Cationic Ruthenium(II) Complex-Catalyzed *ortho* Alkenylation and Benzoxylation of Aromatics via C-H Bond Activation

A Thesis

Submitted in Partial Fulfillment of the Requirements

of the Degree of

Doctor of Philosophy

By

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

April- 2016

Dedicated to

My parents

And

My Beloved family

INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH
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CERTIFICATE

Certified that the work described in this thesis entitled ***"Cationic Ruthenium(II) Complex-Catalyzed ortho Alkenylation and Benzoxylation of Aromatics via C-H Bond Activation***" submitted by *Mr. Kishor Padala* 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: 21st April 2016

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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 this submission. I understand that violation of the above will result in disciplinary actions by the Institute and can also evoke penal action from the sources, which have thus not been properly cited or from whom appropriate permission has not been taken when needed.

Date: 21st April 2016

Kishor Padala

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Kishor Padala

Synopsis

The thesis entitled ***"Cationic Ruthenium(II) Complex-Catalyzed ortho Alkenylation and Benzoxylation of Aromatics via C-H Bond Activation"*** consists of four chapters followed by Experimental details, References and Spectra.

The research area in my doctoral study is focused on a ruthenium-catalyzed C-H bond functionalization of aromatics and heteroaromatics via chelation-assisted deprotonation metalation pathway. The transition metal-catalyzed chelation-assisted coupling of an unreactive C-H bond of aromatics with nucleophiles via C-H bond activation is an efficient method to construct chemical bonds in organic synthesis. By employing this method, various chemical bonds such as C-C, C-N, C-X (X = Halogens) and C-O are efficiently constructed in a highly atom economical and environmentally friendly manner. C-H Bond of aromatics can be activated by several ways in the presence of metal catalysts. However, the control of regioselectivity is key problem in most of cases. But, the regioselectivity can be controlled by activating the C-H bond via chelation-assisted metalation pathway. Heteroatoms such as nitrogen or oxygen containing chelating groups are needed for this reaction. The C-H bond activation by using strong nitrogen containing chelating groups is quite easy and well documented in the literature. But, activation in the presence of weak oxygen containing directing groups such as ketones, aldehydes, esters, sulfoxide and nitrile are very challenging. We have developed an efficient method to construct C–C bond and C–heteroatom bond in presence of weak oxygen containing directing groups by using a ruthenium catalyst via C-H bond activation.

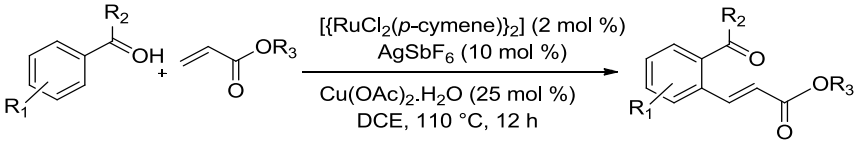
Chapter 1 of this thesis discusses the history of metal-catalyzed particularly a ruthenium-catalyzed C-H bond functionalization of organic molecules. Generally, Pd, Rh and Ru complexes are widely used as catalysts for this type of C-H bond activation reaction. Among these complexes, a ruthenium complex has gained much attention in recent years due to the remarkable reactivity and selectivity. A brief introduction of chelation-assisted C-H bond activation via oxidative addition pathway as well as deprotonation pathway is discussed in this chapter.

Chapter 2 of this thesis describes a ruthenium-catalyzed *ortho* alkenylation of aromatic and heteroaromatic ketones or aldehydes or esters with alkenes, giving the corresponding

ortho-alkenylated aromatics and heteroaromatics in a highly regio- and stereoselective fashion. It contains three sub-divisions as follows:

Section 2A: *ortho* Alkenylation of Aromatic and Heteroaromatic Ketones with Alkenes via C-H Bond Activation

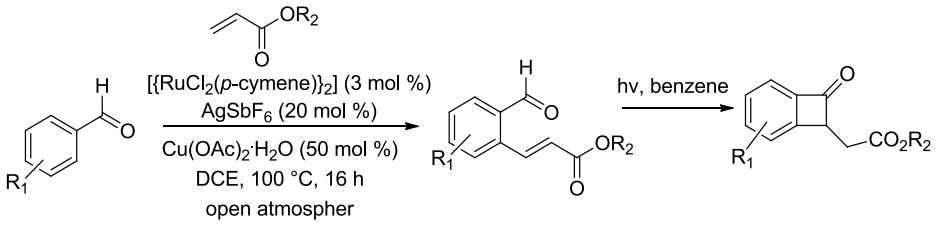
A highly regioselective ruthenium-catalyzed chelation-assisted C-H bond functionalization of an *ortho* C-H bond of aromatic ketones with alkenes to afford substituted alkene derivatives is described. The reaction of 4-bromoacetophenone with *n*-butyl acrylate in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2.H_2O$ (25 mol %) in 1,2-dichloroethane (DCE) at 110 °C for 12 h provided a Heck-type product with excellent *E*-stereo selectivity (Scheme 1). It is important to note that in most of the rhodium-catalyzed C-H activation reactions, stoichiometric amount of oxidant have been used frequently. However, only 25 mol % of oxidant is used in the present reaction. The catalytic reaction was done under air. Control experiments revealed that no corresponding product was obtained in the absence of either ruthenium catalyst or silver salt or copper salt. The catalytic reaction was compatible with various aromatic and heteroaromatic ketones as well as alkenes. A possible recation mechanism was proposed to account for the present recation.



Scheme 1: *ortho* alkenylation of aromatic ketones

Section 2B: *ortho* Alkenylation of Aromatic and Heteroaromatic Aldehydes with Alkenes via C-H Bond Activation

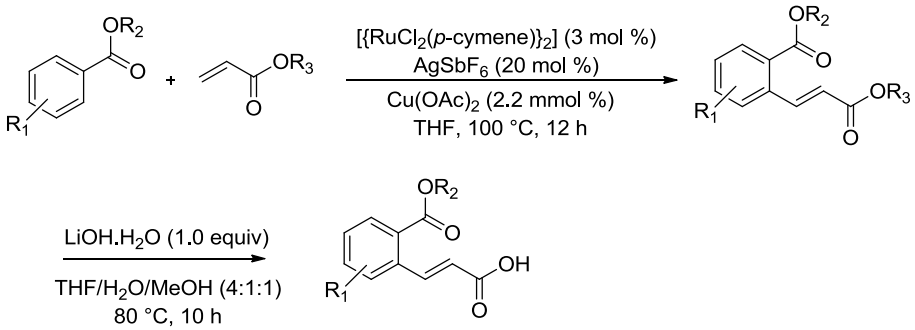
In this section, I have discussed the oxidative coupling of aromatic aldehydes with alkenes in the presence of a catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and $Cu(OAc)_2{\cdot}H_2O$ giving alkene derivatives in good to moderate yields under an air atmosphere in a highly regio- and stereoselective manner. The catalytic reaction was also compatible with heteroaromatic aldehydes. It is important to note that no decarbonylation of aldehydes, hydroacylation of aldehydes with alkenes and oxidation of aldehydes to acids were observed in the reaction. The observed alkene derivatives were further converted into unusual four-membered cyclic ketones or polysubstituted isochromanone derivatives via a photochemical rearrangement (Scheme 2).



Scheme 2: *ortho* alkenylation of aromatic aldehydes followed by photochemical rearrangement

Section 2C: *ortho* Alkenylation of Aromatic and Heteroaromatic Esters with Alkenes via C-H Bond Activation

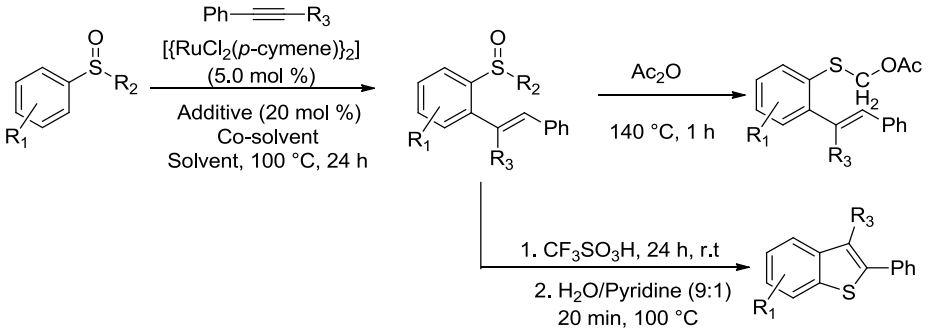
In this section, *ortho* alkenylation of aromatic and heteroaromatic esters with alkenes in the presence of catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and $Cu(OAc)_2$, affording highly substituted alkene derivatives in a highly regio- and stereoselective manner was discussed (Scheme 3). The catalytic reaction was compatible with various heteroaromatic esters. Interestingly, the present ruthenium-catalyzed alkenylation reaction is carried out under an air atmosphere and only a catalytic amount of $Cu(OAc)_2$ has been used as an terminal oxidant and remaining amount of $Cu(OAc)_2$ source has been regenerated under air from the reduced copper source. In the presence of $LiOH{\cdot}H_2O$ (1.0 equiv), selective de-esterification takes place at an alkene substituted ester moiety rather than aromatic ester in THF:H_2O:MeOH (4:1:1) at 80 °C for 12 h.



Scheme 3: *ortho* alkenylation of aromatic aldehydes followed by selective de-esterification

Chapter 3 demonstrates an oxidant free a regio- and stereoselective hydroarylation of aromatic sulfoxides with alkynes in the presence of a less expensive ruthenium catalyst. The reaction provides *ortho* alkenylated aromatic sulfoxides in good to excellent yields in a highly regio- and stereoselective manner. In the reaction, terminal metal oxidant was not used and only Ru(II) species is involved in the whole catalytic cycle without changing the metal oxidation state. It is important to note that the phenyl sulfoxide motif is present in various natural products and drug molecules as well as it have been widely used as

ligands in various enantioselective reactions. By using the observed *ortho* alkenylated aromatic sulfoxides, α-acyloxy thioether were prepeared via Pummerer rearrangement. Later, *ortho* alkenylated phenyl sulfoxide was treated with CF_3SO_3H at room temperature for 24 h followed by addition of a 9:1 ratio of water/pyridine to the reaction mixture, yielding 2,3-disubstituted benzothiophene derivative (Scheme 4).



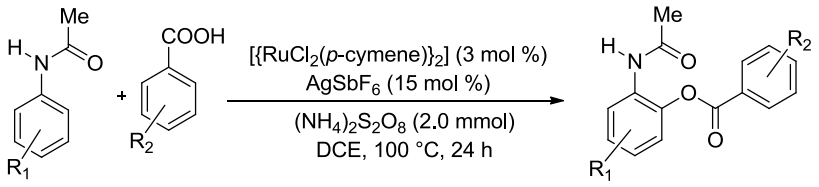
Scheme 4: Hydroarylation of aromatic sulfoxide in the presence of Ru catalyst

Chapter 4 describes an unprecedented oxidative *ortho* benzoxylation of substituted acetanilides or *N*-Alkyl Benzamides with benzoic acids in the presence of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and $(NH_4)_2S_2O_8$ in a highly regioselective manner. This chapter contains two sub-divisions as follows:

Section 4A: Ru-Catalyzed Oxidative *ortho* Benzoxylation of Acetanilides with Aromatic Acids

The transition-metal-catalyzed chelation-assisted transformation of an unreactive *ortho* C-H bond of aromatics to C-C, C-X, C-N and C-O bonds via C-H bond activation is one of the efficient and highly atom-economical methods in organic synthesis. Among them, C-O bond construction is quite difficult and less known in the literature. This is most probably due to high electronegativity of the element and also due to the metal-ligand bond strength. Generally, substituted alcohols and carboxylic acids are widely used as a coupling partner (oxygen source) for the reaction. In fact, coupling of carboxylic acids with aromatics is more challenging due to rapid complex formation of the carboxylic acids with the metals. To avoid the complex formation, carboxylate sources such as $PhI(OR)_2$, anhydride, acid halide, etc., have been used instead of the corresponding carboxylic acid. However, there is no report on *ortho*-benzoxylation of aromatics in the presence of ruthenium catalyst. We have demonstrated an unprecedented oxidative *ortho*-benzoxylation of substituted acetanilides with benzoic acids in the presence of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and $(NH_4)_2S_2O_8$ in a highly regioselective manner. The catalytic

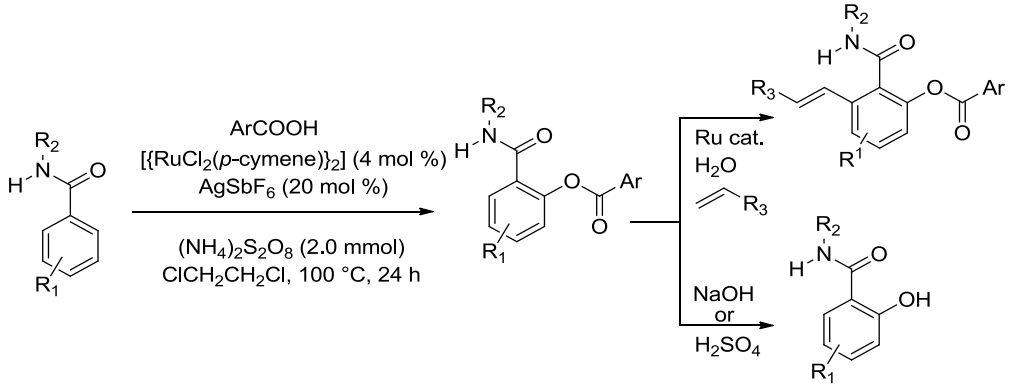
reaction was compatible with various anilides and organic acids. The catalytic reaction was also compatible with acetic acid.



Scheme 5: *ortho* Benzoxylation of acetanilides with aromatic acids

Section 4B: *ortho* Benzoxylation of *N*-Alkyl Benzamides with Aromatic Acids Catalyzed by a Ru(II) Complex

In this section, *ortho* benzoxylation of benzamides with aromatic acids in the presence of a ruthenium catalyst is described. The reaction provides ortho benzoxylated aromatics in good to excellent yields (Scheme 6). It is important to note that the amide is a versatile functional group which has been widely used for various organic transformations. Meanwhile, amide is also a good directing group for metal-catalyzed C-H functionalization reaction. The *ortho* C-H bond of benzoxylated *N*-alkyl benzamides was efficiently alkenylated with methyl acrylate in the presence of [{$RuCl_2$(*p*-cymene)}$_2$], KPF_6 and $Cu(OAc)_2 \cdot H_2O$ (2.0 mmol) in water solvent (Scheme 6). Subsequently, benzoxyl moieties of benzamides were converted into the hydroxyl group, in the presence of NaOH or H_2SO_4 solution (Scheme 6). It is important to mention that this is one of the efficient methods to synthesis *ortho* hydroxy *N*-alkyl benzamides.



Scheme 6: *ortho* Benzoxylation of N- methyl benzamide with aromatic acids

***Publications*:**

1. **Kishor, P.**; Jeganmohan, M.; "Ruthenium Catalyzed *Ortho*-Alkenylation of Aromatic Ketone with Alkene by C-H Bond Activation". *Org. Lett*. **2011,** *13*, 6144-6147. (Highlighted in Organic Chemistry Portal)

2. **Kishor, P.**; Jeganmohan, M.; "Highly Regio and Sterioselective Ruthenium(II) Catalyzed direct *Ortho*-Alkenylation of Aromatic and Heteroaromatic Aldehydes with Activated Alkenes under open Atmosphere". *Org. Lett.* **2012,** *14*, 1134-1137. (Highlighted in Synfacts 2012, 8(5), 0553)

3. **Kishor, P.**; Pimparkar, S.; Madasamy, P.; Jeganmohan, M.; "Ruthenium Catalyzed Regioselective Oxidative Coupling of Aromatic and Hetero Aromatic Esters with Alkenes under an open Atmosphere". *Chem Commun***. 2012**, *48*, 7140-7142.

4. **Kishor, P**; Jeganmohan, M.; "Ruthenium-Catalyzed Oxidative *Ortho*-Benzoxylation of Acetanilides with Aromatic Acids". *Chem. Commun.*, **2013**, *49*, 9651.

5. **Kishor, P.**; Jeganmohan, M.; "Ortho-Benzoxylation of N-Alkyl Benzamides with Aromatic Acids Catalyzed by Ruthenium(II) Complex". *Chem. Eur. J*. **2014**, *20*, 4092-4097. (Highlighted in Chemistry Views)

6. **Kishor, P**.; Jeganmohan, M.; "Ruthenium-catalyzed Highly Regio- and Stereoselective Hydroarylation of Aromatic Sulfoxide with Alkynes via C-H Bond Activation". *Chem. Commun*. **2014**, *50*, 14573-14476.

Review Article:

1. Sandeep, P.; **Kishor, P.**; Jeganmohan, M.; "Ruthenium(II)-Catalyzed *ortho* C-O Bond formation of Substituted Aromatics with Oxygen Nucleophiles through C-H Bond Activation". *Proc Indian Natn SciAcad* 80 No. 5 December 2014 pp. 999-1011

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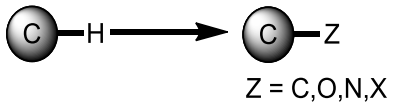
4B: *ortho* Benzoxylation of *N*-Alkyl Benzamides with Aromatic Acids Catalyzed by Ruthenium(II) Complex

Chapter 1

History of Ru(II)-Catalyzed C-H Bond Functionalization of Organic Molecules

1.1: Importance of C–H Bond Functionalization in Organic Synthesis

The transition metal-catalyzed functionalization of unreactive C−H bond of aromatics, heteroaromatics and alkenes has fundamentally revolutionized synthetic concepts for the construction of chemical bonds in organic synthesis.[1] By employing this method, various chemical bonds such as C-C, C-N, C-X (X = halogens), C-O and C-M are efficiently constructed in a highly atom economical and environmentally friendly manner in one pot (Scheme 1.1). These reactions can be widely used for the synthesis of biologically active molecules, pharmaceuticals, natural products, materials and polymers.[1]

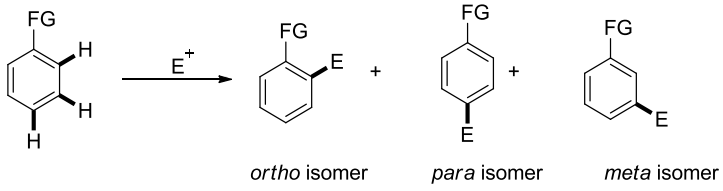


Scheme 1.1: C–H bond functionalization

1.2: C-H Bond Functionalization of Aromatic Compounds

Electrophilic Aromatic Substitution Reactions

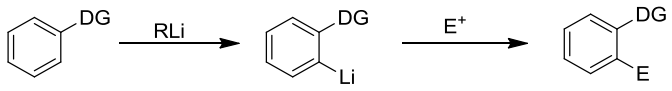
Several methods are available to do C-H bond functionalization on the organic moieties. However, the development of regiocontrolled functionalization of organic moieties has been an important synthetic task among the organic chemists. In earlier decades, researchers have developed electrophilic aromatic substitution reactions such as Friedel-Crafts reaction, nitration, sulfonation, halogenation, etc for the functionalization of organic molecules in an efficient manner. In these reactions, electronic factors on the organic moieties influence the substitution position of the incoming electrophile. On the aromatic moieties, if any electron donating group is present that substitution reaction favors the *ortho* and *para* position of aromatics and if electron withdrawing group is present on the benzene ring that substitution favors *meta* position. In addition, in the reaction, other multi functionalized products were also possible (Scheme 1.2).[2] Thus, mostly in this type of reaction is not completely regioselective. Later, synthetic chemists introduced directing groups on the organic moiety to get the functionalization selectively.



Scheme 1.2: Electrophilic aromatic substitution reactions

Directed *ortho* Metalation

Directed *ortho* metalation (DOM) is one of the best methods to do functionalization on the organic molecules in a highly selective manner. By employing metal bases such as RLi, RMgX, RZnX, etc, an *ortho* C-H bond of directing group substituted aromatics can be deprotonated, forming highly reactive metal reagents. Later, the C-M metal bond can be quenched by various electrophiles (Scheme 1.3).[3] Direct *ortho* metalation by using base is a powerful technique for the construction of 1,2-disubstituted aromatic compounds having a wide variety of functional groups. Unfortunately, these methods face considerable limitations including tedious and/or hazardous reaction procedures, poor site selectivity, harsh reaction conditions and a low chemoselectivity. Later on, synthetic chemists have been devoting considerable amount of time on the development new methodologies for the regioselective C-H functionalization of organic molecules.



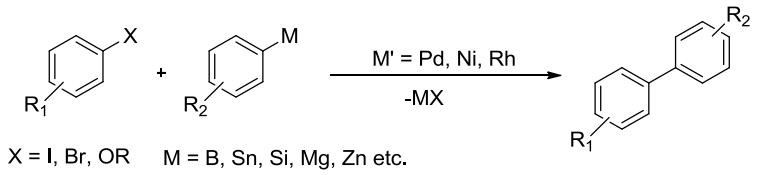
Scheme 1.3: Directed *ortho* metalation

1.3: Typical Cross-Coupling Reaction

Construction of chemical bonds is a back bone in organic synthesis. For making carbon-carbon and carbon-hetero bond, researchers have developed a metal-catalyzed cross-coupling reaction. In these reactions, organic electrophiles react with organometallic reagents in the presence of a metal catalyst providing the corresponding coupling products in a highly efficient manner (Scheme 1.4).[4] It is one of the best methods for the functionalization of organic molecules in an efficient manner. In this reaction, one coupling partner with halogen and another coupling partner with metal are essential. It is important to note that the synthesis of prefunctionalized organic electrophiles and organometallics reagents **(**M = MgX, ZnX, BR_2, SnR_3, SiR_3, etc.) requires more number of steps and the most of organometallic reagents are often sensitive to air and quite expensive. A number of synthetic operations are required to prepare these organometallic reagents. At the end of the reaction, these X and M are wasted as by products. If the functionalization reaction is developed without having X and M wastages, it would be highly interesting in terms of atom economy and environmentally friendly.

This type of functionalization can be done via a metal-catalyzed C-H bond functionalization. It is interesting to note that the preactivated species such as C-X (X = I, Br, OTf and Cl) or C-M (M = B, Si and Sn) on the organic moiety in order to activate the

corresponding carbon is not required for the reaction unlike to the classical catalytic cross-coupling reactions.[2]



Scheme 1.4: Typical cross-coupling

1.4: C-H Bond Activation Classification

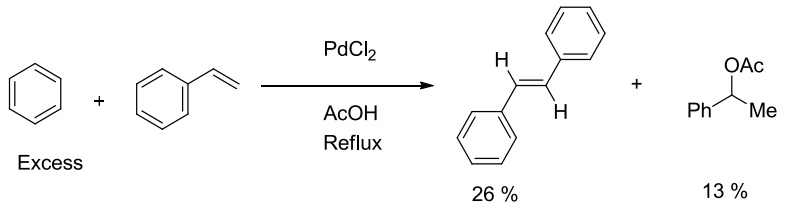
The C-H bond activation is a type of reaction in which C-H bond is cleaved and replaced with electrophiles or nucleophiles such as aryl halides, alkyl halides or organometallics reagents and forming C-C and C-X bond (where X is usually oxygen or nitrogen or halogen). Generally transition-metal catalyzed C-H bond activation reactions are classified in to two types: i) transition-metal catalyzed non chelation assisted C-H bond activation and ii) transition-metal catalyzed chelation assisted C-H bond activation

Transition-Metal Catalyzed Non Chelation Assisted C-H Bond Activation

Fujiwara-Moritani Reaction.

If the C-H bond activation occurs without chelating group that is called as non chelation assisted C-H bond activation. In the reaction, without chelating group the C-H bond is activated. In 1968, Fujiwara's group developed the non chelation assisted C-H bond activation reaction. It is important to note that this is the first report on the metal-mediated C-H bond activation reaction. In this report, benzene reacts with styrene in the presence of a palladium complex giving stilbene derivatives (Scheme 1.5).[5] In the reaction, oxidative dehydrogenative alkenylation takes place *via* a twofold C–H bond activation. This reaction proceeds via Friedel-Craft type electrophilic substitution mechanism. Advantageous of this method is minimisation of unwanted by-products and also reducing the number of reaction steps. Thus, this reaction is highly atom and step economical.

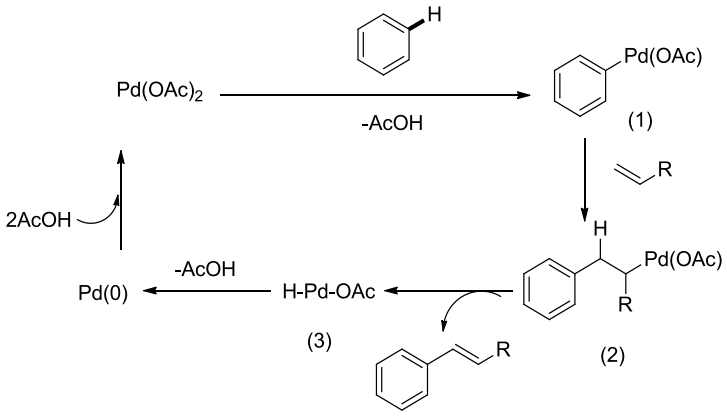
Unfortunately, there are some drawbacks in the reaction. Mostly, in this reaction, a stoichiometric amount of palladium complex is necessary. Mainly, this reaction has the lack of regioselectivity control. On the benzene ring if any substitution is present, this reaction results a mixture of *ortho*, *meta* and *para* functionalized alkene derivatives. This reaction also requires an excess of aromatic hydrocarbon as a solvent.



Scheme 1.5: Fujiwara-Moritani reaction

Mechanism:

The benzene molecule undergoes electrophilic substitution with $Pd(OAc)_2$ to give intermediate **1**. Olefin coordinates to the Pd species and inserts between carbon of aryl and Pd provides intermediate **2.** Intermediate **2** readily undergoes syn β-hydride elimination affords the final coupling product and intermediate **3**. The intermediate **3** undergoes reductive elimination to regenerate Pd(0) for the next catalytic cycle (Scheme 1.6).[5]



Scheme 1.6: General mechanism of Fujiwara- Moritani reaction

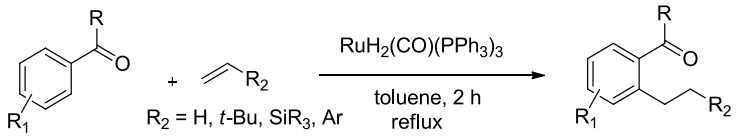
It is important to note that this type of reaction has gained less attention as compared with the cross coupling reaction during the time. In the cross-coupling reaction, in 1968, Heck reported selective alkenylation reaction by using a stoichiometric amount of Pd complex.[6c,d] After the 3 years time, Mizoroki's and Heck's groups independently reported selective alkenylation reaction by using a catalytic amount of Pd complex. Thus, the cross-coupling reactions were developed rapidly as compared with C-H bond activation reaction. But, in the case of C-H bond activation, in 1968, Fujiwara's group developed an alkenylation reaction without selective manner via C-H bond activation reaction in the presence of a stoichiometric amount of palladium complex.[7] But, the catalytic version of C-H bond activation was not developed immediately at the time and chemists have encountered several problems including efficiency and selectivity. Almost the two decades later, Murai's group reported the C-H bond activation reaction by using a

catalytic amount of ruthenium complex in a highly selective manner. This report is emphasized the importance of a chelating group in order to achieve the highly reactivity and selectivity in the C-H activation process.

Transition-Metal Catalyzed Chelation-Assisted C-H Bond Activation

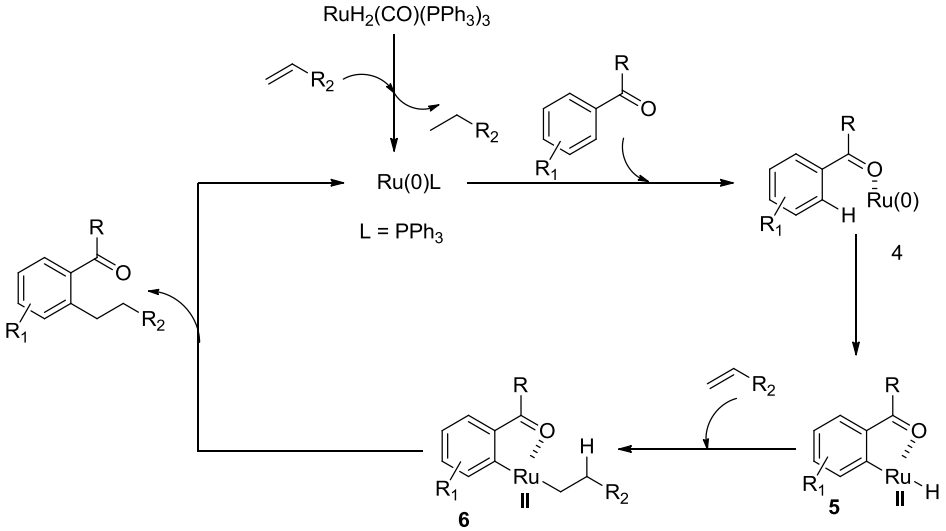
***ortho* Alkylation of Aromatic Ketones with Alkenes by Using Ruthenium Complex**

In 1993, Murai's group reported a ruthenium-catalyzed chelation-assisted *ortho* C–H bond alkylation of aromatic ketones with olefins. This was the first report on the chelation assisted C-H bond activation recation. In this reaction, aromatic ketones reacted with alkenes in the presence of ruthenium catalyst giving *ortho* alkylated aromatic keteones (Scheme 1.7).[8] A remarkable feature of this transformation was the high regioselective C-H bond activation.



Scheme 1.7: Chelation- assisted Ru-catalyzed alkylation *via* oxidative addition

Mechanism:



Scheme 1.8: Mechanism of Ru-catalyzed *ortho* alkylation of aromatic ketones with alkenes

In this reaction, $RuH_2CO(PPh)_3$ catalyst was used which is not the active catalyst. This catalyst reacts with olefin generating the active Ru(0) catalyst and the alkylated product. After the generation of active catalyst, the oxygen atom of carbonyl group coordinates with a ruthenium species giving intermediate **3**. The oxidative addition of *ortho* C-H of aromatic ketone on the Ru(0) provides intermediate **5** with Ru–H bond which is the key intermediate in the reaction. Next, the olefin co-ordinates to the Ru species and inserts

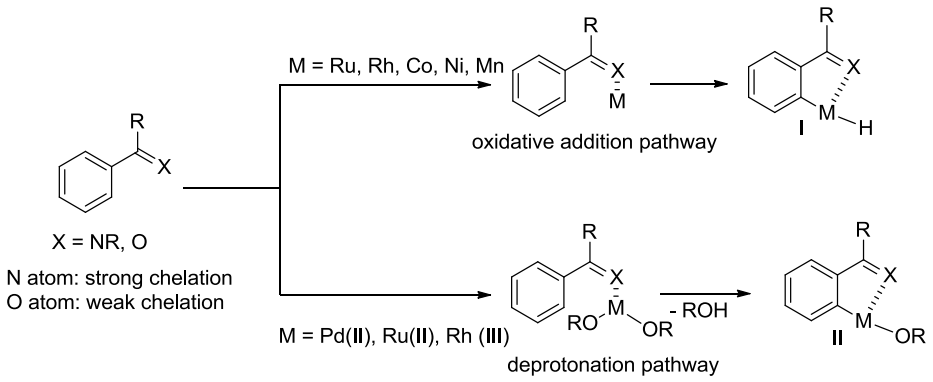
between the Ru-H to give intermediate **6**. Intermediate **6** readily undergoes reductive elimination to give *ortho* alkylated product and regenerates Ru(0) active catalyst for the next catalytic cycle (Scheme 1.8).

1.5: Metal-Catalyzed Chelation-Assisted C-H Bond Activation Pathways

Chelation assisted C-H activation by using a metal catalyst follows two 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 sate favors the oxidation addition step. In the reaction, a five membered hydrometallacycle is the key intermediate.[9]

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 metallacycle intermediate. In the intermediate, there is no M-hydride species. Thus, the mechanism and product formation of these both reactions is completely different (Scheme 1.9).[9]



Scheme 1.9: Metal-catalyzed chelation-assisted C-H bond activation

The C-H bond activation reaction via oxidative addition pathway started with the Ru(0) catalyst and extended to various metals. 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.

Generally Pd, Rh and Ru complexes are widely used as catalysts for this type of C-H bond activation reaction. Among these complexes, we are very much interested with ruthenium complexes due to the remarkable reactivity and selectivity. In addition, a ruthenium complex is less expensive and easily affordable as compared with other

rhodium and palladium complexes. Further, a ruthenium catalyzed C-H bond functionalization can be done under an air atmosphere and/or even water can be used as a solvent. Thus, an inert atmosphere is not required in the reaction.

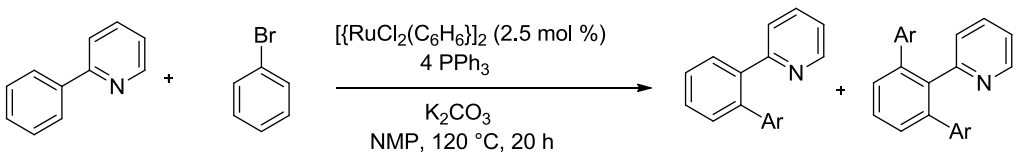
In my thesis, I have focused on the development of new C-H bond functonolization of aromatic and heteroaromatic molecules via a ruthenium-catalyzed chelation assisted deprotonation metalation pathway.

1.6: Early Reports on the C-H Bond Activation by Using a Ru(II) Catalyst via Deprotonation Pathway

ortho Arylation of Aromatics by Using Ru(II) Catalysts with Phoshine Ligands

Ruthenium (II) and (III) complexes are more stable to air and water than in situ generated ruthenium (0) species. Generally, ruthenium (II) catalysts are required to do C-H bond activation via deprotonation metalation pathway.

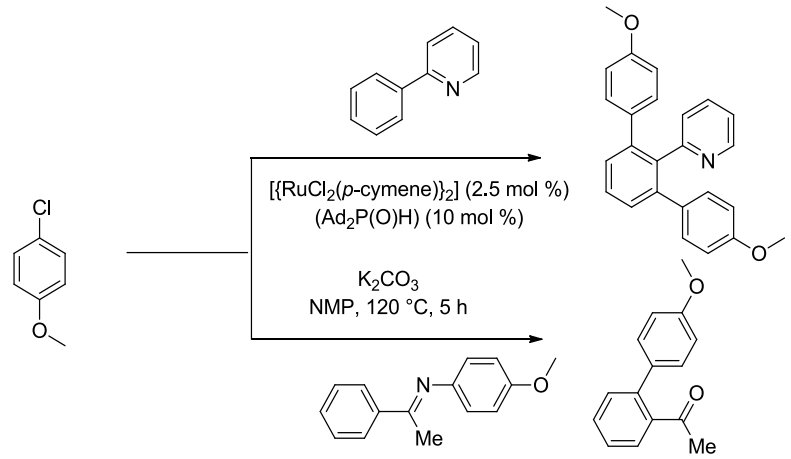
In 2001, Oi and Inoue reported an efficient *ortho* arylation of 2-pyridylbenzene with aromatic halides in the presence of a ruthenium (II) catalyst (Scheme 1.10).[10] In the reaction, $[\{RuCl_2(C_6H_6\}]_2$ along with K_2CO_3 was used to activate the *ortho* C-H bond of phenyl group. 2-Pyridyl group acts as a directing group in the reaction.



Scheme 1.10: Ruthenium-catalyzed direct arylation with aryl halides by Oi and Inoue

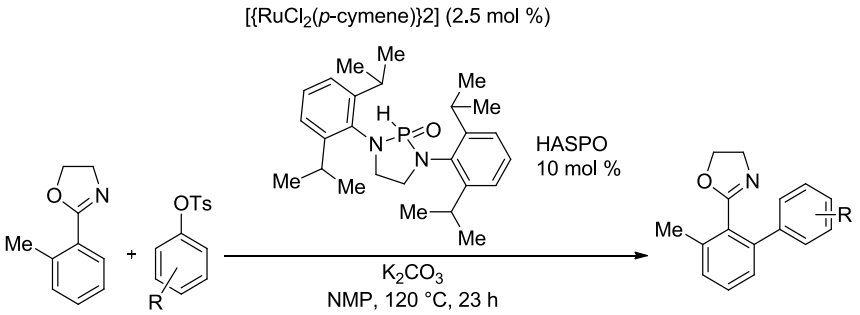
ortho Arylation of Aromatics by using Ru(II) catalyst with $R_2P(O)H$:

In 2005, Ackermann's group introduced the phosphine oxide $R_2P(O)H$ additive along with a ruthenium catalyst and K_2CO_3 base to activate instead of phosphine ligand to activate the C-H bond of 2-phenyl pyridine.[11] In presence of phosphine oxide $R_2P(O)H$ additive, arylation takes place very effectively with readily available aromatic chlorides. In this reaction, $(adamantyl)_2P(O)H$ is more effective additive (Scheme 1.11). Later, this methodology was extended with ketimines also. The arylation of ketimines followed by hydrolysis provided *ortho* arylated aromatic ketones.



Scheme 1.11: Arylation of arene and alkene sp^2 C−H bonds with $R_2P(O)H$ as ruthenium(II) partner

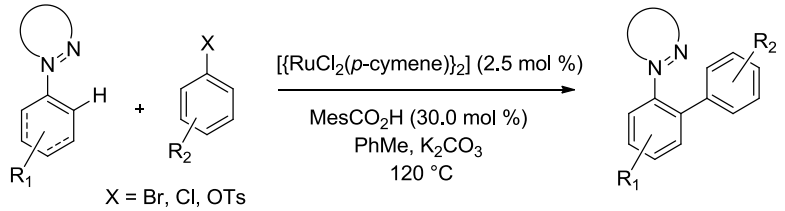
Next, a similar type of selective direct arylation was extended with arylpyrazoles or aryloxazolines and prefunctionalized phenols or aryl chlorides in the presence of secondary phosphine oxide ligand. In 2006, Ackermann's group reported the arylation of 2-aryloxazolines with aryl tosylates in the presence of a ruthenium catalyst. In this reaction, a less reactive aryl tosylates was used as a coupling partner (scheme 1.12).[12]

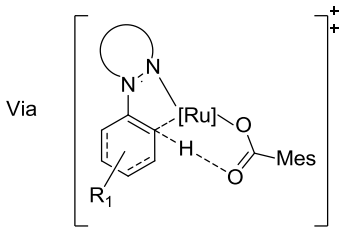


Scheme 1.12: Arylation of arene and alkene sp^2 C−H bonds with $R_2P(O)H$ as ruthenium(II) partner

ortho Arylation of Arenes Through Carboxylic Acid as Cocatalyst in Non-Polar Solvents

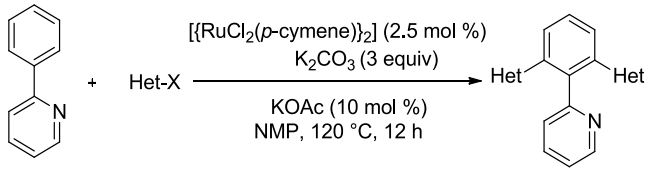
In 2008, Ackermann's group described the selective arylation of triazoles with arylhalides in the presence of 2.5 mol % of $[RuCl_2(p\text{-cymene})]_2$, 30 mol % of carboxylic acid $MesCO_2H$ as an additive and K_2CO_3 as a base in a non polar toluene solvent at 120 °C (Scheme 1.13).[13]



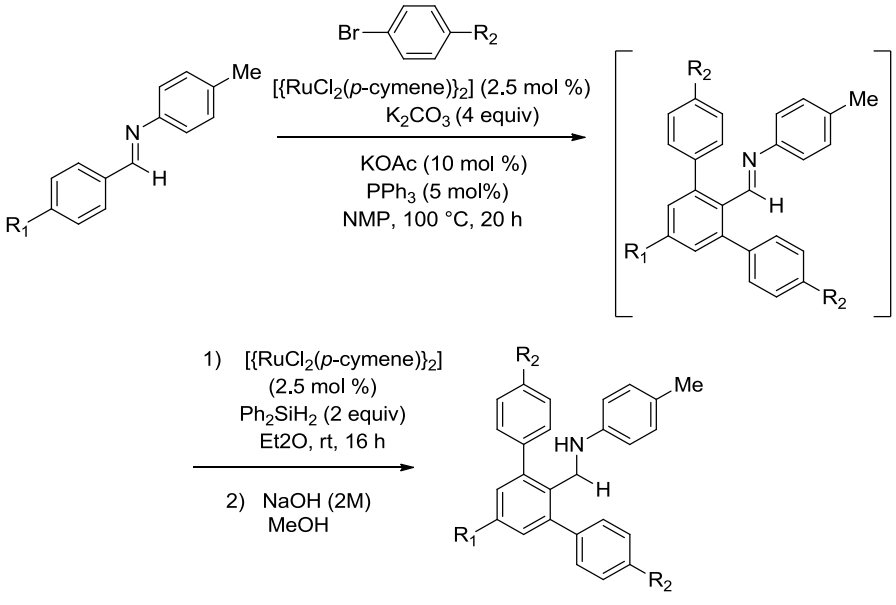


Scheme 1.13: Mesitylate-assisted direct arylation in toluene

In 2009, Dixneuf and Bruneau's groups reported *bis* arylation of 2-phenylpyridines with aromatic halides in the presence of a ruthenium catalyst and K_2CO_3 in NMP solvent (Scheme 1.14).[14a] Later, the arylation reaction was examined with aldimines and aryl bromides in the presence of $[RuCl_2(p\text{-cymene})]_2$, KOAc, PPh_3 ligand and K_2CO_3 in NMP solvent (Scheme 1.15).[14b] In the recation, the expected bis arylated aldimines was observed in good to excellent yields. Subsequently, the double bond of imine was reduced into a single bond on the same recation mixture in the presence of Ph_2SiH_2.



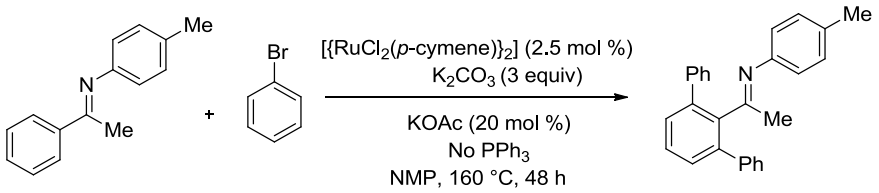
Scheme 1.14: Synthesis of polyheterocycles from phenylpyridine with in situ prepared $Ru(OAc)_2(p$-cymene)**)**



Scheme 1.15: Sequential arylation/hydrosilylation of aldimines

Generally, the bis diarylation of aldimines and ketimines is very difficult to achieve in high yields. In the previous literature, by using PPh_3 in a similar reaction conditions, monoarylation was achieved by Ackermann's group. Interestingly, Dixneuf and

Bruneau's groups succeeded *bis* arylation at the *ortho* position of aromatic ketimines under a similar reaction conditions (Scheme 1.16).[14b]

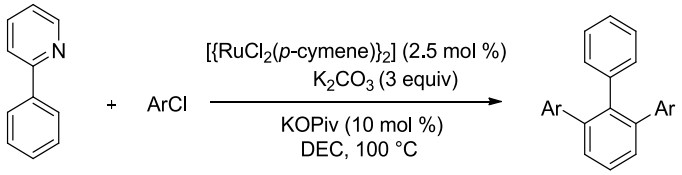


Scheme 1.16: Selective diarylation ketimines with Ru-OAc catalyst

ortho Arylation of Arenes Through Carboxylic Acid as Cocatalyst in "Green" Solvents

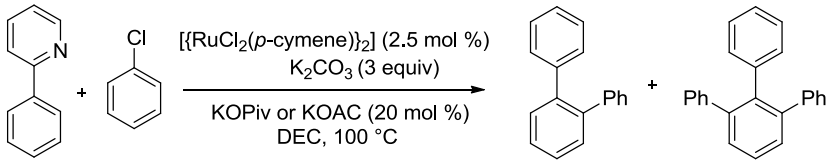
In general, NMP or toluene solvent was used for the direct arylation reaction of substituted aromatics in the presence of a ruthenium catalyst. Afterwards, this chemistry extended into "green solvents" such as diethyl carbonate (DEC) and water.

In 2009, Dixneuf's group reported a ruthenium-catalyzed direct arylation in green diethylcarbonate (DEC) and water solvent. In the reaction, 2-phenylpyridine reacts with aryl chlorides in the presence of $[RuCl_2(p\text{-cymene})]_2$/potassium pivalate catalytic system in diethylcarbonate (DEC) as the solvent at 120 °C affording diarylation products in good to excellent yields (Scheme 1.17).[15]



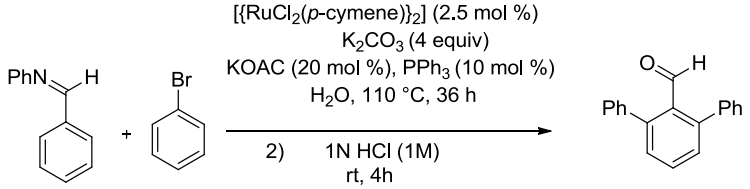
Scheme 1.17: Direct arylations with aryl chlorides in diethylcarbonate

Interestingly, a similar reaction was also worked very well with water solvent. Recently, the same group reported a ruthenium(II)-catalyzed sp^2 C−H bond arylation in water solvent. In the reaction, 2-phenylpyridines reacted with chlorobenzenes in the presence of $[RuCl_2(p\text{-cymene})]_2/KO_2CR$ catalytic system at 100 °C for 2 h providing diarylated 2-phenyl pyridines in water solvent (Scheme 1.18).[16]



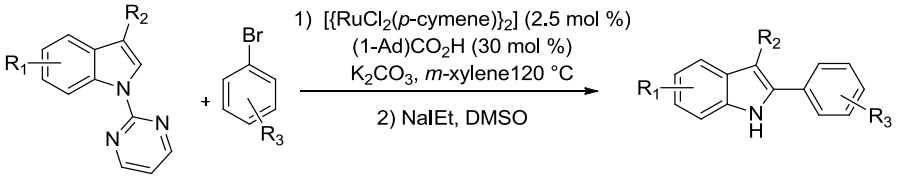
Scheme 1.18: Direct arylations with aryl chlorides in presence water solvent

Subsequently, the same group reported *ortho* diarylation of arylimines with aromatic bromides in water solvent. Later, *bis ortho* arylated aldimines were converted into *bis ortho* arylated benzaldehydes under an acidic reaction conditions (Scheme 1.19).[17]



Scheme 1.19: Synthesis of diarylation of oxazolines in water with Ru(II)-acetate catalyst

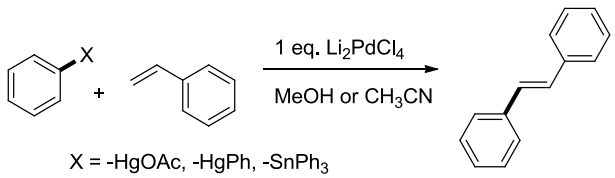
In 2011, Ackermann's group reported a ruthenium-catalyzed direct arylation of substituted 2-pyrimidylindoles with substituted bromobenzenes. In the reaction, C2-arylated 2-pyrimidylindoles derivatives were observed (Scheme 1.20).[18] Later, 2-pyrimidyl directing group was removed by using NaOEt in dimethylsulfoxide (DMSO).



Scheme 1.20: One-pot synthesis of 2-arylated NH-free indoles

Mizoroki-Heck Coupling: A Revolution in Modern Organic Chemistry

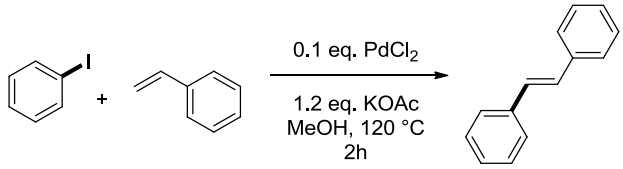
Styrene derivatives are useful synthetic intermediates in various organic transformations. In addition, styrene moieties are present in natural products as well as bioactive molecules. In 1968, Heck's group reported the selective synthesis of alkene derivatives via a metal-mediated cross-coupling of organic electrophiles with alkenes.[6a,b] Initially, styrene derivatives were prepared by the reaction of aryl mercury compounds with styrenes (Scheme 1.21). In this reaction, a stoichiometric amount of palladium complex was used. Thus, in the reaction, a stoichiometric amount of potentially hazardous halide salts was formed as side products and more transmetallation reagents were used.



Scheme 1.21: Heck reaction by using stoichiometric amount of Pd complex

In 1971, Mizoroki's and Heck's groups independently reported the selective alkenylation reaction of aromatic halides and alkenes (Scheme 1.22).[6c,d] In this reaction, only a

catalytic amount of palladium complex was used by introducing the base. The role of base is to assist the reductive elimination in form of quenching HX and regenerates the active Pd(0) complex for the next catalytic reaction.

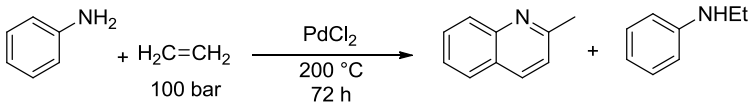


Scheme 1.22: Mizoroki- Heck reaction by using catalytic amount of Pd complex

1.7: History of Heck-type reaction via C-H Bond Activation by using various Metals

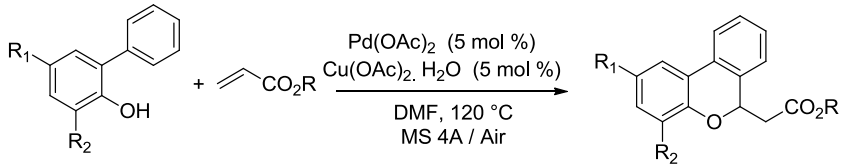
Chelation-assisted alkenylation at the *ortho* position of the aromatic ring with alkenes through a metal-catalyzed C-H bond activation reaction is a highly efficient and beneficial method in organic synthesis.[19,20] In 1968, Fujiwara's group reported the first example of alkenylation of electron-rich aromatics with alkenes catalyzed by palladium complexes.[7a,b] After that, several research groups have devoted substantial effort in the area of alkenylation of electron-rich aromatics and heteroaromatics with alkenes.[19]

In 1979, Diamond and his co-workers reported a palladium-catalyzed chelation assisted alkenylation of the aromatic amines with alkenes.[21] In this reaction, an aniline reacted with ethylene gas in presence of $PdCl_2$ catalyst at 200 °C giving a mixture of 2–methylquinoline and *N*-ethyl aniline derivatives (Scheme 1.23).



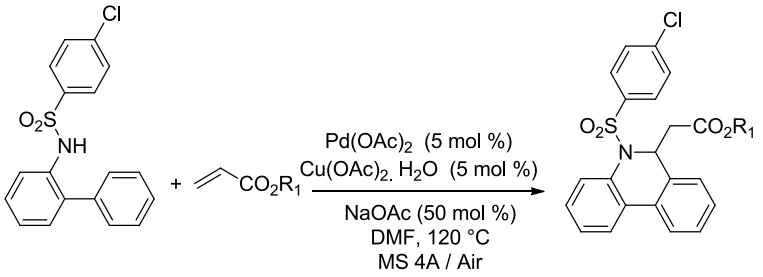
Scheme 1.23: *ortho* alkenylation of aniline by using Pd complex

In 1997, Miura et al. demonstrated the phenol-directed alkenylation of sp^2 C-H bonds in the presence of a palladium complex.[22a] In the reaction, 2-phenylphenols reacted with olefins in the presence of $Pd(OAc)_2$ affording 6-substituted-6*H*-dibenzo[*b,d*]pyran derivatives in good to excellent yields (Scheme 1.24).



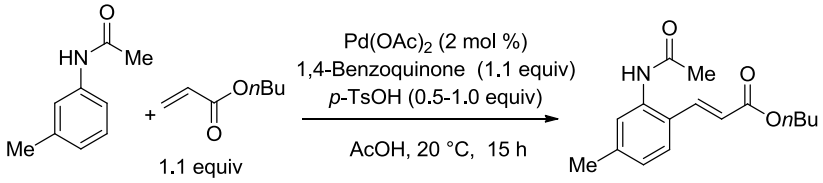
Scheme 1.24: Alkenylation of *ortho* heterosubstituted arylbenzenes

This reaction was further applied into *N*-(arylsulfonyl)-2-phenylanilines (Scheme 1.25).[22b] In these reactions, molecular sieves and copper salt were crucial to increase the yield of the product.



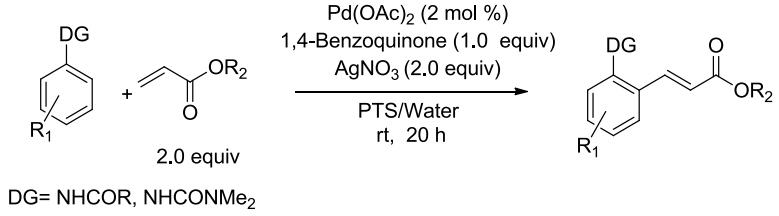
Scheme 1.25: Alkenylation of *ortho* heterosubstituted arylbenzenes

In 2002, the groups of de Vries and van Leeuwen reported a mild oxidative Heck-type olefination of substituted anilides with alkenes in the presence of a palladium catalyst (Scheme 1.26).[23]



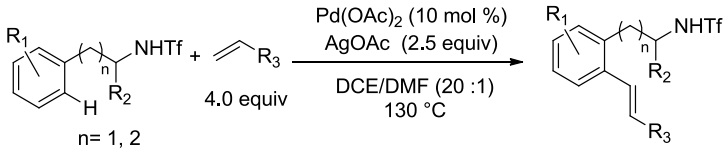
Scheme 1.26: Pd-catalyzed oxidative *ortho* alkenylation of anilides at room temperature

Subsequently, Lipshutz's group reported a similar reaction by using a cationic palladium complex in water in the presence of a PTS surfactant (i.e., polyoxyethanyl R-tocopheryl sebacate). Amide and urea directing groups can be used in the alkenylation recation (Scheme 1.27).[24]



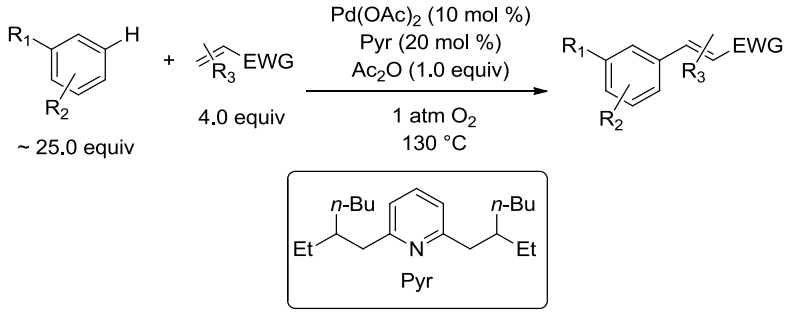
Scheme 1.27: Pd-catalyzed *ortho* alkenylation of anilides at room temperature in water

In 2008, Yu and co-workers developed a novel C-H activation route for the preparation of indolines and tetrahydroisoquinolines by using arylethylamines and alkenes in the presence of a palladium catalyst.[25] Interestingly, electron-deficient and electron-rich olefins were reactive for this reaction (Scheme 1.28).



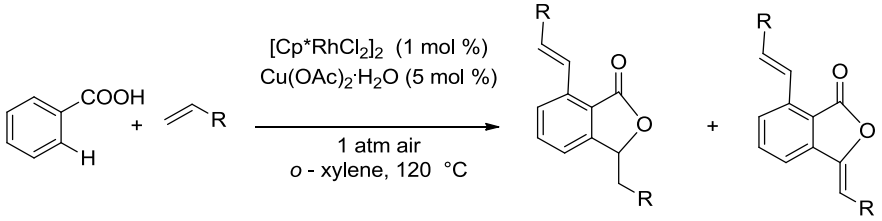
Scheme 1.28: Pd-catalyzed *ortho* alkenylation of homoallyl and bishomoallylamides

In 2009, the same group reported *meta* selective olefination of electron deficient arenes in presence of a Pd catalyst and pyridine ligands.[26] In this reaction, pyridine ligands was for the meta selectivity (Scheme 1.29). Later, the same group reported a series of papers on Pd(II)-catalyzed C-H bond alkenylation reactions.



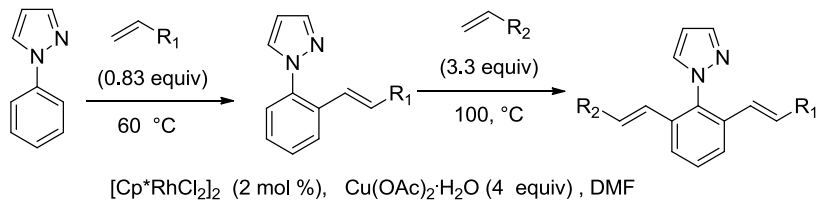
Scheme 1.29: Pd-catalyzed *meta* alkenylation of electron-deficient arenes

In 2007, Miura's group demonstrated a ruthenium-catalyzed oxidative cyclization of benzoic acids with alkenes.[27] The cyclization recation proceeds via *ortho* alkenylation of aromatic acids followed by intramolecular Michael addition (Scheme 1.30).



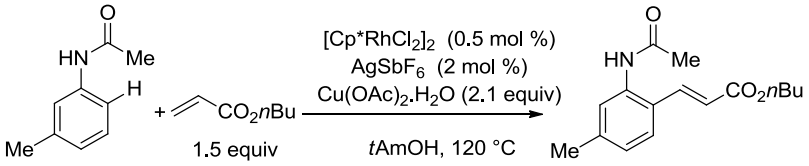
Scheme 1.30: Rh/Cu-catalyzed bis *ortho* alkenylation of benzoic acid

In 2009, the same developed reported a ruthenium-catalyzed alkenylation of 1-phenylpyrazoles with alkenes. In this reaction, 1-phenylpyrazole reacted with styrene in presence of $[Cp^*RhCl_2]_2$ catalyst and $Cu(OAc)_2.H_2O$ oxidant to give the corresponding alkenylated products in good to excellent yields (Scheme 1.31).[28] This olefination reaction has the selectivity of mono- versus divinylation.



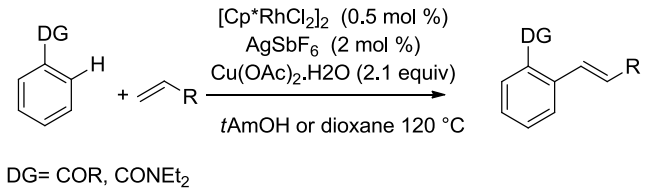
Scheme 1.31: Rh-catalyzed iterative intermolecular oxidative di-*ortho* alkenylation of *N*-phenylpyrazoles

In 2010, Glorius's group reported an *ortho* alkenylation of acetanilides with alkenes in the presence of a rhodium catalyst.[29] In the recation, activated and unactivated alkenes were comfortable for the reaction (Scheme 1.32).



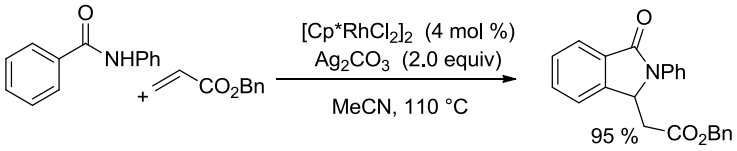
Scheme 1.32: Rh-catalyzed intermolecular oxidative *ortho* alkenylation of anilides

In 2011, the same group reported a rhodium(III)-catalyzed oxidative *ortho* olefination of benzamides and acetophenones under a similar reaction conditions.[30a] In the reaction, benzamides recated with styrenes or acrylates in presence of $[RhCp^*Cl_2]_2/AgSbF_6$ catalyst system and $Cu(OAc)_2$ in *t*-AmOH at 120 °C to give *ortho* alkenylated benzamides in good to excellent yields (Scheme 1.33).



Scheme 1.33: Rh-catalyzed oxidative olefination of C-H bonds in acetophenones and benzamides

In 2010, Li's group reported the synthesis of γ-lactams via oxidative coupling of benzamides or heteroaryl carboxamides with electron-poor olefins in the presence of a rhodium catalyst.[30b] (Scheme 1.34).



Scheme 1.34: Rh-catalyzed intermolecular oxidative *ortho* alkenylation/ hydroamination of benzamides

In the literature, enormous effort has been devoted by the groups of Miura, Yu, Sanford, Cheng, Fagnou, Glorius, and others, to the development of palladium- and rhodium-catalyzed chelation-assisted oxidative alkenylation at the *ortho* position of the aromatic C-H bonds.[25-30] However, these complexes are much expensive and in most of the reactions the stoichiometric amount of oxidant is required to generate the active catalyst. On the other hand, the use of a less-expensive ruthenium complex as a catalyst in the *ortho* alkenylation of aromatics with alkenes has not been explored in literature.

1.8: References

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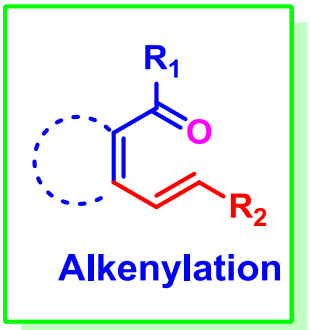
Chapter 2

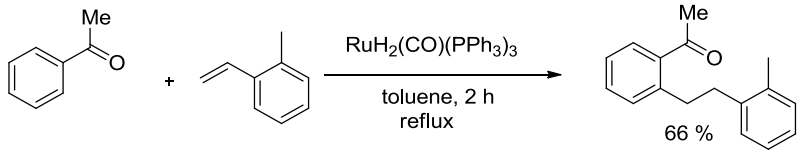
Ru-Catalyzed Selective *ortho* Alkenylation of Aromatic Ketones, Aldehydes and Esters with Alkenes



Introduction

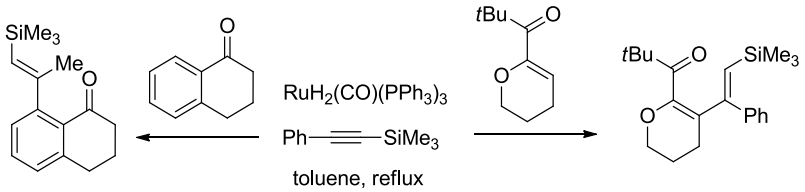
Construction of chemical bonds through a metal-catalyzed chelation-assisted C-H bond activation reaction is a highly efficient and beneficial method in organic synthesis.[1-3] The directing groups frequently used in this C-H bond activation reaction includes imine, alcohol, amine, carboxylic acid, amide, nitrile, ketone and ester. It is known that ruthenium, rhodium and palladium complexes are efficient used as catalysts for this type of reaction.[3] Among them, ruthenium complexes have gained much attention in this type of reaction recently due to their unusual reactivity and the low cost of these metal complexes.[4-8] By using ruthenium catalysts, various C-H bond functionalizations such as alkylations,[5-6] alkenylations[7] and arylation have been reported in the literature via an oxidative addition pathway.[8]

In 1997, Murai's group reported a first paper on the ruthenium-catalyzed chelation-assisted C-H bond functionalization reaction.[5a] In the reaction, aromatic ketones reacted with olefins in the presence of $RuH_2(CO)(PPh_3)_3$ to give alkylated products at the *ortho* C-H bond of aromatic ketones. Later, several research groups have devoted substantial effort in the area of addition reaction of aromatic ketones with alkenes by using different ruthenium complexes as catalysts (Scheme 2.1).[5-6] However, the methods described above generally gave *ortho*-alkylation products. This type of reaction proceeds via an oxidative addition pathway.



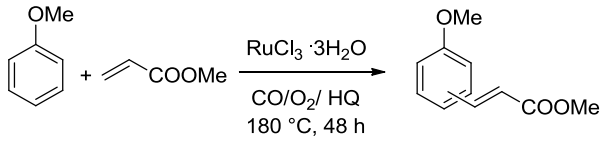
Scheme 2.1: *ortho* alkylation of aromatic ketones

In 1995, the same group reported a ruthenium-catalyzed hydroarylation of aromatic ketones with alkynes leading to trisubstituted alkenes in good to moderate yields (Scheme 2. 2).[9]



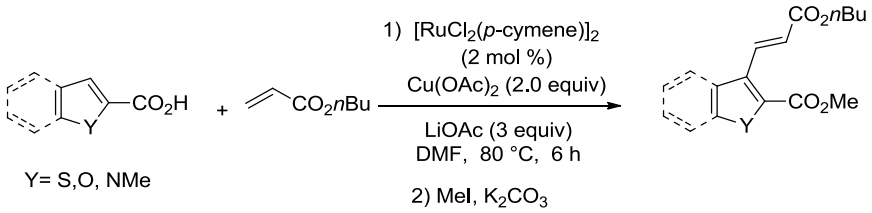
Scheme 2.2: Hydroarylation aromatic ketones with alkynes catalyzed by using Ru complex

In 2001, Milstein's group reported the oxidative alkenylation of electron rich aromatics with alkenes in the presence of $RuCl_3$, hydroquinone and carbon monoxide under the oxygen atmosphere. In the reaction, a mixture of alkenylated products was observed (Scheme 2.3).[10] This alkenylation reaction proceeds via Fujiwara type electrophilic metalation pathway.



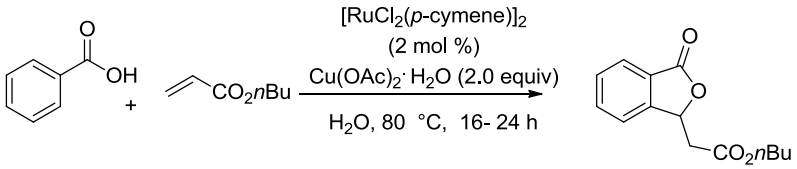
Scheme 2.3: Oxidative coupling of arenes with olefins by using Ru complex

In 2011, Miura's group reported a ruthenium-catalyzed oxidative alkenylation of heteroaromatic carboxylic acids with alkenes providing disubstituted alkene derivatives in good to excellent yields (Scheme 2.4).[11] The alkenylation reaction proceeds via deprotonation metalation pathway.



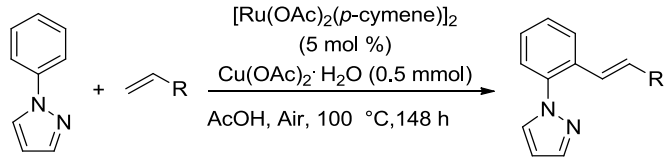
Scheme 2.4: A ruthenium-catalyzed Oxidative alkenylation of heteroaromatic carboxylic acids with alkenes

In the same year, Ackermann's group reported a ruthenium-catalyzed oxidative cyclization of aromatic acids with alkenes in water solvent giving cyclic phthalides in good to excellent yields (Scheme 2.5).[12]



Scheme 2.5: Ruthenium-catalyzed oxidative C-H bond alkenylation in water

Subsequently, Dixneuf's and Bruneau's groups reported a ruthenium-catalyzed oxidative alkenylation of *N*-phenylpyrazoles with alkenes providing disubstituted alkene derivatives in good to excellent yields. In the reaction, $Ru(OAc)_2$(*p*-cymene) and $Cu(OAc)_2 \cdot H_2O$ (20 mol %) were used in a catalytic amount under an air atmosphere (Scheme 2.6).[13]

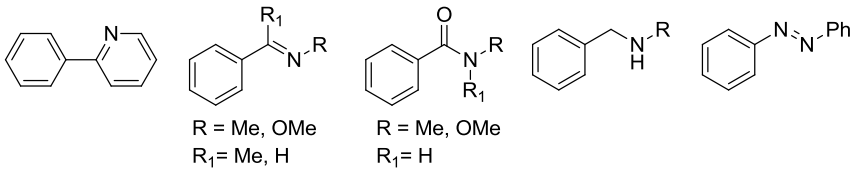


Scheme 2.6: Ruthenium-catalyzed oxidative C-H bond alkenylation of *N*-phenylpyrazoles

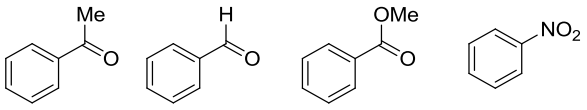
Classification of Directing Groups for C-H Bond Activation

For the chelation assisted C-H bond activation reaction, a directing group is required on the organic moiety. Generally, directing groups are classified into two types, such as a strong directing group and a weak directing group. It depends on the coordinating heteroatom of the directing group into the active metal catalyst. If coordinating hetero atom of directing group is nitrogen, then those functional groups are strong directing groups (Scheme 2.7). By using the strong directing groups, to do the C-H bond activation is very facile and quite easy. It is expected that the nitrogen atom of directing group coordinates with a metal species easily and form the stable metallacycle intermediate. Till that time, in the reported ruthenium-catalyzed C-H bond activation reaction, only strong directing group such as 2-pyridile and imines were used.

In directing group, if the coordinating hetero atom is oxygen, those directing groups are called weak directing groups (Scheme 2.8). It is believed that the oxygen containing functional groups would not coordinate effectively with a Ru(II) catalyst to do C-H bond activation. Because, the oxophilicity of Ru(II) catalyst is not sufficient to coordinate with oxygen contacting directing groups. Until now, there was no report on the weak chelating group assisted C-H bond activation of organic molecules in a ruthenium(II) catalyst via deprotonation metalation pathway. Our interest is to do the C-H bond activation of organic molecules by using a weak directing group in the presence of a less expensive ruthenium catalyst.

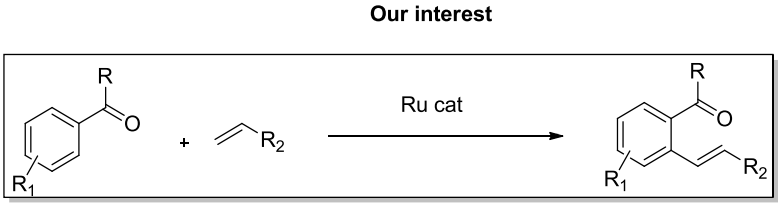


Scheme 2.7: Example of nitrogen containing functional groups



Scheme 2.8: Example of oxygen containing functional groups

While the C-H bond activation reaction in the presence of strong coordinating groups is well documented and facile, activation in the presence of weak coordinating groups such as aldehydes, esters, and ketones is very difficult and a challenging task. We have reported a weak carbonyl chelating group assisted ruthenium-catalyzed alkenylation of aryl ketones, aldehyde or ester with alkenes via deprotonation metalation pathway. This method provides an efficient route to ortho alkenylated aromatics in a highly regio- and stereoselective fashion (Scheme 2.9).

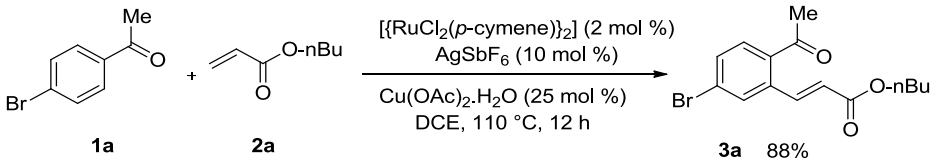


Scheme 2.9: *ortho* alkenylation of aromatic ketones

2A: Ruthenium-Catalyzed *ortho* Alkenylation of Aromatic Ketones with Alkenes by C-H Bond Activation

2A.1: Results and Discussion

The reaction of 4-bromoacetophenone (**1a**) with *n*-butyl acrylate (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2.H_2O$ (25 mol %) in 1,2-dichloroethane (DCE) at 110 °C for 12 h provided a Heck-type product **3a** in 88% isolated yield with excellent *E*-stereoselectivity (Scheme 2.10). It is important to note that in most of the rhodium-catalyzed C-H activation reactions, stoichiometric amount of oxidant have been used frequently. However, only 25 mol % of oxidant is used in the present reaction. It is also worthwhile to mention that only catalytic amount of oxidants (Ag salts or Cu salts or air) were used in the palladium-catalyzed alkenylation reactions.[14] Control experiments revealed that no **3a** was obtained in the absence of either ruthenium catalyst or silver salt or copper salt.



1a **2a** **3a** 88%

Scheme 2.10: *ortho* alkenylation of aromatic ketones

2A.2: Optimization Studies

Table 2.1: Optimization Studies with Various Solvents, Oxidants and Additives.[a]

entry	solvent	oxidant	additive	yield of **3a** (%)[b]
1	DCE	$Cu(OAc)_2.H_2O$	AgOTf	35
2	DCE	$Cu(OAc)_2.H_2O$	$AgBF_4$	20
3	DCE	$Cu(OAc)_2.H_2O$	Ag_2O	NR
4	DCE	$Cu(OAc)_2.H_2O$	AgO_2CCF_3	NR
5	**DCE**	**$Cu(OAc)_2.H_2O$**	**$AgSbF_6$**	**94**
6	DCE	O_2	$AgSbF_6$	NR
7	DCE	oxone	$AgSbF_6$	NR
8	DCE	DDQ	$AgSbF_6$	NR
9	DCE	$PhI(OAc)_2$	$AgSbF_6$	NR
10	DCE	$K_2S_2O_8$	$AgSbF_6$	NR
11	*t*-BuOH	$Cu(OAc)_2.H_2O$	$AgSbF_6$	93
12	THF	$Cu(OAc)_2.H_2O$	$AgSbF_6$	92
13	Toluene	$Cu(OAc)_2.H_2O$	$AgSbF_6$	NR
14	DMF	$Cu(OAc)_2.H_2O$	$AgSbF_6$	NR
15	Acetic acid	$Cu(OAc)_2.H_2O$	$AgSbF_6$	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 oxidants (both 25 mol % as well as 1.5 mmol) 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 AgSbF6. No product **3a** was observed.

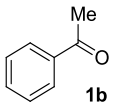
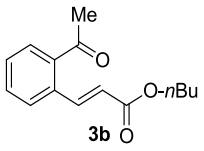
The silver salt and oxidant used were crucial for the success of the foregoing catalytic reaction. First, a variety of silver salts (10 mol %) was examined in the reaction of **1a** (1.0 mmol) with **2a** (1.5 mmol) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %) and $Cu(OAc)_2.H_2O$ (25 mol %) in DCE at 110 °C for 12 h. Among them, $AgSbF_6$ gave the best results and afforded **3a** in 94% NMR yield. AgOTf and $AgBF_4$ were less effective for the reaction giving **3a** in 35% and 20% yields, respectively. Other silver salts including Ag_2O, and AgO_2CCF_3 were totally ineffective for the reaction. The catalytic reaction was tested with various oxidants. $Cu(OAc)_2.H_2O$ was very effective for the reaction providing **3a** in 94% yield. Other oxidants such as O_2, oxone, DDQ, $PhI(OAc)_2$ and $K_2S_2O_8$ were totally ineffective in the reaction (both 25 mol % as well as 1.5 mmol) (Table 2.1). The effect of solvent is also vital to the catalytic reaction. The best solvent is

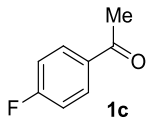
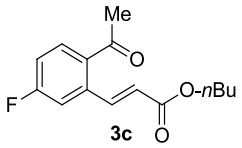
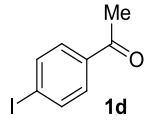
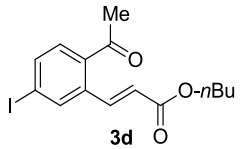
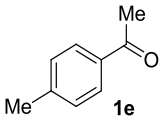
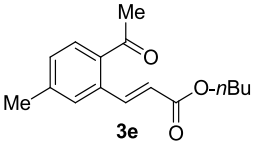
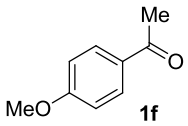
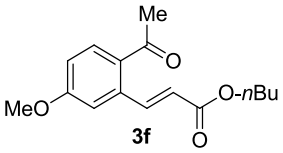
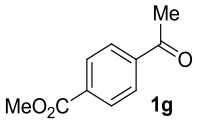
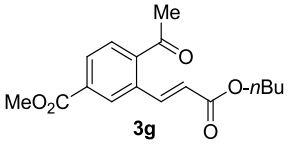
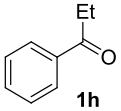
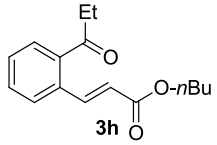
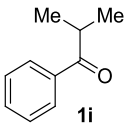
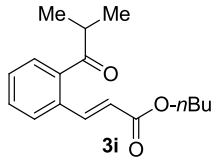
DCE in which **3a** was obtained in 94% yield. THF and *t*-BuOH were also equally effective for the reaction giving **3a** in 92% and 93% yields, respectively. Other solvents such as DMF, acetic acid and toluene were totally ineffective for the catalytic reaction. On the basis of these optimization studies, we chose [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %) as the catalyst, $AgSbF_6$ (10 mol %) as the additive, and $Cu(OAc)_2.H_2O$ (25 mol %) as the oxidant and DCE (1,2-dichloroethane) or THF or *t*-BuOH as the solvent for this ruthenium-catalyzed C-H bond activation reaction.

2A.3: Scope of Aromatic Ketones

Under the optimized reaction conditions, several substituted acetophenones **1b-m** reacted efficiently with *n*-butyl acrylate **(2a)** to give the corresponding alkene derivatives **3b-m** in good to excellent yields with complete E-stereoselectivity (Table 2.2). Thus, acetophenone **(1b),** 4-fluoroacetophenone **(1c),** and 4-iodoacetophenone **(1d)** gave theHecktype products **3b-3d** in 86%, 89%, and 83%yields, respectively (entries 1-3). It is interesting to note that the catalytic reaction is compatible with very sensitive halogen groups such as F and I (Table 2.2 entry 2 and 3). Similarly, 4-methylacetophenone **(1e)** and 4-methoxy acetophenone **(1f)** afforded the corresponding alkene derivatives **3e** and **3f** in 79% and 77% yields, respectively (entries 4 and 5). Surprisingly, 4-methylester acetophenone **1g** reacted with **2a** to give the alkenylation product **3g** at the next carbon to the acetyl group in 85%yield (entry 6). The regiochemistry of compound **3g** was established by NOESY experiments (see SI). It is well-known that the ester group serves as an excellent directing group for the ruthenium-catalyzed C-H bond activation reactions.[15] The present result shows that the acetyl group chelates with Ru better than the ester group. The catalytic reaction was also tested with the effect of changing the methyl group in acetophenone to other substituents. Thus, propiophenone **(1h)** and isobutyrophenone **(1i)** efficiently reacted with **2a** to afford **3h** and **3i** in 85% and 79% yields, respectively (entries 7 and 8).

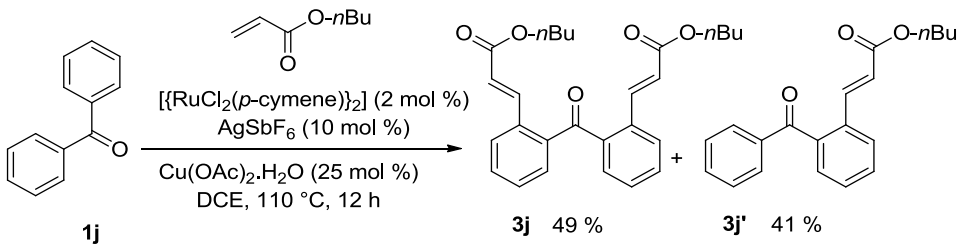
Table 2.2 : Results of the Reaction of Aromatic Ketones **1** with *n*-Butyl Acrylate

entry	**1**	product **3**	yield (%)[b]
1	 **1b**	 **3b**	86

2	 **1c**	 **3c**	89
3	 **1d**	 **3d**	83
4	 **1e**	 **3e**	79
5	 **1f**	 **3f**	77
6	 **1g**	 **3g**	85
7	 **1h**	 **3h**	85
8	 **1i**	 **3i**	79

[a]All reactions were carried out using aromatic ketones **1** (1.0 mmol), *n*-butyl acrylate (**2a**) (1.5 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (10 mol %) and $Cu(OAc)_2.H_2O$ (25 mol %) in DCE (1,2-dichloroethane) (3.0 mL) at 110 °C for 12 h. [b]Isolated yields.

However, benzophenone **(1j)** provided a mixture of monoalkenylated and bis alkenylated products **3j** and **3j'** in 41% and 49% yields, respectively (Scheme 2.11).

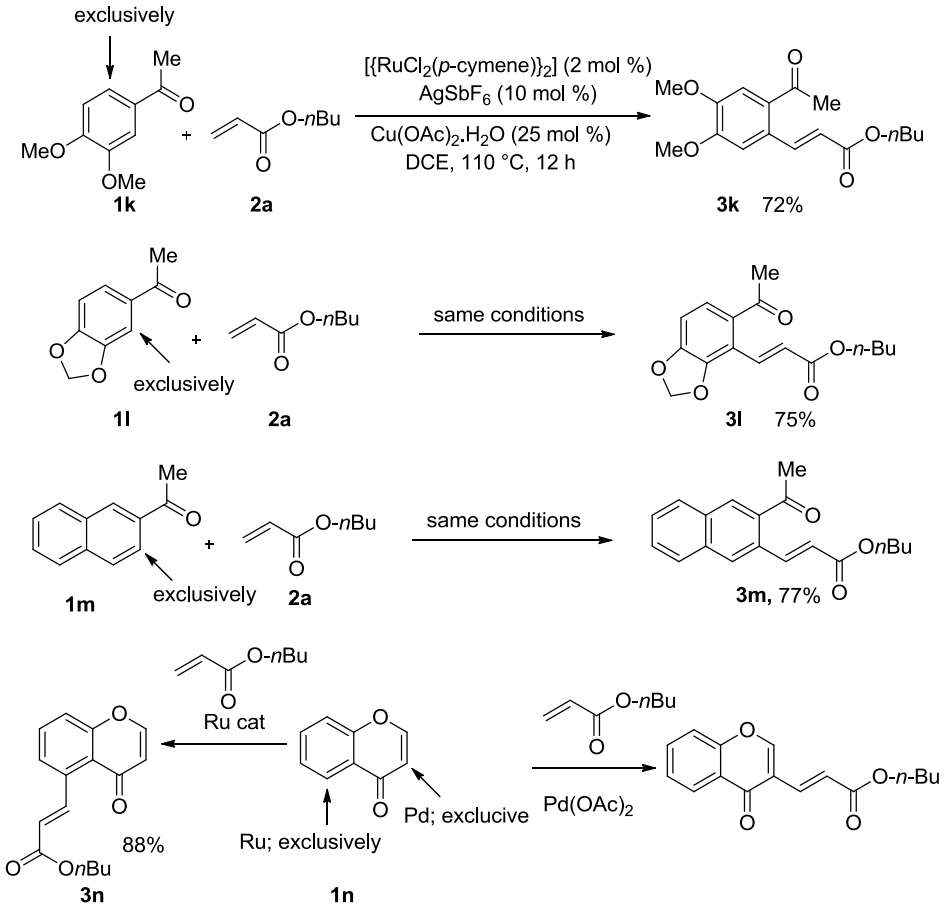


Scheme 2.11: Results of the reaction of benzophenone with *n*-butyl acrylate

2A.4: Regioselectivity Studies

Next, we studied the regioselectivity of the unsymmetrical acetophenones **1k-m** in the reaction (Scheme 2.12). When 3,4-dimethoxyacetophenone **(1k)** was treated with n-butyl acrylate **(2a**), a single regioisomeric product, **3k**, was observed in 72% yield. Clearly, it indicates that formation of **3k** is a sterically controlled process. In contrast, 3,4-(methylenedioxy)acetophenone **(1l)** provided a single product **3l** in 75% yield, in which the alkene had been added at the more sterically hindered site

On the other hand, 2-napthophenone **(1m)** afforded **3m**, with the alkene substituent at C3 carbon, exclusively in 77% yield. The present methodology can be further extended to the heteroaromatic ketone **1n**. Under the optimized reaction conditions, the reaction of chromone **(1n)** with **2a** afforded **3n** in 88%yields. In the reaction, an alkene moiety was incorporated in the C-5 carbon of the chromone. The regiochemistry of compound 3n was established by NOESY experiments.

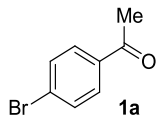
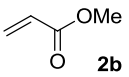
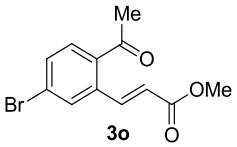
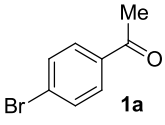
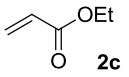
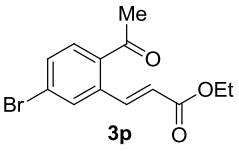
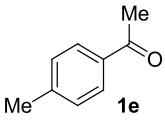
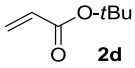
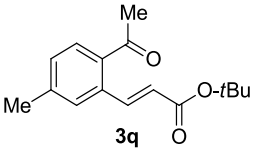
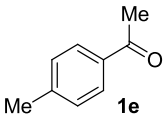
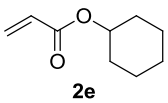
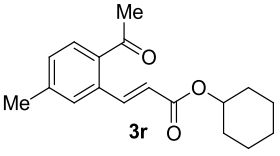


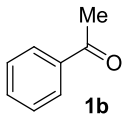
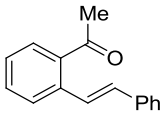
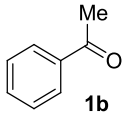
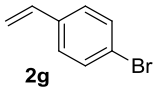
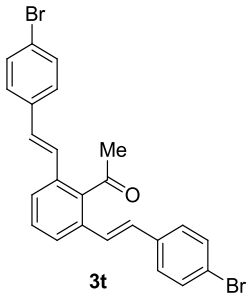
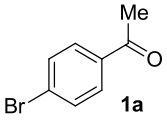
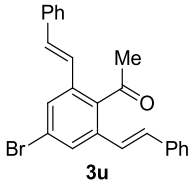
Scheme 2.12: Regioselectivity studies of unsymmetrical acetophenones with *n*-butyl acrylate

2A.5: Scope of Alkenes

The present C-H bond functionalization reaction was successfully extended to various alkenes (Table 2.3). Methyl acrylate **(2b),** ethyl acrylate **(2c),** tert-butyl acrylate **(2d),** and cyclohexyl acrylate **(2e)** efficiently reacted with **1a** or **1e** under the optimized reaction conditions to give the corresponding Heck-type products **3o-r** in 86%, 89%, 75%, and 83% yields, respectively (Table 2.3, entries 1-4). The catalytic reaction was also tested with substituted styrenes. Initially, the reaction of styrene **(2f)** with acetophenone **(1b)** was tested with 1,2-dichloroethane under the optimized reaction conditions. However, in the reaction, the corresponding alkenylated product was not observed. The same reaction was tested with other solvents such as THF and *tert*-butanol. Interestingly, *tert*-butanol worked nicely and gave the expected Heck-type product **3s** in 55% yields (entry 5). But, acetophenone **(1b)** reacted with 4-bromostyrene **(2g)** under similar reaction conditions to give bis alkenylated product **3t** in 59%yield (entry 6). In a similar fashion, 4-bromoacetophenone **(1a)** also reacted efficiently with styrene **(2f)** to afford bis alkenylated product **3u** in 62% yield (entry 7). In these reactions, no monoalkenylated product was observed.

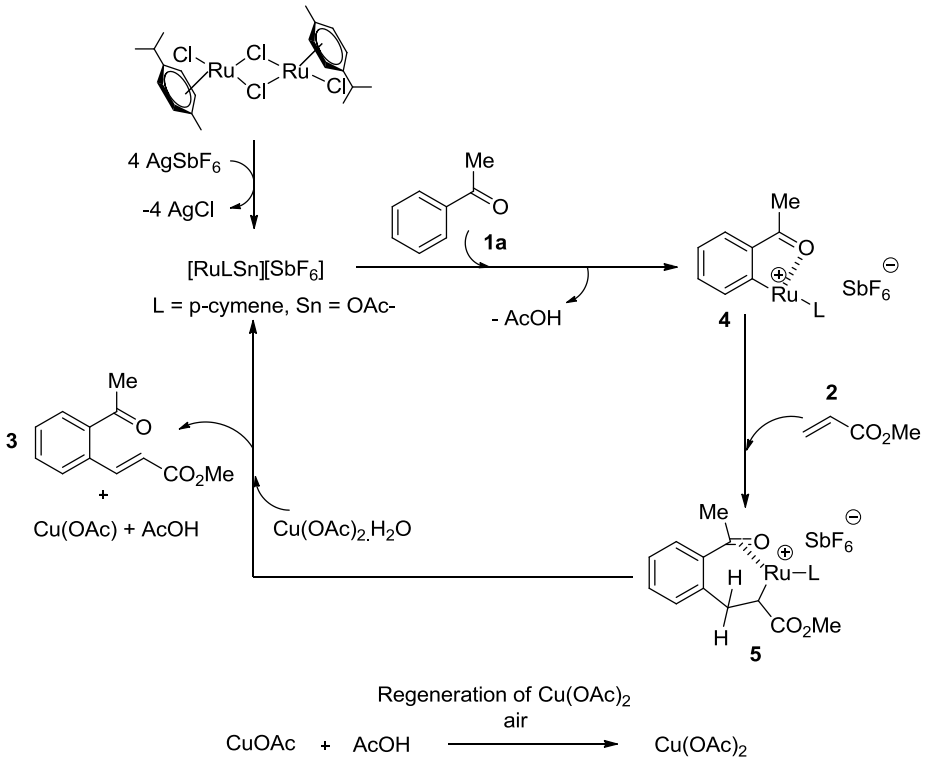
Table 2.3 : Results of the Reaction of 4-Bromoacetophenone (**1a**), Acetophenone **(1b),** or 4-Methylacetophenone (**1e**) with Substituted Alkenes **2b-f**[a]

entry	**1**	**2**	Product **3**	Yield (%)[b]
1	 **1a**	 **2b**	 **3o**	86
2	 **1a**	 **2c**	 **3p**	89
3	 **1e**	 **2d**	 **3q**	75[c]
4	 **1e**	 **2e**	 **3r**	83[c]

5	 **1b**	 **2f**	 **3s**	55[c]
6	 **1b**	 **2g**	 **3t**	59[c]
7	 **1a**	 **2f**	 **3u**	62[c]

[a] All reactions were carried out using aromatic ketones **1a, 1b**, or **1e** (1.0 mmol), alkenes **2 (2b-e** (1.5 mmol), **2f** and **2g** (2.0 mmol)), [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2$. H_2O (25 mol %) in DCE (1, 2-dichloroethane) (3.0 mL) at 110 °C for 12 h. [b] Isolated yields. [c] The reaction was carried out in *tert*-butanol (3.0 mL) instead of DCE.

2A.6: Mechanism



Scheme 2.13: Proposed mechanism

On the basis of known metal-catalyzed directing group assisted C-H bond activation reactions,[1-22] a possible reaction mechanismis proposed to account for the present catalytic reaction (Scheme 2.13). The removal of a chloride ligand by a Ag+ salt from the [{$RuCl_2$(*p*-cymene)}$_2$] complex likely initiates the catalytic reaction. Coordination of the keto oxygen of **1** to the ruthenium cationic species followed by *ortho* metalation gives a five-membered metallacycle 4.[2l] Coordinative insertion of alkene **2** into the Ru-C bond of metallacycle **4** provides an intermediate **5**. β-Hydride elimination from intermediate **5** in the presence of $Cu(OAc)_2 \cdot H_2O$ gives the final product **3** and regenerates the active ruthenium species for the next catalytic cycle. The exact role of the copper source was not clear in the reaction. But, we propose that $Cu(OAc)_2 \cdot H_2O$ provides the OAc^- source to the active rutheniumspecies in order to accelerate the *ortho*-metalation.

It is interesting to compare the mechanistic differences between the present reactions with the previously reported Murai's type alkylation reaction.[26-27] The alkylation reaction proceeds via oxidative addition of an *ortho* C-H bond of acetophenone to the Ru(0) center giving the ruthenium-hydride [(Ar)Ru(II)(H)] species. Coordinative insertion of an alkene into the Ru-H species followed by reductive elimination provides the final alkylated product, whereas, in the present reaction,C-H bond cleavage takes place via a concerted metalation/deprotonation mechanism. Later, coordinative insertion of the olefin into the Ru-C species **4** followed by β-hydride elimination gives the alkenylated product.

2A.7: Conclusion

1. We have developed a ruthenium-catalyzed chelation-assisted C-H bond functionalization of an *ortho* C-H bond of aromatic ketones with alkenes to afford substituted alkene derivatives in good to excellent yields.
2. The amount of $Cu(OAc)_2$ was reduced to catalytic amount by using air as a external oxidant.

2A.8: Experimental Section

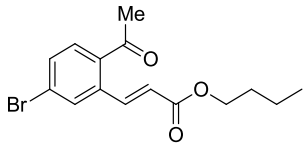
General Procedure for the Coupling of Aromatic Ketones with Alkenes Catalyzed by Ruthenium Complex:

$[RuCl_2$(*p*-cymene)$]_2$ (0.02 mmol, 4 mol%), $AgSbF_6$ (0.10 mmol, 20 mol%), and $Cu(OAc)_2 \cdot H_2O$ (0.25 mmol, 25 mol %) were added to a 15 mL pressure tube, which was

equipped with a magnetic stirrer and septum. (***Note:*** $AgSbF_6$ is moisture-sensitive. Thus, AgSbF6 was handled inside a nitrogen glove box.) To the tube were added by syringe ketones **1** (1.0 equiv.), alkenes **2** (1.2 equiv.), and 1,2-dichloroethane or *tert*-butanol (3.0 mL) as the solvent, and the reaction mixture was allowed to stir at room temperature for 5 min. During this time, the tube was covered with a septum. Then, the septum was removed, and the reaction mixture was stirred under open air for an additional 5 min. [***Note:*** During this time, the nitrogen gas that was initially in the pressure tube dispersed, and air entered the tube. In the reaction, only 25 mol-% of $Cu(OAc)_2 \cdot H_2O$ was used for the internal oxidant. In fact, 2.20 equiv. of $Cu(OAc)_2 \cdot H_2O$ was needed for the reaction. It is strongly believed that the remaining amount of $Cu(OAc)_2 \cdot H_2O$ necessary for the reaction was regenerated under oxygen or air from the reduced copper source CuOAc. Therefore, we conducted the reaction under open air.] Next, the pressure tube was sealed with a screw cap, and the reaction mixture was stirred at 100 °C for 12 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 and then filtered through Celite and silica gel. The filtrate was concentrated, and the crude residue was purified through a silica gel column (hexanes and ethyl acetate) to give pure **3**.

2A.9: Spectral Data of Compounds 3a-u

(*E*)-Butyl 3-(2-acetyl-5-bromophenyl)acrylate (**3a**).



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

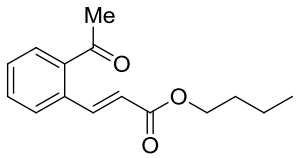
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2959, 1715, 1636, 1582.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, *J* = 16.0 Hz, 1 H), 7.68 (s, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H), 7.54 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.24 (d, *J* = 16 Hz, 1 H), 4.17 (t, *J* = 8.0 Hz, 2 H), 2.56 (s, 3 H), 1.68 – 1.61 (m, 2 H), 1.44 – 1.35 (m, 2 H), 0.92 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.7, 166.3, 142.6, 137.1, 136.6, 132.3, 131.1, 130.8, 126.7, 122.2, 64.7, 30.8, 29.2, 19.2, 13.8.

HRMS (ESI): calc. for $[(C_{15}H_{17}O_3Br)H]$ (M+H) 325.0439, measured 325.0437.

(*E*)-Butyl 3-(2-acetylphenyl)acrylate (**3b**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 1716, 1590, 1262, 1118.

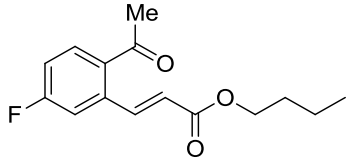
^1H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, *J* = 16.0 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 8.0 Hz, 1 H), 7.44 (t, *J* = 8.0 Hz, 1 H), 6.27 (d, *J* = 16.0 Hz, 1 H), 4.19 (t, *J* = 8.0 Hz, 2 H), 2.60 (s, 3 H), 1.71 – 1.64 (m, 2 H), 1.46 – 1.37 (m, 2 H), 0.94 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.9, 166.7, 143.9, 138.3, 134.9, 132.0, 129.4, 129.2, 128.5, 121.1, 64.6, 30.8, 29.4, 19.3, 13.8.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 247 (M+H), 145, 131, 91.

HRMS (ESI): calc. for [($C_{15}H_{18}O_3$)H] (M+H) 247.1334, measured 247.1335.

(*E*)-Butyl 3-(2-acetyl-5-fluorophenyl)acrylate (**3c**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960, 1715, 1636.

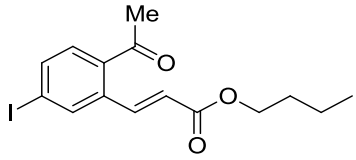
^1H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, *J* = 12.0 Hz, 1 H), 7.74 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.16 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.05 (t, *J* = 8.0, 4.0 Hz, 1 H), 6.20 (d, *J* = 16.0 Hz, 1 H), 4.13 (t, *J* = 8.0 Hz, 2 H), 2.53 (s, 3 H), 1.63 – 1.57 (m, 2 H), 1.39 – 1.32 (m, 2 H), 0.88 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.1, 166.3, 165.6 and 163.1 (C-F), 143.2, 138.4 and 138.3 (C-F), 134.1, 132.2 and 132.1 (C-F), 121.9, 116.3 and 116.1 (C-F), 115.7 and 115.2 (C-F), 64.6, 30.7, 20.1, 19.2, 13.8.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 265 (M+H), 191, 163, 120, 85.

HRMS (ESI): calc. for [($C_{15}H_{17}O_3F$)H] (M+H) 265.1240, measured 265.1228.

(*E*)-Butyl 3-(2-acetyl-5-iodophenyl)acrylate (**3d**).



Pale yellow liquid; eluent (7% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2924, 1710, 1585.

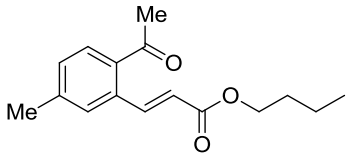
^1H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, *J* = 12.0 Hz, 1 H), 7.92 (s, 1 H), 7.78 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 6.25 (d, *J* = 12 Hz, 1 H), 4.20 (t, *J* = 8.0 Hz, 2 H), 2.57 (s, 3 H), 1.67 – 1.64 (m, 2 H), 1.44 – 1.40 (m, 2 H), 0.95 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.1, 166.5, 142.7, 138.5, 137.6, 137.3, 136.9, 130.7, 122.2, 99.3, 64.8, 30.9, 29.3, 19.4, 13.9.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 373 (M+H), 329, 299, 271, 233, 205.

HRMS (ESI): calc. for [($C_{15}H_{17}O_3I$)H] (M+H) 373.0301, measured 373.0289.

(*E*)-Butyl 3-(2-acetyl-5-methylphenyl)acrylate (**3e**).



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

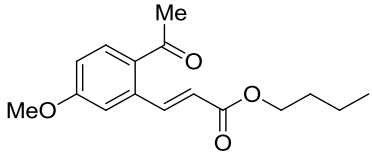
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960, 1713 and 1591.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, *J* = 16.0 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.28 (s, 1 H), 7.16 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.16 (d, *J* = 16 Hz, 1 H), 4.11 (t, *J* = 8.0 Hz, 2 H), 2.49 (s, 3 H), 2.31 (s, 3 H), 1.63 – 1.58 (m, 2 H), 1.37 – 1.29 (m, 2 H), 0.86 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.3, 166.8, 144.5, 142.8, 135.3, 130.1, 129.8, 129.2, 120.7, 64.5, 30.8, 29.1, 21.5, 19.3, 13.8.

HRMS (ESI): calc. for [($C_{16}H_{20}O_3$)H] (M+H) 261.1491, measured 261.1495.

(*E*)-Butyl 3-(2-acetyl-5-methoxyphenyl)acrylate (**3f**).



Pale yellow liquid; eluent (15% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2959, 1707, 1675.

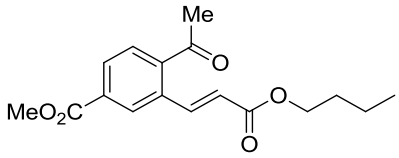
^1H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 12.0 Hz, 1 H), 7.76 (d, *J* = 8.0, Hz, 1 H), 6.98 (s, 1 H), 6.90 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.20 (d, *J* = 16 Hz, 1 H), 4.18 (t, *J* = 8.0 Hz, 2 H), 3.85 (s, 3 H), 2.55 (s, 3 H), 1.69 – 1.64 (m, 2 H), 1.42 – 1.38 (m, 2 H), 0.93 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.9, 166.8, 162.4, 145.1, 138.3, 132.3, 130.4, 121.0, 114.4, 113.9, 64.6, 55.7, 30.9, 28.8, 19.3, 13.9.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 277 (M+H), 175, 161, 132.

HRMS (ESI): calc. for [($C_{16}H_{20}O_4$)H] (M+H) 277.1440, measured 277.1453.

(*E*)-Methyl 4-acetyl-3-(3-butoxy-3-oxoprop-1-en-1-yl)benzoate (**3g**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2925, 1722, 1674 and 1590.

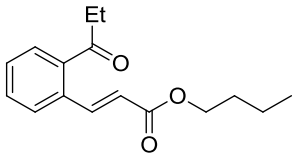
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (s, 1 H), 8.00 – 7.95 (m, 2 H), 7.69 (d, *J* = 8.0, Hz, 1 H), 6.31 (d, *J* = 16 Hz, 1 H), 4.12 (t, *J* = 8.0 Hz, 2 H), 3.87 (s, 3 H), 2.55 (s, 3 H), 1.62 – 1.57 (m, 2 H), 1.38 – 1.32 (m, 2 H), 0.87 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.6, 166.3, 165.7, 142.5, 141.7, 134.7, 132.9, 130.2, 129.3, 129.0, 122.1, 64.6, 52.6, 30.7, 29.6, 19.2, 13.8.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 305 (M+H), 263, 231, 203.

HRMS (ESI): calc. for [($C_{17}H_{20}O_5$)H] (M+H) 305.1389, measured 305.1385.

(*E*)-Butyl 3-(2-propionylphenyl)acrylate (**3h**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 1707 and 1629.

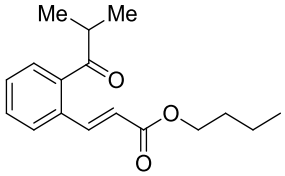
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 12.0 Hz, 1 H), 7.60 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.50 (d, *J* = 8.0, 4.0 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 7.35 (t, *J* = 8.0 Hz, 1 H), 6.21 (d, *J* = 16.0 Hz, 1 H), 4.12 (t, *J* = 8.0 Hz, 2 H), 2.85 (q, *J* = 8.0 Hz, 2 H), 1.64 – 1.57 (m, 2 H), 1.39 – 1.30 (m, 2 H), 1.12 (t, *J* = 8.0 Hz, 3 H), 0.87 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.2, 166.6, 143.8, 138.7, 134.5, 131.6, 129.5, 128.3, 120.8, 64.5, 34.8, 30.8, 19.2, 13.8, 8.4.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 261 (M+H), 187, 159, 131.

HRMS (ESI): calc. for [($C_{16}H_{20}O_3$)H] (M+H) 261.1491, measured 261.1497.

(*E*)-Butyl 3-(2-isobutyrylphenyl)acrylate (**3i**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2963, 1714 and 1636.

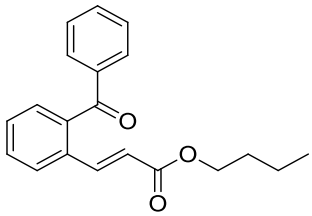
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* = 12.0 Hz, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.47 (t, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 6.29 (d, *J* = 12.0 Hz, 1 H), 4.19 (t, *J* = 8.0 Hz, 2 H), 3.36 – 3.31 (m, 1 H), 1.67 – 1.64 (m, 2 H), 1.42 – 1.39 (m, 2 H), 1.17 (d, *J* = 8.0 Hz, 6 H), 0.94 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 208.6, 166.8, 143.3, 139.7, 134.4, 131.3, 129.6, 128.2, 127.9, 121.1, 64.7, 39.3, 30.9, 19.4, 18.7.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 275 (M+H), 231, 201, 173, 131.

HRMS (ESI): calc. for [($C_{17}H_{22}O_3$)H] (M+H) 275.1647, measured 275.1642.

(*E*)-Butyl 3-(2-benzoylphenyl)acrylate (**3j**).



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

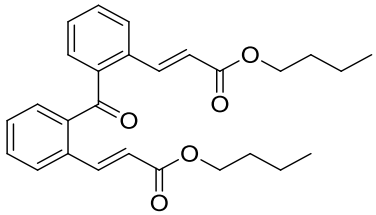
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2927, 1710, 1655.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 – 7.70 (m, 4 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.51 (t, *J* = 8.0 Hz, 1 H), 7.45 – 7.39 (m, 4 H), 6.35 (t, *J* = 16.0 Hz, 1 H), 4.09 (t, *J* = 8.0 Hz, 2 H), 1.61 – 1.54 (m, 2 H), 1.36 – 1.27 (m, 2 H), 0.89 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.3, 166.5, 141.8, 139.5, 137.4, 133.9, 133.6, 130.8, 130.4, 129.3, 128.6, 127.3, 120.9, 64.5, 30.7, 19.2, 13.8.

HRMS (ESI): calc. for [($C_{20}H_{20}O_3$)Na] (M+Na) 331.1310, measured 331.1308.

(2*E*,2'*E*)-Dibutyl 3,3'-(carbonylbis(2,1-phenylene))diacrylate (**3j'**).



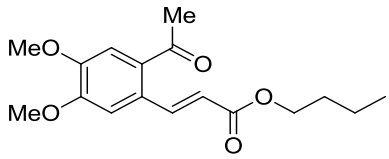
Pale yellow liquid; eluent (12% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, *J* = 12.0 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.61 – 7.57 (m, 2 H), 7.46 – 7.44 (m, 4 H), 6.39 (d, *J* = 12.0 Hz, 2 H), 4.19 (t, *J* = 8.0 Hz, 4 H), 1.70 – 1.65 (m, 4 H), 1.43 – 1.39 (m, 4 H), 0.97 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.9, 166.4, 142.4, 138.8, 135.5, 132.1, 130.9, 129.3, 127.9, 121.4, 65.5, 30.7, 19.2, 13.8.

GC-MS (70 ev, C.I.) [($C_{27}H_{30}O_5$)H] (M+H) 435: measured 435 (M+H), 361, 333, 259, 235.

(*E*)-Butyl 3-(2-acetyl-4,5-dimethoxyphenyl)acrylate (**3k**).



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

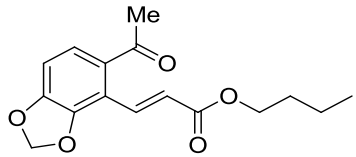
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2923, 1710, 1590.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, *J* = 16.0 Hz, 1 H), 7.19 (s, 1 H), 7.01 (s, 1 H), 6.21 (d, *J* = 16.0 Hz, 1 H), 4.19 (t, *J* = 8.0 Hz, 2 H), 3.94 (s, 6 H), 2.57 (3 H), 1.70 – 1.64 (m, 2 H), 1.44 – 1.39 (m, 2 H), 0.94 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.5, 166.9, 151.7, 149.5, 143.9, 131.5, 129.1, 119.8, 112.0, 110.3, 64.6, 56.2, 56.2, 30.8, 29.6, 19.3, 13.7.

HRMS (ESI): calc. for [($C_{17}H_{22}O_5$)H] (M+H) 307.1545, measured 307.1544.

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



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958, 1708, 1628.

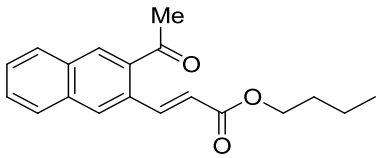
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, *J* = 12.0 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.63 (d, *J* = 12.0 Hz, 1 H), 6.07 (s, 2 H), 4.15 (t, *J* = 8.0 Hz, 2 H), 2.52 (3 H), 1.67 – 1.61 (m, 2 H), 1.41 – 1.36 (m, 2 H), 0.91 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.4, 167.4, 150.8, 137.8, 132.8, 125.7, 123.9, 117.3, 108.0, 102.4, 64.6, 30.9, 29.4, 19.4, 13.9.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 291 (M+H), 217, 275, 189, 175.

HRMS (ESI): calc. for [($C_{16}H_{18}O_5$)H] (M+H) 291.1232, measured 291.1225.

(*E*)-Butyl 3-(3-acetylnaphthalen-2-yl)acrylate (**3m**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958, 1711, 1632.

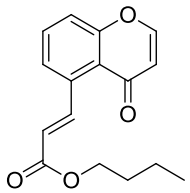
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (d, *J* = 12.0 Hz, 1 H), 8.24 (s, 1 H), 7.95 (s, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.60 – 7.52 (m, 2 H), 6.34 (d, *J* = 12.0 Hz, 1 H), 4.21 (t, *J* = 8.0 Hz, 2 H), 2.70 (s, 3 H), 1.72 – 1.66 (m, 2 H), 1.47 – 1.40 (m, 2 H), 0.95 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.5, 166.9, 145.0, 135.5, 134.6, 132.8, 132.2, 131.2, 129.1, 128.9, 128.6, 128.3, 127.9, 120.5, 64.7, 30.9, 29.1, 19.4, 14.0.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 297 (M+H), 223, 195, 181, 152.

HRMS (ESI): calc. for [($C_{19}H_{20}O_3$)H] (M+H) 297.1491, measured 297.1492.

(*E*)-Butyl 3-(4-oxo-4*H*-chromen-5-yl)acrylate (**3n**).



Pale yellow liquid; eluent (15% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2959, 1712, 1648.

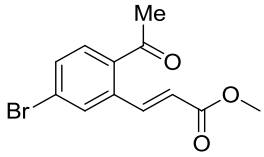
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.89 (d, *J* = 12.0 Hz, 1 H), 7.77 (d, *J* = 4.0 Hz, 1 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 6.26 (d, *J* = 8.0 Hz, 1 H), 6.34 (d, *J* = 12.0 Hz, 1 H), 4.17 (t, *J* = 8.0 Hz, 2 H), 1.68 – 1.63 (m, 2 H), 1.44 – 1.38 (m, 2 H), 0.91 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.9, 166.7, 157.6, 154.5, 144.8, 137.3, 133.3, 124.9, 122.5, 121.8, 119.9, 114.4, 64.7, 30.9, 19.4, 13.9.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 273 (M+H), 217, 199, 171, 115.

HRMS (ESI): calc. for [($C_{16}H_{16}O_4$)H] (M+H) 273.1127, measured 273.1135.

(*E*)-Methyl 3-(2-acetyl-5-bromophenyl)acrylate (**3o**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2941, 1715, 1674.

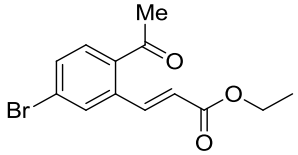
^1H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, *J* = 16.0 Hz, 1 H), 7.68 (s, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 6.24 (d, *J* = 12.0 Hz, 1 H), 3.78 (s, 3 H), 2.57 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.8, 166.8, 143.1, 137.1, 136.7, 132.5, 131.6, 131.0, 126.9, 121.8, 52.1, 29.3.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 283 (M+H), 251, 225, 209, 145, 115.

HRMS (ESI): calc. for [($C_{12}H_{11}O_3Br$)H] (M+H) 282.9970, measured 282.9968.

(*E*)-Ethyl 3-(2-acetyl-5-bromophenyl)acrylate (**3p**).



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

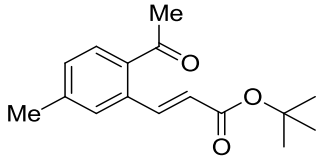
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922, 1714, 1590.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, *J* = 12.0 Hz, 1 H), 7.66 (s, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 6.22 (d, *J* = 16.0 Hz, 1 H), 4.22 (d, *J* = 8.0 Hz, 2 H), 2.55 (s, 3 H), 1.28 (d, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.8, 166.3, 142.8, 137.2, 136.7, 132.4, 131.5, 131.0, 126.9, 122.3, 60.9, 29.3, 14.5.

HRMS (ESI): calc. for [($C_{13}H_{13}O_3Br$)H] (M+H) 297.0126, measured 297.0132.

(*E*)-*tert*-Butyl 3-(2-acetylphenyl)acrylate (**3q**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977, 1708, 1633.

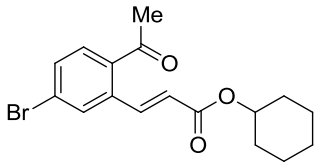
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, *J* = 16.0 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.29 (s, 1 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 6.10 (d, *J* = 16.0 Hz, 1 H), 2.50 (s, 3 H), 2.32 (s, 3 H), 1.45 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.4, 160.0, 143.4, 142.6, 135.4, 129.9, 129.7, 129.2, 122.6, 80.5, 29.2, 28.3, 21.5.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 261 (M+H), 233, 187, 159, 115.

HRMS (ESI): calc. for [($C_{16}H_{20}O_3$)H] (M+H) 261.1491, measured 261.1491.

(*E*)-Cyclohexyl 3-(2-acetyl-5-bromophenyl)acrylate (**3r**).



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

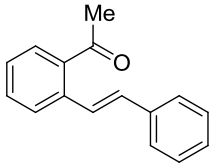
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 1718, 1630.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, *J* = 16.0 Hz, 1 H), 7.70 (s, 1 H), 7.60 – 7.54 (m, 2 H), 6.25 (d, *J* = 16.0 Hz, 1 H), 4.89 – 4.84 (m, 1 H), 2.57 (s, 3 H), 1.90 – 1.87 (m, 2 H), 1.75 – 1.72 (m, 2 H), 1.52 – 1.22 (m, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.8, 165.7, 142.3, 137.1, 136.6, 132.2, 131.5, 130.8, 126.7, 122.8, 73.0, 31.7, 29.3, 25.5, 23.8.

HRMS (ESI): calc. for [($C_{17}H_{19}O_3Br$)Na] (M+Na) 373.0415, measured 373.0399.

(*E*)-1-(2-Styrylphenyl)ethanone (**3s**).



Pale yellow liquid; eluent (2% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922, 1680.

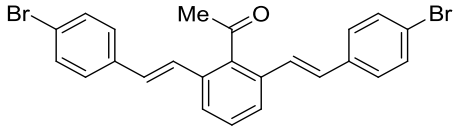
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 8.0 Hz, 1 H), 7.76 – 7.68 (m, 2 H), 7.59 – 7.49 (m, 4 H), 7.40 – 7.36 (m, 2 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 7.00 (d, *J* = 12.0 Hz, 1 H), 2.64 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 217.4, 137.4, 137.2, 131.8, 131.7, 129.2, 128.8, 128.7, 128.4, 127.9, 127.5, 127.3, 126.9, 30.0.

GC-MS (70 ev, C.I.) (M+H): *m/z*: 223 (M+H), 207, 145.

HRMS (ESI): calc. for [($C_{16}H_{14}O$)H] (M+H) 223.1123, measured 223.1117.

1-(2,6-Bis((*E*)-4-bromostyryl)phenyl)ethanone (**3t**).



Pale yellow liquid; eluent (2% ethyl acetate in hexanes).

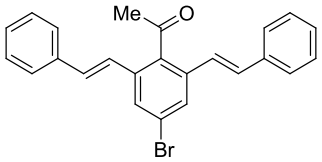
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2935, 1685.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, *J* = 8.0 Hz, 2 H), 7.43 – 7.40 (s, 4 H), 7.33 (t, *J* = 8.0 Hz, 1 H), 7.28 – 7.26 (m, 4 H), 6.94 (d, *J* = 16.0 Hz, 2 H), 6.90 (d, *J* = 16.0 Hz, 2 H), 2.44 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.9, 140.5, 135.8, 133.4, 131.9, 131.2, 129.4, 128.3, 125.6, 125.4, 122.1, 33.7.

HRMS (ESI): calc. for [($C_{24}H_{18}OBr_2$)H] (M+H) 480.9803, measured 480.9801.

1-(4-Bromo-2,6-di((E)-styryl)phenyl)ethanone (**3u**).



Pale yellow liquid; eluent (2% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2937, 1675.

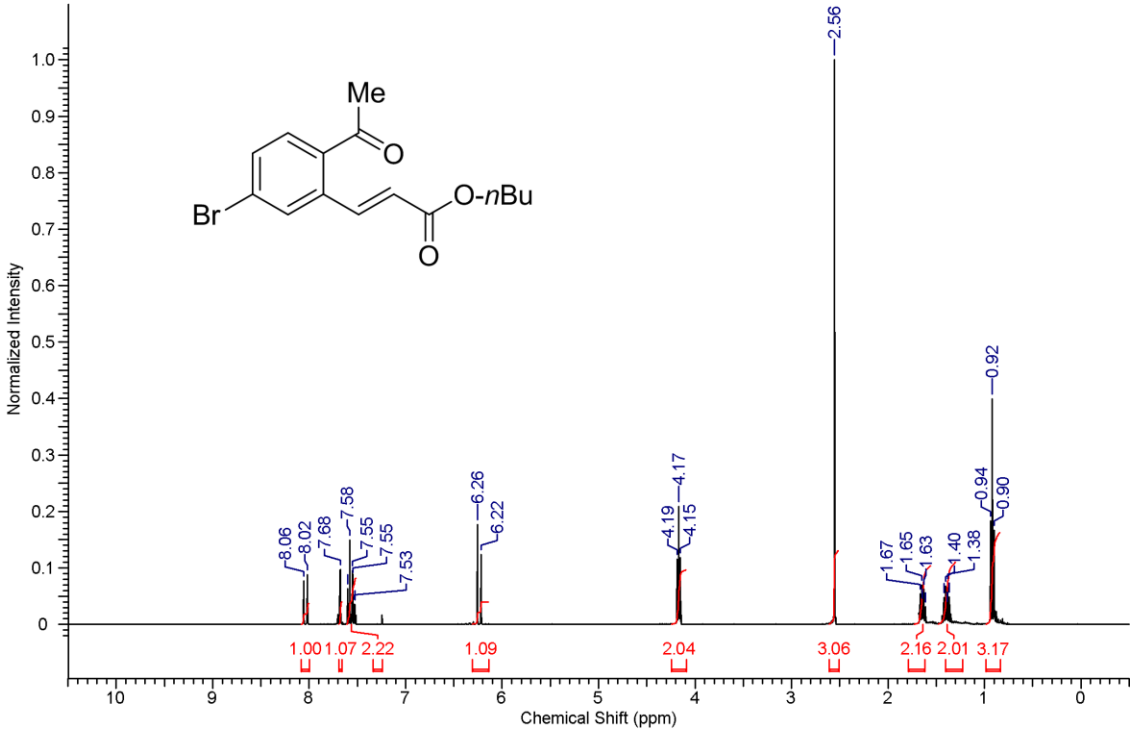
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, *J* = 8.0 Hz, 1 H), 7.63 (s, 2 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.43 – 7.39 (m, 4 H), 7.30 (t, *J* = 8.0 Hz, 3 H), 7.25 – 7.21 (m, 1 H), 6.98 (d, *J* = 16.0 Hz, 2 H), 6.88 (d, *J* = 16.0 Hz, 2 H), 2.42 (s, 3 H).

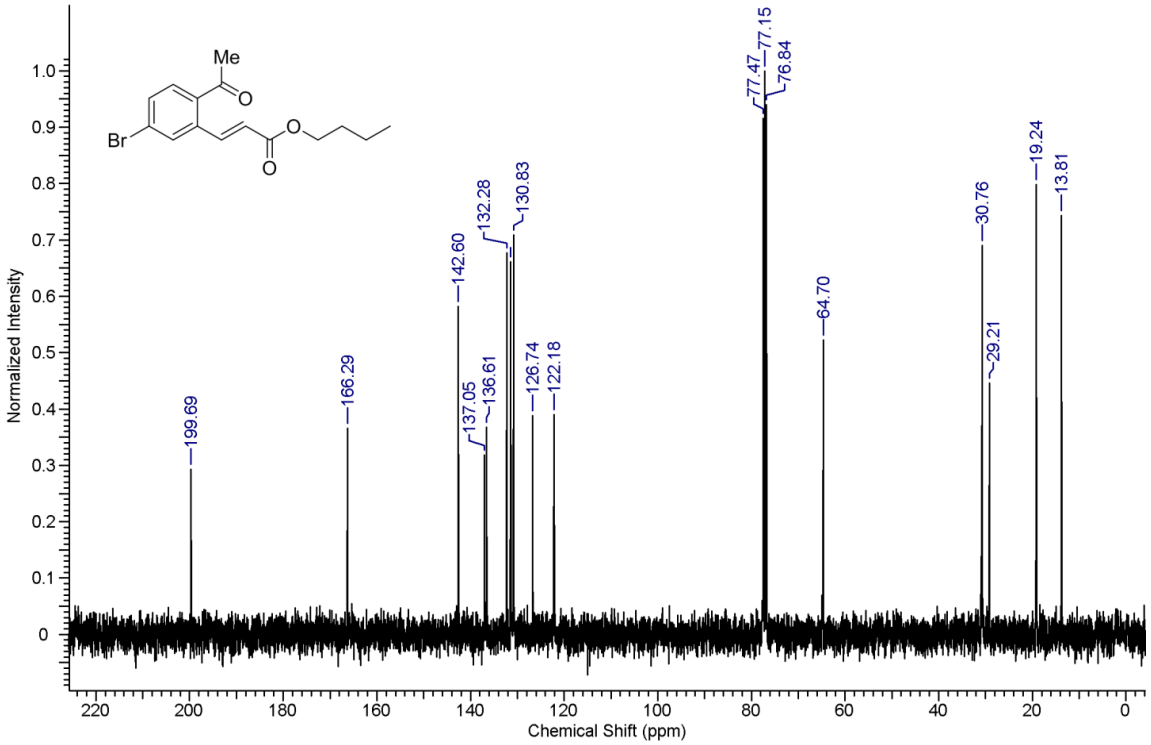
^{13}C NMR ($CDCl_3$, 100 MHz): δ 216.9, 139.1, 136.4, 135.7, 133.6, 132.5, 130.2, 128.9, 128.7, 127.0, 123.5, 33.4.

HRMS (ESI): calc. for [($C_{24}H_{19}OBr$)H] (M+H) 403.0698, measured 403.0703.

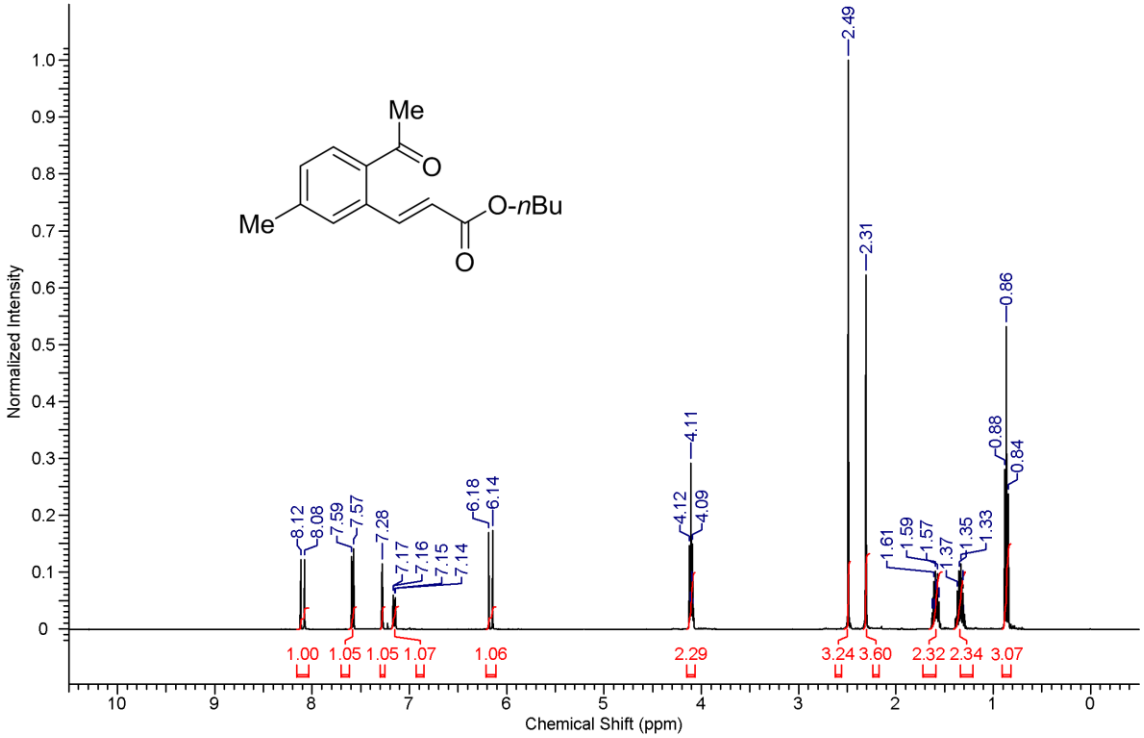
2A.10: Spectral Copies of Selected Compounds

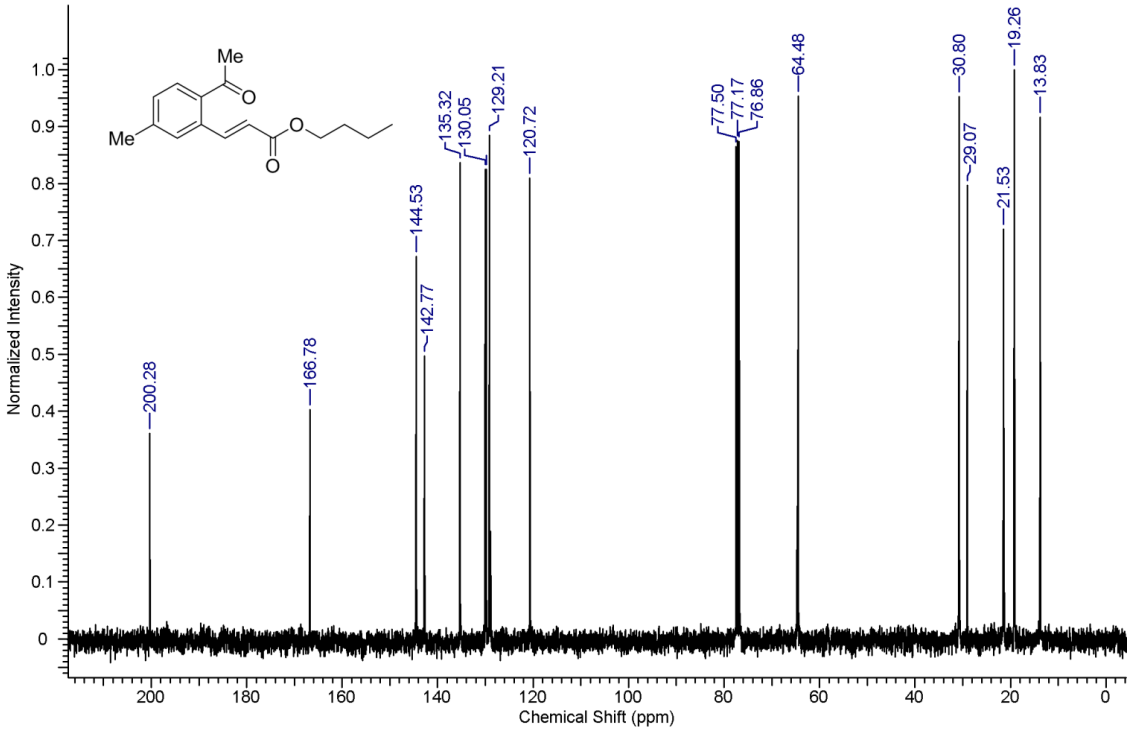
Spectral data of compound **3a**.



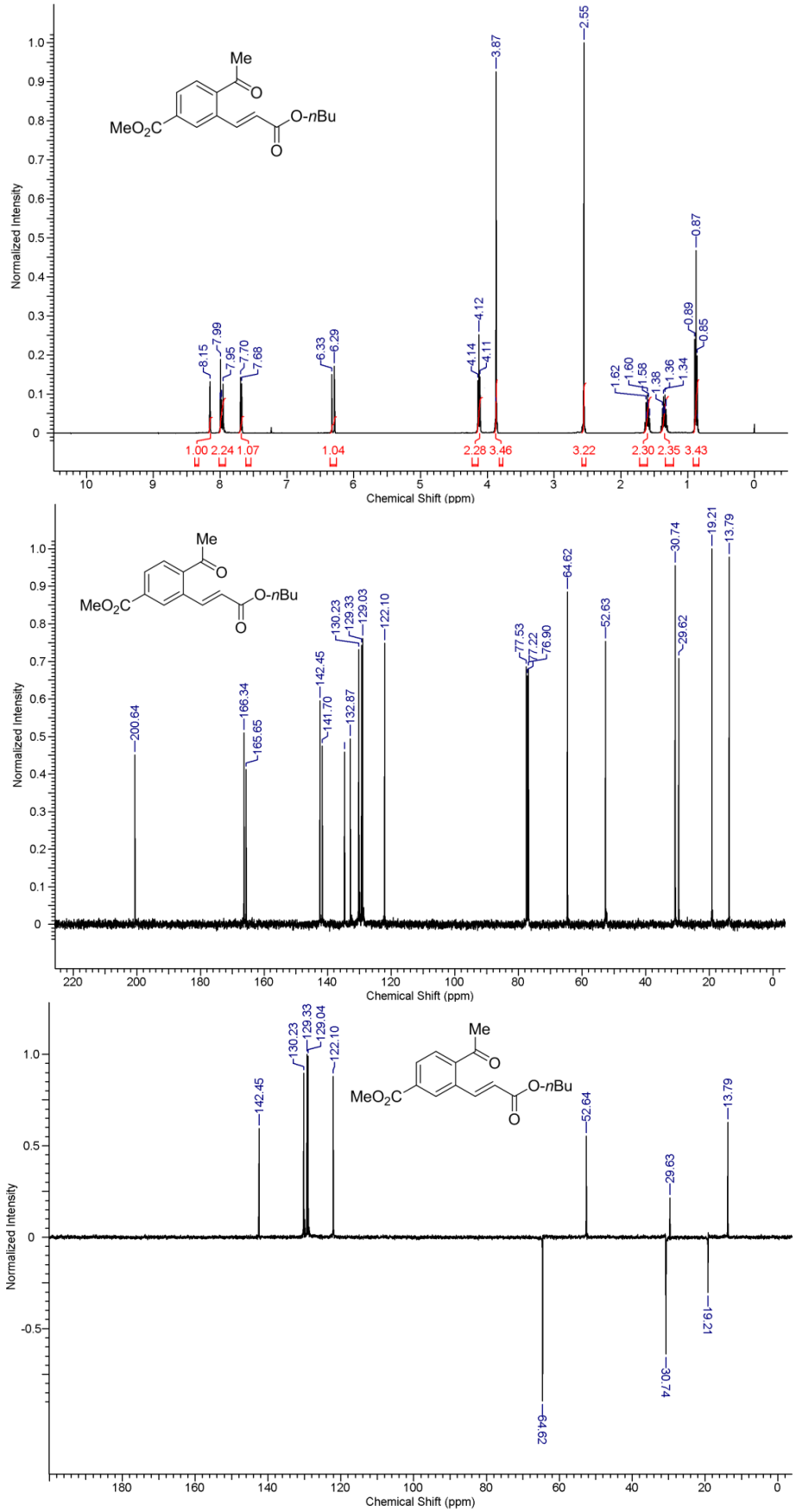


Spectral data of compound **3e**.

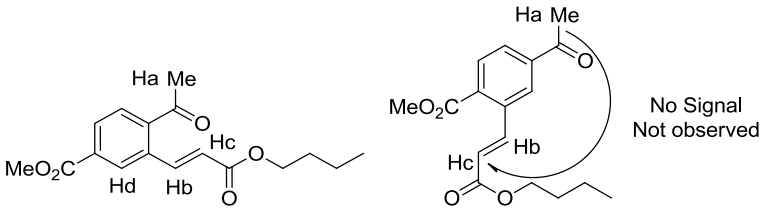




Spectral data of compound **3g**.

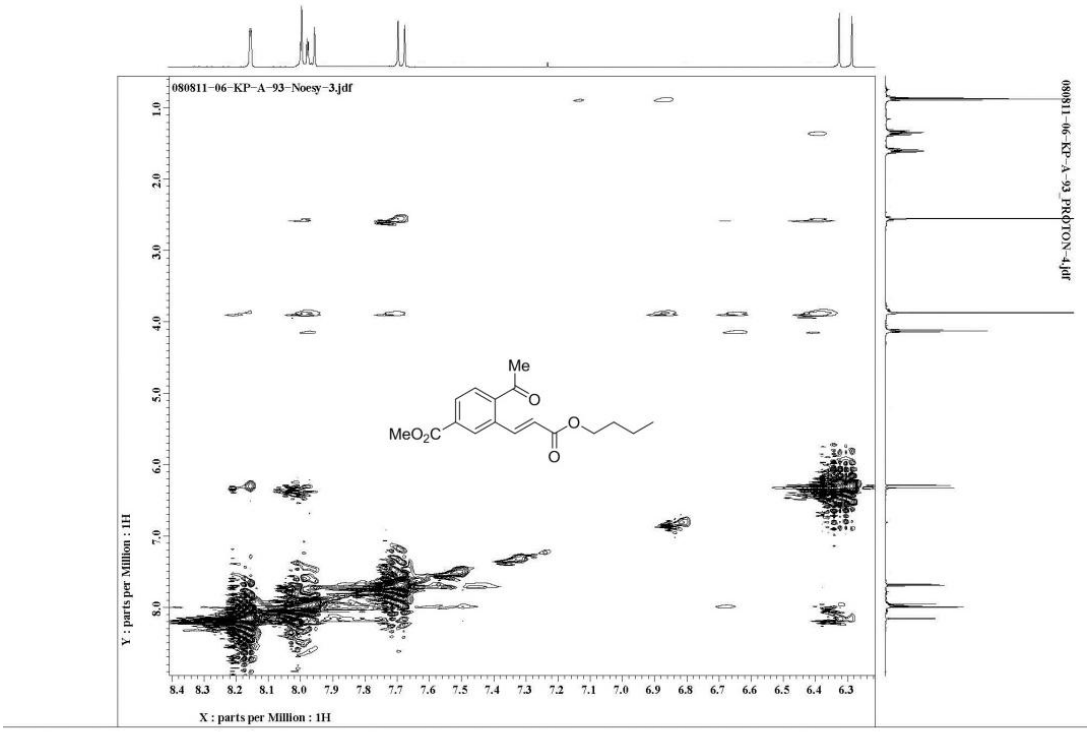


NOESY Spectrumof compound **3g:**

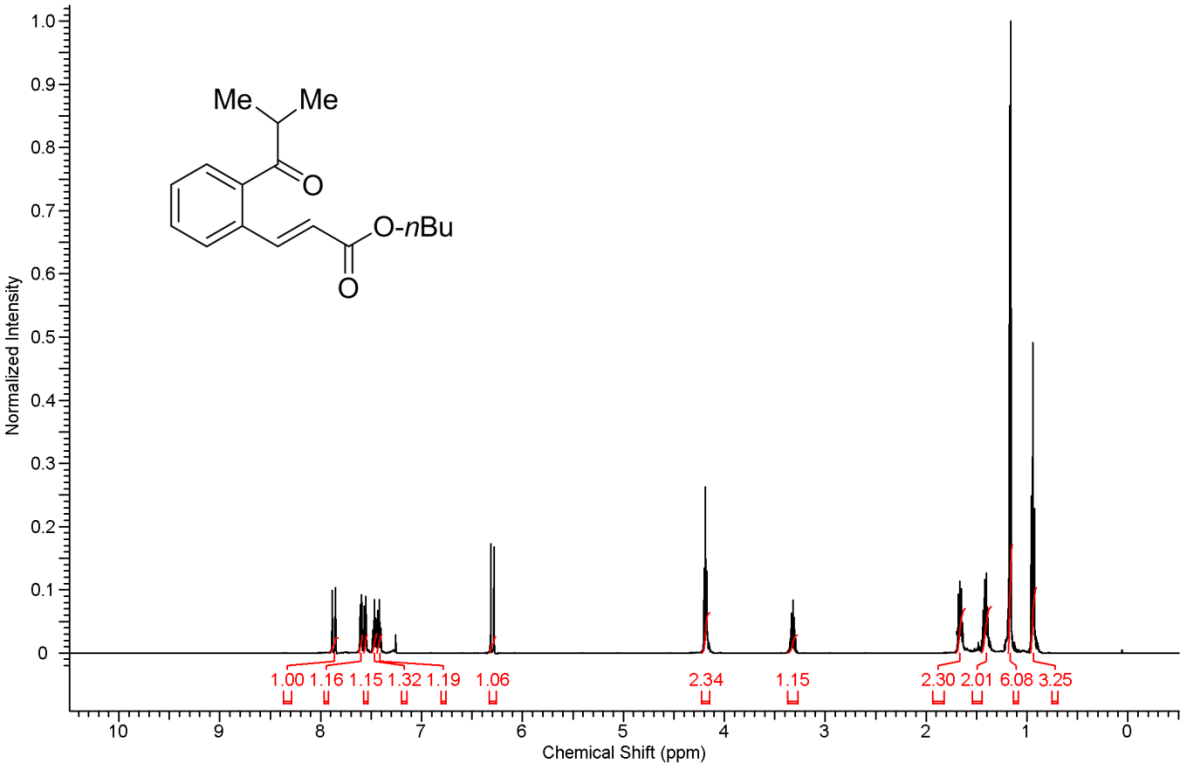


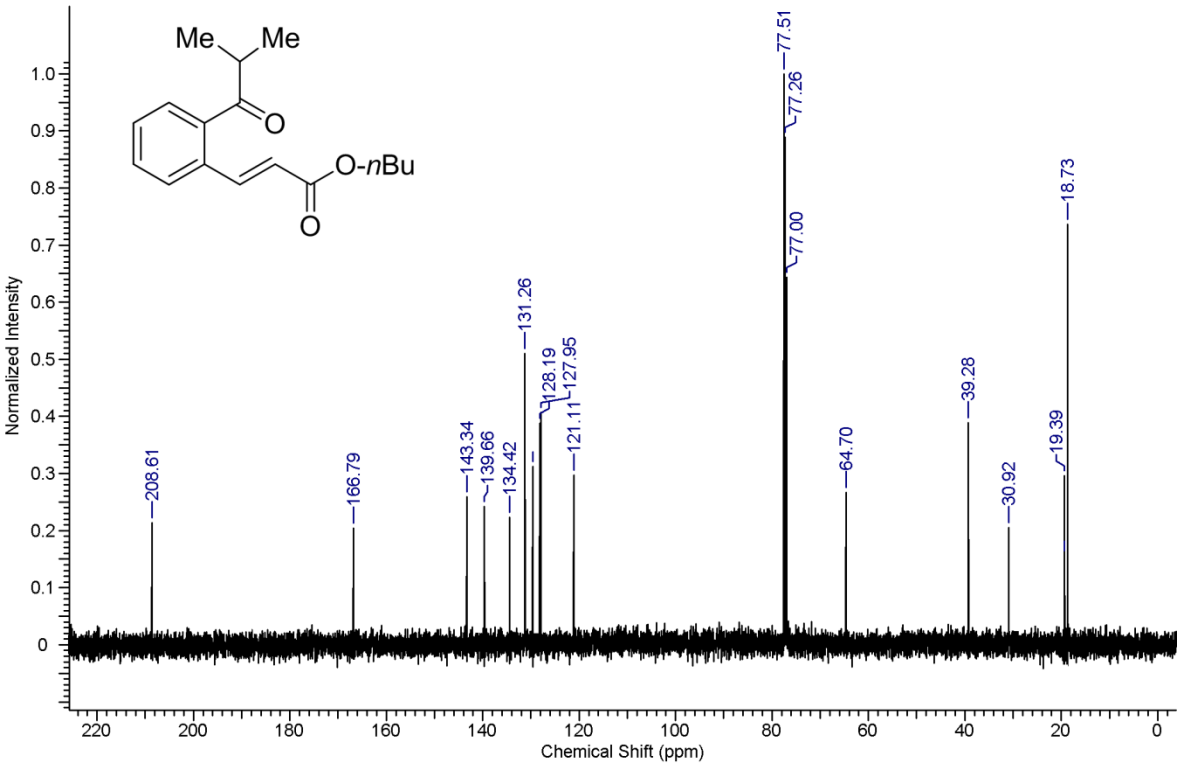
Ha δ= 2.55; Hb δ=8.0-7.95; Hc δ=6.3; Hd δ=8.16

There is a NOE correlation between Ha (δ 2.55, s) and Hc (δ 6.3, d). In meantime, there is also correlation between Hb (δ 8.00 - 7.95, m) and Hd (δ 8.16, s). Thus, these results clearly revealed that the regiochemistry of compound is correct.

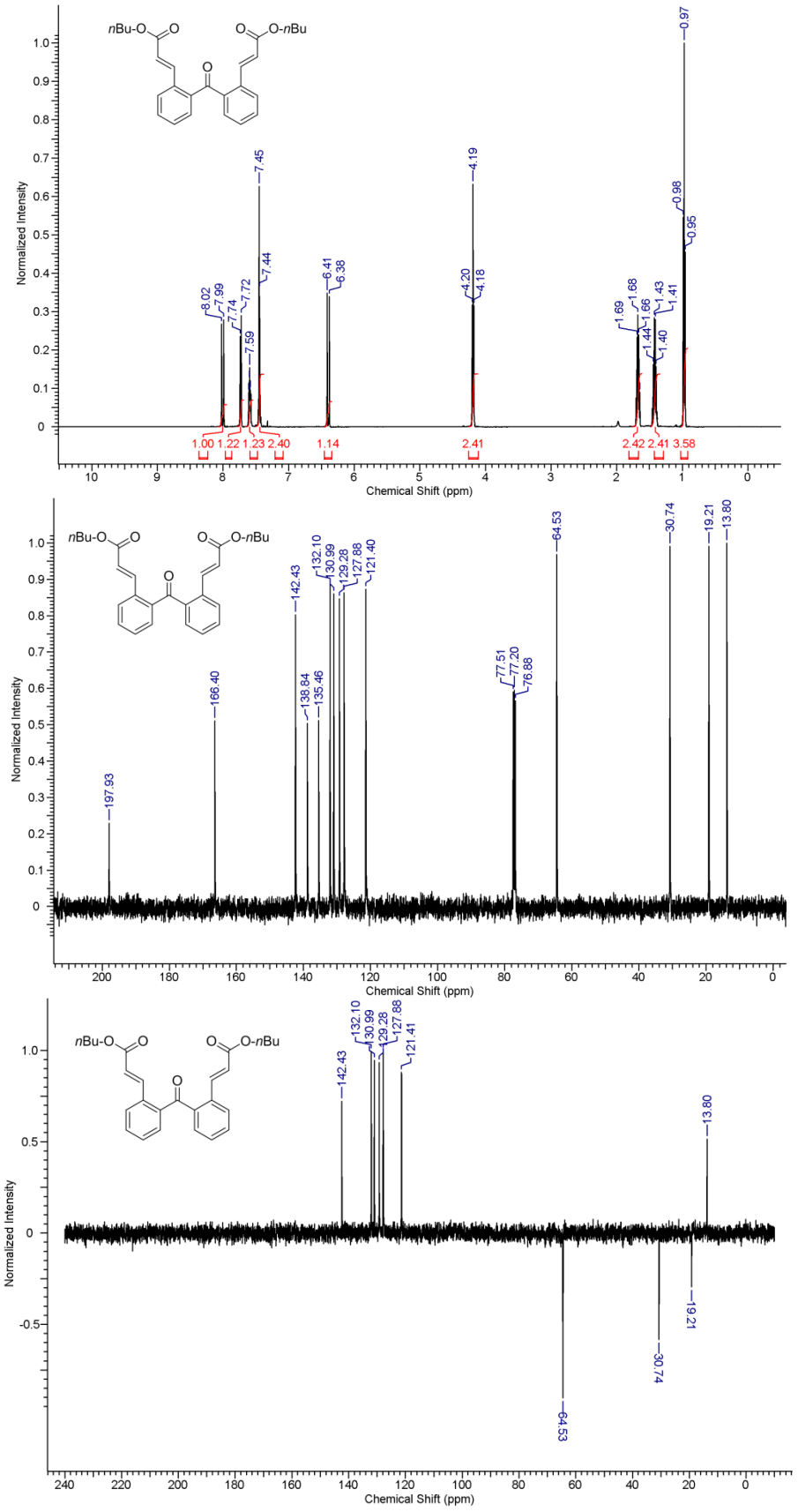


Spectral data of compound **3i**.

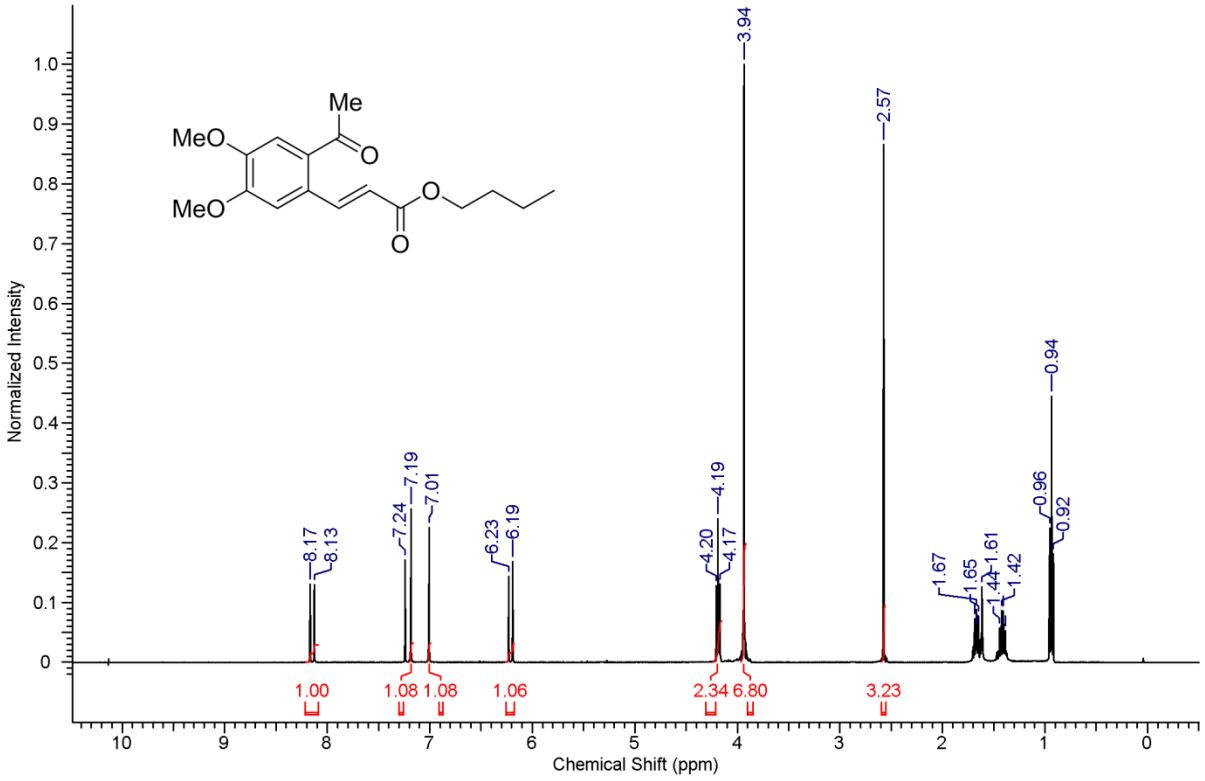


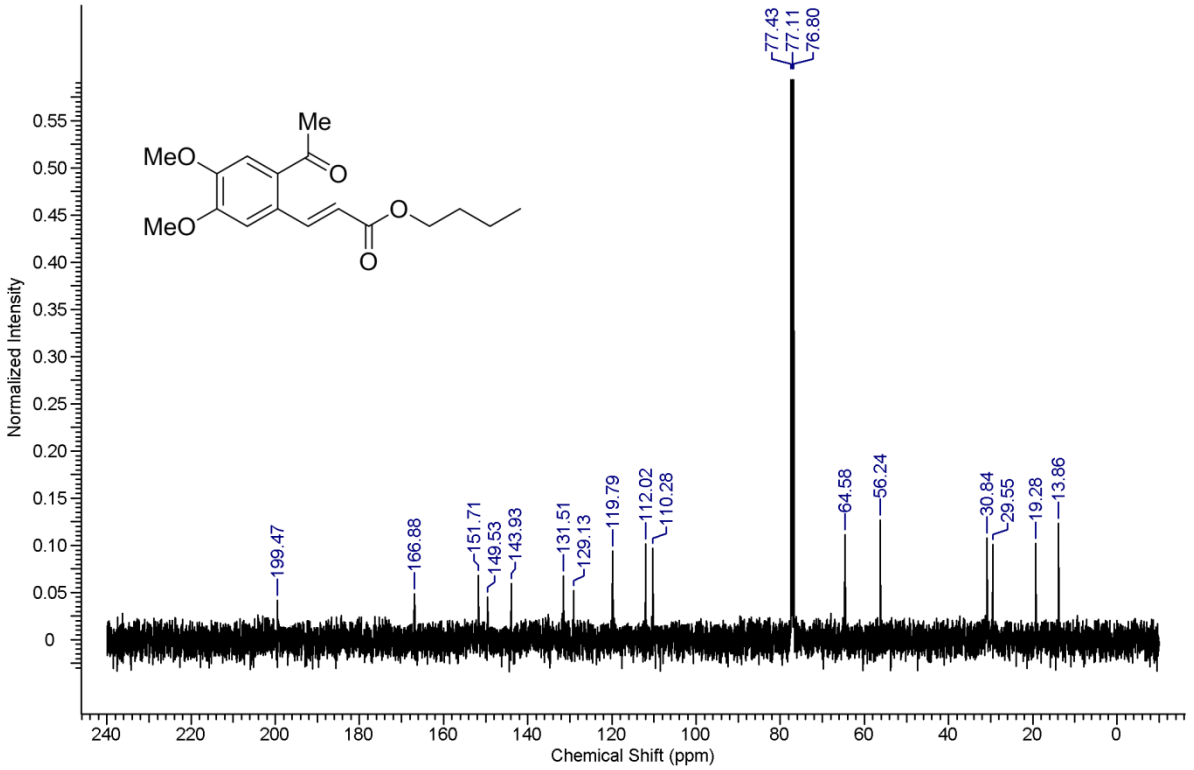


Spectral data of compound **3j'**.

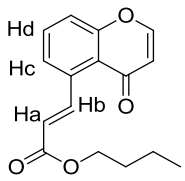


Spectral data of compound **3k**.

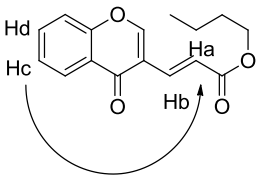




NOESY Spectrumof compound **3n:**



Observed

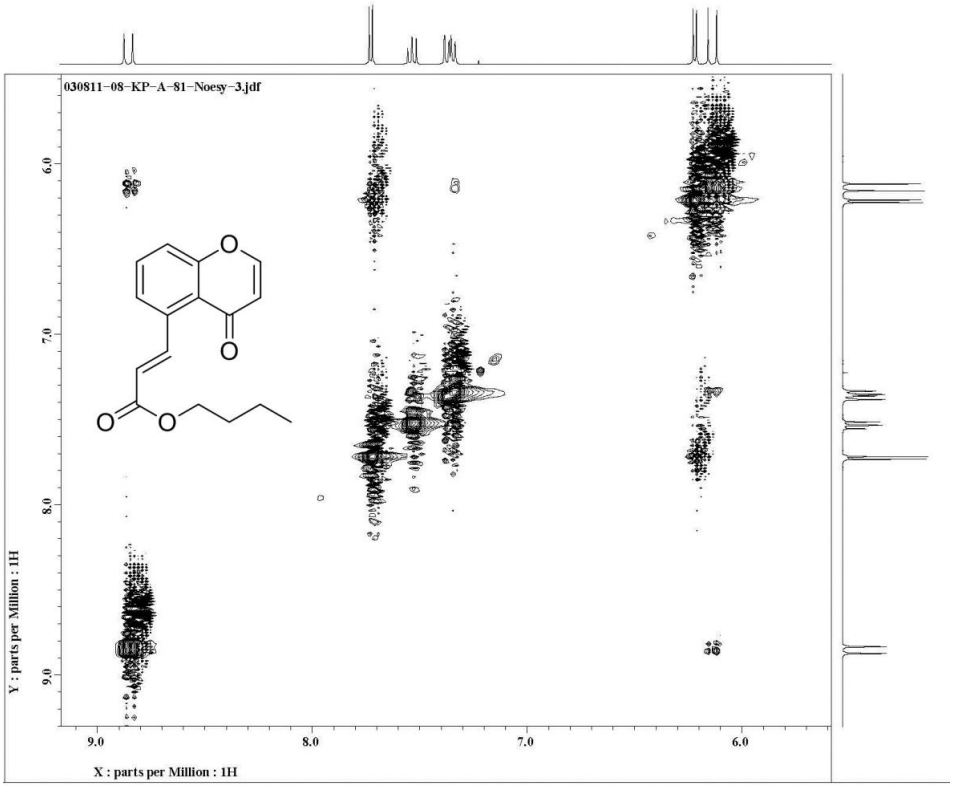


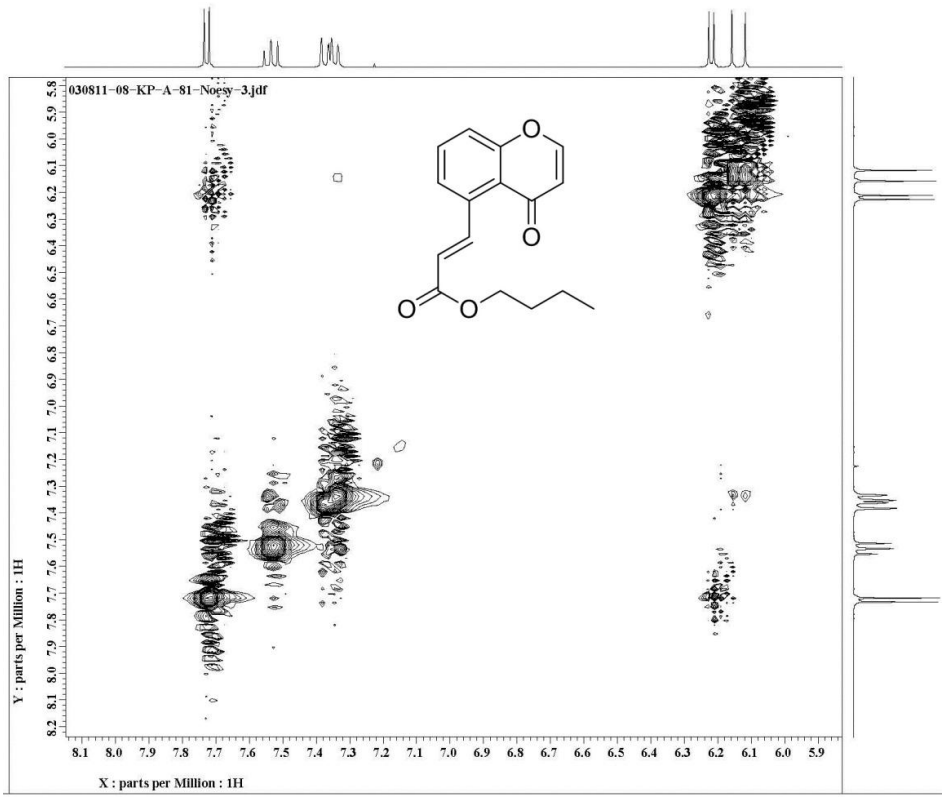
No signal
Not observed

Ha δ= 6.34; Hb δ=8.89; Hc δ=7.77;

Hd δ=7.57;

There is a NOE correlation between Ha (δ 6.34, d) and Hc (δ 7.77, d). In meantime, there is also correlation between Hc (δ 7.77, d) and Hd (δ 7.57, t). Thus, these results clearly revealed that the regiochemistry of compound is correct.



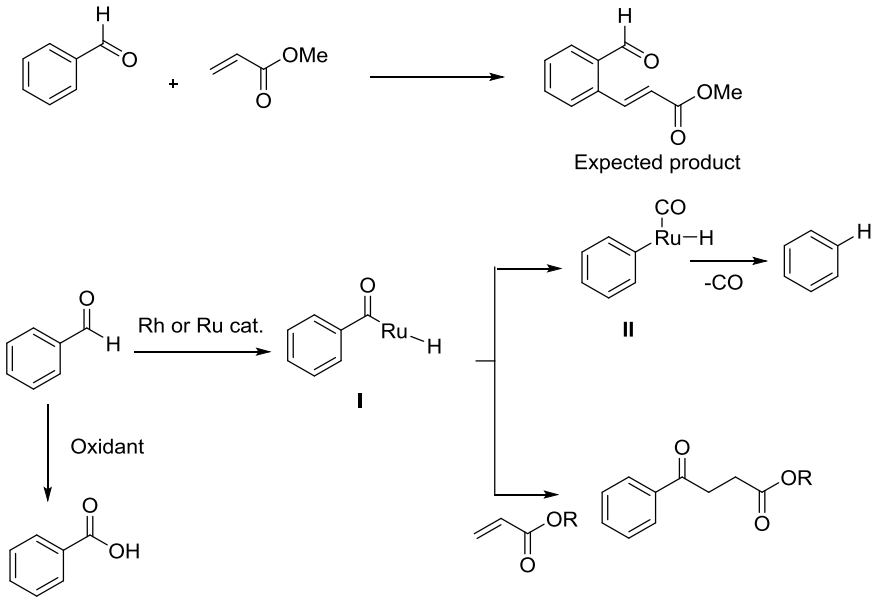

030811-08-KP-A-81-Noesy-3.jdf
Y : parts per Million : 1H
X : parts per Million : 1H
O
O
O
O

2B: Highly Regio- and Stereoselective Ruthenium(II)- Catalyzed Direct *ortho* Alkenylation of Aromatic and Heteroaromatic Aldehydes with Activated Alkenes under Open Atmosphere

2B.1: Results and Discussion

Previously, we have discussed a ruthenium-catalyzed coupling of aromatic and heteroaromatic ketones with alkenes and cyclization of aromatic and heteroaromatic ketones and acids with alkynes in the presence of catalytic amount of silver salt and $Cu(OAc)_2 \cdot H_2O$. In these reactions, $Cu(OAc)_2 \cdot H_2O$ provided the acetate source to the ruthenium species in order to facilitate *ortho* metalation by concerted deprotonation metalation pathway.[21] These reactions were moisture-insensitive and remaining amount of active $Cu(OAc)_2$ source was regenerated by oxygen or atmosphere. These results prompted us to explore the possibility of using a catalytic amount of $Cu(OAc)_2 \cdot H_2O$ as a terminal oxidant in the Heck-type coupling of aromatic aldehydes with alkenes. Herein, we discuss the oxidative coupling of aromatic aldehydes with alkenes in the presence of catalytic amount of $[\{RuCl_2(p\text{-cymene})\}_2]$, $AgSbF_6$ and $Cu(OAc)_2 \cdot H_2O$ giving alkene derivatives in good to moderate yields under open atmosphere in a highly regio- and stereoselective manner. The catalytic reaction was also compatible with heteroaromatic aldehydes. It is important to note that no decarbonylation of aldehydes, hydroacylation of aldehydes with alkenes and oxidation of aldehydes to acids were observed in the reaction. The observed alkene derivatives were further converted into unusual four-membered cyclic ketones or polysubstituted isochromanone derivatives via a photochemical rearrangement.

A number of competitive reactions such as decarbonylation and hydroacylation could be possible in the coupling of substituted aldehydes with alkenes in the presence of metal complexes.[16] This intermediate **I** may undergo decorbonylation to give aryl derivatives. Other possibility with this intermediate **I**, it may react with acrylate to give hydroacylation product. Thus, the control of the competitive reactions is crucial to make this type of reaction beneficial to organic synthesis. Moreover, in most of the metal-catalyzed C-H bond activation reactions, stoichiometric amount of oxidant is used to regenerate the active catalyst. These oxidants most likely oxidize aldehydes into acids subsequently in a facile manner (Scheme 2. 14). These types of competitive reactions seriously restrict the scope of aldehydes in C-H bond functionalization reactions.

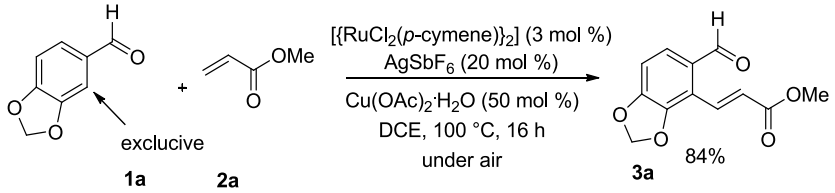


Scheme 2.14: Competitive reactions with aldehyde directing group

2B.2: Optimization Studies

When piperonal (**1a**) was treated with methyl acrylate (**2a**) in the presence of catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (50 mol %) in 1,2-dichloroethane at 100 °C for 16 h under open atmosphere, a substituted alkene derivative **3a** was observed in 47% isolated yield with very high *E*-stereoselectivity. The catalytic reaction was also highly regioselective. In the substrate **1a**, there are two *ortho* aromatic C-H bonds for coupling. Very selectively, the alkenylation reaction takes place at the sterically hindered C-H bond of **1a** moiety predominately. In order to improve the yield, the catalytic reaction was carried out with longer reaction time (24 h), higher reaction temperature (130 °C) and more ruthenium catalytic loading (10 mol %). However, in these conditions, no improvement in the yield of **3a** was observed. Then, the reaction was carried out with an excess amount of methyl acrylate (**2a**) (6.0 equiv). The catalytic reaction proceeded well and gave **3a** in 84 % isolated yield.

Table 2.4: Optimization Studies with Various Solvents, Oxidants and Additives.[a]



entry	solvent	oxidant	additive	yield of **3a** (%)[b]
1	DCE	$Cu(OAc)_2.H_2O$(50 mol %)	AgOTf	NR
2	DCE	$Cu(OAc)_2.H_2O$	$AgBF_4$	NR
3	DCE	$Cu(OAc)_2.H_2O$	Ag_2O	NR
4	DCE	$Cu(OAc)_2.H_2O$	AgO_2CCF_3	NR
5	DCE	$Cu(OAc)_2.H_2O$)(50 mol %)	$AgSbF_6$	47
6	DCE	$Cu(OAc)_2.H_2O$)(50 mol %)	$AgSbF_6$	49[c]
7	**DCE**	**$Cu(OAc)_2.H_2O$)(50 mol %)**	**$AgSbF_6$**	**84[d]**
8	DCE	O_2	$AgSbF_6$	NR
9	DCE	oxone	$AgSbF_6$	NR
10	DCE	DDQ	$AgSbF_6$	NR
11	DCE	$PhI(OAc)_2$	$AgSbF_6$	NR
12	DCE	$K_2S_2O_8$	$AgSbF_6$	NR
13	*t*-BuOH	$Cu(OAc)_2.H_2O$	$AgSbF_6$	NR
14	THF	$Cu(OAc)_2.H_2O$	$AgSbF_6$	NR
15	Toluene	$Cu(OAc)_2.H_2O$	$AgSbF_6$	NR

[a]All reactions were carried out under the following conditions: **1a** (100 mg), **2a** (1.2 equiv), {$RuCl_2$(*p*-cymene)$}_2$] (3 mol %), additive (20 mol %) and oxidants (50 mol %) in solvent (2.5 mL) at 100 °C for 16 h under N_2 atmosphere. [b]GC yield. [c][{$RuCl_2$(*p*-cymene)$}_2$] (10 mol %), at 130 °C for 24 h. [d]**2a** (6 equiv)

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

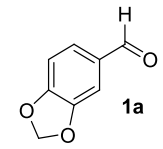
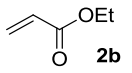
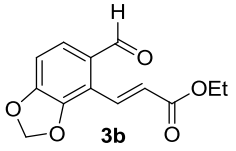
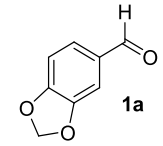
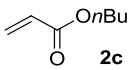
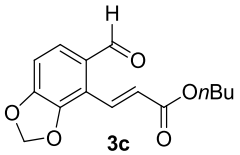
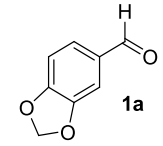
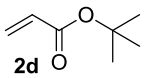
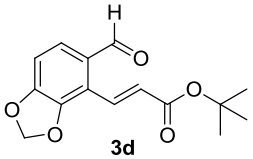
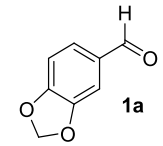
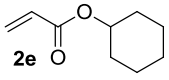
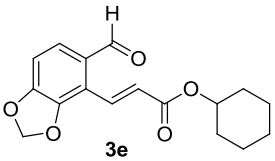
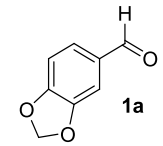
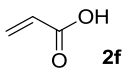
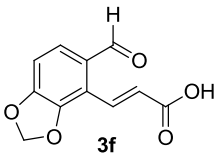
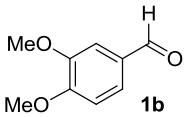
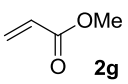
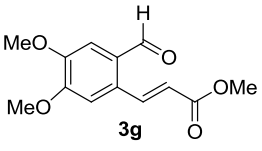
The reaction did not proceed in the absence of either copper source or silver salt. Other solvents such as *t*-BuOH, THF and toluene were totally ineffective for the catalytic reaction. Other silver salts including AgOTf, $AgBF_4$, Ag_2O and AgO_2CCF_3 were totally ineffective for the reaction. Other oxidants such as O_2, oxone, DDQ, $PhI(OAc)_2$ and $K_2S_2O_8$ were totally ineffective in the reaction. Notably, the present ruthenium-catalyzed open atmosphere reaction is inexpensive and environment friendly for synthesizing 2-formyl phenylalkeno-derivatives **3** in a highly regio- and stereoselective manner.

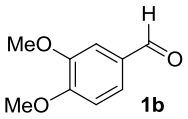
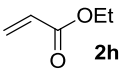
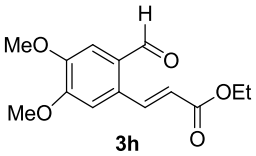
2B.3: Scope of Alkenes

The scope of the present alkenylation reaction was further extended to various substituted activated alkenes. Piperonal (**1a**) underwent alkenylation reaction with ethyl acrylate (**2b**) under similar reaction conditions to afford **3b** in 78% yield. Likewise, *n*-butyl acrylate (**2c**), *tert*-butyl acrylate (**2d**) and cyclohexyl acrylate (**2e**) afforded alkenylation products **3c-e** in 75%, 68% and 79% yields, respectively. An acrylic acid was also a good coupling

partner for this reaction. Thus, acrylic acid (**2f**) underwent coupling with piperonal (**1a**) to give an alkenylated product **3f** in 62% yield. These reactions were also highly regio- and stereoselective as like **3a**. Whereas, 3,4-dimethoxy benzaldehyde (**1b**) reacted with methyl acrylate (**2a**) to give an different type of regioselective product **3g** in 72% yield with very high *E*-stereoselectivity. In the substrate **1b** also, there are two *ortho* aromatic C-H bonds for coupling. Very selectively, the alkenylation reaction takes place predominately at the sterically less hindered C-H bond of **1b** moiety. Similarly, **1b** reacted with ethyl acrylate (**2b**) to provide an alkenylated product **3h** in 67% yield in a highly regio- and stereoselective manner.

Table 2.5 : Results of the Reaction of Piperonal (**1a**), 3, 4-Dimethoxy Benzaldehyde with Substituted Alkenes **2b-h**[a]

entry	**1**	**2**	product **3**	yield (%)[b]
1	 **1a**	 **2b**	 **3b**	78
2	 **1a**	 **2c**	 **3c**	75
3	 **1a**	 **2d**	 **3d**	68[c]
4	 **1a**	 **2e**	 **3e**	79
5	 **1a**	 **2f**	 **3f**	62
6	 **1b**	 **2g**	 **3g**	72[c]

7	 **1b**	 **2h**	 **3h**	67[c]

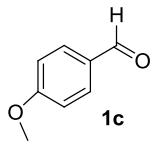
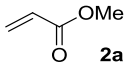
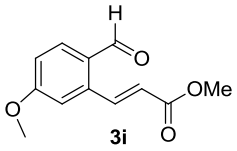
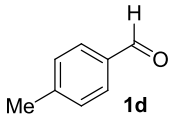
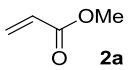
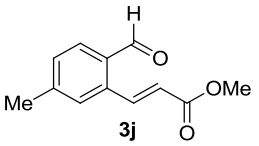
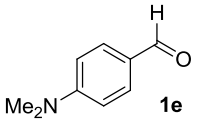
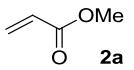
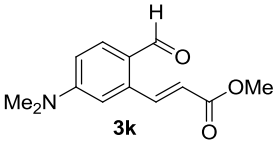
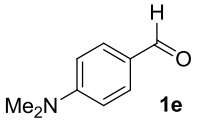
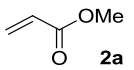
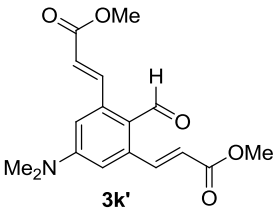
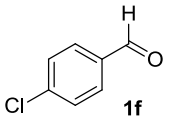
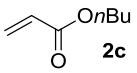
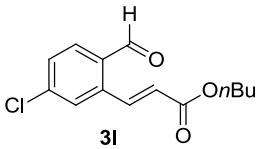
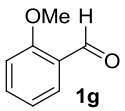
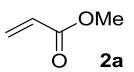
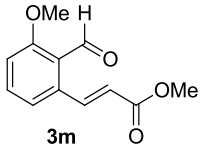
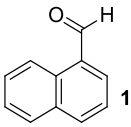
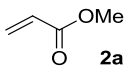
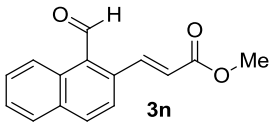
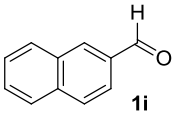
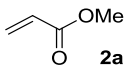
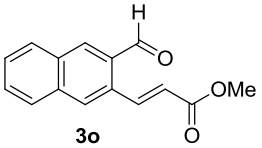
[a]All reactions were carried out using aldehydes **1a** and **1b** (1.0 mmol), alkenes **2** (**2a-b** in 6.0 mmol and **2c-f** in 5.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (50 mol %) in DCE at 100 °C for 16 h. Reported yields are for the isolated products. [b]The reaction was carried out in *tert*-BuOH. [c]$Cu(OAc)_2.H_2O$ (2.0 mmol) was used for the reaction.

2B.4: Scope of Aromatic Aldehydes

alkenylation reaction was successfully extended to various aromatic aldehydes **1** with methyl acrylate (**2a**) (**Table 2.6**). Thus, treatment of 4-methoxy benzaldehyde (**1c**), 4-methyl benzaldehyde (**1d**) and 4-dimethylamino benzaldehyde (**1e**) with methyl acrylate (**2a**) gave the corresponding alkenylated compounds **3i-k** in 60%, 46% and 39% yields, respectively. In the reaction of 4-dimethylamino benzaldehyde **(1e)** with **2a**, in addition to mono alkenylation product **3k** in 39% yield, bis alkenylation product **3k'** was also observed in 49% yield. 4-Chloro benzaldehyde (**1f**) also reacted with *n*-butyl acrylate (**2c**) to provide a 2-formyl phenylalkeno-derivative **3l** in low 25% yield. 2-Methoxy benzaldeyde (**1g**) also participated in the reaction giving an alkenylated product **3m** in 40% yield. The reaction of 1-napthaldehyde (**1h**) with **2a** gave the corresponding coupling product, **3n**, in 41% yield. Under similar reaction conditions, 2-napthaldehyde (**1i**) reacted with **2a** to give an alkenylated product **3o** regioselectively in 43% yield in which C3-H of 2-napthaldehyde involved in the coupling reaction with **2a** selectively. The catalytic reaction was also tested with 4-cyano benzaldehyde and 4-methylester benzaldehyde. However, in these reactions, no expected coupling products were observed. It appears that the yield of this catalytic reaction is highly sensitive to the type of substituent used on the aromatic ring of aldehydes. Electron-rich substituents such as dioxole, OMe, Me and NMe_2 on the aromatic ring gave the highest product yield, while the electron-withdrawing substituents such as Cl, CN and CO_2Me afforded the lowest yield or no product.

Table 2.6: Results of the Reaction of Aromatic Aldehydes **1** with **2a or 2c**[a]

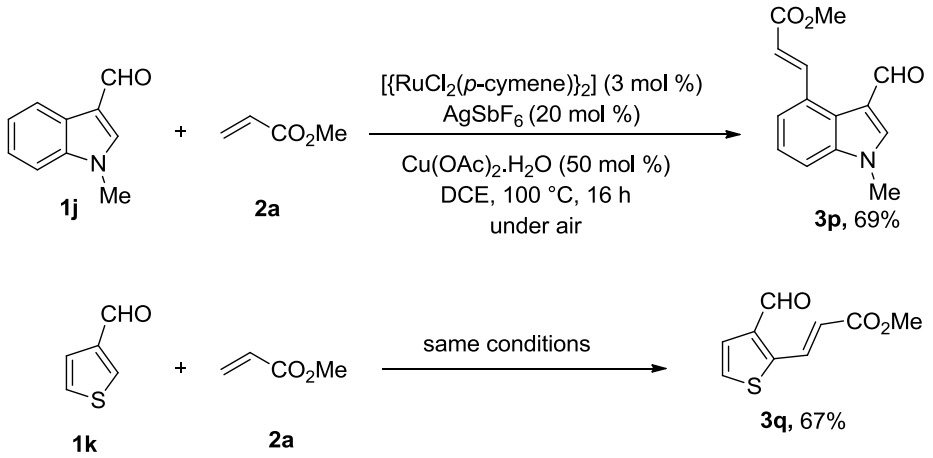
entry	**1**	**2**	product **3**	yield (%)[b]

1	 **1c**	 **2a**	 **3i**	60
2	 **1d**	 **2a**	 **3j**	46
3	 **1e**	 **2a**	 **3k**	39
4	 **1e**	 **2a**	 **3k'**	49
5	 **1f**	 **2c**	 **3l**	25
6	 **1g**	 **2a**	 **3m**	40
7	 **1h**	 **2a**	 **3n**	41
8	 **1i**	 **2a**	 **3o**	43[c]

[a]All were carried out using aldehydes **1** (1.0 mmol), methyl acrylate (**2a**) (6.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (50 mol %) in 1,2-dichloroethane at 100 °C for 16 h under open atmosphere.

2B.5: Heteroaromatic Aldehydes Scope

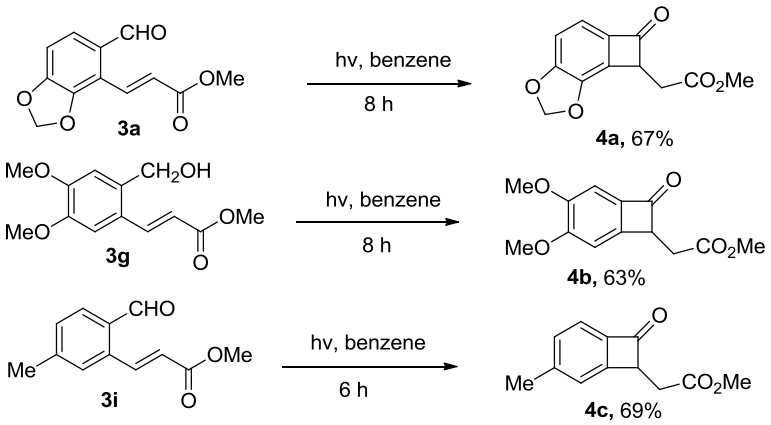
Heterocyclic aldehydes were also compatible for the present C-H bond activation reaction (Scheme 2.15). Thus, 1-methylindole-3-carboxaldehyde (**1j**) and 2-formylthiophene (**1k**) reacted with **2a** to give the corresponding coupling products **3p** and **3q** in 69 and 67% yields, respectively. The reaction tolerates a variety of functional groups such as Br, Cl, OMe, S, dioxole, and NMe_2 on the aromatic and heteroaromatic ring of aldehydes.

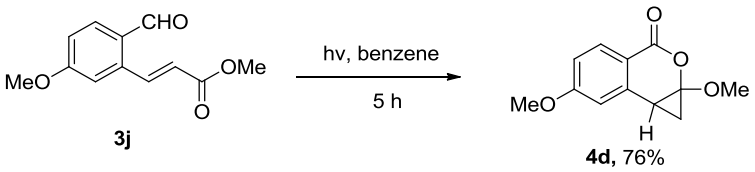


Scheme 2.15: Scope of heteroaromatic aldehydes

2B.6: Photochemical Rearrangement

A synthetic application of product **3** in organic synthesis is shown in Scheme 2.16. The 2-formyl phenylalkeno-derivatives **3** were further converted into unusual four-membered cyclic ketones and a polysubstituted isochromanone derivative via a photochemical rearrangement.[17] Thus, when irradiation of **3a** in a benzene solution with a 450W mediumpressure mercury vapor lamp for 8.0 h was performed, a four-membered cyclic ketone **4a** was observed in 67%yield. Similarly, the irradiation of **3g** under similar reaction conditions for 8 h gave a fourmembered cyclic ketone **4b** in 63%yield. Surprisingly, with the irradiation of **3j** in a benzene solution with a 450 W medium pressure mercury vapor lamp for 5.0 h, a polysubstituted isochromanone derivative **4d** was observed in 76% yield.[17] But, **3i** under similar reaction conditions gave a four-membered cyclic ketone **4c** in 69%yield. It is important to point out that isochromanone derivatives are widely occurring natural products that show various biological activities.[31]

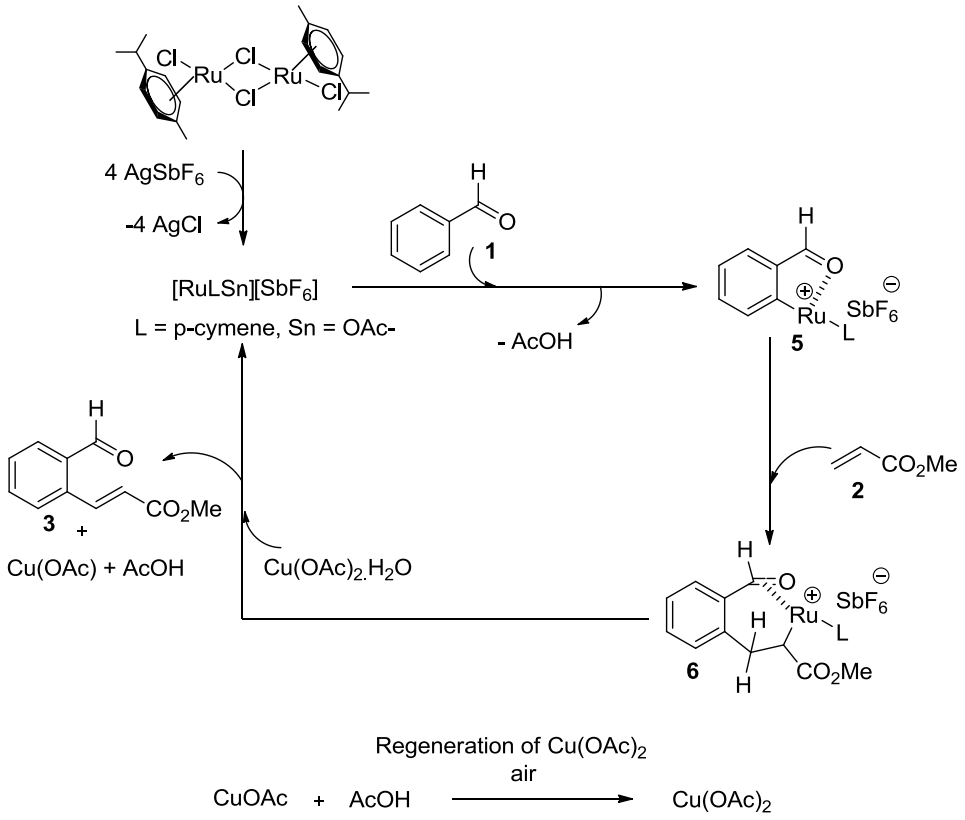




Scheme 2.16: Photochemical rearrangement of 2-formyl phenylalkeno-derivatives

2B.7: Mechanism

A plausible mechanistic rationale of coupling of aromatic and heteroaromatic aldehydes with alkenes is proposed in scheme 2.17. The catalytic reaction is likely initiated by the removal of chloride ligand by Ag^{+} salt from [{$RuCl_2$(*p*-cymene)}$_2$] complex. Coordination of the carbonyl oxygen of to the ruthenium cationic species followed by *ortho* metalation provides a five-membered ruthenacycle **5**.[2l] Coordinative insertion of alkene **2** into the Ru–carbon bond of ruthenacycle **5** affords an intermediate **6**. β-Hydride elimination from intermediate **6** in the presence of $Cu(OAc)_2 \cdot H_2O$ gives the final product **3** and regenerates the active ruthenium species for the next catalytic cycle. In the reaction, remaining amount of active $Cu(OAc)_2$ source was regenerated under oxygen or atmosphere from the reduced copper source.



Scheme 2.17: Proposed mechanism

2B.8: Conclusion

1. We have demonstrated a rutheniumcatalyzed *ortho*-alkenylation of aromatic and Heteroaromatic aldehydes with activated alkenes to afford substituted alkene derivatives in good to moderate yields.
2. The amount of $Cu(OAc)_2$ was reduced to catalytic amount by using air as a external oxidant.
3. The 2-formyl phenylalkeno-derivatives were further converted into unusual four-membered cyclic ketones and a polycyclic isochromanone derivative via a photochemical rearrangement.

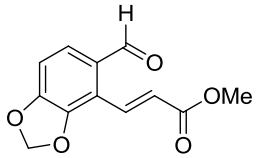
2B.9: Experimental Section

General Procedure for the Oxidative Alkenylation of Aromatic and Heteroaromatic Aldehydes with Activated Alkenes Catalyzed by Ruthenium Complex:

$[\{RuCl_2(p\text{-cymene})\}_2]$ (0.002 mmol, 2 mol %), $Cu(OAc)_2.H_2O$ (0.050mmol, 50 mol %), and aldehydes (if it is solid) were taken in a 15-mL pressure tube equipped with a magnetic stirrer and septum purge with nitrogen 3 times. To the flask or tube were then $AgSbF_6$(0.02 mmol, 20 mol %) (Note: $AgSbF_6$is moisture sensitive. Thus, $AgSbF_6$ was taken inside the nitrogen glove box) added. To the flask or tube were then added aldehyde (**1**) (1.00 mmol)(if it is liquid), alkene **2** (**2a** and **2b**, 6.0 mmol and **2c-f**, 5.0 mmol) and 1,2-dichloroethane or *t*-BuOH (4.0 mL) via syringes and allowed the reaction mixture to stir at room temperature for 5 min. During this time, tube was covered with septum. Then, septum was taken out and the reaction mixture was stirred under an open air for an additional 5 min (Note: During this time, nitrogen gas was in the tube or flask could go away and air goes inside the tube or flask. In the reaction, only 30 mol % of $Cu(OAc)_2{\cdot}H_2O$was used as an internal oxidant. In fact, 2.20 equiv. of $Cu(OAc)_2{\cdot}H_2O$ was needed in the reaction. It is strongly believed that the remaining amount of $Cu(OAc)_2{\cdot}H_2O$ source is regenerated under oxygen or atmosphere from the reduced copper source CuOAc. Thus, we have conducted the reaction under an open air). Then, the pressure tube was covered with a screw cap and the reaction mixture was allowed to stir at 100 °C for 16 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 product.

2B.10: Spectral Data of Compounds

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



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

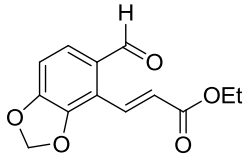
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3083, 3007, 2952, 1706, 1681 and 1451.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.95 (s, 1 H), 8.50 (d, *J* = 16.0 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.73 (d, *J* = 16.0 Hz, 1 H), 6.13 (s, 2 H), 3.77 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.2, 167.5, 152.5, 147.8, 135.5, 132.0, 128.9, 125.1, 117.4, 108.7, 102.8, 51.9.

HRMS (ESI): calc. for [($C_{12}H_{10}O_5$)Na] (M+Na) 257.0425, measured 257.0426.

(*E*)-Ethyl 3-(5-formylbenzo[*d*][1,3]dioxol-4-yl)acrylate (**3b**).



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

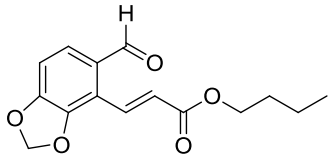
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3070, 2980, 1739, 1683 and 1475.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.99 (s, 1 H), 8.50 (d, *J* = 15.0 Hz, 1 H), 7.39 (d, *J* = 10.0 Hz, 1 H), 6.91 (d, *J* = 10.0 Hz, 1 H), 6.76 (d, *J* = 15.0 Hz, 1 H), 6.16 (s, 2 H), 4.26 (q, *J* = 10.0 Hz, 2 H), 1.32 (t, *J* = 10.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.1, 167.0, 152.4, 147.8, 135.2, 131.8, 128.9, 125.6, 117.5, 108.7, 102.7, 60.7, 14.4.

HRMS (ESI): calc. for [($C_{13}H_{12}O_5$)Na] (M+Na) 271.0582, measured 271.0582.

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



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

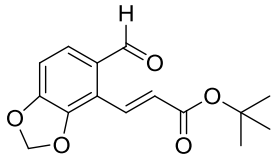
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3089, 2958, 1707, 1683, 1584, 1229 and 1175.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.99 (s, 1 H), 8.52 (d, *J* = 16.0 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 6.76 (d, *J* = 16.0 Hz, 1 H), 6.15 (s, 2 H), 4.19 (t, *J* = 8.0 Hz, 2 H), 1.70 – 1.65 (m, 2 H), 1.45 – 1.39 (m, 2 H), 0.93 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.9, 167.1, 152.5, 147.8, 135.2, 131.8, 128.9, 125.6, 117.6, 108.7, 102.7, 64.7, 30.8, 19.3, 13.8.

HRMS (ESI): calc. for [($C_{15}H_{16}O_5$)Na] (M+Na) 299.0895, measured 299.0907.

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



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

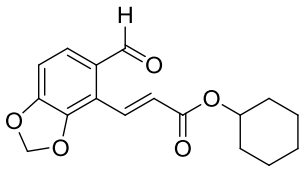
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3060, 2990, 1729, 1689 and 1472.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.00 (s, 1 H), 8.42 (d, *J* = 16.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.67 (d, *J* = 16.0 Hz, 1 H), 6.14 (s, 2 H), 1.50 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.9, 166.3, 152.4, 147.6, 134.1, 131.4, 128.9, 127.5, 117.9, 108.6, 102.7, 80.8, 28.3.

HRMS (ESI): calc. for [($C_{15}H_{16}O_5$)Na] (M+Na) 299.0895, measured 299.0901.

(*E*)-Cyclohexyl 3-(5-formylbenzo[*d*][1,3]dioxol-4-yl)acrylate (**3e**).



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

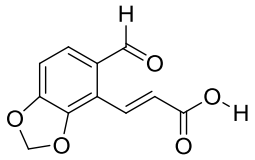
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3086, 2936, 1702, 1684, 1229, 1179 and 801.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.00 (s, 1 H), 8.51 (d, *J* = 16.0 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 6.74 (d, *J* = 16.0 Hz, 1 H), 6.15 (s, 2 H), 4.89 – 4.85 (m, 1 H), 1.89 – 1.86 (m, 2 H), 1.75 – 1.73 (m, 2 H), 1.53 – 1.47 (m, 3 H), 1.45 – 1.36 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.9, 166.5, 152.4, 147.7, 134.9, 131.6, 128.9, 126.2, 117.7, 108.7, 102.7, 72.9, 31.7, 25.5, 23.8.

HRMS (ESI): calc. for [($C_{17}H_{18}O_5$)Na] (M+Na) 325.1051, measured 325.1066.

(*E*)-3-(5-formylbenzo[*d*][1,3]dioxol-4-yl)acrylic acid (**3f**).



Dark black semisolid; eluent (65% ethyl acetate in hexanes).

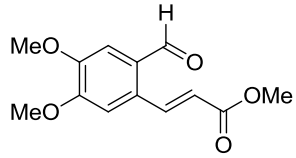
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3221, 3010, 2939, 1709, 1694, 1405 and 1229.

^{1}H NMR (*d*-DMSO, 400 MHz): δ 12.50 (bs, 1 H), 9.89 (s, 1 H), 8.46 (d, *J* = 16.0 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 6.62 (d, *J* = 16.0 Hz, 1 H), 6.27 (s, 2 H).

^{13}C NMR (*d*-DMSO, 100 MHz): δ 193.1, 170.9, 152.8, 148.2, 135.9, 133.9, 128.8, 125.6, 116.3, 109.3, 103.7.

HRMS (ESI): calc. for [($C_{11}H_8O_5$)Na] (M+Na) 243.0269, measured 243.0265.

(*E*)-Methyl 3-(2-formyl-4,5-dimethoxyphenyl)acrylate (**3g**).



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

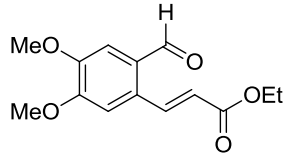
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3080, 3006, 2965, 1716, 1678 and 1264.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.30 (s, 1 H), 8.45 (d, *J* = 16.0 Hz, 1 H), 7.37 (s, 1 H), 7.03 (s, 1 H), 6.33 (d, *J* = 16.0 Hz, 1 H), 3.97 (s, 3 H), 3.94 (s, 3 H), 3.81 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.3, 166.8, 153.7, 150.7, 139.8, 131.6, 127.8, 121.5, 111.3, 109.1, 56.3, 56.2, 52.0.

HRMS (ESI): calc. for [($C_{13}H_{14}O_5$)Na] (M+Na) 273.0739, measured 273.0738.

(*E*)-Ethyl 3-(2-formyl-4,5-dimethoxyphenyl)acrylate (**3h**).



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

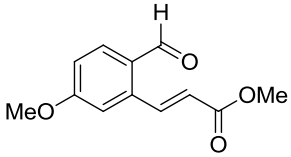
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3081, 2953, 2850, 1720, 1683, 1636, 1286 and 1245.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.26 (s, 1 H), 8.39 (d, *J* = 16.0 Hz, 1 H), 7.33 (s, 1 H), 6.99 (s, 1 H), 6.29 (d, *J* = 12.0 Hz, 1 H), 4.23 (q, *J* = 8.0 Hz, 2 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 1.28 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.6, 166.4, 153.7, 150.7, 139.4, 131.7, 127.8, 121.9, 111.1, 109.1, 60.9, 56.3, 56.2, 14.4.

HRMS (ESI): calc. for [($C_{14}H_{16}O_5$)Na] (M+Na) 287.0895, measured 287.0899.

(*E*)-Methyl 3-(2-formyl-5-methoxyphenyl)acrylate (**3i**).



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

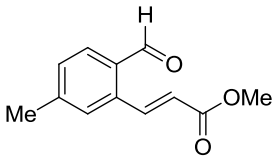
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3078, 2980, 2949, 1715, 1687, 1336 and 1280.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.03 (s, 1 H), 8.42 (d, *J* = 16.0 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 6.98 – 6.93 (m, 2 H), 6.27 (d, *J* = 16.0 Hz, 1 H), 3.82 (s, 3 H), 3.73 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.6, 166.7, 163.8, 141.5, 138.8, 135.3, 127.5, 122.7, 115.1, 113.2, 55.8, 51.9.

HRMS (ESI): calc. for [($C_{12}H_{12}O_4$)Na] (M+Na) 243.0633, measured 243.0634.

(*E*)-Methyl 3-(2-formyl-5-methylphenyl)acrylate (**3j**).



Light yellow semisolid; eluent (6% ethyl acetate in hexanes).

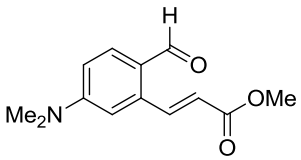
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3088, 2981, 1707, 1684, 1584 and 1230.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.14 (s, 1 H), 8.45 (d, *J* = 16.0 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.35 (s, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 6.29 (d, *J* = 16.0 Hz, 1 H), 3.75 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.7, 166.8, 145.1, 141.6, 136.5, 132.9, 131.7, 130.8, 128.6, 122.4, 51.9, 21.9.

HRMS (ESI): calc. for [($C_{12}H_{12}O_3$)Na] (M+Na) 227.0684, measured 227.0675.

(*E*)-Methyl 3-(5-(dimethylamino)-2-formylphenyl)acrylate (**3k**).



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

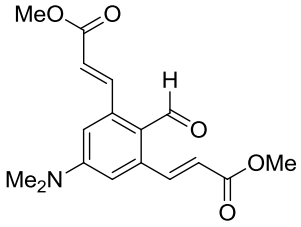
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3076, 2996, 1714, 1668, 1277 and 1194.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.90 (s, 1 H), 8.49 (d, *J* = 16.0 Hz, 1 H), 7.63 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.67 – 6.64 (m, 2 H), 6.26 (d, *J* = 16.0 Hz, 1 H), 3.75 (s, 3 H), 3.03 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.0, 167.0, 153.5, 143.5, 138.6, 135.1, 122.8, 121.8, 111.8, 109.8, 51.9, 40.2.

HRMS (ESI): calc. for [($C_{13}H_{15}NO_3$)Na] (M+Na) 256.0949, measured 256.0941.

(2*E*,2'*E*)-Dimethyl 3,3'-(5-(dimethylamino)-2-formyl-1,3-phenylene)diacrylate (**3k'**).



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

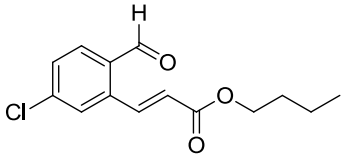
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2994, 2950, 1713, 1665, 1228 and 818.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.22 (s, 1 H), 8.29 (d, *J* = 16.0 Hz, 2 H), 6.59 (s, 2 H), 6.20 (d, *J* = 16.0 Hz, 2 H), 3.76 (s, 6 H), 3.07 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.8, 166.7, 152.8, 144.3, 140.7, 122.5, 111.3, 51.9, 40.2.

HRMS (ESI): calc. for [($C_{17}H_{19}NO_5$)Na] (M+Na) 340.1161, measured 340.1169.

(*E*)-Butyl 3-(5-chloro-2-formylphenyl)acrylate (**3l**).



Pale yellow semisolid; eluent (6% ethyl acetate in hexanes).

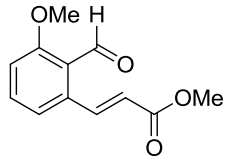
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2961, 2934, 1729, 1699, 1619, 1302 and 1258.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.19 (s, 1 H), 8.37 (d, *J* = 16.0 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.55 (s, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 6.33 (d, *J* = 12.0 Hz, 1 H), 4.17 (t, *J* = 8.0 Hz, 2 H), 1.65 – 1.61 (m, 2 H), 1.40 – 1.35 (m, 2 H), 0.90 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.0, 166.0, 140.6, 139.5, 138.4, 133.4, 130.0, 128.1, 124.5, 115.0, 64.9, 30.8, 19.3, 13.8.

HRMS (ESI): calc. for [($C_{14}H_{15}ClO_3$)Na] (M+Na) 289.0607, measured 286.0605.

(*E*)-Methyl 3-(2-formyl-3-methoxyphenyl)acrylate (**3m**).



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

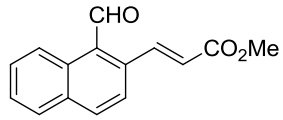
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3006, 2960, 2933, 1708, 1686 and 1332.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.61 (s, 1 H), 8.36 (d, *J* = 16.0 Hz, 1 H), 7.50 (t, *J* = 8.0 Hz, 1 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 6.25 (d, *J* = 16.0 Hz, 1 H), 3.92 (s, 3 H), 3.79 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.6, 167.0, 162.8, 144.1, 137.6, 135.0, 121.7, 120.4, 112.6, 56.1, 51.9.

HRMS (ESI): calc. for [($C_{12}H_{12}O_4$)Na] (M+Na) 243.0633, measured 243.0636.

(*E*)-Methyl 3-(1-formylnaphthalen-2-yl)acrylate (**3n**).



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

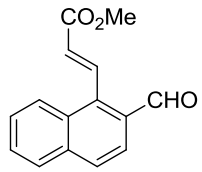
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3108, 3033, 2949, 1746, 1687, 1285 and 1242.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.96 (s, 1 H), 8.82 (d, *J* = 8.0 Hz, 1 H), 8.42 (d, *J* = 16.0 Hz, 1 H), 8.02 (d, *J* = 8.0 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.67 – 7.57 (m, 2 H), 7.46 – 7.43 (t, *J* = 8.0 Hz, 1 H), 6.42 (d, *J* = 16.0 Hz, 1 H), 3.84 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.7, 166.6, 141.8, 134.4, 129.3, 128.7, 128.6, 127.6, 126.6, 125.9, 124.9, 124.7, 124.2, .52.2.

HRMS (ESI): calc. for [($C_{15}H_{12}O_3$)Na] (M+Na) 263.0684, measured 263.0679.

(*E*)-Methyl 3-(2-formylnaphthalen-1-yl)acrylate (**3o**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3056, 2950, 1713, 1693, 1634 and 1215.

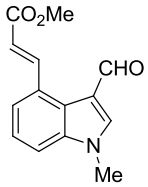
^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.27 (s, 1 H), 8.65 (d, *J* = 16.0 Hz, 1 H), 8.30 (s, 1 H), 8.01 (s, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.65 (t, *J* = 8.0 Hz, 1 H), 7.59 (t, *J* = 8.0 Hz, 1 H), 6.43 (d, *J* = 16.0 Hz, 1

H), 3.82 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.4, 166.9, 142.7, 137.3, 135.3, 132.8, 132.0, 131.9, 129.9, 129.3, 128.5, 128.3, 128.1, 121.6, 51.9.

HRMS (ESI): calc. for [($C_{15}H_{12}O_3$)Na] (M+Na) 263.0684, measured 263.0672.

(E)-methyl 3-(3-formyl-1-methyl-1H-indol-4-yl)acrylate (**3p**).



Pale black semisolid; eluent (20% ethyl acetate in hexanes).

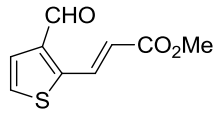
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3091, 3033, 2949, 1697, 1666, 1285 and 740.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.92 (s, 1 H), 9.24 (d, *J* = 16.0 Hz, 1 H), 7.80 (s, 1 H), 7.60 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.38 – 7.35 (m, 2 H), 6.44 (d, *J* = 16.0 Hz, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 183.4, 167.7, 145.4, 142.9, 139.3, 129.6, 124.5, 124.1, 120.9, 119.2, 118.7, 111.7, 51.9, 34.0.

HRMS (ESI): calc. for [($C_{14}H_{13}NO_3$)Na] (M+Na) 266.0793, measured 266.0781.

(*E*)-Methyl 3-(3-formylthiophen-2-yl)acrylate (**3q**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3093, 3029, 2953, 1714, 1670, 1284 and 1239.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.15 (s, 1 H), 8.33 (d, *J* = 16.0 Hz, 1 H), 7.44 (d, *J* = 4.0 Hz, 1 H), 7.29 (d, *J* = 4.0 Hz, 1 H), 6.38 (d, *J* = 16.0 Hz, 2 H), 3.78 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 184.1, 166.4, 146.9, 139.8, 133.5, 129.0, 127.4, 121.8, 52.1.

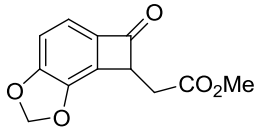
HRMS (ESI): calc. for [($C_9H_8O_3S$)Na] (M+Na) 219.0091, measured 219.0087.

General Procedure for the Photochemical Rearrangement (4a-4d)

The compound **3** dissolved in benzene (1.5 mg/mL) was purged with argon for 30 min then irradiated in an open vessel using a 450 W Hanovia medium pressure mercury vapour lamp. The lamp was immersed in a Pyrex water-jacketed immersion well to allow only wavelengths greater than 280 nm to pass through. After about 5 to 8 h (see specific

timing of the reaction in Scheme 2.16) of irradiation, the consumption of the starting material was found to be almost complete (monitored by TLC) and at this stage the irradiation was discontinued. The solvent was removed under reduced pressure and the crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **4**.

Substituted four-membered ketone (**4a**).



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

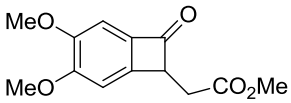
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3055, 2987, 1740, 1713, 1472, 1379 and 731.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (d, *J* = 8.0 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 6.13 (s, 1 H), 6.08 (s, 1 H), 4.25 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.75 (s, 3 H), 2.95 (s, 1 H), 2.93 (d, *J* = 4.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.6, 172.1, 153.4, 144.4, 132.1, 130.5, 119.5, 109.9, 102.7, 52.8, 40.6, 40.4.

HRMS (ESI): calc. for [($C_{12}H_{10}O_5$)Na] (M+Na) 257.0425, measured 257.0428.

Substituted four-membered ketone (**4b**).



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

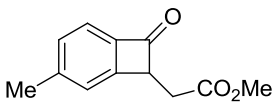
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3004, 2952, 2840, 1732, 1697, 1590 and 1265.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13 (s, 1 H), 7.04 (s, 1 H), 4.16 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.96 (s, 3 H), 3.86 (s, 3 H), 3.73 (s, 3 H), 3.05 (dd, *J* = 16.0, 4.0 Hz, 1 H), 2.82 (dd, *J* = 16.0, 4.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.9, 172.5, 155.6, 150.5, 149.4, 146.2, 107.4, 104.3, 56.5, 56.2, 52.7, 43.4, 39.8.

HRMS (ESI): calc. for [($C_{13}H_{14}O_5$)Na] (M+Na) 273.0739, measured 273.0735.

Substituted isochromen derivative (**4c**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3015, 2977, 1730, 1702 and 1452.

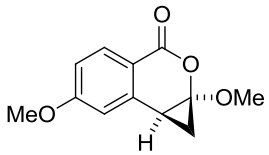
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 8.0 Hz, 1 H), 7.45 (s, 1 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 4.23 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.77 (s, 3 H), 3.09 (dd, *J* = 16.0, 4.0 Hz, 1 H), 2.84 (dd, *J* = 16.0, 4.0 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.8, 172.5, 151.7, 146.5, 130.2, 126.8, 123.9, 115.1, 52.8, 43.6, 39.8, 22.3.

GC-MS (70 ev, C.I.): calc. for [($C_{12}H_{12}O_3$)H] (M+H) 205, measured 205 (M+H).

HRMS (ESI): calc. for [($C_{12}H_{12}O_3$)Na] (M+Na) 227.0684, measured 227.0694.

Substituted isochromen derivative (**4d**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3036, 3015, 2931, 1694, 1252 and 862.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, *J* = 8.0 Hz, 1 H), 6.83 – 6.78 (m, 2 H), 3.82 (s, 3 H), 3.53 (s, 3 H), 2.49 (dd, *J* = 8.0, 4.0 Hz, 1 H), 1.74 (dd, *J* = 8.0, 4.0 Hz, 1 H), 0.76 (t, *J* = 8.0 Hz, 1 H).

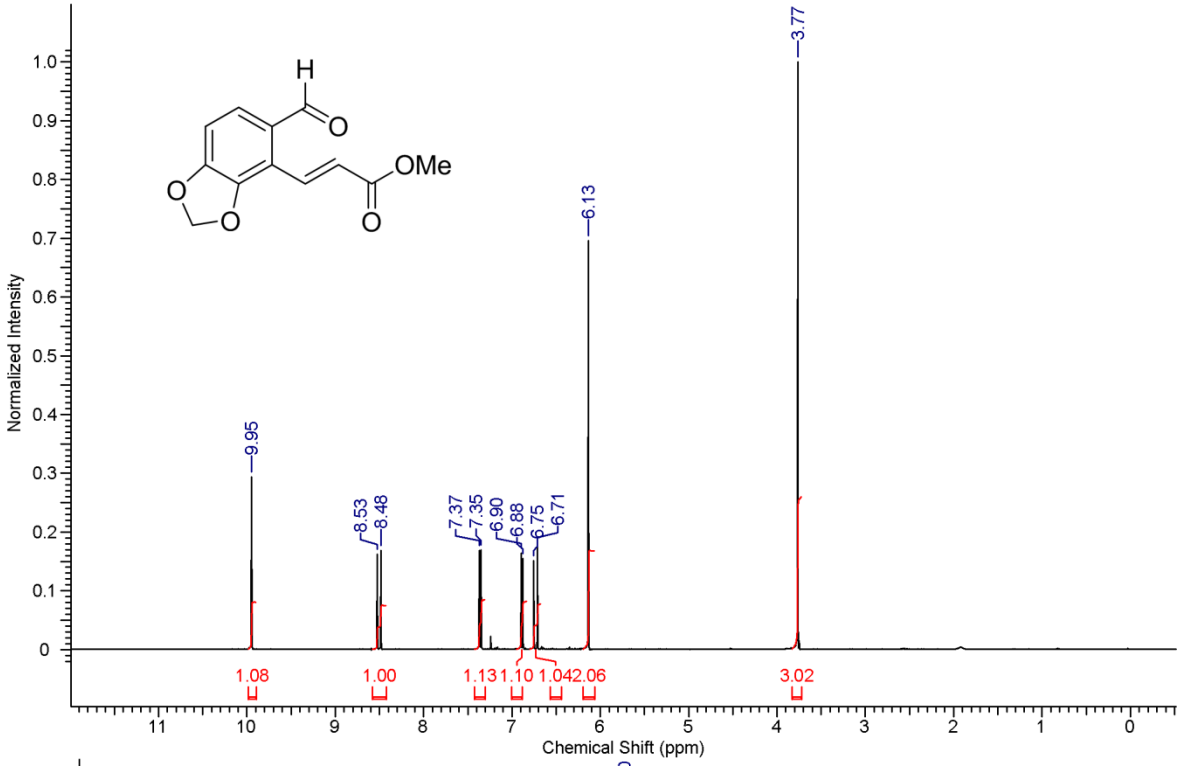
^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.3, 161.7, 142.9, 133.5, 113.9, 112.9, 112.1, 92.2, 55.7, 55.6, 22.2, 21.6.

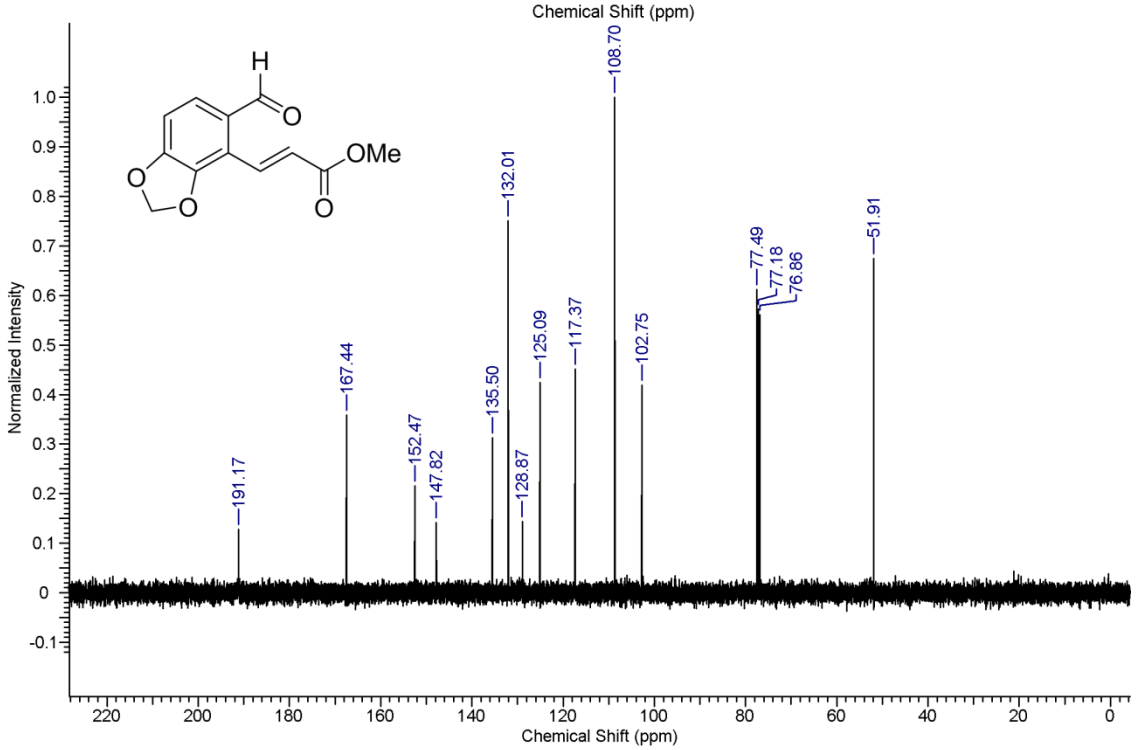
GC-MS (70 ev, C.I.): calc. for [($C_{12}H_{12}O_4$)H] (M+H) 221, measured 221 (M+H).

HRMS (ESI): calc. for [($C_{12}H_{12}O_4$)Na] (M+Na) 243.0633, measured 243.0637.

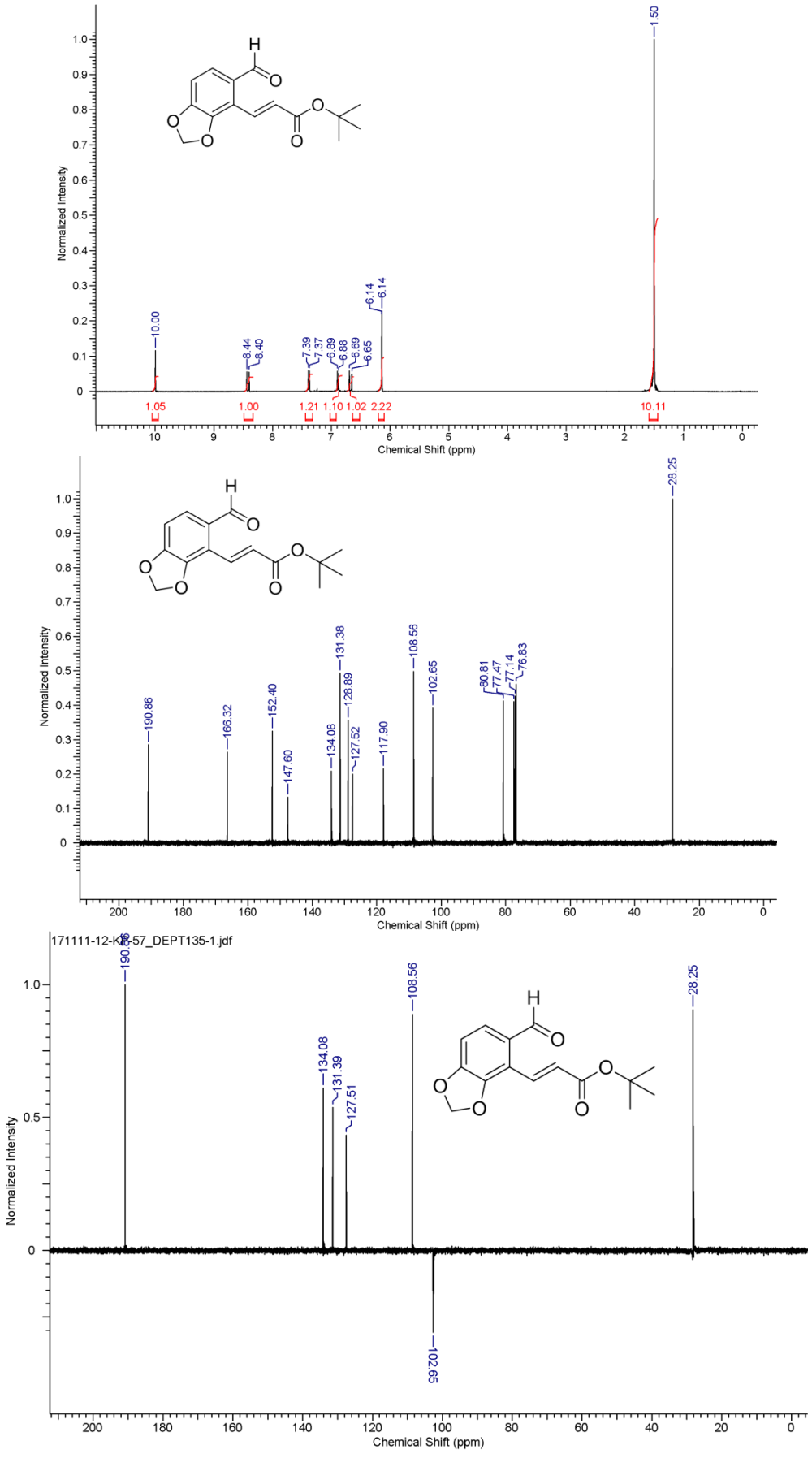
2B.11: Spectral Copies of Selected Compounds

Spectral data of compound **3a**.

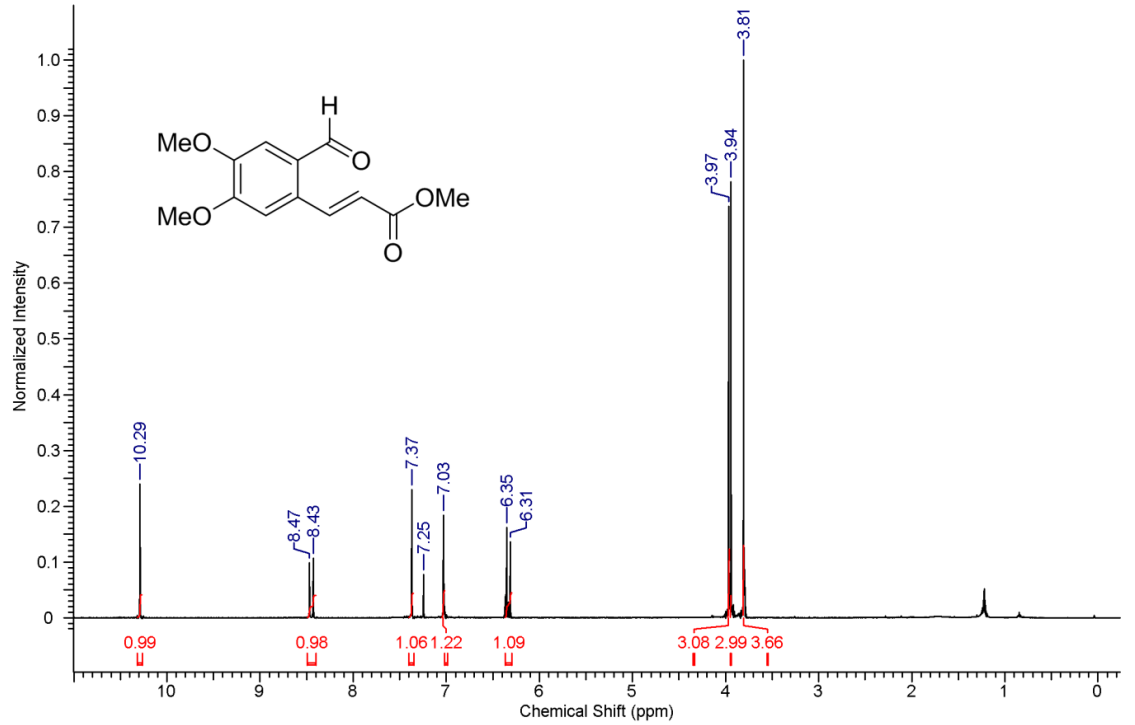


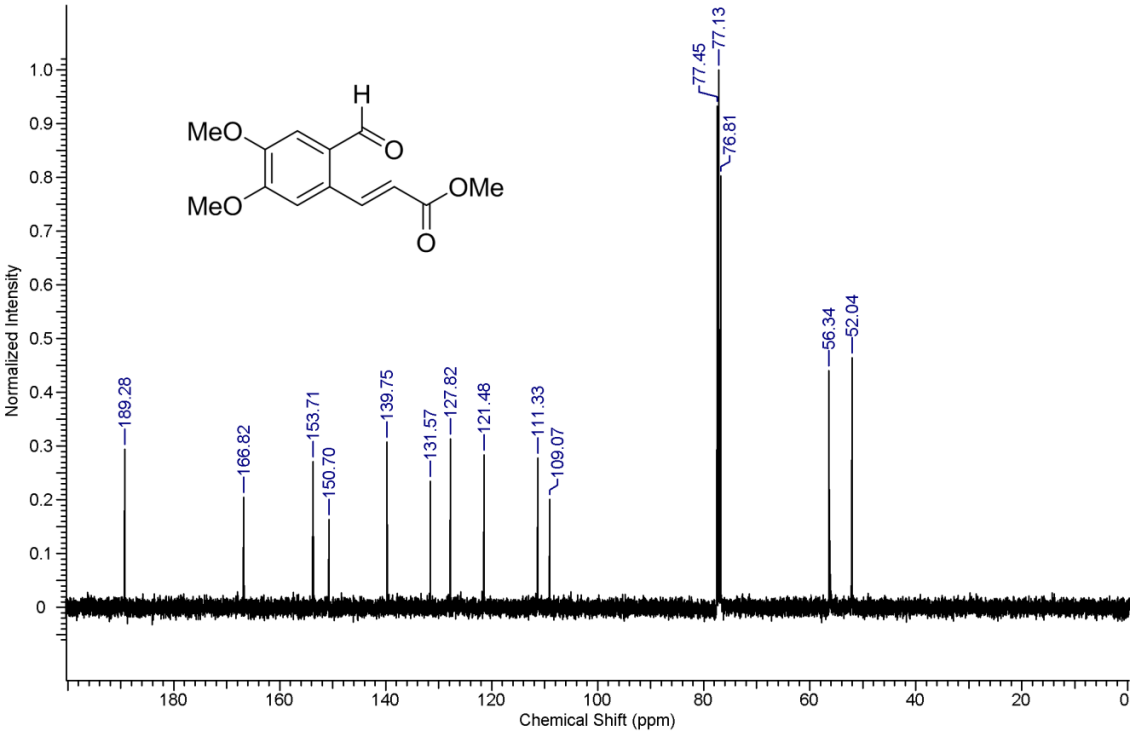


Spectral data of compound **3d**.

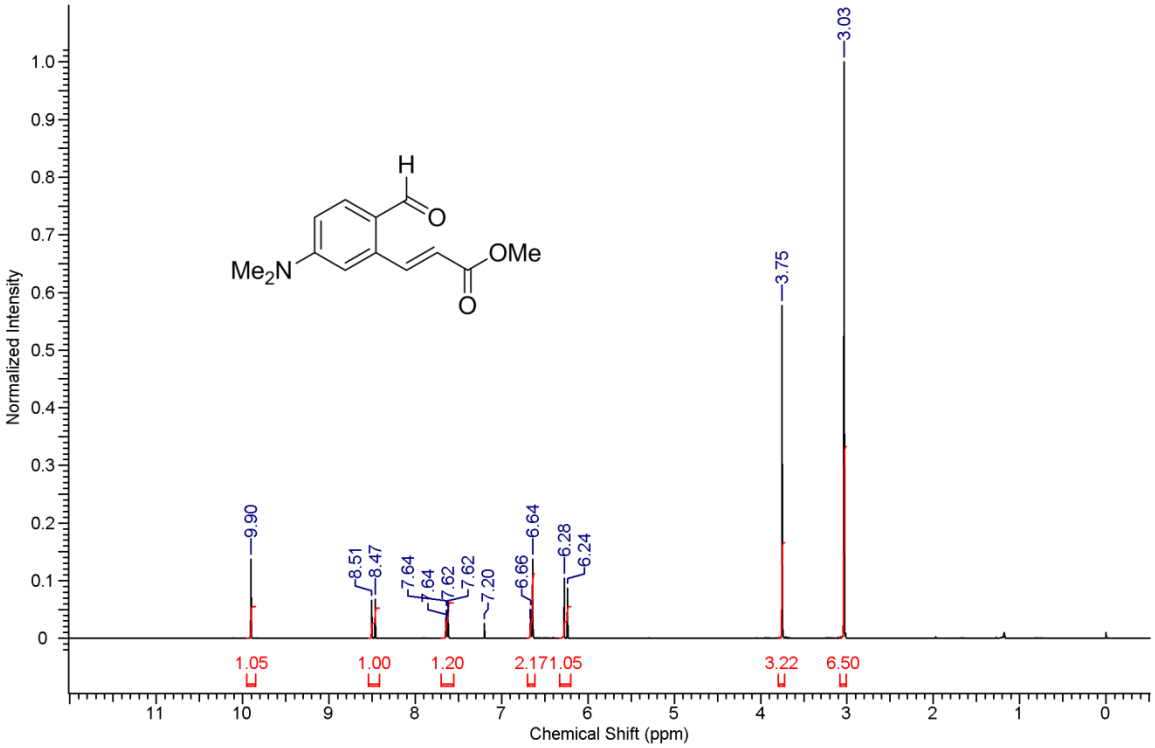


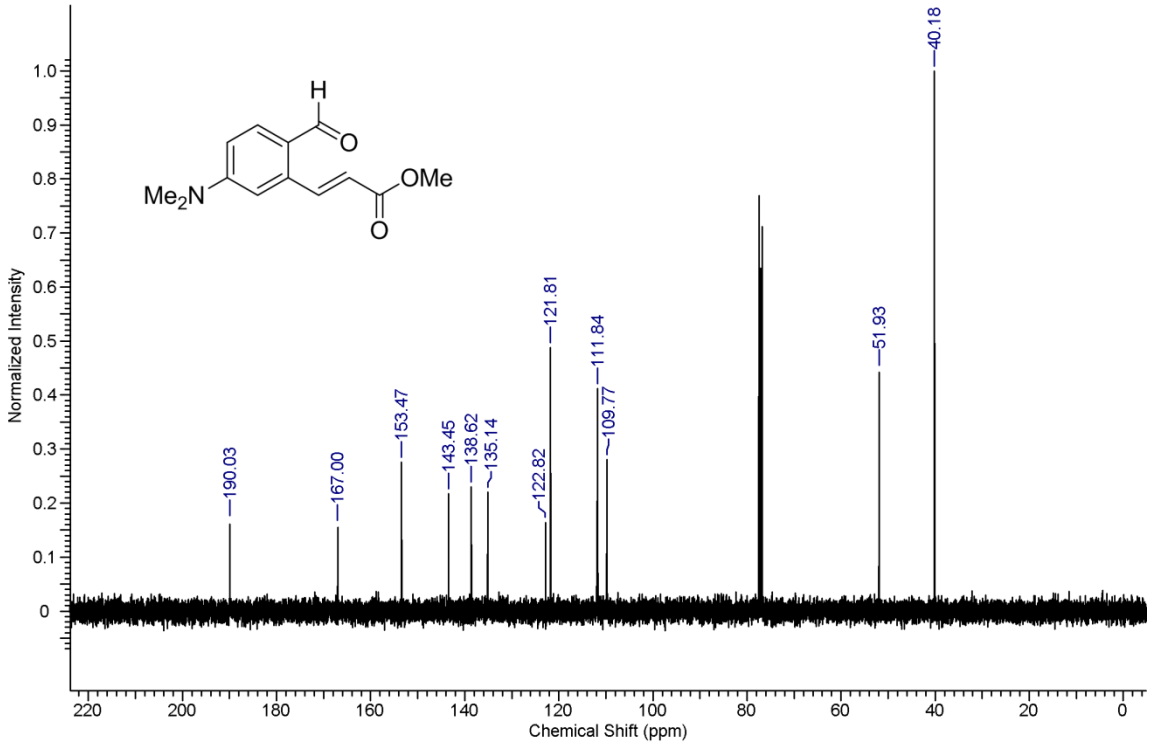
Spectral data of compound **3g**.



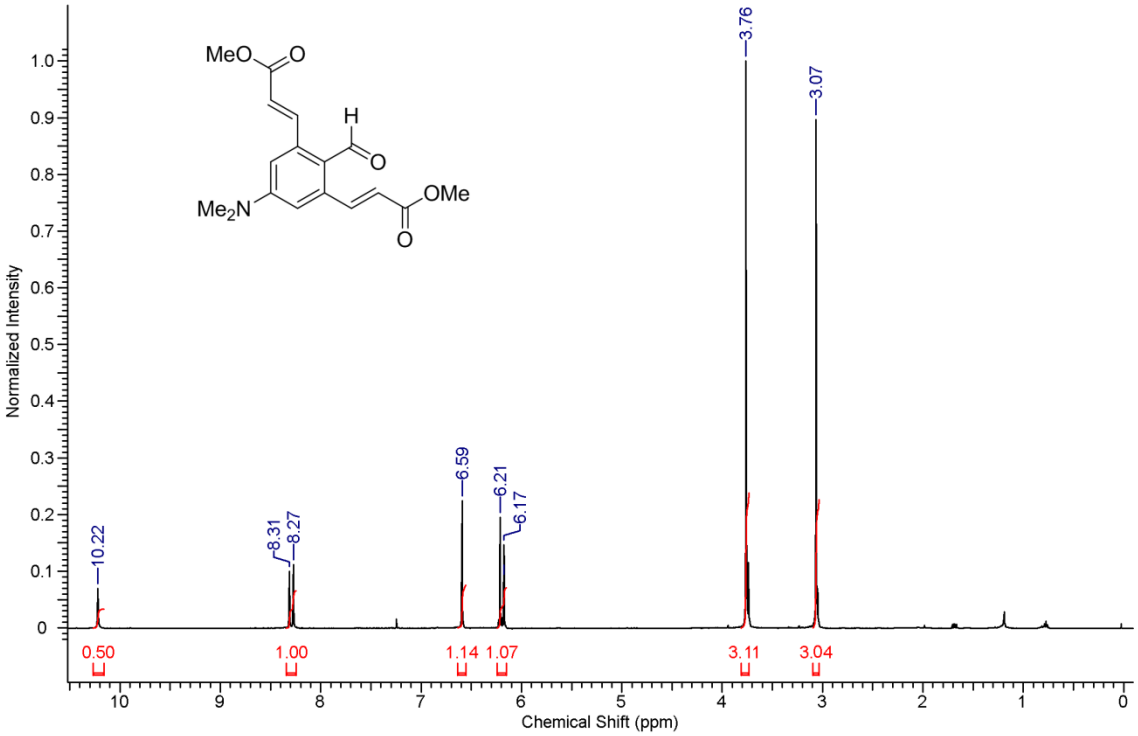


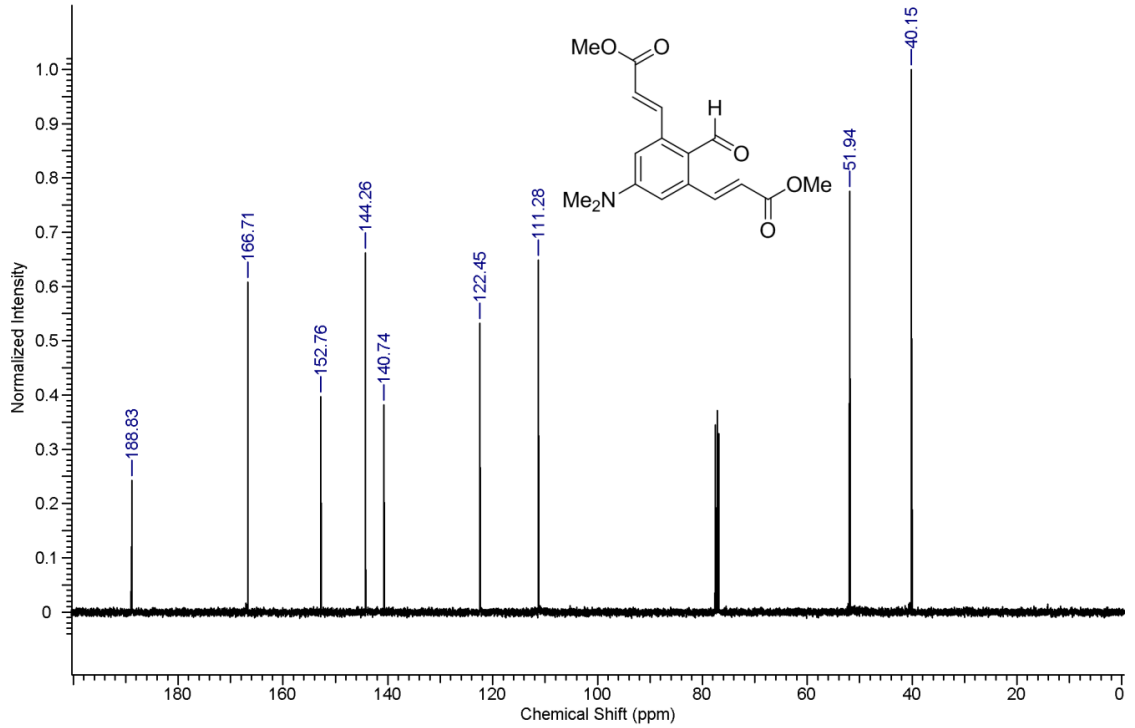
Spectral data of compound **3k**.



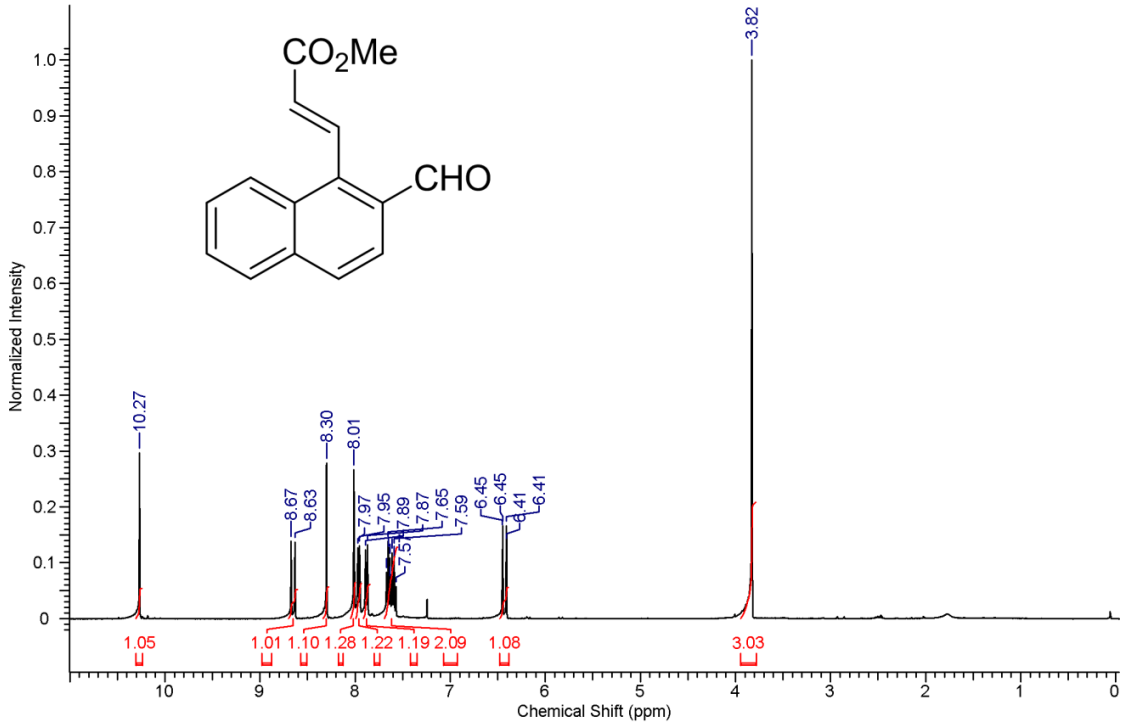


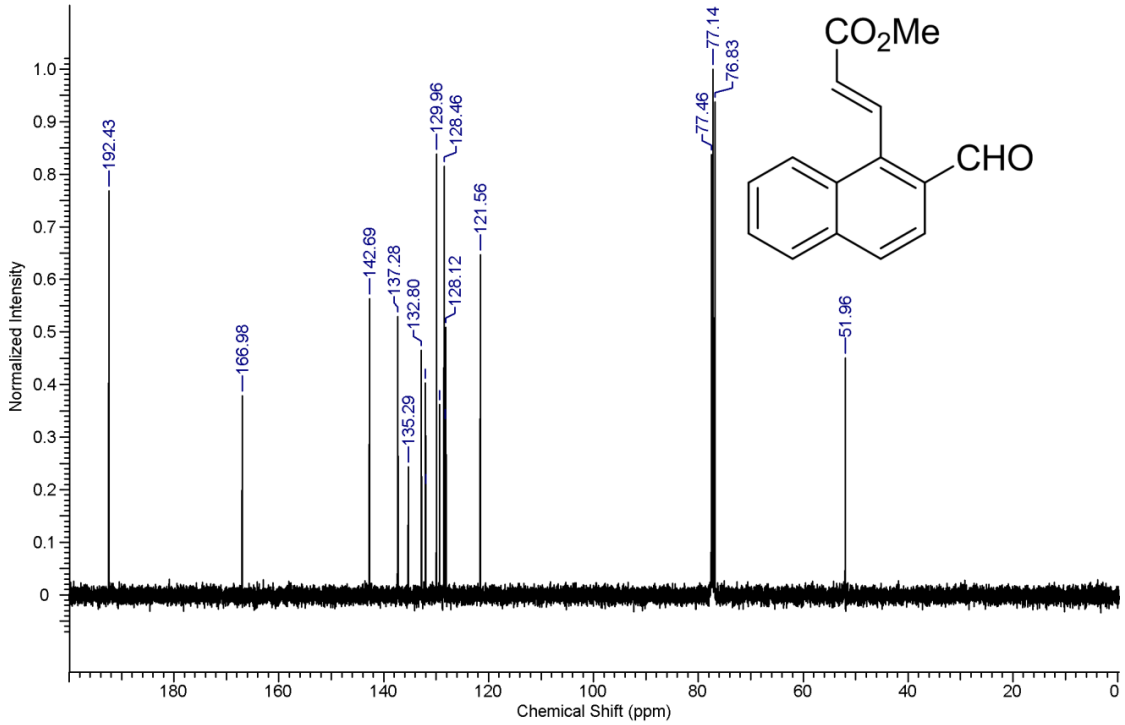
Spectral data of compound **3k'**.



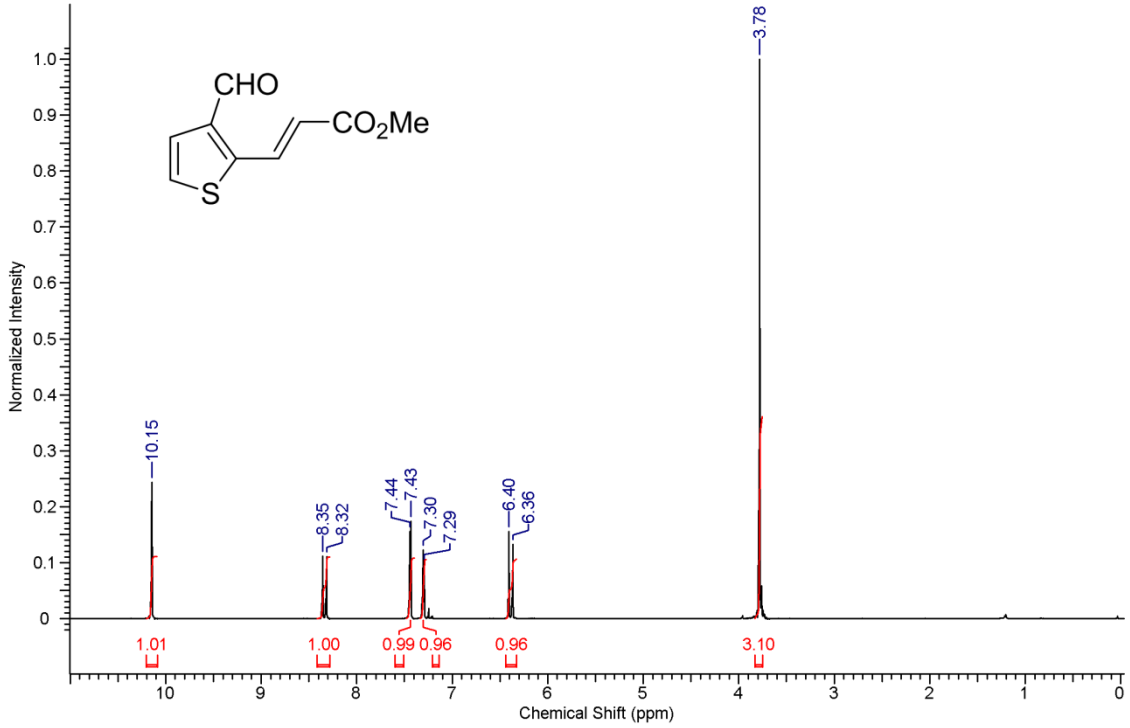


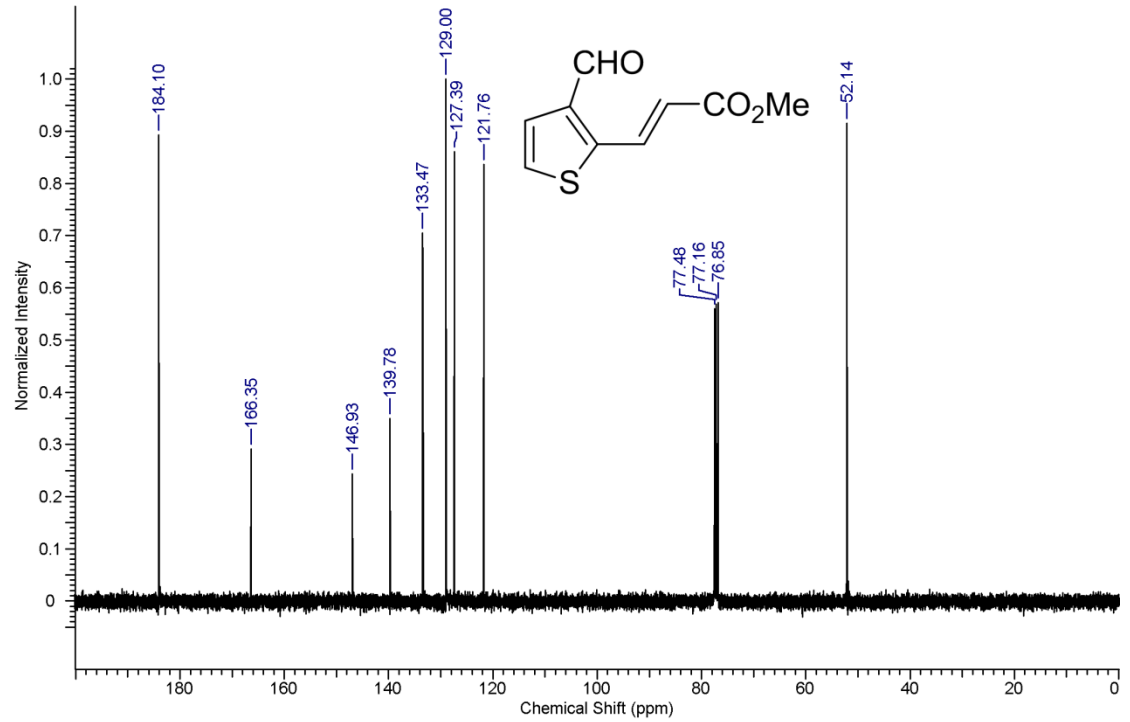
Spectral data of compound **3o**.



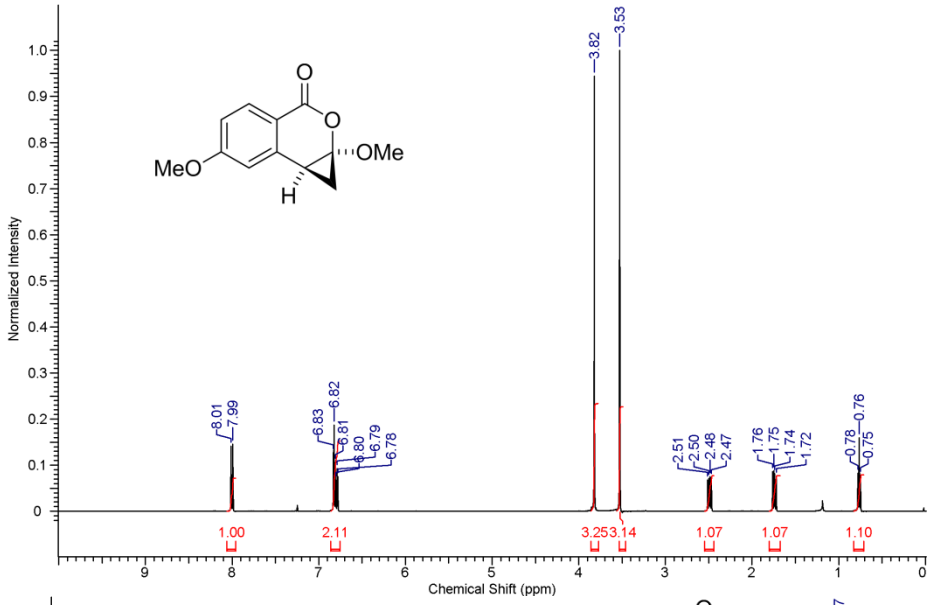


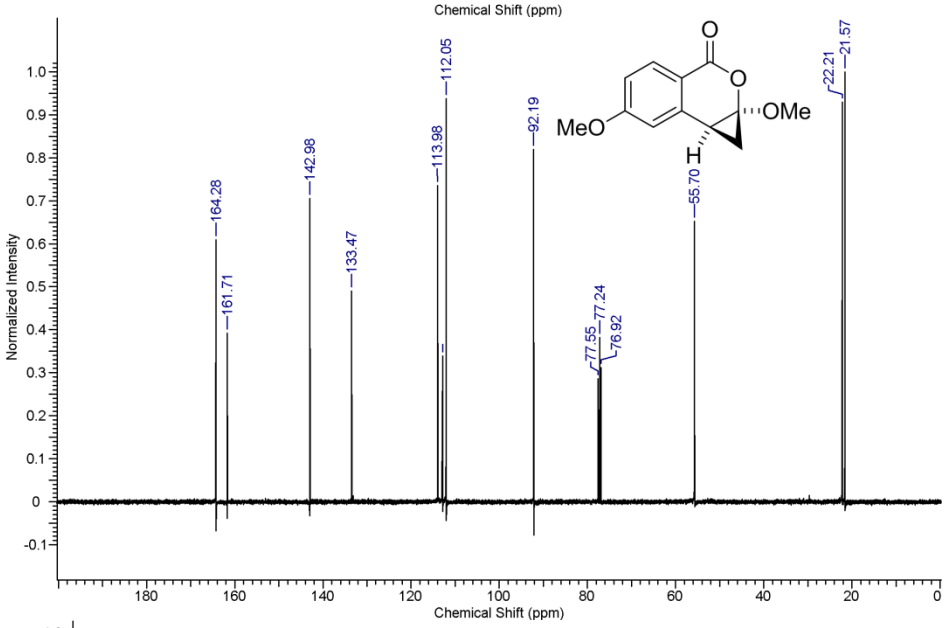
Spectral data of compound **3q**.

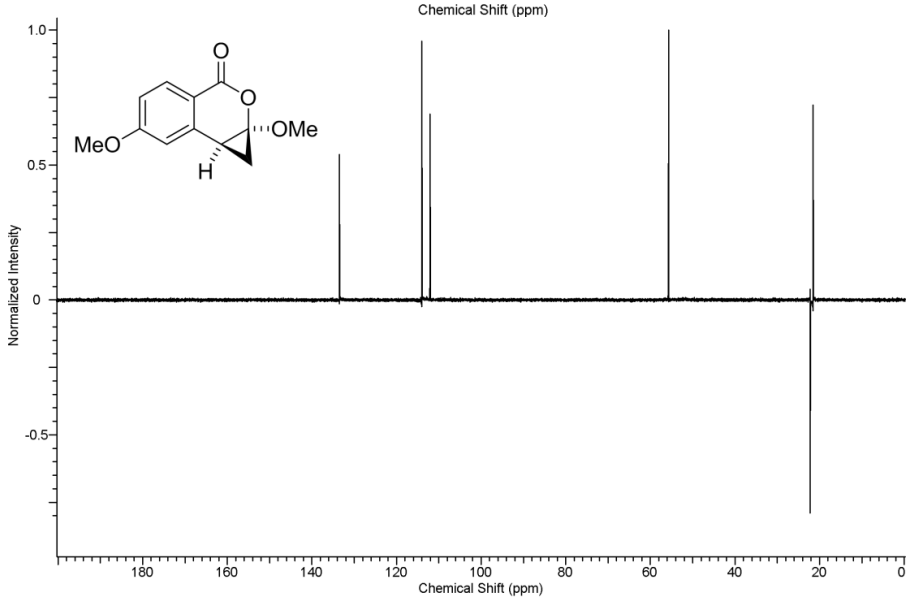




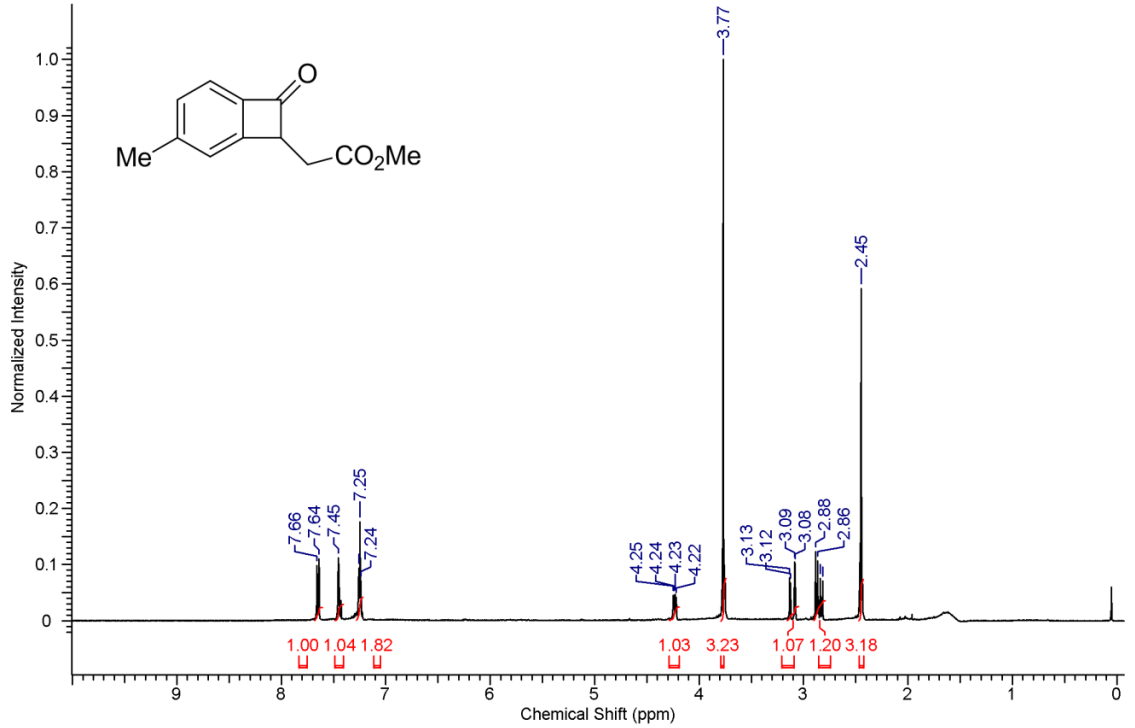
Spectral data of compound **4c**.

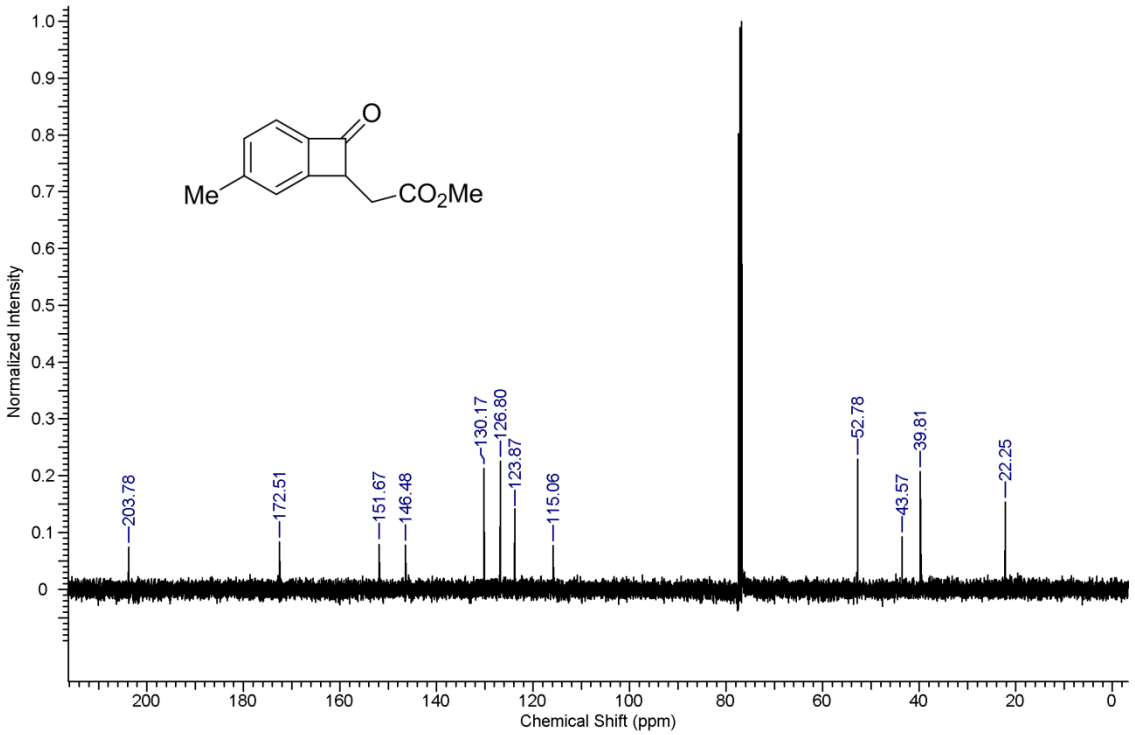






Spectral data of compound **4d**.



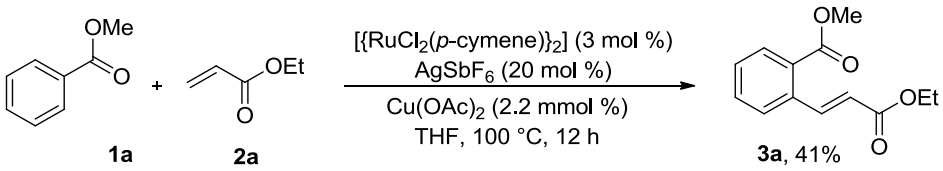


2C: Ruthenium-Catalyzed Regioselective Oxidative Coupling of Aromatic and Heteroaromatic Esters with Alkenes under Open Atmosphere

2C.1: Results and Discussion

Various directing groups such as amine, oxime, amide, pyridyl, COOH, phenol, OH and carbonyl can be used in the metal-catalyzed *ortho* alkenylation reactions. In the presence of strong directing groups, C-H bond activation reactions are facile. But, activation in the presence of weak directing groups are still a challenging task.[8] Herein, we report *ortho* alkenylation of aromatic esters with alkenes in the presence of catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and $Cu(OAc)_2$, affording highly substituted alkene derivatives in a highly regio- and stereoselective manner. The catalytic reaction is also compatible with various heteroaromatic esters. Interestingly, the present ruthenium-catalyzed alkenylation reaction is carried out under open atmosphere and only catalytic amount of $Cu(OAc)_2$ has been used as an terminal oxidant and remaining amount of $Cu(OAc)_2$ source has been regenerated under open atmosphere from the reduced copper source**.**

Treatment of methyl benzoate (**1a**) with ethyl acrylate (**2a**) in the presence of catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2$ (2.2 mmol) in THF at 100 °C for 12 h gave an alkene derivative **3a** in 41% isolated yield (scheme 2.18).



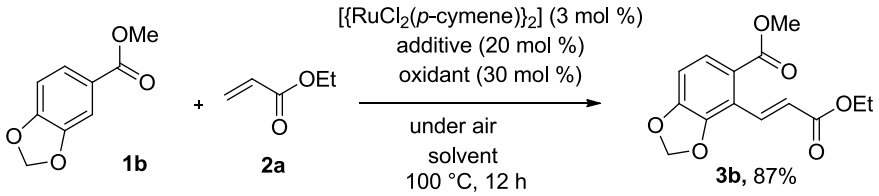
1a **2a** **3a**, 41%

Scheme 2.18: *ortho* alkenylation of methyl piperonate with ethyl acrylate

To improve the yield of the reaction, in addition to ester directing group, a very weak directing group such as 1, 3-dioxol (-O-CH_2-O-) was introduced at 3 and 4 positions of methyl benzoate 1a in order to further activate the aromatic C-H bond efficiently.

2C.2: Optimization Studies

Table 2.7: Optimization Studies with Various Solvents, Oxidants and Additives.[a]



entry	solvent	oxidant	additive	yield of **3a** (%)[b]
1	DCE	$Cu(OAc)_2.H_2O$	AgOTf	NR
2	DCE	$Cu(OAc)_2.H_2O$	$AgBF_4$	NR
3	DCE	$Cu(OAc)_2.H_2O$	Ag_2O	NR
4	DCE	$Cu(OAc)_2.H_2O$	AgO_2CCF_3	NR
5	**DCE**	**$Cu(OAc)_2.H_2O$**	**$AgSbF_6$**	**87**
6	THF	$Cu(OAc)_2.H_2O$	$AgSbF_6$	85[c]
7	THF	$Cu(OAc)_2.H_2O$	$AgSbF_6$	86
8	CH_3CN	$Cu(OAc)_2.H_2O$	$AgSbF_6$	NR
9	MeOH	$Cu(OAc)_2.H_2O$	$AgSbF_6$	NR
10	DMF	$Cu(OAc)_2.H_2O$	$AgSbF_6$	NR
11	DME	$Cu(OAc)_2.H_2O$	$AgSbF_6$	NR
12	*t*-BuOH	$Cu(OAc)_2.H_2O$	$AgSbF_6$	NR
13	DMSO	$Cu(OAc)_2.H_2O$	$AgSbF_6$	NR
14	Toluene	$Cu(OAc)_2.H_2O$	$AgSbF_6$	NR
15	DCE	oxone	$AgSbF_6$	NR
16	DCE	DDQ	$AgSbF_6$	NR
17	DCE	$PhI(OAc)_2$	$AgSbF_6$	NR
18	DCE	$K_2S_2O_8$	$AgSbF_6$	NR

[a]All reactions were carried out under the following conditions: **1a** (100 mg), **2a** (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), additive (20 mol %) and $Cu(OAc)_2.H_2O$ (30 mol % mmol) in solvent (2.5 mL) at 100 °C for 12 h. [b]GC yield.[c] $Cu(OAc)_2.H_2O$ (2.2 mmol). **Note**: The catalytic reaction was tried without ruthenium and $AgSbF_6$. No product **3a** was observed.

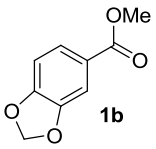
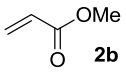
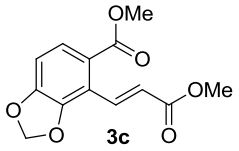
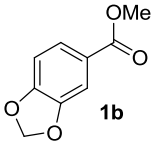
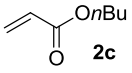
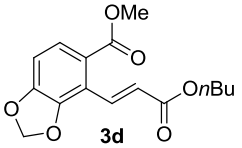
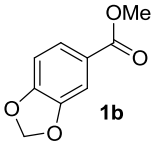
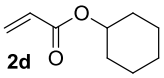
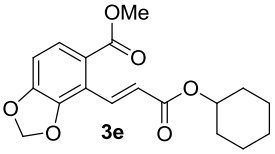
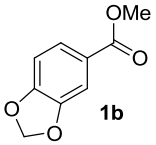
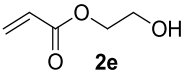
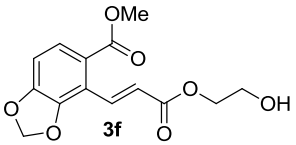
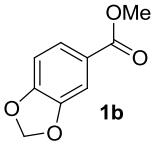
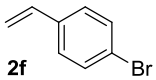
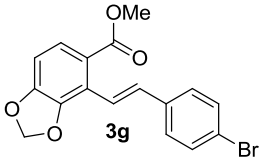
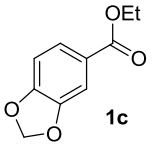
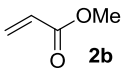
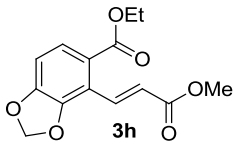
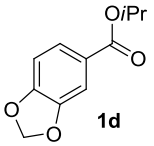
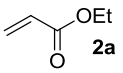
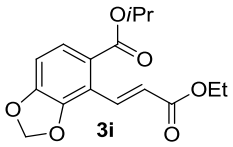
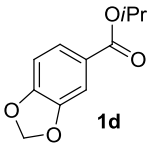
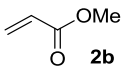
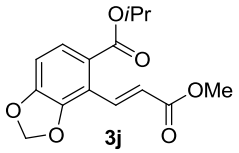
Interestingly, in the reaction of methyl piperonate **(1b)** with ethyl acrylate **(2a)** under similar reaction conditions, the corresponding alkenylated compound **3b** was obtained in excellent 85% isolated yield with a high *E*-stereoselective. The catalytic reaction is also

regioselective. In the substrate **1b,** there are two *ortho* aromatic C-H bonds for alkenylation. Selectively, alkenylation reaction takes place at the sterically hindered C-H bond of **1b** moiety. In the reaction, both ester and 1,3-dioxol moieties act as directing groups. Thus, C-H bond activation takes place selectively at sterically hindered C-H bond. Next, the same coupling reaction was carried out under open atmosphere. Interestingly, the corresponding alkene derivative **3b** was observed in 86% yield (Table 2.7). Other silver salts including AgOTf, $AgBF_4$, Ag_2O and AgO_2CCF_3 were totally ineffective for the reaction (Table 2.7). Other oxidants such as oxone, DDQ, $PhI(OAc)_2$ and $K_2S_2O_8$ were totally ineffective in the reaction. The catalytic reaction was also tested with various solvents such as CH_3CN, toluene, MeOH, *tert*-BuOH, DMF, DME, DMA and DMSO (Table 2.7). Among them, DCE (1, 2-dichloroethane) solvent was equally effective for the reaction, giving the coupling product 3b in 87% yield under open atmosphere. Remaining solvents were totally ineffective for the reaction. However, the catalytic reaction did not proceed in the absence of either copper source or silver salt.

2C.3: Scope of Alkenes

Under similar reaction conditions, various acrylates **2b-e** were effectively coupled with substituted piperonates **1b-d**. Thus, the reaction of methyl piperonate (**1b**) with methyl acrylate (**2b**), *n*-butyl acrylate (**2c**) and cyclohexyl acrylate (**2d**) afforded the corresponding alkenylated products **3c-e** in 89%, 82% and 78% yields, respectively. Very interestingly, 2-hydroxyethyl acrylate (**2e**) is also efficiently involved in the coupling reaction giving product **3f** in 72% yield. The catalytic reaction was also tested with styrenes. Thus, 4-bromostyrene (**2f**) reacted smoothly with **1b** yielding an alkenylated product **3g** in 62% yield. Next, the effect of changing the methyl group in methyl piperonate (**1b**) by other substituents such as ethyl and isopropyl groups was investigated. Thus, ethyl piperonate (**1c**) reacted nicely with methyl acrylate (**2b**) affording compound **3h** in 85% yield. Similarly, isopropyl piperonate (**1d**) underwent coupling with ethyl and methyl acrylates **2a** and **2b** yielding coupling products **3i** and **3j** in 89% and 86% yields, respectively. These reactions were also highly regio- and stereoselective as like **3b**.

Table 2.8 : Results of the Reaction of Piperonates **1b-d** with Substituted Alkenes **2a-f**[a]

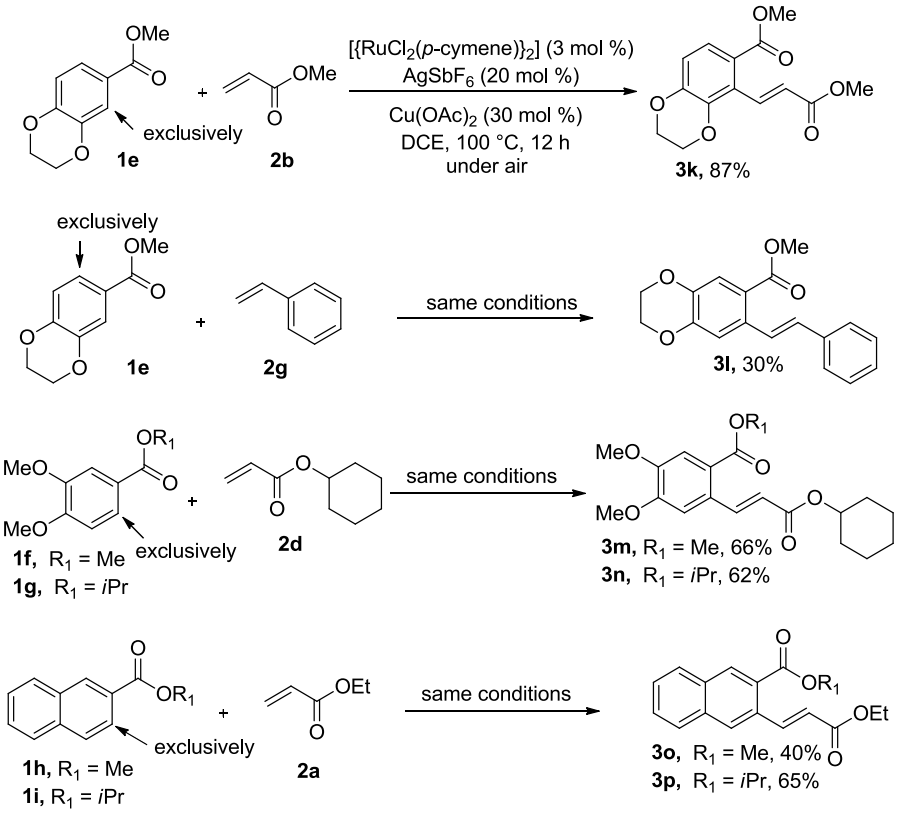
entry	**1**	**2**	product **3**	yield (%)[b]
1	 **1b**	 **2b**	 **3c**	89
2	 **1b**	 **2c**	 **3d**	82
3	 **1b**	 **2d**	 **3e**	78
4	 **1b**	 **2e**	 **3f**	72
5	 **1b**	 **2f**	 **3g**	82
6	 **1c**	 **2b**	 **3h**	85
7	 **1d**	 **2a**	 **3i**	89
8	 **1d**	 **2b**	 **3j**	86

[a]All reactions were carried out using aromatic ester **1** (1.0 mmol), acrylates (**2b-e**) (1.5 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2.H_2O$ (30 mol %) in DCE (1,2-dichloroethane) (3.0 mL) at 100 °C for 12 h. [b]Isolated yields.

2C.4: Regioselective Studies

In addition to **1b-d**, the regioselectivity of other unsymmetrical aromatic esters **1e-i** were also examined under the same reaction conditions (Scheme 2.19). The reaction of methyl

1,4-benzodioxane-6-carboxylate (**1e**) with methyl acrylate (**2b**) provided substituted alkene derivative **3k** in 87% yield in a highly regio- and stereoselective manner. As like **1b-d**, coupling reaction takes place at sterically hindered C-H bond of **1e**. In contrast, **1e** reacted with styrene (**2g**) giving substituted *E*-stilbene derivative **3l**, albeit in only 30% yield in an opposite regiochemistry. In the reaction, the remaining amount of 70% of starting material **1e** was recovered. In the reaction, C-H bond activation takes place at sterically less hindered C-H bond of **1e**. Similarly, methyl 3,4-dimethoxybenzoate (**1f**) and isopropyl 3,4-dimethoxybenzoate (**1g**) also regioselectivity coupled with cyclohexyl acrylate (**2d**) providing coupling products **3m** and **3n** in 66% and 62% yields, respectively, in a highly regio- and stereoselective manner. In this case also, C-H bond activation takes place at sterically less hindered C-H bond of **1f** and **1g**. A similar type of regioselective product **3o** in moderate 40% yield was observed in the reaction of methyl 2-naphthoate (**1h**) with ethyl acrylate (**2a**) under similar reaction conditions. Interestingly, isopropyl 2-naphthoate (**1i**) reacted efficiently with **2a** yielding the corresponding alkene derivative **3p** in good 65% yield.



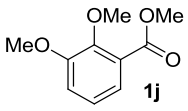
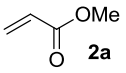
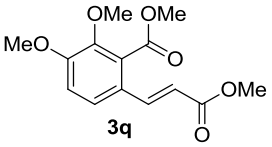
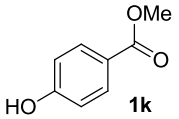
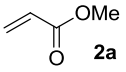
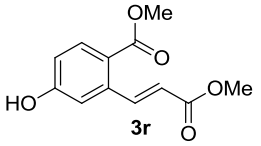
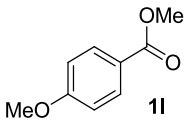
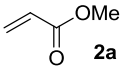
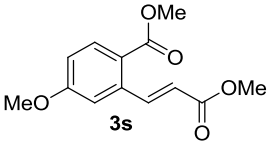
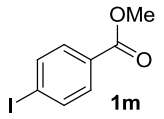
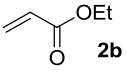
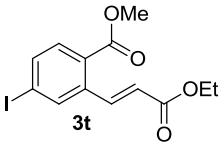
Scheme 2.19: Regioselective studies of substituted aromatic esters

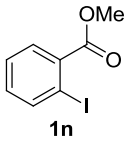
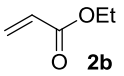
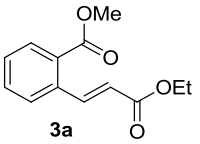
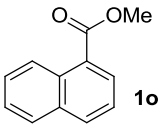
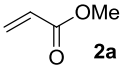
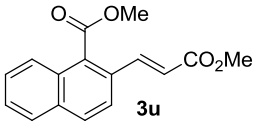
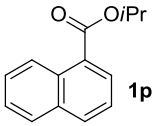
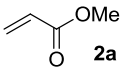
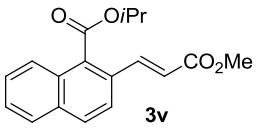
2C.5: Scope of Aromatic Esters

The present alkenylation reaction was tested with various substituted aromatic esters **1**

and ethyl or methyl acrylates (**2a** and **2b**) under the optimized reaction conditions. The reaction of methyl 2,3-dimethoxybenzoate (**1j**) with methyl acrylate (**2b**) afforded coupling product **3q** in 65% yield. Methyl 4-hydroxybenzoate (**1k**) reacted with **2b** providing **3r** albeit in moderate 45% yield. Whereas, methyl 4-methoxybenzoate (**1l**) reacted with **2b** affording **3s** in 61% yield. Methyl 4-iodobenzoate (**1m**) also efficiently participated in the reaction giving the corresponding alkene derivative **3t** in 59% yield. Whereas, methyl 2-iodobenzoate (**1n**) reacted with **2a** providing coupling product **3a** in 75% yield, in which the *ortho* I group of **1n** participates in the coupling reaction via oxidative additionMethyl 1-napthoate (**1o**) reacted with **2b** affording the corresponding alkenylated derivative **3u** only in 52% yield. The yield of coupling product **3v** can be improved up to 75% by changing the methyl group by isopropyl group in 1-naphthoate (**1p**). The catalytic reaction was also tested with various electron-withdrawing group substituted aromatic esters such as methyl 4-nitrobenzoate and methyl 4-trifluorobenzoate under similar reaction conditions. However, in the reaction, no coupling product was observed and only starting material was recovered. It seems that electron-withdrawing group substituted aromatic ester was not compatible substrate for the present coupling reaction.

Table 2.9 : Results of the Reaction of Aromatic Esters **1** with **2a** or **2b.**[a]

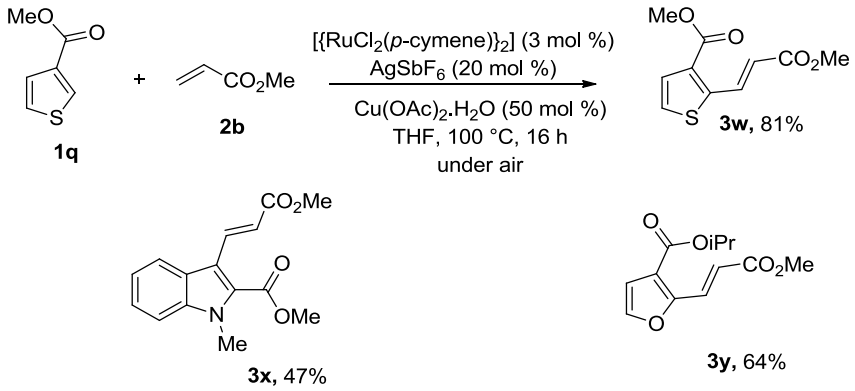
entry	**1**	2	product **3**	yield (%)[b]
1	 **1j**	 **2a**	 **3q**	65
2	 **1k**	 **2a**	 **3r**	45
3	 **1l**	 **2a**	 **3s**	61
4	 **1m**	 **2b**	 **3t**	59

5	 **1n**	 **2b**	 **3a**	75
6	 **1o**	 **2a**	 **3u**	52
7	 **1p**	 **2a**	 **3v**	75

[a]All reactions were carried out using aromatic ester **1j-p** (1.0 mmol), acrylates (**2a** or **2b**) (1.5 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2.H_2O$ (30 mol %) in DCE (1,2-dichloroethane) (3.0 mL) at 100 °C for 12 h. [b]Isolated yields.

2C.6: Scope of Heteroaromatic Esters

The present catalytic reaction was also examined with various heterocyclic esters (Scheme 2.20). Thus, methyl thiophene-3-carboxylate (**1q**) underwent coupling reaction with methyl acrylate (**2b**) providing an alkene derivative **3w** in 81% yield. Substituted indole (**1r**) and isopropyl furan-3-carboxylate(**1s**) also efficiently reacted with methyl acrylate (**2b**) giving the corresponding alkenylated products **3x** and **3y** in 47% and 64% yields, respectively. In the substrate **1r**, C-H bond activation takes place nicely at electron-rich C3-H carbon.

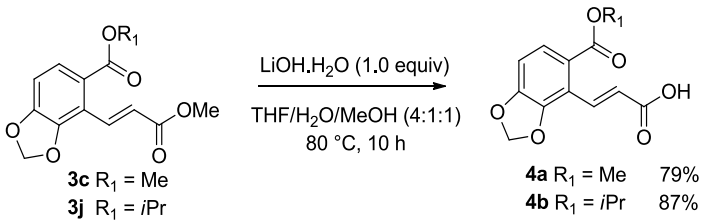


Scheme 2.20: Scope of heteroaromatic esters

2C.7: Selective De-esterification

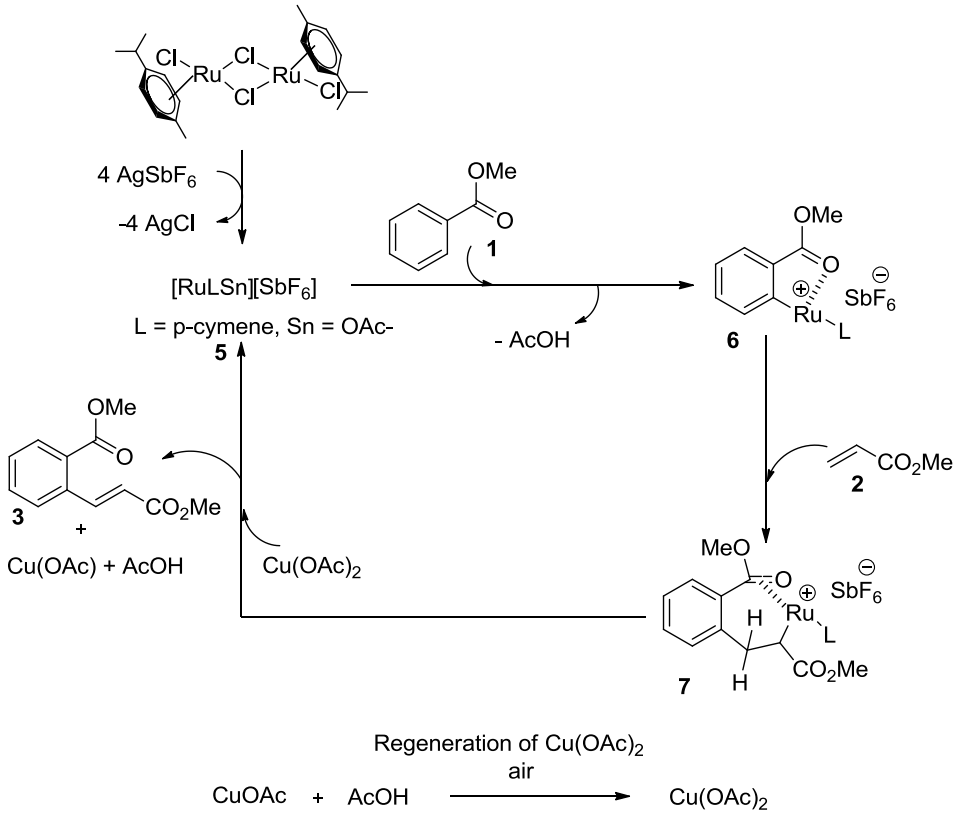
Next, the selective de-esterification of aromatic group substituted ester of compounds **3a** and **3b** were tried in the presence of $LiOH{\cdot}H_2O$ (1.0 equiv) in THF:H_2O:MeOH (4:1:1) at 80 °C for 12 h. Surprisingly, in the reaction, de-esterification takes place very selectively at alkene group substituted ester providing substituted carboxylic acids **4a** and **4b** in 79%

and 87% yields, respectivel. Ester group connected with aromatic moiety of **3a** and **3b** remains intact. For selective de-esterification of aromatic group substituted ester, the reaction was tried with various bases such as NaOH and KOH under the same reaction conditions. In these reactions also, de-esterification selectively takes place at alkene group substituted ester. The coupling reaction of methyl piperonate (**1b**) with acrylic acid was tried under the optimized reaction conditions. However, in the reaction, coupling product **4a** was not observed and only acrylic acid dimerization was observed. By using the present de-esterification reaction, substituted acrylic acid derivatives can be synthesized in excellent yields.



Scheme 2.21: Selective de-esterification

2C.8: Mechanism



Scheme 2.22: Proposed mechanism

A possible reaction mechanism for the present coupling reaction is shown in above. Reaction of [{$RuCl_2$(*p*-cymene)}$_2$] complex with $AgSbF_6$ gives cationic ruthenium

complex **5** (Scheme 2.22). Coordination of the carbonyl oxygen of aromatic ester **1** to the ruthenium cationic species **5** followed by *ortho* metalation affords ruthenacycle intermediate **6**.[21] Insertion of alkene **2** into the Ru–carbon bond of intermediate **6** provides a seven-membered ruthenacycle intermediate **7**. β-Hydride elimination of intermediate in the presence of $Cu(OAc)_2$ yields coupling product **3** and regenerates the active ruthenium species for the next catalytic cycle. The remaining amount of active $Cu(OAc)_2$ source is regenerated under atmosphere from the reduced copper source such as CuOAc.

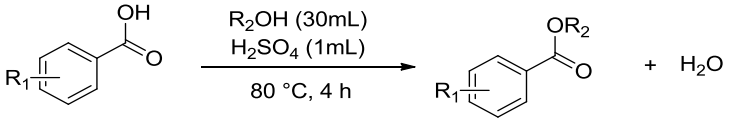
2C.9: Conclusion

1. We have developed a ruthenium-catalyzed highly regioselective *ortho*-alkenylation of aromatic and Heteroaromatic esters with alkenes giving substituted alkene derivatives in a highly stereoselective manner.
2. The amount of $Cu(OAc)_2$ was reduced to catalytic amount by using air as a external oxidant.

2C.10: Experimental Section

Preparation of Aromatic Esters:

A one-neck 100 mL round bottom flask, substituted aromatic acid (1.0 gm), an alcohol (30 mL) and 1.0 mL (1.84 g) conc. sulfuric acid were taken. The sulfuric acid should be added dropwise with swirling. The reaction mixture was refluxed at 80 °C for 4 h. During the reflux period the solution may turn cloudy and a second layer may form. If it does, this is our product. Not all the reaction mixtures will form two layers. Some mixtures will be colorless, others will be yellow or even dark brown. After the reaction, reaction mixture was allowed to cool to room temperature. Later, the reaction mixture was diluted with H_2O (75 mL) and extracted with EtOAc (3 x 75 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under vacuum as eluent to give pure corresponding aromatic ester.[18]



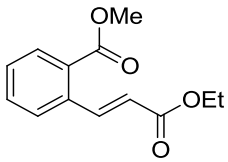
Scheme 2.23: Preparation or aromatic esters

General Procedure for the Coupling of Aromatic and Heteroaromatic Esters with Alkenes Catalyzed by Ruthenium Complex:

$[RuCl_2(p\text{-cymene})]_2$ (0.03 mmol, 3 mol-%), $AgSbF_6$ (0.20 mmol, 20 mol-%), and $Cu(OAc)_2 \cdot H_2O$ (0.30 mmol, 30 mol-%) were added to a 15 mL pressure tube, which was equipped with a magnetic stirrer and septum. (***Note:*** $AgSbF_6$ is moisture-sensitive. Thus, $AgSbF_6$ was handled inside a nitrogen glove box.) To the tube were added by syringe carbamate **1** (1.0 equiv.), alkene **2** (3.0 equiv.), and THF or 1,2-dichloroethane (4.0 mL) as the solvent, and the reaction mixture was allowed to stir at room temperature for 5 min. During this time, the tube was covered with a septum. Then, the septum was removed, and the reaction mixture was stirred under open air for an additional 5 min. [***Note:*** During this time, the nitrogen gas that was initially in the pressure tube dispersed, and air entered the tube. In the reaction, only 30 mol % of $Cu(OAc)_2 \cdot H_2O$ was used for the internal oxidant. In fact, 2.20 equiv. of $Cu(OAc)_2 \cdot H_2O$ was needed for the reaction. It is strongly believed that the remaining amount of $Cu(OAc)_2 \cdot H_2O$ necessary for the reaction was regenerated under oxygen or air from the reduced copper source CuOAc. Therefore, we conducted the reaction under open air.] Next, the pressure tube was sealed with a screw cap, and the reaction mixture was stirred at 100 °C for 12 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 and then filtered through Celite and silica gel. The filtrate was concentrated, and the crude residue was purified through a silica gel column (hexanes and ethyl acetate) to give pure **3**.

2C.11: Spectral Data of Compounds

(*E*)-Methyl 2-(3-ethoxy-3-oxoprop-1-en-1-yl)benzoate (**3a**).



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

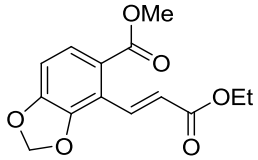
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2975, 1715, 1633, 1266 and 725.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.41 (d, *J* = 16.0 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 6.28 (d, *J* = 16.0 Hz, 1 H), 4.27 (q, *J* = 8.0 Hz, 2 H), 3.92 (s, 3 H), 1.32 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 166.7, 143.7, 136.5, 132.4, 130.9, 129.9, 129.4, 128.0, 121.2, 60.7, 52.5, 14.4.

HRMS (ESI): calc. for $[(C_{13}H_{14}O_4)Na]$ (M+Na) 257.0790, measured 257.0785.

(*E*)-Methyl 4-(3-ethoxy-3-oxoprop-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate (**3b**).



Colorless semisolid; eluent (20% ethyl acetate in hexanes).

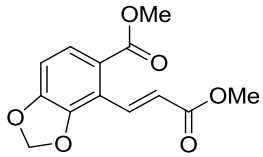
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956, 1716, 1630, 1266 and 777.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (d, *J* = 16.0 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.70 (d, *J* = 16.0 Hz, 1 H), 6.09 (s, 2 H), 4.24 (q, *J* = 8.0 Hz, 2 H), 3.86 (s, 3 H), 1.31 (d, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 166.9, 150.9, 147.3, 137.4, 126.6, 124.1, 123.9, 118.3, 108.3, 102.2, 60.61, 52.4, 14.4.

HRMS (ESI): calc. for [($C_{14}H_{14}O_6$)Na] (M+Na) 301.0688, measured 301.0684.

(*E*)-Methyl 4-(3-methoxy-3-oxoprop-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate (**3c**).



Colorless semisolid; eluent (20% ethyl acetate in hexanes).

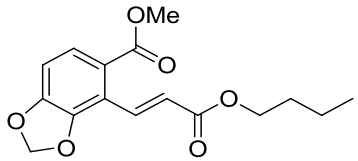
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2923, 1710, 1628, 1590, 1266 and 868.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (d, *J* = 16.0 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.68 (d, *J* = 16.0 Hz, 1 H), 6.08 (s, 2 H), 3.85 (s, 3 H), 3.77 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6, 166.8, 150.9, 147.4, 137.6, 126.6, 123.8, 123.6, 118.2, 108.3, 102.2, 52.4, 51.8.

HRMS (ESI): calc. for [($C_{13}H_{12}O_6$)Na] (M+Na) 287.0532, measured 287.0541.

(*E*)-Methyl 4-(3-butoxy-3-oxoprop-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate (**3d**).



Colorless semisolid; eluent (20% ethyl acetate in hexanes).

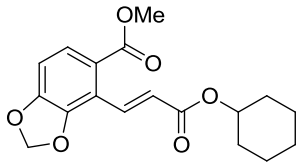
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2912, 1715, 1629, 1266 and 778.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (d, *J* = 16.0 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.65 (d, *J* = 16.0 Hz, 1 H), 6.09 (s, 2 H), 4.18 (t, *J* = 8.0 Hz, 2 H), 3.86 (s, 3 H), 1.68 – 1.66 (m, 2 H), 1.42 – 1.38 (m, 2 H), 0.93 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 166.9, 150.9, 147.3, 137.4, 126.6, 124.1, 124.0, 118.3, 108.3, 102.2, 64.5, 52.3, 30.8, 19.3, 13.8.

HRMS (ESI): calc. for [($C_{16}H_{18}O_6$)Na] (M+Na) 329.1001, measured 329.0995.

(*E*)-Methyl 4-(3-(cyclohexyloxy)-3-oxoprop-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate (**3e**).



Colorless semisolid; eluent (20% ethyl acetate in hexanes).

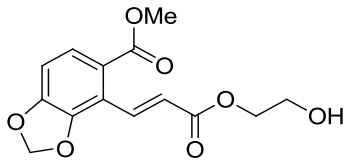
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2933, 1714, 1629, 1584, 1265 and 778.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25 (d, *J* = 16.0 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.69 (d, *J* = 16.0 Hz, 1 H), 6.09 (s, 2 H), 4.89 – 4.83 (m, 1 H), 3.86 (s, 3 H), 1.89 – 1.87 (m, 2 H), 1.75 – 1.72 (m, 2 H), 1.52 – 1.46 (m, 3 H), 1.41 – 1.35 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.9, 166.7, 150.8, 147.3, 137.1, 126.6, 124.6, 123.9, 118.3, 108.2, 102.2, 72.8, 52.3, 31.8, 25.5, 23.9.

HRMS (ESI): calc. for [($C_{18}H_{20}O_6$)Na] (M+Na) 355.1158, measured 355.1159.

(*E*)-Methyl 4-(3-(2-hydroxyethoxy)-3-oxoprop-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate (**3f**).



Colorless semisolid; eluent (30% ethyl acetate in hexanes).

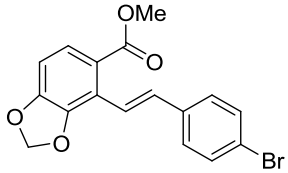
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3477, 2920, 1712, 1630, 1267 and 776.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, *J* = 16.0 Hz, 1 H), 7.52 (d, *J* = 8.0 Hz, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.70 (d, *J* = 16.0 Hz, 1 H), 6.07 (s, 2 H), 4.31 (t, *J* = 4.0 Hz, 2 H), 3.86 (d, *J* = 4.0 Hz, 2 H), 3.84 (s, 3 H), 2.71 (bs, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 166.8, 150.9, 147.4, 138.1, 126.7, 123.6, 123.3, 118.0, 108.4, 102.3, 66.4, 61.3, 52.4.

HRMS (ESI): calc. for [($C_{14}H_{14}O_7$)Na] (M+Na) 317.0637, measured 317.0627.

(*E*)-Methyl 4-(4-bromostyryl)benzo[*d*][1,3]dioxole-5-carboxylate (**3g**).



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

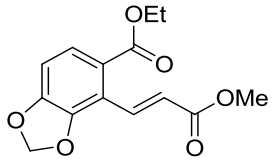
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972, 1715, 1598, 1480, 1293 and 1016.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (d, *J* = 16.0 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 7.41 (d, *J* = 16.0 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 6.72 (d, *J* = 8.0 Hz, 1 H), 6.10 (s, 2 H), 3.87 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 150.7, 146.0, 136.8, 133.6, 131.8, 128.3, 126.8, 122.7, 122.6, 121.8, 121.5, 106.7, 101.9, 52.2.

HRMS (ESI): calc. for [($C_{17}H_{13}BrO_4$)Na] (M+Na) 382.9895, measured 382.9899.

(*E*)-Ethyl 4-(3-methoxy-3-oxoprop-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate (**3h**).



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

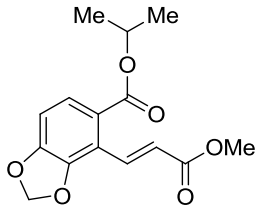
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2990, 1716, 1581, 1279, 819 and 769.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, *J* = 16.0 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 6.70 (d, *J* = 16.0 Hz, 1 H), 6.10 (s, 2 H), 4.32 (q, *J* = 8.0 Hz, 2 H), 3.78 (s, 3 H), 1.37 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 166.5, 150.8, 147.3, 137.8, 126.6, 124.3, 123.5, 118.2, 108.4, 102.2, 61.4, 51.9, 14.4.

HRMS (ESI): calc. for [($C_{14}H_{14}O_6$)Na] (M+Na) 301.0688, measured 301.0685.

(*E*)-Isopropyl 4-(3-methoxy-3-oxoprop-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate (**3i**).



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

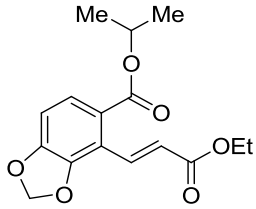
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2995, 1713, 1621, 1289 and 775.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (d, *J* = 16.0 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.66 (d, *J* = 16.0 Hz, 1 H), 6.07 (s, 2 H), 5.22 – 5.16 (m, 1 H), 3.76 (s, 3 H), 1.33 (s, 3 H), 1.32 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 166.0, 150.7, 147.3, 137.9, 126.4, 124.8, 123.2, 117.9, 108.3, 102.2, 69.0, 51.8, 21.9.

HRMS (ESI): calc. for [($C_{15}H_{16}O_6$)Na] (M+Na) 315.0845, measured 315.0840.

(*E*)-Isopropyl 4-(3-ethoxy-3-oxoprop-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate (**3j**).



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

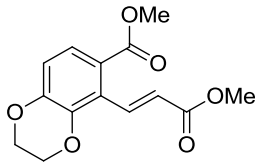
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 1711, 1630, 1260 and 779.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (d, *J* = 16.0 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.66 (d, *J* = 16.0 Hz, 1 H), 6.07 (s, 2 H), 5.23 – 5.16 (m, 1 H), 4.22 (q, *J* = 8.0 Hz, 2 H), 1.34 (s, 3 H), 1.32 (s, 3 H), 1.29 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 166.1, 150.6, 147.2, 137.7, 126.4, 124.9, 123.7, 117.9, 108.3, 102.1, 69.0, 60.6, 21.9, 14.4.

HRMS (ESI): calc. for [($C_{16}H_{18}O_6$)Na] (M+Na) 329.1001, measured 329.0988.

(*E*)-Methyl 5-(3-methoxy-3-oxoprop-1-en-1-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate (**3k**).



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

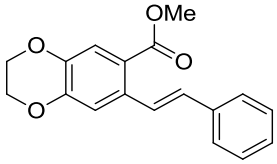
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 1710, 1582, 1272, 1179, 861 and 771.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, *J* = 16.0 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 4.25 (s, 4 H), 3.80 (s, 3 H), 3.74 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 167.2, 146.9, 142.7, 138.6, 125.2, 124.1, 124.0, 123.9, 117.4, 64.2, 64.1, 52.3, 51.8.

HRMS (ESI): calc. for [($C_{14}H_{14}O_6$)Na] (M+Na) 301.0688, measured 301.0678.

(*E*)-Methyl 7-styryl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate (**3l**).



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

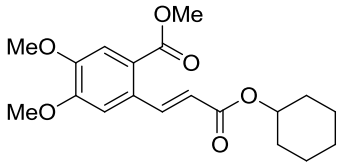
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 1706 and 1270.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 16.0 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.51 (s, 1 H), 7.33 (t, *J* = 8.0 Hz, 2 H), 7.25 (t, *J* = 8.0 Hz, 1 H), 7.19 (s, 1 H), 6.87 (d, *J* = 16.0 Hz, 1 H), 4.31 – 4.27 (m, 4 H), 3.87 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 147.0, 142.6, 137.7, 134.2, 130.2, 128.7, 127.7, 127.2, 126.8, 121.6, 120.2, 115.4, 64.8, 64.4, 52.1.

HRMS (ESI): calc. for [($C_{18}H_{16}O_4$)Na] (M+Na) 319.0946, measured 319.0948.

(*E*)-Methyl 2-(3-(cyclohexyloxy)-3-oxoprop-1-en-1-yl)-4,5-dimethoxybenzoate (**3m**).



Colorless semisolid; eluent (20% ethyl acetate in hexanes).

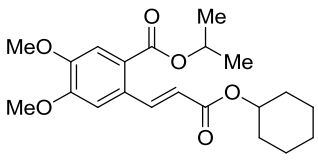
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2938, 2855, 1711, 1597, 1274, 862 and 752.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.46 (d, *J* = 16.0 Hz, 1 H), 7.44 (s, 1 H), 7.02 (s, 1 H), 6.22 (d, *J* = 16.0 Hz, 1 H), 4.90 – 4.84 (m, 1 H), 3.93 (s, 3 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 1.92 – 1.87 (m, 2 H), 1.76 – 1.73 (m, 2 H), 1.55 – 1.42 (m, 3 H), 1.39 – 1.24 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.9, 166.3, 151.9, 149.6, 143.4, 130.5, 125.6, 120.3, 113.1, 109.7, 72.8, 56.2, 56.1, 52.4, 31.8, 25.5, 23.9.

HRMS (ESI): calc. for [($C_{19}H_{24}O_6$)Na] (M+Na) 371.1471, measured 371.1462.

(*E*)-Isopropyl 2-(3-(cyclohexyloxy)-3-oxoprop-1-en-1-yl)-4,5-dimethoxybenzoate (**3n**).



Colorless semisolid; eluent (20% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2948, 1710, 1601, 1279 and 755.

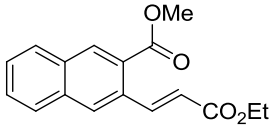
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.42 (d, *J* = 16.0 Hz, 1 H), 7.42 (s, 1 H), 7.01 (s, 1 H), 6.20 (d, *J* = 16.0 Hz, 1 H), 5.27 – 5.21 (m, 1 H), 4.89 – 4.83 (m, 1 H), 3.93 (s, 3 H), 3.92

(s, 3 H), 1.93 – 1.90 (m, 2 H), 1.77 – 1.72 (m, 2 H), 1.54 – 1.41 (m, 3 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.35 – 1.27 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4, 166.3, 151.7, 149.7, 143.7, 129.9, 123.7, 119.9, 113.1, 109.6, 72.9, 69.3, 56.2, 31.9, 25.5, 24.0, 22.1.

HRMS (ESI): calc. for [($C_{21}H_{28}O_6$)Na] (M+Na) 399.1784, measured 399.1778.

(*E*)-Methyl 3-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-naphthoate (**3o**).



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

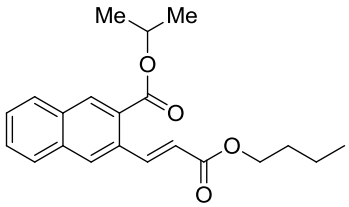
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 1717, 1632, 1276, 863 and 755.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (d, *J* = 16.0 Hz, 1 H), 8.50 (s, 1 H), 8.00 (s, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.58 (t, *J* = 8.0 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 6.38 (d, *J* = 16.0 Hz, 1 H), 4.28 (q, *J* = 8.0 Hz, 2 H), 3.96 (s, 3 H), 1.34 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 166.8, 144.5, 134.7, 132.9, 132.7, 132.4, 128.9, 128.8, 128.2, 127.9, 127.7, 120.7, 60.6, 52.6, 14.5.

HRMS (ESI): calc. for [($C_{17}H_{16}O_4$)Na] (M+Na) 307.0946, measured 307.0950.

(*E*)-Isopropyl 3-(3-butoxy-3-oxoprop-1-en-1-yl)-2-naphthoate (**3p**).



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

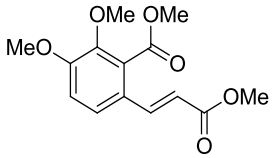
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2963, 1715, 1634, 1270 and 750.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.46 (d, *J* = 16.0 Hz, 1 H), 8.45 (s, 1 H), 7.99 (s, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 7.52 (d, *J* = 8.0 Hz, 1 H), 6.37 (d, *J* = 16.0 Hz, 1 H), 5.34 – 5.28 (m, 1 H), 4.22 (t, *J* = 8.0 Hz, 2 H), 1.72 – 1.65 (m, 2 H), 1.46 – 1.43 (m, 2 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 0.95 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.9, 166.6, 144.7, 134.5, 132.7, 132.6, 132.1, 128.9, 128.7, 128.1, 127.8, 127.6, 120.3, 69.3, 64.5, 30.9, 22.1, 19.3, 13.9.

HRMS (ESI): calc. for [($C_{21}H_{24}O_4$)Na] (M+Na) 363.1572, measured 363.1562.

(*E*)-Methyl 2,3-dimethoxy-6-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate (**3q**).



Colorless semisolid; eluent (20% ethyl acetate in hexanes).

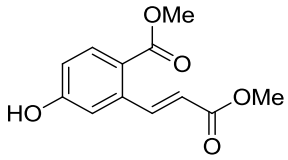
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958, 1714, 1605, 1269 and 765.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (d, *J* = 16.0 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 6.26 (d, *J* = 16.0 Hz, 1 H), 3.94 (s, 3 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.75 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 167.2, 154.1, 146.2, 140.9, 129.9, 124.7, 123.2, 118.5, 113.6, 61.7, 56.1, 52.8, 51.8.

HRMS (ESI): calc. for [($C_{14}H_{16}O_6$)Na] (M+Na) 303.0845, measured 303.0836.

(*E*)-Methyl 4-hydroxy-2-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate (**3r**).



Colorless semisolid; eluent (20% ethyl acetate in hexanes).

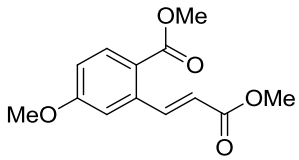
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3356, 2951, 1707, 1601, 1284 and 774.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.50 (d, *J* = 16.0 Hz, 1 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.01 (s, 1 H), 6.89 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.83 (bs, 1 H), 6.22 (d, *J* = 16.0 Hz, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 167.0, 159.7, 144.9, 139.1, 133.5, 132.0, 120.6, 116.6, 114.8, 52.3, 52.2.

HRMS (ESI): calc. for [($C_{12}H_{12}O_5$)Na] (M+Na) 259.0582, measured 259.0579.

(*E*)-Methyl 4-methoxy-2-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate (**3s**).



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

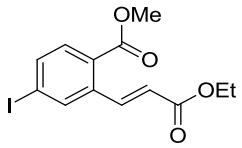
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2949, 1716, 1637, 1272, 861 and 777.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.48 (d, *J* = 16.0 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H), 7.00 (s, 1 H), 6.90 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.24 (d, *J* = 16.0 Hz, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.79 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.1, 166.8, 162.6, 144.6, 139.1, 133.2, 121.8, 120.9, 114.7, 113.2, 55.6, 52.2, 51.9.

HRMS (ESI): calc. for [($C_{13}H_{14}O_5$)Na] (M+Na) 273.0739, measured 273.0734.

(*E*)-Methyl 2-(3-ethoxy-3-oxoprop-1-en-1-yl)-4-iodobenzoate (**3t**).



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

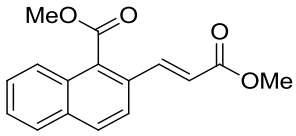
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3420, 2924, 1721, 1684, 1242, 850 and 771.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (d, *J* = 16.0 Hz, 1 H), 7.91 (s, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 6.25 (d, *J* = 16.0 Hz, 1 H), 4.24 (q, *J* = 8.0 Hz, 2 H), 3.89 (s, 3 H), 1.31 (d, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 166.3, 142.3, 138.4, 138.3, 136.9, 132.3, 128.9, 122.3, 60.8, 52.7, 14.4.

HRMS (ESI): calc. for [($C_{13}H_{13}IO_4$)Na] (M+Na) 382.9756, measured 382.9757.

(*E*)-Methyl 2-(3-methoxy-3-oxoprop-1-en-1-yl)-1-naphthoate (**3u**).



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

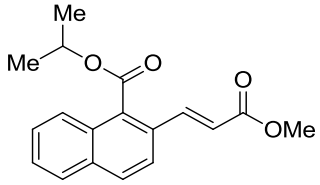
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950, 1722, 1635, 1223, 821 and 755.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* = 16.0 Hz, 1 H), 7.86 – 7.83 (m, 3 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.55 - 7.52 (m, 2 H), 6.52 (d, *J* = 16.0 Hz, 1 H), 4.09 (s, 3 H), 3.81 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.1, 167.0, 141.6, 133.9, 132.7, 130.5, 129.9, 129.7, 128.3, 127.9, 127.6, 125.8, 122.7, 120.9, 52.9, 51.9.

HRMS (ESI): calc. for [($C_{16}H_{14}O_4$)Na] (M+Na) 293.0790, measured 293.0793.

(*E*)-Isopropyl 2-(3-methoxy-3-oxoprop-1-en-1-yl)-1-naphthoate (**3v**).



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

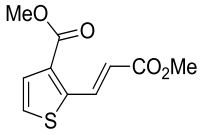
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 1720, 1633, 1220, 815 and 765.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, *J* = 16.0 Hz, 1 H), 7.91 – 7.81 (m, 3 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.55 - 7.51 (m, 2 H), 6.51 (d, *J* = 16.0 Hz, 1 H), 5.55 – 5.49 (m, 1 H), 3.80 (s, 3 H), 1.48 (s, 3 H), 1.46 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 167.0, 141.7, 133.9, 133.2, 130.2, 129.8, 129.3, 128.3, 127.8, 127.6, 125.6, 122.6, 120.5, 70.1, 51.9, 22.1.

HRMS (ESI): calc. for [($C_{18}H_{18}O_4$)Na] (M+Na) 321.1103, measured 321.1099.

(*E*)-Methyl 2-(3-methoxy-3-oxoprop-1-en-1-yl)thiophene-3-carboxylate (**3w**).



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

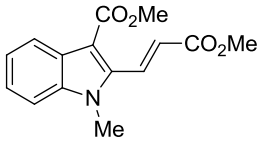
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3107, 2951, 1728, 1624, 1154, 862 and 719.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.54 (d, *J* = 16.0 Hz, 1 H), 7.39 (d, *J* = 4.0 Hz, 1 H), 7.19 (d, *J* = 4.0 Hz, 1 H), 6.28 (d, *J* = 16.0 Hz, 1 H), 3.83 (s, 3 H), 3.73 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.6, 163.2, 145.0, 135.9, 131.9, 130.6, 126.0, 120.0, 52.1, 51.9.

HRMS (ESI): calc. for [($C_{10}H_{10}O_4S$)Na] (M+Na) 249.0197, measured 249.0204.

(*E*)-Methyl 2-(3-methoxy-3-oxoprop-1-en-1-yl)-1-methyl-1*H*-indole-3-carboxylate (**3x**).



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

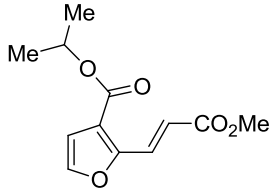
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922, 1718, 1590, 1275 and 753.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45 (d, *J* = 16.0 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 7.28 – 7.25 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 4.02 (s, 3 H), 4.01 (s, 3 H), 3.82 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 162.5, 139.2, 138.4, 128.7, 125.8, 124.6, 122.3, 122.2, 118.2, 117.4, 110.9, 52.4, 51.7, 32.5.

HRMS (ESI): calc. for [($C_{15}H_{15}O_4N$)Na] (M+Na) 296.0899, measured 296.0897.

(*E*)-Isopropyl 2-(3-methoxy-3-oxoprop-1-en-1-yl)furan-3-carboxylate (**3y**).



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

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 1718, 1640, 1263, 830 and 753.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, *J* = 16.0 Hz, 1 H), 7.37 (d, *J* = 4.0 Hz, 1 H), 7.35 (d, *J* = 4.0 Hz, 1 H), 6.47 (d, *J* = 16.0 Hz, 1 H), 5.19 – 5.13 (m, 1 H), 3.76 (s, 3 H), 1.32 (s, 3 H), 1.31 (s, 3 H).

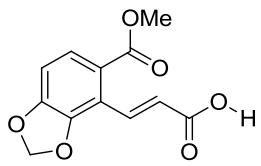
^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.9, 162.2, 153.3, 143.7, 129.9, 120.1, 119.9, 112.8, 68.7, 51.9, 21.9.

HRMS (ESI): calc. for [($C_{12}H_{14}O_5$)Na] (M+Na) 261.0739, measured 261.0737.

General Procedure for De-esterfication Reaction (4a-4b):

A two-neck 50 mL round bottom flask fitted with a condenser containing a mixture of **3a** or **3b** (100 mg) and LiOH (1.0 equiv) in 6 mL of THF/MeOH/H_2O (4:1:l). The reaction mixture was refluxed at 80 °C for 12 h. After the reaction, reaction mixture was allowed to cool to room temperature and the reaction mixture was neutralised (pH = 6) using 1N HCl. The product was extracted with ethyl acetate, washed with water and brine. The extract was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **4**.

(*E*)-3-(5-(Methoxycarbonyl)benzo[*d*][1,3]dioxol-4-yl)acrylic acid (**4a**).



Colorless powder; eluent (75% ethyl acetate in hexanes).

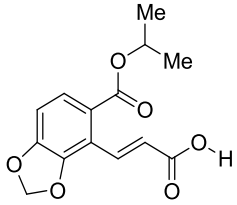
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3013, 2950, 1706, 1685 and 1421.

^{1}H NMR (*d*-MeOH, 400 MHz): δ 8.25 (d, *J* = 16.0 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 6.69 (d, *J* = 16.0 Hz, 1 H), 6.15 (s, 2 H), 3.85 (s, 3 H).

^{13}C NMR (*d*-MeOH, 100 MHz): δ 167.0, 151.2, 147.5, 137.4, 126.3, 123.6, 117.8, 107.9, 102.5, 58.5.

HRMS (ESI): calc. for [($C_{12}H_{10}O_6$)Na] (M+Na) 273.0375, measured 273.0374.

(*E*)-3-(5-(Isopropoxycarbonyl)benzo[*d*][1,3]dioxol-4-yl)acrylic acid (**4b**).



Colorless semisolid; eluent (75% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3017, 1710, 1682, 1421 and 825.

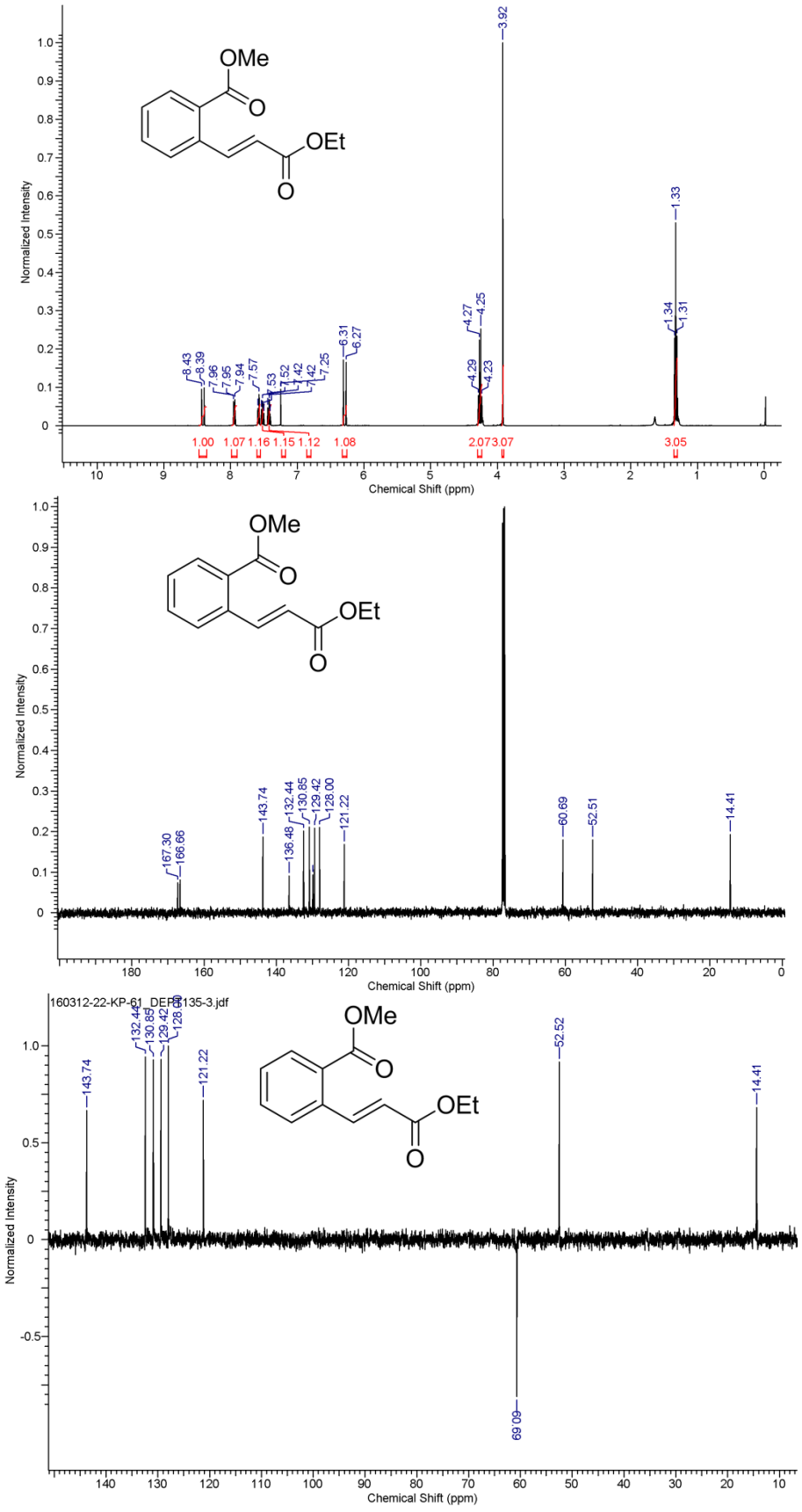
^{1}H NMR (*d*-DMSO, 400 MHz): δ 8.39 (d, *J* = 16.0 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.71 (d, *J* = 16.0 Hz, 1 H), 6.11 (s, 2 H), 5.25 – 5.19 (m, 1 H), 1.36 (s, 3 H), 1.34 (s, 3 H).

^{13}C NMR (*d*-DMSO, 100 MHz): δ 172.7, 166.0, 150.7, 147.5, 139.8, 126.5, 124.9, 123.1, 117.7, 108.6, 102.3, 69.1, 21.9.

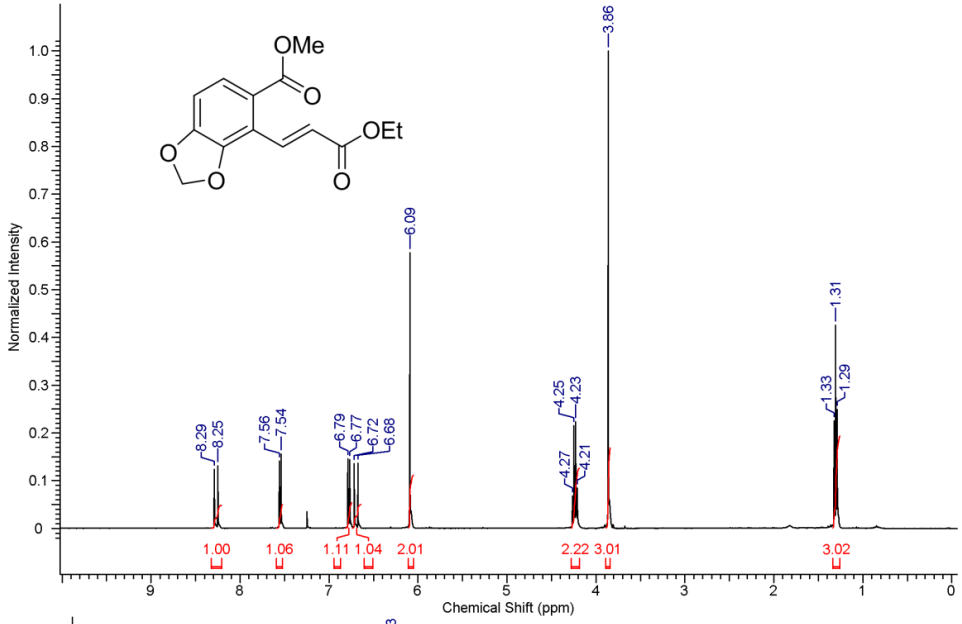
HRMS (ESI): calc. for [($C_{14}H_{14}O_6$)Na] (M+Na) 301.0688, measured 301.0696.

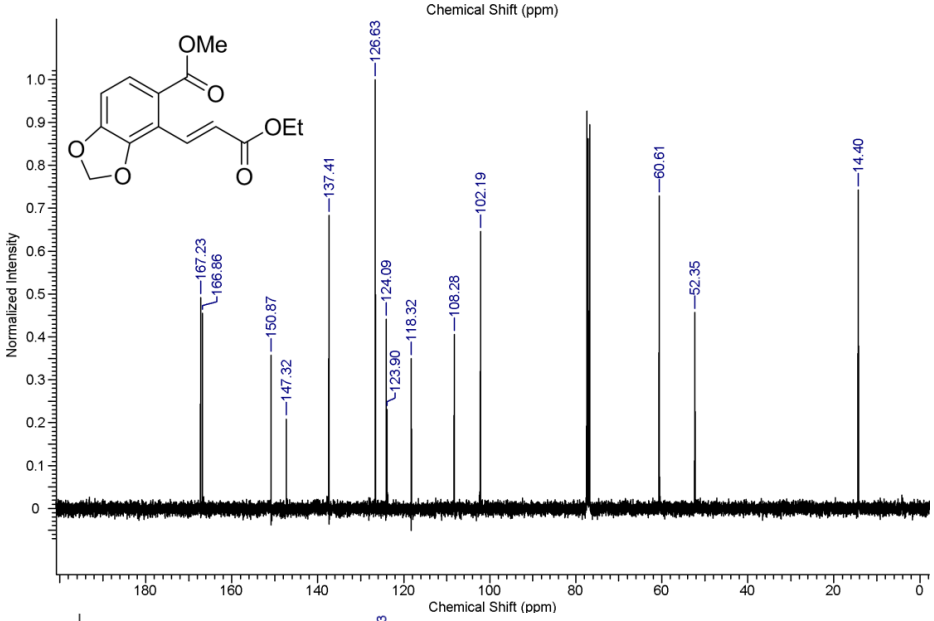
2C.12: Spectral Copies of Selected Compounds

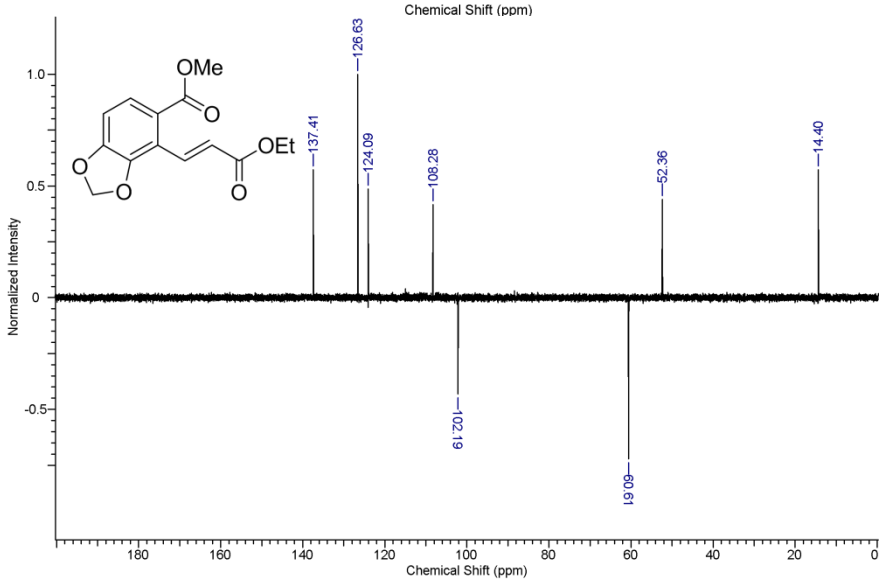
Spectral data of compound **3a**.



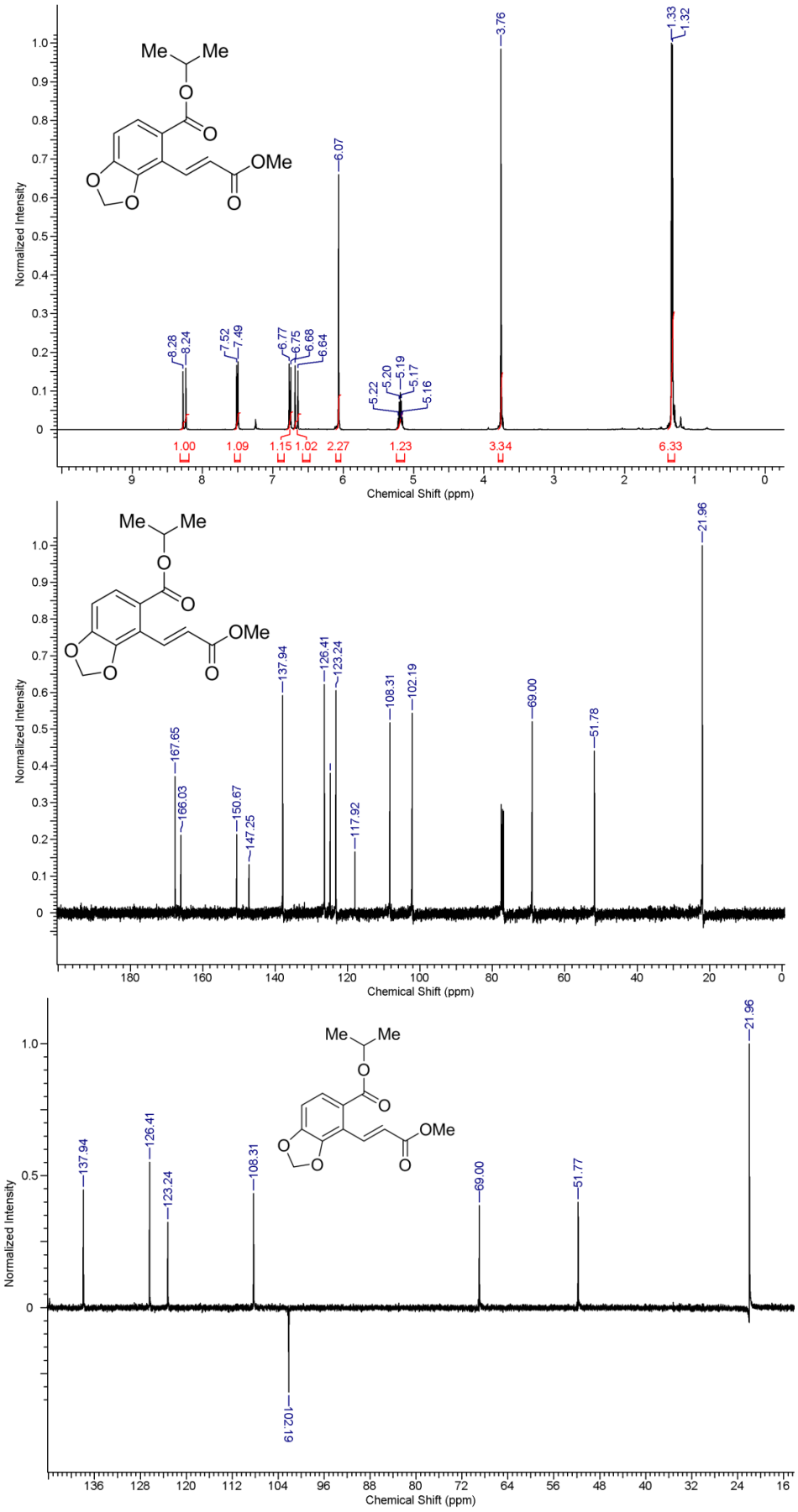
Spectral data of compound **3b**.



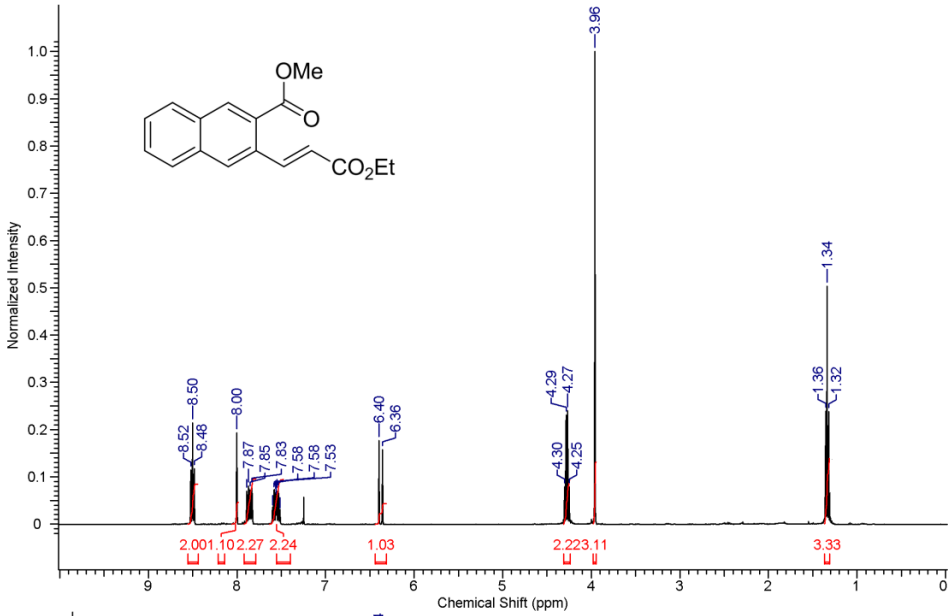


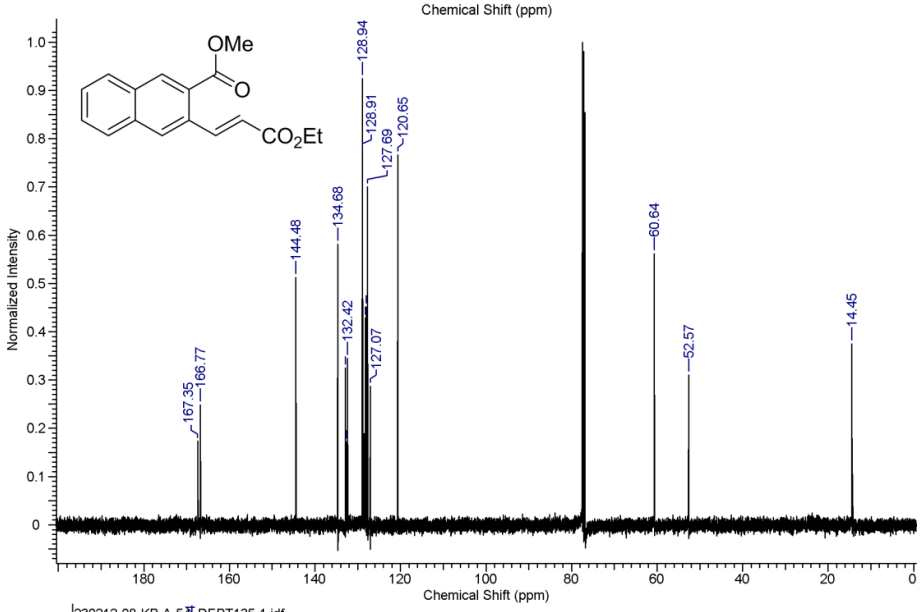


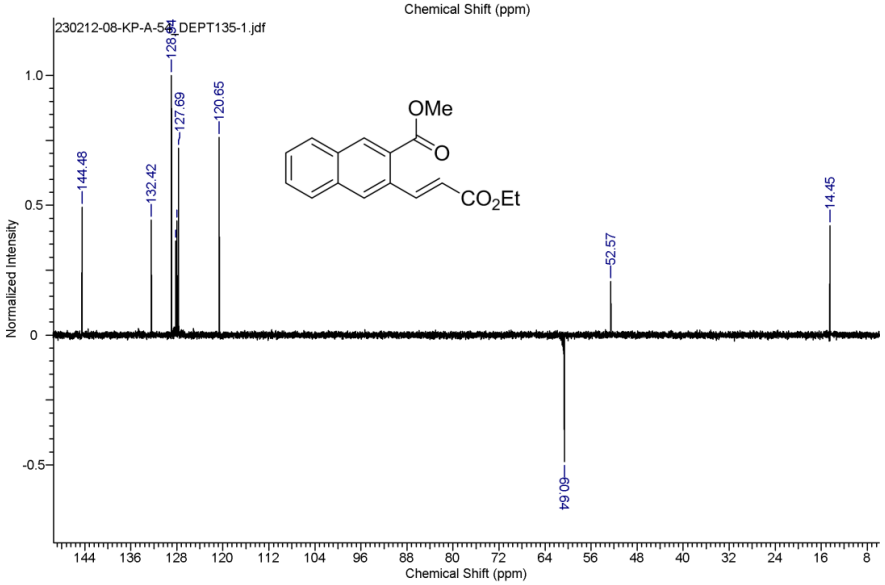
Spectral data of compound **3i**.



Spectral data of compound **3o**.







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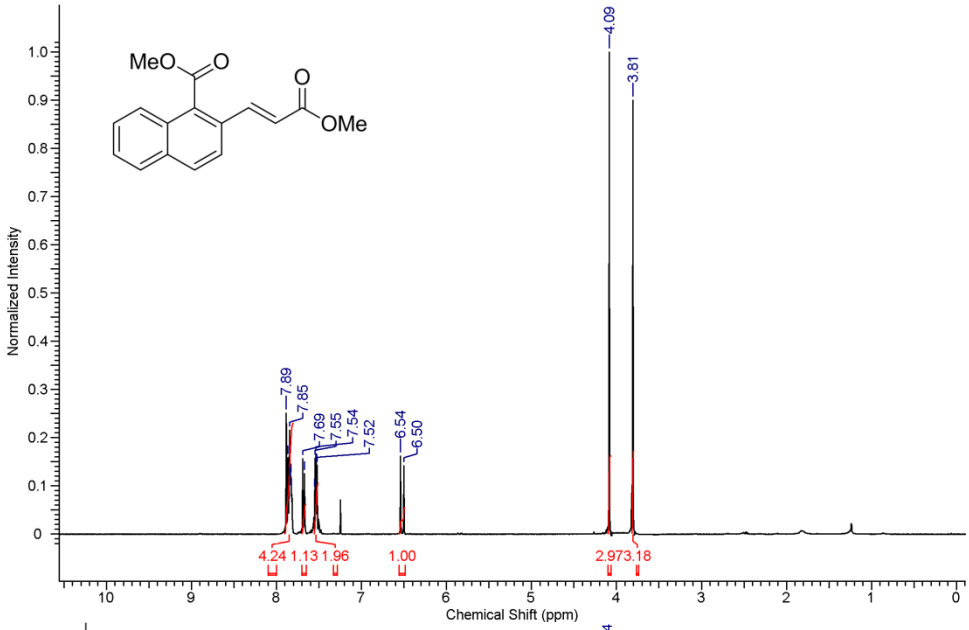

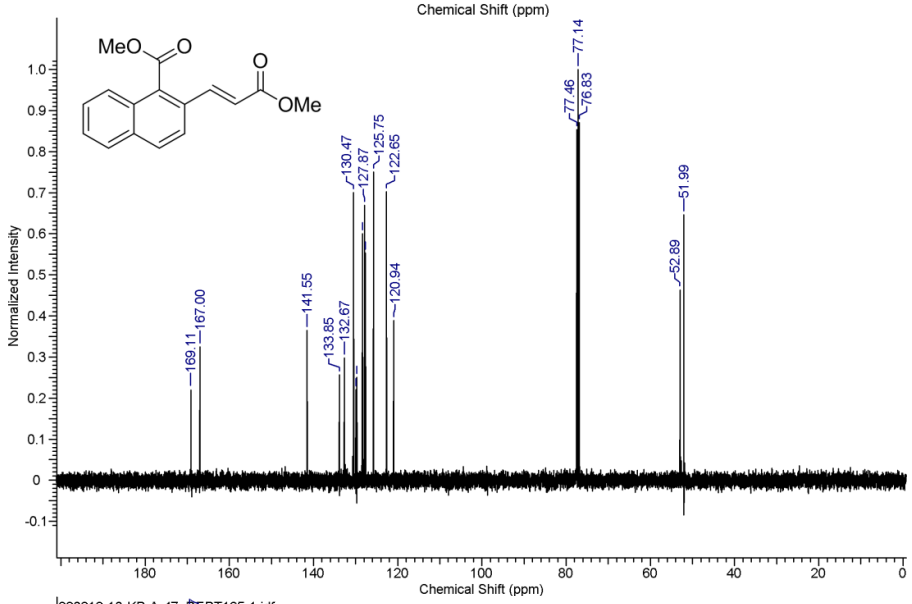

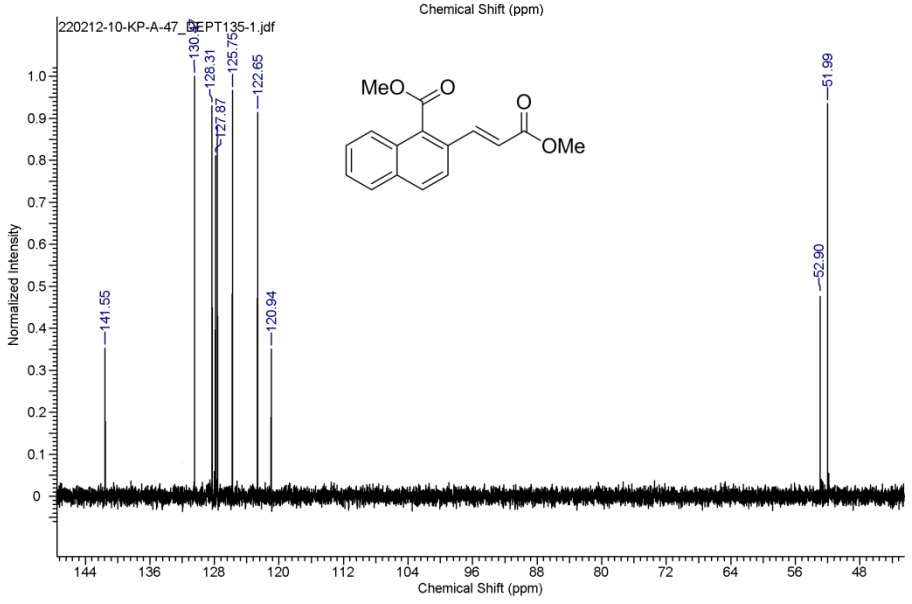

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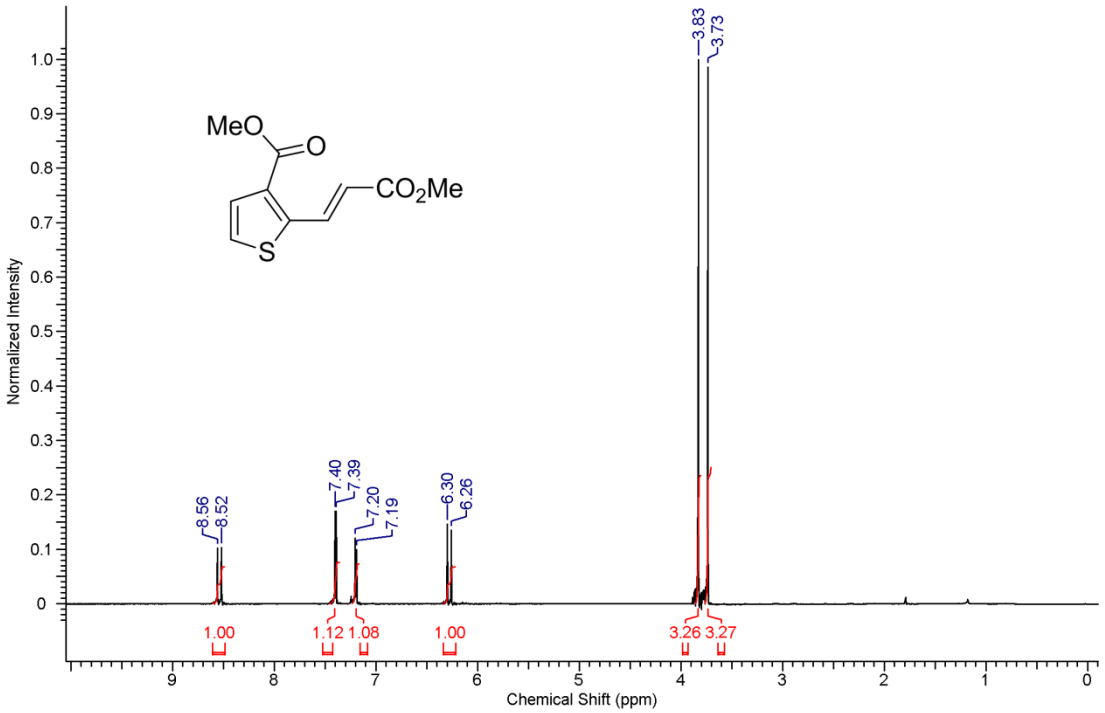

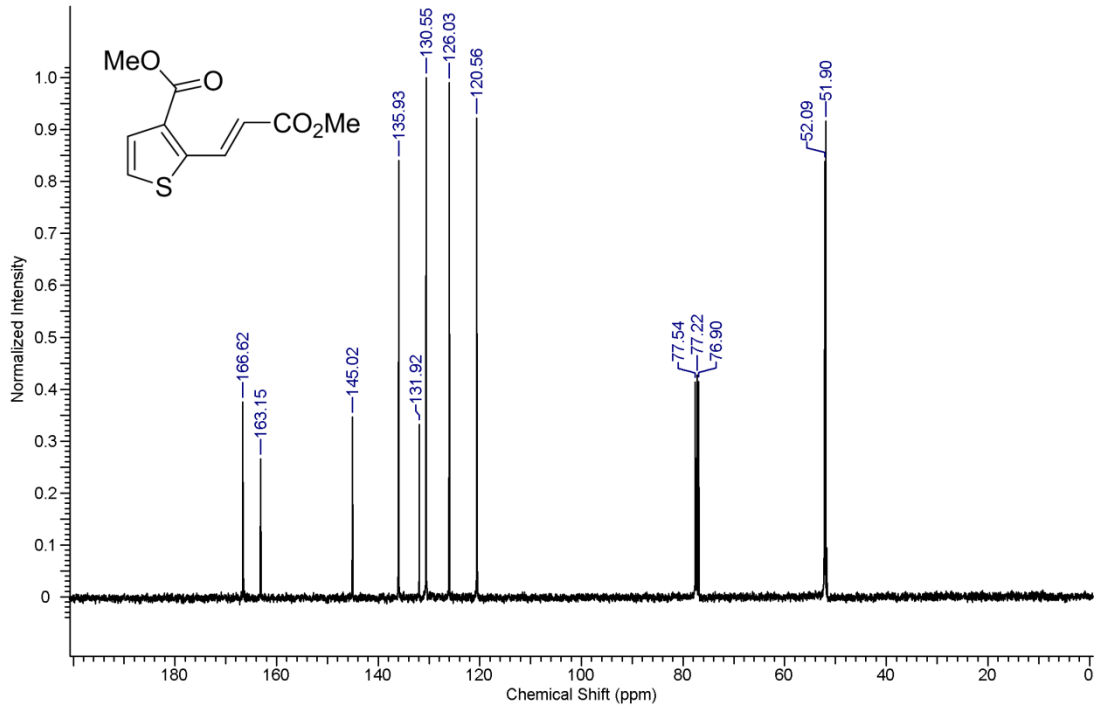

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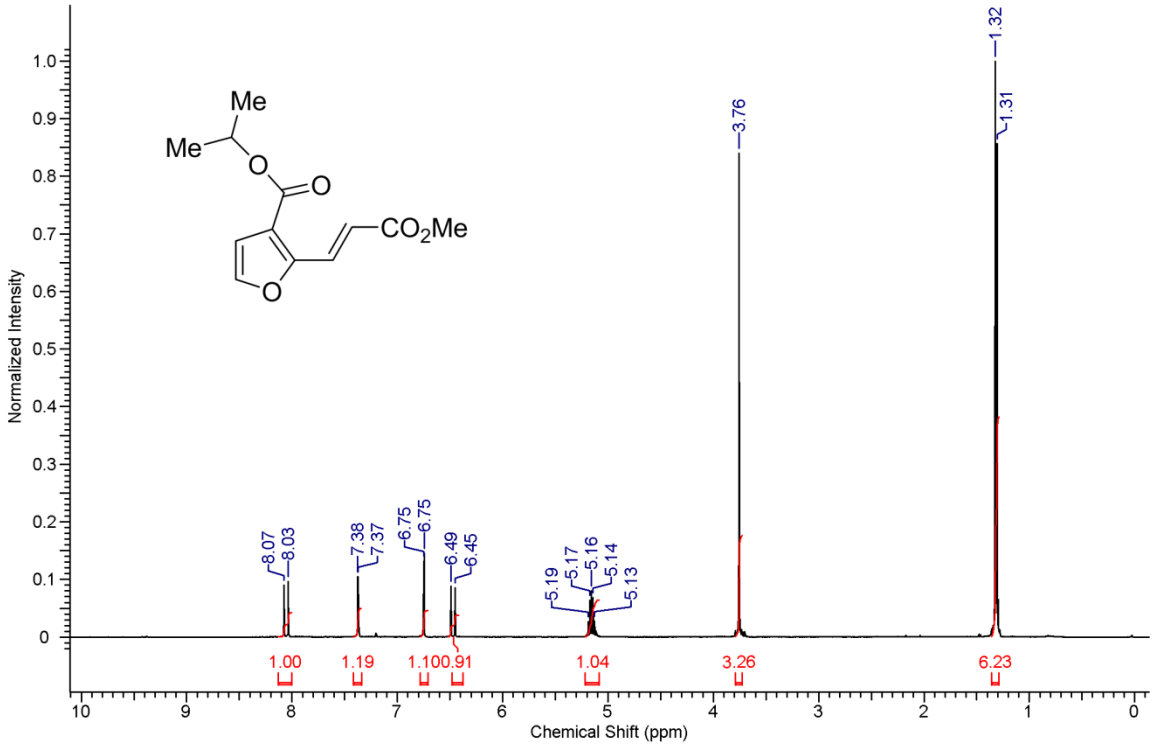

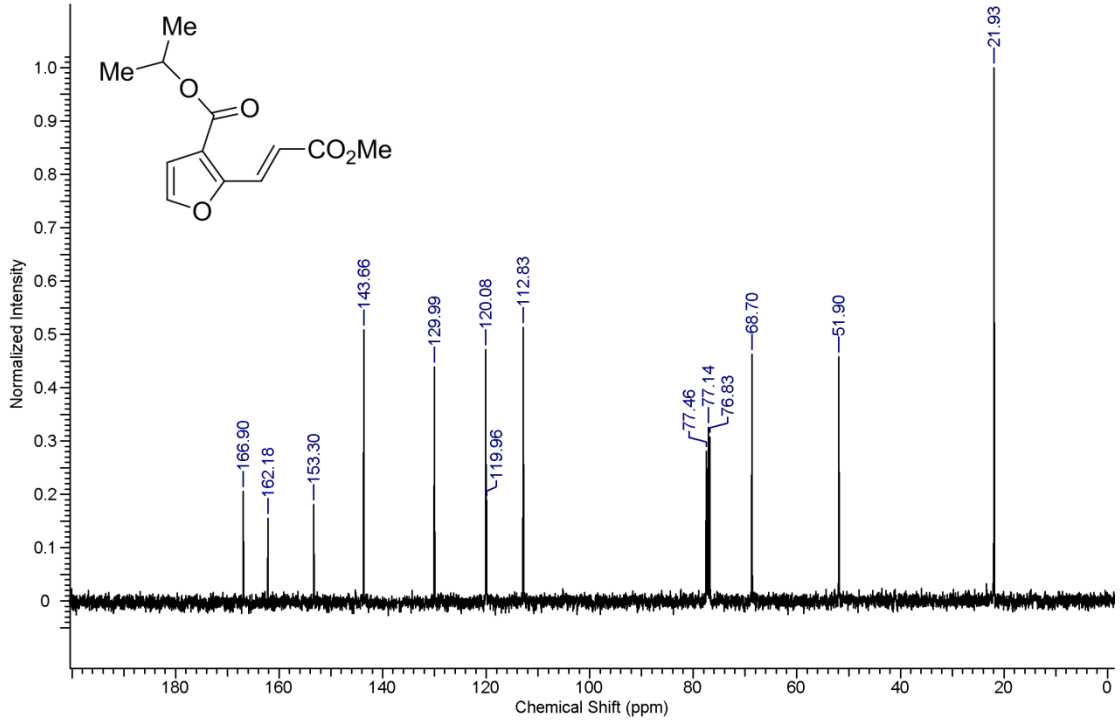

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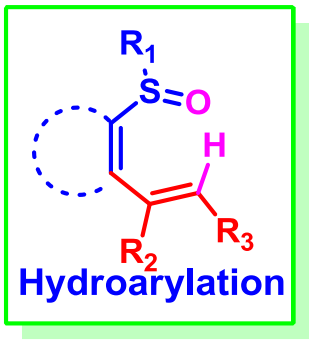
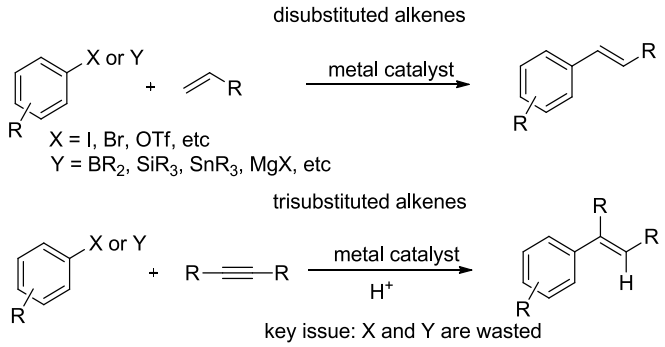
Chapter 3

Ru-Catalyzed Highly Regio- and Stereoselective Hydroarylation of Aromatic Sulfoxides with Alkynes



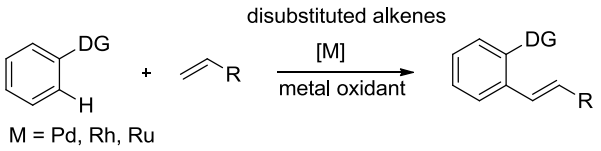
3.1: Introduction

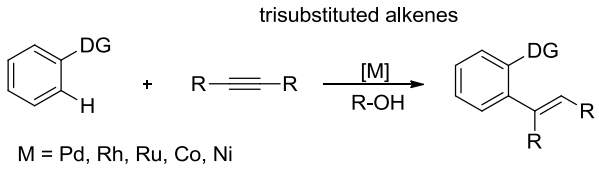
The alkene subunits are present in various natural products, drug molecules and materials. In addition, alkenes are versatile synthetic intermediates which are widely used for various organic transformations.[1] The transition metal-catalyzed coupling of aromatic electrophiles or organometallic reagents with carbon-carbon π-components is a powerful route to synthesize alkene derivatives in a highly regio- and stereoselective manner.



Scheme 3.1: Synthesis of alkenes by cross-coupling reaction

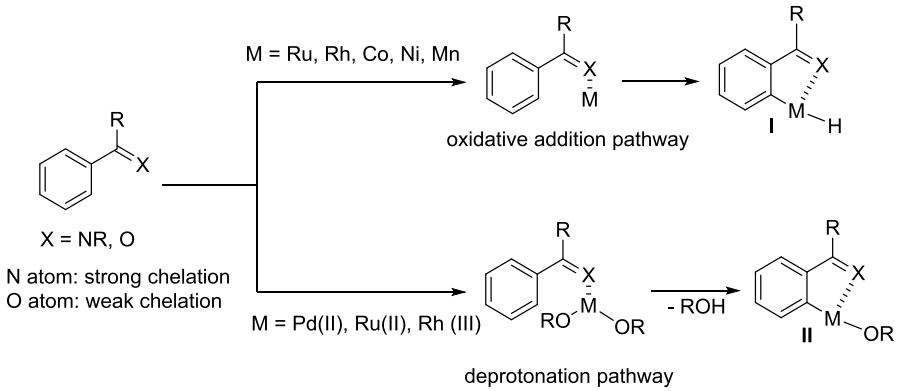
Alkenes and alkynes are widely used as carbon-carbon π-components in the coupling reaction. Usually, alkenes reacted with aromatic electrophiles or organometallic reagents in the presence of a metal catalyst, providing disubstituted alkenes (Scheme 3.1)[2] and alkynes reacted with aromatic electrophiles or organometallic reagents, affording trisubstituted alkenes (scheme 3.1).[3] Various metal complexes such as palladium, nickel, cobalt, rhodium, iron, etc are widely used as catalysts in this type of alkenylation reaction. Aromatic iodides, aromatic bromides and aromatic triflates are frequently used as electrophiles in the reaction. Similarly, aromatic organometallic reagents such as borane, silane, stannane and magnesium are used as a transmetallating agent. Although this type of coupling reaction is very powerful to synthesize substituted alkenes, a preactivated coupling partner such as a C-X or C-Y is usually required on the aromatic moiety. A preactivated species such as X or Y is wasted at end of the reaction. If a similar type of reaction is carried out directly by the C-H bond of aromatic moiety instead of with a C-X or C-M, 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.





Scheme 3.2: Synthesis of alkenes by C-H bond activation

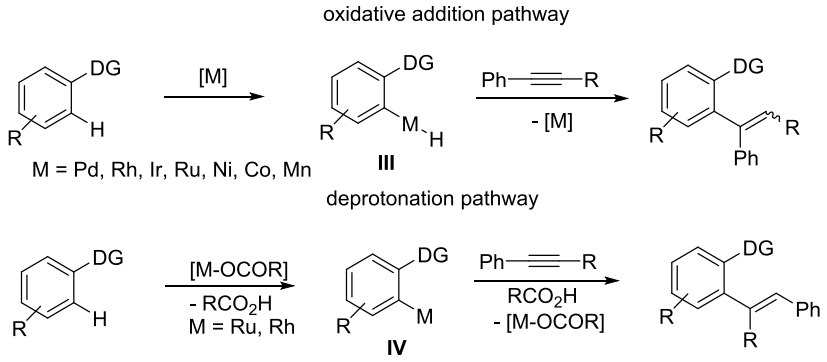
Alternatively, alkene derivatives can also be prepared by a metal-catalyzed chelation-assisted alkenylation at the C-H bond of substituted aromatics with carbon-carbon π-components via C-H bond activation without having any preactivated species on the aromatic moiety (Scheme 3.2).[4] There are several ways to activate the C-H bond of aromatics in the presence of metal catalysts.[5] However, doing the C-H bond activation in a controlled and regioselective manner is a challenging task. This type of regioselective C-H bond activation can be done by a chelation-assisted metalation pathway (Scheme 3.3). Usually, heteroatom such as nitrogen or oxygen containing directing group is needed on the aromatic moiety to activate the C-H bond in a highly regioselective manner. The heteroatom of directing group coordinates with a metal centre via either σ or π bond and allows bringing the *ortho* C-H bond of aromatics to close proximity to the active metal centre. During this time, the C-H bond activation takes place very selectively at the *ortho* position and providing a five membered metalacycle intermediate. There are two pathways such as oxidative addition and deprotonation possible to activate the C-H bond of organic moiety (Scheme 3.3). In the oxidative addition pathway, a five membered hydrometallacycle intermediate **I** is formed and in the deprotonation pathway, a five membered metallacycle intermediate without having a hydride species **II** is formed. It is important to note that in the deprotonation pathway; usually a carbonate or acetate base is required to deprotonate the C-H bond of organic moiety. In the oxidative addition pathway, a metal species undergoes an oxidative addition with a C-H bond of aromatic moiety and providing a hydrometallacycle intermediate **I**. Generally, M(0) or M(I) active catalysts favour oxidative addition pathway and $M(II)(OR)_2$ or $M(III)(OR)_2$ catalysts favours deprotonation pathway. In this context, metal-catalyzed chelation-assisted *ortho* alkenylation of substituted aromatics with alkenes is well explored in the literature.[4] But, an *ortho* alkenylation of substituted aromatics with alkynes has gained much attention quite recently.



Scheme 3.3: Metal-catalyzed chelation assisted C-H bond activation

In 1993, Murai's group reported a ruthenium-catalyzed chelation-assisted *ortho* alkylation of aromatic ketones with alkenes via C-H bond activation. In the reaction, aromatic ketones reacted with alkenes in the presence of $RuH_2(CO)(PPh_3)_3$, giving *ortho* alkylated aromatic ketones in a highly regioselective manner.[6*a*] The C-H bond activation reaction proceeds via an oxidative addition pathway. Later, the same group demonstrated an *ortho* alkenylation of aromatic ketones with alkynes, leading to trisubstituted alkenes in the presence of a ruthenium catalyst (Scheme 3).[6*b*] 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. For example, aromatic ketone reacted with symmetrical alkyne, diphenylacetylene, in the presence of a ruthenium catalyst, yielding a mixture of *cis* and *trans* stereoisomeric trisubstituted alkenes. If an unsymmetrical alkyne is used, a mixture of *cis* and *trans* stereoisomeric as well as regioisomeric trisubstituted alkenes were possible. Later, Murai's group has reported the hydroarylation of various directing groups such as ester, nitrile and aldehyde substituted aromatics with alkynes in the presence of a ruthenium catalyst.[6] Later, a similar type of hydroarylation of heteroatom substituted aromatics with alkynes has been well explored by using various metal complexes such as rhodium, iridium, palladium, nickel, cobalt and manganese complexes as catalysts. Although it is one of the best methods to synthesize trisubstituted alkenes in one pot, the observation of a mixture of *cis*

and *trans* stereoisomeric and regioisomeric products limits the synthetic application in organic synthesis.

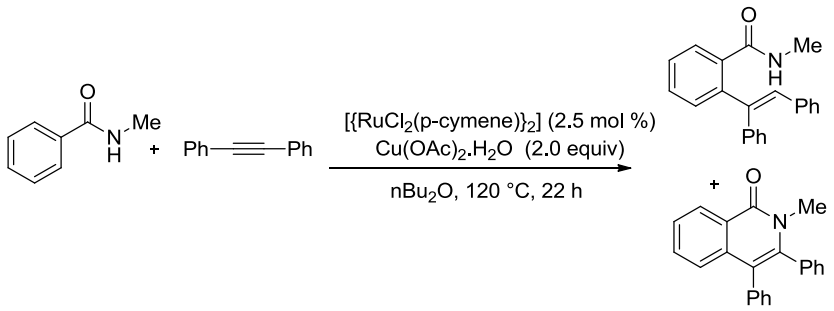


Scheme 3.4: Metal -catalyzed chelation assisted hydroarylation reaction

The recent observation clearly revealed that this type of regio- and stereoisomeric issues can be easily overcome by doing the hydroarylation reaction via a concerted deprotonation metalation pathway.[7] 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. Notably, the metal oxidant is not needed for the hydroarylation reaction unlike the *ortho*-alkenylation of aromatics with alkenes in the presence of metal catalysts. 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 (Fig. 4). The regiochemistry of product of this reaction is completely reversed when compared with the regiochemistry of product observed via an oxidative addition pathway. In the oxidative addition pathway, alkynes preferred to insert into Ru-H bond of intermediate **III** compared with Ru-C bond. In the deprotonation pathway, alkynes preferred to insert into Ru-C bond of metallacycle intermediate **IV**.

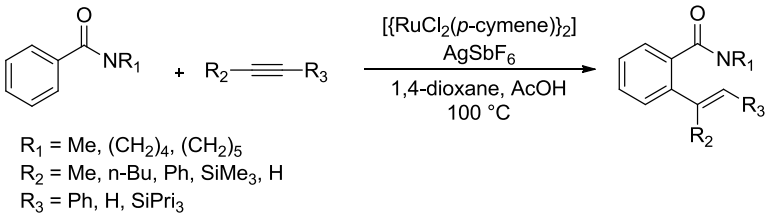
In 2011, Ackermann's group reported an oxidative cyclization of *N*-methyl benzamides with alkynes, providing substituted isoquinolone derivatives (Scheme 3.5).[8] In the reaction of *N*-methyl benzamide with diphenylacetylene in the presence of ruthenium catalyst and $Cu(OAc)_2 \cdot H_2O$ in ether solvent, a minor amount of *ortho* alkenylated benzamide was observed in 15% yield along with isoquinolone derivative in 27% yield,

respectively. This result clearly reveals that the *N*-methyl benzamides prefer cyclization reaction with alkynes rather than the hydroarylation reaction.



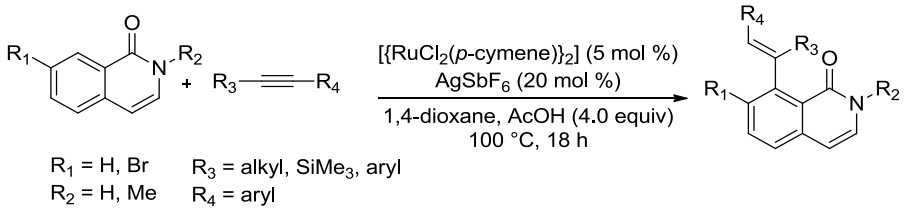
Scheme 3.5: The hydroarylation of *N*-methyl benzamide with diphenylacetylene

In 2012, Miura's group reported a highly regio- and stereoselective hydroarylation of substituted benzamides with alkynes, providing trisubstituted alkenes in a highly regio- and stereoselective manner (Scheme 3.6).[9]



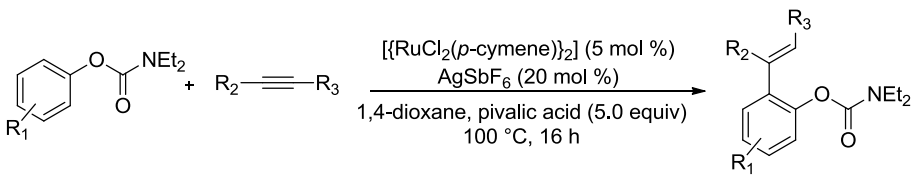
Scheme 3.6: Ruthenium-catalyzed hydroarylation of *N, N*-dialkyl benzamides with alkynes

In the same year, Li's group reported a ruthenium-catalyzed hydroarylation of isoquinolone derivatives with alkynes in the presence of acetic acid (Scheme 3.7).[10]



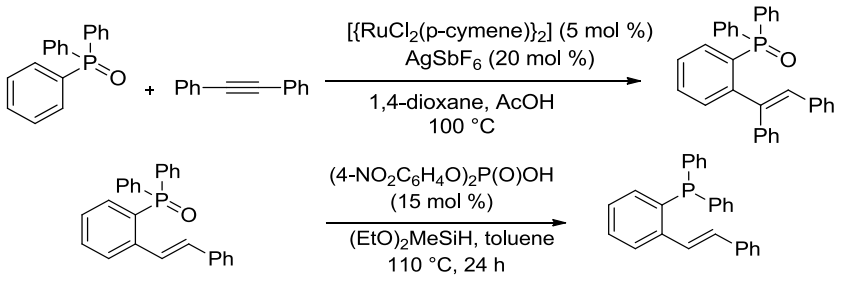
Scheme 3.7: The hydroarylation of isoquinolone derivatives with alkynes

In 2012, Jeganmohan and co workers reported a highly regio- and stereoselective weakly directing carbamate group assisted hydroarylation of aryl carbamates with alkynes in the presence of a ruthenium catalyst and pivalic acid (Scheme 3.8).[11]



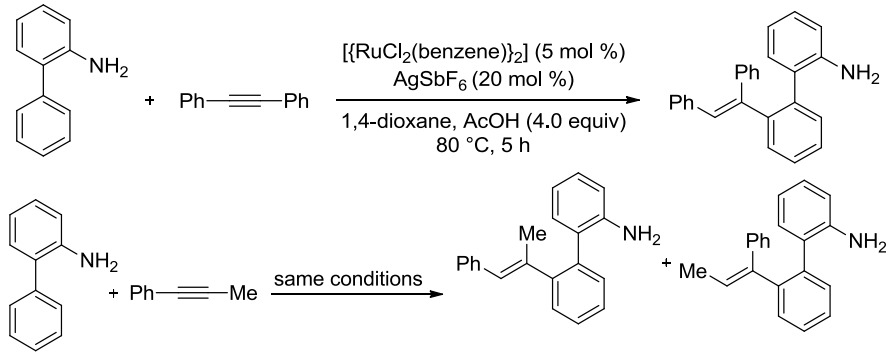
Scheme 3.8: The hydroarylation of aromatic carbamates with alkynes

In the same year, Miura's group demonstrated the hydroarylation of phenylphosphine oxides with alkynes in the presence of a ruthenium catalyst (Scheme 3.9).[12]



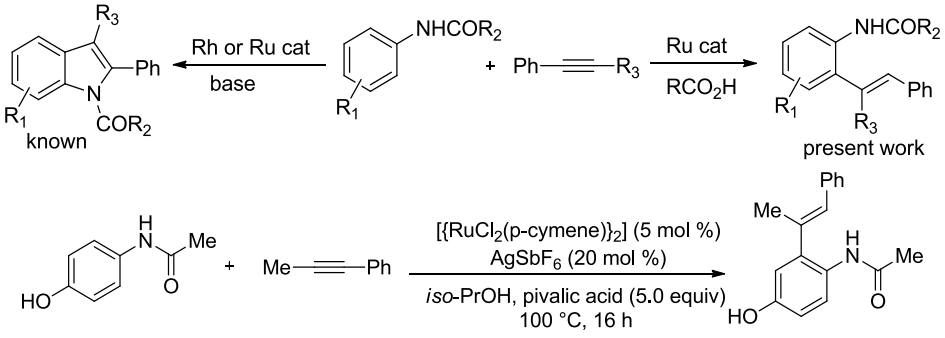
Scheme 3.9: The hydroarylation of phenylphosphine oxide with alkynes

In 2013, Miura's group reported a ruthenium-catalyzed hydroarylation of 2-aminobiphenyls or cumylamine with alkynes.[13] It is important to note that in the reaction a free NH_2 group acts as a directing group without any protection. Later, the reaction was examined with symmetrical and unsymmetrical alkynes. In the reaction of biphenyl aniline with 1-phenyl-1-propyne, a mixture of stereoisomeric products was observed (Scheme 3.10).



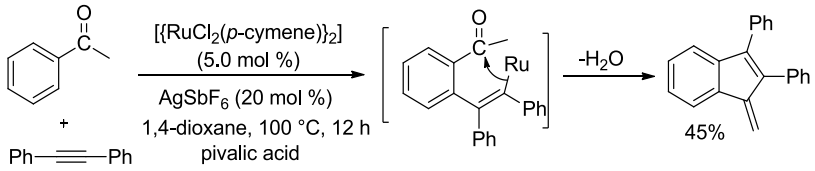
Scheme 3.10: The hydroarylation of 2-aminobiphenyls and cumylamine with alkynes

In 2014, Jeganmohan group reported a ruthenium-catalyzed hydroarylation of acetanilides with alkynes.[14] The catalytic reaction provides *ortho*-alkenylated anilides in good to excellent yields in a highly regio- and stereoselective manner (Scheme 3.11).



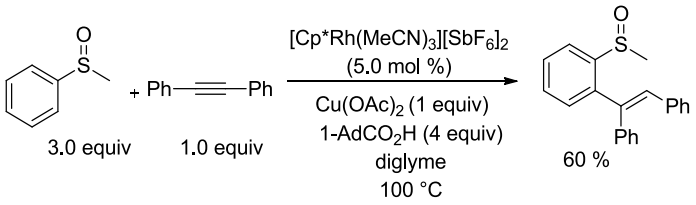
Scheme 3.11: The hydroarylation of anilides with 1-phenyl-1-propyne

Amide, carbamate, phosphine oxide (P=O) and NHCOR substituted aromatics reacted with alkynes in the presence of ruthenium(II) or rhodium(III) catalysts, yielding trisubstituted alkenes in a highly regio- and stereoselective manner.[8-14] This results prompted us to explore the possibility of a weakly coordinating C=O assisted hydroarylation of acetophenone with diphenylacetylene in the presence of ruthenium catalyst. However, in the reaction, only cyclic benzofulvene derivative was observed in 45% yield and the expected hydroarylation product was not observed (Scheme 3.12).[15] After hydroarylation, the C-Ru bond immediately inserts into the carbonyl group leading to cyclic benzofulvene which is very difficult to suppress.



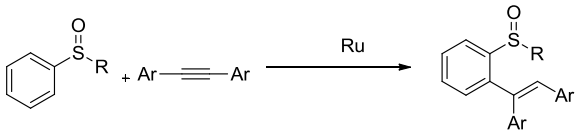
Scheme 3.12: Optimization study with acetophenone

Next, we have paid out attention to explore the possibility of a weakly coordinating S=O assisted hydroarylation of aromatic sulfoxides with alkynes. In the meantime, very recently, Miura's group reported the hydroarylation of aromatic sulfoxides with alkynes in the presence of a highly expensive rhodium complex (Scheme 3.13).[16] However, $Cu(OAc)_2$ is used as a terminal metal oxidant to regenerate the active rhodium catalyst.



Scheme 3.13: Hydroarylation of aromatic sulfoxide by using rhodium catalyst

Herein, we wish to discourse about an oxidant free a regio- and stereoselective hydroarylation of aromatic sulfoxides with alkynes in the presence of a less expensive ruthenium catalyst (Scheme 3.14). In the reaction, terminal metal oxidant is not used and only Ru(II) species is involved in the whole catalytic cycle without changing the metal oxidation state. It is important to note that the phenyl sulfoxide motif is present in various natural products and drug molecules as well as it have been widely used as ligands in various enantioselective reactions.



Scheme 3.14: Hydroarylation of aromatic sulfoxide in the presence of Ru catalyst

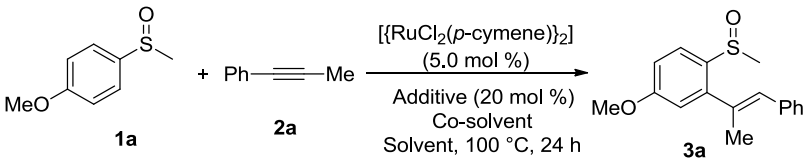
3.2: Results and Discussion

When methyl phenyl sulfoxide (**1a**) was treated with 1-phenyl-1-propyne (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (5.0 equiv) in 1,4-dioxane at 100 °C for 24 h, a hydroarylation product **3a** was observed in 75% isolated yield (detailed optimization studies, Table 3.1). The catalytic reaction is highly regioselective and the *ortho* C-H bond of **1a** selectively inserts at the methyl group substituted carbon of alkyne **2a**. The catalytic reaction is also highly stereoselective giving only *E*-stereoisomer trisubstituted alkene derivative **3a**.

3.3: Optimization Studies

When methyl phenyl sulfoxide (**1a**) was treated with 1-phenyl-1-propyne (**2a**) in the presence of other silver salts including AgOTf and KPF_6 were totally ineffective for the reaction (Table 3.1). But in presence of $AgBF_4$ correspondind hydroarylation product giving the 3a in 52 % yield. The catalytic reaction was tested with various cosolvent such as acetic acid, mesitylenic acid and 1-adamantane carboxylic acid. The catalytic reaction was also tested with various solvents such as CH_3CN, toluene, *tert*-amyl alcohol, trifluoroethanol, THF, DMF, DCE, *i*-propanol and DMSO (Table 3.1). Among them, DCE (1, 2-dichloroethane), THF, and *i*-propanol solvents was slightly effective for the reaction. Remaining solvents were totally ineffective for the reaction. However, the catalytic reaction did not proceed in the absence of either Ruthenium catalyst or silver salt.

Table 3.1: Optimization Studies with Various Solvent and Cosolvent.



entry	solvent	cosolvent	additive	yield of **3a** (%)[b]
1	1,4-Dioxane	No	$AgSbF_6$	5
2	1,4-Dioxane	Pivalic acid (2.0 equiv)	$AgSbF_6$	55
3	1,4-Dioxane	Acetic acid (2.0 equiv)	$AgSbF_6$	10
4	1,4-Dioxane	Mesitylenic acid (2.0 equiv)	$AgSbF_6$	12
5	1,4-Dioxane	1-Adamantane carboxylic acid (2.0 equiv)	$AgSbF_6$	20
6	1,4-Dioxane	Acetic acid (5.0 equiv)	$AgSbF_6$	18
7	1,4-Dioxane	Acetic acid (10.0 equiv)	$AgSbF_6$	25
8	**1,4-Dioxane**	**Pivalic acid (5.0 equiv)**	**$AgSbF_6$**	**80**
9	1,4-Dioxane	Pivalic acid (10.0 equiv)	$AgSbF_6$	81
10	1,4-Dioxane	Pivalic acid (5.0 equiv)	AgOTf	NR
11	1,4-Dioxane	Pivalic acid (5.0 equiv)	$AgBF_4$	52
12	1,4-Dioxane	Pivalic acid (5.0 equiv)	KPF_6	NR
13	*tert*-amyl alcohol	Pivalic acid (5.0 equiv)	$AgSbF_6$	NR
14	trifluoroethanol	Pivalic acid (5.0 equiv)	$AgSbF_6$	NR
15	THF	Pivalic acid (5.0 equiv)	$AgSbF_6$	30
16	$ClCH_2CH_2Cl$	Pivalic acid (5.0 equiv)	$AgSbF_6$	42
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	*i*-propanol	Pivalic acid (5.0 equiv)	$AgSbF_6$	11

[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 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.

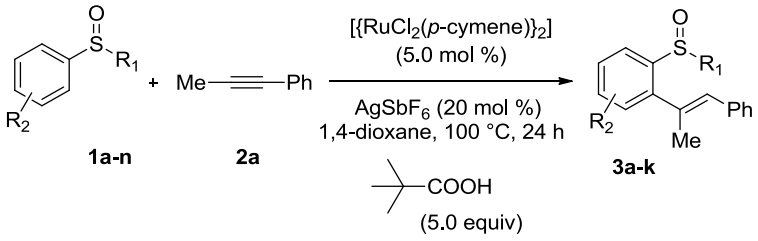
3.4: Scope of Aromatic Sulfoxide

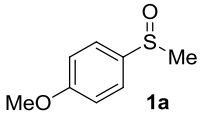
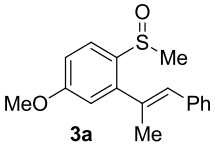
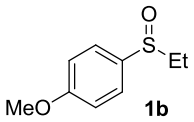
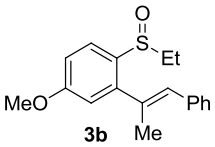
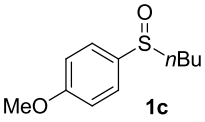
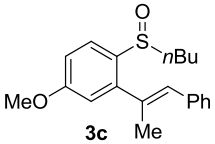
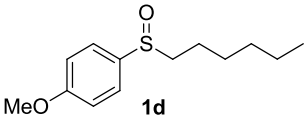
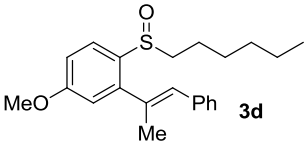
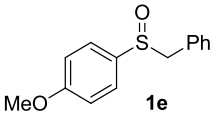
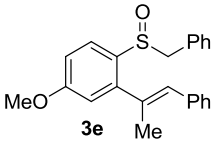
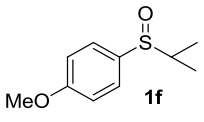
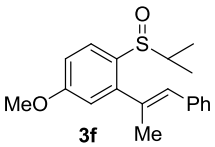
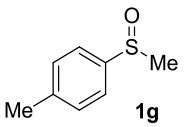
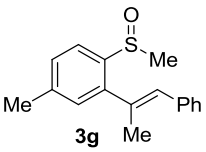
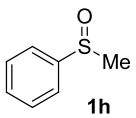
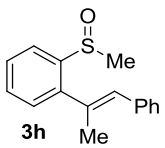
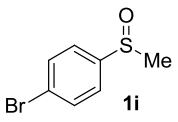
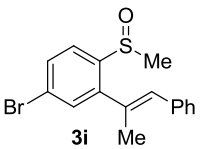
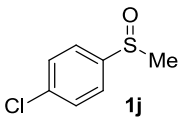
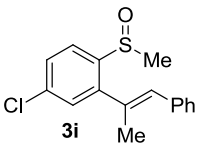
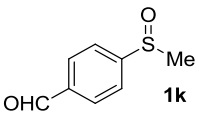
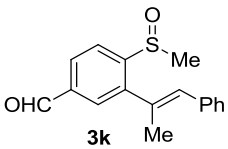
When methyl phenyl sulfoxide (1a) was treated with 1-phenyl-1-propyne (2a) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (5.0

equiv) in 1,4- dioxane at 100 °C for 24 h, a hydroarylation product **3a** was observed in 75% isolated yield (Table 3.2, entry 1) (detailed optimization studies, Table 3.1). The catalytic reaction is highly regioselective and the *ortho* C-H bond of **1a** selectively inserts at the methyl group substituted carbon of alkyne **2a**. The catalytic reaction is also highly stereoselective giving only *E*-stereoisomer trisubstituted alkene derivative **3a**. Next, the methyl group of methyl phenyl sulfoxide (**1a**) was replaced into ethyl, *n*-butyl, *n*-hexyl, benzyl and *iso*-propyl phenyl sulfoxides **1b-f** to know the effect of the reactivity (entries 2-6). Among them, methyl phenyl sulfoxide (**1a**) was very effectively, providing product **3a** in 75% yield. Whereas, *n*-ethyl phenyl sulfoxide (**1b**) and *n*-butyl phenyl sulfoxide (**1c**) yielded products **3b** and **3c** in moderate 52% and 47% yields, respectively (entries 2 and 3). *n*-Hexyl phenyl sulfoxide (**1d**) and benzyl phenyl sulfoxide (**1e**) provided hydroarylation products **3d** and **3e** in less 40% and 43% yields, respectively (entries 4-5). Interestingly, *iso*-propyl phenyl sulfoxide (**1f**) afforded the hydroarylation product **3f** in good 56% yield (entry 6).

Next, the hydroarylation reaction of substituted aryl sulfoxides **1g-k** with **2a** was examined (Table 3.2). The reaction was compatible with functional groups such as Br, Cl and CHO substituted aromatic sulfoxides. Electron-rich Me substituted sulfoxide **1g** reacted with **2a** yielding hydroarylation product **3g** in moderate 55% yield (entry 7). Whereas, unsubstituted methyl phenyl sulfoxide (**1h**) provided hydroarylation product **3h** in good 73% yield (entry 8). A less reactive halogen group such as Br and Cl substituted sulfoxides **1i** and **1j** also efficiently participated in the reaction, affording products **3i** and **3j** in 56%, and 52% yields, respectively (entries 9 and 10). Interestingly, electron-deficient CHO substituted aromatic sulfoxide **1k** provided the corresponding hydroarylation product **3k** in 51% yield without affecting a very sensitive CHO group (entry 11).

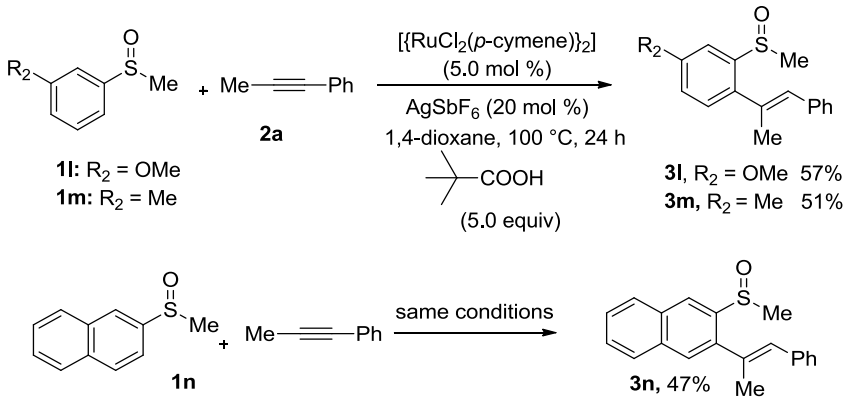
Table 3.2: Scope of Aromatic Sulfoxides **1a-k**[a]



Entry	Sulfoxides **1a-n**	Product **3a-n**	Yield (%)[b]
1	 **1a**	 **3a**	75
2	 **1b**	 **3b**	52
3	 **1c**	 **3c**	47
4	 **1d**	 **3d**	40
5	 **1e**	 **3e**	43
6	 **1f**	 **3f**	56
7	 **1g**	 **3g**	55
8	 **1h**	 **3h**	73
9	 **1i**	 **3i**	56
10	 **1j**	 **3i**	52
11	 **1k**	 **3k**	51

[a]All reactions were carried using **1a-n** (0.5 mmol), **2a** (0.6 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (2.5 mmol) in 1,4-dioxane at 100 °C for 24 h under N_2 atmosphere. [b]Isolated yield.

Subsequently, the hydroarylation reaction was tested with unsymmetrical sulfoxides such as *meta* methoxy **1l** and methyl **1m** substituted phenyl sulfoxides with alkyne **2a** (Scheme 3.15). In the reaction, hydroarylation products **3l** and **3m** were observed in 57% and 51% yields, respectively. The hydroarylation reaction is highly regioselective and methyl attached carbon of alkyne **2a** is connected at the less hindered *ortho* C-H bond of sulfoxides **1l** and **1m**. Similarly, methyl naphthyl sulfoxide **1n** reacted with **2a**, yielding product **3n** in 47% yield, in which also, the *ortho* C-H bond activation takes place at the less hindered side (Scheme 3.15).

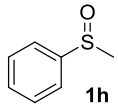
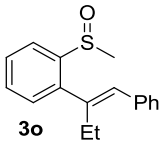
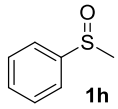
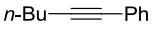
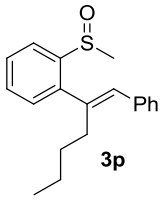
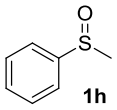
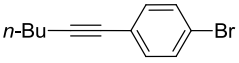
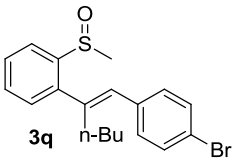
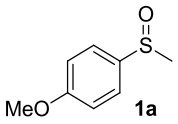
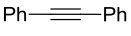
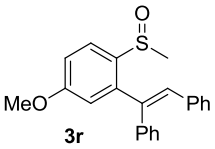
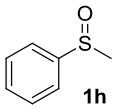
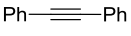
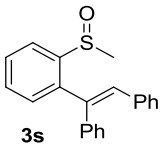
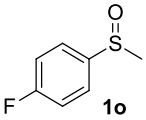
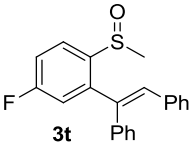
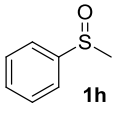
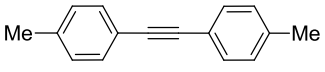
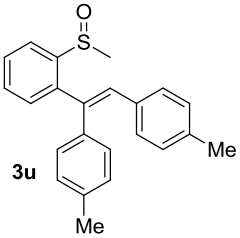


Scheme 3.15: Regioselective studies of unsymmetrical sulfoxides

3.5: Scope of Alkynes

The scope of the hydroarylation reaction was tested with various unsymmetrical and symmetrical alkynes (Table 3.3). Unsymmetrical alkynes such as 1-phenyl-1-butyne (**2b**), 1-phenyl-1-hexyne (**2c**) and bromo substituted alkyne **2d** reacted regioselectively with **1h**, providing the corresponding alkene derivatives **3o-q** in 71%, 67% and 63% yields, respectively (entries 1-3). In these reactions, alkyl substituted alkyne carbon connected at the *ortho* C-H bond of **1h**. A highly reactive symmetrical diphenylacetylene (**2e**) and 1,2-di-*p*-tolylethyne (**2f**) reacted efficiently with **1a** or **1h** or *para* fluoro substituted phenyl sulfoxide **1o** giving the corresponding sterically hindered trisubstituted alkene derivatives **3r-u** in excellent yields (entries 4-7). It is important to note that the electron-deficient *para* fluoro substituted phenyl sulfoxide **1o** was not suitable substrate for hydroarylation reaction with a less reactive 1-phenyl-1-propyne (**2a**). But, it worked nicely with diphenylacetylene (**2e**).

Table 3.3: The Reaction of Sulfoxides **1a** or **1h** or **1o** with Alkynes **2b-f**[a]

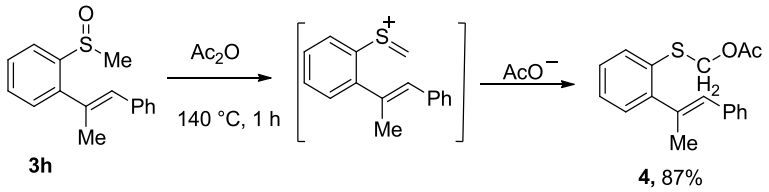
Entry	**1**	Alkynes **2b-j**	Product **3l-u**	Yield (%)[b]
1	 **1h**	**2b**	 **3o**	71
2	 **1h**	 **2c**	 **3p**	67
3	 **1h**	 **2d**	 **3q**	63
4	 **1a**	 **2e**	 **3r**	85[c]
5	 **1h**	 **2e**	 **3s**	83[c]
6	 **1o**	**2e**	 **3t**	45
7	 **1h**	 **2f**	 **3u**	66[c]

[a]All reactions were carried using **1a** or **1h** or **1o** (100 mg), **2b-f** (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (5.0 equiv) in 1,4-dioxane at 100 °C for 24 h under N_2 atmosphere. [b]Isolated yield. [c]The reaction was done at 100 °C for 12 h.

3.6: Application of hydroarylated aromatic sulfoxide

Pummerer Rearrangement

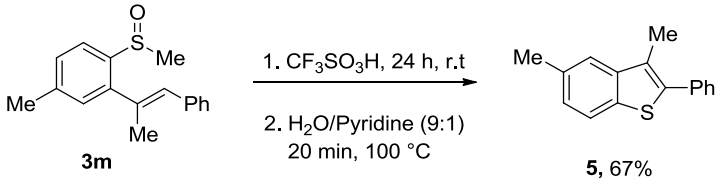
By using aryl sulfoxides **3**, we have tried to prepare α-acyloxy-thioether via Pummerer rearrangement.[17] Treatment of **3h** with acetic anhydride (10.0 equiv) at 140 °C for 1 h gave α-acyloxy-thioether **4** in 87% yield (Scheme 3.16).



Scheme 3.16: Pummerer rearrangement

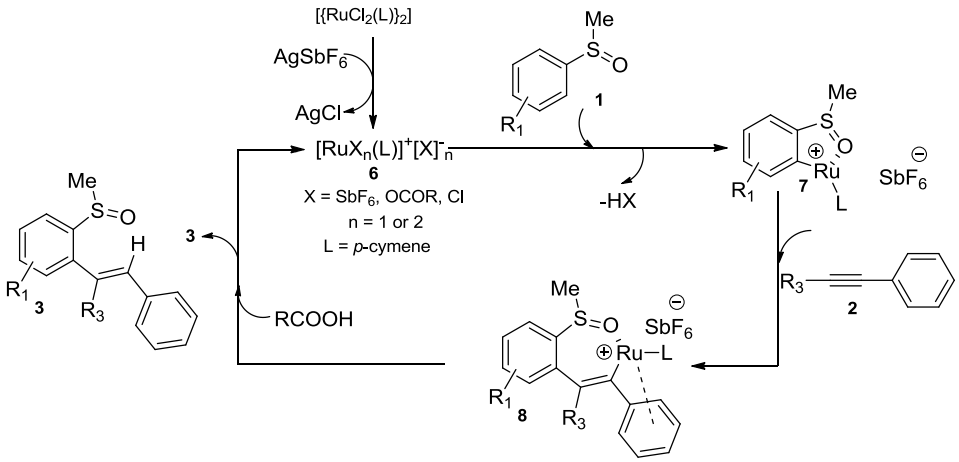
Application: Preparation of 2,3-Disubstituted Benzothiophene Derivative

Later, *ortho* alkenylated phenyl sulfoxide **3m** was treated with CF_3SO_3H at room temperature for 24 h followed by addition of a 9:1 ratio of water/pyridine to the reaction mixture, yielding 2,3-disubstituted benzothiophene derivative **5** in 67% yield (Scheme 3.17). It is well known that aromatic sulfoxides (Ar-S=O-R) can be easily converted into the corresponding aromatic sulfides (Ar-S-R) in good yields.[18]



Scheme 3.17: Preparation of 2,3-disubstituted benzothiophene derivative

3.7: Mechanism



Scheme 3.18: Proposed mechanism

The catalytic reaction proceeds via coordination of oxygen atom of **1** into a cationic ruthenium species **6** followed by *ortho* metalation provides intermediate **7** (Scheme 3.18). Coordinative selective insertion of alkyne **2** into the C-Ru bond of intermediate **7** yields intermediate **8**. Protonation of C-Ru bond of intermediate **8** by pivalic acid affords *ortho* alkenylated product **3** and regenerates the active catalyst **6**. Intramolecular coordination of Ph group to the Ru metal could stabilize the intermediate **8**. Pivalic acid plays dual role in the reaction. It acts as an acetate source for the deprotonation of the *ortho* C-H bond of **1** and the proton source followed by the regeneration of the active catalyst.

3.8: Conclusion

1. We have developed a weakly coordinating S=O assisted hydroarylation of aromatic sulfoxides with alkynes in the presence of ruthenium catalyst.

2. Its leading to trisubstituted alkenes in good to excellent yields in a highly regio- and stereoselective manner.

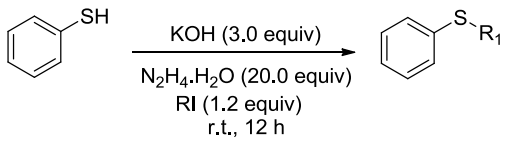
3. By using trisubstituted alkenes, α-acyloxythioether and 2, 3-disubstituted benzothiophene were prepared.

3.9: Experimental Section

General Procedure for the Preparation of Aromatic Sulfoxides.

Step 1:

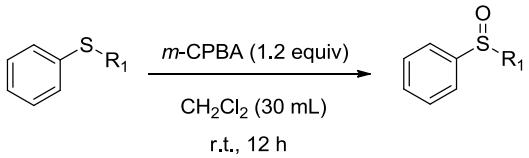
In a 100 mL round bottom flask, substituted aromatic thiol (1.0 gm), KOH (3.0 equiv) and hydrazine hydrate (20.0 equiv) were taken. Then, the reaction mixture was cooled for 15 min at 0 °C. The corresponding alkyl iodide was slowly added to the reaction mixture at 0 °C for 5 min and the reaction mixture was stirred at room temperature for 12 h. Later, the reaction mixture was diluted with H_2O (75 mL) and extracted with EtOAc (3 x 75 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under vacuum and the crude residue was purified through a silica gel column (hexanes and ethyl acetate) to give pure aryl alkyl thioether (Scheme 3.19).



Scheme 3.19: Preparation of aryl alkyl thioether

Step 2:

In a 100 mL round bottom flask, aryl alkyl thioether (1.0 gm) and CH_2Cl_2 (20 mL) were added under the nitrogen atmosphere. In another round bottom flask, *meta*-chloroperoxybenzoic acid (1.2 equiv) was taken in 10 mL CH_2Cl_2. At 0 °C, *meta*-chloroperoxybenzoic acid solution was added into the round bottom flask which containing aryl alkyl thioether solution under the nitrogen atmosphere for 5 min. After addition, the resulting mixture was stirred under nitrogen at room temperature for 12 h. The reaction mixture was extracted with saturated sodium bicarbonate and CH_2Cl_2 (100 mL). The organic layer was dried over Na_2SO_4. After evaporation of the solvents under vacuum, the compound purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure aromatic sulfoxide (Scheme 3.20)**.**



Scheme 3.20: Preparation of aromatic sulfoxide

General Procedure for the Cyclization of Aromatic Ketones with Alkynes: [15]

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 acetophenone (100 mg), diphenylacetylene (1.20 equiv), pivalic acid (5.0 equiv) and 1,4-dioxane (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 benzofulvene derivative in 45% yield.

General Procedure for the Hydroarylation of Aromatic Sulfoxides 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 phenyl sulfoxide **1** (100

mg), alkyne **2** (1.20 equiv), pivalic acid (5.0 equiv) and 1,4-dioxane (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 24 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3**.

Note: For the preparation of compounds **3r**, **3s** and **3u**, the reaction was done at 100 °C for 12 h.

General Procedure for the Pummerer rearrangement.[19]

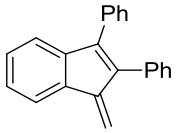
A two-neck 50 mL round bottom flask fitted with a condenser containing a mixture of **3h** (100 mg) and AC_2O (10 equiv). The reaction mixture was refluxed at 140 °C for 4 h. After the reaction, the reaction mixture was allowed to cool to RT. The solvent was removed under reduced pressure and the crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **4.**

The Preparation of Benzothiophene Derivative 5.[16]

A 20 mL two-necked round bottom flask was fitted with a reflux condenser with a nitrogen balloon. In round bottom flask, were added **3m** (100 mg) and CF_3SO_3H (0.5 mL). The resulting mixture was stirred under nitrogen at rt for 24 h. Then, the mixture was poured slowly into water/pyridine (9.0 mL of a 9:1 ratio) and stirred at 120 °C for 20 min. After cooling, the reaction mixture was extracted with ethyl acetate (50 mL). The organic layer was dried over Na_2SO_4. After evaporation of the solvents under vacuum, the compound purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **5.**

3.10: Spectral Data of Compounds

1-Methylene-2, 3-diphenyl-1*H*-indene.



Pale-yellow oil; eluent (hexanes).

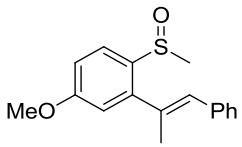
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, *J* = 8.0 Hz, 1 H), 7.34 (t, *J* = 8.0 Hz, 1 H), 7.30–7.25 (m, 10 H), 7.20–7.18 (m, 2 H), 6.25 (s, 1 H), 5.72 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.7, 142.8, 140.9, 137.5, 136.3, 134.7, 134.6, 130.8, 129.4,

128.6, 128.3, 128.1, 127.5, 127.0, 125.8, 120.2, 119.9, 114.2.

HRMS (ESI): calc. for [($C_{22}H_{16}$)H] (M+H) 281.1330, measured 281.1333.

(*E*)-4-Methoxy-1-(methylsulfinyl)-2-(1-phenylprop-1-en-2-yl)benzene (3a).



Colorless semisolid; eluent (50% ethyl acetate in hexanes). **1a** was taken in 100 mg, yield is 75% (126 mg).

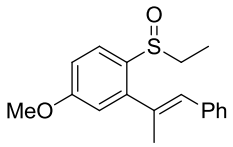
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2390, 1771, 1741, 1084, 734 and 701.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, *J* = 8.0 Hz, 1 H), 7.40 – 7.27 (m, 5 H), 7.05 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 6.43 (s, 1 H), 3.86 (s, 3 H), 2.67 (s, 3 H), 2.22 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 144.9, 136.6, 135.2, 134.3, 132.0, 128.8, 128.4, 127.2, 125.4, 114.1, 113.8, 55.5, 43.3, 20.3.

HRMS (ESI): calc. for [($C_{17}H_{18}O_2S$)H] (M+H) 287.1106, measured 287.1104

(*E*)-1-(Ethylsulfinyl)-4-methoxy-2-(1-phenylprop-1-en-2-yl)benzene (3b).



Colorless semisolid; eluent (50% ethyl acetate in hexanes). **1b** was taken in 100 mg, yield is 52% (84 mg).

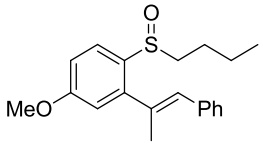
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2850, 1082, 1048, 757 and 701.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, *J* = 12.0 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 2 H),7.32 - 7.27 (m, 3 H), 7.02 (dd, *J* = 12.0, 4.0 Hz, 1 H), 6.80 (d, *J* = 4.0 Hz, 1 H), 6.45 (s, 1 H), 3.85 (s, 3 H), 2.90 – 2.68 (m, 2 H), 2.22 (s, 3 H), 1.16 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 145.3, 136.7, 135.4, 131.9, 131.7, 128.8, 128.4, 127.2, 126.5, 114.3, 113.3, 55.5, 49.2, 20.3, 6.3.

HRMS (ESI): calc. for [($C_{18}H_{20}O_2S$)H] (M+H) 301.1262, measured 301.1265.

(*E*)-1-(Butylsulfinyl)-4-methoxy-2-(1-phenylprop-1-en-2-yl)benzene (3c).



Colorless semisolid; eluent (50% ethyl acetate in hexanes). **1c** was taken in 100 mg, yield is 47% (73 mg).

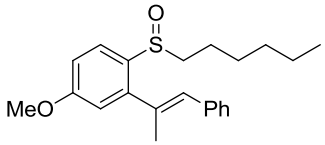
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3055, 2960, 1738, 1496, 1026, 730 and 699.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (d, *J* = 8.0 Hz, 1 H), 7.38, (t, *J* = 8.0 Hz, 2 H), 7.32 - 7.27 (m, 3 H), 7.02 (dd, *J* = 8.0,4.0 Hz, 1 H), 6.79 (d, *J* = 4.0 Hz, 1 H), 6.45 (s, 1 H), 3.85 (s, 3 H), 2.83 – 2.66 (m, 2 H), 2.21 (s, 3 H), 1.74 -1.52 (m, 2 H), 1.44 -1.28 (m, 2 H), 0.84 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.5, 145.1, 136.7, 135.4, 132.6, 131.9, 128.8, 128.4, 127.2, 126.1, 114.3, 113.5, 56.3, 55.5, 24.4, 21.8, 20.3, 13.6.

HRMS (ESI): calc. for [($C_{20}H_{24}O_2S$)H] (M+H) 329.1575, measured 329.1571.

(*E*)-1-(Hexylsulfinyl)-4-methoxy-2-(1-phenylprop-1-en-2-yl)benzene (3d).



Colorless semisolid; eluent (50% ethyl acetate in hexanes). **1d** was taken in 100 mg, yield is 47% (59 mg).

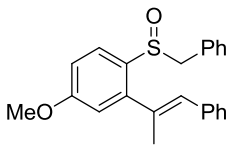
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2956, 1770, 1042, 726 and 699.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (d, *J* = 8.0 Hz, 1 H), 7.37 (t, *J* = 8.0 Hz, 2 H), 7.32 - 7.26 (m, 3 H), 7.02 (dd, *J* = 8.0,4.0 Hz, 1 H), 6.79 (d, *J* = 4.0 Hz, 1 H), 6.45 (s, 1 H), 3.85 (s, 3 H), 2.82 - 2.66 (m, 2 H), 2.22 (s, 3 H),1.75 - 1.54 (m, 3 H), 1.40 – 1.23 (m, 5 H), 0.78 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.5, 145.1, 136.7, 135.4, 132.7, 132.0, 128.8, 128.4, 127.2, 126.1, 114.3, 113.5, 56.7, 55.5, 31.3, 28.3, 22.5, 22.3, 20.2, 13.9.

HRMS (ESI): calc. for [($C_{22}H_{28}O_2S$)H] (M+H) 357.1888, measured 357.1883.

(*E*)-1-(Benzylsulfinyl)-4-methoxy-2-(1-phenylprop-1-en-2-yl)benzene (3e).



Colorless semisolid; eluent (35% ethyl acetate in hexanes), **1e** was taken in 100 mg, yield is 43% (63 mg).

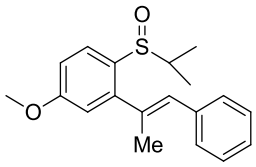
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2985, 1735, 1236, 1098, 1043, 784 and 731.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, *J* = 8.0 Hz, 1 H), 7.28 – 7.24 (m, 4 H), 7.22 - 7.19 (m, 3 H), 7.17 - 7.15 (m, 1 H), 7.11 – 7.09 (m, 1 H), 6.96 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.91 – 6.89 (m, 2 H), 6.53 (s, 1 H), 3.87 (s, 3 H), 3.71 (d, *J* = 12.0 Hz, 1 H), 3.47 (d, *J* = 12.0 Hz, 1 H), 1.26 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 144.5, 139.5, 139.2, 136.3, 133.4, 132.2, 132.2, 130.5, 129.5, 128.6, 128.0, 127.4, 127.2, 115.9, 113.9, 61.2, 55.6, 29.7.

HRMS (ESI): calc. for [($C_{23}H_{22}O_2S$)Na] (M+Na) 385.1238, measured 385.1230.

(*E*)-1-(Isopropylsulfinyl)-4-methoxy-2-(1-phenylprop-1-en-2-yl)benzene (3f).



Colorless semisolid; eluent (40% ethyl acetate in hexanes), **1f** was taken in 100 mg, yield is 56% (88 mg).

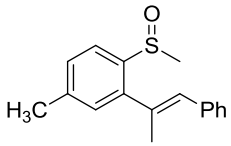
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3057, 2967, 1710, 1046, 732 and 700.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 (d, *J* = 8.0 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 7.32 – 7.25 (m, 3 H), 7.00 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.80 (s, 1 H), 6.49 (s, 1 H), 3.85 (s, 3 H), 2.90 – 2.81 (m, 1 H), 2.22 (s, 3 H), 1.22 (d, *J* = 8.0 Hz, 3 H), 1.06 (d, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 145.8, 136.9, 135.6, 132.1, 130.8, 128.8, 128.4, 127.14, 127.08, 114.4, 113.1, 55.5, 53.2, 20.3, 17.3, 13.1.

HRMS (ESI): calc. for [($C_{19}H_{22}O_2S$)H] (M+H) 315.1419, measured 315.1416.

(*E*)-4-Methyl-1-(methylsulfinyl)-2-(1-phenylprop-1-en-2-yl)benzene (3g).



Colorless semisolid; eluent (40% ethyl acetate in hexanes). **1g** was taken in 100 mg, yield is 55% (96 mg).

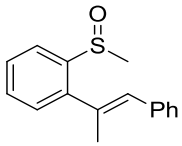
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3055, 2316, 1264, 1031, 734 and 701.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, *J* = 8.0 Hz, 1 H), 7.40 -7.35 (m, 3 H), 7.33 -7.29 (m, 3 H), 7.10 (s, 1 H), 6.42 (s, 1 H), 2.67 (s, 3 H), 2.41 (s, 3 H), 2.22 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.0, 141.2, 140.2, 136.8, 135.5, 132.0, 129.3, 129.2, 128.8, 128.4, 127.2, 123.5, 43.1, 21.3, 20.3.

HRMS (ESI): calc. for [($C_{17}H_{18}OS$)H] (M+H) 271.1157, measured 271.1161.

(*E*)-1-(Methylsulfinyl)-2-(1-phenylprop-1-en-2-yl)benzene (3h).



Colorless semisolid; eluent (40% ethyl acetate in hexanes). **1h** was taken in 100 mg, yield is 73% (133 mg).

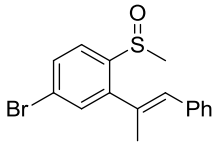
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3055, 1710, 1424, 1264, 1052 and 730.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (d, *J* = 8.0 Hz, 1 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.42 – 7.38 (m, 2 H), 7.36 – 7.34 (m, 2 H), 7.32 -7.29 (m, 2 H), 6.46 (s, 1 H), 2.71 (s, 3 H), 2.25 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.2, 143.0, 136.6, 135.2, 132.2, 130.8, 128.8, 128.5, 128.4, 128.3, 127.2, 123.3, 42.9, 20.2.

HRMS (ESI): calc. for [($C_{16}H_{16}OS$)H] (M+H) 257.1000, measured 257.1001

(*E*)-4-Bromo-1-(methylsulfinyl)-2-(1-phenylprop-1-en-2-yl)benzene (3i).



Colorless semisolid; eluent (40% ethyl acetate in hexanes). **1i** was taken in 100 mg, yield is 56% (86 mg).

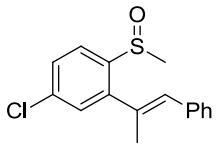
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3057, 2361, 1484, 1031, 744 and 700.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, *J* = 8.0 Hz, 1 H), 7.66 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.41 -7.37 (m, 2 H), 7.32 – 7.29 (m, 3 H), 6.46 (s, 1 H), 2.68 (s, 3 H), 2.22 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.6, 142.7, 136.2, 134.0, 133.0, 131.6, 131.5, 128.8, 128.5, 127.5, 125.34, 125.28, 42.9, 20.1.

HRMS (ESI): calc. for [($C_{16}H_{15}BrOS$)H] (M+H) 335.0105, measured 335.0104.

(*E*)-4-Chloro-1-(methylsulfinyl)-2-(1-phenylprop-1-en-2-yl)benzene (3j).



Pale yellow solid; eluent (40% ethyl acetate in hexanes). **1j** was taken in 100 mg, yield is 52% (87 mg).

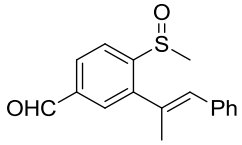
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3055, 2315, 1451,1057, 730 and 703.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, *J* = 12.0 Hz, 1 H), 7.50 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.32 – 7.29 (m, 4 H), 6.46 (s, 1 H), 2.68 (s, 3 H), 2.22 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.5, 142.0, 137.0, 136.2, 134.0, 132.9, 128.9, 128.7, 128.6, 128.5, 127.5, 125.2, 43.0, 20.1.

HRMS (ESI): calc. for [($C_{16}H_{15}ClOS$)H] (M+H) 291.0610, measured 291.0610.

(*E*)-4-(Methylsulfinyl)-3-(1-phenylprop-1-en-2-yl) benzaldehyde (3k).



Colorless semisolid; eluent (45% ethyl acetate in hexanes). **1k** was taken in 100 mg, yield is 51% (86 mg).

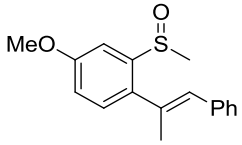
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2962, 2876, 1723, 1037, 743 and 700.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.09 (s, 1 H), 8.26 (d, *J* = 8.0 Hz, 1 H), 8.03 (dd, *J* = 8.0, 4.0 Hz, 1 H) 7.81 (s, 1 H), 7.39 (d, *J* = 8.0 Hz, 2 H) 7.34 -7.30 (m, 3 H), 6.51 (s, 1 H), 2.73 (s, 3 H) 2.26 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.3, 150.4, 143.8, 138.0, 136.2, 134.1, 133.3, 129.7, 129.2, 128.9, 128.5, 127.6, 124.5, 42.6, 20.0.

HRMS (ESI): calc. for [($C_{17}H_{16}O_2S$)H] (M+H) 285.0949, measured 285.0951.

(*E*)-4-Methoxy-2-(methylsulfinyl)-1-(1-phenylprop-1-en-2-yl)benzene (3l).



Colorless solid; eluent (40% ethyl acetate in hexanes). **1l** was taken in 100 mg, yield is 57% (95 mg).

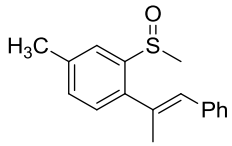
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3052, 1724, 1464, 1052, 723 and 701.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, *J* = 4.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.33 - 7.27 (m, 3 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 7.00 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.43 (s, 1 H), 3.89 (s, 3 H), 2.70 (s, 3 H), 2.20 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 144.4, 136.9, 135.3, 134.9, 132.1, 130.0, 128.8, 128.4, 127.1, 117.8, 107.0, 55.7, 42.8, 20.4.

HRMS (ESI): calc. for [($C_{17}H_{18}O_2S$)H] (M+H) 287.1106, measured 287.1104.

(*E*)-4-Methyl-2-(methylsulfinyl)-1-(1-phenylprop-1-en-2-yl)benzene (3m).



Pale yellow semisolid; eluent (35% ethyl acetate in hexanes). **1m** was taken in 100 mg, yield is 51% (89 mg).

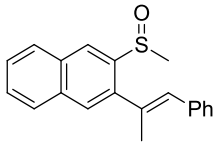
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3024, 2920, 1780, 1055, 760 and 728.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (s, 1 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.18 (d, *J* = 8.0 Hz, 1 H), 6.42 (s, 1 H), 2.68 (s, 3 H), 2.44 (s, 3 H), 2.21 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.9, 140.2, 138.7, 136.8, 135.3, 132.0, 131.5, 128.8, 128.6, 128.3, 127.1, 123.5, 42.9, 21.2, 20.3.

HRMS (ESI): calc. for [($C_{17}H_{18}OS$)Na] (M+Na) 293.0976, measured 293.0981.

(*E*)-2-(Methylsulfinyl)-3-(1-phenylprop-1-en-2-yl)naphthalene (3n).



Colorless semisolid; eluent (45% ethyl acetate in hexanes). **1n** was taken in 100 mg, yield is 47% (75 mg).

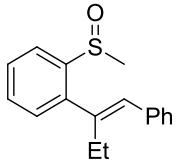
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3056, 2928, 2363, 1646, 1052, 732 and 703.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.56 (s, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.76 (s, 1 H), 7.58 -7.55 (m, 2 H), 7.43 – 7.36 (m, 4 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 6.61 (s, 1 H), 2.75 (s, 3 H), 2.32 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.8, 139.4, 136.8, 135.3, 134.1, 132.5, 132.3, 128.8, 128.4, 127.9, 127.8, 127.6, 127.2, 126.9, 124.1, 43.1, 20.5.

HRMS (ESI): calc. for [($C_{20}H_{18}OS$)H] (M+H) 307.1157, measured 307.1158.

(*E*)-1-(Methylsulfinyl)-2-(1-phenylbut-1-en-2-yl)benzene (3o).



Colorless semisolid; eluent (35% ethyl acetate in hexanes). **1o** was taken in 100 mg, yield is 71% (136 mg).

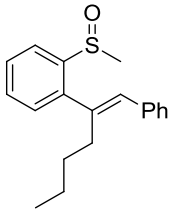
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2977, 1498, 1040, 736 and 701.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 7.31 – 7.25 (m, 4 H), 6.34 (s, 1 H), 2.73 (s, 3 H), 1.23 -1.22 (m, 2 H), 0.99 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 141.9, 141.3, 136.6, 131.9, 130.7, 129.4, 128.6, 128.4, 127.2, 123.3, 43.3, 25.7, 12.7.

HRMS (ESI): calc. for [($C_{17}H_{18}OS$)H] (M+H) 271.1157, measured 271.1151.

(*E*)-1-(Methylsulfinyl)-2-(1-phenylhex-1-en-2-yl)benzene (3p).



Colorless semisolid; eluent (35% ethyl acetate in hexanes). **1p** was taken in 100 mg, yield is 67% (142 mg).

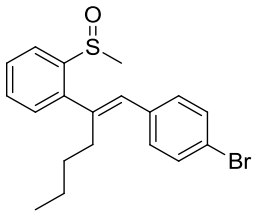
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2985, 1736, 1233, 1099, 1043 and 732.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 7.30 – 7.25 (m, 4 H), 6.34 (s, 1 H), 2.72 (s, 3 H), 2.69 -2.53 (m, 2 H), 1.38 – 1.23 (m, 4 H), 0.80 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 141.7, 141.1, 136.6, 132.2, 130.7, 129.2, 128.6, 128.5, 128.4, 127.2, 123.3, 43.3, 32.4, 30.3, 22.7, 13.8.

HRMS (ESI): calc. for [($C_{19}H_{22}OS$)H] (M+H) 299.1470, measured 299.1473.

(*E*)-1-(1-(4-Bromophenyl)hex-1-en-2-yl)-2-(methylsulfinyl)benzene (3q).



Light red semisolid; eluent (35% ethyl acetate in hexanes). **1q** was taken in 100 mg, yield is 63% (169 mg).

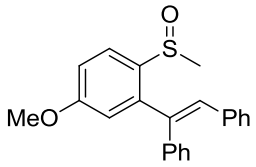
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984, 2362, 1743, 1462, 1043 and 730.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.51 (t, *J* = 8.0 Hz, 1 H), 7.45 -7.41 (m, 3 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 6.22 (s, 1 H), 2.66 (s, 3 H), 2.60 – 2.46 (m, 2 H), 1.32 – 1.14 (m, 4 H), 0.75 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.8, 141.8, 141.3, 135.5, 131.5, 130.9, 130.8, 130.2, 129.1, 128.7, 123.3, 121.1, 43.3, 32.4, 30.1, 22.7, 13.7.

HRMS (ESI): calc. for [($C_{19}H_{21}BrOS$)Na] (M+Na) 399.0394, measured 399.0390.

(*E*)-(1-(5-Methoxy-2-(methylsulfinyl)phenyl)ethene-1,2-diyl)dibenzene (3r).



Colorless semisolid; eluent (40% ethyl acetate in hexanes). **1r** was taken in 100 mg, yield is 85% (174 mg).

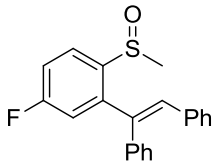
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3054, 2361, 1725,1453, 1021 and 776.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, *J* = 8.0 Hz, 1 H), 7.23 – 7.20 (m, 3 H), 7.18 – 7.16 (m, 3 H), 7.13 – 7.07 (m, 5 H), 6.87 (s, 1 H), 6.68 (s, 1 H), 3.85 (s, 3 H), 2.26 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 143.9, 139.4, 139.3, 136.1, 135.7, 132.2, 130.2, 129.4, 128.5, 128.2, 128.0, 127.5, 125.8, 115.9, 114.4, 55.6, 42.3.

HRMS (ESI): calc. for [($C_{22}H_{20}O_2S$)H] (M+H) 349.1262, measured 349.1369.

(*E*)-(1-(5-Fluoro-2-(methylsulfinyl)phenyl)ethene-1,2-diyl)dibenzene (3s).



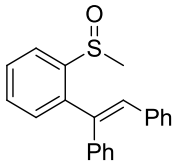
Pale yellow semisolid; eluent (35% ethyl acetate in hexanes). **1s** was taken in 100 mg, yield is 45% (95 mg).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.29 – 7.24 (m, 5 H), 7.21 – 7.19 (m, 3 H), 7.14 – 7.08 (m, 4 H), 6.72 (s, 1 H), 2.35 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.2, 162.7, 144.5 and 144.4 (F coupling), 140.4, 138.8, 138.4, 135.8, 133.0, 130.2, 129.4, 128.7, 128.3 and 128.2 (F coupling), 127.8, 126.5 and 126.4 (F coupling), 117.5 and 117.3 (F coupling), 116.3 and 116.1 (F coupling), 42.4.

HRMS (ESI): calc. for [($C_{21}H_{17}FOS$)H] (M+H) 337.1062, measured 337.1063.

(*E*)-(1-(2-(Methylsulfinyl)phenyl)ethene-1,2-diyl)dibenzene (3t).



Colorless semisolid; eluent (35% ethyl acetate in hexanes). **1t** was taken in 100 mg, yield is 83% (188 mg).

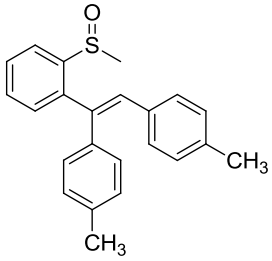
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3054, 2923, 1708, 1266, 1031, 763 and 732.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, *J* = 8.0 Hz, 1 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* =8.0 Hz, 1 H), 7.23 -7.20 (m, 3 H), 7.18 -7.16 (m, 3 H), 7.13 - 7.10 (m, 4 H), 6.69 (s, 1 H), 2.35 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.9, 142.0, 139.5, 139.3, 136.2, 132.3, 130.8, 130.4, 130.2, 129.4, 129.1, 128.6, 128.2, 128.0, 127.5, 123.8, 42.1.

HRMS (ESI): calc. for [($C_{21}H_{18}OS$)H] (M+H) 319.1157, measured 319.1168.

(*E*)-4,4'-(1-(2-(Methylsulfinyl)phenyl)ethene-1,2-diyl)bis(methylbenzene) (3u).



Colorless semisolid; eluent (40% ethyl acetate in hexanes). **1v** was taken in 100 mg, yield is 66% (163 mg).

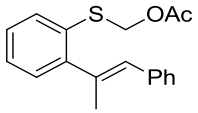
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3050, 2922, 1835, 1032, 756 and 734.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.54 (t, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.04 – 6.98 (m, 8 H), 6.61 (s, 1 H), 2.39 (s, 3 H), 2.31 (s, 3 H), 2.29 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.0, 142.4, 138.6, 137.9, 137.4, 136.5, 133.5, 131.8, 130.6, 130.4, 130.1, 129.3, 128.9, 123.6, 42.2, 21.3, 21.2.

HRMS (ESI): calc. for [($C_{23}H_{22}OS$)H] (M+H) 347.1470, measured 347.1462.

(*E*)-((2-(1-Phenylprop-1-en-2-yl)phenyl)thio)methyl acetate (4).



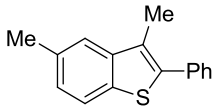
Colorless semisolid; eluent (45% ethyl acetate in hexanes). **3h** was taken in 100 mg, yield is 87% (101 mg).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (dd, *J* = 8.0, 4.0 Hz, 1 H), 738 -7.37 (m, 4 H), 7.31 – 7.25 (m, 3 H), 7.24 -7.23 (m, 1 H), 6.41 (s, 1 H), 5.41 (s, 2 H), 2.22 (s, 3 H), 3.07 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.0 137.6, 133.1, 130.7, 129.6, 128.9, 128.7, 128.2, 127.8, 127.0, 126.7, 67.7, 21.0, 19.9.

HRMS (ESI): calc. for [($C_{18}H_{18}O_2S$)Na] (M+Na) 321.0925, measured 321.0931.

3,5-Dimethyl-2-phenylbenzo[b]thiophene (5).



Colorless semisolid; eluent (4% ethyl acetate in hexanes). **3m** was taken in 100 mg, yield is 67% (59 mg).

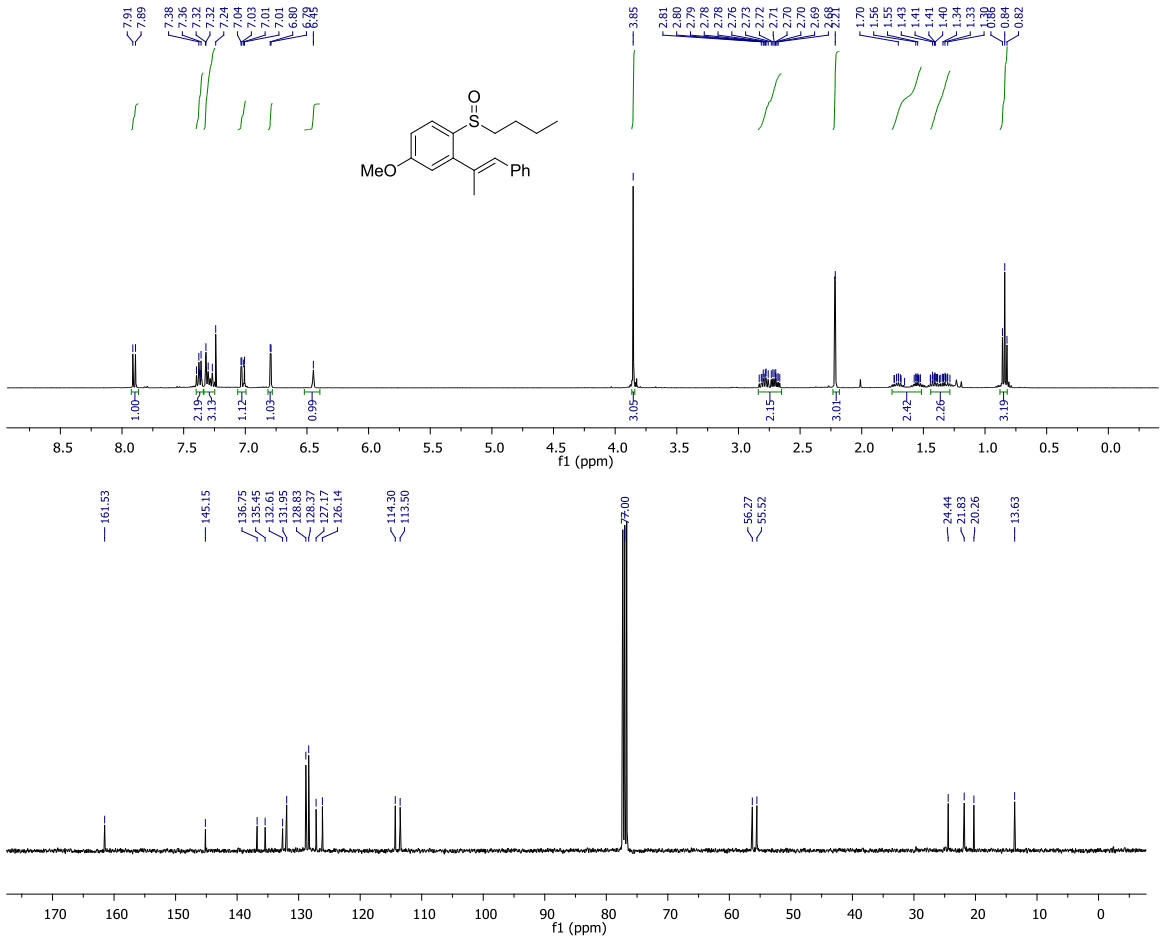
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (s, 1 H), 7.65 - 7.54 (m, 3 H), 7.51 – 7.44 (m, 3 H), 7.29 (dd, *J* = 8.0, 4.0 Hz, 1 H), 2.55 (s, 3 H), 2.51(s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.1, 134.9, 134.2, 129.6, 128.5, 127.6, 127.2, 125.8, 122.0, 121.7, 21.5, 12.6.

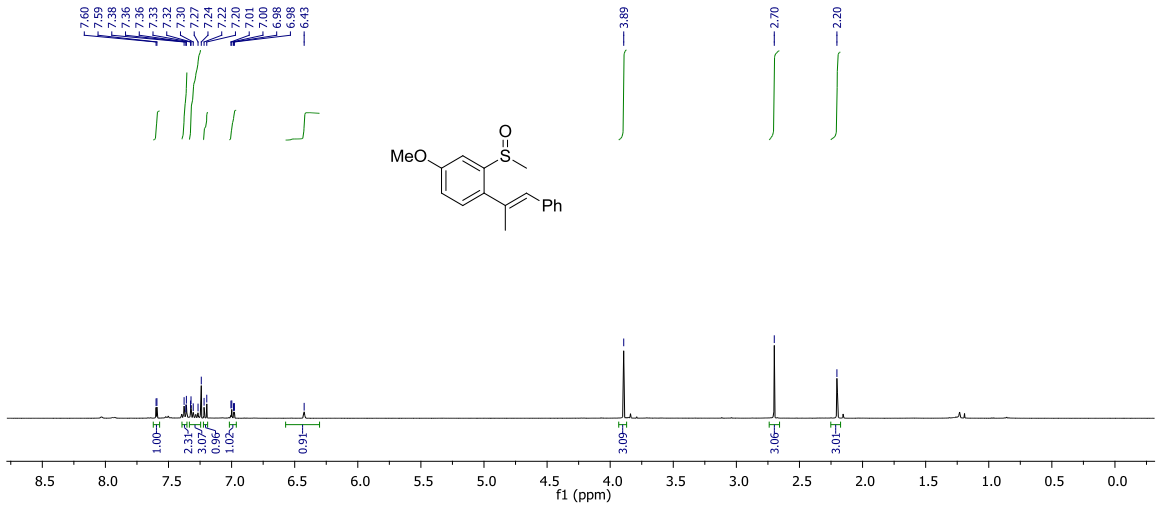
HRMS (ESI): calc. for [($C_{16}H_{15}S$)H] (M+H) 239.0894, measured 239.0885.

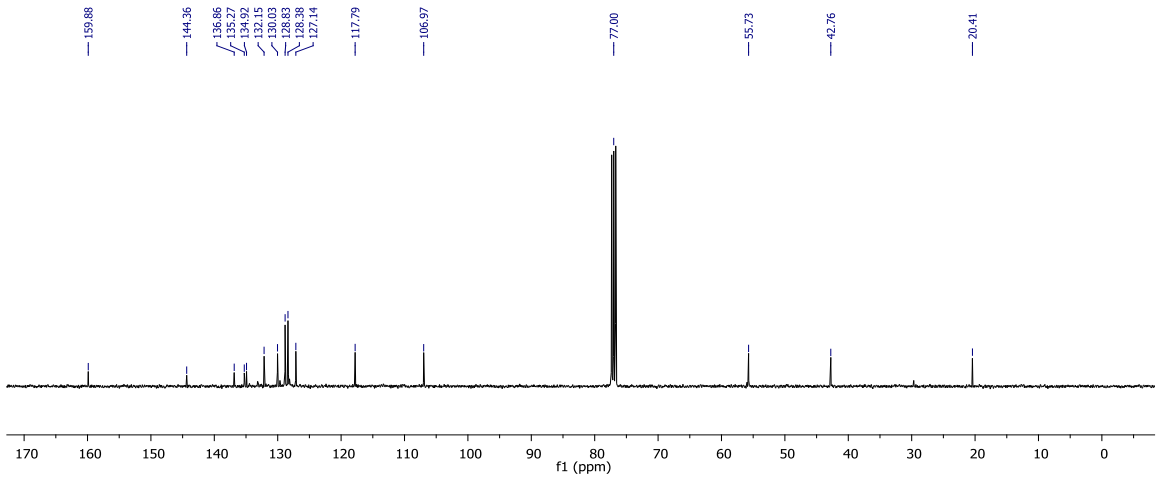
3.11: Spectral Copies of Selected Compounds

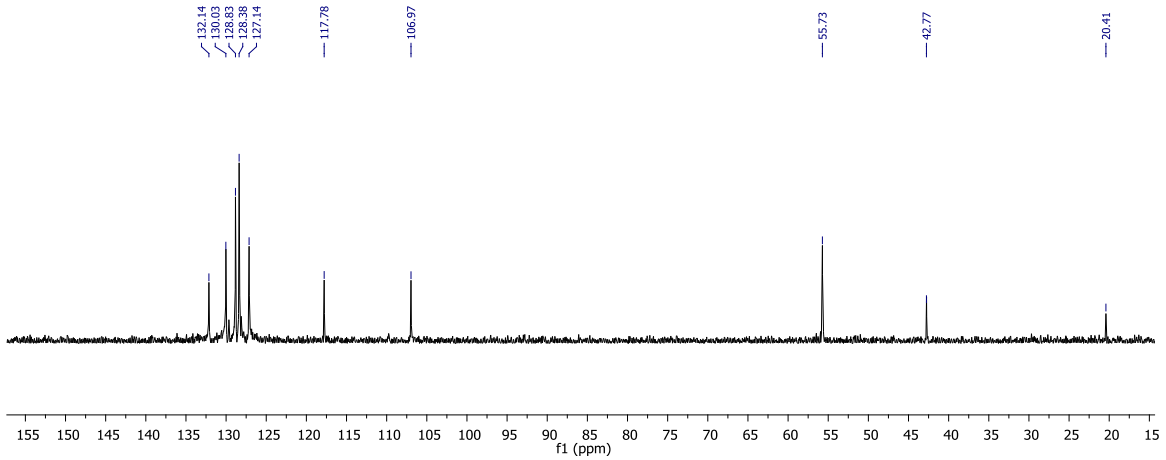
Spectral data of compound **3c**.



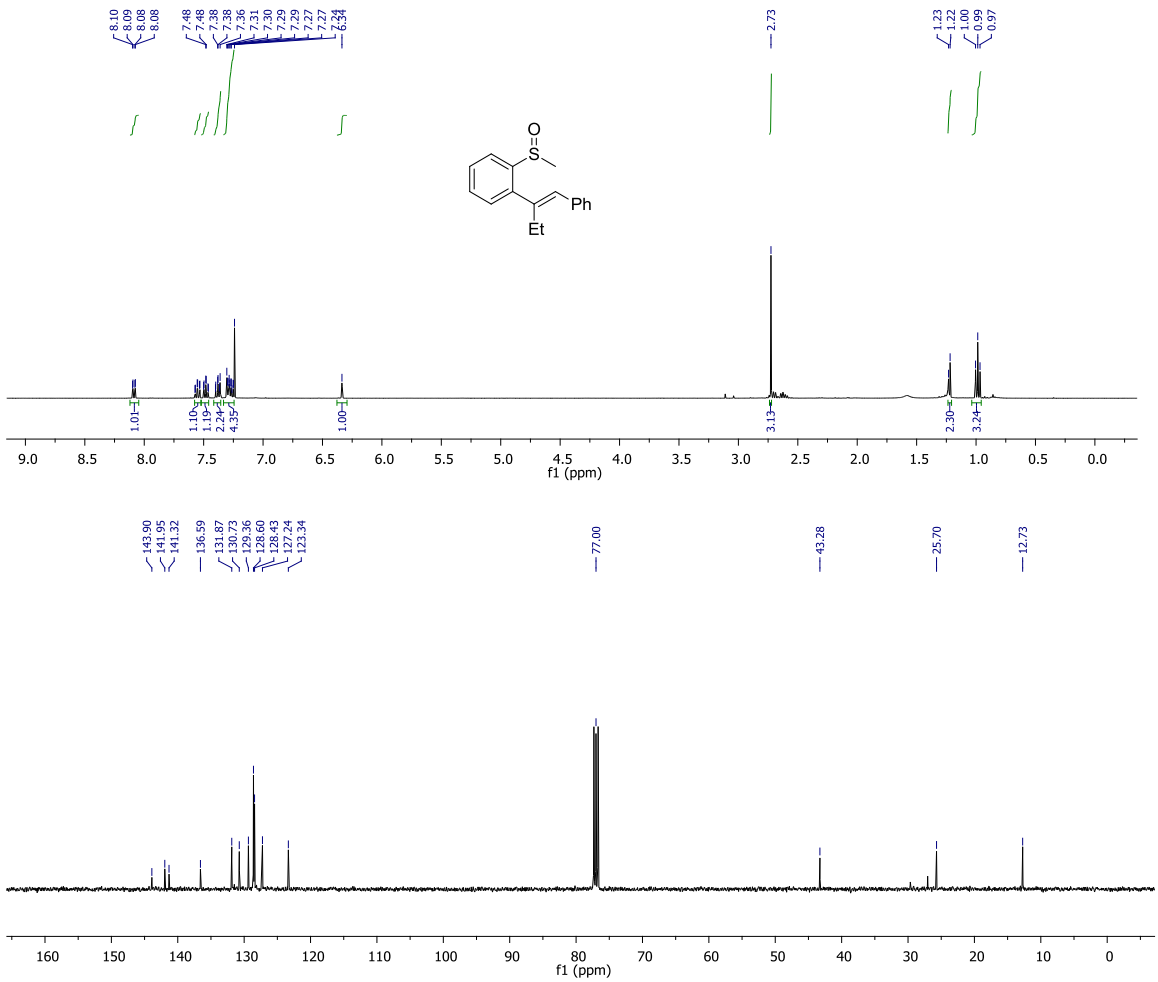
Spectral data of compound **3l**.



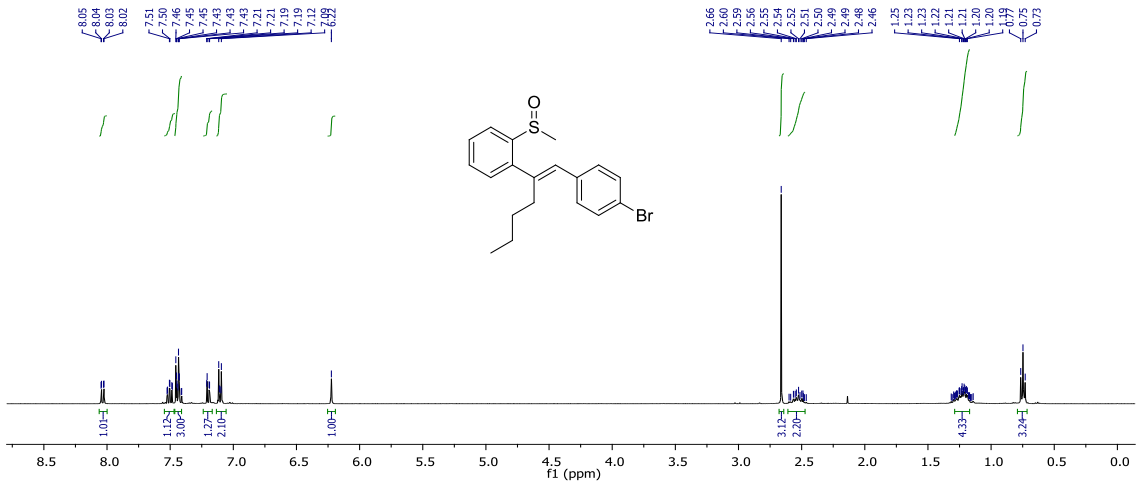


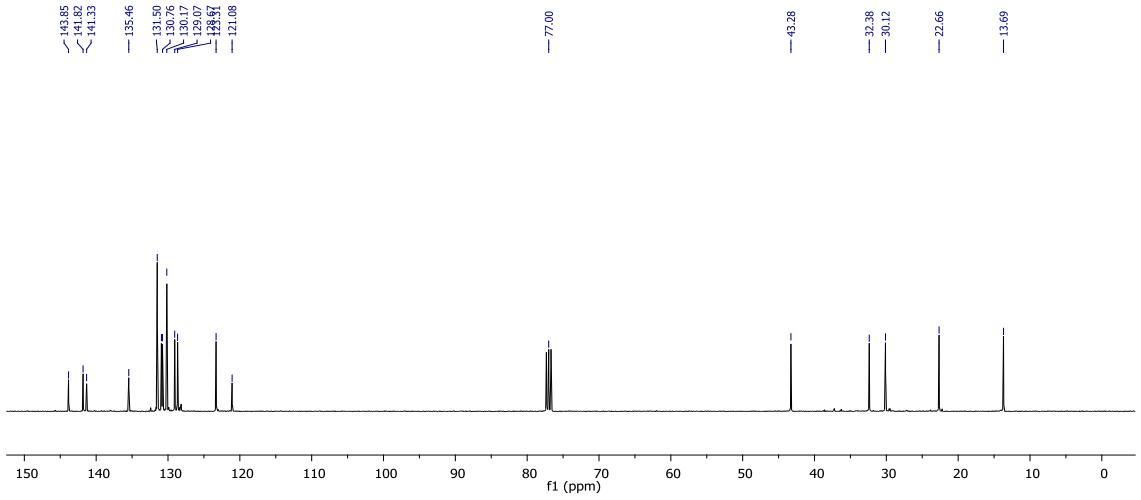


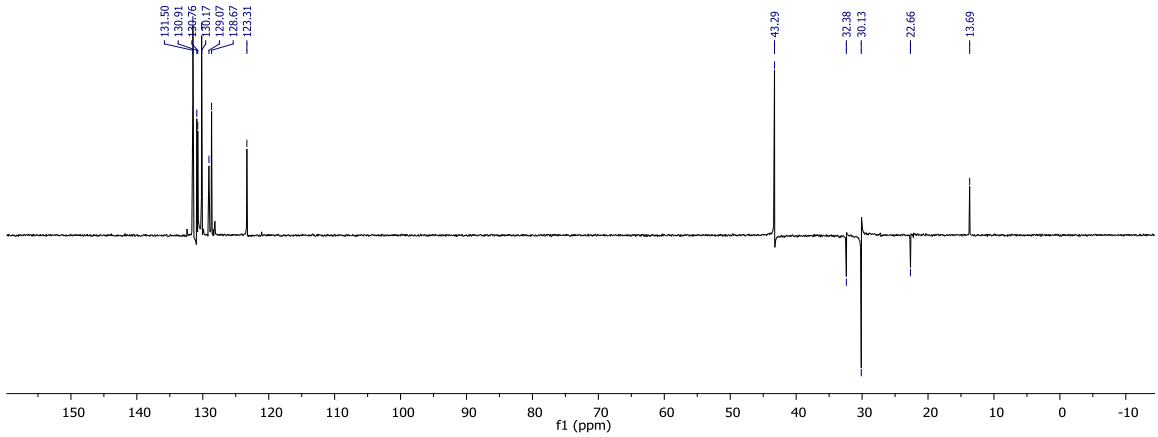
Spectral data of compound **3o**.



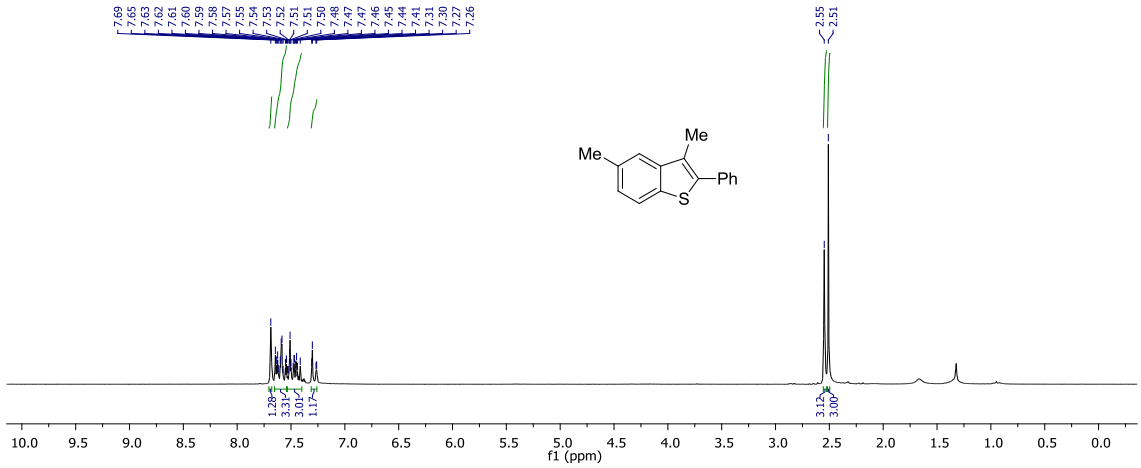
Spectral data of compound **3q**.

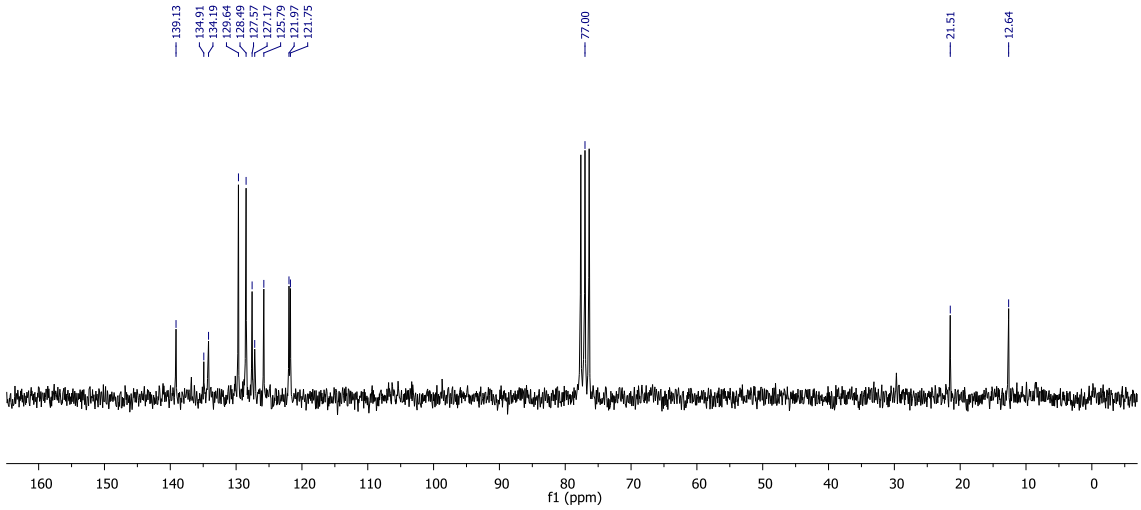


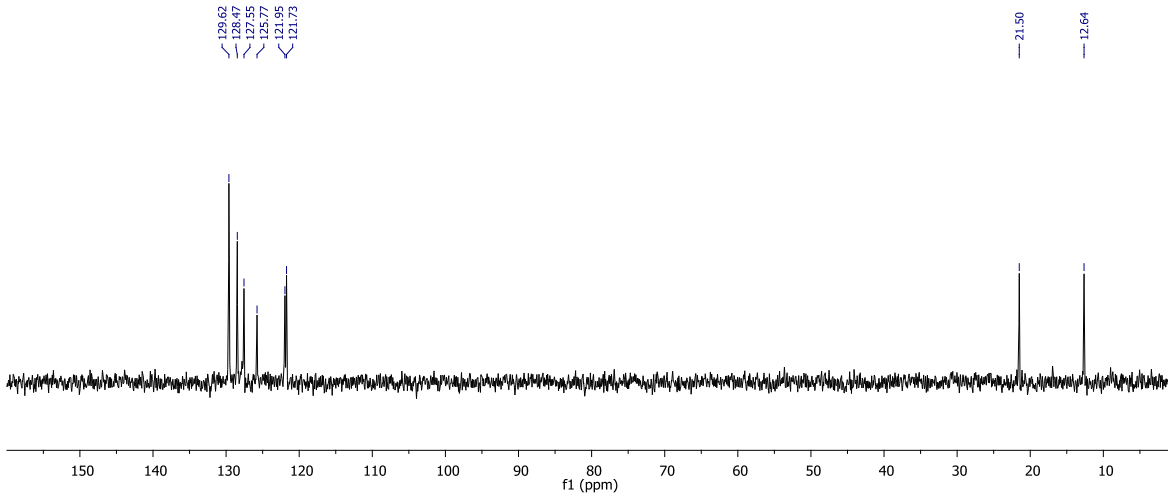




Spectral data of compound **5**.







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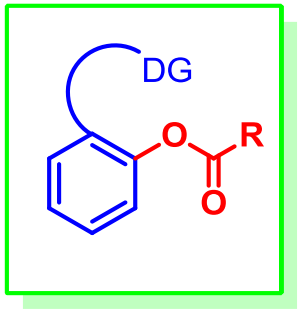
Chapter 4

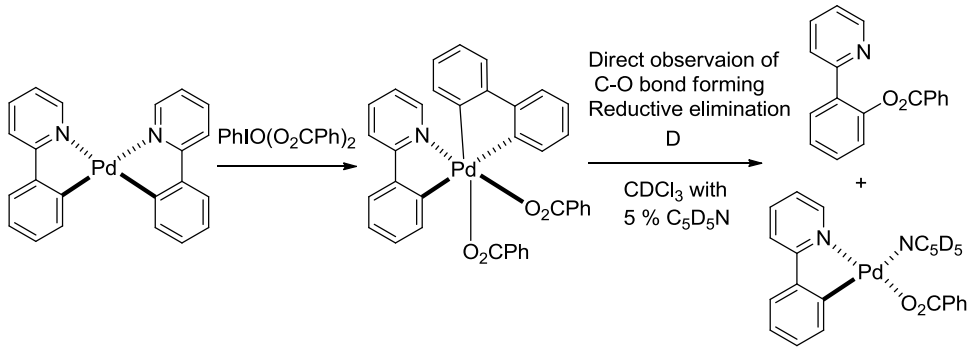
ortho Benzoxylation of *N*-Alkyl Benzamides or Acetanilides with Aromatic Acids Catalyzed by Ru (II) Complex



Introduction:

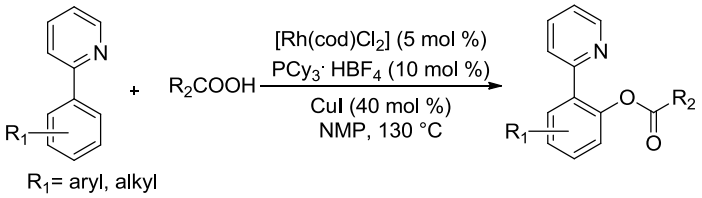
Metal-catalyzed chelation-assisted functionalization at the *ortho* C-H bond of aromatics with nucleophiles via C-H bond activation is an ideal method in organic synthesis.[1] By employing this method, various chemical bonds such as C-C, C-N, C-X and C-O are efficiently constructed in a highly atom economical and environmentally friendly manner. Palladium, rhodium and ruthenium complexes are widely used as catalysts for these types of reactions. In the presence of these catalysts, C-C, C-X and C-N bond formation have been extensively studied in the literature. But, C-O bond formation has not been well explored. This is most probably due to the high electronegativity of the oxygen element and the strong metal-oxygen bond strength.[2]

Various oxygen sources such as acetates, alkoxides, alcohols, aldehydes, anhydrides and carboxylic acids are used as nucleophiles in the reaction. Several directing groups such as 2-pyridyl, carbonyl, ester, nitrile, carboxylic acid and *N*-acetyl can be efficiently used for the reaction. With the assistance of these directing groups, benzoxylation,[4-7] hydroxylation,[8-12] acetoxylation,[15] and alkoxylation[16] at the *ortho* C-H bond of directing group substituted aromatics with various oxygen nucleophiles have been studied. In 2005, Sanford et al. reported benzoxylation of 2-phenylpyridines with benzoate iodonium salts in the presence of palladium catalyst.[3] In this reaction, the series of Pd(IV) complexes containing two rigid cyclometalated bidentate pyridine ligands were synthesized by the oxidation of corresponding Pd(II) complex with a hypervalent iodine(III) reagent $PhI(O_2CPh)_2$ (Scheme 4.1).



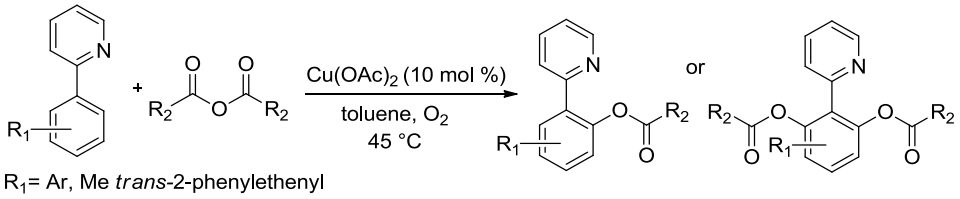
Scheme 4.1: Hypervalent iodine-mediated oxidation to Pd(IV) with subsequent reductive elimination

In 2009, Cheng's group demonstrated the benzoxylation of 2-phenylpyridines with benzoic acids in the presence of a rhodium catalyst.[4] The catalytic reaction showed broad substrate scope and good functional group tolerance.



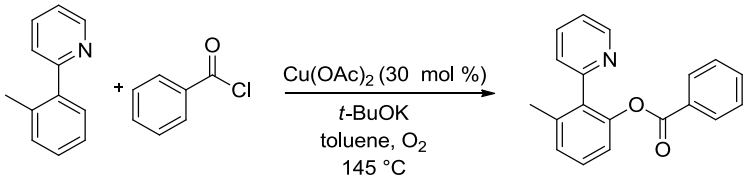
Scheme 4.2: *ortho* benzoxylation reaction of 2-aryl pyridines with benzoic acid

Subsequently, the same group reported an efficient chelation-assisted copper-catalyzed acyloxylation of 2-arylpyridines with anhydrides affording *mono*- or *di*acyloxylation products in moderate to good yields (Scheme 4.3).[5] In the reaction, a less expensive copper complex was used as a catalyst and O_2 as the terminal oxidant.



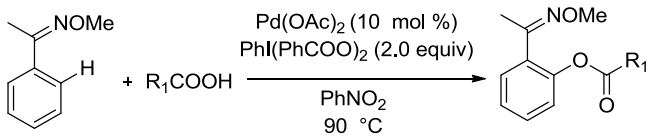
Scheme 4.3: *ortho* acyloxylation of 2-phenylpyridine with anhydrides

This reaction condition was also suitable for benzoxylation of 2-arylpyridines by using the commercially available acyl chlorides in presence of a copper catalyst (Scheme 4.4). Notably, switching of the base from *t*-BuOK to Li_2CO_3 causes chlorination at the C–H bond of 2-aryl pyridines.[6]



Scheme 4.4: Acyloxylation of the 2-phenylpyridine C–H bond

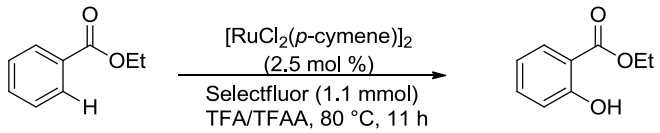
Very recently, Shi's group reported *ortho* benzoxylation of aromatic ketoximes with benzoic acids in the presence of a palladium catalyst (Scheme 4.5).[7] The reaction was also compatible with aliphatic acids.



Scheme 4.5: *ortho* benzoxylation of aromatic ketoximes with benzoic acids

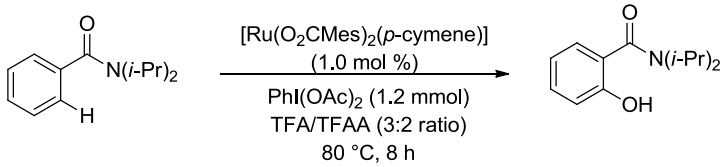
Palladium- or ruthenium-catalyzed hydroxylation of heteroatom substituted aromatics in the presence of a TFA/TFAA combination has been reported recently in the literature. In

2012, Rao's group demonstrated a ruthenium-catalyzed *ortho* hydroxylation of substituted benzoates with trifluoroacetic anhydride.[8]



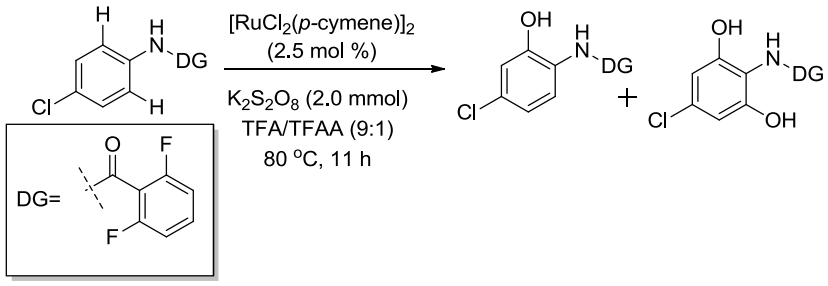
Scheme 4.6: *ortho* hydroxylation of substituted benzoates

In the same year, Ackermann's group showed a ruthenium-catalyzed site-selective *ortho* hydroxylation of substituted benzamides with TFAA.[9]



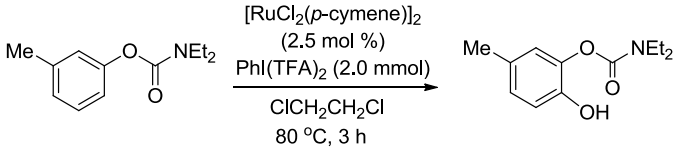
Scheme 4.7: *ortho* hydroxylation of substituted *N*,*N*-di(*iso*-propyl)-benzamides

In 2013, Rao's group reported a ruthenium-catalyzed *ortho* hydroxylation of substituted anilines having a removable directing group (CO-Ar) on the nitrogen moiety (Scheme 4 8).[10]



Scheme 4.8: *ortho* hydroxylation of aniline derivatives

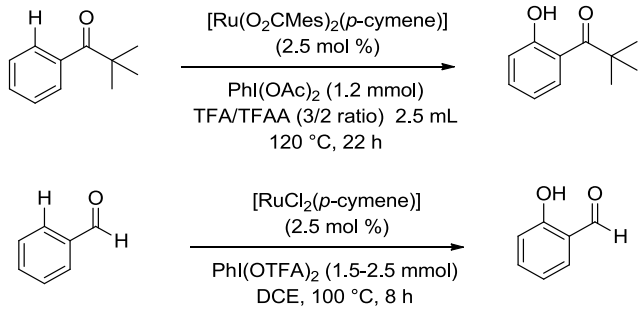
In the same year, Ackermann's group reported a highly regioselective Ru(II)-catalyzed *ortho* hydroxylation of aryl carbamates with TFAA.[11] This methodology provided an efficient method for the synthesis of *ortho* hydroxylated aryl carbamates under the mild reaction conditions.



Scheme 4.9: *ortho* hydroxylation of aryl carbamates

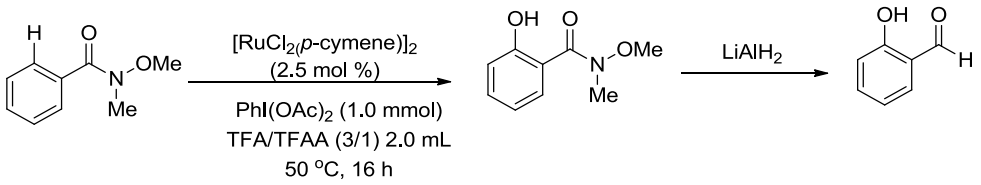
Later, the same group reported a highly chemo- and site-selective *ortho* hydroxylation of substituted aromatic ketones with TFAA.[12a] In addition, the same group reported chemo-

and site-selective *ortho* hydroxylation of substituted aromatic aldehydes with $PhI(OTFA)_2$.[12b]



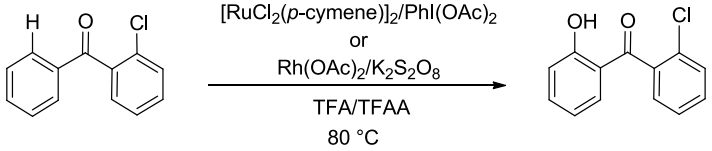
Scheme 4.10: *ortho* hydroxylation of substituted aromatic ketones and aromatic aldehydes

Later, Ackermann's group disclosed *ortho* hydroxylation of aryl Weinreb amides with TFAA under the mild reaction conditions by using Ru(II) catalyst (Scheme 4.11).[13]



Scheme 4.11: *ortho* hydroxylation of weinreb amides

Recently, Rao's group reported a regio- and chemoselective hydroxylation of aromatic ketones with TFAA by using $Rh(OAc)_2$ or Ru(II) catalysts (Scheme 4.12).[14] The practicality of this method was proved by a gram-scale synthesis of substituted 2-acylphenols from substituted acetophenones.



Scheme 4.12: o*rtho* hydroxylation of aromatic ketones

Among these transformations, *ortho* benzoxylation of substituted aromatics is less focused in the literature.[18] Until, only benzoxylation of 2-phenylpyridines and aromatic ketoximes with benzoic acids is known in the literature. This is mainly due to the rapid complex formation of the carboxylic acids with the metal complexes. To suppress the metal carboxylate complex formation, carboxylate sources such as benzoate iodonium salts, benzoyl chlorides, benzaldehydes and aromatic carboxylic anhydrides have been widely used. Also, the known benzoxylation reaction is limited with 2-pyridyl, oxime and *NH*-acetyl directing group substituted aromatics.[4-7]

Recently, a less expensive ruthenium complex has gained tremendous attention in heteroatom directed C–H bond activation of aromatics due to its remarkable reactivity and selectivity. Ruthenium catalyzed *ortho* arylation, alkenylation, hydroxylation and amination of aromatics have been reported in the literature.[17,18] However, there is no report on *ortho* benzoxylation of aromatics in the presence of a ruthenium catalyst. In this chapter we are discourse unprecedented oxidative *ortho* benzoxylation of substituted acetanilides or *N*-Alkyl Benzamides with benzoic acids in the presence of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and $(NH_4)_2S_2O_8$ in a highly regioselective manner.

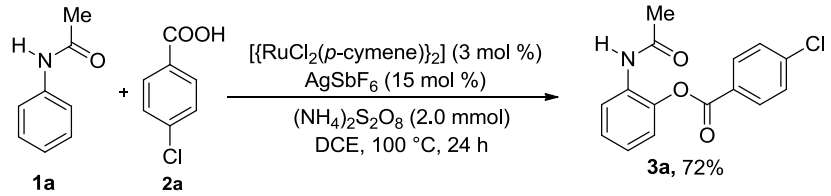
4A: Ru-Catalyzed Oxidative *ortho* Benzoxylation of Acetanilides with Aromatic Acids

4A.1: Results and Discussion

The reaction of acetanilide (**1a**) with 4-chlorobenzoic acid (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (15 mol %) and $(NH_4)_2S_2O_8$ (2.0 equiv) in 1,2-dichloroethane (DCE) at 100 °C for 24 h afforded *ortho* benzoxylated acetanilide **3a** in 72% isolated yield (Scheme 4.13). Initially, the reaction of **1a** and **2a** was tested with various oxidants (2.0 mmol) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] and $AgSbF_6$ in DCE at 100 °C for 24 h. Various oxidants such as Ag_2CO_3, AgOAc, Ag_2O, $Cu(OAc)_2$, CsOAc, KOAc, NaOAc, $K_2S_2O_8$, $PhI(OAc)_2$, $Na_2S_2O_8$ and oxone were examined. Among them, only silver salts such Ag_2CO_3, AgOAc and Ag_2O were active for the reaction, giving **3a** in 78%, 51% and 49% NMR yields, respectively. The yield of product the **3a** was determined by the ^{1}H NMR integration method using mesitylene as an internal standard. Then, the catalytic reaction was tested with $(NH_4)_2S_2O_8$ oxidant in order to avoid the silver salt oxidant. Gratifyingly, product **3a** was observed in 80% NMR yield. Next, the catalytic reaction was tested with various solvents such as DCE, chlorobenzene, THF, DMSO, DMF, DME, 1,2-dioxane, toluene, benzene, MeOH, *tert*-BuOH and AcOH. Among them, DCE solvent was effective for the reaction, providing **3a** in 80% NMR yield. Chlorobenzene was partially effective for the reaction, affording **3a** in moderate 49% yield. Remaining solvents were totally inactive for the reaction. The reaction was tried with a catalytic amount of $AgBF_4$, AgOTf and KPF_6 instead of $AgSbF_6$ (15 mol %). AgOTf was slightly effective for the reaction, yielding **3a** in 42% yield. Remaining additives were not effective for the reaction. The control experiments clearly revealed that a catalytic amount of $AgSbF_6$ and ruthenium complex were crucial for the reaction.

4A.2: Optimization Studies

Table 4.1: Optimization Studies with Various Oxidant and Additives



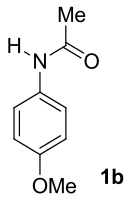
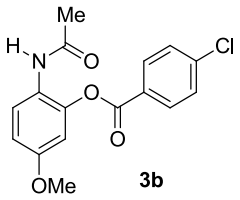
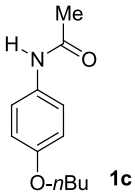
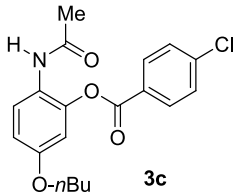
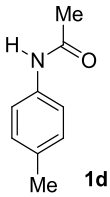
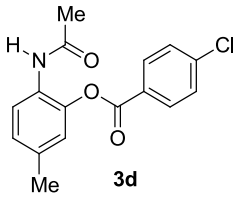
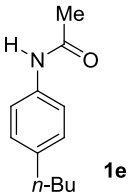
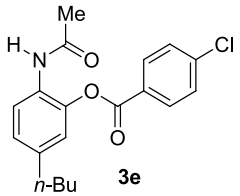
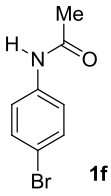
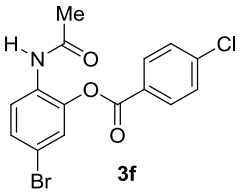
entry	solvent	oxidant	additive	yield of **3a** (%)[b]
1	$ClCH_2CH_2Cl$	$(NH_4)_2S_2O_8$	$AgBF_4$	NR
2	$ClCH_2CH_2Cl$	$(NH_4)_2S_2O_8$	KPF_6	NR
3	$ClCH_2CH_2Cl$	$(NH_4)_2S_2O_8$	AgOTf	42
4	$ClCH_2CH_2Cl$	$(NH_4)_2S_2O_8$	$AgSbF_6$	80
5	$ClCH_2CH_2Cl$	Ag_2CO_3	$AgSbF_6$	78
6	$ClCH_2CH_2Cl$	AgOAc	$AgSbF_6$	51
7	$ClCH_2CH_2Cl$	Ag_2O	$AgSbF_6$	49
8	$ClCH_2CH_2Cl$	$Cu(OAc)_2$	$AgSbF_6$	NR
9	$ClCH_2CH_2Cl$	CsOAc	$AgSbF_6$	NR
10	$ClCH_2CH_2Cl$	KOAc	$AgSbF_6$	NR
11	$ClCH_2CH_2Cl$	NaOAc	$AgSbF_6$	NR
12	$ClCH_2CH_2Cl$	$K_2S_2O_8$	$AgSbF_6$	NR
13	$ClCH_2CH_2Cl$	-	$AgSbF_6$	trace
14	$ClCH_2CH_2Cl$	$(NH_4)_2S_2O_8$	-	NR

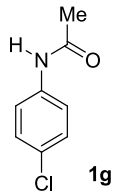
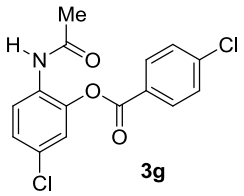
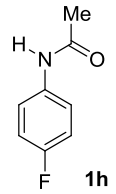
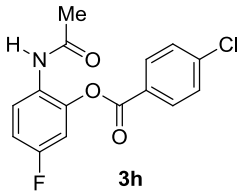
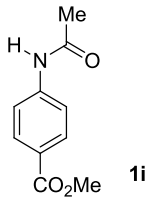
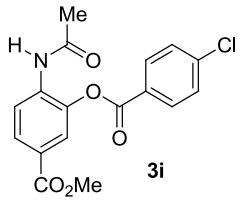
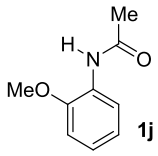
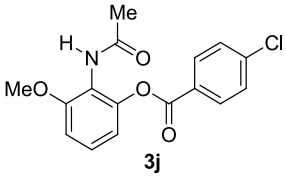
[a]All reactions were carried out under the following conditions: 1a (1.0 mmol), 2a (1.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (4 mol %), additive (15 mol %) and oxidant (2.0 mmol) in solvent (4.0 mL) at 100 °C for 24 h under the nitrogen atmosphere. [b]Yields were determined by the ^{1}H NMR integration method, using mesitylene as an internal standard.

The scope of *ortho* benzoxylation of various substituted acetanilides **1** with 4-chlorobenzoic acid (**2a**) under the optimized reaction conditions was examined (Table 4.1). The reaction of 4-methoxy **1b** and 4-*n*-butoxy **1c** acetanilides with **2a** provided coupling products **3b** and **3c** in 72% and 75% yields, respectively (entries 1 and 2). Similarly, other electron-donating group substituted acetanilides such as 4-methyl **1d** and 4-*n*-butyl **1e** acetanilides yielded the corresponding coupling products **3d** and **3e** in 66% and 72% yields, respectively (entries 3 and 4). This result clearly revealed that more electron releasing substituents such as O-*n*Bu and *n*-Bu gave slightly better yields than a

less electron releasing substituents such as OMe and Me. Halogen group substituted acetanilides were also compatible for the reaction. Thus, the reaction of 4-bromo **1f**, 4-chloro **1g** and 4-fluoro **1h** acetanilides with **2a** gave the corresponding *ortho* benzoxylated acetanilides **3f-h** in 74%, 73% and 71% yields, respectively (entries 5-7). The catalytic reaction also worked effectively with electron-withdrawing group substituted acetanilide **1i**. The reaction of 4-methyl ester acetanilide (**1i**) with **2a** yielded product **3i** in 69% yield (entry 8). It is important to note that an ester is also a good directing group for the C-H bond activation reaction. However, in the reaction, the C-H bond activation takes place only *ortho* to the NHCOMe of the aromatic moiety. *Ortho* Methoxy acetanilide **1j** was also efficiently involved in the reaction with **2a**, providing coupling product **3j** in 67% yield (entry 9).

Table 4.2: The Coupling of Substituted Acetanilides **1** with 4-Chlorobenzoic acid (**2a**) [a]

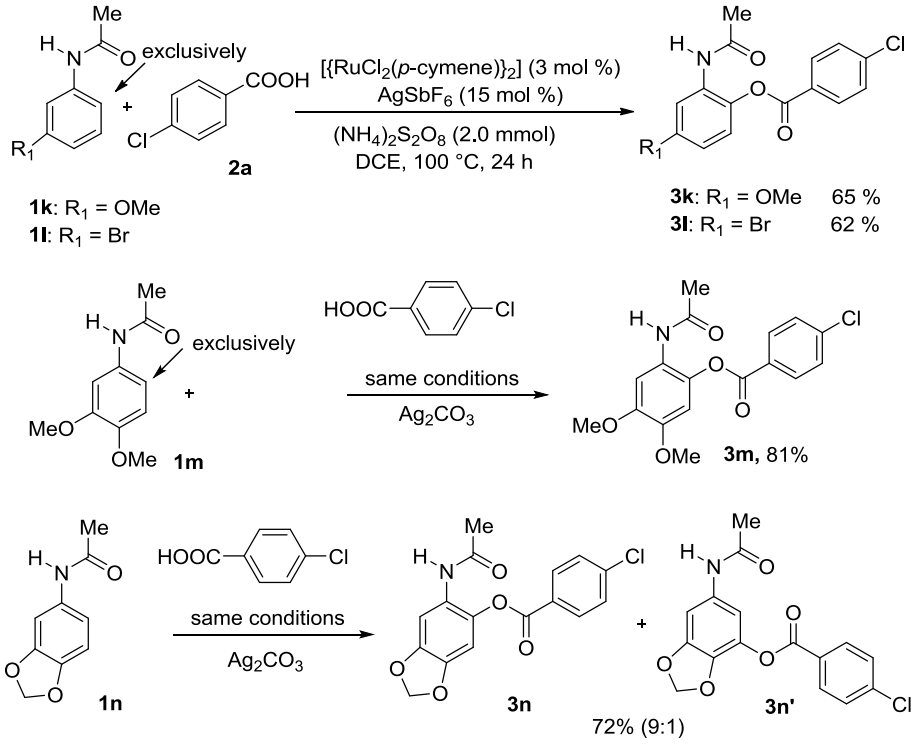
entry	**1**	**3**	yield (%)[b]
1	 **1b**	 **3b**	72
2	 **1c**	 **3c**	75
3	 **1d**	 **3d**	66
4	 **1e**	 **3e**	72
5	 **1f**	 **3f**	74

6	 **1g**	 **3g**	73
7	 **1h**	 **3h**	71
8	 **1i**	 **3i**	69
9	 **1j**	 **3j**	67

[a]All reactions were carried out using **1b-k** (1.0 mmol), **2a** (1.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (15 mol %) and $(NH_4)_2S_2O_8$ (2.0 mmol) in 1,2-dichloroethane at 100 °C for 24 h. [b]Isolated yield.

4A.3: Regioselective Studies

Next, the regioselectivity of unsymmetrical acetanilides 1k-n with 4-chlorobenzoic acid (**2a**) was studied (Scheme 4.13). 3-Methoxy acetanilide (**1k**) underwent *ortho* benzoxylation with **2a** selectively at a less hindered C-H bond under similar reaction conditions, affording **3k** in 65% yield. Likewise, 3-bromo acetanilide (**1l**) reacted with **2a** at a less hindered C-H bond, providing **3l** in 62% yield. Similarly, 3,4-dimethoxy acetanilide (**1m**) and 3,4-(methylenedioxy) acetanilide (**1n**) also underwent coupling with **2a** at a less hindered C-H bond, giving products **3m** and **3n** in 81% and 72% yields, respectively. However, in the reaction of **1n** with **2a**, the other regioisomer **3n'** was also observed in addition to **3n**. For the reaction of **1m** and **1n** with **2a**, Ag_2CO_3 (1.0 mmol) oxidant was used instead of $(NH_4)_2S_2O_8$ in CH_2Cl_2 solvent. Oxidant $(NH_4)_2S_2O_8$ was not effective for these reactions.



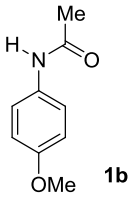
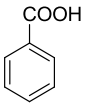
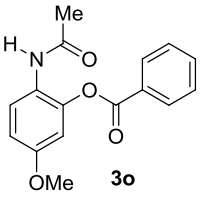
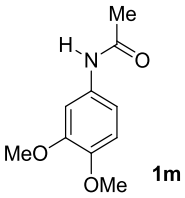
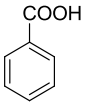
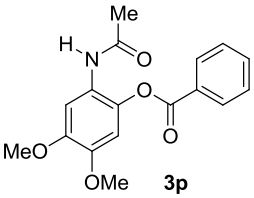
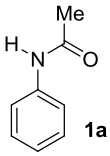
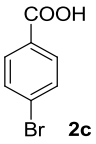
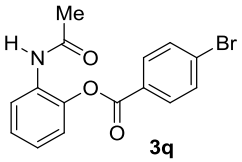
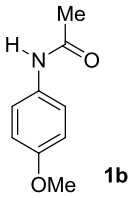
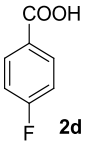
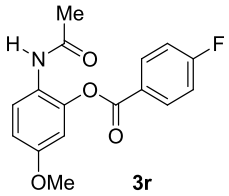
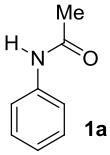
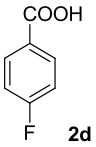
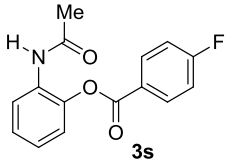
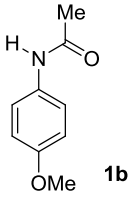
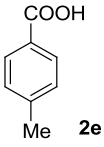
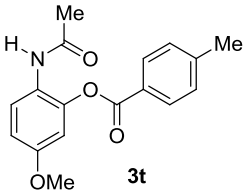
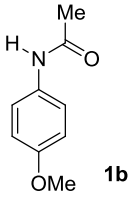
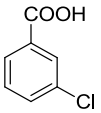
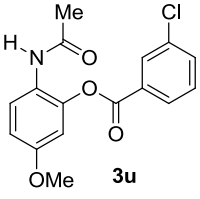
Scheme 4.13: Regioselectivity of unsymmetrical acetanilide

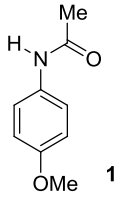
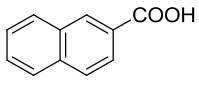
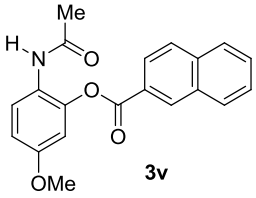
4A.4: Scope of the Substituted Benzoic Acids

This *ortho* benzoxylation reaction was successfully extended with various aromatic acids 2 (Table 4.3). Benzoic acid (**2b**) reacted with **1b** or **1m** under similar reaction conditions to yield the corresponding coupling products **3o** and **3p** in 72% and 78% yields, respectively. In the reaction of **1m** with **2b,** Ag_2CO_3 oxidant was used. 4-Bromobenzoic acid (**2c**) reacted with **1a,** giving coupling product **3q** in 68% yield. Electron deficient 4-fluorobenzoic acid (**2d**) and electron rich 4-methylbenzoic acid (**2e**) also efficiently participated in the reaction with **1a** or **1b**, providing coupling products **3r-t** in 56%, 46% and 51% yields, respectively. Next, the catalytic reaction was tested with *meta* substituted benzoic acid. The reaction of *meta*-chloro benzoic acid **2f** with **1b** gave coupling product **3u** in 58% yield. 2-Naphthoic acid (**2g**) also nicely participated in the reaction, yielding product **3v** in 42% yield. In fact, the catalytic reaction was also tested with 4-cyano, 4-nitro, 4-acetyl and 4-methoxybenzoic acids. However, in these reactions, no expected coupling products were observed. These results clearly showed that the catalytic reaction is highly sensitive to the type of the substituent present on the aromatic ring of the benzoic acids. Moderate electron releasing as well as electron withdrawing substituents such as Me, H, Br, Cl and F on the aromatic acids nicely participated in the reaction. But,

strong electron donating as well as electron withdrawing substituents such as OMe, NO_2, CN and COMe on the aromatic acids were not suitable substrates for the reaction.

Table 4.3: Scope of Substituted Benzoic Acids

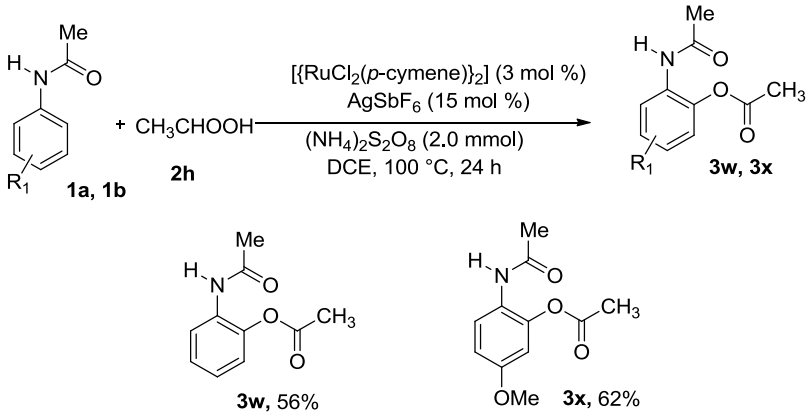
entry	**1**	**2**	**3**	yield (%)[b]
1	 **1b**	 **2b**	 **3o**	72
2	 **1m**	 **2b**	 **3p**	78[c]
3	 **1a**	 **2c**	 **3q**	68
4	 **1b**	 **2d**	 **3r**	56
5	 **1a**	 **2d**	 **3s**	46
6	 **1b**	 **2e**	 **3t**	51
7	 **1b**	 **2f**	 **3u**	58

8	 **1b**	 **2g**	 **3v**	42

[a]All reactions were carried out using **1b-k** (1.0 mmol), **2a** (1.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (15 mol %) and $(NH_4)_2S_2O_8$ (2.0 mmol) in 1,2-dichloroethane at 100 °C for 24 h. [b]Isolated yield. [c]Ag_2CO_3 (2.0 mmol)is used insted of $(NH_4)_2S_2O_8$ (2.0 mmol)

4A.5: The Reaction of 1a or 1b with Acetic Acid

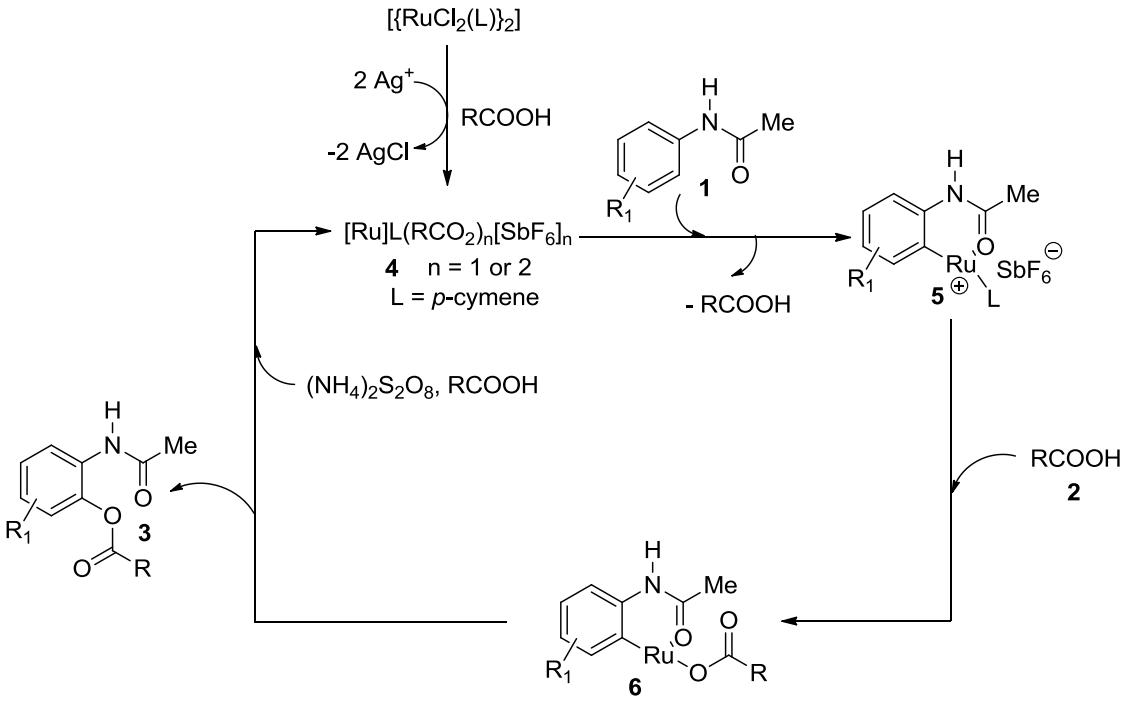
The catalytic reaction was also compatible with acetic acid (**2h**) (Scheme 4.15). Treatment of acetanilide (**1a**) with acetic acid (**2h**) under the optimized reaction conditions gave *ortho* acetoxylation product **3w** in 56% yield. Similarly, 4-methoxy acetanilide **1b** afforded *ortho* acetoxylation product **3x** in 62% yield.



Scheme 4.14: Scope of substituted acetanilide with acetic acid

4A.6: Mechanism

A plausible mechanistic rationale of *ortho* benzoxylation of acetanilides **1** with benzoic acids **2** is proposed in Scheme 4.15. The catalytic reaction likely proceeds via removal of chloride ligand by Ag^+ salt from [{$RuCl_2$(*p*-cymene)}$_2$] complex followed by reaction with aromatic carboxylic acid giving cationic ruthenium carboxylate complex **4**. Coordination of the carbonyl oxygen of acetanilide **1** to the ruthenium cationic species **4** followed by *ortho* metalation provides a six-membered ruthenacycle **5** and RCOOH. Coupling of carboxylic acid **2** into the ruthenacycle **5** affords an intermediate **6**. Reductive elimination of intermediate **6** gives the final product **3** and ruthenium (0) species. Later, $(NH_4)_2S_2O_8$ oxidizes Ru(0) to active ruthenium (II) carboxylate species **4** in the presence of carboxylic acid for the next catalytic cycle.



Scheme 4.15: Proposed mechanism

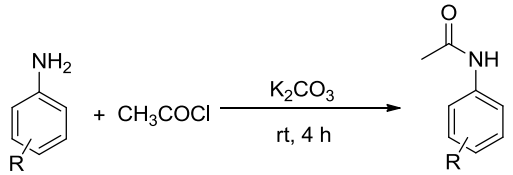
4A.7: Conclusion

1. We have discussed a ruthenium-catalyzed benzoxylation of acetanilides with benzoic acids to provide *ortho* benzoxylated acetanilides in good to moderate yields.
2. The catalytic reaction was also compatible with acetic acid.

4A.8: Experimental Section

Preparation of Acetanilides from Aromatic Amines:

In a 100 mL round bottom flask, substituted aromatic amines (1.0 gm), K_2CO_3 (3.0 equiv) and CH_2Cl_2 (20 mL) were taken. The corresponding acyl chloride was slowly added to the reaction mixture at room temperature stirred for 4 h. The reaction mixture was extracted with water and CH_2Cl_2 (100 mL). The organic layer was dried over Na_2SO_4. After evaporation of the solvents under vacuum, the compound purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure acetanilide (Scheme 4.21)**.**



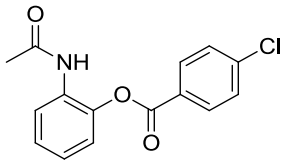
Scheme 4.16: Preparation of substituted acetanilides

General Procedure for the Benzoxylation of Acetanilides with Aromatic Acids Catalyzed by Ruthenium Complex:

[{$RuCl_2$(*p*-cymene)}$_2$] (0.03 mmol, 3 mol %), $AgSbF_6$ (0.15 mmol, 15 mol %), $(NH_4)_2S_2O_8$ (2.0 mmol), acetanilide**1** (1.00 mmol; for only **1a**, 1.20 mmol) and aromatic acid **2** (1.00 mmol) were taken in a 15 mL pressure tube, which was equipped with a magnetic stirrer and septum. The pressure tube was evacuated and purged with nitrogen gas three times (***Note:*** $AgSbF_6$ is moisture sensitive. Thus, $AgSbF_6$ was taken inside the nitrogen glove box). To the tube was then added 1,2-dichloroethane (4.0 mL) as the solvent via syringe and again the tube was evacuated and purged with nitrogen gas three times. Then, the septum was taken out and immediately a screw cap was used to cover the tube. The reaction mixture was allowed to stir at 100 °C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 and then filtered through Celite and silica gel. The filtrate was concentrated, and the crude residue was purified through a silica gel column (hexanes and ethyl acetate) to give pure **3**. For the preparation of compounds **3m**, **3n** and **3p**, oxidant Ag_2CO_3 (1.0 mmol) was used and DCM (4.0 mL) was used as a solvent (***Note:*** Ag_2CO_3 is moisture-sensitive. Thus, Ag_2CO_3 was added inside the nitrogen glove box.)

4A.9: Spectral Data of Compounds

2-Acetamidophenyl 4-chlorobenzoate (3a).



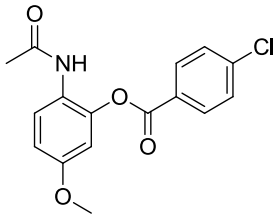
Colorless solid; eluent (30% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, *J* = 8.0 Hz, 2 H), 8.03 (t, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 7.24 – 7.19 (m, 1 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 2.03 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 163.8, 141.1, 140.8, 131.6, 129.9, 129.2, 127.1, 126.8, 125.3, 123.7, 122.2, 24.4.

HRMS (ESI): calc. for [($C_{15}H_{12}ClNO_3$)Na] (M+Na) 312.0403, measured 312.0414.

2-Acetamido-5-methoxyphenyl 4-chlorobenzoate (3b).



Colorless solid; eluent (30% ethyl acetate in hexanes).

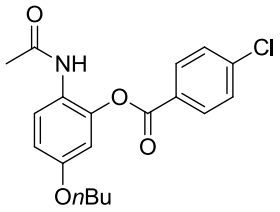
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3334, 2929, 1739, 1688, 1532, 1217 and 686.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, *J* = 8.0 Hz, 2 H), 7.65 (d, *J* = 8.0 Hz, 1 H) 7.42 (d, *J* = 8.0 Hz, 2 H), 7.01 (bs, 1 H), 6.74 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.68 (d, *J* = 8.0 Hz, 1 H), 3.72 (s, 3 H),1.95 (s, 3 H).

^{13}C NMR($CDCl_3$, 100MHz): δ 168.6, 163.8, 157.6, 143.5, 140.7, 131.6, 129.1, 127.1, 126.2, 122.5, 112.2, 108.1, 55.6, 23.8

HRMS (ESI): calc. for [($C_{16}H_{14}ClNO_4$)H] (M+H) 320.0690, measured 320.0689

2-Acetamido-5-butoxyphenyl 4-chlorobenzoate (3c).



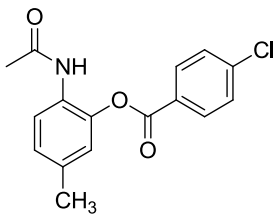
Yellow solid; eluent (40% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, *J* = 8.0 Hz, 2 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 6.93 (s, 1 H), 6.75 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.68 (d, *J* = 8.0 Hz, 1 H), 3.87 (t, *J* = 8.0 Hz, 2 H), 1.97 (s, 3 H), 1.72 – 1.65 (m, 2 H), 1.45 – 1.35 (m, 2 H), 0.89 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 163.8, 157.3, 143.5, 140.7, 131.6, 129.2, 127.1, 126.2, 122.3, 112.8, 108.5, 68.1, 31.1, 23.9, 19.1, 13.8.

HRMS (ESI): calc. for [($C_{19}H_{20}ClNO_4$)H] (M+H)362.1159, measured 362.1167.

2-Acetamido-5-methylphenyl 4-chlorobenzoate (3d).



Colorless solid; eluent (30% ethyl acetate in hexanes).

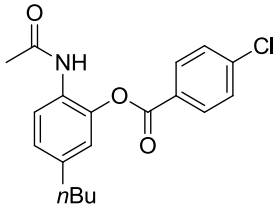
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3353, 2928, 1722, 1681, 1524, and 752.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.0, 3 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 7.08 (d, *J* = 8.0, 1 H), 6.98 (s, 1 H), 2.33 (s, 3 H), 2.32(s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 164.0, 141.5, 140.8, 135.8, 131.6, 129.2, 127.4, 124.1, 122.6, 24.3, 20.9.

HRMS (ESI): calc. for [($C_{16}H_{14}ClNO_3$)Na] (M+Na) 326.0560, measured 326.0565.

2-Acetamido-5-butylphenyl 4-chlorobenzoate (3e).



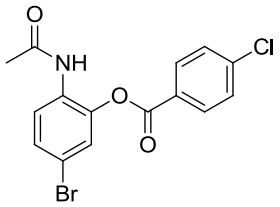
Colorless solid; eluent (30% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, *J* = 8.0 Hz, 2 H) 7.81 (d, *J* = 8.0 Hz, 1 H).7.44 (d, *J* = 8.0 Hz, 2 H), 7.03 (t, *J* = 8.0 Hz, 2 H), 6.94 (s, 1 H) 2.53 (t, *J* = 8.0 Hz, 2 H),1.99 (s, 3 H), 1.56 – 1.48 (m, 2 H), 1.31 – 1.25 (m, 2 H), 0.85 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 164.0, 141.5, 140.9, 140.7, 131.6, 129.2, 127.2, 127.2, 126.7, 124.1, 121.9, 35.0, 33.3, 24.2, 22.2, 13.9.

HRMS (ESI): calc. for [($C_{19}H_{20}ClNO_3$)H] (M+Na) 346.1210, measured 346.1222.

2-Acetamido-5-bromophenyl 4-chlorobenzoate (3f).



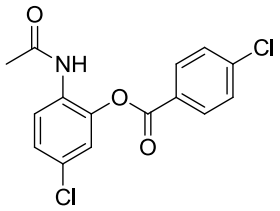
Yellow solid; eluent (25% ethyl acetate in hexanes).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.66 (s, 1 H), 8.13 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.70 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.61 (s, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 2.00 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 168.6, 163.4, 142.4, 138.9, 131.9, 130.4, 129.0, 128.0, 126.2, 125.6, 115.4, 23.5.

HRMS (ESI): calc. for [($C_{15}H_{11}BrClNO_3$)Na] (M+Na) 389.9509, measured 389.9506.

2-Acetamido-5-chlorophenyl 4-chlorobenzoate (3g).



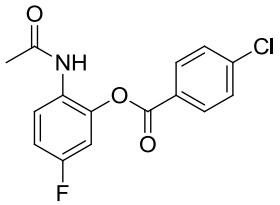
Colorless solid; eluent (25% ethyl acetate in hexanes).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.66 (s, 1 H), 8.13 (d, *J* = 8.0 Hz, 2 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 2 H), 7.49 (d, *J* = 4.0 Hz, 1 H), 7.34 (dd, *J* = 8.0, 4.0 Hz, 1 H), 2.00 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 168.6, 163.3, 142.3, 138.9, 131.9, 130.0, 129.0, 128.0, 127.8, 126.1, 125.3, 123.4, 23.5.

HRMS (ESI): calc. for [($C_{15}H_{11}Cl_2NO_3$)Na] (M+Na) 346.0014 , measured 346.0021.

2-Acetamido-5-fluorophenyl 4-chlorobenzoate (3h).



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

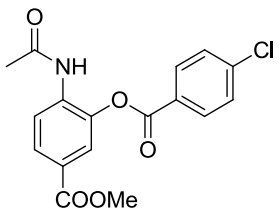
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3348, 1724, 1682, 1265 and 753.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, *J* = 8.0 Hz, 2 H) 7.86 (t, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.14 (s, 1 H), 6.91 (bs, 2 H), 1.99 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.4, 163.4, 158.1, 141.0, 131.6, 129.3, 126.7, 126.1 and 126.06 (F coupling), 125.4 and 125.3 (F coupling), 113.6 and 113.4 (F coupling), 110.3 and 110.0 (F coupling), 24.1.

HRMS (ESI): calc. for [($C_{15}H_{11}ClFNO_3$)Na] (M+Na) 330.0309, measured 330.0315.

Methyl 4-acetamido-3-((4-chlorobenzoyl)oxy)benzoate (3i).



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

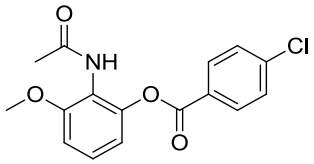
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3366, 2928, 1700, 1597, 1261 and 673.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (bs, 1 H), 8.06 (d, *J* = 8.0 Hz, 2 H), 7.88 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.80 (s, 1 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 3.82 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.8, 163.6, 141.1, 134.4, 131.6, 131.5, 129.3, 128.8, 128.3, 126.7, 123.6, 52.2, 24.8.

HRMS (ESI): calc. for [($C_{17}H_{14}ClNO_5$)Na] (M+Na) 370.0458, measured 370.0454.

2-Acetamido-3-methoxyphenyl 4-chlorobenzoate (3j).



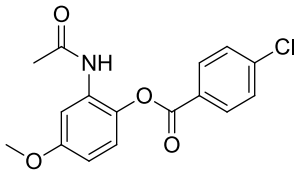
Colorless solid; eluent (30% ethyl acetate in hexanes).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.24 (s, 1 H), 8.05 (d, *J* = 8.0 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 2 H), 7.33 (t, *J* = 8.0 Hz, 1 H), 7.01(d, *J* = 8.0 Hz, 1 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 3.82 (s, 3 H),1.87(s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 168.1, 162.9, 155.3, 147.0, 138.9, 131.4, 129.1, 128.1, 126.9, 119.2, 115.1, 109.2, 55.9, 22.5.

HRMS (ESI): calc. for [($C_{16}H_{14}ClNO_4$)H] (M+H) 320.0690, measured 320.0690.

2-Acetamido-4-methoxyphenyl 4-chlorobenzoate (3k).



Colorless solid; eluent (30% ethyl acetate in hexanes).

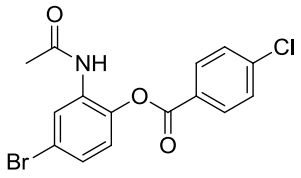
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3450, 2917, 1724, 1685 and 853.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, *J* = 8.0 Hz, 2 H), 7.74 (s, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.13 (b, 1 H), 7.02 (d, *J* = 12.0, 1 H), 6.64 (d, *J* = 8.0 Hz, 1 H), 3.75 (s, 3 H),2.03 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 164.2, 157.8, 140.7, 134.1, 131.6, 130.6, 129.2, 127.2, 122.5, 110.7, 108.0, 55.7, 24.6.

HRMS (ESI): calc. for [($C_{16}H_{14}ClNO_4$)H] (M+H) 320.0690, measured 320.0690.

2-Acetamido-4-bromophenyl 4-chlorobenzoate (3l).



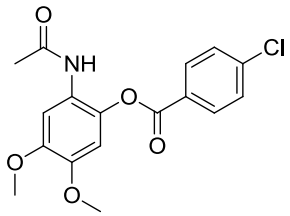
Colorless solid; eluent (30% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (s, 1 H), 8.05 (d, *J* = 8.0 Hz, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H) 7.23 (d, *J* = 8.0, Hz, 1 H) 7.17 (s, 1 H), 7.00 (d, *J* = 8.0, Hz, 1 H), 2.04 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 163.5, 141.1, 139.5, 131.6, 131.2, 129.3, 127.8, 126.7, 125.8, 123.5, 119.7, 24.5.

HRMS (ESI): calc. for [($C_{15}H_{11}BrClNO_3$)Na] (M+Na) 389.9509, measured 389.9508.

2-Acetamido-4,5-dimethoxyphenyl 4-chlorobenzoate (3m).



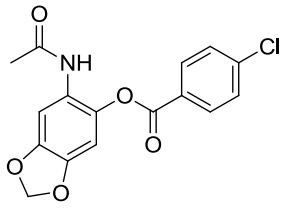
Colorless solid; eluent (50% ethyl acetate in hexanes).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.41 (s, 1 H), 8.12 (d, *J* = 8.0 Hz, 2 H) 7.68 (d, *J* = 8.0 Hz, 2 H),7.34 (s, 1 H), 6.95 (s, 1 H), 3.75 (s, 3 H), 3.72 (s, 3 H),1.94 (s, 3 H).

^{13}CNMR (DMSO-d_6,100 MHz): δ 168.3, 163.7, 146.1, 145.8, 138.7, 135.8, 131.7, 129.0, 128.4, 123.0, 108.6, 107.2, 55.9, 55.8, 23.2.

HRMS (ESI): calc. for [($C_{17}H_{16}ClNO_5$)H] (M+H) 350.0795, measured 350.0805.

6-Acetamidobenzo[*d*][1,3]dioxol-5-yl 4-chlorobenzoate (3n).



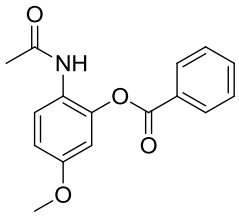
Yellow solid; eluent (40% ethyl acetate in hexanes).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.42 (s, 1 H), 8.11 (d, *J* = 8.0 Hz, 2 H) 7.68 (d, *J* = 8.0 Hz, 2 H),7.25 (s, 1 H), 6.98 (s, 1 H), 6.06 (s, 2 H), 1.93 (s, 3 H).

^{13}CNMR (DMSO-d_6, 100 MHz):δ 168.4, 163.7, 144.6, 144.0, 138.7, 136.6, 131.7, 129.0, 123.9, 106.2, 104.2, 101.8, 23.2.

HRMS (ESI): calc. for [($C_{16}H_{12}ClNO_5$)H] (M+H) 334.0482, measured 334.0491.

2-Acetamido-5-methoxyphenyl benzoate (3o).



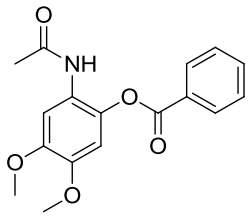
Brown solid; eluent (35% ethyl acetate in hexanes).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.40 (s, 1 H), 8.12 (d, *J* = 8.0 Hz, 2 H), 7.74 (t, *J* = 8.0 Hz, 1 H), 7.61 (t, *J* = 8.0 Hz, 2 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 6.91 (s, 1 H), 6.86 (d, *J* = 8.0 Hz, 1 H), 3.75 (s, 3 H), 1.92 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 168.3, 164.1, 156.7, 144.1, 133.9, 129.9, 129.3, 128.8, 128.4, 127.7, 126.3, 123.5, 111.6, 108.7, 55.6, 23.1.

HRMS (ESI): calc. for [($C_{16}H_{15}NO_4$)H] (M+H) 286.1079, measured 286.1086.

2-Acetamido-4,5-dimethoxyphenyl benzoate (3p).



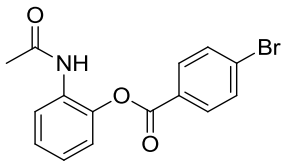
Brown solid; eluent (55% ethyl acetate in hexanes).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.41 (s, 1 H), 8.12 (d, *J* = 8.0 Hz, 2 H), 7.73 (t, *J* = 8.0 Hz, 1 H), 7.61 (t, *J* = 8.0 Hz, 2 H), 7.33 (s, 1 H), 6.94 (s, 1 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 1.94 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 168.3, 164.5, 146.1, 145.9, 136.1, 133.7, 129.9, 129.5, 128.8, 123.0, 108.7, 107.2, 55.9, 55.8, 23.2.

HRMS (ESI): calc. for [($C_{17}H_{17}NO_5$)H] (M+H) 316.1185, measured 316.1190.

2-Acetamidophenyl 4-bromobenzoate (3q).



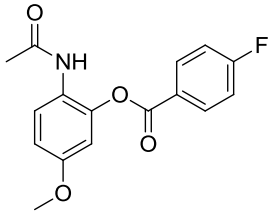
Colorless solid; eluent (25% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, *J* = 8.0 Hz, 1 H), 7.98 (d, *J* = 8.0 Hz, 2 H), 7.61 (d, *J* = 8.0 Hz, 2 H), 7.23 – 7.20 (m, 1 H), 7.16(bs, 1 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 2.02 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.4, 164.0, 141.2, 132.2, 131.6, 129.8, 129.5, 127.6, 126.7, 125.2, 123.8, 122.1, 24.3.

HRMS (ESI): calc. for [($C_{15}H_{12}BrNO_3$)H] (M+H) 334.0079, measured 334.0080.

2-Acetamido-5-methoxyphenyl 4-fluorobenzoate (3r).



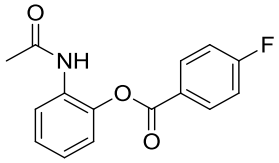
Yellow solid; eluent (30% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.18 (t, *J* = 8.0 Hz, 2 H), 7.00 (bs, 1 H), 6.81 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.73 (s, 1 H), 3.77 (s, 3 H), 2.02 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 167.7, 165.2, 157.7, 143.6, 133.0 and 132.9 (F coupling), 126.2, 124.9, 122.6, 116.2 and 116.0 (F coupling), 112.2, 108.1, 55.6, 23.9.

HRMS (ESI): calc. for [($C_{16}H_{14}FNO_4$)H] (M+H) 304.0985, measured 304.0992.

2-Acetamidophenyl 4-fluorobenzoate (3s).



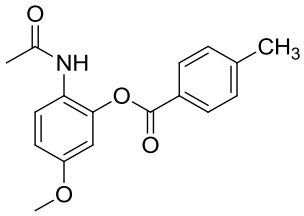
Colorless solid; eluent (30% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (t, *J* = 8.0 Hz, 2 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 7.22 (t, *J* = 8.0 Hz, 1 H), 7.19 – 7.13 (m, 4 H), 2.03 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 167.7, 165.2, 163.7, 141.2, 133.0 and 132.9 (F coupling), 129.9, 126.7, 125.2, 123.7, 122.2, 116.2 and 116.0 (F coupling), 24.5.

HRMS (ESI): calc. for [($C_{15}H_{12}FNO_3$)Na] (M+Na) 296.0699, measured 296.0696.

2-Acetamido-5-methoxyphenyl 4-methylbenzoate (3t).



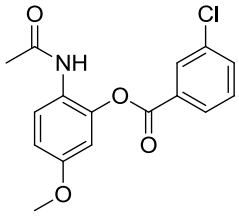
Yellow solid; eluent (30% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 6.99 (s, 1 H), 6.75 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 3.72 (s, 3 H), 2.39 (s, 3 H), 1.97 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.5, 164.7, 157.4, 145.1, 143.3, 130.3, 129.5, 125.84, 125.8, 122.8, 112.0, 108.1, 55.6, 24.0, 21.8.

HRMS (ESI): calc. for [($C_{17}H_{17}NO_4$)Na] (M+Na) 322.1055, measured 322.1067.

2-Acetamido-5-methoxyphenyl 3-chlorobenzoate (3u).



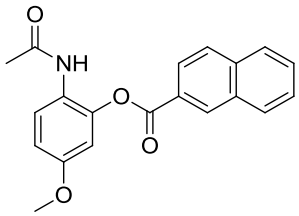
Colorless solid; eluent (35% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (s, 1 H), 8.01(d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 8.0, Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 8.0 Hz, 1 H), 6.94 (bs, 1 H), 6.77 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 3.73 (s, 3 H), 1.99 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 157.6, 143.4, 135.0, 134.1, 130.4, 130.3, 130.1, 128.4, 126.2, 122.5, 112.3, 108.0, 55.7, 24.0.

HRMS (ESI): calc. for [($C_{16}H_{14}ClNO_4$)H] (M+H) 320.0689, measured 320.0691.

2-Acetamido-5-methoxyphenyl 2-naphthoate (3v).



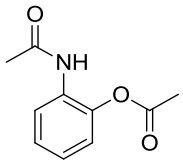
Yellow solid; eluent (30% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.74 (s, 1 H), 8.12 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 7.90 (t, *J* = 8.0 Hz, 2 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.61 (t, *J* = 8.0 Hz, 1 H), 7.56 (t, *J* = 8.0, Hz, 1 H), 7.19 (bs, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 6.80 (s, 1 H), 3.78 (s, 3 H), 2.01 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.7, 164.9, 157.5, 143.5, 135.9, 132.4, 132.3, 129.5, 128.9, 128.6, 127.8, 127.0, 126.0, 125.8, 125.2, 122.8, 112.1, 108.1, 55.6, 23.9.

HRMS (ESI): calc. for [($C_{20}H_{17}NO_4$)Na] (M+Na) 358.1055, measured 355.1057.

2-Acetamidophenyl acetate (3w).



Brown solid; eluent (50% ethyl acetate in hexanes).

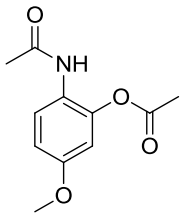
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3279, 2929, 1741, 1653, 1259, 888 and 747.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, *J* = 8.0 Hz, 1 H), 7.25 (bs, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 2.33 (s, 3 H), 2.14 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.8, 168.3, 140.7, 129.6, 126.4, 124.8, 123.1, 122.04, 24.4, 21.0.

HRMS (ESI): calc. for [($C_{10}H_{11}NO_3$)Na] (M+Na) 216.0637, measured 216.0642.

2-Acetamido-5-methoxyphenyl acetate (3x).



Pale yellow solid; eluent (60% ethyl acetate in hexanes).

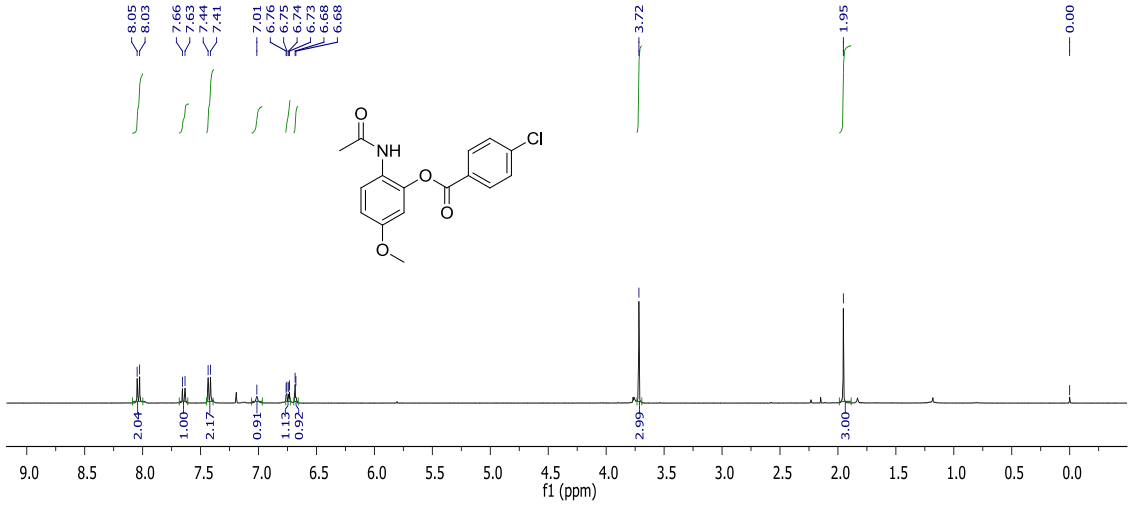
^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.25 (s, 1 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 6.80 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.73 (d, *J* = 4.0 Hz, 1 H), 3.72(s, 3 H), 2.26 (s, 3 H), 2.01 (s, 3 H).

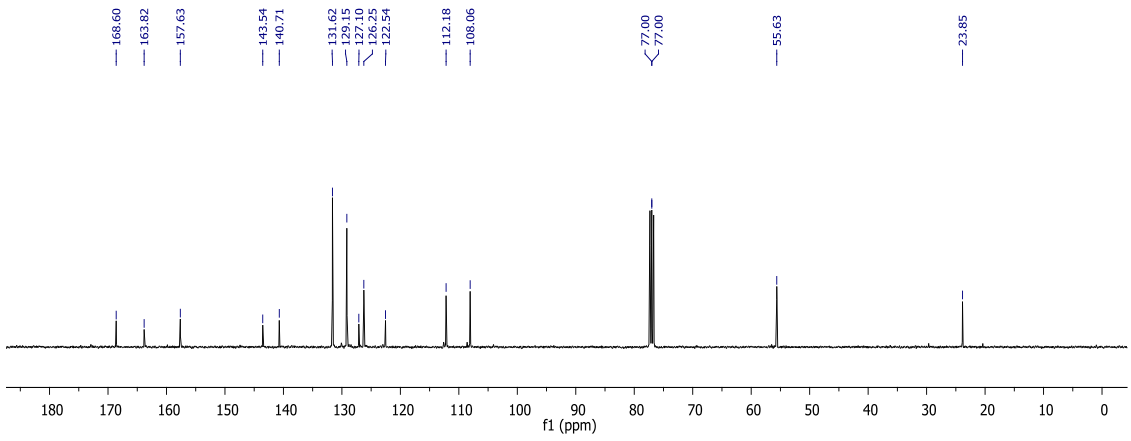
^{13}C NMR (DMSO-d_6, 100 MHz): δ 168.8, 168.2, 156.2, 143.1, 125.4, 123.5, 111.2, 108.7, 55.5, 23.3, 21.1.

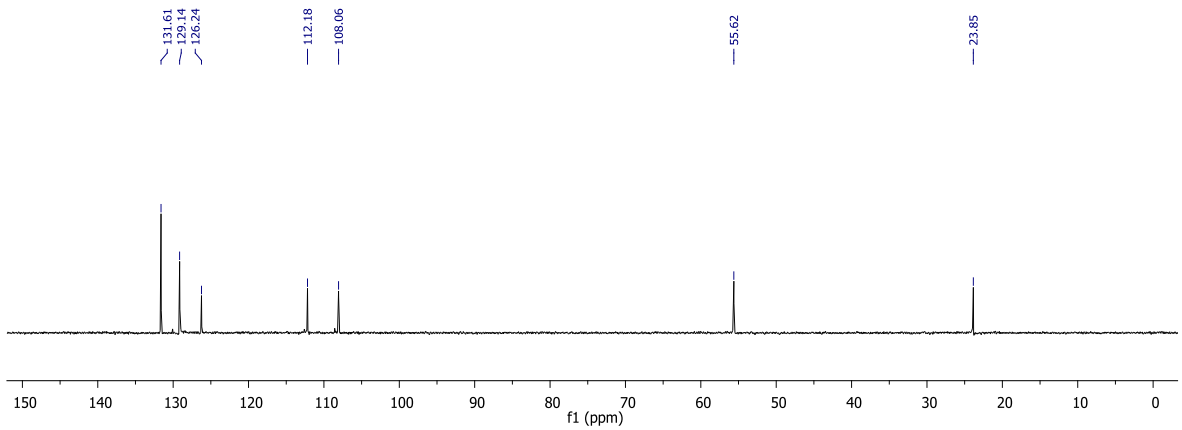
HRMS (ESI): calc. for [($C_{11}H_{13}NO_4$)Na] (M+Na) 246.0742, measured 246.0753.

4A.10: Spectral Copies of Selected Compounds

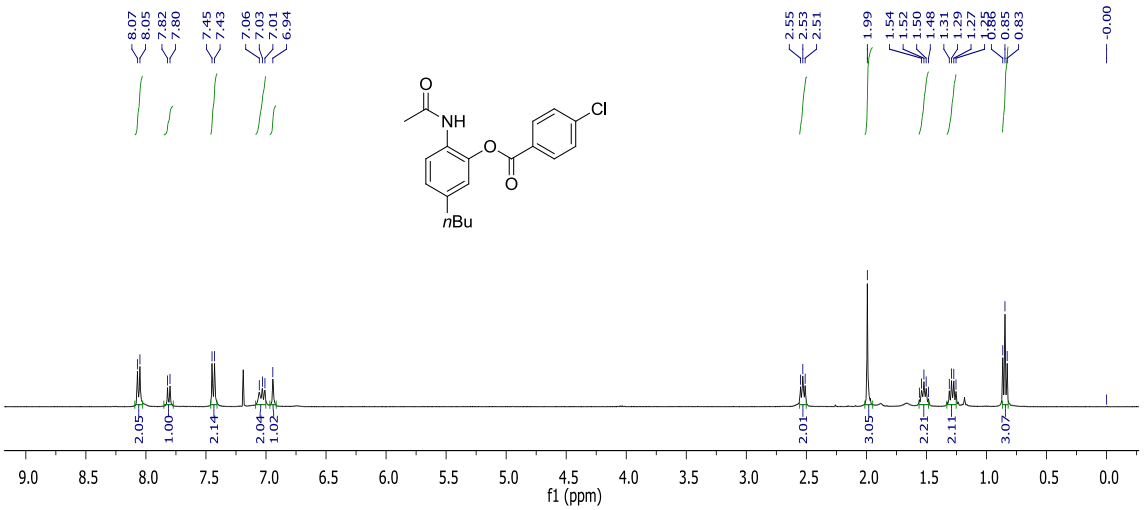
Spectral data of compound **3b**.

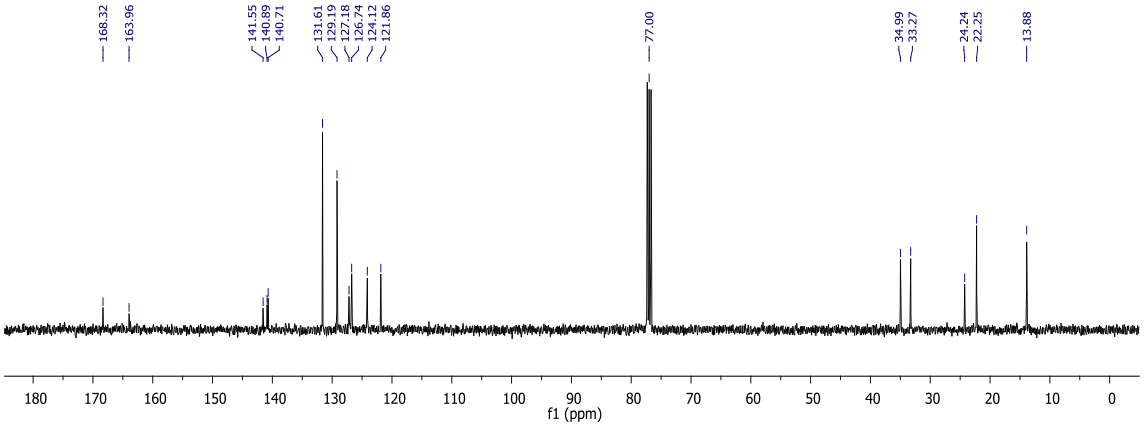




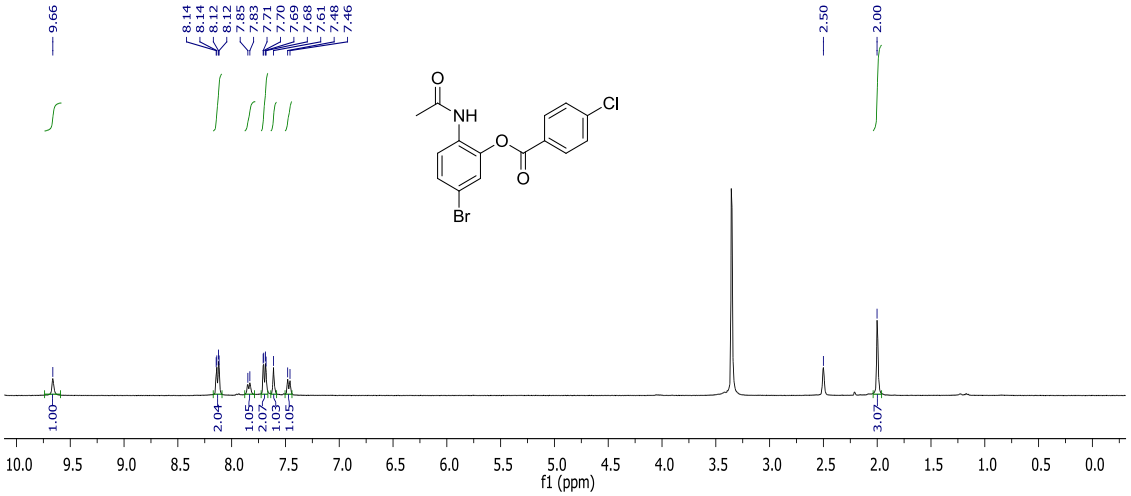


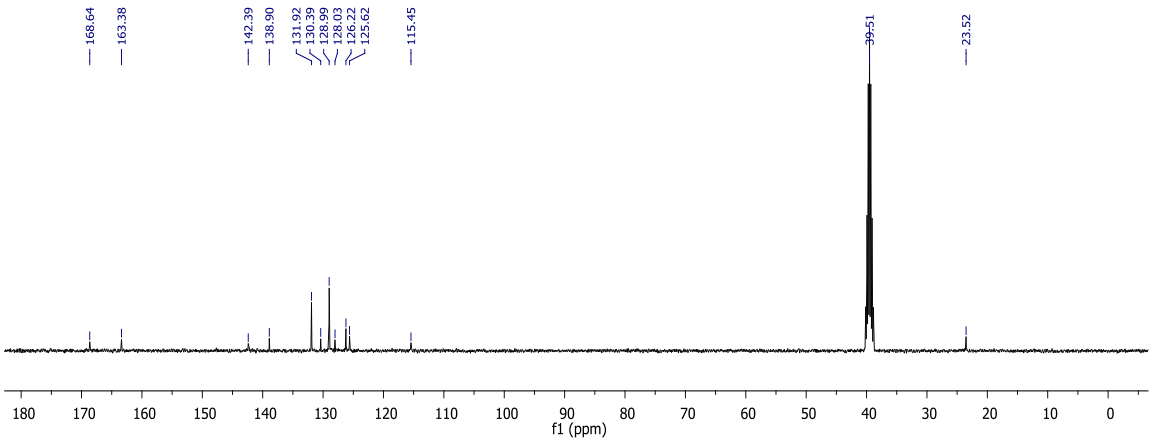
Spectral data of compound **3e**.

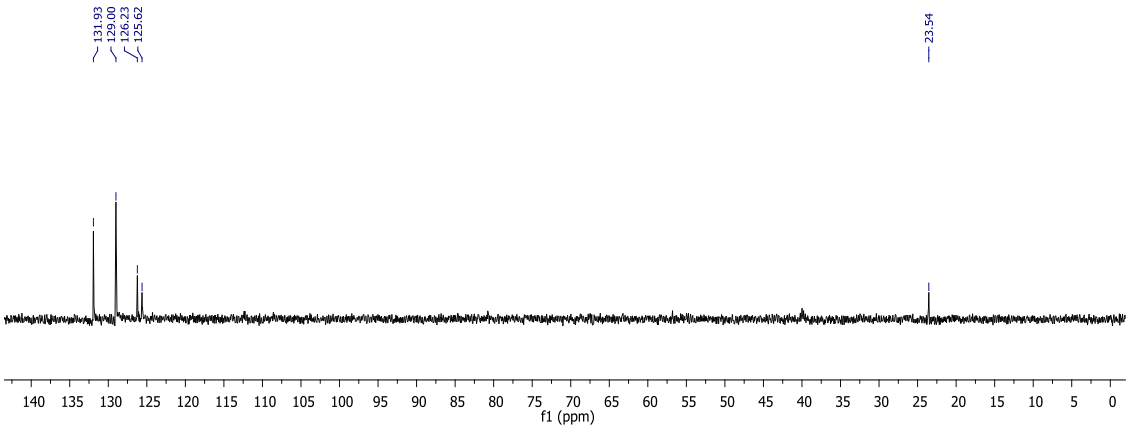




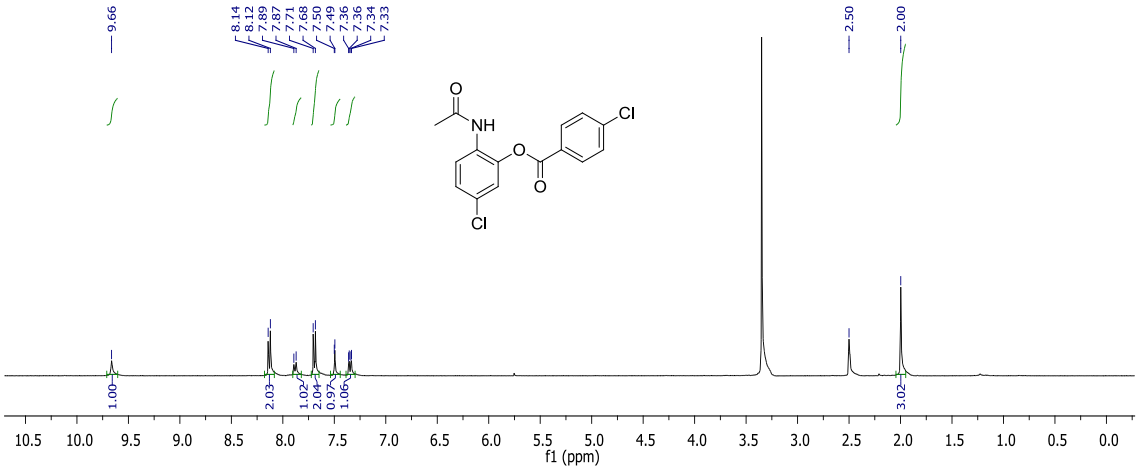
Spectral data of compound **3f**.

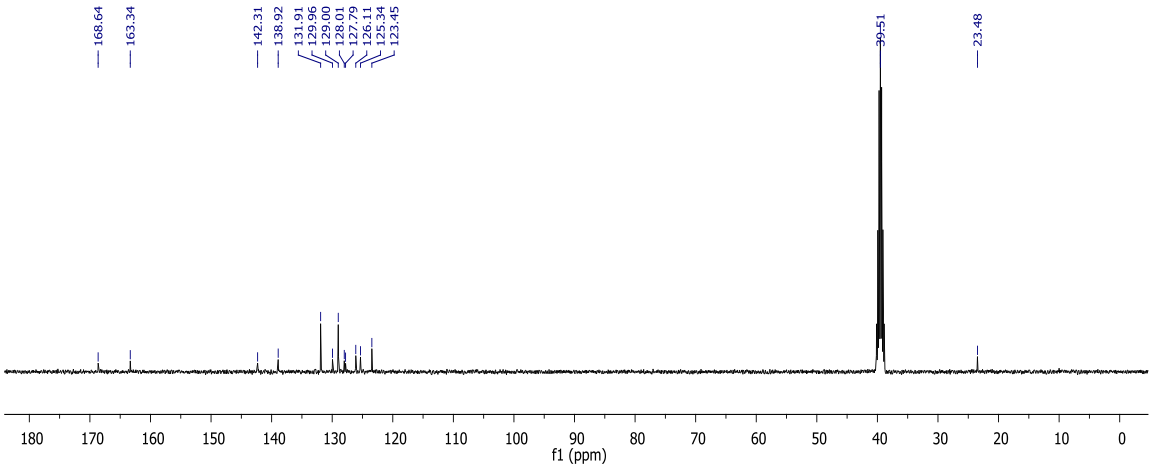


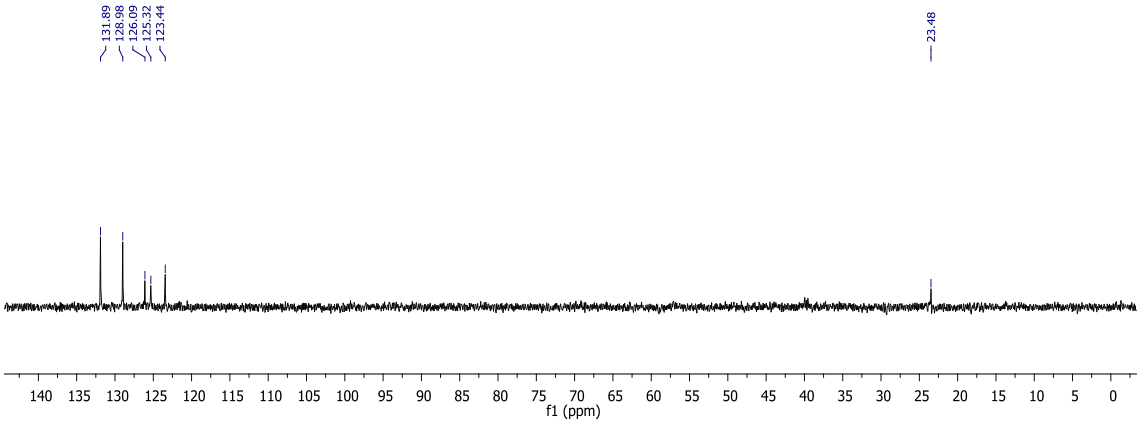




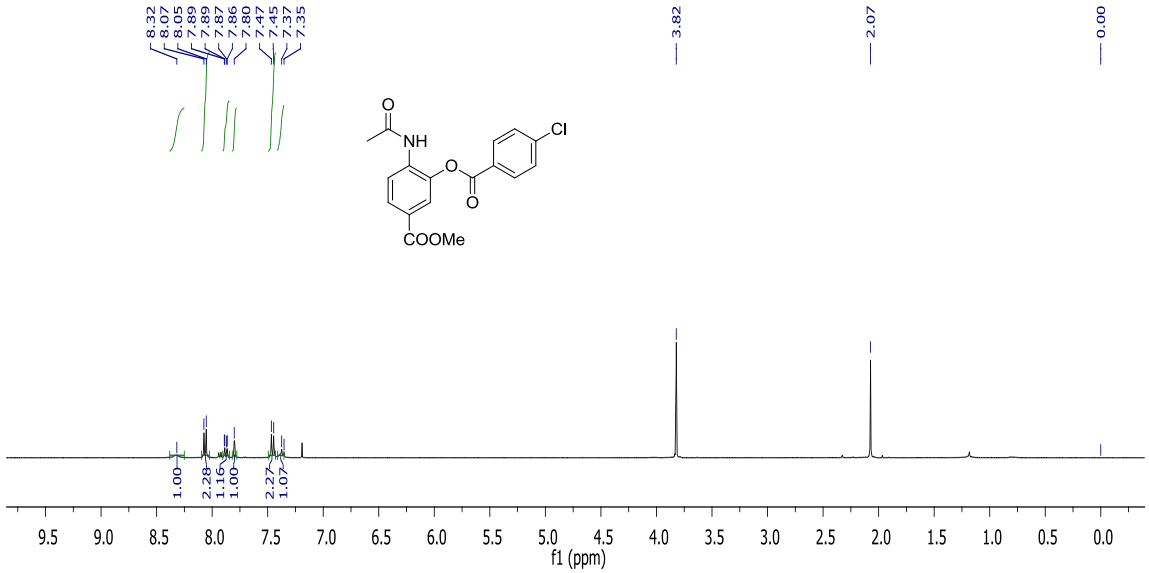
Spectral data of compound **3g**.

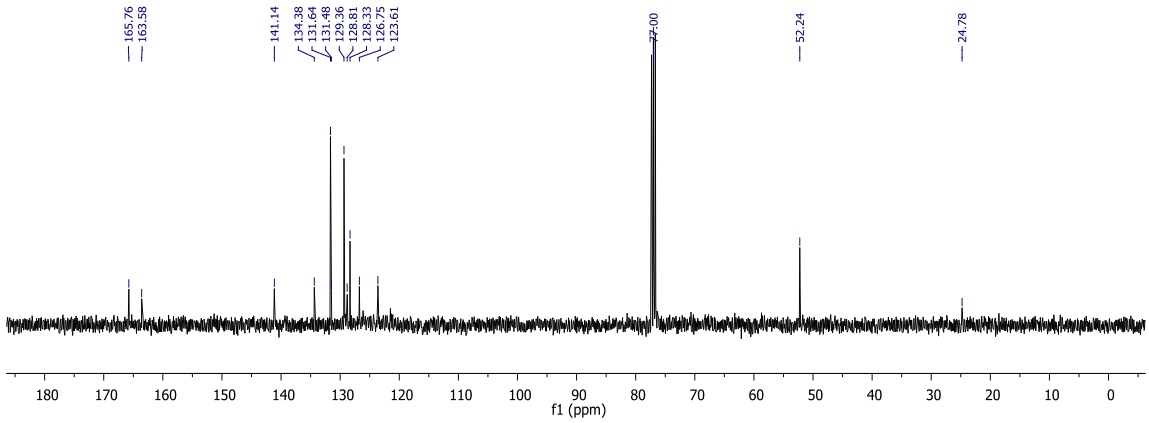




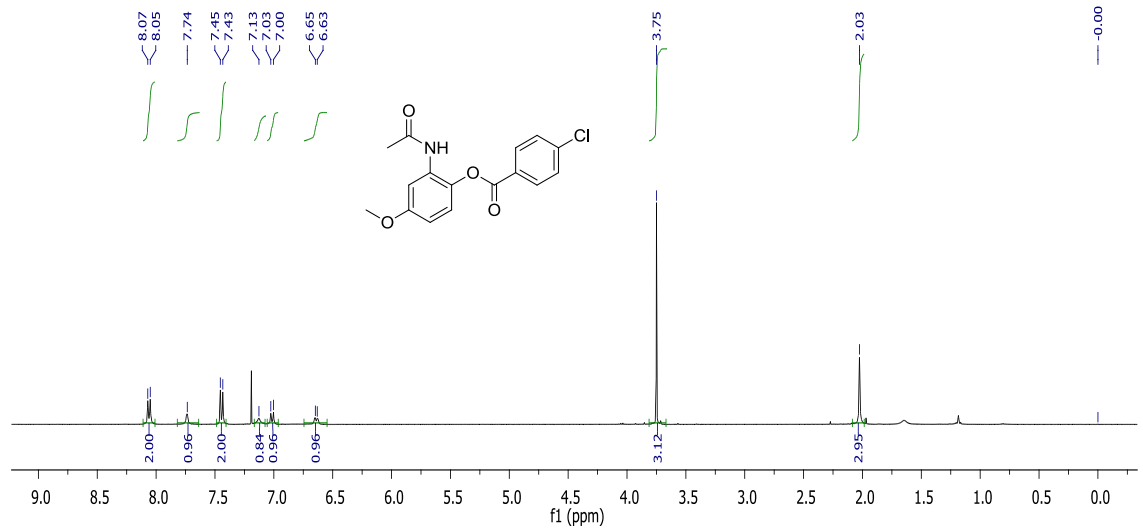


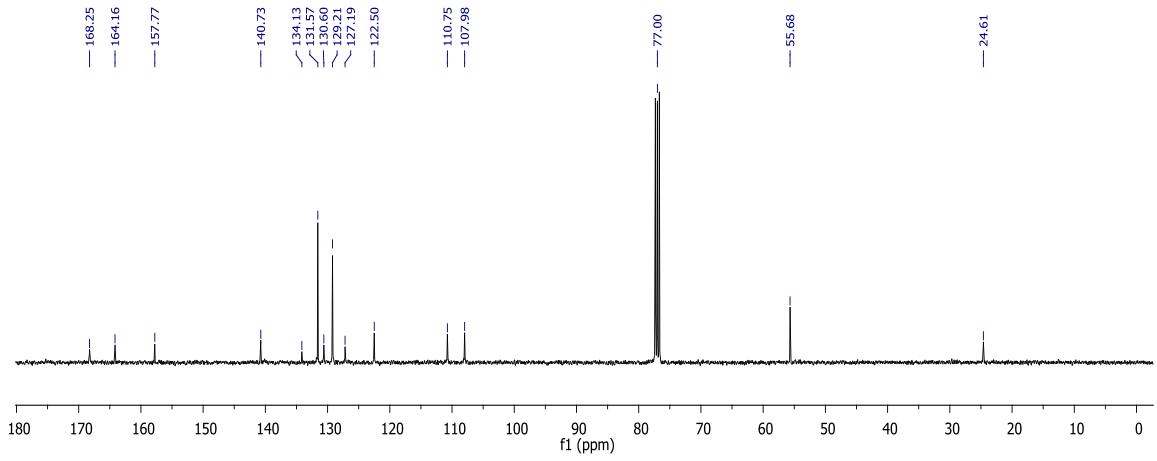
Spectral data of compound **3i**.

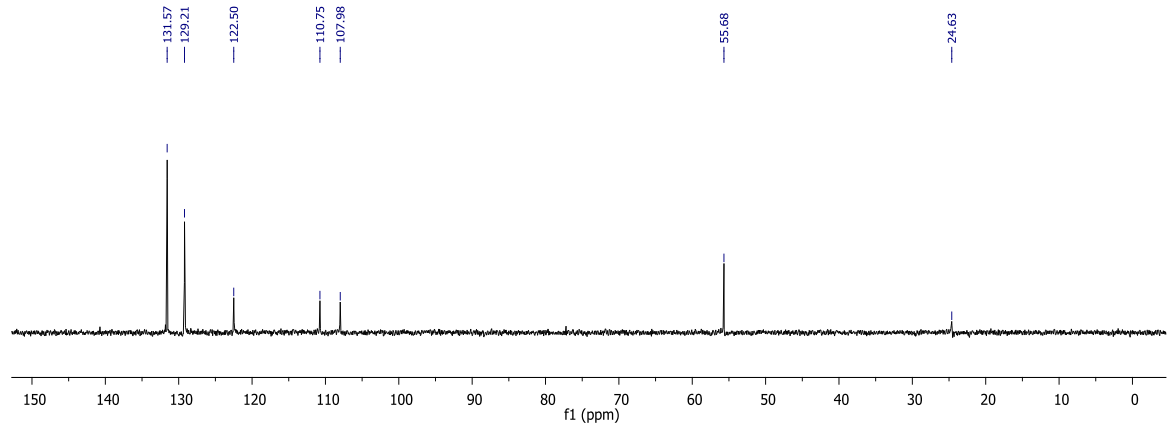




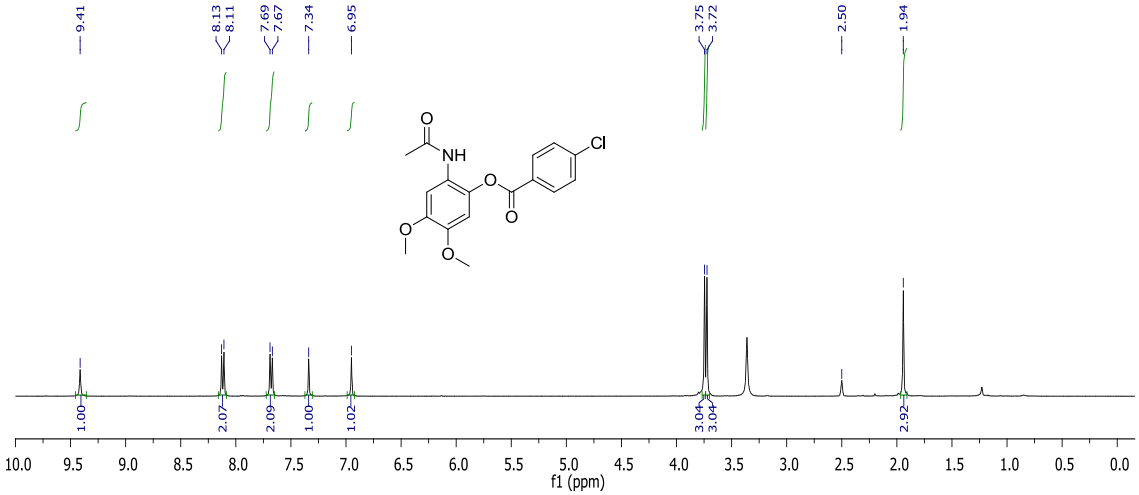
Spectral data of compound **3k**.

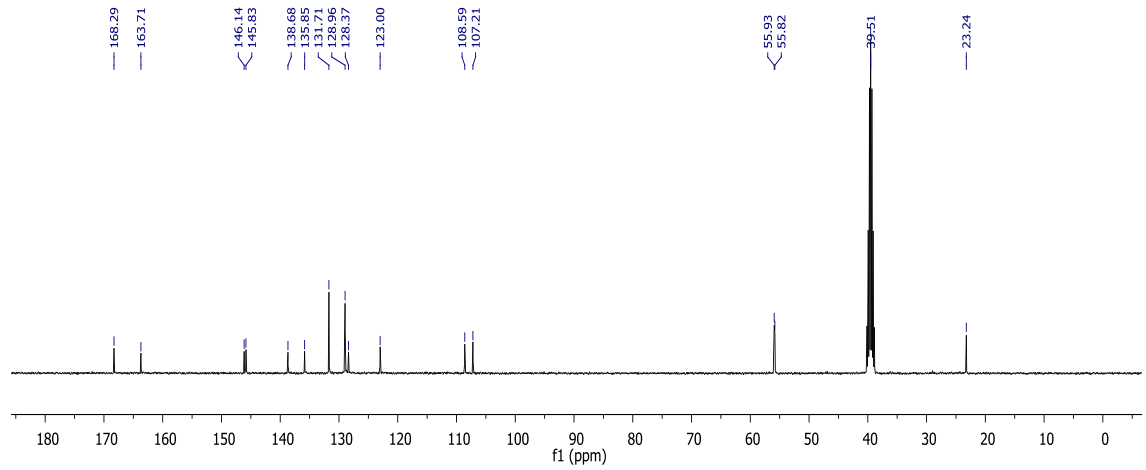


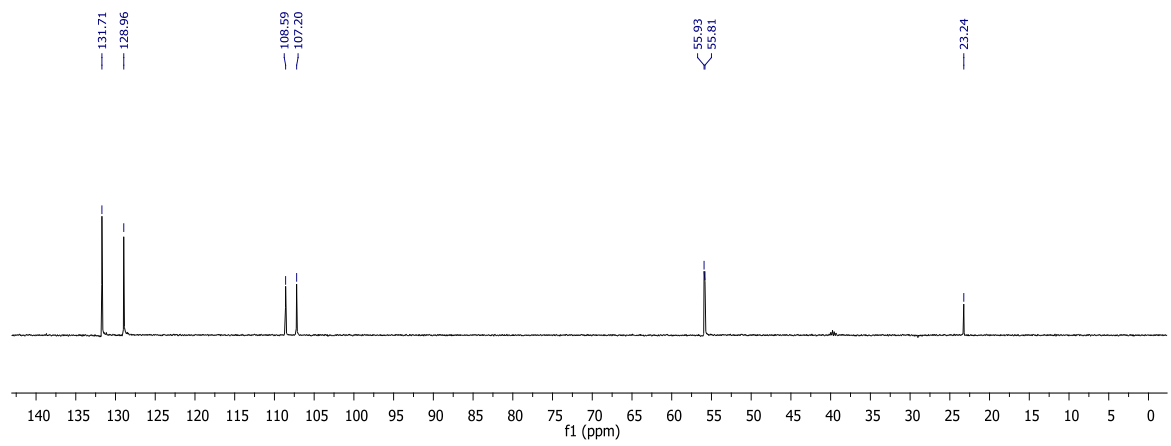




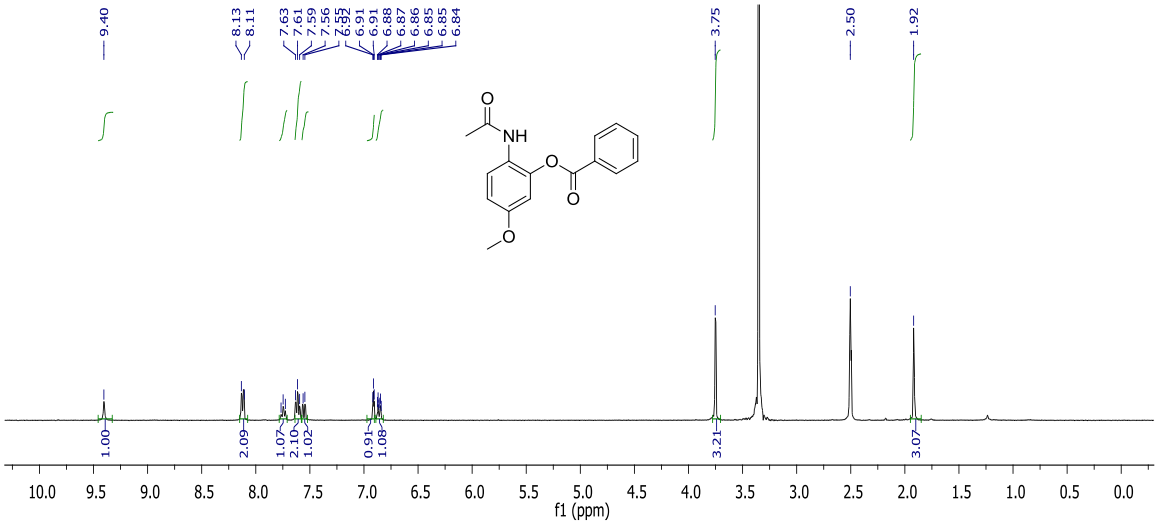
Spectral data of compound **3m**.

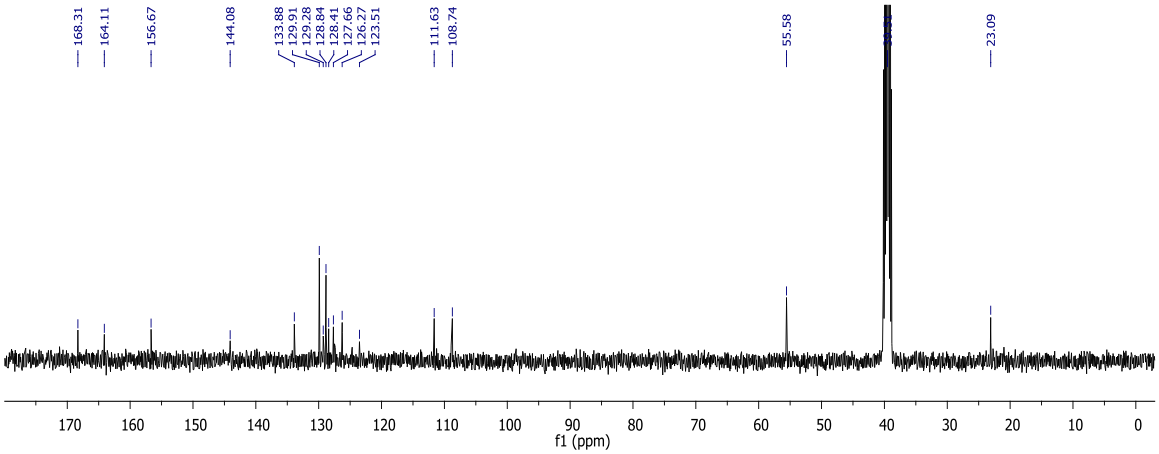




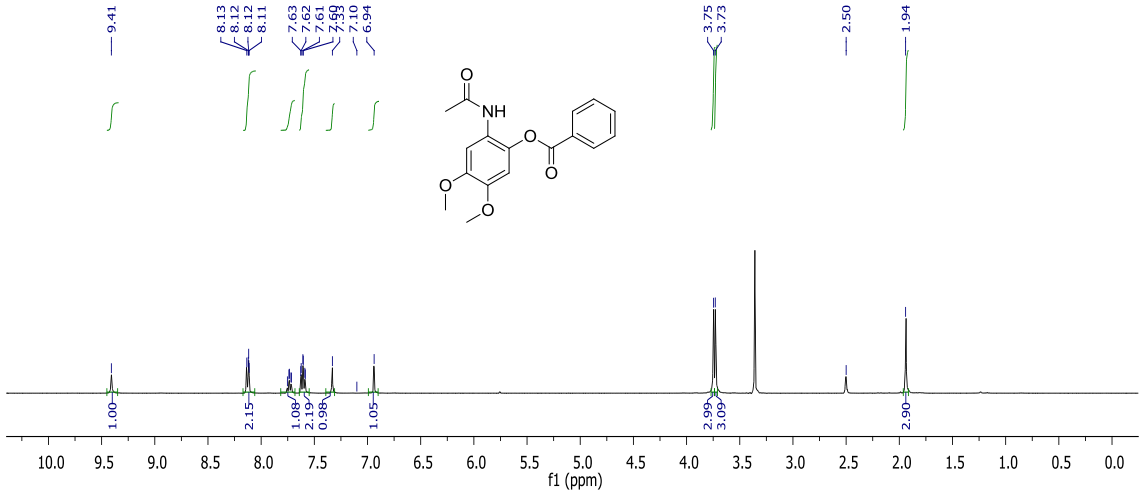


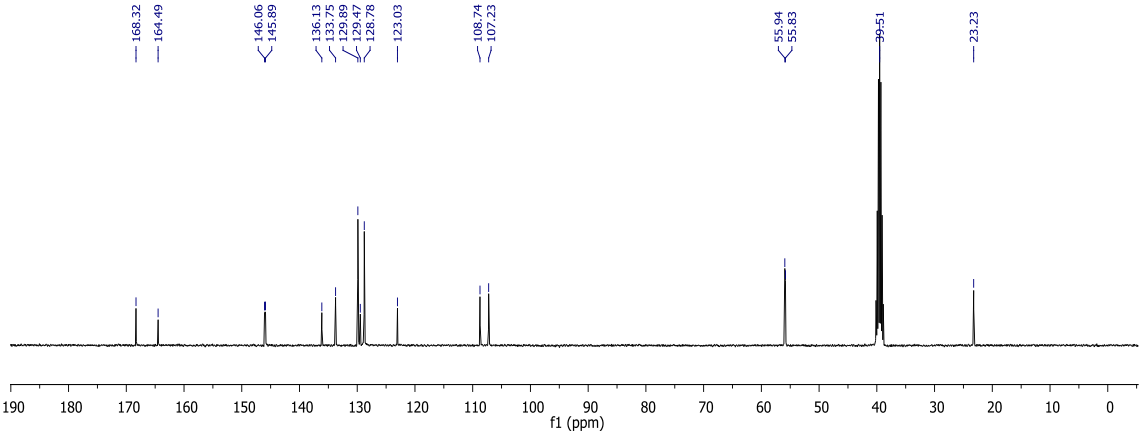
Spectral data of compound **3o**.

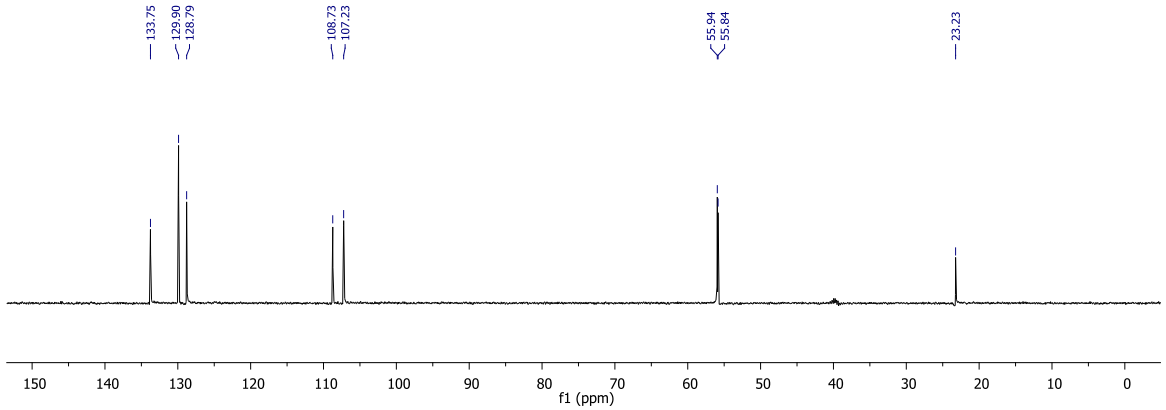




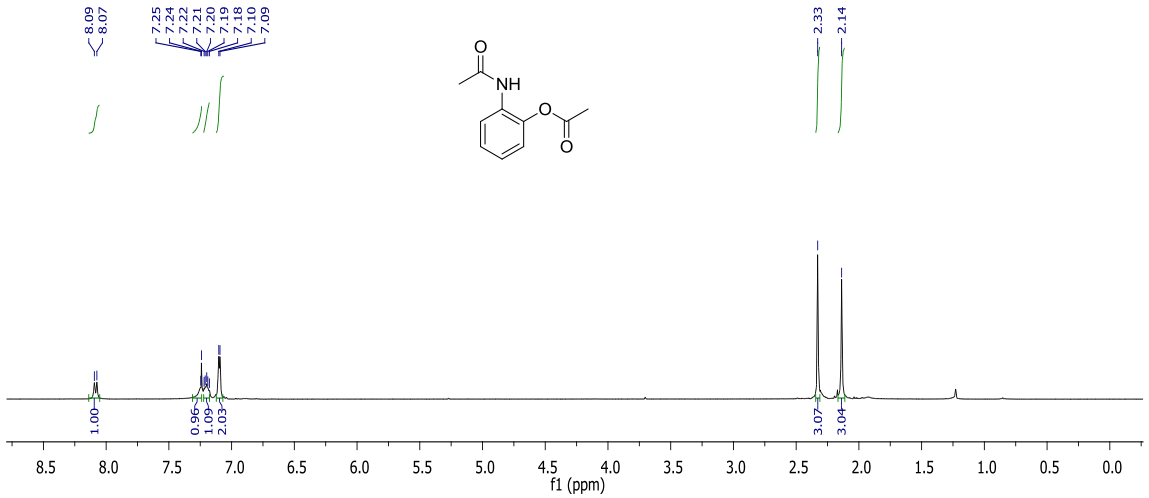
Spectral data of compound **3p**.

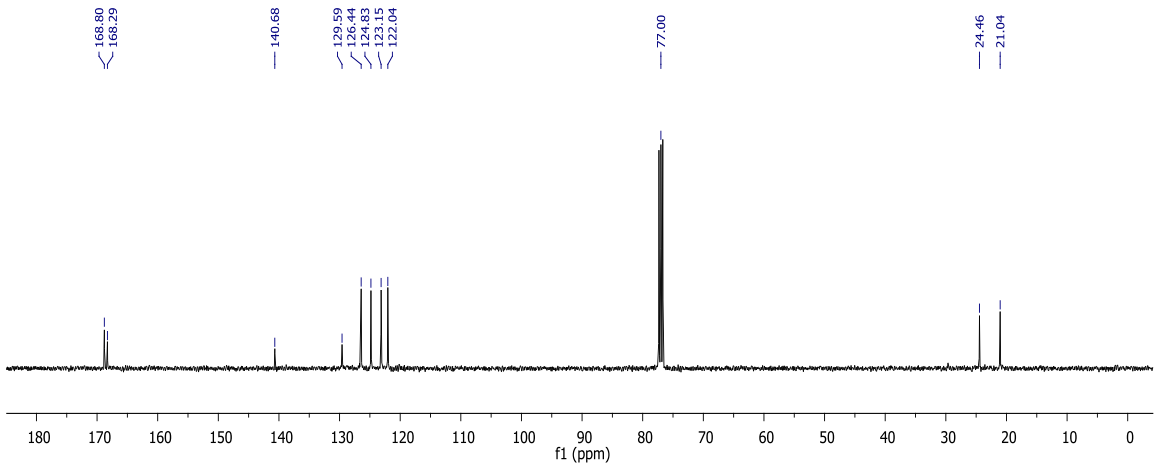


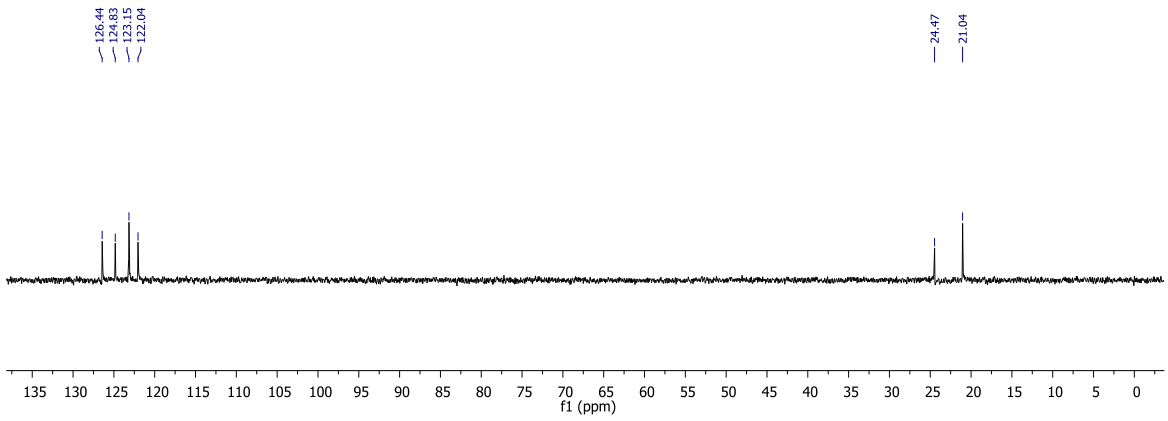




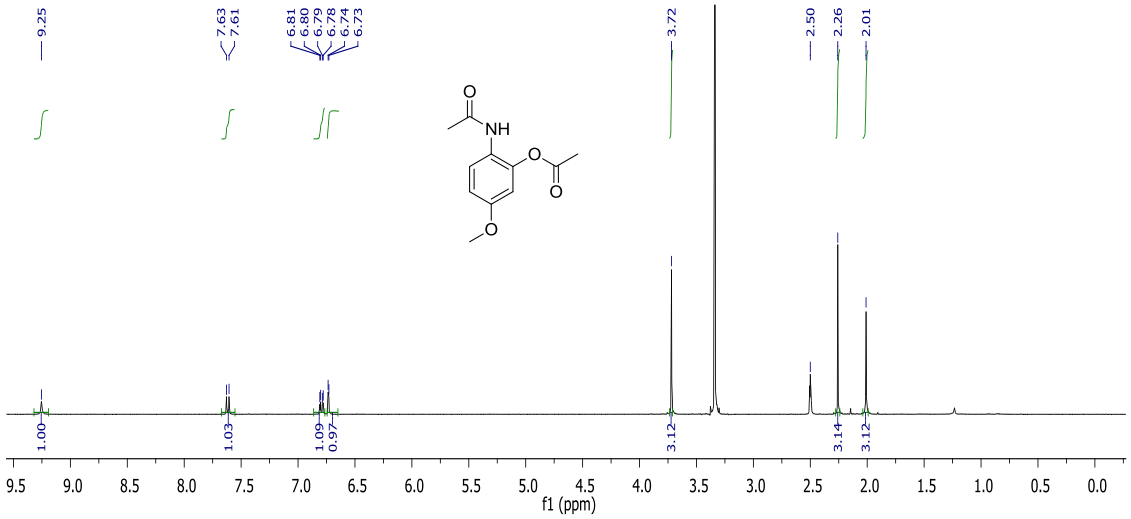
Spectral data of compound **3w**.

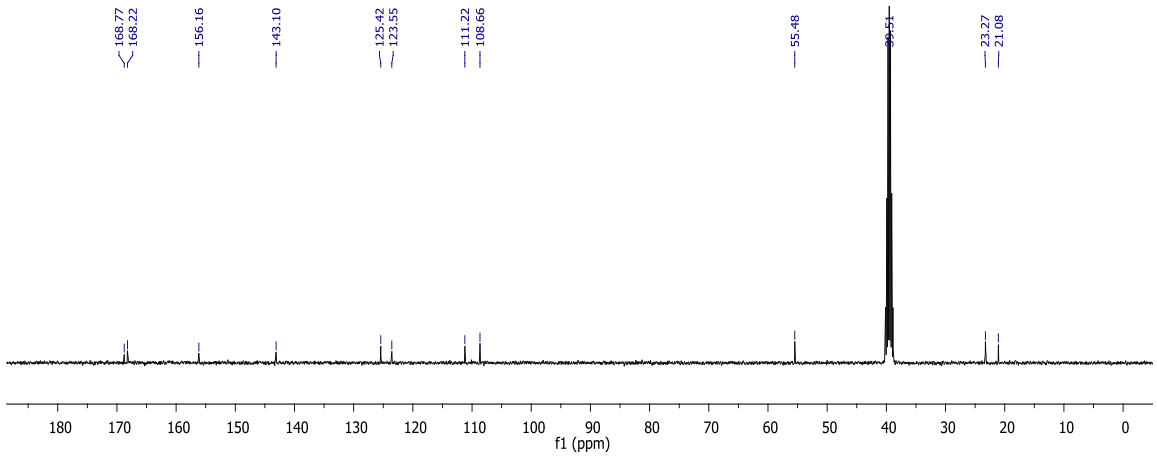


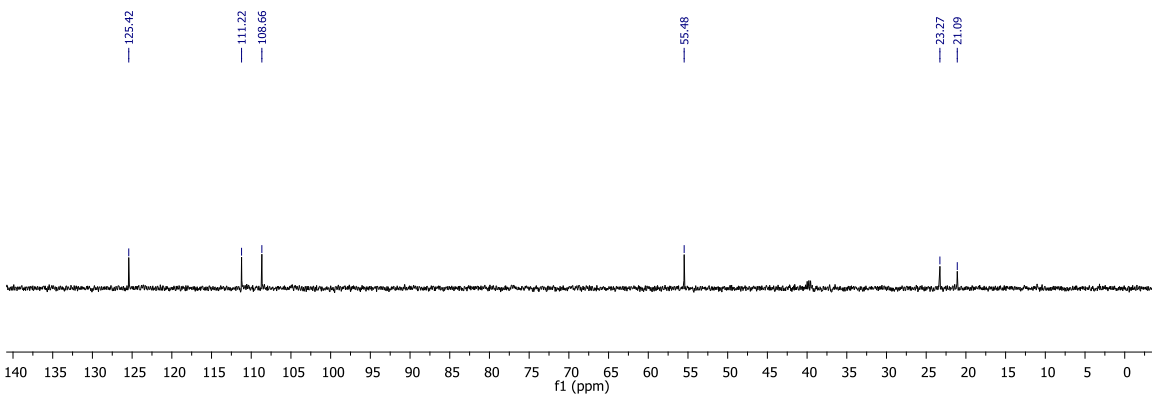




Spectral data of compound **3x**.







4B: *ortho* Benzoxylation of *N*-Alkyl Benzamides with Aromatic Acids Catalyzed by Ruthenium(II) Complex

4B.1: Results and Discussion

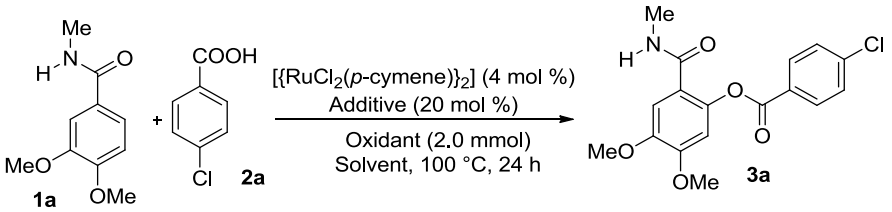
Amide is a versatile functional group which has been widely used for various organic transformations. Meanwhile, amide is also a good directing group for metal-catalyzed C-H functionalization reaction.[1,16] Substituted amides such as Ar-$CONH_2$, Ar-CONHR and Ar-$CONR_2$ are efficiently used for the C-H activation reaction. By using amide directing groups, C-C, C-N and C-X bonds can be formed at the *ortho* C-H bond of aromatics.[1,16] But, amide directed C-O bond is limited in the literature except *ortho* hydroxylation at the *ortho* C-H bond of $CONR_2$ substituted benzamides.[9] Our interest is *ortho* benzoxylation of benzamides with aromatic acids in the presence of ruthenium catalyst.

4B.2: Optimization Studies

A proper selection of oxidant, additive and solvent is highly important to success the catalytic reaction. Initially, the coupling of **1a** and **2a** was tested with various additives (20 mol %) such as $AgBF_4$, AgOTf, KPF_6 and $AgSbF_6$ in the presence of Ru catalyst and $(NH_4)_2S_2O_8$ oxidant in DCE at 100 °C for 24 h (Table 4.4, entries 1-4). $AgBF_4$ was not effective for the reaction (entry 1). KPF_6 and AgOTf were partially effective, yielding **3a** in 64% and 45% yields, respectively (entries 2 and 3). $AgSbF_6$ was very effective for the reaction affording product **3a** in 91% NMR yield (entry 4). Next, the coupling reaction was examined with various oxidants such as oxone, $K_2S_2O_8$, benzoquinone, $Na_2S_2O_8$, Ag_2CO_3, Ag_2O, $Cu(OAc)_2$, AgOAc, $K_2S_2O_8$, $PhI(OAc)_2$ and $(NH_4)_2S_2O_8$. Among them, only $(NH_4)_2S_2O_8$ was very effective, affording product **3a** in 91% yield (entry 4). Ag_2CO_3 was slightly effective, giving **3a** in 62% yield (entry 5). Remaining oxidants were totally ineffective for the reaction. The catalytic reaction was tested with bases such as K_2CO_3 and NaOAc. However, in the reaction, no product **3a** was observed. Then, the catalytic reaction was tested with various solvents such as *tert*-BuOH, THF, DMF, DCE, DMSO, 1,4-dioxane, toluene, MeOH, AcOH and 1,2-dichloroethane. Among them, 1,2-dichloroethane was effective, providing **3a** in 91% yield (entry 4). Remaining solvents were totally ineffective. Based on these optimization studies, we have concluded that $AgSbF_6$, $(NH_4)_2S_2O_8$ and 1,2-dichloroethane in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ at 100 °C for 24 h is the best condition for the reaction. Under the optimized reaction

conditions, the present coupling reaction was tested with *N*-methoxy 3,4-dimethoxy benzamide, *N*-*N*-diethyl 3,4-dimethoxy benzamide and 3,4-dimethoxy benzamide (eq. 1). In these reactions, no coupling product was observed. These results clearly revealed that CO-NHMe is the effective directing group for the reaction compared with CO-NHOMe, CO-NEt_2 and $CONH_2$ substituted benzamide.

Table 4.4: Optimization Studies with Various Oxidant and Additives[a]



Entry	Solvent	Oxidant	Additive	Yield of **3a** (%)[b]
1	$ClCH_2CH_2Cl$	$(NH_4)_2S_2O_8$	$AgBF_4$	NR
2	$ClCH_2CH_2Cl$	$(NH_4)_2S_2O_8$	KPF_6	64
3	$ClCH_2CH_2Cl$	$(NH_4)_2S_2O_8$	AgOTf	45
4	$ClCH_2CH_2Cl$	$(NH_4)_2S_2O_8$	$AgSbF_6$	91
5	$ClCH_2CH_2Cl$	Ag_2CO_3	$AgSbF_6$	62
6	$ClCH_2CH_2Cl$	AgOAc	$AgSbF_6$	NR
7	$ClCH_2CH_2Cl$	Ag_2O	$AgSbF_6$	NR
8	$ClCH_2CH_2Cl$	$Cu(OAc)_2$	$AgSbF_6$	NR
9	$ClCH_2CH_2Cl$	CsOAc	$AgSbF_6$	NR
10	$ClCH_2CH_2Cl$	KOAc	$AgSbF_6$	NR
11	$ClCH_2CH_2Cl$	NaOAc	$AgSbF_6$	NR
12	$ClCH_2CH_2Cl$	$K_2S_2O_8$	$AgSbF_6$	NR
13	$ClCH_2CH_2Cl$	-	$AgSbF_6$	trace
14	$ClCH_2CH_2Cl$	$(NH_4)_2S_2O_8$	-	NR

[a] All reactions were carried out under the following conditions: 1a (1.0 mmol), 2a (1.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (4 mol %), additive (20 mol %) and oxidant (2.0 mmol) in solvent (4.0 mL) at 100 °C for 24 h under the nitrogen atmosphere. [b] Yields were determined by the ^{1}H NMR integration method, using mesitylene as an internal standard.

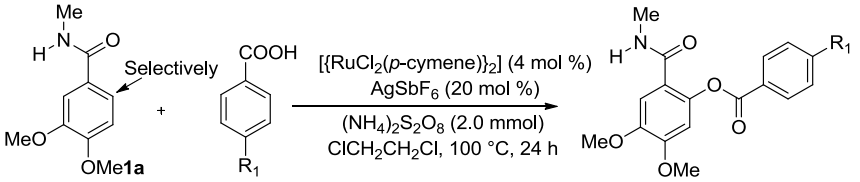
When *N*-methyl 3,4-dimethoxy benzamide **1a** was treated with 4-chlorobenzoic acid (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (4 mol %), $AgSbF_6$ (20 mol %) and $(NH_4)_2S_2O_8$ (2.0 mmol) in 1,2-dichloroethane (DCE) at 100 °C for 24 h, an *ortho* benzoxylated

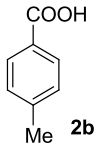
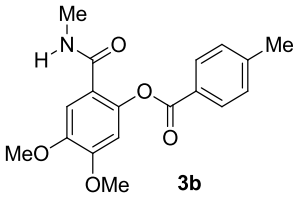
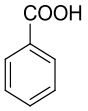
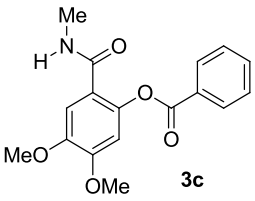
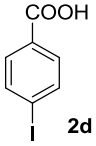
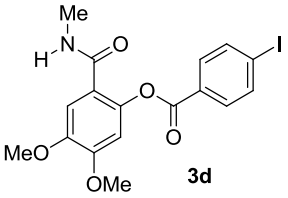
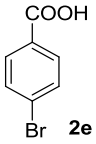
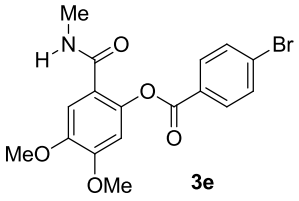
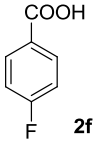
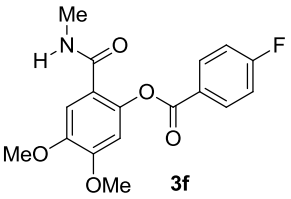
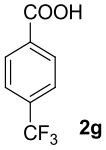
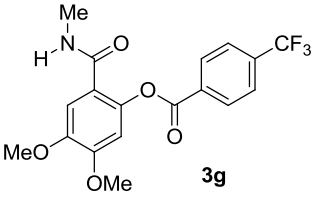
benzamide **3a** was observed in 85% isolated yield (Tabl 4.4). In the substrate **1a**, there are two *ortho* C-H bonds for the activation. The catalytic reaction is highly regioselective; C-H activation takes place selectively at a sterically less hindered C-H bond. It is important to point out that C-O bond formation at the *ortho* C-H bond of *N*-alkyl benzamide is not known in the literature. This is the first report which discloses C-O bond formation at the *ortho* C-H bond of *N*-substituted benzamide in the presence of a less expensive and easily affordable Ru catalyst[9] and $(NH_4)_2S_2O_8$ oxidant.

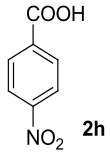
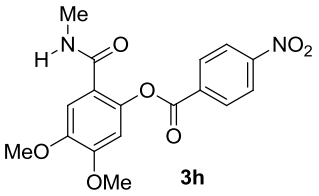
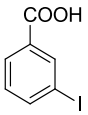
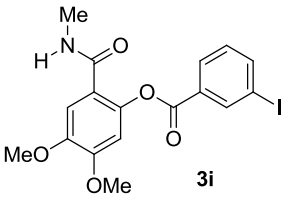
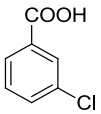
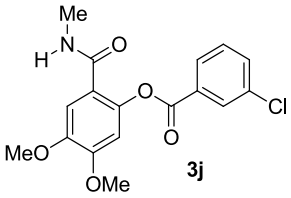
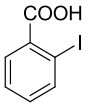
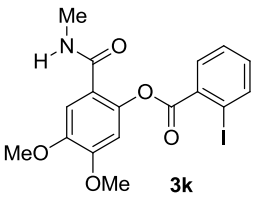
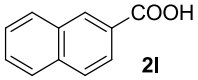
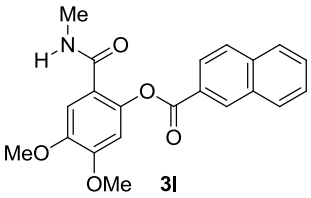
4B.3: Scope of Substituted Benzoic Acids

Under the optimized reaction conditions, the coupling reaction was examined with various *ortho*, *para* and *meta* substituted aromatics acids **2b-l** with **1a** (Table 4.5). The coupling reaction was compatible with electron-donating, halogen and electron-withdrawing functional groups such as Me, H, I, Br, Cl, F, CF_3 and NO_2 substituted aromatic acids **2a-l**. Thus, 4-methylbenzoic acid (**2b**) and benzoic acid (**2c**) reacted with **1a** yielding *ortho* benzoxylated products **3b** and **3c** in 69% and 68% yields, respectively (entries 1 and 2). Halogen groups such as 4-iodo **2d**, 4-bromo **2e** and 4-fluoro **2f** substituted benzoic acids were efficiently involved in the reaction, providing coupling products **3d-f** in 65%, 74% and 66% yields, respectively (entries 3-5). Electron-withdrawing groups such as 4-CF_3 **2g** and 4-nitro **2h** substituted benzoic acids were also nicely involved in the reaction, affording products **3g** and **3h** in 76% and 64% yields, respectively (entries 6 and 7). Next, the coupling reaction was tested with *meta* and *ortho* substituted aromatic acids **2i-k**. *meta* Iodo **2i** or chloro **2j** benzoic acids reacted nicely with **1a** giving the corresponding coupling products **3i** and **3j** in 71% and 75% yields, respectively (entries 8 and 9). Highly sensitive *ortho* iodobenzoic acid (**2k)** also efficiently participated in the reaction, providing coupling product **3k** in 69% yield (entry 10). In the product **3k**, iodo group was retained and not cleaved under the reaction condition which is unusual in the metal-catalyzed reactions. Sterically hindered 2-napthoic acid (**2l**) nicely coupled with **1a**, yielding product **3l** in 73% yield (entry 11). All the catalytic reactions are completely regioselective and only C-H activation takes place at the sterically less hindered C-H bond.

Table 4.5: The Coupling of **1a** with Substituted Benzoic Acids[a]



Entry	**2**	Product **3**	Yield [%][b]
1	 **2b**	 **3b**	69
2	 **2c**	 **3c**	68
3	 **2d**	 **3d**	65
4	 **2e**	 **3e**	74
5	 **2f**	 **3f**	66
6	 **2g**	 **3g**	76

7	 **2h**	 **3h**	64
8	 **2i**	 **3i**	71
9	 **2j**	 **3j**	75
10	 **2k**	 **3k**	69
11	 **2l**	 **3l**	73

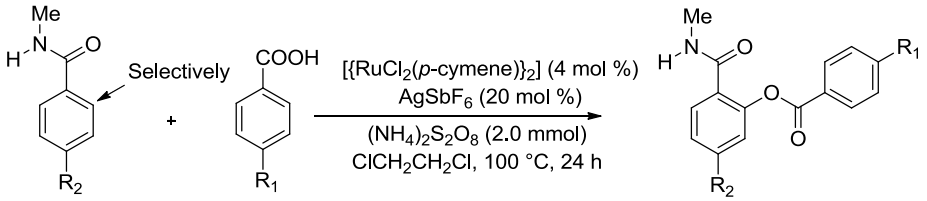
[a]All reactions were carried out using 1a (1.0 mmol), 2b-l (1.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (4 mol %), $AgSbF_6$ (20 mol %) and $(NH_4)_2S_2O_8$ (2.0 mmol) in $ClCH_2CH_2Cl$ (3.0 mL) at 100 °C for 24 h. [b] Isolated yield.

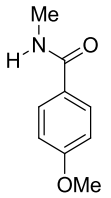
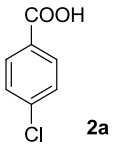
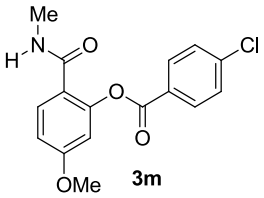
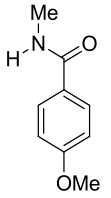
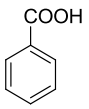
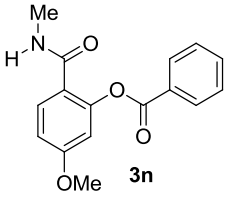
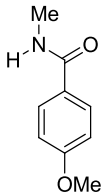
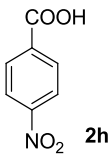
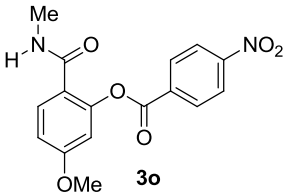
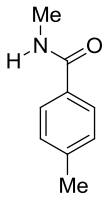
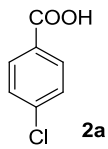
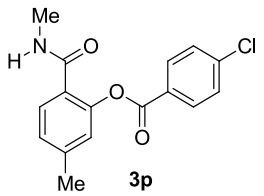
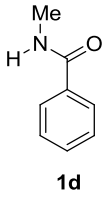
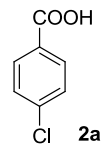
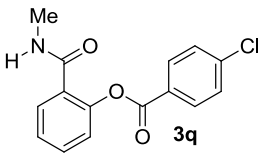
4B.4: Scope of Substituted Benzamides

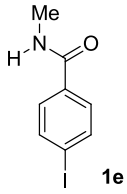
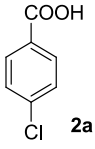
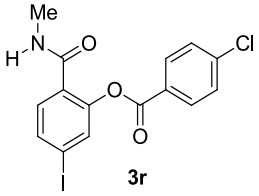
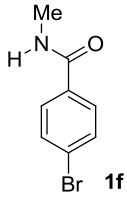
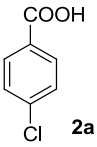
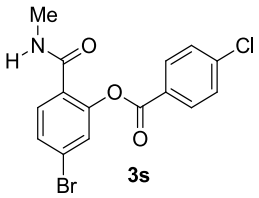
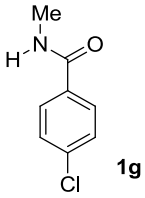
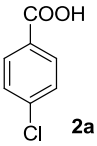
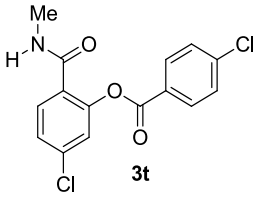
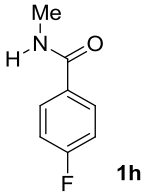
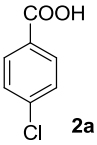
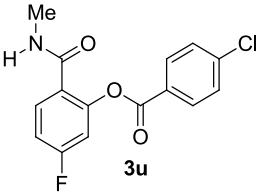
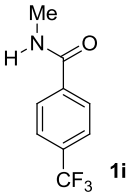
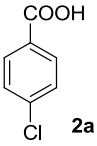
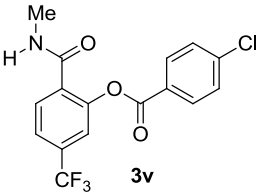
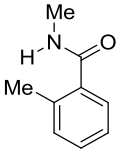
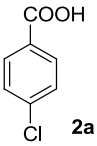
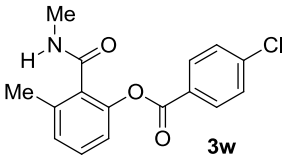
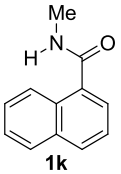
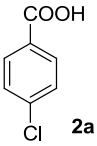
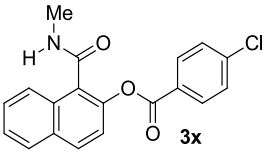
The scope of the catalytic reaction was further examined with various sensitive functional group substituted benzamides **1b-j** (Table 4.6). Treatment of *N*-methyl 4-methoxybenzamide **1b** with substituted benzoic acids **2a**, **2c** and **2h** provided coupling products **3m-o** in 75%, 66% and 56% yields, respectively (entries 1-3). *N*-Methyl 4-methyl benzamide **1c** and *N*-Methyl benzamide **1d** reacted with **2a** yielding *ortho* benzoxylated products **3p** and **3q** in 65% and 69% yields, respectively (entries 4 and 5). Halogen groups such as I, Br, Cl and F substituted benzamides **1e-h** provided the corresponding coupling products **3r-u** in 72%, 69%, 67% and 65% yields, respectively (entries 6-9). Electron-withdrawing group CF_3 substituted benzamide **1i** afforded the

coupling product **3v** in 57% yield (entry 10). *ortho* Methyl benzamide **1j** was also efficiently involved in the reaction, yielding product **3w** in 66% yield (entry 11). *N*-Methyl 1-napthyl benzamide **1k** nicely underwent coupling with **2a**, affording product **3x** in 63% yield (entry 12).

Table 4.6: The Coupling of Benzamides **1b-k** with **2a, 2c** and **2h**



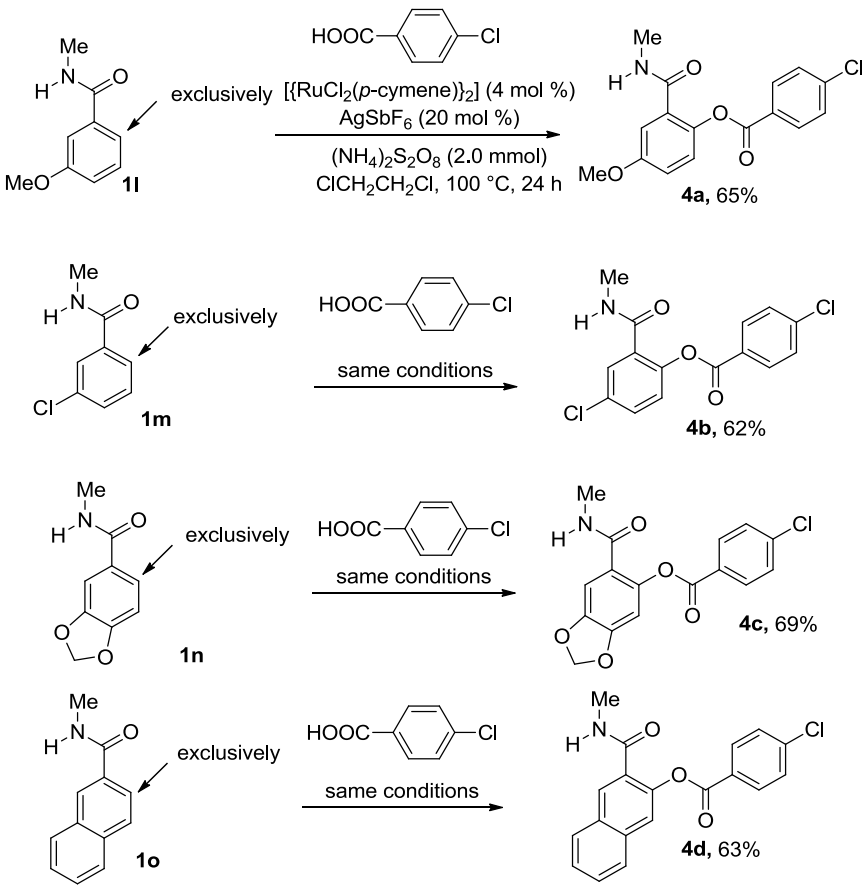
Entry	1	2	Product 3	Yield [%][b]
1	 **1b**	 **2a**	 **3m**	75
2	 **1b**	 **2b**	 **3n**	66
3	 **1b**	 **2h**	 **3o**	56
4	 **1c**	 **2a**	 **3p**	65
5	 **1d**	 **2a**	 **3q**	69

6	 **1e**	 **2a**	 **3r**	72
7	 **1f**	 **2a**	 **3s**	69
8	 **1g**	 **2a**	 **3t**	67
9	 **1h**	 **2a**	 **3u**	65
10	 **1i**	 **2a**	 **3v**	57
11	 **1j**	 **2a**	 **3w**	66
12	 **1k**	 **2a**	 **3x**	63

[a] All reactions were carried out using **1b-k** (1.0 mmol), **2a, c, h** (1.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (4 mol %), $AgSbF_6$ (20 mol %) and $(NH_4)_2S_2O_8$ (2.0 mmol) in $ClCH_2CH_2Cl$ (3.0 mL) at 100 °C for 24 h. [b] Isolated yield.

4B.5: Regioselective Studies

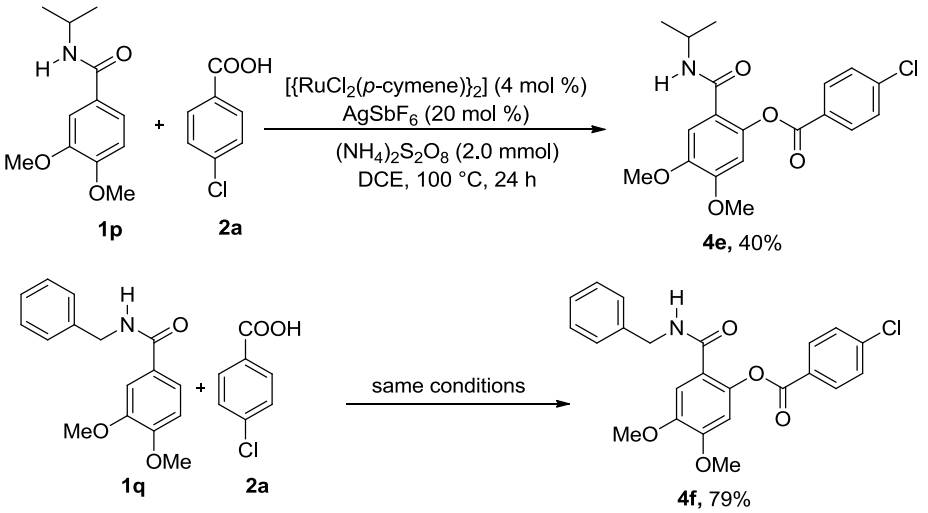
Next, the scope of regioselectivity of the unsymmetrical benzamides **1l-o** with **2a** was examined (Scheme 4.17). The reaction of *N*-methyl 3-methoxy **1l** and 3-chloro 1m substituted benzamides reacted with **2a** providing products **4a** and **4b** in 65% and 62% yields, respectively, in a highly regioselective manner. In the substrates **1l-m,** *ortho* C-H bond activation takes place at a less hindered side. Similarly, substituted benzamides **1n** and **1o** also efficiently coupled with **2a** at a less hindered side, yielding products **4c** and **4d** in 69% and 63% yields, respectively, in a highly regioselective manner.



Scheme 4.17: Regioselective studies

4B.6: Scope of *N*-Substituted Benzamides

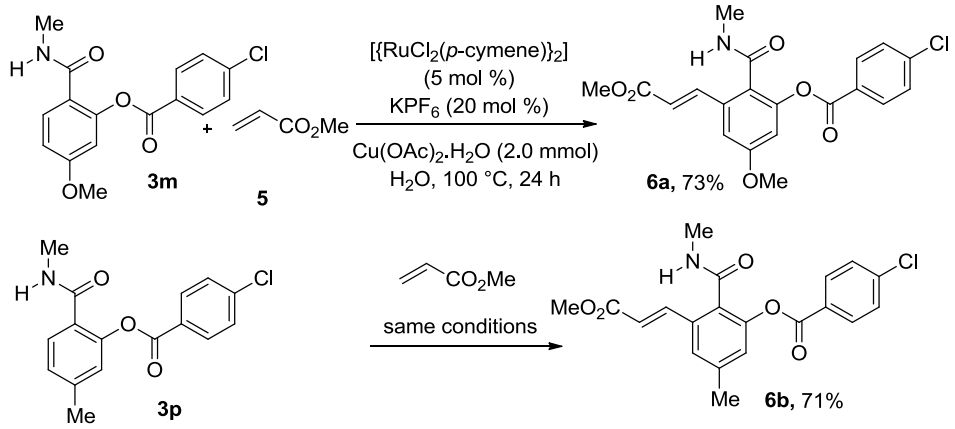
The catalytic reaction was also examined with other *N*-substituted such as *iso*-propyl and benzyl benzamides **1p** and **1q** with **2a** (Scheme 4.18). In the reaction of **1p**, coupling product **4e** was observed only in 40% yield due to the steric hindrance of *iso*-propyl group. Nicely, **1q** provided coupling product **4f** in 79% yield.



Scheme 4.18: Scope of *N*-substituted benzamides

4B.7: Ruthenium-Catalyzed Alkenylation Reaction

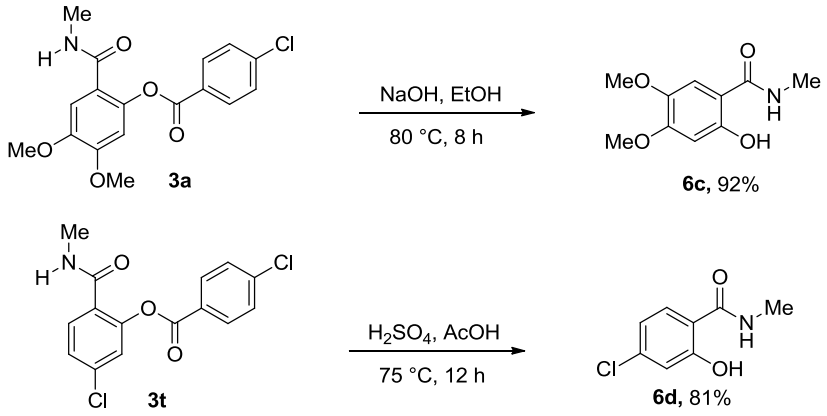
The *ortho* C-H bond of benzoxylated *N*-alkyl benzamides **3m** and **3p** were efficiently alkenylated with methyl acrylate (5) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$], KPF_6 and $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol) in water solvent at 100 °C for 24 h, yielding products **6a** and **6b** in 73% and 71% yields, respectively (Scheme 4.19).[19]



Scheme 4.19: Ruthenium-catalyzed alkenylation reaction

4B.8: Preparation of *ortho* Hydroxy *N*-Alkyl Benzamides

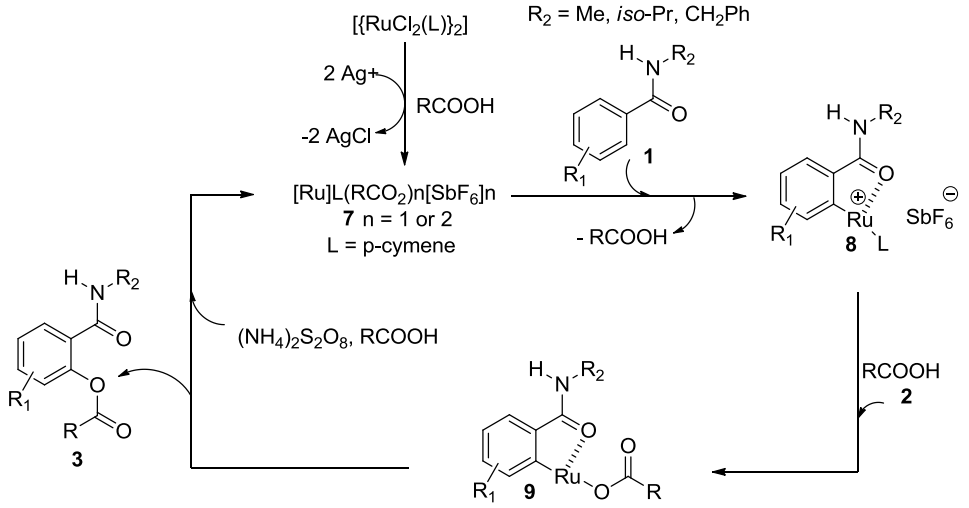
Subsequently, benzoxyl moiety of benzamides **3a** and **3t** were converted into the hydroxyl group, in which products **6c** and **6d** were observed in 92% and 81% yields respectively, in the presence of NaOH or H_2SO_4 solution (Scheme 4.20).[20] It is important to mention that this is one of the efficient methods to synthesis *ortho* hydroxy *N*-alkyl benzamides.



Scheme 4.20: Preparation of *ortho* hydroxy *N*-alkyl benzamides

4B.9: Proposed Mechanism

A possible reaction mechanism is proposed for the present reaction in Scheme 4.21. Silver salt likely removes the chloride ligand from the [{$RuCl_2$(*p*-cymene)}$_2$] complex, providing a cationic ruthenium carboxylate complex **7**.[21] Coordination of the carbonyl oxygen of the benzamide **1** to the cationic species **7** followed by *ortho* metalation affords a five-membered metalacycle **8**. Coupling of **2** into the ruthenacycle **8** affords an intermediate **9**. Reductive elimination of intermediate **9** gives the final product **3** and Ru (0) species.[22] Later, $(NH_4)_2S_2O_8$ oxidizes Ru(0) to active Ru(II) species **7** in the presence of carboxylic acid for the next catalytic cycle.



Scheme 4.21: Proposed mechanism

4B.10: Conclusion

1. We have demonstrated a highly regioselective *ortho* benzoxylation of benzamides with substituted benzoic acids in the presence of ruthenium catalyst. The catalytic reaction worked very efficiently with various functional group substituted

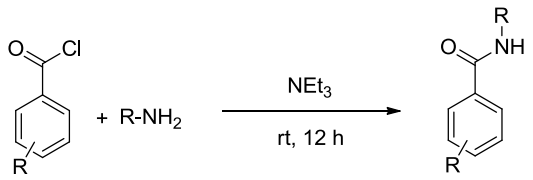
benzamides and benzoic acids yielding *ortho* benzoxylated benzamides in good to excellent yields.

2. Further, a Heck-type alkenylation reaction was done at the *ortho* C-H bond of benzoxylated *N*-alkyl benzamides with alkenes in water solvent in the presence of ruthenium catalyst. *ortho* hydroxy *N*-alkyl benzamides were prepared from benzoxylated *N*-alkyl benzamides in the presence of base or acid.

4B.11: Experimental Section

Preparation of *N*- Alkyl Benzamides:

In a 100 mL round bottom flask, substituted alkyl amine (1.0 gm), NEt_3 (3.0 equiv) and ethyl acetate (20 mL) were taken. The corresponding aromatic acyl chloride dissolved in ethyl acetate and added to the reaction mixture at room temperature was stirred at room temperature for 12 h. The reaction mixture was extracted with water and ethyl acetate (100 mL). The organic layer was dried over Na_2SO_4. After evaporation of the solvents under vacuum, the compound purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure *N*- alkyl benzamides (Scheme 4.23).



Scheme 4.22: Preparation of substituted *N*- alkyl benzamides

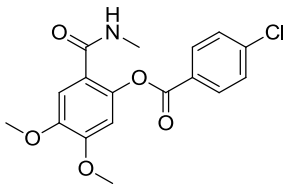
General Procedure for the *ortho* Benzoxylation of *N*-Alkyl Benzamides with Aromatic Acids Catalyzed by Ruthenium Complex

$[\{RuCl_2(p\text{-cymene})\}_2]$ (0.04 mmol, 4 mol %), $AgSbF_6$ (0.20 mmol, 20 mol %), $(NH_4)_2S_2O_8$ (2.0 mmol), benzamides **1** (100 or 150 mg) and aromatic acid **2** (1.0 equiv) were taken in a 15 mL pressure tube, which was equipped with a magnetic stirrer and septum. The pressure tube was evacuated and purged with nitrogen gas three times (***Note:*** $AgSbF_6$ is moisture sensitive. Thus, $AgSbF_6$ was taken inside the nitrogen glove box). To the tube was then added 1,2-dichloroethane (3.0 mL) as the solvent via syringe and again the tube was evacuated and purged with nitrogen gas three times. Then, the septum was taken out and immediately a screw cap was used to cover the tube. The reaction mixture was allowed to stir at 100 °C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 and then filtered through Celite and silica gel. The

filtrate was concentrated, and the crude residue was purified through a silica gel column (hexanes and ethyl acetate) to give pure **3** and **4**.

4B.12: Spectral Data of Compounds

4,5-Dimethoxy-2-(methylcarbamoyl)phenyl 4-chlorobenzoate (3a).



Colorless solid; eluent (60% ethyl acetate in hexanes); **1a** was taken 100 mg, yield is 85%, (152 mg).

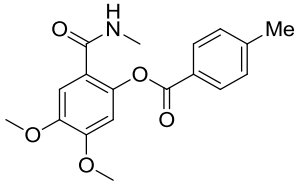
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3391, 2967, 1738, 1642, 1263 and 1215.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (bs, 1 H), 8.11 (d, *J* = 8.0 Hz, 2 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 7.21 (s, 1 H), 6.98 (s, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 2.63 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.0, 163.9, 150.7, 146.1, 142.3, 138.7, 131.7, 129.0, 128.2, 119.9, 111.4, 107.3, 56.0, 55.9, 26.0.

HRMS (ESI): calc. for [($C_{17}H_{16}ClNO_5$)H] (M+H) 350.0795, measured 350.0799.

4,5-Dimethoxy-2-(methylcarbamoyl)phenyl 4-methylbenzoate (3b).



Colorless solid; eluent (55% ethyl acetate in hexanes). **1a** was taken 100 mg, yield is 69%, (115 mg).

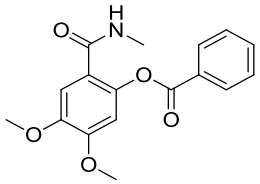
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3303, 2935, 1734, 1634, 1258 and 1214.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, *J* = 8.0 Hz, 2 H), 7.47 (s, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 6.67 (s, 1 H), 6.58 (bs, 1 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 2.83 (d, *J* = 4.0 Hz, 3 H), 2.47 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 165.0, 151.3, 146.9, 145.3, 142.1, 130.1, 129.7, 125.9, 119.3, 112.0, 106.2, 56.2, 26.7, 21.8.

HRMS (ESI): calc. for [($C_{18}H_{19}NO_5$)H] (M+H) 330.1341, measured 330.1347.

4,5-Dimethoxy-2-(methylcarbamoyl)phenyl benzoate (3c).



Colorless solid; eluent (50% ethyl acetate in hexanes). **1a** was taken 100 mg, yield is 68%, (109 mg).

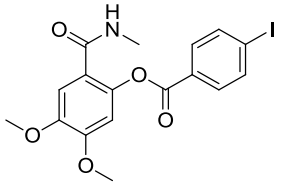
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3449, 3009, 2969, 1739, 1653, 1263 and 1206.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.13 (d, J = 8.0 Hz, 3 H), 7.72 (t, J = 8.0 Hz, 1 H), 7.59 (t, J = 8.0 Hz, 2 H), 7.19 (s, 1 H), 6.97 (s, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 2.63 (d, J = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.1, 164.7, 150.7, 146.0, 142.4, 133.7, 129.9, 129.4, 128.8, 120.2, 111.4, 107.4, 56.0, 55.9, 26.0.

HRMS (ESI): calc. for [($C_{17}H_{17}NO_5$)H] (M+H) 316.1185, measured 316.1195

4,5-dimethoxy-2-(methylcarbamoyl)phenyl 4-iodobenzoate (3d).



Colorless solid; eluent (55% ethyl acetate in hexanes). **1a** was taken 100 mg, yield is 65%, (147 mg).

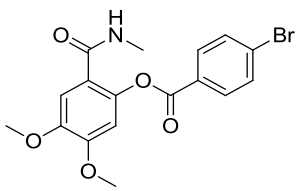
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3296, 3057, 2999, 1738, 1631, 1262 and 1216.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, J = 8.0 Hz, 2 H), 7.85 (d, J = 8.0 Hz, 2 H), 7.34 (s, 1 H), 6.64 (s, 1 H), 6.37 (bs, 1 H), 3.89 (s, 3 H), 3.86 (s, 3 H), 2.81 (d, J = 4.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.7, 164.7, 151.3, 147.0, 141.8, 138.3, 131.3, 128.2, 119.5, 111.7, 106.1, 102.3, 56.22, 56.20, 26.8.

HRMS (ESI): calc. for [($C_{17}H_{16}INO_5$)H] (M+H) 442.0151, measured 442.0157.

4,5-Dimethoxy-2-(methylcarbamoyl)phenyl 4-bromobenzoate (3e).



Colorless solid; eluent (60% ethyl acetate in hexanes). **1a** was taken 100 mg, yield is 74%, (149 mg).

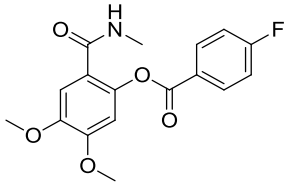
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3392, 2926, 2853, 1734, 1639, 1262 and 1214.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.15 (bs, 1 H), 8.03 (d, *J* = 8.0 Hz, 2 H), 7.82 (d, *J* = 8.0 Hz, 2 H), 7.20 (s, 1 H), 6.98 (s, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 2.63 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.0, 164.1, 150.7, 146.1, 142.3, 132.0, 131.8, 128.6, 127.8, 119.9, 111.3, 107.3, 56.0, 55.9, 26.0.

HRMS (ESI): calc. for [($C_{17}H_{16}BrNO_5$)H] (M+H) 394.0290, measured 394.0289.

4,5-Dimethoxy-2-(methylcarbamoyl)phenyl 4-fluorobenzoate (3f).



Colorless solid; eluent (55% ethyl acetate in hexanes). **1a** was taken 100 mg, yield is 66%, (112 mg).

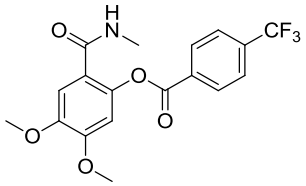
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3396, 3007, 2966, 1738, 1643, 1266 and 1218.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.20-8.16 (m, 3 H), 7.43 (t, *J* = 8.0 Hz, 2 H), 7.19 (s, 1 H), 6.97 (s, 1 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 2.63 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.1, 163.8, 150.7, 146.1, 142.3, 132.85 and 132.76 (F coupling), 126.0, 120.0, 116.1, 115.9, 111.4, 107.4, 56.0, 55.9, 26.0.

HRMS (ESI): calc. for [($C_{17}H_{16}FNO_5$)H] (M+H) 334.1091, measured 334.1096.

4,5-Dimethoxy-2-(methylcarbamoyl)phenyl 4-(trifluoromethyl)benzoate (3g).



Colorless solid; eluent (55% ethyl acetate in hexanes). **1a** was taken 100 mg, yield is 76%, (149 mg).

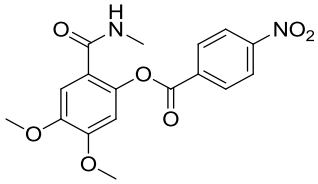
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3309, 3005, 2968, 1741, 1631, 1216 and 1263.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.30 (d, *J* = 8.0 Hz, 2 H), 8.22 (bs, 1 H), 7.97 (d, *J* = 8.0 Hz, 2 H), 7.23 (s, 1 H), 7.02 (s, 1 H), 3.84 (s, 3 H), 3.79 (s, 3 H), 2.63 (d, *J* = 8.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.0, 163.8, 150.8, 146.2, 142.4, 133.2, 130.7, 125.1 and 122.2 (F coupling), 125.9, 119.7, 111.3, 107.3, 56.0, 55.9, 26.0.

HRMS (ESI): calc. for [($C_{18}H_{16}F_3NO_5$)H] (M+H) 384.1059, measured 384.1051.

4,5-Dimethoxy-2-(methylcarbamoyl)phenyl 4-nitrobenzoate (3h).



Colorless solid; eluent (50% ethyl acetate in hexanes). **1a** was taken 100 mg, yield is 64%, (118 mg).

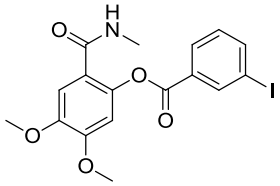
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3383, 3112, 2935, 1741, 1610, 1261 and 1215.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.41 (d, J = 8.0 Hz, 2 H), 8.33 (d, J = 8.0 Hz, 2 H), 8.21 (bs, 1 H), 7.23 (s, 1 H), 7.03 (s, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 2.63 (d, J = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.9, 163.4, 150.8, 150.4, 146.2, 142.3, 134.9, 131.3, 123.9, 119.5, 111.3, 107.3, 56.0, 55.9, 26.0.

HRMS (ESI): calc. for [($C_{17}H_{16}N_2O_7$)H] (M+H) 361.1036, measured 361.1041.

4,5-Dimethoxy-2-(methylcarbamoyl)phenyl 3-iodobenzoate (3i).



Colorless solid; eluent (50% ethyl acetate in hexanes). **1a** was taken 100 mg, yield is 71%, (160 mg).

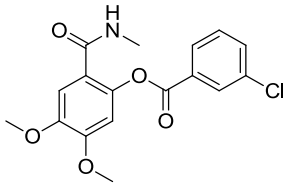
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3389, 3005, 2939, 1738, 1642, 1276 and 1213.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.41 (s, 1 H), 8.19 (bs, 1 H), 8.09 (d, J = 8.0 Hz, 2 H), 7.41 (t, J = 8.0 Hz, 1 H), 7.20 (s, 1 H), 6.99 (s, 1 H), 3.82 (s, 3 H),3.79 (s, 3 H), 2.63 (d, J = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.0, 163.4, 150.7, 146.1, 142.25, 142.17, 138.0, 131.4, 131.0, 129.1, 119.8, 111.3, 107.3, 94.8, 56.0, 55.9, 26.1.

HRMS (ESI): calc. for [($C_{17}H_{16}INO_5$)H] (M+H) 442.0151, measured 442.0155.

4,5-Dimethoxy-2-(methylcarbamoyl)phenyl 3-chlorobenzoate (3j).



Colorless solid; eluent (50% ethyl acetate in hexanes). **1a** was taken 100 mg, yield is 75%, (134 mg).

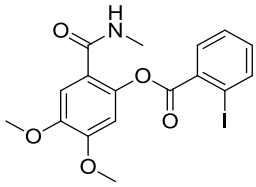
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3393, 3009, 2967, 1740, 1645, 1261 and 1219.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.19 (bs, 1 H), 8.11 (s, 1 H), 8.05 (d, *J* = 8.0 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.64 (t, *J* = 8.0 Hz, 1 H), 7.20 (s, 1 H), 7.00 (s, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 2.63(d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.0, 163.6, 150.7, 146.1, 142.2, 133.5, 131.4, 130.9, 129.4, 128.5, 119.8, 111.3. 107.3, 56.0, 55.9, 26.1.

HRMS (ESI): calc. for [($C_{17}H_{16}ClNO_5$)H] (M+H) 350.0795, measured 350.0800.

4,5-Dimethoxy-2-(methylcarbamoyl)phenyl 2-iodobenzoate (3k).



Colorless solid; eluent (50% ethyl acetate in hexanes). **1a** was taken 100 mg, yield is 69%, (155 mg).

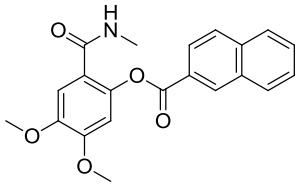
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3301, 3009, 2969, 1742, 1642, 1269 and 1214.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (bs, 1 H), 8.09 (t, *J* = 8.0 Hz, 2 H), 7.60 (t, *J* = 8.0 Hz, 1 H), 7.35 (t, *J* = 8.0 Hz, 1 H), 7.20 (s, 1 H),6.95 (s, 1 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 2.68 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.2, 164.6, 150.7, 146.2, 142.2, 140.9, 134.2, 133.5, 131.6, 128.3, 120.1, 111.4, 107.0, 95.3, 56.0, 55.9, 26.2.

HRMS (ESI): calc. for [($C_{17}H_{16}INO_5$)H] (M+H) 442.0151, measured 442.0146.

4,5-Dimethoxy-2-(methylcarbamoyl)phenyl 2-naphthoate (3l).



Colorless solid; eluent (50% ethyl acetate in hexanes). **1a** was taken 100 mg, yield is 73%, (136 mg).

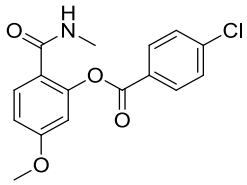
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3393, 3009, 2967, 1738, 1643, 1265 and 1218.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.82 (s, 1 H), 8.18 (d, *J* = 8.0 Hz, 2 H), 8.11 (s, 2 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 7.72-7.64 (m, 2 H),7.22 (s, 1 H), 7.02 (s, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 2.62 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.1, 164.8, 150.7, 146.1, 142.5, 135.3, 132.1, 131.5, 129.5, 128.9, 128.4, 127.8, 127.2, 126.6, 125.3, 120.1, 111.4, 107.4, 56.0, 55.9, 26.1.

HRMS (ESI): calc. for [($C_{21}H_{19}NO_5$)Na] (M+Na) 388.1161, measured 388.1165.

5-Methoxy-2-(methylcarbamoyl)phenyl 4-chlorobenzoate (3m).



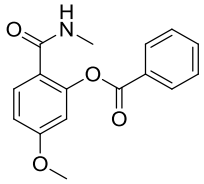
Colorless solid; eluent (30% ethyl acetate in hexanes). **1b** was taken 100 mg, yield is 75%, (144 mg).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.17 (bs, 1 H), 8.11 (d, *J* = 8.0 Hz, 2 H), 7.67 (d, *J* = 8.0 Hz, 2 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 6.96 -6.94 (m, 2 H), 3.81 (s, 3 H), 2.62 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.2, 163.6, 161.5, 149.7, 138.8, 131.8, 130.1, 129.1, 128.1, 121.2, 111.7, 109.1, 55.8, 26.1.

HRMS (ESI): calc. for [($C_{16}H_{14}ClNO_4$)H] (M+H) 320.0690, measured 320.0681.

5-Methoxy-2-(methylcarbamoyl)phenyl benzoate (3n).



Colorless solid; eluent (30% ethyl acetate in hexanes). **1b** was taken 100 mg, yield is 66%, (114 mg).

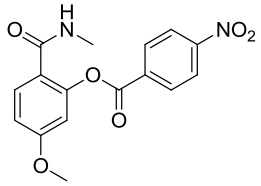
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3395, 2971, 1738, 1647, 1263 and 1238.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.15 (bs, 1 H), 8.11 (d, *J* = 8.0 Hz, 2 H), 7.73 (t, *J* = 8.0 Hz, 1 H), 7.60 (t, *J* = 8.0 Hz, 3 H), 6.94 (d, *J* = 8.0 Hz, 2 H), 3.81 (s, 3 H), 2.61 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.3, 164.4, 161.4, 149.8, 133.9, 130.1, 129.9, 129.2, 128.9, 121.5, 111.6, 109.1, 55.8, 26.1.

HRMS (ESI): calc. for [($C_{16}H_{15}NO_4$)] (M+Na) 308.0899, measured 308.0903.

5-Methoxy-2-(methylcarbamoyl)phenyl 4-nitrobenzoate (3o).



Colorless solid; eluent (30% ethyl acetate in hexanes). **1b** was taken 100 mg, yield is 56%, (112 mg).

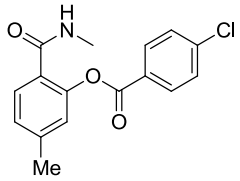
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3361, 3019, 2971, 1740, 1639, 1263 and 1211.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.41 (d, *J* = 8.0 Hz, 2 H), 8.32 (d, *J* = 8.0 Hz, 2 H), 8.22 (bs, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 6.97 (d, *J* = 8.0 Hz, 2 H), 3.82 (s, 3 H), 2.61 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.2, 163.1, 161.6, 150.6, 149.7, 134.8, 131.4, 130.2, 124.0, 120.8, 111.9, 109.1, 55.9, 26.1.

HRMS (ESI): calc. for [($C_{16}H_{14}N_2O_6$)H] (M+H) 331.0930, measured 331.0936.

5-Methyl-2-(methylcarbamoyl)phenyl 4-chlorobenzoate (3p).



Colorless solid; eluent (25% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 65%, (189 mg).

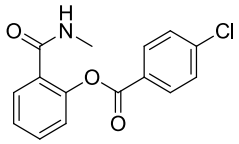
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3391, 3022, 2969, 1785, 1645, 1263 and 1106. **1b** was taken 100 mg, yield is 75%, (144 mg).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.24 (bs, 1 H), 8.10 (d, *J* = 8.0 Hz, 2 H), 7.67 (d, *J* = 8.0 Hz, 2 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 7.15 (s, 1 H), 2.62 (d, *J* = 4.0 Hz, 3 H), 2.36 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.5, 163.7, 148.1, 141.7, 138.8, 131.7, 129.1, 128.8, 128.1, 126.7, 126.3, 123.7, 26.1, 20.7.

HRMS (ESI): calc. for [($C_{16}H_{14}ClNO_3$)H] (M+H) 304.0740, measured 304.0745.

2-(Methylcarbamoyl)phenyl 4-chlorobenzoate (3q).



Colorless solid; eluent (30% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 69%, (191 mg).

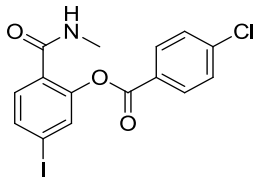
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3308, 3023, 2969, 1738, 1645, 1598, 1261 and 1205.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.34 (bs, 1 H), 8.11 (d, *J* = 8.0 Hz, 2 H), 7.67 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 4.0 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 2.64 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.5, 163.6, 147.9, 138.9, 131.7, 131.3, 129.4, 129.1, 128.9, 128.0, 126.2, 123.4, 26.1.

HRMS (ESI): calc. for [($C_{15}H_{12}ClNO_3$)Na] (M+Na) 312.0403, measured 312.0405.

5-Iodo-2-(methylcarbamoyl)phenyl 4-chlorobenzoate (3r).



Colorless solid; eluent (25% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 72%, (286 mg).

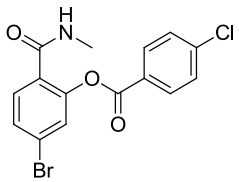
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3297, 3087, 2967, 1737, 1643, 1255 and 1199.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.38 (bs, 1 H), 8.08 (d, *J* = 8.0 Hz, 2 H), 7.82 (s, 1 H), 7.77 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.68 (d, *J* = 8.0 Hz, 2 H), 7.39 (d, *J* = 8.0 Hz, 1 H),, 2.62 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.9, 163.4, 148.2, 139.0, 135.0, 132.0, 131.7, 131.2, 130.4, 129.1, 128.8, 96.6, 26.0.

HRMS (ESI): calc. for [($C_{15}H_{11}ClINO_3$)H] (M+H) 415.9550, measured 415.9549.

5-Bromo-2-(methylcarbamoyl)phenyl 4-chlorobenzoate (3s).



Colorless solid; eluent (25% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 69%, (242 mg).

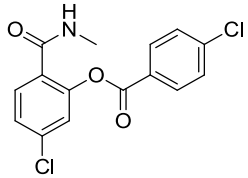
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3301, 2924, 1741, 1647, 1258 and 1201.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.40 (bs, 1 H), 8.09 (d, *J* = 8.0 Hz, 2 H), 7.71 (d, *J* = 4.0 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 2.62 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.7, 163.3, 148.6, 139.0, 131.8, 131.2, 130.6, 129.1, 128.7, 127.6, 126.5, 123.2, 26.0.

HRMS (ESI): calc. for [($C_{15}H_{11}BrClNO_3$)H] (M+H) 367.9689, measured 367.9696.

5-Chloro-2-(methylcarbamoyl)phenyl 4-chlorobenzoate (3t).



Colorless solid; eluent (25% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 67%, (207 mg).

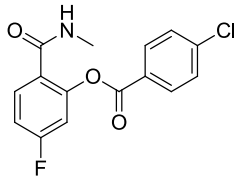
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3292, 2966, 1739, 1636, 1257 and 1205.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.41 (bs, 1 H), 8.09 (d, *J* = 8.0 Hz, 2 H), 7.69 (d, *J* = 8.0 Hz, 2 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.59 (s, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 2.64 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.0, 163.8, 149.1, 139.5, 135.4, 132.3, 131.7, 130.9, 129.6, 128.1, 126.8, 124.2, 26.5.

HRMS (ESI): calc. for [($C_{15}H_{11}Cl_2NO_3$)Na] (M+Na) 346.0014, measured 346.0008.

5-Fluoro-2-(methylcarbamoyl)phenyl 4-chlorobenzoate (3u).



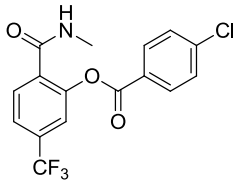
Colorless solid; eluent (30% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 65%, (191 mg).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.36 (bs, 1 H), 8.10 (d, *J* = 8.0 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 3 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.27 (t, *J* = 8.0 Hz, 1 H), 2.64 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.7, 163.3, 149.3, 139.1, 131.8, 131.2, 130.8 and 130.7 (F coupling), 129.2, 128.8, 127.7, 126.0, 113.3 and 113.1(F coupling), 111.5 and 111.2 (F coupling), 26.1.

HRMS (ESI): calc. for [($C_{15}H_{11}ClFNO_3$)Na] (M+Na) 330.0309, measured 330.0321.

2-(Methylcarbamoyl)-5-(trifluoromethyl)phenyl 4-chlorobenzoate (3v).



Colorless solid; eluent (30% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 57%, (195 mg).

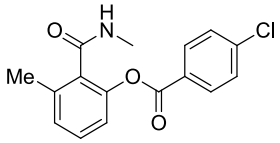
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3275, 3020, 1740, 1663, 1263 and 1222.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.55 (bs, 1 H), 8.10 (d, *J* = 8.0 Hz, 2 H), 7.89 (s, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.70 (d, *J* = 8.0 Hz, 2 H), 2.67 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.4, 163.3, 148.1, 139.1, 133.5, 131.7, 131.1, 130.1, 129.2, 128.7, 127.5, 120.8, 26.0.

HRMS (ESI): calc. for [($C_{16}H_{11}ClNF_3O_3$)] (M+Na) 380.0277, measured 380.0281.

3-Methyl-2-(methylcarbamoyl)phenyl 4-chlorobenzoate (3w).



Colorless solid; eluent (25% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 66%, (192 mg).

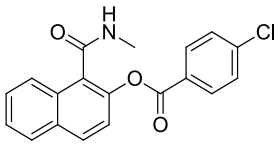
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3274, 3084, 2925, 1736, 1646, 1263 and 1224.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.32 (bs, 1 H), 8.04 (d, *J* = 8.0 Hz, 2 H), 7.69 (d, *J* = 8.0 Hz, 2 H), 7.36 (t, *J* = 8.0 Hz, 1 H), 7.22 -7.19 (m, 2 H), 2.65 (d, *J* = 4.0 Hz, 3 H), 2.28 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.8, 163.3, 146.9, 139.0, 136.2, 131.5, 131.2, 129.3, 129.0, 127.7, 127.6, 120.1, 25.7, 18.7.

HRMS (ESI): calc. for [($C_{16}H_{14}ClNO_3$)] (M+Na) 326.0560, measured 326.0568.

1-(Methylcarbamoyl)naphthalen-2-yl 4-chlorobenzoate (3x).



Colorless solid; eluent (30% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 63%, (205 mg).

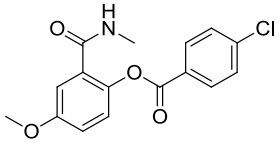
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3282, 3060, 2968, 1739, 1646, 1263 and 1230.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.28 (bs, 1 H), 8.13 (d, *J* = 8.0 Hz, 2 H), 8.07 (d, *J* = 8.0 Hz, 1 H), 7.97 (d, *J* = 8.0 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 2 H), 7.64 (t, *J* = 8.0 Hz, 1 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 2.31(d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 169.9, 163.7, 145.5, 138.8, 134.8, 133.2, 131.7, 129.1, 128.9, 128.1, 126.6, 126.4, 126.1, 125.7, 123.0, 120.9, 25.8.

HRMS (ESI): calc. for [($C_{19}H_{14}ClNO_3$)H] (M+H) 340.0740, measured 340.0741.

4-Methoxy-2-(methylcarbamoyl)phenyl 4-chlorobenzoate (4b).



Colorless solid; eluent (30% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 65%, (199 mg).

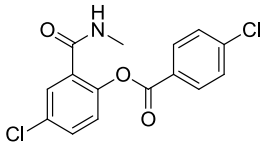
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3306, 2942, 1736, 1648, 1260 and 1194.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.32 (bs, 1 H), 8.09 (d, *J* = 8.0 Hz, 2 H), 7.66 (d, *J* = 8.0.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 1 H), 7.14 (d, *J* = 4.0 Hz, 1 H), 7.10 (dd, *J* = 8.0 ,4.0 Hz, 1 H), 3.82 (s, 3 H), 2.63 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.2, 163.9, 156.7, 141.2, 138.7, 131.6, 129.9, 129.0, 128.1, 124.3, 116.4, 113.6, 55.6, 26.0.

HRMS (ESI): calc. for [($C_{16}H_{14}ClNO_4$)H] (M+H) 320.0690, measured 320.0693.

4-Chloro-2-(methylcarbamoyl)phenyl 4-chlorobenzoate (4c).



Colorless solid; eluent (25% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 62%, (192 mg).

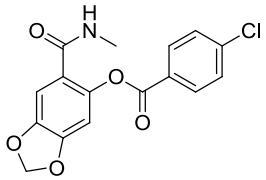
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3392, 3021, 2969, 1741, 1651, 1261 and 1210.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.48 (bs, 1 H), 8.09 (d, *J* = 8.0 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 2 H), 7.66 (t, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 4.0 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 2.63 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.1, 163.4, 146.8, 139.0, 131.7, 131.0, 130.2, 129.2, 128.6, 127.7, 125.5, 26.1.

HRMS (ESI): calc. for [($C_{15}H_{11}Cl_2NO_3$)Na] (M+Na) 346.0014, measured 346.0016.

6-(Methylcarbamoyl)benzo[*d*][1,3]dioxol-5-yl 4-chlorobenzoate (4d).



Colorless solid; eluent (30% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 69%, (220 mg).

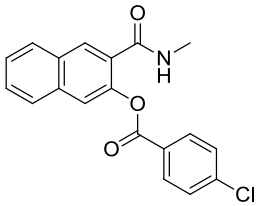
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3019, 1740, 1643, 1263 and 1222.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.16 (bs, 1 H), 8.08 (d, *J* = 8.0, 2 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 7.13 (s, 1 H), 7.02 (s, 1 H), 6.14 (s, 2 H), 2.59 (d, *J* = 4.0, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.8, 163.8, 149.0, 145.0, 143.2, 138.8, 131.7, 129.0, 128.0, 121.9, 107.6, 104.9, 102.4, 26.1.

HRMS (ESI): calc. for [($C_{16}H_{12}ClNO_5$)H] (M+H) 334.0482, measured 334.0488.

3-(Methylcarbamoyl)naphthalen-2-yl 4-chlorobenzoate (4e).



Colorless solid; eluent (30% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 63%, (205 mg).

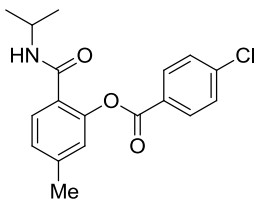
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3007, 2926, 1738, 1654, 1265 and 1225.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.52 (bs, 1 H), 8.23 (s, 1 H), 8.14 (d, *J* = 8.0 Hz, 2 H), 8.05 (d, *J* = 8.0 Hz, 1 H), 7.98 -7.93 (m, 1 H), 7.90 (s, 1 H), 7.71 (d, *J* = 8.0 Hz, 2 H), 7.66 -7.56 (m, 2 H), 2.68 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.7, 163.9, 145.3, 138.9, 133.7, 131.7, 131.1, 130.4, 129.1, 128.8, 128.6, 128.3, 127.9, 127.3, 126.6, 120.4, 26.1.

HRMS (ESI): calc. for [($C_{19}H_{14}ClNO_3$)H] (M+H) 340.0740, measured 340.0737.

2-(Isopropylcarbamoyl)-5-methylphenyl 4-chlorobenzoate (**4f**).



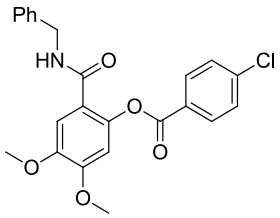
Colorless solid; eluent (50% ethyl acetate in hexanes). **2a** was taken 150 mg, yield is 40%, (127 mg).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.12 (d, *J* = 8.0 Hz, 2 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 2 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 7.15 (s, 1 H), 3.86 (m, 1 H), 2.36 (s, 3 H), 0.96 (d, *J* = 8.0 Hz, 6 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.1, 163.5, 147.7, 141.4, 138.9, 131.7, 129.4, 129.1, 128.0, 127.0, 126.6, 123.4, 40.7, 22.1, 20.7

HRMS (ESI): calc. for [($C_{18}H_{18}ClNO_3$)H] (M+H) 332.1053, measured 332.1060.

2-(Benzylcarbamoyl)-4,5-dimethoxyphenyl 4-chlorobenzoate (4g).



Colorless solid; eluent (60% ethyl acetate in hexanes). **2a** was taken 100 mg, yield is 79%, (215 mg).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3300, 3006, 2938, 1737, 1642, 1263 and 1215.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.74 (t, *J* = 8.0 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.25 (s, 1 H),7.19 – 1.17 (m, 5 H), 7.01 (s, 1 H), 4.33 (d, *J* = 4.0 Hz, 2 H), 3.84 (s, 3 H), 3.80 (s, 3 H).

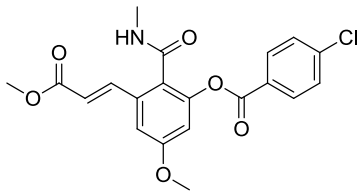
^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.7, 163.9, 150.8, 146.1, 142.2, 139.3, 138.7, 131.7, 128.9, 128.0, 127.0, 126.6, 120.1, 111.5, 107.3, 56.0, 55.9, 42.4.

HRMS (ESI): calc. for [($C_{23}H_{20}ClNO_5$)H] (M+H) 426.1108, measured 426.1112.

General Procedure for the Ruthenium-Catalyzed Alkenylation of Benzamides.[19]

[$RuCl_2$(*p*-cymene)]$_2$ (0.05 mmol, 5 mol %), KPF_6 (0.20 mmol, 20 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.00 mmol) and benzamide **3m** or **3p** (100 mg) were taken in a 15 mL pressure tube, which was equipped with a magnetic stirrer and septum. To the tube were then added methyl acrylate (2.0 mmol) and water (2.0 mL) as the solvent via syringes. Then, the septum was taken out and a screw cap was used to cover the tube. The reaction mixture was allowed to stir at 100 °C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with H_2O (75 mL) and extracted with EtOAc (3 x 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The reaction mixture was concentrated, and the crude residue was purified through a silica gel column (hexanes and ethyl acetate) to give pure **6a** and **6b**.

(*E*)-5-Methoxy-3-(3-methoxy-3-oxoprop-1-en-1-yl)-2-(methylcarbamoyl)phenyl 4-chlorobenzoate (**6a**).



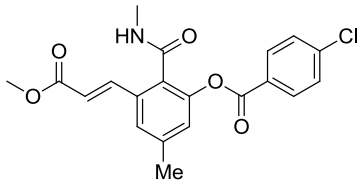
Colorless solid; eluent (40% ethyl acetate in hexanes). **3m** was taken 100 mg, yield is 73%, (94 mg).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 16.0 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 7.06 (s, 1 H), 6.78 (s, 1 H), 6.43 (d, *J* = 16.0 Hz, 1 H), 5.75 (bs, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 2.84 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.6, 165.8, 164.8, 160.7, 148.8, 140.8, 140.7, 134.7, 131.7, 129.2, 126.9, 124.2, 121.5, 110.1, 109.9, 55.7, 51.9, 26.7.

HRMS (ESI): calc. for [($C_{20}H_{18}ClNO_6$)H] (M+H) 404.0901, measured 404.0904

(*E*)-3-(3-Methoxy-3-oxoprop-1-en-1-yl)-5-methyl-2-(methylcarbamoyl) phenyl 4-chlorobenzoate (**6b**).



Colorless solid; eluent (40% ethyl acetate in hexanes). **3p** was taken 100 mg, yield is 71%, (90 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (d, *J* = 8.0 Hz, 2 H), 7.70 (d, *J* = 16.0 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 7.38 (s, 1 H),7.06 (s, 1 H), 6.44 (d, *J* = 16.0 Hz, 1 H) 5.84 (bs, 1 H), 3.79 (s, 3 H), 2.84 (d, *J* = 8.0 Hz, 3 H), 2.41 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.7, 165.9, 165.0, 147.5, 140.9, 140.7, 133.6, 131.6, 130.3, 129.4, 129.1, 127.0, 125.2, 124.6, 121.1, 51.8, 26.7, 21.3.

HRMS (ESI): calc. for [($C_{20}H_{18}ClNO_5$)H] (M+H) 388.0952, measured 388.0952.

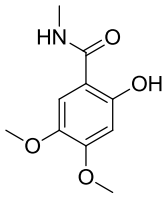
General Procedure for the De-esterification Reaction.[20]

For Base Mediated De-esterification:

A two-neck 50 mL round bottom flask fitted with a condenser containing a mixture of **3a** (100 mg) and NaOH (40 % solution) (2 mL) in 4 mL of Ethanol. The reaction mixture was refluxed at 80 °C for 2 h. After 2 h, 2 mL of water was added to the reaction mixture and refluxed again for another 8 h. After the reaction, the reaction mixture was allowed to

cool to room temperature and the reaction mixture was neutralised (pH = 6) using 1N HCl. The product was extracted with ethyl acetate, washed with water and brine. The extract was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **6c**.

2-Hydroxy-4,5-dimethoxy-*N*-methylbenzamide (**6c**).



Colorless solid; eluent (50% ethyl acetate in hexanes). **3a** was taken 150 mg, yield is 92%, (83 mg).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.42 (s, 1 H), 6.72 (s, 1 H), 6.46 (s, 1 H), 6.20 (bs, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 2.98 (d, *J* = 4.0 Hz, 3 H).

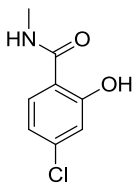
^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 157.9, 154.6, 141.8, 107.7, 104.9, 101.3, 56.8, 56.0, 26.4.

HRMS (ESI): calc. for [($C_{10}H_{13}NO_4$)H] (M+H) 212.0923, measured 212.0925.

For Acid Mediated De-esterification:

A two-neck 50 mL round bottom flask fitted with a condenser containing a mixture of **3a** (100 mg) and Conc. H_2SO_4 (2 mL) in 4 mL of acetic acid. The reaction mixture was refluxed at 75 °C for 12 h. Then, the reaction mixture was allowed to cool to room temperature and the mixture was extracted with ethyl acetate, washed with water and brine. The extract was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **6d**.

4-Chloro-2-hydroxy-*N*-methylbenzamide (**6d**).



Light orange solid; eluent (30% ethyl acetate in hexanes). **3t** was taken 150 mg, yield is 81%, (69 mg).

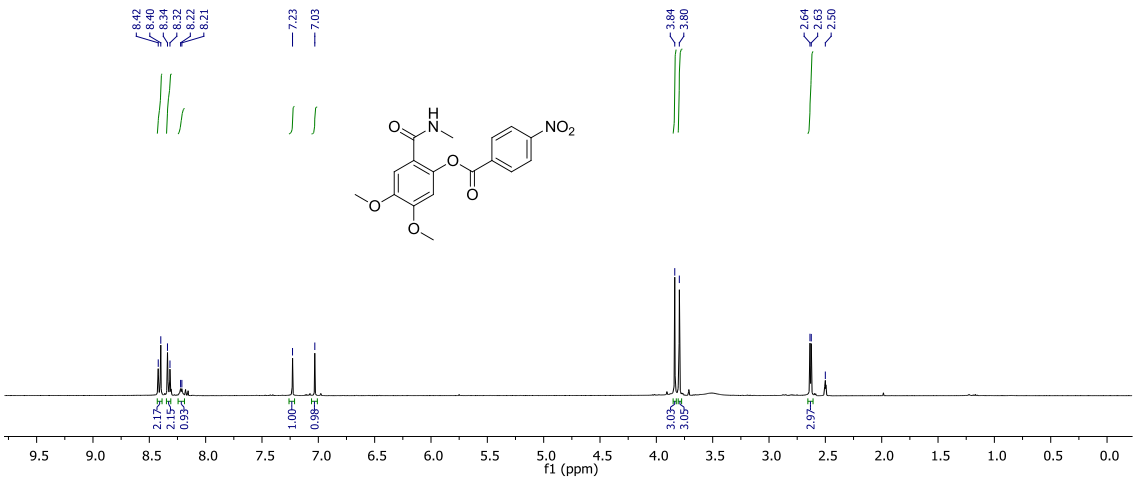
^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.57 (s, 1 H), 7.27 (d, *J* = 8.0 Hz, 1 H). 6.99 (s, 1 H), 6.81 (d, *J* = 8.0 Hz, 1 H). 6.45 (bs, 1 H), 3.00 (d, *J* = 4.0 Hz, 3 H).

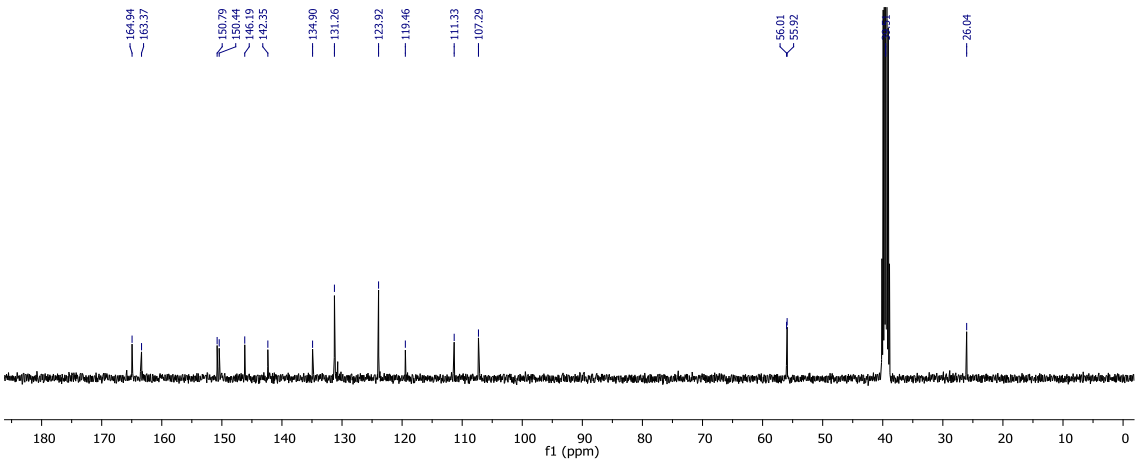
^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 162.1, 139.6, 126.3, 119.1, 118.6, 112.8, 26.5.

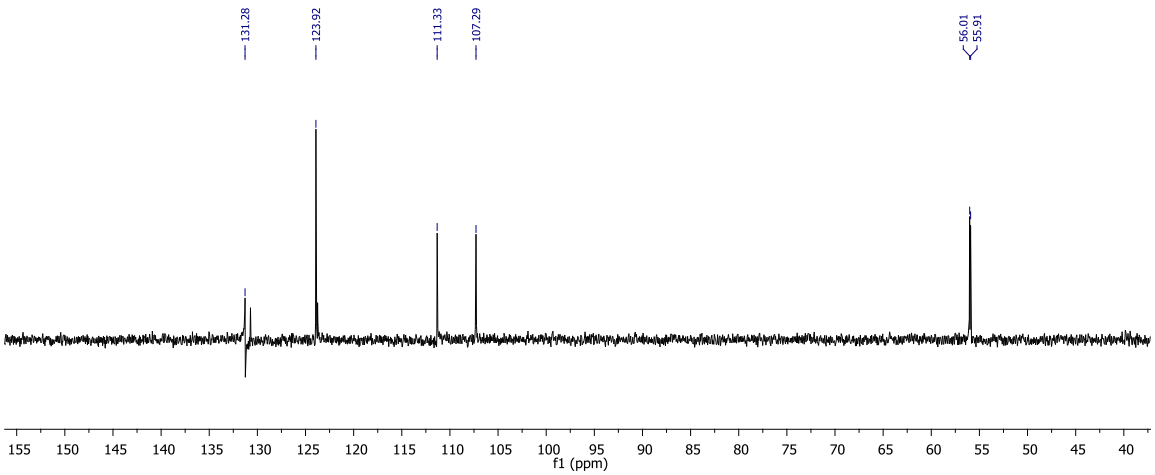
HRMS (ESI): calc. for [($C_8H_8ClNO_2$)H] (M+H) 186.0322, measured 186.0324

4B.13: Spectral Copies of Selected Compounds

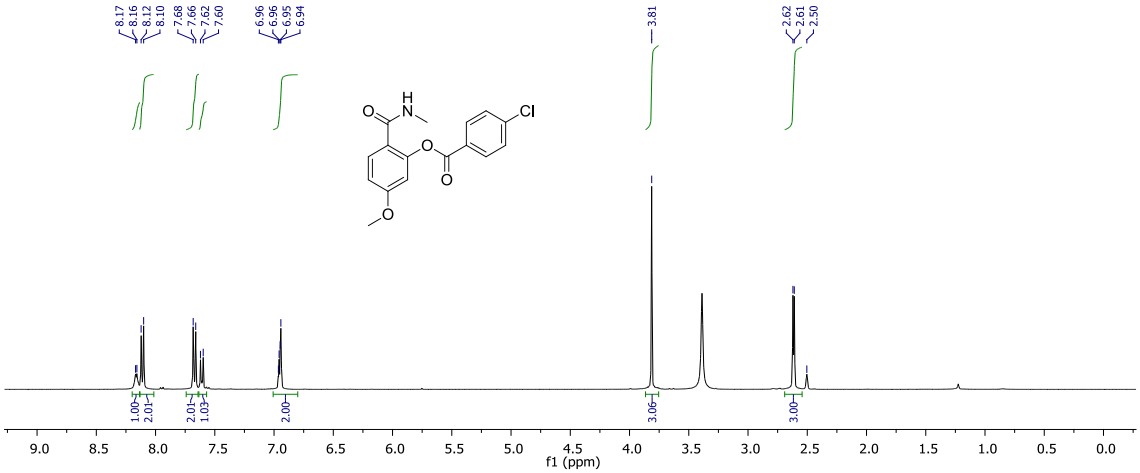
Spectral data of compound **3h**.

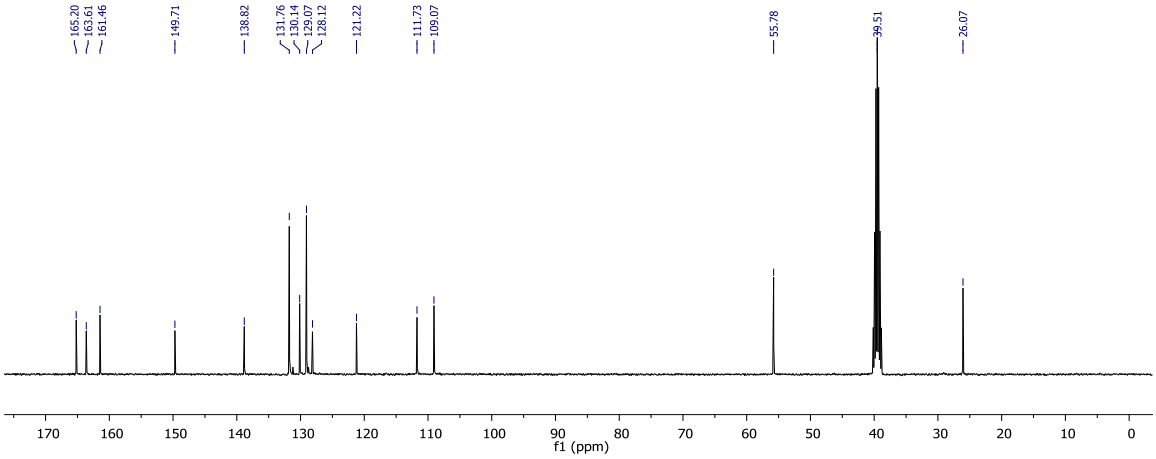


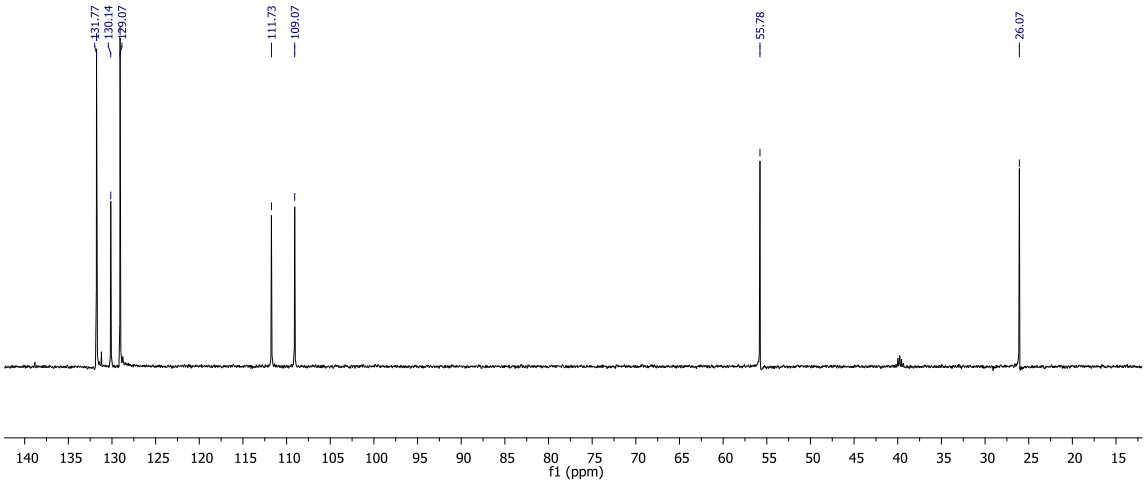




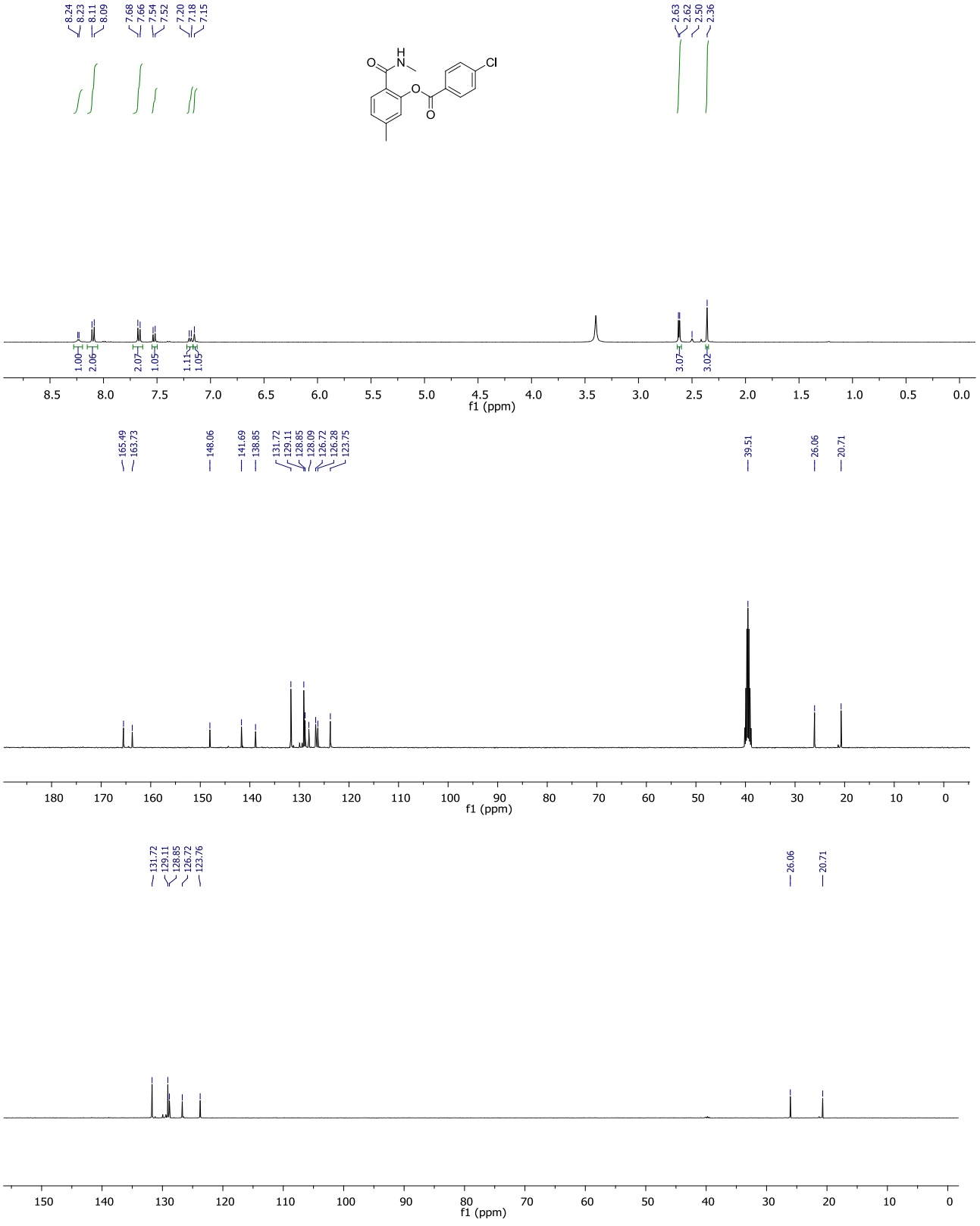
Spectral data of compound **3m**.



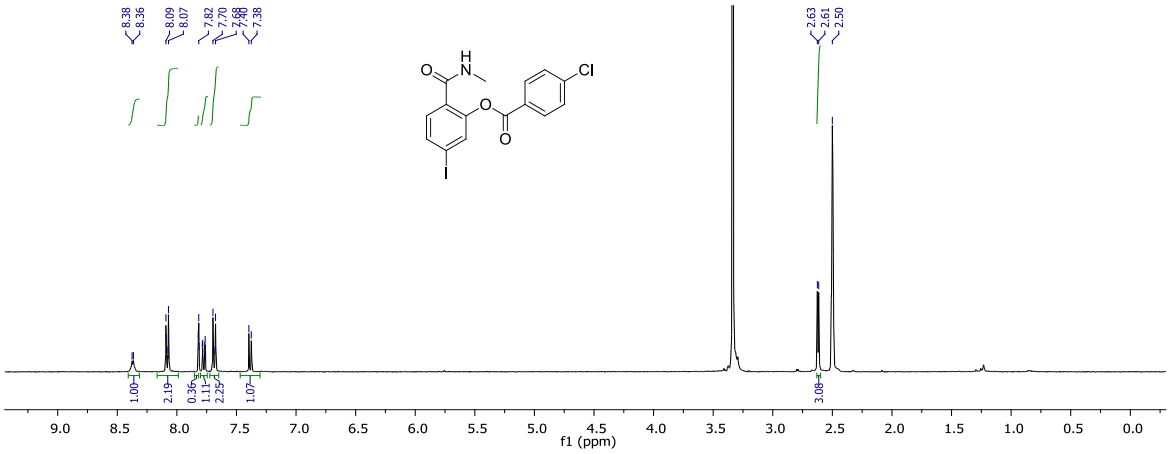


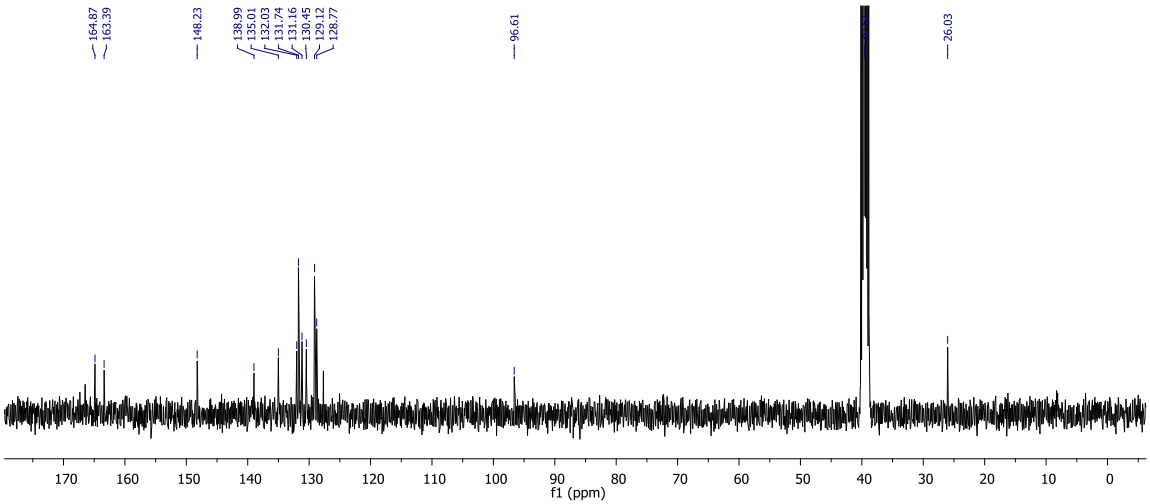


Spectral data of compound **3m**.

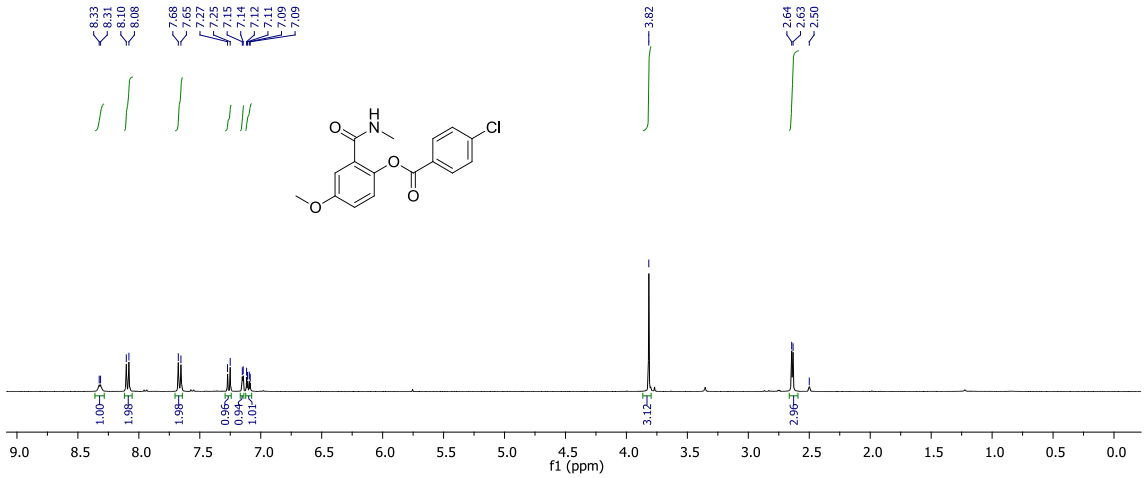


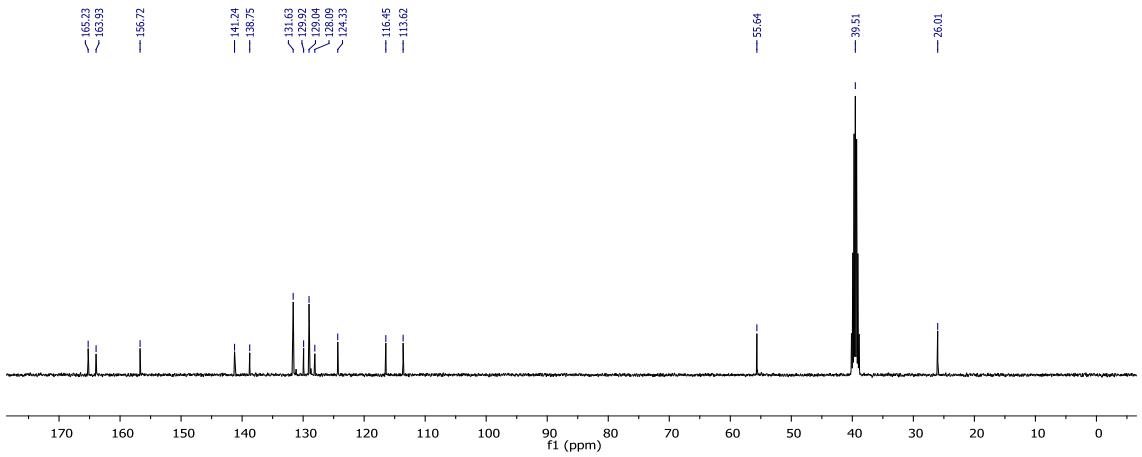
Spectral data of compound **3p**.



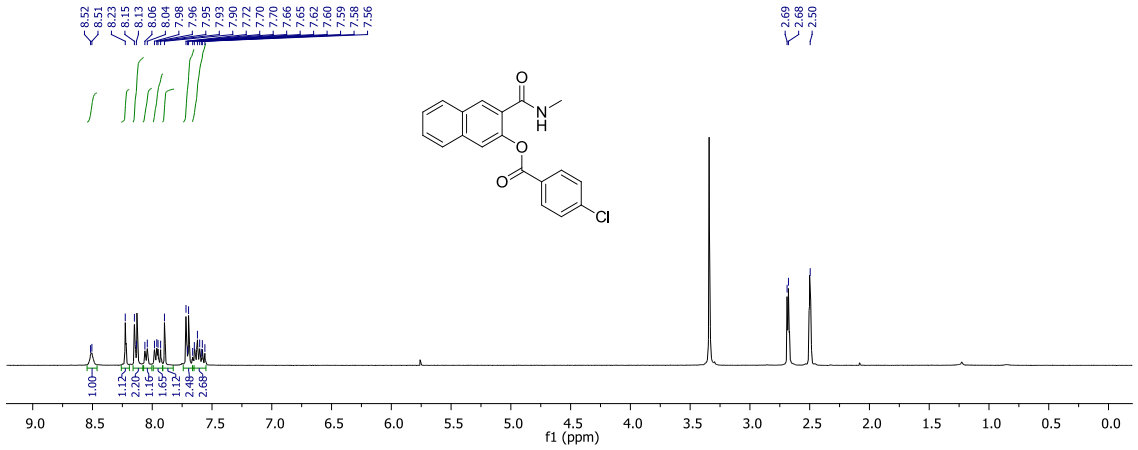


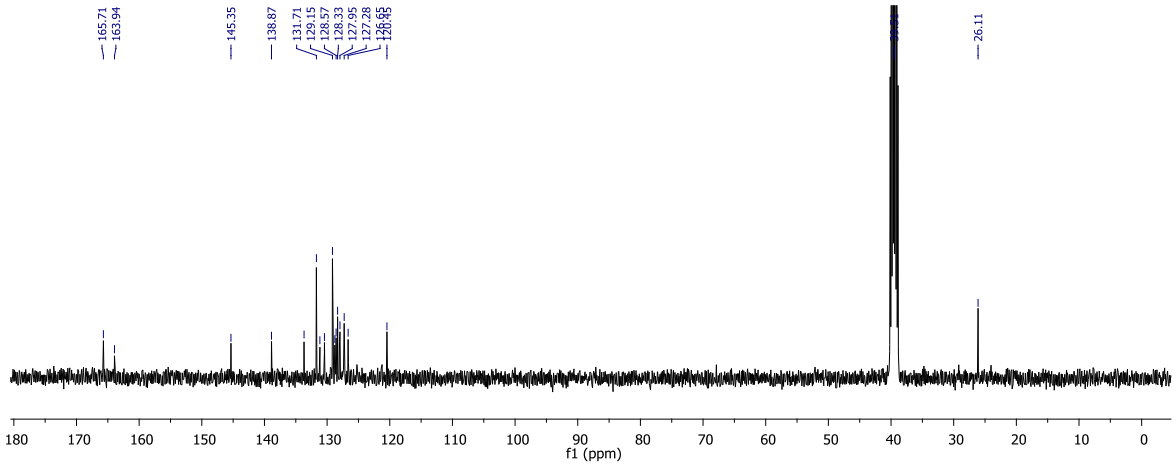
Spectral data of compound **4b**.



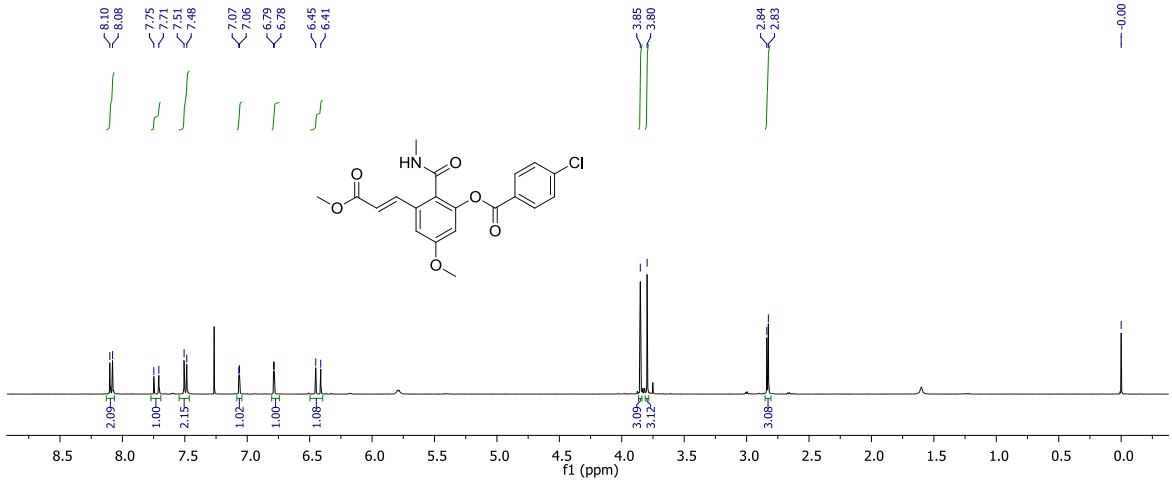


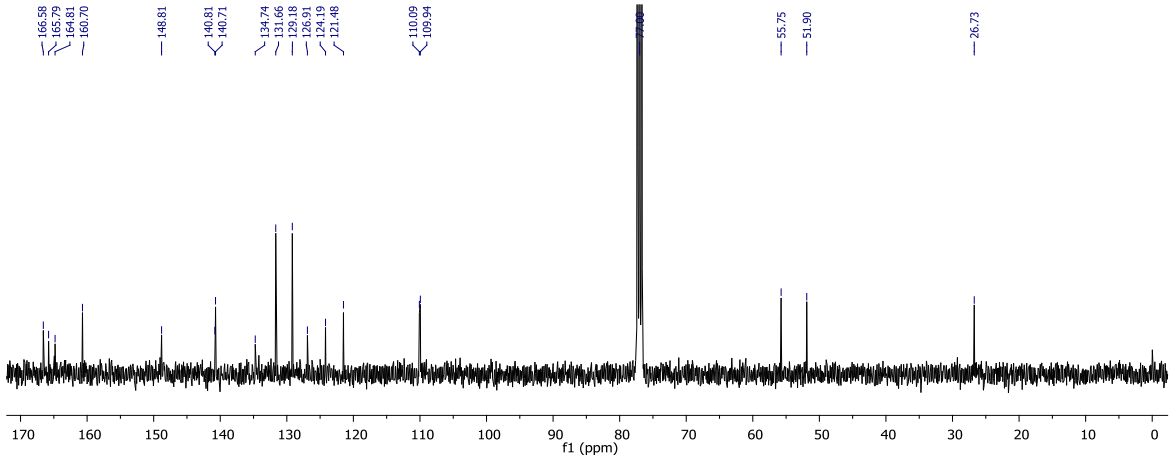
Spectral data of compound **4e**.



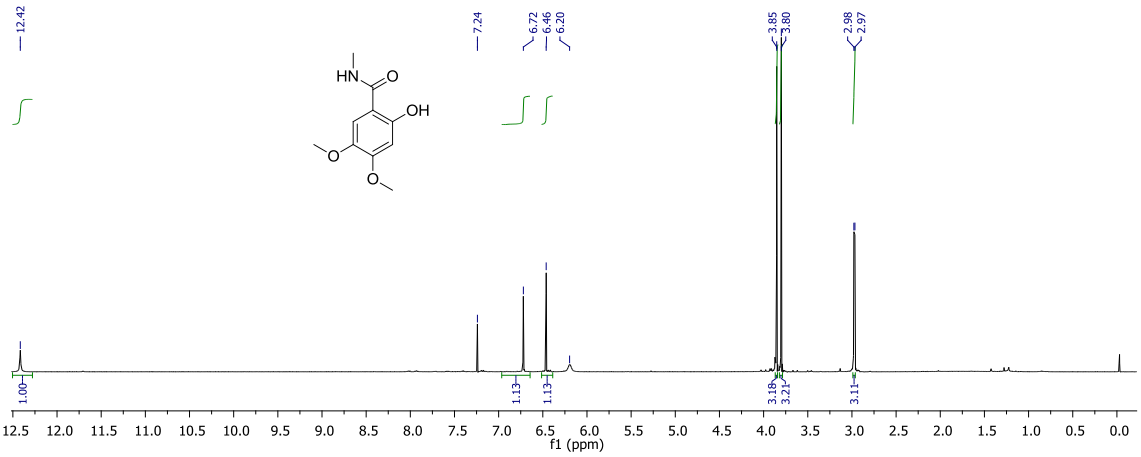


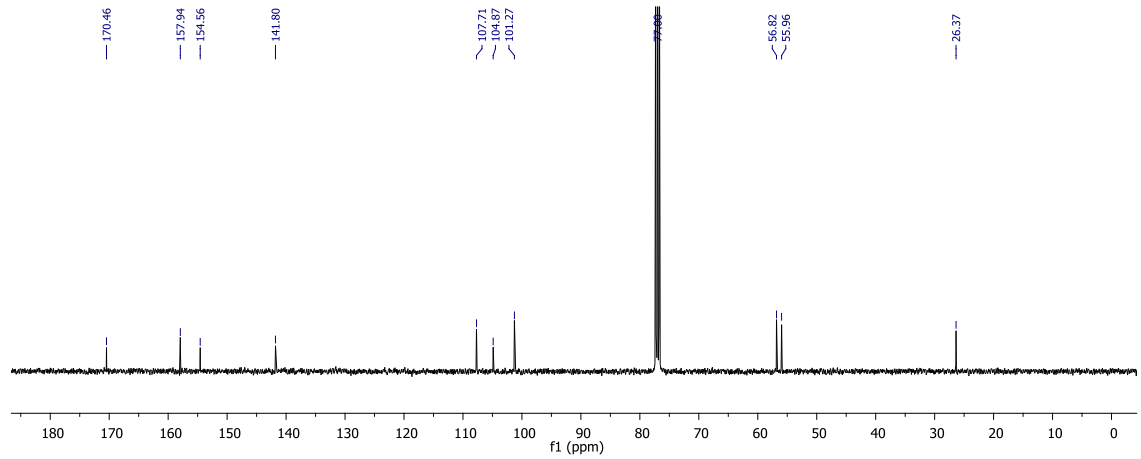
Spectral data of compound **6a**.





Spectral data of compound **6c**.





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