Ruthenium(II)-and Cobalt(III)-Catalyzed Cyclization and Alkenylation of Substituted Aromatics with π-Components

A Thesis

Submitted in Partial Fulfillment of the Requirements

For the Degree of

Doctor of Philosophy

By

R. Manoharan

ID: 20133266

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2019

Dedicated

To

My Mother

And

My Teachers

भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान,पुणे
INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH (IISER), PUNE
(An Autonomous Institution, Ministry of Human Resource Development, Govt. of India)
Dr. HomiBhabha Road, Pashan, Pune – 411 008

Dr. M. Jeganmohan

Associate Professor

Department of Chemistry

IIT Madras

CERTIFICATE

Certified that the work incorporated in this thesis entitled "***Ruthenium(II)-and Cobalt(III)-Catalyzed Cyclization and Alkenylation of Substituted Aromatics with π-Components***" submitted by ***Mr. R. Manoharan*** 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: th February 2019

Chennai

Dr. M. Jeganmohan

Thesis supervisor

Ph: + 91-44-2257-4211 | Mobile: +91- 8903159461 | *Email:* mjeganmohan@iitm.ac.in

DECLARATION

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

Date: th February 2019 **R. Manoharan**

Pune ID: 20133266

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R. Manoharan

Synopsis

The thesis entitled "***Ruthenium(II)-and Cobalt(III)-Catalyzed Cyclization and Alkenylation of Substituted Aromatics with π-Components***" comprises of four chapters.

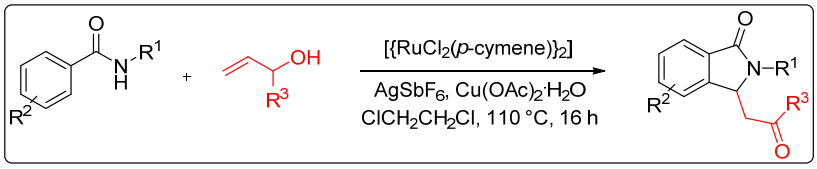
The transition-metal-catalyzed chelation-assisted C–H functionalization of substituted aromatics with electrophiles or nucleophiles is an efficient method to construct chemical bonds in highly atom and step economical manner. Various transition metal complexes of palladium, rhodium, ruthenium and iridium are widely employed as catalysts for this type of transformations. Among them, due to the unique reactivity and selectivity, a less expensive ruthenium arene complex has gained much attention for this type of reactions. In addition, the reactions catalyzed by ruthenium arene complexes can be performed under air atmosphere and water can be employed as solvent. Meanwhile, the development of new C–H bond transformation reactions by using more abundant, biologically tolerated and sustainable first row transition metal catalysts is also highly important. Recently, the air stable and inexpensive cobalt complexes are recognized as one of the efficient catalysts for the C–H functionalization reaction. In this thesis, we aim to develop methods for synthesizing heterocylic moieties using Ru(II) and Co(III) catalysts with a combination of suitable directing groups and C–C π-components.

Chapter 1 of this thesis discusses the history and classification of C–H activation reactions. A brief introduction of chelation-assisted C–H bond activation via oxidative addition pathway as well as deprotonation pathway was also discussed with appropriate examples. In particular this part discusses about the types and the reaction mechanisms of ruthenium and cobalt catalyzed C–H bond activation reactions.

Chapter 2 of this thesis describes an efficient method for the Ru-catalyzed oxidative cyclization reaction to synthesize structurally diverse isoindolines and pyrroloquinolinones. It contains two sub-divisions as follows:

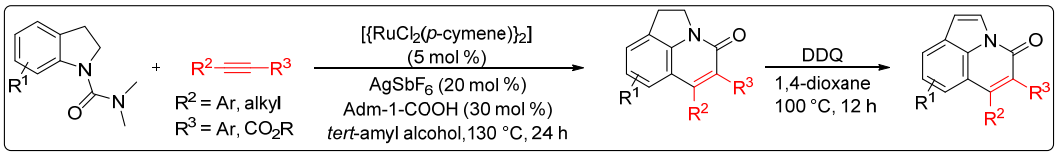
Section 2A: Synthesis of Isoindolinones: Isoindolinone is a core structure unit present in various natural products and biologically active molecules. Particularly, 3-substituted isoindolinone skeleton is found in various biologically active molecules. It has also been serving as a key synthetic intermediate for synthesizing various highly useful organic molecules and natural products. Herein, we describe a ruthenium-catalyzed cyclization of *N*-substituted

benzamides with allylic alcohols to give 3-substituted isoindolinone derivatives in good yields (Scheme 1). A possible reaction mechanism involving a five-membered ruthena cycle intermediate was proposed and strongly supported by experimental evidences. Interestingly, the reaction pathway such as enoloization vs β-hydride elimination can be tuned, by changing the reaction conditions.



Scheme 1: Ruthenium-Catalyzed Cyclization of *N*-substituted Benzamides with Allylic Alcohols

Section 2B: Synthesis of Pyrroloquinolinones: The pyrroloquinoline unit is present in various agrochemicals, drug molecules, natural products and materials. Pyrroloquinoline derivatives show potent biological activities towards asthma, obesity, anti-acetylcholinesterase and epilepsy. In addition, pyrroloquinoline derivative can also be used as a key intermediate for synthesizing various biologically active molecules and natural products. Herein, we describe a convenient route to synthesize pyrroloquinolinone derivatives via a ruthenium-catalyzed oxidative cyclization of *N*-carbamoyl indolines with alkynes (Scheme 2). Generally, a metal acetate base is used to activate the C–H bond of organic moieties. In the reaction, a catalytic amount of organic acid, 1-adamantanecarboxylic acid (1-Adm-COOH), was used. The role of 1-Adm-COOH is unique in the reaction, as it plays a role of proton source as well as base for activating the C7-H bond of indoline moieties.

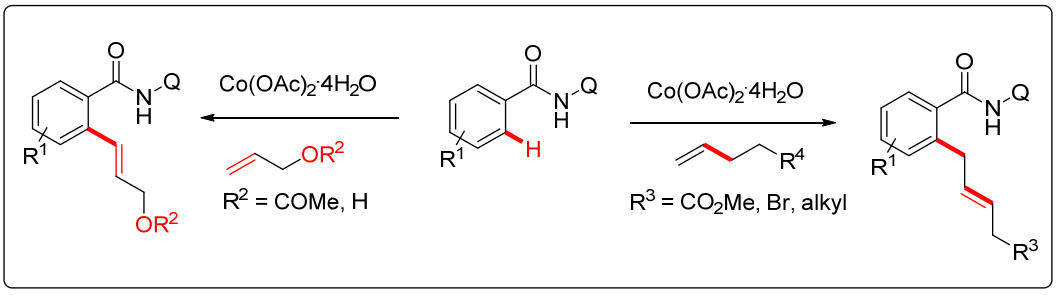


Scheme 2: Ruthenium-Catalyzed Synthesis of Pyrroloquinolinones

The cyclization reaction was compatible with various functional group substituted indolines, symmetrical and unsymmetrical alkynes including substituted propiolates. The cyclization reaction is highly regioselective particularly with unsymmetrical alkynes and the coordinating group such as aryl or ester substituent on the alkyne moiety prefers to stay adjacent to the

carbonyl group of quinolinone derivative. Later, pyrroloquinolinone derivatives were converted into pyrroloindolones in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

Chapter 3 describes a cobalt catalyzed regioselective allyllation and alkenylation of quinoline benzamides with unactivated alkenes and allyl acetates. The transition metal-catalyzed chelation-assisted selective olefination at the inactive C–H bond of substituted aromatics with alkenes is an efficient method for synthesizing arylated alkenes in a highly atom- and step-economical manner from easily available starting materials. However, in this type of alkenylation reactions, only conjugated alkenes such as acrylates, vinyl sulfones, acrylonitriles, acrylamides and styrenes were extensively used. The selective C–H olefination with unactivated alkenes are rare and very challenging to succeed due to the less reactivity of alkenes and formation of mixtures of linear as well as branched isomers. In a metal-catalyzed C–H bond functionalization reaction, allyl acetates or alcohols always serve as an allylating agent, providing allylated product with a removal of OAc or OH. Meanwhile, most of this C–H bond transformation relies on second and third row noble metals such as palladium, rhodium, ruthenium and iridium. However, these noble metals are less abundant in nature and very expensive. Thus, the development of new C–H bond transformation reaction by using more abundant, biologically tolerated and sustainable first row transition metal catalysts is highly important.



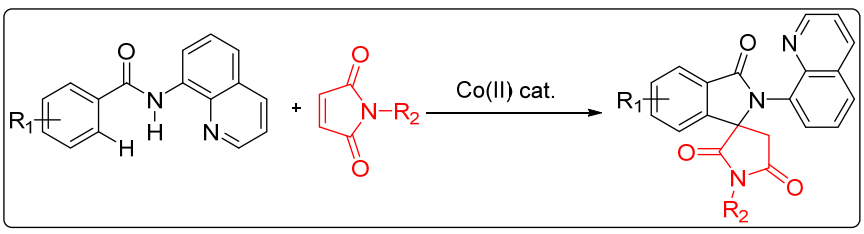
Scheme 3: Cobalt-Catalyzed C–H Allylation and alkenylation

Herein, we describe an unprecedented cobalt-catalyzed C–H olefination of aromatic and heteroaromatic amides with unactivated alkenes, allyl acetates and allyl alcohols. This method offers an efficient route for the synthesis of vinyl and allyl benzamides in a highly stereoselective manner. In the transition metal-catalyzed C–H bond functionalization reaction via chelation-assisted metalation pathway, allyl acetates or alcohols mostly serve as an allylating agent, providing allylated product with a removal of OAc or OH group. This report describes a typical

Heck-type vinylation reaction without cleavage of OAc and OH. Meanwhile, in the other reported alkenylation with unactivated alkenes, a mixture of linear as well as branched vinyl alkenes was observed. In the present method, exclusively a linear allyl aromatics was observed in a highly stereoselective manner.

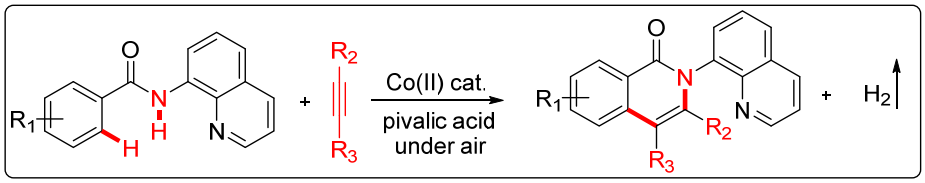
Chapter 4 describes chelation-assisted cobalt-catalyzed oxidative cyclization of arylamides with maleimides and alkynes to synthesize structurally diverse spirosuccinimides and isoquinolinoes respectively. It contains two sub-divisions as follows:

Section 4A: Synthesis of Isoindolone Spirosuccinimides: Isoindolone derivatives are synthesized in a highly atom-economical and environmentally friendly manner by oxidative cyclization of aromatic amides with alkenes by using transition metal catalysts. In this type of cyclization reaction, only terminal alkenes are efficiently involved and internal alkenes including cyclic alkenes are less explored. Recently, maleimides are efficiently used as an alkene source in the C–H alkenylation reaction. Mostly, substituted aromatics undergoes 1,4-addition with maleimides providing *ortho* alkylated aromatics. For this type of alkylation reaction, ruthenium, rhodium, cobalt and manganese complexes are widely used. Herein, we describe a cobalt-catalyzed 8-aminoquinoline directed oxidative cyclization of benzamides with maleimides. The oxidative cyclization reaction provides isoindolone spirosuccinimides in good to excellent yields. The reaction was compatible with various functional group substituted benzamides as well as *N*-substituted maleimides (Scheme 4). A possible reaction mechanism involving the C–H bond activation as a key step was proposed. The competition experiment and deuterium labelling studies were performed to investigate the mechanism of the present cyclization reaction. The competition experiment and deuterium labelling studies clearly reveals that the irreversible C−H bond cleavage might not be the rate-limiting step of the reaction.



Scheme 4: Synthesis of Isoindolone Spirosuccinimides

Section 4B: Synthesis of Isoquinolone: Isoquinolone is an important heterocyclic structural unit which presents in various natural products, biologically active molecules and conjugated materials. In addition, isoquinolone derivatives are widely used as a key intermediate in various organic transformations. Herein, we have described the synthesize of isoquinolone derivatives from benzamides with alkynes assisted by 8-aminoquinoline ligand in the presence of $Co(OAc)_2{\cdot}4H_2O$ and pivalic acid under air. In the reaction, the active Co(III) species is regenerated by the reaction of Co(I) species with pivalic acid under air with hydrogen evolution. The proposed mechanism was supported by competition experiments, deuterium labelling studies, radical scavenger experiment and kinetic studies.



Scheme 6: Synthesis of Isoquinolones

***Publications*:**

1. **Manoharan, R**.; Jeganmohan, M. Cobalt- Catalyzed Cyclization of Benzamides with Alkynes: A Facile Route to Isoquinolones with Evolution of Hydrogen. *Org. Biomol. Chem.*, **2018**, *16*, 7006.
2. **Manoharan, R**.; Jeganmohan, M. Cobalt-Catalyzed Oxidative Cyclization of Benzamides with Maleimides: Synthesis of Isoindolone Spirosuccinimides. *Org. Lett.*, **2017**, *19*, 5884−5887.
3. **Manoharan, R**.; Sivakumar, G.; Jeganmohan, M. Cobalt-catalyzed C-H olefination of aromatics with unactivated alkenes. *Chem. Commun.*, **2016**, *52*, 10533-10536.
4. **Manoharan, R**.; Jeganmohan, M. Ruthenium-Catalyzed C-H Amidation and Alkenylation of CyclicN-Sulfonyl Ketimines. *Eur. J. Org. Chem.*, **2016**, *4013*−4019.
5. **Manoharan, R**.; Jeganmohan, M. Ruthenium-catalyzed cyclization of N-carbamoyl indolines with alkynes: an efficient route to pyrroloquinolinones. *Org. Biomol. Chem.*, **2015**, *13*, *9276*−9284.

6. **Manoharan, R**.; Jeganmohan, M. Synthesis of isoindolinones via a ruthenium-catalyzed cyclization of N-substituted benzamides with allylic alcohols. *Chem. Commun.*, **2015**, *51*, 2929-2932.

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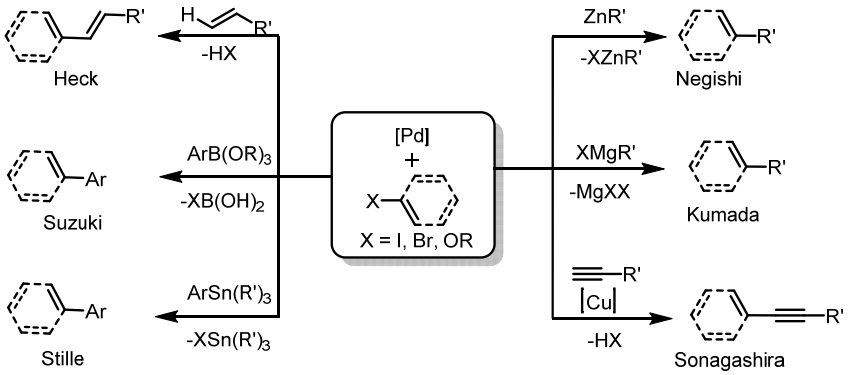
Chapter 1

Introduction

1.1: Cross coupling reactions

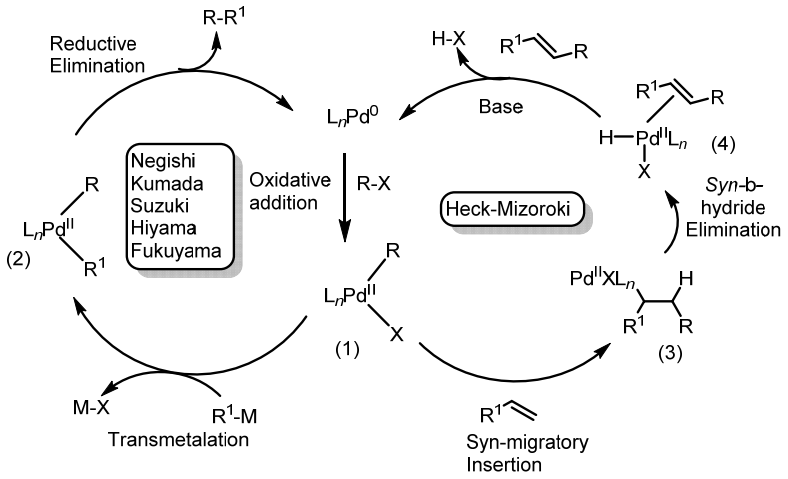
The transition-metal-catalyzed cross-coupling reactions are evolved as indispensable tools for the formation of C–C and C-hetero (especially N and O) bonds in last two decades. These methods have been extensively employed in wide areas of synthetic organic chemistry including natural product synthesis, supramolecular chemistry and medicinal chemistry. These methodologies are playing central role in agrochemical, fine chemical and pharmaceutical industries to make corresponding molecules.[1] In general a typical cross coupling reaction involves in the formation of C–C, C–N, C–O, C–S, C–P, or C–M bond by the synthetic transformation of an organometallic reagent with an organic electrophile in the presence of transition metal catalyst from groups 8–10.[2] Notably palladium complexes are widely employed for this type of transformations. The pioneering experimental discoveries in this area in early 1970's by Kumada, Kochi, Corriu, Murahashi and Heck followed by Suzuki (organoboron), Stille (organotin) and Negishi (organozinc) made these reactions become important tools to make C–C bonds (Scheme 1.1). The revolutionary contribution to this field by R.F. Heck, E. Negishi and A. Suzuki was well recognised and brought Nobel Prize in Chemistry in the year 2010.



Scheme 1.1: Selected palladium-catalyzed cross-coupling reactions

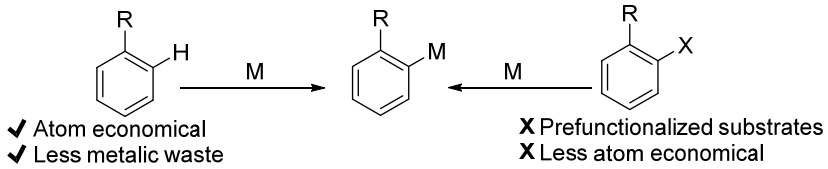
The general catalytic cycle involves the following basic organometallic steps sequentially as follows: Oxidative addition – transmetallation - reductive elimination. In the case of heck reaction, the transformation occurs in the sequence of oxidative addition - syn 1,2-insertion - β-hydride elimination (Scheme 1.2). Even though these reactions are efficient and unique in their way of forming C–C and C–heteroatom bonds, the requirement of prefunctionalized organometallic regents C–M (M = MgX, ZnX, BR_2, SnR_3, SiR_3, etc.) and organo

electrophiles C–X (X = I, Br, OTf, etc.,) are limiting factors of this methodology. In some cases, synthesis of organometallic reagents and electrophiles requires multiple steps and most of them are sensitive to air and moisture. In addition, at the end of the catalytic cycle along with the desired products M and X are eliminated as undesired by products. Hence, it is imperative to develop more atom economical and step economical methodologies to overcome the noted shortcomings.



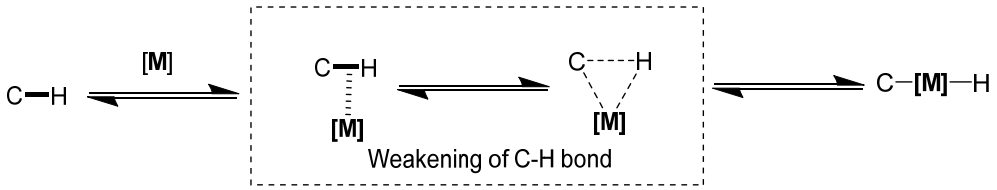
Scheme 1.2: General catalytic cycle

1.2: C–H Bond activation reactions



Scheme 1.3: C–H bond activation *vs* cross-coupling reactions

The transformation would be more atom-economical and step-economical, if the transformation attained by functionalizing the simple C–H bonds, instead of using prefunctionalized starting materials (Scheme 1.3). These types of reactions are coined by the term 'C–H bond activation' reactions. In general, the inactive C–H bonds can be weakened and replaced by transition metal which leads to the formation of C–M intermediate. This transformation occurred majorly by utilizing the agostic interaction between transition metal and C–H bond, which leads to the weakening of the corresponding C–H bond followed by the selective cleavage of the particular C–H bond (Scheme 1.4).

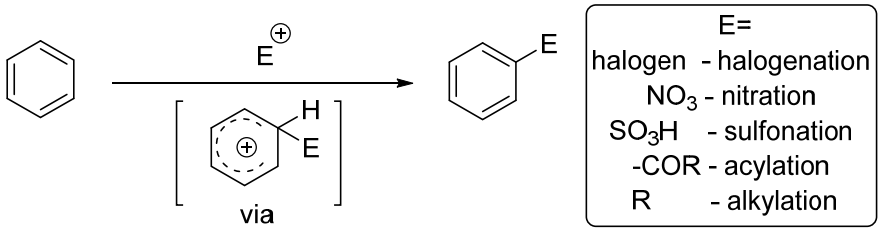


Scheme 1.4: C–H bond activation

Functionalization of aromatics via C–H activation *vs* electrophilic aromatic substitution reactions and directed *ortho* metalation

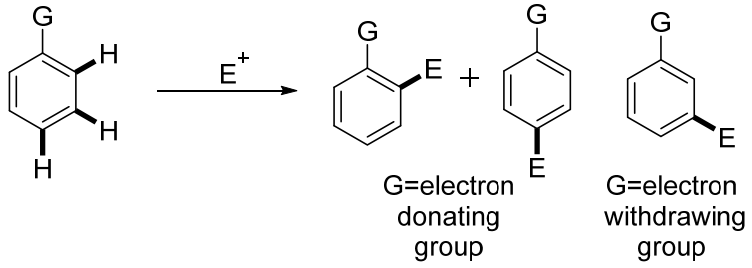
1.3: Electrophilic aromatic substitution reactions

Electrophilic aromatic substitution reactions (EAS) are widely used earlier method to introduce functional groups in the benzene ring and its derivatives. These reactions can be classified as halogenation, nitration, sulfonation, Friedel-Crafts alkyaltion and Friedel-Crafts acylation depends on the electrophile used. Majorly these reactions can be accelerated by using a Lewis acid to increase the electrophilicity of the electrophile (Scheme 1.5).[3]



Scheme 1.5: Electrophilic aromatic substitution

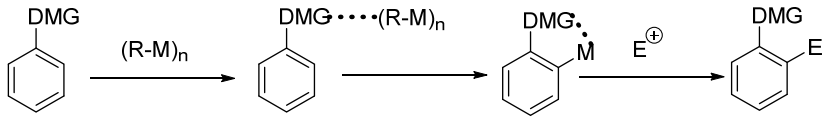
The reaction mechanism starts with the attack of aromatic π-electrons to the electrophilic center which leads to the formation of arenium ion intermediate. In order to retain the aromaticity, arenium ion looses one proton from the methylene group and yields the final product. In these reactions, electronic factors dictate the substitution patterns of the aromatic ring in the final product. The presence of electron donating groups on the aromatic ring directs the incoming electrophile to *ortho* and *para* positions by increasing the nucleophilicity of the aromatic ring by the positive mesomeric effect (+M). Meanwhile electron withdrawing groups directs the incoming electrophile to *meta* position by decreasing the neucleophilicity of the aromatic ring by the negative mesomeric effect (-M). In addition to that multiple substitution products also observed and in some cases products were more reactive than starting materials. Overall these reactions are not regioselective (Scheme 1.6). Later chemists introduced directing groups on the aromatic rings to get *ortho* functionalization selectively.



Scheme 1.6: Effect of substitutions in EAS

1.4: *ortho* Lithiation reactions

ortho Lithiations or directed metalation reactions are used to place the electrophiles adjacent to the hetero atom containing functional group. After the successful *ortho* functionalization of anisole by Gilman and Wittig, these reactions evolved as alternatives to the classical aromatic electrophilic substitution reactions.[4a] In general metal bases like RLi, RMgX, RZnX, etc., are used to deprotonate the C–H bond of aromatics adjacent to the hetero atom containing functional groups. These reactions are called as directed metalation reactions. Later, exposure of various electrophiles to C–M bond furnishes various *ortho* functionalized products. By employing this methodology 1, 2 - di substituted aromatics can be synthesized regioselectively (Scheme 1.7).



Scheme 1.7: Directed *ortho* metalation

This methodology was extended to various nitrogen and oxygen containing directing groups with a range of electrophiles like O_2, Br_2, RX, HCO_2Et, Bu_3SnCl, Ph_2PCl, CO_2, TsN_3, etc., to get 1,2-di-substituted aromatics.[4] Even though these are efficient methods to make *ortho* substituted aromatics but poor chmoselectivity, hazardous reaction procedures and harsh reaction conditions are limitations of this methodology. Later synthetic chemists devoted considerable amount of time in the development of mild reaction conditions for the functionalization of C–H bonds and came up with transition metal catalyzed C–H bond activation reactions.

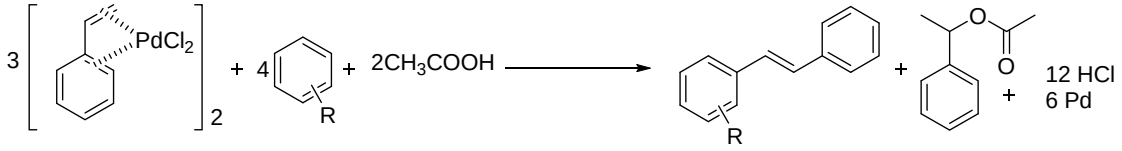
1.5: Classification of C–H bond activation reactions

In general, transition metal catalyzed C–H bond activation reactions can be classified into two major types: a) Non-chelation assisted C–H bond activation reactions b) Chelation assisted C–H bond activation reactions

1.5.1: Non-chelation assisted C-H bond activation reaction

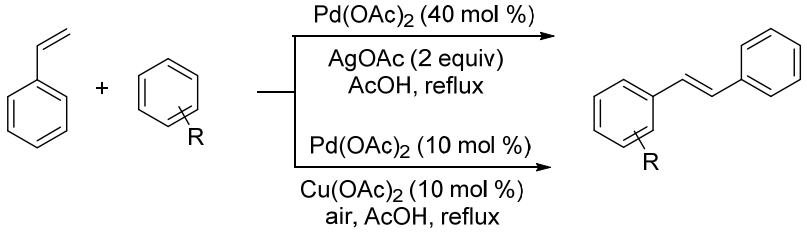
Fujiwara-Moritani reaction

In 1966, Fujiwara and Moritani have reported a new synthetic route to prepare stilbene derivatives. In this reaction olefinic bond of the styrene-palladium complex reacts with aromatic compounds furnishes stilbene derivartives. When styrene-palladium complex refluxed in the mixture of benzene and acetic acid, *trans* stilbene derivative was observed.[5a] Then, this method was extended to substituted benzene derivatives like toluene, xylene and yielded substituted stilbene derivatives. This method provides stilbene derivatives in good to excellent yields. However, an equivalent amount of palladium complex and a large excess of arene as a solvent is necessary for the formation of desired stilbene derivatives (Scheme 1.8).



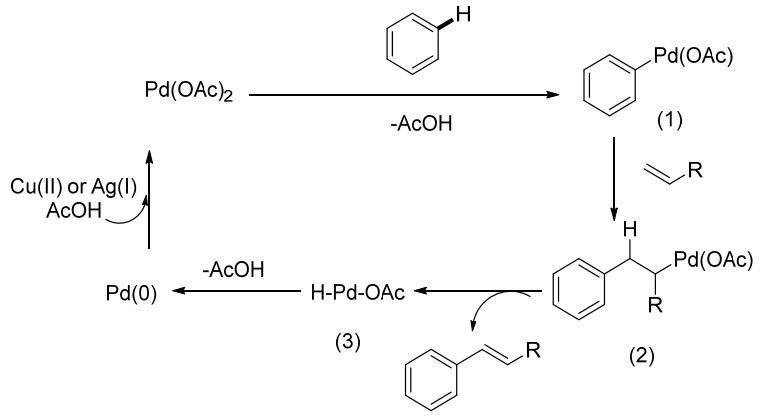
Scheme 1.8: Preparation stilbene derivatives

In 1967, Fujiwara and Moritani reported arylation of styrenes with arenes in the presence of catalytic amount of $Pd(OAc)_2$ and equivalent amount of AgOAc. Here AgOAc used to regenerate Pd (0) to Pd (II).[5b] Later the same group has showed that $Cu(OAc)_2$ can also be used as a co-catalyst in the presense of aectic acid and air to regenerate Pd(II) from Pd (0) (Scheme 1.9).[5c]



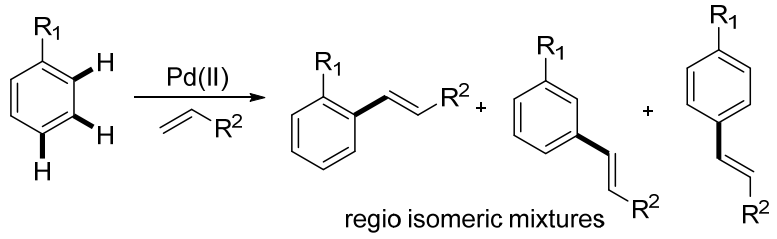
Scheme 1.9: Preparation stilbene derivatives by using catalytic amount of Pd (II)

Reaction mechanism:



Scheme 1.10: General mechanism of Fujiwara- Moritani reaction

The catalytic cycle starts with the electrophilic substitution of benzene with $Pd(OAc)_2$ to furnish intermediate **1**. Olefin insertion followed by syn β-hydride elimination affords the final coupling product and intermediate **3**. The intermediate **3** undergoes reductive elimination to give Pd (0) and AcOH. External oxidants like AgOAc or $Cu(OAc)_2$ regenerates active Pd (II) for the next catalytic cycle (Scheme 1.10).[5] This methodology provides stilbene derivatives in atom and step economical manner with less metallic waste. However substituted arenes provides a mixture of regioisomers in the reaction conditions. In the presence of chemically different types of C–H bonds, this methodology was not regio selective and also it requires harsh reaction conditions (Scheme 1.11).[5c] Because of the aforementioned limitations this reaction did not get much attention in the synthetic organic chemistry community.

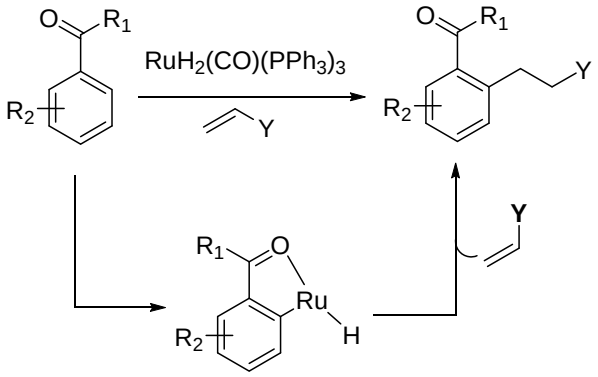


Scheme 1.11: Regioselectivity in Fujiwara- Moritani reaction

1.5.2: Chelation assisted C-H bond activation reaction

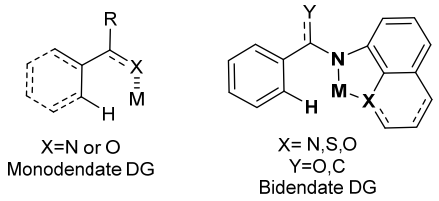
After two decades, in 1993, Murai's group reported *ortho* alkylation of aromatic ketones in the presence of catalytic amount of ruthenium complex.[6a] In this reaction, *ortho* alkylated aromatic ketones were obtained from aromatic ketones with olefins in the presence of low

valent ruthenium complex. It is important to note that in the presence of other C–H bonds, selectively *ortho* C–H bonds functionalized. It is due the coordination between ketone group and the ruthenium complex. This methodology shows the importance of coordinating group or directing group in the C–H bond functionalization reactions. This reaction proceeds through oxidative addition pathway which furnishes desired alkylated products via the formation of Ru–H intermediate (Scheme 1.12).[6]



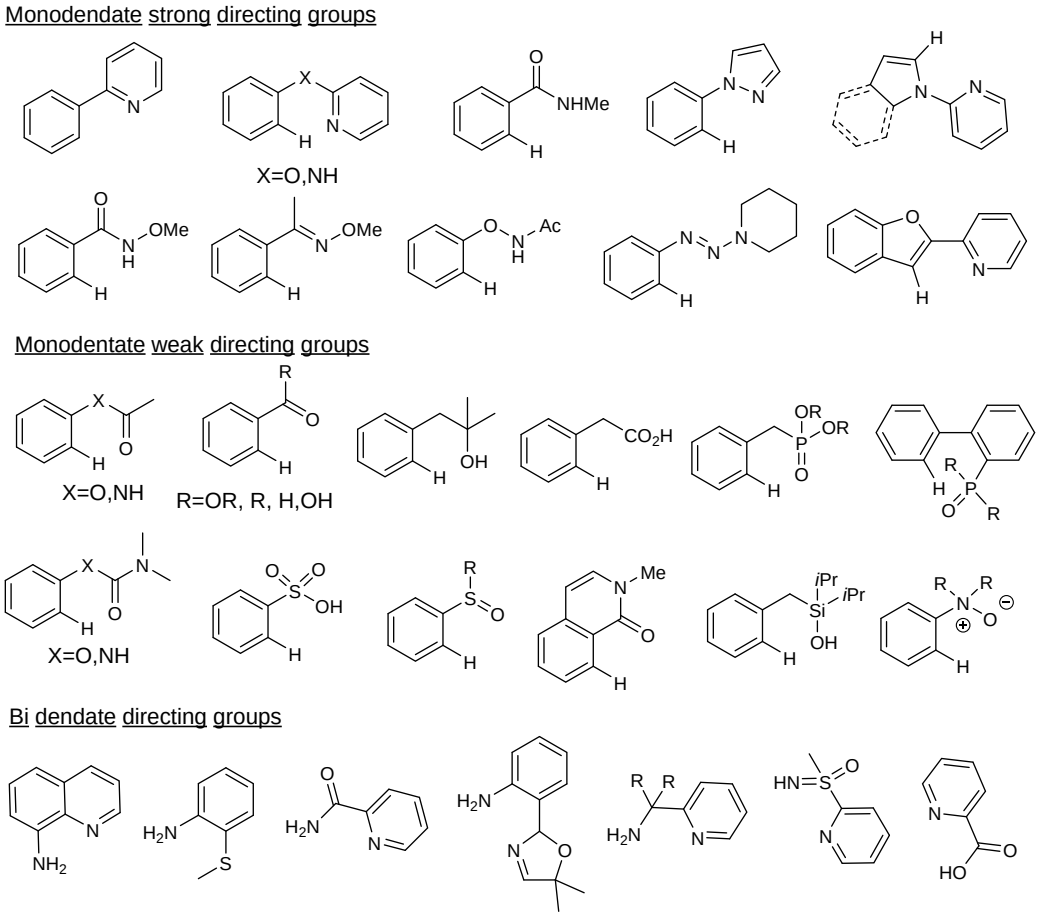
Scheme 1.12: Ru- catalyzed reaction of aromatic ketones with olefins

1.5.3: Directing groups in C–H bond activation reactions



Scheme 1.14: Mono and Bi dendate directing groups

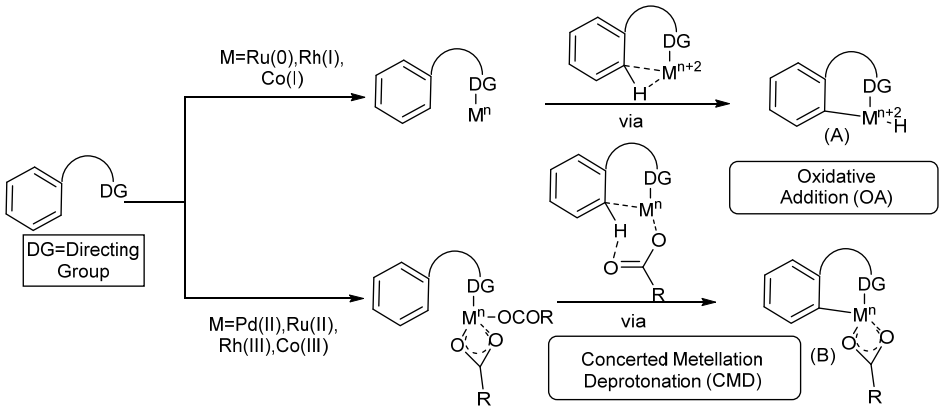
Directing groups or coordinating groups are playing a central importance in chelation assisted C–H bond activation reactions. These groups are chemical functionalities used to direct the transition metal towards C–H bond by using mostly by the lone pair of electrons.[7-8] Based on the number of donor atoms present; a directing group can be classified into two types as follows: 1.Monodendate directing group 2. Bidentate directing group. A monodendate directing group can be further classified into two types based on the hetero atom present in it. The directing groups can be categorized as strong directing groups if the coordinating atom from the chemical functionality possesses reduced electronegativity such as nitrogen atom. On the other hand, weak directing groups are more electronegative in nature compared to nitrogen as in the cases of directing groups with oxygen as the coordinating atom.



Scheme 1.15: Examples of directing groups

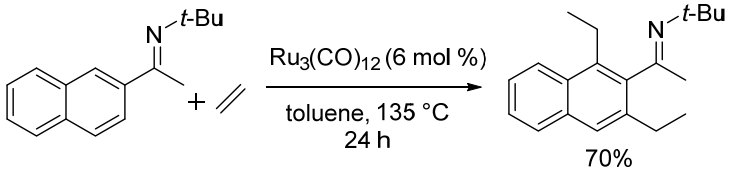
1.6: Classification of chelation assisted C–H bond activation reactions

In general, these reaction pathways are classified into two major types based on the oxidation state of the transition metal catalyst used and the nature of the intermediates involved: 1) Oxidative addition pathway 2) Deprotonation pathway. These two reactions proceed via different intermediates and resulting in different products. In oxidative addition pathway, alkylation of aromatics and hetero aromatics with alkenes can be achieved in the presence of low valent transition metal catalyst. In this class of reactions, after oxidative addition of the metal into *ortho* C–H bond, the M–H bond of the metalacycle intermediate (A) inserts into the double bond of alkene followed by reductive elimination yields *ortho* alkylated aromatics. In deprotonation pathway, aromatics and hetero aromatics react with alkenes in the presence of high-valent transition metal catalyst furnishes *ortho* alkenylated products. In this reaction, a high-valent metal acetate species deprotonates the aromatic C–H bond providing a five membered metalacycle intermediate (B) (Scheme 1.13).[7]



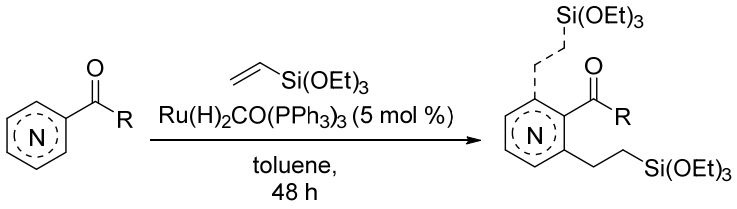
Scheme 1.13: Oxidative addition vs concerted metellation deprotonation

1.6.1: C–H activation of Aromatics with olefins under oxidative addition pathway



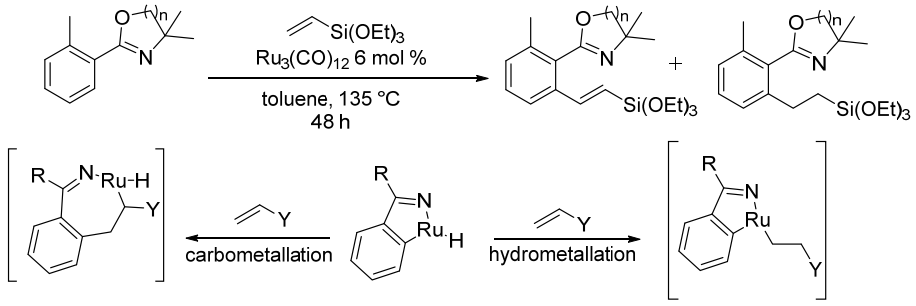
Scheme 1.16: *ortho* Alkylation of ketimines with ethylene

After his seminal findings, Murai and co-workers extended this methodology into aldimines and ketimines. Remarkably, ethlylene also participated in the C–H alkylation reactions and furnished *ortho* alkylated products (Scheme 1.16).[8a]



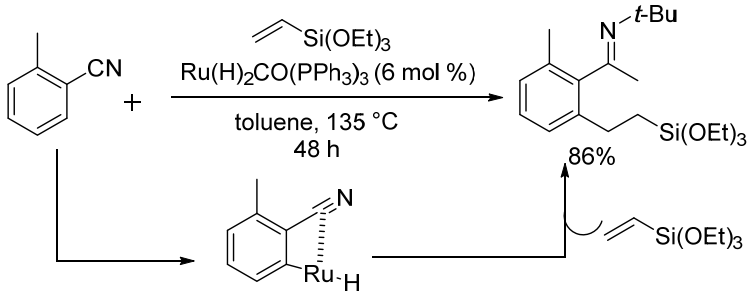
Scheme 1.17: *ortho* Alkylation of acyl pyridines

In 1997, Grigg and co-workers reported alkylation of 3- and 4-acyl pyridine derivatives in the presence of *in situ* generated Ru(0) complex. In this reaction, 3- and 4-acyl pyridine derivatives reacts with olefins yielded desired alkylated products. In the case of 2-acylated pyridines there was no expected product formed this is due to the combined bidendate chelation from nitrogen and oxygen (Scheme 1.17).[8b]



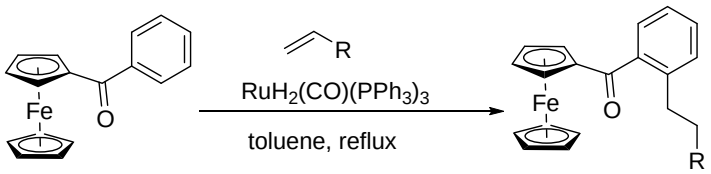
Scheme 1.18: *ortho* Alkenylation and alkylation of oxzazines

In 1999, Murai and co-workers found that when oxazines were employed as directing groups a mixture of *ortho* alkenylation and alkylation products were observed in equal ratios (Scheme 1.18).[8c]



Scheme 1.19: *ortho* Alkylation of nitriles via π-coordination

Aromatic nitriles also efficiently direct the ruthenium complex in C–H bond activation reaction and furnished *ortho* alkylated nitrile derivatives in quantitative yields. Interestingly in this reaction unlike ketones and imines, nitriles directed ruthenium complex through π-coordination mode (Scheme 1.19).[8d]

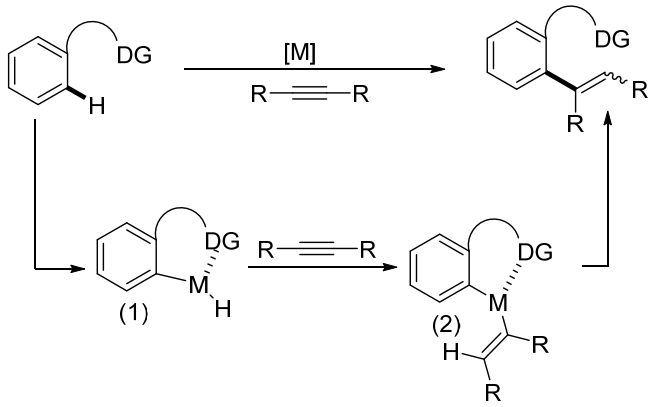


Scheme 1.20: Alkylation of ferrocenes

In 2001, Du and co-workers extended the ruthenium catalyzed alkylation reactions to ferrocenecs. In this reaction ferrocenyl ketones furnished the corresponding alkylated products in the presence of $RuH_2(CO)(PPh_3)_3$ complex (Scheme 1.20).[8e]

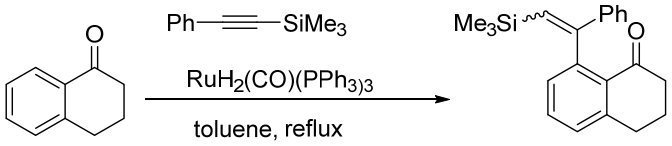
1.6.2: C–H activation of Aromatics with alkynes under oxidative addition pathway

Alkylated aromatics and heteroaromatics can be obtained from aromatics and olefins in the presence of low valent metal catalysts. Similiarly *ortho* alkenylated aromatics and hetero aromatics can be obtained by employing alkynes as coupling partners instead of olefins. A general catalytic cycle depicted in the scheme 1.21. The catalytic cycle starts with the coordination of the directing group with the metal catalyst followed by oxidative addition of the metal with the *ortho* C–H bond leads to the formation of the intermediate (1). The 1,2-insertion of M–H bond with alkyne furnishes intermediate (2), which produces the required alkenylated product by reductive elimination.



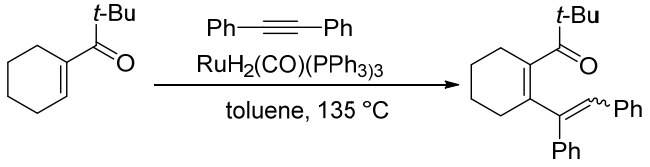
Scheme 1.21: *ortho* Alkenylation with alkynes

In 1999, Woodgate and co-workers reported the addition of alkynes into olefinic C–H bond of the enones. In this reaction 10 mol% of the ruthenium complex used to obtain the corresponding conjugated dienones in quantitative yields (Scheme 1.22).[9a]



Scheme 1.22: *ortho* Alkenylation of ketones

In 2001, Murai and co-workers reported the addition of alkynes into olefinic C–H bond of the enones. In this reaction also 10 mol% of the catalyst used to obtain the corresponding conjugated dienones in quantitative yields (Scheme 1.23).[9b]

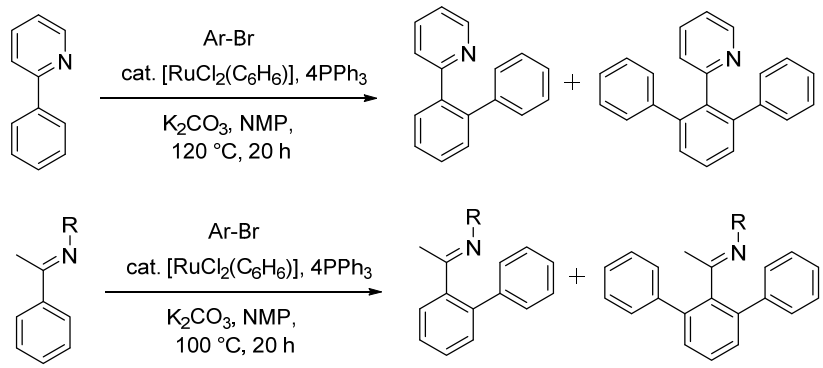


Scheme 1.23: *ortho* Alkenylation of enones

The C–H bond activation reactions proceeds via oxidative addition pathway initiated by Ru (0) and further extended to other low valent metals. These methodologies were well documented in literature.[7] On the other hand methodologies proceeds via deprotonation path way was quite recently got attention.

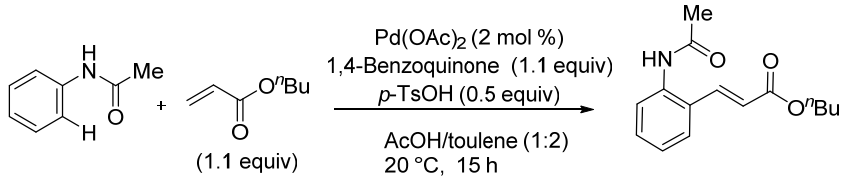
1.6.3: C–H activation of Aromatics with olefins under deprotonation pathway

In 2001, Oi and co-workers discovered the arylation of 2-phenylpyridine with arylbromides catalyzed by Ru (II) catalyst with the combination of triphenyl phosphine and potassium carbonate. The same group successfully extended this transformation into aromatic imines (Scheme 1.33).[12a-b] It is important to note that here stable Ru (II) complex used to catalyze the transformation and the reaction follows deprotonation pathway. This reaction proceeds via deprotonation path way. After Oi's initial findings, several research groups utilized high-valent metal complexes of Pd (II), Rh (III) and Ru (II) to functionalize C–H bonds of aromatic compounds.[7-8, 20-21]



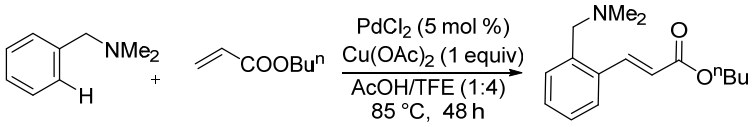
Scheme 1.33: C–H functionalization of aromatics by Ru(II)

In 2002, de Vries and van Leeuwen reported oxidative dehydrogenative alkenylayion of anilides with olefins via C–H bond activation strategy. Interestingly this reaction proceeds smoothly in room temperature (Scheme 1.24).[10a]



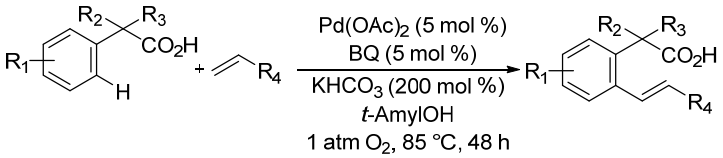
Scheme 1.24: *ortho* Alkenylation of anilides

Later, in 2007, Shi and co-workers reported a *ortho* olefination of *N*,*N*-dimethylbenzylamines catalyzed by $PdCl_2$. In this reaction AcOH used to acidify the reaction medium (Scheme 1.25).[10b]

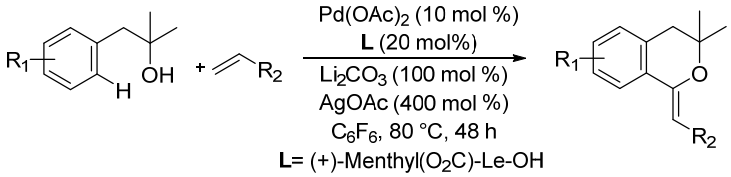


Scheme 1.25: *ortho* Olefination of *N*,*N*-Dimethylbenzylamines

In 2010, Yu and co-workers reported C–H olefination of phenyl acetic acid derivatives. In this reaction a higher degree of α-substitution resulted in the higher degree of product formation due to Thorpe-Ingold effect (Scheme 1.26).[10c] The same group successfully developed C–H olefination of aromatics using tertiary alcohol as directing group (Scheme 1.27).[10d]

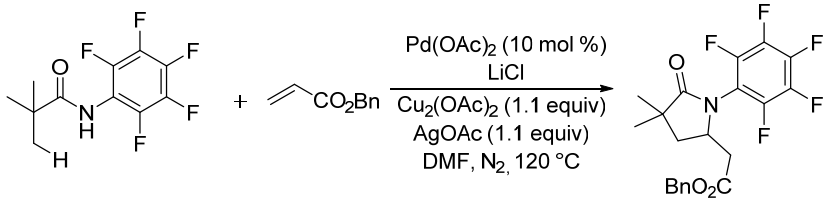


Scheme 1.26: *ortho* Olefination of phenyl acetic acid derivatives



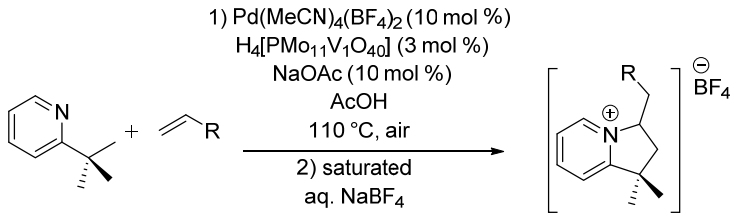
Scheme 1.27: Hydroxyl directed *ortho*-Olefination

In 2010, Yu's group reported a sp^3 C–H olefination of *N*-arylpivalamides in the presence of $Pd(OAc)_2$ (Scheme 1.28).[10e]



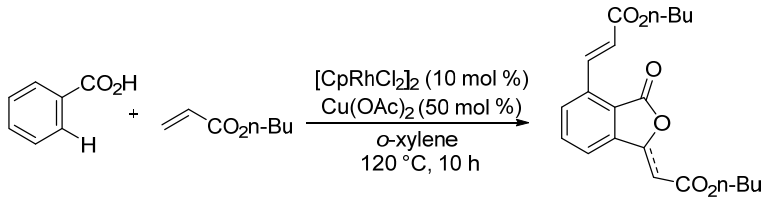
Scheme 1.28: olefination of *N*-arylpivalamides

In 2011, Sanford and co-workers reported an aerobic olefination of sp^3 C–H bonds in the presence of Pd(II) complex (Scheme 1.29).[10f]



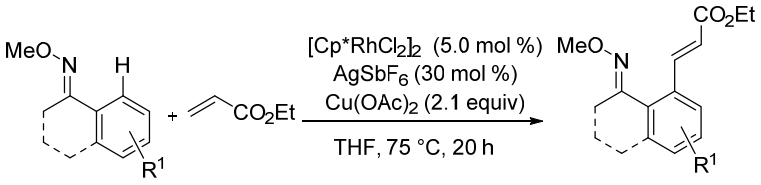
Scheme 1.29: Olefination of *N*-arylpivalamides

After all this bench mark findings, several methods were developed to functionalize sp^2 C–H as well as sp^3 C–H bonds by employing palladium complexes as catalysts. Simultaneously rhodium catalysis also developed to activate C–H bonds of aromatics and hetero aromatics. In 2007, Miura's group employed Rh(III) complex for the aerobic oxidation of the ortho C–H bonds of benzoic acid derivatives (Scheme 1.30).[11a]



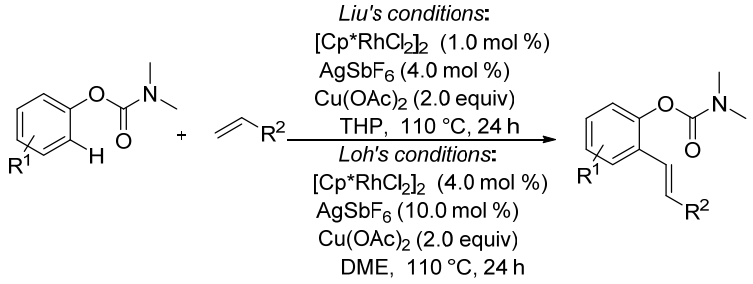
Scheme 1.30: *ortho* Olefination of benzoic acid derivatives

In 2011, Bergman and Ellman reported olefination of oxime derivatives by using Rh(III) complex (Scheme 1.31).[11b]



Scheme 1.31: C–H Olefination of oxime

In 2011, Liu's and Loh's groups independently disclosed rhodium-catalyzed selective C-H alkenylationof phenol carbamates with alkenes (Scheme 1.32).[11c-d]



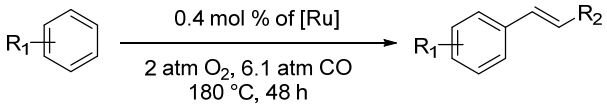
Scheme 1.32: C–H Olefination of carbamates

After these seminal findings, several catalytic systems of palladium and rhodium efficiently used for the C−H functionalization reactions.[7] Later, ruthenium arene complexes were drawn attention of synthetic organic chemistry community due to their stability under air and less expensive compare to rhodium and palladium. In addition, the reactions can be performed under air atmosphere and water can be employed as solvent.

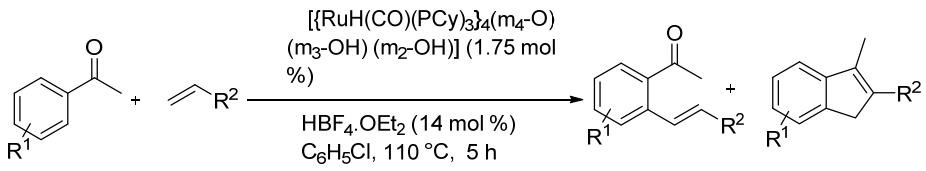
1.7. Ruthenium catalyzed C–H bond activation reactions via deprotonation pathway

1.7.1: Ruthenium catalyzed C–H olefination of aromatics under deprotonation pathway

In 2001, Milstein's group reported a cross dehydrogenative coupling of arenes with olefins in presence of ruthenium complexes like $RuCl_3.H_2O$, $[Ru(CO)_3Cl_2]_2$, $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$, $Ru(NO)Cl_3.5H_2O$ and $[Ru\ (F_3CCOCHCOCF_3)]_3$. This reaction was conducted under CO atmosphere and O_2 was used as sole oxidant (Scheme 1.34).[13a]

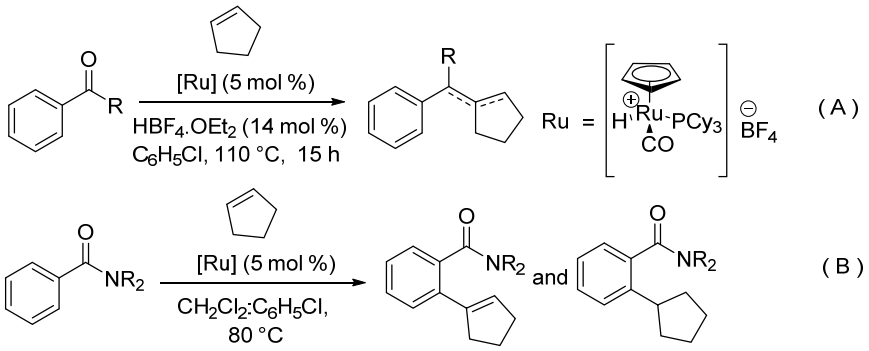


Scheme 1.34: Cross dehydrogenative coupling of arenes with olefins



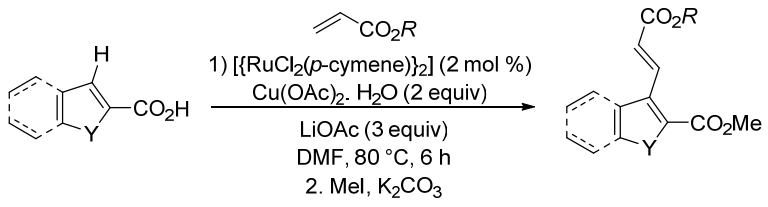
Scheme 1.35: Cross dehydrogenative coupling of arenes with olefins

In the year of 2009, Yi and Lee reported the formation of indene derivatives from aromatic ketones with alkenes in the presence of *in situ* generated ruthenium cationic complex (Scheme 1.35).[13b] The same group extended this methodology for the intermolecular olefination of arylketones with cycloalkenes by employing a ruthenium cataonic complex as a catalyst (Scheme 1.36A).[13c]



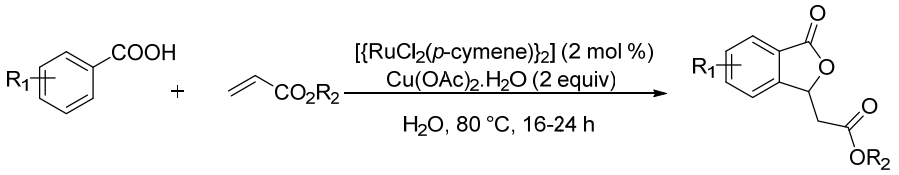
Scheme 1.36: Cross dehydrogenative coupling of arenes with olefins catalyzed by cationic ruthenium complex

Here the formation of electrophilic ruthenium-vinyl complex is the key step which leads to the formation of the desired olefinated products. When aryl amides were employed instead of aryl ketones a mixture of *ortho* alkenylated and alkylated amides derivatives obtained (Scheme 1.36B).[13d] These intersting findings reveal that ketone and amide functional groups are capable of assisting the formation of ruthenium(II)−hydride complex. This process helps to achieve *ortho*-C−H olefination *via* dehydrogenative cross-coupling reaction. By following this principle Miura's group disclosed the C−H bond alkenylation of heterocyles containing carboxylic acids as directing groups in 2011 (Scheme 1.37).[14a]



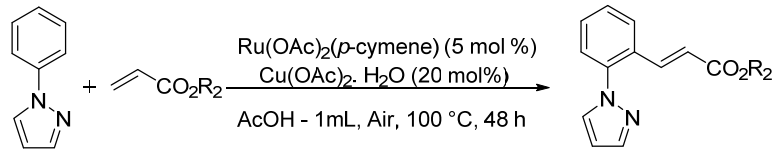
Scheme 1.37: Cross dehydrogenative coupling of arenes with olefins

In 2011, Ackermann and Pospech reported a ruthenium catalyzed oxidative C−H alkenylation of benzoicacid derivatives. In this reaction water was employed as a solvent and this methodology leads to the formation of annulated lactones via oxa-micheal addition (Scheme 1.38).[14b]



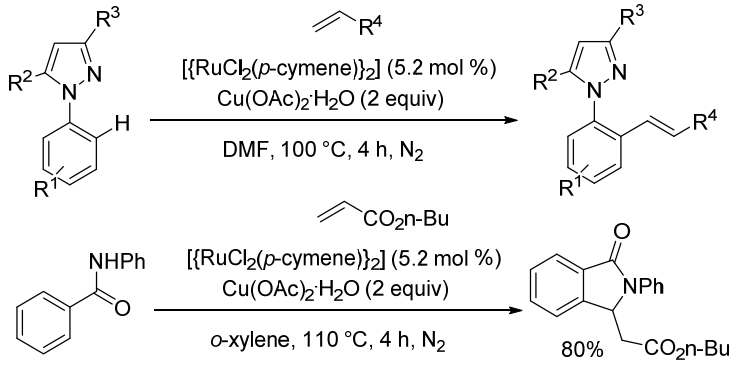
Scheme 1.38: Cross dehydrogenative coupling of arenes with olefins in water

Later, in 2011, Dixneuf's group reported an oxidative dehydrognative alkenylation of nitrogen containing heterocycle *N*-arylpyrazole. In this reaction also water was employed as solvent (Scheme 1.39).[14c]



Scheme 1.39: Dehydrognative alkenylation of *N*-arylpyrazole

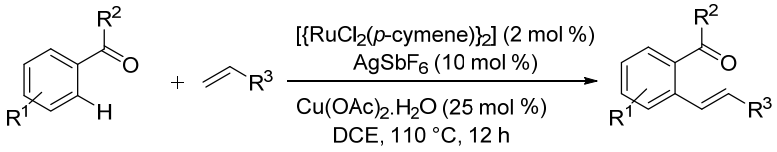
A similar transformation was attained by Miura's group in 2011. *N*-phenyl benzamide furnished isoindoline derivative by following alkenylation and aza-Micheal addition sequence under slightly modified reaction conditions (Scheme 1.40).[14d]



Scheme 1.40: Cross dehydrogenative coupling of *N*-arylpyrazoles and *N*-phenyl benzamide with olefins

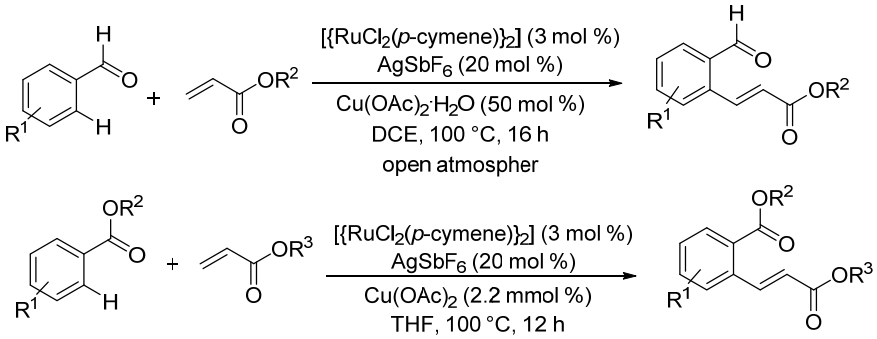
Our group's research focuses on C−H functionalization of aromatics and hetero aromatics containing weak directing groups. Majorly weak directing groups chelate with transition metal by oxygen atom present in it. Consequently, it is important to increase the binding ability of transition metal for the efficient coordination and C−H functionalization. In 2011, our group successfully developed catalytic conditions for the *ortho* olefination of weak coordinating aromatic ketone derivatives.[15a] This transformation attained by adding an

external additive $AgSbF_6$ which will produce a non-coordinating counter anion hexafluoro antimanate to stabilize the Ru (II) cationic complex (Scheme 1.41).[15]



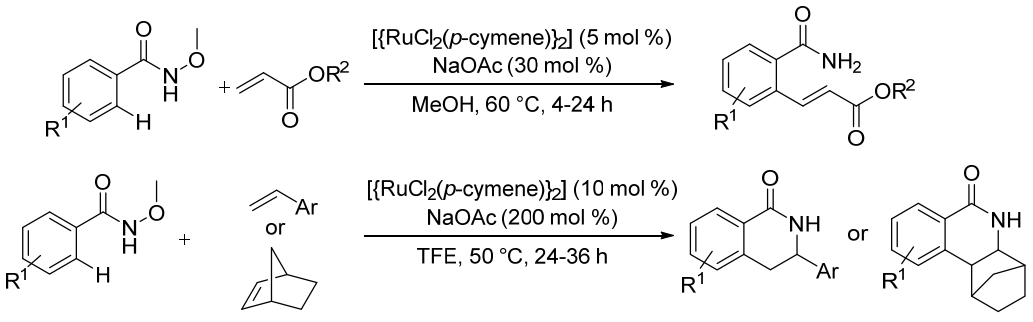
Scheme 1.41: Dehydrogenative coupling of ketones

This catalytic system can be extented to aldehyde and ester directing groups containing aromatics and furnished *ortho* olefinated products.[15b-c] It is important to note that aldehydes employed as directing groups for the first time in C−H functionalization reactions (Scheme 1.42).[15b]



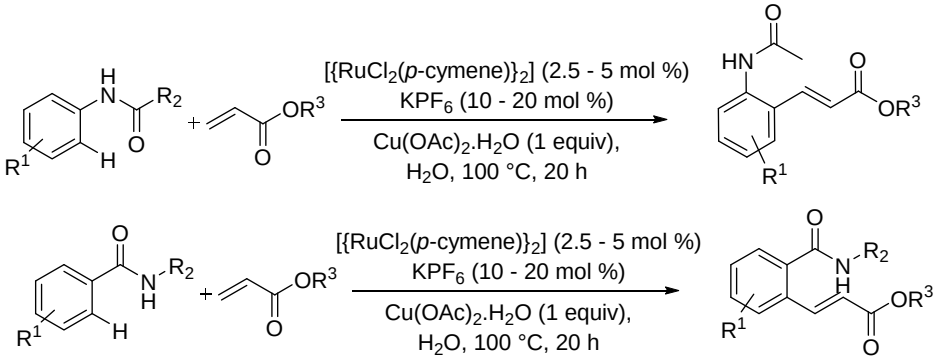
Scheme 1.42: Dehydrogenative coupling of aromatic aldehydes and esters

In 2012, Wang's group employed *N*-Methoxy benzamides as directing groups to achieve *ortho* olefination of benzamide derivatives. Styrene and norborene provides dihydro isoquinolinone derivatives under slightly modified conditions from the reaction conditions for alkyl acrylates (Scheme 1.43).[15d]



Scheme 1.43: *ortho* alkenylation of of *N*-Methoxy benzamides

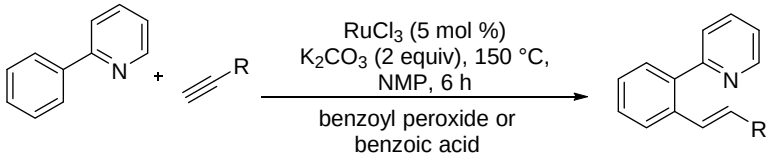
In 2012, Ackermann's group disclosed an oxidative *ortho* alkenylation of *N*-substituted benzamides and anilides with alkenes in the presence of ruthenium catalyst. Interestingly in this reaction water was used as solvent (Scheme 1.44).[15e]



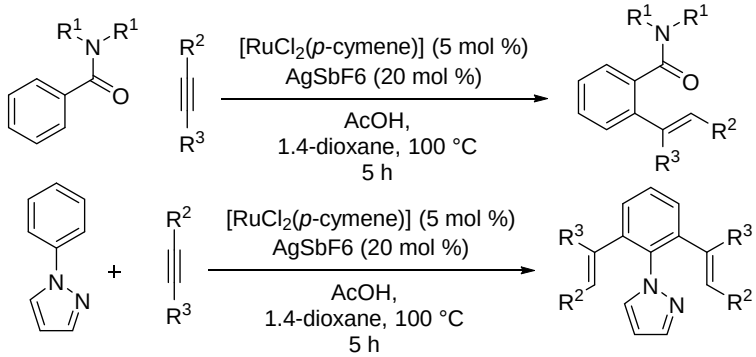
Scheme 1.44 *ortho* alkenylation of of *N*-substituted benzamides and anilides in water

1.7.2: Insertion of alkynes into C−H bonds via deprotonation pathway

In 2008, Zhang's group disclosed alkenylation of aromatic C−H bonds with alkynes in the presence of $RuCl_3$ catalyst. It is important to note that this reaction does not requires any external oxidant and benzoyl peroxide used to deprotonate C−H bond by generating carboxylate anion in the reaction mixture (Scheme 1.45).[16a]



Scheme 1.45: *ortho* alkenylation of 2-phenyl pyridines with alkynes

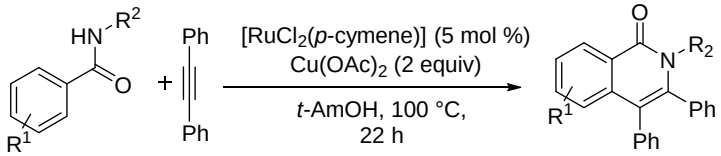


Scheme 1.46: *ortho* Alkenylation of *N*, *N* – disubstituted benzamides and 1-phenyl pyrazole

In 2012, Miura's group reported a ruthenium-catalyzed region- and stereoselective hyroarylation of alkynes via C−H bond functionalization as a key step. In this report *N*, *N*-dialkyl amides and pyrazoles employed as directing groups (Scheme 1.46).[16b] After these seminal findings, several directing groups were explored to achieve region- and stereoselective hyroarylation of alkynes via C−H bond activation reactions.[16c]

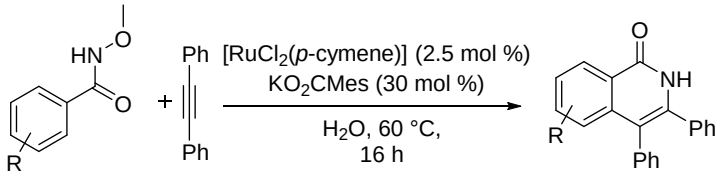
1.7.3: Insertion of alkynes between C−H and Heteroatom-H bonds via deprotonation pathway

In 2011, Ackermann's group disclosed synthesis of isoquinolone derivatives from *N*-alkyl benzamides with alkynes in the presence of $[RuCl_2(p\text{-cymene})]_2$ in *t*-amyl alcohol (Scheme 1.47).[17a]



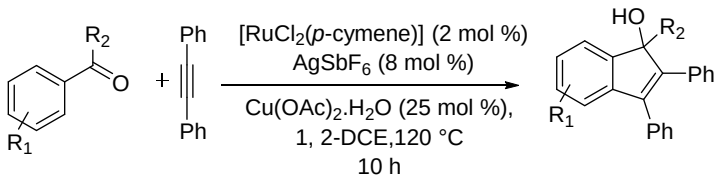
Scheme 1.47: Ruthenium-catalyzed oxidative annulation of benzamides

The same group disclosed synthesis of isoquinolone synthesis by using benzamides having internal oxidant group (-OMe) with alkyne in H_2O (Scheme 1.48).[17b]



Scheme 1.48: Ruthenium-catalyzed annulation of benzamides in water

In 2012, our group successfully synthesized Indenols and benzofulvenes from aromatic ketones with alkynes (Scheme 1.49).[17c]



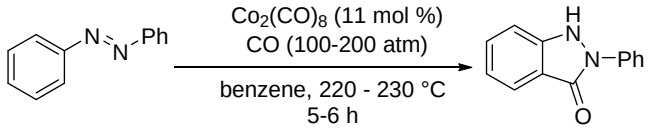
Scheme 1.49: Ruthenium-catalyzed annulation of benzamides in water

1.8: First row transition metal catalyzed C–H bond activation reactions

Most of the aforementioned methodologies rely upon the second and third row transition metals like Ru, Rh, Pd and Ir. However, these noble metals are less abundant in nature and very expensive. Hence, these metal salts and its complexes are not desired for their applications in large scales industries. Consequently it is very important to develop methodologies using first row transition metals like Fe, Co, Ni and Cu which are highly earth abundant and environmentally friendly when compared with their second and third row counterparts. Thus, the development of new C-H bond transformation reaction by using more abundant and sustainable first row transition metal catalysts is highly important. In particular, numerous experiments have been commenced on cobalt catalyzed C–H bond activation reactions. However the electronic properties of the 3d transition metal cobalt substantially varies from 4d and 5d counterparts. Consequently cobalt-carbon bonds are more polarized than rhodium-carbon and iridium-carbon bonds. This difference in property which allows the cobalt catalyzed reactions to proceed in unprecedented pathways with significant chemo and regio selectivities.[19-21]

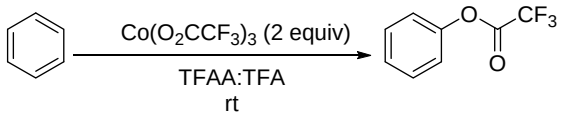
1.9: History of Cobalt catalyzed C–H bond activation reactions

In 1955, Murahashi reported the synthesize of pthalimidines from Schiff bases and carbon monoxide in the presence of $Co_2(CO)_8$(Scheme 1.50). [18a] This was considered as the earliest example of low valent cobalt catalyzed C–H bond activation reaction. After this significant finding cobalt catalyzed reactions become powerful tool to make C–C bonds.



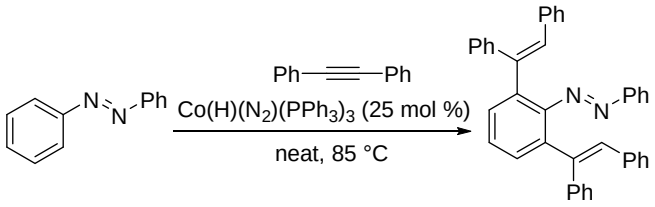
Scheme 1.50: Preparation of pthalimidines from Schiff bases

Almost two decades later in 1972, Kochi's group successfully oxidized benzene into phenyl trifluoro acetate in the presence of $Co(O_2CCF_3)$ complex. This reaction proceeds via a one electron transfer process and this reaction needs two equivalent of cobalt complex (Scheme 1.51).[18b-c]



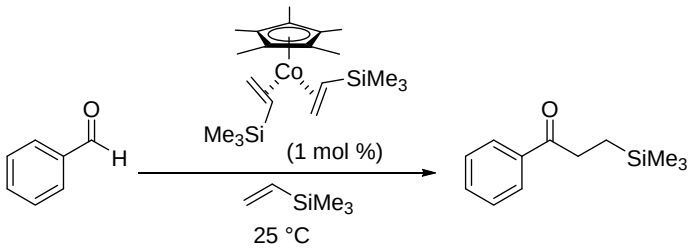
Scheme 1.51: Oxidation of benzene by Co(III) complex

In 1994, Kish's group disclosed *ortho* alkenylation of aromatic azo compounds using low valent Co (I) system. The formation of products in this system is depends on the substitution on the ring (Scheme 1.52).[18d]



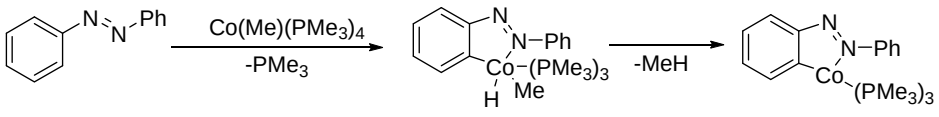
Scheme 1.52: *ortho* alkenylation of aromatic azo compounds

In continuation with Kish's report, Brookhart in 1998 reported an addition of aldehydes with vinyl silanes in presence of low valent half sandwich cobalt complex (Scheme 1.53).[18e-f]



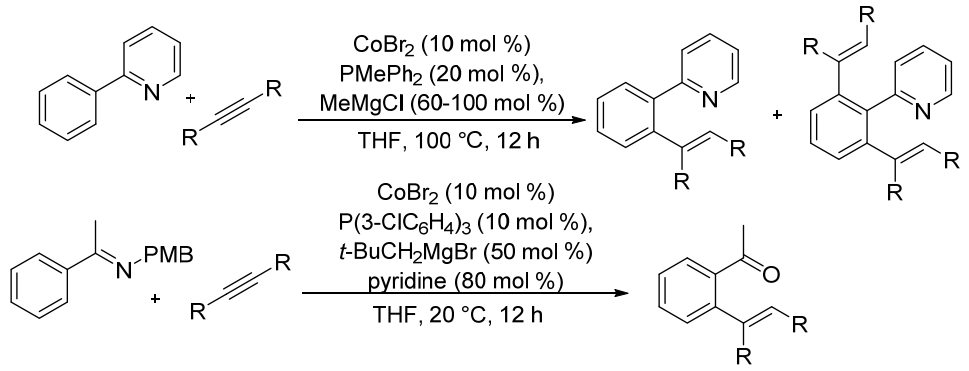
Scheme 1.53: Addition of aldehydes with vinyl silanes

A break through finding was disclosed in 1993 by Klein, where a cobalt complex was isolated and characterized. When $Co(Me)(PMe_3)_4$ reacts with azobenzene and liberates methane gas along with the formation of low valent cobalt complex.[18g] This observation clearly indicates that the reaction proceeds via a cobalt-hydride intermediate which might formed by oxidative addition of cobalt complex with *ortho* C–H bond of the azobenzene (Scheme 1.54).



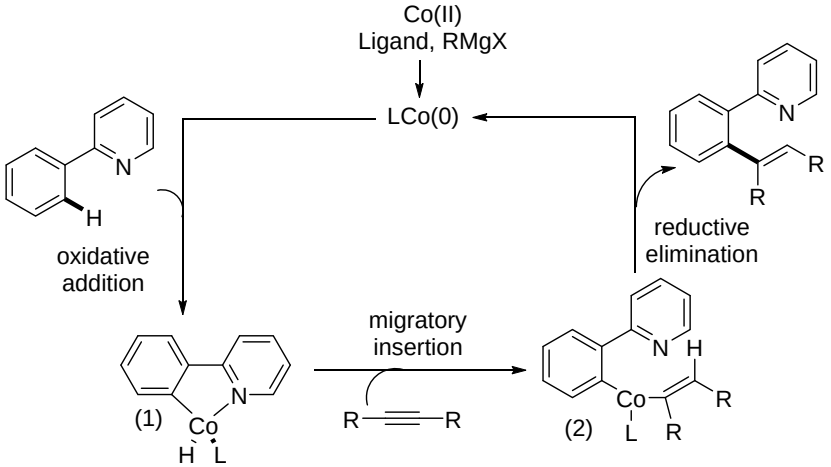
Scheme 1.54: Isolation of aryl-Co(I) complex

1.10: Low valent Cobalt catalyzed C–H bond activation reactions



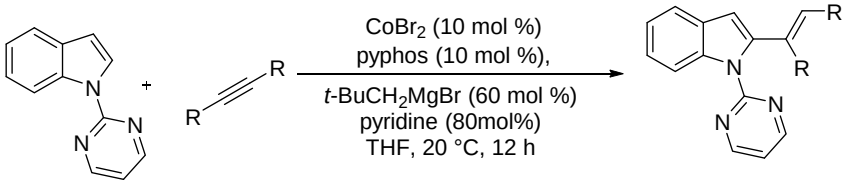
Scheme 1.55: *ortho* alkenylation of 2-phenyl pyridines with alkynes

In 2010, Yoshikai's group reported *ortho* alkenylation of 2-phenylpyridines from 2-phenyl pyridine and alkyne. This catalytic system employs the combination of $CoBr_2$, phosphine ligand and Grignard reagent which produces a low valent Co species in the reaction medium (Scheme 1.55).[19a] This reaction proceeds via oxidative addition pathway where oxidative addition of *ortho* C–H to the cobalt center leads to the formation of the cylometalated species (1). Insertion of the alkyne into Co–H bond (2) followed by reductive elimination leads to the formation of desired alkenylated product and regenerates active catalyst for the next cycle (Scheme 1.56).[19a]



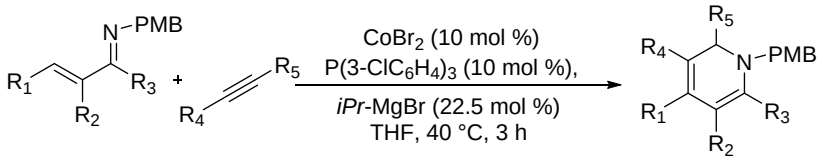
Scheme 1.56: *ortho*-alkenylation with alkynes

The same group extended this methodology to make C-2 alkenylated indoles by using *N*-pyrimidylindoles and alkynes. Among the various ligands examined, pyphos found to be more efficient and furnished desired alkenylated products (Scheme 1.57).[19b]



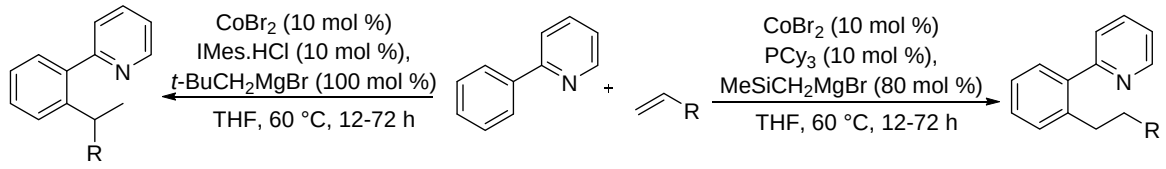
Scheme 1.57: C-2 alkenylation of indoles with alkynes

After finding the optimal catalytic system the same group extended this methodology with various directing groups.[18-19] When α, β-unsaturated imines reacted with internal alkynes under similar conditions, dihydropyridine derivatives were observed. This reaction proceeds through the sequence of C–H activation via oxidative addition followed by 6π-electrocylization (Scheme 1.58).[19c]



Scheme 1.58: C-2 alkenylation of indoles with alkynes

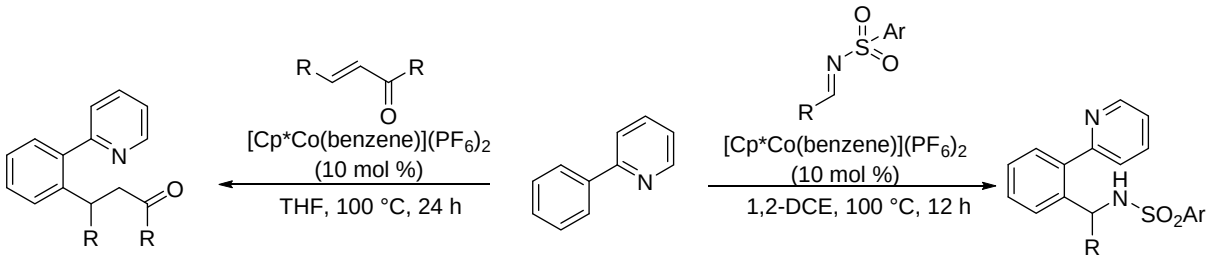
These methodologies are not restricted only to alkynes but also extended with alkenes. In 2011, Yoshikai disclosed alkylation of 2-phenyl pyridine derivatives. Interestingly, depending on the ligand used different regioisomeric products were observed (Scheme 1.59).[19d]



Scheme 1.59: *ortho* alkylation of 2-phenyl pyridines with alkenes

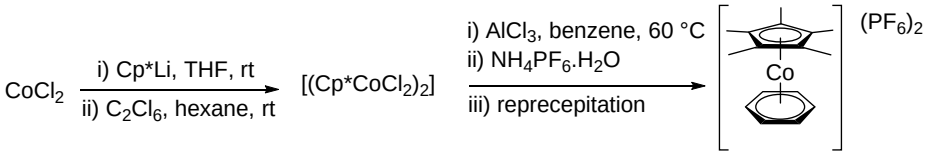
Even though these methodologies are very effective in C–C bond forming reactions, the requirement of Grignard reagents and inert conditions are reducing their functional group tolerance and applicability in large scale industries. It is very important to develop milder reaction conditions with high functional group tolerance. Very recently, a high-valent cobalt catalyzed C–H bond activation drawn considerable attention in organic synthesis.

1.11: High-valent half-sandwich cobalt catalyzed C–H bond activation reactions

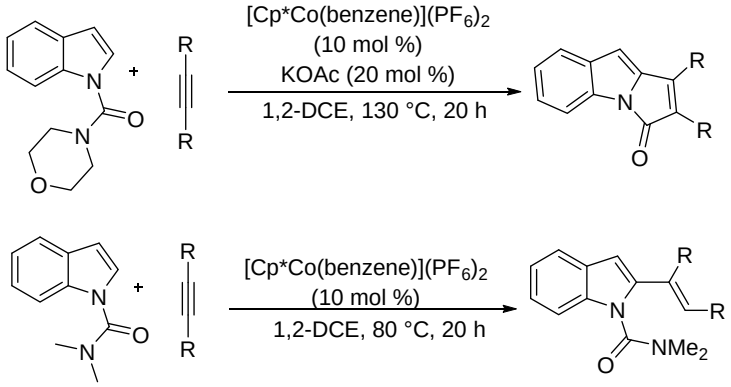


Scheme 1.60: *ortho* alkylation and amidation of 2-phenyl pyridines

In 2013, Kanai and Matsunaga reported arylation of imines and α, β- unsaturated carbonyl compounds with 2-phenyl pyridine derivatives. This reaction was catalyzed by a Cp*Co(III) complex (Scheme 1.60).[20a] This reaction proceeds via deprotonation pathway and does not require any reagent for the oxidative generation of active catalyst to cleave C–H bond. This report was the major breakthrough in the progress of cobalt catalyzed C–H bond functionalization reactions and opened new paths for the high-valent cobalt catalysis in C–H bond functionalization reactions. The active catalyst can prepared from $CoCl_2$ with Cp* ligand as depicted in scheme (Scheme 1.61).[20a]



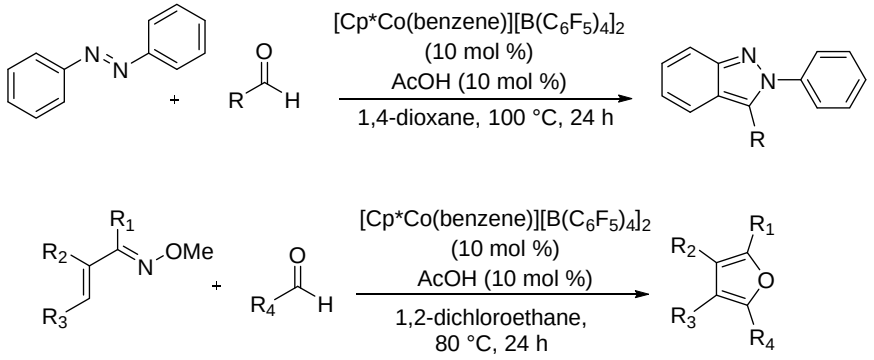
Scheme 1.61: Preperation of active catalyst



Scheme 1.62: C-2 functionalization of indoles

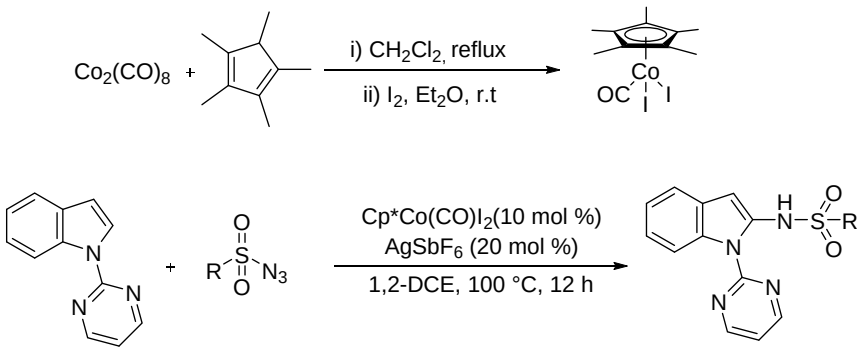
The same group reported the C-2 functionalization of indoles by using same catalyst with alkynes. It is very important to note that in this reaction weakly directing carbamoyl group acts as a directing group (Scheme 1.62).[20b]

In 2015, Ellman's disclosed the synthesis of indazoles and furans from azobenzenes and enamides respectively. In this cobalt catalyzed redox neutral reactions, [Cp*Co(benzene)] complex with $B(C_6F_5)_4^-$ anion furnishes desired products in good yields (Scheme 1.63).[20c]



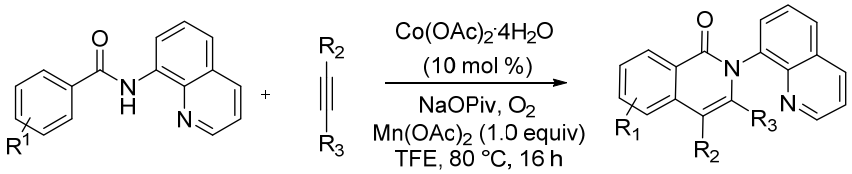
Scheme 1.63: synthesis of indazoles and furans

In 2014, Kani and Matsunaga came up with another breakthrough contribution by disclosing amidation of indoles with sulfonyl azides.[20d] It is very important to note that their previous catalyst $[Cp^*Co(benzene)](PF_6)_2$ was not efficient enough for this transformation but a combination of bench stable $[Cp^*Co(CO)I_2]$ catalyst and $AgSbF_6$ furnishes desired products in good to excellent yields (Scheme 1.64). This complex can be readily prepared from $Co_2(CO)_8$.[20d] After this seminal finding, the half sandwich high-valent cobalt catalyzed C–H bond functionalization with various directing groups and coupling partners were disclosed in literature by various research groups.[20]



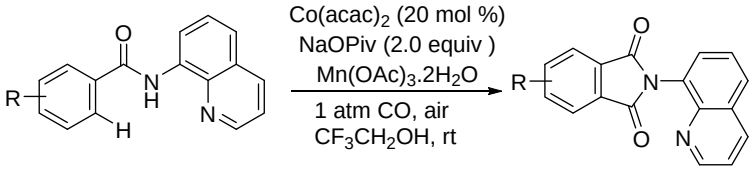
Scheme 1.64: Preparation of $CpCo(CO)I_2$ and amidation of indoles

1.12: High-valent cobalt catalyzed C–H bond activation reactions by using bidendate directing groups



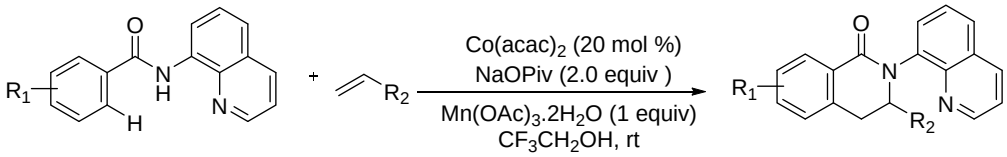
Scheme 1.65: Oxidative cyclization of amides with alkynes

After the contribution of Kanai and Matsunaga, the Cp*Co(III) catalyzed C–H bond functionalization started growing enormously. Meanwhile, in 2014, Daugulis disclosed a high-valent cobalt catalyzed C–H functionalization using bidendate 8-aminoquinoline and 2-picolinamide directing groups (Scheme 1.65).[21a] In this method, active catalyst can be generated by using oxidants like Ag(I), Mn(III) and air. This reaction proceeds through deprotonation pathway. The same group reported direct carbonylation of aminoquinoline benzamides using high-valent cobalt catalyzed C–H functionalization strategy (Scheme 1.66).[21b]



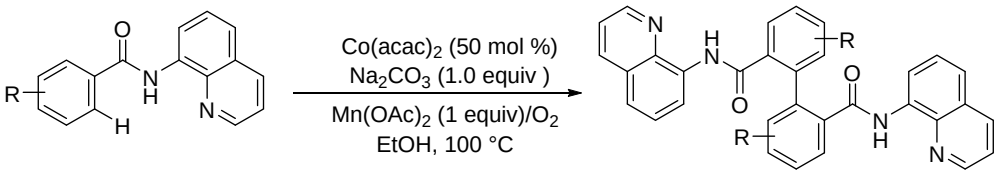
Scheme 1.66: Carbonylation of aminoquinoline amides with CO

In 2015, Daugulis's group disclosed the synthesis of dihydro isoquinolonecs from aminoquinoline benzamides with olefins in the presence of Co (II) catalyst (Scheme 1.67).[21c]



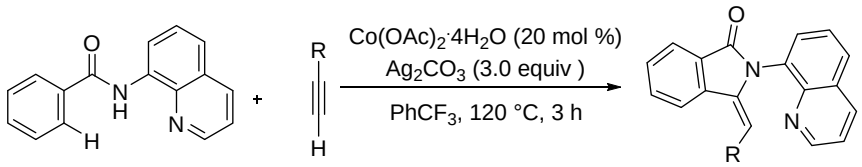
Scheme 1.67: Oxidative cyclization of amides with alkenes

Daugulis's group also observed dimerization of quinoline amides in the presence of cobalt catalyst (Scheme 1.68).[21d]



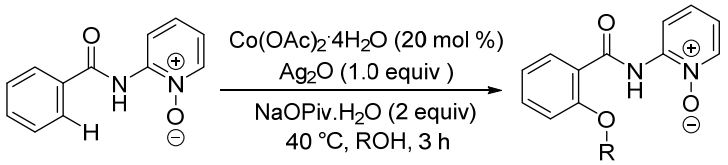
Scheme 1.68: Dimerization of quinoline amides

After the contributions from Daugulis, a number of reports came from various research groups to make C–C and C–heteroatom bonds by using this methodology.[21] Among them, in 2015, Zhang and co-workers disclosed cyclization of aromatic amides with terminal alkynes. In this report unlike Daugulis's report, a five membered cylization observed (Scheme 1.69).[21e]



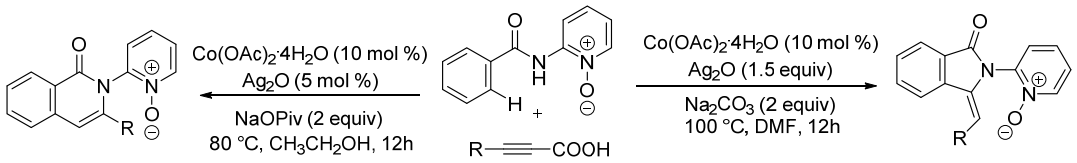
Scheme 1.69: Oxidative cyclization of amides with terminal alkynes

This methodology was not restricted only to aminoquinoline directing group and it can be extended to other bi dendate directing groups. For example, in 2015, Song's group reported alkoxylation of olefinic carbamides having pyridine *N*-oxide as directing group (Scheme 1.70).[21f]



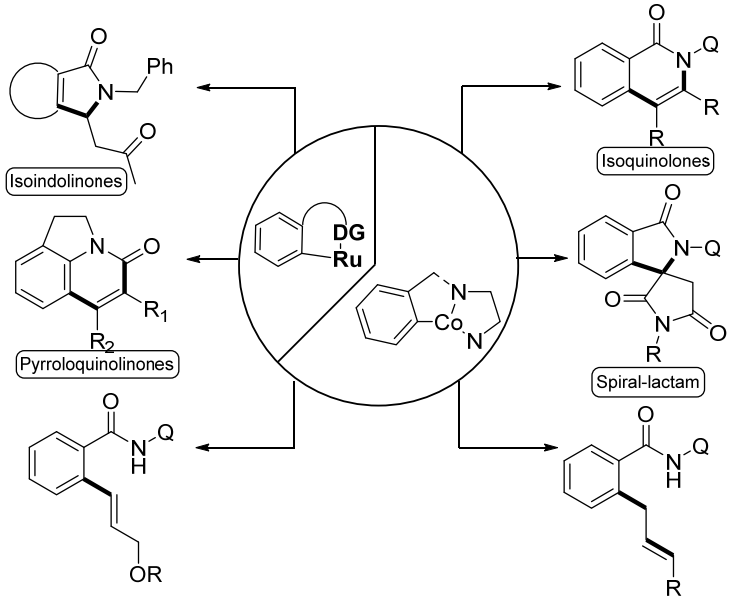
Scheme 1.70: Alkoxylation of amides

In 2016, the same group successfully developed two different catalytic conditions to obtain isoquinolone and isoindolinones derivatives from carbamides having pyridine *N*-oxide as directing group. By varying the proportion of the oxidant, the formation of silver acetylinide species can be controlled which reflects in the in the reductive elimination step and ended up in two different product formation (Scheme 1.71).[21g]



Scheme 1.71: Synthesis of isoquinolone and isoindolinones

1.13: Chelation Assisted Ruthenium and Cobalt Catalyzed Carbon-Carbon Bond Formation Reactions of Aromatics and Heteroaromatics



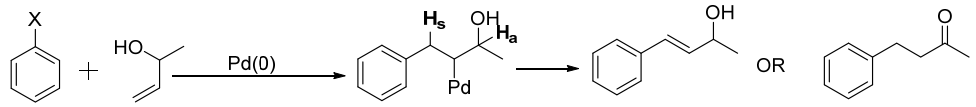
Scheme 1.72: Thesis overview

Despite significant developments in the metal-mediated C-H activation reactions to achieve diverse organic structural fragments, the scope of these catalysts could be explored further to accomplish several synthetically challenging chemical intermediates. In this thesis, we aim to develop methods for the synthesizing heterocylic moieties using Ru(II) and Co(III) catalysts with a combination of suitable directing groups and C–C π-components. In addition, to reduce the amount of metallic waste generated, we also aimed to develop metal oxidant free C–H activation reactions (Scheme 1.72). Here, we explore Ru-catalyzed oxidative cyclization reaction to synthesize structurally diverse isoindolines (Methodology 1a) and pyrroloquinolinones (Methodology: 1b). Further, we utilize chelation assistance in cobalt-catalysis to achieve C-H functionalization of arylamides with unactivated alkenes and ally lactates (Methodology: 3). Finally, we use chelation-assisted cobalt-catalyzed oxidative cyclization of arylamides with maleimides and alkynes to synthesize structurally diverse spirosuccinimides (Methodology: 3a) and isoquinolinoes respectively (Methodology: 3b).

1.13.1: Methodology 1: Synthesis of Isoindolinone and Pyrroloquinolone Derivatives *via* a Ruthenium Catalyzed *ortho* C–H Bond Funtionalization

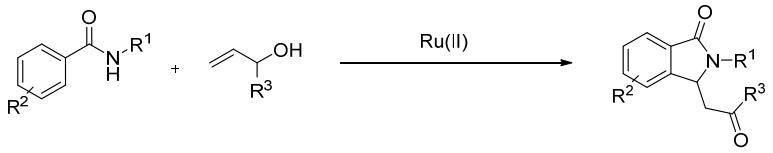
Methodology 1A: Synthesis of Isoindolinones from *N*-Substituted Benzamides and Allylic Alcohols

Isoindolinone is a core structure unit present in various natural products and biologically active molecules. Particularly, 3-substituted isoindolinone skeleton is found in various biologically active molecules. It has also been serving as a key synthetic intermediate for synthesizing various highly useful organic molecules and natural products. By using the traditional methods and metal-catalyzed reactions, 3-substituted isoindolinone derivatives are efficiently prepared in the literature. In these reactions, mostly activated alkenes such as acrylates, ethyl vinyl ketone, acrylamide and conjugated 1, 2-diketones were used.



Scheme 1.73: Reactivity of allyl alcohols

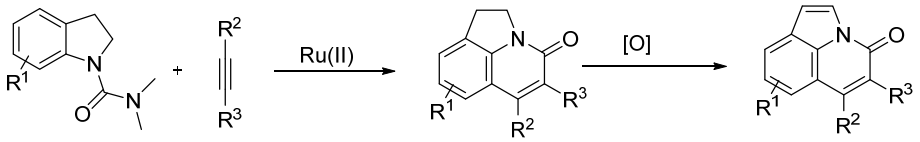
Due to the vast availability, easy accessibility and simple preparation of allylic alcohols, it has been widely used as an alkene partner in the coupling reaction with aromatic electrophiles or organometallic reagents in the presence of metal catalysts. Depending upon the reaction conditions allyl alcohol can furnishes different products. In this chapter we develop a strategy to synthesize isoindolinoe derivatives by using ruthenium catalyzed C–H activation method. We propose possible reaction mechanism for the cyclization reaction and strongly support the mechanistic route with experimental evidences. Remarkably, we show that the reaction pathway such as enoloization vs β-hydride elimination can be tuned, by changing the reaction conditions.



Scheme 1.73: Synthesize isoindolinoes

Methodology 1B: Ruthenium-catalyzed cyclization of *N*-carbamoyl indolines with alkynes: an efficient route to pyrroloquinolinones

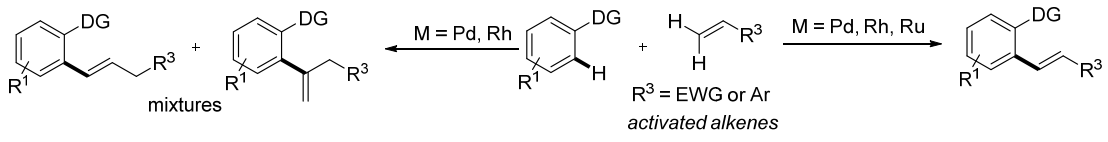
The pyrroloquinoline unit is present in various agrochemicals, drug molecules, natural products and materials. Pyrroloquinoline derivatives show potent biological activities towards asthma, obesity, anti-acetylcholinesterase, melatoninergic and epilepsy. In addition, pyrroloquinoline derivative can also be used as a key intermediate for synthesizing various biologically active molecules and natural products. Traditionally, pyrroloquinoline derivatives are prepared by Fischer indole cyclization, a free radical cyclization, sigmatropic rearrangement, and Michael-type cyclization. In addition, pyrroloquinoline derivatives can also be prepared by using metal catalysts. However, these methods suffer by several drawbacks such as a limited number of substrates scope, a number of steps is needed for synthesizing pyrroloquinolines, poor regioselectivity and requirement of prefunctionalized substrates for the reaction.



Scheme 1.74: Synthesize pyrroloquinolines

In this chapter we have develope a route to synthesize pyrroloquinolinone derivatives via a ruthenium-catalyzed base free oxidative cyclization of *N*-carbamoyl indolines with alkynes. Later, we convert pyrroloquinolinone derivatives into pyrroloindolones in the presence of organic oxidants.

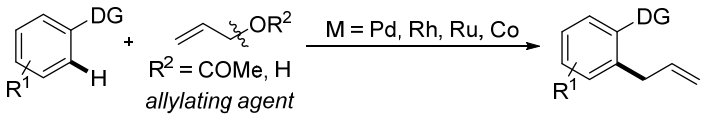
1.13.2: Methodology 2: Cobalt‑Catalyzed C–H Olefination of Aromatics with Unactivated Alkenes



Scheme 1.75: Reactivity of activted and unactivated olefins

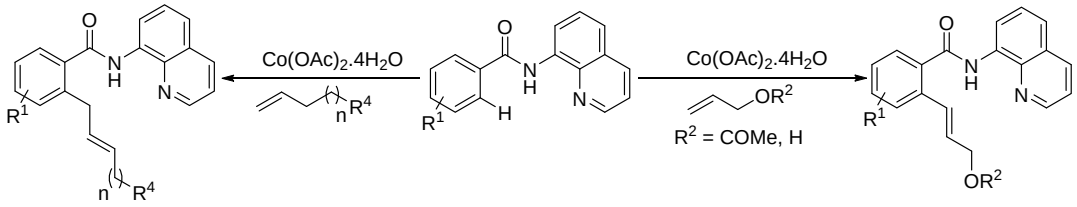
The transition metal-catalyzed chelation-assisted selective olefination at the inactive C–H bond of substituted aromatics with alkenes is an efficient method for synthesizing arylated alkenes in a highly atom- and step-economical manner from easily available starting

materials. However, in this type of alkenylation reaction, only conjugated alkenes such as acrylates, vinyl sulfones, acrylonitriles, acrylamides and styrenes are extensively used. The selective C–H olefination with unactivated alkenes are rare and very challenging to succeed due to the less reactivity of alkenes and formation of mixtures of linear as well as branched isomers. In a metal-catalyzed C–H bond functionalization reaction, allyl acetates or alcohols always serve as an allylating agent, providing allylated product with a removal of OAc or OH.



Scheme 1.76: Reactivity of allyl alcetates and allyl alcohols

Meanwhile, most of this C–H bond transformation relies on second and third row noble metals such as palladium, rhodium, ruthenium and iridium. However, these noble metals are less abundant in nature and expensive. Thus, the development of new C–H bond transformation reaction by using more abundant, biologically tolerated and sustainable first row transition metal catalysts is highly important. In this chapter we have disclosed an unprecedented cobalt-catalyzed C–H olefination of aromatic and heteroaromatic amides with unactivated alkenes, allyl acetates and allyl alcohols. This method offers an efficient route for the synthesis of vinyl and allyl benzamides in a highly stereoselective manner.

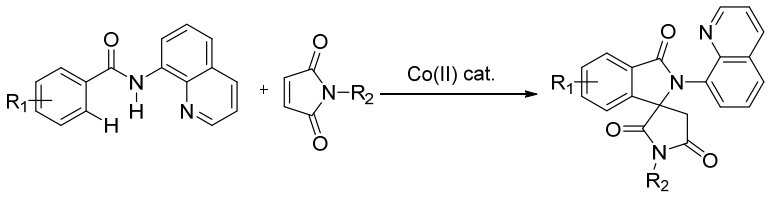


Scheme 1.77: Synthesis of vinyl and allyl benzamides

1.13.3: Methodology 3: Chelation Assisted Cobalt-Catalyzed Oxidative Cyclization of Benzamides with Maleimides and Alkynes

Methodology 3A: Cobalt Catalyzed Oxidative Cyclization of Benzamides with Maleimides: Synthesis of Isoindolone Spirosuccinimides

In general olefins will give ortho olefinated product via facile β-hydride elimination in transition metal catalysed reactions like cross coupling reactions and C–H bond activation reactions. Recently, maleimides are efficiently used as an alkene source in the C-H alkenylation reaction and mostly furnishes, 1,4-addition products due to the absence of β-hydrogen in synperi planner manner . By using ruthenium arene complex as a catalyst, this result was initially disclosed by Prabhu's group and it was extended to other transition metal complexes of rhodium, cobalt and manganese. Meanwhile in 2015, Miura's group disclosed an unusual and very interesting copper-mediated oxidative cyclization of benzamides with maleimides assisted by 8-aminoquinoline. In the reaction, highly useful isoindolone spiro succinimides were prepared. It is interesting to note that the first row copper complex gives cyclized product and second row ruthenium and rhodium complexes provide the Michael-type alkylated product. Our continuous interest in the cobalt-catalyzed oxidative cyclization reaction prompted us to explore the possibility of a catalytic version of cyclization of benzamides with maleimides. In this chapter we report a cobalt-catalyzed 8-aminoquinoline-directed oxidative cyclization of benzamides with maleimides. The oxidative cyclization reaction provides isoindolone spirosuccinimides in good to excellent yields. The reaction was compatible with various functional group substituted benzamides as well as *N*-substituted maleimides.

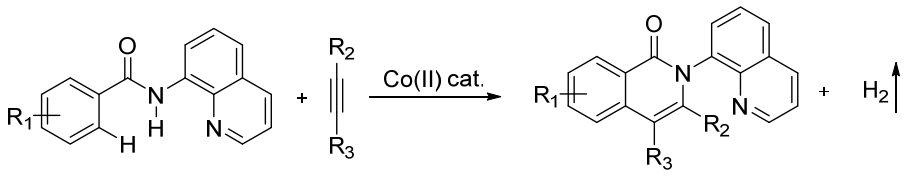


Scheme 1.78: Oxidative cyclization of benzamides with maleimides

Methodology 3B: Chelation assisted cobalt-catalyzed ortho C–H olefination of aromatic benzamides

Isoquinolone is an important heterocyclic structural unit which presents in various natural products, biologically active molecules and conjugated materials. In addition, isoquinolone derivatives are widely used as a key intermediate in various organic transformations. Several methods are available in literature for synthesizing isoquinolone derivatives. Among them, the transition metal catalyzed oxidative cyclization of benzamides with carbon-carbon π-components via C–H bond activation is an efficient method to construct isoquinolones from easily available starting materials. For this type of transformation, the second and third row

transition metal complexes such as Pd, Rh, Ru and Ir are widely employed which are less abundant in the nature. The use of cheaper, more abundant and environmentally benign first row transition metal complexes such as Fe, Co, Cu and Ni as catalysts in the C-H bond activation reaction is highly desirable.In this final chapter we have developed a cobalt-catalyzed 8-aminoquinoline-directed oxidative cyclization of benzamides with alkynes which furnishes substituted isoquinolones with the liberation of hydrogen gas in good to excellent yields. The present cyclization reaction was compatible with various functional group substituted benzamides as well as internal alkynes, terminal alkynes and 1,3-diynes. In the reaction, the active Co(III) species is regenerated by the reaction of Co(I) species with pivalic acid under air.



Scheme 1.79: Oxidative cyclization of benzamides with alkynes

1.14: References

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Chapter 2

Synthesis of Isoindolinone and Pyrroloquinolone Derivatives *via* a Ruthenium Catalyzed *ortho* C–H Bond Funtionalization

Section 2A: Synthesis of Isoindolinones via a Ruthenium-Catalyzed Cyclization of *N*-substituted Benzamides with Allylic Alcohols

2A.1 Introduction

The isoindolinone core unit is present in various natural products, biologically active molecules and pharmaceuticals (Figure 2A.1).[1] It has been serving as a key synthetic intermediate for synthesizing various highly useful organic molecules and natural products.[2] Particularly, the 3-substituted isoindolinone skeleton is found in various biologically active molecules.[3] As a result, various synthetic methods are available in the literature to synthesize 3-substituted isoindolinone derivatives.[4-7]

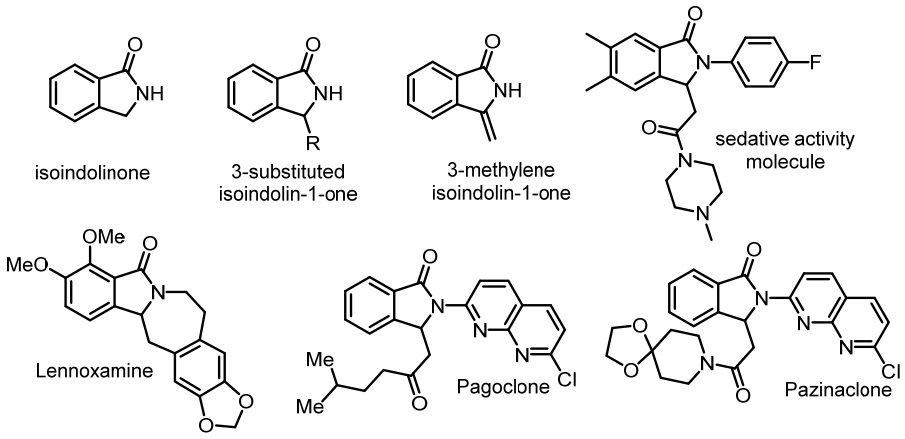
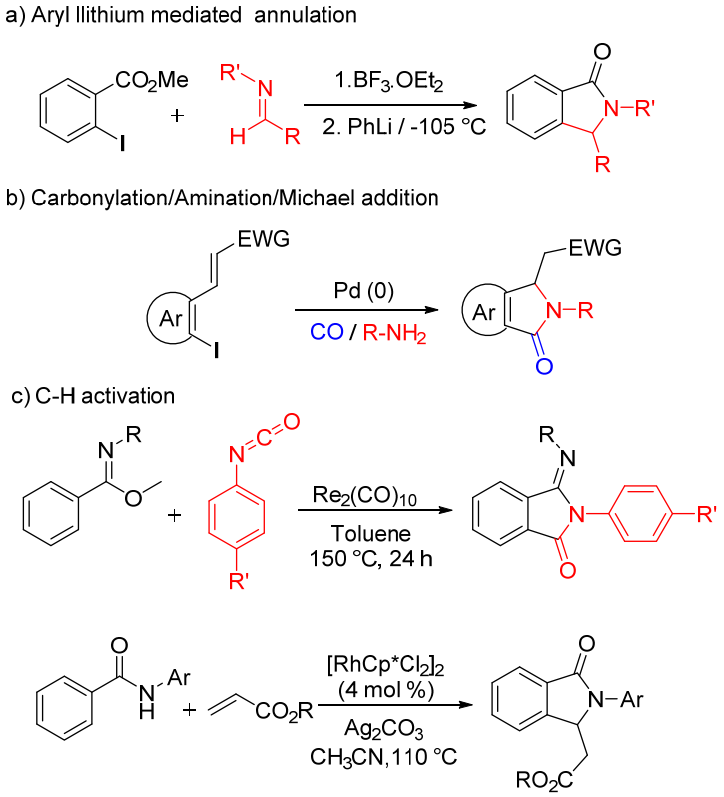


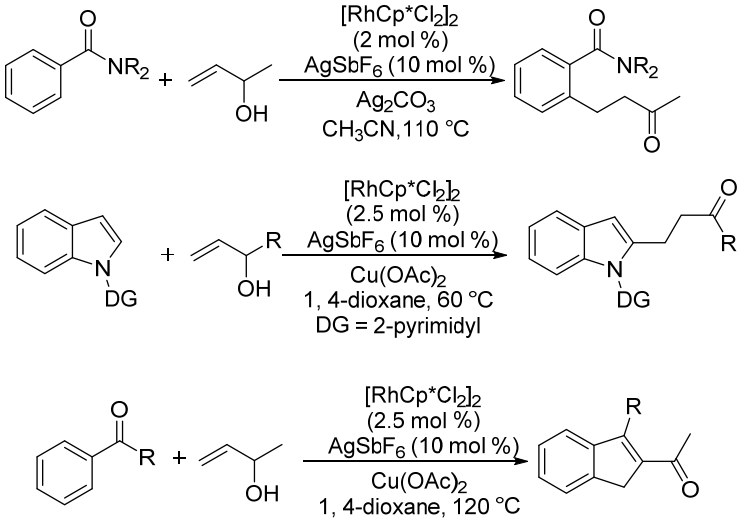
Figure 2A.1: Biologically active molecules with isoindolinone core

Generally, 3-substituted isoindolinones are prepared by nucleophilic addition of metal reagents into isoindoline-1,3-diones,[4a] the cyclization of *ortho*-substituted aryllithiums with imines,[4b-c] or strong base-induced metalation followed by functionalization at the 3-position of isoindolinones.[4d] Additionally, 3-substituted isoindolinones can be prepared by metal-catalyzed cyclization of *ortho*-halo substituted aromatics with imines[5a] and tandem cyclization of *ortho* halo substituted aromatics with CO and amines.[5b] Generally, 3-substituted isoindolinones were efficiently prepared by using metal catalysts via C−H bond activation in a highly atom economical and environmentally friendly manner.[6-8] Aromatic imines underwent cyclization with isocyanates in the presence of a rhenium catalyst, providing 3-substituted isoindolinones.[8a] *N*-Substituted benzamides reacted with alkenes in the presence of metal catalysts, giving isoindolinones in good to excellent yields.[8b-g] In the reaction, mostly activated alkenes such as acrylates, ethyl vinyl ketone, acrylamide and conjugated 1,2-diketones were used (Scheme 2A.1).[8]



Scheme 2A.1: Selected examples of isoindolinone synthesis

Due to the vast availability, easy accessibility and simple preparation of allylic alcohols, these have been widely used as alkene partners in the coupling reaction with aromatic electrophiles or organometallic reagents in the presence of metal catalysts.[9] It is important to note that in most of the catalytic reactions, allylic alcohols are chemically equivalent to α,β-unsaturated enones and aldehydes.



Scheme 2A.2: Reactivity of allyl alcohols in C−H bond activation reactions

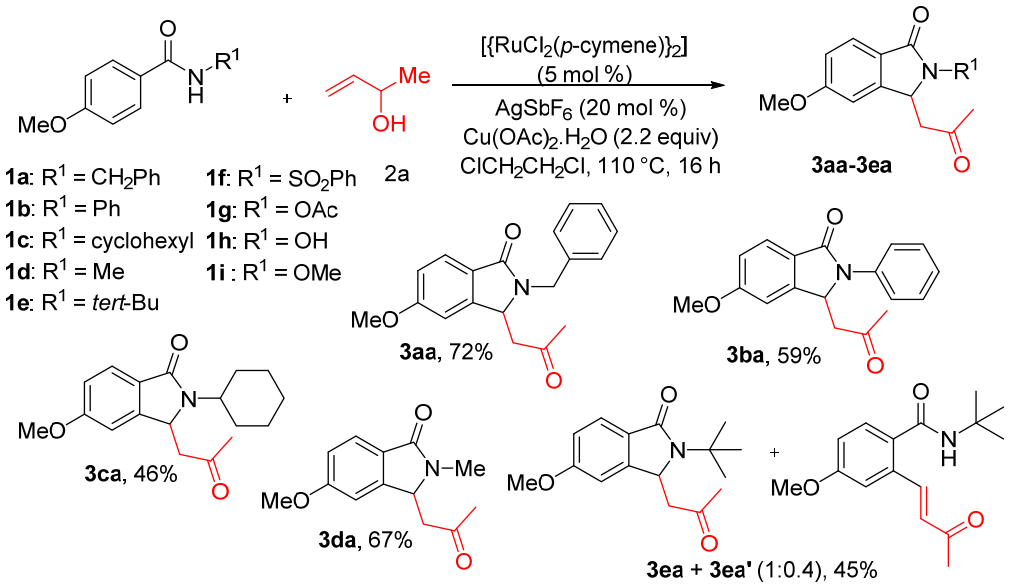
Recently, allylic alcohols are also efficiently used as a coupling partner in the reaction with heteroatom substituted aromatics, and this transformation leads to *ortho* alkylated aromatics in the presence of metal catalysts via C−H bond activation (Scheme 2A.2).[10] Herein, we report a ruthenium-catalyzed cyclization of *N*-substituted benzamides with allylic alcohols to give 3-substituted isoindolinone derivatives in good yields. A possible reaction mechanism involving a five-membered ruthenacycle intermediate was proposed and strongly supported by experimental evidence.

2A.2 Results and Discussion

2A.2.1 Optimization Studies

Treatment of *n*-benzyl 4-methoxy benzamide (**1a**) with 3-buten-2-ol (**2a**) (2.2 equiv) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (2.2 equiv) in 1,2-dichloroethane at 110 °C for 16 h gave 3-substituted isoindolinone derivative **3aa** in 72% isolated yield (Scheme 2A.3). Initially, the cyclization reaction was examined with various solvents such as MeOH, *iso*-PrOH, THF, DMF, 1,2-dimethoxyethane and toluene under similar reaction conditions. Among them, $ClCH_2CH_2Cl$ was very effective, giving **3aa** in 79% GC yield (*n*-docane was used as an internal standard). THF, 1,4-dioxane and 1,2-dimethoxyethane were partially effective, affording product **3aa** in 34%, 45% and 48% GC yields, where as remaining solvents were totally ineffective. The reaction was also tested with additives such as $AgSbF_6$, $AgBF_4$, AgOTf and KPF_6. Among them, $AgSbF_6$ was very effective, giving product **3aa** in 79% GC yield. $AgBF_4$ and AgOTf were partially effective, yielding **3aa** in 47% and 27% GC yields, respectively. KPF_6 was not suitable for the reaction. The cyclization reaction was also tested with various acetate and oxidant sources such as AgOAc, CsOAc, KOAc, NaOAc, Ag_2O and $Cu(OAc)_2{\cdot}H_2O$. Among them, $Cu(OAc)_2{\cdot}H_2O$ was very effective, providing **3aa** in 79% GC yield. Remaining acetate sources were not effective. The reaction was also tested with less than 50 mol % of $Cu(OAc)_2{\cdot}H_2O$ under an air atmosphere. However, in the reaction, product **3aa** was observed only in 38% GC yield. The reaction was tested with other catalysts (5 mol %) such as $Ru(COD)Cl_2$, $Ru(PPh_3)_3Cl_2$ and $RuCl_3{\cdot}H_2O$ apart from [{$RuCl_2$(*p*-cymene)}$_2$]. However, no cyclization product **3aa** was observed in these complexes. The amount of catalyst [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %) and (10 mol %) was also examined. In 2 mol % and 10 mol % of catalyst, product **3aa** was observed in 32% and 80% GC yields, respectively. Thus, 5 mol

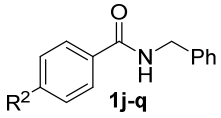
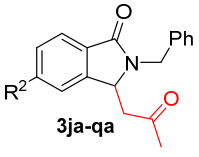
% of catalyst amount is sufficient for the reaction. The amount of reactant **2a** (1.2 equiv and 3.0 equiv apart from 2.2 equiv) was also tested. In 1.2 equiv of **2a**, product **3aa** was observed in 55% GC yield and in 3.0 equiv of **2a**, product **3aa** was observed in 79% GC yield. The cyclization reaction was also tested at 60 °C and 80 °C apart from 110 °C. In 60 °C, no product **3aa** was observed and at 80 °C product **3aa** was observed in 35% GC yield. Control experiments showed that in the absence of $AgSbF_6$ or [{$RuCl_2$(*p*-cymene)}$_2$] or $Cu(OAc)_2{\cdot}H_2O$, no **3aa** was obtained. Under the optimized reaction conditions, the cyclization of other *N*-substituted benzamides **1b-i** with **2a** was tested (Scheme 2A.3). *N*-Phenyl **1b** and cyclohexyl **1c** substituted benzamides reacted with **2a**, providing cyclization products **3ba** and **3ca** in 59% and 46% yields, respectively. *N*-Methyl substituted benzamide **1d** gave isoindolinone derivative **3da** in 67% yield. But, *N*-*tert* butyl benzamide **1e** provided a mixture of cyclic product **3ea** and *ortho* alkenylated product **3ea'** in 45% combined yield in a 1:0.4 ratio. In other *N*-substituted benzamides **1f-i**, the expected cyclization product was not observed.

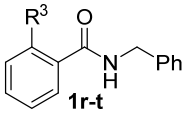
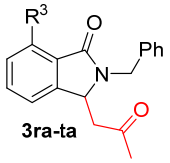
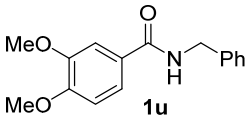
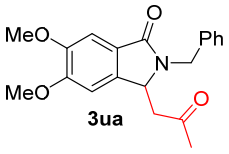
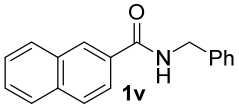
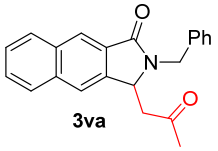
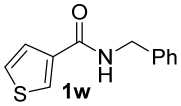
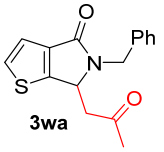


Scheme 2A.3: Cyclization of *N*-substituted benzamides with **2a**

2A.2.2 Scope of Substituted Aromatic Amides

Table 2A.1: Scope of the *N*-benzyl substituted benzamides[a]

Entry	Benzamides **1**	Product **3**	Yield (%)[b]
	 **1j-q**	 **3ja-qa**	

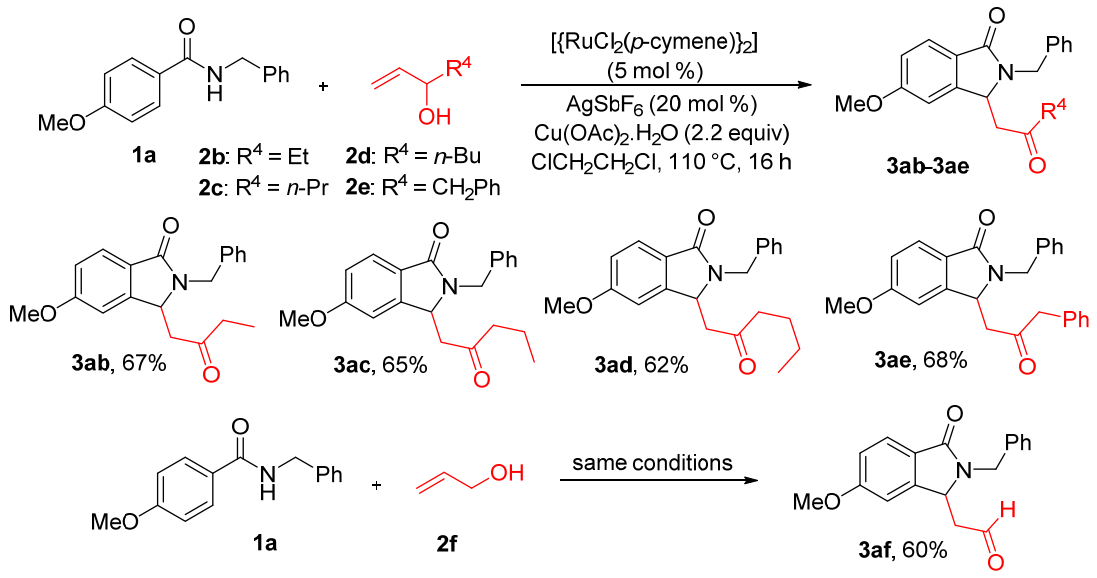
1	**1j**: R^2 = Me	**3ja**: R^2 = Me	69
2	**1k**: R^2 = H	**3ka**: R^2 = H	60
3	**1l**: R^2 = I	**3la**: R^2 = I	61
4	**1m**: R^2 = Br	**3ma**: R^2 = Br	59
5	**1n**: R^2 = Cl	**3na**: R^2 = Cl	58
6	**1o**: R^2 = F	**3oa**: R^2 = F	47
7	**1p**: R^2 = CF_3	**3pa**: R^2 = CF_3	54
8	**1q**: R^2 = NO_2	**3qa**: R^2 = NO_2	46
	 **1r-t**	 **3ra-ta**	
9	**1r**: R^3 = OMe	**3ra**: R^3 = OMe	80
10	**1s**: R^3 = Me	**3sa**: R^3 = Me	65
11	**1t**: R^3 = Br	**3ta**: R^3 = Br	62
12	 **1u**	 **3ua**	53
13	 **1v**	 **3va**	58
14	 **1w**	 **3wa**	60[c]

[a]All reactions were carried out using **1j-w** (100 mg), ethyl-2- buten-2-ol (**2a**) (2.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (2.2 equiv) in $ClCH_2CH_2Cl$ (3.0 mL) at 110 °C for 16 h. [b]Isolated yield. [c]The reaction was carried at 110 °C for 28 h.

The scope of the cyclization reaction was examined with *N*-benzyl substituted benzamides **1j-v** (Table 2A.1). Benzamides **1j** and **1k** reacted efficiently with **2a**, providing the cyclization products **3ja** and **3ka** in 69% and 60% yields, respectively (entries 1 and 2). Halogen groups such as I, Br, Cl and F substituted benzamides **1l-o** reacted efficiently with **2a**, affording products **3la-3oa** in good to moderate yields, respectively (entries 3-6). Interestingly, electron-withdrawing groups such as CF_3 and

NO_2 substituted benzamides **1p** and **1q** reacted with **2a,** giving cyclization products **3pa** and **3qa** in 54% and 46% yields, respectively (entries 7 and 8). Apart from the *para* substituted benzamides, *ortho* OMe, Me and Br substituted benzamides **1r-t** also efficiently participated in the reaction, yielding products **3ra-ta** in 80%, 65% and 62% yields, respectively (entries 9-11). Unsymmetrical 3,4-dimethoxy **(1u)** and 2-naphthyl **(1v)** substituted benzamides regioselectively reacted with **2a** yielding products **3ua** and **3va** in 53% and 58% yields, respectively (entries 12 and 13). In the substrates **1u** and **1v,** the C−H bond activation takes place at the C-6 position of benzene ring and the C-3 position of naphthalene ring selectively. Interestingly, heteroaromatic amide **1w** also efficiently participated in the reaction, affording product **3wa** in 60% yield (entry 14).

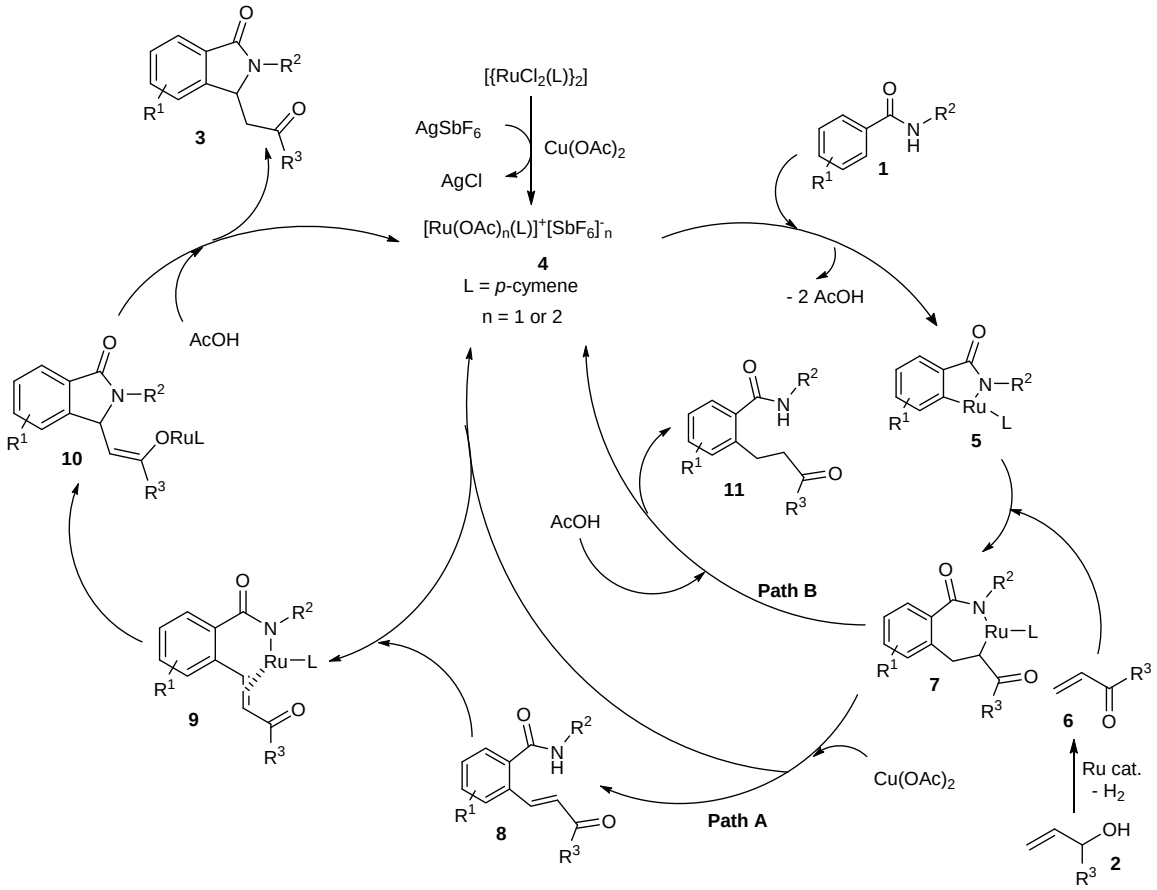
2A.2.3 Scope of Allylic Alcohols



Scheme 2A.4: Scope of the substituted allylic alcohols

The scope of the cyclization reaction was also further examined with substituted allylic alcohols (Scheme 2A.4). Treatment of pent-1-en-3-ol **(2b),** hex-1-en-3-ol **(2c)** and hept-1-en-3-ol **(2d)** with benzamide **1a** under similar reaction conditions gave cyclization products **3ab-ad** in 67%, 65% and 62% yields, respectively. 1-Phenylbut-3-en-2-ol **(2e)** also nicely participated in the reaction, affording the corresponding cyclization product **3ae** in 68% yield. Interestingly, prop-2-en-1-ol **(2f)** reacted efficiently with **1a,** giving a formyl substituted cyclic compound **3af** in 60% yield.

2A.2.4 Proposed Mechanism



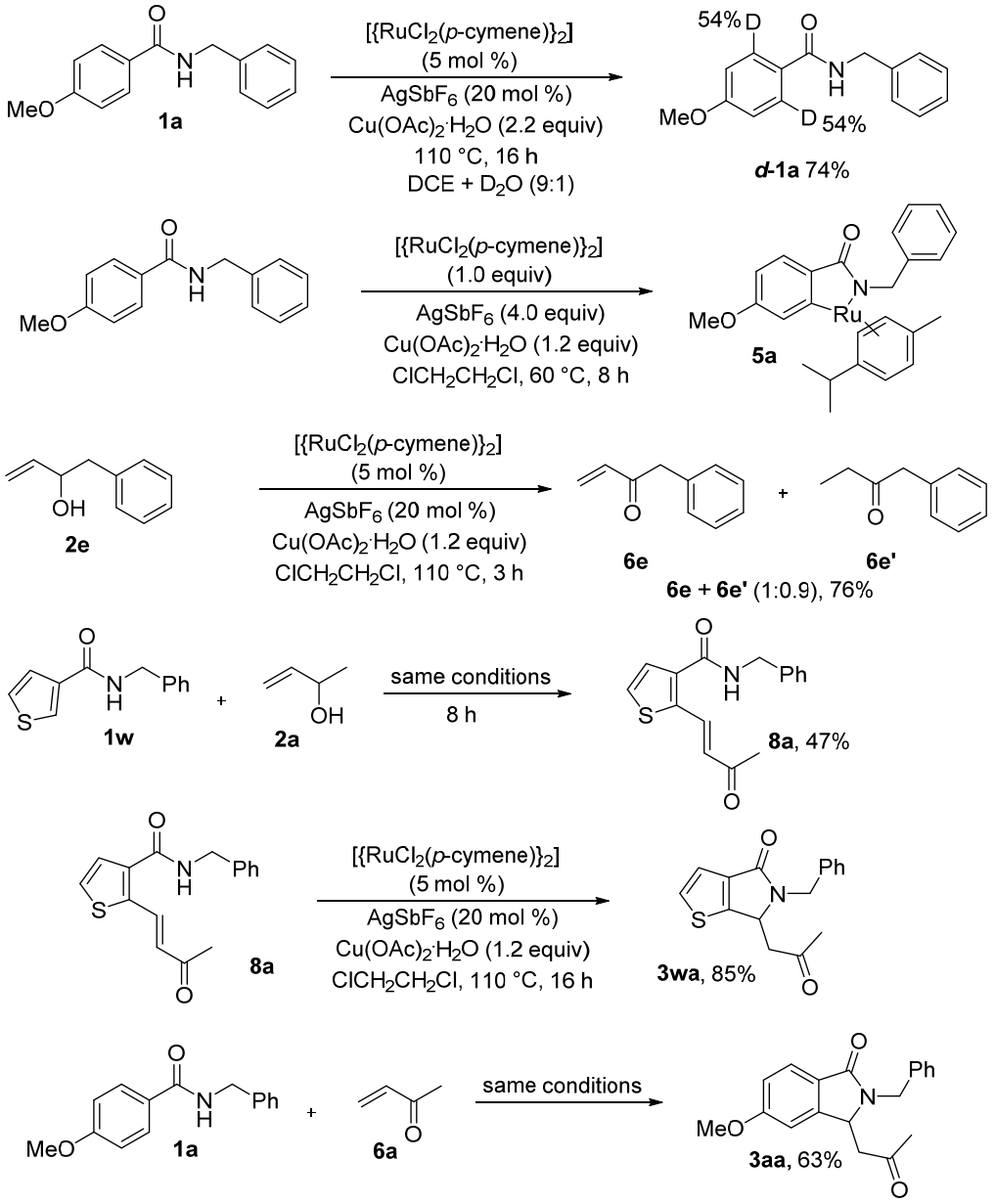
Scheme 2A.5: Proposed mechanism

Based on the previous reports[6-10] and our observation, a possible reaction mechanism is proposed in Scheme 2A.5. Basically, a multi-step reaction is involved in the cyclization reaction. First, $AgSbF_6$ likely removes the Cl^- ligand from $[\{RuCl_2(p\text{-cymene})\}_2]$ complex in the presence of $Cu(OAc)_2$ providing a cationic ruthenium acetate species **4**. Coordination of the nitrogen atom of **1** to the ruthenium species **4** followed by *ortho*-metalation provides ruthenacycle intermediate **5**. Coordinative insertion of α,β-unsaturated enone **6** into the Ru–carbon bond of intermediate **5** gives intermediate **7**. We strongly believe that the allylic alcohols **2** convert into *α,β*-unsaturated enones **6** in the presence of ruthenium catalyst and $Cu(OAc)_2$.[11] β-Deprotonation of intermediate **7** by acetate source followed by protonation of nitrogen affords *ortho*-alkenylated benzamide **8** and regenerates the ruthenium species **4** (proceeds via **path A**).[11c] Later, coordination of the nitrogen atom of *ortho*-alkenylated benzamide **8** into ruthenium species **4** followed by intramolecular coordination of double bond into ruthenium affords intermediate **9** and AcOH. Intramolecular coordinative insertion of N-Ru bond of intermediate **9** into the

alkene moiety followed by enolization provides ruthenium enolate intermediate **10.** Protonation of intermediate **10** in the presence of AcOH provides product **3** and regenerates the active ruthenium species **4**. The control of the product formation **11** which proceeds via enolization of intermediate **7** followed by protonation is highly important to success the present cyclization reaction (via **path B**).[10]

2A.2.5 Mechanistic Studies

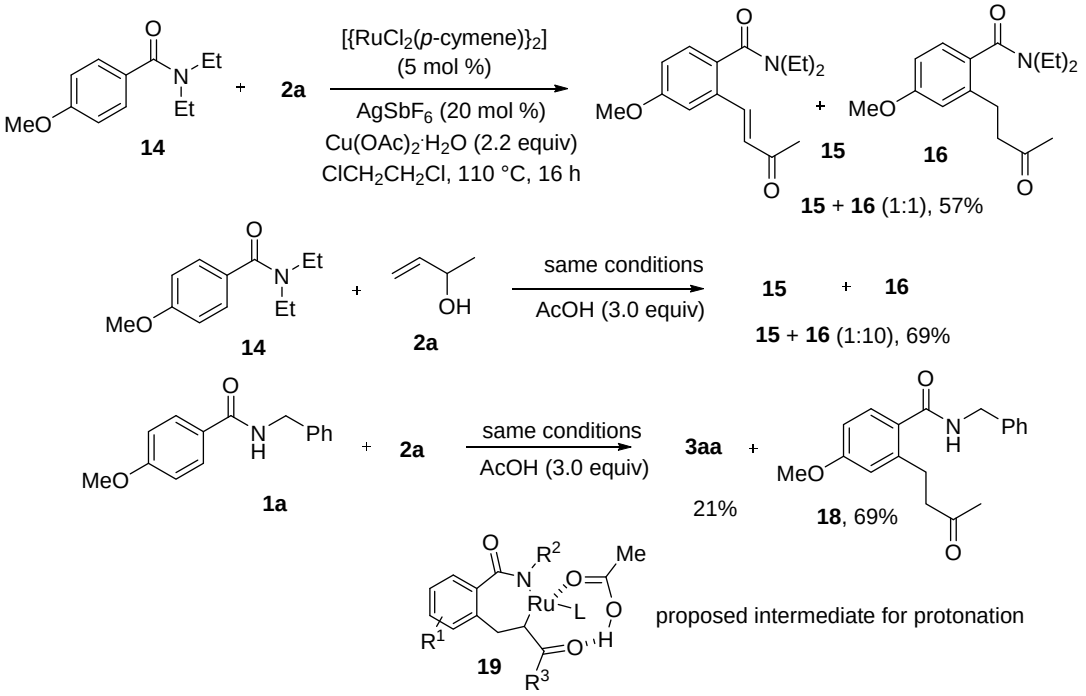
The formation of a key five-membered ruthenacycle intermediate **5** is a rate determining reversible step in the reaction. To support the reversible step, *N*-benzyl 4-methoxy benzamide **(1a)** was treated with ruthenium catalyst, $AgSbF_6$ and $Cu(OAc)_2{\cdot}H_2O$, D_2O in DCE solvent at 110 °C for 16 h. As expected, 54% deuterium incorporations were observed at both *ortho* carbons of benzamide ***d*-1a** in a combined 74 % yield (Scheme 2A.6). In the meantime, we have tried to isolate the key ruthenacycle intermediate **5** in the reaction of 4-methoxy benzamide **1a** with a stoichiometric amount of ruthenium complex (1.0 equiv), $AgSbF_6$ (4.0 equiv) and $Cu(OAc)_2{\cdot}H_2O$ (1.2 equiv) in DCE solvent at 60 °C for 8 h. In the reaction, metalacycle intermediate **5** was isolated. However, we were not able to crystallize the intermediate **5**. But, the complex **5** was tentatively assigned by ^1H, ^{13}C NMR, HRMS and MALDI-TOF spectroscopic techniques. To confirm the formation of activated alkene **6**, 1-phenylbut-3-en-2-ol **(2e)** was treated with ruthenium catalyst, $AgSbF_6$ and $Cu(OAc)_2{\cdot}H_2O$ at 110 °C for 3 h. In the reaction, approx. 1:1 mixture of 1-phenylbut-3-en-2-one **(6e)** and the reduced 1-phenylbutan-2-one **(6e')** were observed in a combined 76% yield. It seems in the cyclization reaction, initially product **6e** is formed which further reacted with benzamide **1** providing the cyclization product **3**. If benzamide is not present in the reaction mixture, alkene moiety of **6e** subsequently reduced. Further, we have tried to isolate *ortho* alkenylated benzamide **8** in the reaction of 2-thienyl amide **(1w)** with **2a** under the optimized reaction conditions at the shorter reaction time 8 h. In the reaction, the expected alkenylated product **8a** was observed in 47% yield. Later, *ortho* alkylated benzamide **8a** was treated with ruthenium catalyst, $AgSbF_6$ and $Cu(OAc)_2{\cdot}H_2O$ at 110 °C for 16 h giving the expected cyclic compound **3wa** in 85% yield. Further, benzamide **1a** reacted with methyl vinyl ketone **(6a)** under the optimized reaction conditions providing the expected cyclic product **3aa** in 63% yield. This experimental evidence clearly supports the proposed mechanism in Scheme 2A.5.



Scheme 2A.6: Mechanistic evidence

To success the present cyclization reaction, to suppress the enolization of intermediate **7** into **11** is highly important. It is known that *N*-*N*-disubstituted benzamides reacted with allylic alcohols leading to *ortho* alkylated benzamides in the presence of rhodium or ruthenium complexes.[10] But, in the present reaction, *N*-substituted benzamides reacted with allylic alcohols yielding isoindolinone derivatives **3**. To know the clear mechanism, we have tried the reaction of *N*-*N*-diethyl benzamide **14** with **2a** under the optimized reaction conditions (Scheme 2A.7). In the reaction, *ortho* alkenylated benzamide **15** and *ortho* alkylated benzamide **16** were observed in combined 57% yields in a 1:1 ratio. But, in the presence of AcOH (3.0 equiv) under similar reaction conditions, the same reaction provided a major amount of *ortho* alkylated benzamide **16** along with a minor amount of

15 in 69% yield in a 10:1 ratio. Similarly, the reaction of *N*-substituted benzamide **1a** with **2a** was tried in the presence of 3.0 equiv of AcOH under the optimized reaction conditions. In the reaction, cyclization product **3aa** and *ortho* alkylated benzamide **18** were observed in 21% and 69% yields, respectively. In this stage, we conclude that an excess amount of AcOH might increases the electrophilicity of carbonyl group in intermediate **7** via protonation. It is likely that intermediate **19** could be formed. Thus, instead of β-hydride elimination, enoloization takes place effectively.[10c, 12]



Scheme 2A.7: Reaction of *N*-*N*-Diethyl Benzamide with **2a**

2A.3 Conclusion

In conclusion, we have demonstrated a ruthenium-catalyzed cyclization of *N*-substituted benzamides with allylic alcohols in the presence of ruthenium catalyst. A possible reaction mechanism involving a five-membered ruthenacycle intermediate was proposed and strongly supported by experimental evidence.

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2A.5: Experimental section

2A.5.1: General Procedure for the Cyclization Reaction.

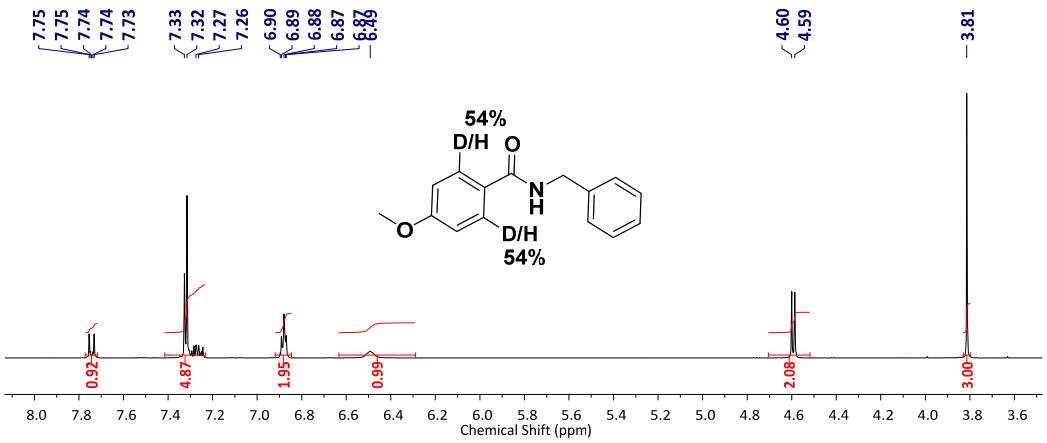
A 15 mL pressure tube with septum containing [{$RuCl_2$(p-cymene)}$_2$] (5.0 mol %), aromatic or heteroaromatic amide **1** (100 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.20 equiv) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube were then added allylic alcohol **2** (2.20 equiv) and $ClCH_2CH_2Cl$ (3.0 mL) via syringes after that the reaction mixture was evacuated and purged with nitrogen gas three times. After that, the septum was taken out immediately and a screw cap was used to cover the tube under the nitrogen atmosphere and again the reaction mixture stirred at room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 110 °C for 16 h. After cooling to the ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite 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 **3**.

2A.5.2: Mechanistic Studies

Procedure for the Deuteration reaction.

A 15 mL pressure tube with septum containing [{$RuCl_2$(p-cymene)}$_2$] (5.0 mol %), N-benzyl-4-methoxybenzamide (**1a**) (100 mg), $Cu(OAc)_2.H_2O$ (2.20 equiv) 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 $ClCH_2CH_2Cl$ (2.70 mL) and deuterium oxide (0.3 mL) via syringes and again the reaction mixture was evacuated and

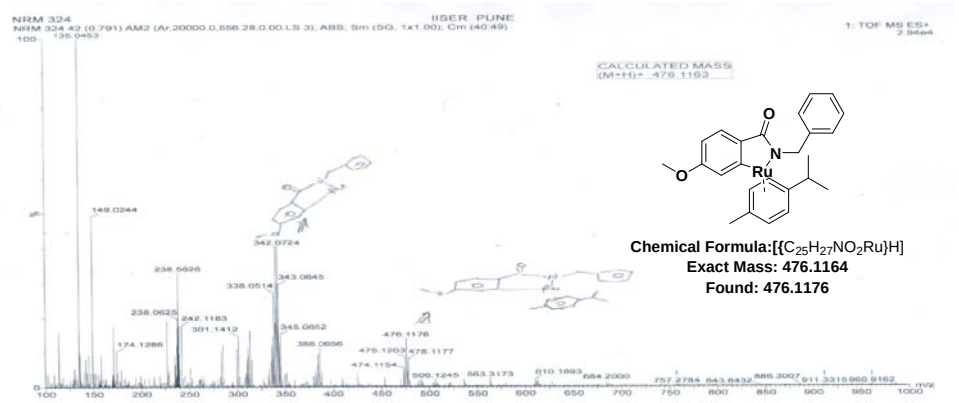
purged with nitrogen gas three times. After that, the septum was taken out and immediately a screw cap was used to cover the tube under the nitrogen atmosphere. Then, the reaction mixture was allowed to stir at 110 °C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and the filtrate was concentrated. The crude residue was purified through a very short silica gel column using hexanes and ethyl acetate as eluent to give duterated N-benzyl-4-methoxybenzamide (**d-1a**).



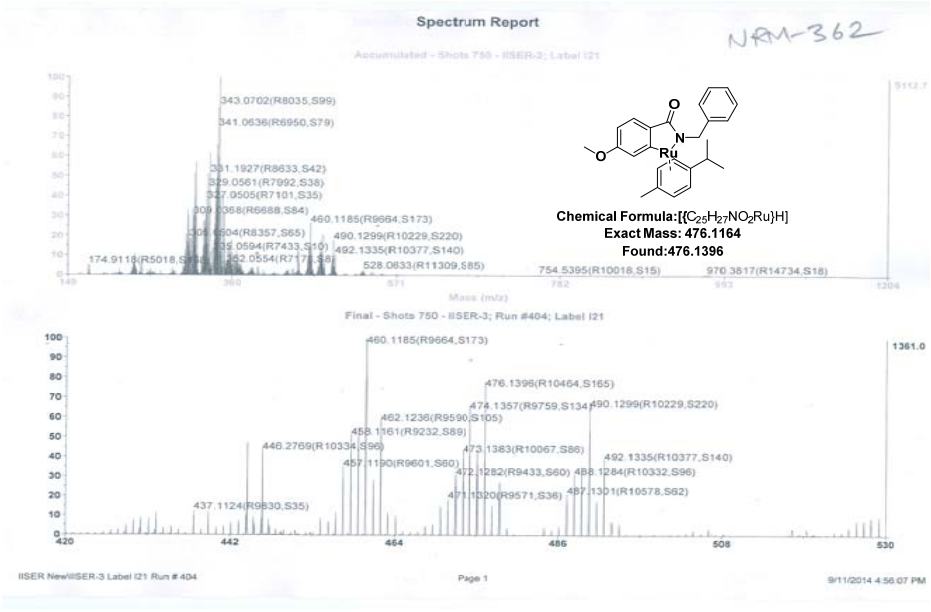
Procedure for the Preparation of a Five-Membered Ruthenacycle 5.

A 15 mL pressure tube with septum containing [{$RuCl_2$(p-cymene)}$_2$] (50 mg), benzamide **1a** (1.10 equiv), $Cu(OAc)_2 \cdot H_2O$ (1.20 equiv) and $AgSbF_6$ (4.0 equiv) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube were then added $ClCH_2CH_2Cl$ (2.0 mL) via syringe and again the reaction mixture was evacuated and purged with nitrogen gas three times. After that, the septum was 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 60 °C for 8 h. After cooling to ambient temperature, the reaction mixture was diluted with methanol, filtered through Celite and the filtrate was concentrated and taken for further analysis without any further purification.

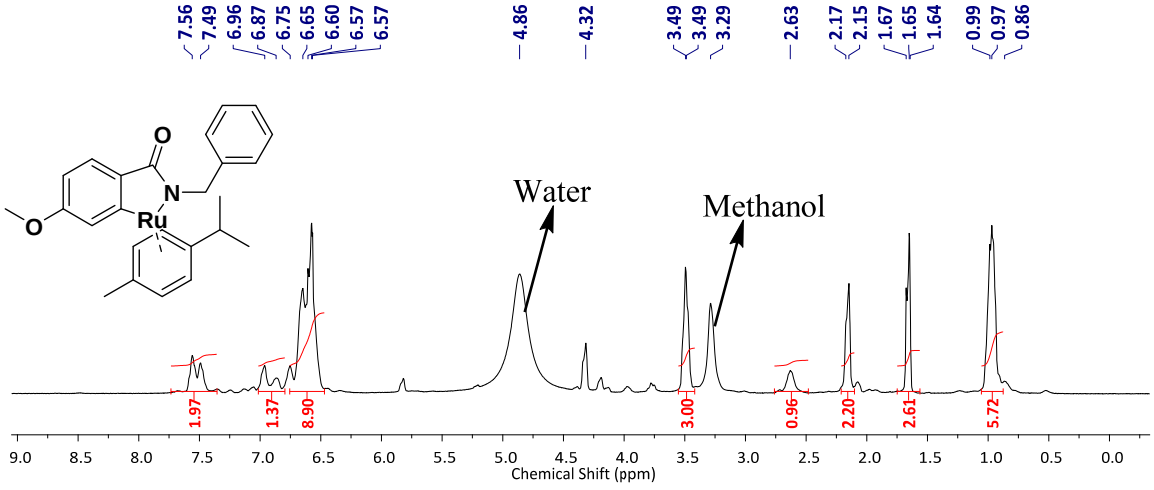
HRMS Spectra of Ruthenacycle 5

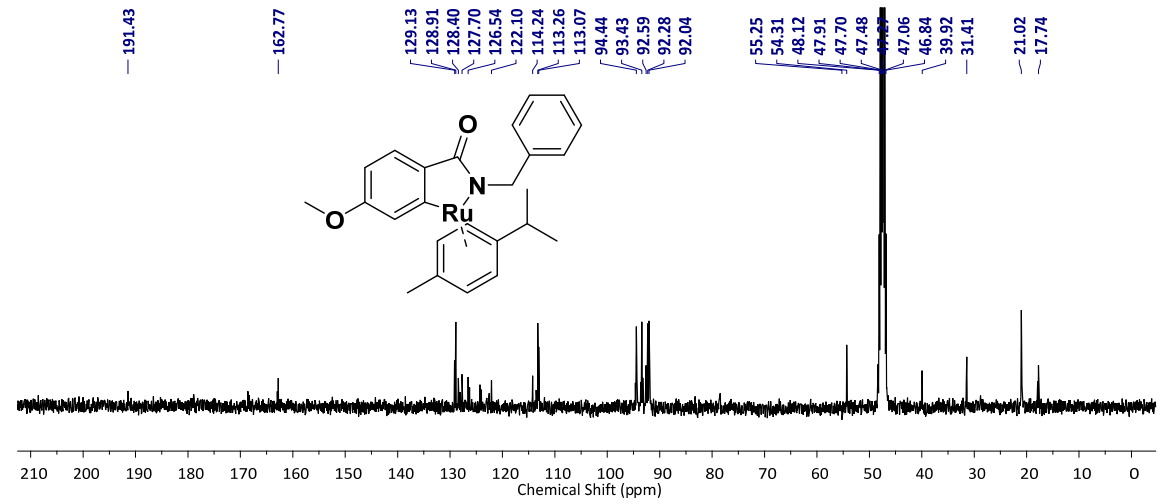


MALDI-TOF Spectra of Ruthenacycle 5

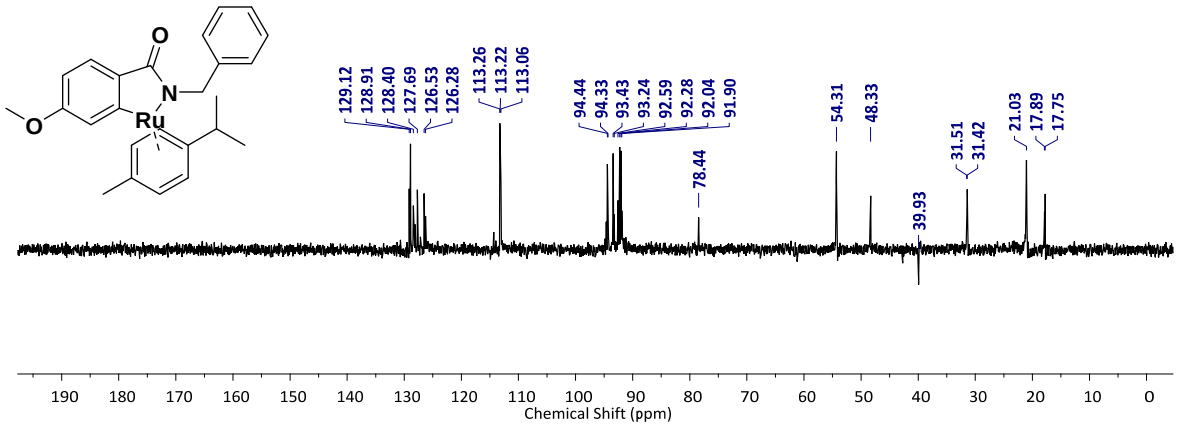


H[1] and C[13] NMR Spectra of Ruthenacycle 5



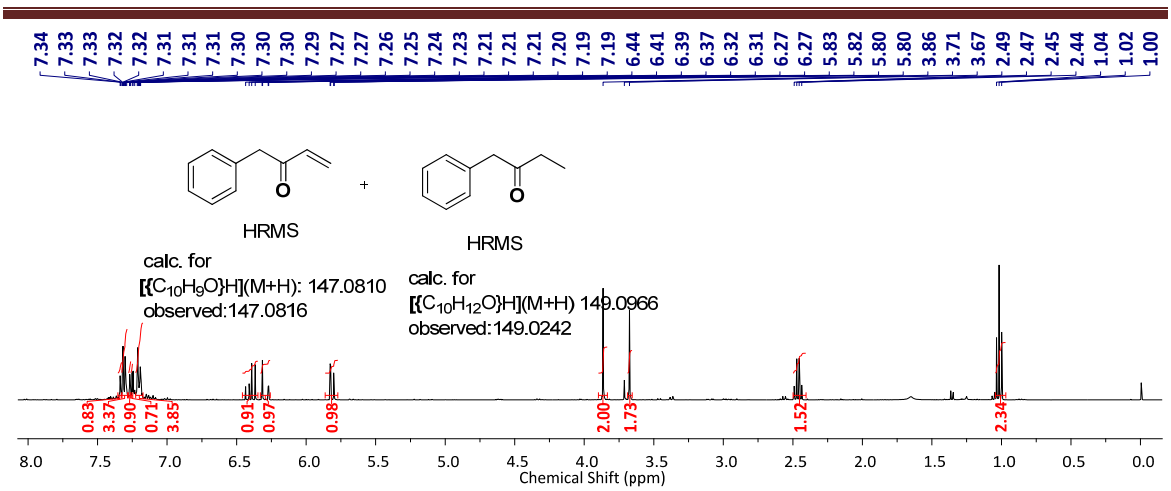


Note: *In ^{13}C NMR, we think C-Ru peak comes at δ 191.4 due to the deshilding of C-Ru.*



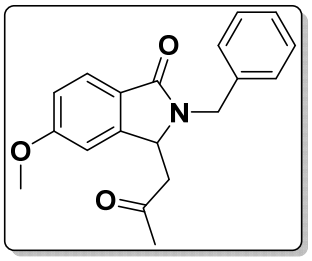
Procedure for the reaction of Phenylbut-3-en-2-ol (2e) with Ru(II) catalyst.

A 15-mL pressure tube with septum containing [{$RuCl_2$(p-cymene)}$_2$] (5.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.20 equiv) 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 1-phenylbut-3-en-2-ol (100 mg), $ClCH_2CH_2Cl$ (3.0 mL) via syringes and 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 and further the reaction mixture stirred at room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 110 °C for 3 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and the filtrate was concentrated. The crude residue was purified through a very short silica gel column using hexanes and ethyl acetate as eluent.


7.34 7.33 7.33 7.32 7.32 7.31 7.31 7.31 7.30 7.30 7.30 7.29 7.27 7.27 7.26 7.25 7.24 7.23 7.21 7.21 7.21 7.20 7.19 7.19 6.44 6.41 6.39 6.37 6.32 6.31 6.27 6.27 5.83 5.82 5.80 5.80 3.86 3.71 3.67 2.49 2.47 2.45 2.44 1.04 1.02 1.00
HRMS
calc. for
[{C10H9O}H](M+H): 147.0810
observed:147.0816
HRMS
calc. for
[{C10H12O}H](M+H) 149.0966
observed:149.0242
0.83 3.37 0.90 0.71 3.85 0.91 0.97 0.98 2.00 1.73 1.52 2.34
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)

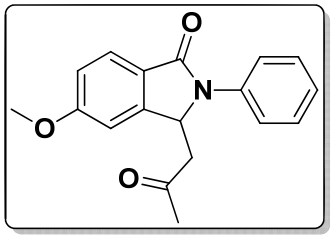
2A.6: Spectral Data of Compounds

2-Benzyl-5-methoxy-3-(2-oxopropyl)isoindolin-1-one (3aa).



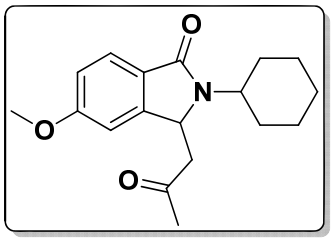
White semisolid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 72% (92 mg). **IR (ATR)** ṽ (cm-1): 2960, 1721, 1515, 1277, 1071 and 743. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.78 (d, *J* = 8.4 Hz, 1 H), 7.31 – 7.25 (m, 2 H), 7.24 – 7.20 (m, 3 H), 6.97 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.81 (d, *J* = 2.2 Hz, 1 H), 4.93 (t, *J* = 6.0 Hz, 1 H), 4.85 (d, *J* = 15.4 Hz, 1 H), 4.55 (d, *J* = 15.4 Hz, 1 H), 3.81 (s, 3 H), 2.87 (dd, *J* = 17.8, 5.6 Hz, 1 H), 2.64 (dd, *J* = 17.8, 6.6 Hz, 1 H), 1.90 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.8, 168.5, 163.1, 147.9, 137.5, 128.8, 127.9, 127.5, 125.4, 124.3, 114.9, 107.6, 55.7, 55.3, 46.9, 44.7, 30.4. **HRMS (ESI):** calc. for $[(C_{19}H_{19}NO_3)H]$ (M+H) 310.1443, measured 310.1443.

5-Methoxy-3-(2-oxopropyl)-2-phenylisoindolin-1-one (3ba).



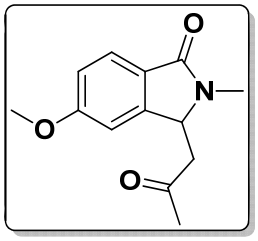
Colorless semisolid; eluent (40 % ethyl acetate in hexanes); **1b** was taken in 100 mg; yield is 59 % (77 mg). **IR (ATR)** ṽ (cm^{-1}): 1692, 1614, 1497, 1461, 1373, 1263, 1084, and 729. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.81 (d, *J* = 8.4 Hz, 1 H), 7.56 – 7.47 (m, 2 H), 7.45 – 7.34 (m, 2 H), 7.23 – 7.16 (m, 1 H), 7.01 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.94 (d, *J* = 2.2 Hz, 1 H), 5.64 (dd, *J* = 9.4, 3.0 Hz, 1 H), 3.85 (s, 3 H), 3.04 (dd, *J* = 18, 3 Hz, 1 H), 2.61 (dd, *J* = 18, 9.4 Hz, 1 H), 2.09 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 206.5, 166.8, 163.4, 147.4, 136.8, 129.4, 125.6, 125.5, 124.4, 123.2, 115.5, 107.6, 56.1, 55.7, 46.7, 30.8. **HRMS (ESI):** calc. for $[(C_{18}H_{17}NO_3)H]$ (M+H) 296.1287, measured 296.1291.

2-Cyclohexyl-5-methoxy-3-(2-oxopropyl)isoindolin-1-one (3ca).



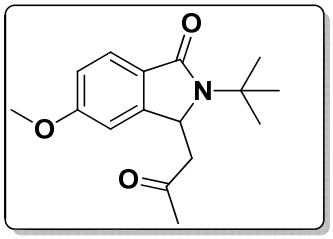
Colorless semisolid; eluent (35% ethyl acetate in hexanes); **1c** was taken in 100 mg; yield is 46 % (59 mg). ***IR (ATR)*** *$\tilde{\nu}$ (cm^{-1}):* 1708, 1677, 1615, 1515, 1424, 1367, 1262, and 729. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66 (d, *J* = 8.4 Hz, 1 H), 6.90 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.78 (d, *J* = 2.2 Hz, 1 H), 5.00 (dd, *J* = 9, 3.4 Hz, 1 H), 3.78 (s, 3 H), 3.71 – 3.65 (m, 1 H), 3.15 (dd, *J* = 17.8, 3.4 Hz, 1 H), 2.65 (dd, *J* = 17.8, 9.2 Hz, 1 H), 2.17 (s, 3 H), 1.94 (dd, *J* = 12.4, 3.6 Hz, 1 H), 1.87 – 1.74 (m, 4 H), 1.76 – 1.69 (m, 2 H), 1.36 – 1.28 (m, 2 H), 1.19 – 1.14 (m, 1 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 206.4, 168.3, 162.8, 148.3, 125.1, 124.8, 114.8, 107.5, 55.7, 55.3, 53.8, 48.2, 31.5, 31.1, 30.9, 26.2, 26.1, 25.5. **HRMS (ESI):** calc. for [($C_{18}H_{23}NO_3$)H] (M+H) 302.1756, measured 302.1758.

5-Methoxy-2-methyl-3-(2-oxopropyl)isoindolin-1-one (3da).



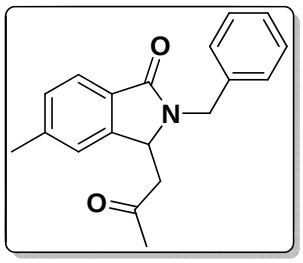
Yellow semisolid; eluent (55 % ethyl acetate in hexanes); **1d** was taken in 100 mg; yield is 67%, 94 mg). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2962, 1722, 1463, 1374, 1275, 1124, 1071, and 734. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.69 (d, *J* = 8.4 Hz, 1 H), 6.93 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.85 (d, *J* = 2 Hz, 1 H), 4.87 (dd, *J* = 7.4, 5.2 Hz, 1 H), 3.81 (s, 3 H), 3.05 – 2.97 (m, 4 H), 2.71 (dd, *J* = 17.8, 7.4 Hz, 1 H), 2.21 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 206.0, 168.1, 162.8, 147.6, 124.9, 124.6, 114.8, 107.7, 57.0, 55.7, 46.6, 30.8, 27.7. **HRMS (ESI):** calc. for [($C_{13}H_{15}NO_3$)Na] (M+Na) 256.0950, measured 256.0946.

2-(*tert*-Butyl)-5-Methoxy-3-(2-oxopropyl)isoindolin-1-one (3ea).



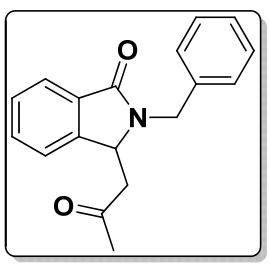
Yellow semisolid; eluent (55 % ethyl acetate in hexanes); **1d** was taken in 100 mg; combined yield is 45% (62 mg). **IR (ATR)** ṽ (cm^{-1}): 2962, 1722, 1463, 1374, 1275, 1124, 1071, and 734. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.62 (d, *J* = 8.4 Hz, 1 H), 6.89 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.75 (d, *J* = 2.2 Hz, 1 H), 5.17 (dd, *J* = 9.6, 2.0 Hz, 1 H), 3.79 (s, 3 H), 3.29 (dd, *J* = 18.2, 2 Hz, 1 H), 2.59 (dd, *J* = 18.2, 9.6 Hz, 1 H), 2.14 (s, 3 H), 1.53 (s, 9 H). **HRMS (ESI):** calc. for [($C_{16}H_{21}NO_3$)H] (M+Na) 276.1600 measured 276.1601.

2-Benzyl-5-methyl-3-(2-oxopropyl) isoindolin-1-one (3ja).



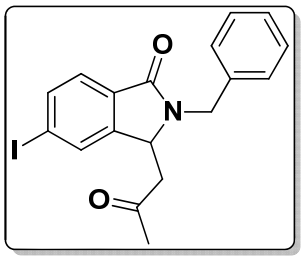
White semisolid; eluent (30% ethyl acetate in hexanes); **1j** was taken in 100 mg; yield is 69% (90 mg). **IR (ATR)** ṽ (cm^{-1}): 1681, 1619, 1409, 1360, 1292, 1266, 1156, and 733. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.76 (d, *J* = 7.8 Hz, 1 H), 7.32 – 7.25 (m, 3 H), 7.22 (m, 3 H), 7.12 (s, 1 H), 4.95 (t, *J* = 6 Hz, 1 H), 4.86 (d, *J* = 15.4 Hz, 1 H), 4.57 (d, *J* = 15.4 Hz, 1 H), 2.85 (dd, *J* = 17.8, 5.8 Hz, 1 H), 2.65 (dd, *J* = 17.8, 6.4 Hz, 1 H), 2.40 (s, 3 H), 1.89 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.7, 168.7, 146.0, 142.6, 137.4, 129.5, 129.2, 128.8, 127.9, 127.5, 123.8, 122.9, 55.4, 46.9, 44.8, 30.4, 22.0. **HRMS (ESI):** calc. for [($C_{19}H_{19}NO_2$)H] (M+H) 294.1494, measured 294.1498.

2-Benzyl-3-(2-oxopropyl) isoindolin-1-one (3ka).



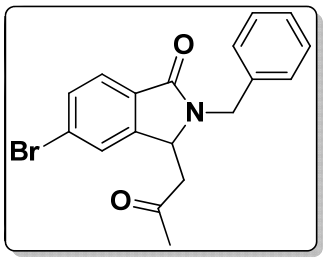
Colorless semisolid; eluent (35% ethyl acetate in hexanes); **1k** was taken in 100 mg; yield is 60% (71 mg). **IR (ATR)** ṽ (cm^{-1}): 1684, 1517, 1464, 1408, 1360, 1266, 1154 and 730. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88 (dd, *J* = 6.6, 1 Hz, 1 H), 7.51 – 7.46 (m, 2 H), 7.35 – 7.27 (m, 4 H), 7.24 – 7.22 (m, 2 H), 5.01 (t, *J* = 6.2 Hz, 1 H), 4.88 (d, *J* = 15.4 Hz, 1 H), 4.60 (d, *J* = 15.2 Hz, 1 H), 2.87 (dd, *J* = 17.8, 5.8 Hz, 1 H), 2.67 (dd, *J* = 17.8, 6.4 Hz, 1 H), 1.89 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.6, 168.6, 145.6, 137.9, 131.9, 131.7, 128.8, 128.7, 127.9, 127.6, 124.0, 122.5, 55.6, 46.8, 44.8, 30.4. **HRMS (ESI):** calc. for [($C_{18}H_{17}NO_2$)H] (M+H) 280.1338, measured 280.1333.

2-Benzyl-5-iodo-3-(2-oxopropyl) isoindolin-1-one (3la).



Brown solid; eluent (30% ethyl acetate in hexanes); **1l** was taken in 100 mg; yield is 61% (74 mg). **IR (ATR)** ṽ (cm^{-1}): 1684, 1605, 1497, 1411, 1360, 1299, 1163, and 733. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.81 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.72 (s, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H), 7.31 – 7.22 (m, 3 H), 7.21 – 7.19 (m, 2 H), 4.95 (t, *J* = 6 Hz, 1 H), 4.84 (d, *J* = 15.4 Hz, 1 H), 4.56 (d, *J* = 15.4 Hz, 1 H), 2.87 (dd, *J* = 18, 5.6 Hz, 1 H), 2.64 (dd, *J* = 18, 6.6 Hz, 1 H), 1.91 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.2, 167.8, 147.4, 137.8, 136.9, 131.9, 131.3, 128.8, 127.9, 127.7, 125.4, 98.8, 55.1, 46.5, 44.8, 30.3. **HRMS (ESI):** calc. for [($C_{18}H_{16}INO_2$)H] (M+H) 406.0304, measured 406.0306.

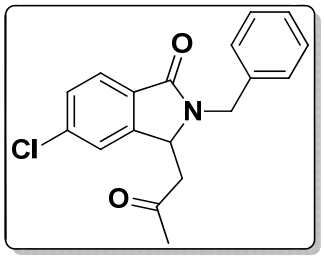
2-Benzyl-5-bromo-3-(2-oxopropyl) isoindolin-1-one (3ma).



Colorless semisolid; eluent (30% ethyl acetate in hexanes); **1m** was taken in 100 mg; yield is 59% (73 mg). **IR (ATR)** ṽ (cm^{-1}): 1683, 1608, 1409, 1359, 1163, and 734. **^{1}H**

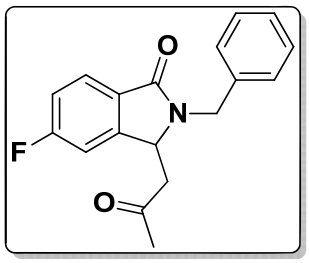
NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 1 H), 7.59 (dd, *J* = 8, 1.4 Hz, 1 H), 7.51 (d, *J* = 1.4 Hz, 1 H), 7.30 – 7.24 (m, 3 H), 7.22 – 7.17 (m, 2 H), 4.96 (t, *J* = 6 Hz, 1 H), 4.85 (d, *J* = 15.4 Hz, 1 H), 4.56 (d, *J* = 15.4 Hz, 1 H), 2.88 (dd, *J* = 18, 5.6 Hz, 1 H), 2.63 (dd, *J* = 18, 6.6 Hz, 1 H), 1.92 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.2, 167.7, 147.6, 136.9, 132.0, 130.7, 128.8, 127.9, 127.7, 126.6, 126.1, 125.4, 55.2, 46.5, 44.8, 30.3. **HRMS (ESI):** calc. for [($C_{18}H_{16}BrNO_2$)H] (M+H) 358.0443, measured 358.0450.

2-Benzyl-5-chloro-3-(2-oxopropyl) isoindolin-1-one (3na).



Brown semisolid; eluent (30% ethyl acetate in hexanes); **1n** was taken in 100 mg; yield is 58% (74 mg). **IR (ATR)** ṽ (cm^{-1}): 1683, 1612, 1406, 1359, 1318, 1164, 1073 and 840. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.78 (d, *J* = 8.0 Hz, 1 H), 7.42 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.34 (m, 1 H), 7.30 – 7.19 (m, 5 H), 4.96 (t, *J* = 6.2 Hz, 1 H), 4.85 (d, *J* = 15.4 Hz, 1 H), 4.56 (d, *J* = 15.4 Hz, 1 H), 2.89 (dd, *J* = 18, 5.6 Hz, 1 H), 2.63 (dd, *J* = 18, 6.8 Hz, 1 H), 1.92 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.3, 167.6, 147.3, 138.3, 136.9, 130.2, 129.1, 128.8, 127.9, 127.7, 125.2, 123.2, 55.3, 46.4, 44.8, 30.3. **HRMS (ESI):** calc. for [($C_{18}H_{16}ClNO_2$)H] (M+H) 314.0948, measured 314.0948.

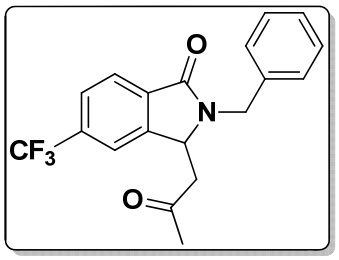
2-Benzyl-5-fluoro-3-(2-oxopropyl) isoindolin-1-one (3oa).



Brown solid; eluent (35% ethyl acetate in hexanes); **1o** was taken in 100 mg; yield is 47% (61 mg). **IR (ATR)** ṽ (cm^{-1}): 1684, 1599, 1534, 1486, 1409, 1360, 1269, and 1220. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.84 (dd, *J* = 8.4, 5.0 Hz, 1 H), 7.29 – 7.24 (m, 3 H), 7.23 – 7.19 (m, 2 H), 7.14 (td, *J* = 8.6, 2.2 Hz, 1 H), 7.04 (dd, *J* = 8.4, 2.2 Hz, 1 H), 4.95 (t, *J* =

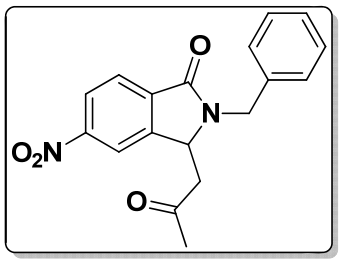
6.2 Hz, 1 H), 4.86 (d, *J* = 15.4 Hz, 1 H), 4.55 (d, *J* = 15.4 Hz, 1 H), 2.90 (dd, *J* = 18.0, 5.4 Hz, 1 H), 2.62 (dd, *J* = 18.0, 6.8 Hz, 1 H), 1.92 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.3, 167.6, 166.5, 164.0, 148.1 and 148.0 (F coupling), 137.0, 128.8, 127.7, 126.0, 125.9, 116.4 and 116.1 (F coupling), 110.4 and 110.1 (F coupling), 55.3, 46.5, 44.8, 30.3. **HRMS (ESI):** calc. for [($C_{18}H_{16}FNO_2$)H] (M+H) 298.1243, measured 298.1242.

2-Benzyl-3-(2-oxopropyl)-5-(trifluoromethyl)isoindolin-1-one (3pa).



White solid; eluent (35% ethyl acetate in hexanes); **1p** was taken in 100 mg; yield is 54 % (67 mg). **IR (ATR)** ṽ (cm^{-1}): 1693, 1516, 1429, 1362, 1325, 1265, 1166, and 729. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 8.2 Hz, 1 H), 7.74 (d, *J* = 8.2 Hz, 1 H), 7.62 (s, 1 H), 7.33 – 7.19 (m, 5 H), 5.06 (t, *J* = 6 Hz, 1 H), 4.89 (d, *J* = 15.4 Hz, 1 H), 4.62 (d, *J* = 15.4 Hz, 1 H), 2.92 (dd, *J* = 18.2, 5.6 Hz, 1 H), 2.68 (dd, *J* = 18.2, 6.6 Hz, 1 H), 1.93 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.1, 167.2, 146.0, 136.7, 135.0, 134.0, 133.7, 128.9, 127.9, 127.8, 125.9 and 125.8 (F coupling), 124.5, 120.0 and 120.0 (F coupling), 55.6, 46.4, 45.0, 30.2. **HRMS (ESI):** calc. for [($C_{19}H_{16}F_3NO_2$)H] (M+H) 348.1211, measured 348.1220.

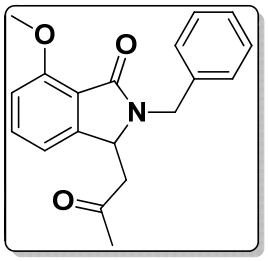
2-Benzyl-5-nitro-3-(2-oxopropyl) isoindolin-1-one (3qa).



White solid; eluent (35% ethyl acetate in hexanes); **1q** was taken in 100 mg; yield is 46 % (58 mg). **IR (ATR)** ṽ (cm^{-1}): 1691, 1530, 1409, 1344, 1267, 1163, 1087, and 732. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.34 (dd, *J* = 8.2, 1.8 Hz, 1 H), 8.22 (d, *J* = 1.8 Hz, 1 H), 8.02 (d, *J* = 8.2 Hz, 1 H), 7.32 – 7.26 (m, 3 H), 7.23 – 7.21 (m, 2 H), 5.09 (t, *J* = 6.0 Hz, 1

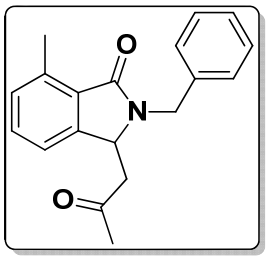
H), 4.88 (d, *J* = 15.4 Hz, 1 H), 4.64 (d, *J* = 15.4 Hz, 1 H), 2.95 (dd, *J* = 18.4, 5.6 Hz, 1 H), 2.73 (dd, *J* = 18.4, 6.6 Hz, 1 H), 1.94 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 204.7, 166.4, 150.3, 146.6, 137.1, 136.4, 129.0, 127.9, 125.0, 124.3, 118.5, 55.7, 46.0, 45.2, 30.2. **HRMS (ESI):** calc. for [($C_{18}H_{16}N_2O_4$)H] (M+H) 325.1188, measured 325.1191.

2-Benzyl-7-methoxy-3-(2-oxopropyl) isoindolin-1-one (3ra).



White solid; eluent (35% ethyl acetate in hexanes) **1r** was taken in 100 mg; yield is 80 % (102 mg). **IR (ATR)** ṽ (cm^{-1}): 1683, 1607, 1486, 1406, 1362, 1265, 1084, and 729. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42 (dd, *J* = 8.2, 7.4 Hz, 1 H), 7.23 – 7.18 (m, 5 H), 6.87 (dd, *J* = 6.0, 2.4 Hz, 2 H), 4.92 (t, *J* = 6.0 Hz, 1 H), 4.75 (d, *J* = 15.4 Hz, 1 H), 4.55 (d, *J* = 15.4 Hz, 1 H), 3.94 (s, 3 H), 2.79 (dd, *J* = 17.8, 6 Hz, 1 H), 2.64 (dd, *J* = 17.8, 5.8 Hz, 1 H), 1.84 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.7, 167.5, 157.4, 148.3, 137.5, 133.6, 128.7, 128.0, 127.4, 118.8, 114.4, 110.5, 55.9, 55.1, 47.0, 44.6, 30.4. **HRMS (ESI):** calc. for [($C_{19}H_{19}NO_3$)H] (M+H) 310.1443, measured 310.1449.

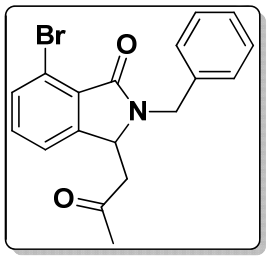
2-Benzyl-7-methyl-3-(2-oxopropyl) isoindolin-1-one (3sa).



White solid; eluent (30% ethyl acetate in hexanes) **1s** was taken in 100 mg; yield is 65% (85 mg). **IR (ATR)** ṽ (cm^{-1}): 1687, 1624, 1419, 1364, 1293, 1273, 1181 and 746. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 (t, *J* = 7.6 Hz, 1 H), 7.31 – 7.25 (m, 2 H), 7.24 (s, 2 H), 7.23 (d, *J* = 2.4 Hz, 1 H), 7.21 – 7.17 (m, 1 H), 7.12 (d, *J* = 7.2 Hz, 1 H), 4.95 (t, *J* = 6.0 Hz, 1 H), 4.82 (d, *J* = 15.4 Hz, 1 H), 4.59 (d, *J* = 15.4 Hz, 1 H), 2.82 (dd, *J* = 17.6, 6.0 Hz, 1 H), 2.75 (s, 3 H), 2.65 (dd, *J* = 17.6, 6.0 Hz, 1 H), 1.86 (s, 3 H). **^{13}C NMR (100 MHz,**

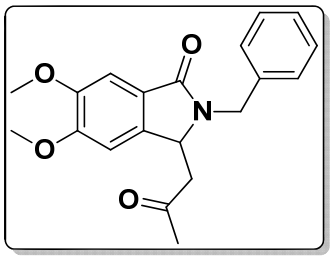
$CDCl_3$): δ 205.7, 169.3, 146.1, 138.0, 137.5, 131.4, 130.5, 128.7, 128.0, 127.5, 119.7, 55.0, 47.1, 44.6, 30.4, 17.4. **HRMS (ESI):** calc. for [($C_{19}H_{19}NO_2$)H] (M+H) 294.1494, measured 294.1490.

2-Benzyl-7-bromo-3-(2-oxopropyl) isoindolin-1-one (3ta).



Brown oil; eluent (30% ethyl acetate in hexanes) **1t** was taken in 100 mg, yield is 62% (77 mg). **IR (ATR)** ṽ (cm^{-1}): 1693, 1515, 1264, 1409, 1386, 1206, 1084, and 729. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88 (dd, *J* = 6.6, 1.4 Hz, 1 H), 7.48 (m, 2 H), 7.33 (d, *J* = 7.2 Hz, 1 H), 7.30 – 7.27 (m, 2 H), 7.24 – 7.21 (m, 2 H), 5.01 (t, *J* = 6.2 Hz, 1 H), 4.88 (d, *J* = 15.4 Hz, 1 H), 4.60 (d, *J* = 15.4 Hz, 1 H), 2.86 (dd, *J* = 17.8, 5.8 Hz, 1 H), 2.66 (dd, *J* = 17.8, 6.4 Hz, 1 H), 1.89 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.6, 168.6, 145.6, 137.3, 131.9, 131.7, 128.8, 128.5, 127.9, 127.6, 124.0, 122.5, 55.6, 46.8, 44.8, 30.4. **HRMS (ESI):** calc. for [($C_{18}H_{16}BrNO_2$)H] (M+H) 358.0443, measured 358.0448.

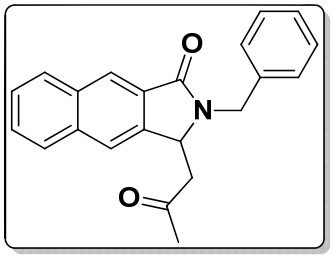
2-Benzyl-5, 6-dimethoxy-3-(2-oxopropyl)isoindolin-1-one (3ua).



White solid; eluent (35% ethyl acetate in hexanes). **1u** was taken in 100 mg, yield is 53 % (66 mg). **IR (ATR)** ṽ (cm^{-1}): 1682, 1510, 1464, 1426, 1264, 1220, 1084, and 730. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34 (s, 1 H), 7.31 – 7.25 (m, 2 H), 7.23 – 7.20 (m, 3 H), 6.82 (s, 1 H), 4.96 – 4.83 (m, 2 H), 4.51 (d, *J* = 15.4 Hz, 1 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 2.90 (dd, *J* = 17.8, 5.4 Hz, 1 H), 2.60 (dd, *J* = 17.8, 7.0 Hz, 1 H), 1.94 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 206.0, 168.8, 152.8, 149.9, 139.2, 137.4, 128.7, 127.8, 127.5,

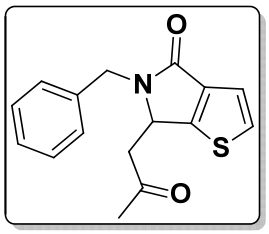
123.9, 105.4, 104.9, 56.3, 55.2, 46.9, 44.7, 30.4. **HRMS (ESI):** calc. for [($C_{20}H_{21}NO_4$)H] (M+H) 340.1549, measured 340.1551.

2-Benzyl-3-(2-oxopropyl)-2, 3-dihydro-1H-benzo[*f*]isoindol-1-one (3va).



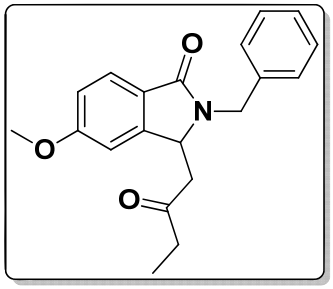
White waxysolid; eluent (35% ethyl acetate in hexanes) **1v** was taken in 100 mg, yield is 58 % (73 mg). **IR (ATR)** ṽ (cm^{-1}): 1685, 1515, 1417, 1364, 1264, 1125, 1084, and 730. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.40 (s, 1 H), 8.00 (dd, *J* = 6.8, 2 Hz, 1 H), 7.88 – 7.83 (m, 1 H), 7.76 (s, 1 H), 7.54 (m, 2 H), 7.34 – 7.19 (m, 5 H), 5.14 (t, *J* = 5.8 Hz, 1 H), 4.97 (d, *J* = 15.4 Hz, 1 H), 4.63 (d, *J* = 15.4 Hz, 1 H), 2.98 (dd, *J* = 17.8, 5.4 Hz, 1 H), 2.74 (dd, *J* = 17.8, 6.8 Hz, 1 H), 1.94 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.8, 168.4, 140.6, 137.1, 135.3, 133.1, 129.5, 128.8, 128.2, 128.0, 127.8, 127.6, 126.6, 124.3, 121.6, 55.5, 47.4, 45.0, 30.5. **HRMS (ESI):** calc. for [($C_{22}H_{19}NO_2$)H] (M+H) 330.1494, measured 330.1496.

5-Benzyl-6-(2-oxopropyl)-5,6-dihydro-4H-thieno[2,3-c]pyrrol-4-one (3wa).



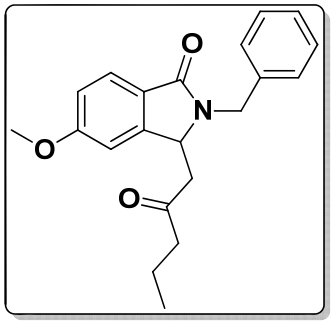
White semisolid; eluent (35% ethyl acetate in hexanes) 1w was taken in 100 mg; yield is 60 % (79 mg). **IR (ATR)** ṽ (cm^{-1}): 1681, 1532, 1516, 1397, 1362, 1265, 908 and 730. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.58 (d, *J* = 4.8 Hz, 1 H), 7.31 – 7.27 (m, 2 H), 7.25 – 7.22 (m, 3 H), 6.91 (d, *J* = 4.8 Hz, 1 H), 4.94 (d, *J* = 15.6 Hz, 1 H), 4.80 (dd, *J* = 8.4, 5.2 Hz, 1 H), 4.43 (d, *J* = 15.6 Hz, 1 H), 2.95 (dd, *J* = 17.8, 5.2 Hz, 1 H), 2.54 (dd, *J* = 17.8, 8.4 Hz, 1 H), 1.98 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.5, 164.5, 155.6, 137.3, 135.1, 134.9, 128.8, 127.8, 127.6, 121.7, 54.8, 45.7, 45.1, 30.4. **HRMS (ESI):** calc. for [($C_{16}H_{15}NO_2S$)H] (M+H) 286.0902, measured 286.0898.

2-Benzyl-5-methoxy-3-(2-oxobutyl) isoindolin-1-one (3ab).



White solid; eluent (35% ethyl acetate in hexanes) **1a** was taken in 100 mg; yield is 67% (90 mg). **IR (ATR)** ṽ (cm^{-1}): 1676, 1613, 1489, 1405, 1281, 1107, 1027, and 699. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.78 (d, *J* = 8.4 Hz, 1 H), 7.29 – 7.24 (m, 2 H), 7.22 – 7.19 (m, 3 H), 6.96 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.79 (d, *J* = 2.2 Hz, 1 H), 4.96 (t, *J* = 6.2 Hz, 1 H), 4.81 (d, *J* = 15.4 Hz, 1 H), 4.56 (d, *J* = 15.4 Hz, 1 H), 3.81 (s, 3 H), 2.82 (dd, *J* = 17.6, 6.0 Hz, 1 H), 2.60 (dd, *J* = 17.6, 6.4 Hz, 1 H), 2.20 (dq, *J* = 18, 7.2 Hz, 1 H), 1.97 (dq, *J* = 18.0, 7.2 Hz, 1 H), 0.94 (t, *J* = 7.2 Hz, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 208.4, 168.5, 163.0, 148.0, 137.5, 128.7, 127.9, 127.5, 125.3, 124.3, 114.9, 107.5, 55.7, 55.5, 45.8, 44.8, 36.4, 7.5. **HRMS (ESI):** calc. for [($C_{20}H_{21}NO_3$)H] (M+H) 324.1600, measured 324.1598.

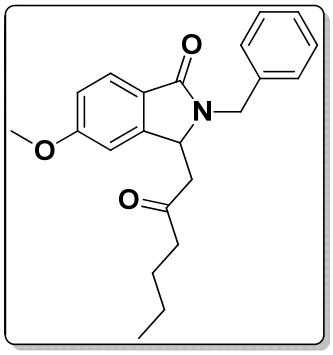
2-Benzyl-5-methoxy-3-(2-oxopentyl) isoindolin-1-one (3ac).



White solid; eluent (30% ethyl acetate in hexanes) **1a** was taken in 100 mg; yield is 65% (91 mg). **IR (ATR)** ṽ (cm^{-1}): 1676, 1612, 1488, 1403, 1252, 1184, 1027, and 735. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.77 (d, *J* = 8.4 Hz, 1 H), 7.29 – 7.24 (m, 2 H), 7.23 – 7.17 (m, 3 H), 6.96 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.79 (d, *J* = 2.2 Hz, 1 H), 4.95 (t, *J* = 6.2 Hz, 1 H), 4.84 (d, *J* = 15.4 Hz, 1 H), 4.53 (d, *J* = 15.4 Hz, 1 H), 3.80 (s, 3 H), 2.83 (dd, *J* = 17.6, 5.8 Hz, 1 H), 2.59 (dd, *J* = 17.6, 6.6 Hz, 1 H), 2.16 (dd, *J* = 17.0, 6.6 Hz, 1 H), 1.96 (dd, *J* = 17.2, 6.6 Hz, 1 H), 1.54 – 1.43 (m, 2 H), 0.82 (t, *J* = 7.4 Hz, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 206.9, 167.3, 161.8, 146.8, 136.3, 127.5, 126.7, 126.3, 124.1, 123.1,

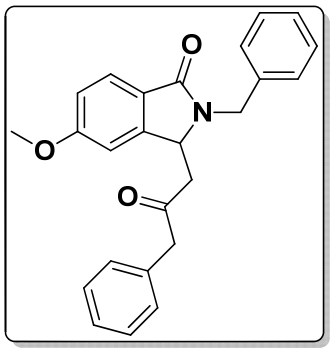
113.8, 106.3, 54.5, 54.2, 44.9, 43.9, 43.6, 15.7, 12.4. **HRMS (ESI):** calc. for $[(C_{21}H_{23}NO_3)H]$ (M+H) 338.1756, measured 338.1754.

2-Benzyl-5-methoxy-3-(2-oxohexyl) isoindolin-1-one (3ad).



White solid; eluent (30 % ethyl acetate in hexanes) 1a was taken in 100 mg, yield is 62 % (90 mg). **IR (ATR)** ṽ (cm^{-1}): 1683, 1615, 1494, 1408, 1262, 1180, 1084, and 730. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.78 (d, *J* = 8.4 Hz, 1 H), 7.29 – 7.25 (m, 2 H), 7.24 – 7.20 (m, 3 H), 6.97 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.80 (d, *J* = 2.2 Hz, 1 H), 4.95 (t, *J* = 6.2 Hz, 1 H), 4.85 (d, *J* = 15.4 Hz, 1 H), 4.54 (d, *J* = 15.4 Hz, 1 H), 3.81 (s, 3 H), 2.83 (dd, *J* = 17.6, 5.8 Hz, 1 H), 2.60 (dd, *J* = 17.6, 6.6 Hz, 1 H), 2.18 (dd, *J* = 17.0, 6.6 Hz, 1 H), 1.99 (dd, *J* = 17.0, 6.6 Hz, 1 H), 1.48 – 1.39 (m, 2 H), 1.25 (d, *J* = 7.4 Hz, 1 H), 1.19 (d, *J* = 7.6 Hz, 1 H), 0.84 (t, *J* = 7.2 Hz, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 208.2, 168.5, 163.0, 148.0, 137.5, 128.7, 127.9, 127.5, 125.3, 124.3, 114.9, 107.5, 55.7, 55.4, 46.1, 44.8, 43.0, 25.5, 22.2, 13.8. **HRMS (ESI):** calc. for $[(C_{22}H_{25}NO_3)H]$ (M+H) 352.1913, measured 352.1920.

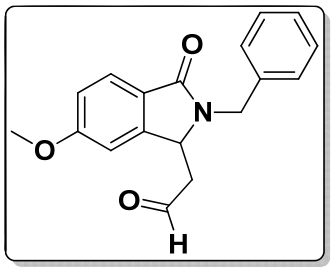
2-Benzyl-5-methoxy-3-(2-oxo-3-phenylpropyl)isoindolin-1-one (3ae).



Colorless semisolid; eluent (35% ethyl acetate in hexanes), **1a** was taken in 100 mg; yield is 65 % (104 mg). **IR (ATR)** ṽ (cm^{-1}): 1683, 1614, 1495, 1451, 1406, 1255, 1045, and 700. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.76 (d, *J* = 8.4 Hz, 1 H), 7.31 – 7.23 (m, 6 H), 7.18

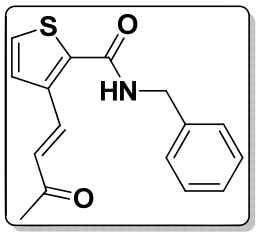
– 7.16 (m, 2 H), 7.06 – 7.04 (m, 2 H), 6.95 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.73 (d, *J* = 2 Hz, 1 H), 4.89 (t, *J* = 6 Hz, 1.0 H), 4.82 (d, *J* = 15.4 Hz, 1 H), 4.44 (d, *J* = 15.4 Hz, 1 H), 3.78 (s, 3 H), 3.39 (s, 2 H), 2.90 (dd, *J* = 18, 5.6 Hz, 1 H), 2.63 (dd, *J* = 18, 6.4 Hz, 1 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 205.5, 168.5, 163.0, 147.8, 137.4, 133.3, 129.4, 128.9, 128.8, 127.9, 127.5, 127.4, 125.3, 124.3, 115.0, 107.5, 55.7, 55.3, 50.4, 45.3, 44.7. **HRMS (ESI):** calc. for [($C_{25}H_{23}NO_3$)H] (M+H) 386.1756, measured 386.1765.

2-(2-Benzyl-6-methoxy-3-oxoisoindolin-1-yl) acetaldehyde (3af).



Colorless semisolid; eluent (35% ethyl acetate in hexanes), **1a** was taken in 100 mg; yield is 60% (73 mg). **IR (ATR)** ṽ (cm^{-1}): 1678, 1614, 1531, 1494, 1257, 1220, 1029 and 735. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.54 (t, *J* = 1.2 Hz, 1 H), 7.80 (d, *J* = 8.4 Hz, 1 H), 7.32 – 7.28 (m, 4 H), 7.23 (s, 1 H), 7.00 (dd, *J* = 8.4, 2.2 Hz, 1 H), 6.85 (d, *J* = 2.2 Hz, 1 H), 5.11 (d, *J* = 15.4 Hz, 1 H), 4.85 – 4.76 (m, 1 H), 4.36 (d, *J* = 15.4 Hz, 1 H), 3.83 (s, 3 H), 2.94 (dd, *J* = 17.8, 4.6 Hz, 1 H), 2.77 (dd, *J* = 17.8, 6.4, 1 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 199.1, 168.4, 163.2, 147.0, 136.9, 128.9, 128.0, 127.8, 125.5, 124.3, 115.2, 107.7, 55.7, 54.2, 45.9, 44.5. **HRMS (ESI):** calc. for [($C_{18}H_{17}NO_3$)H] (M+H) 296.1287, measured 296.1290.

(*E*)-*N*-Benzyl-3-(3-oxobut-1-en-1-yl)thiophene-2-carboxamide (8).



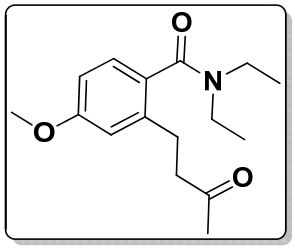
White semisolid; eluent (35% ethyl acetate in hexanes), **1w** was taken in 100 mg; yield is 47 % (62 mg). **IR (ATR)** ṽ (cm^{-1}): 1648, 1530, 1425, 1262 and 730. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.30 (d, *J* = 16.6 Hz, 1 H), 7.40 – 7.25 (m, 7 H), 6.49 (d, *J* = 16.6 Hz, 1 H), 6.35 (s, 1 H), 4.60 (d, *J* = 5.6 Hz, 2 H), 2.35 (s, 3 H). **^{13}C NMR (50 MHz, $CDCl_3$):** δ

199.6, 161.9, 139.9, 137.6, 136.2, 135.4, 130.4, 128.9, 127.8, 127.8, 127.1, 126.9, 44.2, 26.5. **HRMS (ESI):** calc. for [($C_{16}H_{15}NO_2S$)H] (M+H) 286.0902, measured 286.0887.

Procedure for the Reaction of *N*-*N*-diethyl benzamide 14 with 2a.

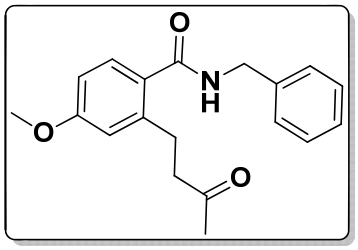
A 15-mL pressure tube with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.20 eq) and $AgSbF_6$ (20 mol %) was evacuated and purged with nitrogen gas three times ($AgSbF_6$ was taken inside the glove box). To the tube were then added $ClCH_2CH_2Cl$ (3.0 mL), amide **14** or **1a** (100 mg, 1.0 equiv), acetic acid (2.0 equiv) and allyl alcohol **2** (2.2 equiv) via syringe after that 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 and the reaction mixture stirred in room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 110 °C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and the filtrate was concentrated. The crude residue was purified through a very short silica gel column using hexanes and ethyl acetate as eluent.

***N,N*-Diethyl-4-methoxy-2-(3-oxobutyl)benzamide (16).**



Yellow liquid: eluent (35% ethyl acetate in hexanes), **14** was taken in 100 mg, combined yield is 69% (920mg). **IR (ATR)** ṽ (cm^{-1}): 1712, 1611, 1463, 1430, 1243, 1088, 905 and 819. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.04 (d, *J* = 9.0 Hz, 1 H), 6.74 – 6.68 (m, 2 H), 3.75 (s, 3 H), 3.56 (s, 2 H), 3.15 – 3.04 (m, 2 H), 2.73 (s, 4 H), 2.07 (s, 3 H), 1.18 (t, *J* = 7.8 Hz, 3 H), 0.99 (t, *J* = 7.0 Hz, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 207.9, 170.6, 159.8, 139.3, 129.4, 127.1, 115.1, 111.5, 55.3, 45.1, 43.0, 38.9, 29.9, 27.5, 14.1, 12.8. **HRMS (ESI):** calc. for [($C_{16}H_{23}NO_3$)H] (M+H) 278.1756, measured 278.1758.

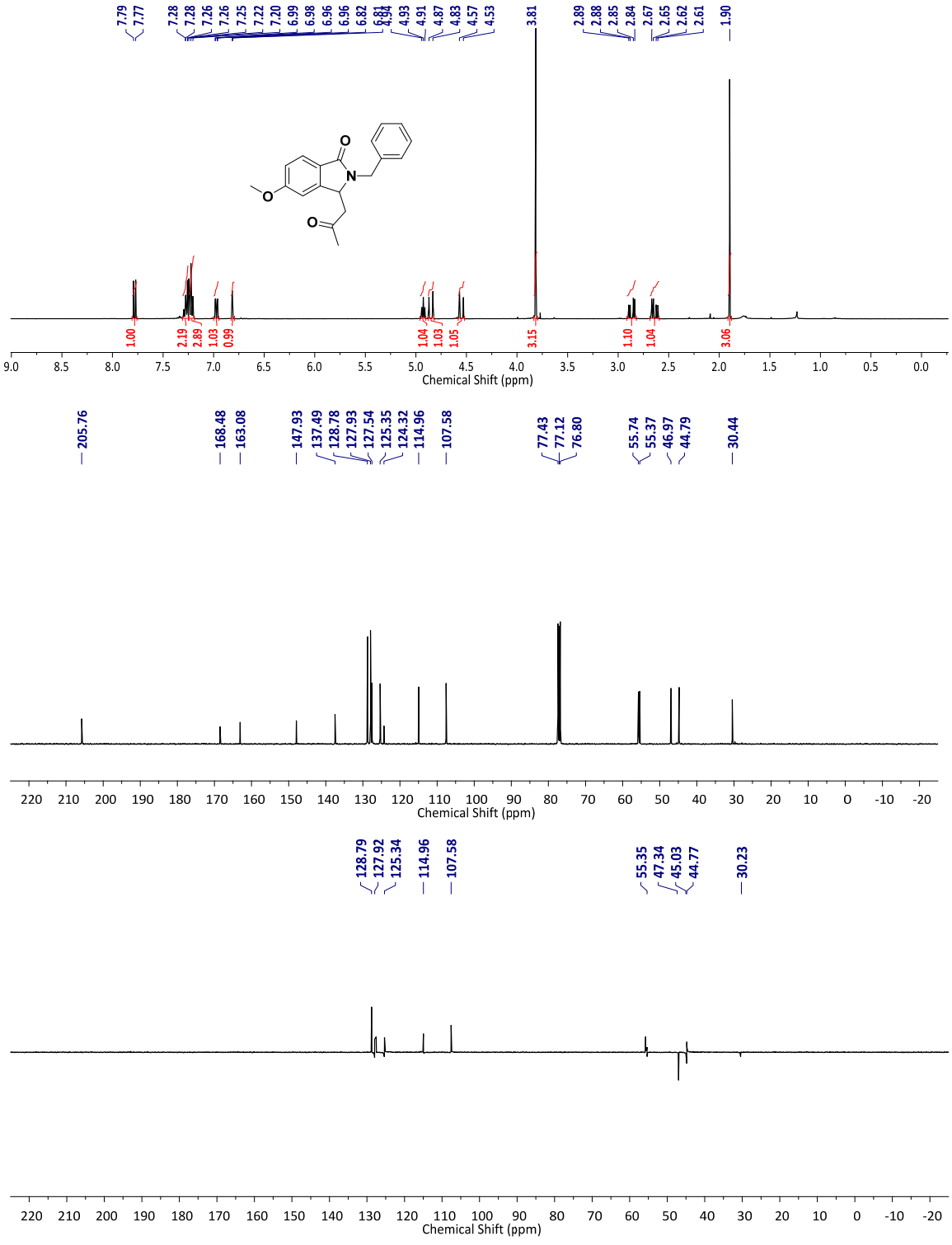
***N*-Benzyl-4-methoxy-2-(3-oxobutyl)benzamide (18).**



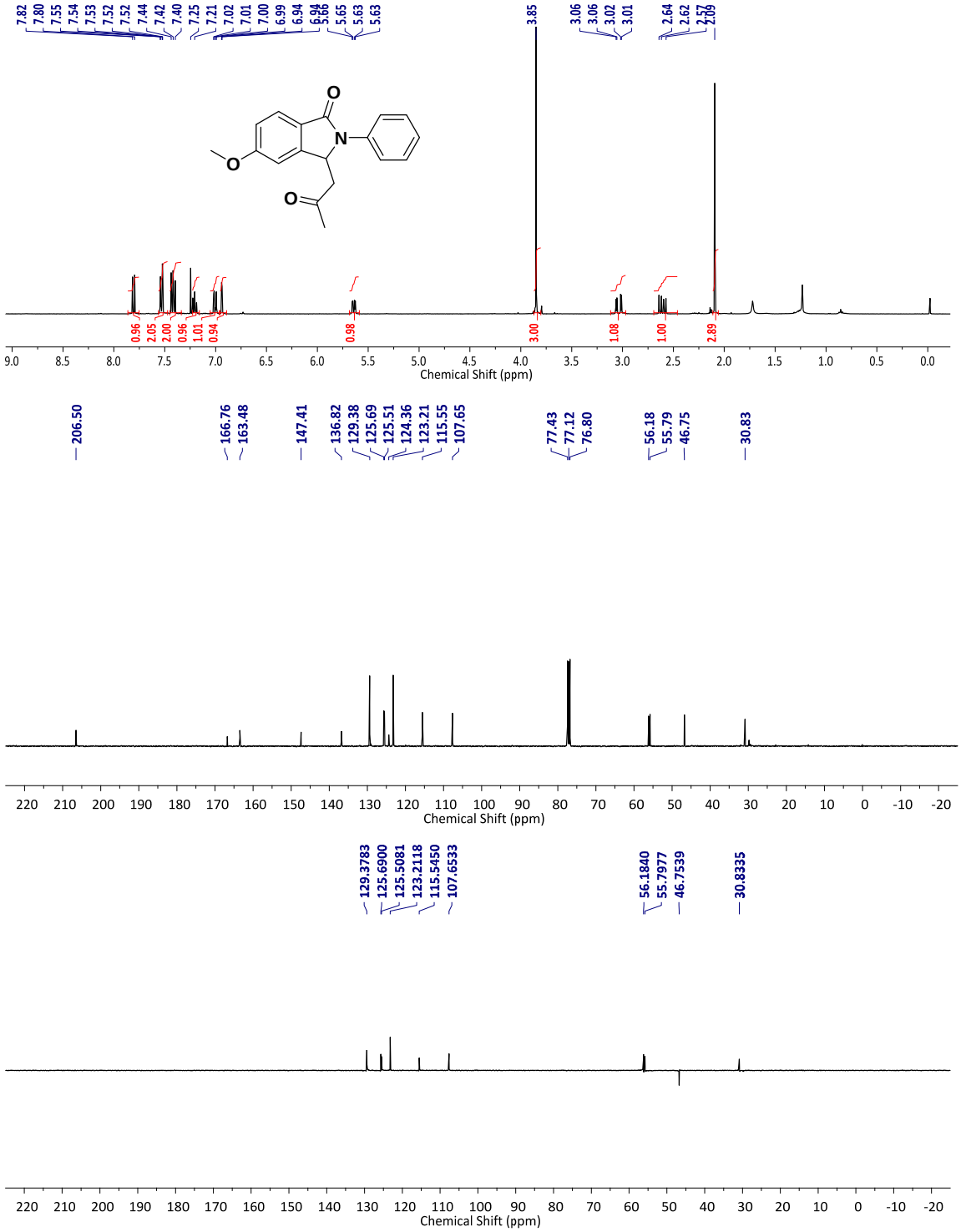
White solid: eluent (35% ethyl acetate in hexanes), **1a** was taken in 100 mg, yield is 69 % (89 mg). **IR (ATR)** ṽ (cm^{-1}): 1705, 1627, 1419, 1306, 1247, 1166, 1054 and 735. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 – 7.31 (m, 5 H), 7.30 – 7.25 (m, 1 H), 6.73 (d, *J* = 2.4 Hz, 1 H), 6.69 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.55 (s, 1 H), 4.57 (d, *J* = 5.8 Hz, 2 H), 3.77 (s, 3 H), 2.98 (t, *J* = 7.2 Hz, 2 H), 2.84 (t, *J* = 7.2 Hz, 2 H), 2.08 (s, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 208.6, 169.5, 160.9, 141.9, 138.4, 129.0, 128.8, 128.7, 127.9, 127.6, 115.7, 111.4, 55.4, 45.4, 44.0, 30.0, 27.8. **HRMS (ESI):** calc. for [($C_{19}H_{21}NO_3$)H] (M+H) 312.1600, measured 312.1594.

2A.7: Spectral Copies of Selected Compounds

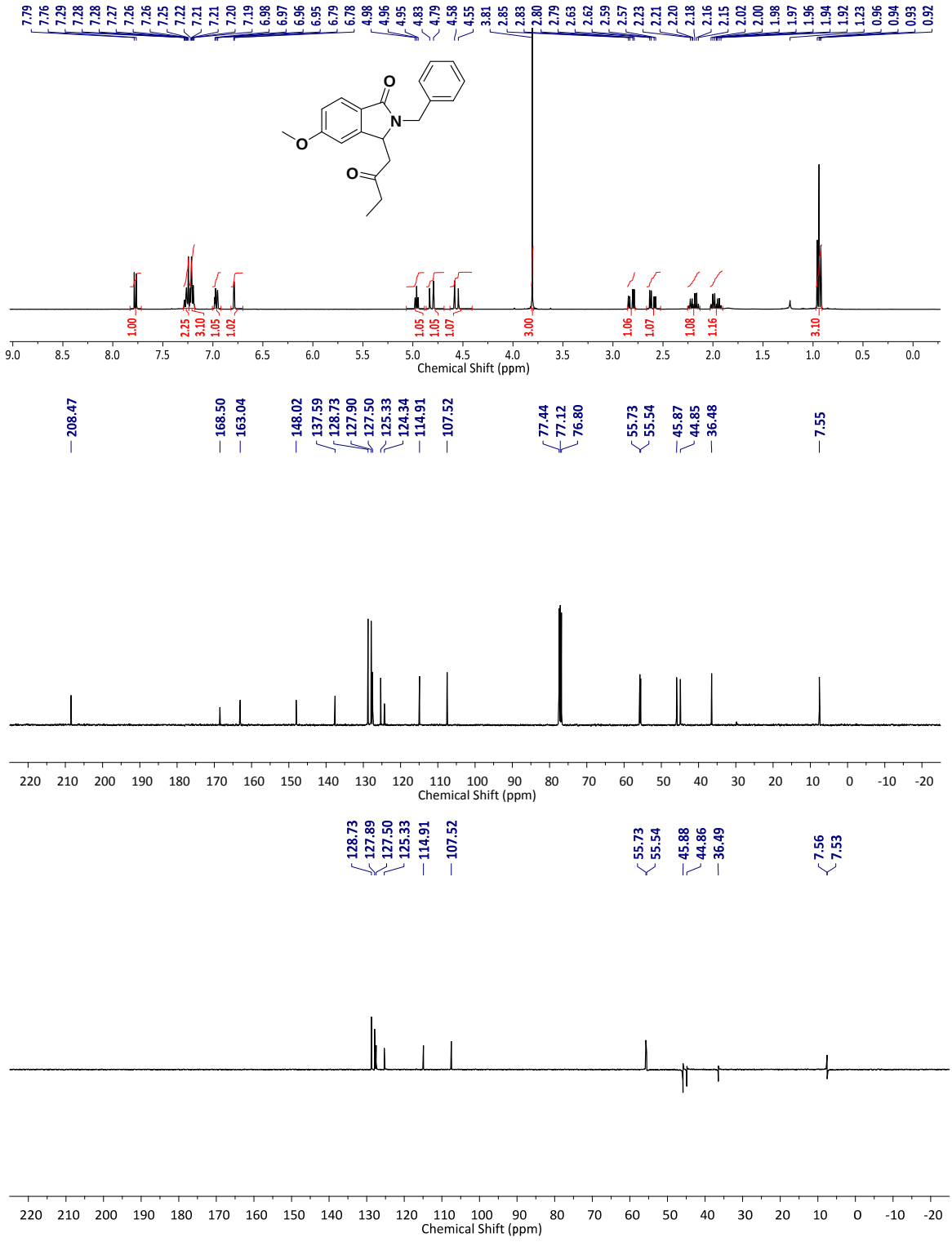
^{1}H and ^{13}C NMR Spectra of compound **3aa.**



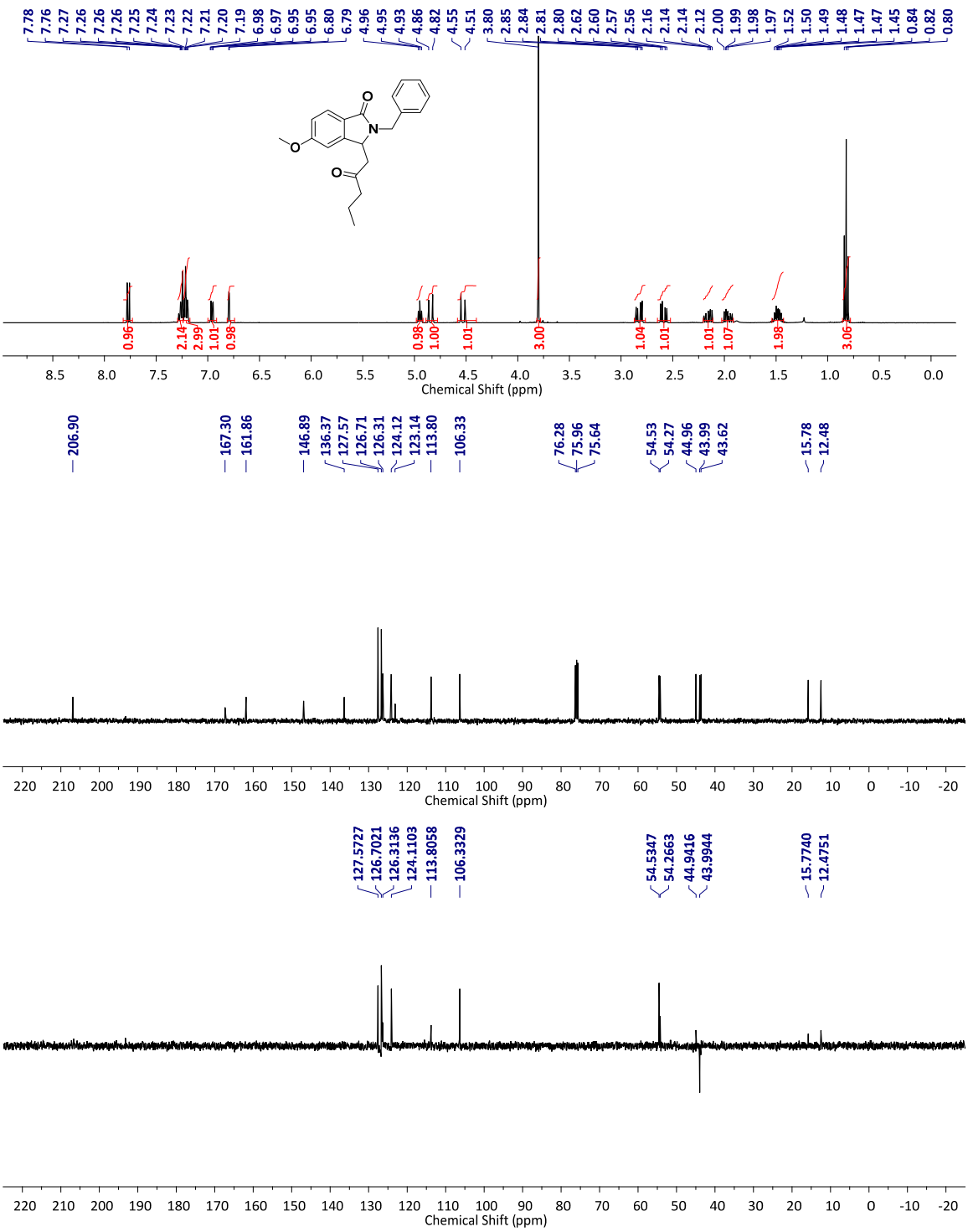
^{1}H and ^{13}C NMR Spectra of compound **3ba.**



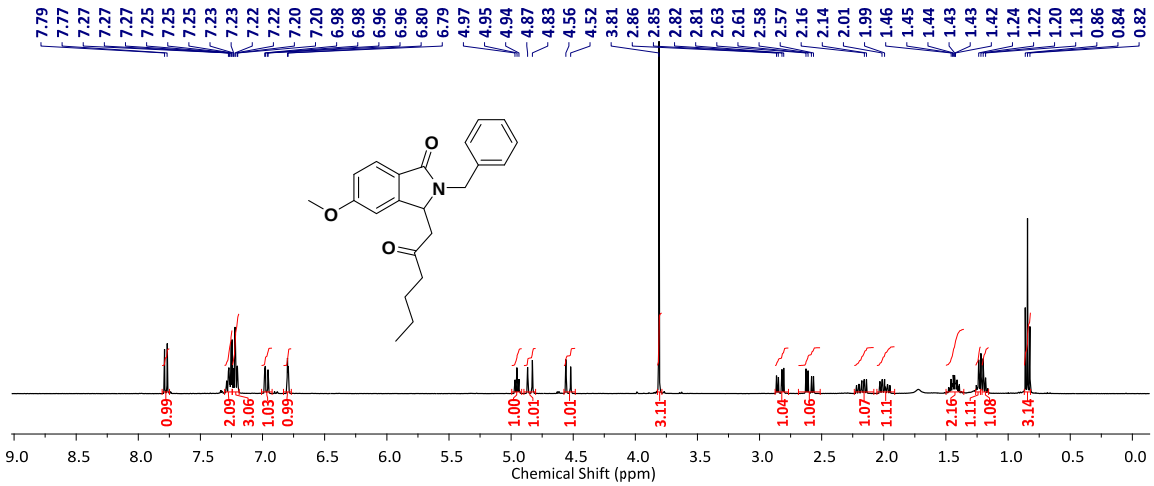
^{1}H and ^{13}C NMR Spectra of compound **3ab.**

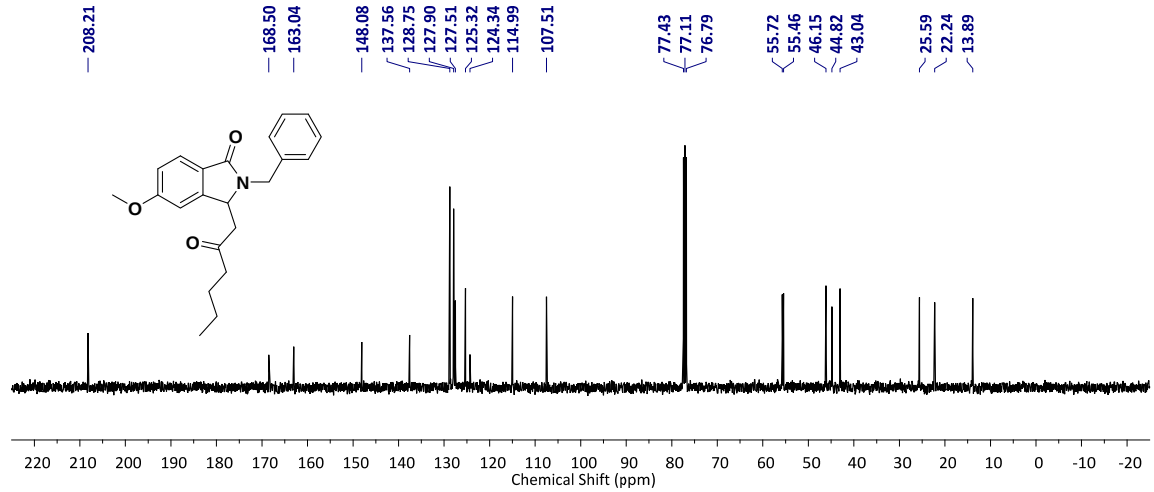


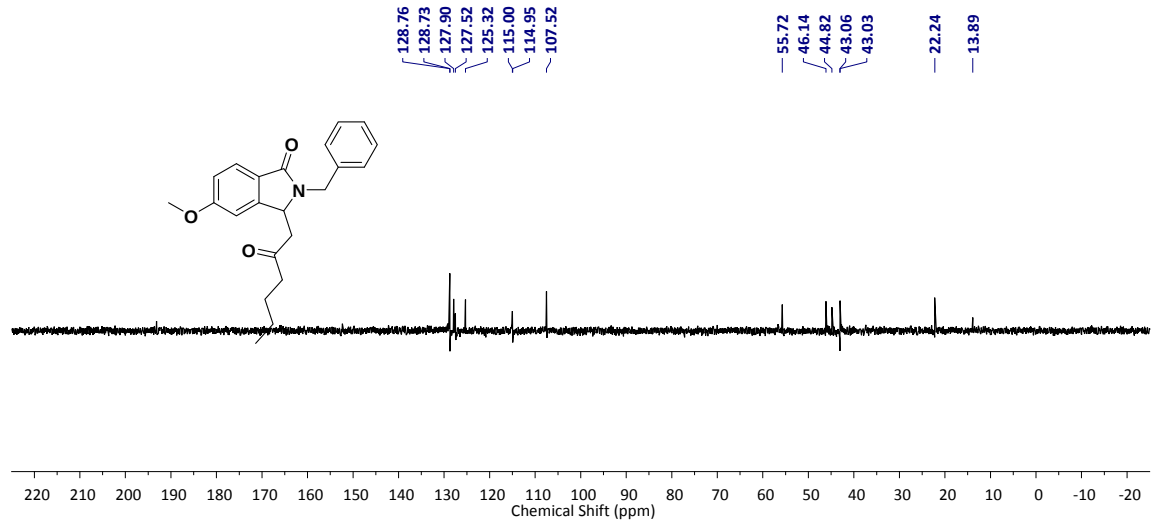
^{1}H and ^{13}C NMR Spectra of compound **3ac.**



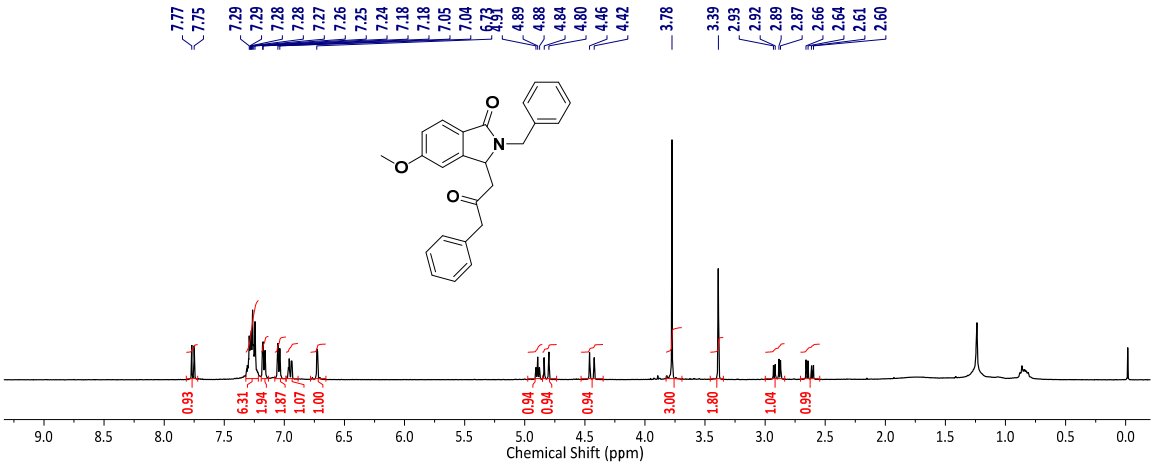
^{1}H and ^{13}C NMR Spectra of compound **3ad.**

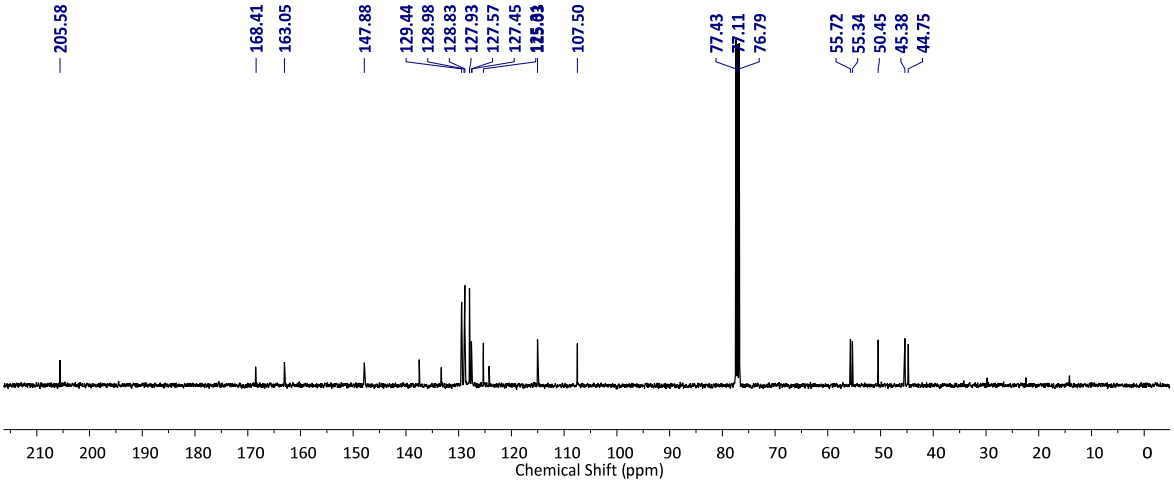


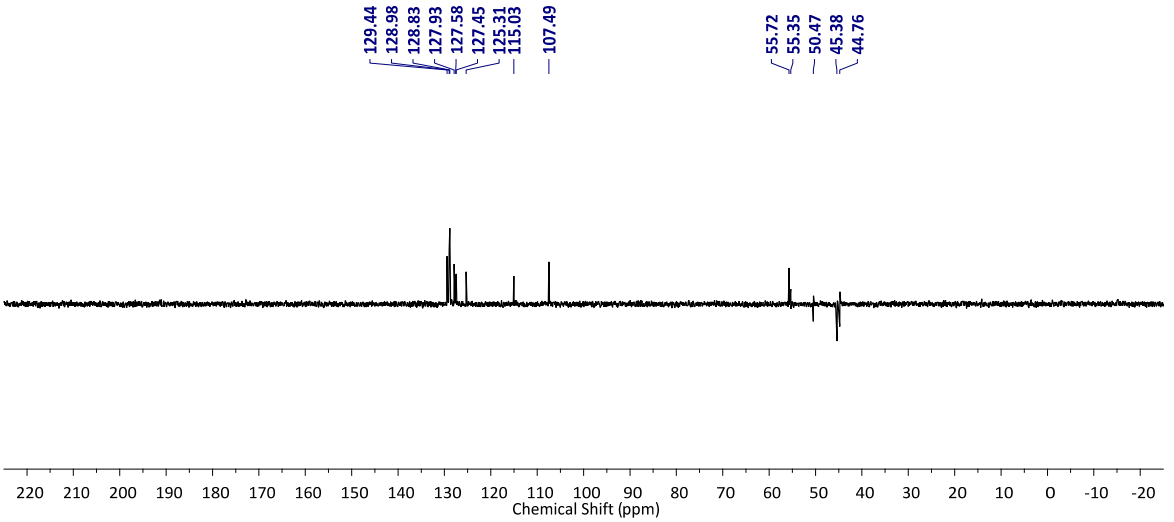




^{1}H and ^{13}C NMR Spectra of compound **3ae.**





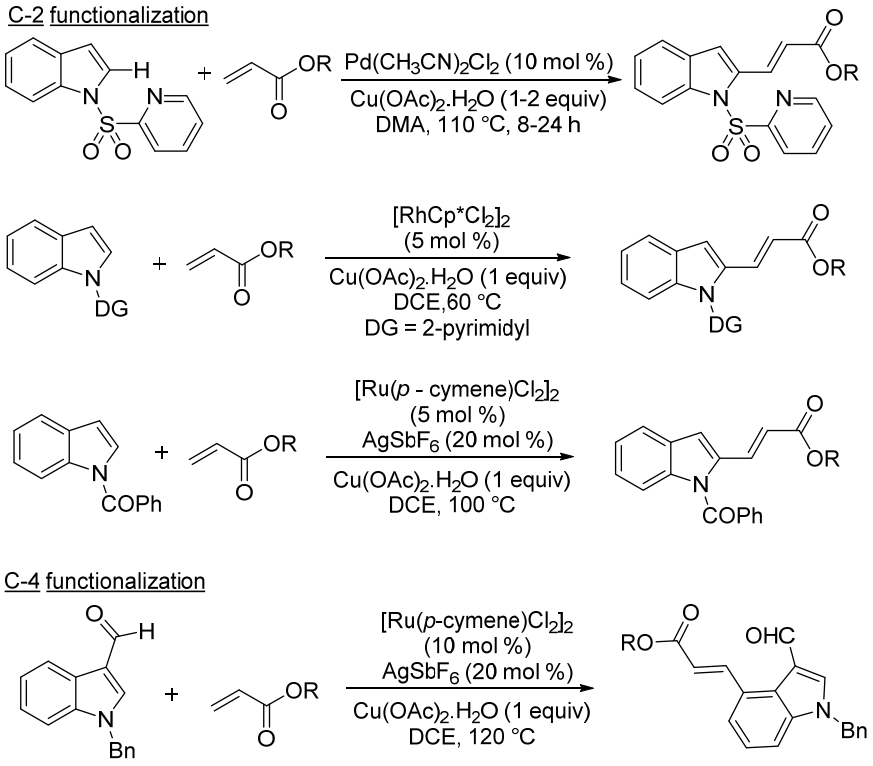


Section 2B: Ruthenium-catalyzed cyclization of *N*-carbamoyl indolines with alkynes: an efficient route to pyrroloquinolinones

2B.1 Introduction

The pyrroloquinoline unit is present in various agrochemicals, drug molecules, natural products and materials.[1] Pyrroloquinoline derivatives show potent biological activities towards asthma, obesity, anti-acetylcholinesterase, melatoninergic and epilepsy.[2] In addition, pyrroloquinoline derivative can also be used as a key intermediate for synthesizing various biologically active molecules and natural products.[3] Due to the rising importance of pyrroloquinoline molecules in medicinal and material chemistry, the synthesis of pyrroloquinoline framework has gained considerable attention in organic synthesis for the past three decades.[4] Traditionally, pyrroloquinoline derivatives are prepared by Fischer indole cyclization,[2a-c] a free radical cyclization,[4a] sigmatropic rearrangement,[4b-c] and Michael-type cyclization.[4d] In addition, pyrroloquinoline derivatives can also be prepared by using metal catalysts.[5] However, these methods suffers several drawbacks such as a limited number of substrates scope, a number of steps is needed, poor regioselectivity and requirement of prefunctionalized substrates for the reaction.

Transition metal-catalyzed oxidative cyclization of heteroatom substituted aromatics with carbon-carbon π-components is one of the powerful methods for synthesizing heterocyclic molecules in one pot without having any pre-functionalized substrates. [6-7] This method provides a step and atom economical route to synthesize various heterocyclic molecules from the readily available starting materials. Meanwhile, due to the high abundance of nitrogen containing heterocyclic moieties in natural products and biologically active molecules, the C−H bond functionalization of *N*-heterocycles has gained much attention in organic synthesis. Particularly, C−H bond functionalization of indole derivatives is highly focused. By employing a suitable directing group on the indole nitrogen atom, C2-H of indole can be functionalized selectively. Subsequently, by having a directing group at C3 position of indole, C4-H or C2-H can be activated (Scheme 2B.1).[8]



Scheme 2B.1: C-2 and C-4 Functionalization of indoles

However, the direct C−H bond activation at C7-H of indole skeleton is very challenging task. But, this type of C−H bond functionalization can be indirectly achieved by the C−H bond activation at C7-H of indoline moiety which having a directing group such as acetyl (COR), carbamoyl ($CONR_2$) or pyridyl on the nitrogen atom in the presence of metal catalysts. Later, indoline moiety can be converted easily into indole moiety by using the suitable oxidizing agent.

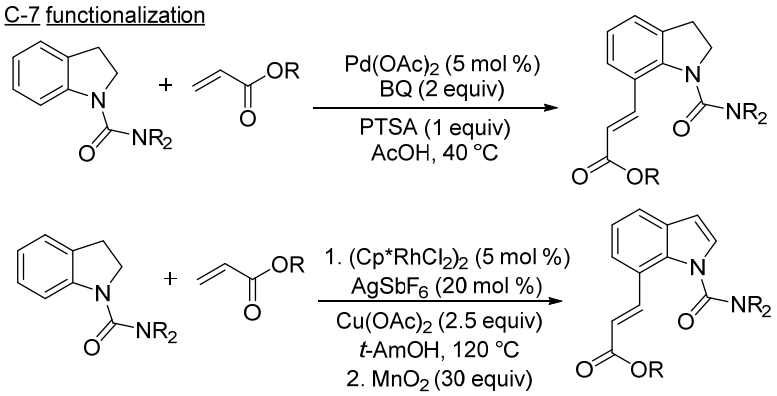
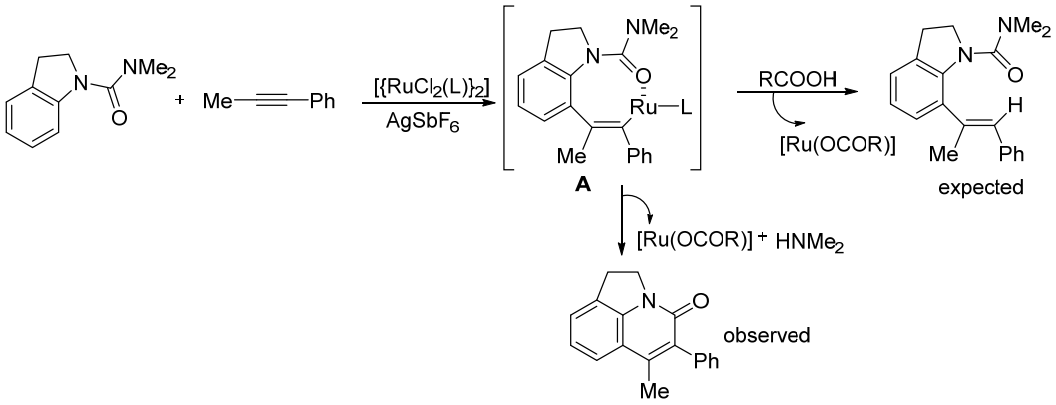


Figure 2B.2: C-4 Functionalization of indoles

By employing this protocol, various functionalizations such as arylation, alkenylation, alkylation, acylation and amination were done at C-7 position of indoline moiety (Scheme 2B.2).[9]

Recently, we have reported the hydroarylation of substituted aromatics with alkynes in the presence of a less expensive ruthenium catalyst and carboxylic acid, providing trisubstituted alkenes in a highly regio- and stereoselective manner. Our continuous interest in a ruthenium-catalyzed hydroarylation and oxidative cyclization reaction prompted us to explore the possibility of hydroarylation at C7-H of *N*-carbamoyl indolines with alkynes.[10] Herein, we wish to report a convenient route to synthesize pyrroloquinolinone derivatives via a ruthenium-catalyzed base free oxidative cyclization of *N*-carbamoyl indolines with alkynes. In the reaction, we have expected the *ortho* alkenylation of *N*-carbamoyl indolines with alkynes in the presence of ruthenium catalyst and carboxylic acid (Scheme 2B.3).

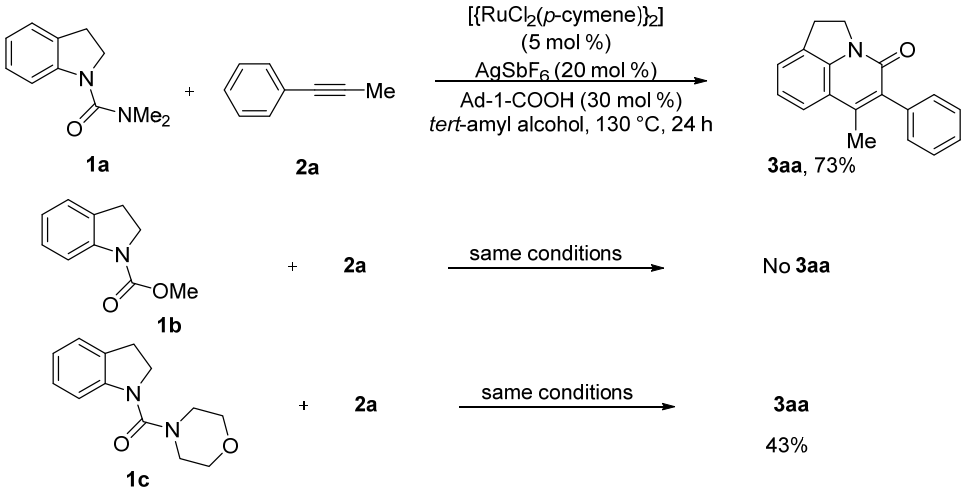


Scheme 2B.3: Observed cyclization of N-carbamoyl indoline with alkyne

However, we observed an unexpected pyrroloquinolinone derivative via an intramolecular nucleophilic addition of C-Ru bond into carbamoyl group of intermediate **A**. Generally, a metal acetate base is used to activate the C−H bond of organic moieties. In the reaction, a catalytic amount of carboxylic acid, 1-adamantanecarboxylic acid (Ad-1-COOH), was used. The role of Ad-1-COOH is unique in the reaction, as it plays a role of proton source as well as base for activating the C7-H bond of indoline moiety. The cyclization reaction was compatible with various hydrocarbon containing alkynes as well as functional group such as ester containing alkynes. The cyclization reaction was also compatible with various functional group substituted indolines. The cyclization

reaction is highly regioselective particularly with unsymmetrical alkynes and the coordinating groups such as aryl or ester substituent on the alkyne moiety prefers to stay adjacent to the carbonyl group of quinolinone derivative. Later, pyrroloquinolinone derivatives were aromatized into indole derivatives in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

2B.2 Results and Discussion



Scheme 2B.4: Cyclization of *N*-Carbamoyl Indolines (**1a-c**)

When *N*-carbamoyl indoline (**1a)** was treated with unsymmetrical alkyne, 1-phenyl-1-propyne (**2a)**, in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), $AgSbF_6$ (20 mol %) and Ad-1-COOH (30 mol %) in *tert*-amyl alcohol at 130 °C for 24 h, pyrroloquinolinone derivative **3aa** was observed in 73% isolated yield in a highly regioselective manner (Scheme 2B.4). In the product **3aa**, methyl substituted carbon of alkyne **2a** was connected at C7 position of **1a** and phenyl ring substituted carbon of **2a** was connected adjacent to the carbonyl group of **3aa**. The structure and regiochemistry of compound **3aa** was confirmed by a single crystal X-ray analysis (Figure 2B.1).

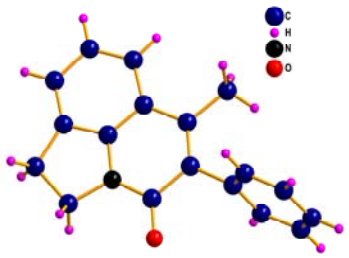
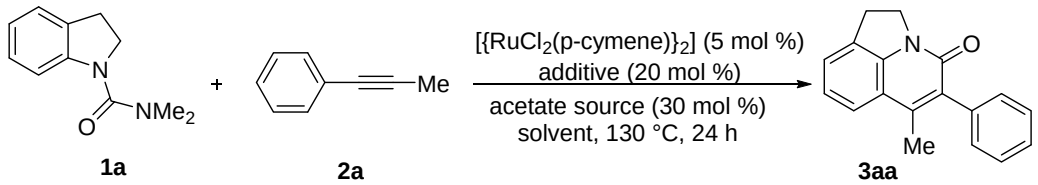


Figure 2B.1 Crystal structure of compound **3aa**

2B.2.1 Optimization Studies

The cyclization reaction was examined with various carboxylic acid sources such as acetic acid (10.0 equiv), pivalic acid (5.0 equiv), mesitoic acid(30 mol %), CF_3COOH (5.0 equiv) and Ad-1-COOH (30 mol %). Pivalic acid and mesitoic acidwere partially effective, providing **3aa** in 51% and 47% GC yields (*n*-docane was used as an internal standard), respectively (Table 2B.1, entries 1 and 2). Ad-1-COOH was superior for the reaction, yielding **3aa** in 79% GC yield (entry 3). Other carboxylic acids were not effective. The cyclization reaction was examined with various metal acetate sources (1.0 equiv) such as AgOAc, CsOAc, LiOAc, NaOAc, Ag_2CO_3, $Cu(OAc)_2{\cdot}H_2O$ and CsOPiv instead of carboxylic acid. AgOAc, $Cu(OAc)_2{\cdot}H_2O$ and NaOAc were less effective, producing product **3aa** in 29%, 37% and 25% GC yields, respectively (entries 4-6). Remaining salts were not effective. This result clearly revealed that the Ad-1-COOH was the best acetate source for the reaction (entry 3). The cyclization reaction was also examined with various solvents such as THF, DCE, CH_3CN, *iso*-PrOH, DMSO, DMF, *tert*-amyl alcohol, 1,2-dimethoxy ethane and toluene under similar reaction conditions. Among them, *tert*-amyl alcohol was very effective, providing **3aa** in 79% GC yield (entry 3). DCE was partially effective, giving **3aa** in 58% GC yield (entry 7). THF, *iso*-PrOH and 1,2-dimethoxyethane were less effective, affording product **3aa** in 15%, 20% and 32% GC yields, respectively (entries 8-10). Remaining solvents were not effective. The reaction was also tested with additives such as $AgSbF_6$, $AgBF_4$, AgOTf and KPF_6. Among them, $AgSbF_6$ was very effective, giving product **3aa** in 79% GC yield (entries 3). $AgBF_4$ was partially effective, yielding **3aa** in 41% GC yield (entry 11). AgOTf and KPF_6 were not suitable for the reaction (entries 12 and 13). The reaction temperature 130 °C was also crucial to get the better yield of product **3aa**. Product **3aa** was observed only in 45% yield at reaction temperature 110 °C (entry 14). Under the optimized reaction conditions, the cyclization reaction was tested with other *N*-substituted indolines **1b-c** with **2a** (Scheme 2B.4). In the substrate **1c**, product **3aa** was observed only in 43% yield. In the substrate **1b**, no product **3aa** was observed. No cyclization product **3aa** was observed in the blank reaction such as without $AgSbF_6$, $[\{RuCl_2(p\text{-cymene})\}_2]$ catalyst and Ad-1-COOH. This optimization studies clearly revealed that $[\{RuCl_2(p\text{-cymene})\}_2]$ (5.0 mol %), $AgSbF_6$ (20 mol %) and Ad-1-COOH (30 mol %) in *tert*-amyl alcohol at 130 °C is the best conditions for the cyclization reaction.

Table 2B.1 Optimization studies[a]



Entry	Solvent	Acetate source	Additive	Yield (%)[b]
1	*tert*-amyl alcohol	pivalic acid	$AgSbF_6$	51
2	*tert*-amyl alcohol	mesitylenic acid	$AgSbF_6$	47
3	*tert*-amyl alcohol	Ad-1-COOH	$AgSbF_6$	79
4	*tert*-amyl alcohol	AgOAc	$AgSbF_6$	29
5	*tert*-amyl alcohol	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	37
6	*tert*-amyl alcohol	NaOAc	$AgSbF_6$	25
7	1,2-dicholoroethane	Ad-1-COOH	$AgSbF_6$	58
8	THF	Ad-1-COOH	$AgSbF_6$	15
9	*iso*-PrOH	Ad-1-COOH	$AgSbF_6$	20
10	1,2-dimethoxyethane	Ad-1-COOH	$AgSbF_6$	32
11	*tert*-amyl alcohol	Ad-1-COOH	$AgBF_4$	41
12	*tert*-amyl alcohol	Ad-1-COOH	AgOTf	-
13	*tert*-amyl alcohol	Ad-1-COOH	KPF_6	-
14	*tert*-amyl alcohol	Ad-1-COOH	$AgSbF_6$	45[c]

[a]All reactions were carried out using **1a** (100 mg), alkyne **2a** (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %), acetate source and solvent (3.0 mL) at 130 °C for 24 h. [b] GC yield (*n*-docane was used as an internal standard).[c] Reaction was done at 110 °C for 24 h.

2B.2.2 Scope of Alkynes

The scope of the cyclization reaction was examined with other unsymmetrical alkynes **2b-g** (Table 2B.2). Thus, 1-phenyl-1-butyne (**2b**), 1-phenyl-1-hexyne (**2c**) and 2-thienyl substituted alkyne **2d** reacted with **1a** under the optimized reaction conditions, yielding the corresponding cyclization products **3ab-ad** in 65%, 60% and 61% yields, respectively (entries 1-3). In these reactions, C7−H of **1a** was selectively inserted at the alkyl substituted carbon of alkynes **2b-d**. Encouraged by this result, we further examined with substituted propiolates such as ethyl 2-butynoate (**2e**), methyl hex-2-ynoate (**2f**), and methyl oct-2-ynoate (**2g**).

Interestingly, these alkynes also nicely participated in the reaction, yielding products **3ae-ag** in 56%, 53%, and 48% yields, respectively (entries 4-6). In these reactions also, the alkyl substituted carbon of alkynes **2e-g** was regioselectively connected at the carbon-7 position of **1a**. The structure and regiochemistry of compound **3af** was confirmed by a single crystal X-ray analysis (Figure 2B.2).

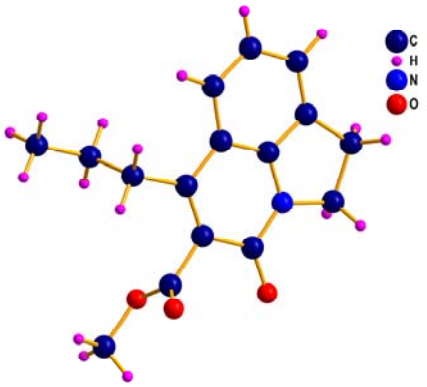
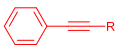
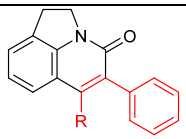
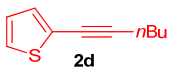
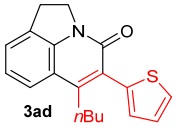
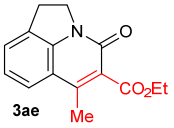
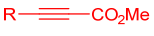
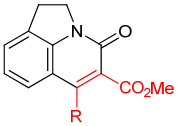
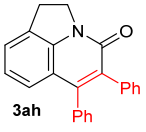
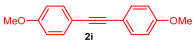
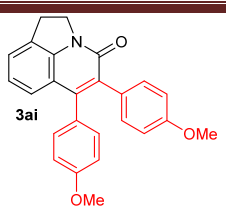
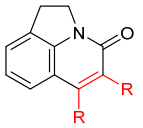
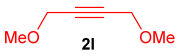
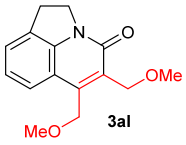


Figure 2B.2. Crystal structure of compound **3af**

Table 2B.2 Scope of alkynes **2b-l** [a]

Entry	Alkyne **2**	Product **3**	Yield (%)[b]
			
1	**2b**: R = Et	**3ab**: R = Et	65
2	**2c**: R = n-Bu	**3ac**: R = n-Bu	60
3			61
4			56
			
5	**2f**: R = n-Pr	**3af**: R = n-Pr	53
6	**2g**: R = n-Pentyl	**3ag**: R = n-Pentyl	48
7			67

8			68
			
9	**2j**: R = Me	**3aj**: R = Me	47
10	**2k**: R = Et	**3ak**: R = Et	61
11			65

[a]All reactions were carried out using **1a** (100 mg, 0.46 mmol), alkynes **2a-l** (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and Ad-1-COOH (30 mol %) in *tert*-amyl alcohol (3.0 mL) at 130 °C for 24 h. [b]Isolated yield.

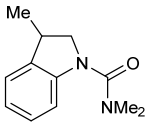
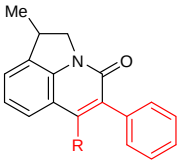
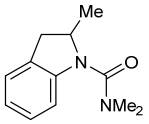
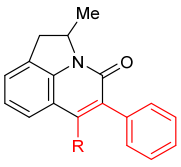
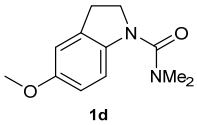
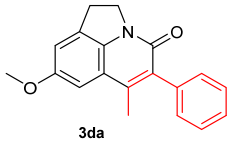
Next, the cyclization reaction was examined with symmetrical alkynes **2h-l**. Diphenylacetylene (**2h**) and 1,2-*bis*(4-methoxyphenyl)ethyne (**2i**) nicely reacted with **1a**, providing the corresponding cyclization products **3ah-ai** in 67% and 68% yields, respectively (entries 7 and 8). A less reactive aliphatic alkynes such as 2-butyne (**2j)** and 3-hexyne (**2k**) were also nicely involved in the reaction, affording products **3aj-ak** in 47% and 61% yields, respectively (entries 9 and 10). 1, 4-Dimethoxy-2-butyne (**2l**) also nicely reacted with **1a**, giving product **3al** in 65% yield (entry 11). Meanwhile, the cyclization reaction was also examined with terminal alkynes such as phenylacetylene and 1-butyne. However, terminal alkynes were not compatible for the reaction.

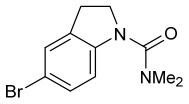
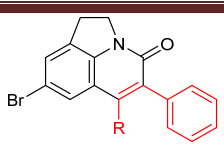
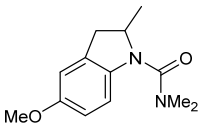
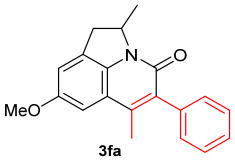
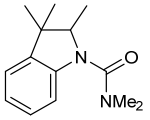
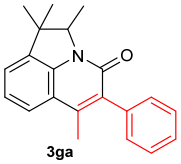
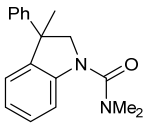
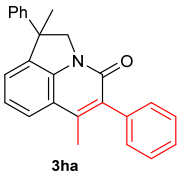
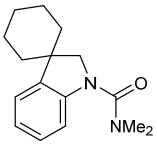
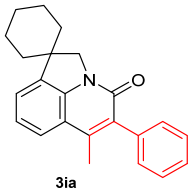
2B.2.3 Scope of substituted *N*-carbamoyl indolines

The cyclization reaction was further examined with substituted *N*-carbamoyl indolines **1b-i** (Table 2B.3). In the cyclization reaction, a less reactive 1-phenyl-1-propyne (**2a**) efficiently reacted with indoline derivatives, yielding the corresponding cyclization products in good yields compared with a highly reactive diphenylacetylene (**2h**). 3-Methyl *N*-carbamoyl indoline (**1b**) reacted with 1-

phenyl-1-propyne (**2a**) or diphenylacetylene (**2h**) under similar reaction conditions, affording the cyclization products **3ba** and **3bh** in 76% and 62% yields, respectively (entries 1 and 2). Similarly, 2-methyl *N*-carbamoyl indoline (**1c**) reacted with **2a** or **2h**, providing the cyclization products **3ca** and **3ch** in 57% and 55% yields, respectively (entries 3 and 4). The cyclization reaction was also compatible with OMe and Br substituted indolines **1d-f**. Thus, 5-methoxy (**1d**) and bromo (**1e**) substituted *N*-carbamoyl indolines reacted nicely with **2a** or **2h**, giving pyrroloquinolinones **3da-3eh** in 68%, 56% and 51% yields, respectively (entries 5-7). Similarly, 5-methoxy-2-methyl *N*-carbamoyl indoline (**1f**) provided the corresponding cyclic compound **3fa** in 63% yield (entry 8). Substituted indolines **1g-h** also efficiently reacted with **2a**, giving pyrroloquinolinones **3ga** and **3ha** in 73% and 47% yields, respectively (entries 9 and 10). Interestingly, spiro indoline **1i** was also nicely involved in the reaction with **2a**, affording a multi cyclic sipro compound **3ia** in 69% yield (entry 11).

Table 2B.3 Reaction of substituted *N*-carbamoyl indolines **1** with 1-phenyl-1-propyne (**2a**) or diphenylacetylene (**2h**)[a]

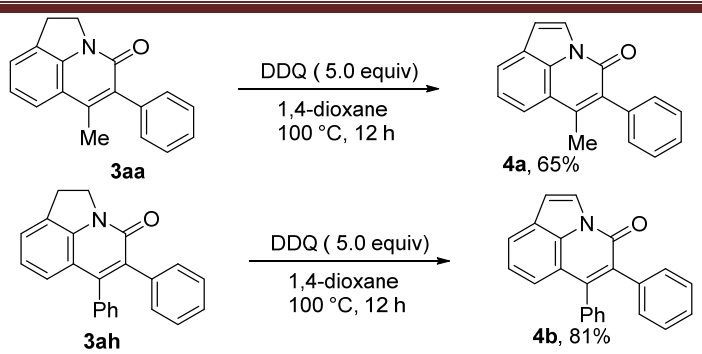
Entry	Indoline **1**	Product **3**	Yield (%)[b]
			
1	**1b**	**3ba**: R = Me	76
2	**1b**	**3bh**: R = Ph	62
			
3	**1c**	**3ca**: R = Me	57
4	**1c**	**3ch**: R = Ph	55
5	 1d	 3da	68

			
6	**1e**	**3ea**: R = Me	56
7	**1e**	**3eh**: R = Ph	51
8	 **1f**	 **3fa**	63
9	 **1g**	 **3ga**	73
10	 **1h**	 **3ha**	47
11	 **1i**	 **3ia**	69

[a] All reactions were carried out using **1b-i** (100 mg), alkynes **2a** and **2h** (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and Ad-1-COOH (30 mol %) in *tert*-amyl alcohol (3.0 mL) at 130 °C for 24 h. [b]Isolated yield.

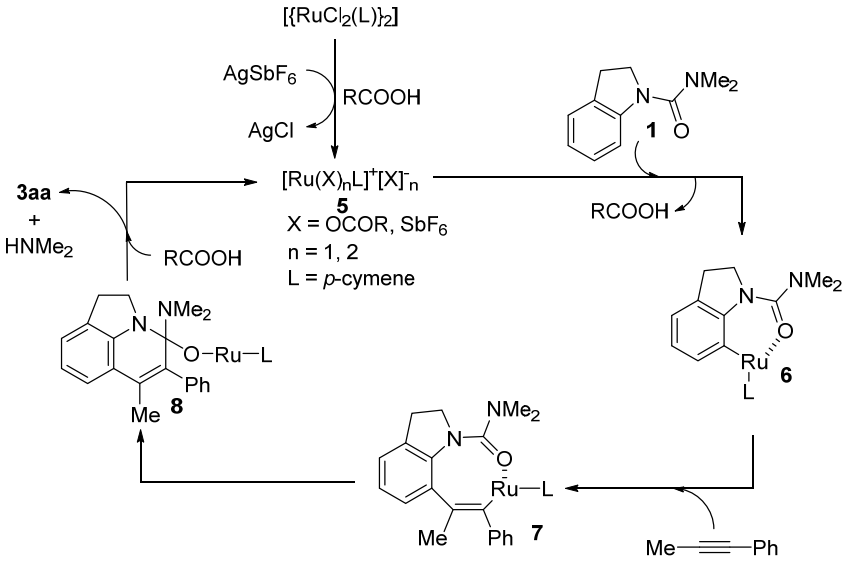
2B.2.4 Aromatization of Pyrroloquinolinones

Later, we have tried to aromatize pyrroloquinolinones into indole derivatives in the presence of DDQ (Scheme 2B.5). Treatment of **3aa** and **3ah** with DDQ in 1,4-dioxane at 130 °C for 12 h gave indole derivatives **4a** and **4b** in 65% and 81% yields, respectively. It is important to note that the pyrroloindolone unit is highly useful and presents in various natural products and biologically active molecules.[11]



Scheme 2B.5: Aromatization of pyrroquinolinones

2B.2.5 Proposed Mechanism



Scheme 2B.6: Plausible mechanism

A plausible reaction mechanism is proposed to account for the present cyclization reaction in Scheme 2B.6. The active cationic ruthenium species **5** was generated by the ligand exchange reaction between [{$RuCl_2$(*p*-cymene)}$_2$] and $AgSbF_6$. Chelation of oxygen atom of carbamoyl group into the active ruthenium species **5** followed by selective deprotonation at C7-H of indoline moiety affords a six-membered ruthenacycle **6**. Regioselective coordinative insertion of an alkyne into the C-Ru bond of intermediate **6** provides an alkenyl−Ru intermediate **7**. It is important to note that the coordinating group Ph or ester of unsymmetrical alkynes always prefer to stay near to the ruthenium metal of intermediate **7**. An intramolecular nucleophilic addition of the alkene−Ru bond of intermediate **7** into the carbamoyl group produces intermediate **8**. Later, protonation at the O-Ru bond of intermediate **8** in the presence of 1-Ad-COOH affords the cyclization product **3**

along with the release of *N*, *N*-dimethyl amine and regenerates the active cationic Ru complex **5** for the next catalytic cycle.

2B.3 Conclusions

In conclusions, we have described a highly regioselective, atom and step-economical route to synthesize very useful pyrroloquinolinone derivatives by a ruthenium-catalyzed cyclization of *N*-carbamoyl indolines with alkynes. The cyclization reaction was compatible with various functional group substituted indolines and symmetrical as well as unsymmetrical alkynes including substituted propiolates. Later, we have done the aromatization of pyrroloquinolinones in the presence of DDQ.

2B.4 References

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9. Indoline C7-H activation: (a) Yi, C. S.; Yun, S. Y.; Guzei, I. A. *J. Am. Chem. Soc.* **2005**, *127*, 5782; (b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330; (c) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068; (d) Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E.; Smith, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 15552; (e) Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y.; *Angew. Chem. Int. Ed.* **2007**, *46*, 5554; (f) Pan, C.; Abdukader, A.; Han, J.; Cheng, Y.; Zhu, C. *Chem. Eur. J.* **2014**, *20*, 3606; (g) Song, Z.; Samanta, R.; Antonchick, A. P. *Org. Lett.* **2013**, *15*, 5662; (h) Jiao, L.-Y.; Oestreich, M.; *Org. Lett.* **2013**, *15*, 5374; (i) Pan, S.; Ryu, N.; Shibata, T. *Adv. Synth. Catal.* **2014**, *356*, 929; (j) Shin, Y.; Sharma, S.; Mishra, N. K.; Han, S.; Park, J.; Oh, H.; Ha, J.; Yoo, H.; Jung, Y. H.; Kim, I. S. *Adv. Synth. Catal.* **2015**, *357*, 594; (k) Yang, X.-F.; Hu, X.-H.; Loh, T.-P. *Org. Lett*. **2015**, *17*, 1481.

10. Hydroarylation: (a) Reddy, M. C.; Jeganmohan, M. *Chem. Commun.* **2013**, *49,* 481; (b) Manikandan, R.; Jeganmohan, M. *Org. Lett.* **2014**, *16,* 912; (c) Kishor, P.; Jeganmohan, M.; *Chem. Commun.* **2014***, 50,* 14573; Oxidative cyclization: (d) Reddy, M. C.; Jeganmohan, M. *Org. Lett*. **2014**, *16*, 4866; (e) Pimparkar, S.; Jeganmohan, M. *Chem. Commun.* **2014**, *50,* 12116; (f) Manikandan, R.; Jeganmohan, M. *Org. Lett.* **2014**, *16*, 3568; (g) Ravi Kiran, CG.; Pimparkar, S.; Jeganmohan, M. *Org. Lett.* **2012**, 14, 3032; (h) Manoharan, R.; Jeganmohan, M. *Chem. Commun.* **2015***,* **52***,* 2029.

10. Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S.; *Chem. Commun.* **2012**, *48*, 10337.

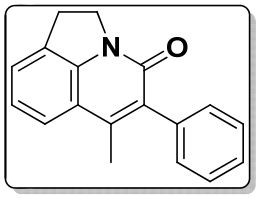
2B.5 Experimental Section

2B.5.1 General Information: All reactions were carried out under the nitrogen atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use (three times). Dry solvents were used for the reaction. Column chromatographical purifications were performed using SiO_2 (120-200 mesh ASTM) from Merck if not indicated otherwise. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Starting Materials: Commercial available starting materials, metal complexes and metal salts were purchased from commercial sources and used without further purification.

2B.5.2 A. General procedure for the preparation of pyrroloquinolinones catalyzed by ruthenium complex: A 15-mL pressure tube with septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), *N*-carbamoyl indolines 1 (100 mg), Ad-1-COOH (30 mol %), alkyne 2 (1.2 equiv) (if alkyne is solid) 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 *tert*-amyl alcohol (3.0 mL) via syringe after that the reaction mixture was evacuated and purged with nitrogen gas three times (liquid alkynes were added at this stage via syringe). After that, the septum was taken out and immediately a screw cap was used to cover the tube under the nitrogen atmosphere and the reaction mixture stirred at room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 130 °C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and 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 3.

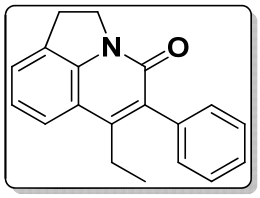
2B.6 Spectral Data of Compounds

6-Methyl-5-phenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3aa):



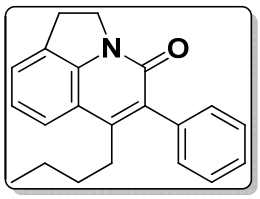
White solid; eluent (40% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1a** (100 mg); yield is 73% (99 mg). IR (ATR) ṽ (cm^{-1}): 2960, 1611, 1231, 793, 608 and 653. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.30 – 7.23 (m, 2H), 7.20 – 7.14 (m, 1H), 4.47 – 4.41 (t, *J* = 8.0 Hz, 2H), 3.42 (t, *J* = 8.0 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 142.6, 141.2, 136.3, 133.6, 130.8, 130.3, 128.3, 127.6, 124.8, 123.2, 121.7, 119.00, 47.3, 27.3, 16.3. HRMS (ESI): calc. for $[(C_{18}H_{15}NO)H]$ (M+H) 262.1232, measured 262.1233.

6-Ethyl-5-phenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ab):



Half white solid; eluent (35% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1a** (100 mg); yield is 65% (95 mg). IR (ATR) ṽ (cm^{-1}): 2956, 1620, 1606, 1277, 1066 and 706. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.39 – 7.31 (m, 2H), 7.28 – 7.22 (m, 2H), 7.21 – 7.14 (m, 1H), 4.43 (t, *J* = 8.0, 2H), 3.41 (t, *J* = 8.0 Hz, 2H), 2.67 (q, *J* = 7.6 Hz, 2H), 1.15 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 148.3, 141.8, 136.5, 133.4, 131.0, 129.9, 128.4, 127.5, 124.6, 123.0, 121.7, 117.6, 47.11, 27.2, 22.9, 14.6. HRMS (ESI): calc. for $[(C_{19}H_{17}NO)H]$ (M+H) 276.1388, measured 276.1389.

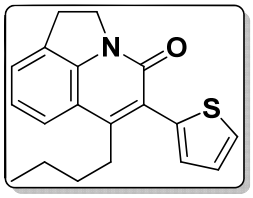
6-Butyl-5-phenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ac):



White solid; eluent (40% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1a** (100 mg); yield is 60% (96 mg). IR (ATR) ṽ (cm^{-1}): 2960, 1621, 1615, 1277, 1071 and 743. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* =8.2 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.38 – 7.29 (m, 2H), 7.28 – 7.20 (m, 2H), 7.20 – 7.11 (m, 1H), 4.44 (t, *J* = 8.0 Hz, 2H), 3.41 (t, *J* = 8.0 Hz, 2H), 2.70 –

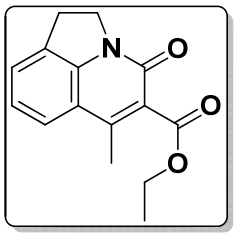
2.59 (m, 2H), 1.52 (dd, *J* = 11.4, 4.6 Hz, 2H), 1.26 (dd, *J* = 14.6, 7.2 Hz, 2H), 0.78 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 147.4, 141.7, 136.4, 133.6, 130.9, 129.9, 128.3, 127.5, 124.6, 122.9, 121.8, 118.0, 47.1, 32.3, 29.4, 27.2, 22.9, 13.7. HRMS (ESI): calc. for [($C_{21}H_{21}NO$)H] (M+H) 304.1701, measured 304.1707.

6-Butyl-5-(thiophen-2-yl)-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ad):



Brown solid; eluent (45% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1a** (100 mg); yield is 61% (99 mg).IR (ATR) ṽ (cm^{-1}): 2850, 1641, 1232, 823, 697 and 743. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.8 Hz, 1H), 7.43 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.21 – 7.13 (m, 1H), 7.10 (dd, *J* = 5.2, 3.6 Hz, 1H), 7.02 (dd, *J* = 3.6, 1.2 Hz, 1H), 4.48 – 4.37 (m, 2H), 3.45 – 3.34 (m, 2H), 2.85 – 2.74 (m, 2H), 1.66 – 1.55 (m, 2H), 1.37 (dd, *J* = 14.8, 7.4 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 149.7, 141.8, 136.5, 131.0, 128.3, 126.6, 126.6, 126.1, 125.0, 123.1, 121.9, 117.7, 47.2, 32.8, 29.9, 27.2, 23.1, 13.8. HRMS (ESI): calc. for [($C_{19}H_{19}NOS$)H] (M+H) 310.1266, measured 310.1261.

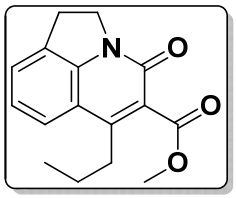
Ethyl 6-methyl-4-oxo-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-5-carboxylate (3ae):



Thick brown liquid; eluent (50% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1a** (100 mg); yield is 56% (72 mg). IR (ATR) ṽ (cm^{-1}): 3006, 1725, 1644, 1614, 1161 and 741. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.2, 1H), 7.36 (d, *J* = 7.4, 1H), 7.17 (dd, *J* = 8.2, 7.4 Hz,

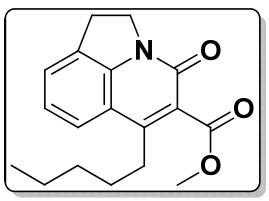
1H), 4.49 – 4.36 (m, 4H), 3.40 (t, *J* = 8.2 Hz, 2H), 2.44 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 157.8, 144.3, 141.7, 130.9, 127.6, 126.0, 123.5, 121.8, 117.8, 61.9, 46.9, 27.2, 15.5, 14.4. HRMS (ESI): calc. for [($C_{15}H_{15}NO_3$)H] (M+H) 258.1130, measured 258.1133.

4 Methyl 4-oxo-6-propyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-5-carboxylate (3af):



Thick brown liquid; eluent (45% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1a** (100 mg); yield is 53% (76 mg). IR (ATR) ṽ (cm-1): 2920, 1727, 1640, 1606, 1231 and 809.1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.2 Hz, 1H), 7.35 (d, J = 7.4 Hz, 1H), 7.16 (dd, J = 8.2, 7.4 Hz, 1H), 4.51 – 4.33 (m, 2H), 3.93 (s, 3H), 3.39 (t, J = 8.0 Hz, 2H), 2.84 – 2.69 (m, 2H), 1.75 – 1.62 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H). 13C NMR (100 MHz, $CDCl_3$): δ 167.4, 157.9, 148.8, 142.1, 131.2, 127.0, 125.9, 123.5, 122.0, 116.9, 52.6, 46.9, 32.0, 27.2, 23.5, 14.5. HRMS (ESI): calc. for [($C_{16}H_{17}NO_3$)Na] (M+Na) 294.1106, measured 294.1105.

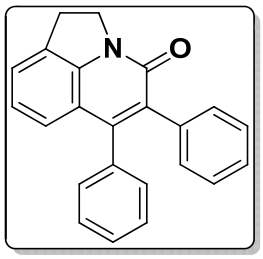
Methyl 4-oxo-6-pentyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-5-carboxylate (3ag):



Brown solid; eluent (45% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1a** (100 mg); yield is 48% (76 mg).IR (ATR) ṽ (cm-1): 2956, 1728, 1643, 1612, 1154 and 744. 1H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 8.2 Hz, 1H), 7.35 (d, J = 7.2, Hz, 1H), 7.17 (dd, J = 8.0, 7.2 Hz, 1H), 4.53 – 4.18 (m, 2H), 3.93 (s, 3H), 3.39 (t, J = 8.0 Hz, 2H), 2.76 (dd, J = 9.2, 7.2 Hz, 2H), 1.65 (dd, J = 8.8, 6.6 Hz, 2H), 1.43 – 1.27 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H). 13C NMR (100 MHz, $CDCl_3$): δ 167.4, 157.9, 149.1, 142.1, 131.2, 126.8, 125.9,

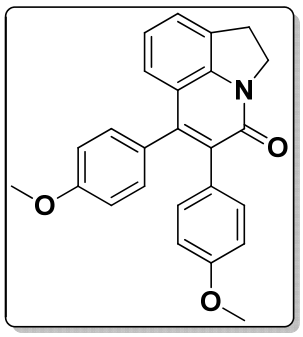
123.5, 121.9, 116.9, 52.6, 46.9, 32.1, 30.0, 29.8, 27.2, 22.4, 14.0. HRMS (ESI): calc. for [($C_{18}H_{21}NO_3$)H] (M+H) 300.1599, measured 300.1600.

5,6-Diphenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ah):



White solid; eluent (40% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1a** (100 mg); yield is 67% (114 mg). IR (ATR) ṽ (cm^{-1}): 2997, 1636, 1604, 1443, 1237, 1070 and 772. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 6.8, 1.2 Hz, 1H), 7.28 – 7.22 (m, 3H), 7.18 – 7.02 (m, 9H), 4.53 (t, *J* = 8.2 Hz, 2H).3.48 (t, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 146.9, 141.7, 136.0, 135.5, 133.4, 130.9, 130.4, 129.8, 127.9, 127.6, 127.4, 126.9, 124.8, 123.7, 122.9, 118.6, 47.3, 27.2. HRMS (ESI): calc. for [($C_{23}H_{17}NO$)H] (M+H) 324.1388, measured 324.1393.

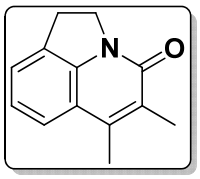
5,6-bis(4-Methoxyphenyl)-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ai):



Half white semisolid; eluent (40% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1a** (100 mg); yield is 68% (137mg). IR (ATR) ṽ (cm^{-1}): 2867, 1640, 1630, 1501, 1247, 1085 and 748.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 7.09 – 6.99 (m, 5H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.73 – 6.67 (m, 2H), 4.60 – 4.45 (m, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.46 (t, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 158.8, 158.3, 146.8, 141.4, 132.6, 132.3, 131.1, 130.6, 128.3, 127.8, 124.7, 123.7, 123.2,

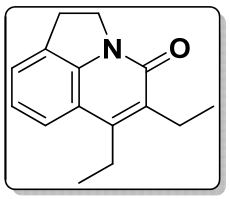
119.0, 113.6, 113.0, 55.2, 55.1, 47.5, 27.2. HRMS (ESI): calc. for [($C_{25}H_{21}NO_3$)H] (M+H) 384.1600, measured 384.1607.

5,6-Dimethyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3aj):



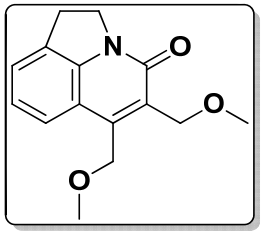
White solid; eluent (30% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1a** (100 mg); yield is 47% (49 mg). IR (ATR) ṽ (cm^{-1}): 2924, 1637, 1620, 1597, 1245, 1022 and 809.^{1}H NMR (400 MHz, CDCl3): δ 7.43 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.18 – 7.07 (m, 1H), 4.49 – 4.32 (m, 2H), 3.38 (t, *J* = 8.0 Hz, 2H), 2.41 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 140.8, 140.4, 130.6, 128.5, 123.8, 122.9, 120.9, 118.9, 47.0, 27.3, 14.7, 13.2. HRMS (ESI): calc. for [($C_{13}H_{13}NO$)H] (M+H) 200.1075, measured 200.1076.

5,6-Diethyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ak):



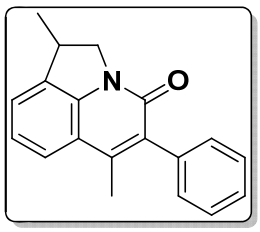
White solid; eluent (35% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1a** (100 mg); yield is 61% (73 mg). IR (ATR) ṽ (cm^{-1}): 2960, 1651, 1615, 1247, 1041 and 643.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 7.0, Hz, 1H), 7.18 – 7.06 (m, 1H), 4.43 (t, *J* = 8.0 Hz, 2H), 3.39 (t, *J* = 8.0 Hz, 2H), 2.89 (q, *J* = 7.6 Hz, 2H), 2.76 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H), 1.18 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 146.1, 140.9, 133.8, 130.8, 123.7, 122.8, 120.9, 117.9, 46.9, 27.2, 21.7, 20.4, 14.4, 14.0. HRMS (ESI): calc. for [($C_{15}H_{17}NO$)H] (M+H) 228.1388, measured 228.1392.

5,6-bis(Methoxymethyl)-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3al):



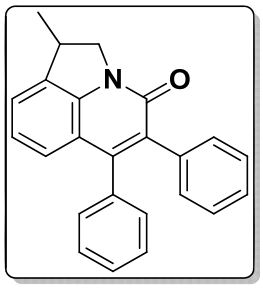
White solid; eluent (35% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1a** (100 mg); yield is 65% (89mg). IR (ATR) ṽ (cm^{-1}): 2975, 1644, 1525, 1177, 1071, 950 and 743.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 7.0 Hz, 1H), 7.18 – 7.09 (m, 1H), 4.79 (s, 2H), 4.67 (s, 2H), 4.41 (t, *J* = 8.0 Hz, 2H), 3.42 (s, 3H), 3.41 (s, 3H), 3.38 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 144.6, 141.8, 130.7, 129.7, 125.4, 123.5, 122.7, 117.7, 67.7, 65.0, 58.6, 47.4, 27.2. HRMS (ESI): calc. for [($C_{15}H_{17}NO_3$)Na] (M+Na) 282.1106, measured 282.1107.

1,6-Dimethyl-5-phenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ba):



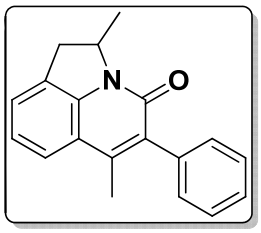
White solid; eluent (40% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1b** (100 mg); yield is 76% (102 mg). IR (ATR) ṽ (cm^{-1}): 2870, 1640, 1609, 1229, 860 and 752. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.42 – 7.34 (m, 2H), 7.34 – 7.27 (m, 2H), 7.27 – 7.21 (m, 1H), 4.65 (dd, *J* = 12.6, 9.4 Hz, 1H), 4.03 (dd, *J* = 12.6, 5.6 Hz, 1H), 3.89 – 3.74 (m, 1H), 2.33 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 142.3, 140.6, 136.3, 135.8, 133.8, 130.2, 128.2, 127.4, 123.7, 123.0, 121.8, 118.8, 55.0, 34.8, 20.9, 16.2. HRMS (ESI): calc. for [($C_{19}H_{17}NO$)H] (M+H) 276.1388, measured 276.1389.

1-Methyl-5,6-diphenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3bh):



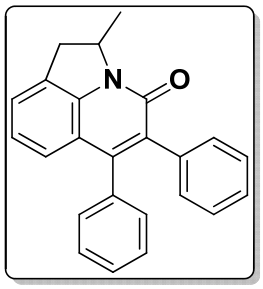
White solid; eluent (40% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1b** (100 mg); yield is 62% (103 mg). IR (ATR) ṽ (cm^{-1}): 2770, 1629, 1596, 1123, 830 and 736.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.0 Hz, 1H), 7.31 – 7.26 (m, 3H), 7.21 – 7.10 (m, 9H), 4.74 (dd, *J* = 12.0, 8.0 Hz, 1H), 4.13 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.88 (dq, *J* = 13.6, 7.0 Hz, 1H), 1.55 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 147.0, 141.0, 136.0, 135.6, 135.5, 133.5, 130.9, 129.8, 128.0, 127.5, 127.4, 126.9, 123.9, 123.8, 123.1, 118.5, 55.3, 34.8, 20.8. HRMS (ESI): calc. for [($C_{24}H_{19}NO$)H] (M+H) 338.1545, measured 338.1549.

2,6-Dimethyl-5-phenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ca):



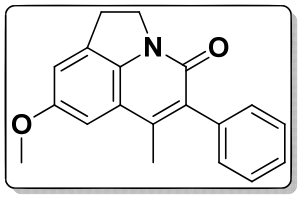
Half white solid; eluent (30% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1c** (100 mg); yield is 57% (77 mg). IR (ATR) ṽ (cm^{-1}): 2960, 1650, 1620, 1240, 873 and 740. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.42 – 7.34 (m, 2H), 7.33 (m, 1H), 7.33 – 7.31 (m, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 5.15 – 5.02 (m, 1H), 3.67 (dd, *J* = 16.8, 9.4 Hz, 1H), 3.03 (dd, *J* = 16.8, 3.8 Hz, 1H), 2.34 (s, 3H), 1.65 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 142.1, 140.6, 136.4, 134.2, 130.3, 129.2, 128.1, 127.4, 124.7, 122.9, 121.6, 118.7, 56.9, 36.3, 20.6, 16.1. HRMS (ESI): calc. for [($C_{19}H_{17}NO$)H] (M+H) 276.1388, measured 276.1396.

2-Methyl-5,6-diphenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ch).



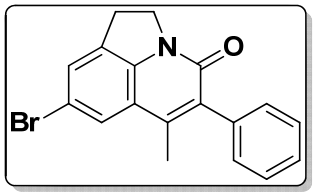
Half white solid; eluent (30% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1c** (100 mg); yield is 55% (91 mg).IR (ATR) ṽ (cm^{-1}): 2973, 1640, 1613, 1206, 793 and 720. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (t, *J* = 8.4 Hz, 2H), 7.31 – 7.24 (m, 3H), 7.22 – 7.15 (m, 5H), 7.14 – 7.01 (m, 3H), 5.19 (m, 1H), 3.72 (dd, *J* = 16.6, 9.4 Hz, 1H), 3.08 (dd, *J* = 16.6, 3.8 Hz, 1H), 1.73 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3): δ 160.2, 146.9, 141.0, 136.0, 135.6, 133.8, 131.0, 129.8, 129.0, 128.0, 127.9, 127.5, 127.4, 126.8, 124.9, 123.7, 123.0, 118.4, 57.2, 36.3, 20.6. HRMS (ESI): calc. for [($C_{24}H_{19}NO$)H] (M+H) 338.1545, measured 338.1549.

8-Methoxy-6-methyl-5-phenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3da).



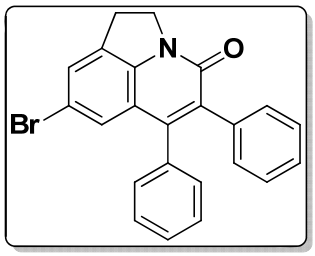
White solid; eluent (45% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1d** (100 mg); yield is 68% (90mg). IR (ATR) ṽ (cm^{-1}): 2965, 1640, 1607, 1483, 1314 and 780. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (t, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.30 (dd, *J* = 8.6, 2.0 Hz, 2H), 7.09 – 7.03 (m, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 4.55 – 4.43 (m, 2H), 3.90 (s, 3H), 3.43 (t, *J* = 8.0 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 156.6, 141.8, 136.4, 136.0, 134.0, 132.1, 130.2, 128.1, 127.4, 118.7, 114.7, 103.5, 56.1, 47.3, 27.2, 16.3. HRMS (ESI): calc. for [($C_{19}H_{17}NO_2$)H] (M+H) 292.1338, measured 292.1337.

8-Bromo-6-methyl-5-phenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ea):



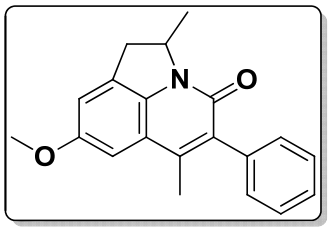
Brown solid; eluent (40% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1e** (100 mg); yield is 56% (71 mg). IR (ATR) ṽ (cm^{-1}): 3742, 2998, 1639, 1611, 1072 and 856. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.46 (t, *J* = 7.8 Hz, 3H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.29 (dd, *J* = 6.8, 1.6 Hz, 2H), 4.59 – 4.37 (m, 2H), 3.44 (t, *J* = 8.0 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 141.3, 140.2, 135.8, 134.6, 132.6, 130.1, 128.2, 127.8, 127.7, 124.3, 119.9, 115.6, 47.2, 27.0, 16.2. HRMS (ESI): calc. for $[(C_{18}H_{14}BrNO)H]$ (M+H) 340.0337, measured 340.0339.

8-Bromo-5,6-diphenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3eh):



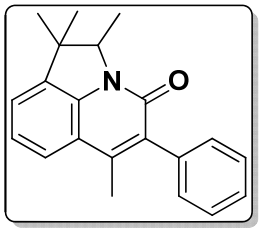
Brown solid; eluent (40% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1e** (100 mg); yield is 51% (76 mg).IR (ATR) ṽ (cm^{-1}): 3693, 2898, 1647, 1603, 1046 and 826.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 1.6 Hz, 1H), 7.31 (s, 1H), 7.30 (d, *J* = 1.6 Hz, 2 H), 7.26 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 3H), 7.15 – 7.09 (m, 4H), 4.58 (t, *J* = 8.2 Hz, 2H), 3.51 (t, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ^{13}C NMR (101 MHz, CDCl3): δ 160.0, 146.0, 135.3, 135.1, 132.5, 130.8, 129.6, 128.2, 128.0, 127.8, 127.5, 127.1, 126.1, 119.6, 115.7, 47.5, 27.0. HRMS (ESI): calc. for $[(C_{23}H_{16}BrNO)H]$ (M+H) 402.0494, measured 402.0500.

8-Methoxy-2,6-dimethyl-5-phenyl-1,2-dihydro-4H-yrrolo[3,2,1-ij]quinolin-4-one (3fa):



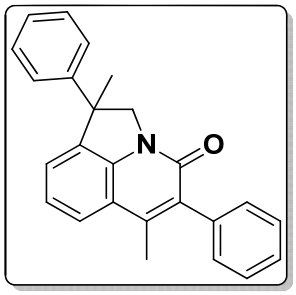
Yellow oil; eluent (45% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1f** (80 mg); yield is 63% (66 mg). IR (ATR) ṽ (cm^{-1}): 3012, 1653, 1621, 1260, 1069 and 783. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 6.8 Hz, 2H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 5.15 – 4.97 (m, 1H), 3.88 (s, 3H), 3.67 – 3.57 (m, 1H), 2.97 (dd, *J* = 16.0, 3.8 Hz, 1H), 2.28 (s, 3H), 1.62 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 156.6, 141.6, 136.5, 135.5, 134.6, 130.7, 130.3, 128.1, 127.3, 118.6, 114.6, 103.6, 57.1, 56.1, 36.3, 20.6, 16.3. HRMS (ESI): calc. for [($C_{20}H_{19}NO_2$)H] (M+H) 306.1494, measured 306.1495.

1,1,2,6-Tetramethyl-5-phenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ga):



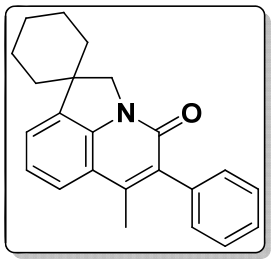
White semisolid; eluent (30% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1g** (100 mg); yield is 73% (99 mg). IR (ATR) ṽ (cm^{-1}): 2989, 1640, 1607, 1265, 1077 and 893. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0, Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.34 – 7.31 (m, 3H), 7.28 – 7.23 (m, 1H), 4.66 (q, *J* = 6.8 Hz, 1H), 2.34 (s, 3H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.46 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 142.2, 139.2, 138.7, 136.4, 134.4, 130.3, 128.1, 127.4, 123.2, 122.4, 121.8, 118.7, 67.7, 44.1, 31.3, 22.3, 16.1, 14.7. HRMS (ESI): calc. for [($C_{21}H_{21}NO$)H] (M+H) 304.1701, measured 304.1707.

1,6-Dimethyl-1,5-diphenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ha):



White semisolid; eluent (20% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1h** (100 mg); yield is 47% (59 mg). IR (ATR) ṽ (cm^{-1}): 2354, 1693, 1646, 1531, 1231 and 772. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.39 – 7.29 (m, 6H), 7.26 (t, *J* = 2.4 Hz, 3H), 4.62 (d, *J* = 12.6 Hz, 1H), 4.52 (d, *J* = 12.6 Hz, 1H), 2.38 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 146.4, 142.5, 140.1, 138.7, 136.2, 134.1, 130.2, 128.6, 128.2, 127.5, 126.8, 126.3, 124.3, 123.3, 122.2, 118.9, 64.1, 48.7, 28.0, 16.2. HRMS (ESI): calc. for $[(C_{25}H_{21}NO)H]$ (M+H) 352.1701, measured 352.1709.

2,6-Dimethyl-5-phenyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (3ia):

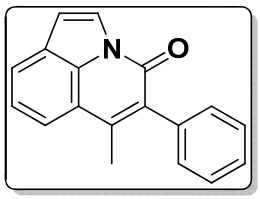


Yellow thick oil; eluent (25% ethyl acetate in hexanes); The representative general procedure **A** was followed using **1i** (100 mg); yield is 69% (88 mg). IR (ATR) ṽ (cm^{-1}): 2960, 1651, 1515, 1277, 1071 and 743. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0, Hz, 1H), 7.51 – 7.44 (m, 2H), 7.42 – 7.36 (m, 1H), 7.36 – 7.29 (m, 3H), 7.24 (dd, *J* = 8.0, 7.4 Hz, 1H), 4.30 (s, 2H), 2.33 (s, 3H), 1.92 – 1.73 (m, 7H), 1.58 – 1.35 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 142.3, 140.0, 139.8, 136.4, 133.8, 130.2, 128.2, 127.4, 123.0, 122.8, 121.8, 118.8, 57.9, 45.6, 37.8, 25.2, 22.9, 16.1. HRMS (ESI): calc. for $[(C_{23}H_{23}NO)H]$ (M+H) 330.1858, measured 330.1862.

2B.5.4 B. General Procedure for the Aromatization of Pyrroloquinolinones. A 15-mL pressure tube with septum containing pyrroloquinolinone **3aa** or **3ah** (50 mg) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (5.0 equiv) was evacuated and

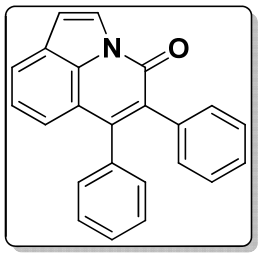
purged with nitrogen gas three times. To the tube was then added 1,4-dioxane (2.0 mL) via syringe after that the reaction mixture was evacuated and purged with nitrogen gas three times. After that, the septum was taken out and immediately a screw cap was used to cover the tube under the nitrogen atmosphere and the reaction mixture was stirred at room temperature for 5 minutes. 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 CH2Cl2, and concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure aromatized product **4a** or **4b**.

6-Methyl-5-phenyl-4H-pyrrolo[3,2,1-ij]quinolin-4-one (4a):



Half white solid; eluent (10% ethyl acetate in hexanes); The representative general procedure **B** was followed using **3aa** (50 mg); yield is 65% (32 mg). IR (ATR) ṽ (cm^{-1}): 3056, 2993, 1643, 1626, 1379, 1293 and 1119. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.56 – 7.41 (m, 4H), 7.39 – 7.32 (m, 2H), 6.90 (d, *J* = 3.6 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 158.9, 144.5, 135.7, 133.7, 131.5, 130.2, 128.3, 127.8, 127.8, 124.7, 123.9, 123.8, 121.9, 118.8, 110.4, 16.1. HRMS (ESI): calc. for [($C_{18}H_{13}NO$] (M+H) 260.1075, measured 260.1082.

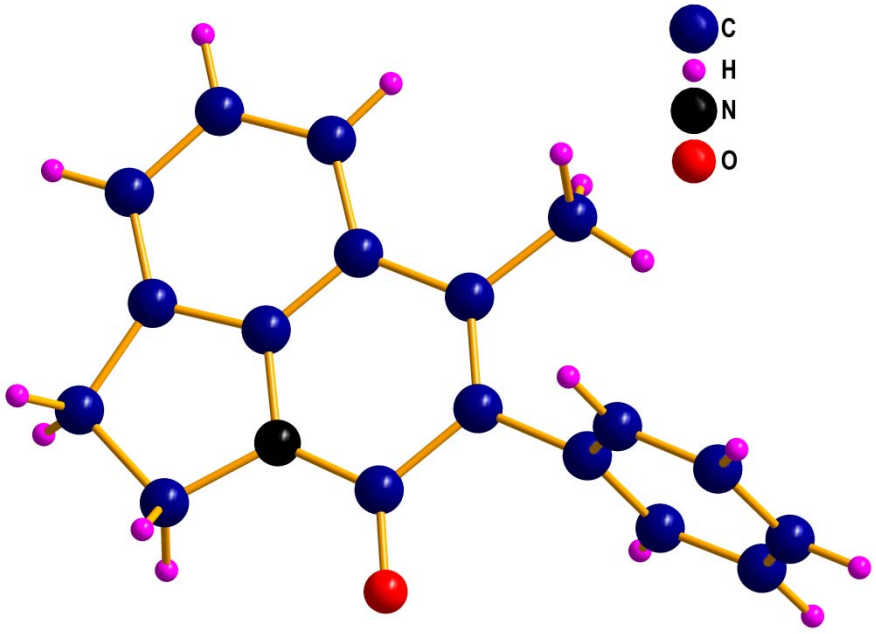
5,6-Diphenyl-4H-pyrrolo[3,2,1-ij]quinolin-4-one (4b):



Grey solid; eluent (10% ethyl acetate in hexanes); The representative general procedure **B** was followed using **3ah** (50 mg); yield is 81% (40 mg). IR (ATR) ṽ (cm^{-1}): 3046, 2979, 1669, 1638, 1400, 1373, and 1243. ^{1}H NMR (400 MHz,

$CDCl_3$): δ 8.09 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 7.6, Hz, 1H), 7.43 – 7.38 (m, 1H), 7.38 – 7.30 (m, 4H), 7.27 – 7.17 (m, 7H), 6.99 (d, *J* = 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 148.6, 135.4, 135.0, 133.4, 131.6, 131.0, 130.0, 127.9, 127.9, 127.8, 127.6, 127.3, 124.9, 124.8, 124.0, 118.5, 110.9. HRMS (ESI): calc. for [$(C_{23}H_{15}NO)H$] (M+H) 322.1232, measured 322.1239.

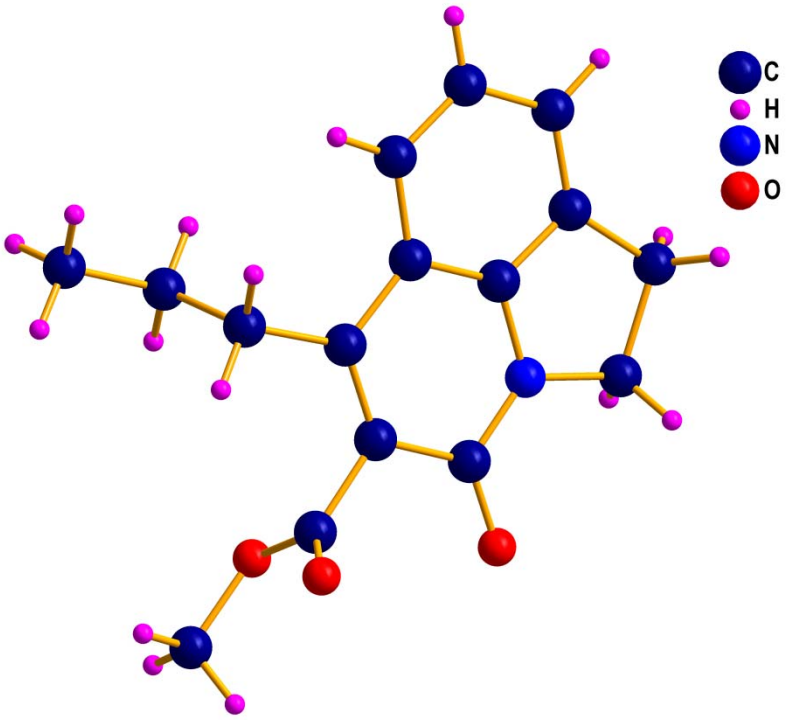
Crystal structure of Compound 3aa.



Identification code	**3aa**	
Empirical formula	$C_{18}H_{15}NO$	
Formula weight	261.31	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 7.6266(8) Å	□= 90°.
	b = 18.5193(18) Å	□= 108.801(5)°.
	c = 10.0793(10) Å	□ = 90°.
Volume	1347.6(2) $Å^3$	
Z	4	
Density (calculated)	1.288 Mg/m^3	
Absorption coefficient	0.625 mm^{-1}	
F(000)	594	
Crystal size	?x ?x ? mm^3	

Theta range for data collection	4.776 to 68.371°.
Index ranges	-9<=h<=9, -22<=k<=22, -10<=l<=12
Reflections collected	16428
Independent reflections	2475 [R(int) = 0.0426]
Completeness to theta = 67.679°	100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2475 / 0 / 182
Goodness-of-fit on F^2	0.882
Final R indices [I>2sigma(I)]	R1 = 0.0405, wR2 = 0.1216
R indices (all data)	R1 = 0.0540, wR2 = 0.1389
Extinction coefficient	n/a
Largest diff. peak and hole	0.190 and -0.115 e.$Å^{-3}$

Crystal structure of Compound 3af.

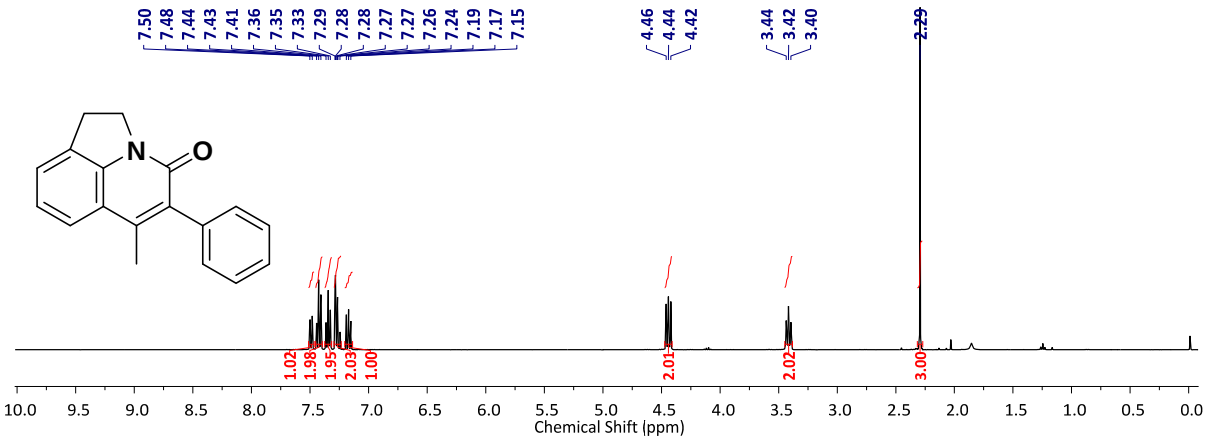


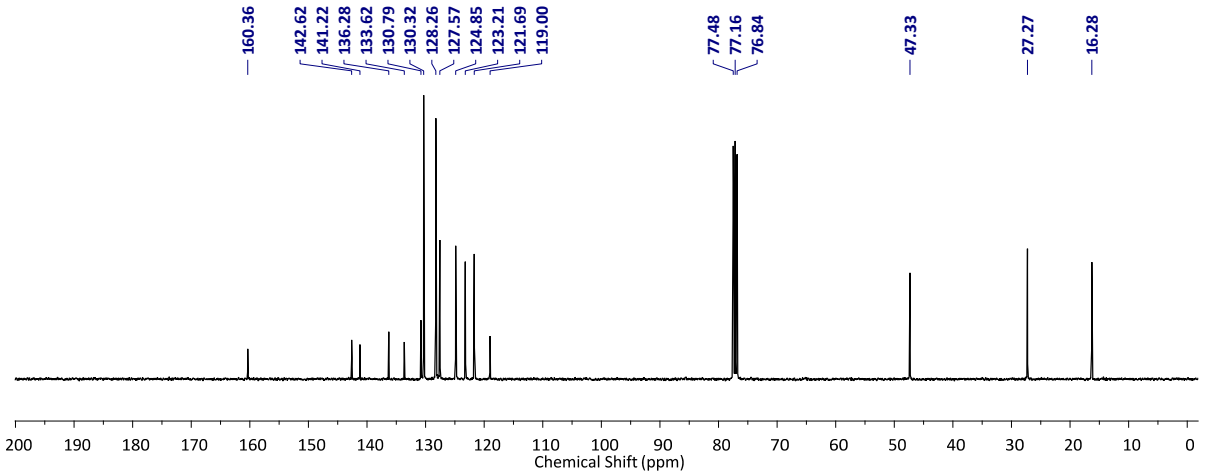
Identification code	**3af**
Empirical formula	$C_{16}H_{17}N\ O_3$
Formula weight	271.31
Temperature	100(2) K

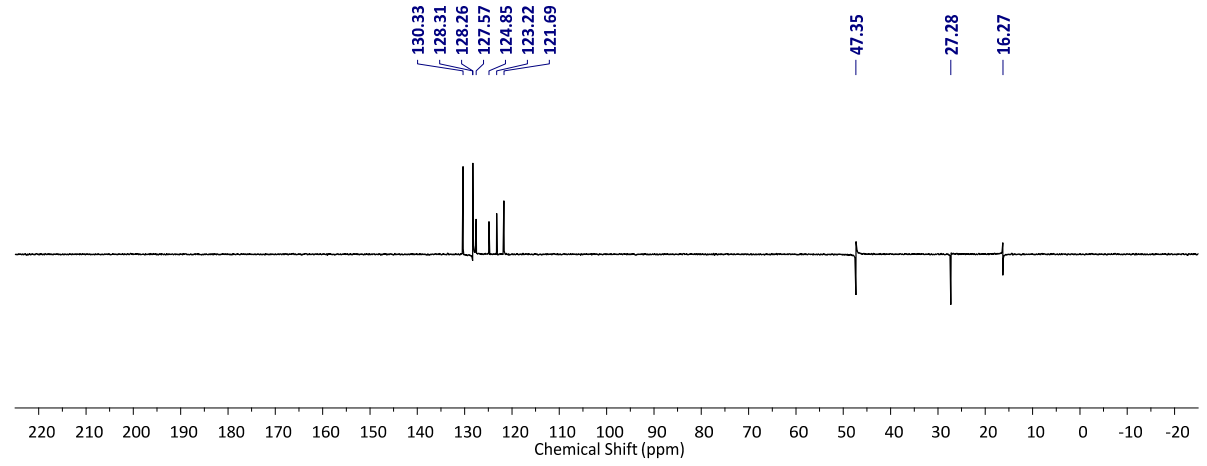
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.1792(3) Å	□= 91.062(2)°.
	b = 8.2361(3) Å	□= 95.422(2)°.
	c = 11.9209(4) Å	□ = 119.402(2)°.
Volume	694.53(4) $Å^3$	
Z	2	
Density (calculated)	1.297 Mg/m^3	
Absorption coefficient	0.730 mm^{-1}	
F(000)	308	
Crystal size	0.230 x 0.100 x 0.050 mm^3	
Theta range for data collection	3.735 to 68.392°.	
Index ranges	-9<=h<=9, -9<=k<=9, -13<=l<=14	
Reflections collected	7560	
Independent reflections	2525 [R(int) = 0.0259]	
Completeness to theta = 67.679°	99.4 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2525 / 0 / 183	
Goodness-of-fit on F^2	0.639	
Final R indices [I>2sigma(I)]	R1 = 0.0445, wR2 = 0.1168	
R indices (all data)	R1 = 0.0551, wR2 = 0.1311	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.297 and -0.247 $e.Å^{-3}$	

2B.7 Spectral Copies of Selected Compounds

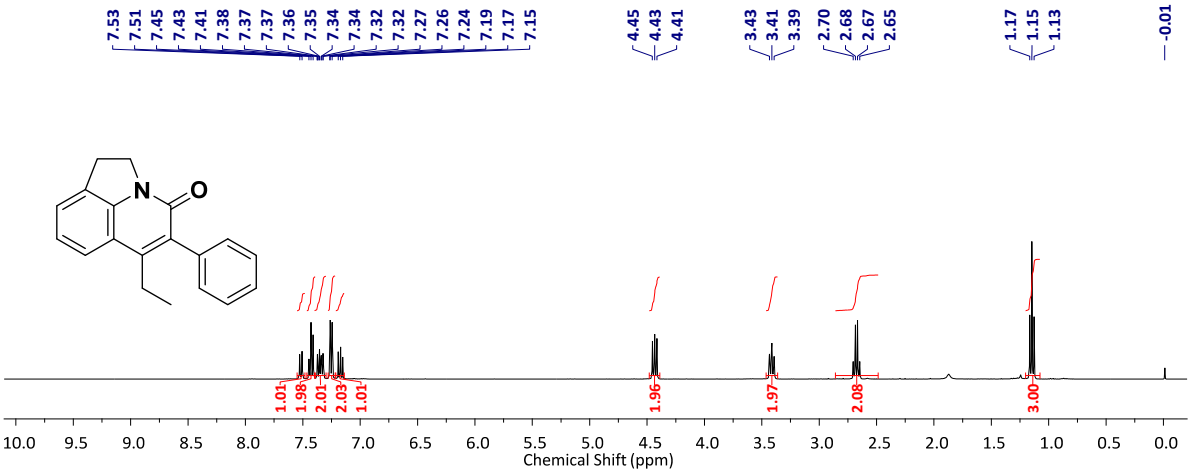
^{1}H and ^{13}C NMR Spectra of Compound **3aa**.

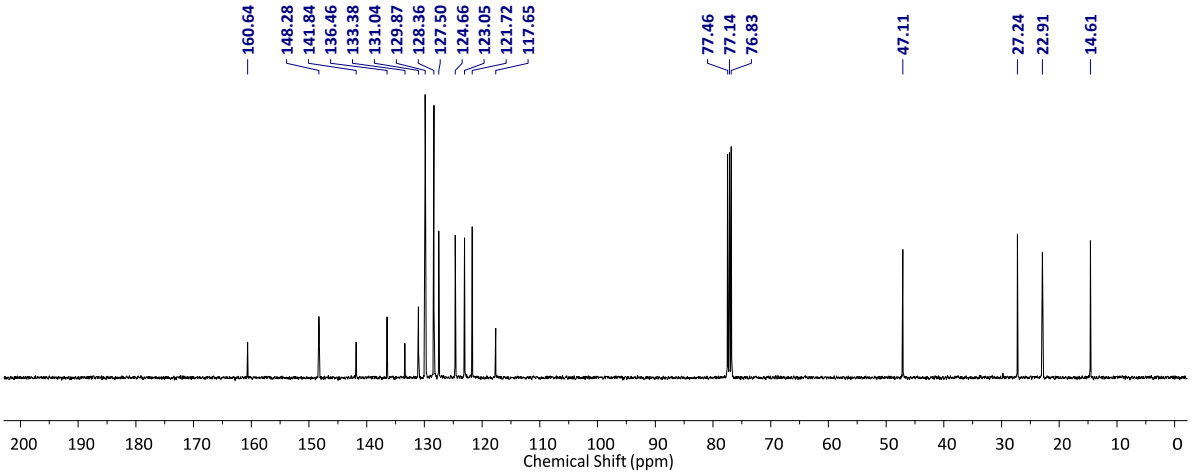


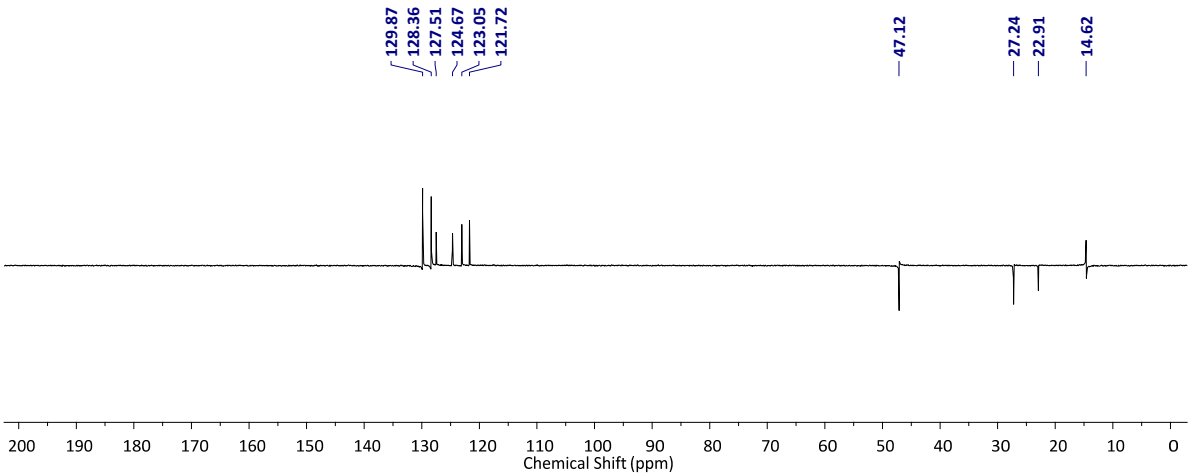




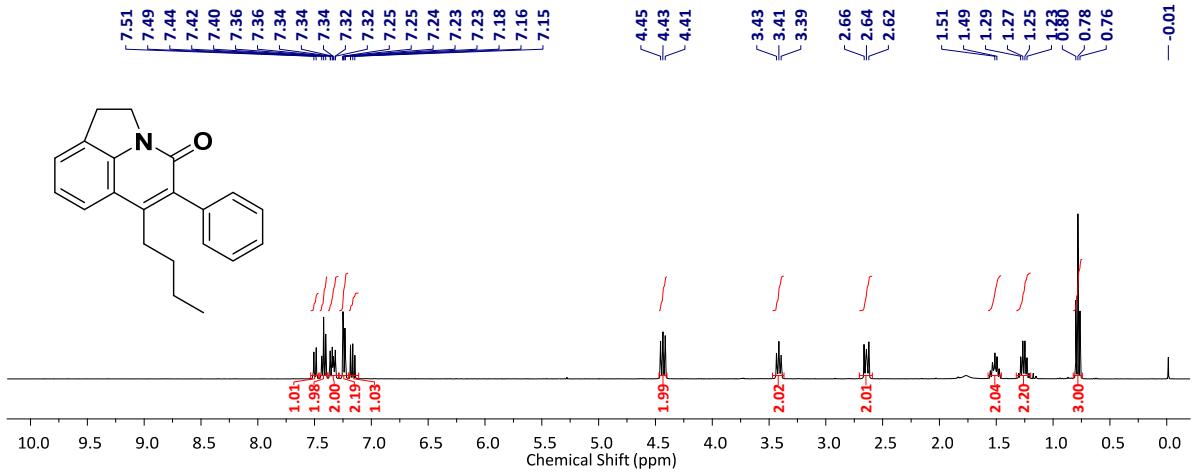
^{1}H and ^{13}C NMR Spectra of Compound **3ab.**

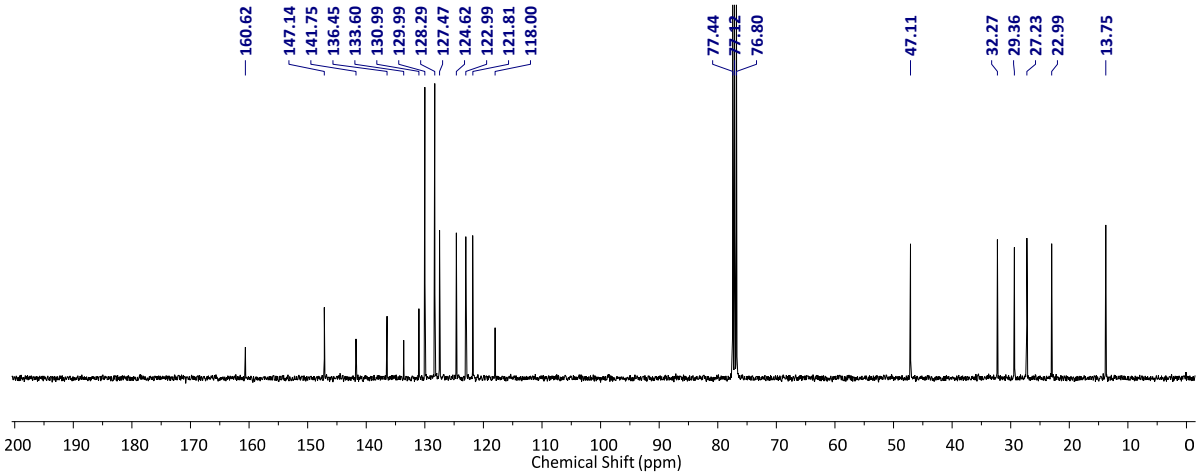


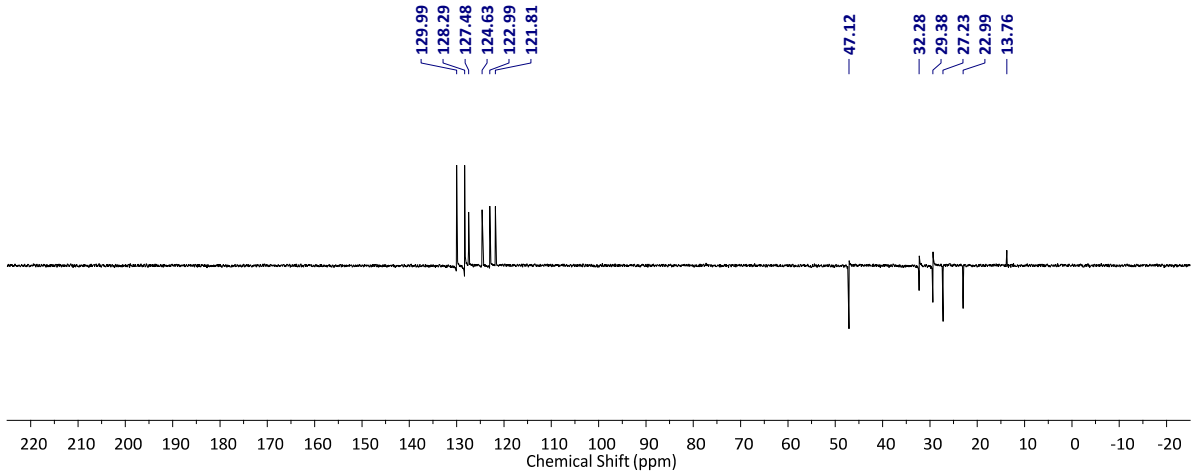




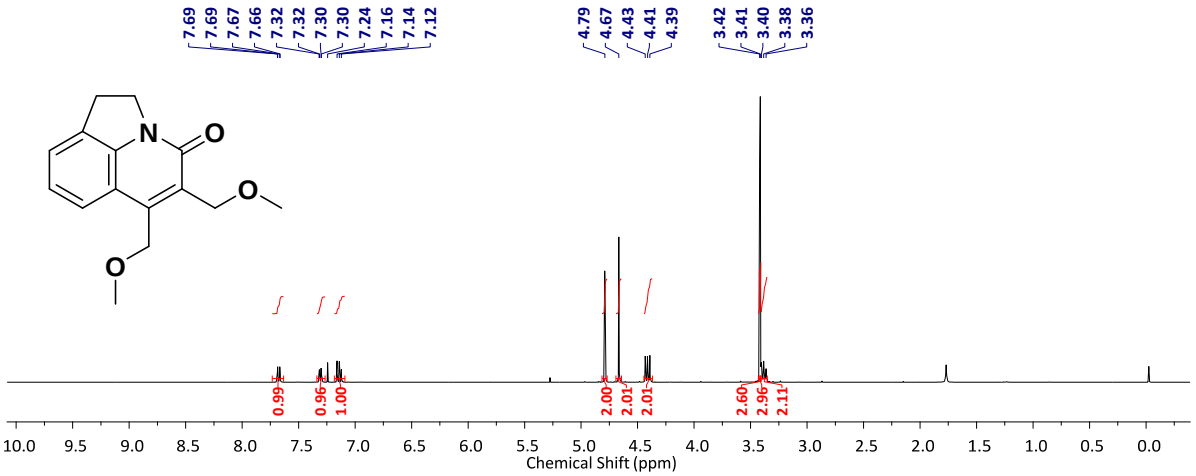
^{1}H and ^{13}C NMR Spectra of Compound **3ac.**

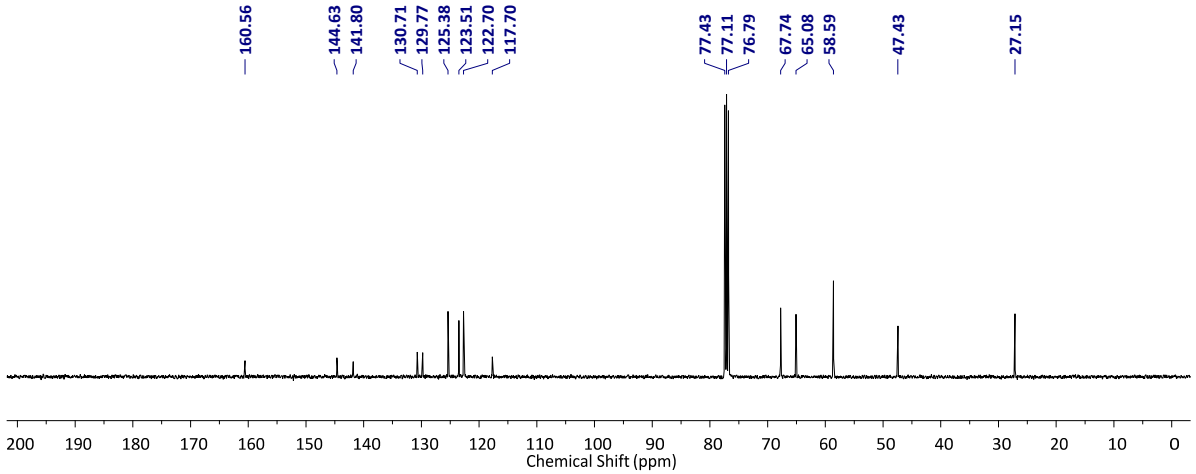


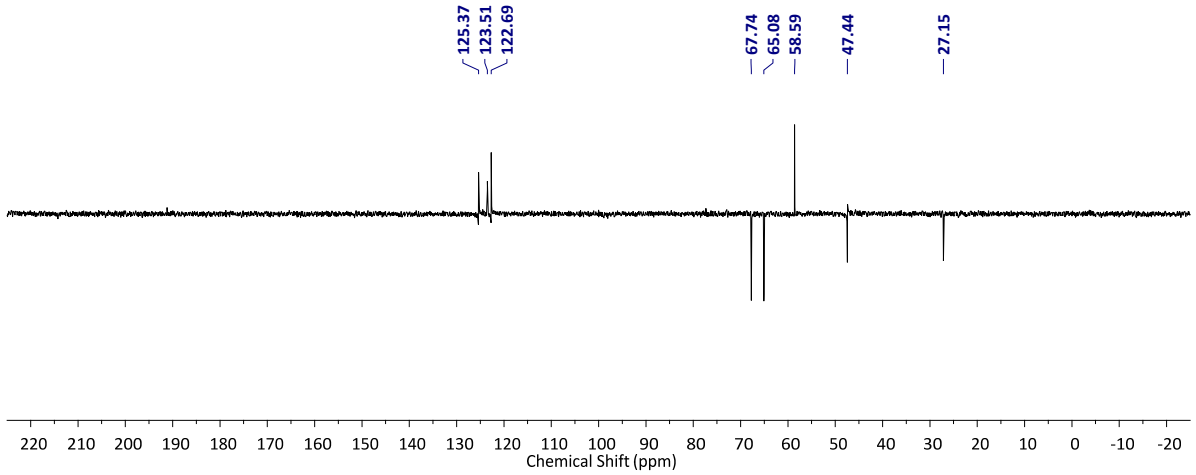




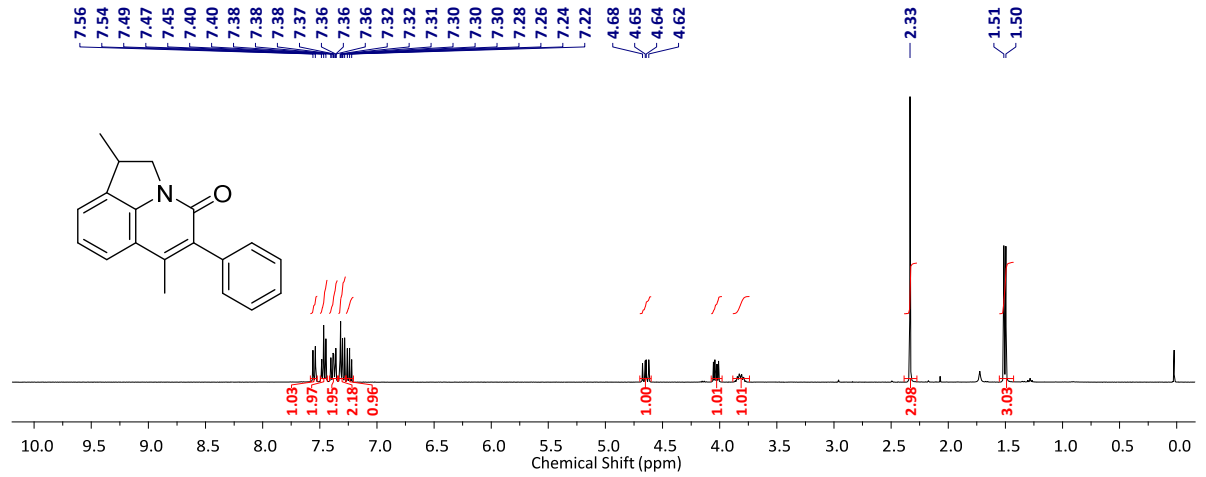
^{1}H and ^{13}C NMR Spectra of Compound **3al.**

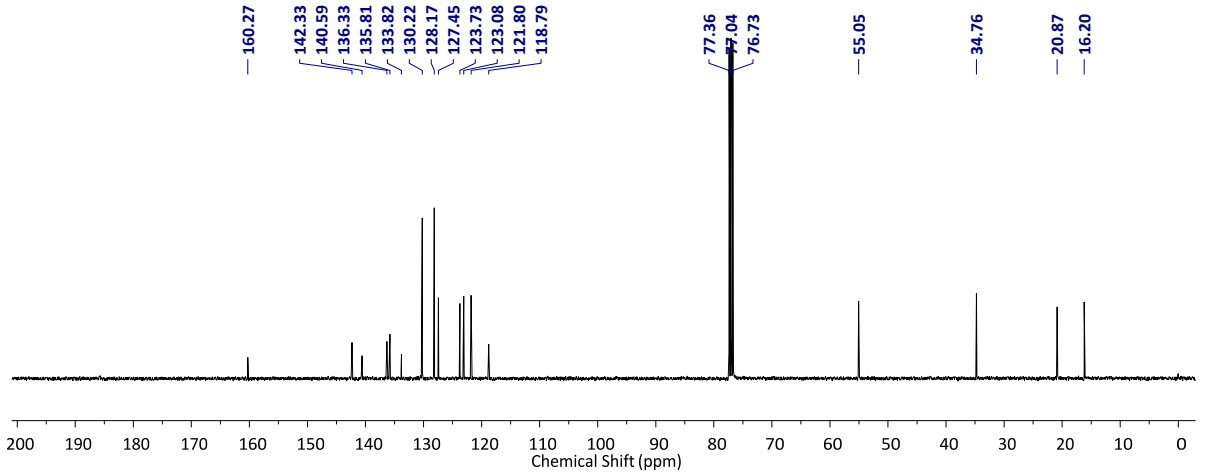


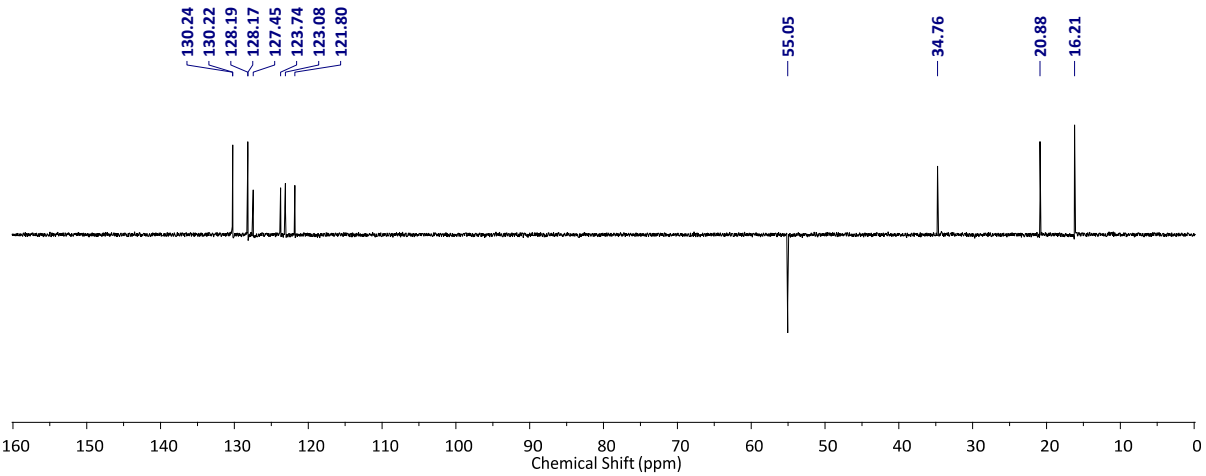




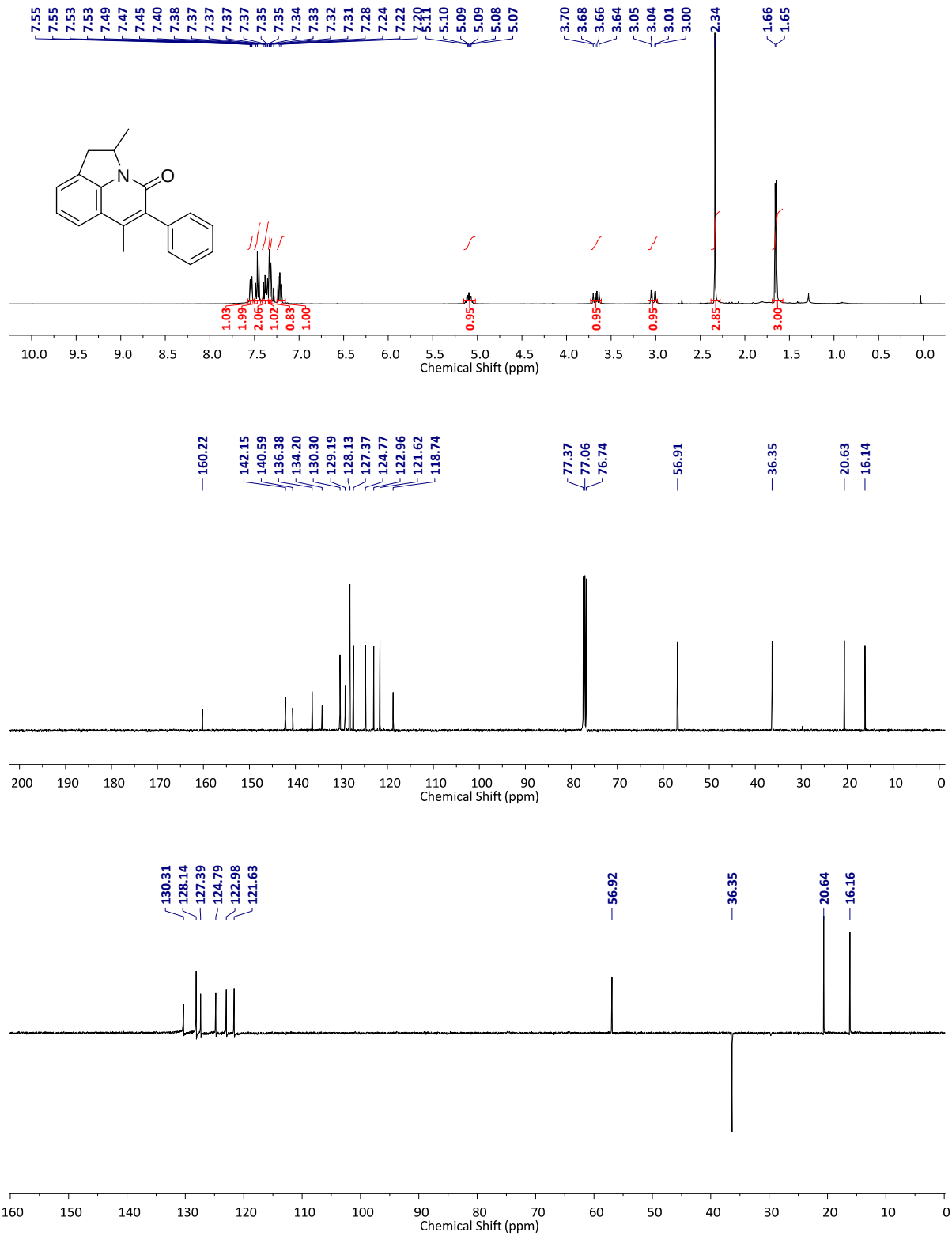
^{1}H and ^{13}C NMR Spectra of Compound **3ba.**







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



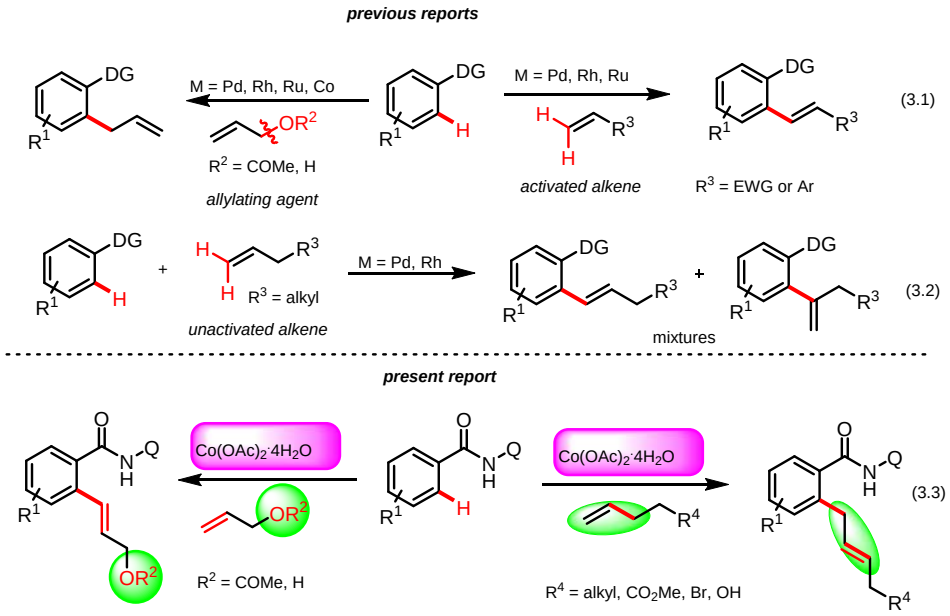
Chapter 3

Chelation Assisted Cobalt-Catalyzed *ortho* C-H Olefination of Aromatic Benzamides

3.1 Introduction

The C−H bond functionalization of substituted aromatics and heteroaromatics is a subject of intense interest in modern organic synthesis. Particularly, a metal-catalyzed chelation-assisted selective olefination at the inactive C−H bond of substituted aromatics with alkenes is an efficient method for synthesizing arylated alkenes in a highly atom- and step-economical manner from easily available starting materials.[1] Traditionally, arylated alkenes are efficiently prepared by a palladium-catalyzed cross-coupling of organic electrophiles or organometallic reagents with alkenes in a highly stereoselective manner.[2] Alternatively, arylated alkenes are prepared by a palladium-catalyzed C−H olefination of electron-rich aromatics with alkenes via an electrophilic metalation pathway.[3] However, controlling the selectivity of this reaction is very difficult and also a large excess amount of aromatics is required to perform the reaction. Meanwhile, the C−H olefination of aromatics with alkenes is achieved selectively in the presence of a metal catalyst via chelation-assisted metalation pathway by taking the advantage of coordinating ability of heteroatom with a metal.[4] By employing this pathway, an alkene moiety can be successfully installed at the *ortho* as well as *meta* position of substituted aromatics selectively.[5-7] However, in this type of alkenylation reaction, only conjugated alkenes such as acrylates, vinyl sulfones, acrylonitriles, acrylamides and styrenes are extensively used (eq 3.1). The selective C−H olefination with unactivated alkenes are rare and very challenging to succeed due to the less reactivity of alkenes and formation of mixtures of linear as well as branched isomers (eq 3.2).[8] Meanwhile, most of this transformation relies on second and third row noble metals such as palladium, rhodium, ruthenium and iridium. However, these noble metals are less abundant in nature and very expensive. Thus, the development of new C−H bond transformation reaction by using more abundant and sustainable first row transition metal catalysts is highly important. Very recently, a cobalt complex has been identified as an efficient catalyst for the C−H bond transformation reaction.[9-11] Herein, we report an unprecedented cobalt-catalyzed aminoquinoline directed C−H olefination of aromatics with unactivated alkenes, allyl acetates and allyl alcohols. The present method provides synthetically highly useful alkenylated benzamides in a highly stereoselective manner (eq 3.3). Interestingly, allyl acetates and allyl alcohols provided vinylated benzamides without cleavage of OAc or OH groups on the alkene moiety. Meanwhile, unactivated alkenes afforded allyl benzamides exclusively in a highly stereoselective manner. It is observed that the *ortho*

substituent on the benzamide moiety is crucial for the observation of allylated products in the reaction with unactivated alkenes in a highly regioselective manner.



3.2. Results and Discussion

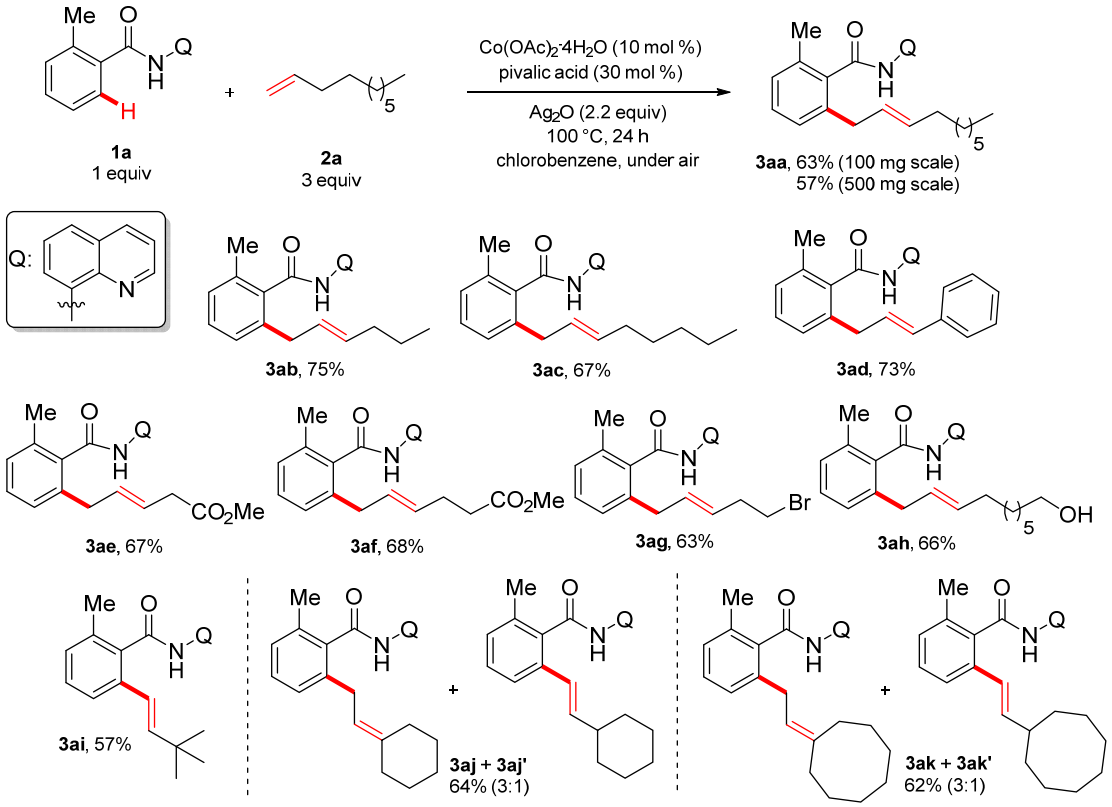
3.2.1 Optimization Studies

Treatment of 2-methyl benzamide **1a** with 1-decene (**2a**) (3.0 equiv) in the presence of $Co(OAc)_2{\cdot}4H_2O$ (10 mol %), Ag_2O (2.2 equiv) and pivalic acid (30 mol %) in chlorobenzene under air at 100 °C for 24 h provided *ortho* allylated benzamide **3aa** in 63% yield. In most of the reported C−H olefination of aromatics with unactivated alkenes, a mixture of linear as well as branched vinylated products was observed.[8] Interestingly, in the present reaction, only a linear type allylated product was observed in a highly stereoselective manner.

3.2.2 Scope of Unactivated Alkenes

The scope of allylation reaction was examined with various unactivated alkenes (Scheme 3.1). 1-Hexene (**2b**), 1-octene (**2c**) and allylbenzene (**2d**) reacted efficiently with **1a**, providing allylated aromatics **3ab-ad** in good yields. Further, functional group such as ester, bromo and OH substituted unactivated alkenes **2e-h** provided products **3ae-ah** without affecting the sensitive groups. In all these alkenes including allylbenzene (**2d**), only linear type allylated product was observed. 3,3-Dimethylbut-1-ene (**2i**) reacted with **1a** giving vinylated benzamide **3ai** in 57% yield. But, in vinylcyclohexane (**2j**) and

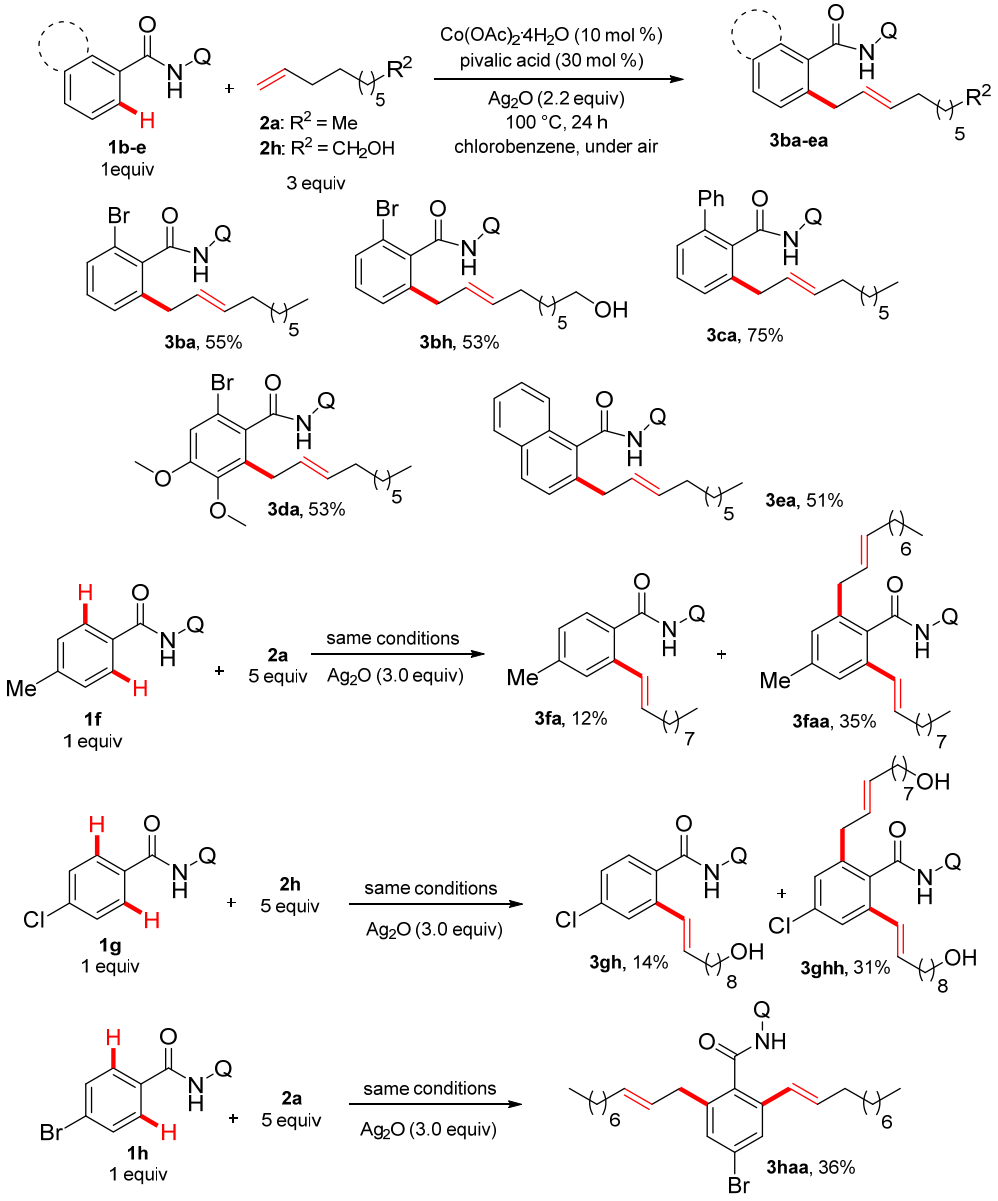
vinylcyclooctane (**2k**), an approx. 3:1 ratio of allyl and vinyl benzamides **3aj-ak'** were observed.



Scheme 3.1 Scope of unactivated alkenes **2a-k**

3.2.3 Scope of Substituted Benzamides

The allylation reaction was further examined with substituted benzamides **1b-h** (Scheme 3.2). *ortho* Bromo **1b** and phenyl **1c** substituted benzamides reacted with unactivated alkenes such as 1-decene (**2a**) or 9-decen-1-ol (**2h**) providing the expected allylated products **3ba-ca** in good yields. Sterically hindered 2-bromo-4,5-dimethoxy benzamide **1d** and 1-naphthyl amide **1e** also efficiently participated in the reaction affording products **3da** and **3ea** in good yields. However, the reaction of *para* methyl **1f** and chloro **1g** substituted benzamides provided a mixture of mono as well as *bis* olefinated benzamides **3fa-gh** and **3faa-ghh** in moderate yields. In *para* bromo benzamide **1h**, only *bis* olefinated product **3haa** was observed in 36% yield. It is very interesting to note that in products **3fa** and **3gh**, a typical Heck-type vinylated product was observed. Surprisingly, in *bis* olefinated products **3faa**, **3ghh** and **3haa**, vinylation was observed at one of the *ortho* carbons and allylation was found in another *ortho* carbon.



Scheme 3.2 Scope of substituted benzamides **1b-h**

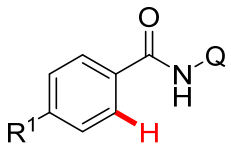
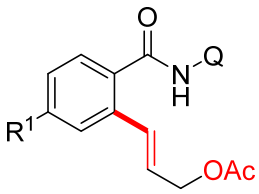
This results clearly reveals that a sterically hindered *ortho* substituted benzamides including *ortho* alkenylated benzamides prefer to give allylated products in a highly stereoselective manner. Whereas, a less hindered *para* substituted benzamides prefer to give a vinyl type coupling product.

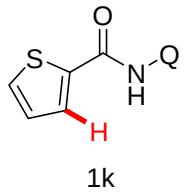
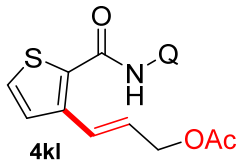
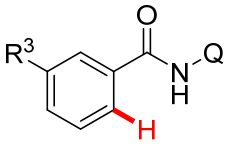
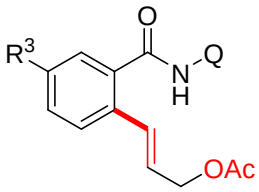
3.2.4 Vinylation of Substituted Benzamides with Allyl Acetate

Impressed by these results, the olefination reaction was examined with allyl acetates and alcohols (Table 3.1 and Scheme 3.3). Treatment of 4-chlorobenzamide (**1g**) with allyl acetate (**2l**) under the optimized reaction conditions in the presence of 3.0 equiv of pivalic

acid gave *ortho* vinylated product **4gl** in 42% yield. It is surprising that in product **4gl**, acetate moiety of **2l** was not cleaved and only a Heck-type vinylation product was observed. In the reported metal-catalyzed C−H bond functionalization reaction, allylic acetates mostly serve as an allylating agent, providing allylated product.[12d] In the present report, a typical Heck type vinylation product was observed in allyl acetate without cleavage of OAc group. The scope of olefination reaction was examined with substituted benzamides having functional groups such as I, Br, and OMe by using allylic acetate (**2l**) (Table 1). In all these reactions, the expected vinylated products **4hl-jl** were observed in moderate yields without acetate cleavage (entries 2-5). A heteroaromatic amide **1k** reacted with **2l**, affording product **4kl** in 30% yield. The alkenylation reaction of unsymmetrical benzamides **1l-m** with **2l** was highly site selective, providing vinylated products **4ll-lm** in moderate yields (entries 7 and 8). In benzamides **1l-m**, regioselectively a less hindered C6-H was involved

Table 3.1 Vinylation of substituted benzamides with allyl acetate[a]

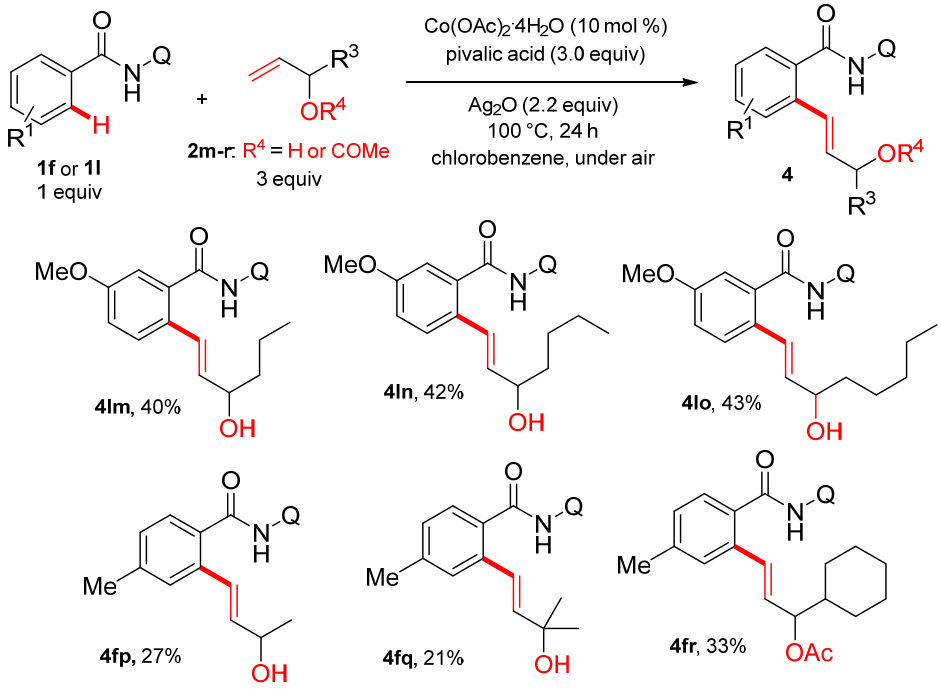
Entry	Alkenes **2**	Product **3**	Yield (%)[b]
			
1	**1g**: R^1 = Cl	**4gl**: R^1 = Cl	42
2	**1h**: R^1 = Br	**4hl**: R^1 = Br	37
3	**1i**: R^1 = I	**4il**: R^1 = I	33
4	**1f**: R^1 = Me	**4fl**: R^1 = Me	32
5	**1j**: R^1 = OMe	**4jl**: R^1 = OMe	29

6	 1k	 **4kl**	30
			
7	**1l**: R^3 = OMe	**4ll**: R^3 = OMe	33
8	**1m**: R^3 = I	**4ml**: R^3 = I	32

[a]All reactions were carried out using **1f-m** (100 mg), allyl acetate (**2l**) (3.0 equiv), $Co(OAc)_2{\cdot}4H_2O$ (10 mol %), pivalic acid (3.0 equiv), and Ag_2O (2.2 equiv) in chlorobenzene (4.0 mL) under air at 100 °C for 24 h. [b]Isolated yield.

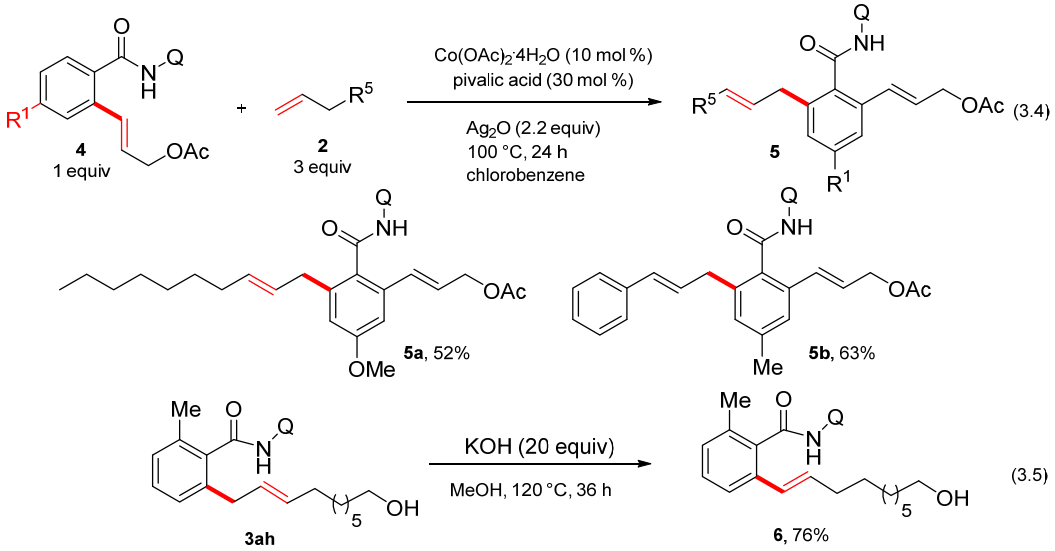
3.2.5 Scope of allyl alcohols and acetates

The olefination reaction was further examined with substituted allyl alcohols and allyl acetates (Scheme 3.3). Various allyl alcohols and acetates **2m-r** were efficiently involved in the reaction with *para* or *meta* substituted benzamides **1f** or **1l**, yielding the expected vinyl benzamides **4lm-fr** in moderate yields. Particularly, in *meta* substituted benzamide **1l**, vinylation selectively takes place at the C-6 position. It is observed that if any coordinating group such as ester is present at the γ-carbon of alkene, vinyl type product was observed exclusively (Scheme 3.3). If there is no coordinating group in γ-carbon, only allyl type products were observed (Scheme 3.1). A possibility of sequential C−H olefination at the *ortho* C−H bond of *ortho* olefinated benzamides **4** with unactivated alkenes **2** was examined (eq 3.4).



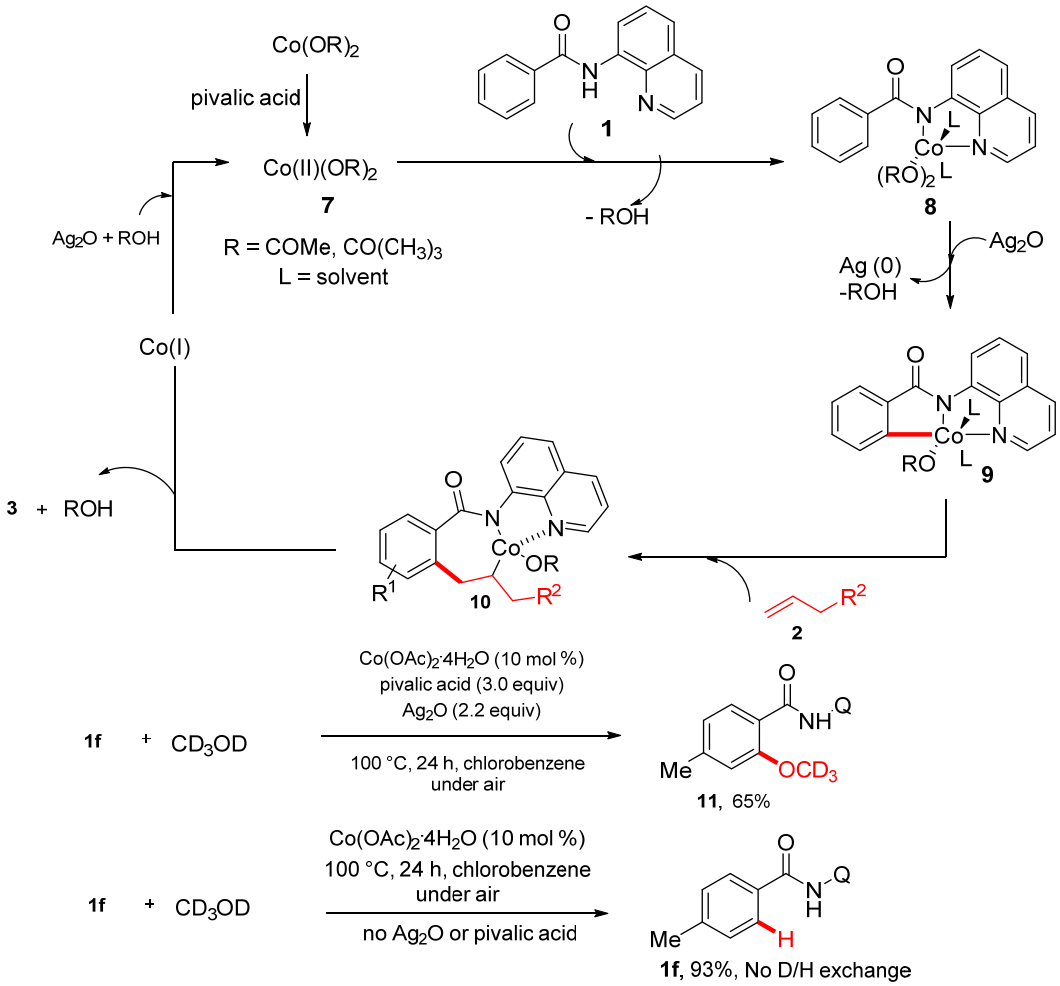
Scheme 3.3 Scope of allyl alcohols and acetates

When products **4jl** or **4fl** was treated with 1-octene (**2a**) or allylbenzene (**2d**), allyl aromatic alkenes **5a-b** were observed in good yields in a highly regioselective manner. In this way, unsymmetrical 2,6-diolefinated benzamides can be prepared selectively in good yields. Surprisingly, product **3ah** underwent double bond migration towards aromatic moiety in the presence of base, affording *ortho* vinylated aromatic amide **6** in 76% yield (eq 3.5).



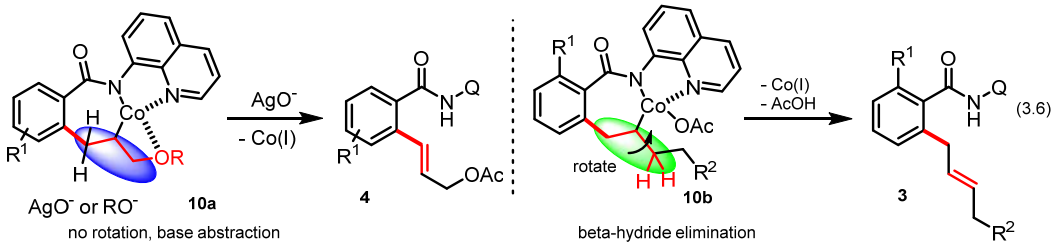
3.2.6 Proposed Mechanism

A possible reaction mechanism is proposed to account for the present reaction in 3.4. The catalytic cycle starts with the coordination of amide **1** with cobalt(II) catalyst which leads to the formation of intermediate **8**. Silver oxide likely oxidizes Co(II) to Co(III) in the presence of pivalic acid followed by acetate-mediated, irreversible C−H bond cleavage provides a cobaltacycle intermediate **9**. Coordinative insertion of the double bond of alkene **2** into a C−Co bond of intermediate **9** affords intermediate **10**. β-Hydride elimination of intermediate **10** gives olefinated product **3** and regenerates the active cobalt(II) species **7** by the reaction of Co(I) with Ag_2O and ROH.[11m] The reaction of **1f** with CD_3OD clearly reveals that the reaction starts with a Co(III) species **9** (Scheme 3.4). The reaction did not proceed in the absence of either Ag_2O or pivalic acid.



Scheme 3.4 Proposed mechanism

It is believed that the β-hydride elimination proceeds via a different mechanism in intermediate **10** based on the alkene coupling partner and substituent on the benzamide moiety. In allyl acetates and alcohols, intermediate **10a** would be formed. The OAc or OH substituent at the γ-carbon of alkene intramolecularly coordinates with a cobalt species in intermediate **10a** and stabilizes it (eq 3.6). The *syn* coplanarity arrangement of metal with C_β-H is required for β-hydride elimination. In intermediate **10a**, the rotation of a single bond to obtain *syn* coplanarity is restricted in both sides due to the strong coordination of aminoquinoline ligand as well as OR of alkene into a cobalt metal.[12] It is likely that the base AgO^- or RO^- could deprotonates the benzylic C−H bond to form vinylated product **4**.[7e] In unactivated alkenes, there is no coordinating group present at the γ-carbon.



Thus, to obtain the coplanarity, a single bond rotation takes place towards alkyl side easily in intermediate **10b** without any restriction (eq 3.6). After rotation, β-hydride elimination takes place at alkyl side efficiently and giving allyl benzamides **3**. In this case, β-hydride elimination was not found at the benzylic C−H bond due the strong complex formation of aminoquinoline ligand into a cobalt species. It is also further believed that an *ortho* substituent in benzamide can able to give a more conformational strain in the intermediate **10b**. Thus, the allylic selectivity is better in *ortho* substituted benzamides (particularly products **3faa**, **3ghh**, **3haa** and **5a-b**). It is unclear that the observation of vinylated products **3fa** and **3gh** in the reaction of *para* substituted benzamides **1f** or **1g** with alkenes **2a** or **2h**.

3.3 Conclusion

In conclusion, we have demonstrated a cobalt-catalyzed C−H olefination of benzamides with unactivated alkenes, allyl acetates and allyl alcohols. The present protocol allows an efficient route to synthesize vinyl and allyl benzamides in a highly stereoselective manner. It is observed that the *ortho* substituent on the benzamide moiety is crucial for

the observation of allylated products in unactivated alkenes. The mechanistic investigation suggest that a Co(III) acetate species is involved in the C−H bond activation. A detailed mechanistic investigation and the extension of a similar reaction in other organic molecules are in progress in our laboratory.

3.4 References

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3.5: Experimental section

3.5.1: General Procedure for the Cyclization Reaction.

All reactions were carried out under the air atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use (three times). Dry solvents were used for the reaction. Column chromatographical purifications were performed using SiO_2 (120-200 mesh ASTM) from Merck if not indicated otherwise. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Starting Materials: commercial available starting materials, metal complexes and metal salts were purchased from commercial sources and used without further purification.

3.5.2: General Procedure for the Synthesis of Allyl Benzamides via A Cobalt-Catalyzed alkenylation of Benzamides with Unactivated Alkenes (GP 1).

To a 15-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amides **1** (100 mg, 1 equiv) and Ag_2O (2.2 equiv) was added chlorobenzene (4.0 mL) via syringe. After that, unactivated alkenes **2** (3.0 equiv) and *pivalic acid (30 mol %, freshly distilled)* were added via syringe sequentially. After that, a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. 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 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 **3**.

Note: For compounds **3ab** and **3ai**, a 5.0 equiv of corresponding alkenes **2b** and **2i** were used. Because of their low boiling point, an excess amount was used.

Note: For reactions **1f, 1g** and **1h**, 5.0 equiv of corresponding alkenes **2a** and 3.0 equivalent of Ag_2O were used.

Note: The reaction is not air sensitive and nitrogen gas purging is not needed.

Note: A similar procedure was used to synthesize compounds **5a** and **5b**.

3.5.3: General Procedure for the Synthesis of Vinyl Benzamides via A Cobalt-Catalyzed Vinylation of Benzamides with Substituted Allyl Acetates or Allyl Alcohols (GP 2).

To a 15-mL pressure tube containing $Co(OAc)_2 \cdot 4H_2O$ (10 mol %), amides **1** (100 mg, 1.0 equiv) and Ag_2O (2.2 equiv) was added cholorobenzene (4.0 mL) via syringe. After that, allyl acetates or alcohols **2** (3.0 equiv) and *pivalic acid (3.0 equiv, freshly distilled)* were added via syringe sequentially. After that, a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. 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 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 **4**.

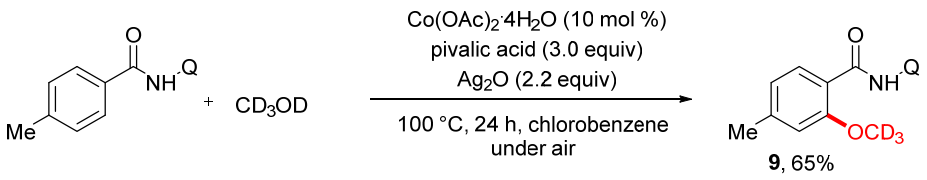
Note: The reaction is not air sensitive and nitrogen gas purging is not needed.

Note: For compound **4fr**, 1.5 equiv of corresponding allyl acetate **2r** were used.

3.5.4 Procedure for the Preparation of Compound 6 (GP 3).

Compound **3ah** (75 mg, 1.0 equiv) was dissolved in MeOH (3.0 mL) was taken in a 15-mL pressure tube containing KOH (0.65g, 20 equiv). Then, the pressure tube was closed with screw cap under air and allowed to stir at 120 ^oC for 36 h. After that pressure tube was taken out from oil bath and allowed to cool to room temperature. The reaction mixture was neutralised with 10% aq. HCl solution and extracted with EtOAc (10mL X 3). Organic layer was separated and concentrated after drying by using Na_2SO_4. Then, crude product **6** purified through a silica gel column using hexanes and ethyl acetate as eluent to give isomerised product **6**.

3.5.5: Procedure for Preparation of *ortho* Methoxy Benzamide 10 by Using CD_3OD (GP 4).

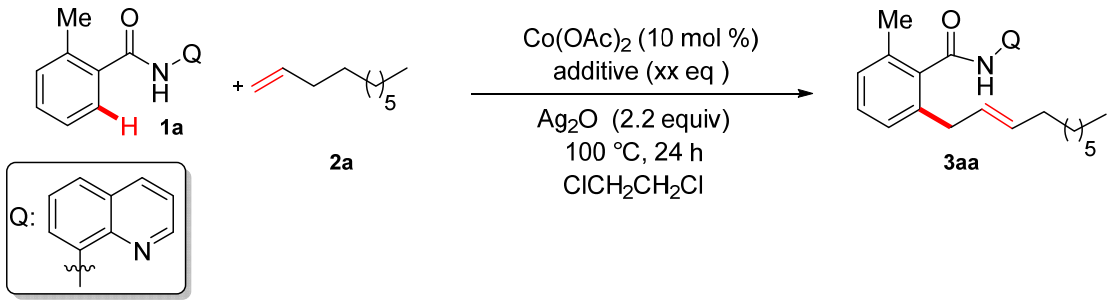


To a 15-mL pressure tube containing $Co(OAc)_2 \cdot 4H_2O$ (10 mol %), benzamide **1f** (100 mg, 1.0 equiv) and Ag_2O (2.2 equiv) was added cholorobenzene (4.0 mL) via syringe. Then, deuterated CD_3OD (1.0 mL) and pivalic acid (30 mol %, *freshly distilled*) were added via syringes. After that, a screw cap was used to cover the tube. Later, the reaction mixture

stirred at room temperature for 5 minutes. 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 the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give *ortho* methoxylated product **10**.

3.5.6 Optimization Studies

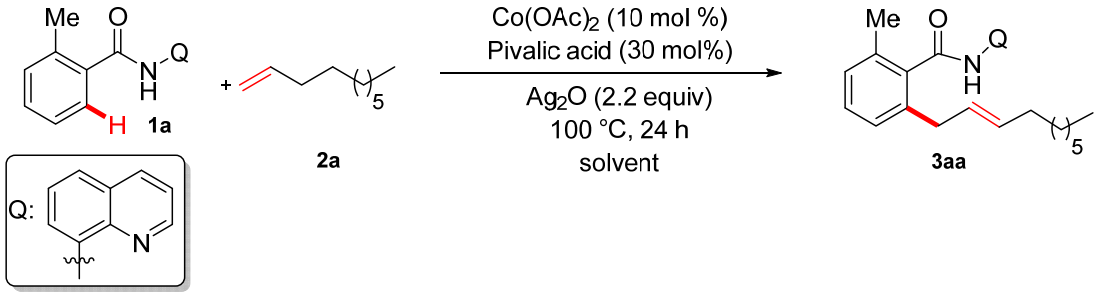
Table 3.2: Additive Optimization[a]



Entry	Additive (xx equiv)	Yield **3aa** (%)[b]
1	AcOH (3 equiv)	NR
2	Adm-1-COOH (30 mol %)	22
3	**PivOH (30 mol %)**	34
4	Mesitylenic acid (30 mol %)	trace

[a]All reactions were carried out under the following conditions: **1a** (100 mg), **2a** (3.0 equiv), $Co(OAc)_2$ (10 mol %), additive (specified) and oxidant (2.2 equiv) in solvent (4 mL) at 100 ^oC for 24 h under air atmosphere. [b]Isolated yield.

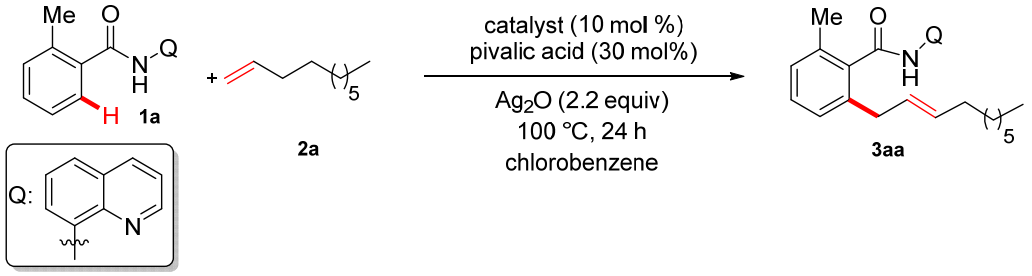
Table 3.3: Solvent Optimization[a]



Entry	Solvent	Yield **3aa** (%)[b]
1	1,4-dioxane	NR
2	Toluene	23
3	*tert*-amyl alcohol	NR
4	*tert*-BuOH	NR
5	*iso*-PrOH	NR
6	CF_3CH_2OH	21
7	CH_3CN	NR
8	DMF	NR
9	**cholorobenzene**	**60**
10	DMSO	NR
11	THF	NR

[a]All reactions were carried out under the following conditions: **1a** (100 mg), **2a** (3.0 equiv), $Co(OAc)_2$ (10 mol %), PivOH (30 mol %) and Ag_2O (2.2 equiv) in solvent (4.0 mL) at 100 ^oC for 24 h under air atmosphere. [b] Isolated yield.

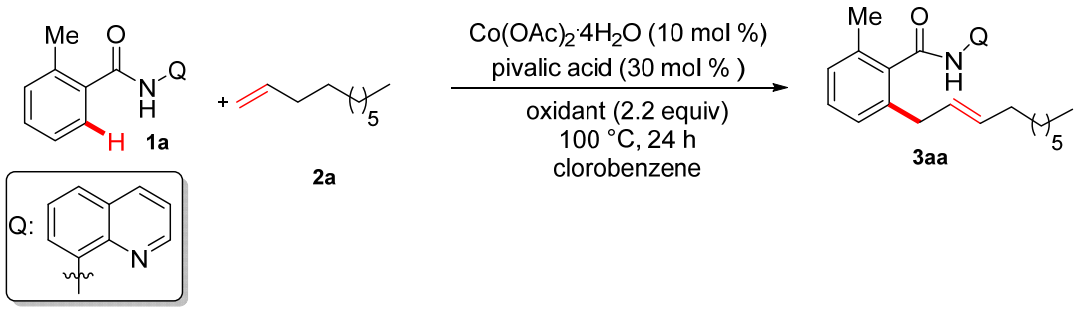
Table 3.4: Cobalt Source Optimization[a]



Entry	Cobalt source	Yield **3aa** (%)[b]
1	$Co(acac)_2$	37
2	$CoBr_2$	NR
3	$Co(acac)_3$	NR
4	**$Co(OAc)_2{\cdot}4H_2O$**	**63**

[a]All reactions were carried out under the following conditions: **1a** (100 mg), **2a** (3.0 equiv), catalyst (10 mol %), PivOH (30 mol %) and Ag_2O (2.2 equiv) in solvent (4.0 mL) at 100 °C for 24 h under air atmosphere. [b] Isolated yield.

Table 3.5: Oxidant Optimization[a]

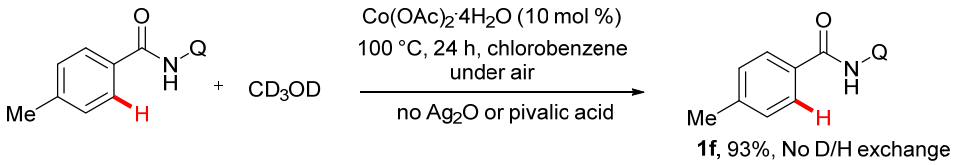


Entry	Oxidant (equiv)	Yield **3aa** (%)[b]
1	$Cu(OAc)_2{\cdot}H_2O$ (2.2 equiv)	NR
2	AgOTf (2.2 equiv)	23
3	AgOAc (2.2 equiv)	41

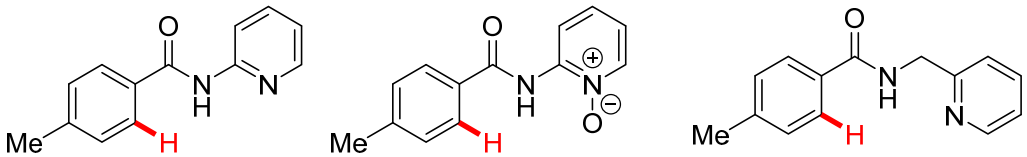
4	Ag_2CO_3 (2.2 equiv)	46
5	**Ag_2O (2.2 equiv)**	**63**
6	$Ag(CF_3CO_2)$ (2.2 equiv)	24
7	$K_2S_2O_8$ (2.2 equiv)	NR
8	$(NH_4)_2S_2O_8$ (2.2 equiv)	NR
9	Ag_2O (1.2 equiv)	43

[a]All reactions were carried out under the following conditions: **1a** (100 mg), **2a** (3.0 equiv), $Co(OAc)_2{\cdot}4H_2O$ (10 mol %), PivOH (30 mol %) and oxidant (specified) in solvent (4.0 mL) at 100 ^oC for 24 h under air atmosphere. [b] Isolated yield.

Controlled experiments:

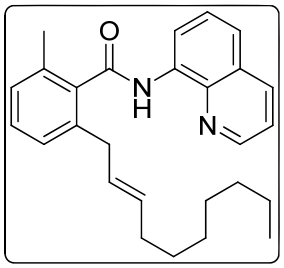


Other Failure Directing Groups Examined



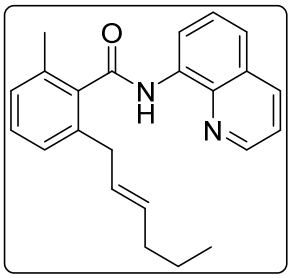
3.6 Spectral Data of Compounds

(*E*)-2-Methyl-6-(dec-2-en-1-yl)-*N*-(quinolin-8-yl)benzamide (3aa).



Prepared according to **GP 1**; Coloueless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 63% (96 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.94 (s, 1H), 9.02 (d, *J* = 7.4 Hz, 1H), 8.75 (d, *J* = 4.2 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.60 (dd, *J* = 15.2, 7.8 Hz, 2H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.16 (dd, *J* = 7.2, 4.4 Hz, 2H), 5.57 (dd, *J* = 14.6, 7.4 Hz, 1H), 5.44 (dd, *J* = 14.6, 7.2 Hz, 1H), 3.47 (d, *J* = 6.6 Hz, 2H), 2.46 (s, 3H), 1.91 – 1.77 (m, 2H), 1.33 – 1.21 (m, 2H), 1.14 (brs, 8H), 0.87 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 168.7, 148.3, 138.6, 137.8, 137.8, 136.4, 134.6, 134.5, 132.5, 129.2, 128.2, 128.1, 128.1, 127.5, 127.1, 121.9, 121.7, 116.8, 36.8, 32.5, 31.8, 29.3, 29.2, 29.2, 22.7, 19.6, 14.2. **IR (ATR)** ṽ (cm^{-1}): 3346, 2922, 2853, 1722, 1675, 1517, 1477, 1382, 1324 and 1074. **HRMS (ESI):** calc. for [($C_{27}H_{32}N_2O$)H] (M+H) 401.2593, measured 401.2597.

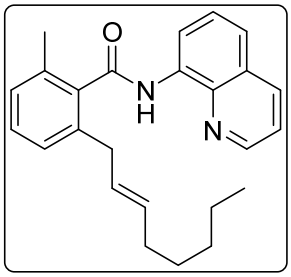
(*E*)-2-(Hex-2-en-1-yl)-6-methyl-*N*-(quinolin-8-yl)benzamide (3ab).



Prepared according to **GP 1**; colourless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 75% (98 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.95 (s, 1H), 9.02 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.71 – 7.56 (m, 2H), 7.47 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.31 (dd, *J* = 13.4, 5.8 Hz, 1H), 7.19 – 7.13 (m, 2H), 5.69 – 5.51 (m, 1H), 5.51 – 5.28 (m, 1H), 3.47 (d, *J* = 6.8 Hz, 2H), 2.46 (s, 3H), 1.85 (td, *J* = 7.8, 1.2 Hz, 2H), 1.23 (dq, *J* = 14.6, 7.4 Hz, 2H), 0.77 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 168.8, 148.3, 138.6, 137.8, 137.8, 136.4, 134.8, 134.5, 132.3, 129.2, 128.4, 128.1, 128.1, 127.5, 127.1, 122.0, 121.7, 116.9, 36.7, 34.6, 22.4, 19.6, 13.7. **IR (ATR)** ṽ (cm^{-1}): 3340, 2911, 2842, 1706, 1666, 1526, 1474, 1354,

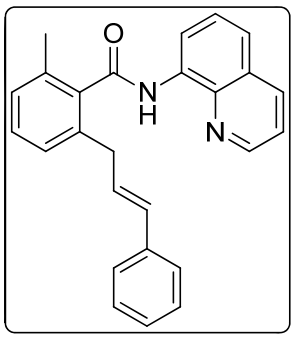
1319 and 1103. **HRMS (ESI):** calc. for [($C_{23}H_{24}N_2O$)H] (M+H) 345.1967, measured 345.1972.

(*E*)-2-(Oct-2-en-1-yl)-6-methyl-*N*-(quinolin-8-yl)benzamide (3ac).



Prepared according to **GP 1**; coloueless oil; eluent (15 % ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 67% (95 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.94 (s, 1H), 9.01 (d, *J* = 7.4 Hz, 1H), 8.75 (d, *J* = 4.0 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.70 – 7.54 (m, 2H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.30 (dd, *J* = 13.2, 5.4 Hz, 1H), 7.16 (dd, *J* = 7.4, 4.2 Hz, 2H), 5.64 – 5.53 (m, 1H), 5.48 – 5.37 (m, 1H), 3.46 (d, *J* = 6.6 Hz, 2H), 2.46 (s, 3H), 1.84 (q, *J* = 6.6 Hz, 2H), 1.23 – 1.03 (m, 6H), 0.81 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 168.7, 148.3, 138.6, 137.8, 137.8, 136.4, 134.8, 134.5, 132.5, 129.2, 128.2, 128.1, 128.1, 127.6, 127.1, 121.9, 121.7, 116.8, 36.8, 32.4, 31.5, 28.9, 22.5, 19.6, 14.1. **IR (ATR)** ṽ (cm^{-1}): 3333, 2906, 2823, 1716, 1665, 1506, 1465, 1379, 1319 and 1063.**HRMS (ESI):** calc. for [($C_{25}H_{28}N_2O$)H] (M+H) 373.2280, measured 373.2285.

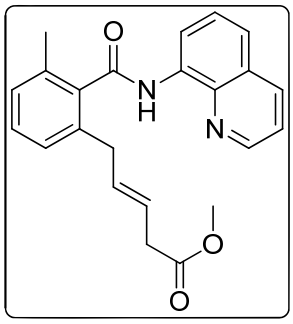
2-Cinnamyl-6-methyl-*N*-(quinolin-8-yl)benzamide (3ad).



Prepared according to **GP 1**; Colourless thick oil; eluent (25% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 73% (105 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.01 (s, 1H), 9.05 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.52 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.69 – 7.60 (m, 1H), 7.57 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.42 – 7.31 (m, 2H), 7.22

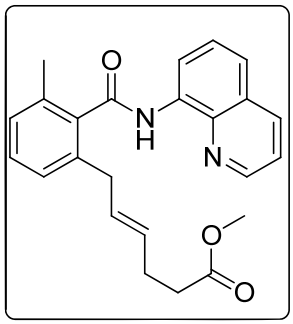
(dd, *J* = 14.2, 7.6 Hz, 2H), 7.17 – 7.08 (m, 5H), 6.42 – 6.31 (m, 2H), 3.69 (d, *J* = 6.0 Hz, 2H), 2.50 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$):** 168.6, 148.2, 138.4, 137.9, 137.3, 136.8, 136.2, 134.9, 134.3, 131.3, 129.3, 128.7, 128.4, 128.2, 127.9, 127.3, 127.3, 126.8, 126.0, 122.0, 121.6, 116.8, 37.1, 19.5. **IR (ATR)** ṽ (cm^{-1}): 3744, 3405, 2855, 1709, 1527, 1465, 1376, 1337, 1203 and 1125. **HRMS (ESI):** calc. for [($C_{26}H_{22}N_2O$)H] (M+H) 379.1810, measured 379.1804.

Methyl (*E*)-5-(3-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)pent-3-enoate (3ae).



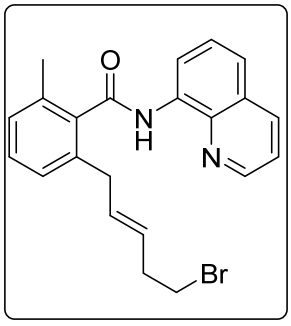
Prepared according to **GP 1**; Colourless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 67% (96 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.95 (s, 1H), 9.01 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.82 – 7.54 (m, 2H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.31 (dd, *J* = 13.8, 6.2 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 5.78 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.58 (dt, *J* = 15.2, 6.8 Hz, 1H), 3.61 (s, 3H), 3.53 (d, *J* = 6.8 Hz, 2H), 2.95 (d, *J* = 6.8 Hz, 2H), 2.47 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 172.2, 168.5, 148.3, 138.5, 137.7, 136.7, 136.4, 134.9, 134.3, 132.7, 129.3, 128.3, 128.1, 127.4, 127.1, 123.3, 122.1, 121.7, 116.8, 51.7, 37.6, 36.7, 19.5. **IR (ATR)** ṽ (cm^{-1}): 3743, 3343, 2921, 1737, 1676, 1521, 1481, 1425, 1385, 1236 and 1128. **HRMS (ESI):** calc. for [($C_{23}H_{22}N_2O_3$)H] (M+H) 375.1709, measured 375.1714.

Methyl (*E*)-5-(3-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)hex-3-enoate (3af).



Prepared according to **GP 1**; Colourless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 68% (101 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.94 (s, 1H), 9.01 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.70 – 7.54 (m, 2H), 7.47 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.30 (dd, *J* = 12.8, 5.0 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 2H), 5.75 – 5.57 (m, 1H), 5.51 – 5.37 (m, 1H), 3.61 (s, 3H), 3.47 (d, *J* = 6.8 Hz, 2H), 2.46 (s, 3H), 2.31 – 2.15 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$):** 173.6, 168.7, 148.4, 138.6, 137.7, 137.3, 136.4, 134.8, 134.4, 130.0, 129.7, 129.2, 128.3, 128.1, 127.5, 127.1, 122.1, 121.8, 116.8, 51.5, 36.6, 33.71, 27.7, 19.6. **IR (ATR)** ṽ (cm^{-1}): 3346, 3007, 2950, 1733, 1672, 1517, 1426, 1383, 1323 and 1082. **HRMS (ESI):** calc. for $[(C_{24}H_{24}N_2O_3)H]$ (M+H) 389.1865 measured 389.1874.

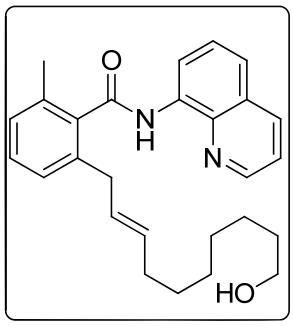
(*E*)-2-(5-Bromopent-2-en-1-yl)-6-methyl-*N*-(quinolin-8-yl)benzamide (3ag).



Prepared according to **GP 1**; Colourless oil; eluent (15 % ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 63% (98 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.94 (s, 1H), 9.02 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.21 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.62 (ddd, *J* = 10.7, 9.8, 4.8 Hz, 2H), 7.47 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.37 – 7.28 (m, 1H), 7.18 (d, *J* = 7.6 Hz, 2H), 5.74 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.42 (dt, *J* = 15.2, 6.8 Hz, 1H), 3.51 (d, *J* = 6.8 Hz, 2H), 3.21 (t, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 2.43 (dd, *J* = 14.2, 7.2 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** 168.6, 148.3, 138.5, 137.7, 136.9, 136.4, 134.8, 134.3, 131.7, 129.2, 128.4, 128.4, 128.1, 127.4, 127.2, 122.1, 121.7, 116.8, 36.6, 35.8,

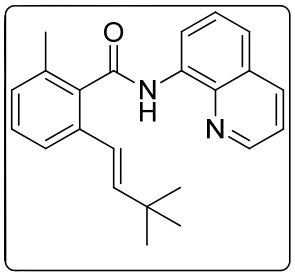
32.3, 19.5. **IR (ATR)** ṽ (cm^{-1}): 3343, 3050, 1671, 1590, 1518, 1477, 1424, 1324 and 1089. **HRMS (ESI):** calc. for [($C_{22}H_{21}BrN_2O$)H] (M+H) 409.0916, measured 409.0924.

(*E*)-2-(10-Hydroxydec-2-en-1-yl)-6-methyl-N-(quinolin-8-yl)benzamide (3ah).



Prepared according to **GP 1**; Colourless oil; eluent (15 % ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 66% (105 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.96 (s, 1H), 9.02 (d, *J* = 7.4 Hz, 1H), 8.75 (d, *J* = 4.0 Hz, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.67 – 7.53 (m, 2H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.20 – 7.12 (m, 2H), 5.67 – 5.52 (m, 1H), 5.49 – 5.36 (m, 1H), 3.60 (t, *J* = 6.8 Hz, 2H), 3.47 (d, *J* = 6.8 Hz, 2H), 2.46 (s, 3H), 1.93 – 1.79 (m, 2H), 1.56 – 1.44 (m, 2H), 1.32 – 1.00 (m, 9H). **^{13}C NMR (100 MHz, $CDCl_3$):** 168.8, 148.2, 138.5, 137.7, 137.6, 136.4, 134.7, 134.4, 132.3, 129.1, 128.2, 128.0, 128.0, 127.4, 127.0, 121.9, 121.6, 116.8, 62.9, 36.7, 32.7, 32.3, 29.2, 29.0, 25.6, 19.5. **IR (ATR)** ṽ (cm^{-1}): 3344, 3043, 2853, 1731, 1665, 1506, 1456, 1379, 1319 and 1024. **HRMS (ESI):** calc. for [($C_{27}H_{32}N_2O_2$)Na] (M+Na) 439.2361, measured 439.2355.

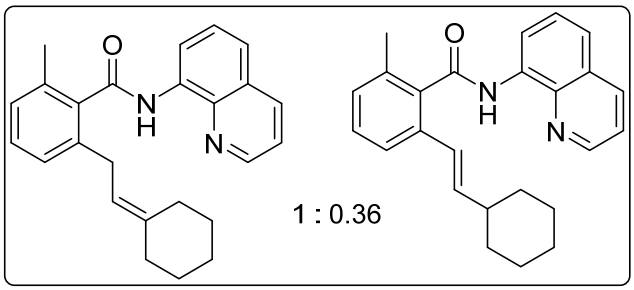
(*E*)-2-(3,3-Dimethylbut-1-en-1-yl)-6-methyl-*N*-(quinolin-8-yl)benzamide (3ai).



Prepared according to **GP 1**; Colourless oil; eluent (15 % ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 57% (78 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.92 (s, 1H), 9.02 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.8 Hz,

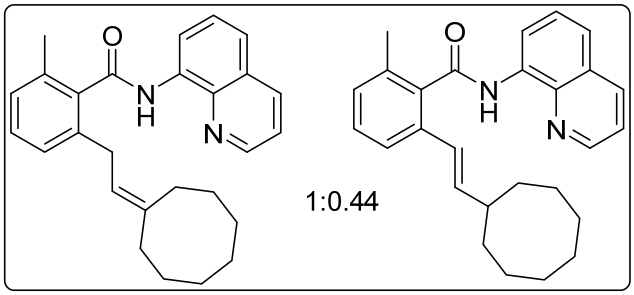
1H), 7.70 – 7.55 (m, 2H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.25 (d, *J* = 16.0 Hz, 1H), 2.47 (s, 3H), 0.93 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$):** 168.6, 148.3, 145.2, 138.6, 136.4, 135.7, 135.3, 134.6, 129.2, 128.8, 128.1, 127.5, 123.5, 122.1, 121.9, 121.7, 116.8, 33.6, 29.4, 19.6. **IR (ATR)** ṽ (cm^{-1}): 3743, 3344, 2955, 1719, 1517, 1475, 1382, 1324, 1259 and 1125. **HRMS (ESI):** calc. for [($C_{23}H_{24}N_2O$)Na] (M+Na) 367.1786, measured 367.1797.

2-(2-Cyclohexylideneethyl)-6-methyl-*N*-(quinolin-8-yl)benzamide (3aj and **3aj').**



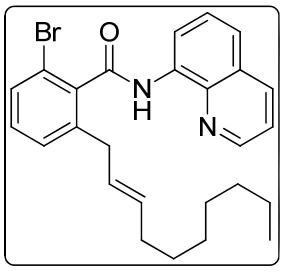
Prepared according to **GP 1**; Colourless oil; eluent (15 % ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 64% (combined with minor isomer ratio 1:0.36) (94 mg). Only major isomer data is mentioned here. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.95 (s, 1H), 9.01 (d, *J* = 7.6 Hz, 1H), 8.76 (d, *J* = 4.2 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.68 – 7.55 (m, 2H), 7.46 (dd, *J* = 8.2, 3.8 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.15 (t, *J* = 8.2 Hz, 2H), 5.29 (t, *J* = 7.2 Hz, 1H), 3.49 (d, *J* = 7.2 Hz, 1H), 2.45 (s, 3H), 2.16 – 2.06 (m, 2H), 1.98 (t, *J* = 5.2 Hz, 2H), 1.33 – 0.94 (m, 6H).**^{13}C NMR (100 MHz, $CDCl_3$):** 168.8, 148.2, 140.8, 138.7, 138.6, 137.7, 136.3, 134.6, 134.5, 129.1, 128.0, 127.9, 127.4, 126.8, 121.9, 121.7, 119.4, 116.8, 37.1, 31.1, 28.7, 28.4, 27.6, 26.8, 19.5. **IR (ATR)** ṽ (cm^{-1}): 3743, 3333, 2920, 1663, 1509, 1466, 1421, 1373, 1247 and 1058. **HRMS (ESI):** calc. for [($C_{25}H_{26}N_2O$)H] (M+H) 371.2123 measured 317.2132.

2-(2-Cyclooctylideneethyl)-6-methyl-N-(quinolin-8-yl)benzamide (3ak and **3ak').**



Prepared according to **GP 1**; Colourless oil; eluent (15 % ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 62% (combined with minor isomer ratio 1: 0.44) (95 mg). Only major isomer data is mentioned here. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.95 (s, 1H), 9.02 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.63 (dd, *J* = 10.8, 4.6 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.17 (dd, *J* = 10.6, 7.8 Hz, 2H), 5.38 (t, *J* = 7.2 Hz, 1H), 3.51 (d, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 2.16 – 2.06 (m, 2H), 2.06 – 1.99 (m, 2H), 1.73 – 1.66 (m, 2H), 1.59 – 1.51 (m, 8H).**^{13}C NMR (100 MHz, $CDCl_3$):** 168.8, 148.2, 142. 2, 140.8, 138.7, 138.5, 137.8, 136.3, 134.6, 134.5, 129.1, 127.8, 127.4, 126.8, 123.4, 121.8, 121.6, 116.9, 37.4, 31.3, 29.1, 27.2, 26.3, 26.3, 25.9, 25.1, 24.8. **IR (ATR)** ṽ (cm^{-1}): 3744, 3343, 2917, 1673, 1518, 1476, 1425, 1383, 1260 and 1168. **HRMS (ESI):** calc. for [($C_{27}H_{30}N_2O$)H] (M+H) 399.2436, measured 299.2435.

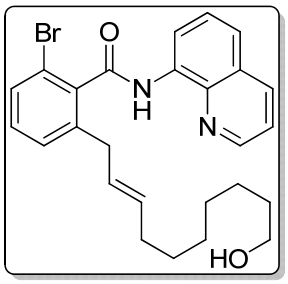
(*E*)-2-Bromo-6-(dec-2-en-1-yl)-*N*-(quinolin-8-yl)benzamide (3ba).



Prepared according to **GP 1**; Colourless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 55 % (78 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.99 (s, 1H), 9.01 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.78 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.59 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.52 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.47 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.37 – 7.22 (m, 2H), 5.56 (dt, *J* = 14.2, 6.6 Hz, 1H), 5.46 (dt, *J* = 14.0, 6.4 Hz, 1H), 3.50 (d, *J* = 6.4 Hz, 2H), 1.86 (q, *J* = 6.6 Hz, 2H), 1.34 – 1.15

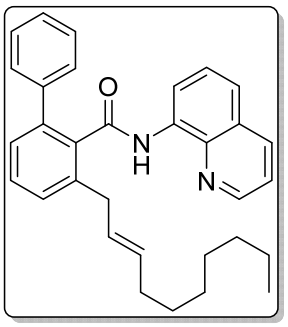
(m, 10 H), 0.88 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 166.3, 148.3, 140.6, 138.7, 138.5, 136.3, 134.2, 133.3, 130.5, 128.6, 128.0, 127.4, 127.2, 122.2, 121.7, 119.8, 116.9, 36.9, 32.4, 31.8, 29.1, 29.1, 29.1, 22.6, 14.1. **HRMS (ESI):** calc. for [($C_{26}H_{29}BrN_2O$)H] (M+H) 465.1542, measured 465.1540.

(*E*)-2-Bromo-6-(10-hydroxydec-2-en-1-yl)-*N*-(quinolin-8-yl)benzamide (3bh).



Prepared according to **GP 1**; Colourless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 53% (78 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.98 (s, 1H), 8.99 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.67 – 7.57 (m, 2H), 7.52 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.47 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.31 – 7.23 (m, 2H), 5.56 (dt, *J* = 14.4, 6.6 Hz, 1H), 5.50 – 5.38 (m, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.49 (d, *J* = 6.4 Hz, 2H), 1.91 – 1.79 (m, 2H), 1.57 – 1.45 (m, 3H), 1.37 – 1.16 (m, 8H). **^{13}C NMR (100 MHz, $CDCl_3$):** 166.4, 148.4, 140.7, 138.8, 138.6, 136.4, 134.2, 133.2, 130.6, 128.7, 128.1, 127.5, 127.4, 122.3, 121.8, 119.9, 117.1, 63.1, 36.9, 32.8, 32.4, 29.2, 29.1, 29.1, 25.7. **HRMS (ESI):** calc. for [($C_{26}H_{29}BrN_2O_2$)H] (M+H) 481.1491, measured 481.1493.

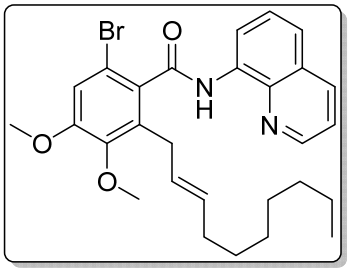
(*E*)-3-(Dec-2-en-1-yl)-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (3ca).



Prepared according to **GP 1**; Colourless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 75% (107 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.67 (s, 1H),

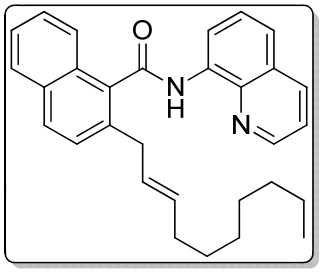
8.81 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.63 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.08 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.57 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.40 – 7.33 (m, 3H), 7.29 – 7.21 (m, 2H), 7.15 – 7.07 (m, 1H), 5.65 (ddd, *J* = 14.8, 7.2, 6.2 Hz, 1H), 5.58 – 5.44 (m, 1H), 3.63 (d, *J* = 6.6 Hz, 2H), 1.87 (q, *J* = 6.6 Hz, 2H), 1.34 – 1.14 (m, 10H), 0.88 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 168.1, 147.9, 140.4, 139.8, 139.1, 138.4, 136.6, 136.0, 134.4, 132.6, 129.3, 128.8, 128.7, 128.2, 128.0, 128.0, 127.8, 127.3, 121.6, 121.4, 116.5, 36.8, 32.5, 31.8, 29.2, 29.2, 29.1, 22.6, 14.1. **HRMS (ESI):** calc. for [($C_{32}H_{34}N_2O$)H] (M+H) 463.2749, measured 463.2750.

(*E*)-6-Bromo-2-(dec-2-en-1-yl)-3,4-dimethoxy-*N*-(quinolin-8-yl)benzamide (3da).



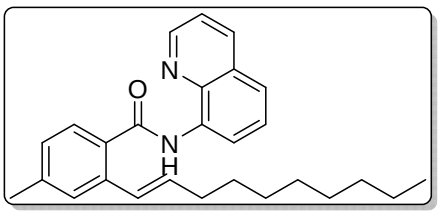
Prepared according to **GP 1**; Colourless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 53 % (75 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.94 (s, 1H), 8.99 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.72 – 7.56 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.06 (s, 1H), 5.63 – 5.47 (m, 1H), 5.38 (dt, *J* = 15.2, 6.5 Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.50 (d, *J* = 5.9 Hz, 2H), 1.73 (d, *J* = 6.2 Hz, 2H), 1.23 – 1.16 (m, 2H), 1.16 – 1.00 (m, 8H), 0.85 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 166.0, 153.8, 148.2, 146.7, 138.5, 136.3, 134.3, 134.2, 132.4, 132.4, 128.0, 127.4, 127.2, 122.1, 121.6, 116.8, 114.6, 113.9, 60.8, 56.1, 32.4, 31.7, 31.3, 29.2, 29.0, 22.6, 14.1. **HRMS (ESI):** calc. for [($C_{28}H_{33}BrN_2O_3$)H] (M+H) 525.1753, measured 525.1748.

(*E*)-2-(Dec-2-en-1-yl)-*N*-(quinolin-8-yl)-1-naphthamide (3ea).



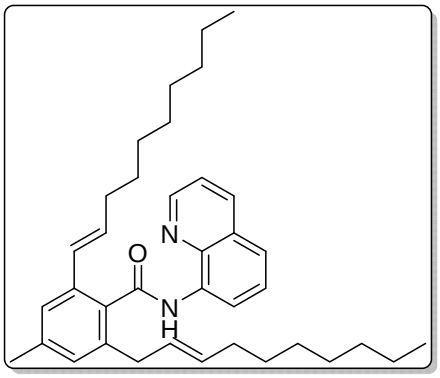
Prepared according to **GP 1**; Colourless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 51 % (75 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.17 (s, 1H), 9.17 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.68 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.04 (dd, *J* = 6.2, 3.6 Hz, 1H), 7.99 – 7.86 (m, 2H), 7.72 – 7.65 (m, 1H), 7.62 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.48 – 7.40 (m, 2H), 5.78 – 5.61 (m, 1H), 5.52 (ddd, *J* = 15.2, 10.2, 6.0 Hz, 1H), 3.65 (d, *J* = 6.4 Hz, 2H), 1.92 (d, *J* = 6.8 Hz, 2H), 1.38 – 1.14 (m, 9H), 0.88 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 168.2, 148.2, 138.5, 136.3, 135.3, 134.5, 134.0, 132.8, 132.0, 130.4, 129.4, 128.1, 127.9, 127.9, 127.7, 127.5, 127.0, 125.8, 125.0, 122.1, 121.6, 116.9, 37.1, 32.5, 31.8, 29.2, 29.1, 29.1, 22.6, 14.1. **HRMS (ESI):** calc. for [($C_{30}H_{32}N_2O$)H] (M+H) 437.2593, measured 437.2587.

(*E*)-2-(Dec-1-en-1-yl)-4-methyl-*N*-(quinolin-8-yl)benzamide (3fa).



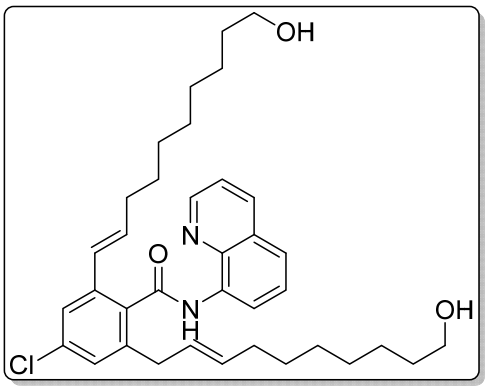
Prepared according to **GP 1**; Colourless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 12 % (18 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.24 (s, 1H), 8.98 (d, *J* = 7.6 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.19 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.64 (dd, *J* = 18.6, 7.8 Hz, 2H), 7.59 – 7.54 (m, 1H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.42 (s, 1H), 7.17 (s, 1H), 6.90 (d, *J* = 15.6 Hz, 1H), 6.29 (dt, *J* = 15.6, 6.8 Hz, 1H), 2.44 (s, 3H), 2.21 (td, *J* = 8.2, 1.2 Hz, 2H), 1.47 – 1.37 (m, 2H), 1.35 – 1.21 (m, 10H), 0.88 (t, *J* = 4.8 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 167.9, 148.2, 140.6, 138.7, 136.7, 136.2, 134.9, 134.8, 132.4, 128.9, 128.2, 128.0, 127.7, 127.5, 127.5, 127.3, 121.6, 121.6, 116.5, 33.2, 31.8, 29.4, 29.2, 29.2, 22.6, 21.5, 14.1.

2-((*E*)-Dec-1-en-1-yl)-6-((*E*)-dec-2-en-1-yl)-4-methyl-*N*-(quinolin-8-yl)benzamide (3faa).



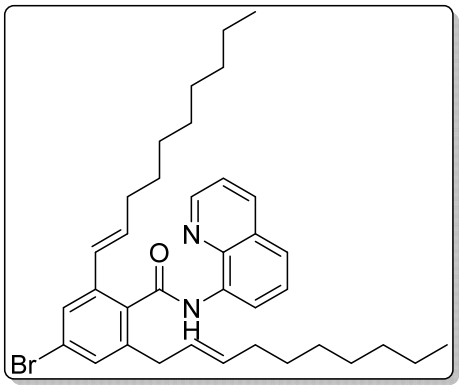
Prepared according to **GP 1**; Colourless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 35 % (72 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.93 (s, 1H), 9.04 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.73 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.18 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.68 – 7.55 (m, 2H), 7.48 – 7.39 (m, 1H), 7.28 (d, *J* = 3.2 Hz, 1H), 7.00 (s, 1H), 6.57 (d, *J* = 15.6 Hz, 1H), 6.25 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.57 (dt, *J* = 13.2, 6.8 Hz, 1H), 5.49 – 5.38 (m, 1H), 3.45 (d, *J* = 6.6 Hz, 2H), 2.40 (s, 3H), 2.09 (q, *J* = 6.6 Hz, 1H), 1.91 – 1.81 (m, 2H), 1.38 – 1.11 (m, 23H), 0.89 – 0.85 (m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** 168.6, 148.0, 138.8, 138.5, 138.1, 137.8, 136.2, 135.4, 134.6, 134.1, 133.4, 132.4, 132.4, 128.8, 128.2, 128.2, 128.0, 128.0, 127.4, 126.9, 124.1, 121.7, 121.6, 116.6, 36.6, 36.6, 33.2, 32.4, 31.9, 31.8, 29.2, 29.1, 29.1, 22.6, 22.6, 21.4, 14.1. **HRMS (ESI):** calc. for $[(C_{37}H_{50}N_2O)H]$ (M+H) 539.4001, measured 539.4003.

4-Chloro-2-((*E*)-dec-1-en-1-yl)-6-((*E*)-dec-2-en-1-yl)-*N*-(quinolin-8-yl)benzamide (3ghh).



Prepared according to **GP 1**; Colourless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 31% (61 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.92 (s, 1H), 8.98 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.70 – 7.55 (m, 3H), 7.47 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.43 (d, *J* = 1.8 Hz, 1H), 7.17 – 7.14 (m, 1H), 6.51 (d, *J* = 15.6 Hz, 1H), 6.26 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.52 (dd, *J* = 13.6, 7.8 Hz, 1H), 5.45 (dd, *J* = 14.0, 7.6 Hz, 1H), 3.61 (dt, *J* = 6.6, 5.4 Hz, 5H), 3.43 (d, *J* = 6.2 Hz, 2H), 2.09 (d, *J* = 6.6 Hz, 2H), 1.92 – 1.81 (m, 3H), 1.53 – 1.48 (m, 5H), 1.37 – 1.14 (m, 16H). **^{13}C NMR (100 MHz, $CDCl_3$):** 167.5, 148.2, 140.2, 138.5, 137.3, 136.3, 135.7, 135.1, 134.2, 134.1, 133.2, 128.0, 127.6, 127.4, 127.3, 127.2, 125.8, 123.4, 122.1, 121.7, 116.8, 63.0, 36.4, 33.0, 32.7, 32.7, 32.3, 29.2, 29.2, 29.1, 29.0, 28.9, 28.9, 28.8, 25.6. **HRMS (ESI):** calc. for [($C_{36}H_{47}ClN_2O_3$)H] (M+H) 591.3353, measured 591.3349.

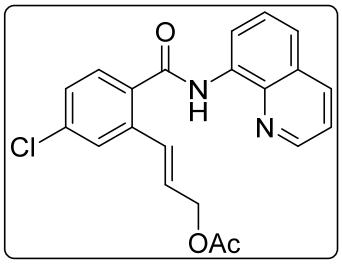
4-Bromo-2-((*E*)-dec-1-en-1-yl)-6-((*E*)-dec-2-en-1-yl)-*N*-(quinolin-8-yl)benzamide (3haa).



Prepared according to **GP 1**; Colourless oil; eluent (15% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 36% (66 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.93 (s, 1H), 9.00 (d, *J* = 7.2 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.19 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.68 – 7.57 (m, 3H), 7.50 – 7.42 (m, 1H), 7.34 – 7.29 (m, 1H), 6.51 (d, *J* = 15.6 Hz, 1H), 6.27 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.57 – 5.41 (m, 2H), 3.44 (d, *J* = 6.2 Hz, 2H), 2.10 (q, *J* = 7.2 Hz, 1H), 1.88 – 1.83(m, 2H), 1.48 – 1.10 (m, 23H), 0.89 – 0.84(m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** 167.4, 148.2, 140.4, 140.2, 138.5, 137.5, 136.3, 135.8, 134.6, 134.3,

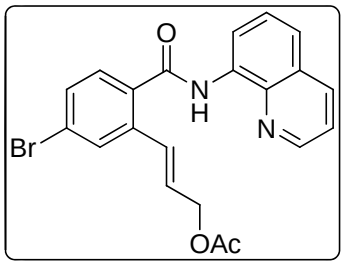
133.3, 130.6, 130.2, 128.0, 127.4, 127.2, 127.1, 126.4, 125.6, 123.5, 122.1, 121.7, 116.8, 36.3, 33.1, 32.4, 31.8, 31.8, 29.3, 29.1, 29.1, 29.0, 22.6, 22.6, 14.1. **HRMS (ESI):** calc. for [($C_{36}H_{47}BrN_2O$)H] (M+H) 603.2950, measured 603.2941.

(*E*)- 3-(5-Chloro-2-(quinolin-8-ylcarbamoyl)phenyl)allyl acetate (4gl).



Prepared according to **GP 2**; White solid; eluent (20% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 42% (57 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.21 (s, 1H), 8.89 (d, *J* = 7.2 Hz, 1H), 8.76 (d, *J* = 4.2 Hz, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.57 (m, 3H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 15.8 Hz, 1H), 6.33 (dt, *J* = 15.8, 6.2 Hz, 1H), 4.70 (d, *J* = 6.2 Hz, 2H), 1.97 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.7, 166.3, 148.5, 138.6, 137.2, 136.9, 136.5, 134.5, 133.9, 130.1, 129.6, 128.2, 128.1, 128.1, 127.5, 127.2, 122.3, 121.9, 116.8, 64.7, 20.9. **IR (ATR)** ṽ (cm^{-1}): 3744, 1737, 1671, 1588, 1524, 1425, 1233 and 1028. **HRMS (ESI):** calc. for [($C_{21}H_{17}ClN_2O_3$)H] (M+H) 381.1006, measured 381.1013.

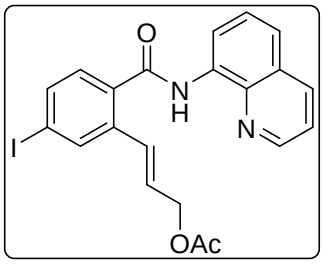
(*E*)- 3-(5-Bromo-2-(quinolin-8-ylcarbamoyl)phenyl)allyl acetate (4hl).



Prepared according to **GP 2**; Half white solid; eluent (20% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 37% (48 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.21 (s, 1H), 8.89 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.18 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.77 (d, *J* = 1.8 Hz, 1H), 7.70 – 7.51 (m, 4H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.13 (d, *J* = 15.8 Hz, 1H), 6.33 (dt, *J* = 15.8, 6.2 Hz, 1H), 4.70 (dd, *J* = 6.2, 1.4 Hz, 2H), 1.98 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.8, 166.4, 148.5, 138.7, 137.4, 136.5,

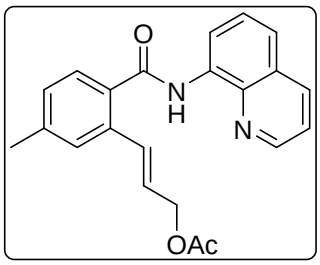
134.4, 134.3, 131.1, 130.2, 130.0, 129.7, 128.2, 128.1, 127.5, 125.3, 122.3, 121.9, 116.8, 64.7, 20.9. **IR (ATR)** ṽ (cm^{-1}): 3472, 3332, 1728, 1673, 1523, 1477, 1239 and 958. **HRMS (ESI):** calc. for [($C_{21}H_{17}BrN_2O_3$)H] (M+H) 425.0501, measured 425.0509.

(*E*)- 3-(5-Methoxy-2-(quinolin-8-ylcarbamoyl)phenyl)allyl acetate (4il).



Prepared according to **GP 2**; Half white solid; eluent (20% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 33 % (39 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.25 (s, 1H), 8.93 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.22 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.01 (d, *J* = 1.6 Hz, 1H), 7.78 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.69 – 7.55 (m, 2H), 7.54 – 7.42 (m, 2H), 7.13 (d, *J* = 15.8 Hz, 1H), 6.35 (dt, *J* = 15.8, 6.2 Hz, 1H), 4.73 (dd, *J* = 6.2, 1.4 Hz, 2H), 2.01 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.7, 166.4, 148.4, 138.6, 137.2, 137.0, 136.4, 136.1, 134.8, 134.4, 129.8, 129.5, 128.1, 128.0, 127.4, 122.2, 121.8, 116.7, 97.3, 64.6, 20.8. **IR (ATR)** ṽ (cm^{-1}): 3743, 3333, 3061, 1735, 1668, 1521, 1479, 1380, 1324 and 1227.**HRMS (ESI):** calc. for [($C_{21}H_{17}IN_2O_3$)H] (M+H) 473.0362, measured 473.0358.

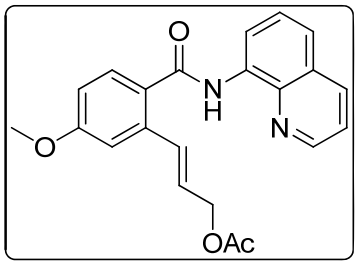
***(E)*-3-(5-Methyl-2-(quinolin-8-ylcarbamoyl)phenyl)allyl acetate (4fl).**



Prepared according to **GP 2**; Half white solid; eluent (20% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 32% (42 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.26 (s, 1H), 8.96 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.66 – 7.55 (m, 2H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 2H), 7.28 – 7.21 (m, 2H), 6.34 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.74 (dd, *J* = 6.4, 1.2 Hz, 2H), 2.45

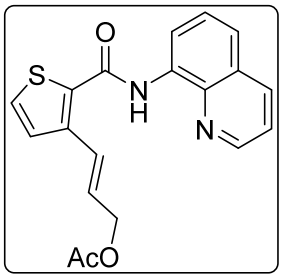
(s, 3H), 2.02 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.8, 167.3, 148.3, 140.9, 138.7, 136.3, 135.3, 134.7, 132.8, 131.7, 130.2, 128.8, 128.1, 127.8, 127.4, 126.3, 121.8, 121.6, 116.6, 65.0, 21.4, 20.8. **IR (ATR)** ṽ (cm^{-1}): 3744, 3342, 3043, 1734, 1688, 1522, 1481, 1425, 1381, 1325 and 1232. **HRMS (ESI):** calc. for [($C_{22}H_{20}N_2O_3$)H] (M+H) 361.1552, measured 361.1559.

(*E*)- 3-(5-Methoxy-2-(quinolin-8-ylcarbamoyl)phenyl)allyl acetate (4jl).



Prepared according to **GP 2**; White solid; eluent (25 % ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 29% (39 mg, 8% of *Z* isomer was also observed along with major *E* isomer 92%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.22 (s, 1H), 8.93 – 8.89 (m, 1H), 8.76 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.62 – 7.51 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.25 (d, *J* = 15.8 Hz, 1H), 7.09 (d, *J* = 2.6 Hz, 1H), 6.93 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.30 (dt, *J* = 15.8, 6.2 Hz, 1H), 4.72 (dd, *J* = 6.2, 1.2 Hz, 2H), 3.88 (s, 3H), 1.99 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.9, 167.0, 161.4, 148.3, 138.7, 137.6, 136.5, 134.8, 132.3, 131.8, 130.1, 128.1, 127.5, 126.8, 121.7, 116.6, 113.8, 113.7, 112.4, 65.0, 55.5, 20.9. **IR (ATR)** ṽ (cm^{-1}): 3337, 3058, 1725, 1667, 1595, 1519, 1479, 1379, 1323 and 1222. **HRMS (ESI):** calc. for [($C_{22}H_{20}N_2O_4$)Na] (M+Na) 399.1320, measured 399.1311.

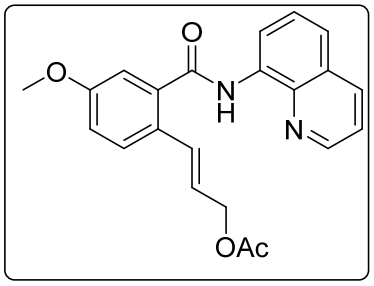
(*E*)-3-(2-(Quinolin-8-ylcarbamoyl)thiophen-3-yl)allyl acetate (4kl).



Prepared according to **GP 2**; Half white solid; eluent (20% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 30% (42 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.48 (s,

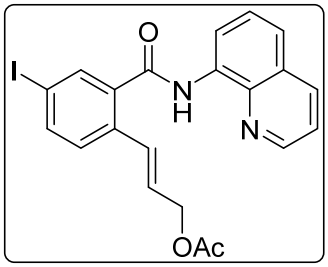
1H), 8.86 (t, *J* = 6.8 Hz, 2H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.53 (m, 3H), 7.50 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.44 (d, *J* = 5.2 Hz, 1H), 7.33 (d, *J* = 5.2 Hz, 1H), 6.37 (dt, *J* = 15.8, 6.2 Hz, 1H), 4.84 (d, *J* = 6.2 Hz, 2H), 2.10 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.9, 160.7, 148.5, 140.9, 138.7, 136.5, 134.6, 133.4, 128.1, 128.1 (one carbon merged), 127.6, 127.5, 127.1, 121.9, 121.7, 116.7, 65.1, 21.1. **IR (ATR)** ṽ (cm^{-1}): 3743, 3317, 2925, 1734, 1645, 1524, 1480, 1422, 1326 and 1054. **HRMS (ESI):** calc. for [($C_{19}H_{16}N_2O_3S$)H] (M+H) 353.0960, measured 353.0964.

(*E*)-3-(4-Methoxy-2-(quinolin-8-ylcarbamoyl)phenyl)allyl acetate (4ll).



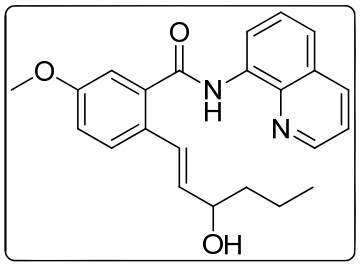
Prepared according to **GP 2**; White solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 33% (45 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.24 (s, 1H), 8.96 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.78 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.72 – 7.54 (m, 3H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.36 – 7.22 (m, 1H), 7.13 (d, *J* = 15.8 Hz, 1H), 7.05 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.25 (dt, *J* = 15.8, 6.5 Hz, 1H), 4.70 (dd, *J* = 6.4, 1.2 Hz, 2H), 3.89 (s, 3H), 1.99 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.9, 167.2, 159.4, 148.4, 138.7, 136.9, 136.5, 134.6, 131.2, 128.6, 128.1, 127.6, 127.5, 124.8, 122.2, 121.8, 116.9, 116.8, 112.8, 65.3, 55.6, 20.9. **IR (ATR)** ṽ (cm^{-1}): 3744, 3339, 1733, 1668, 1602, 1519, 1479, 1379 and 1217. **HRMS (ESI):** calc. for [($C_{22}H_{20}N_2O_4$)Na] (M+Na) 399.1320, measured 399.1308.

(*E*)-3-(4-Iodo-2-(quinolin-8-ylcarbamoyl)phenyl)allyl acetate (4ml).



Prepared according to **GP 2**; Half white solid; eluent (25% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 32% (40 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.24 (s, 1H), 8.93 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.79 (dd, *J* = 8.2, 5.8 Hz, 1H), 7.67 – 7.56 (m, 2H), 7.49 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.34 (dd, *J* = 10.0, 2.6 Hz, 1H), 7.22 (dd, *J* = 15.8, 1.4 Hz, 1H), 7.12 (td, *J* = 8.2, 2.6 Hz, 1H), 6.35 (dt, *J* = 15.8, 6.2 Hz, 1H), 4.74 (dd, *J* = 6.2, 1.4 Hz, 2H), 2.01 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.8, 166.4, 148.4, 138.7, 138.3, 138.2, 136.5, 134.5, 131.8, 130.5, 130.4, 128.1, 127.9, 127.5, 122.2, 121.9, 116.6, 115.3, 115.1, 113.9, 113.8, 64.7, 20.9. **IR (ATR)** ṽ (cm^{-1}): 3744, 3339, 3047, 1739, 1664, 1521, 1369, 1340, 1324 and 1207. **HRMS (ESI):** calc. for [($C_{21}H_{17}IN_2O_3$)H] (M+H) 473.0362, measured 473.0360.

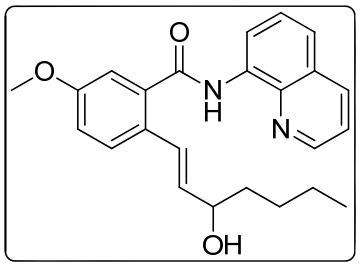
(*E*)-2-(3-Hydroxyhex-1-en-1-yl)-5-methoxy-N-(quinolin-8-yl)benzamide (4lm).



Prepared according to **GP 2**; Thick oil; eluent (35% ethyl acetate in hexanes); **1l** was taken in 100 mg; yield is 40% (54 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.17 (s, 1H), 9.00 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.67 – 7.57 (m, 2H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.32 (d, *J* = 2.6 Hz, 1H), 7.08 – 7.05 (m, 1H), 7.05 – 7.02 (m, 1H), 6.21 (dd, *J* = 15.8, 6.8 Hz, 1H), 4.27 (q, *J* = 6.2 Hz, 1H), 3.90 (s, 3H), 1.67 – 1.51 (m, 2H), 1.48 – 1.32 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 167.2, 159.1, 148.5, 138.7, 136.6, 136.4, 135.3, 134.5, 128.7, 128.1, 128.1, 127.6, 127.5, 122.1, 121.8, 117.3, 117.0, 112.9, 72.8, 55.6, 39.0, 18.7, 13.9. **IR (ATR)** ṽ (cm^{-1}): 3744, 3333, 2933, 2867, 1649, 1593,

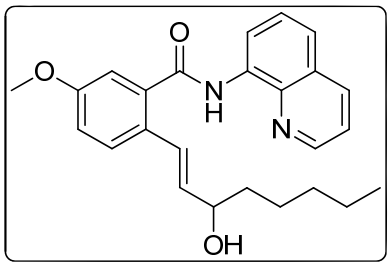
1503, 1482, 1323, 1125 and 1026. **HRMS (ESI):** calc. for [($C_{23}H_{24}N_2O_3$)H] (M+H) 377.1865 measured 377.1866.

(*E*)-2-(3-Hydroxyhept-1-en-1-yl)-5-methoxy-N-(quinolin-8-yl)benzamide (4ln).



Prepared according to **GP 2**; Thick oil; eluent (30% ethyl acetate in hexanes); **1l** was taken in 100 mg; yield is 42% (59 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.18 (s, 1H), 9.00 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.67 – 7.57 (m, 2H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.32 (d, *J* = 2.8 Hz, 1H), 7.09 – 7.02 (m, 2H), 6.22 (dd, *J* = 15.8, 6.8 Hz, 1H), 4.26 (q, *J* = 6.2 Hz, 1H), 3.90 (s, 3H), 1.65 – 1.55 (m, 2H), 1.35 – 1.25 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR (100 MHz, $CDCl_3$):** δ 167.2, 159.1, 148.5, 138.7, 136.6, 136.4, 135.3, 134.5, 128.7, 128.1, 128.1, 127.6, 127.5, 122.1, 121.8, 117.2, 117.0, 112.9, 73.0, 55.6, 36.6, 27.6, 22.6, 13.9. **IR (ATR)** ṽ (cm^{-1}): 3743, 3339, 2929, 2860, 1655, 1603, 1522, 1482, 1323, 1036 and 969. **HRMS (ESI):** calc. for [($C_{24}H_{26}N_2O_3$)H] (M+H) 391.2022, measured 391.2023.

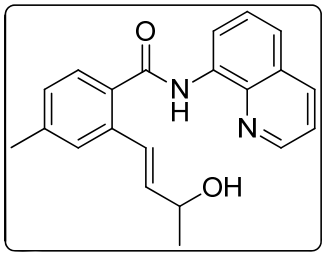
(*E*)-2-(3-Hydroxyoct-1-en-1-yl)-5-methoxy-*N*-(quinolin-8-yl)benzamide (4lo).



Prepared according to **GP 2**; Thick oil; eluent (30% ethyl acetate in hexanes); **1l** was taken in 100 mg; yield is 43% (62 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.18 (s, 1H), 9.00 (d, *J* = 7.4 Hz, 1H), 8.79 (d, *J* = 4.2 Hz, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.68 – 7.57 (m, 2H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.49 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.06 (dd, *J* = 8.6, 6.2 Hz, 2H), 6.22 (dd, *J* = 15.8, 6.9 Hz, 1H), 4.26 (q, *J* = 6.6 Hz, 1H),

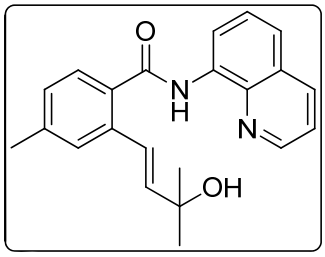
3.90 (s, 3H), 1.66 – 1.52 (m, 2H), 1.48 – 1.22 (m, 6H), 3.90 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 167.2, 159.1, 148.5, 138.7, 136.6, 136.4, 135.4, 134.5, 128.7, 128.1, 128.1, 127.6, 127.5, 122.1, 121.8, 117.2, 117.0, 112.9, 73.0, 55.8, 36.9, 31.8, 25.1, 22.5, 14.0. **IR (ATR)** ṽ (cm^{-1}): 3744, 3343, 2932, 2861, 1675, 1643, 1532, 1492, 1323, 1136 and 1021. **HRMS (ESI):** calc. for [($C_{25}H_{28}N_2O_3$)H] (M+H) 405.2178, measured 405.2171.

(*E*)-2-(3-Hydroxybut-1-en-1-yl)-4-methyl-*N*-(quinolin-8-yl)benzamide (4fq).



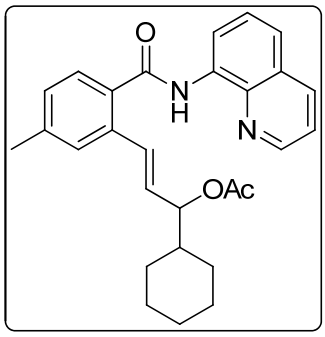
Prepared according to **GP 2**; Half white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 27% (34 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.18 (s, 1H), 8.99 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.47 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.41 (s, 1H), 7.22 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.15 (d, *J* = 15.8 Hz, 1H), 6.33 (dd, *J* = 15.8, 6.4 Hz, 1H), 4.51 (pd, *J* = 6.4, 1.1 Hz, 1H), 2.44 (s, 3H), 1.36 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 167.5, 148.4, 141.0, 138.7, 137.6, 136.6, 135.8, 134.7, 132.6, 128.6, 128.5, 128.1, 127.9, 127.5, 127.5, 121.9, 121.7, 116.9, 68.8, 22.8, 21.4. **IR (ATR)** ṽ (cm^{-1}): 3603, 3333, 2984, 1660, 1617, 1521, 1479, 1379, 1319, 1239 and 1205. **HRMS (ESI):** calc. for [($C_{21}H_{20}N_2O_2$)H] (M+H) 333.1603, measured 333.1600.

(*E*)-2-(3-Hydroxy-3-methylbut-1-en-1-yl)-4-methyl-*N*-(quinolin-8-yl)benzamide (4fr).



Prepared according to **GP 2**; White solid; eluent (35 % ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 21% (28 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.09 (s, 1H), 8.99 (d, *J* = 7.2 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.53 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.36 (s, 1H), 7.16 (d, *J* = 15.8 Hz, 2H), 6.40 (d, *J* = 15.8 Hz, 1H), 2.41 (s, 3H), 1.37 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 167.5, 148.5, 141.8, 141.0, 138.7, 136.7, 135.8, 134.7, 132.6, 130.1, 128.9, 128.4, 128.2, 127.8, 127.5, 124.6, 121.9, 121.7, 117.1, 70.9, 29.6, 21.4. **IR (ATR)** ṽ (cm^{-1}): 3743, 3343, 2970, 1663, 1605, 1524, 1482, 1383, 1325, 1243 and 1142. **HRMS (ESI):** calc. for [($C_{22}H_{22}N_2O_2$)H] (M+H) 347.1760, measured 347.1756.

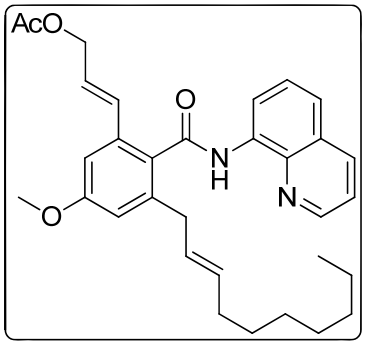
(*E*)-1-Cyclohexyl-3-(5-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)allyl acetate (4fp).



Prepared according to **GP 2**; White solid; eluent (25 % ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 33 % (56 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.12 (s, 1H), 8.96 (d, *J* = 7.2 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.63 (dt, *J* = 7.8, 4.2 Hz, 2H), 7.60 – 7.54 (m, 1H), 7.47 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.43 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 15.8 Hz, 1H), 6.19 (dd, *J* = 15.8, 7.2 Hz, 1H), 5.21 (t, *J* = 6.8 Hz, 1H), 2.45 (s, 3H), 1.89 (s, 3H), 1.70 (t, *J* = 10.4 Hz, 4H), 1.19 – 1.03

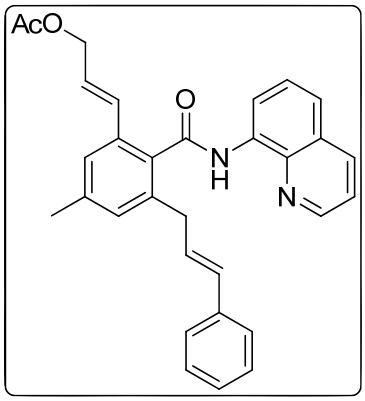
(m, 4H), 1.04 – 0.89 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.1, 167.7, 148.3, 140.5, 138.6, 136.3, 135.1, 134.7, 133.3, 130.1, 129.6, 128.6, 128.0, 127.6, 127.4, 121.7, 121.6, 116.6, 78.4, 42.0, 28.6, 28.5, 26.2, 25.8, 21.4, 20.9. **IR (ATR)** ṽ (cm^{-1}): 3744, 3346, 2926, 1732, 1671, 1520, 1480, 1376, 1325 and 1233. **HRMS (ESI):** calc. for $[(C_{28}H_{30}N_2O_3)H]$ (M+H) 443.2335, measured 443.2345.

(*E*)-3-(3-((*E*)-Dec-2-en-1-yl)-5-methoxy-2-(quinolin-8-ylcarbamoyl)phenyl)allyl acetate (5a).



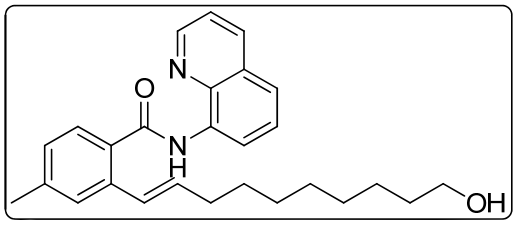
Prepared according to **GP 1**; Colourless thick oil; eluent (25 % ethyl acetate in hexanes); **3jl** was taken in 50 mg; yield is 52% (35 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.92 (s, 1H), 8.99 (d, *J* = 7.4 Hz, 1H), 8.74 (d, *J* = 4.0 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.69 – 7.55 (m, 2H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 6.99 (s, 1H), 6.86 (d, *J* = 15.8 Hz, 1H), 6.81 (s, 1H), 6.32 (dt, *J* = 15.8, 6.2 Hz, 1H), 5.64 – 5.49 (m, 1H), 5.50 – 5.36 (m, 1H), 4.61 (d, *J* = 6.2 Hz, 2H), 3.89 (s, 3H), 3.46 (d, *J* = 6.6 Hz, 2H), 1.91 (s, 3H), 1.89 – 1.78 (m, 2H), 1.36 – 1.09 (m, 10H), 0.87 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR (100 MHz, $CDCl_3$):** 170.6, 167.9, 160.1, 148.2, 140.4, 138.5, 136.3, 135.5, 134.4, 132.9, 130.9, 129.8, 128.0, 127.6, 127.4, 126.2, 121.9, 121.6, 116.7, 115.3, 108.5, 64.7, 55.4, 36.7, 32.4, 31.8, 29.2, 29.1, 29.1, 22.6, 20.7, 14.1. **HRMS (ESI):** calc. for $[(C_{32}H_{38}N_2O_4)H]$ (M+H) 515.2910, measured 515.2917.

(*E*)-3-(3-Cinnamyl-5-methoxy-2-(quinolin-8-ylcarbamoyl)phenyl)allyl acetate (5b).



Prepared according to **GP 1**; Colourless thick oil; eluent (25 % ethyl acetate in hexanes); **4fl** was taken in 50 mg; yield is 63% (42 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.98 (s, 1H), 9.01 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.51 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.57 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.16 – 7.09 (m, 6H), 6.87 (d, *J* = 15.8 Hz, 1H), 6.43 – 6.29 (m, 3H), 4.63 (dd, *J* = 6.4, 1.2 Hz, 2H), 3.65 (d, *J* = 5.6 Hz, 2H), 2.42 (s, 3H), 1.94 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 170.2, 167.2, 148.4, 148.3, 145.2, 139.4, 138.7, 138.4, 137.3, 137.2, 136.2, 134.3, 131.4, 131.0, 130.4, 128.5, 128.3, 127.4, 126.1, 126.0, 124.7, 122.2, 121.7, 116.8, 113.0, 65.0, 37.3, 37.1, 21.5. **HRMS (ESI):** calc. for [($C_{31}H_{28}N_2O_3$)H] (M+H) 477.2178, measured 477.2178.

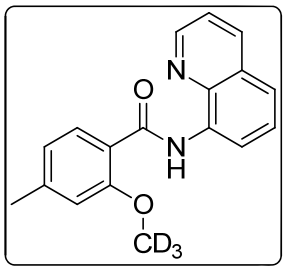
(*E*)-2-(10-Hydroxydec-1-en-1-yl)-4-methyl-*N*-(quinolin-8-yl)benzamide (6).



Prepared according to **GP 3**; Colourless thick oil; eluent (15 % ethyl acetate in hexanes); **1a** was taken in 75 mg; yield is 76% (57 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.95 (s, 1H), 9.04 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.19 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.69 – 7.56 (m, 2H), 7.51 – 7.41 (m, 2H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.58 (d, *J* = 15.6 Hz, 1H), 6.25 (dt, *J* = 15.6, 7.2 Hz, 1H), 4.03 (t, *J* = 6.8 Hz, 2H), 2.45 (s, 3H), 2.10 (dd, *J* = 14.8, 7.8 Hz, 2H), 2.06 (s, 3H), 1.60 – 1.51 (m, 2H), 1.38 – 1.16 (m, 8H). **^{13}C NMR (100 MHz, $CDCl_3$):** 171.2, 168.6, 148.2, 138.5, 136.3, 135.3, 134.9, 134.5, 134.2, 129.1, 128.7, 128.0, 127.4, 126.8, 123.2, 121.9, 121.7, 116.8, 64.6,

33.1, 29.2, 29.0, 28.8, 28.5, 25.8, 21.0, 19.4. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3343, 3041, 2847, 1729, 1645, 1504, 1454, 1368, 1329 and 1016. **HRMS (ESI):** calc. for [($C_{27}H_{32}N_2O_2$)H] (M+H) 417.2542, measured 417.2546.

2-Methoxy-4-methyl-*N*-(quinolin-8-yl)benzamide (10).



Prepared according to **GP 4**; white solid; eluent (15 % ethyl acetate in hexanes); **1a** was taken in 100 mg; yield is 65 % (73 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 12.32 (s, 1H), 9.03 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.86 (dd, *J* = 6.0, 1.6 Hz, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.49 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 6.94 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.86 (s, 1H), 2.42 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 163.8, 157.7, 148.2, 144.1, 139.3, 136.3, 135.9, 132.4, 128.1, 127.6, 122.2, 121.4, 121.3, 119.7, 117.3, 112.3, 26.9, 21.8. **HRMS (ESI):** calc. for $C_{18}H_{13}D_3N_2O_2$ (M+H) 296.1478, measured 296.1483.

3A.9.8 NOESY Studies

Copy of NOESY Experiment of Compound **3ad**

There is a NOE correlation between Ha 10.01 (s, 1H) and benzylic CH_2 Hb 3.68 (d, *J* = 6.0 Hz, 2H) (Fig. 3A.s1). In the meantime, there is a correlation between Hb 3.68 (d, *J* = 6.0 Hz, 2H) and Hc (7.20 (d, *J* = 7.5 Hz, 1H) (Fig 3A.s2). But, no correlation between Hb 3.68 (d, *J* = 6.0 Hz, 2H) and Hd 7.16 – 7.09 (m, 5H). These results clearly revealed that the regiochemistry of compound **3pn** is correct.

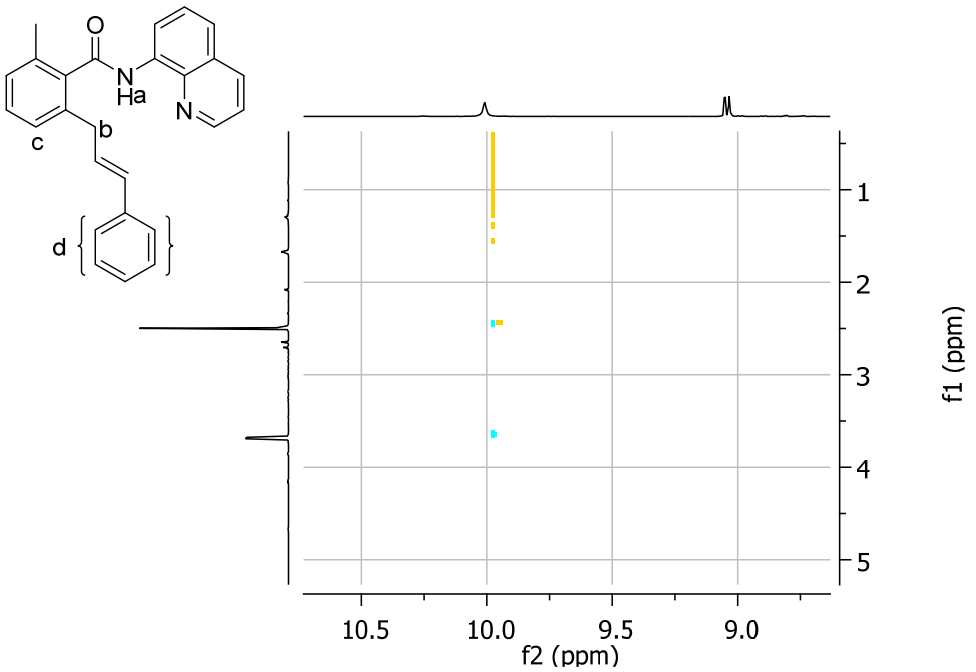


Figure 3.1

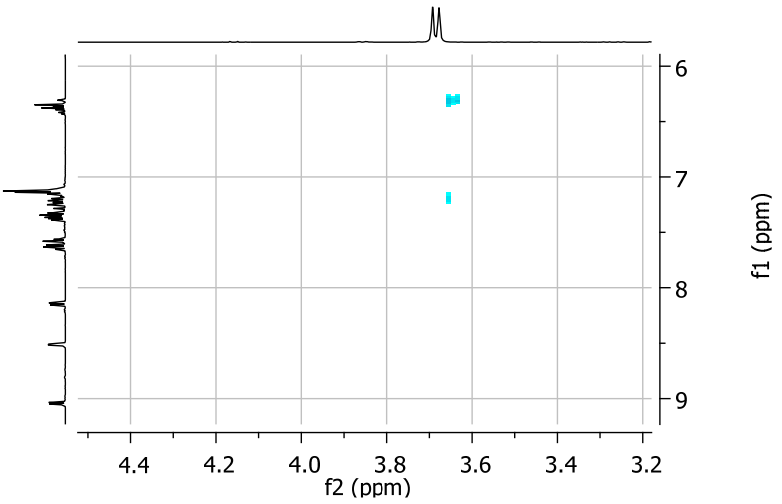


Figure 3.2

Full 2D-NOSY spectrum of compound **3pn**

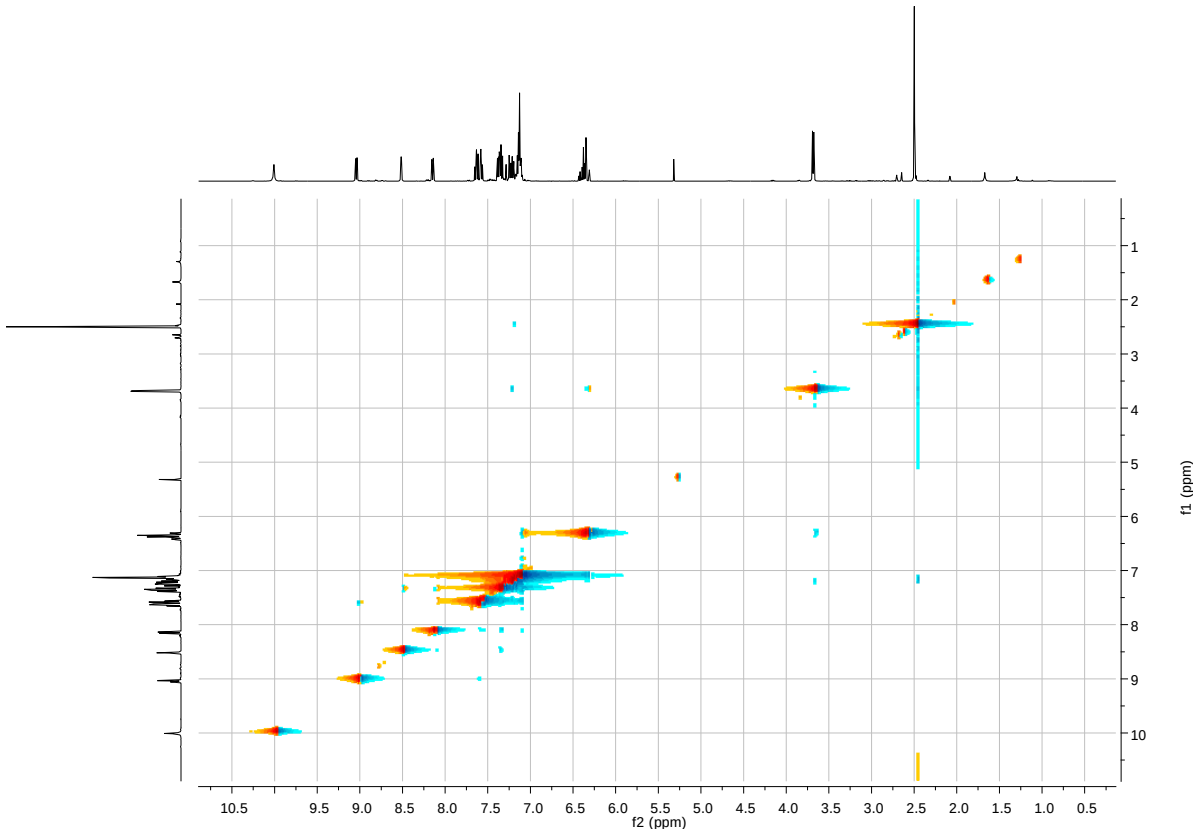


Figure 3.3

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

There is a NOE correlation between Ha (9.95, s) and benzylic CH_2 Hb (3.47 (d, J = 6.6 Hz, 2H) (Fig. 3A.s4). In the meantime, there is a correlation between Hc 7.16 (dd, J = 7.6, 4.2 Hz, 1H) and Hb (3.47 (d, J = 6.6 Hz, 2H) (Fig 3A.s5). These results clearly revealed that the regiochemistry of compound **3ah** is correct.

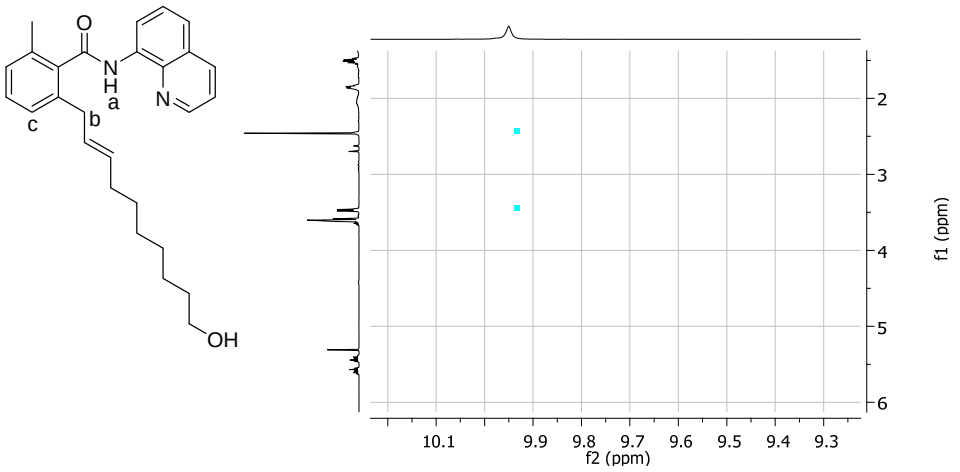


Figure 3.4

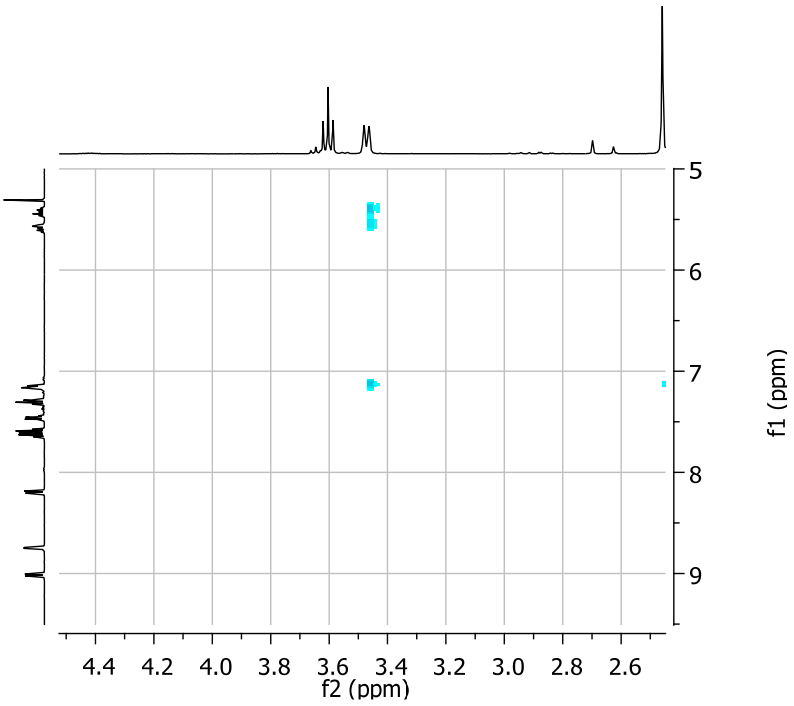


Figure 3.5

Full 2D-NOSY spectrum of compound **3ah**

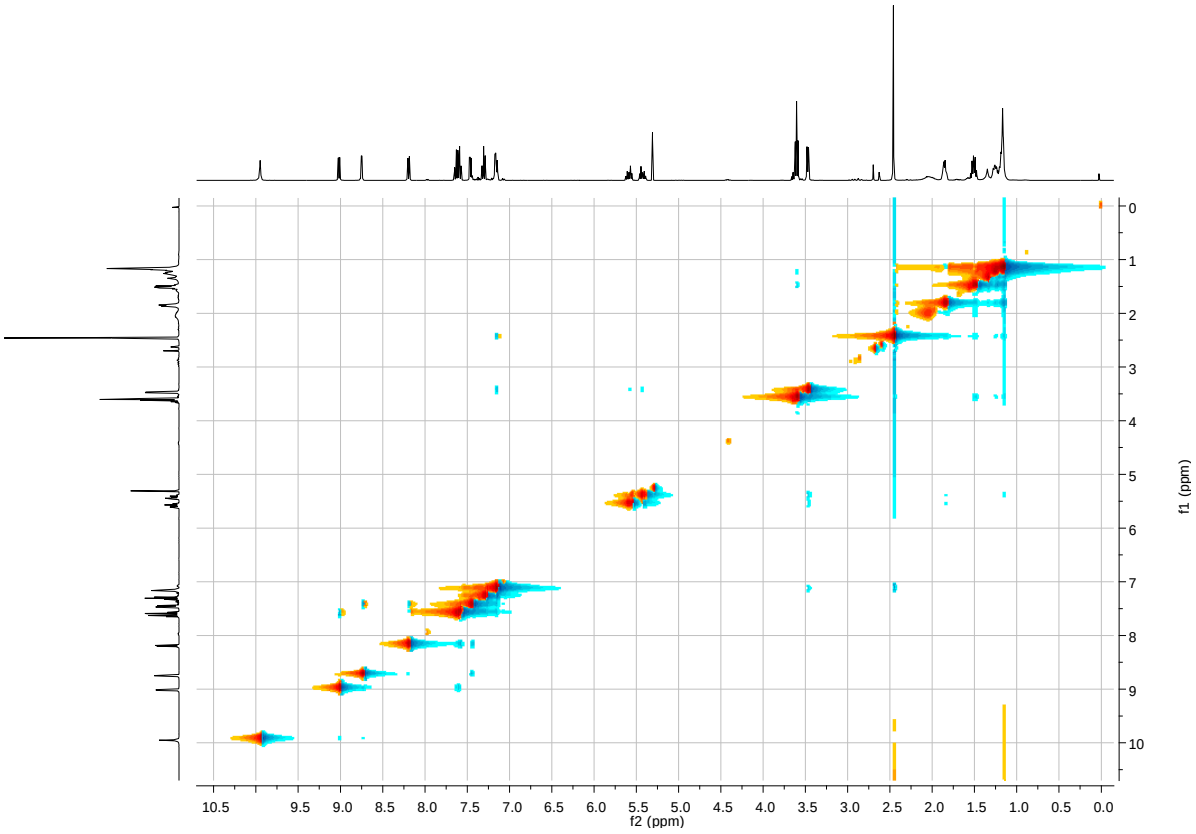
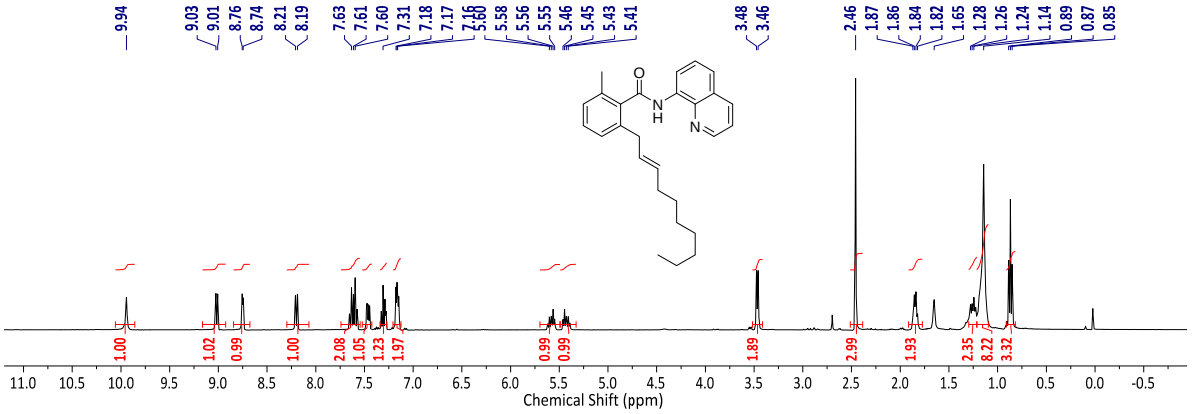
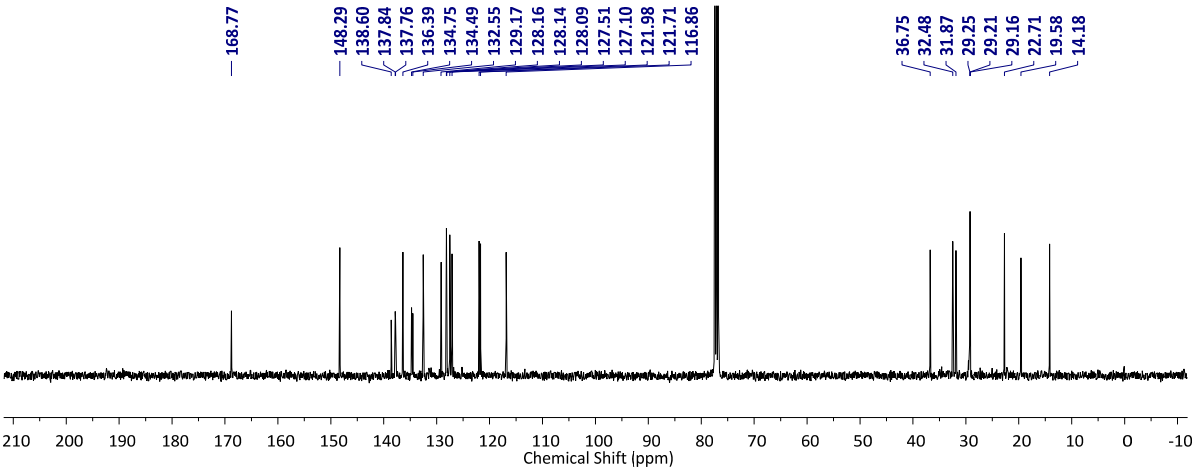


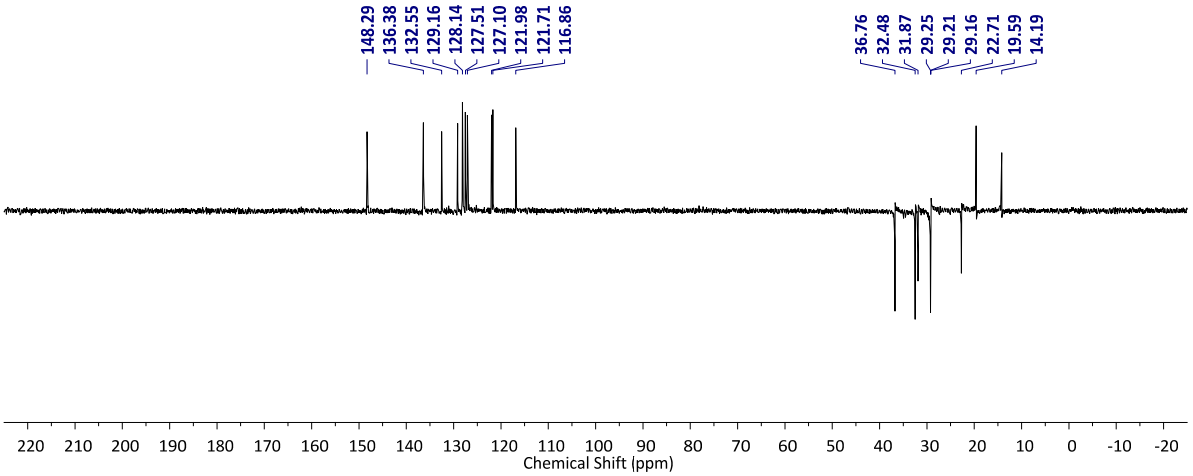
Figure 3.6

3.7: Spectral Copies of Selected Compounds

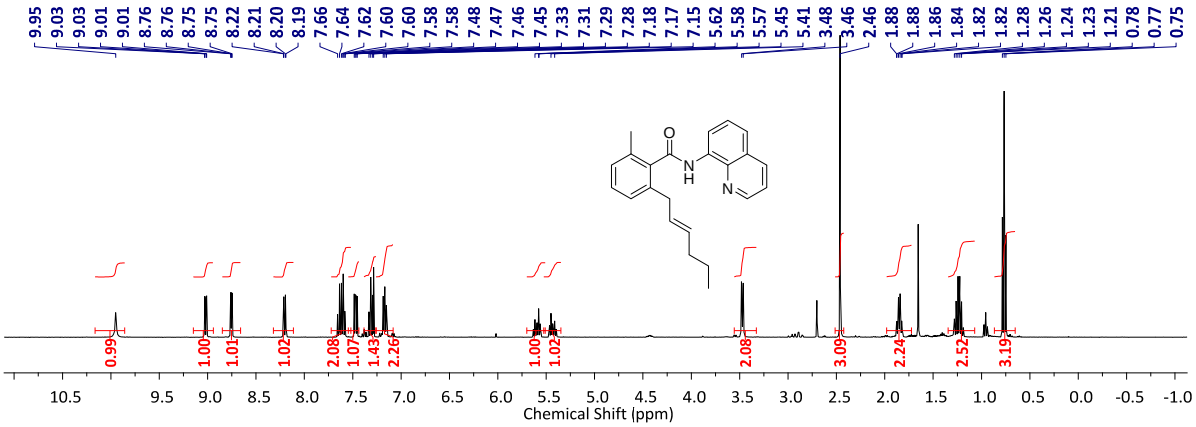
Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **3aa**

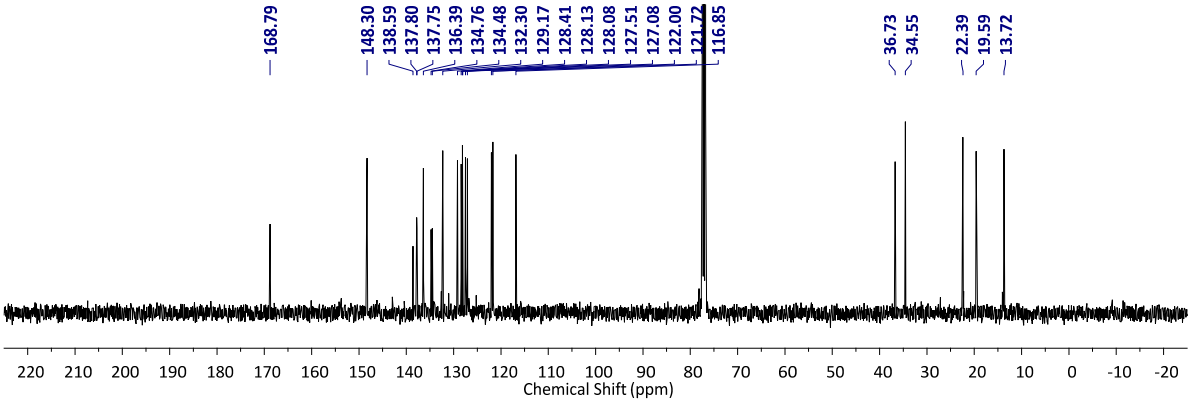


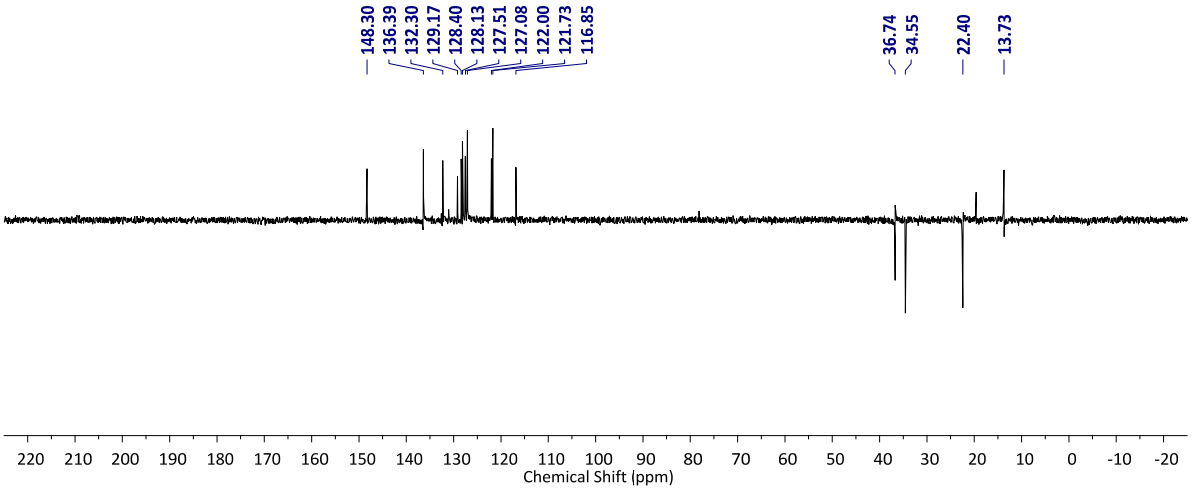




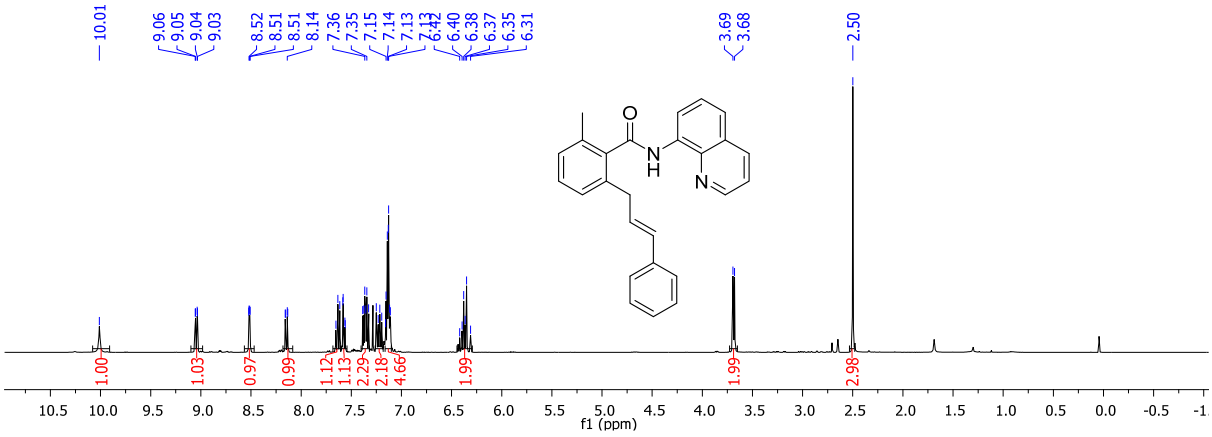
Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **3ab**.

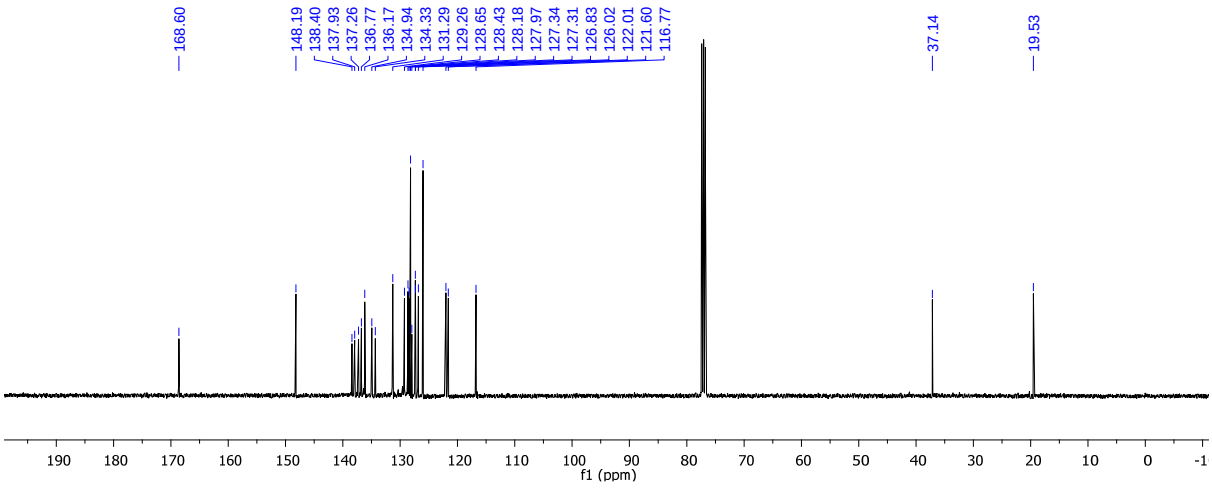


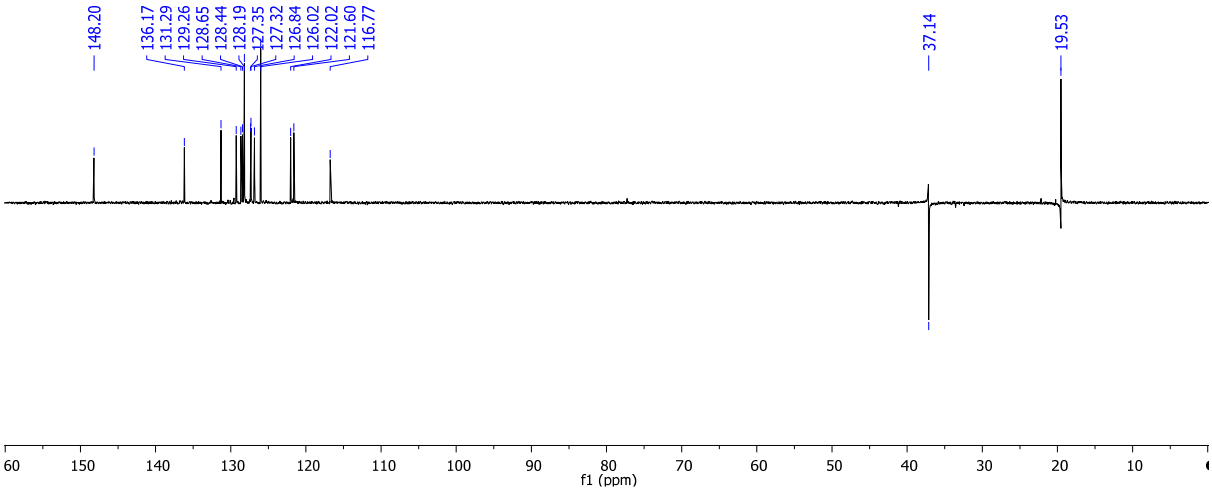




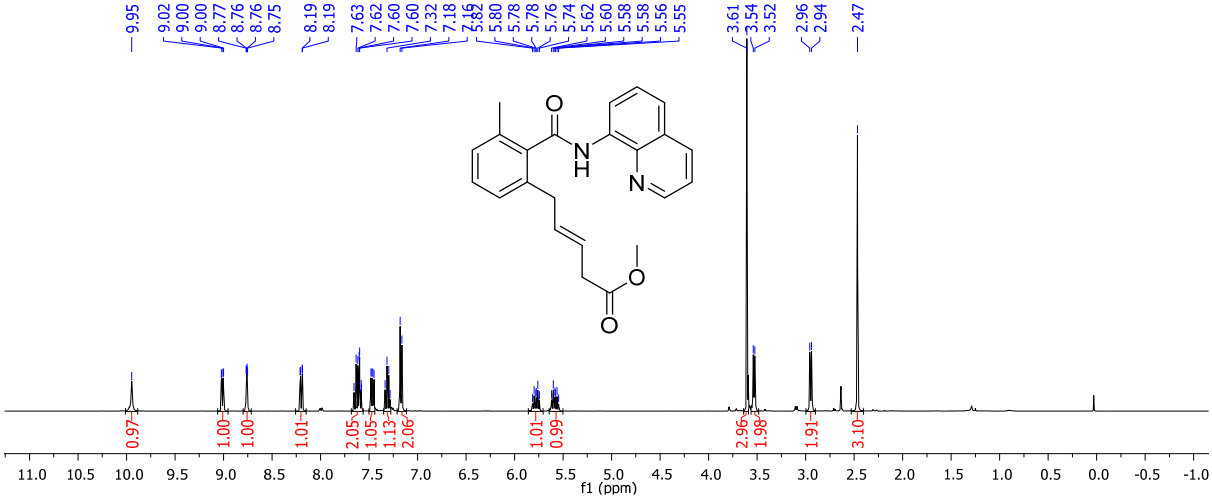
Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **3ad**.

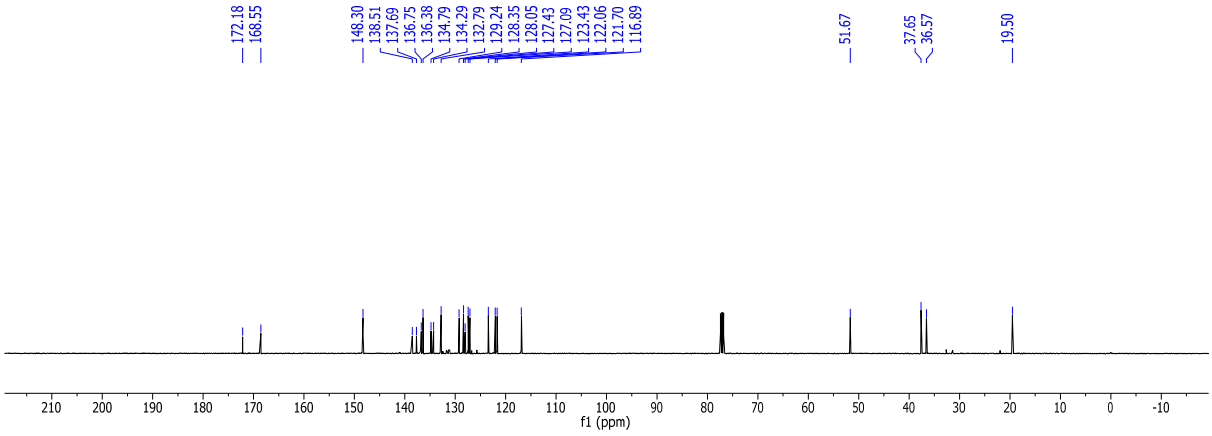


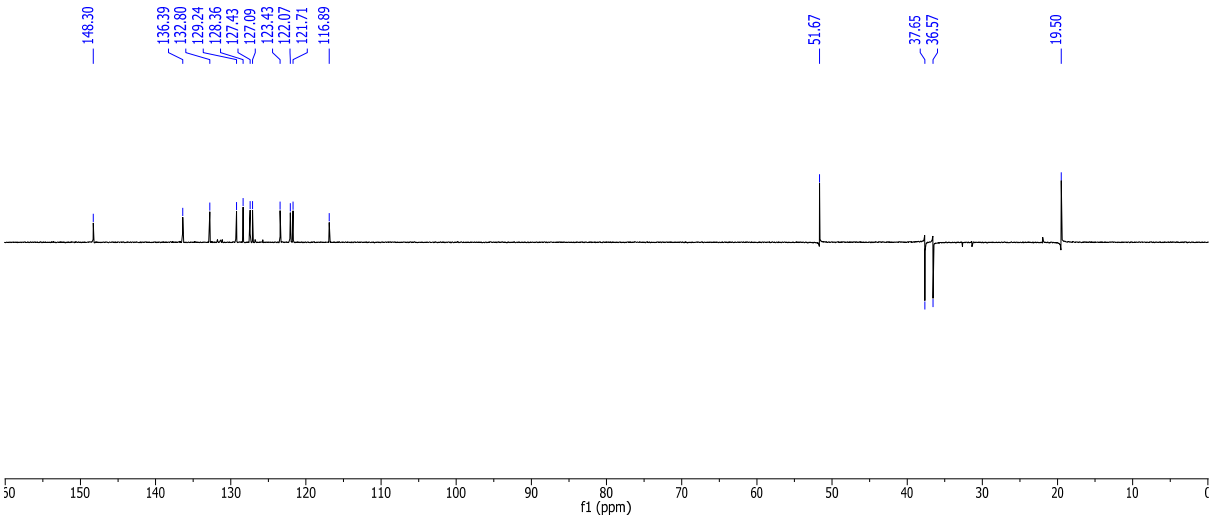




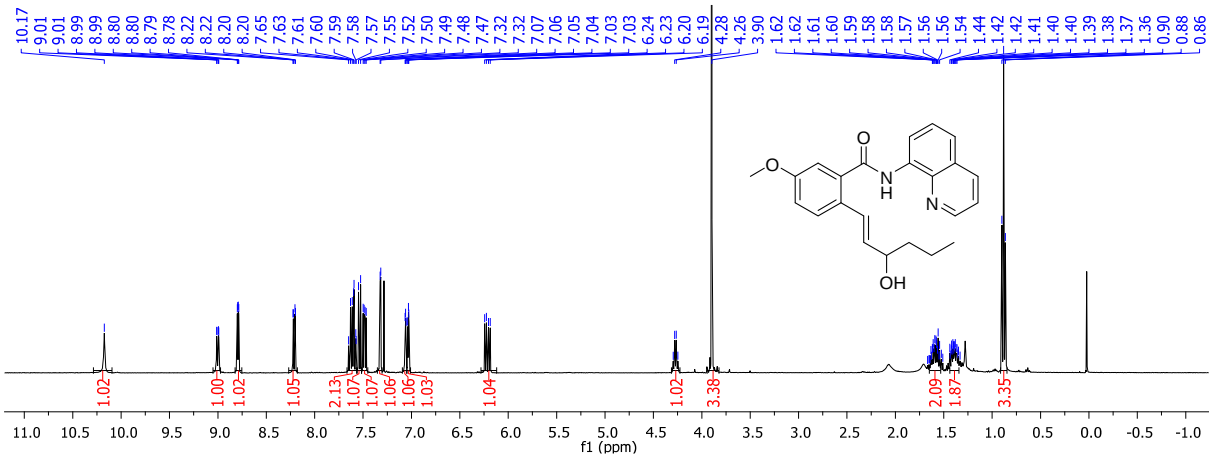
Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **3ae**.

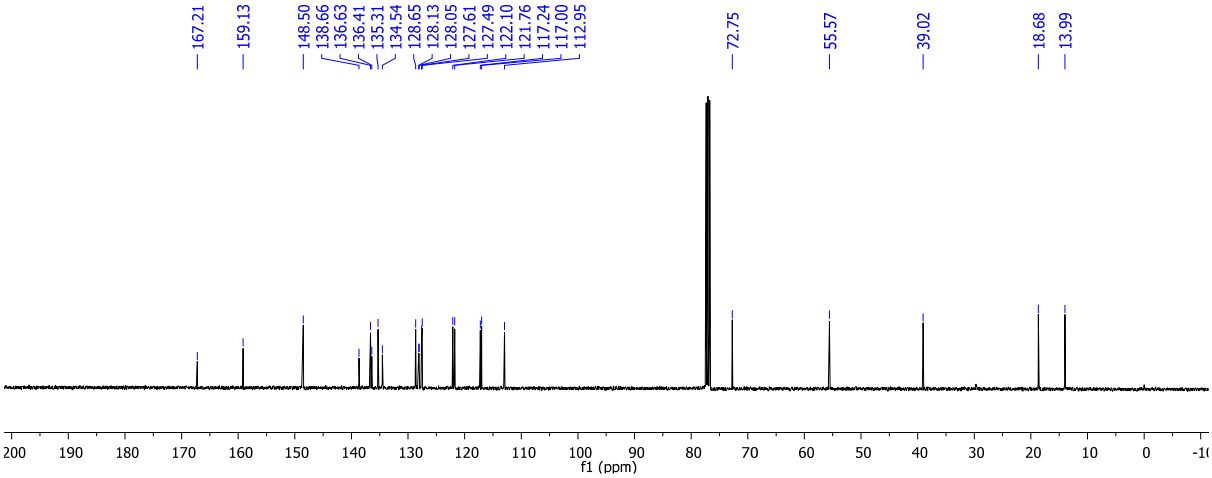


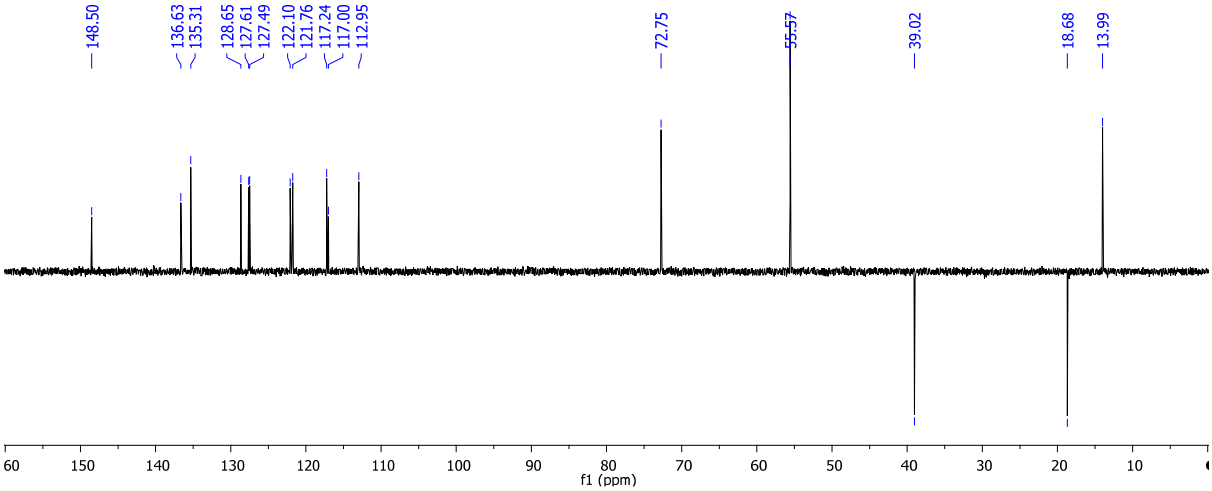




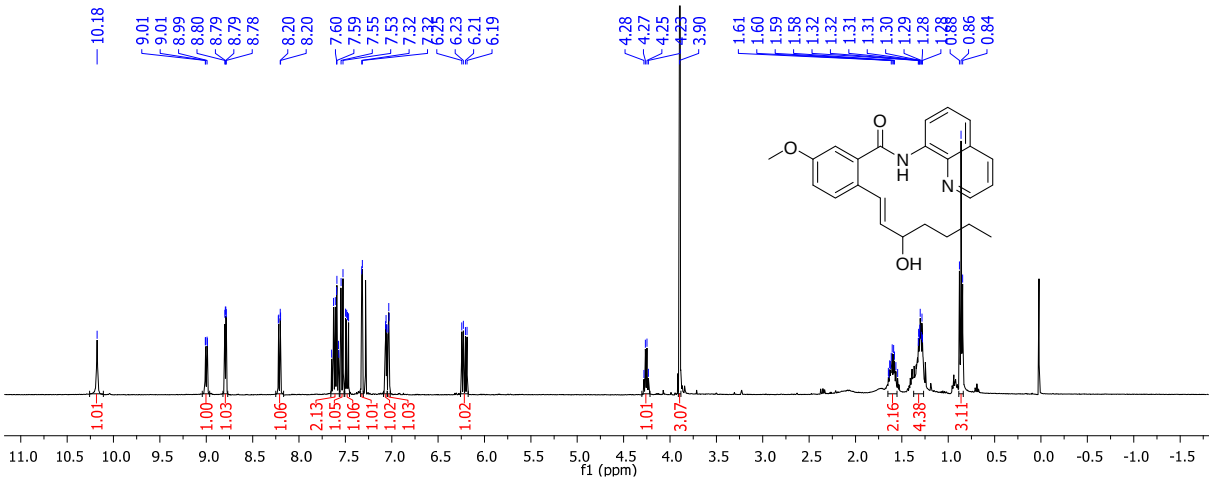
Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **4lm**

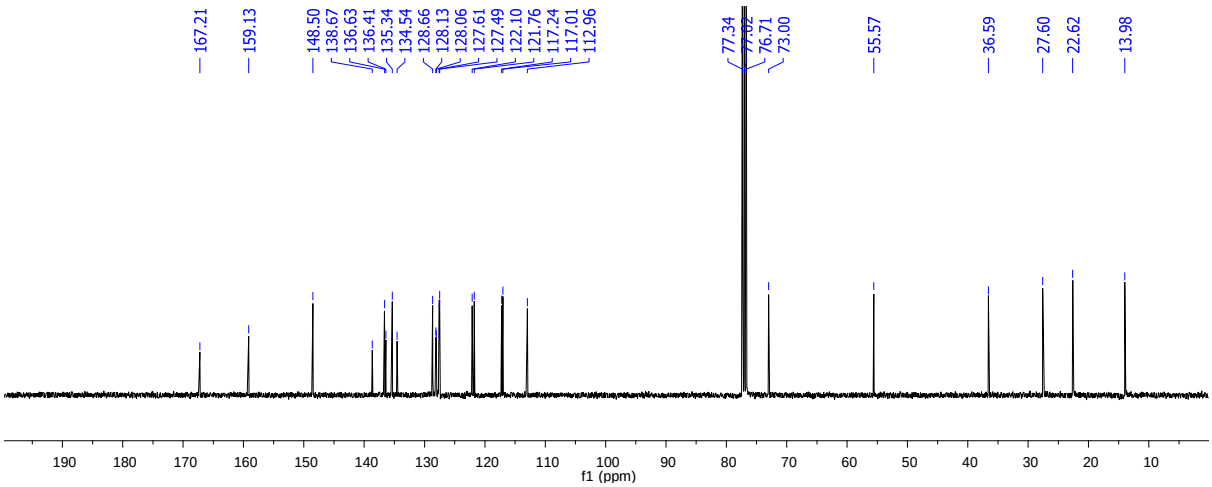


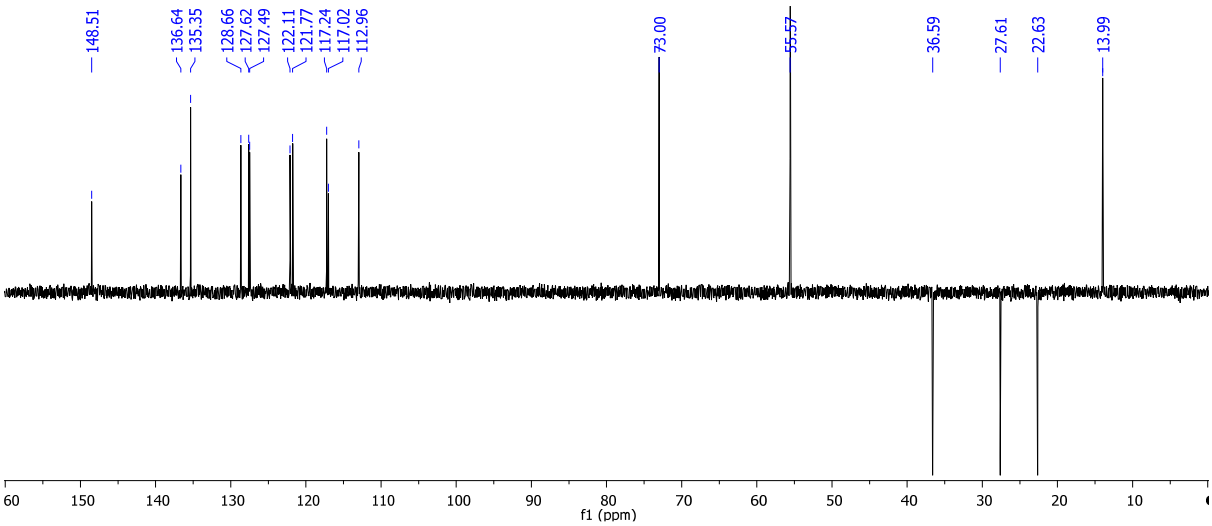




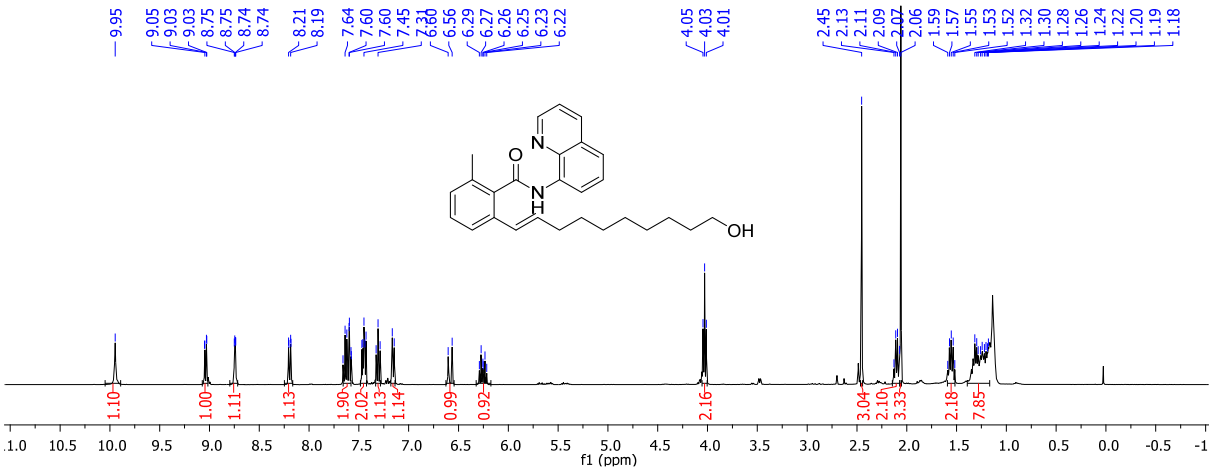
Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **4ln**

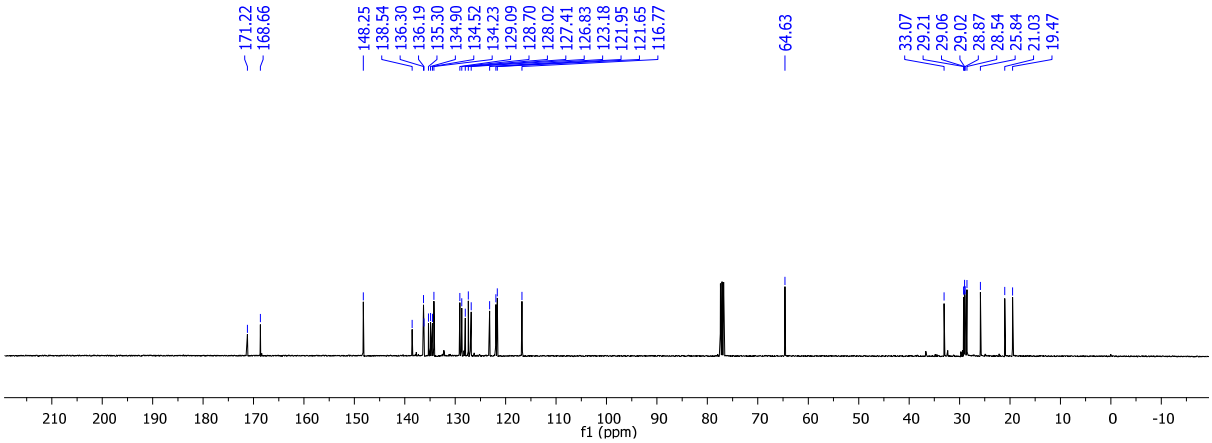


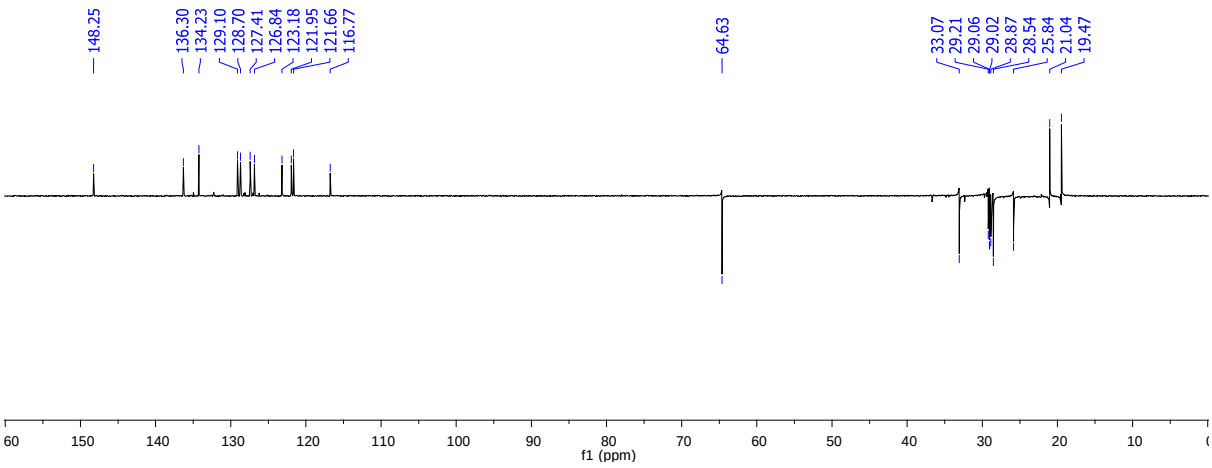




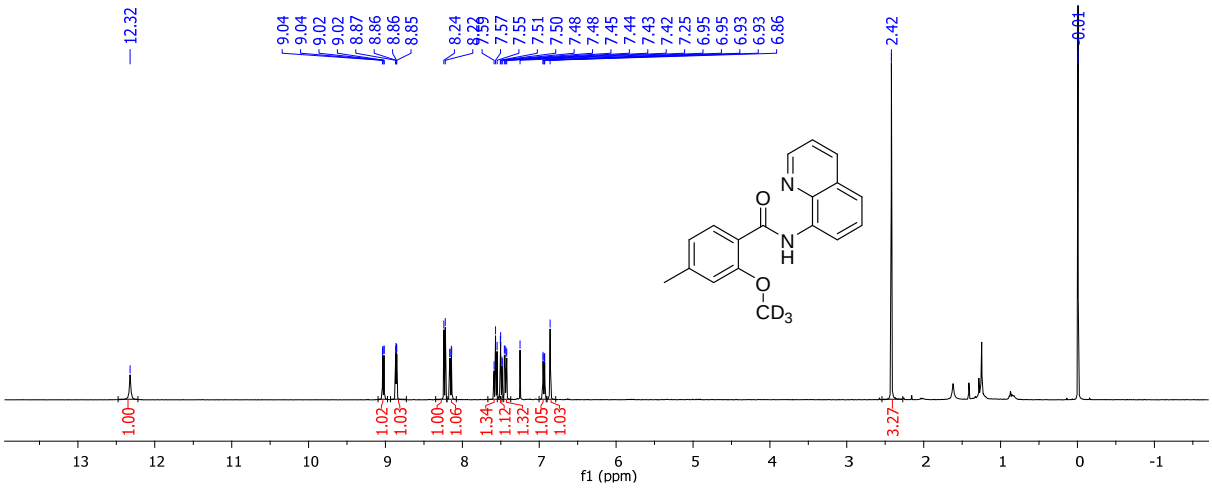
Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **6**

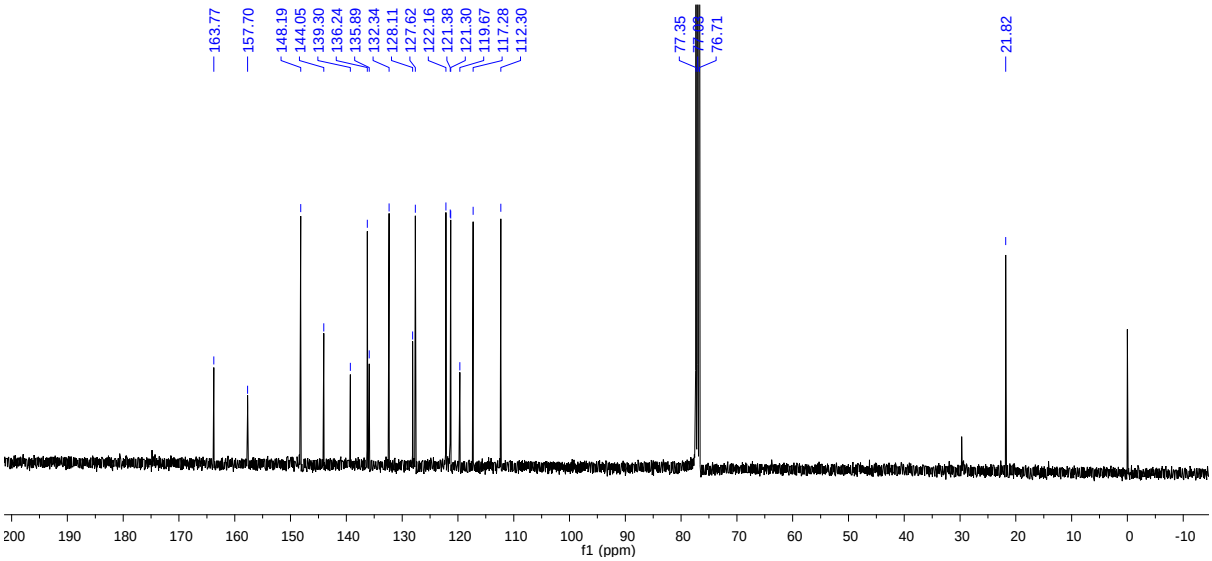


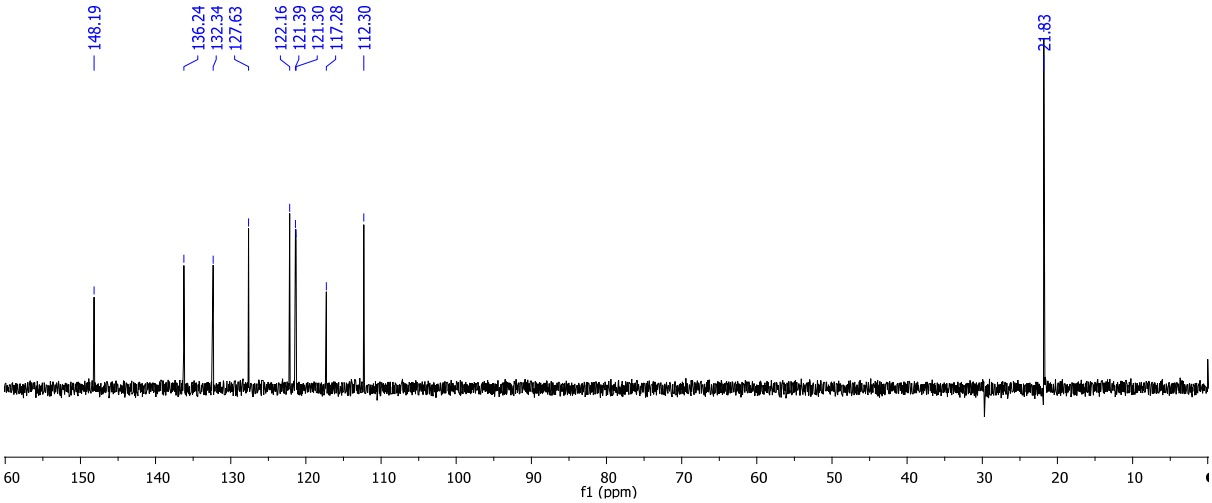




Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **11**







Chapter 4

Chelation Assisted Cobalt-Catalyzed Oxidative Cyclization of Benzamides with Maleimides and Alkynes

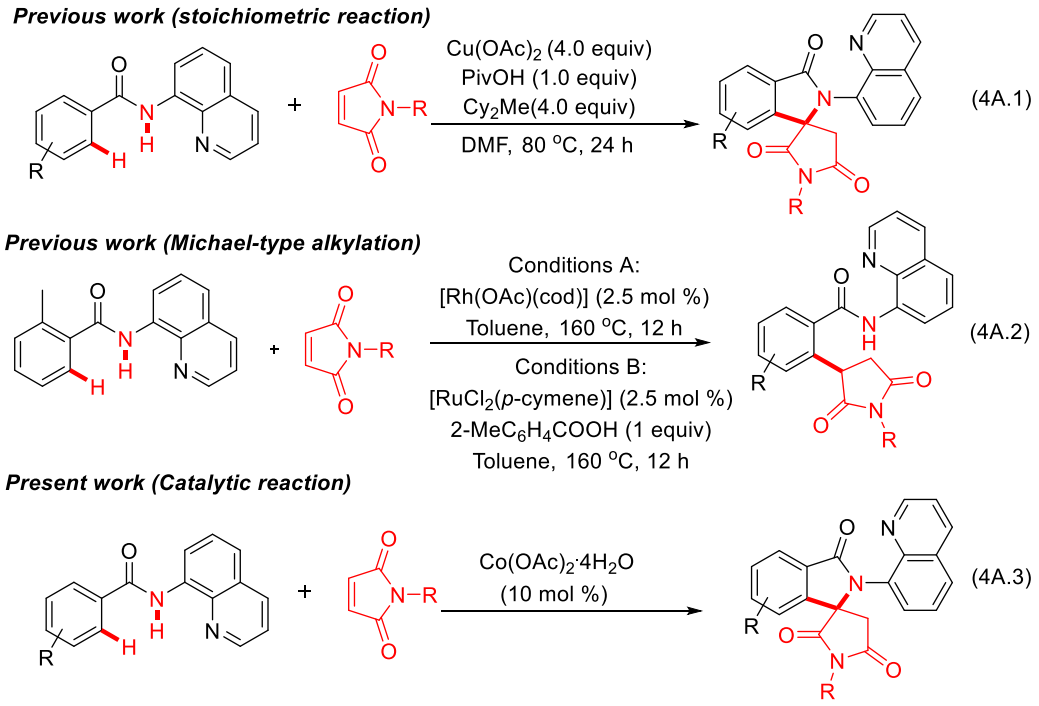
Section 4A: Cobalt-Catalyzed Oxidative Cyclization of Benzamides with Maleimides: Synthesis of Isoindolone Spirosuccinimides

4A.1 Introduction

Isoindolone is an important class of nitrogen containing heterocyclic molecule.[1] This core unit is present in various natural products, biologically active molecules, and pigments.[2] Importantly, the 3-substituted isoindolinone skeleton shows diverse biological properties.[3] Meanwhile, it has also been observed that the spiro ring substituent at the 3-position of isoindolone derivatives shows an interesting array of biological properties.[4] It is also important to note that the succinimides having substitution at the 3-position are key structural motifs found in various natural products and pharmaceuticals.[5] Thus, the development of effective methods for synthesizing isoindolone spirosuccinimides is highly desirable in organic synthesis. Several methods are available in the literature for synthesizing isoindolone derivatives and 3-substituted isoindolone derivatives.[6-8] However, only a few reports are available for synthesizing a spiro ring substituent at the 3-position of isoindolone derivatives.[6]

The transition metal-catalyzed oxidative cyclization of aromatic amides with alkenes via C−H bond activation is one of the effective methods for synthesizing isoindolone derivatives in a highly atom-economical and environmentally friendly manner.[7] By employing this protocol, isoindolone derivatives, particularly 3-substituted isoindolone, are synthesized efficiently from easily available starting materials.[7] In this type of cyclization reaction, only terminal alkenes are efficiently involved, and internal alkenes, including cyclic alkenes, are less explored. Recently, maleimides are efficiently used as an alkene source in the C−H alkenylation reaction. Mostly, substituted aromatics undergo 1,4-addition with maleimides providing Michael-type *ortho* alkylated aromatics.[8-10] For this type of alkylation reaction, ruthenium,[9a-c] rhodium,[9d-f] cobalt[9g-j] and manganese[9k] complexes are used.[9] In 2015, Miura's group[10a-b] found an unusual and very interesting copper-mediated oxidative cyclization of benzamides with maleimides assisted by 8-aminoquinoline (eq 4A.1). In the reaction, highly useful isoindolone spiro succinimides were prepared. However, it is stoichiometric reaction, and 4.0

equiv of $Cu(OAc)_2$ was needed. Very recently, Chatani's group found the Michael-type addition of benzamides with maleimides assisted by 8-aminoquinoline in the presence of ruthenium and rhodium catalysts (eq 4A.2).[10c] It is interesting to note that the first row copper complex gives cyclized product and second row ruthenium and rhodium complexes provide the Michael-type alkylated product. Our continuous interest in the metal-catalyzed oxidative cyclization reaction prompted us to explore the possibility of a catalytic version of cyclization of benzamides with maleimides by using the first row transition metal.[11-12] Herein, we report a cobalt-catalyzed 8-aminoquinoline-directed oxidative cyclization of benzamides with maleimides (4A.3). The oxidative cyclization reaction provides isoindolone spirosuccinimides in good to excellent yields. The reaction was compatible with various functional group substituted benzamides as well as *N*-substituted maleimides.

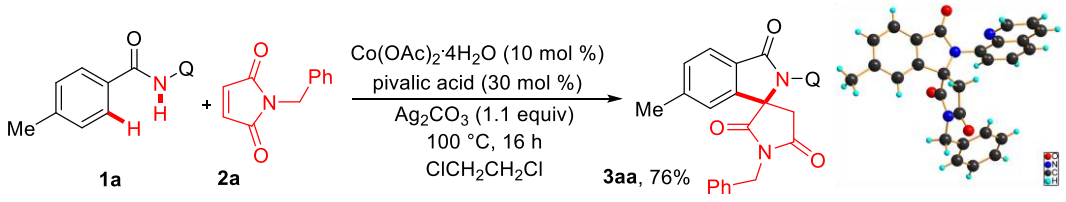


4A.2 Results and Discussion

4A.2.1 Optimization Studies

When benzamide having 8-aminoquinoline **1a** was treated with *N*-benzyl maleimide (**2a**) (1.3 equiv) in the presence of $Co(OAc)_2{\cdot}4H_2O$ (10 mol %), Ag_2CO_3 (1.1 equiv) and pivalic acid (30 mol %) in 1,2-dichloroethane at 100 °C for 16 h, isoindolone

spirosuccinimide **3aa** was observed in 76% yield (Scheme 4A.1). The structure of compound **3aa** was confirmed by a single crystal X-ray analysis (see Section 4A. 5. 7). The oxidative cyclization reaction was examined with *N*-OMe and Me-substituted benzamides. In the reaction, no expected product was observed. This result clearly reveals that the 8-aminoquinoline auxiliary ligand is crucial for the success of the reaction. The olefination reaction was also examined with other auxiliary ligands such as 2-aminopyridine and 2-aminomethylpyridine. However, in these substrates no expected cyclization product was observed.

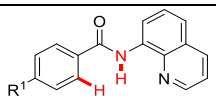
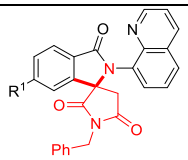
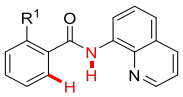
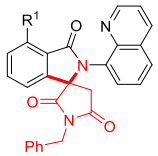
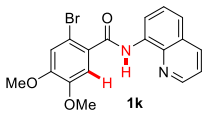
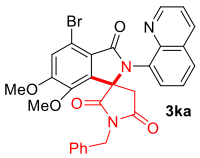


Scheme 4A.1 Oxidative Cyclization of Benzamide **1a** with **2a**

The oxidative cyclization of **1a** with **2a** was examined in the presence of $Co(OAc)_2{\cdot}4H_2O$ (10 mol %), NaOPiv (1.0 equiv) and oxidant (1.1 equiv) in $ClCH_2CH_2Cl$ at 100 °C for 16 h (see Section 4A.5.4). The base NaOPiv was used to deprotonate the NH group of amide **1a**. The oxidant is needed to oxidize Co(II) to the active Co(III) species. Several oxidants such as AgOAc, AgOTf, Ag_2O, $Mn(OAc)_3.2H_2O$, $K_2S_2O_8$ and Ag_2CO_3 were examined. Among them, Ag_2CO_3 was very effective, yielding **3aa** in 63% yield. AgOAc and AgOTf were less effective, providing **3aa** in 57% and 27% yields, respectively. Ag_2O, $Mn(OAc)_3{\cdot}2H_2O$ and $K_2S_2O_8$ were not effective. Meanwhile, the cyclization reaction was examined with various solvents such as toluene, CH_3CN, DMF, 1,2-dichloroethane, 1,4-dioxane, CF_3CH_2OH and *tert*-amyl alcohol. Among them, 1,2-dichloroethane was effective, giving product **3aa** in 63% yield. Remaining solvents CF_3CH_2OH, CH_3CN, DMF, toluene and 1,4-dioxane were partially effective, providing **3aa** in 56-33% yields. *tert*-amyl alcohol was not effective for the reaction. The reaction was also examined with various additives such as NaOAc, CsOAc, K_2CO_3, AcOH, 1-Adm-COOH, mesitylenic acid and pivalic acid. Among them, pivalic acid was very effective, affording **3aa** in 73% yield AcOH, 1-Adm-COOH, NaOAc, CsOAc, K_2CO_3 and mesitylenic acid provided product **3aa** in 53-37% yields. The reaction was examined with 30 mol % of pivalic acid. In the reaction, product **3aa** was observed in 76% yield. This result clearly reveals that

the $Co(OAc)_2{\cdot}4H_2O$ (10 mol %), pivalic acid (30 mol %), Ag_2CO_3 (1.1 equiv) in $ClCH_2CH_2Cl$ at 100 °C for 16 h is the optimized conditions for the reaction.

Table 4A.1 Scope of Substituted Benzamides[a]

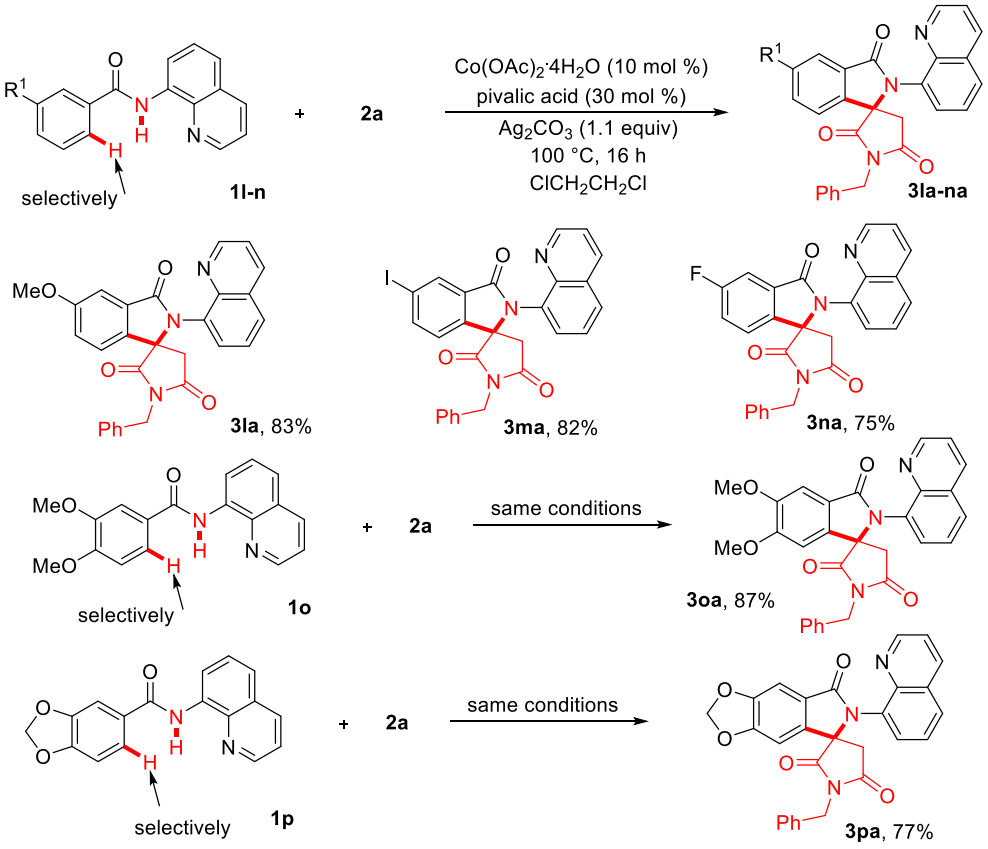
Entry	Benzamide **1**	Product **3**	Yield (%)[b]
			
1	**1b**: R^1 = OMe	**3ba:** R^1 = OMe	72
2	**1c**: R^1 = H	**3ca:** R^1 = H	60
3	**1d**: R^1 = I	**3da:** R^1 = I	89
4	**1e**: R^1 = Br	**3ea:** R^1 = Br	76
5	**1f**: R^1 = Cl	**3fa:** R^1 = Cl	73
6	**1g**: R^1 = F	**3ga:** R^1 = F	63
7	**1h**: R^1 = CF_3	**3ha:** R^1 = CF_3	64
			
8	**1i**: R^1 = Me	**3ia:** R^1 = Me	60
9	**1j**: R^1 = Ph	**3ja:** R^1 = Ph	88
10			58

[a]All reactions were carried out using **1b-k** (50 mg), **2a** (1.3 equiv), $Co(OAc)_2{\cdot}4H_2O$ (10 mol %), pivalic acid (30 mol %), and Ag_2CO_3 (1.1 equiv) in $ClCH_2CH_2Cl$ (3.0 mL) under N_2 at 100 °C for 16 h. [b]Isolated yield.

4A.2.2 Scope of substituted benzamides

The scope of oxidative cyclization of various substituted benzamides with *N*-benzyl maleimide (**2a**) was examined under the optimized reaction conditions (Table 4A.1). The cyclization reaction was compatible with various sensitive functional groups including I, Br, Cl, F, OMe and CF_3 substituted benzamides. 4-Methoxybenzamide **1b** and benzamide **1c** reacted with **2a**, providing the expected

cyclization products **3ba** and **3ca** in 72% and 60% yields, respectively (entries 1 and 2). Halogens such as I, Br, Cl and F substituted benzamides **1d-g** nicely reacted with **2a**, yielding the corresponding cyclized products **3da-ga** in 89%, 76%, 73% and 63% yields, respectively (entries 3-6). Electron-withdrawing CF_3-substituted benzamide **1h** was also effective for the reaction, providing the cyclized product **3ha** in 64% yield (entry 7). *ortho* Methyl-**1i** and phenyl-**1j** substituted benzamides (**1i** and **1j**) reacted with **2a**, giving products **3ia** and **3ja** in 60% and 88% yields, respectively (entries 8 and 9). A sterically hindered 2-bromo-4,5-dimethoxy benzamide **1k** efficiently reacted with **2a**, affording cyclization product **3ka** in 58% yield (entry 10). The cyclization reaction was not compatible with α-methyl vinyl amide under the optimized reaction conditions.

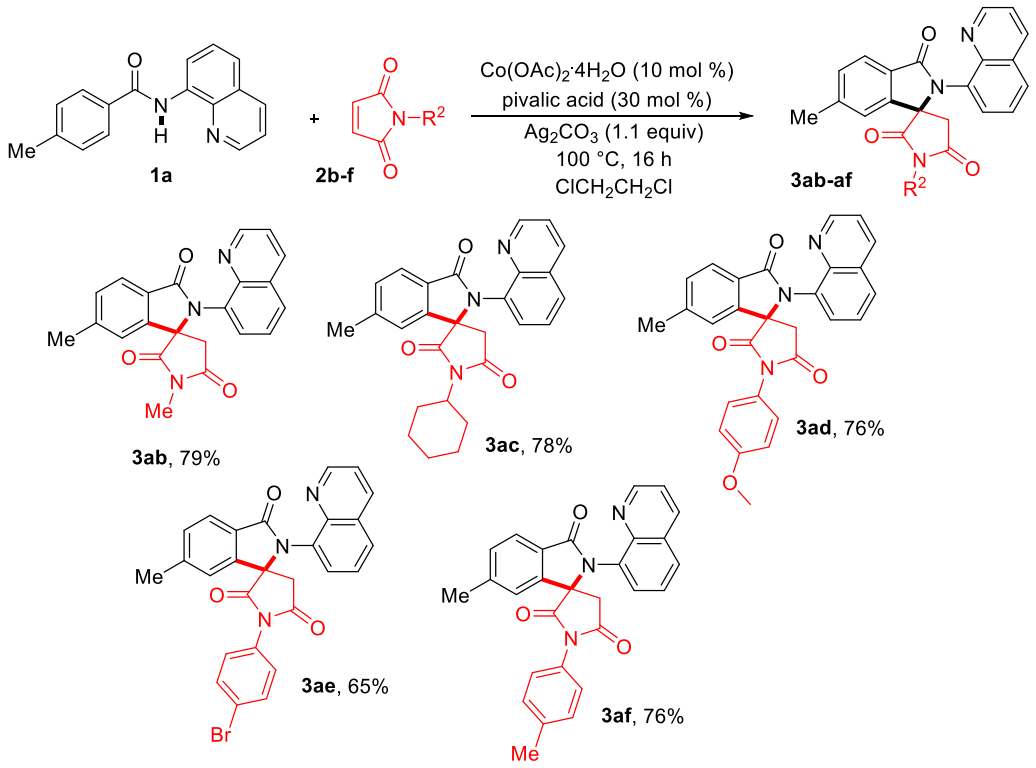


Scheme 4A.2 Scope of unsymmetrical benzamides

The oxidative cyclization reaction was examined with unsymmetrical benzamides **1l-p** to investigate the regioselective outcome of the reaction (Scheme 4A.2). In all reactions, the expected products **3la-pa** was observed in a highly regioselective manner. The reaction of *meta* methoxy-**1l**, iodo-**1m** and fluoro-**1n** substituted

benzamides (**1l-1m**) with **2a** under similar reaction conditions produced the expected products **3la-na** in 83%, 82% and 75% yields, respectively. In the reaction, the C−H bond functionalization takes place at the less hindered C-6 position. Similarly, 3,4-dimethoxybenzamide **1o** and piperonylic amide **1p** also efficiently participated in the reaction at a less hindered C-6 position with **2a**, yielding cyclized products **3oa** and **3pa** in 87% and 77% yields, respectively.

4A.2.3 Scope of *N*-Substituted Maleimides

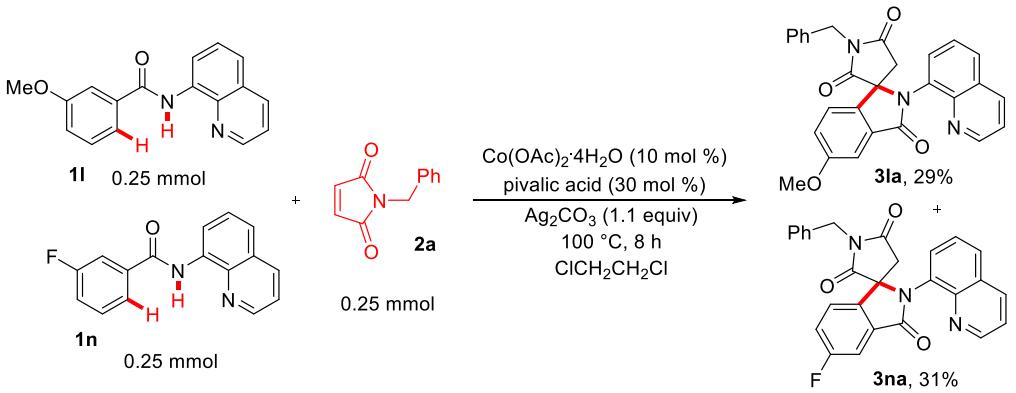


Scheme 4A.3 Scope of *N*-Substituted Maleimides

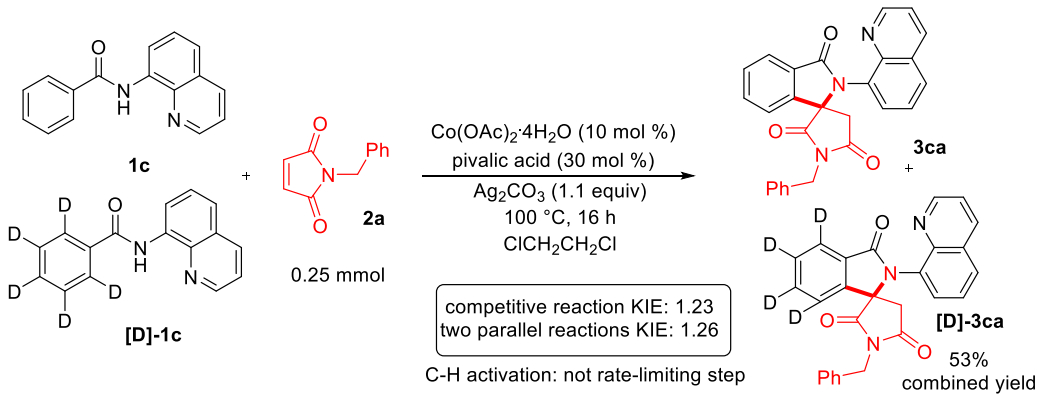
The oxidative cyclization reaction was further examined with various *N*-substituted maleimides **2b-f** (Scheme 4A.3). Treatment of *N*-methyl and cyclohexyl maleimides (**2b** and **2c**) with **1a** under the optimized reaction conditions gave cyclized products **3ab** and **3ac** in 79% and 78% yields, respectively. The reaction of **1a** with *N*-phenyl-substituted maleimides **2d-f** having 4-OMe, 4-Me, and 4-Br substituents on the phenyl ring yielded the expected cyclized products **3ad-af** in 76%, 65% and 76% yields, respectively. The reaction was compatible with OMe and Br substituents on the phenyl group of maleimides. The reaction was tried with

maleic anhydride and NH-free maleimide. However, no cyclization product was observed.

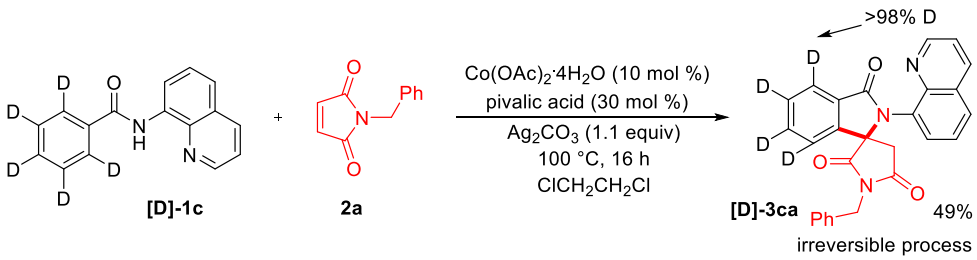
4A.2.4 Mechanistic studies



Scheme4A.4 Competition experiment between amides



Scheme 4A.5 Competition experiment between [D]-**1c** and **1c** amides

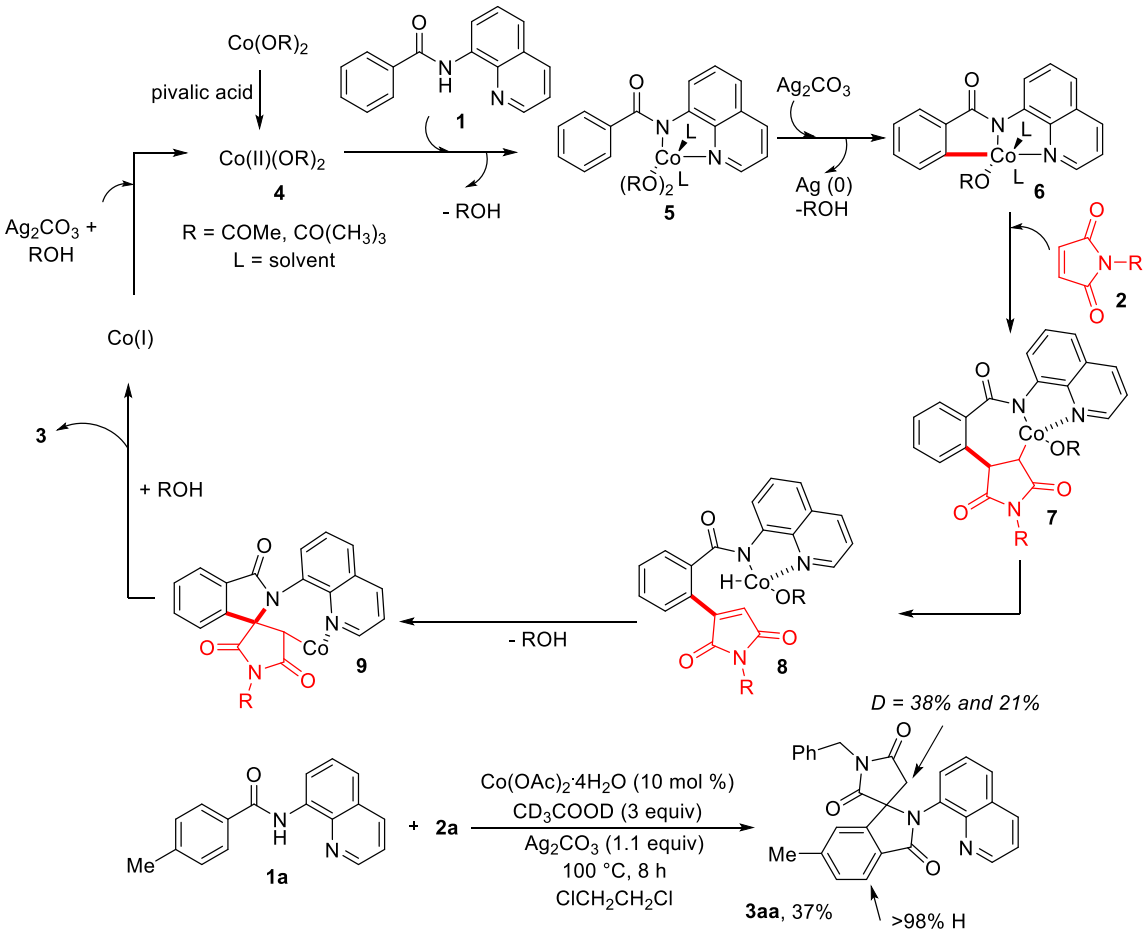


Scheme 4A.6 Competition experiment between [D]-**1c** and **1c** amides

To investigate the mechanism of the cyclization reaction, competition experiments and deuterium labelling studies were performed. Treatment of a 1:1 mixture of 3-methoxybenzamide (**1l**) and 3-fluorobenzamide (**1n**) with **2a** under similar reaction

conditions provided products **3la** and **3na** in 29% and 31% yields, respectively (Scheme 4A.4). This result clearly reveals that the electrophilic cobaltation is unlikely in the reaction. Further, in the competition reaction of **1c** and **[D]-1c** with **2a** under similar reaction conditions, the expected cyclization products **3ca** and **[D]-3ca** were observed in the distribution value of 1.22 by NMR analysis (Scheme 4A.5). A similar type of result was also observed when the reaction was carried out in the two parallel manners. Furthermore, in the reaction of **[D]-1c** with **2a**, product [**D]-3ca** was observed in 49% yield without the loss of *ortho* deuterium (98% deuterium retained, Scheme 4A.6). It indicates that the irreversible C−H bond cleavage could not be the rate-limiting step.

4A.2.5 Proposed Mechanism



Scheme 4A.7 Plausible mechanism

Based on the known cobalt-catalyzed C−H bond cleavage reactions and present competition and deuterium labelling experiments, a possible reaction mechanism is proposed in Scheme 4A.7. The catalytic cycle starts with the coordination of amide

1 with cobalt(II) catalyst which leads to the formation of intermediate **5**. Silver carbonate likely oxidizes Co(II) to Co(III) in the presence of pivalic acid followed by acetate-mediated, irreversible C−H bond cleavage provides a cobaltacycle intermediate **6**. Coordinative insertion of the double bond of maleimide **2** into a C−Co bond of intermediate **6** affords intermediate **7**. β-Hydride elimination of intermediate **7** gives intermediate **8** and ROH. Intramolecular insertion of N−Co into the double bond of maleimide of intermediate **9** followed by protonation in the presence of ROH provides cyclized product **3** and cobalt species. Later the active cobalt(III) species **6** was regenerated in the presence of Ag_2CO_3 and ROH.[12o] In the reaction, carboxylic acid plays a dual role; it acts as a base to deprotonate the *ortho* C−H bond and protonate the Co−C bond in intermediate **8**. Further to know the role of RCOOH, the reaction of **1a** with **2a** was examined in CD_3COOD under similar reaction conditions. In the reaction, deuterium incorporation of 38% and 21% was observed at the β-carbon of succinimides product **3aa** in 37% yield. This result clearly reveals that the RCOOH protonates the Co−C bond in intermediate **8**.

4A.3 Conclusions

In conclusion, we have demonstrated a cobalt-catalyzed oxidative cyclization of benzamides with maleimides assisted by 8-aminoquinoline ligand. The present protocol allows an efficient route to synthesize isoindolone spirosuccinimides in good to excellent yields. The competition experiment and deuterium labelling studies clearly reveals that the irreversible C−H bond cleavage might not be the rate-limiting step of the reaction.

4A.4 References

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4A.5 Experimental Section

4A.5.1 General Information: All reactions were carried out under the nitrogen atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use (three times). Dry solvents were used for the reaction. Column chromatographical purifications were performed using SiO_2 (120-200 mesh ASTM) from Merck if not indicated otherwise. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Starting Materials: Commercial available starting materials, metal complexes and metal salts were purchased from commercial sources and used without further purification.

4A.5.2 General Procedure for Synthesis of Isoindolone Spirosuccinimides (GP 1)

To a 15-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amides **1** (50 mg, 1 equiv), malemides **2** (1.3 equiv) and Ag_2CO_3 (1.1 equiv) was evacuated and purged with nitrogen gas three times. (Ag_2CO_3 was taken inside the glove box). To the tube were then added,1,2- dichloroethane (3.0 mL) and pivalic acid(30 mol %) were added via syringe sequentially. After that, the tube was evacuated and purged with nitrogen gas three times and a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, 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 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 **3**.

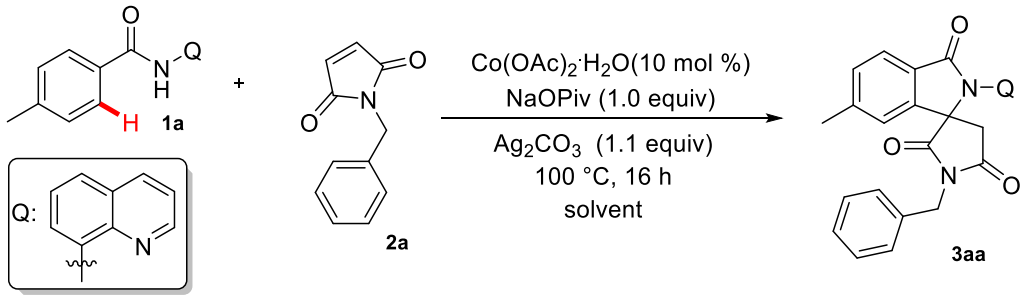
4A.5.3 Procedure for Synthesis of Isoindolone Spirosuccinimide 3aa in 1mmol scale (GP 2)

To a 50-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %, 12.5 mg), amide **1a** (1mmol, 262 mg), malemide **2a** (1.3 mmol, 243 mg) and Ag_2CO_3 (1.1 mmol, 304 mg) was evacuated and purged with nitrogen gas three times. (Ag_2CO_3 was taken inside the glove box). To the tube were then added 1, 2- dichloroethane (8.0 mL) and pivalic acid (30 mol %) were added via syringe sequentially. After that, the tube was evacuated and purged with nitrogen gas three times and a screw cap was used to cover the tube. Again,

the reaction mixture was stirred at room temperature for 5 minutes. Then, 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 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 **3aa** in 68% (306 mg) as a half white solid yield.

4A.5.4 Optimization Studies

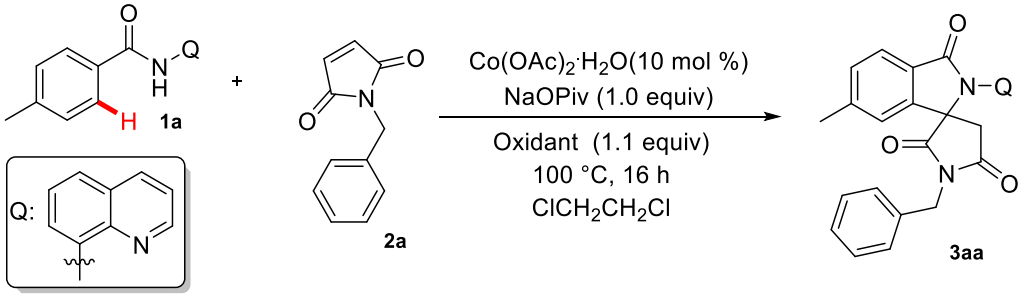
Table 4A.2 Solvent Optimization[a]



Entry	Solvent	Yield **3aa** (%)[b]
1	1,4-dioxane	33
2	Toluene	41
3	*tert*-amyl alcohol	NR
4	*tert*-BuOH	NR
5	*iso*-PrOH	39
6	CF_3CH_2OH	56
7	CH_3CN	51
8	DMF	47
9	**$ClCH_2CH_2Cl$**	**63**
10	DMSO	NR
11	THF	27

[a]All reactions were carried out under the following conditions: **1a** (50 mg), **2a** (1.3 equiv), $Co(OAc)_2.4H_2O$ (10 mol %), NaOPiv (1 eq) and Ag_2CO_3(1.1 equiv) in solvent (3.0 mL) at 100 °C for 16 h under N_2 atmosphere. [b] Isolated yield.

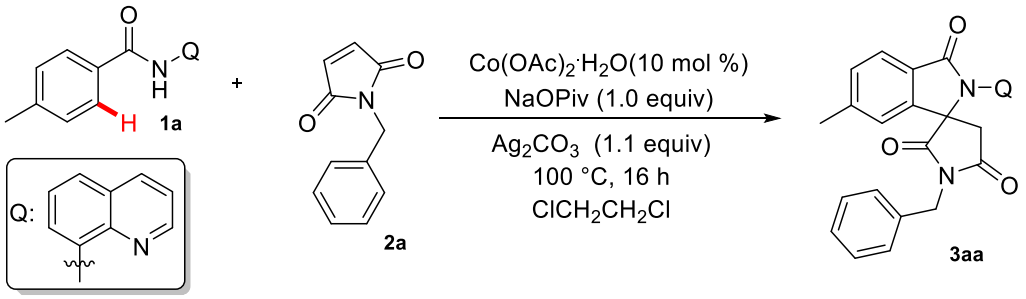
Table 4A.3 Oxidant Optimization[a]



Entry	Oxidant (equiv)	Yield **3aa** (%)[b]
1	AgOTf(1.1 equiv)	27
2	AgOAc(1.1 equiv)	57
3	$AgSbF_6$(1.1 equiv)	trace
4	Ag_2O (1.1 equiv)	NR
5	$Mn(OAc)_3.2H_2O$	NR
6	$Ag(CF_3CO_2)$ (1.1 equiv)	24
7	$K_2S_2O_8$(1.1 equiv)	NR
8	$(NH_4)_2S_2O_8$(1.1 equiv)	NR
9	**Ag_2CO_3(1.1 equiv)**	**63**
10	Ag_2CO_3(2.2 equiv)	69

[a]All reactions were carried out under the following conditions: **1a** (50 mg), **2a** (1.3 equiv), $Co(OAc)_2{\cdot}4H_2O$ (10 mol %), NaOPiv (1 eq) and oxidant (specified) in solvent (3.0 mL) at 100 ^oC for 16 h under N_2 atmosphere. [b] Isolated yield.

Table 4A.4 Cobalt Source Optimization[a]

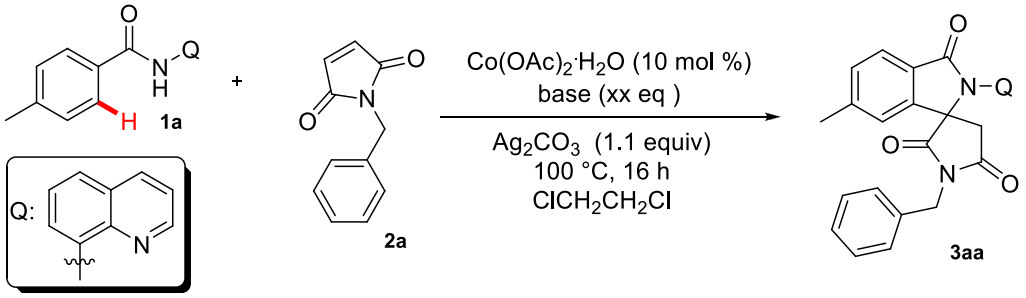


Entry	Cobalt source	Yield **3aa** (%)[b]
1	$Co(acac)_2$	37
2	$CoBr_2$	NR
3	$Co(acac)_3$	43

4	**$Co(OAc)_2{\cdot}4H_2O$**	**63**

[a]All reactions were carried out under the following conditions: **1a** (100 mg), **2a** (3.0 equiv), catalyst (10 mol %), NaOPiv (1 eq) and Ag_2CO_3(1.1 equiv) in solvent (3.0 mL) at 100 ^oC for 16 h under N_2 atmosphere. [b] Isolated yield.

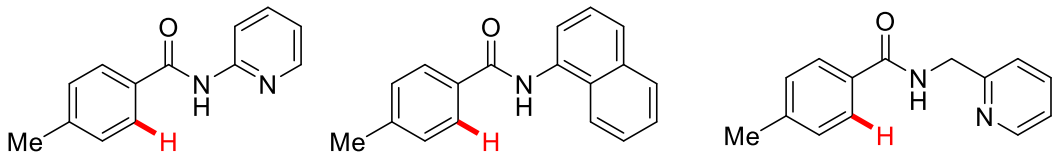
Table 4A.5 AdditiveOptimization[a]



Entry	Additive (xx equiv)	Yield **3aa** (%)[b]
1	AcOH(3.0 equiv)	37
2	Adm-1-COOH (1.0 equiv)	53
3	PivOH(3.0 equiv)	73
4	**PivOH(30 mol %)**	**76**
5	CsOAc(1.0 equiv)	41
6	Mesitylenic acid (1.0 equiv)	47
7	NaOAc (1.0 equiv)	44
8	K_2CO_3(1.0 equiv)	42

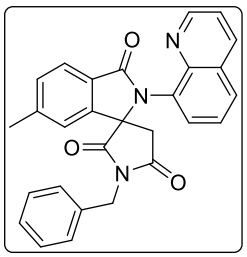
[a]All reactions were carried out under the following conditions: **1a** (50 mg), **2a** (1.3 equiv), $Co(OAc)_2$ (10 mol %), additive (specified) and oxidant (1.1 equiv) in solvent (3 mL) at 100 ^oC for 16 h under N_2 atmosphere. [b]Isolated yield.

Other Failure Directing Groups



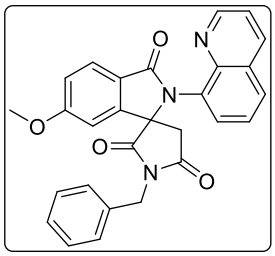
4A.6 Spectral Data of Compounds

1'-benzyl-6-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3aa).



Prepared according to **GP 1**; Half-white solid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 76% (65 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.74 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.18 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.72 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.39 – 7.34 (m, 1H), 7.34 – 7.26 (m, 5H), 6.83 (s, 1H), 4.75 (d, *J* = 13.8 Hz, 1H), 4.70 (d, *J* = 13.8 Hz, 1H), 3.27 (d, *J* = 18.8 Hz, 1H), 3.10 (d, *J* = 18.8 Hz, 1H), 2.36 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 174.7, 173.4, 168.8, 150.9, 145.1, 144.9, 144.0, 136.6, 135.3, 132.5, 131.4, 130.8, 129.5, 129.5, 128.8, 128.7, 128.6, 128.3, 126.7, 124.8, 121.9, 120.5, 70.8, 43.1, 37.6, 21.9. **IR (ATR)** ṽ (cm^{-1}): 3053, 2932, 1784, 1706, 1613, 1496, 1429, 1388, 1346 and 1263. **HRMS (ESI):** calc. for [($C_{28}H_{21}N_3O_3$)H] (M+H) 448.1661, measured 448.1662.

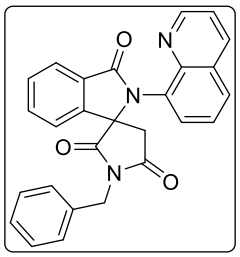
1'-benzyl-6-methoxy-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ba)



Prepared according to **GP 1**; Brown solid; eluent (55% ethyl acetate in hexanes); **1b** was taken in 50 mg; yield is 72% (60 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.70 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.81 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.66 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.48 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.36 (dd, *J* = 5.4, 2.8 Hz, 1H), 7.31 – 7.18 (m, 5H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.76 – 6.56 (m, 1H), 4.73 (d, *J* = 14.0 Hz, 1H), 4.66 (d, *J* = 14.0 Hz, 1H), 3.96 (s, 3H), 3.28 (d, *J* = 18.8 Hz, 1H), 3.09 (d, *J* = 18.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 174.7, 173.6, 167.5, 158.1, 150.9, 147.1, 145.2, 136.6, 135.2, 134.8, 132.6, 131.4, 129.6, 129.5, 128.8, 128.8, 128.3, 126.7, 121.8, 118.5, 112.3, 112.1, 70.3, 56.2, 43.2, 37.9. **IR (ATR)** ṽ (cm^{-1}): 3053, 2846, 1784, 1705,

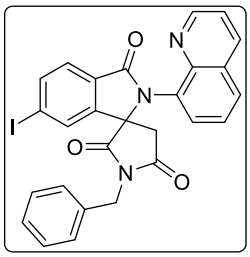
1602, 1487, 1432, 1389, 1342 and 1266. **HRMS (ESI):** calc. for [($C_{28}H_{21}N_3O_4$)H] (M+H) 464.1610, measured 464.1616.

1'-benzyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ca)



Prepared according to **GP 1**; Half-white solid; eluent (60% ethyl acetate in hexanes); **1c** was taken in 50 mg; yield is 60% (52 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.21 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.08 – 7.96 (m, 1H), 7.88 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.70 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.49 – 7.37 (m, 2H), 7.31 – 7.27(m, 5H), 7.16 – 7.11 (m, 1H), 4.75 (d, *J* = 13.8 Hz, 1H), 4.69 (d, *J* = 13.8 Hz, 1H), 3.34 (d, *J* = 18.8 Hz, 1H), 3.14 (d, *J* = 18.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 174.7, 173.5, 151.2, 145.2, 144.6, 136.7, 135.2, 133.1, 132.4, 131.5, 131.4, 129.9, 129.7, 129.6, 128.9, 128.8, 128.7, 128.3, 126.8, 125.2, 122.1, 120.2, 71.0, 43.2, 37.6. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2924, 2855, 2315, 1783, 1706, 1604, 1497, 1465, 1431 and 1263. **HRMS (ESI):** calc. for [($C_{27}H_{19}N_3O_3$)H] (M+H) 434.1505, measured 434.1510.

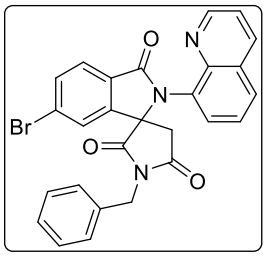
1'-benzyl-6-iodo-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3da)



Prepared according to **GP 1**; Half-white solid; eluent (35% ethyl acetate in hexanes); **1d** was taken in 50 mg; yield is 89% (67 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.23 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.90 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.69 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.51 – 7.43 (m, 3H), 7.38 – 7.33 (m, 3H), 7.32 – 7.29 (m, 2H), 4.78 (d, *J* = 13.8 Hz, 1H), 4.72 (d, *J* = 13.8 Hz, 1H), 3.30 (d, *J* = 18.8 Hz, 1H), 3.14 (d, *J* = 18.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 174.1, 172.9, 168.0, 151.2, 146.2, 145.0, 139.3, 136.7, 135.1, 131.9, 131.4, 130.9, 129.9, 129.6, 129.6, 129.0, 128.7, 128.5, 126.8, 126.5, 122.1, 99.7, 70.5, 43.3,

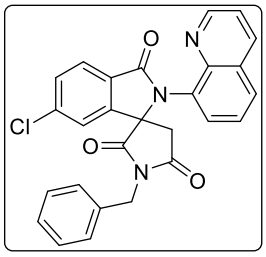
37.4. **IR (ATR)** ṽ (cm^{-1}): 3055, 2929, 1785, 1707, 1597, 1497, 1468, 1427, 1389 and 1263. **HRMS (ESI):** calc. for [($C_{27}H_{18}IN_3O_3$)H] (M+H) 560.0471, measured 560.0460.

1'-benzyl-6-bromo-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ea)



Prepared according to **GP 1**; Brown solid; eluent (35% ethyl acetate in hexanes); **1e** was taken in 50 mg; yield is 76% (59 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.79 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.22 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.89 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.68 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.38 – 7.28 m, 5H), 7.12 (d, *J* = 1.4 Hz, 1H), 4.78 (d, *J* = 13.8 Hz, 1H), 4.72 (d, *J* = 13.8 Hz, 1H), 3.33 (d, *J* = 19.2 Hz, 1H), 3.14 (d, *J* = 19.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 174.1, 172.2, 151.2, 146.2, 144.9, 136.9, 135.0, 133.4, 131.9, 131.6, 131.5, 131.3, 129.9, 129.7, 128.9, 128.8, 128.5, 127.6, 126.8, 126.5, 123.9, 122.2, 70.6, 43.4, 37.4. **IR (ATR)** ṽ (cm^{-1}): 3059, 2922, 1784, 1713, 1609, 1493, 1477, 1382, 1284 and 1181. **HRMS (ESI):** calc. for [($C_{27}H_{18}BrN_3O_3$)H] (M+H) 512.0610, measured 512.0618.

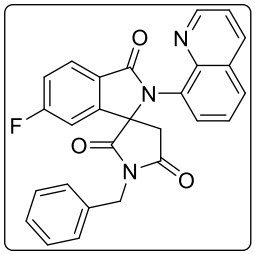
1'-benzyl-6-chloro-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3fa)



Prepared according to **GP 1**; Half-white solid; eluent (30% ethyl acetate in hexanes); **1f** was taken in 50 mg; yield is 73% (60 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.79 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.22 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.89 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.68 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.38 – 7.28 m, 5H), 7.12 (d, *J* = 1.4 Hz, 1H), 4.78 (d, *J* = 13.8 Hz, 1H), 4.72 (d, *J* = 13.8 Hz, 1H), 3.33 (d, *J* = 19.2 Hz, 1H), 3.14 (d, *J* = 19.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 174.0, 172.8, 167.6, 151.1, 145.9, 144.9, 139.3, 136.6, 134.9, 132.0, 131.3, 130.4, 129.8, 129.8, 129.5, 128.8, 128.7, 128.4, 126.7, 126.2, 122.0, 120.8, 70.6,

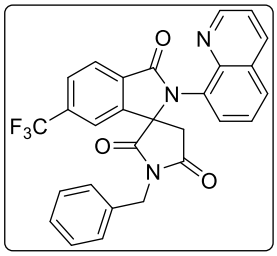
43.3, 37.3. **IR (ATR)** ṽ (cm^{-1}): 3062, 2927, 1786, 1717, 1613, 1497, 1482, 1387, 1289 and 1187. **HRMS (ESI):** calc. for [($C_{27}H_{18}ClN_3O_3$)H] (M+H) 468.1115, measured 468.1112.

1'-benzyl-6-fluoro-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ga)



Prepared according to **GP 1**; Brown solid; eluent (35% ethyl acetate in hexanes); **1g** was taken in 50 mg; yield is 63% (53 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.79 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.23 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.09 – 7.97 (m, 1H), 7.89 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.68 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.50 – 7.41 (m, 3H), 7.36 – 7.28 (m, 5H), 6.83 (dd, *J* = 7.6, 2.0 Hz, 1H), 4.77 (d, *J* = 13.8 Hz, 1H), 4.71 (d, *J* = 13.8 Hz, 1H), 3.37 (d, *J* = 19.2 Hz, 1H), 3.14 (d, *J* = 19.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 174.2, 173.0, 167.6 and 167.1 (F coupling), 164.6, 151.2, 146.7 and 146.7 (F coupling), 145.1, 136.7, 135.1, 132.2, 131.4, 129.8, 129.6, 128.9, 128.8, 128.5, 127.5, 127.4 and 127.3 (F coupling), 126.8, 122.1, 117.8 and 117.6 (F coupling), 108.2 and 107.9 (F coupling), 70.6, 43.3, 37.5. **IR (ATR)** ṽ (cm^{-1}): 3056, 2925, 2312, 1781, 1710, 1620, 1494, 1432, 1390 and 1347. **HRMS (ESI):** calc. for [($C_{27}H_{18}FN_3O_3$)H] (M+H) 452.1410, measured 452.1416.

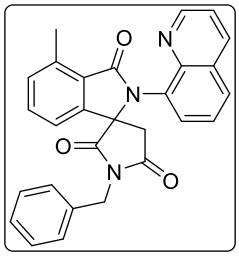
1'-benzyl-2-(quinolin-8-yl)-6-(trifluoromethyl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ha)



Prepared according to **GP 1**; Half-white solid; eluent (30% ethyl acetate in hexanes); **1h** was taken in 50 mg; yield is 64% (51 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.78 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.21 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.97 – 7.81 (m, 2H), 7.65 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.49 – 7.38 (m, 2H), 7.34 (s, 1H), 7.36 – 7.25 (m, 5H), 4.76 (d, *J* = 13.8 Hz, 1H), 4.70 (d, *J* = 13.8 Hz, 1H), 3.32 (d, *J* = 19.2 Hz, 1H), 3.15

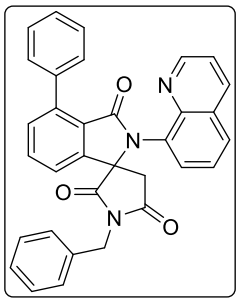
(d, *J* = 19.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 173.90, 172.82, 167.26, 151.32, 144.92, 136.82, 134.98, 131.78, 131.37, 130.10, 129.67, 129.01, 128.99, 128.98, 128.71, 128.55, 127.34, 127.31, 126.82, 125.80, 122.24, 117.71, 117.67, 71.04, 43.42, 37.26. **IR (ATR)** ṽ (cm^{-1}): 3063, 2926, 2856, 1786, 1711, 1603, 1497, 1432, 1390 and 1324. **HRMS (ESI):** calc. for [($C_{28}H_{18}F_3N_3O_3$)H] (M+H) 502.1379, measured 502.1372.

1'-benzyl-4-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ia)



Prepared according to **GP 1**; Half-white solid; eluent (40% ethyl acetate in hexanes); **1i** was taken in 50 mg; yield is 60% (51 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.82 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.23 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.89 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.74 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.52 – 7.40 (m, 3H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.32 – 7.28 (m, 5H), 6.95 (d, *J* = 7.6 Hz, 1H), 4.76 (d, *J* = 14.0 Hz, 1H), 4.70 (d, *J* = 14.0 Hz, 1H), 3.38 (d, *J* = 19.2 Hz, 1H), 3.16 (d, *J* = 19.2 Hz, 1H), 2.79 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 174.9, 173.5, 169.4, 151.1, 145.3, 145.0, 139.3, 136.6, 135.2, 132.6, 132.4, 131.9, 131.7, 129.6, 129.5, 128.7, 128.7, 128.2, 128.2, 126.7, 121.9, 117.5, 70.3, 43.1, 37.9, 17.3. **IR (ATR)** ṽ (cm^{-1}): 3045, 2926, 2855, 1784, 1705, 1599, 1481, 1429, 1389 and 1344. **HRMS (ESI):** calc. for [($C_{28}H_{21}N_3O_3$)H] (M+H) 448.1661, measured 448.1663.

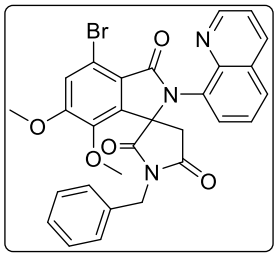
1'-benzyl-4-phenyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ja)



Prepared according to **GP 1**; Half-white solid; eluent (35% ethyl acetate in hexanes); **1j** was taken in 50 mg; yield is 88% (69 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.74 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.68 – 7.59 (m, 3H), 7.58 – 7.53 (m, 1H), 7.46 (d, *J* = 7.6 Hz, 1H),

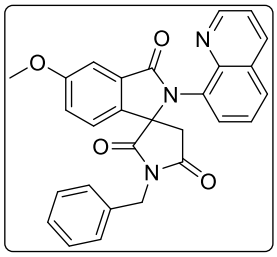
7.44 – 7.38 (m, 4H), 7.36 – 7.29 (m, 5H), 7.13 (dd, *J* = 7.6, 0.8 Hz, 1H), 4.79 (d, *J* = 14.0 Hz, 1H), 4.74 (d, *J* = 14.0 Hz, 1H), 3.48 (d, *J* = 18.8 Hz, 1H), 3.24 (d, *J* = 18.8 Hz, 1H).**^{13}C NMR (100 MHz, $CDCl_3$):** 174.9, 173.6, 168.1, 151.1, 145.9, 145.3, 142.3, 136.7, 136.6, 135.2, 132.7, 132.6, 132.0, 131.8, 130.0, 129.6, 129.5, 128.8, 128.7, 128.3, 128.1, 127.7, 127.0, 126.7, 121.9, 119.1, 70.2, 43.3, 38.0. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3056, 2926, 2854, 2312, 1784, 1706, 1594, 1497, 1470 and 1429. **HRMS (ESI):** calc. for [($C_{33}H_{23}N_3O_3$)H] (M+H) 510.1818, measured 510.1817.

1'-benzyl-4-bromo-6,7-dimethoxy-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ka)



Prepared according to **GP 1**; Half-white solid; eluent (40% ethyl acetate in hexanes); **1k** was taken in 50 mg; yield is 58% (43 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.21 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.88 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.58 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.33 – 7.26 (m, 5H), 4.72 (d, *J* = 14.0 Hz, 1H), 4.68 (d, *J* = 14.0 Hz, 1H), 3.95 (s, 3H), 3.58 (s, 3H), 3.36 (d, *J* = 18.8 Hz, 1H), 3.23 (d, *J* = 18.8 Hz, 1H).**^{13}C NMR (100 MHz, $CDCl_3$):** 174.9, 173.8, 166.0, 155.5, 151.4, 145.4, 142.3, 138.3, 136.6, 135.1, 132.1, 131.5, 129.9, 129.5, 128.9, 128.6, 128.1, 126.5, 121.9, 119.1, 113.5, 68.2, 60.2, 56.6, 43.1, 36.8. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3062, 2961, 1786, 1717, 1613, 1497, 1482, 1433, 1283 and 1232. **HRMS (ESI):** calc. for [($C_{29}H_{22}BrN_3O_5$)H] (M+H) 572.0821, measured 572.0825.

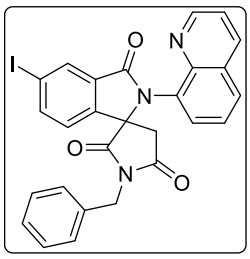
1'-benzyl-5-methoxy-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3la)



Prepared according to **GP 1**; Half-white solid; eluent (45% ethyl acetate in hexanes); **1l** was taken in 50 mg; yield is 83% (69 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.79 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.22 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.88 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.70 (dd, *J*

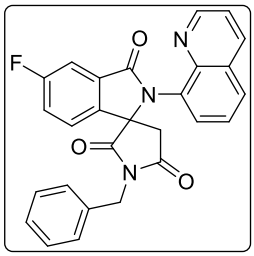
= 7.4, 1.2 Hz, 1H), 7.50 (d, *J* = 2.4 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.33 – 7.27 (m, 5H), 7.13 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 4.76 (d, *J* = 13.8 Hz, 1H), 4.70 (d, *J* = 13.8 Hz, 1H), 3.91 (s, 3H), 3.31 (d, *J* = 19.2 Hz, 1H), 3.13 (d, *J* = 19.2 Hz, 1H).**^{13}C NMR (100 MHz, $CDCl_3$):** 174.8, 173.4, 168.6, 161.2, 151.1, 145.1, 136.6, 136.5, 135.1, 132.9, 132.4, 131.3, 129.6, 129.5, 128.7, 128.7, 128.2, 126.7, 121.9, 121.2, 121.1, 107.7, 70.6, 55.9, 43.1, 37.5. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2924, 2856, 2314, 1786, 1710, 1608, 1488, 1432, 1388 and 1261. **HRMS (ESI):** calc. for [($C_{28}H_{21}N_3O_4$)H] (M+H) 464.1610, measured 464.1614.

1'-benzyl-5-iodo-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ma)



Prepared according to **GP 1**; Half-white solid; eluent (35% ethyl acetate in hexanes); **1m** was taken in 50 mg; yield is 82% (61 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.78 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.37 (d, *J* = 1.2 Hz, 1H), 8.22 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.90 (ddd, *J* = 8.2, 3.8, 1.4 Hz, 2H), 7.67 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.37 – 7.26 (m, 5H), 6.90 (d, *J* = 8.0 Hz, 1H), 4.76 (d, *J* = 13.8 Hz, 1H), 4.70 (d, *J* = 13.8 Hz, 1H), 3.32 (d, *J* = 19.2 Hz, 1H), 3.12 (d, *J* = 19.2 Hz, 1H).**^{13}C NMR (100 MHz, $CDCl_3$):** 174.0, 173.0, 167.0, 151.2, 144.9, 143.8, 141.6, 136.6, 135.0, 134.1, 133.3, 131.9, 131.2, 129.8, 129.5, 128.8, 128.7, 128.4, 126.6, 122.1, 121.9, 95.3, 70.8, 43.3, 37.2. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3346, 2922, 2853, 1722, 1675, 1517, 1477, 1382, 1324 and 1074. **HRMS (ESI):** calc. for [($C_{27}H_{18}IN_3O_3$)H] (M+H) 560.0471, measured 560.0478.

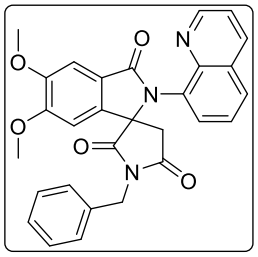
1'-benzyl-5-fluoro-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3na)



Prepared according to **GP 1**; Colourless oil; eluent (55% ethyl acetate in hexanes); **1n** was taken in 50 mg; yield is 75% (64 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.80 (dd, *J* =

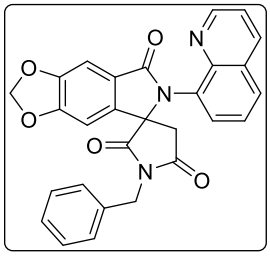
4.2, 1.6 Hz, 1H), 8.23 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.90 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.76 – 7.64 (m, 2H), 7.52 – 7.39 (m, 2H), 7.35 – 7.24 (m, 6H), 7.11 (dd, *J* = 8.4, 4.2 Hz, 1H), 4.77 (d, *J* = 13.8 Hz, 1H), 4.70 (d, *J* = 13.8 Hz, 1H), 3.35 (d, *J* = 18.8 Hz, 1H), 3.14 (d, *J* = 18.8 Hz, 1H).**^{13}C NMR (100 MHz, $CDCl_3$):** δ 174.39, 173.17, 167.56 and 167.53 (F-Coupling), 165.06, 162.56, 151.27, 145.05, 139.98 and 139.96 (F-Coupling), 136.71, 135.13, 133.85 and 133.76 (F-Coupling), 132.10, 131.33, 129.94, 129.64, 128.90, 128.83, 128.40, 126.76, 122.15, 122.07 and 121.98 (F-Coupling), 120.69 and 120.45 (F-Coupling), 112.2 and 111.9 (F-Coupling), 70.72, 43.29, 37.49. **IR (ATR)** ṽ (cm^{-1}): 2924, 2855, 1783, 1710, 1611, 1488, 1438, 1390, 1347 and 1267. **HRMS (ESI):** calc. for [($C_{27}H_{18}FN_3O_3$)H] (M+H) 452.1410, measured 452.1421.

1'-benzyl-5,6-dimethoxy-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3oa)



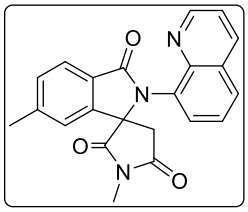
Prepared according to **GP 1**; Half-white solid; eluent (45% ethyl acetate in hexanes); **1o** was taken in 50 mg; yield is 87% (70 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.81 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.22 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.89 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.77 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.46 (s, 1H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.38 – 7.29 (m, 5H), 6.40 (s, 1H), 4.78 (d, *J* = 13.8 Hz, 1H), 4.73 (d, *J* = 13.8 Hz, 1H), 3.98 (s, 3H), 3.69 (s, 3H), 3.30 (d, *J* = 18.8 Hz, 1H), 3.11 (d, *J* = 18.8 Hz, 1H).**^{13}C NMR (100 MHz, $CDCl_3$):** 174.8, 173.5, 169.0, 153.8, 150.9, 145.2, 138.0, 136.6, 135.5, 132.7, 131.4, 129.6, 129.5, 129.0, 128.9, 128.4, 126.8, 123.7, 121.9, 106.4, 101.8, 70.6, 56.5, 56.3, 43.1, 37.5. **IR (ATR)** ṽ (cm^{-1}): 3059, 2936, 1782, 1702, 1604, 1500, 1466, 1428, 1388 and 1164. **HRMS (ESI):** calc. for [($C_{29}H_{23}N_3O_5$)H] (M+H) 494.1716, measured 496.1714.

1-benzyl-6'-(quinolin-8-yl)spiro[pyrrolidine-3,5'-[1,3]dioxolo[4,5-f]isoindole]-2,5,7'(6'H)-trione (3pa)



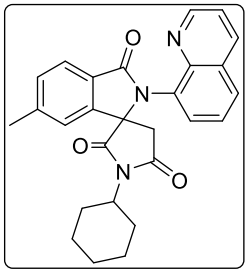
Prepared according to **GP 1**; White solid; eluent (35% ethyl acetate in hexanes); **1p** was taken in 50 mg; yield is 77% (71 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.78 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.21 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.71 – 7.64 (m, 1H), 7.47 – 7.46 – 7.42 (m, 2H), 7.38 (s, 1H), 7.33 – 7.28 (m, 6H), 6.53 (s, 1H), 6.10 (d, *J* = 3.4 Hz, 1H), 4.76 (d, *J* = 14.2 Hz, 1H), 4.69 (d, *J* = 14.2 Hz, 1H), 3.33 (d, *J* = 18.8 Hz, 1H), 3.10 (d, *J* = 18.8 Hz, 1H).**^{13}C NMR (100 MHz, $CDCl_3$):** 174.7, 173.4, 168.4, 152.5, 151.1, 149.7, 145.2, 139.9, 136.7, 135.2, 132.5, 131.4, 131.6, 131.4, 129.6, 128.8, 128.8, 128.4, 126.8, 122.0, 104.6, 102.6, 100.6, 70.6, 43.2, 37.5. **IR (ATR)** ṽ (cm^{-1}): 3061, 2939, 1787, 1697, 1604, 1507, 1463, 1429, 1374 and 1184. **HRMS (ESI):** calc. for [($C_{28}H_{19}N_3O_5$)H] (M+H) 478.1403, measured 478.1407.

1',6-dimethyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ab)



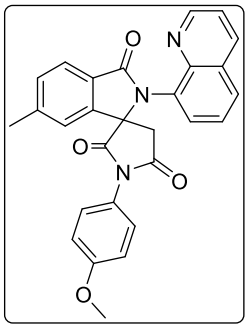
Prepared according to **GP 1**; Half-white solid; eluent (55% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 79% (56 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.24 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.97 – 7.90 (m, 2H), 7.86 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.62 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.15 (s, 1H), 3.37 (d, *J* = 18.8 Hz, 1H), 3.16 (d, *J* = 18.8 Hz, 1H), 3.10 (s, 3H), 2.51 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$):** 175.1, 174.0, 168.8, 151.0, 145.3, 144.9, 144.1, 136.6, 132.7, 131.6, 130.8, 129.7, 129.6, 128.7, 126.8, 124.8, 121.9, 120.6, 71.1, 37.7, 25.6, 22.0. **IR (ATR)** ṽ (cm^{-1}): 3056, 2932, 2859, 1780, 1701, 1619, 1498, 1469, 1359 and 1191. **HRMS (ESI):** calc. for [($C_{22}H_{17}N_3O_3$)H] (M+H) 372.1348, measured 372.1352.

1'-cyclohexyl-6-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ac)



Prepared according to **GP 1**; Half-white solid; eluent (45% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 78% (65 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.83 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.95 – 7.84 (m, 2H), 7.79 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.64 – 7.52 (m, 1H), 7.48 – 7.35 (m, 2H), 7.08 (s, 1H), 3.99 (tt, *J* = 12.3, 3.8 Hz, 1H), 3.24 (d, *J* = 18.8 Hz, 1H), 3.06 (d, *J* = 18.8 Hz, 1H), 2.46 (s, 3H), 2.14 (qd, *J* = 12.4, 3.6 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.82 (dd, *J* = 21.1, 18.1 Hz, 2H), 1.63 (d, *J* = 11.7 Hz, 1H), 1.49 (d, *J* = 11.4 Hz, 2H), 1.38 – 1.11 (m, 3H).**^{13}C NMR (100 MHz, $CDCl_3$):** δ 175.1, 174.1, 168.9, 151.3, 145.5, 145.3, 144.1, 136.7, 132.8, 131.6, 130.9, 129.9, 129.7, 128.9, 126.7, 124.9, 122.1, 120.5, 70.6, 52.6, 37.6, 28.9, 28.8, 25.9, 25.8, 24.9, 22.1. **IR (ATR)** ṽ (cm^{-1}): 3053, 2931, 2859, 1780, 1701, 1614, 1496, 1467, 1357 and 1261. **HRMS (ESI):** calc. for [($C_{27}H_{25}N_3O_3$)H] (M+H) 440.1974, measured 440.1967.

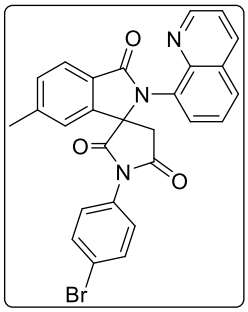
1'-(4-methoxyphenyl)-6-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ad)



Prepared according to **GP 1**; Half-white solid; eluent (45% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 76% (69 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.89 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.27 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.98 – 7.96 (m, 3H), 7.65 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.29 (d, *J* = 6.6 Hz, 1H), 7.19 – 7.14 (m, 2H), 7.01 – 6.97 (m, 2H), 3.84 (s, 3H), 3.54 (d, *J* = 18.8 Hz, 1H), 3.31 (d, *J* = 18.8 Hz, 1H), 2.55 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$):** 174.4, 173.2, 168.9, 159.8, 151.2, 145.3, 145.1, 144.3, 136.8, 132.7, 131.6, 131.1, 129.8, 129.7, 128.9, 127.4, 126.8, 125.1, 124.1, 122.1, 120.6, 114.7, 71.1, 55.6, 37.9, 22.2. **IR (ATR)** ṽ (cm^{-1}): 3054, 2966, 2843, 1787, 1711,

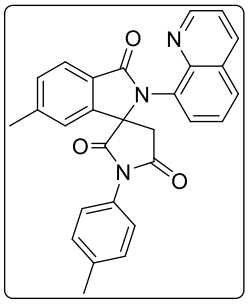
1611, 1509, 1468, 1383 and 1254. **HRMS (ESI):** calc. for [($C_{28}H_{21}N_3O_4$)H] (M+H) 464.1610, measured 464.1615.

1'-(4-bromophenyl)-6-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ae)



Prepared according to **GP 1**; Brown solid; eluent (35% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 65% (64 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.87 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.27 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.05 – 7.88 (m, 3H), 7.73 – 7.57 (m, 3H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 2H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.22 – 7.13 (m, 2H), 3.54 (d, *J* = 18.8 Hz, 1H), 3.31 (d, *J* = 18.8 Hz, 1H), 2.54 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$):** 173.8, 172.5, 168.8, 150.9, 144.9, 144.8, 144.4, 136.7, 132.6, 132.5, 131.4, 131.1, 130.5, 129.7, 129.6, 128.7, 127.5, 126.8, 125.1, 122.8, 122.0, 120.5, 70.9, 37.8, 22.1. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3054, 2966, 2843, 1787, 1711, 1611, 1509, 1468, 1383 and 1300. **HRMS (ESI):** calc. for [($C_{27}H_{18}BrN_3O_3$)H] (M+H) 512.0610, measured 512.0606.

6-methyl-2-(quinolin-8-yl)-1'-(p-tolyl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trion (3af)



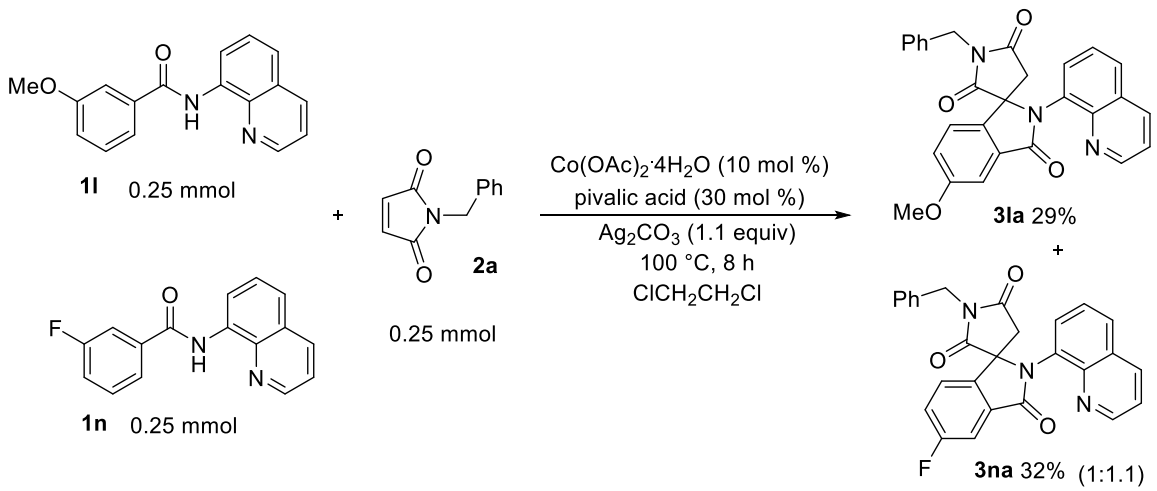
Prepared according to **GP 1**; Half-white solid; eluent (45% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 76% (65 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.24 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.95 – 7.89 (m, 3H), 7.64 – 7.60 (m, 1H), 7.47 – 7.43 (m, 2H), 7.26 – 7.65 (m, 3H), 7.09 (d, *J* = 8.2 Hz, 2H), 3.50 (d, *J* = 18.8 Hz, 1H), 3.27 (d, *J* = 18.8 Hz, 1H), 2.51 (s, 3H), 2.37 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$):** 174.1, 173.0, 168.8, 151.1, 145.2, 145.0, 144.2, 139.2, 136.6, 132.7, 131.6, 130.9, 129.9,

129.7, 128.9, 126.8, 125.7, 125.0, 121.9, 120.5, 71.0, 37.8, 22.1, 21.2. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3058, 2939, 1782, 1715, 1612, 1469, 1428, 1386, 1349 and 1261. **HRMS (ESI):** calc. for [($C_{28}H_{21}N_3O_3$)H] (M+H) 448.1661, measured 448.1661.

Mechanistic Studies

General Procedure for Competition reaction between amides(GP 3)

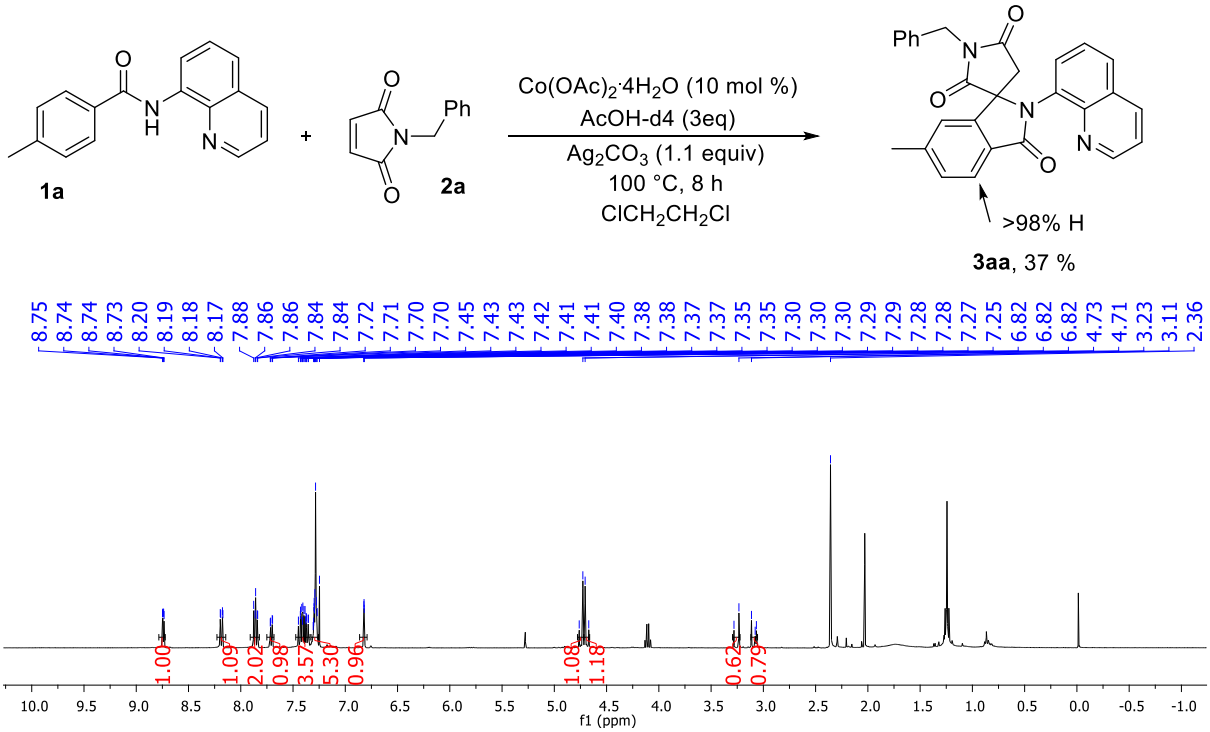
To a 15-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amides **1l** (0.25 mmol, 1 equiv), amide **1n** (0.25 mmol, 1 equiv), malemide **2a** (0.25 mmol, 1 eq) and Ag_2CO_3 (1.1 equiv) was evacuated and purged with nitrogen gas three times. (Ag_2CO_3 was taken inside the glove box). To the tube were then added 1, 2- dichloroethane (3.0 mL) and pivalic acid*(30 mol %)* were added via syringe sequentially. After that, the tube was evacuated and purged with nitrogen gas three times and a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 100 °C for 8 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite 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 products **3la** and **3na** 29% and 32% respectively (ratio 1:1.1).



Procedure for the Studies with Isotopically Labelled Compounds of Isoindolone Spirosuccinimides

A)H/D Exchange studies with AcOH-$d_4$as Additive (GP 4)

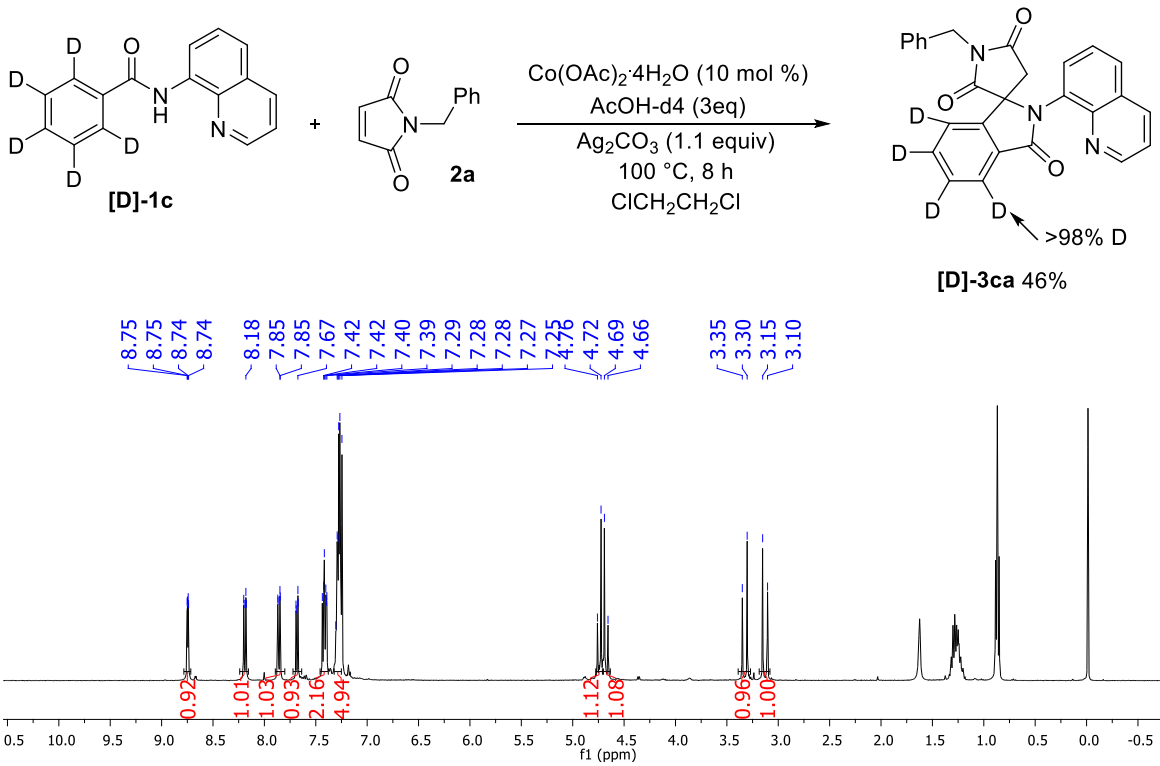
To a 15-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amides **1a** (50 mg, 1 equiv), malemide **2a** (1.3 equiv) and Ag_2CO_3 (1.1 equiv) was evacuated and purged with nitrogen gas three times. (Ag_2CO_3 was taken inside the glove box). To the tube were then added 1,2- dichloroethane (3.0 mL) and AcOH-d_4(3 eq) were added via syringe sequentially. After that, the tube was evacuated and purged with nitrogen gas three times and a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, 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 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 **3aa**.



B) H/D Exchange studies [D]-1c (GP 5)

To a 15-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amides **[D]-1c** (50 mg, 1 equiv), malemide **2a** (1.3 equiv) and Ag_2CO_3 (1.1 equiv) was evacuated and purged with nitrogen gas three times. (Ag_2CO_3 was taken inside the glove box). To the tube were then added 1, 2- dichloroethane (3.0 mL) and pivalic acid *(30 mol %)* were added via

syringe sequentially. After that, the tube was evacuated and purged with nitrogen gas three times and a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, 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 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 **[D]-3ca** in 46% yield.

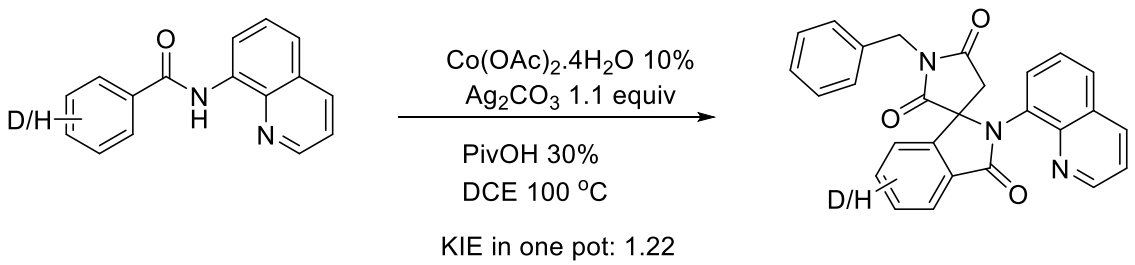


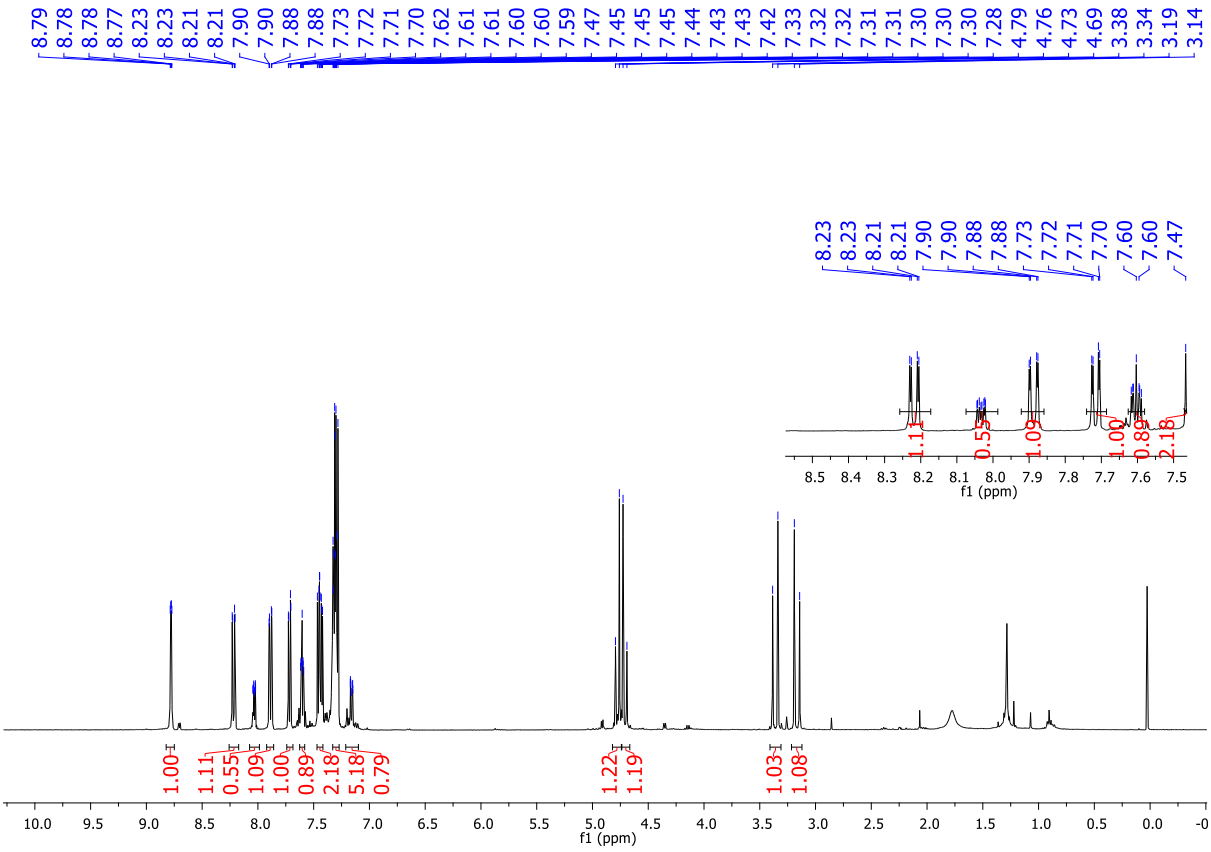
Studies on the Kinetic Isotope Effect.

A) By competition reaction

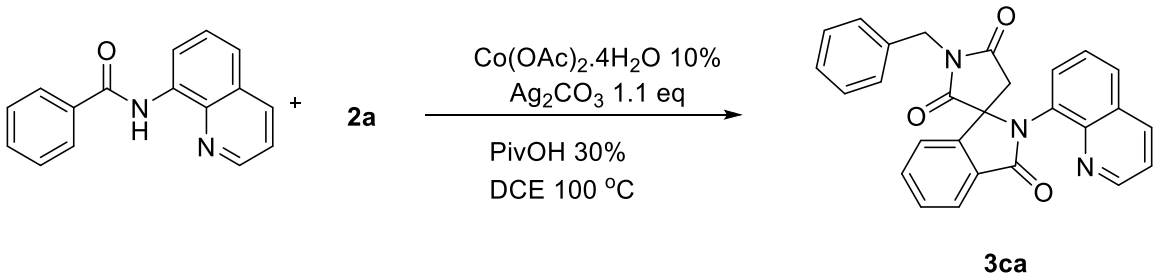
To a 15-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amides **1c**(50 mg, 1eq)and**[D]-1c** (50 mg, 1 equiv), malemide **2a** (1.3 equiv) and Ag_2CO_3 (1.1 equiv) was evacuated and purged with nitrogen gas three times. (Ag_2CO_3 was taken inside the glove box). To the tube were then added 1, 2- dichloroethane (3.0 mL) and pivalic acid*(30 mol %)* were added via syringe sequentially. After that, the tube was evacuated and purged with nitrogen gas three times and a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, 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 the filtrate was

concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give combined products **3ca**and **[D]-3ca**in 54% yield.



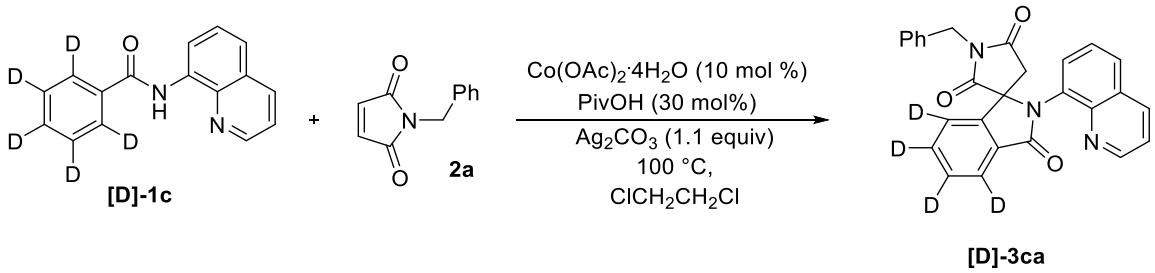


B) By two parallel reactions

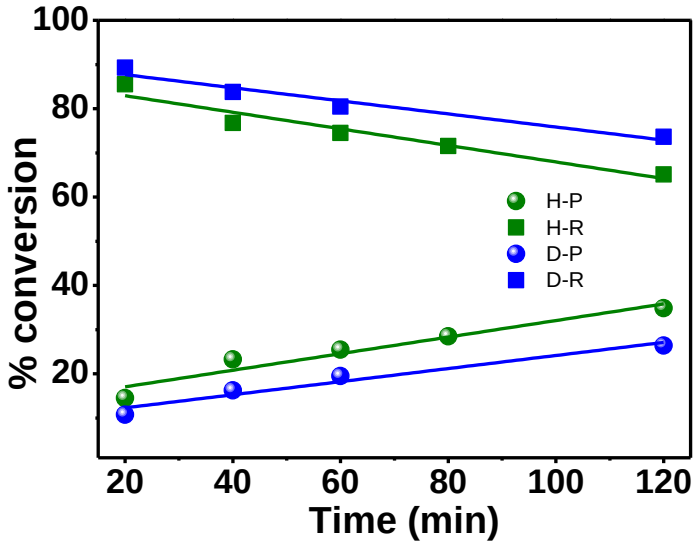


3ca

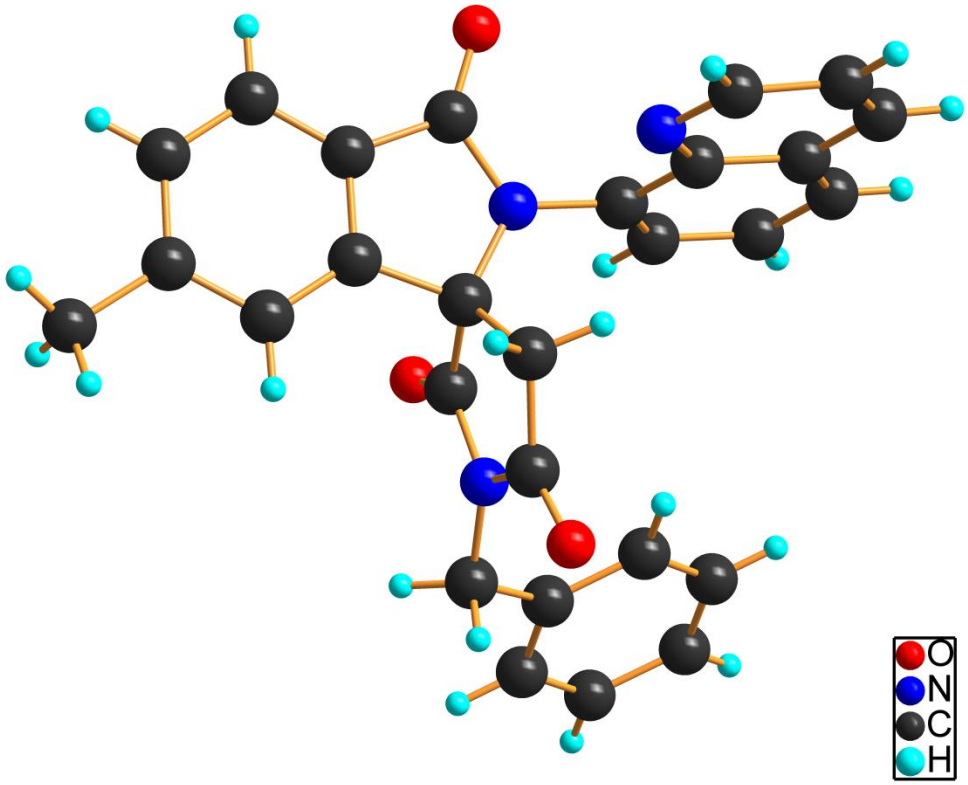
To a 15-mL pressure tube containing $Co(OAc)_2 \cdot 4H_2O$ (10 mol %), amides **1c**(100 mg, 1eq)and malemide **2a** (1.3 equiv) and Ag_2CO_3 (1.1 equiv) was evacuated and purged with nitrogen gas three times. (Ag_2CO_3 was taken inside the glove box). To the tube were then added 1, 2- dichloroethane (3.0 mL) and pivalic acid*(30 mol %)* were added via syringe sequentially. After that, the tube was evacuated and purged with nitrogen gas three times and a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 100 °C. For 120 min, an aliquot (0.1 mL) wasremoved by a syringe every 20 min and directly analyzed by 1H-NMR.



The procedure above was followed using **[D]-1c**(100 mg,). Data from independent kinetic isotope studies are collected in the figure below and KIE wasfound to be $k_H/k_D \approx 1.26$



X-Ray analysis: Single crystal structure of **3aa**



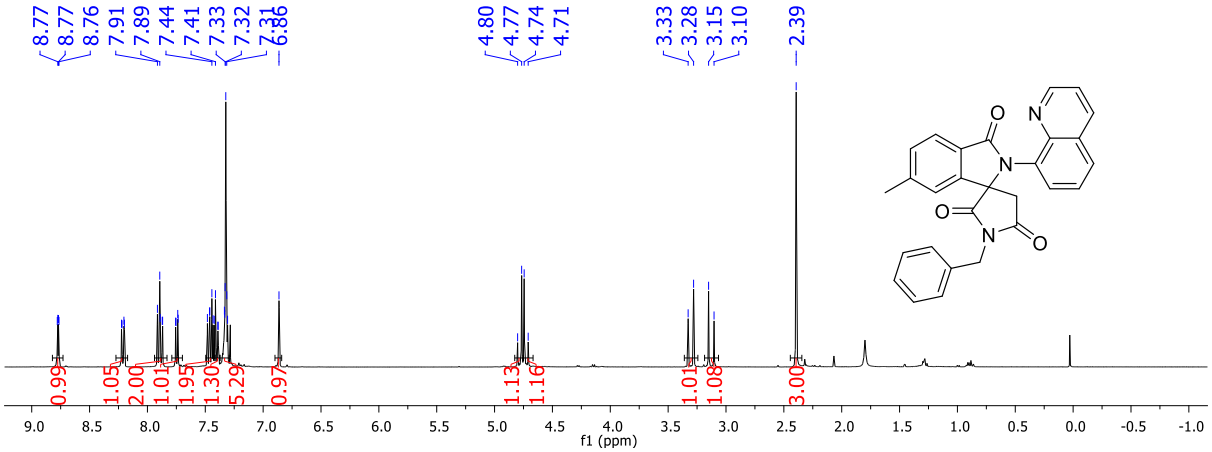
Crystal data and structure refinement for tr1_a.

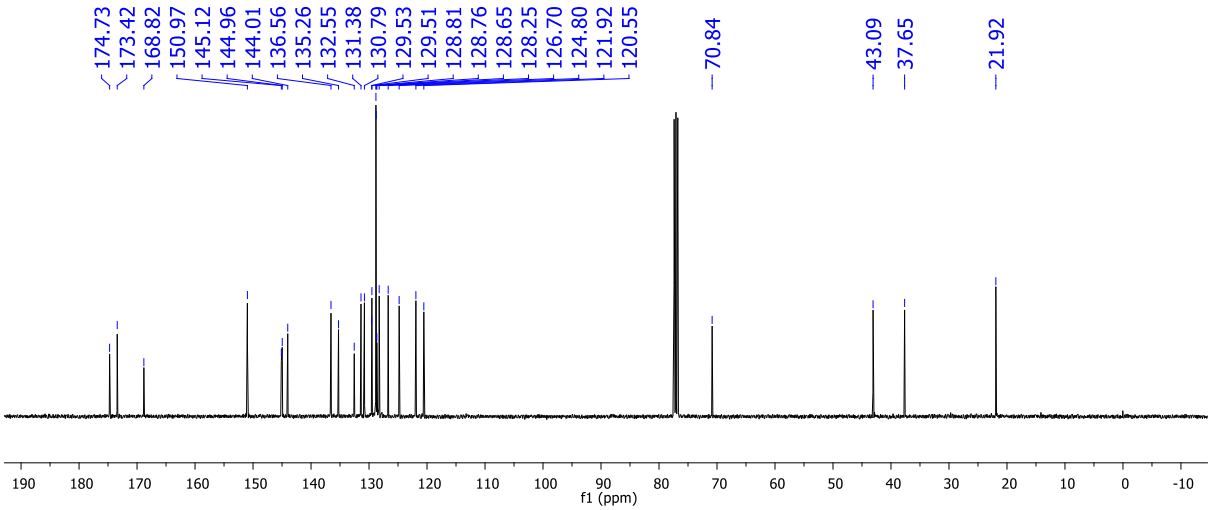
Identification code	NRM-3430_a	
Empirical formula	C28 H21 N3 O3	
Formula weight	447.48	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.3542(12) Å	α= 102.671(4)°.
	b = 11.7504(15) Å	β= 106.404(4)°.
	c = 11.9494(15) Å	γ = 97.121(4)°.
Volume	1076.0(2) $Å^3$	
Z	2	
Density (calculated)	1.381 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	468	
Theta range for data collection	2.59 to 26.11°.	
Index ranges	-10<=h<=10, -14<=k<=14, -12<=l<=14	
Reflections collected	21952	
Independent reflections	4372 [R(int) = 0.0749]	

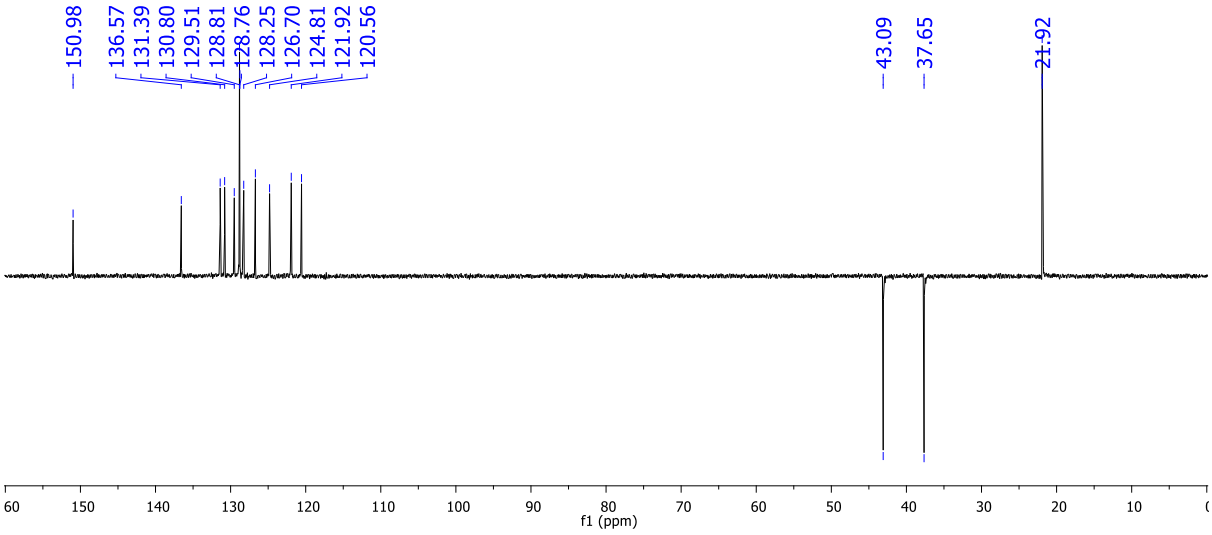
Completeness to theta = 25.242°	99.6 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4372/ 0/ 308
Goodness-of-fit on F^2	1.004
Final R indices [I>2sigma(I)]	R1 = 0.0471, wR2 = 0.1199
R indices (all data)	R1 = 0.0875, wR2 = 0.1479
Extinction coefficient	n/a
Largest diff. peak and hole	0.203and -0.257 e.$Å^{-3}$

4A.7 Spectral Copies of Selected Compounds

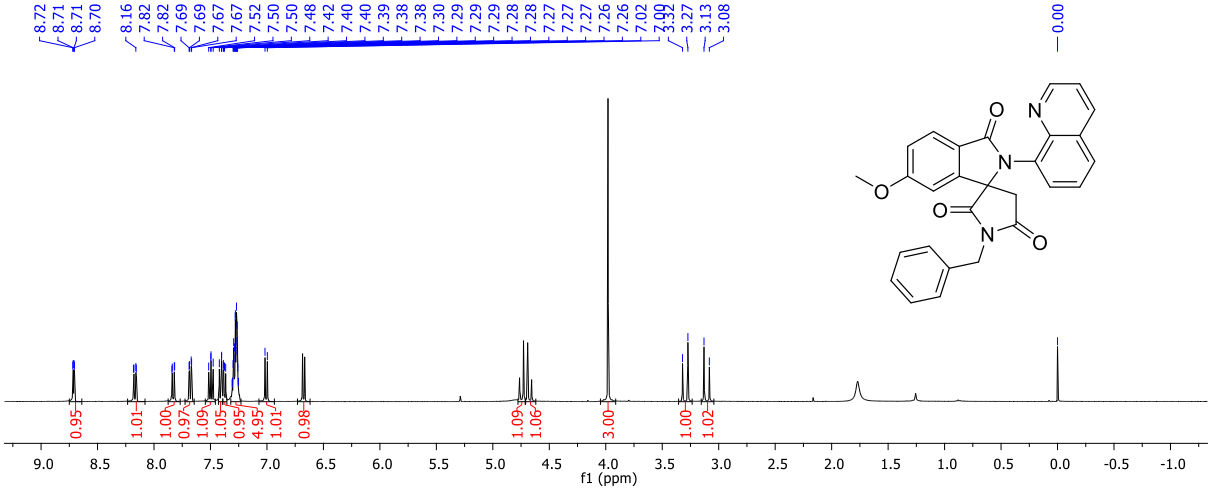
Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **3aa**

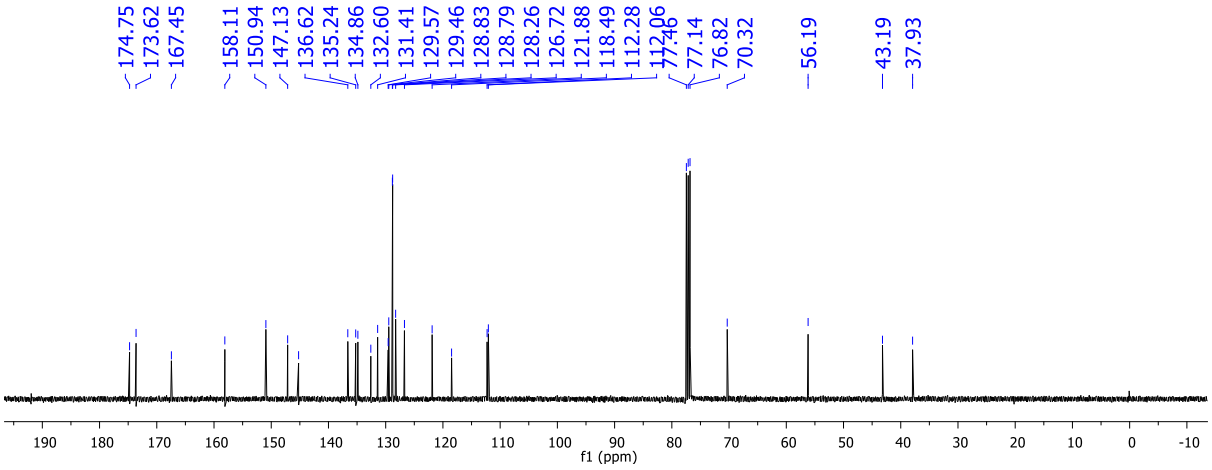


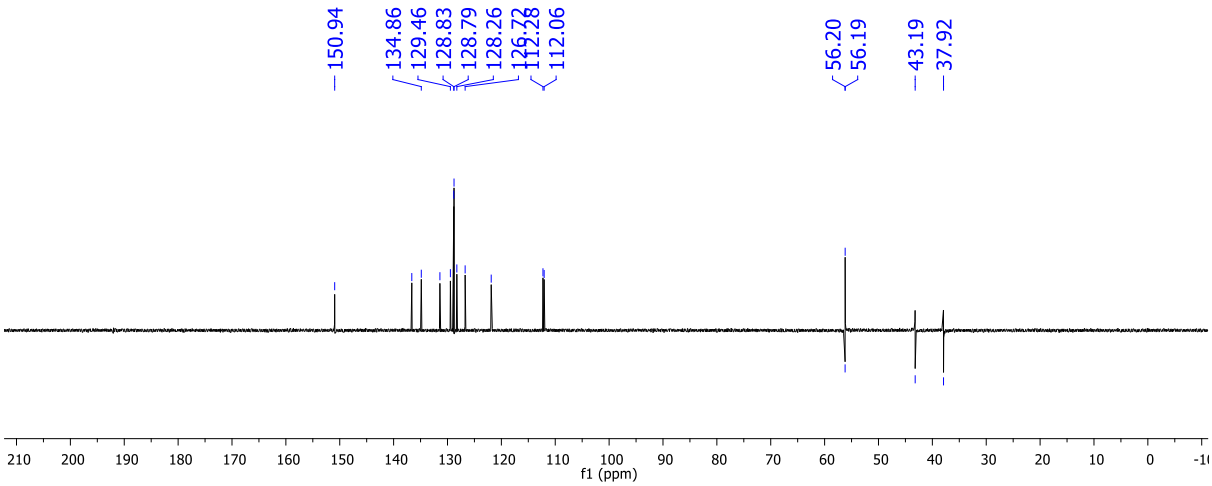




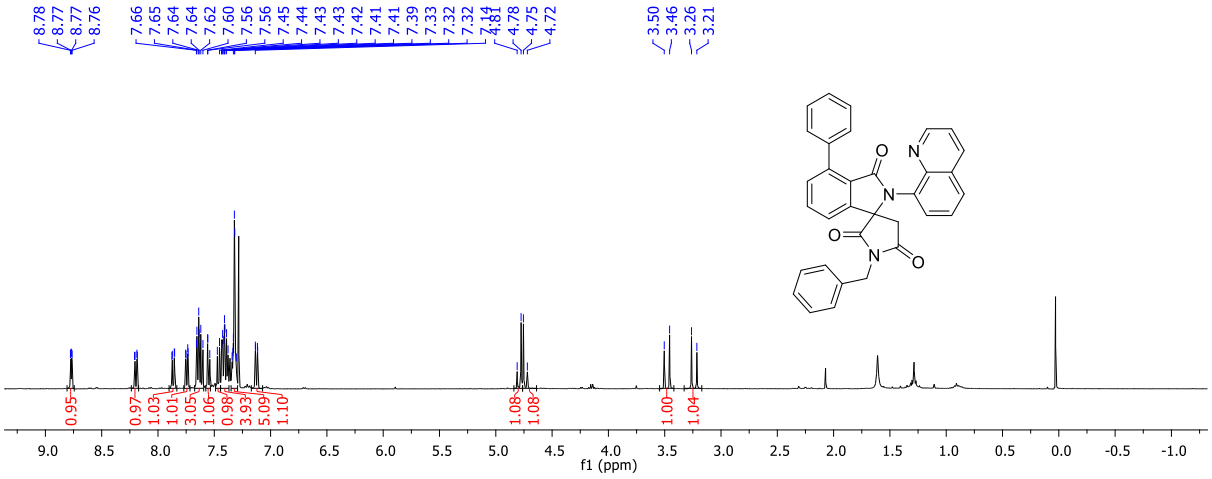
Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **3ba**

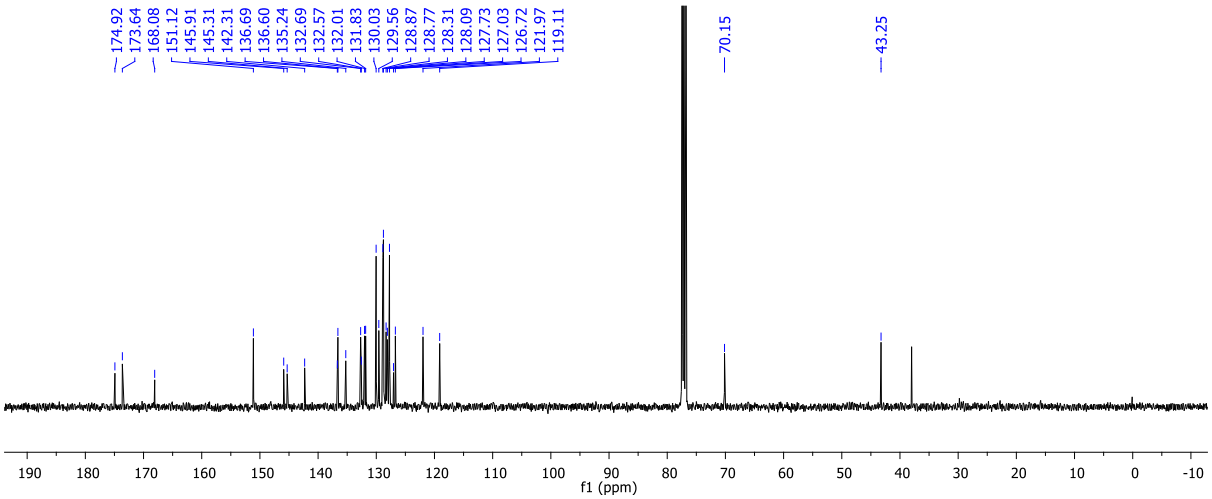


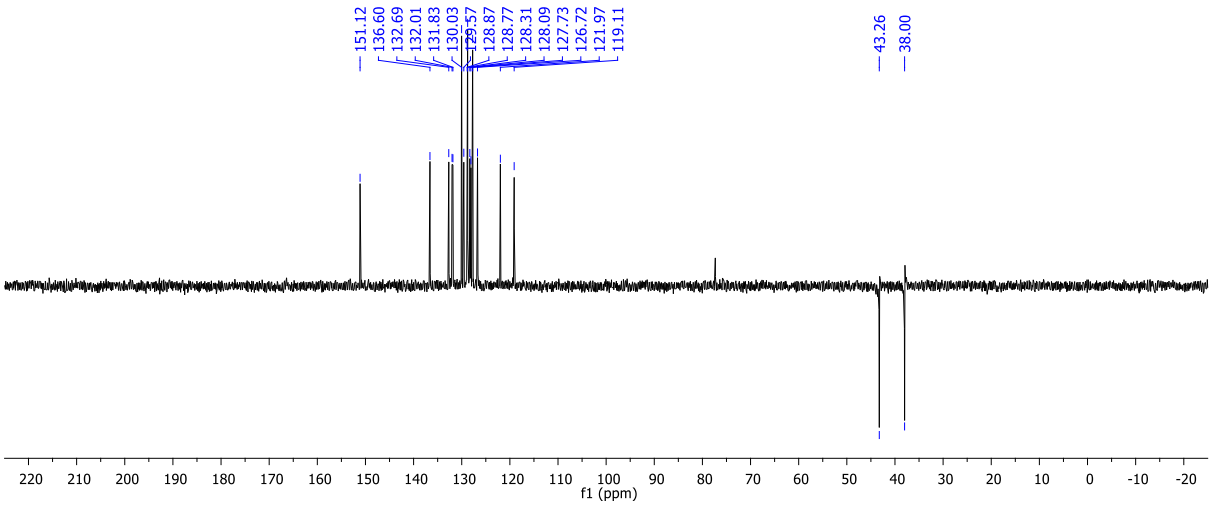




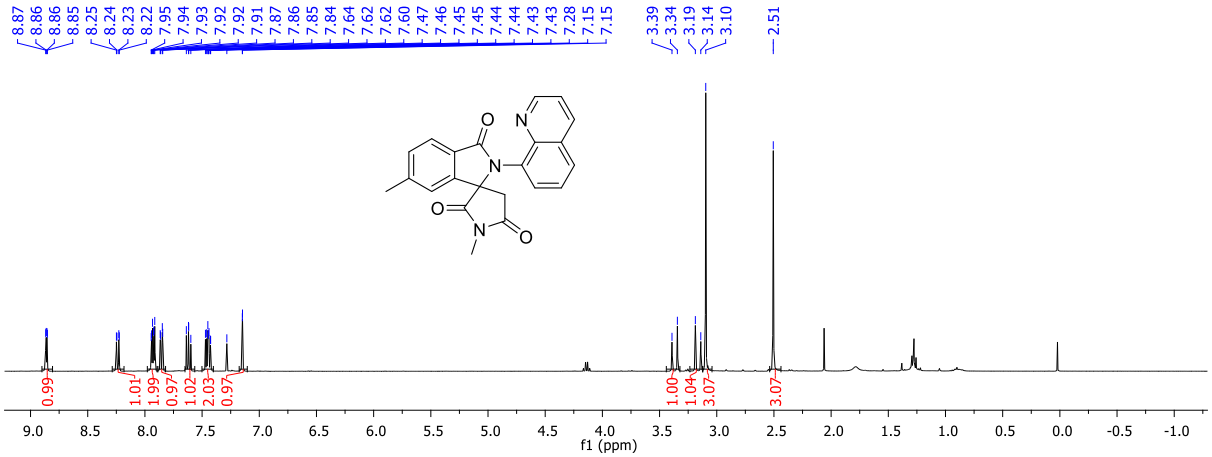
Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **3ja**

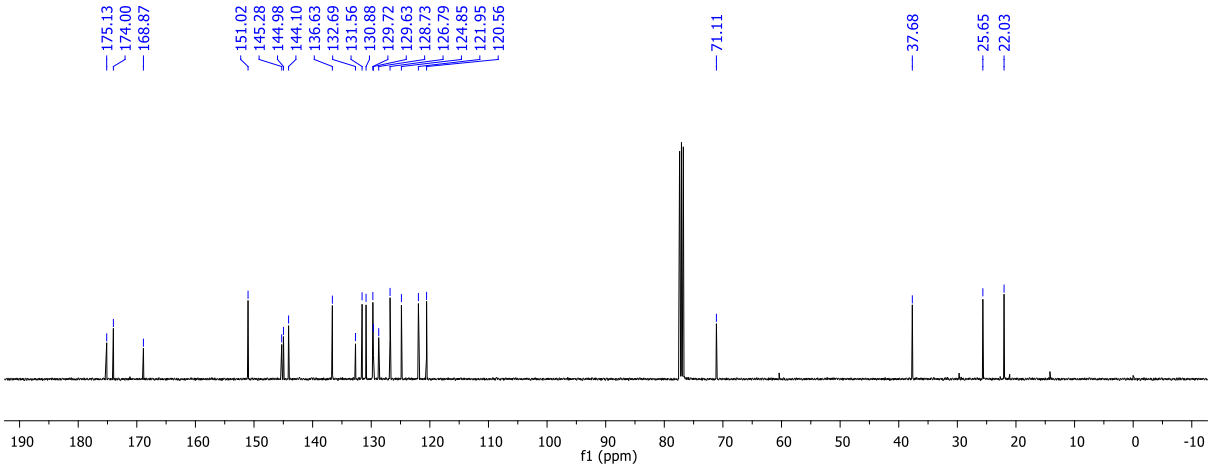


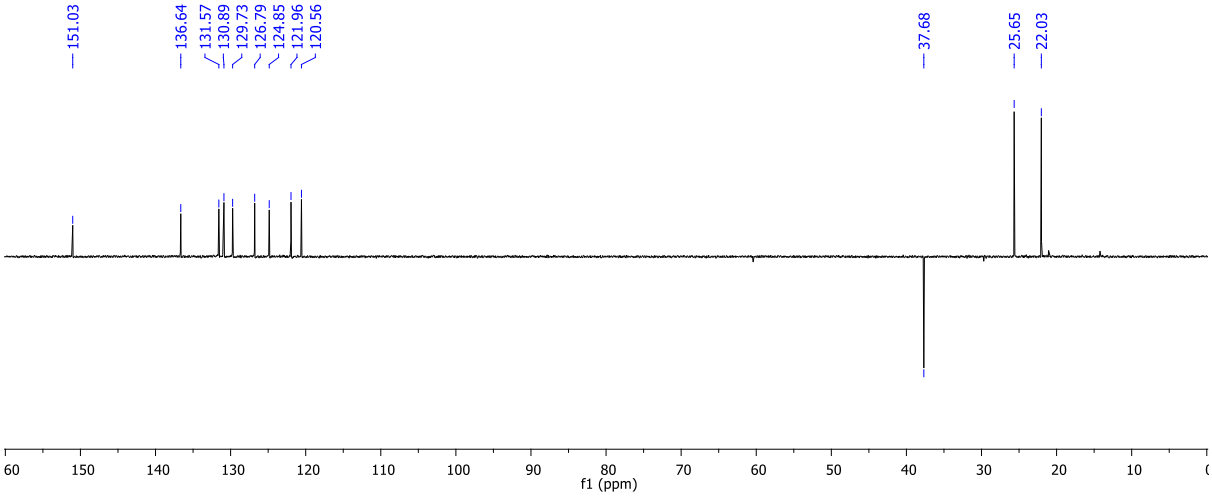




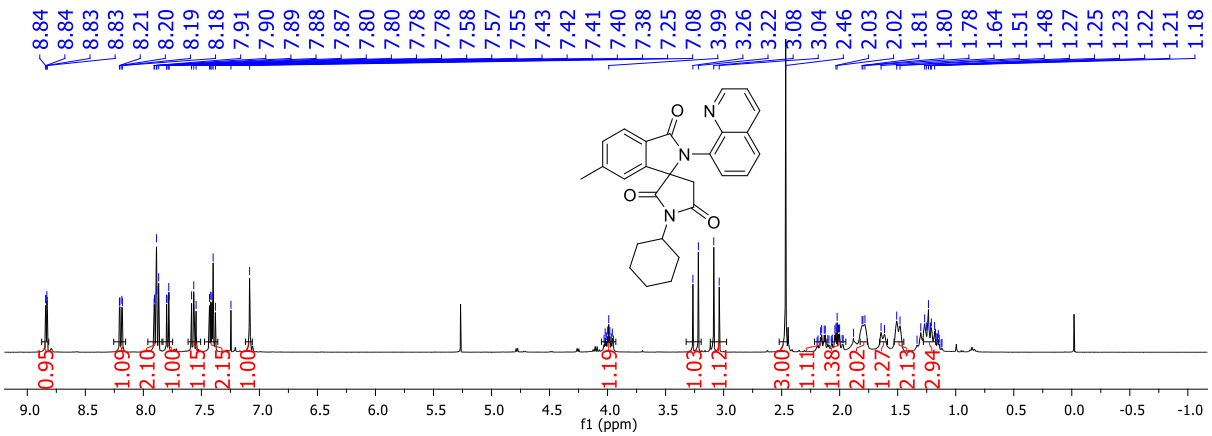
Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **3ab**

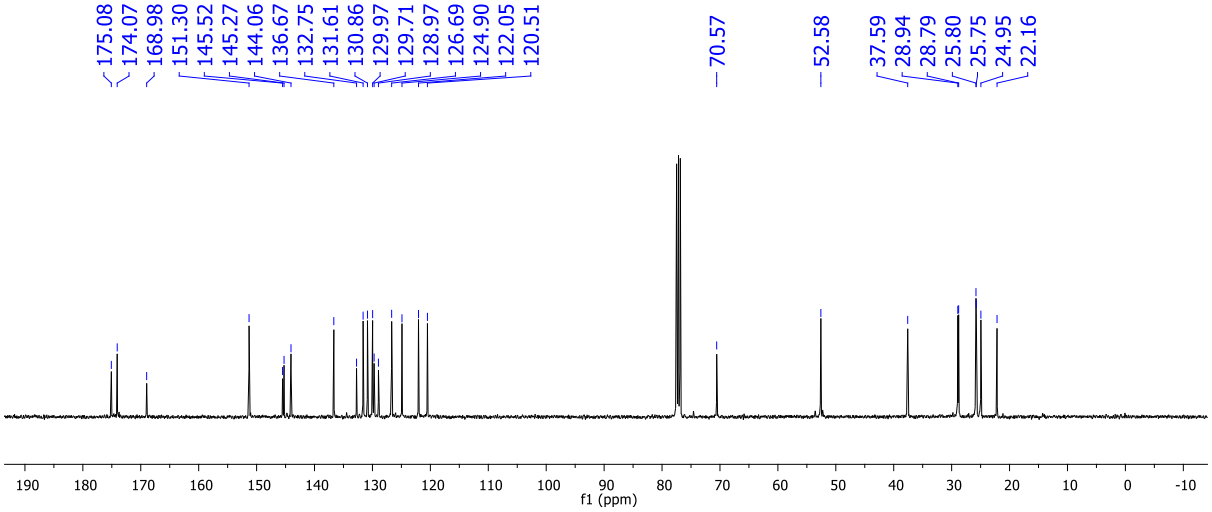


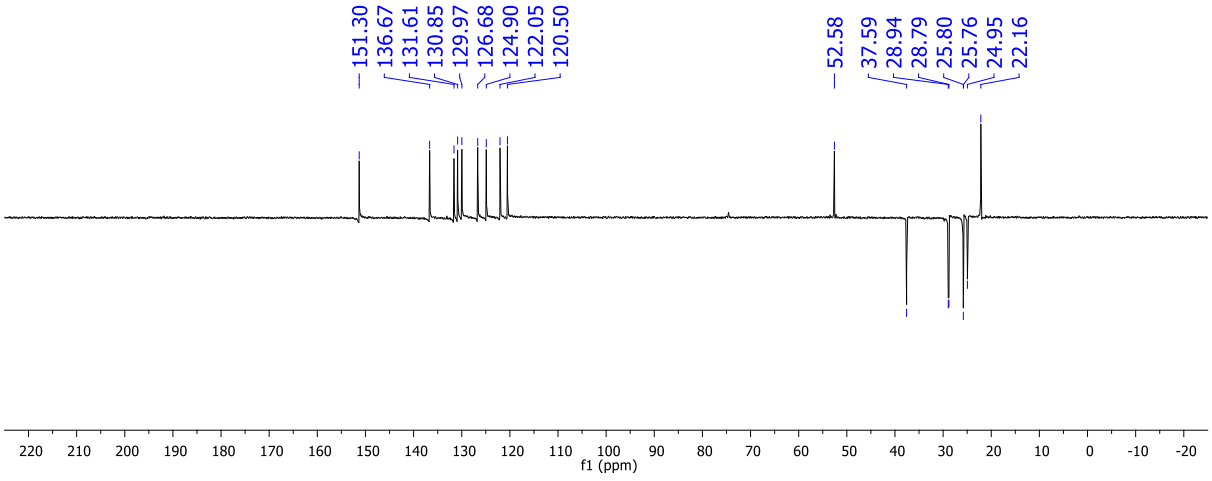




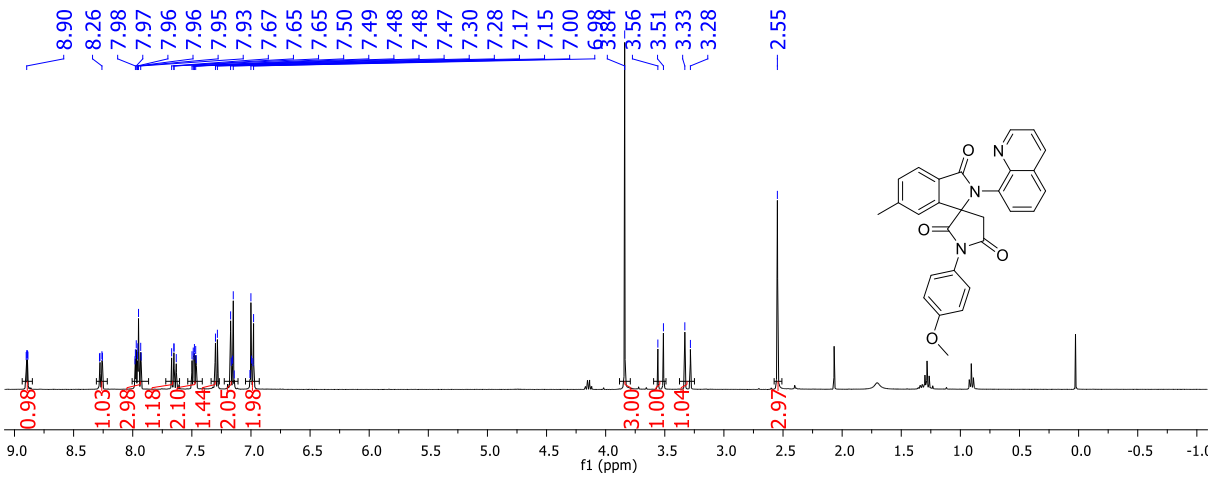
Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **3ac**

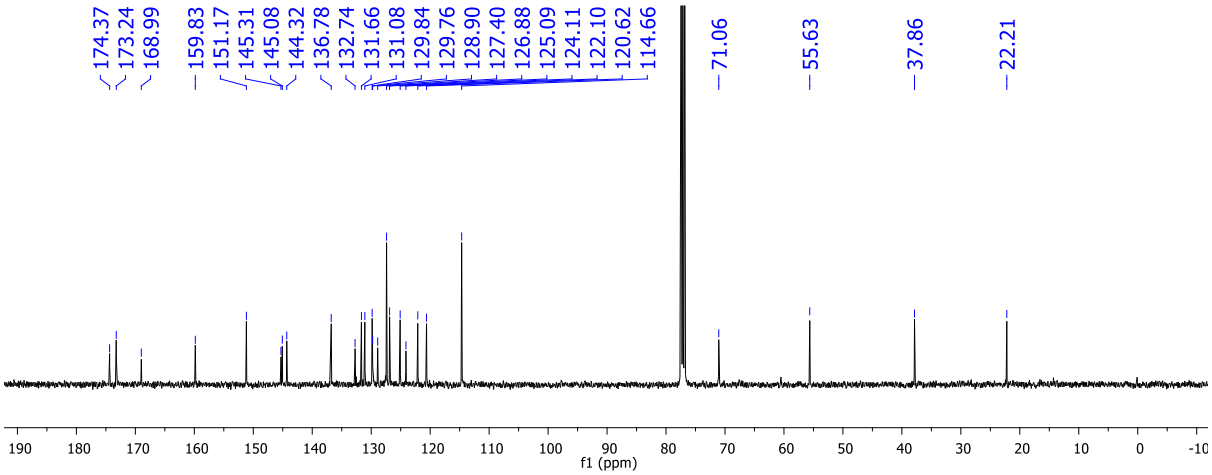


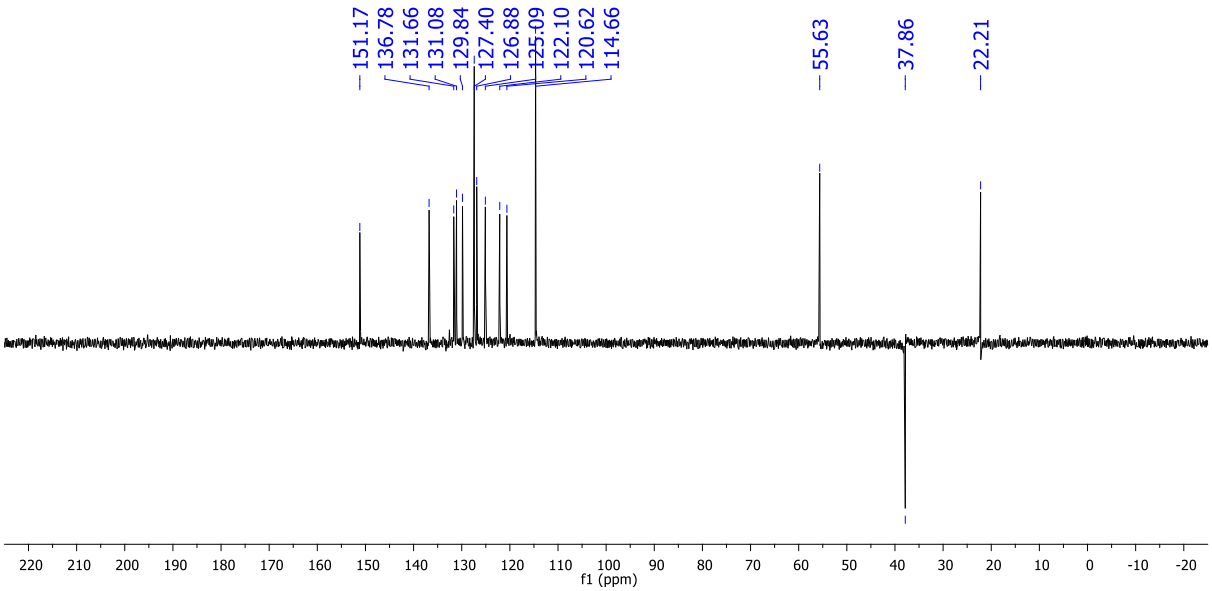




Copies of H^1, C^{13} and DEPT 135 NMR spectra of compound **3ad**



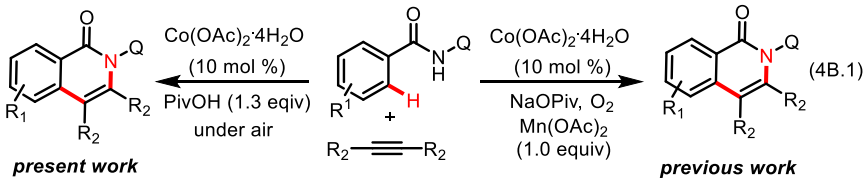




Section 4B: Cobalt-Catalyzed Cyclization of Benzamides with Alkynes: A Facile Route to Isoquinolones with Hydrogen Evolution

4B.1 Introduction

Isoquinolone is an important heterocyclic structural unit which presents in various natural products, biologically active molecules and conjugated materials.[1] In addition, isoquinolone derivatives are widely used as a key intermediate in various organic transformations.[1] Several methods are available in literature for synthesizing isoquinolone derivatives.[2] Among them, the transition-metal-catalyzed oxidative cyclization of benzamides with carbon-carbon π-components via C−H bond activation is an efficient method to construct isoquinolones from easily available starting materials.[3] For this type of transformation, the second and third row transition metal complexes such as Pd, Rh, Ru and Ir are widely employed which are less abundant in the nature.[3] The use of cheaper, more abundant and environmentally benign first row transition metal complexes such as Fe, Co, Cu and Ni as catalysts in the C−H bond activation reaction is highly desirable.[4] In this context, very recently, a cobalt complex has gained tremendous attention in the C−H bond functionalization reaction due to the low toxicity as compared with other early transition metals.[5] Particularly, a simple and easily affordable $Co(OR)_2$-catalyzed C−H bond functionalization reaction assisted by the auxiliary ligand has gained much attention in recent years.[5] In 2014, Daugulis's group reported the oxidative cyclization of benzamides with alkynes assisted by 8-aminoquinoline ligand in the presence of $Co(OAc)_2{\cdot}4H_2O$ as a catalyst, stoichiometric amount of $Mn(OAc)_2$ (1.0 equiv) as a co-oxidant, NaOPiv (2.0 equiv) as a base and O_2 as a terminal oxidant providing isoquinolone derivatives. In the reaction, $Mn(OAc)_2$ and NaOPiv was used to regenerate the active Co(III) species from Co(I) species (eq 4B.1).[5b] Later, this concept has been successfully extended for various heterocyclic molecules in the presence of metal oxidants and base.[5]



In the metal-catalyzed oxidative cyclization reaction, the oxidation step such as a metal with lower oxidation state into the higher oxidation state [Rh(I) to Rh(III), Co(I) to

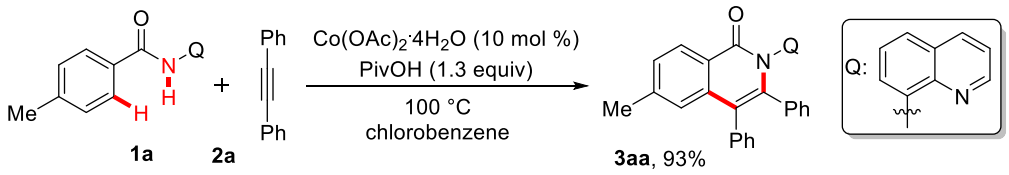
Co(III), Pd(0) to Pd(II), and Ru(0) to Ru(II)] is required to regenerate the active catalyst. Generally, a stoichiometric amount of inorganic or organic oxidants is required to regenerate the active catalyst. Particularly, in the Co(II)-catalyzed reaction, a stoichiometric amount $Mn(OAc)_2$ or silver salt along with O_2 was used as an oxidant.[4-5] An equivalent amount of reduced form of metal salt was formed as a by-product. To avoid the oxidants, several new methods such as having internal oxidant on the directing group,[6] molecular oxygen as a terminal oxidant[7] and electrochemical oxidations[8] are developed in the literature. Recently, we have reported redox-neutral ruthenium(II)-catalyzed C−H alkenylation reaction by using carboxylic acid with the elimination of hydrogen.[9] In the reaction, the alkenylation was done in the ruthenium (II) oxidation state and the typical Ru(0) to Ru(II) oxidation step was avoided. This result prompted us to explore the possibility of cobalt-catalyzed cyclization of aromatic amides with alkynes in the presence of carboxylic acid in the redox-neutral version.

4B.2 Results and Discussion

4B.2.1 Optimization Studies

Herein, we report a cobalt-catalyzed 8-aminoquinoline-directed oxidative cyclization of benzamides with alkynes giving substituted isoquinolones with the liberation of hydrogen in good to excellent yields (eq 4B.1). The present cyclization reaction was compatible with various functional group substituted benzamides as well as internal and terminal alkynes and 1,3-diynes. Treatment of benzamide having 8-aminoquinoline ligand **1a**with diphenylacetylene **(2a)** (1.3equiv) in the presence of $Co(OAc)_2{\cdot}4H_2O$ (10 mol %) and pivalic acid (1.3equiv) in chlorobenzene under air at 100 °C for 4 h gave isoquinolone derivative**3aa** in 93% yield (Scheme 1). Along with product **3aa**, H_2 gas was formed as a side product in the reaction. It was confirmed by GC analysis with a TCD detector (see section 4B.5.6 for more details). It is important to note that the cyclization reaction proceeds very smoothly without any metal oxidant. Initially, the cyclization reaction was examined with various solvents such as toluene, *tert*-amyl alcohol, NMP, *iso*-PrOH, CF_3CH_2OH, CH_3CN, DMF, chlorobenzene, 1,2-dichloroethane, DMSO and THF. Among them, chlorobenzene was very effective, giving product **3aa** in 93% yield. 1,4-Dioxane, toluene, *iso*-PrOH, CF_3CH_2OH, and THF were partially effective, providing **3aa** in 56-29% yields. Other solvents were totally ineffective. The same reaction was tried without pivalic acid under air in the presence of $Co(OAc)_2{\cdot}4H_2O$. However, product **3aa** was

observed only in 27% yield. This result clearly reveals that the pivalic acid is crucial for the success of the reaction. This observation prompted us to examine various carboxylic acid sources such as Adm-1-COOH, *p*-toluic acid, trifluoroacetic acid, *p*-toluene sulfonic acid and mesitylenic acid. Among them, Adm-1-COOH and *p*-toluic acid were partially effective, giving **3aa** in 72% and 67% yields, respectively. Mesitylenic acid was less effective, giving product **3aa** in 43% yield. The cyclization reaction was tried in the presence of NaOPiv (1.3 equiv) instead of PivOH under similar reaction conditions. In the reaction, product **3aa** was not observed. The cyclization reaction was tried under inert atmosphere with degassed chlorobenzene. In the reaction, only trace amount of product **3aa** was observed. This result clearly reveals that the air atmosphere along with pivalic acid is crucial for the reaction (see section 4B.5.4 for detailed optimization studies).

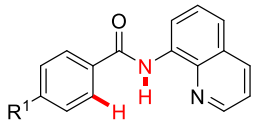
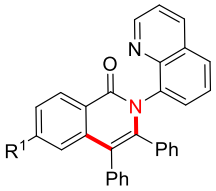
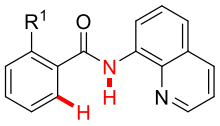
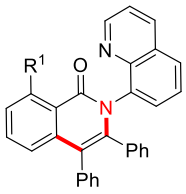
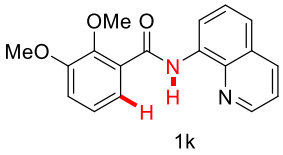
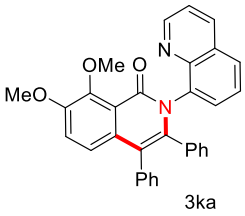
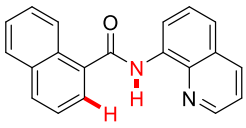
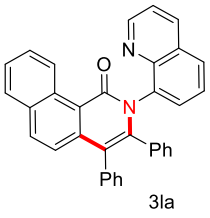
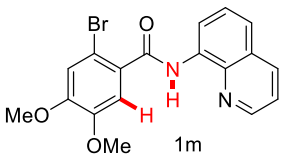
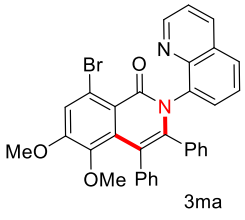


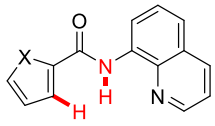
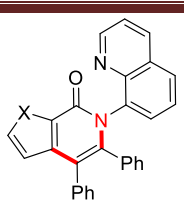
Scheme 4B.1 Oxidative cyclization of benzamide **1a** with **2a**

4B.2.2 Scope of Substituted Benzamides

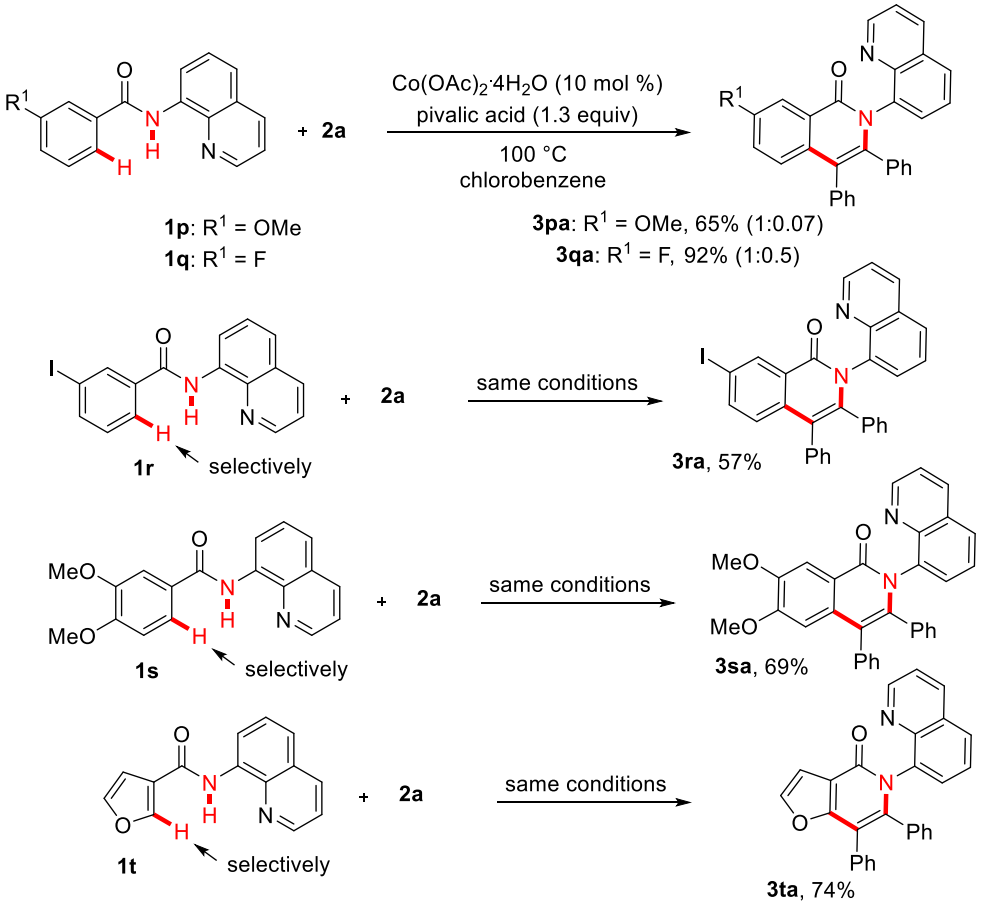
The scope of cyclization reaction was examined with various substituted benzamides under the optimized reaction conditions (Table 1). Benzamide **1b** and 4-methoxybenzamide **1c** reacted with **2a** providing the expected isoquinolone derivatives **3ba** and **3ca** in 94% and 58% yields, respectively (entries 1 and 2). Benzamides having halogen groups such as I, Br, Cl and F at the *para* position **1d-g** reacted with **2a** providing cyclized products **3da-ga** in 46%, 82%, 87% and 54% yields, respectively (entries 3-6). An electron-withdrawing CF_3-substituted benzamide **1h** was also effective for the reaction, affording **3ha** in 66% yield (entry 7). *ortho* Methyl-**1i** and phenyl-**1j** substituted benzamides reacted with **2a** giving products **3ia** and **3ja** in 92% and 95% yields, respectively (entries 8 and 9). 2,3-Dimethoxy benzamide **1k** and 1-naphthylamide **1l** yielded cyclized products **3ka** and **3la** in 84% and 60% yields, respectively (entries 10 and 11).

Table 4B.1 Scope of substituted benzamides[a]

Entry	Benzamide**1**	Product **3**	Yield (%)[b]
			
1	**1b**: R^1 = H	**3ba**: R^1 = H	94
2	**1c**: R^1 = OMe	**3ca**: R^1 = OMe	58
3	**1d**: R^1 = I	**3da**: R^1 = I	46
4	**1e**: R^1 = Br	**3ea**: R^1 = Br	82
5	**1f**: R^1 = Cl	**3fa**: R^1 = Cl	87
6	**1g**: R^1 = F	**3ga**: R^1 = F	54
7	**1h**: R^1 = CF_3	**3ha**: R^1 = CF_3	66
			
8	**1i**: R^1 = Me	**3ia**: R^1 = Me	92
9	**1j**: R^1 = Ph	**3ja**: R^1 = Ph	95
10	 1k	 3ka	84
11	 1l	 3la	60
12	 1m	 3ma	51

			
13	**1n**: X=S	**3na**: X=S	89
14	**1o** : X=O	**3oa**: X=O	79

[a]All reactions were carried out using **1b-n** (50 mg), **2a** (1.3 equiv), $Co(OAc)_2.4H_2O$ (10 mol %) and pivalic acid (1.3 equiv) in chlorobenzene (3.0 mL) under air at 100 °C for 4-36 h.bIsolated yield.

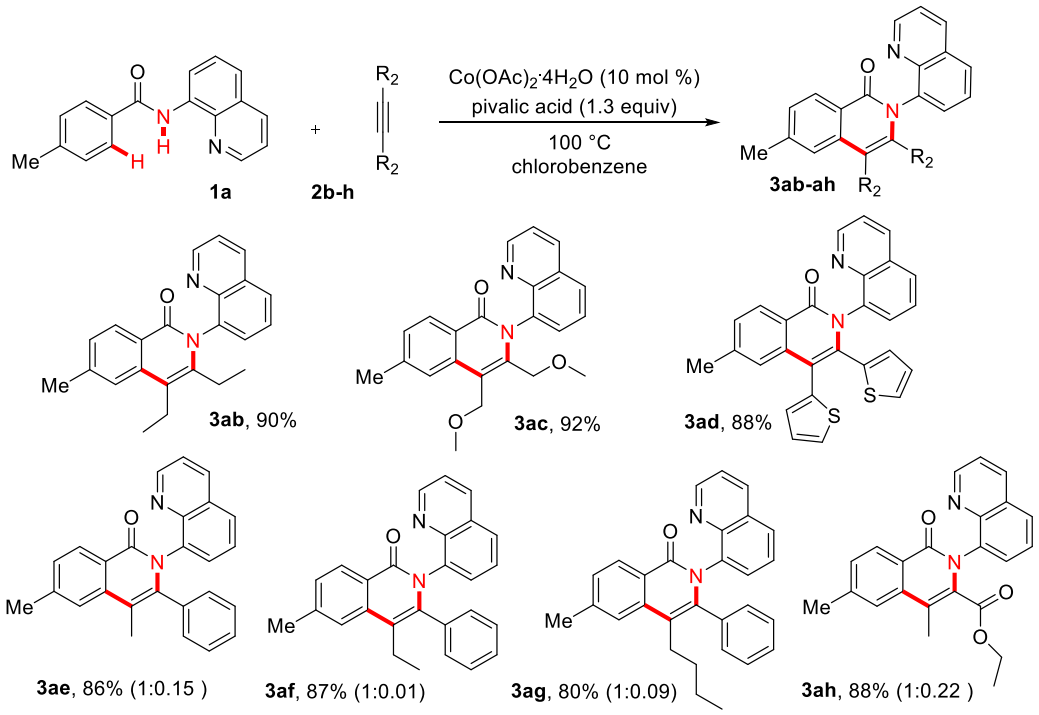


Scheme 4B.2 Scope of unsymmetrical benzamides

A sterically hindered 2-bromo-4,5-dimethoxy benzamide **1m** reacted with **2a** giving cyclized product **3ma** in 51% yield (entry 12). The present reaction was compatible with heterocyclic 2-thiophene and 2-furan amides **1n** and **1o**. In these reactions, products **3na** and **3oa** were observed in 89% and 79% yields respectively (entry 13 and 14). To examine the regioselective outcome of benzamides, unsymmetrical benzamides **1p-t** were subjected for the cyclization reaction with **2a** (Scheme 2). The reaction of *meta* methoxy

1p and *meta* fluoro **1q** substituted benzamides with **2a** produced regioisomeric cyclized products **3pa** and **3pa'** in combined 65% yields with 1:0.07 ratio and **3qa** and **3qa'** in combined 92% yields in 1:0.5 ratio, respectively. Interestingly, *meta* iodo benzamide **1r** reacted with **2a** at the C-6 position producing cyclized product **3ra** in 57% yield in a highly regioselective manner. Similarly, 3,4-dimethoxybenzamide **1s** reacted with **2a** at the C-6 position giving product **3sa** in 69% yield in a regioselective manner.Finally, 3-furan amide **1t**reacted with **2a** furnishing corresponding cyclized product **3ta** in 74% yield, in which, the C−H activation takes place at the C-2 position.

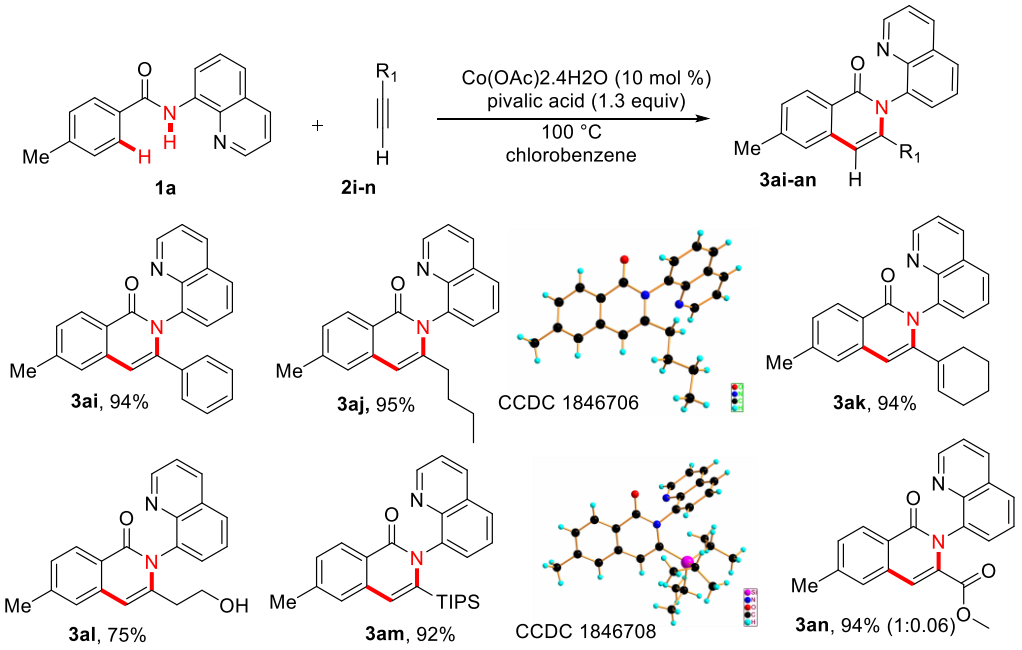
4B.2.3 Scope of Symmetrical and Unsymmetrical Alkynes



Scheme 4B.3 Scope of symmetrical and unsymmetrical alkynes

The scope of cyclization reaction was examined with symmetrical and unsymmetrical alkynes **2b-n**(Scheme 3). The reaction of less reactive symmetrical aliphatic alkynes such as 3-hexyne (**2b**) and 1,4-dimethoxybut-2-yne (**2c**) with **1a** yielding cyclized products **3ab** and **3ac**in 90% and 92% yields, respectively. Similarly, 1,2-di(thiophen-2-yl)ethyne (**2d**) reacted with **1a** providing cyclized product **3ad** in 88% yield. Unsymmetrical alkynes such as 1-phenyl-1-propyne (**2e**), 1-phenyl-1-butyne (**2f**) and 1-phenyl-1-hexyne (**2g**) reacted with **1a** giving regioisomeric mixtures of cyclized products **3ae** and **3ae**', **3af** and **3af**' and **3ag** and **3ag**' in 80-87% yields in 1:0.09 to 1:0.15 ratios, respectively. Ethyl

2-butynoate (**2h**) reacted with **1a** providing regioisomeric mixture of products **3ah** and **3ah**' in 88% yield in a 1:0.22 ratio.



Scheme 4B.4 Scope of terminal alkynes

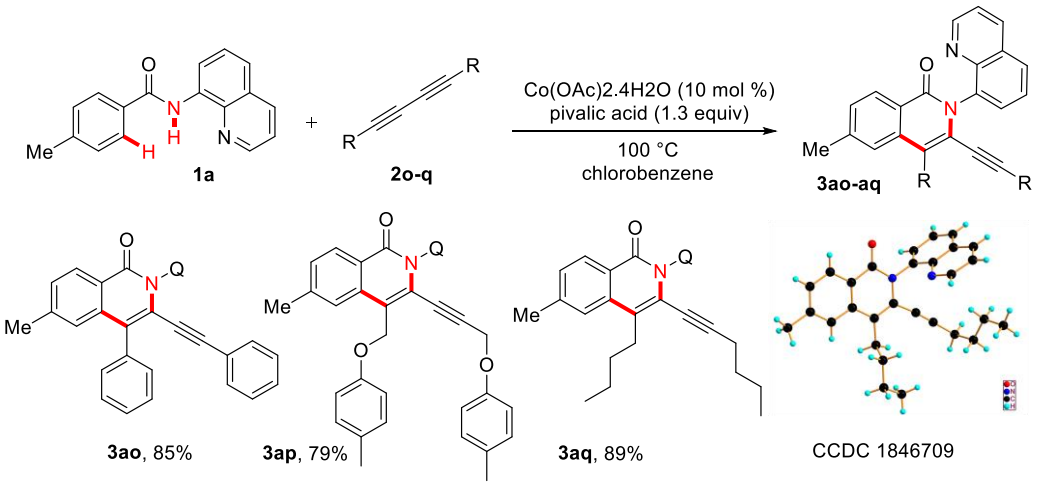
4B.2.4 Scope of Terminal Alkynes

It is important to note that the substituted terminal alkyne was also compatible for the reaction (Scheme 4). Phenylacetylene (**2i**), 1-hexyne (**2j**) and cyclohexylacetylene (**2k**) reacted with **1a** providing cyclized products **3ai**, **3aj** and **3ak** in 94%, 95% and 94% yields, respectively, in a highly selective manner. Functional group such as OH **2l** and silyl **2m** substituted alkynes were also effectively involved in the reaction, providing cyclized products **3al** and **3am** in 75% and 92% yields, respectively, in a highly selective manner. Methyl propiolate (**2n**) was also compatible for the reaction giving cyclized products **3an** and **3an**' in 94% yield in a 1:0.08 regioisomeric mixtures. It was expected that the reaction proceeds via a Co-alkynyl intermediate which leads to the regioselectivity observed in products **3ai-an** in the case of terminal alkynes.[5s]

4B.2.5 Scope of 1,3-Diynes

The present methodology was further extended with substituted 1,3-diynes (Scheme 5). Symmetrical 1,3-diynes having phenyl **2o**, ether **2p** and *n*-hexyl **2q** groups reacted with **1a** providing cyclized products having internal alkynes **3ao-aq** in 85%, 79% and 89%

yields, respectively.In case of 1,3-diynes there would be a coordination between neighbouring alkyne and cobalt intermediate formed during insertion which resulted in the observed regioselectivity of products **3ao-aq**.[5t]

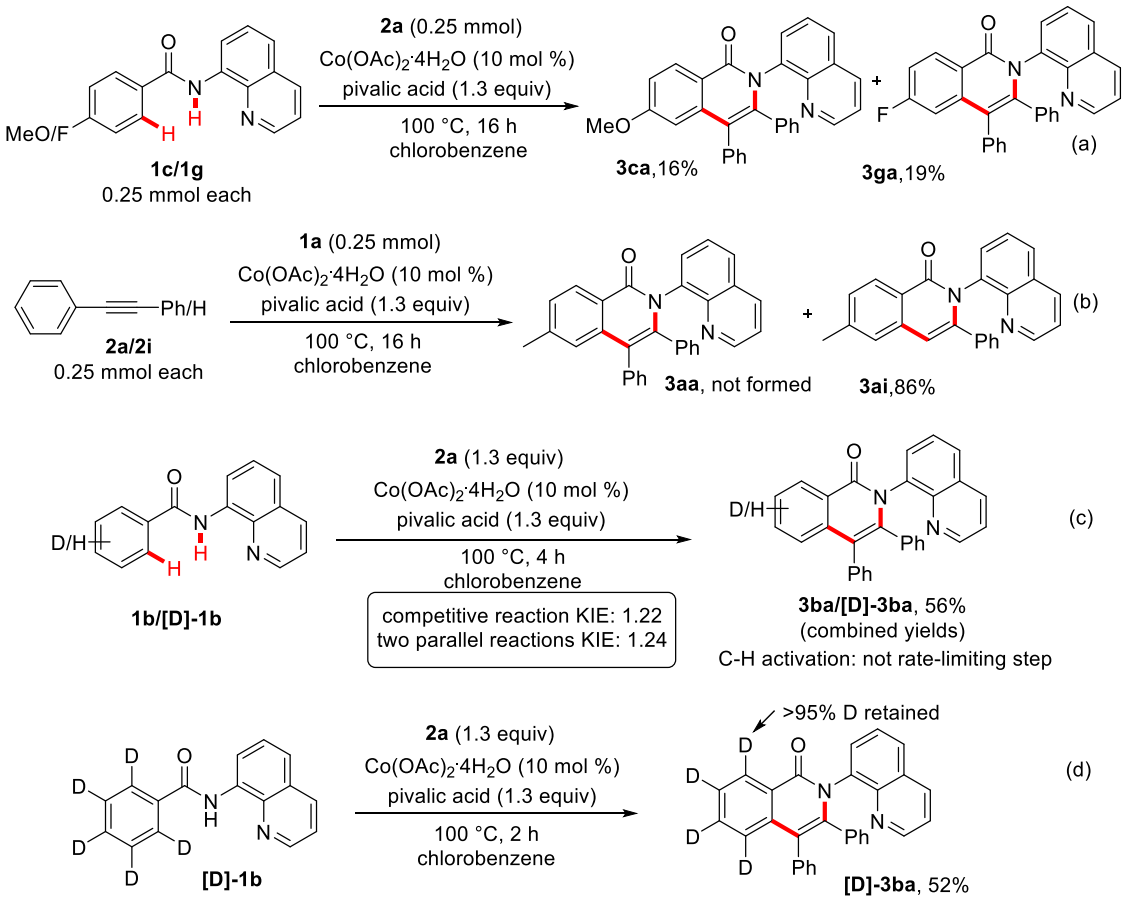


Scheme 4B.5 Scope of 1,3-diynes

4B.2.6 Mechanistic Studies

To understand the reaction mechanism, competition experiments and deuterium labelling studies were performed (Scheme 6). The reaction between a 1:1 mixture of 4-methoxybenzamide (**1c**) and 4-fluorobenzamide (**1g**) with **2a** under similar reaction conditions provided products **3ba** and **3ga** in 16% and 19% yields, respectively (Scheme 6a). This result clearly reveals that the electrophilic cobaltation as a key step is unlikely in the reaction. Meanwhile, the competition reaction of **2a** and **2i** with **1a** under similar reaction conditions givingonly cyclization product **3ia** in 86% yield (Scheme 6b). In the reaction, product **3aa** was not observed. In the competition experiment between **1b** and **[D]-1b**, the distribution value of 1.12 of the products **3ba** and **[D]-3ba** were observed by NMR analysis (Scheme 6c). A similar type of result was also observed when the reaction was carried out in the two parallel manners. Furthermore, amide **[D]-1b**with **2a**under the reaction conditions, yielding product [**D]-3ba** in 52% yield with the loss of 5% of *ortho* deuterium (95% of deuterium was retained, Scheme 6d). These results clearly indicating that the irreversible C−H bond cleavage could not be the rate-limiting step (see SI). The present cyclization reaction was completely inhibited in the presence of radical scavengers TEMPO and BHT under the reaction conditions. This observation shows that the radical intermediate may be involved in the reaction. Further, the kinetic experiments

were performed to determine the rate laws of the reaction. The order with respect to benzamide was found to be approximately -0.5 which shows that there may be some non-productive coordination of amide with cobalt involved which renders the formation of desired product and alkyne exhibited first order kinetics. It is important to mention that the order of benzamide can vary depending upon the reaction conditions and coupling partner. [5l,5p]

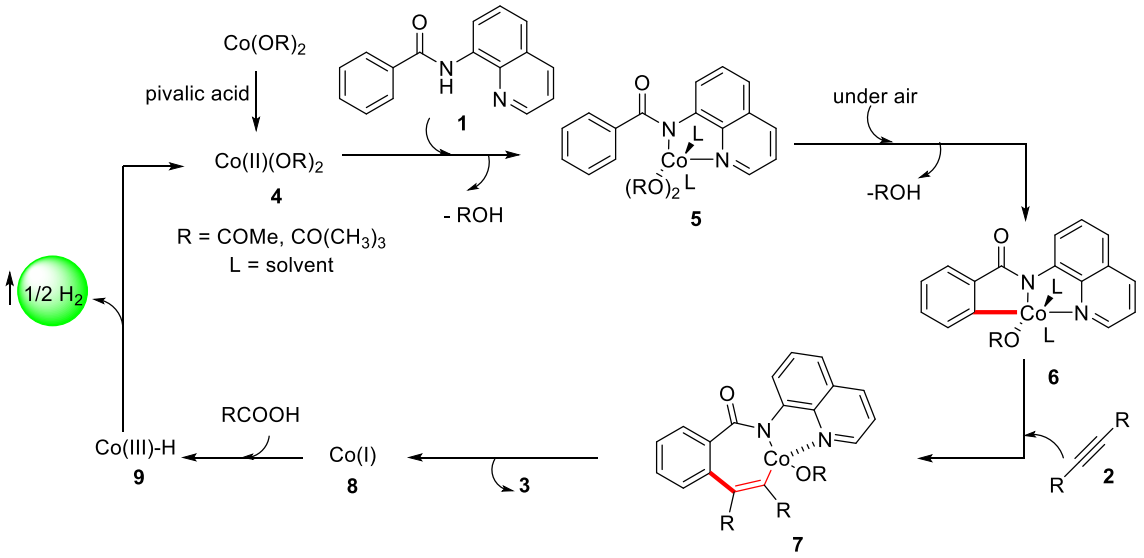


Scheme 4B.6 Preliminary Mechanistic Studies

4B.2.7 Proposed Mechanism

Based on the known cobalt-catalyzed C−H bond cleavage reactions and the observation of hydrogen gas, a possible reaction mechanism is proposed in Scheme 7. The catalytic cycle starts with the coordination of amide **1** with cobalt(II) catalyst followed by aerobic oxidation of cobalt(II) to Co(III) in the presence of pivalic acid under air which leads to the formation of intermediate **5**. Then an irreversible C−H bond cleavage provides intermediate **6**. Coordinative insertion of **2** into a C−Co bond of intermediate **6** affords intermediate **7**. Reductive elimination of intermediate **7** provides cyclized product **3** and

Co(I) species **8**. Later,the Co(I) species **8** converts into Co(III)−H intermediate **9** in the presence of PivOH.[10] Later, intermediate **9** converts into Co(II) spices **4** probably *via* a homolytic or heterolytic cleavage along with the liberation of hydrogen gas. Finally, the active catalyst **4** was generated by the aerobic oxidation of cobalt(II) to Co(III) in the presence of pivalic acid. In the reaction, carboxylic acid plays a dual role; it acts as a base to deprotonate the *ortho* aromatic C−H bond and oxidizing the reduced form of Co(I) to Co(III).



Scheme 4B.7 Proposed mechanism

4B.3 Conclusion

In conclusion, we have demonstrated a cobalt-catalyzed cyclization of benzamides with alkynes assisted by 8-aminoquinoline ligand providing isoquinolones in good yields. In the reaction, the active Co(III) species was regenerated by the reaction of Co(I) species with pivalic acid under air with the evolution of hydrogen gas. The mechanistic investigation clearly reveals that the irreversible C−H bond cleavage might not be the rate-limiting step and the radical intermediate may be involved in the reaction.

4B.4 References

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4B.5: Experimental section

4B.5.1: General information: All reactions were carried out under the air atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use (three times). Dry solvents were used for the reaction. Column chromatographical purifications were performed using SiO_2 (120-200 mesh ASTM) from Merck if not indicated otherwise. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Commercially available metal salts were purchased from Sigma-Aldrich and used without further purification.

4B.5.2: General Procedure for Synthesis of Isoquinolone derivatives (GP 1)

To a 15-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amides **1** (50 mg, 1 equiv), alkynes **2** (1.3 equiv), chlororobenzene 3 mL and pivalic acid (1.3 equiv) were added under open air conditions.*(Liquid alkynes were added via a micro pipette after the addition of pivalic acid)*. After that, a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 100 °C for indicated time. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite 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 products **3**.

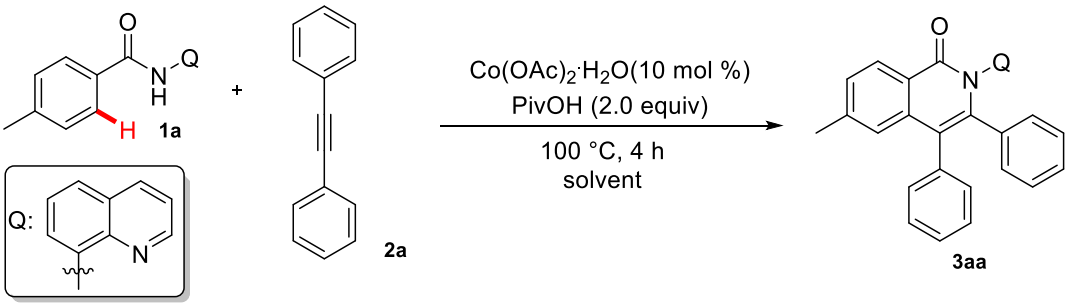
4B.5.3: General Procedure for Synthesis of Isoquinolone derivatives (GP 2)

To a 10-mL R. B flask fitted with reflux condenser containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amides **1** (50 mg, 1 equiv), alkynes **2** (1.3 equiv), chlororobenzene 3 mL and pivalic

acid (1.3 equiv) were added under open air conditions.*(Liquid alkynes were added via a micro pipette after the addition of pivalic acid)*. After that, the reaction mixture was stirred at room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 100 °C for indicated time. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite 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 products **3**.

4B.5.4: Optimization Studies

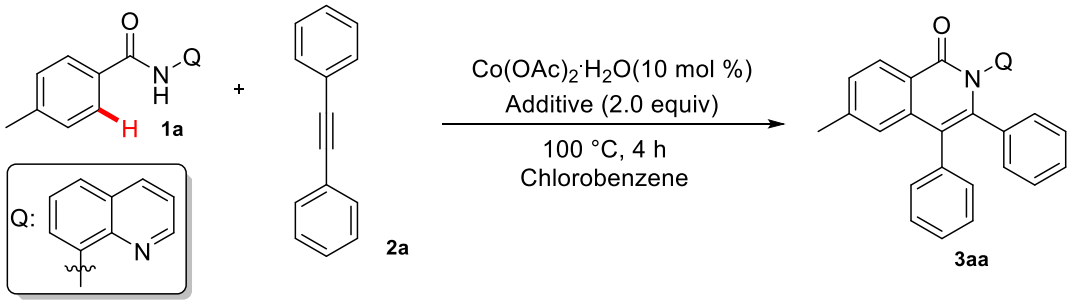
Table 4B.2. Solvent Optimization[a]



entry	solvent	yield **3aa** (%)[b]
1	1,4-dioxane	31
2	Toluene	39
3	*tert*-amyl alcohol	NR
4	NMP	NR
5	*iso*-PrOH	56
6	CF_3CH_2OH	31
7	CH_3CN	29
8	DMF	NR
9	**Chlorobenzene**	**94**
10	$ClCH_2CH_2Cl$	NR
11	DMSO	NR
12	THF	39

[a]All reactions were carried out under the following conditions: **1a** (50 mg), **2a** (1.3 equiv), $Co(OAc)_2.4H_2O$ (10 mol %) and PivOH (2.0 eq) in solvent (3.0 mL) at 100 ^oC for 4 h under air atmosphere. [b] Isolated yield.

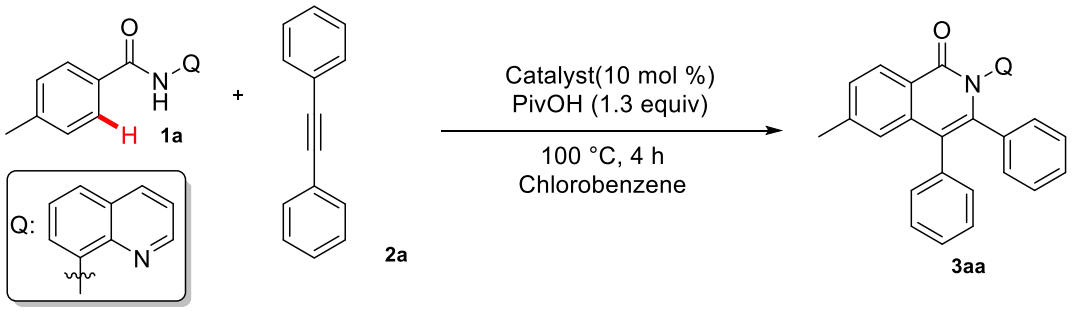
Table 4B.3. AdditiveOptimization[a]



entry	additive	yield **3aa** (%)[b]
1	AcOH	NR
2	Adm-1-COOH	72
3	*p*-Toluic acid	67
4	PivOH	94
5	Trifluoro aceticacid	NR
6	*p*-TsOH	NR
7	Mesitylenic acid	43
8	NaOAc	NR
9	NaOPiv	NR
10	K_2CO_3	NR
11	Sodium benzoate	NR
12	PivOH (3eq)	95
13	PivOH (30 mol%)	41
14	**PivOH (1.3eq)**	**93**
15	PivOH (1.3eq)	NR[c]
16	PivOH (30 mol%)	NR[d]
17	PivOH (0 %)	27

[a]All reactions were carried out under the following conditions: **1a** (50 mg), **2a** (1.3 equiv), $Co(OAc)_2$ (10 mol %) and additive (specified) in solvent (3 mL) at 100 °C for 4 h under air atmosphere. [b]Isolated yield. [c] Solvent was degassed by Freeze-Pump-Thaw technique and reaction was carried under argon atmosphere. [d] Without $Co(OAc)_2.4H_2O$.

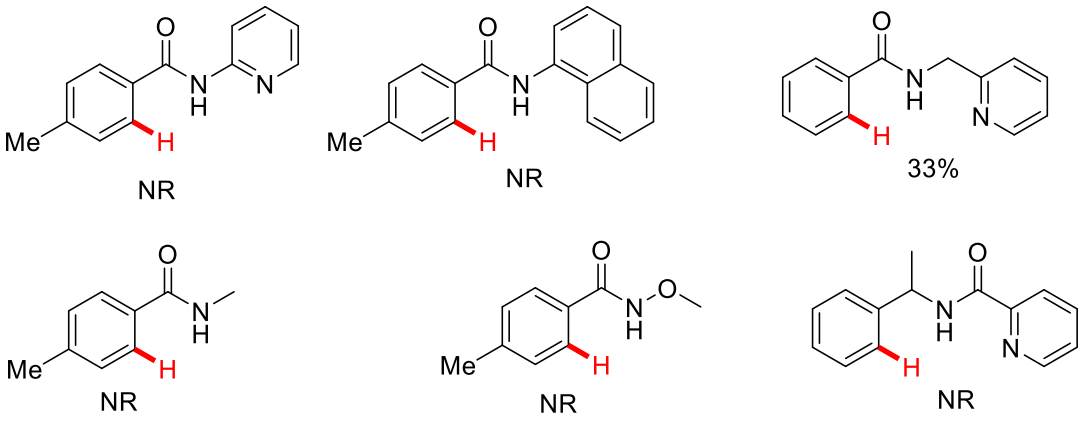
Table 4B.4. Catalyst Optimization[a]



entry	cobalt source	yield **3aa** (%)[b]
1	$Co(acac)_2$	21
2	$CoBr_2$	NR
3	$Co(acac)_3$	14
4	**$Co(OAc)_2{\cdot}4H_2O$**	**93**
5	$Cu(OAc)_2{\cdot}\ H_2O$	NR
6	$Pd(OAc)_2$	NR
7	{$RuCl_2$(*p*-cymene)}	NR

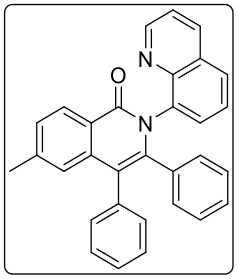
[a]All reactions were carried out under the following conditions: **1a** (50 mg), **2a** (1.3 equiv), catalyst (10 mol %) and PivOH (1.3 eq) in solvent (3.0 mL) at 100 °C for 4 h air atmosphere. [b] Isolated yield.

Other Directing groups tried:



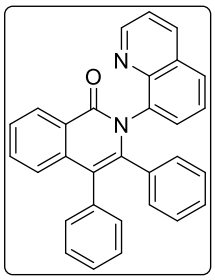
4B.6: Spectral Data of Compounds

6-methyl-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3aa)



Prepared according to **GP 1,** Time - 4h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 93% (78 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.92 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.48 (d, *J* = 8.2 Hz, 1H), 8.02 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.63 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.49 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.40 – 7.30 (m, 3H), 7.24 (dd, *J* = 5.2, 2.6 Hz, 2H), 7.15 (tdd, *J* = 7.0, 4.6, 2.4 Hz, 3H), 7.08 (s, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.81 (td, *J* = 7.6, 0.8 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.70 (tt, *J* = 7.4, 1.2 Hz, 1H), 6.47 (td, *J* = 7.6, 0.8 Hz, 1H), 2.38 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.7, 150.8, 144.8, 143.1, 141.9, 138.3, 137.8, 136.7, 136.0, 135.1, 131.9, 131.7, 130.9, 130.8, 129.8, 128.8, 128.5, 128.5, 128.3, 128.0, 127.9, 127.2, 126.7, 126.6, 126.4, 125.7, 125.4, 123.5, 121.5, 118.4, 22.1. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3802, 3736, 2923, 2310, 1737, 1654, 1606, 1490, 1377 and 1324. **HRMS (ESI):** calc. for [($C_{31}H_{22}N_2O$)H] (M+H) 439.1810, measured 439.1826.

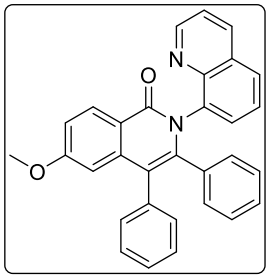
3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ba)



Prepared according to **GP 1,** Time - 4h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 94% (80 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.97 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.64 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.08 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.68 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.59 – 7.52 (m, 2H), 7.44 – 7.37 (m, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.24 – 7.15 (m, 3H), 7.02 (d, *J* =

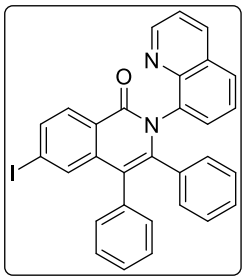
7.8 Hz, 1H), 6.87 (td, *J* = 7.6, 0.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.75 (tt, *J* = 7.6, 1.2 Hz, 1H), 6.53 (td, *J* = 7.6, 0.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.8, 150.9, 144.7, 141.9, 138.2, 137.7, 136.6, 136.0, 134.9, 132.5, 131.9, 131.7, 130.9, 130.8, 129.8, 128.8, 128.6, 128.4, 128.1, 127.8, 127.2, 126.8, 126.7, 126.7, 126.4, 125.8, 125.7, 125.6, 121.5, 118.6. **IR (ATR)** ṽ (cm^{-1}): 3854, 3626, 2920, 1960, 1705, 1655, 1597, 1486, 1324 and 1258. **HRMS (ESI):** calc. for [($C_{30}H_{20}N_2O$)H] (M+H) 425.1654, measured 425.1654.

6-methoxy-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ca)



Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (60% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 58% (47 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.96 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.54 (d, *J* = 8.8 Hz, 1H), 8.07 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.67 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.52 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.28 – 7.24 (m, 2H), 7.19 – 7.15 (m, 3H), 7.13 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.03 – 6.97 (m, 1H), 6.85 (td, *J* = 7.6, 0.8 Hz, 1H), 6.80 – 6.76 (m, 1H), 6.74 – 6.73 (m, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 6.51 (td, *J* = 7.6, 0.8 Hz, 1H), 3.77 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 163.0, 162.4, 150.8, 144.8, 142.5, 140.3, 137.8, 136.6, 135.9, 135.0, 131.8, 131.6, 130.9, 130.7, 130.6, 129.8, 128.7, 128.5, 128.1, 127.8, 127.2, 126.8, 126.6, 126.4, 125.8, 121.4, 119.6, 118.3, 115.3, 107.6, 55.3. **IR (ATR)** ṽ (cm^{-1}): 3852, 3734, 2919, 2311, 1738, 1652, 1599, 1482, 1377 and 1226. **HRMS (ESI):** calc. for [($C_{31}H_{22}N_2O_2$)H] (M+H) 455.1759, measured 455.1763.

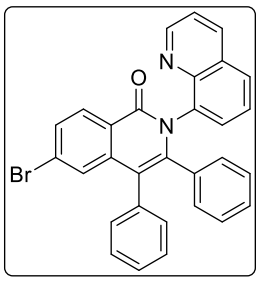
6-iodo-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3da)



Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 46% (34 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ

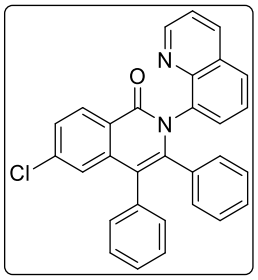
8.94 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.07 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.86 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.70 – 7.67(m, 2H), 7.51 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.28 – 7.11 (m, 5H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.77 – 6.72 (m, 2H), 6.51 (td, *J* = 7.6, 0.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.5, 150.8, 144.6, 143.2, 139.6, 137.4, 136.0, 135.8, 135.7, 134.6, 134.4, 131.8, 131.5, 130.8, 130.6, 130.0, 129.6, 128.7, 128.7, 128.2, 128.0, 127.4, 127.1, 126.7, 126.5, 125.7, 124.8, 121.6, 117.4, 100.9. **IR (ATR)** ṽ (cm^{-1}): 3870, 3740, 2918, 2854, 1732, 1649, 1581, 1537, 1455 and 1312. **HRMS (ESI):** calc. for [($C_{30}H_{19}IN_2O$)H] (M+H) 551.0620, measured 551.0618.

6-bromo-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ea)



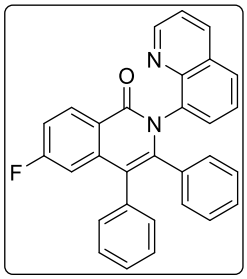
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (35% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 82% (63 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.96 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.45 (d, *J* = 8.6 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.69 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.65 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.51 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.47 (d, *J* = 1.6 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.28 – 7.11 (m, 5H), 7.02 – 6.96 (m, 1H), 6.86 (td, *J* = 7.8, 1.2 Hz, 1H), 6.75 (ddd, *J* = 8.0, 2.6, 1.4 Hz, 2H), 6.56 – 6.44 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.3, 150.8, 144.5, 143.3, 139.7, 137.4, 136.1, 135.8, 134.6, 131.8, 131.5, 130.8, 130.6, 130.3, 129.9, 129.6, 128.8, 128.7, 128.2, 128.1, 128.03, 127.9, 127.4, 127.1, 126.7, 126.5, 125.8, 124.3, 121.6, 117.6. **IR (ATR)** ṽ (cm^{-1}): 3864, 3737, 3026, 2312, 1745, 1651, 1604, 1495, 1341 and 1031. **HRMS (ESI):** calc. for [($C_{30}H_{19}BrN_2O$)H] (M+H) 503.0759, measured 503.0767.

6-chloro-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3fa)



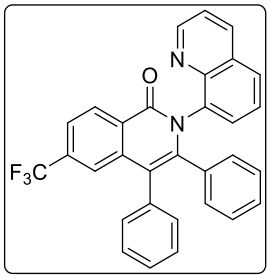
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 87% (71 mg).**^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.97 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.56 (d, *J* = 8.6 Hz, 1H), 8.08 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.69 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.53 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.33 (d, *J* = 1.8 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.21 – 7.19 (m, 3H), 7.04 – 6.97 (m, 1H), 6.88 (td, *J* = 7.8, 1.4 Hz, 1H), 6.82 – 6.72 (m, 2H), 6.53 (td, *J* = 7.6, 0.8 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$):** 162.3, 150.9, 144.7, 143.4, 139.6, 139.2, 137.5, 136.1, 135.9, 134.7, 131.8, 131.6, 130.8, 130.7, 130.4, 129.7, 128.8, 128.3, 128.1, 127.5, 127.3, 127.2, 126.8, 126.6, 125.8, 125.1, 124.0, 121.7, 117.8. **IR (ATR)** ṽ (cm^{-1}): 3860, 3739, 2921, 2313, 1735, 1655, 1593, 1472, 1321 and 1079. **HRMS (ESI):** calc. for [($C_{30}H_{19}ClN_2O$)H] (M+H) 459.1264, measured 459.1263.

6-fluoro-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ga)



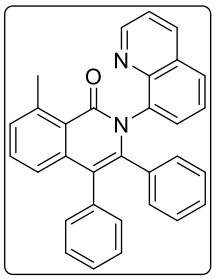
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (35% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 54% (45 mg).**^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.96 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.61 (dd, *J* = 8.8, 5.8 Hz, 1H), 8.08 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.69 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.52 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.28 – 7.22 (m, 3H), 7.21 – 7.15 (m, 3H), 7.00 – 6.94 (m, 2H), 6.86 (td, *J* = 8.0, 1.4 Hz, 1H), 6.77 – 6.73 (m, 2H), 6.52 (td, *J* = 7.6, 0.8 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$):** 166.9 and 164.4 (F-coupling), 162.1, 150.8, 144.6, 143.2, 140.7 and 140.6 (F-coupling), 137.4, 136.0, 134.6, 131.7, 131.6, 131.5, 130.8, 130.6, 129.6, 128.8, 128.7, 128.2, 127.9, 127.4, 127.0, 126.7, 126.5, 125.7, 122.2, 121.5, 118.1, 118.0, 115.3 and 115.1 (F-coupling), 110.9 and 110.7 (F-coupling). **IR (ATR)** ṽ (cm^{-1}): 3863, 3732, 2927, 1740, 1652, 1589, 1489, 1330, 1245 and 809. **HRMS (ESI):** calc. for [($C_{30}H_{19}FN_2O$)H] (M+H) 443.1560, measured 443.1559.

3,4-diphenyl-2-(quinolin-8-yl)-6-(trifluoromethyl)isoquinolin-1(2H)-one (3ha)



Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 66% (51 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.91 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.67 (d, *J* = 8.2 Hz, 1H), 8.05 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.72 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.66 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.58 (s, 1H), 7.48 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.24 – 7.08 (m, 5H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.78 – 6.65 (m, 2H), 6.54 – 6.39 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.03, 150.86, 144.44, 143.51, 138.29, 137.22, 136.10, 135.52, 134.42, 134.07 (q, *J-F* = 32.4 Hz), 131.71, 131.47, 130.73, 130.58, 129.6, 129.5, 128.8, 128.78, 128.32, 128.11, 127.51, 127.25, 126.77, 126.54, 125.77, 125.20, 122.93, 122.89 (m), 122.59 (m), 121.64, 118.31. **IR (ATR)** ṽ (cm^{-1}): 3868, 3733, 3606, 2928, 2312, 1739, 1657, 1502, 1317 and 1128. **HRMS (ESI):** calc. for [($C_{31}H_{19}F_3N_2O$)H] (M+H) 493.1528, measured 493.1541.

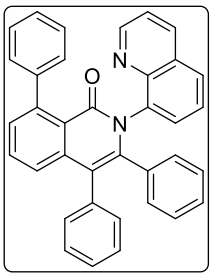
8-methyl-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ia)



Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 92% (77 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.94 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.02 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.63 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.53 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.46 – 7.30 (m, 3H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.23 – 7.09 (m, 6H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.85 – 6.78 (m, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.71 – 6.65 (m, 1H), 6.46 (t, *J* = 7.6 Hz, 1H), 2.96 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 163.5, 150.7, 144.8, 142.5, 141.9, 140.0, 138.2, 137.3, 136.0, 135.0, 131.9, 131.8, 131.6, 131.1, 130.7, 129.9, 129.7, 128.9, 128.4, 128.0, 127.8, 127.1, 126.7, 126.6, 126.3, 125.8, 124.1, 124.1, 121.5, 118.6, 24.4. **IR (ATR)** ṽ (cm^{-1}): 3865, 3733, 2921, 1653, 1598, 1477,

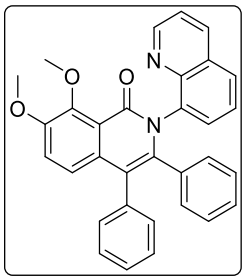
1297, 1175, 1026 and 760. **HRMS (ESI):** calc. for [($C_{31}H_{22}N_2O$)H] (M+H) 439.1810, measured 439.1821.

3,4,8-triphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ja)



Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 95% (73 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.95 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.99 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.58 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.53 – 7.42 (m, 3H), 7.39 – 7.16 (m, 12H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.81 – 6.68 (m, 2H), 6.50 (td, *J* = 7.6, 0.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 161.9, 150.5, 144.9, 144.8, 143.9, 142.6, 139.8, 137.9, 137.3, 135.9, 135.1, 132.1, 131.9, 131.4, 131.2, 130.8, 130.7, 129.8, 128.9, 128.4, 128.2, 127.9, 127.4, 127.2, 126.8, 126.6, 126.4, 125.7, 125.7, 122.9, 121.5, 118.2. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3742, 3603, 2313, 1881, 1732, 1659, 1548, 1486, 1149 and 1023. **HRMS (ESI):** calc. for [($C_{36}H_{24}N_2O$)H] (M+H) 501.1967, measured 501.1975.

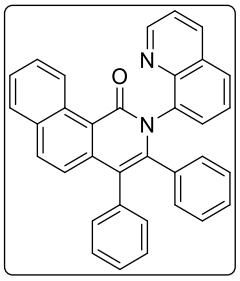
7,8-dimethoxy-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ka)



Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (65% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 84% (66 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.95 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.05 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.65 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.56 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.38 – 7.34 (m, 1H), 7.29 (d, *J* = 4.8 Hz, 1H), 7.27 – 7.13 (m, 5H), 7.05 (d, *J* =8.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.83 (td, *J* = 7.6, 0.8 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.71 (tt, *J* = 7.6, 1.2 Hz, 1H), 6.49 (td, *J* = 7.6, 0.9 Hz, 1H), 4.02 (s, 3H), 3.95 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 160.7, 151.8, 150.6, 150.1, 144.8, 140.2, 138.0, 137.1, 135.9, 135.0, 133.9, 131.9, 131.8, 131.3, 130.8, 129.9, 128.8, 128.4, 127.9, 127.8, 127.0, 126.7, 126.5, 126.3, 125.8, 122.0, 121.4,

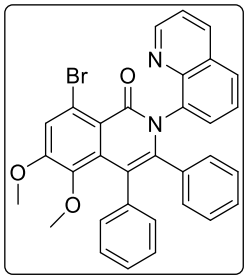
120.5, 118.4, 117.7, 61.7, 56.8. **IR (ATR)** ṽ (cm^{-1}): 3862, 3738, 2310, 1736, 1651, 1487, 1379, 1278, and 1081. **HRMS (ESI):** calc. for [($C_{32}H_{24}N_2O_3$)H] (M+H) 485.1865, measured 485.1852.

3,4-diphenyl-2-(quinolin-8-yl)benzo[h]isoquinolin-1(2H)-one (3la)



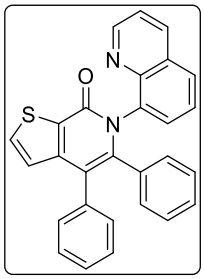
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (45% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 60% (48 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.24 (d, *J* = 8.8 Hz, 1H), 8.91 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.06 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.88 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.72 – 7.63 (m, 2H), 7.60 – 7.56 (m, 2H), 7.43 – 7.35 (m, 3H), 7.27 – 7.24 (m, 2H), 7.23 – 7.21 (m, 1H), 7.20 – 7.16 (m, 2H), 7.02 – 6.93 (m, 1H), 6.88 – 6.81 (m, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.72 (tt, *J* = 7.6, 1.2 Hz, 1H), 6.50 (td, *J* = 7.6, 0.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 163.1, 150.8, 144.7, 143.5, 139.6, 138.3, 137.1, 136.0, 134.9, 133.8, 132.3, 132.2, 132.1, 131.9, 130.8, 130.6, 129.6, 128.8, 128.6, 128.3, 128.1, 128.1, 128.0, 127.9, 127.3, 126.8, 126.6, 126.4, 126.3, 125.8, 123.8, 121.6, 119.0. **IR (ATR)** ṽ (cm^{-1}): 3876, 3738, 3625, 2922, 2589, 2316, 1731, 1649, 1582, 1487 and 1313. **HRMS (ESI):** calc. for [($C_{34}H_{22}N_2O$)H] (M+H) 475.1810, measured 475.1811.

8-bromo-5,6-dimethoxy-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ma)



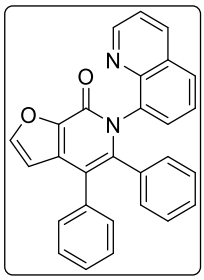
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (65% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 51% (37 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.96 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.03 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.63 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.38 – 7.34(m, 2H), 7.16 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.11 – 6.96 (m, 3H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.78 (t, *J* = 7.6 Hz, 1H), 6.68 – 6.64 (m, 2H), 6.42 (td, *J* = 7.6, 0.8 Hz, 1H), 3.96 (s, 3H), 3.10 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 160.6, 155.5, 150.6, 144.6, 143.9, 143.8, 139.8, 137.7, 135.9, 134.8, 134.7, 131.1, 130.9, 130.9, 130.8, 129.7, 128.8, 128.4, 126.9, 126.6, 126.6, 126.3, 126.0, 125.7, 125.4, 121.4, 119.4, 119.3, 117.7, 114.9, 60.4, 56.2. **IR (ATR)** ṽ (cm^{-1}): 3861, 3735, 3611, 2917, 2312, 1737, 1656, 1567, 1451 and 1355. **HRMS (ESI):** calc. for [($C_{32}H_{23}BrN_2O_3$)H] (M+H) 563.0970, measured 563.0966.

6,7-diphenyl-5-(quinolin-8-yl)thieno[3,2-c]pyridin-4(5H)-one (3na)



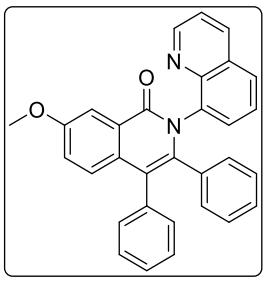
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 89% (75 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.92 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.03 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.67 – 7.64 (m, 2H), 7.49 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.22 – 7.14 (m, 5H), 7.03 (d, *J* = 5.0 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.84 (t, *J* = 7.6, 1H), 6.75 (ddt, *J* = 8.6, 7.6, 1.2 Hz, 2H), 6.51 (td, *J* = 7.6, 0.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 158.7, 150.9, 146.8, 144.8, 143.2, 137.3, 137.1, 136.1, 134.6, 133.4, 131.1, 131.0, 130.1, 130.08 (br s), 129.4, 128.9, 128.8, 127.9, 127.5, 126.9, 126.6, 125.8, 125.2, 121.6, 117.5. **IR (ATR)** ṽ (cm^{-1}): 3871, 3738, 2920, 1733, 1639, 1555, 1490, 1267, 865 and 699. **HRMS (ESI):** calc. for [($C_{28}H_{18}N_2OS$)H] (M+H) 431.1218, measured 431.1220.

4,5-diphenyl-6-(quinolin-8-yl)furo[2,3-c]pyridin-7(6H)-one (3oa)



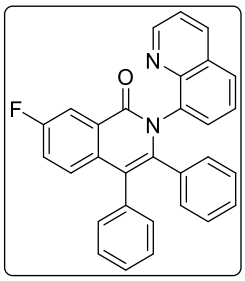
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 79% (69 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.94 (d, *J* = 3.2 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 1.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.45 – 7.33 (m, 2H), 7.19 – 7.13 (m, 5H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 1.0 Hz, 1H), 6.55 (t, *J* = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 153.6, 150.9, 148.4, 144.6, 142.5, 142.3, 136.9, 136.2, 134.7, 134.4, 131.2, 131.1, 130.4, 130.2, 128.9, 128.8, 127.9, 127.5, 126.9, 126.7, 126.6, 125.8, 121.6, 114.8, 107.8. **HRMS (ESI):** calc. for [($C_{28}H_{18}N_2O_2$)H] (M+H) 415.1447, measured 415.1446.

7-methoxy-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3pa)



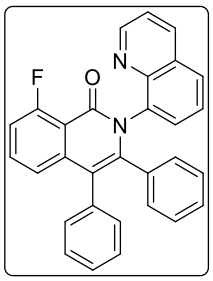
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (60% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 65% (53 mg, (Major isomer shown) 1:0.07 mixtrue of regioisomers inseparable by flash column chromatography).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.97 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.06 (d, *J* = 2.4 Hz, 1H), 7.69 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.51 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.33 – 7.24 (m, 4H), 7.22 – 7.14 (m, 3H), 7.05 – 6.97 (m, 1H), 6.86 (td, *J* = 7.6, 0.8 Hz, 1H), 6.81 – 6.72 (m, 2H), 6.52 (td, *J* = 7.6, 0.8 Hz, 1H), 3.96 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.5, 158.8, 150.9, 144.8, 139.6, 137.9, 136.8, 136.1, 135.0, 132.3, 131.9, 131.7, 131.1, 130.8, 130.0, 128.8, 128.6, 128.1, 127.8, 127.5, 127.2, 126.8, 126.7, 126.5, 125.8, 122.9, 121.5, 118.6, 108.3, 55.7. **IR (ATR)** ṽ (cm^{-1}): 3865, 3739, 2919, 1739, 1653, 1586, 1462, 1317, 1138 and 822. **HRMS (ESI):** calc. for [($C_{31}H_{22}N_2O_2$)H] (M+H) 455.1760, measured 455.1763.

7-fluoro-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3qa)



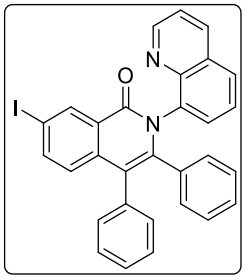
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 61% (52 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.97 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.27 – 8.24 (m 1H), 8.09 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.70 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.52 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.37 – 7.34 (m, 2H), 7.29 – 7.26 (m, 2H), 7.22 – 7.17 (m, 3H), 7.00 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.87 (td, *J* = 7.8, 1.4 Hz, 1H), 6.81 – 6.73 (m, 2H), 6.52 (td, *J* = 7.6, 0.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.8, 162.0 and 161.9 (F-coupling), 160.4, 150.9, 144.7, 141.2, 137.6, 136.4, 136.1, 134.8 and 134.7 (F-coupling), 131.8, 131.6, 130.9, 129.9, 128.8, 128.8, 128.3 and 128.2 (F-coupling), 128.2, 127.9, 127.4, 127.3 and 127.2 (F-coupling), 127.0, 126.8, 126.5, 125.8, 121.6, 121.2, 120.9, 118.2, 113.6 and 113.4 (F-coupling). **IR (ATR)** ṽ (cm^{-1}): 3860, 3736, 2920, 1734, 1649, 1592, 1487, 1326, 1247 and 811. **HRMS (ESI):** calc. for [($C_{30}H_{19}FN_2O$)H] (M+H) 443.1560, measured 443.1562.

8-fluoro-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3qa')



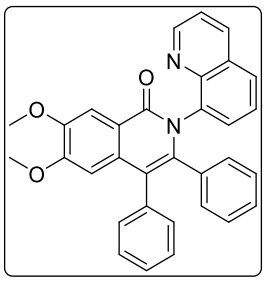
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (35% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 31% (26 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.97 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.47 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.08 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.69 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.44 – 7.37 (m, 2H), 7.36 – 7.30 (m, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.21 – 7.15 (m, 1H), 7.14 – 7.10 (m, 2H), 6.98 (dt, *J* = 7.8, 1.2 Hz, 1H), 6.85 (td, *J* = 7.8, 1.2 Hz, 1H), 6.77 – 6.67 (m, 2H), 6.49 (td, *J* = 7.8, 0.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 161.8 and 161.7 (F-coupling), 159.90, 157.37, 150.90, 144.54, 143.32, 138.50, 137.47, 136.10, 134.46, 131.02, 130.99, 130.93, 130.90, 130.84, 129.85, 128.79, 127.90, 127.41, 127.31, 127.16, 126.60, 126.42, 126.37, 125.80, 124.7 and 124.6 (F-coupling), 121.65, 119.67, 119.45, 114.4 and 114.3 (F-coupling). **IR (ATR)** ṽ (cm^{-1}): 3735, 3389, 2922, 2856, 1731, 1658, 1594, 1492, 1459 and 1256. **HRMS (ESI):** calc. for [($C_{30}H_{19}FN_2O$)H] (M+H) 443.1560, measured 443.1564.

7-iodo-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ra)



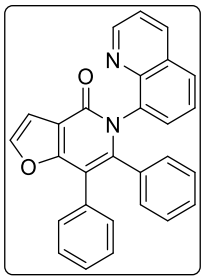
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 57% (42 mg).**^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.97 – 8.94 (m, 2H), 8.09 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.89 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.70 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.51 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.29 – 7.22 (m, 2H), 7.22 – 7.14 (m, 3H), 7.07 (d, *J* = 8.6 Hz, 1H), 7.02 – 6.95 (m, 1H), 6.87 (td, *J* = 7.6, 0.8 Hz, 1H), 6.80 – 6.71 (m, 2H), 6.52 (td, *J* = 7.6, 0.8 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$):** 161.41, 150.90, 144.62, 142.73, 141.16, 137.47, 137.41, 137.26, 136.12, 136.07, 134.68, 131.81, 131.60, 130.80, 130.68, 129.67, 128.82, 128.22, 128.00, 127.58, 127.45, 127.18, 127.05, 126.80, 126.56, 125.82, 121.65, 118.23, 91.70. **IR (ATR)** ṽ (cm^{-1}): 3863, 3738, 3616, 2309, 1743, 1652, 1488, 1323 and 775. **HRMS (ESI):** calc. for [($C_{30}H_{19}IN_2O$)H] (M+H) 551.0620, measured 551.0627.

6,7-dimethoxy-3,4-diphenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3sa)



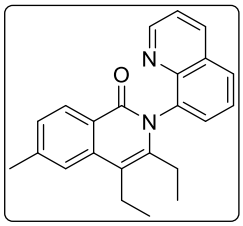
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (70% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 69% (54 mg). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.96 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.07 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.02 (s, 1H), 7.67 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.49 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.33 – 7.24 (m, 2H), 7.21 – 7.12 (m, 3H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.85 (td, *J* = 7.6, 0.8 Hz, 1H), 6.80 – 6.71 (m, 2H), 6.70 (s, 1H), 6.52 (dd, *J* = 7.6, 0.8 Hz, 1H), 4.03 (s, 3H), 3.76 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$):** 162.1, 153.5, 150.9, 149.2, 144.9, 140.7, 138.0, 136.9, 136.1, 135.2, 133.7, 131.9, 131.6, 130.9, 130.9, 129.9, 128.8, 128.6, 128.2, 127.9, 127.2, 126.9, 126.7, 126.5, 125.8, 121.5, 119.6, 118.3, 108.4, 106.2, 56.3, 55.9. **IR (ATR)** ṽ (cm^{-1}): 3860, 3736, 2919, 2584, 1732, 1650, 1587, 1492, 1386 and 1255. **HRMS (ESI):** calc. for [($C_{32}H_{24}N_2O_3$)H] (M+H) 485.1865, measured 485.1868.

6,7-diphenyl-5-(quinolin-8-yl)furo[3,2-c]pyridin-4(5H)-one (3ta)



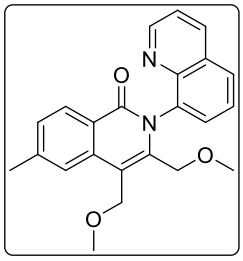
Prepared according to **GP 2,** Time - 36h; Half-white solid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 74% (64 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.96 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 6.4 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.32 – 7.17 (m, 5H), 7.15 (d, *J* = 1.8 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.87 – 6.74 (m, 2H), 6.57 (t, *J* = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 159.6, 159.2, 150.9, 144.7, 144.2, 143.6, 137.3, 136.2, 133.9, 132.8, 131.1, 130.9, 130.0, 128.8, 128.7, 127.9, 127.7, 127.2, 126.9, 126.7, 125.8, 121.6, 115.3, 111.1, 108.2. **HRMS (ESI):** calc. for [($C_{28}H_{18}N_2O_2$)H] (M+H) 415.1447, measured 415.1443.

3,4-diethyl-6-methyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ab)



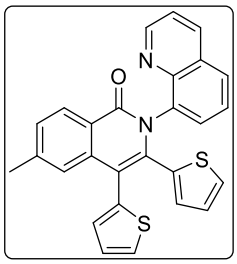
Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 90% (59 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.88 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.39 (d, *J* = 8.2 Hz, 1H), 8.24 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.97 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.80 – 7.66 (m, 2H), 7.58 (s, 1H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.33 – 7.22 (m, 1H), 2.65 – 2.58 (m, 1H), 2.57 (s, 3H), 2.88 (q, *J* = 7.6 Hz, 2H), 2.10 (dq, *J* = 14.8, 7.6 Hz, 1H), 1.36 (t, *J* = 7.6 Hz, 3H), 0.91 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 163.2, 151.4, 145.0, 142.8, 141.8, 137.6, 137.6, 136.3, 130.5, 129.4, 129.1, 128.8, 127.3, 126.2, 123.4, 122.7, 121.8, 114.5, 23.7, 22.4, 20.7, 15.0, 14.2. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3866, 3736, 3624, 2311, 1740, 1640, 1596, 1490, 1319 and 1102. **HRMS (ESI):** calc. for [($C_{23}H_{22}N_2O$)H] (M+H) 343.1810, measured 343.1801.

3,4-bis(methoxymethyl)-6-methyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ac)



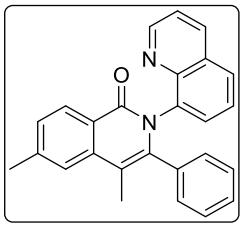
Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 92% (66 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.84 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.38 (d, *J* = 8.2 Hz, 1H), 8.25 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.98 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.81 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.78 – 7.65 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.37 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.87 – 4.67 (m, 2H), 4.41 (d, *J* = 11.8 Hz, 1H), 3.63 (d, *J* = 11.8 Hz, 1H), 3.54 (s, 3H), 2.91 (s, 3H), 2.58 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 163.1, 151.3, 144.8, 143.2, 139.2, 136.9, 136.4, 136.2, 130.9, 129.2, 128.9, 128.7, 128.5, 126.1, 124.2, 123.8, 121.7, 113.0, 67.5, 58.1, 57.9, 22.3. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3863, 3732, 3638, 2918, 2863, 1737, 1649, 1605, 1486, 1376 and 1074. **HRMS (ESI):** calc. for [($C_{23}H_{22}N_2O_3$)H] (M+H) 375.1709, measured 375.1715.

6-methyl-2-(quinolin-8-yl)-3,4-di(thiophen-2-yl)isoquinolin-1(2H)-one (3ad)



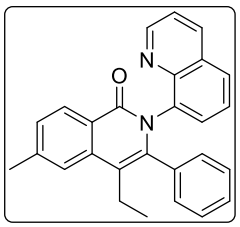
Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (35% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 88% (76 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.96 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.49 (d, *J* = 8.2 Hz, 1H), 8.13 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.76 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.60 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.35 (d, *J* = 0.8 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.03 – 6.96 (m, 2H), 6.87 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.51 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.38 (dd, *J* = 5.2, 3.6 Hz, 1H), 2.47 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.7, 151.0, 144.9, 143.5, 138.2, 137.6, 137.4, 137.1, 136.2, 135.1, 130.6, 130.5, 129.9, 129.1, 128.9, 128.5, 127.2, 126.6, 126.6, 125.9, 125.6, 125.3, 123.6, 121.7, 113.8, 22.3. **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3868, 3801, 3737, 3628, 3578, 1735, 1651, 1601, 1517 and 1316. **HRMS (ESI):** calc. for [($C_{27}H_{18}N_2OS_2$)H] (M+H) 451.0939, measured 451.0944.

4,6-dimethyl-3-phenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ae)



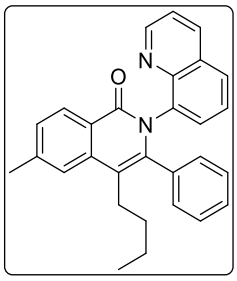
Prepared according to **GP 1,** Time - 16h; White solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 86% (62 mg, (Major isomer shown) 1:0.15 mixtrue of regioisomers inseparable by flash column chromatography).**^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.98 – 8.91 (m, 1H), 8.48 (d, *J* = 8.2 Hz, 1H), 8.07 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.67 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.62 (s, 1H), 7.49 – 7.34 (m, 5H)7.22 – 7.18 (m, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.94 – 6.84 (m, 1H), 6.76 (t, *J* = 7.6 Hz, 1H), 2.60 (s, 3H), 2.13 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$):** 162.7, 150.9, 144.8, 143.1, 140.9, 138.3, 138.0, 136.1, 135.7, 131.1, 130.4, 129.3, 128.8, 128.5, 128.2, 128.9, 127.8, 127.4, 127.2, 125.8, 123.7, 123.5, 121.5, 110.1, 22.4, 14.9. **IR (ATR)** ṽ (cm^{-1}): 3053, 2932, 1784, 1706, 1613, 1496, 1429, 1388, 1346 and 1263. **HRMS (ESI):** calc. for [($C_{26}H_{20}N_2O$)H] (M+H) 377.1654, measured 377.1649.

4-ethyl-6-methyl-3-phenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3af)



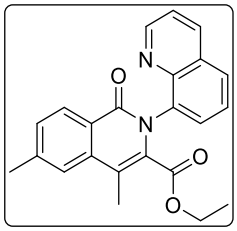
Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 87% (65 mg, (Major isomer shown) 1:0.01 mixtrue of regioisomers inseparable by flash column chromatography).**^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.87 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.46 (d, *J* = 8.2 Hz, 1H), 8.00 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.43 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.38 – 7.29 (m, 3H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.99 – 6.92 (m, 1H), 6.90 – 6.83 (m, 1H), 6.70 (td, *J* = 7.8, 1.2 Hz, 1H), 2.55 (d, *J* = 2.6 Hz, 3H), 2.54 – 2.42 (m, 2H), 1.13 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$):** 162.5, 150.7, 144.8, 142.9, 140.9, 137.9, 137.2, 135.9, 135.4, 130.9, 130.2, 129.1, 128.9, 128.7, 128.4, 127.9, 127.7, 127.3, 127.1, 125.7, 124.1, 123.3, 121.4, 116.1, 22.3, 21.6, 14.9. **IR (ATR)** ṽ (cm^{-1}): 3855, 3739, 3631, 2311, 1740, 1695, 1497, 1372, 1325 and 1267. **HRMS (ESI):** calc. for [($C_{27}H_{22}N_2O$)H] (M+H) 391.1810, measured 391.1813.

4-butyl-6-methyl-3-phenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ag)



Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 80% (64 mg, (Major isomer shown) 1:0.09 mixtrue of regioisomers inseparable by flash column chromatography). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.93 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.49 (d, *J* = 8.2 Hz, 1H), 8.05 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.47 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.40 – 7.34 (m, 3H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.13 (td, *J* = 7.4, 0.8 Hz, 1H), 6.98 (tt, *J* = 7.4, 1.2 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.74 (td, *J* = 7.6, 0.8 Hz, 1H), 2.60 (s, 3H), 2.53 – 2.41 (m, 2H), 1.59 – 1.57 (m, 2H), 1.29 – 1.24 (m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$):** 162.6, 150.7, 144.7, 142.8, 141.0, 137.9, 137.4, 136.0, 135.3, 131.1, 130.3, 129.2, 128.9, 128.7, 128.4, 127.9, 127.7, 127.2, 126.9, 125.7, 124.1, 123.4, 121.4, 115.1, 32.5, 28.1, 22.9, 22.4, 13.7. **IR (ATR)** ṽ (cm^{-1}): 3860, 3742, 3636, 2313, 1745, 1694, 1499, 1371, 1324 and 1267. **HRMS (ESI):** calc. for [($C_{29}H_{26}N_2O$)H] (M+H) 419.2123, measured 419.2126.

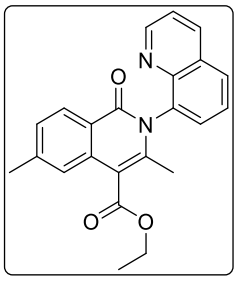
ethyl 4,6-dimethyl-1-oxo-2-(quinolin-8-yl)-1,2-dihydroisoquinoline-3-carboxylate (Major isomer) (3ah)



Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (35% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 72% (51 mg).**^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.95 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.43 (d, *J* = 8.2 Hz, 1H), 8.21 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.93 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.72 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.64 – 7.61 (m, 1H), 7.58 (s, 1H), 7.47 – 7.38 (m, 2H), 3.89 – 3.55 (m, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 0.48 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$):** 163.6, 161.7, 151.3, 144.9, 143.4, 137.2, 136.0, 133.9, 129.7, 129.4, 129.4, 128.9, 128.7, 125.9, 124.3, 123.9, 121.8, 110.9, 61.3, 22.2, 14.1, 12.9. **IR (ATR)** ṽ (cm^{-1}): 3863, 3742, 3623, 2927, 1732, 1660, 1504, 1380, 1213

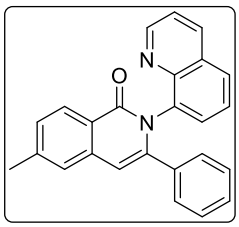
and 1102. **HRMS (ESI):** calc. for [($C_{23}H_{20}N_2O_3$)H] (M+H) 373.1552, measured 373.1551.

ethyl 3,6-dimethyl-1-oxo-2-(quinolin-8-yl)-1,2-dihydroisoquinoline-4-carboxylate-(Minor isomer) (3ah')



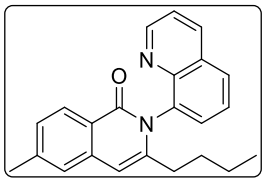
Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 16% (11 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.89 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.32 (d, *J* = 8.2 Hz, 1H), 8.26 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.00 (dd, *J* = 5.2, 4.4 Hz, 1H), 7.76 – 7.65 (m, 2H), 7.51 (s, 1H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.32 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.50 (qd, *J* = 7.2, 0.8 Hz, 2H), 2.53 (s, 3H), 2.01 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 168.2, 162.9, 151.5, 144.4, 143.6, 141.3, 136.7, 136.3, 134.6, 129.9, 129.4, 128.4, 128.2, 126.4, 123.5, 122.4, 121.9, 110.9, 61.4, 22.2, 19.1, 14.3. **IR (ATR)** ṽ (cm^{-1}): 3858, 3737, 3612, 2924, 1727, 1657, 1502, 1378, 1211 and 1098. **HRMS (ESI):** calc. for [($C_{23}H_{20}N_2O_3$)H] (M+H) 373.1552, measured 373.1548.

6-methyl-3-phenyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ai)



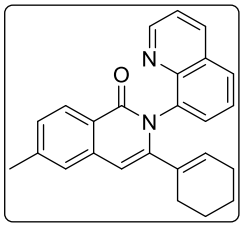
Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 94% (65 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.93 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.40 (d, *J* = 8.2 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.74 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.52 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.48 – 7.33 (m, 4H), 7.17 – 7.11 (m, 2H), 7.08 – 7.02 (m, 1H), 7.01 – 6.94 (m, 2H), 6.62 (s, 1H), 2.55 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 163.2, 150.9, 144.9, 144.7, 143.2, 137.5, 137.4, 136.5, 136.0, 130.8, 128.8, 128.8, 128.6, 128.4, 128.4, 127.9, 127.3, 125.9, 125.8, 123.3, 121.5, 107.3, 21.9. **IR (ATR)** ṽ (cm^{-1}): 3047, 2932, 1775, 1653, 1619, 1491, 1427, 1388, 1347 and 12661. **HRMS (ESI):** calc. for [($C_{25}H_{18}N_2O$)H] (M+H) 363.1497, measured 363.1499.

3-butyl-6-methyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3aj)



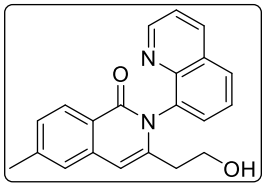
Prepared according to **GP 1,** Time - 4h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 95% (62 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.88 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 8.25 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.98 (dd, *J* = 7.4, 2.2 Hz, 1H), 7.75 – 7.68 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.36 (s, 1H), 7.27 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.49 (s, 1H), 2.52 (s, 3H), 2.25 – 2.07 (m, 2H), 1.53 – 1.35 (m, 2H), 1.13 (dd, *J* = 14.8, 7.4 Hz, 2H), 0.69 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 163.9, 151.4, 144.8, 144.4, 143.0, 137.8, 136.7, 136.4, 130.4, 129.4, 129.2, 128.2, 127.7, 126.3, 125.4, 122.7, 121.9, 104.2, 33.0, 30.2, 22.2, 21.9, 13.7. **IR (ATR)** ṽ (cm^{-1}): 3859, 3737, 3488, 2928, 2868, 1644, 1606, 1560, 1487 and 1373. **HRMS (ESI):** calc. for [($C_{23}H_{22}N_2O$)H] (M+H) 343.1810, measured 343.1809.

3-(cyclohex-1-en-1-yl)-6-methyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ak)



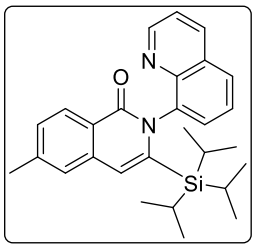
Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 94% (66 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.89 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.33 (d, *J* = 8.2 Hz, 1H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.90 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.36 (s, 1H), 7.29 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.45 (s, 1H), 5.81 – 5.62 (m, 1H), 2.52 (s, 3H), 1.92 – 1.76 (m, 2H), 1.71 – 1.59 (m, 1H), 1.58 – 1.42 (m, 1H), 1.30 – 1.15 (m, 2H), 1.16 – 0.92 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** 163.3, 150.9, 147.2, 145.0, 142.9, 137.9, 137.5, 136.0, 134.3, 130.5, 130.5, 128.9, 128.7, 128.3, 127.8, 125.8, 125.6, 123.1, 121.5, 105.0, 28.9, 25.1, 22.2, 21.9, 21.4. **IR (ATR)** ṽ (cm^{-1}): 3945 , 3893, 3737, 2918, 2311, 1739, 1648, 1606, 1553, 1368 and 790. **HRMS (ESI):** calc. for [($C_{25}H_{22}N_2O$)H] (M+H) 367.1810, measured 367.1806.

3-(2-hydroxyethyl)-6-methyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3al)



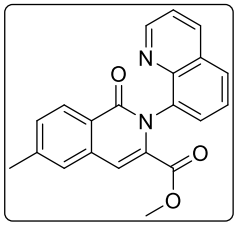
Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (65% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 75% (47 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.81 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.30 – 8.08 (m, 2H), 7.96 (p, *J* = 3.2 Hz, 1H), 7.72 – 7.58 (m, 2H), 7.42 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.34 (s, 1H), 7.32 – 7.19 (m, 1H), 6.50 (s, 1H), 3.68 – 3.25 (m, 2H), 2.59 (s, 1H), 2.51 (s, 3H), 2.44 (td, *J* = 6.2, 2.0 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** 163.8, 151.4, 144.8, 143.2, 140.4, 137.4, 136.6, 136.4, 130.4, 129.4, 129.3, 128.1, 127.9, 126.4, 125.4, 122.8, 121.9, 105.9, 60.1, 36.5, 21.9. **IR (ATR)** ṽ (cm^{-1}): 3862, 3737, 3619, 3374, 2920, 2800, 2310, 1738, 1647, 1596, 1499 and 1039. **HRMS (ESI):** calc. for [($C_{21}H_{18}N_2O_2$)H] (M+H) 331.1447, measured 331.1452.

6-methyl-2-(quinolin-8-yl)-3-(triisopropylsilyl)isoquinolin-1(2H)-one (3am)



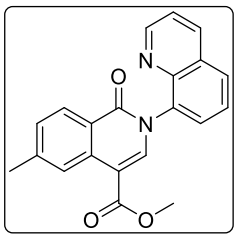
Prepared according to **GP 1,** Time - 16h; Half-white solid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 92% (78 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.84 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.21 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.96 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.79 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.65 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.43 (s, 1H), 7.40 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.36 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.90 (s, 1H), 2.55 (s, 3H), 1.00 (d, *J* = 7.4 Hz, 9H), 0.78 (d, *J* = 7.4 Hz, 9H), 0.69 – 0.57 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 164.3, 150.9, 145.6, 143.6, 142.8, 140.3, 136.7, 136.0, 130.1, 129.2, 128.9, 128.1, 125.9, 125.8, 124.2, 121.8, 117.6, 21.9, 19.4, 18.7, 12.5. **IR (ATR)** ṽ (cm^{-1}): 3883, 3735, 3622, 2929, 2862, 2310, 1739, 1646, 1549 and 1343. **HRMS (ESI):** calc. for [($C_{28}H_{34}N_2OSi$)H] (M+H) 443.2519, measured 443.2524.

Methyl 6-methyl-1-oxo-2-(quinolin-8-yl)-1,2-dihydroisoquinoline-3-carboxylate (3an)



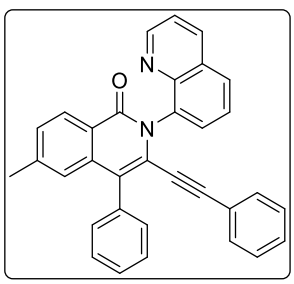
Prepared according to **GP 1,** Time - 4h; Half-white solid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 88% (58 mg)(Major isomer).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.81 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 8.19 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.90 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.74 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.65 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.47 (s, 1H), 7.45 – 7.40 (m, 2H), 7.37 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.45 (s, 3H), 2.52 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.7, 150.7, 144.6, 143.7, 137.3, 136.3, 135.3, 133.7, 130.7, 129.2, 128.9, 128.6, 128.5, 127.3, 126.0, 125.6, 121.4, 112.3, 52.4, 21.7. **IR (ATR)** ṽ (cm^{-1}): 3811, 3740, 2383, 1709, 1657, 1607, 1427, 1378, 1292 and 1218. **HRMS (ESI):** calc. for [($C_{21}H_{16}N_2O_3$)H] (M+H) 345.1239, measured 345.1251.

Methyl 6-methyl-1-oxo-2-(quinolin-8-yl)-1,2-dihydroisoquinoline-4-carboxylate (3an')



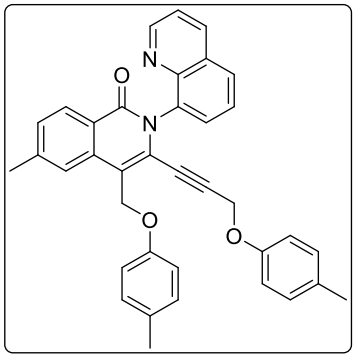
Half-white solid; 6% (4 mg) (minor isomer).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.93 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.75 (s, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 8.33 – 8.24 (m, 2H), 8.02 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.85 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.71 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.50 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.41 (dd, *J* = 8.2, 1.4 Hz, 1H), 3.87 (s, 3H), 2.59 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 165.9, 151.4, 144.2, 143.6, 141.7, 137.8, 136.3, 134.8, 129.5, 129.4, 128.9, 128.8, 128.5, 126.2, 125.3, 123.6, 122.0, 106.1, 51.6, 29.7, 22.4. **HRMS (ESI):** calc. for [($C_{21}H_{16}N_2O_3$)H] (M+H) 345.1239, measured 345.1246.

6-methyl-4-phenyl-3-(phenylethynyl)-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3ao)



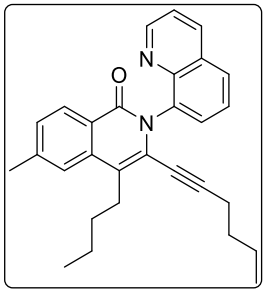
Prepared according to **GP 1,** Time - 36h; Half-white solid; eluent (35% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 85% (75 mg). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.99 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.52 (d, *J* = 8.2 Hz, 1H), 8.30 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.05 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.94 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.76 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.67 – 7.49 (m, 5H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.41 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.23 (s, 1H), 7.16 – 7.10 (m, 1H), 7.03 (t, *J* = 7.6 Hz, 2H), 6.39 – 6.27 (m, 2H), 2.46 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.3, 151.3, 144.9, 143.3, 138.0, 137.3, 136.5, 136.4, 131.7, 131.3, 131.1, 130.9, 130.6, 129.3, 129.17, 128.72, 128.58, 128.36, 128.23, 128.03, 127.88, 126.30, 125.66, 125.56, 124.65, 124.45, 121.82, 121.75, 99.09, 84.24, 22.13. **IR (ATR)** ṽ (cm^{-1}): 3864, 3702, 2311, 1736, 1645, 1594, 1476, 1347 and 985. **HRMS (ESI):** calc. for [($C_{33}H_{22}N_2O$)H] (M+H) 463.1810, measured 463.1819.

6-methyl-2-(quinolin-8-yl)-4-((p-tolyloxy)methyl)-3-(3-(p-tolyloxy)prop-1-yn-1-yl)isoquinolin-1(2H)-one (3ap)



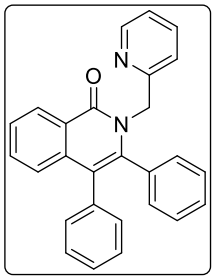
Prepared according to **GP 1,** Time - 36h; Half-white solid; eluent (40% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 79% (83 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.81 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.70 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.43 – 7.33 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.96 – 6.89 (m, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.42 – 6.25 (m, 2H), 5.33 (d, *J* = 10.8 Hz, 1H), 5.28 (d, *J* = 10.8 Hz, 1H), 4.30 (d, *J* = 16.6 Hz, 1H), 4.24 (d, *J* = 16.6 Hz, 1H), 2.48 (s, 3H), 2.32 (s, 3H), 2.25 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.3, 156.6, 154.9, 151.1, 144.6, 143.6, 137.4, 136.1, 136.1, 130.6, 130.5, 130.1, 129.9, 129.8, 129.6, 129.2, 129.0, 128.6, 127.0, 125.9, 124.6, 124.1, 121.6, 116.9, 115.0, 114.3, 95.2, 79.6, 66.0, 55.6, 22.2, 20.6, 20.5. **IR (ATR)** ṽ (cm^{-1}): 3859, 3737, 2918, 2311, 1734, 1639, 1585, 1472, 1342 and 977. **HRMS (ESI):** calc. for [($C_{37}H_{30}N_2O_3$)H] (M+H) 551.2335, measured 551.2330.

4-butyl-3-(hex-1-yn-1-yl)-6-methyl-2-(quinolin-8-yl)isoquinolin-1(2H)-one (3aq)



Prepared according to **GP 1,** Time - 36h; Half-white solid; eluent (35% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 89% (72 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.85 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.38 (d, *J* = 8.2 Hz, 1H), 8.19 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.90 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.72 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.63 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.51 (s, 1H), 7.38 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.30 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.25 (s, 1H), 3.04 – 2.88 (m, 2H), 2.53 (s, 3H), 1.89 (t, *J* = 6.8 Hz, 2H), 1.75 – 1.58 (m, 2H), 1.53 – 1.42 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.92 – 0.69 (m, 3H), 0.60 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.3, 151.1, 145.0, 142.9, 138.6, 136.9, 136.0, 130.2, 129.2, 128.9, 128.8, 128.4, 126.2, 125.2, 124.5, 123.4, 121.5, 121.4, 100.7, 75.0, 32.1, 29.9, 29.12, 22.9, 22.4, 21.4, 18.9, 14.1, 13.5. **IR (ATR)** ṽ (cm^{-1}): 3752, 2921, 2317, 1710, 1639, 1585, 1463 and 1341. **HRMS (ESI):** calc. for [($C_{29}H_{30}N_2O$)H] (M+H) 423.2436, measured 423.2438.

3,4-diphenyl-2-(pyridin-2-ylmethyl)isoquinolin-1(2H)-one (4aa)



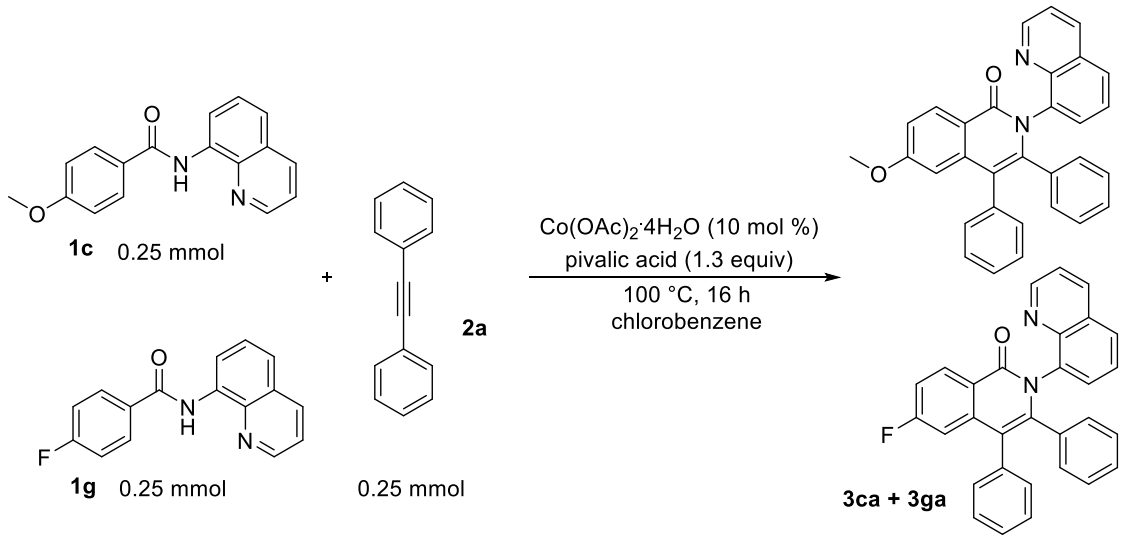
Prepared according to **GP 1,** Time - 36h; Half-white solid; eluent (30% ethyl acetate in hexanes); **1a** was taken in 50 mg; yield is 33% (30 mg).**^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.64 – 8.55 (m, 1H), 8.45 – 8.43 (m, 1H), 7.63 – 7.51 (m, 3H), 7.25 – 7.15 (m, 4H), 7.15 – 6.98 (m, 9H), 5.30 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** 162.6, 157.2, 149.1, 141.5, 137.5, 136.5, 136.3, 134.5, 132.4, 131.6, 130.2, 128.2, 127.9, 127.7, 126.8, 126.7, 125.5, 125.1, 121.7, 120.8, 119.3, 51.1. **IR (ATR)** ṽ (cm^{-1}): 1653, 1593, 1494, 1479, 1339, 928, 734, 704. **HRMS (ESI):** calc. for [($C_{27}H_{20}N_2O$)H] (M+H) 389.1654, measured 389.1660.

4B.7 Mechanistic Studies

Competition Experiments:

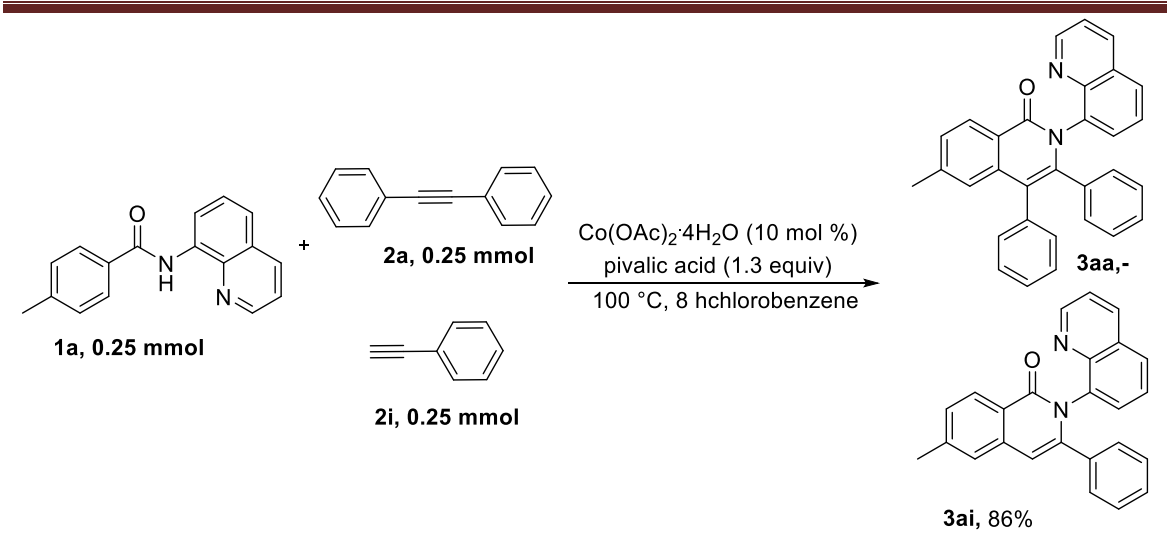
General Procedure for Competition reaction between amides (GP 3)

To a 15-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amides **1c** (0.25 mmol, 1 equiv), amide **1g** (0.25 mmol, 1 equiv) and alkyne **2a** (0.25 mmol, 1 eq), chlororobenzene 3 mL and pivalic acid (1.3 equiv) were added under open air conditions. After that, a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, 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 the filtrate was concentrated.The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure products **3ca** and **3ga** 16% and 19% respectively (ratio 0.84:1).



General Procedure for Competition reaction between alkynes (GP 4)

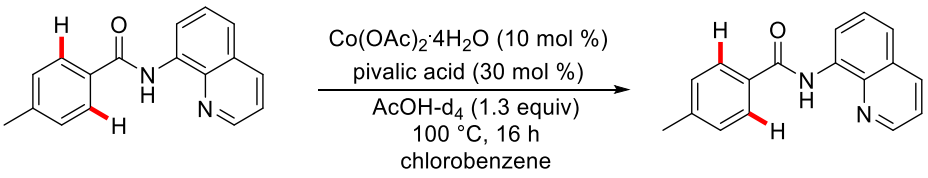
To a 15-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amide **1a** (0.25 mmol, 1 equiv), alkyne **2a** (0.25 mmol, 1 equiv) and alkyne **2i** (0.25 mmol, 1 eq), chlororobenzene 3 mL and pivalic acid (1.3 equiv) were added under open air conditions. After that, a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 100 °C for 8 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluents to give pure product **3ai** in 86% yield.

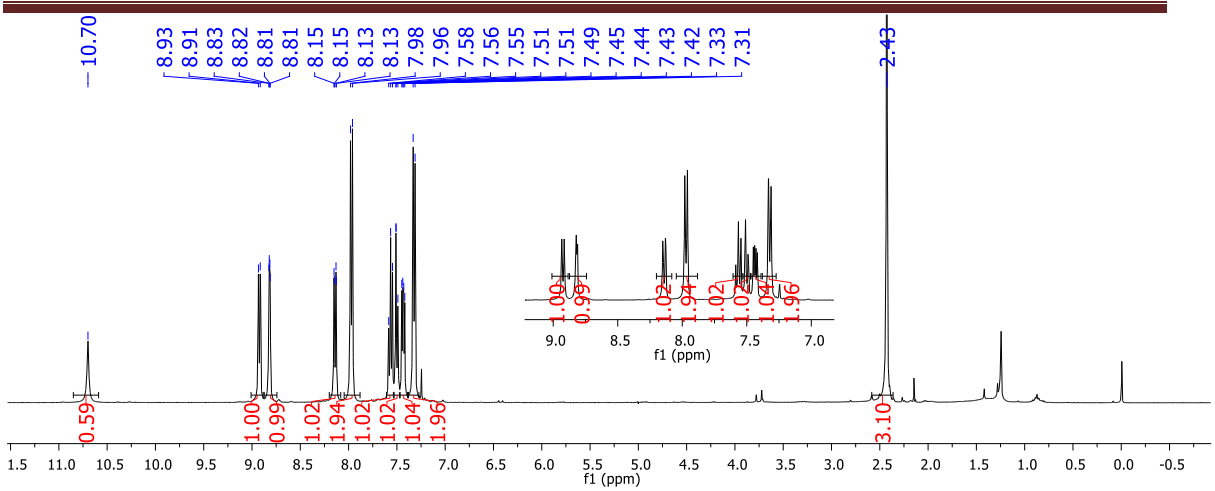


Procedure for the Studies with Isotopically Labelled Compounds

A) H/D Exchange studies with AcOH-d4as Additive (GP 5)

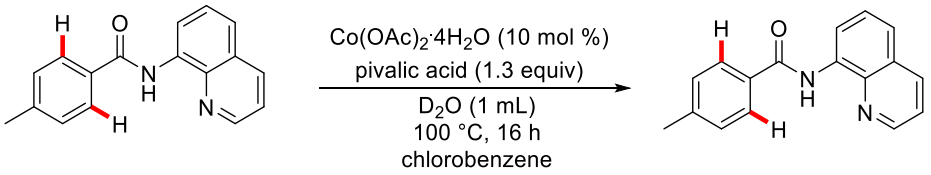
To a 15-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amide **1a** (50 mg, 1 equiv), chlororobenzene 3 mL, pivalic acid (30 mol%) and **AcOH-d4** (1.3 eq) were added under open air conditions. After that, a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, 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 the filtrate was concentrated. The crude residue was directly analysed by 1H NMR.

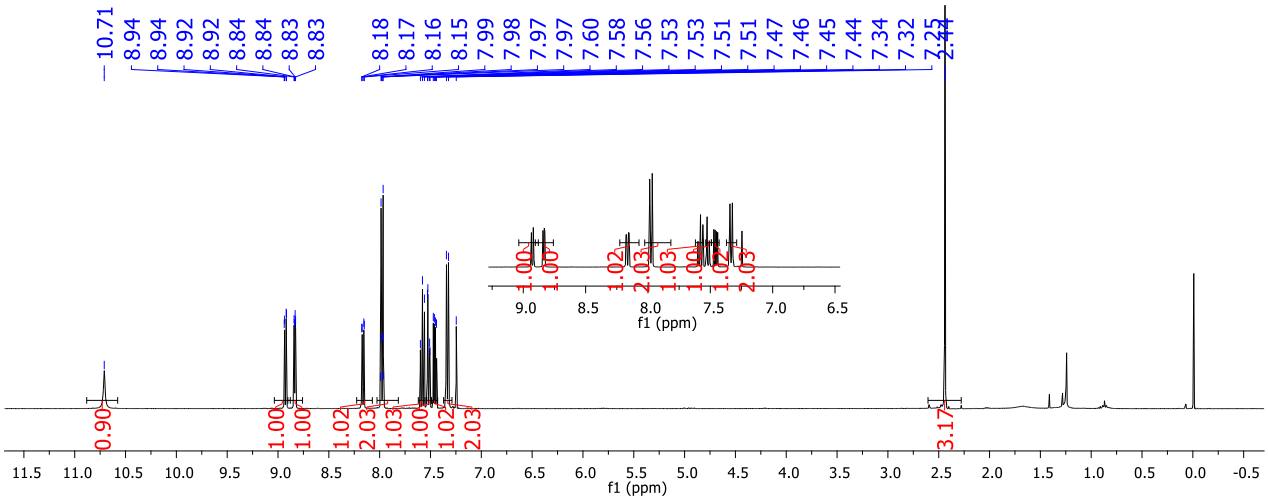




B) H/D Exchange studies with D_2O as Additive (GP 6)

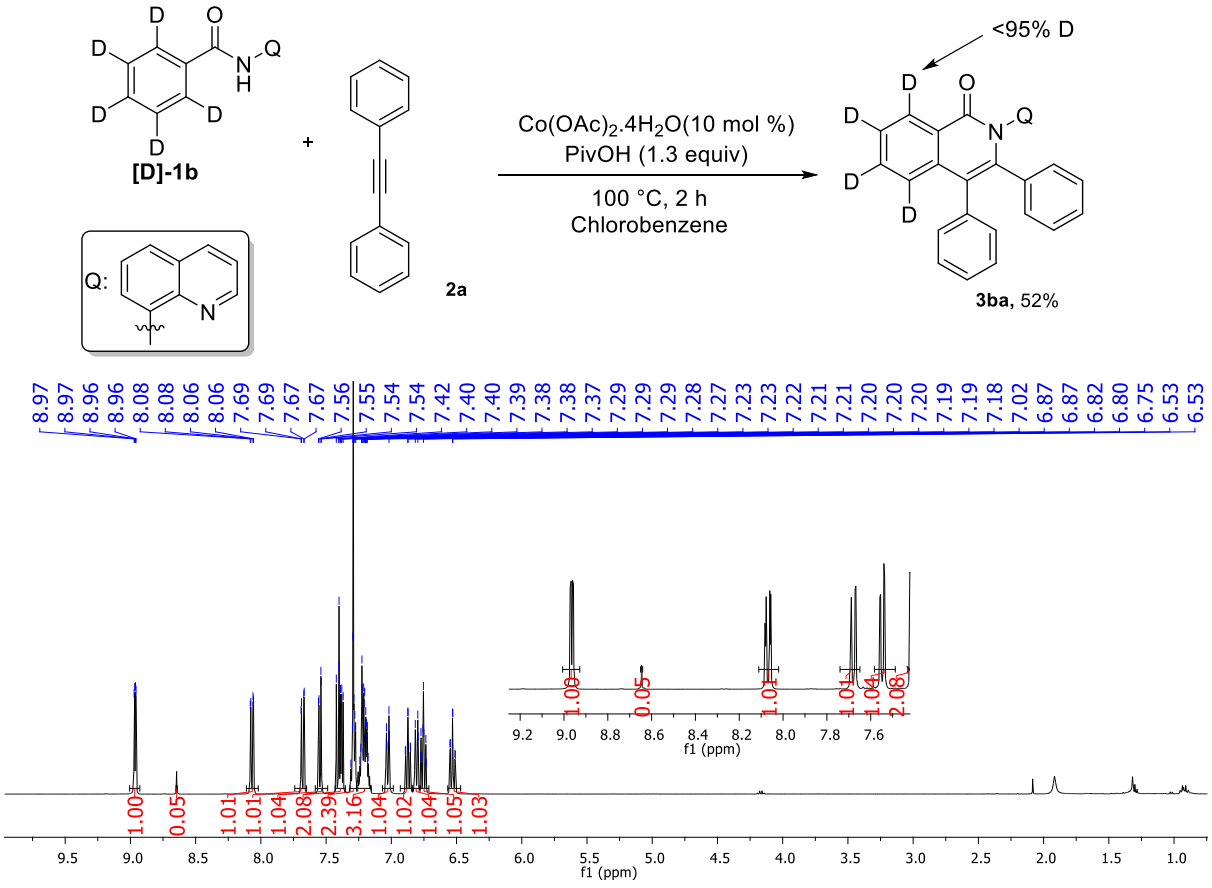
To a 15-mL pressure tube containing $Co(OAc)_2 \cdot 4H_2O$ (10 mol %), amide **1a** (50 mg, 1 equiv), chlororobenzene 3 mL, pivalic acid (1.3 equiv) and **D_2O** (1 mL) were added under open air conditions. After that, a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, 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 the filtrate was concentrated. The crude residue was directly analysed by 1H NMR.





C) H/D Exchange studies [D]-1b (GP 7)

To a 15-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amide **[D]-1b** (50 mg, 1 equiv), alkyne **2a** (1.3 equiv), chlororobenzene 3 mL and pivalic acid (1.3 equiv) were added under open air conditions. After that, a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 100 °C for 2 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite 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 **[D]-3ba** in 46% yield.

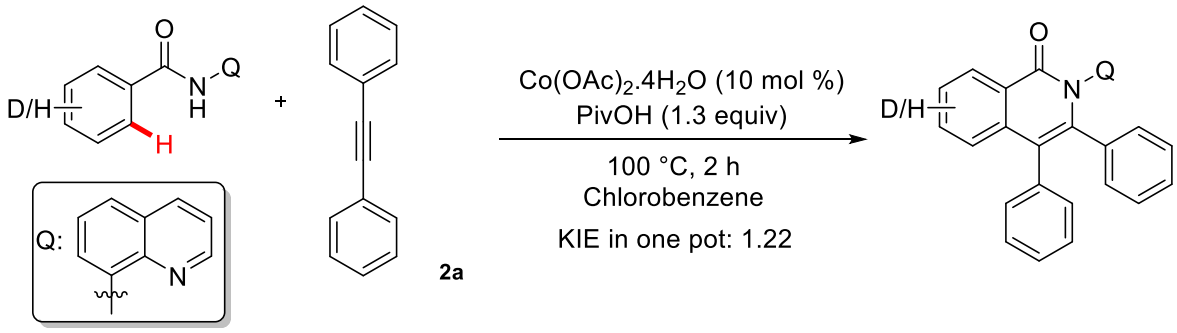


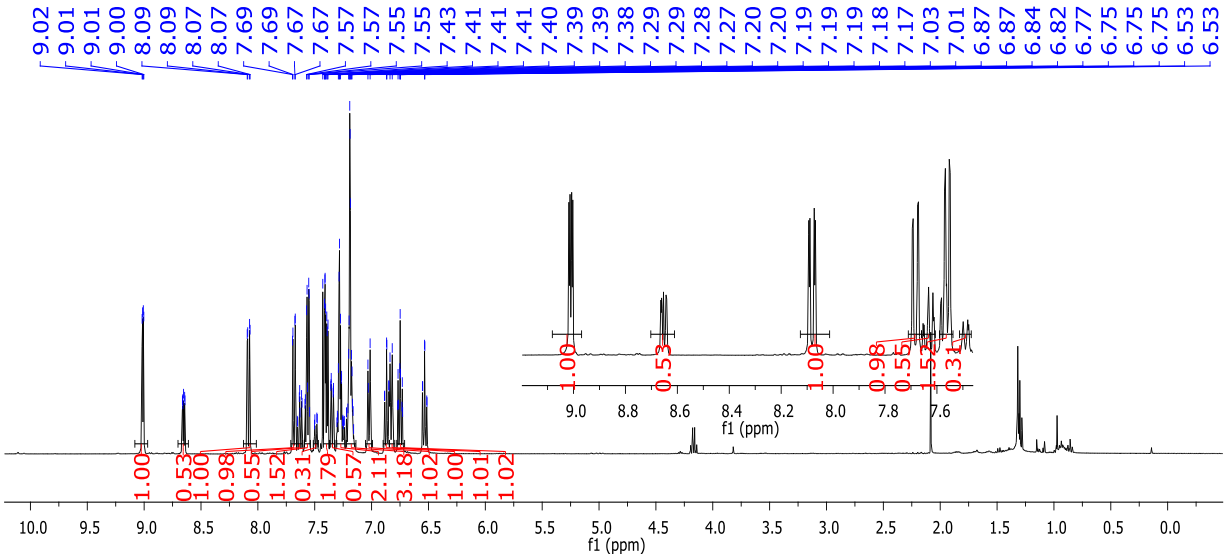
Studies on the Kinetic Isotope Effect.

A) By competition reaction (GP 8)

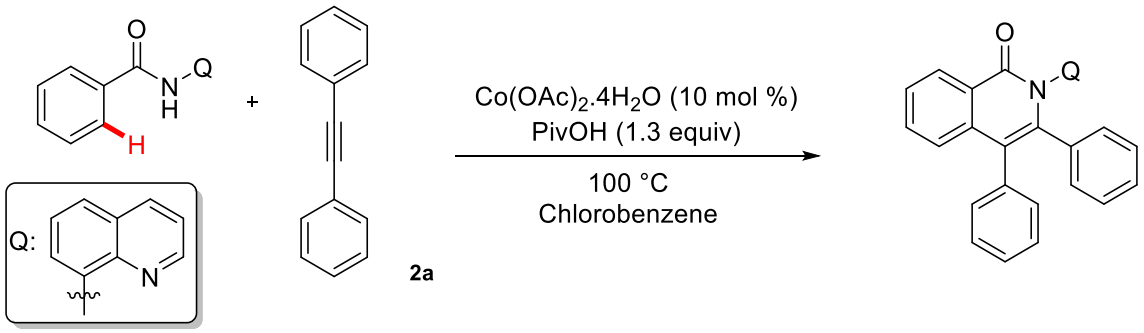
To a 15-mL pressure tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amide **1b** (50 mg, 1 equiv), amide **[D]-1b** (50 mg, 1 equiv) and alkyne **2a** (1.3 equiv), chlororobenzene 3 mL and pivalic acid (1.3 equiv) were added under open air conditions. After that, a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 100 °C for 2 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and the filtrate was concentrated. The crude residue was purified through a

silica gel column using hexanes and ethyl acetate as eluent to give combined products **3ba**and **[D]-3ba**in 56% yield.



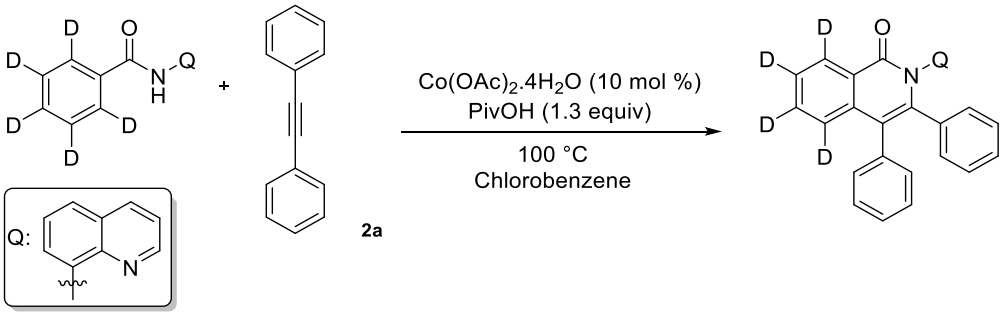


B) By two parallel reactions

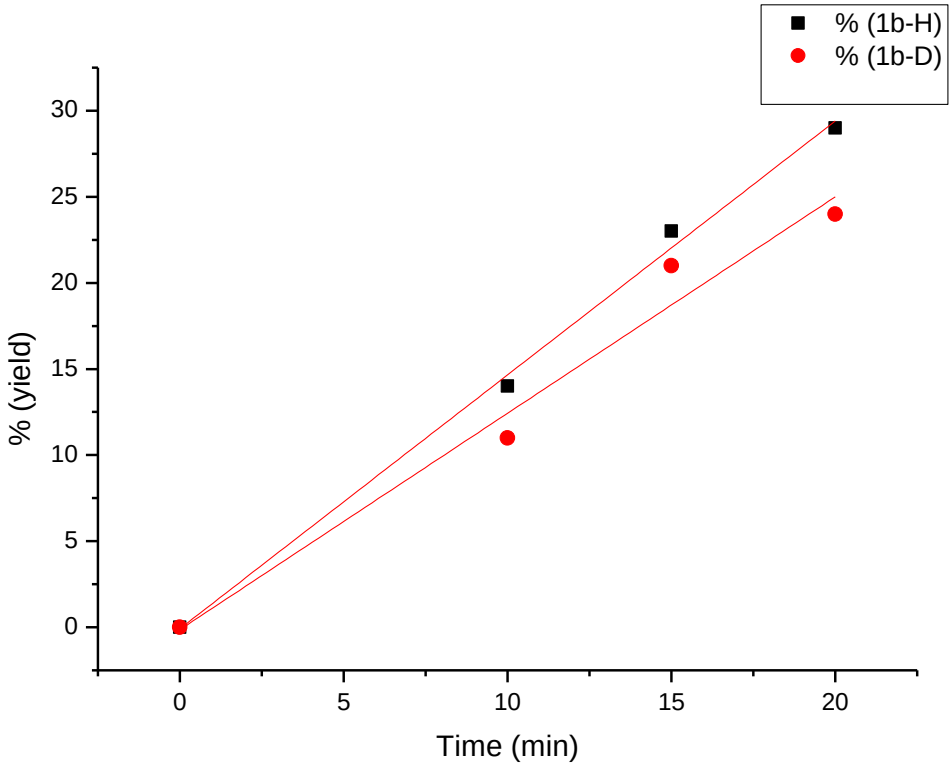


Three 15-mL pressure tubes containing Co(OAc)·4H_2O (10 mol %), amide **1b** (25 mg, 1 equiv), alkyne **2a** (1.3 equiv), chlororobenzene 2 mL and pivalic acid (1.3 equiv) were added under open air conditions. After that, a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, the

reaction mixture was allowed to stir at 100 °C. The reactions were stopped sequentially at 10, 15 and 20 mins. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluents to give pure product **3ba** in 14%, 23% and 29% yields respectively.



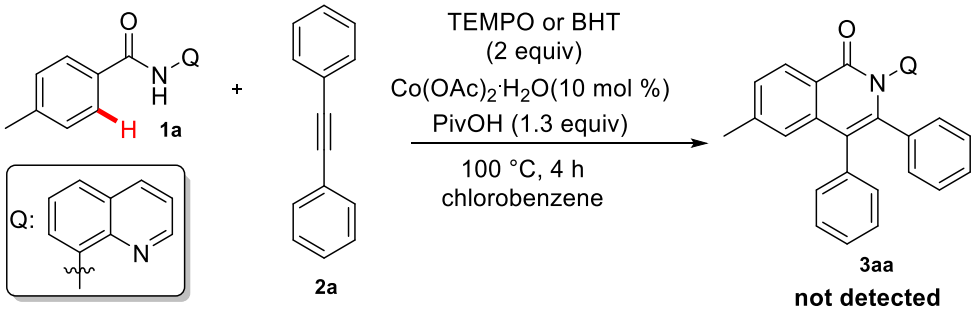
The procedure above was followed using **[D]-1b**(25 mg,) and product **[D]-3ba** was isolated in 11%, 21% and 24% yields respectivly. Data from independent kinetic isotope studies are collected in the figure below and KIE was found to be $k_H/k_D \approx 1.16 \approx 1.2$



Radical trapping experiments (GP 9)

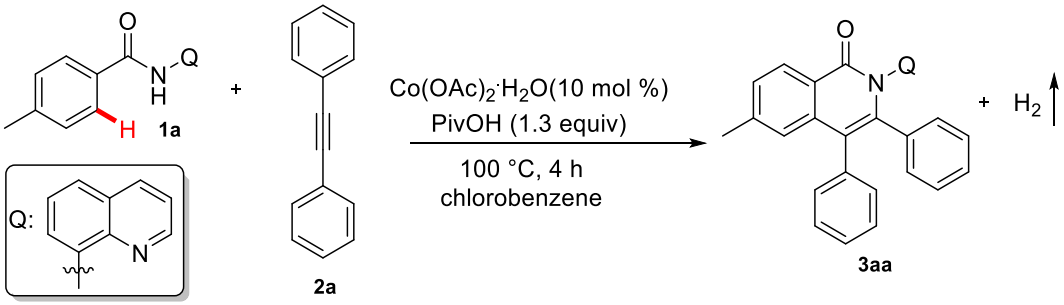
To a 15-mL pressure tube containing Co(OAc)·4H$_2$O (10 mol %), amide **1a** (50 mg, 1 equiv), TEMPO or BHT (2 equiv) and alkyne **2a** (1 eq), chlororobenzene 3 mL and

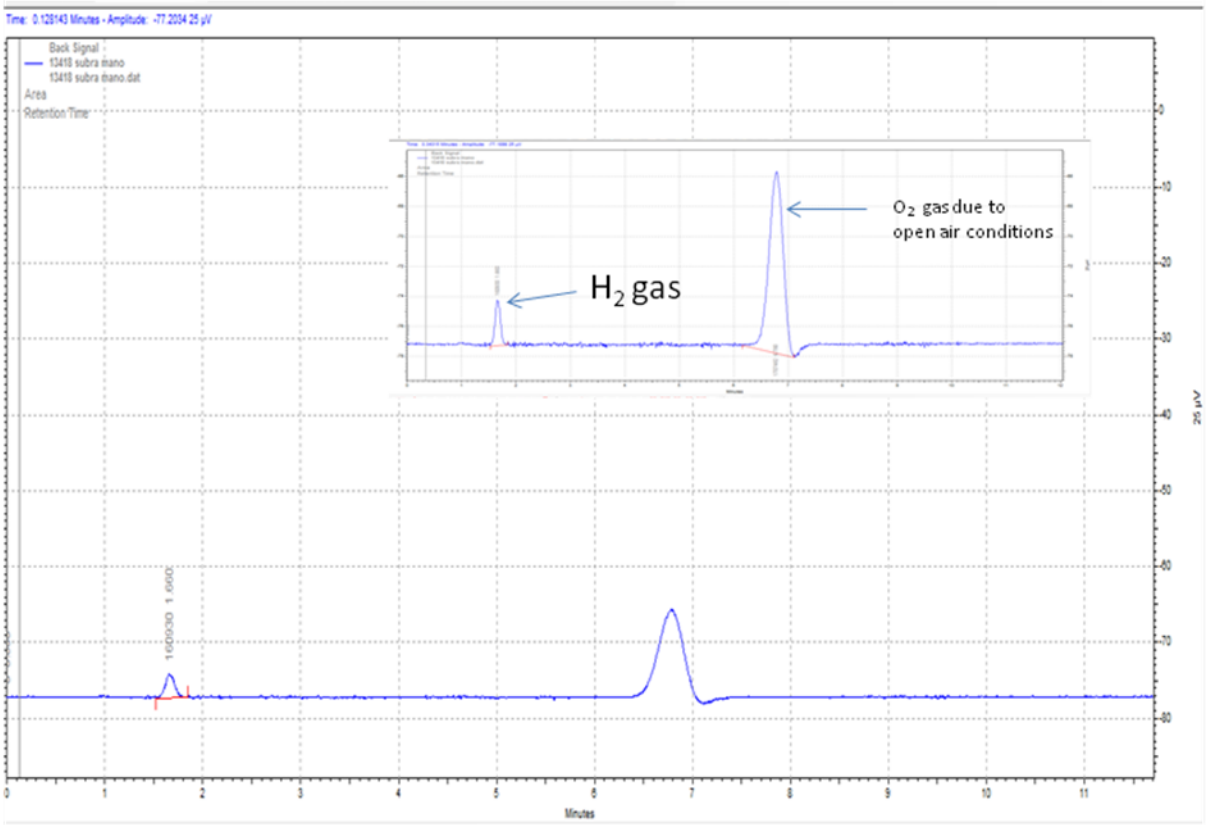
pivalic acid (1.3 equiv) were added under open air conditions. After that, a screw cap was used to cover the tube. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 100 °C for 4 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and the filtrate was concentrated. In crude reaction mixture expected product **3aa** was not observed.



Procedure for the Determination of H_2 gas Evolution by GC (GP 10)

To a 5-mL sealed tube containing $Co(OAc)\cdot 4H_2O$ (10 mol %), amide **1a** (50 mg, 1 equiv), and alkyne **2a** (1 eq), chlororobenzene 3 mL and pivalic acid (1.3 equiv) were added. After that, tube was tightly sealed. Again, the reaction mixture was stirred at room temperature for 5 minutes. Then, the reaction mixture was allowed to stir at 100 °C for 4 h. After that, the gaseous reaction mixture was taken by the syringe and injected into the gas chromatograph (GC) equipped with a TCD detector (Agilent 7890). The characteristic peak for H_2 gas was observed in the exact region (retention time 1-1.2 minutes).

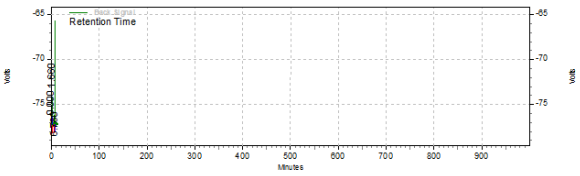




Page 1 of 1

Area % Report

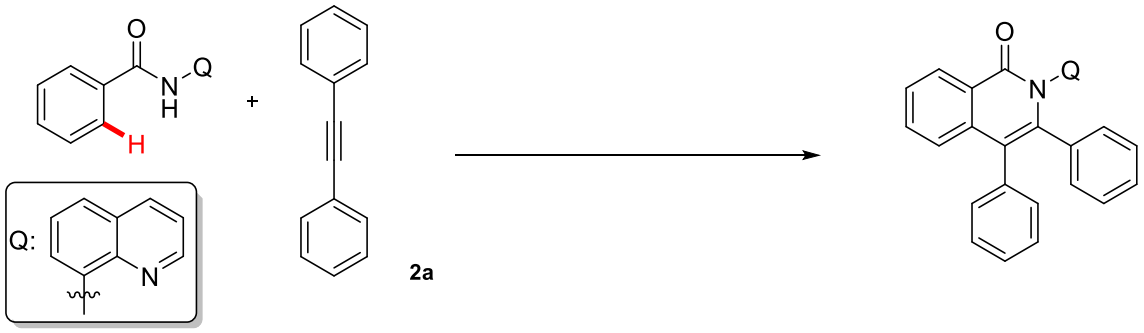
Data File: C:\EZChrom rElite\Data\himanshu\nicu1h\13418 subra mano.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\test 24_10_2016.met
Acquired: 4/13/2018 12:06:14 PM
Printed: 4/13/2018 12:20:06 PM



Back Signal
Results

Retention Time	Area	Area %	Height	Height %
0.000	0	0.00	0	0.00
1.660	160930	8.61	23381	20.10
6.780	1707482	91.39	92926	79.90
Totals	1868412	100.00	116307	100.00

Procedure for Kinetic experiments:



All kinectic experiments were performed by taking standard reaction between amide **1a** and alkyne **2a** by following standard reaction procedure **GP1**. The ratio between products and reactants were calculated by 1H NMR analysis using 1, 3, 5 - Trimethoxy benzene as an internal standard.

Amide and alkyne were involved in the reaction. So we assumed that rate of the reaction is dependent on the concentration of amide and olefin.

So, Rate = k.[amide]^{x} [olefin]^{y} ……..(1)

[x = order with respect to amide; y = order with respect to olefin; k = rate constant]

Order with respect to amide:

Reaction No	Amide **1a**	Alkyne **2a**	$Co(OAc)_2.4H_2O$	Pivalic acid
1	50 mg (0.2016 mmol)	46.6 mg (0.2620mmol)	5 mol%	1.3 equiv
2	100 mg (0.4032 mmol)	46.6 mg (0.2620mmol)	5 mol%	1.3 equiv

By two different sets of reactions where only the concentration of amide varied others kept constant. The following plot was obtained by analysing the product ratio in H^1 NMR.

From the equation (1) we got, Rate = k. [Amide]^{x} [Olefin]^{y}

For reaction number 1, initial rate = R1

So, R1 = k. [Amide]^{x} [Olefin]^{y}

0.024 = k [0.2016]^{x} [0.2620]^{y} ……(2)

For reaction number 2, initial rate = R2

So, R2= k. [Amide]^{x} [Olefin]^{y}

0.023= k. [0.4032]^{x} [0.2620]^{y} …….(3)

Hence, from equation (2) and (3)

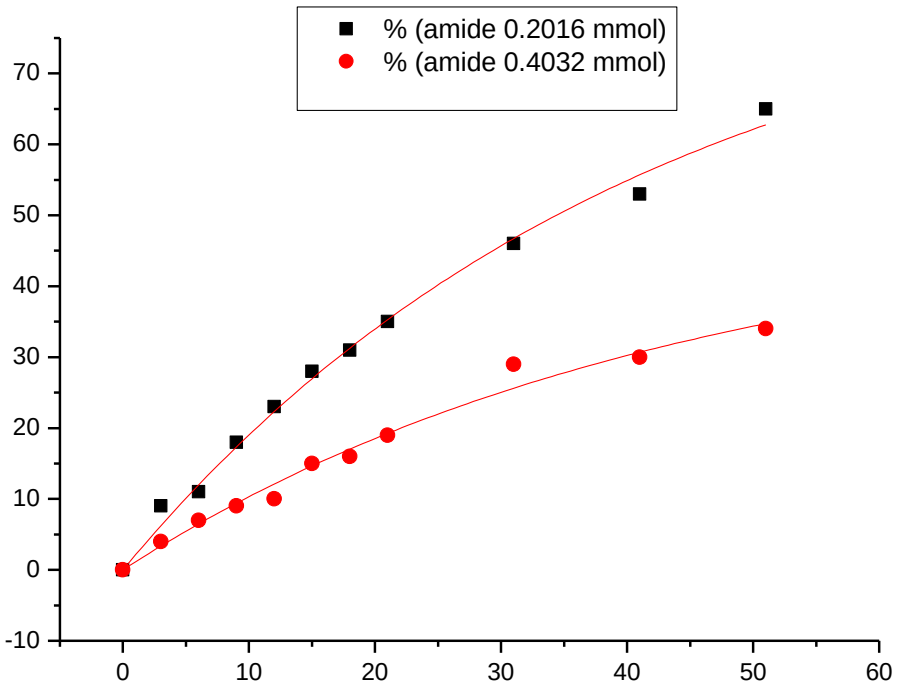
[R2/R1] = [0.023 /0.024]x

x = [log(Rate 2) - log(Rate 1)] / [log(0.4032) - log(0.2016)]

x = [log(0.023) – log(0.024)] / [log(0.4032) – log(0.2016)]

x = ~ -0.5

So, order with respect to amide is ~ -0.5



Order with respect to alkyne:

Reaction No	Amide **1a**	Alkyne **2a**	$Co(OAc)_2.4H_2O$	Pivalic acid
1	50 mg (0.2016 mmol)	46.6 mg (0.2620mmol)	10 mol%	1.3 equiv
2	50 mg (0.2016 mmol)	93.2 mg (0.5240mmol)	10 mol%	1.3 equiv

By two different sets of reactions where only the concentration of amide varied others kept constant. The following plot was obtained by analysing the product ratio in H^1 NMR. From the equation (1) we got, Rate = k. $[Amide]^x$ $[Olefin]^y$

For reaction number 1, initial rate = R1

So, R1 = k. $[Amide]^x$ $[Olefin]^y$

0.051 = k.$[0.2016]^x$ $[0.2620]^y$ ……(4)

For reaction number 2, initial rate = R2

So, R2= k. $[Amide]^x$ $[Olefin]^y$

or, 0.086= k. $[0.2016]^x$ $[0.5240]^y$ ……(5)

Hence, from equation (2) and (3)

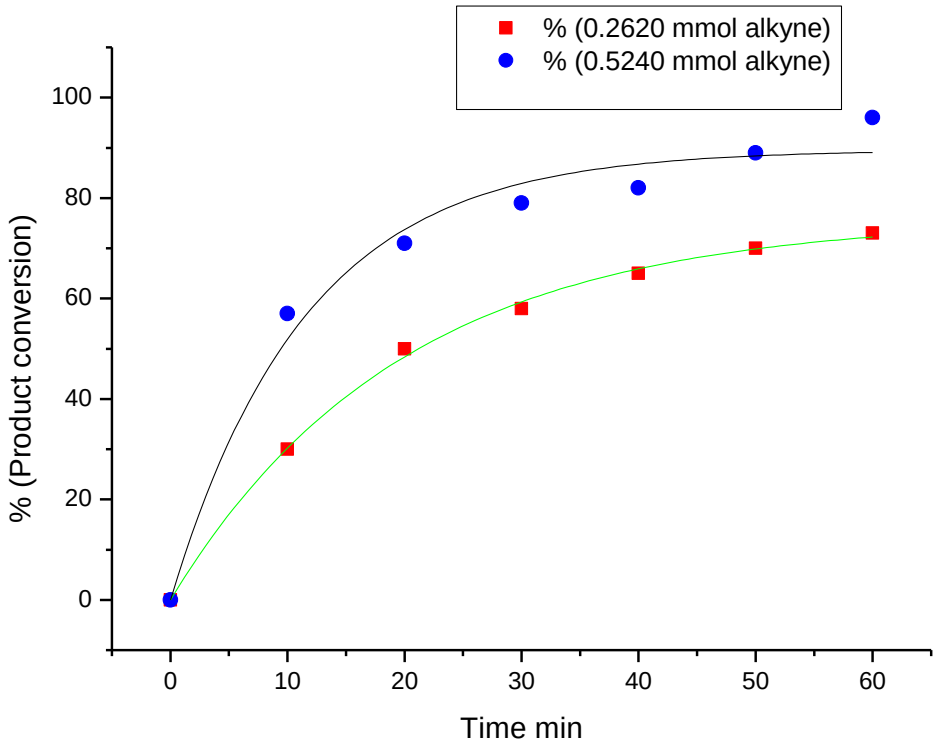
$[R2/R1] = [0.086 /0.051]^y$

y = [log(Rate 2) - log(Rate 1)] / [log(0.5240) - log(0.0.2620)]

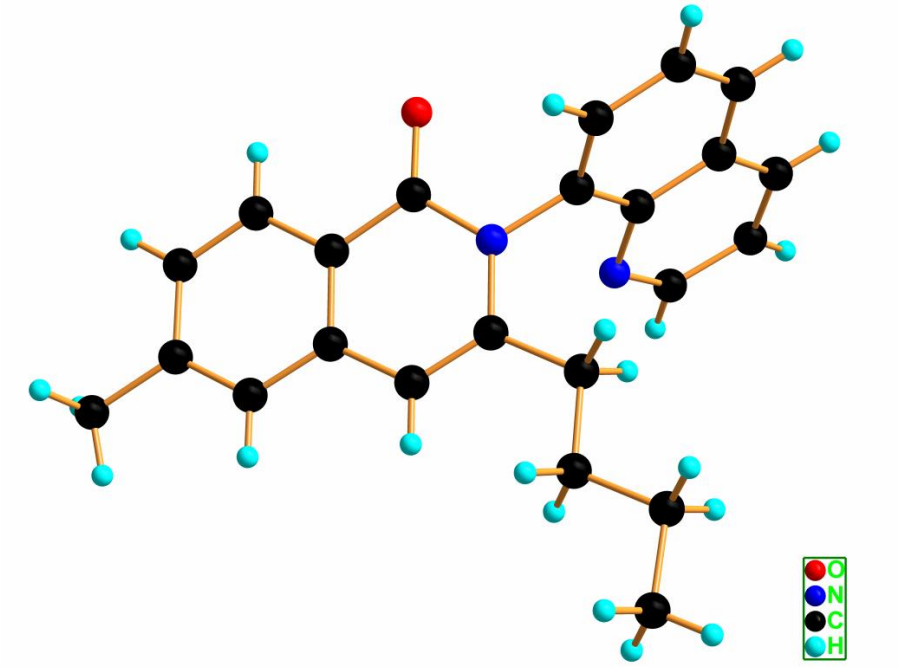
y = [log(0.086) – log(0.051)] / [log(0.5240) – log(0.2620)]

y = ~ 0.75

So, order with respect to alkyne is ~ 0.8



Crystallographic Data of Compound 3aj.

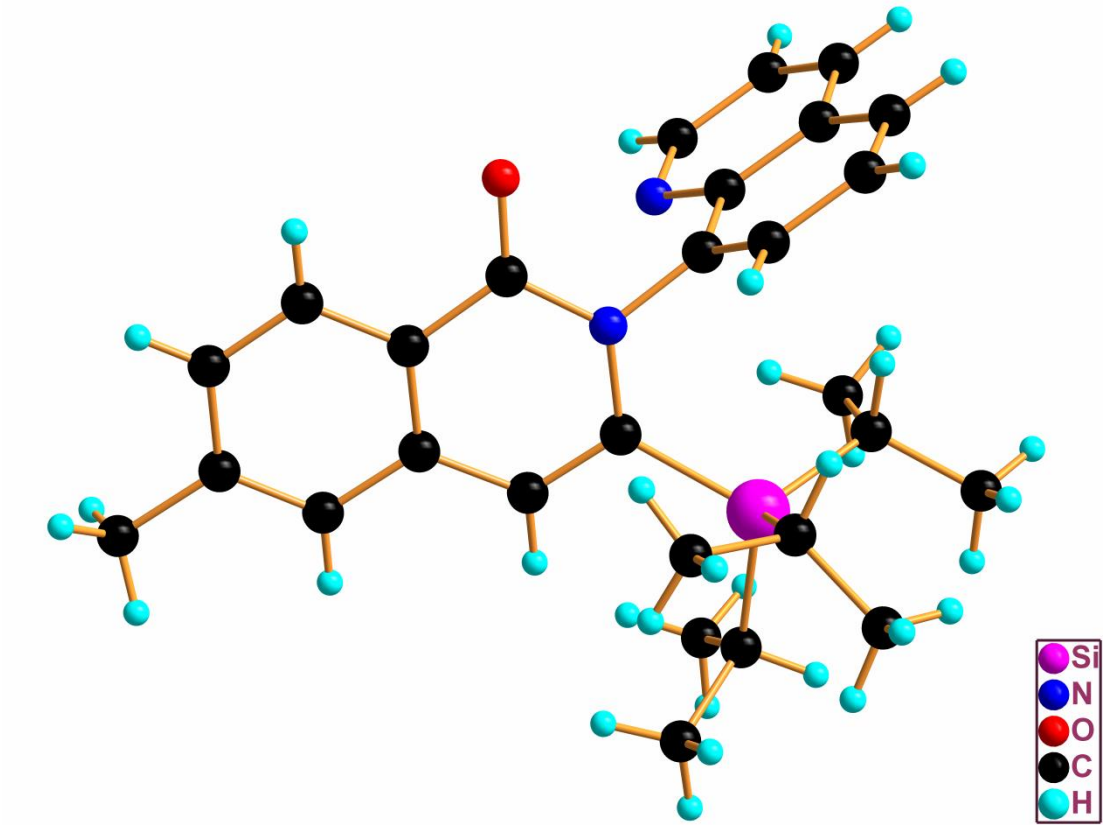


Crystal data and structure refinement for compound **3aj**.

Identification code	nrm-4146	
Empirical formula	$C_{23}H_{22}N_2O$	
Formula weight	342.42	
Temperature	150 (2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 5.1215(15) Å	a= 98.617(11) °.
	b = 9.156(3) Å	b= 95.001(10) °.
	c = 20.332(6) Å	g = 97.261(10) °.
Volume	929.6(5) $Å^3$	
Z	2	
Density (calculated)	1.223 Mg/m^3	
Absorption coefficient	0.075 mm^{-1}	
F(000)	364	
Theta range for data collection	2.273 to 25.247 °.	
Index ranges	-5<=h<=6, -10<=k<=10, -24<=l<=24	
Reflections collected	14300	
Independent reflections	3348 [R(int) = 0.0881]	
Completeness to theta = 25.242°	99.9 %	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	3348 / 0 /237
Goodness-of-fit on F^2	1.025
Final R indices [I>2sigma(I)]	R1 = 0.0690, wR2 = 0.1476
R indices (all data)	R1 = 0.1265, wR2 = 0.1673
Extinction coefficient	n/a
Largest diff. peak and hole	0.219 and -0.243 e.$Å^{-3}$

Crystallographic Data of Compound 3am.

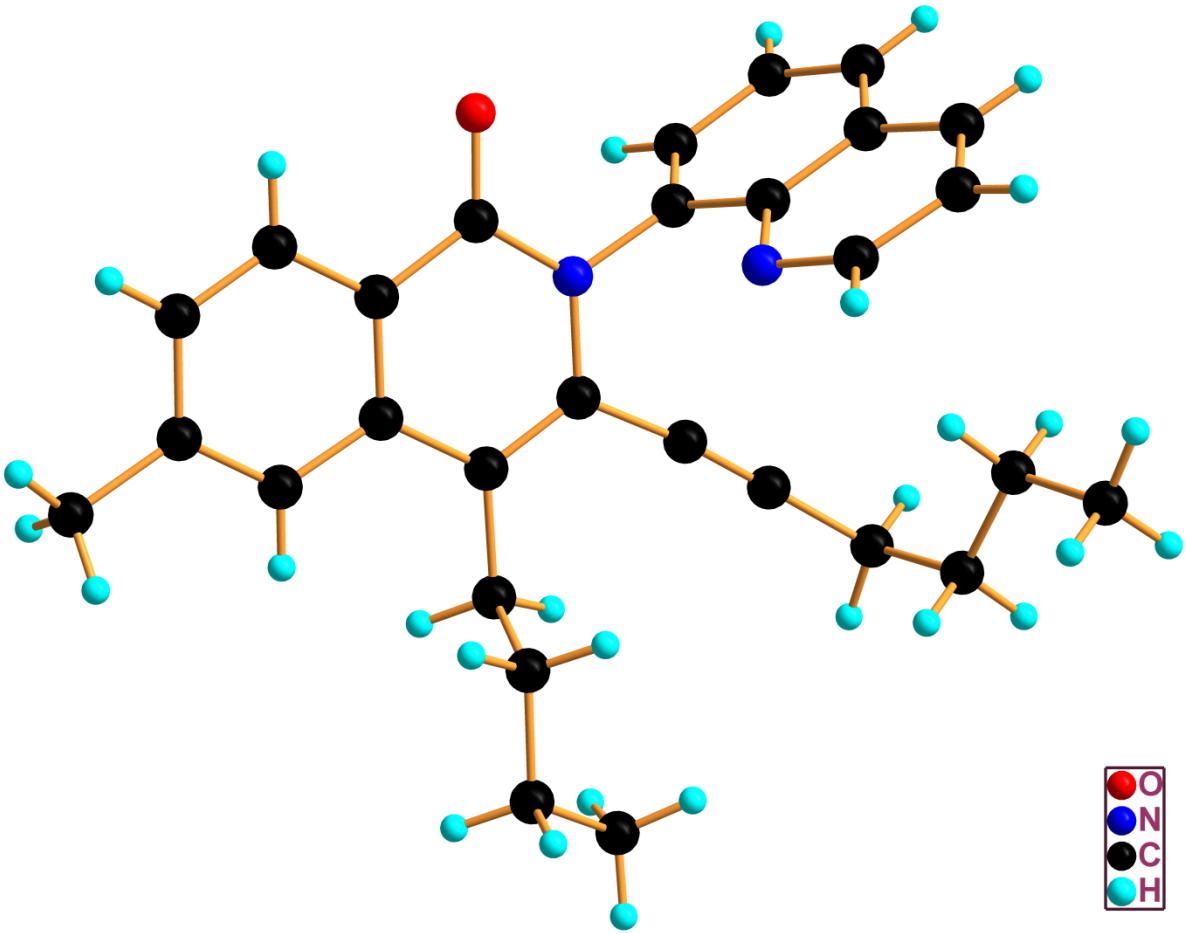


Crystal data and structure refinement for compound **3am**.

Identification code	nrm-4147	
Empirical formula	$C_{28}H_{34}N_2OSi$	
Formula weight	442.66	
Temperature	150 (2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 18.218(4)Å	α = 90 °.
	b = 7.7675(18) Å	β = 111.106(5) °.
	c = 18.549(4) Å	γ = 90 °.
Volume	2448.8(9) $Å^3$	

Z	4
Density (calculated)	1.201 Mg/m^3
Absorption coefficient	0.118 mm^{-1}
F(000)	952
Theta range for data collection	1.959 to 28.401°.
Index ranges	-22<=h<=24, -10<=k<=7, -24<=l<=19
Reflections collected	44246
Independent reflections	6144 [R(int) = 0.1315]
Completeness to theta = 25.242°	100 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6144 / 0 /296
Goodness-of-fit on F^2	0.993
Final R indices [I>2sigma(I)]	R1 = 0.0592, wR2 = 0.1460
R indices (all data)	R1 = 0.1056,wR2 = 0.1782
Extinction coefficient	n/a
Largest diff. peak and hole	0.380 and -0.448 $e.Å^{-3}$

4B.5.9 Crystallographic Data of Compound 3aq

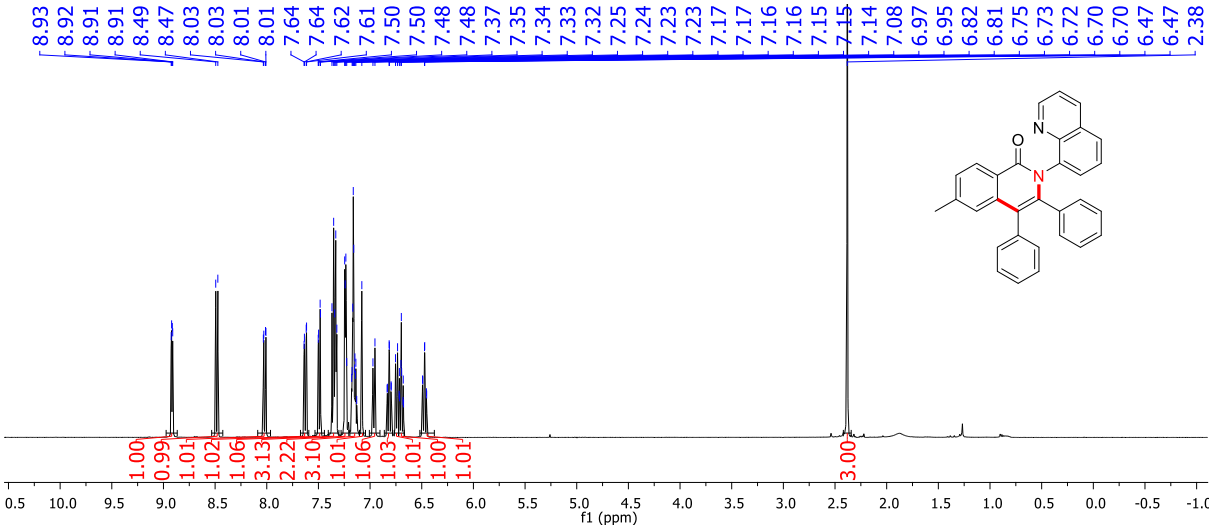


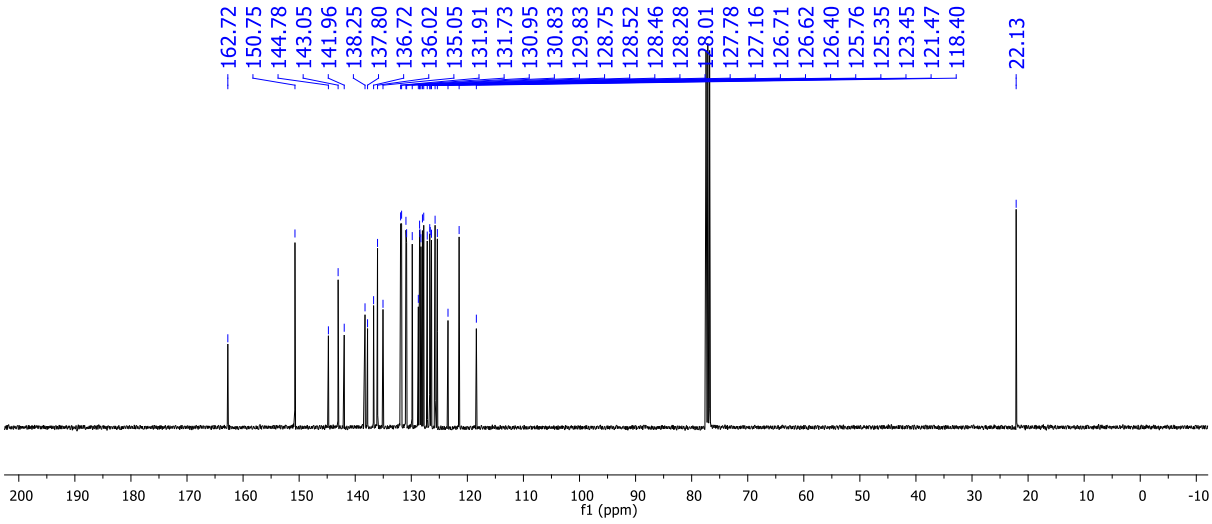
Crystal data and structure refinement for compound **3aq**.

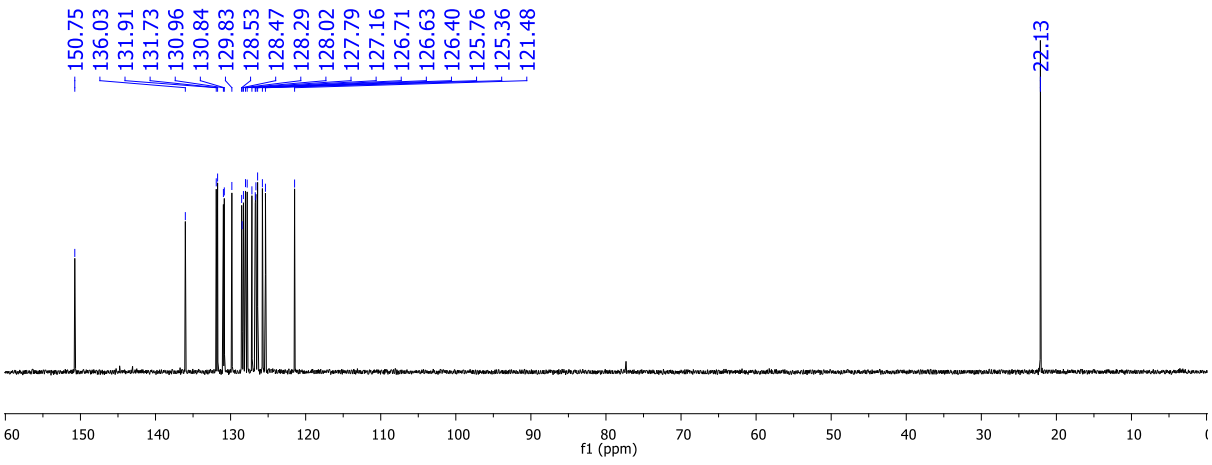
Identification code	nrm-4163	
Empirical formula	$C_{29}H_{30}N_2O$	
Formula weight	422.55	
Temperature	296 (2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.697(4)Å	α = 93.694(9) °.
	b = 11.477(4) Å	β = 96.086(10) °.
	c = 12.404(5) Å	γ = 106.015(10)°.
Volume	1177.7(8)$Å^3$	
Z	2	
Density (calculated)	1.192 Mg/m^3	
Absorption coefficient	0.072 mm^{-1}	
F(000)	452	
Theta range for data collection	1.659 to 25.248°.	
Index ranges	-10<=h<=9, -13<=k<=13, -14<=l<=14	
Reflections collected	11388	
Independent reflections	4269 [R(int) = 0.0589]	
Completeness to theta = 25.242°	100 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4269/ 0 /292	
Goodness-of-fit on F^2	1.019	
Final R indices [I>2sigma(I)]	R1 = 0.0657, wR2 = 0.1645	
R indices (all data)	R1 = 0.1124, wR2 = 0.1978	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.562 and -0.307 $e.Å^{-3}$	

4B.8: Spectral Copies of Selected Compounds

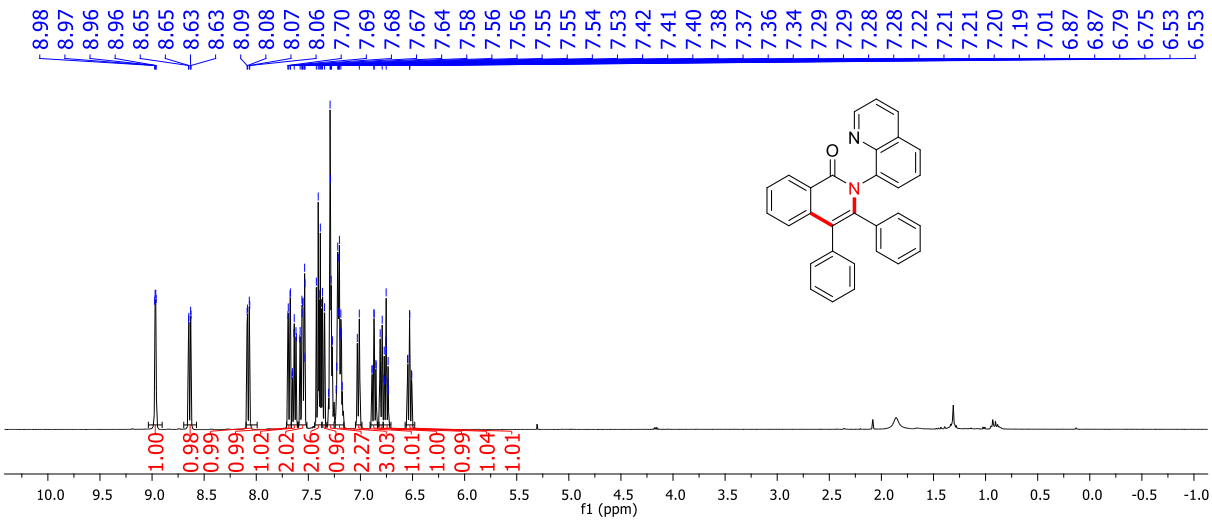
Copies of ^{1}H, ^{13}C and DEPT 135 NMR spectra of compound **3aa**

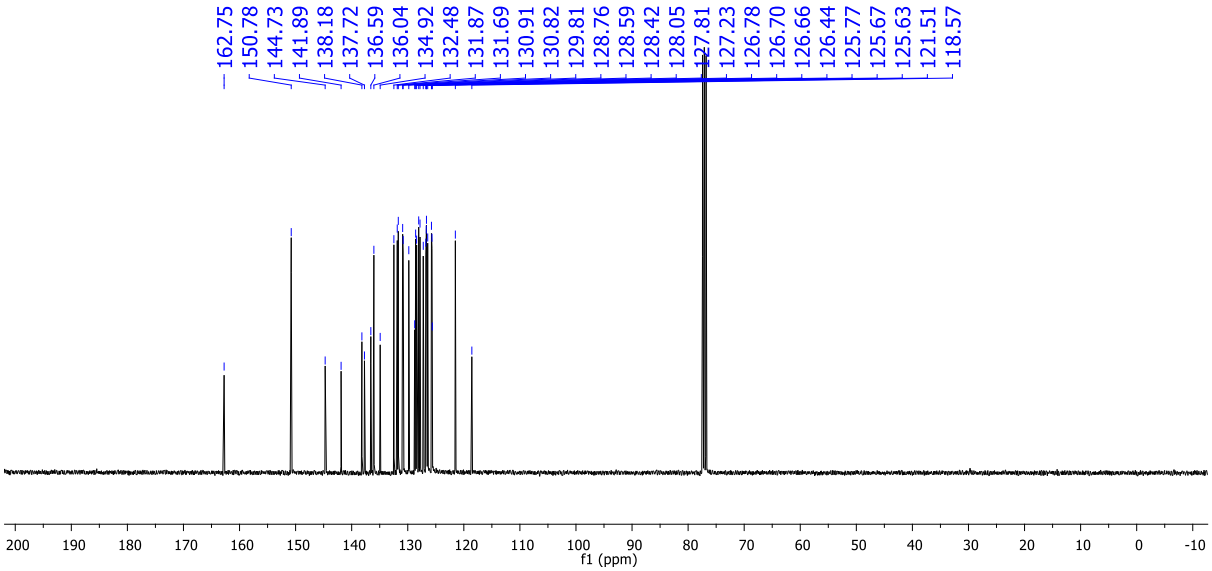


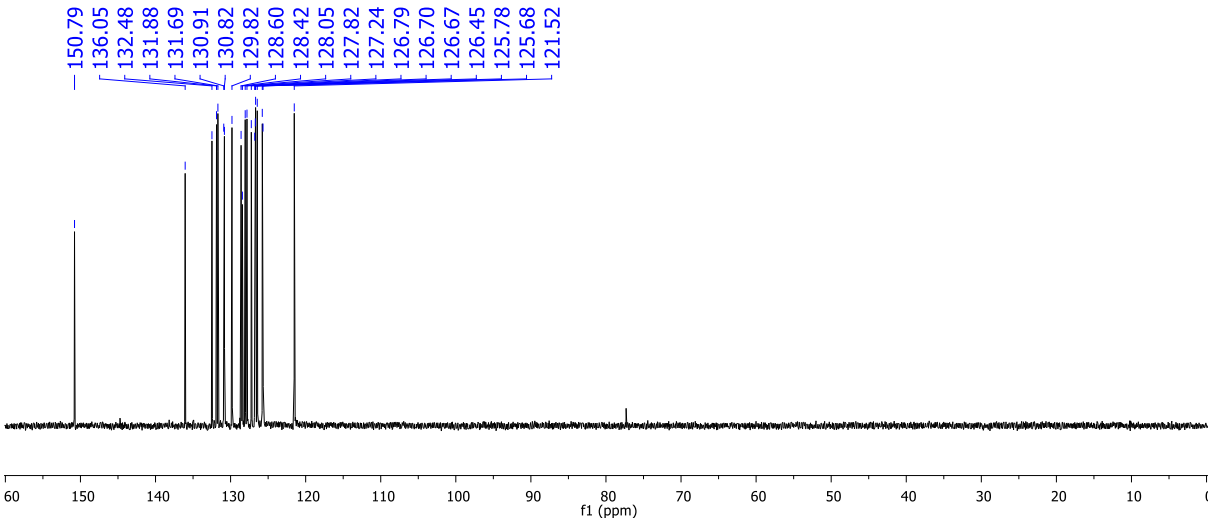




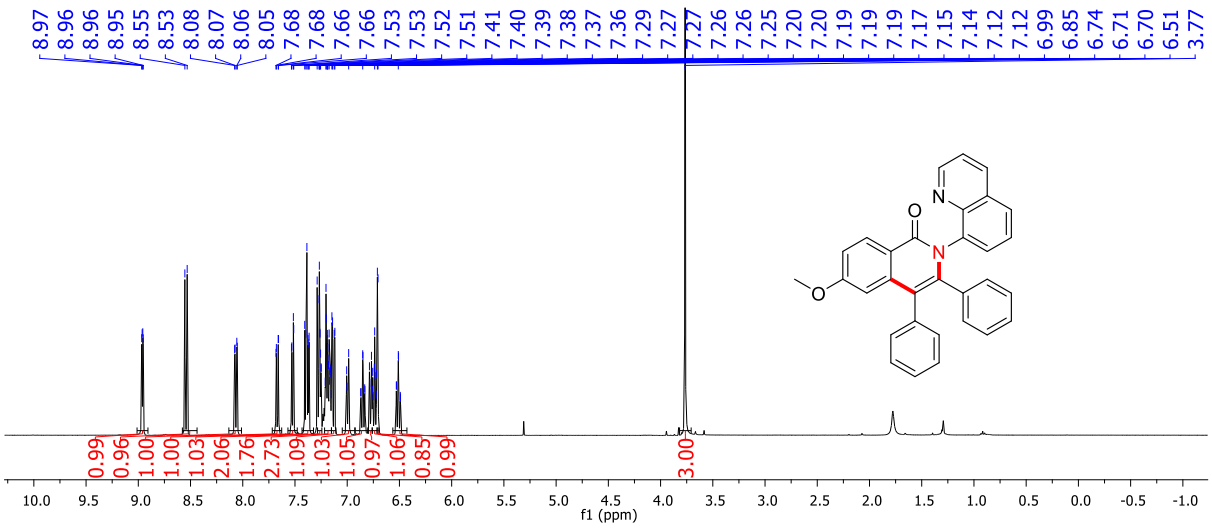
Copies of ^{1}H, ^{13}C and DEPT 135 NMR spectra of compound **3ba**

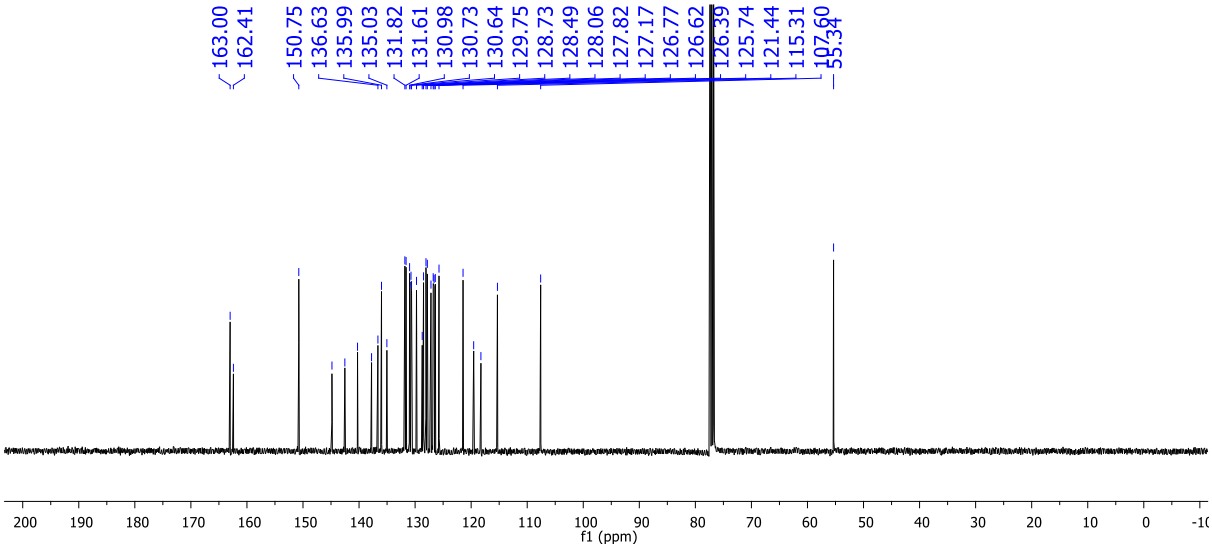


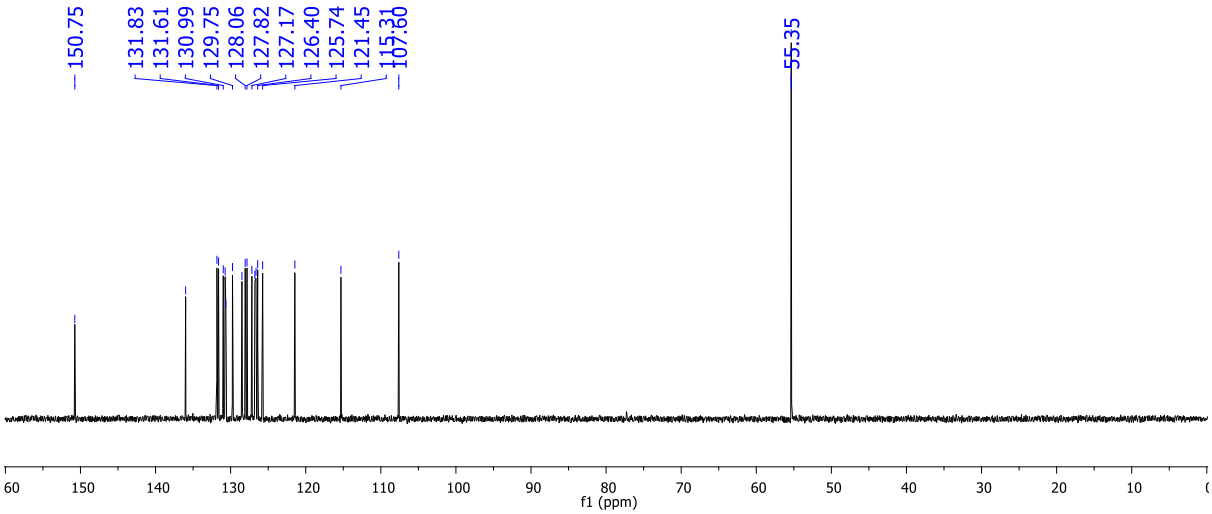




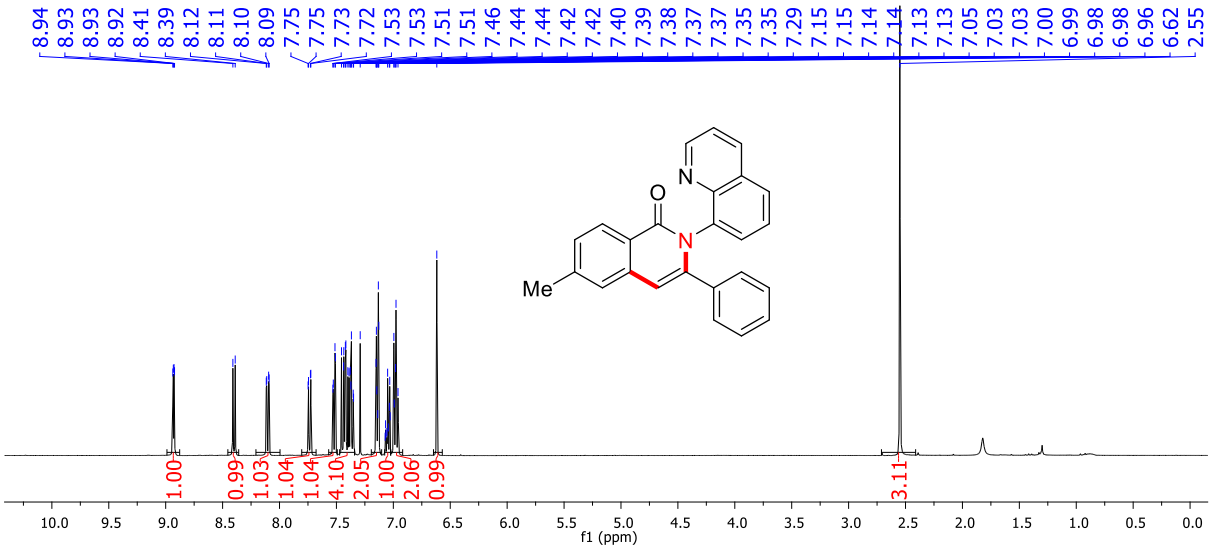
Copies of ^{1}H, ^{13}C and DEPT 135 NMR spectra of compound **3ca**

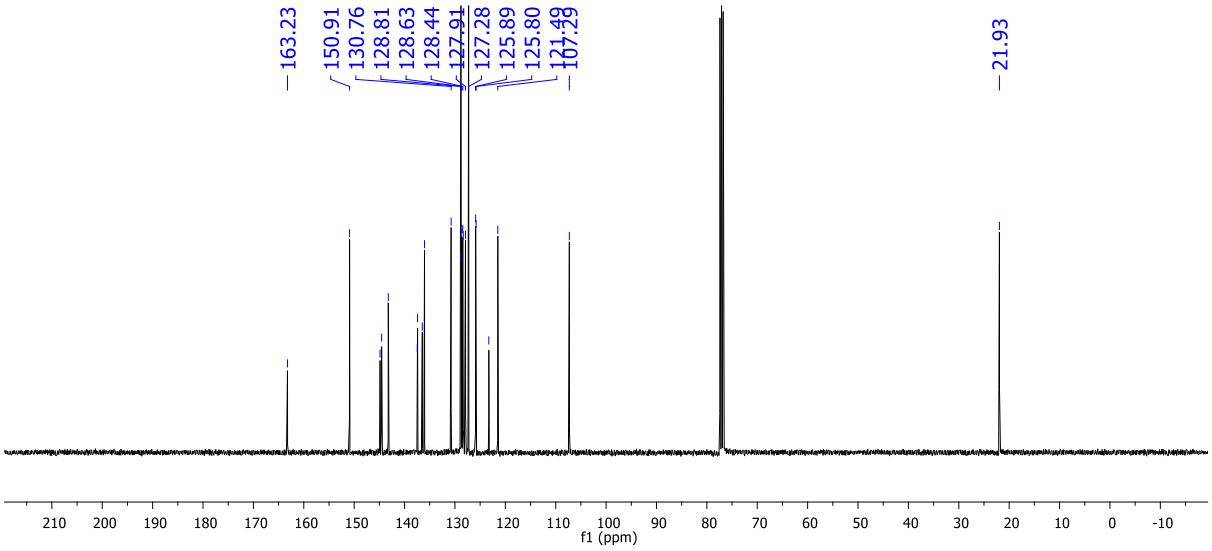


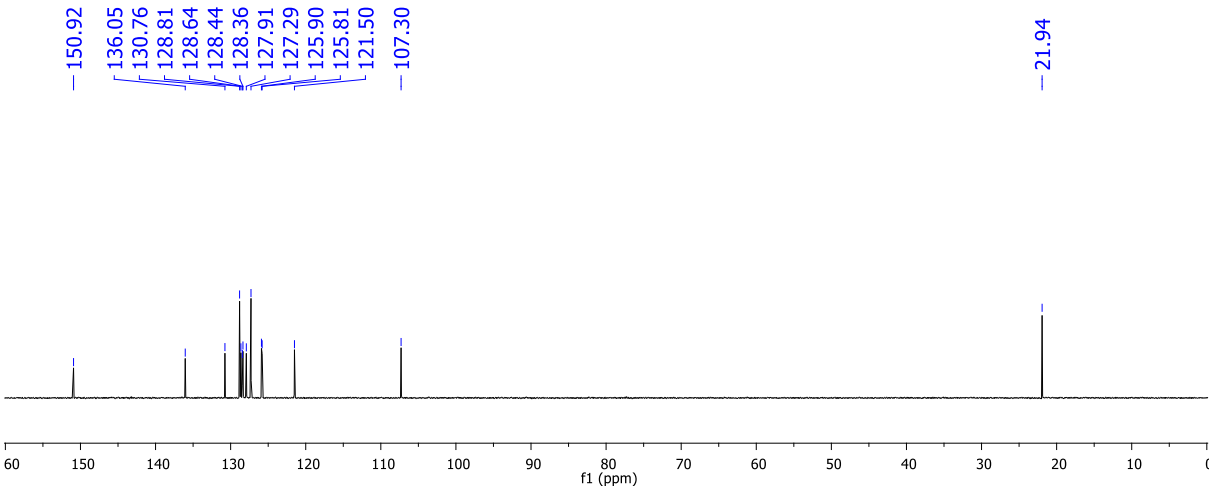




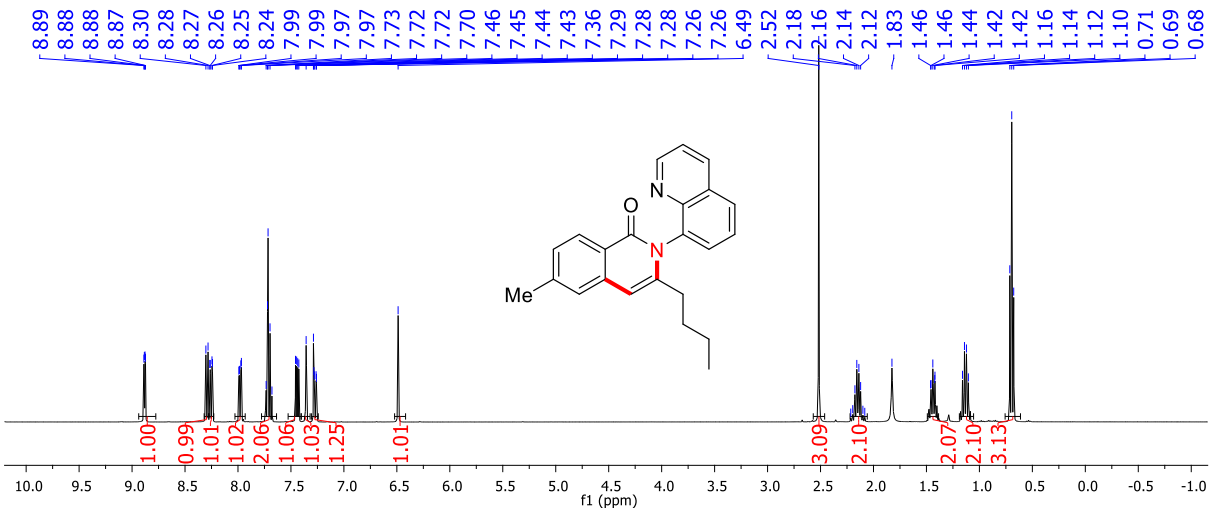
Copies of ^{1}H, ^{13}C and DEPT 135 NMR spectra of compound**3ai**

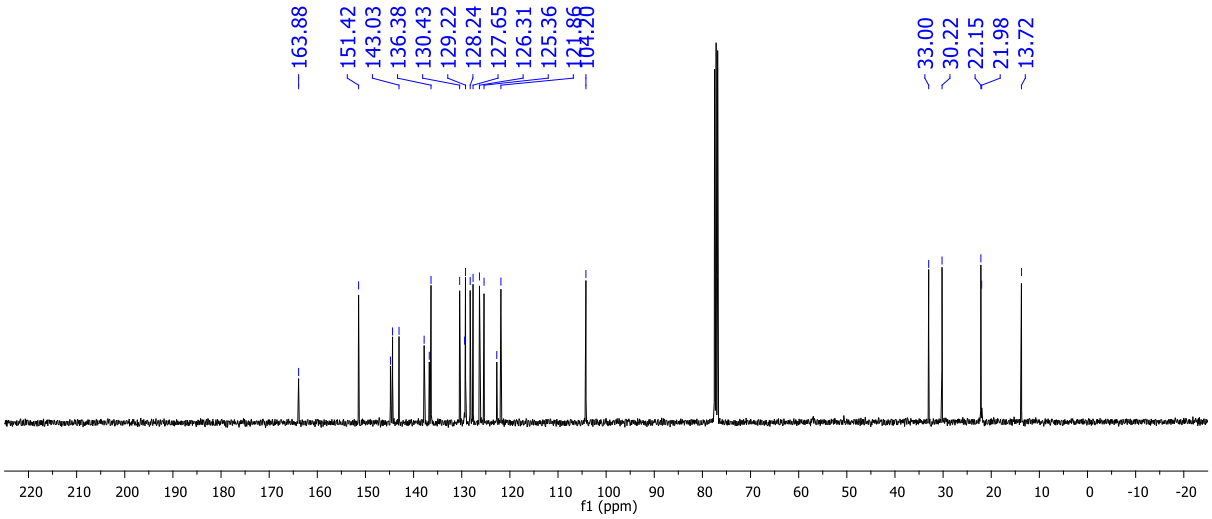


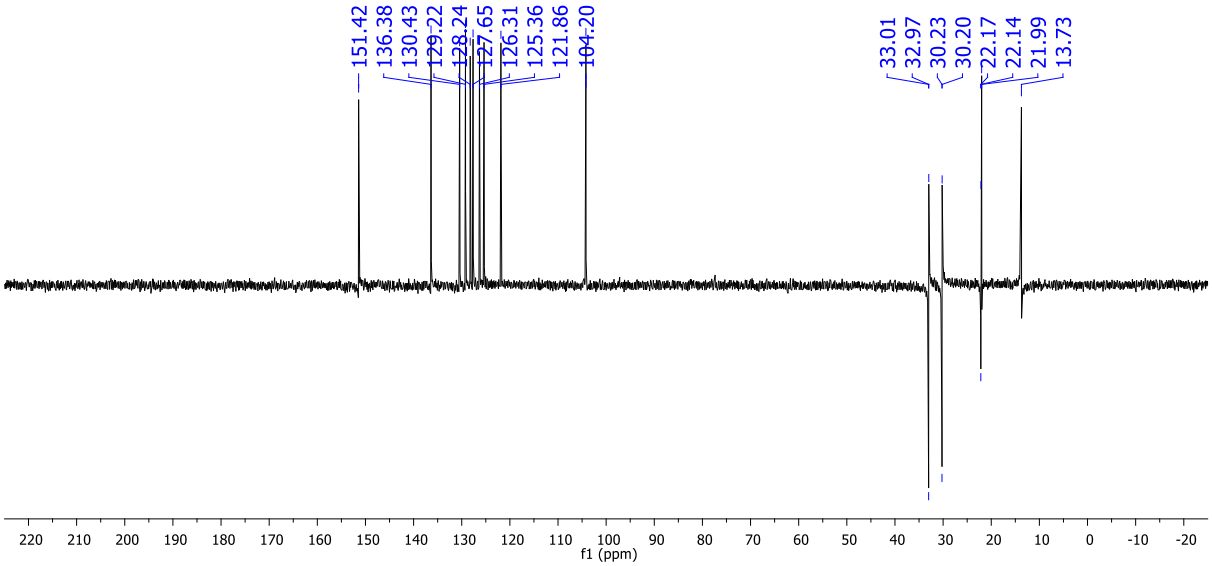




Copies of ^{1}H, ^{13}C and DEPT 135 NMR spectra of compound **3aj**







Copies of ^{1}H, ^{13}C and DEPT 135 NMR spectra of compound **3ak**