-dimethylbenzonitrile (**1r**) with **2c** or **2g** (Scheme 3C.2). In these substrates, two different regioselective products are possible. But, the reaction is highly regioselective, and the *ortho* C-H activation takes place at the less hindered side, giving products **3pg-3rg** in 45%, 59% and 59% yields, respectively (Scheme 3C.2). Whereas, in the substrate **1s**, the *ortho* C-H bond activation takes place at the sterically hindered side, providing cyclization product **3sg** in 77% yield (Scheme 3C.2).



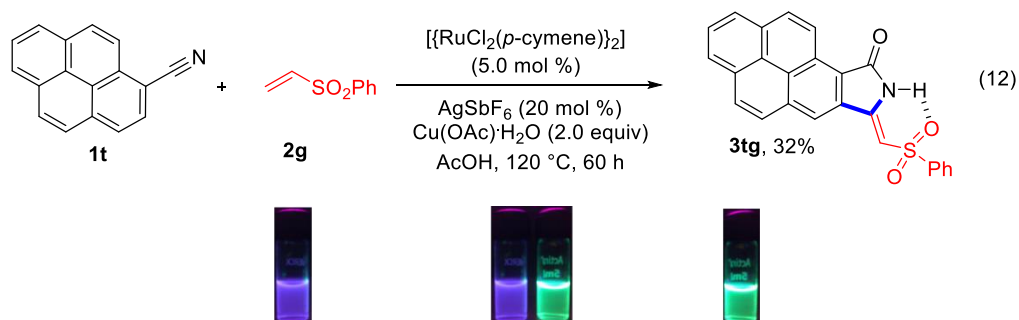
Scheme 3C.2: Regioselective studies

3C.8: Applications of (Z)-3-Methyleneisoindolin-1-ones

3C.8a: Synthesis of New Isoindolin-1-one Fluorophosphoric Pyrene Derivative

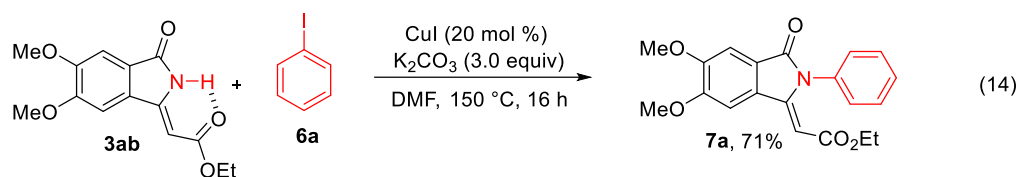
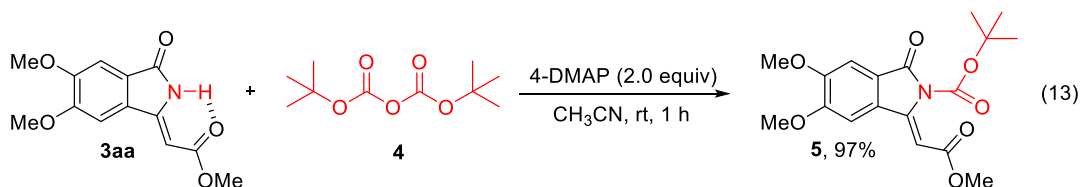
Isoindolin-1-one derivatives are widely used as a fluorescent marker for labeling biomolecules.² To learn the optical behaviour, we have done the following reaction and monitored the absorbance and fluorescence of the product (eq 12). Treatment of pyrene-1-carbonitrile (**1t**) with **2g** provided cyclization product **3tg** in 32% yield. Compound **3tg** shows absorbance at 415 nm and fluorescence at 470 nm (see SI). The starting material pyrene-1-carbonitrile (**1t**) shows absorbance at 355 nm and fluorescence shows three characteristic bands at 383 nm, 402 nm and 425 nm. After installation of isoindolin-1-one

moiety, fluorescence has been enhanced 55 nm and a broad single emission band with red shift was observed.



3C.8b: Synthesis of N-Substituted (Z)-3-Methyleneisoindolin-1-ones

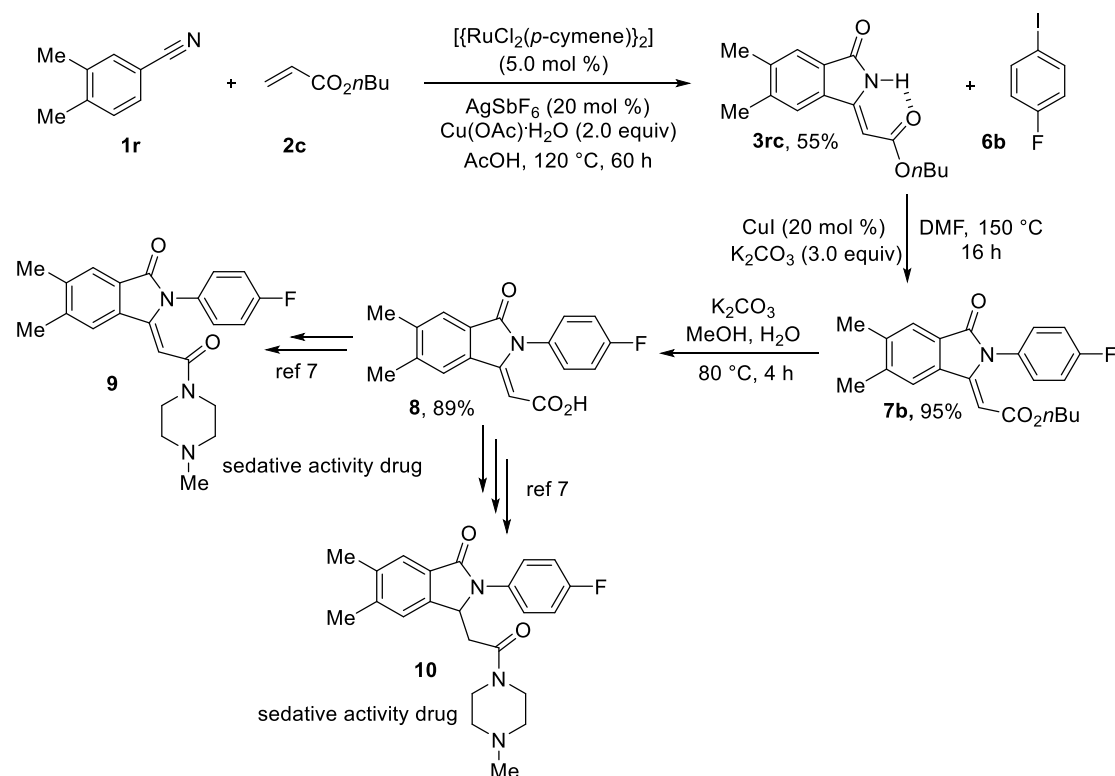
Next, the free N-H group of **3aa** was tried to protect with di-*tert*-butyl dicarbonate (**4**) (2.0 equiv) in the presence 4-dimethylaminopyridine (4-DMAP) (2.0 equiv) in CH₃CN at room temperature for 1 h (eq 13). In the reaction, *N*-BOC protected compound **5** was observed in 97% yield. It is very interesting to note that in the product **5**, alkene *Z*-stereoselectivity was retained (NOE experiments, see SI). Similarly, the N-H group of **3ab** was tried by arylating with iodobenzene (**6a**) in the presence of CuI (20 mol %) and K₂CO₃ (3.0 equiv) in DMF at 150 °C for 16 h (eq 14). In the reaction, *N*-arylated product **7a** was observed in 71% yield, in which also, alkene *Z*-stereoselectivity was retained.



3C.8c: A Route for The Synthesis of Pharmaceutical Molecules

The *N*-arylation reaction prompted us to explore the possibility of preparation of pharmaceutical molecules **9** and **10** (Scheme 3C.3).^{7, 10} These molecules show sedative activity.¹⁰ Treatment of 3,4-dimethylbenzonitrile (**1r**) with *N*-butyl acrylate (**2c**) under the optimized reaction conditions provided cyclic compound **3rc** in 55% yield in a highly regio- and stereoselective manner (Scheme 3C.3). Later, the free N-H group of compound

3rc was arylated with 4-fluorophenyl iodide (**6b**) under similar reaction conditions, providing *N*-arylated product **7b** in 95% yield. Then, the ester group of compound **7b** was converted into COOH derivative **8** in 89% yield in the presence of 15% aqueous K₂CO₃ (2.0 mL) in MeOH at 80 °C for 4 h. It is known that the compound **8** can be easily converted into the pharmaceutical molecule **9** and **10**.⁷



Scheme 3C.3: Synthesis of sedative active molecules

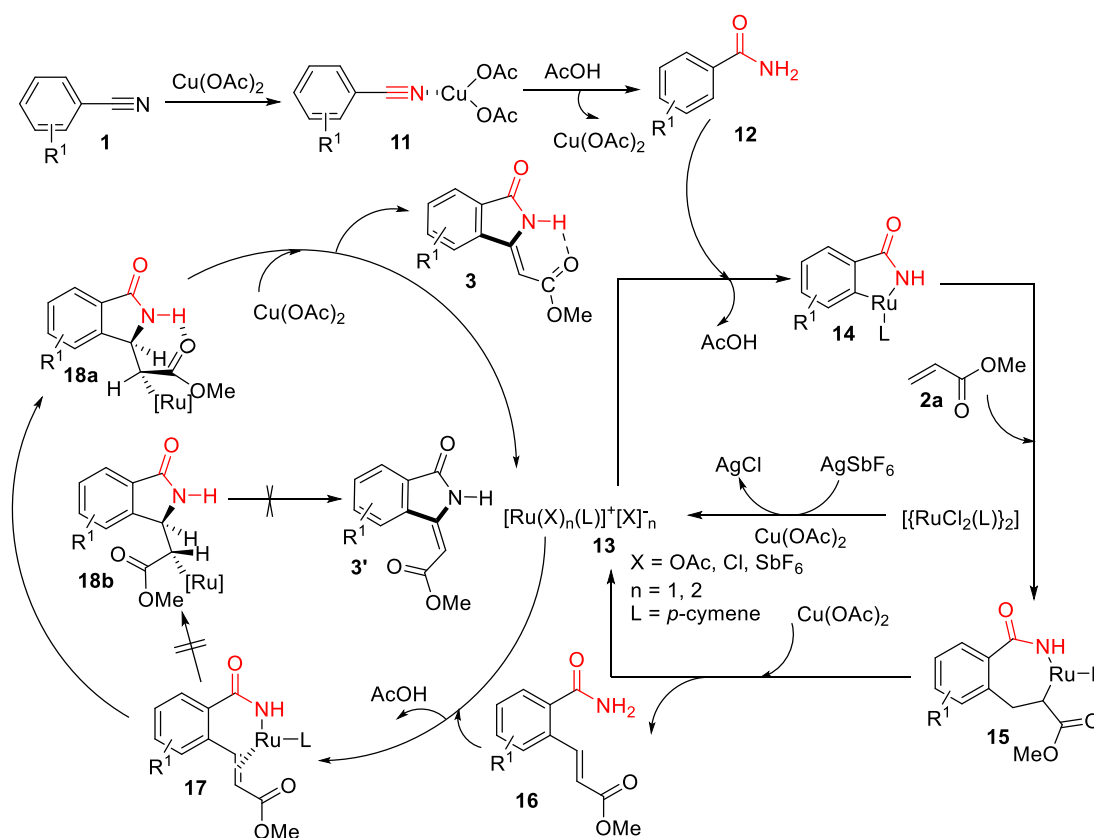
3C.9: Proposed Mechanism

A possible reaction mechanism is proposed in Scheme 3C.4 to account for the present cyclization reaction.⁵⁻⁹ Three different catalytic reactions were involved in the reaction. In the first step, Cu(OAc)₂ likely acts as a Lewis acid to which the nitrile group of benzonitrile **1** is coordinated to provide intermediate **11**. In this stage, the Lewis acid likely reduces the electron density of the nitrile group followed by hydration, providing benzamide **12** and regenerates the active Cu(OAc)₂.^{11a}

In the second catalytic cycle, AgSbF₆ likely removes the chloride ligand from [{RuCl₂(*p*-cymene)}₂] complex followed by the ligand exchange with Cu(OAc)₂ giving a cationic ruthenium species **13**. Coordination of the amide group of **12** into the ruthenium cationic species **13** followed by the *ortho*-metalation provides a five membered ruthenacycle **14** and AcOH.^{11b-c} Coordinative insertion of alkene **2** into the Ru–carbon bond of

ruthenacycle **14** affords ruthenacycle intermediate **15**. β -Hydride elimination of intermediate **15** in the presence of $\text{Cu}(\text{OAc})_2$ provides alkenylated product **16** and regenerates the active ruthenium species **13**.

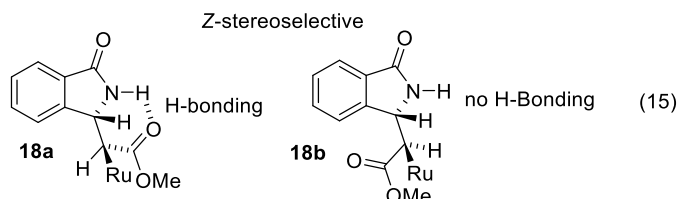
In the third catalytic cycle, the amide group of product **16** coordinates with ruthenium species **13** followed by the intramolecular coordination of double bond affords intermediate **17** and AcOH . Intramolecular coordinative insertion of N-Ru bond of intermediate **17** into the alkene moiety via aza-Michael addition provides intermediate **18a**. Subsequent β -hydride elimination of intermediate **18a** in the presence of $\text{Cu}(\text{OAc})_2$ provides product **3** and regenerates ruthenium species **16**.



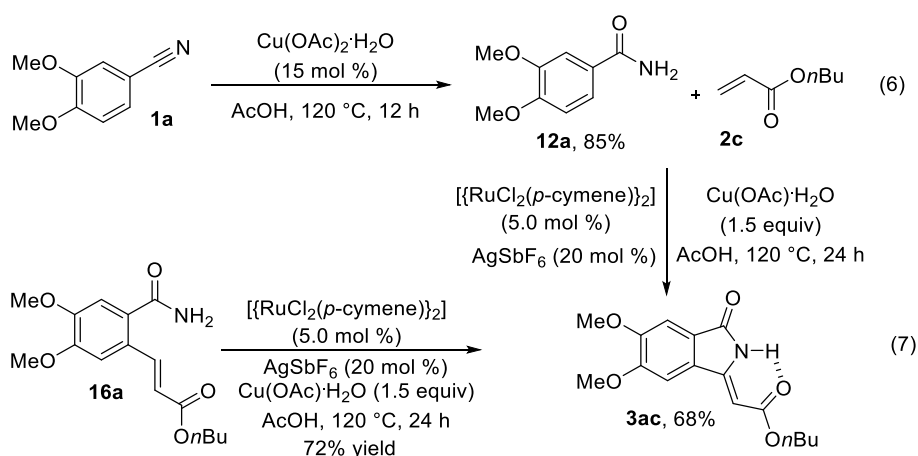
Scheme 3C.4: Proposed Mechanism

In fact, in the intramolecular insertion of N-Ru bond of intermediate **17** into the double bond of alkene moiety, two different diastereoselective intermediates such as ester moiety of alkene and cyclic tertiary C-N-H bond are *syn* to each other **18a** and *anti* to each other **18b** are possible via aza-Michael addition (eq 5). These intermediates only decide the nature of product. If ester and C-N-H are *syn* to each other as like intermediate **18a**, only *Z*-stereoselective product **3** would be formed. If both are *anti* to each other as like intermediate **18b**, *E*-stereoselective product **3'** would be expected. In the cyclization of

aromatic nitrile **1** with **2**, intermediate **18a** was only formed (eq 5). This is mainly due to the intramolecular hydrogen bonding of C-N-H bond to C=O bond of intermediate **18a**.



To support the proposed mechanism, aromatic nitrile **3a** was treated with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (15 mol %) in acetic acid at 120 °C for 12 h, giving the corresponding benzamide **12a** in 85% yield (eq 6). Later, benzamide **12a** was treated with *n*-butyl acrylate (**2c**) under similar reaction conditions, providing product **3ac** in 68% yield (eq 7). Further, *ortho*-alkenylated benzamide **16a** was prepared separately and treated with $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (5.0 mol %), AgSbF_6 (20 mol %) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.5 equiv) in acetic acid at 120 °C for 24 h. In the reaction, product **3ac** was observed in 72% yield (eq 7). However, the corresponding conversion did not proceed in the absence of ruthenium catalyst with or without the Lewis acid.



3C.10: Conclusion

1. We have developed a highly regio and stereoselective synthesis of *Z*-3-methyleneisindolin-1-ones in good to moderate yields by a ruthenium catalyzed annulation of aromatic nitriles with activated alkenes.
2. This developed method applied to synthesis of precursor for preparation of sedative active molecules and *N*-substituted substituted (*Z*)-3-Methyleneisindolin-1-ones.

3C.11: References

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3C.12: Experimental Section

General Procedure for the Cyclization of Aromatic Nitriles with Alkenes Catalyzed by Ruthenium Complex.

Substituted nitriles **1** (0.5 mmol, 1.0 equiv), if alkene is solid (for example phenyl vinyl sulfone **2g** (0.6 mmol, 1.20 equiv)), [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (0.025 mmol, 5 mol %), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.0 mmol, 2.0 equiv), AgSbF_6 (0.10 mmol, 20 mol %) were taken in a 15-mL pressure tube equipped with a magnetic stirrer and septum. (Note: AgSbF_6 is moisture sensitive. Thus, AgSbF_6 was taken inside the nitrogen glove box). The tube was evacuated and purged with nitrogen gas three times. To the tube were then added liquid alkenes **2** (**2a-c** (2.0 mmol, 4.0 equiv) and **2d-f** (1.5 mmol, 3.0 equiv)) and acetic acid solvent (3.0 mL) via syringes, allowed the reaction mixture to stir at room temperature for few seconds and again the tube was evacuated and purged with nitrogen gas three times. Then, the septum was taken out and immediately a screw cap was used to cover the tube. Then, the reaction mixture was allowed to stir at 120 °C. After 16 h, the reaction was monitored by TLC. The reaction mixture was allowed to cool to room temperature and a screw was taken out and a few drops were collected from the tube through small dropper for checking TLC. If the reaction is not completed, the tube was covered with screw cap and then, the reaction mixture was allowed to stir at 120 °C (Note: In this stage, the reaction is not moisture sensitive). The reaction was monitored by TLC until the maximum conversion. After maximum conversion observed by TLC, the reaction mixture cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 , filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3**.

Procedure for the Preparation of Compound 5.

To a stirred solution of compound **3aa** (75 mg) in CH_3CN (10.0 mL) at room temperature were added di-*tert*-butyl dicarbonate (Boc_2O) (2.0 equiv) and DMAP (2.0 equiv) and the reaction mixture was stirred for 1 h. After removal of volatiles in vacuo, the residue was diluted with EtOAc and the solution was washed with H_2O and brine. The organic layer was dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give compound **5** (101 mg, 97% yield).

General Procedure for the N-Arylation Reaction.

Compound **3ab** or **3rc** (0.5 mmol, 1.0 equiv), K_2CO_3 (1.5 mmol, 3.0 equiv), CuI (0.1 mmol, 20 mol %) were added to a 15-mL pressure tube equipped with a magnetic stirrer and septum. The tube was evacuated and purged with nitrogen gas three times. DMF (3.0 mL), iodobenzene (**6a**) or 4-fluorophenyl iodide (**6b**) (1.0 mmol, 2.0 equiv) were added to the tube under N_2 atmosphere by syringe at room temperature. Again the tube was

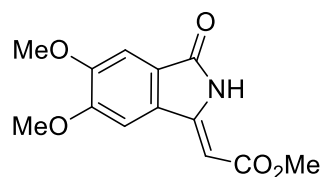
evacuated and purged with nitrogen gas three times. After that, the septum of tube was substituted with screw-cap. Then, the reaction mixture was heated at 150 °C for 16 h, and then allowed to cool to room temperature. The product was extracted with ethyl acetate, washed with water and brine. The extract was dried with anhydrous Na₂SO₄. The solvents were evaporated under reduced pressure and the crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **7a** and **7b**.

General Procedure for the Preparation of Compound 8.

A solution of compound **7b** (75 mg) in MeOH (8.0 mL) and 15% of aqueous K₂CO₃ (2.0 mL) was stirred at 80 °C for 4 h and concentrated under reduced pressure. H₂O was added to the residue, followed by extraction with EtOAc. The aqueous layer was acidified with concentrated hydrochloric acid and the precipitate was collected by filtration, washed with water, and dried to afford compound **8**.

3C.13: Spectral Data of all Compounds

Methyl (Z)-2-(5,6-dimethoxy-3-oxoisindolin-1-ylidene)acetate (**3aa**).



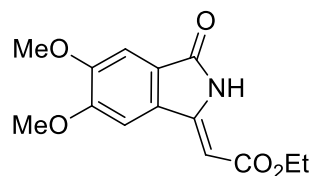
Golden yellow solid; eluent (40% ethyl acetate in hexanes). The reaction scale is 75 mg, 94 mg of **3aa** was isolated and yield is 75%. The reaction was done for 36 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.06 (bs, 1 H), 7.69 (s, 1 H), 7.25 (s, 1 H), 6.04 (s, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.72 (s, 3 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 168.3, 166.8, 153.3, 152.1, 147.1, 130.1, 121.7, 105.1, 104.8, 90.9, 56.3, 56.0, 51.3.

HRMS (ESI): calc. for [(C₁₃H₁₃NO₅)] (M+H) 264.0872, measured 264.0880.

Ethyl (Z)-2-(5,6-dimethoxy-3-oxoisindolin-1-ylidene)acetate (**3ab**).



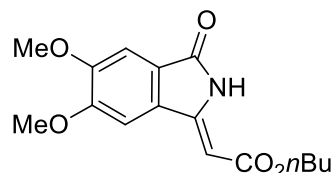
Pale yellow solid; eluent (35% ethyl acetate in hexanes). The reaction scale is 75 mg, 85 mg of **3ab** was isolated and yield is 67%. The reaction was done for 36 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.00 (bs, 1 H), 7.71 (s, 1 H), 7.25 (s, 1 H), 6.06 (s, 1 H), 4.19 (q, *J* = 8.0 Hz, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 1.26 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 168.2, 166.5, 153.3, 152.1, 147.2, 130.1, 121.6, 105.0, 104.7, 91.2, 59.8, 56.3, 56.0, 14.3.

HRMS (ESI): calc. for $[(\text{C}_{14}\text{H}_{15}\text{NO}_5)\text{H}]$ (M+H) 278.1028, measured 278.1032.

Butyl (Z)-2-(5,6-dimethoxy-3-oxoisindolin-1-ylidene)acetate (3ac).



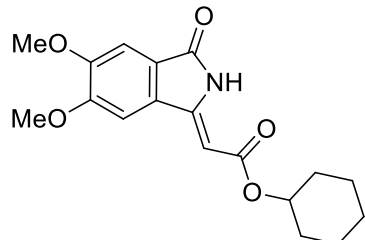
Colorless solid; eluent (35% ethyl acetate in hexanes). The reaction scale is 75 mg, 98 mg of **3c** was isolated and yield is 70%. The reaction was done for 36 h at 120 °C.

^1H NMR (DMSO- d_6 , 400 MHz): δ 9.97 (bs, 1 H), 7.72 (s, 1 H), 7.25 (s, 1 H), 6.07 (s, 1 H), 4.14 (t, J = 8 Hz, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 1.66 - 1.59 (m, 2 H), 1.42 - 1.32 (m, 2 H), 0.91 (t, J = 8 Hz, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 168.2, 166.7, 153.3, 152.1, 147.3, 130.1, 121.6, 105.0, 104.8, 91.0, 63.5, 56.3, 56.0, 30.3, 18.7, 13.6.

HRMS (ESI): calc. for $[(\text{C}_{16}\text{H}_{19}\text{NO}_5)\text{H}]$ (M+H) 306.1341, measured 306.1345.

Cyclohexyl (Z)-2-(5,6-dimethoxy-3-oxoisindolin-1-ylidene)acetate (3ad).



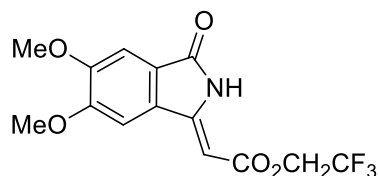
Colorless solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 113 mg of **3ad** was isolated and yield is 74%. The reaction was done for 36 h at 120 °C.

^1H NMR (DMSO- d_6 , 400 MHz): δ 9.92 (bs, 1 H), 7.74 (s, 1 H), 7.26 (s, 1 H), 6.07 (s, 1 H), 4.80 - 4.76 (m, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 1.86 - 1.84 (m, 2 H), 1.72 - 1.69 (m, 2 H), 1.51 - 1.38 (m, 4 H), 1.33 - 1.21 (m, 2 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 168.2, 166.1, 153.3, 152.1, 147.3, 130.1, 121.6, 105.0, 104.8, 91.4, 71.9, 56.3, 56.0, 30.3, 24.9, 23.3.

HRMS (ESI): calc. for $[(\text{C}_{18}\text{H}_{21}\text{NO}_5)\text{H}]$ (M+H) 332.1498, measured 332.1496.

2,2,2-Trifluoroethyl (Z)-2-(5,6-dimethoxy-3-oxoisindolin-1-ylidene)acetate (3ae).



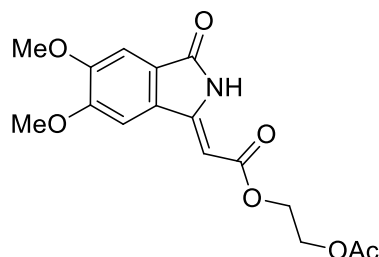
Colorless solid; eluent (35% ethyl acetate in hexanes). The reaction scale is 75 mg, 94 mg of **3ae** was isolated and yield is 62%. The reaction was done for 36 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.23 (bs, 1 H), 7.80 (s, 1 H), 7.28 (s, 1 H), 6.21 (s, 1 H), 4.85 (q, *J* = 8.0 Hz, 2 H), 3.88 (s, 6 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 168.5, 164.7, 153.4, 152.4, 149.4, 129.9, 121.6, 105.18, 105.12, 89.9, 88.8, 59.90 - 59.55 - 59.20 and 58.86 (F coupling), 56.4, 56.1.

HRMS (ESI): calc. for [(C₁₄H₁₂F₃NO₅)H] (M+H) 332.0746, measured 332.0742.

2-Acetoxyethyl (Z)-2-(5,6-dimethoxy-3-oxoisindolin-1-ylidene)acetate (3af).



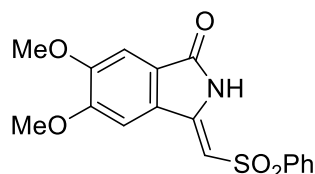
Colorless solid; eluent (35% ethyl acetate in hexanes). The reaction scale is 75 mg, 94 mg of **3af** was isolated and yield is 61%. The reaction was done for 36 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.01 (bs, 1 H), 7.75 (s, 1 H), 7.26 (s, 1 H), 6.10 (s, 1 H), 4.36 - 4.34 (m, 2 H), 4.30 - 4.28 (m, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 2.04 (s, 3 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 170.4, 168.3, 166.3, 153.3, 152.2, 147.6, 130.1, 121.6, 105.1, 104.9, 90.6, 62.1, 61.9, 56.3, 56.0, 20.7.

HRMS (ESI): calc. for [(C₁₆H₁₇NO₇)Na] (M+Na) 358.0903, measured 358.0901.

(Z)-5,6-dimethoxy-3-((phenylsulfonyl)methylene)isindolin-1-one (3ag).



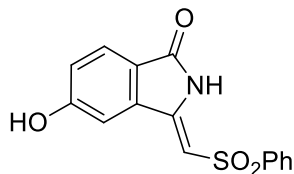
Pale yellow solid; eluent (50% ethyl acetate in hexanes). The reaction scale is 75 mg, 96 mg of **3ag** was isolated and yield is 61%. The reaction was done for 36 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.07 (bs, 1 H), 8.06 - 8.04 (m, 2 H), 7.74 - 7.64 (m, 4 H), 7.28 (s, 1 H), 6.83 (s, 1 H), 3.87 (s, 3 H), 3.84 (s, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 167.9, 153.3, 152.5, 144.0, 142.1, 133.6, 129.7, 129.5, 126.8, 121.2, 105.1, 100.3, 56.2, 56.1.

HRMS (ESI): calc. for $[(\text{C}_{17}\text{H}_{15}\text{NO}_5\text{S})\text{H}]$ (M+H) 346.0749, measured 346.0744.

(Z)-5-Hydroxy-3-((phenylsulfonyl)methylene)isoindolin-1-one (3bg).



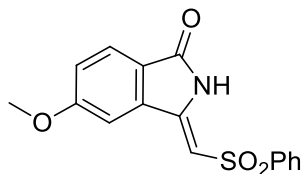
Off white solid; eluent (45% ethyl acetate in hexanes). The reaction scale is 75 mg, 115 mg of **3bg** was isolated and yield is 61%. The reaction was done for 36 h at 120 °C.

^1H NMR (DMSO- d_6 , 400 MHz): δ 10.69 (s, 1 H), 10.07 (bs, 1 H), 8.06 (d, J = 8.0 Hz, 2 H), 7.74 - 7.62 (m, 4 H), 7.35 (s, 1 H), 7.05 (d, J = 8.0, Hz, 1 H), 6.83 (s, 1 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 167.6, 162.5, 143.8, 142.0, 138.7, 133.6, 129.6, 126.9, 125.2, 119.4, 119.1, 108.9, 100.6.

HRMS (ESI): calc. for $[(\text{C}_{15}\text{H}_{11}\text{NO}_4\text{S})\text{H}]$ (M+H) 302.0487, measured 302.0486.

(Z)-5-methoxy-3-((phenylsulfonyl)methylene)isoindolin-1-one (3cg).



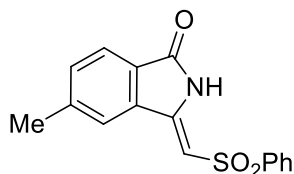
Colorless solid; eluent (40% ethyl acetate in hexanes). The reaction scale is 75 mg, 133 mg of **3cg** was isolated and yield is 75%. The reaction was done for 36 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 9.29 (bs, 1 H), 7.97 (d, J = 8.0 Hz, 2 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.65 (t, J = 8.0 Hz, 1 H), 7.57 (t, J = 8.0 Hz, 2 H), 7.12 (dd, J = 8.0, 4.0 Hz, 1 H), 7.04 (d, J = 4.0 Hz, 1 H), 6.05 (s, 1 H), 3.88 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.2, 163.9, 143.9, 141.5, 138.1, 133.7, 129.4, 127.0, 125.7, 121.2, 118.6, 106.1, 99.7, 55.9.

HRMS (ESI): calc. for $[(\text{C}_{16}\text{H}_{13}\text{NO}_4\text{S})\text{H}]$ (M+H) 316.0644, measured 316.0648.

(Z)-5-Methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3dg).



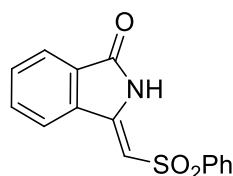
Colorless solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 61 mg of **3dg** was isolated and the yield is 41%. The reaction was done for 42 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 9.37 (bs, 1 H), 7.98 - 7.96 (m, 2 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.67 - 7.63 (m, 1 H), 7.60 - 7.55 (m, 2 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.39 (s, 1 H), 6.05 (s, 1 H), 2.47 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.5, 144.2, 144.0, 141.5, 136.1, 133.6, 133.2, 129.4, 127.9, 127.0, 124.1, 121.8, 99.7, 77.0, 21.9.

HRMS (ESI): calc. for [(C₁₆H₁₃NO₃S)H] (M+H) 300.0694, measured 300.0694.

(Z)-3-((Phenylsulfonyl)methylene)isoindolin-1-one (3eg).



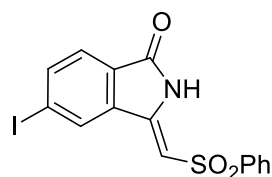
Off white solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 149 mg of **3eg** was isolated and yield is 72%. The reaction was done for 36 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.43 (bs, 1 H), 8.09 - 8.05 (m, 3 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.76 - 7.64 (m, 5 H), 6.95 (s, 1 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 167.8, 143.6, 141.9, 136.1, 133.7, 133.4, 132.4, 129.6, 128.3, 126.9, 123.4, 122.5, 101.5.

HRMS (ESI): calc. for [(C₁₅H₁₁NO₃S)H] (M+H) 286.0538, measured 286.0539.

(Z)-5-Iodo-3-((phenylsulfonyl)methylene)isoindolin-1-one (3fg).



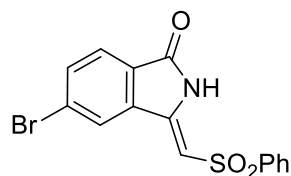
Off white solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 93 mg of **3eg** was isolated and yield is 69%. The reaction was done for 39 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.46 (bs, 1 H), 8.54 (s, 1 H), 8.06 - 8.03 (m, 3 H), 7.74 (t, *J* = 8.0 Hz, 1 H), 7.67 (t, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.02 (s, 1 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 167.3, 142.2, 141.7, 140.8, 137.8, 133.8, 131.2, 129.6, 127.7, 126.9, 124.9, 102.4, 101.2.

HRMS (ESI): calc. for [(C₁₅H₁₀INO₃S)H] (M+H) 411.9504, measured 411.9510.

(Z)-5-Bromo-3-((phenylsulfonyl)methylene)isoindolin-1-one (3gg).



Colorless solid; eluent (30% ethyl acetate in hexanes).

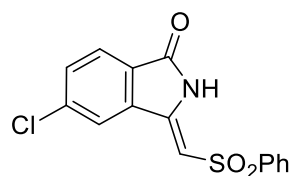
The reaction scale is 75 mg, 107 mg of **3eg** was isolated and yield is 71%. The reaction was done for 39 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.55 (bs, 1 H), 8.40 (s, 1 H), 8.07 - 8.04 (m, 2 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.76 - 7.72 (m, 2 H), 7.69 - 7.65 (m, 2 H), 7.03 (s, 1 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 167.1, 142.2, 141.7, 138.2, 135.1, 133.9, 129.7, 127.5, 127.1, 126.9, 125.6, 125.2, 102.7.

HRMS (ESI): calc. for [(C₁₅H₁₀BrNO₃S)] (M+H) 363.9643, measured 363.9637.

(Z)-5-Chloro-3-((phenylsulfonyl)methylene)isoindolin-1-one (3hg).



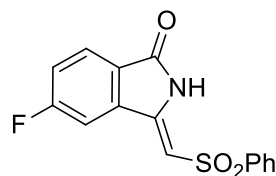
Colorless solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 117 mg of **3gg** was isolated and yield is 67%. The reaction was done for 39 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 9.47 (bs, 1 H), 7.98 - 7.95 (m, 2 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.68 - 7.56 (m, 5 H), 6.08 (s, 1 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.3, 142.5, 141.1, 139.8, 137.4, 133.9, 132.6, 129.6, 127.2, 125.5, 121.8, 101.3.

HRMS (ESI): calc. for [(C₁₅H₁₀ClNO₃S)H] (M+H) 320.0148, measured 320.0140.

(Z)-5-Fluoro-3-((phenylsulfonyl)methylene)isoindolin-1-one (3ig).



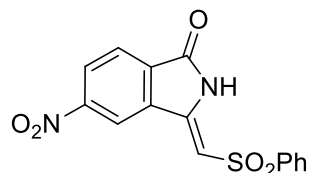
Colorless solid; eluent (35% ethyl acetate in hexanes). The reaction scale is 75 mg, 122 mg of **3hg** was isolated and yield is 65%. The reaction was done for 42 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.52 (bs, 1 H), 8.07 - 8.05 (m, 2 H), 8.00 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.87 - 7.84 (m, 1 H), 7.75 - 7.71 (m, 1 H), 7.69 - 7.64 (m, 2 H), 7.54 - 7.49 (m, 1 H), 6.97 (s, 1 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 166.8, 166.5 and 163.9 (F coupling), 142.5, 141.7, 138.9 and 138.8 (F coupling), 133.8, 129.7, 126.9, 126.0 and 125.9 (F coupling), 124.8, 119.9 and 119.6 (F coupling), 110.1 and 109.8 (F coupling), 102.5.

HRMS (ESI): calc. for $[(\text{C}_{15}\text{H}_{10}\text{FNO}_3\text{S})\text{H}]$ (M+H) 304.0444, measured 304.0449.

(Z)-5-Nitro-3-((phenylsulfonyl)methylene)isoindolin-1-one (3jg).



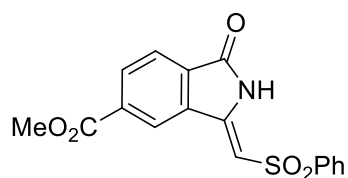
Off white solid; eluent (40% ethyl acetate in hexanes). The reaction scale is 75 mg, 102 mg of **3ig** was isolated and yield is 61%. The reaction was done for 45 h at 120 °C.

^1H NMR (DMSO- d_6 , 400 MHz): δ 10.89 (bs, 1 H), 9.02 (d, J = 4.0 Hz, 1 H), 8.47 (dd, J = 8.0, 4.0 Hz, 1 H), 8.08 - 8.03 (m, 3 H), 7.77 - 7.72 (m, 1 H), 7.70 - 7.66 (m, 2 H), 7.35 (s, 1 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 166.2, 150.9, 141.6, 141.5, 137.4, 133.9, 133.1, 129.7, 127.2, 127.1, 124.8, 118.3, 104.0.

HRMS (ESI): calc. for $[(\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_5\text{S})\text{Na}]$ (M+H) 353.0208, measured 353.0212.

Methyl (Z)-1-oxo-3-((phenylsulfonyl)methylene)isoindoline-5-carboxylate (3kg).



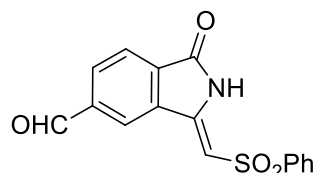
Orange solid; eluent (40% ethyl acetate in hexanes). The reaction scale is 75 mg, 86 mg of **3jg** was isolated and yield is 56%. The reaction was done for 42 h at 120 °C.

^1H NMR (DMSO- d_6 , 400 MHz): δ 10.64 (bs, 1 H), 8.66 (s, 1 H), 8.21 (d, J = 8.0 Hz, 1 H), 8.05 (d, J = 8.0 Hz, 2 H), 7.93 (d, J = 8.0 Hz, 1 H), 7.73 (t, J = 8.0 Hz, 1 H), 7.67 (t, J = 8.0 Hz, 2 H), 7.26 (s, 1 H), 3.89 (s, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 166.9, 165.2, 142.4, 141.7, 136.5, 134.1, 133.8, 132.9, 131.9, 129.6, 127.0, 123.8, 123.5, 102.9, 52.7.

HRMS (ESI): calc. for $[(\text{C}_{17}\text{H}_{13}\text{NO}_5\text{S})\text{H}]$ (M+H) 344.0593, measured 344.0588.

(Z)-1-Oxo-3-((phenylsulfonyl)methylene)isoindoline-5-carbaldehyde (3lg).



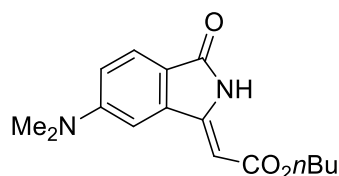
Pale yellow solid; eluent (45% ethyl acetate in hexanes). The reaction scale is 75 mg, 93 mg of **3kg** was isolated and yield is 52%. The reaction was done for 42 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.72 (bs, 1 H), 10.09 (s, 1 H), 8.60 (s, 1 H), 8.20 (d, *J* = 8.0 Hz, 1 H), 8.08 (d, *J* = 8.0 Hz, 2 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.74 (t, *J* = 8.0 Hz, 1 H), 7.67 (t, *J* = 8.0 Hz, 2 H), 7.18 (s, 1 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 192.3, 166.9, 142.5, 141.7, 139.8, 136.8, 133.8, 133.7, 132.6, 129.6, 127.0, 124.2, 123.1, 102.8.

HRMS (ESI): calc. for [(C₁₆H₁₁NO₄S)H] (M+H) 314.0487, measured 314.0489.

Butyl (Z)-2-(6-(dimethylamino)-3-oxoisindolin-1-ylidene)acetate (3mc).



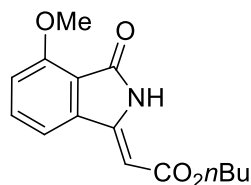
Yellow solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 87 mg of **3md** was isolated and yield is 59%. The reaction was done for 36 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 9.76 (bs, 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 4.0 Hz, 1 H), 6.87 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.09 (s, 1 H), 4.14 (t, *J* = 8 Hz, 2 H), 3.05 (s, 6 H), 1.66 - 1.58 (m, 2 H), 1.42 - 1.32 (m, 2 H), 0.91 (t, *J* = 8 Hz, 3 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 168.3, 167.0, 153.9, 148.2, 138.9, 124.4, 115.1, 114.1, 104.1, 90.1, 63.5, 40.1, 30.3, 18.7, 13.6.

HRMS (ESI): calc. for [(C₁₆H₂₀N₂O₃)H] (M+H) 289.1552, measured 289.1554.

Butyl (Z)-2-(4-methoxy-3-oxoisindolin-1-ylidene)acetate (3nc).



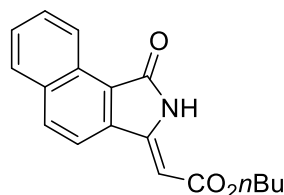
Colorless solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 79 mg of **3nd** was isolated and yield is 51%. The reaction was done for 39 h at 120 °C.

^1H NMR (DMSO- d_6 , 400 MHz): δ 10.03 (bs, 1 H), 7.69 - 7.63 (m, 2 H), 7.25 (d, J = 8.0 Hz, 1 H), 6.02 (s, 1 H), 4.14 (t, J = 8.0 Hz, 2 H), 3.90 (s, 3 H), 1.65 - 1.58 (m, 2 H), 1.40 - 1.31 (m, 2 H), 0.90 (t, J = 8 Hz, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): 166.6, 166.4, 156.9, 146.7, 138.8, 135.2, 114.9, 114.8, 113.9, 91.1, 63.6, 55.8, 30.3, 18.7, 13.6.

HRMS (ESI): calc. for $[(\text{C}_{15}\text{H}_{17}\text{NO}_4)\text{H}]$ (M+H) 276.1236, measured 276.1241.

Butyl (Z)-2-(1-oxo-1,2-dihydro-3H-benzo[e]isoindol-3-ylidene)acetate (3oc).



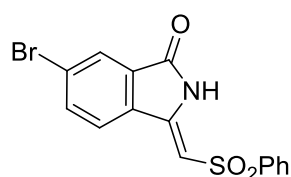
Colorless solid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg, 81 mg of **3md** was isolated and yield is 56%. The reaction was done for 36 h at 120 °C.

^1H NMR (DMSO- d_6 , 400 MHz): δ 10.32 (s, 1 H), 8.87 (d, J = 8.0 Hz, 1 H), 8.25 (d, J = 8.0 Hz, 1 H), 8.12 (d, J = 8.0 Hz, 1 H), 8.09 (d, J = 8.0 Hz, 1 H), 7.74 (t, J = 8.0 Hz, 1 H), 7.67 (t, J = 8.0 Hz, 1 H), 6.23 (s, 1 H), 4.18 (t, J = 8.0 Hz, 2 H), 1.67 - 1.60 (m, 2 H), 1.42 - 1.33 (m, 2 H), 0.91 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 169.1, 166.3, 146.5, 136.6, 134.7, 128.9, 128.8, 127.9, 127.7, 123.3, 122.9, 118.4, 93.6, 63.8, 30.3, 18.7, 13.6.

HRMS (ESI): calc. for $[(\text{C}_{18}\text{H}_{17}\text{NO}_3)\text{H}]$ (M+H) 296.1287, measured 296.1293.

(Z)-6-Bromo-3-((phenylsulfonyl)methylene)isoindolin-1-one (3pg).

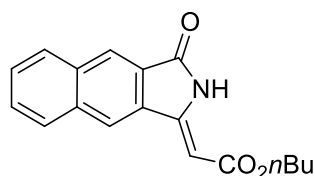


Pale yellow solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 68 mg of **3pg** was isolated and yield is 45%. The reaction was done for 36 h at 120 °C.

^1H NMR (DMSO- d_6 , 400 MHz): δ 10.58 (bs, 1 H), 8.05 (d, J = 8.0 Hz, 2 H), 8.02 (d, J = 8.0 Hz, 1 H), 7.98 (s, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 7.74 (t, J = 8.0 Hz, 1 H), 7.67 (t, J = 8.0 Hz, 2 H), 7.01 (s, 1 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 166.5, 142.7, 141.7, 136.1, 135.1, 133.8, 130.4, 129.7, 126.9, 126.2, 125.7, 124.5, 102.4.

HRMS (ESI): calc. for $[(\text{C}_{15}\text{H}_{10}\text{BrNO}_3\text{S})\text{H}]$ (M+H) 363.9643, measured 363.9633.

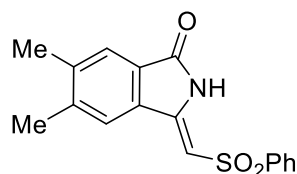
Butyl (Z)-2-(3-oxo-2,3-dihydro-1H-benzo[*f*]isoindol-1-ylidene)acetate (3qc).

Off white solid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg, 85 mg of **3qg** was isolated and yield is 59%. The reaction was done for 36 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 9.88 (bs, 1 H), 8.38 (s, 1 H), 8.15 (s, 1 H), 8.03 (d, *J* = 8.0 Hz, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 7.68 - 7.61 (m, 2 H), 5.89 (s, 1 H), 4.24 (t, *J* = 8.0 Hz, 2 H), 1.75 - 1.68 (m, 2 H), 1.51 – 1.41 (m, 2 H), 0.99 (t, *J* = 8.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.9, 167.8, 147.7, 135.1, 134.4, 131.8, 130.0, 129.1, 128.7, 128.0, 126.4, 125.0, 121.2, 90.2, 64.4, 30.7, 19.1, 13.7.

HRMS (ESI): calc. for [(C₁₈H₁₇NO₃)H] (*M*+*H*) 296.1293, measured 296.1287.

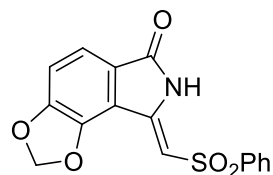
(Z)-5,6-dimethyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3rg).

Pale yellow solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 78 mg of **3rg** was isolated and yield is 59%. The reaction was done for 48 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.21 (bs, 1 H), 8.06 (d, *J* = 8.0 Hz, 2 H), 7.81 (s, 1 H), 7.72 (t, *J* = 8.0 Hz, 1 H), 7.65 (t, *J* = 8.0 Hz, 2 H), 7.56 (s, 1 H), 6.77 (s, 1 H), 2.31 (s, 3 H), 2.29 (s, 3 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 167.9, 143.9, 142.9, 142.1, 141.8, 134.0, 133.6, 129.6, 126.9, 126.3, 123.9, 123.0, 100.4, 20.1, 19.8.

HRMS (ESI): calc. for [(C₁₇H₁₅NO₃S)Na] (*M*+*Na*) 336.0670, measured 336.0672.

(Z)-8-((Phenylsulfonyl)methylene)-7,8-dihydro-6H-[1,3]dioxolo[4,5-*e*]isoindol-6-one (3sg).

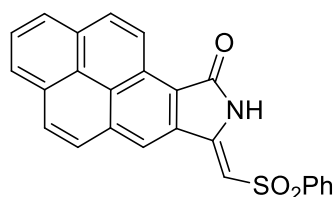
Yellow solid; eluent (45% ethyl acetate in hexanes). The reaction scale is 75 mg, 129 mg of **3sg** was isolated and yield is 77%. The reaction was done for 36 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.48 (bs, 1 H), 8.09 (d, J = 8.0 Hz, 2 H), 7.72 (t, J = 8.0 Hz, 1 H), 7.65 (t, J = 8.0 Hz, 2 H), 7.36 (d, J = 8.0 Hz, 1 H), 7.18 (d, J = 8.0 Hz, 1 H), 6.30 (s, 2 H), 6.05 (s, 1 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 167.0, 152.7, 142.8, 141.8, 141.4, 133.8, 129.7, 127.0, 122.1, 118.8, 115.7, 111.2, 104.2, 102.3.

HRMS (ESI): calc. for [(C₁₆H₁₁NO₅S)H] (M+H) 330.0436, measured 330.0445.

(Z)-7-((Phenylsulfonyl)methylene)-7,8-dihydro-9H-phenaleno[1,9-*ef*]isoindol-9-one (3tg).



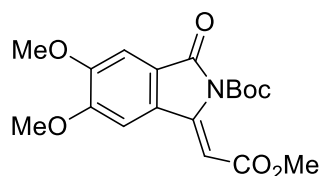
Colorless solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg, 43 mg of **3tg** was isolated and yield is 32%. The reaction was done for 60 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.58 (bs, 1 H), 9.03 (d, J = 8.0 Hz, 1 H), 8.78 (s, 1 H), 8.42 - 8.40 (m, 3 H), 8.33 (d, J = 8.0 Hz, 1 H), 8.19 - 8.11 (m, 4 H), 7.77 - 7.69 (m, 3 H), 7.14 (s, 1 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 168.9, 143.9, 142.1, 134.1, 133.9, 133.8, 131.0, 130.7, 130.3, 130.2, 129.7, 127.7, 127.6, 127.5, 127.39, 127.35, 127.1, 125.2, 123.2, 121.6, 118.2, 118.0, 101.2.

HRMS (ESI): calc. for [(C₂₅H₁₅NO₃S)H] (M+H) 410.0851, measured 410.0861.

***tert*-Butyl (Z)-5,6-dimethoxy-1-(2-methoxy-2-oxoethylidene)-3-oxoisindoline-2-carboxylate (5).**

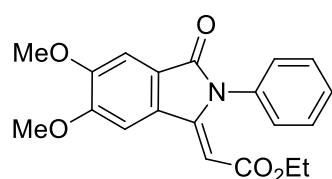


Off white solid; eluent (30% ethyl acetate in hexanes).

¹H NMR (CDCl₃, 400 MHz): δ 7.26 (s, 1 H), 7.07 (s, 1 H), 5.96 (s, 1 H), 4.00 (s, 3 H), 3.96 (s, 3 H), 3.78 (s, 3 H), 1.62 (s, 9 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.8, 165.4, 154.5, 152.7, 148.8, 142.0, 131.3, 120.5, 105.3, 101.8, 97.5, 84.7, 56.4, 51.8, 27.9.

HRMS (ESI): calc. for [(C₁₈H₂₁NO₇)Na] (M+Na) 386.1216, measured 386.1215.

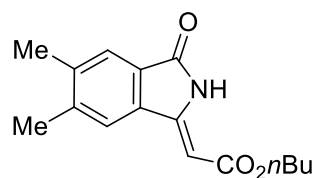
Ethyl (Z)-2-(5,6-dimethoxy-3-oxo-2-phenylisoindolin-1-ylidene)acetate (7a).

Yellow solid; eluent (25% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 8.87 (s, 1 H), 7.55 (t, J = 8 Hz, 2 H), 7.48 (t, J = 8 Hz, 1 H), 7.39 (s, 1 H), 7.31 (d, J = 8 Hz, 2 H), 5.46 (s, 1 H), 4.21 (q, J = 8 Hz, 2 H), 4.08 (s, 3 H), 4.02 (s, 3 H), 1.28 (t, J = 8 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.1, 166.4, 153.1, 151.9, 150.3, 133.9, 129.7, 129.0, 128.9, 127.5, 123.2, 110.5, 104.9, 99.3, 60.4, 56.43, 56.38, 14.3.

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{19}\text{NO}_5)\text{H}]$ ($\text{M}+\text{H}$) 354.1341, measured 354.1336.

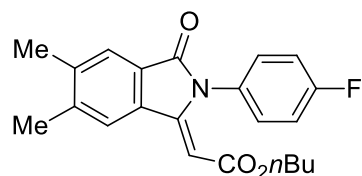
Butyl (Z)-2-(5,6-dimethyl-3-oxoisoindolin-1-ylidene)acetate (3rc).

Colorless solid; eluent (35% ethyl acetate in hexanes). The reaction scale is 75 mg, 86 mg of **6g** was isolated and yield is 55%.

^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 10.07 (bs, 1 H), 7.80 (s, 1 H), 7.51 (s, 1 H), 5.91 (s, 1 H), 4.14 (t, J = 8 Hz, 2 H), 2.31 (s, 6 H), 1.65 - 1.58 (m, 2 H), 1.40 - 1.31 (m, 2 H), 0.90 (t, J = 8 Hz, 3 H).

^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz): δ 168.2, 166.6, 147.2, 142.5, 141.0, 134.5, 126.8, 123.7, 122.6, 90.8, 63.6, 30.3, 20.1, 19.8, 18.7, 13.6.

HRMS (ESI): calc. for $[(\text{C}_{16}\text{H}_{19}\text{NO}_3)\text{H}]$ ($\text{M}+\text{H}$) 274.1443, measured 274.1445.

(Z)-2-(2-(4-Fluorophenyl)-5,6-dimethyl-3-oxoisoindolin-1-ylidene)acetate (7b).

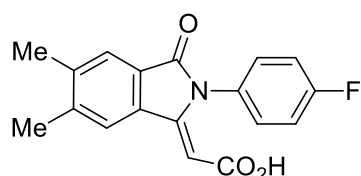
Colorless solid; eluent (25% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 8.87 (bs, 1 H), 7.67 (s, 1 H), 7.28 - 7.19 (m, 4 H), 5.38 (s, 1 H), 4.15 (t, J = 8.0 Hz, 2 H), 2.44 (s, 3 H), 2.39 (s, 3 H), 1.66 - 1.59 (m, 2 H), 1.41 - 1.32 (m, 2 H), 0.92 (t, J = 8.0 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.31, 166.25, 163.76 and 161.29 (F coupling), 150.3, 143.1, 141.2, 131.6, 130.86 and 130.78 (F coupling), 129.83 and 129.80 (F coupling), 128.9, 127.6, 124.3, 116.92 and 116.69 (F coupling), 99.4, 64.4, 30.7, 20.9, 20.3, 19.1, 13.7.

HRMS (ESI): calc. for $[(\text{C}_{22}\text{H}_{22}\text{FNO}_3)\text{H}]$ (M+H) 368.1662, measured 368.1660.

(Z)-2-(2-(4-Fluorophenyl)-5,6-dimethyl-3-oxoisindolin-1-ylidene)acetate (8).



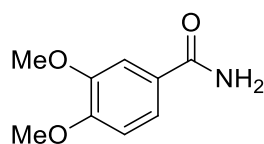
Colorless solid; eluent (25% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 8.81 (s, 1 H), 7.72 (s, 1 H), 7.31 - 7.28 (m, 2 H), 7.27 - 7.22 (m, 2 H), 5.44 (s, 1 H), 2.44 (s, 3 H), 2.43 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 170.3, 167.3, 163.90 and 161.42 (F coupling), 152.3, 143.2, 141.7, 131.4, 130.86 and 130.77 (F coupling), 129.61 and 129.58 (F coupling), 129.2, 127.6, 124.5, 117.02 and 116.79 (F coupling), 97.8, 20.9, 20.4.

HRMS (ESI): calc. for $[(\text{C}_{18}\text{H}_{14}\text{FNO}_3)\text{H}]$ (M+H) 312.1036, measured 312.1032.

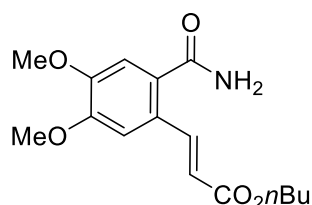
3,4-Dimethoxybenzamide (12a).



Pale yellow solid; eluent (70% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 7.46 (s, 1 H), 7.34 (d, J = 8.0 Hz, 1 H), 6.87 (d, J = 8.0 Hz, 1 H), 6.04 (bs, 2 H), 3.93 (s, 6 H).

Butyl (E)-3-(2-carbamoyl-4,5-dimethoxyphenyl)acrylate (16a).³



Colorless solid; eluent (65% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 8.11 (d, J = 16.0 Hz, 1 H), 7.12 (s, 1 H), 7.07 (s, 1 H), 6.33 (d, J = 16.0 Hz, 1 H), 5.93 (bs, 1 H), 5.79 (bs, 1 H), 4.21 (t, J = 8 Hz, 2 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 1.73 - 1.61 (m, 2 H), 1.49 - 1.32 (m, 2 H), 0.97 (t, J = 8 Hz, 3 H).

Ref. 3. Li, B.; Ma, J.; Wang N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.*, **2011**, 14, 736.

3C.12: X-Ray Analysis

Crystallographic Data of Compound 3cg.

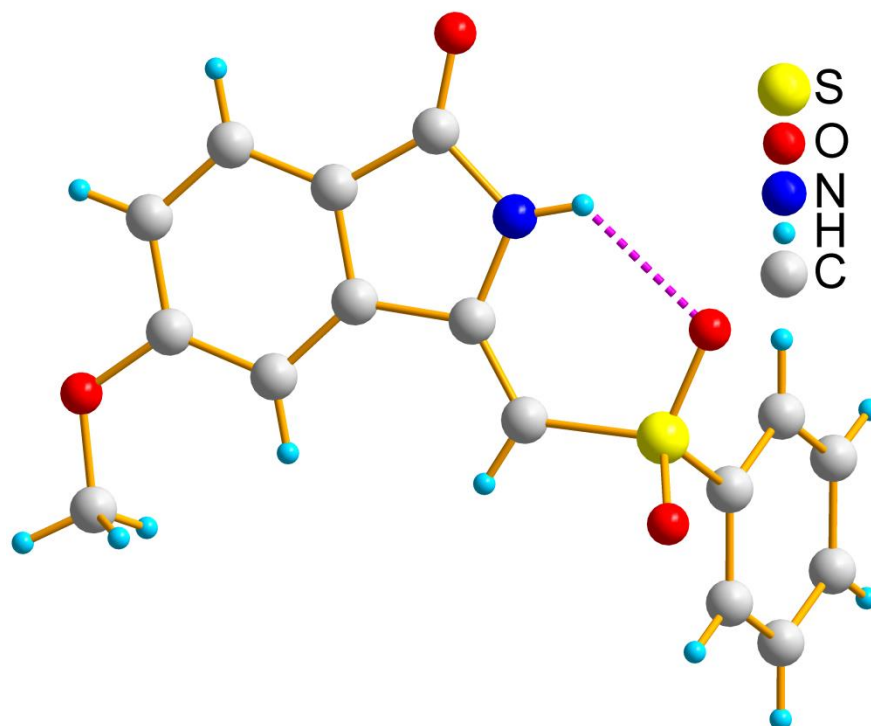


Table S2. Crystal data and structure refinement for compound **3cg**.

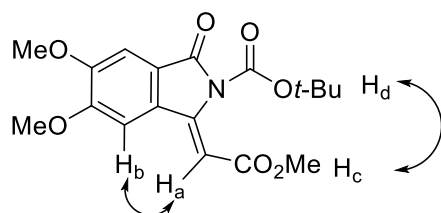
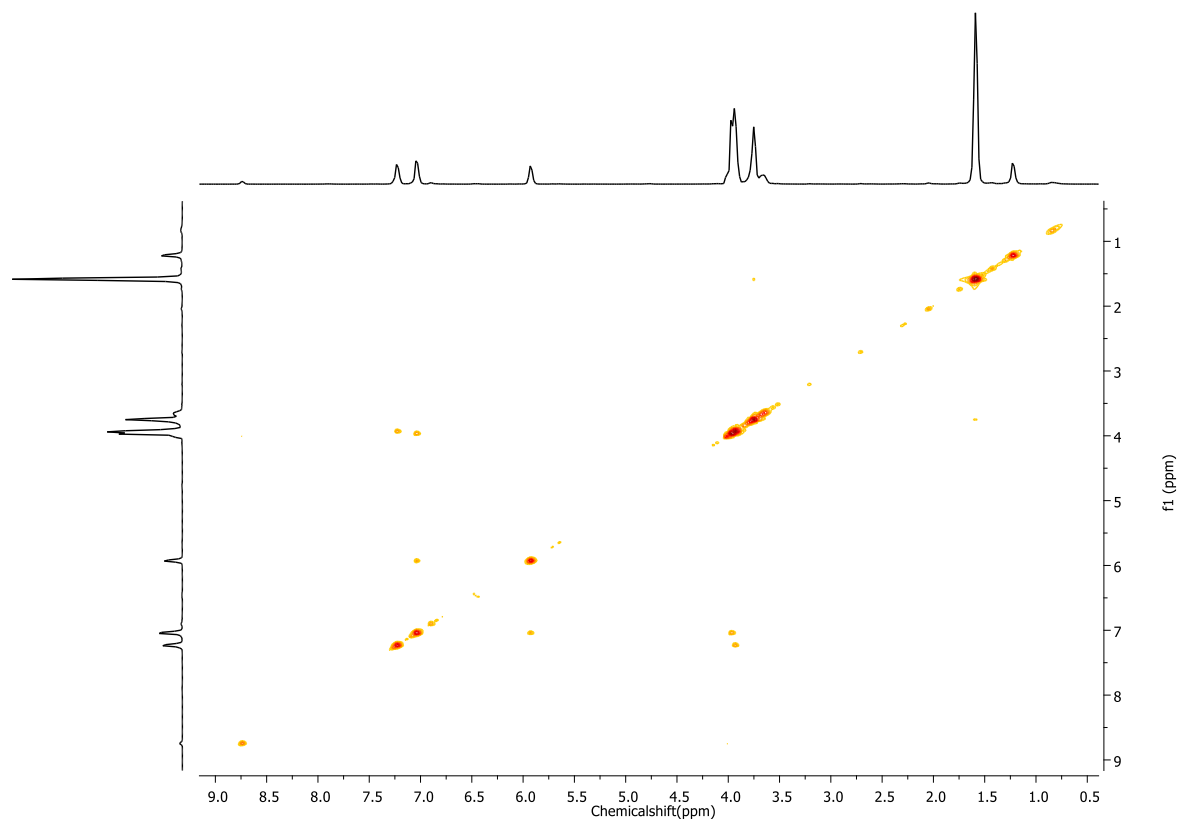
Identification code	compound 3cg	
Empirical formula	C ₁₆ H ₁₃ N O ₄ S	
Formula weight	315.33	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P b c n	
Unit cell dimensions	a = 18.8157(16) Å	a = 90°.
	b = 10.5029(9) Å	b = 90°.
	c = 15.0591(15) Å	c = 90°.
Volume	2976.0(5) Å ³	
Z	8	
Density (calculated)	1.408 Mg/m ³	
Absorption coefficient	0.235 mm ⁻¹	

F(000)	1312
Theta range for data collection	2.165 to 26.371°.
Index ranges	-23<=h<=23, -13<=k<=12, -18<=l<=18
Reflections collected	40742
Independent reflections	3043 [R(int) = 0.0646]
Completeness to theta = 25.242°	100.0 %
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3043 / 59 / 200
Goodness-of-fit on F ²	1.004
Final R indices [I>2sigma(I)]	R1 = 0.0397, wR2 = 0.1231
R indices (all data)	R1 = 0.0651, wR2 = 0.1462
Extinction coefficient	n/a
Largest diff. peak and hole	0.219 and -0.366 e.Å ⁻³

A clear intramolecular hydrogen bonding between N-H and oxygen of SO₂ of compound **3cg** was observed. The distance between hydrogen of N-H and oxygen of SO₂ is 2.16 Å. The angle between N-H-O is 127.10° and the dihedral angle of N-C-S-O is +0.25.

3C.14: Stereo Selective Studies: NOESY Experiments

NOESY Studies of Compound 5.



There is a NOE correlation between H_a (δ 5.96, s) and H_b (δ 7.07, s). In meantime, there is also a correlation between H_c (δ 3.78, s) and H_d (δ 1.62, s). These results clearly revealed that the stereochemistry of compound 5 is correct.

3C.15: Absorbance (Black) and Fluorescence (Blue) Spectra:

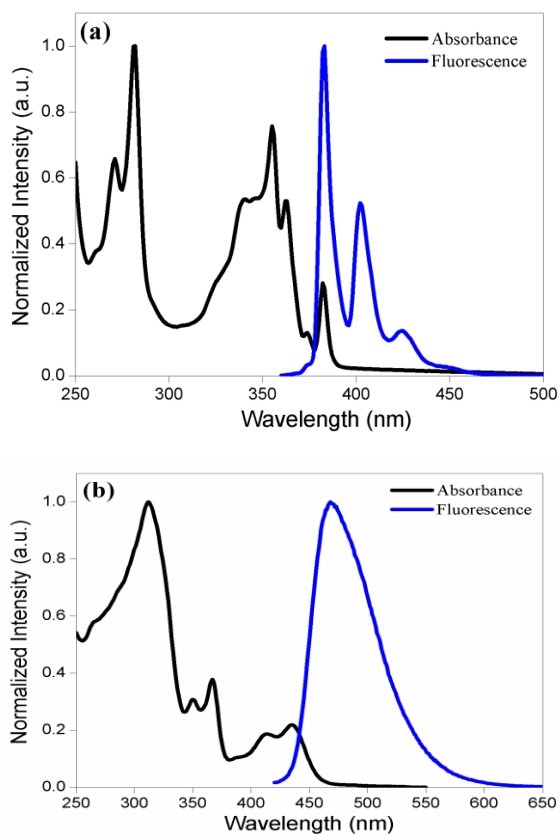
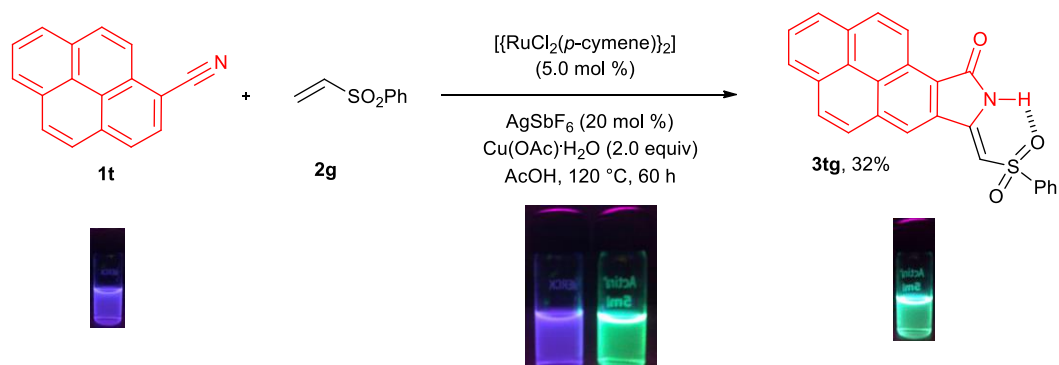
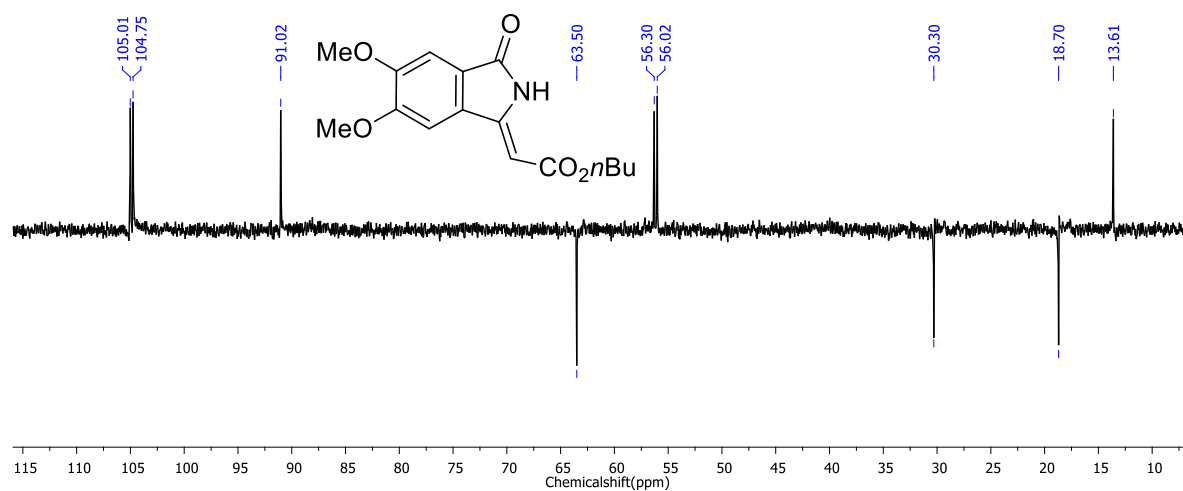
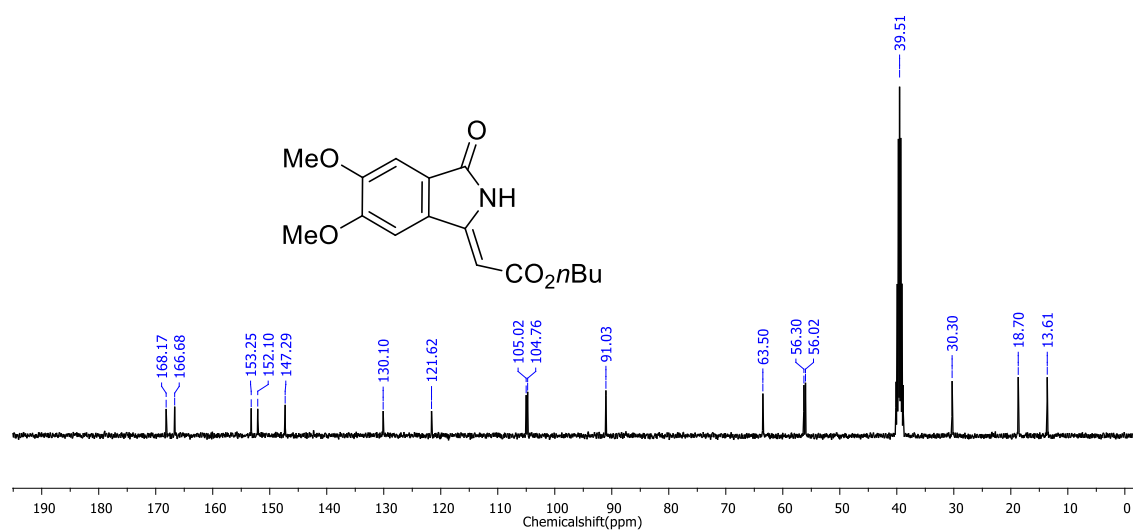
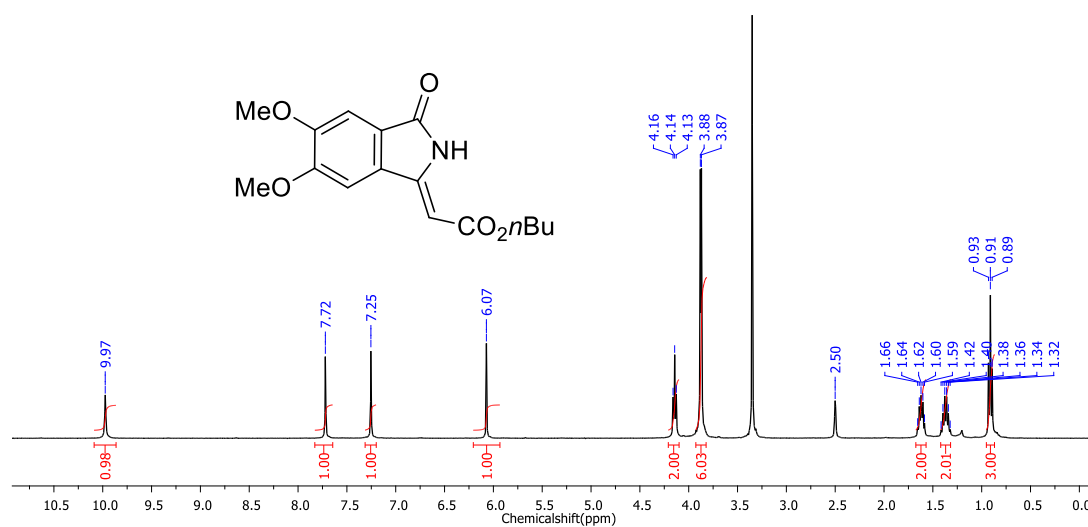
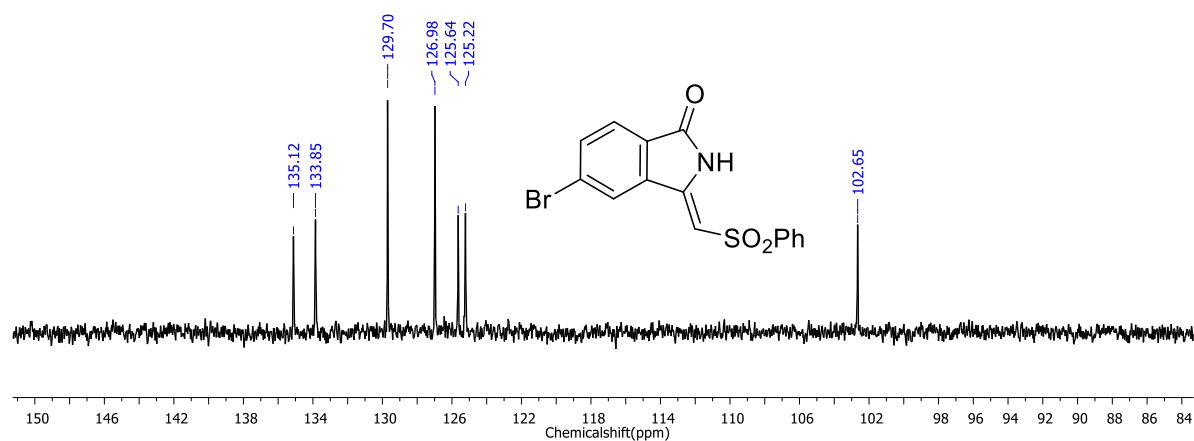
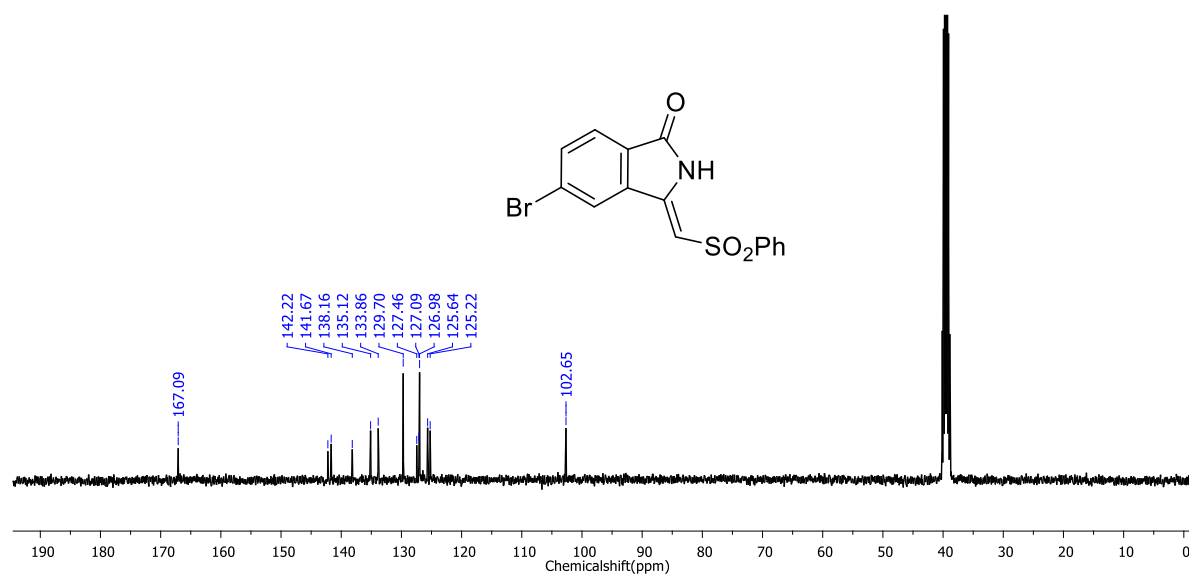
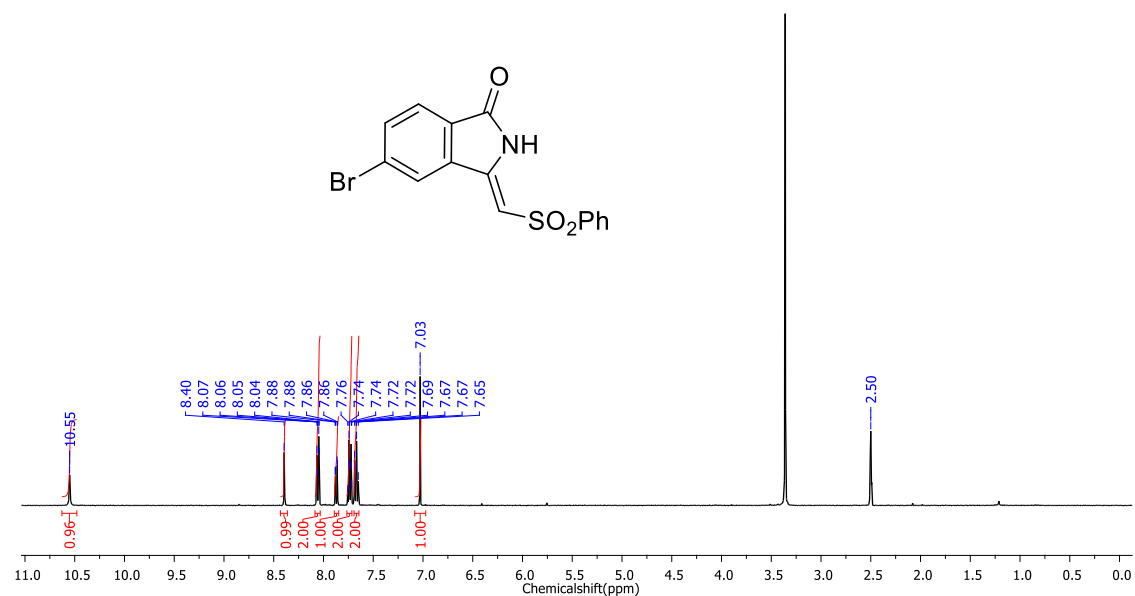
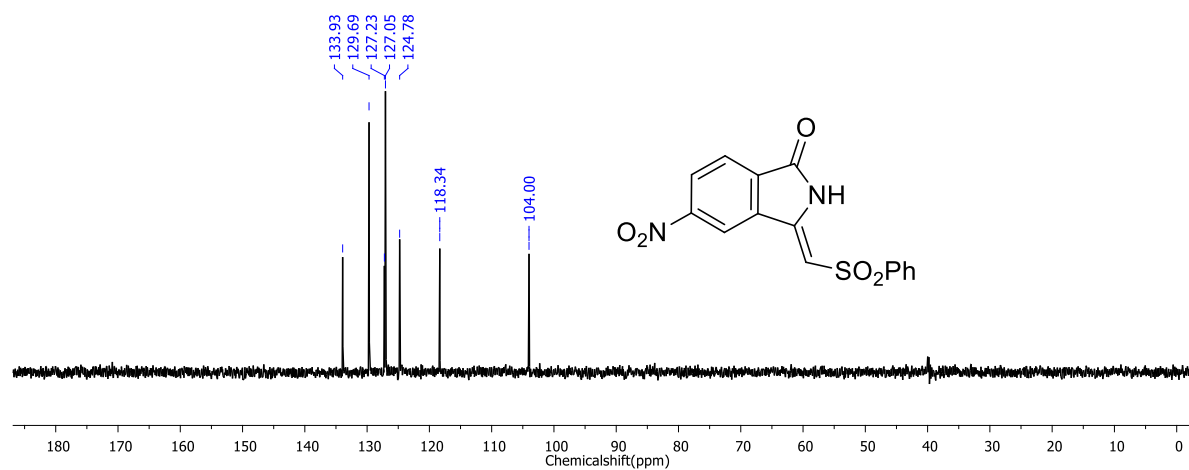
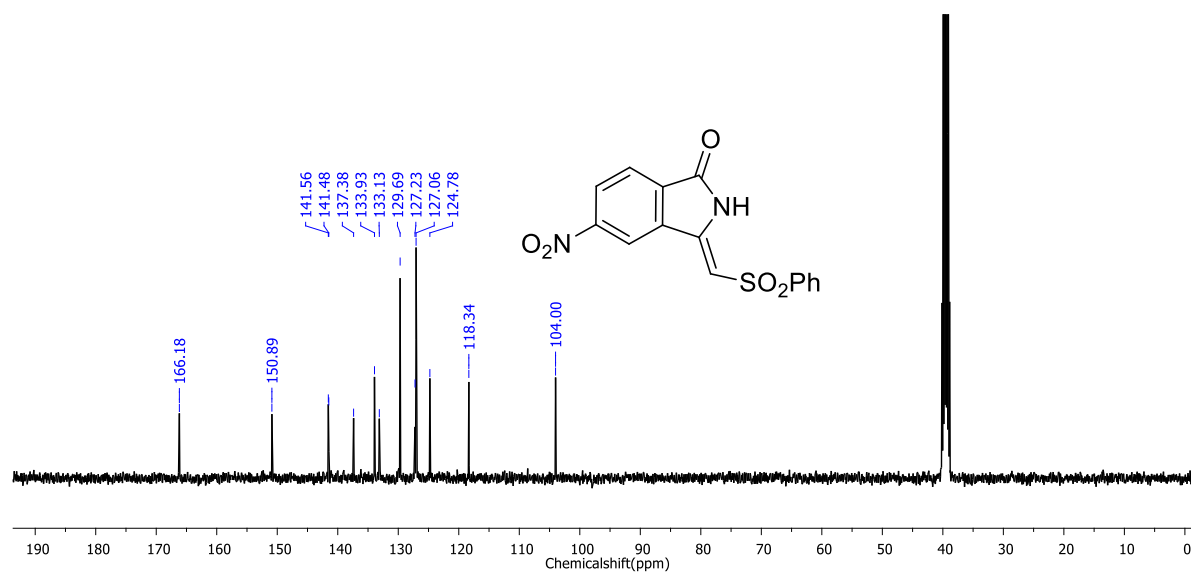
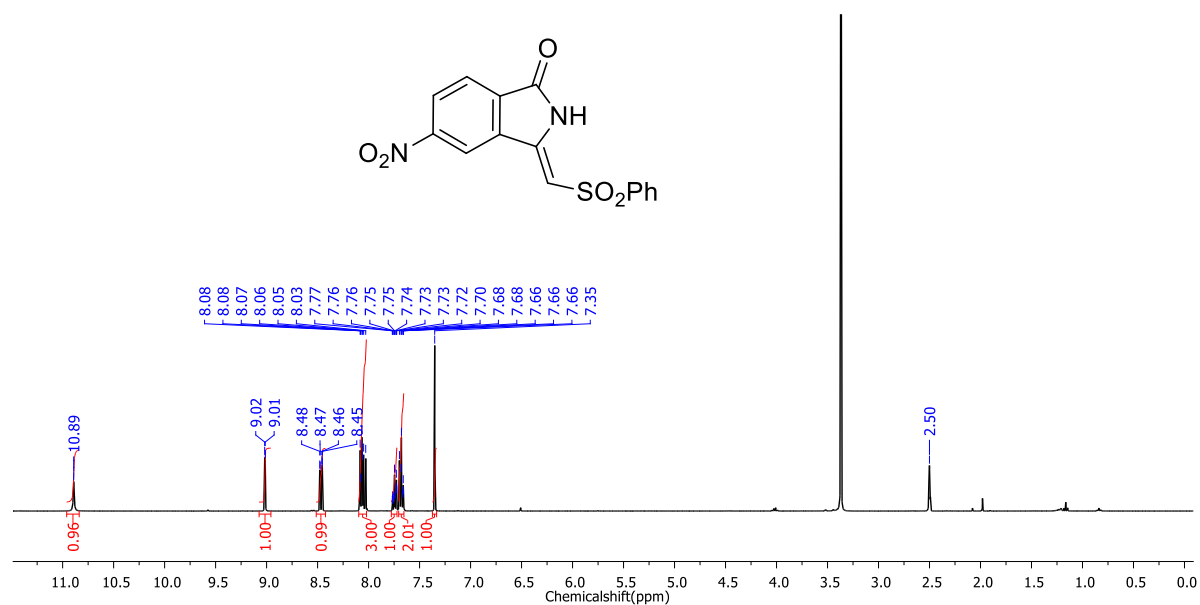


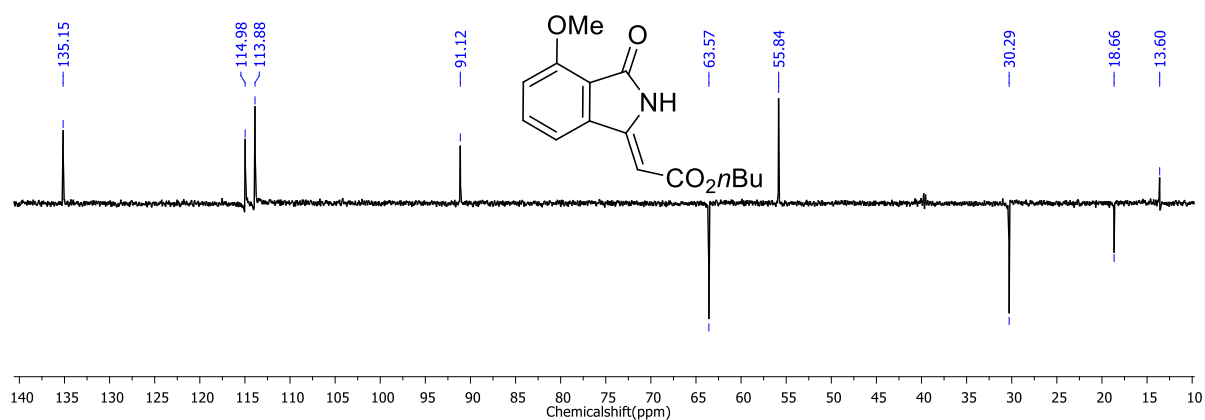
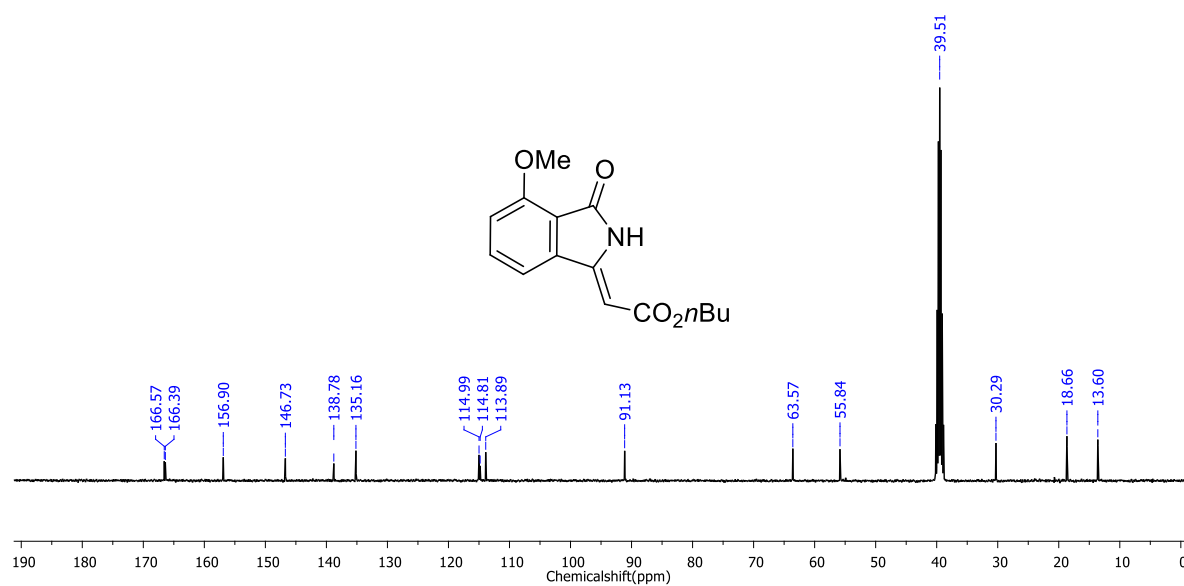
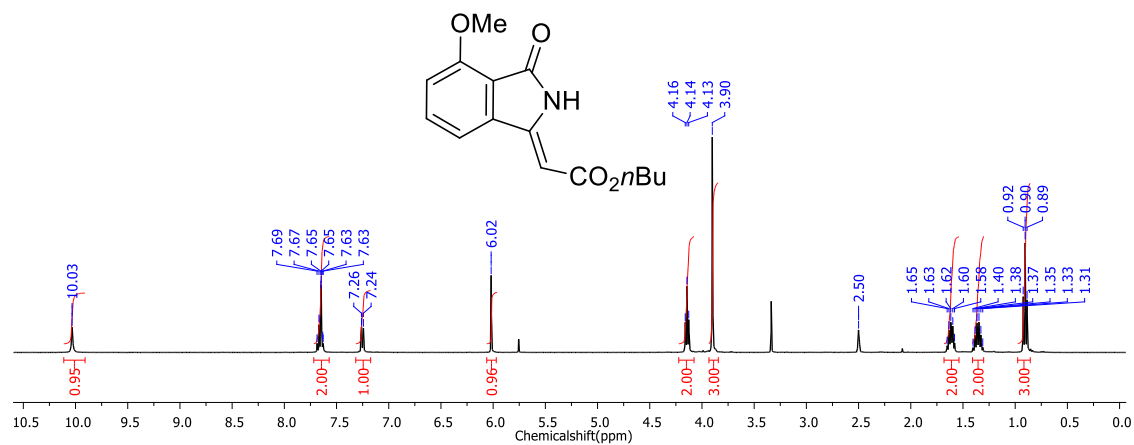
Figure 1 Absorbance (black) and Fluorescence (blue) spectra of (a) pyrene-1-carbonitrile (**1t**) and (b) 3-methyleneisoindolin-1-one (**3tg**) in dichloromethane solvent

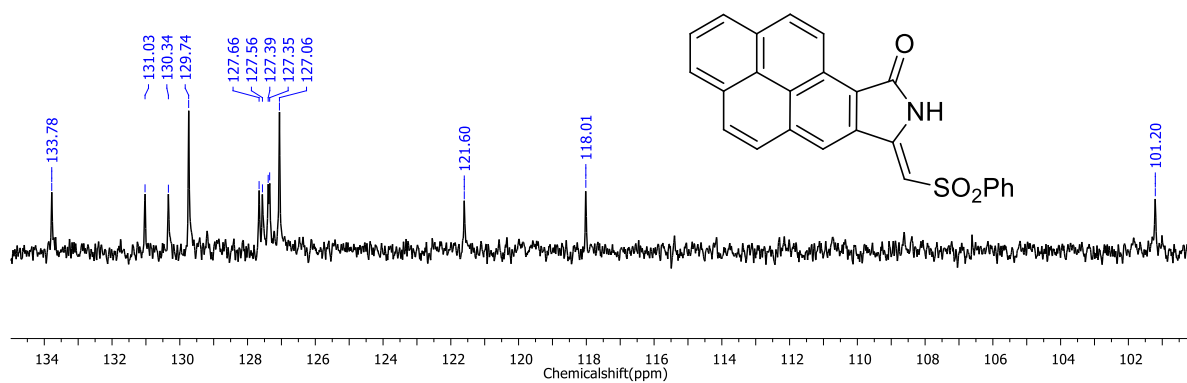
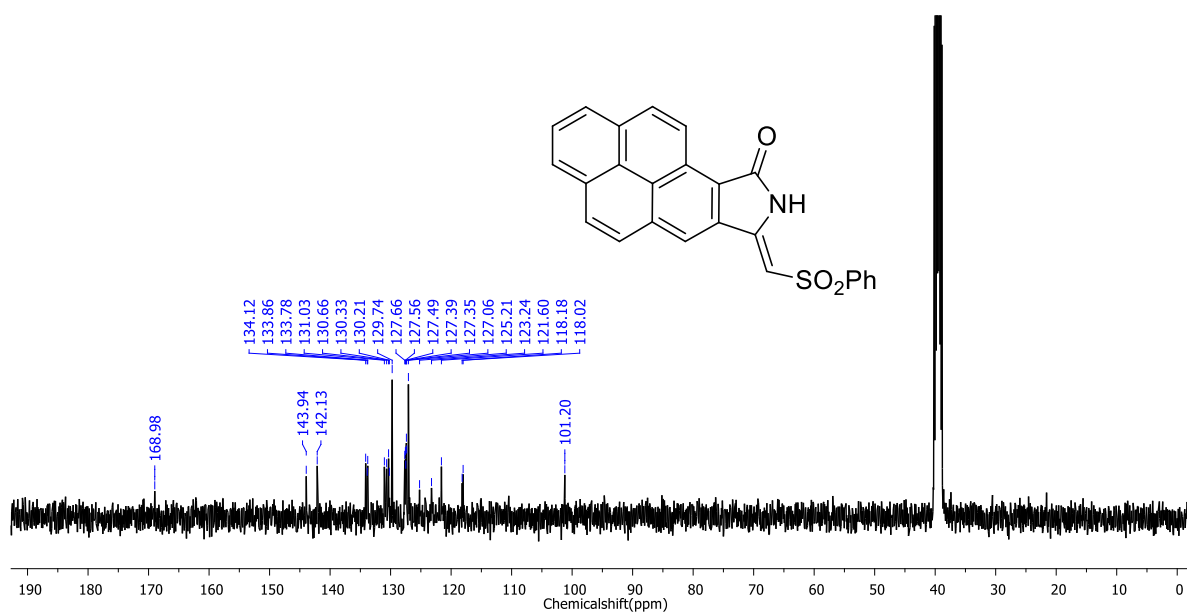
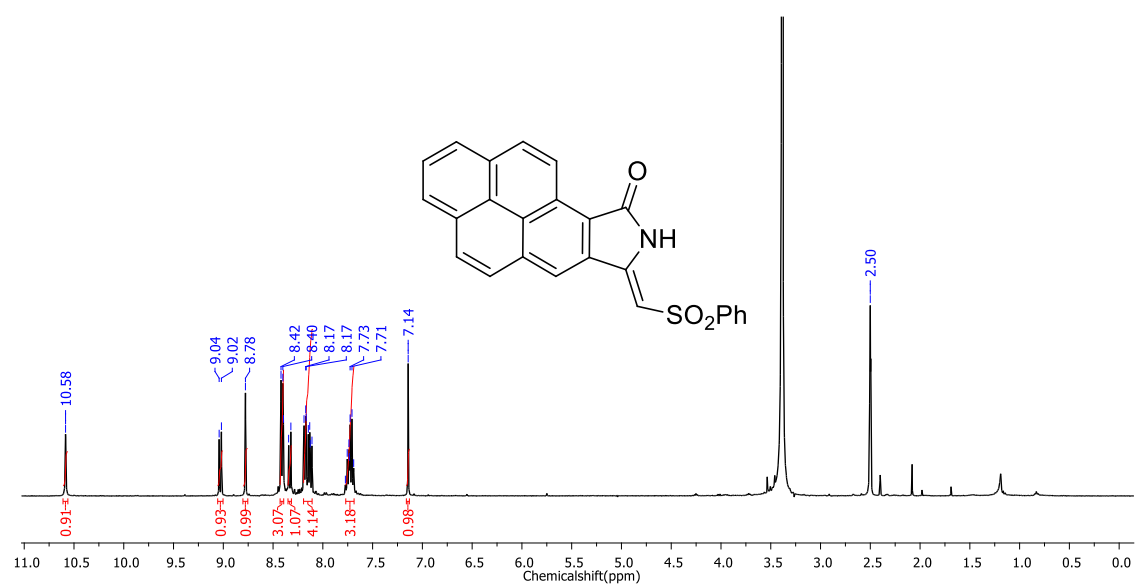
3C.16: Spectral Copies of Selected Compounds

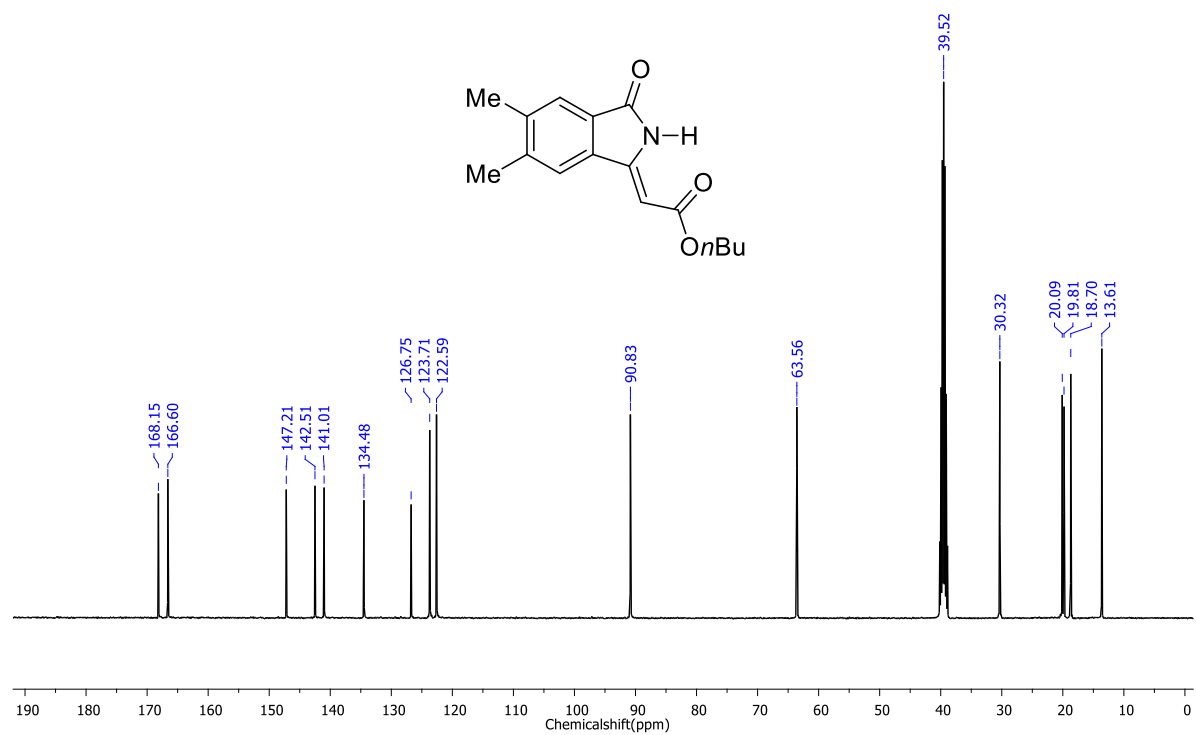
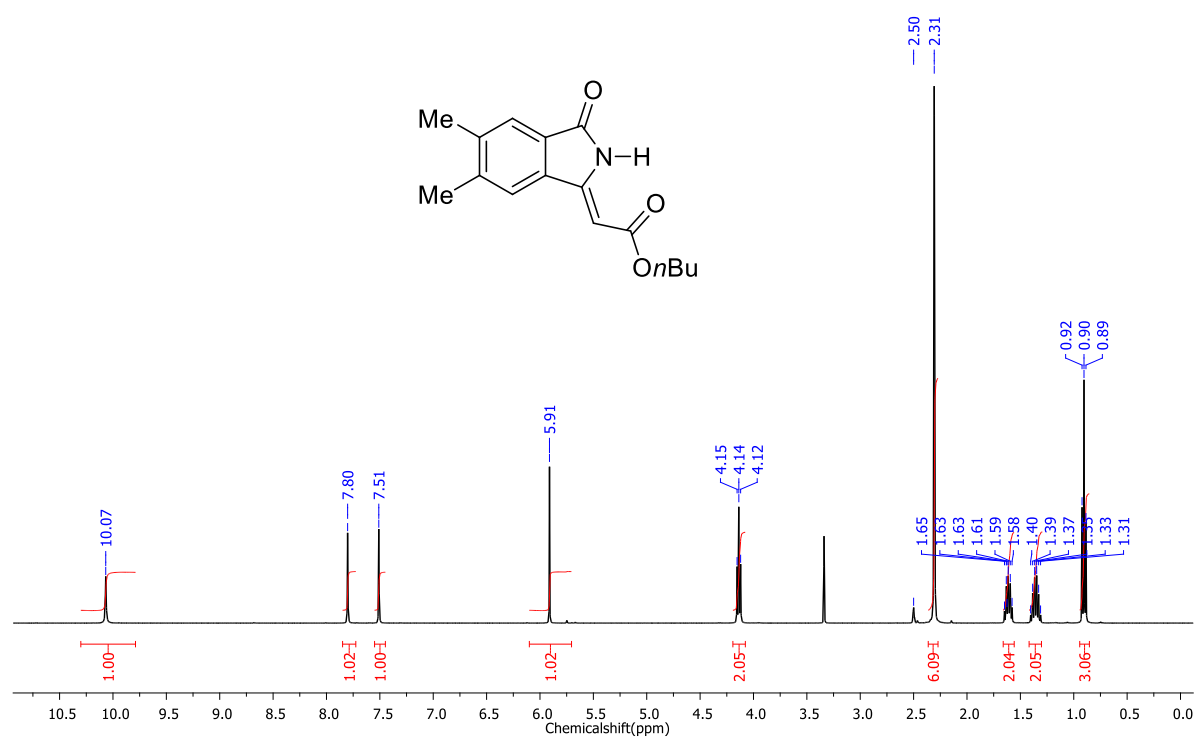
Spectral Data of Compound **3ac**.

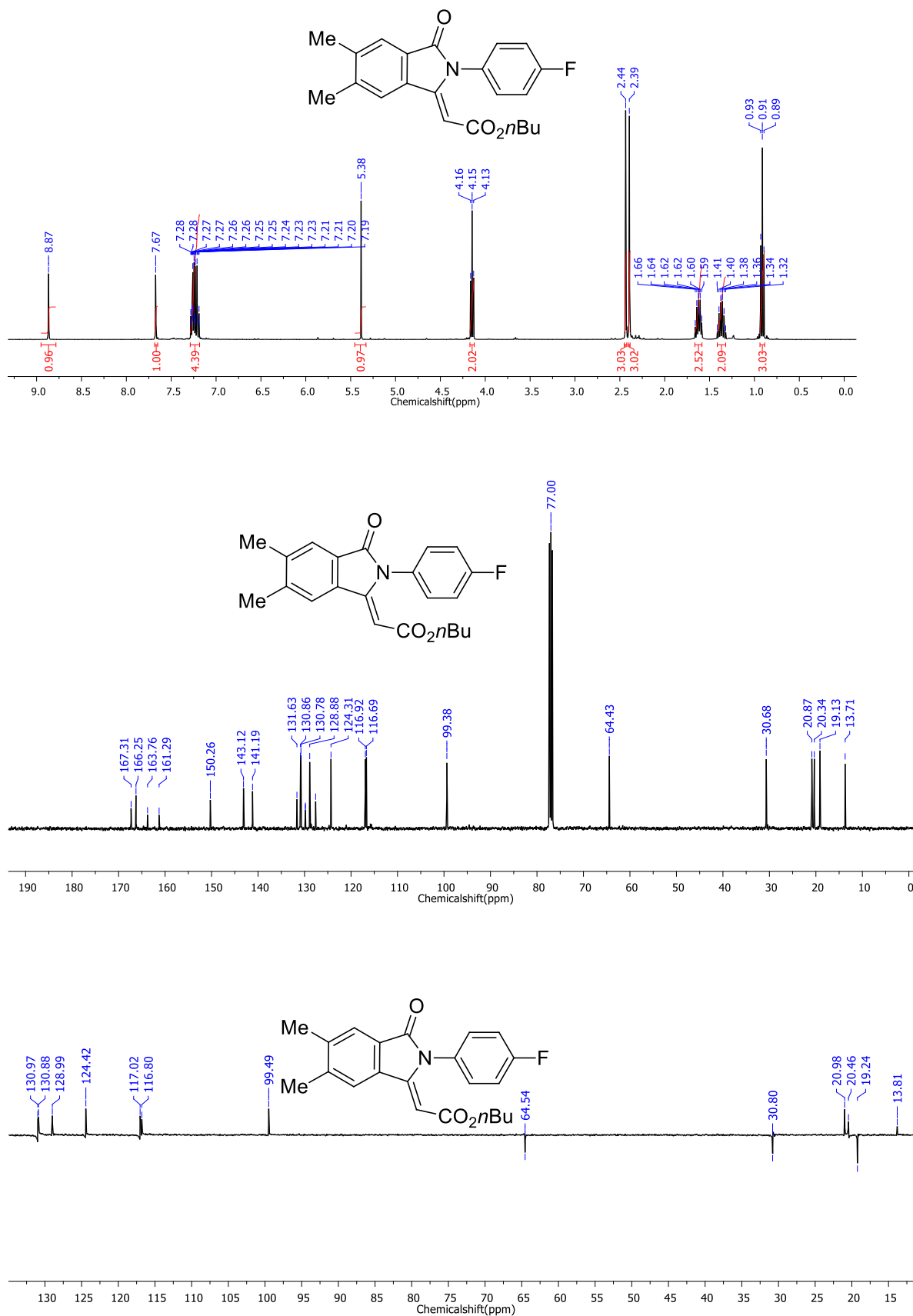
Spectral Data of Compound **3gg**.

Spectral Data of Compound **3jg**.

Spectral Data of Compound **3nc**.

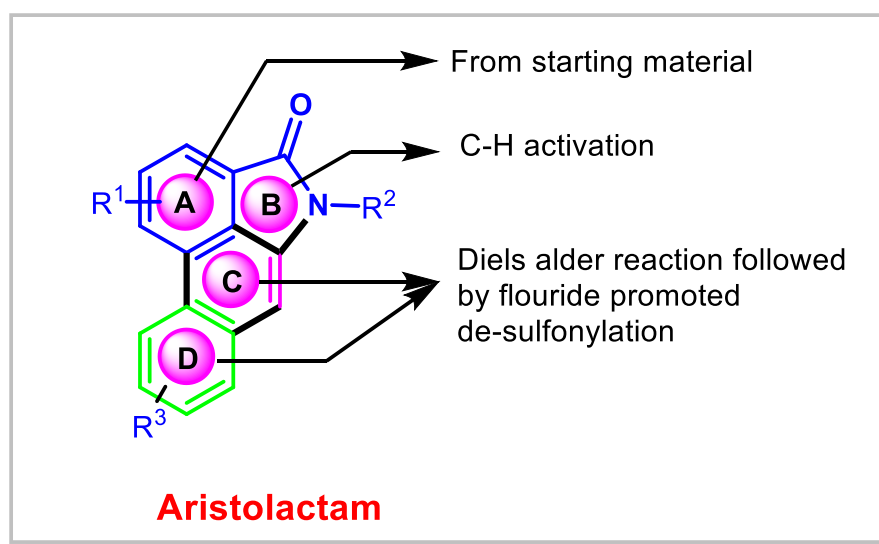
Spectral Data of Compound **3tg**.

Spectral Data of Compound **3rc**.

Spectral Data of Compound **7b**.

Chapter 4

Total Synthesis of Aristolactam Alkaloids via Synergistic C-H Bond Activation and Dehydro-Diels-Alder Reactions



4.1 Introduction

Aristolactams are naturally occurring phenanthrene lactam alkaloids (Figure1). These alkaloids are isolated from *Aristolochiaceae*, *Annonaceae*, *Piper* *Piperaceae*, and *Saururaceae* plant species.¹⁻³ Aristolactams are frequently used as folk medicines in several countries.^{2g-i} Meanwhile, these molecules show an interesting array of biological properties such as anti-inflammatory, antiplatelet, antimycobacterial, neuro-protective and anticancer activities.²⁻³ Due to the unique structural features and potential biological activities, considerable amount of effort has been devoted to synthesize these molecules by several research groups.⁴

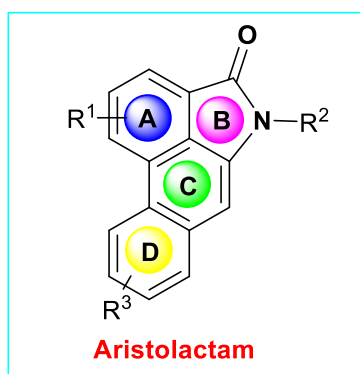
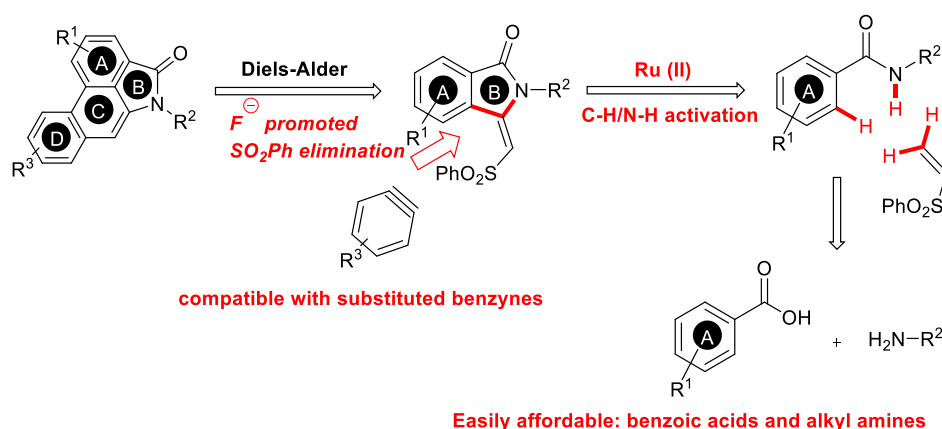


Figure1: Structure of aristolactam alkaloid.

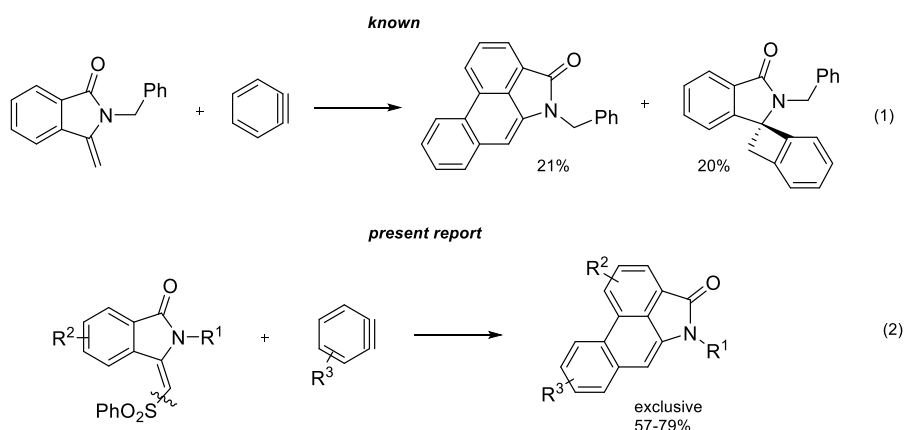
4.2: Aim of The Present Work

After surveying all these elegant contributions, we understood that a general and easily approachable method for synthesizing these alkaloids with minimum number of steps from easily affordable starting materials is needed. Meanwhile, the new method should be general for the preparation of numerous aristolactam derivatives in order to explore the utility of these molecules in various areas. Particularly, the utility of these alkaloids in various biological applications have been extensively increased in the past two decades.



Scheme 4.1: Retrosynthetic Analysis

Herein, we aimed to develop an efficient two steps synthesis of aristolactam alkaloids from easily available and affordable starting materials such as aromatic acids, alkyl amines and alkenes. To execute the synthesis, two new synthetic methodologies such as preparation of 3-methyleneisindolin-1-ones via a ruthenium-catalyzed oxidative cyclization of aromatic amides with vinyl sulphone and dehydro-Diels-Alder reaction followed by SO_2Ph cleavage of 3-methyleneisindolin-1-ones with benzyne were developed. The present method was compatible for the preparation of various aristolactam derivatives including sensitive I, Br, Cl, F and CF_3 functional groups. The combination of C-H bond activation and dehydro-Diels-Alder reactions allow a short and efficient synthesis of several aristolactam alkaloids in good yields.



The goal of this work is to construct cyclic rings of aristolactam **A-D** in a simple manner from easily affordable starting materials (Scheme 1). Rings **A** and **B** having 3-methylene-isindolone can be constructed via a metal-catalyzed C-H/N-H annulation of substituted benzamides with alkenes in one pot.⁵⁻⁷ Substituted benzamides can be easily prepared from benzoic acids and amines. Rings **C** and **D** can be constructed in one pot via

the Dihydro-Diels-Alder reaction of 3-methyleneisindolin-1-ones with benzyne.⁸⁻⁹ However, this type of cycloaddition reaction is not very effective, because it provides competitive side products along with the expected product (eq 1).⁴ⁱ To overcome this problem, we engineered a molecule having a cleavable SO₂Ph group at the β-carbon of alkene of 3-methyleneisindolin-1-one. After the cycloaddition reaction, the sulfonyl group can be easily cleaved by fluoride source in the same step (eq 2). Thus, the cycloaddition reaction can be done in a highly selective manner.

4.3: Ruthenium-Catalyzed Cyclization of Aromatic Benzamides with Alkenes: Stereoselective Synthesis of (E)-3- Methyleneisindolin-1-ones

4.4: Results and Discussion

Our continuous interest on ruthenium-catalyzed C-H bond activation reaction prompted us to explore the possibility of development of new synthetic route for the synthesis of key intermediate 3-methyleneisindolin-1-ones via ruthenium-catalyzed oxidative cyclization of benzamides with vinyl phenyl sulfone.^{6c-d, 7l} The oxidative cyclization of *N*-methyl benzamide **1a** with phenyl vinyl sulfone (**2a**) in the presence of [{RuCl₂(*p*-cymene)}₂] (5 mol %), AgSbF₆ (20 mol %) and Cu(OAc)₂·H₂O (0.5 equiv) under oxygen at 120 °C for 36 h provided 3-methyleneisindolin-1-one **3a** in 78% yield in an 95:5 *E/Z* ratio.

4.5: Optimization Studies

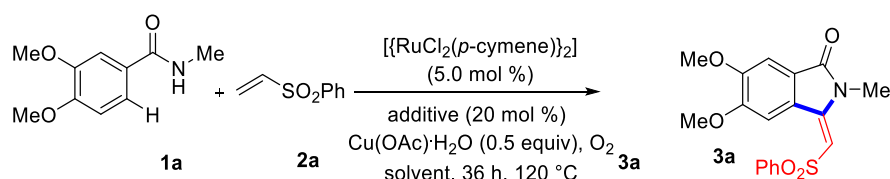


Table 4.1: Optimization Studies ^a

entry	solvent	additive	yield of 3a (%) ^b
1	ClCH ₂ CH ₂ Cl	AgSbF ₆	-
2	THF	AgSbF ₆	15
3	1,4-dioxane	AgSbF ₆	-
4	DMF	AgSbF ₆	-
5	toluene	AgSbF ₆	20
6	CF ₃ COOH	AgSbF ₆	-
7	CH₃COOH	AgSbF₆	78
8	CH ₃ COOH	AgBF ₄	42
9	CH ₃ COOH	AgOTf	46
10	CH ₃ COOH	KPF ₆	15
11	CH ₃ COOH	-	NR

^aAll reactions were carried out under the following conditions: **1a** (75 mg), **2a** (1.5 equiv), [{RuCl₂(*p*-cymene)}₂] (5 mol %), additive (20 mol %) and Cu(OAc)₂·H₂O (50 mol %) in solvent at 120 °C for 36 h under oxygen atmosphere. ^b Isolated yield.

Initially, the cyclization reaction was examined with various solvents such as 1,2-dichloroethane, THF, 1,4-dioxane, DMF, toluene, CF₃COOH and CH₃COOH (Table 4.1). Among them, acetic acid was effective yielding product **3a** in 78% yield (entry 7). Other solvents such as toluene and THF were less effective affording product **3a** in 20% and 15% yields, respectively (entries 2 and 5). Remaining solvents were not effective. The cyclization reaction was further examined with additives AgSbF₆, AgBF₄, AgOTf and KPF₆. Among them, AgSbF₆ was effective providing product **3a** in 78% yield (entry 7). Remaining additives were less effective for the cyclization reaction (entries 8-10). The cyclization reaction did not proceed without AgSbF₆ (entry 11). AgSbF₆ is used to generate a cationic ruthenium species for activating weak amide group assisted C-H bond.^{5c-d} Cu(OAc)₂·H₂O has been widely used as an oxidant for a weak chelating group assisted C-H bond activation.^{5c} Usually, a 2.0 equiv amount of copper source is needed for this type of reaction. However, in the present reaction, 0.5 equiv amount of copper source is used and the remaining amount of copper source has been regenerated under oxygen.

4.6: Scope of *N*-Substituted Benzamides

The cyclization reaction was examined with various *N*-substituted such as methyl, propyl, butyl, isopropyl, cyclohexyl and benzyl substituted benzamides **1b-f** (Table 4.2). These reactions worked very well, providing the expected cyclization products **3b-f** in 69%, 67%, 58%, 56% and 71% yields in 95:4 to 99:1 *E/Z* ratios, respectively (Table 4.2, entries 2-6).

Table 4.2: Results of the Reaction of Aromatic *N*-Substituted Benzamides **1** with Vinyl Phenyl Sulfone **2a**

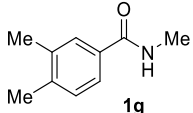
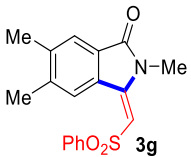
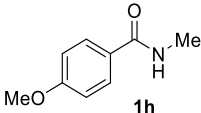
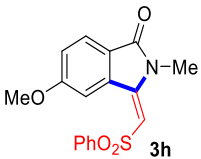
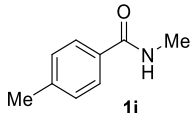
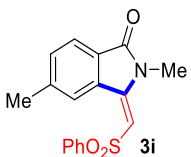
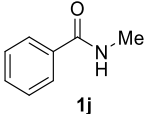
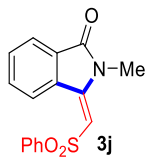
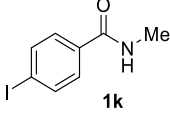
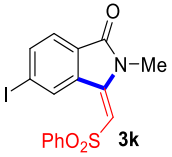
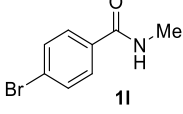
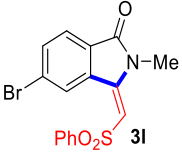
entry	1	product 3	yield (%) ^b
1			78% (<i>E/Z</i> 95:5)
2			69% (<i>E/Z</i> 98:2)
3			67% (<i>E/Z</i> 98:2)
4			58% (<i>E/Z</i> 98:2)
5			56% (<i>E/Z</i> 99:1)
6			71% (<i>E/Z</i> 96:4)

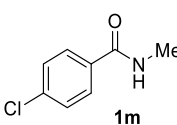
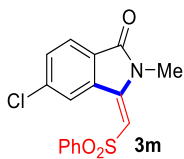
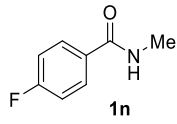
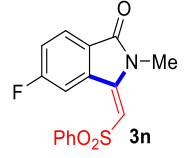
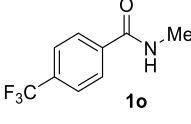
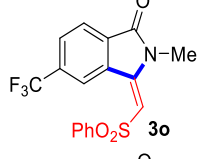
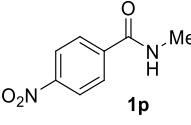
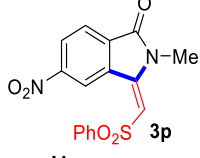
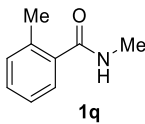
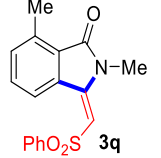
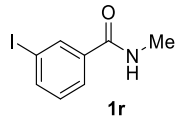
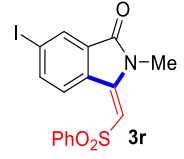
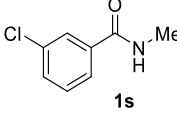
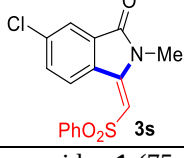
^aAll reactions were carried out using aromatic benzamides **1** (75 mg), vinyl phenyl sulfone **2a** (1.5 equiv), [{RuCl₂(*p*-cymene)}₂] (5 mol %), AgSbF₆ (20 mol %) and Cu(OAc)₂·H₂O (50 mol %) under O₂ atmosphere in dry acetic acid (3.0 mL) at 120 °C for 36 h. ^bIsolated yields.

4.7: Scope of Substituted Benzamides

A variety of substituted benzamides **1g-s** was compatible for the cyclization reaction (Table 4.3). Electron-releasing OMe, Me and halogen I, Br, Cl and F substituted benzamides **1g-n** efficiently reacted with **2a** affording isoindolin-1-ones **3g-n** in good yields (Table 4.3, entries 1-8). A less reactive electron-withdrawing CF₃ and NO₂ substituted benzamides **1o-p** also efficiently reacted with **2a** providing products **3o** and **3p** in good yields (Table 4.3, entries 9-10). Similarly, *ortho* and *meta* substituted benzamides **1q-s** also efficiently participated in the reaction, giving products **3q-s** in 47%, 64% and 61% yields, respectively (Table 4.3, entries 11-13). Particularly, in the *meta* substituted benzamides **1r-s**, the C-H bond activation takes place at a less hindered C6-H.

Table 4.3: Results of the Reaction of Aromatic Substituted Benzamides **1** with Vinyl Phenyl Sulfone **2a**

entry	1	product 3	yield (%) ^b
1	 1g	 3g	66% (E:Z 98:2)
2	 1h	 3h	75% (E:Z 97:3)
3	 1i	 3i	71% (E:Z 99:1)
4	 1j	 3j	65%
5	 1k	 3k	69%
6	 1l	 3l	67%

7			65%
8			59%
9			66%
10			58%
11			47%
12			64%
13			61%

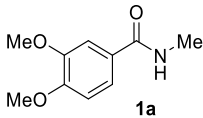
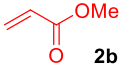
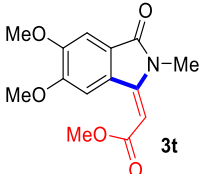
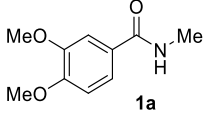
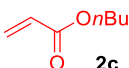
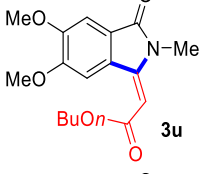
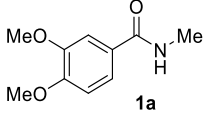
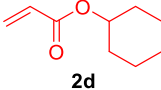
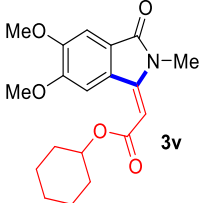
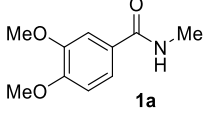
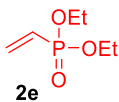
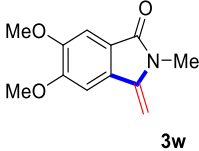
^aAll reactions were carried out using aromatic benzamides **1** (75 mg), vinyl phenyl sulfone **2a** (1.5 equiv), [{RuCl₂(*p*-cymene)}₂] (5 mol %), AgSbF₆ (20 mol %) and Cu(OAc)₂·H₂O (50 mol %) under O₂ atmosphere in dry acetic acid (3.0 mL) at 120 °C for 72 h. ^bIsolated yields.

4.8: Scope of Alkenes

The cyclization reaction was further examined with various alkenes (Table 4.4). Methyl, *n*-butyl and cyclohexyl acrylates **2b-d** efficiently reacted with **1a** yielding cyclization products **3t-v** in good yields (Table 4.4, entries 1-3). In the reaction, only *E* stereoselective compound was observed. Diethyl vinylphosphonate (**2e**) was also efficiently involved in the reaction, giving product **3w** in 54% yield with a free *exo* double bond (Table 4.4, entry 4). In the product **3w**, phosphonate (P=O(OEt)₂) was cleaved under the present reaction

conditions. The cyclization reaction was not compatible with acrylonitrile, methyl vinyl ketone and styrene.

Table 4.4 : Scope of the Activated Alkenes **2b-e**^a

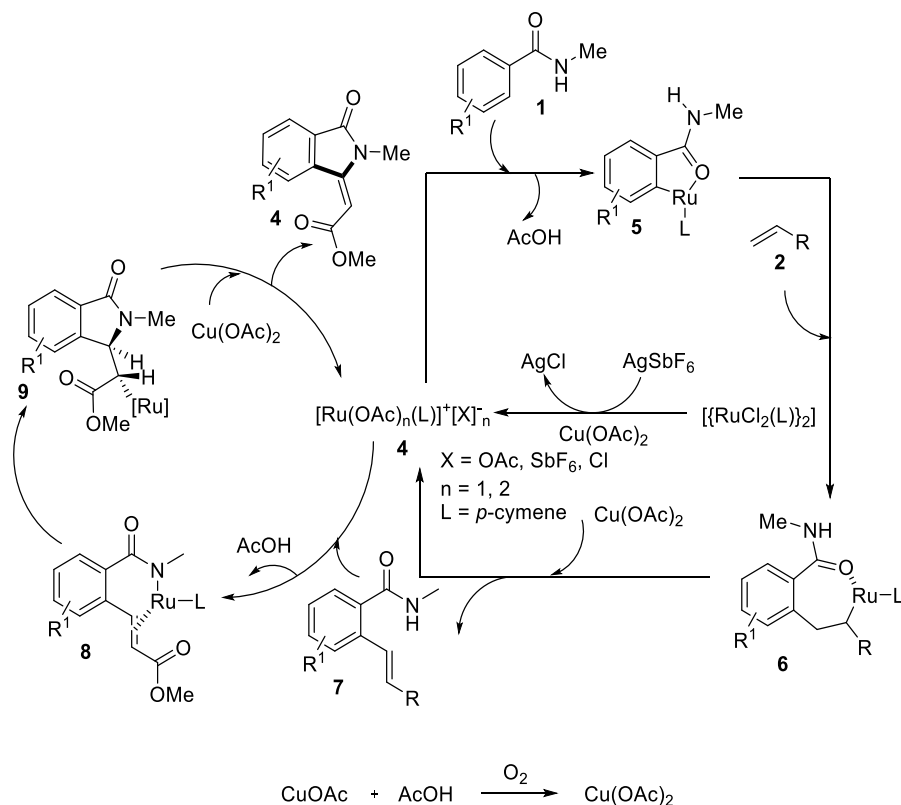
entry	1	alkenes 2	product 3	yield (%) ^b
1				74
2				72
3				72
4				54

^aAll reactions were carried out using **1a**, alkenes **2b-c** (4.0 equiv), **2d-e** (2.0 equiv), [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (5 mol %), AgSbF₆ (20 mol %) and Cu(OAc)₂·H₂O (50 mol %) under O₂ atmosphere in AcOH (3.0 mL) at 120 °C for 36 h. ^bIsolated yield.

4.9: Proposed Mechanism

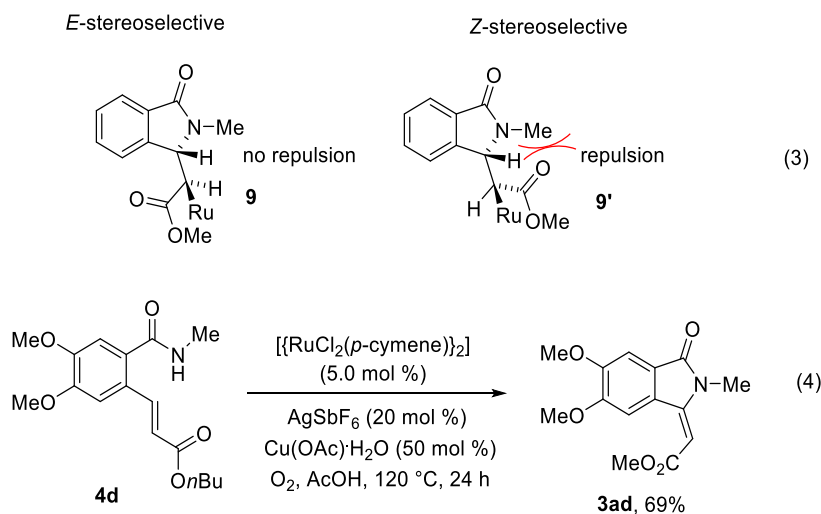
A possible reaction mechanism for oxidative cyclization of *N*-substituted benzamides **1** with alkenes **2** is discussed in Scheme S1. AgSbF₆ likely removes the chloride ligand from [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] complex followed by the ligand exchange with Cu(OAc)₂ giving a cationic ruthenium species **4**. Coordination of the carbonyl group of amide **1** into the ruthenium cationic species followed by *ortho*-metalation provides a five-membered ruthenacycle **5** and AcOH. Coordinative insertion of alkene **2** into the Ru–carbon bond of ruthenacycle **5** affords a seven membered ruthenacycle intermediate **6**. β-Hydride elimination of intermediate **6** in the presence of Cu(OAc)₂ provides a Heck-type

alkenylated product **7** and regenerates the active ruthenium species **4** for the next catalytic cycle.



Scheme 4.5: Proposed mechanism

Later, the amide group of product **7** coordinates with a ruthenium species **4** followed by the intramolecular coordination of double bond affords intermediate **8** and AcOH. Intramolecular coordinative insertion of N-Ru bond of intermediate **8** into an alkene moiety provides intermediate **9**. Subsequent β -hydride elimination of intermediate **9** in the presence of Cu(OAc)_2 provides product **3** and regenerates the active ruthenium species **4** for the next catalytic cycle.

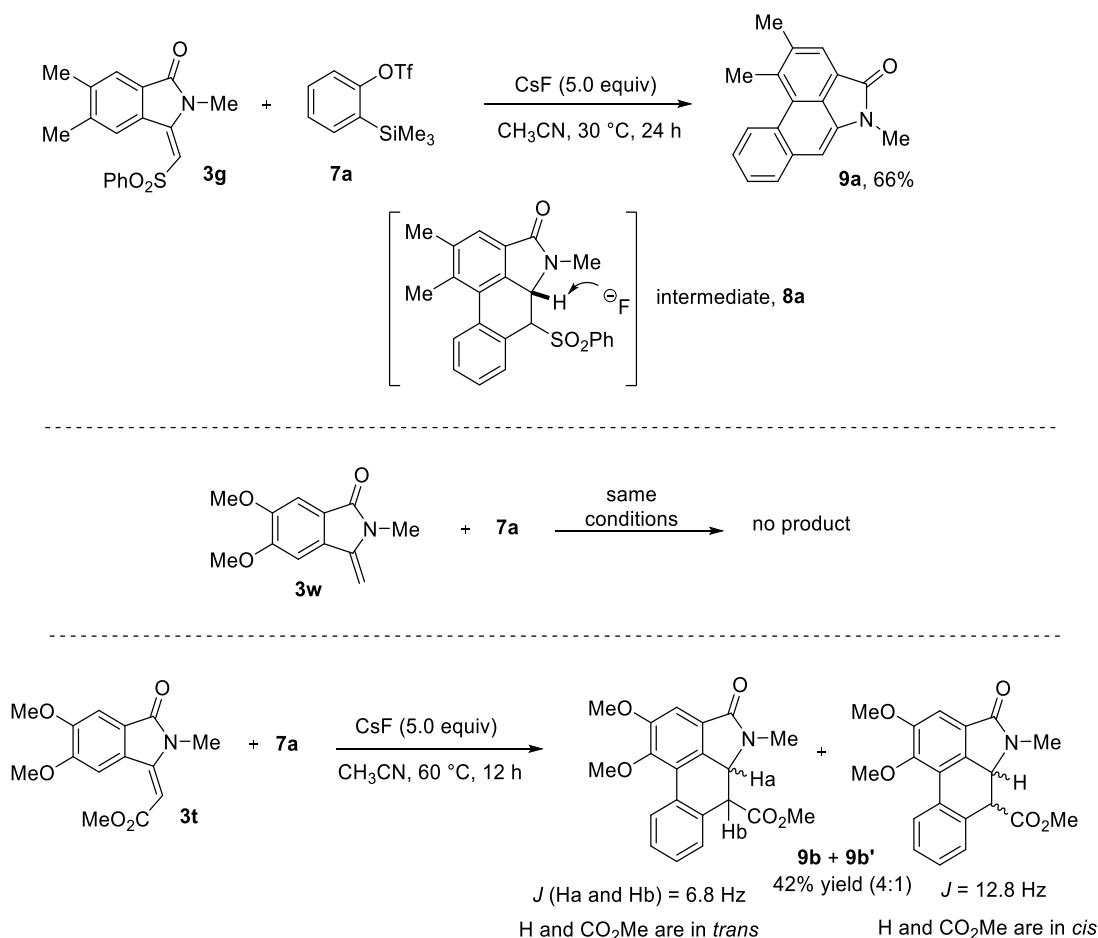


The stereoselectivity highly depends on the coordinative intramolecular insertion of N-Ru bond to the double of alkene in intermediate **8**. In the reaction, intermediate **9** was observed (eq 3). After that, β -Hydride elimination takes place of intermediate **9** in the presence of $\text{Cu}(\text{OAc})_2$ providing *E*-stereoselective product **3** and regenerates the active ruthenium species **4**. In the intermediate **9**, an ester group of alkene and tertiary C-N Me of intermediate **9** stay anti to each other. This is mainly due to avoid the steric hindrance of *N*-Me group and ester moiety of intermediate **9'**. Meanwhile, intermediate **9'** accounts for the *Z*-stereoselective product. In the reaction, only 30 mol % of $\text{Cu}(\text{OAc})_2$ was used. In fact, a stoichiometric amount of 2.0 equiv $\text{Cu}(\text{OAc})_2$ is needed for the reaction. The remaining amount of $\text{Cu}(\text{OAc})_2$ has been regenerated by the reaction of CuOAc with AcOH under oxygen. It has been previously observed from our group that a cationic ruthenium species **4** is very selective to the coordination of carbonyl group instead of the nitrogen group in benzamide **1**.^{6d}

4.10: Dehydro-Diels-Alder Reaction Followed by SO_2Ph Cleavage of 3-Methyleneisoindolin-1-ones with Benzyne: Synthesis of Aristolactams

To explore the possibility for the preparation of aristolactam derivatives, the dehydro-Diels-Alder reaction of **3** with benzyne was examined (Scheme 4.6). The cycloaddition of **3g** with benzyne precursor **7a** in the presence of CsF in CH_3CN at 30°C for 24 h gave aristolactam derivative **9a** in 66% yield. It is believed that after cycloaddition reaction, intermediate **8a** is formed in which SO_2Ph is cleaved by fluoride ion. The formation of intermediate **8a** was confirmed by MALDI-TOF experiment (for detailed mechanism, see experimental data).⁸ However, in the cycloaddition reaction of **3w** with **7a**, no product

was observed. In the cycloaddition of **3t** in which an ester substituent present at the β -carbon of alkene with **7a**, a mixture of heterocyclic molecules **9b** and **9b'** were observed in 42% combined yield in a 4:1 diastereoselective ratio. In the reaction, CO₂Me group did not eliminate as like SO₂Ph. This result clearly reveals that the SO₂Ph is crucial to get aristolactams in more yields with high selectivity.



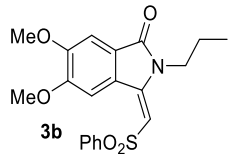
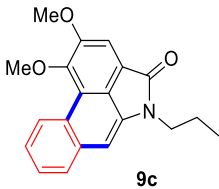
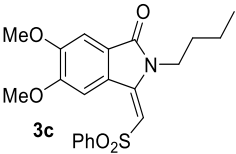
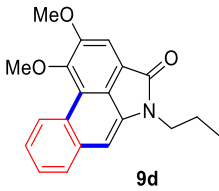
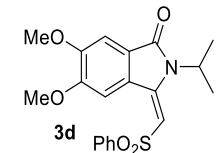
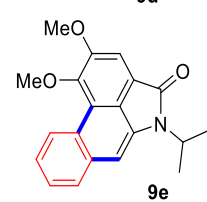
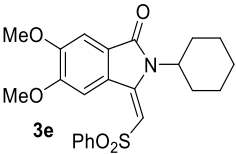
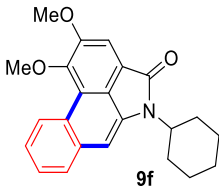
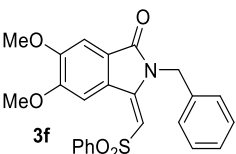
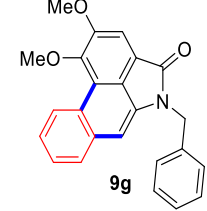
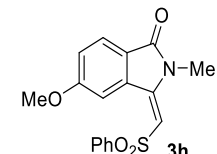
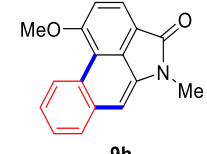
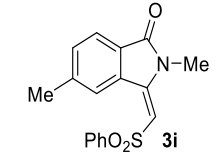
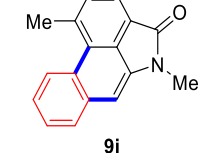
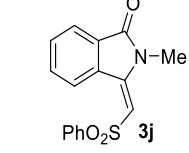
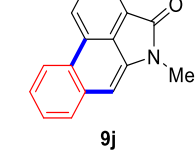
Scheme 4.6: Dehydro-Diels-Alder reaction with benzyne

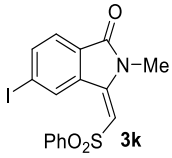
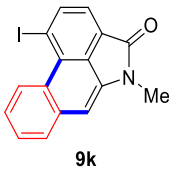
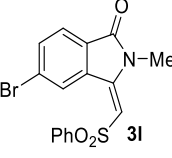
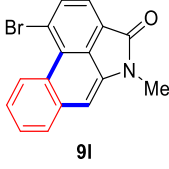
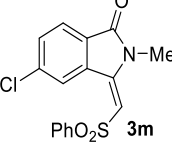
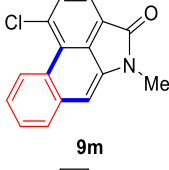
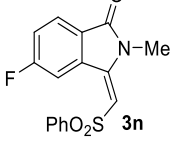
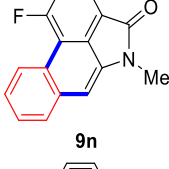
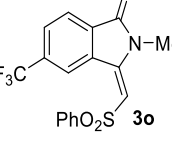
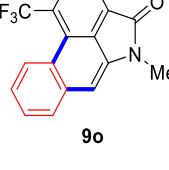
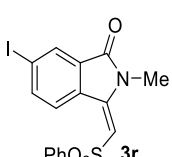
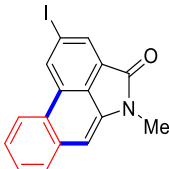
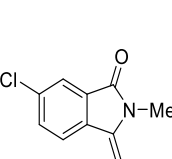
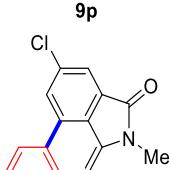
4.11: Scope of Substituted Isoindolin-1-ones

The cycloaddition reaction was examined with various *N*-substituted indolin-1-one derivatives **3b-f** (Table 4.5). *N*-propyl, butyl, *iso*-propyl, cyclohexyl and benzyl substituted isoindolin-1-ones **3b-f** underwent cycloaddition with **7a** providing aristolactam derivatives **9c-g** in good yields (Table 4.5, entries 1-5). Meanwhile, OMe, Me, I, Br, I, Cl, F, and CF₃ substituted

isoindolin-1-ones **3h-s** also efficiently participated in the reaction yielding products **9h-q** in good yields (Table 4.5, entries 6-15).

Table 4.5: Results of the Reaction of Substituted Isoindolin-1-ones **3** with benzyne **7a**^a

entry	1	product 9	yield (%) ^b
1	 3b	 9c	66%
2	 3c	 9d	68%
3	 3d	 9e	56%
4	 3e	 9f	59%
5	 3f	 9g	65%
6	 3h	 9h	75%
7	 3i	 9i	79%
8	 3j	 9j	71%

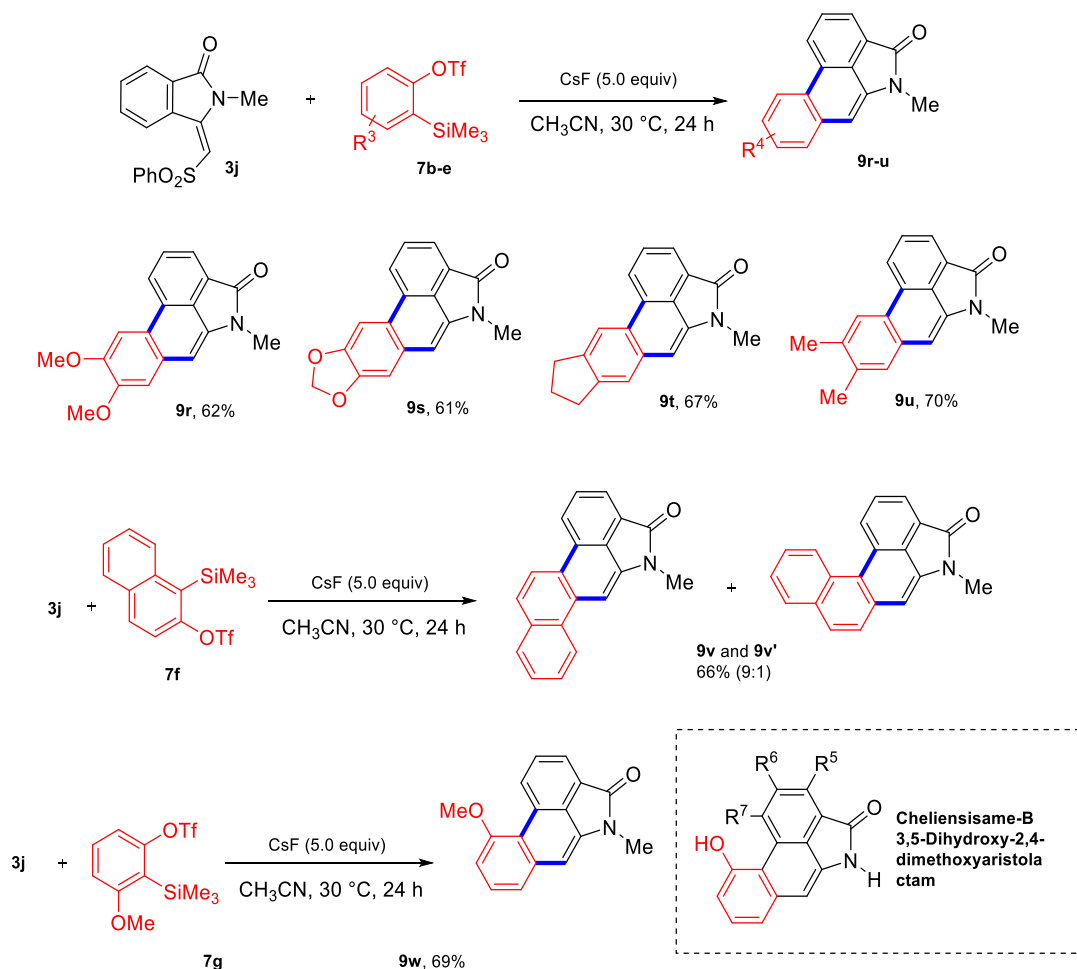
9	 <chem>CN1C(=O)c2cc(I)ccc2C1=SPh</chem> 3k	 9k	68%
10	 <chem>CN1C(=O)c2cc(Br)ccc2C1=SPh</chem> 3l	 9l	74%
11	 <chem>CN1C(=O)c2cc(Cl)ccc2C1=SPh</chem> 3m	 9m	77%
12	 <chem>CN1C(=O)c2cc(F)ccc2C1=SPh</chem> 3n	 9n	71%
13	 <chem>CN1C(=O)c2cc(C(F)(F)F)ccc2C1=SPh</chem> 3o	 9o	48%
14	 <chem>CN1C(=O)c2cc(I)ccc2C1=SPh</chem> 3r	 9p	65%
15	 <chem>CN1C(=O)c2cc(Cl)ccc2C1=SPh</chem> 3s	 9q	67%

^aAll reactions were carried out using substituted isoindolin-1-ones **3** (80 mg), benzyne precursor **7a** (2.0 equiv), CsF (5.0 equiv) in dry CH₃CN (8.0 mL) at 30 °C for 24 h. ^bIsolated yields.

4.12: Scope of Substituted Benzyne

The scope of cycloaddition reaction was further examined with substituted benzyne **7b-g** (Scheme 4.8). Symmetrical benzyne such as 3,4-dimethoxy benzyne, 3,4-dimethyl benzyne, indene derivative and 1,3-benzodioxale reacted with **3j**, providing cyclization products **9r-u** in good yields. When unsymmetrical benzyne **7f** was used, a regioisomeric products **9v** and **9v'** was observed in 66% yield in a 9:1 ratio. Interestingly,

unsymmetrical benzyne precursor **7g** provided aristolactam **9w** in 69% yield in a highly regioselective manner. The structure of compound **9w** was supported by a single crystal X-ray diffraction. It is important to note that by using benzyne precursor **7g**, several natural products can be prepared by changing the substituent on the benzamides.

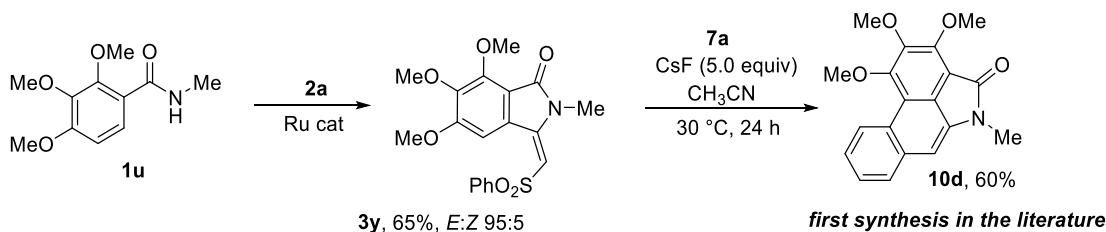
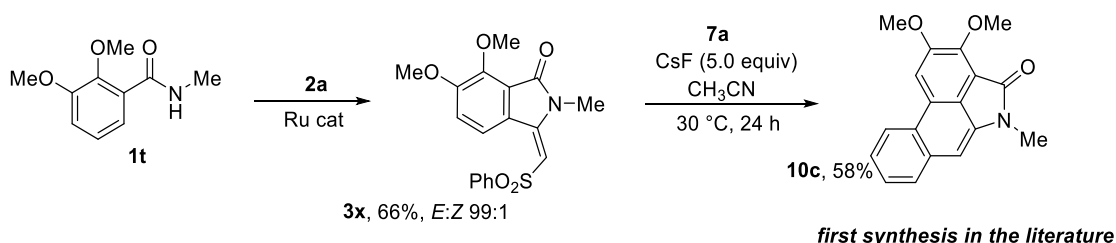
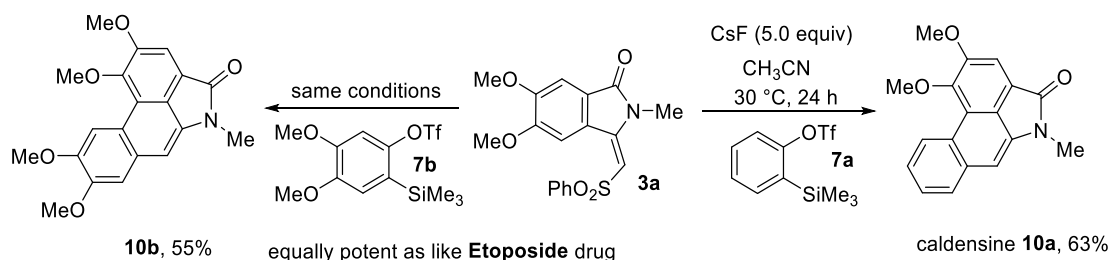


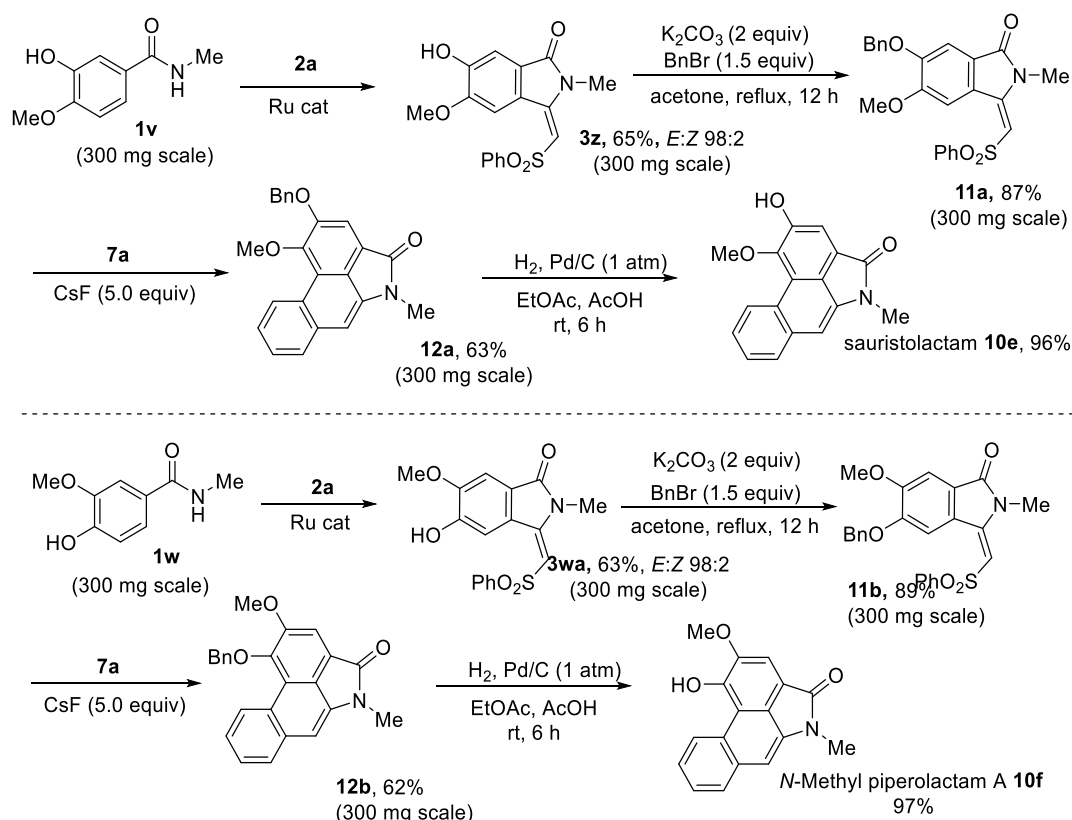
Scheme 4.8: Scope of substituted benzyne

4.13: Synthesis of *N*-Methyl Aristolactam Alkaloids

This result prompted us to explore the possibility for the preparation of *N*-methyl aristolactam alkaloids (Scheme 4.9). Treatment of compound **3a** with benzyne precursors **7a** or **7b** in the presence of CsF in CH₃CN at 30 °C for 24 h gave Caldensine **10a** and **10b** in 63% and 55% yields, respectively. Caldensine exhibited an IC₅₀ value of 25 mM against the chloroquine-sensitive and also shows antiplasmodial activity.^{3a} Compound **10b** is equally potent towards multidrug-resistant cell lines as compared with the commercially available drug Etoposide.^{2a} In a similar fashion, other alkaloids such as 2,3-dimethoxy-*N*-methyl-aristolactam **10c** and 2,3,4-trimethoxy-*N*-methyl-aristolactam **10d**

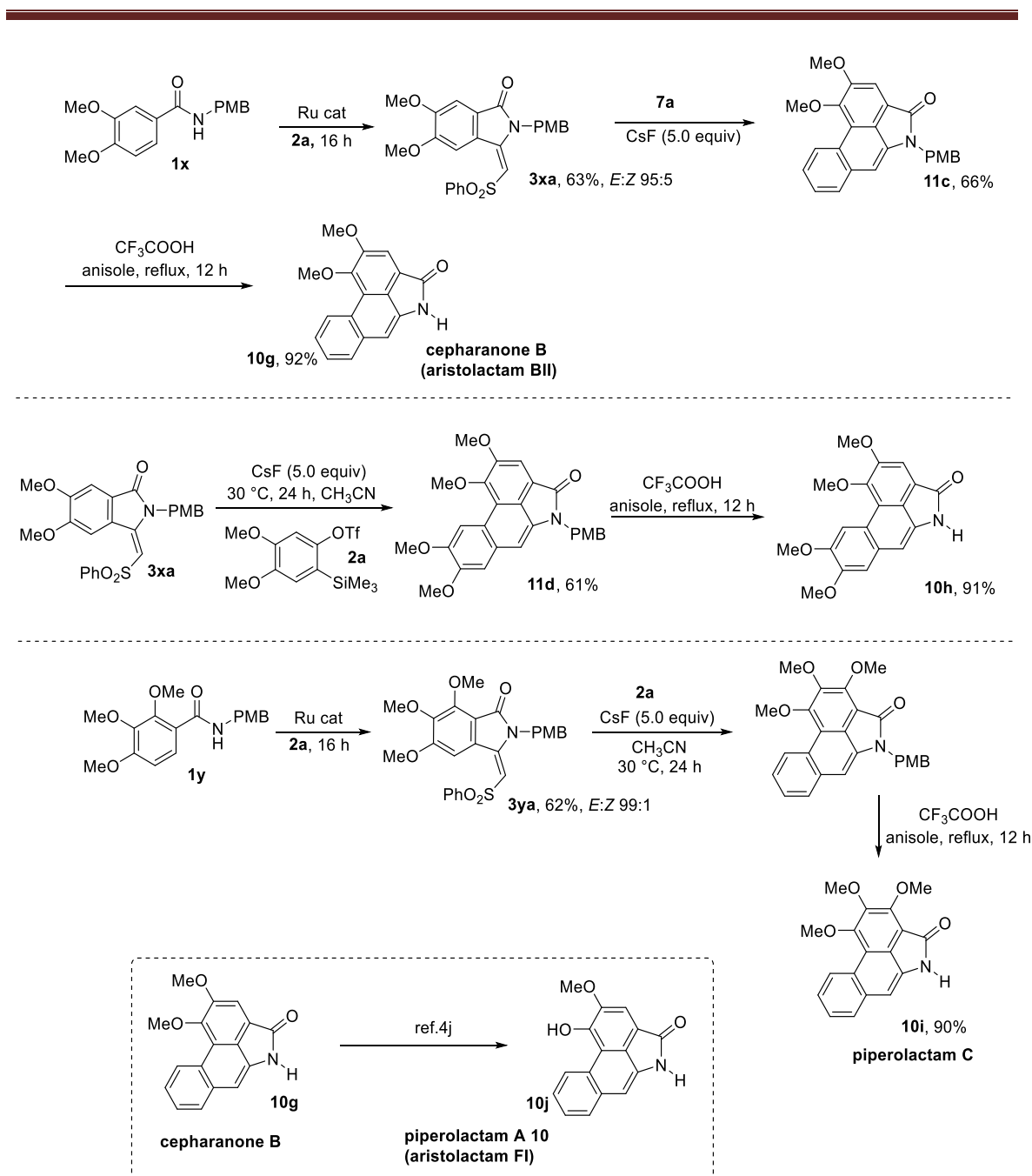
were prepared in good yields. It is important to note that the alkaloids **10c-d** were prepared for the first time in the literature. A highly useful sauristolactam (**10e**) and *N*-methyl piperolactam A (**10f**) were prepared in three steps. The reaction of 3-hydroxy-4-methoxy **1v** and 3-methoxy-4-hydroxy **1w** benzamides with **2a** provided products **3z** and **3wa** in good yields. Later, a free hydroxy group of **3z** and **3wa** was protected with benzyl bromide followed by cycloaddition reaction with **7a** affording products **12a-b**. Later, the benzyl group was deprotected by a palladium-catalyzed hydrogenation reaction, yielding alkaloids **10e-f** in excellent yields. Sauristolactam (**10e**) and *N*-methyl piperolactam A (**10f**) have shown cytotoxic activity against several cancer cell lines^{1c, 2a} and neuroprotective activity.^{3b}



Scheme 4.9: *N*-Methyl Aristolactam Alkaloids

4.14: Synthesis of *N*-H Aristolactam Alkaloids

By employing the present protocol, *N*-H aristolactams were also prepared by using *N*-PMB substituted benzamides (Scheme 4.10). The reaction of **1x** with **2a** at 120 °C for 16 h under similar reaction conditions provided product **3xa** in 63% yield. Later, **3xa** was treated with benzyne precursors **7a** or **7b** in the presence of CsF in CH_3CN at 30 °C for 24 h followed by PMB cleavage yielding Cepharanone B (**10g**) and Norcepharanone (**10h**) in good yields. In a similar fashion, Piperolactam C alkaloid (**10i**) was prepared by the cyclization of **1y** with **2a** in the presence of a ruthenium catalyst followed by cycloaddition with **7a** and subsequent PMB cleavage. Meanwhile, by using Cepharanone B (**10g**), aristolactam FI (**10j**) can be prepared easily in the known procedure.^{4j} Cepharanone B (**10g**) showed antimalarial activity with IC_{50} values of 7.51–11.01 $\mu g mL^{-1}$ ^{3c} and also exhibited significant cytotoxic activity against human CNS carcinoma cells.^{3d} Piperolactam C showed cytotoxicity against P-388 cells with IC_{50} value of 78 μM .^{3e} It is important to note that the *E/Z* ratio of indolin-1-one does not affect the yield of benzyne cycloaddition reaction.

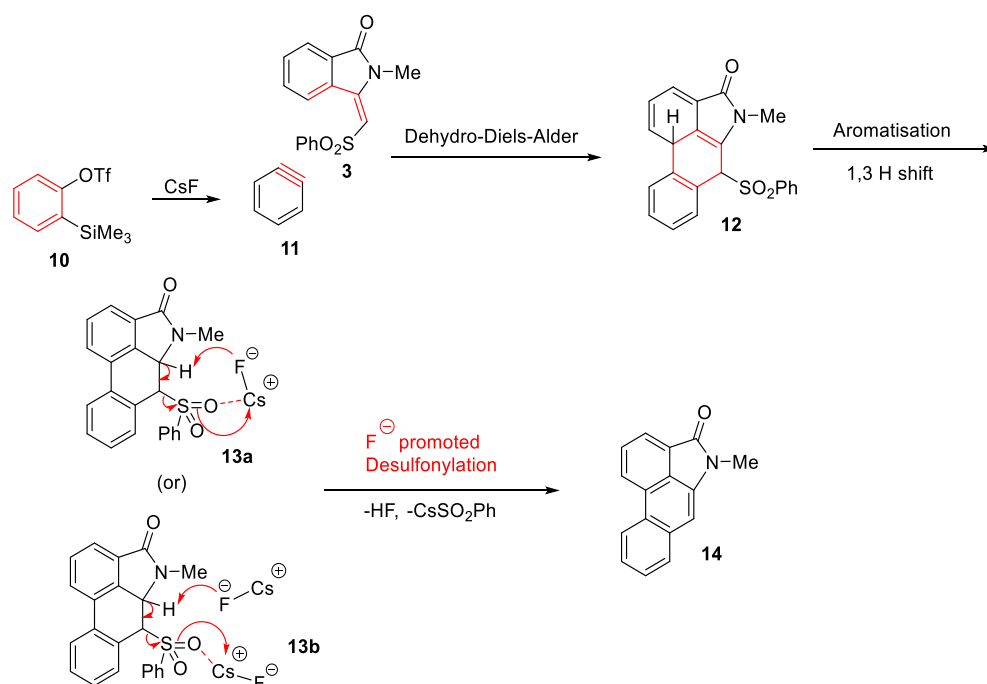


Scheme 4.10: Synthesis of N-H Aristolactam Alkaloids

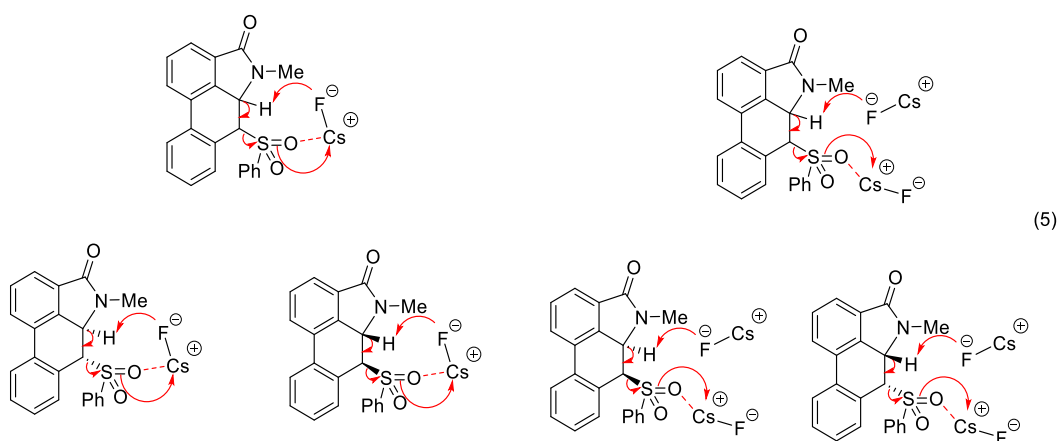
4.15: Proposed Mechanism for Cycloaddition Reaction

A possible reaction mechanism is proposed in Scheme 4.11 for the cycloaddition of product **3** with benzyne **11**. Isoindolone molecule **3** acts as a dienophile which undergoes dehydro-Diels-Alder reaction with benzyne **11** giving intermediate **12**. CsF likely cleaves SiMe₃ of **10** followed by elimination of OTf generating benzyne **11**. Intermediate **12** undergoes 1,3-H shift due to aromatization as a driving force giving intermediate **13a** or

13b. Later, fluoride ion abstracts the hydrogen which is adjacent to SO₂Ph carbon and promoted desulfonation either in inter- or intramolecular fashion providing the final cycloaddition product **14**.^{8c} It is important to note that the formation of key intermediate **13** by MALDI-TOF experiment.^{8a} According to Woodward rules of [4+2] cycloaddition, there are four intermediates possible which is given below (eq 5).



Scheme 4.11: Proposed Mechanism for Cycloaddition Reaction



4.16: Conclusion

1. We have demonstrated an efficient route to synthesize aristolactam alkaloids in good yields by a synergistic combination of C-H bond activation, dehydro-Diels-Alder and desulfonylation reactions.
2. A library of aristolactam derivatives having substituents at all rings and naturally occurring aristolactams were prepared from easily available starting materials in less number of steps by employing present method.

4.17: References

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4.18: Experimental Section

General Procedure for the Cyclization of Aromatic Amides with Alkenes Catalyzed by Ruthenium Complex.

In a Schlenk tube (3cm width, 18cm high) with a magnetic stirrer and septum containing [$\{\text{RuCl}_2(p\text{-cymene})\}_2$] (5.0 mol %), Cu(OAc)₂·H₂O (0.50 equiv, 50 mol %), AgSbF₆ (20 mol %), benzamide **1** (75 mg, if solid) and alkene **2** (particularly **2a**, 1.5 equiv, if solid) was evacuated and purged with nitrogen gas three times (AgSbF₆ was taken inside the glove box). To the tube, were then added benzamide **1** (75 mg, if semisolid or liquid) and alkene **2** (**2b-c** 4.00 equiv and **2d-e** 2.0 equiv) in dry acetic acid solvent (3.0 mL) via

syringes. Then, the reaction was evacuated and purged with nitrogen gas three times and stir at room temperature for 5 min (during this type a cationic ruthenium complex was formed). Later, the tube was evacuated and purged with the oxygen gas three times. Then, the reaction mixture was allowed to stir at 120 °C for 16-72 h (the exact reaction time is mentioned in the spectral data information) under oxygen atmosphere which was taken in a balloon. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 , filtered through Celite pad, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3**.

Note: The reaction of **3z** or **3wa** with **2a** was done in a 300 mg scale. In the reaction, 12 mL AcOH solvent was used. After reaction, the reaction mixture was diluted with CH_2Cl_2 and MeOH solvents, filtered through Celite pad, and the filtrate was concentrated.

General Procedure for the Cycloaddition reaction.

In a single neck tube (5cm width, 20cm high) with a medium size magnetic stirrer and septum containing compound **3** (80 mg) in dry CH_3CN solvent (7.0 mL) was evacuated and purged with nitrogen gas three times. Later, benzyne precursor **7** (2.0 equiv) in 1.0 mL of dry CH_3CN was added into the tube via syringes. After stirring at room temperature for 3 min, CsF (5.0 equiv) was added into the tube and the reaction was evacuated and purged with nitrogen gas three times (CsF was taken inside the glove box). Then, the reaction mixture was allowed to stir at 30 °C for 24 h. Later, the reaction mixture was diluted with CH_2Cl_2 , filtered through Celite pad, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **9**.

General Procedure for the Benzylation Reaction (preparation of 11a-b).

In a single neck 25-mL round bottom flask with a magnetic stirrer and septum containing compound **3z** or **3wa** (300 mg) and K_2CO_3 (2.0 equiv) in dry acetone solvent (15.0 mL) was evacuated and purged with nitrogen gas three times. Then, benzyl bromide (1.5 equiv) in a 5.0 mL acetone was added via syringe. Immediately, a spectrum was taken out and fitted with a condenser and the top of condenser was covered with a septum. Again, the reaction mixture was evacuated and purged with nitrogen gas three times. Then, the reaction mixture was refluxed under the nitrogen atmosphere which was taken in a

balloon for 6 h. Later, the reaction mixture was diluted with DCM, filtered through Celite pad, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **11a-b**.

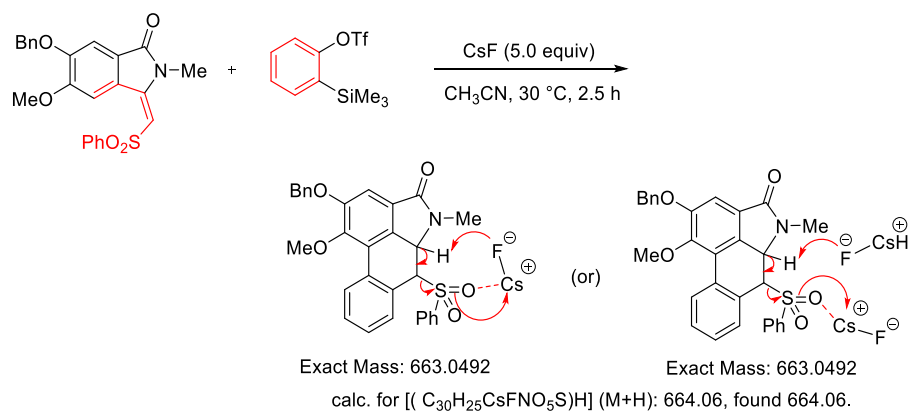
General Procedure for the Cleavage of Benzyl Group (preparation of 12a-b).

In a single neck 25-mL round bottom flask with a magnetic stirrer and septum containing compound **11a** or **11b** (300 mg) with a mixture of dry ethyl acetate solvent (15.0 mL) and dry acetic acid (0.4 mL) was evacuated and purged with nitrogen gas three times. The reaction mixture was allowed to stir at room temperature for 10 min (to make uniform solubility). Later, Pd/C (45 mg, 10% w/w) was added into the round bottom flask. Again, the reaction was evacuated and purged with nitrogen gas three times. Then, the reaction mixture was allowed to stir at 25 °C under a hydrogen atmosphere which was taken in a balloon for 6 h. Later, the reaction mixture was diluted with MeOH, filtered through Celite pad, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **10e** or **10f**.

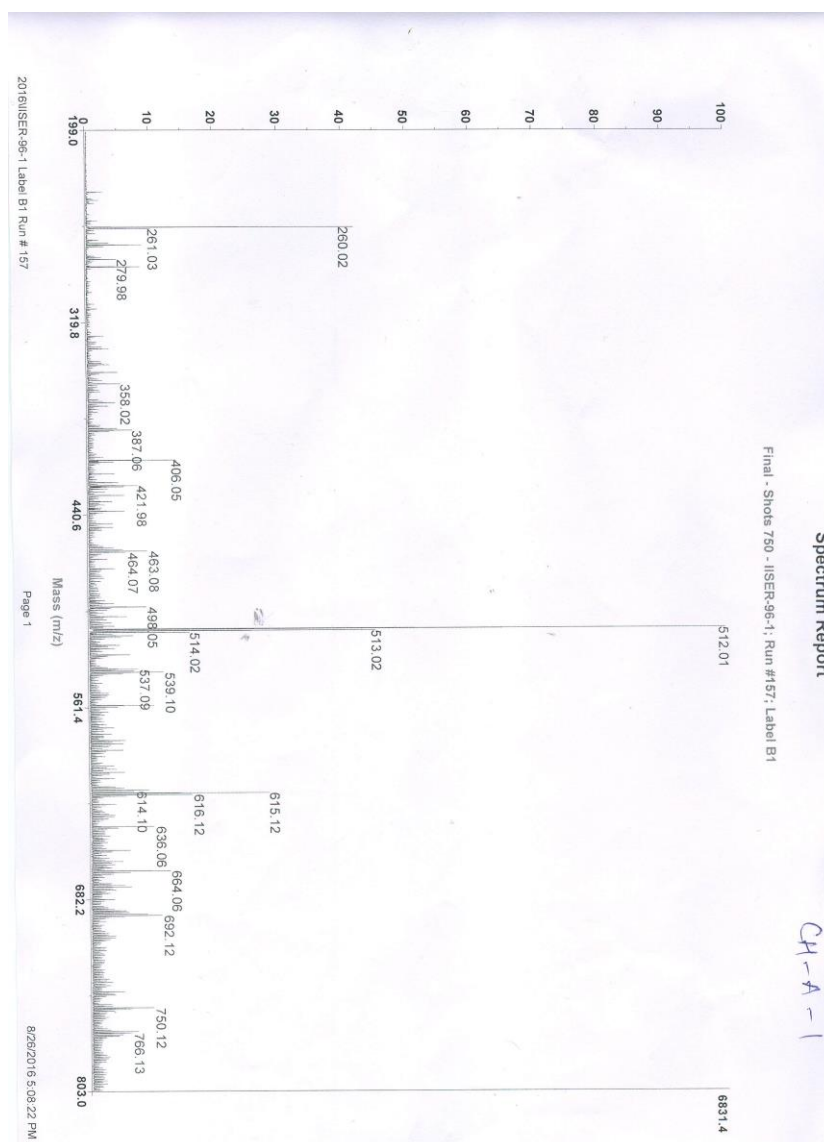
General Procedure for the PMB Group Cleavage (preparation of 10h-i).

In a single neck 50-mL round bottom flask with a magnetic stirrer and septum containing compound **11c-e** (100 mg) and anisole (20 equiv) in trifluoroacetic acid solvent (10.0 mL) was evacuated and purged with nitrogen gas three times. Immediately, a spectrum was taken out and fitted with a condenser and the top of condenser was covered with a septum. Again, the reaction mixture was evacuated and purged with nitrogen gas three times. Then, the reaction mixture was allowed to reflux for 12 h under the nitrogen atmosphere. Later, the reaction mixture was diluted with MeOH and DCM, filtered through Celite pad, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **10h-i**.

MALDI-TOF experiment

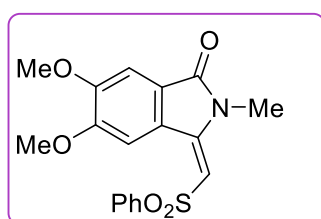


Copy of MALDI-TOF Experiment



4.19: Spectral Copies of Selected Compounds

(*E*)-5,6-Dimethoxy-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (**3a**).



Yellow semi solid; eluent (35% ethyl acetate in hexanes). The reaction scale 75 mg (**1a** (75 mg), **2a** (1.5 equiv)), 108 mg of **3a** was isolated and yield is 78%. The reaction was done for 36 h at 120 °C.

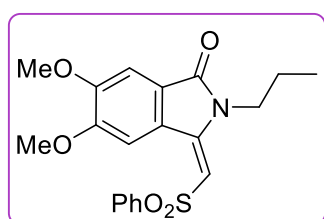
¹H NMR (CDCl₃, 400 MHz): δ 8.37 (s, 1 H), 7.99 - 7.97 (m, 2 H), 7.62 - 7.50 (m, 3 H), 7.24 (s, 1 H), 6.02 (s, 1 H), 3.97 (s, 3 H), 3.94 (s, 3 H), 3.14 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.9, 152.9, 152.3, 147.7, 142.7, 133.6, 129.5, 127.1, 126.7, 125.7, 123.7, 110.5, 106.5, 105.3, 56.6, 56.5, 26.5 (One carbon signal is missing due to overlap).

HRMS (ESI): calc. for [(C₁₈H₁₇NO₅S)H] (M+H) 360.0906, measured 360.0898.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3059, 2927, 2850, 1723, 1596, 1466, 1306, 1222, 1145, 1082, 1038, 856, 760.

(*E*)-5,6-Dimethoxy-3-((phenylsulfonyl)methylene)-2-propylisoindolin-1-one (**3b**).



Light yellow semisolid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg (**1b** (75 mg), **2a** (1.5 equiv)), 90 mg of **3b** was isolated and yield is 69 %. The reaction was done for 36 h at 120 °C .

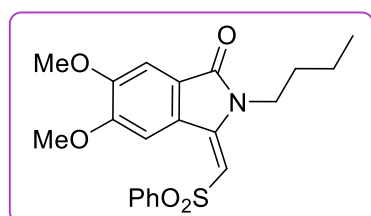
^1H NMR (CDCl_3 , 400 MHz): δ 8.33 (s, 1 H), 7.99 - 7.96 (m, 2 H), 7.62 - 7.51 (m, 3 H), 7.25 (s, 1 H), 6.07 (s, 1 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.62 (t, J = 7.2 Hz, 2 H), 1.63 - 1.55 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.2, 152.9, 152.5, 147.0, 143.1, 133.5, 129.5, 126.6, 125.8, 123.6, 110.7, 106.2, 105.4, 56.6, 56.5, 41.4, 21.4, 11.4 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{21}\text{NO}_5\text{S})\text{H}]$ ($\text{M}+\text{H}$) 388.1219, measured 388.1222.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3059, 2964, 2839, 1722, 1591, 1499, 1463, 1303, 1051, 856, 721.

(E)-2-Butyl-5,6-dimethoxy-3-((phenylsulfonyl)methylene)isoindolin-1-one (3c).



Off-white semisolid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg (**1c** (75 mg), **2a** (1.5 equiv)), 85 mg of **3c** was isolated and yield is 67 %. The reaction was done for 36 h at 120 °C.

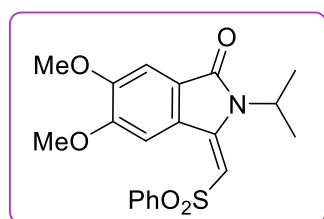
^1H NMR (CDCl_3 , 400 MHz): δ 8.33 (s, 1 H), 7.99 - 7.97 (m, 2 H), 7.62 - 7.58 (m, 1 H), 7.54 - 7.50 (m, 2 H), 7.24 (s, 1 H), 6.07 (s, 1 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.65 (t, J = 7.2 Hz, 2 H), 1.57 - 1.50 (m, 2 H), 1.35 - 1.26 (m, 2 H), 0.89 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.1, 152.9, 152.4, 146.9, 143.0, 133.5, 129.5, 126.5, 125.8, 123.6, 110.6, 106.2, 105.3, 56.6, 56.5, 39.6, 30.1, 20.2, 13.8 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{21}\text{H}_{23}\text{NO}_5\text{S})\text{H}]$ ($\text{M}+\text{H}$) 402.1375, measured 402.1379.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3090, 2957, 1719, 1590, 1497, 1463, 1393, 1302, 1180, 1039, 994, 854, 753.

(E)-2-Isopropyl-5,6-dimethoxy-3-((phenylsulfonyl)methylene)isoindolin-1-one (3d).



Brown semisolid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg (**1d** (75 mg), **2a** (1.5 equiv)), 76 mg of **3d** was isolated and yield is 58 %. The reaction was done for 36 h at 120 °C.

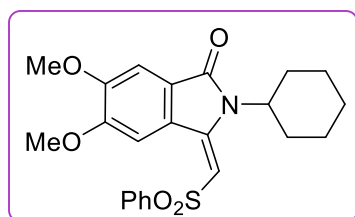
^1H NMR (CDCl_3 , 400 MHz): δ 8.31 (s, 1 H), 8.03 - 8.01 (m, 2 H), 7.66 - 7.55 (m, 3 H), 7.27 (s, 1 H), 6.26 (s, 1 H), 4.45 - 4.38 (m, 1 H), 3.98 (s, 3 H), 3.97 (s, 3 H), 1.51 (s, 3 H), 1.49 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): 167.4, 152.9, 152.4, 146.8, 143.1, 133.5, 129.5, 126.5, 125.8, 123.8, 110.5, 106.7, 105.1, 56.6, 56.5, 44.9, 20.1 (Three carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{21}\text{NO}_5\text{S})\text{H}]$ (M+H) 388.1219, measured 388.1218.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3060, 2929, 2848, 1722, 1590, 1500, 1461, 1305, 1143, 691.

(E)-2-Cyclohexyl-5,6-dimethoxy-3-((phenylsulfonyl)methylene)isoindolin-1-one (3e).



Off-white semisolid; eluent (30% ethyl acetate in hexanes).

The reaction scale is 75 mg (**1e** (75 mg), **2a** (1.5 equiv)), 69 mg of **3e** was isolated and yield is 56 %. The reaction was done for 36 h at 120 °C.

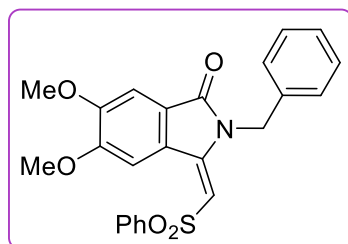
^1H NMR (CDCl_3 , 400 MHz): δ 8.22 (s, 1 H), 7.99 (d, J = 7.6 Hz, 2 H), 7.62 - 7.51 (m, 3 H), 7.19 (s, 1 H), 6.27 (s, 1 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.85 - 3.74 (m, 1 H), 2.25 - 2.16 (m, 2 H), 1.88 - 1.67 (m, 5 H), 1.38 - 1.17 (m, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.4, 152.8, 152.4, 147.5, 143.1, 133.5, 129.5, 126.4, 125.6, 123.8, 110.4, 106.2, 104.9, 56.6, 56.5, 29.8, 26.4, 25.3 (Five carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{23}\text{H}_{25}\text{NO}_5\text{S})\text{H}]$ (M+H) 428.1532, measured 428.1537.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3302, 2930, 2855, 1719, 1587, 1499, 1464, 1304, 1080, 753.

(E)-2-Benzyl-5,6-dimethoxy-3-((phenylsulfonyl)methylene)isoindolin-1-one (3f).



Yellow semisolid; eluent (30% ethyl acetate in hexanes).

The reaction scale is 75 mg (**1f** (75 mg), **2a** (1.5 equiv)), 86 mg of **3f** was isolated and yield is 71 %. The reaction was done for 36 h at 120 °C.

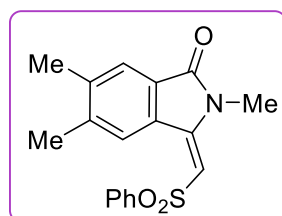
^1H NMR (CDCl_3 , 400 MHz): δ 8.34 (s, 1 H), 7.72 (d, J = 7.2 Hz, 2 H), 7.54 (t, J = 7.2 Hz, 1 H), 7.42 (t, J = 7.6 Hz, 2 H), 7.33 (s, 1 H), 7.28 - 7.24 (m, 3 H), 7.12 - 7.10 (m, 2 H), 6.02 (s, 1 H), 4.92 (s, 2 H), 3.98 (s, 3 H), 3.97 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.2, 153.1, 152.4, 146.1, 142.8, 135.4, 133.3, 129.2, 129.0, 127.9, 126.8, 126.3, 125.9, 123.3, 110.6, 108.0, 105.5, 56.6, 56.5, 43.5 (Four carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{24}\text{H}_{21}\text{NO}_5\text{S})\text{H}]$ (M+H) 436.1219, measured 436.1222.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3061, 2936, 2836, 1723, 1592, 1498, 1305, 1142, 1079, 854, 732.

(E)-2,5,6-Trimethyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3g).



Colorless semisolid; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg (**1g** (75 mg), **2a** (1.5 equiv)), 99 mg of **3g** was isolated and yield is 66%. The reaction was done for 72 h at 120 °C.

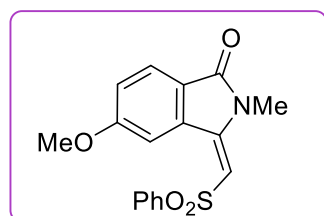
¹H NMR (CDCl₃, 400 MHz): δ 8.52 (s, 1 H), 8.00 (d, J = 7.2 Hz, 2 H), 7.61 - 7.50 (m, 4 H), 6.04 (s, 1 H), 3.14 (s, 3 H), 2.37 (s, 3 H), 2.33 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.1, 147.8, 142.9, 142.7, 141.6, 133.5, 130.1, 129.4, 128.8, 128.1, 126.9, 124.5, 106.9, 26.4, 20.9, 20.4 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₁₈H₁₇NO₃S)H] (M+H) 328.1007, measured 328.1013.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3052, 2925, 1724, 1599, 1431, 1389, 1311, 1145, 1020, 757, 723.

(E)-5-Methoxy-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3h).



Colorless semisolid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg (**1h** (75 mg), **2a** (1.5 equiv)), 113 mg of **3h** was isolated and yield is 75 %. The reaction was done for 72 h at 120 °C.

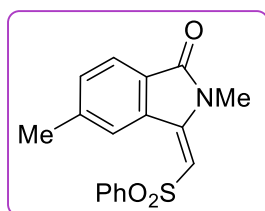
¹H NMR (CDCl₃, 400 MHz): δ 8.38 (d, J = 2.4 Hz, 1 H), 8.01 - 7.99 (m, 2 H), 7.70 (d, J = 7.6 Hz, 1 H), 7.63 - 7.59 (m, 1 H), 7.55 - 7.52 (m, 2 H), 7.05 (dd, J = 7.6, 2.4 Hz, 1 H), 6.07 (s, 1 H), 3.90 (s, 3 H), 3.14 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.6, 164.0, 147.4, 142.6, 134.4, 133.6, 129.5, 126.8, 125.0, 122.4, 118.4, 112.9, 107.6, 56.1, 26.5 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₁₇H₁₅NO₄S)H] (M+H) 330.0800, measured 330.0796.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2932, 2850, 1727, 1600, 1480, 1434, 1383, 1320, 1291, 1147, 1081, 1040, 841, 761.

(E)-2,5-Dimethyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3i).



Colorless semisolid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg (**1i** (75 mg), **2a** (1.5 equiv)), 112 mg of **3i** was isolated and yield is 71 %. The reaction was done for 72 h at 120 °C.

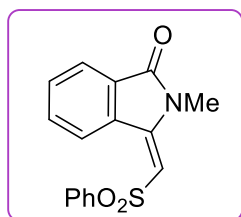
¹H NMR (CDCl₃, 400 MHz): δ 8.58 (s, 1 H), 8.02 – 7.99 (m, 2 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.62 – 7.51 (m, 3 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 6.08 (s, 1 H), 3.15 (s, 3 H), 2.48 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.8, 147.5, 144.3, 142.6, 133.6, 132.7, 132.5, 129.4, 128.5, 127.6, 126.9, 123.5, 107.8, 26.4, 22.4 (Two carbon signals are missing due to overlap) .

HRMS (ESI): calc. for [(C₁₇H₁₅NO₃S)H] (M+H) 314.0851, measured 314.0857.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3063, 2312, 1734, 1609, 1435, 1323, 1287, 1144, 1091, 1050, 910, 827, 761.

(E)-2-Methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3j).



Colorless semisolid ; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg (**1j** (75 mg), **2a** (1.5 equiv)), 108 mg of **3j** was isolated and yield is 65 %. The reaction was done for 72 h at 120 °C.

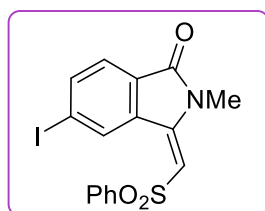
¹H NMR (CDCl₃, 400 MHz): δ 8.83 (d, *J* = 7.6 Hz, 1 H), 8.02 - 8.00 (m, 2 H), 7.81 (d, *J* = 7.6 Hz, 1 H), 7.68 - 7.58 (m, 3 H), 7.56 - 7.51 (m, 2 H), 6.12 (s, 1 H), 3.17 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.8, 147.3, 142.5, 133.7, 133.4, 132.1, 131.9, 130.1, 129.5, 127.9, 126.9, 123.7, 108.2, 26.5 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₁₆H₁₃NO₃S)H] (M+H) 300.0694, measured 300.0703.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3058, 2922, 1726, 1606, 1436, 1391, 1319, 1145, 1082, 1041, 758, 690.

(E)-5-Iodo-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3k).



Off-white semisolid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg (**1k** (75 mg), **2a** (1.5 equiv)), 85 mg of **3k**

was isolated and yield is 69 %. The reaction was done for 72 h at 120 °C.

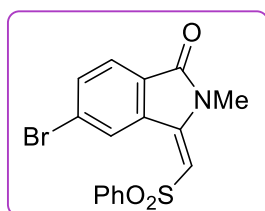
^1H NMR (CDCl_3 , 400 MHz): δ 9.17 (d, J = 1.2 Hz, 1 H), 8.01 – 8.98 (m, 2 H), 7.94 (dd, J = 8.0, 1.6 Hz, 1 H), 7.65 – 7.56 (m, 3 H), 7.52 (dd, J = 7.6, 0.4 Hz, 1 H), 6.15 (s, 1 H), 3.17 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.1, 145.7, 142.1, 140.9, 136.9, 133.9, 133.5, 129.6, 129.4, 127.1, 124.8, 109.3, 100.4, 26.6 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{16}\text{H}_{12}\text{INO}_3\text{S})\text{H}]$ (M+H) 425.9661, measured 425.9656.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3059, 1727, 1605, 1386, 1317, 1147, 1084, 1043, 894, 753.

(E)-5-Bromo-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3l).



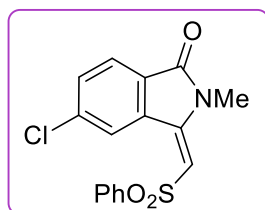
Colorless semisolid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg (**1l** (75 mg), **2a** (1.5 equiv)), 89 mg of **3l** was isolated and yield is 67 %. The reaction was done for 72 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 9.01 (d, J = 1.2 Hz, 1 H), 8.01 – 7.98 (m, 2 H), 7.73 (dd, J = 9.6, 1.6 Hz, 1 H), 7.67 – 7.53 (m, 4 H), 6.15 (s, 1 H), 3.16 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 165.8, 145.7, 142.2, 135.1, 133.8, 133.7, 131.2, 129.6, 128.9, 128.3, 127.1, 124.8, 109.4, 26.6 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{16}\text{H}_{12}\text{BrNO}_3\text{S})\text{H}]$ (M+H) 377.9800, measured 377.9805.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3115, 3063, 2311, 1727, 1605, 1429, 1386, 1083, 1042, 847, 808.

(E)-5-Chloro-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3m).

Off-white semisolid; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg (**1m** (75 mg), **2a** (1.5 equiv)), 96 mg of **3m** was isolated and yield is 65 %. The reaction was done for 72 h at 120 °C.

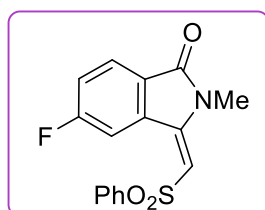
¹H NMR (CDCl₃, 400 MHz): δ 8.86 (d, *J* = 1.2 Hz, 1 H), 8.00 –

7.98 (m, 2 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.64 – 7.53 (m, 4 H), 6.14 (s, 1 H), 3.16 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.7, 145.8, 142.2, 139.9, 133.8, 133.6, 132.1, 129.6, 128.4, 128.4, 127.1, 124.6, 109.4, 26.6 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₁₆H₁₂ClNO₃S)H] (M+H) 334.0305, measured 334.0317.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3117, 3061, 2943, 2312, 1725, 1604, 1430, 1386, 1315, 1146, 1080, 1042, 902, 753.

(E)-5-Fluoro-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3n).

Yellow semisolid; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg (**1n** (75 mg), **2a** (1.5 equiv)), 92 mg of **3n** was isolated and yield is 59 %. The reaction was done for 72 h at 120 °C.

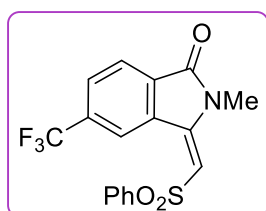
¹H NMR (CDCl₃, 400 MHz): δ 8.63 (dd, *J* = 9.6, 2.4 Hz, 1 H),

8.01 – 7.99 (m, 2 H), 7.81 (dd, *J* = 8.4, 5.2 Hz, 1 H), 7.65 – 7.53 (m, 3 H), 7.30 – 7.25 (m, 1 H), 6.12 (s, 1 H), 3.16 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.15 and 164.64 (F coupling), 165.7, 145.95 and 145.92 (F coupling), 142.3, 134.53 and 134.42 (F coupling), 133.9, 129.6, 128.4, 127.0, 126.2, 125.65 and 125.55 (F coupling), 119.40 and 119.17 (F coupling), 116.15 and 115.88 (F coupling), 109.2, 26.7 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₁₆H₁₂FNO₃S)H] (M+H) 318.0600, measured 318.0612.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3119, 3058, 2922, 1726, 1603, 1473, 1437, 1186, 1075, 848, 721.

(E)-2-Methyl-3-((phenylsulfonyl)methylene)-5-(trifluoromethyl)isoindolin-1-one (3o).

Off-white semisolid; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg (**1o** (75 mg), **2a** (1.5 equiv)), 90 mg of **3o**

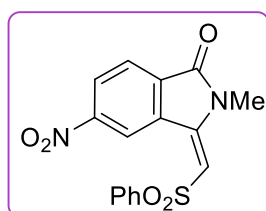
was isolated and yield is 66 %. The reaction was done for 72 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 9.14 (s, 1 H), 8.01 – 7.99 (m, 2 H), 7.93 (d, J = 8.0 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 7.64 – 7.53 (m, 3 H), 6.25 (s, 1 H), 3.22 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 165.4, 145.7, 142.1, (135.67, 135.35, 135.02, 134.70) F coupling, 133.9, 133.0, 132.6, 129.6, (129.04, 129.00, 128.97, 128.93) F coupling, 127.1, (125.40, 125.36, 125.32, 125.28) F coupling, (127.59, 124.88, 122.16, 119.45) F coupling, 124.1, 111.2, 26.8 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{17}\text{H}_{12}\text{F}_3\text{NO}_3\text{S})\text{H}]$ (M+H) 368.0568, measured 368.0578.

(E)-2-Methyl-5-nitro-3-((phenylsulfonyl)methylene)isoindolin-1-one (3p).



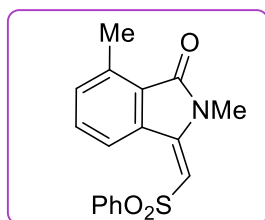
Tan semisolid; eluent (30% ethyl acetate in hexanes). The reaction scale is 75 mg (**1p** (75 mg), **2a** (1.5 equiv)), 83 mg of **3p** was isolated and yield is 58 %. The reaction was done for 72 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 9.72 (d, J = 1.6 Hz, 1 H), 8.45 (dd, J = 8.0, 1.6 Hz, 1 H), 8.04 (d, J = 7.2 Hz, 2 H), 7.97 (d, J = 8.0 Hz, 1 H), 7.65 – 7.55 (m, 3 H), 6.32 (s, 1 H), 3.25 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 164.6, 151.1, 144.8, 141.7, 134.7, 134.1, 133.2, 129.7, 127.3, 127.1, 124.5, 123.6, 111.1, 27.0 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_5\text{S})\text{H}]$ (M+H) 345.0545, measured 345.0561.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3129, 3060, 2312, 1731, 1610, 1536, 1436, 1346, 1148, 1074, 855, 746.

(E)-2,7-Dimethyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3q).

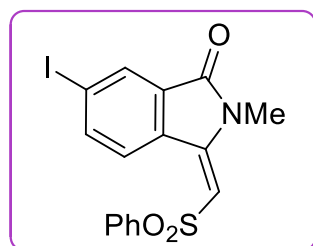
Yellow semisolid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg (**1q** (75 mg), **2a** (1.5 equiv)), 74 mg of **3q** was isolated and yield is 47 %. The reaction was done for 72 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.64 (d, *J* = 8.0 Hz, 1 H), 8.02 – 7.99 (m, 2 H), 7.62 – 7.57 (m, 1 H), 7.54 – 7.48 (m, 3 H), 7.32 (d, *J* = 7.6 Hz, 1 H), 6.06 (s, 1 H), 3.15 (s, 3 H), 2.66 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.4, 147.4, 142.7, 138.1, 134.4, 133.5, 132.8, 129.5, 126.9, 125.6, 107.1, 26.3, 17.6 (Four carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₁₇H₁₅NO₃S)H] (M+H) 314.0851, measured 314.0863.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3058, 2929, 1720, 1600, 1435, 1145, 1045, 754.

(E)-6-Iodo-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3r).

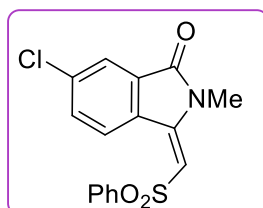
Colorless semisolid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg (**1r** (75 mg), **2a** (1.5 equiv)), 78 mg of **3r** was isolated and yield is 64 %. The reaction was done for 72 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.58 (d, *J* = 8.4 Hz, 1 H), 8.15 (d, *J* = 1.2 Hz, 1 H), 8.00 – 7.97 (m, 3 H), 7.64 – 7.59 (m, 1 H), 7.56 – 7.52 (m, 2 H), 6.13 (s, 1 H), 3.16 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.3, 146.4, 142.3, 133.9, 132.8, 131.7, 131.4, 129.6, 129.3, 126.9, 109.1, 98.67, 26.6 (Three carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₁₆H₁₂INO₃S)H] (M+H) 425.9661, measured 425.9658.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3048, 1725, 1598, 1431, 1311, 1148, 1084, 841, 720.

(E)-6-Chloro-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3s).

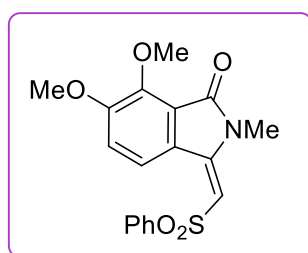
Yellow semisolid; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg (**1s** (75 mg), **2a** (1.5 equiv)), 90 mg of **3s** was isolated and yield is 61 %. The reaction was done for 72 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.80 (d, *J* = 8.4 Hz, 1 H), 8.00 – 7.97 (m, 2 H), 7.77 (d, *J* = 2.0 Hz, 1 H), 7.64 – 7.60 (m, 2 H), 7.56 – 7.52 (m, 2 H), 6.12 (s, 1 H), 3.17 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.5, 146.1, 142.2, 138.6, 133.8, 133.4, 131.9, 130.3, 129.6, 129.3, 126.9, 123.9, 108.9, 26.7 (Three carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₁₆H₁₂ClNO₃S)H] (M+H) 334.0305, measured 334.0306.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3123, 3065, 2925, 1726, 1601, 1458, 1323, 1149, 1083, 901, 756.

(E)-6,7-Dimethoxy-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3x).

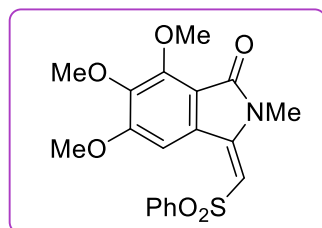
Yellow semisolid; eluent (35% ethyl acetate in hexanes). The reaction scale is 75 mg (**1t** (75 mg), **2a** (2.0 equiv)), 91 mg of **3x** was isolated and yield is 66 %. The reaction was done for 36 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 8.50 (d, *J* = 8.8 Hz, 1 H), 7.98 (d, *J* = 7.6 Hz, 2 H), 7.60 – 7.49 (m, 3 H), 7.07 (d, *J* = 8.8 Hz, 1 H), 5.97 (s, 1 H), 4.00 (s, 3 H), 3.91 (s, 3 H), 3.12 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 164.8, 155.9, 147.3, 147.1, 142.9, 133.4, 129.4, 126.8, 124.8, 124.5, 121.8, 115.9, 105.6, 62.5, 56.6, 26.4 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₁₈H₁₇NO₅S)H] (M+H) 360.0906, measured 360.0907.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3060, 2942, 2839, 1723, 1596, 1499, 1434, 1390, 1275, 1144, 941, 754.

(E)-5,6,7-Trimethoxy-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3y).

Yellow semisolid; eluent (40% ethyl acetate in hexanes). The reaction scale 75 mg (**1u** (75 mg), **2a** (2.0 equiv)), 84 mg of **3y** was isolated and yield is 65%. The reaction was done for 36 h at 120 °C.

^1H NMR (CDCl_3 , 400 MHz): δ 8.24 (s, 1 H), 7.99 - 7.97 (m, 2 H), 7.62 - 7.58 (m, 1 H), 7.54 - 7.51 (m, 2 H), 5.99 (s, 1 H), 4.03 (s, 3 H), 3.94 (s, 3 H), 3.89 (s, 3 H), 3.10 (s, 3 H).

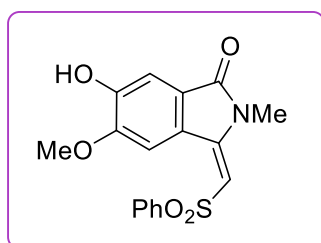
^{13}C NMR (CDCl_3 , 100 MHz): δ 164.9, 157.7, 151.4, 147.2, 144.9, 142.8, 133.6, 129.5, 128.8, 126.7, 114.7, 107.9, 106.2, 62.6, 61.6, 56.7, 26.3 (Two carbon signals are missing due to overlap).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3133, 2938, 2849, 1720, 1685, 1594, 1423, 1386, 1139, 1074, 739

HRMS (ESI): calc. for $[(\text{C}_{19}\text{H}_{19}\text{NO}_6\text{S})\text{H}]$ (M+H) 390.1011, measured 390.1009.

(E)-6-Hydroxy-5-methoxy-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one

(3z).



Yellow solid; eluent (50% ethyl acetate in hexanes). The reaction scale is 300 mg (**1v** (300 mg), **2a** (2.0 equiv)), 372 mg of **3z** was isolated and the yield is 65%. The reaction was done for 36 h at 120 °C.

^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 10.46 (bs, 1 H), 8.06 - 8.04 (m, 3 H), 7.70 - 7.61 (m, 3 H), 7.08 (s, 1 H), 6.51 (s, 1 H), 3.82 (s, 3 H), 3.12 (s, 3 H).

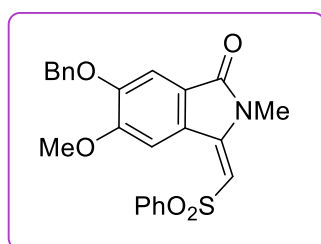
^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz): δ 166.2, 151.4, 150.5, 147.6, 142.8, 133.7, 129.7, 126.4, 123.6, 123.3, 110.6, 109.3, 105.9, 56.1, 26.4 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{17}\text{H}_{15}\text{NO}_5\text{S})\text{H}]$ (M+H) 346.0749, measured 346.0753.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3003, 2945, 2836, 1714, 1597, 1499, 1307, 1143, 1082, 721.

(E)-6-(Benzyloxy)-5-methoxy-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one

(11a).



Light yellow solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 300 mg (**3z**), 329 mg of **11a** was isolated and the yield is 87%.

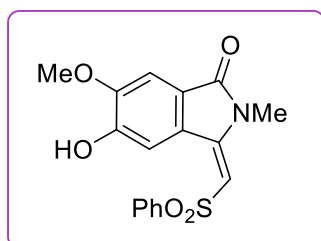
^1H NMR (CDCl_3 , 400 MHz): δ 8.43 (s, 1 H), 8.04 - 8.02 (m, 2 H), 7.65 - 7.54 (m, 3 H), 7.45 - 7.28 (m, 6 H), 6.06 (s, 1 H), 5.23 (s, 2 H), 4.01 (s, 3 H), 3.16 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.9, 153.4, 151.3, 147.7, 142.8, 135.9, 133.6, 129.5, 128.8, 128.4, 127.5, 126.7, 125.9, 123.5, 110.8, 107.1, 106.4, 71.0, 56.6, 26.4 (Four carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{24}\text{H}_{21}\text{NO}_5\text{S})\text{H}]$ (M+H) 436.1219, measured 436.1223.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3060, 2928, 1715, 1596, 1465, 1300, 1214, 1033, 733.

(E)-5-Hydroxy-6-methoxy-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (3wa).



Yellow solid; **m.p.** 197-198 °C, eluent (50% ethyl acetate in hexanes). The reaction scale is 300 mg (**1w** (300 mg), **2a** (2.0 equiv)), 361 mg of **3wa** was isolated and the yield is 63%. The reaction was done for 48 h at 120 °C.

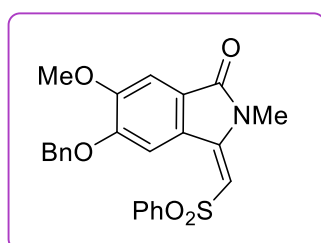
^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 10.37 (s, 1 H), 8.12 (s, 1 H), 8.08 - 8.06 (m, 2 H), 7.71 - 7.67 (m, 1 H), 7.65 - 7.61 (m, 2 H), 7.26 (s, 1 H), 6.51 (s, 1 H), 3.87 (s, 3 H), 3.12 (s, 3 H).

^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz): δ 166.2, 150.9, 150.9, 147.2, 142.6, 133.5, 129.5, 126.6, 124.9, 121.7, 114.1, 106.6, 106.1, 56.1, 26.3 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{17}\text{H}_{15}\text{NO}_5\text{S})\text{H}]$ (M+H) 346.0749, measured 346.0745.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3000, 2845, 2311, 1736, 1598, 1495, 1371, 1313, 1217, 1144, 1083, 1037, 863.

(E)-5-(Benzyloxy)-6-methoxy-2-methyl-3-((phenylsulfonyl)methylene)isoindolin-1-one (11b).



Light Yellow solid; **m.p.** 195-196 °C, eluent (30% ethyl acetate in hexanes). The reaction scale is 300 mg (**3wa**), 337 mg of **11b** was isolated and the yield is 89%.

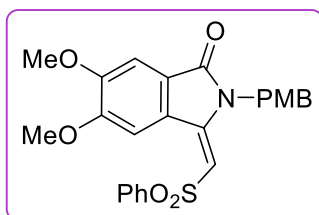
^1H NMR (CDCl_3 , 400 MHz): δ 8.51 (s, 1 H), 7.81 (d, $J = 7.6$ Hz, 2 H), 7.58 - 7.27 (m, 9 H), 5.96 (s, 1 H), 5.28 (s, 2 H), 3.95 (s, 3 H), 3.11 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.9, 152.8, 151.9, 147.5, 142.8, 136.0, 133.4, 129.5, 128.8, 128.3, 127.7, 126.7, 125.6, 123.9, 112.2, 106.7, 105.6, 71.1, 56.5, 26.5 (Four carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(C_{24}H_{21}NO_5S)H]$ (M+H) 436.1219, measured 436.1223.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3059, 2935, 1722, 1595, 1496, 1430, 1303, 1145, 1034, 855, 750.

(E)-5,6-Dimethoxy-2-(4-methoxybenzyl)-3-((phenylsulfonyl)methylene)isoindolin-1-one (3xa).



Yellow semisolid; eluent (35% ethyl acetate in hexanes). The reaction scale 75 mg (**1v** (75 mg), **2a** (2.0 equiv)), 79 mg of **3xa** was isolated and yield is 63%. The reaction was done for 16 h at 120 °C.

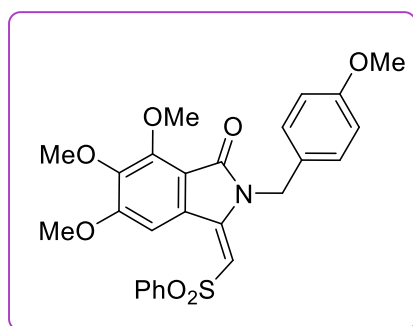
¹H NMR (CDCl₃, 400 MHz): δ 8.31 (s, 1 H), 7.72 (d, J = 7.6 Hz, 2 H), 7.53 (t, J = 7.6 Hz, 1 H), 7.42 (t, J = 7.6 Hz, 2 H), 7.31 (s, 1 H), 7.02 (d, J = 8.0 Hz, 2 H), 6.76 (d, J = 8.0 Hz, 2 H), 6.02 (s, 1 H), 4.84 (s, 2 H), 3.96 (s, 3 H), 3.96 (s, 3 H), 3.76 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 162.9, 159.1, 149.4, 134.1, 133.3, 129.6, 129.4, 129.3, 128.2, 126.4, 125.3, 114.5, 114.4, 114.2, 108.0, 107.2, 105.5, 55.8, 55.4, 54.7, 43.2, 18.2 (Three carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(C_{25}H_{23}NO_6S)H]$ (M+H) 466.1324, measured 466.1326.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2923, 2845, 1727, 1596, 1507, 1459, 1309, 1009, 831, 752.

(E)-5,6,7-Trimethoxy-2-(4-methoxybenzyl)-3-((phenylsulfonyl)methylene)isoindolin-1-one (3ya).



Brickred semisolid; eluent (35% ethyl acetate in hexanes). The reaction scale is 75 mg (**1y** (75 mg), **2a** (2.0 equiv)), 70 mg of **5cg** was isolated and yield is 62%. The reaction was done for 16 h at 120 °C.

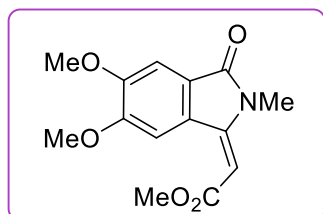
¹H NMR (CDCl₃, 400 MHz): δ 8.28 (s, 1 H), 7.72 (d, J = 8.0 Hz, 2 H), 7.54 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.04 (d, J = 7.6 Hz, 2 H), 6.76 (d, J = 7.6 Hz, 2 H), 6.00 (s, 1 H), 4.80 (s, 2 H), 4.09 (s, 3 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.76 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.2, 159.3, 157.9, 151.6, 145.6, 144.9, 142.8, 133.3, 129.3, 129.0, 128.4, 127.4, 126.4, 114.4, 107.9, 107.7, 62.6, 61.6, 56.8, 55.4, 42.8 (Five carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(C_{26}H_{25}NO_7S)H]$ (M+H) 496.1430, measured 496.1434.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3003, 2944, 1737, 1598, 1514, 1448, 1367, 1216.

Methyl (*E*)-2-(5,6-dimethoxy-2-methyl-3-oxoisindolin-1-ylidene)acetate (3t).



Golden yellow semisolid; eluent (25% ethyl acetate in hexanes). The reaction scale is 75 mg (**1a** (75 mg), **2b** (4.0 equiv)), 79 mg of **3t** was isolated and yield is 74%. The reaction was done for 36 h at 120 °C.

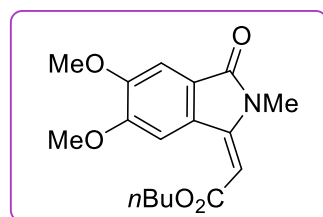
¹H NMR (DMSO-*d*₆, 400 MHz): δ 8.59 (s, 1 H), 7.24 (s, 1 H), 5.69 (s, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.74 (s, 3 H), 3.13 (s, 3 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 166.3, 152.3, 151.5, 149.2, 126.4, 123.0, 109.9, 104.9, 96.6, 55.9, 55.7, 51.5, 26.0 (One carbon signal is missing due to overlap).

HRMS (ESI): calc. for $[(C_{14}H_{15}NO_5)H]$ (M+H) 278.1028, measured 278.1038.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2928, 2848, 1712, 1624, 1592, 1429, 1337, 1298, 1166, 1045, 774.

Butyl (*E*)-2-(5,6-dimethoxy-2-methyl-3-oxoisindolin-1-ylidene)acetate (3u).



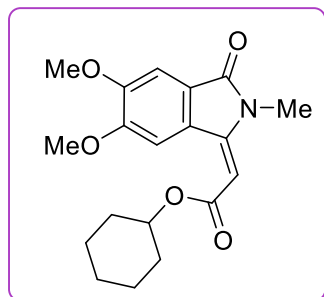
Golden yellow semisolid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg (**1a** (75 mg), **2c** (4.0 equiv)), 88 mg of **3u** was isolated and yield is 72%. The reaction was done for 36 h at 120 °C.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 8.54 (s, 1 H), 7.16 (s, 1 H), 5.62 (s, 1 H), 4.15 (t, *J* = 6.8 Hz, 2 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 3.11 (s, 3 H), 1.67 - 1.60 (m, 2 H), 1.44 - 1.35 (m, 2 H), 0.92 (t, *J* = 7.2 Hz, 3 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 166.2, 165.8, 152.1, 151.4, 149.1, 126.4, 122.9, 109.9, 104.7, 96.7, 63.7, 55.8, 55.6, 30.3, 25.9, 18.7, 13.6.

HRMS (ESI): calc. for $[(C_{17}H_{21}NO_5)H]$ (M+H) 320.1498, measured 320.1496.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2923, 1713, 1626, 1501, 1466, 1380, 1300, 1167, 1040.

Cyclohexyl (*E*)-2-(5,6-dimethoxy-2-methyl-3-oxoisindolin-1-ylidene)acetate (3v**).**

Colorless semisolid; eluent (20% ethyl acetate in hexanes).

The reaction scale is 75 mg (**1a** (75 mg), **2d** (2.0 equiv)), 84 mg of **3v** was isolated and yield is 63%. The reaction was done for 36 h at 120 °C.

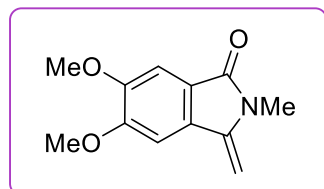
¹H NMR (CDCl₃, 400 MHz): δ 8.75 (s, 1 H), 7.26 (s, 1 H), 5.60 (s, 1 H), 4.89 - 4.83 (m, 1 H), 4.01 (s, 3 H), 3.95 (s, 3 H),

3.22 (s, 3 H), 1.95 – 1.91 (m, 2 H), 1.78 – 1.74 (m, 2 H), 1.59 – 1.55 (m, 1 H), 1.51 – 1.36 (m, 4 H), 1.31 – 1.22 (m, 1 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.6, 165.9, 152.9, 151.7, 149.6, 127.7, 123.8, 110.8, 104.9, 98.3, 72.8, 56.6, 56.4, 32.0, 26.4, 25.6, 24.1 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₁₉H₂₃NO₅)H] (M+H) 346.1654, measured 346.1662.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2934, 2857, 1711, 1627, 1495, 1336, 1169, 1042, 826, 732.

5,6-Dimethoxy-2-methyl-3-methyleneisindolin-1-one (3w**).**

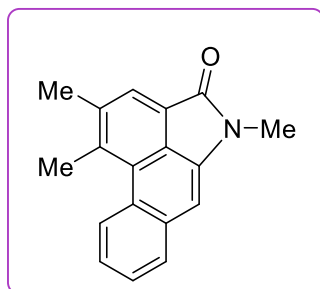
Pale yellow solid; eluent (20% ethyl acetate in hexanes). The reaction scale is 75 mg (**1a** (75 mg), **2e** (2.0 equiv)), 45 mg of **3w** was isolated and yield is 54%. The reaction was done for 36 h at 120 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.25 (s, 1 H), 7.09 (s, 1 H), 5.03 (d, *J* = 2.0 Hz, 1 H), 4.76 (d, *J* = 2.0 Hz, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.23 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.5, 152.9, 151.1, 143.2, 130.0, 122.7, 104.8, 102.1, 87.7, 56.5, 56.4, 25.9.

HRMS (ESI): calc. for [(C₁₂H₁₃NO₃)H] (M+H) 220.0974, measured 220.0970.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2924, 2847, 2312, 1740, 1705, 1612, 1498, 1433, 1305, 1218, 1030, 779, 741.

1,2,5-Trimethyldibenzo[cd,f]indol-4(5H)-one (9a).

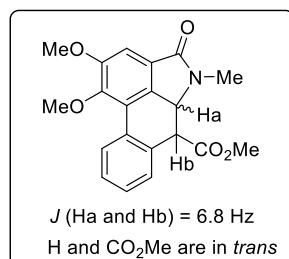
Off-white solid; **m.p.** 194-195 °C, eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3g** (80 mg), **7a** (2.0 equiv)), 42 mg of **9a** was isolated and yield is 66%.

¹H NMR (CDCl₃, 400 MHz): δ 8.74 (d, *J* = 7.6 Hz, 1 H), 7.90 (s, 1 H), 7.85 (d, *J* = 7.6 Hz, 1 H), 7.57 - 7.50 (m, 2 H),

6.99 (s, 1 H), 3.44 (s, 3 H), 2.97 (s, 3 H), 2.61 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 168.5, 139.6, 138.7, 137.9, 135.6, 129.7, 129.1, 127.6, 127.0, 126.7, 126.7, 125.8, 125.1, 123.9, 104.7, 26.3, 22.7, 20.5. **HRMS (ESI):** calc. for [(C₁₈H₁₅NO)H] (M+H) 262.1232, measured 262.1223.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3048, 2920, 1697, 1650, 1458, 1338, 1306, 1249, 1085, 836, 750.

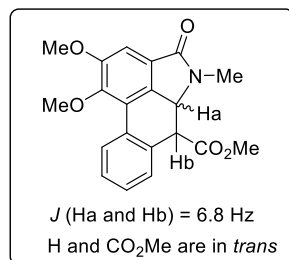
Compounds 9b (major isomer).

Pale yellow solid; eluent (40% ethyl acetate in hexanes).

¹H NMR (CDCl₃, 400 MHz): δ 8.42 (d, *J* = 8.0 Hz, 1 H), 7.47 - 7.42 (m, 1 H), 7.33 - 7.30 (m, 2 H), 7.24 (s, 1 H), 4.57 (d, *J* = 6.8 Hz, 1 H), 4.22 (d, *J* = 6.8 Hz, 1 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 3.37 (s, 3 H), 3.20 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): 169.8, 169.1, 155.4, 149.3, 134.4, 132.9, 132.27, 130.5, 129.6, 128.6, 128.5, 126.3, 123.8, 105.7, 60.4, 58.9, 56.4, 52.3, 48.7, 28.3.

HRMS (ESI): calc. for [(C₂₀H₁₉NO₅)H] (M+H) 354.1341, measured 354.1332.

Compounds 9b (major isomer).

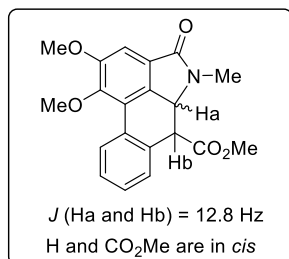
Pale yellow solid; eluent (40% ethyl acetate in hexanes).

¹H NMR (CDCl₃, 400 MHz): δ 8.42 (d, *J* = 8.0 Hz, 1 H), 7.47 - 7.42 (m, 1 H), 7.33 - 7.30 (m, 2 H), 7.24 (s, 1 H), 4.57 (d, *J* = 6.8 Hz, 1 H), 4.22 (d, *J* = 6.8 Hz, 1 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 3.37 (s, 3 H), 3.20 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): 169.8, 169.1, 155.4, 149.3, 134.4, 132.9, 132.27, 130.5, 129.6, 128.6, 128.5, 126.3, 123.8, 105.7, 60.4, 58.9, 56.4, 52.3, 48.7, 28.3.

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{19}\text{NO}_5)\text{H}]$ ($\text{M}+\text{H}$) 354.1341, measured 354.1332.

Compound 9b' (minor isomer).



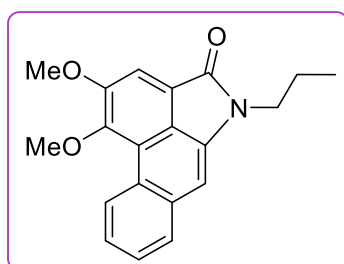
Pale yellow solid; eluent (40% ethyl acetate in hexanes).

^1H NMR (CDCl_3 , 400 MHz): δ 8.40 (dd, J = 8.0, 4.0 Hz, 1 H), 7.44 - 7.40 (m, 1 H), 7.34 - 7.30 (m, 2 H), 7.05 (d, J = 8.0 Hz, 1 H), 4.72 (d, J = 12.8 Hz, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.84 (s, 3 H), 3.61 (d, J = 12.8 Hz, 1 H), 3.07 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 173.7, 169.8, 155.4, 149.3, 135.2, 133.3, 131.3, 128.9, 128.9, 128.2, 127.1, 125.6, 122.9, 105.9, 60.5, 59.8, 56.5, 52.8, 52.1, 28.8.

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{19}\text{NO}_5)\text{H}]$ ($\text{M}+\text{H}$) 354.1341, measured 354.1333.

1,2-Dimethoxy-5-propyldibenzo[*cd*,*f*]indol-4(5*H*)-one (9c).



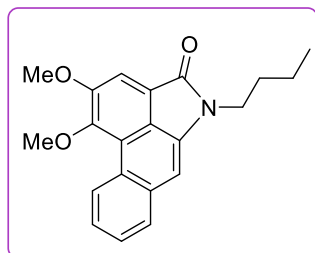
Pale yellow solid; **m.p.** 153-154 °C, eluent (20% ethyl acetate in hexanes). The reaction scale is 80 mg (**3b** (80 mg), **7a** (2.0 equiv)), 44 mg of **9c** was isolated and yield is 66%.

^1H NMR (CDCl_3 , 400 MHz): δ 9.22 – 9.20 (m, 1 H), 7.82 – 7.79 (m, 2 H), 7.58 – 7.51 (m, 2 H), 6.99 (s, 1 H), 4.09 (s, 3 H), 4.05 (s, 3 H), 3.92 (t, J = 8.0 Hz, 2 H), 1.89 – 1.80 (m, 2 H), 1.01 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 168.1, 154.6, 151.2, 136.8, 134.9, 129.1, 127.7, 127.6, 127.2, 125.9, 123.2, 121.5, 120.9, 109.7, 104.5, 60.5, 57.1, 42.1, 22.4, 11.6.

HRMS (ESI): calc. for $[(\text{C}_{20}\text{H}_{19}\text{NO}_3)\text{H}]$ ($\text{M}+\text{H}$) 322.1443, measured 322.1448.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 2854, 1698, 1644, 1607, 1498, 1456, 1281, 1038, 751.

5-Butyl-1,2-dimethoxydibenzo[cd,f]indol-4(5H)-one (9d).

Brick red solid; **m.p.** 108-109 °C, eluent (20% ethyl acetate in hexanes). The reaction scale is 80 mg (**3c** (80 mg), **7a** (2.0 equiv)), 46 mg of **9d** was isolated and yield is 68%.

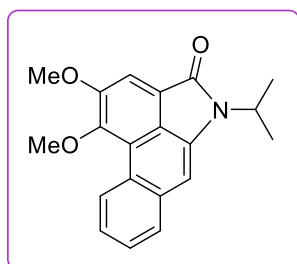
¹H NMR (CDCl₃, 400 MHz): δ 9.22-9.20 (m, 1 H), 7.82 - 7.78 (m, 2 H), 7.57 - 7.52 (m, 2 H), 6.98 (s, 1 H), 4.09 (s, 3 H),

4.05 (s, 3 H), 3.95 (t, *J* = 7.2 Hz, 2 H), 1.83 - 1.76 (m, 2 H), 1.48 - 1.39 (m, 2 H), 0.96 (t, *J* = 7.2 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 168.0, 154.5, 151.2, 136.8, 134.9, 129.1, 127.7, 127.6, 127.2, 125.9, 123.2, 121.5, 120.9, 109.7, 104.5, 60.5, 57.1, 40.2, 31.2, 20.4, 13.9.

HRMS (ESI): calc. for [(C₂₁H₂₁NO₃)H] (M+H) 336.1600, measured 336.1599.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2931, 2864, 1697, 1645, 1405, 1317, 979, 752.

5-Isopropyl-1,2-dimethoxydibenzo[cd,f]indol-4(5H)-one (9e).

Colorless solid; **m.p.** 158-159 °C, eluent (20% ethyl acetate in hexanes). The reaction scale is 80 mg (**3d** (80 mg), **7a** (2.0 equiv)), 37 mg of **9e** was isolated and yield is 56%.

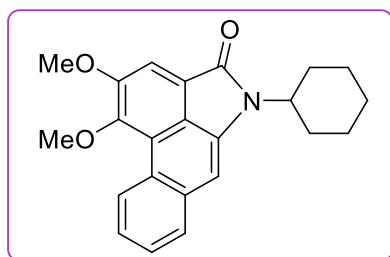
¹H NMR (CDCl₃, 400 MHz): δ 9.21 (d, *J* = 6.8 Hz, 1 H), 7.82 - 7.77 (m, 2 H), 7.57 - 7.52 (m, 2 H), 7.14 (s, 1 H), 4.92 - 4.82

(m, 1 H), 4.08 (s, 3 H), 4.05 (s, 3 H), 1.60 (d, *J* = 7.2 Hz, 6 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.7, 154.5, 151.3, 135.4, 134.9, 129.2, 127.6, 126.9, 126.0, 123.3, 121.5, 121.1, 109.5, 106.3, 60.5, 57.1, 44.0, 21.0 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₂₀H₁₉NO₃)H] (M+H) 322.1443, measured 322.1439.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2959, 2309, 1697, 1641, 1606, 1511, 1210, 746.

5-Cyclohexyl-1,2-dimethoxydibenzo[cd,f]indol-4(5H)-one (9f).

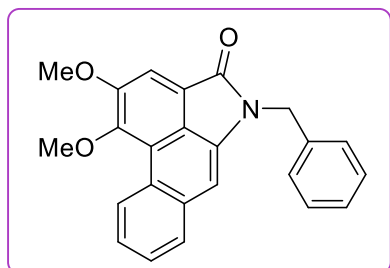
Paleyellow semisolid; **m.p.** 171-172 °C, eluent (20% ethyl acetate in hexanes). The reaction scale is 80 mg (**3e** (80 mg), **7a** (2.0 equiv)), 40 mg of **9f** was isolated and yield is 59%.

¹H NMR (CDCl₃, 400 MHz): δ 9.22 – 9.19 (m, 1 H), 7.83 – 7.80 (m, 1 H), 7.77 (s, 1 H), 7.58 – 7.51 (m, 2 H), 7.17 (s, 1 H), 4.46 – 4.38 (m, 1 H), 4.08 (s, 3 H), 4.05 (s, 3 H), 2.25 – 2.15 (m, 2 H), 1.96 – 1.78 (m, 5 H), 1.56 – 1.45 (m, 2 H), 1.40 – 1.32 (m, 1 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.7, 154.5, 151.3, 135.9, 134.9, 129.2, 127.6, 127.6, 126.9, 125.9, 123.3, 121.5, 121.0, 109.6, 106.5, 60.5, 57.1, 52.2, 31.0, 26.3, 25.7 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₂₃H₂₃NO₃)H] (M+H) 362.1756, measured 362.1756.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3055, 2926, 2854, 1729, 1694, 1640, 1539, 1399, 1280, 1042, 849, 737.

5-Benzyl-1,2-dimethoxydibenzo[cd,f]indol-4(5H)-one(9g).

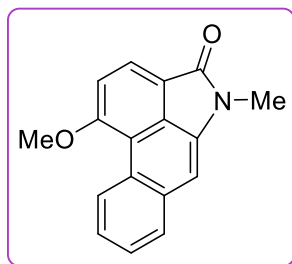
Greenish yellow solid; **m.p.** 166-167 °C, eluent (20% ethyl acetate in hexanes). The reaction scale is 80 mg (**3f** (80 mg), **7a** (2.0 equiv)), 44 mg of **9g** was isolated and yield is 65%.

¹H NMR (CDCl₃, 400 MHz): δ 9.24 – 9.23 (m, 1 H), 7.87 (s, 1 H), 7.76 – 7.74 (m, 1 H), 7.56 – 7.28 (m, 7 H), 6.90 (s, 1 H), 5.20 (s, 2 H), 4.13 (s, 3 H), 4.10 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 168.0, 154.6, 151.5, 137.0, 136.3, 134.8, 129.2, 128.9, 127.7, 127.6, 127.4, 127.2, 126.0, 123.4, 121.1, 120.9, 109.9, 105.4, 60.5, 57.1, 44.1 (Three carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₂₄H₁₉NO₃)H] (M+H) 370.1443, measured 370.1450.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2932, 2847, 1698, 1646, 1454, 1316, 1279, 1070, 702.

1-Methoxy-5-methyldibenzo[cd,f]indol-4(5H)-one (9h).

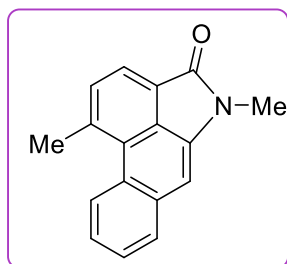
Pale yellow solid; eluent (20% ethyl acetate in hexanes). The reaction scale 80 mg (**3h** (80 mg), **7a** (2.0 equiv)), 48 mg of **9h** was isolated and yield is 75%.

¹H NMR (CDCl₃, 400 MHz): δ 9.24 - 9.22 (m, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 7.87 - 7.84 (m, 1 H), 7.57 - 7.52 (m, 2 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 7.09 (s, 1 H), 4.19 (s, 3 H), 3.47 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 168.1, 162.3, 137.4, 134.3, 129.6, 128.9, 128.3, 127.5, 126.9, 125.7, 125.5, 118.8, 116.9, 110.2, 105.5, 56.4, 26.4.

HRMS (ESI): calc. for [(C₁₇H₁₃NO₂)H] (M+H) 264.1025, measured 264.1018.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2924, 2847, 1740, 1705, 1612, 1498, 1433, 1305, 1218, 1030, 779, 741.

1,5-Dimethyldibenzo[cd,f]indol-4(5H)-one (9i).

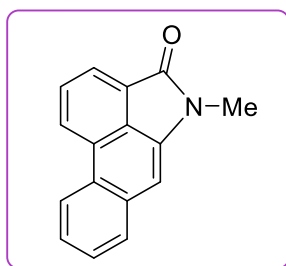
Yellow solid; **m.p.** 185-185 °C, eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3i** (80 mg), **7a** (2.0 equiv)), 50 mg of **9i** was isolated and yield is 79%.

¹H NMR (CDCl₃, 400 MHz): δ 8.70 (dd, *J* = 7.6, 2.0 Hz, 1 H), 7.95 (d, *J* = 7.6 Hz, 1 H), 7.87 (dd, *J* = 7.6, 2.0 Hz, 1 H), 7.59 - 7.53 (m, 3 H), 7.05 (s, 1 H), 3.46 (s, 3 H), 3.10 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 168.2, 141.2, 138.0, 135.2, 132.9, 129.6, 129.1, 128.5, 127.2, 126.9, 126.3, 125.4, 124.9, 123.5, 105.4, 26.3, 25.9.

HRMS (ESI): calc. for [(C₁₇H₁₃NO)H] (M+H) 248.1075, measured 248.1078.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3034, 2956, 1701, 1649, 1606, 1514, 1393, 716.

5-Methyldibenzo[cd,f]indol-4(5H)-one (9j).

Yellowish green solid; **m.p.** 174-175 °C. (lit.² 176 °C), eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3j** (80 mg), **7a** (2.0 equiv)), 45 mg of **9j** was isolated and yield is 71%.

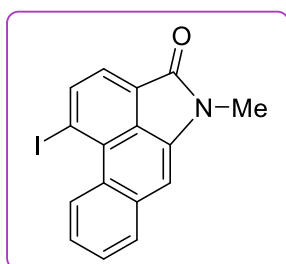
¹H NMR (CDCl₃, 400 MHz): δ 8.56 (d, *J* = 8.0 Hz, 1 H), 8.50 (dd, *J* = 7.6, 1.6 Hz, 1 H), 8.08 (d, *J* = 7.6 Hz, 1 H), 7.86 – 7.79

(m, 2 H), 7.60 – 7.54 (m, 2 H), 7.07 (s, 1 H), 3.49 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 168.5, 137.9, 134.5, 129.2, 127.8, 127.7, 127.4, 127.2, 126.7, 126.3, 125.6, 123.8, 123.4, 104.8, 26.5 (One carbon signal is missing due to overlap).

HRMS (ESI): calc. for [(C₁₆H₁₁NO)H] (M+H) 234.0919, measured 234.0926.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3054, 2932, 1722, 1647, 1438, 1318, 1147, 1082, 921, 726.

1-Iodo-5-methyldibenzo[cd,f]indol-4(5H)-one (9k).

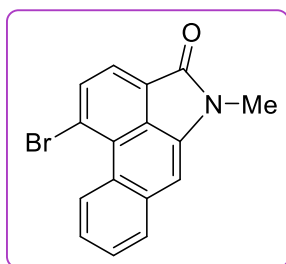
Brickred solid; **m.p.** 239-240 °C, eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3k** (80 mg), **7a** (2.0 equiv)), 46 mg of **9k** was isolated and yield is 68%.

¹H NMR (CDCl₃, 400 MHz): δ 10.02 – 10.00 (m, 1 H), 8.45 (d, *J* = 7.2 Hz, 1 H), 7.82 – 7.80 (m, 1 H), 7.64 – 7.60 (m, 3 H), 7.06 (s, 1 H), 3.44 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.6, 144.6, 137.2, 135.1, 129.6, 128.5, 128.4, 127.8, 127.4, 126.9, 124.8, 124.3, 123.9, 106.6, 95.8, 26.3.

HRMS (ESI): calc. for [(C₁₆H₁₀INO)H] (M+H) 359.9885, measured 359.9892.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2941, 1738, 1649, 1488, 1434, 1370, 1217.

1-Bromo-5-methyldibenzo[cd,f]indol-4(5H)-one (9l).

Yellow solid; **m.p.** 206-207 °C, eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3l** (80 mg), **7a** (2.0 equiv)), 49 mg of **9l** was isolated and yield is 74%.

¹H NMR (CDCl₃, 400 MHz): δ 9.75 (d, *J* = 8.0 Hz, 1 H), 7.98 (d, *J* = 7.6 Hz, 1 H), 7.76 (d, *J* = 7.6 Hz, 2 H), 7.60 – 7.3 (m, 2 H), 6.96 (s, 1 H), 3.40 (s, 3 H).

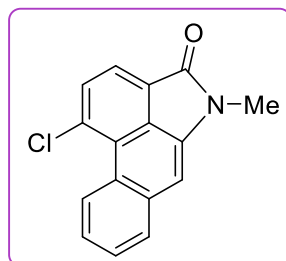
¹³C NMR (CDCl₃, 100 MHz): δ 167.3, 137.1, 136.4, 135.1, 129.5, 129.3, 128.2, 127.3, 126.0, 125.6, 125.4, 124.3, 123.8, 106.5, 26.3 (One carbon signal is missing due to overlap).

HRMS (ESI): calc. for [(C₁₆H₁₀BrNO)H] (M+H) 312.0024, measured 312.0021.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3050, 2921, 1708, 1649, 1596, 1439, 1387, 1307, 1027, 906, 745.

1-Chloro-5-methyldibenzo[cd,f]indol-4(5H)-one (9m).

Golden yellow solid; **m.p.** 215-216 °C, eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3m** (80 mg), **7a** (2.0 equiv)), 50 mg of **9m** was isolated and yield is 77%.

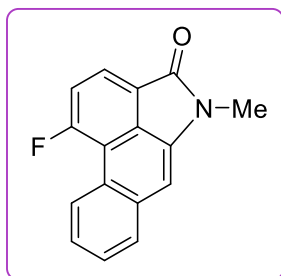


¹H NMR (CDCl₃, 400 MHz): δ 9.52 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H), 7.78 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.73 (d, *J* = 7.6 Hz, 1 H), 7.60 – 7.52 (m, 2 H), 6.97 (s, 1 H), 3.41 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.2, 137.1, 135.9, 135.0, 132.4, 129.4, 129.4, 128.1, 127.1, 126.9, 125.8, 125.4, 124.2, 123.7, 106.4, 26.3.

HRMS (ESI): calc. for [(C₁₆H₁₀ClNO)H] (M+H) 268.0529, measured 268.0532.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3047, 2940, 2379, 1706, 1647, 1445, 1389, 1069, 1029, 869, 745.

1-Fluoro-5-methyldibenzo[cd,f]indol-4(5H)-one (9n).

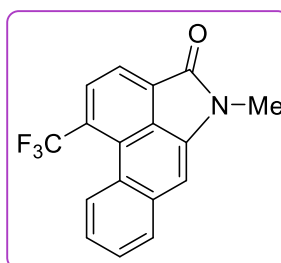
Golden yellow solid; **m.p.** 176-177 °C, eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3n** (80 mg), **7a** (2.0 equiv)), 45 mg of **9n** was isolated and yield is 71%.

¹H NMR (CDCl₃, 400 MHz): δ 8.78 - 8.75 (m, 1 H), 8.01 - 7.98 (m, 1 H), 7.85 - 7.83 (m, 1 H), 7.61 - 7.55 (m, 2 H), 7.46 - 7.40 (m, 1 H), 7.06 (s, 1 H), 3.46 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.4, 164.59 and 161.99 (F coupling), 137.01 and 136.97 (F coupling), 134.4, 129.99 and 129.91 (F coupling), 129.2, 128.03 and 128.01 (F coupling), 127.82 and 127.67 (F coupling), 126.3, 125.50 and 125.45 (F coupling), 125.31 and 125.21 (F coupling), 122.41 and 122.37 (F coupling), 116.34 and 116.09 (F coupling), 116.05 and 115.92 (F coupling), 105.8, 26.5 (One carbon signal is missing due to overlap).

HRMS (ESI): calc. for [(C₁₆H₁₀FNO)H] (M+H) 252.0825, measured 252.0830.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3053, 1701, 1649, 1615, 1419, 1263, 997, 895, 729.

5-Methyl-1-(trifluoromethyl)dibenzo[cd,f]indol-4(5H)-one (9o).

Greenish yellow solid; **m.p.** 164-165 °C, eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3o** (80 mg), **7a** (2.0 equiv)), 32 mg of **9o** was isolated and yield is 48%.

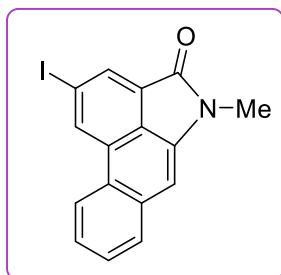
¹H NMR (CDCl₃, 400 MHz): δ 8.79 (d, *J* = 8.4 Hz, 1 H), 8.25 (d, *J* = 7.6 Hz, 1 H), 8.12 (d, *J* = 8.4 Hz, 1 H), 7.84 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.63 - 7.54 (m, 2 H), 7.13 (s, 1 H), 3.49 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.8, 137.4, 135.7, 130.6, 129.8, (129.25, 128.99, 128.81, 128.76) F coupling, 128.8, 128.6, (128.01, 127.93, 127.85, 127.76) F coupling, 126.2, 125.9, 125.5, 122.8, 107.1, 26.5 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₁₇H₁₀F₃NO)H] (M+H) 302.0793, measured 302.0794.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3064, 2921, 2851, 1714, 1654, 1605, 1494, 1463, 1202, 1085, 905, 753.

2-Iodo-5-methyldibenzo[cd,f]indol-4(5H)-one (9p).



Colorless semisolid; eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3r** (80 mg), **7a** (2.0 equiv)), 44 mg of **9p** was isolated and yield is 65%.

¹H NMR (CDCl₃, 400 MHz): δ 8.81 (s, 1 H), 8.35 - 8.30 (m, 2 H), 7.79 (d, *J* = 7.2 Hz, 1 H), 7.60 - 7.52 (m, 2 H), 6.98 (s, 1 H), 3.43 (s, 3 H).

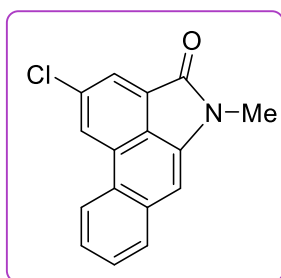
¹³C NMR (CDCl₃, 100 MHz): δ 166.8, 137.3, 134.9, 134.5, 132.2, 129.3, 128.7, 128.4, 128.1, 126.3, 125.9, 123.4, 105.3, 94.6, 26.5.

HRMS (ESI): calc. for [(C₁₆H₁₀INO)H] (M+H) 359.9885, measured 359.9881.

IR (ATR)ν̃ (cm⁻¹): 2926, 1703, 1646, 1391, 1308, 1020, 749.

2-Chloro-5-methyldibenzo[cd,f]indol-4(5H)-one (**9q**).

Greenishyellow solid; **m.p.** 185-186 °C, eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3s** (80 mg), **7a** (2.0 equiv)), 43 mg of **9q** was isolated and yield is 66%.



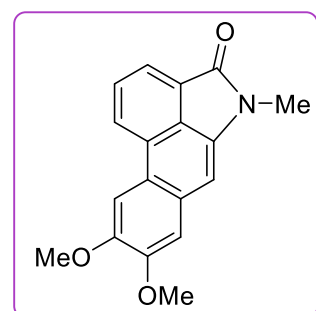
¹H NMR (CDCl₃, 400 MHz): δ 8.40 (d, *J* = 1.2 Hz, 1 H), 8.32 (d, *J* = 7.6 Hz, 1 H), 7.95 (d, *J* = 1.2 Hz, 1 H), 7.79 (d, *J* = 7.6 Hz, 1 H), 7.60 - 7.51 (m, 2 H), 6.95 (s, 1 H), 3.42 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.0, 137.2, 135.5, 134.7, 129.3, 128.4, 127.9, 126.6, 125.9, 125.9, 125.4, 124.1, 123.4, 105.0, 26.5 (One carbon signal is missing due to overlap).

HRMS (ESI): calc. for [(C₁₆H₁₀ClNO)Na] (M+Na) 290.0349, measured 290.0362.

IR (ATR)ν̃ (cm⁻¹): 2925, 1696, 1646, 1467, 1351, 1080, 746.

8,9-Dimethoxy-5-methyldibenzo[cd,f]indol-4(5H)-one (**9r**).



Yellow solid; **m.p.** 207-208 °C, eluent (20% ethyl acetate in hexanes). The reaction scale is 80 mg (**3j** (80 mg), **7b** (2.0 equiv)), 49 mg of **9r** was isolated and yield is 62%.

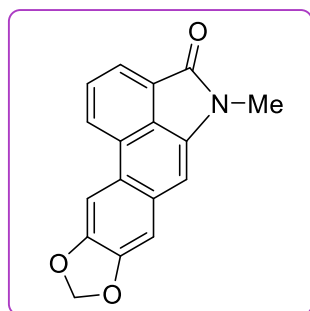
¹H NMR (CDCl₃, 400 MHz): δ 8.43 (d, *J* = 8.0 Hz, 1 H), 8.02 (d, *J* = 7.6 Hz, 1 H), 7.84 (s, 1 H), 7.76 (t, *J* = 7.6 Hz, 1 H), 7.23 (s, 1 H), 6.98 (s, 1 H), 4.08 (s, 3 H), 4.02 (s, 3 H), 3.46 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 168.2, 149.7, 148.2, 136.6, 129.0, 128.6, 126.7, 126.5, 126.0, 125.6, 122.7, 121.5, 109.5, 104.2, 104.1, 56.1, 55.9, 26.3.

HRMS (ESI): calc. for $[(\text{C}_{18}\text{H}_{15}\text{NO}_3)\text{H}]$ (M+H) 294.1130, measured 294.1137.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3003, 2938, 2845, 1738, 1693, 1646, 1500, 1252, 1060, 867, 761.

5-Methyl-[1,3]dioxolo[4',5':4,5]benzo[1,2-*f*]benzo[*cd*]indol-4(5*H*)-one (9s).



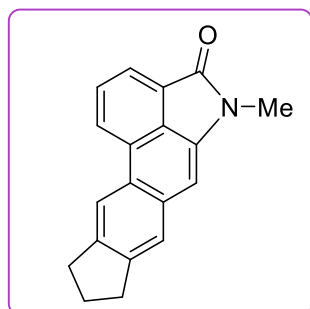
Darkyellow solid; **m.p.** 297-298 °C, eluent (25% ethyl acetate in hexanes). The reaction scale is 80 mg (**3j** (80 mg), **7c** (2.0 equiv)), 45 mg of **9s** was isolated and yield is 61%.

^1H NMR (CDCl_3 , 400 MHz): δ 8.41 (d, J = 7.6 Hz, 1 H), 8.05 (d, J = 7.0 Hz, 1 H), 7.87 (s, 1 H), 7.78 (t, J = 7.6 Hz, 1 H), 7.25 (s, 1 H), 7.00 (s, 1 H), 6.11 (s, 2 H), 3.49 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 168.4, 148.4, 147.1, 136.9, 130.6, 128.9, 127.2, 126.9, 126.2, 126.1, 123.2, 123.2, 107.1, 104.9, 101.9, 101.7, 26.5.

HRMS (ESI): calc. for $[(\text{C}_{17}\text{H}_{11}\text{NO}_3)\text{H}]$ (M+H) 278.0817, measured 278.0824.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2951, 2311, 1701, 1646, 1516, 1160, 742.

5-Methyl-5,8,9,10-tetrahydro-4H-benzo[cd]indeno[5,6-f]indol-4-one (9t).

Yellow solid; **m.p.** 179-180 °C, eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3j** (80 mg), **7d** (2.0 equiv)), 49 mg of **9t** was isolated and yield is 67%.

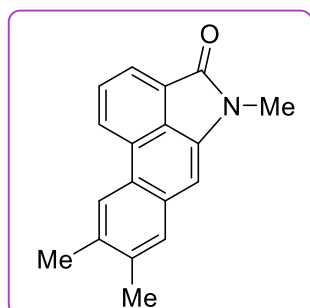
¹H NMR (CDCl₃, 400 MHz): δ 8.48 (d, *J* = 8.0 Hz, 1 H), 8.30 (s, 1 H), 8.01 (d, *J* = 7.0 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.63 (s, 1 H), 6.96 (s, 1 H), 3.45 (s, 3 H), 3.12 - 3.05 (m, 4 H),

2.22 - 2.15 (m, 2 H).

¹³C NMR (CDCl₃, 100 MHz): δ 168.5, 144.9, 142.8, 136.9, 133.3, 128.8, 127.2, 126.9, 126.6, 126.4, 126.0, 124.2, 123.1, 118.4, 105.1, 33.0, 32.9, 26.4, 26.1.

HRMS (ESI): calc. for [(C₁₉H₁₅NO)H] (M+H) 274.1232, measured 274.1236.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2945, 1698, 1648, 1487, 1028, 876, 765.

5,8,9-Trimethyldibenzo[cd,f]indol-4(5H)-one (9u).

Yellow solid; **m.p.** 153-154 °C, eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3j** (80 mg), **7e** (2.0 equiv)), 49 mg of **9u** was isolated and yield is 70%.

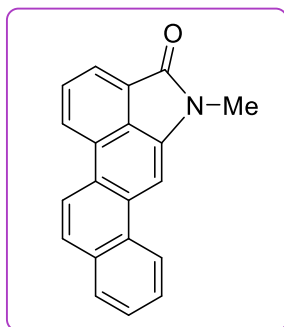
¹H NMR (CDCl₃, 400 MHz): δ 8.52 (d, *J* = 7.6 Hz, 1 H), 8.24 (s, 1 H), 8.03 (d, *J* = 7.0 Hz, 1 H), 7.77 (t, *J* = 7.6 Hz, 1 H), 7.60 (s, 1 H), 6.99 (s, 1 H), 3.48 (s, 3 H), 2.48 (s, 3 H), 2.44 (s,

3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 168.5, 137.2, 137.1, 134.9, 132.7, 129.6, 128.9, 127.1, 127.0, 126.7, 126.0, 125.8, 123.8, 123.2, 104.5, 26.5, 20.4, 20.3.

HRMS (ESI): calc. for [(C₁₈H₁₅NO)H] (M+H) 262.1232, measured 262.1233.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2993, 1699, 1644, 1515, 1165.

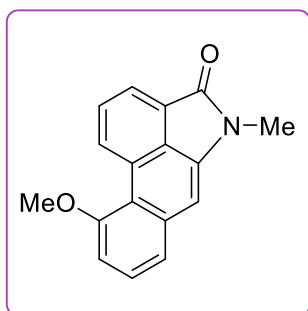
5-Methylbenzo[cd]naphtho[2,1-f]indol-4(5H)-one (9v) (major isomer).

Yellow solid; eluent (15% ethyl acetate in hexanes). The reaction scale is 80 mg (**3j** (80 mg), **7f** (2.0 equiv)), 50 mg of **9v** + **9v'** was isolated and yield is 66%.

¹H NMR (CDCl₃, 400 MHz): δ 9.22 (d, *J* = 8.4 Hz, 1 H), 9.12 (d, *J* = 8.4 Hz, 1 H), 8.16 (d, *J* = 7.6 Hz, 1 H), 8.01 - 7.89 (m, 3 H), 7.85 (d, *J* = 8.4 Hz, 1 H), 7.76 - 7.72 (m, 1 H), 7.64 - 7.60 (m, 1 H), 7.26 (s, 1 H), 3.55 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 168.6, 138.9, 134.1, 132.9, 131.7, 131.5, 129.4, 129.1, 128.6, 128.0, 127.2, 127.2, 126.9, 125.7, 123.7, 123.7, 106.2, 26.5 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₂₀H₁₃NO)H] (M+H) 284.1075, measured 284.1088.

7-Methoxy-5-methyldibenzo[cd,f]indol-4(5H)-one (9w).

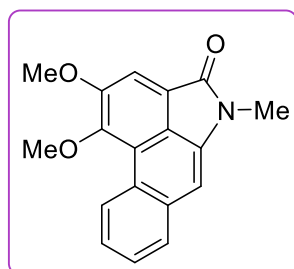
Brown solid; **m.p.** 154-155 °C, eluent (20% ethyl acetate in hexanes). The reaction scale is 80 mg (**3j** (80 mg), **7g** (2.0 equiv)), 49 mg of **9w** was isolated and yield is 69%.

¹H NMR (CDCl₃, 400 MHz): δ 9.32 (d, *J* = 8.4 Hz, 1 H), 8.06 (d, *J* = 7.6 Hz, 1 H), 7.81 - 7.77 (m, 1 H), 7.54 - 7.48 (m, 2 H), 7.09 - 7.07 (m, 2 H), 4.14 (s, 3 H), 3.49 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 159.4, 138.4, 136.5, 132.9, 129.1, 127.8, 126.7, 125.9, 123.2, 122.1, 117.6, 107.4, 105.1, 55.7, 26.4 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₁₇H₁₃NO₂)H] (M+H) 264.1025, measured 264.1031.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2925, 1700, 1649, 1470, 1329, 1275, 1094, 716.

Caldensine (10a).

Yellowish green solid; **m.p.** 188-189 °C. (lit.² 189 °C, lit.³ 193–194 °C), eluent (25% ethyl acetate in hexanes). The reaction scale is 80 mg (**3a** (80 mg), **7a** (2.0 equiv)), 41 mg of **10a** was isolated and yield is 63%.

¹H NMR (CDCl₃, 400 MHz): δ 9.21 - 9.19 (m, 1 H), 7.82 - 7.79 (m, 1 H), 7.77 (s, 1 H), 7.58 - 7.52 (m, 2 H), 6.97 (s, 1 H),

4.09 (s, 3 H), 4.05 (s, 3 H), 3.47 (s, 3 H).

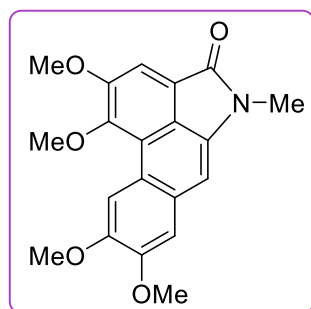
¹³C NMR (CDCl₃, 100 MHz): δ 168.2, 154.6, 151.3, 137.4, 134.9, 129.1, 127.8, 127.6, 127.3, 125.9, 123.2, 121.5, 120.9, 109.7, 104.2, 60.5, 57.1, 26.5.

HRMS (ESI): calc. for [(C₁₈H₁₅NO₃)Na] (M+Na) 316.0950, measured 316.0952.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2953, 2905, 1697, 1646, 1513, 1341.

1,2,8,9-Tetramethoxy-5-methyldibenzo[cd,f]indol-4(5H)-one (10b).

Yellow solid; **m.p.** 218-219 °C. (lit.² 218 °C, lit.¹ 216–217 °C), eluent (35% ethyl acetate in hexanes). The reaction scale is 80 mg (**3a** (80 mg), **7b** (2.0 equiv)), 43 mg of **10b** was isolated and yield is 55%.



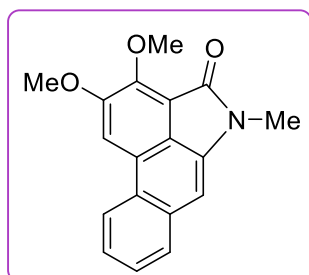
¹H NMR (CDCl₃, 400 MHz): δ 8.72 (s, 1 H), 7.71 (s, 1 H), 7.18 (s, 1 H), 6.86 (s, 1 H), 4.08 (s, 3 H), 4.05 (s, 3 H), 4.02 (s, 3 H), 4.01 (s, 3 H), 3.42 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.9, 154.1, 150.2, 149.3, 147.9, 136.2, 129.8, 122.1, 121.6, 121.1, 120.4, 109.6, 109.1, 108.8, 103.7, 60.4, 57.0, 55.9, 26.4 (One carbon signal is

missing due to overlap).

HRMS (ESI): calc. for [(C₂₀H₁₉NO₅)H] (M+H) 354.1341, measured 354.1343.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3000, 2941, 2848, 1737, 1691, 1505, 1403, 1296, 1250, 1025, 758.

2,3-Dimethoxy-5-methyldibenzo[cd,f]indol-4(5H)-one (10c).

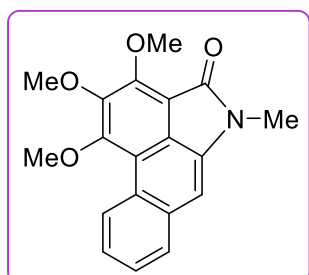
Yellow solid; **m.p.** 150-151 °C. eluent (20% ethyl acetate in hexanes). The reaction scale is 80 mg, 38 mg of **10c** was isolated and yield is 58%.

¹H NMR (CDCl₃, 400 MHz): δ 8.36 – 8.34 (m, 1 H), 7.89 (s, 1 H), 7.84 – 7.82 (m, 1 H), 7.54 – 7.49 (m, 2 H), 7.00 (s, 1 H), 4.56 (s, 3 H), 4.07 (s, 3 H), 3.45 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 166.1, 153.5, 150.2, 136.8, 133.5, 128.9, 126.9, 126.6, 124.9, 122.6, 121.8, 121.3, 112.2, 108.1, 102.6, 63.3, 57.2, 26.7.

HRMS (ESI): calc. for [(C₁₈H₁₅NO₃)H] (M+H) 294.1130, measured 294.1131.

IR (ATR)ν̄ (cm⁻¹): 2996, 2948, 1691, 1647, 1492, 1375, 1061, 750.

1,2,3-Trimethoxy-5-methyldibenzo[cd,f]indol-4(5H)-one(10d).

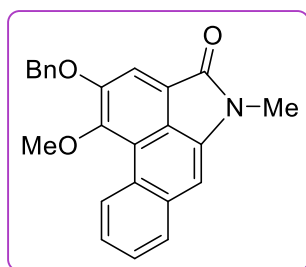
Yellow solid; **m.p.** 115-116 °C, eluent (35% ethyl acetate in hexanes). The reaction scale is 80 mg, 40 mg of **10d** was isolated and yield is 60%.

¹H NMR (CDCl₃, 400 MHz): δ 9.18 – 9.16 (m, 1 H), 7.85 – 7.82 (m, 1 H), 7.55 – 7.51 (m, 2 H), 7.08 (s, 1 H), 4.52 (s, 3 H), 4.16 (s, 3 H), 3.97 (s, 3 H), 3.47 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 165.8, 156.9, 154.0, 146.4, 136.6, 133.5, 128.8, 127.0, 126.7, 126.6, 125.8, 124.7, 116.2, 108.9, 104.6, 63.2, 61.8, 60.9, 26.5.

HRMS (ESI): calc. for [(C₁₉H₁₇NO₄)H] (M+H) 324.1236, measured 324.1238.

IR (ATR)ν̄ (cm⁻¹): 2940, 1742, 1689, 1563, 1515, 1457, 1395.

2-(Benzyloxy)-1-methoxy-5-methyldibenzo[*cd*,*f*]indol-4(5*H*)-one (12a).

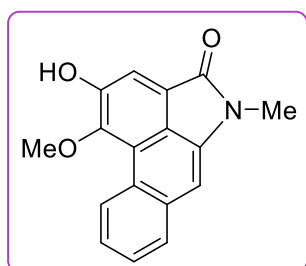
Off-white solid; **m.p.** 151-152 °C, eluent (20% ethyl acetate in hexanes). The reaction scale is 300 mg, 161 mg of **12a** was isolated and yield is 63 %.

¹H NMR (CDCl₃, 400 MHz): δ 9.23 – 9.20 (m, 1 H), 7.83 – 7.80 (m, 2 H), 7.58 – 7.50 (m, 4 H), 7.41 (t, *J* = 7.6 Hz, 2 H), 7.34 (t, *J* = 7.6 Hz, 1 H), 6.98 (s, 1 H), 5.28 (s, 2 H), 4.13 (s, 3 H), 3.46 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 168.1, 153.5, 151.9, 137.3, 136.6, 134.9, 129.1, 128.86, 128.4, 127.7, 127.7, 127.6, 127.4, 126.0, 123.5, 121.4, 121.0, 111.8, 104.4, 72.2, 60.6, 26.5 (One carbon signal is missing due to overlap).

HRMS (ESI): calc. for [(C₂₄H₁₉NO₃)H] (*M*+*H*) 370.1443, measured 370.1441.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3054, 2927, 1696, 1458, 1312, 1183, 1018, 842, 735.

Sauristolactam (10e).

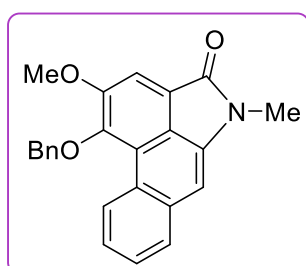
Yellow solid; **m.p.** 293-294 °C (lit.² 276 °C, lit.³ > 290 °C), eluent (55% ethyl acetate in hexanes). The reaction scale is 300 mg, 218 mg of **5cg** was isolated and yield is 66%.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.35 (s, 1 H), 9.10 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.92 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.62 (s, 1 H), 7.60 – 7.53 (m, 2 H), 7.25 (s, 1 H), 4.01 (s, 3 H), 3.36 (s, 3 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 166.8, 152.2, 148.8, 136.9, 134.7, 129.1, 127.5, 126.9, 126.3, 125.6, 120.9, 120.2, 113.6, 103.5, 59.5, 26.2 (One carbon signal is missing due to overlap).

HRMS (ESI): calc. for [(C₁₇H₁₃NO₃)H] (*M*+*H*) 280.0974, measured 280.0983.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2926, 2856, 2311, 1697, 1645, 1509, 1448, 1149, 750.

1-(Benzyloxy)-2-methoxy-5-methyldibenzo[*cd*,*f*]indol-4(5*H*)-one (12b).

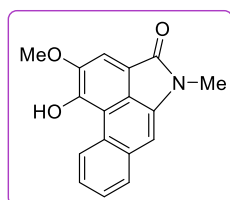
Greenish yellow solid; eluent (20% ethyl acetate in hexanes). The reaction scale is 300 mg, 158 mg of **12b** was isolated and yield is 62%.

¹H NMR (CDCl₃, 400 MHz): δ 9.22 (d, *J* = 8.0 Hz, 1 H), 7.77 – 7.73 (m, 2 H), 7.57 (d, *J* = 7.2 Hz, 2 H), 7.51 (t, *J* = 7.2 Hz, 1 H), 7.43 – 7.34 (m, 4 H), 6.92 (s, 1 H), 5.22 (s, 2 H), 4.01 (s, 3 H), 3.44 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 168.1, 154.4, 149.8, 137.2, 137.1, 134.8, 129.0, 128.7, 128.4, 127.9, 127.5, 127.2, 125.8, 123.0, 121.4, 121.0, 109.5, 104.2, 74.9, 56.9, 26.4 (Three carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{24}\text{H}_{19}\text{NO}_3)\text{H}]$ (M+H) 370.1443, measured 370.1446.

N-Methyl piperolactam A (10f).



Grey solid; eluent (55% ethyl acetate in hexanes). **m.p.** 204-205 °C (lit.² 201 °C, lit.⁶ 249-251 °C), The reaction scale is 300 mg, 220 mg of **10f** was isolated and yield is 97%.

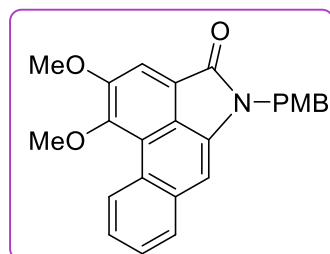
^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 10.68 (s, 1 H), 9.25 – 9.22 (m, 1 H), 7.90 – 7.87 (m, 1 H), 7.75 (s, 1 H), 7.55 – 7.53 (m, 2 H), 7.22 (s, 1 H), 4.03 (s, 3 H), 3.36 (s, 3 H).

^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz): δ 167.2, 149.3, 148.1, 136.7, 133.9, 128.7, 127.5, 126.9, 126.7, 125.1, 122.9, 115.1, 114.2, 108.7, 103.8, 57.9, 26.0.

HRMS (ESI): calc. for $[(\text{C}_{17}\text{H}_{13}\text{NO}_3)\text{H}]$ (M+H) 280.0974, measured 280.0981.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2387, 1685, 1645, 1514, 1421, 1364.

1,2-Dimethoxy-5-(4-methoxybenzyl)dibenzo[cd,f]indol-4(5H)-one (11c).



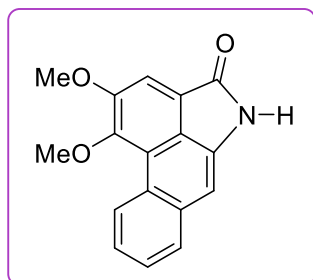
Yellow solid; **m.p.** 190-191 °C; eluent (25% ethyl acetate in hexanes). The reaction scale is 80 mg, 46 mg of **11c** was isolated and yield is 66%.

^1H NMR (CDCl_3 , 400 MHz): δ 9.19 – 9.17 (m, 1 H), 7.81 (s, 1 H), 7.73 – 7.71 (m, 1 H), 7.52 – 7.50 (m, 1 H), 7.30 (d, J = 8.4 Hz, 2 H), 6.87 (s, 1 H), 6.82 (d, J = 8.4 Hz, 2 H), 5.09 (s, 2 H), 4.08 (s, 3 H), 4.06 (s, 3 H), 3.74 (s, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 167.9, 159.2, 154.6, 151.5, 136.4, 134.8, 129.2, 128.9, 127.7, 127.6, 127.2, 126.0, 123.4, 121.2, 120.9, 114.3, 109.9, 105.3, 60.5, 57.1, 55.4, 43.6 (Three carbon signals are missing due to overlap).

HRMS (ESI): calc. for $[(\text{C}_{25}\text{H}_{21}\text{NO}_4)\text{H}]$ (M+H) 400.1549, measured 400.1556.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2942, 2837, 1698, 1646, 1404, 1243, 1076, 996, 752.

Cepharanone B (aristolactam BII) (10g).

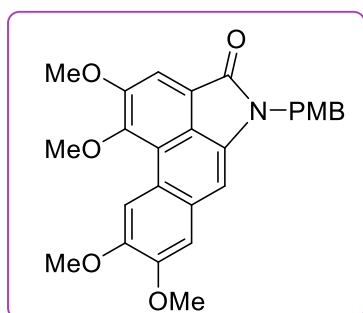
Light yellow solid; **m.p.** 252-253 °C. (lit.² 254 °C, lit.⁴ 249-251), eluent (55% ethyl acetate in hexanes). The reaction scale is 100 mg, 65 mg of **10g** was isolated and yield is 92%.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.87 (bs, 1 H), 9.1 (d, *J* = 7.6 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.84 (s, 1 H), 7.60 – 7.53 (m, 2 H), 7.14 (s, 1 H), 4.03 (s, 3 H), 4.02 (s, 3 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 168.5, 154.3, 150.5, 135.2, 134.9, 129.1, 127.6, 126.9, 126.0, 125.6, 123.4, 121.6, 120.0, 109.9, 104.8, 60.0, 57.0.

HRMS (ESI): calc. for [(C₁₇H₁₃NO₃)H] (M+H) 280.0974, measured 280.0977.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2923, 2855, 1698, 1512, 1462, 1262, 1025, 741.

1,2,8,9-Tetramethoxy-5-(4-methoxybenzyl)dibenzo[*cd,f*]indol-4(5*H*)-one (11d).

yellow solid; eluent (35% ethyl acetate in hexanes). The reaction scale is 80 mg, 79 mg of **11d** was isolated and yield is 61%.

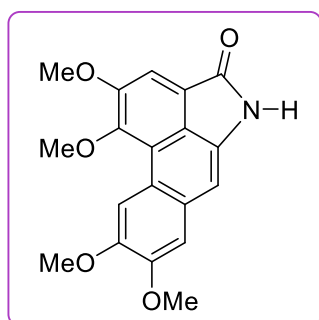
¹H NMR (CDCl₃, 400 MHz): δ 8.73 (s, 1 H), 7.79 (s, 1 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.12 (s, 1 H), 6.83 – 6.80 (m, 3 H), 5.07 (s, 2 H), 4.08 (s, 3 H), 4.05 (s, 3 H), 4.04 (s, 3

H), 3.98 (s, 3 H), 3.74 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 167.9, 159.1, 154.2, 150.5, 149.4, 148.0, 135.3, 129.8, 129.4, 128.8, 122.5, 121.4, 121.1, 120.7, 114.3, 109.8, 109.5, 108.9, 104.8, 60.5, 57.2, 56.0, 55.9, 55.4, 43.6 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₂₇H₂₅NO₆)H] (M+H) 460.1760, measured 460.1757.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2946, 2836, 1689, 1506, 1403, 1032, 864.

Norcepharanone (10h).

Yellow solid; eluent (65% ethyl acetate in hexanes). **m.p.** 209-210 °C (lit.⁵ 208-209 °C), The reaction scale is 100 mg, 67 mg of **10h** was isolated and yield is 91%. **¹H NMR (DMSO-*d*₆, 400 MHz):** δ 10.76 (bs, 1 H), 8.61 (s, 1 H), 7.78 (s, 1 H), 7.50 (s, 1 H), 7.09 (s, 1 H), 4.04 (s, 3 H), 4.03 (s, 3 H), 3.93 (s, 3 H), 3.91 (s, 3 H).

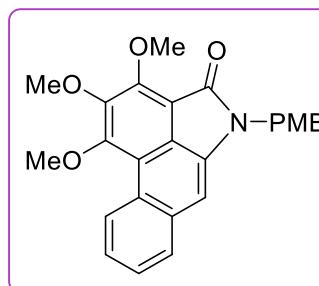
¹³C NMR (DMSO-*d*₆, 100 MHz): δ 168.3, 153.8, 149.5, 149.1, 147.3, 133.7, 129.9, 122.5, 121.7, 119.8, 119.6, 110.2, 109.2, 108.2, 104.5, 59.9, 56.9, 55.5, 55.3.

HRMS (ESI): calc. for [(C₁₉H₁₇NO₅)H] (M+H) 340.1185, measured 340.1186.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2950, 1685, 1503, 1465, 1353, 1314, 1215.

1,2,3-Trimethoxy-5-(4-methoxybenzyl)dibenzo[*cd*,*f*]indol-4(5*H*)-one (11e).

Yellow solid; eluent (30% ethyl acetate in hexanes). The reaction scale is 80 mg, 45 mg of **11e** was isolated and yield is 65%.



¹H NMR (CDCl₃, 400 MHz): δ 9.16 (d, *J* = 8.4 Hz, 1 H), 7.76 (d, *J* = 7.2 Hz, 1 H), 7.53 – 7.47 (m, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.01 (s, 1 H), 6.82 (d, *J* = 8.4 Hz, 2 H), 5.10 (s, 2 H), 4.55 (s, 3 H), 4.16 (s, 3 H), 4.98 (s, 3 H), 3.74 (s, 3 H).

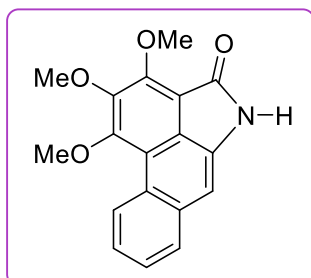
¹³C NMR (CDCl₃, 100 MHz): δ 165.7, 159.1, 157.1, 154.2, 146.5, 135.7, 133.4, 129.2, 128.9, 128.9, 126.9, 126.6, 126.6, 125.8, 124.9, 116.3, 114.3, 108.8, 105.7, 63.2, 61.8, 60.9, 55.4, 43.6 (Two carbon signals are missing due to overlap).

HRMS (ESI): calc. for [(C₂₆H₂₃NO₅)H] (M+H) 430.1654, measured 430.1652.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2928, 2851, 1692, 1645, 1513, 1462, 1389, 1040, 738.

Piperolactam C (10i).

Yellow color solid; **m.p.** 190-191 °C, eluent (65% ethyl acetate in hexanes). The reaction scale is 100 mg, 65 mg of **10i** was isolated and yield is 90%.



¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.98 (bs, 1 H), 9.09 – 9.07 (m, 1 H), 7.97 – 7.95 (m, 1 H), 7.55 – 7.53 (m, 2 H), 7.25 (s, 1 H), 4.39 (s, 3 H), 4.11 (s, 3 H), 3.91 (s, 3 H).

¹³C NMR (DMSO-*d*₆, 100 MHz): δ 166.3, 156.1, 153.3, 146.0, 134.4, 133.4, 128.8, 126.5, 125.9, 125.6, 125.4, 125.1, 115.5, 109.6, 105.3, 62.5, 61.4, 60.8.

HRMS (ESI): calc. for [(C₁₈H₁₅NO₄)H] (M+H) 310.1079, measured 310.1085.

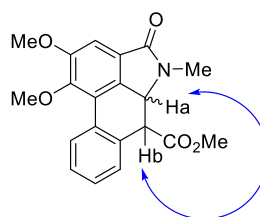
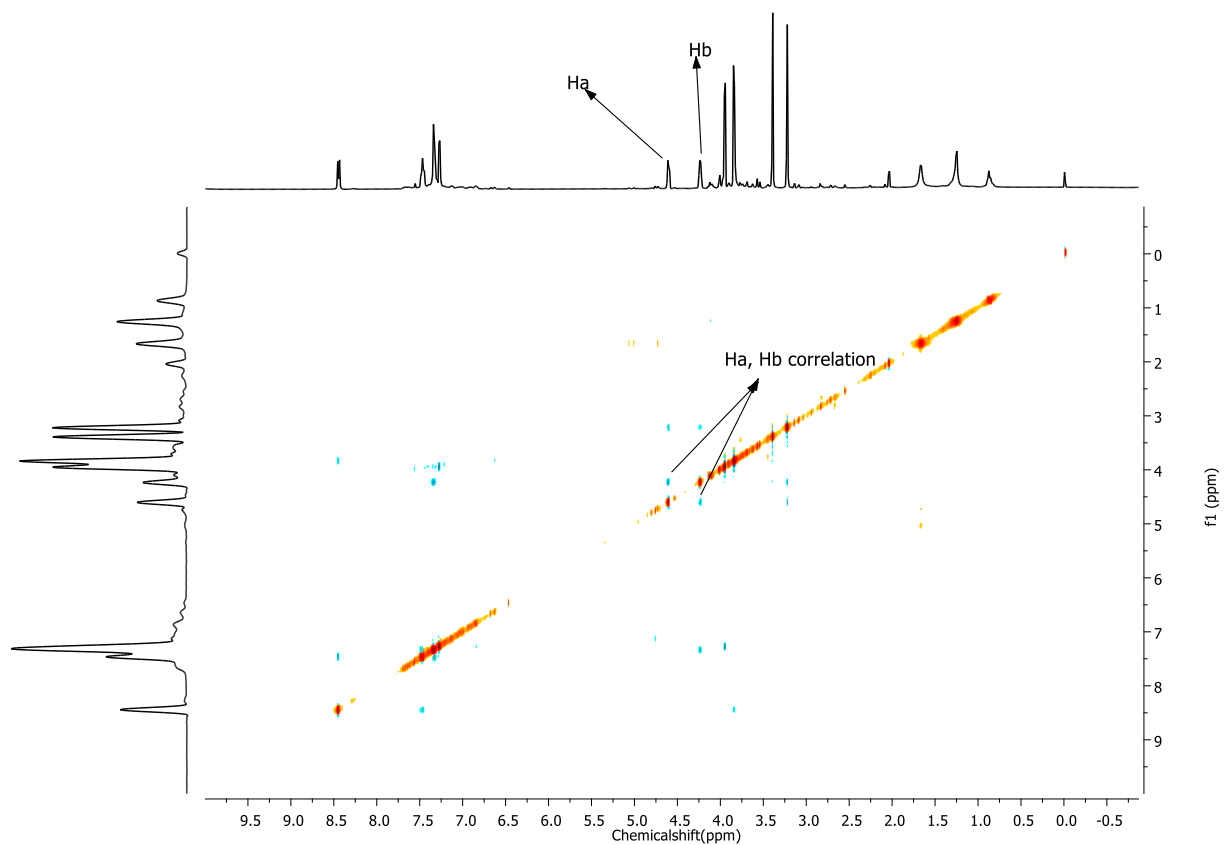
IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2943, 1690, 1604, 1518, 1461, 1386, 1314, 1121, 1083, 752.

References

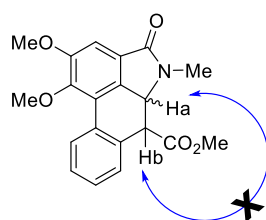
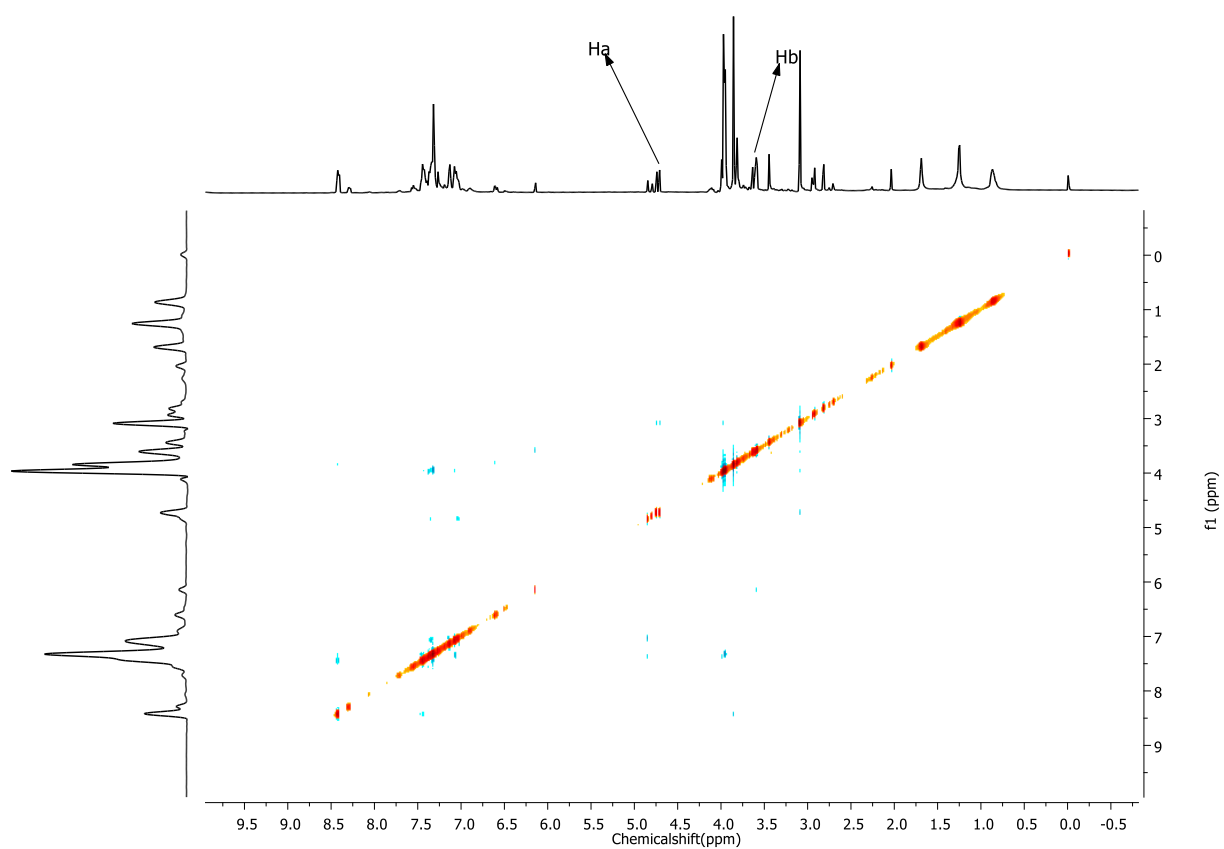
- (1) Castedo, L.; Suau, R.; Mouriño, A. *Tetrahedron Lett.* **1976**, 6, 501.
- (2) Kim, J. K.; Kim, Y. H.; Nam, H. T.; Kim, B. T.; Heo, J.-N. *Org. Lett.* **2008**, 10, 3543.
- (3) Rao, K. V.; Reddy, G. C. S. *J. Nat. Prod.* **1990**, 53, 309–312.
- (4) Castedo, L.; Guitian, E.; Saa, J. M.; Suau, R. *Heterocycles* **1982**, 19, 279–280.
- (5) Estevez, J.C.; Villaverde, M. C.; Estevez, R.J.; Castedo, L. *Tetrahedron* **1995**, 51, 4075.
- (6) Ruangrungsi, N.; Prathanturug, S.; Lange, G. L.; Organ, M. G. *Phytochemistry* **1992**, 31, 2397.

4.20: NOESY Experiments

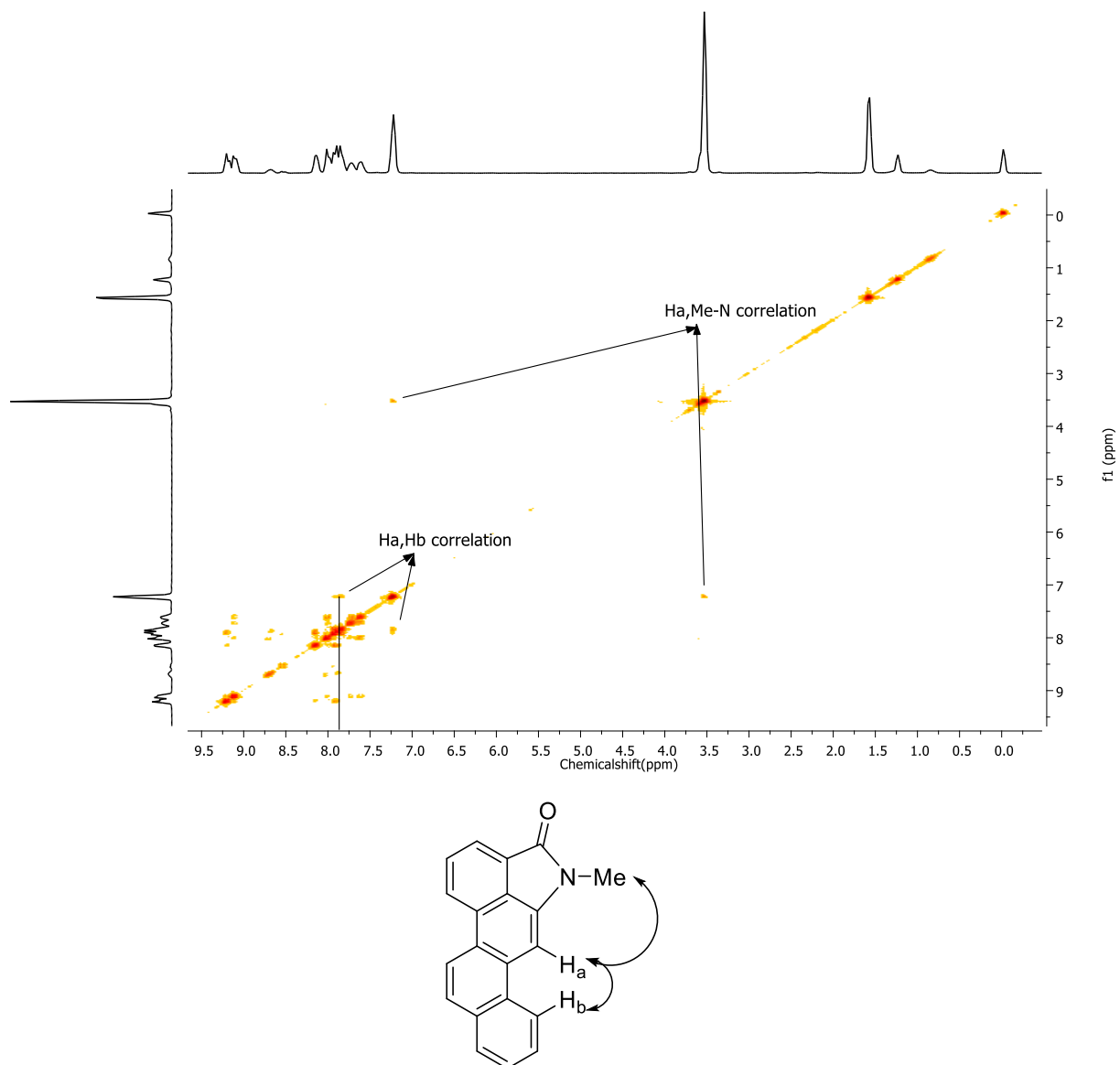
NOESY of compound 9b (major isomer).



There is a strong NOE correlation between H_a (δ 4.57, d) and H_b (δ 4.22, d). It clearly indicates that H_a and CO₂Me are in trans to each other.

NOESY of Compound 9b' (minor isomer).

There is no NOE correlation between H_a (δ 4.57, d) and H_b (δ 4.22, d). It clearly indicates that H_a and CO_2Me are in cis to each other.

NOESY of compound (9v) (major isomer).

There is a NOE correlation between H_a (δ 7.29, s) and H_b (δ 7.88, d). And there is other NOE correlation between H_a (δ 7.29, s) and Me-N (δ 3.58, s). It clearly indicates that above structure is correct.

4.21: X-ray Analysis

Crystallographic Data of Compound 9w.

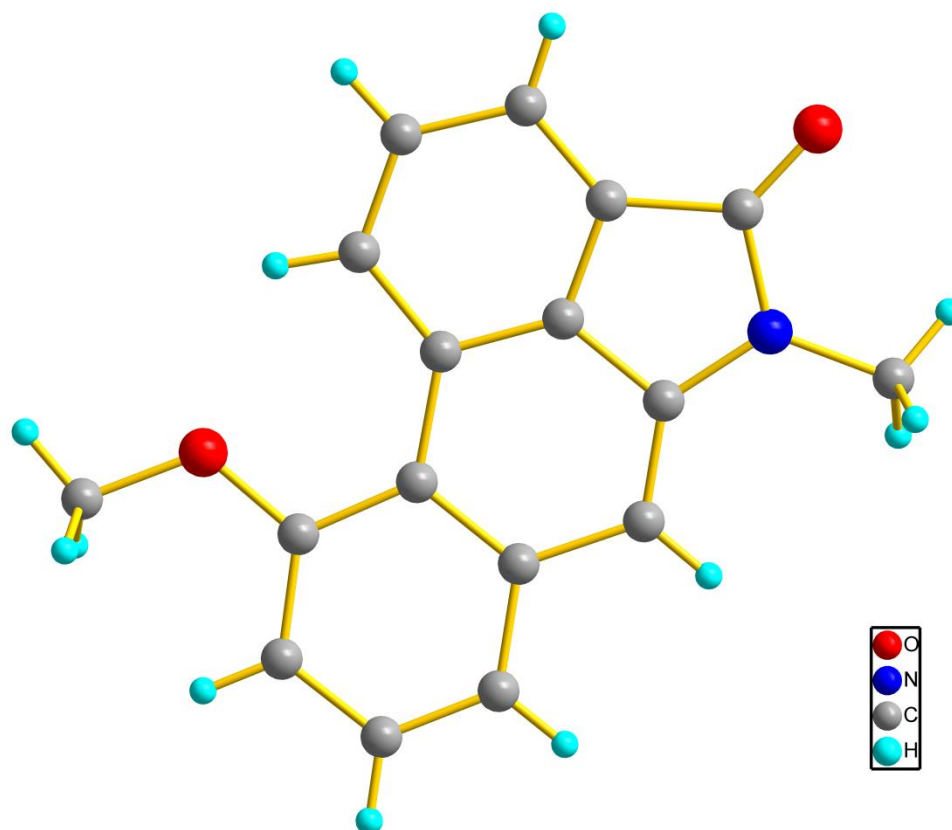
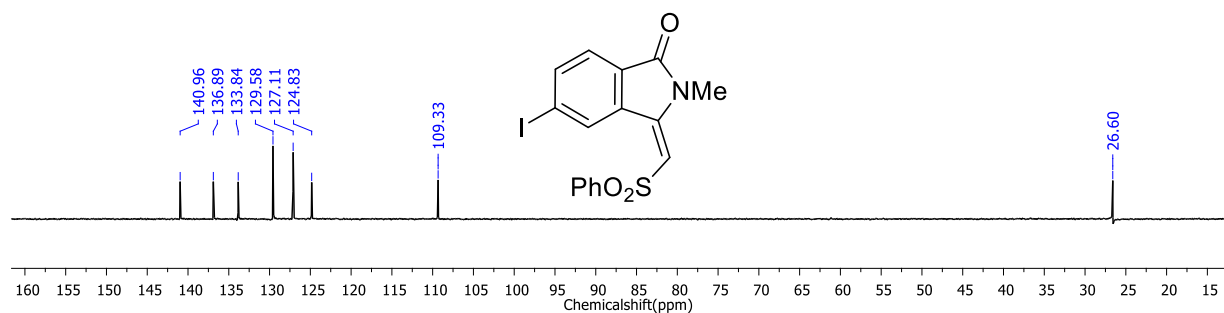
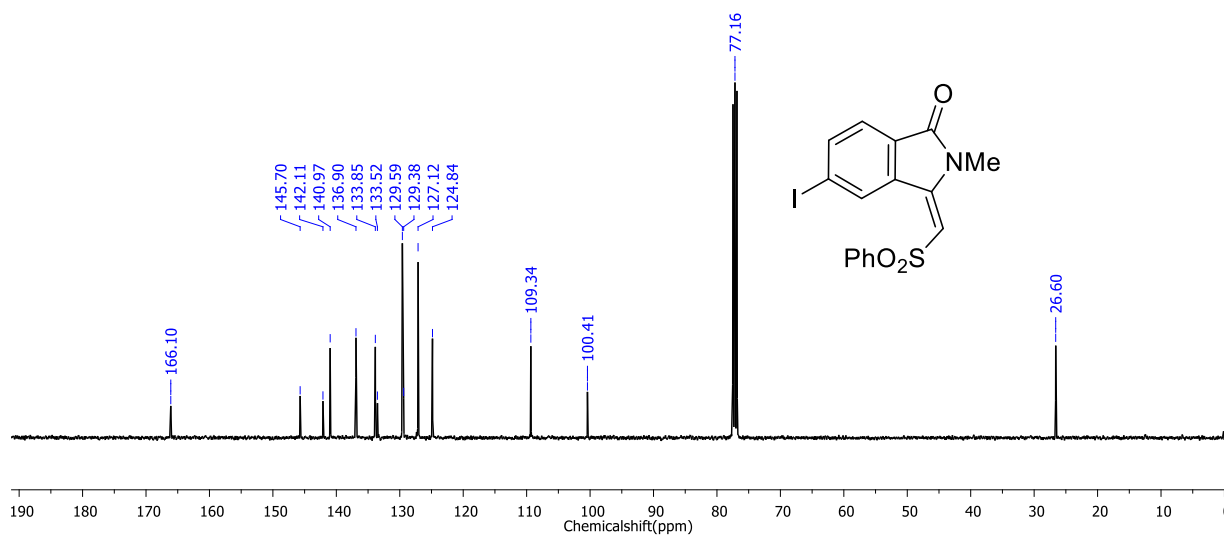
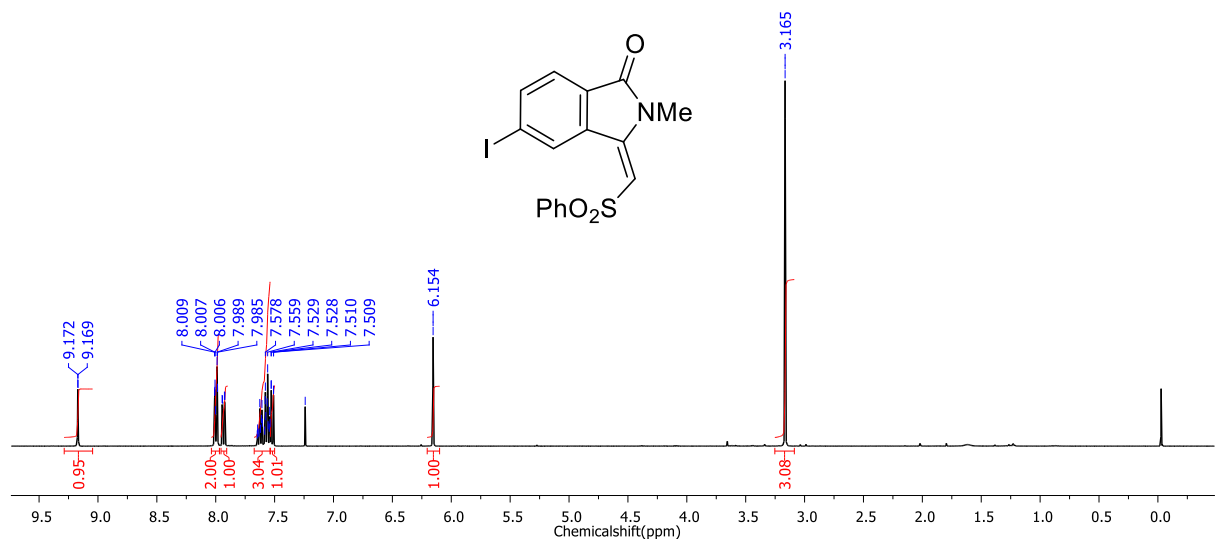


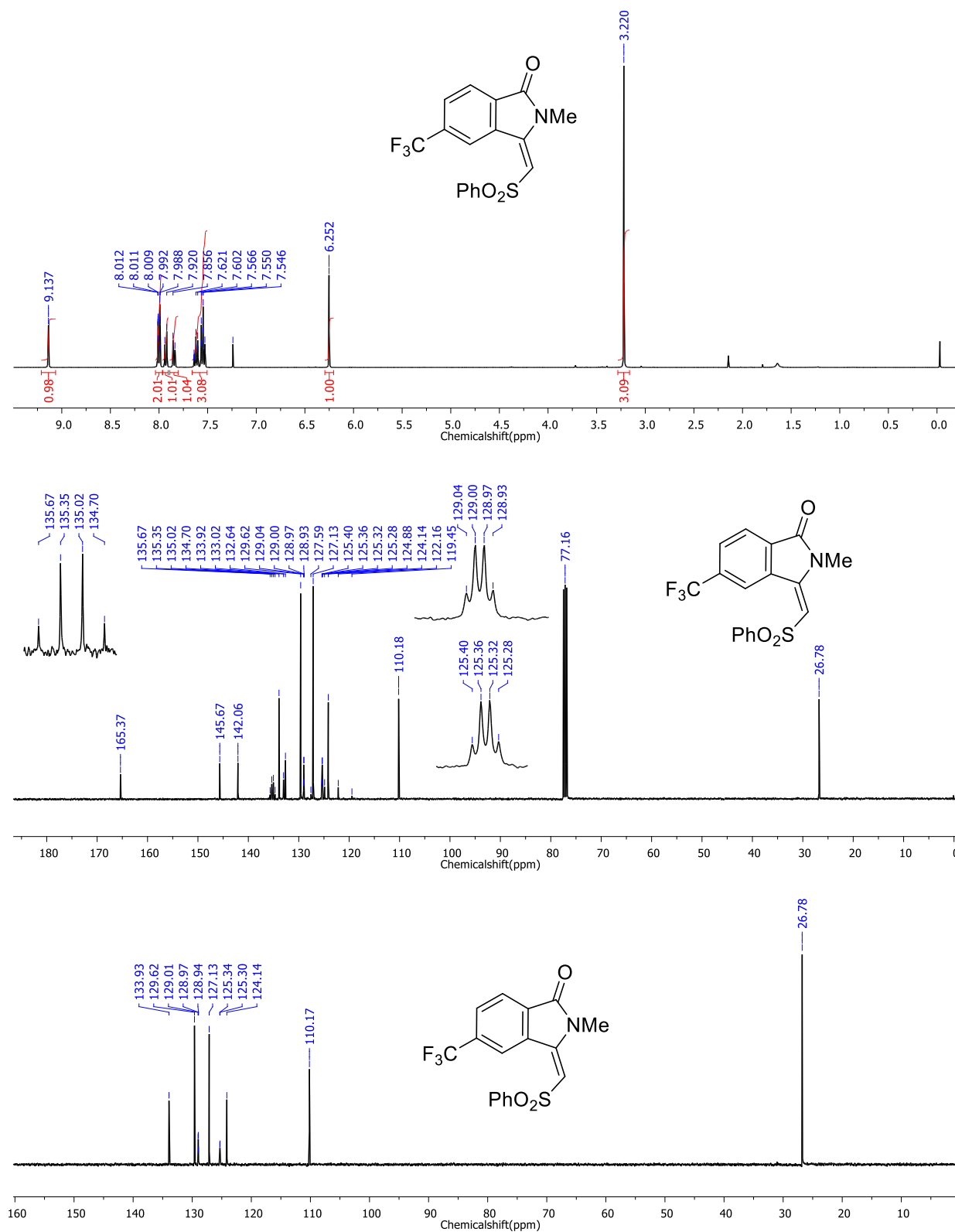
Table 1. Crystal data and structure refinement for TR1_a.

Identification code	TR1_a	
Empirical formula	C ₁₇ H ₁₃ N O ₂	
Formula weight	263.28	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 2 ₁ /c	
Unit cell dimensions	a = 8.3660(14) Å b = 21.114(3) Å c = 7.4894(14) Å	a = 90°. b = 111.841(9) °. g = 90°.
Volume	1228.0(4) Å ³	
Z	4	

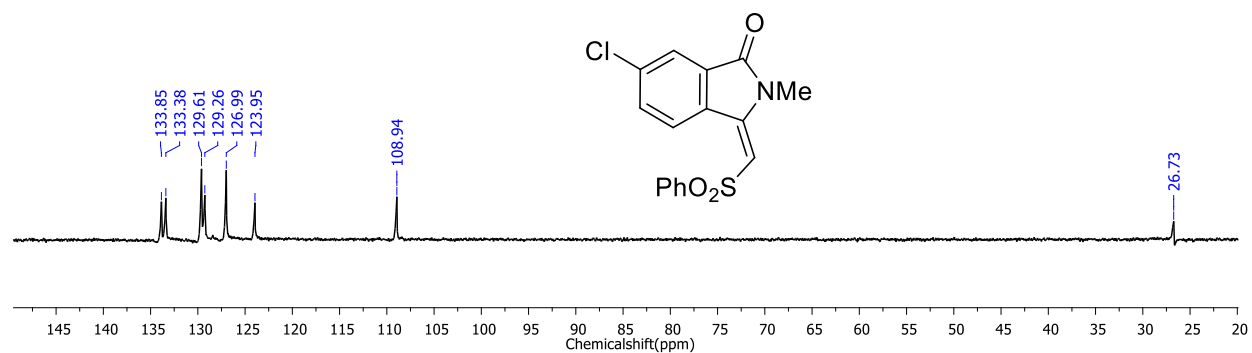
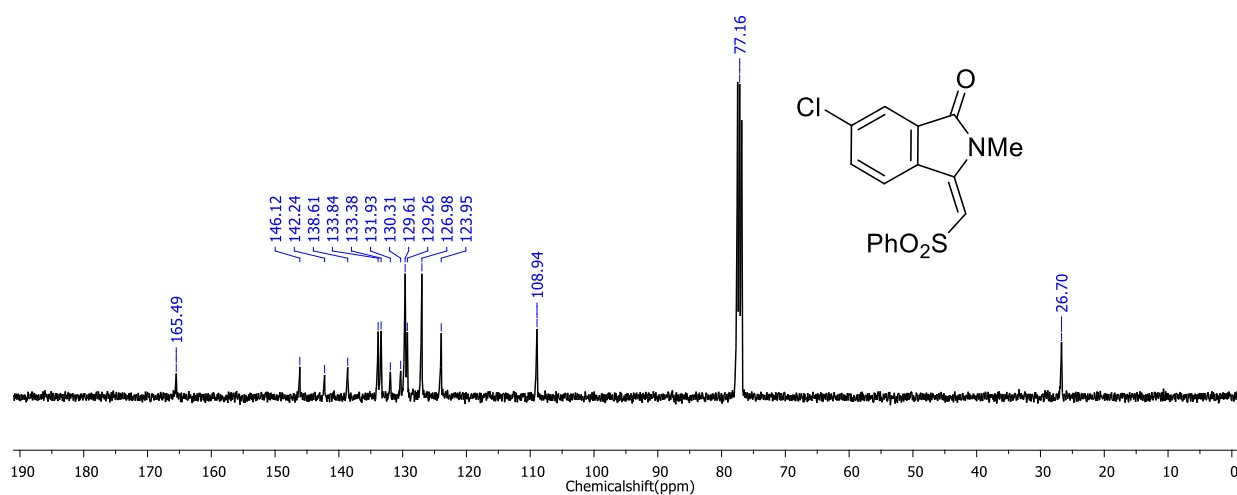
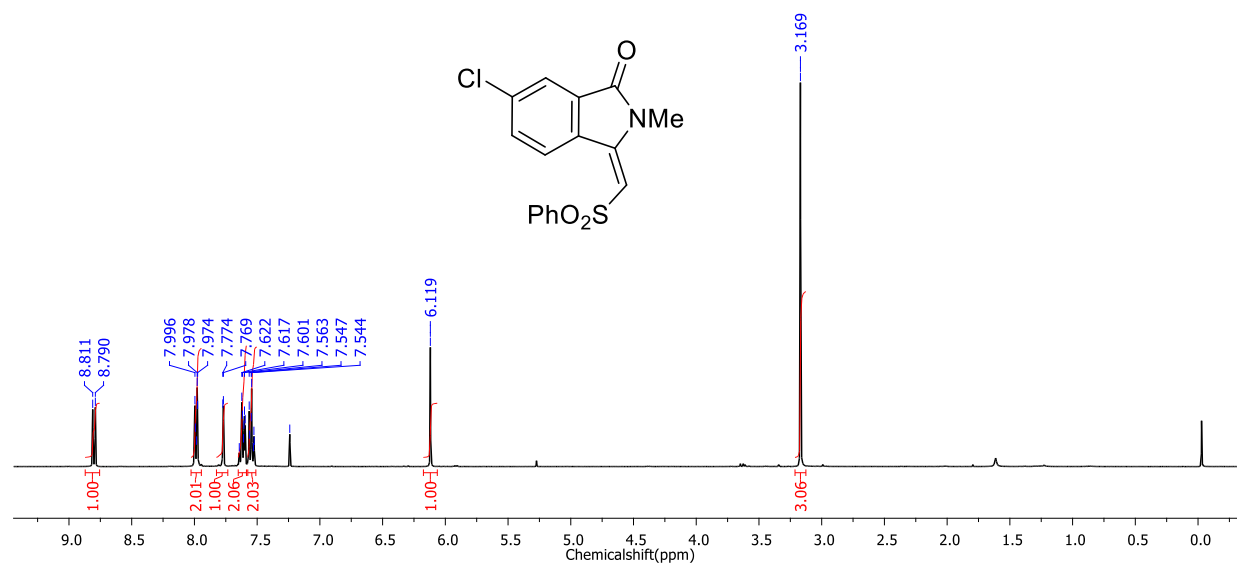
Density (calculated)	1.424 Mg/m ³
Absorption coefficient	0.094 mm ⁻¹
F(000)	552.0
Theta range for data collection	2.623 to 28.550 °.
Index ranges	-11<=h<=11, -28<=k<=28, -9<=l<=10
Reflections collected	40781
Independent reflections	3119 [R(int) = 0.0581]
Completeness to theta = 25.242°	98.7 %
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3080 / 0 / 183
Goodness-of-fit on F ²	0.897
Final R indices [I>2sigma(I)]	R1 = 0.0581, wR2 = 0.1742
R indices (all data)	R1 = 0.1164, wR2 = 0.1462
Largest diff. peak and hole	0.228 and -0.308 e.Å ⁻³

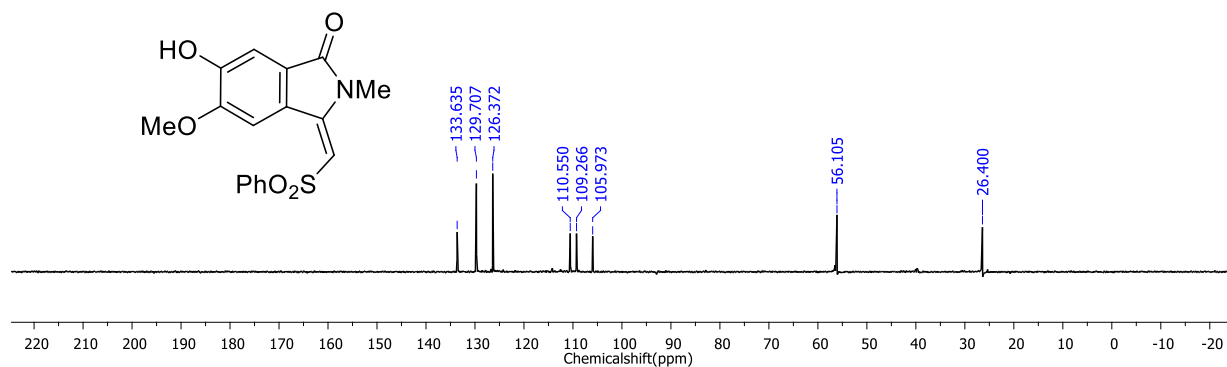
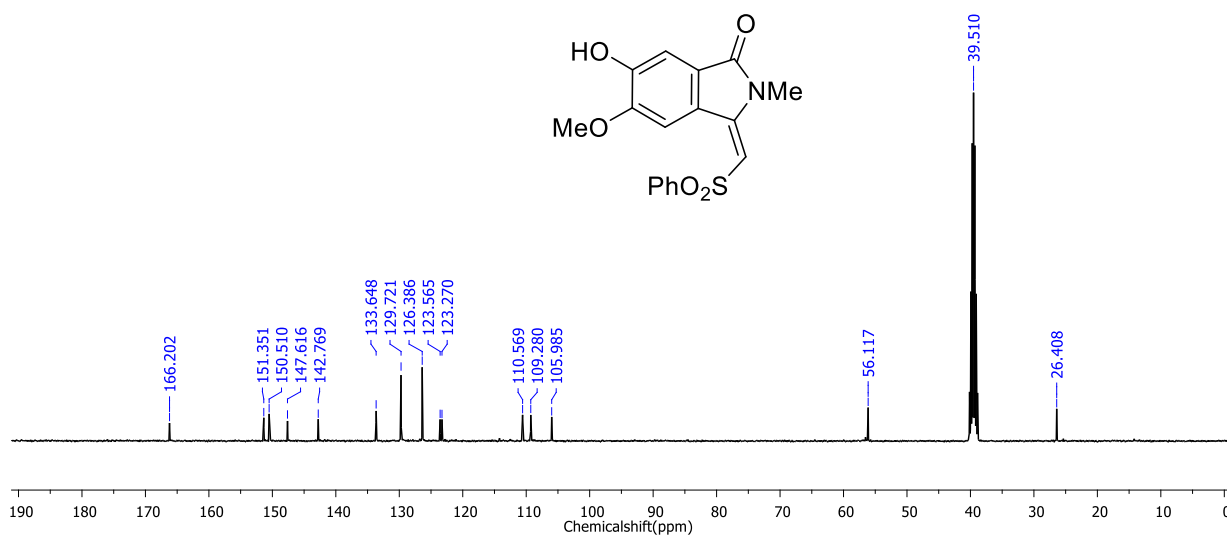
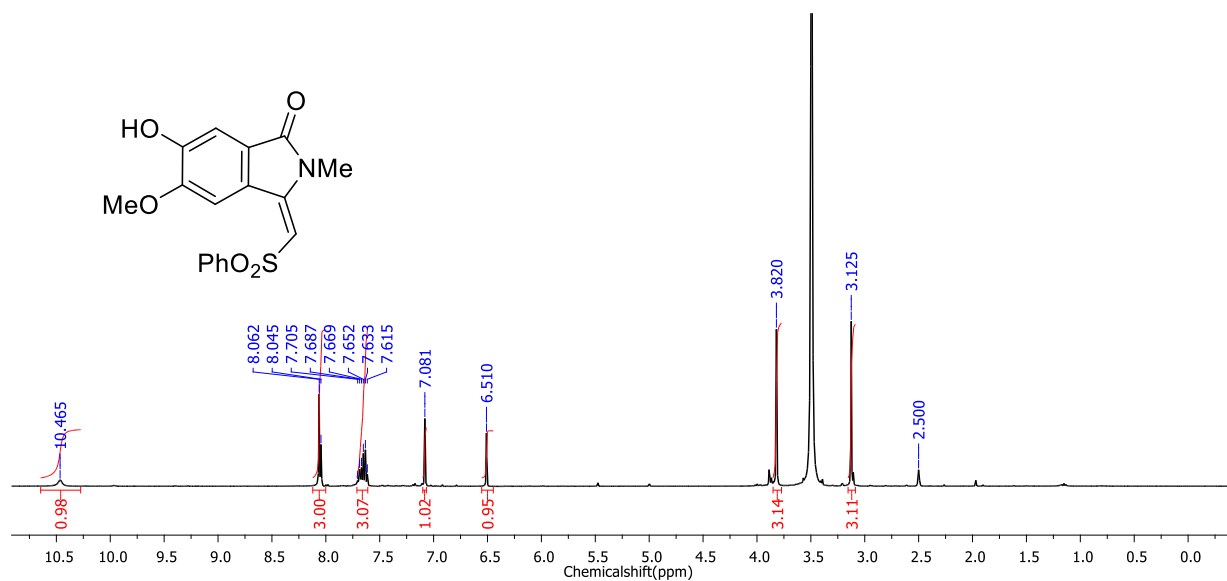
4.22: Spectral Copies of Selected Compounds

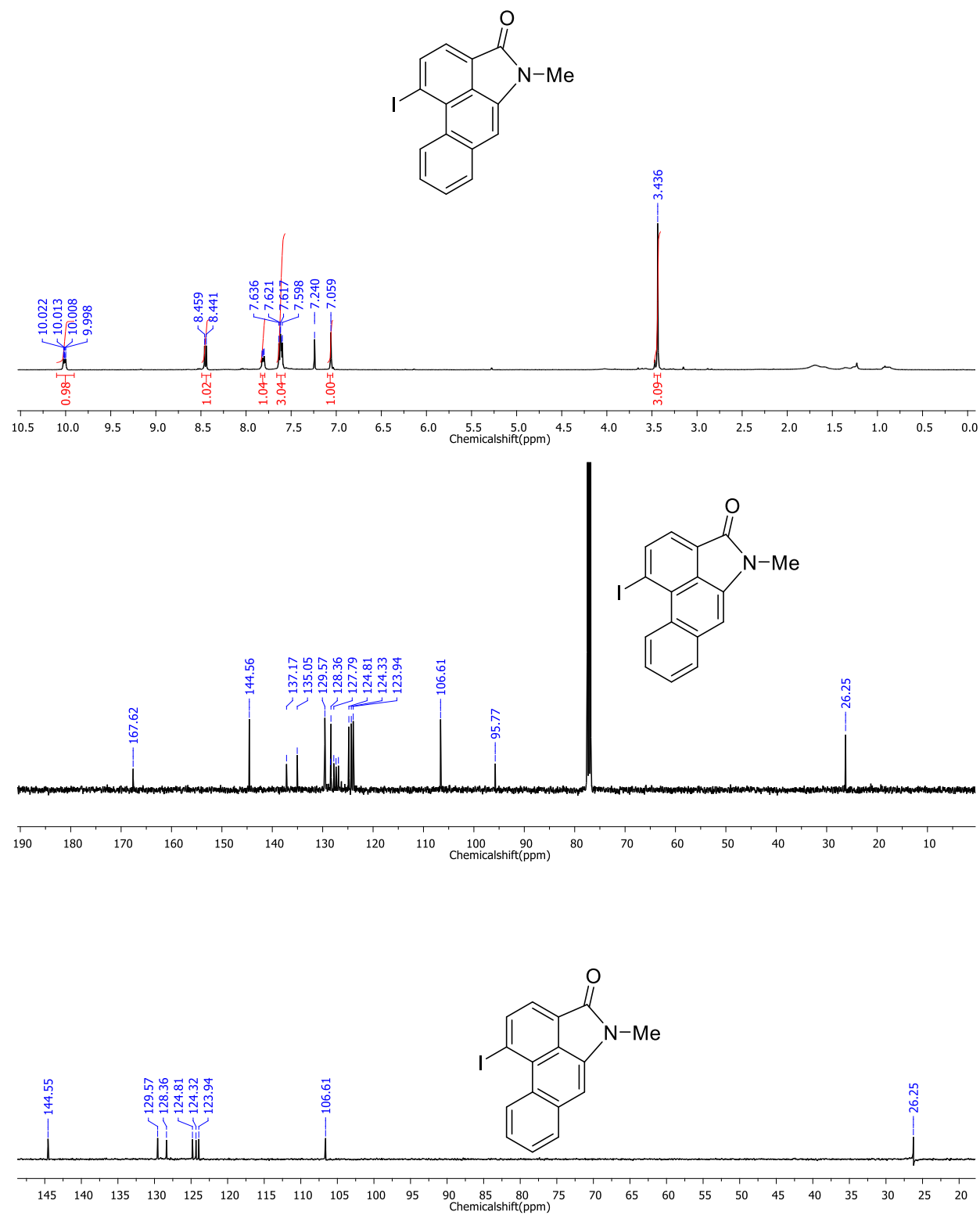
Spectral Data of Compound **3k**.

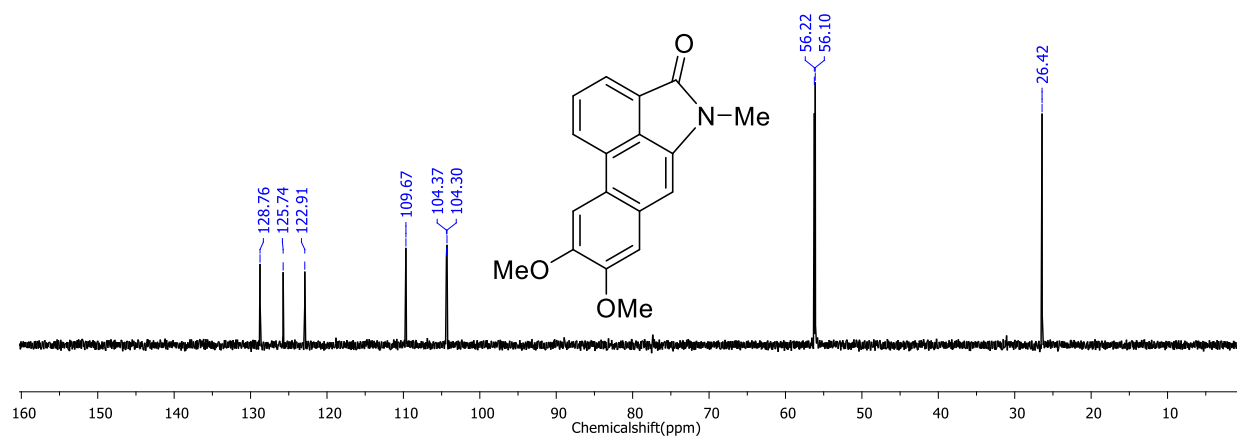
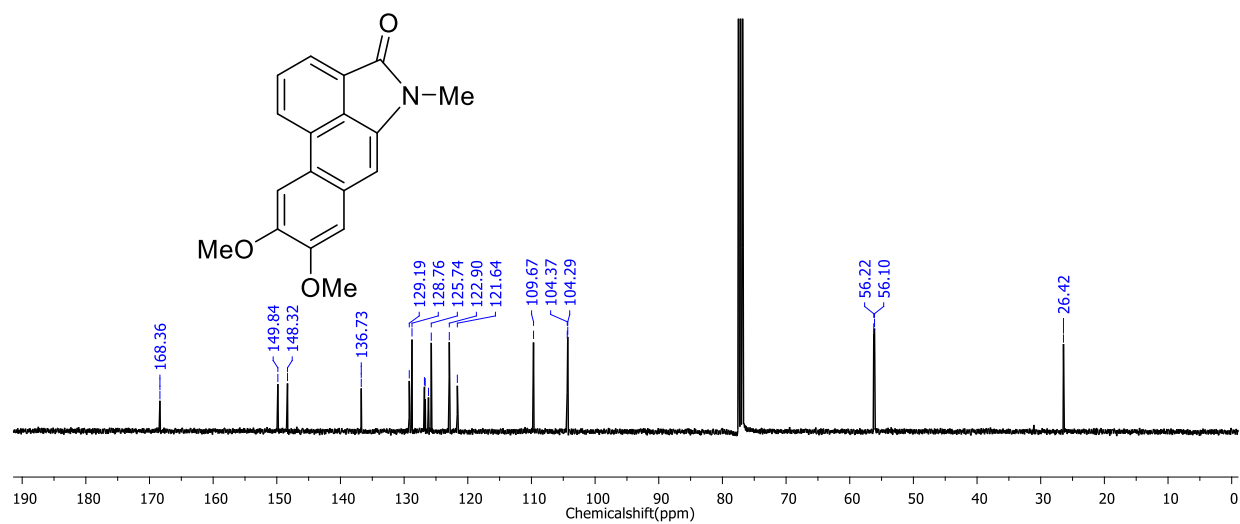
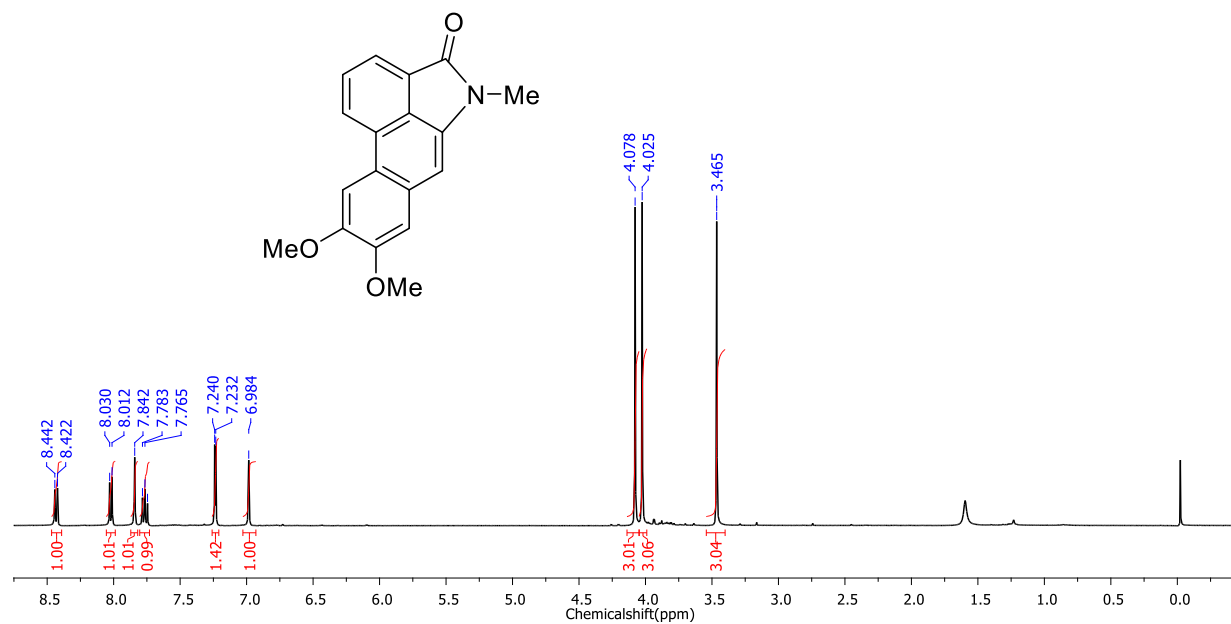
Spectral Data of Compound **3o**.

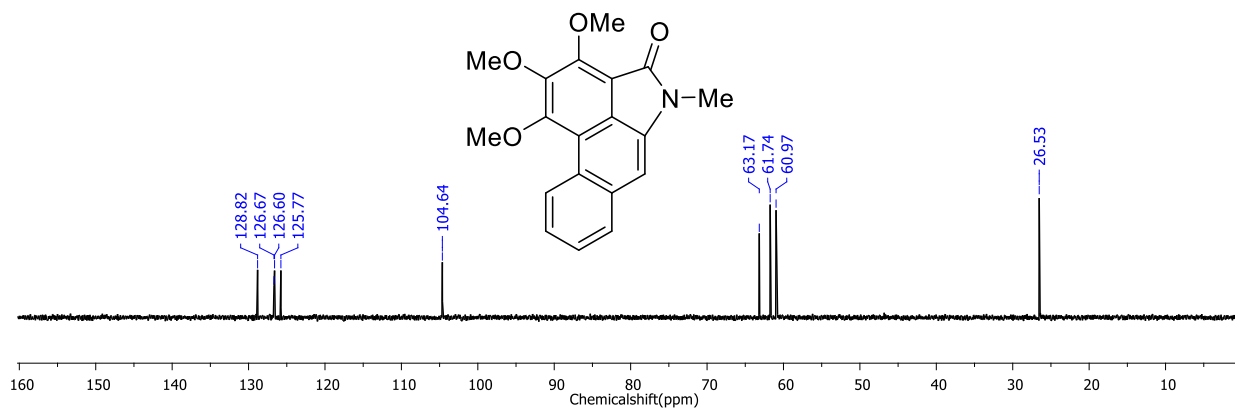
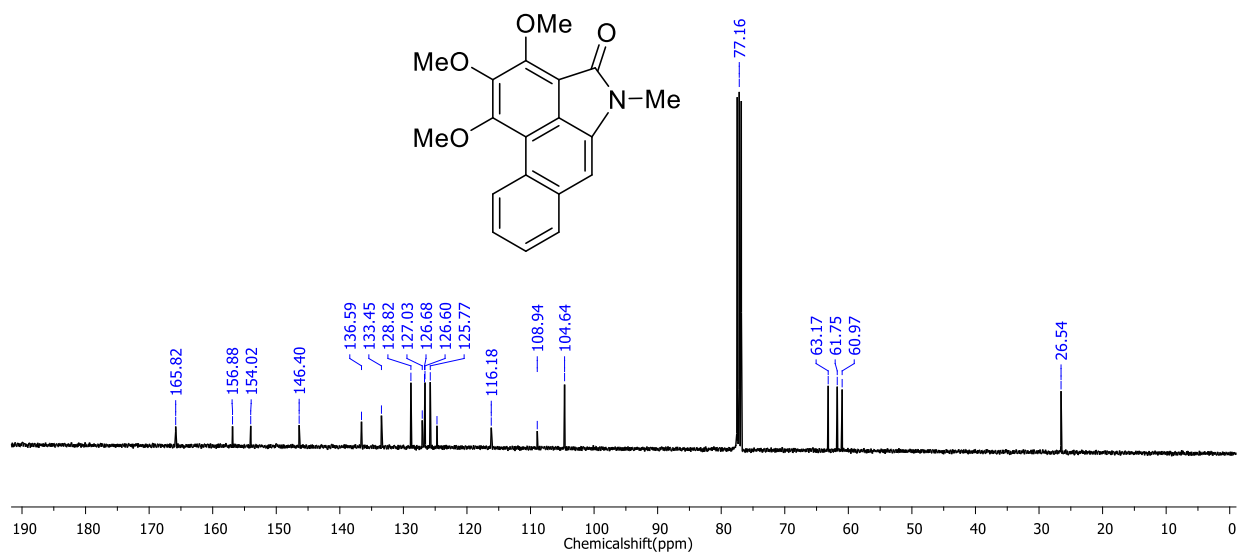
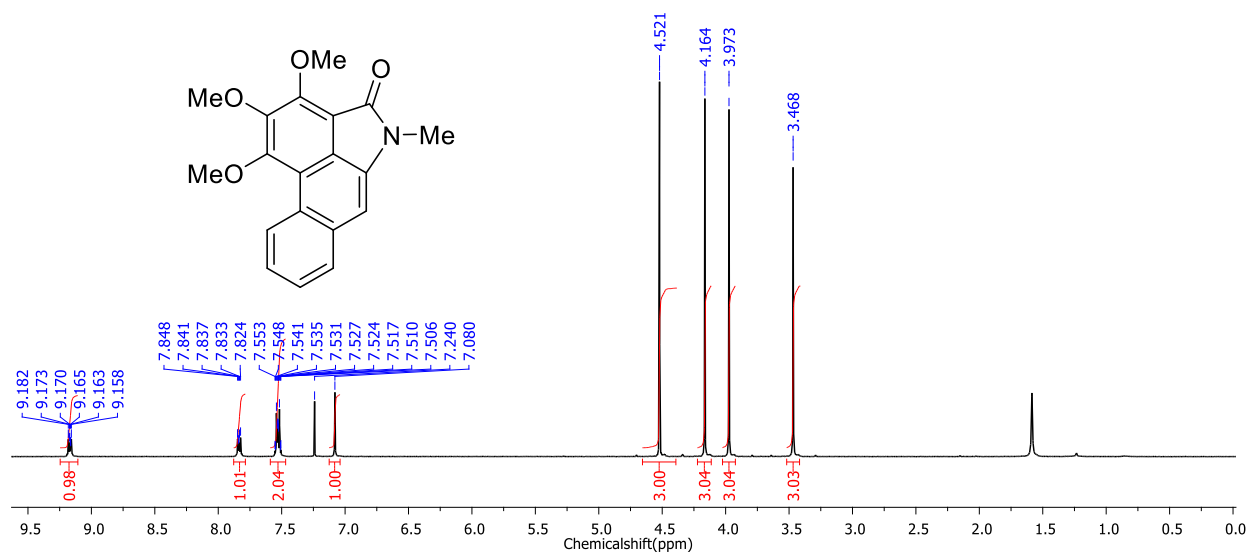
Spectral Data of Compound 3s.

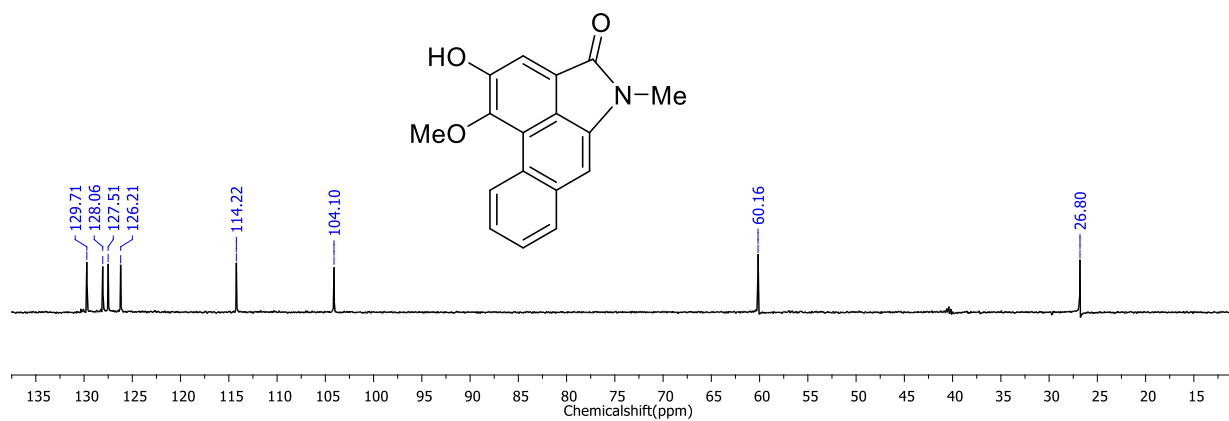
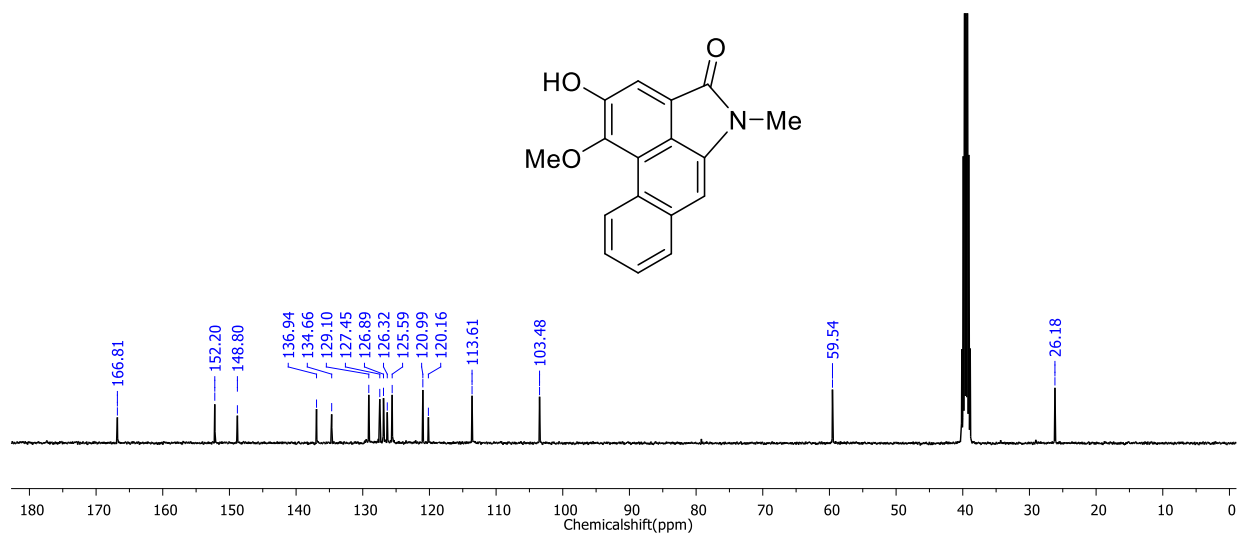
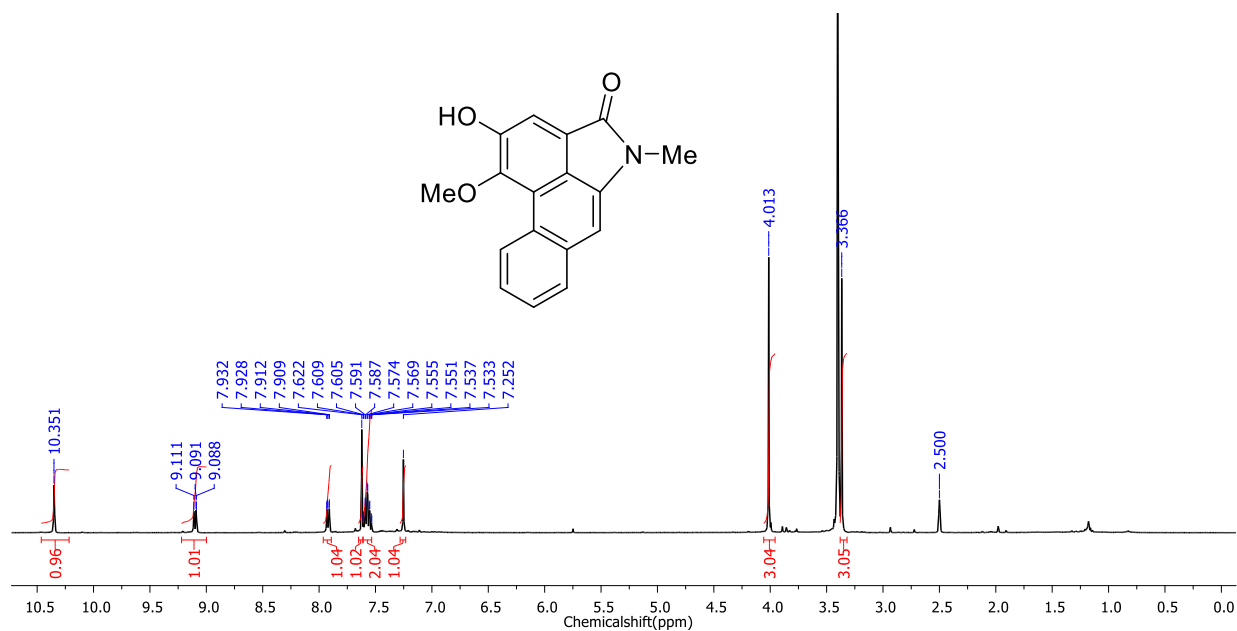


Spectral Data of Compound **3z**.

Spectral Data of Compound **9k**.

Spectral Data of Compound **9r**.

Spectral Data of Compound **10d**.

Spectral Data of Compound **10e**.

Spectral Data of Compound **10i**.