Ruthenium-Catalyzed Redox-Neutral C–H Bond Functionalization Reaction: an Efficient Route to Substituted Alkenes and Heterocycles

A Thesis

Submitted in Partial Fulfillment of the Requirements

For the Degree of

Doctor of Philosophy

by

R. Manikandan

ID: 20133240

Indian Institute of Science Education and Research (IISER), Pune

2018

Dedicated

To

My Parents, brothers

And

My Beloved Family Members

भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान,पुणे
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CERTIFICATE

Certified that the work incorporated in this thesis entitled "***Ruthenium Catalyzed Redox-neutral C–H Bond Functionalization Reaction: an Efficient Route to Substituted Alkenes and Heterocycles***" submitted by ***Mr. R.Manikandan*** 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: 12th March 2018

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DECLARATION

I declare that this written submission represents my ideas in my own words and wherever other's ideas have been included; I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea /data /fact /source in my submission. I understand that violation of the above will cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

Date: 12th March **R. Manikandan**

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It's been an incredible journey and I am so grateful to all of the amazing people that have helped me along the way. In fact, the phrase "Thank you" can never capture the gratitude I want to express.

R. Manikandan

Synopsis

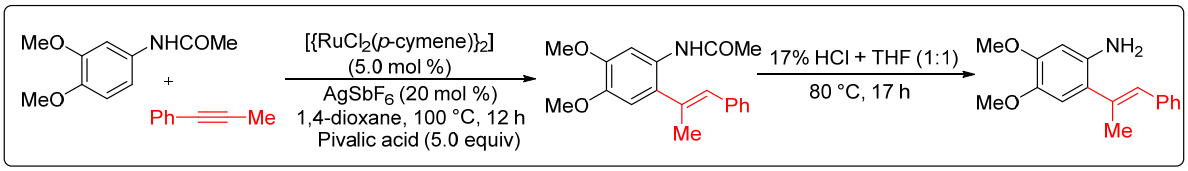
The thesis entitled "***Ruthenium-Catalyzed Redox-Neutral C–H Bond Functionalization Reaction: an Efficient Route to Substituted Alkenes and Heterocycles***" comprises of four chapters.

The research area in my doctoral study is targeted on the development of new synthetic methods for the synthesis of various substituted alkenes and valuable heterocyclic compounds via a ruthenium-catalyzed chelation assisted redox-neutral C–H bond activation reaction. The transition metal catalyzed chelation assisted C–H bond activation is one of the efficient method to construct various carbon-carbon bonds in a highly efficient manner, by employing this methodology various substituted aromatics and heterocycles were prepared in a highly atom economical and environmentally friendly manner compared to classical cross coupling reactions. Various transition metal complexes such as palladium, rhodium and ruthenium have been widely used as catalysts in this type of reaction. Among them a less expensive ruthenium complexes gained tremendous attention in this type of reaction, due to their remarkable reactivity, compatibility and selectivity. Synthesize of substituted alkenes via ruthenium catalyzed C–H bond activation is excellent method to synthesize various substituted alkene derivatives in a highly regio and stereo selective manner. However Till now, in the ruthenium-catalyzed alkenylation reaction, a stoichiometric amount or a catalytic amount of oxidant or base was used to execute the reaction. We have developed a redox-neutral method to synthesize of tri, di and mono substituted alkenes with high regio selectivity without using any oxidant with cheaper ruthenium catalyst, in addition biologically important heterocycles also prepared by employing the same methodology.

Chapter 1 of this thesis discusses the importance, classification and general synthetic methods for various substituted alkenes and heterocycles. Various synthetic methods for synthesizing alkenes and heterocyclic compounds including metal-catalyzed coupling reactions and C–H bond activation methods were discussed. A brief introduction of chelation-assisted C–H bond activation via oxidative addition pathway as well as deprotonation pathway was also discussed in this chapter.

Chapter 2 of this thesis describes an efficient method for the synthesis of *ortho*-alkenylated anilines and biologically important 2-Quinolinone derivatives via a ruthenium-catalyzed hydroarylation of alkynes with substituted aromatic anilides. It contains two sub-divisions as follows:

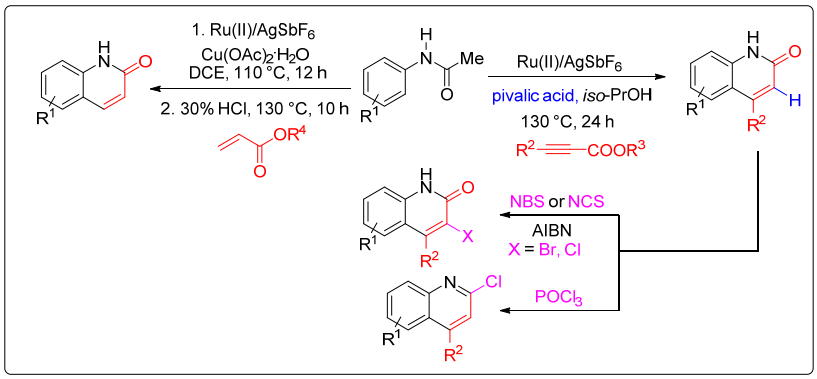
Section 2A: Synthesis of *ortho*-alkenylated anilines: The transition metal-catalyzed hydroarylation of alkynes with substituted aromatics is one of the convenient routes to synthesize tri-substituted alkenes in a highly regio- and stereoselective manner. Herein, we have discussed a highly regio- and stereoselective ruthenium-catalyzed hydroarylation of acetanilides with symmetrical and unsymmetrical alkynes (Scheme 1). The catalytic reaction provides *ortho*-alkenylated anilides in good to excellent yields. The alkyne substituents decide the regiochemistry of the product. Coordinating groups such as Ph or ester from the alkynes are *trans* to the anilides. Later, *ortho*-alkenylated anilides were converted into *ortho*-alkenylated anilines in the presence of HCl. It is important to note that *ortho*-alkenylated anilines are versatile synthetic precursors in a number of organic transformations and also efficiently used to synthesize biologically active molecules.



Scheme 1: Ruthenium-Catalyzed Hydroarylation of Acetanilides with alkynes

Section 2B: Synthesis of 2-Quinolinones: 2-Quinolinones are a naturally occurring heterocyclic moiety which exhibits a broad range of biological activities including antibiotic, anticancer, antiviral and antihypersensitive. Transition metal-catalyzed cyclization of heteroatom substituted aromatics with carbon-carbon π-component via chelation-assisted C–H bond activation is one of the powerful methods to synthesize heterocyclic molecules in one pot. But, the synthesis of 2-quinolinone derivatives via chelation-assisted C–H bond activation pathway is limited in the literature. Herein, we wish to report the synthesis of 4-substituted-2-quinolinone derivatives from easily available starting materials via a ruthenium-catalyzed cyclization of anilides with substituted propiolates (Scheme 2**)**. By using acrylates instead of propiolates, unsubstituted 2-quinolinone derivatives were prepared. Later, a halo group such as Cl or Br was introduced at the

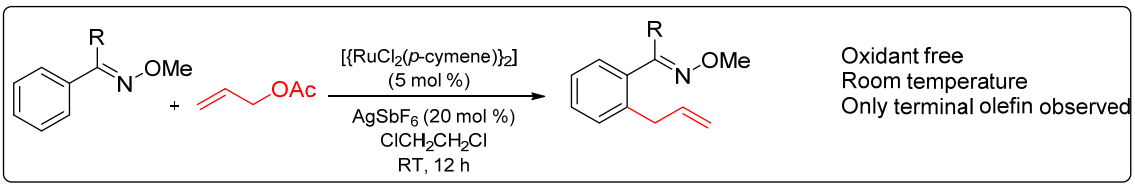
C-3 position of 4-substituted-2-quinolinones in the presence of NBS or NCS. Further, a highly useful 2-chloroquinolines were prepared from 2-quinolinones in the presence of $POCl_3$.



Scheme 2: Ruthenium-Catalyzed Synthesis of 2-Quinolinones

Chapter 3 demonstrates the regioselective synthesis of *ortho*-allyl and vinylated substituted aromatics via a ruthenium-catalyzed oxidant-free allylation of substituted aromatics with allylic acetates. It contains two sub-divisions as follows:

Section 3A: Synthesis of *Ortho*-allylated Aromatic Ketoximes : The allylarene unit is present in various natural products and medicinally relevant molecules. In addition, substituted allylic derivatives are a versatile synthetic intermediate which is widely used to synthesize natural products and pharmaceutical molecules. In earlier reports in allylation via C–H bond activation reaction, requires a stoichiometric amount of oxidant or base or acid to activate the C–H bond of aromatics. Further, the high temperature is required for the reaction and also mostly a mixture of double bond migration products were observed. Herein, we report an oxidant free *ortho* allylation of substituted aromatic ketoximes with allylic acetates in the presence of ruthenium catalyst at room temperature under mild reaction conditions (Scheme 3**)**. In the reaction, allyl

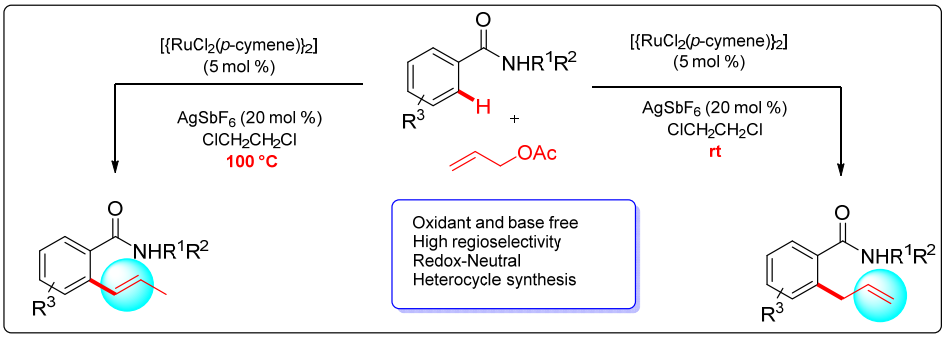


Scheme 3: Ruthenium-Catalyzed *Ortho*-allylation of Aromatic Ketoximes

acetate plays dual role, it acts as an allylating agent and also provides an acetate anion source for activating the C–H bond of aromatics. Thus, an external acetate source is not required for the

reaction. Very interestingly, the double bond migration product was not observed and only terminal olefin product was observed

Section 3B: Synthesis of *Ortho* Allyl and vinylated benzamides: In this section, we have showed the redox-neutral ruthenium-catalyzed allylation of benzamides with allylic acetates without any oxidant or base at room temperature (Scheme 4**)**. The whole catalytic reaction has occurred in a Ru (II) oxidation state. In the reaction, acetate moiety of allylic acetate acts as a base to deprotonate the C–H bond. The acetate moiety of allylic acetate intramolecularly transferred into a ruthenium species via β-acetate elimination and maintains the Ru (II) oxidation state. It is important to note that the C–H bond activation as well as allylation reaction takes place at room temperature. But, a higher reaction temperature is needed for the double bond migration. The reaction temperature decides the outcome of regioselectivity of the product. A possible reaction mechanism for allylation reaction was proposed. The alkene migration mechanism was supported by a deuterium labelling experiment. *Ortho* allyl and vinylated benzamides were converted into biologically useful six- and five-membered benzolactones in the presence of HCl.

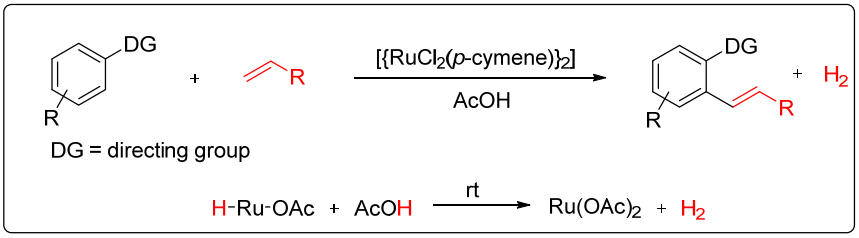


Scheme 3: Ruthenium-Catalyzed *Ortho*-allyl and vnylation of Aromatic Amides

Chapter 4 describes an efficient route to synthesize of disubstituted alkenes and Isoindoles via a ruthenium-catalyzed oxidant-free *ortho* alkenylation of substituted aromatics with alkenes at room temperature with hydrogen evolution. It contains two sub-divisions as follows:

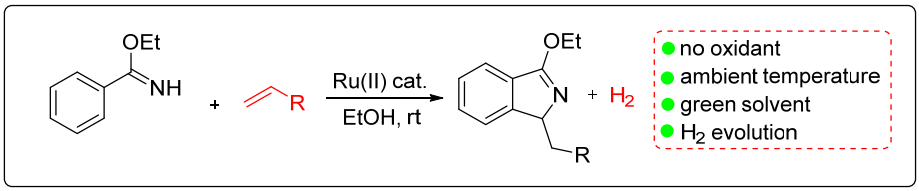
Section 4A: Synthesis of disubstituted alkenes: The transition metal-catalyzed chelation assisted *ortho* alkenylation of substituted aromatics with alkenes via C–H bond activation is one of the powerful methods to synthesize substituted alkenes in a highly regio- and stereoselective manner. Till now, in the ruthenium-catalyzed alkenylation reaction, a stoichiometric amount of

$Cu(OAc)_2$ or a catalytic amount of $Cu(OAc)_2$ along with air or oxygen oxidant was used. In this type of reaction, after β-hydride elimination, a ruthenium hydride intermediate is formed. It is known that a metal hydride species readily reacts with water or organic acids forming a metal hydroxide or carboxylate species along with hydrogen evolution. With this background, we have planned to use acetic acid in the reaction which could readily reacts with H-Ru species giving the active Ru-OAc catalyst without using any oxidizing agent (Scheme 5**)**. By this way, the oxidation step such as the oxidation of Ru(0) to Ru(II) can be avoided and the catalytic reaction can be done without changing the oxidation state of metal via redox-neutral C–H bond functionalization.



Scheme 5: Ruthenium-Catalyzed *Ortho*-alkenylation of substituted Aromatics with Alkenes

Section 4B: Synthesis of Isoindoles: Isoindoles are an important class of heterocyclic compounds, and their structural units are present in various natural products, biologically active molecules, and dyes. In addition, it also shows excellent fluorescent and electroluminescent properties. However, only a few reports are available for synthesizing 1*H*-isoindoles due to its lower stability. Herein, we have showed an unprecedented redox-neutral ruthenium (II)-catalyzed cyclization of benzimidates with alkenes in green ethanol solvent at ambient temperature, giving 1*H*-isoindoles and 2*H*-isoindoles with the liberation of renewable hydrogen source (Scheme 6). The cyclization was done in a redox-neutral version without changing the oxidation state of Ru(II), and thus no oxidant is needed.



Scheme 6: Ruthenium-Catalyzed Oxidant free Synthesis of Isoindoles

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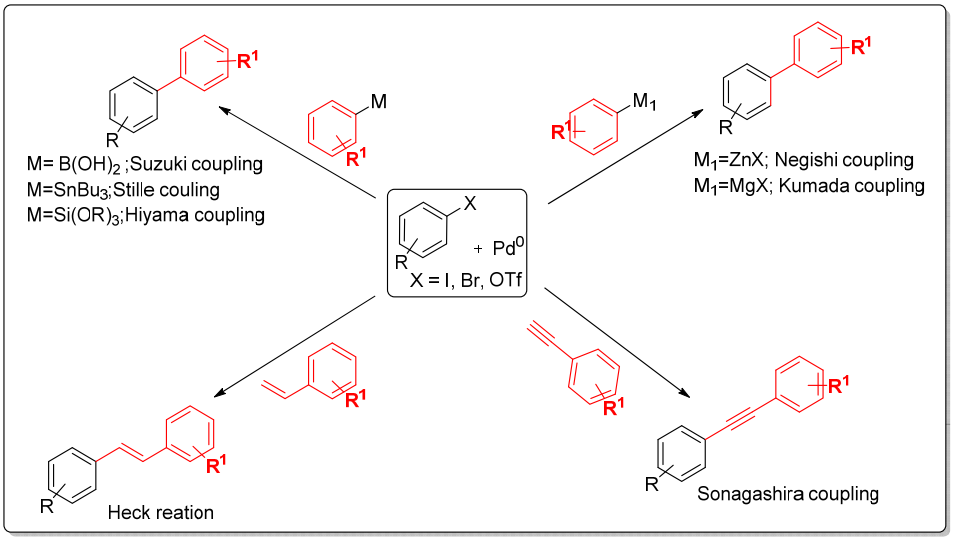
Chapter 1

History of Ru (II)-Catalyzed Redox- Neutral C–H Bond Functionalization Reactions

1. Introduction

1.1: Importance of Cross-Coupling Reactions in Organic Synthesis

The transition metal-catalyzed formation of new carbon-carbon and carbon-heteroatom bonds (especially oxygen and nitrogen) is a mandatory step in modern organic synthesis for synthesizing of various biologically active molecules, agrochemicals, and novel materials.[1] Last few decades, the outstanding performance in the area of carbon-carbon and carbon-heteroatom bond formation was achieved by using classical cross-coupling reactions with very reactive precious metals, like palladium and rhodium.[2] Such an importance of these transformations was recognized by the Nobel prize academy. In 2010, Nobel prize in chemistry was awarded to R.F. Heck, E. Negishi and A. Suzuki for their excellent contribution in the field of palladium-catalyzed cross-coupling reactions. In cross-coupling reactions, organic electrophiles coupled with organometallic reagents or simple organic molecules in the presence of the transition metal catalyst providing the corresponding coupling products in a highly efficient manner (Scheme 1.1).[2]



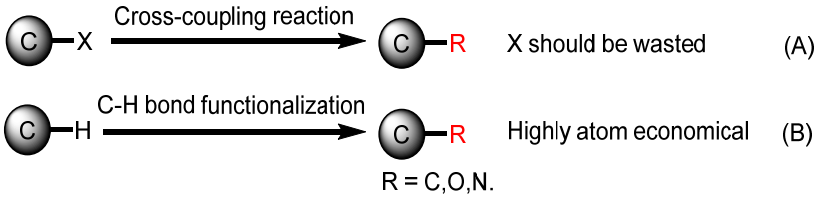
Scheme 1.1: Palladium-catalyzed cross-coupling reactions.

Although these type of reactions are very effective for construction of various chemical bonds, a preactivated coupling partner such as C-X or C-M on the aromatic moiety is required. The synthesis of prefunctionalized organic electrophiles and organometallics reagents **(**M = MgX, ZnX, BR_2, SnR_3, SiR_3, etc.) requires the number of steps and the most of organometallic reagents are often sensitive to air and quite expensive. In addition, at the end of the reaction, these X and M are wasted as by-products. This situation clearly means, if the functionalization reaction was developed without using any pre-

functionalised starting materials via direct C–H bond functionalization, it would be highly interesting in terms of the atom economy and environmentally friendly.

1.2: Necessity of C–H Bond Functionalization Reaction

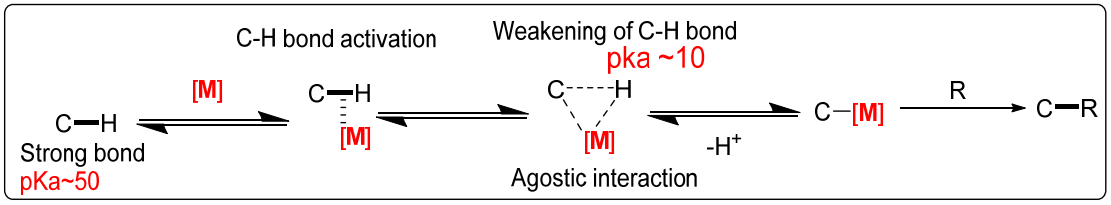
The functionalization of organic molecules using alternative C–H bond activation strategies, also promoted by transition metals, is now a well-established methodology.[3] The benefits of C–H activation methods are clear, even though precious metals are involved such as palladium and rhodium. Prefunctionalization of the reagents is not always necessary and the amount of waste materials can be reduced by following this method (Scheme 1.2B).[2]



Scheme 1.2: Importance of C–H bond functionalization reaction.

1.3: Mechanism of C–H Bond Activation

The C–H bond activation is a type of reaction in which C–H bond is activated, cleaved and replaced by a new C-R bond (R = usually C, N, and O) in the presence of metal catalyst. In this reaction, initially, the metal interacts with the unreactive C–H bond. The agostic interaction causes weakening of the C–H bond, which leads to cleavage of that and forms a C-M intermediate. Further, the C-M intermediate can undergo functionalization with various chemical reagents to replace C–H with C-R. This process is called as C–H bond functionalization (Scheme 1.3).



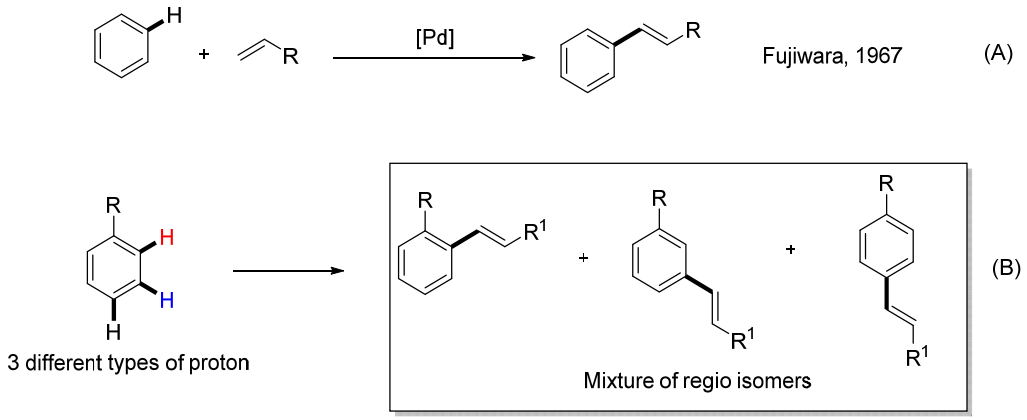
Scheme 1.3: mechanism of C–H bond activation.

1.4 Regio Selective Problem in Simple C–H Bond Activation Reactions

The major drawback in the simple C–H bond activation reaction is the lack of regioselectivity. Generally, an organic molecule contains number of C–H bonds, so activation of one specific C–H bond is highly difficult.

In 1968, Fujiwara's group has reported the Pd-catalyzed coupling of simple benzene with an alkene to produce a highly valuable stilbene derivative. It is highly atom-economical

and environmentally friendly reaction (Scheme 1.4A). However, the substituted benzene contains several C–H bonds, thus mixture of regioisomeric products was observed (Scheme 1.4B).[3]



Scheme 1.4: Fujiwara-Moritani reaction

1.5 Attaining the Regioselectivity in C–H Bond Activation Reactions

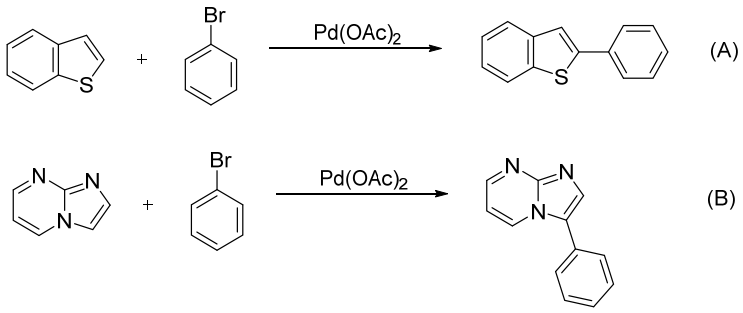
The regioselectivity in C–H bond activation reaction was achieved by following two major pathways.

a) Non-chelation assisted C–H bond activation reaction

b) Chelation assisted C–H bond activation reaction

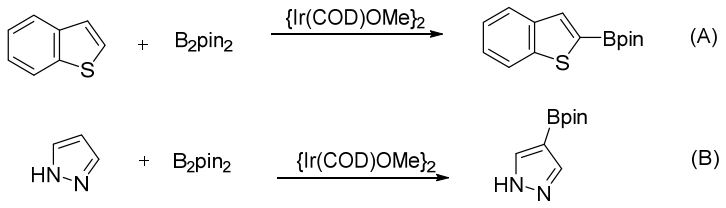
a) Non-Chelation Assisted C–H bond Activation Reaction

In non-chelation assisted C–H bond activation reaction, the selective C–H bond functionalization was attained based on the electronic and steric factor. Generally, the most acidic or electron rich and the most sterically available site could be the most reactive for this type of reaction. The Pd-catalyzed direct C–H arylation of heteroaromatic system occurred selectively at the highly acidic C–H bond.



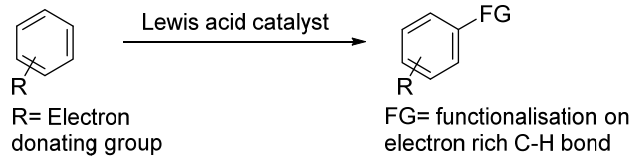
Scheme 1.5: Palladium-catalyzed regioselective arylation of heteroarenes

In 2006, Fagnou's group has reported the selective arylation of heteroarenes with aryl halides in the presence of palladium catalyst (Scheme 1.5).[4a-b] Subsequently, the iridium-catalyzed selective C–H borylation of heteroarenes were reported by Hartwig co-workers (Scheme 1.6).[4c]



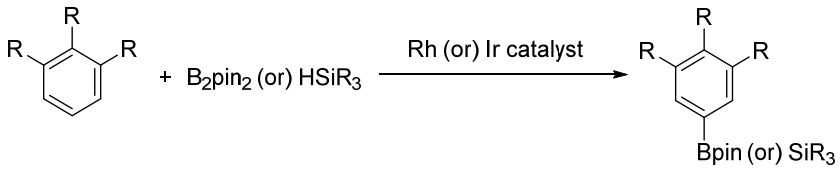
Scheme 1.6: Iridium-catalyzed regioselective borylation of heteroarenes

Later, various electrophilic C–H bond functionalization reactions at the highly acidic C–H bonds in the presence of Pd, Cu, Ir and Rh catalyst have been reported in the literature.[4d] In contrast to the electrophilic C–H bond functionalization reaction, highly electron rich C–H bond was also selectively functionalized in the presence of Lewis acid catalysts (Scheme 1.7).[4e-f]



Scheme 1.7: Lewis acid mediated C–H bond functionalization of electron-rich arenes.

Apart from this, the steric factor also plays important role in selective C–H bond functionalization of aromatics. In iridium or rhodium-catalyzed borylation and silylation of multi-substituted arenes, the functionalization selectively occurred at sterically less hindered C–H bond of the arenes (Scheme 1.8).[4g]



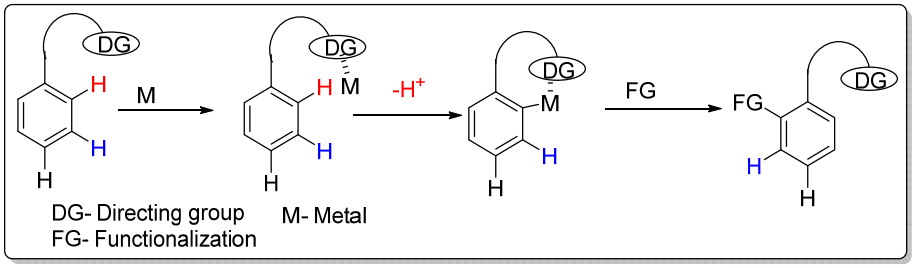
Scheme 1.8: Transition metal-catalyzed regioselective borylation, silylation of multi-substituted arenes

The non-chelation assisted C−H bond functionalization reactions are highly atom economical. However, the substrate scope was highly limited and also achieving the complete regioselectivity is quite difficult. Thus it was less developed compared to chelation assisted C−H bond functionalization reactions.

b) Chelation-Assisted C–H Bond Functionalization Reactions

The introduction of directing group (DG) has allowed considerable progress to be made in the development of metal-mediated regioselective C–H activation processes. In chelation-assisted C–H bond activation, initially metal coordinates with heteroatom of the directing group and deprotonates the *ortho* proton (close proximity to the metal) selectively to form metallacycle intermediate. Further, the metallacycle intermediate can

undergo functionalization by adding various chemical reagents to give the desired product. The directing group present in the molecule does not only control the regioselectivity of C–H bond activation, further, the interaction of a directing group with the catalyst also increases the rate of the overall reaction (Scheme 1.9).[6]

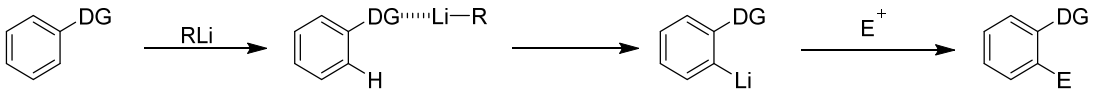


Scheme 1.9: Transition metal-catalyzed directing group assisted C–H bond functionalization.

In earlier days, directed *ortho* metalation (DOM) with organometallic bases (RLi, RMgX) is used for the functionalization on the organic molecules in a highly selective manner.

1.6 Directed O*rtho* Metalation by using Organometallic Reagent

In directed *ortho* metalation (DOM) process, the metal present in the organometallic reagent coordinates with the heteroatom of directing groups present in the organic molecule followed by selective deprotonation leads to an ortho-metallated intermediate. Later, the C-M metal bond can be quenched with various electrophiles (CO_2, TsN_3, O_2, Br_2, MeI, HCO_2Et, Bu_3SnCl) (Scheme 1.10).[5] Direct *ortho* metalation by using organometallic base is a powerful technique for the construction of various chemical bonds. However, this method contains considerable limitations including hazardous reaction procedures, poor site selectivity, harsh reaction conditions and a low chemoselectivity.



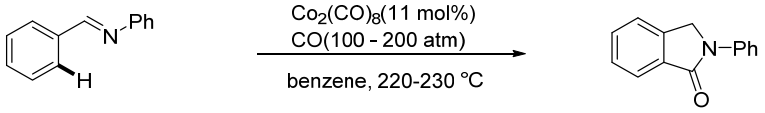
Scheme 1.10: Directed *ortho* metalation using organometallic reagents

Later on, by taking inspiration from directed *ortho* metalation (DOM) process, synthetic chemists have developed the transition metal-catalyzed chelation-assisted C–H Bond activation reactions for more convenient regioselective C–H functionalization of organic molecules. The operating mechanism of this reaction is also same as *ortho* metalation (DOM) process. However, instead of using stoichiometric amount of the organometallic reagents, only catalytic amount of transition metal catalyst was used for this type of reaction.

1.7 Transition Metal-Catalyzed Chelation-Assisted C–H Bond Activation Reactions

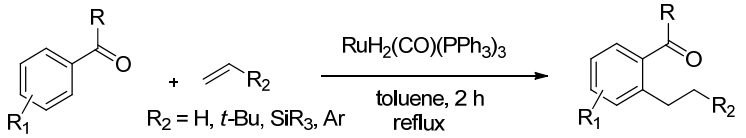
The transition metal-catalyzed chelation assisted C–H bond activation is one of the efficient methods to construct various chemical bonds in a highly efficient manner, by employing this methodology various substituted aromatics and heterocycles were prepared in a highly atom-economical and environmentally friendly manner compared to classical cross-coupling reactions.[7]

The first report in transition metal-catalyzed chelation-assisted C–H bond activation was reported by Murahashi's group in 1955. They have synthesized isoindolinone product from the reaction of imine with CO in the presence of a cobalt catalyst. (Scheme 1.11).[6a]



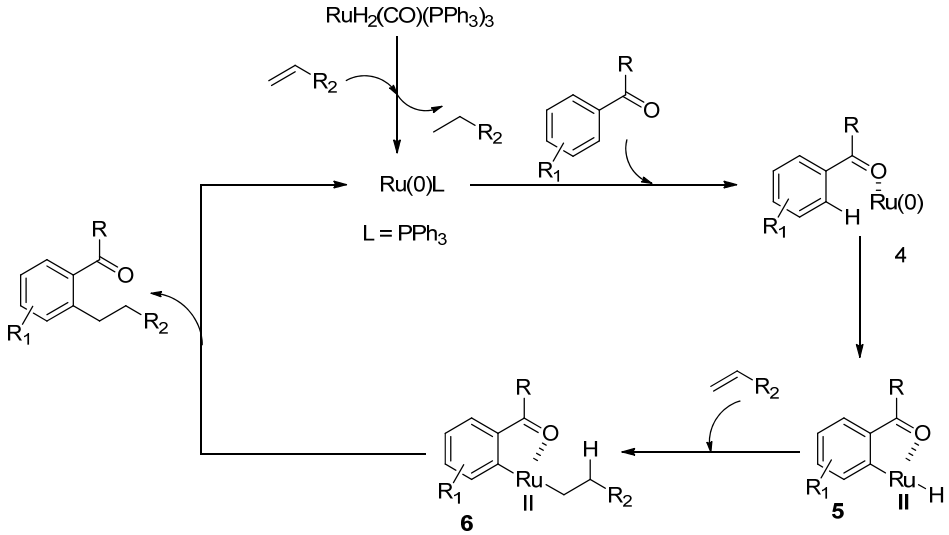
Scheme 1.11: Cobalt-catalyzed C–H activation of imines.

However, this type of reaction was extremely developed after Murai's report. In 1993, Murai's group has reported a ruthenium-catalyzed chelation-assisted *ortho* C–H bond alkylation of aromatic ketones with olefins. In this reaction, aromatic ketones reacted with alkenes in the presence of ruthenium catalyst yielding *ortho* alkylated aromatic ketones (Scheme 1.12).[6b]



Scheme 1.12: Chelation- assisted Ru-catalyzed alkylation *via* oxidative addition

Mechanism



Scheme 1.13: Mechanism of Ru-catalyzed *ortho* alkylation of aromatic ketones with alkenes

In this reaction, the active ruthenium (0) catalyst was generated from the reaction of $RuH_2CO(PPh)_3$ with an alkene. After the generation of active catalyst, the oxygen atom of carbonyl group coordinates with a ruthenium species produce intermediate **4**. The oxidative addition of *ortho* C–H bond of aromatic ketone on the Ru (0) provides a ruthenium hydride intermediate **5.** Next, the olefin co-ordinates to the Ru species and inserts between the Ru-H to give intermediate **6**. Intermediate **6** readily undergoes reductive elimination to give *ortho* alkylated product and regenerates Ru (0) active catalyst for the next catalytic cycle (Scheme 1.13).

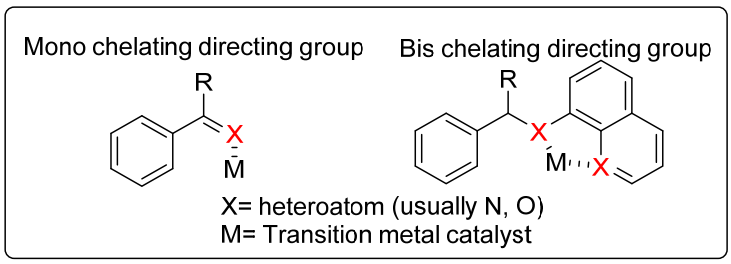
After Murai's report, the transition metal-catalyzed chelation-assisted C–H bond activation reactions were explored by several research groups by using different directing groups, and transition metal catalysts.[7-10]

1.8 Directing Groups in C–H Bond Activation Reaction

Generally, the directing group is a neutral or anionic functional group present in the molecule to be functionalized and contains at least one heteroatom (generally oxygen, and nitrogen) with bonding ability. Generally, it was classified into two types based on the number of coordinating atom present in the molecule (Scheme 1.14).

a) Mono chelating directing group (contain single donor atom).

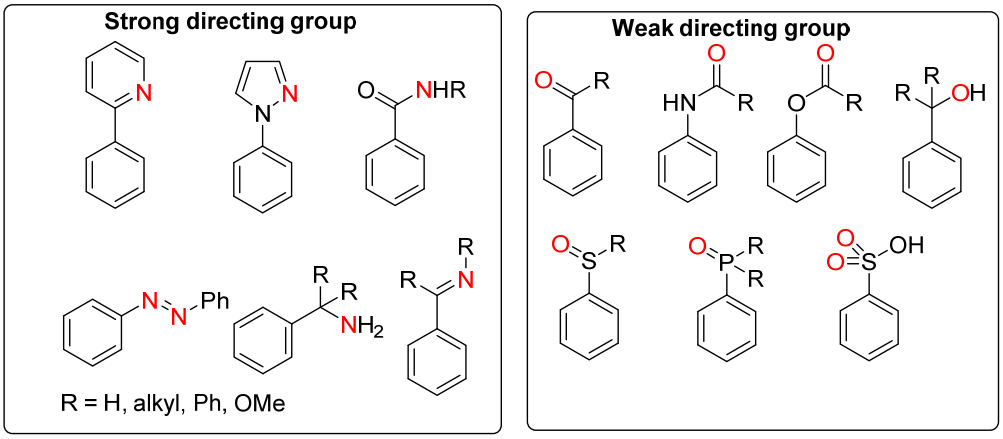
b) Bis chelating directing group (contain two donor atoms).



Scheme 1.14: Classification of directing group based on the number of coordinating atoms.

Initially, mono chelating directing groups were frequently used for achieving various C–H bond functionalization reactions. Recently, bis chelating directing groups were explored especially for C–H bond functionalization with the first-row transition metal catalysts (Fe, Co, Mn,..etc).

Further, it was classified into two types based on the coordinating ability of the heteroatom with metal (Scheme 1.15). Generally, the less electronegative nitrogen can coordinate effectively with transition metals compared to oxygen. Thus nitrogen-containing directing groups are called as strong directing groups and the oxygen-containing directing groups are called as weak directing groups.

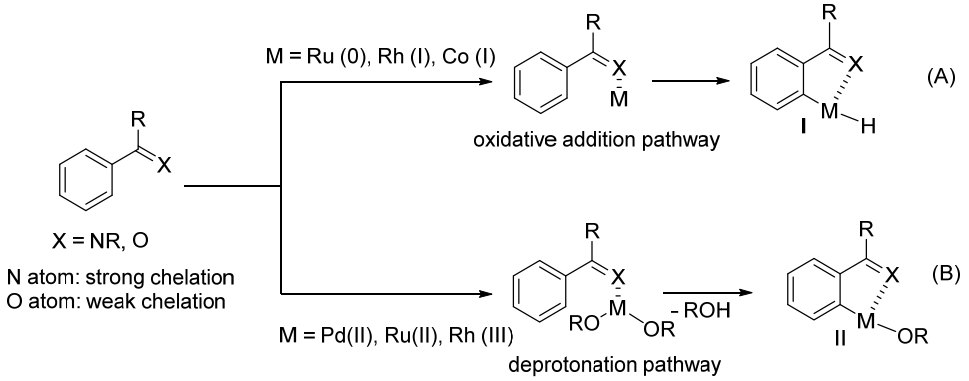


Scheme 1.15: Classification of directing group based on the coordinating ability of heteroatom.

1.9: Mechanistic Pathways of Transition Metal-Catalyzed Chelation-Assisted C–H Bond Activation Reaction

Chelation assisted C–H activation by using a metal catalyst follows two types of mechanistic pathways 1) oxidative addition pathway and 2) deprotonation pathway.

In the oxidative addition pathway, M (0) or (I) is the active catalyst. Generally metal with the lower oxidation state favors the oxidation addition step. In the reaction, a five-membered hydro metallacycle is the key intermediate (Scheme 1.16A).[9]

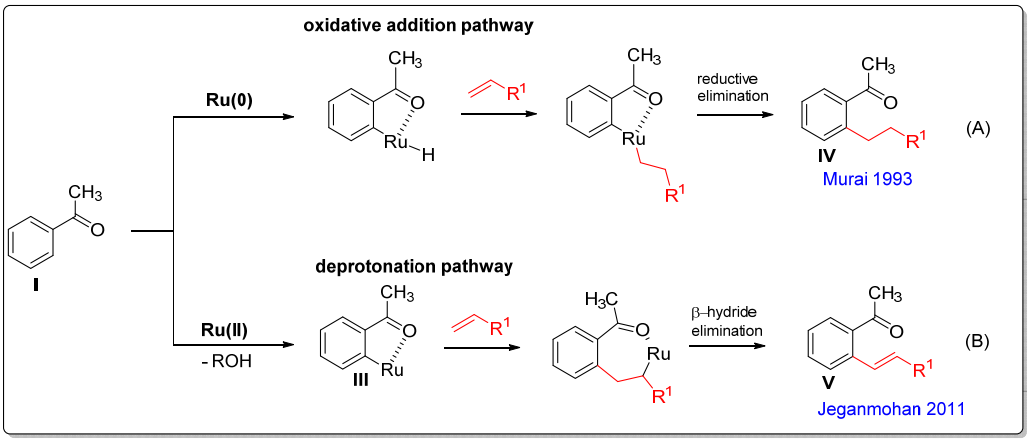


Scheme 1.16: Mechanism of metal-catalyzed chelation-assisted C–H bond activation

In deprotonation pathway, M (II) or (III) is the active catalyst. Generally, metal with the higher oxidation along with acetate ligand favors the deprotonation pathway. The catalytic reaction proceeds via the chelation-assisted acetate accelerated deprotonation at

the *ortho* C–H bond of the heteroatom group substituted aromatic compounds in the presence of metal acetate bases, providing a five-membered metallacycle intermediate (Scheme 1.16B). In the intermediate, there are no M-hydride species.

Thus, the mechanism and product formation of these both reactions are entirely different in these two pathways (Scheme 1.17). The reaction of aromatic ketones with alkenes in the presence of Ru (0) catalyst yielded the ortho alkylated aromatic ketones (Scheme 1.17A).[6b] In contrast, the same reaction in the presence of ruthenium (II) catalyst provided ortho alkenylated aromatic ketones selectively (Scheme 1.17B).[9j]



Scheme 1.17: Ru-catalyzed *ortho* C–H bond functionalization of aromatic ketones with alkenes.

1.10 Transition Metal Catalysts used for C–H Bond Functionalization Reactions

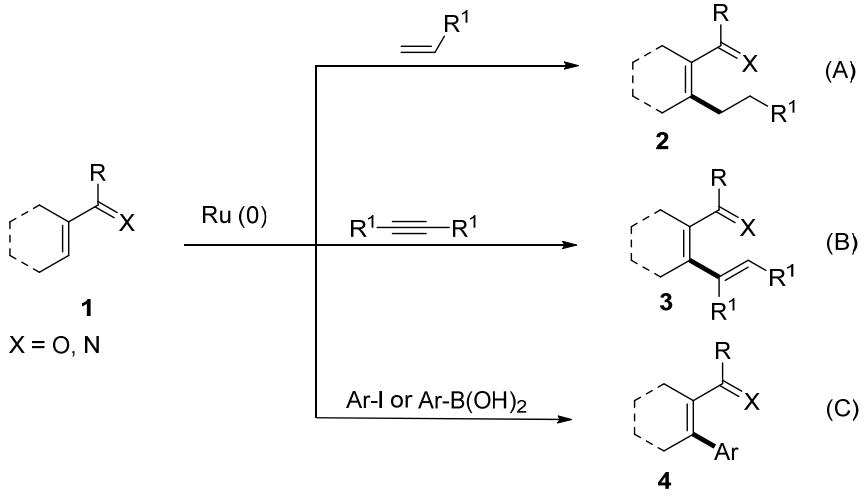
Initially, palladium and rhodium complexes were frequently used for C–H bond functionalization reaction. Later, ruthenium has been widely used as a catalyst for this type of reaction. Very recently, highly cheap and earth-abundant first-row transition metal catalysts like iron, cobalt, and manganese also explored for C–H bond functionalization reactions. However, our focus is ruthenium catalyst, because it is less expensive than palladium and rhodium. In addition, it has superior reactivity towards weak chelating groups substituted aromatics compared to the first-row transition metal catalysts.

In addition, the ruthenium-catalyzed C–H bond functionalization can be done under an air atmosphere, even water can be used as a solvent. Thus, an inert atmosphere is not required for the reaction.

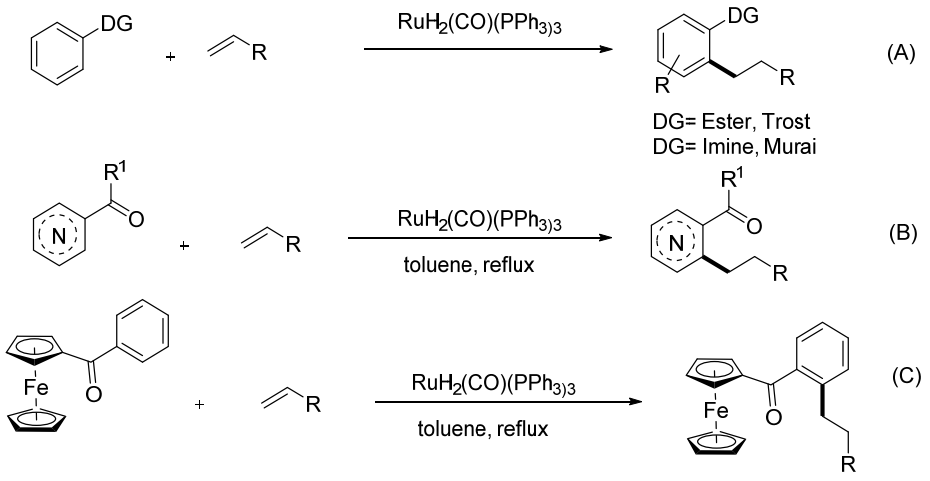
1.11 Earlier Reports in Ruthenium-Catalyzed C–H bond Functioanalization reactions

1.11.1: Ru (0) -Catalyzed C–H Bond Functioanalization Reactions via Oxidative Addition Pathway

Inspired from the Murai's report, the ruthenium (0)- catalyzed C–H bond functioanalization of substituted aromatics via oxidative addition pathway was explored in various functionalizations like alkylation, alkenylation, and arylation using different directing groups by several research groups (Scheme 1.18).[7]



Scheme 1.18: Ru (0)-catalyzed *ortho* C–H bond functionalization of substituted aromatics via oxidative addition pathway.

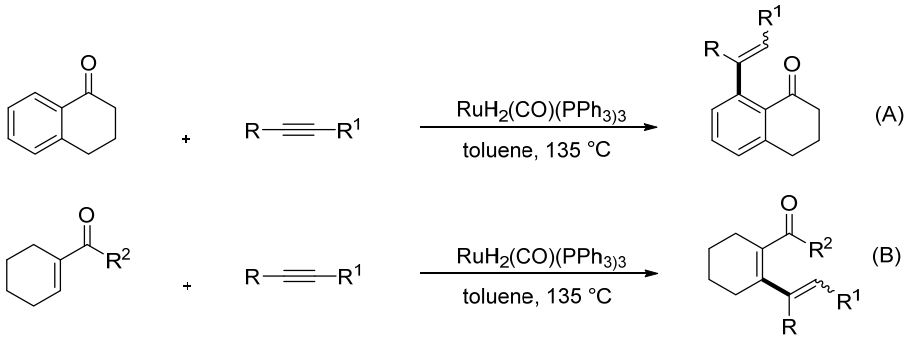


Scheme 1.19: Ru (0)-catalyzed *Ortho*-alkylation of substituted aromatics.

Initially, the ruthenium (0)-catalyzed *ortho*-alkylation of aromatics were explored by using various directing groups (Scheme 1.19). B. M. Trost and co-workers successfully extended the alkylation with ester directing group by using $RuH_2(CO)(PPh_3)_3$.[7b]

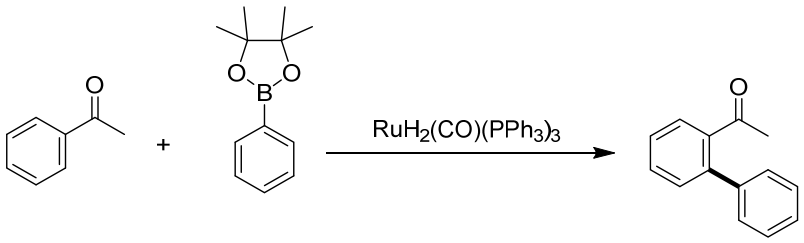
Subsequently, Murai's group has reported *ortho*-alkylation of aromatic imines with alkenes by using the same Ru (0) catalyst.[7c-d] Later, *ortho*-alkylation of aromatic ketones were extended with pyridine[7e] and ferrocene substituted ketones.[7f]

Next, the same Murai's group showed *ortho* alkenylation of aromatic ketones with alkynes in the presence of a ruthenium catalyst. This *ortho*-alkenylation reaction was not completely stereoselective and provided mixture of cis and trans trisubstituted alkenes (Scheme 1.20).[7f-g]



Scheme 1.20: Ru (0)-catalyzed *Ortho*-Alkenylation of aromatic ketones

Later, the *ortho*-arylation of aromatic ketones was also reported by using pinacol ester as an arylating reagent in the presence of a ruthenium (0) catalyst (Scheme 1.21).[7h]

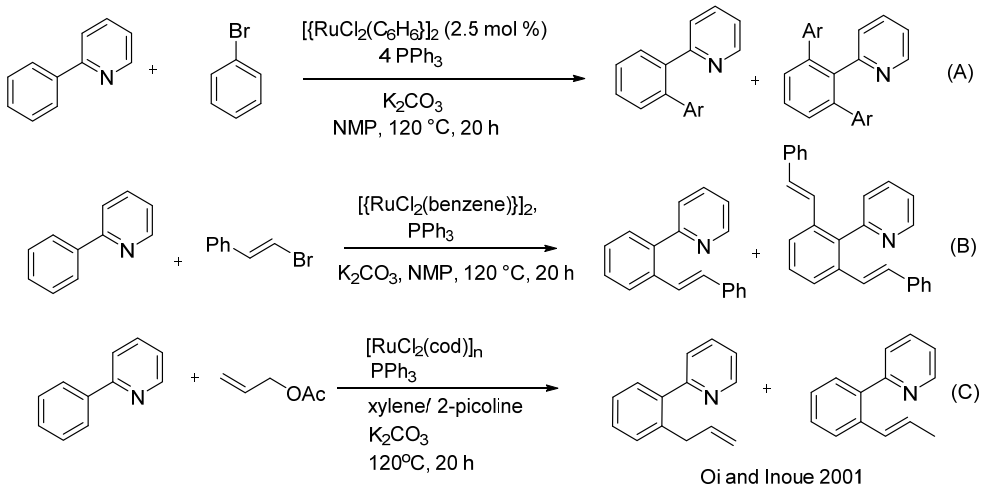


Scheme 1.21: Ru (0)-catalyzed *Ortho*-Arylation of aromatic ketones

The C–H bond activation reaction via oxidative addition pathway started with the Ru (0) catalyst and extended to various metals.[8] This type of reaction has gained much attention for the past two decades and well documented in the literature. However, the C–H bond activation via the deprotonation pathway has gained much attention quite recently.[9]

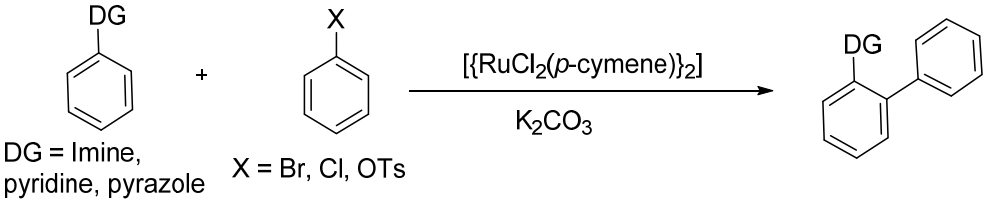
1.11.2: Ru (II) -Catalyzed C–H Bond Functionalization Reactions via Deprotonation Pathway

Generally, ruthenium (II) arene complexes are widely used for C–H bond activation via deprotonation metalation pathway. In 2001, Oi and Inoue have described an efficient *ortho* arylation, alkenylation and allylation of 2-pyridyl benzene with aromatic, vinyl halides and allylic acetates in the presence of a ruthenium (II) catalyst and base (Scheme 1.22).[9a]



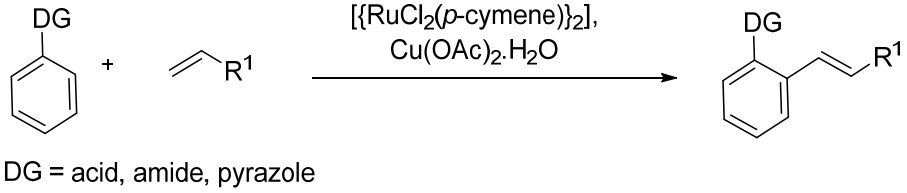
Scheme 1.22: Ru (II)-catalyzed *ortho* C–H bond functionalization of 2-phenyl pyridine.

Later, Ackermann and Dixneuf's groups have explored a similar type of arylation reaction with various strong directing group by using catalytic amount of phosphine ligand (or) carboxylic acid along with [{$RuCl_2$(p-cymene)}$_2$] catalyst and K_2CO_3 base (Scheme 1.23).[9b-e]



Scheme 1.23: Ru (II)-catalyzed *ortho* arylation of strong directing group containing aromatics.

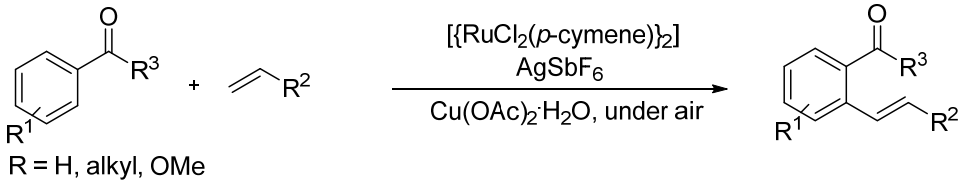
Subsequently, a ruthenium-catalyzed *ortho* alkenylation of carboxylic acids, amides, and 1-phenyl pyrazole with substituted alkenes was explored by Murai, Ackermann, and Dixneuf's groups (Scheme 1.24).[9f-i]



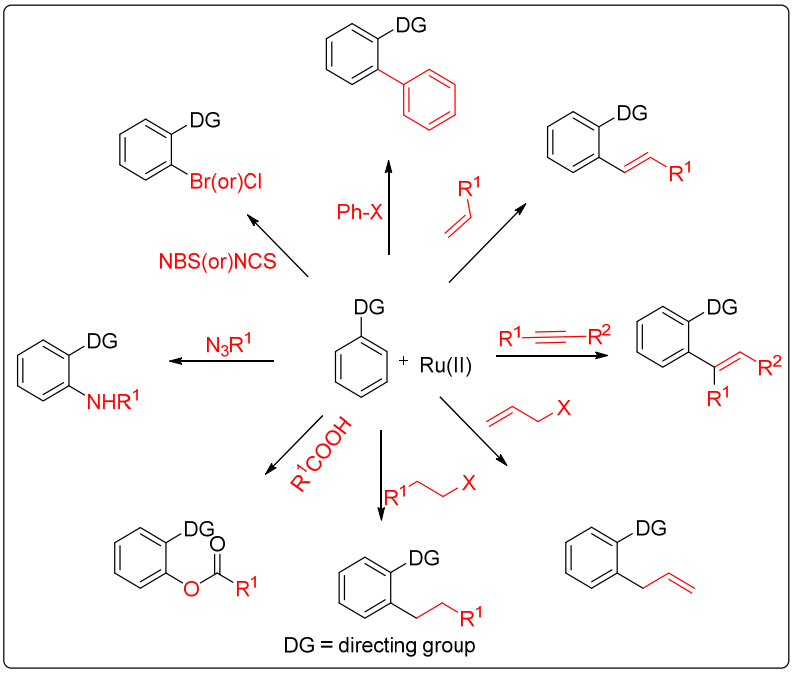
Scheme 1.24: Ru (II)-catalyzed *ortho* alkenylation of strong directing group containing aromatics.

In addition, the ruthenium-catalyzed C–H bond functionalization of the weak chelating group was described by our group (Scheme 1.25).[9j-l] We have disclosed *ortho* alkenylation of aromatic and heteroaromatic aldehyde, ketone, and esters with alkenes in the presence of *in situ* generated cationic ruthenium complex along with the catalytic amount of $Cu(OAc)_2$ as an oxidant. It is important to note that to regenerate the $Cu(OAc)_2$

from the reduced CuOAc, air is needed along with the *in situ* formed AcOH. Thus, these reactions have been done under an air atmosphere.



Scheme 1.25: Ru (II)-catalyzed *ortho* alkenylation of weak directing group containing aromatics.

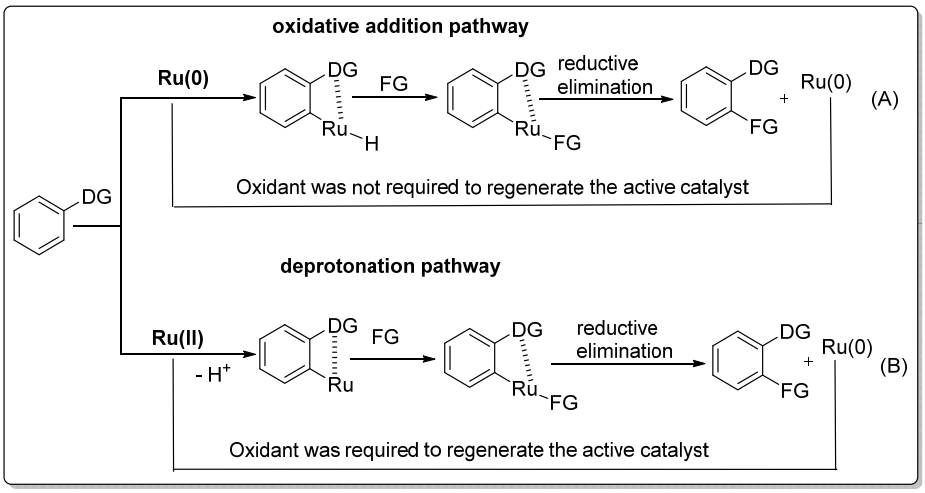


Scheme 1.26: Ru (II)-catalyzed *ortho* C–H bond functionalization of substituted aromatics.

After these reports, the ruthenium-catalyzed C–H bond activation via deprotonation pathway was explored in various functionalizations like alkenylation, arylation, alkylation, allylation, amination, halogenation and benzoxylation with various directing groups by several research groups (Scheme 1.26).[10]

1.12 Regeneration of Active Ruthenium –Catalyst in C–H Bond Functioanalization Reactions

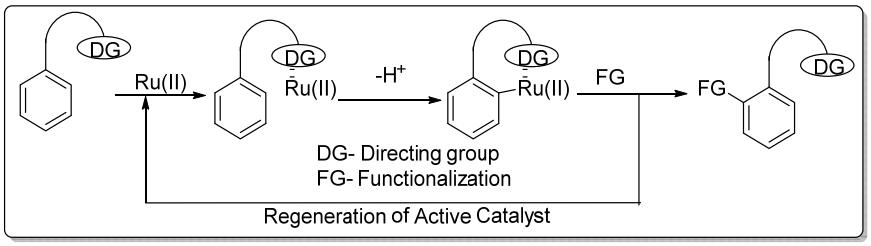
Normally, in the C–H bond functionalization reaction via deprotonation pathway, the oxidation step such as a metal with lower oxidation state into the higher oxidation state [Ru(0) to Ru(II)] is required to regenerate the active catalyst (Scheme 1.27). Generally, a stoichiometric amount of inorganic or organic oxidants such as AgOAc, Ag_2O, $Cu(OAc)_2$, $Fe(OAc)_2$ $PhI(OAc)_2$, benzoquinone, and $K_2S_2O_8$ is required to regenerate the active catalyst.[10] It is one of the major disadvantages in deprotonation pathway.



Scheme 1.27: Regeneration of active Ru (0) and Ru (II) catalysts.

1.13: Ru (II)–catalyzed Redox-neutral C–H Bond Functionalization Reaction

This oxidant can be avoided performing the C–H bond functionalization reaction via the redox-neutral method. Here, the whole catalytic cycle ruthenium (II) oxidation state is maintained and thus the oxidant was not required for this kind of C–H bond functionalization reactions (Scheme 1.28).

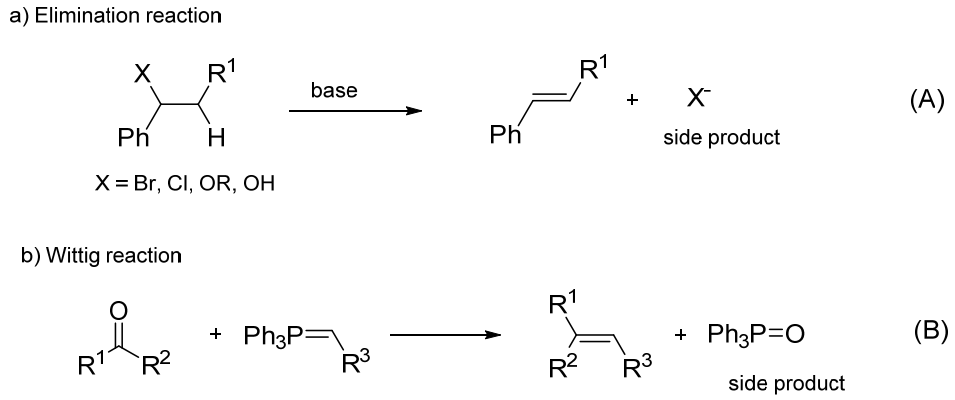


Scheme 1.28: Ru (II)–catalyzed redox-neutral C–H bond functionalization of substituted aromatics.

1.14: Synthesize of Substituted Alkenes and Heterocycles via Ru (II)–Catalyzed Redox-neutral C–H bond Functionalization Reactions

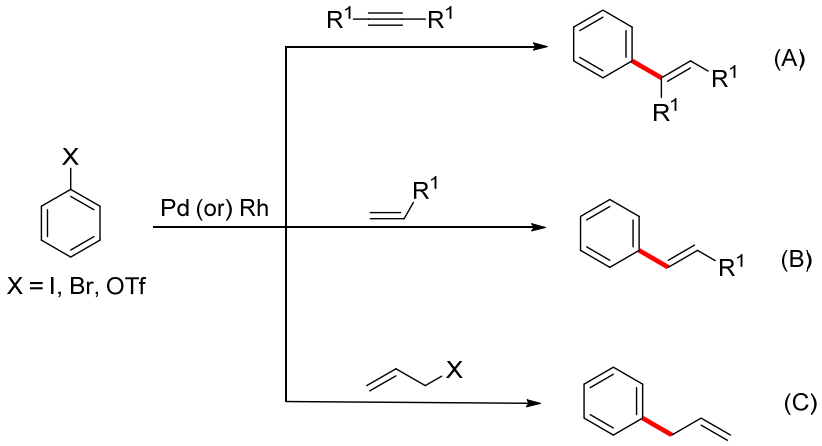
Here, our focus is synthesizing of various substituted alkene derivatives and valuable heterocycles by using ruthenium (II)-catalyzed redox-neutral C–H bond functionalization reactions via deprotonation pathway.

Substituted alkenes are synthetically versatile compounds that have been widely used as key intermediates in various organic transformations and for synthesizing various natural products, heterocyclic molecules, biologically active molecules, and organic materials.[11] In traditionally, alkenes are synthesized by the base-mediated elimination of organic halides or alcohols and the Wittig reaction of carbonyl compounds with organic phosphonium salts (Scheme 1.29).[12]

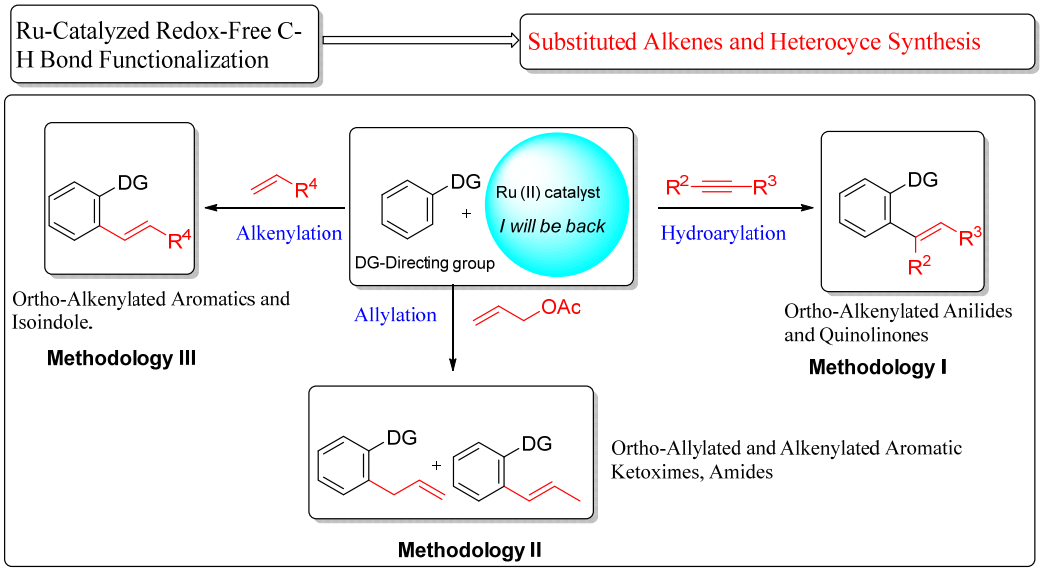


Scheme 1.29: Traditional methods to synthesize of substituted alkene derivatives.

Subsequently, alkenes are efficiently prepared by the cross-coupling of organic halides or organometallic reagents with alkynes, alkenes and allylic electrophiles in the presence of a metal catalyst in a highly regio- and stereoselective manner (Scheme 1.30).[13].



Scheme 1.30: Synthesize of substituted alkene derivatives by cross-coupling reactions.

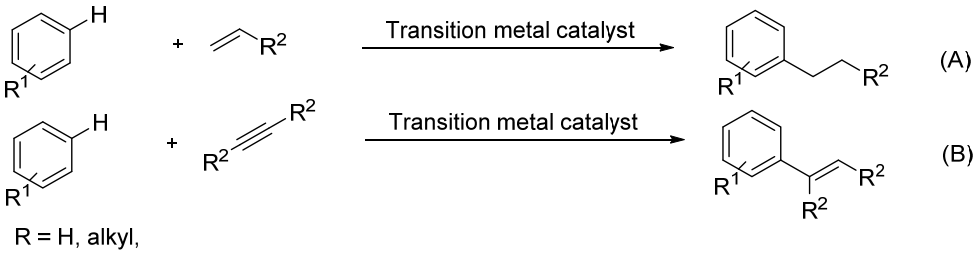


Scheme 1.31: Synthesize of substituted alkene derivatives via Ru (II)–catalyzed redox-neutral C–H bond functionalization reactions.

Very recently, the substituted alkenes also effectively synthesized by the transition metal-catalyzed directing group assisted C–H bond functionalization reactions.[14] However, in most of the reactions oxidant was used to regenerate the active catalyst. Here, our aim is by employing ruthenium-catalyzed redox-neutral C–H bond functionalization reaction, we would like to synthesize variously substituted alkenes and biologically important heterocycles with high regioselectivity without using any oxidant by using three different methodologies (Scheme 1.31).

1.14.1 Methodology I: Ruthenium-Catalyzed Hydro Arylation of Alkynes with Substituted Aromatics

Addition of phenyl ring and hydrogen across the carbon-carbon multiple bonds is called as hydroarylation. Generally, the hydroarylation of alkene gives substituted alkyl derivatives and hydroarylation of alkyne produce substituted alkene derivatives (Scheme 1.32).[14] Hydroarylation of alkynes with substituted aromatics is one of the efficient method to synthesize of trisubstituted alkenes.

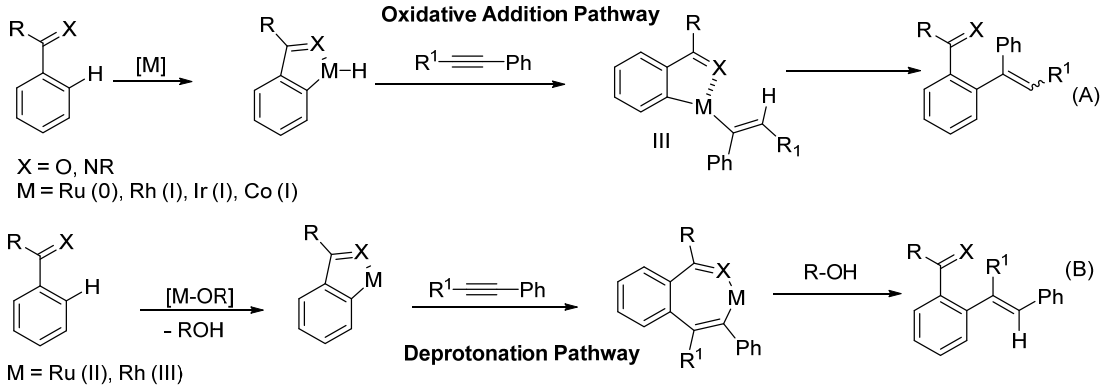


Scheme 1.32: Transition metal-catalyzed hydroarylation of alkenes and alkynes with substituted aromatics

Initially, the hydroarylation of alkyne was done by coupling of aromatic electrophiles or organometallic reagents with alkynes.[13] Instead of using a preactivated partner, a similar type of reaction is done by C–H bond activation, it would be even more attractive in organic synthesis.

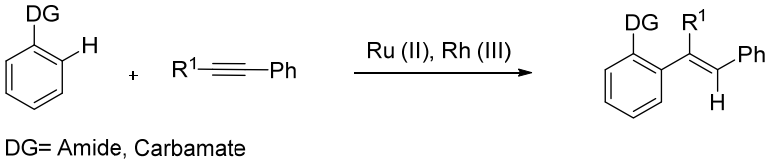
Later, this type of hydroarylation reaction also done via C–H bond activation, with various heteroatom substituted aromatics by several groups in the presence of low valent transition metal catalysts such as Ru, Rh, Ir, Pd, Ni and Co.[14] This hydroarylation reaction mechanistically proceeds via oxidative addition pathway. This reaction is not completely regio- and stereoselective with unsymmetrical alkynes and mostly provides a mixture of alkene derivatives (Scheme 1.33A). This type of regio- and stereoselective problem can

be solved by doing the hydroarylation reaction via chelation-assisted concerted deprotonation-metalation pathway (Scheme 1.33B).[15]

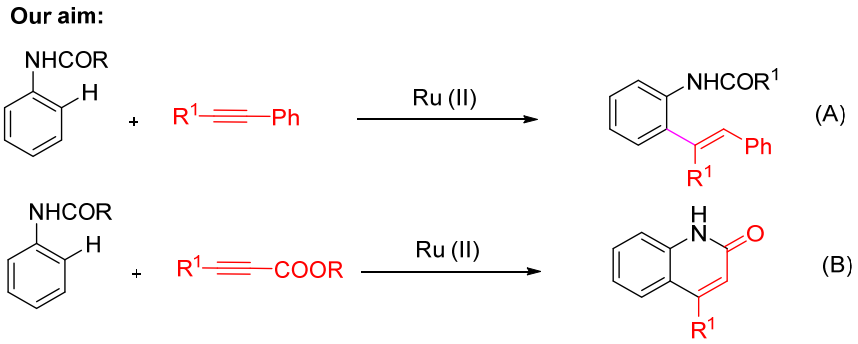


Scheme 1.33: Mechanistic pathways of hydroarylation of alkynes with substituted aromatics

In fact, both reactions proceed entirely in a different mechanistic pathway and also provide the hydroarylation product in a reverse regiochemistry. Very recently, Chelating groups such as amide and carbamate substituted aromatics underwent hydroarylation with alkynes in the presence of ruthenium(II) or rhodium(III) complexes as catalysts, yielding trisubstituted alkenes in a highly regio- and stereoselective manner via deprotonation pathway (Scheme 1.34).[15]



Scheme 1.34: Transition metal-catalyzed hydroarylation of alkynes via deprotonation pathway.

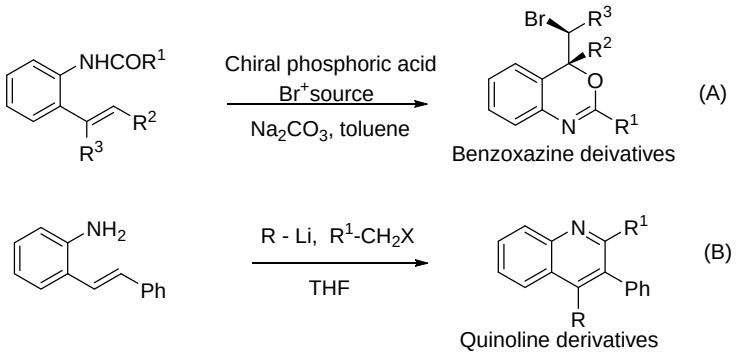


Scheme 1.35: Ru (II)–catalyzed hydroarylation of anilides with alkynes

Here, our aim is to synthesize of highly regio- and stereoselective *ortho*-alkenylated anilines via ruthenium-catalyzed hydroarylation of acetanilides with symmetrical and

unsymmetrical alkynes (Scheme 1.35 A). In addition, by using the same methodology, we have also aimed to synthesize of 2-Quinolinone derivatives by the reaction of acetanilides with substituted propiolates (Scheme 1.35 B).

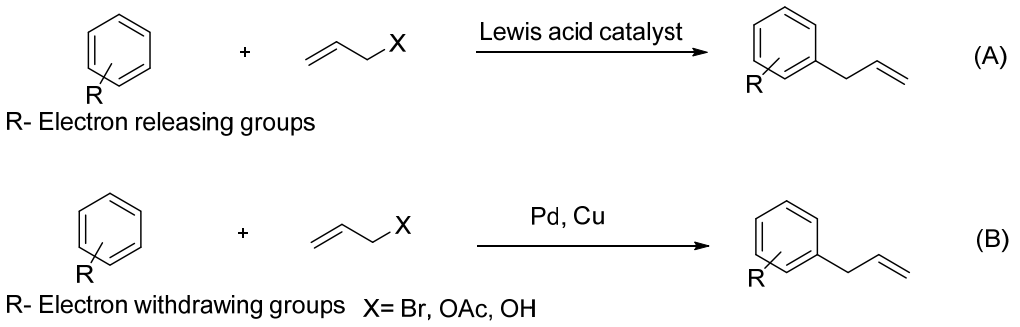
It is also important to note that *ortho*-alkenylated anilines are versatile synthetic precursors in a number of organic transformations and also efficiently used to synthesize biologically active molecules (Scheme 1.36).[16] However, the existing methods for synthesizing of *ortho*-alkenylated aniline derivatives are required multiple steps and harsh reaction conditions.



Scheme 1.36: Synthetic importance of *ortho*-alkenylated aniline derivatives

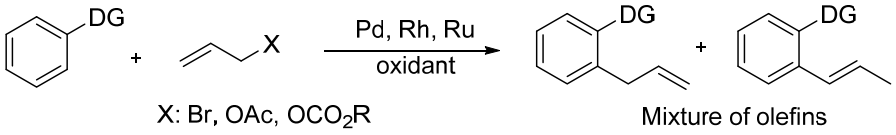
1.14.2 Methodology II: Ruthenium-Catalyzed Oxidant-Free Allylation of Substituted Aromatics with Allylic Acetates

The transition metal-catalyzed allylation at the C–H bond of substituted aromatics with allylic electrophiles is one of the effective methods for synthesizing allyl aromatics in a highly regioselective manner.[19] Allylarenes are widely used as key intermediates for synthesizing various natural products and medicinally relevant molecules.[17] Traditionally, allylarenes are prepared via a Lewis acid-mediated Friedel-Crafts type allylation of electron-rich aromatics with allylic electrophiles (Scheme 1.37 A).[18] Meanwhile, The allylation of electron-deficient polyfluoroarenes with allylic electrophiles was done in the presence of palladium or copper complexes as catalysts via C–H bond activation (Scheme 1.37 B).[19] However, both of these methods are highly suffered by limited substrate scopes.



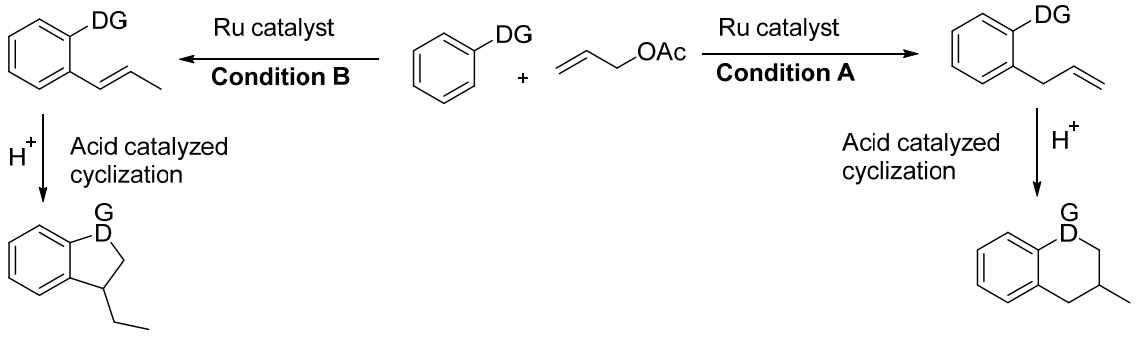
Scheme 1.37: Synthesize of substituted allyl arenes via non-chelation assisted C–H bond functionalization.

By employing the chelating groups, allylation can also be done at the *ortho* C–H bond of substituted aromatics with allylic electrophiles in the presence of various metal catalysts. In these reactions, a stoichiometric amount of oxidant or base or acid was used to activate the C–H bond of aromatics. Further, the high temperature is required for the reaction and also mostly a mixture of double bond migration products were observed (Scheme 1.38).[20]



Scheme 1.38: Synthesize of substituted allyl arenes via chelation assisted C–H bond functionalization.

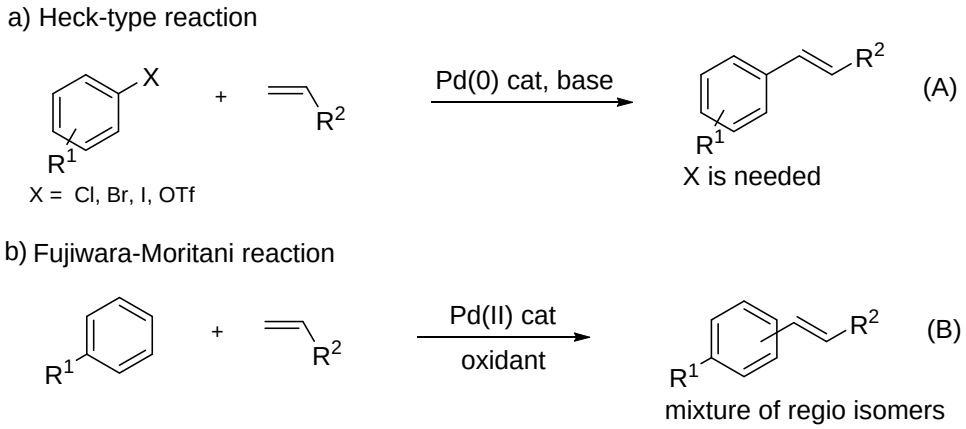
We have planned ruthenium-catalyzed regio-specific synthesize of *ortho* allyl and vinyl substituted arenes via coupling of substituted aromatics with allylic acetates, without using any oxidant at mild reaction conditions. Later, our aim was to convert both *ortho* allyl and vinyl substituted arenes into biologically important heterocycles by employing acid-catalyzed nucleophilic cyclization (Scheme 1.39).



Scheme 1.39: Ru (II)–catalyzed *ortho* allylation of substituted aromatics with allylic acetates.

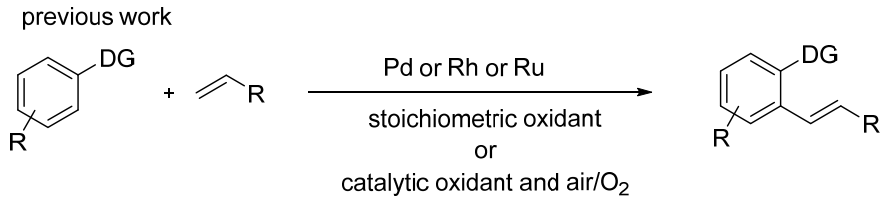
1.14.3 Methodology III: Ruthenium-Catalyzed *ortho* Alkenylation of Aromatics with Alkenes

The transition metal-catalyzed *ortho* alkenylation of substituted aromatics with alkenes is one of the excellent methods to synthesize of disubstituted alkenes in a highly regio- and stereoselective manner. Initially, the disubstituted alkenes are efficiently prepared by the cross-coupling of organic halides or organometallic reagents with alkenes in the presence of a metal catalyst in a highly regio- and stereoselective manner (Scheme 1.40 A).[2]. Alternatively, vinyl arenes are also efficiently prepared by the dehydrogenative coupling of electron-rich aromatics or heteroaromatics with alkenes in the presence of a metal catalyst in a highly atom economical manner (Scheme 1.40 B).[3] However, controlling the regioselectivity is a key issue in the Fujiwara–Moritani type reaction.



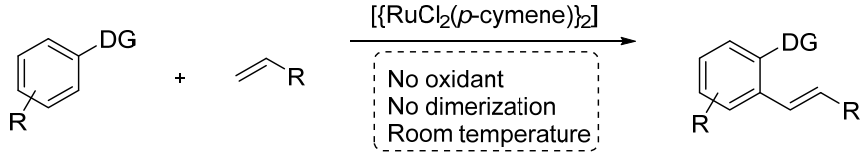
Scheme 1.40: Palladium–catalyzed alkenylation of substituted aromatics with alkenes.

Transition metal-catalyzed chelation-assisted alkenylation at the inactive C–H bond of aromatics, alkenes, and heteroaromatics with alkenes is an efficient method for synthesizing vinyl arenes in a highly regio- and stereoselective manner.[21] This method is highly atom-economical and environmentally friendly as compared with the classical cross-coupling of organic electrophiles or organometallic reagents with alkenes. Till now, in the reported transition metal-catalyzed alkenylation reaction, a stoichiometric amount of $Cu(OAc)_2$ or a catalytic amount of $Cu(OAc)_2$ along with air or oxygen oxidant was used (Scheme 1.41).[21] In addition, in the ruthenium-catalyzed alkenylation reaction, a higher reaction temperature is required. Due to a higher reaction temperature, in the alkenylation of substituted aromatics with alkenes, the dimerization of alkenes was observed as a side product in most of the cases.



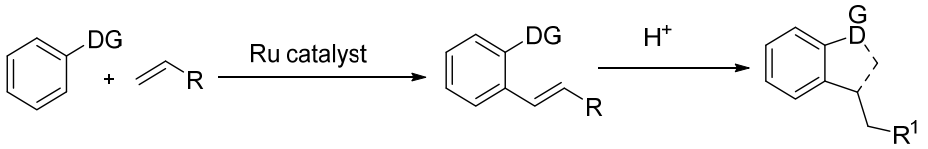
Scheme 1.41: Transition metal-catalyzed *ortho* alkenylation of substituted aromatics with alkenes.

We have decided to develop a convenient protocol for the alkenylation reaction such as alkenylation at room temperature, avoiding oxidants and suppressing the formation of alkene dimerization (Scheme 1.42).



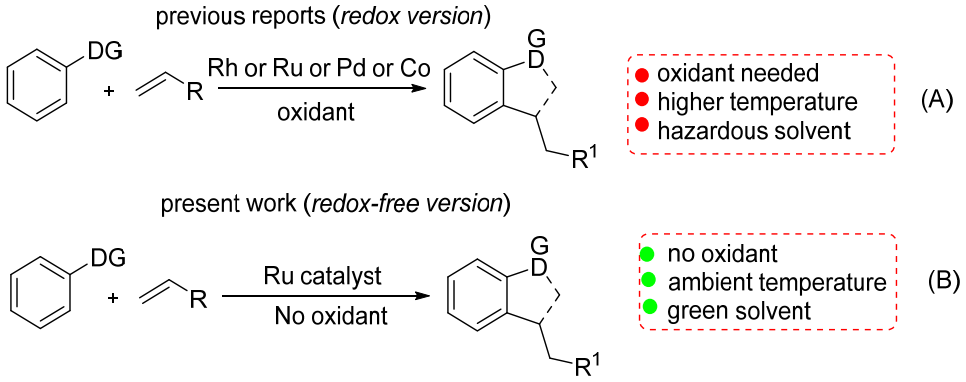
Scheme 1.42: Ru (II)-catalyzed oxidant-free *ortho* alkenylation of substituted aromatics with alkenes.

Ruthenium-catalyzed alkenylation followed by cyclization of aromatics and heteroaromatics with alkenes is the powerful method to synthesize nitrogen and oxygen-containing heterocyclic molecules in one pot (Scheme 1.43).[21] In the reaction, alkenylation takes place at the *ortho* C–H bond of aromatics followed by the nucleophilic addition of heteroatom of directing group to the olefinic bond followed by protonation providing the cyclic product. By employing this protocol, various heterocycle molecules were prepared efficiently.



Scheme 1.43: Ru (II)-catalyzed oxidant-free *ortho* alkenylation followed by cyclization of substituted aromatics with alkenes.

However, most of the reported reactions required higher reaction temperature, oxidant and hazardous solvent (Scheme 1.44 A).[21]Our main focus was to synthesize nitrogen-containing heterocyclic molecules by using, redox-neutral ruthenium (II)-catalyzed oxidative cyclization of substituted aromatics with alkenes in green solvent at ambient temperature (Scheme 1.44 B).



Scheme 1.44: Ru (II)-catalyzed oxidant-free *ortho* alkenylation followed by cyclization of substituted aromatics with alkenes.

1.15: References

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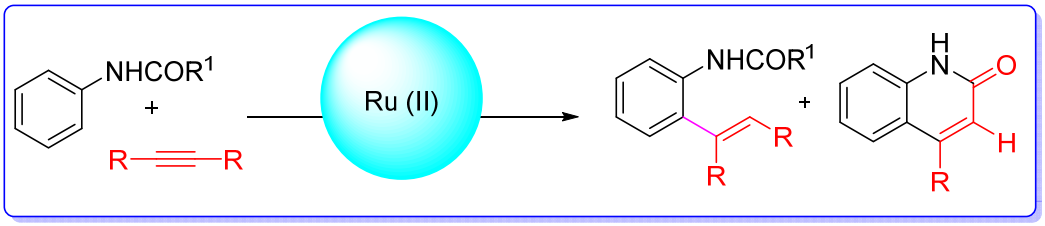
Chapter-2



Ruthenium-Catalyzed Highly Regio- and Stereoselective Hydroarylation of Alkynes with Anilides: an Efficient Route to *ortho*-Alkenylated Anilines and 2-Quinolinones

Section 2A: Ruthenium-Catalyzed Hydroarylation of Anilides with Alkynes: an Efficient Route to *ortho*-Alkenylated Anilines

2A.1 Introduction

The transition metal-catalyzed hydroarylation of alkynes with substituted aromatics is one of the convenient routes to synthesize tri-substituted alkenes in a highly regio- and stereoselective manner.[1] Substituted alkenes are versatile synthetic precursors which are widely used for several organic transformations. Alkene unit is also present in various drug molecules and materials (Figure 1).[1]

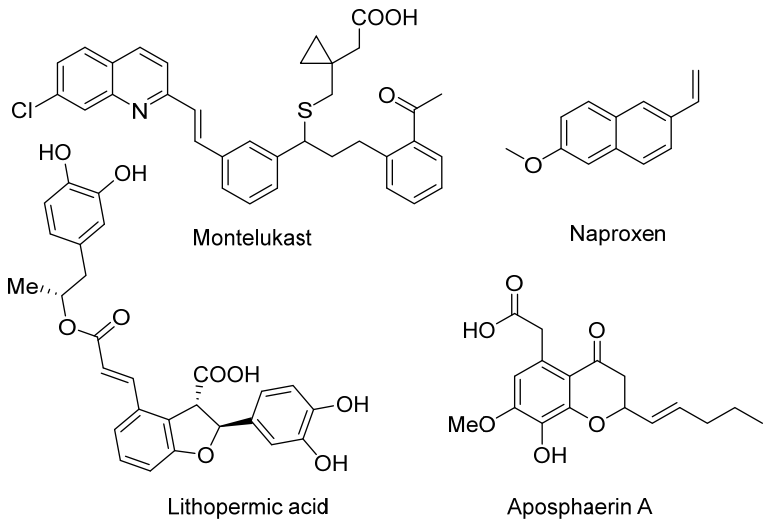
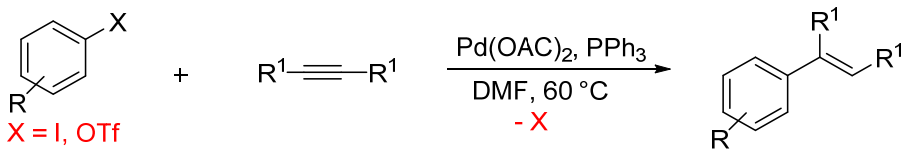


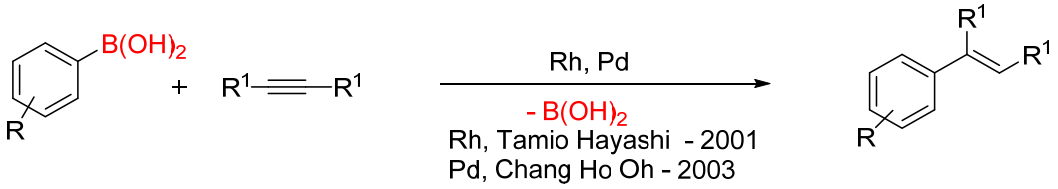
Figure 1: Selected biologically active molecules containing alkene structural units.

Initially, the hydroarylation of alkyne was done by the cross-coupling reaction using aromatic halides or triflates or organometallic reagents as a coupling partner.[2] In 1999, Cacchi's group has reported the hydroarylation of alkynes with aromatic halides and triflates in the presence of a palladium catalyst. This method provides highly useful substituted alkene derivatives in a highly stereoselective manner (Scheme 2A.1).[2a]



Scheme 2A.1: Transition metal-catalyzed hydroarylation of alkynes with aryl halides.

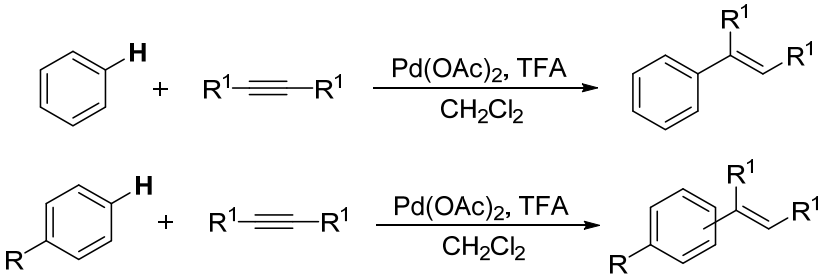
Later, Hayashi's group has showed a rhodium-catalyzed hydroarylation of alkynes with aryl boronic acids as a coupling partner.[2b] Subsequently, Oh's group described a palladium-catalyzed hydroarylation of alkynes with organoboronic acids and the mechanistic studies were done based on the isotope-labelling study(Scheme 2A.2).[2c.]



Scheme 2A.2: Transition metal-catalyzed hydroarylation of alkynes with aryl boronic acids.

After these initial reports, the hydroarylation of alkyne was done by using various metal complexes such as palladium, nickel, cobalt, rhodium and ironwith preactivated coupling partners such as aromatic halides or triflates or organometallic reagents. Although this type of coupling reaction is excellent method to synthesize substituted alkenes, a preactivated coupling partner is usually required on the aromatic moiety. A preactivated species waswasted at end of the reaction. If a similar type of reaction is carried out directly by activating the C–H bond of aromatic moiety, it would be more useful in organic synthesis. Because, this method would be highly atom- and step economical as well as an environmentally friendly process.

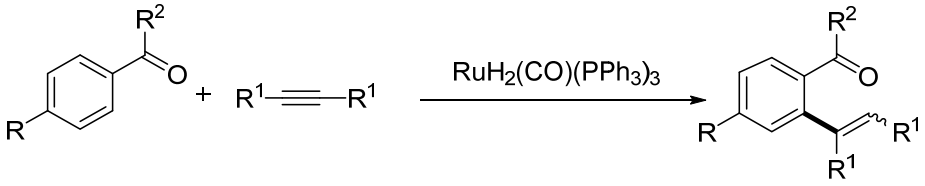
Fujiwara's group reported the hydroarylation of alkynes with simple arenes in the presence of a palladium catalyst. This method provides the highly atom-economical route for synthesizing substituted alkene derivatives. However, the regioisomeric mixtures were observed in the case of substituted arenes (Scheme 2A.3).[2d]



Scheme 2A.3: Transition metal-catalyzed hydroarylation of alkynes with substituted arenes.

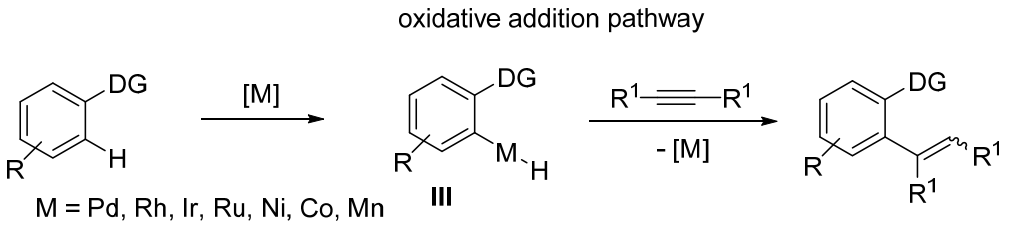
The selective C–H bond functionalization reaction was achieved on the C–H bond of substituted aromatics by assisting the directing group. In 1993, Murai's group demonstrated an *ortho*

alkenylation of aromatic ketones with alkynes, leading to trisubstituted alkenes in the presence of a ruthenium catalyst (Scheme 2A.4).[2e]



Scheme 2A.4: Ruthenium-catalyzed hydroarylation of alkynes with aromatic ketones.

The hydroarylation reaction proceeds via a chelation-assisted oxidative addition of *ortho* C–H bond of aromatic ketone with a ruthenium catalyst providing a five-membered hydrometallacycle intermediate **III**. Later, an alkyne undergoes coordinative insertion into a metal-hydride bond of intermediate **III** followed by reductive elimination, providing a trisubstituted alkene derivative and regenerates a active Ru(0) catalyst for the next catalytic cycle. However, this type of hydroarylation reaction is not completely regio- and stereoselective. Mostly, a mixture of regio- and stereoisomeric trisubstituted alkenes were observed (Scheme 2A.5).[4]

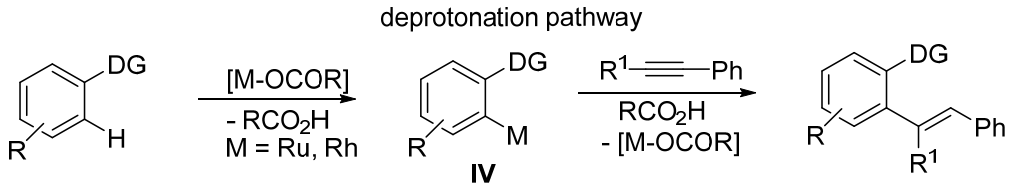


Scheme 2A.5: Transition metal-catalyzed hydroarylation of alkynes via oxidative addition pathway.

Later, Murai's group has extended the hydroarylation of alkyne with various directing groups such as ester, nitrile and aldehyde in the presence of a ruthenium catalyst.[3] Subsequently, a similar type of hydroarylation of heteroatom substituted aromatics with alkynes has been well explored by using various low valent metal complexes such as rhodium, iridium, palladium, nickel, cobalt and manganese.[3]Although it is one of the best methods to synthesize trisubstituted alkenes in one pot, however the observation of a mixture of *cis* and *trans* stereoisomeric and regioisomeric products limits synthetic application of this transformation in organic synthesis.

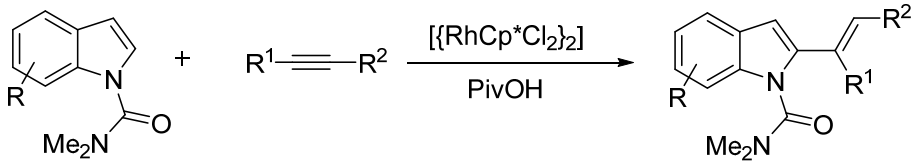
This type of regio- and stereoisomeric issues can be easily overcome by performing the hydroarylation reaction via a concerted deprotonation metalation pathway. In the reaction,

substituted aromatics reacted with alkynes in the presence of a ruthenium catalyst, providing trisubstituted alkene derivatives in a highly regio- and stereoselective manner without using any metal oxidant. The catalytic reaction proceeds via a chelation-assisted acetate accelerated deprotonation at the *ortho* C–H bond of hetero atom substituted aromatic with a metal complex (Rh or Ru), providing a metallacycle intermediate **IV**. Coordinative insertion of an alkyne into the metal–carbon bond of metallacycle followed by protonation in the presence of organic acid provides trisubstituted alkene derivative in a highly regio- and stereoselective manner (Scheme 2A.6).[5]



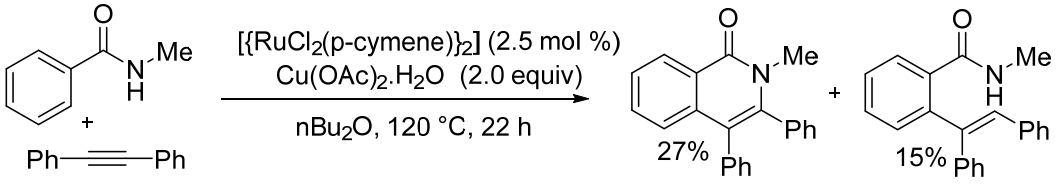
Scheme 2A.6: Transition metal-catalyzed hydroarylation of alkynes via deprotanation pathway.

In 2010, Fagnou's group reported a rhodium-catalyzed hydroarylation of symmetrical and unsymmetrical alkynes with *N*-substituted indoles in the presence of pivalic acid via a concerted deprotonation metalation pathway (eq. 2A.7).[5a]



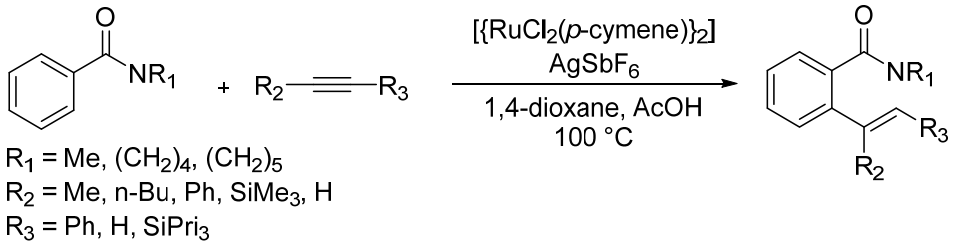
Scheme 2A.7: Rhodium-catalyzed hydroarylation of alkynes with substituted indoles

Subsequently, Ackermann's group was observed a minor amount of *ortho* alkenylated benzamide along with isoquinolone derivative, in the reaction of *N*-methyl benzamide with diphenylacetylene in the presence of ruthenium catalyst and $Cu(OAc)_2 \cdot H_2O$. This result clearly reveals that the *N*-methyl benzamides prefer cyclization reaction with alkynes rather than the hydroarylation reaction (Scheme 2A.8).[5b]



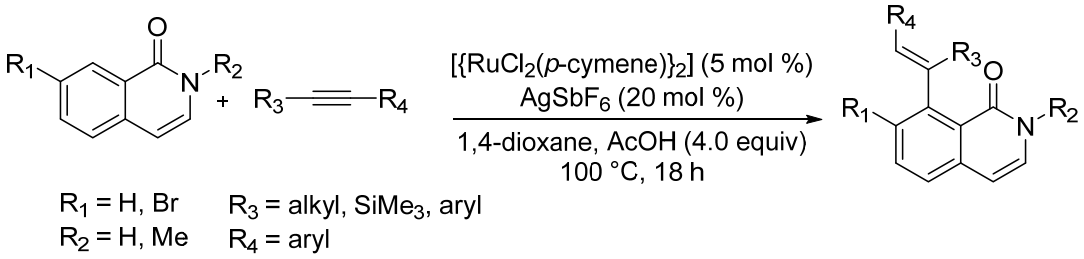
Scheme 2A.8: Ruthenium-catalyzed hydroarylation of alkynes with secondary amides

In 2012, Miura's group showed a highly regio- and stereoselective hydroarylation of alkynes with substituted benzamides, providing trisubstituted alkenes in a good to excellent yields (Scheme 2A.9).[5c]



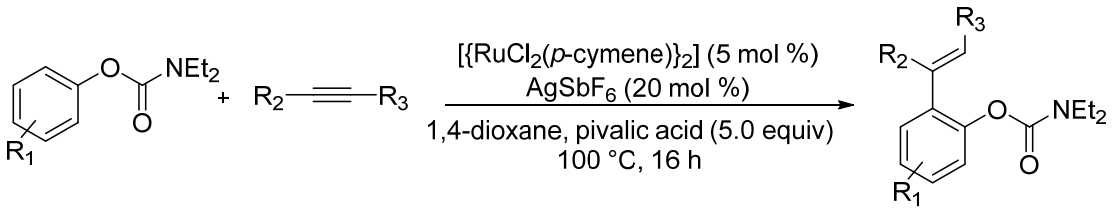
Scheme 2A.9: Ruthenium-catalyzed hydroarylation of alkynes with tertiary amides

In the same year, Li's group reported a ruthenium-catalyzed hydroarylation of alkynes with biologically important isoquinolone derivatives in the presence of acetic acid (Scheme 2A.10).[5d]



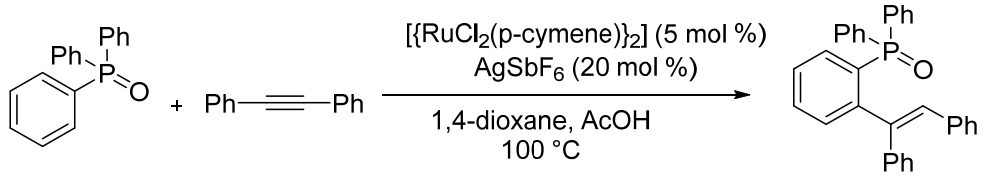
Scheme 2A.10: Ruthenium-catalyzed hydroarylation of alkynes with isoquinolone derivatives.

Later, Jeganmohan and co-workers described the hydroarylation of alkynes with weakly co-coordinating carbonyl group assisted aryl carbamates in the presence of a ruthenium catalyst and pivalic acid (Scheme 2A.11).[5e]



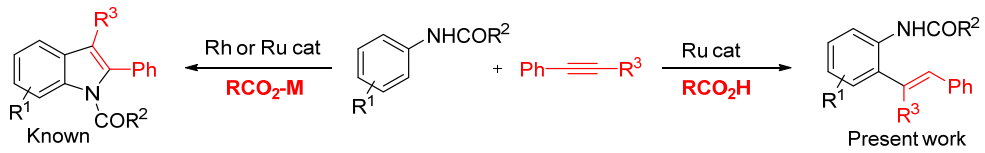
Scheme 2A.11: Ruthenium-catalyzed hydroarylation of alkynes with aryl carbamates.

In the same year,Miura's group demonstrated a ruthenium-catalyzed hydroarylation of alkynes with unexploredphenylphosphine oxides as a directing group (Scheme 2A.12).[5f]



Scheme 2A.12: Ruthenium-catalyzed hydroarylation of alkynes with phenylphosphine oxides.

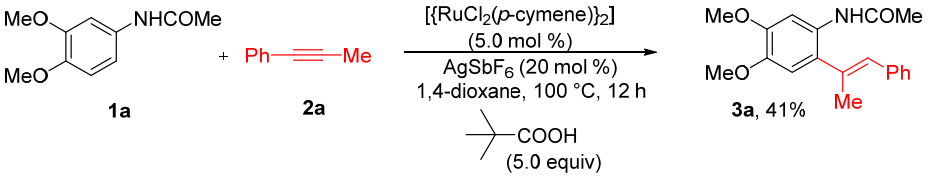
Herein, we report a highly regio- and stereoselective ruthenium-catalyzed hydroarylation of acetanilides with symmetrical and unsymmetrical alkynes. The catalytic reaction provides *ortho*-alkenylated anilides in good to excellent yields. The alkyne substituents decide the regiochemistry of the product. Coordinating groups such as Ph or ester from the alkynes are *trans* to the anilides. Later, *ortho*-alkenylated anilides were converted into *ortho*-alkenylated anilines in the presence of HCl. It is important to note that *ortho*-alkenylated anilines are versatile synthetic precursors in a number of organic transformations and also efficiently used to synthesize biologically active molecules. It is known that acetanilides reacted with alkynes in the presence of rhodium or ruthenium catalysts and acetate base to give indole derivatives (Scheme 2A.13).[5g] Interestingly, if the same reaction is done in the presence of organic acid instead of a base, a different type of *ortho*-alkenylated anilides are observed. It is interesting to note that organic acids or acetate base completely changes the reaction pattern.



Scheme 2A.13: Rhodium and ruthenium-catalyzed reaction of anilide with alkyne

2A.2 Results and Discussion

Initially, the hydroarylation of 3,4-dimethoxy aniline with 1-phenyl-1-propyne (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (5.0 equiv) in 1,4-dioxane at 100 °C for 12 h was carried out. However, in the reaction, no expected *ortho*-alkenylated aniline was observed. Next, the hydroarylation reaction was tested with anilines having a removable directing group at the nitrogen atom such as acetanilide **1a** (NH-COMe), sulfonamide (NH-SO_2Me) and aryl urea (NHCONMe_2). In the reaction of acetanilide **1a** with **2a**, hydroarylation product **3a** was observed in 41% yield (Scheme 2A.14). In other substrates, no hydroarylation products were observed. The hydroarylation reaction of **1a** and **2a** is highly regio- and stereoselective, a less hindered C–H bond of **1a** coupled with the methyl substituted carbon of alkyne **2a.**

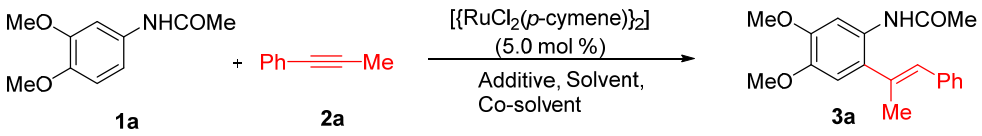


Scheme 2A.14: Ruthenium-catalyzed hydroarylation of alkyne with aromatic anilide.

2A.3 Optimization studies

To increase the yield of hydroarylation product **3a**, the reaction of 3,4-dimethoxy acetanilide (**1a**) with **2a** in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) with various organic acids and solvents were examined(Table 2A.1). First, the reaction was examined in various solvents such as *iso*-PrOH, *tert*-amyl alcohol, trifluoroethanol, DCE, THF, DMSO, DMF, CH_3CN and toluene in the presence of pivalic acid (5.0 equiv). Among them, *iso*-PrOH was very effective giving **3a** in 93% GC yield. *tert*-Amyl alcohol and trifluoroethanol were partially effective affording **3a** in 75% and 65% yields, respectively. DCE and THF were less effective yielding product **3a** in 32% and 40% yields, respectively.

Table 2A.1: Optimization Studies with Various Additive, Solvent and Cosolvent.



entry	solvent	cosolvent	additive	yield of **3a** (%)[b]
1	Isopropanol	No	$AgSbF_6$	5
2	Isopropanol	Pivalic acid (2.0 equiv)	$AgSbF_6$	74
3	Isopropanol	Acetic acid (2.0 equiv)	$AgSbF_6$	51
4	Isopropanol	Mesitylenic acid (2.0 equiv)	$AgSbF_6$	12
5	Isopropanol	1-Adamantane carboxylic acid (2.0 equiv)	$AgSbF_6$	NR
6	Isopropanol	Acetic acid (5.0 equiv)	$AgSbF_6$	60
7	Isopropanol	Mesitylenic acid (5.0 equiv)	$AgSbF_6$	25
8	**Isopropanol**	**Pivalic acid (5.0 equiv)**	**$AgSbF_6$**	**93**
9	Isopropanol	Pivalic acid (10.0 equiv)	$AgSbF_6$	93
10	Isopropanol	Pivalic acid (5.0 equiv)	AgOTf	73
11	Isopropanol	Pivalic acid (5.0 equiv)	$AgBF_4$	58
12	Isopropanol	Pivalic acid (5.0 equiv)	KPF_6	NR
13	*tert*-amyl alcohol	Pivalic acid (5.0 equiv)	$AgSbF_6$	75
14	trifluoroethanol	Pivalic acid (5.0 equiv)	$AgSbF_6$	65
15	THF	Pivalic acid (5.0 equiv)	$AgSbF_6$	40
16	$ClCH_2CH_2Cl$	Pivalic acid (5.0 equiv)	$AgSbF_6$	32
17	DMSO	Pivalic acid (5.0 equiv)	$AgSbF_6$	NR
18	Toluene	Pivalic acid (5.0 equiv)	$AgSbF_6$	NR
19	DMF	Pivalic acid (5.0 equiv)	$AgSbF_6$	NR
20	CH_3CN	Pivalic acid (5.0 equiv)	$AgSbF_6$	NR
21	DME	Pivalic acid (5.0 equiv)	$AgSbF_6$	NR

[a]All reactions were carried out under the following conditions: **1a** (100 mg), **2a** (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), additive (20 mol %) and co-solvent (specified) in solvent (2.5 mL) at 100 °C for 12 h under N_2 atmosphere. [b]GC yield.

Note: The catalytic reaction was tried without ruthenium and $AgSbF_6$. No product **3a** was observed.

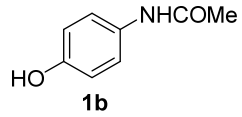
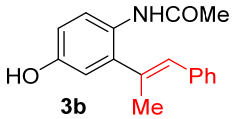
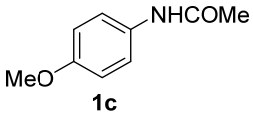
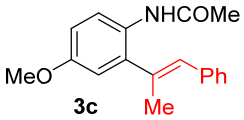
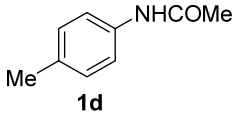
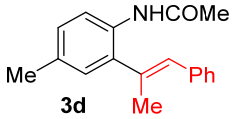
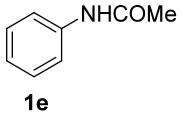
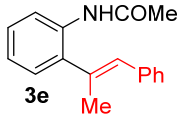
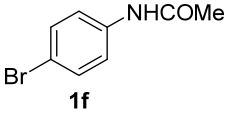
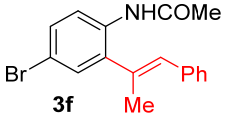
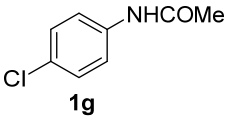
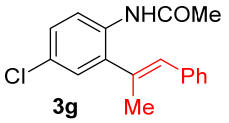
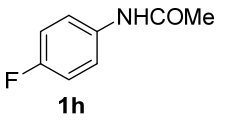
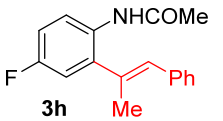
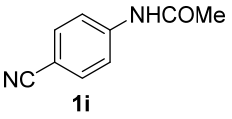
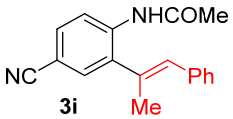
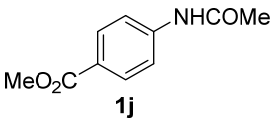
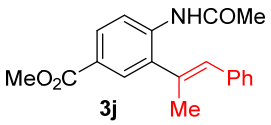
Remaining solvents were totally ineffective. Next, various organic acids (5.0 equiv) such as acetic acid, 3,5-dimethylbenzoic acid, pivalic acid and 1-adamantanecarboxylic acid were examined in *iso*-PrOH solvent. Among them, pivalic acid was very effective giving product **3a** in 93% yield. Acetic acid and 3,5-dimethylbenzoic acid were partially effective providing **3a** in 60% and 25% yields, respectively. But, 1-adamantane carboxylic acid was totally ineffective. The amount of organic acid is also highly important for the reaction. 2.0 equiv of Pivalic acid provides **3a** in 74% yield. But, 5.0 equiv or 10.0 equiv of pivalic acid affords product **3a** in same 93% yield. The catalytic reaction was examined without ruthenium catalyst and silver salt. In these reactions, no desired product **3a** was formed.

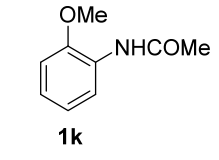
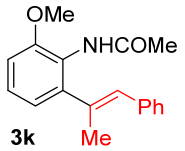
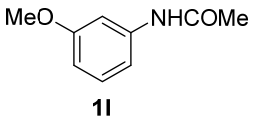
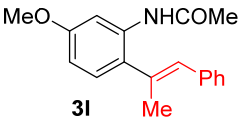
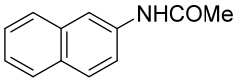
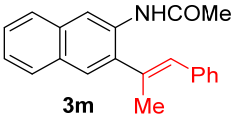
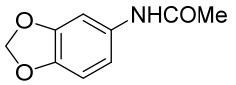
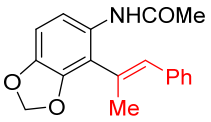
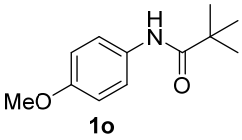
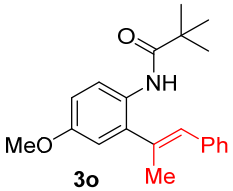
2A.4 Scope of Substituted Aromatic Anilides

The scope of the catalytic reaction was tested with various substituted anilides**1b-o** (Table 2A.2). The reaction was compatible with various functional groups such as OMe, F, Cl, Br, I, ester, CN and OH substituted anilides. Thus, electron-donating group such as OH, OMe and Me substituted anilides**1b-d** reacted efficiently with **2a** yielding hydroarylation products **3b-d** in 78%, 85%, 81% yields, respectively, in a highly regio- and stereoselective manner (entries 1-3). It is very interesting to note that a free hydroxyl group substituted acetanilide **1b** was also effective for the reaction. Acetanilide (**1e**) reacted nicely with **2a** giving product **3e** in 80% yield (entry 4). Halogen groups such as Br, Cl and F substituted anilides**1f-h** also efficiently participated in the reaction, providing products **3f-h** in 79%, 76% and 69% yields, respectively, in a highly regio- and stereoselective manner (entries 5-7). A less reactive electron-withdrawing group such as CN or ester substituted anilides**1i** and **1j** also reacted efficiently with **2a** giving trisubstituted alkenes **3i** and **3j** in 68%, and 71% yields, respectively (entries 8 and 9). The regiochemistry of **3j** was assigned based on the NOESY experiment. It is also important to note that CN and ester groups are known as a directing group for C–H bond activation reaction.[2] The present result shows that NHCOMe is a best directing group for the reaction compared with ester and CN. Sterically hindered *ortho*-methoxy acetanilide **1k** was effectively involved in the reaction, giving product **3k** in 84% yield (entry 10). Next, the reaction was tested with unsymmetrical acetanilides**1l-n**. A sterically less hindered C–H bondof *meta*-methoxy acetanilide **1l** and 2-napthyl acetamide**1m** underwent hydroarylation with **2a** providing alkene derivatives **3l** and **3m** in excellent 83% and 82% yields, respectively (entries 11 and 12). The structure of **3l** was confirmed by a single

crystal X-ray diffraction. In contrast, in the reaction of 3,4-(Methylenedioxy)anilide (**1n**) with **2a**, hydroarylation takes place at a sterically hindered C–H bond of **1n**, yielding product **3n** in 81% yield (entry 13). The hydroarylation reaction was tested with 4-methoxyphenyl pivalamide (**1o**). In the reaction, product **3o** was observed in 20% yield (entry 14).

Table 2A.2 The Hydroarylation of Substituted Anilides **1b-o** with 1-Phenyl-1-propyne (**2a**)[a]

Entry	Aromatic amide (1)	Compound (3)	Yield[b]
1	 **1b**	 **3b**	78%
2	 **1c**	 **3c**	85%[c]
3	 **1d**	 **3d**	81%[d]
4	 **1e**	 **3e**	80%[d]
5	 **1f**	 **3f**	79%
6	 **1g**	 **3g**	76%
7	 **1h**	 **3h**	69%
8	 **1i**	 **3i**	68%
9	 **1j**	 **3j**	71%

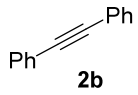
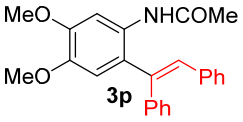
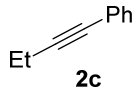
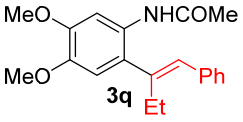
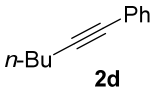
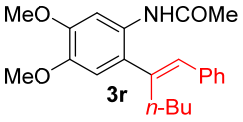
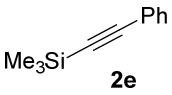
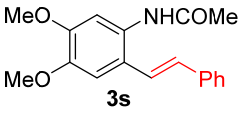
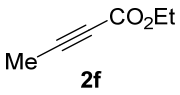
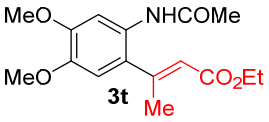
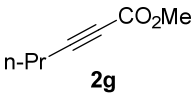
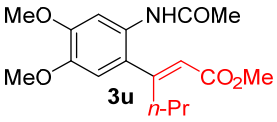
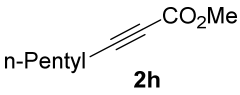
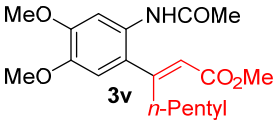
10	 **1k**	 **3k**	84%
11	 **1l**	 **3l**	83%
12	 **1m**	 **3m**	82%
13	 **1n**	 **3n**	81%
14	 **1o**	 **3o**	20%

[a]All reactions were carried out using **1b-o** (100 mg), 1-phenyl-1-propyne (**2a**) (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv) and pivalic acid (5.0 equiv) in *iso*-PrOH (2.5 mL) at 100 °C for 12 h. [b]Isolated yield. [c]Thereaction was carried out for 4 h. [d]Thereaction was carried out for 3 h.

2A.5 Scope of Alkynes

The scope of the catalytic reaction was further examined with substituted alkynes **2b-k** (Table 2A.3). Thus, diphenylacetylene (**2b**), 1-phenyl-1-butyne (**2c**), 1-phenyl-1-hexyne (**2d**) and 1-phenyl-2-(trimethylsilyl) acetylene (**2e**) reacted very selectively at the sterically less hindered C–H bond of **1a** providing alkene derivatives **3p-s** in 87%, 83%, 81% and 61% yields, respectively (entries 1-4). In alkynes **2c-d**, aromatic C–H bond of **1a** selectively inserted at the alkyl substituted carbon of alkynes. In the product **3s**, sensitive $SiMe_3$ was cleaved under the reaction conditions. Interestingly, ethyl 2-butynoate (**2f**), methyl hex-2-ynoate (**2g**) and methyl oct-2-ynoate (**2h**) also nicely participated in the reaction, yielding products **3t-v** in 88%, 80%, 78% yields, respectively (entries 5-7). In these reactions also, alkyl substituted carbon of alkynes **2f-h** was regioselectively connected at the *ortho* carbon of **1a**. The regiochemistry of **3t** was assigned based on the NOESY experiment.

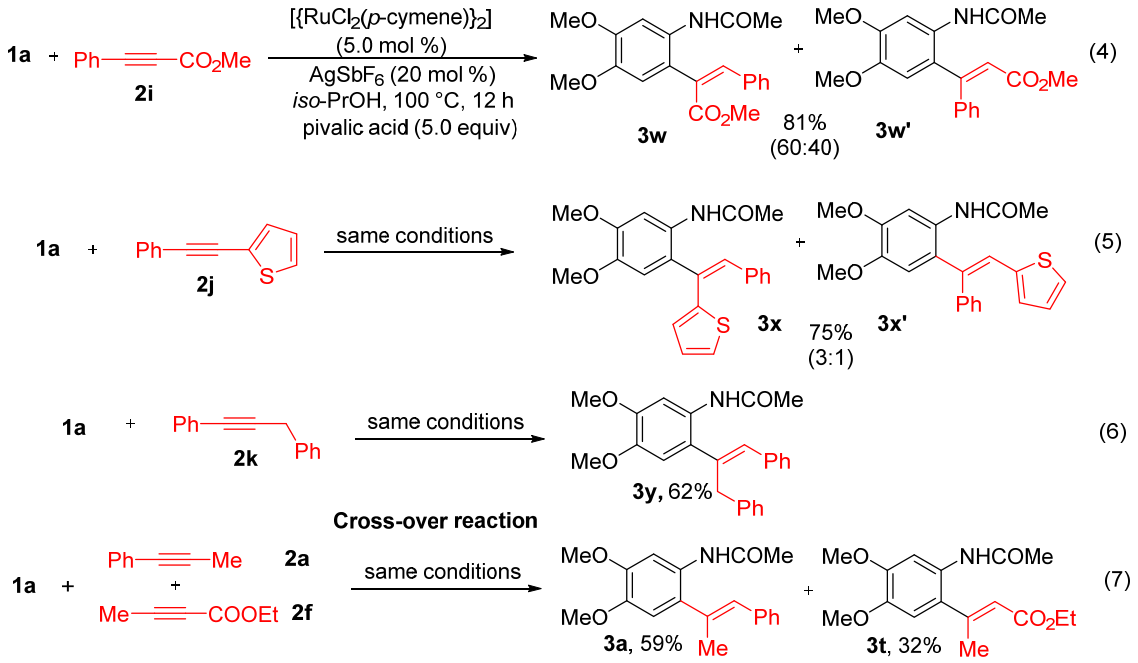
Table 2A.3 The Hydroarylation of 3,4-Dimethoxy Acetanilde (**1a**) with Substituted Alkynes **2b-h**[a]

Entry	Alkyne (1)	Compound (4)	Yield[b]
1	 **2b**	 **3p**	87%
2	 **2c**	 **3q**	83%
3	 **2d**	 **3r**	81%
4	 **2e**	 **3s**	61%
5	 **2f**	 **3t**	88%
6	 **2g**	 **3u**	80%
7	 **2h**	 **3v**	78%

[a]All reactions were carried out using **1a** (100 mg), **2a-h** (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv) and pivalic acid (5.0 equiv) in *iso*-PrOH (2.5 mL) at 100 °C for 12 h. [b]Isolated yield.

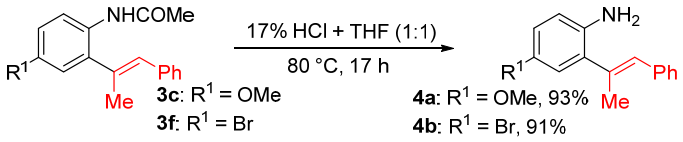
But, an alkyne, methyl phenyl propiolate (**2i**), having two chelating groups such as Ph and ester, gave a mixture of hydroarylation products **3w** and **3w'** in 81% combined yields in a 60:40 ratio (eq 4). Interestingly, 2-thienyl substituted alkyne **2j** provided hydroarylation products **3x** and **3x'** in 75% combined yields in a 3:1 ratio (eq 5). In the major product **3x**, 2-thienyl attached carbon of alkyne **2j** was connected with a less hindered carbon of **1a**. Surprisingly, in the reaction of alkyne **2k** having Ph and elongated Ph (CH_2Ph) with **1a**, a single coupling product **3y** in 62% yield was obtained (eq 6). In the reaction, **1a** was connected selectively at the CH_2Ph attached carbon of alkyne **2k**. To know the chelating effect of Ph and ester groups, the following cross-over reaction was examined (eq 7). Treatment of **1a** with **2a** (1.0 equiv) and **2f** (1.0 equiv) under

similar reaction conditions gave alkyne **2a** coupling product **3a** in a major 59% yield and alkyne **2f** coupling product **3t** in a less 32% yield, respectively (Scheme 2A.15). This result clearly reveals that Ph ring chelates with Ru than ester.

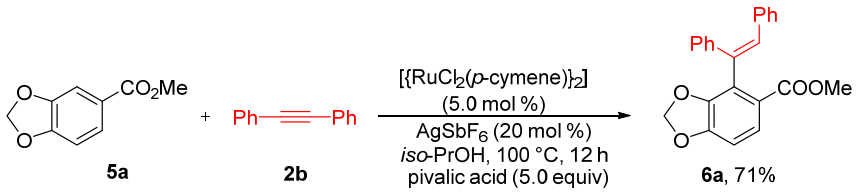


Scheme 2A.15: Regio chemistry studies and cross-over experiments.

Later, *ortho*-alkenylated acetanilides **3c** and **3f** were converted into *ortho*-alkenylated anilines **4a** and **4b** in 93% and 91% yields, respectively, in the presence of a 1:1 mixture of 17% HCl and THF at 100 °C for 17 h (Scheme 2A.16).



Scheme 2A.16: Applications.

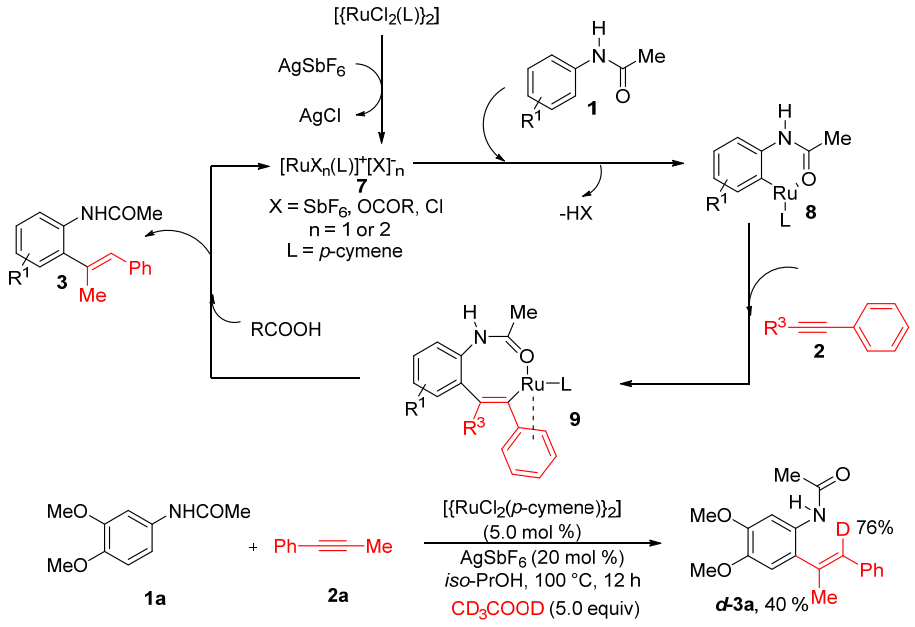


Scheme 2A.17: Ruthenium-catalyzed hydroarylation of alkyne with aromatic ester.

The catalytic reaction was successfully extended with a weak ester directing group substituted aromatic moiety. Methyl piperonate (**5a**) reacted with diphenylacetylene (**2b**) under similar reaction conditions yielding hydroarylation product **6a** in 71% in a highly regioselective manner (Scheme 2A.17).

2A.6 Proposed mechanism

A possible reaction mechanism for the hydroarylation reaction is proposed in Scheme 2A.18. $AgSbF_6$ likely removes Cl^- ligand from $[\{RuCl_2(p\text{-cymene})\}_2]$ complex giving a cationic ruthenium species **7**. Coordination of the carbonylgroup of **1** to a cationic species**7** followed by *ortho*-metalation provides a six-membered ruthenacycle intermediate**8**. Coordinative regioselective insertion of alkyne **2** into the Ru–carbon bond of intermediate **8** gives intermediate **9**. Protonation at Ru-C bond of intermediate **9** in the presence of RCOOH affords hydroarylationproduct**3** and regenerates the active ruthenium species **7** for the next catalytic cycle. In the reaction, organic acid acts as a proton source. To support the role of organic acid, the following deuterium labelling experiment was done. Treatment of **1a** with **2a** under similar reaction conditions in the presence of CD_3COOD instead of pivalic acid gave product ***d*-3a** in 40% yield with 76% of deuterium incorporation at the alkene carbon.



Scheme 2A.18 Proposed mechanism

2A.7 Conclusions

In conclusion, we have described a highly regio- and stereoselective ruthenium-catalyzed hydroarylation of alkynes with acetanilides. The catalytic reaction was compatible with various sensitive functional group substituted acetanilides and alkynes. The mechanism of the reaction was proposed based on experimental evidence. Later, *ortho*-alkenylated acetanilides were converted into biologically important *ortho*-alkenylated anilines in the presence of HCl.

2A.8 References

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2A.9 Experimental Section

2A.9.1 General Procedure for the Hydroarylation of Acetanilides with Alkynes Catalyzed by Ruthenium Complex:

A 15-mL pressure tube with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube were then added acetanilide **1** (100 mg), alkyne **2** (1.20 equiv), pivalic acid (5.0 equiv) and *iso*-propanol (2.5 mL) via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, the septum was taken out and immediately a screw cap was used to cover the tube under the nitrogen atmosphere. Then, 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 **2**.

a) The reaction of 4-methoxy acetanilide (**1c**) with **2a** was carried out for 4 h (The excess reaction time leads to a minor amount of ortho *bis* alkenylation product).

b) Thereaction of 4-methyl acetanilide (**1d**) and acetanilide (**1e**) with **2a** were carried out for 3 h (The excess reaction time leads to a minor amount of ortho *bis* alkenylation product).

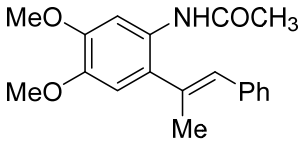
2A.9.2 General Procedure for the Deacetylation Reaction.[1]

In a 15-mL pressure tube, *ortho*-alkenylated anilide **3** (100 mg), 1.5 mL of 17% HCl and 1.5 mL of THF were taken. The tube was covered with a screw cap. Then, the reaction mixture was allowed to stir at 80 °C for 17 h. After cooling to ambient temperature, the reaction mixture was neutralized with saturated $NaHCO_3$, extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4 and the solution was concentrated under reduced pressure. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure to provide crude *ortho*-alkenylated anilines **4**.

Ref. 1: Yang, X.; Shan, G.; Rao .Y. *Org.lett*, **2013,***15*, 10.

2A.10 Spectral Data of Compounds 3a-y, 5a, 6a-b.

(*E*)-*N*-(4,5-Dimethoxy-2-(1-phenylprop-1-en-2-yl)phenyl)acetamide (3a).



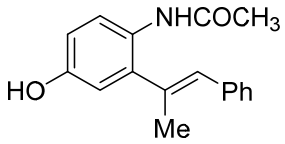
Brown solid; eluent (45% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.75 (s, 1 H), 7.36-7.34 (m, 5 H), 7.24 - 7.21 (m, 1 H), 6.68 (s, 1 H), 6.45 (s, 1 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 2.16 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 168.2, 147.9, 145.5, 136.9, 135.3, 131.1, 128.8, 128.4, 128.3, 127.3, 127.0, 127.6, 127.0, 56.1, 55.9, 24.5, 19.8.

HRMS (ESI): calc. for [($C_{19}H_{21}NO_3$)H] (M+H) 312.1600, measured 312.1618.

(*E*)-*N*-(4-Hydroxy-2-(1-phenylprop-1-en-2-yl)phenyl)acetamide (3b).



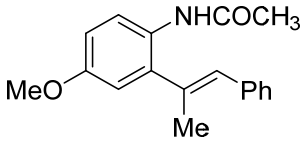
Black solid; eluent (40% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.66 (s, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.32 - 7.24 (m, 5 H), 7.21-7.17 (m, 1 H), 6.64 (s, 1 H), 6.60 (d, *J* = 8.0 Hz, 1 H), 6.35 (s, 1 H), 2.06 (s, 3 H), 2.03 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 169.6, 154.1, 139.9, 137.0, 135.5, 130.6, 128.9, 128.3, 126.9, 125.5, 115.5, 114.7, 23.9, 19.4.

HRMS (ESI): calc. for [($C_{17}H_{17}NO_2$)H] (M+H) 268.1338, measured 268.1342.

(*E*)-*N*-(4-Methoxy-2-(1-phenylprop-1-en-2-yl)phenyl)acetamide (3c).



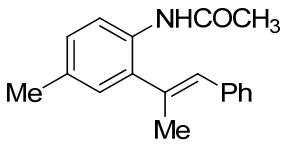
Yellow solid; eluent (32% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.96 - 7.92 (m, 1 H), 7.41-7.37 (m,4 H), 7.29-7.24 (m,2 H), 6.85 - 6.80 (m, 1 H), 6.76 (s, 1 H), 6.48 (s, 1 H), 3.79 (s, 3 H), 2.19 (s, 3 H), 2.10 (s, 3 H).

($CDCl_3$, 100 MHz):δ 168.2, 156.3, 138.5, 136.9, 135.5, 130.9, 128.8, 128.3, 127.1, 124.1, 113.9, 112.7, 55.4, 24.3, 19.5.

HRMS (ESI): calc. for [($C_{18}H_{19}NO_2$)H] (M+H) 282.1494, measured 282.1499.

(*E*)-*N*-(4-Methyl-2-(1-phenylprop-1-en-2-yl)phenyl)acetamide (3d).



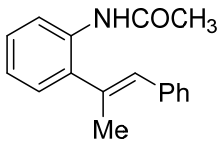
Colourless liquid; eluent (25% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.99 (d, *J* = 8.0 Hz, 1 H), 7.42 – 7.36 (m, 5 H), 7.28 (t, *J* = 8.0 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 1 H), 7.04 (s, 1 H), 6.48 (s, 1 H), 2.33 (s, 3 H), 2.20 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 136.9, 136.3, 135.7, 133.9, 131.4, 130.8, 128.8, 128.7, 128.3, 126.9, 122.1, 24.4, 20.8, 19.7.

HRMS (ESI): calc. for [($C_{18}H_{19}NO$)H] (M+H) 266.1545, measured 266.1549.

(*E*)-*N*-(2-(1-Phenylprop-1-en-2-yl)phenyl)acetamide (3e).



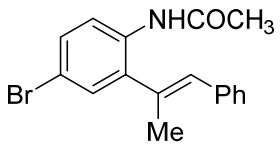
Colorless liquid; eluent (22% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.18 (d, *J*=8.0 Hz, 1 H), 7.42 –7.34 (m, 5 H), 7.28 (d, *J*=8.0 Hz, 2 H), 7.21 (d, *J*=8.0 Hz, 1 H), 7.11 (t, *J*=8.0 Hz, 1 H), 6.50 (s, 1 H), 2.21 (s, 3 H), 2.12 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 168.2, 136.9, 135.5, 133.9, 135.9, 131.2, 128.9, 128.2, 127.8, 127.1, 124.2, 121.6, 24.7, 19.8.

HRMS (ESI): calc. for [($C_{17}H_{17}NO$)H] (M+H) 252.1388, measured 252.1393.

(*E*)-*N*-(4-Bromo-2-(1-phenylprop-1-en-2-yl)phenyl)acetamide (3f).



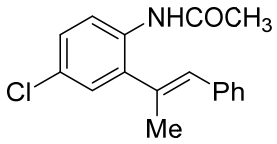
white solid; eluent (22% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.10 (d, *J* = 8.0, 1 H), 7.42 - 7.29 (m, 7 H), 7.29 (t, *J* = 8.0, 1 H), 6.50 (s, 1 H), 2.18 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 168.2, 137.6, 136.4, 134.1, 133.2, 132.0, 131.0, 130.7, 128.9, 128.5, 127.4, 123.1, 116.9, 24.7, 19.6.

HRMS (ESI): calc. for [($C_{17}H_{16}BrNO$)H] (M+H) 330.0494, measured 330.0485.

(*E*)-*N*-(4-Chloro-2-(1-phenylprop-1-en-2-yl)phenyl)acetamide (3g).



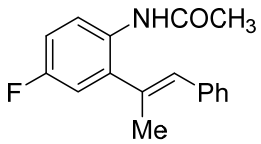
White solid; eluent (23% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.15 (d, *J* = 8.0 Hz, 1 H), 7.41 - 7.30 (m, 5 H), 7.29 - 7.27 (m, 1 H), 7.23 - 7.21 (m, 1 H), 7.18 (s, 1 H), 6.49 (s, 1 H), 2.18 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 137.3, 136.4, 134.2, 132.7, 131.9, 129.2, 128.9, 128.5, 128.2, 127.7, 127.4, 122.8, 24.7, 19.6.

HRMS (ESI): calc. for [($C_{17}H_{16}ClNO$)H] (M+H) 286.0999, measured 286.1007.

(*E*)-*N*-(4-Fluoro-2-(1-phenylprop-1-en-2-yl)phenyl)acetamide (3h).



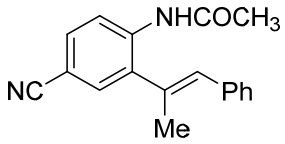
White solid; eluent (21% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.08 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.42 - 7.35 (m, 5 H), 7.31 - 7.29 (m, 2 H), 7.00 - 6.91 (m, 2 H), 6.50 (s ,1 H), 2.19 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 168.2, 151.9, 151.2, 138.3, 138.25, 138.2, 136.5, 134.5, 131.7, 128.9, 128.5, 127.4, 123.9, 123.8, 115.1, 114.9, 114.5, 114.3, 24.5, 19.5.

HRMS (ESI): calc. for [($C_{17}H_{16}FNO$)H] (M+H) 270.1294, measured 270.1296.

(*E*)-*N*-(4-Cyano-2-(1-phenylprop-1-en-2-yl)phenyl)acetamide (3i).



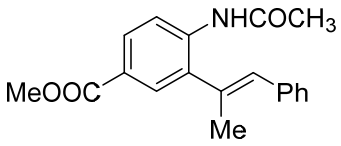
Yellow solid; eluent (24% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.48 (d, *J* = 8.0 Hz, 1 H), 7.59-7.55 (m, 1 H), 7.49 (d, *J* = 4.0 Hz, 1 H), 7.42 – 7.32 (m, 6 H), 6.53 (s, 1 H), 2.21 (s, 3 H), 2.16 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 168.4, 138.3, 136.0, 132.9, 132.2, 132.1, 132.0, 128.9, 128.6, 127.8, 120.8, 118.7, 107.0, 24.9, 19.6.

HRMS (ESI): calc. for [($C_{18}H_{16}N_2O$)H] (M+H) 277.1341, measured 277.1337.

Methyl (*E*)-4-acetamido-3-(1-phenylprop-1-en-2-yl)benzoate (3j).



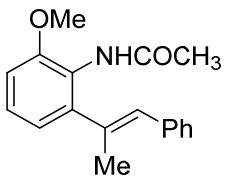
Pale yellow solid; eluent (25% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.38 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H) 7.88 (s, 1 H), 7.65 (s, 1 H), 7.39 – 7.34 (m, 4 H) ,7.30 – 7.28 (m, 1 H) ,6.51 (s, 1 H), 3.87 (s, 3 H), 2.21 (s, 3 H), 2.14 (s, 3 H) .

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 166.6, 138.3, 136.5, 134.8, 134.4, 132.1, 129.8, 129.5, 128.9, 128.5, 127.4, 125.2, 120.2, 52.0, 24.9, 19.7.

HRMS (ESI): calc. for [($C_{19}H_{19}NO_3$)H] (M+H) 310.1443, measured 310.1448.

(*E*)-*N*-(2-Methoxy-6-(1-phenylprop-1-en-2-yl)phenyl)acetamide (3k).



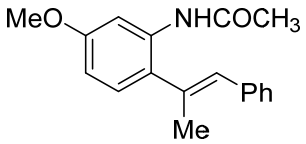
Colorless solid; eluent (28% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.36 – 7.31 (m,4 H), 7.24 – 7.22 (m,2 H), 6.92 – 6.84 (m,3 H), 6.40 (s, 1 H), 3.83 (s, 3 H), 2.19 (s, 3 H), 2.10 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 168.9, 154.3, 144.2, 137.9, 136.6, 128.9, 128.8, 128.7, 128.1, 127.4, 126.4, 122.4, 120.7, 109.8, 55.8, 23.4, 18.8.

HRMS (ESI): calc. for [($C_{18}H_{19}NO_2$)H] (M+H) 282.1494, measured 282.1499.

(*E*)-*N*-(5-Methoxy-2-(1-phenylprop-1-en-2-yl)phenyl) acetamide (3l).



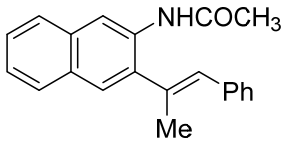
White solid; eluent (24% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.90 (s, 1 H), 7.46 (s, 1 H), 7.36 – 7.33 (m, 4 H), 7.26 –7.20 (m,1 H), 7.07 (d, *J* = 8.0 Hz, 1 H), 6.63 (d, *J* = 8.0 Hz, 1 H), 6.44 (s, 1 H), 3.80 (s, 3 H), 2.20 (s, 3 H), 2.10 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 168.2, 158.9, 137.0, 135.2, 135.1, 131.2, 128.9, 128.8, 128.4, 127.9, 127.0, 110.3, 106.2, 55.4, 24.9, 20.0.

HRMS (ESI): calc. for [($C_{18}H_{19}NO_2$)H] (M+H) 282.1494, measured 282.1497.

(*E*)-*N*-(3-(1-Phenylprop-1-en-2-yl)naphthalen-2-yl)acetamide (3m).



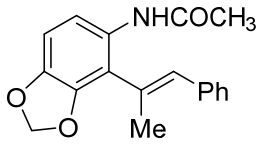
Yellow solid; eluent (24% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.75 (s, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.67 (s, 1 H), 7.55 (s, 1 H), 7.43 – 7.39 (m, 6 H), 7.33 –7.31 (m,1 H), 6.61 (s, 1 H), 2.30 (s, 3 H), 2.19 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 168.2, 136.8, 135.7, 135.3, 133.1, 132.1, 131.0, 130.1, 128.9, 128.4, 127.7, 127.3, 127.2, 126.3, 125.3, 118.0, 24.9, 20.2.

HRMS (ESI): calc. for [($C_{21}H_{19}NO$)H] (M+H) 302.1545, measured 302.1550.

(*E*)-*N*-(4-(1-Phenylprop-1-en-2-yl)benzo[d][1,3]dioxol-5-yl)acetamide (3n).



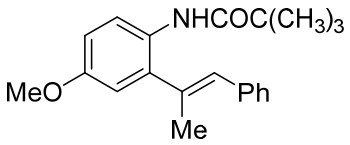
Brown solid; eluent (35% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.52 (d, *J* = 8.0 Hz, 1 H), 7.38 – 7.37 (m, 4 H), 7.33 (s, 1 H), 7.30 – 7.27 (m, 1 H), 6.72 (d, *J* = 8.0, 1 H), 6.53 (s, 1 H), 5.93 (s, 2 H), 2.19 (s, 3 H), 2.08 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 172.7, 168.4, 144.6, 144.1, 136.5, 132.4, 130.1, 128.9, 128.3, 127.2, 120.1, 115.7, 106.9, 101.1, 24.31, 18.5.

HRMS (ESI): calc. for [($C_{18}H_{17}NO_3$)H] (M+H) 296.1287, measured 296.1291.

(*E*)-*N*-(4-Methoxy-2-(1-phenylprop-1-en-2-yl)phenyl)pivalamide (3o).



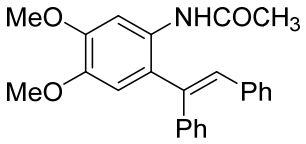
Yellow solid; eluent (12% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.13 (d, *J* = 8.0 Hz, 1 H),7.70 (s, 1 H), 7.39 - 7.34 (m,4 H), 7.30 - 7.26 (m,1 H), 6.83 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.76 (d, *J* = 4.0 Hz, 2 H), 6.51 (s, 1 H), 3.80 (s, 3 H), 2.19 (s, 3 H), 1.23 (s, 9 H).

($CDCl_3$, 100 MHz):δ 176.1, 155.9, 137.5, 136.7, 135.6, 131.0, 129.1, 128.8, 128.4, 122.9, 122.6, 114.1, 112.9, 55.4, 39.7, 27.7.

HRMS (ESI): calc. for [($C_{21}H_{25}NO_2$)H] (M+H) 324.1972, measured 324.1963.

(*E*)-*N*-(2-(1,2-Diphenylvinyl)-4,5-dimethoxyphenyl)acetamide (3p).



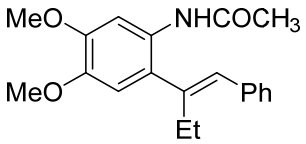
Yellow solid; eluent (43% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.58 (s, 1 H), 7.24 - 7.21 (m, 3 H), 7.18-7.16 (m, 2 H), 7.14 - 7.13 (m, 3 H), 7.09 - 7.07 (m, 2 H), 6.84 (s, 1 H), 6.72 (s, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 1.63 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 167.9, 148.8, 145.6, 139.6, 139.4, 136.7, 131.5, 129.5, 129.4, 129.0, 128.8, 128.1, 128.0, 127.2, 126.9, 113.5, 106.9, 56.1, 55.9, 23.9.

HRMS (ESI): calc. for [($C_{24}H_{23}NO_3$)H] (M+H) 374.1756, measured 374.1759.

(*E*)-*N*-(4,5-Dimethoxy-2-(1-phenylbut-1-en-2-yl)phenyl)acetamide (3q).



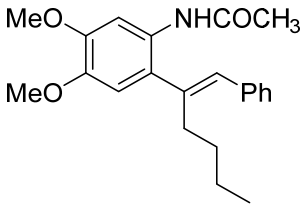
Colorless solid; eluent (43% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.88 (s, 1 H), 7.39 - 7.28 (m, 6 H), 6.66 (s, 1 H), 6.44 (s, 1 H), 3.90 (s, 3 H), 3.85 (s, 3 H), 2.59 (q, J = 8.0 Hz, 2 H), 2.09 (s, 3 H), 1.01 (t, J = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 161.7, 156.5, 140.2, 139.2, 135.6, 131.4, 130.5, 128.4, 128.3, 127.9, 127.6, 127.4, 126.9, 125.9, 119.6, 115.5, 114.2, 58.3.

HRMS (ESI): calc. for [($C_{20}H_{23}NO_3$)H] (M+H) 326.1756, measured 326.1758.

(*E*)-*N*-(4,5-Dimethoxy-2-(1-phenylhex-1-en-2-yl)phenyl)acetamide (3r).



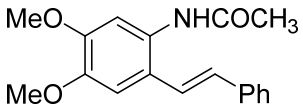
Colorless solid; eluent (34% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.87 (s, 1 H), 7.39 – 7.26 (m, 3 H), 7.30 – 7.26 (m, 3 H), 6.66 (s, 1 H), 6.44 (S, 1 H), 3.88 (s, 3 H),3.84 (s, 3 H), 2.54 (t, *J* = 8.0 Hz, 3 H), 2.08 (s, 3 H), 1.37-1.23 (m, 4 H), 0.82 (t, *J* = 8.0 Hz, 3 H),

^{13}C NMR ($CDCl_3$, 100 MHz):δ 167.9, 147.9, 145.2, 140.6, 136.8, 131.0, 128.5, 128.4, 128.2, 127.0, 126.3, 111.3, 105.5, 56.1, 55.8, 32.4, 30.5, 24.5, 22.8, 13.7.

HRMS (ESI): calc. for [($C_{22}H_{27}NO_3$)H] (M+H) 354.2024, measured 354.2032.

(*E*)-*N*-(4,5-Dimethoxy-2-styrylphenyl) acetamide (3s).



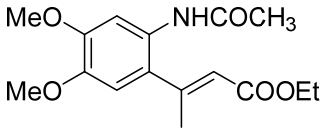
Brown solid; eluent (47% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.41 (d, *J* = 8.0 Hz, 2 H), 7.31 (t, *J* = 8.0 Hz, 2 H), 7.24 - 7.20 (m, 3 H), 7.02 (d, *J* = 16.0 Hz, 1 H), 6.94 (s, 1 H), 6.83 (d, *J* = 16.0 Hz, 1 H),3.85 (s, 3 H), 3.82 (s, 3 H), 2.15 (s, 3 H) .

^{13}C NMR ($CDCl_3$, 100 MHz):δ 181.2, 148.3, 149.1, 147.0, 137.3, 130.1, 128.7, 128.0, 127.8, 126.4, 123.3, 108.5, 108.4, 56.1, 56.0, 24.1.

HRMS (ESI): calc. for [($C_{18}H_{19}NO_3$)H] (M+H) 298.1443, measured 298.1441.

Ethyl (*E*)-3-(2-acetamido-4,5-dimethoxyphenyl)but-2-enoate (3t).



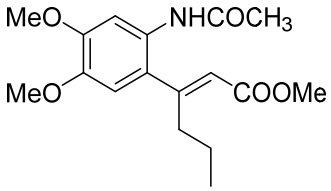
Pale yellow solid; eluent (45% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.54 (s, 1 H), 7.11 (s, 1 H), 6.60 (s, 1 H), 5.84 (s, 1 H), 4.18 (q, *J* = 8.0 Hz, 2 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 2.42 (s, 3 H), 2.12 (s, 3 H), 1.28 (t, *J* = 8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100MHz):δ 168.6, 166.2, 154.4, 148.8, 145.9, 127.6, 126.8, 120.7, 110.4, 107.4, 60.1, 56.1, 55.9, 24.3, 20.5, 14.2.

HRMS (ESI): calc. for [($C_{16}H_{21}NO_5$)H] (M+H) 308.1498, measured 308.1504.

Methyl (*E*)-3-(2-acetamido-4,5-dimethoxyphenyl)hex-2-enoate (3u).



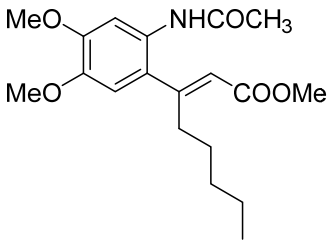
Pale yellow solid; eluent (35% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.68 (s, 1 H), 6.99 (s, 1 H), 6.55 (s, 1 H), 5.82 (s, 1 H), 3.88(s, 3 H), 3.82 (s, 3 H), 3.74(s, 3 H), 2.87 (t, *J* = 8.0 Hz, 2 H), 2.11 (s, 3 H), 1.41 – 1.35 (m, 2H) , 1.26-1.21 (m, 2H), 0.90 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 168.3, 166.2, 159.4, 148.7, 145.6, 127.3, 125.5, 120.6, 110.6, 106.6, 56.2, 55.8, 51.2, 35.3, 24.1, 21.8, 14.1.

HRMS (ESI): calc. for [($C_{17}H_{23}NO_5$)H] (M+H) 322.1654, measured 322.1642.

Methyl (*E*)-3-(2-acetamido-4,5-dimethoxyphenyl)oct-2-enoate (3v).



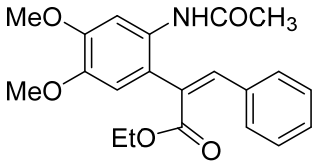
Light-yellowsolid; eluent (35% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.69(s, 1 H), 7.0 (s, 1 H), 6.55 (s, 1 H), 5.80 (s, 1 H), 3.87(s, 3 H), 3.82 (s, 3 H), 3.82 (s, 3 H), 3.73(s, 3 H), 2.88 (t, *J* = 8.0 Hz, 2 H), 2.10 (s, 3 H), 1.34 – 1.27(m, 2H) , 1.26-1.24 (m, 4H), 0.81 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 168.2, 166.2, 159.6, 148.6, 145.6, 127.4, 125.5, 120.3, 110.6, 106.6, 56.1, 55.9, 51.3, 33.4, 31.9, 28.1, 24.5, 22.3, 13.9.

HRMS (ESI): calc. for [($C_{19}H_{27}NO_5$)H] (M+H) 350.1967, measured 350.1965.

Ethyl (Z)-2-(2-acetamido-4,5-dimethoxyphenyl)-3-phenylacrylate (3w).



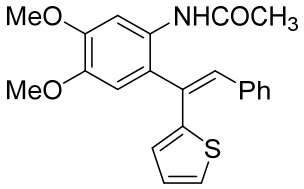
Pale yellow solid; eluent (45% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.14 (s, 1 H), 7.75 (s, 1 H), 7.59 (s, 1 H), 7.33 - 7.28 (m, 6 H), 6.78 (s, 2 H), 4.16 (q, *J* = 8.0 Hz, 2 H), 2.80 (s, 3 H), 3.82- 3.80 (m, 6 H), 2.08 (s, 3 H), 0.81 (t, *J* = 8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100MHz):δ 168.6, 168.5, 148.9, 145.4, 137.4, 134.9, 132.2, 131.5, 128.6, 128.0, 120.4, 112.9, 110.5, 106.9, 106.8, 61.9, 60.4, 55.1, 24.3, 13.9, 13.7.

HRMS (ESI): calc. for [($C_{21}H_{23}NO_5$)Na] (M+Na) 392.1475, measured 392.1473.

(Z)-N-(4,5-dimethoxy-2-(2-phenyl-1-(thiophen-2-yl)vinyl)phenyl)acetamide (3x).



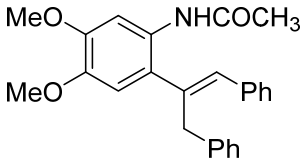
Yellow solid; eluent (41% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.07 (s, 1 H), 7.49 (s, 1 H), 7.33-7.30 (m, 4 H), 7.28-7.24 (m, 2 H), 7.16-7.14 (m, 1 H), 7.12 (d, *J* = 4.0 Hz, 1 H), 6.92-6.90 (m, 1 H), 3.97 (s, 3 H), 3.76 (s, 3 H), 1.83 (s, 3 H) .

^{13}C NMR ($CDCl_3$, 100 MHz):δ 168.1, 159.5, 155.5, 149.4, 146.4, 140.0, 139.8, 129.7, 128.7, 128.5, 127.9, 127.8, 126.1, 123.1, 119.6, 112.5, 105.7, 90.0, 55.1, 55.0, 21.60.

HRMS (ESI): calc. for [($C_{22}H_{21}NO_3S$)H] (M+H) 380.1320, measured 380.1324.

(*E*)-*N*-(2-(1,3-Diphenylprop-1-en-2-yl)-4,5-dimethoxyphenyl) acetamide(3y)



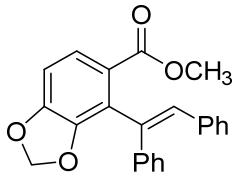
Yellow solid; eluent (40% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.68 (s, 1 H), 7.42 (d, *J* = 8.0 Hz, 4 H), 7.32 (t, *J* = 8.0 Hz, 1 H), 7.19 - 7.17 (m, 3 H), 6.99 (d, *J* = 8.0 Hz, 2 H),6.89 (s, 1 H), 6.58 (s, 1 H), 6.56 (s, 1 H), 3.89 (s, 2 H), 3.86 (s, 3 H), 3.74 (s, 3 H), 1.91 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 167.9, 147.9, 145.1, 138.6, 138.3, 136.6, 132.3, 128.7, 128.65, 128.6, 128.5, 128.1, 127.4, 126.5, 126.2, 111.6, 105.7, 55.9, 55.8, 38.8, 24.3.

HRMS (ESI): calc. for [($C_{25}H_{25}NO_3$)H] (M+H) 388.1913, measured 388.1914.

Methyl (*E*)-4-(1,2-diphenylvinyl)benzo[d][1,3]dioxole-5-carboxylate (5a).



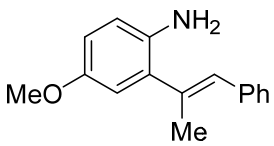
Colorless solid; eluent (2% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.43 (d, *J* = 8.0 Hz,2 H), 7.25 – 7.24 (m, 2 H), 7.20 – 7.18 (m, 3 H), 7.14 (s, 5 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 6.66 (s, 1 H), 5.95 (s, 2 H),3.62 (s, 3 H) .

^{13}C NMR ($CDCl_3$, 100 MHz):δ 167.7, 150.1, 146.4, 139.0, 136.9, 135.7, 130.7, 129.9, 129.4, 127.9, 127.2, 126.9, 125.3, 106.9, 101.6, 51.9.

HRMS (ESI): calc. for [($C_{23}H_{19}O_4$)H] (M+H) 359.1283, measured 359.1289.

(*E*)-4-Methoxy-2-(1-phenylprop-1-en-2-yl)aniline (6a)



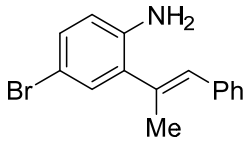
Yellow solid; eluent (14% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.37-7.36 (m, 4 H), 7.26-7.22 (m, 1 H), 6.70 – 6.68 (m, 3 H), 6.54 (s, 1 H), 3.75 (s, 3 H), 3.54 (s, 2 H), 2.22 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 152.5, 137.5, 136.5, 136.4, 132.7, 129.9, 128.9, 128.2, 126.6, 116.8, 114.2, 113.5, 55.7, 19.0.

HRMS (ESI): calc. for [($C_{16}H_{17}NO$)H] (M+H) 240.1388, measured 240.1393.

(*E*)-4-Bromo-2-(1-phenylprop-1-en-2-yl)aniline (6b)



Colourless liquid ; eluent (12% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.39-7.38 (m, 4 H), 7.29-7.27 (m, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 6.90 (d, *J* = 4.0 Hz, 1 H), 6.87 (m, 1 H), 6.54 (s, 1 H), 3.86 (s, 2 H), 2.20 (s, 3 H).

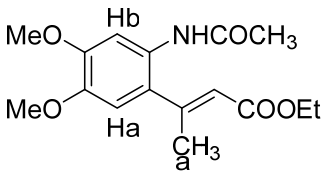
^{13}C NMR ($CDCl_3$, 100 MHz):δ 144.3, 137.2, 135.4, 130.9, 130.4, 130.2, 129.5, 129.0, 128.5, 127.9, 126.3, 121.5, 120.6, 118.4, 117.5, 19.06.

HRMS (ESI): calc. for [($C_{15}H_{14}BrN$)H] (M+H) 288.0388, measured 288.0398.

2A.11. Regioselective Studies

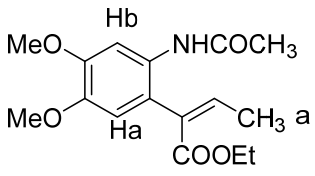
A. NOESY Studies

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



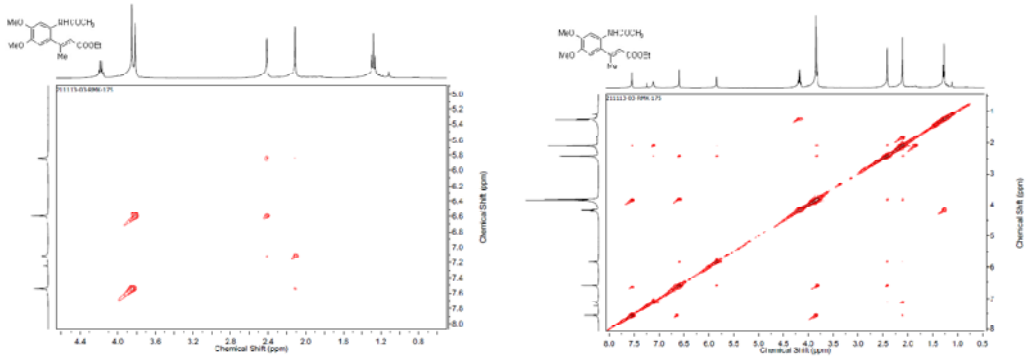
Ha δ = 7.11; Hb = 7.54; Me(a) = 2.42

Observed

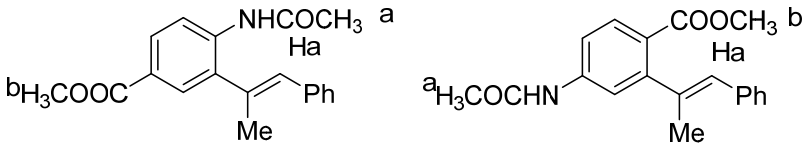


Not observed

There is a NOE correlation between Ha (δ 7.11, s) and Me (a) (δ 2.42, s). In meantime, there is a no correlation between Ha (δ 7.11, s) and ester carbonyl attatched ethyl group. These results clearly revealed that the regiochemistry of compound **3t** is correct.



Copy of NOESY Experiment of Compound **3j**

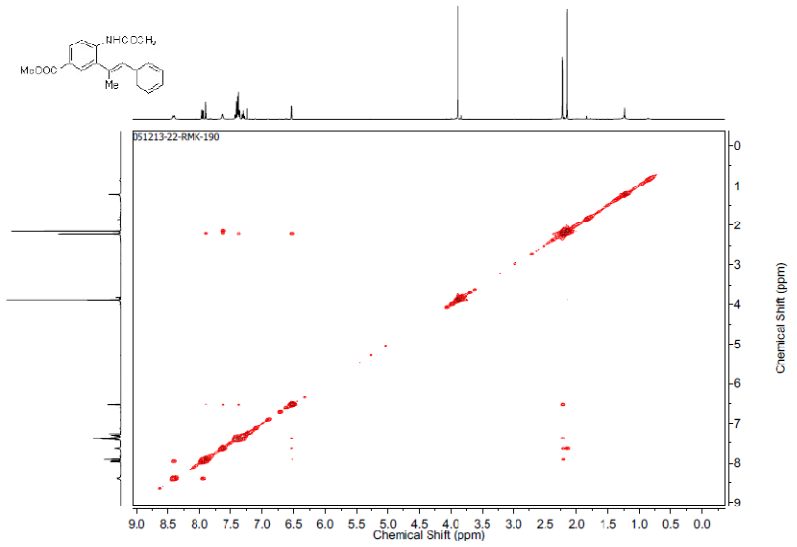


Ha δ = 6.51; CH_3(a) = 2.14; CH_3(b) = 3.87

Observed

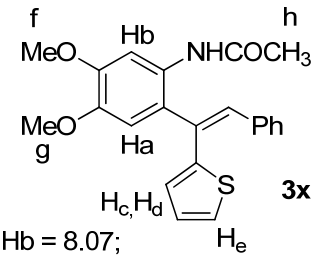
Not observed

There is a NOE correlation between Ha (δ 6.51, s) and CH_3 (a) (δ 2.14, s). In meantime, there is a no correlation between Ha (δ 6.51, s) and CH_3 (b) (δ 3.87, s). These results clearly revealed that the regiochemistry of compound **3j** is correct.



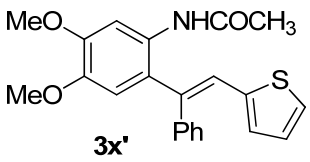
NOESY Studies

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



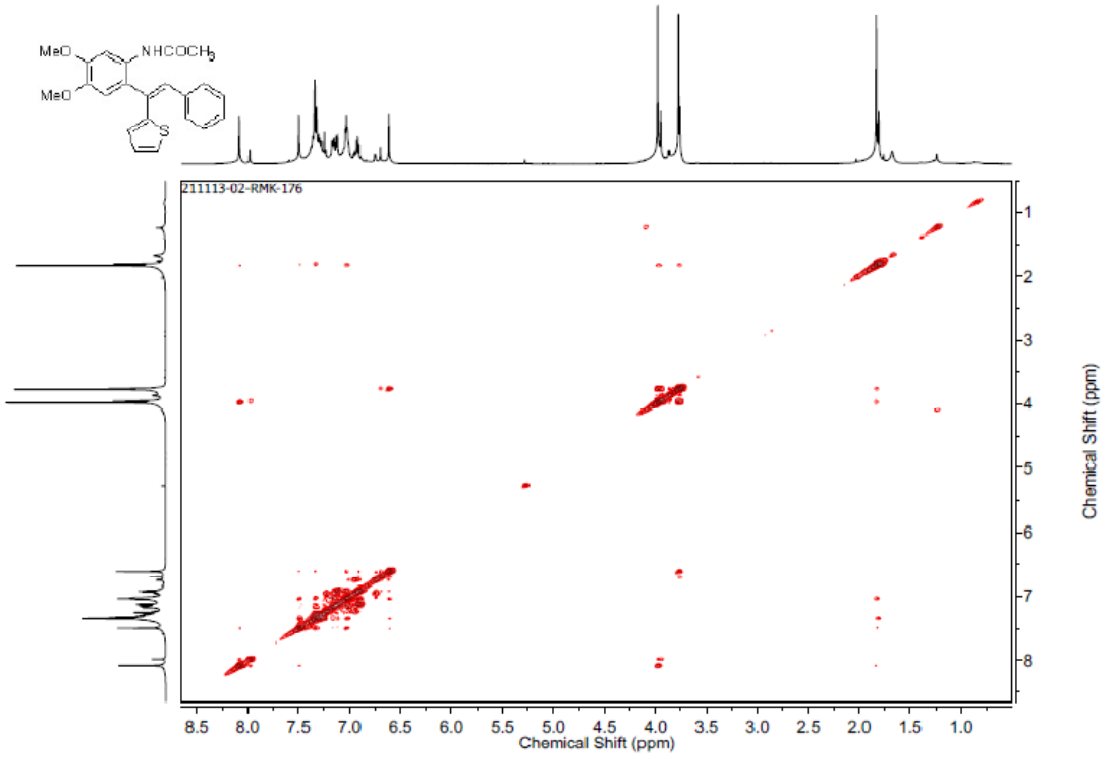
Ha δ = 6.61; Hb = 8.07;
H_c,H_d=7.15,7.11;H_e = 6.91
$Me_{f,g}$=3.91,3.76,Me_h=1.83

Major isomer

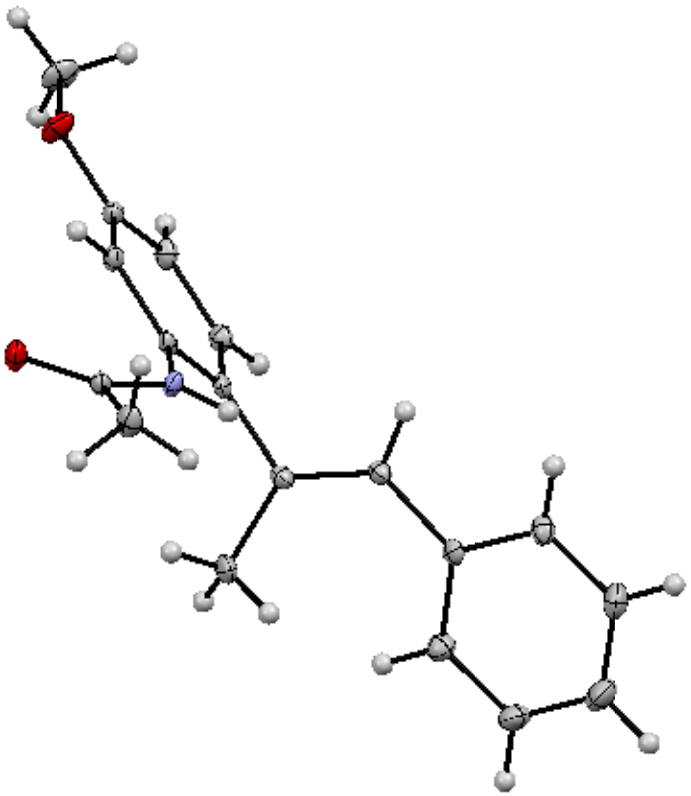


Minor isomer

There is a NOE correlation between Ha (δ 6.61, s) and thiophene protons H_e, H_d, H_e This result clearly reveals that the major isomer is **3x**.



X-Ray crystal structure of compound **3l**.



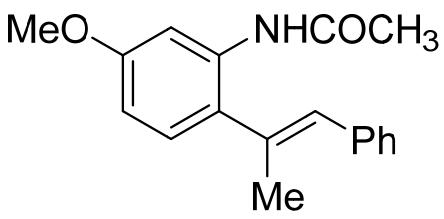


Table 1. Crystal data and structure refinement for compound 3l

Identification code	3l	
Empirical formula	$C_{18}H_{19}NO_2$	
Formula weight	281.134	
Temperature	296 K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P 21/n	
Unit cell dimensions	a = 9.4559 (5) Å	α= 87.305°.
	b = 11.7099(8) Å	β= 85.178(3)°.

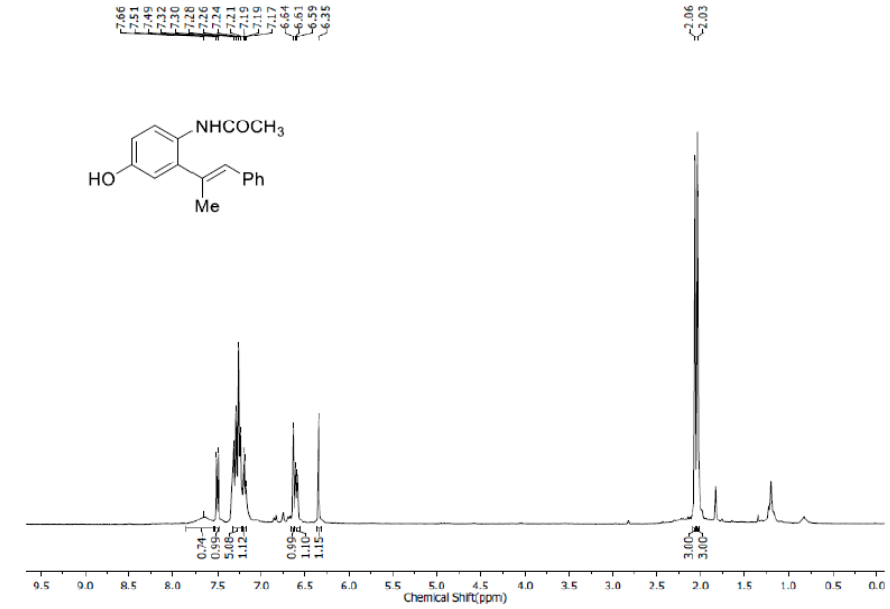
	c = 27.9417(18) Å γ = 89°.
Volume	1051.88(14) $Å^3$
Z	8
Density (calculated)	1.214Mg/m^3
Absorption coefficient	0.713 mm^{-1}
F(000)	448.0
Crystal size	0.236 x 0.101 x 0.032 mm^3
Theta range for data collection	8.98 to 66.94°.
Index ranges	-12<=h<=7, -6<=k<=6, -22<=l<=22
Reflections collected	7330
Independent reflections	1864 [R(int) = 0.0442]
Completeness to theta = 66.94°	94.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.977 and 0.917
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1764 / 0 / 146
Goodness-of-fit on F^2	0.977
Final R indices [I>2sigma(I)]	R1 = 0.0459, wR2 = 0.1214
R indices (all data)	R1 = 0.0478, wR2 = 0.1234
Largest diff. peak and hole	0.248 and -0.196 $e.Å^{-3}$

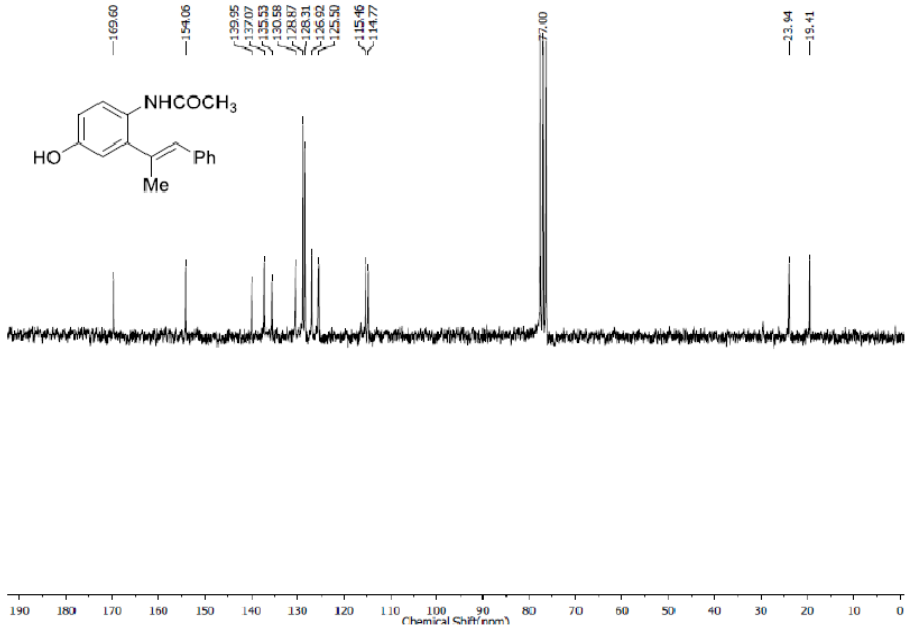
of Compound **3b**

2A.12: Spectral Copies of Selected Compounds

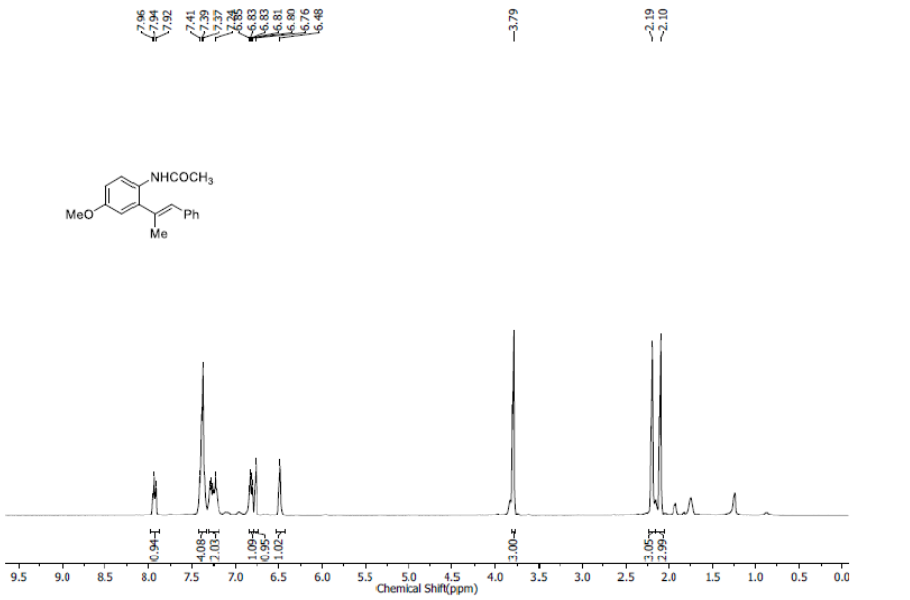
^{1}H and ^{13}C Spectra of Compound **3a.**

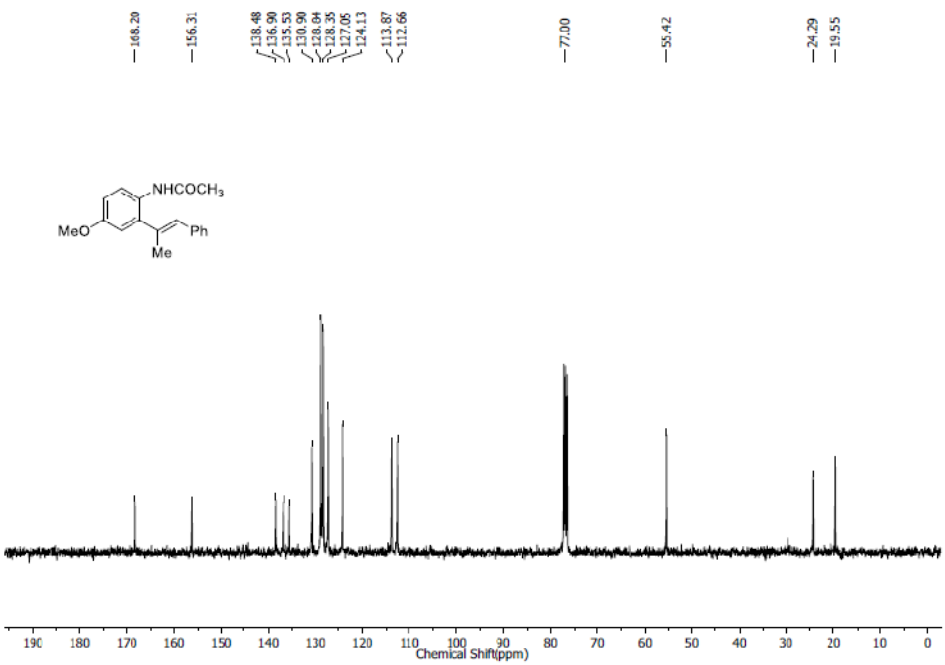
^{1}H and ^{13}C Spectra of Compound **3b.**



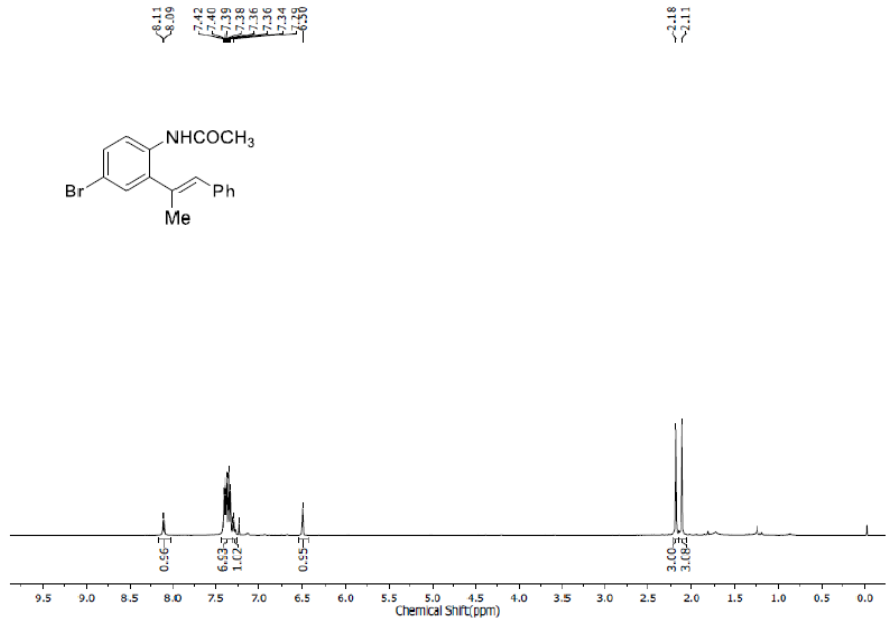


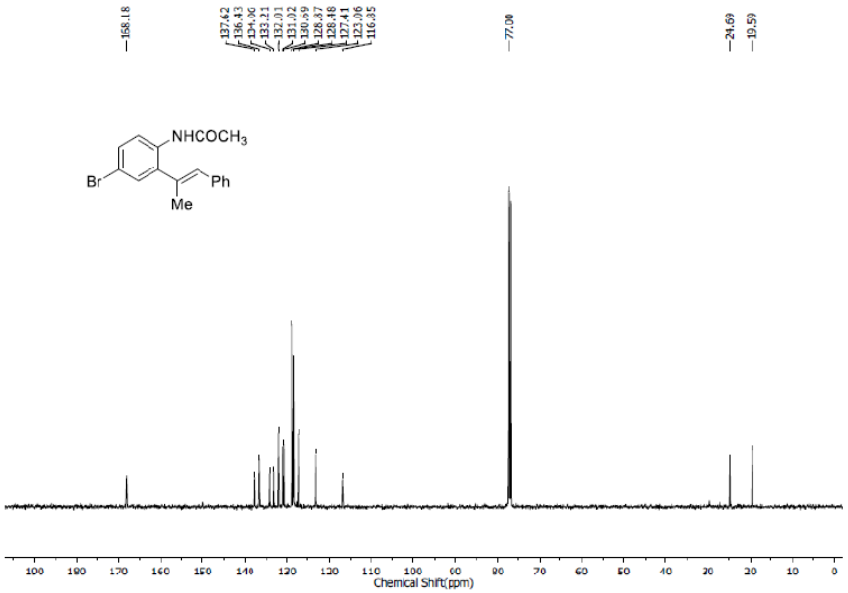
^{1}H and ^{13}C Spectra of Compound **3c.**



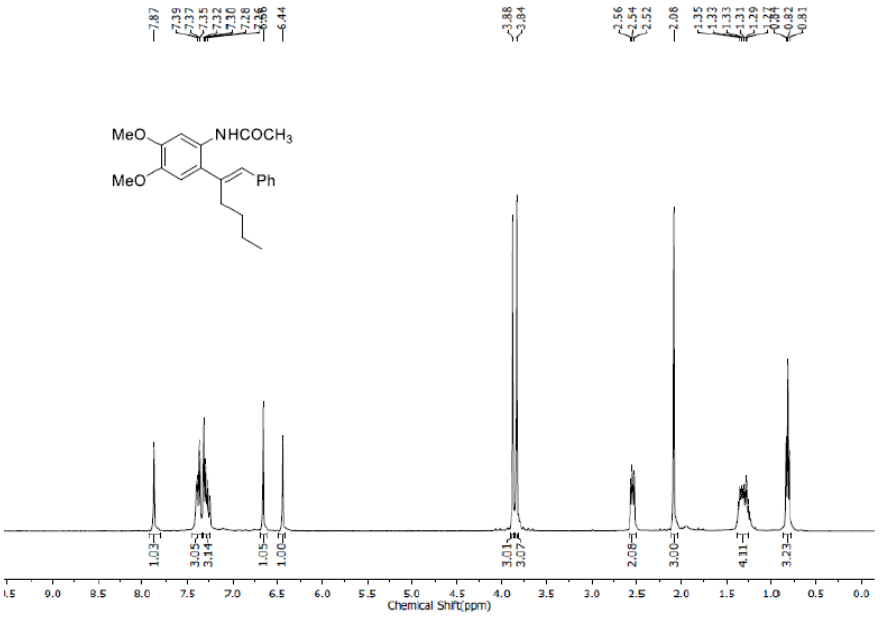


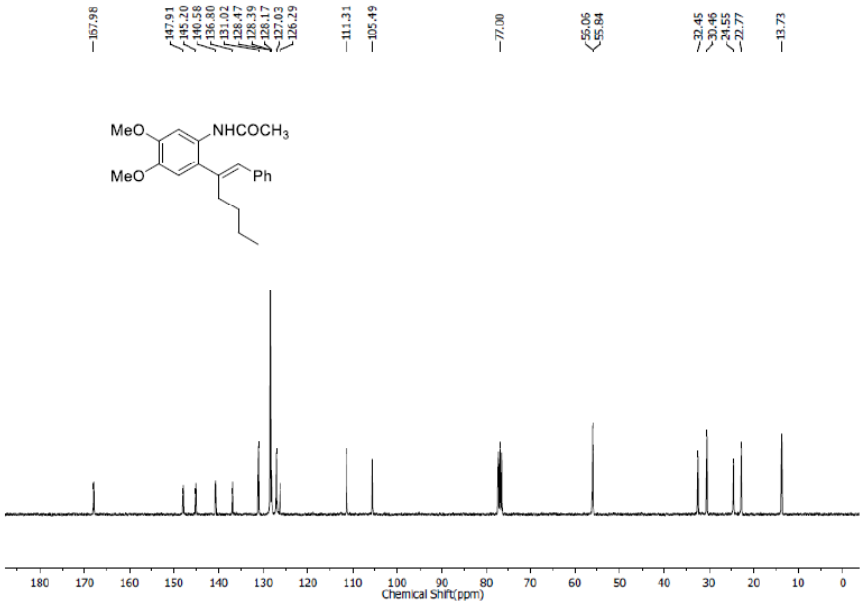
^{1}H and ^{13}C Spectra of Compound **3f.**



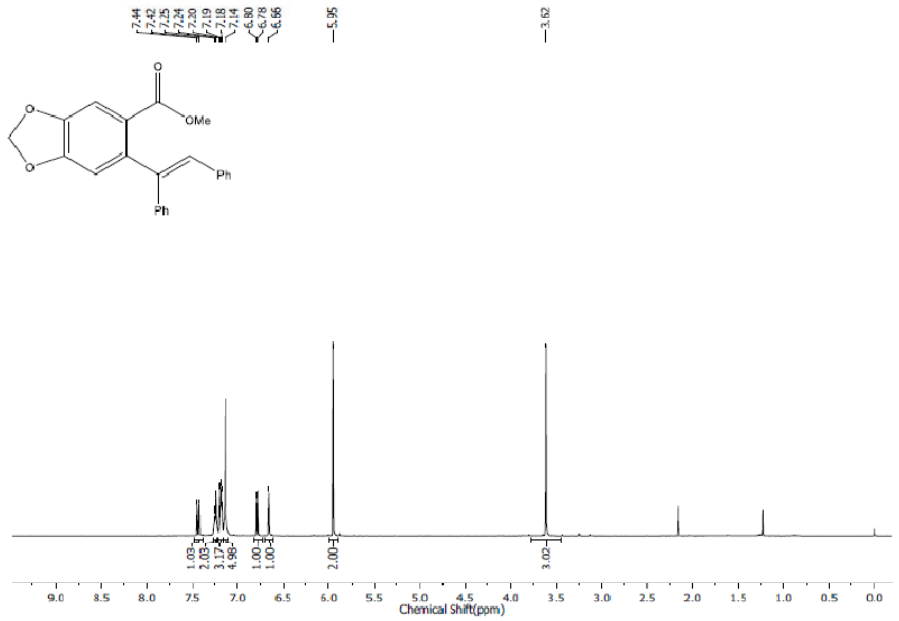


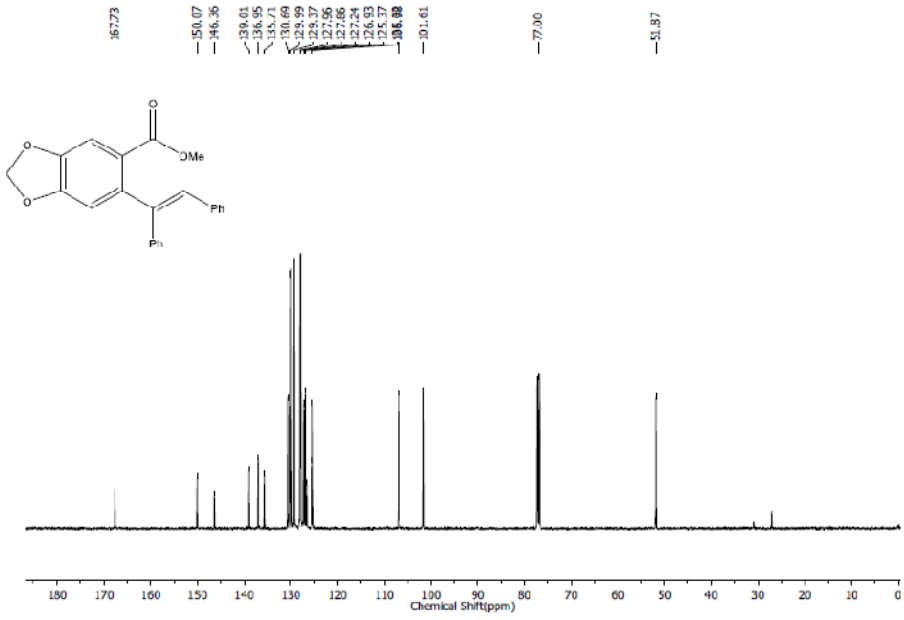
^{1}H and ^{13}C Spectra of Compound **3r.**



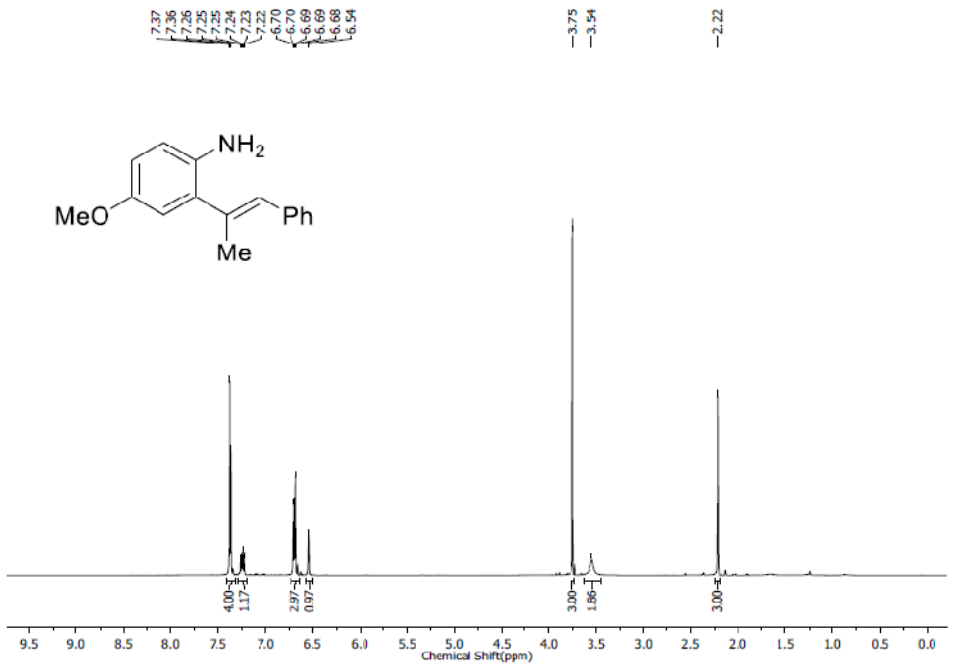


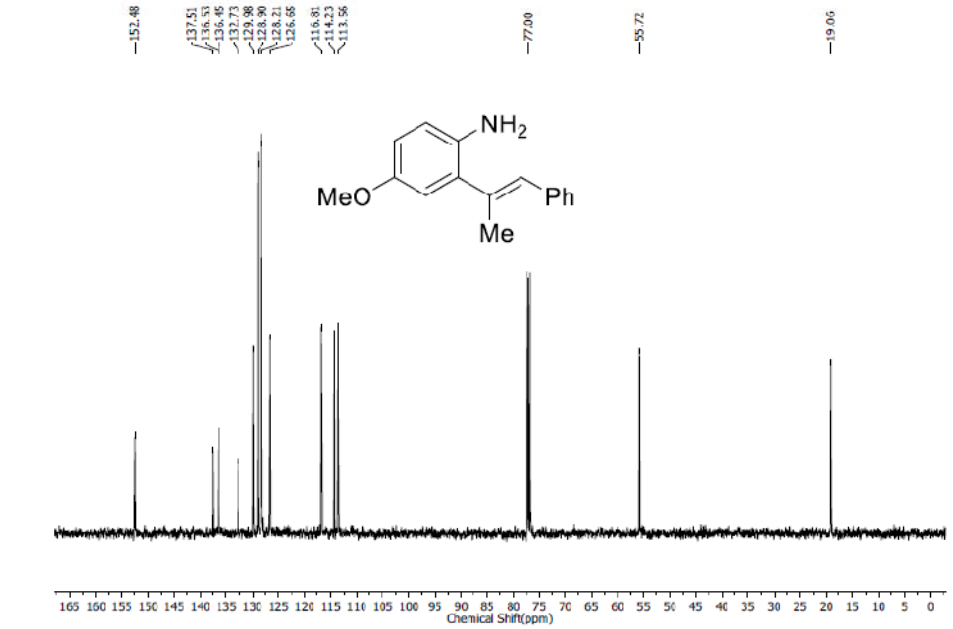
^{1}H and ^{13}C Spectra of Compound **5a**





^{1}H and ^{13}C Spectra of Compound **4a.**

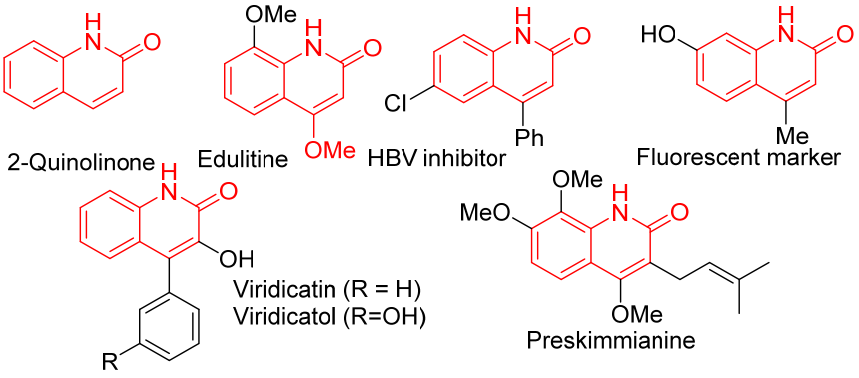




Section 2B: Ruthenium-Catalyzed Cyclization of Anilides with Substituted Propiolates or Acrylates: an Efficient Route to 2-Quinolinones

2B.1 Introduction

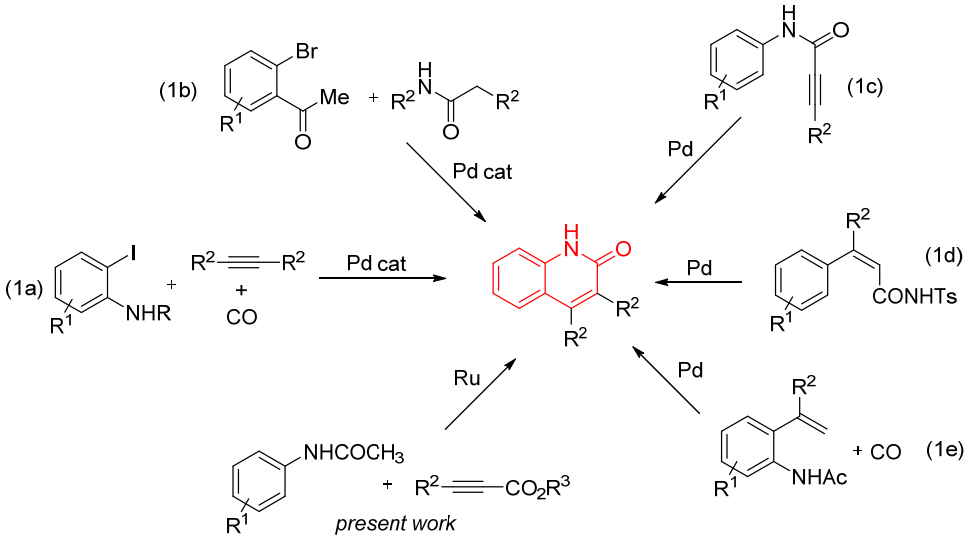
2-Quinolinones are a naturally occurring heterocyclic moiety which exhibits a broad range of biological activities including antibiotic, anticancer, antiviral and antihypersensitive.[1] This core is also present in various natural products (Scheme 2B.1).[2] 2-Quinolinones are also efficient fluorescent markers for amino acids, peptides, amino carbohydrates, and amino polysaccharides. In addition, 2-quinolinones are key synthetic intermediates for synthesizing 2-halo, 2-alkoxy and 2-amino substituted quinolines.[4]



Scheme 2B.1: Selected Biologically Active 2-Quinolinones

As a result, various synthetic methods are reported in the literature for the synthesis of 2-quinolinone derivatives (Scheme 2B.2).[5-7] Traditionally, 2-quinolinone derivatives are prepared by the acid-mediated intramolecular cyclization of β-ketoanilides (Knorr synthesis) and a base-mediated intramolecular aldol condensation of 2-aminophenyl substituted carbonyl compounds (Friedlander synthesis).[5] Recently, 2-quinolinones are efficiently prepared by using the palladium catalyst.[6]Larock's group reported the synthesis of 3,4-disubstituted quinolinones by a palladium-catalyzed carbonylative annulation of 2-iodoanilides with alkynes and CO (eq. 1a).[6a] Manley's group reported a Pd-catalyzed amidation of *ortho*-halo acetophenone withalkyl amides leading to 4-substituted quinolinones (eq. 1b).[6b] Fujiwara's group reported the synthesis of 4-substituted quinolinones via a palladium-catalyzed intramolecular electrophilic cyclization *of ortho*-alkynylanilides (eq. 1c).[6c]Doi's group reported the synthesis of 2-quinolinones through a palladium-catalyzed intramolecular amidation of phenyl substituted enamides (eq. 1d).[6d] Very

recently, Alper's group reported the synthesis of 2-quinolinones via the oxidative cyclo carbonylation of 2-vinyl anilines in the presence of palladium catalyst (eq. 1e).[6e] In most of these methods, a preactivated species such as C–X or C–M having starting material is required to synthesize the key starting materials or for the reaction and the key starting material preparation needs a number of steps. In the meantime, the synthesis of 2-quinolinones are also achieved by the other protocols without metal catalyst.[7]

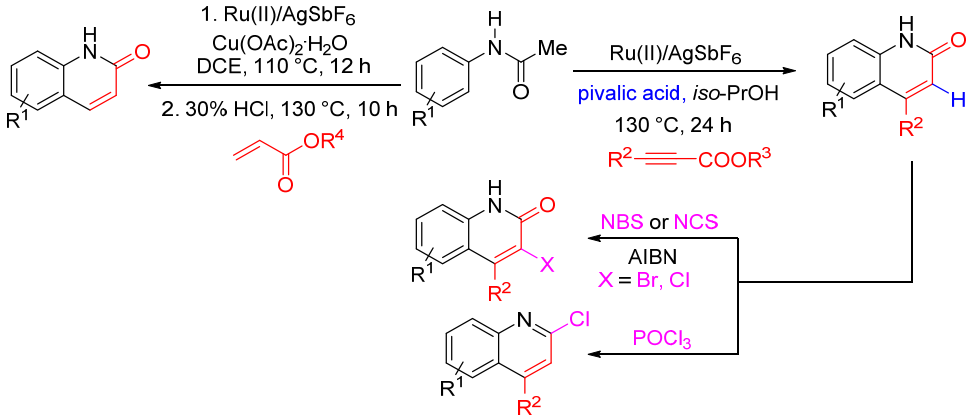


Scheme 2B.2: Previous methods to synthesize of 2-Quinolinone derivatives

2B.2 Notion of our work

Transition metal-catalyzed cyclization of heteroatom substituted aromatics with carbon-carbon π-component via chelation-assisted C–H bond activation is one of the powerful methods to synthesize heterocyclic molecules in one pot.[8] In this method, a preactivated species such as C-X or C-M having starting material is not required to activate the carbon of aromatic moiety. By using this method, various heterocyclic compounds were synthesized efficiently in a highly atom economical and environmentally friendly manner.[8] But, the synthesis of 2-quinolinone derivatives via chelation-assisted C–H bond activation pathway is limited in the literature. Herein, we wish to report the synthesis of 4-substituted-2-quinolinone derivatives from easily available starting materials via a ruthenium-catalyzed cyclization of anilides with substituted propiolates (Scheme 2B.3**)**. By using acrylates instead of propiolates, unsubstituted 2-quinolinone derivatives were prepared. Later, a halo group such as Cl or Br was introduced at the

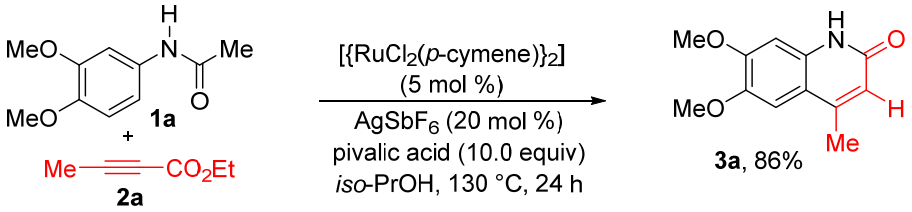
C-3 position of 4-substituted-2-quinolinones in the presence of NBS or NCS. Further, a highly useful 2-chloroquinolines were prepared from 2-quinolinones in the presence of $POCl_3$.



Scheme 2B.3: Summary of our work

2B.3 Results and Discussion

The cyclization of 3,4-dimethoxy acetanilide (**1a**) with ethyl-2-butynoate (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (10.0 equiv) in *iso*-PrOH at 130 °C for 24 h gave 4-methyl substituted-2-quinolinone **3a** in 86% isolated yield. The *ortho* C–H bond activation of substrate **1a** is very selective, and the activation selectively takes place at a sterically less hindered side (Scheme 2B.4).



Scheme 2B.4: Ruthenium-catalyzed synthesize of 2-Quinolinone derivatives

2B.4 Optimization Studies

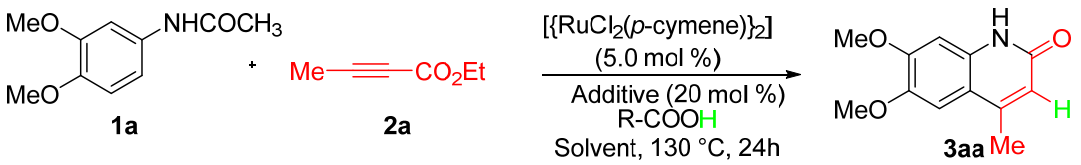


Table 2B.1 Ruthenium-catalyzed cyclization of 3,4-dimethoxy acetanilide (**1a**) with ethyl-2-butynoate (**2a**) [a]

entry	Solvent	cosolvent	additive	yield of **3a** (%)[b]
1	Isopropanol	No	$AgSbF_6$	NR
2	Isopropanol	Pivalic acid (5.0 equiv)	$AgSbF_6$	67
3	Isopropanol	Acetic acid (1.0 mL)	$AgSbF_6$	62
4	Isopropanol	Mesitylenic acid (2.0 equiv)	$AgSbF_6$	15
5	**Isopropanol**	**Pivalic acid (10.0 equiv)**	**$AgSbF_6$**	**86**
6	Isopropanol	Pivalic acid (10.0 equiv)	AgOTf	76
7	Isopropanol	Pivalic acid (10.0 equiv)	$AgBF_4$	68
8	Isopropanol	Pivalic acid (10.0 equiv)	KPF_6	NR
9	Methanol	Pivalic acid (10.0 equiv)	$AgSbF_6$	61
10	DCE	Pivalic acid (10.0 equiv)	$AgSbF_6$	54
11	THF	Pivalic acid (10.0 equiv)	$AgSbF_6$	41
12	DMF	Pivalic acid (10.0 equiv)	$AgSbF_6$	NR
13	DMSO	Pivalic acid (10.0 equiv)	$AgSbF_6$	NR
14	Toluene	Pivalic acid (10.0 equiv)	$AgSbF_6$	NR
15	1,4 Dioxane	Pivalic acid (10.0 equiv)	$AgSbF_6$	37

[a]All reactions were carried out under the following conditions: **1a** (100 mg), **2a** (1.5equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), additive (20 mol %) and co-solvent (specified) in solvent (2.5 mL) at 130 °C for 24 h under N_2 atmosphere. [b]GC yield.

Note: The catalytic reaction was tried without ruthenium and $AgSbF_6$. No product **3a** was observed.

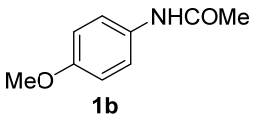
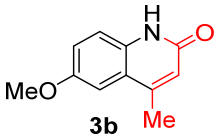
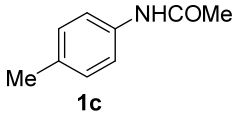
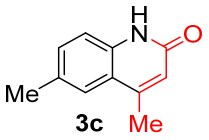
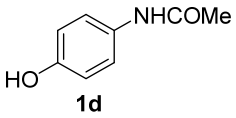
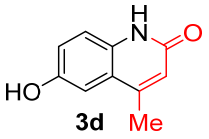
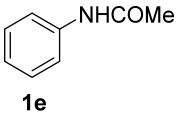
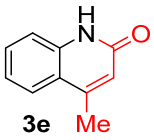
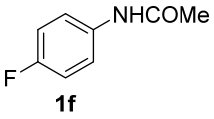
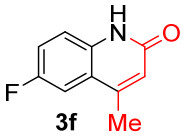
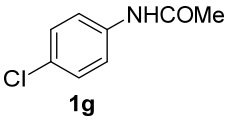
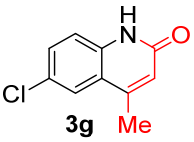
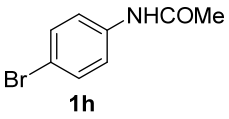
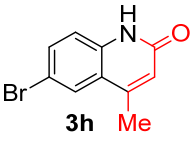
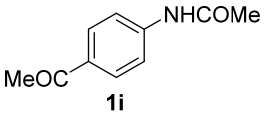
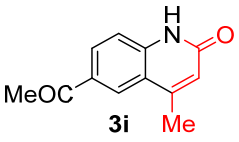
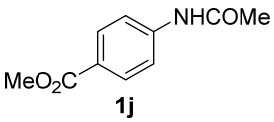
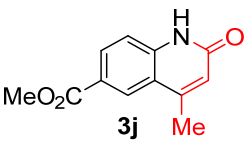
Initially, the cyclization reaction was examined with various solvents such as MeOH, *iso*-PrOH, DCE, THF, DMF and toluene under similar reaction conditions (Table 2B.1). Among them, *iso*-PrOH was effective, giving **3a** in 86% yield. MeOH was partially effective, providing **3a**in 61% yield. THF and DCE were less effective, giving **3a** in 41% and 54% yields, respectively. Remaining solvents such as DMF, DMSO and toluene were totally ineffective. The cyclization reaction was also tested with organic acids such as pivalic acid (10.0 equiv), AcOH (1.0 mL), adamantane-1-carboxylic acid (2.0 equiv) and mesitylenic acid (2.0 equiv) in *iso*-PrOH. Among them, pivalic acid was very effective, providing **3a** in 86% yield. Remaining acids were partially effective, giving **3a** in 62%, 10% and 15% yields, respectively. The reaction was also tested with

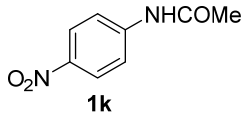
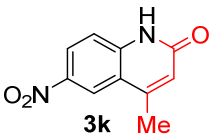
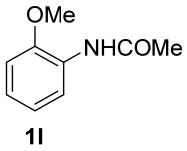
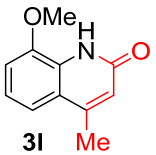
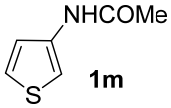
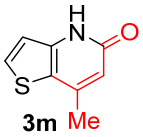
other additives such as $AgBF_4$, AgOTf and KPF_6 instead of $AgSbF_6$. $AgBF_4$ and AgOTf were partially effective, yielding **3a** in 68% and 76% yields, respectively. KPF_6 was not suitable for the reaction. The selection of reaction temperature 130 °C is crucial for the success of the reaction. If the reaction is carried out at 100 °C, only *ortho*-alkenylated anilide was observed in 85% yield.[9] At 110 °C, product **3a** was observed only in 10% yield and *ortho*-alkenylated anilide was observed in 71% yield. At 130 °C only, product **3a** was observed in 86% yield and no *ortho*-alkenylated anilide was observed. Based on this optimization studies, we have choosed that [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (10.0 equiv) in *iso*-PrOH at 130 °C for 24 h is the best conditions for the reaction.

2B.5 Substrate scope of substituted anilides

Under the optimized reaction conditions, the cyclization was examined with various substituted anilides**1b-p** and ethyl-2-butynoate (**2a**) (Table 2B.2). In all these reactions, the expected 4-methyl substituted-2-quinolinone derivatives were observed in good to excellent yields. In addition, the reaction was compatible with various sensitive functional groups such as OMe, F, Cl, Br, NO_2, ester, keto and OH substituted anilides. The reaction of electron-donating group such as OMe, Me and OH substituted anilides **1b-e** with **2a** gave the corresponding quinolinones **3b-e** in excellent 81%, 79%, 76% and 80% yields, respectively (entries 1-4). But, the optimized reaction condition was not superior for the halogen and electron-withdrawing groups substituted anilides **1f-k**. For these substrates, acetic acid solvent was superior compared with pivalic acid/*iso*-PrOH. Under the reaction conditions, halogen group such as F, Cl and Br substituted anilides**1f-h** provided products **3f-h** in 62%, 64% and 69% yields, respectively (entries 5-7). A less reactive electron-withdrawing group such as keto, ester and nitro substituted anilides**1i-k** also efficiently participated in the reaction, giving quinolinone derivatives **3i-k** in 66%, 71% and 69% yields, respectively (entries 8-10). It is important to note that in the substrates **1i-j**, the C–H bond activation selectively takes place at the *ortho* to NHCOMe group and the keto and ester groups remain intact. Sterically hindered *ortho*-methoxy acetanilide **1l** was also involved in the reaction, yielding product **3l** in 77% yield (entry 11). Very interestingly, heteroaromatic thiophene-2-acetamine (**1m**) also efficiently reacted with **2a**, affording the cyclization product **3m** in excellent 83% yield (entry 12).

Table 2B.2 The Cyclization of Substituted Anilides 1b-m with Ethyl-2-butynoate (2a)[a]

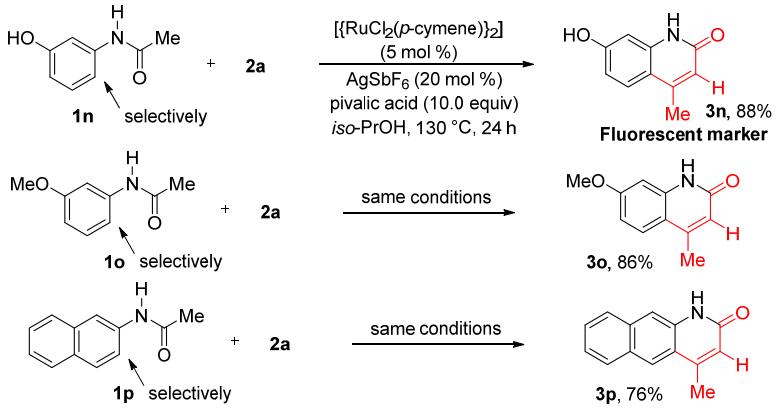
Entry	Anilide (1)	Product (3)	Yield[b]
1	 **1b**	 **3b**	81%
2	 **1c**	 **3c**	79%
3	 **1d**	 **3d**	76%
4	 **1e**	 **3e**	80%
5	 **1f**	 **3f**	62%[c]
6	 **1g**	 **3g**	64%[c]
7	 **1h**	 **3h**	69%[c]
8	 **1i**	 **3i**	66%[c]
9	 **1j**	 **3j**	71%[c]

10	 **1k**	 **3k** Me	69% [c]
11	 **1l**	 **3l** Me	77%
12	 **1m**	 **3m** Me	83%

[a]All reactions were carried out using **1b-p** (100 mg), ethyl-2-butynoate (**2a**) (1.5 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv) and pivalic acid (10.0 equiv) in *iso*-PrOH (2.5 mL) at 130 °C for 24 h. [b]Isolated yield. [c]Thereaction was carried out using AcOH as a solvent. Pivalic acid was not used.

2B.6 Regio selective studies

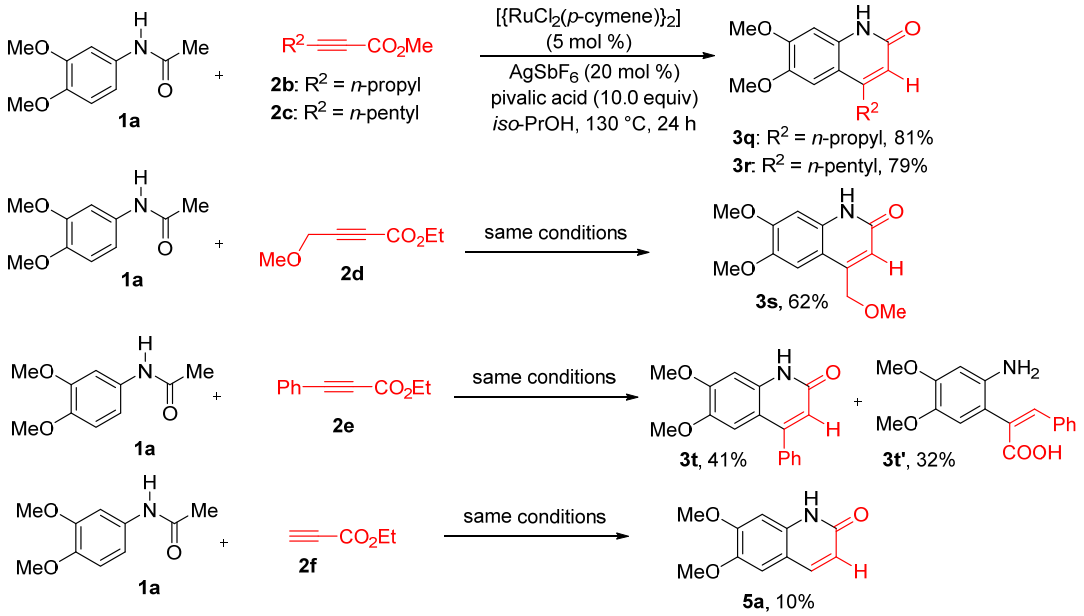
The scope of the reaction was further tested with unsymmetrical acetanilides **1n-p** (Scheme 2B.5). In all these reactions, a less hindered *ortho* C–H bondof anilide participated in the reaction in a highly regioselective manner. *meta* Hydroxy **1n** and methoxy**1o** acetanilides underwent cyclization with **2a**, giving the corresponding 2-quinolinone derivatives **3n** and **3o** in excellent 88% and 86% yields, respectively. It is important to note that the compound **3n** is used as a reference material for study and analysis of carcinogenicity and quinolone metabolism activity. 2-Naphthyl acetamide (**1o**) also efficiently reacted with **2a**, providing quinolinone derivative **3p** in 76% yield.



Scheme 2B.5 Regioselective studies

2B.7 Substrate scope of substituted propiolates

The scope of the catalytic reaction was examined with substituted alkynes **2b-f** (Scheme 2B.6). Thus, methyl-2-hexynoate (**2b**), methyl-2-octynoate (**2c**) and ethyl 4-methoxy but-2-ynoate (**2d**) nicely reacted with **1a** to give the corresponding quinolinone derivatives **3q-3s** in 81%, 79% and 62% yields, respectively. The structure of compound **3r** was confirmed by a single-crystal X-ray diffraction. Ethylphenyl propiolate (**2e**) also reacted with **1a** providing 4-aryl substituted quinolinone **3t** in 41% yield. However, in the reaction, the other alkyne regioisomer product **3t'** was observed in 32% yield. It is important to note that 4-aryl-2-quinolinone unit present in various natural products and medicinal compounds.[10] Terminal alkyne, ethyl propiolate (**2f**), was also compatible for the reaction. However, in the reaction, quinolinone derivative **3u** was observed only in 10% yield.

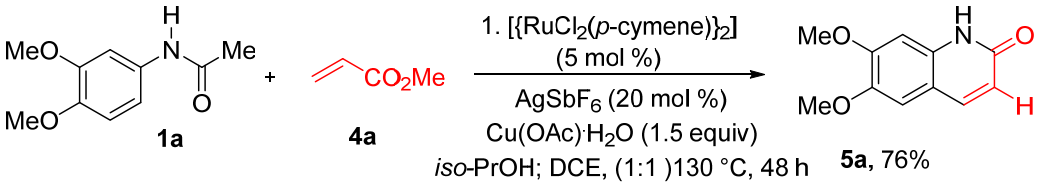


Scheme 2B.6 Scope of Substituted Propiolates

2B.8 The Cyclization of substituted anilides 1 with acrylates 4

Next, the alkyne cyclization reaction prompted us to explore the possibility of cyclization of anilides**1** with acrylates **4**. Thus, we have tried the cyclization of **1a** with methyl acrylate (**4a**) under the optimized reaction conditions (Scheme 2B.7). In the reaction, the cyclization product **5a** was observed only in 32% yield. To increase the yield, we have added 1.50 equiv of $Cu(OAc)_2 \cdot H_2O$ in the reaction mixture instead of pivalic acid. It is important to note that

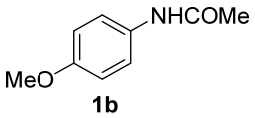
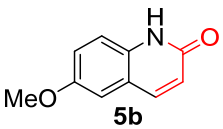
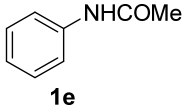
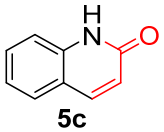
$Cu(OAc)_2{\cdot}H_2O$ is an efficient oxidant for the alkenylation reaction of anilides with alkenes.[11] However, in the reaction also, product **5a** was observed only in 32% yield. Then, the reaction was done with a 1:1 mixture of $ClCH_2CH_2Cl$ (DCE) and *iso*-PrOH solvents. Interestingly, product **5a** was observed in 76% yield. The cyclization reaction was also tested with other acrylates such as ethyl acrylate (**4b**) and *n*-butyl acrylate (**4c**). However, product **5a** was observed only in 65% and 45% yields, respectively.

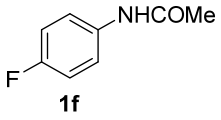
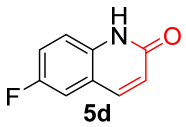
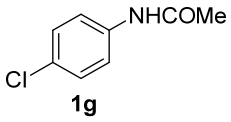
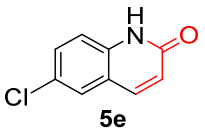
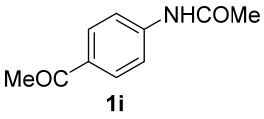
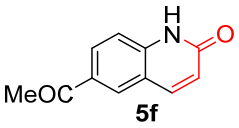
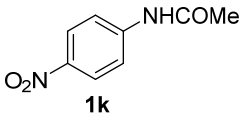
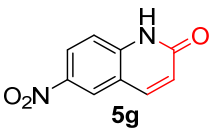


Scheme 2B.7: Ruthenium-catalyzed Cyclization of substituted anilides 1 with acrylates 4

But, the above reaction conditions such as $Cu(OAc)_2{\cdot}H_2O$ in a 1:1 mixture of solvents is not suitable for the cyclization of anilides **1b**, **1e-g**, **1i** and **1k** with **4a**. To increase the yield, the reaction of anilides**1** with **4a** was done in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (5.0 mol %), $AgSbF_6$ (20 mol %), $Cu(OAC)_2{\cdot}H_2O$ (1.5 equiv)in DCE at 110 °C. After that, 0.5 mL of 30% of HCl was added into the reaction mixture directly and further allowed to stir at 130 °C. Under the reaction conditions, the cyclization products **5b-5g** were observed in 64%, 60%, 54%, 56%, 46%, and 48% yields, respectively (Table 2A.3). In the substrate, 4-acetyl acetanilide (**1i**), the C–H bond activation takes place only at the *ortho* to NHCOMe.

Table 2A.3 The Cyclization of Substituted Anilides **1b-m** with methyl acrylate (**4a**)[a]

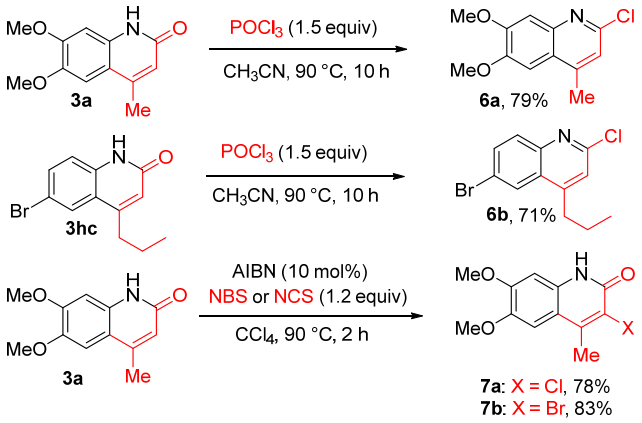
Entry	Anilide (1)	Product (3)	Yield[b]
1	 **1b**	 **5b**	64%[c]
2	 **1e**	 **5c**	60%[c]

3	 **1f**	 **5d**	54%
4	 **1g**	 **5e**	56%
5	 **1i**	 **5f**	46%
6	 **1k**	 **5g**	48%

[a]All reactions were carried out using **1** (100 mg), **4a** (1.5 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv) and $Cu(OAC)_2.H_2O$ (1.5 equiv) in DCE (2.5 mL) at 110 °C for 12 h. After that, 30% of HCl was added and heated at 130 °C for 10 h.[b]Isolated yield. [c]The frist step was allowed for only 5 h. After that, 30% of HCl was added and heated at 130°C for 5 h.

2B.9 Applications

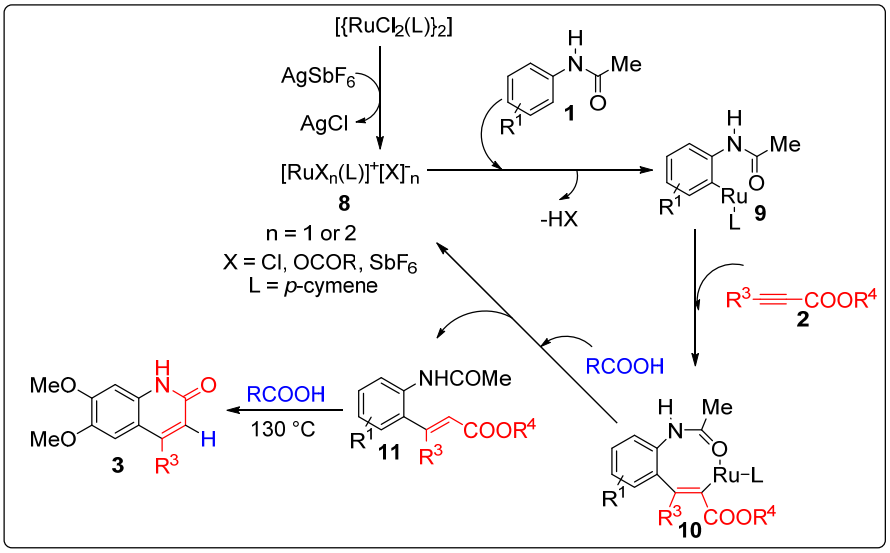
Later, quinolinone derivatives **3a** and **3hc** were converted into useful 2-chloroquinolines **6a** and **6b** in 79% and 71% yields, respectively, in the presence of $POCl_3$ in CH_3CN at 90 °C for 10 h (Scheme 2B.8). Further, **3a** reacted with NCS or NBS in the presence of AIBN (10 mol %) in CCl_4 at 90 °C for 2 h, yielding 3-Cl or Br substituted quinolinones**7a-b** in 78% and 83% yields, respectively. By using compounds **7a-b**, various functionalizations can be done at the carbon-3 position of quinolinones ring.



Scheme 2B.8: Synthetic Transformation of 2-Quinolinones

2B.10 Proposed mechanism

A possible reaction mechanism is proposed to account for the present cyclization reaction in (Scheme 2B.9). $AgSbF_6$ likely removes the Cl^- ligand from [{$RuCl_2$(*p*-cymene)}$_2$] complex, providing a cationic ruthenium species **8**. Coordination of the carbonyl group of **1** to the ruthenium species **8** followed by *ortho*-metalation provides ruthenacycle **9**. Coordinative insertion of alkyne **2** into the Ru–carbon bond of intermediate **9** gives intermediate **10**. Protonation at the Ru-carbon bond of intermediate **10** by RCOOH affords *ortho*-alkenylated anilide **11** and regenerates the ruthenium species **8**. Later, organic acid accelerates *trans-cis* isomerization of double bond of compound **11**, subsequent acid-mediated deacylation of NHCOMe to NH_2 of compound **11** and intramolecular nucleophilic addition of NH_2 to ester moiety leads to cyclic compound **3**. In the reaction, organic acid plays multiple roles such as acting as a proton source, accelerates *cis-trans* isomerization and deacylation of anilide to aniline.

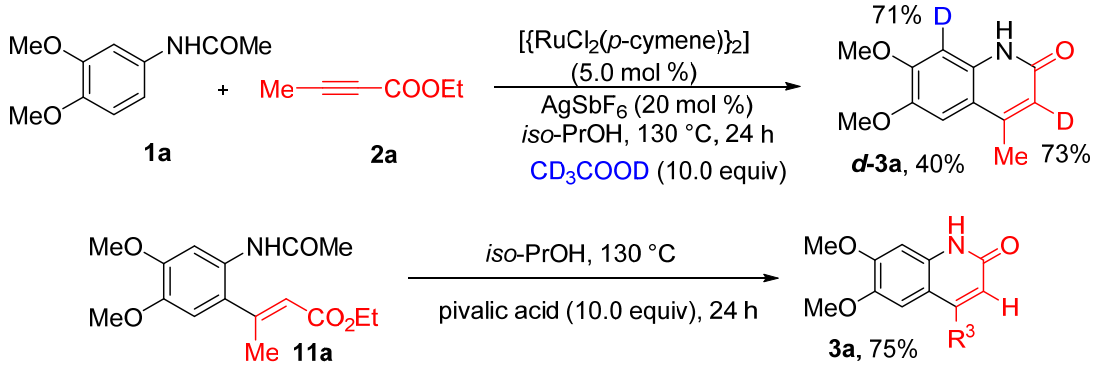


Scheme 2B.9: Proposed Mechanism.

2B.11 Mechanistic Studies

To support the multiple roles of organic acid, the reaction of **1a** with **2a** was done in the presence of CD_3COOD instead of pivalic acid under similar reaction conditions (Scheme 2B.10). In the reaction, product ***d*-3a** was observed in 40% yield, in which 73% of deuterium

incorporation was observed at the C-3 carbon of quinolinone. In the meantime, 71% deuterium incorporation was also observed at C-8 carbon of ***d*-3a**. This result clearly supports that the *ortho* C–H bond cleavage of anilide **1** is a reversible process. Further, to support the conversation of product **11** into **3**, product **11a** was prepared separately and treated with pivalic acid (10.0 equiv) in *iso*-PrOH at 130 °C for 12 h without catalyst. As expected, product **3a** was observed in 75% yield. But, the same reaction did not produce product **3a** without acid source. This result clearly reveals the multiple role of organic acid in the cyclization reaction.



Scheme 2B.10: Mechanistic studies

2B.12 Conclusions

In conclusions, we have demonstrated a ruthenium-catalyzed cyclization of anilides with substituted propiolates or acrylates in the presence of organic acid. The reaction provides 4-substituted-2-quinolinones and 2-quinolinones in good to excellent yields. 3-Halo-4-substituted-2-quinolinones and 2-chloroquinolines were prepared by using 2-quinolinones.

2B.13 References

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2B.14 Experimental Section

2B.14.1 General Procedure for the Synthesis of Quinolinones via Cyclization of Acetanilides with Propiolates Catalyzed by Ruthenium Complex

A 15-mL pressure tube with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube, were then added acetanilide **1** (100 mg), propiolate**2** (1.50 equiv), pivalic acid (10.0 equiv) and *iso*-propanol (2.5 mL) via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, the septum was taken out immediately a screw cap was used to cover the tube. Then, the reaction mixture was allowed to stir at 130 °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 dichloromethane and methanol as eluent to give pure **3**. For acetanilides **3f-3k and 3s** Acetic acid solvent (3.0 mL) was used instead of pivalic acid (10.0 equiv) and *iso*-propanol (2.5 mL).

2B.14.2 Procedure for the Synthesis of Quinolinones (5a)

A 15-mL pressure tube with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube, were then added acetanilide **1a** (100 mg), acrylate **4** (1.50 equiv), pivalic acid (10.0 equiv) and 1:1 mixture of $ClCH_2CH_2Cl$ (DCE) and *iso*-PrOH solvents(2.5 mL) via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, the septum was taken out immediately a screw cap was used to cover the tube. Then, the reaction mixture was allowed to stir at 130 °C for 48 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 dichloromethane and methanol as eluent to give pure **5a.**

2B.14.3 General Procedure for the Synthesis of Quinolinones (5b - 5k) via the cyclization of Acetanilides with Acrylates Catalyzed by Ruthenium Complex.

A 15-mL pressure tube with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube, were then added acetanilide **1** (100 mg), acrylate **4** (1.50 equiv), $Cu(OAC)_2.H_2O$ (1.50 equiv) and 1,2 dichloroethane (3.0 mL) via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, 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 110 °C for 12 h (for compounds **5b** and **5e** only 5 h). After 12 h, the reaction mixture was cooled to the room temperature. In the tube, the screw cap was removed and 0.5 mL of (30% HCl) was added to the reaction mixture and again the tube was covered with a screw cap. Then, the reaction mixture was allowed to stir at 130 °C for 10 h (for substance **5b**, **5e** only 5 h). After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, and 0.5 mL of methanol filtered through Celite. After that, the filtrate was washed with water and the organic layer was extracted with DCM and dried over Na_2SO_4. Later, the solution was concentrated under the reduced pressure. The crude residue was purified through a silica gel column using dichloromethane and methanol as eluent to give pure **5.**

2B.14.4 General Procedure for the Synthesis of 2-Chloro Substituted Quinolines 6a-b.

6,7-Dimethoxy-4-methylquinolin-2(1*H*)-one (**3a)** or 6-bromo-4-propylquinolin-2(1*H*)-one (100 mg) was taken in a 25-mL round bottom flask and dissolved with 3.0 mL of CH_3CN. To the flask, was then added phosphorous oxychloride ($POCl_3$) (1.2 equiv). Then, the condenser was fitted with water circulation into the round bottom flask and the reaction mixture was allowed to reflux at 90 °C for 4 h under an air atmosphere. Then, the reaction mixture was cooled to ambient temperature and ice water was poured and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over Na_2SO_4. The solution was concentrated

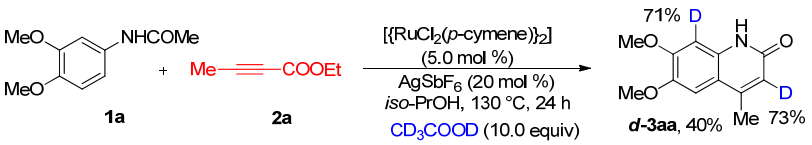
under the reduced pressure. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **6**.

2B.14.5 General Procedure for the Synthesis of 3-Bromo and 3-Chloro Substituted Quinolinones 7a-b

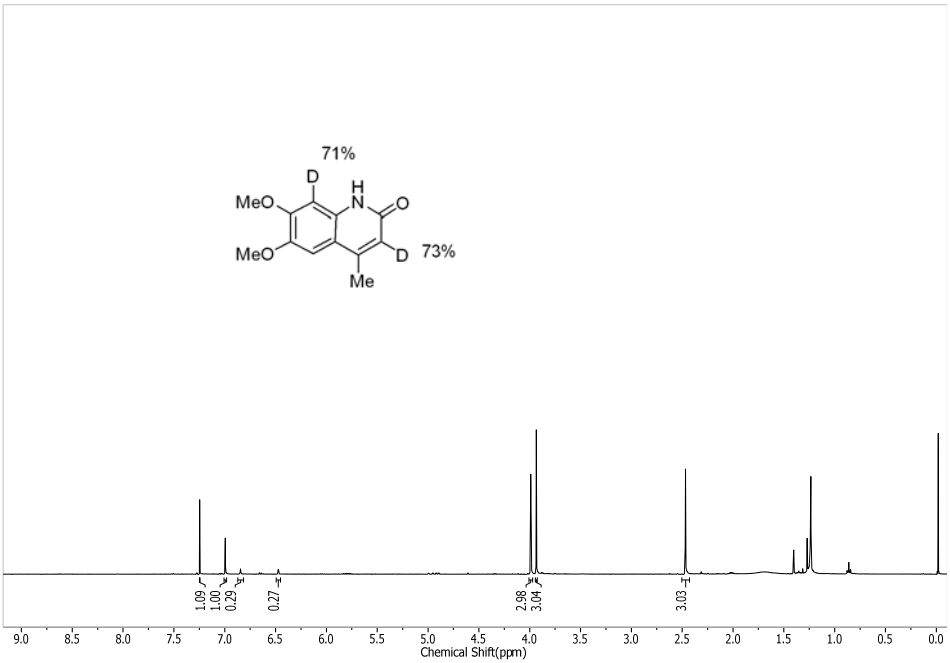
6,7-Dimethoxy-4-methylquinolin-2(1*H*)-one (**3a)** (100 mg) was taken in a 25-mL round bottom flask and dissolved with 3.0 mL of CCl_4. To the flask, were then added *N*-bromosuccinimide (or) *N*-chlorosuccinimide (1.2 mmol) and AIBN (10 mol %). Then, the condenser was fitted with water circulation in the round bottom flask and the reaction mixture was allowed to reflux at 90 °C for 2 h under an air atmosphere. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2. The crude residue was purified through a silica gel column using dichloromethane and methanol as eluent to give pure **7.**

2B.15 Mechanistic Investigation(Deuterium Studies)

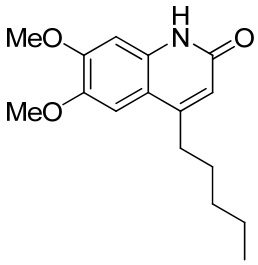
The observed results for the mechanistic investigations of the present reaction were shown below.



^{1}H NMR Spectrum of Compound ***d*-3a**.



Crystal structure of compound 3r.



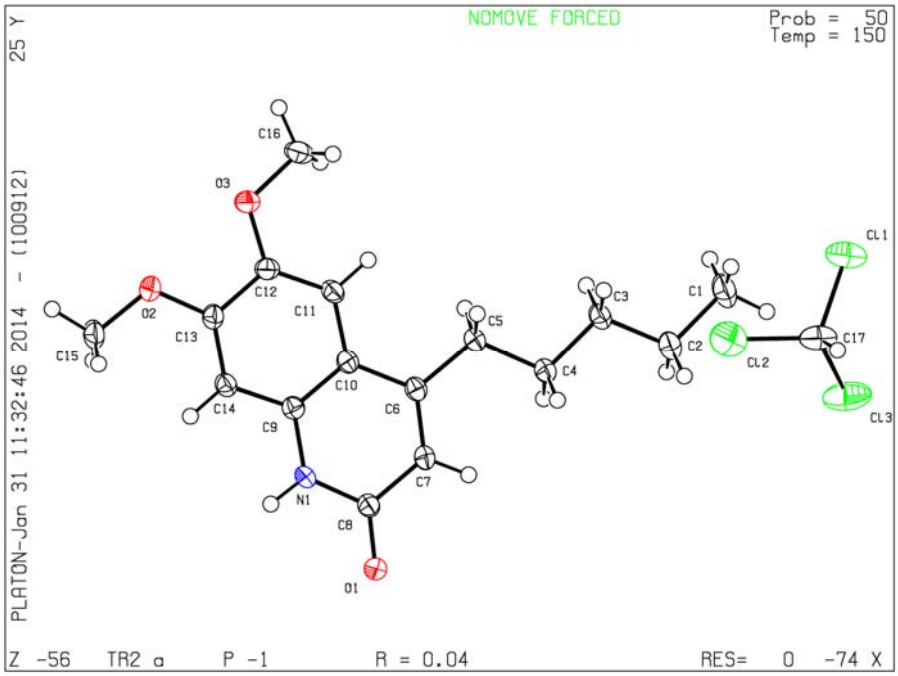


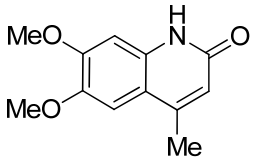
Table 1. Crystal data and structure refinement for mani 03.

Identification code	3ac
Empirical formula	$C_{16}H_{21}NO_3$, $CHCl_3$
Formula weight	394.71
Temperature	150 K
Wavelength	1.54178 Å
Crystal system	Triclinic
Space group	P -1

Unit cell dimensions	a = 7.1463 (3) Å	α= 99.6700(15)°.
	b = 10.1770(4) Å	β= 92.9420(16).
	c = 13.3296(5) Å	γ = 99.2950(15).
Volume	940.04 (6) $Å^3$	
Z	2	
Density (calculated)	1.395Mg/m^3	
Absorption coefficient	0.713 mm^{-1}	
F(000)	412.0	
Crystal size	0.236 x 0.101 x 0.032 mm^3	
Theta range for data collection	8.98 to 66.94°.	
Index ranges	-12<=h<=7, -6<=k<=6, -22<=l<=22	
Reflections collected	3529	
Independent reflections	1864 [R(int) = 0.0442]	
Completeness to theta = 66.94°	94.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.977 and 0.917	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1764 / 0 / 146	
Goodness-of-fit on F^2	0.977	
Final R indices [I>2sigma(I)]	R1 = 0.0430, wR2 = 0.1621	
R indices (all data)	R1 = 0.0470, wR2 = 0.1634	
Largest diff. peak and hole	0.248 and -0.196 $e.Å^{-3}$	

2B.15 Spectral Data of Compounds 3a-t, 5a-g, 6a-b, and 7a-b

6,7-Dimethoxy-4-methylquinolin-2(1*H*)-one(3a).



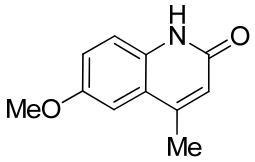
Brown colour solid; eluent (4% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 96 mg, 86% yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.38 (s, 1 H), 7.07 (s, 1 H),6.85 (s, 1 H),6.22 (s, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 2.38 (s, 3 H).

^{13}C NMR(DMSO-d_6, 400 MHz):δ161.6, 151.7, 147.6, 144.6, 134.2, 118.1, 112.6, 106.1, 97.9, 55.8, 55.5, 18.8.

HRMS (ESI): calc. for [($C_{12}H_{13}NO_3$)H] (M+H) 220.0973, measured 220.0978.

6-Methoxy-4-methylquinolin-2(1*H*)-one(3b).



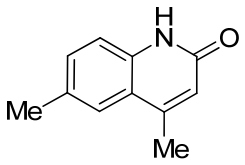
Brown colour solid; eluent (3% DCM in Methanol).The reaction scale is 100 mg, product was isolated in 92 mg, 81 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.49 (s, 1 H), 7.25 (d, J = 8.0Hz, 1 H), 7.15 (dd, J = 8.0, 4.0 Hz, 1 H), 7.13 (s, 1 H), 6.39 (s, 1 H), 3.81 (s, 3 H), 2.41 (s, 3 H).

^{13}C NMR(DMSO-d_6,100MHz):δ 161.2, 154.1, 147.4, 133.0, 121.2, 120.2, 119.0, 116.6, 106.8, 55.5, 18.6.

HRMS (ESI): calc. for [($C_{11}H_{11}NO_2$)H] (M+H) 190.0868, measured 190.0872.

4,6-Dimethylquinolin-2(1*H*)-one (3c).



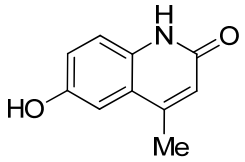
White colour solid; eluent (2% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 91 mg, 79 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.52 (s, 1 H), 7.47 (s, 1 H), 7.30 (d, J = 8.0Hz, 1 H), 7.20 (d, J = 4.0Hz, 1 H), 6.35 (s, 1 H), 2.39 (s, 3 H), 2.35 (s, 3 H).

^{13}C NMR(DMSO-d_6,100MHz):δ 161.5, 147.6, 136.6, 131.4, 130.5, 124.3, 120.8, 119.5, 115.3, 20.6, 18.5.

HRMS (ESI): calc. for [($C_{11}H_{11}NO$)H] (M+H) 174.0919, measured 174.0924.

6-Hydroxy-4-methylquinolin-2(1*H*)-one (3d).



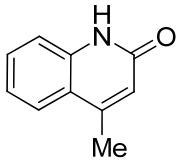
Brown colour solid; eluent (5% DCM in Methanol).The reaction scale is 100 mg, product was isolated in 88 mg, 76 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.40 (s, 1 H), 9.41 (s, 1 H), 7.16 (d, J = 8.0Hz, 1 H), 7.00 (d, J = 8.0Hz, 1 H), 6.99 (s, 1 H), 6.35 (s, 1 H), 2.34 (s, 3 H).

^{13}C NMR(DMSO-d_6,100MHz):δ 161.1, 152.1, 147.1, 131.9, 121.0, 120.5, 119.5, 116.5, 108.6, 18.5.

HRMS (ESI): calc. for [($C_{10}H_9NO_2$)H] (M+H)176.0711, measured 176.0716.

4-Methylquinolin-2(1*H*)-one (3e).



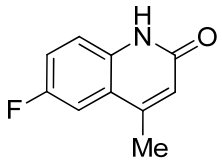
Light yellow colour solid; eluent (2% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 94 mg, 80 % yield was observed.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.65 (d, *J* = 8.0Hz, 1 H)7.50 - 7.44 (m, 2 H), 7.21 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.58 (s, 1 H), 2.49 (s, 3 H).

^{13}C NMR($CDCl_3$, 100MHz):δ 164.4, 149.3, 138.2, 130.4, 124.3, 122.5, 120.5, 120.4, 116.7, 19.1.

HRMS (ESI): calc. for [($C_{10}H_9NO$)H] (M+H) 160.0762, measured 160.0768.

6-Fluoro-4-methylquinolin-2(1*H*)-one (3f).



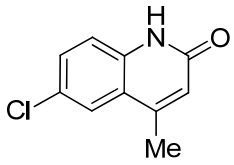
White colour solid; eluent (2% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 72 mg, 62 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.67 (s, 1 H), 7.57 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.40 (td, *J* = 8.0, 4.0 Hz, 1 H) 7.33 - 7.30 (m, 1 H), 6.45 (s, 1 H), 2.39 (s, 3 H).

^{13}C NMR(DMSO-d_6,100MHz):δ 161.3, 158.2, 147.4, 135.3, 121.9, 120.4, 118.3 and 118.1 (F-coupling), 117.1, 110.1 and 109.9(F-coupling), 18.5.

HRMS (ESI): calc. for [($C_{10}H_8FNO$)H] (M+H) 178.0668, measured 178.0672.

6-Chloro-4-methylquinolin-2(1*H*)-one(3g).



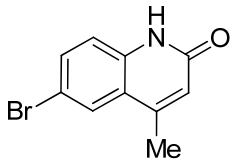
Light green colour solid; eluent (2% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 73 mg, 64% yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.72 (s, 1 H), 7.71 (s, 1 H), 7.53 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.30(d, *J* = 8.0 Hz, 1 H),6.44 (s, 1 H), 2.40 (s, 3 H).

^{13}C NMR(DMSO-d_6,100MHz):δ 161.4, 147.2, 137.4, 130.2, 125.7, 124.0, 121.9, 120.9, 117.2, 18.4.

HRMS (ESI): calc. for [($C_{10}H_8ClNO$)H] (M+H) 194.0372, measured 194.0375.

6-Bromo-4-methylquinolin-2(1*H*)-one (3h).



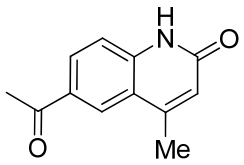
Yellow solid; eluent (2% DCM in Methanol).The reaction scale is 100 mg, product was isolated 77 mg, 69% yield.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.73 (s, 1 H), 7.84 (s, 1 H), 7.65 (d, *J* = 8.0, Hz, 1 H), 7.25(d, *J* = 12.0 Hz, 1 H),6.44 (s, 1 H), 2.50 (s, 3 H).

^{13}C NMR(DMSO-d_6,100MHz):δ 161.4, 147.2, 137.8, 132.9, 127.0, 121.8, 121.4, 117.7, 113.6, 18.4.

HRMS (ESI): calc. for [($C_{10}H_8BrNO$)H] (M+H) 237.9867, measured 237.9868.

6-Acetyl-4-methylquinolin-2(1*H*)-one(3i).



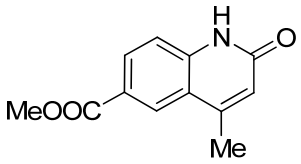
Yellow solid; eluent (2% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 75 mg, 66 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.91 (s, 1 H), 8.24(s, 1 H), 8.05 (d,*J* = 8.0Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 6.47 (s, 1 H), 2.62 (s, 3 H), 2.49 (s, 3 H).

^{13}C NMR(DMSO-d_6, 100 MHz):δ 196.6, 161.8, 148.4, 141.9, 130.4, 129.8, 125.9, 121.6, 119.0, 115.6, 26.6, 18.4.

HRMS (ESI): calc. for [($C_{12}H_{11}NO_2$)H] (M+H) 202.0868, measured 202.0864.

Methyl 4-methyl-2-oxo-1,2-dihydroquinoline-6-carboxylate(3j).



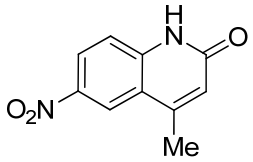
Light red colour solid; eluent (3% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 79 mg, 71 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.94 (s, 1 H), 8.23 (s, 1 H), 8.03 (dd,*J*= 8.0, 4.0 Hz, 1 H), 7. 36 (d,*J* = 12.0 Hz, 1 H),6.48 (s, 1 H), 3.86 (s, 3 H), 2.45 (s, 3 H).

^{13}C NMR(DMSO-d_6,100MHz):δ 165.8, 161.7, 148.0, 142.0, 130.6, 126.4, 122.7, 121.7, 119.2, 115.8, 52.1, 18.4.

HRMS (ESI): calc. for [($C_{12}H_{11}NO_3$)H] (M+H) 218.0871, measured 218.0871.

4-Methyl-6-nitroquinolin-2(1*H*)-one(3k).



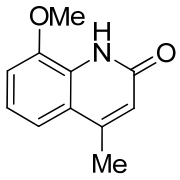
Yellow colour solid; eluent (2% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 78 mg, 69 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ12.18 (s, 1 H), 8.49 (s, 1 H), 8.33(d, *J* = 8.0 Hz, 1 H),7.42 (d, *J* = 8.0 Hz, 1 H),6.57 (s, 1 H), 2.50 (s, 3 H).

^{13}C NMR(DMSO-d_6,100MHz):δ 161.7, 148.1, 143.2, 141.4, 125.2, 122.6, 121.2, 119.1, 116.4, 18.3.

HRMS (ESI): calc. for [($C_{10}H_8N_2O_3$)H] (M+H) 205.0613, measured 205.0620.

8-Methoxy-4-methylquinolin-2(1*H*)-one (3l).



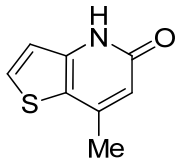
Light yellow colour solid; eluent (3% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 88 mg, 77 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ10.59 (s, 1 H), 7.29 – 7.27 (m,2 H),7.15 (d, J = 8.0 Hz, 1 H),6.42 (s, 1 H),3.89 (s, 3 H), 2.41 (s, 3 H).

^{13}C NMR(DMSO-d_6,100MHz):δ 161.1, 148.1, 145.8, 128.6, 121.5, 121.4, 120.0, 116.4, 110.9, 56.0, 18.7.

HRMS (ESI): calc. for [($C_{11}H_{11}NO_2$)H] (M+H) 190.0868, measured 190.0872.

7-Methylthieno[3,2-*b*]pyridin-5(4*H*)-one (3m).



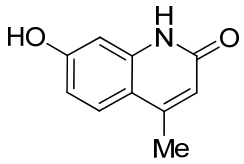
Light yellow solid; eluent (2% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 93 mg, 83 % yield was observed.

^{1}H NMR (CD_3OD, 400 MHz):δ7.20(d, J = 8.0 Hz, 1 H),7.16 (d, J = 8.0 Hz, 1 H),6.32 (s, 1 H), 2.46 (s, 3 H).

^{13}C NMR(CD_3OD,100MHz):δ 165.6, 150.2, 147.9, 125.0, 122.0, 119.4, 115.5, 19.9.

HRMS (ESI): calc. for [(C_8H_7NOS)H] (M+H) 166.0326, measured 166.0329.

7-Hydroxy-4-methylquinolin-2(1*H*)-one (3n).



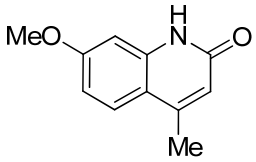
White colour solid; eluent (5% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 101 mg, 88 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.38 (s, 1 H), 10.08 (s, 1 H), 7.50 (d, J = 8.0 Hz, 1 H),6.70 (d, J = 4.0 Hz, 1 H), 6.63 - 6.65 (m, 1 H), 6.13 (s, 1 H), 2.33 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100MHz):δ 162.2, 159.5, 147.9, 140.6, 126.2, 117.0, 112.8, 111.3, 100.1, 18.6.

HRMS (ESI): calc. for [($C_{10}H_9NO_2$)H] (M+H) 176.0711, measured 176.0716.

7-Methoxy-4-methylquinolin-2(1*H*)-one (3o).



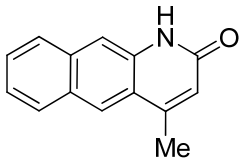
Light yellow solid; eluent (3% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 98 mg, 86 % yield was observed.

^{1}H NMR (CD_3OD, 400 MHz):δ 7.69 (d, J = 12.0 Hz, 1 H), 6.89 (dd, J = 8.0, 4.0Hz, 1 H),6.84 (d, J = 4.0 Hz, 1 H), 6.33 (s, 1 H), 3.88 (s, 3 H), 2.47 (s, 3 H).

^{13}C NMR(CD_3OD,100MHz):δ 165.7, 163.6, 151.9, 141.4, 127.5, 117.8, 116.2, 113.4, 99.5, 56.2, 19.3.

HRMS (ESI): calc. for [($C_{11}H_{11}NO_2$)H] (M+H) 190.0868, measured 190.0872.

4-Methylbenzo[*g*]quinolin-2(1*H*)-one (3p).



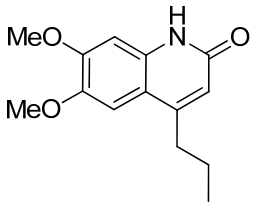
White colour solid; eluent (2% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 86 mg, 76 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.61 (s, 1 H), 8.35 (s, 1 H), 8.03(d, *J* = 8.0 Hz, 1 H),7.87 (d, *J* = 8.0 Hz, 1 H),7.66 (s, 1 H),7.52(t, *J* = 8.0 Hz, 1 H), 7.42(t, *J* = 8.0 Hz, 1 H),6.46 (s, 1 H), 2.50 (s, 3 H).

^{13}C NMR(DMSO-d_6,100MHz):δ 161.9, 147.6, 136.2, 133.7, 128.8, 128.4, 127.4, 126.5, 125.0, 124.9, 121.6, 120.7, 110.2, 18.5.

HRMS (ESI): calc. for [($C_{14}H_{11}NO$)H] (M+H) 210.0919, measured 210.0971.

6,7-dimethoxy-4-propylquinolin-2(1*H*)-one (3q).



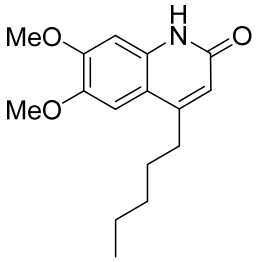
Brown solid; eluent (3% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 102 mg, 81 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.31 (s, 1 H), 7.00 (s, 1 H),6.77 (s, 1 H),6.08 (s, 1 H), 3.71 (s, 3 H), 3.70 (s, 3 H),2.64 (t, *J* = 8.0 Hz, 2 H), 1.57 - 1.52 (m, 2 H), 0.87 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 400 MHz):δ161.6, 151.6, 151.1, 144.6, 134.6, 117.1, 111.8, 105.8, 98.1, 55.9, 55.5, 33.4, 21.6, 13.8.

HRMS (ESI): calc. for [($C_{14}H_{17}NO_3$)H] (M+H), 248.1286 measured 248.1291.

6,7-Dimethoxy-4-pentylquinolin-2(1*H*)-one(3r).



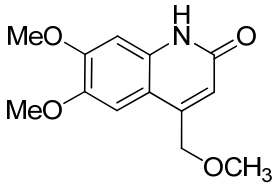
Brown colour solid; eluent (3% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 111 mg, 79 % yield was observed.

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.02 (s, 1 H),6.91 (s, 1 H),6.46 (s, 1 H), 3.98 (s, 3 H), 3.91 (s, 3 H),2.77 (t, *J* = 8.0 Hz, 2 H),1.71 (t, *J* = 8.0 Hz, 2 H), 1.38 - 1.37(m, 4 H) , 0.89 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$,100 MHz):δ 164.6, 152.8, 152.3, 145.6, 134.6, 116.6, 113.2, 104.7, 98.7, 56.3, 56.2, 32.4, 31.6, 28.3, 22.4, 13.9.

HRMS (ESI): calc. for [($C_{16}H_{21}NO_3$)H] (M+H) 276.1600 measured 276.1606.

6,7-Dimethoxy-4-(methoxymethyl)quinolin-2(1H)-one(3s).



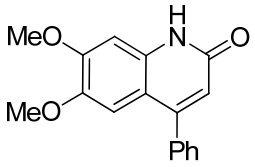
Dark yellow solid; eluent (4% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 79 mg, 62 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.50 (s, 1 H), 7.05(s, 1 H),6.87 (s, 1 H),6.34 (s, 1 H), 4.64 (s, 2 H), 3.80 (s, 3 H),3.79 (s, 3 H),3.40 (s, 3 H).

^{13}C NMR (DMSO-d_6, 400 MHz): δ161.6, 151.7, 146.9, 144.6, 134.6, 116.0, 110.3, 105.4, 97.9, 70.4, 58.1, 55.8, 55.5.

HRMS (ESI): calc. for [($C_{13}H_{15}NO_4$)H] (M+H) 250.1079, measured 250.1078.

6,7-Dimethoxy-4-phenylquinolin-2(1*H*)-one(3t).



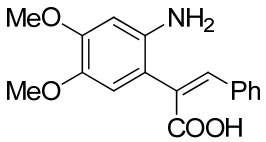
Light yellow colour solid; eluent (3% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 59 mg, 41 % yield was observed.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.50 - 7.45 (m, 5 H), 7.00 (s, 1 H),6.91 (s, 1 H), 6.57 (s, 1 H), 4.0 (s, 3 H), 3.72 (s, 3 H).

^{13}C NMR($CDCl_3$,100 MHz): δ 164.3, 152.9, 152.6, 145.7, 137.7, 135.0, 128.7, 128.6, 117.9, 112.9, 106.9, 98.6, 56.4, 56.0.

HRMS (ESI): calc. for [($C_{17}H_{15}NO_3$)H] (M+H) 282.1130, measured 282.1139.

(Z)-2-(2-Amino-4,5-dimethoxyphenyl)-3-phenylacrylic acid(3t').



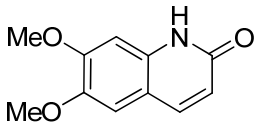
Red colour solid; eluent (2% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 49 mg, 32 % yield was observed.

^{1}H NMR ($CDCl_3$ 400 MHz):δ8.76 (s, 1 H), 7.67 (s, 1 H), 7.64(d, *J* = 8.0 Hz, 2 H), 7.47 -7.37 (m, 3 H), 7.18 (s, 1 H), 6.51 (s, 1 H),3.88 (s, 3 H),3.65 (s, 3 H), 1.64 (s, 2 H).

^{13}C NMR ($CDCl_3$ 100 MHz):δ 170.9, 151.2, 144.0, 136.7, 135.1, 134.4, 129.4, 129.2, 128.5, 112.8, 107.8, 95.3, 56.5, 56.2.

HRMS (ESI): calc. for [($C_{17}H_{17}NO_4$)Na] (M+Na) 322.1055, measured 322.1046.

6,7-Dimethoxyquinolin-2(1*H*)-one (5a).



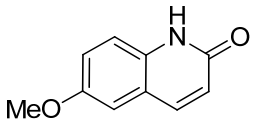
Dark brown colour solid; eluent (3% DCM in Methanol) The reaction scale is 100 mg, product was isolated in 79 mg, 76 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.54 (s, 1 H), 7.77(d, *J* = 12.0 Hz, 1 H), 7.17(s, 1 H), 6.84 (s, 1 H), 6.31 (d, *J* = 8.0 Hz, 1 H), 3.80 (s, 3 H),3.77 (s, 3 H).

^{13}C NMR (DMSO-d_6 100 MHz):δ 161.8, 151.8, 144.7, 139.7, 134.5, 118.7, 112.3, 108.8, 97.6, 55.7, 55.5.

HRMS (ESI): calc. for [($C_{11}H_{11}NO_3$)H] (M+H) 206.0817, measured 206.0821.

6-Methoxyquinolin-2(1*H*)-one(5b).



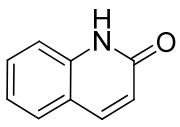
Brown colour solid; eluent (3% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 68 mg, 64 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.64 (s, 1 H), 7.84(d, *J* = 12.0 Hz, 1 H), 7.25 - 7.20 (m, 2 H), 7.14 (dd, *J* = 8.0 , 4.0 Hz, 1 H), 6.49 (d, *J* = 12.0 Hz, 1 H),3.77 (s, 3 H).

^{13}CNMR (DMSO-d_6 100 MHz):δ 161.5, 154.1, 139.8, 133.3, 122.3, 119.7, 119.5, 116.4, 109.3, 55.4.

HRMS (ESI): calc. for [($C_{10}H_9NO_2$)H] (M+H) 176.0711, measured 176.0716.

Quinolin-2(1*H*)-one (5c).



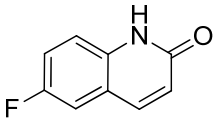
Light yellow colour solid; eluent (2% DCM in Methanol).The reaction scale is 100 mg, product was isolated in 64 mg, 60 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.75 (s, 1 H), 7.89(d, J = 8.0 Hz, 1 H), 7.64(d, J = 8.0 Hz, 1 H), 7.48(t, J = 8.0 Hz, 1 H), 7.30(d, J = 8.0 Hz, 1 H), 7.16(t, J = 8.0 Hz, 1 H), 6.49(d, J = 8.0 Hz, 1 H).

^{13}C NMR (DMSO-d_6 100 MHz):δ 161.9, 140.2, 138.9, 130.3, 127.9, 121.9, 121.7, 119.1, 115.1.

HRMS (ESI): calc. for [(C_9H_7NO)H] (M+H) 146.0606, measured 146.0609.

6-Fluoroquinolin-2(1*H*)-one (5d).



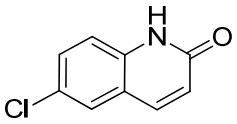
White colour solid; eluent (2% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 57 mg, 54% yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.82 (s, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.54(dd, J = 8.0, 4.0 Hz, 1 H), 7.40(td, J = 8.0, 4.0 Hz, 1 H), 7.33 - 7.30(m, 1 H), 6.56(d, J = 8.0 Hz, 1 H).

^{13}C NMR (DMSO-d_6 100 MHz):δ 161.6, 155.7, 150.4, 139.4, 135.6, 123.2, 119.8, 118.5 and 118.3 (F-coupling), 112.8 and 112.5 (F-coupling).

HRMS (ESI): calc. for [(C_9H_6FNO)H] (M+H) 164.0511, measured 164.0509.

6-Chloroquinolin-2(1*H*)-one (5e).



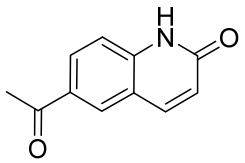
Grey colour solid; eluent (3% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 59 mg, 56 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ11.87 (s, 1 H), 7.87(d, J = 12.0 Hz, 1 H), 7.78(d, J = 4.0 Hz, 1 H), 7.52 (dd, J = 8.0, 4.0 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 6.56 (d, J = 12.0 Hz, 1 H).

^{13}C NMR (DMSO-d_6 100 MHz):δ 161.7, 139.2, 137.6, 130.2, 126.9, 125.6, 123.2, 120.3, 117.0.

HRMS (ESI): calc. for [(C_9H_6ClNO\)H] (M+H) 180.0216, measured180.0220.

6-Acetylquinolin-2(1*H*)-one (5f).



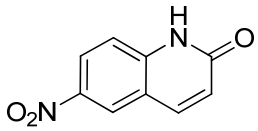
White colour solid; eluent (3% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 48 mg, 46 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ12.06 (s, 1 H), 8.36(d, *J* = 4.0 Hz, 1 H), 8.05 - 8.02(m, 2 H), 7.36 (d, *J* = 12.0 Hz, 1 H), 6.58 (d, *J* = 12.0 Hz, 1 H), 2.59 (s, 3 H) .

^{13}C NMR (DMSO-d_6 100 MHz):δ 196.5, 162.2, 142.1, 140.7, 130.7, 129.7, 129.5, 122.7, 118.5, 115.4, 26.6.

HRMS (ESI): calc. for [($C_{11}H_9NO_2$)H] (M+H) 188.0711, measured 188.0713.

6-Nitroquinolin-2(1*H*)-one (5g).



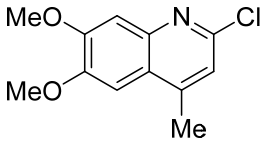
Light yellow colour solid; eluent (2% DCM in Methanol).The reaction scale is 100 mg, product was isolated in 50 mg, 48 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz):δ12.31 (s, 1 H), 8.70 (s, 1 H), 8.33(dd, *J* = 8.0, 4.0 Hz, 1 H), 8.13 (d, *J* = 8.0 Hz, 1 H), 7.43 (d, *J* = 12.0 Hz, 1 H), 6.68 (d, *J* = 12.0 Hz, 1 H).

^{13}C NMR (DMSO-d_6 100 MHz):δ 162.0, 143.3, 141.5, 140.2, 125.1, 124.4, 123.9, 118.6, 116.1.

HRMS (ESI): calc. for [($C_9H_6N_2O_3$)H] (M+H) 191.0456, measured 191.0457.

2-chloro-6,7-dimethoxy-4-methylquinoline (6a).



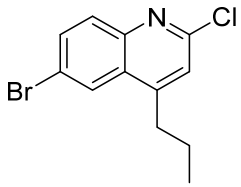
White colour solid; eluent (7% petether in ethylacetate) The reaction scale is 100 mg, product was isolated in 85 mg, 79 % yield was observed.

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.30 (s, 1 H), 7.07 (s, 1 H), 7.04 (s, 1 H), 3.98 (s, 3 H), 3.97 (s, 3 H) 2.57 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ152.6, 149.6 148.2, 145.7, 144.6, 122.0, 120.6, 107.9, 101.6, 56.1, 55.1, 18.8.

HRMS (ESI): calc. for [($C_{12}H_{12}ClNO_2$)H] (M+H) 238.0635, measured 238.0626.

6-bromo-2-chloro-4-propylquinoline (6b).



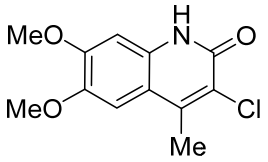
White colour solid; eluent ((3% petether in ethylacetate) The reaction scale is 100 mg, product was isolated in 75 mg, 71 % yield was observed.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 8.10 (d, *J* = 4.0 Hz, 1 H), 7.85 (d, *J* = 4.0 Hz, 1 H), 7.75 dd, (*J* = 8.0, 4.0 Hz, 1 H) 7.22 (s, 1 H), 2.94 (t, *J* = 8.0 Hz, 2 H), 1.75 (sex, *J* = 8.0 Hz, 2 H), 1.04 (t, *J* = 8.0 Hz, 3 H) .

^{13}C NMR ($CDCl_3$,100 MHz):δ151.0, 146.6 133.5, 130.9, 127.5, 126.2, 122.3, 120.7, 33.8, 22.8, 14.0.

HRMS (ESI): calc. for [($C_{12}H_{11}BrCl$)H] (M+H) 283.9841, measured 283.9842.

3-Chloro-6,7-dimethoxy-4-methylquinolin-2(1H)-one (7a).



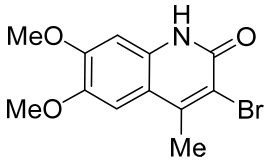
White colour solid; eluent (2% DCM in Methanol) reaction scale is 100 mg, product was isolated in 90 mg, 78 % yield was observed.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.94 (s, 1 H), 7.09 (s, 1 H), 6.82 (s, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H) 2.52 (s, 3 H).

^{13}C NMR (DMSO-d_6 100 MHz):δ 156.9, 151.7 145.1, 143.6, 132.2, 122.2, 112.2, 106.1, 97.7, 55.8, 55.6, 16.4.

HRMS (ESI): calc. for [($C_{12}H_{13}ClNO_3$)H] (M+H) 254.0584, measured 254.0577.

3-Bromo-6,7-dimethoxy-4-methylquinolin-2(1*H*)-one (7b).



White colour solid; eluent (2% DCM in Methanol). The reaction scale is 100 mg, product was isolated in 112 mg, 83 % yield was observed.

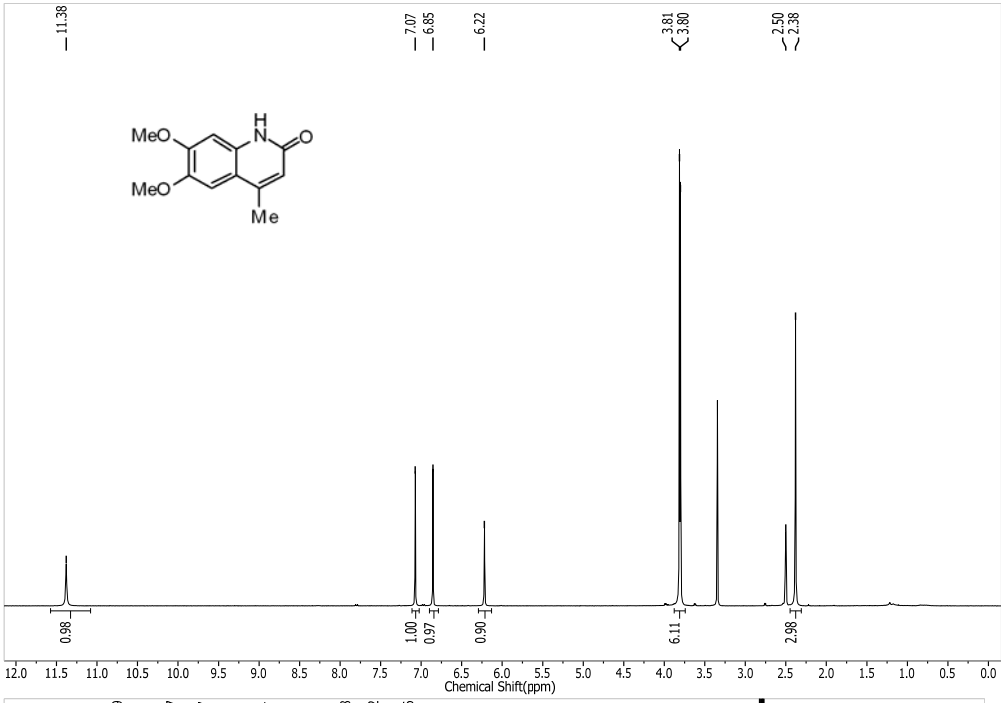
^{1}H NMR (DMSO-d_6, 400 MHz):δ11.96 (s, 1 H), 7.18 (s, 1 H), 6.87 (s, 1 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 2.61(s, 3 H).

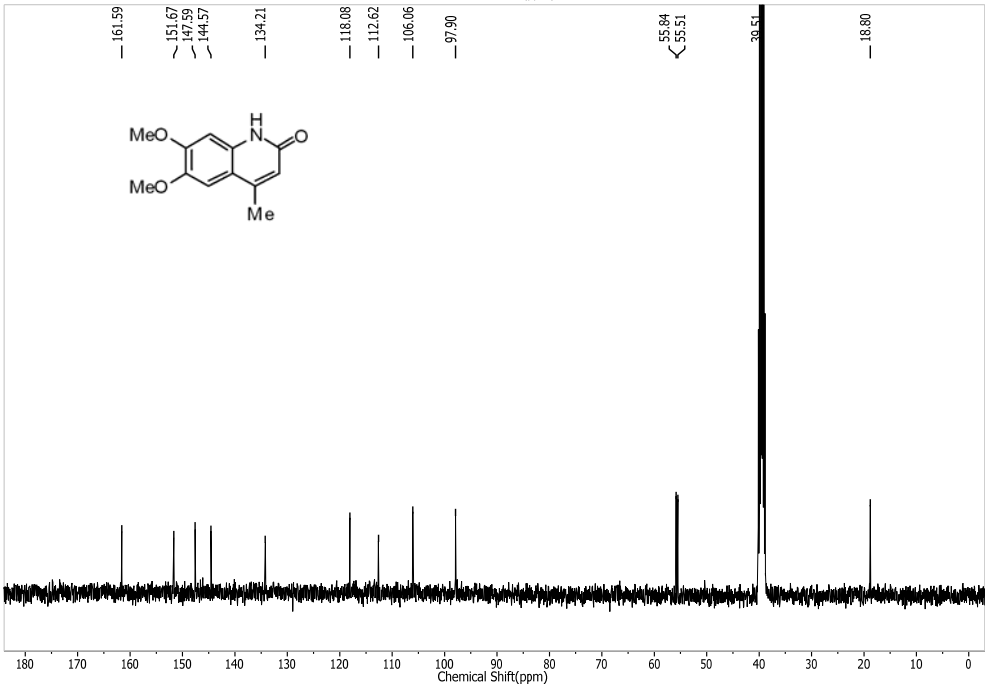
(DMSO-d_6 100 MHz):δ 157.2, 151.9, 146.4, 145.0, 132.7, 116.1, 112.3, 106.4, 97.7, 55.9, 55.6,19.9.

HRMS (ESI): calc. for [($C_{12}H_{12}BrNO_3$)H] (M+H), 298.0079 measured 298.0071.

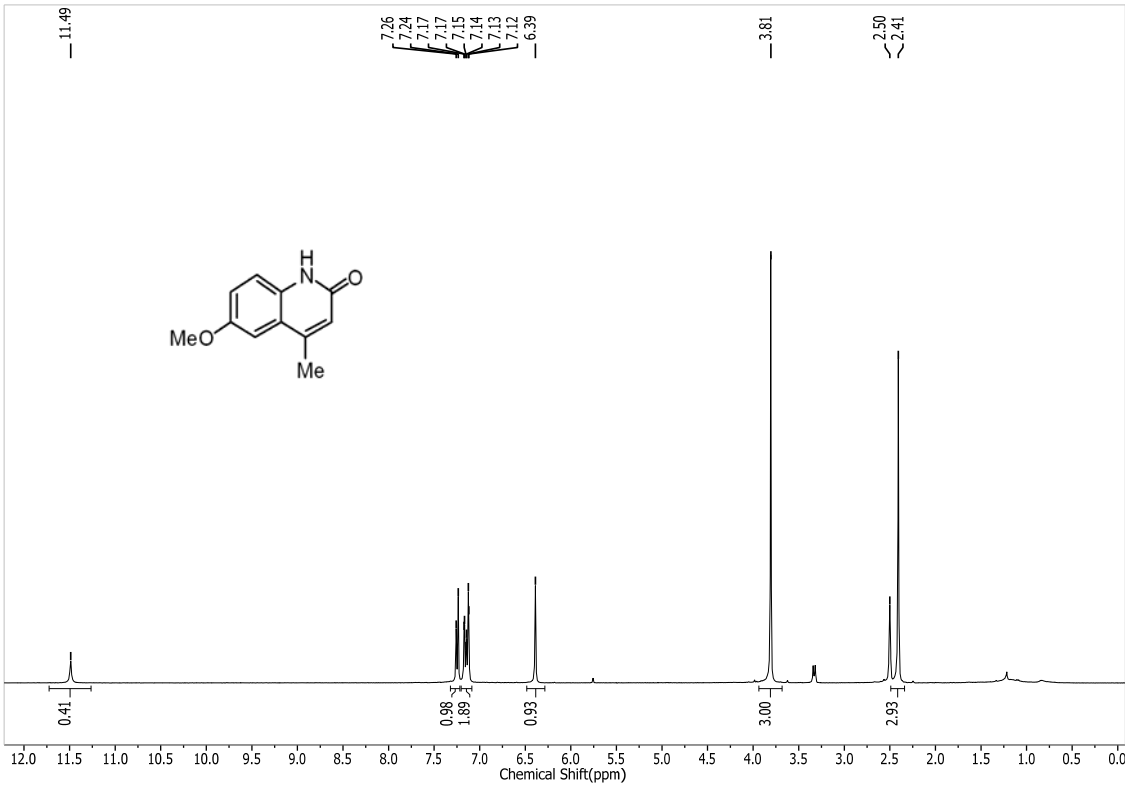
2B.16 Spectral Copies of Selected Compounds

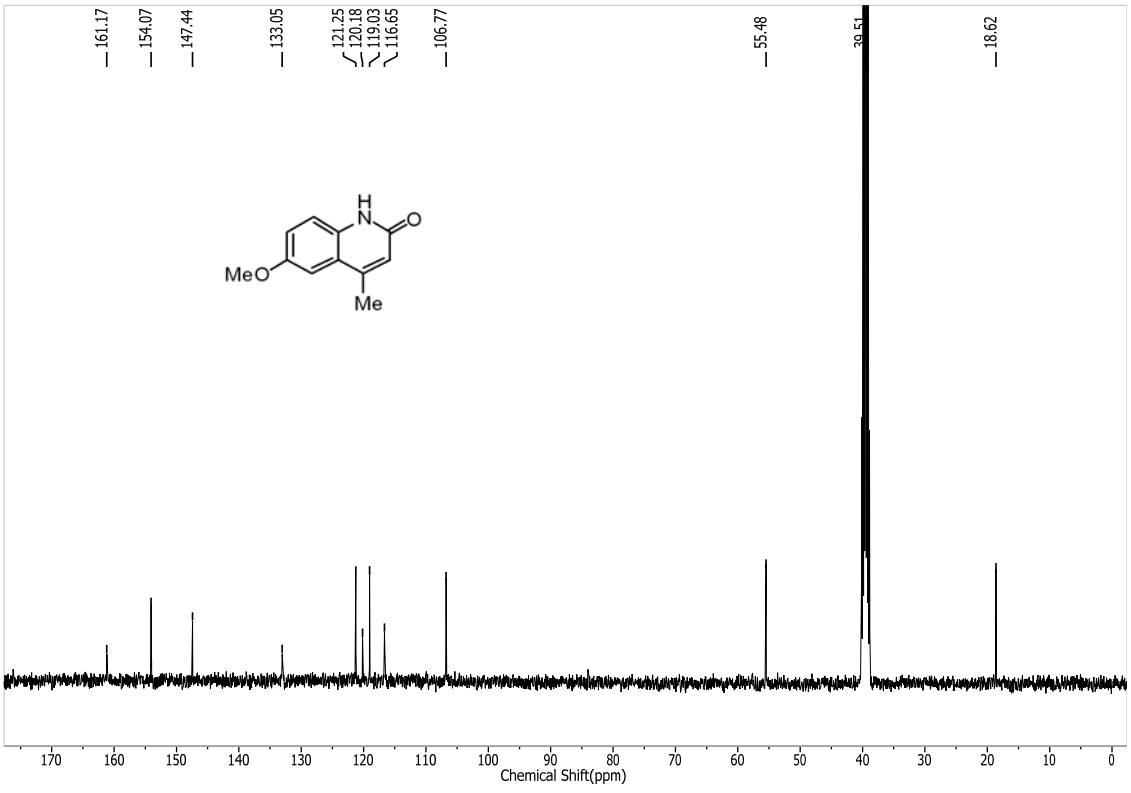
^{1}H and ^{13}CNMR Spectra of Compound **3a.**



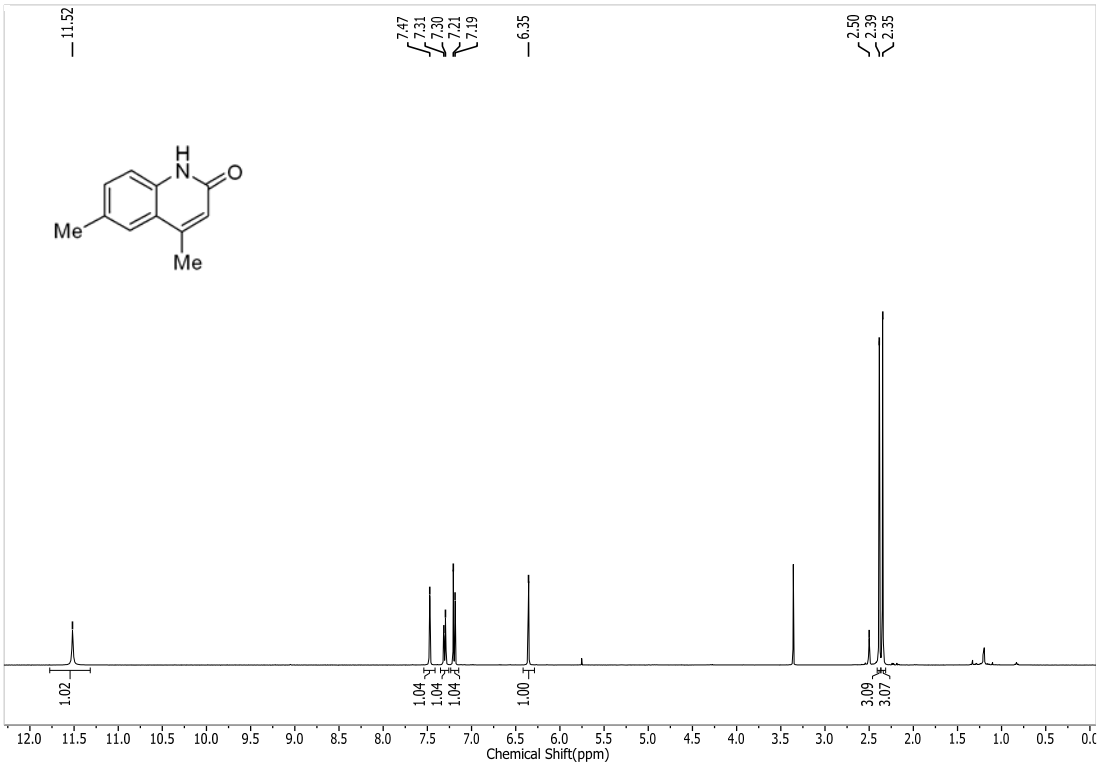


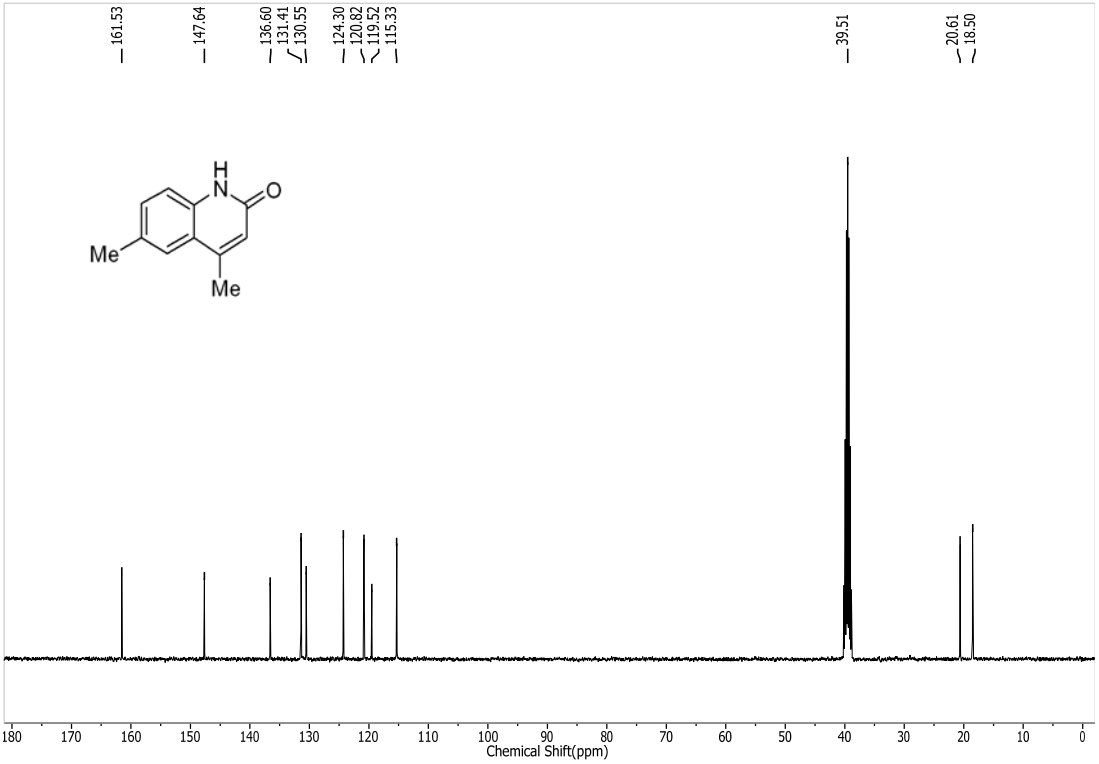
^{1}H and $^{13}CNMR$ Spectra of Compound **3b.**



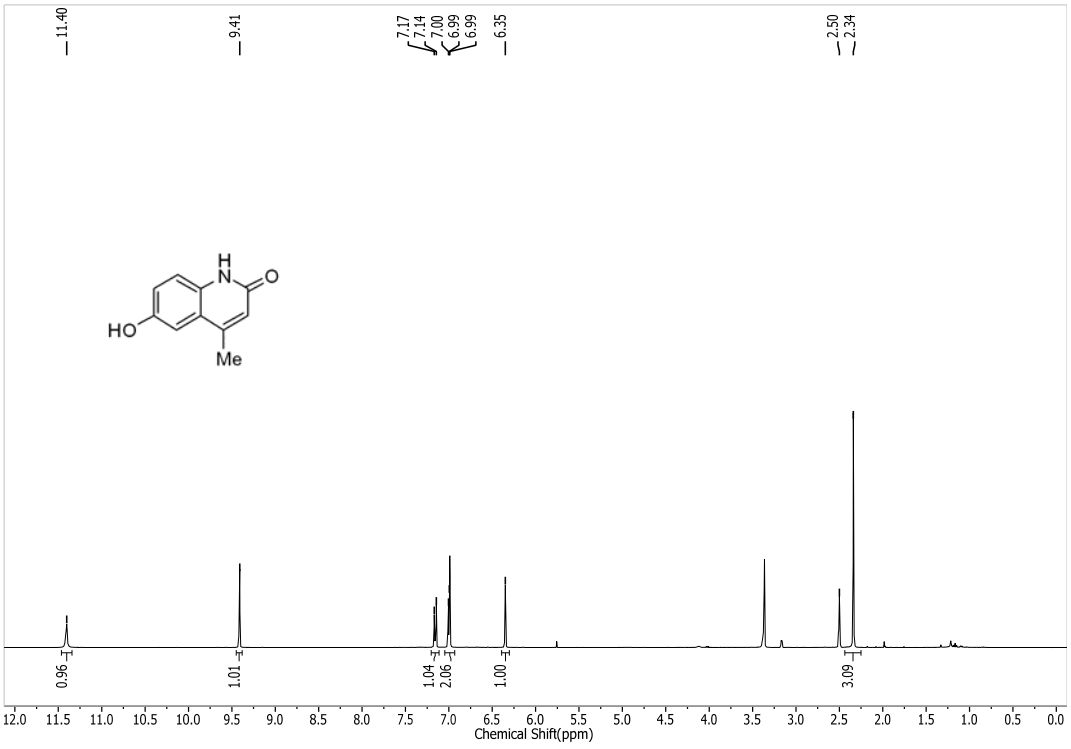


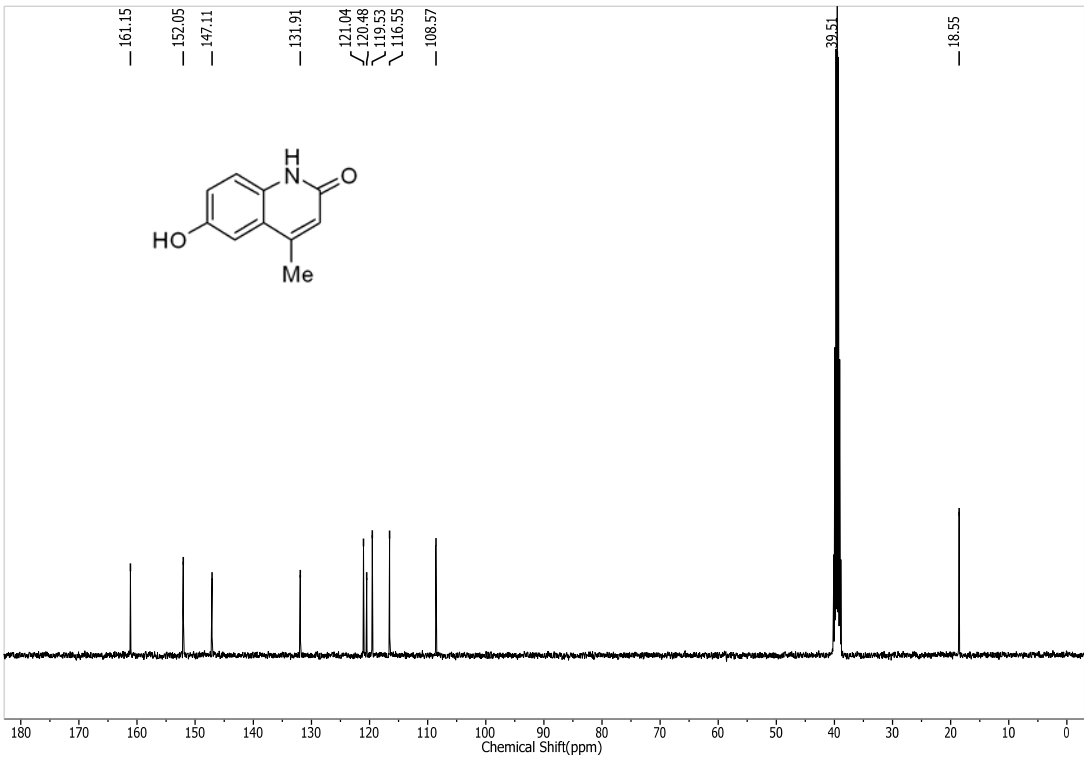
^{1}H and $^{13}CNMR$ Spectra of Compound **3c.**



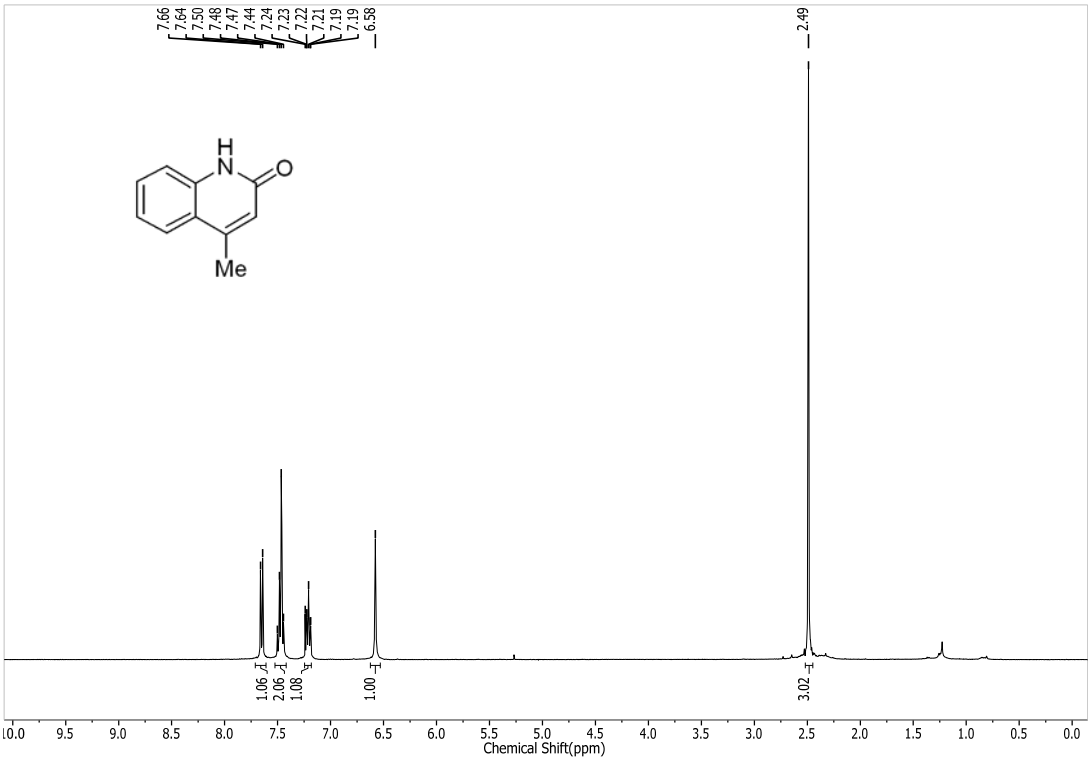


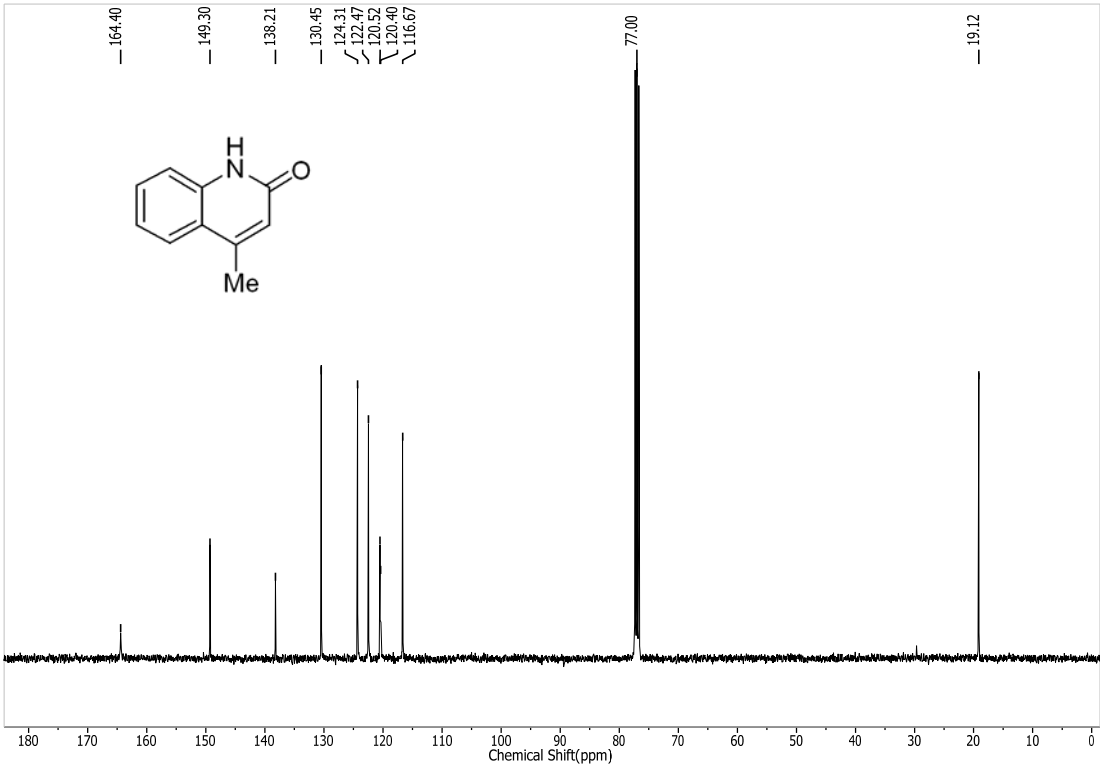
^{1}H and $^{13}CNMR$ Spectra of Compound **3d.**



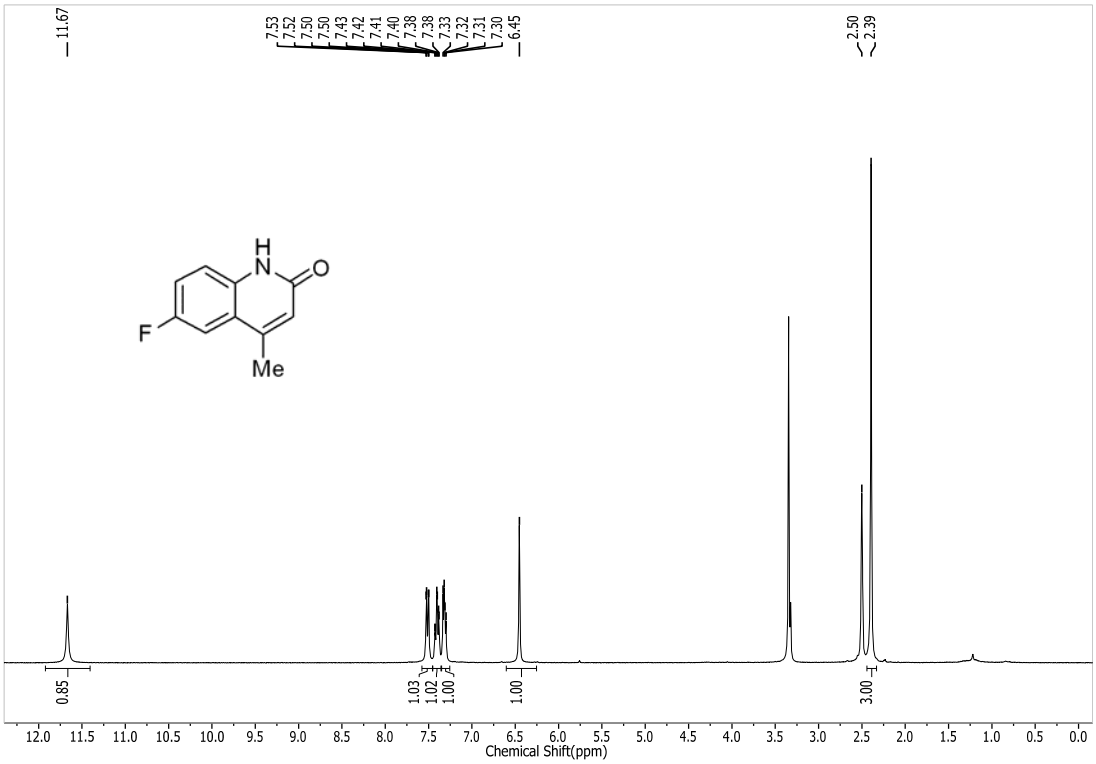


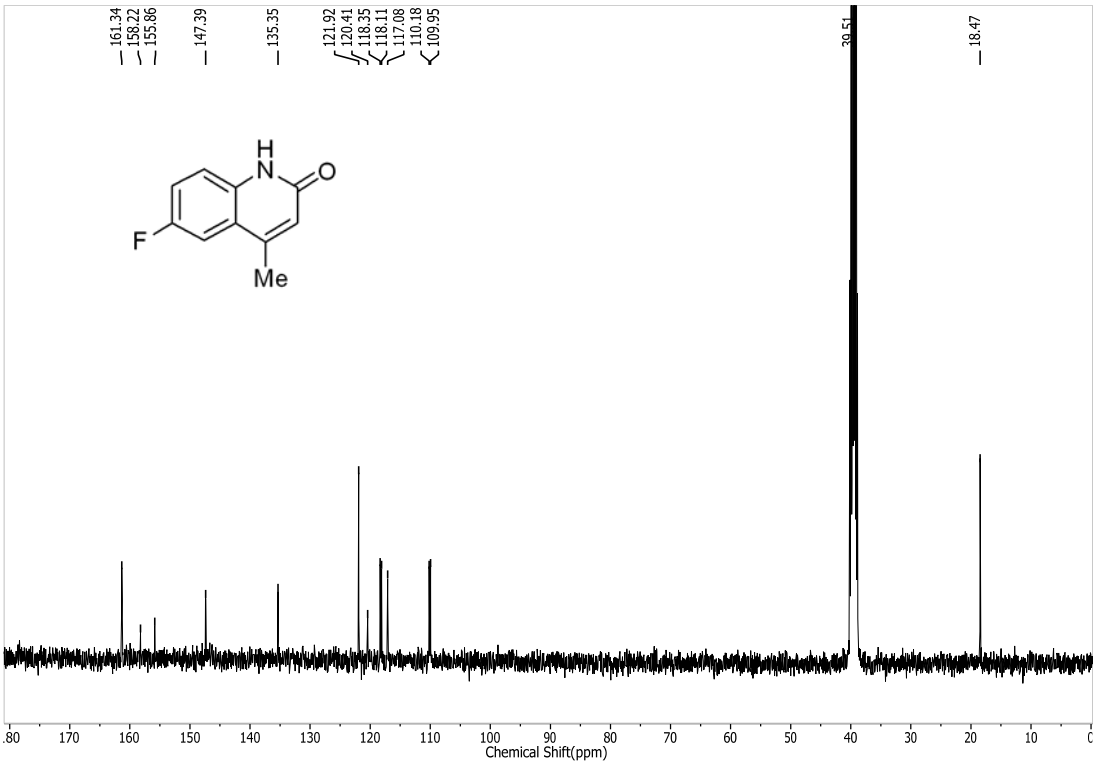
^{1}H and ^{13}CNMR Spectra of Compound **3e.**



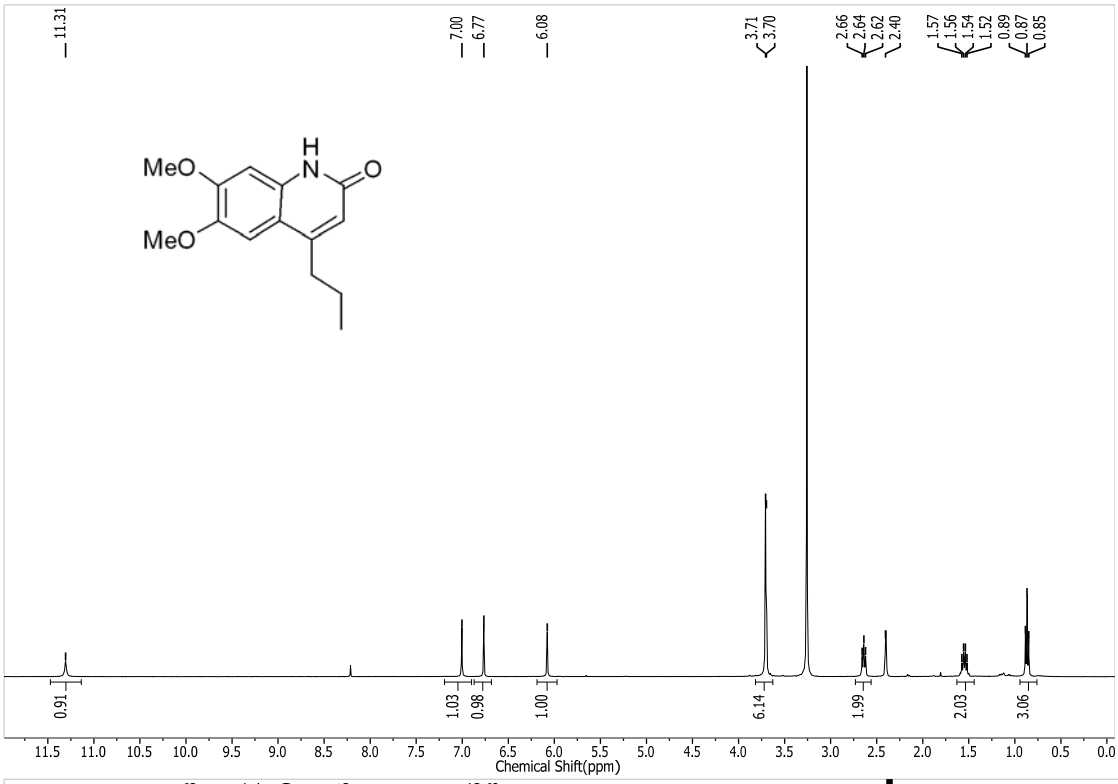


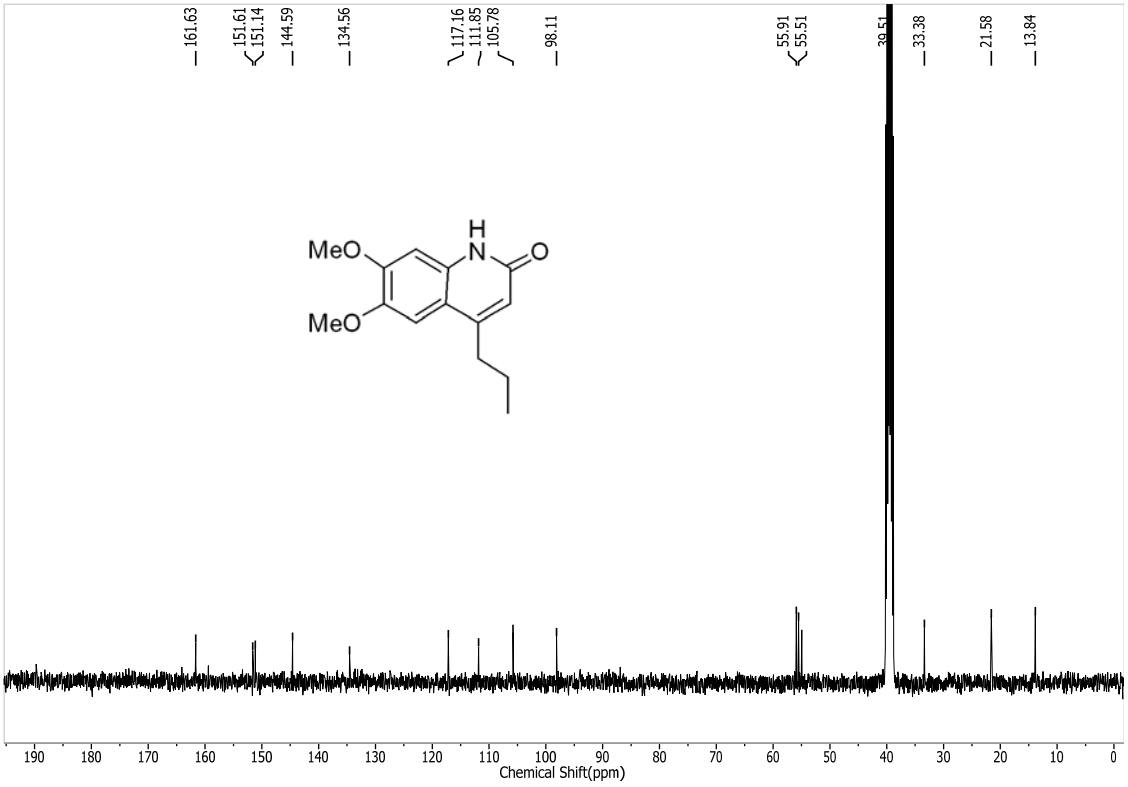
^{1}H and ^{13}CNMR Spectra of Compound **3f.**



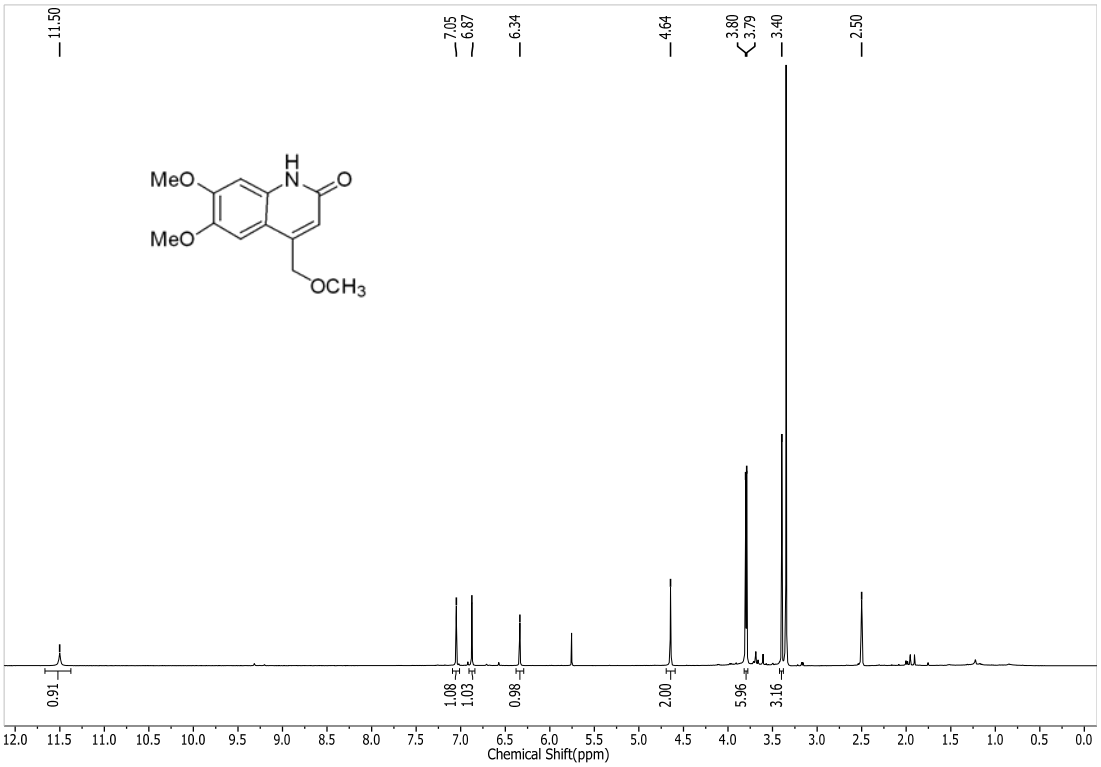


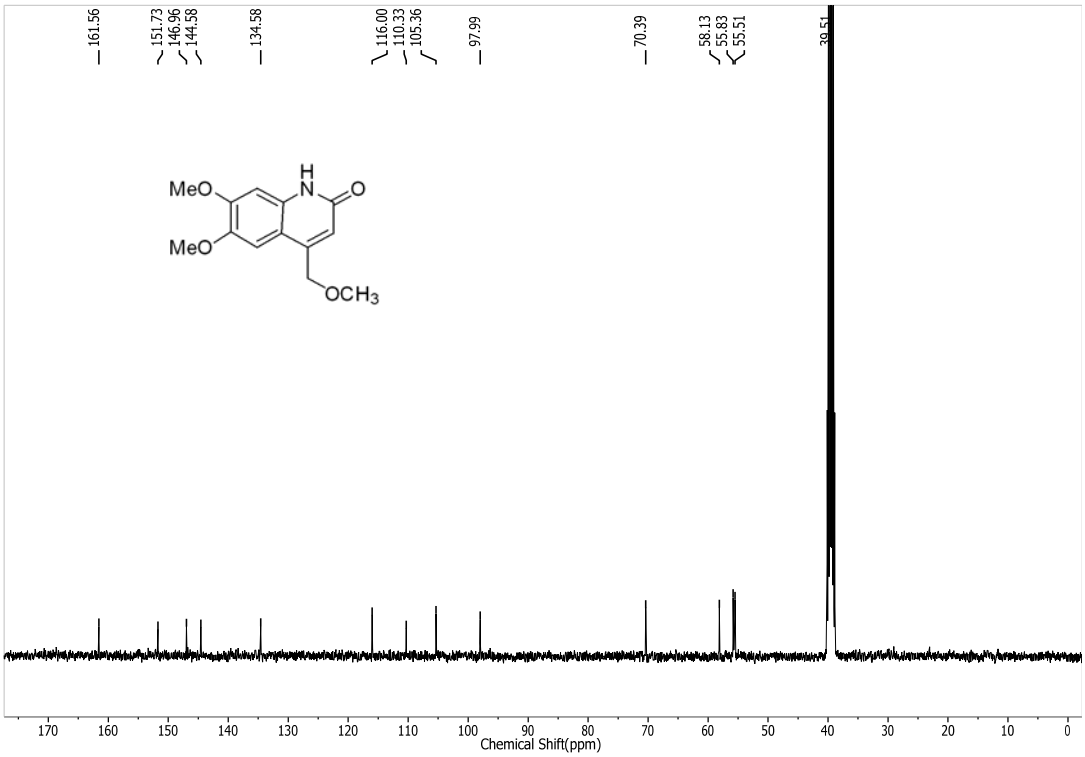
^{1}H and $^{13}CNMR$ Spectra of Compound **3q.**



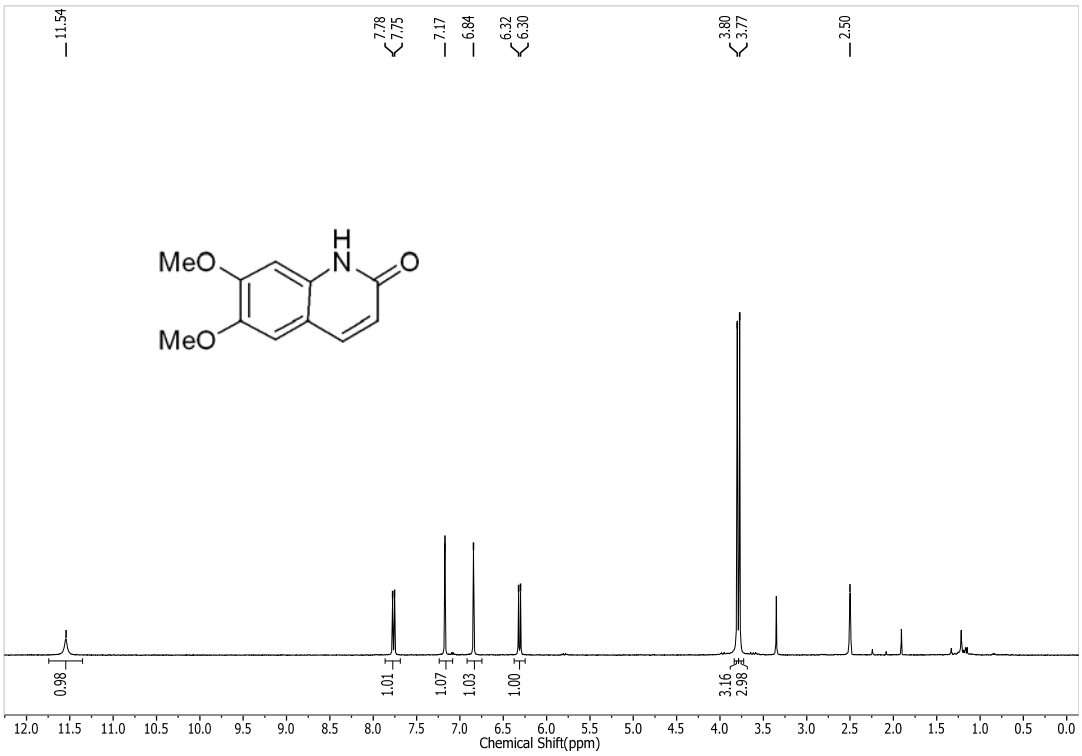


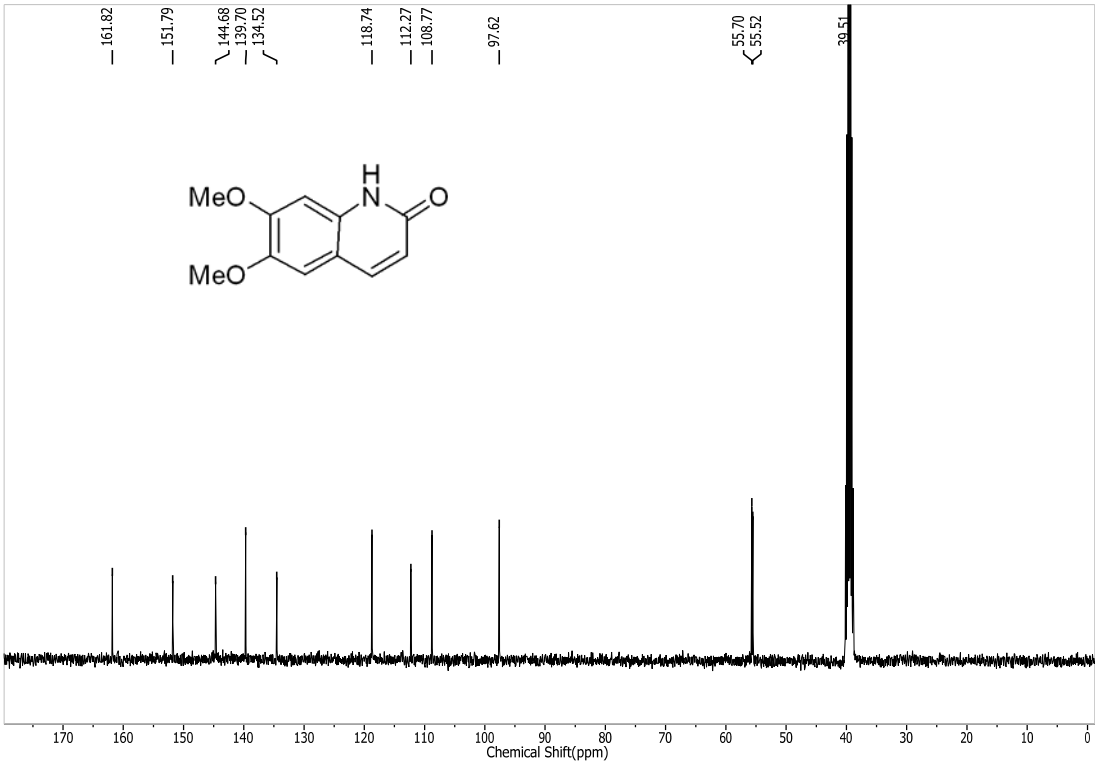
^{1}H and ^{13}CNMR Spectra of Compound **3s.**



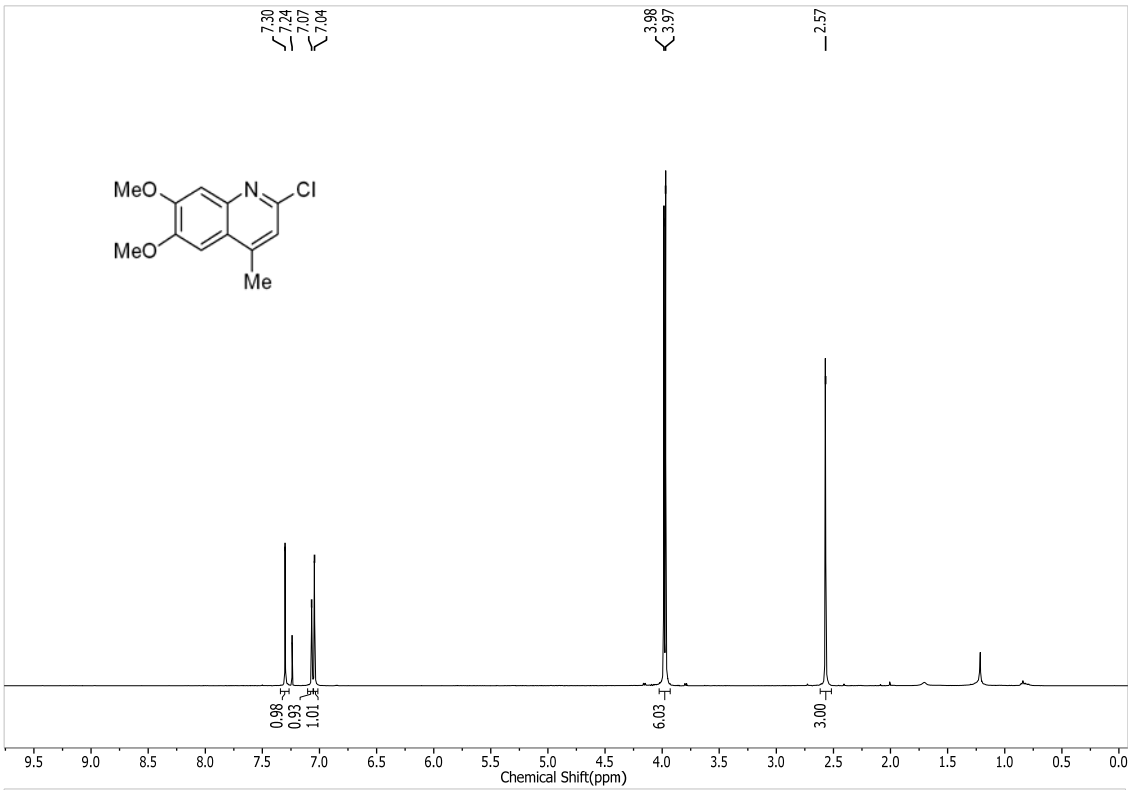


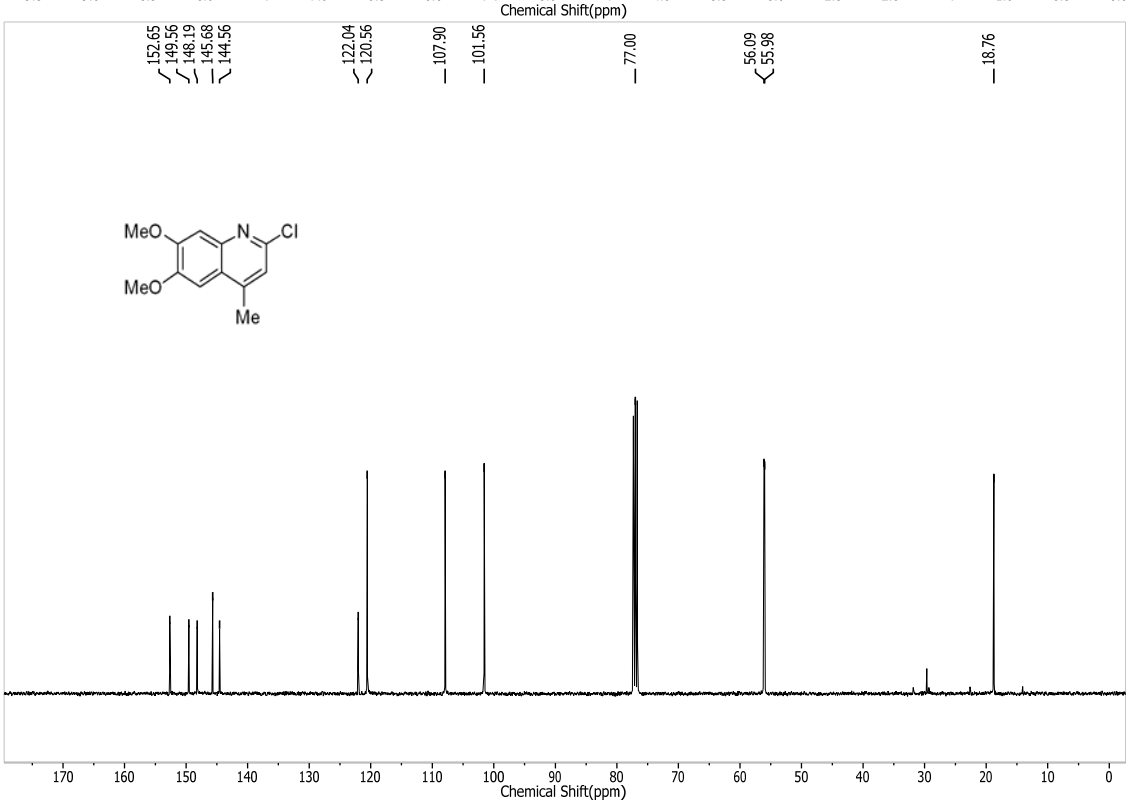
^{1}H and $^{13}CNMR$ Spectra of Compound **5a.**



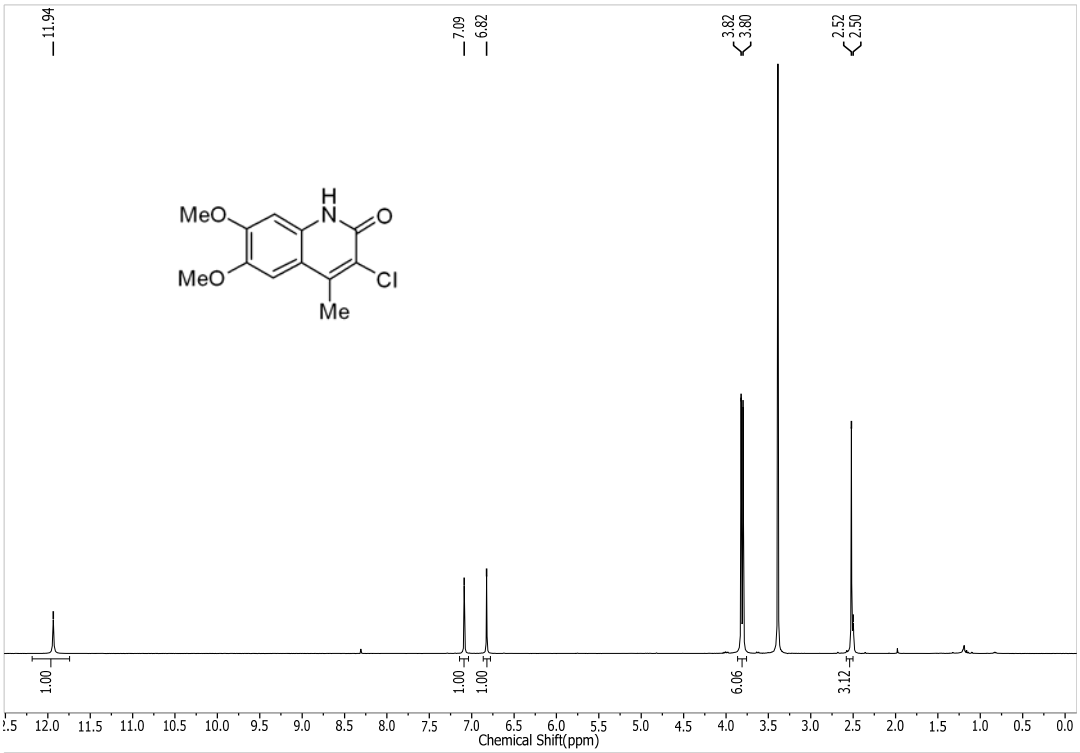


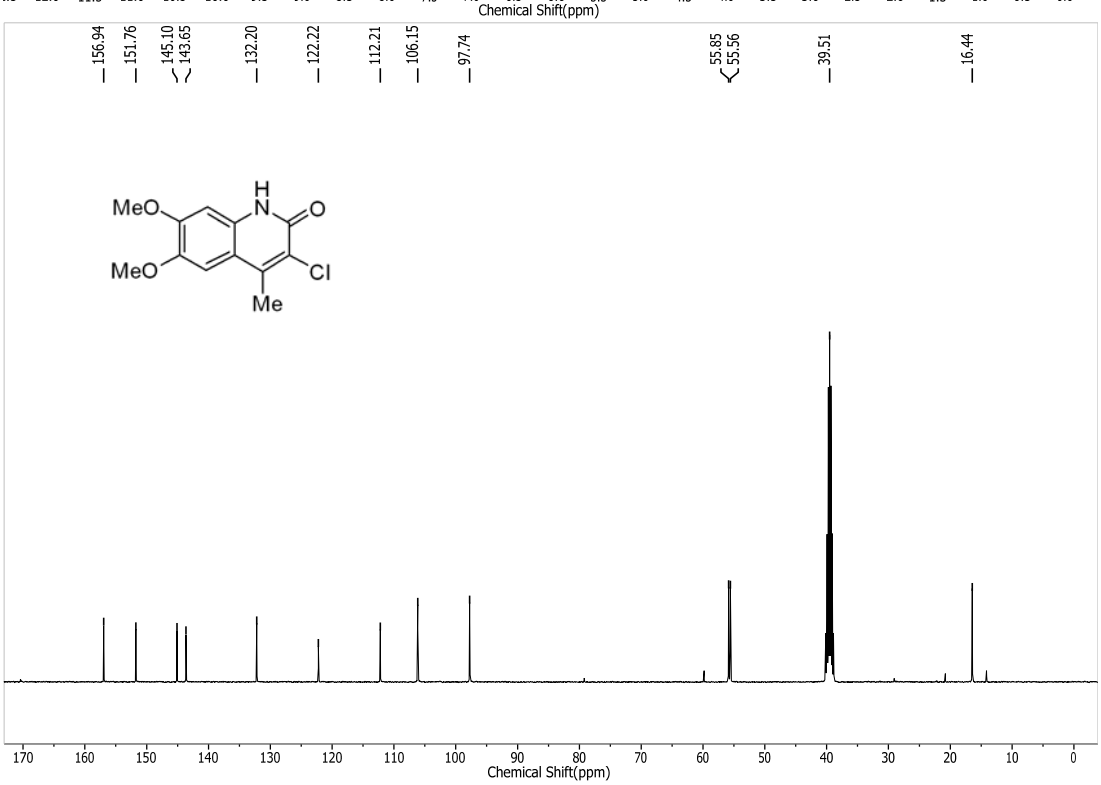
^{1}H and $^{13}CNMR$ Spectra of Compound **6a.**



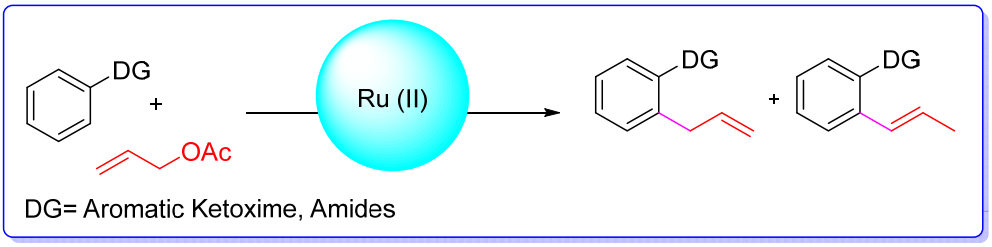


^{1}H and ^{13}CNMR Spectra of Compound **7a.**





Chapter-3



Ruthenium-Catalyzed Oxidant-Free Regioselective *Ortho*-Allylation and vinylation of Substituted Aromatics with Allylic acetates

Section 3A: Ruthenium-Catalyzed Oxidant-Free Allylation of Aromatic Ketoximes with Allylic Acetates at Room Temperature

3A.1 Introduction

The allylarene unit is present in various natural products and medicinally relevant molecules.[1] In addition, substituted allylic derivatives are a versatile synthetic intermediate which is widely used to synthesize natural products and pharmaceutical molecules (Figure 1).[2]

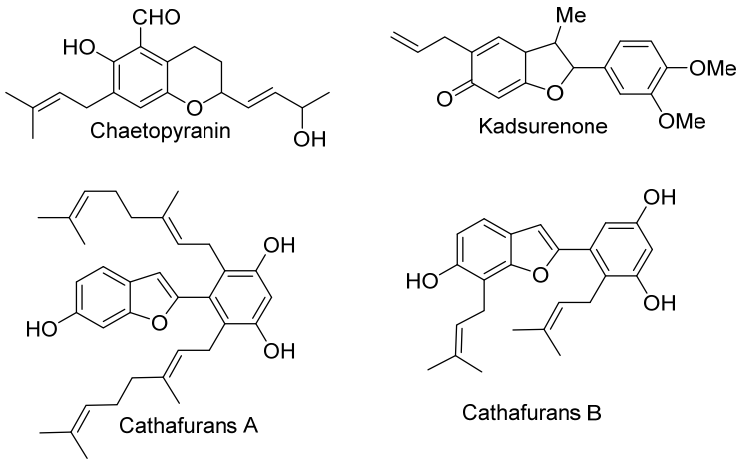
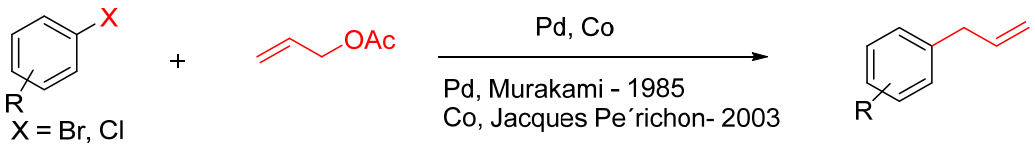


Figure 1: Selected biologically active molecules containing allyl moieties.

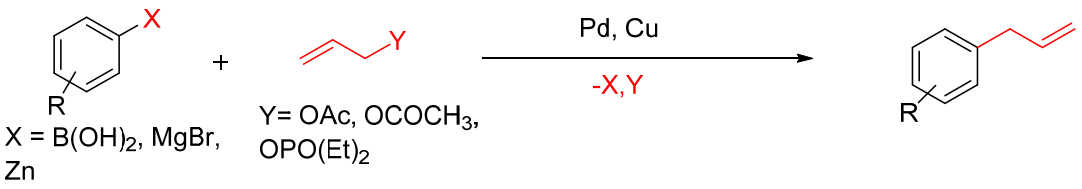
Various routes are available in the literature for synthesizing allylaromatics in organic synthesis.Cross-couplingreactions based on a prefunctionalized arene is one of the powerful methods to synthesize of substituted allylarenes in a highly effective manner.[3,4] In these reactions, aromatic halide (or) organometallic reagents coupled with allylating reagents in the presence of various transition metal catalysts.

In 1985, Murakami's group reported a palladium-catalyzed direct allylation of aryl bromides with allylic acetates.[3a] Later, Pe´richon's group showed the synthesize of allylarenes via a cobalt-catalyzed coupling of aryl halides with allylic acetates at room temperature (Scheme 3A.1).[3b]



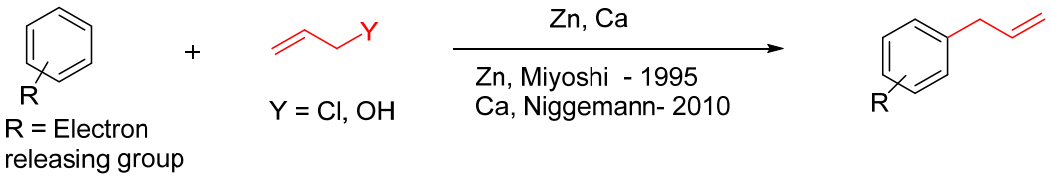
Scheme 3A.1: Transition metal-catalyzed allyation of aryl halides with allylic acetate.

Subsequently, substitution reactions of allylic derivatives with various aromatic organometallic reagents such as aryl magnesium halides, diaryl zinc, and aryl boronic acids have reported in the presence of palladium and copper catalysts (Scheme 3A.2).[4] However, in these previous reports, a preactivated halogen or metal species is needed.



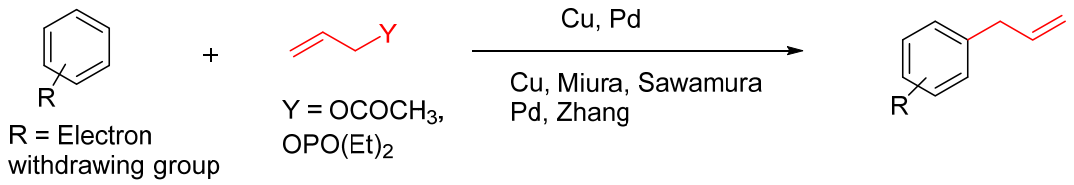
Scheme 3A.2: Transition metal-catalyzed allyation of organometallic reagents with allylic electrophiles.

Allylarenes are also efficiently prepared by the reaction of allylic electrophiles with substituted aromatics without having any preactivated species. Electron-rich allylarenes are prepared by a Lewis acid-mediated Friedel-Crafts type allylation of electron-rich aromatics with allylic electrophiles (Scheme 3A.3).[5] Miyoshi's group described the $ZnCl_2$ mediated Friedel-crafts allylation of aromatic compounds using allylchloride at room temperature.[5a] Later, calcium-catalyzed coupilng of allyl alcohol with electron-rich aromatics was reported by Niggemann's group.[5b]



Scheme 3A.3: Friedel-crafts allylation of electron-rich aromatics with allylic electrophiles.

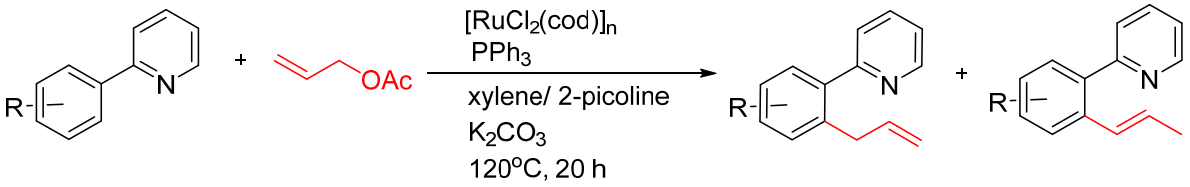
The allylation of electron-deficient polyfluoroarenes with allylic electrophiles was done in the presence of palladium or copper complexes as catalysts via the C–H bond activation (Scheme 3A.4).[6] Miura's[6a] and sawamura's[6b] groups showed the copper-catalyzed region- and stereo-selective allylation of electron-deficient arenes with allylic phosphates. Eventually, Zhang's group described a palladium-catalyzed allylation of electron-deficient polyfluoroarenes with allylic carbonates.[6c,d] This method is highly atom-economical. However, the substrate scope of aromatics is highly limited and only highly electron rich (or) electron defficient arenes are suitable for the allylation reaction.



Scheme 3A.4: Transition metal-catalyzed allyation of electron defficient arenes with allylic electrophiles

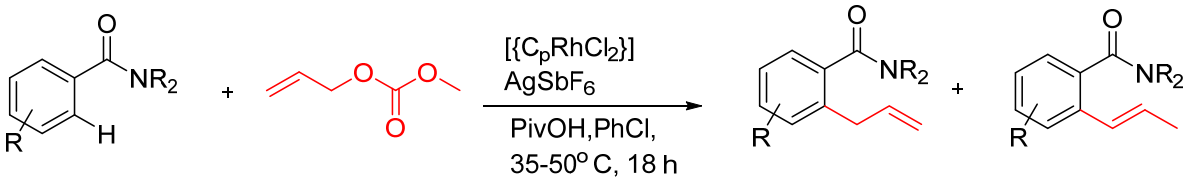
Recently, the transition-metal catalyzed directing group assisted carbon-carbon bond formation reactions via the C–H bond functionalization has grown rapidly as a potentially more efficient and highly regioselective process.[7] By employing the chelating groups, allylation can also be done at the *ortho* C–H bond of substituted aromatics with allylic electrophiles in the presence of various metal catalysts.[8]

In 2001, Inoue's group showed a highly selective *ortho*-allylation of 2-phenylpyridine with allyl acetates in the presence of a ruthenium(II)-phosphine complex (Scheme 3A.5). However, in this reaction, linear aliphatic allyl acetates afforded a mixture of linear and branched products.[8a]



Scheme 3A.5: Ruthenium-Catalyzed *ortho*Allylation of 2-Phenyl pyridine with Allylic Acetates

Later, a rhodium-catalyzed *ortho* allylation of benzamides with allylic carbonates at ambient temperature was reported by the Glorius's group (Scheme 3A.6).[8b] The catalytic reaction was explored with various substituted amides and allylic acetates. However, along with *ortho* allylated benzamides, a minor amount of *ortho* vinylated benzamide product was also observed.

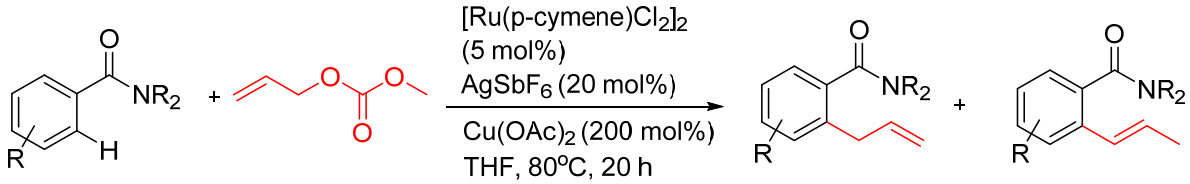


Scheme 3A.6: Rhodium-Catalyzed *ortho*Allylation of Aromatic amides with Allylic carbonates

Interestingly, by using the same rhodium catalyst, the regioselective synthesis of *ortho*-vinylated benzamide was synthesized by Loh's group via coupling of aromatic amides with allylic acetates at higher tempature (Scheme 3A.7).[8c]

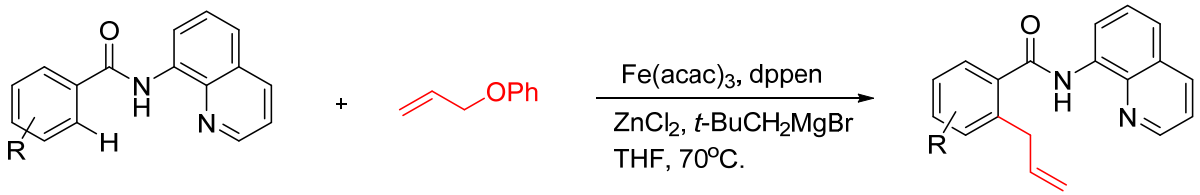
Scheme 3A.7: Rhodium-Catalyzed *ortho*vinylation of Aromatic amides with Allylic acetates

Later, by using a less expensive ruthenium-catalyzed *ortho* allylation of benzamides was reported by Kim and his co-workers at the moderate temperature with 2 equivalent of $Cu(OAc)_2 \cdot H_2O$ (Scheme 3A.8).[8d] As expected, the mixture of *ortho*-allylated and vinylated products were observed.



Scheme 3A.8: Ruthenium-Catalyzed *ortho*Allylation of Aromatic amides with Allylic carbonates

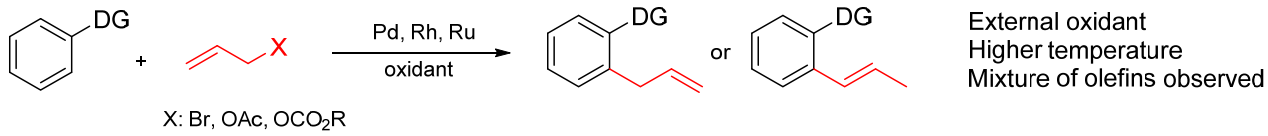
The Allylation of aromatics was also done by using the highly earth-abundant and a less expensive iron catalyst. Nakamura's group reported an iron-catalyzed *ortho* allylation of quinoline substituted amides with allyl ethers using diphosphine ligand and organomettalic reagent as a base (Scheme 3A.9).[8e]



Scheme 3A.9: Iron-Catalyzed *ortho*Allylation of Aromatic amides with Allylic ethers

In all these earlier reports, a stoichiometric amount of oxidant or base or acid was used to activate the C–H bond of aromatics. Further, the high temperature is required for the reaction and also mostly a mixture of double bond migration products were observed (Scheme 3A.10).

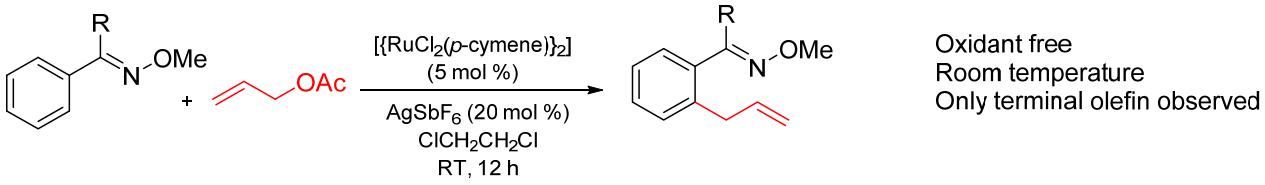
Previous reports



Scheme 3A.10: Transition metal-catalyzed allyation of substituted aromatics with allylic electrophiles.

Our continuous interest on the ruthenium-catalyzed C–H bond functionalization reaction[9] prompted us to explore the possibility of preparation of allylarenes from the easily affordable allylic acetate source without having any external oxidant at room temperature. Herein, we report an oxidant free *ortho* allylation of substituted aromatic ketoximes with allylic acetates in the presence of ruthenium catalyst at room temperature under mild reaction conditions. In the reaction, allyl acetate plays dual role, it acts as an allylating agent and also provides an acetate anion source for activating the C–H bond of aromatics. Thus, an external acetate source is not required for the reaction. Very interestingly, the double bond migration product was not observed and only terminal olefin product was observed (Scheme 3A.11).

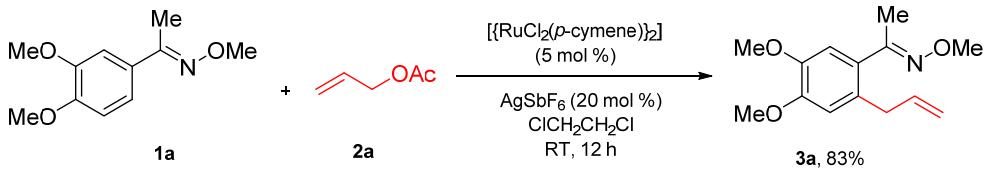
Present work



Scheme 3A.11: Ruthenium-Catalyzed Oxidant-Free Allylation of Aromatic Ketoximes with Allylic Acetates.

3A.2 Results and Discussion

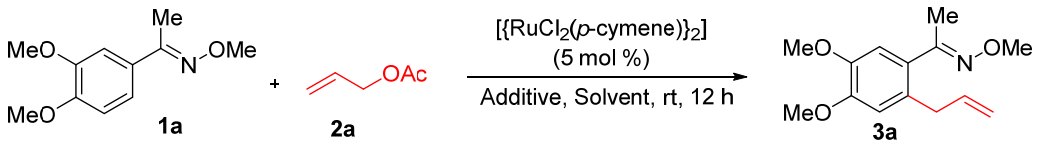
When 3,4-dimethoxy ketoxime (**1a**) was treated with allyl acetate (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), $AgSbF_6$ (20 mol %) in 1,2-dichloroethane at room temperature for 12 h, *ortho* allylated 3,4-dimethoxy ketoxime (**3a**) was observed in 83% yield (Scheme 3A.12). The allylation reaction is highly regioselective and the C–H bond activation takes place at a less hindered C6-H of **1a**. In the reaction, no external oxidant or acetate source was used. It is strongly believed that the acetate moiety of **2a** would deprotonates the C–H bond of **1a**.



Scheme 3A.12: Ruthenium-Catalyzed *ortho* Allylation of 3,4-Dimethoxy Ketoxime (1a) with Allyl Acetate (2a).

3A.3 Optimization Studies

Table 3A.1: Optimization Studies with Various Additive, Solvent and Cosolvent.



entry	solvent	Allyl source	Additive	yield of **3a** (%)[b]
1	Isopropanol	Allyl acetate (1.5 equiv)	$AgSbF_6$	NR
2	Methanol	Allyl acetate (1.5 equiv)	$AgSbF_6$	NR
3	THF	Allyl acetate (1.5 equiv)	$AgSbF_6$	NR
4	DME	Allyl acetate (1.5 equiv)	$AgSbF_6$	NR
5	DMF	Allyl acetate (1.5 equiv)	$AgSbF_6$	NR
6	DMSO	Allyl acetate (1.5 equiv)	$AgSbF_6$	NR
7	Toluene	Allyl acetate (1.5 equiv)	$AgSbF_6$	NR
8	Dichloromethane	Allyl acetate (1.5 equiv)	$AgSbF_6$	52
9	Chlorobenzene	Allyl acetate (1.5 equiv)	$AgSbF_6$	34
10	**$ClCH_2CH_2Cl$**	**Allyl acetate (1.5 equiv)**	**$AgSbF_6$**	**83**
11	$ClCH_2CH_2Cl$	Allyl acetate (1.5 equiv)	AgOTf	68
12	$ClCH_2CH_2Cl$	Allyl acetate (1.5 equiv)	$AgBF_4$	59
13	$ClCH_2CH_2Cl$	Allyl acetate (1.5 equiv)	KPF_6	NR
14	$ClCH_2CH_2Cl$	Allyl bromide (1.5 equiv)	$AgSbF_6$	NR
15	$ClCH_2CH_2Cl$	Allyl carbonate (1.5 equiv)	$AgSbF_6$	NR
16	$ClCH_2CH_2Cl$	Allyl alcohol (1.5 equiv)	$AgSbF_6$	NR
17	$ClCH_2CH_2Cl$	Pivalic acid (5.0 equiv)	$AgSbF_6$	NR

[a]All reactions were carried out under the following conditions: **1a** (100 mg), **2a** (2.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), additive (20 mol %) and solvent (3.0 mL) at rt for 12 h under N_2 atmosphere. [b]GC yield.

Note: The catalytic reaction was tried without ruthenium and $AgSbF_6$. No product **3a** was observed.

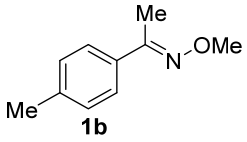
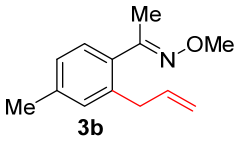
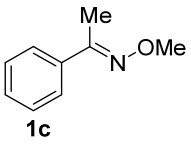
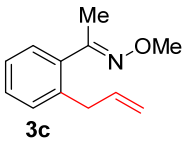
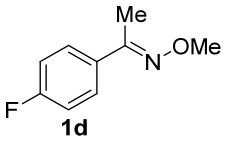
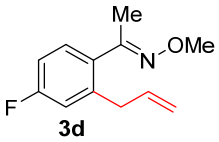
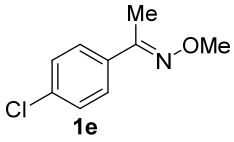
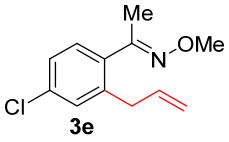
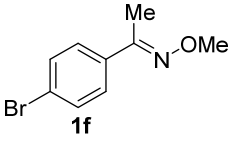
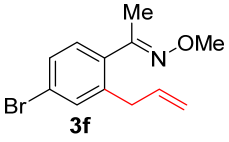
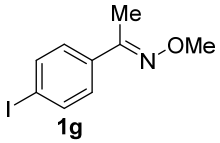
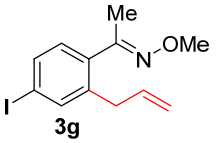
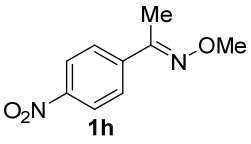
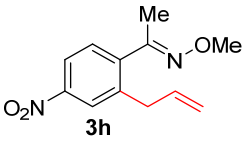
The selection of silver salt additive and solvent were crucial for the success of the reaction (Table 3A.1). The catalytic reaction was screened with various solvents such as *iso*-PrOH, THF, MeOH, AcOH, DMF, toluene, DMSO, $ClCH_2Cl$, chlorobenzenes and 1,2-dichloroethane. Dichloromethane and chlorobenzene were partially effective, providing **3a** in 52% and 34% yields, respectively (entries 8-9). 1,2-Dichloroethane was very effective, yielding product **3a** in 83% yield (entry 10). Remaining solvents were not effective. Next, the catalytic reaction was screened with various additives such as $AgSbF_6$, $AgBF_4$, AgOTf, KPF_6 and $CuBF_4$. Among them, $AgSbF_6$ was effective for the reaction, yielding product **3a** in 83% isolated yield (entry 10). $AgBF_4$ and AgOTf were partially effective, providing product **3a** in 59% and 68% yields, respectively (entries 11-12). Remaining additives were not effective.Under the optimized reaction conditions, the allylation reaction was examined with other allyl sources such as allyl bromide, allyl alcohol and allyl carbonate. However, in these reactions, no allylated product **3a** was observed. This result clearly reveals that the allyl acetate is the best allylating source in the reaction.

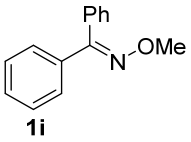
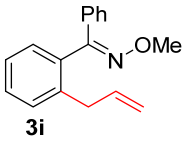
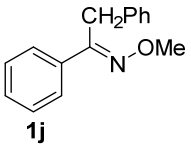
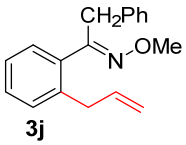
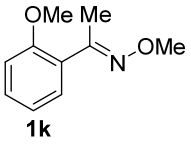
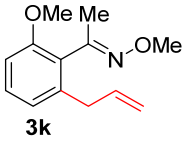
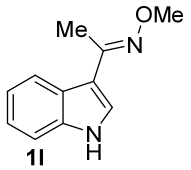
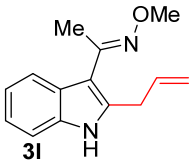
3A.4 Scope of Substituted Aromatic Ketoximes

The scope of allylation reaction was examined with various substituted aromatic and heteroaromatic ketoximes **1b-l** with allyl acetate (**2a**) (Table 3A.2). In all these reactions, the expected allylated products **3** were observed in good to excellent yields. In addition, the allylation reaction was compatible with a variety of sensitive functional groups such as Me, F, Cl, Br, I and NO_2 substituted aromatic ketoximes. The *ortho* allylation of electron-donating Me group substituted ketoxime **1b** or acetophenone oxime (**1c**) with **2a** gave the corresponding allylated products **3b** and **3c** in 75% and 74% yields, respectively (entries 1 and 2). In the reaction of **1b-c** with **2a**, a negligible amount of *bisortho* allylated product was observed. These products could not be able to isolate and a small peak was found with the corresponding molecular weight in the GC-MS. Halogen groups F, Cl, Br and I substituted oximes **1d-g** provided *ortho* allylated aromatic ketoximes **3d-g** in 55%, 64%, 67% and 69% yields, respectively (entries 3-6). A less reactive electron-withdrawing NO_2 group substituted oxime **1h** also efficiently participated in the reaction, giving allylated product **3h**in 60% yield (entry 7). The catalytic reaction was further examined with benzophenone oxime (**1i**) and benzyl methyl ketoxime (**1j**) with **2a**. In the reaction, allylated products **3i** and **3j** were observed in 72% and

70% yields, respectively (entries 8 and 9). Sterically hindered *ortho*-methoxy acetophenone oxime (**1k**) was also effectively involved in the reaction, giving product **3k** in 78% yield (entry 10). Very interestingly, heteroaromatic indole substituted oxime **1l** also efficiently reacted with **2a**, affording the corresponding allylated product **3l** in moderate 37% yield (entry 11).

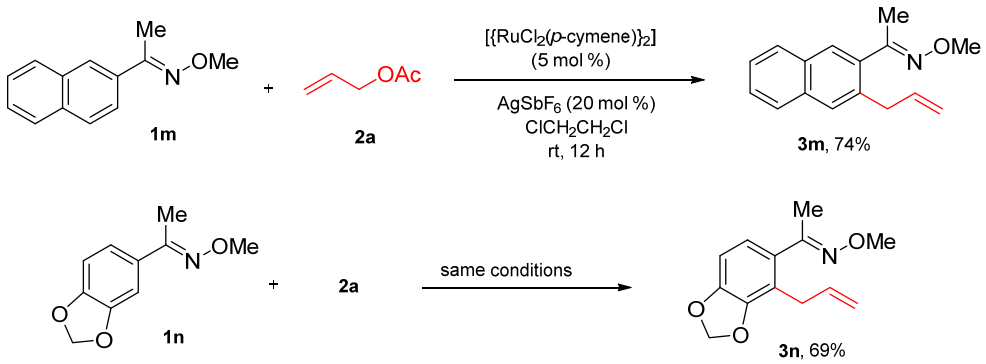
Table 3A.2 Ruthenium-Catalyzed *ortho* allyllation of aromatic ketoximes **1b-o** with allyl acetate (**2a**)[a]

Entry	Aromatic ketoxime (1)	Compound (3)	Yield[b]
1	 **1b**	 **3b**	75%
2	 **1c**	 **3c**	74%
3	 **1d**	 **3d**	55%
4	 **1e**	 **3e**	64%
5	 **1f**	 **3f**	67%
6	 **1g**	 **3g**	69%[c]
7	 **1h**	 **3h**	60%[c]

8	 **1i**	 **3i**	72%
9	 **1j**	 **3j**	70%
10	 **1k**	 **3k**	78%
11	 **1l**	 **3l**	37%

[a]All reactions were carried out using substituted oximes **1b-l** (100 mg), allyl acetate **(2a)** (2.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv) in 1,2-dichloroethane (3.0 mL) at room temperature for 12 h. (b)Isolated yield.(c)Allyl acetate **(2a)** (1.0 equiv) was used.

The allylation reaction was tested with unsymmetrical aromatic ketoximes **1m-n** (Scheme 3A.13). 2-Naphthyl ketoxime (**1m**) underwent allylation at the less hindered C3-H with **2a**, providing allylated product **3m** in 74% yield. In contrast, in the reaction of 3,4-(methylenedioxy)oxime (**1n**) with **2a**, allylation takes place at a hindered C6-H of **1n**, yielding product **3n** in 69% yield. Interestingly, in both cases, only a single regioisomeric product was observed.

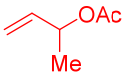
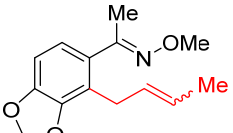
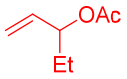
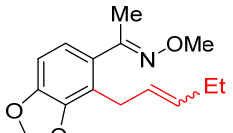
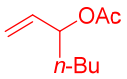
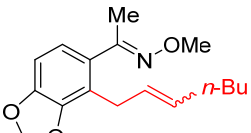


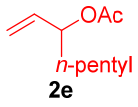
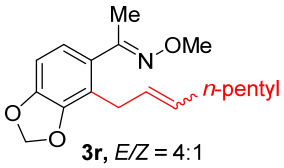
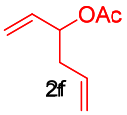
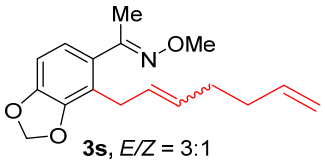
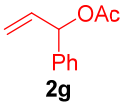
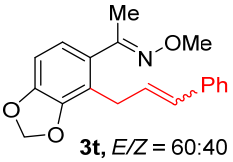
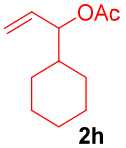
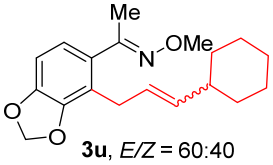
Scheme 3A.13: Regioselective studies.

3A.5 Scope of Substituted Allylic acetates

The scope of allylation reaction was further examined with substituted allylic acetates **2b-h** (Table 3A.3). γ-Alkyl group such as methyl (**2b**), ethyl (**2c**), *n*-butyl (**2d**) and *n*-pentyl (**2e**) substituted allylic acetates nicely reacted with **1n**, giving the corresponding allylated products **3o-r** in 84%, 87%, 85%, and 71% yields, respectively (entries 1-4). However, in all these products, a mixture of stereoisomeric products with *E*/*Z* ratios from 2:1 to 4:1 was observed. The allylation reaction was also compatible with γ-allyl (**2f**), phenyl (**2g**) and cyclohexyl (**2h**) substituted allylic acetates. In the reaction of **2f** with **1n**, synthetically useful 1,4-diene derivative **3s** in 69% yield with a 3:1 *E*/*Z* ratio was observed (entry 5). In the reaction of sterically hindered allylic acetates **2g-h**, the expected allylation products **3t** and **3u** were observed in 73% and 61% yields with a 60:40 *E*/*Z* ratio (entries 6-7). The *E*/*Z* ratios were determined by using ^{1}H NMR integration method. However α- as well as β-substituted allylic acetates were not suitable for the reaction. It is important to note that the bulky group such as Ph and cyclohexyl at the γ position of allylic acetates decreases the stereoselectivity of the product, a less bulky group such as alkyl and allyl increases the stereoselectivity of the products.

Table 2A.3 Ruthenium-catalyzed allylation reaction of substituted aromatic ketoxime **1n** with allyl acetates **2b-h.**[a]

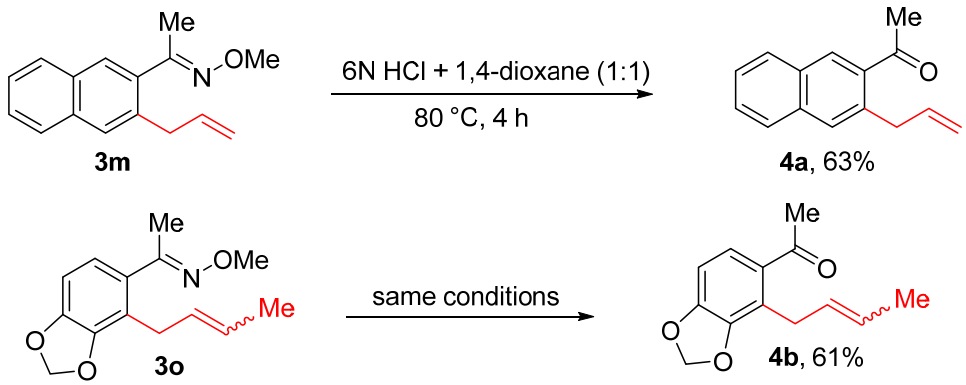
Entry	Allylic acetates (2)	Compound (3)	Yield[b]
1	 **2b**	 **3o**, *E*/*Z* = 2:1	84%
2	 **2c**	 **3p**, *E*/*Z* = 3:1	87%
3	 **2d**	 **3q**, *E*/*Z* = 3:1	85%

4	 **2e**	 **3r**, *E*/*Z* = 4:1	71%
5	 **2f**	 **3s**, *E*/*Z* = 3:1	69%
6	 **2g**	 **3t**, *E*/*Z* = 60:40	73%
7	 **2h**	 **3u**, *E*/*Z* = 60:40	61%

[a]All reactions were carried out using **1n** (1.0 equiv), allylic acetates **2b-h** (2.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv) in 1,2 dichloroethane (3.0 mL) at room temperature for 12 h.[b]Isolated yield.

3A.6 Applications

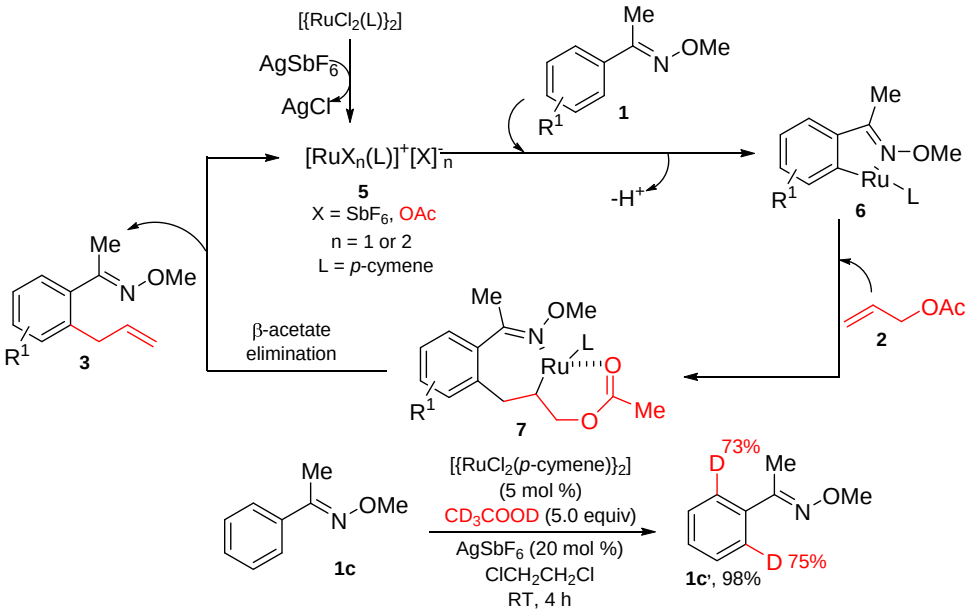
Later, *ortho* allylated aromatic ketoximes **3m** and **3o** were converted into *ortho*-allyl aromatic ketones **4a** and **4b** in 63% and 61% yields, respectively, in the presence of a 1:1 mixture of 6 N HCl and 1,4-dioxane at 80 °C for 4 h (Scheme 3A.14). It is important to note that *ortho* allylation of aromatic ketones with allylating agent is not known in the literature.



Scheme 3A.14: Applications.

3A.7 Proposed Mechanism

A possible reaction mechanism for *ortho* allylation of substituted aromatics with allylic acetates is proposed in Scheme 3A.15. $AgSbF_6$ likely removes all Cl^- ligand from [{$RuCl_2$(*p*-cymene)}$_2$] complex, giving a cationic ruthenium complexes **5**. Later, the nitrogen atom of ketoxime **1** coordinates with ruthenium species **5** followed by *ortho*-metalation providing a five-membered ruthenacycle intermediate **6**. Coordinative regioselective insertion of allyl acetate **2** into the Ru–carbon bond of intermediate **6** gives intermediate **7**. β-Acetate elimination of intermediate **7** affords *ortho* allyl aromatic ketoxime **3** and regenerates the active ruthenium acetate species **5** for the next catalytic cycle. It is important to note that the acetate group of allyl acetate would be transferred into the ruthenium species **5** and the corresponding acetate species deprotonates the *ortho* C–H bond of aromatic moiety. To know the feasibility of C–H bond activation of aromatic ketoxime at room temperature, the following deuterium labelling experiment was done. Treatment of **1c** with CD_3COOD in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) in 1,2-dichloroethane at room temperature for 4 h gave product **1c'** in 98% yield with 75% and 73% of deuterium incorporation at the both *ortho* carbons, respectively. It clearly indicates that the *ortho* C–H bond cleavage of aromatic ketoxime in intermediate **6** is a reversible process.



Scheme 3A.15: Proposed Mechanism.

3A.8 Conclusions

In conclusion, we have described a highly regioselective *ortho* allylation of aromatic ketoximes with allylic acetates in the presence of ruthenium catalyst and $AgSbF_6$ at room temperature. In the reaction, the acetate group of allyl acetate acts as a base to activate the C–H bond of aromatics.

3A.9 References

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3A.10 Experimental Section

3A.10.1 General procedure for the allylation of aromatic ketoximes with allylic acetates catalyzed by ruthenium complex

A 15-mL pressure with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube, were then added oxime **1** (100 mg), allylacetate **2** (2.0 equiv) and 1,2 dichloroethane (3.0 mL) via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, 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 rt for 12 h. Then, 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 petroleum

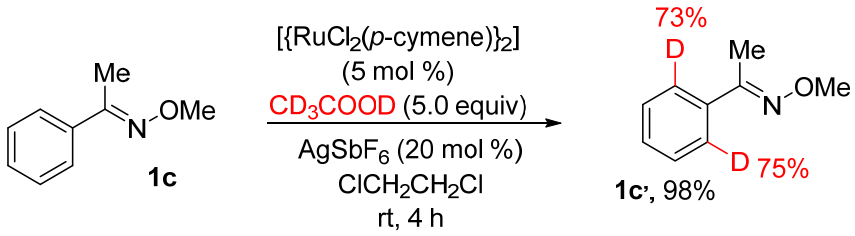
ether and ethyl acetate as eluent to give pure **3**. **Note**: For product **3a,** 1.5 equiv of allyl acetate (**2a**) was used. For products **3i and 3k,** 1.0 equiv of **2a** was used.

3A.10.2 General Procedure for the Hydrolysis of *ortho* Allyl Aromatic Ketoximes

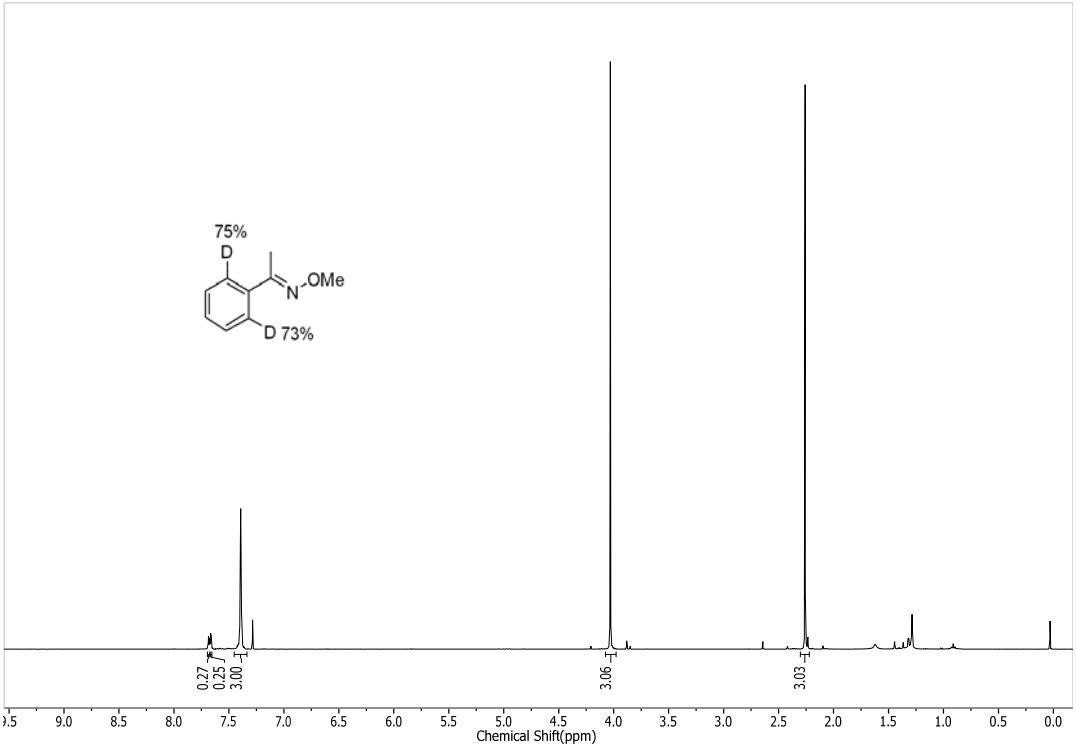
ortho Allyl Aromatic ketoximes (**3m** and **3o**) (100 mg) was taken in a 25-mL round bottom flask and dissolved with 1.0 mL of 1,4 dioxane and 1.0 mL of 6N HCl. Then the reaction mixture heated at 80°C for 4 h under an air atmosphere along with the condenser and water circulation. After cooling to ambient temperature, water was poured in to the reaction mixture and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over Na_2SO_4. The solution was concentrated under the reduced pressure. The crude residue was purified through a silica gel column using petroleum ether and ethyl acetate as eluent to give pure **4**.

3A.11 Mechanistic Investigation (Deuterium Studies)

To know the feasibility of C–H bond activation of aromatic ketoxime at room temperature, the following deuterium labelling experiment was done. Treatment of **1c**with CD_3COOD in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) in 1,2-dichloroethane at room temperature for 4 h gave product **1c'** in 98% yield with 75% and 73% of deuterium incorporation at the both *ortho* carbons. It clearly indicates that the *ortho* C–H bond cleavage of aromatic ketoxime in intermediate **5** is a reversible process.

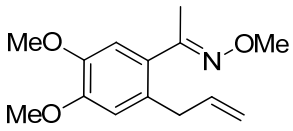


^{1}H NMR Spectra of Compound **1c'**



3A.12 Spectral Data of Compounds 3a-u and 4a-b.

(*E*)-1-(2-Allyl-4,5-dimethoxyphenyl)ethan-1-one*O*-methyloxime(3a).



Colourless liquid;eluent (3% ethylacetate in hexanes).The reaction scale is 100mg, 99mg of product was isolated and yield is 83%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 6.70 (s, 1 H), 6.69 (s, 1 H), 5.95 – 5.85 (m, 1 H), 5.04 (t,*J* = 4.0Hz, 1 H), 5.01- 4.99 (m, 1 H), 3.93 (s, 3 H), 3.84 (s, 6 H), 3.37 (d, *J* = 8.0Hz,2 H), 2.12 (s, 3 H).

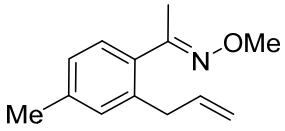
^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.5, 148.9, 147.1, 137.6, 130.2, 129.4, 115.7, 112.8, 111.4, 61.6, 55.9, 55.8, 37.2, 16.8.

HRMS (ESI): calc. for [($C_{14}H_{19}NO_3$)H] (M+H) 250.1443, measured 250.1444.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3078, 2931, 1634, 1589, 1463, 1259, 1041, 874, 747, 668.

Rf (hexane/ethyl acetate = 95:5): 0.61.

(*E*)-1-(2-Allyl-4-methylphenyl)ethan-1-one *O*-methyl oxime (3b).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 93mg of product was isolated and yield is 75%

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.10 (d, *J* = 8.0Hz, 1 H), 7.03-7.01 (m, 2 H), 5.96 – 5.88 (m, 1 H), 5.06 (m, 1 H), 5.02 (dd, *J* =8.0, 4.0 Hz, 1 H), 3.95 (s, 3 H), 3.44 (d, *J* = 4.0Hz,2 H), 2.31 (s, 3 H), 2.13 (s, 3 H).

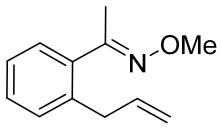
^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.5, 138.3, 137.5, 134.4, 130.6, 128.3, 126.9, 115.7, 61.6, 37.6, 21.1, 16.7.

HRMS (ESI): calc. for [($C_{13}H_{17}NO$)H] (M+H) 204.1388, measured 204.1390.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2931, 2817, 1727, 1637, 1435, 1312, 1041, 908, 875, 661.

Rf (hexane/ethyl acetate = 98:2): 0.63.

(*E*)-1-(2-Allylphenyl)ethan-1-one *O*-methyl oxime(3c).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 94mg of product was isolated and yield is 74%

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.28-7.25 (m, 2 H), 7.22-7.19 (m, 2 H), 5.97 – 5.87 (m, 1 H), 5.04 (dd, *J* = 4.0 Hz, 1 H), 5.02 – 4.99 (m, 1 H), 3.94 (s, 3 H), 3.45 (d, *J* = 8.0Hz,2 H), 2.14 (s, 3 H).

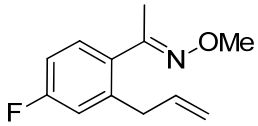
^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.6, 137.7, 137.4, 137.3, 129.9, 128.5, 128.4, 126.3, 115.8, 61.7, 37.6, 16.7.

HRMS (ESI): calc. for [($C_{12}H_{15}NO$)H] (M+H) 190.1232, measured 190.1236.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2929, 1727, 1637, 1522, 1451, 1248, 1048, 877, 762, 674.

Rf (hexane/ethyl acetate = 98:2): 0.63.

(*E*)-1-(2-Allyl-4-fluorophenyl)ethan-1-one *O*-methyl oxime (3d).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 68mg of product was isolated and yield is 55%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.18 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.93 (dd, *J* = 8.0, 4.0 Hz, 1 H),6.89 (dd, *J* = 8.0, 4.0 Hz, 1 H), 5.95 - 5.85 (m, 1 H), 5.10 - 5.02 (m, 2 H), 3.94 (s, 3 H), 3.44 (d, *J* = 8.0Hz,2 H),2.12 (s, 3 H).

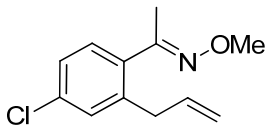
^{13}C NMR ($CDCl_3$, 400 MHz):δ 163.8, 161.4, 155.8, 140.6 and 140.5(F-coupling), 136.4, 133.3, 130.2 and 130.1 (F-coupling), 116.7, 116.6 and 116.4 (F-coupling), 113.3 and 113.1(F-coupling), 61.7, 37.5, 16.7.

HRMS (ESI): calc. for [($C_{12}H_{14}FNO$)H] (M+H) 208.1137, measured 208.1131.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3077, 2935, 2362, 1637, 1591, 1483, 1365, 1044, 886, 772, 681.

Rf (hexane/ethyl acetate = 98:2): 0.42

(*E*)-1-(2-Allyl-4-chlorophenyl)ethan-1-one *O*-methyl oxime (3e).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 80mg of product was isolated and yield is 64%

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.21 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.18 (d, *J* = 4.0Hz,1 H),7.13 (d, *J* = 8.0Hz,1 H),5.92 - 5.84 (m, 1 H), 5.09 - 5.0 (m, 2 H),3.94 (s, 3 H), 3.43 (d, *J* = 4.0Hz,2 H),2.12 (s, 3 H).

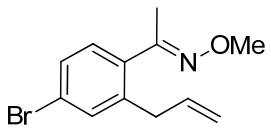
^{13}C NMR ($CDCl_3$, 400 MHz):δ 155.6, 139.8, 136.4, 135.7, 134.3, 129.9, 129.7, 126.4, 116.7, 61.8, 37.4, 16.6.

HRMS (ESI): calc. for [($C_{12}H_{14}ClNO$)H] (M+H) 224.0842, measured 224.0838.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3077, 2935, 2362, 1637, 1591, 1483, 1365, 1044, 886, 772, 681.

Rf (hexane/ethyl acetate = 98:2): 0.48.

(*E*)-1-(2-Allyl-4-bromophenyl)ethan-1-one *O*-methyl oxime (3f).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 79mg of product was isolated and yield is 67%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.36 (d, *J* = 8.0Hz,1 H), 7.34 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.07 (d, *J* = 8.0Hz,1 H),5.93 - 5.83 (m, 1 H), 5.09 - 5.01(m, 2 H), 3.94 (s, 3 H), 3.42 (d, *J* = 8.0Hz,2 H),2.11 (s, 3 H).

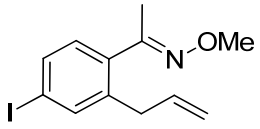
^{13}C NMR ($CDCl_3$, 400 MHz):δ 155.6, 140.1, 136.4, 136.2, 132.9, 130.0, 129.4, 122.6, 116.7, 61.8, 37.4, 16.5.

HRMS (ESI): calc. for [($C_{12}H_{14}BrNO$)H] (M+H) 268.0337, measured 268.0334.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3077, 2926, 2362, 1728, 1638, 1454, 1043, 883, 765, 675.

Rf (hexane/ethyl acetate = 98:2): 0.46.

(*E*)-1-(2-Allyl-4-iodophenyl)ethan-1-one *O*-methyl oxime (3g).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 79mg of product was isolated and yield is 69%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.57 (d, *J* = 4.0Hz,1 H), 7.54 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.93 (d, *J* = 8.0Hz,1 H),5.91 - 5.84 (m, 1 H), 5.08- 5.01 (m, 2 H), 3.94 (s, 3 H), 3.40 (d, *J* = 4.0Hz, 2 H), 2.11 (s, 3 H).

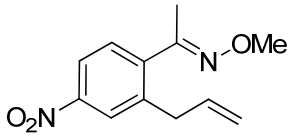
^{13}C NMR ($CDCl_3$, 400 MHz):δ 155.6, 140.1, 138.8, 136.8, 136.5, 135.4, 130.1, 116.6, 94.5, 61.8, 37.2, 16.5.

HRMS (ESI): calc. for [($C_{12}H_{14}INO$)H] (M+H) 316.0198, measured 316.0201.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3075, 2933, 1637, 1578, 1434, 1309, 1041, 880, 817, 769, 672.

Rf (hexane/ethyl acetate = 98:2): 0.44.

(*E*)-1-(2-Allyl-4-nitrophenyl)ethan-1-one *O*-methyl oxime (3h).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 72mg of product was isolated and yield is 60%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 8.10 (d, *J* = 4.0Hz,1 H), 8.06 (dd, *J* = 8.0, 4.0 Hz,1 H), 7.37 (d, *J* = 8.0Hz,1 H), 5.96 - 5.86(m, 1 H), 5.14 (dq,*J* = 8.0, 4.0 Hz,1 H),5.08 (dq,*J* = 16.0, 4.0 Hz,1 H),3.97 (s, 3 H), 3.54 (d, *J* = 8.0Hz,2 H), 2.16(s, 3 H).

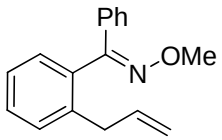
^{13}C NMR ($CDCl_3$, 400 MHz):δ 154.7, 147.7, 143.5, 140.1, 135.6, 129.5, 124.9, 121.3, 117.5, 62.1, 37.4, 16.3.

HRMS (ESI): calc. for [($C_{12}H_{14}NO_3$)H] (M+H) 235.1083, measured 235.1080.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3079, 2969, 1730, 1624, 1468, 1296, 1051, 848, 657.

Rf (hexane/ethyl acetate = 98:2): 0.41.

(*E*)-(2-Allylphenyl)(phenyl)methanone*O*-methyl oxime (3i).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 85mg of product was isolated and yield is 72%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.52-7.49 (d, *J* = 8.0 Hz, 2 H), 7.36-7.31 (m, 5 H), 7.28-7.23 (m, 2 H), 5.83 – 5.73 (m, 1 H), 4.97 – 4.95 (m, 1 H), 4.94 – 4.91 (m, 1 H), 4.01 (s, 3 H), 3.31 (d, *J* = 8.0Hz, 2 H).

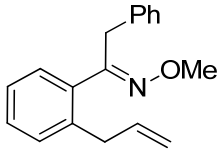
^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.2, 139.1, 136.9, 136.3, 133.5, 130.5, 129.9, 129.8, 129.3, 128.9, 127.9, 126.1, 115.8, 62.3, 37.6.

HRMS (ESI): calc. for [($C_{17}H_{17}NO$)H] (M+H) 252.1388, measured 252.1387.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3063, 2934, 1725, 1637, 1488, 1324, 1041, 974, 870, 692, 662.

Rf (hexane/ethyl acetate = 98:2): 0.38.

(*E*)-1-(2-Allylphenyl)-2-phenylethan-1-one *O*-methyl oxime (3j).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 82mg of product was isolated and yield is 70%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.15-7.23 (m, 5 H), 7.09-7.11 (m, 3 H), 7.01 (dd, *J* = 8.0, 4.0 Hz, 1 H), 5.00 (t,*J* = 8.0Hz, 1 H), 4.97(dd, *J* = 8.0, 4.0 Hz,2 H), 3.99(s, 5H), 3.31 (d, *J* = 8.0Hz,2 H).

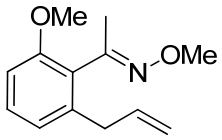
^{13}C NMR ($CDCl_3$, 400 MHz):δ 157.8, 138.2, 137.5, 135.9, 135.7, 129.8, 129.3, 128.9, 128.5, 128.4, 126.4, 125.9, 115.8, 61.8, 37.4, 36.4.

HRMS (ESI): calc. for [($C_{18}H_{19}NO$)H] (M+H) 266.1545, measured 266.1546.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3065, 2927, 2817, 1728, 1637, 1601, 1444, 1042, 910, 877, 759.

Rf (hexane/ethyl acetate = 98:2): 0.40.

(*E*)-1-(2-Allyl-6-methoxyphenyl)ethan-1-one *O*-methyl oxime (3k).



Colourless liquid; eluent (3% ethylacetate in hexanes).The reaction scale is 100mg, 95mg of product was isolated and yield is 78%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.22 (t, *J* = 8.0Hz,1 H), 6.81 (d, *J* = 8.0Hz,1 H), 6.75 (d, *J* = 8.0Hz,1 H), 5.93 - 5.85 (m, 1 H), 5.04 - 5.02 (m, 1 H), 5.00 – 4.99 (m, 1 H), 3.95 (s, 3 H), 3.77 (s, 3 H), 3.39 (d, *J* = 8.0Hz,2 H),2.08 (s, 3 H).

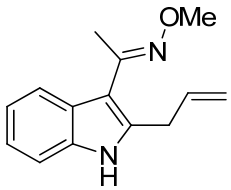
^{13} CNMR ($CDCl_3$, 400 MHz):δ 157.5, 154.8, 139.5, 137.4, 129.2, 126.3, 121.8, 115.7, 108.6, 61.6, 55.5, 37.4, 16.5.

HRMS (ESI): calc. for [($C_{13}H_{17}NO_2$)H] (M+H) 220.1337, measured 220.1333.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3074, 2937, 1632, 1580, 1463, 1255, 1040, 874, 746, 665.

Rf (hexane/ethyl acetate = 95:5): 0.37.

(*E*)-1-(2-Allyl-1*H*-indol-3-yl)ethan-1-one *O*-methyl oxime (3l).



Colourless liquid; eluent (15% ethylacetate in hexanes).The reaction scale is 100mg, 45mg of product was isolated and yield is 37%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.05 (s, 1 H), 7.73 (d, *J* = 8.0Hz, 1 H), 7.27(d,*J* = 8.0Hz, 1 H), 7.16-7.09 (m, 2 H),6.03 - 5.93 (m, 1 H), 5.25 - 5.19 (m, 2 H), 3.98 (s, 3 H), 3.72 (d, *J* = 4.0Hz, 2 H), 2.33 (s, 3 H).

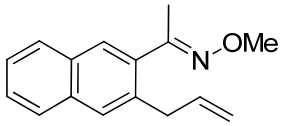
^{13}C NMR ($CDCl_3$, 400 MHz):δ 152.4, 135.3, 135.1, 134.7, 127.1, 121.8, 120.3, 120.0, 117.8, 110.6, 110.3, 61.6, 31.9, 15.8.

HRMS (ESI): calc. for [($C_{14}H_{16}N_2O$)H] (M+H) 229.1341, measured 229.1335.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3288(broad), 2930, 2361, 1716, 1610, 1452, 1046, 879, 754, 671.

Rf (hexane/ethyl acetate = 80:20): 0.37.

(*E*)-1-(3-Allylnaphthalen-2-yl)ethan-1-one *O*-methyl oxime(3m).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 89mg of product was isolated and yield is 74%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.81-7.76(m,2 H), 7.73 (s, 1 H), 7.68 (s, 1 H), 7.48-7.43(m,2 H), 6.07-5.99(m,1 H), 5.14-5.08(m,2 H), 4.01 (s, 3 H), 3.65 (d, *J* = 8.0Hz,2 H),2.25 (s, 3 H).

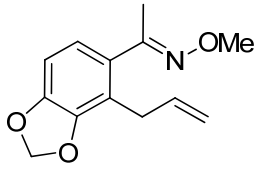
^{13}C NMR ($CDCl_3$, 400 MHz):δ 156.6, 137.1, 135.9, 135.4, 133.3, 131.8, 128.4, 127.8, 127.7, 127.2, 126.4, 125.7, 116.2, 61.8, 37.8, 16.9.

HRMS (ESI): calc. for [($C_{16}H_{17}NO$)H] (M+H) 240.1388, measured 240.1384.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3068, 2937, 1729, 1637, 1488, 1324, 1048, 977, 870, 699, 668.

Rf (hexane/ethyl acetate = 98:2): 0.44.

(*E*)-1-(4-allylbenzo[*d*][1,3]dioxol-5-yl)ethan-1-one *O*-methyl oxime (3n).



Colourless liquid; eluent (2% ethylacetate in hexanes).The reaction scale is 100mg, 83mg of product was isolated and yield is 69%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 6.70 (d, *J* = 8.0Hz, 1 H), 6.68 (d, *J* = 8.0Hz, 1 H), 5.87 – 5.96 (m, 1 H), 5.93 (s, 2 H), 5.02 (t,*J* = 8.0Hz, 1 H), 4.99 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.93 (s, 3 H), 3.43 (d, *J* = 8.0Hz,2 H), 2.10 (s, 3 H).

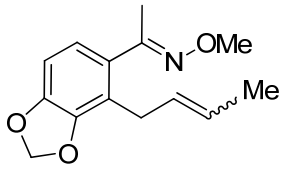
^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8, 147.1, 146.5, 135.8, 131.6, 122.1, 119.8, 115.5, 106.4, 101.0, 61.7, 31.2, 16.7.

HRMS (ESI): calc. for [($C_{13}H_{15}NO_3$)H] (M+H) 234.1130, measured 234.1129.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2930, 2818, 1634, 1450, 1251, 1048, 916, 877, 668.

Rf (hexane/ethyl acetate = 95:5): 0.61.

(1*E*)-1-(4-(But-2-en-1-yl)benzo[*d*][1,3]dioxol-5-yl)ethan-1-one *O*-methyl oxime (3o).



Colourless liquid; eluent (2% ethylacetate in hexanes).The reaction scale is 100mg, 107mg of product was isolated and yield is 84%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 6.71 (d, *J* = 8.0Hz, 1 H), 6.66 (d, *J* = 8.0Hz, 1 H), 5.94 (s, 2 H), 5.51 – 5.41 (m, 2 H), 3.93 (s, 3 H), 3.41 (d, *J* = 8.0Hz,2 H), 2.11 (s, 3 H), 1.69 (dd, *J* = 8.0, 4.0 Hz,3 H).

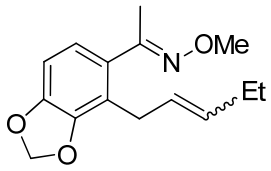
^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 147.0, 146.2, 131.5, 127.8, 124.4, 122.1, 121.1, 106.1, 100.9, 61.6, 24.8, 16.8, 12.8.

HRMS (ESI): calc. for [($C_{14}H_{17}NO_3$)H] (M+H) 248.1286, measured 248.1281.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2933, 2895, 1604, 1447, 1307, 1044, 967, 935, 873, 805, 664.

Rf (hexane/ethyl acetate = 95:5): 0.59.

(1*E*)-1-(4-(Pent-2-en-1-yl)benzo[*d*][1,3]dioxol-5-yl)ethan-1-one *O*-methyl oxime (3p).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 117mg of product was isolated and yield is 87%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 6.71 (d, *J* = 8.0Hz, 1 H), 6.66 (d, *J* = 8.0Hz, 1 H), 5.93 (s, 2 H), 5.39 – 5.36 (m, 2 H), 3.93 (s, 3 H), 3.43 (d, *J* = 8.0Hz,2 H), 2.11 (s, 3 H), 2.05 (q, *J* = 4.0Hz, 2 H), 0.98 (t, *J* = 8.0Hz,3 H).

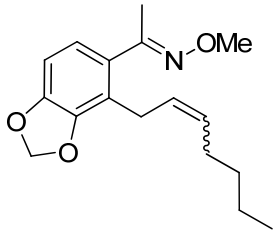
^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 147.0, 146.2, 133.2, 132.2, 131.5, 126.2, 122.1, 106.1, 100.1, 61.6, 25.1, 20.6, 16.8, 14.0.

HRMS (ESI): calc. for [($C_{15}H_{19}NO_3$)H] (M+H) 262.1443, measured 262.1438.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2933, 2895, 1605, 1448, 1307, 1045, 967, 934, 876, 804, 673.

Rf (hexane/ethyl acetate = 95:5): 0.61.

(1*E*)-1-(4-(Hept-2-en-1-yl)benzo[*d*][1,3]dioxol-5-yl)ethan-1-one *O*-methyl oxime(3q).



Colourless liquid; eluent (2% ethylacetate in hexanes).The reaction scale is 100mg, 127mg of product was isolated and yield is 85%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 6.71 (d, *J* = 8.0Hz, 1 H), 6.66 (d, *J* = 8.0Hz, 1 H), 5.93 (s, 2 H), 5.41 – 5.37 (m, 2 H), 3.93 (s, 3 H), 3.43 (d, *J* = 8.0Hz,2 H), 2.11 (s, 3 H), 1.35 – 1.32 (m, 6 H),0.98 (m,3 H).

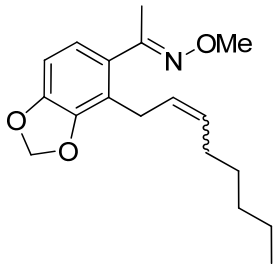
^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 147.0, 146.2, 136.6, 130.7, 126.7, 122.1, 116.4, 106.1, 100.9, 61.6, 31.7, 27.1, 25.2, 22.4, 16.8, 13.9.

HRMS (ESI): calc. for [($C_{17}H_{23}NO_3$)H] (M+H) 290.1756, measured 290.1753.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2933, 2895, 1604, 1447, 1307, 1044, 967, 935, 873, 805, 664.

Rf (hexane/ethyl acetate = 95:5): 0.63.

(1*E*)-1-(4-(Oct-2-en-1-yl)benzo[*d*][1,3]dioxol-5-yl)ethan-1-one *O*-methyl oxime (3r).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 111mg of product was isolated and yield is 71%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.71 (d, *J* = 8.0Hz, 1 H), 6.66 (d, *J* = 8.0Hz, 1 H), 5.93 (s, 2 H), 5.40 – 5.37 (m, 2 H), 3.93 (s, 3 H), 3.42 (d, *J* = 8.0Hz,2 H), 2.11 (s, 3 H), 1.32 – 1.28 (m, 8 H),0.86 (m,3 H).

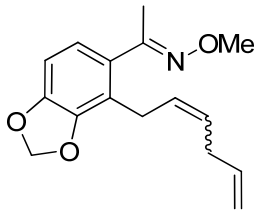
^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 147.1, 146.2, 131.9, 130.8, 126.7, 122.1, 121.3, 106.2, 100.9, 61.7, 32.5, 31.6, 27.3, 25.2, 22.6, 16.9, 14.1.

HRMS (ESI): calc. for [($C_{18}H_{25}NO_3$)H] (M+H) 304.1912, measured 304.1909.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2929, 2362, 1604, 1450, 1308, 1049, 971, 879, 735, 672.

Rf (hexane/ethyl acetate = 95:5): 0.65

(1*E*)-1-(4-(Hexa-2,5-dien-1-yl)benzo[d][1,3]dioxol-5-yl)ethanone O-methyl oxime(3s).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 98mg of product was isolated and yield is 69%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 6.72 (d, *J* = 8.0Hz, 1 H), 6.67 (d, *J* = 8.0Hz, 1 H), 5.94 (s, 2 H), 5.50 – 5.42 (m, 2 H), 5.07 – 4.95 (m, 2 H), 3.93 (s, 3 H), 3.44 (d, *J* = 8.0Hz,2 H), 2.89 (t, *J* = 8.0Hz,2 H), 2.65 (t, *J* = 4.0Hz,1 H), 2.11 (s, 3 H).

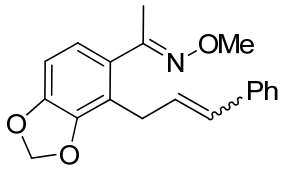
^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8, 147.1, 146.3, 136.9, 136.7, 131.4, 128.1, 127.4, 122.1, 114.8, 106.2, 100.9, 61.6, 31.6, 25.1, 16.8.

HRMS (ESI): calc. for [($C_{16}H_{19}NO_3$)H] (M+H) 274.1443, measured 274.1448.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2933, 2818, 1636, 1448, 1364, 1250, 1043, 969, 805, 637.

Rf (hexane/ethyl acetate = 95:5): 0.61.

(1*E*)-1-(4-(3-Phenylallyl)benzo[*d*][1,3]dioxol-5-yl)ethan-1-one *O*-methyl oxime (3t)



Colourlessliquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 116mg of product was isolated and yield is 73%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.39 – 7.35 (m, 5 H), 6.81 (d, *J* = 8.0Hz, 1 H), 6.73 (d, *J* = 8.0Hz, 1 H), 6.41 – 6.32 (m, 2 H), 6.02 (d, *J* = 4.0 Hz, 2 H), 4.00 (s, 3 H), 3.64 (d, *J* = 8.0Hz, 2 H), 2.11 (s, 3 H).

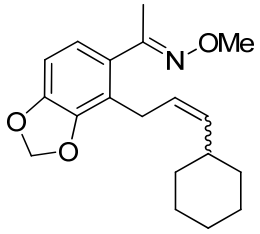
^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8, 147.2, 146.5, 137.6, 131.7, 130.9, 129.9, 127.7, 126.9, 122.2, 120.1, 119.9, 106.5, 101.1, 61.7, 30.5, 26.7, 16.8.

HRMS (ESI): calc. for [($C_{19}H_{19}NO_3$)H] (M+H) 310.1443, measured 310.1444.

IR (ATR)$\tilde{\nu}$ (cm^{-1}):3061,2921, 2367, 1725, 1674, 1447, 1358, 1256, 1053, 976, 855, 662.

Rf (hexane/ethyl acetate = 95:5): 0.59.

(1*E*)-1-(4-(3-Cyclohexylallyl)benzo[*d*][1,3]dioxol-5-yl)ethan-1-one *O*-methyl oxime (3u).



Colourless liquid; eluent (1% ethylacetate in hexanes).The reaction scale is 100mg, 99mg of product was isolated and yield is 61%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 6.70 (d, *J* = 8.0Hz, 1 H), 6.66 (d, *J* = 8.0Hz, 1 H), 5.93 (s, 2 H), 5.44 – 5.29 (m, 2 H), 3.93 (s, 3 H), 3.35 (d, *J* = 4.0Hz,2 H), 2.09 (s, 3 H), 1.72 – 1.59 (m, 11 H).

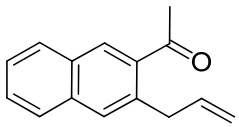
^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.0, 147.1, 137.7, 131.7, 124.4, 122.2, 121.5, 120.1, 106.2, 100.9, 61.6, 40.6, 36.4, 32.9, 30.2, 26.1, 16.9.

HRMS (ESI): calc. for [($C_{19}H_{25}NO_3$)H] (M+H) 316.1913, measured 316.1916.

IR (ATR)$\tilde{\nu}$ (cm^{-1}):3061,2921, 2367, 1725, 1674, 1447, 1358, 1256, 1053, 976, 855, 662.

Rf (hexane/ethyl acetate = 95:5): 0.61.

1-(3-Allylnaphthalen-2-yl)ethan-1-one(4a).



Colourless liquid; eluent (4% ethylacetate in hexanes).The reaction scale is 100mg, 56mg of product was isolated and yield is 63%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 8.17 (s, 1 H), 7.86 (d, *J* = 8.0Hz, 1 H), 7.78 (d, *J* = 8.0Hz, 1 H), 7.67 (s, 1 H), 7.56-7.46(m,2 H), 6.07 – 6.01(m,1 H), 5.07 - 4.98(m,2 H), 3.81 (d, *J* = 4.0Hz,2 H),2.68(s, 3 H).

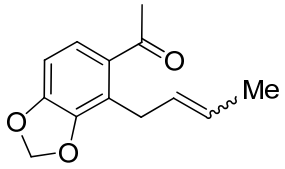
^{13}C NMR ($CDCl_3$, 400 MHz):δ 201.8, 137.7, 136.9, 136.2, 134.7, 131.2, 130.2, 129.6, 128.4, 128.1, 127.2, 126.2, 115.9, 38.0, 29.7.

HRMS (ESI): .calc. for [($C_{15}H_{14}O$)H] (M+H) 211.1123, measured 211.1128.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3058, 2923, 2361, 1680, 1632, 1493, 1355, 1272, 1156, 889, 750, 660.

Rf (hexane/ethyl acetate = 90:10): 0.41.

1-(4-(But-2-en-1-yl)benzo[d][1,3]dioxol-5-yl)ethan-1-one (4b).



Colourless liquid; eluent (4% ethylacetate in hexanes).The reaction scale is 100mg, 54mg of product was isolated and yield is 61%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.33 (d, *J* = 8.0Hz, 1 H), 6.68 (d, *J* = 8.0Hz, 1 H), 6.00(s, 2 H), 5.49 – 5.45(m, 2 H), 3.66 (d, *J* = 8.0Hz,2 H), 2.51 (s, 3 H), 1.72 (d, *J* = 8.0Hz,3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.5, 149.8, 131.9, 127.9, 126.0, 125.7, 124.7, 123.7, 105.4, 101.4, 29.3, 24.7, 12.9.

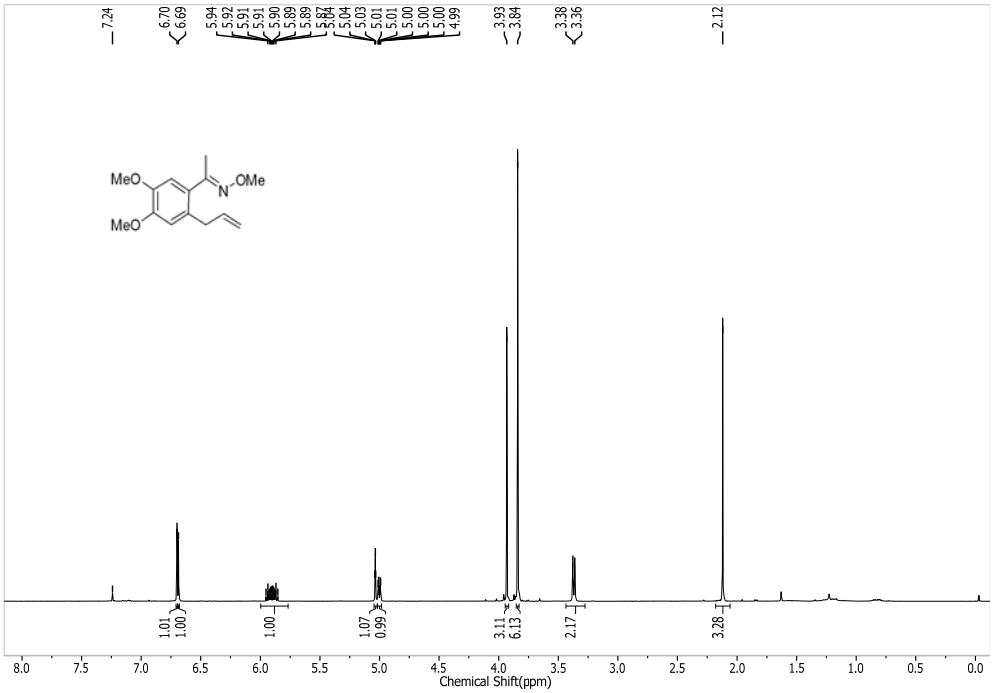
HRMS (ESI): calc. for [($C_{13}H_{14}O_3$)H] (M+H) 219.1021, measured 219.1031.

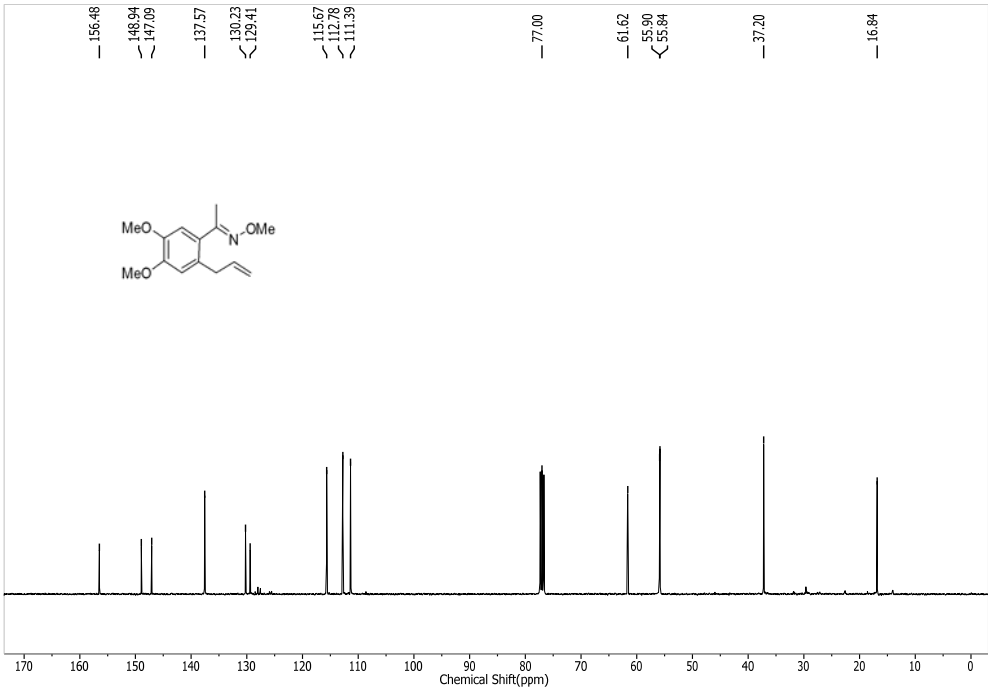
IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2933, 2818, 2318, 1681, 1630, 1495, 1358, 1274, 1158, 891, 758, 663.

Rf (hexane/ethyl acetate = 90:10): 0.48.

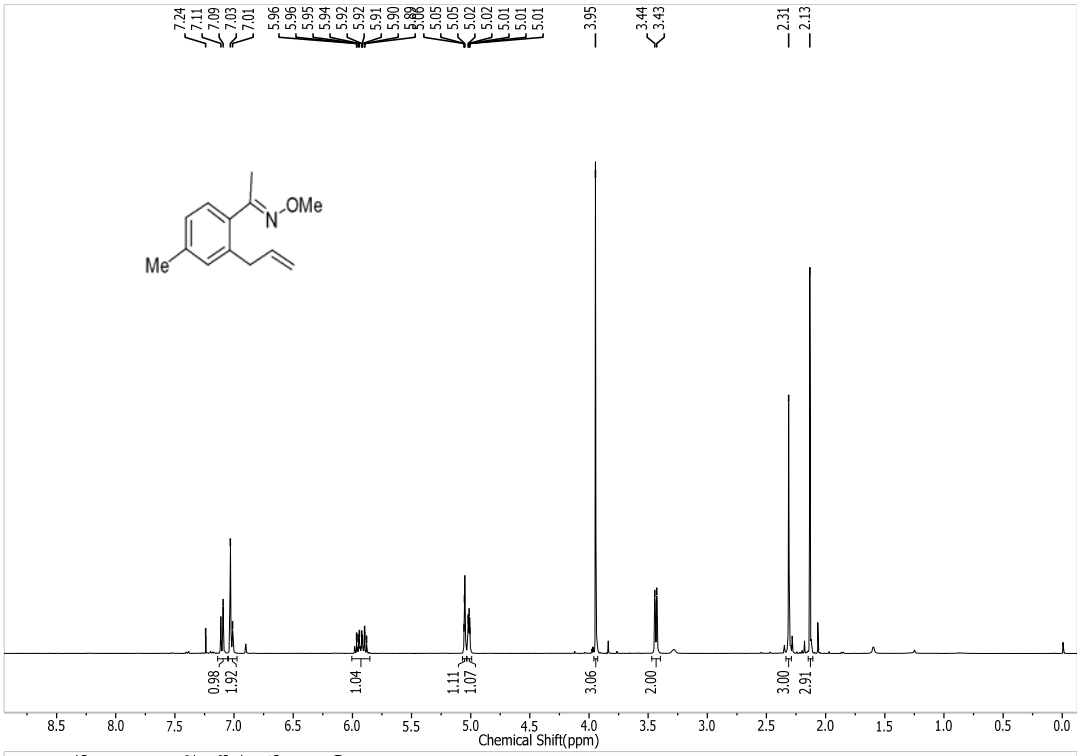
3A.13: SpectralCopies of Selected Compounds

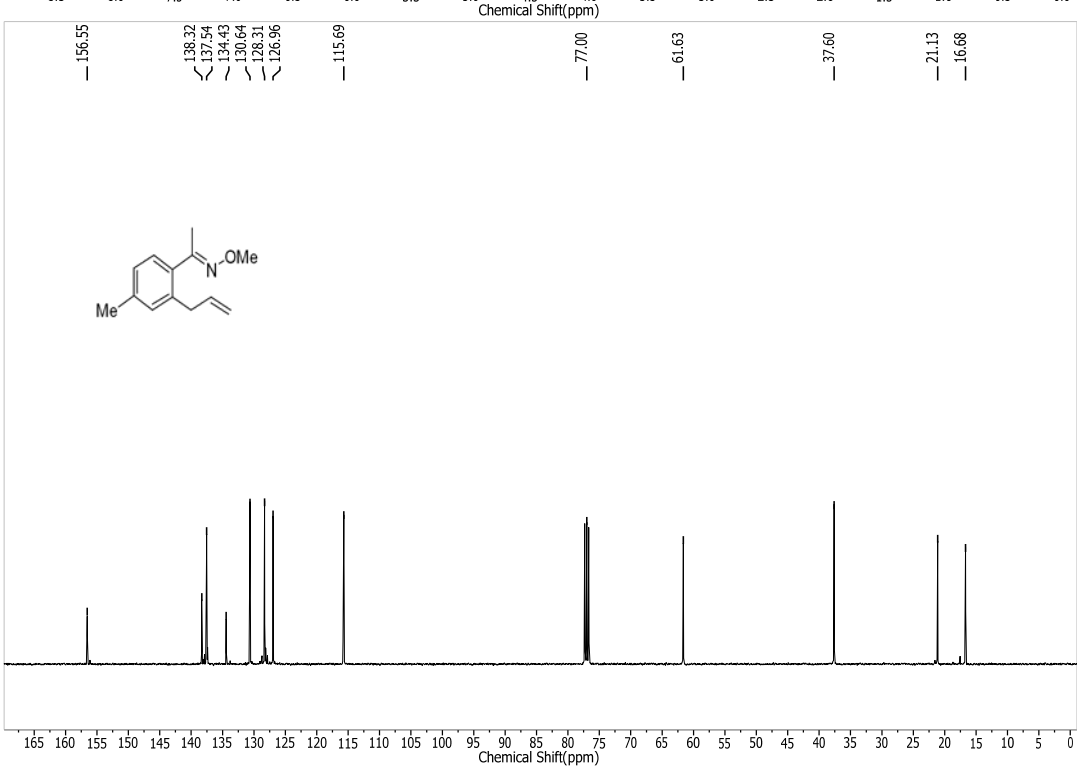
^{1}H and ^{13}C NMR Spectra of Compound **3a.**



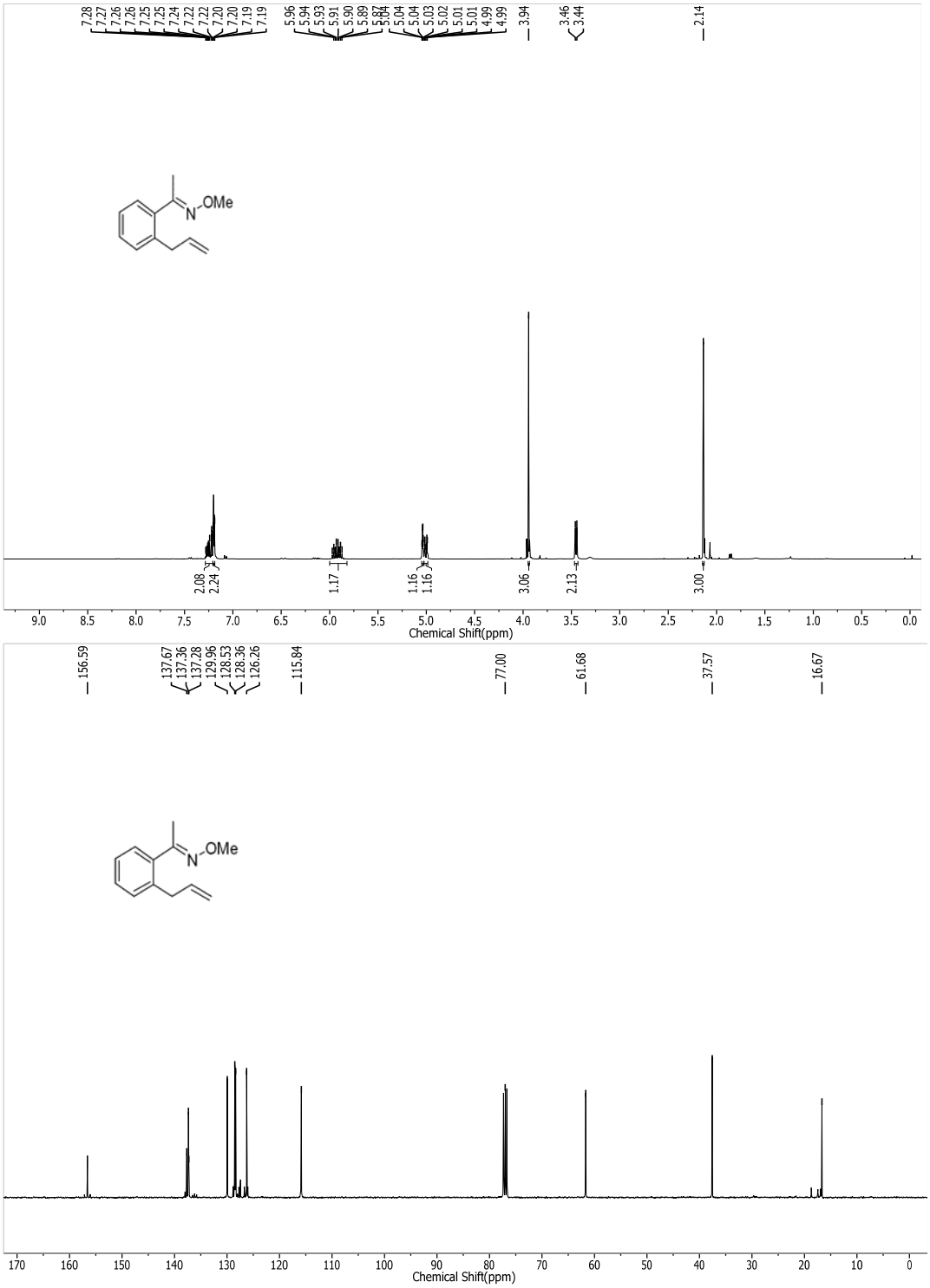


^{1}H and ^{13}C NMR Spectra of Compound **3b.**

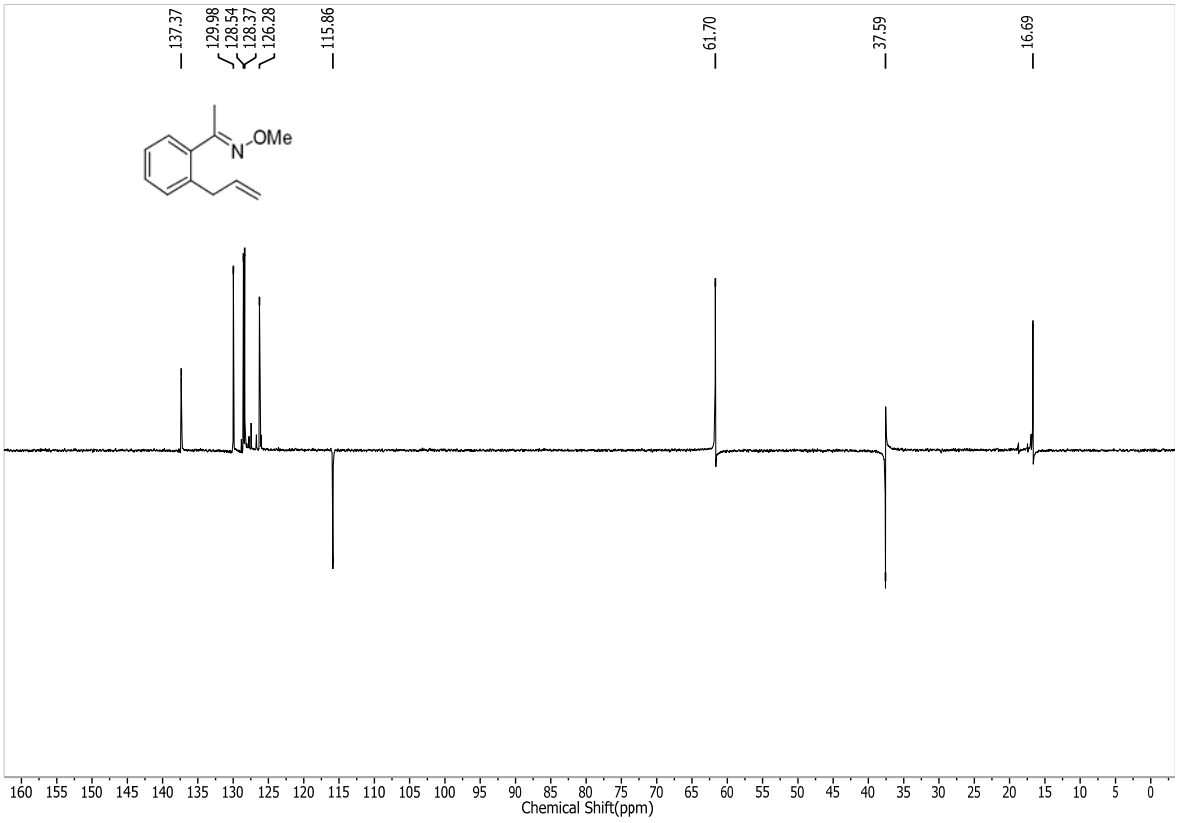




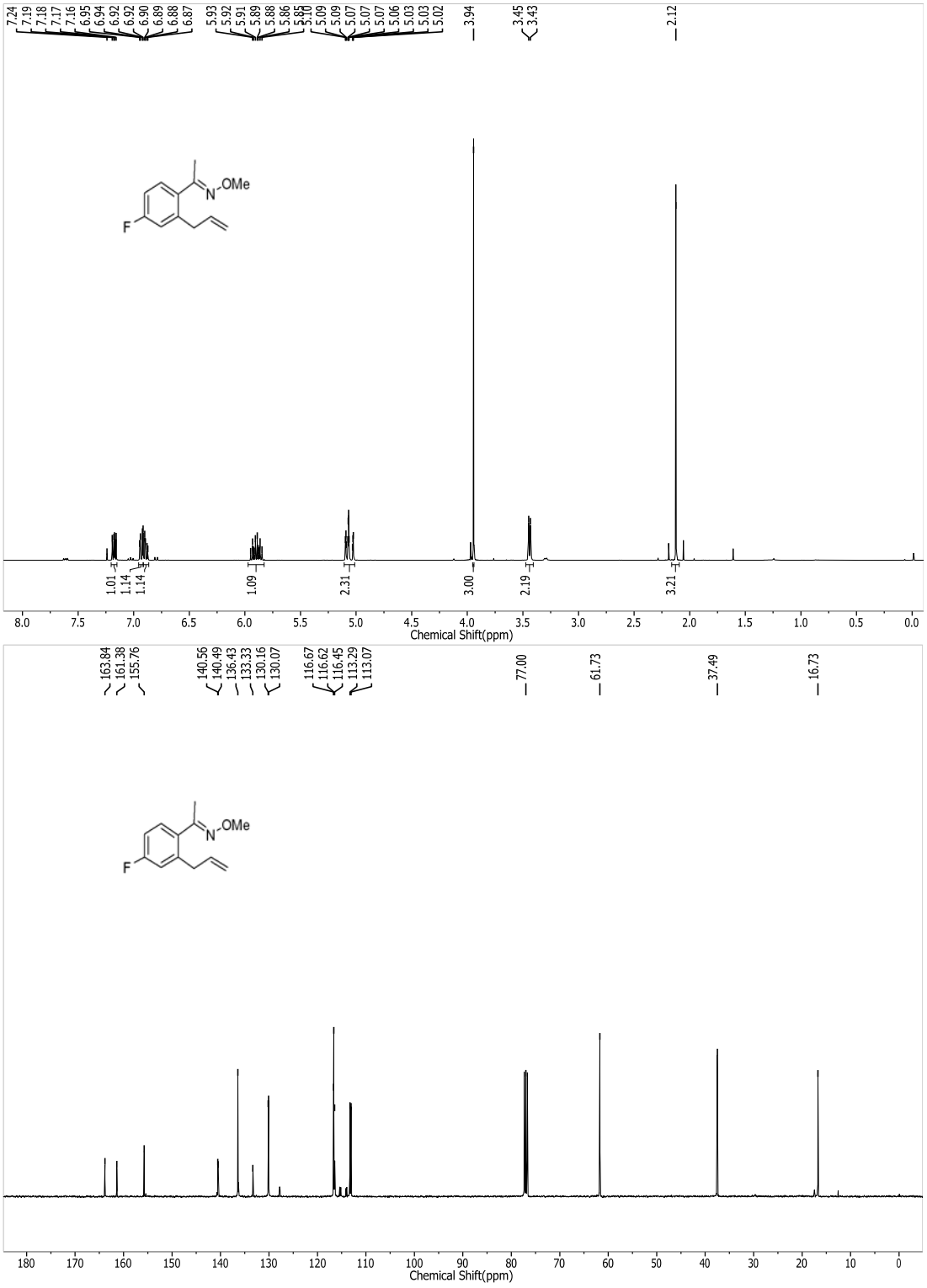
^{1}H and ^{13}C NMR Spectra of Compound **3c.**



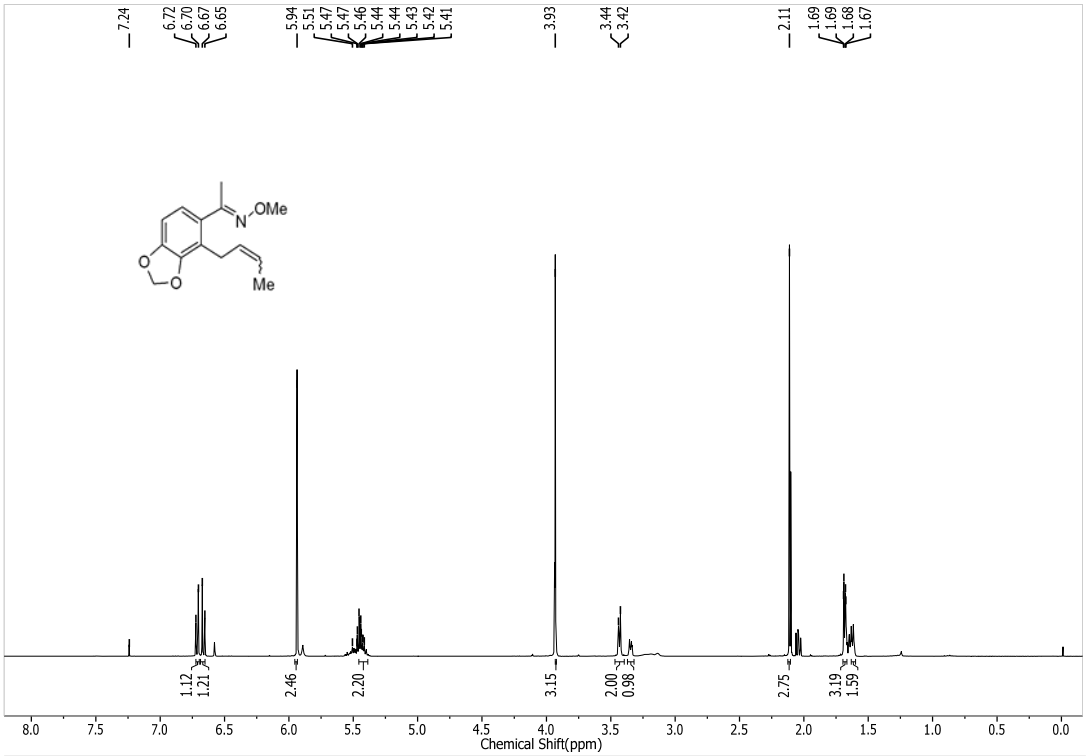
DEPT (135) NMR Spectrum of Compound **3c.**

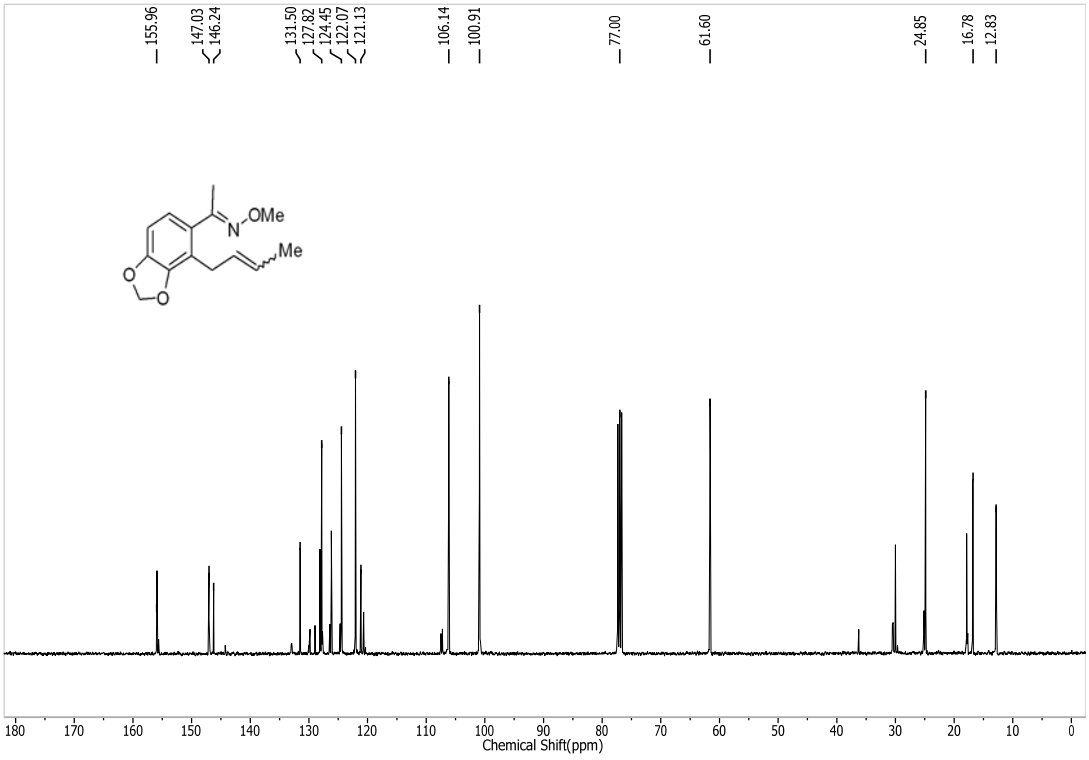


^{1}H and ^{13}C NMR Spectra of Compound **3d.**

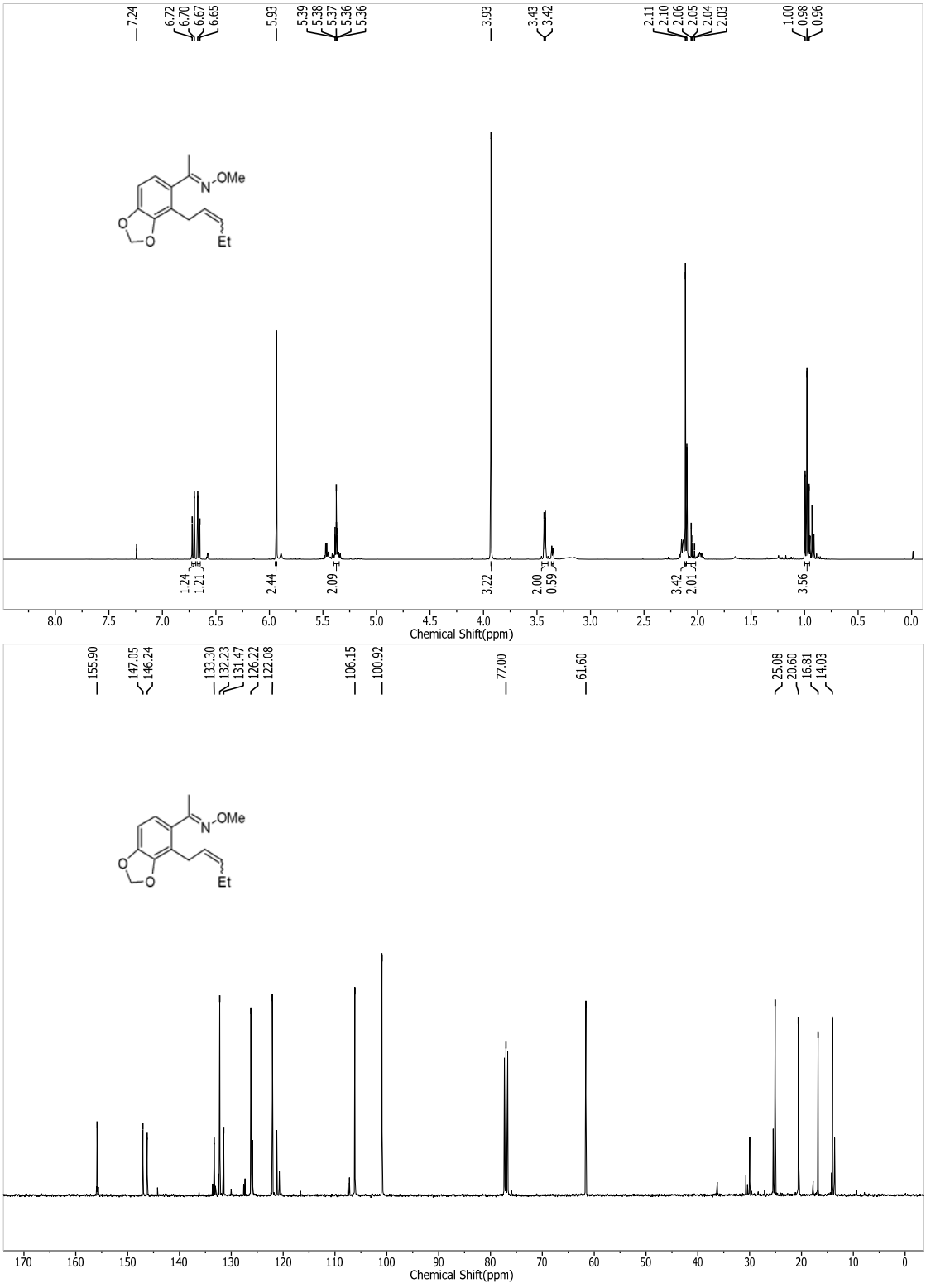


^{1}H and ^{13}C NMR Spectra of Compound **3o.**

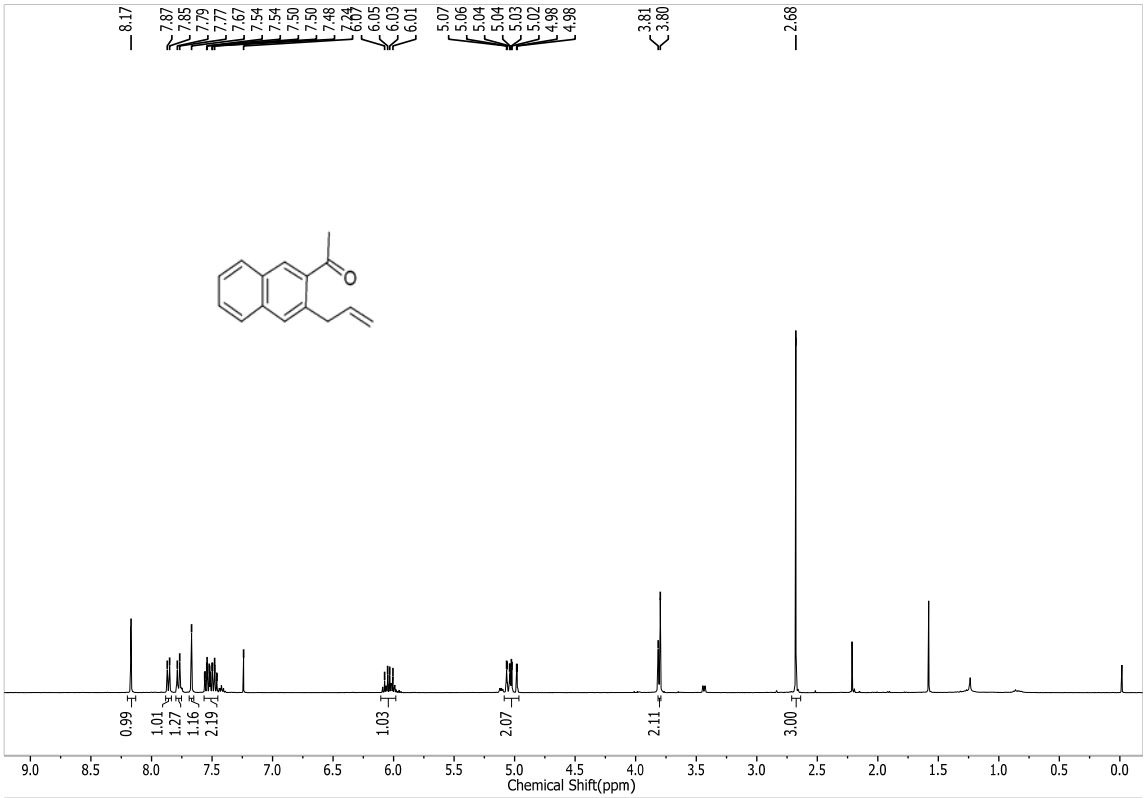


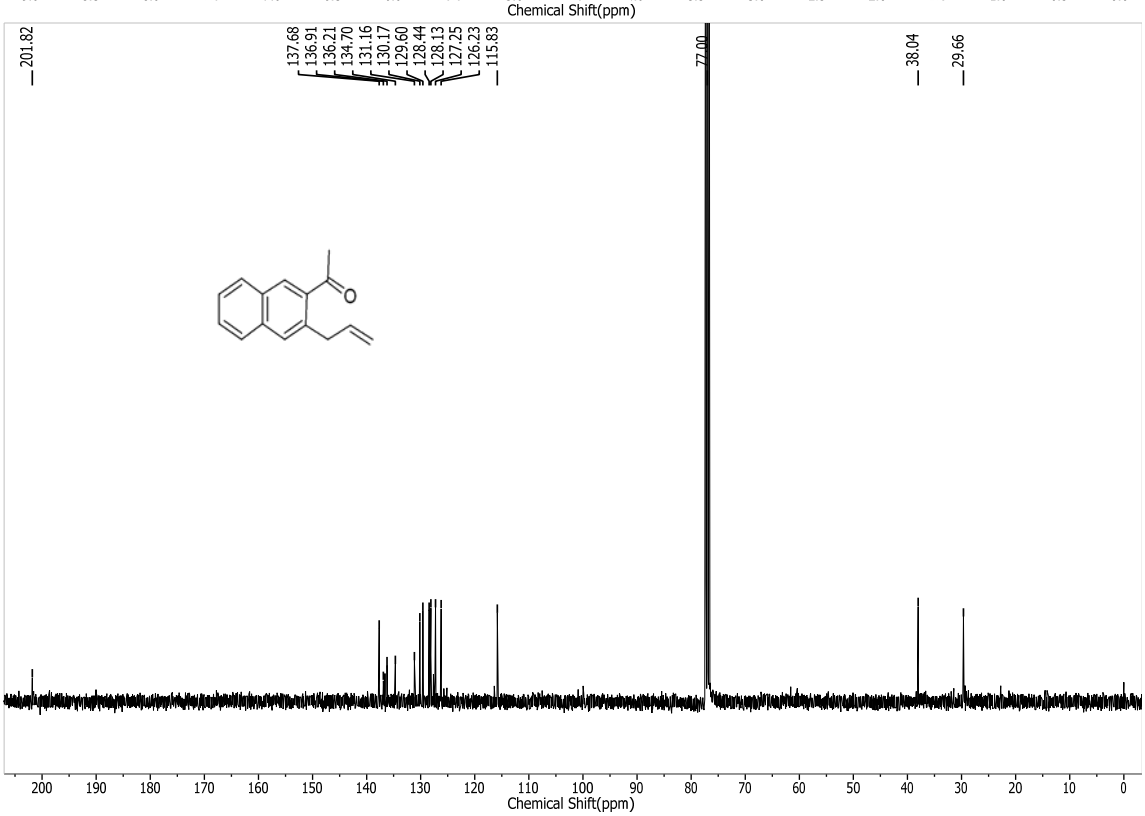


^{1}H and ^{13}C NMR Spectra of Compound **3p.**



^{1}H and ^{13}C NMR Spectra of Compound **4a.**


8.17
7.87
7.85
7.79
7.77
7.67
7.54
7.54
7.50
7.50
7.48
6.05
6.03
6.01
5.07
5.06
5.04
5.04
5.03
5.02
4.98
4.98
3.81
3.80
2.68
O
0.99
1.01
1.27
1.16
2.19
1.03
2.07
2.11
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shift(ppm)


201.82
137.68
136.91
136.21
134.70
131.16
130.17
129.60
128.44
128.13
127.25
126.23
115.83
77.00
38.04
29.66
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift(ppm)

Section 3B: Temperature-Controlled Redox-Neutral Ruthenium (II)-Catalyzed Regioselective Allylation of Benzamides with Allylic Acetates

3B.1 Introduction

The transition metal-catalyzed allylation at the C–H bond of substituted aromatics with allylic electrophiles is one of the effective methods for synthesizing allylaromatics in a highly regioselective manner.[1] Allylarenes are widely used as key intermediates for synthesizing various natural products and medicinally relevant molecules.[2] Recently, allylarenes are efficiently prepared in a highly step- and atom-economical manner via C–H bond activation reaction.[3-5] However, in most of the reported reactions, mixtures of allyl as well as vinyl arenes were observed. Internal olefins are thermodynamically more stable than the terminal olefins. Thus, after allylation, the double bond migration takes place towards thermodynamically more stable internal olefins in the presence of a metal catalyst. Meanwhile, the mechanism of this type of allylation reaction as well as the mechanism and driving force for the double bond migration of allylarenes is not clearly studied.

In the reported allylation reaction via the C–H bond activation, a stoichiometric amount of oxidant or acetate base or acid is needed. The oxidation step such as a metal with lower oxidation state into the higher oxidation state [Pd(0) to Pd(II), Co(I) to Co(III), Rh(I) to Rh(III) and Ru(0) to Ru(II)] is required for this type of transformation.[5] Usually, this source is used for the regeneration of active catalyst. However, a stoichiometric amount of oxidant waste is produced. In addition, the elevated reaction temperature is required for the reaction.

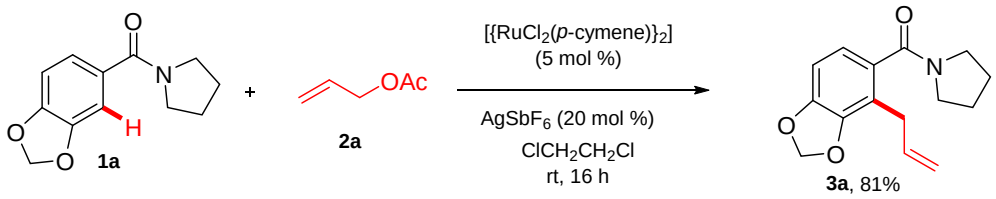
3B.2 Notion of Our work

Herein, we report a redox-neutral ruthenium-catalyzed allylation of benzamides with allylic acetates without any oxidant or base at room temperature. The whole catalytic reaction has occurred in a Ru (II) oxidation state. In the reaction, acetate moiety of allylic acetate acts as a base to deprotonate the C–H bond. The acetate moiety of allylic acetate intramolecularly transferred into a ruthenium species via β-acetate elimination and maintains the Ru(II) oxidation state. It is important to note that the C–H bond activation as well as allylation reaction takes place at room temperature. But, a higher reaction temperature is needed for the double bond migration. The reaction temperature decides the outcome of regioselectivity of the product. A

possible reaction mechanism for allylation reaction was proposed. The alkene migration mechanism was supported by a deuterium labelling experiment. *Ortho* Allyl and vinylated benzamides were converted into biologically useful six- and five-membered benzolactones in the presence of HCl.

3B.3 Results and Discussion

When benzamide **1a** was treated with allyl acetate (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) in 1,2-dichloroethane (DCE) at room temperature for 16 h, *ortho* allylated benzamide **3a** was observed in 81% yield (Scheme 3B.1). In the reaction, no double bond isomerization product of **3a** was observed and the C–H bond activation regioselectively takes place at the C2-H position.



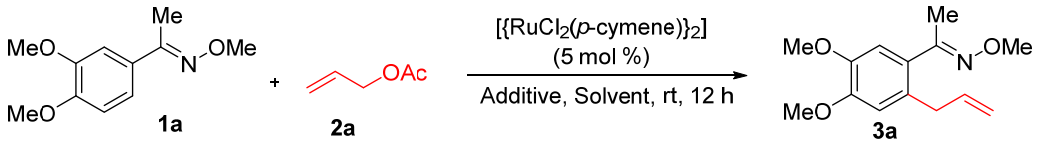
Scheme 3B.1: Rhodium-Catalyzed *ortho*vinylation of Aromatic amides with Allylic acetates

3B.4 Optimization Studies

Initially, the allylation reaction was screened with various additives, solvents and allyl sources (Table 3B.1).The allylation reaction of **1a** with **2a** was tried in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) in various solvents such as *iso*-PrOH, MeOH, 1,4-dioxane, THF, DME, $ClCH_2CH_2Cl$, methanol, toluene, CH_3CN, DMSO, DMF and water at room temperature for 16 h (entries 1-10). Among them, $ClCH_2CH_2Cl$ was very effective, yielding product **3a** in 81% yield (entry 10). *iso*-PrOH, MeOH, THF, DME and 1,4-dioxane were partially effective, providing product **3a** in 38%, 44%, 68%, 66% and 50% yields, respectively. Remaining solvents were not effective. Further, the allylation reaction was examined with various additives such as $AgSbF_6$, $AgBF_4$, AgOTf, KPF_6 and $CuBF_4$ (entries 10-13). Among them, $AgSbF_6$ was effective, affording product **3a** in 81% yield. $AgBF_4$ and AgOTf were partially effective, providing product **3a** in 69% and 71% yields, respectively. KPF_6 and $CuBF_4$ were not effective. The catalytic reaction was also tested with other allyl sources such as

allyl bromide, allyl alcohol and allyl carbonate. However, in these reactions, no allylated product **3a** was observed (entries 14-16).

Table 3B.1: Optimization Studies with Various Additive, Solvent and Cosolvent



entry	solvent	Allyl source	additive	yield of **3a** (%)[b]
1	Isopropanol	Allyl acetate (1.5 equiv)	$AgSbF_6$	38
2	Methanol	Allyl acetate (1.5 equiv)	$AgSbF_6$	44
3	THF	Allyl acetate (1.5 equiv)	$AgSbF_6$	68
4	DME	Allyl acetate (1.5 equiv)	$AgSbF_6$	66
5	DMF	Allyl acetate (1.5 equiv)	$AgSbF_6$	NR
6	DMSO	Allyl acetate (1.5 equiv)	$AgSbF_6$	NR
7	Toluene	Allyl acetate (1.5 equiv)	$AgSbF_6$	NR
8	1,4 Dioxane	Allyl acetate (1.5 equiv)	$AgSbF_6$	50
9	CH_3CN	Allyl acetate (1.5 equiv)	$AgSbF_6$	NR
10	**$ClCH_2CH_2Cl$**	**Allyl acetate (1.5 equiv)**	**$AgSbF_6$**	**81**
11	$ClCH_2CH_2Cl$	Allyl acetate (1.5 equiv)	AgOTf	71
12	$ClCH_2CH_2Cl$	Allyl acetate (1.5 equiv)	$AgBF_4$	69
13	$ClCH_2CH_2Cl$	Allyl acetate (1.5 equiv)	KPF_6	NR
14	$ClCH_2CH_2Cl$	Allyl bromide (1.5 equiv)	$AgSbF_6$	NR
15	$ClCH_2CH_2Cl$	Allyl carbonate (1.5 equiv)	$AgSbF_6$	NR
16	$ClCH_2CH_2Cl$	Allyl alcohol (1.5 equiv)	$AgSbF_6$	NR

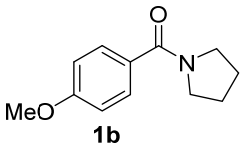
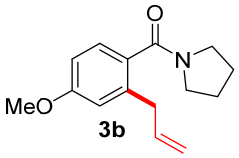
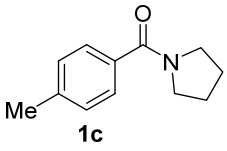
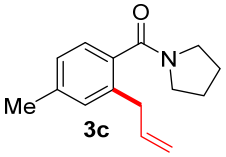
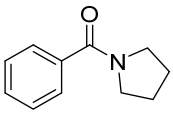
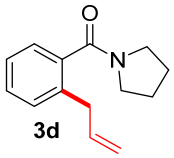
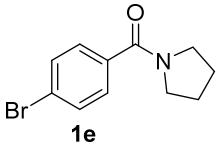
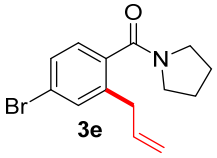
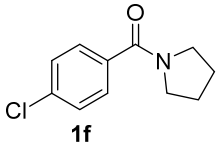
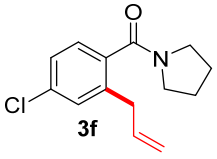
[a]All reactions were carried out under the following conditions: **1a** (100 mg), **2a** (2.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), additive (20 mol %) and solvent (3.0 mL) at rt for 12 h under N_2 atmosphere. [b]GC yield.

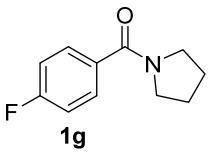
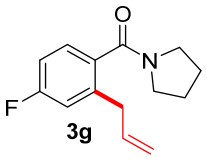
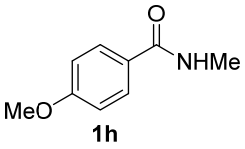
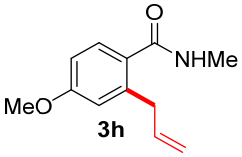
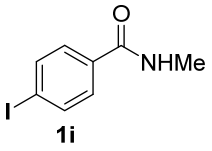
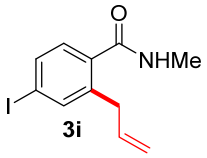
Note: The catalytic reaction was tried without ruthenium and $AgSbF_6$. No product **3a** was observed.

3B.5 *Ortho* Allylation of substituted Benzamides

The scope of the allylation reaction was examined with various *N*-*N*-disubstituted aromatic amides **1b-i** (Table 3A.2). The allylation reaction was compatible with sensitive functional group such as F, Cl, Br and I substituted benzamides. In all these reactions, the expected allylation products **3b-g** were observed in good to excellent yields. An electron-releasing substituent on the benzamides was very effective for the reaction as compared with electron-withdrawing substituent. *N*-Monosubstituted benzamides **1h-i** were also involved in the reaction, affording *ortho* allylated *N*-methyl benzamides **3h-3i** in moderate yields and the remaining unreacted *N*-monosubstituted benzamides starting materials were recovered.

Table 3A.2 Ruthenium-Catalyzed *ortho* allyllation of aromatic amides **1b-i** with allyl acetate (**2a**)[a]

Entry	Aromatic amide (1)	Compound (3)	Yield[b]
1	 **1b**	 **3b**	71%
2	 **1c**	 **3c**	63%
3	 **1d**	 **3d**	69%
4	 **1e**	 **3e**	66%
5	 **1f**	 **3f**	61%

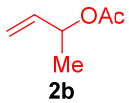
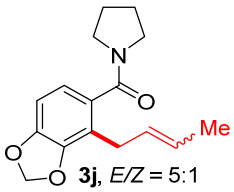
6	 **1g**	 **3g**	52%
7	 **1h**	 **3h**	51%[c]
8	 **1i**	 **3i**	42%[c]

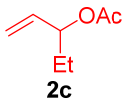
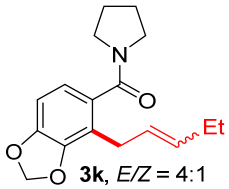
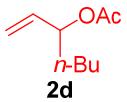
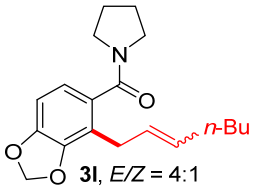
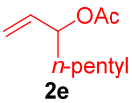
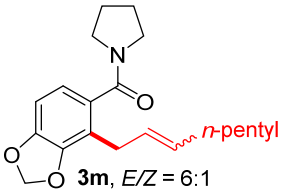
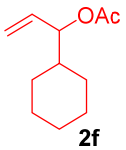
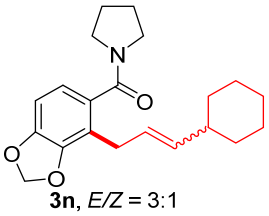
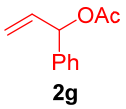
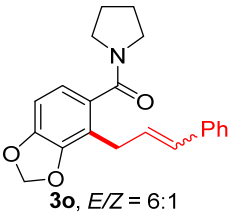
[a]All reactions were carried out using substituted amides **1b-l** (100 mg), allyl acetate **(2a)** (2.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv) in 1,2-dichloroethane (3.0 mL) at room temperature for 16 h. (b)Isolated yield.(c)Reaction was done for 36 h**.**

3B.6 Scope of Allylic Acetates

The scope of allylation reaction was further examined with substituted allylic acetates **2b-g** (Table 3B.2). γ-Alkyl group such as methyl (**2b**), ethyl (**2c**), *n*-propyl (**2d**) and *n*-pentyl (**2e**) substituted allylic acetates reacted efficiently with **1a**, giving the corresponding allylated products **3j-m** in excellent yields in 3:1 to 6:1 *E*:*Z* stereoisomeric ratios. The allylation reaction was also compatible with hindered γ- cyclohexyl (**2f**) and phenyl (**2g**) substituted allylic acetates. In the reaction, the expected allylation products **3n** and **3o** were observed in excellent yields in a 3:1 and 6:1 *E*:*Z* stereoisomeric ratios. However, the present allylation reaction was not compatible with α- as well as β-substituted allylic acetates.

Table 3B.2 Ruthenium-catalyzed allylation reaction of substituted aromatic amide **1n** with allyl acetates **2b-g.**[a]

Entry	Allylic acetates (2)	Compound (3)	Yield[b]
1	 **2b**	 **3j**, *E*/*Z* = 5:1	78%

2	 **2c**	 **3k**, *E*/*Z* = 4:1	77%
3	 **2d**	 **3l**, *E*/*Z* = 4:1	76%
4	 **2e**	 **3m**, *E*/*Z* = 6:1	68%
5	 **2f**	 **3n**, *E*/*Z* = 3:1	62%
6	 **2g**	 **3o**, *E*/*Z* = 6:1	74%

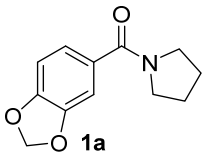
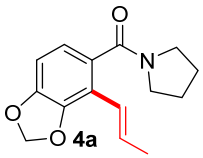
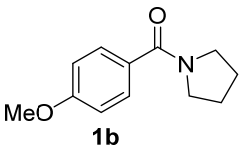
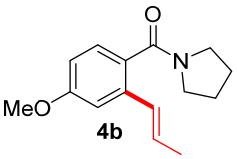
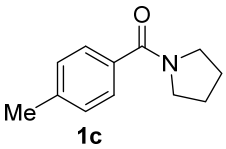
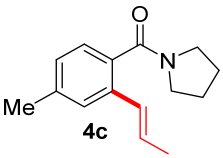
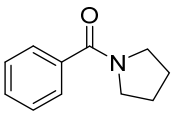
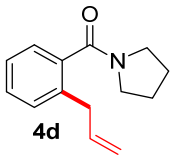
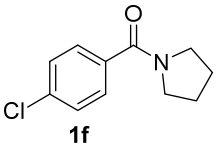
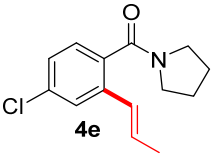
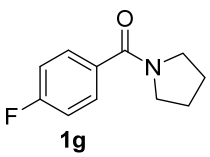
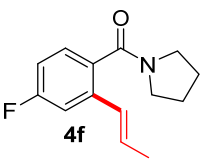
[a]All reactions were carried out using **1n** (1.0 equiv), allylic acetates **2b-h** (2.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv) in 1,2 dichloroethane (3.0 mL) at room temperature for 12 h.[b]Isolated yield.

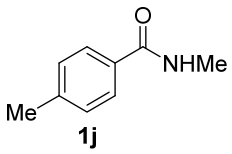
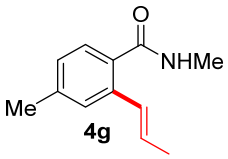
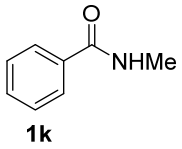
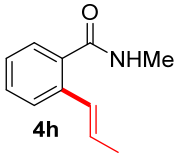
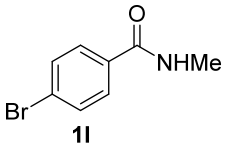
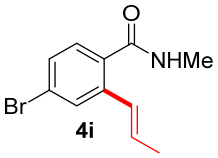
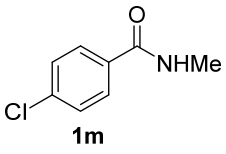
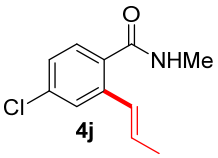
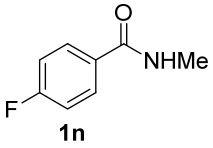
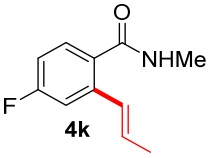
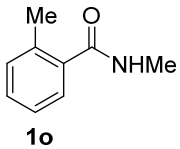
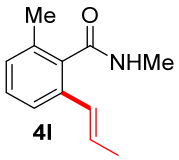
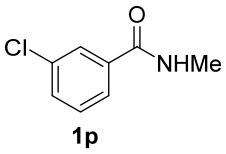
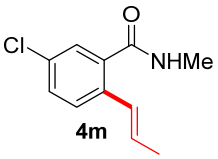
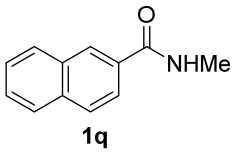
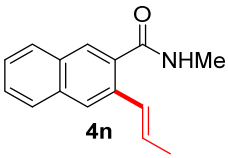
3B.7 *Ortho* Vinylation of Substituted Benzamides

When the allylation reaction of **1a** with **2a** was tried under the optimized reaction conditions at 100 °C, *ortho* vinylated benzamide **4a** was product in 76% yield (Table 3B.3). .*N*-*N*-Disubstituted benzamides **1b-g** as well as *N*-methyl benzamides **1j-q**were equally reactive with **2a**, providing *ortho* vinylated benzamides **4b-q** in good to excellent yields in a highly *E* stereoselectivity. Generally, *N*-substituted benzamides were not suitable substrates for allylation as well as vinylation reaction. It is important to mention that the electron-withdrawing substituted benzamides **1f-g**, **1l-n** and **1p**need 120 °C to provide *ortho* vinylated benzamides

exclusively. At 100 °C, mixtures of internal as well as terminal olefins were observed. This result clearly indicates that the double bond isomerization is most favorable for electron rich benzamides as compared with electron-deficient benzamides. In products **4m** and **4n**, vinylation was observed selectively at the less hindered C-6 or C-3 position. Meanwhile, γ-substituted allylic acetates were not selective for the reaction which providing regio- and stereoisomeric mixtures of internal as well as terminal olefins even at 120 °C.

Table 3B.3 Ruthenium-Catalyzed *ortho* vinylation of aromatic amides **1a-q** with allyl acetate (**2a**)[a]

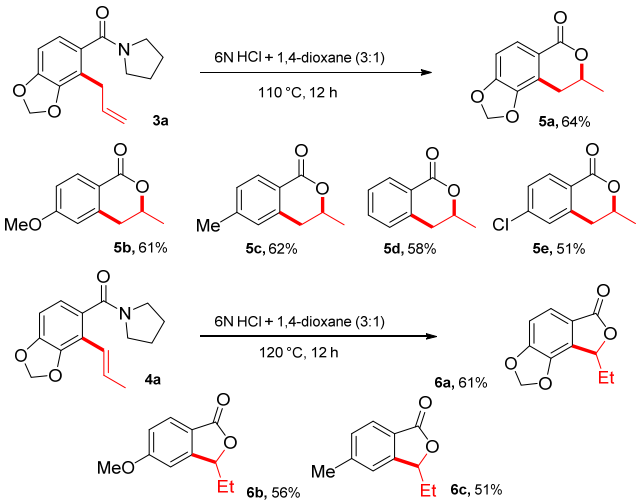
Entry	Aromatic amide (1)	Compound (3)	Yield[b]
1	 **1a**	 **4a**	76%
2	 **1b**	 **4b**	74%
3	 **1c**	 **4c**	81%
4	 **1d**	 **4d**	75%
5	 **1f**	 **4e**	73%[c]
6	 **1g**	 **4f**	62%[c]

7	 **1j**	 **4g**	63%
8	 **1k**	 **4h**	65%
9	 **1l**	 **4i**	56%[c]
10	 **1m**	 **4j**	54%[c]
11	 **1n**	 **4k**	42%[c]
12	 **1o**	 **4l**	83%
13	 **1p**	 **4m**	51%[c]
14	 **1q**	 **4n**	77%

[a]All reactions were carried out using substituted amides **1a-q** (100 mg), allyl acetate **(2a)** (2.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv) in 1,2-dichloroethane (3.0 mL) at 100 °Cfor 16 h. (b)Isolated yield.(c)Reaction was done at 120 °C.

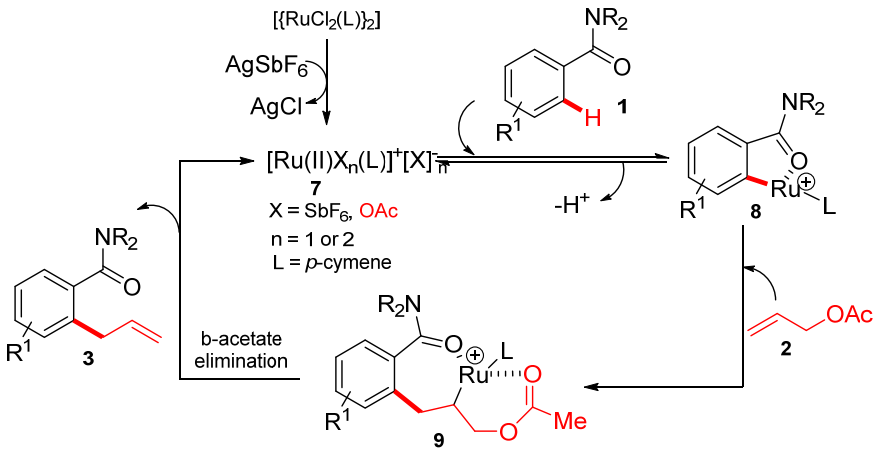
3B.8 Application

Substituted *ortho* allylated benzamides **3a-d** and **3f** were efficiently converted into a six-membered benzolactones **5a-e** in good yields in the presence of a 3:1 mixture of 6 N HCl and 1,4-dioxane at 110 °C for 12 h (Scheme 3B.2). Under similar reaction conditions, *ortho* vinylated benzamides **4a-c** provided a five-membered benzolactones **6a-c** in good yields. It is important to note that these structural units are present in various natural products and biologically active molecules.



Scheme 3B.2: Acid-Mediated Cyclization

3B.9 Proposed Mechanism

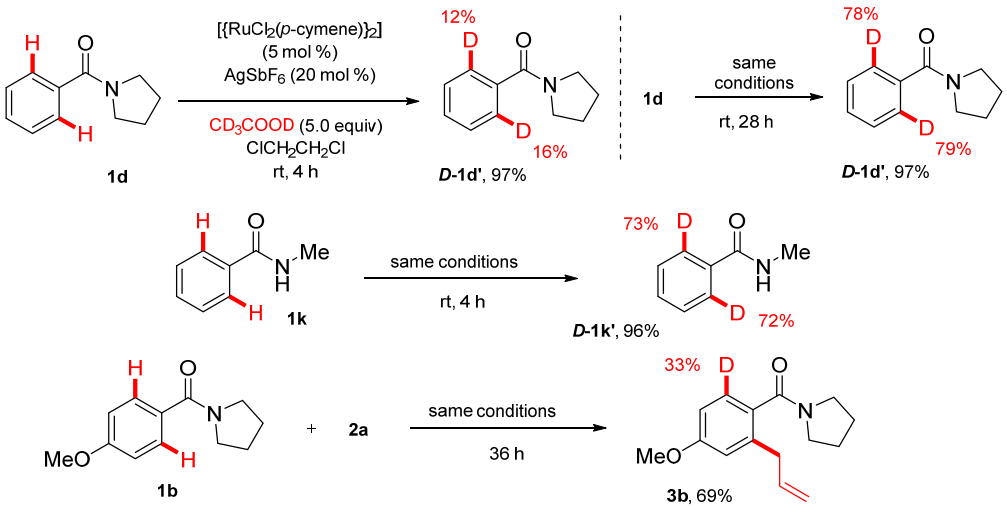


Scheme 3B.3: Proposed mechanism.

A possible reaction mechanism for *ortho* allylation of benzamides with allylic acetates is proposed in Scheme 3B.3. $AgSbF_6$ likely removes Cl^- ligand from $[\{RuCl_2(p\text{-cymene})\}_2]$ complex, giving a cationic ruthenium complexes **7**. Later, the oxygen atom of amide **1** coordinates with a ruthenium species **7** followed by *ortho*-metalation providing a five-membered ruthenacycle intermediate **8**. Coordinative regioselective insertion of allyl acetate **2a** into the Ru–carbon bond of intermediate **8** gives intermediate **9**. β-Acetate elimination of intermediate **9** affords *ortho* allyl benzamide **3** and regenerates catalyst **7** for the next catalytic cycle. It is important to note that the acetate group of **2a** would be transferred into the ruthenium species **7** intramolecularly and the corresponding acetate species deprotonates the C–H bond. The whole catalytic reaction has occurred in a Ru(II) oxidation state without changing the oxidation state of ruthenium and thus oxidant is not required for the present allylation reaction.

3B.10 Mechanistic Investigation

The reactivity of benzamides varies based on the substituent on the nitrogen atom. To know more about the reactivity, the rate of the C–H bond activation of benzamides was studied via deuterium labelling experiment (Scheme 3B.4). *N*, *N*-Disubstituted benzamide **1d** was treated with CD_3COOD at room temperature for 4 h, yielding product ***D*-1d‘**in 97% yield with 12% and 16% of deuterium incorporation at the both *ortho* carbons. But, the same reaction provided product ***D*-1d‘** in the maximum deuterium incorporation at the both *ortho* carbons in 78% and 79% at room temperature for 28 h. Further, *N*-methyl benzamide (**1k**) was treated with CD_3COOD at room temperature for 4 h, yielding product **D-1k‘**in 96% yield with 72% and 73% of deuterium incorporation at the both *ortho* carbons.

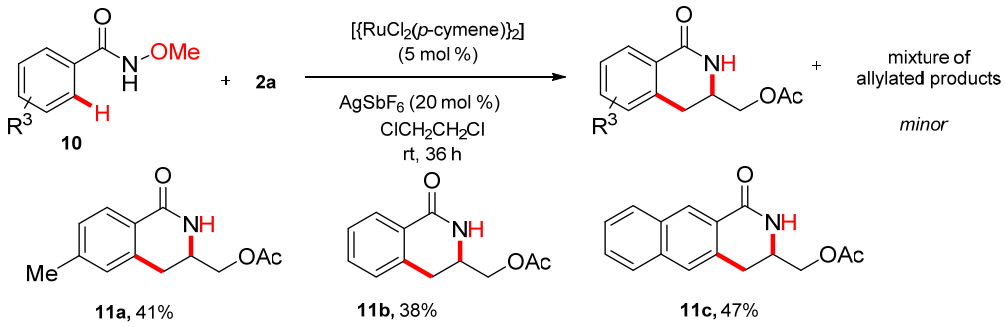


Scheme 3B.4: Deuterium labelling experiment of Aromatic amides

Based on these deuterium studies, we concluded that the C–H bond of *N*-methyl benzamides can be activated at room temperature for 4 h, but the allylation step needs a longer reaction time. But, in the case of *N*,*N*-disubstituted benzamide, the C–H bond activation can be activated at room temperature, but the process is slow and needs a longer reaction time. Further, to prove the formation of intermediate **8** is a reversible process, **1b**was treated with **2a** and CD_3COOD in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] and $AgSbF_6$ in DCE at room temperature for 36 h. In the reaction, product **3b** was observed in 69% yield with 33% deuterium incorporation at the *ortho* carbon.

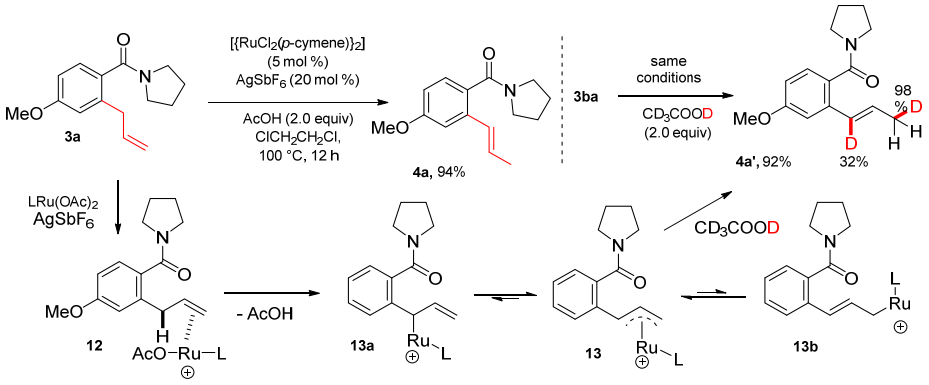
Subsequently, the formation of a seven-membered ruthenacycle intermediate **9** was supported by the reaction of *N*-methoxy benzamides **10** with allyl acetate (**2a**) under the optimized reaction conditions. In the reaction, cyclic 3,4-dihydroisoquinolin-1(2*H*)-ones **11a-c** were observed in moderate yields along with the formation of a minor amount of allylated products (Scheme 3B.5). It is very interesting to note that in the metal-catalyzed allylation reaction, allylic acetates mostly act as an allylating agent with a leaving of acetate group. Surprisingly, in the reaction, an acetate group was not cleaved and stayed as such. In the particular reaction, a ruthenium species can eliminate from intermediate **9** by two ways; a) β-acetate elimination along with the formation of allylated product as suggested in Scheme 3B.3; b) coupling of C-Ru with the free NH group of intermediate **9** via reductive elimination forming a cyclic product followed by cleavage of *N*-methoxy group of cyclic product **11**. In the reaction, both products such as a major amount of

cyclic products along with a minor amount of allylated products were observed. This result provides indirect evidence that the allylation reaction occurred via a seven membered metalacycle intermediate **9** as well as the β-acetate elimination.



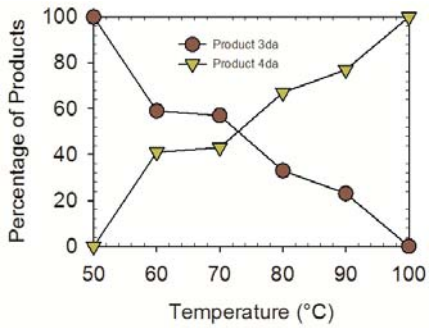
Scheme 3B.5: Synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones.

To know more about the insight of isomerization mechanism, *ortho* allylated benzamide **3b** was treated with [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) in DCE at 100 °C. In the reaction, no double bond isomerization product **4b** was observed. Later, the same reaction was examined in the presence of NaOAc. In the reaction, a mixture of **3b** and **4b** was observed in an 1:1 ratio. Interestingly, in the presence of 2.0 equiv of AcOH, the same reaction provided exclusively internal alkene **4b** in 94% yield. This result clearly reveals that the AcOH is crucial for the isomerization reaction along with a catalyst. In the present allylation reaction, a stoichiometric amount of AcOH is formed at the C–H bond activation step. It has been used for the isomerization reaction. To find out the exact role of AcOH, the same reaction was done by using CD_3COOD (Scheme 3B.6). Interestingly, in the reaction, product **4b** was observed in 92% yield with 98% deuterium incorporation at the CH_3 group of alkene and 32% at the benzylic CH_2. This study reveals that the isomerization reaction proceeds via π-allyl ruthenium intermediate 13 and not in a typical oxidative addition pathway. In most of the reported allylation reaction, it has been proposed that the reaction proceeds via an oxidative addition pathway. The present reaction proceeds via coordination of double bond of alkene with a cationic ruthenium species followed by OAc mediated deprotonation at the benzylic CH_2 provides π-allyl ruthenium intermediate **13**. Protonation at the C-Ru bond of intermediate **13** by acetic acid affords isomerization product **4b**' and regenerates the active catalyst.



Scheme 3B.6: Mechanism for isomerization reaction

Meanwhile, the reaction temperature is also crucial for the isomerization reaction. The isomerization reaction of **3a** into **4a** was carried out at different temperature such as 50 °C, 60 °C, 70 °C, 80 °C, 90 °C and 100 °C (Scheme 3B.7). The result shows that the reaction temperature up to 50 °C does not play any role for the isomerization reaction. At 60 °C to 90 °C, a mixture of terminal and internal olefins was observed in a higher ratio towards internal olefin. At 100 °C, terminal olefin was completely converted into internal olefin.To know further about the isomerization reaction, the energy of molecules **3d** and **4d** were calculated based on the DFT calculation. Based on the energy calculation, compound **4d** is stabilized by 19.2 kJ/mol than compound **3d.**



Scheme 3B.7: Temperature effect in Isomerization reaction.

3B.11 Conclusion

In conclusion, we have described a ruthenium-catalyzed highly regioselective *ortho*allylation of aromatic amides with allylic acetates at room temperature without any oxidant. In the reaction, two different regioisomeric alkene derivatives were observed exclusively by tuning the reaction

temperature. Later, biologically active six- and five-membered containing benzolactones were preparedby HCl hydrolysis. The detailed mechanistic investigation for the allylation and isomerization reactions was carried out.

3B.12 References

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3B.13 Experimental Section

3B.13.1 General Procedure for the Allylation of Aromatic amides with Allylic Acetates Catalyzed by a Ruthenium Complex

A 15-mL pressure tube with septum containing amide **1** (100 mg), [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube,was then added 1,2-dichloroethane(1.0 mL) via syringe. After that, allylicacetate **2** (2.0-2.5 equiv) and 1,2-dichloroethane(2.0 mL) were added via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, 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 rt for 16-36 h.Then, 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 petroleum ether and ethyl acetate(for some compounds CH_2Cl_2 and MeOH combination were used. It has been mentioned in the substrates below) as eluent to give pure **3**.

Note: Liquid amide reactants are added after adding 1.0 mL of solvent.For product **3aa,** 2.0equivofallylacetate (**2a**) was used.

3B.13.2 General Procedure for the Vinylation of Aromatic amides with Allylic Acetates catalyzed by Ruthenium Complex.

A 15-mL pressure A 15-mL pressure tube with septum containing amide **1** (100 mg), [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube, was then added 1,2-dichloroethane (1.0 mL) via syringe.After that, allylacetate **2a** (1.2-2.0equiv) and 1,2-dichloroethane (2.0 mL) were added via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, 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 100-120°C for 12-20 h. Then, 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 petroleum ether and ethyl acetate as eluent (for some compounds CH_2Cl_2 and MeOH combination were used. It has been mentioned in the substrates below) to give pure **4**.

3B.13.3 General Procedure for the Synthesis of Isochromanone Derivatives.

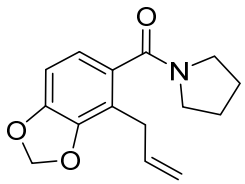
Ortho Allylated aromatic amides (**3**) (50 mg) was taken in a 10-mL sealed tube and dissolved with 0.5 mL of 1,4 dioxane and 2.0 mL of 6N HCl. Then, the reaction mixture heated at 110°C for 12 h. After cooling to ambient temperature, water was poured into the reaction mixture and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over Na_2SO_4. The solution was concentrated under the reduced pressure. The crude residue was purified through a silica gel column using petroleum ether and ethyl acetate as eluent to give pure **5.**

3B.13.4 General Procedure for the Synthesis of Isobenzofuranone Derivatives.

Ortho Vinylated aromatic amides (**4**) (50 mg) was taken in a 10-mL sealed tube and dissolved with 0.5 mL of 1,4-dioxane and 2.0 mL of 6N HCl. Then the reaction mixture heated at 120°C for 12 h. After cooling to ambient temperature, water was poured in to the reaction mixture and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over Na_2SO_4. The solution was concentrated under the reduced pressure. The crude residue was purified through a silica gel column using petroleum ether and ethyl acetate as eluent to give pure **6**.

3B.14 Spectral Data of Compounds 3a-o, 4a-n, 5a-e, and 6a-c

(4-Allylbenzo[*d*][1,3]dioxol-5-yl)(pyrrolidin-1-yl)methanone (3a).



The representative general procedure was followed using **1a** (100 mg), **2a** (2.0 equiv) and the reaction was done at rt for 16 h.The desired product was isolated in 96 mg and yield is 81%. Colorless solid; eluent (30% ethylacetate in hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ6.66 (d, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 5.91 (s, 2H), 5.89 – 5.77 (m, 1H), 4.98 (dq, *J* = 16.0, 4.0 Hz, 1H), 4.93 (dt, *J* = 12.0, 4.0 Hz, 1H), 3.53 (t, *J*= 8.0 Hz, 2H), 3.36 (d, *J* = 8.0 Hz, 2H), 3.12 (t, *J* = 8.0 Hz, 2H), 1.87 (p, *J* = 8.0 Hz, 2H), 1.75 (p, *J* = 8.0 Hz, 2H).

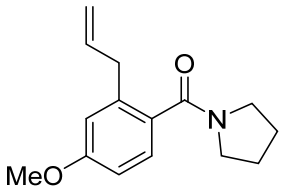
^{13}C NMR ($CDCl_3$, 100 MHz): δ168.9, 147.3, 146.2, 135.2, 131.8, 119.7, 118.6, 115.5, 106.3, 100.9, 48.9, 45.4, 30.9, 25.9, 24.5.

HRMS (ESI): calc. for [($C_{15}H_{17}NO_3$)H] (M+H) 260.1287, measured 260.1289.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3011, 2931, 2817, 1651, 1425, 1317, 1049, 918, 871, 668.

Rf (hexane/ethyl acetate = 70:30): 0.23.

(2-Allyl-4-methoxyphenyl)(pyrrolidin-1-yl)methanone(3b).



The representative general procedure was followed using **1b**(100 mg), **2a** (2.5 equiv)and the reaction was done at rt for 36 h.The desired product was isolated in 85 mg and yield is 71%. Colorless solid; eluent (28% ethylacetate in hexane).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.10 (d, *J* = 8.0Hz,1H),6.74 (d, *J* = 4.0Hz,1H),6.71 (dd, *J* = 8.0, 4.0 Hz,1H),5.90 -5.80 (m, 1H), 5.06 – 4.97 (m, 2H), 3.76(s, 3H), 3.57 (t, *J* = 8.0Hz,2H), 3.34 (d, *J* = 8.0Hz,2H), 3.11 (d, *J* = 8.0Hz,2H), 1.88 (p, *J* = 4.0Hz,2H), 1.79 (p, *J* = 4.0Hz,2 H).

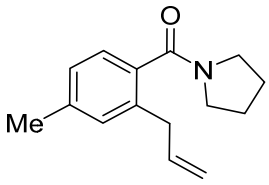
^{13}CNMR($CDCl_3$, 100 MHz): δ 169.7, 159.8, 138.3, 136.5, 130.2, 127.4, 115.9, 115.3, 111.3, 55.2, 48.8, 45.4, 37.5, 25.9, 24.5.

HRMS (ESI): calc. for [($C_{15}H_{19}NO_2$)H] (M+H) 246.1494, measured 246.1502.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2978, 2901, 1614, 1579, 1468, 1219, 1031, 858, 744, 598.

Rf (hexane/ethyl acetate = 70:30): 0.31.

(2-Allyl-4-methylphenyl)(pyrrolidin-1-yl)methanone (3c).



The representative general procedure was followed using **1c**(100 mg), **2a** (2.5 equiv)and the reaction was done at rt for 36 h.The desired product was isolated in 76 mg and yield is 63%. Colorless solid; eluent (30% ethylacetate in hexane).

^{1}H NMR ($CDCl_3$, 400 MHz): δ7.06 (d, *J* = 8.0 Hz, 1H), 7.02 (s, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 5.91 – 5.81 (m, 1H), 5.02 (dq, *J* = 16.0, 4.0 Hz, 1H), 4.98 (dq, *J* = 8.0, 4.0 Hz, 1H), 3.58 (t, *J* = 8.0 Hz, 2H), 3.37 (d, *J* = 8.0 Hz, 2H), 3.10 (t, *J* = 8.0 Hz, 2H), 2.29 (s, 3H), 1.90 (p, *J* = 8.0 Hz, 2H), 1.79 (p, *J* = 8.0 Hz, 2H).

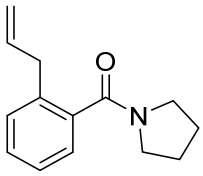
^{13}C NMR ($CDCl_3$, 100 MHz): δ169.8, 138.7, 136.9, 136.1, 134.8, 130.4, 126.8, 125.9, 115.7, 48.7, 45.3, 37.3, 25.9, 24.5, 21.2.

HRMS (ESI): calc. for [($C_{15}H_{19}NO$)H] (M+H) 230.1545, measured 230.1553.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2931, 2817, 1727, 1637, 1435, 1312, 1041, 908, 875, 661.

Rf (hexane/ethyl acetate = 70:30): 0.38.

(2-Allylphenyl)(pyrrolidin-1-yl)methanone (3d).



The representative general procedure was followed using **1d**(100 mg), **2a** (2.5 equiv)and the reaction was done at rt for 36 h.The desired product was isolated in 85 mg and yield is 69%. Colorless solid; eluent (30% ethylacetate in hexane).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.31 (td, *J* = 8.0, 4.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.21 (td, *J* = 8.0, 4.0 Hz, 2H),5.94 -5.86 (m, 1H), 5.09 – 5.01 (m, 2H), 3.63 (t, *J* = 8.0Hz,2H), 3.44 (d, *J* = 8.0Hz,2H), 3.14 (t, *J* = 8.0Hz,2H), 1.94 (p, *J* = 4.0Hz,2H), 1.84 (p, *J* = 4.0Hz,2 H).

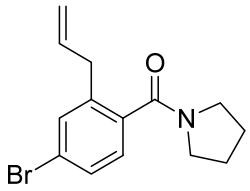
^{13}C NMR($CDCl_3$, 100 MHz): δ 168.6, 138.7, 136.4, 135.7, 132.8, 129.4, 127.5,122.9, 116.7,48.7, 45.5, 37.1, 25.9, 24.5.

HRMS (ESI): calc. for [($C_{14}H_{17}NO$)H] (M+H) 216.1388, measured 216.1395.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2979, 1614, 1570, 1413, 1261, 1048, 879, 717, 628.

Rf (hexane/ethyl acetate = 70:30): 0.31.

(2-Allyl-4-bromophenyl)(pyrrolidin-1-yl)methanone (3e).



The representative general procedure was followed using **1e**(100 mg), **2a** (2.5 equiv)and the reaction was done at rt for 36 h.The desired product was isolated in 77 mg and yield is 66%. Colorless solid; eluent (24% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.38 (d, *J* = 4.0Hz,1H),7.34 (dd, *J* = 8.0, 4.0 Hz,1H),7.05 (d, *J* = 8.0Hz,1H), 5.88 -5.78 (m, 1H), 5.08 – 5.02 (m, 2H), 3.58 (t, *J* = 8.0Hz,2H), 3.37 (d, *J* = 8.0Hz,2H), 3.09 (t, *J* = 8.0Hz,2H), 1.90 (p, *J* = 4.0Hz,2H), 1.81 (p, *J* = 4.0Hz,2H).

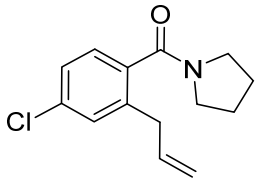
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.6, 137.5, 136.7, 136.1, 129.8, 128.9, 126.2, 125.9, 115.8, 48.7, 45.3, 37.4, 25.9, 24.5.

HRMS (ESI): calc. for [($C_{14}H_{16}BrNO$)H] (M+H) 294.0494, measured 294.0495.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3078, 2931, 1634, 1589, 1463, 1259, 1041, 874, 747, 668.

Rf (hexane/ethyl acetate = 70:30): 0.29.

(2-Allyl-4-chlorophenyl)(pyrrolidin-1-yl)methanone (3f).



The representative general procedure was followed using **1f**(100 mg), **2a** (2.5 equiv)and the reaction was done at rt for 36 h.The desired product was isolated in 73 mg and yield is 61%. Colorless solid; eluent (30% ethylacetate in hexane).

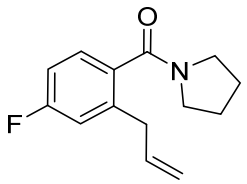
^{1}H NMR ($CDCl_3$, 400 MHz): δ7.21 (d, *J* = 4.0 Hz, 1H), 7.17 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 5.87 – 5.77 (m, 1H), 5.05 (dq, *J* = 12.0, 4.0 Hz, 1H), 5.02 (dq, *J* = 8.0, 4.0 Hz, 1H), 3.57 (t, *J* = 8.0 Hz, 2H), 3.37 (dd, *J* = 8.0, 4.0 Hz, 2H), 3.08 (t, *J* = 8.0 Hz, 2H), 1.90 (p, *J* = 8.0 Hz, 2H), 1.79 (p, *J* = 8.0 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ168.5, 138.5, 135.9, 135.7, 134.6, 129.8, 127.3, 126.4, 116.7, 48.6, 45.4, 37.1, 25.9, 24.5.

HRMS (ESI): calc. for [($C_{14}H_{16}ClNO$)H] (M+H) 250.0999, measured 250.1003.

Rf (hexane/ethyl acetate = 70:30): 0.31.

(2-Allyl-4-Fluorophenyl)(pyrrolidin-1-yl)methanone (3g).



The representative general procedure was followed using **1g**(100 mg), **2a** (2.5 equiv)and the reaction was done at rt for 36 h.The desired product was isolated in 62 mg and yield is 52%. Colorless liquid;eluent (25% ethylacetate in hexane).

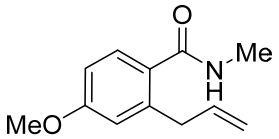
^{1}H NMR ($CDCl_3$, 400 MHz): δ7.16 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.93 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.89 (td, *J* = 8.0, 4.0 Hz, 1H), 5.88 – 5.79 (m, 1H), 5.06 (dq, *J* = 8.0, 4.0 Hz, 1H), 5.03 (dq, *J* = 8.0, 4.0 Hz, 1H), 3.59 (t, *J* = 8.0 Hz, 2H), 3.39 (d, *J* = 8.0 Hz, 2H), 3.10 (t, *J* = 8.0 Hz, 2H), 1.91 (p, *J* = 8.0 Hz, 2H), 1.81 (p, *J* = 8.0 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.9, 163.9, 161.5, 139.4 and 139.3(F-coupling), 135.8, 133.6, 127.8 and 127.7(F-coupling), 116.7 and 116.5(F-coupling), 113.3 and 113.1(F-coupling),48.7, 45.5, 37.2, 25.9, 24.4.

HRMS (ESI): calc. for [($C_{14}H_{16}FNO$)H] (M+H) 234.1294, measured 234.1299.

Rf (hexane/ethyl acetate = 70:30): 0.33.

2-Allyl-4-methoxy-*N*-methylbenzamide (3h).



The representative general procedure was followed using **1h**(100 mg), **2a** (2.5 equiv)and the reaction was done at rt for 36 h.The desired product was isolated in 63 mg and yield is 51%. Colorless solid; eluent (30% ethylacetate in hexanes).

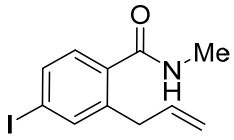
^{1}H NMR ($CDCl_3$, 400 MHz):δ7.33(d, *J* = 8.0Hz,1H), 6.73 – 6.69 (m, 2H), 6.02 – 5.92 (m, 1H), 5.87 (s, 1H), 5.05 (dq, *J* = 8.0, 4.0 Hz, 1H), 5.0 (dq, *J* = 12.0, 4.0 Hz, 1H), 3.78 (s, 3H), 3.53 (d, *J* = 8.0Hz,2H), 2.91 (d, *J* = 8.0Hz,3H).

^{13}C NMR($CDCl_3$, 100 MHz): δ 170.2, 160.7, 139.9, 137.5, 129.0, 128.9, 116.0, 115.9, 111.3, 55.2, 37.8, 26.6.

HRMS (ESI): calc. for [($C_{12}H_{15}NO_2$)H] (M+H) 206.1181, measured 206.1187.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3289, 2922, 1630, 1536, 1403, 1157, 1041, 999.

2-Allyl-4-iodo-*N*-methylbenzamide (3i).



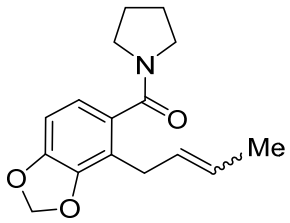
The representative general procedure was followed using **1i**(100 mg), **2a** (2.5 equiv)and the reaction was done at rt for 36 h.The desired product was isolated in 49 mg and yield is 42%. Colorless solid; eluent (30% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.57 (d, *J* = 4.0Hz,1H), 7.54 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.06 (d, *J* = 8.0Hz,1H),5.98 (s, 1H), 5.96 – 5.86 (m, 1H), 5.07 (dq, *J* = 8.0, 4.0 Hz, 1H), 4.99 (dq, *J* = 12.0, 4.0 Hz, 1H), 3.44 (d, *J* = 8.0Hz,2H), 2.91 (d, *J* = 4.0Hz,3H).

^{13}C NMR($CDCl_3$, 100 MHz): δ 169.7, 139.8, 139.2, 136.7, 135.9, 135.4, 128.7, 116.7, 96.3 37.1, 26.6.

HRMS (ESI): calc. for [($C_{11}H_{12}INO$)H] (M+H) 302.0042, measured 302.0049.

(4-(But-2-en-1-yl)benzo[*d*][1,3]dioxol-5-yl)(pyrrolidin-1-yl)methanone (3j).



The representative general procedure was followed using **1a**(100 mg), **2b**(2.5 equiv)and the reaction was done at rt for 16 h.The desired product was isolated in 98 mg and yield is 78%. Colorless liquid; eluent (27% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): **E isomer:**δ6.66 (d, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 5.93 (s, 2H), 5.51 – 5.34 (m, 2H), 3.55 (t, *J* = 8.0 Hz, 2H), 3.37 (d, *J*= 8.0 Hz, 2H), 3.13 (t, *J* = 8.0 Hz, 2H), 1.89 (p, *J* = 8.0 Hz, 2H), 1.78 (p, *J* = 8.0 Hz, 2H), 1.64 (d, *J* = 8.0 Hz, 3H).

Z isomer:δ6.66 (d, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 5.93 (s, 2H), 5.51 – 5.34 (m, 2H), 3.55 (t, *J* = 8.0 Hz, 2H), 3.29 (d, *J* = 4.0 Hz, 1H), 3.13 (t, *J* = 8.0 Hz, 2H), 1.89 (p, *J* = 8.0 Hz, 2H), 1.78 (p, *J* = 8.0 Hz, 2H), 1.58 (d, *J* = 4.0 Hz, 1H).

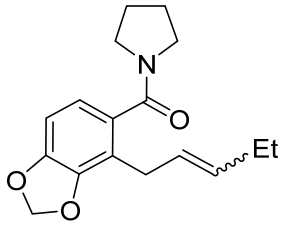
^{13}C NMR ($CDCl_3$, 100 MHz): **E isomer:** δ169.2, 147.3, 146.1, 131.7, 127.7, 127.1, 126.3, 124.8, 106.2, 100.9, 48.9, 45.4, 29.8, 25.9, 24.6, 12.8. **Z isomer:** δ169.1, 147.3, 146.1, 131.7, 127.7, 126.3, 119.8, 119.7, 106.2, 100.9, 48.9, 45.4, 29.6, 25.9, 24.6, 17.8.

HRMS (ESI): calc. for [($C_{16}H_{19}NO_3$)H] (M+H) 274.1443, measured 274.1446.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2989, 2717, 1637, 1485, 1212, 1041, 908, 875, 652.

Rf (hexane/ethyl acetate = 70:30): 0.23.

(4-(Pent-2-en-1-yl)benzo[*d*][1,3]dioxol-5-yl)(pyrrolidin-1-yl)methanone (3k).



The representative general procedure was followed using **1a**(100 mg), **2c**(2.5 equiv)and the reaction was done at rt for 16 h.The desired product was isolated in 101 mg and yield is 77%. Colorless liquid; eluent (30% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): **E isomer:**δ6.66 (d, *J* = 8.0 Hz, 1H),6.63 (d, *J* = 8.0 Hz, 1H),5.93 (s, 2H), 5.38 – 5.32 (m, 2H), 3.55 (t, *J* = 8.0 Hz, 2H), 3.37 (d, *J* = 8.0 Hz, 2H), 3.14 (t, *J* = 8.0 Hz, 2H), 2.08 (p, *J* = 8.0 Hz, 2H), 1.89 (p, *J* = 8.0 Hz, 2H), 1.78 (p, *J* = 8.0 Hz, 2H), 0.93 (t, *J* = 8.0 Hz, 3H).**Z isomer:** δ6.66 (d, *J* = 8.0 Hz, 1H),6.63 (d, *J* = 8.0 Hz, 1H), 5.93 (s, 2H), 5.48 – 5.43 (m, 2H), 3.55 (t, *J* = 8.0 Hz, 2H), 3.31 (d, *J* = 8.0 Hz, 2H), 3.14 (t, *J* = 8.0 Hz, 2H), 2.08 (p, *J* = 8.0 Hz, 2H), 1.89 (p, *J* = 8.0 Hz, 2H), 1.78 (p, *J* = 8.0 Hz, 2H), 0.93 (t, *J* = 8.0 Hz, 3H).

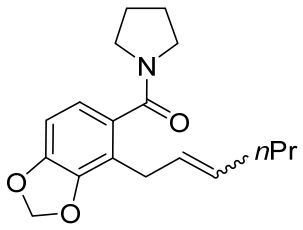
^{13}C NMR ($CDCl_3$, 100 MHz): **E isomer:**δ 169.1, 147.3, 146.1, 133.4, 132.6, 131.7, 125.5, 119.9, 106.1, 100.9, 48.9, 45.4, 25.9, 24.8, 24.6, 20.5, 14.1. **Z isomer:** δ170.7, 147.3, 146.1, 130.5, 125.4, 125.3, 119.7, 119.6, 106.1, 100.9, 48.9, 45.4, 39.0, 34.7, 29.8, 25.9, 25.4, 24.9, 24.8, 24.6, 20.5, 14.1, 13.5.

HRMS (ESI): calc. for [($C_{17}H_{21}NO_3$)H] (M+H) 288.1600, measured 288.1610.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2948, 2811, 1616, 1435, 1212, 1021, 905, 875, 669.

Rf (hexane/ethyl acetate = 70:30): 0.23.

(4-(Hex-2-en-1-yl)benzo[*d*][1,3]dioxol-5-yl)(pyrrolidin-1-yl)methanone (3l).



The representative general procedure was followed using **1a**(100 mg), **2d**(2.5 equiv)andthe reaction was done at rt for 16 h.The desired product was isolated in 103 mg and yield is 76%. Colorless liquid; eluent (26% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): **E isomer:**δ6.66 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 5.92 (s, 2H), 5.38 – 5.33 (m, 2H), 3.55 (t, *J* = 8.0 Hz, 2H), 3.36 (d, *J* = 4.0 Hz, 2H), 3.13 (t, *J* = 8.0 Hz, 2H), 2.05 (q, *J* = 8.0 Hz, 2H), 1.89 (p, *J* = 8.0 Hz, 2H), 1.77 (p, *J* = 8.0 Hz, 2H), 5.38 – 5.33 (m, 2H), 0.87 (t, *J* = 8.0 Hz, 3H).

Z isomer: δ6.66 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 5.92 (s, 2H), 5.47 – 5.41 (m, 2H), 3.55 (t, *J* = 8.0 Hz, 2H), 3.31 (d, *J* = 4.0 Hz, 2H), 3.13 (t, *J* = 8.0 Hz, 2H), 2.05 (q, *J* = 8.0 Hz, 2H), 1.89 (p, *J* = 8.0 Hz, 2H), 1.77 (p, *J* = 8.0 Hz, 2H), 5.38 – 5.33 (m, 2H), 0.81 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): **E isomer:**δ170.7, 147.2, 146.0, 131.7, 130.8, 126.2, 126.0, 119.7, 106.2, 100.9, 48.8, 45.4, 29.2, 25.8, 24.9, 24.5, 22.7, 13.7.

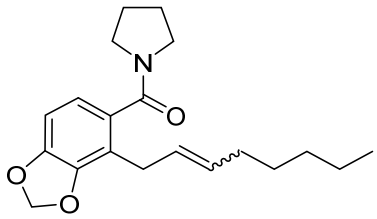
Z isomer:δ 169.1, 147.2, 146.0, 130.4, 126.5, 120.1, 119.9, 119.7, 106.2, 100.9, 48.8, 39.0, 34.7, 34.5, 29.9, 25.0, 22.4, 13.6.

HRMS (ESI): calc. for [($C_{18}H_{23}NO_3$)H] (M+H) 302.1756, measured 302.1762.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2967, 2819, 1614, 1435, 1312, 1041, 908, 818, 695.

Rf (hexane/ethyl acetate = 70:30): 0.29.

(4-(Oct-2-en-1-yl)benzo[*d*][1,3]dioxol-5-yl)(pyrrolidin-1-yl)methanone (3m).



The representative general procedure was followed using **1a**(100 mg), **2e**(2.5 equiv)and the reaction was done at rt for 16 h.The desired product was isolated in 102 mg and yield is 68%. Colorless liquid; eluent (28% ethylacetate in hexane).

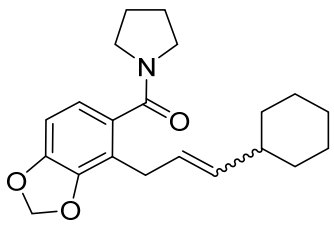
^{1}H NMR ($CDCl_3$, 400 MHz): **E isomer:**δ6.65 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 5.91 (s, 2H), 5.37 – 5.35 (m, 2H), 3.54 (t, *J* = 8.0 Hz, 2H), 3.35 (d, *J* = 4.0 Hz, 2H), 3.13 (t, *J* = 8.0 Hz, 2H), 2.06 (q, *J* = 8.0 Hz, 2H), 1.88 (p, *J* = 8.0 Hz, 2H), 1.77 (p, *J*= 8.0 Hz, 2H), 1.36 – 1.16 (m, 6H), 0.84 (t, *J* = 8.0 Hz, 3H).**Z isomer:** δ6.65 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 5.91 (s, 2H), 5.43 – 5.40 (m, 1H), 3.54 (t, *J* = 8.0 Hz, 2H), 3.29 (d, *J* = 4.0 Hz, 2H), 3.13 (t, *J* = 8.0 Hz, 2H), 2.06 (q, *J* = 8.0 Hz, 2H), 1.88 (p, *J* = 8.0 Hz, 2H), 1.77 (p, *J*= 8.0 Hz, 2H), 1.36 – 1.16 (m, 6H), 0.84 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): **E isomer:**δ169.1, 147.2, 146.1, 131.7, 131.1, 125.9, 119.9, 119.7, 106.1, 100.9, 48.8, 45.4, 31.4, 29.2, 27.1, 25.9, 24.9, 24.5, 22.5, 13.9.**Z isomer:**δ 169.1, 147.2, 146.1, 131.9, 131.1, 126.2, 119.9, 119.7, 106.1, 100.9, 48.8, 36.5, 34.7, 32.4, 31.3, 29.9, 29.6, 28.9, 22.4, 13.9.

HRMS (ESI): calc. for [($C_{20}H_{27}NO_3$)H] (M+H) 330.2069, measured 330.2077.

Rf (hexane/ethyl acetate = 70:30): 0.23.

(4-(3-Cyclohexylallyl)benzo[*d*][1,3]dioxol-5-yl)(pyrrolidin-1-yl)methanone (3n).



The representative general procedure was followed using **1a**(100 mg), **2f**(2.5 equiv)and the reaction was done at rt for 16 h.The desired product was isolated in 96 mg and yield is 62%. Colorless liquid; eluent (30% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): **E isomer:** δ 6.67 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.93 (s, 2H), 5.31 – 5.18 (m, 2H), 3.57 (t, *J* = 8.0 Hz, 2H), 3.38 (d, *J* = 8.0 Hz, 2H), 3.16 (t, *J* = 8.0 Hz, 2H), 2.39 – 2.32 (m, 1H), 1.90 (p, *J* = 8.0 Hz, 2H), 1.79 (p, *J* = 8.0 Hz, 2H), 1.68 – 1.56 (m, 6H), 1.35 – 1.19 (m, 2H), 1.19 – 1.07 (m, 2H), 1.07 – 0.93 (m, 2H).

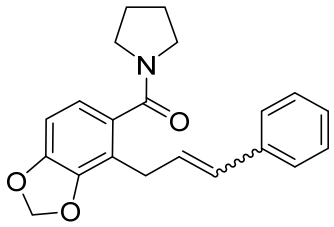
Z isomer:δ 6.67 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.93 (s, 2H), 5.41 – 5.38 (m, 2H), 3.57 (t, *J* = 8.0 Hz, 2H), 3.30 (d, *J* = 8.0 Hz, 2H), 3.16 (t, *J* = 8.0 Hz, 2H), 2.39 – 2.32 (m, 1H), 1.90 (p, *J* = 8.0 Hz, 2H), 1.79 (p, *J* = 8.0 Hz, 2H), 1.68 – 1.56 (m, 6H), 1.35 – 1.19 (m, 2H), 1.19 – 1.07 (m, 2H), 1.07 – 0.93 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): **E isomer:**δ169.1, 147.3, 146.1, 137.1, 131.7, 124.3, 120.2, 119.8, 106.2, 100.9, 48.9, 45.5, 36.2, 33.1, 26.0, 25.9, 25.8, 25.1, 24.6.**Z isomer:**δ 169.1, 137.9, 137.8, 137.1, 130.5, 124.1, 123.9, 119.8, 106.2, 100.9, 48.9, 45.5, 40.5, 39.1, 34.8, 32.9, 30.2, 29.6, 26.1.

HRMS (ESI): calc. for [($C_{21}H_{27}NO_3$)H] (M+H) 342.2069, measured 342.2073.

Rf (hexane/ethyl acetate = 98:2): 0.63.

(4-(3-Phenylallyl)benzo[*d*][1,3]dioxol-5-yl)(pyrrolidin-1-yl)methanone (3o).



The representative general procedure was followed using **1a**(100 mg), **2g**(2.5 equiv)and the reaction was done at rt for 16 h.The desired product was isolated in 113 mg and yield is 74%. Colorless liquid; eluent (27% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): **E isomer:**δ 7.35 – 7.17 (m, 6H), 6.67 (s, 2H), 6.43 (dt, *J* = 12.0, 4.0 Hz, 1H), 5.94 (s, 2H), 5.74 (dt, *J* = 12.0, 8.0 Hz, 1H), 3.68 (dd, *J* = 8.0, 4.0 Hz, 2H), 3.29 (t, *J* = 8.0 Hz, 2H), 3.05 (t, *J* = 8.0 Hz, 2H), 1.74 – 1.62 (m, 4H).

Z isomer:δ 7.35 – 7.17 (m, 6H), 6.67 (s, 2H), 6.43 (dt, *J* = 12.0, 4.0 Hz, 1H), 5.94 (s, 2H), 5.74 (dt, *J* = 12.0, 8.0 Hz, 1H), 3.56 (dd, *J* = 8.0, 4.0 Hz, 2H), 3.52 (t, *J* = 8.0 Hz, 2H), 3.11 (t, *J* = 8.0 Hz, 2H), 1.74 – 1.62 (m, 4H).

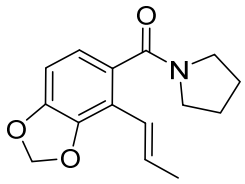
^{13}C NMR ($CDCl_3$, 100 MHz): **E isomer:**δ168.7, 147.3, 145.9, 136.8, 131.9, 129.4, 128.7, 128.1, 126.7, 119.6, 119.1, 106.6, 101.0, 48.6, 45.5, 26.5, 25.7, 24.3.

Z isomer:δ168.9, 146.1, 137.1, 131.7, 131.1, 128.4, 127.1, 126.6, 125.9, 119.9, 118.8, 106.2, 101.0, 49.0, 45.1, 29.9, 29.6, 25.6.

HRMS (ESI): calc. for [($C_{21}H_{21}NO_3$)H] (M+H) 336.1600, measured 336.1607.

Rf (hexane/ethyl acetate = 70:30): 0.27.

(*E*)-(4-(Prop-1-en-1-yl)benzo[*d*][1,3]dioxol-5-yl)(pyrrolidin-1-yl)methanone (4a).



The representative general procedure was followed using **1a**(100 mg), **2a**(1.2 equiv)and the reaction was done at 100^{o}Cfor12 h.The desired product was isolated in 89 mg and yield is 76%. Colorless solid; eluent (30% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.71 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.55 (dq, *J* = 16.0, 8.0 Hz, 1H), 6.22(dq, *J* = 16.0, 4.0 Hz, 1H), 5.98 (s, 2H), 3.61 (t, *J* = 8.0 Hz, 2H), 3.12 (t, *J* = 8.0 Hz, 2H), 1.91 (p, *J* = 8.0 Hz, 2H), 1.84 (dd, *J* = 8.0, 4.0 Hz, 3H), 1.84 – 1.78 (m, 2H).

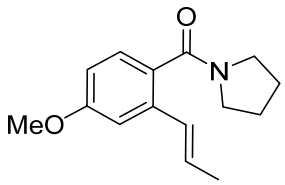
^{13}C NMR ($CDCl_3$, 100 MHz): δ169.1, 147.6, 144.8, 132.6, 130.7, 122.9, 119.9, 117.5, 106.6, 100.9, 48.4, 45.5, 25.9, 24.6, 19.4.

HRMS (ESI): calc. for [($C_{15}H_{17}NO_3$)H] (M+H) 260.1287, measured 260.1289.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2881, 2797, 1647, 1435, 1312, 1041, 918, 874, 680.

Rf (hexane/ethyl acetate = 70:30): 0.22.

(*E*)-(4-Methoxy-2-(prop-1-en-1-yl)phenyl)(pyrrolidin-1-yl)methanone (4b).



The representative general procedure was followed using **1b**(100 mg), **2a**(1.2 equiv)and the reaction was done at 100^{o}C for12 h.The desired product was isolated in 88 mg and yield is 74%. Colorless solid; eluent (28% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ7.13 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 4.0 Hz, 1H), 6.74 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.25 – 6.16 (m, 1H), 3.79 (s, 3H), 3.62 (t, *J* = 8.0 Hz, 2H), 3.09 (t, *J* = 8.0 Hz, 2H), 1.91 (p, *J* = 8.0 Hz, 2H), 1.83 (dd, *J* = 8.0, 4.0 Hz, 2H), 1.82 – 1.77 (m, 2H).

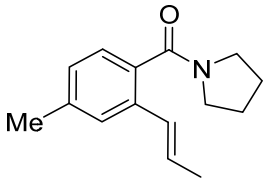
^{13}C NMR ($CDCl_3$, 100 MHz): δ169.7, 159.8, 135.9, 129.1, 128.5, 127.8, 127.6, 112.6, 110.4, 55.2, 48.3, 45.5, 25.9, 24.6, 18.7.

HRMS (ESI): calc. for [($C_{15}H_{19}NO_2$)H] (M+H) 246.1494, measured 246.1502.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2931, 2817, 1727, 1637, 1435, 1312, 1041, 908, 875, 661.

Rf (hexane/ethyl acetate = 70:30): 0.32.

(*E*)-(4-Methyl-2-(prop-1-en-1-yl)phenyl)(pyrrolidin-1-yl)methanone (4c).



The representative general procedure was followed using **1c**(100 mg), **2a**(1.2 equiv)and the reaction was done at 100^{o}Cfor12 h.The desired product was isolated in 98 mg and yield is 81%. Colorless solid; eluent (28% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ7.25 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 6.23- 6.15 (m, 1H), 3.61 (t, *J* = 8.0 Hz, 2H), 3.06 (t, *J* = 8.0 Hz, 2H), 2.29 (s, 3H), 1.90 (p, *J* = 8.0 Hz, 2H), 1.81 (dd, *J* = 8.0, 4.0 Hz, 3H), 1.81 – 1.75(m, 2 H).

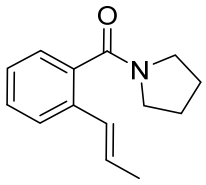
^{13}C NMR ($CDCl_3$, 100 MHz): δ169.9, 138.5, 133.9, 133.3, 127.9, 127.6, 127.5, 126.0, 125.9, 48.2, 45.4, 25.8, 24.5, 21.3, 18.7.

HRMS (ESI): calc. for [($C_{15}H_{19}NO$)H] (M+H) 230.1545, measured 230.1553.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2942, 2617, 1647, 1415, 1317, 1047, 918, 875, 598.

Rf (hexane/ethyl acetate = 70:30): 0.29.

(*E*)-(2-(Prop-1-en-1-yl)phenyl)(pyrrolidin-1-yl)methanone (4d).



The representative general procedure was followed using **1d**(100 mg), **2a**(1.2 equiv)andthe reaction was done at 100^{o}Cfor12 h.The desired product was isolated in 92 mg and yield is 75%. Colorless solid; eluent (27% ethylacetate in hexanes).

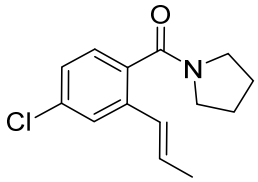
^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.40 (d, *J* = 8.0Hz,1H),7.24 -7.18 (m, 1H), 7.12 (t, *J* = 4.0Hz,2H),6.33 (d, *J* = 16.0Hz,1H),6.20 -6.13(m, 1H), 3.57 (t, *J* = 8.0Hz,2 H), 3.00 (t, *J* = 8.0Hz,2 H), 1.85 (p, *J* = 4.0Hz,2 H), 1.77(dt, *J* = 8.0, 4.0Hz,3 H), 1.76 – 1.72 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.5, 135.8, 133.8, 128.7, 128.2, 127.4, 126.7, 125.8, 125.2, 48.0, 45.2, 25.7, 24.4, 18.6.

HRMS (ESI): calc. for [($C_{14}H_{17}NO$)H] (M+H) 216.1388, measured 216.1395.

Rf (hexane/ethyl acetate = 70:30): 0.33.

(*E*)-(4-Chloro-2-(prop-1-en-1-yl)phenyl)(pyrrolidin-1-yl)methanone (4e).



The representative general procedure was followed using **1f**(100 mg), **2a**(1.2 equiv)and the reaction was done at 120^{o}C for12 h.The desired product was isolated in 86 mg and yield is 73%. Colorless solid; eluent (28% ethylacetate in hexanes).

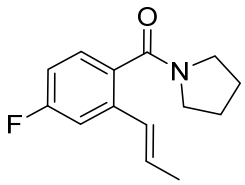
^{1}H NMR ($CDCl_3$, 400 MHz): δ7.45 (d, *J* = 4.0 Hz, 1H), 7.17 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.29 – 6.21 (m, 1H), 3.63 (t, *J* = 8.0 Hz, 2H), 3.07 (t, *J* = 8.0 Hz, 2H), 1.93 (p, *J* = 6.5 Hz, 2H), 1.85 (dd, *J* = 8.0, 2.0 Hz, 3H), 1.84 – 1.78 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ168.7, 136.1, 134.8, 134.5, 129.3, 127.6, 126.9, 126.6, 125.5, 48.2, 45.5, 25.9, 24.6, 18.7.

HRMS (ESI): calc. for [($C_{14}H_{16}ClNO$)H] (M+H) 250.0999, measured 250.1003.

Rf (hexane/ethyl acetate = 70:30): 0.29.

(*E*)-(4-Fluoro-2-(Prop-1-en-1-yl)phenyl)(pyrrolidin-1-yl)methanone (4f).



The representative general procedure was followed using **1g**(100 mg), **2a**(1.2 equiv)and the reaction was done at 120^{o}C for12 h.The desired product was isolated in 75 mg and yield is 62%. Colorless solid; eluent (28% ethylacetate in hexanes).

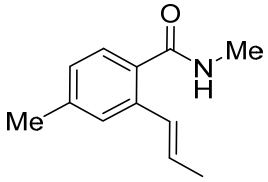
^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.17 (d, *J* = 8.0Hz,1H),7.13 (dd, *J* = 8.0, 4.0Hz,1H),6.88(dt, *J* = 8.0, 4.0 Hz,1H),6.35 (d, *J* = 16.0Hz,1H),6.27 -6.18(m, 1H), 3.61 (t, *J* = 8.0Hz,2H), 3.06 (t, *J* = 8.0Hz,2H), 1.91 (p, *J* = 4.0Hz,2H), 1.83(dd, *J* = 8.0, 4.0Hz,3H), 1.81 – 1.77(m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.9, 164.1 and 161.6(F-coupling), 136.8 and 136.7(F-coupling), 132.1, 129.8, 128.1 and 127.9(F-coupling), 126.7, 114.0 and 113.8(F-coupling), 111.9 and 111.7(F-coupling), 48.3, 45.5, 25.9, 24.5, 18.7.

HRMS (ESI): calc. for [($C_{14}H_{16}FNO$)H] (M+H) 234.1294, measured 234.1299.

Rf (hexane/ethyl acetate = 98:2): 0.63.

(*E*)-*N*,4-Dimethyl-2-(prop-1-en-1-yl)benzamide (4g).



The representative general procedure was followed using **1j**(100 mg), **2a**(2.0 equiv)and the reaction was done at 100^{o}C for16 h.The desired product was isolated in 79 mg and yield is 63%. White Colour solid; eluent (0.3% methanol in DCM).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.29 (d, *J* = 4.0Hz, 1H), 7.25 (d, *J* = 4.0 Hz, 1H), 7.00 (d, *J* = 8.0Hz, 1H), 6.67 (dd, *J* = 16.0, 4.0 Hz, 1H), 6.20-6.11 (m, 1H), 5.81 (s, 1H), 2.95(d, *J* = 4.0 Hz,3 H), 2.32 (s, 3 H), 1.86 (dd, *J* = 8.0, 4.0Hz, 3 H).

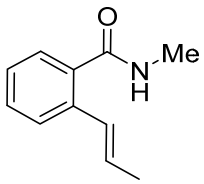
^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 139.9, 135.9, 132.0, 128.6, 128.4, 127.5, 127.4, 126.9, 26.7, 21.3, 18.7.

HRMS (ESI): calc. for [($C_{12}H_{15}NO$)H] (M+H) 190.1232, measured 190.1236.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3289, 2922, 1630, 1536, 1403, 1157, 1041, 999.

Rf (hexane/ethyl acetate = 70:30): 0.27.

(*E*)-*N*-Methyl-2-(prop-1-en-1-yl)benzamide(4h).



The representative general procedure was followed using **1k**(100 mg), **2a**(2.0 equiv)and the reaction was done at 100°C for16 h.The desired product was isolated in 84 mg and yield is 65%. White Colour solid; eluent (0.3% methanol in DCM).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.44 (d, *J* = 4.0Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H),7.16 (t, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 12.0Hz, 1H), 6.20-6.11 (m, 1H), 5.92 (s, 1 H), 2.93(d, *J* = 4.0 Hz,3 H), 1.85 (dd, *J* = 8.0, 4.0Hz, 3 H).

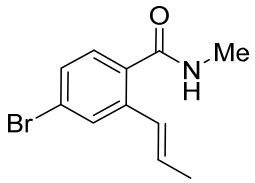
^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 135.8, 134.8, 129.8, 128.6, 128.3, 127.3, 126.6, 126.1, 26.6, 18.6.

HRMS (ESI): calc. for [($C_{11}H_{13}NO$)H] (M+H) 176.1075, measured 176.1073.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3294, 2935, 1635, 1546, 1444, 1319, 1005, 954, 687.

Rf (hexane/ethyl acetate = 70:30): 0.21.

(*E*)-4-Bromo-*N*-methyl-2-(prop-1-en-1-yl)benzamide (4i).



The representative general procedure was followed using **1l**(100 mg), **2a**(2.0 equiv)and the reaction was done at 120°C for20 h.The desired product was isolated in 66 mg and yield is 56%. Colorless solid; eluent (0.3% methanol in DCM).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.59 (d, *J* = 4.0Hz, 1 H), 7.31 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.24 (d, *J* = 8.0 Hz, 1 H), 6.60 (dd, *J* = 16.0, 4.0 Hz, 1 H), 6.23-6.14 (m, 1 H), 5.83 (s, 1 H), 2.96(d, *J* = 4.0 Hz,3 H), 1.87 (dd, *J* = 8.0, 4.0Hz, 3 H).

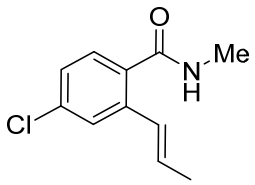
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4, 137.9, 133.5, 130.3, 129.6, 129.2, 128.9, 127.2, 124.3, 26.7, 18.7.

HRMS (ESI): calc. for [($C_{11}H_{12}BrNO$)H] (M+H) 254.0181, measured 254.0188.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3282, 2945, 2817, 1635, 1547, 1441, 1312, 1041, 935, 875, 661.

Rf (hexane/ethyl acetate = 70:30): 0.29.

(*E*)-4-Chloro-*N*-methyl-2-(prop-1-en-1-yl)benzamide (4j).



The representative general procedure was followed using **1m**(100 mg), **2a**(2.0 equiv)and the reaction was done at 120^{o}Cfor20 h.The desired product was isolated in 66 mg and yield is 54%. Colorless solid; eluent (0.3% methanol in DCM).

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.42 (d, *J* = 4.0Hz, 1 H), 7.29 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.14 (dt, *J* = 8.0, 4.0 Hz, 1 H), 6.60 (d, *J* = 16.0Hz, 1 H), 6.23-6.14 (m, 1 H), 5.89 (s, 1 H), 2.94(dd, *J* =8.0, 4.0 Hz,3 H), 1.87 (d, *J* = 4.0Hz, 3 H).

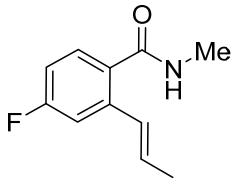
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4, 137.8, 135.9, 133.1, 130.2, 128.8, 127.3, 126.7,126.2, 26.7, 18.7.

HRMS (ESI): calc. for [($C_{11}H_{12}ClNO$)H] (M+H) 210.0686, measured 210.0691.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3078, 2931, 1634, 1589, 1463, 1259, 1041, 874, 747, 668.

Rf (hexane/ethyl acetate = 70:30): 0.30.

(*E*)-4-Fluoro-*N*-methyl-2-(prop-1-en-1-yl)benzamide (4q).



The representative general procedure was followed using **1n**(100 mg), **2a**(2.0 equiv)and the reaction was done at 120^{o}C for20 h.The desired product was isolated in 47 mg and yield is 42%. Colorless solid; eluent (0.3% methanol in DCM).

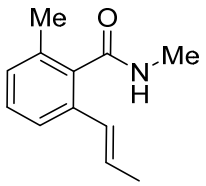
^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.38 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.14 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.88 (td, *J* = 8.0, 4.0 Hz, 1H), 6.67 (dt, *J* = 16.0, 4.0 Hz, 1H), 6.20 (dq, *J* = 12.0, 4.0 Hz, 1H), 5.78(s, 1H), 2.97 (d, *J* = 4.0Hz, 3H), 1.88(dd, *J* = 8.0, 4.0 Hz,3H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 169.5, 164.8, 162.3, 138.7 and 138.6(F-coupling), 130.9, 130.1, 129.6 and 129.5 (F-coupling), 127.5, 113.8 and 113.6 (F-coupling), 112.8 and 112.6 (F-coupling), 26.8, 18.7.

HRMS (ESI): calc. for [($C_{11}H_{12}FNO$)H] (M+H) 194.0981, measured 194.0988.

Rf(hexane/ethyl acetate = 70:30): 0.31.

(*E*)-*N*,2-Dimethyl-6-(prop-1-en-1-yl)benzamide (4l).



The representative general procedure was followed using **1o**(100 mg), **2a**(2.0 equiv)and the reaction was done at 100^{o}C for16 h.The desired product was isolated in 104 mg and yield is 83%. Colorless solid; eluent (0.3% methanol in DCM).

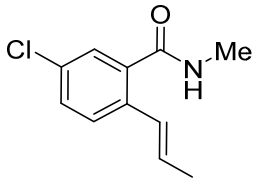
^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.27 (d, *J* = 8.0Hz, 1 H), 7.14 (t, *J* = 8.0 Hz, 1 H), 6.99 (d, *J* = 4.0 Hz, 1 H), 6.36 (d, *J* = 16.0,Hz, 1 H), 6.19-6.13 (m, 1 H), 5.75 (s, 1 H), 2.95 (d, *J* = 8.0 Hz,3 H), 2.25 (s, 3 H), 1.82 (dd, *J* = 8.0, 4.0Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 135.7, 134.7, 134.5, 128.7, 128.4, 128.2, 127.8, 122.5, 26.4, 19.1, 18.7.

HRMS (ESI): calc. for [($C_{12}H_{15}NO$)H] (M+H) 190.1232, measured 190.1236.

Rf (hexane/ethyl acetate = 70:30): 0.28.

(*E*)-5-Chloro-*N*-methyl-2-(prop-1-en-1-yl)benzamide (4m).



The representative general procedure was followed using **1m**(100 mg), **2a**(2.0 equiv)and the reaction was done at 120^{o}C for20 h.The desired product was isolated in 64 mg and yield is 51%. Colorless solid; eluent (0.3% methanol in DCM).

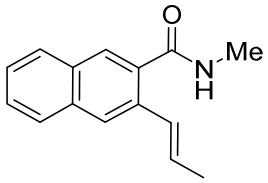
^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.39 (d, *J* = 8.0Hz, 1 H), 7.35 (d, *J* = 4.0 Hz, 1 H), 7.27 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.59 (d, *J* = 16.0Hz, 1 H), 6.21-6.12 (m, 1 H), 5.86 (s, 1 H), 2.96 (d, *J* = 8.0 Hz,3 H), 1.86 (dd, *J* = 8.0, 4.0Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.9, 136.0, 134.4, 132.4, 130.0, 129.5, 127.6, 127.4, 127.3, 26.7, 18.7.

HRMS (ESI): calc. for [($C_{11}H_{12}ClNO$)H] (M+H) 210.0686, measured 210.0685.

Rf (hexane/ethyl acetate = 70:30): 0.21.

(*E*)-*N*-Methyl-3-(prop-1-en-1-yl)-2-naphthamide (4n).



The representative general procedure was followed using **1i**(100 mg), **2a**(2.0 equiv)and the reaction was done at 100^{o}C for16 h.The desired product was isolated in 93 mg and yield is 77%. Colorless solid; eluent (0.3% methanol in DCM).

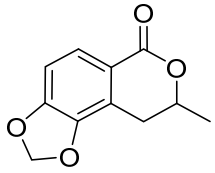
^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.88 (s, 1 H), 7.86 (s, 1 H), 7.76 (t, *J* = 8.0 Hz,2 H), 7.47 (t, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 8.0 Hz, 1 H), 6.76 (d, *J* = 16.0Hz, 1 H), 6.31-6.22 (m, 1 H), 5.99 (s, 1 H), 3.01 (d, *J* = 8.0 Hz,3 H), 1.91 (dd, *J* = 8.0, 4.0Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ170.3, 133.9, 133.5, 133.5, 131.6, 128.8, 128.6, 127.9, 127.6, 127.3, 127.2, 126.1, 125.2, 26.8, 18.8.

HRMS (ESI): calc. for [($C_{15}H_{15}NO$)H] (M+H) 226.1232, measured 226.1236.

Rf (hexane/ethyl acetate = 98:2): 0.63.

8-Methyl-8,9-dihydro-6*H*-[1,3]dioxolo[4,5-*f*]isochromen-6-one (5a).



The representative general procedure was followed using **3a**(50 mg)and the reaction was done at 110^{o}C for12 h.The desired product was isolated in 25 mg and yield is 64%. Colorless solid; eluent (11% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ7.45 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.12 (d, *J*= 4.0 Hz, 1H), 6.09 (d, *J* = 4.0 Hz, 1H), 5.42 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.16 – 2.08 (m, 1H), 1.88 – 1.78 (m, 1H), 0.99 (t, *J* = 8.0 Hz, 3H).

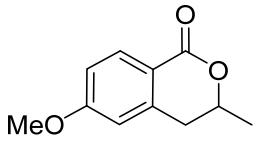
^{13}C NMR ($CDCl_3$, 100 MHz): δ165.1, 151.6, 143.8, 126.3, 119.8, 118.8, 107.6, 102.3, 74.6, 28.6, 20.9.

HRMS (ESI): calc. for [($C_{11}H_{10}O_4$)H] (M+H) 207.0657, measured 207.0659.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2927, 2854, 1707, 1589, 1232, 1116, 1041, 908, 845, 664.

Rf (hexane/ethyl acetate = 80:20): 0.38.

6-Methoxy-3-methylisochroman-1-one (5b).



The representative general procedure was followed using **3b**(50 mg)and the reaction was done at 110^{o}C for12 h.The desired product was isolated in 27 mg and yield is 61%. Colorless solid; eluent (10% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, *J* = 8.0 Hz, 1H), 6.86 (dd, *J* = 8.0, 4.0 Hz, 1H),6.67 (d, *J* = 4.0 Hz, 1H), 4.67 – 4.59 (m, 1H), 3.84 (s, 3H), 2.92 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1H),1.48 (d, *J* = 8.0 Hz, 3H).

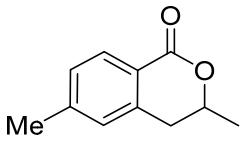
^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.5, 163.7, 141.4, 132.6, 117.5, 113.4, 112.1, 74.7, 55.5, 35.2, 20.9.

HRMS (ESI): calc. for [($C_{11}H_{12}O_3$)H] (M+H) 193.0865, measured 193.0874.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2980, 2935, 1713, 1607, 1458, 1117, 1041, 908, 741, 691.

Rf (hexane/ethyl acetate = 80:20): 0.48.

3,6-Dimethylisochroman-1-one (5c).



The representative general procedure was followed using **3c**(50 mg)and the reaction was done at 110^{o}C for12 h.The desired product was isolated in 24 mg and yield is 62%. Colorless solid; eluent (10% ethylacetate in hexanes).

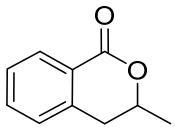
^{1}H NMR ($CDCl_3$, 400 MHz): δ7.95 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 4.67 -4.58 (m, 1 H), 2.90 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.83 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.37 (s, 3H), 1.48 (d, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.8, 144.6, 139.1, 130.3, 128.5, 127.8, 122.3, 74.9, 34.9, 21.7, 20.9.

HRMS (ESI): calc. for [($C_{11}H_{12}O_2$)H] (M+H) 177.0916, measured 177.0923.

Rf (hexane/ethyl acetate = 80:20): 0.43.

3-Methylisochroman-1-one (5d).



The representative general procedure was followed using **3d**(50 mg)and the reaction was done at 110^{o}Cfor12 h.The desired product was isolated in 22 mg and yield is 58%. Colorless solid; eluent (10% ethylacetate in hexanes).

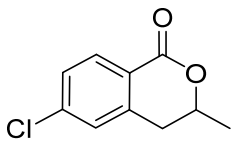
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.51 (td, *J* = 8.0, 4.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 4.69 -4.64(m, 1 H), 2.96 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.90 (dd, *J* = 16.0, 4.0 Hz, 1H),1.50 (d, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ165.6, 139.1, 133.6, 130.2, 127.6, 127.2, 124.9, 75.1, 34.9, 20.9.

HRMS (ESI): calc. for [($C_{10}H_{10}O_2$)H] (M+H) 163.0759, measured 163.0770.

Rf (hexane/ethyl acetate = 80:20): 0.43.

6-Chloro-3-methylisochroman-1-one (5e).



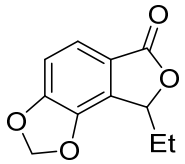
The representative general procedure was followed using **3fa** (50 mg) and the reaction was done at 110^{o}C for12 h.The desired product was isolated in 20 mg and yield is 51%. Colorless solid; eluent (10% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.22 (d, *J* = 4.0 Hz, 1H), 4.69 -4.61 (m, 1 H), 2.94 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.87 (dd, *J* = 16.0, 4.0 Hz, 1H),), 1.49 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.7, 140.7, 139.9, 131.8, 128.1, 127.4, 123.4, 74.9, 34.6, 20.8.

Rf (hexane/ethyl acetate = 98:2): 0.63.

8-Ethyl-[1,3]dioxolo[4,5-*e*]isobenzofuran-6(8*H*)-one (6a).



The representative general procedure was followed using **4a**(50 mg)and the reaction was done at 120^{o}Cfor12 h.The desired product was isolated in 25 mg and yield is 61%. Colorless solid; eluent (10% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.12 (d, *J* = 4.0 Hz, 1H), 6.09 (d, *J* = 4.0 Hz, 1H), 5.42 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.16 -2.08(m, 1 H), 1.83 (dq, *J* = 12.0, 4.0 Hz, 1H), 0.99 (t, *J* = 8.0 Hz, 3H).

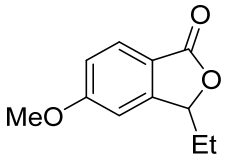
^{13}C NMR ($CDCl_3$, 100 MHz): δ169.7, 152.4, 141.1, 129.2, 121.3, 120.8, 109.9, 102.6, 79.6, 26.7, 8.8.

HRMS (ESI): calc. for [($C_{11}H_{10}O_4$)H] (M+H) 207.0657, measured 207.0666.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2931, 2817, 1727, 1637, 1435, 1312, 1041, 908, 875, 661.

Rf (hexane/ethyl acetate = 80:20): 0.33.

3-Ethyl-5-methoxyisobenzofuran-1(3*H*)-one (6b).



The representative general procedure was followed using **4b**(50 mg)andthe reaction was done at 120^{o}Cfor12 h.The desired product was isolated in 22 mg and yield is 56%. Colorless solid; eluent (12% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ7.78 (d, *J* = 8.0 Hz, 1H), 7.00(dd, *J* = 8.0, 4.0 Hz, 1H), 6.82(d, *J* = 8.0 Hz, 1H), 5.35 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.88 (s, 3H), 2.15 – 2.04 (m, 1H),1.84 – 1.73 (m, 1H), 0.98 (t, *J* = 8.0 Hz, 3H).

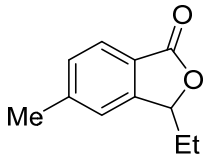
^{13}C NMR ($CDCl_3$, 100 MHz): δ170.4, 164.6, 152.5, 127.2, 118.7, 116.1, 105.8, 81.5, 55.8, 27.6, 8.7.

HRMS (ESI): calc. for [($C_{11}H_{12}O_3$)H] (M+H) 193.0865, measured 193.0874.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2972, 2933, 1702, 1604, 1495, 1255, 1083, 1019, 689.

Rf (hexane/ethyl acetate = 80:20): 0.31.

3-Ethyl-5-methylisobenzofuran-1(3*H*)-one (6c).



The representative general procedure was followed using **4c**(50 mg)andthe reaction was done at 120^{o}Cfor12 h.The desired product was isolated in 19 mg and yield is 51%. Colorless solid; eluent (12% ethylacetate in hexanes).

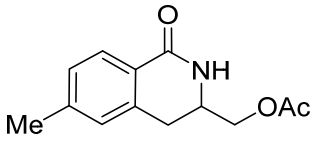
^{1}H NMR ($CDCl_3$, 400 MHz): δ7.74 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.21 – 7.17 (m, 1H), 5.36 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.46 (s, 3H), 2.13 – 2.02 (m, 1H),1.81 – 1.74 (m, 1H), 0.96 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ170.7, 150.3, 145.1, 130.2, 125.4, 123.7, 122.0, 82.0, 27.7, 22.1, 8.8.

HRMS (ESI): calc. for [($C_{11}H_{12}O_2$)H] (M+H) 177.0916, measured 177.0923.

Rf (hexane/ethyl acetate = 80:20): 0.30.

(6-Methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl acetate (11a).



The representative general procedure was followed using **10a**(100 mg), **2a** (2.5 equiv)andthe reaction was done at rt for 36 h.The desired product was isolated in 58 mg and yield is 41%. Colorless solid; eluent (32% ethylacetate in hexanes).

^{1}H NMR (DMSO d_6, 400 MHz): δ7.96 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.10 (s, 1H), 4.08 (dd, J= 12.0, 4.0 Hz, 1H), 3.92 (dd, J= 12.0, 4.0 Hz, 1H), 3.82 – 3.78 (m, 1H), 3.02 (dd, J = 16.0, 4.0 Hz, 1H), 2.81 (dd, J = 16.0, 8.0 Hz, 1H), 2.33 (s, 3H), 1.97 (s, 3H).

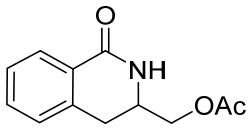
^{13}C NMR (DMSO d_6, 100 MHz): δ170.3, 164.3, 142.0, 137.2, 128.3, 127.5, 127.0, 126.1, 65.1, 48.7, 29.5, 21.1, 20.6.

HRMS (ESI): calc. for [($C_{13}H_{15}NO_3$)H] (M+H) 234.1130, measured 234.1141.

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3300 (broad), 2926, 2315, 1649, 1615, 1454, 1337, 1080, 657.

Rf (hexane/ethyl acetate = 60:40): 0.23.

(1-Oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl acetate (11b).



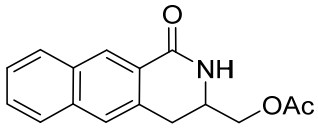
The representative general procedure was followed using **10b**(100 mg), **2a** (2.5 equiv)and the reaction was done at rt for 36 h.The desired product was isolated in 55 mg and yield is 38%. Colorless solid; eluent (32% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 6.42 (s, 1H), 4.24 (dd, J = 12.0, 4.0 Hz, 1H), 4.05 (dd, J = 12.0, 8.0 Hz, 1H), 4.02 – 3.91 (m, 1H), 3.02 (dd, J = 16.0, 4.0 Hz, 1H), 2.89 (dd, J = 16.0, 8.0 Hz, 1H), 2.06 (s, 3H).

IR (ATR)$\tilde{\nu}$ (cm^{-1}): 2931, 2817, 1727, 1637, 1435, 1312, 1041, 908, 875, 661.

Rf (hexane/ethyl acetate = 60:40): 0.24.

(1-Oxo-1,2,3,4-tetrahydrobenzo[g]isoquinolin-3-yl)methyl acetate (11c).



The representative general procedure was followed using **10c**(100 mg), **2a** (2.5 equiv)and the reaction was done at rt for 36 h.The desired product was isolated in 63 mg and yield is 47%. Colorless solid; eluent (32% ethylacetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ8.62 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.53 (d, *J* = 8.20 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 6.47 (s, 1H), 4.27 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.07 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.02 – 3.98 (m, 1H), 3.20 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.04 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.06 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ170.7, 166.3, 135.4, 132.3, 132.1, 129.6, 129.4, 128.7, 128.5, 127.1, 126.3, 126.2, 65.9, 50.2, 30.6, 20.7.

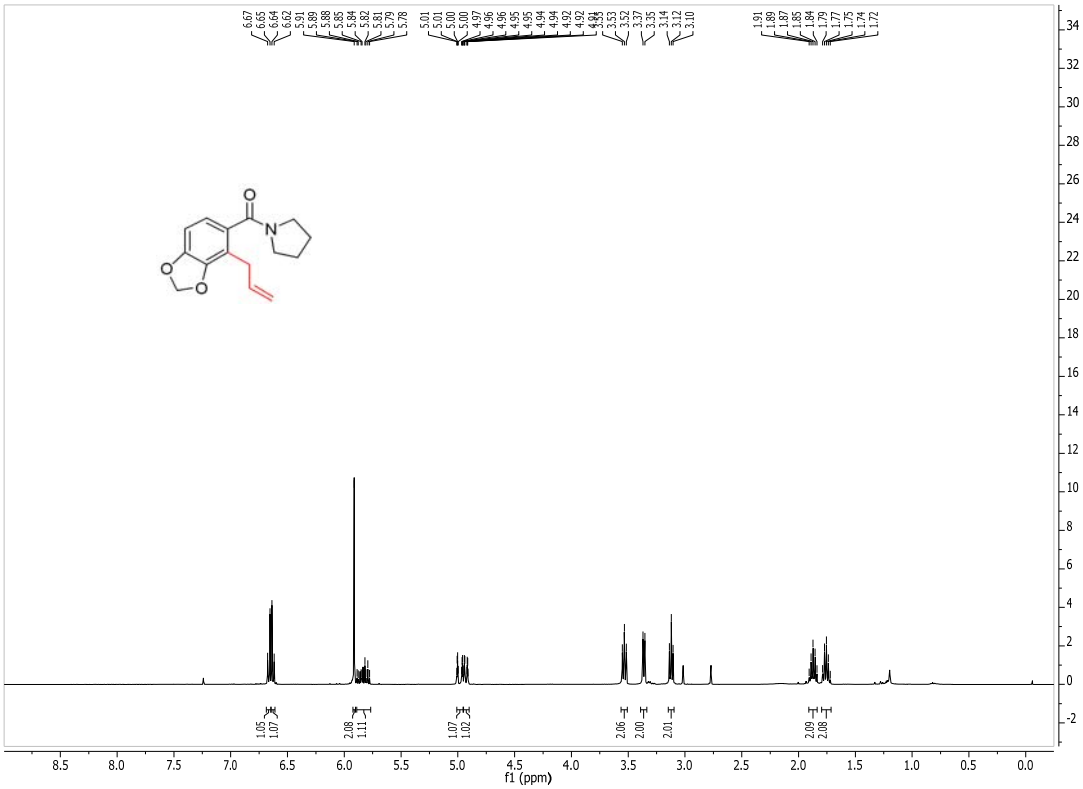
HRMS (ESI): calc. for [($C_{16}H_{16}NO_3$)H] (M+H) 270.1130, measured 270.1140.

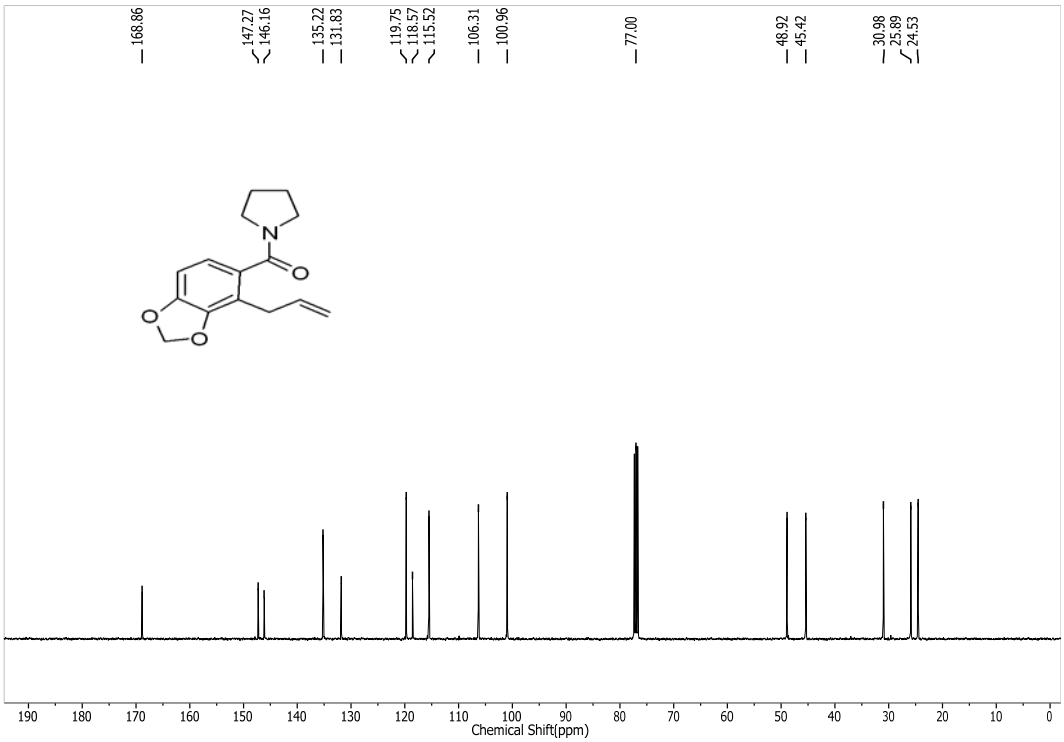
IR (ATR)$\tilde{\nu}$ (cm^{-1}): 3267 (broad), 1734, 1727, 1656, 1413, 1229, 1042, 730.

Rf (hexane/ethyl acetate = 60:40): 0.28.

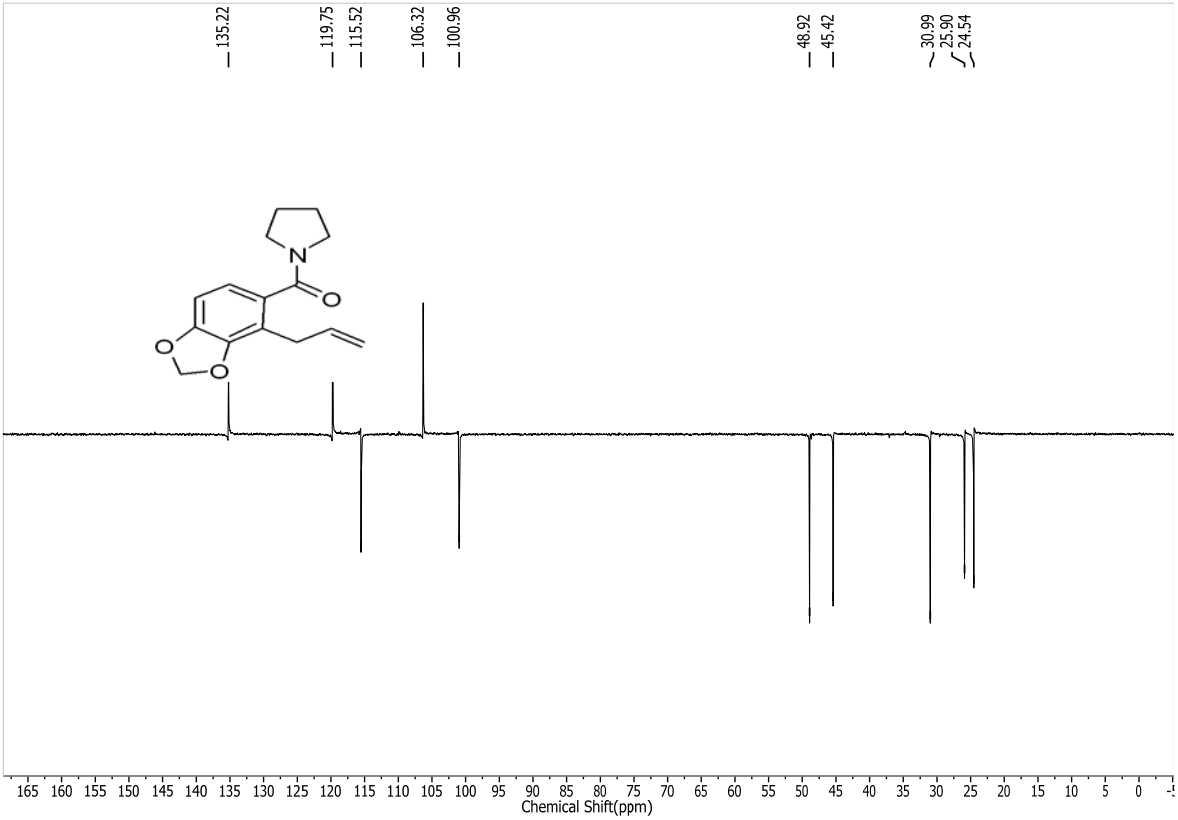
3B.15: SpectralCopies of Selected Compounds

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

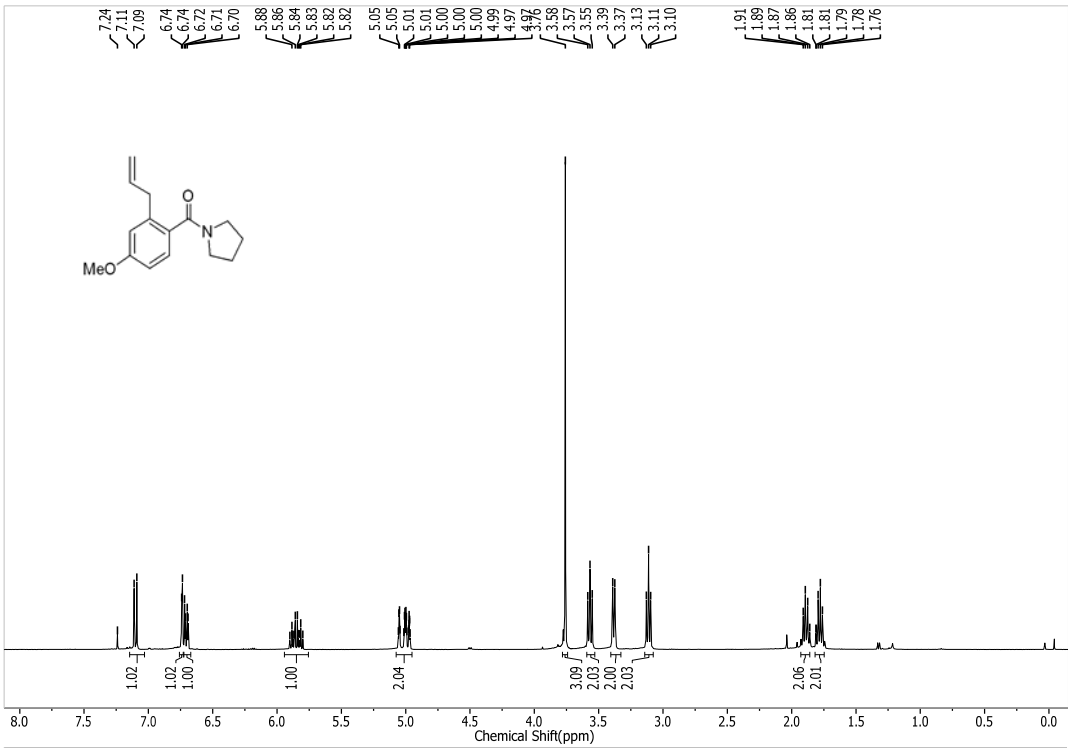


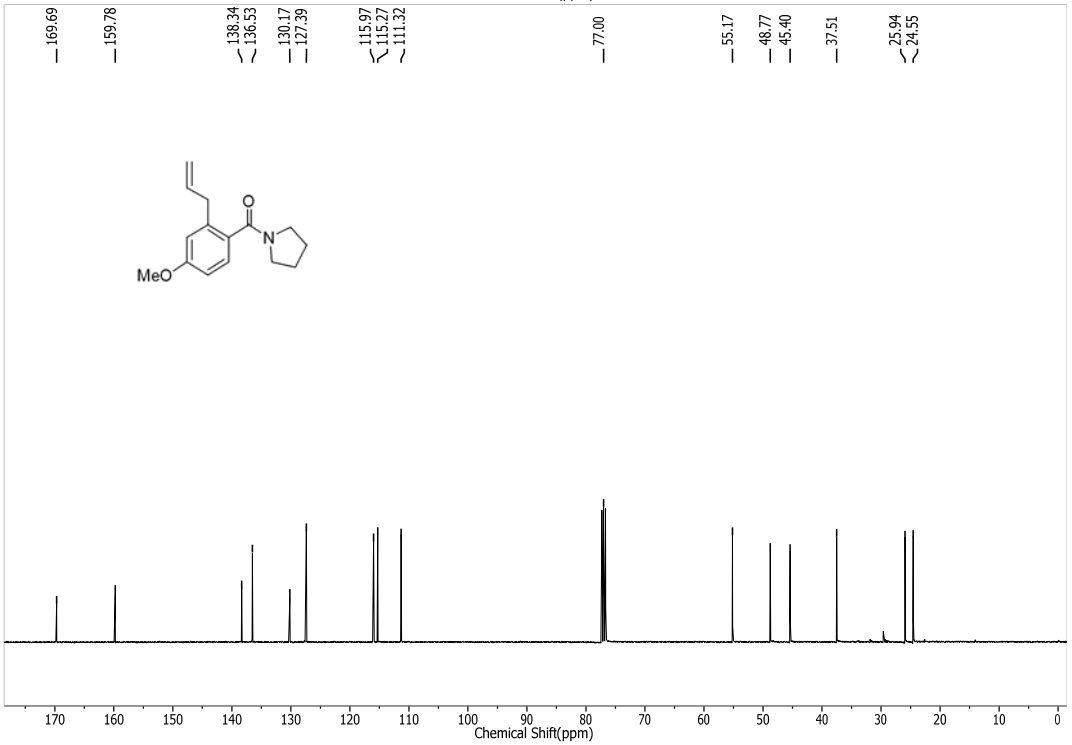


DEPT (135) NMR Spectrum of Compound **3a.**

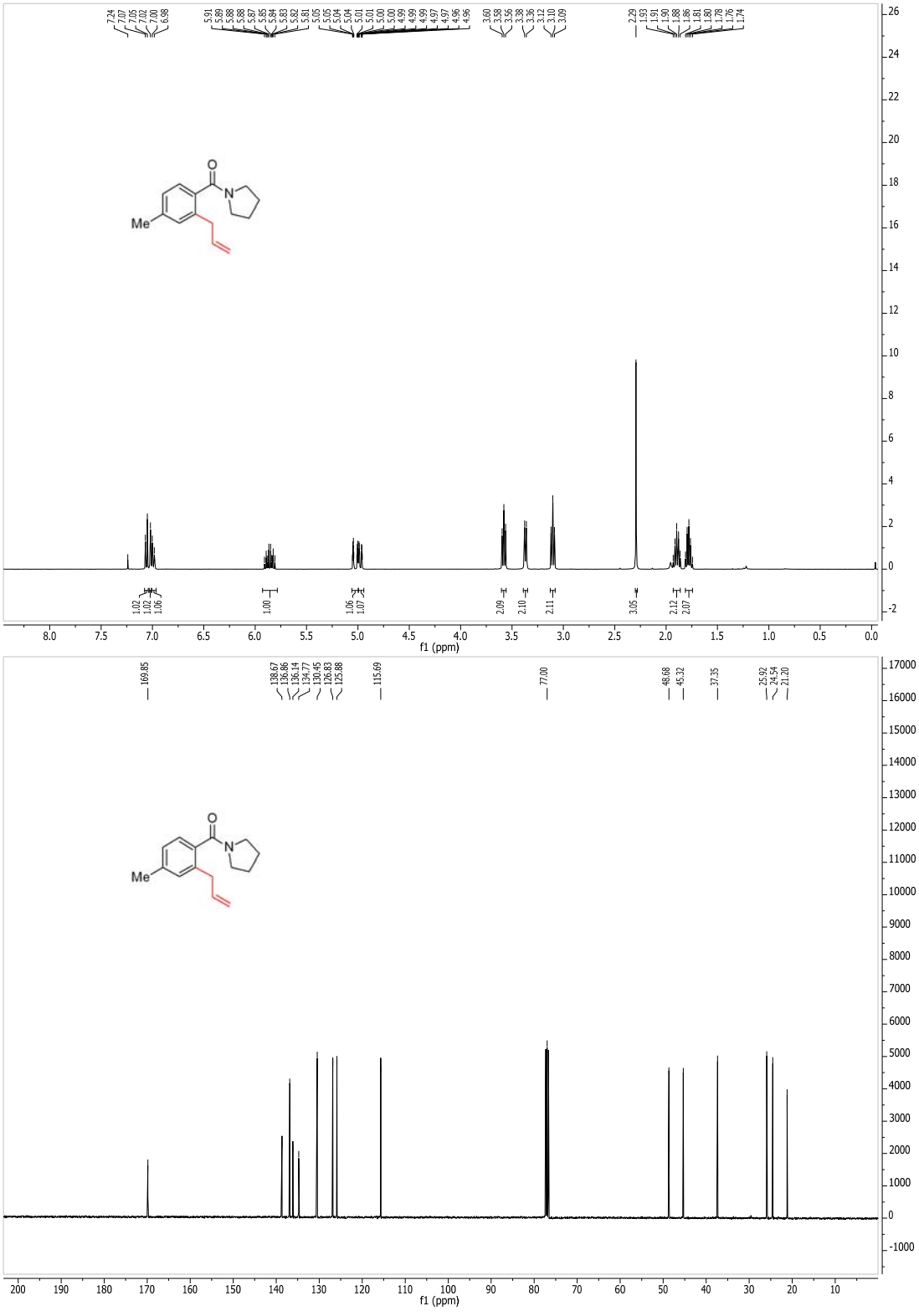


^{1}H and ^{13}C NMR Spectra of Compound **3b.**

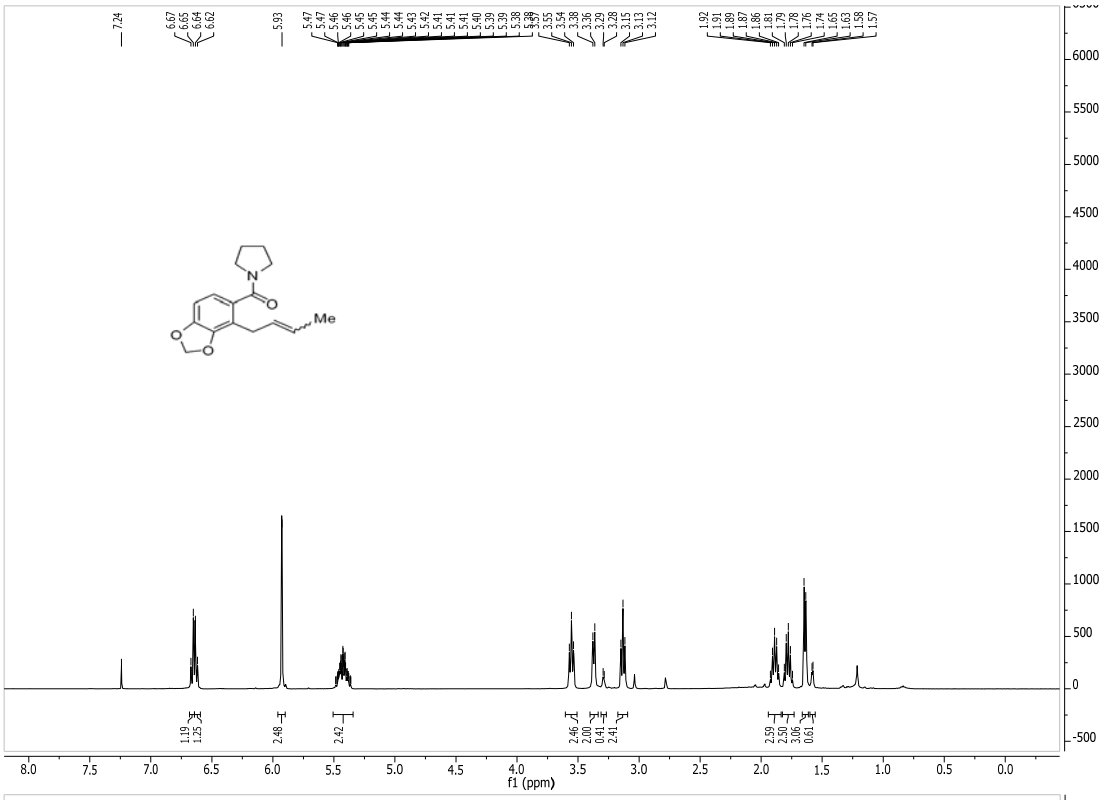


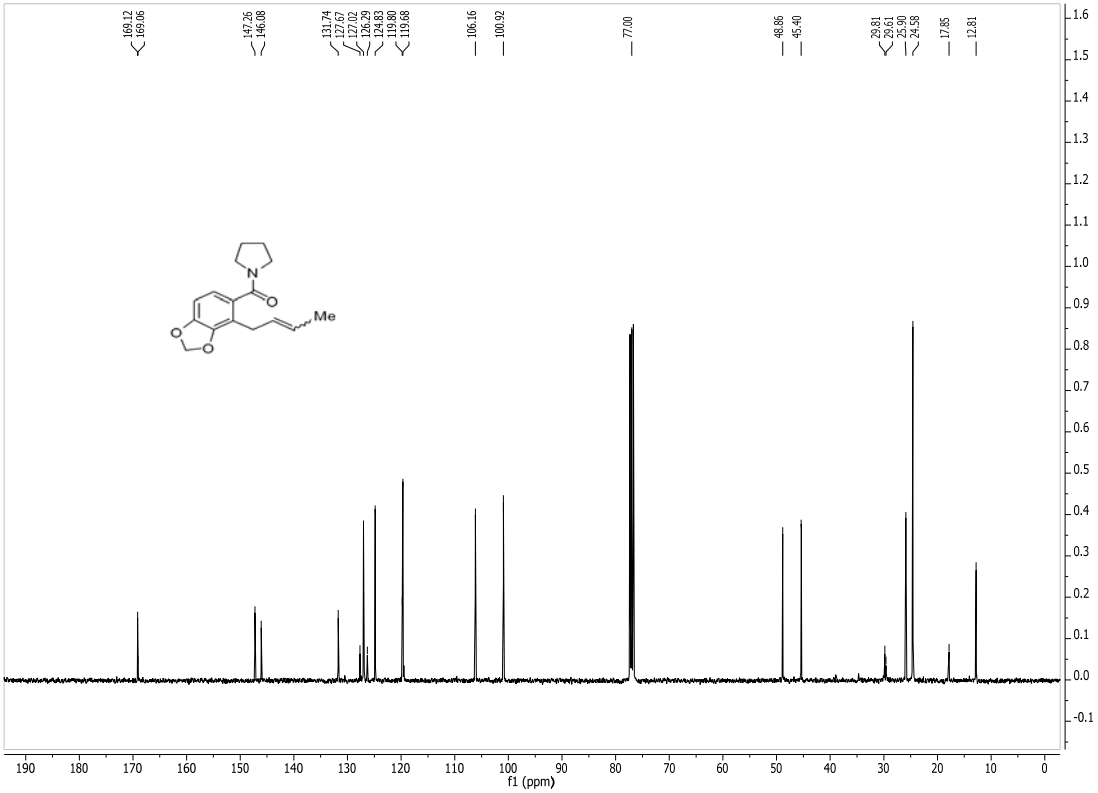


^{1}H and ^{13}C NMR Spectra of Compound **3c.**

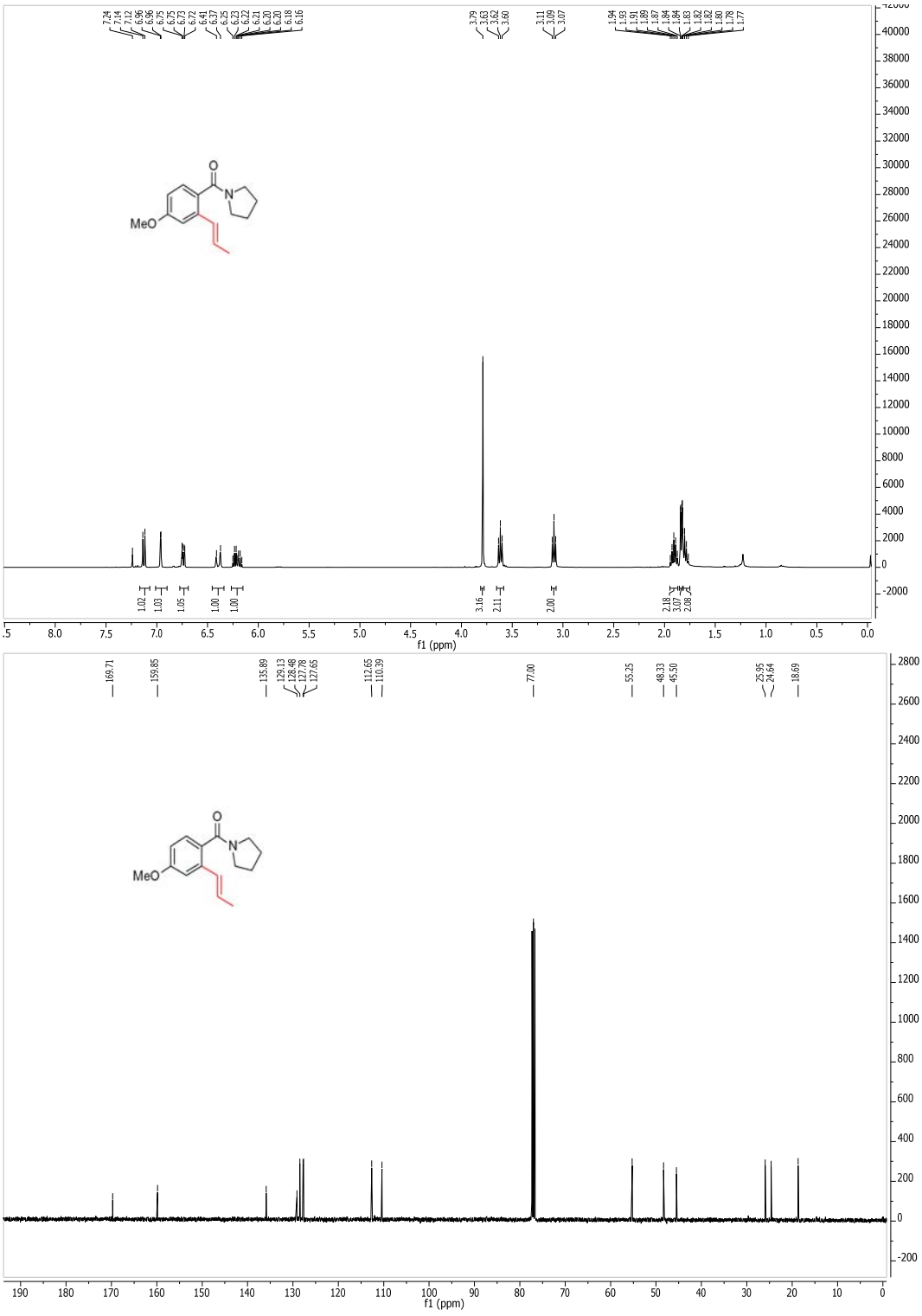


^{1}H and ^{13}C NMR Spectra of Compound **3j.**

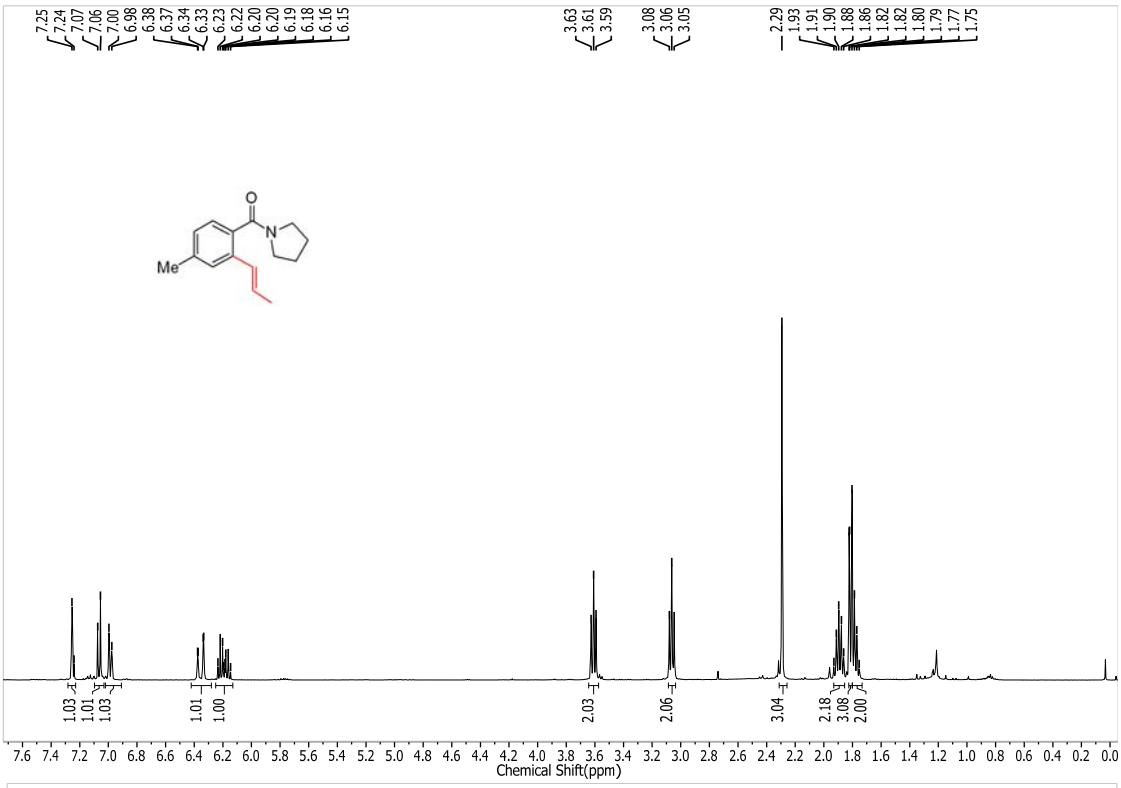


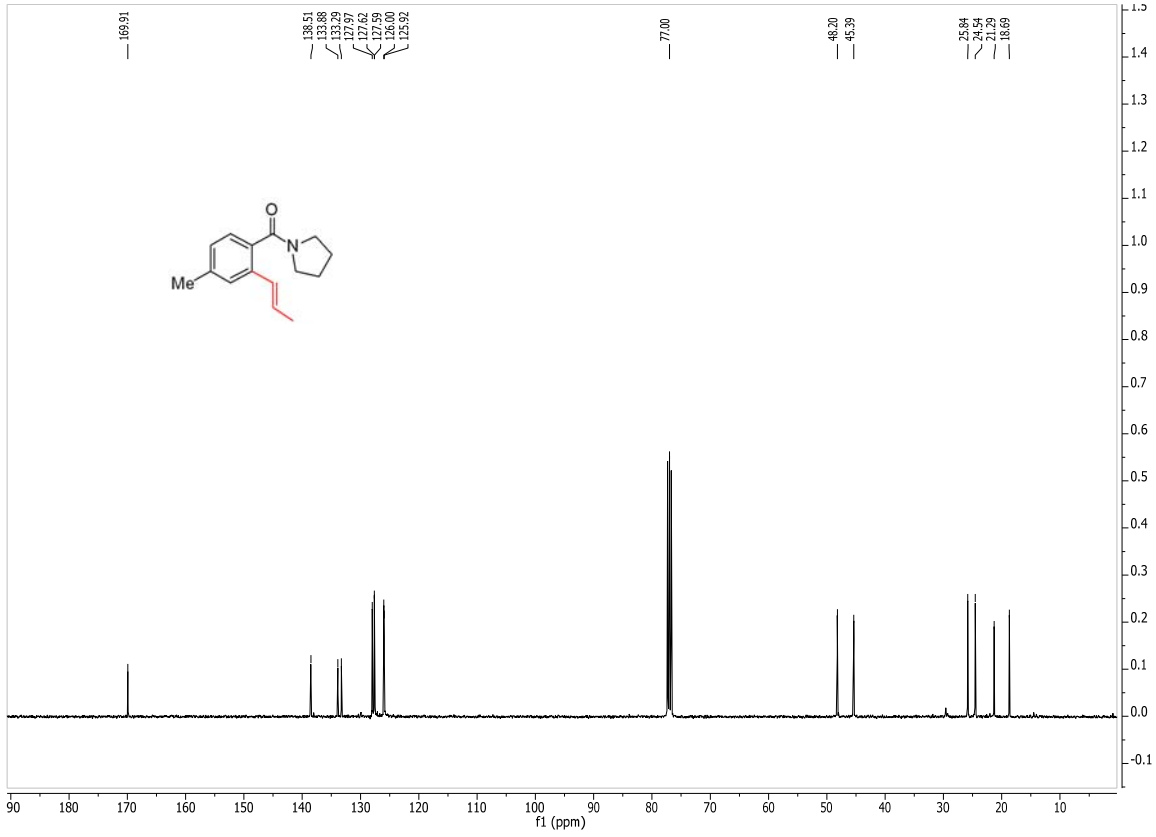


^{1}H and ^{13}C NMR Spectra of Compound **4b.**

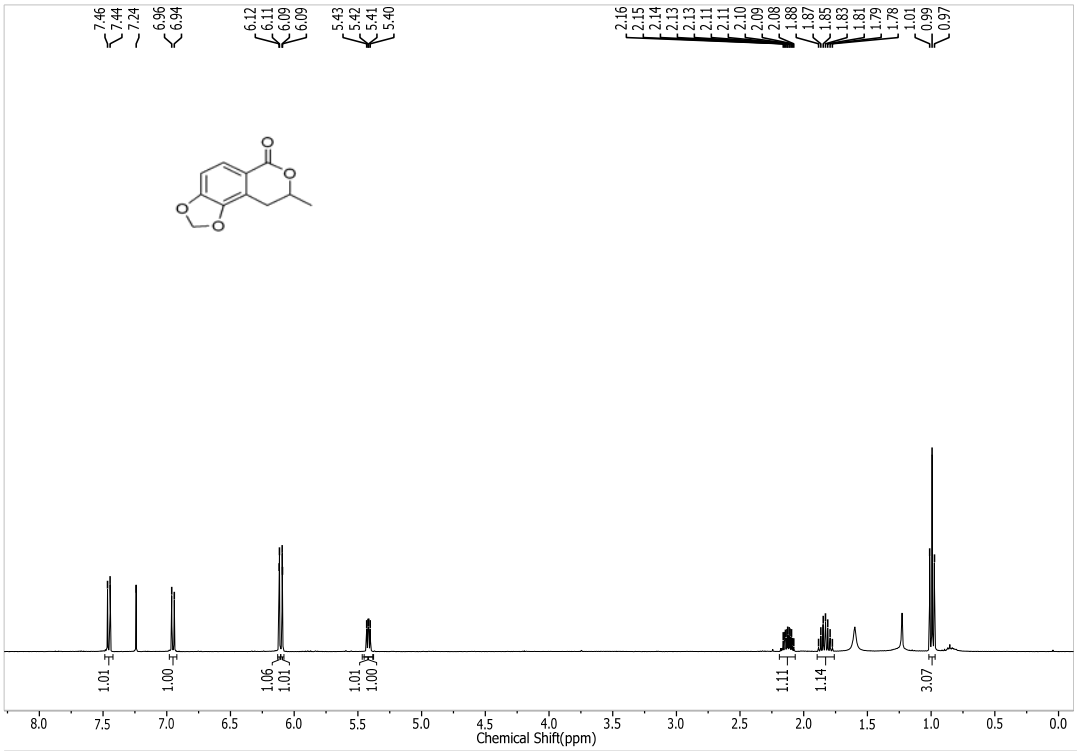


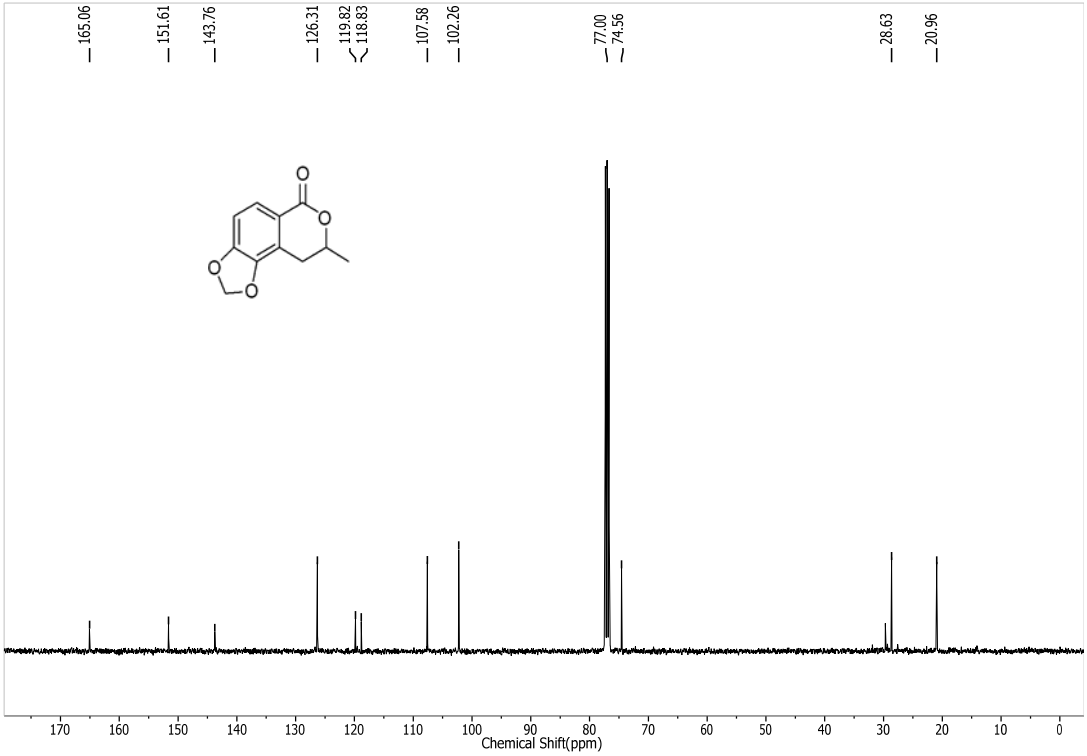
^{1}H and ^{13}C NMR Spectra of Compound **4c.**



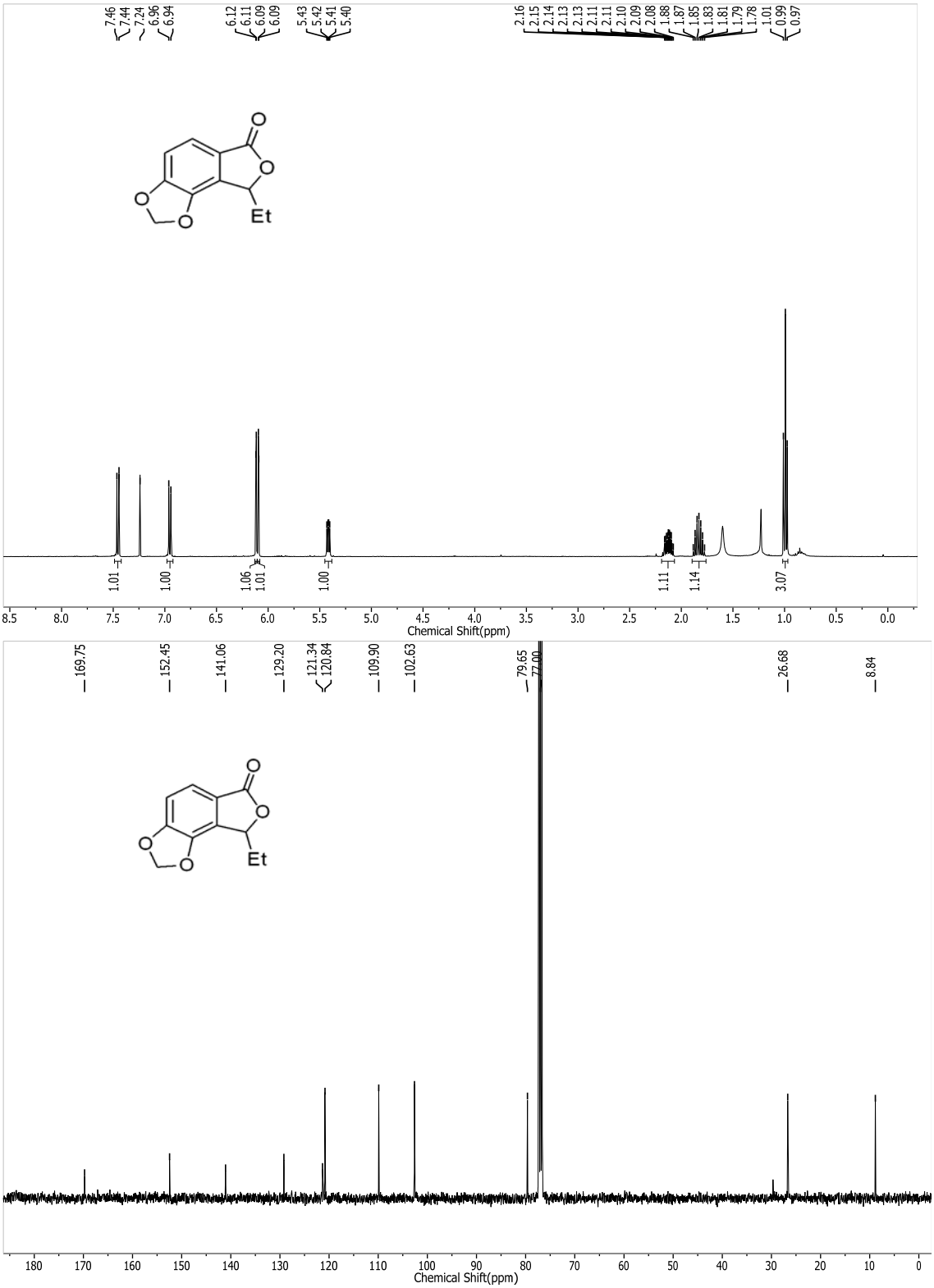


^{1}H and ^{13}C NMR Spectra of Compound **5a.**

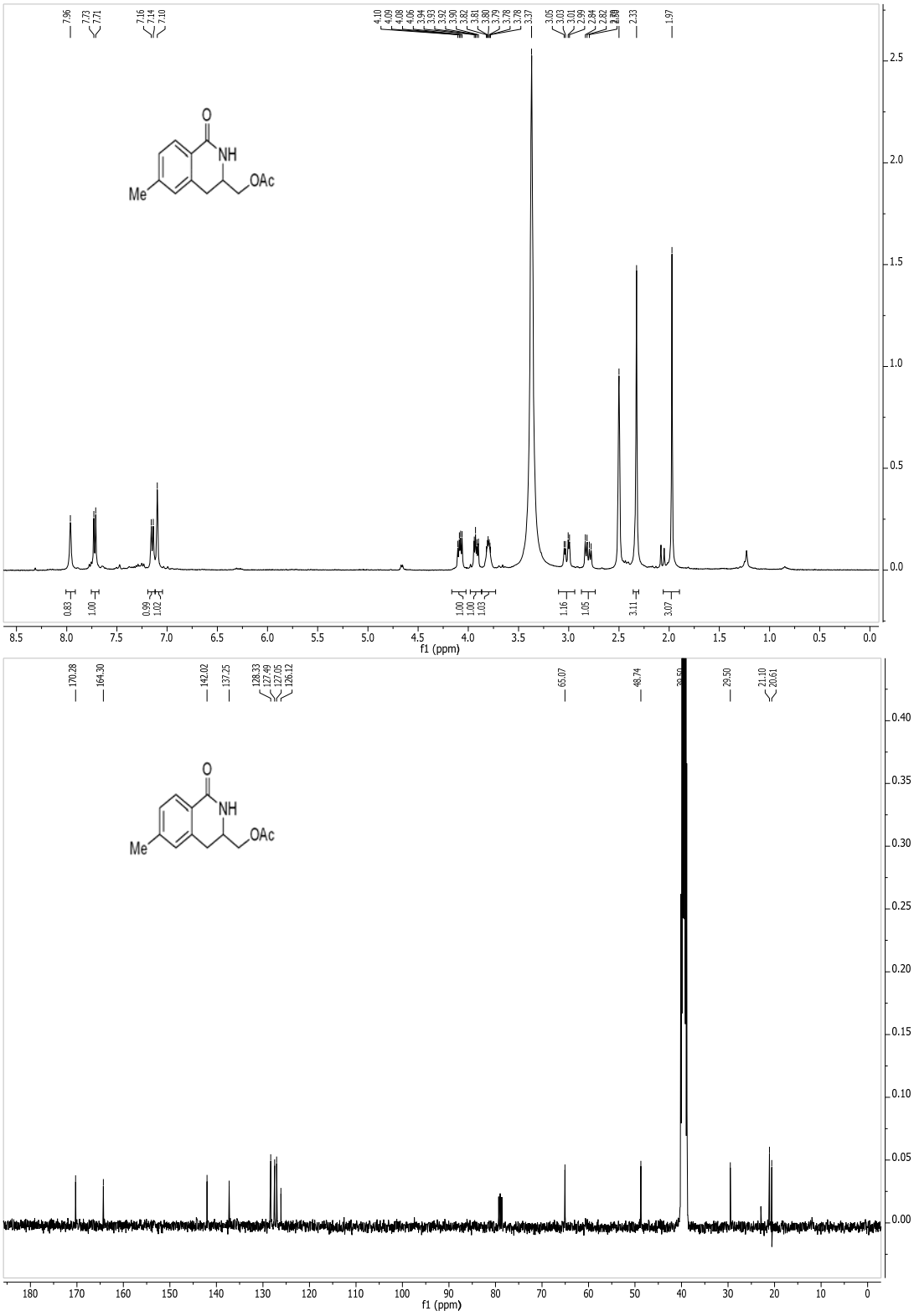




^{1}H and ^{13}C NMR Spectra of Compound **6a.**



^{1}H and ^{13}C NMR Spectra of Compound **11a.**



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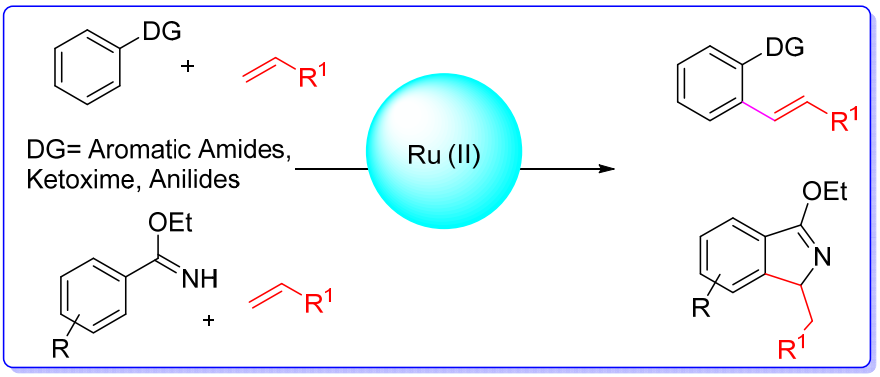
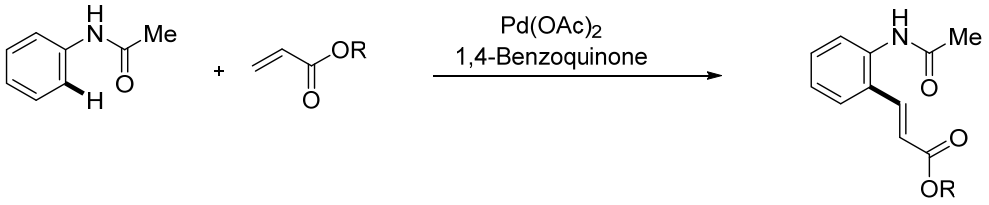


Ruthenium-Catalyzed Oxidant free *Ortho*-Alkenylation of Substituted Aromatics with Alkenes at Room Temperature with Hydrogen Evolution

Section 4A: Ruthenium-Catalyzed *ortho* Alkenylation of Aromatics with Alkenes at Room Temperature with Hydrogen Evolution

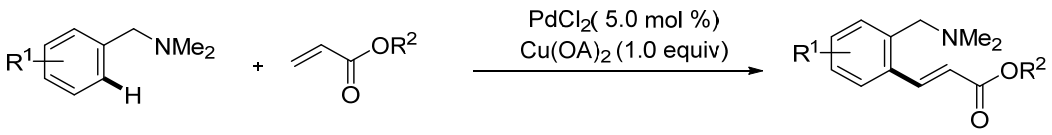
4A.1 Introduction

The transition metal-catalyzed chelation assisted *ortho* alkenylation of substituted aromatics with alkenes via C–H bond activation is one of the powerful methods to synthesize substituted alkenes in a highly regio- and stereoselective manner. Initially, palladium complexes are widely used as catalysts in this type of alkenylation reaction. In 2002, van Leeuwen's group has reported the palladium-catalyzed *ortho* alkenylation of substituted anilide with alkenes. Here, benzoquinone was used as an oxidant to regenerate the active Pd(II) catalyst (Scheme 4A.1).[4b]



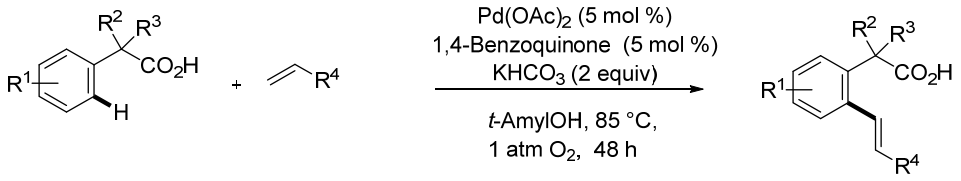
Scheme 4A.1: Palladium-catalyzed *ortho* olefination of substituted anilides with alkenes

Next, Zhang Shi's group has developed o*rtho* olefination of substituted *N*, *N*-dimethyl benzylamines with alkenes in the presence of palladium chloride. In this reaction, various substituted *N*, *N*-dimethyl benzylamines reacted with acrylates in presence of the $PdCl_2$ catalyst and $Cu(OAc)_2$ oxidant to give the corresponding alkenylated products in good yields (Scheme 4A.2).[4c]



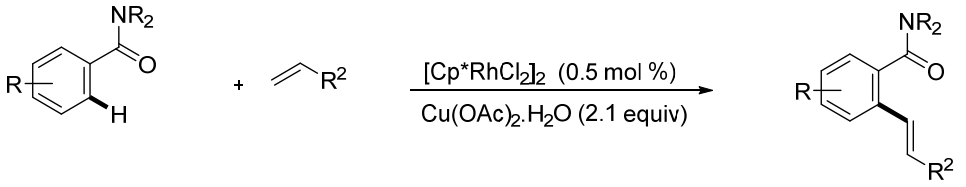
Scheme 4A.2: Palladium-catalyzed *ortho* olefination of *N*,*N*-dimethyl benzylamines with alkenes

Later, Yu's group showed a Pd(II)-catalyzed C–H alkenylation of substituted phenylacetic acid with alkenes by using a catalytic amount of benzoquinone as the terminal oxidant and $KHCO_3$ as a base (Scheme 4A.3).[4d]



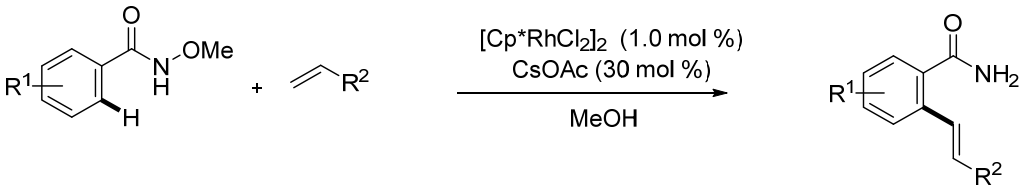
Scheme 4A.3: Palladium-catalyzed *ortho* olefination of substituted phenylacetic acid with alkenes

Eventually, the same type of alkenylation reaction has been successfully extended with the rhodium catalyst. In 2011, Glorius's group has demonstrated a rhodium (III)-catalyzed oxidative alkenylation of substituted benzamides with alkenes in the presence of a stoichiometric amount of $Cu(OAc)_2$ as an oxidant (Scheme 4A.4).[5a]



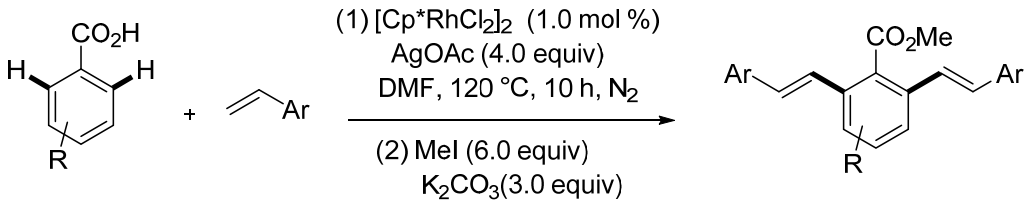
Scheme 4A.4: Rhodium-catalyzed *ortho* olefination of substituted benzamides with alkenes

Next, the same group has explored external oxidant-free Rh(III)-catalyzed C–H olefination reaction of *N*-methoxy benzamides with alkenes. In this reaction, N-O bond present in the *N*-methoxy benzamide itself acts as an internal oxidant thus external oxidant was not required for regeneration of the active catalyst (Scheme 4A.5).[5b]



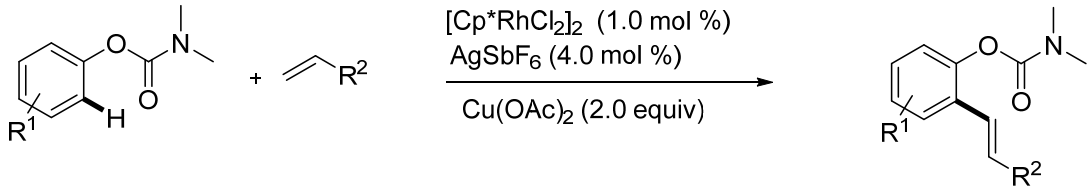
Scheme 4A.5: Rhodium-catalyzed external oxidant-free *ortho* olefination of substituted benzamides with alkenes

Later, Miura's group showed one pot synthesize of *ortho* alkenylated aromatic esters by the reaction of aromatic carboxylic acids with alkenes in the presence of Rh(III) catalyst.(Scheme 4A.6).[5c]



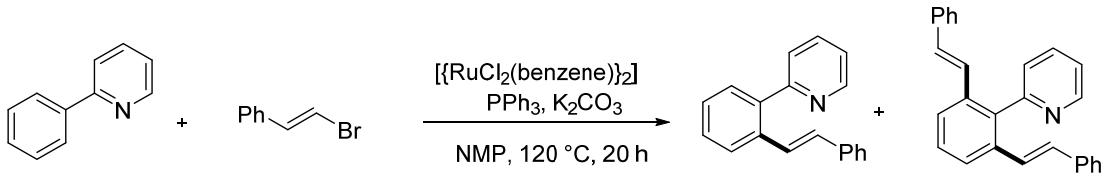
Scheme 4A.6: Rhodium-catalyzed *ortho* olefination of aromatic acid with alkenes

In 2011, Liu and Loh's groups independently reported *in-situ* generated cationic rhodium-catalyzed selective C–H alkenylation of phenol carbamates with alkenes (Scheme 4A.7).[5d-e]



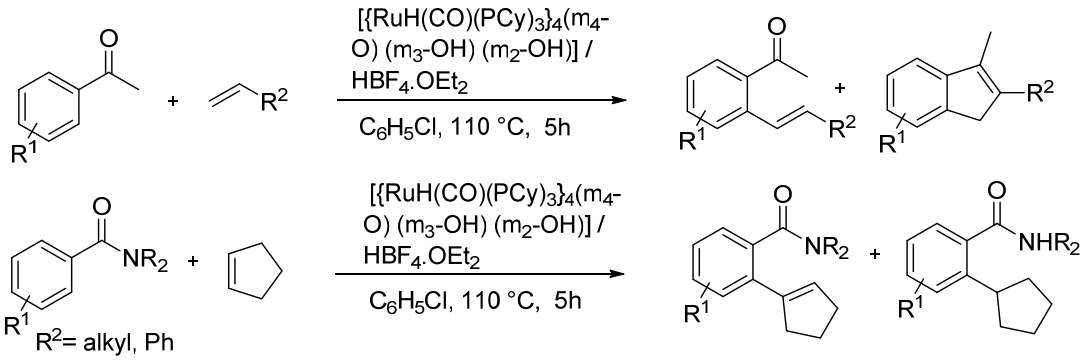
Scheme 4A.7: Rhodium-catalyzed *ortho* olefination of phenol carbamates with alkenes

Recently, a less expensive and easily affordable ruthenium catalyst has gained much attention in this reaction. In 2001, Oi and Inoue have reported the successive usage of ruthenium (II) complexes in *ortho* alkenylation reaction. In this reaction, 2-Aryl pyridines reacted with vinyl halides gives *ortho* alkenylated 2-Aryl pyridines in the presence of [{$RuCl_2$(benzene)}$_2$] catalyst (Scheme 4A.8).[5a]



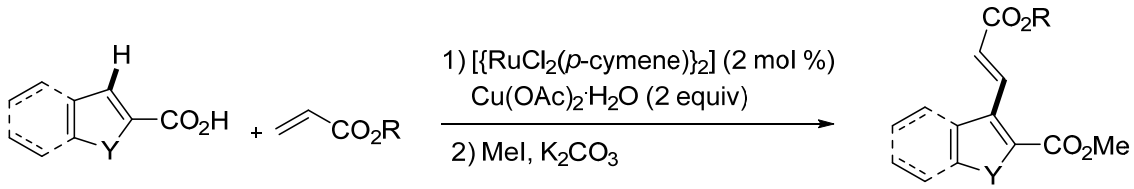
Scheme 4A.8: Ruthenium-catalyzed *ortho* olefination of 2-Aryl pyridine with alkenes

The ruthenium-hydride catalyzed *ortho* alkenylation of aromatic ketone was reported by Yi's group. In this reaction, along with alkenylated product minor amount of cyclic indene also observed as a side product (Scheme 4A.9).[5b]Later, the similar type of reaction was extended to aromatic amides with alkenes including cyclic alkenes.[5c]



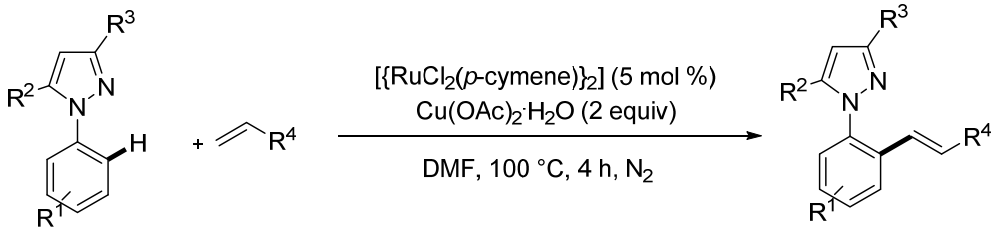
Scheme 4A.9: Ruthenium-hydride catalyzed *ortho* olefination of substituted aromatics with alkenes

In 2011, Satoh and Miura have disclosed a less expensive ruthenium-catalyzed C–H alkenylation of heteroaromatic acids with alkenes in the presence of a stoichiometric amount of $Cu(OAc)_2$ oxidant (Scheme 4A.10).[5d]



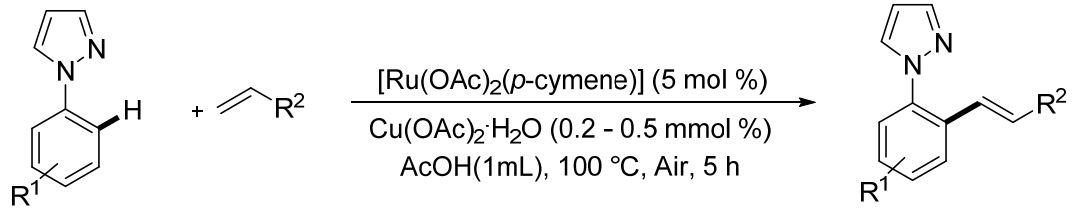
Scheme 4A.10: Ruthenium-catalyzed *ortho* olefination of heteroaromatic acids with alkenes

Next, the same group has extended the alkenylation of arylpyrazoles in the presence of $[RuCl_2(p\text{-cymene})]_2$ catalyst with alkenes and 2 equiv of $Cu(OAc)_2 \cdot H_2O$ in DMF under the nitrogen atmosphere (Scheme 4A.11).[5e] Generally, for this type of alkenylation reaction, Ru(II) is a active catalyst which converts into Ru (0) after the alkenylation reaction. To regenerate the active catalyst, the stoichiometric amount of oxidant mostly $Cu(OAc)_2$ was used.



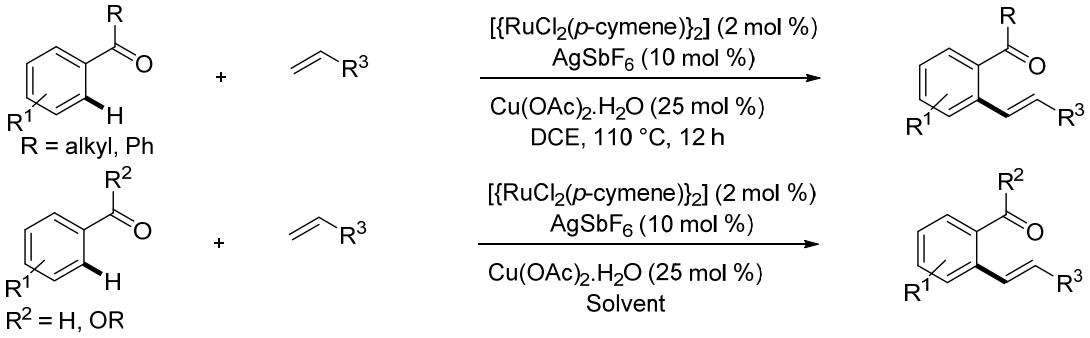
Scheme 4A.11: Ruthenium-catalyzed *ortho* olefination of arylpyrazoles with alkenes using stoichiometric amount of oxidant

Later, with the contribution of Bruneau, Dixneuf, and Jeganmohan, the oxidant amount has been reduced and only catalytic amount of copper acetate was used. Dixneuf and Bruneau have reported the oxidative alkenylation of a nitrogen-containing heterocycle such as *N*-arylpyrazoles with alkenes in the presence of $Ru(OAc)_2$(p-cymene) catalyst (Scheme 4A.12).[5f]



Scheme 4A.12: Ruthenium-catalyzed *ortho* olefination of arylpyrazoles with alkenes using catalytic amount of oxidant

Subsequently, we have disclosed *ortho* alkenylation of aromatic and heteroaromatic ketones with alkenes in the presence of a cationic ruthenium complex (Scheme 4A.13A).[5g] Since carbonyl is a weak chelating group, a cationic ruthenium complex is used for the reaction.

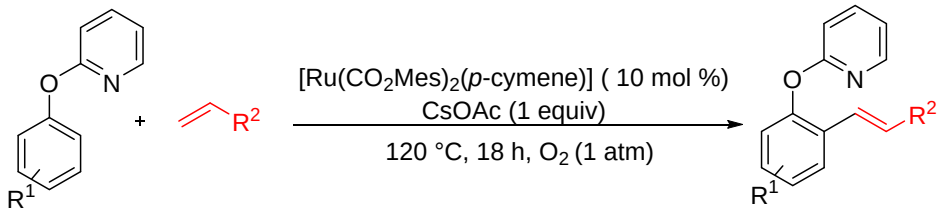


Scheme 4A.13: Ruthenium-catalyzed *ortho* olefination of carbonyl compounds with alkenes.

It is important to note that to regenerate the $Cu(OAc)_2$ from the reduced CuOAc, air is needed along with the *in situ* formed AcOH. Thus, these reactions have done under an air atmosphere. Next, our group have extended the same catalytic reaction with aromatic aldehyde and esters by using same cationic ruthenium complex (Scheme 4A.13B).[5h-i]

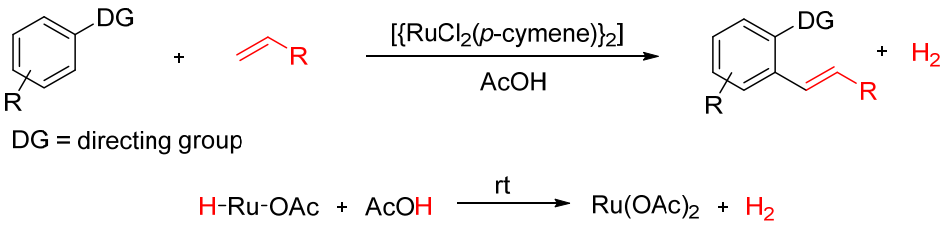
Very recently, Ackermann's group has disclosed the *ortho* alkenylation of phenol pyridine derivatives using oxygen as a sole oxidant (Scheme 4A.14).[5j] In the reaction, oxygen was used as a sole oxidant which oxidizes the Ru(0) into Ru(II) catalyst. In the reaction, after β-hydride

elimination, the ruthenium (0) species was generated which further oxidized into Ru(II) species in the presence of oxygen at ambient pressure.



Scheme 4A.14: Ruthenium-catalyzed *ortho* olefination of phenol pyridine using oxygen as a sole oxidant

Till now, in the ruthenium-catalyzed alkenylation reaction, a stoichiometric amount of $Cu(OAc)_2$ or a catalytic amount of $Cu(OAc)_2$ along with air or oxygen oxidant was used.[3-5] In this type of reaction, after β-hydride elimination, a ruthenium hydride intermediate is formed. It is known that a metal hydride species readily reacts with water or organic acids forming a metal hydroxide or carboxylate species along with hydrogen evolution.[7] With this background, we have planned to use acetic acid in the reaction which could readily reacts with H-Ru species giving the active Ru-OAc catalyst without using any oxidizing agent. By this way, the oxidation step such as the oxidation of Ru(0) to Ru(II) can be avoided and the catalytic reaction can be done without changing the oxidation state of metal via redox-neutral C–H bond functionalization (Scheme 4A.15).

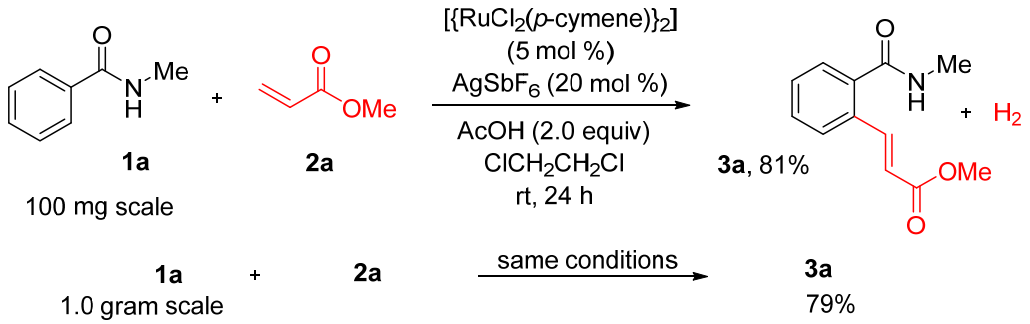


Scheme 4A.15: Ruthenium-catalyzed oxidant-free *ortho* olefination of substituted aromatics with alkenes

4A.2 Results and Discussion

Treatment of *N*-methyl benzamide (**1a**) with methyl acrylate (**2a**) (2.0 equiv) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (5.0 mol %), $AgSbF_6$ (20 mol %) and acetic acid (2.0 equiv) in $ClCH_2CH_2Cl$ (DCE) at room temperature for 24 h gave product **3a** in 81% isolated yield along with H_2 gas evolution (Scheme 4A.16). The liberation of H_2 gas was confirmed by gas chromatograph with a TCD detector. In the reaction, no methyl acrylate (**2a**) dimerization

product and reduced product of **2a** such as methyl propionate (Et-CO_2Me) was observed. Under the same reaction condition, the alkenylation reaction of **1a** was tried in a gram scale with **2a**. The reaction worked nicely and providing product **3a** in 79% isolated yield

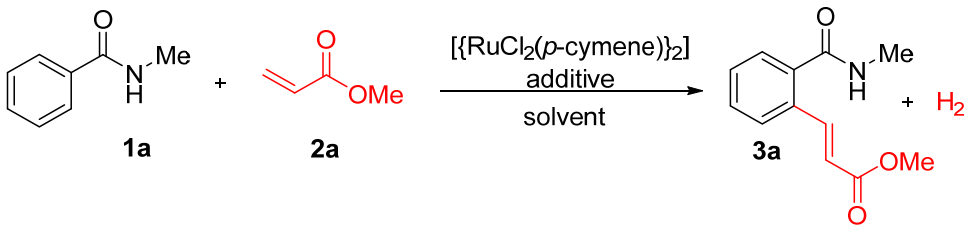


Scheme 4A.16: Ruthenium-catalyzed *ortho* alkenylation of *N*-Methyl Benzamide **(1a)** with Methyl Acrylate **(2a)**

4A.3 Optimization Studies

The alkenylation reaction was also examined with other solvents such as 1,4-dioxane, THF, DME, methanol, toluene, CH_3CN, DMSO, DMF and water instead of DCE. THF, DME and 1,4-dioxane were partially effective, providing product **3a** in 52%, 54% and 40% isolated yields, respectively. Remaining solvents were not effective. Further, the alkenylation reaction was examined with other organic acids such as pivalic acid, 2,6-dimethylbenzoic acid, 1-adamantanecarboxylic acid and benzoic acid instead of acetic acid. These acids were partially effective, yielding product **3a** in 69%, 64%, 61% and 38% yields, respectively. The catalytic reaction was also tested with other additives such as $AgBF_4$, AgOTf, KPF_6 and $CuBF_4$ instead of $AgSbF_6$. $AgBF_4$ and AgOTf were partially effective, providing product **3a** in 52% and 64% yields, respectively. KPF_6 and $CuBF_4$ were not effective. It is important to note that no product **3a** was observed without additive $AgSbF_6$. **(Table 4A.1).**

Table 4A.1: Optimization Studies with Various Additive, Solvent and Cosolvent.



entry	solvent	cosolvent	additive	yield of **3a** (%)[b]
1	Acetonitrile	Acetic acid (2.0equiv)	$AgSbF_6$	NR
2	Methanol	Acetic acid (2.0equiv)	$AgSbF_6$	NR
3	THF	Acetic acid (2.0equiv)	$AgSbF_6$	52
4	DME	Acetic acid (2.0equiv)	$AgSbF_6$	54
5	1,4-dioxane	Acetic acid (2.0equiv)	$AgSbF_6$	40
6	Water	Acetic acid (2.0equiv)	$AgSbF_6$	NR
7	Toluene	Acetic acid (2.0equiv)	$AgSbF_6$	NR
8	$ClCH_2CH_2Cl$	Acetic acid (2.0equiv)	$AgSbF_6$	NR
9	**$ClCH_2CH_2Cl$**	**Acetic acid (2.0equiv)**	**$AgSbF_6$**	**81**
	$ClCH_2CH_2Cl$	Acetic acid (2.0equiv)	$AgSbF_6$	74
11	$ClCH_2CH_2Cl$	Pivalic acid (2.0 equiv)	$AgSbF_6$	61
12	$ClCH_2CH_2Cl$	Adamantane carboxylic acid (1.0 equiv)	$AgSbF_6$	69
13	$ClCH_2CH_2Cl$	Mesitylinic acid (1.0 equiv)	$AgSbF_6$	64
14	$ClCH_2CH_2Cl$	Benzoic acid (1.0 equiv)	$AgSbF_6$	38
15	$ClCH_2CH_2Cl$	Acetic acid (2.0equiv)	AgOTf	64
16	$ClCH_2CH_2Cl$	Acetic acid (2.0equiv)	$AgBF_4$	52
17	$ClCH_2CH_2Cl$	Acetic acid (2.0equiv)	KPF_6	NR

[a]All reactions were carried out under the following conditions: **1a** (100 mg), **2a** (2.0equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5mol %), additive (20 mol %) andsolvent (3.0 mL) at rt for 24 h under the N_2 atmosphere. [b] Isolated yield.

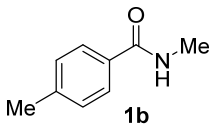
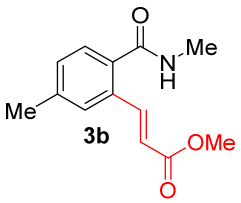
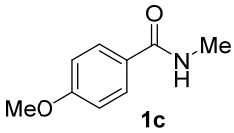
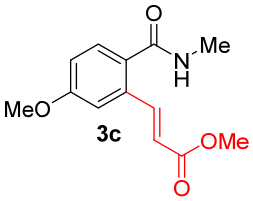
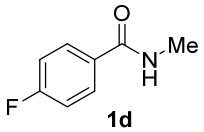
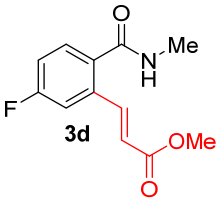
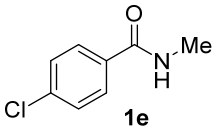
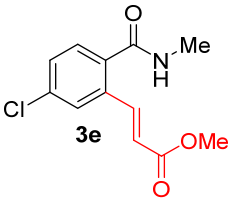
Note: The catalytic reaction was tried without ruthenium and $AgSbF_6$. No product **3a** was observed.

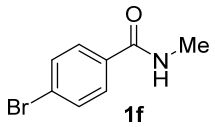
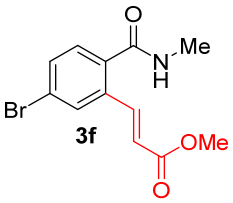
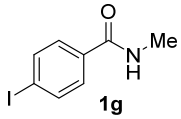
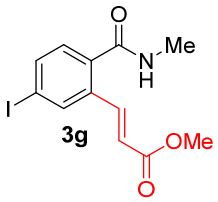
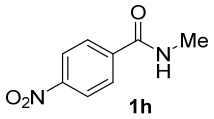
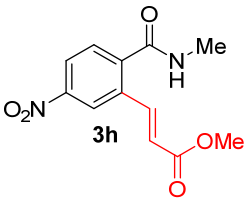
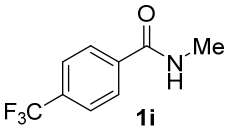
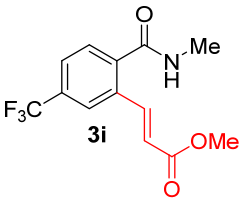
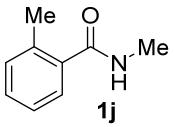
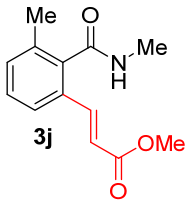
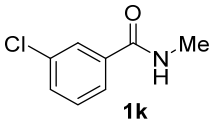
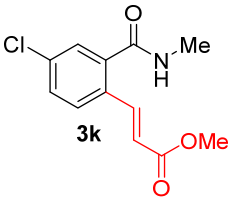
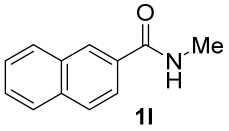
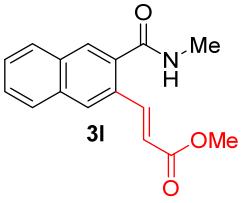
4A.4 Scope of Substituted Aromatic amides.

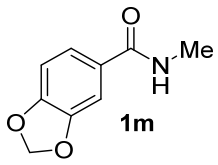
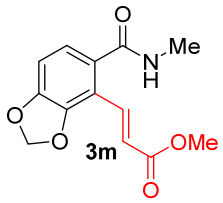
The scope of the alkenylation reaction was examined with various substituted aromatic amides **1b-m** (Table 4A.2). The alkenylation reaction was compatible with various sensitive functional groups such as F, Cl, Br, I, CF_3 and NO_2 substituted aromatic amides. The reaction of electron-donating groups such as Me and OMe substituted benzamides **1b-c** with **2a** provided *ortho* alkenylated benzamides **3b** and **3c** in 78% and 46% yields, respectively (Table 1, entries 1 and

2). Halogen groups such as F, Cl, Br and I substituted benzamides **1d-g** provided *ortho* alkenylated aromatic amides **3d-g** in 71%, 64%, 61% and 55% yields, respectively (entries 3-6). Less reactive electron-withdrawing groups such as NO_2 and CF_3 substituted benzamides **1h-i** also efficiently participated in the reaction, giving alkene derivatives **3h** and **3i** in 53% and 69% yields respectively (entries 7-8). *Ortho* Methyl benzamide (**1j**) was also effectively involved in the reaction, giving product **3j** in 70% yield (entry 9). Next, the alkenylation reaction was tested with unsymmetrical aromatic amides **1k-m** (entries 10-12). *meta* Chloro benzamide (**1k**) and 2-naphthyl benzamide (**1l**) underwent alkenylation at the less hindered C–H bond with **2a**, providing alkene derivatives **3k** and **3l** in 68% and 78% yields, respectively. In contrast, in the reaction of **1m** with **2a**, an alkenylation takes place at a hindered C6-H of **1m**, yielding product **3m** in 62% yield.

Table 4A.2*ortho* Alkenyation of substituted *N*-alkyl benzamides **1b**–**m** with methyl acrylate **2a**[a]

Entry	*N*-alkyl benzamide (**1**)	Compound (**3**)	Yield[b]
1	 **1b**	 **3b**	78%
2	 **1c**	 **3c**	46%
3	 **1d**	 **3d**	71%
4	 **1e**	 **3e**	64%

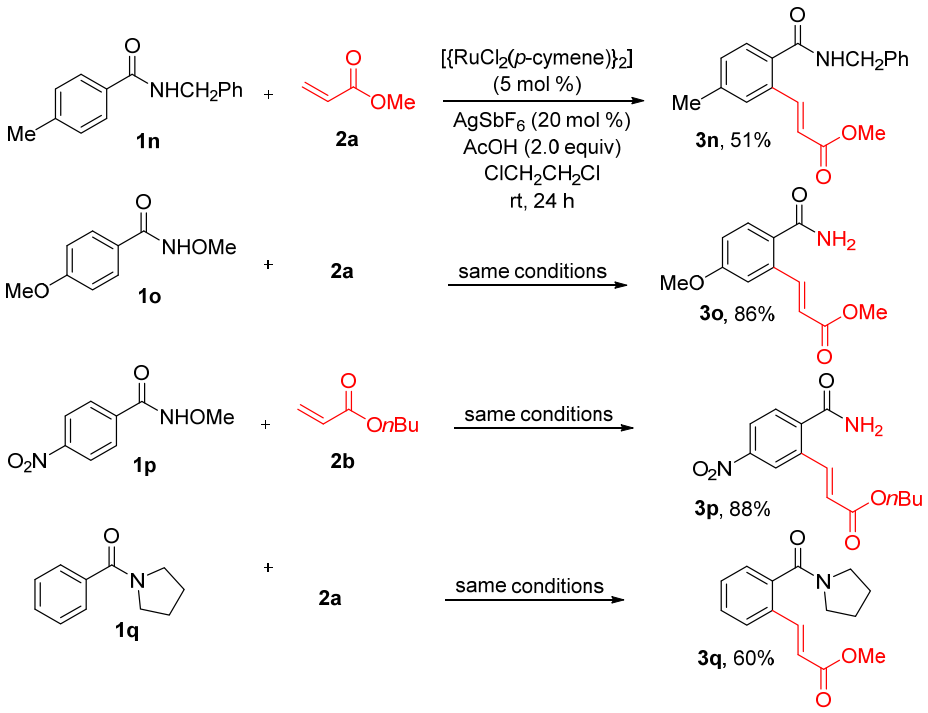
5	 1f	 3f	61%
6	 1g	 3g	55%
7	 1h	 3h	53%[c]
8	 1i	 3i	69%
9	 1j	 3j	70%
10	 1k	 3k	68%
11	 1l	 3l	68%

12			62%

[a]All reactions were carried out using substituted amides **1b-m** (100 mg), methyl acrylate (**2a**) (2.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv), AcOH (2.0 equiv) in 1,2-dichloroethane (3.0 mL) at room temperature for 24 h. [b]Isolated yield. [c]AcOH (4.0 equiv) was used.

4A.5 Substrate Scope of *N*-Substituted Aromatic amides

The alkenylation reaction was examined with *N*-substituted aromatic amides **1n-q** with **2a** or **2b** (Scheme 4A.17). *N*-Benzyl and *N*-OMe substituted benzamides **1n-p** efficiently reacted with **2a** or **2b**, giving the corresponding alkene derivatives **3n, 3o** and **3p** in 51%, 86% and 88% yields, respectively. In the reaction of **1o-p** with **2**, OMe moiety of the amide group was cleaved and acts as an internal oxidant. Tertiary amide **1q** also efficiently reacted with **2a**, affording **3q** in 60% yield.

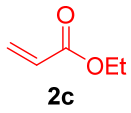
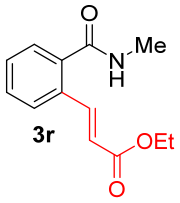
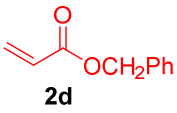
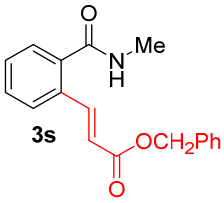
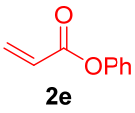
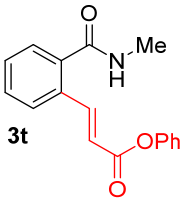
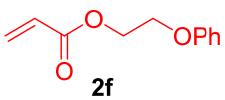
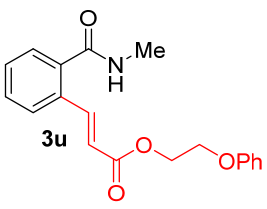


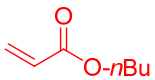
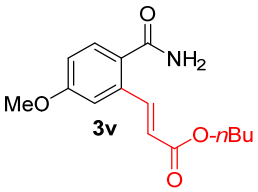
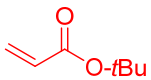
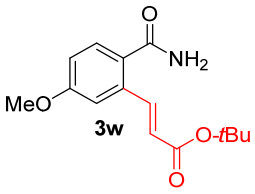
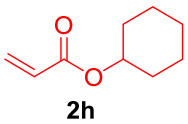
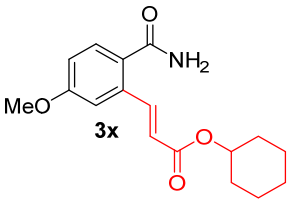
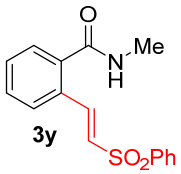
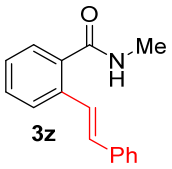
Scheme 4A.17 Scope of *N*-Substituted Benzamides.

4A.6 Substrate Scope of Alkenes

The scope of the alkenylation reaction was further examined with substituted alkenes **2b-j** (Table 4A.3). Ethyl (**2c**), benzyl (**2d**) and phenyl (**2e**) acrylates nicely reacted with **1a**, giving alkene derivatives **3r-t** in 80%, 76% and 71% yields, respectively (entries 1-3). 2-Methoxyethyl acrylate (**2f**) was also nicely involved in the reaction, yielding an alkene derivative **3u** in 61% yield (entry 4). *n*-Butyl (**2b**), *tert*-butyl (**2g**) and cyclohexyl (**2h**) acrylates reacted with **1l**, providing *ortho* alkenylated benzamides **3w-y** in 91%, 88% and 90% yields, respectively (entries 5-7). Phenyl vinyl sulphone (**2g**) also participated in the reaction, providing product **3ai** in 61% yield (entry 8). However, styrene (**2j**) did not react with **1a** at room temperature. At 100 °C, styrene (**2j**) reacted with **1a** in 1,4-dioxane, yielding product **3z** in 43% yield (entry 9).

Table 4A.3 *ortho* Alkenyation of substituted *N*-alkyl benzamide **1a**(or) **1o** with alkenes **2b-j**[a]

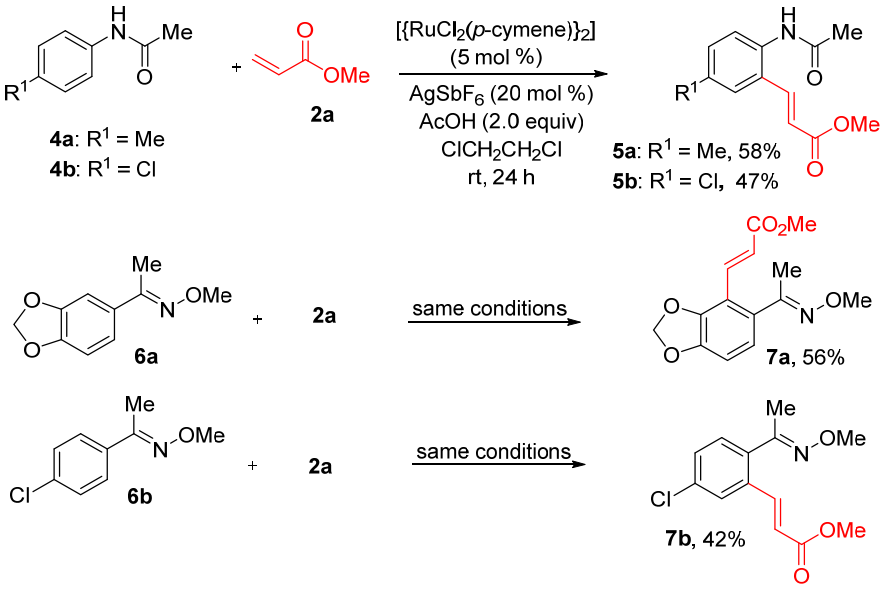
Entry	Alkene (**1**)	Compound (**3**)	Yield[b]
1	 **2c**	 **3r**	80%
2	 **2d**	 **3s**	76%
3	 **2e**	 **3t**	71%
4	 **2f**	 **3u**	61%

5	 **2b**	 **3v**	91%
6	 **2g**	 **3w**	88%
7	 **2h**	 **3x**	90%[c]
8	 **2i**	 **3y**	61%
9	 **2j**	 **3z**	43%[c]

[a]All reactions were carried out using **1a** or **1o** (100 mg), alkenes **2b-j** (2.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv), AcOH (2.0 equiv) in 1,2-dichloroethane (3.0 mL) at room temperature for 24 h. [b]Isolated yield. [c]1,4-dioxane solvent was used and the reaction was done at 100 °C.

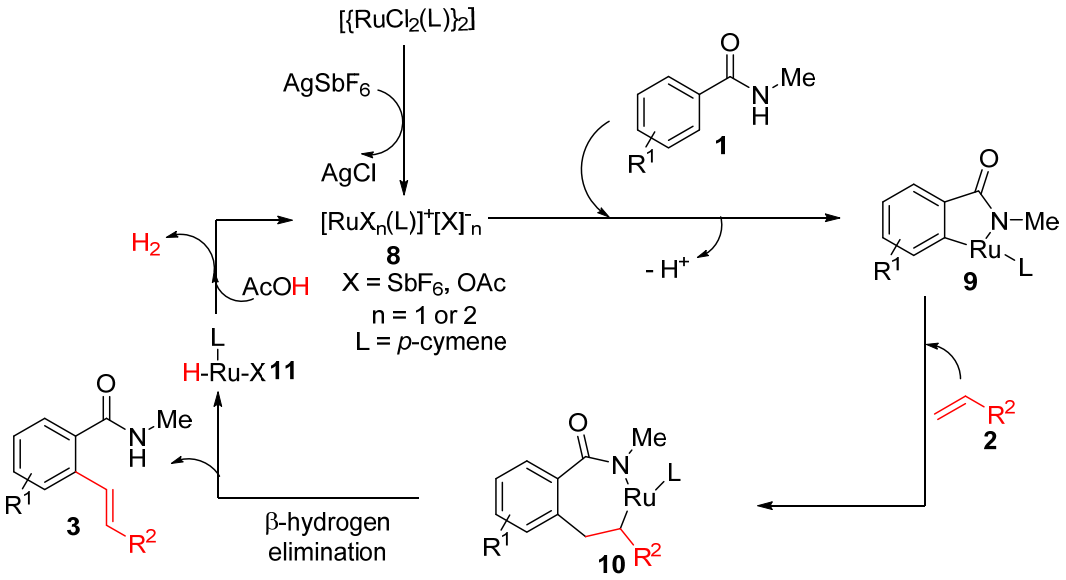
4A.7 Substrate Scope of Substituted Aromatic amides and Ketoximes

The alkenylation reaction was successfully extended to substituted anilides **4** and aromatic ketoximes **6** (Scheme 4A.18). Treatment of substituted anilides **4a-b** with methyl acrylate (**2a**) under the optimized reaction conditions at ambient temperature gave *ortho* alkenylated anilides **5a-b** in 58% and 47% yields, respectively. In a similar fashion, substituted aromatic ketoximes **6a-b** reacted with **2a** at ambient temperature, affording *ortho* alkenylated aromatic ketoximes **7a-b** in 56% and 42% yields, respectively.



Scheme 4A.18 *ortho* Alkenylation of Anilides and Aromatic Ketoximes of benzamides

4A.8 Proposed Mechanism



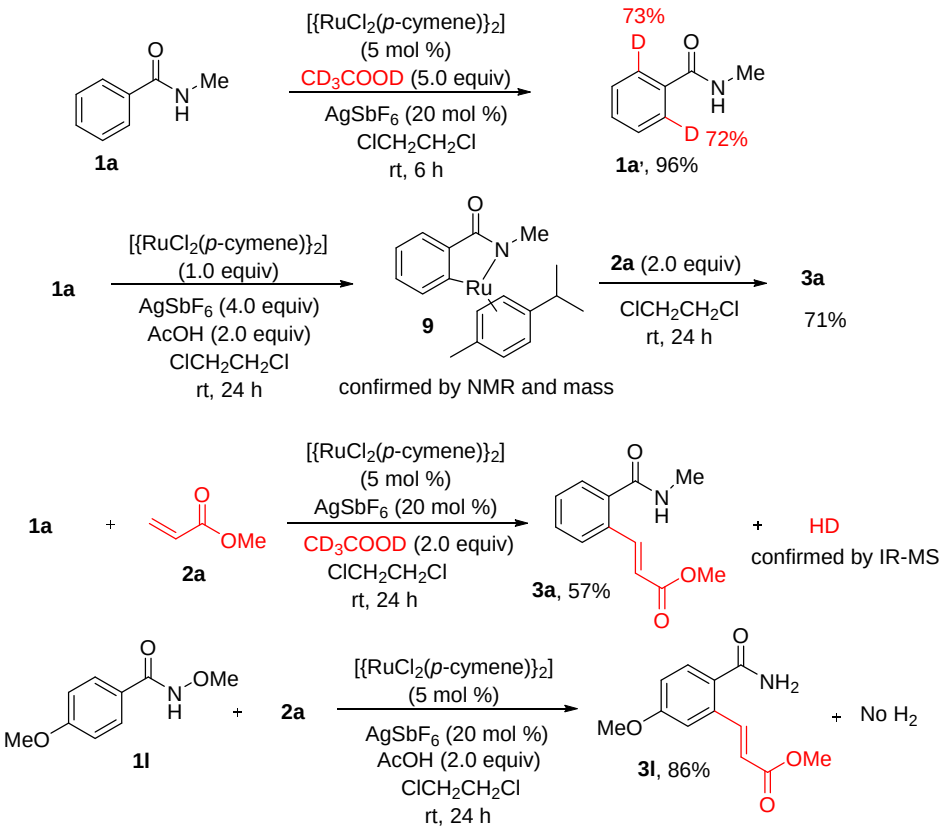
Scheme 4A.19. Proposed Mechanism

A possible reaction mechanism for *ortho* alkenylation of substituted aromatics with alkenes is proposed in Scheme 4A.19. $AgSbF_6$ likely removes Cl ligand from $[\{RuCl_2(p\text{-cymene})\}_2]$ complex, giving a cationic ruthenium species **8**. Later, the nitrogen atom of amide **1** coordinates with a ruthenium species **8** followed by *ortho* metalation providing a five-membered

ruthenacycle intermediate **9**. Coordinative insertion of alkene **2** into the Ru–carbon bond of intermediate **9** gives intermediate **10**. β-Hydride elimination of intermediate **10** affords *ortho* alkenylated aromatic amides **3** and a ruthenium hydride species **11**. Later, a ruthenium hydride species **11** reacts with acetic acid liberating H_2 gas and regenerates the active catalyst **8**.

4A.9 Mechanistic studies

To prove the formation of intermediate **9** step is a reversible process, **1a** was treated with CD_3COOD in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) in 1,2-dichloroethane at room temperature for 6 h. In the reaction, product **d-1a'** was observed in 96% yield with 72% and 73% of deuterium incorporation at the both *ortho* carbons, respectively (Scheme 4A.20). In the meantime, we have tried to isolate the key ruthenacycle intermediate **9** in the reaction of **1a** with a stoichiometric amount of [{$RuCl_2$(*p*-cymene)}$_2$] (1.0 equiv), $AgSbF_6$ (4.0 equiv) and AcOH (2.0 equiv) in 1,2-dichloroethane at room temperature for 24 h. As expected, in the reaction, metalacycle intermediate **9** was isolated. However, a suitable single crystal was not formed for the X-ray analysis. But, the complex **9** was tentatively assigned by ^1H, ^{13}C NMR and MALDI-TOF techniques. It is important to note that the metalacycle intermediate **9** was not observed without AcOH. Later, intermediate **9** reacted with **2a** to give the expected alkene derivative **3a** in 71% yield. Further, the alkenylation reaction of **1a** was examined with **2a** in the presence of CD_3COOD under the optimized reaction conditions. In the reaction, product **3a** was observed in 57% yield along with the liberation of HD gas. Initially, the liberation of HD gas was tried to confirm by GC. However, we were not able to confirm it, due to a similar retention time of H_2 and HD gases. Later, the formation of HD gas was confirmed by Isotope-ratio mass spectrometry (IR-MS) analysis. The expected molecular mass of HD 3 was observed in the spectrum (see Supporting Information). This result clearly reveals that in the H_2 gas evolution, one of the hydrogen comes from the acetic acid and another one from the Ru-H species. It is interesting to note that the H_2 evolution was not observed in the reaction of *N*-methoxy substituted benzamide **1l** with methyl acrylate (**2a)**. In the reaction, N-OMe group of **1l** acts as an internal oxidant. But, this reaction did not proceed without AcOH.



Scheme 4A.20 Mechanistic studies

4A.10 Conclusions

In conclusion, we have described a highly regioselective *ortho* alkenylation of aromatic amides and ketoximes or anilides with alkenes in the presence of a ruthenium catalyst, $AgSbF_6$ and AcOH at room temperature without an oxidant. Interestingly, a clean and renewable H_2 fuel was observed at room temperature. The proposed reaction mechanism was supported by experemental evidence.

4A.11 References

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4A.12 Experimental Section

4A.12.1 General Procedure for the Alkenylation of Aromatic amides, oximes and anilides with Alkenes catalyzed by Ruthenium Complex

A 15-mL pressure tube with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube, were then added aromatic amides or oximes or anilides **1** or **4** or **6** (100 mg), alkenes **2** (2.0equiv), acetic acid (2.0 equiv) and 1,2-dichloroethane (3.0 mL) via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, 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 room temperature (~ 24 °C) for 24 h. Then, 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 petroleum ether and ethyl acetate as eluent to give pure alkenylated product **3** or **5** or **7**.

The alkenylation reaction can also be done in a round bottom flask under the nitrogen atmosphere.

Note: a) For substrate **3h**, AcOH (4.0 equiv) was used. b) For compound **3z**, 1,4-dioxane solvent was used and the reaction was done at 100 °C.

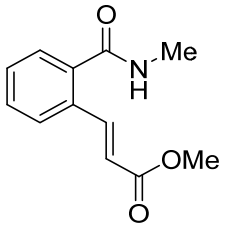
Procedure for the 1.0 Gram Scale Reaction of *N*-methyl benzamide (1a) with methyl acrylate (2a).

A 50 mL single neck round bottom flask with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$

was taken inside the glove box). To the flask, were then added *N*-methyl benzamide (**1a**) (1.0 gram), methyl acrylate (**2a**) (2.0 equiv), acetic acid (2.0 equiv) and 1,2-dichloroethane (15.0 mL) via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, the nitrogen balloon was kept on the septum. The reaction mixture was allowed to stir at room temperature for 24 h. Then, 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 petroleum ether and ethyl acetate as eluent to give pure alkenylated product **3a** in 79% yield.

4A.13 Spectral Data of Compounds 3a-z, 5a-b, and 7a-b

Methyl (*E*)-3-(2-(methylcarbamoyl)phenyl)acrylate (3a).



White solid; eluent (29% ethylacetate in hexanes).The reaction scale is 100mg (**1a)**, 132mg of product was isolated and yield is 81%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, *J* = 16.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.39 – 7.36 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 6.52 (s, 1H), 6.29 (d, *J* = 16.0 Hz, 1H), 3.73 (s, 3H), 2.92 (s, 3H).

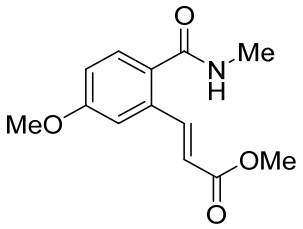
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.5, 166.9, 142.1, 136.9, 132.5, 130.1, 129.7, 127.4, 126.9, 119.9, 51.6, 26.7.

HRMS (ESI): calc. for [($C_{12}H_{13}NO_3$)Na] (M+Na) 242.0793, measured 242.0798.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3281, 2978, 2360, 1705, 1628, 1545, 1264, 1040, 763.

Rf (hexane/ethyl acetate = 2:1): 0.31.

Methyl (*E*)-3-(5-methoxy-2-(methylcarbamoyl)phenyl)acrylate (3b).



White solid; eluent (32% ethylacetate in hexanes).The reaction scale is 100mg (**1b)**, 69mg of product was isolated and yield is 46%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, *J* = 16.0 Hz, 1H), 7.42 (d, *J* = 8.0Hz, 1H), 7.05 (d, *J* = 4.0 Hz, 1H), 6.88 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.33 (d, *J* = 16.0.Hz, 1H), 5.84 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 2.97 (d, *J* = 4.0 Hz, 3H).

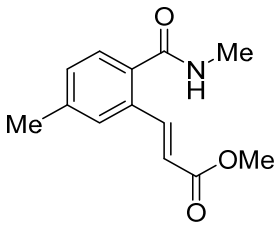
^{13}C NMR ($CDCl_3$, 100 MHz):δ168.9, 166.8, 160.9, 142.5, 134.9, 129.5, 129.3, 120.5, 115.3, 112.2, 55.4, 51.8, 26.9.

HRMS (ESI): calc. for [($C_{13}H_{15}NO_4$)Na] (M+Na) 272.0899, measured 272.0906.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3301, 3080, 2948, 1710, 1624, 1540, 1284, 1033, 863.

Rf (hexane/ethyl acetate = 1:1): 0.61.

Methyl (*E*)-3-(5-methyl-2-(methylcarbamoyl)phenyl)acrylate (3c).



White solid; eluent (29% ethylacetate in hexanes).The reaction scale is 100mg (**1c**), 122mg of product was isolated and yield is 78%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, *J* = 16.0 Hz, 1H), 7.37 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.31 (d, *J* = 16.0 Hz, 1H), 6.00 (s, 1H), 3.75 (s, 3H), 2.95 (d, *J* = 4.0 Hz, 3H), 2.34 (s, 3H).

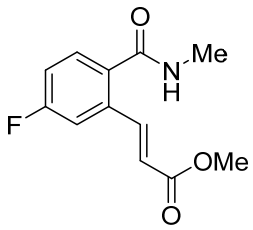
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4, 166.9, 142.3, 140.5, 134.2, 132.8, 130.5, 127.7, 127.6, 120.0, 51.7, 26.9, 21.3.

HRMS (ESI): calc. for [($C_{13}H_{15}NO_3$)Na] (M+Na) 256.0950, measured 256.0954.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3294, 2950, 1707, 1627, 1545, 1432, 1219, 1034, 705.

Rf (hexane/ethyl acetate = 1:1): 0.65.

Methyl (*E*)-3-(5-fluoro-2-(methylcarbamoyl)phenyl)acrylate (3d).



White solid; eluent (27% ethylacetate in hexanes).The reaction scale is 100mg (**1d**), 110mg of product was isolated and yield is 71%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, *J* = 16.0 Hz, 1H), 7.47 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.29 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.07 (td, *J* = 8.0, 4.0 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.11 (s, 1H), 3.80 (s, 3H), 3.00 (d, *J* = 4.0 Hz, 3H).

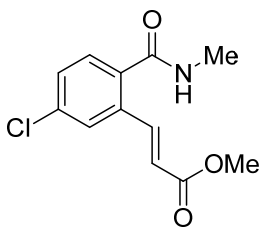
^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.4, 166.5, 164.6, 162.1, 141.0 and 140.9 (F-coupling), 135.4, 133.2, 129.7, 121.4, 116.8 and 116.6(F-coupling), 113.9 and 113.6(F-coupling), 51.9, 26.9.

HRMS (ESI): calc. for [($C_{12}H_{12}FNO_3$)Na] (M+Na) 260.0699, measured 260.0711.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3285, 3079, 2923, 1718, 1633, 1550, 1318, 1265, 1162, 1010.

Rf (hexane/ethyl acetate = 2:1): 0.32.

Methyl (*E*)-3-(5-chloro-2-(methylcarbamoyl)phenyl)acrylate (3e).



White solid; eluent (26% ethylacetate in hexanes).The reaction scale is 100mg (**1e**), 96mg of product was isolated and yield is 64%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (d, *J* = 16.0 Hz, 1H), 7.55 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 6.34 (d, *J* = 16.0 Hz, 1H), 5.92 (s, 1H), 3.77 (s, 3H), 2.98 (d, *J* = 6.0 Hz, 3H).

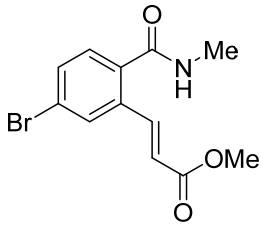
^{13}C NMR ($CDCl_3$, 100 MHz):δ168.3, 166.5, 140.7, 136.4, 135.2, 134.6, 129.7, 128.9, 127.1, 121.5, 51.9, 26.9.

HRMS (ESI): calc. for [($C_{12}H_{12}ClNO_3$)H] (M+H) 254.0584, measured 254.0593.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3280, 2947, 1717, 1634, 1554, 1264, 1040.

Rf (hexane/ethyl acetate = 2:1): 0.37.

Methyl (*E*)-3-(5-bromo-2-(methylcarbamoyl)phenyl)acrylate (3f).



Pale yellow solid; eluent (29% ethylacetate in hexanes).The reaction scale is 100mg (**1f**), 85mg of product was isolated and yield is 61%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, *J* = 16.0 Hz, 1H), 7.74 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.25 (m, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 6.08 (s, 1H), 3.81 (s, 3H), 3.00 (d, *J* = 6.0 Hz, 3H).

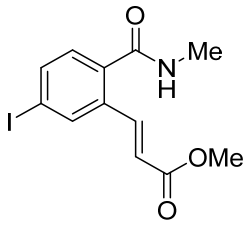
^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 166.5, 140.6, 135.6, 134.8, 132.6, 130.0, 129.1, 124.6, 121.5, 51.9, 26.9.

HRMS (ESI): calc. for [($C_{12}H_{12}BrNO_3$)Na] (M+Na) 319.9898, measured 319.9912.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3281, 3075, 2947, 1719, 1637, 1555, 1312, 1167, 1006.

Rf (hexane/ethyl acetate = 2:1): 0.34.

Methyl (*E*)-3-(5-iodo-2-(methylcarbamoyl)phenyl)acrylate (3g).



White solid; eluent (28% ethylacetate in hexanes).The reaction scale is 100mg (**1g**), 73mg of product was isolated and yield is 55%.

^{1}H NMR (DMSO d_6, 400 MHz):δ 8.48 (d, J = 4.0 Hz, 1H), 8.25 (d, J = 4.0 Hz, 1H), 7.83 (dd, J = 8.0, 4.0 Hz, 1H), 7.78 (d, J = 16.0 Hz, 1H), 7.22 (d, J = 8.0Hz, 1H), 6.67 (d, J = 16.0 Hz, 1H), 3.72 (s, 3H), 2.76 (d, J = 4.0 Hz, 3H).

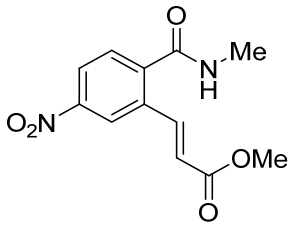
^{13}C NMR (DMSO d_6, 100 MHz): δ 167.8, 166.3, 140.5, 140.91, 138.4, 136.9, 133.9, 129.5, 120.5, 96.7, 51.6, 26.1.

HRMS (ESI): calc. for [($C_{12}H_{12}INO_3$)Na] (M+Na) 367.9760, measured 367.9764.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3288, 2957, 1719, 1634, 1554, 1264, 1042.

Rf (hexane/ethyl acetate = 2:1): 0.33.

Methyl (*E*)-3-(2-(methylcarbamoyl)-5-nitrophenyl)acrylate (3h).



White solid; eluent (27% ethylacetate in hexanes).The reaction scale is 100mg (**1h**), 78mg of product was isolated and yield is 53%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.42 (d, J = 4.0 Hz, 1H), 8.21 (dd, J = 8.0, 4.0 Hz, 1H), 7.90 (d, J = 16.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 6.49 (d, J = 16.0 Hz, 1H), 6.09 (s, 1H), 3.79 (s, 3H), 3.02 (d, J = 4.0 Hz, 3H).

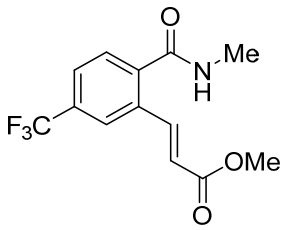
^{13}C NMR (DMSO d_6, 100 MHz):δ166.9, 166.1, 148.3, 142.9, 139.7, 133.4, 129.3, 128.6, 124.3, 123.5, 122.2, 121.8, 51.8, 26.1.

HRMS (ESI): calc. for [($C_{12}H_{12}N_2O_5$)Na] (M+Na) 287.0644, measured 287.0651.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3292,3081, 2949, 1714, 1638, 1549, 1279, 788.

Rf (hexane/ethyl acetate = 2:1): 0.39.

Methyl (*E*)-3-(2-(methylcarbamoyl)-5-(trifluoromethyl)phenyl)acrylate (3i).



White solid; eluent (31% ethylacetate in hexanes).The reaction scale is 100mg (**1i**), 98 mg of product was isolated and yield is 69%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.93 (d, J = 16.0 Hz, 1H), 7.82 (s, 1H),7.61 (dd, J = 8.0, 4.0 Hz, 1H), 7.56 (dd, J = 8.0, 4.0 Hz, 1H), 6.42 (d, J = 16.0 Hz, 1H), 5.94 (s, 1H), 3.78 (s, 3H), 3.01 (d, J = 8.0 Hz, 3H).

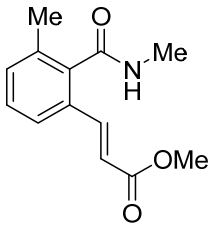
^{13}C NMR ($CDCl_3$, 100 MHz):δ168.0, 166.4, 140.4, 139.9, 133.6, 132.7, 132.3, 128.2, 126.3 and 126.2, (F-coupling), 124.1, 122.2, 51.9, 26.9.

HRMS (ESI): calc. for [($C_{13}H_{12}F_3NO_3$)H] (M+H) 288.0848, measured 288.0856.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3283, 2939, 1718, 1631, 1554, 1264, 1162.

Rf (hexane/ethyl acetate = 2:1): 0.31.

Methyl (*E*)-3-(3-methyl-2-(methylcarbamoyl)phenyl)acrylate (3j).



White solid; eluent (29% ethylacetate in hexanes).The reaction scale is 100mg (**1j**), 109mg of product was isolated and yield is 70%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, *J* = 16.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 5.74 (s, 1H), 3.75 (s, 3H), 3.02 (d, *J* = 4.0 Hz, 3H), 2.32 (s, 3H).

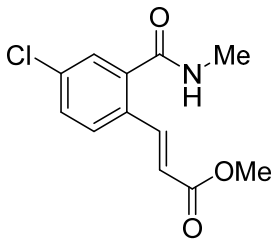
^{13}C NMR ($CDCl_3$, 100 MHz): δ169.6, 166.9, 141.7, 138.1, 135.3, 131.8, 131.4, 129.0, 123.8, 120.0, 51.7, 26.5, 19.1.

HRMS (ESI): calc. for [($C_{13}H_{15}NO_3$)H] (M+H) 256.0950, measured 256.0958.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3293, 2949, 1707, 1634, 1545, 1214, 1034.

Rf (hexane/ethyl acetate = 2:1): 0.38.

Methyl (*E*)-3-(4-chloro-2-(methylcarbamoyl)phenyl)acrylate (3k).



White solid; eluent (27% ethylacetate in hexanes).The reaction scale is 100mg (**1k**), 101mg of product was isolated and yield is 68%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, *J* = 16.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 4.0 Hz, 1H), 7.37 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 5.95 (s, 1H), 3.77 (s, 3H), 2.99 (d, *J* = 4.0 Hz, 3H).

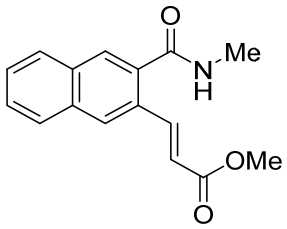
^{13}C NMR ($CDCl_3$, 100 MHz):δ167.8, 166.6, 140.8, 138.4, 135.8, 131.2, 130.4, 128.5, 127.8, 120.8, 51.8, 26.9.

HRMS (ESI): calc. for [($C_{12}H_{12}ClNO_3$)Na] (M+Na) 276.0403, measured 276.0407.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3280, 2947, 1718, 1631, 1559, 1312, 1040.

Rf (hexane/ethyl acetate = 2:1): 0.41.

Methyl (*E*)-3-(2-(methylcarbamoyl)naphthalen-2-yl)acrylate (3l).



White solid; eluent (26% ethylacetate in hexanes).The reaction scale is 100mg (**1l**), 114mg of product was isolated and yield is 78%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, *J* = 16.0 Hz, 1H),8.03 (s, 1H), 7.91 (s, 1H), 7.83(dd, *J* = 8.0, 4.0 Hz, 1H), 7.79 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.52 (t, *J* = 4.0 Hz, 1H), 7.53 (t, *J* = 4.0 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.06 (s, 1H), 3.79 (s, 3H), 3.04 (d, *J* = 8.0 Hz, 3H).

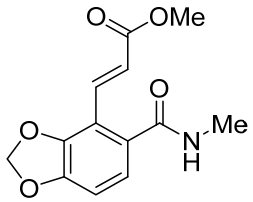
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.5, 166.9, 142.6, 136.9, 133.9, 133.4, 132.9, 130.1, 128.2, 128.0, 127.8, 127.7, 127.5, 120.0, 51.7, 26.9.

HRMS (ESI): calc. for [($C_{16}H_{15}NO_3$)Na] (M+Na) 292.0950, measured 292.0958.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3279, 3054, 2941, 1710, 1624, 1545, 1302, 1159, 1034, 747.

Rf (hexane/ethyl acetate = 2:1): 0.33.

Methyl (*E*)-3-(5-(methylcarbamoyl)benzo[*d*][1,3]dioxol-4-yl)acrylate (3m).



White solid; eluent (32% ethylacetate in hexanes).The reaction scale is 100 mg (**1m**), 91 mg of product was isolated and yield is 62%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 16.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 16.0 Hz, 1H), 6.27 (s, 1H), 6.05 (s, 2H), 3.74 (d, *J* = 4.0 Hz, 3H), 2.93 (d, *J* = 4.0 Hz, 3H).

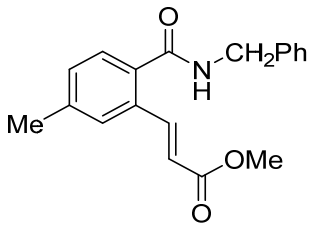
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.1, 167.4, 149.1, 147.1, 136.6, 130.8, 123.1, 121.7, 115.7, 108.6, 101.9, 51.7, 26.9.

HRMS (ESI): calc. for [($C_{13}H_{13}NO_5$)Na] (M+Na) 286.0691, measured 286.0702.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3295, 2947, 1707, 1635, 1548,1449, 1301, 1170, 901, 823.

Rf (hexane/ethyl acetate = 1:1): 0.41.

Methyl (*E*)-3-(2-(benzylcarbamoyl)-5-methylphenyl)acrylate (3n).



White solid; eluent (28% ethylacetate in hexanes).The reaction scale is 100mg (**1n**), 70mg of product was isolated and yield is 51%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, *J* = 16.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 4.0 Hz, 3H), 7.33 (s, 1H), 7.28 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.16 (d,*J* = 8.0 Hz, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 6.14 (s, 1H), 4.60 (s, 2H), 3.76 (s, 3H), 2.35 (s, 3H).

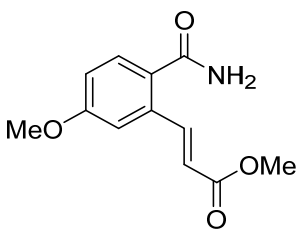
^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.5, 166.9, 142.4, 140.6, 137.8, 133.9, 132.9, 130.5, 128.8, 127.9, 127.8, 127.7, 127.6, 120.2, 51.7, 44.2, 21.3.

HRMS (ESI): calc. for [($C_{19}H_{19}NO_3$)H] (M+H) 310.1443, measured 310.1454.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3311, 2937, 1724, 1628, 1543, 1310, 1130, 975, 760.

Rf (hexane/ethyl acetate = 2:1): 0.40.

Methyl (*E*)-3-(2-carbamoyl-5-methoxyphenyl)acrylate (3o).



White solid; eluent (34% ethylacetate in hexanes).The reaction scale is 100 mg (**1o**), 111 mg of product was isolated and yield is 86%.

^{1}H NMR (DMSO d_6, 400 MHz): δ 8.07 (d, J = 16.0 Hz, 1H), 7.85 (s, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.42 (s, 1H), 7.35 (d, J = 4.0 Hz, 1H), 7.02 (dd, J = 8.0, 4.0 Hz, 1H), 6.62 (d, J = 16.0 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H).

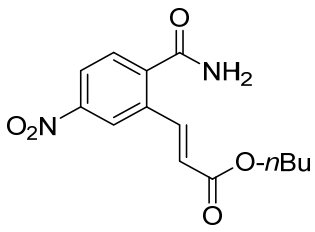
^{13}C NMR (DMSO d_6, 100 MHz): δ 169.8, 166.7, 160.2, 142.6, 133.9, 130.1, 129.6, 119.3, 115.7, 111.5, 55.6, 51.6.

HRMS (ESI): calc. for [($C_{12}H_{13}NO_4$)H] (M+H) 236.0923, measured 236.0932.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3322, 2927, 1721, 1638, 1541, 1319, 1130, 975, 860.

Rf (hexane/ethyl acetate = 1:1): 0.32.

Butyl (*E*)-3-(2-carbamoyl-5-methoxyphenyl)acrylate (3p).



White solid; eluent (34% ethylacetate in hexanes).The reaction scale is 100 mg (**1p**), 131 mg of product was isolated and yield is 88%.

^{1}H NMR (DMSO d_6,400 MHz): δ 8.65 (d, J = 4.0 Hz, 1H), 8.27 (dd, J = 8.0, 4.0 Hz, 1H), 8.22 (s, 1H), 7.93 (s, 1H), 7.88 (d, J = 16.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 16.0 Hz, 1H), 4.17 (t, J = 8.0 Hz, 2H), 1.63 (quintet, J = 8.0 Hz, 2H), 1.38 (m, 2H), 0.92 (t, J = 8.0 Hz, 3H).

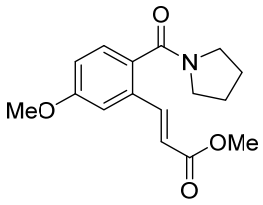
^{13}C NMR (DMSO d_6, 100 MHz): δ 168.6, 165.7, 148.2, 143.2, 139.6, 133.1, 129.0, 124.2, 122.4, 121.7, 64.0, 30.2, 18.6, 13.5.

HRMS (ESI): calc. for [($C_{14}H_{16}N_2O_5$)Na] (M+Na) 315.0957, measured 315.0962.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3322, 2837, 1734, 1618, 1541, 1319, 1137, 979, 761.

Rf (hexane/ethyl acetate = 1:1): 0.31.

Methyl (*E*)-3-(5-methoxy-2-(pyrrolidine-1-carbonyl)phenyl)acrylate (3q).



Colourless liquid; eluent (26% ethylacetate in hexanes).The reaction scale is 100mg (**1q**), 85 mg of product was isolated and yield is 60%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J* = 16.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 4.0 Hz, 1H), 6.93 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.65 (t, *J* = 4.0 Hz, 2H), 3.54 (t, *J* = 4.0 Hz, 2H), 1.93 (q, *J* = 4.0 Hz, 2H), 1.82 (q, *J* = 4.0 Hz, 2H).

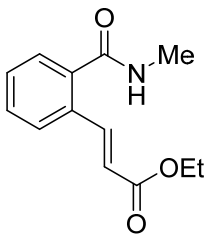
^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.4, 166.8, 159.9, 141.5, 132.4, 131.1, 128.3, 120.2, 115.9, 111.5, 55.4, 51.7, 48.6, 45.7, 25.9, 24.5.

HRMS (ESI): calc. for [($C_{16}H_{19}NO_4$)H] (M+H) 290.1392, measured 290.1397.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3434, 2954, 1710, 1599, 1429, 1310, 1169, 1031, 828.

Rf (hexane/ethyl acetate = 2:1): 0.29.

Ethyl (*E*)-3-(2-(methylcarbamoyl)phenyl)acrylate (3r).



White solid; eluent (31% ethylacetate in hexanes).The reaction scale is 100mg (**1a**), 138mg of product was isolated and yield is 80%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, *J* = 16.0 Hz, 1H), 7.57 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.42 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.39 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.34 (td, *J* = 8.0, 4.0 Hz, 1H), 6.33 (d, *J* = 16.0 Hz, 1H), 5.99 (s, 1H), 4.21 (q, *J* = 8.0 Hz, 2H), 2.97 (d, *J* = 4.0 Hz, 3H), 1.29 (t, *J* = 8.0 Hz, 3H).

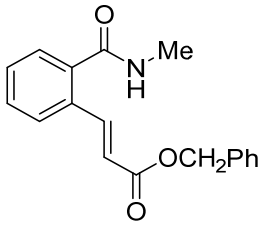
^{13}C NMR ($CDCl_3$, 100 MHz): δ169.3, 166.5, 141.8, 137.2, 132.7, 130.2, 129.7, 127.6, 127.1, 120.8, 60.5, 26.8, 14.2.

HRMS (ESI): calc. for [($C_{13}H_{15}NO_3$)Na] (M+Na) 256.0950, measured 256.0957.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3281, 3065, 2978, 1705, 1628, 1545, 1432, 1264, 1040, 765.

Rf (hexane/ethyl acetate = 2:1): 0.38.

Benzyl (*E*)-3-(2-(methylcarbamoyl)phenyl)acrylate (3s).



White solid;eluent (28% ethylacetate in hexanes).The reaction scale is 100mg (**1a**), 166mg of product was isolated and yield is 76%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.02 (d, *J* = 16.0 Hz, 1H), 7.60 (d, *J* = 4.0 Hz, 1H), 7.45 (td, *J* = 8.0, 4.0 Hz, 1H), 7.41 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.39 (t,*J* = 4.0 Hz, 3H), 7.36 (dt, *J* = 8.0, 4.0 Hz, 2H), 7.33 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 5.85 (s, 1H), 5.23 (s, 2H), 2.99 (d, *J* = 4.0 Hz, 3H).

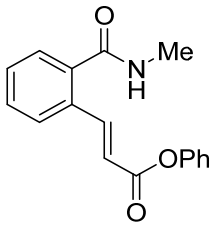
^{13}C NMR ($CDCl_3$, 100 MHz): δ169.2, 166.2, 142.4, 137.2, 135.9, 132.6, 131.3, 130.2, 129.8, 128.5, 128.4, 128.2, 127.6, 127.1, 126.8, 120.3, 66.3, 26.8.

HRMS (ESI): calc. for [($C_{18}H_{17}NO_3$)Na] (M+Na) 318.1106, measured 318.1112.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3311, 2937, 1724, 1628, 1543, 1310, 1130, 975, 760.

Rf (hexane/ethyl acetate = 2:1): 0.38.

Phenyl (*E*)-3-(2-(methylcarbamoyl)phenyl)acrylate (3t).



White solid; eluent (27% ethylacetate in hexanes).The reaction scale is 100mg (**1a**), 148mg of product was isolated and yield is 71%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ8.22 (d, *J* = 16.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.40 (m, 5H), 7.28 (d, *J* = 4.0 Hz, 1H), 7.19 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.18 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.60 (d, *J* = 16.0 Hz, 1H), 5.96 (s, 1H), 3.04 (d, *J* = 4.0 Hz, 3H).

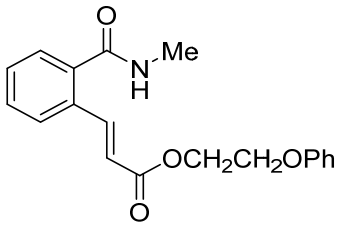
^{13}C NMR ($CDCl_3$, 100 MHz):δ169.2, 164.9, 150.7, 143.8, 137.3, 132.6, 130.4, 130.2, 129.4, 127.6, 127.3, 125.7, 121.6, 119.8, 26.9.

HRMS (ESI): calc. for [($C_{17}H_{15}NO_3$)Na] (M+Na) 304.0950, measured 304.0953.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3310, 3068, 2935, 1728, 1631, 1543, 1310, 1138, 975, 766.

Rf (hexane/ethyl acetate = 2:1): 0.39.

2-Phenoxyethyl (*E*)-3-(2-(methylcarbamoyl)phenyl)acrylate (3u).



White solid; eluent (31% ethylacetate in hexanes).The reaction scale is 100mg (**1a**), 146mg of product was isolated and yield is 61%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, *J* = 16.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.48-7.38 (m, 3H) 7.32 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.29 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.00 (d,*J* = 4.0 Hz, 1H),, 6.97-6.94 (m, 2H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.03 (s, 1H), 4.56 (t, *J* = 4.0 Hz, 2H), 4.25 (t, *J* = 4.0 Hz, 2H), 2.99 (d, *J* = 4.0 Hz, 3H).

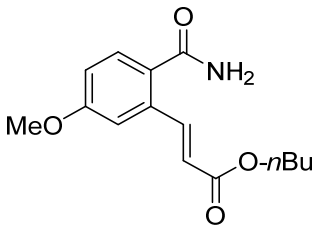
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.3, 166.3, 158.4, 142.6, 137.0, 132.5, 130.3, 129.9, 129.5, 127.6, 127.1, 121.1, 120.0, 114.6, 65.8, 62.9, 26.9.

HRMS (ESI): calc. for [($C_{19}H_{19}NO_4$)H] (M+H) 326.1392, measured 326.1400.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3312, 3057, 2931, 1725, 1637, 1540, 1310, 1138, 975, 760.

Rf(hexane/ethyl acetate = 2:1): 0.29.

Butyl (*E*)-3-(2-carbamoyl-5-methoxyphenyl)acrylate (3v).



White solid; eluent (34% ethylacetate in hexanes).The reaction scale is 100 mg (**1o**), 139 mg of product was isolated and yield is 91%.

^{1}H NMR (DMSO d_6, 400 MHz): δ 8.07 (d, J = 16.0 Hz, 1H), 7.85 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.37 (d, J = 4.0 Hz, 1H), 7.02 (dd, J = 8.0, 4.0 Hz, 1H), 6.63 (d, J = 16.0 Hz, 1H), 4.15 (t, J = 8.0 Hz, 2H), 3.84 (s, 3H), 1.62 (quintet, J = 8.0 Hz, 2H), 1.38 (m, 2H), 0.91 (t, J = 8.0 Hz, 3H).

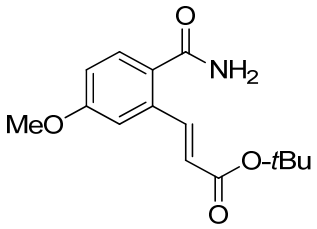
^{13}C NMR (DMSO d_6, 100 MHz): δ 169.9, 166.4, 160.2, 142.6, 134.0, 130.2, 129.7, 119.6, 115.9, 111.4, 63.9, 55.7, 30.5, 18.7, 14.0.

HRMS (ESI): calc. for [($C_{15}H_{19}NO_4$)Na] (M+Na) 300.1212, measured 300.1216.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3323, 2939, 1728, 1627, 1541, 1319, 1127, 968, 758.

Rf (hexane/ethyl acetate = 1:1): 0.29.

***tert*-Butyl (*E*)-3-(2-carbamoyl-5-methoxyphenyl)acrylate (3w**).



White solid; eluent (34% ethylacetate in hexanes).The reaction scale is 100 mg (**1o**), 134 mg of product was isolated and yield is 88%.

^{1}H NMR (DMSO d_6, 400 MHz): δ 7.99 (d, J = 16.0 Hz, 1H), 7.83 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.33 (d, J = 4.0 Hz, 1H), 6.99 (dd, J = 8.0, 4.0 Hz, 1H), 6.51 (d, J = 16.0 Hz, 1H), 3.83 (s, 3H), 1.48 (s, 9H).

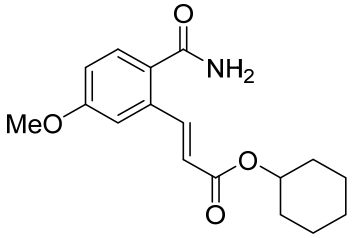
^{13}C NMR (DMSO d_6, 100 MHz): δ 169.9, 165.6, 160.2, 141.8, 134.0, 130.2, 129.6, 121.2, 115.8, 111.1, 80.1, 55.6, 28.1.

HRMS (ESI): calc. for [($C_{15}H_{19}NO_4$)Na] (M+Na) 300.1212, measured 300.1216.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3319, 2934, 1729, 1618, 1549, 1318, 1134, 971, 769.

Rf (hexane/ethyl acetate = 1:1): 0.29.

Cyclohexyl (*E*)-3-(2-carbamoyl-5-methoxyphenyl)acrylate (3x).



White solid; eluent (34% ethylacetate in hexanes).The reaction scale is 100 mg (**1o**), 150 mg of product was isolated and yield is 90%.

^{1}H NMR (DMSO d_6, 400 MHz): δ 8.07 (d, J = 16.0 Hz, 1H), 7.85 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.46 (s, 1H), 7.37 (d, J = 4.0 Hz, 1H), 7.01 (dd, J = 8.0, 4.0 Hz, 1H), 6.61 (d, J = 16.0 Hz,

1H), 4.78 (m, 1H), 3.84 (s, 3H), 1.87 - 1.83 (m, 2H), 1.72 - 1.69 (m, 2H), 1.54 - 1.47 (m, 1H), 1.40 (quintet, J = 4.0 Hz, 4H), 1.29 - 1.24 (m, 1H).

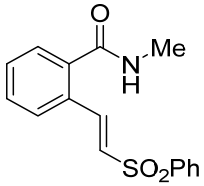
^{13}C NMR (DMSO d_6, 100 MHz): δ 169.9, 165.7, 160.2, 142.5, 134.0, 130.2, 129.6, 119.9, 116.0, 111.3, 72.2, 55.6, 31.4, 25.2, 23.5.

HRMS (ESI): calc. for [($C_{17}H_{21}NO_4$)Na] (M+Na) 326.1368, measured 326.1378.

FT-IR $\tilde{v}$ (cm^{-1}): 3319, 2927, 1722, 1625, 1545, 1310, 1130, 981, 860.

Rf (hexane/ethyl acetate = 1:1): 0.30.

(*E*)-N-Methyl-2-(2-(phenylsulfonyl)vinyl)benzamide (3y).



White solid; eluent (35% ethylacetate in hexanes).The reaction scale is 100mg (**1a**), 131mg of product was isolated and yield is 59%.

^{1}H NMR (DMSO d_6,400 MHz): δ 8.51 (s, 1H), 7.91 (dd, J = 8.0, 4.0 Hz, 1H), 7.90(d, J = 12.0 Hz, 1H), 7.85 (t, J = 4.0 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.67 (t, J = 8.0 Hz, 2H), 7.57 (d, J = 12.0 Hz, 1H), 7.50 – 7.48 (m, 3H),2.79 (d, J = 4.0 Hz, 3H).

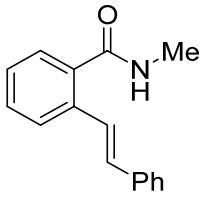
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.1, 140.5, 140.3, 136.9, 133.5, 130.9, 130.7, 130.6, 129.5, 129.3, 128.6, 127.8, 127.7, 27.1.

HRMS (ESI): calc. for [($C_{16}H_{15}NO_3S$)Na] (M+Na) 324.0670, measured 324.0676.

FT-IR $\tilde{v}$ (cm^{-1}): 3210, 3053, 2925, 2363, 1694, 1642, 1616, 1296, 1135, 1075, 999, 741.

Rf(hexane/ethyl acetate = 1:1): 0.39.

(*E*)-*N*-Methyl-2-styrylbenzamide (3z).



White solid; eluent (29% ethylacetate in hexanes).The reaction scale is 100mg (**1a**), 76mg of product was isolated and yield is 43%.

^{1}H NMR ($CDCl_3$, 400 MHz):δ7.72 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H),7.43 (d, *J* = 4.0 Hz, 1H),7.40 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 2H),7.27 (t, *J* = 8.0 Hz, 2H),7.04 (d, *J* = 16.0 Hz, 2H), 5.81 (s, 1H), 3.00 (d, *J* = 4.0 Hz, 3H).

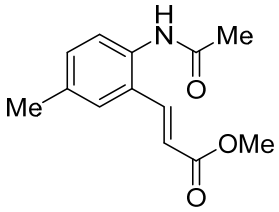
^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.4, 135.3, 135.1, 134.7, 127.1, 121.8, 120.3, 120.0, 117.8, 110.6, 110.3, 61.6, 31.9, 15.8.

HRMS (ESI): calc. for [($C_{16}H_{15}NO$)H] (M+H) 238.1232, measured 238.1231.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3309, 3052, 2930, 2361, 1625, 1527, 1310, 1154, 953, 755.

Rf (hexane/ethyl acetate = 2:1): 0.32.

Methyl (*E*)-3-(2-acetamido-5-methylphenyl)acrylate (5a).



White solid; eluent (31% ethylacetate in hexanes).The reaction scale is 100mg (**4a**), 91mg of product was isolated and yield is 58%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ7.79 (d, *J* = 16.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.50 (s, 1H), 7.35 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.38 (d, *J* = 16.0 Hz, 1H), 3.80 (s, 3H), 2.34 (s, 3H), 2.21 (s, 3H).

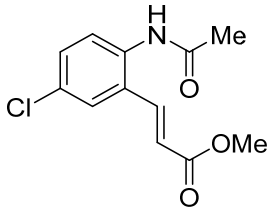
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2, 167.7, 139.8, 135.7, 133.4, 131.5, 127.9, 127.2, 125.7, 119.4, 51.7, 23.8, 20.9.

HRMS (ESI): calc. for [($C_{13}H_{15}NO_3$)Na] (M+Na) 256.0950, measured 256.0960.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3265, 3068, 2950, 1703, 1647, 1526, 1430, 1268, 1229,1030, 974, 815.

Rf (hexane/ethyl acetate = 2:1): 0.28.

Methyl (*E*)-3-(2-acetamido-5-chlorophenyl)acrylate (5b).



White solid; eluent (29% ethylacetate in hexanes).The reaction scale is 100mg (**4b**), 70mg of product was isolated and yield is 47%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 16.0 Hz, 1H), 7.49 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.27 (s, 1H), 6.38 (d, *J* = 16.0 Hz, 1H), 3.80 (s, 3H), 2.22 (s, 3H).

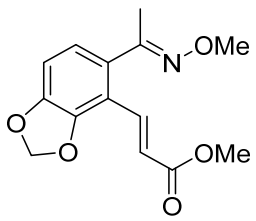
^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.9, 166.8, 138.2, 134.3, 131.2, 130.6, 128.9, 126.7, 126.4, 121.4, 51.9, 24.1.

HRMS (ESI): calc. for [($C_{12}H_{12}ClNO_3$)Na] (M+Na) 276.0403, measured 276.0406.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3268, 3080, 2950, 1710, 1653, 1517, 1517, 1268, 1229,1022, 973, 819.

Rf (hexane/ethyl acetate = 2:1): 0.31.

Methyl(*E*)-3-(5-((E)-1-(methoxyimino)ethyl)benzo[*d*][1,3]dioxol-4-yl)acrylate (7a).



White solid; eluent (7% ethylacetate in hexanes).The reaction scale is 100mg (**6a**), 80mg of product was isolated and yield is 56%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ7.70 (d, *J* = 16.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 16.0 Hz, 1H), 6.05 (s, 2H), 3.95 (s, 3H), 3.77 (s, 3H), 2.15 (s, 3H).

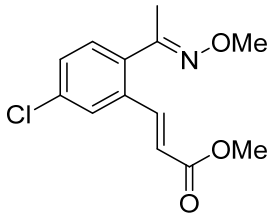
^{13}C NMR ($CDCl_3$, 100 MHz): δ167.7, 155.1, 147.9, 147.2, 137.8, 132.3, 122.5, 122.2, 115.9, 109.1, 101.7, 61.9, 51.6, 17.1.

HRMS (ESI): calc. for [($C_{14}H_{15}NO_5$)H] (M+H) 278.1028, measured 278.1034.

FT-IR $\tilde{\nu}$ (cm^{-1}): 2902, 1713, 1629, 1526, 1463, 1244, 1181, 1038, 864, 809.

Rf (hexane/ethyl acetate = 90:10): 0.31.

Methyl (*E*)-3-(5-chloro-2-((*E*)-1-(methoxyimino)ethyl)phenyl)acrylate (7b).



Colourless liquid; eluent (5% ethylacetate in hexanes).The reaction scale is 100mg (**6b**), 61mg of product was isolated and yield is 42%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ7.86 (d, *J* = 16.0 Hz, 1H), 7.56 (s, 1H), 7.34 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 6.33 (d, *J* = 16.0 Hz, 1H), 3.97 (s, 3H), 3.79 (s, 3H), 2.16 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.9, 154.3, 142.3, 136.2, 134.8, 134.7, 130.1, 129.7, 127.1, 120.2, 62.2, 51.8, 16.3.

HRMS (ESI): calc. for [($C_{13}H_{14}ClNO_3$)H] (M+H) 268.0740, measured 268.0745.

FT-IR $\tilde{\nu}$ (cm^{-1}): 2892, 1719, 1620, 1521, 1469, 1241, 1181, 1038, 864, 817.

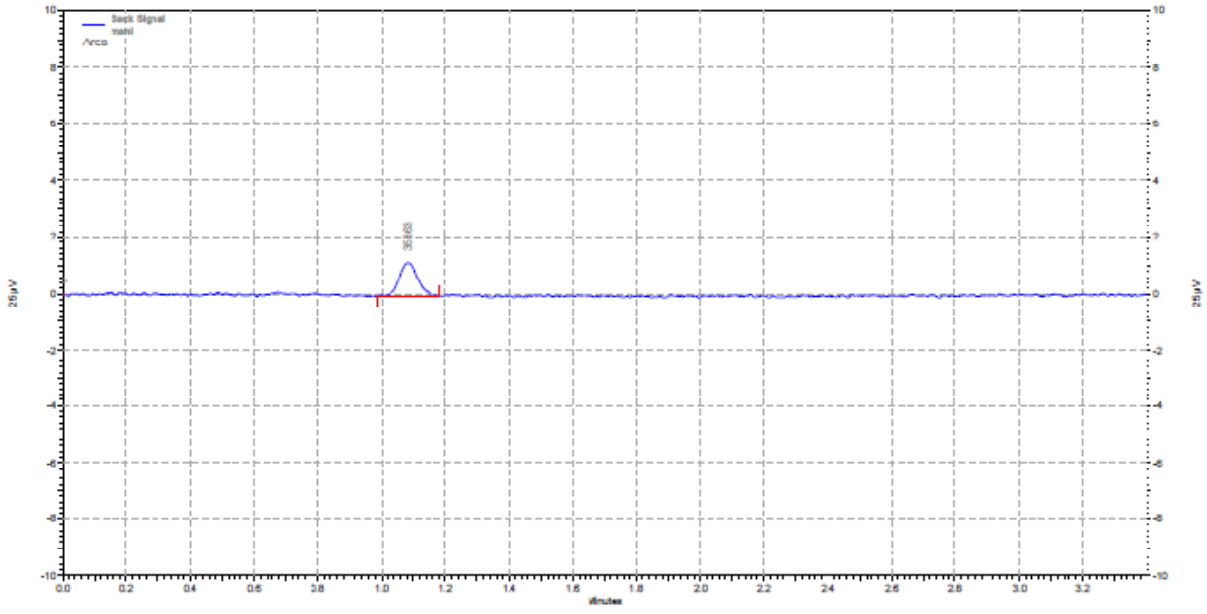
Rf (hexane/ethyl acetate = 90:10): 0.53.

4A.14 Mechanistic Studies

4A.14.1 Procedure for the Determination of H_2 gas Evolution by GC.

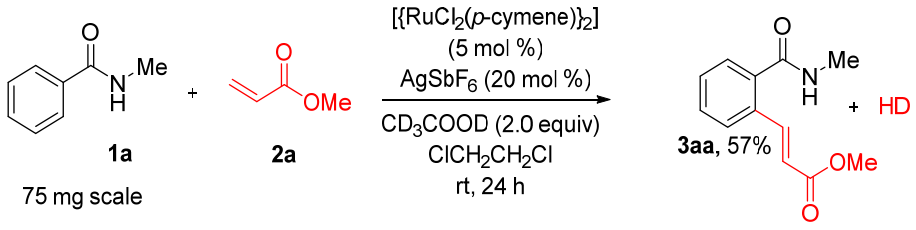
A 25-mL schlenk tube with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube, were then added *N*-methyl benzamide (**1a**) (100 mg), methyl acrylate (**2a**) (2.0 equiv), acetic acid (2.0 equiv) and 1,2-dichloroethane (3.0 mL) via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, the septum was completely covered by Teflon tape. Then, the reaction mixture was allowed to stir at room temperature (~ 24 °C) for 24 h. After that, the gaseous reaction mixture was taken by the syringe and injected into the gas chromatograph (GC) equipped with a TCD detector (Agilent 7890). The characteristic peak for H_2 gas was observed in the exact region (retention time 1-1.2 minutes).

Gas Chromatograph Spectrum



4A.14.2 Procedure for the Determination of HD Evolution by Isotope-Ratio Mass Spectrometry (IR-MS).

A 10-mL glass tube with a screw cap containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube, were then added *N*-methyl benzamide (**1a**) (75 mg), methyl acrylate (**2a**) (2.0 equiv), acetic acid (2.0 equiv) and 1,2-dichloroethane (2.0 mL) via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. Then, the reaction mixture was allowed to stir at room temperature (~ 24 °C) for 24 h. IR-MS (Delta V Plus model) analysis was done with the reaction mixture.



In the spectra, brown line indicating the molecular mass is 2 and it is for H_2 gas.

The green line indicating that the molecular mass is 3 and it is for HD gas.

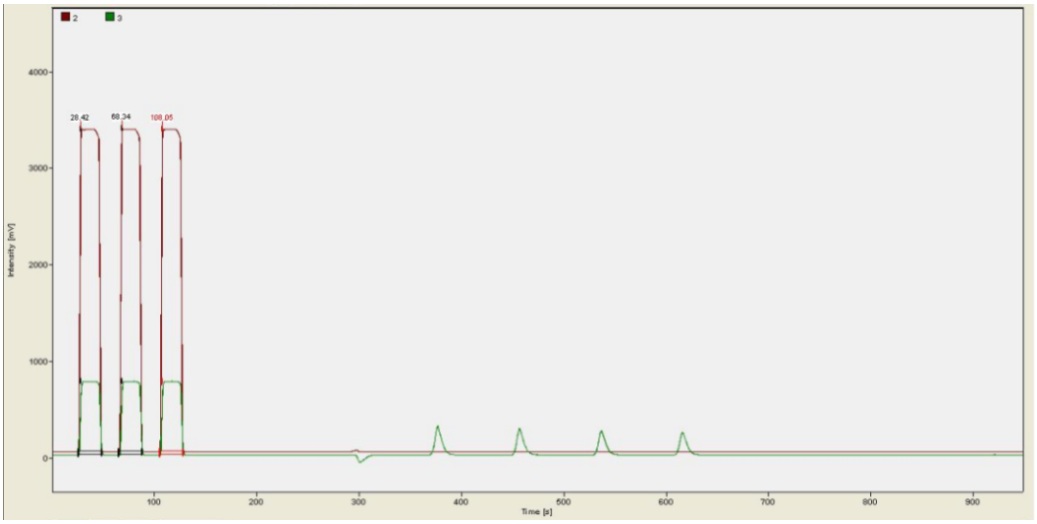
The first 3 peaks are corresponding to the reference gas. The reference gas has both (H_2+HD) mixtures. So that, we observed both brown and green colour peak in a particular ratio. The remaining 4 peaks are corresponding to the reaction mixture. Here, only green colour peaks are observed which clearly indicates that HD gas was formed in the reaction. Generally, in the IR-MS analysis, the instrument takes reference gas 3 times and the reaction mixture gas for 4 times consecutively. Thus, we have observed 3 peaks in the reference region followed by 4 peaks for the reaction mixture.

(**Notes**: It is important to note that the intensity of HD detection in the IR-MS spectrum for the four consecutive injection of reaction mixture is in decreasing order (see the spectra 1 and 2). It is expected that in the first injection concentration of HD is high and in the following peaks intensity could decrease a little bit.

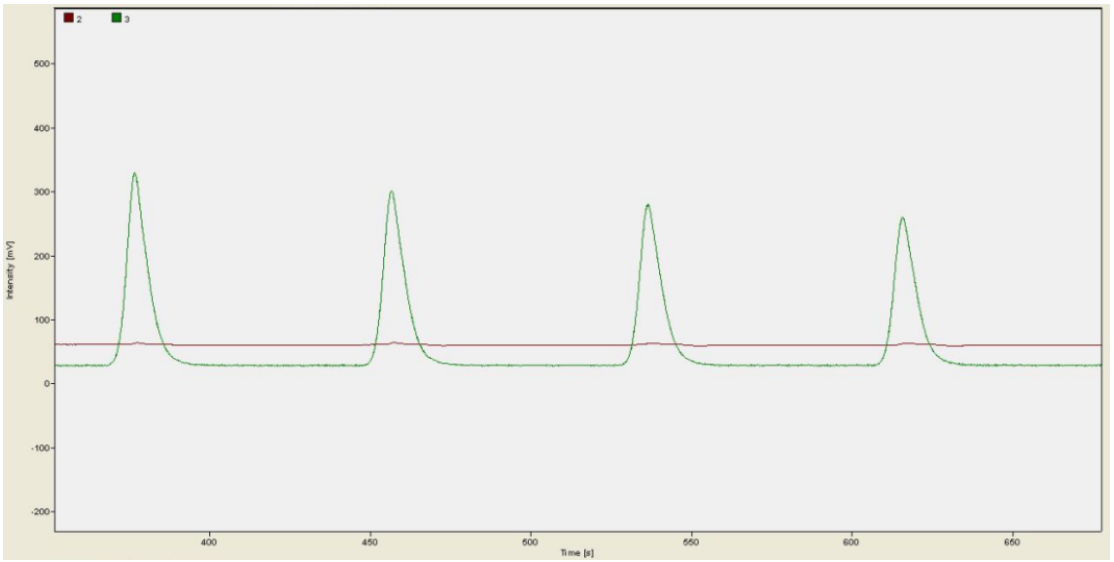
Next, we have tried the same reaction in 150 mg scale of *N*-methyl benzamide (**1a**). Previously, we have done in 75 mg scale corresponding to **1a**. Interestingly, the intensity of HD gas is also

increased almost twice in the IR-MS spectra (see spectra 1 and 2). For 75 mg scale reaction, the intensity of HD gas was around 330 mV. For 150 mg scale reaction, the intensity of HD gas was increased 750 mV. This result clearly indicates that the amount of HD gas production in the reaction is highly depends on the concentration of the reaction.

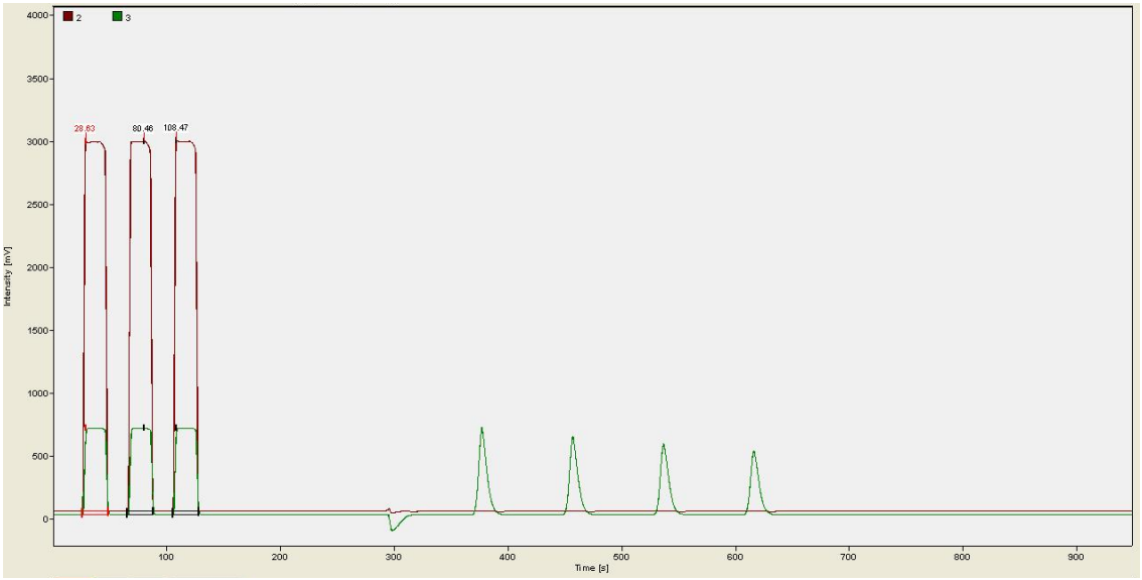
IR-MS Spectra of 75 mg scale reaction (spectra 1)



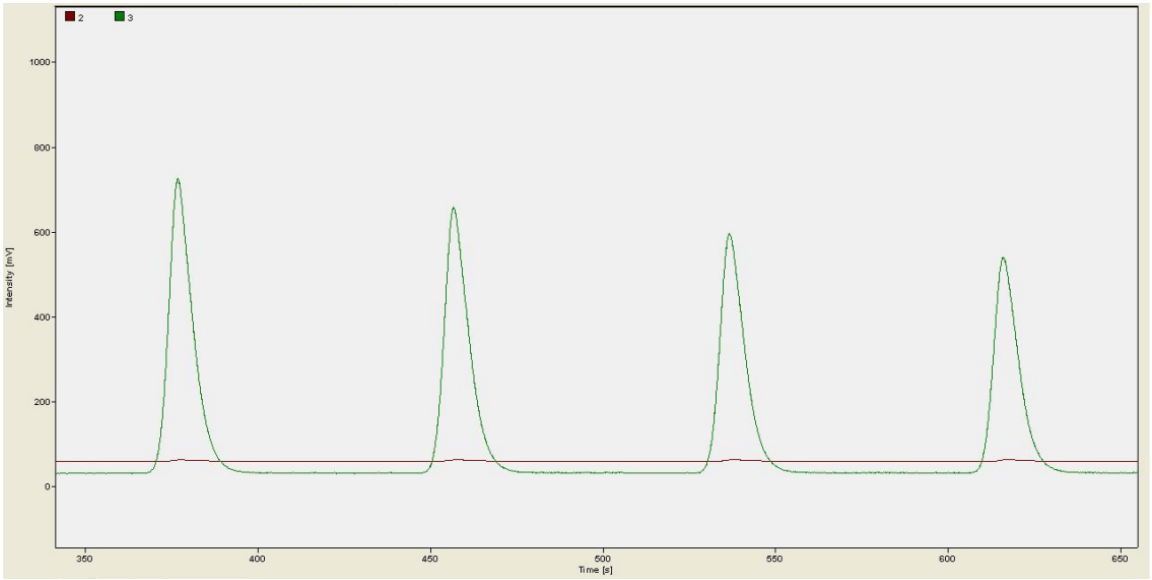
Maximized area for characteristic peak in spectra 1



IR-MS Spectra of 150 mg scale reaction (spectra 2)

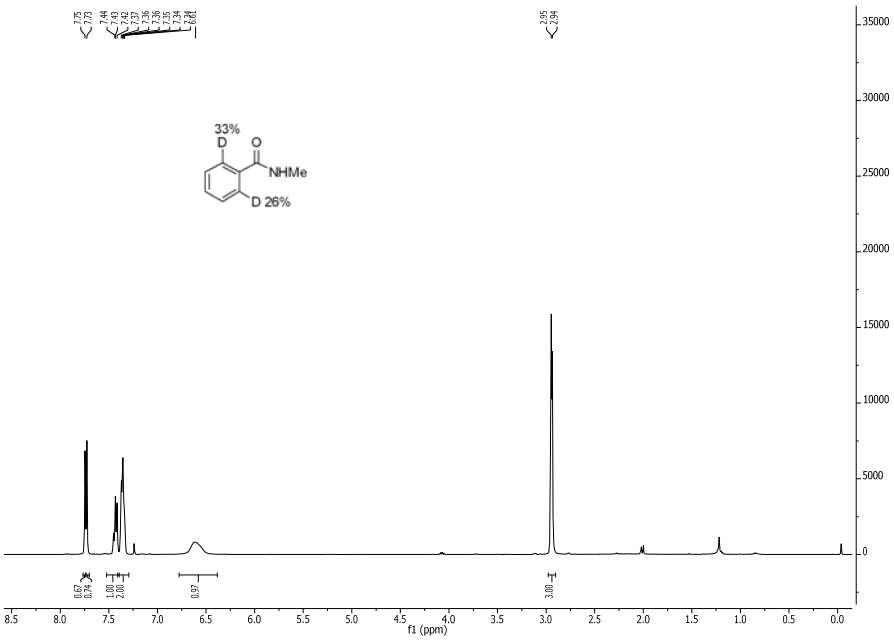


Maximized area for characteristic peak in spectra 2

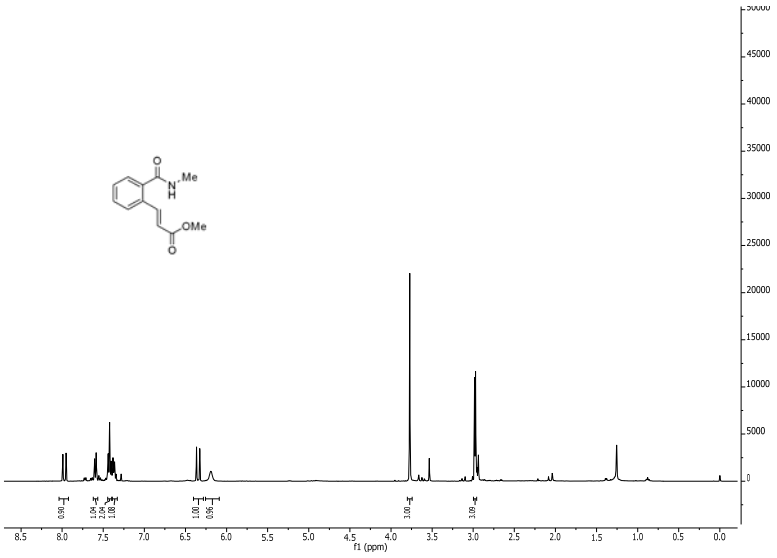


4A.14.3 NMR Spectra of the HD Evolution reaction mixture.

^{1}H NMR Spectra of Compound **1a** obtained at the end of the reaction. Deuterium incorporation was observed at both ortho carbons of **1a**.

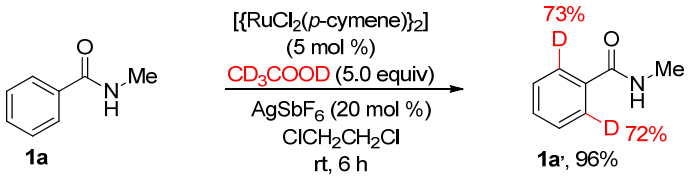


^{1}H NMR Spectra of Compound **3aa** obtained at the end of the reaction. No deuterium incorporation was observed in the compound.

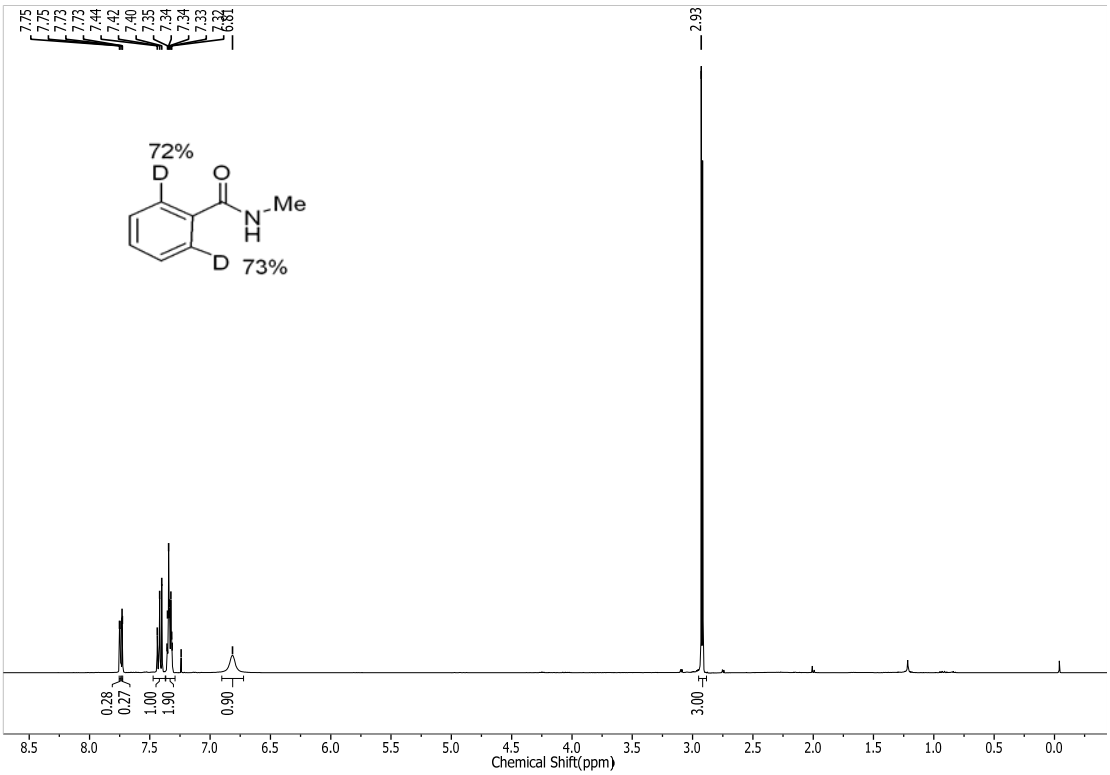


4A.14.4 Deuterium studies

To know the feasibility of C–H bond activation of aromatic amide at room temperature, the following deuterium labelling experiment was done. Treatment of **1a** with CD_3COOD in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) in 1,2-dichloroethane at room temperature for 6 h gave product **1a'** in 96% yield with 72% and 73% of deuterium incorporation at the both *ortho* carbons. It clearly indicates that the *ortho* C–H bond cleavage of aromatic amide in intermediate **9** is a reversible process.



^{1}H NMR Spectra of Compound **1a'.**

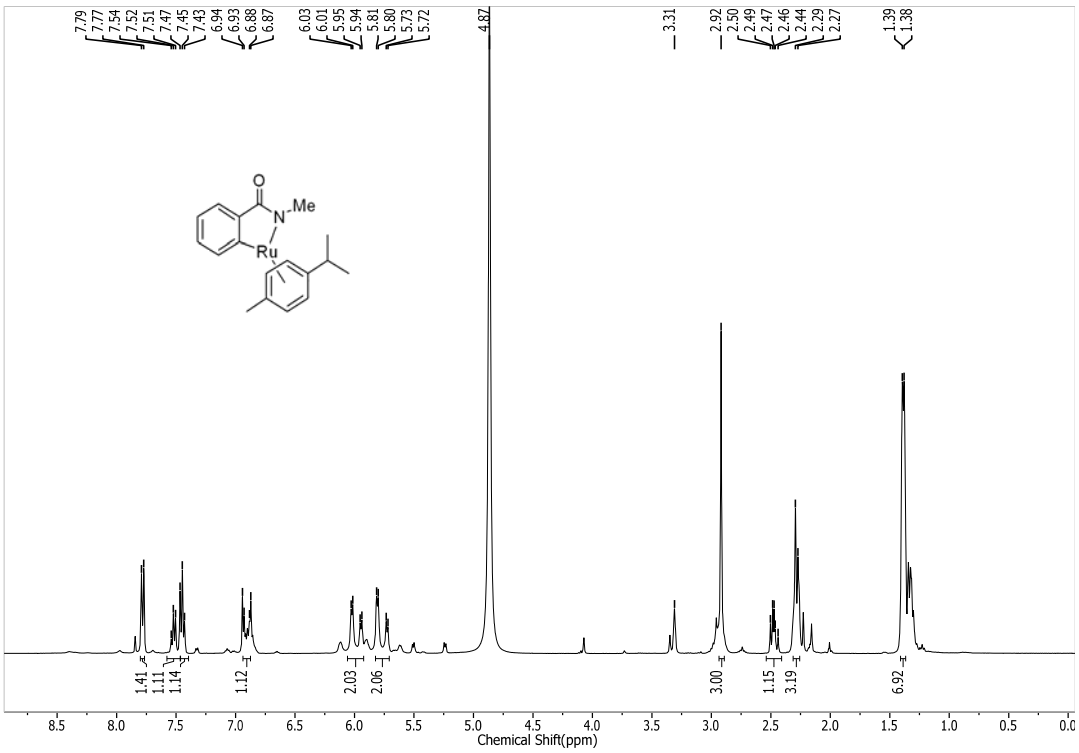


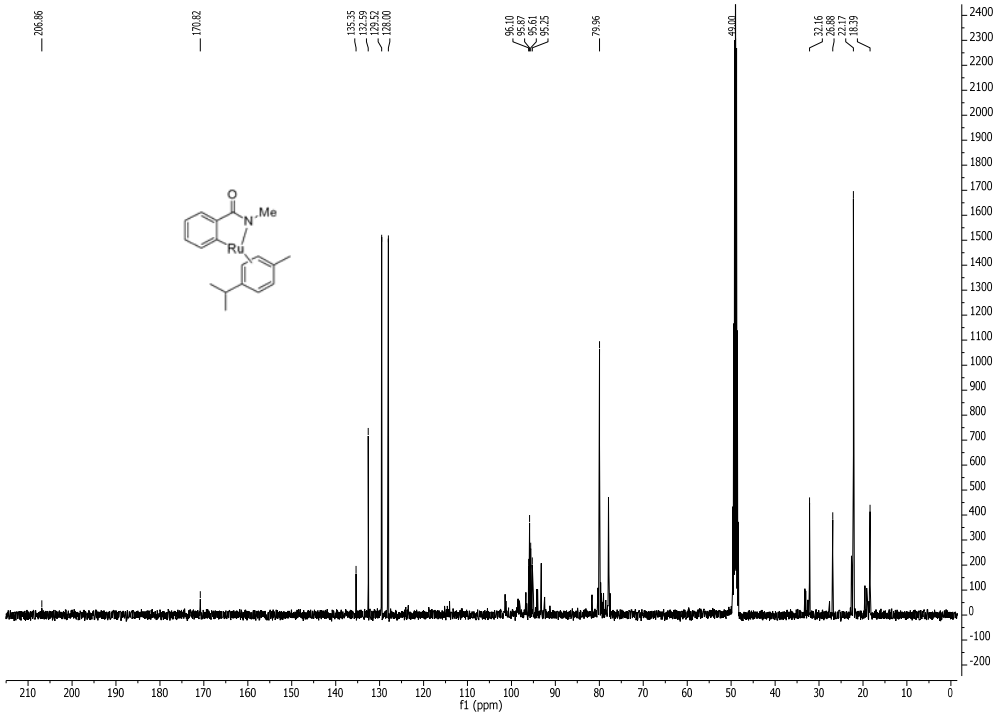
4A.14.5 Procedure for the Preparation of a Five-Membered Ruthenacycle Intermediate 9.

A 25-mL schlenk tube with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (50 mg), and $AgSbF_6$ (4.0 equiv) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube, were then added benzamide **1a** (1.0 equiv), AcOH (2.0 equiv) and $ClCH_2CH_2Cl$ (2.0 mL) via syringe and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that the septum was completely covered by Teflon tape. Then, the reaction mixture was allowed to stir at room temperature for 24 h. After the reaction mixture was diluted with methanol, filtered through Celite and the filtrate was concentrated and taken for further analysis without any further purification. We have tried to get a single crystal. However, we could not make it. The NMR spectra was recorded with the crude reaction mixture without further purification.

NMR Data

^{1}H and ^{13}C NMR Spectra of Compound **9.**

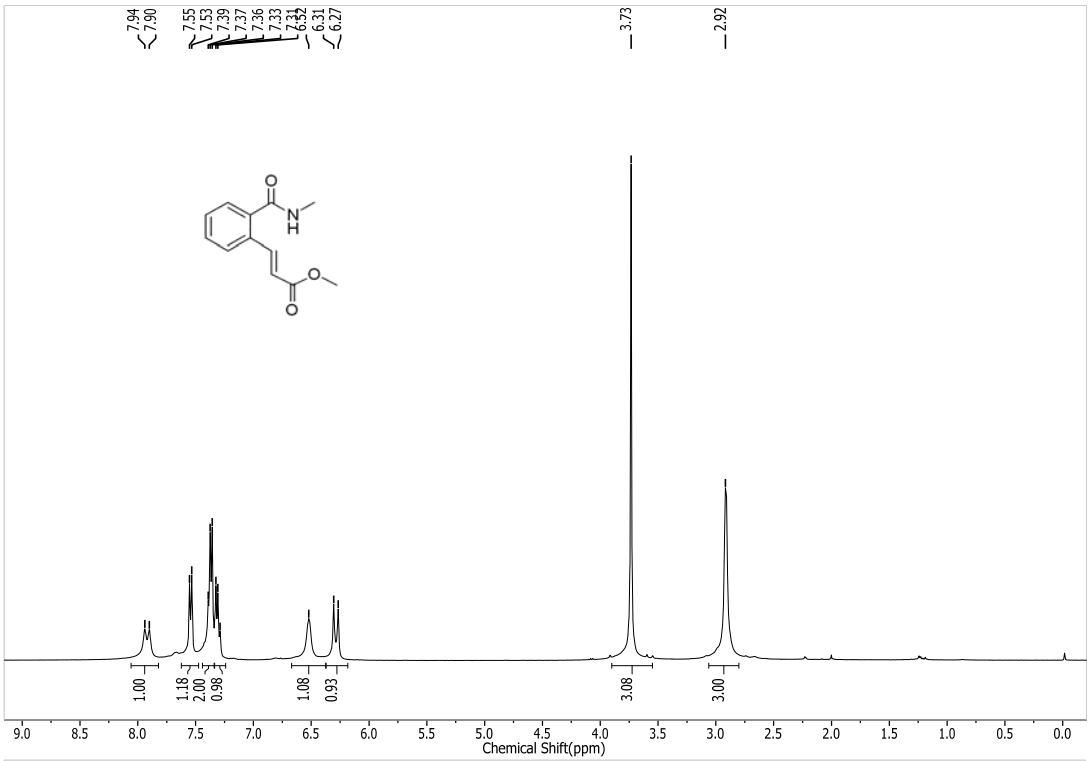


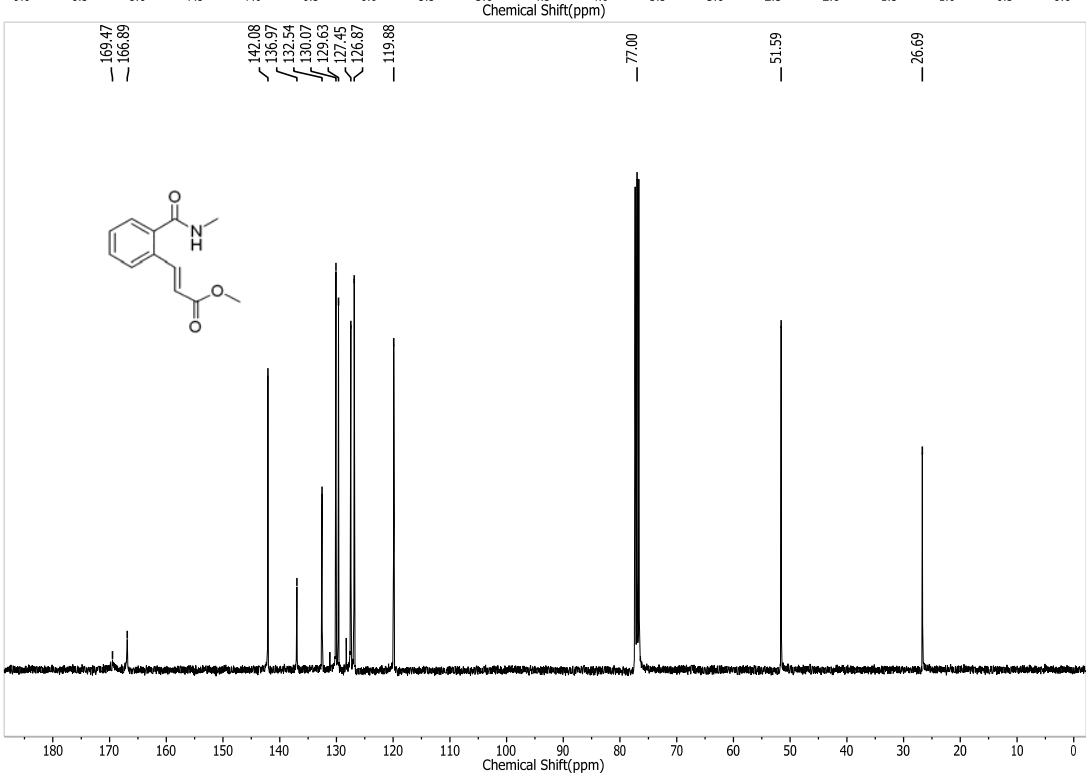


Note: In ^{13}C NMR, a characteristic C-Ru peak found at δ 206.86 due to the deshilding of C-Ru.

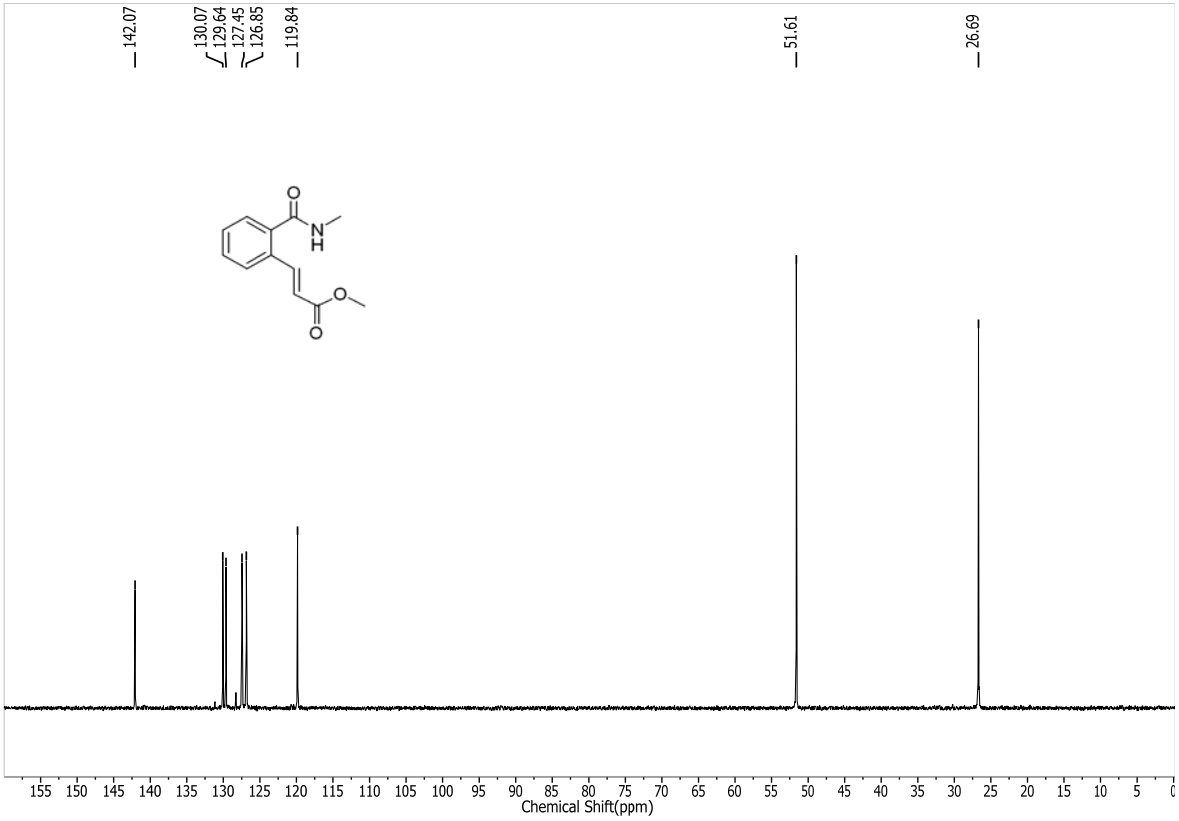
4A.15 Spectral Copies of Selected Compounds

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

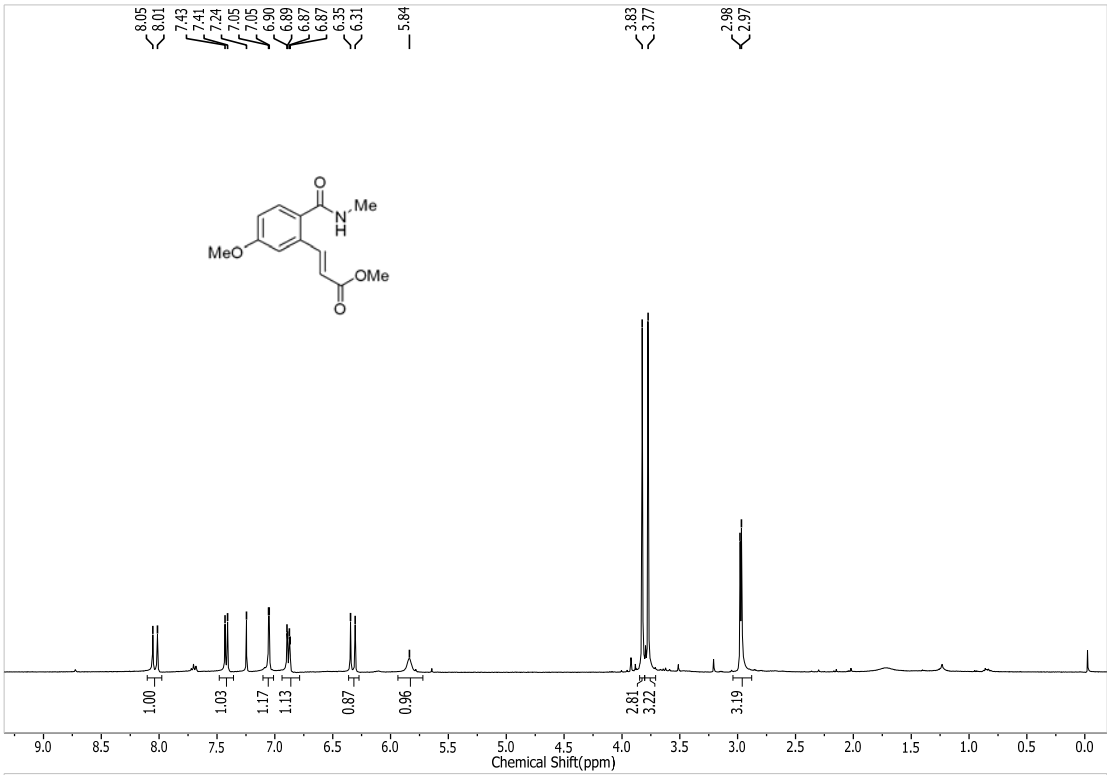


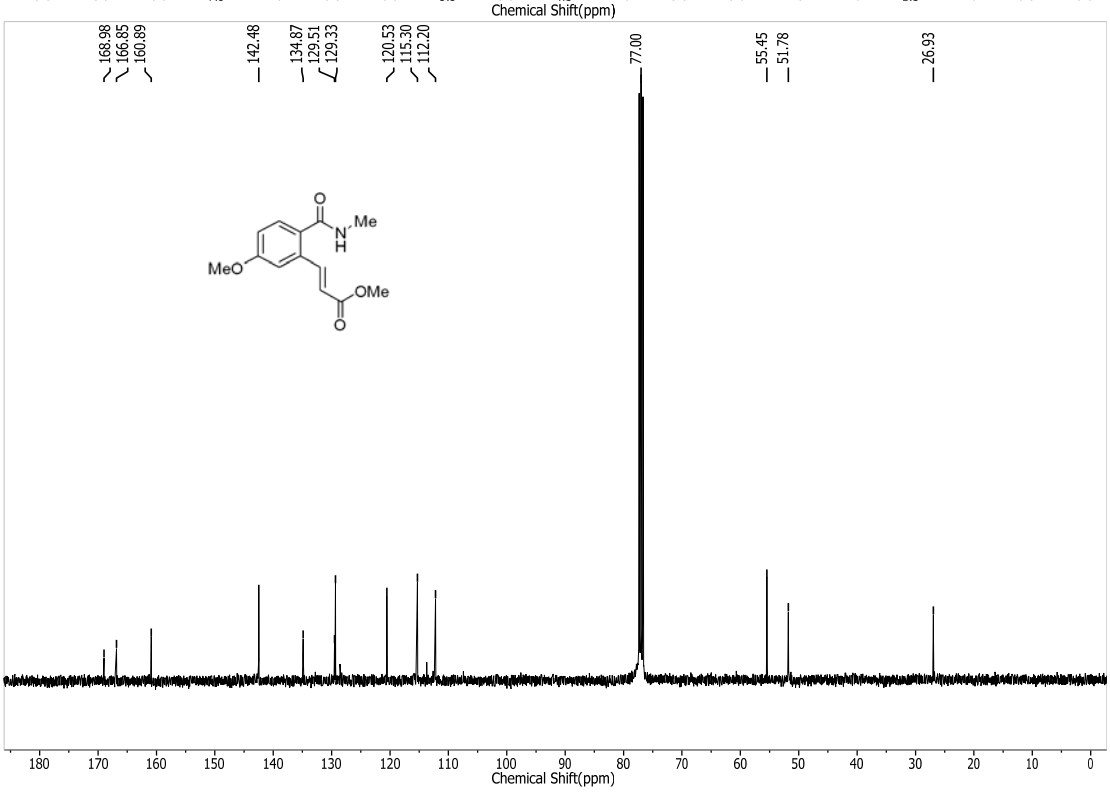


DEPT (135) NMR Spectrum of Compound 3a.

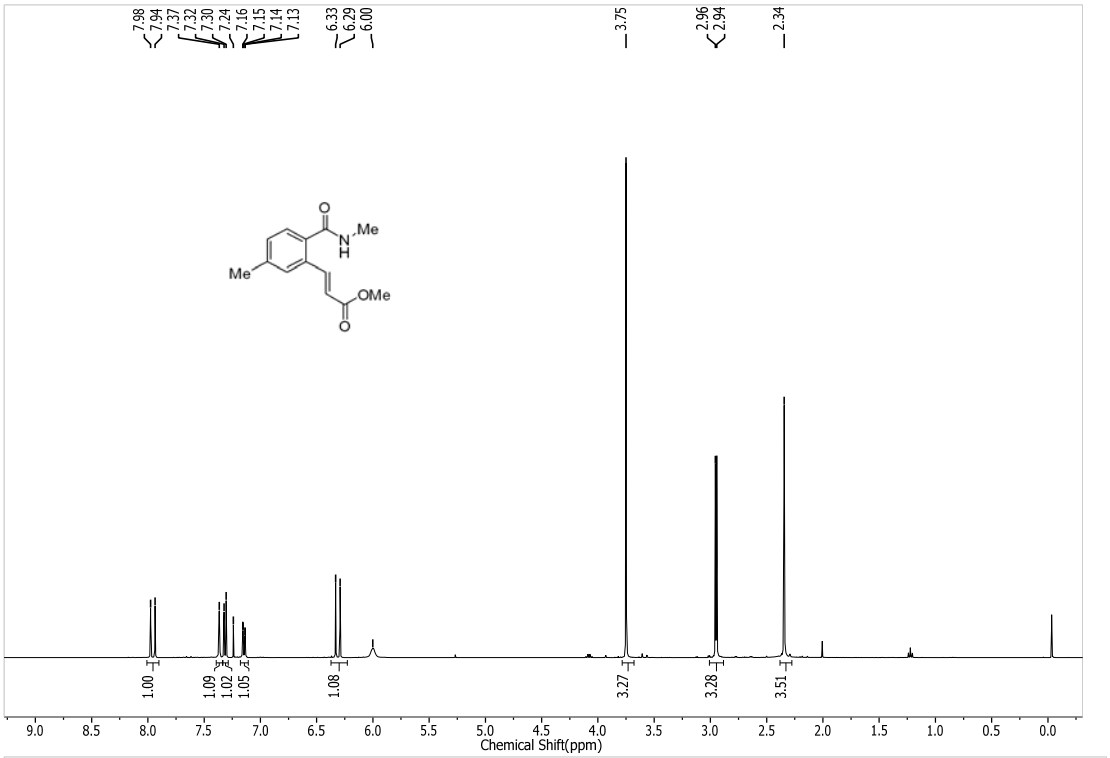


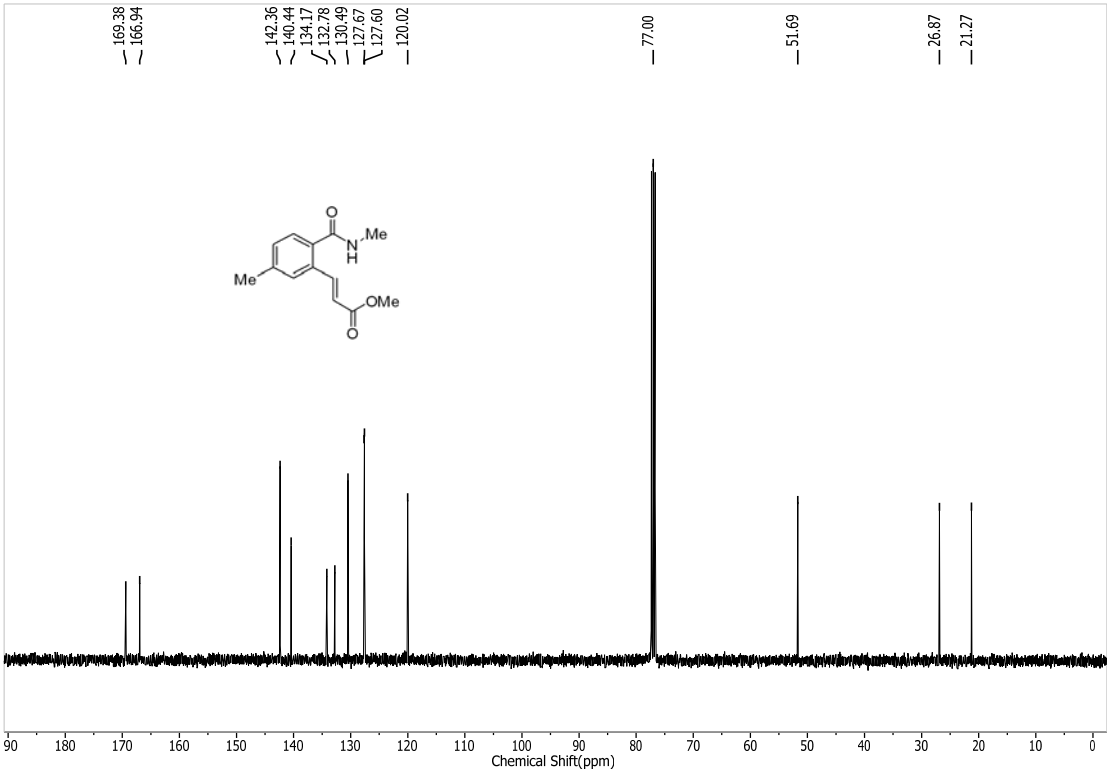
^{1}H and ^{13}C NMR Spectra of Compound 3b.



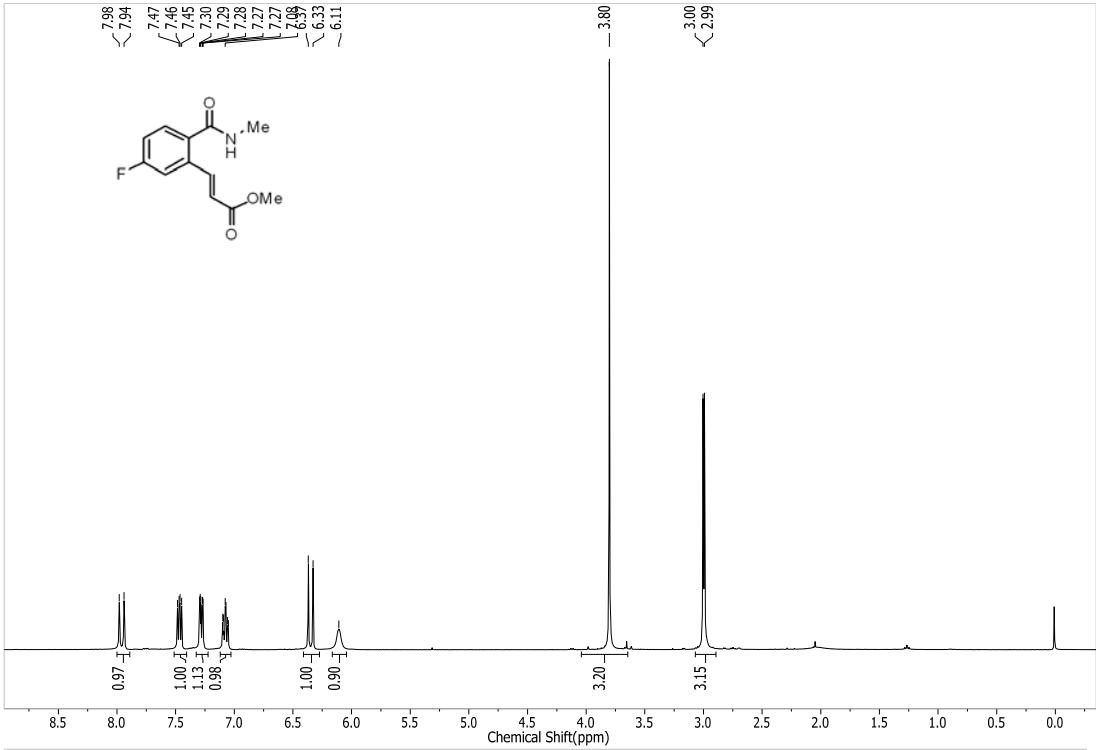


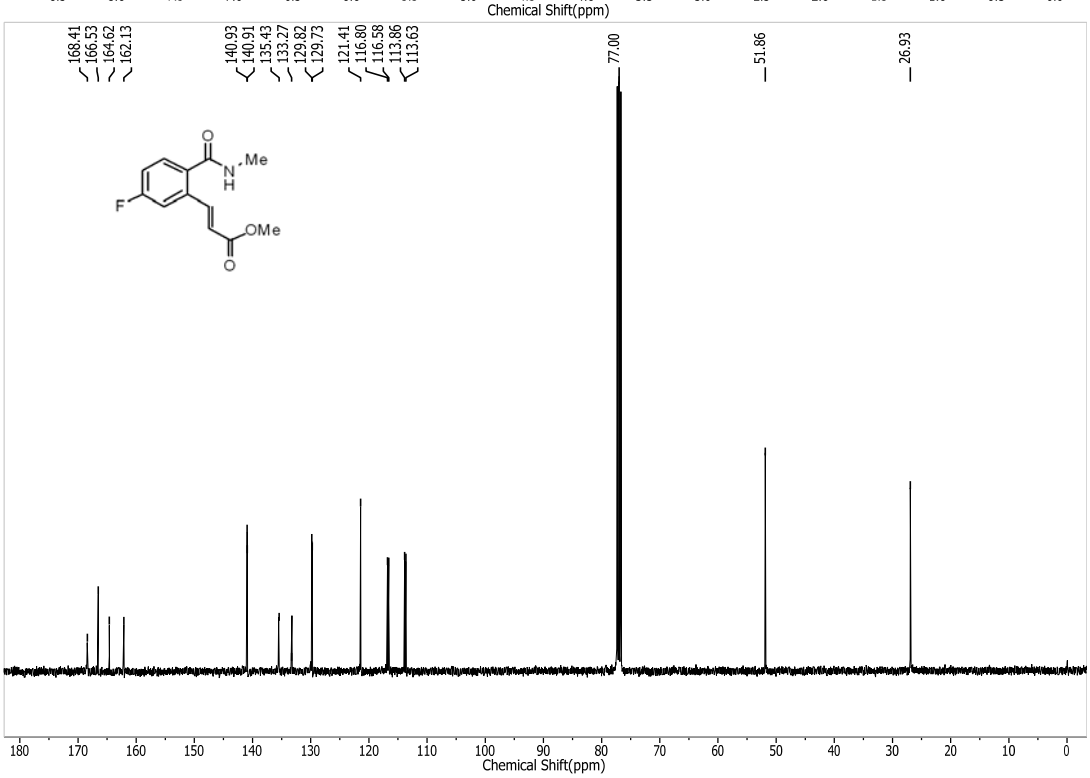
^{1}H and ^{13}C NMR Spectra of Compound 3c.



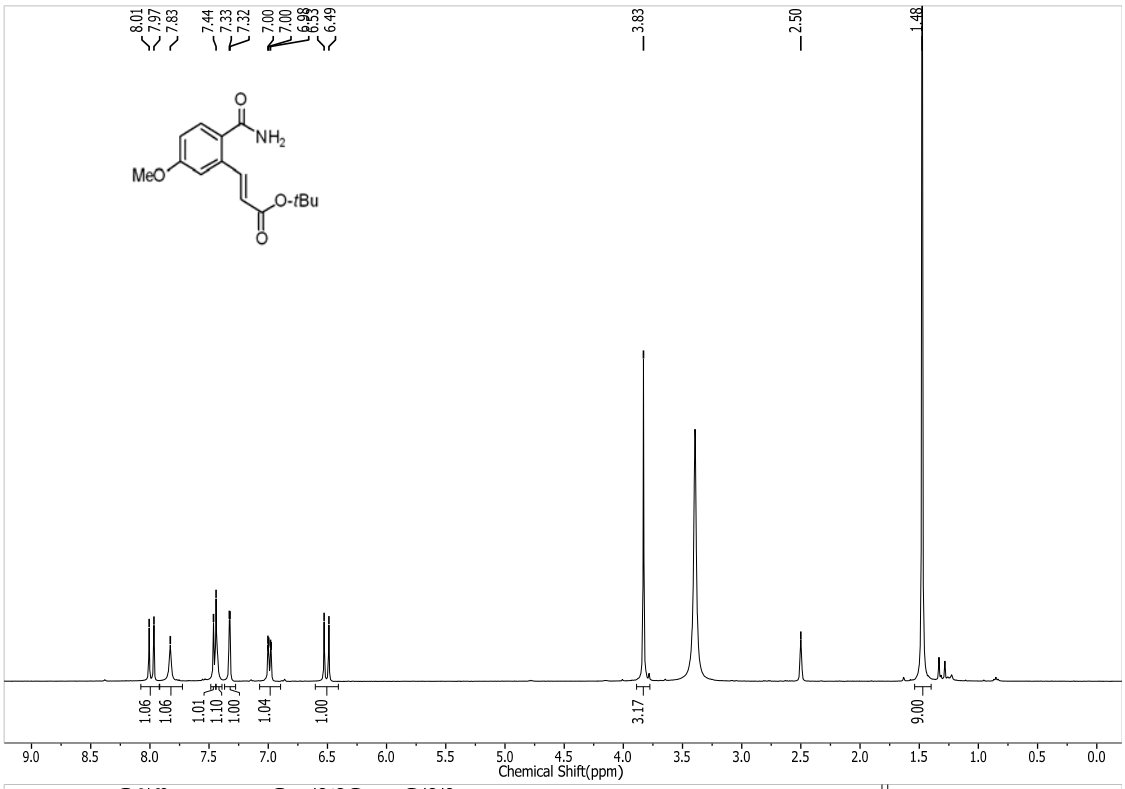


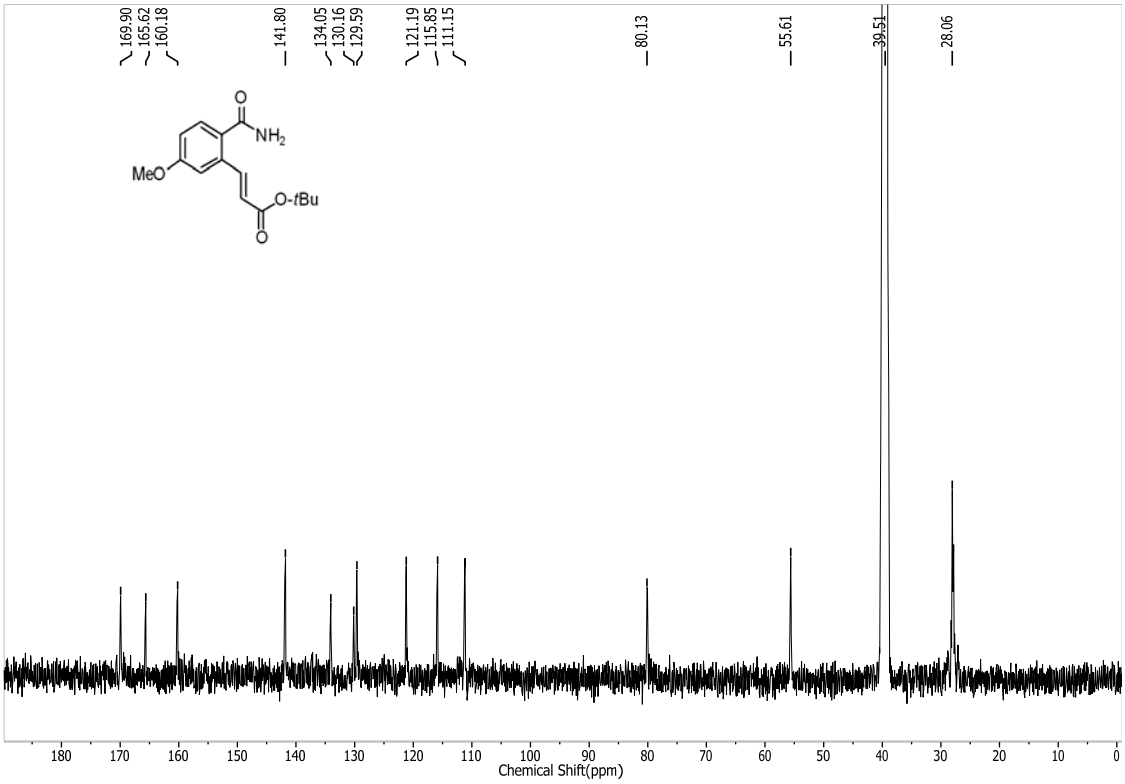
^{1}H and ^{13}C NMR Spectra of Compound 3d.



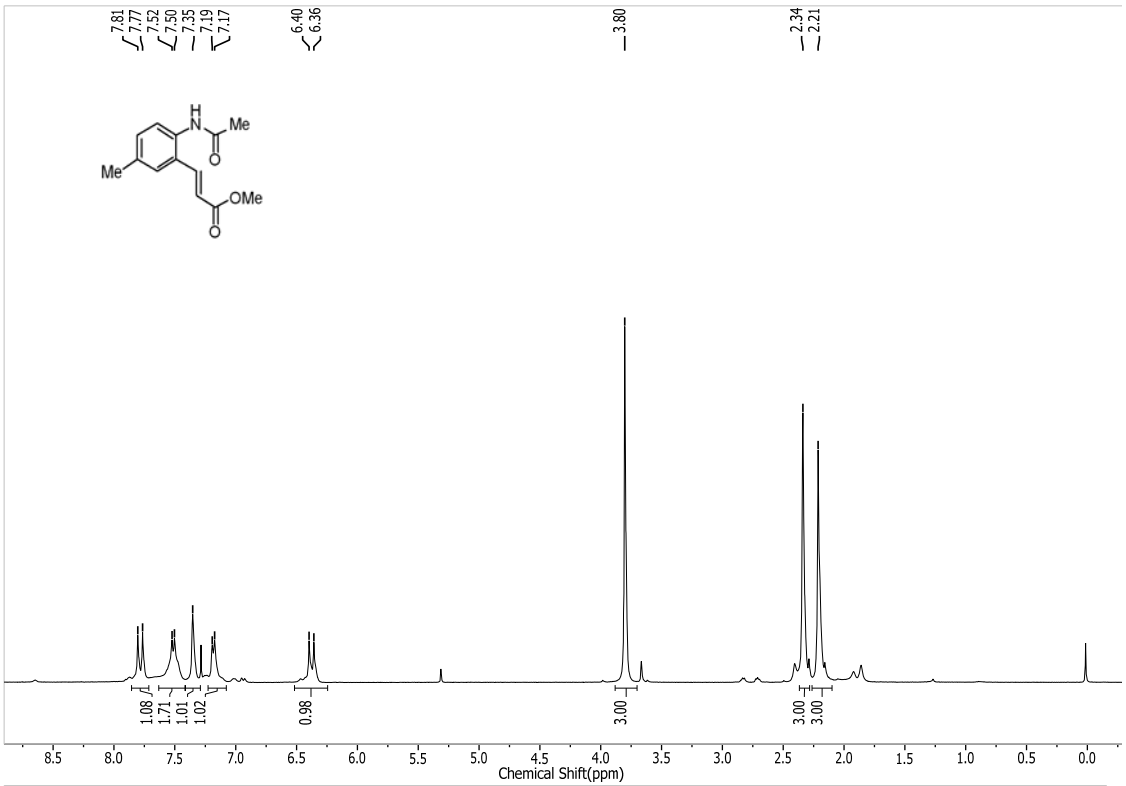


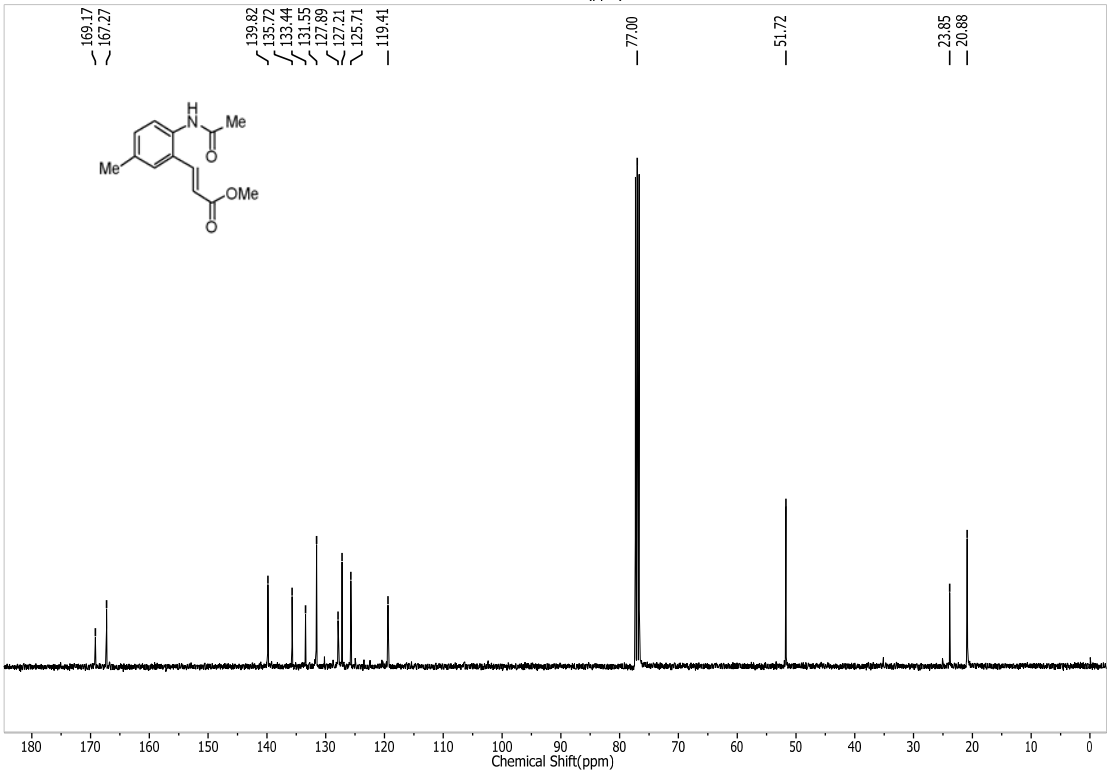
^{1}H and ^{13}C NMR Spectra of Compound **3w.**



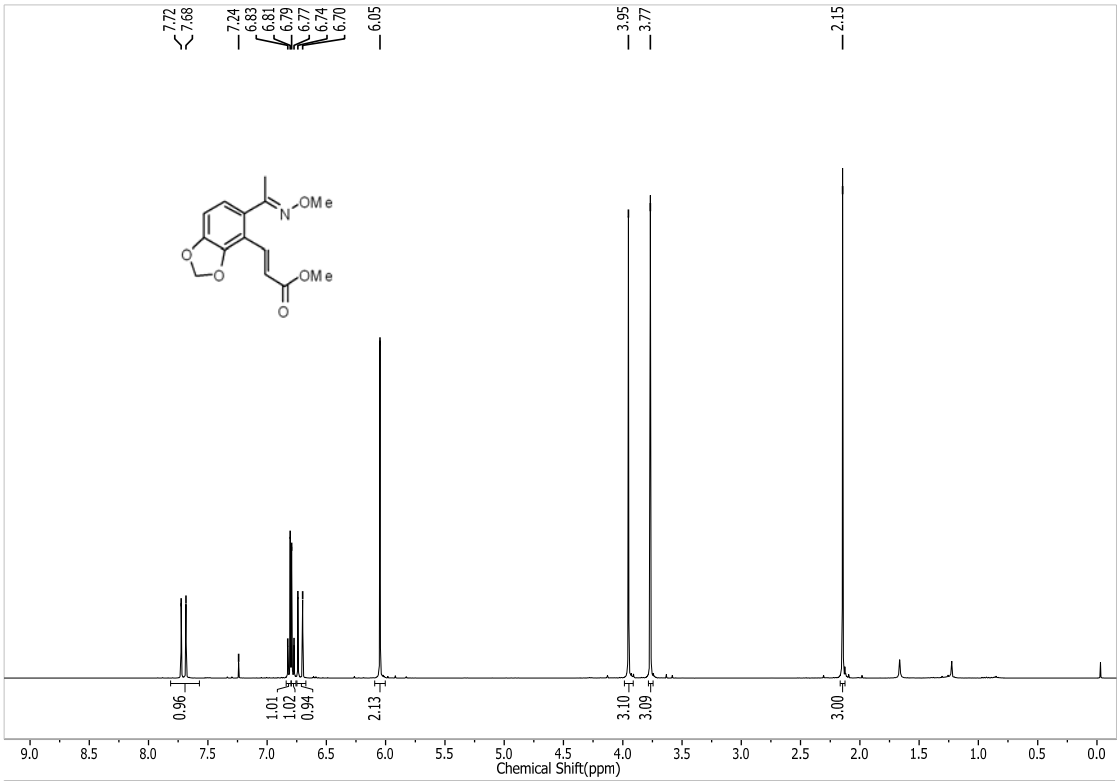


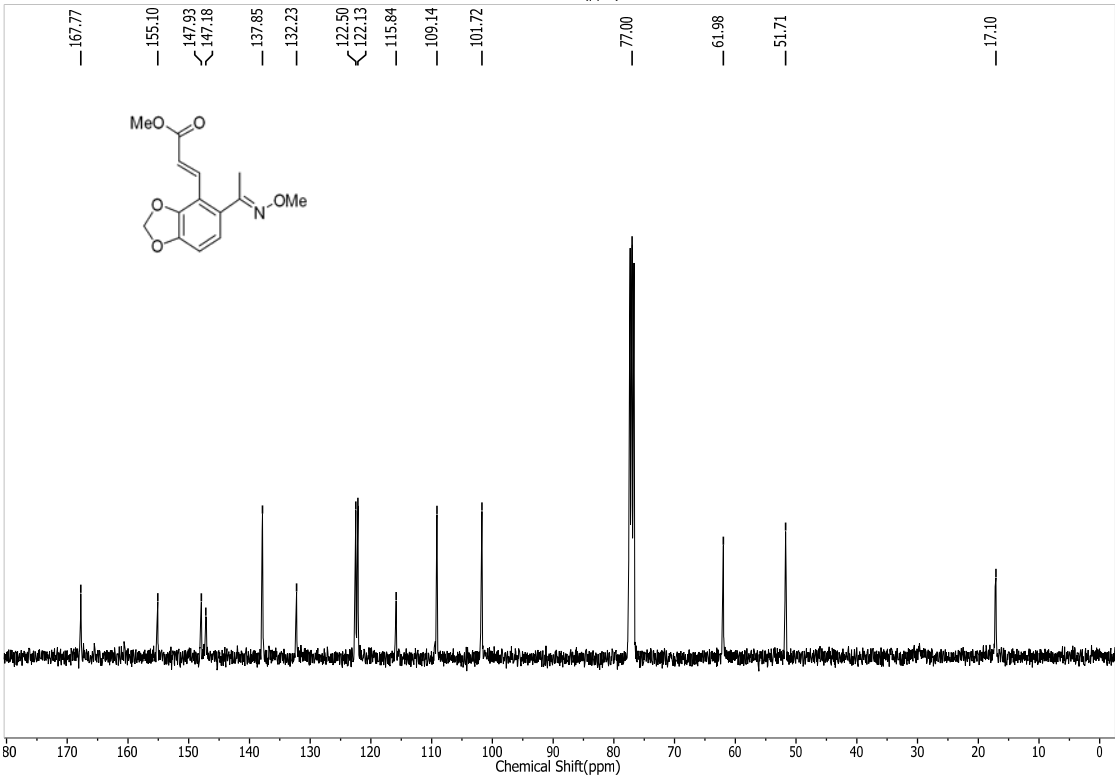
^{1}H and ^{13}C NMR Spectra of Compound **5a.**





^{1}H and ^{13}C NMR Spectra of Compound **7a.**





Section 4B: Ruthenium (II)-Catalyzed Redox-Neutral Cyclization of Benzimidates with Alkenes with Hydrogen Evolution

4B.1 Introduction

Isoindoles are an important class of heterocyclic compounds, and their structural units are present in various natural products, biologically active molecules, and dyes (Figure 1). In addition, it also shows excellent fluorescent and electroluminescent properties.[1a]

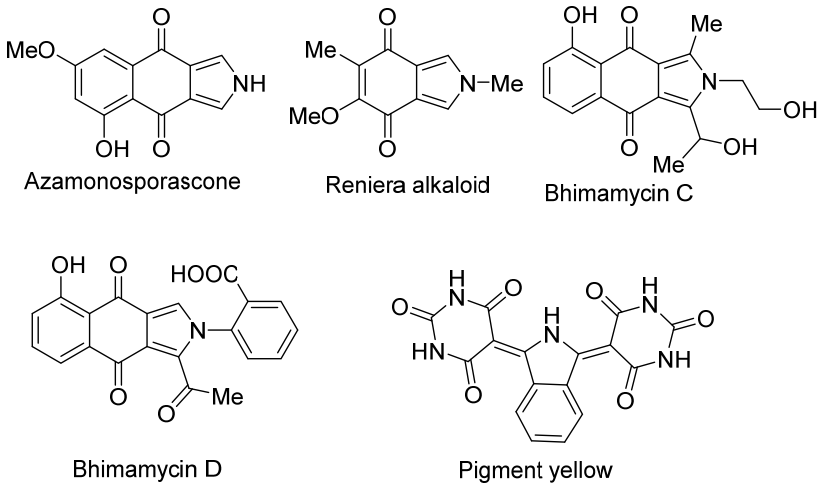
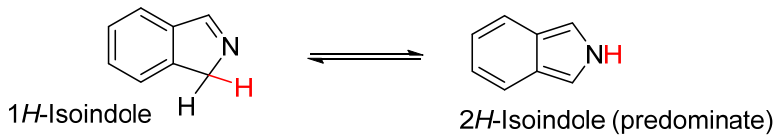


Figure 1: Selected biologically active Isoindole derivatives.

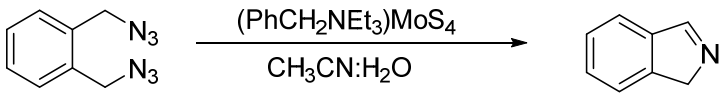
The isoindole derivatives exist in two tautomeric forms such as 1*H*-isoindole and 2*H*-isoindole (Scheme 4B.1). Generally, in the solution, 2*H*-isoindole is a more predominant tautomer than the 1*H*-isoindole.[1b]



Scheme 4B.1: Tautomerism of Isoindole.

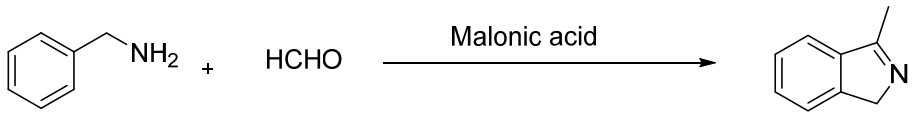
Due to the high stability, several reports are available in the literature to synthesize 2*H*-isoindoles. However, only a few reports are available for synthesizing 1*H*-isoindoles due to its lower stability.[1a-b] Traditionally, 1*H*-isoindoles are prepared by the intramolecular reduction of

diazides in the presence of the tetrathiomolybdate complex. In the reaction, 1*H*-isoindole was observed in lower yield (Scheme 4B.2).[1c]



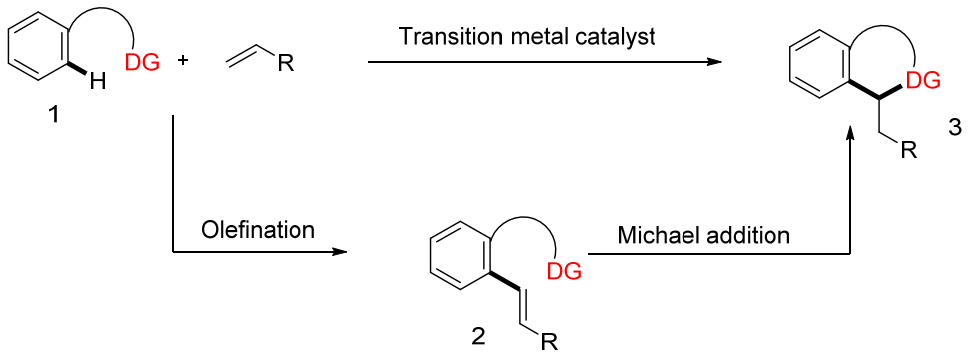
Scheme 4B.2: Tetrathiomolybdate complex catalyzed intramolecular reduction of diazides.

1*H*-Isoindoles are also synthesized by intramolecular condensation of benzylamines with aldehydes. However, mixtures of 1*H*-isoindoles and 2*H*-isoindoles were observed (Scheme 4B.3).[1d] The literature report clearly reveals that the OR or NR_2 substituent at the C3 position of 1*H*-isoindole makes the system more stable. The stability arises due to the conjugation of the lone pair of OR or NR_2 with the C=N of 1*H*-isoindole.[1]



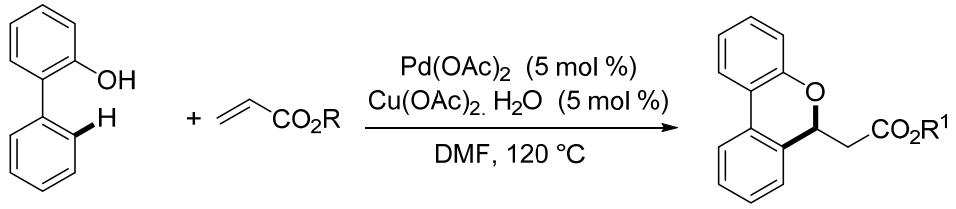
Scheme 4B.3: Malonic acid-catalyzed coupling of benzylamine with formaldehyde.

The transition metal-catalyzed alkenylation followed by cyclization of substituted aromatics with alkenes represents one of the efficient methods to synthesize heterocyclic molecules in one pot from easily available starting materials (Scheme 4B.4).[2] In the reaction, the alkenylation takes place at the *ortho* C–H bond of directing group substituted aromatics followed by intramolecular nucleophilic addition of nitrogen or oxygen atom of the directing group into an alkene, producing cyclic molecules.



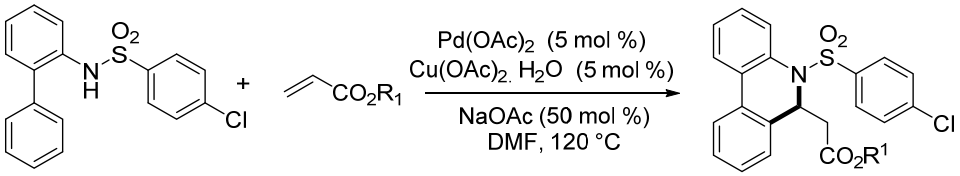
Scheme 4B.4: Transition metal-catalyzed cyclization of substituted aromatics with alkenes.

In the reaction, Rh(III), Ru(II), Pd(II) and Co(III) complexes are widely used as an active catalyst. Initially, palladium complexes are widely used as catalysts for this type of cyclization reaction. In 1997, Miura's group showed the reaction of 2-phenyl phenol with olefins in the presence of $Pd(OAc)_2$ catalyst and $Cu(OAc)_2{\cdot}H_2O$ as an oxidant to produce 6-substituted-6*H*-dibenzo[*b,d*]pyran derivatives in good to excellent yields (Scheme 4B.5).[3a]



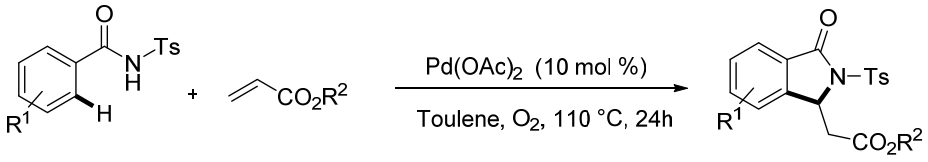
Scheme 4B.5: Palladium-catalyzed cyclization of phenol derivatives with alkenes.

Later, the same group has explored the cyclization reaction of *N*-(Arylsulfonyl)-2-phenyl aniline with alkenes in the presence of $Pd(OAc)_2$ catalyst (Scheme 4B.6).[3b]



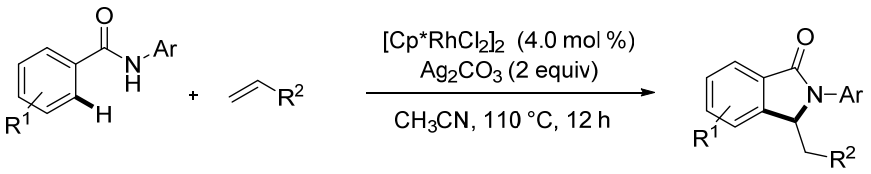
Scheme 4B.6: Palladium-catalyzed cyclization of aniline derivatives with alkenes..

The Pd(II)-catalyzed effective synthesis of isoindolinone derivatives was reported by Zhu's group. In this reaction, *N*- tosyl amides underwent tandem C−H olefination/annulation with alkenes (Scheme 4B.7).[3c]



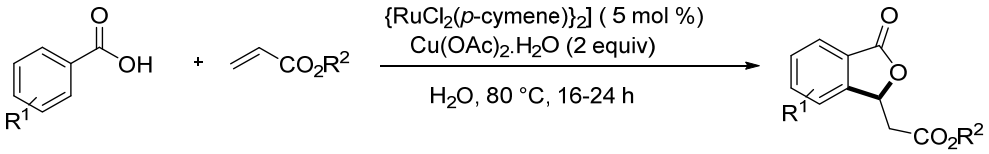
Scheme 4B.7: Palladium-catalyzed cyclization of substituted amides with alkenes..

Eventually, the same type of reaction also explored with a rhodium catalyst. In 2010, Li's group showed the tandem cyclization of *N*-aryl benzamides with alkenes to produce isoindolinone derivatives in the presence of Rh(III)-catalyst (Scheme 4B.8).[3d]



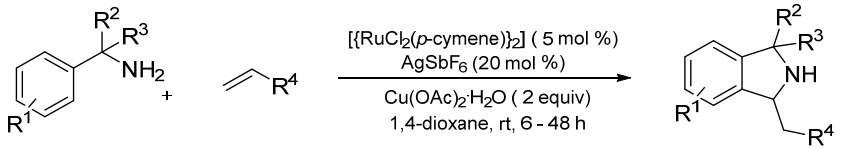
Scheme 4B.8: Rhodium-catalyzed cyclization of amide derivatives with alkenes.

Recently, a less expensive and easily affordable ruthenium catalyst has been widely used for these type of reactions. In 2012, Ackermann's group described the *ortho* alkenylation followed by Michael-type addition of aromatic benzoic acids with alkenes to give cyclic products in the presence of $\{RuCl_2(p\text{-cymene})\}_2]$ and $Cu(OAc)_2.H_2O$ (Scheme 4B.9).[3e]



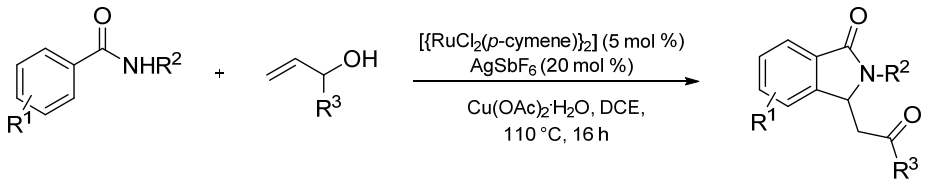
Scheme 4B.9: Ruthenium-catalyzed cyclization of aromatic carboxylic acids with alkenes.

Miura and Satoh have reported the *ortho* alkenylation and followed by cyclization of α,α-disubstituted benzyl amines with alkenes at room temperature (Scheme 4B.10).[3f] It is important to note that the alkenylation reaction was done with the free amine without protection of the amine group.



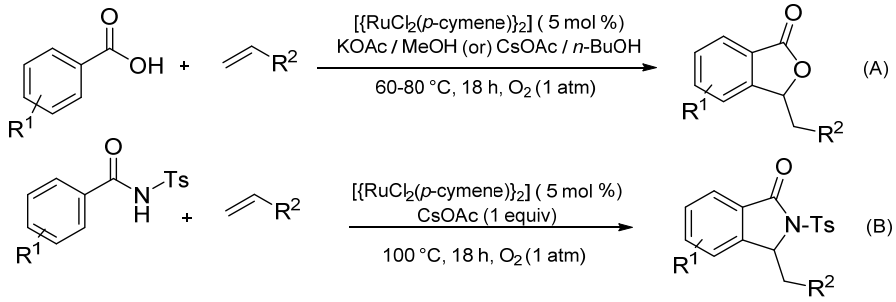
Scheme 4B.10: Ruthenium-catalyzed cyclization of α,α-disubstituted benzyl amines with alkenes.

Subsequently, we have disclosed the oxidative cyclization of *N*-substituted benzamides with allylic alcohols affording 3-substituted isoindolinone derivatives in the presence of ruthenium (II) catalyst (Scheme 4B.11).[3g]



Scheme 4B.11: Ruthenium-catalyzed cyclization of *N*-substituted benzamides with allylic alcohols.

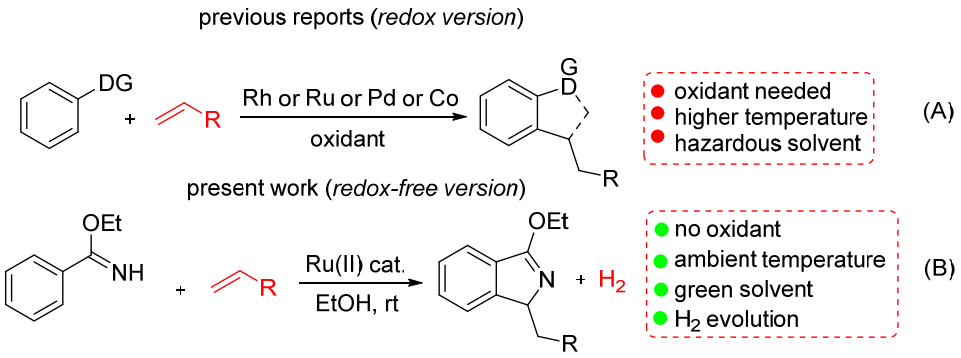
Very recently, Ackermann's group has reported a ruthenium-catalyzed oxidative cyclization of benzoic acids and tosyl benzamides with alkenes to produce the corresponding cyclic products using oxygen as a sole oxidant (Scheme 4B.12).[3h] In the reaction, oxygen was used as an oxidant which oxidizes the Ru(0) into Ru(II) catalyst.



Scheme 4B.12: Ruthenium-catalyzed cyclization of substituted aromatics with alkenes using O_2 as a sole oxidant.

Till now, in the reported cyclizations of aromatics with alkenes was done in the redox version and thus an oxidant is needed to regenerate the active catalyst [Rh(I) to Rh (III), Ru(0) to Ru(II), Pd(0) to Pd(II) and Co(I) to Co(III)) (eq 3]. In addition, generally, higher reaction temperatures and hazardous solvents are needed for the reaction (Scheme 4B.13A).[2] To the best of our knowledge, there is no report available in the literature for doing cyclizations of aromatics with alkenes in the redox-neutral version. Herein, we report an unprecedented redox-neutral ruthenium (II)-catalyzed of benzimidates with alkenes in green ethanol solvent at ambient temperature, giving 1*H*-isoindoles and 2*H*-isoindoles with the liberation of renewable hydrogen

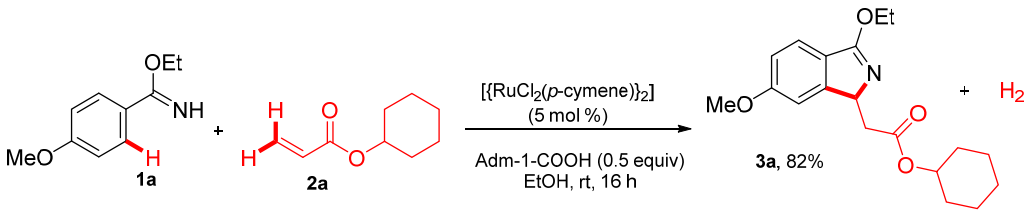
source (Scheme 4B.13B). The cyclization was done in a redox-neutral version without changing the oxidation state of Ru(II), and thus no oxidant is needed.



Scheme 4B.13: Tetrathiomolybdate complex catalyzed intramolecular reduction of diazides.

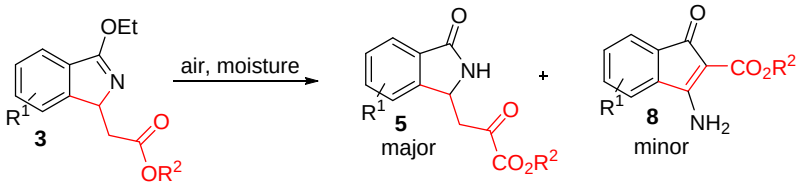
4B.2 Results and Discussion

Treatment of ethyl 4-methoxybenzimidate **(1a)** with cyclohexyl acrylate **(2a)** (2.0 equiv) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and adamantane-1-carboxylic acid (Adm-1-COOH) (0.5 equiv) in EtOH at ambient temperature for 16 h gave 1*H*-isoindole **3a** in 82% isolated yield along with H_2 gas evolution (Scheme 4B.14). The liberation of H_2 gas was confirmed by gas chromatography with a TCD detector.[8]



Scheme 4B.14: Ruthenium-catalyzed cyclization of 4-methoxybenzimidate (**1a)** with cyclohexyl acrylate (**2a)**

The product **3a** is highly moisture and air sensitive in the neat form. In the presence of air and moisture product **3** is slowly start to decompose and forms maximum amount of hydrolyzed isoindolinone **5** and minor amount of indenone **8** product (Scheme 4B.15).[7e] Apart from that, product is very stable under inert atmosphere or mixed with any organic solvent.

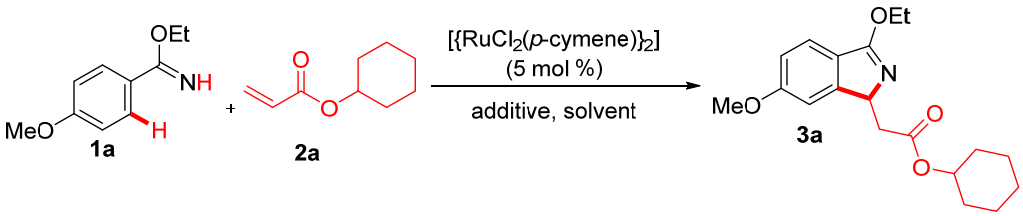


Scheme 4B.15: Decomposition of Isoindole in the presence of air and moisture

4B.3 Optimization studies

The cyclization reaction was also examined with other solvents such as 1,4-dioxane, THF, DME, methanol, toluene, CH_3CN, DMSO, DMF and DCE instead of EtOH (Table 4B.1). CH_3CN, methanol, and DCE, were partially effective, providing product **3a** in 30%, 68% and 51% isolated yields, respectively. Remaining solvents were not effective. Further, the alkenylation reaction was examined with other organic acids such as acetic acid, pivalic acid, 2,6-dimethylbenzoic acid, and benzoic acid instead of 1-adamantanecarboxylic acid. These acids were partially effective, yielding product 3a in 64%, 61%, 75% and 62% yields, respectively. It is important to note that no product **3a** was observed without a ruthenium catalyst and carboxylic acid source.

Table 4B.1: Optimization Studies with Various Additive, Solvent and Cosolvent.



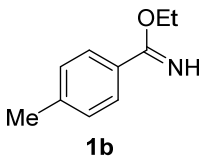
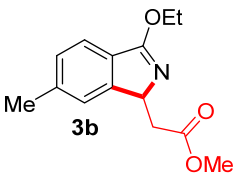
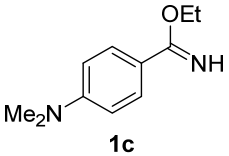
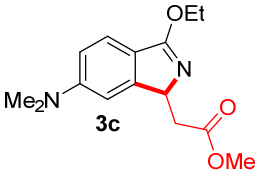
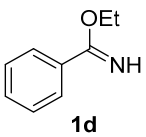
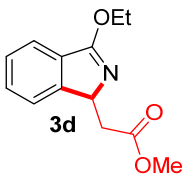
entry	Solvent	cosolvent	yield of **3a** (%)[b]
1	Acetonitrile	1-Adamantane carboxylic acid (0.5 equiv)	30
2	Methanol	1-Adamantane carboxylic acid (0.5 equiv)	68
3	THF	1-Adamantane carboxylic acid (0.5 equiv)	NR
4	DME	1-Adamantane carboxylic acid (0.5 equiv)	NR
5	1,4-dioxane	1-Adamantane carboxylic acid (0.5 equiv)	NR
6	DMF	1-Adamantane carboxylic acid (0.5 equiv)	NR
7	Toluene	1-Adamantane carboxylic acid (0.5 equiv)	NR
8	$ClCH_2CH_2Cl$	1-Adamantane carboxylic acid (0.5 equiv)	51
9	**Ethanol**	**1-Adamantane carboxylic acid (0.5 equiv)**	**82**
10	Ethanol	Acetic acid (0.5equiv)	64
11	Ethanol	Pivalic acid (0.5 equiv)	61
12	Ethanol	Mesitylinic acid (0.5 equiv)	75
13	Ethanol	Benzoic acid (0.5 equiv)	62
14	Ethanol	1-Adamantane carboxylic acid (0.5 equiv)	68
15	Ethanol	1-Adamantane carboxylic acid (0.3 equiv)	66
16	Ethanol	1-Adamantane carboxylic acid (1 equiv)	79
17	Ethanol	_	NR

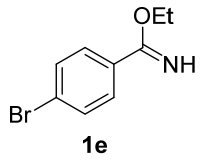
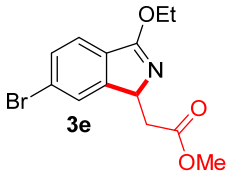
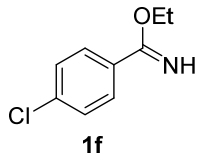
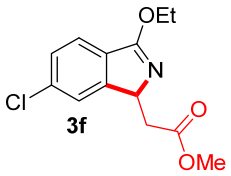
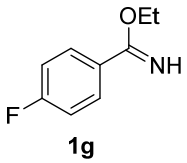
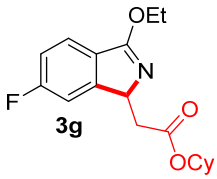
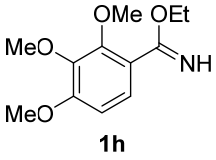
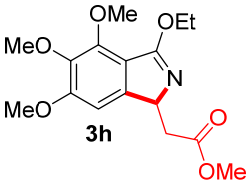
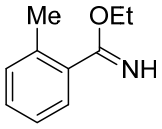
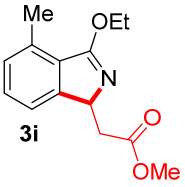
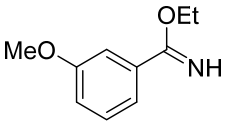
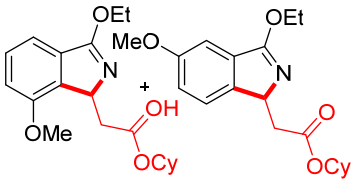
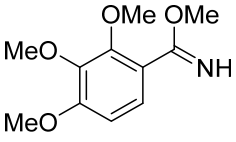
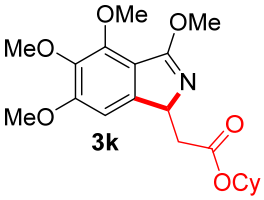
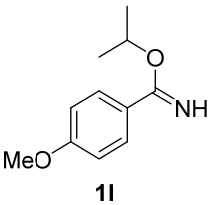
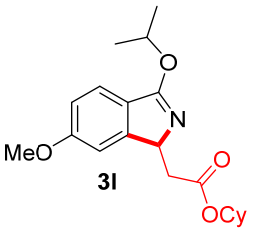
[a]All reactions were carried out under the following conditions: **1a** (50 mg), **2a** (2.0equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5mol %), acid source andsolvent (1.0 mL) at rt for 16 h under the N_2 atmosphere. [b] Isolated yield. [c]1.0 equivalent of **2a** was used.

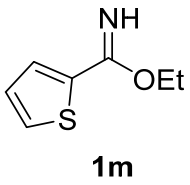
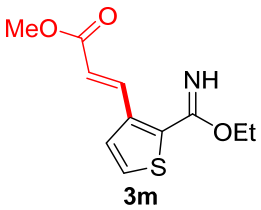
4B.4 Scope of Substituted Aromatic imidates

The scope of the alkenylation reaction was examined with various substituted benzimidates **1b-m** (Table 4B.2). The alkenylation reaction was compatible with sensitive functional groups such as F, Cl, Br, OMe, and NMe_2-substituted benzimidates. The reaction of electron-donating 4-Me- and 4-NMe_2-substituted benzimidates **1b-c** with methyl acrylate **(2b)** provided products **3b** and **3c** in 61% and 71% yields, respectively (entries 1-2). Ethyl benzimidate **(1d)** and halogen group such as 4-Br-, 4-Cl- and 4-F-substituted benzimidates **1e-g** afforded substituted isoindoles **3d-g** in 64%, 48%, 56% and 61% yields, respectively (entries 3-6). Ethyl 3,4,5-trimethoxy benzimidate **(1h)** and *ortho* methyl benzimidate **(1i)** were also effectively involved in the reaction, giving products 3hb and 3ib in 87% and 66% yields, respectively (entries 7-8). Unsymmetrical ethyl 3-methoxybenzimidate **(1j)** reacted with **2a,** yielding products **3j** and **3j'** in a 2:1 regioisomeric mixture with 72% combined yield. The cyclization reaction was tested with alkoxy-substituted benzimidates 1k-l. Methyl 2,3,4-trimethoxybenzimidate **(1k)** and *iso*propyl 4-methoxy-benzimidate **(1l)** underwent cyclization with **2a,** providing isoindole derivatives **3k** and **3l** in 68% and 72% yields, respectively (entries 10 and 11). In contrast, in the reaction of ethyl thiophene-2-carbimidate **(1m)** with **2b,** only alkenylated product **3m** was observed in 41% yield.

Table 4B.2 Cyclization of substituted benzimidates **1b–m** with alkene **2**[a]

Entry	Aromatic imidate (**1**)	Compound (**3**)	Yield[b]
1	 **1b**	 **3b**	61%
2	 **1c**	 **3c**	71%
3	 **1d**	 **3d**	64%

4	 **1e**	 **3e**	48%
5	 **1f**	 **3f**	56%
6	 **1g**	 **3g**	61%
7	 **1h**	 **3h**	87%[c]
8	 **1i**	 **3i**	66%
9	 **1j**	 **3j + 3j'** (2:1)	72%
10	 **1k**	 **3k**	68%
11	 **1l**	 **3l**	72%

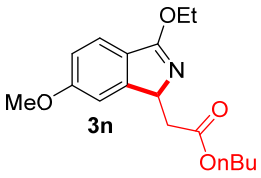
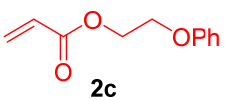
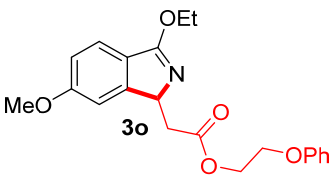
12	 **1m**	 **3m**	41%

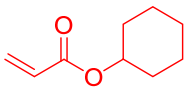
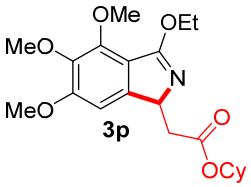
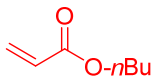
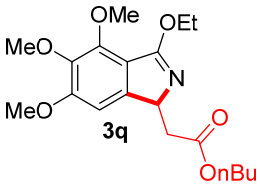
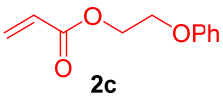
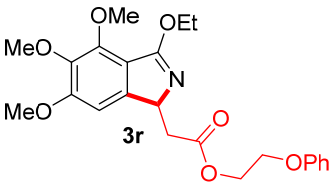
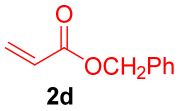
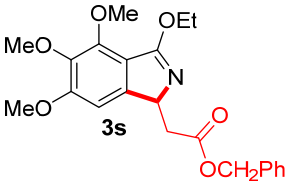
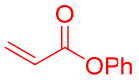
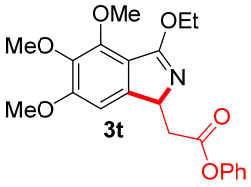
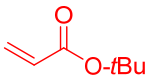
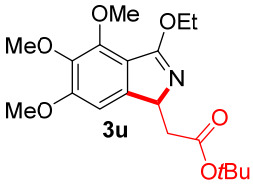
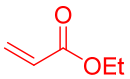
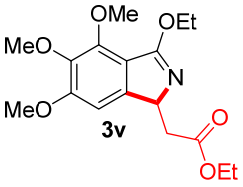
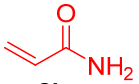
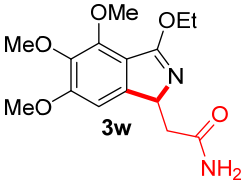
[a]All reactions [a]All reactions were carried out using imidates **1b-m** (50 mg), alkene **2a** or **2b** (2.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), Adm-1-COOH (0.5 equiv) in EtOH (1.0 mL) at room temperature for 8-24 h [b]Isolated yield.

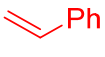
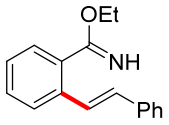
4B.5 Substrate Scope of Alkenes

The scope of the cyclization reaction was further examined with substituted alkenes **2a-j** (Table 4B.3). *n*-Butyl acrylate **(2c)** and 2-phenoxyethyl acrylate **(2d)** reacted with 1a, giving 1*H*-isoindoles **3n** and **3o** in 80% and 56% yields, respectively (entries 1 and 2). The cyclization reaction of **1h** with various acrylates such as **2a, 2c, 2d**, phenyl acrylate **(2e),** benzyl acrylate **(2f),** *tert*-butyl acrylate **(2g)** and ethyl acrylate **(2h)** provided cyclized products **3p-3v** in good to excellent 45-94% yields, respectively (entries 3-9). However, acrylamide **(2i)** and styrene **(2j)** did not participate in the reaction at room temperature. At 60 °C, acrylamide **(2i)** participated in the reaction, yielding cyclic product **3w** in 21% yield (entry 10). At the same temperature, styrene (2j) provided *ortho* alkenylated product **3x** in 43% yield (entry 11).

Table 4B.3 Scope of substituted alkenes **2a-i** with Benzimidates **1**[a]

Entry	Alkene (**1**)	Compound (**3**)	Yield[b]
1	 **2b**	 **3n**	80%
2	 **2c**	 **3o**	56%

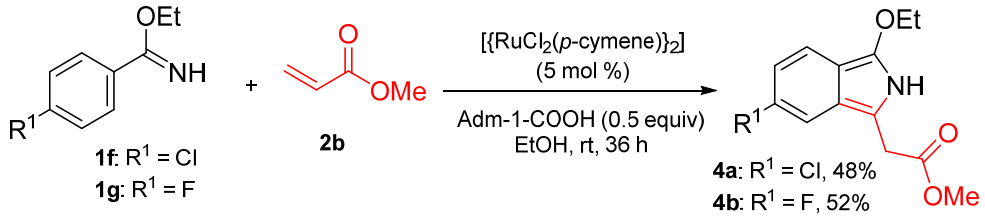
3	 **2a**	 **3p**	94%
4	 **2b**	 **3q**	78%
5	 **2c**	 **3r**	58%
6	 **2d**	 **3s**	76%
7	 **2e**	 **3t**	66%[c]
8	 **2f**	 **3u**	45%
9	 **2g**	 **3v**	70%
10	 **2h**	 **3w**	21%

11	 **2i**	 **3x**	43%[c]

[a]All reactions were carried out using **1a** or **1o** (100 mg), alkenes **2b-j** (2.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv), AcOH (2.0 equiv) in 1,2-dichloroethane (3.0 mL) at room temperature for 24 h. [b]Isolated yield. [c]1,4-dioxane solvent was used and the reaction was done at 100 °C.

4B.6 Synthesis of 2*H*-isoindoles.

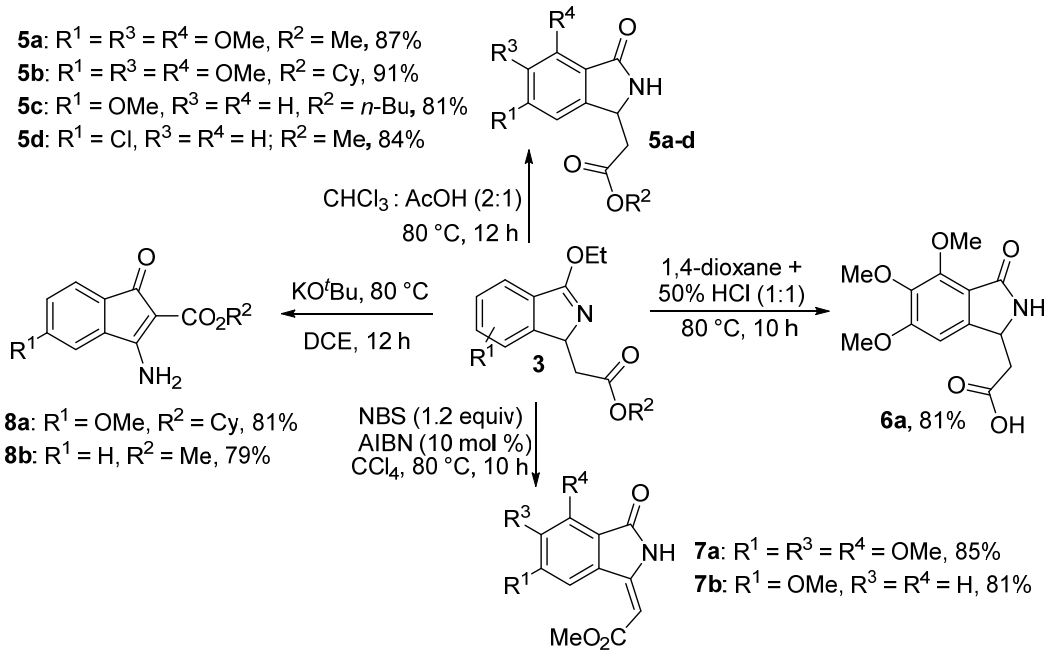
It is important to mention that the halogen group such as 4-Cl- and 4-F-substituted benzimidates **1f-g** reacted with **2b** under similar reaction conditions at a longer 36 h reaction time at ambient temperature with vigorous stirring, giving 2*H*-isoindoles **4a-b** in 48% and 52% yields, respectively (Scheme 4B.16). However, a similar type of product was not observed in electron rich benzimidates **1a-d.**



Scheme 4B.16: Ruthenium-catalyzed synthesis of 2*H*-isoindoles.

4B.7 Synthetic Transformation of 1*H*-Isoindole

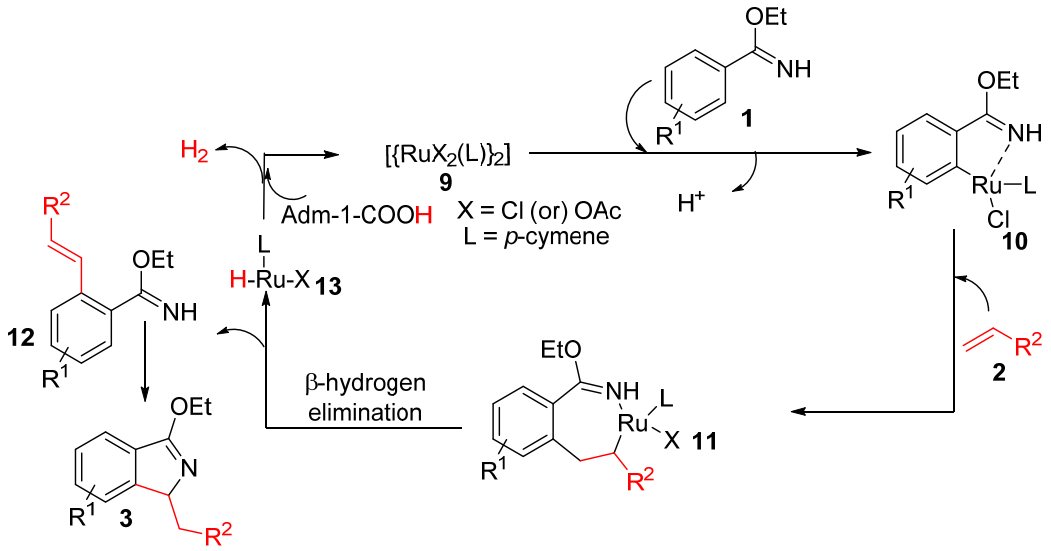
1*H*-Isoindole is a versatile molecule which can be further converted into various useful heterocycles (Scheme 4B.17). Substituted 1*H*-isoindole derivatives were converted into isoindolinones **5a-d** in excellent 81-91% yields, by a mild hydrolysis with AcOH at 80 °C for 12 h. When the hydrolysis was done with 50% HCl, the ester group of 3ha was also cleaved along with OEt, producing isoindole carboxylic acid **6** in 81% yield. Meanwhile, 3-methyleneisoindolin-1-ones **7a-b** were prepared in excellent yields by the reaction of 1*H*-isoindoles **3** with NBS (1.2 equiv) and AIBN (10 mol %) in CCl_4 at 80 °C for 10 h. Finally, indenones having free amine **8a-b** were synthesized in 74% and 79% yields, respectively, in the reaction of **3a** or **3d** in the presence of *t*BuOK base in $ClCH_2CH_2Cl$ at 80 °C.



Scheme 4B.17: Synthetic Transformation of 1*H*-Isoindole**.**

4B.8 Proposed reaction mechanism

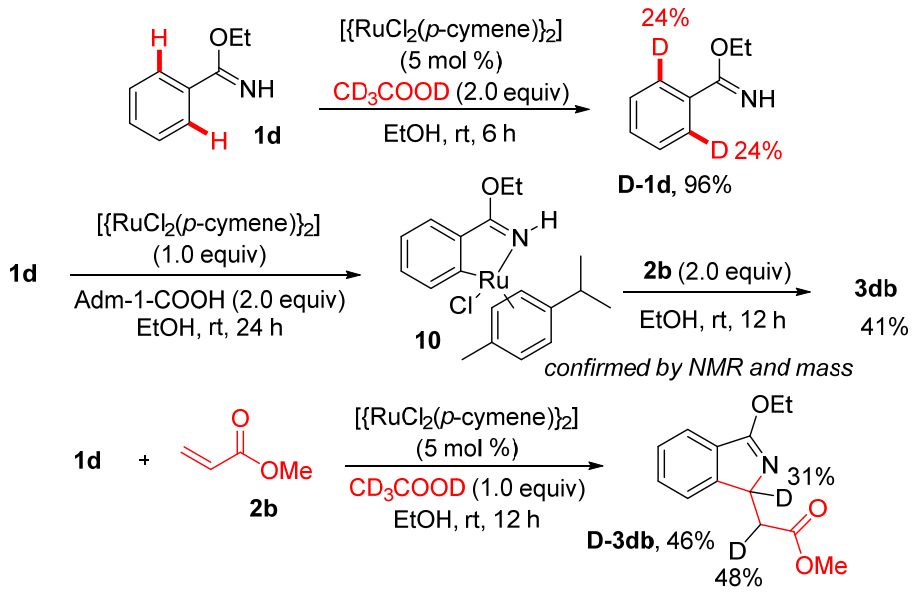
A possible reaction mechanism for the redox-neutral cyclization of benzimidates **1** with alkenes **2** is proposed in Scheme 4B.18. The lone pair of the nitrogen atom of benzimidate **1** coordinates with a ruthenium catalyst **9** followed by *ortho* metalation providing a five-membered ruthenacycle intermediate **10.** Coordinative insertion of alkene **2** into the Ru–carbon bond of intermediate **10** gives intermediate **11**. β-Hydride elimination of intermediate **11** affords *ortho* alkenylated benzimidate **12** and a ruthenium hydride species **13**. The ruthenium hydride species **13** reacts with carboxylic acid, providing H_2 gas and regenerates the active catalyst **9**. It is also possible that ruthenium hydride can react with the N-H bond of imidate to produce H_2 gas, later protonation of the Ru-N bond provide ortho alkenylated benzimidate **12** and regenerates the active catalyst **9.** However, the reaction of ruthenium hydride with highly acetic carboxylic acid proton is more favourable, in addition, our previous report and DFT calculation also suggest that proposed reaction mechanism is more feasible. Later, the *ortho* alkenylated benzimidate **12** undergoes successive intramolecular aza-Michael reaction to provide 1H-isoindole **3** derivatives.



Scheme 4B.18: Proposed reaction mechanism.

4B.9 Mechanistic Studies

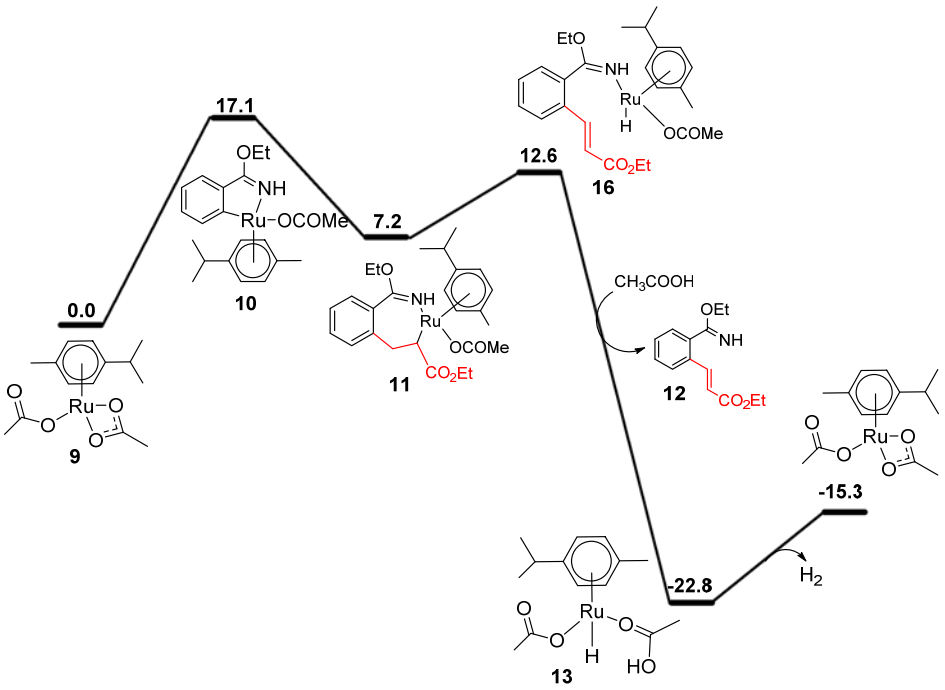
To prove the formation of a five-membered ruthenacycle **10** is a reversible process, 1d was treated with CD_3COOD in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) in ethanol at room temperature for 6 h. In the reaction, product **D-1d** was observed in 96% yield with 24% of deuterium incorporation at the both *ortho* carbons, respectively (Scheme 4B.19). In the meantime, we have tried to isolate the key ruthenacycle intermediate **10** in the reaction of **1d** with a stoichiometric amount of [{$RuCl_2$(*p*-cymene)}$_2$] and AcOH (2.0 equiv) in EtOH at room temperature for 24 h. As expected, the metalacycle intermediate 10 was observed in 78% yield. The complex **10** was assigned by ^{1}H, ^{13}C NMR and HRMS techniques. Later, intermediate **10** was treated with **2b,** giving cyclic product 3db in 41% yield. Further, the reaction of 1d was examined with **2b** in the presence of CD_3COOD under the optimized reaction conditions. In the reaction, product **D-3db** was observed in 46% yield along with 48% of deuterium incorporation at the adjacent carbon of the ester group of **D-3db.** It clearly reveals that the carboxylic acid protonates the C-Ru bond of intermediate **15**. Due to the highly acidic nature of C1 position of **D-3db,** 31% of deuterium incorporation was observed.



Scheme 4B.19: Synthetic Transformation of 1*H*-Isoindole**.**

4B.10 DFT calculations for Proposed Mechanism

DFT calculations were carried out to understand the experimental observation of the reaction of benzimidate 1d with alkene 2 in the presence of a ruthenium catalyst. Benzimidate **1d** reacts with complex **9** via C–H bond activation, giving complex **10** and is calculated to be slightly endergonic by 17.1 kcal mol-1 which indicates that the formation of ruthenacycle intermediate **10** is thermodynamically feasible by the losing of acetic acid (Scheme 4B.20). The insertion of alkene **2** into the ruthenacycle intermediate **10** to give intermediate **11** is calculated to be exergonic by 9.9 kcal.mol^{-1}. The β-hydride shift to a ruthenium metal of intermediate **11** requires only 5.4 kcal.mol^{-1} in which adduct **16** is observed. Addition of acetic acid to adduct **16** affords product **12**, and a ruthenium hydride complex **13** is calculated to be more exergonic by -22.8 kcal.mol^{-1}. Later, the liberation of hydrogen gas and generation of active catalyst **9** is calculated to be only 7.5 kcal.mol^{-1} and hence it is thermodynamically feasible. Overall, the calculated energy barrier clearly indicates that the proposed mechanism in Scheme 4B.20 is energetically feasible process



Scheme 4B.20: DFT-computed energy profiles**.**

4B.11 Conclusion

In conclusion, we have described an efficient synthesis of 1*H*-isoindoles and 2*H*-isoindoles via a ruthenium(II)-catalyzed redox-neutral oxidative cyclization of benzimidates with alkenes at room temperature with evolution of hydrogen. In the whole catalytic cycle, a ruthenium with +2 oxidation state was involved and thus external oxidant was not needed. Useful nitrogen-containing heterocycles were prepared by using 1*H*-isoindoles. The DFT calculations and experimental evidence strongly supports the proposed reaction mechanism.

4B.12 References

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4B.13 Experimental Section

4B.13.1 General Procedure for Synthesis of Imidate Ester 1

Alcohol (200 mmol) and aryl nitrile (20 mmol) were stirred in a round bottom flask. Then AcCl (200 mmol) was added dropwise within 15 minutes in an ice bath. The reaction mixture was stirred at room temperature for 6 h, and the solvent was removed under reduced pressure to give a white solid. The white solid was washed with Et_2O, and saturated $NaHCO_3$ solution was then added till gas evolution ceased. The resulting mixture was extracted with EtOAc three times. The organic layers were collected and concentrated under reduced pressure to give the desired product **1**.

4B.13.2 General Procedure for the oxidative cyclization of Aromatic imidates with Alkenes catalyzed by Ruthenium Complex

A 15-mL schlenk tube (or) pressure tube with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) was evacuated and purged with nitrogen gas three times. To the tube, were then added aromatic imitades **1** (50 mg), alkenes **2** (2.0equiv), adamantine -1-carboxylic acid (0.5 equiv) and Ehanol (1.0 mL) via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, 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 room temperature (~ 24 °C) for 8 - 36 h. Then, 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 petroleum ether and ethyl acetate as eluent to give pure isoindole product **3 (or) 4.**

The oxidativecyclization reaction can also be done in a round bottom flask under the nitrogen atmosphere.

4B.13.3 General Procedure for the Synthesis of Isoindolinone Derivatives 5.

1H-Isoindole derivative (**3**) (50 mg) was taken in a 10-mL sealed tube and dissolved with 1 mL of $CHCl_3$ and 0.5 mL AcOH. Then, the reaction mixture was heated at 80°C for 12 h. After cooling to ambient temperature, The solution was concentrated under the reduced pressure. The crude residue was purified through a silica gel column using petroleum ether and ethyl acetate as eluent to give pure **5.**

4B.13.4 General Procedure for the Synthesis of Isoindolinone carboxylic acid Derivatives 6.

1H-Iso indole derivative (**3**) (50 mg) was taken in a 10-mL round bottom flask and dissolved with 1 mL of 1,4 dioxane and 1.0 mL of 6N HCl. Then, the reaction mixture heated at 80°C for 10 h. After cooling to ambient temperature, water was poured into the reaction mixture and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over Na_2SO_4. The solution was concentrated under the reduced pressure. The crude residue was purified through a silica gel column using DCM and ethyl nethanol as eluent to give pure **6.**

4B.13.5 General Procedure for the Synthesis of Isoindolinone Derivatives 7.

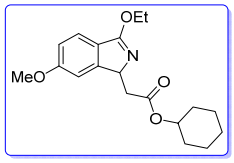
1H-Iso indole derivative (**3**) (50 mg) was taken in a 10-mL round bottom flask and dissolved with 2.0 mL of CCl_4. To the flask, were then added *N*-bromo succinimide (1.2 mmol) and AIBN (10 mol %). Then, the condenser was fitted with water circulation in the round bottom flask and the reaction mixture was allowed to reflux at 90 °C for 10 h under an air atmosphere. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2. The crude residue was purified through a silica gel column using dichloromethane and methanol as eluent to give pure **7.**

4B.13.6 General Procedure for the Synthesis of Indenone Derivatives 8.

1H-Iso indole derivative (**3**) (50 mg) was taken in a 10-mL sealed tube and dissolved with 2.0 mL of $ClCH_2CH_2Cl$. To the tube, were then added KO^tBu (1.2 equiv) Then, the reaction mixture heated at 80°C for 12 h. After cooling to ambient temperature, The solution was concentrated under the reduced pressure. The crude residue was purified through a silica gel column using petroleum ether and ethyl acetate as eluent to give pure

4B.14 Spectral Data of Compounds 3a-x, 4a-b, 5a-d, 6a, 7a-b, and 8a-b.

Cyclohexyl 2-(3-ethoxy-6-methoxy-1H-isoindol-1-yl)acetate (3a).



Colourless liquid; eluent (12% ethylacetate in hexanes). The representative general procedure was followed using **1a** (50 mg), **2a** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 76 mg and yield is 82%.

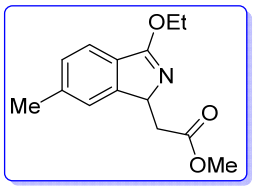
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 4.0 Hz, 1H), 6.87 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.97 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.82 – 4.77 (m, 1H), 4.44 – 4.37 (m, 2H), 3.79 (s, 3H), 2.88 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.48 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.87 – 1.80 (m, 2H), 1.73 – 1.60 (m, 2H), 1.54 – 1.49 (m, 2H), 1.39 (t, *J* = 8.0 Hz, 3H), 1.38 – 1.30 (m, 2H), 1.23 – 1.20 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9, 168.9, 161.2, 155.1, 125.8, 121.4, 114.2, 107.50, 72.9, 64.5, 63.82, 55.5, 38.9, 31.5, 25.3, 23.6, 14.4.

HRMS (ESI): calc. for [($C_{19}H_{25}NO_4$)H] (M+H) 332.1862, measured 332.1864.

Rf (hexane/ethyl acetate = 4:1): 0.31.

Methyl 2-(3-ethoxy-6-methyl-1H-isoindol-1-yl)acetate (3b).



Colourless liquid; eluent (7% ethylacetate in hexanes). The representative general procedure was followed using **1b** (50 mg), **2b** (2.0 equiv) and the reaction was done at rt for 20 h. The desired product was isolated in 46 mg and yield is 61%.

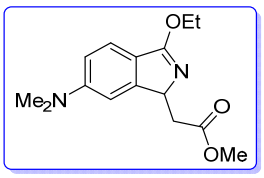
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (d, *J* = 8.0 Hz, 1H), 7.24 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 5.01 (t, *J* = 8.0 Hz, 1H), 4.48 – 4.39 (m, 2H), 3.74 (s, 3H), 2.81 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.53 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.40 (s, 3H), 1.41 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.1, 169.3, 153.1, 139.7, 130.4, 128.6, 122.9, 120.4, 64.5, 63.9, 51.7, 38.4, 21.7, 14.4.

HRMS (ESI): calc. for [($C_{14}H_{17}NO_3$)H] (M+H) 248.1286, measured 248.1292.

Rf (hexane/ethyl acetate = 9:1): 0.36.

Methyl 2-(6-(dimethylamino)-3-ethoxy-1H-isoindol-1-yl)acetate (3c).



Colourless liquid; eluent (10% ethylacetate in hexanes). The representative general procedure was followed using **1c** (50 mg), **2b** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 51 mg and yield is 71%.

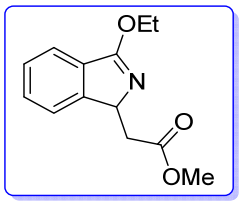
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 4.0 Hz, 1H), 6.65 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.96 (t, *J* = 8.0 Hz, 1H), 4.44 – 4.33 (m, 2H), 3.72 (s, 3H), 2.98 (s, 6H), 2.80 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.51 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.39 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3, 169.6, 154.7, 151.6, 121.2, 121.1, 111.5, 105.2, 64.3, 63.7, 51.6, 40.6, 39.0, 14.5.

HRMS (ESI): calc. for [($C_{15}H_{20}N_2O_3$)H] (M+H) 277.1552, measured 277.1556.

Rf (hexane/ethyl acetate = 9:1): 0.25.

Methyl 2-(3-ethoxy-1H-isoindol-1-yl)acetate (3d).



Colourless liquid; eluent (8% ethylacetate in hexanes). The representative general procedure was followed using **1d** (50 mg), **2b** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 50 mg and yield is 64%.

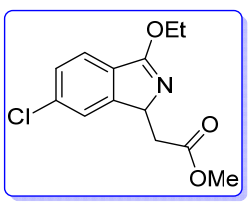
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 – 7.50 (m, 1H), 7.44 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.36 (dd, *J* = 8.0, 4.0 Hz, 1H), 5.06 (t, *J* = 8.0 Hz, 1H), 4.50 – 4.42 (m, 2H), 3.73 (s, 3H), 2.84 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.53 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.42 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.9, 169.3, 152.6, 132.83, 129.30, 127.63, 122.3, 120.7, 64.9, 64.02, 51.8, 38.3, 14.4.

HRMS (ESI): calc. for [($C_{13}H_{15}NO_3$)H] (M+H) 234.1130, measured 234.1134.

Rf (hexane/ethyl acetate = 9:1): 0.35.

Methyl 2-(6-chloro-3-ethoxy-1H-isoindol-1-yl)acetate (3e).



Colourless liquid; eluent (5% ethylacetate in hexanes). The representative general procedure was followed using **1e** (50 mg), **2b** (2.0 equiv) and the reaction was done at rt for 20 h. The desired product was isolated in 41 mg and yield is 56%.

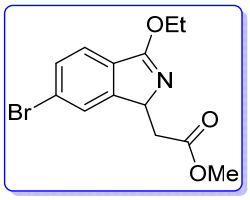
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, *J* = 4.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H),7.34 (dd, *J* = 8.0, 4.0 Hz, 1H), 5.03 (t, *J* = 8.0 Hz, 1H), 4.48 – 4.36 (m, 2H), 3.73 (s, 3H), 2.86 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.50 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.41 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.7, 168.5, 154.4, 135.92, 131.4, 128.2, 123.0, 121.6, 64.6, 64.2, 51.9, 37.9, 14.4.

HRMS (ESI): calc. for $[(C_{13}H_{14}ClNO_3)H]$ (M+H) 268.0740, measured 268.0560.

Rf (hexane/ethyl acetate = 9:1): 0.40.

Methyl 2-(6-bromo-3-ethoxy-1H-isoindol-1-yl)acetate (3f).



Colourless liquid; eluent (5% ethylacetate in hexanes). The representative general procedure was followed using **1f** (50 mg), **2b** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 33 mg and yield is 48%.

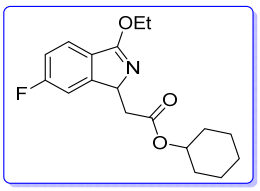
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (d, *J* = 4.0 Hz, 1H), 7.51 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 5.03 (t, *J* = 8.0 Hz, 1H), 4.48 – 4.39 (m, 2H), 3.74 (s, 3H), 2.87 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.52 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.41 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 169.2, 147.5, 137.3, 132.2, 126.9, 125.8, 125.0, 64.6, 64.3, 52.4, 39.0, 14.31.

HRMS (ESI): calc. for $[(C_{13}H_{14}BrNO_3)H]$ (M+H) 312.0235, measured 312.0294.

Rf (hexane/ethyl acetate = 9:1): 0.42.

Methyl 2-(6-fluoro-3-ethoxy-1H-isoindol-1-yl)acetate (3g).



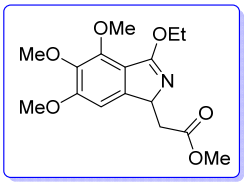
Colourless liquid; eluent (6% ethylacetate in hexanes). The representative general procedure was followed using **1g** (50 mg), **2a** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 58 mg and yield is 61%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.23 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 5.05 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.87 – 4.82 (m, 1H), 4.51 – 4.43 (m, 2H), 2.96 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.53 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.94 – 1.85 (m, 2H), 1.74 – 1.69 (m, 2H), 1.56 – 1.53 (m, 2H), 1.86 (d, *J* = 12.0 Hz, 2H), 1.41 – 1.35 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 168.4, 165.2, 155.5, 155.4 (F-Coupling), 128.9, 122.0, 121.9 (F-Coupling), 115.2, 115.0 (F-Coupling), 110.3, 110.0 (F-Coupling), 73.1, 64.6, 64.1 (F-Coupling), 38.5, 31.6, 31.5 (F-Coupling), 25.3, 23.7, 23.6, 14.4.
HRMS (ESI): calc. for [($C_{18}H_{22}FNO_3$)H] (M+H) 320.1662, measured 320.1666.

Rf (hexane/ethyl acetate = 9:1): 0.44.

Methyl 2-(3-ethoxy-4,5,6-trimethoxy-1H-isoindol-1-yl)acetate (3h).



Colorless liquid; eluent (20% ethylacetate in hexanes).

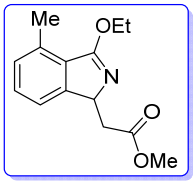
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.79 (s, 1H), 5.04 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.46 – 4.37 (m, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.67 (s, 3H), 3.06 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.42 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.39 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.8, 168.6, 154.5, 148.3, 143.1, 136.8, 128.5, 98.9, 64.1, 63.8, 61.0, 60.6, 56.2, 51.6, 37.3, 14.4.

HRMS (ESI): calc. for [($C_{16}H_{21}NO_6$)H] (M+H) 324.1447, measured 324.1444.

Rf (hexane/ethyl acetate = 2:1): 0.28.

Methyl 2-(3-ethoxy-4-methyl-1H-isoindol-1-yl)acetate (3i).



Colourless liquid; eluent (6% ethylacetate in hexanes). The representative general procedure was followed using **1a** (50 mg), **2a** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 52 mg and yield is 66%.

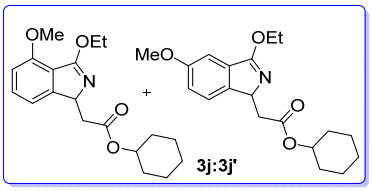
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.33 (d, *J* = 4.0 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 5.01 (t, *J* = 8.0 Hz, 1H), 4.47 – 4.42 (m, 2H), 3.74 (s, 3H), 2.86 – 2.79 (m, 1H), 2.56 – 2.49 (m, 1H), 2.40 (s, 3H), 1.41 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.9, 169.3, 154.3, 151.3, 120.9, 120.8, 111.2, 104.9, 63.9, 63.4, 51.3, 40.2, 38.7, 14.2.

HRMS (ESI): calc. for [($C_{14}H_{17}NO_3$)H] (M+H) 248.1286, measured 248.1292.

Rf (hexane/ethyl acetate = 9:1): 0.34.

Cyclohexyl 2-(3-ethoxy-6-methoxy-1H-isoindol-1-yl)acetate (3j).



Colourless liquid; eluent (20% ethylacetate in hexanes). The representative general procedure was followed using **1a** (50 mg), **2a** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 76 mg and yield is 82%.

^{1}H NMR ($CDCl_3$, 400 MHz) 3j: δ 7.30 (t, *J* = 8.0 Hz, 1H), 7.11 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 5.05 (dd, *J* = 8.0, 4.0 Hz, 2H), 4.72 – 4.65 (m, 1H), 4.74 – 4.63 (m, 2H), 3.84

(s, 6H), 3.13 (dd, *J* = 14.8, 4.9 Hz, 2H), 2.58 (dd, *J* = 14.8, 7.7 Hz, 2H), 2.00 – 1.88 (m, 4H), 1.72 – 1.60 (m, 18H), 1.43 – 1.35 (m, 2H), 1.40 (t, *J* = 12.0, 8.0 Hz, 2H), 1.33 – 1.13 (m, 2H).

^{1}H NMR ($CDCl_3$, 400 MHz) 3j': δ 7.33 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.93 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.99 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.82 – 4.76 (m, 1H), 4.48 – 4.38 (m, 2H), 3.81 (s, 3H), 2.89 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.45 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.85 – 1.76 (m, 2H), 1.43 – 1.35 (m, 12H), 1.40 (t, *J* = 12.0, 8.0 Hz, 2H), 1.33 – 1.13 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) 3j: δ 170.8, 169.0, 159.7, 145.0, 134.8, 129.4, 116.9, 110.8, 104.3, 72.3, 55.6, 55.2, 38.7, 36.9, 31.6, 27.9, 23.6, 14.4.

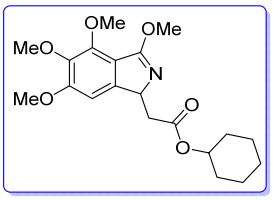
^{13}C NMR ($CDCl_3$, 100 MHz) 3j': δ 170.9, 168.9, 154.6, 139.8, 134.0, 123.0, 116.1, 112.9, 96.8, 64.0, 55.6, 55.2, 36.5, 31.3, 25.3, 14.4.

HRMS (ESI): calc. for [($C_{19}H_{25}NO_4$)H] (M+H) 332.1862, measured 332.1864.

FT-IR $\tilde{\nu}$ (cm^{-1}): 3281, 2978, 2360, 1705, 1628, 1545, 1264, 1040, 763.

Rf (hexane/ethyl acetate = 3:1): 0.21.

Cyclohexyl 2-(3,4,5,6-tetramethoxy-1H-isoindol-1-yl)acetate (3k).



Colourless liquid; eluent (18% ethylacetate in hexanes). The representative general procedure was followed using **1k** (50 mg), **2a** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 57 mg and yield is 68%.

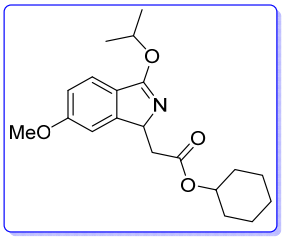
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.78 (s, 1H), 5.01 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.76 – 4.65 (m, 1H), 4.01 (s, 3H), 3.94 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.09 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.54 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.78 – 1.68 (m, 2H), 1.64 – 1.61 (m, 2H), 1.48 – 1.22 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 169.1, 154.5, 148.3, 143.1, 137.2, 128.3, 98.8, 72.5, 63.8, 60.9, 60.6, 56.3, 55.5, 37.5, 31.5, 25.3, 23.6.

HRMS (ESI): calc. for [($C_{20}H_{27}NO_6$)H] (M+H) 378.1916, measured 378.1921.

Rf (hexane/ethyl acetate = 2:1): 0.31.

Cyclohexyl 2-(3,4,5,6-tetramethoxy-1H-isoindol-1-yl)acetate (3l).



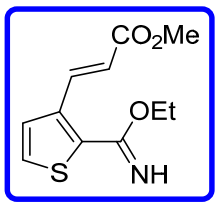
Colourless liquid; eluent (14% ethylacetate in hexanes). The representative general procedure was followed using **1l** (50 mg), **2a** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 62 mg and yield is 74%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 4.0 Hz, 1H), 6.88 (dd, *J* = 8.0, 4.0 Hz, 1H), 5.25 – 5.19 (m, 1H), 5.01 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.82 – 4.76 (m, 1H), 3.81 (s, 3H), 2.94 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.50 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.02 – 1.97 (m, 2H), 1.83 – 1.76 (m, 2H), 1.73 – 1.66 (m, 4H), 1.53 – 1.47 (m, 2H), 1.38 (d, *J* = 4.0 Hz, 3H), 1.37 (d, *J* = 4.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 163.2, 148.5, 132.2, 125.5, 114.9, 112.2, 107.4, 73.9, 64.4, 55.7, 52.9, 40.2, 38.6, 36.4, 27.8.
HRMS (ESI): calc. for [($C_{20}H_{27}NO_4$)H] (M+H) 346.2018, measured 346.2021.

Rf (hexane/ethyl acetate = 3:1): 0.27.

Methyl (E)-3-(2-(ethoxy(imino)methyl)thiophen-3-yl)acrylate (3m).



Colourless liquid; eluent (8% ethylacetate in hexanes). The representative general procedure was followed using **1m** (50 mg), **2b** (2.0 equiv) and the reaction was done at rt for 20 h. The desired product was isolated in 41 mg and yield is 32%.

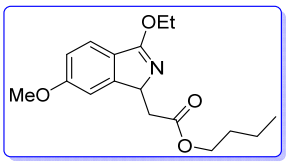
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, *J* = 16.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H) 6.29 (d, *J* = 16.0 Hz, 1H), 4.27 (q, *J* = 8.0 Hz, 2H), 3.77 (s, 3H), 1.42 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 161.9, 137.0, 136.9, 136.3, 127.4, 126.5, 120.4, 62.1, 51.8, 14.0.

HRMS (ESI): calc. for [($C_{11}H_{13}NO_3S$)H] (M+H) 240.0694, measured 240.0702.

Rf (hexane/ethyl acetate = 9:1): 0.30.

Butyl 2-(3-ethoxy-6-methoxy-1H-isoindol-1-yl)acetate (3n).



Colourless liquid; eluent (15% ethylacetate in hexanes). The representative general procedure was followed using **1a** (50 mg), **2d** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 68 mg and yield is 80%.

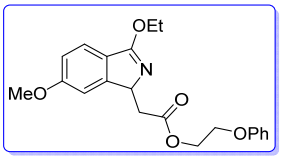
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 4.0 Hz, 1H), 6.88 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.98 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.45 – 4.36 (m, 2H), 4.12 (t, *J* = 8.0 Hz, 2H), 3.80 (s, 3H), 2.86 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.50 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.61 – 1.54 (m, 2H), 1.40 (t, *J* = 8.0 Hz, 2H), 1.35 – 1.29 (m, 2H), 0.89 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.6, 169.0, 161.2, 155.0, 125.7, 121.5, 114.2, 107.6, 64.5, 64.4, 63.9, 55.5, 38.6, 30.6, 19.1, 14.4, 13.7.

HRMS (ESI): calc. for [($C_{17}H_{23}NO_4$)H] (M+H) 306.1705, measured 306.1608.

Rf (hexane/ethyl acetate = 3:1): 0.38.

2-phenoxyethyl 2-(3-ethoxy-6-methoxy-1H-isoindol-1-yl)acetate (3o).



Colourless liquid; eluent (25% ethylacetate in hexanes). The representative general procedure was followed using **1a** (50 mg), **2h** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 58 mg and yield is 56%.

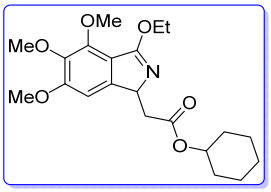
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 4.0 Hz, 1H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 3H), 5.00 (t, *J* = 7.2 Hz, 1H), 4.53 – 4.47 (m, 2H), 4.44 – 4.37 (m, 2H), 4.15 (t, *J* = 4.0 Hz, 2H), 3.79 (s, 3H), 2.87 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.61 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.39 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.4, 169.1, 161.2, 158.4, 154.8, 129.4, 125.8, 121.5, 121.1, 114.5, 114.1, 107.7, 65.7, 64.3, 63.9, 62.9, 55.5, 38.6, 14.41.

HRMS (ESI): calc. for [($C_{21}H_{23}NO_5$)H] (M+H) 370.1654, measured 370.1670.

Rf (hexane/ethyl acetate = 2:1): 0.21.

Cyclohexyl 2-(3-ethoxy-4,5,6-trimethoxy-1H-isoindol-1-yl)acetate (3p).



Colourless liquid; eluent (16% ethylacetate in hexanes). The representative general procedure was followed using **1h** (50 mg), **2a** (2.0 equiv) and the reaction was done at rt for 14 h. The desired product was isolated in 90 mg and yield is 94%.

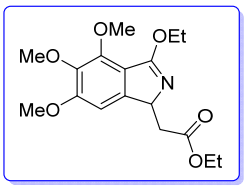
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.79 (s, 1H), 5.00 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.74 – 4.66 (m, 1H),), 4.46 – 4.35 (m, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.08 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.55 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.75 – 1.69 (m, 2H), 1.64 – 1.60 (m, 2H), 1.55 – 1.44 (m, 2H), 1.40 (t, *J* = 8.0 Hz, 3H), 1.29 – 1.22 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.5, 154.5, 148.3, 143.1, 137.0, 128.7, 98.8, 72.5, 64.1, 63.8, 61.0, 60.6, 56.3, 37.5, 31.4, 25.3, 23.6, 14.5.

HRMS (ESI): calc. for [($C_{21}H_{29}NO_6$)H] (M+H) 400.1760, measured 400.1765.

Rf (hexane/ethyl acetate = 2:1): 0.30.

Ethyl 2-(3-ethoxy-4,5,6-trimethoxy-1H-isoindol-1-yl)acetate (3q).



Colourless liquid; eluent (21% ethylacetate in hexanes). The representative general procedure was followed using **1h** (50 mg), **2c** (2.0 equiv) and the reaction was done at rt for 8 h. The desired product was isolated in 52 mg and yield is 70%.

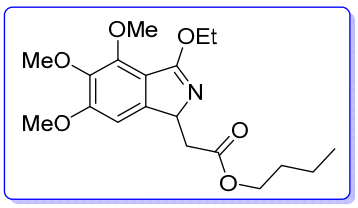
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.79 (s, 1H), 5.04 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.46 – 4.37 (m, 2H), 4.13 – 4.08 (m, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.06 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.42 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.39 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 168.5, 154.5, 148.3, 143.05, 136.9, 128.6, 98.8, 64.1, 63.8, 60.9, 60.6, 60.3, 56.2, 37.4, 14.4, 14.1.

HRMS (ESI): calc. for [($C_{17}H_{23}NO_6$)H] (M+H) 338.1604, measured 338.1606.

Rf (hexane/ethyl acetate = 2:1): 0.27.

Butyl 2-(3-ethoxy-4,5,6-trimethoxy-1H-isoindol-1-yl)acetate (3r).



Colourless liquid; eluent (20% ethylacetate in hexanes). The representative general procedure was followed using **1h** (50 mg), **2d** (2.0 equiv) and the reaction was done at rt for 14 h. The desired product was isolated in 67 mg and yield is 78%.

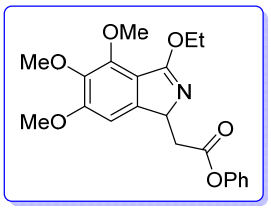
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.78 (s, 1H), 5.01 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.45 – 4.34 (m, 2H), 4.06 – 4.00 (m, 2H), 3.92 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.05 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.47 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.54 – 1.47 (m, 2H), 1.38 (t, *J* = 8.0 Hz, 3H), 1.25 – 1.33 (m, 2H), 0.85 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 168.5, 154.5, 148.3, 143.0, 136.9, 128.6, 98.8, 64.1, 63.8, 60.9, 60.6, 60.3, 56.2, 37.4, 30.6, 18.9, 14.4, 14.1.

HRMS (ESI): calc. for [($C_{19}H_{27}NO_6$)H] (M+H) 366.1916, measured 366.1921.

Rf (hexane/ethyl acetate = 2:1): 0.38.

Phenyl 2-(3-ethoxy-4,5,6-trimethoxy-1H-isoindol-1-yl)acetate (3s).



Colourless liquid; eluent (20% ethylacetate in hexanes). The representative general procedure was followed using **1h** (50 mg), **2e** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 70 mg and yield is 76%.

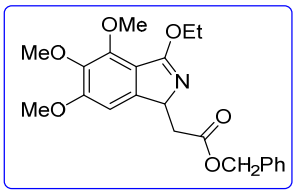
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (t, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.01 (dd, *J* = 8.0, 4.0 Hz, 2H), 6.83 (s, 1H), 5.14 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.52 – 4.40 (m, 2H), 3.97 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.31 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.80 (dd, *J* = 12.0, 8.0 Hz, 1H), 1.42 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.6, 168.8, 154.7, 150.7, 148.3, 143.2, 136.4, 129.2, 128.5, 125.6, 121.5, 98.99, 64.3, 63.6, 60.9, 60.6, 56.2, 37.3, 14.4.

HRMS (ESI): calc. for [($C_{21}H_{23}NO_6$)H] (M+H) 386.1603, measured 386.1600.

Rf (hexane/ethyl acetate = 2:1): 0.31.

Benzyl 2-(3-ethoxy-4,5,6-trimethoxy-1H-isoindol-1-yl)acetate (3t).



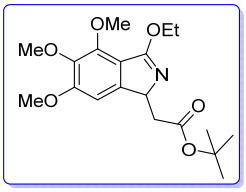
Colourless liquid; eluent (21% ethylacetate in hexanes). The representative general procedure was followed using **1h** (50 mg), **2f** (2.0 equiv) and the reaction was done at rt for 14 h. The desired product was isolated in 62 mg and yield is 66%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 – 7.22 (m, 5H), 6.78 (s, 1H), 5.09 (d, *J* = 4.0 Hz, 2H), 5.06 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.45 – 4.34 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.14 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.55 (dd, *J* = 12.0, 8.0 Hz, 1H), 1.39 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.2, 168.6, 154.5, 148.3, 143.1, 136.7, 136.0, 128.6, 128.3, 128.0, 127.9, 98.9, 66.1, 64.1, 63.7, 60.9, 60.6, 56.2, 37.4, 14.4.
HRMS (ESI): calc. for [($C_{22}H_{25}NO_6$)H] (M+H) 400.1760, measured 400.1765.

Rf (hexane/ethyl acetate = 2:1): 0.33.

***tert*-Butyl 2-(3-ethoxy-4,5,6-trimethoxy-1H-isoindol-1-yl)acetate (3u**).



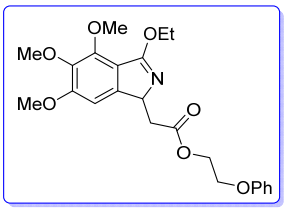
Colourless liquid; eluent (20% ethylacetate in hexanes). The representative general procedure was followed using **1h** (50 mg), **2g** (2.0 equiv) and the reaction was done at rt for 14 h. The desired product was isolated in 45 mg and yield is 52%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.79 (s, 1H), 4.96 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.48 – 4.37 (m, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.02 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.54 (dd, *J* = 16.0, 4.0 Hz, 1H), 1.40 (t, *J* = 8.0 Hz, 3H), 1.28 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 168.4, 154.4, 148.3, 143.1, 137.2, 128.7, 98.8, 80.1, 64.1, 63.9, 61.0, 60.6, 56.3, 38.3, 27.9, 14.5.
HRMS (ESI): calc. for [($C_{19}H_{27}NO_6$)H] (M+H) 366.1916, measured 366.1919.

Rf (hexane/ethyl acetate = 2:1): 0.42.

2-phenoxyethyl 2-(3-ethoxy-4,5,6-trimethoxy-1H-isoindol-1-yl)acetate (3v).



Colourless liquid; eluent (30% ethylacetate in hexanes). The representative general procedure was followed using **1h** (50 mg), **2h** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 58 mg and yield is 57%.

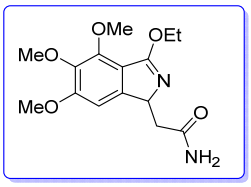
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (t, *J* = 8.0 Hz, 2H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.77 (s, 1H), 5.05 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.46 – 4.36 (m, 4H), 4.08 (t, *J* = 4.0 Hz, 2H), 3.93 (s, 3H), 3.84 (s, 6H), 3.13 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.53 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.36 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 168.7, 158.4, 154.6, 148.3, 143.1, 136.7, 129.4, 128.5, 121.0, 114.5, 98.9, 65.8, 64.2, 63.7, 62.7, 60.9, 60.6, 56.2, 37.3, 14.4.

HRMS (ESI): calc. for [($C_{23}H_{27}NO_7$)H] (M+H) 430.1866, measured 430.1874.

Rf (hexane/ethyl acetate = 2:1): 0.21.

2-(3-Ethoxy-4,5,6-trimethoxy-1H-isoindol-1-yl)acetamide (3w).



Colourless liquid; eluent (5% methanol in DCM). The representative general procedure was followed using **1h** (50 mg), **2i** (2.0 equiv) and the reaction was done at 80^0 C for 16 h. The desired product was isolated in 14 mg and yield is 21%.

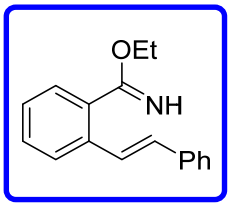
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (s, 1H), 6.81 (s, 1H), 4.86 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.42 (q, *J* = 8.0 Hz, 2H), 3.96 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.19 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.06 (dd, *J* = 16.0, 12.0 Hz, 1H), 1.43 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.53, 168.48, 167.7, 154.8, 148.4, 143.4, 136.7, 98.9, 64.3, 63.8, 61.0, 60.7, 56.3, 39.1, 14.4.

HRMS (ESI): calc. for [($C_{25}H_{20}N_2O_5$)H] (M+H) 309.1450, measured 309.1448.

Rf (hexane/ethyl acetate = 2:1): 0.31.

Ethyl (E)-2-styrylbenzimidate (3x).



Colourless liquid; eluent (5% ethylacetate in hexanes). The representative general procedure was followed using **1d** (50 mg), **2j** (2.0 equiv) and the reaction was done at rt for 16 h. The desired product was isolated in 36 mg and yield is 43%.

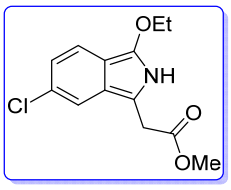
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.42 (dd, *J* = 12.0, 8.0 Hz, 3H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 16.0 Hz, 1H), 4.34 (q, *J* = 8.0 Hz, 2H), 1.37 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.6, 137.0, 131.3, 129.9, 128.7, 127.9, 127.5, 126.7, 126.1, 62.06, 14.31.

HRMS (ESI): calc. for [($C_{17}H_{17}NO$)H] (M+H) 252.1388, measured 252.1392.

Rf (hexane/ethyl acetate = 9:1): 0.37.

Methyl 2-(6-chloro-3-ethoxy-2H-isoindol-1-yl)acetate (4a).



Colourless liquid; eluent (30% ethylacetate in hexanes). The representative general procedure was followed using **1f** (50 mg), **2b** (2.0 equiv) and the reaction was done at rt for 36 h. The desired product was isolated in 35 mg and yield is 48%.

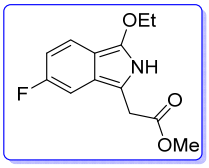
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (t, *J* = 4.0 Hz, 1H), 7.36 (d, *J* = 4.0 Hz, 2H), 4.43 (q, *J* = 8.0 Hz, 2H), 3.68 (s, 3H), 2.96 (d, *J* = 16.0 Hz, 1H), 2.80 (d, *J* = 16.0 Hz, 1H), 1.41 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.8, 168.5, 153.6, 131.4, 137.0, 130.6, 129.5, 123.0, 121.9, 94.8, 64.8, 52.0, 43.1, 14.2.

HRMS (ESI): calc. for [($C_{13}H_{14}ClNO_3$)H] (M+H) 268.0740, measured 268.0560.

Rf (hexane/ethyl acetate = 2:1): 0.36.

Methyl 2-(6-fluoro-3-ethoxy-2H-isoindol-1-yl)acetate (4b).



Colourless liquid; eluent (32% ethylacetate in hexanes). The representative general procedure was followed using **1e** (50 mg), **2b** (2.0 equiv) and the reaction was done at rt for 36 h. The desired product was isolated in 39 mg and yield is 52%.

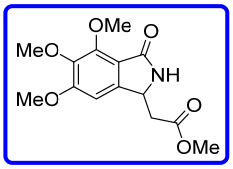
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.24 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.10 – 7.04 (m, 1H), 5.66 (s, 1H), 4.43 (q, *J* = 8.0 Hz, 2H), 3.68 (s, 3H), 2.94 (d, *J* = 16.0 Hz, 1H), 2.82 (d, *J* = 16.0 Hz, 1H), 1.41 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 168.6, 165.8, 163.3, 154.5, 154.4 (F-Coupling), 128.0, 128.1(F-Coupling), 122.6, 116.5, 116.3 (F-Coupling), 110.5, 110.3 (F-Coupling), 94.6, 94.5 (F-Coupling), 64.9, 51.9, 43.4, 14.3.

HRMS (ESI): calc. for [($C_{13}H_{14}FNO_3$)H] (M+H) 252.1036, measured 252.1042.

Rf (hexane/ethyl acetate = 2:1): 0.31.

Methyl 2-(4,5,6-trimethoxy-3-oxoisoindolin-1-yl)acetate (5a).



Colourless liquid; eluent (40% ethylacetate in hexanes). The representative general procedure was followed using **3hb** (50 mg) and the reaction was done at 80^0C for 12 h. The desired product was isolated in 40 mg and yield is 87%.

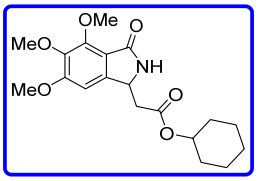
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11 (s, 1H), 6.81 (s, 1H), 4.84 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.96 (s, 3H), 3.88 (s, 6H), 3.73 (s, 3H), 3.33 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.27 (dd, *J* = 16.0, 8.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.2, 169.7, 155.3, 148.4, 144.9, 130.3, 127.2, 101.7, 61.0, 60.8, 56.3, 52.1, 51.1, 37.9.

HRMS (ESI): calc. for $[(C_{14}H_{17}NO_6)H]$ (M+H) 296.1134, measured 296.1140.

Rf (hexane/ethyl acetate = 2:1): 0.24.

Cyclohexyl 2-(4,5,6-trimethoxy-3-oxoisoindolin-1-yl)acetate (5b).



Colourless liquid; eluent (38% ethylacetate in hexanes). The representative general procedure was followed using **3ha** (50 mg), and the reaction was done at 80 °C for 12 h. The desired product was isolated in 42 mg and yield is 91%.

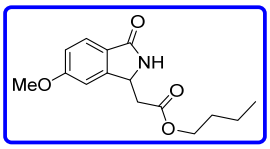
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10 (s, 1H), 6.83 (s, 1H), 4.87 – 4.73 (m, 2H), 3.97 (s, 3H), 3.87 (s, 6H), 3.34 – 3.22 (m, 1H), 2.26 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.83 (t, *J* = 12.0 Hz, 2H), 1.75 – 1.63 (m, 2H), 1.54 – 1.39 (m, 2H), 1.36 – 1.21 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.1, 169.7, 155.2, 148.4, 144.9, 130.5, 127.3, 101.6, 73.7, 61.0, 60.8, 56.3, 51.3, 38.3, 31.5, 25.2, 23.7.

HRMS (ESI): calc. for $[(C_{19}H_{25}NO_6)H]$ (M+H) 364.1760, measured 364.1763.

Rf (hexane/ethyl acetate = 2:1): 0.28.

Butyl 2-(6-methoxy-3-oxoisoindolin-1-yl)acetate (5c).



Colourless liquid; eluent (30% ethylacetate in hexanes). The representative general procedure was followed using **1a** (50 mg), and the reaction was done at 80 °C for 16 h. The desired product was isolated in 37 mg and yield is 81%

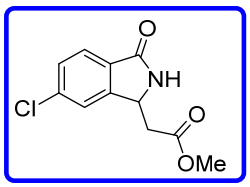
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.86 (s, 1H), 6.60 (s, 1H), 4.84 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.15 (t, *J* = 8.0 Hz, 2H), 3.85 (s, 3H), 2.96 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.44 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.63 – 1.59 (m, 2H), 1.40 – 1.34 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 169.9, 163.2, 148.2, 125.5, 124.2, 115.0, 107.3, 65.2, 55.7, 52.5, 39.7, 30.6, 19.1, 13.7.

HRMS (ESI): calc. for [($C_{15}H_{19}NO_4$)H] (M+H) 278.1392, measured 278.1394.

Rf (hexane/ethyl acetate = 2:1): 0.33.

Methyl 2-(6-chloro-3-oxoisoindolin-1-yl)acetate (5d).



Colourless liquid; eluent (30% ethylacetate in hexanes). The representative general procedure was followed using **3fb** (50 mg), and the reaction was done at 80 °C for 16 h. The desired product was isolated in 38 mg and yield is 84%

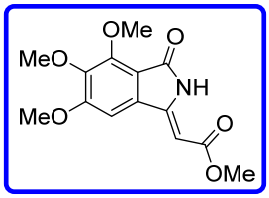
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 6.79 (s, 1H), 4.89 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.77 (s, 3H), 2.99 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.46 (dd, *J* = 16.0, 8.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.4, 168.9, 147.3, 138.6, 130.3, 129.40, 125.3, 122.9, 52.4, 39.1.

HRMS (ESI): calc. for [($C_{11}H_{10}ClNO_3$)H] (M+H) 240.0427, measured 240.0432.

Rf (hexane/ethyl acetate = 2:1): 0.34.

Methyl (Z)-2-(4,5,6-trimethoxy-3-oxoisoindolin-1-ylidene)acetate (6a).



Colourless liquid; eluent (21% ethylacetate in hexanes). The representative general procedure was followed using **3hb** (50 mg), and the reaction was done at 80 °C for 16 h. The desired product was isolated in 39 mg and yield is 85%

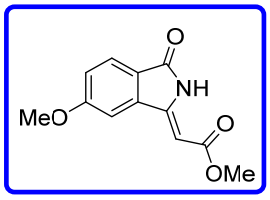
^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.61 (s, 1H), 7.15 (s, 1H), 6.08 (s, 1H), 4.03 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.78 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 167.7, 157.2, 150.3, 146.3, 145.7, 125.9, 120.8, 102.4, 94.3, 61.2, 60.8, 56.5, 51.6.

HRMS (ESI): calc. for [($C_{14}H_{15}NO_6$)H] (M+H) 294.0977, measured 294.0981.

Rf (hexane/ethyl acetate = 3:1): 0.31.

Methyl (Z)-2-(6-methoxy-3-oxoisoindolin-1-ylidene)acetate (6b).



Colourless liquid; eluent (18% ethylacetate in hexanes). The representative general procedure was followed using **3ab** (50 mg), and the reaction was done at 80 °C for 16 h. The desired product was isolated in 37 mg and yield is 81%

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.43 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 4.0 Hz, 1H), 7.08 (dd, J = 8.0, 4.0 Hz, 1H), 5.71 (s, 1H), 3.90 (s, 3H), 3.79 (s, 3H).

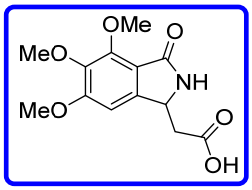
^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.9, 163.8, 147.6, 138.8, 128.6, 125.6, 122.0, 117.8, 105.9,

90.8, 55.9, 51.7.

HRMS (ESI): calc. for [($C_{12}H_{11}NO_4$)H] (M+H) 234.0766, measured 234.0772.

Rf (hexane/ethyl acetate = 4:1): 0.30.

2-(4,5,6-Trimethoxy-3-oxoisoindolin-1-yl)acetic acid (7a).



Colourless liquid; eluent (30% methanol in DCM). The representative general procedure was followed using **3ha** (50 mg), and the reaction was done at 80 °C for 12 h. The desired product was isolated in 30 mg and yield is 81%

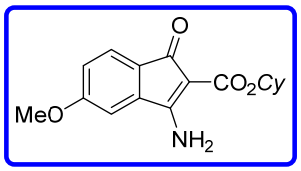
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.43 (s, 1H), 7.00 (s, 1H), 4.78 (d, *J* = 8.0 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 2.97 (d, *J* = 16.0 Hz, 1H), 2.08 (t, *J* = 12.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.7, 168.6, 154.5, 148.2, 144.3, 131.3, 127.8, 101.4, 60.6, 60.5, 56.2.

HRMS (ESI): calc. for [($C_{13}H_{15}NO_6$)H] (M+H) 282.0977, measured 282.0976.

Rf (hexane/ethyl acetate = 2:1): 0.31.

Cyclohexyl 3-amino-5-methoxy-1-oxo-1H-indene-2-carboxylate (8a).



Colourless liquid; eluent (40% ethylacetate in hexanes). The representative general procedure was followed using **3ad** (50 mg), and the reaction was done at 80 °C for 16 h. The desired product was isolated in 40 mg and yield is 81%

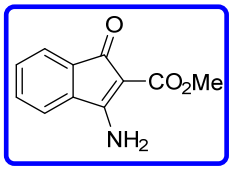
^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.56 (s, 1H), 8.92 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.07 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.96 (d, *J* = 4.0 Hz, 1H), 4.84 – 4.79 (m, 1H), 3.84 (s, 3H), 1.80 – 1.73 (m, 4H), 1.52 – 1.45 (m, 2H), 1.40 – 1.25 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 185.3, 170.9, 164.5, 163.5, 138.7, 126.7, 122.9, 115.8, 107.3, 93.6, 69.9, 55.8, 31.4, 25.1, 23.1.

HRMS (ESI): calc. for [($C_{17}H_{19}NO_4$)H] (M+H) 302.1392, measured 302.1395.

Rf (hexane/ethyl acetate = 2:1): 0.31.

Methyl 3-amino-1-oxo-1H-indene-2-carboxylate (8b).



Colourless liquid; eluent (40% ethylacetate in hexanes). The representative general procedure was followed using **3db** (50 mg), and the reaction was done at 80 °C for 16 h. The desired product was isolated in 39 mg and yield is 79%

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.67 (s, 1H), 9.05 (s, 1H), 7.98 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.47 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.68 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 186.5, 170.5, 165.2, 135.6, 135.2, 132.9, 131.9, 121.2, 120.9, 93.2, 43.9.

HRMS (ESI): calc. for [($C_{11}H_9NO_3$)Na] (M+Na) 226.0479, measured 226.0488.

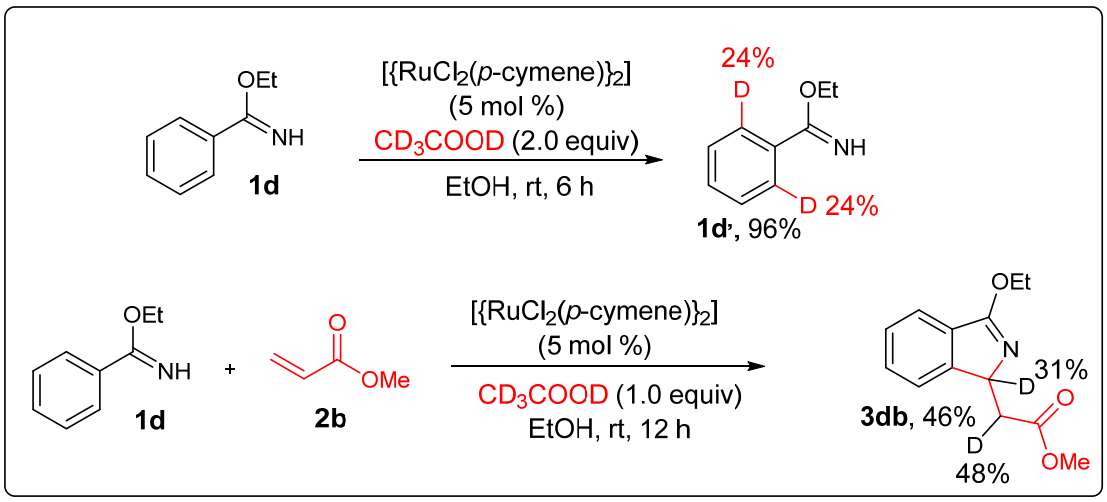
Rf (hexane/ethyl acetate = 2:1): 0.21.

4B.15 Mechanistic Studies.

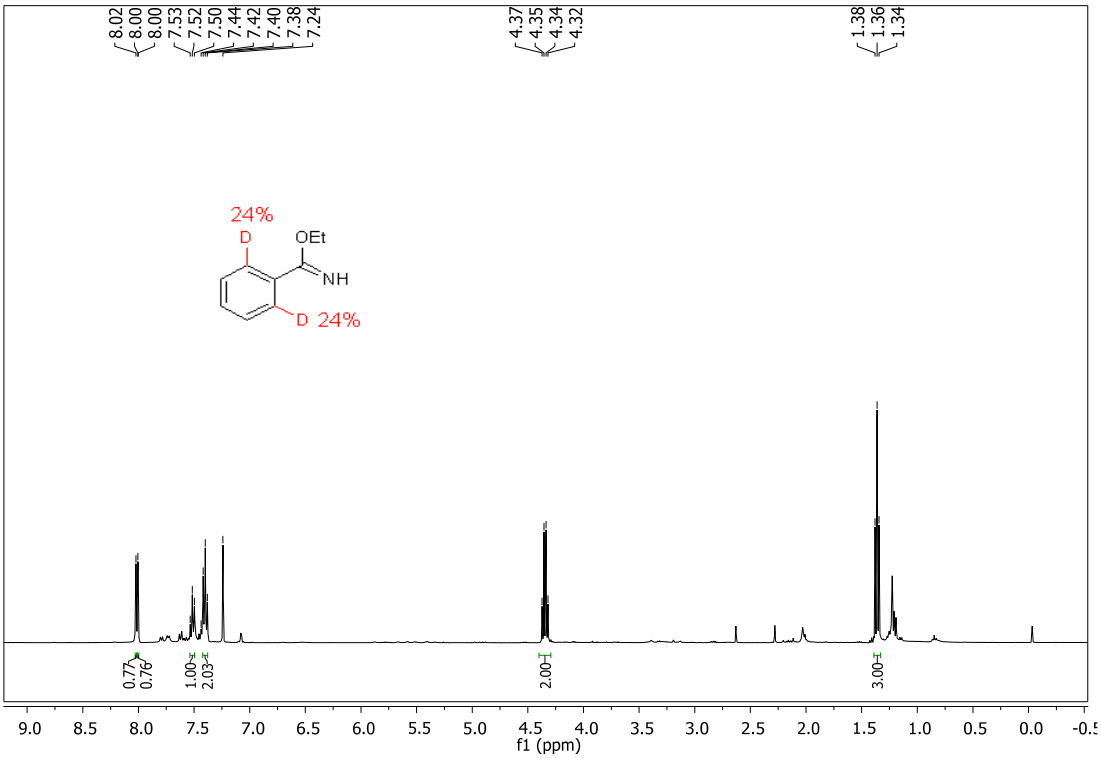
4B.15.1 Deuterium studies

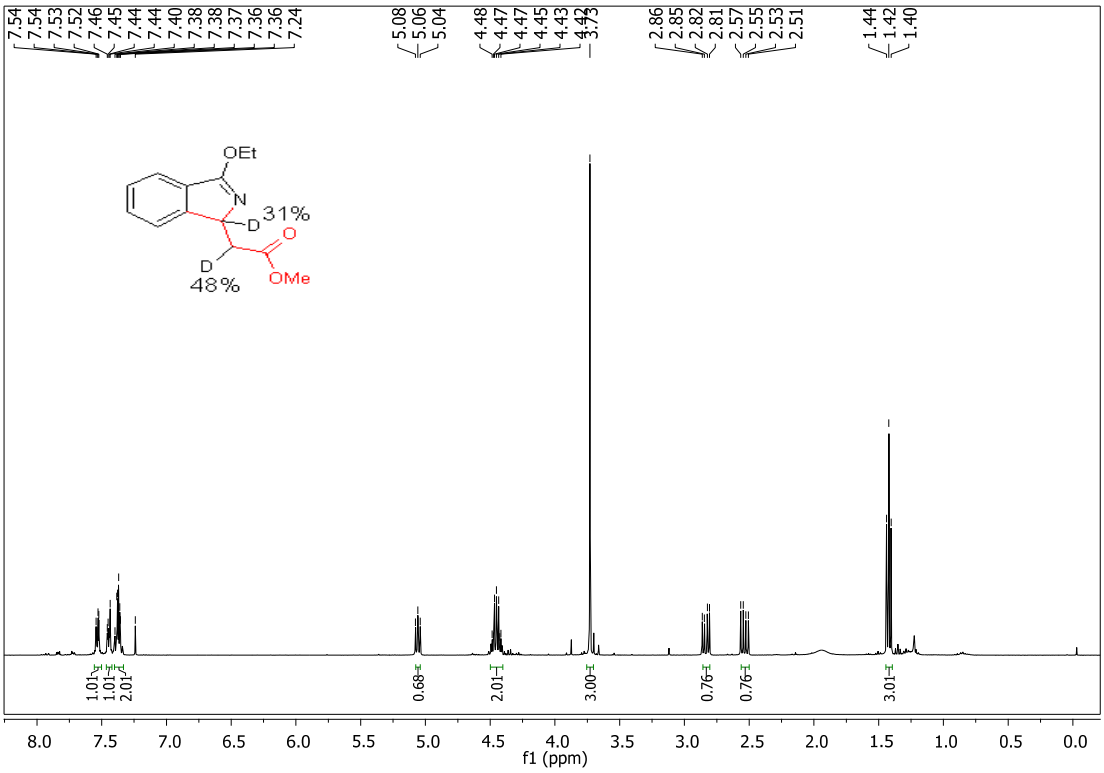
To know the feasibility of C–H bond activation of aromatic imidate at room temperature, the following deuterium labelling experiment was done. **1d** was treated with CD_3COOD in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) in ethanol at room temperature for 6 h. In the reaction, product **D-1d** was observed in 96% yield with 24% of deuterium incorporation at the both *ortho* carbons, respectively It clearly indicates that the *ortho* C–H bond cleavage of aromatic amide in intermediate **9** is a reversible process. . Further, the reaction of **1d** was examined with **2b** in the presence of CD_3COOD under the optimized reaction conditions. In the reaction, product **3db** was observed in 46% yield. In the obtained product **D-3db**, the deuterium incorporation was found at β position of the carbonyl group of alkene clearly indicates that the

product **3** formed via alkenylation followed by intramolecular nucleophilic addition of imidate nitrogen followed by protonation of C-Ru at the β position of the alkene double bond.



^{1}H NMR Spectra of Compound **1d' and 3db.**



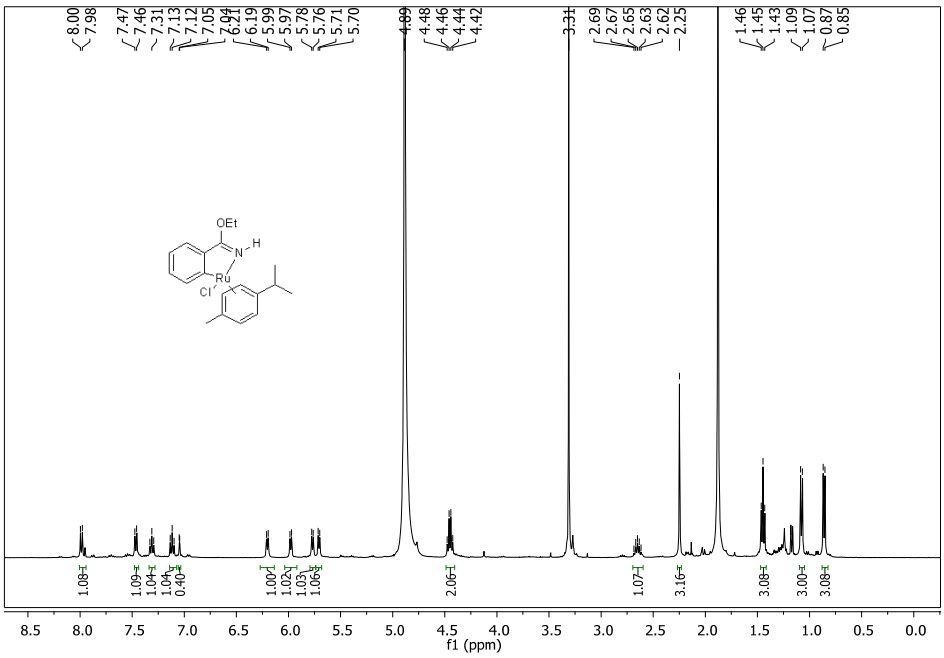


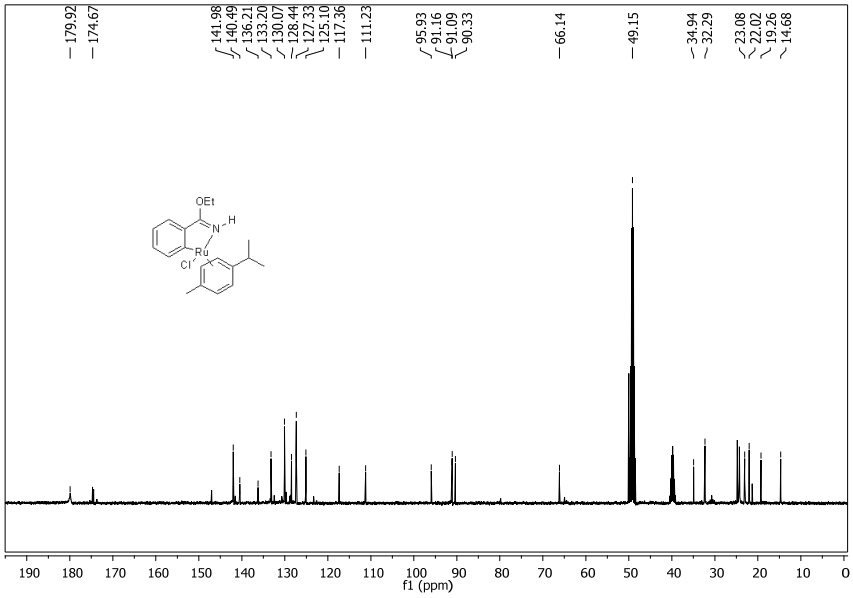
4B.15.2 Procedure for the Preparation of a Five-Membered Ruthenacycle Intermediate 11.

A 25-mL schlenk tube with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (50 mg), was evacuated and purged with nitrogen gas three times To the tube, were then added benzimidate **1d** (1.0 equiv), AcOH (2.0 equiv) and EtOH (2.0 mL) via syringe and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that the septum was completely covered by Teflon tape. Then, the reaction mixture was allowed to stir at room temperature for 24 h. After the reaction mixture was diluted with methanol, filtered through Celite and the filtrate was concentrated and taken for further analysis without any further purification. We have tried to get a single crystal. However, we could not make it. The NMR spectra was recorded with the crude reaction mixture without further purification.

NMR Data

^{1}H and ^{13}C NMR Spectra of Compound **11.**



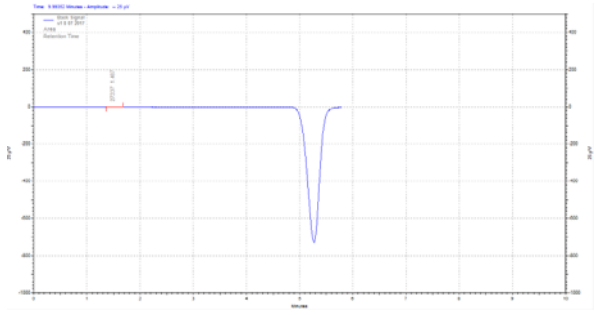


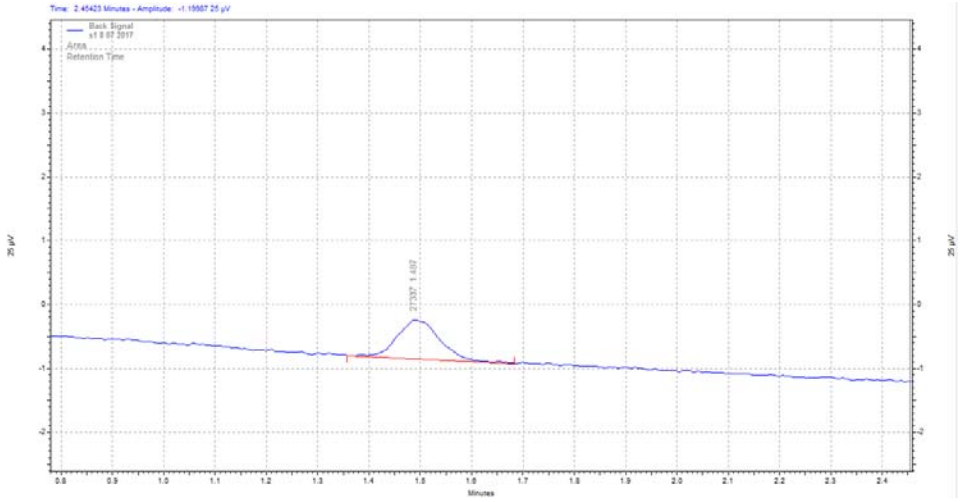
Note: In ^{13}C NMR, a characteristic C-Ru peak found at δ 179.92 due to the deshilding of C-Ru.

4B.15.3 Procedure for the Determination of H_2 gas Evolution by GC.

A 15-mL schlenk tube (or) pressure tube with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) was evacuated and purged with nitrogen gas three times. To the tube, were then added aromatic imitades **1** (50 mg), alkenes **2** (2.0equiv), adamantane -1-carboxylic acid (0.5 equiv) and Ehanol (1.0 mL) via syringes and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, the septum was completely covered by Teflon tape. Then, the reaction mixture was allowed to stir at room temperature (~ 24 °C) for 16 h. After that, the gaseous reaction mixture was taken by the syringe and injected into the gas chromatograph (GC) equipped with a TCD detector (Agilent 7890). The characteristic peak for H_2 gas was observed in the exact region (retention time 1-1.2 minutes).

Gas Chromatograph Spectrum





Area % Report

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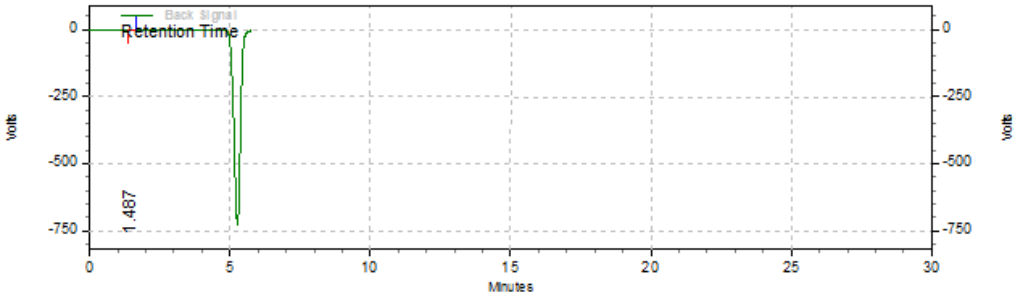
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\sleep mode.met
Acquired: 7/8/2017 1:43:51 PM
Printed: 7/8/2017 6:49:28 PM



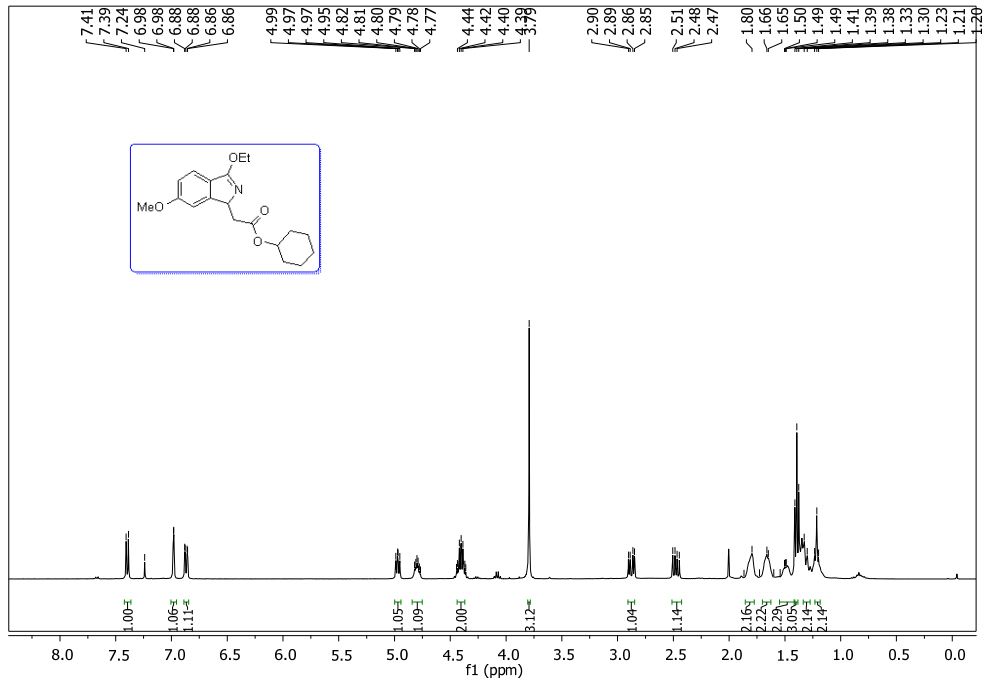
Back Signal
Results

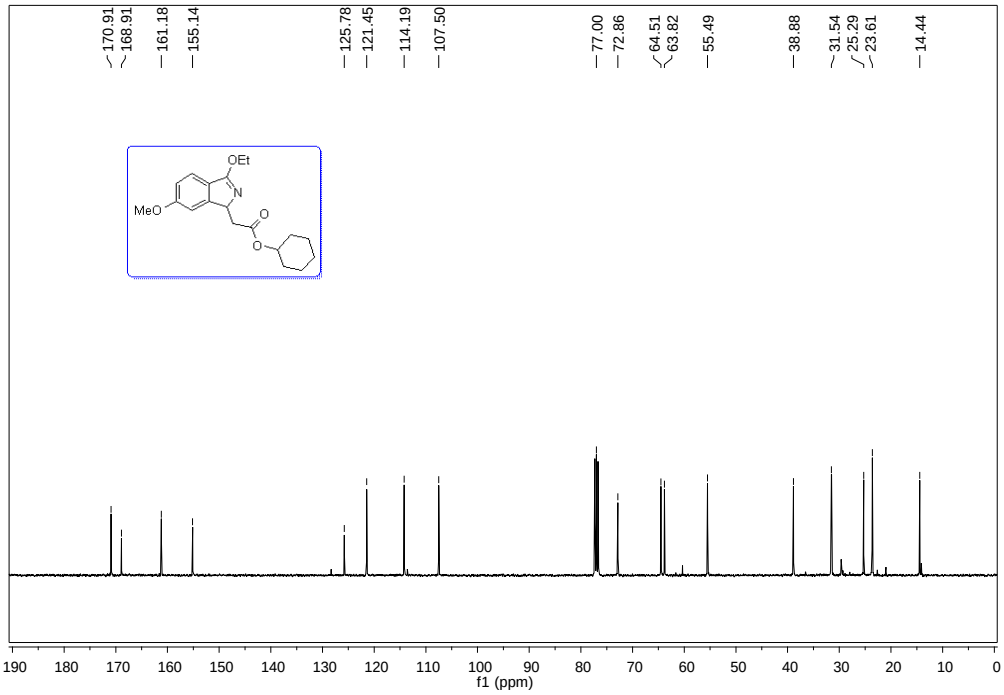
Retention Time	Area	Area %	Height	Height %
1.487	27337	100.00	4659	100.00

Totals	27337	100.00	4659	100.00

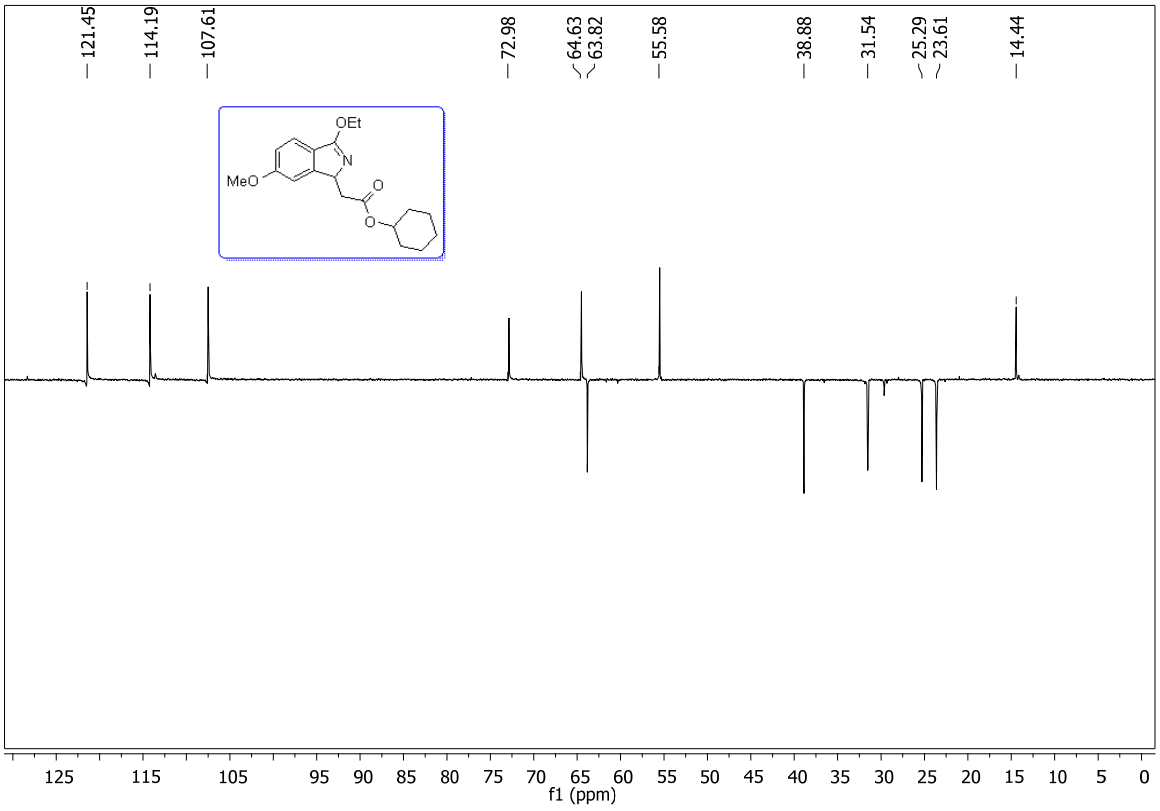
4B.16. Copies of ^{1}H and ^{13}C NMR Spectra of selected Compounds

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

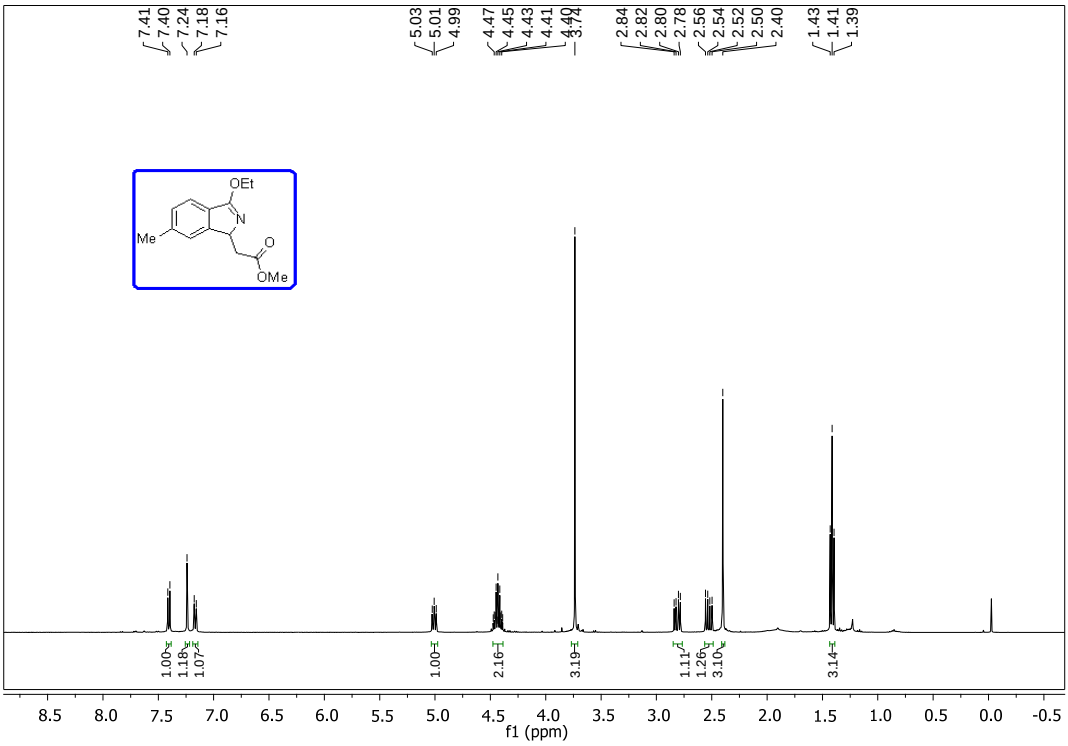


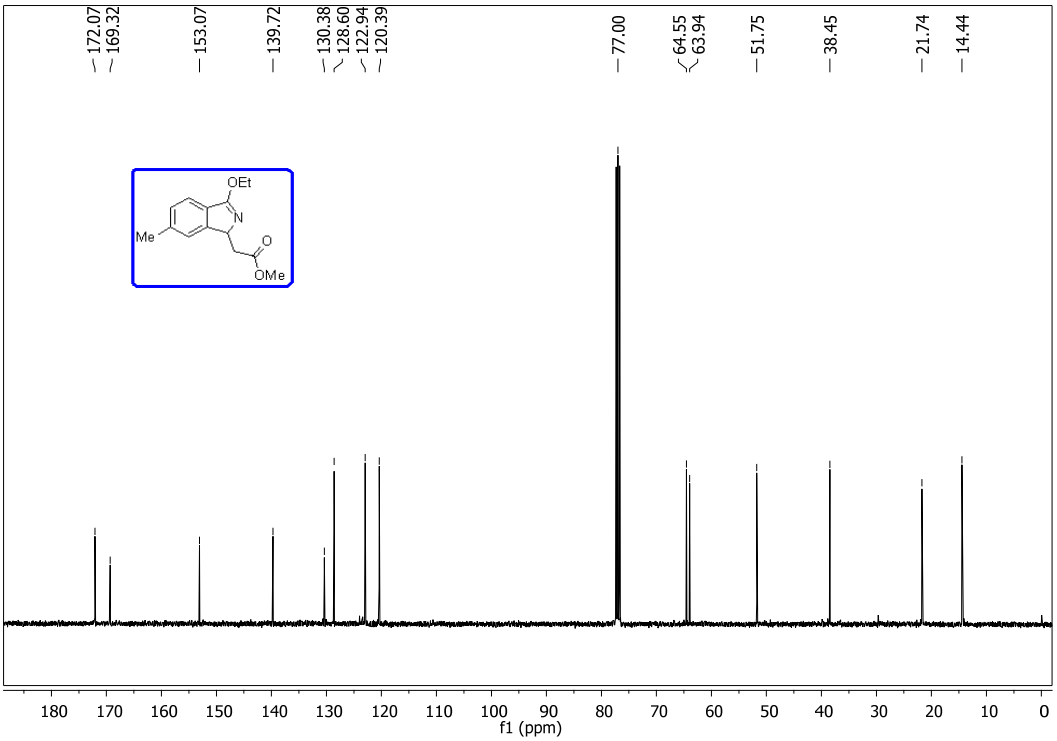


DEPT (135) NMR Spectrum of Compound **3a.**

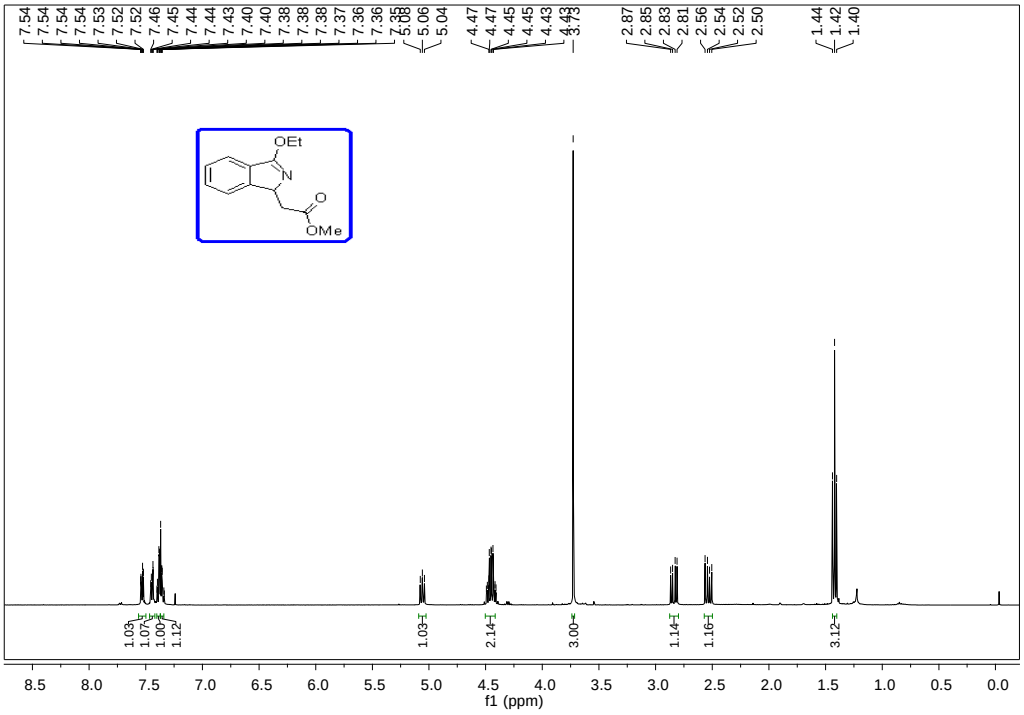


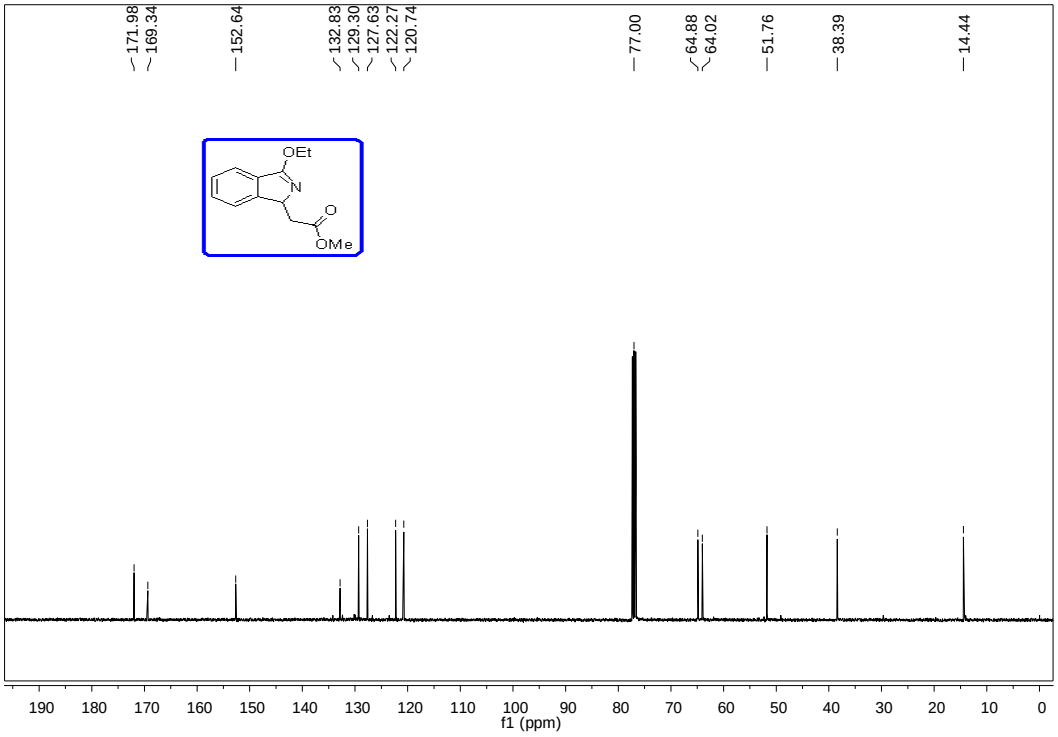
^{1}H and ^{13}C NMR Spectra of Compound **3b.**



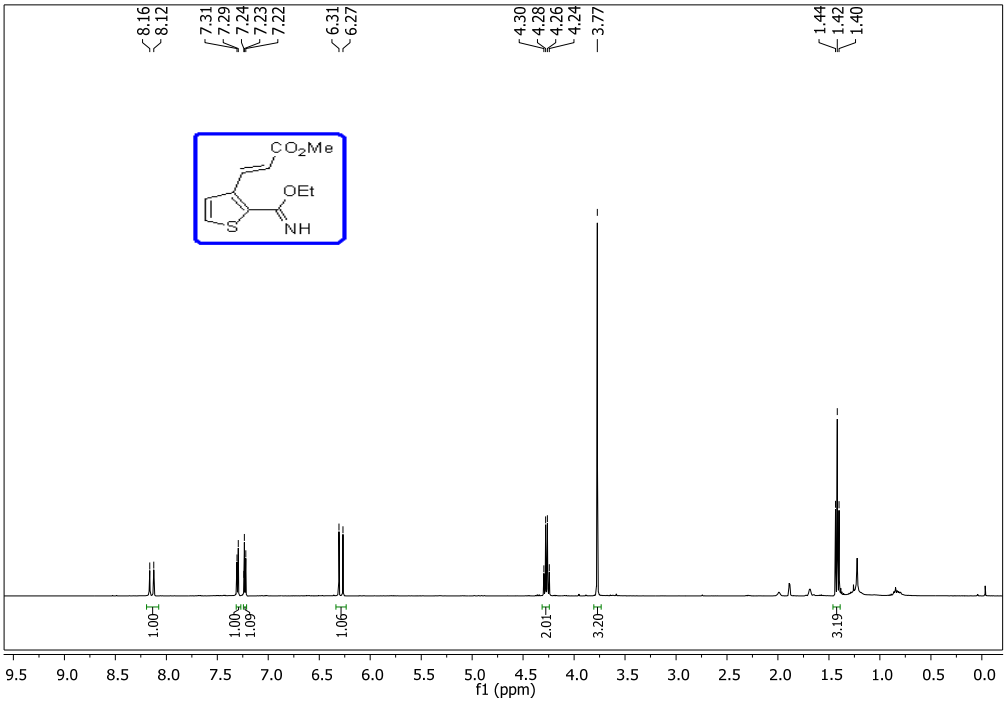


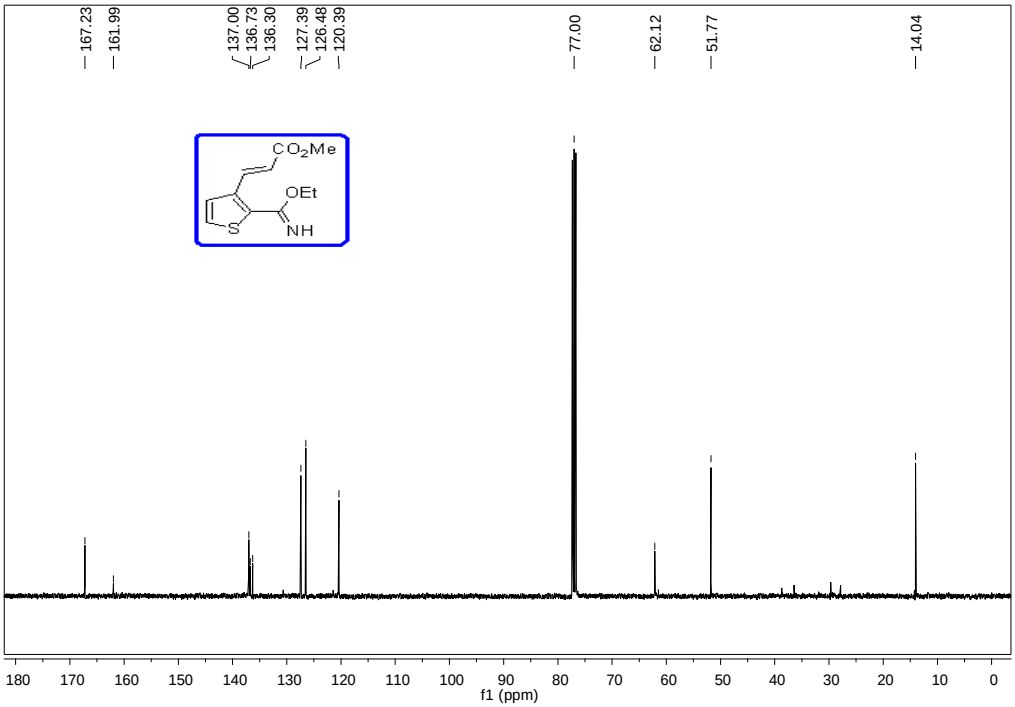
^{1}H and ^{13}C NMR Spectra of Compound **3d**



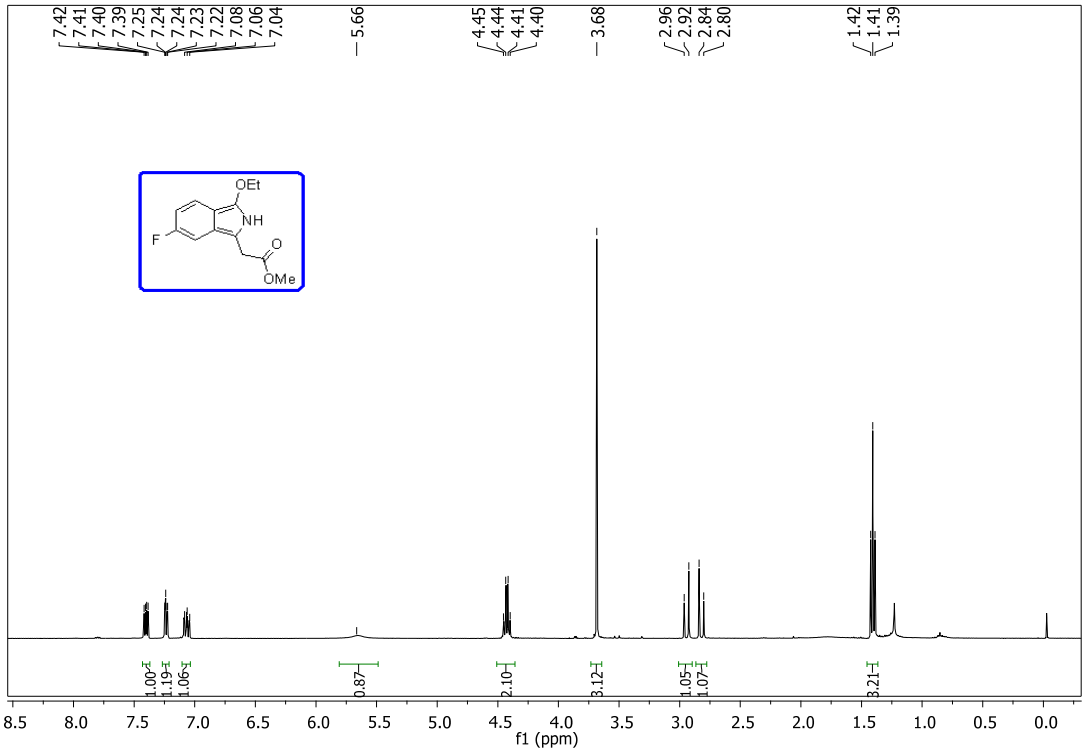


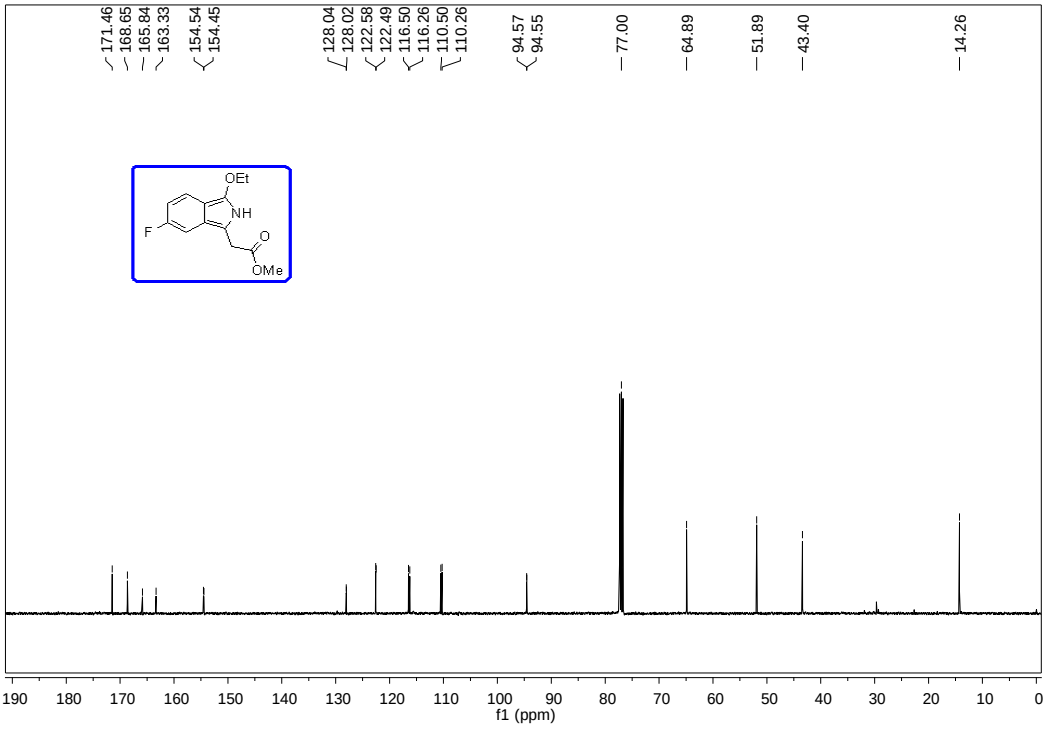
^{1}H and ^{13}C NMR Spectra of Compound **3m.**



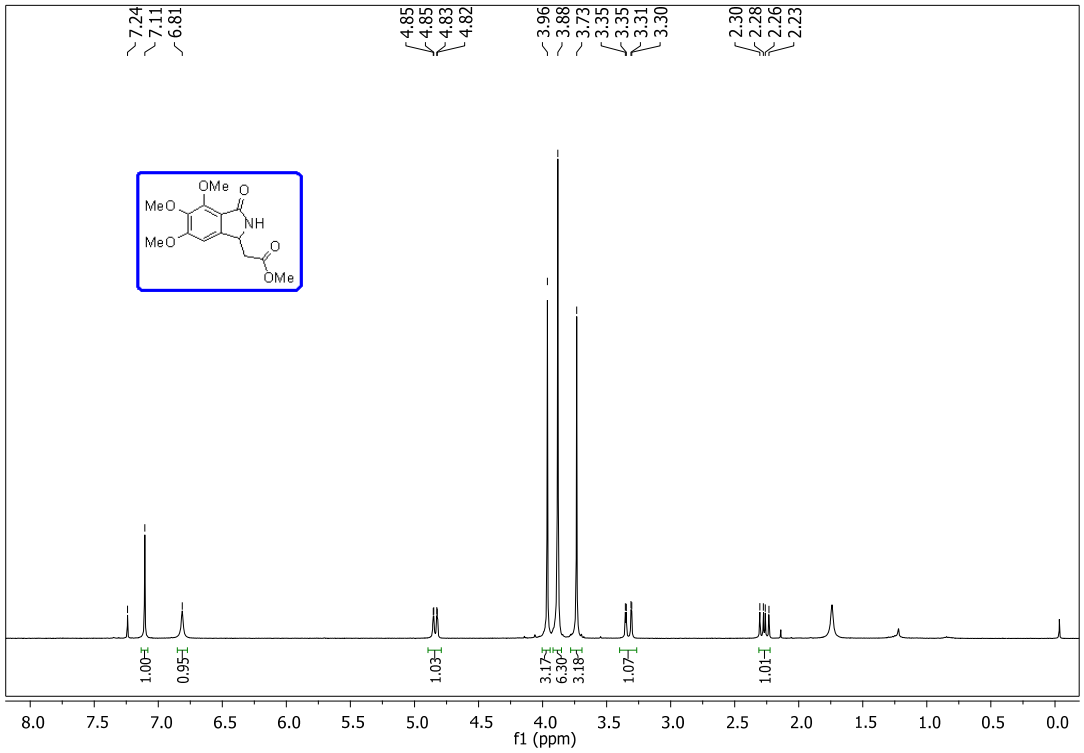


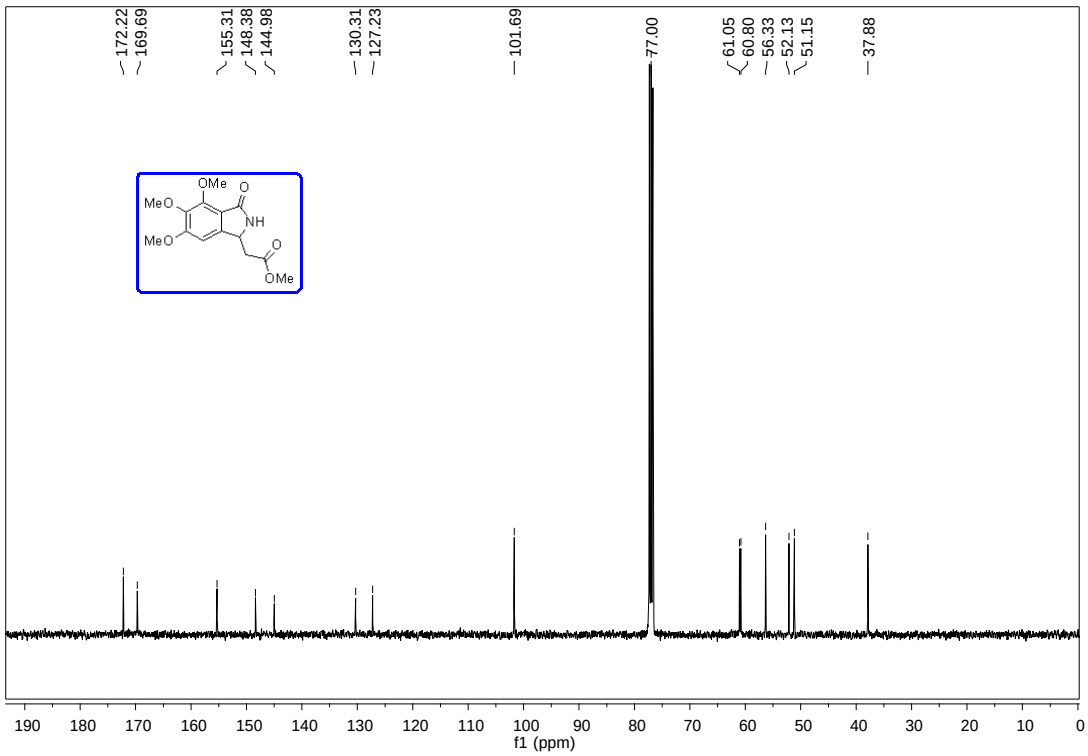
^{1}H and ^{13}C NMR Spectra of Compound **4b.**



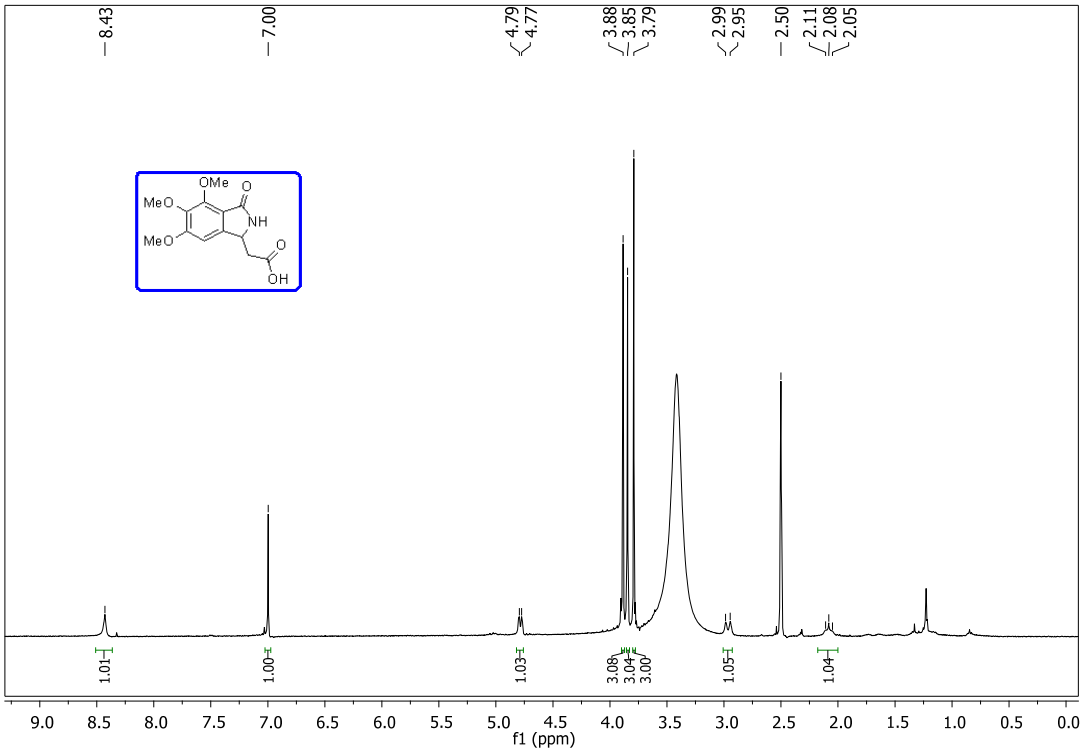


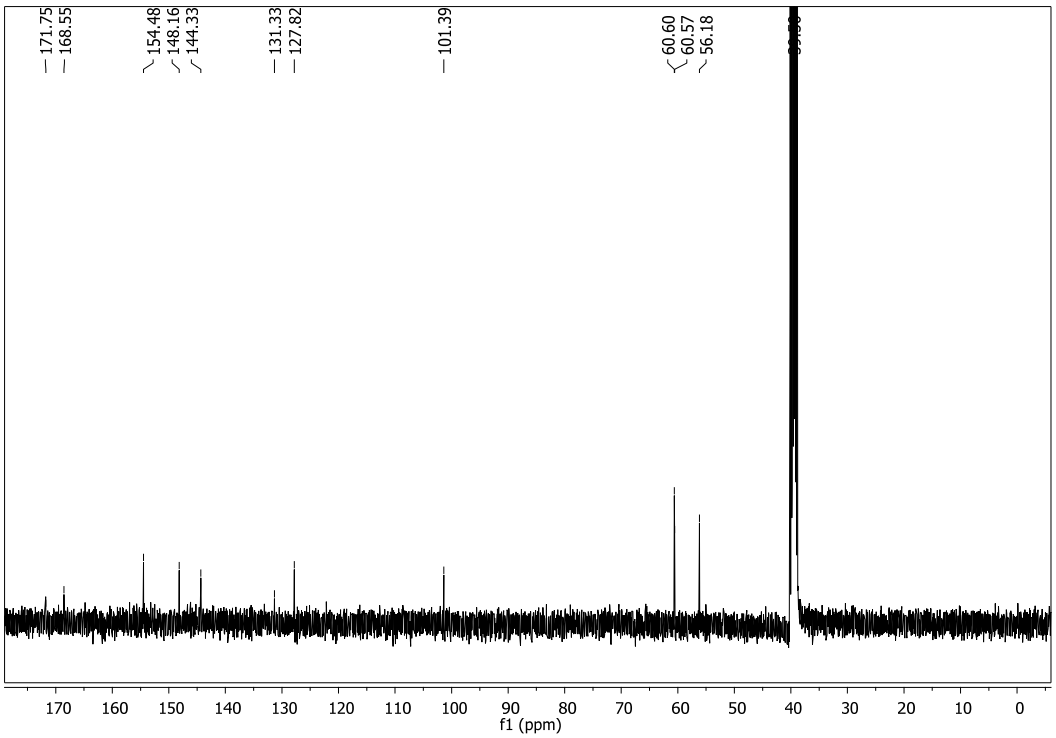
^{1}H and ^{13}C NMR Spectra of Compound **5a.**



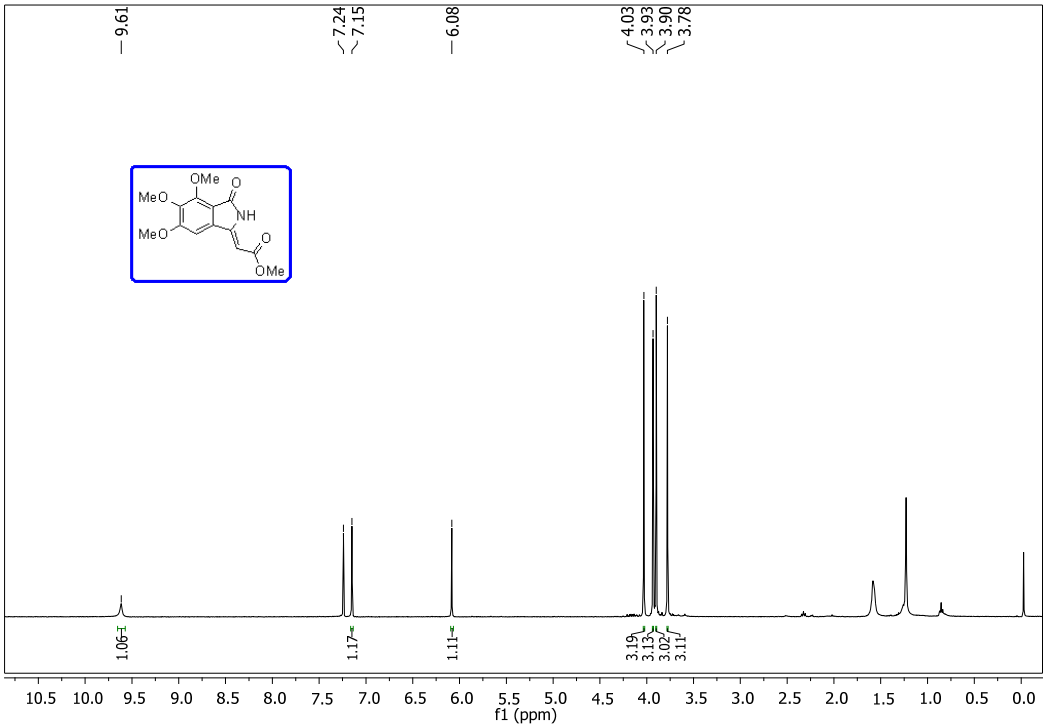


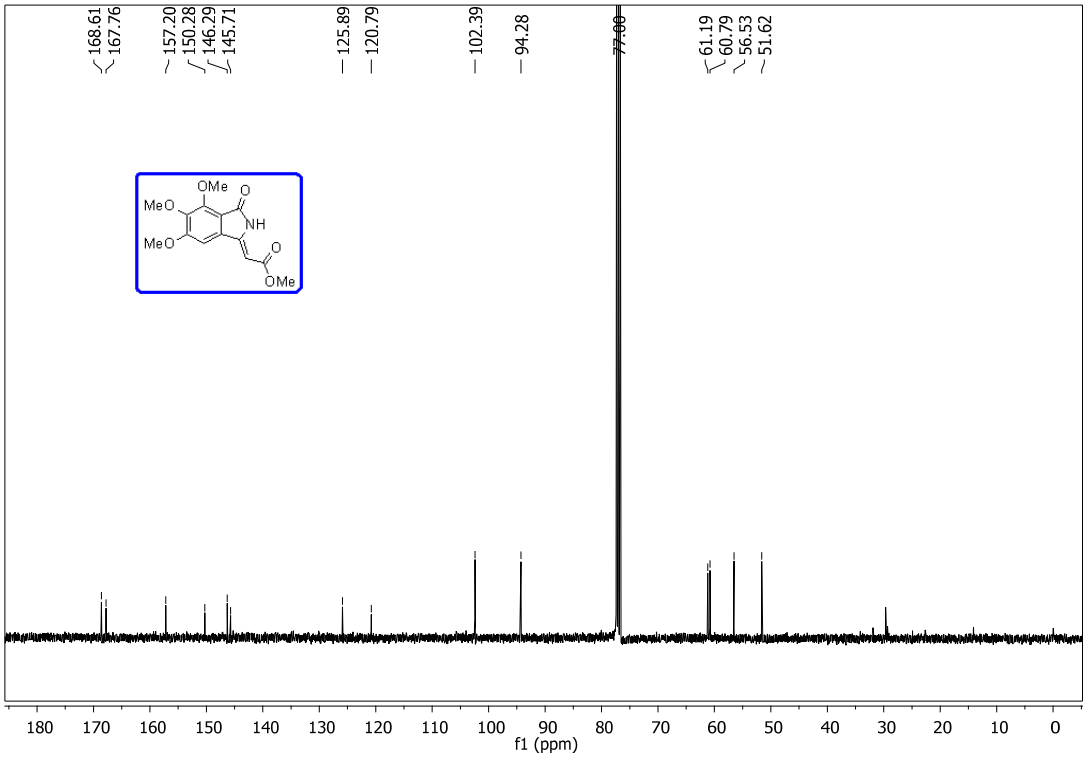
^{1}H and ^{13}C NMR Spectra of Compound **6a.**





^{1}H and ^{13}C NMR Spectra of Compound **7a.**





^{1}H and ^{13}C NMR Spectra of Compound **8a.**