Synthesis of Annulated Heterocycles *via* a Ruthenium-Catalyzed C-H Bond Activation

A Thesis

Submitted in Partial Fulfillment of the Requirements

For the Degree of

Doctor of Philosophy

by

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ID: 20113107

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

2016

Dedicated

To

My Parents

And

My Beloved Family Members

भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान, पुणे
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CERTIFICATE

Certified that the work incorporated in this thesis entitled "***Synthesis of Annulated Heterocycles via a Ruthenium-Catalyzed C-H Bond Activation***" submitted by ***Mr. Ravi Kiran Chinnagolla*** 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: 9th March 2016

Pune

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DECLARATION

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

Date: 9th March 2016

Pune

Ravi Kiran Chinnagolla

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I would like to thank my parents (Late) and my brother Raju Kumar and my family. I am grateful to my parents gave me endless support, unconditional love and encouragement. I owe much to them for their help to overcome difficulties I have encountered.

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

Ravi Kiran Chinnagolla

Synopsis

The thesis entitled "***Synthesis of Annulated Heterocycles via a Ruthenium-Catalyzed C-H Bond Activation***" comprises of four chapters.

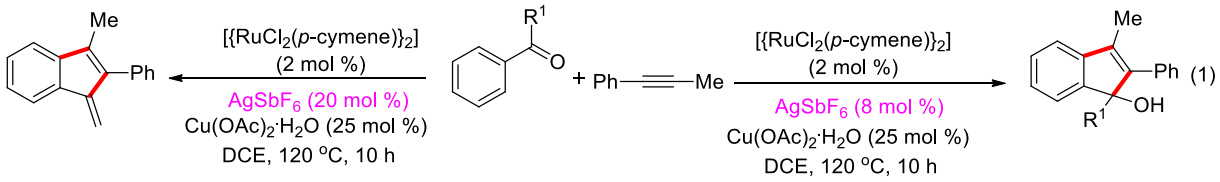
The research area in my doctoral study is targeted on the development of new synthetic methods for the synthesis of different class of annulated heterocyclic compounds *via* ruthenium-catalyzed chelation assisted C-H bond activation. Transition metal-catalyzed chelation-assisted oxidative cyclization of substituted aromatics or alkenes with carbon–carbon π-components is a powerful method to synthesize heterocyclic molecules in a highly regioselective manner. This type of reaction is highly atom economical and an environmentally friendly. In the oxidative cyclization reaction, rhodium complexes are widely used as catalysts. However, the most of rhodium-catalyzed cyclization reaction is not completely regioselective. Particularly, a mixture of regioselective products was observed in case of the reaction of substituted aromatics with unsymmetrical carbon–carbon π-components. Our recent observation clearly reveals that this type of oxidative cyclization reaction can be done in a highly regioselective manner by using a less-expensive ruthenium catalyst. We have developed a highly regioselective method to synthesize annulated heterocycles via a ruthenium-catalyzed oxidative cyclization of substituted aromatics or alkenes with alkynes under an air atmosphere in one pot.

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

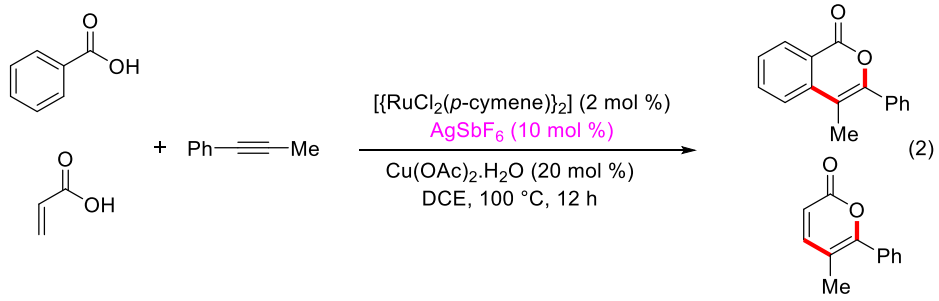
Chapter 2 of this thesis describes an efficient method for the synthesis of indenols, benzofulvenes, isocoumarins and α-pyrones via a ruthenium-catalyzed oxidative cyclization of substituted aromatics with alkynes. It contains two sub-divisions as follows:

Section 2A: Synthesis of Indenols and Benzofulvenes: A highly regioselective ruthenium-catalyzed cyclization of substituted aromatic ketones with alkynes through C-H bond activation is described. This reaction proceeds via a chelation-assisted deprotonation metalation pathway.

This methodology offers a simple and mild method for the synthesis of indenols and benzofulvenes in a highly regioselective manner. The cyclization reaction of aromatic ketones with unsymmetrical alkynes is highly regioselective and provided exclusively a single regioisomeric indenols derivatives. The amount of silver salt used determined the nature of the product. A 2 mol % of the ruthenium catalyst and 8 mol % of the silver salt favored the formation of indenols derivatives and 20 mol % of the silver salt in the presence of same amount of ruthenium catalyst afforded benzofulvenes in a highly regioselective manner (eq. 1).



Section 2B: Synthesis of Isocoumarins and α-Pyrones: Isocoumarins are an important class of naturally occurring lactones that show various biological activities such as antifungal, antitumor, antiallergic, antimicrobial, anti-inflammatory, antidiabetic, phytotoxic, and anticancer activities. We have disclosed a highly regioselective method to synthesize substituted isocoumarins and α-pyrones via a ruthenium-catalyzed oxidative cyclization. Treatment of aromatic acids with unsymmetrical alkynes in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %) and $Cu(OAc)_2.H_2O$ (20 mol %) without using $AgSbF_6$ in 1,2-dichloroethane at 100 °C for 12 h gave a mixture of alkyne regioisomeric isocoumarin derivatives. In addition, 1:2 decarboxylative cyclization of acid with alkyne to give a mixture of naphthalene derivative was observed. Surprisingly, when the same reaction was carried out in the presence of a catalytic amount of $AgSbF_6$ (10 mol %) under the same reaction conditions, exclusively isocoumarin derivative was observed without the naphthalene derivatives in a highly regioselective manner.

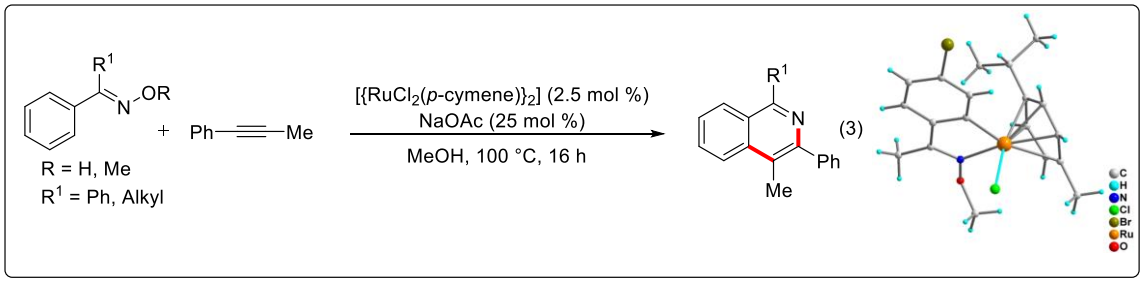


In the reaction, $AgSbF_6$ played an important role to control the regioselectivity of the reaction and also completely suppressed the formation of decarboxylative naphthalene derivatives.This

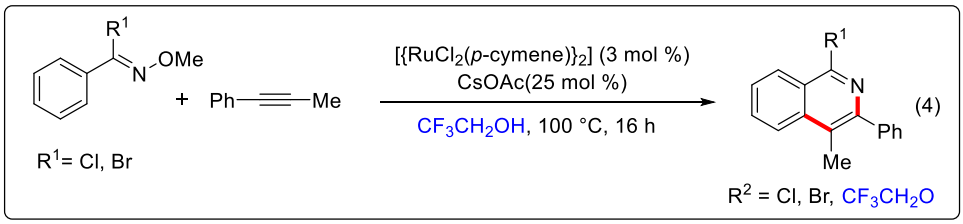
reaction is suitable for all types of substituted aromatic and hetero aromatic acids to synthesis isocoumarin derivatives. The scope of cyclization reaction was further examined with alkenylacids. The cyclization reaction worked efficiently and provided the expected α-pyrone derivatives in good to excellent yields (eq. 2).

Chapter 3 demonstrates the synthesis of substituted isoquinolines, 1-haloisoquinolines, 1-alkoxyisoquinolines and isoquinolones via a ruthenium-catalyzed oxidative cyclization of aromatics with alkynes.

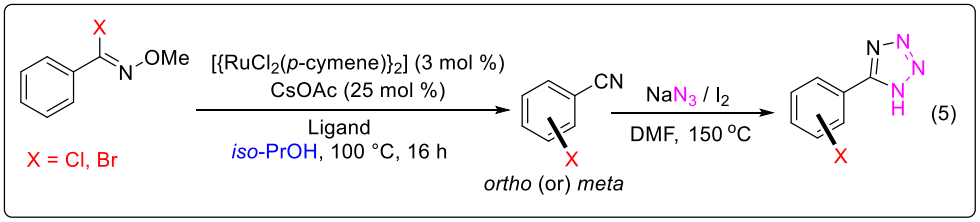
Section 3A: Synthesis of Isoquinolines and 1-Haloisoquinolines: Isoquinoline derivatives are an important class of heterocyclic compounds. This core is present in various biologically active molecules and natural products. Several reports are available in the literature to synthesize isoquinoline derivatives via C-H bond activation; however the control of regioselectivity in the cyclization of ketoximes with unsymmetrical alkynes is still a challenging task. Till now, there is no report discussing the complete regioselective synthesis of isoquinolines by cyclization of ketoximes with unsymmetrical alkynes. We have described a highly regioselective cyclization of aromatic and heteroaromatic ketoximes with substituted alkynes in the presence of catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$] and NaOAc to afford highly substituted isoquinoline derivatives in good to excellent yields. The present catalytic reaction was compatible with various sensitive functional groups substituted unsymmetrical internal alkynes. In all cases, the corresponding isoquinoline derivatives were observed in a highly regioselective manner. It is important to note that terminal alkynes were also compatible for the present reaction. The proposed mechanism of the cyclization reaction was strongly supported by isolation of a key five-membered ruthenacycle intermediate (eq. 3).



Section 3B: Synthesis of 1-Haloisoquinolines, 1-Alkoxyisoquinolines and Isoquinolones: In this section, we have showed for the first time an imidoyl halide (X-C = N-OMe; X = Cl or Br) moiety as a directing group for the cyclization of *O*-methylbenzohydroximoyl halides with substituted alkynes in the presence of a catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$] and CsOAc. In the reaction, various highly substituted 1-haloisoquinoline and 1-alkoxyisoquinoline derivatives are prepared in good to excellent yields in a highly regioselective manner. It is important to point out that the halide groups in the observed 1-haloisoquinoline derivatives can be used for further functionalization (eq. 4).

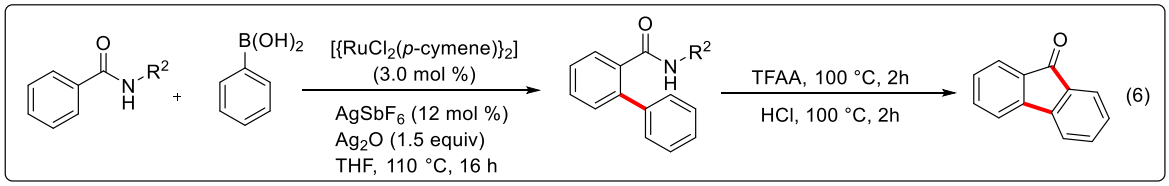


Section 3C: Intramolecular Selective Halogenation of Benzonitriles: In this section, we have described an unprecedented ruthenium-catalyzed intramolecular halogenation at the *meta* and *ortho* carbon position of *O*-methylbenzohydroximoyl halides. The reaction provides an efficient route to *meta* halo substituted aromatic nitriles in good to excellent yields in a highly regioselective manner. In this reaction, for the first time we have described the halogenation at the meta C-H bond of substituted aromatics and also halogenation of aromatics via intramolecular fashion. It is noteworthy to say that the present halogenation reaction is conducted under the base and oxidant free conditions. Further, substituted nitriles were converted into substituted tetrazole derivatives in the presence of NaN_3 and I_2 (eq. 5). It is also important to point out that substituted aromatic nitriles are key structural units in various natural products and also key intermediates for synthesising various pharmaceutically active molecules, agricultural molecules, dyes and organic materials.



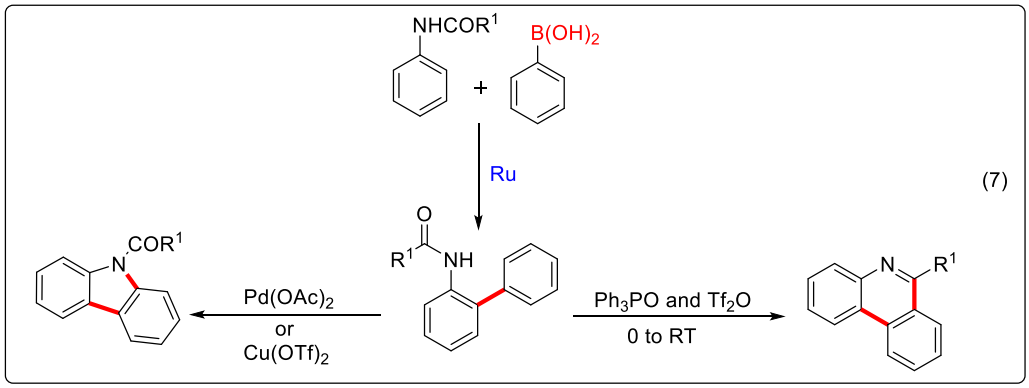
Chapter 4 describes an efficient route to synthesize of tricyclic heterocyclic compounds such as fluorenones, phenanthridine, carbazole and dibenzothiazines via a ruthenium-catalyzed *ortho*-arylation fallowed by intramolecular cyclization of substituted aromatics with phenylboronic acids.

Section 4A: Synthesis of Fluorenones; We have described a highly regioselective mono *ortho*-arylation of *N*-alkyl benzamides with substituted aromatic boronic acids in the presence of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$, and Ag_2O. Biaryl structural unit is present in various natural products, drug and agrochemical molecules, and also key intermediates in various material syntheses. Metal-catalyzed *ortho*-arylation of heteroatom directed aromatics with aromatic electrophiles has been extensively studied in the literature. However, in the reaction of aromatic substrate with aromatic electrophiles, a mixture of mono- and di-arylated compounds were observed. The di-arylated compounds cannot be suppressed in the reaction, but, they can be suppressed by arylation using aromatic organometallic reagents. An *ortho*-alkenylation of *N*-alkyl benzamides with substituted alkenylboronic acids was also shown. To show the synthetic utility of *ortho*-arylated *N*-alkylbenzamides, the *ortho*-arylated *N*-alkyl benzamides were successfully converted into fluorenones in the presence of TFAA and HCl (eq. 6). Fluorenone is an important structural scaffold present in various natural products and biologically active molecules.



Section 4B: Synthesis of Carbazoles and Phenanthridines; *ortho*-Arylated *N*-substituted anilines are key synthetic intermediates for various organic transformations and also for synthesizing heterocyclic moieties. We have described a less coordinating oxygen atom directed *ortho*-arylation of acetanilides with aromatic boronic acids in the presence of a Ru(II) catalyst. The catalytic reaction was compatible with various functional groups such as electron-rich, electron-deficient and halogen substituted aromatic anilides and aromatic boronic acids. In the reaction, no diarylated products or *N*-arylated acetanilides were observed. Later, *ortho*-arylated anilides were converted phenanthridine derivatives *via* intramolecular cyclization of *ortho*-

arylated acetanilides in the presence of Ph_3PO and Tf_2O. In the meantime, *ortho*-arylated anilides were converted into highly useful carbazole derivatives in presence of palladium and copper catalysts (eq. 7). It is important to note that the phenanthridine and carbazole scaffolds are present in natural products and biologically active molecules.



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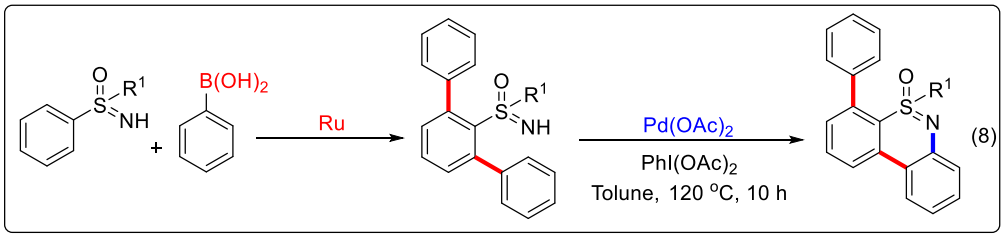
Section 4C: Synthesis of Dibenzothiazines: Sulfoximine is a pivotal structural motif which is present in various biologically active molecules, pharmaceuticals and agrochemicals. The sulfoximine derivatives are also successfully used as chiral auxiliaries and ligands in asymmetric synthesis of various chiral organic molecules. In all previous reports, sulfoximine containing bicyclic benzothiazine derivatives were synthesized efficiently. We have disclosed the synthesis of tricyclic dibenzothiazines by a ruthenium-catalyzed *ortho*-arylation of phenyl sulfoximines with aromatic boronic acids followed by a palladium-catalyzed intramolecular cyclization in two consecutive steps. The present reaction was compatible with various sensitive and useful functional group substituted phenyl sulfoximines and aromatic boronic acids. An enantioselective version of *ortho*-arylation of phenyl sulfoximines with phenylboronic acids followed by cyclization, and this transformation leads to chiral dibenzothiazines with an excellent ee ratio of 99% (eq. 8).



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List of Publications

1. **Ravi Kiran Chinnagolla** and Masilamani Jeganmohan* *"Ruthenium-Catalyzed Regioselective Cyclization of Aromatic Ketones with Alkynes: An Efficient Route to Indenols and Benzofulvenes" Eur. J. Org. Chem.* **2012**, 417-423.

2. **Ravi Kiran Chinnagolla** and Masilamani Jeganmohan* *"Regioselective Synthesis of Isocoumarins by Ruthenium-Catalyzed Aerobic Oxidative Cyclization of Aromatic Acids with Alkynes*" *Chem. Commun.* **2012**, *48*, 2030-2032.

3. **Ravi Kiran Chinnagolla**, Sandeep Pimparkar and Masilamani Jeganmohan* "*Ruthenium-Catalyzed Highly Regioselective Cyclization of Ketoximes with Alkynes by C-H Bond Activation: A Practical Route to Synthesize Substituted Isoquinolines" Org. Lett.* 2**012**, *14*, 3032-3035.

4. **Ravi Kiran Chinnagolla** and Masilamani Jeganmohan* "*Regioselective ortho-Arylation and Alkenylation of N-Alkyl Benzamides with Boronic acids via Ruthenium-Catalyzed C-H Bond Activation: An Easy Route to Fluorenones Synthesis*" *Org. Lett.* 2**012**, *14*, 5246-5249.

5. **Ravi Kiran Chinnagolla**, Sandeep Pimparkar and Masilamani Jeganmohan* *"Ruthenium-Catalyzed Intramolecular Selective Halogenation of O-Methylbenzohydroximoyl halides: A New Route to Halogenated Aromatic nitriles" Chem. Commun.* **2013**, *49*, 3146-3148.

6. **Ravi Kiran Chinnagolla**, Sandeep Pimparkar and Masilamani Jeganmohan* "*A Regioselective Synthesis of 1-Haloisoquinolines via Ruthenium-Catalyzed Cyclization of O-Methylbenzohydroximoyl halides with Alkynes*." *Chem. Commun.* **2013**, *49*, 3703-3705.

7. **Ravi Kiran Chinnagolla** and Masilamani Jeganmohan* "*Ruthenium-Catalyzed ortho-Arylation of Acetanilides with Aromatic Boronic acids: An Easy Route to Prepare Phenanthridines and Carbazoles*" *Chem. Commun.* **2014**, *50*, 2442-2444.

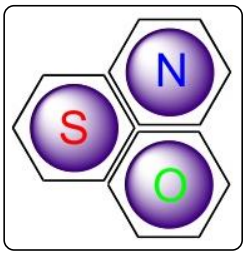
8. **Ravi Kiran Chinnagolla**, Arjun Vijeta and Masilamani Jeganmohan* "*Ruthenium- and Palladium-Catalyzed Consecutive Coupling and Cyclization of Aromatic Sulfoximines with Phenylboronic acids: An Efficient Route to Dibenzothiazines*" *Chem. Commun.* **2015**, *51*, 12992-12995.

9. **Ravi Kiran Chinnagolla**, Arjun Vijeta and Masilamani Jeganmohan* "*Palladium-Catalyzed Cyclization of Aromatic Sulfoximines with Arynes: An Easy Route to Dibenzothiazines*" manuscript under submission.

Table of Contents

Section 4C: Ruthenium- and Palladium-Catalyzed Consecutive Coupling and Cyclization of Aromatic Sulfoximines with Phenylboronic acids: An Efficient Route to Dibenzothiazines

Chapter-1



Synthetic Methods for Heterocyclic Compounds and their Importance

Synthetic Methods for Heterocyclic Compounds and their Importance

1.0 Introduction:

Heterocyclic molecules are highly essential for life process. Literature survey clearly revealed that scientifically the history of heterocyclic chemistry has been started in the period of 18th century and afterwards gained tremendous attention in organic chemistry.[1] In fact, two thirds of organic compounds that known in the literature are heterocyclic molecules. Heterocyclic compounds usually contain at least one hetero atom such as sulfur, oxygen, nitrogen, selenium, etc within the skeleton of organic molecules.[2] In addition, a ring with only carbon and hydrogen atoms is named as carbocyclic compounds and a ring with only heteroatoms without carbon atom is called homocyclic compound. The incorporation of oxygen, nitrogen, sulfur or other heteroatoms into the organic structural moiety in place of a carbon atom gives a wide variety of heterocyclic molecules (Fig. 1.0).[3]

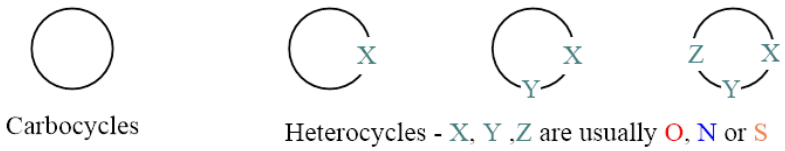


Fig. 1.0 Heterocyclic structures

Heterocyclic compounds are generally classified into two types such as *aliphatic* and *aromatic heterocycles*. The aliphatic heterocycles are the cyclic analogues of amines, ethers, thio ethers and amides. These compounds usually contain of small (3- to 4-cyclic systems) and common (5 to 7 cyclic systems) ring systems.[4a-b] The aromatic heterocyclic compounds almost behaves like benzene derivatives in terms of properties and reactivity. Mostly, these analogs also obey with the general rule proposed by Huckel.[4c] The heterocyclic compounds normally have a stable ring which are not simply cleaved by other sources. Generally, stable heterocyclic compounds having one heteroatom within the ring. The heterocyclic molecules having two or more heteroatoms are more likely as highly reactive species as compared with one hetero atom containing hetero aromatic molecules.

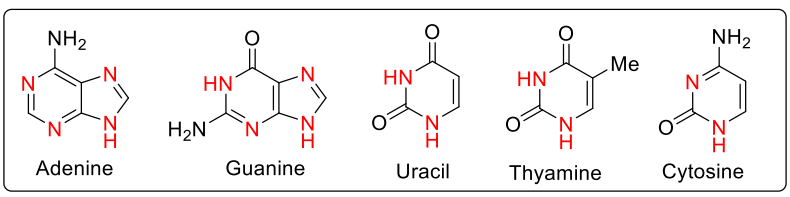


Fig. 1.1 Purines & Pyrimidines

Heterocycle skeletons are enormously found in natural products and biologically active molecules and also the basic subunit of biological molecules such as DNA and RNA. DNA and Nucleotides are the building blocks of generating genes and pyrimidine and purine ring structures are present these biological molecules (Fig. 1.1).[5]

Heme (a large heterocyclic porphyrin ring) is an essential core unit of chlorophyll and hemoglobin which acts as a carrier of oxygen in plants and animals, respectively (Fig 1.2).[5a]

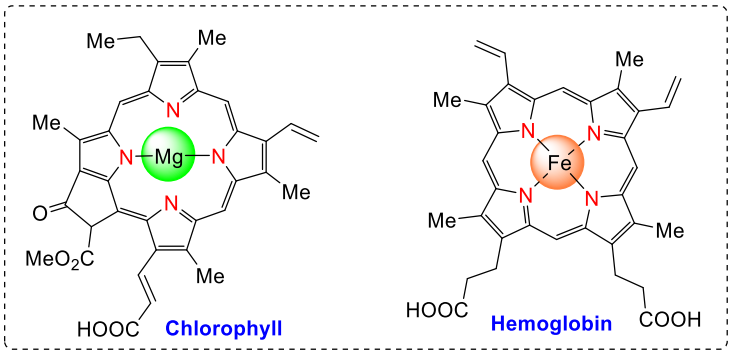


Fig. 1.2 Macromolecules

Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, biomolecules and biologically active molecules including antitumor, anti-inflammatory, antibiotic, antimalarial, antidepressant, anti-HIV, antibacterial, antimicrobial, antiviral, antifungal, antidiabetic, fungicidal, herbicidal and insecticidal agents. Also, it has been generally found as an essential structural unit in synthetic pharmaceuticals and agrochemicals. Thus, the development of highly efficient and easily applicable method to synthesize heterocyclic molecules is always highly important in organic synthesis.

1.1 Nitrogen Heterocycles and Importance:

The nitrogen atom containing heterocycles whether it is natural or synthetic one is always highly important in organic chemistry due to their exciting biological properties. Many synthetic nitrogen heterocycles such as indole, carbazole, pyridine, quinoline, isoquinoline, phenanthridines, quinolone, isoquinolone and phenanthridones (Fig. 1.3) shows various biological activities such antibacterial, antiviral, antifungal, antioxidants, anti- inflammatory, analgesics, anticancer, anticonvulsants sedatives, hypnotics agents, etc. In addition, several

pesticides and insecticides having this type of core subunits. Certain nitrogen heterocycles are used as anti AIDS agents and has been found to be a potent inhibitor of HIV reverse transcription.[6a]

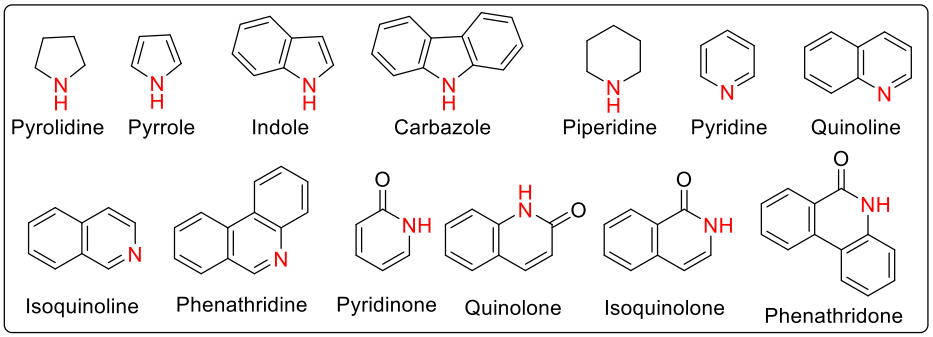


Fig. 1.3 Nitrogen heterocycles

The pyridine ring is one of the most important units of heterocycles in drug discovery. This core unit is present in more number of marketed drugs including the blockbuster drugs such as esomeprazole (Nexium) and loratadine (Claritin). In addition, quinoline containing heterocyclic compounds is used for the treatment of malaria. Structural alteration of quinoline moiety led to the powerful and inexpensive 4-aminoquinoline drug, chloroquine (CQ), and other related drugs (Fig. 1.4). In addition, nitrogen contains natural products such as isoquinoline, phenthridine, phenathridone and carbazole ring containing papavarine, sanguinarine, oxyavicine and tubingensin-A are useful for the treatment of smooth muscle relaxation, antibacterial, anti-inflammatory, antiviral and anticancer, respectively (Fig. 1.4).[6b-c]

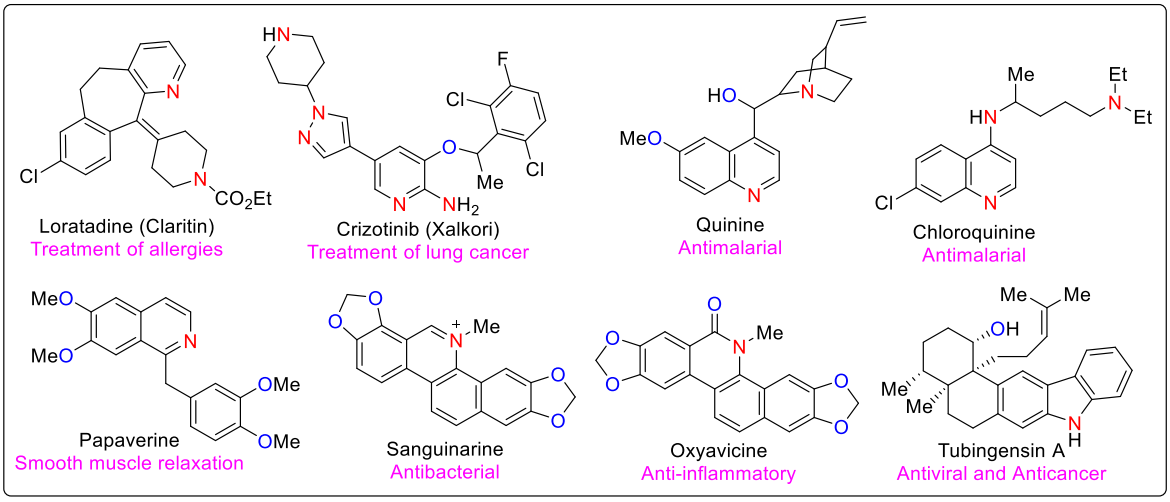


Fig. 1.4 Nitrogen containing natural products

1.2 Oxygen Heterocycles and Importance:

Oxygen atom containing heterocycles such as furan, α-pyrone and its benzo-fused oxygen heterocycles are found as a key structural unit in various natural products, pharmaceuticals and biologically active molecules (Fig. 1.5). Particularly, oxygen atom containing heterocycles such as furan, benzofuran, coumarin, isocoumarin and dibenzoisocoumarins are of great synthetic importance in various fields.[7a-b]

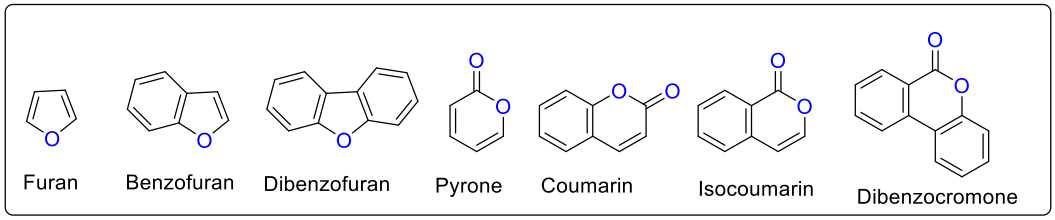


Fig. 1.5 Oxygen heterocycles

These molecules have great medicinal importance for curing various diseases such as anti HIV (coriandrine), antifungal (3-Methyl-6-methoxy-8-hydroxy-3,4-dihydro-isocoumarin), antitumor (cytogenin), phytotoxic (glomellin), antidiabetic (arnotin), anti-inflammatory (erythrocentaurin), antimicrobial (phylloducinol), antiallergic (thunberginol B), and anticancer activities (Fig. 1.6). A five as well as six membered containing lactones are also found in numerous natural products and biologically active molecules.[7c-g]

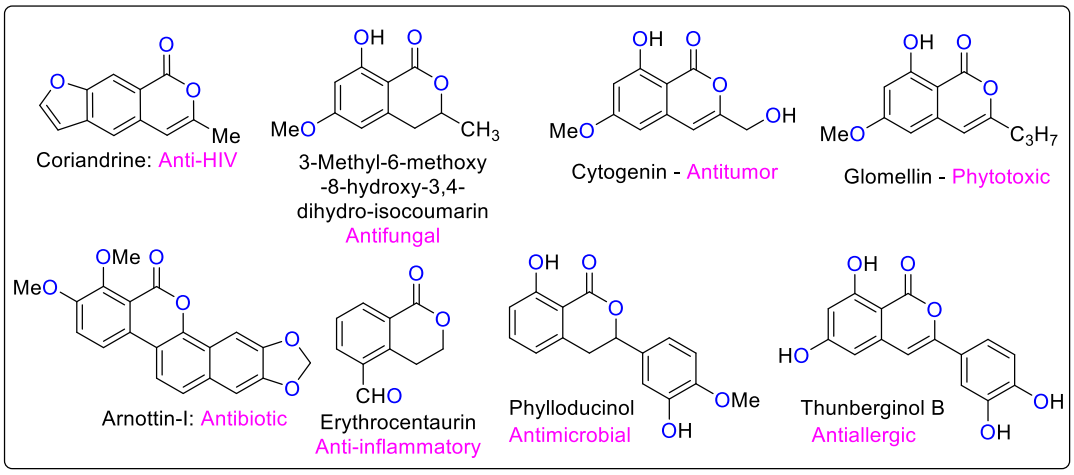


Fig. 1.6 Naturally occurring isocoumarin derivatives

1.3 Synthetic Methods for Heterocyclic Compounds

Synthetic chemistry is the science of constructing complex molecules from the simply available starting materials. It is probable to divide it into two great landscapes: the total synthesis, where

the synthetic chemists study how step by step it is possible to build a structure usually with biologically importance, and the methodologies which introduce new reactions. Our interest is focusing on the development of new methodologies for the construction of heterocyclic and carbocyclic molecules *via* a metal-catalyzed C-X (coupling reactions) and C-H bond (C-H bond activation).

1.3.1 Coupling Reactions Method:

The transition-metal catalyzed cross-coupling cyclization of halo substituted organic molecules into carbon-carbon π-components is of great interest in organic synthesis. For this type of reaction, various metal complexes such as palladium, nickel, cobalt, rhodium etc. are widely used. Among them, a palladium-catalyzed intermolecular annulation of alkynes is most effective for the synthesis of a variety of heterocycles.[8a-d] The reaction usually takes place starting from an organic halide bearing a neighboring heteroatom, which is oxidative palladated of R-X bond to provide R-Pd-X **I**, After subsequent ciscarbopalladation of the alkyne leading to **II**, the internal nucleophile may affect intramolecular displacement of the palladium towards heterocycle, probably by prior formation of a palladacycle **III** and reductive elimination (Fig. 1.7).[8e]

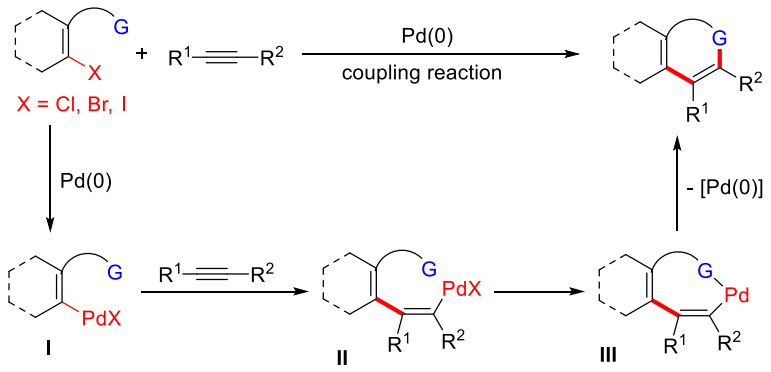


Fig. 1.7 Mechanism of coupling reaction

Among the established methodologies, the inter-molecular palladium-catalyzed reaction of *ortho*-iodoaromatic derivatives with internal alkynes (Larock's intermolecular cyclization reaction) has proven as a powerful procedure for the preparation of mono and bi cyclic heterocyclic molecules in a highly regioselective manner.[8c] By applying this methodology, various heterocyclic molecules including indoles, 1,2-dihydroisoquinolines, benzofurans, benzopyrans, isoquinolines and isocoumarins were prepared in a highly regioselective manner.[8d] Although this type of coupling reactions are very powerful method to synthesize heterocyclic

compounds, but a pre-activated coupling partner such as organic halides (C-X or C-Y) and organometallic reagents (R-M-X) are usually required as a starting material. A pre-activated species such as X or Y is wasted at end of the reaction. If a similar type of reaction is carried out directly by the C-H bond of the aromatic moiety instead of an organic halides C-X or organometallic reagents C-M, it would be highly useful in organic chemistry as well as heterocyclic chemistry. Because, this method would be a highly atom- and step economical as well as an environmentally friendly process.[9]

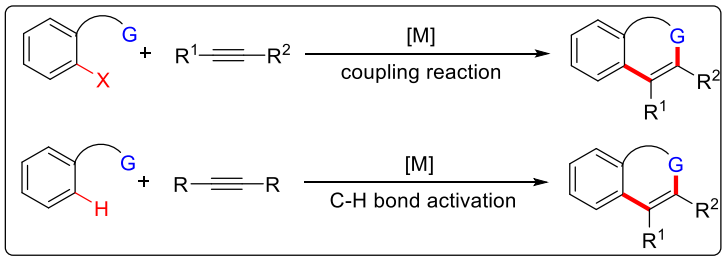
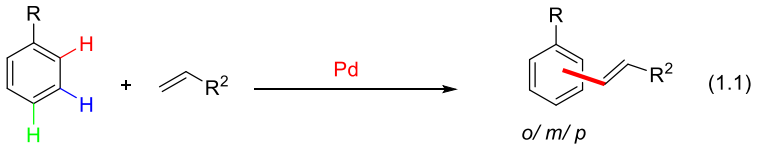


Fig. 1.8 Synthesis of heterocyclic compounds

1.3.2 C-H Bond Activation Method

C-H bond activation method is one of the most attractive alternative methods for the synthesis of heterocyclic compounds from the easily available starting materials. Several methods are available in the literature to activate the C-H bond of aromatics in the presence of metal catalysts.[10] But, activating the C-H bond selectively in a controlled and regioselective manner is a big challenge. For example, Fujiwara-Moritani reaction gave a mixture of regio isomeric products in the presence of a palladium complex. The reaction of substituted aromatics with substituted olefins provided mixture of *ortho*-, *meta*-, *para*- alkenyled products in presence of a palladium complex (eq. 1.1).[10a-d] However, this type of regioselective C-H bond activation can be achieved by a chelation-assisted metalation pathway.



1.3.3 Chelation-Assisted C-H Bond Activation:

Metal-catalyzed chelation-assisted C-H bond activation is a highly regioselective method for activating the C-H bond of organic molecules in a highly selective manner. Generally, a

heteroatom such as a nitrogen or an oxygen containing chelating group is required on the aromatic moiety to activate the C-H bond in a highly regioselective manner. The heteroatom of the directing group chelates with a metal complex *via* either σ or π bond and allows bringing the *ortho* C-H bond of aromatics in close proximity to the active metal complex. During this time, the C-H bond activation takes place very selectively at the *ortho* position of directing group providing a five membered metallacycle intermediate. Later on, the carbon-carbon π-components undergoes coordinative insertion into M-C bond provides 7-membered cyclic intermediate followed by reductive elimination providing functionalization compound (Fig. 1.9).[11]

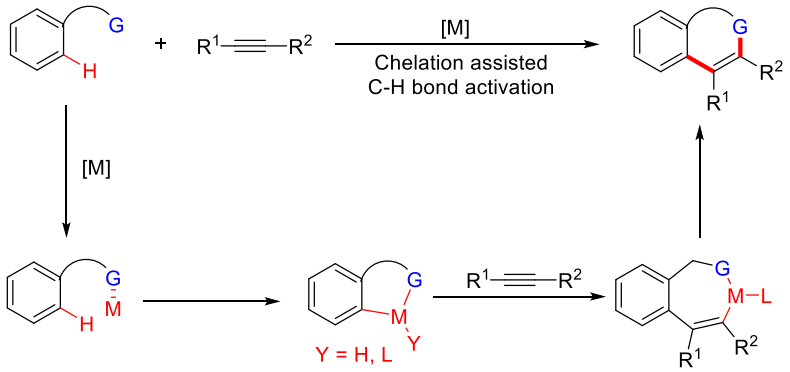


Fig. 1.9 Chelation assisted C-H bond activation

Recently, heterocyclic compounds are efficiently prepared by a metal-catalyzed chelation-assisted cyclization at the C-H bond of substituted aromatics with carbon-carbon π-components without having any pre-functionalized starting material on the aromatic moiety. In particular, nitrogen-based functional groups such as 2-pyridinyl, amide, anilide, azo and oxime substituted aromatics easily reacts with metal complexes form well-defined cyclometalated metal complexes efficiently. Nitrogen-containing functional groups provide azo-cyclic heterocyclic compounds from highly reactive nitrogen cyclometalated intermediates. Aromatic compounds with oxygen-containing functional groups including ketones, aldehydes, carboxylic acids and alcohols are commonly available organic molecules which provide oxo-cyclic heterocyclic compounds. However, oxygen-containing functional groups chelating capacity is very weak with a metal complex as compared with nitrogen atom containing chelating groups. Generally, oxygen-containing functional groups is called as week directing groups and nitrogen containing directing groups is called as strong chelating groups. By employing this methodology, a variety of carbocyclic and polycyclic heterocyclic compounds were prepared (Fig. 1.10).[12]

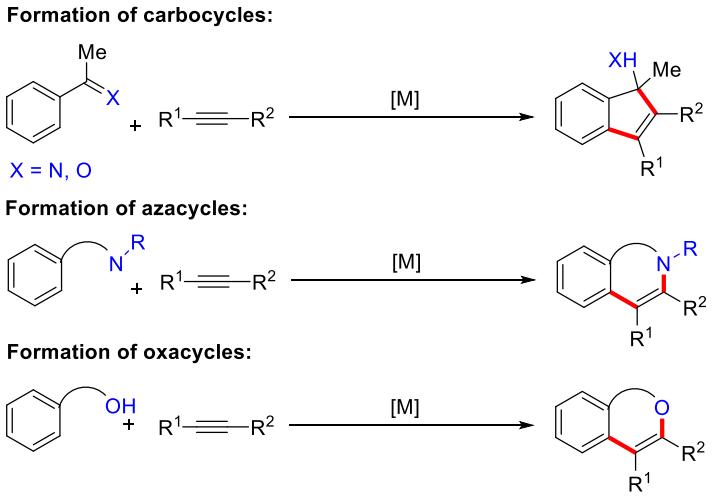


Fig. 1.10 Synthesis of heterocyclic compounds

Chelation-assisted C-H bond activation generally classified into two types based on the formation of a five membered metallacycle intermediate; a) oxidative addition pathway and b) deprotonation pathway. (a) In the oxidative addition pathway, the heteroatom of the directing group chelate with a metal complex and followed by the oxidative addition of metal in to the *ortho* C-H bond of aromatics provide a five membered hydrometallacycle (R-M-H) intermediate. (b) In the deprotonation pathway, the heteroatom of the directing group chelate with a metal complex and metal contain base deprotonates the *otho* C-H bond provide a five membered metallacycle intermediate without having a metal hydride intermediate. It is important to note that in the deprotonation pathway; generally a carbonate or acetate base is required to deprotonate the *ortho* C-H bond of organic moiety. In the oxidative addition pathway, a metal species undergoes an oxidative addition with an *ortho* C-H bond of aromatic moiety and providing a hydrometallacycle intermediate. Generally, M(0) or M(I) metal complexes are widely used as a catalysts in oxidative addition pathway and $M(II)(OR)_2$ or $M(III)(OR)_2$ catalysts are most favor catalysts for deprotonation pathway (Fig. 1.11).[13]

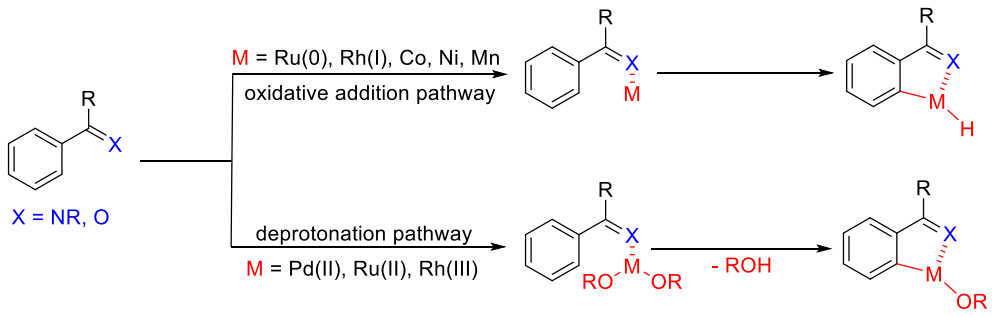


Fig. 1.11 Chelation-assisted *ortho* C-H bond activation pathways

(a) Oxidative Addition Pathway:

Chelation-assisted *ortho* C-H bond activation *via* an oxidative addition pathway provides mechanistically a five-membered metallacycle hydride intermediate. These metallacycle hydride intermediates were further converted into various useful organic molecules *via* coupling reactions with organic halides or organometallic reagents and addition reaction with carbon-carbon multiple bonds such as alkynes or alkenes (Fig. 1.12).[14]

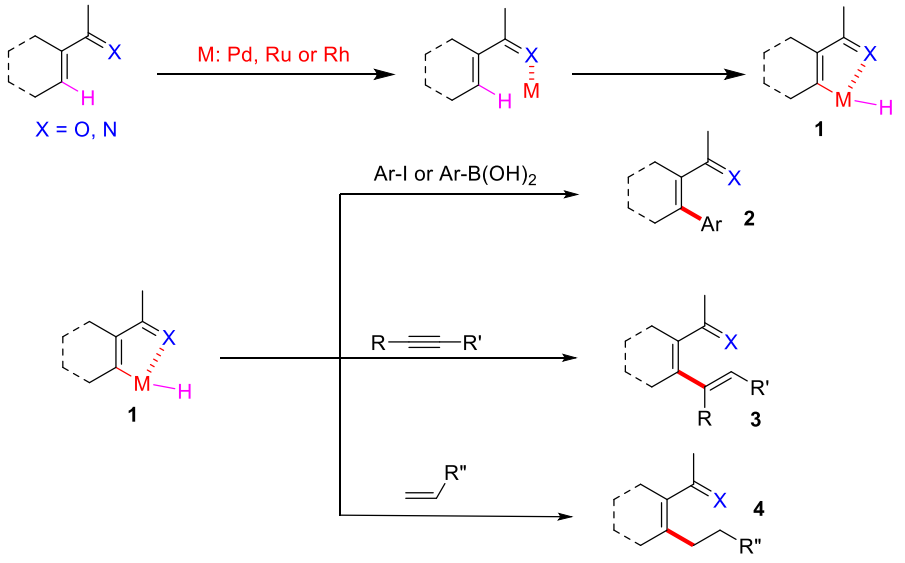
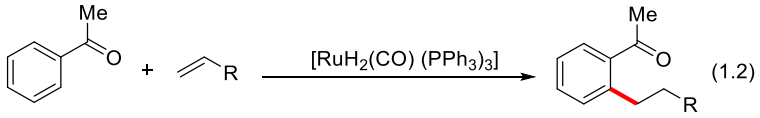


Fig. 1.12 β-Functionalized-α,β-unsaturated ketones in oxidative addition pathway

In 1993, for the first time, Murai's group reported a ruthenium-catalyzed chelation-assisted *ortho* alkylation of aromatic ketones with alkenes *via* C-H bond activation. In the reaction, aromatic ketones reacted with alkenes in the presence of $[RuH_2(CO)(PPh_3)_3]$, giving *ortho* alkylated aromatic ketones in a highly regioselective manner (eq. 1.2).[14a] This reaction proceeds *via* a chelation-assisted oxidative addition pathway.



Later, the same group described an *ortho* alkenylation of aromatic ketones with alkynes in the presence of a ruthenium catalyst (eq. 1.3).[14b] The *ortho* alkenylation reaction proceeds via a chelation-assisted oxidative addition of the *ortho* C-H bond of the aromatic ketone with a

ruthenium catalyst providing a five-membered hydrometallacycle intermediate **II**. Later, an alkyne undergoes coordinative insertion into a ruthenium-hydride bond of intermediate **II** provides 7-membered cyclic intermediate **III** followed by reductive elimination of intermediate **III**, providing a *ortho* alkenylaromatic ketone derivatives and regenerates an active Ru(0) catalyst for the next catalytic cycle. However, this type of hydroarylation reaction is not completely regio- and stereoselective. Mostly, a mixture of regio- and stereoisomeric substituted alkenes was observed. For example, the aromatic ketone reacted with the unsymmetrical alkyne, 1-phenyl-1-propyne, in the presence of a ruthenium catalyst, yielding a mixture of *cis* and *trans* stereoisomeric trisubstituted alkenes (Fig. 1.13).[14]

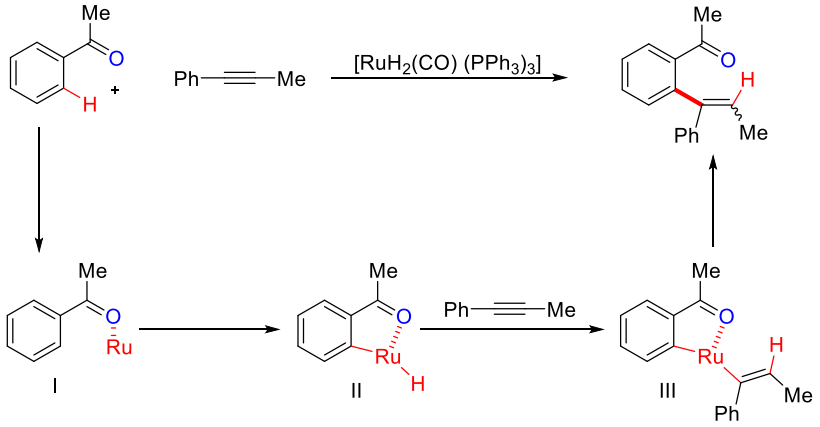
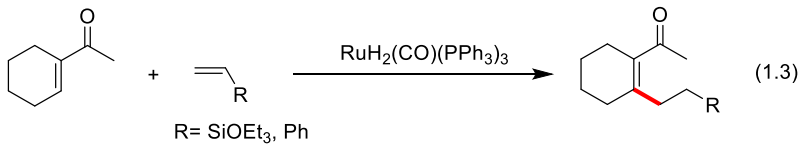
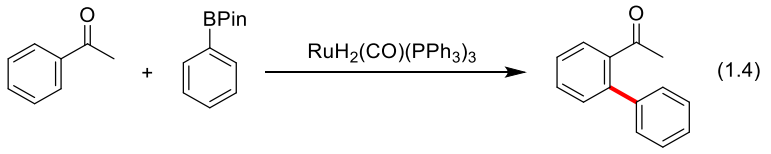


Fig. 1.13 *ortho*-Alkenylation of aromatic ketones in oxidative addition pathway

In 1994, Murai and coworkers described a ruthenium-catalyzed β-alkylation of α,β-unsaturated ketones with triethoxyvinylsilanes. The β-alkylation reaction of 1-acetylcyclohexenes with triethoxyvinylsilanes providing the corresponding β-alkyl-α,β-unsaturated ketone coupling products (eq. 1.3).[15a]

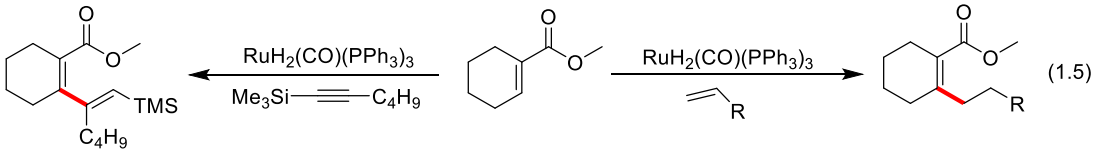


Later, the same group has reported *ortho*-arylation of aromatic ketones with phenylboronic acid pinacol esters in presence of a ruthenium catalyst (eq. 1.4).[15b]



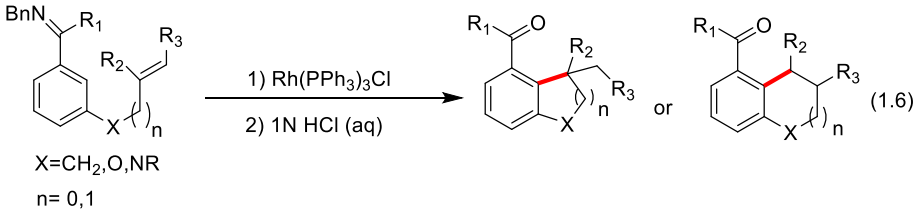
(1.4)

Subsequently, Trost and coworkers showed that methyl 1-cyclohexenecarboxylates reacted efficiently with alkenes as well as silylalkynes in the presence of a ruthenium catalyst giving the desired products in good to excellent yields (eq. 1.5).[15c]



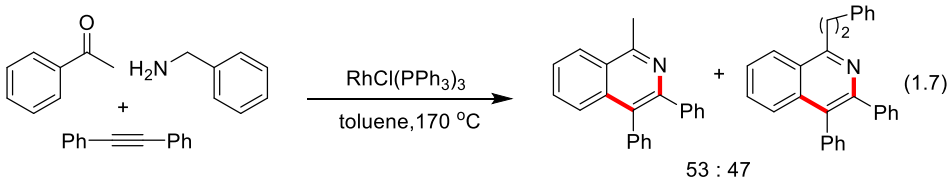
(1.5)

In this regard, metal-catalyzed chelation-assisted *ortho* alkenylation of substituted aromatics with alkenes is well explored in the literature. Recently, cyclization of substituted aromatics with alkynes has gained much attention to synthesize valuable heterocyclic compounds. Ellman and coworkers reported an intramolecular cyclization reaction of aromatic imines having internal alkene *meta* to the imine. The cyclization reaction of the aromatic ketimines in the presence of $RhCl(PPh_3)_3$ catalyst afforded annulation products in a highly regioselective manner. This intramolecular reaction can provide linear as well as branched coupling products depending on the alkene substituent (eq. 1.6).[16a]

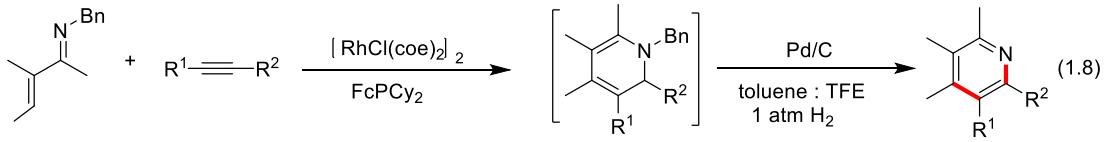


(1.6)

In 2003, Jun's group for the first time reported the synthesis of isoquinoline derivatives via transition metal-catalyzed chelation-assisted oxidative addition pathway. In the reaction, aromatic ketimines added with alkynes followed by intramolecular electrocyclization provided isoquinoline derivatives in the presence of a rhodium catalyst. However, the synthetic utility of this reaction is limited due to the formation of two different types of isoquinoline derivatives in one pot and higher temperature (> 170 ºC) is required for the electrocyclization (eq. 1.7).[16b]



In 2006, Ellman and coworkers described a rhodium-catalyzed synthesis of substituted pyridines from α,β-unsaturated imines and alkynes that proceeds through dihydropyridine intermediate. This method is quite difficult to compare with other available methods as well as pyridine synthesis takes three-step (eq. 1.8).[16c]



Later, Cheng's group reported a new method for the synthesis of highly substituted pyridines and isoquinolines from α,β-unsaturated ketoximes or aromatic ketoximes and alkynes.

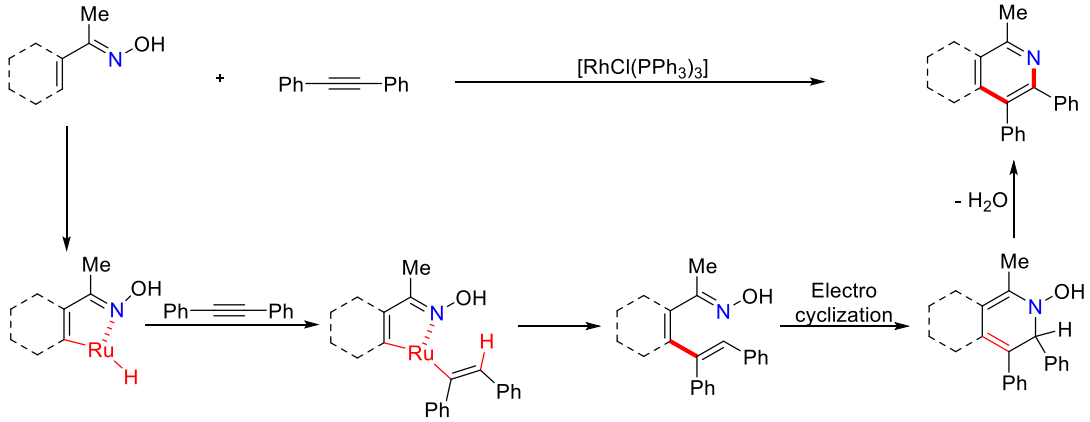


Fig. 1.14 Oxidative addition pathway for cyclization

The present reaction proceeds via a rhodium-catalyzed chelation-assisted *ortho* C-H activation in oxidative addition pathway. The formation of product can be viewed as β-alkenylation of alkenyl oximes or *ortho* alkenylation of aromatic ketoximes to provide a 1-azatriene intermediate, followed by a [4+2] 6π-cycloaddition of Diels-Alder and dehydration (Fig. 1.14).[16d] After that, this type of reactions has been widely explored to synthesize various heterocyclic molecules in the presence of various metal complexes.

(b) Deprotonation Pathway:

In the deprotonation pathway, the heteroatom of the directing group chelates with a metal catalyst have base which deprotonates the *otho* C-H bond provides a five membered metallacycle intermediate (**1**) without forming a metal hydride intermediate. The corresponding five membered metallacycle intermediate was further converted into valuable organic molecules such as alkenylation (**2**), cyclization (**3**) and arylation (**4**) in presence of olefins, aryl halides or phenyboronic acids and alkynes, correspondingly (Fig 1.15).

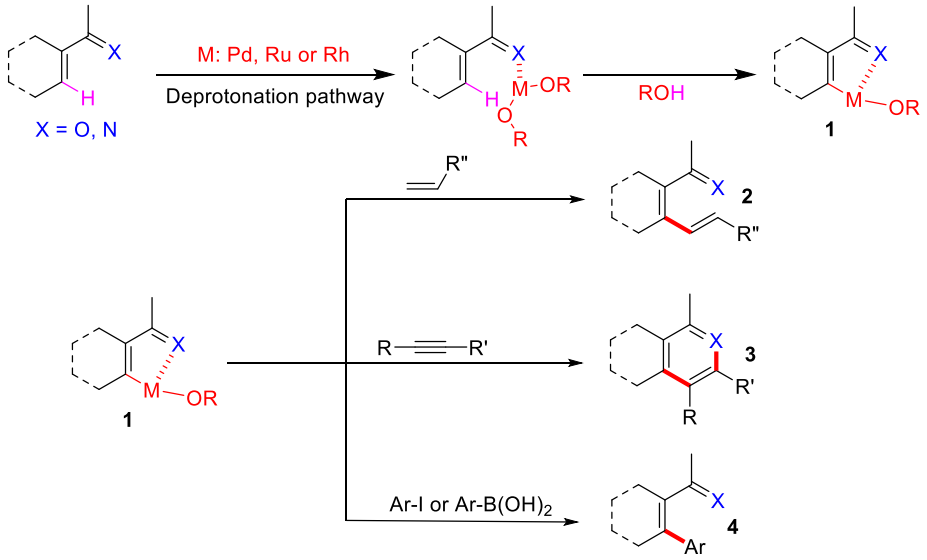
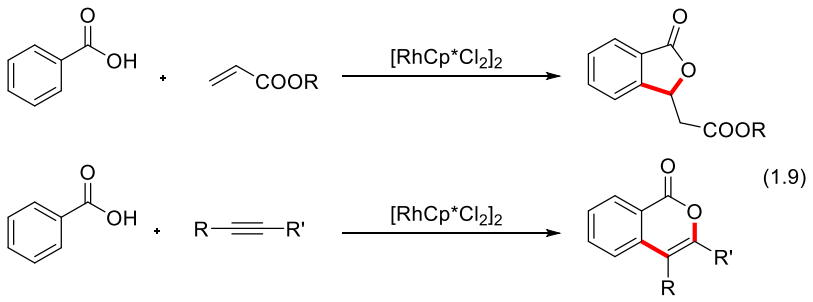


Fig. 1.15 Functionalization in deprotonation pathway

By employing this method, a variety of highly useful carbocyclic and heterocyclic compounds such as isoquinolones, pyridines, isoquinolines, benzofulvenes, naphthalenes, indoles, indenols, pyrroles, quinolines, pyridones, phthalimidines, phthalide and isocoumarines have been synthesized efficiently in one pot. Initially, rhodium complexes are widely used for this type of reactions. A rhodium-catalyzed chelation assisted *ortho* functionalization of aromatics via deprotonation pathway has been fairly studied by several research groups including Bergman, Glorious, Cheng, Chiba, Muira and Fagnou.[17]

In 2007, Miura and Satoh reported the first [RhCp*Cl_2]$_2$-catalyzed olefination followed by oxa-michael cyclization in the coupling of benzoic acids with acrylates. The same group has reported the synthesis of isocoumarin derivatives from the cyclization reaction of benzoic acids with alkynes in the presence of a rhodium complex (eq. 1.9).[18a-c]



(1.9)

Fagnou's group has reported chelation assisted cyclization of *N*-*tert*-butylbenzaldimines with internal alkynes in presence of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ catalyst leading to isoquinoline derivatives via deprotonation pathway (Fig. 1.16).[18d] After that, this type of cyclization reaction has been explored by several groups.

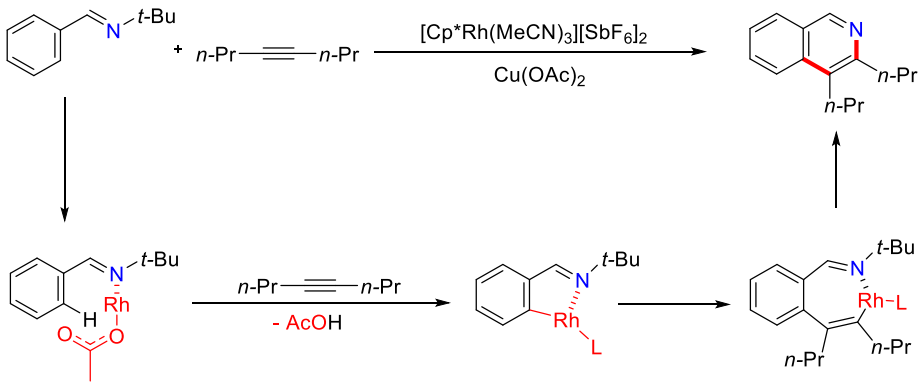


Fig. 1.16 Deprotonation pathway for cyclization

Regioselective issue: In the oxidative cyclization reaction, rhodium complexes are widely used as catalysts. However, most of a rhodium-catalyzed cyclization reaction is not completely regioselective. Particularly, a mixture of regioselective products was observed in case of the reaction of substituted aromatics with unsymmetrical carbon–carbon π-components.

Recently, a less-expensive ruthenium catalysts has gained much attention in this type of cyclization reactions, due to its remarkable reactivity and selectivity.[19] Owing to the extraordinary reactivity and selectivity, $[\{RuCl_2(p\text{-cymene})\}_2]$ complex has been efficiently used as a catalyst for various C-H bond functionalization reactions. Ruthenium(II)-catalyzed arylation of 2-pyridyl, oxazoline, azole and oxime substituted aromatics with aromatic electrophiles has been elaborately studied by Dixneuf and Ackermann research group's.[20] The biaryl structural unit is present in various natural products, drug and agrochemical molecules and also key

intermediates in various material synthesis (Fig. 1.17). However, in all these reported reactions the reaction of symmetrical aromatics with aromatic electrophiles, a mixture of *mono*- and *di*-arylated compounds were observed. The diarylated compounds cannot be suppressed in the reaction, but, it can be suppressed by doing arylation using aromatic organometallic reagents.[20]

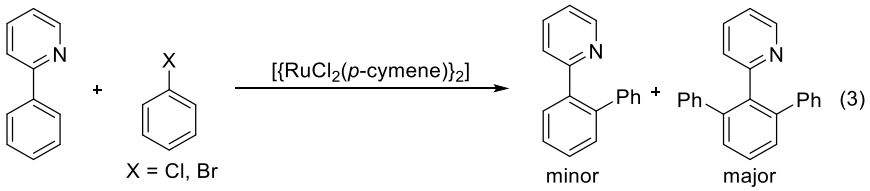
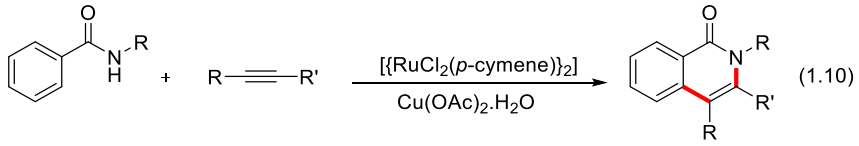


Fig. 1.17 *ortho*-Arylation of 2-phenylpyridine

In 2011, Ackermann's group reported a ruthenium-catalyzed oxidative cyclization of *N*-alkyl benzamides with alkynes providing isoquinolone derivatives. This reaction proceeds via chelation-assisted deprotonation pathway. In the reaction, copper (II) acetate was used as a base to deprotonate the *ortho* C-H bond of aromatic amides (eq. 1.10).[21]



- In a ruthenium-catalyzed cyclization reaction, a better coordinating strong chelating group was used for the C-H bond activation. Till that time, there was no report discussing on the C-H bond activation by using weak oxygen containing cheating groups in the presence of a less expensive ruthenium catalyst. Thus, we have focused our research towards activating C-H bond of organic molecules by using weak oxygen containing chelating groups. In my thesis, I would like to discuss our recent accomplishments of a ruthenium-catalyzed oxidative annulation of aromatic compounds with alkynes through weakly chelation-assisted C−H activation. By employing this methodology, we have prepared a variety of heterocyclic molecules in a highly regioselective manner in good to excellent yields in one pot from easily available starting materials.

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19. The cost of 1 gm of [{$RuCl_2$(*p*-cymene)}$_2$] in Alfa-Asear is $36. Whereas 1gm of [{Cp*$RhCl_2$}$_2$] in Alfa-Asear is $702.

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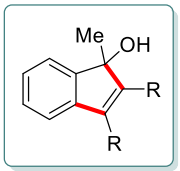
Chapter-2



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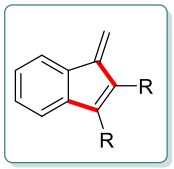

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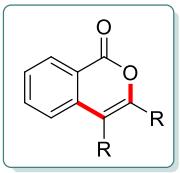

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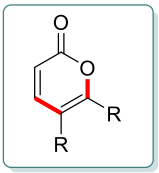


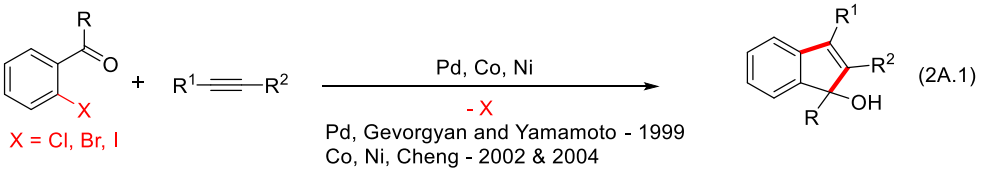
Pyrones

Synthesis of Indenols, Indenes, Isocoumarins and α-Pyrones

Section 2A: Ruthenium-Catalyzed Regioselective Cyclization of Aromatic Ketones with Alkynes: An Efficient Route to Indenols and Benzofulvenes

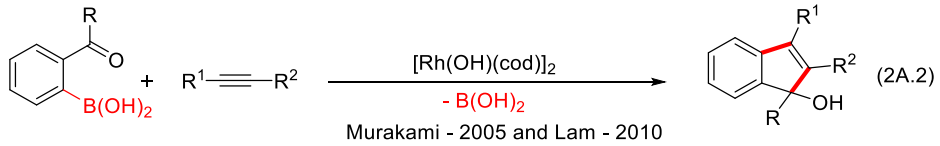
2A.1 Introduction

Transition metal-catalyzed oxidative cyclization reaction is one of the most efficient methods for the synthesis of carbocyclic and heterocyclic compounds in one pot. In the literature, several methods are available for the synthesis of cyclic compounds in the presence of metal catalysts.[1] Of these methods, Gevorgyan's and Yamamoto's groups independently reported the cyclization reaction of *o*-haloaromatic carbonyls with alkynes in presence of palladium catalyst.[2a-b] This method provides powerful synthetic route for the synthesis of cyclic indenole derivatives. Subsequently, Cheng's group reported nickel- and cobalt-catalyzed cyclization of *o*-iodophenyl ketones with alkynes leading to indenole derivatives (eq. 2A.1).[2c-f]



(2A.1)

Later on, Murakami's and Lam's groups described the cyclization of *o*-acylphenylboronic acids with alkynes by using a rhodium complex as a catalyst providing cyclic indenole derivatives (eq. 2A.2).[3]

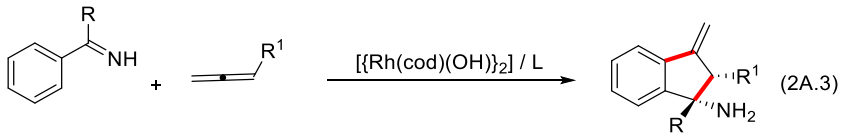


(2A.2)

Generally, in all these carbocyclization reactions, a pre-activated coupling partner such as aryl halides or organometallic reagents are usually required as a starting material to construct carbocyclic and heterocyclic compounds. Instead of pre-activated species, if the cyclization could be carried out by direct C-H bond activation, it would be even very useful in organic synthesis, since it is highly atom-economical as well as environmentally friendly process.[4-6] In this regard, metal-catalyzed chelation-assisted oxidative cyclization of the *ortho* aromatic or alkenyl C-H bond with carbon-carbon π-components has gained considerable attention to

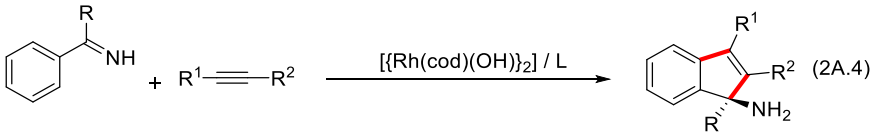
synthesize cyclic compounds in the past five years. In this cyclization reaction, mostly rhodium complexes have been widely used as catalysts by several research groups.[7]

In 2010, Cramer's group reported a rhodium(I)-catalyzed cyclization of aromatic ketimines with allenes giving cyclic 1-methyl-3-methylene-2,3-dihydro-1*H*-inden-1-amine derivatives in an enantioselective version (eq. 2A.3).[8a]



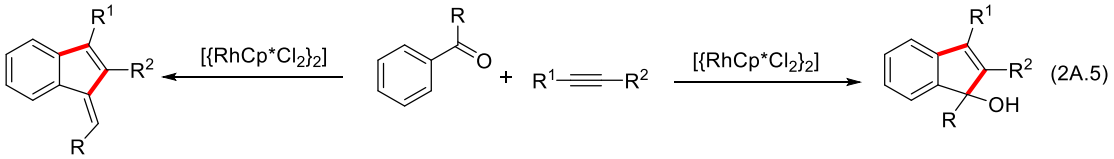
(2A.3)

Later, the same group described an enantioselective rhodium(I)-catalyzed [3+2] cyclization of aromatic ketimines with alkynes providing 1-methyl-2,3-diphenyl-1*H*-inden-1-amine derivatives in good to excellent yields (eq. 2A.4).[8b]



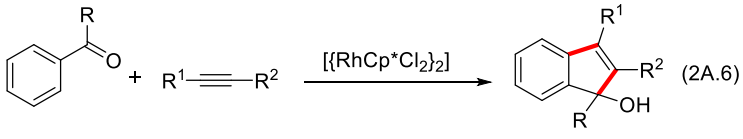
(2A.4)

Recently, Glorious's group showed a rhodium-catalyzed oxidative cyclization of aromatic ketones with alkynes leading to a mixture of cyclic indenol and benzofulvene derivatives. In the reaction, if R^2 is *i*-Pr or electron-withdrawing group, fulvene derivatives were not observed and exclusively indenol derivatives were observed (eq. 2A.5).[8c]



(2A.5)

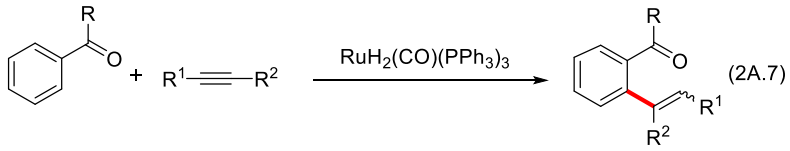
Subsequently, Cheng's group reported the synthesis of substituted indenols from aryl ketones and alkynes by using a rhodium catalyst (eq. 2A.6).[8d]



(2A.6)

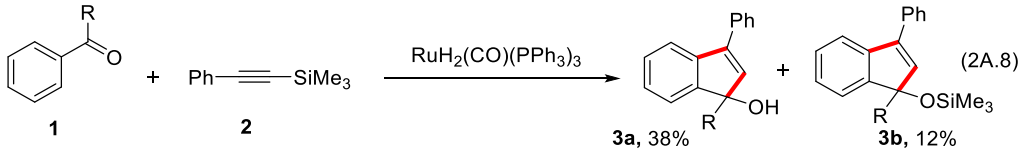
It is very important to note that the most of the rhodium-catalyzed cyclization reaction provides a mixture of regioisomeric products particularly in the case of unsymmetrical alkynes. In addition,

rhodium complexes are highly expensive and not easy to afford. Recently, less-expensive ruthenium catalysts have gained much attention in this type of cyclization reactions, due to their remarkable reactivity and selectivity.[9-10] In 1995, Murai's group reported the reaction of aromatic ketones with alkynes in the presence of $RuH_2(CO)(PPh_3)_3$ catalyst.[11a] However, in the reaction, only *ortho* alkenylated aromatic ketones were observed with a mixture of stereoisomeric products (eq. 2A.7). A similar type of carbonyl directed C-H bond alkenylation reactions with alkynes have also been studied by other research groups.[11]



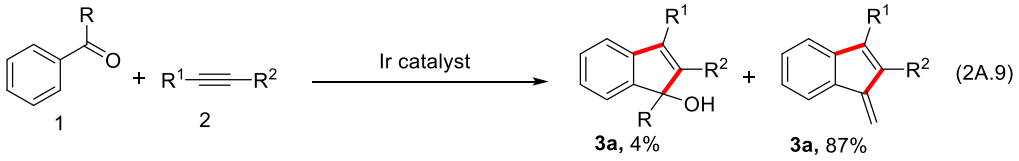
(2A.7)

In 1999, Woodgate's group reported the first example of a ruthenium-catalyzed ketone-assisted cyclization reaction of aromatic ketones with alkynes providing a mixture of cyclic indenol derivatives. In the reaction mixture, products **3a** and **3b** were observed in 38% and 12% yields, respectively, in the reaction of 1-phenyl-2-trimethylsilylethyne with acetophenone (eq. 2A.8).[11b]



(2A.8)

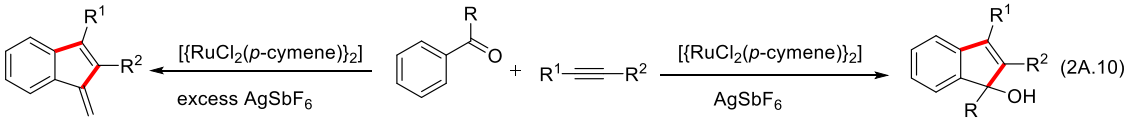
Recently, Shibata and his coworkers reported the synthesis of benzofulvene derivatives in which indenols were obtained as minor products in a different mechanastic pathway. The recation proceeds via a iridium-catalyzed hydroarylation of *ortho* C-H bond of aryl ketones with alkynes followed by cyclization and dehydration (eq. 2A.9).[11c] It is significant that benzofulvene derivatives find the versatile applications in materials science, organometallics and medicinal chemistry.[12]



(2A.9)

Herein, we report a highly regioselective synthesis of cyclic indenol as well as benzofulvene derivatives separately by a [{$RuCl_2$(*p*-cymene)}$_2$]-catalyzed cyclization reaction of aromatic

ketones with alkynes. In this section, I would like to discuss about the highly regioselective cyclization of aromatic ketones with alkynes in the presence of catalytic amount of less expensive ruthenium catalyst [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and $Cu(OAc)_2.H_2O$. This method offers a general method to synthesis of indenols and benzofulvenes in a highly regioselective manner with good to excellent yields (eq. 2A.10).



(2A.10)

2A.2 Results and Discussion

The oxidative cyclization of 4-bromoacetophenone (**1a**) with diphenylacetylene (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (8 mol %), and $Cu(OAc)_2 \cdot H_2O$ (25 mol %), in 1,2-dichloroethane (DCE) at 120 °C for 10 h to give cyclic indenol derivative **3a** in 89% isolated yield (Table 1). Interestingly, only a catalytic amount of oxidant $Cu(OAc)_2 \cdot H_2O$ (25 mol %) was required, whereas in most rhodium-catalyzed reactions stoichiometric amounts of oxidant were used.[7,8] Control experiments revealed that no reaction occurred at all in the absence of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$, or $Cu(OAc)_2 \cdot H_2O$. Note that substituted indenol derivatives are known to show important biological properties such as analgesic, insecticidal, and myorelaxation activity.[13]

2A.2.1 Optimization Studies

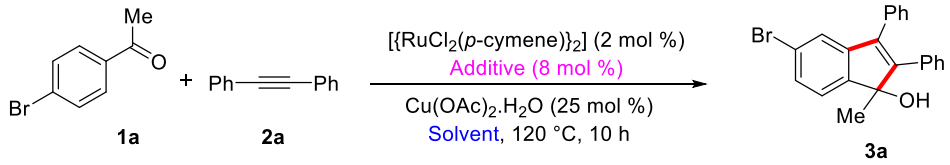


Table 2A.1 Cyclization reaction of 4-bromoacetophenone (**1a**) with diphenylacetylene (**2a**).[a]

Entry	Additive (8 mol %)	Solvent	Yield % (3a)[b]
1	$AgSbF_6$	Tolune	55
2	$AgSbF_6$	THF	25
3	$AgSbF_6$	*tert*-amyl alcohol	15

4	**$AgSbF_6$**	**DCE**	**96**
5	$AgSbF_6$	DMF	nr
6	$AgSbF_6$	CH_3CN	nr
7	$AgSbF_6$	CH_3COOH	nr
8	AgOTf	DCE	40
9	$AgBF_4$	DCE	21
10	AgOAc	DCE	nr
11	AgO_2CCF_3	DCE	nr
12	Ag_2O	DCE	nr

[a]All reactions were carried out using 1a (100 mg), alkyne (2a) (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.02 equiv), Additive (0.08equiv) and $Cu(OAc)_2.H_2O$ (0.25 equiv) in solvent (3.0 mL) at 120 °C for 10 h. [b]GC yield

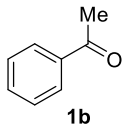
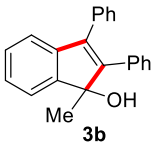
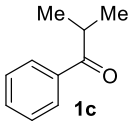
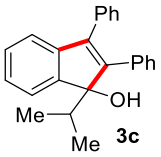
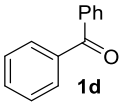
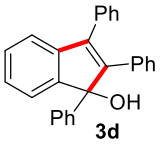
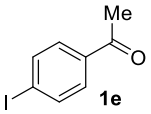
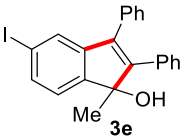
To optimize the present ruthenium-catalyzed cyclization reaction, the reaction of **1a** with **2a** in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %) was examined with various solvents, additives (8 mol %) and oxidants (25 mol %). The reaction was first tested with various solvents. Of the solvents tested, 1,2-dichloromethane (DCE) was most effective, affording **3a** in 96% yield (Table 2A.1, entry 4). The yield of **3a** was determined based on the ^{1}H NMR integration method using mesitylene as an internal standard. Toluene was also effective providing **3a** in 55% yield (entry 1). Other solvents such as THF and *tert*-amyl alcohol were less effective giving **3a** in 25% and 15% yields, respectively (entry 2 and 3). The other solvents such as DMF, CH_3CN and CH_3COOH were totally ineffective for the reaction (entry 5-7). Next, the effect of silver salt (8 mol %) was examined. A variety of silver salts such as $AgSbF_6$, AgOTf, $AgBF_4$, AgOAc, AgO_2CCF_3 and Ag_2O were tested. Among them, $AgSbF_6$ was very effective for the reaction, giving **3a** in 96% yield (entry 4). AgOTf and $AgBF_4$ were less effective giving **3a** in 40% and 21% yields, respectively. Remaining silver salts AgOAc, AgO_2CCF_3 and Ag_2O were totally ineffective for the reaction (entry 10-12).

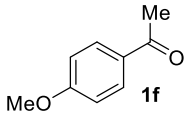
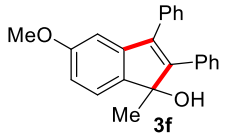
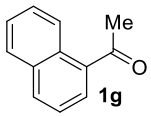
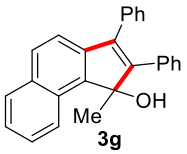
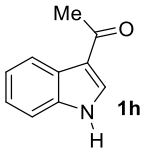
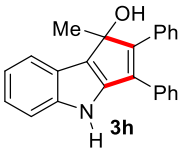
2A.2.2 Synthesis of Indenols

This ruthenium-catalyzed cyclization reaction was successfully extended to different substituted aromatic ketones **1b-h** and substituted alkynes **2b-e** (Table 2A.2). The reaction of acetophenone

(**1b**) with diphenylacetylene (**2a**) under the optimized reaction conditions, i.e., [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (8 mol %) and $Cu(OAc)_2.H_2O$ (25 mol %) in the presence of 1,2-dichloroethane, afforded product **3b** in 83% yield (Table 2A.2, entry 1). Similarly, isobutyroacetophenone (**1c**) and benzophenone (**1d**) reacted with **1a** giving the corresponding cyclization product 3c and 3d in 76% and 73% yields, respectively (entry 2 and 3),. Under similar reaction conditions, 4-iodoacetophenone (**1e**) and 4-methoxyacetophenone (**1f**) worked well with **1a** to afford indenols **3e** and **3f** in 88% and 85% yields, respectively (entry 4 and 5),. The reaction of 1-napthophenone (**1g**) with **2a** provided **3g**, with the C-H bond activation takes place at adjacent carbon to acetyl group of **1g**, exclusively in 82% yield (entry 6),. The present catalytic reaction was also tested with heteroaromatic ketones. Treatment of indole-3-acetophenone (**1h**) with **2a** gave **3h** in 69% yield (entry 7). It is significant that, the present catalytic reaction tolerated a variety of sensitive functional groups such as I, Br, OMe, and NH on the aromatic and heteraromatic rings of **1**.

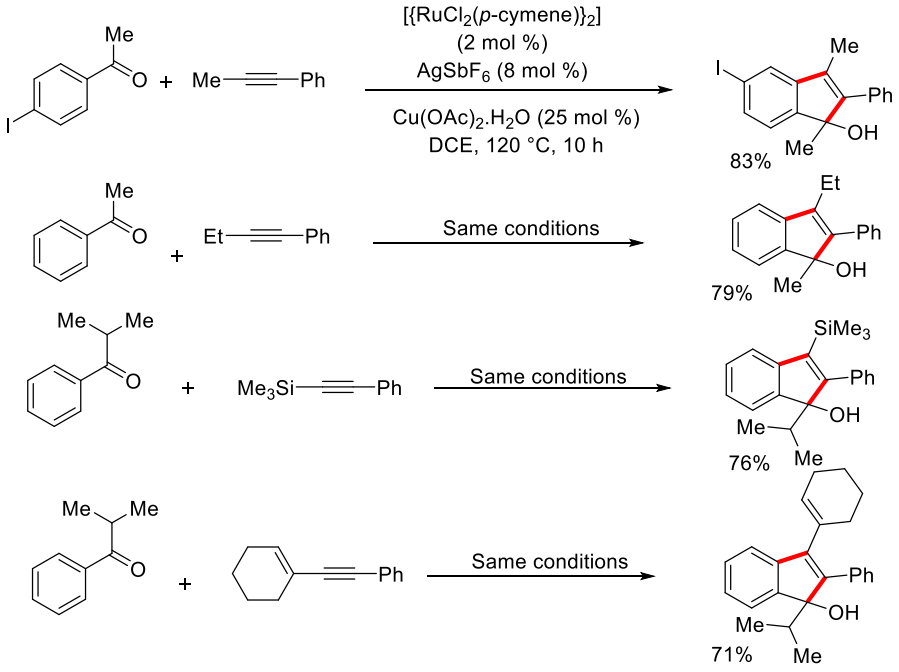
Table 2A.2 Cyclization reaction of substituted aromatic ketones **1b**–**h** with diphenylacetylene (**2a**).[a]

Entry	Aromatic ketone (1)	Compound (3)	Yeild[b]
1	 **1b**	 **3b**	83%
2	 **1c**	 **3c**	76%
3	 **1d**	 **3d**	73%
4	 **1e**	 **3e**	88%

5			85%
6			82%
7			69%

[a]All reactions were carried out with substituted aromatic ketones **1** (1.00 mmol), diphenylacetylene (**2a**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (8 mol %), $Cu(OAc)_2 \cdot H_2O$ (25 mol %), and 1,2-dichloroethane (3.0 mL) at 120 °C for 10 h. [b]Isolated yields.

Next, we examined the reaction of various substituted unsymmetrical alkynes **2b-e** with substituted aromatic ketones **1** (Scheme 2A.1). In all these reactions, complete regioselective cyclic indenole derivatives were observed. Thus, 1-phenyl-1-propyne (**2b**) and 1-phenyl-1-butyne (**2c**) underwent cyclization reaction with 4-iodoacetophenone (**1e)** or acetophenone (**1b**) giving products **3i** and **3j** in 83% and 79% yields, respectively, in a highly regioselective manner (Scheme 2A.1). In the reaction, phenyl group of alkynes placed the next carbon C-2 to alcohol group and alkyl group in C-3 carbon of indenols **3i** and **3j**. The regiochemistry was completely established by NOESY experiments (see the Experimental Section). Similarly, in the reaction of 1-phenyl-2-(trimethylsilyl)acetylene (**2d**) with **1c** provided silylated indenol derivative **3k** in 76% yield in a high regioselective manner in which Ph group was attached to C-2 and silyl group to C-3 of an indenol moiety **3k** (Scheme 2A.1)**.** It is significant that most of the metal-catalyzed chelation-assisted cyclization of *ortho* aromatic C-H bond with **2d** provides only desilylated compounds.[7d, 13] The catalytic reaction was also tested with substituted unsymmetrical enyne **2e**. Substituted enyne **2e** reacted with **1c** to give a single regioisomeric product **3l** in 71% yield in which Ph group present in the C-2 carbon of **3l.** In the cyclization reaction, the alkyne carbon bearing a less electron-donating substituent (Ph) is connected to the keto group of **1** and the alkyne carbon with a more electron-donating substituent (Me, Et and $SiMe_3$) is attached to the *ortho* carbon of aryl ketone moiety (Scheme 2A.1). The present regiochemistry is exactly matching with the regiochemistry observed from the cyclization reaction of *ortho* halophenyl ketones with unsymmetrical alkynes in the presence of cobalt and nickel catalysts.[2a-d]

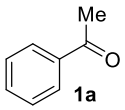
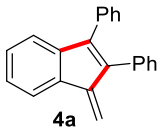
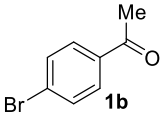
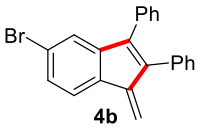
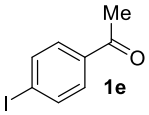
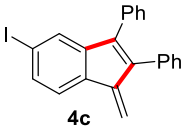
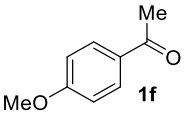
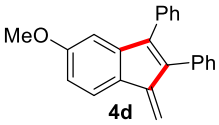
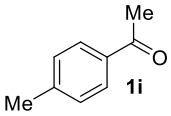
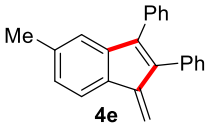
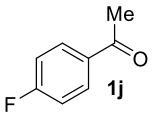
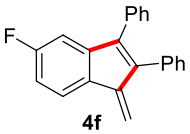
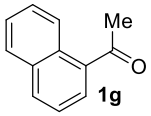
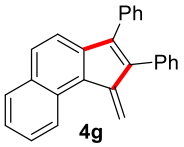
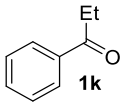
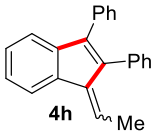
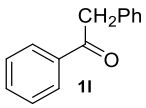
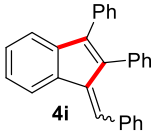


Scheme 2A.1 Scope of the unsymmetrical alkynes **2b-e**

2A.2.3 Synthesis of Indenes

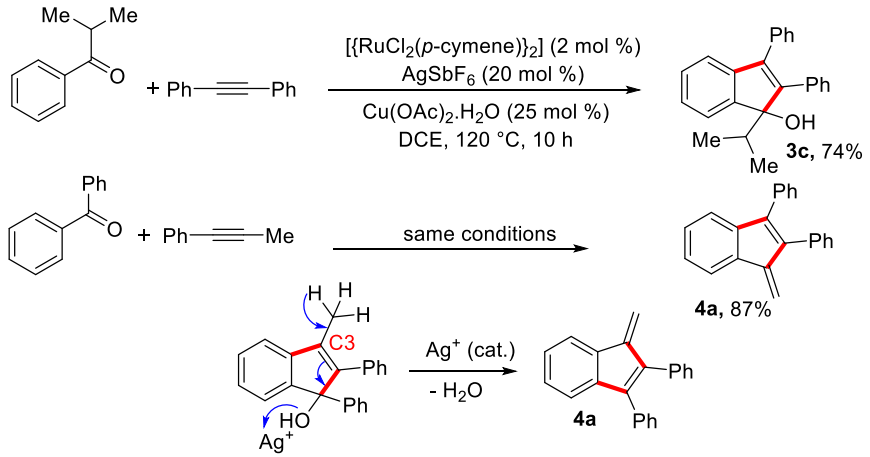
The amount of silver salt plays an important role in the product formation. When the silver salt amount exceeded more than 8 mol % in the presence of 2 mol % of [{$RuCl_2$(*p*-cymene)}$_2$], a different type of dehydration product, benzofulvene derivative started to appear in the reaction. Thus, treatment of Acetophenone (**1a**) with diphenylacetylene (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2.H_2O$ (25 mol %) in 1,2-dichloroethane at 120 °C for 10 h afforded benzofulvene derivative **4a** in 89% isolated yield (Table 2A.3, entry 1) In the presence of excess amount of silver salt (20 mol %), various substituted acetophenones such as 4-bromoacetophenone (**1b**), 4-iodoacetophenone (**1e**), 4-methoxyacetophenone (**1f**), 4-methylacetophenone (**1i**) and 4-fluoroacetophenone (**1j**) efficiently reacted with **2a** to provide benzofulvene derivatives **4b-f** in 86–92% excellent yields (entry 1-6). Similarly, 1-napthophenone (**1g**) afforded **4g** with the C-H bond activation took place at adjacent carbon of acetyl group, exclusively in 80% yield (entry 7). Likewise, propiophenone (**1k**) and 2-phenylacetophenone (**1l**) also efficiently reacted with **2a** to give benzofulvene derivatives **4h** and **4i** in 85% and 82% yields with *E*/*Z* ratios 85:15 and 98:2, respectively (entry 8 and 9).

Table 2A.3 Cyclization reaction of substituted aromatic ketones **(1)** with diphenylacetylene (**2a**).[a]

Entry	Aromatic ketone (1)	Compound (4)	Yeild[b]
1	 **1a**	 **4a**	89%
2	 **1b**	 **4b**	93%
3	 **1e**	 **4c**	91%
4	 **1f**	 **4d**	86%
5	 **1i**	 **4e**	87%
6	 **1j**	 **4f**	92%
7	 **1g**	 **4g**	80%
8	 **1k**	 **4h**	85% (85:15)
9	 **1l**	 **4i**	82% (98:2)

[a]All reactions were carried out with substituted aromatic ketones **1** (1.00 mmol), diphenylacetylene (**2a**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (25 mol %), and 1,2-dichloroethane (3.0 mL) at 120 °C for 10 h. [b]Isolated yields.

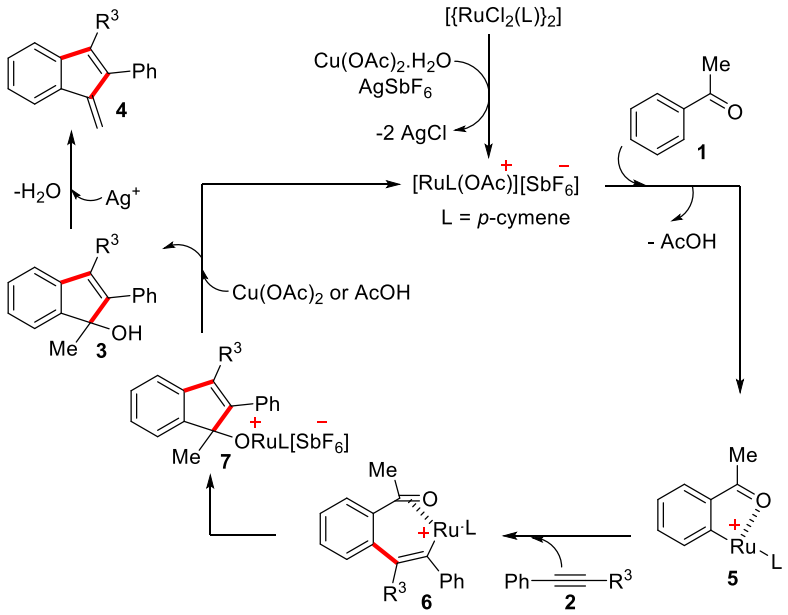
It is important to note that no dehydration product was observed in the reaction of isobutylacetophenone (**1c**) with diphenylacetylene (**2a**), even in the presence of excess amount (20 mol %) of silver salt (Scheme 2A.2). Interestingly, benzophenone (**1e**) reacted with unsymmetrical alkyne, 1-pheny-1-propyne (**2b**), to give **4a** in 87% yield (Scheme 2A.2). In the reaction, one of the hydrogen of methyl group of C-3 carbon of an indenol moiety (intermediate) involved in the intramolecular dehydration with OH group.



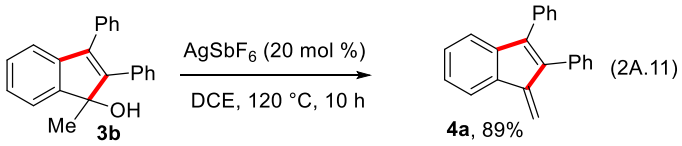
Scheme 2A.2 Substituted aromatic ketones with alkynes.

Based on the above observations and the known metal-catalyzed C-H bond activation reactions,[4-10] a conceivable reaction mechanism is proposed in Scheme 2A.3. The first step formation of ruthenium cationic complex in presence of $Cu(OAc)_2.H_2O$ and $AgSbF_6$ from [{$RuCl_2$(*p*-cymene)}$_2$] complex. Next, the coordination of the carbonyl oxygen of **1** to the active ruthenium cationic species followed by *ortho* metalation provided intermediate **5**. Coordinative insertion of alkyne **2** into the Ru–carbon bond of intermediate **5** afforded intermediate **6**. Further intramolecular insertion of the C=O group into the Ru–alkenyl bond of **6** afforded a five-membered ruthenium alkoxide intermediate **7**. Protonation of the intermediate **7** by $Cu(OAc)_2$ provided the final product **3** and regenerated the active ruthenium species for the next catalytic cycle. The exact role of copper source in catalytic reaction $Cu(OAc)_2.H_2O$ provides the OAc^- source to the active ruthenium species in order to accelerate the *ortho*-metalation and also replace the ruthenium species in intermediate **7** via transmetalation for the first catalytic cycle. On the next catalytic cycle onwards, protonation of the intermediate **7** by AcOH provides the final product **3** and regenerates the active ruthenium species for the next catalytic cycle (Scheme 2A.3).

2A.2.4 Mechanism



Scheme 2A.3 Proposed mechanism for cyclization reaction.



In the reaction, the amount of silver salt ($AgSbF_6$) added, decided the product formation. The role of silver salt was likely to remove chloride ligand to form ruthenium cationic complex from [{$RuCl_2$(*p*-cymene)}$_2$]. In the reaction, 2 mol % of [{$RuCl_2$(*p*-cymene)}$_2$] was used. In fact, 8 mol % of $AgSbF_6$ salt was good enough to remove all four chloride ligand. When the amount of silver salt increased up to 20 mol %, a dehydration product benzofulvene was observed. The product formation can be explained by the coordination of alcohol group of indenol **3** to the excess silver salt followed by subsequent dehydration. The proposed silver-catalyzed dehydration pathway was strongly supported by the results of the following reaction (eq. 2A.11). Treatment of indenol **3b** (1.0 mmol) with $AgSbF_6$ (20 mol %) in the presence of DCE at 120 °C for 10 h gave product **4a** in 89% yield.

2A.3 Conclusions

In conclusion, we have developed a highly regioselective ruthenium-catalyzed cyclization of substituted aromatic ketones with alkynes via week chelation-assisted C-H bond activation. This methodology offered a simple and mild method for the synthesis of indenols and benzofulvenes in a highly regioselective manner. In the reaction, the amount of silver salt used, decided the product formation. 8 mol % of silver salt favored indenols and 20 mol % of silver salts provided benzofulvenes in the presence of 2 mol % of ruthenium catalyst.

2A.4 References

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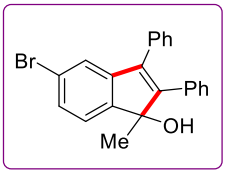
2A.5 Experimental Section

2A.5.1 General Procedure for the Cyclization Reaction of Aromatic Ketones 1 with Alkynes 2

A 15 mL pressure tube containing [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (8 mol %) and $Cu(OAc)_2.H_2O$ (25 mol %) was evacuated and purged with nitrogen gas three times. Freshly distilled 1,2-dichloroethane (3.0 mL), aromatic ketones (1.00 mmol) and alkynes (1.20 mmol) were sequentially added to the system and the reaction mixture was stirred at 120 °C for 10 h. The mixture was filtered through a short Celite and silica gel pad and washed with dichloromethane several times. The filtrate was concentrated and the residue was purified on a silica gel column using hexanes-ethyl acetate as eluent to afford the cyclization product **3**. Products **4a-i** were synthesized according to this procedure, but 20 mol % of $AgSbF_6$ were required.

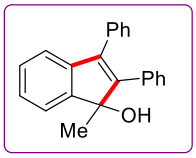
2A.5.2 Spectral Data of Compounds 3a-u

5-Bromo-1-methyl-2,3-diphenyl-1*H*-inden-1-ol (**3a**): Yellow solid; m.p. 127-129 °C, eluent



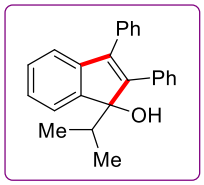
(10% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3396, 2923, 1589, 1453, 1264, 1082. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.41 – 7.38 (m, 4 H), 7.34 – 7.30 (m, 4 H), 7.28 – 7.21 (m, 5 H), 2.02 (bs, 1 H), 1.55 (s, 3 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 148.3, 148.2, 144.3, 137.8, 134.3, 134.0, 129.5, 129.3, 129.2, 128.8, 128.2, 127.9, 127.7, 124.0, 123.3, 122.6, 83.0, 24.0 ppm. **GC-MS** (70 ev, C.I.) (M+H): *m/z*: 377 (M+H), 201, 199, 119, 92. **HRMS** (EI): calc. for $C_{22}H_{17}OBr$ 376.0463, measured 376.0468.

1-Methyl-2,3-diphenyl-1*H*-inden-1-ol (**3b**): Pale yellow solid; m.p. 123-125 °C, eluent (10% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3369, 2924, 1596, 1451, 1269. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.52 (d, *J* = 8.0 Hz, 1 H), 7.44 - 7.41 (d, *J* = 8.0 Hz, 2 H), 7.34 - 7.29 (m, 5 H),



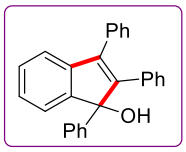
7.26 - 7.24 (m, 2 H), 7.23 - 7.20 (m, 4 H), 2.01 (bs, 1 H), 1.59 (s, 3 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 149.6, 147.0, 142.3, 138.8, 134.8, 129.5, 129.3, 128.9, 128.6, 127.9, 127.4, 127.2, 127.2, 126.7, 122.0, 120.9, 83.4, 24.0 ppm. **GC-MS** (70 ev, C.I.) (M+H): *m/z*: 298 (M+H), 252, 123. **HRMS** (ESI): calc. For [($C_{22}H_{18}O$)Na] (M+Na) 321.1255, measured 321.1263.

1-Isopropyl-2,3-diphenyl-1H-inden-1-ol (**3c**): Pale yellow solid; m.p. 151-153 °C, eluent (10% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3439, 2925, 1596, 1456, 1026. **^{1}H NMR** ($CDCl_3$,



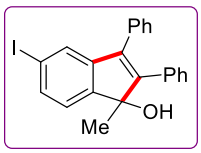
400 MHz): δ = 7.51 (d, *J* = 8.0 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.34 – 7.29 (m, 3 H), 7.28 – 7.23 (m, 4 H), 7.22 – 7.18 (m, 5 H), 2.21 – 2.16 (m, 1 H), 2.14 (bs, 1 H), 1.21 (d, *J* = 8.0 Hz, 3 H), 0.57 (d, *J* = 8.0 Hz, 3 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 146.6, 146.4, 143.9, 140.4, 135.4, 134.8, 129.6, 129.4, 128.5, 128.4, 128.0, 127.5, 127.3, 126.1, 123.6, 120.7, 89.2, 34.0, 16.9, 16.8 ppm. **GC-MS** (70 ev, C.I.) (M+H): *m/z*: 327 (M+H), 315, 298, 221. **HRMS** (ESI): calc. for [($C_{24}H_{22}O$)Na] (M+Na) 349.1568, measured 349.1568.

1,2,3-Triphenyl-1*H*-inden-1-ol (**3d**): Colorless solid; m.p. 206-208 °C, eluent (10% ethyl



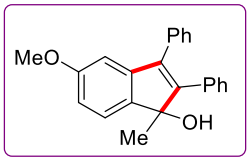
acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3438, 2922, 1591, 1449, 1125. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.66 (d, *J* = 8.0 Hz, 2 H), 7.53 (t, *J* = 8.0 Hz, 2 H), 7.49 – 7.45 (m, 3 H), 7.36 - 7.31 (m, 6 H), 7.27 - 7.23 (m, 3 H), 7.15 - 7.12 (m, 3 H), 2.91 (bs, 1 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 151.2, 147.7, 142.9, 141.9, 140.8, 135.1, 133.9, 129.8, 129.2, 128.7, 128.5, 128.4, 127.8, 127.3, 127.1, 125.3, 123.1, 121.2, 87.2 ppm. **GC-MS** (70 ev, C.I.) [($C_{27}H_{20}O$)H] (M+H) 361: *m/z*: 361 (M+H), 294, 176, 142, 134. **HRMS** (ESI): calc. for [($C_{27}H_{20}O$)Na] (M+Na) 383.1412, measured 383.1412.

5-Iodo-1-methyl-2,3-diphenyl-1H-inden-1-ol (**3e**): Pale yellow solid; m.p. 151-153 °C, eluent

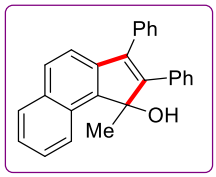


(10% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3367, 2923, 1589, 1449, 1085. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.51 (d, *J* = 8.0 Hz, 1 H), 7.43 (s, 1 H), 7.31 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.26 – 7.22 (m, 3 H), 7.19 – 7.16 (m, 2 H), 7.15 – 7.12 (m, 4 H), 1.57 (s, 3 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 149.1, 148.0, 144.5, 137.9, 135.5, 134.3, 134.1, 129.8, 129.5, 129.2, 128.9, 128.2, 127.9, 127.7, 123.8, 94.2, 83.2, 24.0 ppm. **HRMS** (EI): calc. for $C_{22}H_{17}OI$ 424.0324, measured 424.0331.

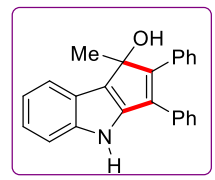
5-Methoxy-1-methyl-2,3-diphenyl-1H-inden-1-ol (**3f**): Pale yellow solid; m.p. 142-144 °C, eluent (15% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3356, 2924, 1591, 1474, 1030. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.39 – 7.36 (m, 3 H), 7.27 – 7.24 (m, 5 H), 7.14 – 7.13 (m, 3 H), 6.72 (s, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 3.71 (s, 3 H), 2.04 (bs, 1 H), 1.50 (s, 3 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 160.5, 148.3, 143.9, 141.8, 138.4, 134.9, 134.7, 129.5, 129.4, 128.7, 128.1, 127.7, 127.4, 122.6, 111.1, 107.6, 82.9, 55.7, 24.2 ppm. **HRMS** (EI): calc. for $C_{23}H_{20}O_2$ 328.1463, measured 328.1460.



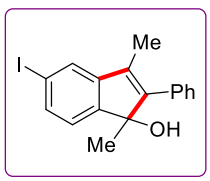
1-Methyl-2,3-diphenyl-1*H*-cyclopenta[a]naphthalen-1-ol (**3g**): Red semisolid; eluent (10% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3417, 2922, 1589, 1127. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.29 (d, *J* = 8.0 Hz, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.43 – 7.37 (m, 3 H), 7.35 – 7.31 (m, 3 H), 7.26 – 7.20 (m, 5 H), 7.14 – 7.07 (m, 2 H), 2.21 (bs, 1 H), 1.65 (s, 3 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 148.5, 143.2, 139.2, 138.6, 135.1, 134.8, 133.1, 129.7, 129.5, 129.2, 129.1, 128.7, 128.6, 128.1, 127.7, 127.4, 126.6, 125.0, 124.0, 119.6, 85.1, 25.1 ppm. **GC-MS** (70 ev, C.I.) [($C_{26}H_{20}O$)H] (M+H): *m/z*: 349 (M+H), 346, 338, 328, 128. **HRMS** (EI): calc. for $C_{26}H_{20}O$ 348.1514, measured 348.1509.



1-Methyl-2,3-diphenyl-1,4-dihydrocyclopenta[*b*]indol-1-ol (**3h**): Red semisolid; eluent (35% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3372 (bs), 2923, 1611, 1430, 1025. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 8.51 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.37 – 7.28 (m, 6 H), 7.16 – 7.11 (m, 3 H), 7.05 – 6.99 (m, 3 H), 1.26 (s, 3 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 142.0, 140.3, 135.6, 135.5, 133.1, 132.6, 129.8, 129.7, 117.0, 129.2, 129.1, 129.0, 128.7, 126.5, 123.9, 123.3, 122.9, 111.3, 90.3, 14.3 ppm. **HRMS** (ESI): calc. for [($C_{24}H_{19}NO$)H] (M+H) 338.1545, measured 338.1530.

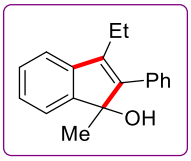


5-Iodo-1,3-dimethyl-2-phenyl-1*H*-inden-1-ol (**3i**): Orange oil; eluent (10% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3345, 2923, 1447, 1081. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.58 (d, *J* = 8.0, 4.0 Hz, 1 H) 7.56 (s, 1 H), 7.52 – 7.50 (m, 2 H), 7.43 – 7.40 (m, 2 H), 7.35 (t, *J* = 8.0 Hz, 1 H), 7.18 (d, *J* = 8.0 Hz, 1 H), 2.05 (s, 3 H), 1.92 (bs, 1 H), 1.45 (s, 3 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 148.9,

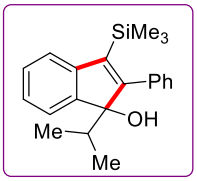


147.8, 145.8, 135.3, 134.9, 133.6, 129.2, 128.8, 128.5, 127.8, 123.4, 94.2, 83.0, 23.8, 11.7 ppm. **HRMS** (ESI): calc. for [($C_{17}H_{15}IO$)H] (M+H) 363.0246, measured 363.0242.

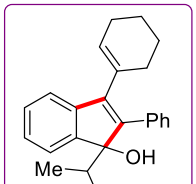
3-Ethyl-1-methyl-2-phenyl-1*H*-inden-1-ol (**3j**): Orange semisolid; eluent (10% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3349, 2969, 1597, 1457, 1363, 1088. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.45 – 7.42 (m, 2 H), 7.41 – 7.36 (m, 3 H), 7.33 – 7.28 (m, 2 H), 7.26 – 7.18 (m, 2 H), 2.46 (q, *J* = 8.0 Hz, 2 H), 1.88 (bs, 1 H), 1.44 (s, 3 H), 1.17 (t, *J* = 8.0 Hz, 3 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 149.6, 146.5, 142.3, 140.1, 135.4, 129.1, 128.5, 128.3, 127.5, 126.3, 121.8, 119.9, 83.1, 23.8, 19.3, 13.6 ppm. **HRMS** (EI): calc. for $C_{18}H_{18}O$ 250.1358, measured 250.1363.



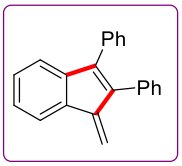
1-Isopropyl-2-phenyl-3-(trimethylsilyl)-1*H*-inden-1-ol (**3k**): Orange oil; eluent (4% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3402, 1580, 1128. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.45 (d, *J* = 8.0 Hz, 1 H), 7.38 – 7.31 (m, 4 H), 7.29 – 7.24 (m, 3 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 2.00 – 1.97 (m, 1 H), 1.95 (bs, 1 H), 1.15 (d, *J* = 8.0 Hz, 3 H), 0.56 (d, *J* = 8.0 Hz, 3 H), 0.02 (s, 9 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 146.8, 146.1, 139.8, 137.6, 129.5, 128.5, 128.3, 128.0, 127.8, 125.1, 123.5, 122.6, 89.7, 33.2, 17.1, 16.4, 0.3 ppm. **HRMS** (EI): calc. for $C_{21}H_{26}OSi$ 322.1753, measured 322.1758.



3-(Cyclohex-1-en-1-yl)-1-isopropyl-2-phenyl-1*H*-inden-1-ol (**3l**): Orange oil; eluent (10% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3422, 2930, 1591, 1456, 1370, 1267, 1035. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.65 (d, *J* = 8.0 Hz, 1 H), 7.39 – 7.31 (m, 4 H), 7.29 – 7.23 (m, 3 H), 7.10 (t, *J* = 8.0 Hz, 1 H), 5.77 (t, *J* = 4.0 Hz, 1 H), 2.31 – 2.25 (m, 1 H), 2.18 – 2.11 (m, 2 H), 2.09 – 2.01 (m, 1 H), 1.91 – 1.85 (m, 2 H), 1.79 – 1.61 (m, 3 H), 1.13 (d, *J* = 8.0 Hz, 3 H), 0.51 (d, *J* = 8.0 Hz, 3 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 146.7, 143.7, 136.2, 135.9, 132.3, 129.1, 128.8, 128.2, 127.9, 127.2, 125.7, 123.4, 120.5, 88.9, 34.1, 28.0, 25.5, 22.9, 22.2, 16.9, 16.7 ppm. **HRMS** (EI): calc. for $C_{24}H_{26}O$ 330.1984, measured 330.1983.

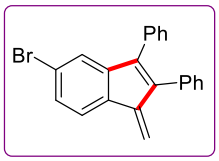


1-Methylene-2,3-diphenyl-1*H*-indene (**4a**): Pale yellow oil; eluent (only hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.71 (d, *J* = 8.0 Hz, 1 H), 7.34 (t, *J* = 8.0 Hz, 1 H), 7.30 – 7.25 (m, 10 H), 7.20 – 7.18 (m, 2 H), 6.25 (s, 1 H), 5.72 (s, 1 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 147.7, 142.8, 140.9, 137.5, 136.3, 134.7, 134.6, 130.8,

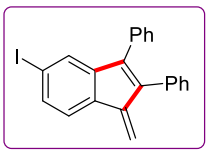


129.4, 128.6, 128.3, 128.1, 127.5, 127.0, 125.8, 120.2, 119.9, 114.2 ppm. **GC-MS** (70 ev, C.I.): calc. for [($C_{22}H_{16}$)H] (M+H) 281, measured 281 (M+H), 265, 220.

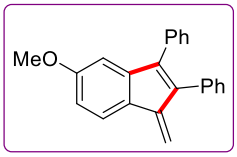
5-Bromo-1-methylene-2,3-diphenyl-1*H*-indene (**4b**): Pale yellow semisolid; eluent (only hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.56 (d, *J* = 8.0 Hz, 1 H), 7.46 (s, 1 H), 7.40 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.35 – 7.29 (m, 4 H), 7.28 – 7.25 (m, 4 H), 7.19 – 7.17 (m, 2 H), 6.25 (s, 1 H), 5.77 (s, 1 H) ppm.**^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 146.8, 144.7, 141.1, 138.7, 135.0, 134.2, 133.9, 130.7, 129.4, 128.5, 128.4, 128.2, 127.8, 127.3, 123.3, 122.4, 121.2, 115.4 ppm. **GC-MS** (70 ev, C.I.): calc. for [($C_{22}H_{15}Br$)H] (M+H) 359, measured 359 (M+H), 338, 294, 272, 196.



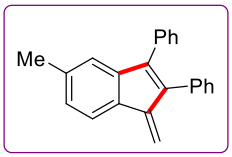
5-Iodo-1-methylene-2,3-diphenyl-1*H*-indene (**4c**): Pale yellow solid; eluent (only hexanes). m.p. 172-175 °C, **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.67 (s, 1 H), 7.62 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.35 – 7.30 (m, 4 H), 7.29 – 7.25 (m, 4 H), 7.20 – 7.18 (m, 2 H), 6.28 (s, 1 H), 5.78 (s, 1 H) ppm. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 147.0, 144.9, 138.6, 135.8, 134.6, 134.3, 134.1, 130.9, 129.8, 129.6, 129.2, 128.7, 128.3, 127.9, 127.5, 121.7, 115.6, 94.1 ppm. **GC-MS** (70 ev, C.I.): calc. for [($C_{22}H_{15}I$)H] (M+H) 407, measured 407 (M+H), 330, 266, 225, 108.



5-Methoxy-1-methylene-2,3-diphenyl-1*H*-indene (**4d**): Orange semisolid; eluent (1% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (d, *J* = 8.0 Hz, 1 H), 7.34 – 7.28 (m, 8 H), 7.25 – 7.22 (m, 2 H), 6.96 (s, 1 H), 6.83 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.15 (s, 1 H), 5.66 (s, 1 H), 3.84 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.6, 147.2, 144.5, 141.5, 138.9, 134.8, 134.6, 130.8, 129.6, 129.1, 128.4, 128.1, 127.6, 127.1, 120.9, 112.9, 110.8, 106.6, 55.7 ppm. GC-MS (70 ev, C.I.): calc. for [($C_{23}H_{18}O$)H] (M+H) 311, measured 311 (M+H), 179, 167, 119.

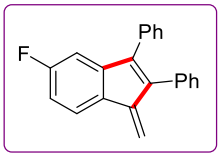


5-Methyl-1-methylene-2,3-diphenyl-1*H*-indene (**4e**): Pale yellow oil; eluent (only hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.62 (d, *J* = 8.0 Hz, 1 H), 7.35 – 7.31 (m, 4 H), 7.30 – 7.27 (m, 4 H), 7.22 – 7.20 (m, 2 H), 7.17 (s, 1 H), 7.10 (d, *J* = 4.0 Hz, 1 H), 6.21 (s, 1 H), 5.70 (s, 1 H), 2.40 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.7, 143.2, 142.0, 138.5, 137.9, 134.9, 133.9, 130.9, 129.7,



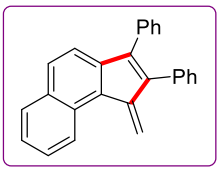
128.5, 128.2, 127.6, 127.1, 126.5, 121.1, 119.9, 113.6, 22.0 ppm. GC-MS (70 ev, C.I.): calc. for [($C_{23}H_{18}$)H] (M+H) 295, measured 295 (M+H), 181, 152, 129.

5-Fluoro-1-methylene-2,3-diphenyl-1*H*-indene (**4f**): Pale yellow oil; eluent (only hexanes). ^{1}H



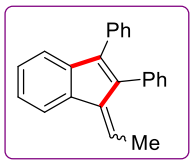
NMR ($CDCl_3$, 400 MHz): δ = 7.52 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.22 – 7.15 (m, 8 H), 7.10 – 7.07 (m, 2 H), 6.95 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.86 – 6.81 (m, 1 H), 6.08 (s, 1 H), 5.61 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.9 and 162.4 (C-F coupling), 146.7, 144.9 and 144.8 (C-F coupling), 141.0, 139.2, 134.4, 134.1, 132.0, 130.8, 129.4, 128.5, 128.2, 127.8, 127.3, 121.0 and 120.9 (C-F coupling), 114.6, 112.3 and 112.1 (C-F coupling), 107.8 and 107.6 (C-F coupling) ppm. GC-MS (70 ev, C.I.): calc. for [($C_{22}H_{15}F$)H] (M+H) 299, measured 299 (M+H), 279, 221. HRMS (ESI): calc. for [($C_{22}H_{15}F$)H] (M+H) 299.1236, measured 299.1232.

1-Methylene-2,3-diphenyl-1*H*-cyclopenta[*a*]naphthalene (**4g**): Red semisolid; eluent (only in



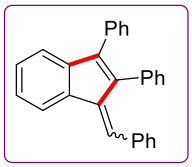
hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.52 (d, *J* = 8.0 Hz, 1 H), 7.86 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.58 – 7.52 (m, 2 H), 7.44 – 7.33 (m, 8 H), 7.30 – 7.23 (m, 3 H), 7.12 (s, 1 H), 6.88 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.1, 139.6, 138.9, 138.1, 134.5, 134.2, 132.6, 129.1, 128.9, 129.1, 128.7, 128.1, 128.2, 127.8, 127.2, 127.0, 126.1, 124.0, 123.6, 119.6, 110.9 ppm. GC-MS (70 ev, C.I.): calc. for [($C_{26}H_{18}$)H] (M+H) 331, measured 331 (M+H), 281, 268, 209, 191. HRMS (ESI): calc. for [($C_{26}H_{18}$)H] (M+H) 331.1487, measured 331.1487.

(*E*)- and (Z)- mixtures of 1-Ethylidene-2,3-diphenyl-1*H*-indene (4h) (*E*:*Z* ratio; 85:15): Pale



yellow oil; eluent (only hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.89 (d, *J* = 8.0 Hz, 1 H) (major isomer), 7.65 (d, *J* = 8.0 Hz, 1 H) (minor isomer), 7.42 (t, *J* = 8.0 Hz, 1 H), 7.33 – 7.22 (m, 10 H), 7.19 – 7.16 (m, 2 H), 6.90 (q, *J* = 8.0 Hz, 1 H) (minor isomer), 6.37 (q, *J* = 8.0 Hz, 1 H) (major isomer), 2.40 (d, *J* = 8.0 Hz, 3 H) (major isomer), 1.68 (d, *J* = 8.0 Hz, 1 H) (minor isomer) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.6, 141.7, 139.5, 138.7, 137.8, 135.4, 135.3, 135.0, 132.9, 131.2, 130.4, 129.7, 129.5, 128.2, 128.1, 127.9, 127.3, 127.1, 127.0, 126.9, 125.4, 125.3, 123.9, 120.3, 120.0, 118.4, 15.9, 15.6 ppm. GC-MS (70 ev, C.I.): calc. for [($C_{23}H_{18}$)H] (M+H) 295, measured 295 (M+H), 278, 217, 145.

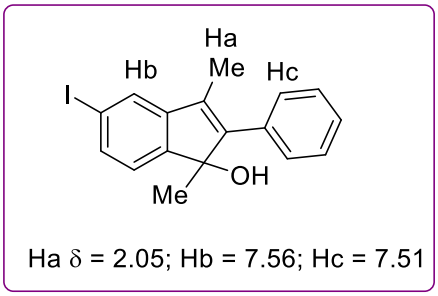
(*E*)-1-Benzylidene-2,3-diphenyl-1*H*-indene (**4i**): Pale yellow semisolid; eluent (only hexanes).



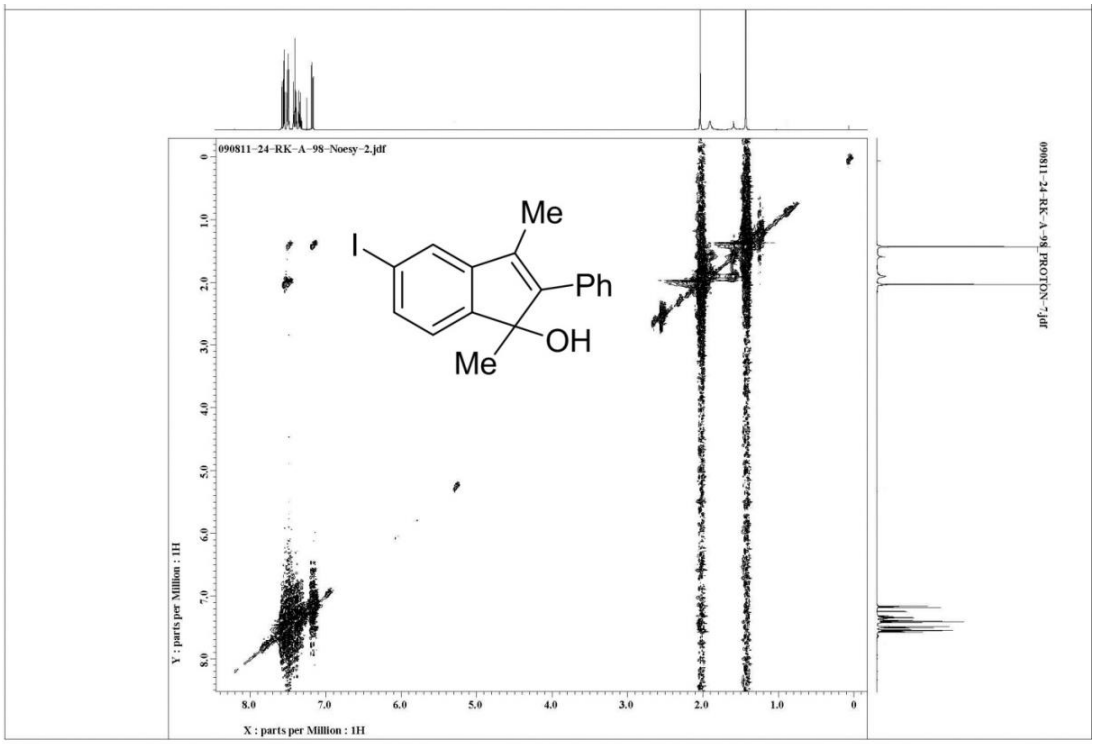
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.60 – 7.56 (m, 3 H), 7.45 (t, *J* = 8.0 Hz, 2 H), 7.39 (t, *J* = 8.0 Hz, 2 H), 7.35 – 7.26 (m, 11 H), 7.20 (s, 1 H), 7.05 (t, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 144.0, 141.7, 140.7, 139.9, 137.3, 135.3, 134.9, 134.8, 134.7, 131.5, 130.4, 129.9, 129.8, 129.6, 128.7, 128.4, 128.3, 128.2, 127.5, 127.2, 125.5, 123.5, 120.3 ppm. GC-MS (70 ev, C.I.): calc. for [($C_{28}H_{20}$)H] (M+H) 357, measured 357 (M+H), 325, 295, 217, 167.

2A.5.3 Regioselective Studies: NOESY Experiments

NOESY Experiments Spectra of Compound **3i**

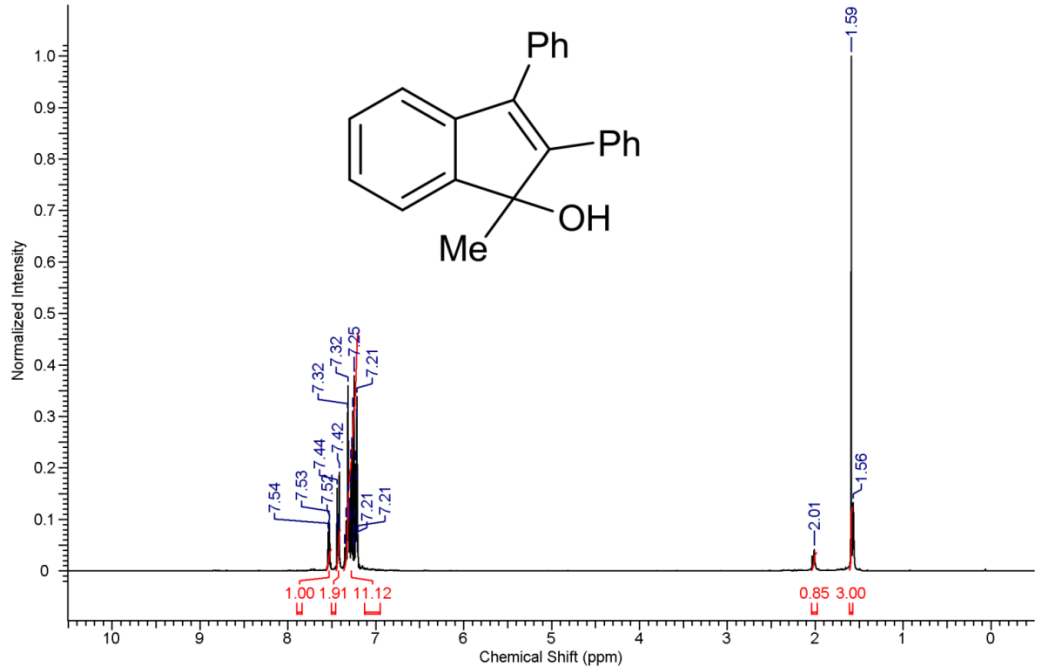


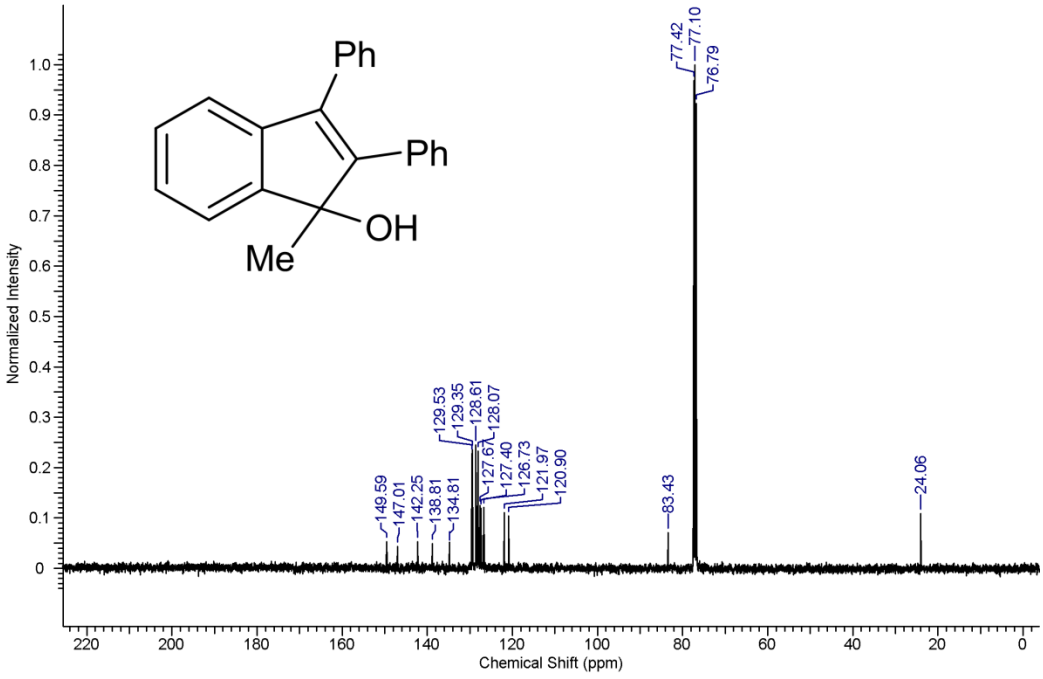
There is a NOE correlation between Ha (δ 2.05, s) and Hb (δ 7.56, s). In meantime, there is also a NOE correlation between Ha (δ 2.05, s) and Hc (δ 7.51, d). However, there is no correlation between Hb (δ 7.56, s) and Hc (δ 7.51, d). These results clearly revealed that the regiochemistry of compound **3i** is correct.



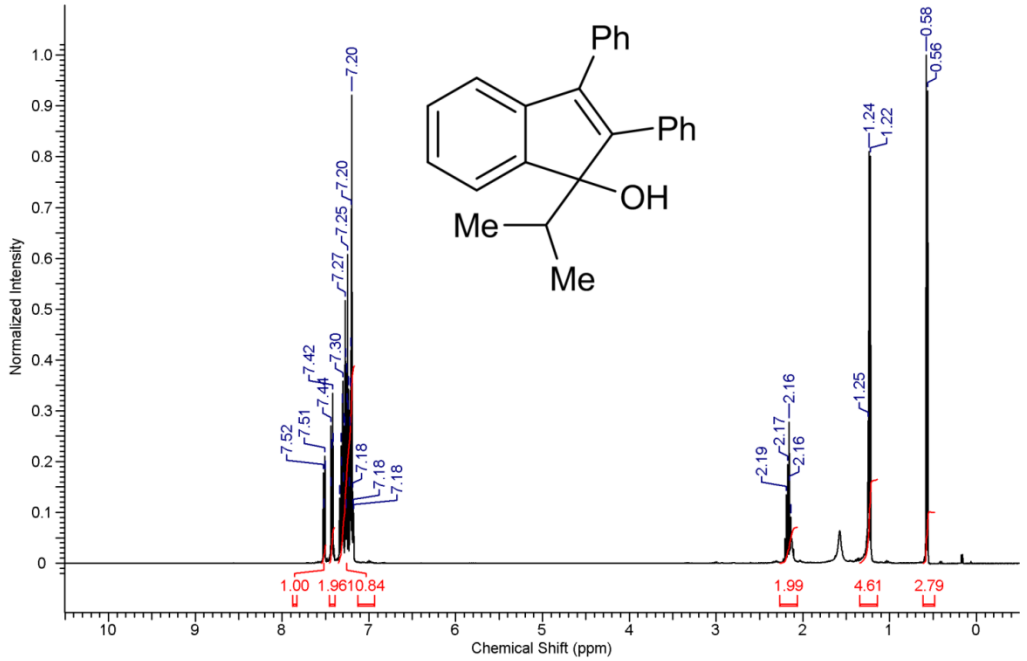
2A.5.4 Spectral Copies of Selected Compounds

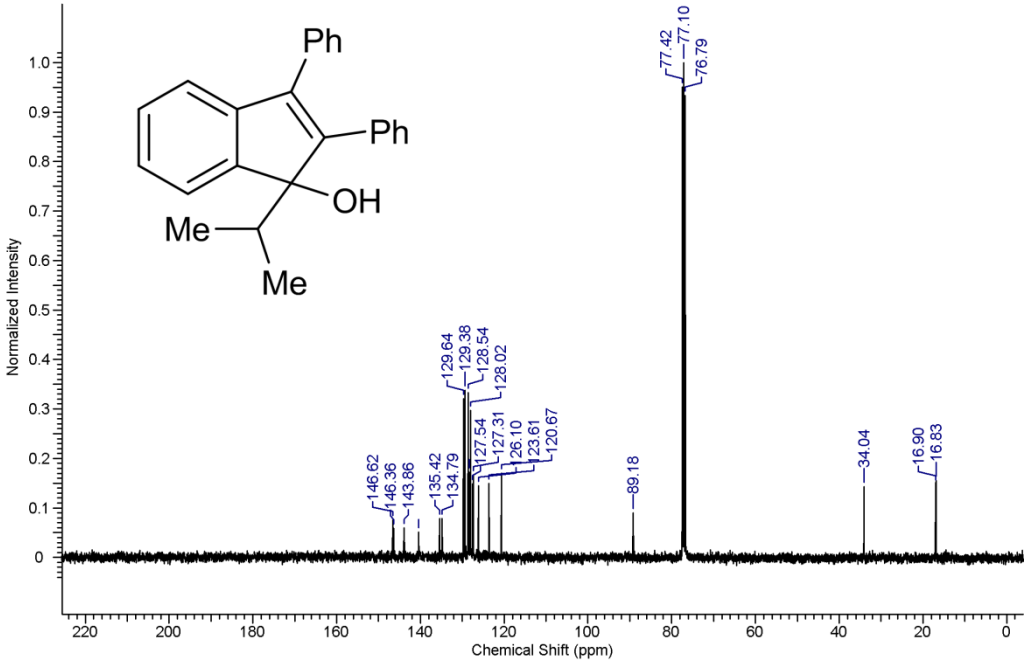
^{1}H and ^{13}C NMR Spectra of Compound **3b**



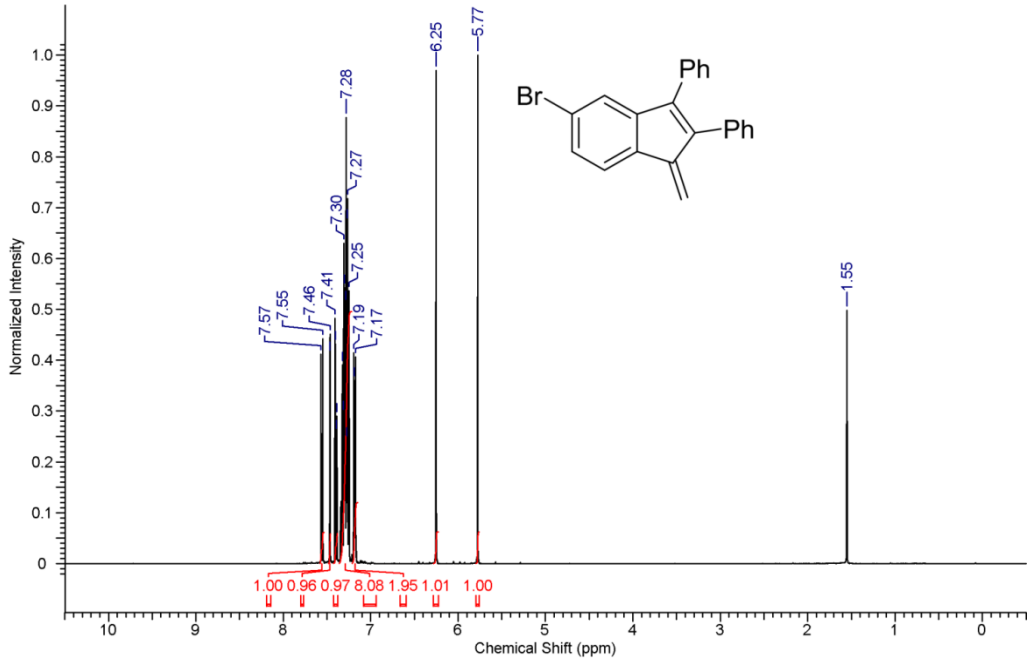


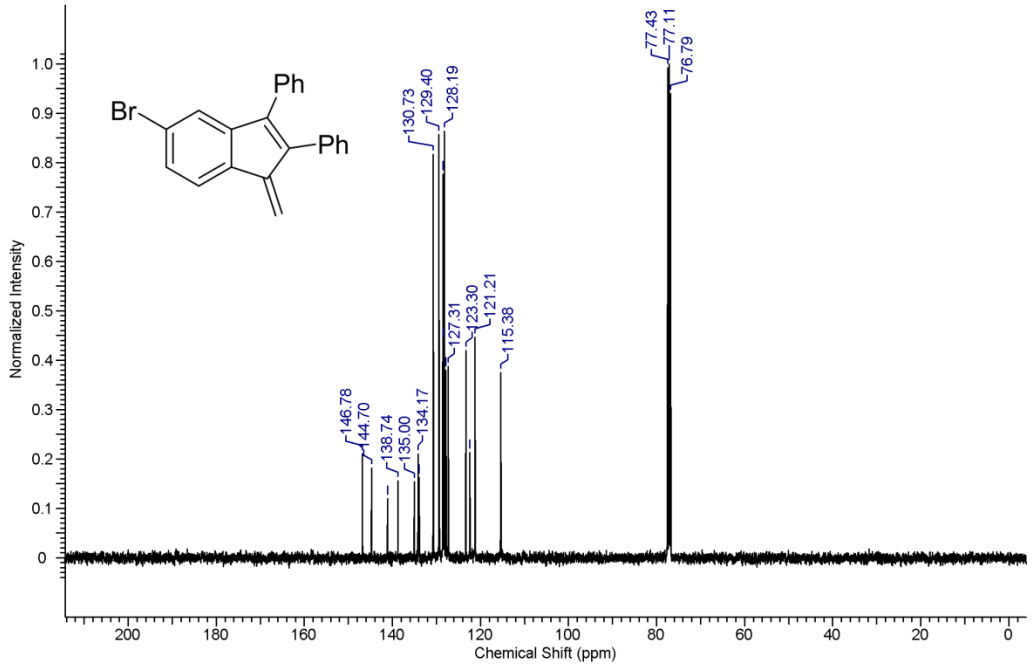
^{1}H and ^{13}C NMR Spectra of Compound **3c**



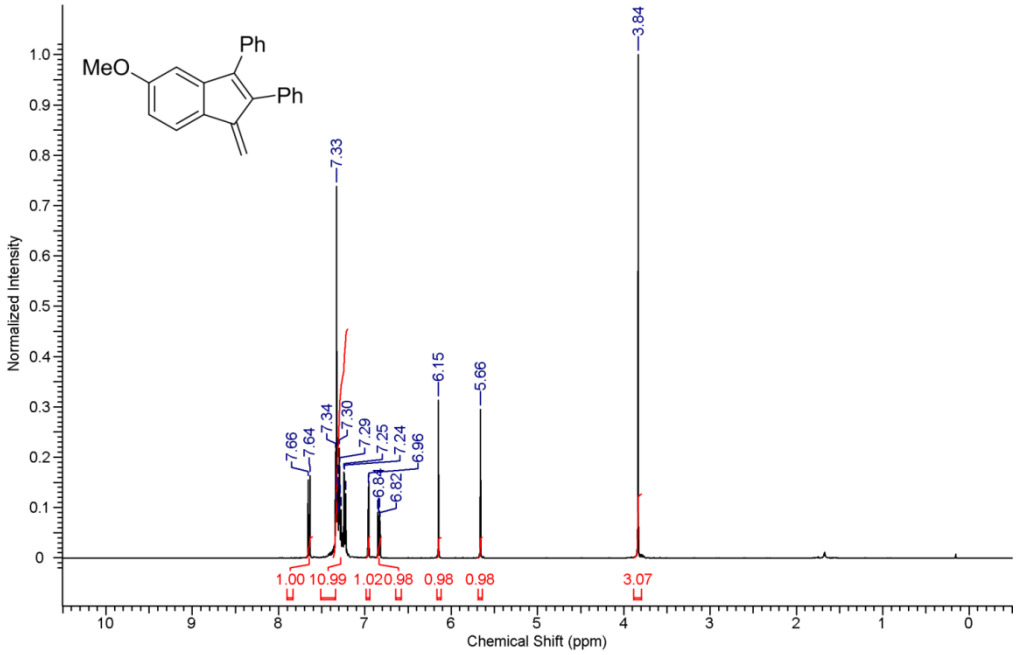


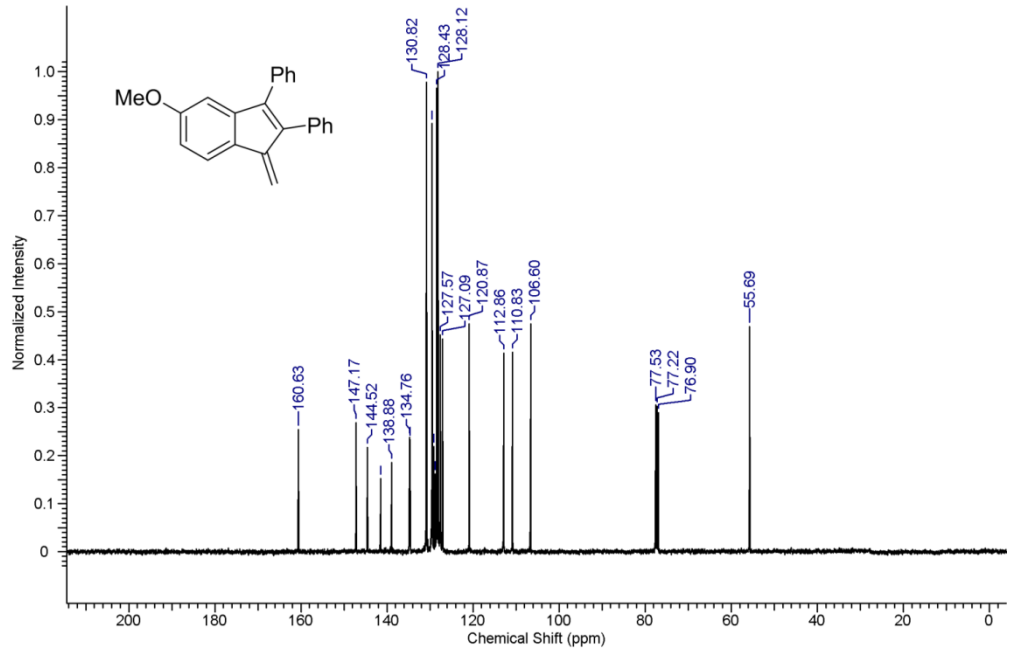
^{1}H and ^{13}C NMR Spectra of Compound **4a**



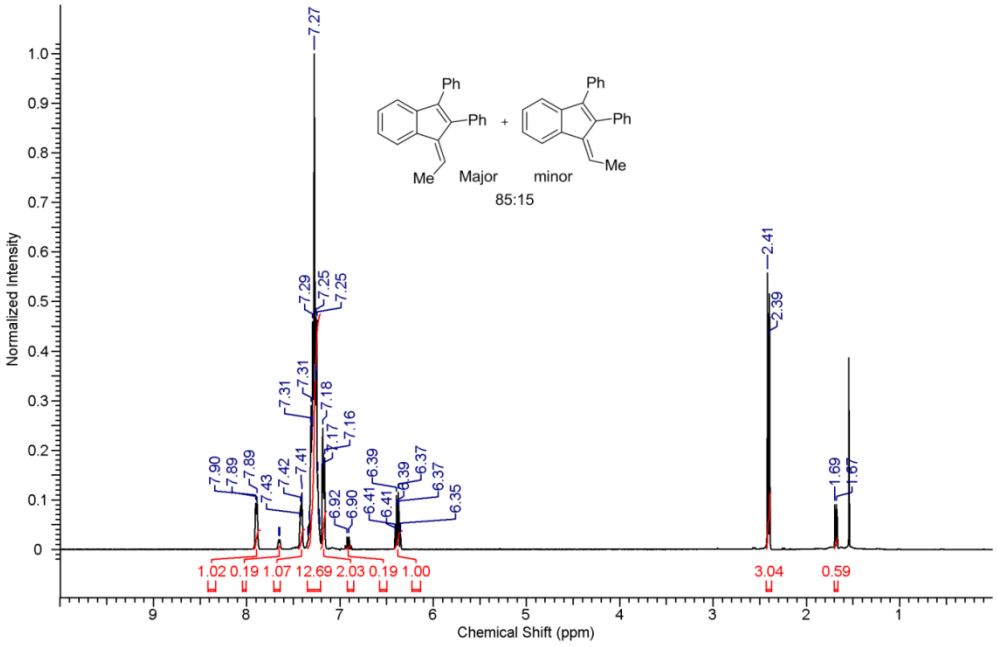


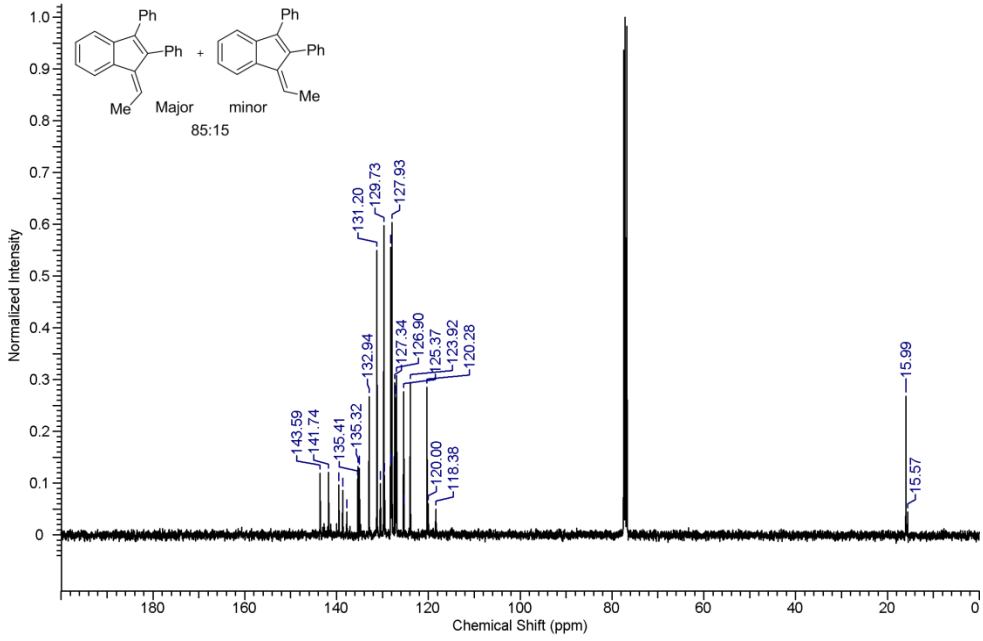
1H and 13C NMR Spectra of Compound **4d**





^{1}H and ^{13}C NMR Spectra of Compound **4h**

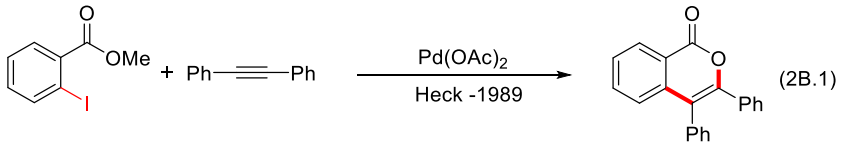




Section 2B: Regioselective Synthesis of Isocoumarins by a Ruthenium-Catalyzed Aerobic Oxidative Cyclization of Aromatic acids with Alkynes

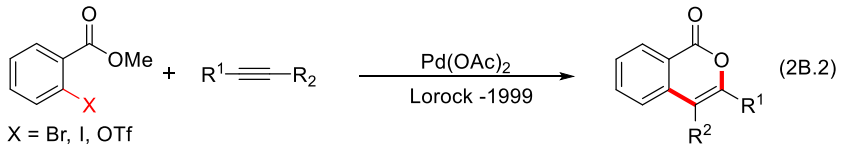
2B.1 Introduction

Isocoumarins are an important class of naturally occurring lactones that show various biological activities such as antifungal, antitumor, antiallergic, antimicrobial, anti-inflammatory, antidiabetic, phytotoxic, and anticancer activities. These lactones are also found in numerous natural products and biologically active molecules.[1,2] Due to their interesting biological properties, a great attention has been focused on the synthesis of isocoumarin derivatives. The transition-metal-catalyzed cyclization of *o*-haloaromatic acids (or) esters with π-components have been recognized as an efficient method to synthesize isocoumarin derivatives (eq. 2B.1).[3] In 1989, Heck's group described the direct synthesis of 3,4-diphenylisocoumarin derivatives via a palladium-mediated coupling of methyl 2-iodobenzoate with diphenylacetylene in 56% yield (eq. 2B.1).[3a]



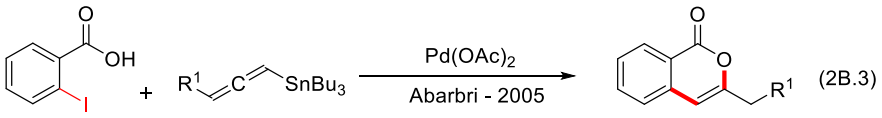
(2B.1)

Later, Larock's developed a palladium-catalyzed cyclization of *ortho* halogen or triflate substituted aromatic esters with alkynes. This method provides an efficient route to synthesize isocoumarins derivatives in good to excellent yields. In the reaction, *ortho*-iodobenzoate gave the higher yields in a shorter reaction time compared with *ortho*-bromobenzoate. However, unsymmetrical alkynes provided a mixture of regioisomers isocoumarins derivatives (eq. 2B.2).[3b-e]



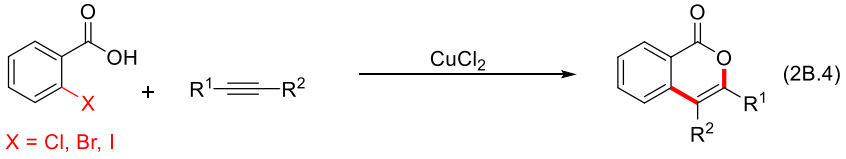
(2B.2)

Subsequently, Abarbri's group reported consecutive coupling followed by intramolecular cyclization of *o*-iodobenzoic acids with allenyl stannenes in the presence of a palladium catalyst providing 3-substituted isocoumarins derivatives (eq. 2B.3).[3f]



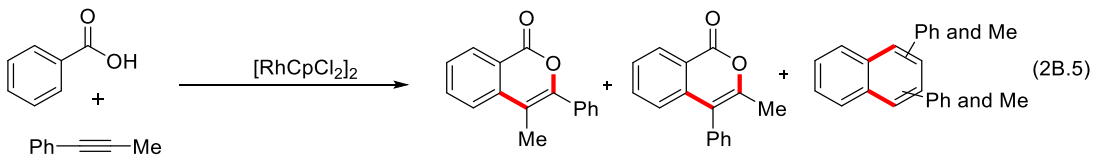
(2B.3)

Very recently, Guo's group reported a copper-catalyzed cyclization reaction of o-halobenzoic acids with alkynes providing 3,4-disubstituted isocoumarins in good to excellent yields (eq. 2B.4).[3g] However, in all these reactions, a pre-activated coupling partner such as organic halides or organometallic reagents are used as a starting material to construct isocoumarin derivatives.[3]



(2B.4)

In this regard, transition metal-catalyzed chelation-assisted oxidative annulation of the *ortho* aromatic or alkenyl C-H bond with carbon-carbon π-components reactions are one of the most efficient method to construct heterocyclic compounds.[4,5] This reaction is highly atom-economical and environmentally friendly. By using this method, a variety of highly useful carbocyclic and heterocyclic compounds have been synthesized efficiently.[6,7] In this oxidative cyclization reaction, mostly rhodium and palladium complexes have been widely used as catalysts. Recently, less-expensive ruthenium catalysts have gained much attention in this type of cyclization reactions, due to their remarkable reactivity and selectivity. Recently, Miura's group reported a rhodium-catalyzed oxidative cyclization of aromatic acids with alkynes in the presence of rhodium catalyst.[8-9] However, in the reaction of aromatic acids with unsymmetrical alkynes, a mixture of regioisomeric products (ca. 6:1 to 8:1 ratios) were observed. In addition to that, a 1:2 decarboxylative cyclization of aromatic acids with alkynes to give naphthalene derivatives (eq. 2B.5).[8]

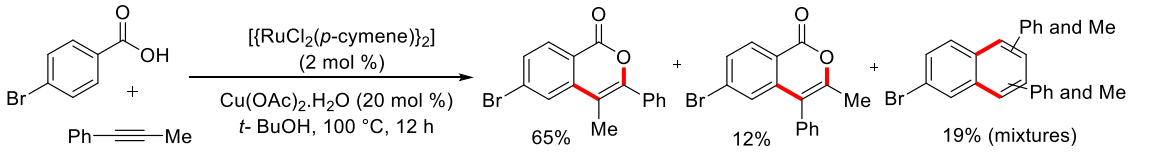


(2B.5)

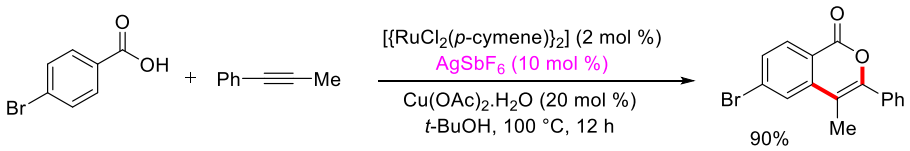
Herein, we report a highly regioselective oxidative cyclization of aromatic acids with alkynes in the presence of catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and $Cu(OAc)_2.H_2O$ providing highly substituted isocoumarin derivatives in good to excellent yields. Interestingly, in the present ruthenium- and silver-catalyzed reaction, exclusively a single regioisomeric product was observed with unsymmetrical alkynes and no naphthalene product was observed.

2B.2 Results and Discussion

The treatment of 4-bromobenzoic acid (**1a**) with 1-phenyl-1-propyne (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %) and $Cu(OAc)_2.H_2O$ (20 mol %) in 1,2-dichloroethane at 100 °C for 12 h gave a mixture of regioisomeric isocoumarin derivatives **3a** and **3a'** in 65% and 12% isolated yields, respectively. In addition, 1:2 decarboxylative cyclization of **1a** with **2a** to give a mixture of naphthalene derivative **4** was observed in combined 19% yield. Surprisingly, when the same reaction was carried out in the presence of a catalytic amount of $AgSbF_6$ (10 mol %) under the same reaction conditions, exclusively isocoumarin derivative **3a** was observed in 90% isolated yield without the naphthalene derivatives **4** in a highly regioselective manner (eq. 2B.6).



(2B.6)



The catalytic reaction was also nicely undergoing cyclization with **1a** and **2a** under an air atmosphere, providing **3a** in 89% isolated yield. The catalytic reaction is highly regioselective in which the alkyne carbon bearing Ph group is attached to the COOH group of **1a** and the alkyne carbon bearing Me group is connected to the *ortho* carbon of aromatic acid. In the reaction, $AgSbF_6$ played an important role to control the regioselectivity and completely suppressed the decarboxylative naphthalene derivatives **4**.

2B.2.1 Optimization Studies

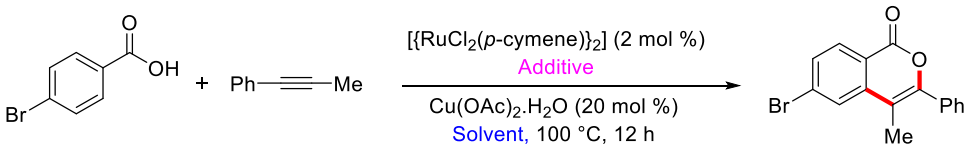


Table 2B.1 Cyclization reaction of 4-bromo benzoic acid (**1**) with 1-phenyl-1-propyne (**2a**).[a]

Entry	Additives	Solvents	Yield[b]
1	$AgSbF_6$	THF	23
2	$AgSbF_6$	Toluene	10
3	$AgSbF_6$	*tert*-Amyl alcohol	65
4	$AgSbF_6$	*t*-BuOH	87
5	**$AgSbF_6$**	**DCE**	**90**
6	$AgSbF_6$	DMF	nr
7	$AgSbF_6$	CH_3CN	nr
8	$AgSbF_6$	CH_3COOH	nr
9	$AgBF_4$	DCE	43
10	AgOTf	DCE	25
11	AgO_2CCF_3	DCE	nr
12	AgOAc	DCE	nr
13	Ag_2O	DCE	nr

[a]All reactions were carried out with4-bromo benzoic acid **1** (1.00 mmol), diphenylacetylene (**2a**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2 \cdot H_2O$ (20 mol %), and 1,2-Dichloroethane (3.0 mL) at 100 °C for 10 h. [b]Isolated yields.

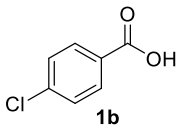
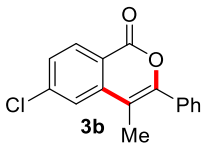
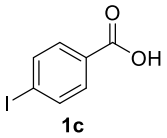
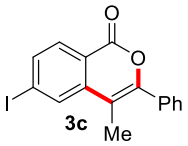
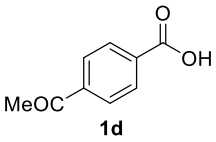
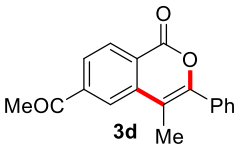
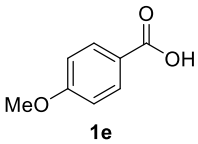
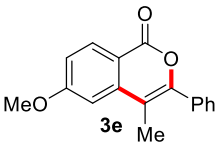
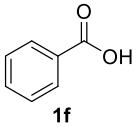
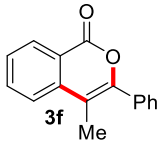
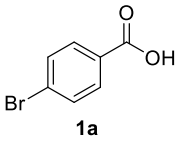
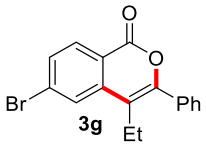
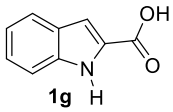
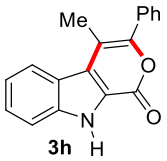
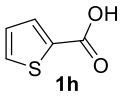
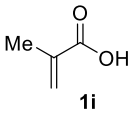
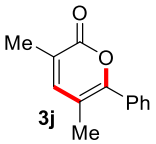
For optimizing the present ruthenium-catalyzed cyclization reaction, the reaction of **1a** with **2a** in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %) was examined with different type of solvents, additives (8 mol %) and oxidants (25 mol %). The reaction was first tested with various solvents. Of the solvents tested, 1,2-dichloroethane (DCE) and *t*-BuOH were most effective, affording **3a** in 90% and 87% yield (Table 2B.1, entry 4 and 5). The yield of **3a** was determined based on the

^{1}H NMR integration method using mesitylene as an internal standard. *tert*-amyl alcohol was also effective providing **3a** in 65% yield (entry 3). Other solvents such as THF and Toluene were less effective giving **3a** in 23% and 10% yields, respectively (entry 1 and 2). The other solvents such as DMF, DME, CH_3CN and CH_3COOH were totally ineffective for the reaction (entry 6-8). Next, the effect of silver salt was examined. A variety of silver salts such as $AgSbF_6$, $AgBF_4$, AgOTf, AgO_2CCF_3, AgOAc and Ag_2O were tested. Among them, $AgSbF_6$ was very effective for the reaction, giving **3a** in 90% yield (entry 5). $AgBF_4$ and AgOTf were less effective giving **3a** in 43% and 25% yields, respectively (entry 9 and 10). Remaining silver salts AgO_2CCF_3, AgOAc and Ag_2O were totally ineffective for the reaction (entry 11-13). The catalytic reaction provided almost equal yield in the presence of catalytic amount of $Cu(OAc)_2.H_2O$ (20 mol %, 90% yield) as well as stoichiometric amount of $Cu(OAc)_2.H_2O$ (2.20 equiv, 88% yield). But, the reaction did not proceed in the absence of $Cu(OAc)_2.H_2O$. *t*-BuOH was also a highly effective solvent for the reaction, giving **3a** in 87% isolated yield.

2B.2.2 Synthesis of Isocoumarins

The oxidative cyclization reaction was successfully extended with various substituted acids **1b-i** and unsymmetrical alkynes **2a-b** under the best optimized conditions. 4-Chlorobenzoic acid (**1b**), 4-iodobenzoic acid (**1c**), 4-acetylbenzoic acid (**1d**), 4-methoxybenzoic acid (**1e)**, and benzoic acid (**1f**) reacted with 1-phenyl-1-propyne (**2a**) to give the corresponding isocoumarin derivatives **3b-3f** in excellent yields with very high regioselectivity (Table 2B.2, entry 1-5). The catalytic reaction tolerates a variety of sensitive functional groups such as COMe and iodo on the aromatic ring of acids. It is noteworthy to say that both acid and keto groups act as excellent directing groups for the oxidative cyclization reaction. Interestingly, in the present reaction, the COOH group chelates better with ruthenium than the keto group (product **3d**). An unsymmetrical alkyne, 1-phenyl-1-butyne (**2b**), also regioselectively reacted with **1a** to afford **3g** in 87% yield (entry 6). The catalytic reaction was also compatible with heteroaromatic and alkenyl acids. Indole-2-carboxylic acid (**1g**), 2-thiophenecarboxylic acid (**1h**) and 2-methylacrylic acid (**1i**) reacted efficiently with **2a** to afford the expected cyclization products **3h-3j** in good to excellent yields (entry 7-9). Meanwhile, the catalytic reaction was also tested with 1-phenyl-2-(trimethylsilyl)acetylene, tributyl(phenylethynyl) tin and various terminal alkynes. However, in these reactions, no expected cyclization products were observed.

Table 2B.2 Cyclization reaction of substituted aromatic acids **1b-j** with substituted alkynes (**2a-b**).[a]

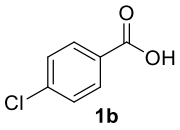
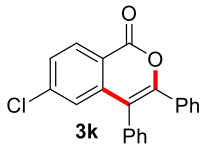
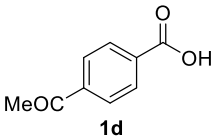
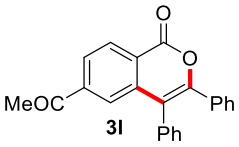
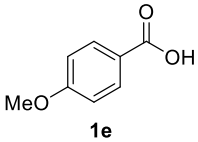
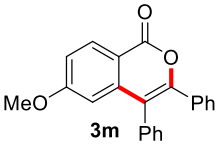
Entry	Aromatic acid (1)	Compound (3)	Yeild[b]
1	 **1b**	 **3b**	86%
2	 **1c**	 **3c**	92%
3	 **1d**	 **3d**	81%
4	 **1e**	 **3e**	93%
5	 **1f**	 **3f**	85%
6	 **1a**	 **3g**	87%
7	 **1g**	 **3h**	56%
8	 **1h**	 **3i**	80%
9	 **1i**	 **3j**	78%

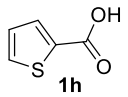
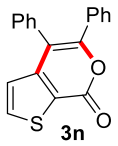
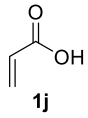
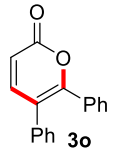
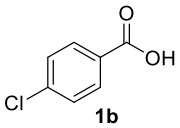
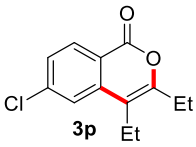
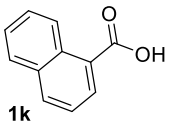
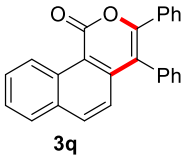
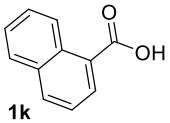
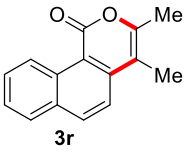
[a]All reactions were carried out with substituted aromatic acid **1** (1.00 mmol), substituted alkyne (**2a-b)**

(1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2 \cdot H_2O$ (20 mol %), and 1,2-dichloroethane (3.0 mL) at 100 °C for 10 h. [b]Isolated yields.

Next, we have examined the scope of symmetrical alkynes in the cyclization reaction with substituted acids **1** (Table 2B.3). 4-Chlorobenzoic acid (**1b**), 4-acetylbenzoic acid (**1d**) and 4-methoxybenzoic acid (**1e**) underwent cyclization reaction with diphenylacetylene (**2c**) to give substituted isocoumarin derivatives **3k**-**3m** in good yields (entry 1-3). In these reactions, no decarboxylative naphthalene products **4** were observed. Heteroaromatic and alkenyl acids also worked well for the reaction. Thus, 2-thiophenecarboxylic acid (**1h**) and acrylic acid (**1j**) reacted with diphenylacetylene (**2c**) to give the corresponding cyclic compounds **3n** and **3o** in 70% and 85% yields, respectively (entry 4 and 5). The less reactive 3-hexyne (**2d**) and 2-butyne (**2e**) also efficiently participated in the reaction. Thus, 4-chlorobenzoic acid (**1b)** reacted with 3-hexyne (**2d**) to afford an isocoumarin derivative **3p** in 87% yield (Table 2, entry 6). The present methodology can be further extended to 1-napthoic acid (**1k**). Thus, 1-napthoic acid (**1k**) reacted with diphenylacetylene (**2c**) to afford **3q** in a moderate 54% yield (Table 2, entry 7). But, 1-napthoic acid (**1k**) reacted with 2-butyne (**2e**) to give an isocoumarin derivatives **3r** in an excellent 88% yield (entry 8). This result clearly indicated that the less reactive aliphatic alkynes **2d-e** reacted with acids **1** better than diphenylacetylene (**2c**).

Table 2B.3 Cyclization of substituted aromatic acids **1** with symmetrical alkynes (**2**).[a]

Entry	Aromatic acid (1)	Compound (3)	Yeild[b]
1	 **1b**	 **3k**	71%
2	 **1d**	 **3l**	66%
3	 **1e**	 **3m**	72%

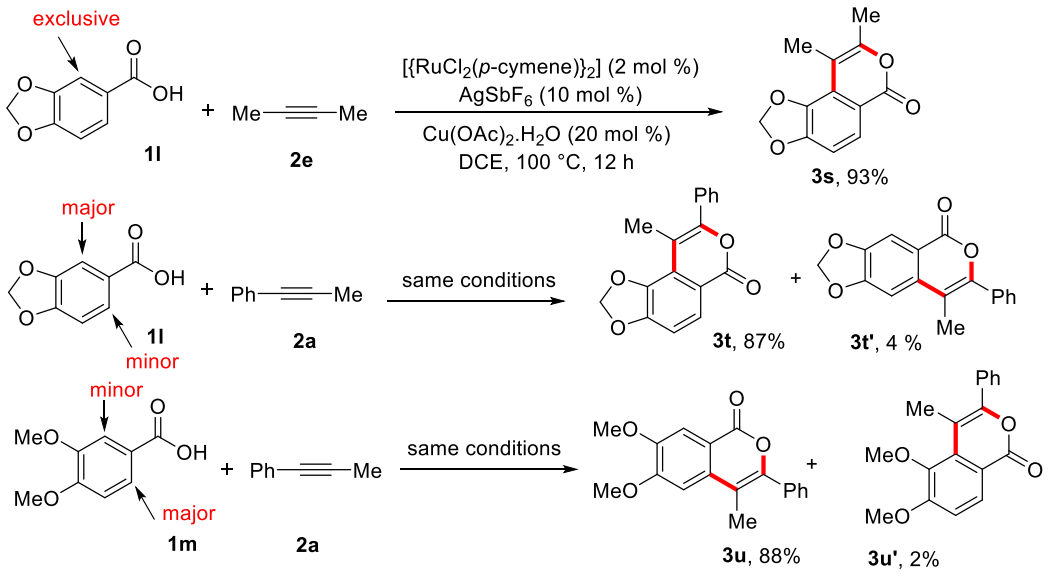
4	 1h	 3n	70%
5	 1j	 3o	85%
6	 1b	 3p	87%
7	 1k	 3q	54%
8	 1k	 3r	88%

[a]All reactions were carried out with substituted aromatic acid **1** (1.00 mmol), symmetrical alkynes (**2**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2 \cdot H_2O$ (20 mol %), and 1,2-dichloroethane (3.0 mL) at 100 °C for 10 h. [b]Isolated yields.

2B.2.3 Regioselective Studies

Subsequently, we studied the regioselectivity of unsymmetrical aromatic acids **1l** and **1m** with alkynes **2** (Scheme 2B.1). The reaction of piperonylic acid (**1l**) with 2-butyne (**2e**) proceeded smoothly to give the corresponding isocoumarin derivative **3s** in 93% yield with high regioselectivity. In the substrate **1l**, there are two *ortho* aromatic C-H bonds for cyclization. Very selectively, oxidative cyclization takes place at the sterically hindered C-H bond of **1l**. The exact reason for the high regioselectivity is unclear in the reaction. We think that in the reaction, in addition to COOH directing group, O group of dioxole moiety of **1l** also assists C-H bond activation.[12] But, the same substrate **1l** reacts with an unsymmetrical alkyne, 1-phenyl-1-propyne (**2a**), to give a mixture of isocoumarin derivatives **3t** and **3t**' in 87% and 4% yields, respectively (Scheme 2B.1). This reaction clearly indicated that formation of major product **3t** was a sterically controlled process as in the case of **3s**. In contrast, 3,4-dimethoxybenzoic acid (**1m**) reacted with **2a** to provide a mixture of products **3u** in 88% yield and **3u'** in 2% yield,

respectively. In the substrate **1m** also, there are two *ortho* aromatic C-H bonds for cyclization. But, oxidative cyclization takes place at the less hindered C-H bond of **1m** moiety predominately. In these reactions, alkyne regiochemistry was highly selective and remained the same as in the case of **3a-j** (Table 2B.1), but the aromatic C-H bond regioselectivity was found to change based on the alkyne reactant.

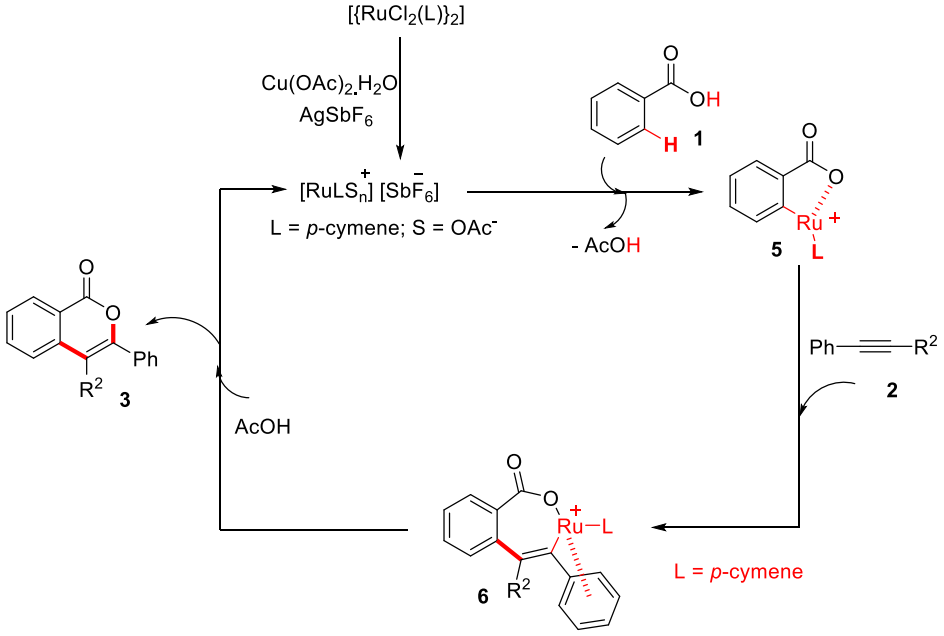


Scheme 2B.1 Regioselective studies

2B.2.4 Mechanism

A possible mechanism of the present oxidative cyclization reaction is shown in Scheme 2B.2. The catalytic reaction is likely initiated by the removal of chloride ligand by Ag^+ in [{$RuCl_2$(*p*-cymene)}$_2$] complex. Coordination of the carboxylate oxygen of **1** to the ruthenium species followed by *ortho* metalation affords a five-membered metallacycle intermediate **5** (for detailed mechanism see experimental section). Regioselective coordinative insertion of an alkyne **2** into the Ru-carbon bond of metallacycle **5** provides intermediate **6**. Subsequent reductive elimination of intermediate **6** in the presence of $Cu(OAc)_2$ gives the final product **3** and regenerates the active ruthenium species for the next catalytic cycle. In the reaction, only catalytic amount of $Cu(OAc)_2$ was used to regenerate the active ruthenium species. It is assumed that the remaining active copper salt can be regenerated under oxygen from the reduced copper source. In our reaction, no decarboxylative product **4** was observed. This is probably because of the possibility that the cationic nature of the ruthenium species increases the relative rate of *ortho* metalation

than that of decarboxylation. The silver salt also played an important role to control the selectivity of the reaction. The exact reason for the high selectivity was unclear in the reaction. The exact role of copper source is $Cu(OAc)_2$ offers an OAc^- source to the active ruthenium species in order to accelerate *ortho*-metalation.



Scheme 2B.2 Proposed mechanism

2B.3 Conclusions

In conclusion, we have developed the oxidative cyclization of substituted acids with alkynes in the presence of catalytic amounts of ruthenium, silver and copper catalysts to provide isocoumarin derivatives in a highly regioselective manner in good to excellent yields. In the reaction, $AgSbF_6$ played an important role to control the regioselectivity of the reaction and also completely suppressed the formation of decarboxylative naphthalene derivatives.

2B.4 References

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2B.5 Experimental Section

2B.5.1 General Procedure for the Oxidative Cyclization of Aromatic acids with Alkynes Catalyzed by Ruthenium Complex

A 25-mL round bottom flask or a 15-mL pressure tube containing [{$RuCl_2$(*p*-cymene)}$_2$] (0.002 mmol, 2 mol %), $AgSbF_6$ (0.010 mmol, 10 mol %) and $Cu(OAc)_2.H_2O$ (0.020mmol, 20 mol %) was evacuated and purged with nitrogen gas three times (Silver salt is moisture sensitive. Thus, the reaction mixture was purged with nitrogen gas). To the flask or tube were then added

aromatic acids (**1**) (1.00 mmol), alkynes **2** (1.20 mmol) and 1,2-dichloroethane or *t*-BuOH (3.0 mL) via syringes and allowed the reaction mixture to stir at room temperature for 5 min. Then, the reaction mixture was allowed to stir at 100 °C for 12 h under open air (for a 15-mL pressure tube, a screw cap was used to cover the tube). After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3**. The reaction worked equally in the both reaction setups. For low boiling reactants (for example, alkynes **2d-e** and acids **1i-j**), a 15-mL pressure tube setup is recommended in order to get more yields.

1.5 mmol of 2-methylacrylic acid (**1i**) was used for the reaction with an alkyne **2a** (1.0 mmol). Yield was calculated based on **2a**.

Similarly, 2.0 mmol of acrylic acid **1j** was used for the reaction with an alkyne **2c** (1.0 mmol).

2B.5.2 Mechanistic Investigation

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

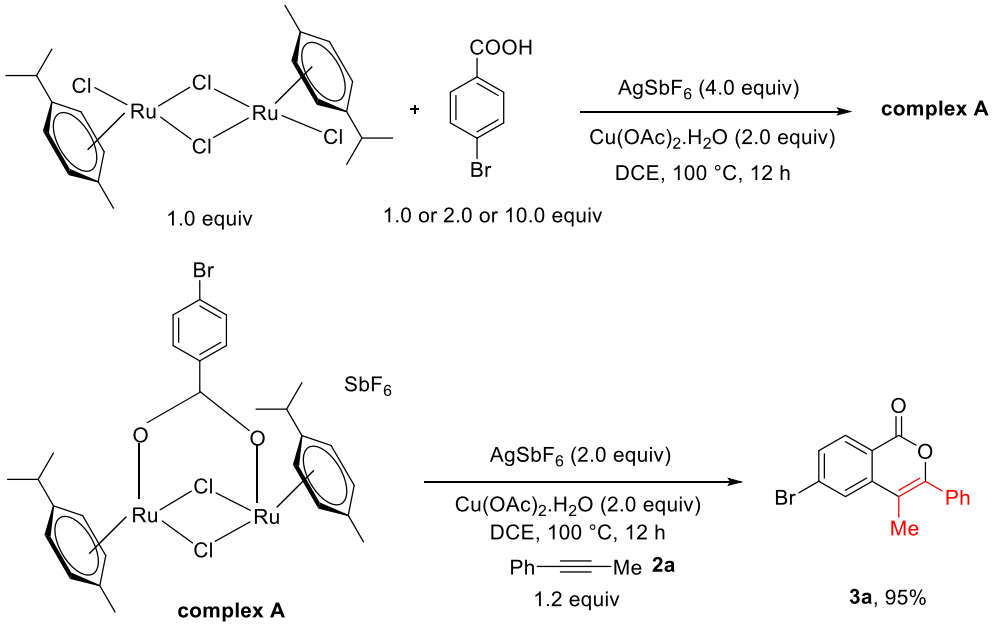
a) To isolate a key five-membered metallacycle intermediate **5,** the reaction of 4-bromobenzoic acid (1.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (1.0 equiv), $AgSbF_6$ (4.0 equiv) and $Cu(OAc)_2.H_2O$ (2.0 equiv) in 1,2-dichloroethane at 100 °C for 12 h was carried out. In the reaction, the expected five-membered metallacycle intermediate **5** cannot be isolated. However, a different type of intermediate **A** was isolated in the reaction mixture (complex **A** is highly stable at room temperature as well as under open atmosphere). The structure of intermediate **A** was determined by a single crystal X-ray diffraction (eq. 2B.7).

In order to get the key intermediate **5**, the ratio of 4-bromobenzoic acid has been changed as:

i) 4-bromobenzoic acid (**1.0 equiv**), [{$RuCl_2$(*p*-cymene)}$_2$] (1.0 equiv), $AgSbF_6$ (4.0 equiv) and $Cu(OAc)_2.H_2O$ (2.0 equiv) in 1,2-dichloroethane at 100 °C for 12 h.

ii) 4-bromobenzoic acid (**2.0 equiv**), [{$RuCl_2$(*p*-cymene)}$_2$] (1.0 equiv), $AgSbF_6$ (4.0 equiv) and $Cu(OAc)_2.H_2O$ (2.0 equiv) in 1,2-dichloroethane at 100 °C for 12 h.

iii) 4-bromobenzoic acid (**10.0 equiv**), [{$RuCl_2$(*p*-cymene)}$_2$] (1.0 equiv), $AgSbF_6$ (4.0 equiv) and $Cu(OAc)_2.H_2O$ (2.0 equiv) in 1,2-dichloroethane at 100 °C for 12 h.



(2B.7)

In all these conditions, only intermediate **A** was observed. Again, the structure of intermediate **A** was determined by a single crystal X-ray diffraction. The expected key intermediate **5** was not observed in these reactions. Complex **A** was also isolated without $Cu(OAc)_2.H_2O$ under similar reaction conditions.

b) Next, the observed complex **A** was further treated with 1-phenyl-1-propyne (**2a**) (1.2 equiv), $AgSbF_6$ (2.0 equiv) and $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv) in 1,2-dichloroethane at 100 °C for 12 h. Again, the expected key intermediate **5** cannot be isolated. But, the cyclization product **3a** was observed exclusively in 95% yield. The reaction of complex **A** with 1-phenyl-1-propyne (**2a**) (1.2 equiv) was also tried without $AgSbF_6$ under similar reaction conditions. In the reaction also, the expected cyclization product **3a** was observed in 92% yield.

We have tried many times to isolate intermediate **5**. Unfortunately, we were not able to isolate it. Meanwhile, we have also tried to record NMR spectrum of intermediate **5**. Due to the high

reactivity and less stable of complex **5**, we were not able to record NMR spectrum of intermediate **5.**

Based on these observations, we concluded that a five-membered metallacycle intermediate **5** was formed during the reaction in the presence of alkyne **2** and further undergo cyclization reaction rapidly with alkyne to give the cyclization product **3**. It seems that intermediate **5** is highly reactive species and difficult to isolate under our reaction conditions. But, the reaction of 1-phenyl-1-propyne (**2a**) with complex **A** clearly revealed that the complex **A** is one of the intermediate of the present reaction.

2B.5.3 Procedure for the Preparation of Ruthenium Complex A

A 15-mL pressure tube containing [{$RuCl_2$(*p*-cymene)}$_2$] (0.100 mg, 1.0 equiv), $AgSbF_6$ (4.0 equiv) and $Cu(OAc)_2.H_2O$ (2.0 equiv) and 4-bromobenzoic acid (1.0 or 2.0 or 4.0 equiv) was evacuated and purged with nitrogen gas three times. Then, 1,2-dichloroethane (4.0 mL) was added via syringe to the tube and allowed the reaction mixture to stir at 100 °C for 12 h. After cooling to ambient temperature, the mixture was filtered through a short Celite pad and the Celite pad was washed with MeOH several times and the filtrate was concentrated by vacuum. Recrystallization from EtOAc/MeOH (9:1) gave single crystals suitable for X-ray analysis.

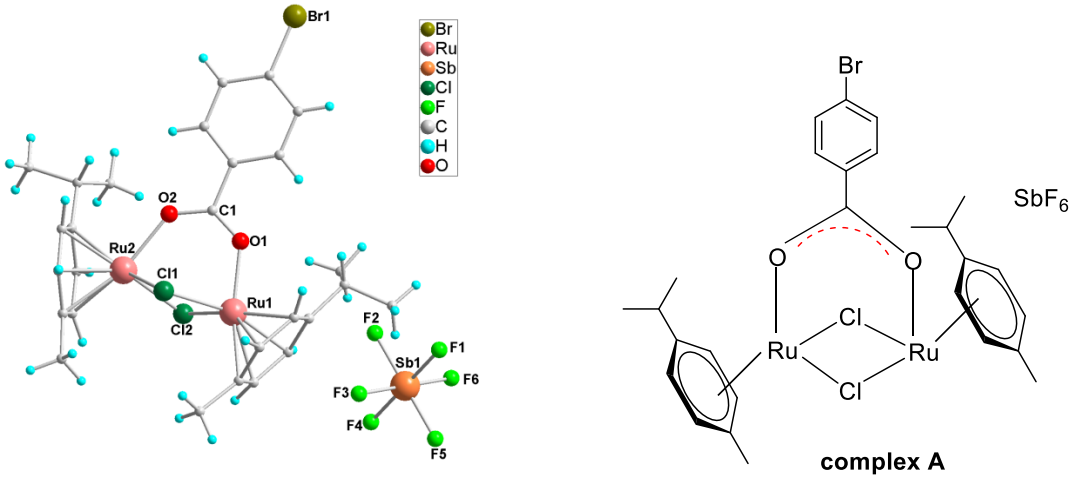


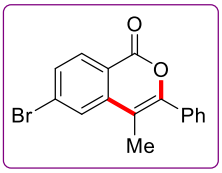
Table 2B.4 Crystal data and structure refinement for intermediate (complex-A).

Identification code	Complex-A
Identification code	$C_{27}H_{32}BrCl_2F_6O_2Ru_2Sb$
Formula weight	977.23

Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
space group	Pnma
Unit cell dimensions	a = 12.7425(16) Å α = 90°. b = 23.711(3) Å β = 90° c = 10.2862(13) Å ϒ = 90°.
Volume	3107.8(7) A^3
Z, Calculated density	4, 2.089 Mg/m^3
Absorption coefficient	3.341 mm^{-1}
F(000)	1888
Crystal size	0.3 x 0.2 x 0.2 mm^3
Theta range for data collection	1.72 to 28.34°.
Limiting indices	-16<=h<=17, -31<=k<=31, -13<=l<=13
Reflections collected / unique	28307 / 3962 [R(int) = 0.0704]
Completeness to theta = 28.34	99.9 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3962 / 0 / 199
Goodness-of-fit on F^2	0.571
Final R indices [I>2sigma(I)]	R_1 = 0.0373, wR_2 = 0.0994
R indices (all data)	R_1 = 0.0701, wR_2 = 0.1446
Largest diff. peak and hole	0.694 and -1.532 $e.A^{-3}$

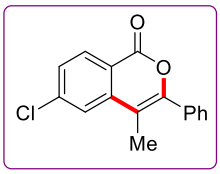
2B.5.4 Spectral Data of Compounds 3a-u

6-Bromo-4-methyl-3-phenyl-1*H*-isochromen-1-one (**3a**): Colorless solid; mp 130-132 °C; eluent (5% ethyl acetate in hexanes); 90% yield (0.282 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3020, 2915, 1710, 1593, 1476 and 1214. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.20 (d, *J*= 8.0 Hz, 1 H), 7.77 (s, 1 H), 7.64 (dd, *J*= 8.0, 4.0 Hz, 1 H), 7.56 – 7.53 (m, 2 H), 7.47 – 7.42 (s, 3 H), 2.27 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz):



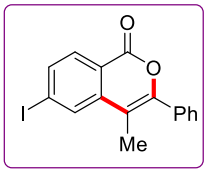
δ 161.9, 152.5, 140.5, 132.9, 131.5, 131.3, 130.6, 129.8, 129.6, 128.5, 126.5, 119.6, 108.4, 13.7. **HRMS** (ESI): calc. for [($C_{16}H_{11}O_2Br$)H] (M+H) 315.0020, measured 315.0034.

6-Chloro-4-methyl-3-phenyl-1*H*-isochromen-1-one (**3b**): Colorless solid; mp 119-121 °C;



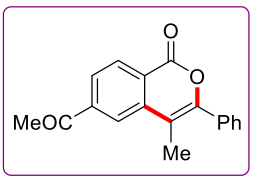
eluent (5% ethyl acetate in hexanes); 86% yield (0.232 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3033, 2925, 1699, 1610, 1593, 1174 and 1096**.** **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.23 (d, *J*= 8.0 Hz, 1 H), 7.54 – 7.50 (m, 3 H), 7.44 – 7.38 (m, 4 H), 2.22 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 161.8, 152.6, 141.8, 140.4, 132.9, 131.5, 129.7, 129.6, 128.5, 123.4, 119.2, 108.5, 13.7. **HRMS** (ESI): calc. for [($C_{16}H_{11}O_2Cl$)H] (M+H) 271.0525, measured 271.0532.

6-Iodo-4-methyl-3-phenyl-1*H*-isochromen-1-one (**3c**): Colorless solid; mp 163-165 °C; eluent



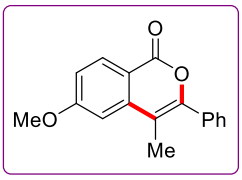
(5% ethyl acetate in hexanes); 92% yield (0.332 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3013, 2922, 1720, 1602, 1586, 1475, 1214 and 1096. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.03 (d, *J*= 8.0 Hz, 1 H), 7.99 (s, 1 H), 7.87 (dd, *J*= 8.0, 4.0 Hz, 1 H), 7.57 – 7.54 (m, 2 H), 7.47 – 7.43 (s, 3 H), 2.26 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 162.2, 152.4, 140.2, 137.2, 133.0, 132.8, 131.1, 129.7, 129.6, 128.4, 120.1, 103.6, 95.6, 13.7. **HRMS** (ESI): calc. for [($C_{16}H_{11}O_2I$)H] (M+H) 362.9882, measured 362.9867.

6-Acetyl-4-methyl-3-phenyl-1*H*-isochromen-1-one (**3d**): Colorless solid; mp 131-133 °C; eluent (8% ethyl acetate in hexanes); 81% yield (0.225 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2925, 1740,



1695, 1605, 1593 and 1174. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.75 (dd, *J*= 8.0, 4.0 Hz, 1 H), 7.62 (d, *J*= 4.0 Hz, 1 H), 7.51 – 7.49 (m, 2 H), 7.41 – 7.37 (m, 3 H), 7.23 (dd, *J*= 8.0, 4.0 Hz, 1 H), 2.52 (s, 3 H), 2.25 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 204.6, 161.1, 151.9, 145.9, 139.6, 134.9, 132.9, 129.7, 129.6, 128.4, 124.8, 124.3, 116.9, 109.8, 31.3, 13.8. **HRMS** (ESI): calc. for [($C_{18}H_{14}O_3$)H] (M+H) 279.1021, measured 279.1018.

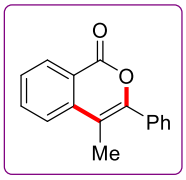
6-Methoxy-4-methyl-3-phenyl-1*H*-isochromen-1-one (**3e**): Colorless solid; mp 127-129 °C;



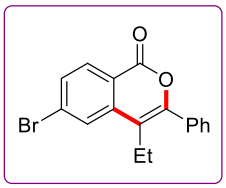
eluent (8% ethyl acetate in hexanes); 93% yield (0.247 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3003, 2932, 1708, 1602, 1488, 1362, 1230 and 1139. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.23 (d, *J*= 8.0 Hz, 1 H), 7.52 – 7.49 (m, 2 H), 7.40 – 7.36 (m, 3 H), 7.01 (dd, *J*= 8.0, 4.0 Hz, 1 H), 6.92(s, 1 H), 3.88 (s, 3 H), 2.20 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.9, 162.4, 152.9, 141.2, 133.4, 132.2, 129.6, 129.4, 128.3, 115.4, 114.0, 109.6, 106.7, 55.8, 13.8. **HRMS** (ESI): calc. for [($C_{17}H_{14}O_3$)H] (M+H) 267.1021, measured 267.1018.

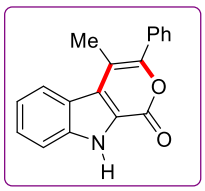
4-Methyl-3-phenyl-1*H*-isochromen-1-one (**3f**): Colorless Semi solid; eluent (5% ethyl acetate in hexanes); 75% yield (0.117 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2922, 1690, 1634, 1605, 1486 and 1317. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.36 (d, *J*= 8.0 Hz, 1 H), 7.78 (t, *J*= 8.0 Hz, 1 H), 7.62 (d, *J*= 8.0 Hz, 1 H), 7.59 – 7.52 (m, 2 H), 7.53 (t, *J*= 8.0 Hz, 1 H), 7.48 – 7.41 (m, 3 H), 2.20 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 162.7, 151.3, 138.4, 134.9, 133.3, 129.8, 129.6, 129.4, 128.5, 128.0, 123.5, 120.9, 109.3, 13.7. **HRMS** (ESI): calc. for [($C_{16}H_{12}O_2$)H] (M+H) 237.0915, measured 237.0924.



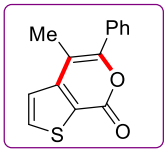
6-Bromo-4-ethyl-3-phenyl-1*H*-isochromen-1-one (**3g**): Colorless solid; mp 129-131 °C; eluent (5% ethyl acetate in hexanes); 87% yield (0.285 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2987, 1710, 1593, 1476, 1214. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.16 (d, *J*= 12.0 Hz, 1 H), 7.72 (s, 1 H), 7.58 (d, *J*= 8.0 Hz, 1 H), 7.49 – 7.47 (m, 2 H), 7.41 – 7.39 (s, 3 H), 2.62 (q, *J*= 8.0 Hz, 2 H), 1.21 (t, *J*= 8.0 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 161.9, 152.7, 139.4, 133.1, 131.7, 131.3, 130.5, 129.8, 128.9, 128.5, 126.5, 120.1, 114.5, 20.2, 14.7. **HRMS** (ESI): calc. for [($C_{17}H_{13}O_2Br$)Na] (M+Na) 350.9996, measured 350.9981.



4-Methyl-3-phenylpyrano[4,3-*b*]indol-1(5*H*)-one (**3h**): Colorless solid; mp 279-281 °C; eluent (30% ethyl acetate in hexanes); 56% yield (0.154 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3359, 2947, 1690, 1567, 1477, 1360 and 1078. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.66 (d, *J*= 8.0 Hz, 1 H), 7.46 – 7.36 (m, 5 H), 7.28 (dd, *J*= 8.0, 4.0 Hz, 2 H), 7.13 (t, *J*= 8.0 Hz, 1 H), 2.26 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 158.1, 152.5, 145.6, 135.8, 132.3, 128.9, 128.6, 127.8, 127.5, 127.4, 126.0, 123.7, 121.5, 120.7, 119.5, 13.9. **HRMS** (ESI): calc. for [($C_{18}H_{13}NO_2$)H] (M+H) 276.1024, measured 276.1037.

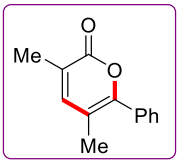


4-Methyl-5-phenyl-7*H*-thieno[2,3-*c*]pyran-7-one (**3i**): Colorless solid; mp 93-95 °C; eluent (8% ethyl acetate in hexanes); 80% yield (0.193 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2988, 1685, 1522, 1427, 1281, 1043. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.78 (d, *J*= 4.0 Hz, 1 H), 7.51 – 7.48 (m, 2 H), 7.38 – 7.33 (m, 3 H), 7.20 (d, *J*= 4.0 Hz, 1 H), 2.29 (s, 3

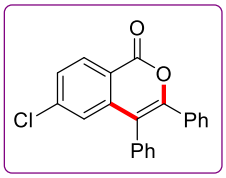


H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 158.8, 153.3, 150.0, 135.0, 132.6, 129.3, 128.4, 128.2, 123.8, 123.0, 109.0, 14.6. **HRMS** (ESI): calc. for [($C_{14}H_{10}O_2S$)H] (M+H) 243.0479, measured 243.0489.

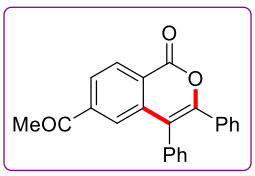
3,5-Dimethyl-6-phenyl-2*H*-pyran-2-one (**3j**): Colorless oil; eluent (5% ethyl acetate in hexanes); 78% yield (0.156 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2987, 1685, 1577, 1425, 1320 and 1178. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.50 – 7.48 (m, 2 H), 7.38 – 7.33 (m, 3 H), 7.04 (s, 1 H), 2.07 (s, 6 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 163.7, 155.0, 144.9, 132.7, 129.5, 128.7, 128.4, 123.9, 111.5, 16.8, 16.5. **HRMS** (ESI): calc. for [($C_{13}H_{12}O_2$)H] (M+H) 201.0915, measured 201.0918.



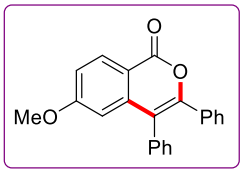
6-Chloro-3,4-diphenyl-1*H*-isochromen-1-one (**3k**): Colorless solid; mp 168-170 °C; eluent (5% ethyl acetate in hexanes); 71% yield (0.228 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2937, 1701, 1573 and 1134. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (d, *J*= 8.0 Hz, 1 H), 7.40 (d, *J*= 8.0, 4.0 Hz, 1 H), 7.37 – 7.35 (m, 3 H), 7.25 (s, 1 H), 7.23 (d, *J*= 8.0 Hz, 1 H), 7.18 – 7.16 (m, 2 H), 7.14 – 7.12 (m, 2 H), 7.10 (t, *J*= 8.0 Hz, 1 H), 7.08 (d, *J*= 4.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 152.3, 141.7, 140.5, 133.7, 132.6, 131.3, 131.2, 129.4, 129.3, 129.2, 128.7, 128.6, 128.0, 125.0, 118.8, 116.2. HRMS (ESI): calc. for [($C_{21}H_{13}O_2Cl$)H] (M+H) 333.0682, measured 333.0682.



6-Acetyl-3,4-diphenyl-1*H*-isochromen-1-one (**3l**): Colorless solid; mp 175-177 °C; eluent (8% ethyl acetate in hexanes); 66% yield (0.224 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2940, 1735, 1688, 1609 and 1154. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (dd, *J*= 8.0, 4.0 Hz, 1 H), 7.37 – 7.35 (m, 2 H), 7.26 – 7.21 (m, 3 H), 7.19 – 7.16 (m, 4 H), 7.15 – 7.10 (m, 3 H), 2.58 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.6, 160.9, 145.7, 134.8, 132.5, 131.3, 129.4, 129.3, 129.2, 129.1, 129.0, 128.6, 128.4, 128.3, 128.0, 126.3, 125.0, 116.8, 31.4. HRMS (ESI): calc. for [($C_{23}H_{16}O_3$)H] (M+H) 341.1177, measured 341.1180.

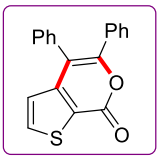


6-Methoxy-3,4-diphenyl-1*H*-isochromen-1-one (**3m**): Colorless solid; mp 170-173 °C; eluent (8% ethyl acetate in hexanes); 72% yield (0.236 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2922, 2850, 1715, 1599, 1487, 1364, 1230 and 1072. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (d, *J*= 8.0 Hz, 1 H), 7.35 – 7.31 (m, 3 H), 7.25 (dd, *J*= 8.0, 4.0

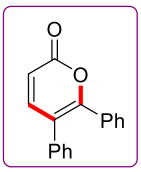


Hz, 2 H), 7.19 – 7.15 (m, 3 H), 7.14 – 7.09 (m, 2 H), 7.00 (dd, *J*= 8.0, 4.0 Hz, 1 H), 6.50 (d, *J*= 4.0 Hz, 1 H), 3.69 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.7, 162.1, 151.6, 141.3, 133.1, 132.0, 131.3, 129.3, 129.2, 129.1, 129.0, 128.2, 127.9, 116.9, 115.7, 113.8, 108.6, 55.6. HRMS (ESI): calc. for [($C_{22}H_{16}O_3$)H] (M+H) 329.1177, measured 329.1180.

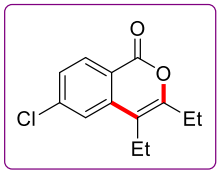
4,5-Diphenyl-7*H*-thieno[2,3-*c*]pyran-7-one (**3n**): Colorless solid; mp 165-167 °C; eluent (8% ethyl acetate in hexanes); 70% yield (0.212 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2922, 2850, 1707, 1576, 1424, 1405 and 1076. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, *J*= 4.0 Hz, 1 H), 7.33 – 7.30 (m, 3 H), 7.29 (t, *J*= 8.0 Hz, 1 H), 7.27 (d, *J*= 4.0 Hz, 1 H), 7.21 – 7.19 (m, 2 H), 7.17 (t, *J*= 8.0 Hz, 1 H), 7.15 – 7.11 (m, 2 H), 6.88 (d, *J*= 4.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 153.5, 149.6, 136.4, 134.9, 132.4, 130.4, 129.4, 129.3, 129.2, 128.3, 128.1, 125.3, 122.9, 115.9. HRMS (ESI): calc. for [($C_{19}H_{12}O_2S$)H] (M+H) 305.0636, measured 305.0648.



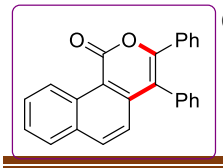
5,6-Diphenyl-2*H*-pyran-2-one (**3o**): Colorless solid; mp 83-85 °C; eluent (5% ethyl acetate in hexanes); 85% yield (0.210 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2966, 1692, 1579, 1415 and 1167. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, *J*= 12.0 Hz, 1 H), 7.30 – 7.28 (m, 2 H), 7.27 – 7.23 (m, 4 H), 7.19 – 7.15 (m, 2 H), 7.10 (dd, *J*= 8.0, 4.0 Hz, 2 H), 6.31 (d, *J*= 8.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.3, 154.5, 147.9, 136.3, 132.2, 130.1, 129.3, 129.2, 129.1, 128.3, 128.0, 117.8, 114.1. HRMS (ESI): calc. for [($C_{17}H_{12}O_2$)H] (M+H) 249.0915, measured 249.0927.



6-Chloro-3,4-diethyl-1*H*-isochromen-1-one (**3p**): Colorless solid; mp 82-84 °C; eluent (5% ethyl acetate in hexanes); 87% yield (0.205 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2973, 1705, 1563, 1433 and 1147. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, *J*= 8.0 Hz, 1 H), 7.42 (s, 1 H), 7.32 (dd, *J*= 8.0, 4.0 Hz, 1 H), 2.57 – 2.51 (m, 4 H), 1.21 (d, *J*= 8.0 Hz, 3 H), 1.12 (d, *J*= 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.2, 156.5, 141.6, 139.4, 131.7, 127.6, 122.4, 112.5, 24.3, 19.4, 14.3, 12.5. HRMS (ESI): calc. for [($C_{13}H_{13}O_2Cl$)H] (M+H) 237.0682, measured 237.0690.

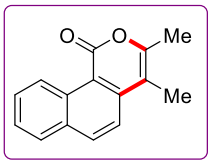


3,4-Diphenyl-1*H*-benzo[*h*]isochromen-1-one (**3q**): Colorless solid; mp 182-184 °C; eluent (5% ethyl acetate in hexanes); 54% yield (0.187 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2989, 1709, 1592, 1453, 1290, 1108. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.85 (d, *J*= 8.0

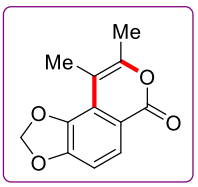


Hz, 1 H), 8.00 (d, *J*= 8.0 Hz, 1 H), 7.88 (d, *J*= 8.0 Hz, 1 H), 7.79 (d, *J*= 8.0 Hz, 1 H), 7.63 (d, *J*= 8.0 Hz, 1 H), 7.45 – 7.42 (m, 3 H), 7.37 (d, *J*= 8.0 Hz, 2 H), 7.30 – 7.28 (m, 2 H), 7.26 – 7.18 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.3, 152.6, 141.1, 135.8, 134.7, 132.8, 132.7, 131.5, 131.4, 129.3, 129.2, 129.1, 129.0, 128.5, 128.2, 127.8, 127.1, 122.8, 117.3, 114.0. HRMS (ESI): calc. for [($C_{25}H_{16}O_2$)H] (M+H) 349.1228, measured 349.1236.

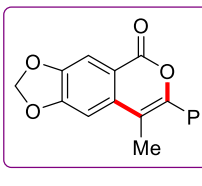
3,4-Dimethyl-1*H*-benzo[*h*]isochromen-1-one (**3r**): Colorless solid; mp 127-129 °C; eluent (5% ethyl acetate in hexanes); 88% yield (0.197 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2924, 1697, 1592, 1508 and 1297. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.76 (d, *J*= 8.0 Hz, 1 H), 8.11 (d, *J*= 8.0 Hz, 1 H), 7.88 (t, *J*= 8.0 Hz, 1 H), 7.73 (d, *J*= 8.0 Hz, 1 H), 7.58 – 7.51 (m, 2 H), 2.37 (s, 3 H), 2.33 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.3, 152.2, 141.1, 134.7, 134.0, 132.2, 131.9, 131.7, 129.4, 128.8, 128.5, 126.4, 120.3, 17.7, 13.0. HRMS (ESI): calc. for [($C_{15}H_{12}O_2$)H] (M+H) 225.0916, measured 225.0923.

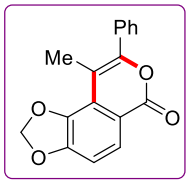


8,9-Dimethyl-6*H*-[1,3]dioxolo[4,5-*f*]isochromen-6-one (**3s**): Colorless solid; mp 88-90 °C; eluent (10% ethyl acetate in hexanes); 93% yield (0.202 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3020, 1709, 1626, 1450, 1288, 1214 and 1051. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J*= 8.0 Hz, 1 H), 6.87 (d, *J*= 8.0 Hz, 1 H), 6.03 (s, 2 H), 2.19 (s, 3 H), 2.17 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.2, 152.7, 149.9, 141.9, 126.1, 122.9, 115.4, 108.8, 105.8, 101.9, 17.0, 14.0. HRMS (ESI): calc. for [($C_{12}H_{10}O_4$)H] (M+H) 219.0657, measured 219.0668.



9-Methyl-8-phenyl-6*H*-[1,3]dioxolo[4,5-*f*]isochromen-6-one (**3t**): Colorless solid; mp 170-174 °C; eluent (10% ethyl acetate in hexanes); 87% yield (0.243 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2964, 2917, 2855, 1714, 1620, 1577, 1497, 1455, 1361 and 1267. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, *J*= 8.0 Hz, 1 H), 7.51 – 7.48 (m, 2 H), 7.39 – 7.35 (m, 3 H), 6.95 (d, *J*= 12.0 Hz, 1 H), 6.07 (s, 2 H), 2.31 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.9, 152.9, 150.7, 142.9, 133.1, 129.6, 129.4, 128.3, 126.2, 123.1, 115.0, 109.5, 107.4, 102.1, 15.7. HRMS (ESI): calc. for [($C_{17}H_{12}O_4$)H] (M+H) 281.0813, measured 281.0821. **8-Methyl-7-phenyl-5*H*-[1,3]dioxolo[4,5-*g*]isochromen-5-one** (**3t'**): Colorless solid; eluent (10% ethyl acetate in hexanes); 4% yield (0.112 gm). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.65 (s,



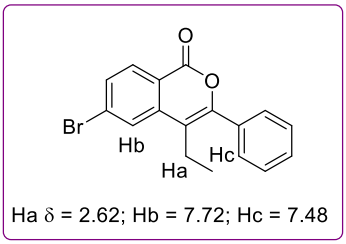


1 H), 7.51 – 7.49 (m, 2 H), 7.39 – 7.36 (m, 3 H), 6.95 (s, 1 H), 6.07 (s, 2 H), 2.20 (s, 3 H).

6,7-Dimethoxy-4-methyl-3-phenyl-1*H*-isochromen-1-one (**3u**): Colorless solid; mp 177-179 °C; eluent (10% ethyl acetate in hexanes); 88% yield (0.264 gm). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2938, 2868, 1706, 1607, 1508, 1464, 1391, 1266 and 1228. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (s, 1 H), 7.55 (dd, *J*= 8.0, 4.0 Hz, 2 H), 7.46 – 7.40 (m, 3 H), 6.94 (s, 1 H), 4.02 (s, 3 H), 3.99 (s, 3 H), 2.29 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9, 155.1, 149.5, 134.6, 133.5, 129.6, 129.2, 128.3, 115.0, 114.1, 109.8, 108.9, 104.3, 56.4, 56.3, 13.9. HRMS (ESI): calc. for [($C_{18}H_{16}O_4$)H] (M+H) 297.1126, measured 297.1128. **5,6-Dimethoxy-4-methyl-3-phenyl-1*H*-isochromen-1-one** (**3u'**): Colorless solid; eluent (10% ethyl acetate in hexanes); 2% yield (0.059 gm). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, *J*= 8.0 Hz, 1 H), 7.55 (dd, *J*= 8.0, 4.0 Hz, 2 H), 7.45 – 7.41 (m, 3 H), 7.12 (d, *J*= 8.0 Hz, 1 H), 3.99 (s, 3 H), 3.85 (s, 3 H), 2.43 (s, 3 H).

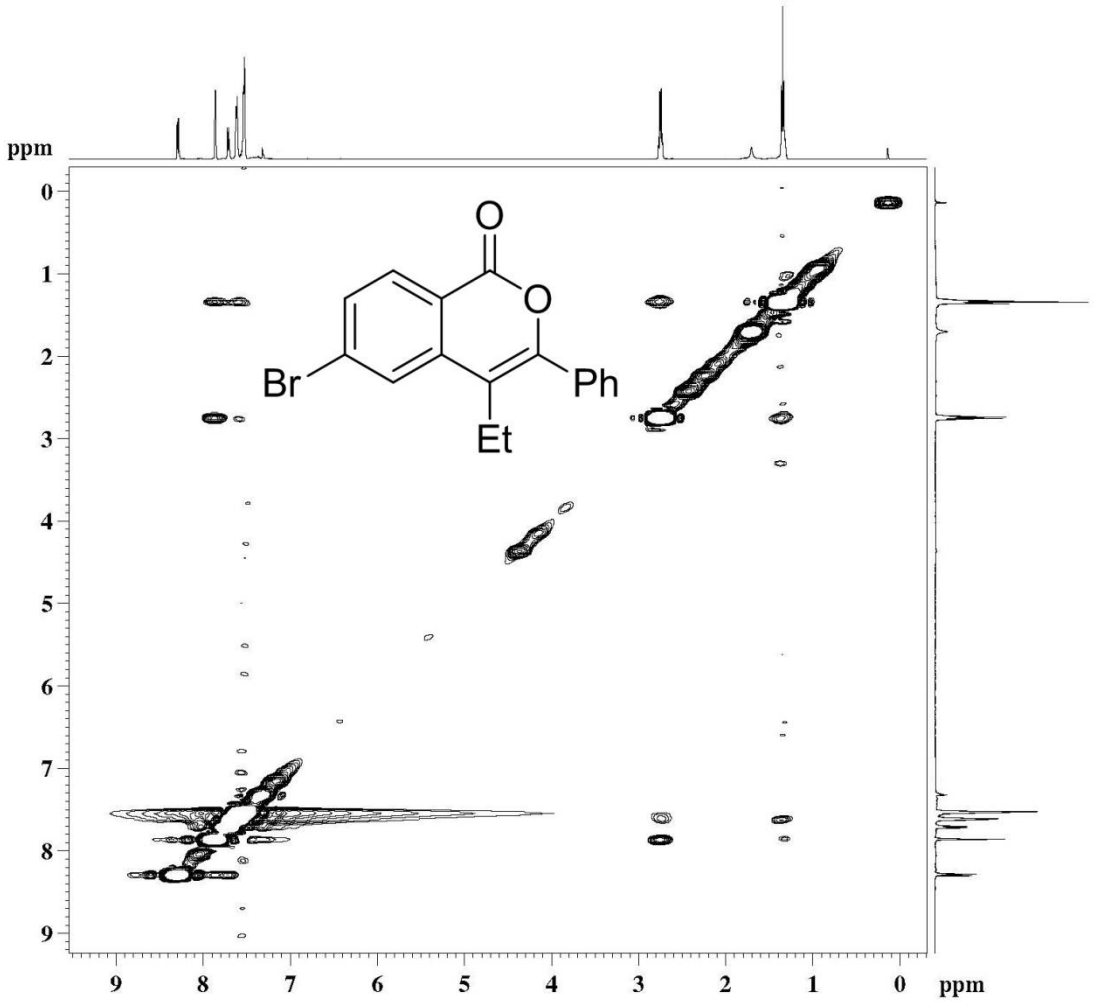
2B.5.3 Regioselective Studies: NOESY Experiments

NOESY Experiments Spectra of Compound **3g**



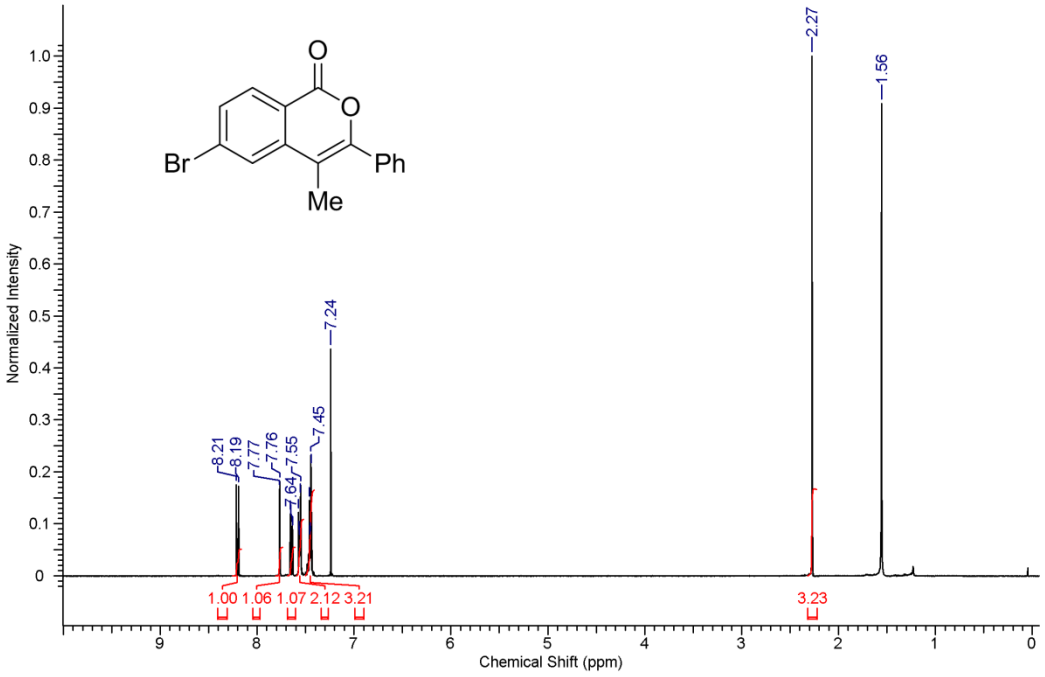
Ha δ = 2.62; Hb = 7.72; Hc = 7.48

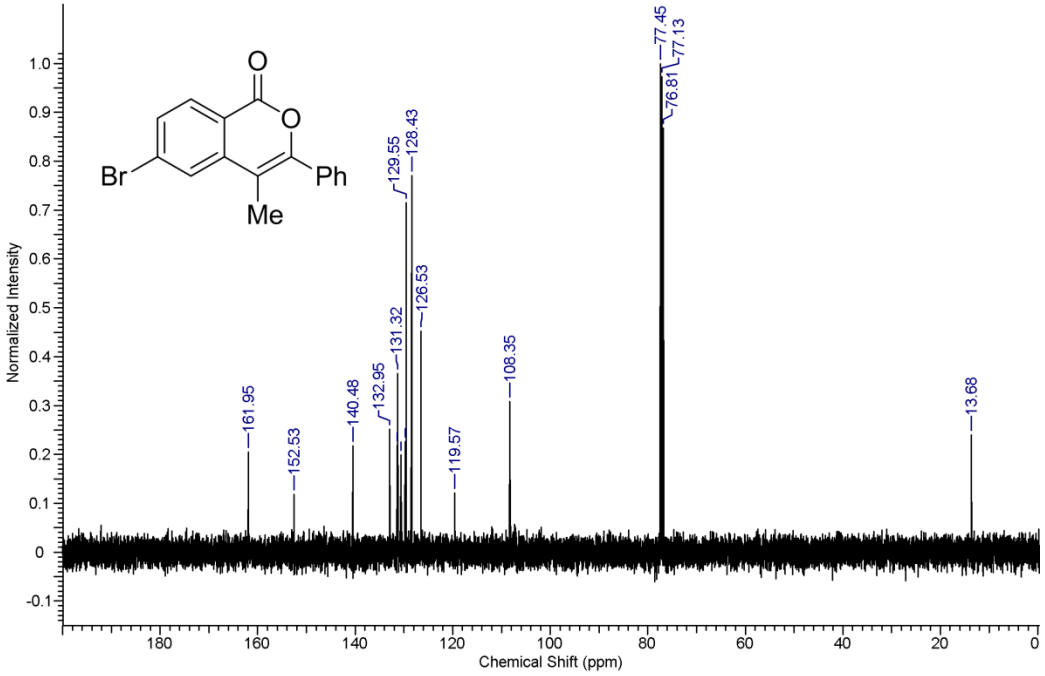
There is a NOE correlation between Ha (δ 2.62, s) and Hb (δ 7.72, s). In meantime, there is also a NOE correlation between Ha (δ 2.62, s) and Hc (δ 7.48, d). However, there is no correlation between Hb (δ 7.72, s) and Hc (δ 7.48, d). These results clearly revealed that the regiochemistry of compound **3g** is correct.



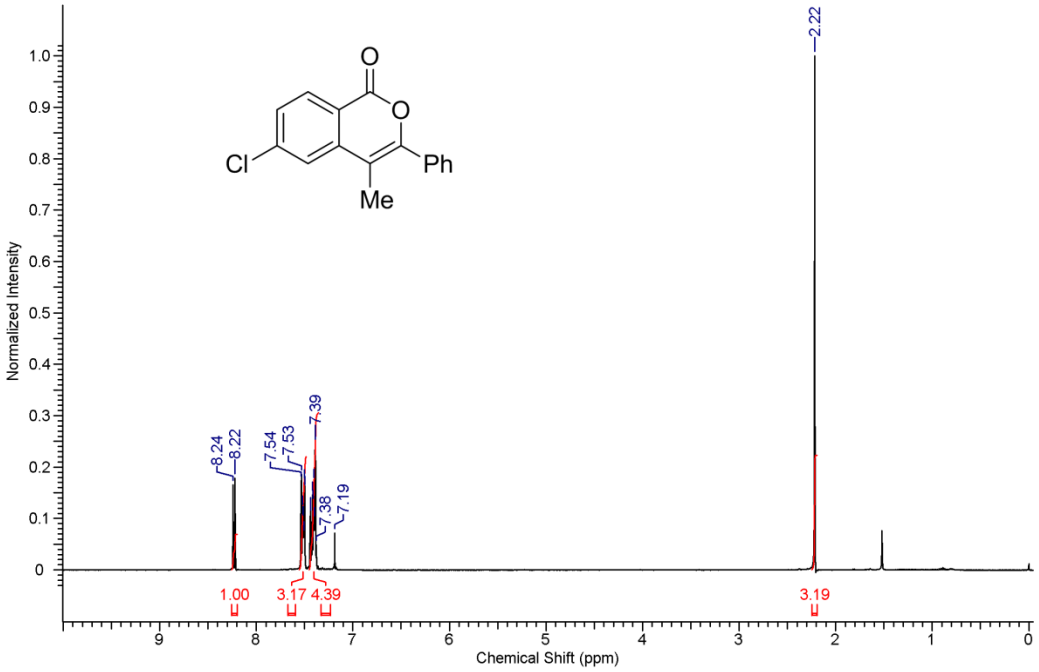
2B.5.4 Spectral Copies of Selected Compounds

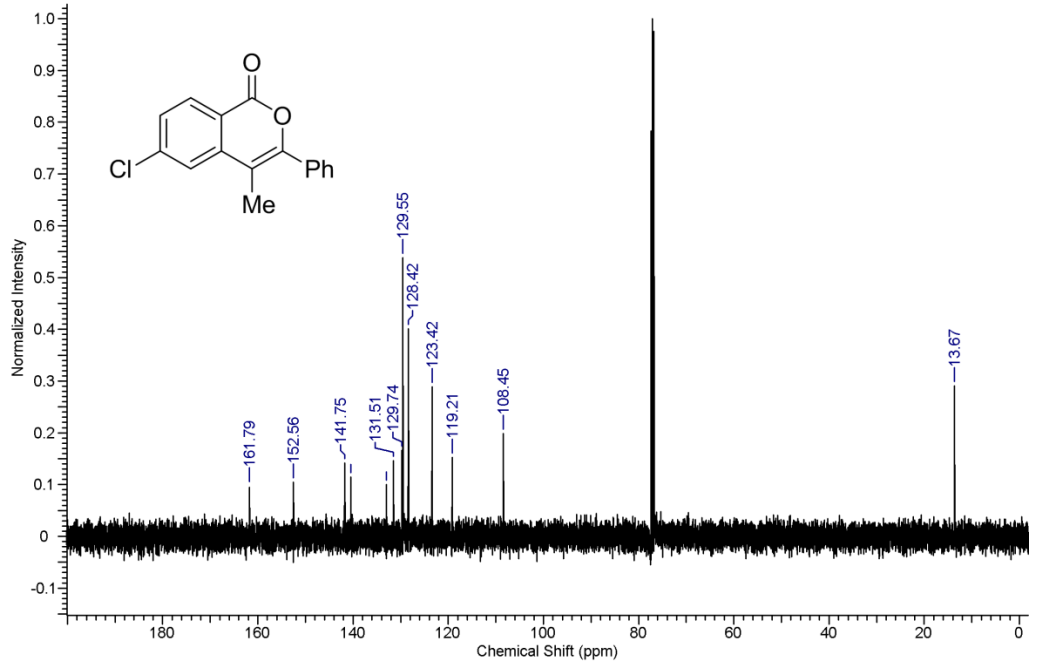
^{1}H and ^{13}C NMR Spectra of Compound **3a**



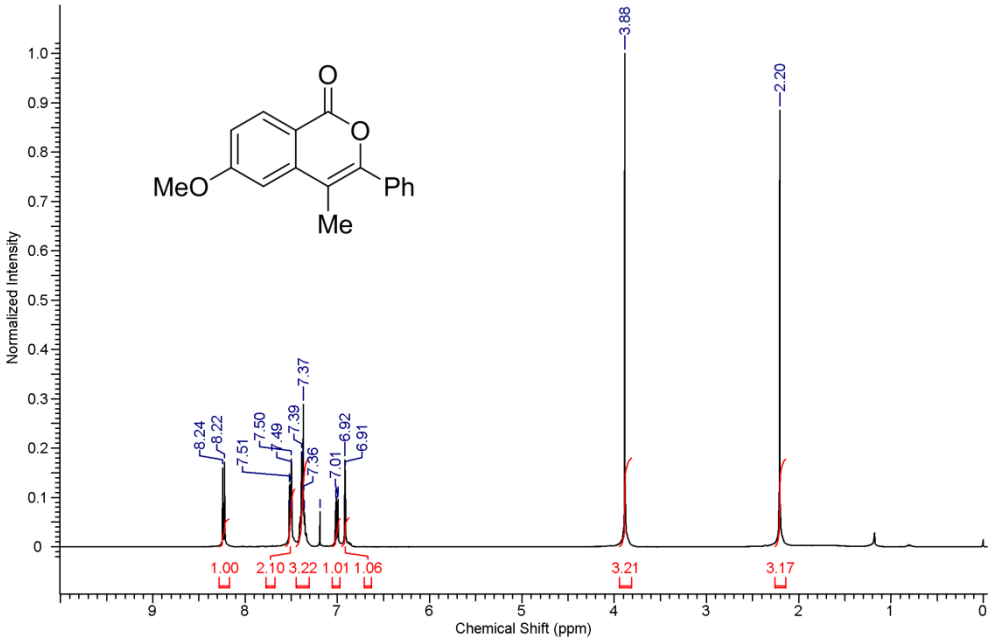


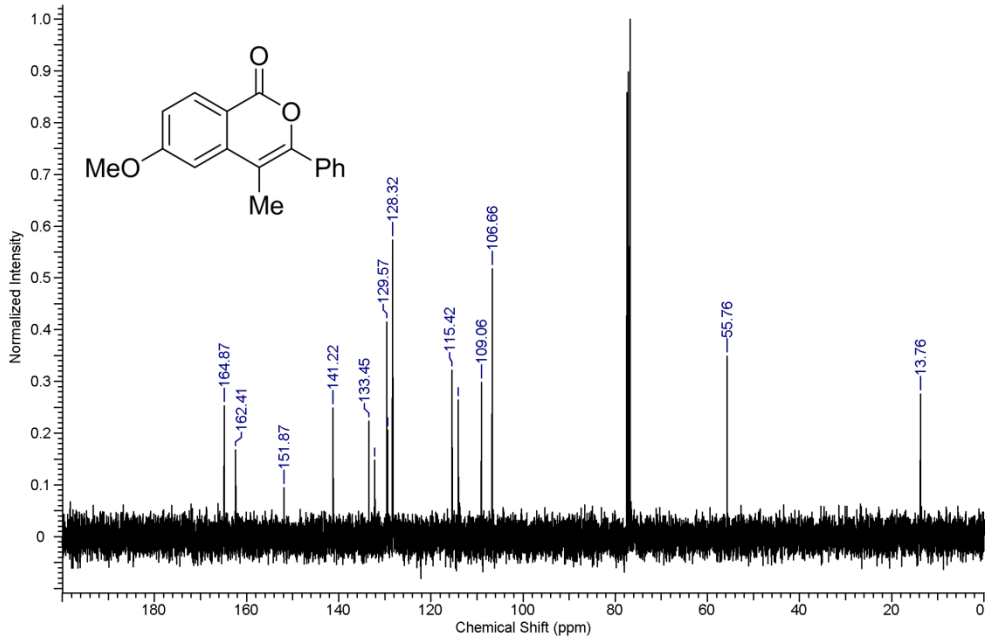
^{1}H and ^{13}C NMR Spectra of Compound **3b**



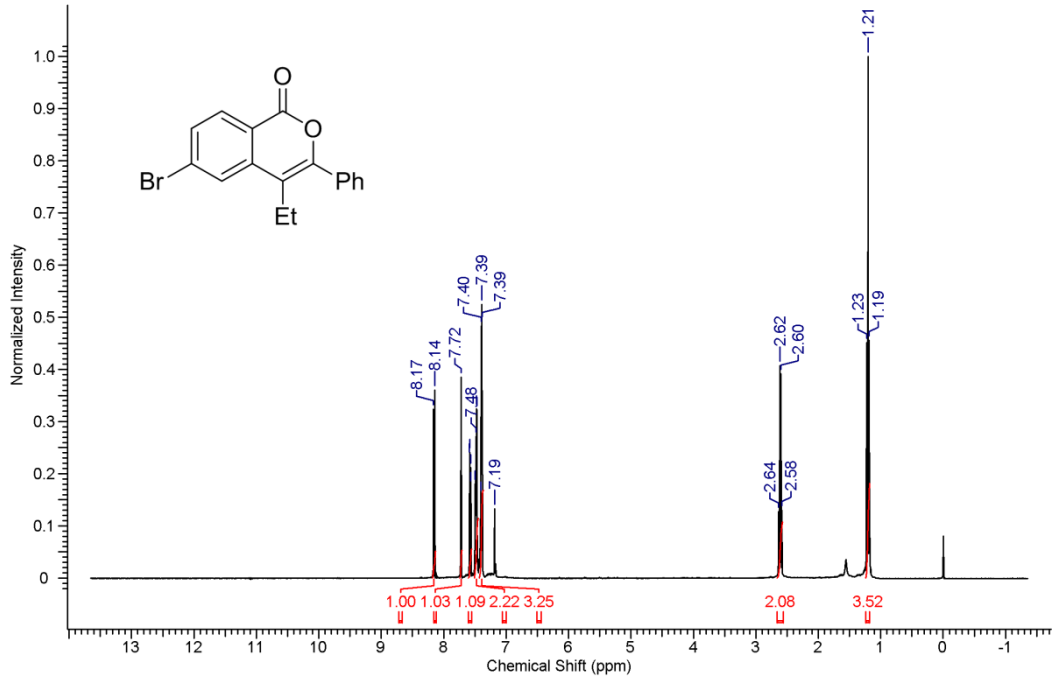


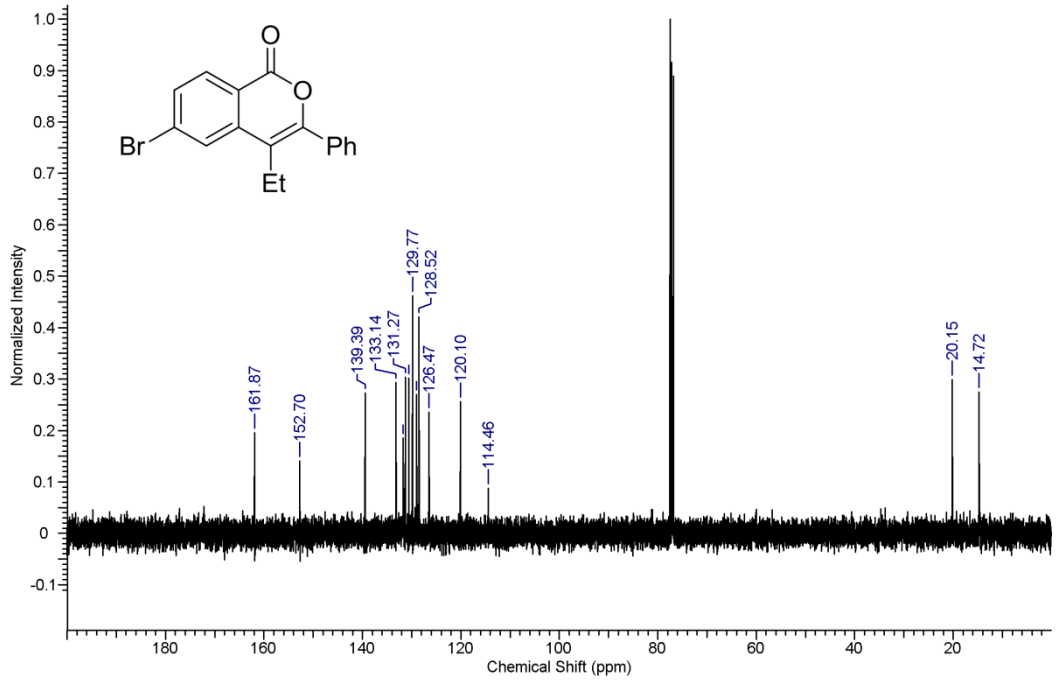
^{1}H and ^{13}C NMR Spectra of Compound **3e**



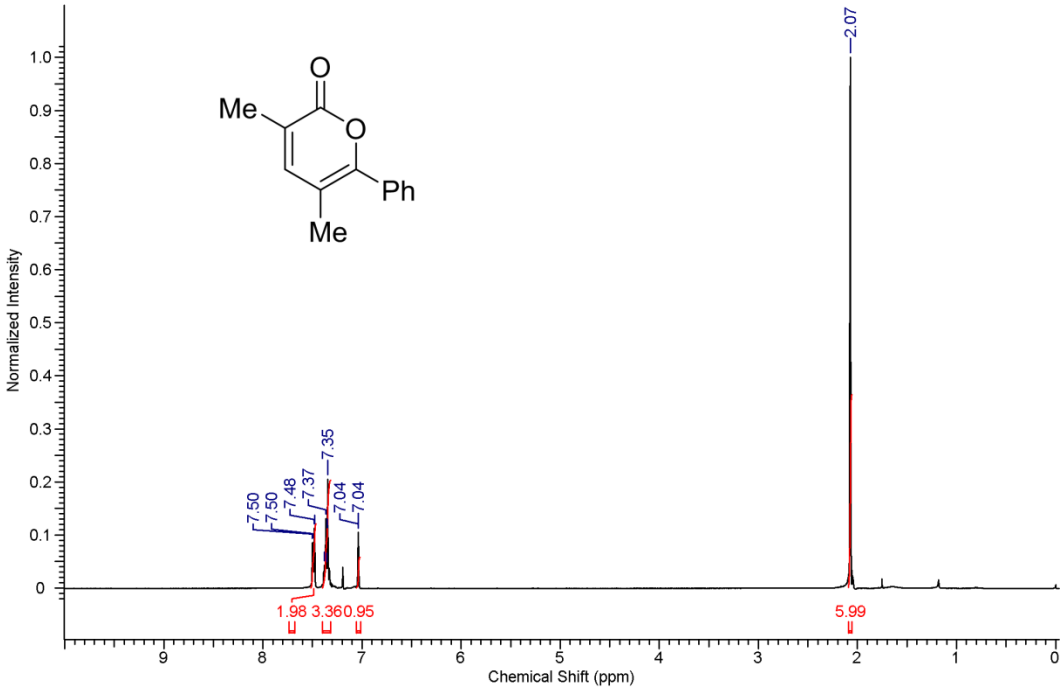


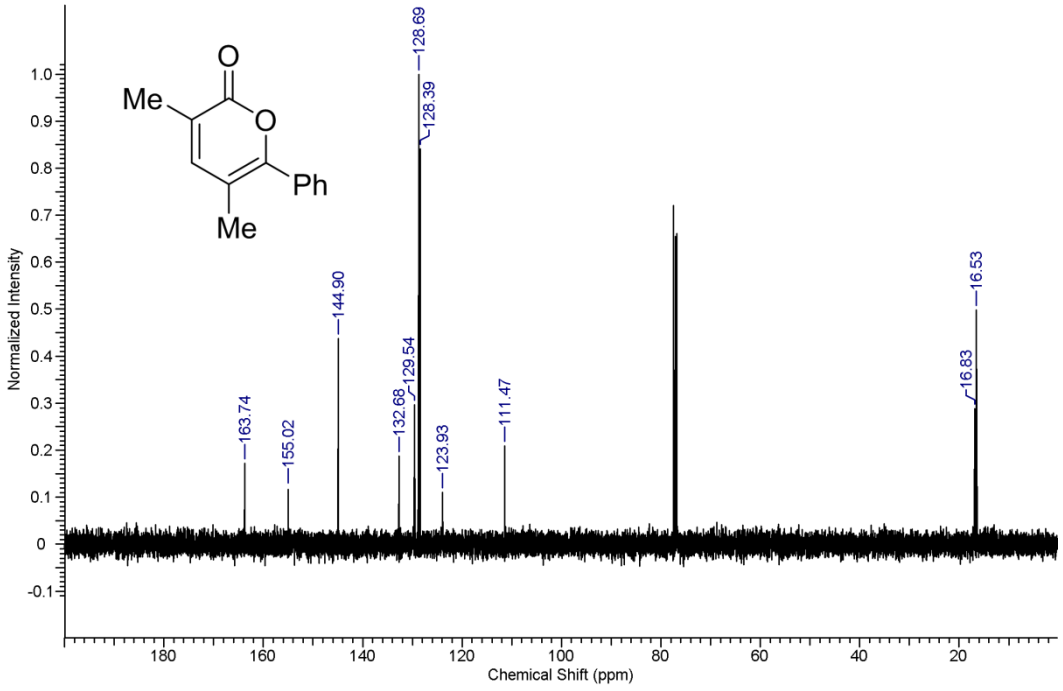
^{1}H and ^{13}C NMR Spectra of Compound **3g**



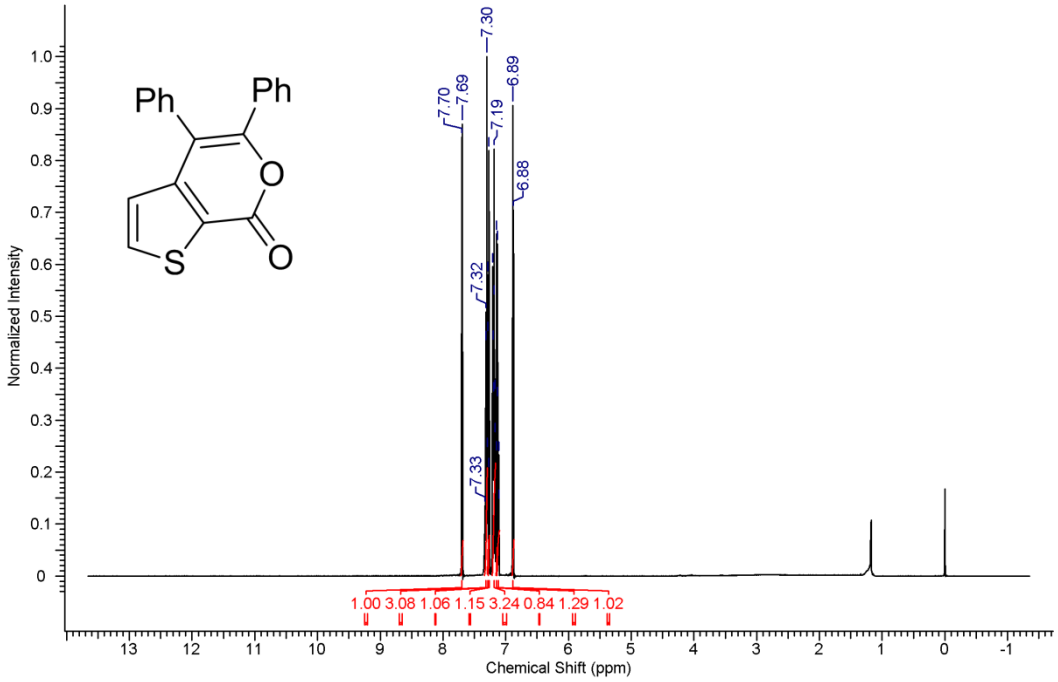


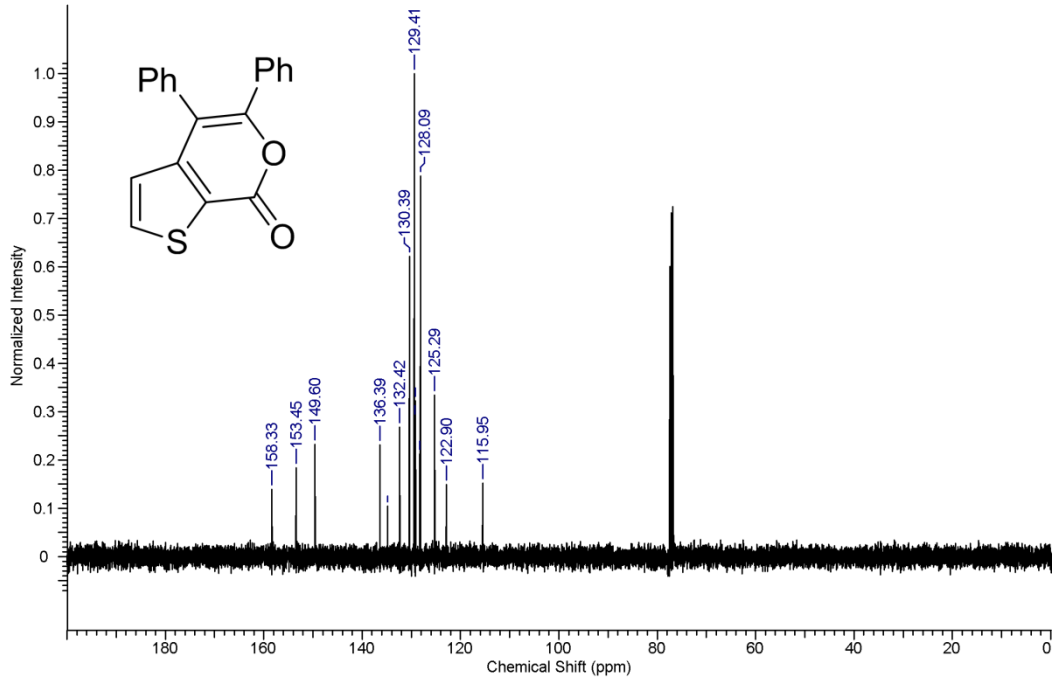
^{1}H and ^{13}C NMR Spectra of Compound **3j**



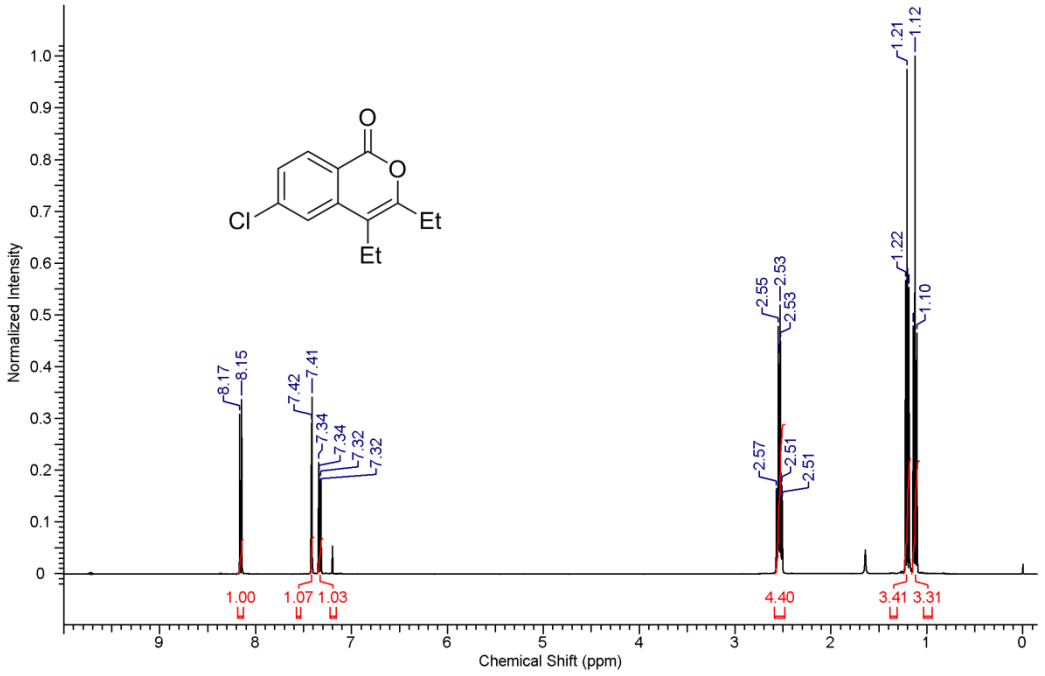


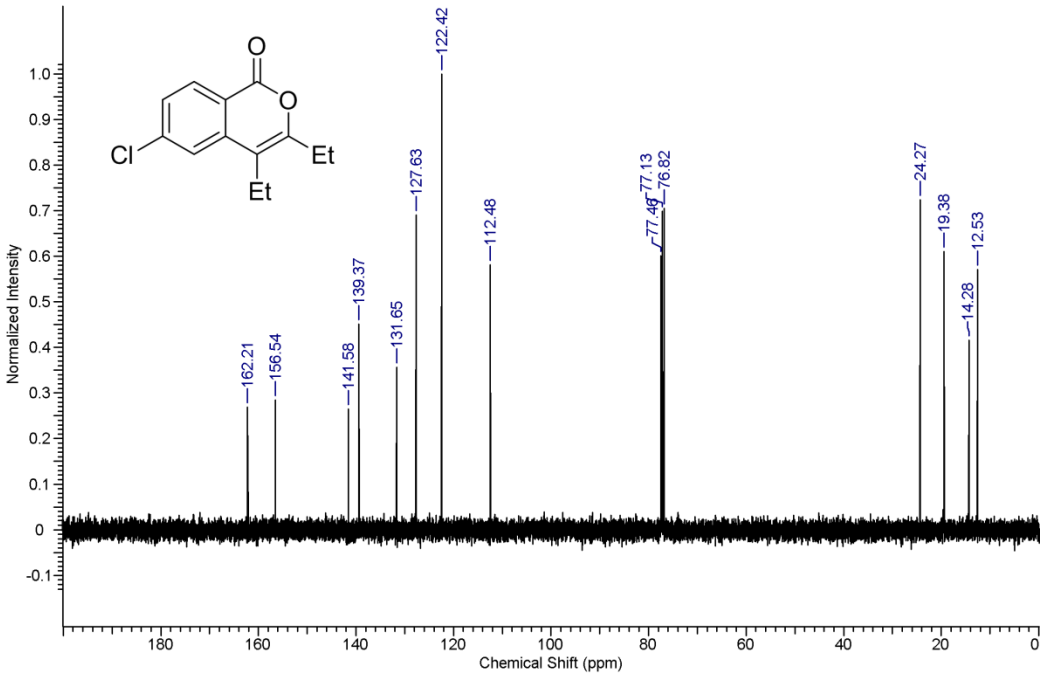
^{1}H and ^{13}C NMR Spectra of Compound **3n**



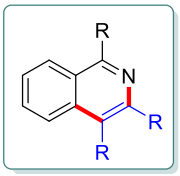


^{1}H and ^{13}C NMR Spectra of Compound **3p**

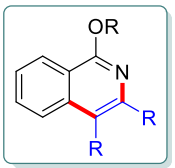




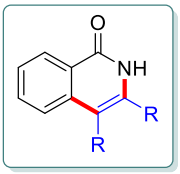
Chapter-3



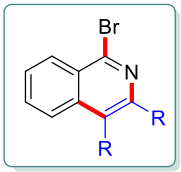
Isoquinolines



1-Alkoxyisoquinolines



Isoquinolones



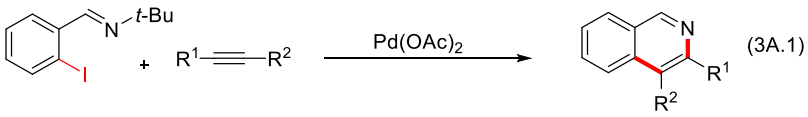
1-Haloisoquinolines

Synthesis of Isoquinolines, 1-Alkoxyisoquinolines, Isoquinolones and 1-Haloisoquinolines

Section 3A: Ruthenium-Catalyzed Highly Regioselective Cyclization of Ketoximes with Alkynes by C-H Bond Activation: A Practical Route to Synthesize Substituted Isoquinolines

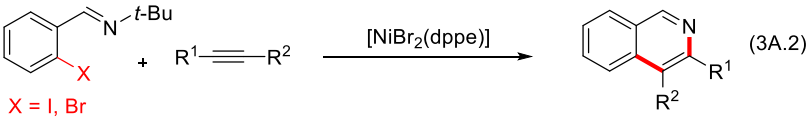
3A.1 Introduction

Isoquinoline derivatives are an important class of heterocyclic compounds. This core is present in various biologically active molecules and natural products.[1] In the literature, several methods are available to synthesize isoquinoline derivatives.[2] Palladium- or nickel-catalyzed cyclization of *o*-halobenzimines with carbon-carbon π-components is one of the promising methods to synthesize isoquinoline derivatives.[3] Lorock's goup reported a palladium-catalyzed cyclization of *tert*-butylimine of o-iodobenzaldehydes with substituted alkynes providing disubstituted isoquinoline derivatives in good to excellent yields (eq. 3A.1).[3a-d]



(3A.1)

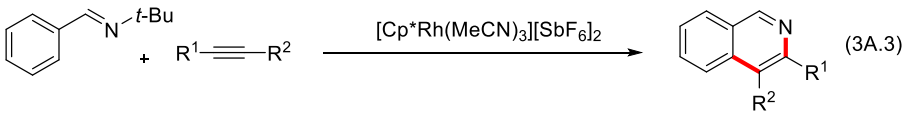
Later, Cheng's group described a less expensive nickel-catalyzed cyclization of *tert*-butylamines of 2-iodobenzaldehydes with substituted alkynes giving isoquinoline derivatives (eq. 3A.2).[3e-f] However, in these reactions, a preactivated halogen group such as I or Br was used to activate *ortho*-carbon of the aromatic imines. However, if the cyclization reaction could be carried out by direct C-H bond activation, it would be highly useful in heterocyclic chemistry, because it is highly atom-economical as well as environmentally friendly process.[4,5]



(3A.2)

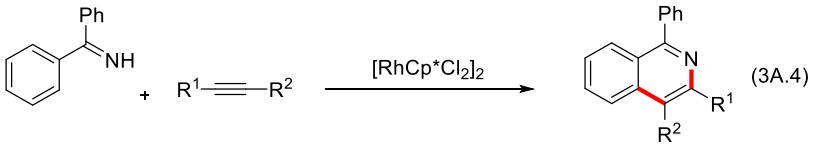
Recently, metal-catalyzed chelation-assisted oxidative annulation of the *ortho* aromatic or alkenyl C-H bond with carbon-carbon π-components has potential application to synthesize heterocyclic compounds. In this cyclization reaction, mostly rhodium complexes have been used as catalysts by several research groups. Rhodium(I)-catalyzed chelation-assisted C-H bond activation of aromatic and alkene imines or oximes followed by alkenylation with alkynes and subsequent intramolecular electrocyclization providing isoquinolines and pyridines have been

reported by several research groups.[4-6] In these reactions, the *ortho* aromatic or alkene C-H bond was activated by imine or oxime directing groups instead of using a preactivated halogen group. This C-H bond activation reaction proceeds via oxidative addition pathway. Later, Fagnou et al. reported a rhodium(III)-catalyzed oxidative cyclization of benzaldimines with alkynes via chelation-assisted deprotonation metalation pathway (eq. 3A.3).[6a]



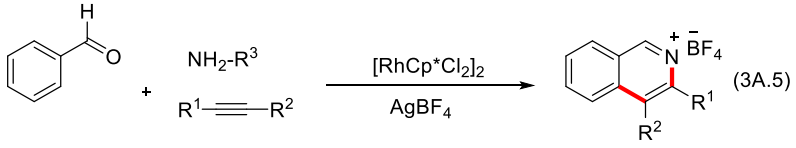
(3A.3)

Later, Miura et al. described a rhodium-catalyzed oxidative cyclization of aromatic imines such as benzylideneanilines and benzophenone imine with alkynes providing indenone imine and isoquinoline derivatives, respectively (eq. 3A.4).[6b]



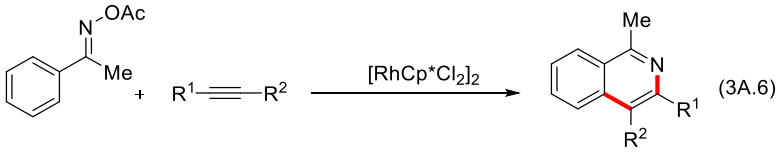
(3A.4)

Subsequently, Cheng's group established a nice method to synthesize isoquinolinium salts from aromatic aldehydes, amines and alkynes in the presence of rhodium(III) catalysts by C-H bond activation (eq. 3A.5).[6c]



(3A.5)

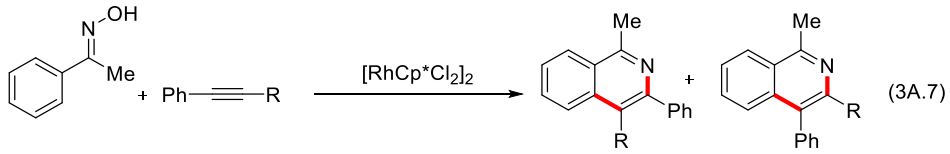
Chiba's group reported a Rh(III)-catalyzed cyclization of aryl ketone *O*-acyloximes with alkynes to construct isoquinoline derivatives by C-H bond activation (eq. 3A.6).[6d-f]



(3A.6)

Very recently, Rovis et al. and Li et al. demonstrated a rhodium-catalyzed cyclization of aromatic ketoximes with alkynes by C-H bond activation.[6g] Although several reports have been known to synthesize isoquinolines by C-H bond activation in the literature, the control of regioselectivity in the cyclization of ketoximes with unsymmetrical alkynes is still a challenging

task. In all reported reactions, a mixture of regioisomeric products was observed with unsymmetrical alkynes (except 1-phenyl-1-propyne). In all these reactions, only a highly expensive rhodium complex was used as catalysts (eq. 3A.7).[6]



(3A.7)

3A.2 Results and Discussion

Recently, a less-expensive ruthenium catalyst has been widely used in the cyclization reaction due to remarkable regioselectivity and low cost of the metal.[7,8] To the best of our knowledge, there is no report discussing the complete regioselective synthesis of isoquinolines by cyclization of ketoximes with unsymmetrical alkynes. Herein, we wish to report a highly regioselective cyclization of aromatic and heteroaromatic ketoximes with substituted alkynes in the presence of catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$] and NaOAc to afford highly substituted isoquinoline derivatives in good to excellent yields. The present catalytic reaction was compatible with various sensitive functional groups substituted unsymmetrical internal as well as terminal alkynes. In all cases, the corresponding isoquinoline derivatives were observed in a highly regioselective manner. It is important to note that terminal alkynes were also compatible for the present reaction. The proposed mechanism of the cyclization reaction was strongly supported by isolation of a key five-membered ruthenacycle intermediate. Experimental evidence was also provided to support the proposed mechanism.

3A.2.1 Optimization Studies

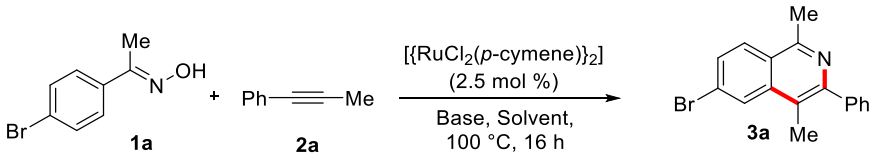


Table 3A.1 Cyclization reaction of 4-bromo oxime (**1**) with 1-phenyl-1-propyne (**2a**).[a]

Entry	Base	Solvents	Yield[b]
1	KOAc	MeOH	75

2	CsOAc	MeOH	65
3	LiOAc	MeOH	35
4	NaOAc	MeOH	81
5	AgOAc	MeOH	43
6	$Cu(OAc)_2$	MeOH	10
7	--	MeOH	25
8	NaOAc	CH_3CN	43
9	NaOAc	DMF	25
10	NaOAc	THF	Nr
11	NaOAc	Tolune	Nr
12	NaOAc	DMSO	Nr
13	NaOAc	DCE	Nr

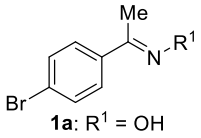
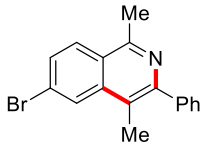
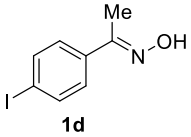
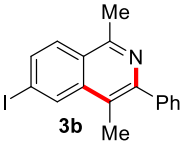
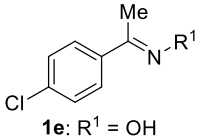
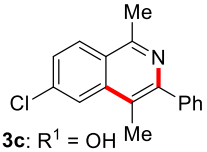
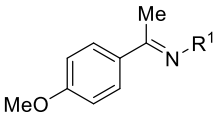
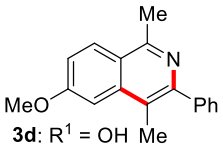
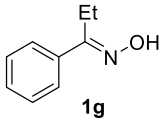
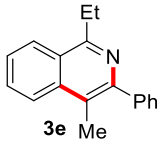
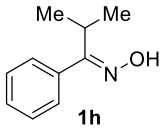
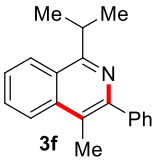
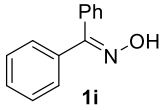
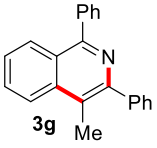
[a]All reactions were carried out with substituted 4-bromo oxime (**1)** (1.00 mmol), 1-phenyl-1-propyne (**2a**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol %), base (25 mol %), and MeOH (3.0 mL) at 100 °C for 16 h. [b]Isolated yields.

When 4-bromoacetophenone oxime (**1a**) was treated with unsymmetrical alkyne, 1-phenyl-1-propyne (**2a**), in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol %) and NaOAc (25 mol %) in MeOH at 100 °C for 16 h, an isoquinoline derivative **3a** was observed in 81% isolated yield Table 3A.1, entry 4). The catalytic reaction afforded almost equal 79% yield in the presence of stoichiometric amount of NaOAc (1.20 equiv). Interestingly, the catalytic reaction also proceeded nicely under open atmosphere to give product **3a** in 80% isolated yield under similar reaction conditions. The catalytic reaction seems to be moisture insensitive. The catalytic reaction was also tested in the absence of NaOAc. In the reaction, product **3a** was observed only in 25% yield (entry 7). The catalytic reaction was also tested with other acetates such as KOAc, CsOAc, LiOAc, NaOAc,AgOAc and $Cu(OAc)_2$. In these reactions, product **3a** was observed only in 75%, 65%, 35%, 81%, 43% and 10% yields, respectively (entry 1-6). The catalytic reaction was also tested with other solvents such as CH_3CN, DMF, THF, toluene, DMSO and DCE. Among them CH_3CN, DMF solvents are less effective **3a** was 43% and 25 yields were

observed (entry 8 and 9). Other solvents were not effective for the catalytic reaction (entry 10-13).

3A.2.2 Synthesis of Isoquinolines

Table 3A.2 Cyclization reaction of substituted aromatic oximes **1a**–**i** with 1-phenyl-1-propyne (**2a**).[a]

Entry	Aromatic oxime (1)	Compound (3)	Yeild[b]
1	 **1a**: R^1 = OH **1b**: R^1 = OMe	 **3a**: R^1 = OH **3a**: R^1 = OMe	81% 70%
2	 **1d**	 **3b**	82%
3	 **1e**: R^1 = OH **1e'**: R^1 = OMe	 **3c**: R^1 = OH **3c**: R^1 = OMe	80% 73%
4	 **1f**: R^1 = OH **1f'**: R^1 = OMe	 **3d**: R^1 = OH **3d**: R^1 = OMe	78% 69%
5	 **1g**	 **3e**	78%
6	 **1h**	 **3f**	84%
7	 **1i**	 **3g**	82%

[a]All reactions were carried out with substituted aromatic oximes **1** (1.00 mmol), 1-phenyl-1-propyne

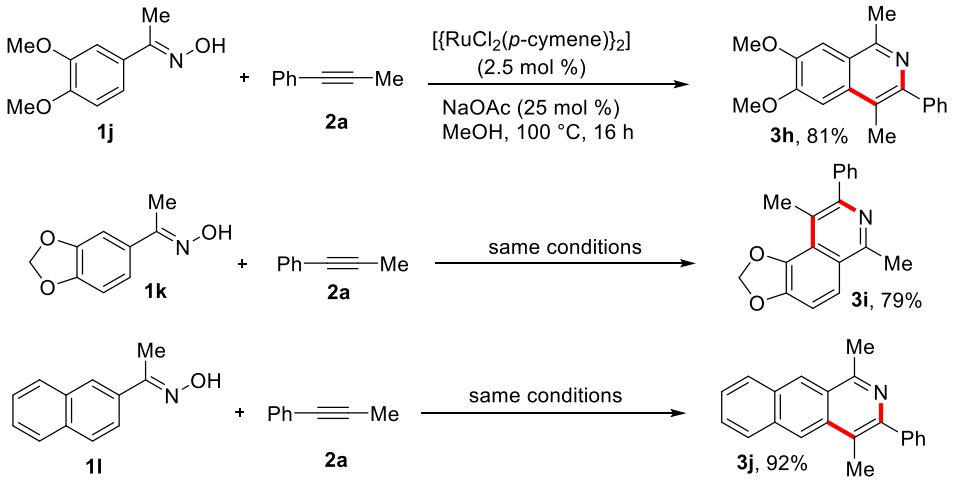
(**2a**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol %), NaOAc (25 mol %), and MeOH (3.0 mL) at 100 °C for 16 h. [b]Isolated yields.

A variety of aromatic ketoximes **1** was compatible for the present cyclization reaction (Table 3A.2). When 4-bromoacetophenone oxime (**1a**) was treated with unsymmetrical alkyne, 1-phenyl-1-propyne (**2a**), in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol %) and NaOAc (25 mol %) in MeOH at 100 °C for 16 h, an isoquinoline derivative **3a** was observed in 81% isolated yield in a highly regioselective manner. The cyclization of *o*-methyl 4-bromoacetophenone oxime (**1b**) and *o*-acetyl 4-bromoacetophenone oxime (**1c**) with **2a** under similar reaction conditions was also examined. In case of *o*-methyl oxime **1b**, the corresponding cyclization product **3a** was observed in 70% yield (entry 1), whereas no cyclization product **3a** was observed in case of *o*-acetyl oxime **1c** with 1-phenyl-1-propyne (**2a**). The cyclization of 4-iodoacetophenone oxime **1d**, 4-chloroacetophenone oxime **1e** and 4-methoxyacetophenone oxime **1f** with 1-phenyl-1-propyne (**2a**) gave isoquinoline derivatives **3b-d** in excellent yields with very high regioselectivity (entry 2-4). The effect of changing the methyl group in acetophenone oxime to some other groups such as ethyl, isopropyl and phenyl was also investigated. Thus, propiophenone oxime **1g**, isobutyrophenone oxime **1h** and benzophenone oxime **1i** efficiently underwent cyclization with **2a** to provide isoquinoline derivatives **3e-g** in 78%, 84% and 82% yields, respectively (entry 5-7). The cyclization reaction of various substituted *o*-methyl oximes with **2a** was also tested. Thus, the reaction of *o*-methyl 4-chloroacetophenone oxime and *o*-methyl 4-methoxyacetophenone oxime with **2a** produced corresponding cyclization products **3c** and **3d** in 73% and 69% yields, respectively (entry 3 and 4). It is important to note that cyclization of substituted *o*-methyl oximes with alkynes affording isoquinoline derivatives is unprecedented in the literature.

3A.2.3 Regioselective Studies

Next, the regioselectivity of unsymmetrical aromatic ketoximes **1j-l** with an unsymmetrical alkyne, 1-phenyl-1-propyne (**2a**), was examined. Thus, 3,4-dimethoxyacetophenone oxime **1j** reacted with **2a** regioselectively to afford **3h** in 81% yield. In the substrate **1j**, there are two *ortho* aromatic C-H bonds for cyclization. Regioselectively, the cyclization takes place at the less hindered C-H bond of **1j** moiety exclusively. In contrast, 3,4-methylenedioxy acetophenone oxime **1k** reacted with **2a** to produce a reverse regioselective product **3i** exclusively in 79% yield. In **1k** also, there are two *ortho* aromatic C-H bonds for cyclization. But, oxidative

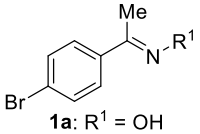
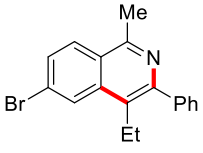
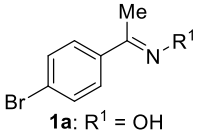
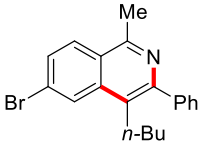
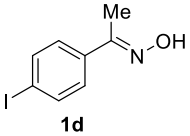
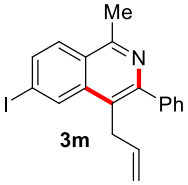
cyclization takes place at the sterically hindered C-H bond of **1k** moiety predominately. As like **1j**, 2-acetonaphthone oxime **1l** also underwent cyclization regioselectively with **2a** at the less substituted C-H bond of **1l** to give **3j** in excellent 92% yield (Scheme 3A.1).

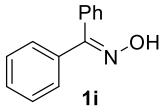
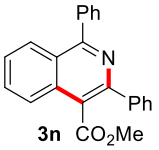
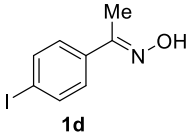
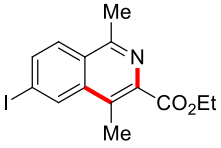
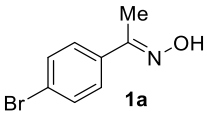
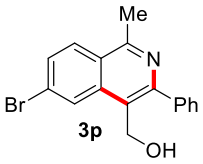
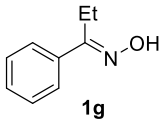
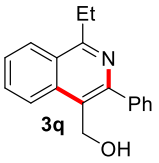
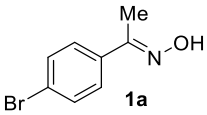
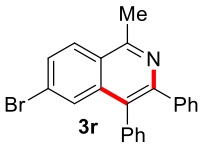
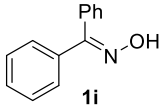
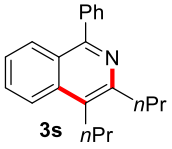


Scheme 3A.1 Regioselective studies

3A.2.4 Scope of the Substituted and Unsymmetrical Alkynes

Table 3A.3 Cyclization reaction of substituted aromatic oximes **1a**–**i** with alkynes (**2a**).[a]

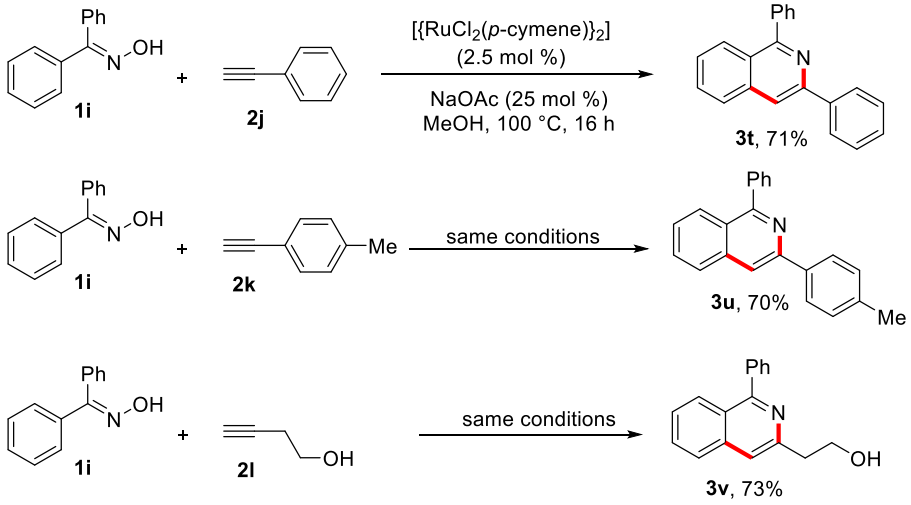
Entry	Aromatic oxime (1)	Compound (3)	Yeild[b]
1	 **1a**: R^1 = OH **1b**: R^1 = OMe	 **3k**: R^1 = OH **3k**: R^1 = OMe	72% 63%
2	 **1a**: R^1 = OH **1b**: R^1 = OMe	 **3l**: R^1 = OH **3l**: R^1 = OMe	74% 65%
3	 **1d**	 **3m**	55%

4	 **1i**	 **3n** CO_2Me	65%
5	 **1d**	 **3o**: R^1 = OH **3o**: R^1 = OMe	63% 54%
6	 **1a**	 **3p**	77%
7	 **1g**	 **3q**	81%
8	 **1a**	 **3r**	80%
9	 **1i**	 **3s**	76%

[a]All reactions were carried out with substituted aromatic oximes **1** (1.00 mmol), alkynes (**2a**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol %), NaOAc (25 mol %), and MeOH (3.0 mL) at 100 °C for 16 h. [b]Isolated yields.

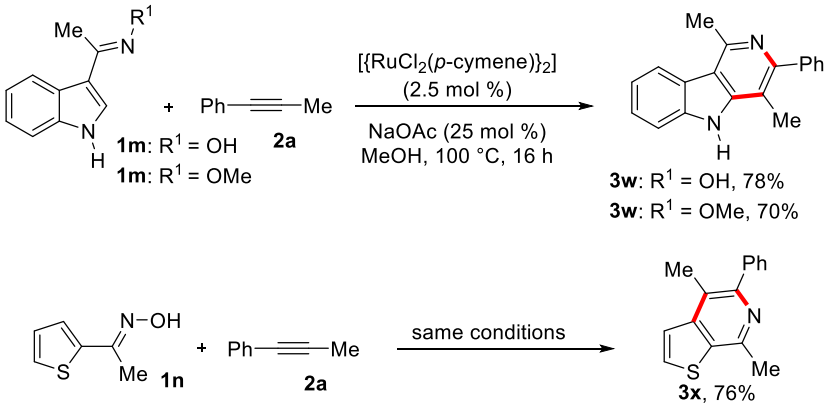
For further understanding the regioselectivity of the present reaction, cyclization of ketoximes **1** with various unsymmetrical alkynes was examined under similar reaction conditions (Table 3A.3). Unsymmetrical alkynes, 1-phenyl-1-butyne (**2b**), 1-phenyl-1-hexyne (**2c**) and 1-phenyl-4-penten-1-yne (**2d**) reacted with 4-bromoacetophenone oxime **1a** or 4-iodoacetophenone oxime **1d** regioselectively to afford **3k-m** in 72%, 74% and 55% yields, respectively (entry 1-3). Surprisingly, bulky benzophenone oxime **1i** reacted efficiently with methyl phenylpropiolate (**2e**) to provide the corresponding isoquinoline derivative **3n** in 65% yield (entry 4). Ethyl 2-butynoate (**2f**) also reacted efficiently with 4-iodoacetophenone oxime **1d** to afford isoquinoline derivative **3o** in 63% yield in a highly regioselective manner. Interestingly (entry 5), 3-phenyl-2-

propyn-1-ol (**2g**) also efficiently participated in the cyclization reaction with 4-bromoacetophenone oxime **1a** and propiophenone oxime **1g** to give the corresponding isoquinoline derivatives **3p** and **3q** in 77% and 81% yields, respectively (entry 6 and 7), in a highly regioselective manner. Also, *o*-methyl 4-bromoacetophenone oxime **1b** and *o*-methyl 4-iodoacetophenone oxime underwent cyclization reaction with 1-phenyl-1-butyne (**2b**), 1-phenyl-1-hexyne (**2c**) and ethyl 2-butynoate (**2f**) to provide the corresponding isoquinoline derivatives **3k**, **3l** and **3o** in 63%, 65% and 54% yields, respectively (entry 1,2 and 5). The catalytic reaction was also tested with symmetrical alkynes. Thus, diphenyl acetylene (**2h**) and 3-hexyne (**2i**) underwent cyclization with 4-bromoacetophenone oxime **1a** or benzophenone oxime **1i** to afford isoquinoline derivatives **3r** and **3s** in 80% and 76% yields, respectively (entry 8 and 9).



Scheme 3A.2 Studies of the terminal alkynes

Terminal alkynes were also compatible for the present cyclization reaction (Scheme 3A.2). Thus, phenylacetylene (**2j**) reacted efficiently with **1i** to give isoquinoline derivative **3t** in 71% yield in a highly regioselective manner. Similarly, 4-methyl phenylacetylene (**2k**) and pent-4-yn-1-ol (**2l**) also efficiently participated in the cyclization reaction with **1i** to afford the corresponding isoquinoline derivatives **3u** and **3v** in 70% and 73% yields, respectively, in a highly regioselective manner. In the reaction, highly substituted carbon of terminal alkyne was connected to the nitrogen atom of oxime **1i** and terminal carbon of alkyne was attached to the *ortho* carbon of oxime **1i** (Scheme 3A.2).

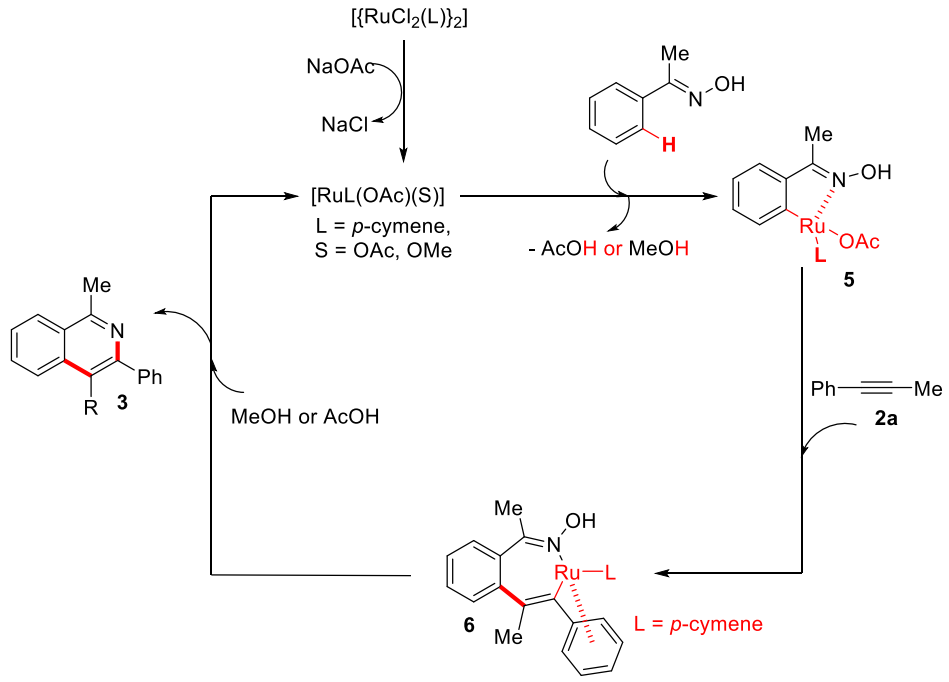


Scheme 3A.3 Studies of the hetero aromatic oximes

The catalytic reaction was also tested with heteroaromatic oximes **1m** and **1n**. Treatment of 3-acetylindole oxime **1m** with **2a** under the optimized reaction conditions gave isoquinoline derivative **3w** in 78% yield, in a highly regioselective manner. The *o*-methyl 3-acetylindole oxime also underwent cyclization reaction with **2a** to provide **3w** in 70% yield. 2-Acetylthiophene oxime **1n** reacted with **2a** regioselectively to afford the corresponding cyclization product **3x** in 76% yield (Scheme 3A.3).

3A.2.5 Mechanism

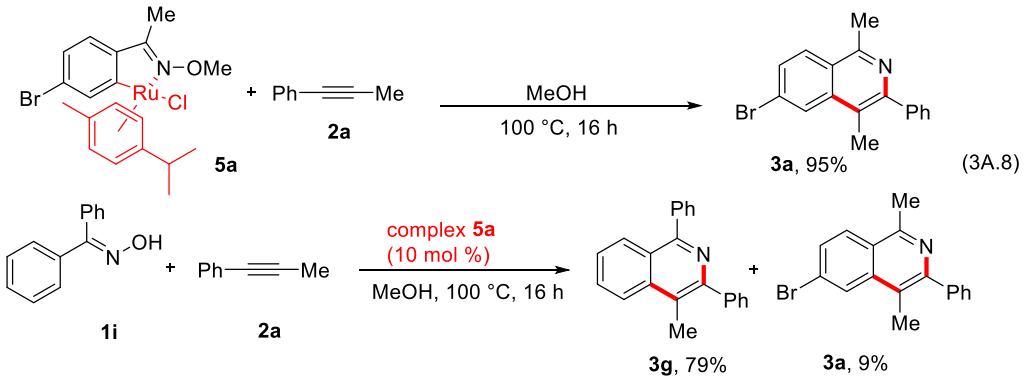
Based on the known metal-catalyzed C-H bond activation,[4-8] a reasonable mechanism is proposed to account for the present cyclization reaction in Scheme 3A.4. The dissociation of dimeric form of ruthenium complex to monomer followed by ligand exchange with NaOAc gives a ruthenium acetate species **4** to initiate the catalytic reaction. Coordination of the nitrogen atom of oxime **1** to the ruthenium acetate species **4** followed by acetate accelerated *ortho*-metalation affords a five-membered metalacycle intermediate **5**. Coordinative regioselective insertion of alkyne **2** into the Ru–carbon bond of intermediate **5** provides a seven-membered intermediate **6**. Subsequent C-N bond formation and N-O bond cleavage of intermediate **6** in the presence of MeOH or AcOH affords product **3** and regenerates the active ruthenium species **4** for the next catalytic cycle. The exact reason for high regioselectivity is not very clear in the reaction. The phenyl group of alkyne **2** might coordinates intramolecularly with ruthenium metal in intermediate **6** and stabilizes it. This may be the reason for the high regioselectivity (Scheme 3A.4).



Scheme 3A.4 Proposed mechanism

The proposed mechanism in scheme 4 is strongly supported by the isolation of key ruthenacycle intermediate **5a** (eq. 3A. 8). When *o*-methyl 4-bromoacetophenone oxime (**1b**) was treated with stoichiometric amount of [{$RuCl_2$(*p*-cymene)}$_2$] and NaOAc in MeOH at 100 °C for 16 h, a five-membered ruthenacycle intermediate **5a** was observed in 69% yield (eq. 8). The structure of complex **5a** was determined by single crystal X-ray diffraction. Subsequently, when intermediate **5a** was treated with alkyne **2a** in the presence of MeOH at 100 °C for 10 h, an isoquinoline derivative **3a** was obtained in 95% yield. In the present cyclization reaction of oximes **1** with alkynes **2**, only catalytic amount of NaOAc (25 mol %) was used. However, a stoichiometric amount of NaOAc (1.2 equiv) is crucial for the acetate mediated *ortho*-metalation.[9] It is likely that during the C-N bond formation of intermediate **6**, MeOH protonates OH group of intermediate **6** and regenerates the active ruthenium methoxide catalyst **4** for next catalytic cycle (assuming that due to the intramolecular coordination of the nitrogen to ruthenium in intermediate **6**, the OH group at the nitrogen side in intermediate **6** could be basic character). This assumption is strongly supported by the following experimental evidence. Treatment of benzophenone oxime (**1i**) with 1-phenyl-1-propyne (**2a**) in the presence of catalytic amount of complex **5a** (10 mol %) in MeOH at 100 °C for 16 h gave isoquinoline derivatives **3g** in 79% and **3a** in 9% yields (Scheme 3A.1). In the cyclization reaction, NaOAc was not used. This result

clearly reveals that in the cyclization reaction, NaOAc provides the OAc^- source to the ruthenium species to initiate the *ortho*-metalation of the first catalytic cycle. In the subsequent catalytic cycles, MeOH protonates the OH of intermediate **6** and regenerates the active ruthenium methoxide **4** for the next *ortho*-metalation.



Based on these studies, the cyclization reaction of some of the substituted oximes **1** with alkynes **2** was examined in the absence of NaOAc and only in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol %) in MeOH at 100 °C for 16 h. The observed results showed that in some reactions such as propiophenone oxime **1g** and isobutyrophenone oxime **1h** with 1-phenyl-1-propyne (**2a**) gave corresponding isoquinoline derivatives **3e** and **3f** in excellent 79% and 82% isolated yields, respectively, even in the absence of NaOAc (Table 2, entry 4 and 5). But, in other oximes such as benzophenone oxime **1i** and 2-acetonaphthone oxime **1l** with **2a**, isoquinoline derivatives **3g** and **3i** were observed only in 25% and 62% yields, respectively (Scheme 3A.1). In remaining reactions such as benzophenone oxime **1i** with methyl phenylpropiolate (**2e**) or phenylacetylene (**2j**), cyclization compounds **3n** and **3t** were observed only in very less 25% and 10% yields, respectively. In the reaction of benzophenone oxime **1i** with 3-hexyne (**2i**), no cyclization compound **3s** was observed (Scheme 3A.2). Based on these observations, we conclude that OAc^- anion is an efficient base to initiate the catalytic reaction when compared to Cl^- anion which is present in the ruthenium catalyst.

3A.3 Conclusions

In conclusion, we have demonstrated a ruthenium-catalyzed regioselective cyclization of substituted aromatic and heteroaromatic ketoximes with internal as well as terminal alkynes in

the presence of catalytic amount of NaOAc to afford isoquinoline derivatives in good to excellent yields.

3A.4 References

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3A.5 Experimental Section

3A.5.1 General Procedure for the Cyclization of Oximes with Alkynes Catalyzed by Ruthenium Complex

A 15-mL pressure tube containing [{$RuCl_2$(*p*-cymene)}$_2$] (0.0025 mmol, 2.5 mol %) and NaOAc (0.025mmol, 25 mol %) was evacuated and purged with nitrogen gas three times (This reaction is moisture insensitive. The reaction can also be done without nitrogen purge). To the tube were then added oximes (**1**) (1.00 mmol), alkynes **2** (1.20 mmol) and MeOH (3.0 mL) via syringes. Then, the reaction mixture was allowed to stir at 100 °C for 16 h (a screw cap was used to cover the tube). After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3**.

3A.5.2 Procedure for the Preparation of Ruthenium Complex 5a

A 15-mL pressure tube containing [{$RuCl_2$(*p*-cymene)}$_2$] (0.100 mg, 1.0 equiv), NaOAc (1.2 equiv) and oxime (1.0 equiv) was evacuated and purged with nitrogen gas three times. Then,

MeOH (3.0 mL) was added via syringe to the tube and allowed the reaction mixture to stir at 100 °C for 16 h. After cooling to ambient temperature, the mixture was filtered through a short Celite pad and the Celite pad was washed with MeOH several times and the filtrate was concentrated by vacuum. Recrystallization from EtOAc/MeOH (9:1) gave single crystals suitable for X-ray analysis.

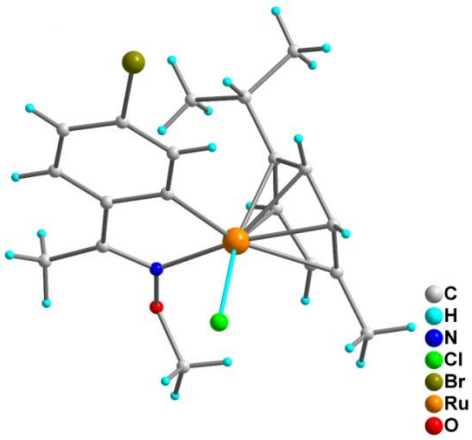


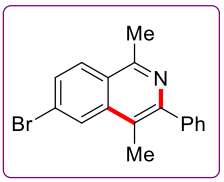
Table 3A.4 Crystal data and structure refinement for complex **5a**

Identification code	Complex 5a
Empirical formula	C_{19} H_{23} Br Cl N O Ru
Formula weight	497.81
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$p^2(1)/c$
Unit cell dimensions	a = 11.9632(13) Å α = 90°.
	b = 9.4235(10) Å β = 97.487(3)°.
	c = 17.273(2) Å ϒ = 90°.
Volume	1930.7(4) A^3

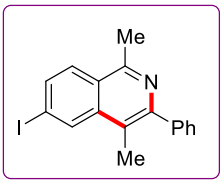
Z	4
Density (calculated)	1.713 Mg/m^3
Absorption coefficien	3.025 mm^{-1}
F(000)	992
Crystal size	0.20 x 0.16 x 0.08 mm^3
Theta range for data collection	1.72 to 25.00°.
Index ranges	-12<=h<=14, -11<=k<=11, -12<=l<=20
Reflections collected	14591
Independent reflections	3401 [R(int) = 0.0682]
Completeness to theta = 25.00	99.9 %
Absorption correction	
Semi-empirical from equivalents	
Max. and min. transmission	0.785 and 0.565
Refinement method	
Full-matrix least-squares on F^2	
Data / restraints / parameters	3401 / 36 / 222
Goodness-of-fit on F^2	1.453
Final R indices [I>2sigma(I)]	R_1 = 0.0611, wR_2 = 0.1239
R indices (all data)	R_1 = 0.0912, wR_2 = 0.1336
Largest diff. peak and hole	2.512 and -1.038 $e.A^{-3}$

3A.5.3 Spectral Data of Compounds 3a-u

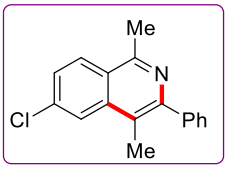
6-Bromo-1,4-dimethyl-3-phenylisoquinoline (**3a**): Colorless semisolid; eluent (5% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 2920, 1620, 1483, 1244, 1185. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.19 (s, 1 H), 8.01 (d, *J*= 8.0 Hz, 1 H), 7.67 (d, *J*= 8.0 Hz, 1 H), 7.54 (d, *J*= 8.0 Hz, 2 H), 7.45 (t, *J*= 8.0 Hz, 2 H), 7.38 (t, *J*= 8.0 Hz, 1 H), 2.95 (s, 3 H), 2.54 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 156.0, 151.8, 141.1, 137.8, 129.9, 129.8, 128.3, 127.9, 127.8, 126.8, 125.1, 124.7, 121.5, 22.5, 15.6. **HRMS** (ESI): calc. for [($C_{17}H_{14}BrN$)H] (M+H) 312.0382, measured 312.0384.



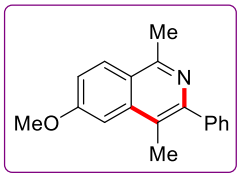
6-Iodo-1,4-dimethyl-3-phenylisoquinoline (**3b**): Colorless semisolid; eluent (5% ethyl acetate in hexanes). **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 2950, 1632, 1455, 1228, 1146. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.42 (s, 1 H), 7.84 – 7.82 (m, 2 H), 7.51 (d, *J*= 8.0 Hz, 2 H), 7.45 (t, *J*= 8.0 Hz, 2 H), 7.37 (t, *J*= 8.0 Hz, 1 H), 2.94 (s, 3 H), 2.53 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 156.2, 151.5, 140.9, 138.0, 135.2, 133.6, 129.9, 128.3, 127.9, 127.6, 124.9, 121.4, 97.9, 22.3, 15.5. **HRMS** (ESI): calc. for [($C_{17}H_{14}IN$)H] (M+H) 360.0249, measured 360.0242.

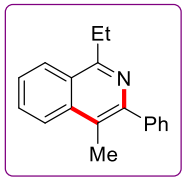


6-Chloro-1,4-dimethyl-3-phenylisoquinoline (**3c**): Colorless liquid; eluent (7% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, *J*= 8.0 Hz, 1 H), 7.98 (s, 1 H), 7.58 – 7.53 (m, 2 H), 7.51 – 7.43 (m, 3 H), 7.39 (t, *J*= 8.0 Hz, 1 H), 2.94 (s, 3 H), 2.53 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 151.8, 141.2, 137.5, 136.3, 129.9, 128.3, 127.9, 127.8, 127.2, 124.5, 123.5, 121.6, 22.6, 15.6. HRMS (ESI): calc. for [($C_{17}H_{14}ClN$)H] (M+H) 268.0888, measured 268.0897.

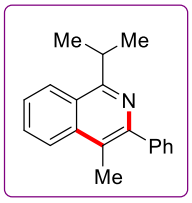


6-Methoxy-1,4-dimethyl-3-phenylisoquinoline (**3d**): Colorless semisolid; eluent (10% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, *J*= 8.0 Hz, 1 H), 7.54 (d, *J*= 8.0 Hz, 2 H), 7.45 (t, *J*= 8.0 Hz, 2 H), 7.36 (t, *J*= 8.0 Hz, 1 H), 7.23 – 7.20 (m, 2 H), 3.97 (s, 3 H), 2.92 (s, 3 H), 2.52 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.7, 155.3, 151.4, 141.8, 138.4, 129.9, 128.2, 128.1, 127.5, 121.9, 121.5, 118.5, 102.3, 55.5, 22.5, 15.8. HRMS (ESI): calc. for [($C_{18}H_{17}NO$)H] (M+H) 264.1388, measured 264.1393.

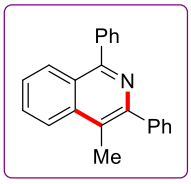


1-Ethyl-4-methyl-3-phenylisoquinoline (**3e**): Colorless liquid; eluent (5% ethyl acetate in hexanes). 

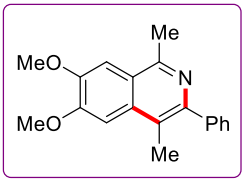
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, *J*= 8.0 Hz, 1 H), 8.06 (d, *J*= 8.0 Hz, 1 H), 7.73 (t, *J*= 8.0 Hz, 1 H), 7.61 – 7.57 (m, 3 H), 7.46 (t, *J*= 8.0 Hz, 2 H), 7.38 (t, *J*= 8.0 Hz, 1 H), 3.36 (q, *J*= 8.0 Hz, 2 H), 2.60 (s, 3 H), 1.44 (t, *J*= 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.8, 136.8, 130.1, 129.9, 128.7, 128.2, 127.5, 126.3, 125.9, 125.4, 124.4, 122.2, 28.7, 15.6, 14.4. HRMS (ESI): calc. for [($C_{18}H_{17}N$)H] (M+H) 248.1434, measured 248.1434.

1-Isopropyl-4-methyl-3-phenylisoquinoline (**3f**): Colorless liquid; eluent (3% ethyl acetate in hexanes). 

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (d, *J*= 8.0 Hz, 1 H), 8.08 (d, *J*= 8.0 Hz, 1 H), 7.71 (d, *J*= 8.0 Hz, 3 H), 7.60 (t, *J*= 8.0 Hz, 1 H), 7.50 (t, *J*= 8.0 Hz, 2 H), 7.41 (t, *J*= 8.0 Hz, 1 H), 4.00 – 3.94 (m, 1 H), 2.67 (s, 3 H), 1.49 (s, 3 H), 1.48 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.4, 150.2, 142.0, 136.9, 130.5, 129.5, 127.9, 127.4, 126.1, 125.2, 124.9, 124.5, 121.5, 31.24, 22.4, 15.9. HRMS (ESI): calc. for [($C_{19}H_{19}N$)H] (M+H) 262.1590, measured 262.1591.

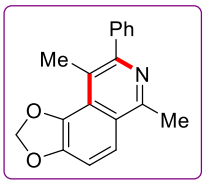
4-Methyl-1,3-diphenylisoquinoline (**3g**): Colorless liquid; eluent (5% ethyl acetate in hexanes). 

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (dd, *J*= 8.0, 4.0 Hz, 2 H), 7.77 – 7.70 (m, 3 H), 7.63 (d, *J*= 8.0 Hz, 2 H), 7.55 – 7.70 (m, 2 H), 7.49 – 7.44 (m, 4 H), 7.37 (t, *J*= 8.0 Hz, 1 H), 2.69 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 151.1, 141.6, 139.9, 137.2, 130.3, 130.2, 130.1, 128.4, 128.3, 128.2, 128.1, 127.6, 126.5, 125.5, 124.0, 123.3, 15.9. HRMS (ESI): calc. for [($C_{22}H_{17}N$)H] (M+H) 296.1434, measured 296.1436.

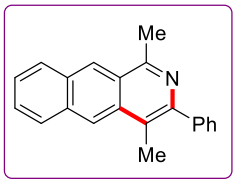
6,7-Dimethoxy-1,4-dimethyl-3-phenylisoquinoline (**3h**): Colorless semisolid; eluent (15% ethyl acetate in hexanes). 

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (d, *J*= 8.0 Hz, 2 H), 7.44 (t, *J*= 8.0 Hz, 2 H), 7.37 (t, *J*= 8.0 Hz, 1 H), 7.31 (s, 1 H), 7.21 (s, 1 H), 4.06 (s, 3 H), 4.05 (s, 3 H), 2.96 (s, 3 H), 2.52 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.2, 152.9, 149.6, 132.3, 131.1, 130.1, 128.2, 127.7, 122.0, 121.9, 115.0, 104.5, 102.8, 56.2, 56.1, 21.8, 15.8. HRMS (ESI): calc. for [($C_{19}H_{19}O_2N$)H] (M+H) 294.1489, measured 294.1491.

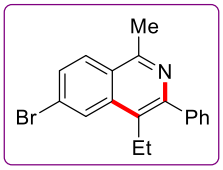
6,9-Dimethyl-8-phenyl-[1,3]dioxolo[4,5-*f*]isoquinoline (**3i**): Colorless semisolid; eluent (15% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, *J*= 8.0 Hz, 1 H), 7.52 (d, *J*= 8.0 Hz, 2 H), 7.44 (t, *J*= 8.0 Hz, 2 H), 7.36 (t, *J*= 8.0 Hz, 1 H), 7.24 (d, *J*= 8.0 Hz, 1 H), 6.16 (s, 2 H), 2.91 (s, 3 H), 2.64 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.7, 151.2, 147.4, 142.3, 140.9, 129.9, 128.2, 127.6, 123.7, 121.3, 120.1, 110.8, 101.5, 23.0, 17.8. HRMS (ESI): calc. for [($C_{18}H_{15}O_2N$)H] (M+H) 278.1176, measured 278.1181.



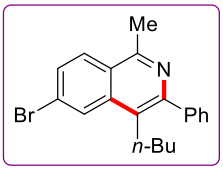
1,4-Dimethyl-3-phenylbenzo[*g*]isoquinoline (**3j**): Colorless semisolid; eluent (5% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.71 (s, 1 H), 8.51 (s, 1 H), 8.05 (d, *J*= 8.0 Hz, 1 H), 8.03 (d, *J*= 8.0 Hz, 1 H), 7.63 (d, *J*= 8.0 Hz, 2 H), 7.59 – 7.52 (m, 2 H), 7.49 (t, *J*= 8.0 Hz, 2 H), 7.40 (t, *J*= 8.0 Hz, 1 H), 3.11 (s, 3 H), 2.70 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.7, 148.0, 141.5, 134.1, 133.3, 131.5, 130.2, 128.9, 128.3, 128.2, 127.5, 127.4, 126.1, 124.9, 122.9, 121.6, 23.0, 15.8. HRMS (ESI): calc. for [($C_{21}H_{17}N$)H] (M+H) 284.1434, measured 284.1438.



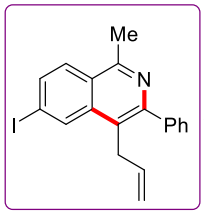
6-Bromo-4-ethyl-1-methyl-3-phenylisoquinoline (**3k**): Colorless semisolid; eluent (5% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (s, 1 H), 8.01 (d, *J*= 8.0 Hz, 1 H), 7.65 (dd, *J*= 8.0, 4.0 Hz, 1 H), 7.49 – 7.46 (m, 3 H), 7.45 – 7.38 (m, 2 H), 2.93 (s, 3 H), 2.92 (q, *J*= 8.0 Hz, 2 H), 1.23 (t, *J*= 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.0, 136.7, 129.8, 129.2, 128.4, 128.2, 127.9, 127.8, 126.7, 125.2, 125.1, 115.0, 22.5, 21.7, 15.8. HRMS (ESI): calc. for [($C_{18}H_{16}BrN$)H] (M+H) 326.0538, measured 326.0545.



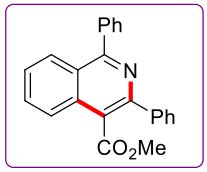
6-Bromo-4-butyl-1-methyl-3-phenylisoquinoline (**3l**): Colorless semisolid; eluent (5% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (s, 1 H), 8.02 (d, *J*= 8.0 Hz, 1 H), 7.66 (dd, *J*= 8.0, 4.0 Hz, 1 H), 7.47 – 7.42 (m, 4 H), 7.40 – 7.38 (m, 1 H), 2.96 (s, 3 H), 2.89 (t, *J*= 8.0 Hz, 2 H), 1.60 – 1.53 (m, 2 H), 1.33 – 1.27 (m, 2 H), 0.82 (t, *J*= 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 137.0, 132.0, 129.9, 129.4, 128.3, 128.2, 127.9, 127.6, 127.1, 126.9, 125.2, 115.0, 33.4, 28.2, 22.9, 22.3, 13.8. HRMS (ESI): calc. for [($C_{20}H_{20}BrN$)H] (M+H) 354.0851, measured 354.0862.



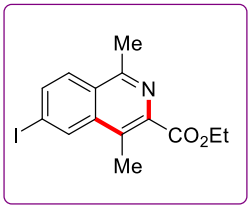
4-Allyl-6-iodo-1-methyl-3-phenylisoquinoline (**3m**): Colorless semisolid; eluent (5% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (s, 1 H), 7.89 – 7.84 (m, 2 H (two H merged and showed like singlet), 7.56 (d, *J* = 8.0 Hz, 2 H), 7.45 – 7.39 (m, 3 H), 6.13 – 6.04 (m, 1 H), 5.15 (dd, *J*= 8.0, 4.0 Hz, 1 H), 4.84 (dd, *J* = 16.0, 4.0 Hz, 1 H), 3.67 (d, *J*= 4.0 Hz, 2 H), 2.98 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.2, 150.9, 147.9, 146.3, 138.4, 137.6, 137.7, 136.6, 136.1, 124.3, 129.4, 128.4, 128.3, 127.8, 117.2, 32.9, 12.0. HRMS (ESI): calc. for [($C_{19}H_{16}IN$)H] (M+H) 386.0400, measured 386.0408.



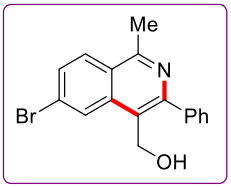
Methyl 1,3-diphenylisoquinoline-4-carboxylate (**3n**): Colorless liquid; eluent (7% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2959, 1726, 1591, 1449, 1280, 1126 and 1071. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, *J*= 8.0 Hz, 1 H), 8.05 (d, *J*= 8.0 Hz, 1 H), 7.79 – 7.73 (m, 4 H), 7.58 – 7.50 (m, 3 H), 7.48 – 7.38 (m, 4 H), 7.31 (m, 1 H), 3.78 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 161.9, 149.9, 140.3, 139.3, 134.6, 131.3, 130.3, 129.1, 128.9, 128.7, 128.5, 128.4, 128.1, 127.5, 125.0, 124.5, 122.3, 52.7. HRMS (ESI): calc. for [($C_{23}H_{17}O_2N$)H] (M+H) 340.1332, measured 340.1329.



Ethyl 6-iodo-1,3-dimethylisoquinoline-4-carboxylate (**3o**): Colorless liquid; eluent (7% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2978, 1715, 1422, 1272 and 1065. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (s, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 4.32-4.29 (m, 2 H), 3.18 (s, 3 H), 2.44 (s, 3 H), 1.38 (t, *J* = 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.0, 150.3, 149.3, 144.9, 137.2, 134.8, 130.7, 124.4, 93.3, 63.1, 20.6, 14.4, 13.0. HRMS (ESI): calc. for [($C_{14}H_{14}O_2IN$)H] (M+H) 356.0142, measured 356.0149.

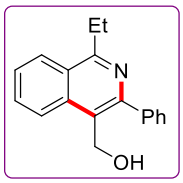


(6-Bromo-1-methyl-3-phenylisoquinolin-4-yl)methanol (**3p**): Colorless semisolid; eluent (20% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3422, 2252, 1656 and 1018. ^{1}H NMR (*d*-DMSO, 400 MHz): δ 8.46 (s, 1 H), 8.15 (d, *J* = 8.0 Hz, 1 H), 7.77 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 7.48 – 7.41 (m, 3 H), 5.43 (t, *J* = 4.0 Hz, 1 H), 4.72 (d, *J* = 4.0 Hz, 2 H), 2.86 (s, 3 H). ^{13}C NMR

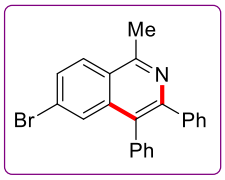


(*d*-DMSO, 100 MHz): δ 158.3, 151.9, 140.5, 137.6, 130.4, 130.3, 128.9, 128.5, 128.4, 127.9, 125.0, 124.9, 124.7, 58.0, 22.9. HRMS (ESI): calc. for [($C_{17}H_{14}OBrN$)H] (M+H) 328.0332, measured 328.0335.

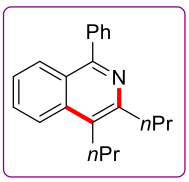
(1-Ethyl-3-phenylisoquinolin-4-yl)methanol (**3q**): Colorless liquid; eluent (5% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3428, 2960, 2932, 1599, 1458, 1287 and 1122. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (d, *J* = 8.0 Hz, 1 H), 8.22 (d, *J* = 8.0 Hz, 1 H), 7.76 (t, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 7.61 (t, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 8.0 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 4.99 (s, 2 H), 3.37 (q, *J* = 8.0 Hz, 2 H), 1.43 (t, *J* = 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.4, 159.0, 137.8, 136.3, 130.7, 129.9, 128.3, 128.1, 126.8, 125.9, 125.8, 124.7, 124.2, 59.5, 28.8, 14.2. HRMS (ESI): calc. for [($C_{18}H_{17}ON$)H] (M+H) 264.1383, measured 264.1395.



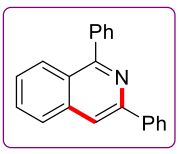
6-Bromo-1-methyl-3,4-diphenylisoquinoline (**3r**): Colorless solid; mp 191-193 °C; eluent (3% ethyl acetate in hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.04 (d, *J* = 8.0 Hz, 1 H), 7.81 (s, 1 H), 7.65 (dd, *J* = 8.0 Hz, 1 H), 7.36 – 7.33 (m, 5 H), 7.20 – 7.17 (m, 5 H), 3.05 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 157.8, 150.6, 140.6, 137.5, 136.9, 131.6, 131.4, 130.3, 130.2, 128.6, 128.5, 128.4, 127.8, 127.6, 127.4, 125.3, 124.7, 22.8. **HRMS** (ESI): calc. for [($C_{22}H_{16}BrN$)H] (M+H) 374.0538, measured 374.0542.



3,4-Diethyl-1-phenylisoquinoline (**3s**): Colorless liquid; eluent (3% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (t, *J* = 8.0 Hz, 2 H), 7.68 – 7.64 (m, 2 H), 7.51 (t, *J* = 8.0 Hz, 2 H), 7.47 – 7.40 (m, 3 H), 3.16 – 3.04 (m, 4 H), 1.38 (t, *J* = 8.0 Hz, 3 H), 1.35 (t, *J* = 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.4, 153.2, 140.1, 135.9, 130.1, 129.9, 129.7, 128.4, 128.3, 128.2, 125.5, 125.4, 123.2, 28.6, 21.0, 15.3, 15.0. HRMS (ESI): calc. for [($C_{19}H_{19}N$)H] (M+H) 262.1590, measured 262.1593.

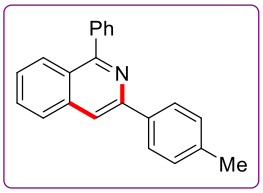


1,3-Diphenylisoquinoline (**3t**): Colorless liquid; eluent (3% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, *J* = 8.0 Hz, 2 H), 8.12 (d, *J* = 8.0 Hz, 1 H), 8.07 (s, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.80 (dd, *J* = 8.0 Hz, 2 H), 7.69 (t, *J* = 8.0 Hz, 1 H), 7.56 – 7.47 (m, 6 H), 7.40 (t, *J* = 8.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz):



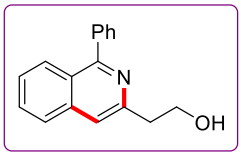
δ 160.5, 150.2, 139.9, 139.7, 137.9, 130.3, 130.2, 128.8, 128.7, 128.6, 128.4, 127.7, 127.6, 127.2, 127.0, 125.9, 115.8. HRMS (ESI): calc. for [($C_{21}H_{15}N$)H] (M+H) 282.1277, measured 282.1279.

1-Phenyl-3-(*p*-tolyl)isoquinoline (**3u**): Colorless liquid; eluent (3% ethyl acetate in hexanes).

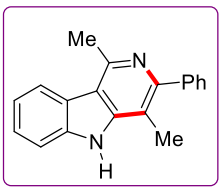


^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 – 8.09 (m, 3 H), 8.03 (s, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.79 (dd, *J* = 8.0 Hz, 2 H), 7.66 (t, *J* = 8.0 Hz, 1 H), 7.57 – 7.46 (m, 4 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 2.40 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 150.2, 149.7, 137.9, 135.0, 130.4, 130.2, 129.5, 128.7, 128.4, 127.7, 127.5, 127.1, 126.9, 125.7, 115.4, 114.8, 21.4. HRMS (ESI): calc. for [($C_{22}H_{17}N$)H] (M+H) 296.1434, measured 296.1433.

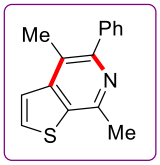
2-(1-Phenylisoquinolin-3-yl)ethanol (**3v**): Colorless liquid; eluent (20% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3394, 2925, 1590, 1444, 1388, 1347 and 1047. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, *J* = 8.0 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.69 – 7.63 (m, 3 H), 7.53 – 7.44 (m, 5 H), 4.07 (t, *J* = 8.0 Hz, 2 H), 3.18 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.0, 152.9, 139.2, 137.7, 130.0, 128.9, 128.6, 128.5, 127.7, 126.9, 126.8, 125.3, 118.5, 62.6, 38.8. HRMS (ESI): calc. for [($C_{17}H_{15}ON$)H] (M+H) 250.1226, measured 250.1217.



1,4-Dimethyl-3-phenyl-5*H*-pyrido[4,3-*b*]indole (**3w**): Colorless semisolid; eluent (20% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3372, 2961, 1592, 1456, 1288 and 1127. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.80 (bs, 1 H), 8.13 (d, *J* = 8.0 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 7.50 (t, *J* = 8.0 Hz, 1 H), 7.45 – 7.40 (m, 3 H), 7.36 – 7.31 (m, 2 H), 3.05 (s, 3 H), 2.45 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.9, 150.4, 144.8, 140.7, 139.7, 129.8, 128.2, 127.6, 126.0, 123.0, 122.5, 120.9, 116.7, 111.0, 110.6, 23.5, 13.9. HRMS (ESI): calc. for [($C_{19}H_{16}N_2$)H] (M+H) 273.1381, measured 273.1395.

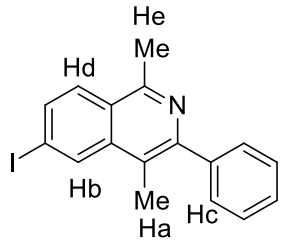


4,7-Dimethyl-5-phenylthieno[2,3-*c*]pyridine (**3x**): Colorless semisolid; eluent (5% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 8.0 Hz, 1 H), 7.53 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 2 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.37 (t, *J* = 8.0 Hz, 1 H), 2.81 (s, 3 H), 2.54 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.1, 149.7, 146.1, 140.8, 134.1, 131.1, 129.8, 128.3, 127.6, 122.9, 122.3, 23.5, 16.7. HRMS (ESI): calc. for [($C_{15}H_{13}SN$)H] (M+H) 240.0841, measured 240.0850.



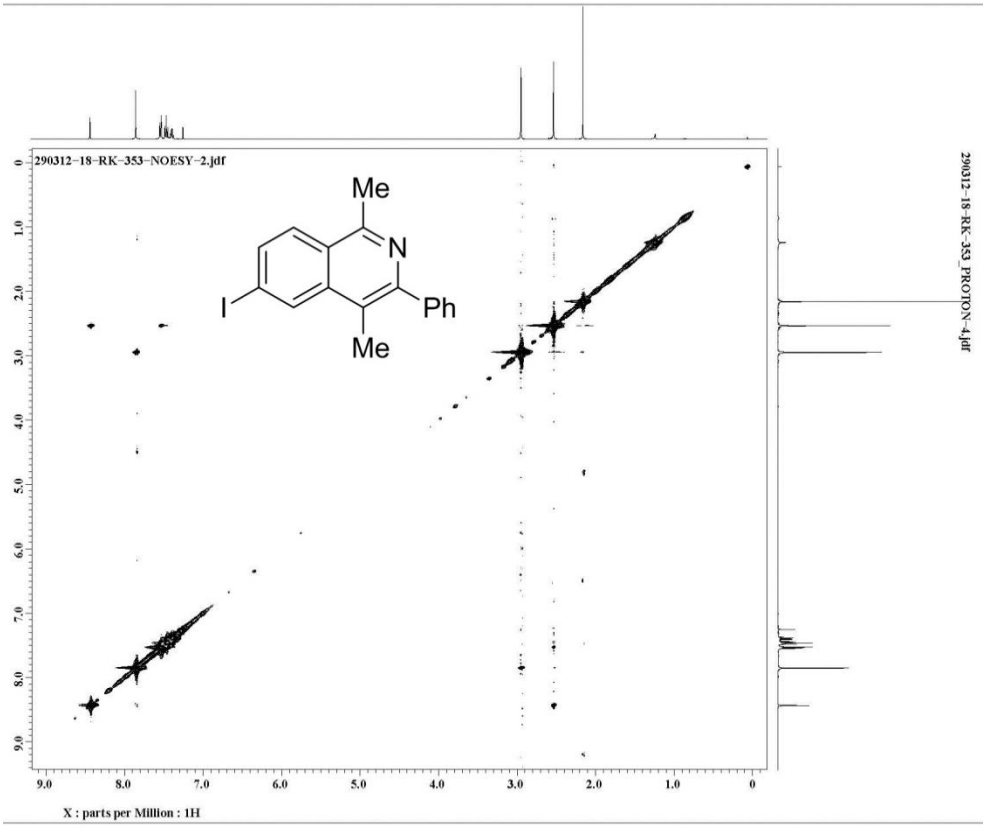
3A.5.4 Regioselective Studies: NOESY Experiments

Copy of NOESY Experiment of Compound **3b**

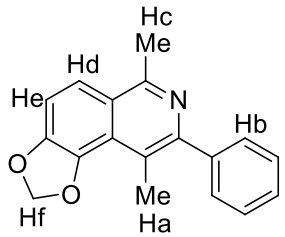


Ha δ = 2.53; Hb = 8.42; Hc = 7.52
Hd δ = 7.84; He = 2.94

There is a NOE correlation between Ha (δ 2.53, s) and Hb (δ 8.42, s). In meantime, there is also a NOE correlation between Ha (δ 2.53, s) and Hc (δ 7.52, d). However, there is no correlation between Hb (δ 8.42, s) and Hc (δ 7.52, d). These results clearly revealed that the regiochemistry of compound **3b** is correct.

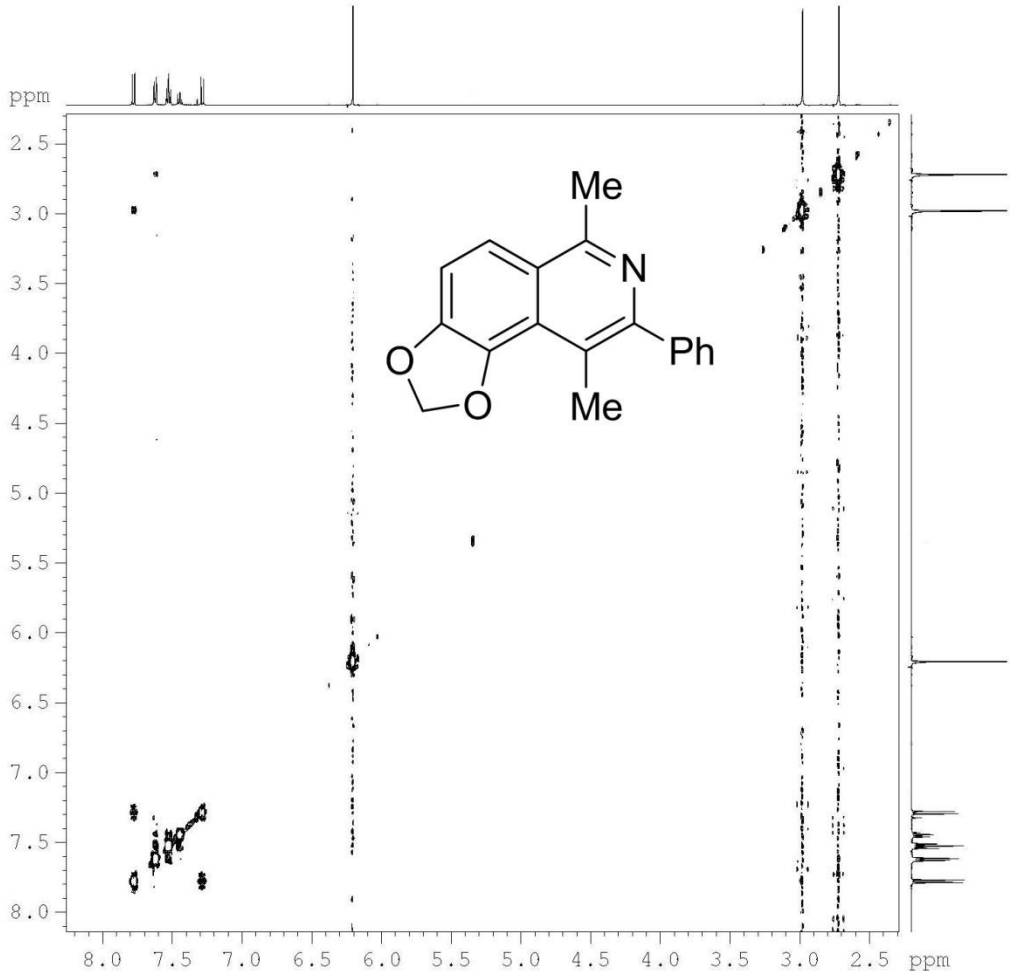


Copy of NOESY Experiment of Compound **3i**

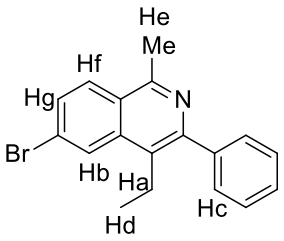


Ha δ = 2.64; Hb = 7.52; Hc = 2.91
Hd δ = 7.74; He = 7.24; Hf = 6.16

There is a NOE correlation between Ha (δ 2.64, s) and Hb (δ 7.52, d). In meantime, there is also a NOE correlation between Hc (δ 2.91, s) and Hd (δ 7.74, d). However, there is no correlation between Hb (δ 7.52, d) and Hf (δ 6.16, d). These results clearly revealed that the regiochemistry of compound **3i** is correct.

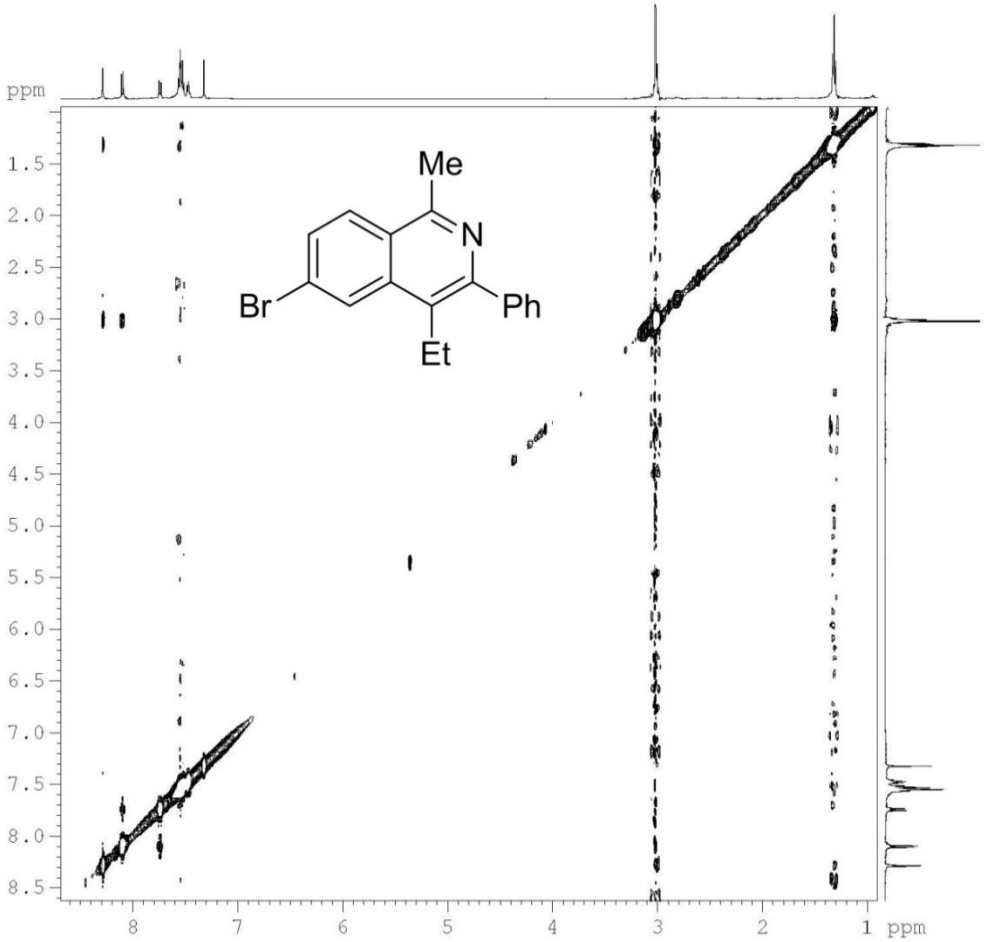


Copy of NOESY Experiment of Compound **3k**

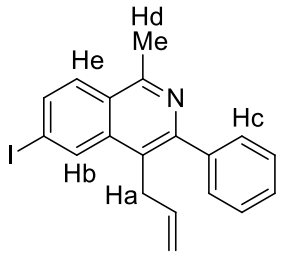


Ha δ = 2.92; Hb = 8.20; Hc = 7.49
Hd δ = 1.23; He = 2.93; Hf = 8.01; Hg = 7.65

There is a NOE correlation between Ha (δ 2.92, q) and Hb (δ 8.20, s). In meantime, there is also a NOE correlation between Ha (δ 2.92, q) and Hc (δ 7.49, m). There is also a NOE correlation between Hd (δ 1.23, t) with Hb (δ 8.20, s) as well as with Hc (δ 7.49, m). However, there is no a NOE correlation between Hb (δ 8.20, s) and Hc (δ 7.49, m). These results clearly revealed that the regiochemistry of compound **3k** is correct.

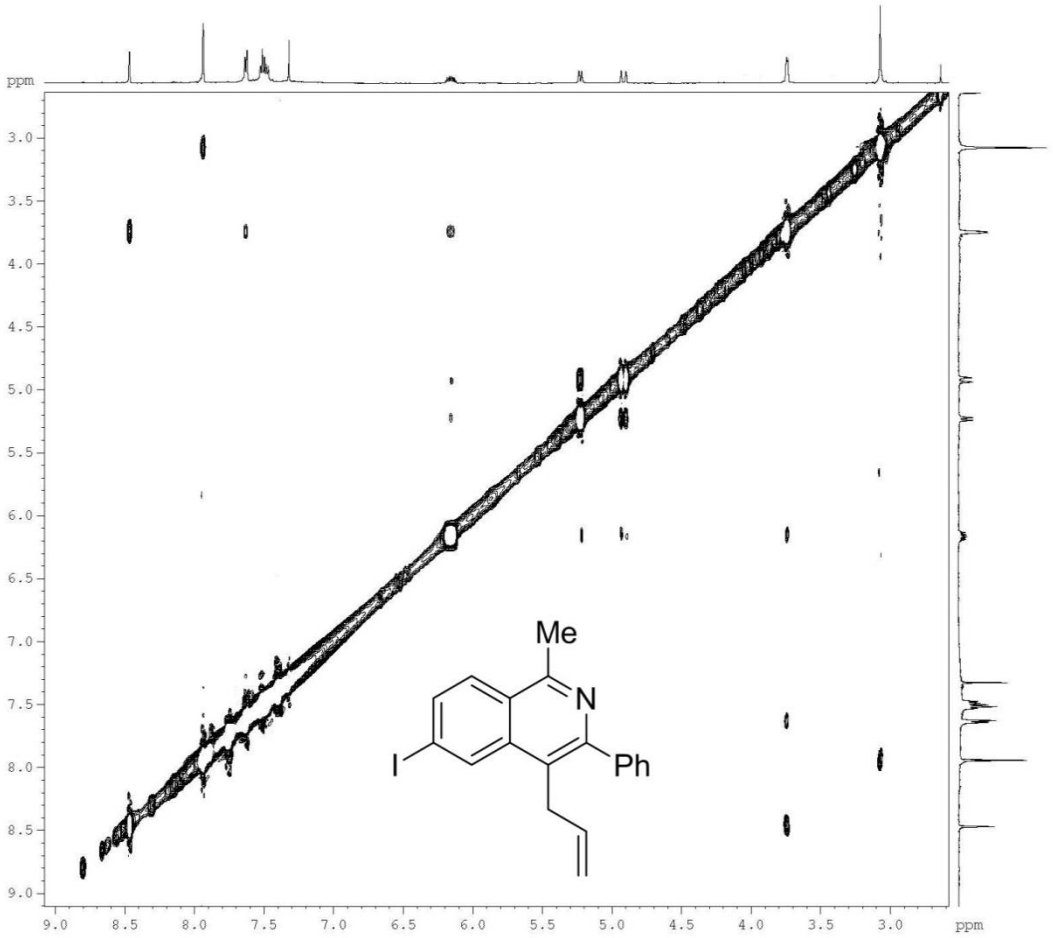


Copy of NOESY Experiment of Compound **3m**

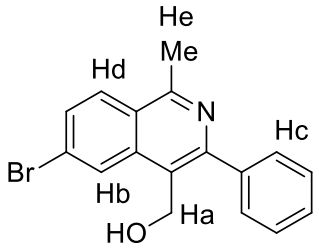


Ha δ = 3.67; Hb: 8.38; Hc = 7.56
Hd δ = 2.98; He: 7.87

There is a NOE correlation between Ha (δ 3.67, d) and Hb (δ 8.38, s). In meantime, there is also a NOE correlation between Ha (δ 3.67, s) and Hc (δ 7.56, d). However, there is no correlation between Hb (δ 8.38, s) and Hc (δ 7.56, d). These results clearly revealed that the regiochemistry of compound **3m** is correct.

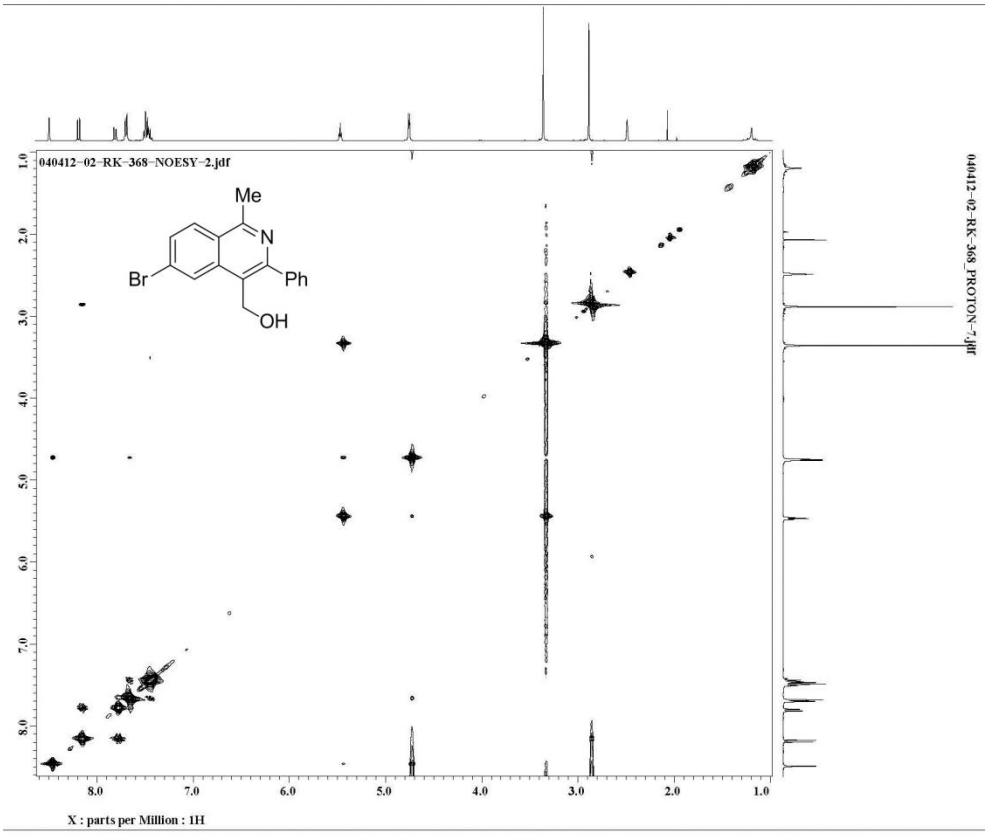


Copy of NOESY Experiment of Compound **3p**

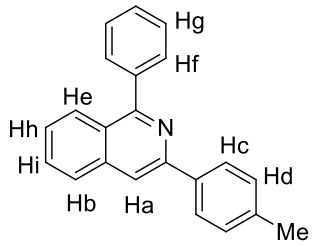


Ha δ = 4.72; Hb: 8.46; Hc = 7.66
Hd δ = 8.15; He: 2.86

There is a NOE correlation between Ha (δ 4.72, d) and Hb (δ 8.46, s). In meantime, there is also a NOE correlation between Ha (δ 4.72, d) and Hc (δ 7.66, d). However, there is no a NOE correlation between Hb (δ 8.46, s) and Hc (δ 7.66, d). These results clearly revealed that the regiochemistry of compound **3p** is correct.



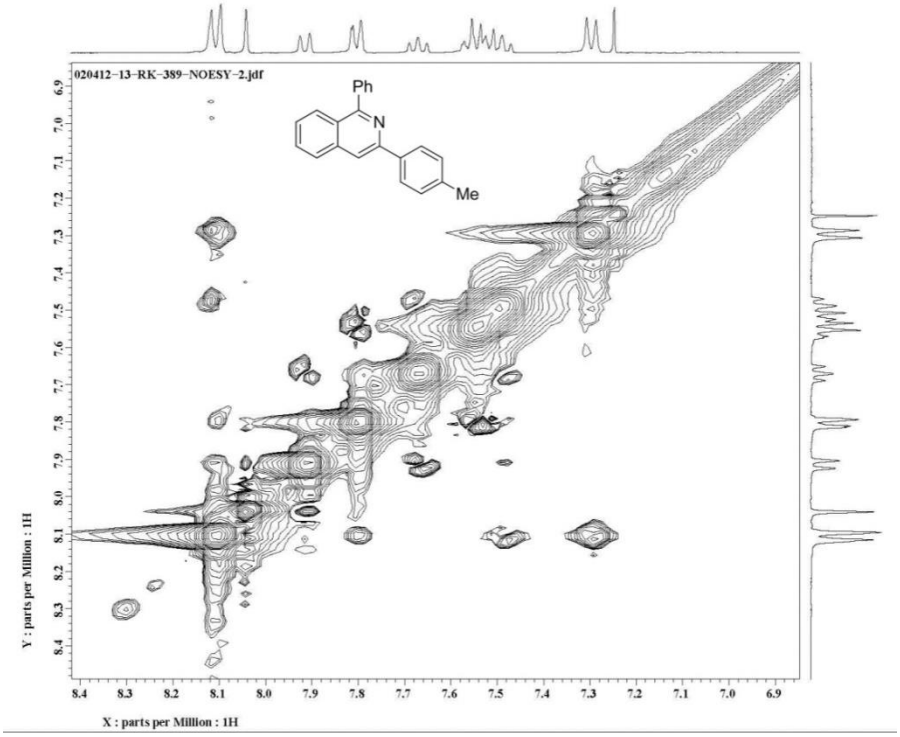
Copy of NOESY Experiment of Compound **3u**



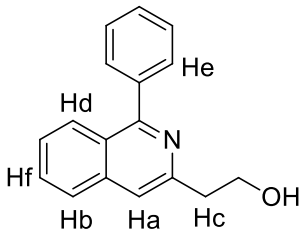
Ha δ = 8.03; Hb: 7.90; Hc = 8.11; Hd = 7.29
He δ = 8.11; Hf: 7.79; Hg = 7.55 (m)
Hh δ = 7.66; Hi: 7.50 (m)

There is a NOE correlation between Ha (δ 8.03, s) and Hb (δ 7.90, d). In meantime, there is also a NOE correlation between Ha (δ 8.03, s) with Hc (δ 8.11, d (merged with one more doublet and showed as multiplet)). However, there is no a NOE correlation between Hb (δ 7.90, d) and Hc (δ 8.11, d). These results clearly revealed that the regiochemistry of compound **3u** is correct.

Hc proton is assigned based on Hd proton (7.29, d). Hd proton is assigned based on Me group protons of **3u**. He (δ 8.11, d (merged with one more doublet and showed as multiplet)) proton is assigned based on Hf protons (7.79, d). These protons are assigned by NOESY experiments.

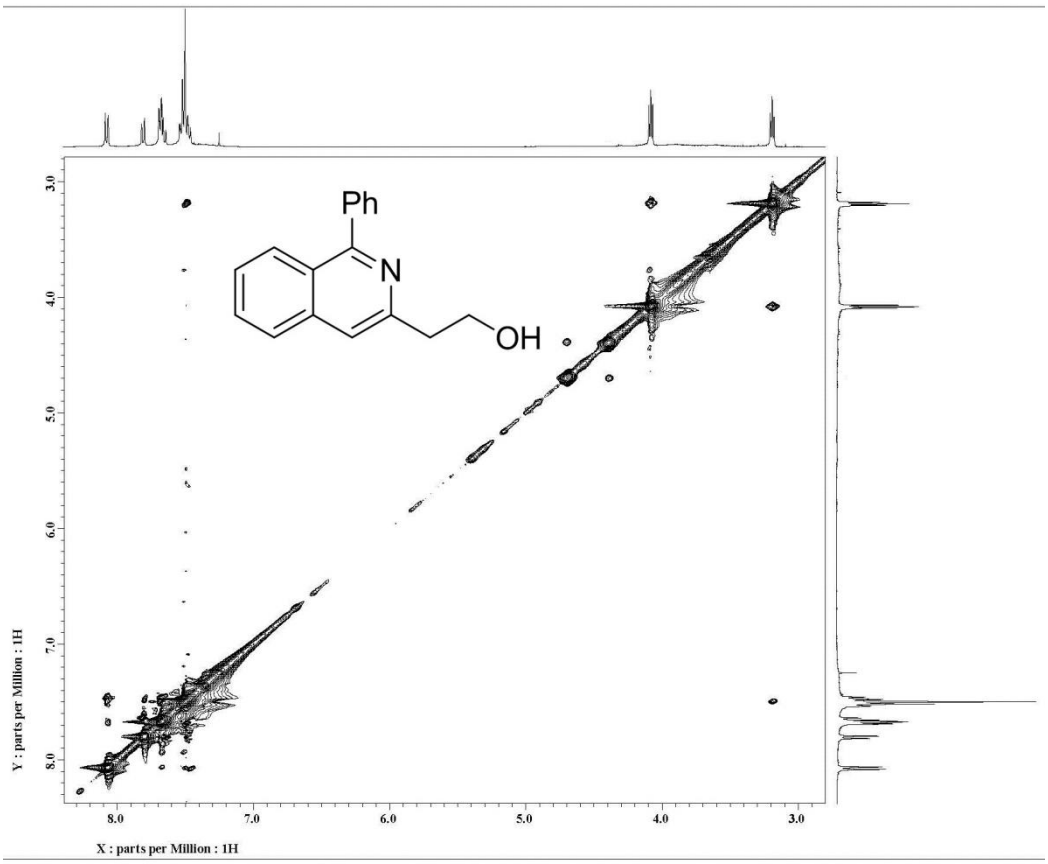


Copy of NOESY Experiment of Compound **3v**

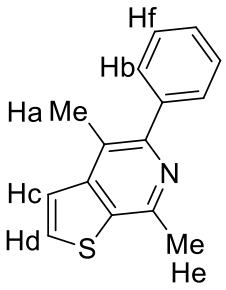


Ha δ = 7.49; Hb: 8.05; Hc = 3.18
Hd δ = 7.79; He = 7.67 (m); Hf = 7.67 (m)

There is a NOE correlation between Ha (δ 7.49, singlet is merged with multiplet; but can view in expansion NMR) and Hb (δ 8.05, d). In meantime, there is also a NOE correlation between Ha (δ 7.49, s) and Hc (δ 3.18, d). However, there is no a NOE correlation between Hb (δ 8.05, d) and Hc (δ 3.18, d). These results clearly revealed that the regiochemistry of compound **3v** is correct.

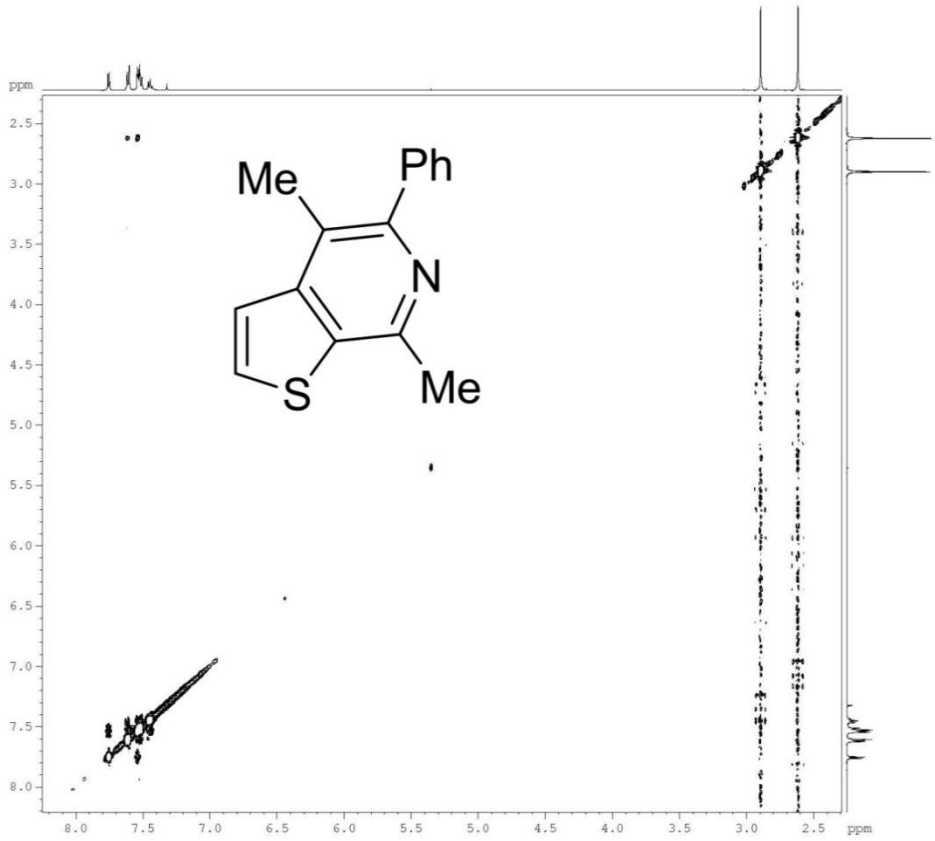


Copy of NOESY Experiment of Compound **3x**



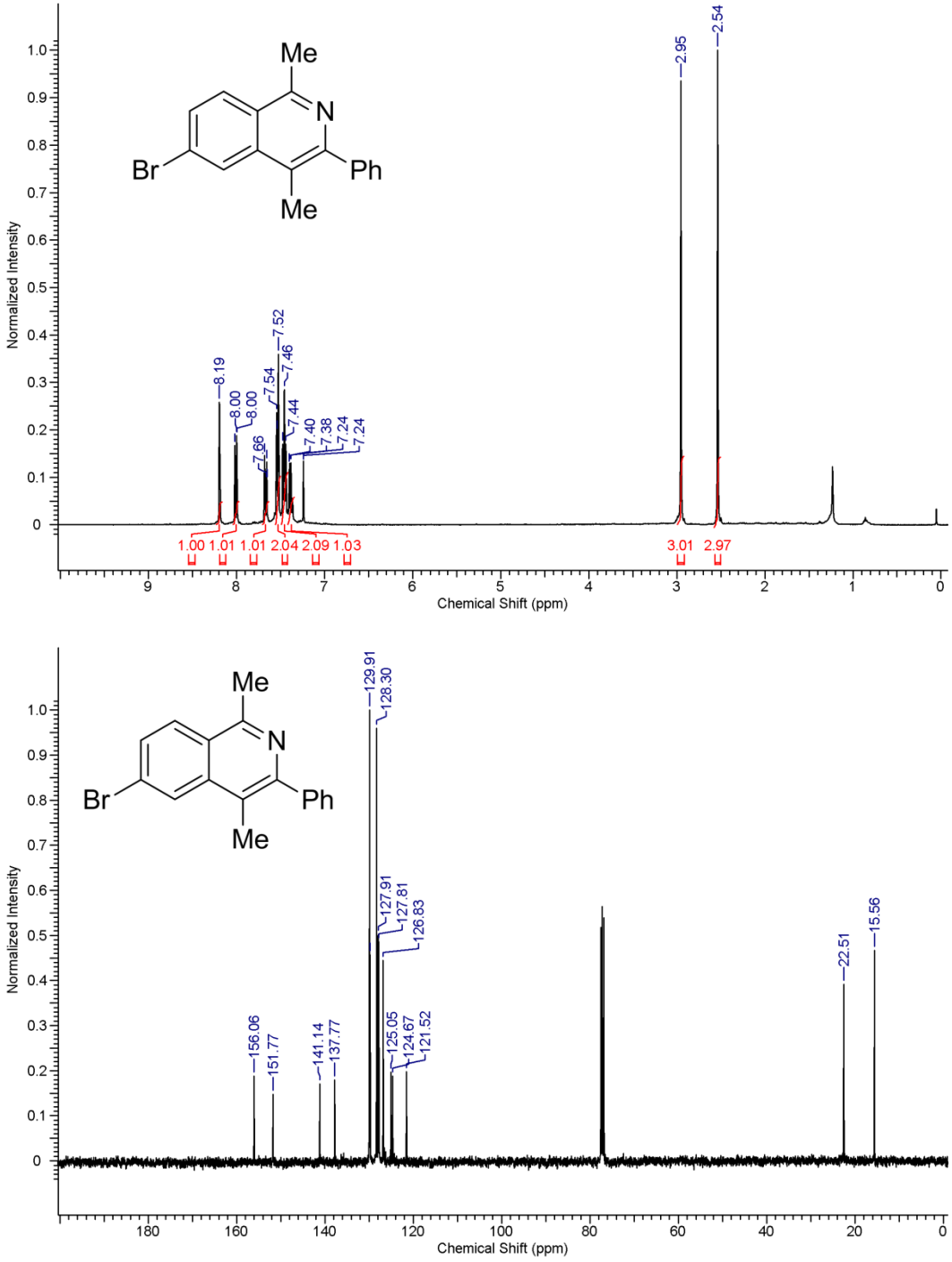
Ha δ = 2.54; Hb = 7.53; Hc = 7.44
Hd δ = 7.68; He = 2.81; Hf = 7.46

There is a NOE correlation between Ha (δ 2.54, s) and Hb (δ 7.53, d). In meantime, there is also a NOE correlation between Ha (δ 2.54, s) with Hc (δ 7.44, d). However, there is no a NOE correlation between Hb (δ 7.53, d) and Hc (δ 7.44, d). These results clearly revealed that the regiochemistry of compound **3x** is correct. Hc (merged with triplet and showed as multiplet) proton is assigned based on Ha proton (2.54, s). Hd (7.68, d) proton is assigned based on Hc proton. These protons are assigned by NOESY experiments.

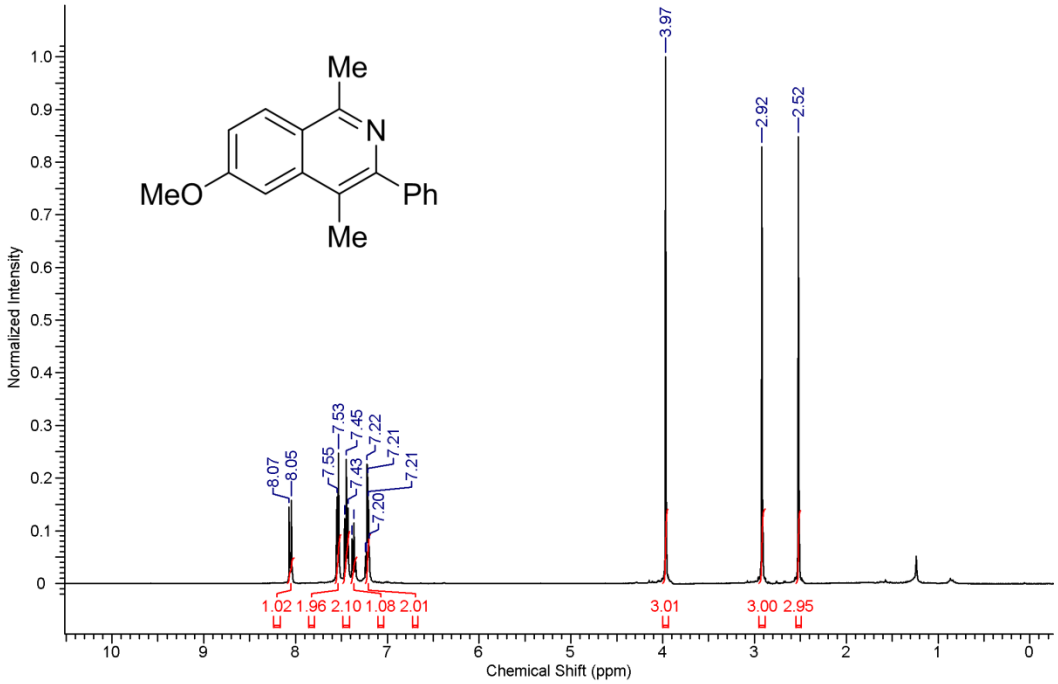


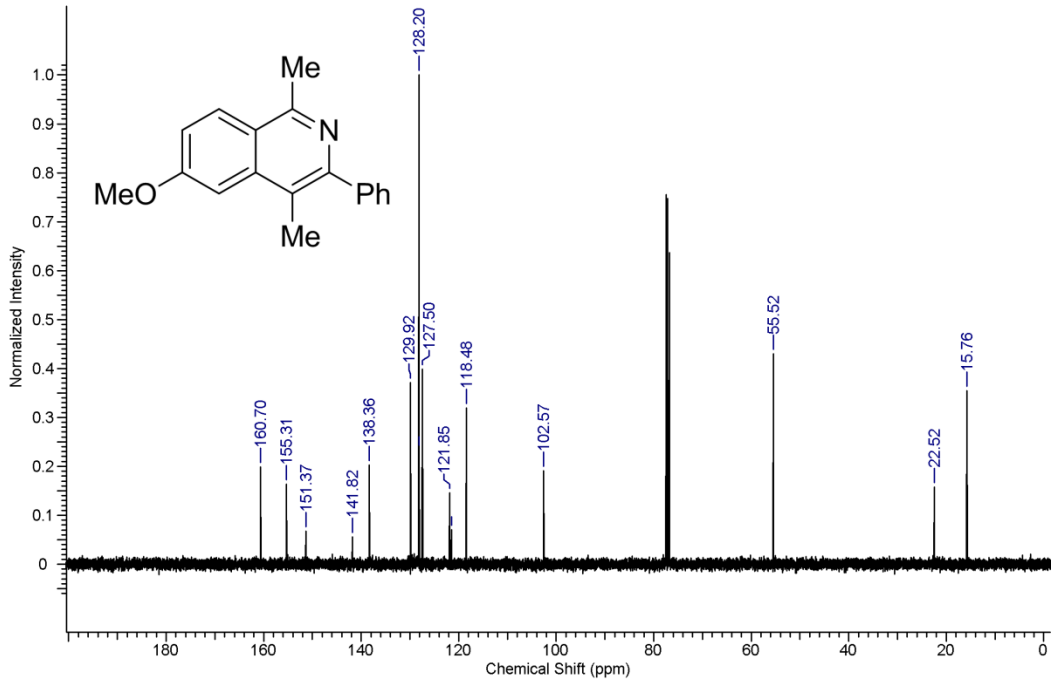
3A.5.5 Spectral Copies of Selected Compounds

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

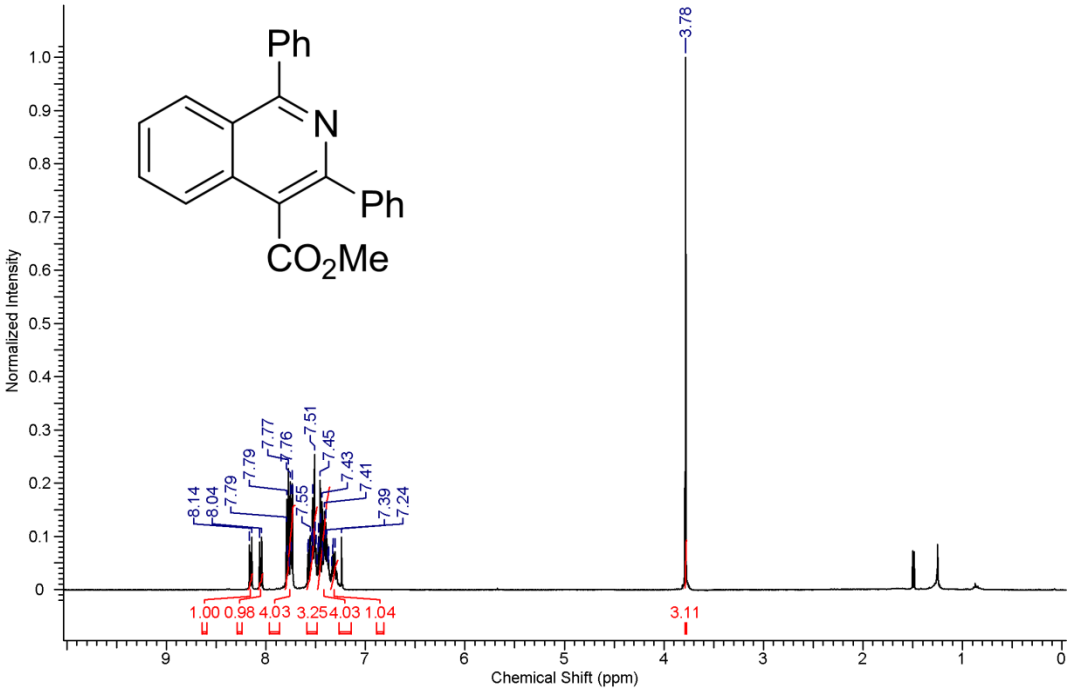


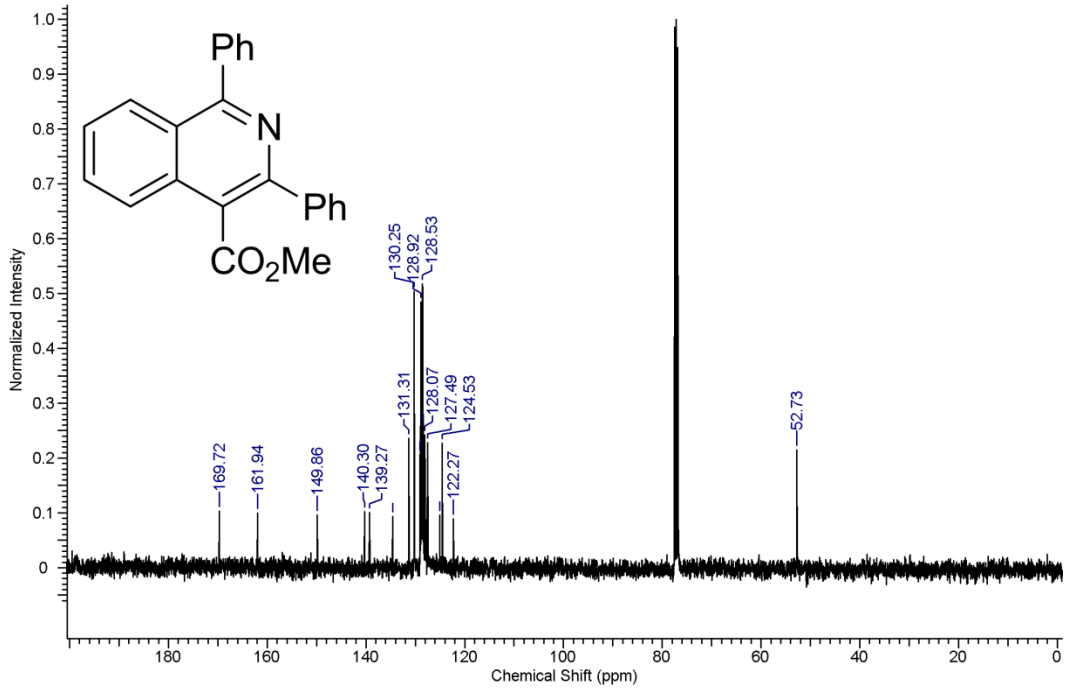
^{1}H and ^{13}C NMR Spectra of Compound **3d**



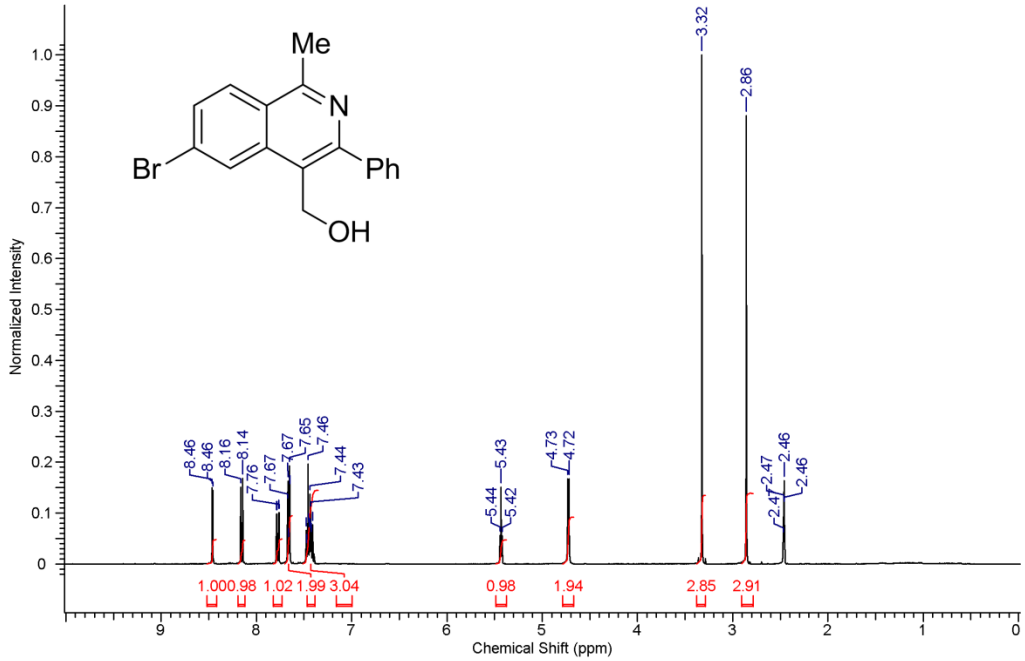


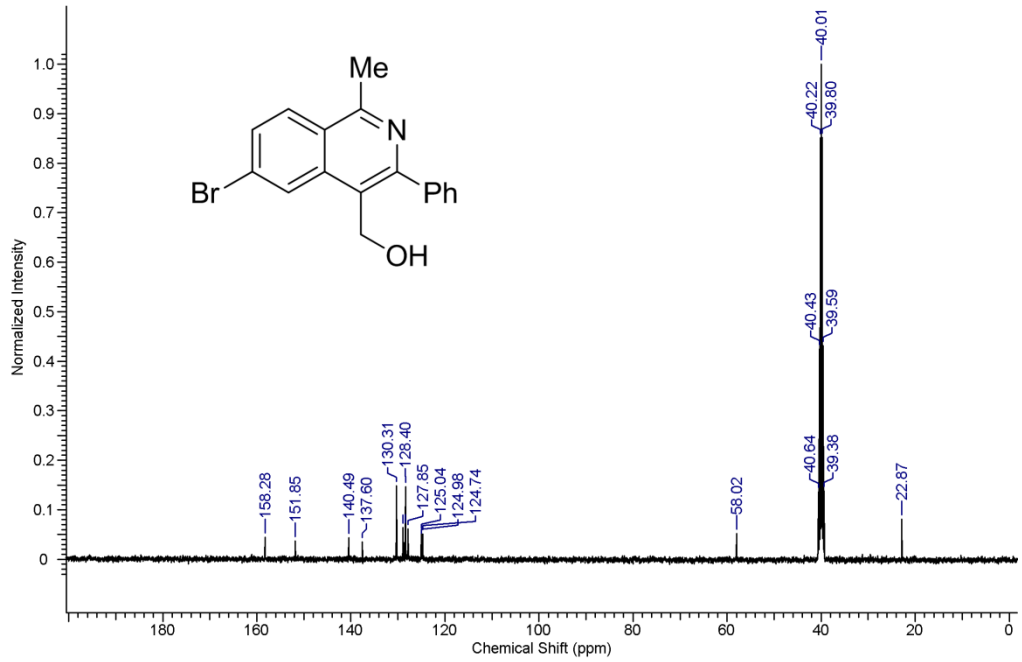
^{1}H and ^{13}C NMR Spectra of Compound **3n**



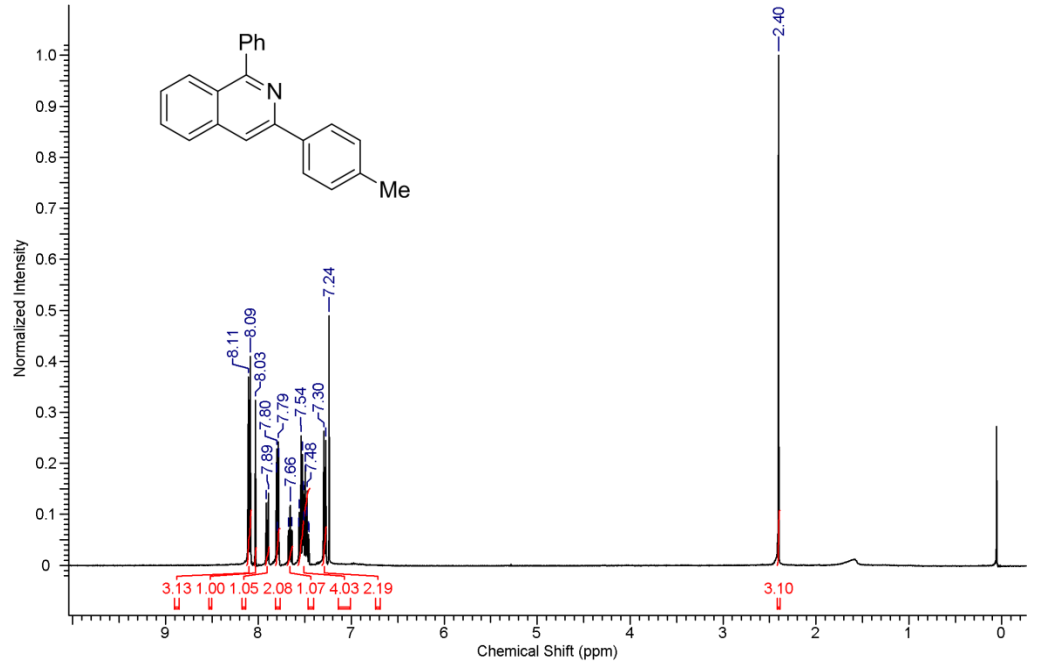


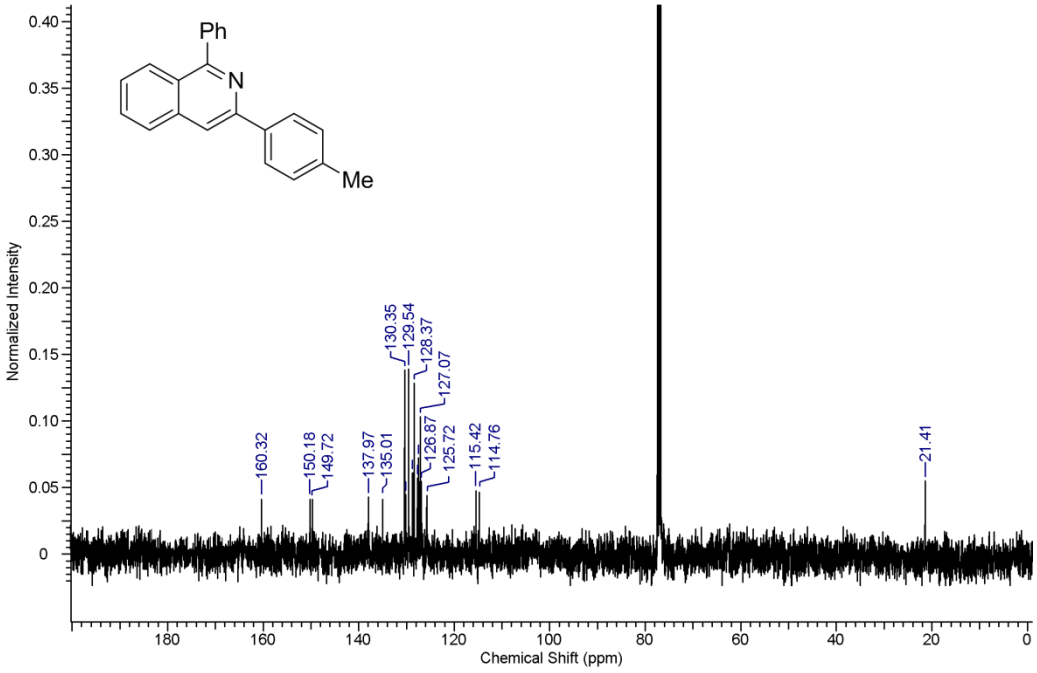
^{1}H and ^{13}C NMR Spectra of Compound **3p** (The NMR was measured in *d*-DMSO)**.**



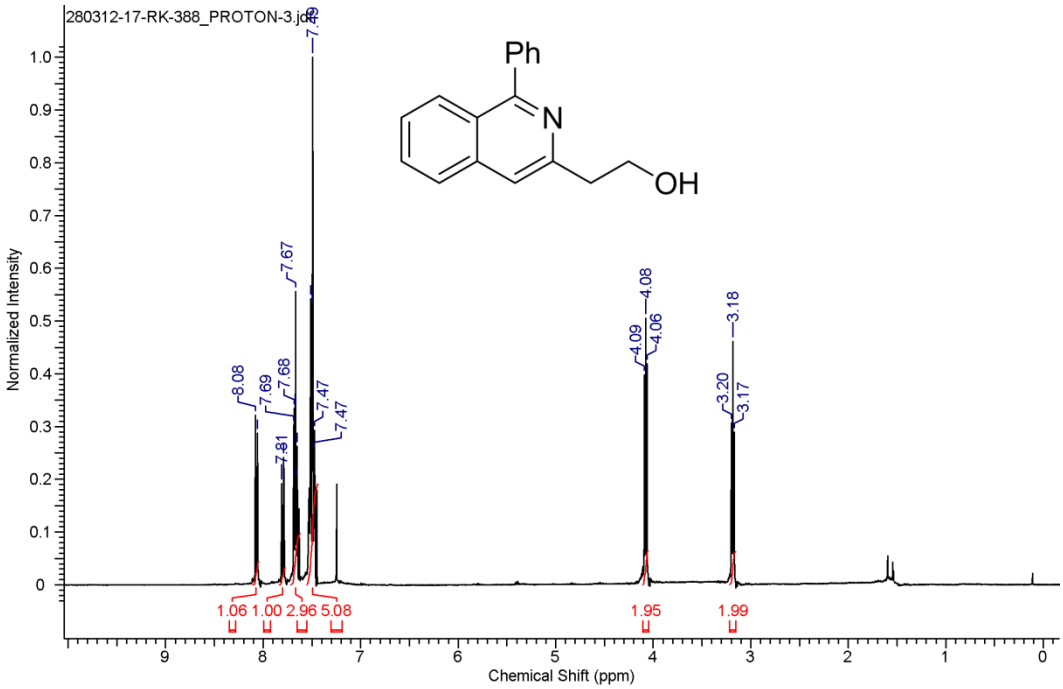


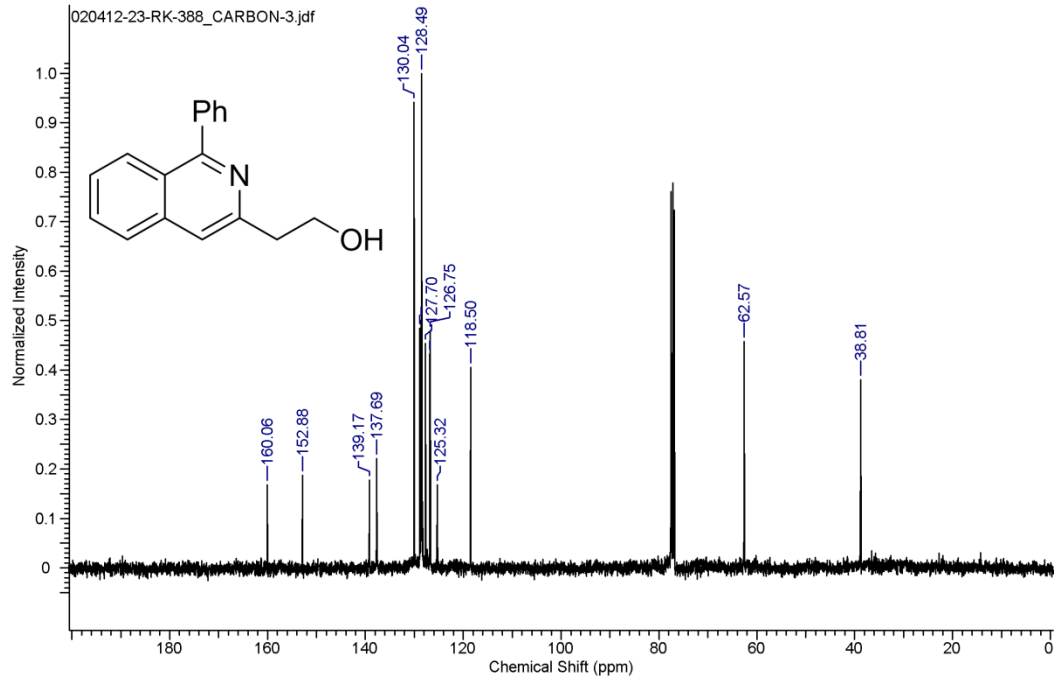
^{1}H and ^{13}C NMR Spectra of Compound **3u**





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

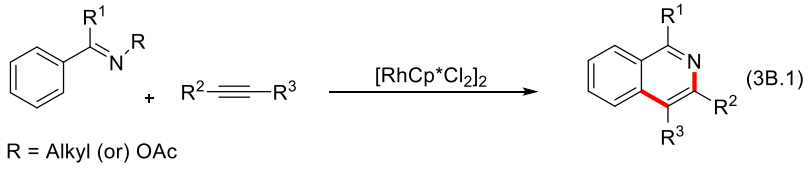




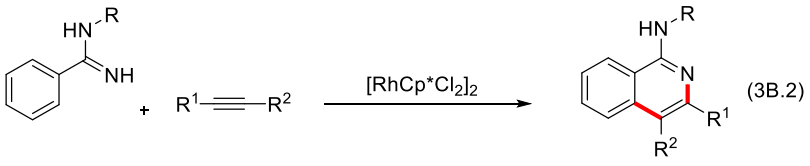
Section 3B: A Regioselective Synthesis of 1-Haloisoquinolines *via* Ruthenium-Catalyzed Cyclization of *O*-Methylbenzohydroximoyl halides with Alkynes

3B.1 Introduction

The transition-metal catalyzed chelation-assisted cyclization of aromatic and alkene imines or oximes with alkynes is one of the powerful methods to synthesis isoquinoline and pyridine derivatives.[1] This reaction is highly atom-economical and environmentally friendly when compared with other methods such as organic halides or organometallic functionalization. It is important to note that isoquinoline is a highly useful heterocyclic compound which is present in various natural products and biologically active molecules.[2] Initially, Rh(I) complex has been efficiently used as a catalyst for this type of reaction.[3,4] This catalytic reaction proceeds via chelation-assisted oxidative addition of *ortho* C-H bond of aromatic imines or oximes with rhodium(I) complex followed by hydroarylation with alkynes and subsequent intramolecular electrocyclization, providing the corresponding isoquinoline derivatives. Later, Rh(III) complex has been used as a catalyst for this type of cyclization reaction. This reaction proceeds via chelation-assisted acetate accelerated deprotonation at the ortho C-H bond of aromatic imines or oximes with rhodium(III) complex followed by cyclization with alkynes (eq. 3B.1).[5]

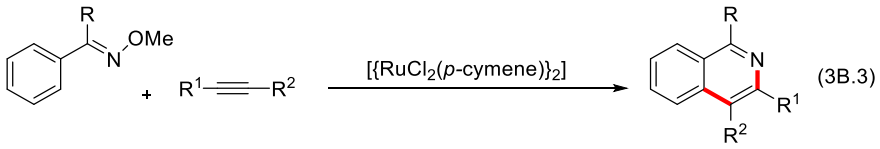


Recently, Li's group reported the synthesis of *N*-substituted 1-aminoisoquinolines via a Rh(III)-catalyzed oxidative cyclization of *N*-alkyl benzamidines with alkynes. This reaction possess via ortho C-H activation of the C-aryl ring of benzamidine ring. The coupling of *N*-aryl benzamidines gave cyclic isoquonilines in moderate to good yield, and *N*-^{t}Bu and *N*-Cy benzamidines provided even greater efficiency and selectivity (eq. 3B.2).[6]



In these reactions, the control of regioselectivity is a key problem. In most of the cases, unsymmetrical alkynes lead to mixture of regioisomeric products. This kind of regioselective problem was solved by conducting a similar type of cyclization reaction using a less expensive ruthenium(II) complex as a catalyst via deprotonation pathway.[7] In meantime, in the reported rhodium- and ruthenium-catalyzed reactions, mostly ketoximes, aldehyde imines and amidines have been used as a directing group to activate *ortho* C-H bond of aromatics.[4-7]

In 2012, we have described the synthesis of highly regio selective synthesis of isoquinoline derivatives by less expensive ruthenium-catalyzed oxidative cyclization of aromatic ketoximes with alkynes (eq. 3B.3).[8]



(3B.3)

3B.2 Results and Discussion

Till now, there is no report available in the literature discussing imidoyl halide moiety (X-C=N-OMe; X = Cl or Br) as a directing group to activate ortho C-H bond of aromatics. Herein, we wish to statement for the first time an imidoyl halide moiety as a directing group for the cyclization of *O*-methylbenzohydroximoyl halides with substituted alkynes in the presence of catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$] and CsOAc. In the reaction, various highly substituted 1-haloisoquinoline and 1-alkoxyisoquinoline derivatives are prepared in good to excellent yields in a highly regioselective manner. It is important to point out that halide group in the observed 1-haloisoquinoline derivatives can be used for further functionalization.

3B.2.1 Optimization Studies

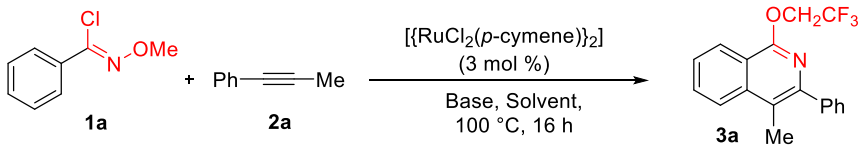


Table 3B.1 Cyclization reaction of imidoyl halide (**1**) with 1-phenyl-1-propyne (**2a**).[a]

Entry	Base	Solvents	Yield(%)[b]
1	NaOAc	MeOH	nr

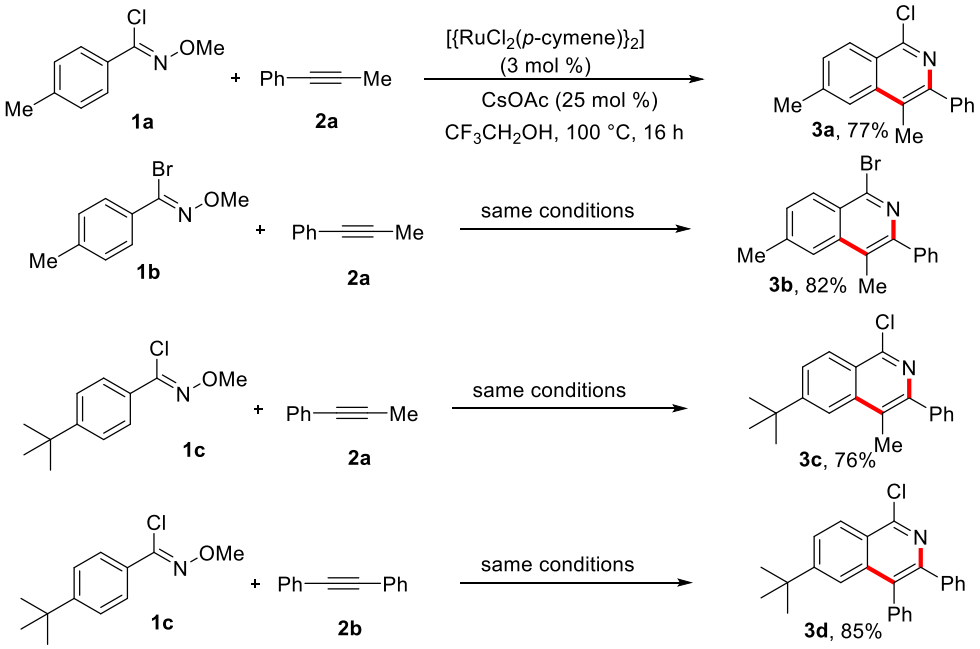
2	NaOAc	*iso*-PrOH	nr
3	NaOAc	*tert*-BuOH	nr
4	NaOAc	*tert*-amyl alcohol	nr
5	NaOAc	CF_3CH_2OH	76
6	NaOAc	Tolune	nr
7	NaOAc	DMSO	nr
8	NaOAc	DCE	nr
9	KOAc	CF_3CH_2OH	50
10	LiOAc	CF_3CH_2OH	60
11	CsOAc	CF_3CH_2OH	78
12	$Cu(OAc)_2$	CF_3CH_2OH	10
13	--	CF_3CH_2OH	nr

[a]All reactions were carried out with substituted imidoyl halide (**1a)** (1.00 mmol), 1-phenyl-1-propyne (**2a**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), base (25 mol %), and solvent (3.0 mL) at 100 °C for 16 h. [b]Isolated yields.

Initially, the ruthenium-catalyzed cyclization of **1a** and **2a** was conducted in the presence of catalytic amount of NaOAc (25 mol %) in MeOH at 100 °C for 16 h. usually, alcoholic solvent and acetate base is suitable for this type of cyclization reaction. Thus, the catalytic reaction was tested with various alcoholic solvents such as MeOH, *iso*-PrOH, *tert*-BuOH, *tert*-amyl alcohol, Tolune, DMSO and DCE in the presence of NaOAc (Table 3B.1, entry 1-4 and 6-8). However, no cyclization product **3a** was observed in the reaction. Finally, the catalytic reaction was carried out in the presence of CF_3CH_2OH. Surprisingly, in the reaction, product **3a** was observed in 76% NMR yield (entry 5). The yield of product **3a** was determined by the ^{1}H NMR integration method using mesitylene as an internal standard. In order to increase the yield of **3a**, the catalytic reaction was carried out in the presence of various acetate bases such as KOAc, LiOAc, CsOAc and $Cu(OAc)_2$. As like NaOAc, CsOAc base was also equally effective, yielding product **3a** in 78% NMR yield. The remaining bases were less effective, giving **3a** in 50%, 60% and 10% NMR yields, respectively (entry 9-12).

3B.2.2 Synthesis of 1-Haloisoquinolines

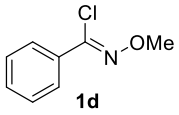
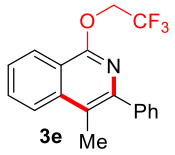
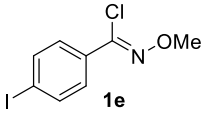
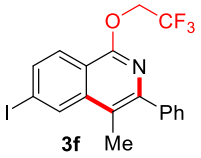
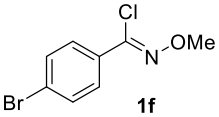
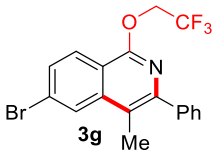
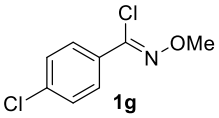
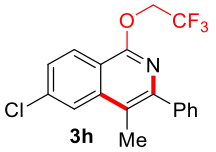
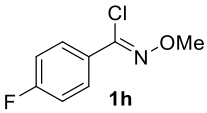
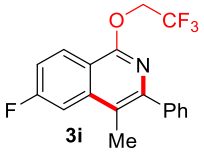
Treatment of 4-methyl substituted *N*-methoxy benzimidoyl chloride **1a** with unsymmetrical alkyne, 1-phenyl-1-propyne (**2a**), in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (3.0 mol %) and CsOAc (25 mol %) in CF_3CH_2OH (TFE) at 100 °C for 16 h gave substituted 1-chloro isoquinoline derivative **3a** in 77% isolated yield (Scheme 3B.1). The cyclization reaction is highly regioselective, so that, Ph group attached carbon of alkyne is connected to the nitrogen atom of imidoyl moiety of **1a** and Me substituted carbon of alkyne is attached to the *ortho* carbon of **1a** (for detailed studies, see in experimental section). In meantime, instead of imidoyl chloride moiety, the catalytic reaction was extended with imidoyl bromide moiety. Thus, 4-methyl benzohydroximoyl bromide **1b** reacted with **2a** yielding substituted 1-bromoisoquinoline **3b** in 82% isolated yield in a highly regioselective manner. Under the optimized reaction conditions, the cyclization reaction of 4-*tert*-butyl substituted *N*-methoxy benzimidoyl chloride **1c** with **2a** was carried out. In the reaction, the corresponding 1-chloro isoquinoline derivative **3c** was observed in 76% isolated yield. Symmetrical alkyne, diphenylacetylene **2b**, efficiently reacted with **1c** to give 1-chloro isoquinoline derivative **3d** in 85% yield (Scheme 3B.1).



Scheme 3B.1 Synthesis of substituted 1-haloisoquinolines.

3B.2.3 Synthesis of 1-Alkoxyisoquinolines

Table 3B.2 Cyclization reaction of substituted imidoyl halide **1d**–**h** with 1-phenyl-1-propyne (**2a**).[a]

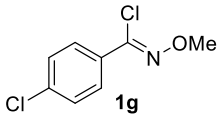
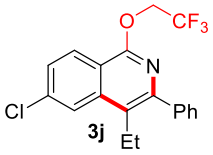
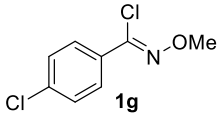
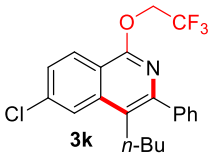
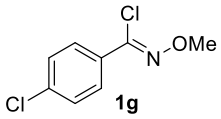
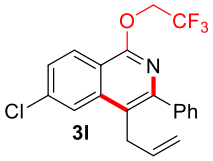
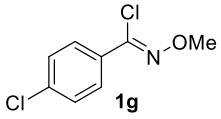
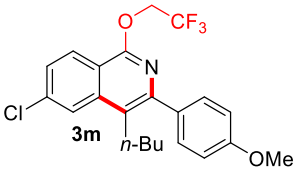
Entry	Imidoyl halide (1)	Compound (3)	Yeild[b]
1	 **1d**	 **3e**	78%
2	 **1e**	 **3f**	79%
3	 **1f**	 **3g**	76%
4	 **1g**	 **3h**	74%
5	 **1h**	 **3i**	71%

[a]All reactions were carried out with substituted imidoyl halide **1** (1.00 mmol), 1-phenyl-1-propyne (**2a**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3.0 mol %), CsOAc (25 mol %), and TFE (3.0 mL) at 100 °C for 16 h. [b]Isolated yields.

The present reaction was further examined with various substituted *O*-methylbenzohydroximoyl chlorides **1d-h** (Table 3B.2). The cyclization of *N*-methoxybenzimidoyl chloride (**1d**) with 1-phenyl-1-propyne (**2a**) under the optimized reaction conditions gave the corresponding cyclization compound **3e** in 78% yield (entry 1). But, during the cyclization, solvent CF_3CH_2OH was also involved in the reaction and added at the Cl connected carbon of imidoyl moiety. It is important to note that fluorinated heterocyclic compounds show several biological activites.[8] Further, 4-iodo **1e**, 4-bromo **1f**, 4-chloro **1g** and 4-fluoro **1h** benzohydroximoyl chlorides also reacted nicely with **2a** yielding the corresponding isoquinoline derivatives **3f-i** in 79%, 76%,

74% and 71% yields, respectively (entry 2-5). The structure of **3h** was confirmed by a single crystal X-ray diffraction (see in experimental section).

Table 3B.3 Cyclization reaction of substituted imidoyl halide **1a**–**i** with alkynes (**2a**).[a]

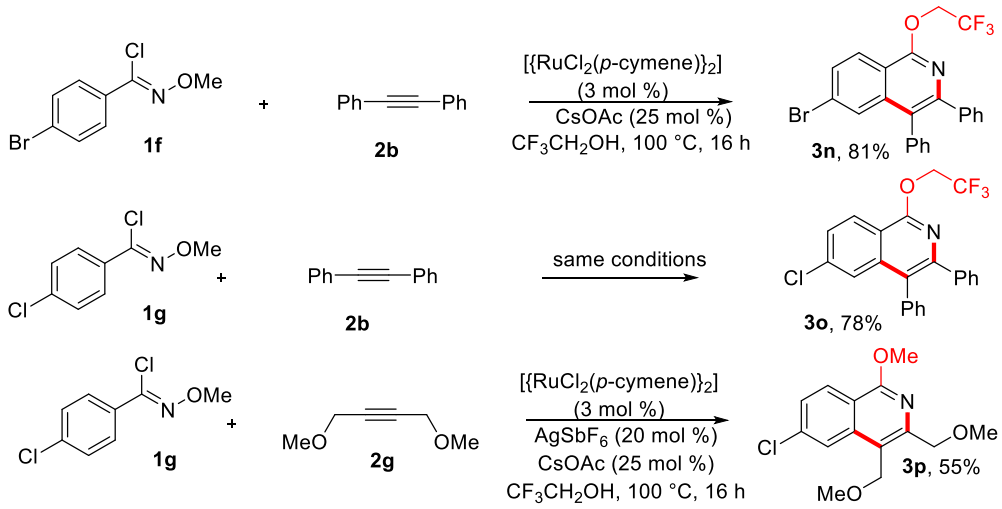
Entry	Aromatic oxime (1)	Compound (3)	Yeild[b]
1	 **1g**	 **3j**	77%
2	 **1g**	 **3k**	79%
3	 **1g**	 **3l**	61%
4	 **1g**	 **3m**	67%

[a]All reactions were carried out with substituted imidoyl halide **1** (1.00 mmol), alkynes (**2a**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3.0 mol %), NaOAc (25 mol %), and TFE (3.0 mL) at 100 °C for 16 h. [b]Isolated yields.

In meantime, the catalytic reaction was tested with electron-withdrawing group substituted 4-nitro benzohydroximoyl chloride. However, in the reaction, no cyclization product was observed. Subsequently, the scope of the cyclization reaction was tested with various unsymmetrical alkynes **2c-f** (Table 3B.3). Thus, 1-pheny-1-butyne (**2c**), 1-phenyl-1-hexyne (**2d**), substituted enyne **2e** and methoxy group substituted alkyne **2f** reacted efficiently with **1g** providing isoquinoline derivatives **3j-m** in 77%, 79% and 61% and 67% yields, respectively (entry 1-4), in a highly regioselective manner. In the substituted enyne **2e**, selectively the alkyne part was involved in the reaction.

Further, diphenylacetylene (**2b**) reacted with **1f** and **1g** affording isoquinoline derivatives **3n** and **3o** in 81% and 78% yields, respectively. Interestingly, 1,4-dimethoxybut-2-yne (**2g**) reacted with

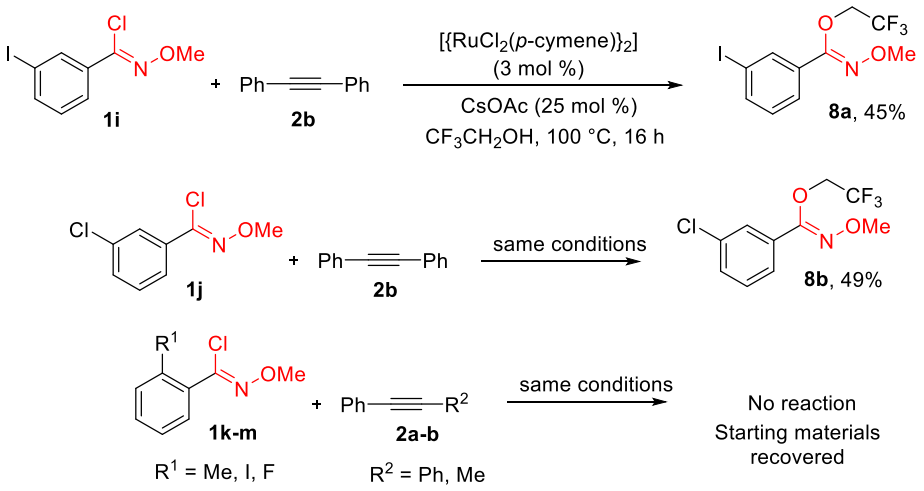
1g in the presence of $AgSbF_6$ giving 1-methoxy isoquinoline derivative **3p** in 55% yield (Scheme 3B.2). The catalytic reaction did not proceed in the absence of $AgSbF_6$. It is important to point out that unlike former reactions; TFE did not add at Cl substituted carbon of imidoyl moiety rather OMe moiety was added. The exact reason for the addition of OMe moiety instead of TFE at the Cl substituted carbon of imidoyl moiety is unclear to us (Scheme 3B.2).



Scheme 3B.2 Scope of the symmetrical alkynes

In fact, the cyclization reaction of various *meta* and *ortho* substituted I, Cl and F substituted *N*-methoxybenzimidoyl halides with diphenylacetylene (**2b**) was tested. However, in these reactions, no expected cyclization product **3** was observed; instead a different type of nucleophilic addition of solvent TFE at the Cl group substituted carbon of imidoyl moiety was observed. For example, in the reaction of meta iodo **1i** or chloro **1j** substituted *N*-methoxybenzimidoyl halides with diphenylacetylene (**2b**), only TFE addition products **8a-b** were observed instead of cyclization products. Whereas, no cyclization as well as TFE addition products were observed in the reaction of ortho Me **1k** or Cl **1l** or F **1m** substituted *N*-methoxybenzimidoyl halides with diphenylacetylene (**2b**) (Scheme 3B.3). Based on these reactions, we have concluded that in the *meta* substituted *N*-methoxybenzimidoyl halide substrates **1i-j**, nucleophilic addition of solvent TFE at the Cl substituted carbon of imidoyl moiety takes place before the cyclization reaction. At this stage, further cyclization reaction was stopped completely. Thus, the cyclization product was not observed. Whereas, in the *para* substituted *N*-methoxybenzimidoyl halide substrates **1a-i**, nucleophilic addition of the solvent

TFE at the Cl substituted carbon of imidoyl moiety takes place after the cyclization reaction. Thus, the expected cyclization product was observed **3** without any problem. In the meantime, *ortho* substituted *N*-methoxybenzimidoyl halides were not suitable substrates for the reaction (Scheme 3B.3).



Scheme 3B.3 Studies of the substituted imidoyl halides

In addition, nature of the substituent present on the aromatic ring of **1** also plays an important role especially for the nucleophilic addition of TFE. Electron-donating alkyl substituents do not encourage the TFE addition at the Cl substituted carbon of imidoyl moiety. But, electron-withdrawing substituents such as I, Br, Cl and F favor the TFE addition at the Cl substituted carbon of imidoyl moiety.

3B.2.4 Synthesis of Isoquinolones and 1-Haloisoquinolines

The trifluoroethoxy substituted isoquinoline derivatives **3f**, **3g**, and **3o** are easily converted into isoquinolone derivatives **4a-c** in excellent 89%, 91% and 87% yields, respectively (Table 3B.4, entry 1-3), in the presence of HBr/AcOH hydrolysis. Further, isoquinolone derivatives **4a-c** were converted into 1-chloroisoquinoline derivatives **5a-c** in excellent 90%, 89% and 93% yields, respectively (entry 1-3), by HBr hydrolysis followed by chlorination with $POCl_3$. Similarly, 1-alkoxyisoquinoline derivatives **4b** and **4c** were converted into 1-bromoisoqunoline derivatives **4h** and **5d** and **5e** in 91% and 94% yields, respectively, by HBr hydrolysis followed by bromination with PBr_3 (Table 4, entry 4 and 5). Whereas, in the substrate **3m**, OMe moiety was hydrolysed instead of trifluoroethoxy moiety, yielding isoquinoline derivative **4d** in 81% yield.

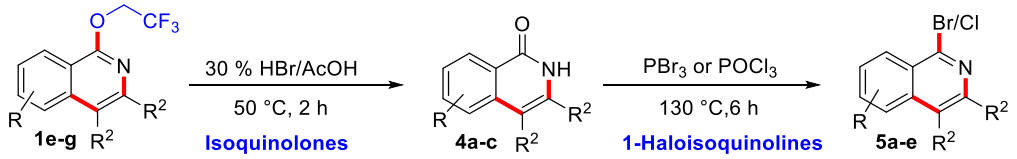
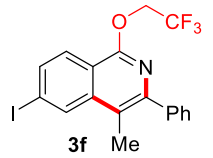
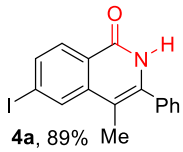
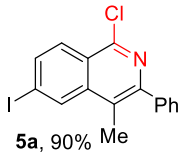
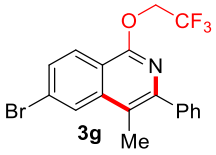
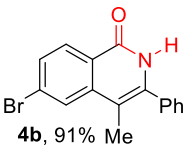
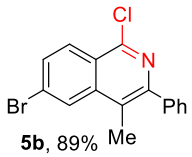
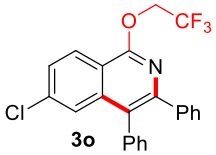
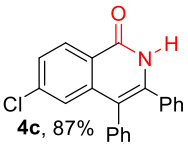
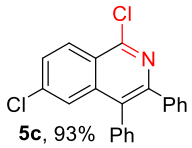
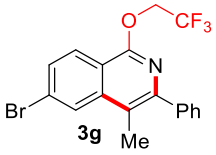
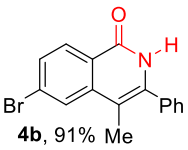
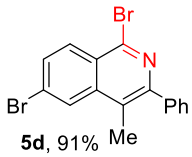
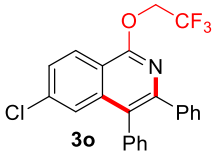
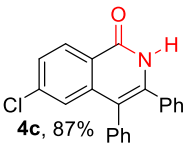
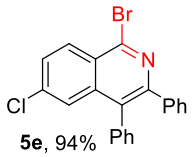
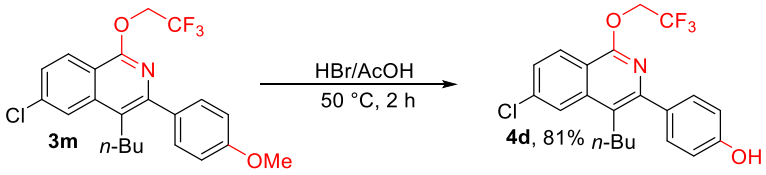


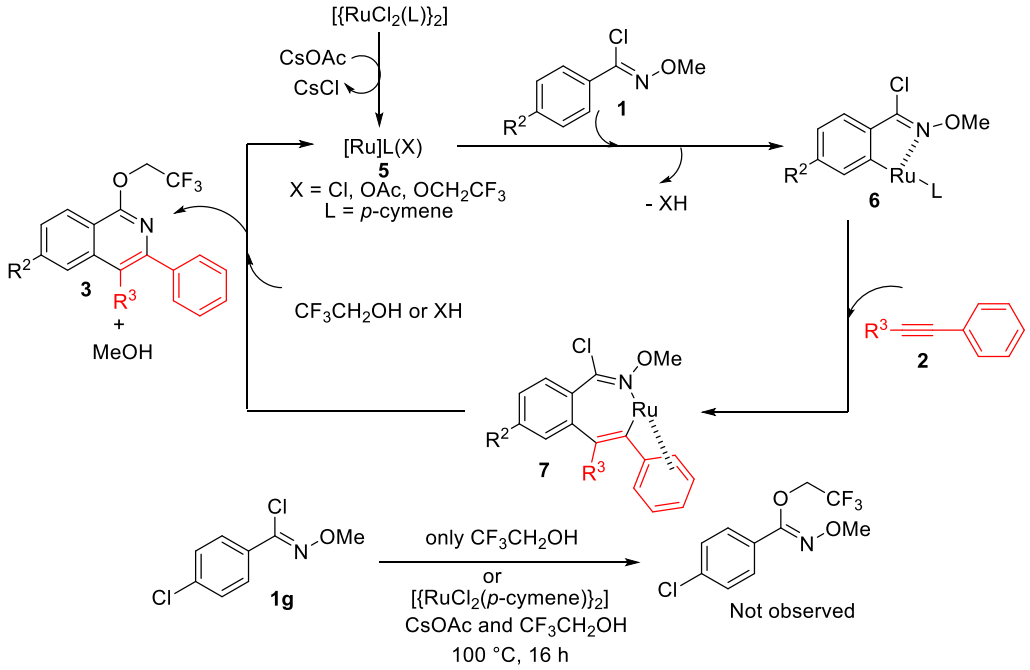
Table 3B.4 Synthesis of isoquinolones (4) and 1-haloisoquinolines (5).[a]

Entry	Isoquinoline (3)	Compound (4)	Compound (5)[b]
1	 **3f**	 **4a**, 89%	 **5a**, 90%
2	 **3g**	 **4b**, 91%	 **5b**, 89%
3	 **3o**	 **4c**, 87%	 **5c**, 93%
4	 **3g**	 **4b**, 91%	 **5d**, 91%
5	 **3o**	 **4c**, 87%	 **5e**, 94%

[a]All reactions were carried out with substituted 1-alkoxyisoquinolines **3** (150 mg) with 30% HBr/AcOH (3.0 mmol) at 50 °C for 2 h. and all reactions were carried out with substituted isoquinolones **4** (100 mg) with $POCl_3$ or PBr_3 (3.0 mmol) at 130 °C for 6 h. [b]Isolated yields.



3B.2.5 Mechanism



Scheme 4B.4 Proposed mechanism

A possible reaction mechanism for the cyclization of **1** with **2** is proposed in Scheme 3B.4. The catalytic reaction is likely initiated by the dissociation of dimeric form of ruthenium complex to monomer followed by ligand exchange with CsOAc providing a ruthenium acetate species **5**. Coordination of the nitrogen atom of imidoyl moiety **1** to the ruthenium species **5** followed by acetate accelerated *ortho*-metalation provides intermediate **6**. Coordinative regioselective insertion of alkyne **2** into the Ru–carbon bond of ruthenacycle **6** gives an intermediate **7**. Subsequent C-N bond formation followed by nucleophilic addition of CF_3CH_2OH (TFE) at Cl connected carbon of imidoyl moiety and N-OMe bond cleavage of intermediate **7** in the presence of TFE yields product **3** and regenerates the active ruthenium catalyst **5**. In the reaction, only 25 mol % of CsOAc base was used for the ortho C-H bond activation. In the reaction, acetate base initiates the catalytic reaction. Subsequently, alcoholic solvent acts as a base for the deprotonation of ortho C-H of aromatic.[6c] Solvent TFE acts as a base as well as proton donor in the reaction. TFE protonates OMe group of intermediate **7** providing product **3** and regenerates Ru-OCH_2CF_3. To know exactly when TFE is added at Cl connected carbon of imidoyl moiety **1**, the following reactions were carried out. The reaction of TFE with **1g** was tested in the presence of ruthenium catalyst and CsOAc and also carried out without ruthenium catalyst and CsOAc in

the absence of alkyne **2a** (Scheme 3B.4). In these reactions, no TFE addition product was observed. This result clearly revealed that TFE was added to the imidoyl moiety after insertion of alkyne into metalacycle intermediate **7**. In the reaction of **1a-c** with **2a-b** (Scheme 3B.1), no TFE addition was observed at the halogen substituted carbon of imidoyl moiety.

3B.3 Conclusions

In conclusion, we have shown a highly regioselective ruthenium-catalyzed cyclization of substituted *N*-methoxy benzimidoyl halide with alkynes in the presence of base to provide 1-halo and 1-alkoxyisoquinolines in good to excellent yields.

3B.4 References

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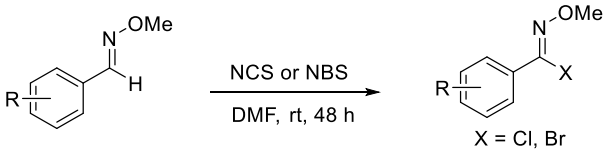
3B.5 Experimental Section

3B.5.1 General Procedure for the Preparation of Starting Materials 1[1]



The appropriate *O*-alkyl benzaldehyde oxime (20 mmol, 1.0 equiv) and DMF (50 mL) was charged in a 250 mL round-bottom flask fitted with a septum. Then, *N*-chlorosuccinimide (NCS, 20 mmol, 1.0 equiv) or *N*-bromosuccinimide (NBS, 20 mmol, 1.0 equiv) was slowly added to the reaction mixture. After the addition was complete, the reaction mixture was stirred at room temperature for 48 h. Then, the reaction mixture was poured into ice water (70 mL) and the resulting mixture was extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **1**.

Ref. 1: Lijser, H. J. P.; Burke, C. R.; Rosenberg, J.; Hunter, J. *J. Org. Chem*. **2009**, *74*, 1679.

3B.5.2 General Procedure for the Cyclization of *O*-Methylbenzohydroximoyl halides with Alkynes Catalyzed by Ruthenium Complex

A 15-mL pressure tube equipped with a magnetic stirrer and septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (0.03 mmol, 3 mol %) and CsOAc (25 mol %) was evacuated and purged with nitrogen gas three times. To the tube were then added *O*-methylbenzohydroximoyl halides **1** (1.00 mmol), alkynes **2** (1.20 mmol) and CF_3CH_2OH (2.0 mL) via syringes and again the tube was evacuated and purged with nitrogen gas three times. Then, in the pressure tube, septum was taken out and covered with a screw cap immediately under nitrogen atmosphere and the reaction mixture was allowed to stir at 100 °C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3**.

3B.5.3 General Procedure for the HBr Hydrolysis[2]

A mixture of *O*-alkyl isoquinoline **3f** (0.30 mmol, 70 mg) and 48% HBr in AcOH (2.0 mL) n a sealed tube was heated at 50 ˚C for 2 h. The reaction mixture was cooled to room temperature and poured into a mixture of ice and saturated aq. $NaHCO_3$ solution. The reaction mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure to yield the corresponding pure isoquinolone derivative **4a** (purification is not necessary). A similar procedure was used for the preparation of compounds **4b-d**. For the chlorination and bromination reactions, the corresponding compounds were used directly without further purification.

Ref. 2: Li, J.; Chen, L.; Chin, E.; Lui, A. S.; Zecic, H. *Tetrahedron Lett*. **2010**, *51*, 6422.

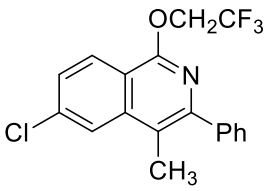
3B.5.4 General Procedure for the Chlorination or Bromination reaction[3]

In a 50 mL round-bottom flask fitted with a condenser, a suspension of isoquinolone (100 mg) in phosphorus oxychloride ($POCl_3$) or phosphorus tribromide (PBr_3) (2.0 mL) was heated at 100 ˚C for 2 h (100 ˚C for chlorination and 130 ˚C for bromination). The reaction was monitored on TLC. After completion the reaction (approx. 2.0 h for chlorination and approx. 6.0 h for bromination), the reaction mixture was cooled to ambient temperature, and poured in ice and added saturated $NaHCO_3$, extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4. The solution was concentrated under reduced pressure to provide crude 1-halo isoquinolines **4e-i**. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **4e-i**.

Ref. 3: Tobe, M.; Isobe, Y.; Tomizawa, H.; Nagasaki, T.; Takahashi, H.; Fukazawa, T.; Hayashi, H. *Bioorg. Med. Chem*. **2003**, *11*, 383.

3B.5.5 X-Ray Analysis

6-Chloro-4-methyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (3h)



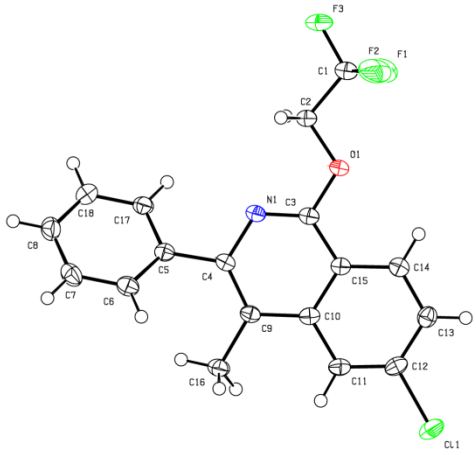


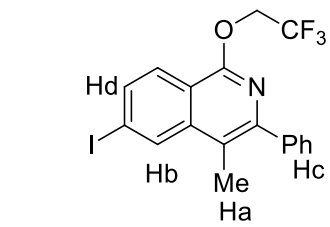
Table 3B.4 Crystal data and structure refinement for (**3h**)

Identification code	**3h**	
Empirical formula	C_{18} H_{13} Cl F_3 N O	
Formula weight	351.74	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	'Monoclinic'	
Space group	'P121/n1'	
Unit cell dimensions	a = 11.5379(13) Å	α= 90°.
	b = 7.0208(8) Å	β= 94.958(3)°.
	c = 19.335(2) Å	γ = 90°.
Volume	1560.4(3) A^3	
Z	4	
Density (calculated)	1.497 Mg/m^3	
Absorption coefficient	0.282 mm^{-1}	
F(000)	720	
Crystal size	0.14 x 0.12 x 0.06 mm^3	
Theta range for data collection	1.98 to 28.36°.	
Index ranges	-15<=h<=15, -9<=k<=8, -25<=l<=25	
Reflections collected	27160	
Independent reflections	3907 [R(int) = 0.0437]	

Completeness to theta = 28.36°	99.9 %
Max. and min. transmission	0.9833 and 0.9616
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3907 / 0 / 219
Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R_1 = 0.0361, wR_2 = 0.0901
R indices (all data)	R_1 = 0.0544, wR_2 = 0.1004
Extinction coefficient	0.0009(5)
Largest diff. peak and hole	0.345 and -0.287 e.Å^{-3}

3B.5.6 Regioselective Studies: NOESY Experiments

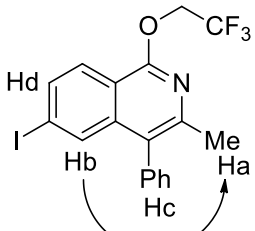
Copy of NOESY Experiment of Compound 3f



Ha δ = 2.52; Hb = 8.36; Hc = 7.48 - 7.42

Hd δ = 8.01

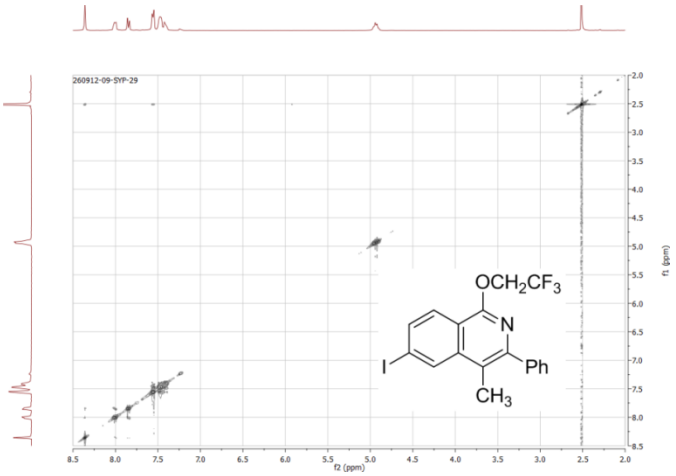
Observed



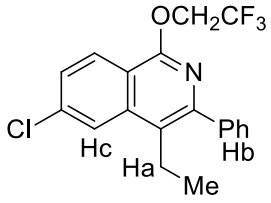
No signal

Not observed

There is a NOE correlation between Ha (δ 2.52, s) and Hb (δ 8.36, s). In meantime, there is also correlation between Ha (δ 2.52, s) and Hc (δ 7.48 - 7.42, m). However, there is no correlation between Hb (δ 8.36, s) and Hc (δ 7.48 - 7.42, m). These results clearly revealed that the regiochemistry of compound **3f** is correct.

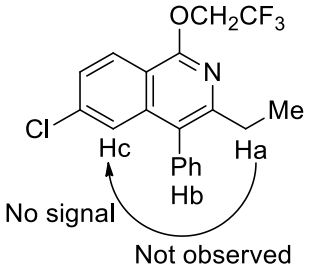


Copy of NOESY experiment of compound 3j



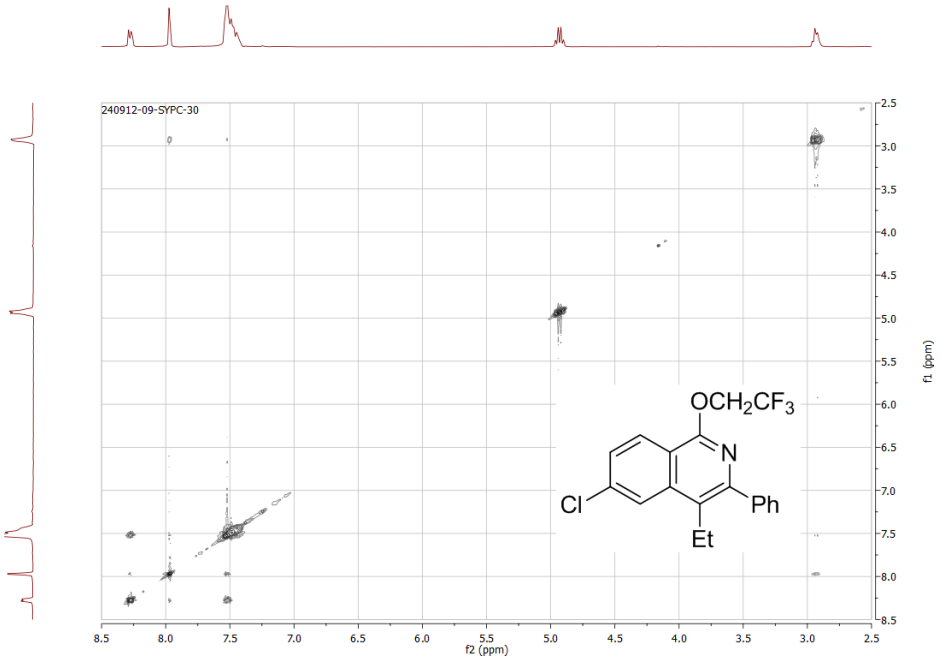
Ha δ = 2.93; Hb = 7.54 - 7.43; Hc = 7.97

Observed

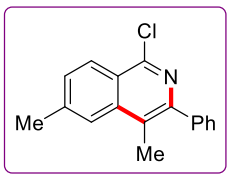


Not observed

There is a NOE correlation between Ha (δ 2.93, q) and Hc (δ 7.97, s). In meantime, there is also correlation between Ha (δ2.93, q) and Hb (δ 7.54 - 7.43, m). If the other regioisomer is formed, there should not be correlation between Ha (δ 2.93, q) and Hc (δ 7.97, s). However, there is correlation between Ha (δ 2.93, q) and Hc ((δ 7.97, s). Thus, these results clearly revealed that the regiochemistry of compound **3j** is correct.



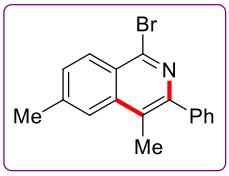
3B.5.7 Spectral Data of all Compounds



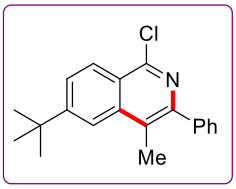
1-Chloro-4,6-dimethyl-3-phenylisoquinoline (**3a**): Brown semisolid; eluent (3% ethyl acetate in hexanes) **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2922, 1722, 1621, 1482, 1308, 1242 and 1091. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.25(d, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 2 H), 7.47 – 7.42 (m, 3 H), 7.40 (s, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 2.52 (s,

3 H), 2.28 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6, 151.2, 145.8, 138.9, 133.4, 129.7, 129.5, 129.3, 128.2, 123.5, 118.4, 109.1, 22.3, 13.6. HRMS (ESI): calc. for [($C_{17}H_{14}ClN$)H] (M+H) 268.0893, measured 268.0897.

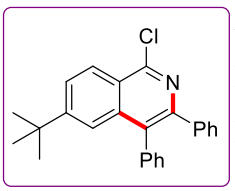
1-Bromo-4,6-dimethyl-3-phenylisoquinoline (3b): Brown semisolid; eluent (3% ethyl acetate in hexanes) **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2911, 1591, 1417, 1121 and 1038. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 8.0 Hz, 1 H), 7.56 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.46 – 7.40 (m, 4 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 2.51 (s, 3 H), 2.28 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 151.3, 145.9, 138.9, 133.5, 129.8, 129.6, 129.3, 128.3, 123.6, 118.5, 109.1, 22.4, 13.7. HRMS (ESI): calc. for [($C_{17}H_{14}BrN$)H] (M+H) 312.0388, measured 312.0385.



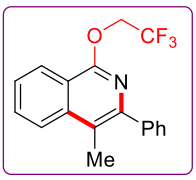
6-(*tert*-Butyl)-1-chloro-4-methyl-3-phenylisoquinoline (**3c**): Yellow liquid; eluent (3% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2961, 1728, 1601, 1482, 1308, 1247, 1100 and 1037. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, *J* = 8.0 Hz, 1 H), 7.60 – 7.58 (m, 3 H), 7.56 (d, *J* = 4.0 Hz, 1 H), 7.47 – 7.41 (m, 3 H), 2.32 (s, 3 H), 1.40 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6, 158.7, 151.2, 138.7, 133.5, 129.6, 129.5, 129.3, 128.3, 125.9, 119.6, 118.4, 109.4, 35.7, 31.2, 13.6. HRMS (ESI): calc. for [($C_{20}H_{20}ClN$)H] (M+H) 310.1363, measured 310.1366.



6-(*tert*-Butyl)-1-chloro-3,4-diphenylisoquinoline (3d): Colorless solid; eluent (3% ethyl acetate in hexanes). m.p. 152-154 °C, **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.32 (d, *J* = 8.0 Hz, 1 H), 7.57 (dd, *J* = 4.0, 4.0 Hz, 1 H) 7.42 – 7.38 (m, 3 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.26 – 7.23 (m, 2 H), 7.21 – 7.15 (m, 4 H), 1.22 (s, 9 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 162.3, 158.6, 150.9, 138.7, 134.4, 133.1, 131.3, 129.4, 129.3, 129.0, 128.8, 128.1, 127.9, 126.0, 121.7, 118.0, 117.3, 35.5, 30.9. **HRMS** (ESI): calc. for [($C_{25}H_{22}ClN$)H] (M+H) 372.1519, measured 372.1516.

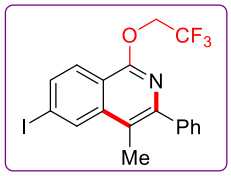


4-Methyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3e**): Colorless solid; eluent (1% ethyl acetate in hexanes). m.p. 135-137 °C, **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2923, 2855, 1729, 1624, 1580, 1454, 1350, 1272, 1107 and 1034. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.33 (d, *J* = 8.0 Hz, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 7.77 (t, *J* = 8.0 Hz, 1 H), 7.60 (t, *J* = 8.0 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 2 H), 7.48 (t, *J* = 8.0 Hz, 2),



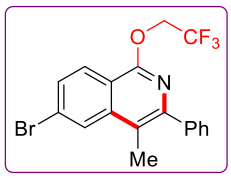
7.42 – 7.38 (m, 1 H), 4.96 (q, *J* = 8.0 Hz, 2 H), 2.57 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 156.1, 147.2, 140.8, 138.8, 130.9, 130.0, 128.0, 127.7, 126.5, 125.4 (due to F – Coupling), 124.2, 123.7, 122.6 (due to F – Coupling), 119.2, 118.0, 62.1 (q, *J* = 36.0 Hz), 15.2. **HRMS** (ESI): calc. for [($C_{18}H_{14}F_3NO$)H] (M+H) 318.1106, measured 318.1109.

6-Iodo-4-methyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3f**): Colorless solid; eluent



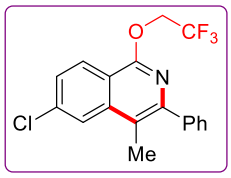
(1% ethyl acetate in hexanes) m.p. 181-183 °C, **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 1605, 1415, 1268, 1168, 1109 and 1054. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.36 (s, 1 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.42 (t, *J* = 8.0 Hz, 1 H) 4.94 (q, *J* = 8.0 Hz, 2 H) 2.52 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 156.1, 148.4, 140.4, 140.3, 135.3, 133.0, 129.9, 128.1, 127.9, 125.6, 125.3 and 122.5 (due to F – coupling), 118.0, 116.7, 98.9, 62.1 (d, *J* = 37.0 Hz), 15.2. **HRMS** (ESI): calc. for [($C_{18}H_{13}F_3INO$)H] (M+H) 444.0072, measured 444.0076.

6-Bromo-4-methyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3g**): Colorless solid;



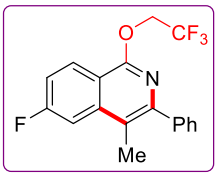
eluent (1% ethyl acetate in hexanes). m.p. 195-197 °C, **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 1584, 1414, 1264, 1169, 1109 and 1034. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.17 (d, *J* = 8.0 Hz, 1 H), 8.13 (s, 1 H), 7.66 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.56 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 4.94 (q, *J* = 8.0 Hz, 2 H), 2.52 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 156.0, 148.6, 140.4, 140.2, 129.9, 128.1, 127.9, 126.4, 126.2, 126.0, 125.3 and 122.5 (due to F – coupling), 118.4, 116.4, 62.0 (q, *J* = 36), 15.2. **HRMS** (ESI): calc. for [($C_{18}H_{13}BrF_3NO$)H] (M+H) 396.0211, measured 396.0214.

6-Chloro-4-methyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (3h): Colorless solid;



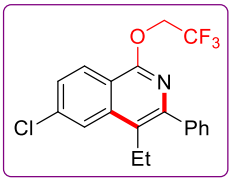
eluent (1% ethyl acetate in hexanes). m.p. 201-203 °C, **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 1585, 1414, 1263, 1166, 1107 and 1035. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 8.0 Hz, 1 H), 7.93 (s, 1 H), 7.58 (d, *J* = 8.0, Hz, 2 H), 7.53 – 7.47 (m, 3 H) 7.42 (t, *J* = 8.0, Hz, 1 H), 4.95 (q, *J* = 8.0, Hz, 2 H), 2.53 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 155.9, 148.6, 140.4, 139.9, 137.5, 129.9, 128.1, 127.9, 127.3, 126.0, 125.3 (due to F – coupling), 123.1, 122.5 (due to F – coupling), 118.5, 116.2, 62.2 (q, *J* = 35.0 Hz), 15.2. **HRMS** (ESI): calc. for [($C_{18}H_{13}ClF_3NO$)H] (M+H) 352.0716, measured 352.0713.

6-Fluoro-4-methyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3i**): Colorless solid; eluent



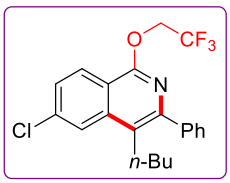
(1% ethyl acetate in hexanes) m.p. 220-223 °C, **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 1568, 1417, 1260, 1150, 1109 and 1035. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.34 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.59 – 7.54 (m, 3 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.33 (t, *J* = 8.0 Hz, 1 H), 4.95 (q, *J* = 8.0 Hz, 2 H), 2.51 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.4, 162.9, 155.9, 148.5, 141.0 (d, *J* = 9.0 Hz), 140.5, 129.9, 128.1 (d, *J* = 18.0 Hz), 127.4 (d, *J* = 10.0 Hz), 125.3 and 122.5 (due to F – coupling), 118.9 (d, *J* = 5.0 Hz), 116.4 (d, *J* = 24.0 Hz), 114.9, 108.3 (d, *J* = 22.0 Hz), 62.1 (q, *J* = 36.0 Hz), 15.3. **HRMS** (ESI): calc. for [($C_{18}H_{13}F_4NO$)H] (M+H) 336.1012, measured 336.1017.

6-Chloro-4-ethyl-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3j**): Colorless solid; eluent



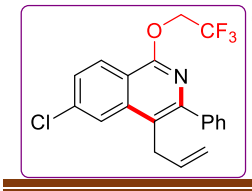
(1% ethyl acetate in hexanes) m.p. 185-187 °C, **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2970, 1612, 1579, 1416, 1269, 1167, 1109 and 1054. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.27 (d, *J* = 8.0 Hz, 1 H), 7.97 (s, 1 H), 7.54 – 7.43 (m, 6 H), 4.93 (q, *J* = 8.0 Hz, 2 H), 2.93 (q, *J* = 8.0 Hz, 2 H), 1.28 (t, *J* = 8.0 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 155.9, 148.8, 140.8, 138.9, 137.5, 129.2, 128.2, 127.9, 127.3, 126.2, 125.3 (due to F – coupling), 125.0, 123.1, 122.5 (F – coupling), 116.7, 62.2 (q, *J* = 35.0 Hz), 21.4, 15.7. **HRMS** (ESI): calc. for [($C_{19}H_{15}ClF_3NO$)H] (M+H) 366.0873, measured 366.0878.

4-Butyl-6-chloro-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3k**): Colorless solid; eluent



(1% ethyl acetate in hexanes) m.p. 174-176 °C, **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2951, 2868, 1614, 1510, 1467, 1371, 1254, 1162 and 1037. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.25 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.92 (s 1 H), 7.52 – 7.40 (m, 6 H), 4.90 (q, *J* = 8.0 Hz, 2 H), 2.87 (t, *J* = 8.0 Hz, 2 H), 1.63 – 1.55 (m, 2 H), 1.37 – 1.28 (m, 2 H), 0.85 (t, *J* = 8.0 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 155.8, 149.0, 140.8, 139.1, 137.4, 129.3, 128.1, 127.8, 127.2, 126.2, 125.3 (due to F – coupling), 123.8, 123.1, 122.5 (due to F – coupling), 116.6, 62.2 (q, *J* = 36.0 Hz), 33.3, 27.9, 22.8, 13.8. **HRMS** (ESI): calc. for [($C_{21}H_{19}ClF_3NO$)H] (M+H) 394.1186, measured 394.1189.

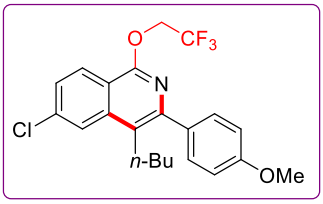
4-Allyl-6-chloro-3-phenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3l**): Yellow liquid; eluent



(1% ethyl acetate in hexanes) **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 1614, 1580, 1490, 1414, 1376, 1271, 1166 and 1030. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (d, *J* = 8.0

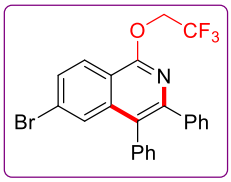
Hz, 1 H), 7.90 (s, 1 H), 7.61 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.52 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.48 – 7.42 (m, 2 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 6.19 – 6.10 (m, 1 H) 5.20 (dd, *J* = 8.0, 4.0 Hz, 1 H), 4.96 (q, *J* = 8.0 Hz, 2 H), 4.90 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.67 (q, *J* = 8.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.4, 149.8, 140.2, 139.5, 137.6, 136.9, 131.5, 129.2, 128.2, 128.1, 127.4, 126.0, 125.3 (due to F – coupling), 123.8, 122.5 (due to F – coupling), 120.0, 117.1, 116.5, 62.2 (q, *J* = 36.0 Hz), 32.8. HRMS (ESI): calc. for [($C_{20}H_{15}ClF_3NO$)H] (M+H) 378.0873, measured 378.0874.

4-Butyl-6-chloro-3-(4-methoxyphenyl)-1-(2,2,2-trifluoroethoxy)isoquinoline (**3m**): Yellow



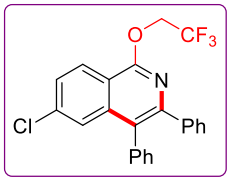
semi solid; eluent (3% ethyl acetate in hexanes) **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2957, 2863, 1610, 1515, 1462, 1375, 1259, 1169 and 1034. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 8.0 Hz, 1 H), 7.91 (s, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 4.91 (q, *J* = 8.0 Hz, 2 H) 3.88 (s, 3 H), 2.90 (t, *J* = 8.0 Hz, 2 H), 1.64 – 1.57 (m, 2 H), 1.40 – 1.31 (m, 2 H), 0.88 (t, *J* = 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 155.7, 148.7, 139.2, 137.3, 133.4 133.3, 130.6, 127.0, 126.2, 125.3 (due to F – coupling), 123.6, 123.1, 122.5 (due to F – coupling), 116.5, 113.5, 62.1 (q, *J* = 37.0 Hz), 55.4, 33.3, 28.0, 22.9, 13.8. HRMS (ESI): calc. for [($C_{22}H_{21}ClF_3NO_2$)H] (M+H) 424.1291, measured 424.1296.

6-Bromo-3,4-diphenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3n**): Yellow solid; eluent (1%



ethyl acetate in hexanes) **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2926, 1581, 1454, 1361, 1272, 1132 and 1045. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21(d, *J* = 8.0 Hz, 1 H), 7.72 (s, 1 H), 7.66 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.38 – 7.32 (m, 5 H), 7.20 – 7.18 (m, 5 H), 5.04 (q, *J* = 8.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.1, 147.8, 140.1, 139.8, 136.6, 131.4, 130.3, 130.2, 128.7, 128.4, 128.0, 127.7, 127.6, 126.4, 125.9, 125.6, 125.3 and 122.5 (due to F – coupling), 116.3, 62.4 (q, *J* = 36.0 Hz). HRMS (ESI): calc. for [($C_{23}H_{15}BrF_3NO$)H] (M+H) 458.0367, measured 458.0367.

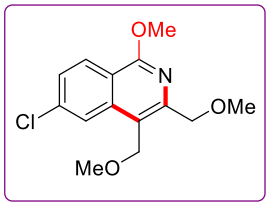
6-Chloro-3,4-diphenyl-1-(2,2,2-trifluoroethoxy)isoquinoline (**3o**): Yellow solid; eluent (1%



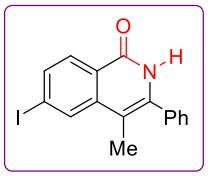
ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2922, 1584, 1458, 1419, 1364, 1270, 1122 and 1040. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, *J* = 8.0 Hz, 1 H), 7.54 (s, 1 H), 7.51 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.38 – 7.32 (m, 5 H), 7.20 –

7.18 (m, 5 H), 5.04 (q, *J* = 8.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.0, 147.8, 139.9, 139.8, 137.7, 136.7, 131.4, 130.4, 130.2, 128.7, 128.4, 127.7, 127.3, 125.9, 125.8 (due to F – coupling), 125.6, 125.2 (due to F – coupling), 124.8, 116.0, 62.3 (q, *J* = 37 Hz). HRMS (ESI): calc. for [($C_{23}H_{15}ClF_3NO$)H] (M+H) 414.0873, measured 414.0871.

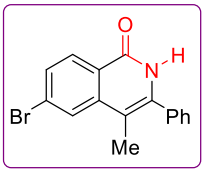
6-Chloro-1-methoxy-3,4-bis(methoxymethyl)isoquinoline (3p): Pale yellow semisolid; eluent (20% ethyl acetate in hexanes) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (d, *J* = 8.0 Hz, 1 H), 7.40 (s, 1 H), 7.16 (dd, *J* = 8.0, 4.0 Hz, 1 H), 4.55 (s, 2 H), 4.54 (s, 2 H), 4.11 (s, 3 H), 3.37 (s, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.1, 145.9, 142.6, 135.0, 132.7, 129.2, 126.9, 121.6, 121.0, 67.1, 66.0, 63.8, 58.5, 58.3. HRMS (ESI): calc. for [($C_{14}H_{16}ClNO_3$)H] (M+H) 282.0897, measured 282.0903.



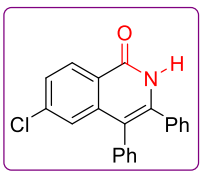
6-Iodo-4-methyl-3-phenylisoquinolin-1(2*H*)-one (4a): Colorless solid; eluent (25% ethyl acetate in hexanes). m.p. 221-223 °C, **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3390, 2933, 1569, 1443, 1254, 1042. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 9.08 (bs, 1H), 8.10 (d, *J* = 4.0 Hz, 1 H), 8.09 (s, 1H), 7.80 (dd, *J* = 4.0, 4.0 Hz, 1 H), 7.50 – 7.46 (m, 3 H) 7.45 – 7.41 (m, 2 H), 2.20 (s, 3 H). **^{13}C NMR** (DMSO-d_6, 100 MHz): δ 161.7, 140.3, 139.5, 135.2, 135.0, 132.8, 130.1, 129.3, 129.2, 128.7, 125.0, 106.7, 102.0, 13.9. **HRMS** (ESI): calc. for [($C_{16}H_{12}INO$)H] (M+H) 362.0042, measured 362.0040.



6-Bromo-4-methyl-3-phenylisoquinolin-1(2*H*)-one (4b): Colorless solid; eluent (25% ethyl acetate in hexanes). m.p. 228-230 °C, **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3394, 2922, 1585, 1457, 1268, 1081. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 9.14 (bs, 1H), 8.25 (d, *J* = 8.0 Hz, 1 H), 7.87 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1 H) 7.51 – 7.42 (m, 5 H), 2.21 (s, 3 H). **^{13}C NMR** (DMSO-d_6, 100 MHz): δ 181.4, 140.5, 139.8, 134.9, 130.1, 129.7, 129.5, 129.4, 128.8, 127.5, 126.7, 124.7, 106.9, 13.9. HRMS (ESI): calc. for [($C_{16}H_{12}BrNO$)H] (M+H) 314.0181, measured 314.0183.

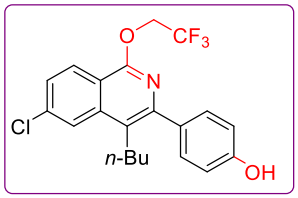


6-Chloro-3,4-diphenylisoquinolin-1(2*H*)-one (4c): Colorless solid; eluent (25% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.77 (bs, 1H), 8.36 (d, *J* = 8.0 Hz, 1 H), 7.41 (dd, *J* = 4.0, 4.0 Hz, 1 H) 7.32 – 7.29 (m, 4 H), 7.27 – 7.20 (m, 5 H), 7.15 – 7.13 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4, 154.9, 140.1,

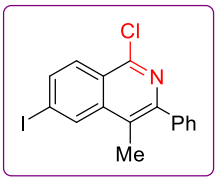


139.5, 138.7, 135.0, 134.6, 131.7, 129.3, 128.9, 128.7, 128.4, 127.7, 127.2, 125.1, 123.4, 116.5. HRMS (ESI): calc. for [($C_{21}H_{14}ClNO$)H] (M+H) 332.0842, measured 332.0840.

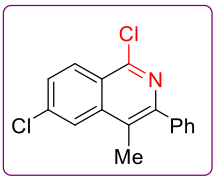
4-(4-Butyl-6-chloro-1-(2,2,2-trifluoroethoxy)isoquinolin-3-yl)phenol (4d): Colorless solid; eluent (15% ethyl acetate in hexanes). m.p. 246-248 °C, **IR** (ATR) $\tilde{\nu}$ (cm^{-1}): 3385, 2936, 1591, 1462, 1255, 1075. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 8.0 Hz, 1 H), 7.90 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1 H) 7.39 (d, *J* = 8.0 Hz, 2 H), 6.92 (d, *J* = 8.0 Hz, 2 H), 5.13 (bs, 1H), 4.90 (q, *J* = 8.0 Hz, 2 H), 2.88 (d, *J* = 8.0 Hz, 2 H), 1.59 (qt, *J* = 8.0 Hz, 2 H), 1.35 (m, 2 H), 0.88 (t, *J* = 8.0 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 155.7, 155.3, 148.6, 139.2, 137.4, 133.5, 130.8, 127.1, 126.2, 123.6, 123.1, 122.5, 116.5, 115.0, 62.9 - 62.2 (q), 33.3, 28.0, 22.9, 13.8. **HRMS** (ESI): calc. for [($C_{22}H_{19}ClF_3NO_2$)H] (M+H) 410.1135, measured 410.1133.



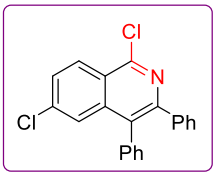
1-Chloro-6-iodo-4-methyl-3-phenylisoquinoline (4e): Pale yellow oil; eluent (5% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.44 (s, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 2.57 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.9, 148.9, 139.7, 139.6, 136.6, 133.6, 129.9, 128.3, 128.2, 124.4, 123.2, 99.3, 15.6. HRMS (ESI): calc. for [($C_{16}H_{11}ClIN$)H] (M+H) 379.9703, measured 379.9711.



1,6-Dichloro-4-methyl-3-phenylisoquinoline (4f): Pale yellow oil; eluent (5% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (d, *J* = 8.0 Hz, 1 H), 8.01 (s, 1 H), 7.60 (dd, *J* = 8.0 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 2 H), 7.41 (t, *J* = 8.0 Hz, 1 H), 2.58 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.0, 148.8, 139.5, 139.3, 137.9, 129.9, 128.8, 128.7, 128.3, 128.2, 123.9, 123.6, 123.5, 15.6. HRMS (ESI): calc. for [($C_{16}H_{11}Cl_2N$)H] (M+H) 288.0347, measured 288.0353.

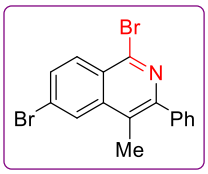


1,6-Dichloro-3,4-diphenylisoquinoline (4g): Pale yellow oil; eluent (5% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (d, *J* = 8.0 Hz, 1 H), 7.62 (s, 1 H), 7.59 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.39 – 7.37 (m, 3 H), 7.34 – 7.32 (m, 2 H), 7.21 – 7.18 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.9, 150.4, 139.1, 139.0, 138.0, 135.9, 131.1, 130.3, 130.1, 129.0, 128.8, 128.3, 128.1, 127.9,

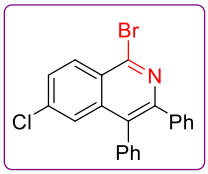


125.3, 123.9. HRMS (ESI): calc. for [($C_{21}H_{13}Cl_2N$)H] (M+H) 350.0503, measured 350.0510.

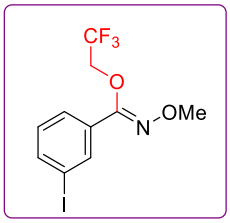
1,6-Dibromo-4-methyl-3-phenylisoquinoline (4h): Pale yellow oil; eluent (5% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 – 8.16 (m, 2 H), 7.73 (t, *J* = 8.0 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 2.56 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.6, 142.3, 139.4, 139.1, 131.5, 131.0, 129.9, 128.3, 126.9, 126.6, 126.1, 123.8, 14.6. HRMS (ESI): calc. for [($C_{16}H_{11}Br_2N$)H] (M+H) 375.9336, measured 375.9335.



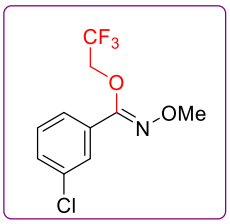
1-Bromo-6-chloro-3,4-diphenylisoquinoline (4i): Pale yellow oil; eluent (5% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.47 – 7.45 (m, 2 H), 7.25 – 7.23 (m, 3 H), 7.20 – 7.18 (m, 2 H), 7.10 – 7.03 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.2, 143.8, 138.8, 138.6, 137.9, 135.7, 130.9, 130.5, 130.2, 129.1, 128.7, 128.0, 127.7, 125.9, 125.2. HRMS (ESI): calc. for [($C_{21}H_{13}BrClN$)H] (M+H) 393.9998, measured 394.0007.



(*Z*)-2,2,2-Trifluoroethyl 3-iodo-*N*-methoxybenzimidate (8a): Pale Yellow semi solid; eluent (1% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (s, 1 H), 7.76 (d, *J* = 8.0, Hz, 1 H), 7.74 (d, *J* = 8.0, Hz, 1 H), 7.12 (t, *J* = 8.0, Hz, 1 H), 4.73 (q, *J* = 8.0, Hz, 2 H), 3.96 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.4, 139.4, 135.4, 132.1, 130.1, 125.7, 124.5 – 121.7 (F coupling), 94.1, 69.0 – 67.9 (q, due to fluorine coupling), 63.0. HRMS (ESI): calc. for [($C_{10}H_9F_3INO_2$)H] (M+H) 359.9708, measured 359.9703.

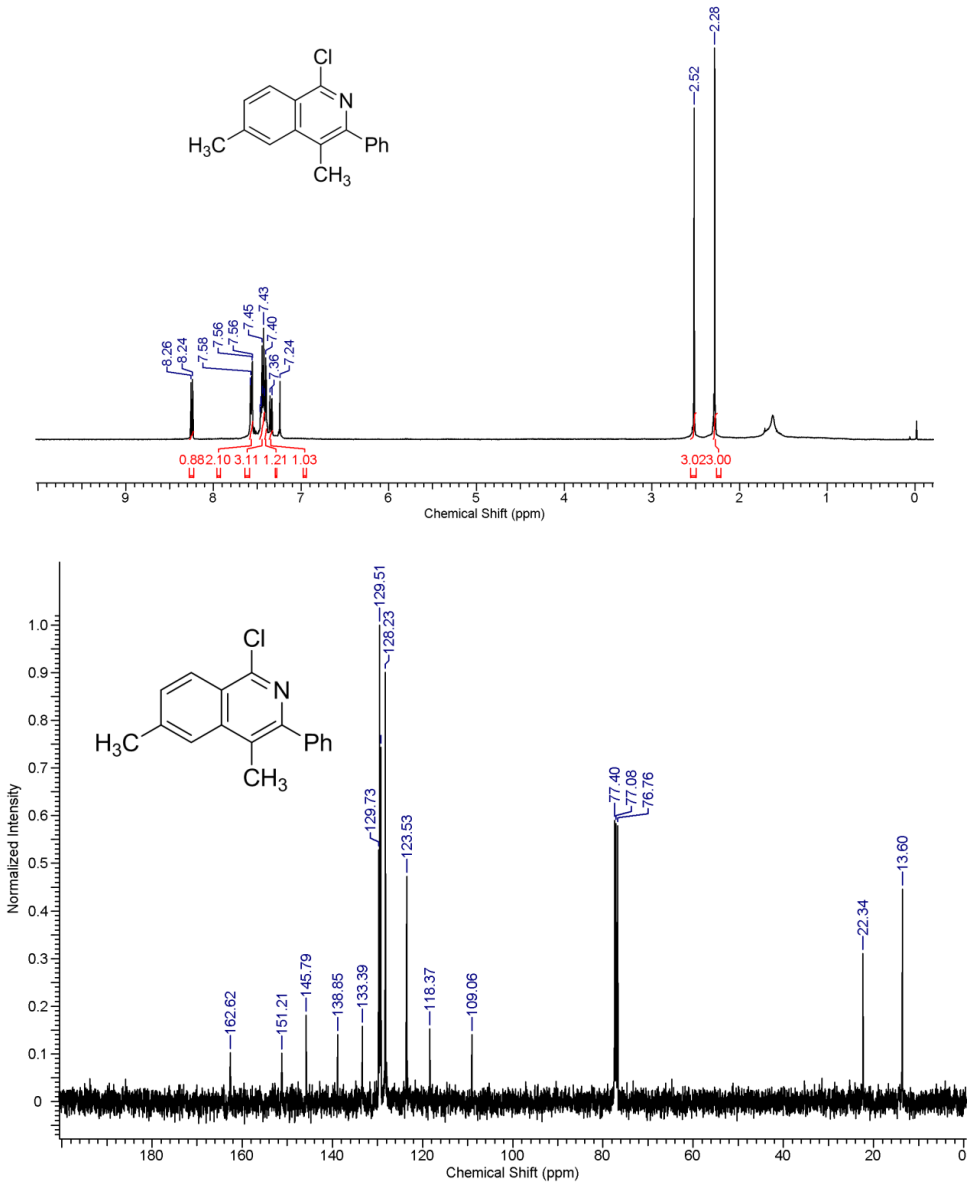


(*Z*)-2,2,2-Trifluoroethyl 3-chloro-*N*-methoxybenzimidate (8b): Pale Yellow semi solid; eluent (1% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (s, 1 H), 7.67 (d, *J* = 8.0, Hz, 1 H), 7.39 (d, *J* = 8.0, Hz, 1 H), 7.32 (t, *J* = 8.0, Hz, 1 H), 4.74 (q, *J* = 8.0, Hz, 2 H), 3.96 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.7, 134.6, 131.9, 130.5, 129.7, 126.6, 124.6, 124.5 – 121.7 (F coupling), 69.0 – 67.9 (q, due to fluorine coupling), 63.0. HRMS (ESI): calc. for [($C_{10}H_9ClF_3NO_2$)H] (M+H) 268.0352, measured 268.0350.

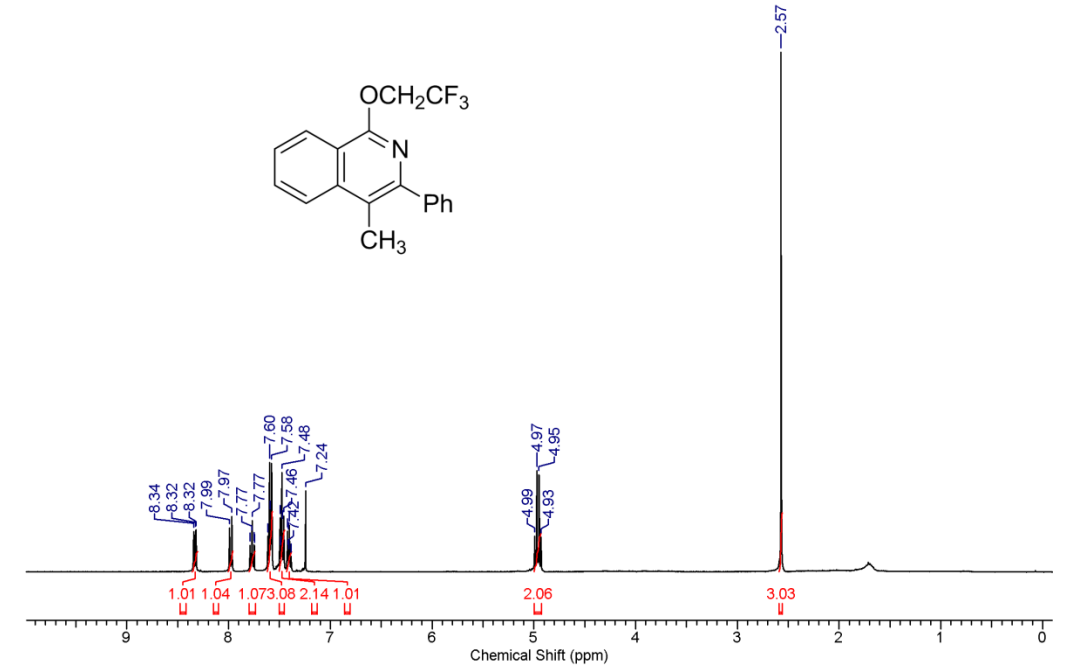


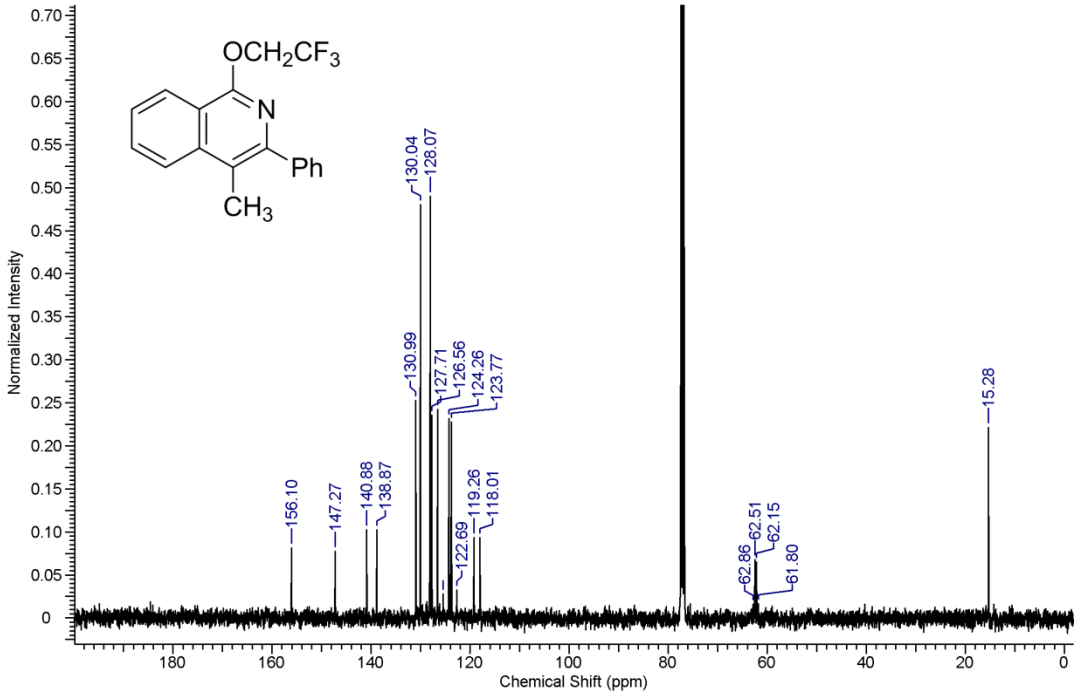
3B.5.7 Spectral Copies of Selected Compounds

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

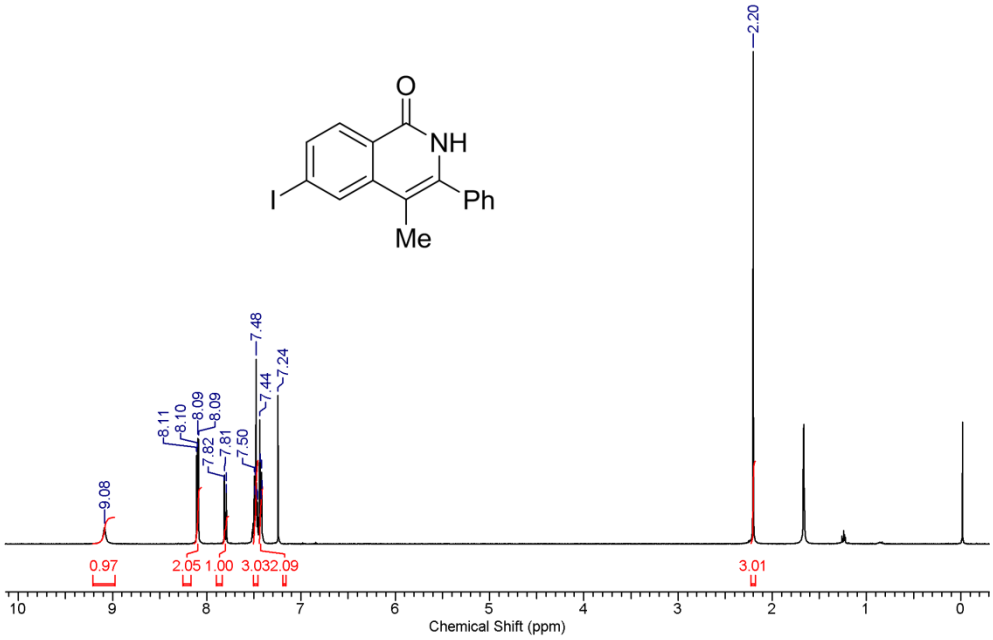


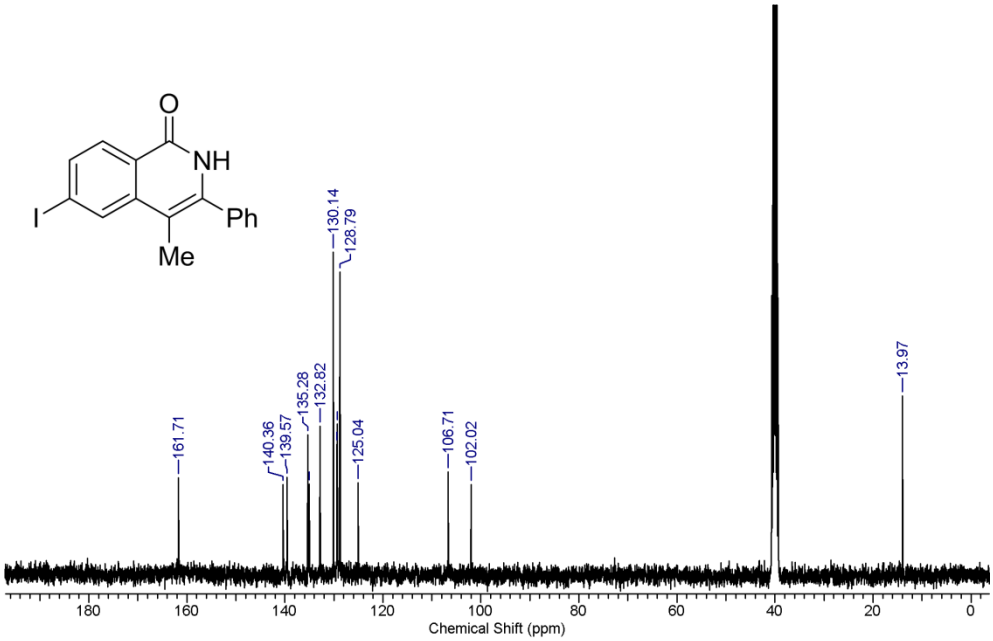
^{1}H and ^{13}C NMR Spectra of Compound **3e**



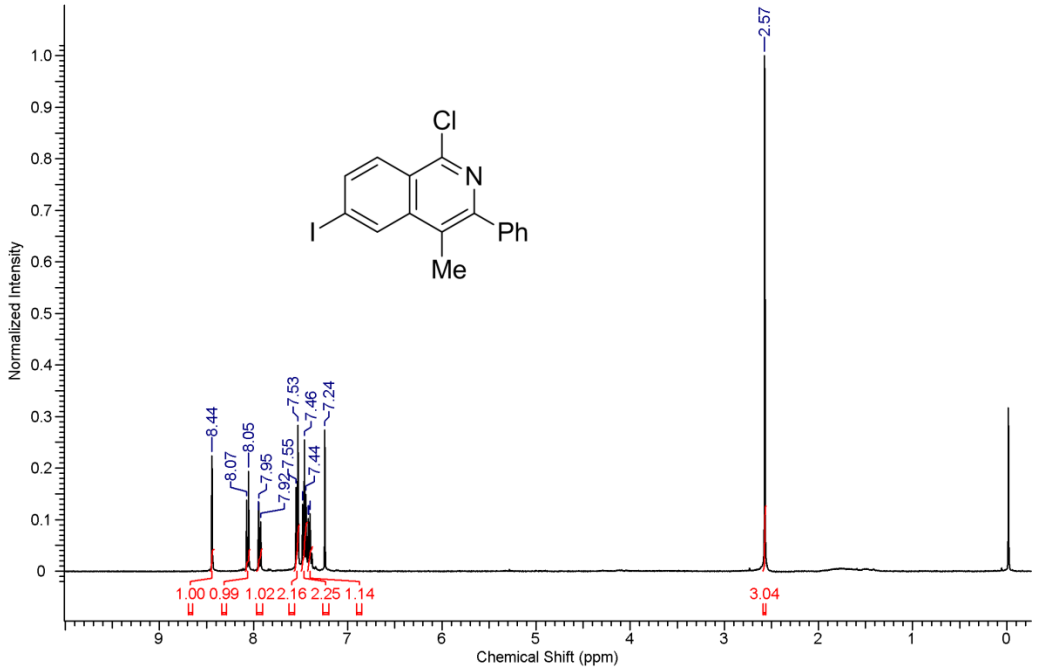


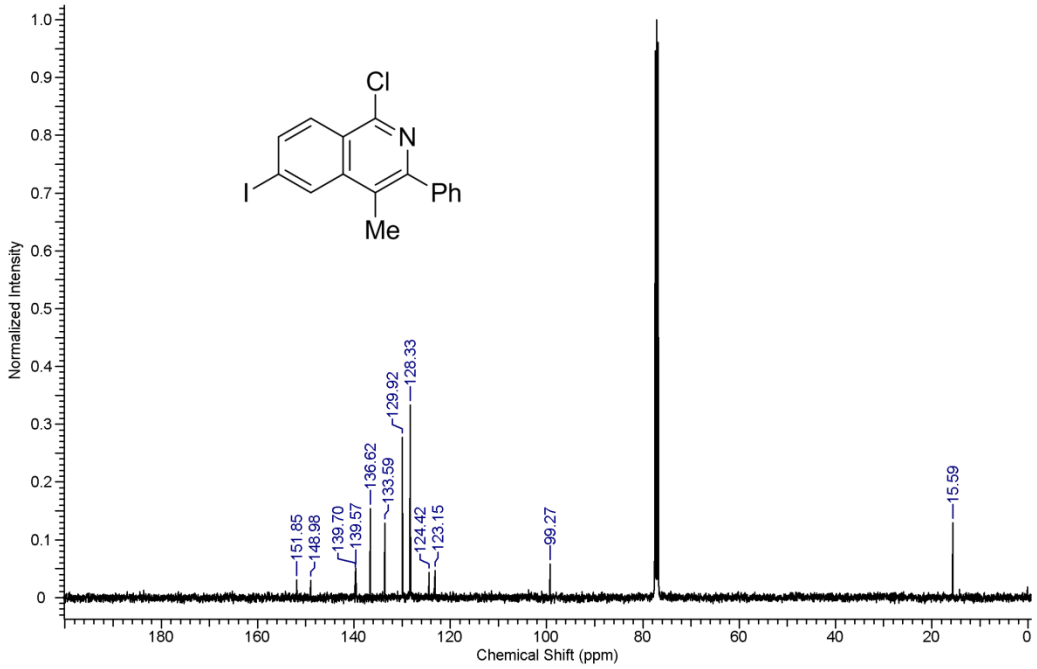
^{1}H and ^{13}C NMR Spectra of Compound **4a**





^{1}H and ^{13}C NMR Spectra of Compound **4e**





Section 3C: Ruthenium-Catalyzed Intramolecular Selective Halogenation of *O*-Methylbenzohydroximoyl halides: A New Route to Halogenated Aromatic nitriles

3C.1 Introduction

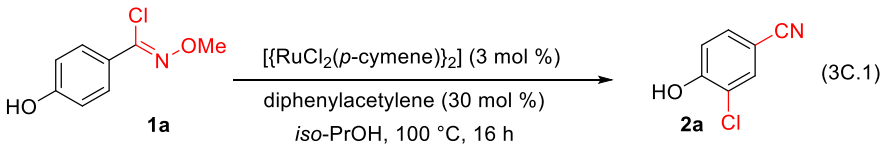
Aromatic halides are synthetically useful compounds that have been widely used as precursors in various organic transformations and for synthesizing various organometallic reagents, heterocyclic compounds, natural products, biologically active molecules and organic materials.[1] Traditionally, substituted aromatic halides are prepared by aromatic electrophilic substitution of electron-rich aromatics.[2] However, many of these reactions generally provide mixtures of regioisomeric *ortho* and *para* substituted aromatic halides. Alternatively, *ortho*-halo substituted aromatics are efficiently prepared by chelation-assisted metal-base mediated C-H bond activation of substituted aromatics followed by halogen quenching.[3] Recently, metal-catalyzed directing group assisted transformation of *ortho* aromatic C-H bonds to C-X bonds by utilizing NXS sources (X = Cl, Br and I) or XOAc or CuX_2 have been reported.[4] By using these methods, various *ortho*-bromo and iodo substituted aromatic compounds are conveniently prepared. However, still chlorobenzenes synthesis is a challenging task. In all reported reactions, halogenation of aromatics proceeded via intermolecular fashion.[5]

The *ortho* C-H bond activation of aromatics has been fairly studied in the literature.[4-5] But, the meta selective C-H bond activation of aromatics is much limited in the literature.[6] In this context, metal-catalyzed meta selective arylation and alkenylation of substituted aromatics have been reported by the groups of Gaunt, Yu and Sanford.[6*a-d*] In addition, Ru(II)-catalyzed meta selective sulfonation of 2-phenylpyridines has been demonstrated by Frost and co-workers in 2011.[6*e*]

3C.2 Results and Discussion

To date, no report is available in the literature for halogenation at the *meta* C-H bond of substituted aromatics. In the meantime, there is also no example available in the literature for halogenation of aromatics via intramolecular fashion. With this in mind, and also our continuous interest in the Ru(II)-catalyzed C-H activation reactions,[7,8] prompted us to explore the possibility of doing halogenation at the meta C-H bond of substituted aromatics via intramolecular fashion. Herein, we wish to account for the first time an unprecedented ruthenium-catalyzed

intramolecular halogenation at the *meta* and *ortho* carbon position of *O*-methylbenzohydroximoyl halides. It is noteworthy to say that the present halogenation reaction is conducted under the base and oxidant free conditions. It is also important to point out that substituted aromatic nitriles are key structural units in various natural products and also key intermediates for synthesising various pharmaceutically active molecules, agricultural molecules, dyes and organic materials.[9,10]



(3C.1)

The halogenation of 4-hydroxy-*N*-methoxybenzimidoyl chloride (**1a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %) and ligand diphenylacetylene (30 mol %) in *iso*-PrOH at 100 °C for 16 h gave 3-chloro-4-hydroxybenzonitrile (**2a**) in 83% isolated yield (eq. 3C.1). In the reaction, chlorination takes place very selectively at the *meta* carbon position of **1a** and the imidoyl moiety of **1a** is converted into the nitrile moiety.

3C.2.1 Optimization Studies

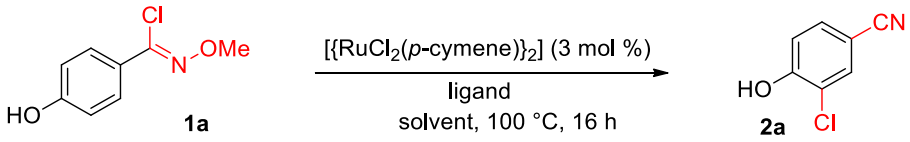


Table 3C.1 Ruthenium catalyzed selective halogenation of benzonitriles.[a]

Entry	Ligand	Solvent	Yield % (2a)[b]
1	No ligand	MeOH	nr
2	PPh_3 (20 mol %)	MeOH	nr
3	dppe (10 mol %)	MeOH	nr
4	L_1 (30 mol %)	MeOH	72
5	styrene (30 mol %)	MeOH	nr
6	L_2 (50 mol %)	MeOH	71
7	norbornadiene (50 mol %)	MeOH	nr

8	cyclooctadiene (50 mol %)	MeOH	nr
9	norbornene (50 mol %)	MeOH	nr
10	L_1 (30 mol %)	MeOH	nr
11	L_1 (30 mol %)	*iso*-PrOH	93
12	L_1 (30 mol %)	*tert*-BuOH	55
13	L_1 (30 mol %)	DMF	60
14	L_1 (30 mol %)	THF	nr
15	L_1 (30 mol %)	CH_3CN	nr
16	L_1 (30 mol %)	toluene	nr
17	L_1 (30 mol %)	DCE	nr
18	L_1 (30 mol %)	CH_3COOH	nr
19	L_1 (30 mol %)	1,4-dioxane	nr

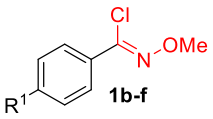
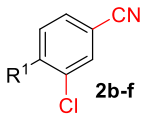
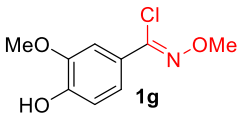
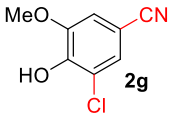
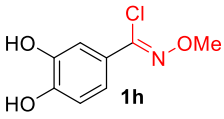
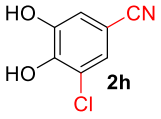
[a]All reactions were carried out using 1a (1.0 mmol), ligand and [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), L_1 = diphenylacetylene, L_2 = methyl acrylate, in solvent (3.0 mL) at 100 °C for 16 h. [b]Yields were determined by the ^{1}H NMR integration method, using mesitylene as an internal standard.

In the beginning of the project, the intramolecular chlorination of **1a** was examined in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %) in MeOH at 100 °C for 16 h. However, in the reaction, no chlorination product **2a** was observed (Table 3C.1, entry 1). Then, the catalytic reaction was tested in the presence of phosphine ligands PPh_3 and dppe and carbon-carbon π-component ligands such as diphenylacetylene, styrene, methyl acrylate, norbornene, norbornadiene and cyclooctadiene (entry 2-9). The corresponding chlorination product **2a** was observed in the presence of ligand, diphenylacetylene, in 72% yield (entry 4). The yield of product **2a** was determined by the ^{1}H NMR integration methods using mesitylene as an internal standard. Methyl acrylate (50 mol %) also worked equally, giving **2a** in 71% yield (entry 6). Other ligands were totally inactive for the reaction. Usually, less coordinating carbon-carbon π-component moieties are suitable ligands for C-H bond activation reaction. Importantly, diphenylacetylene or methyl acrylate was not involved in the reaction. In the crude reaction mixture, diphenylacetylene or methyl acrylate was found. This was isolated and confirmed by NMR spectroscopy. The reaction was tested without ruthenium catalyst and just only in the presence of ligand. In the reaction, no **2a** was observed. This result clearly revealed that both ruthenium and ligand such as diphenylacetylene or methyl acrylate are crucial for the reaction. In order to increase the yield of **2a**, the catalytic reaction was tested with various solvents such as

iso-PrOH, *tert*-BuOH, DMF, THF, CH_3CN, toluene, 1,2-dichloroethane, acetic acid and 1,4-dioxane (entries 11-19). Among them, *iso*-PrOH was the best solvent, providing **2a** in excellent 93% yield (entry 11). *tert*-BuOH and DMF were also partially active solvent, giving **2a** in 55% and 60% yields, respectively (entries 12 and 13). The remaining solvents were totally ineffective for the reaction.

3C.2.2 *meta*-Chlorination of Benzonitriles

Table 3C.2 Scope of the selective *meta*-chlorination reaction[a]

Entry	Imidoyl halide (1b-h)	Compound (2b-h)	Yeild[b]
			
1	**1b**: R^1 = OMe	**2b**: R^1 = OMe	85%
2	**1c**: R^1 = OEt	**2c**: R^1 = OEt	90%
3	**1d**: R^1 = O-*n*Pr	**2d**: R^1 = O-*n*Pr	92%
4	**1e**: R^1 = NMe_2	**2e**: R^1 = NMe_2	84%
5	**1f**: R^1 = NHMe	**2f**: R^1 = NHMe	91%[c]
6			85%
4			87%

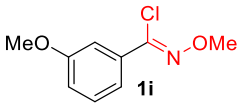
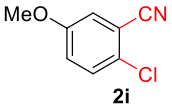
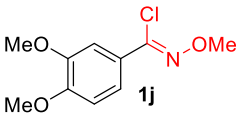
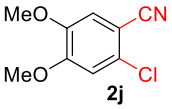
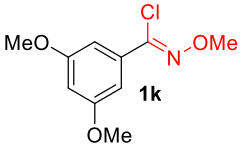
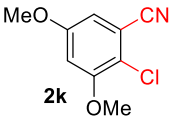
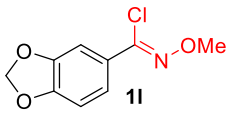
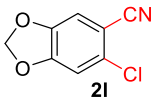
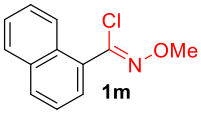
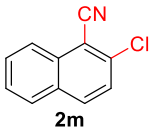
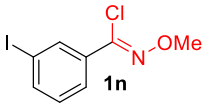
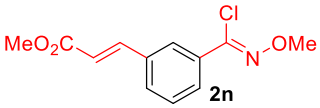
[a] All reactions were carried out using 1b-h (1.0 mmol), diphenylacetylene (30 mol %) and [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %) in *iso*-PrOH (3.0 mL) at 100 °C for 16 h. [b] Isolated yield. [c] The reaction was conducted in the presence of methyl acrylate (50 mol %).

Under similar reaction conditions, the catalytic reaction was examined with various substituted *O*-methylbenzohydroximoyl chlorides **1b-h** (Table 3C.2). Thus, 4-methoxy **1b**, 4-ethoxy **1c**, 4-*n*-propoxy **1d** substituted *N*-methoxybenzimidoyl chlorides underwent chlorination selectively at the *meta* carbon position yielding the corresponding *meta*-chlorobenzonitriles 2b-d in excellent 85%, 90% and 92% yields, respectively (entries 1-3). The structure of **2c** was confirmed by single crystal X-ray diffraction (see in experimantal section). 4-Dimethylamino **1e** and 4-

methylamino **1f** substituted *N*-methoxybenzimidoyl chlorides also proceeded smoothly under similar reaction conditions affording the corresponding *meta*-chlorobenzonitriles **2e** and **2f** in excellent 84% and 91% yields, respectively (entries 4 and 5). In these reactions also, chlorination takes place at the meta carbon position of **1e** and **1f** exclusively. Interestingly, 4-hydroxy-3-methoxy **1g** and 3,4-dihydroxy **1h** substituted *N*-methoxybenzimidoyl chlorides provided substituted *meta*-chlorobenzonitriles **2g** and **2h** in 85% and 87% yields, respectively, also in which chlorination takes place at the meta carbon position of **1g** and **1h** (entries 6 and 7).

3C.2.3 *ortho*-Chlorination of Benzonitriles

Table 3C.3 Scope of the selective *ortho*-chlorination reaction[a]

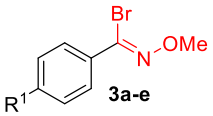
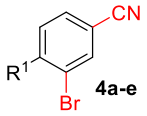
Entry	Imidoyl halide (1i-m)	Compound (2i-m)	Yeild[b]
1	 1i	 2i	93[c]
2	 1j	 2j	81
3	 1k	 2k	89[c]
4	 1l	 2l	85
5	 1m	 2m	81[c]
6	 1n	 2n	42[c]

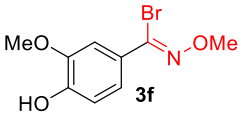
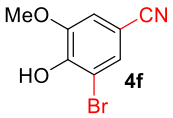
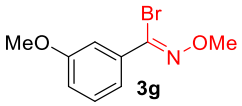
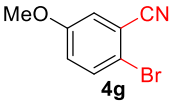
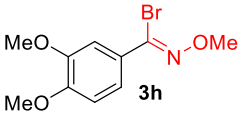
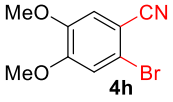
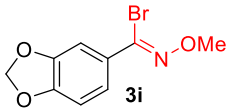
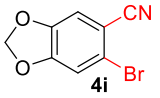
[a]All reactions were carried out using **1i-n** (1.0 mmol), diphenylacetylene (30 mol %) and [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %) in *iso*-PrOH (3.0 mL) at 100 °C for 16 h. [b]Isolated yield. [c]The reaction was conducted in the presence of methyl acrylate (50 mol %).

Next, the scope of the regioselectivity of the chlorination of substituted unsymmetrical *N*-methoxybenzimidoyl chlorides **1i-n** was examined under the optimized reaction conditions (Table 3). Initially, the reaction was tested with 3-methoxy substituted *N*-methoxybenzimidoyl chloride **1i**. In contrast to the previous reactions (Table 3C.2), surprisingly, in the reaction, chlorination takes place selectively at the less hindered *ortho* carbon position of **1i** providing 2-chloro-5-methoxybenzonitrile (**2i**) in 93% yield (Table 3C.3, entry 1). As like **1i**, 3,4-dimethoxy **1j** and 3,5-dimethoxy **1k** substituted *N*-methoxybenzimidoyl chlorides underwent chlorination at the less hindered *ortho* carbon position of **1j** and **1k** affording the corresponding substituted *ortho*-chlorobenzonitriles **2j** and **2k** in 81% and 89% yields, respectively (entries 2 and 3). Similarly, 1,3-dioxale group substituted *N*-methoxybenzimidoyl chloride **1l** yielded *ortho*-chloro piperonylonitrile **2l** in 85% yield (entry 4). The structure of **2l** was confirmed by single crystal X-ray diffraction (see experimantal section). Further, *N*-methoxy-1-naphthimidoyl chloride **1m** provided 2-chloro-1-naphthonitrile **2m** in 81% yield (entry 5). Next, the reaction was tested with 3-iodo substituted *N*-methoxybenzimidoyl chloride **1n**. In the reaction, the C-I bond of **1n** underwent a Heck-type alkenylation with methyl acrylate ligand giving an alkene derivative **2n** in 42% yield (entry 6).

3C.2.4 Selective Bromination of Benzonitriles

Table 3C.4 Scope of the selective bromination reaction.[a]

Entry	Imidoyl halide (3)	Compound (4)	Yeild[b]
	 **3a-e**	 **4a-e**	
1	**3a**: R^1 = OH	**4a**: R^1 = OH	93%
2	**3b**: R^1 = OMe	**4b**: R^1 = OMe	96%
3	**3c**: R^1 = OEt	**4c**: R^1 = OEt	96%
4	**3d**: R^1 = O-*n*Pr	**4d**: R^1 = O-*n*Pr	97%
5	**3e**: R^1 = NMe_2	**4e**: R^1 = NMe_2	84%

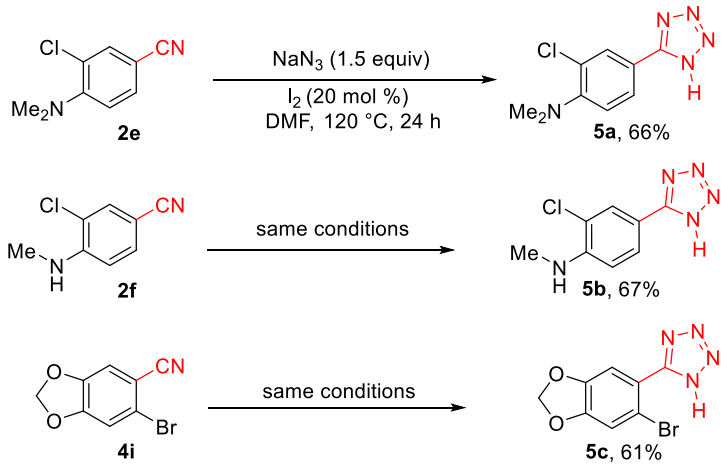
6			88
7			94[c]
8			83
9			85

[a]All reactions were carried out using 3a-i (1.0 mmol), diphenylacetylene (30 mol %) and [{RuCl2(p-cymene)}2] (3 mol %) in *iso*-PrOH (3.0 mL) at 100 °C for 16 h. [b]Isolated yield. [c]The reaction was conducted in the presence of methyl acrylate (50 mol %).

The current method can also be successfully extended to prepare various meta and ortho bromo substituted benzonitriles **4a-i** (Table 3C.4). The bromination at the *meta* carbon position of 4-hydroxy substituted *N*-methoxybenzimidoyl bromide **3a** proceeded smoothly under the optimized reaction conditions affording 3-bromo-4-hydroxybenzonitrile **4a** in 93% yield in a highly regioselective manner (entry 1). Similar to **3a**, 4-methoxy **3b**, 4-ethoxy **3c**, and 4-*n*-propoxy **3d** substituted *N*-methoxybenzimidoyl bromides gave the corresponding *meta*-bromo substituted benzonitriles **4b-d** in 96%, 96% and 97% yields, respectively (entries 2-4), in a highly regioselective manner. Similarly, 4-dimetylamino substituted *N*-methoxybenzimidoyl bromide **3e** provided the corresponding *meta*-bromo substituted benzonitrile **4e** in 84% yield (entry 5). Likewise, in the reaction of 4-hydroxy-3-methoxy substituted *N*-methoxybenzimidoyl bromide **3f**, bromination took place regioselectively at the meta carbon position yielding **4f** in 88% yield (entry 6). The structure of **4f** was confirmed by single crystal X-ray diffraction (see experimantal section). In contrast to **3a-f**, 3-methoxy, 3,4-dimethoxy and 1,3-dioxale substituted *N*-methoxybenzimidoyl bromides **3g-i** provided *ortho*-bromo substituted benzonitriles **4g-i** in 94%, 83% and 85% yields, respectively, in a highly regioselective manner (entries 7-9).

3C.2.5 Synthesis of Tetrazoles from Benzonitriles

To demonstrate the synthetic utility of CN group in organic synthesis, the [3+2] cycloaddition of aromatic nitriles with NaN_3 was carried out (Scheme 1)). The cycloaddition of aromatic nitrile 2e with NaN_3 (1.5 equiv) in the presence of catalytic amount of I_2 (20 mol %) in DMF at 120 °C for 24 h yielded the corresponding substituted tetrazole 5a in 66% yield. Similarly, aromatic nitriles 2f and 4i also underwent cycloaddition with NaN_3 under similar reaction conditions giving tetrazoles 5b and 5c in 67% and 61% yields, respectively (Scheme 3C.1).



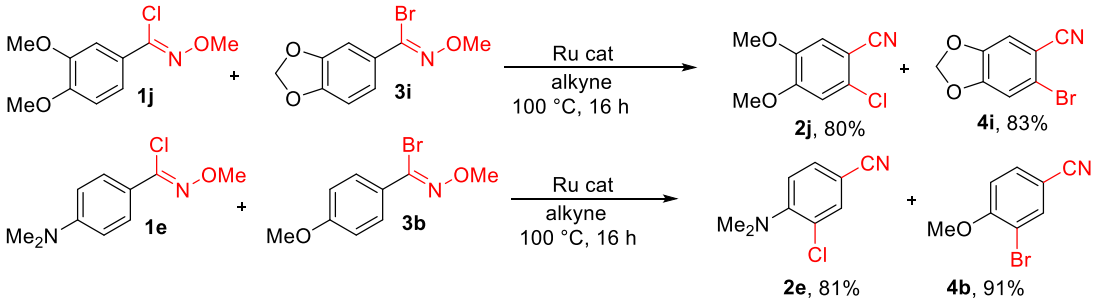
Scheme 3C.1 Synthesis of tetrazoles

At present, the exact mechanism for the halogenation of **1** or **3** is not very clear to us. Possibly, the imidoyl moiety of **1** or **3** is converted into cyano group[9b] followed by halogen transfer via electrophilic substitution at the aromatic carbon of **1** or **3** in the presence of ruthenium catalyst. The exact role of co-catalyst diphenylacetylene or methyl acrylate is unclear to us. It might be possible that this ligand coordinates with ruthenium metal and decreases the electron-density on the metal via π-back bonding. In fact the halogenation reaction was tested with various para and meta I, Br, Cl, F, CF_3 and NO_2 substituted *N*-methoxybenzimidoyl halides. However, in these reactions, no halogenation product was observed. This is probably due to electron-withdrawing nature of these substituents. In the meantime, no halogenation product was observed in the reaction of 4-methyl or 4-*tert*-butyl substituted *N*-methoxybenzimidoyl halides. These results clearly revealed that in the present halogenation reaction, electron mesomeric donating groups such as OH, OR, NHR and NR_2 are highly important compared to the electron inductive donating groups such as alkyls. In all reactions, halogenation takes place selectively at the *ortho*

and *meta* carbon of aromatics **1** and **3**. This is most likely due to the ortho and para directing nature of OH, OR, NHR and NR_2 groups in the electrophilic aromatic substitution reaction.

3C.2.6 Cross-Over Experiments

To see whether the halogenation reaction proceeds via inter or intramolecular manner, the following competitive reactions were done. The reaction of **1j** was conducted with **3i** under the optimized reaction conditions. In the reaction if cross products, **4h** and **2l** are observed in addition to the expected **2j** and **4i**, the reaction should be an intermolecular. However, in the reaction, as expected only compound **2j** and **4i** were observed exclusively in 80% and 83% yields, respectively, and no cross products were observed. Similarly, in the reaction of **1e** with **3b**, only compound **2e** and **4b** were observed exclusively in 81% and 91% yields, respectively, and no cross products **4e** and **2b** were observed. These results very clearly revealed that the present halogenation reaction proceeds via intramolecular fashion (Scheme 3C.2).



Scheme 3C.2 Cross-over experimants

3C.3 Conclusions

In conclusion, we have described a ruthenium-catalyzed intramolecular halogenation of *O*-methylbenzohydroximoyl halides. The catalytic reaction is highly regioselective, yielding substituted halo aromatic nitriles under base and oxidant free conditions.

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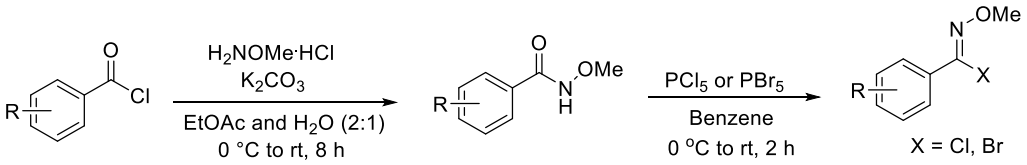
3C.5 Experimental Section

3C.5.1 General Procedure for the Preparation of Starting Materials 1 and 3



O-Methylhydroxylamine hydrochloride (2.0 g, 24.0 mmol, 1.2 equiv) and K_2CO_3 (5.98 g, 48.0 mmol, 2 equiv) were dissolved in 120 mL of mixture of ethyl acetate and water (2:1) in a round-bottomed flask. The solution was cooled to 0 °C in an ice bath. The corresponding benzoyl chloride (20.0 mmol, 1.0 equiv) was added via syringe and the reaction mixture was stirred at room temperature for 8 h. Then, the aqueous layer in the reaction mixture was separated out and organic layer was washed with water and then brine. After drying over $MgSO_4$, solvents were evaporated under reduced pressure. The crude reaction mixture was transferred into a round-bottom flask with a stir bar, and dry benzene (60 mL) was added. The solution was cooled to 5 °C and PCl_5 (6.25 g, 30.0 mmol, 1.5 equiv) or PBr_5 (6.50 g, 30.0 mmol, 1.5 equiv) was added. The reaction mixture was stirred at 5 °C for 2 h and then allowed to warm at room temperature for 30 min. The resulting mixture was extracted three times with hexane. The combined organic layers were dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure.

The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **1** or **3**.

Ref: 1. Y. Lian, R. G. Bergman and J. A. Ellman, *Chem. Sci*. **2012**, *3*, 3088.

3C.5.2 General Procedure for Intramolecular Halogenation of *O*-Methylbenzohydroximoyl Halides Catalyzed by Ruthenium Complex

A 15-mL pressure tube equipped with a magnetic stirrer and septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (0.03 mmol, 3 mol %) and diphenylacetylene (30 mol %) or methyl acrylate (50 mol %) was evacuated and purged with nitrogen gas three times. To the tube were then added *O*-methylbenzohydroximoyl halides **1** or **3** (1.00 mmol) and *iso*-propanol (3.0 mL) via syringes and again the tube was evacuated and purged with nitrogen gas three times. Then, in the pressure tube, septum was taken out and covered with a screw cap immediately under nitrogen atmosphere and the reaction mixture was allowed to stir at 100 °C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **2** and **4**.

3C.5.3 General Procedure for the Preparation of Substituted Tetrazoles

A 50-mL two-neck round bottom flask equipped with a magnetic stirrer, septum and condenser containing I_2 (20 mol %), NaN_3 (1.5 mmol) and aromatic nitriles **2** (1.0 mmol). To the round bottom flask was then added solvent DMF (3.0 mL) via syringe. Then, the reaction mixture was allowed to stir at 120 °C for 24 h. After cooling to ambient temperature, the reaction mixture was extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **5**.

3C.5.4 X-Ray Analysis

3-Chloro-4-ethoxybenzonitrile (2c)

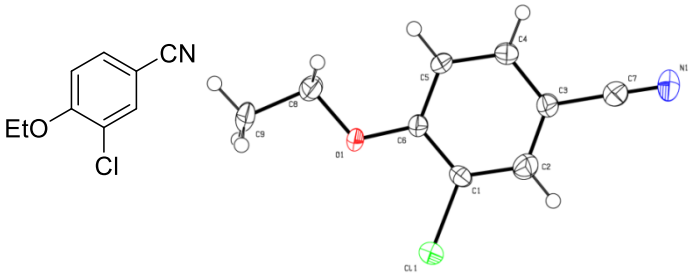


Table **3C.3** Crystal data and structure refinement for (**2c**)

Identification code	**2c**	
Empirical formula	$C_9 H_8 Cl N O$	
Formula weight	181.61	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	'Monoclinic'	
Space group	'C1c1'	
Unit cell dimensions	a = 8.511(5) Å	α = 90°.
	b = 17.062(10) Å	β = 123.831(10)°.
	c = 7.200(4) Å	ϒ = 90°.
Volume	868.6(9) A^3	
Z	4	
Density (calculated)	1.389 Mg/m^3	
Absorption coefficient	0.386 mm^{-1}	
F(000)	376	
Crystal size	0.16 x 0.12 x 0.08 mm3	
Theta range for data collection	2.39 to 28.29°.	

Index ranges	-11<=h<=11, -18<=k<=22, -9<=l<=9
Reflections collected	2102
Independent reflections	1251 [R(int) = 0.0411]
Completeness to theta = 25.00°	84.0 %
Max. and min. transmission	0.9698 and 0.9408
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	1251 / 2 / 110
Goodness-of-fit on F2	1.001
Final R indices [I>2sigma(I)]	R_1 = 0.0571, wR_2 = 0.1374
R indices (all data)	R_1 = 0.0838, wR_2 = 0.1513
Absolute structure parameter	0.02(17)
Largest diff. peak and hole	0.571 and -0.268 e.A^{-3}

6-Chlorobenzo[*d*][1,3]dioxole-5-carbonitrile (**2l**)

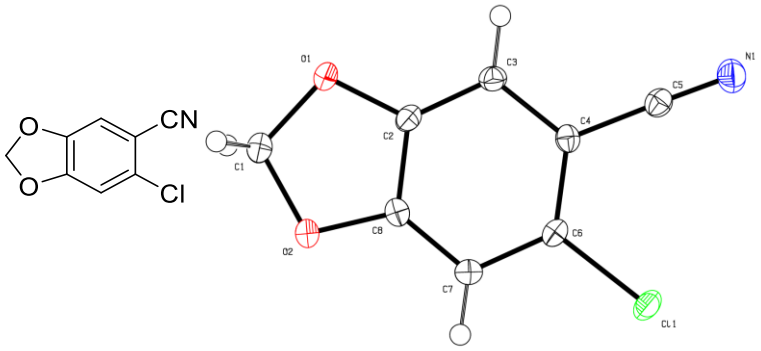


Table **3C.4** Crystal data and structure refinement for **2l**

Identification code	**2l**
Empirical formula	C8 H4 Cl N O2
Formula weight	181.57

Temperature	150(2) K
Wavelength	71.073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 1233.7(3) pm α = 90°.
	b = 380.23(10) pm β = 99.168(4)°.
	c = 1560.3(4) pm ϒ = 90°.
Volume	0.7226(3) nm^3
Z	4
Density (calculated)	1.669 Mg/m^3
Absorption coefficient	0.474 mm^{-1}
F(000)	368
Crystal size	0.490 x 0.320 x 0.160 mm^3
Theta range for data collection	1.96 to 28.41°.
Index ranges	-15<=h<=16, -4<=k<=5, -20<=l<=20
Reflections collected	7021
Independent reflections	1788 [R(int) = 0.0263]
Completeness to theta = 28.41°	98.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.927 and 0.834
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	1788 / 0 / 110
Goodness-of-fit on F2	1.075

Final R indices [I>2sigma(I)]	R_1 = 0.0262, wR_2 = 0.0719
R indices (all data)	R_1 = 0.0275, wR_2 = 0.0729
Extinction coefficient	0.006(3)
Largest diff. peak and hole	0.352 and -0.227 e.A^{-3}

3-Bromo-4-hydroxy-5-methoxybenzonitrile (**4f**)

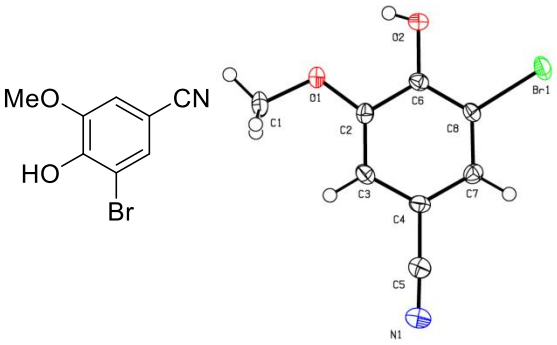


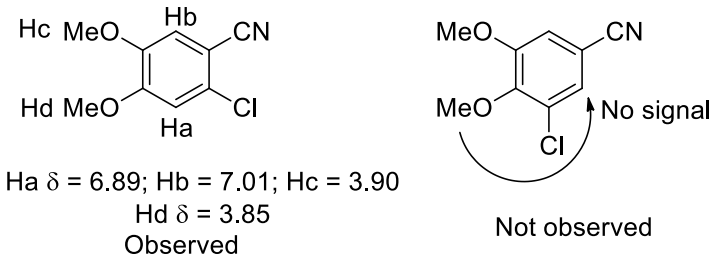
Table 3C.5 Crystal data and structure refinement for (**4f**)

Identification code	4f
Empirical formula	C_{16} H_{12} Br_2 N_2 O_4
Formula weight	456.10
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	'Triclinic'
Space group	'P-1'
Unit cell dimensions	a = 7.2030(10) Å α = 85.645(3)°.

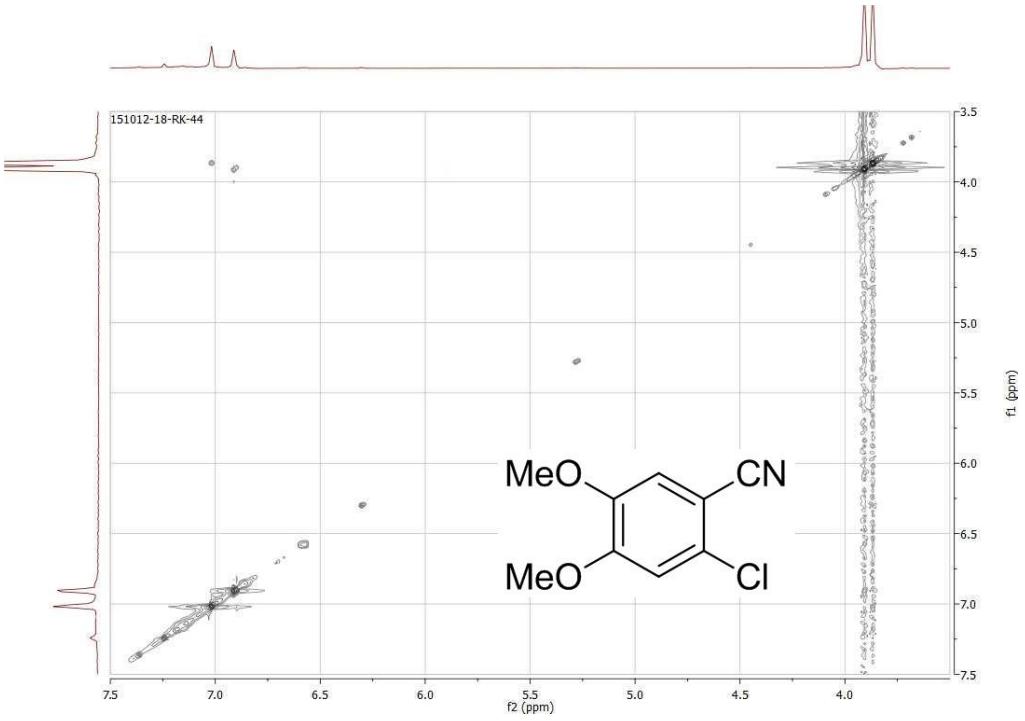
	b = 9.5004(12) Å β = 89.563(3)°.
	c = 12.9717(16) Å ϒ = 70.248(3)°.
Volume	832.88(19) A^3
Z	2
Density (calculated)	1.819 Mg/m^3
Absorption coefficient	4.889 mm^{-1}
F(000)	448
Crystal size	0.16 x 0.13 x 0.11 mm^3
Theta range for data collection	1.57 to 28.53°.
Index ranges	-9<=h<=6, -12<=k<=12, -17<=l<=17
Reflections collected	13496
Independent reflections	4127 [R(int) = 0.0244]
Completeness to theta = 28.53°	97.4 %
Max. and min. transmission	0.6153 and 0.5084
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	4127 / 0 / 225
Goodness-of-fit on F2	1.043
Final R indices [I>2sigma(I)]	R_1 = 0.0255, wR_2 = 0.0592
R indices (all data)	R_1 = 0.0325, wR_2 = 0.0613
Largest diff. peak and hole	1.059 and -0.417 $e.A^{-3}$

3C.5.5 Regioselective Studies: NOESY Studies

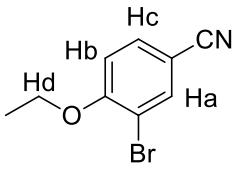
Copy of NOESY Experiment of Compound 2j



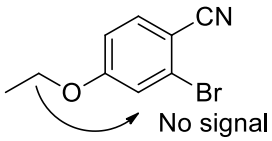
There is a NOE correlation between Ha (δ 6.89, s) and Hd (δ 3.85, s). In meantime, there is also a correlation between Hb (δ 7.01, s) and Hc (δ 3.90, s). These results clearly revealed that the regiochemistry of compound **2j** is correct.



Copy of NOESY experiment of compound 4c

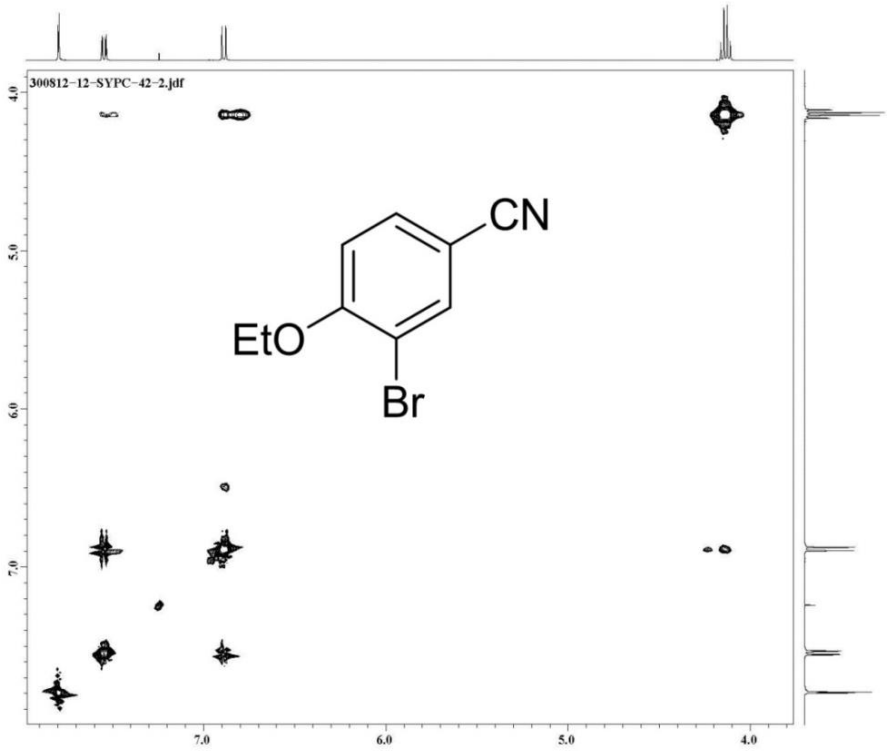


Ha δ = 7.79; Hb = 6.89; Hc = 7.54
Hd δ = 4.14
Observed

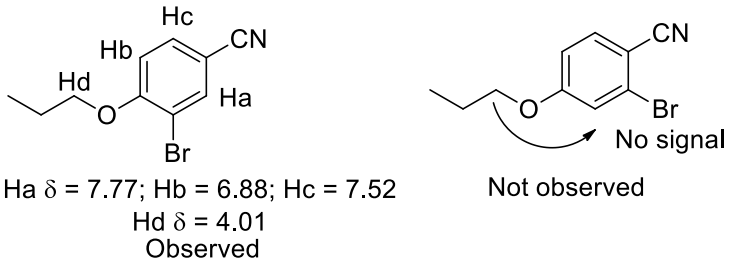


Not observed

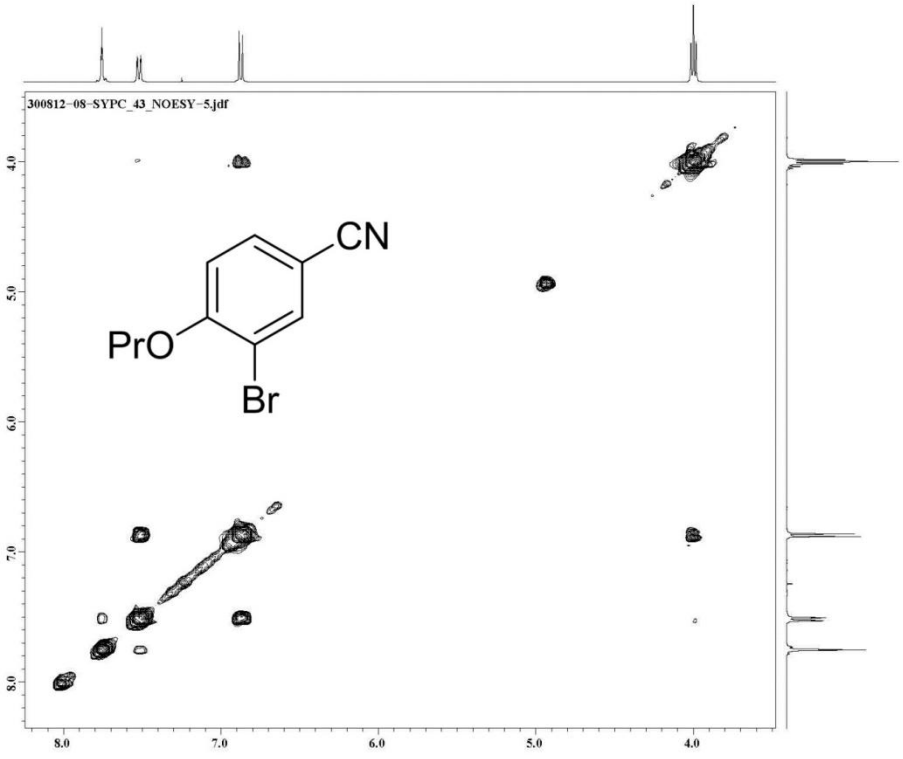
There is a NOE correlation between Hb (δ 6.89, d) and Hd (δ 4.14, q). In meantime, there is also a very weak NOE correlation between Hc (δ 7.54, dd) and Hd (δ 4.14, d). However, there is no correlation between Ha (δ 7.79, s) and Hd (δ 4.14, q). These results clearly revealed that the regiochemistry of compound **4c** is correct.



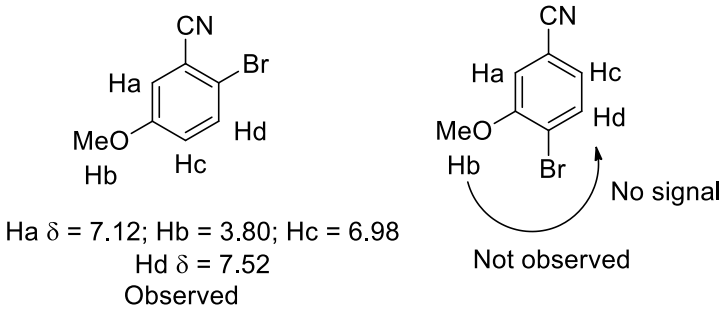
Copy of NOESY Experiment of Compound 4d



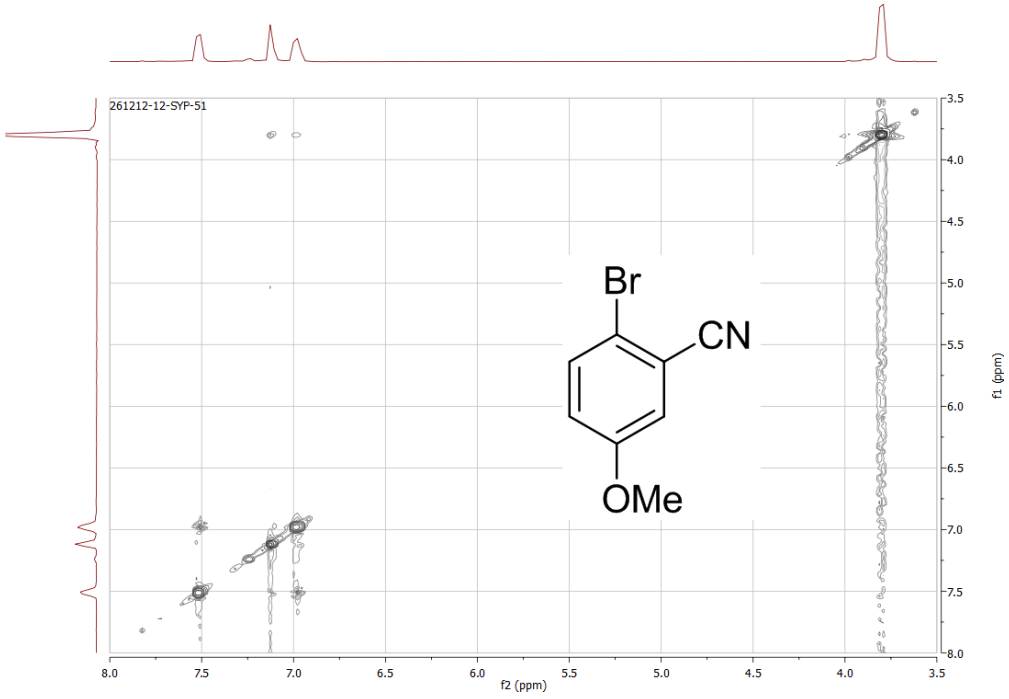
There is a NOE correlation between Hb (δ 6.88, d) and Hd (δ 4.01, q). In meantime, there is also a very weak NOE correlation between Hc (δ 7.52, dd) and Hd (δ 4.01, d). However, there is no correlation between Ha (δ 7.77, s) and Hd (δ 4.01, q). These results clearly revealed that the regiochemistry of compound **4d** is correct.



Copy of NOESY Experiment of Compound 4g

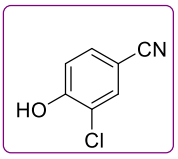


There is a NOE correlation between Ha (δ 7.12, s) and Hb (δ 3.80, s). In meantime, there is also a correlation between Hc (δ 6.98, dd) and Hb (δ 3.80, s). These results clearly revealed that the regiochemistry of compound **4g** is correct. If there is a no correlation between Hc (δ 6.98, dd) and Hb (δ 3.80, s), then the other regiochemistry is possible. But, there is a signal.

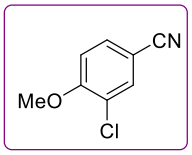


3C.5.6 Spectral Data of all Compounds

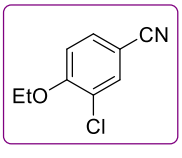
3-Chloro-4-hydroxybenzonitrile (2a): Colorless solid; m.p. 155-157 °C, eluent (10% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3419, 2234, 1593, 1411, 1305, 1123 and 1044. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (s, 1 H), 7.46 (dd, *J* = 8.0, 4.0, Hz, 1 H), 7.06 (d, *J* = 8.0 Hz, 1 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 155.8, 133.3, 132.7, 121.0, 117.9, 117.3, 104.7. **HRMS** (ESI): calc. for [(C_7H_4ClNO)H] (M+H) 154.0060, measured 154.0063.



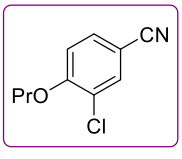
3-Chloro-4-methoxybenzonitrile (**2b**): Colorless solid; m.p. 182-184 °C, eluent (5% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2923, 2228, 1595, 1500, 1270, 1192 and 1064. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.62 (s, 1 H), 7.53 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.96 (d, *J* = 8.0 Hz, 1 H), 3.94 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 158.6, 133.6, 132.5, 123.6, 117.9, 112.2, 104.7, 56.5. **HRMS** (ESI): calc. for [(C_8H_6ClNO)H] (M+H) 168.0217 measured 168.0217.



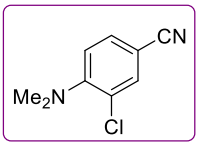
3-Chloro-4-ethoxybenzonitrile (**2c**): Colorless solid; m.p. 133-135 °C, eluent (5% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2229, 1591, 1477, 1298, 1262, 1167, 1125 and 1033. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (s, 1 H), 7.50 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.93 (d, *J* = 8.0 Hz, 1 H), 4.14 (q, *J* = 8.0 Hz, 2 H), 1.48 (t, *J* = 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.1, 133.6, 132.4, 123.7, 118.1, 112.9, 104.4, 65.2, 14.5. **HRMS** (ESI): calc. for [(C_9H_8ClNO)H] (M+H) 182.0373, measured 182.0371.



3-Chloro-4-propoxybenzonitrile (**2d**): Brown liquid; eluent (5% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2968, 2228, 1690, 1594, 1463, 1394, 1270 and 1061. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (s, 1 H), 7.50 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 4.02 (t, *J* = 4.0 Hz, 2 H), 1.89 – 1.84 (m, 2 H), 1.06 (t, *J* = 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 133.6, 132.4, 123.8, 118.1, 113.0, 104.3, 70.9, 22.3, 10.4. HRMS (ESI): calc. for [($C_{10}H_{10}ClNO$)H] (M+H) 196.0529, measured 196.0526.

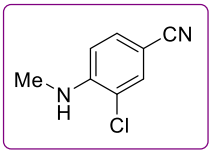


3-Chloro-4-(dimethylamino)benzonitrile (**2e**): Brown liquid; eluent (5% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2968, 2228, 1690, 1594, 1463, 1270, 1195 and 1061. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (s, 1 H), 7.42 (dd, *J* = 8.0, 4.0 Hz 1 H), 6.96 (d, *J* = 8.0 Hz 1 H), 2.89 (s, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.1,

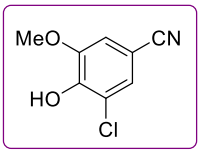


134.4, 131.5, 126.4, 119.4, 118.4, 104.4, 42.9. HRMS (ESI): calc. for $[(C_9H_9ClN_2)H]$ (M+H) 181.0533 measured 181.0532.

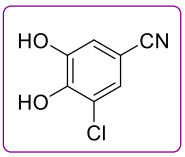
3-Chloro-4-(methylamino)benzonitrile (**2f**): Colorless solid; m.p. 201-203 °C, eluent (20% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3325, 2361, 1517, 1235 and 1037. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.46 (s, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 6.58 (d, *J* = 8.0 Hz, 1 H), 4.91 (bs, 1 H), 2.93 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 148.9, 132.5, 132.3, 119.3, 118.5, 109.9, 98.7, 30.0. **HRMS** (ESI): calc. for $[(C_8H_7ClN_2)H]$ (M+H) 167.0376, measured 167.0371.



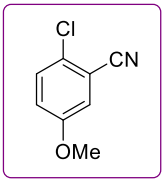
3-Chloro-4-hydroxy-5-methoxybenzonitrile (**2g**): Colorless solid; m.p. 182-184 °C, eluent (10% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3427, 2215, 1588, 1500, 1415, 1363, 1293, 1124 and 1044. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.29 (s, 1 H), 7.00 (s, 1 H), 3.93 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 147.5, 146.5, 126.9, 120.4, 118.1, 112.4, 103.6, 56.8. **HRMS** (ESI): calc. for $[(C_8H_6ClNO_2)H]$ (M+H) 184.0165, measured 184.0164.



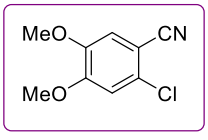
3-Chloro-4,5-dihydroxybenzonitrile (**2h**): Colorless solid; eluent (20% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3433, 2234, 1593, 1411, 1305, 1123 and 1044. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.43 (s, 1 H), 7.03 (s, 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 148.8, 146.9, 127.9, 118.7, 117.6, 110.2, 102.4. HRMS (ESI): calc. for $[(C_7H_4ClNO_2)H]$ (M+H) 170.0009, measured 170.0005.



2-Chloro-5-methoxybenzonitrile (**2i**): Colorless solid; eluent (5% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2365, 1599, 1265, and 1121. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 (d, *J* = 8.0 Hz, 1 H), 7.12 (s, 1 H), 7.05 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.1, 130.9, 120.7, 118.2, 116.0, 115.8, 113.7, 55.9. HRMS (ESI): calc. for $[(C_8H_6ClNO)H]$ (M+H) 168.0216, measured 168.0212.

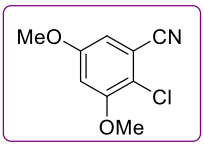


2-Chloro-4,5-dimethoxybenzonitrile (**2j**): Colorless solid; m.p. 193-195 °C, eluent (7% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2229, 1595, 1459, 1382, 1274, 1220, 1121 and 1042. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.01 (s, 1 H), 6.89 (s, 1 H), 3.90 (s, 3 H), 3.85 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.3, 148.0, 130.2,

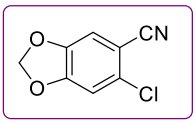


116.5, 114.6, 112.6, 104.2, 56.5, 56.4. **HRMS** (ESI): calc. for [($C_9H_8ClNO_2$)H] (M+H) 198.0322, measured 198.0319.

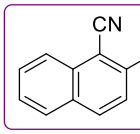
2-Chloro-3,5-dimethoxybenzonitrile (**2k**): Colorless solid; eluent (7% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2230, 1589, 1387, 1225 and 1123. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.71 (s, 1 H), 6.67 (s, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 156.4, 117.8, 116.1, 114.2, 108.3, 104.6, 56.5, 56.0. HRMS (ESI): calc. for [($C_9H_8ClNO_2$)H] (M+H) 198.0322, measured 198.0320.



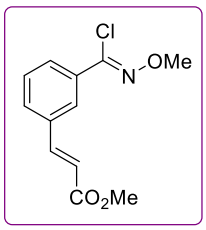
6-Chlorobenzo[*d*][1,3]dioxole-5-carbonitrile (**2l**): Yellow solid; eluent (7% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2235, 1590, 1472, 1414, 1261, 1121 and 1036. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.99 (s, 1 H), 6.90 (s, 1 H), 6.08 (s, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.3, 146.9, 131.8, 116.2, 111.9, 110.6, 105.3, 103.2. HRMS (ESI): calc. for [($C_8H_4ClNO_2$)H] (M+H) 182.0009, measured 182.0009.



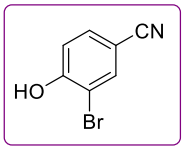
2-Chloro-1-naphthonitrile (**2m**): Colorless solid; m.p. 208-210 °C, eluent (5% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2355, 1597, 1479, 1135 and 1051. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (d, *J* = 8.0 Hz, 1 H), 8.23 (d, *J* = 8.0 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.77 – 7.69 (m, 2 H), 7.60 (d, *J* = 8.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.0, 133.3, 132.2, 130.6, 129.5, 128.7, 125.7, 125.6, 125.3, 117.3, 109.4. HRMS (ESI): calc. for [($C_{11}H_6ClN$)H] (M+H) 188.0267, measured 188.0265.



(*E*)-Methyl 3-(3-((Z)-chloro(methoxyimino)methyl)phenyl)acrylate (2n): Pale yellow semisolid; eluent (15% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.01 (s, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.72 (d, *J* = 16.0 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 6.51 (d, *J* = 16.0 Hz, 1 H), 4.13 (s, 3 H), 3.82 (s, 3 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.2, 143.9, 136.5, 134.8, 133.5, 129.8, 129.1, 128.7, 126.6, 119.0, 63.4, 51.8. HRMS (ESI): calc. for [($C_{12}H_{12}ClNO_3$)H] (M+H) 254.0584, measured 254.0579.

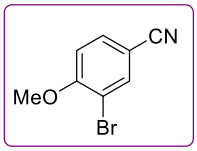


3-Bromo-4-hydroxybenzonitrile (**4a**): Brown solid; eluent (10% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3431, 2237, 1600, 1507, 1410, 1303, 1222 and 1046. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (s, 1 H), 7.48 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.04 (d, *J* = 8.0

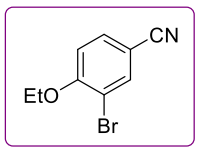


Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.7, 136.3, 133.3, 117.7, 116.9, 110.6, 105.0. HRMS (ESI): calc. for [(C_7H_4BrNO)H] (M+H) 197.9555, measured 197.9559.

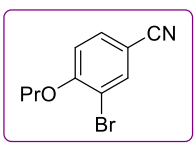
3-Bromo-4-methoxybenzonitrile (**4b**): Colorless solid; eluent (5% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2235, 1589, 1488, 1294, 1190, 1121 and 1046. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (s, 1 H), 7.58 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 3.94 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 136.7, 133.2, 117.8, 112.3, 111.9, 105.2, 56.6. HRMS (ESI): calc. for [(C_8H_6BrNO)H] (M+H) 211.9711, measured 211.9713.



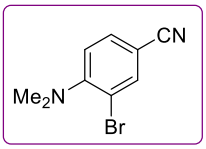
3-Bromo-4-ethoxybenzonitrile (**4c**): Colorless solid; eluent (5% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2224, 1594, 1471, 1295, 1266, 1161, 1120 and 1036. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (s, 1 H), 7.54 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 4.14 (d, *J* = 8.0 Hz, 2 H), 1.48 (t, *J* = 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.0, 136.7, 133.1, 117.9, 112.7, 112.6, 104.9, 65.3, 14.5. HRMS (ESI): calc. for [(C_9H_8BrNO)H] (M+H) 225.9868, measured 225.9863.



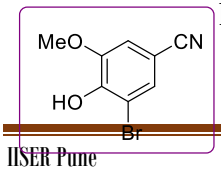
3-Bromo-4-propoxybenzonitrile (**4d**): Brown liquid; eluent (5% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2971, 2227, 1593, 1491, 1267, 1191 and 1051. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (s, 1 H), 7.52 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 4.01 (t, *J* = 8.0 Hz, 2 H), 1.88 – 1.83 (m, 2 H), 1.05 (t, *J* = 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 136.6, 133.1, 117.9, 112.7, 112.6, 104.8, 71.0, 22.3, 10.5. HRMS (ESI): calc. for [($C_{10}H_{10}BrNO$)H] (M+H) 240.0024, measured 240.0020.



3-Bromo-4-(dimethylamino)benzonitrile (**4e**): Brown liquid; eluent (5% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2223, 1593, 1445, 1339, 1133 and 1045. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (s, 1 H), 7.48 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 2.88 (s, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.7, 137.7, 132.1, 119.8, 118.2, 116.5, 105.3, 43.4. HRMS (ESI): calc. for [($C_9H_9BrN_2$)H] (M+H) 225.0027, measured 225.0028.

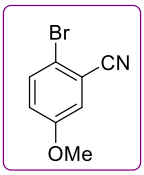


3-Bromo-4-hydroxy-5-methoxybenzonitrile (**4f**): Colorless solid; eluent (10% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3454, 2223, 1587, 1492, 1285, 1175, 1126 and

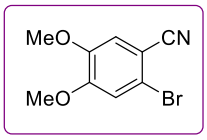


1040. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (s, 1 H), 7.03 (s, 1 H), 3.92 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.6, 147.2, 129.7, 117.9, 112.9, 108.6, 104.2, 56.8. HRMS (ESI): calc. for [($C_8H_6BrNO_2$)H] (M+H) 227.9660, measured 227.9664.

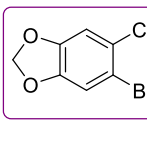
2-Bromo-5-methoxybenzonitrile(4g): Colorless solid; eluent (5% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2237, 1587, 1425, 1141 and 1045. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (d, *J* = 8.0 Hz, 1 H), 7.12 (s, 1 H), 6.98 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.7, 134.0, 120.9, 118.9, 117.1, 116.2, 115.6, 55.9. HRMS (ESI): calc. for [(C_8H_6BrNO)H] (M+H) 211.9711, measured 211.9710.



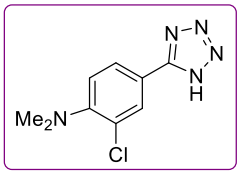
2-Bromo-4,5-dimethoxybenzonitrile (**4h**): Colorless solid; eluent (7% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2925, 2227, 1980, 1590, 1419, 1349, 12367, 1122 and 1036. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.04 (s, 1 H), 7.02 (s, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.2, 148.5, 117.7, 117.6, 115.5, 115.3, 106.9, 56.5, 56.4. HRMS (ESI): calc. for [($C_9H_8BrNO_2$)H] (M+H) 241.9817, measured 241.9812.



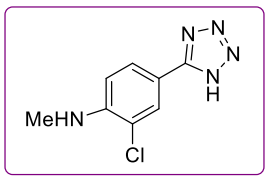
6-Bromobenzo[*d*][1,3]dioxole-5-carbonitrile (**4i**): Yellow solid; eluent (7% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 2360, 1591, 1470, 1259, 1119 and 1031. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.05 (s, 1 H), 6.99 (s, 1 H), 6.08 (s, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.3, 147.5, 119.0, 117.4, 113.4, 112.6, 107.9, 103.1. HRMS (ESI): calc. for [($C_8H_4BrNO_2$)H] (M+H) 225.9504, measured 225.9500.



2-Chloro-*N*,*N*-dimethyl-4-(1*H*-tetrazol-5-yl)aniline (5a):[3] Yellow solid; m.p. 225-227 °C, eluent (20% ethyl acetate in hexanes). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.56 (s, 1 H), 7.49 (dd, *J* = 10.0, 5.0 Hz, 1 H), 6.67 (d, *J* = 10.0 Hz, 1 H), 4.98 (bs, 1 H), 3.02 (s, 3 H), 3.01 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 148.1, 132.5, 132.3, 119.3, 118.5, 109.9, 98.7, 30.0. **HRMS** (ESI): calc. for [($C_9H_{10}ClN_5$)H] (M+H) 224.0703, measured 224.0710.

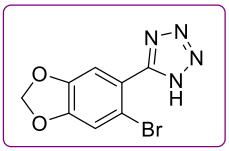


2-Chloro-*N*-methyl-4-(1*H*-tetrazol-5-yl)aniline (5b):[3] Pale yellow solid; m.p. 199-201 °C, eluent (45% ethyl acetate in hexanes). **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 7.52 (s, 1 H), 7.32 (t, *J* = 8.0 Hz, 1 H), 6.72 (d, *J* = 8.0 Hz, 1 H), 4.62 (bs, 2 H),



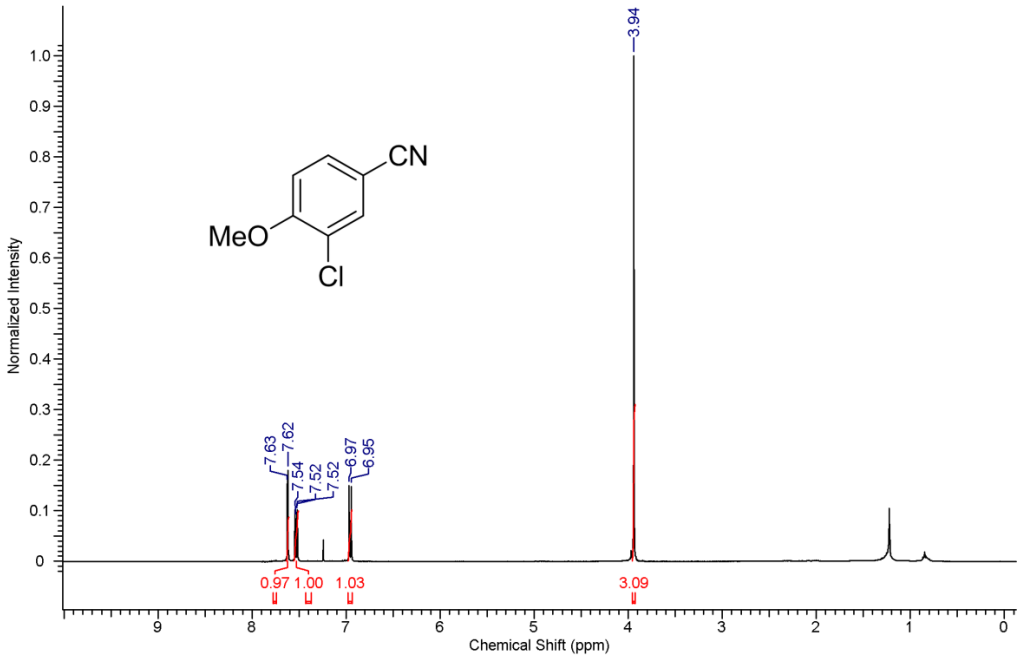
2.94 (d, *J* = 16.0 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 147.1, 133.2, 131.9, 118.9, 118.4, 115.1, 100.7, 36.7. **HRMS** (ESI): calc. for [($C_8H_8ClN_5$)H] (M+H) 210.0546, measured 210.0556.

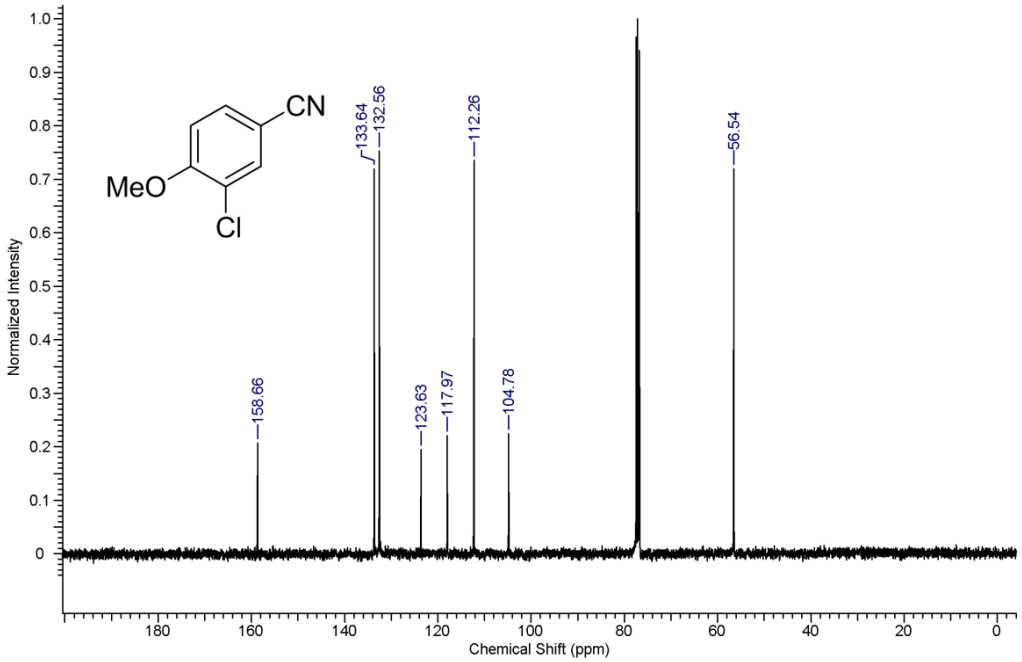
5-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-1*H*-tetrazole (5c): Colorless solid; eluent (25% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (s, 1 H), 7.23 (s, 1 H), 6.36 (bs, 1H), 5.23 (s, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.9, 143.0, 120.4, 120.1, 119.1, 117.2, 106.7, 81.0. HRMS (ESI): calc. for [($C_8H_5BrN_4O_2$)H] (M+H) 268.9674, measured 268.9670



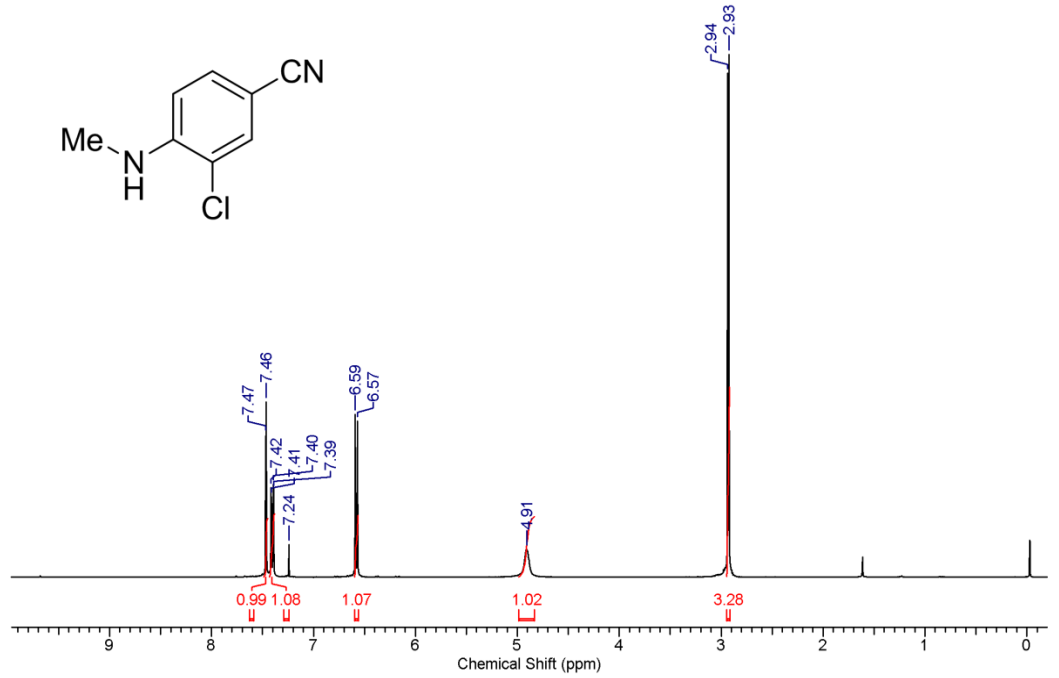
3C.5.7 Spectral Copies of Selected Compounds

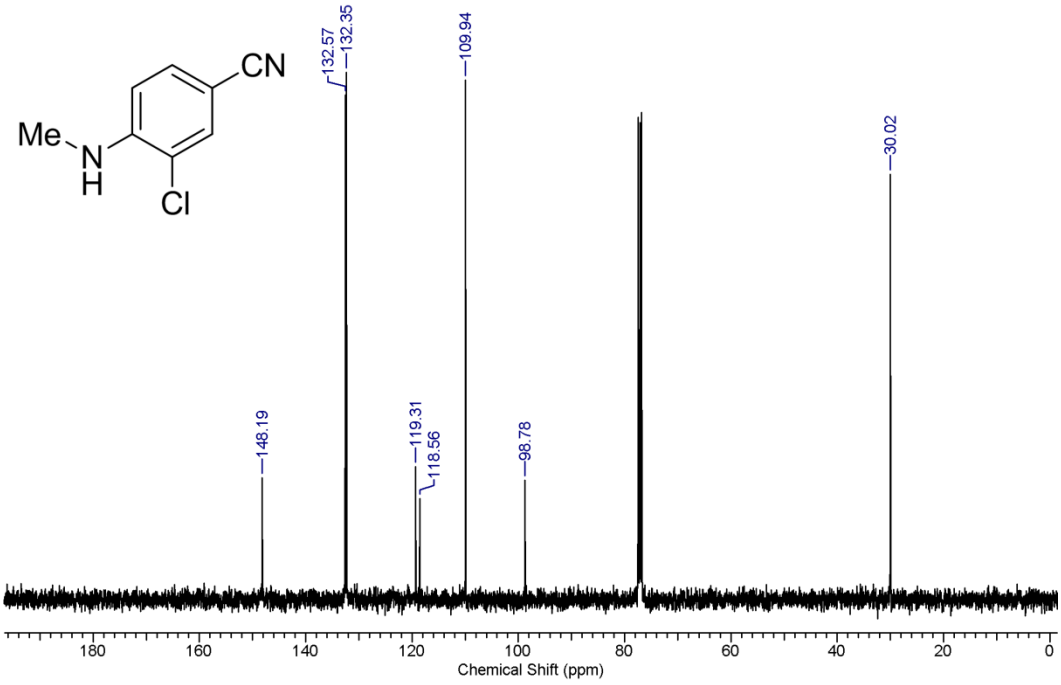
^{1}H and ^{13}C NMR Spectra of Compound **2b**



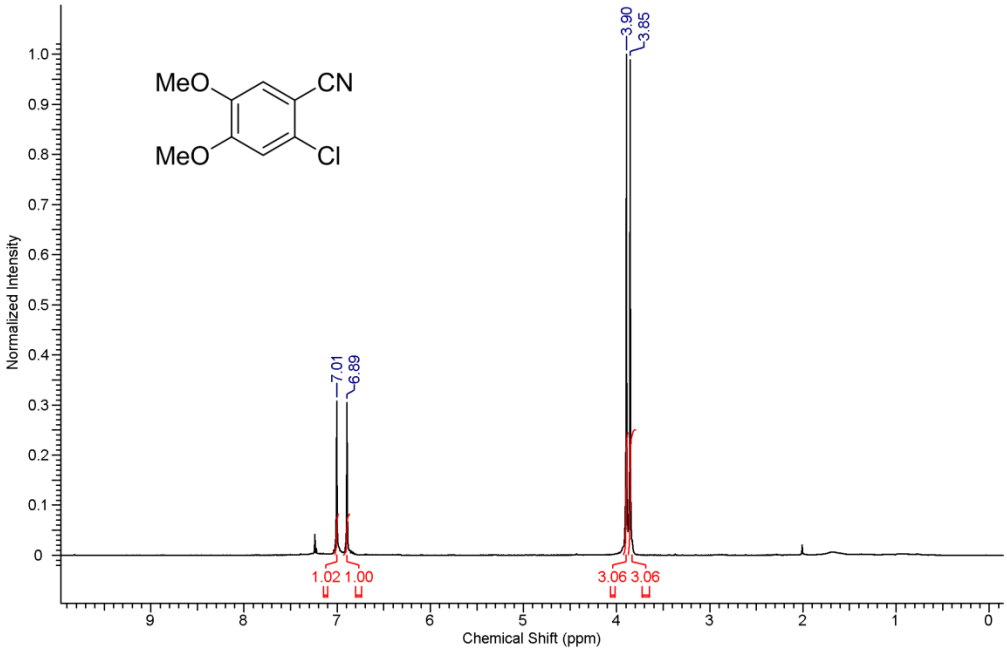

CN
MeO
Cl
133.64
132.56
112.26
56.54
158.66
123.63
117.97
104.78
Normalized Intensity
Chemical Shift (ppm)

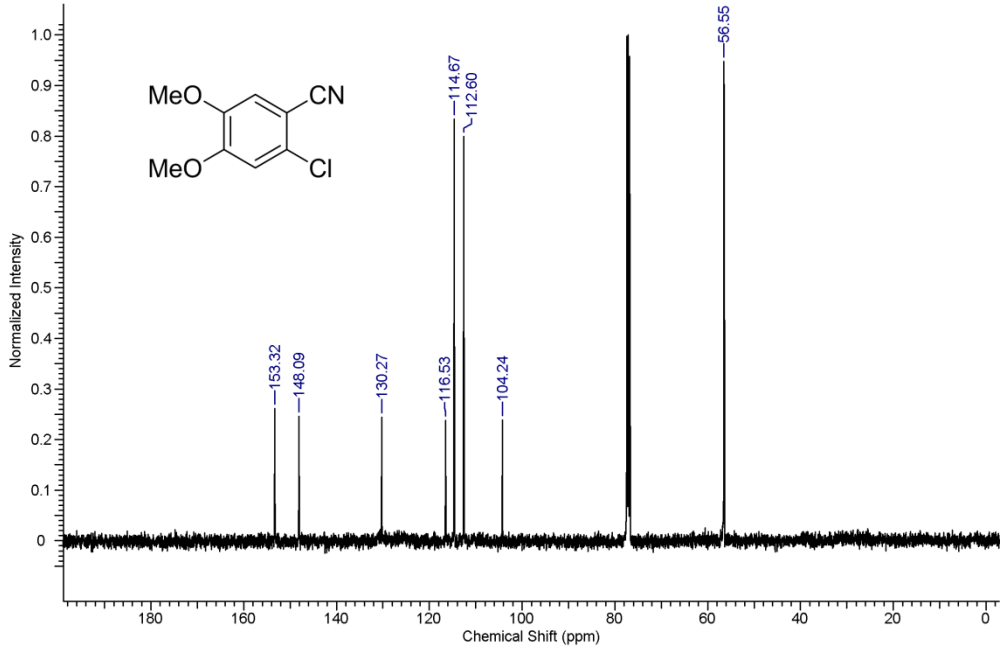
^{1}H and ^{13}C NMR Spectra of Compound **2f**



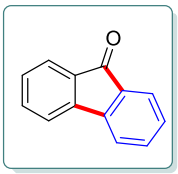


^{1}H and ^{13}C NMR Spectra of Compound **2j**

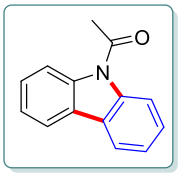




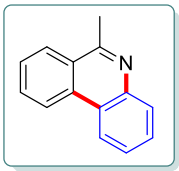
Chapter-4



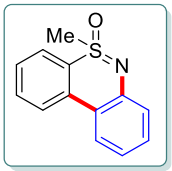
Fluorenones



Carbazoles



Phenanthridines



Dibenzothiazines

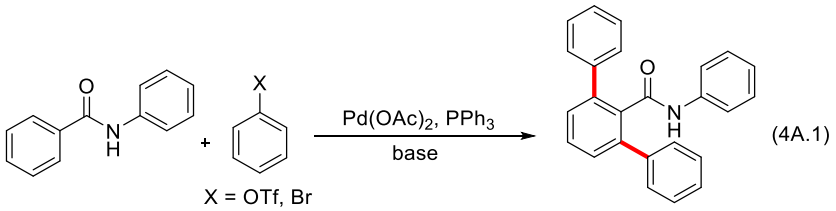
Synthesis of Tricyclic Heterocyclic Compounds Fluorenones, Phenanthridines, Carbazoles and Dibenzothiazines

Section 4A: Regioselective *ortho*-Arylation and Alkenylation of *N*-Alkyl Benzamides with Boronic acids via Ruthenium-Catalyzed C-H Bond Activation: An Easy Route to Fluorenones Synthesis

4A.1 Introduction

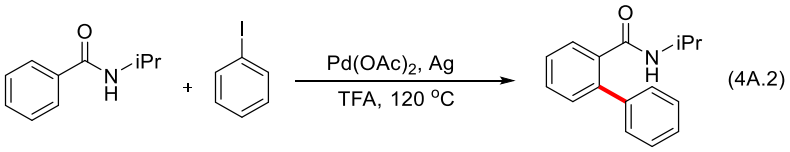
The transition-metal-catalyzed heteroatom-directed *ortho*-arylation of substituted aromatics with aryl electrophiles or organometallic reagents by C-H bond activation is one of the most efficient and environmentally friendly methods to synthesize biaryl derivatives with minimum waste.[1,2] The biaryl structural unit is present in various natural products, drug and agrochemical molecules and also key intermediates in various material syntheses.[3] Palladium,- rhodium- or ruthenium-catalyzed *ortho*-arylations of heteroatom group substituted aromatics with aryl electrophiles such as aryl halides and aryl pseudohalides have been extensively studied by the groups of Miura, Daugulis, Yu, Cheng, Kakiuchi, Dixneuf, Ackermann and others.[4,5] An alternative strategy such as *ortho*-arylation by using aryl organometallic reagents has not been well explored in the literature. Organoborons, organosilanes and organostannanes are commonly used transmetallating agents in this type of reaction. Among them, organoboron reagents display multifarious advantages including availability, air and moisture stability, low toxicity and easy removal of boron-derived by-products unlike other organometallic reagents.[6]

In 2000, Miura's group reported a palladium-catalyzed direct *ortho*-arylation of benzanilides with aryl triflates or bromides. In the reaction, only the corresponding di arylated compounds were observed (eq. 4A.1).[7a]



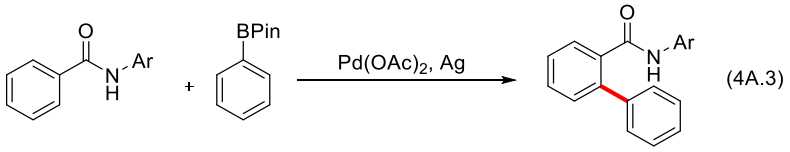
(4A.1)

Dauguli's group described a palladium-catalyzed *ortho*-arylation of *N*-alkyl benzamides with aryl iodides. This reaction is one of the most useful methods for *ortho*-arylation of *N*-alkyl benzamides. But, in the reaction symmetrical aromatic benzamides provided *ortho*-diarylated compound predominantly (eq. 4A.2).[7b]



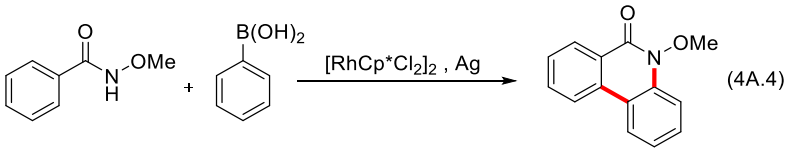
(4A.2)

Later, Yu's group showed a palladium-catalyzed direct arylation of substituted aromatics amides with organoboron reagents. In this reaction excess amount of reagents were used such as $Pd(OAc)_2$ (10 mol %) as the catalyst, Ag_2CO_3 (1.5 equiv) as the terminal oxidant, and $NaHCO_3$ (3.0 equiv) as the base in *t*-AmylOH (*tert*-amyl alcohol). In addition to that 1,4-benzoquinone (BQ), (0.5 equiv) DMSO (0.5 equiv) and 5 equiv of H_2O to the reaction improves reaction yields (eq. 4A.3).[7c]



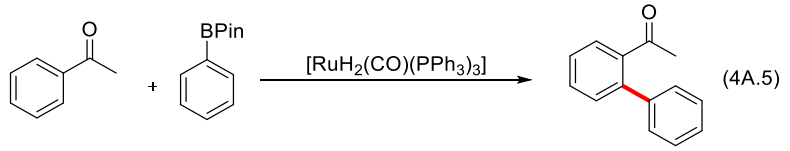
(4A.3)

Subsequently, Cheng's group demonstrated rhodium-catalyzed cyclization of *N*-methoxybenzamides with aryl boronic acids under mild conditions. The catalytic reaction proceeds with high regioselectivity and affords various substituted phenanthridinones concluded C-C and C-N bond formation. But, in this reaction excess amount of Ag_2O (4.0 equiv) was used for the cyclization reaction (eq. 4A.4).[7d]



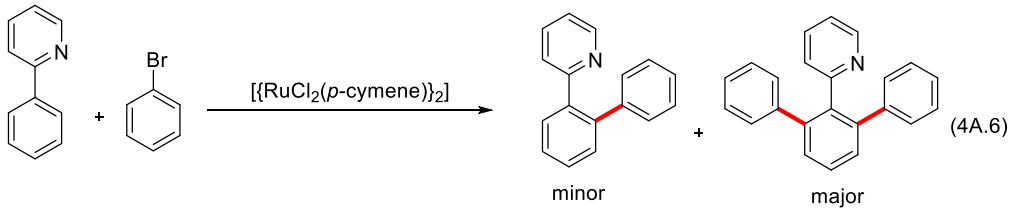
(4A.4)

In most of the reported C-H bond activation reactions, the palladium complex has been used as a catalyst. In contrast, ruthenium catalyst was found suitable only for C-H bond activation of aromatic ketones with aryl boronates. In 2003, Kakiuchi's group reported a ruthenium(0)-catalyzed direct arylation of aromatic ketones with aryl boronates (eq. 4A.5).[8a-c]



(4A.5)

Owing to the extraordinary reactivity and selectivity, [{$RuCl_2$(*p*-cymene)}$_2$] complex has been efficiently used as a catalyst for various C-H bond functionalization reactions. Ru(II)-catalyzed arylation of 2-pyridyl, oxazoline, azole, amide and oxime substituted aromatics with aromatic electrophiles has been elaborately studied in the literature. Dixneuf and Ackerman group's described ruthenium(II)-catalyzed *ortho*-arylation of 2-phenylpyridines or aromatic imines with organic electrophiles. This reaction is compitable for aromatic or hetero aromatic arylbromides as a coupling partner (eq. 4A.6).[9]



(4A.6)

Metal-catalyzed *ortho*-arylation of hetero atom directed aromatics with aromatic electrophiles has been extensively studied in the literature. However, in the reaction of symmetrical substrates with aromatic electrophiles, a mixture of *mono*- and *di*-arylated compounds were observed.[7-9] The diarylated compounds cannot be suppressed in the reaction, but, it can be suppressed by doing arylation using aromatic organometallic reagents. Aromatic boranes, aromatic stannenes and aromatic silanes are commonly used arylating agents in the coupling reaction. Among them, organoborane reagents display multifarious advantages and the observed boron-derived byproducts are not harmful unlike other organometallic reagents. In addition, in most of the reported reactions, organoboronates have been widely used as a coupling partner.[10] The corresponding organoboronic acid was not a suitable coupling partner for the reaction, mainly with ruthenium-catalyzed reactions. Therefore, hydroxy groups of boronic acid were masked and the masked reagent was used. Due to the vast availability and easy preparation of boronic acids, if a new arylation reaction is developed by organoboronic acid, it would be very useful in organic synthesis. However, the major challenge in this reaction is to suppress other competitive reactions such as homo coupling of boronic acids, addition of boronic acid to the directing groups and decomposition of directing groups by *in situ* generated proton of boronic acid.

4A.2 Results and Discussion

Recently, [{$RuCl_2$(*p*-cymene)}$_2$] complex has been widely used as a catalyst in various C-H bond activation reactions due to remarkable reactivity, compatibility and low cost of the complex.[11,12] In this section, we wish to account a highly regioselective *ortho*-arylation of *N*-alkyl benzamides with substituted aromaticboronic acids in the presence of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and Ag_2O. An *ortho*-alkenylation of *N*-alkyl benzamides with substituted alkenylboronic acids was also shown. Later, the *ortho* arylated *N*-alkyl benzamides were successfully converted into fluorenones in the presence of $(CF_3CO)_2O$ and HCl.

4A.2.1 Optimization Studies

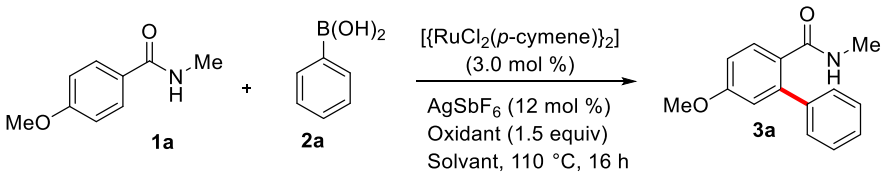


Table 4A.1 *ortho*-Arylation of 4-methoxy *N*-methyl benzamide (**1**) with phenylboronic acid (**2a**).[a]

Entry	Oxidant	Solvent	Yield[b]
1	$Cu(OAc)_2$	THF	nr
2	AgOTf	THF	40
3	$AgBF_4$	THF	21
4	AgOAc	THF	nr
5	AgO_2CCF_3	THF	nr
6	Ag_2O	THF	87
7	AgCl	THF	nr
8	AgBr	THF	nr
9	Ag_2CO_3	THF	50
10	$AgClO_4$	THF	nr
11	AgF	THF	nr

12	Ag_2O	1,4-dioxane	45
13	Ag_2O	DCE	nr
14	Ag_2O	DMF	27
15	Ag_2O	CH_3CN	nr
16	Ag_2O	CH_3COOH	nr
17	Ag_2O	MeOH	nr
18	Ag_2O	*tert*-BuOH	15
19	Ag_2O	DMSO	nr
20	Ag_2O	toluene	nr

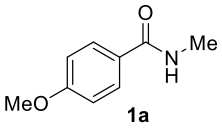
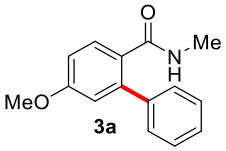
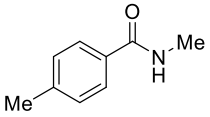
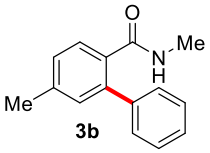
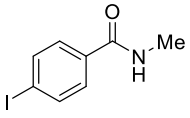
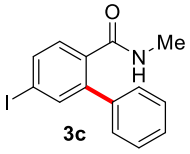
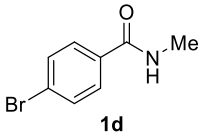
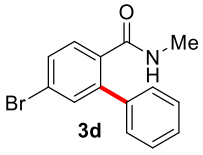
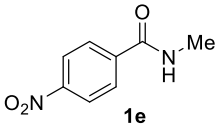
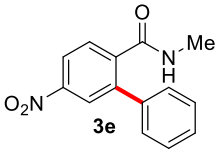
[a]All reactions were carried out with 4-methoxy *N*-methyl benzamide (**1)** (1.00 mmol), phenylboronic acid (**2a**) (1.50 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), oxidant (1.5 equiv), $AgSbF_6$ (12 mol %) and solvent (3.0 mL) at 110 °C for 16 h. [b]Isolated yields.

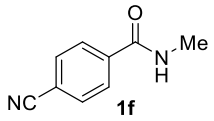
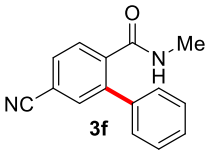
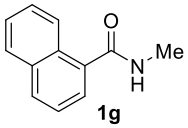
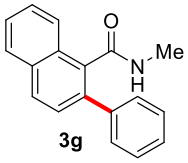
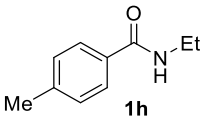
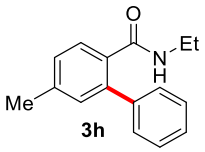
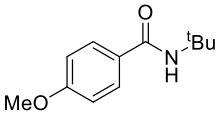
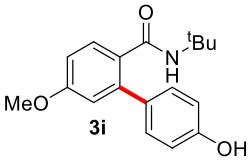
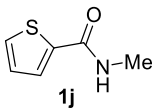
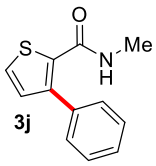
The reaction optimization was carried out with 4-methoxy *N*-methylbenzamide (**1a**) (1.0 mmol) and phenylboronic acid (**2a**) (1.50 mmol) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %) and $AgSbF_6$ (12 mol %) in THF at 110 °C for 16 h. The reaction was first tested with various terminal oxidants such as $Cu(OAc)_2$, AgOTf, $AgBF_4$, AgOAc, AgO_2CCF_3, Ag_2O, AgCl, AgBr, Ag_2CO_3, $AgClO_4$ and AgF (Table 4A.1, entry 1-11). Among them, Ag_2O was very effective for the reaction, giving **3a** in 87% yield (entry 6). The yield of **3a** was determined based on ^{1}H NMR integration method using mesitylene as an internal standard. Ag_2CO_3, AgOTf and $AgBF_4$ were less effective giving **3a** in 50%, 40% and 21% yields respectively (entry 2-3 and 9),. Remaining silver salts AgOAc, AgO_2CCF_3, $Cu(OAc)_2$, AgCl, AgBr, $AgClO_4$ and AgF were totally ineffective for the reaction. Next, the reaction was tested with various solvents such as 1,4-dioxane, DCE, DMF, CH_3CN, CH_3COOH, THF, MeOH, *tert*-BuOH, DMSO and toluene (entry 12-20). Of the solvents tested, THF was most effective, affording **3a** in 87% yield (entry 6). 1,4-Dioxane was also effective for the reaction, providing **3a** in 45% yield (entry 12). Other solvents such as DMF and *tert*-BuOH were less effective for the reaction, providing **3a** in 27% and 15% yields, respectively (entry 14 and 18). Remaining solvents such as DCE, CH_3CN, CH_3COOH, MeOH and DMSO were totally ineffective for the reaction. Next, the reaction was tested with different amounts of Ag_2O (0.5 equiv, 1.0 equiv, 1.5 equiv and 2.0 equiv). The coupling reaction

showed a better yield of 87% in 1.0 equiv of Ag_2O. In the remaining reactions, product **3a** was observed only in 75-55% yields. Further, the reaction was tested without $AgSbF_6$ and only in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] and Ag_2O. However, in this reaction, coupling product **3a** was not observed. The catalytic reaction was also tested with stoichiometric amount of $AgSbF_6$ (1.0 equiv) without Ag_2O under similar reaction conditions. In this reaction as well, no coupling product **3a** was observed. These results clearly revealed that both $AgSbF_6$ (12 mol %) and Ag_2O (1.0 equiv) were crucial for the reaction. The optimization studies revealed that $AgSbF_6$ (12 mol %) was the best additive, Ag_2O (1.0 equiv) was the best terminal oxidant and THF was the best solvent at 110 °C for 16 h for the present catalytic reaction. Under the optimized reaction conditions, **1a** reacted with **2a** providing coupling product **3a** in 81% isolated yield (Table 4A.1).

4A.2.2 *ortho*-Arylation of *N*-Alkyl Benzamides

Table 4A.2 *ortho*-Arylation of substituted *N*-alkyl benzamides **1a**–**j** with phenylboronic acids (**2a-b**).[a]

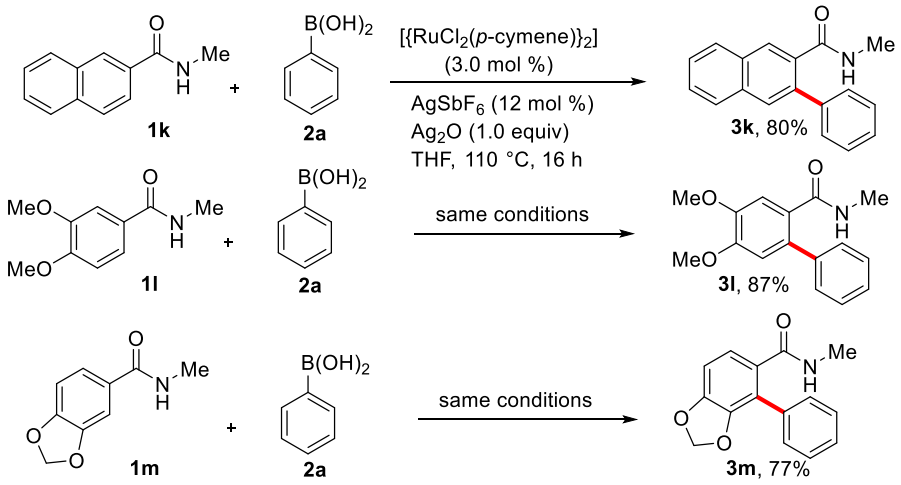
Entry	*N*-alkyl benzamide (**1**)	Compound (**3**)	Yeild[b]
1	 **1a**	 **3a**	81%
2	 **1b**	 **3b**	77%
3	 **1c**	 **3c**	79%
4	 **1d**	 **3d**	76%
5	 **1e**	 **3e**	73%

6			64%
7			77%
8			76%
9			74%
10			75%

[a]All reactions were carried out with substituted *N*-alkyl benzamides **1** (1.00 mmol), phenylboronic acids (**2**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3.0 mol %), $AgSbF_6$ (12 mol %), Ag_2O (1.0 equiv), and THF (3.0 mL) at 110 °C for 16 h. [b]Isolated yields.

Under the optimized reaction conditions, various substituted *N*-methyl benzamides **1a-j** reacted efficiently with phenylboronic acid **2a** to give the corresponding *ortho*-arylated compounds **3a-j** in good to excellent yields (Table 4A.2). Thus, 4-methoxy *N*-methylbenzamide **1a** and 4-methyl *N*-methylbenzamide **1b** afforded the corresponding *ortho*-arylated product 3a and **3b** in 81% and 77% yields (entry 1 and 2). Halogen group substituted benzamides such as 4-iodo *N*-methylbenzamide **1c** and 4-bromo *N*-methylbenzamide **1d** provided coupling products **3c** and **3d** in 79% and 76% yields, respectively (entry 3 and 4). Interestingly, electron-withdrawing group substituted benzamides such as 4-nitro *N*-methylbenzamide **1e** and 4-cyano *N*-methylbenzamide **1f** also efficiently participated in the reaction giving the corresponding *ortho*-arylated products **3e** and **3f** in 73% and 64% yields, respectively (entry 5 and 6). Bulky *N*-methyl-1-naphthamide **1g** also successfully involved in the reaction providing coupling product **3g** in 77% yield (entry 7). The effect of changing substituents on the *N*-group of the benzamides to Et and *tert*-Bu were also tested. Thus, 4-methyl *N*-ethylbenzamide **1h** reacted with phenylboronic acid **2a** to give

coupling product **3h** in 76% yield (entry 8). Similarly, 4-methoxy *N*-*tert*-butylbenzamide **1i** reacted with 4-hydroxyphenylboronic acid **2b** to give the corresponding *ortho*-arylated product **3i** in 74% yield (entry 9). A sensitive free hydroxy group on the benzene ring of boronic acid **2b** was not affected in the reaction. The catalytic reaction was also tested with heteroaromatic group substituted amide. Thus, *N*-methylthiophene-2-carboxamide **1j** underwent coupling with **2a** to afford **3j** in 75% yield. The coupling reaction was also tested with various *N*-phenyl substituted benzamides. However, no coupling product was observed in the reaction.

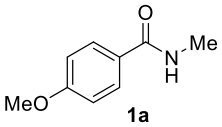
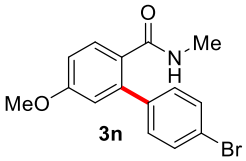
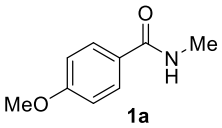
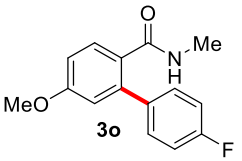
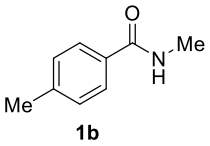
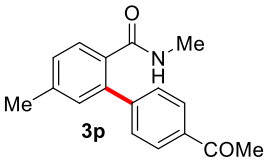
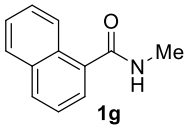
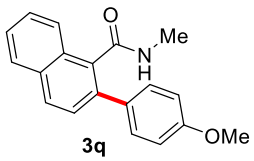
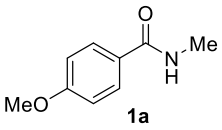
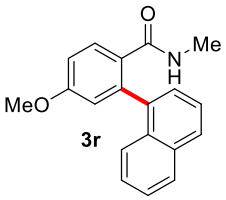
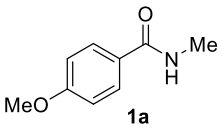
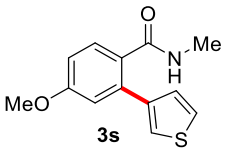


Scheme 4A.1 Regioselective studies

We next examined the scope of the regioselectivity of the present reaction. Thus, the coupling reaction was tested with various unsymmetrical benzamides **1k-m** (Scheme 4A.1). *N*-Methyl-2-naphthamide **1k** underwent arylation reaction with phenylboronic acid **2a** affording coupling product **3k** in 80% yield in a highly regioselective manner. In this reaction, there are two *ortho* C-H bonds for arylation. Regioselectively, arylation takes place at sterically less hindered C-H bond of **1k**. Similarly, 3,4-dimethoxy *N*-methylbenzamide **1l** also regioselectively reacted with **2a** at the sterically less hindered C-H bond of **1l** moiety exclusively providing coupling product **3l** in 87% yield. In contrast, 1,3-dioxol group substituted benzamide **1m** reacted with **2a** giving coupling product **3m** in 77% yield in a reverse regiochemistry. In this reaction, arylation takes place selectively at the sterically hindered C-H bond of **1m** moiety (Scheme 4A.1).

Table 4A.3 *ortho*-Arylation of substituted *N*-alkyl benzamides **1** with phenylboronic acids (**2c-f**).[a]

Entry	*N*-Alkyl benzamide (1)	Compound (3)	Yeild[b]

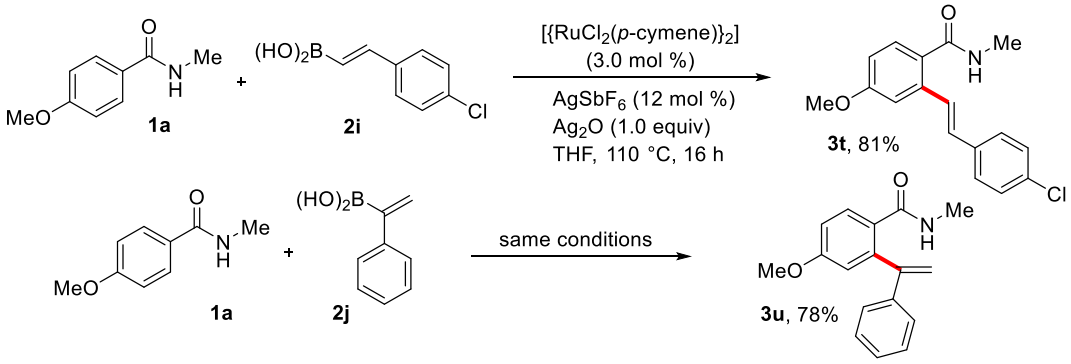
1	 1a	 3n	77%
2	 1a	 3o	76%
3	 1b	 3p	65%
4	 1g	 3q	77%
5	 1a	 3r	78%
6	 1a	 3s	75%

[a]All reactions were carried out with substituted *N*-alkyl benzamides **1** (1.00 mmol), substituted phenylboronic acids (**2**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3.0 mol %), $AgSbF_6$ (12 mol %), Ag_2O (1.0 equiv), and THF (3.0 mL) at 110 °C for 16 h. [b]Isolated yields.

The scope of the present *ortho*-arylation reaction was further examined with various substituted aromatic and heteroaromatic boronic acids (Table 4A.3). Thus, electron-withdrawing group substituted boronic acids such as 4-bromophenylboronic acid **2c**, 4-fluorophenylboronic acid **2d** and 4-acetylphenylboronic acid **2e** reacted efficiently with **1a** or 4-methyl *N*-methylbenzamide **1b** providing coupling products **3n-p** in 77%, 76% and 65% yields, respectively (entry 1-3). 4-Methoxyphenylbornoic acid **2f** coupled nicely with bulky *N*-methyl-1-naphthamide **1g** yielding biaryl derivative **3q** in 77% yield (entry 4). Similarly, bulkier 1-naphthoboronic acid **2g** also efficiently coupled with **1a** to give the corresponding biaryl derivative **3r** in 78% yield (entry 5).

Heteroaromatic boronic acid was also compatible for the reaction. Thus, 3-thienylboronic acid **2h** efficiently participated in the coupling reaction with **1a** affording substituted 3-phenylthiophene derivative **3s** in 75% yield (entry 6).

4A.2.3 *ortho*-Alkenylation of Benzamides



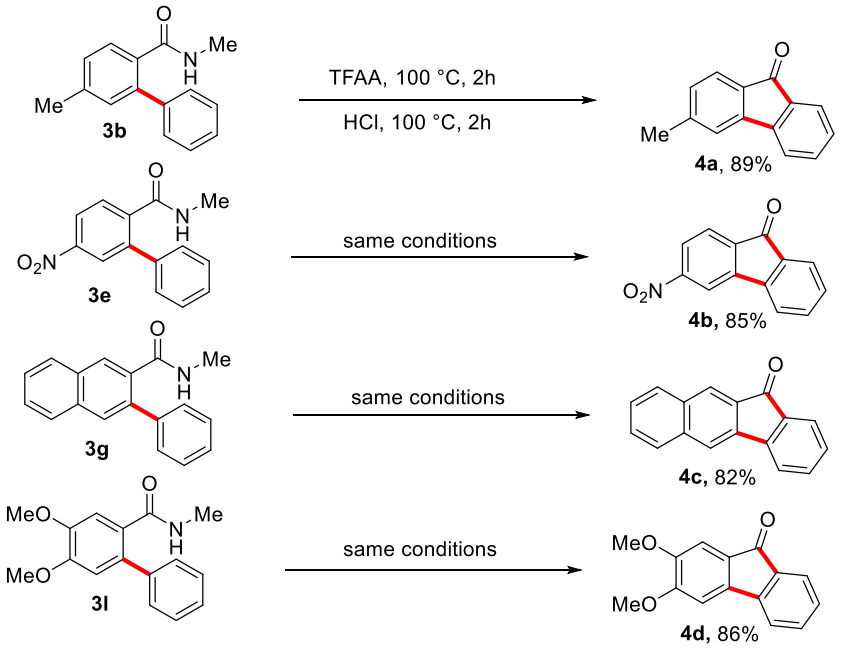
Scheme 4A.2 *ortho*-Alkenylation of benzamides

Subsequently, the present coupling reaction was tested with alkenylboronic acids **2i** and **2j** (Scheme 4A.2). Thus, 4-chlorostyrylboronic acid **2i** underwent coupling with **1a** to give the corresponding alkene derivative **3t** in 81% yield in a highly *E*-stereoselective manner. Surprisingly, highly sterically hindered 1-phenylvinylboronic acid **2j** also efficiently reacted with **1a** to yield an alkene derivative **3u** in 78% yield. It is noteworthy to say that various functional groups such as I, Br, Cl, F, CN, NO_2, OMe, S, COMe and OH on the amides or boronic acids were compatible for the present reaction.

4A.2.4 Synthesis of Fluorenones

To demonstrate the synthetic utility of *ortho*-arylated *N*-alkylbenzamides **3** in organic synthesis, we carried out intramolecular cyclization of *ortho*-arylated *N*-alkylbenzamides in the presence of trifluoroacetic anhydride and HCl (Scheme 4A.3). The intramolecular cyclization of **3h** proceeded smoothly in the presence of $(CF_3CO)_2O$ in 100 °C for 2 h followed by HCl hydrolysis in 100 °C for another 2 h yielding fluorenone derivative **4a** in 89% yield. Whereas, **3b** underwent intramolecular cyclization under similar reaction conditions, giving **4a** only in 70% yield. Similarly, *ortho* arylated *N*-ethyl benzamides of **3e**, **3j** and **3k** also nicely converted into substituted fluorenone derivatives **4b-d** in excellent 85%, 82% and 86% yields, respectively

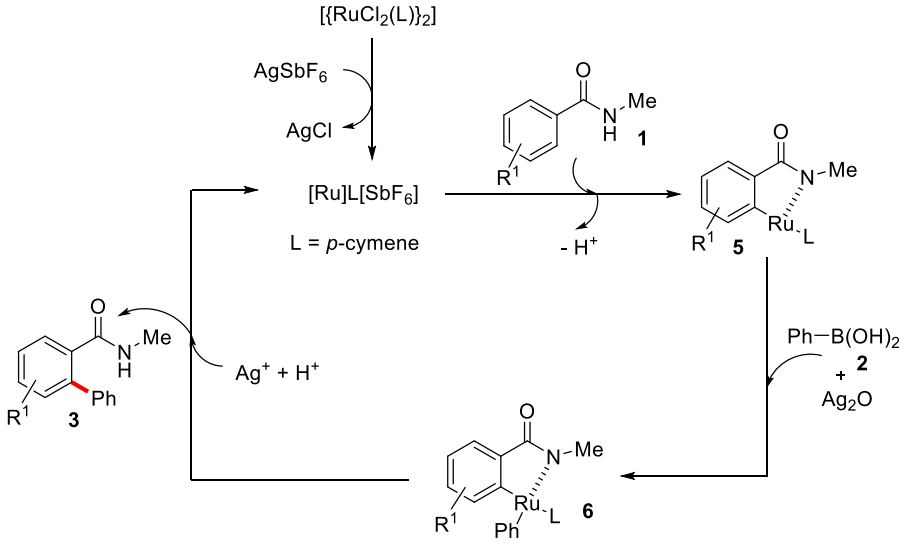
(Scheme 4A.3). Fluorenone is an important structural scaffold present in various natural products and biologically active molecules.[5h]



Scheme 4A.3. Synthesis of fluorenones

4A.2.5 Mechanism

On the basis of known metal-catalyzed C-H activation possible reaction mechanism is proposed to account for the present *ortho*-arylation reaction (Scheme 4A.4). The first step involves removal of chloride ligand from ruthenium complex by $AgSbF_6$ providing cationic ruthenium complex. Coordination of the carbonyl oxygen of benzamide **1** to the cationic ruthenium species followed by *ortho*-metalation gives ruthenacycle intermediate **5**.[5] Transmetallation of boronic acid **2** into intermediate **5** in the presence of Ag_2O provides intermediate **6**. Subsequent reductive elimination of intermediate **6** in the presence of Ag_2O affords product **3** and regenerates the active ruthenium species for the next catalytic cycle. While the exact role of Ag_2O is not clear, we think Ag_2O might play dual role in the reaction. It acts as a base to accelerate transmetallation of boronic acid **2** into intermediate **5**. In addition, Ag^+ ion acts as a terminal oxidant to oxidize Ru(0) to Ru(II).



Scheme 4A.4 Reaction mechanism

4A.3 Conclusions

In conclusion, we have described a ruthenium-catalyzed highly regioselective *ortho*-arylation of substituted *N*-alkylbenzamides with substituted aromatic and heteroaromatic boronic acids in the presence of $AgSbF_6$ and Ag_2O. Later, the observed coupling products were further converted into fluorenones in the presence of trifluoroacetic anhydride and HCl.

4A.4 References

1. Selected recent reviews: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev*. **2007**, *107*, 174. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed*. **2009**, *48*, 5094. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*. **2010**, *110*, 624. (d) Lyons, T. W.; Sanford M. S. *Chem. Rev*. **2010**, *110*, 1147. (e) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev*. **2011**, *111*, 1780. (f) Ackermann, L. *Chem. Rev*. **2011**, *111*, 1351.

2. Oxidative arylation reviews see: (a) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett*, **2008**, 949. (b) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Tetrahedron* **2012**, *68*, 5130. (c) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev*, **2012**, *41*, 5588. Cross-coupling reaction: (d) *Metal-Catalyzed Cross-Coupling Reactions*; Dieterich, F., Stang, P. J., Eds; Wiley-VCH: New York, 1998. (e) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev*. **2002**, *102*, 1359.

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4A.5 Experimental Section

4A.5.1 General Procedure for the Coupling of *N*-Alkyl Benzamides 1 with Boronic acids 2 Catalyzed by Ruthenium Complex

A 15-mL pressure tube equipped with a magnetic stirrer and septum containing [{$RuCl_2$(*p*-cymene)}$_2$] (0.03 mmol, 3 mol %), $AgSbF_6$ (0.12 mmol, 12 mol %), boronic acid **2** (1.5 mmol, 1.5 equiv) and Ag_2O (1.0 mmol, 1.0 equiv) was evacuated and purged with nitrogen gas three times. To the tube were then added benzamide (**1**) (1.00 mmol) and THF (3.0 mL) via syringes. Then, in the pressure tube, septum was taken out and covered with a screw cap immediately and 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 silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3**.

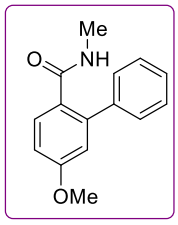
4A.5.2 General Procedure for the Preparation of Fluorenones

Note: For fluorenones synthesis, crude product **3** was taken directly without column purification. In the reaction, pure as well as crude product **3** worked equally.

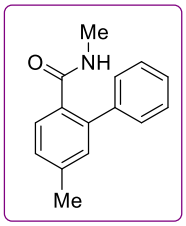
Crude product **3** (1.00 mmol scale reaction) and $(CF_3CO)_2O$ (1.5 mL) were taken in a 25-mL two-neck round bottom flask equipped with a magnetic stirrer, septum and condenser with water circulation. The reaction mixture was allowed to stir at 100 °C for 2 h. Then, the reaction mixture was refluxed in the presence of conc. HCl (1.5 mL) at 100 °C for additional 2 h. After the reaction, the reaction mixture was allowed to cool to room temperature and the reaction mixture was extracted with ethyl acetate, washed with water and brine. The extract was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **4**.

4A.5.3 Spectral Data of Compounds 3a-u and 4a-d

5-Methoxy-*N*-methyl-[1,1`-biphenyl]-2-carbaxamide (**3a**): Colorless solid; m.p.: 126 - 132 °C, eluent (30% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3297, 2925, 1735, 1640, 1556, 1407, 1291, 1132 and 1030. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 8.0 Hz, 1 H), 7.42 - 7.36 (m, 5 H), 6.90 (d, *J* = 4.0 Hz, 1 H), 6.82 (s, 1 H), 5.17 (bs, 1 H), 3.83 (s, 3 H), 2.63 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 170.0, 160.8, 141.4, 140.2, 131.2, 128.7, 128.0, 127.7, 115.5, 113.3, 55.7, 27.0. **HRMS** (ESI): calc. for $[(C_{15}H_{15}NO_2)H]$ (M+H) 242.1181 measured 242.1173.

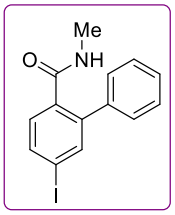


5-Methyl-*N*-methyl-[1,1`-biphenyl]-2-carboxamide (3b):Colorless solid; mp.: 118 – 123 °C, eluent (25% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3290, 2925, 1721, 1643, 1408, 1310 and 1159. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.57 (d, *J* = 8.0 Hz, 1 H), 7.38 - 7.33 (m, 5 H), 7.18 (d, *J* = 8.0, Hz, 1 H), 7.14 (s, 1 H), 5.22 (bs, 1 H), 2.62 (d, *J* = 4.0 Hz, 3 H), 2.38 (s, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 170.3, 140.4, 140.3, 139.4, 132.8, 130.9, 129.0, 128.7, 128.6, 128.3, 127.7, 26.7, 21.4.

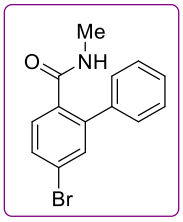


HRMS (ESI): calc. for [($C_{15}H_{15}NO$)H] (M+H) 226.1232, measured 226.1240.

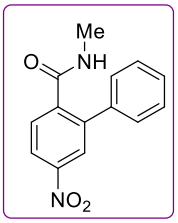
5-Iodo-*N*-methyl-[1,1`-biphenyl]-2-carboxamide (**3c**): Colorless solid; mp.: 161-165 °C, eluent (25% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3307, 2926, 1722, 1638, 1568, 1442, 1313 and 1165. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.73 -7.70 (m, 2 H), 7.42 – 7.33 (m, 6 H), 5.25 (bs, 1 H), 2.62 (d, *J* = 4.0 Hz 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 169.4, 141.2, 138.9, 138.6, 136.6, 135.0, 130.5, 128.8, 128.5, 128.3, 96.5, 26.7. **HRMS** (ESI): calc. for [($C_{14}H_{12}INO$)H] (M+H) 338.0042 measured 338.0035.



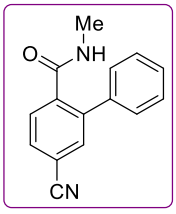
5-Bromo-*N*-methyl-[1,1`biphenyl]-2-carboxamide (**3d**): Colorless solid; mp.: 146 – 152 °C, eluent (25% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3300, 2927, 1722, 1642, 1579, 1465, 1309, 1159 and 1083. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.55 – 7.50 (m, 3 H), 7.43 – 7.35 (m, 5 H), 5.22 (bs, 1 H), 2.64 (d, *J* = 4.0 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 169.3, 141.3, 138.7, 134.4, 133.0, 130.7, 130.6, 128.8, 128.5, 128.4, 124.3, 26.84. **HRMS** (ESI): calc. for [($C_{14}H_{12}BrNO$)H] (M+H) 290.0181, measured 290.0187.



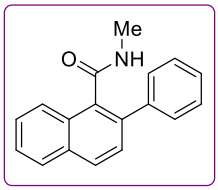
***N*-Methyl-5-nitro-[1,1`-biphenyl]-2-carboxamide** (**3e**): Colorless solid; mp.: 145 – 148 °C, eluent (30% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3284, 2926, 1650, 1527, 1408, 1350, 1160 and 1031. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.23 (s, 1 H), 8.20 (dd, *J* = 4.0, 4.0 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.45 – 7.41 (m, 5 H), 5.33 (bs, *J* = 1 H), 2.69 (d, *J* = 4.0 Hz 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 168.4, 148.6, 141.3, 141.0, 137.9, 130.2, 129.1, 129.0, 128.5, 125.1, 122.4, 26.8. **HRMS** (ESI): calc. for [($C_{14}H_{12}N_2O_3$)H] (M+H) 257.0926, measured 257.0934.



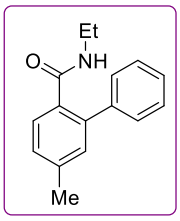
5-Cyano-*N*-methyl-[1,1`-biphenyl]-2-carboxamide (**3f**): Colorless semisolid; eluent (25% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3415, 2923, 2241, 1633, 1404, 1263 and 1027. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, *J* = 8.0, 1 H), 7.67 – 7.65 (m, 2 H), 7.44 – 7.41 (m, 3 H), 7.38 – 7.36 (m, 2 H), 5.28 (bs, 1 H), 2.67 (d, *J* = 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.5, 140.5, 139.7, 137.8, 133.8, 131.0, 129.7, 129.0, 128.9, 128.5, 118.0, 114.0, 26.8. HRMS (ESI): calc. for [($C_{15}H_{12}N_2O$)H] (M+H) 237.1028, measured 237.1035.



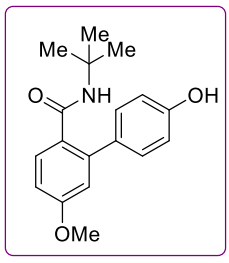
***N*-Methyl-2-phenyl-1-napthamide** (**3g**): Colorless solid; mp.: 170 – 180 °C, eluent (20% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3277, 2925, 1743, 1629, 1539, 1400, 1260, 1155 and 1080. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.06 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.56 – 7.49 (m, 5 H), 7.43 (t, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 1 H) 5.43 (bs, 1 H), 2.75 (d, *J* = 4.0 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 170.3, 140.4, 136.4, 133.5, 132.5, 130.4, 129.5, 128.8, 128.6, 128.0, 127.7, 127.48, 127.41, 126.4, 125.7, 26.8. **HRMS** (ESI): calc. for [($C_{18}H_{15}NO$)H] (M+H) 262.1232, measured 262.1236.



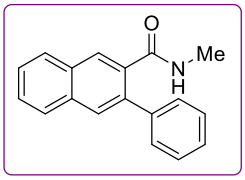
***N*-Ethyl-5-methyl-[1,1`-biphenyl]-2-carboxamide** (**3h**): Colorless semisolid; eluent (25% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3300, 2927, 1725, 1646, 1533, 1451, 1380, 1129 and 1074. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, *J* = 8.0 Hz, 1 H), 7.39 – 7.34 (m, 5 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 7.14 (s, 1 H), 5.10 (bs, 1 H), 3.15 (q, *J* = 8.0 Hz, 2 H), 2.38 (s, 3 H) 0.76 (t, *J* = 16.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2, 140.5, 140.2, 139.5, 133.0, 130.8, 129.1, 128.8, 128.6, 128.3, 127.7, 34.6, 21.3, 14.1. HRMS (ESI): calc. for [($C_{16}H_{17}NO$)H] (M+H) 240.1388, measured 240.1394.



***N*-(tert-butyl)-4`-Hydroxy-5-methoxy-[1,1`-biphenyl]-2-carboxamide** (**3i**): Colorless semisolid; eluent (40% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3423, 2923, 1626, 1394, 1270, 1374 and 1091. ^{1}H NMR (*d*-DMSO, 400 MHz): δ 9.44 (bs, 1 H), 7.26 (d, *J* = 8.0 Hz, 1 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 7.14 (s, 1 H), 6.83 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.72 (d, *J* = 8.0 Hz, 2 H), 3.75 (s, 3 H), 1.92 (s, 9 H). ^{13}C NMR (*d*-DMSO, 100 MHz): δ 169.0, 159.9, 157.4, 141.3, 131.4, 131.0, 130.1, 129.9, 115.3, 115.0, 112.1, 55.7, 50.8, 28.7. HRMS (ESI): calc. for [($C_{18}H_{21}NO_3$)H] (M+H) 300.1600, measured 300.1607.

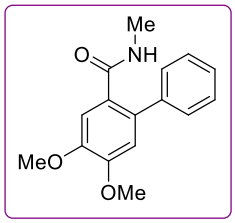


***N*-Methyl-3-phenyl-2-naphthamide** (**3j**): Colorless solid; mp.: 170 – 180 °C, eluent (20% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3277, 2925, 1743, 1629, 1539, 1400, 1260, 1155 and 1080. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (s, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.80 (s, 1 H), 7.55 – 7.35 (m, 7 H), 5.41 (bs, 1 H), 2.70 (d, *J* = 4.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ



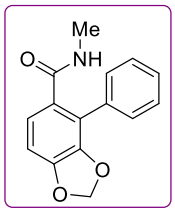
170.1, 140.3, 136.7, 133.8, 132.0, 129.4, 129.2, 128.8, 128.6, 128.4, 127.8, 127.7, 127.6, 126.8, 26.8. HRMS (ESI): calc. for [($C_{18}H_{15}NO$)H] (M+H) 262.1232, measured 262.1236.

4,5-Dimethoxy-*N*-methyl-[1,1`-biphenyl]-2-carboxamide (**3k**): Colorless solid; mp.: 132 – 140



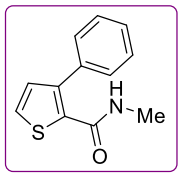
°C, eluent (35% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3376, 2926, 1735, 1642, 1518, 1455, 1349, 1269, 1176 and 1020. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 – 7.34 (m, 5 H), 7.29 (s, 1 H), 6.77 (s, 1 H), 5.14 (bs, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 2.61 (d, *J* = 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 150.2, 148.3, 140.2, 132.7, 128.8, 128.7, 127.7, 127.4, 112.8, 112.0, 56.15, 56.12, 26.8. HRMS (ESI): calc. for [($C_{16}H_{17}NO_3$)H] (M+H) 272.1287, measured 272.1281.

***N*-Methyl-4-phenylbenzo[*d*][1,3]dioxole-5-carboxamide** (**3l**): Colorless solid; mp.: 136 – 140



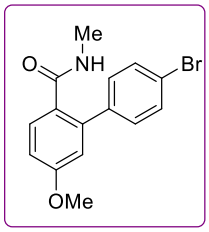
°C, eluent (35% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3393, 2919, 1733, 1646, 1543, 1306, 1248 and 1049. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 – 7.34 (m, 5 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 5.95 (s, 2 H), 5.25 (bs, 1 H), 2.61 (d, *J* = 4.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2, 148.8, 145.4, 133.8, 129.8, 129.3, 128.6, 128.3, 123.6, 121.5, 107.6, 101.5, 26.7. HRMS (ESI): calc. for [($C_{15}H_{13}NO_3$)H] (M+H) 256.0974, measured 256.0981.

***N*-Methyl-3-phenylthiophene-2-carboxamide** (**3m**): Colorless solid; mp.: 100 -106 °C, eluent



(20% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3430, 2968, 1641, 1540, 1452, 1290, 1166 and 1078. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.43 – 7.39 (m, 6 H), 6.97 (d, *J* = 8.0, Hz, 1 H), 5.57 (bs, 1 H), 2.71 (d, *J* = 4.0 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 163.0, 141.7, 135.5, 134.7, 130.7, 129.1, 129.0, 128.6, 128.5, 26.6. **HRMS** (ESI): calc. for [($C_{12}H_{11}NOS$)H] (M+H) 218.0640, measured 218.0634.

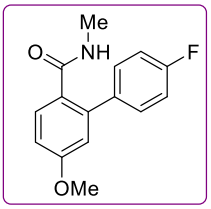
4`-Bromo-5-methoxy-*N*-[1,1`-biphenyl]-2-carboxamide (**3n**): Colorless solid; mp.: 152 – 157



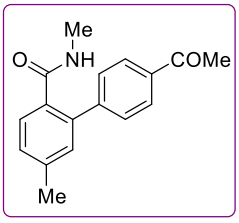
°C, eluent (30% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3295, 2924, 1630, 1542, 1289, 1170, 1160 and 1068. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (d, *J* = 8.0 Hz, 1 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 6.77 (s, 1 H), 5.27 (bs, 1 H), 3.82 (s, 3 H), 2.68 (d, *J* = 4.0 Hz,

3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 160.7, 140.1, 139.2, 131.7, 130.7, 130.2, 128.1, 122.2, 115.5, 113.1, 55.5, 26.6. HRMS (ESI): calc. for [($C_{15}H_{14}BrNO_2$)H] (M+H) 320.0286, measured 320.0290.

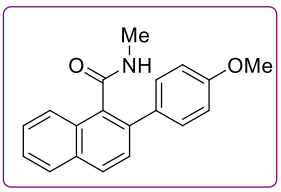
4`-Fluro-5-methoxy-*N*-methyl-[1,1`-biphenyl]-2-carboxamide (**3o**): Colorless solid; m.p.: 140 – 142 °C, eluent (30% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3256, 2925, 1640, 1553, 1499, 1293, 1166 and 1028. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, *J* = 8.0 Hz, 1 H), 7.33 and F coupling(t, *J* = 8.0 Hz, 2 H), 7.08 and F coupling (t, *J* = 8.0 Hz, 2 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.79 (s, 1 H), 5.23 (bs, 1 H), 3.82 (s, 3 H), 2.66 (d, *J* = 8.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.8, 163.8, 161.3, 160.7, 140.2, 136.3 and 130.2 (F coupling), 130.7, 130.3 and 130.2 (F coupling), 115.7, 115.6 and 115.5 (F coupling), 112.9, 55.5, 26.7. HRMS (ESI): calc. for [($C_{15}H_{14}FNO_2$)H] (M+H) 260.1087, measured 260.1089.



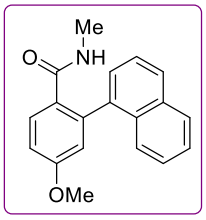
4'-Acetyl-*N*,5-dimethyl-[1,1'-biphenyl]-2-carboxamide (**3p**): Colorless semisolid; eluent (35% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3309, 2924 1673, 1548, 1362, 1268 and 1081. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, *J* = 8.0 Hz, 2 H), 7.41 (d, *J* = 8.0, Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.18 (d, *J* = 8.0 Hz, 1 H), 7.15 (s, 1 H), 5.80 (bs, 1 H), 2.66 (d, *J* = 4.0 Hz, 3 H), 2.59 (s, 3 H), 2.38(s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.9, 170.9, 145.0, 140.9, 138.6, 136.1, 132.1, 129.8, 128.8, 128.7, 128.5, 126.6, 27.0, 26.7, 21.4. HRMS (ESI): calc. for [($C_{17}H_{17}NO_2$)H] (M+H) 268.1338, measured 268.1344.



2-(4-Methoxyphenyl)-*N*-methyl-1-napthamide (**3q**): Colorless solid; mp.: 185 – 189 °C, eluent (25% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3288, 2975, 1627, 1534, 1240, 1169 and 1038. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, *J* = 8.0 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.52 – 7.49 (m, 2 H), 7.47 – 7.45 (m, 3 H), 6.94 (d, *J* = 8.0 Hz, 2 H), 5.49 (bs, 1 H), 3.83 (s, 3 H), 2.76 (d, *J* = 4.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 159.2, 136.0, 133.1, 132.7, 132.3, 130.5, 129.9, 129.4, 127.9, 127.5, 127.3, 126.2, 125.6, 114.0, 55.3, 26.8. HRMS (ESI): calc. for [($C_{19}H_{17}NO_2$)H] (M+H) 292.1338, measured 292.1342.

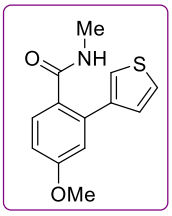


4-Methoxy-*N*-methyl-2-(naphthalen-1-yl)benzamide (**3r**): Colorless solid; mp.: 178 -183 °C,



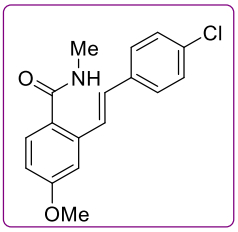
eluent (20% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3302, 2929, 1646, 1544, 1485, 1293, 1226, 1171 and 1037. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, *J* = 8.0, 1 H), 7.88 (d, *J* = 8.0, 2 H), 7.60 (d, *J* = 8.0, Hz, 1 H), 7.53 – 7.46 (m, 2 H), 7.43 – 7.39 (m, 2 H), 7.02 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 5.11 (bs, 1 H), 3.81 (s, 3 H), 2.28 (d, *J* = 4.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 160.8, 139.5, 138.3, 133.5, 131.7, 131.4, 128.6, 128.4, 126.9, 126.7, 126.6, 126.4, 125.5, 125.4, 116.5, 113.6, 55.5, 20.5. HRMS (ESI): calc. for [($C_{19}H_{17}NO_2$)H] (M+H) 292.1338, measured 292.1344.

4-Methoxy-*N*-methyl-2-(thiophen-3-yl)benzamide (3s): Colorless solid; mp.: 118 – 123 °C,



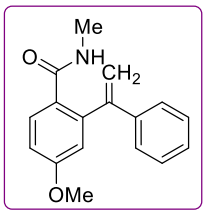
eluent (20% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3292, 2925, 1732, 1640, 1560, 1483, 1282 and 1173. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (d, *J* = 8.0 Hz, 1 H), 7.36 – 7.32 (m, 2 H), 7.12 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H) 6.86 (s, 1 H), 5.34 (bs, 1 H), 3.82 (s, 3 H), 2.71 (d, *J* = 4.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 160.7, 140.7, 135.7, 130.7, 128.3, 128.1, 126.1, 123.0, 115.2, 113.0, 55.5, 26.8. HRMS (ESI): calc. for [($C_{13}H_{13}SNO_2$)H] (M+H) 248.0745, measured 248.0749.

(*E*)-2-(4-Chlorostyryl)-4-methoxy-*N*-methylbenzamide (**3t**): Colorless semisolid; eluent (25%



ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3288, 2924, 1624, 1535, 1485, 1394, 1213, 1161 and 1090. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, *J* = 16.0 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 3 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.12 (s, 1 H), 6.93 (d, *J* = 16.0 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 5.86 (bs, 1 H), 3.84 (s, 3 H), 2.96 (d, *J* = 4.0 Hz 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 160.9, 137.4, 135.6, 133.6, 130.0, 129.4, 128.9, 128.2, 128.0, 126.9, 113.1, 111.4, 55.4, 25.9. HRMS (ESI): calc. for [($C_{17}H_{16}ClNO_2$)H] (M+H) 302.0948, measured 302.0951.

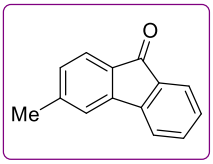
4-Methoxy-*N*-methyl-2-(1-phenylvinyl)benzamide (**3u**): Colorless solid; mp.: 150 – 155 °C,



eluent (25% ethyl acetate in hexanes). **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3299, 2923, 1735, 1616, 1527, 1393, 1271, 1158 and 1030. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, *J* = 8.0 Hz, 3 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.32 (t, *J* = 8.0 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 7.10 (s, 1 H), 6.96 (d, *J* = 16.0 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H),

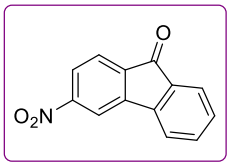
6.01 (bs, 1 H), 3.81 (s, 3 H), 2.92 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0, 160.8, 137.6, 137.0, 131.4, 129.5, 128.7, 128.3, 128.0, 126.9, 126.3, 113.0, 111.3, 55.4, 26.9. HRMS (ESI): calc. for [($C_{17}H_{17}NO_2$)H] (M+H) 268.1338, measured 268.1342.

3-Methyl-9*H*-fluoren-9-one (4a): Yellow viscous liquid; eluent (5% ethyl acetate in hexanes).



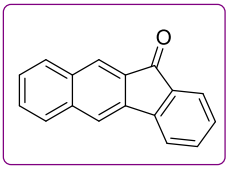
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, *J* = 8.0 Hz, 1 H), 7.52 (d, *J* = 8.0 Hz, 1 H), 7.45 – 7.41 (m, 2 H), 7.28 (s, 1 H), 7.27 – 7.23 (m, 1 H), 7.06 (d, *J* = 8.0 Hz, 1 H), 2.39 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.7, 145.9, 144.8, 144.3, 134.7, 134.5, 131.9, 129.6, 129.0, 124.3, 124.2, 121.3, 120.1, 22.2. HRMS (ESI): calc. for [($C_{14}H_{10}O$)H] (M+H) 195.0810, measured 195.0811.

3-Nitro-9*H*-fluoren-9-one (4b): Yellow solid; m.p. 211 – 215 ^{o}C, eluent (10% ethyl acetate in hexanes).



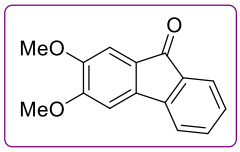
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (s, 1 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 4.0 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.59 (t, *J* = 8.0 Hz, 1 H) 7.40 (t, *J* = 8.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.7, 152.5, 145.8, 142.5, 138.4, 135.8, 134.2, 130.6, 125.1, 124.87, 124.81, 121.3, 115.4. HRMS (ESI): calc. for [($C_{13}H_7NO_3$)H] (M+H) 226.0504, measured 226.0507.

11*H*-Benzo[*b*]fluoren-11-one (4c): Yellow solid; m.p. 141 – 143 ^{o}C, eluent (5% ethyl acetate in hexanes).



^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (s, 1 H), 8.88 (d, *J* = 8.0 Hz, 1 H), 7.87 (s, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H) 7.58 – 7.52 (m, 2 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 7.34 (t, *J* = 8.0 Hz, 1 H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.2, 144.9, 138.5, 136.9, 136.2, 135.1, 133.7, 132.8, 130.9, 129.3, 129.1, 128.9, 127.0, 125.8, 124.5, 121.1, 119.2. **HRMS** (ESI): calc. for [($C_{17}H_{10}O$)H] (M+H) 231.0810, measured 231.0815.

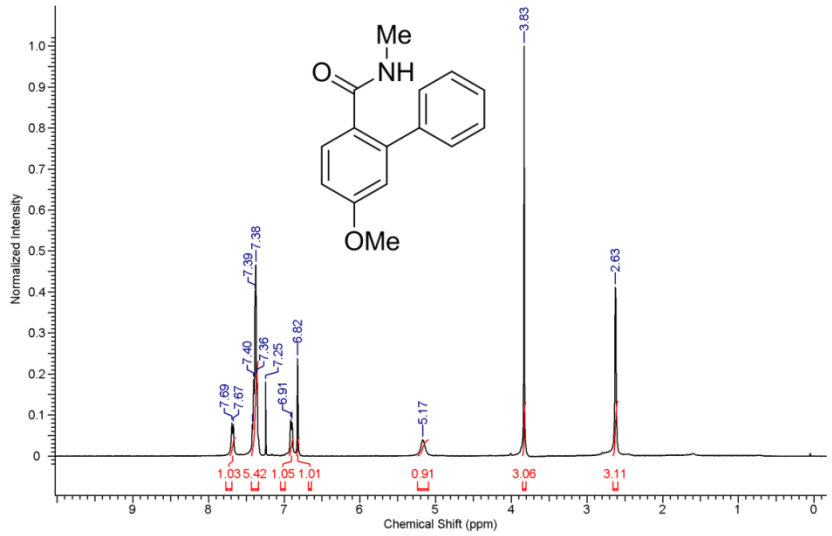
2,3-Dimethoxy-9*H*-fluoren-9-one (4d): Yellow semi solid; eluent (10% ethyl acetate in hexanes).

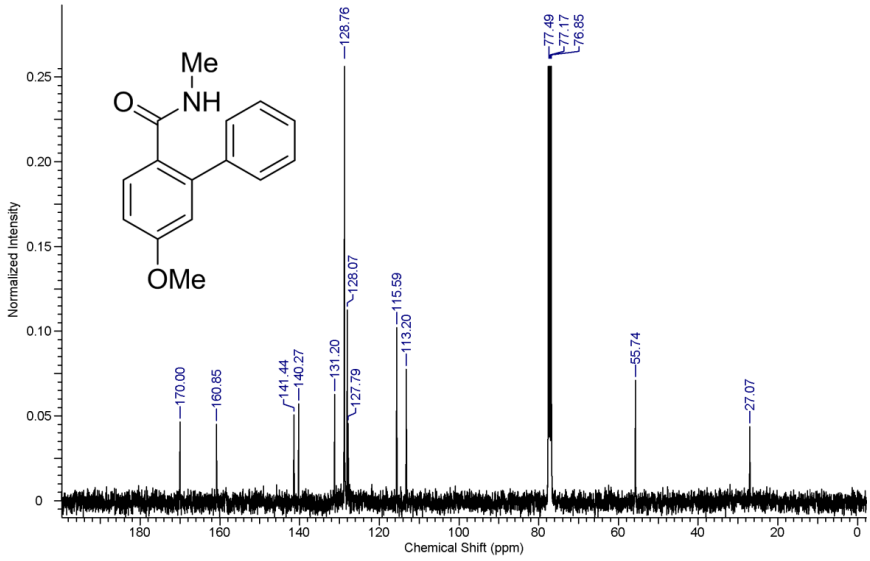


^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (d, *J* = 8.0 Hz, 1 H), 7.37 (t, *J* = 8.0 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.16 (t, *J* = 8.0 Hz, 1 H), 7.15 (s, 1 H), 6.96 (s, 1 H) 3.98 (s, 3 H) 3.90 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.3, 154.6, 149.7, 144.0, 139.5, 134.8, 134.3, 128.2, 126.9, 123.8, 119.1, 107.1, 103.4, 56.4, 56.3. HRMS (ESI): calc. for [($C_{15}H_{12}O_3$)H] (M+H) 241.0865, measured 241.0864

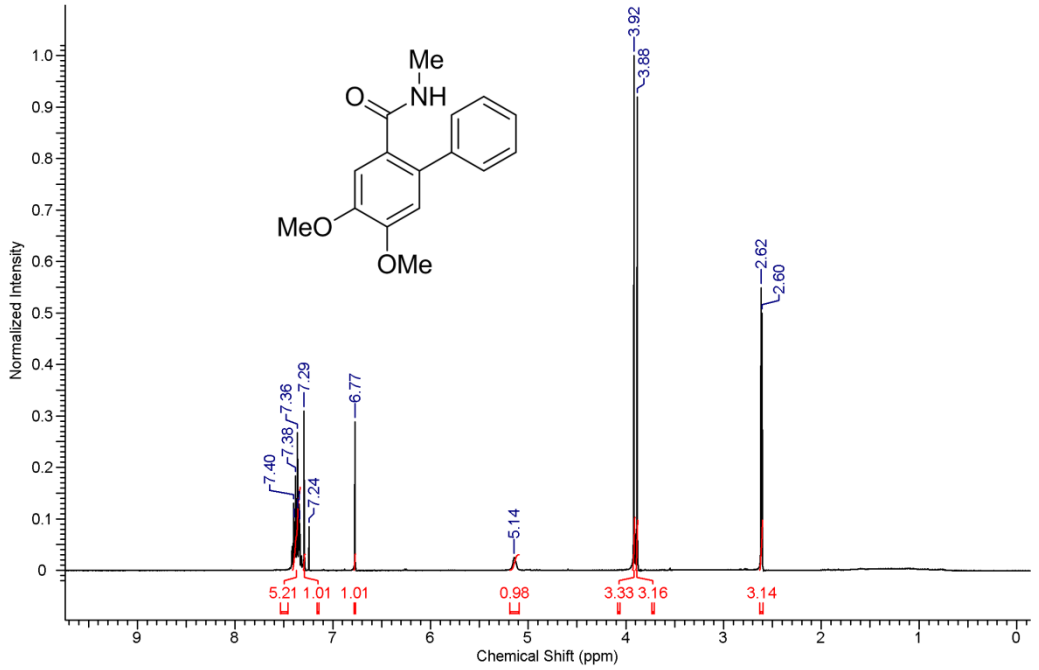
4A.5.4 Spectral Copies of Selected Compounds

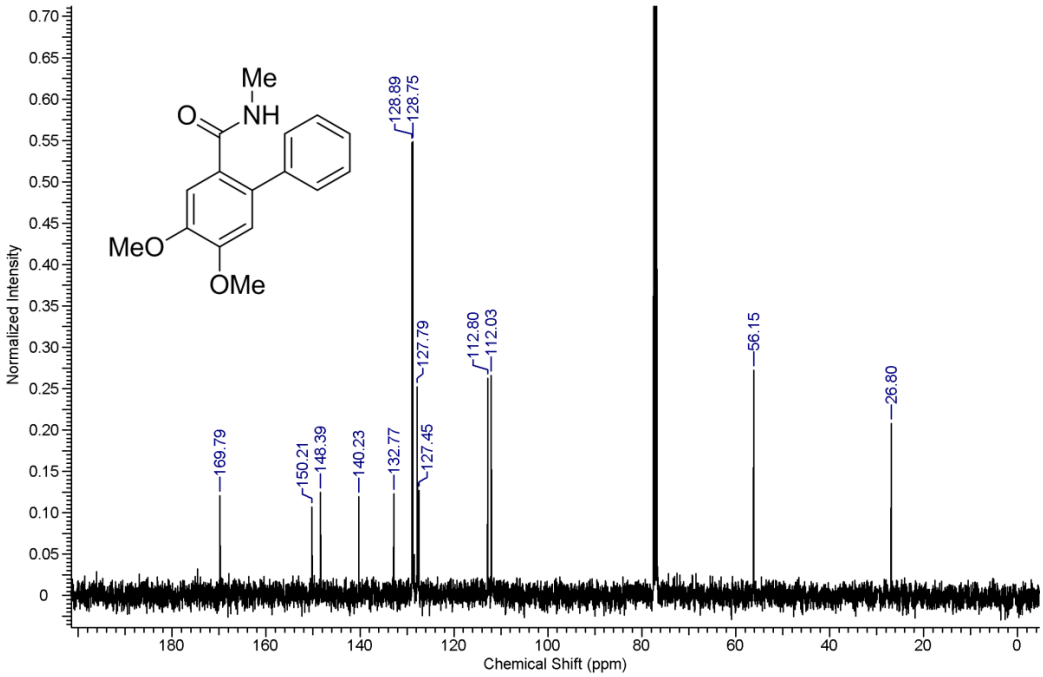
^{1}H and ^{13}C NMR Spectra of Compound **3a**



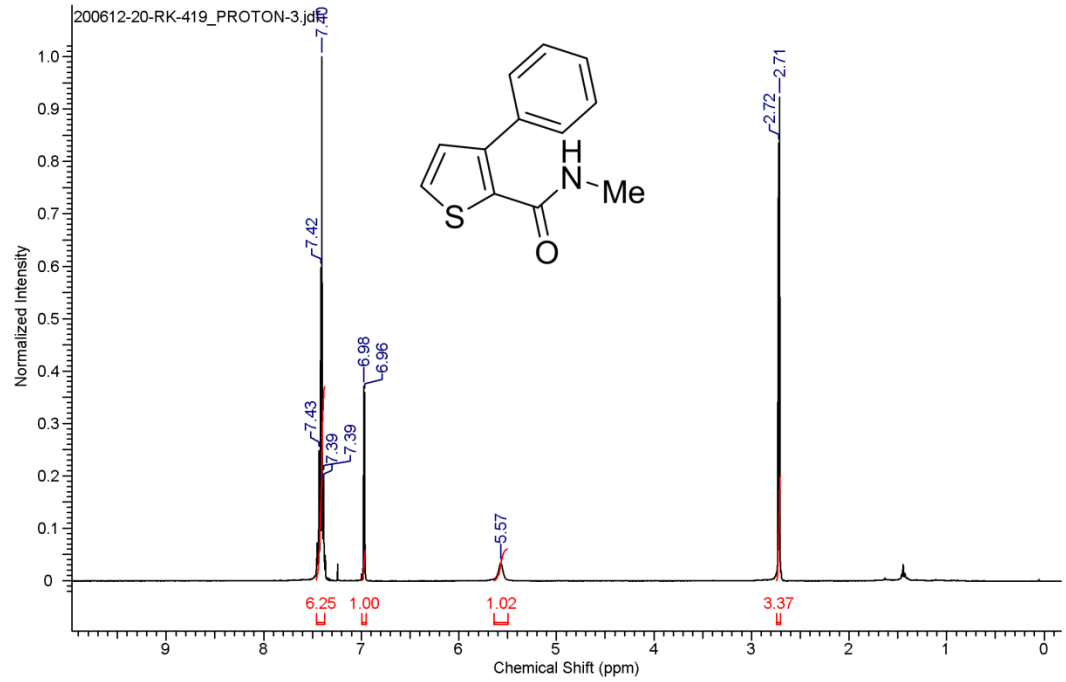


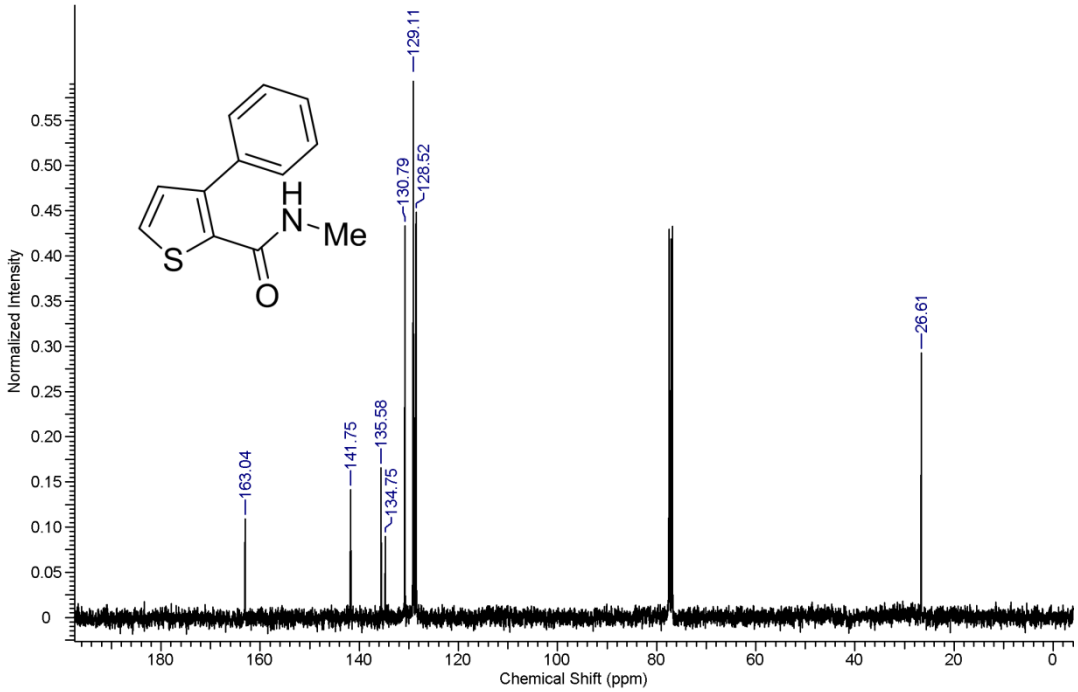
^{1}H and ^{13}C NMR Spectra of Compound **3k**



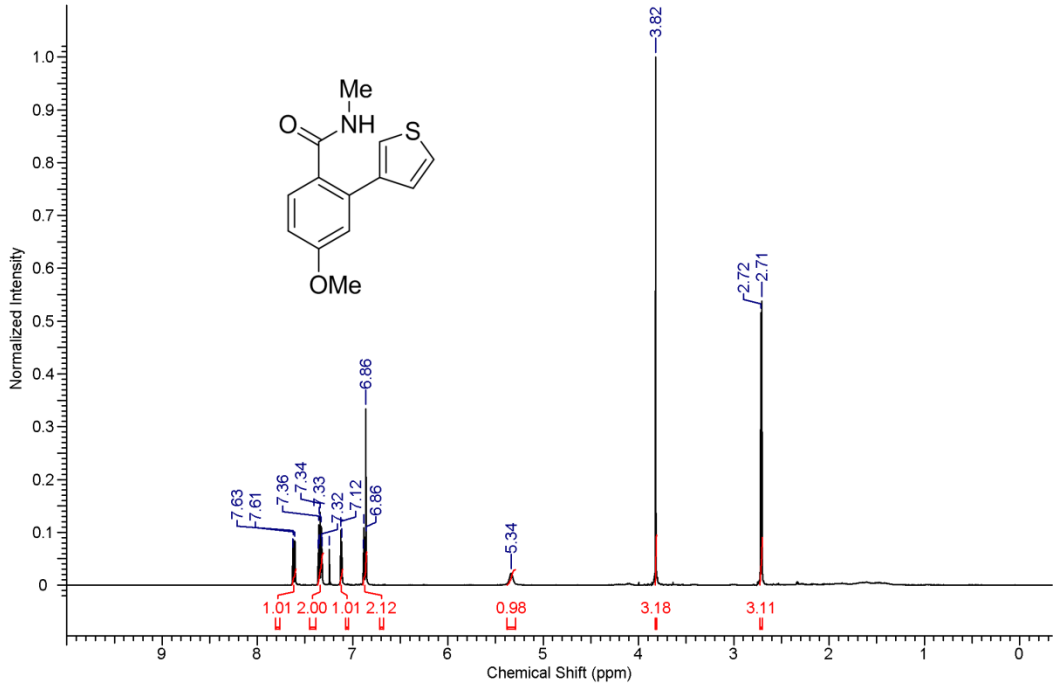


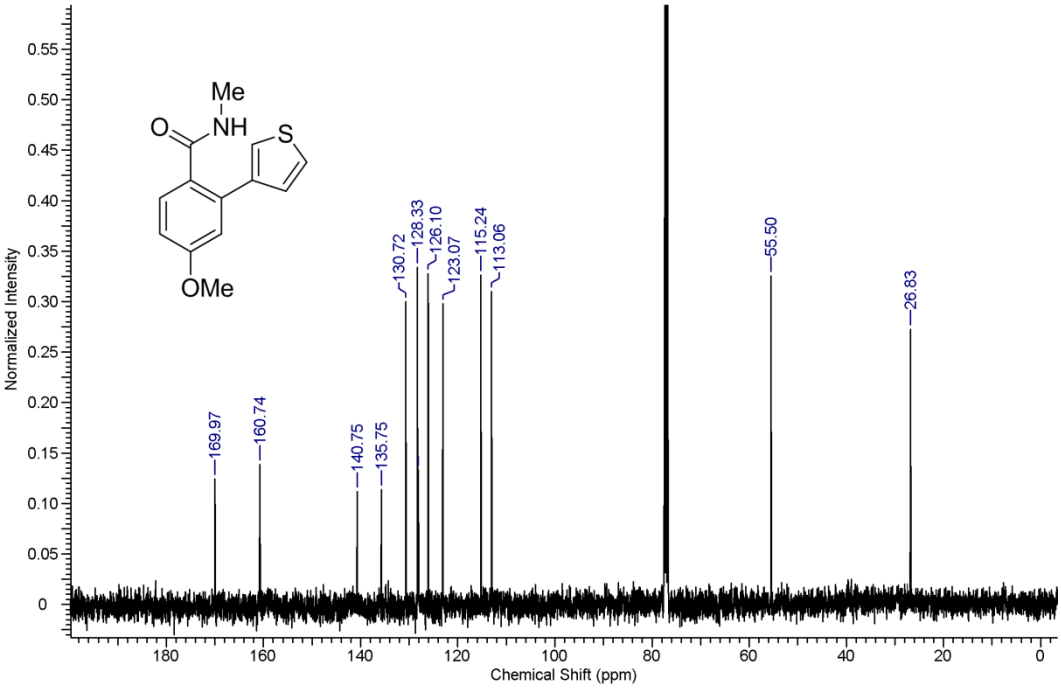
^{1}H and ^{13}C NMR Spectra of Compound **3m**



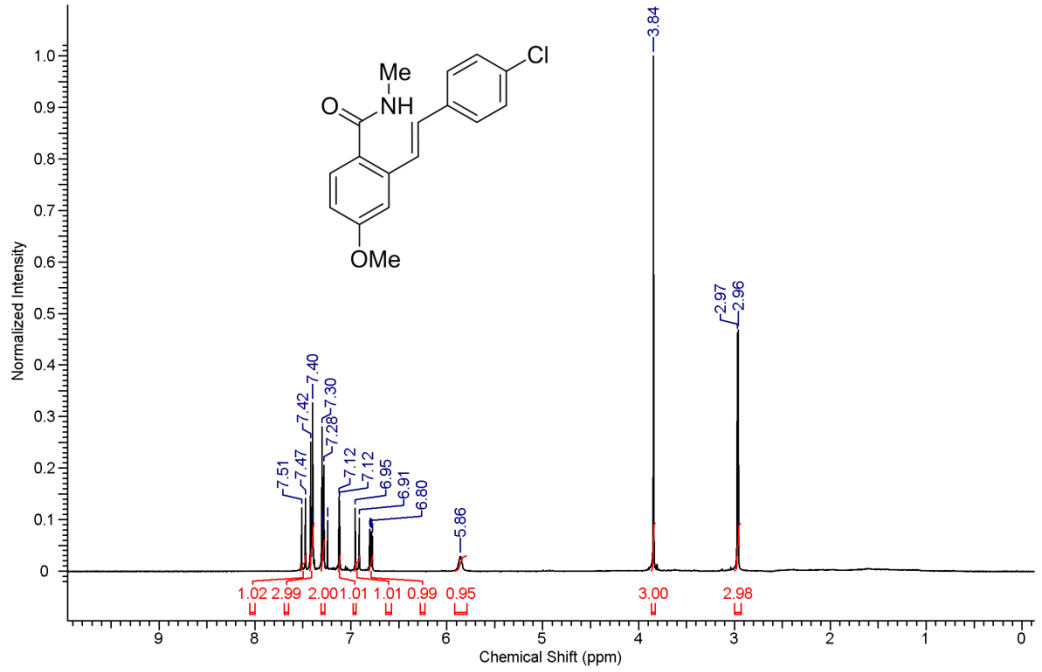


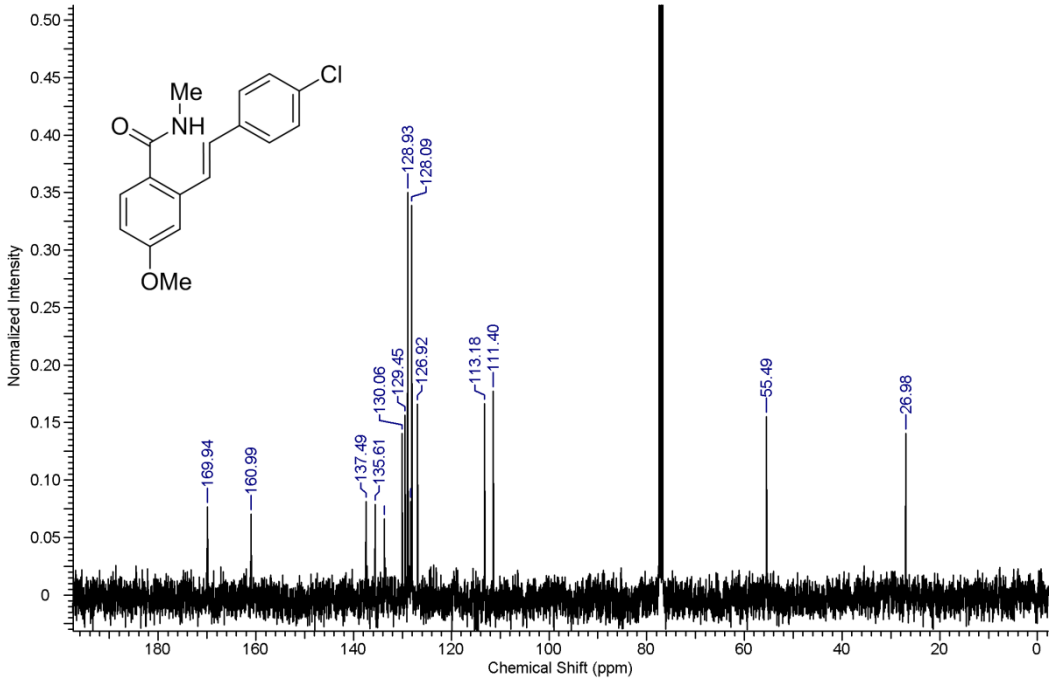
^{1}H and ^{13}C NMR Spectra of Compound **3s**



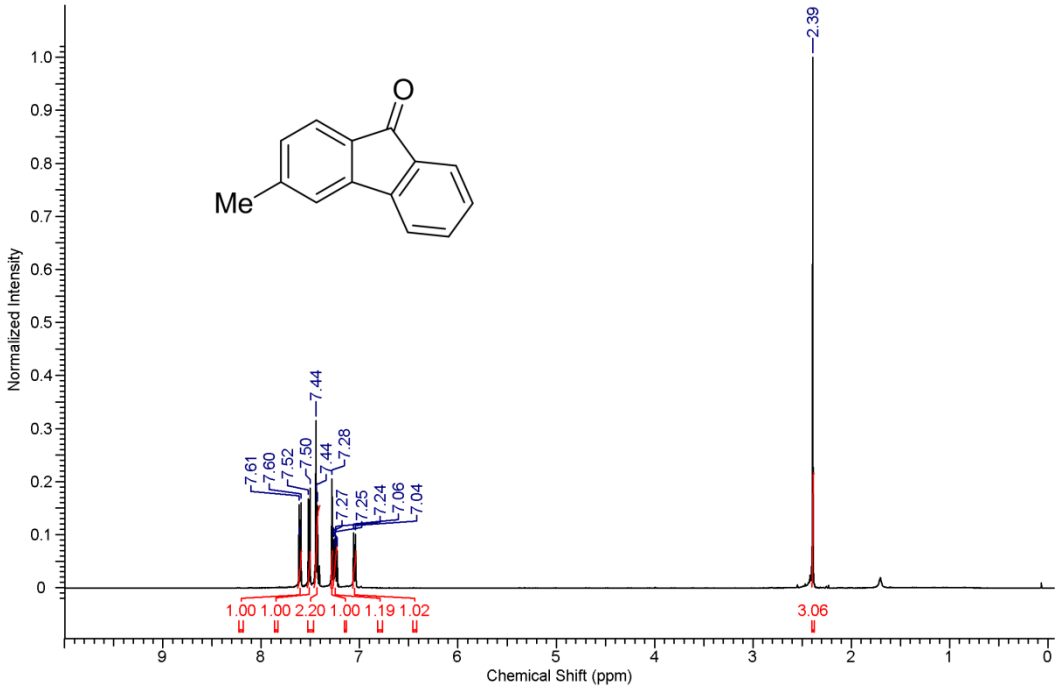


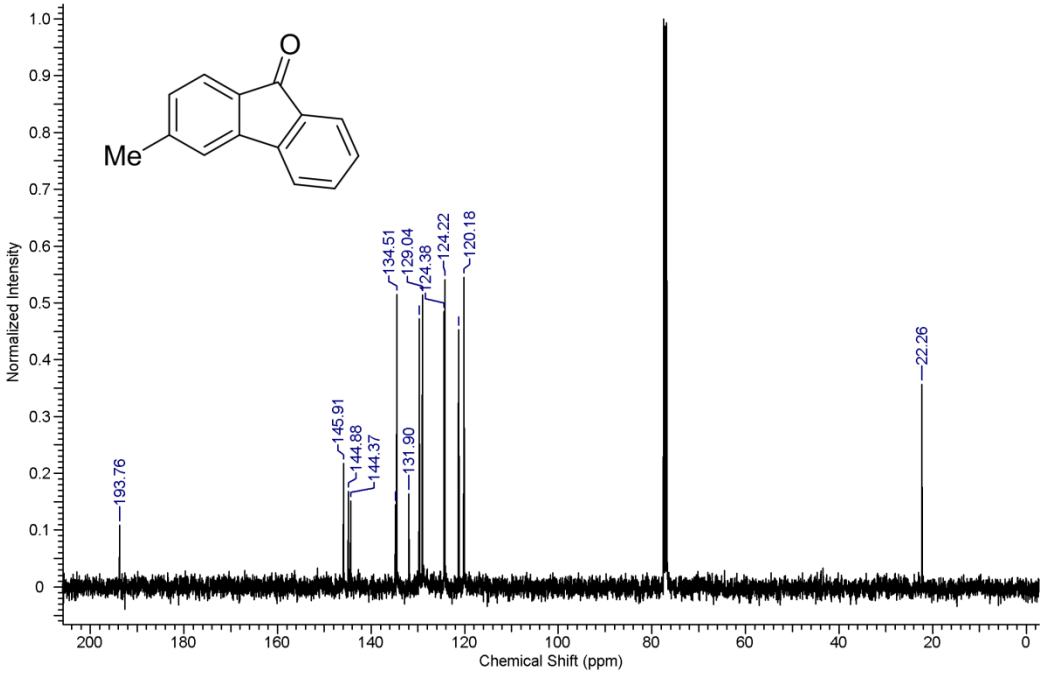
^{1}H and ^{13}C NMR Spectra of Compound **3t**



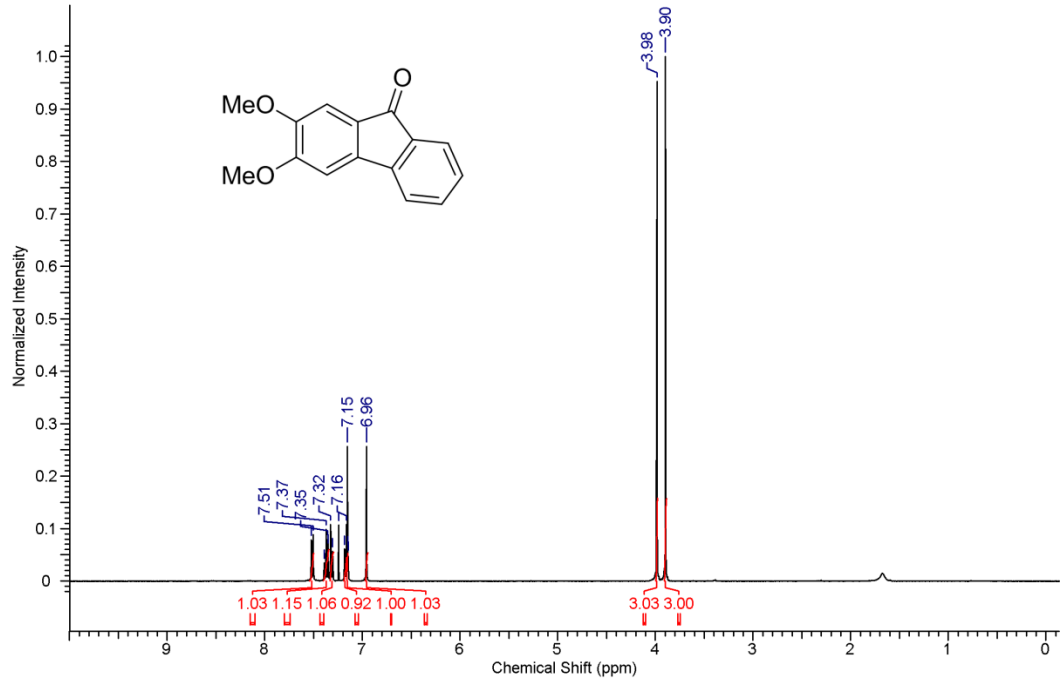


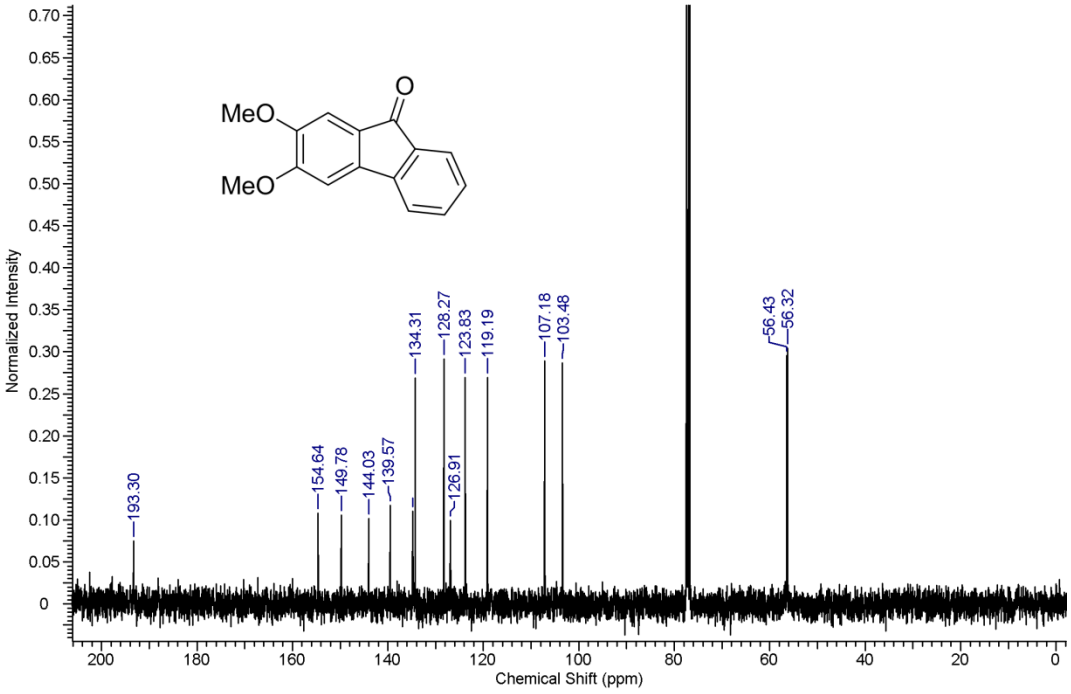
^{1}H and ^{13}C NMR Spectra of Compound **4a**





^{1}H and ^{13}C NMR Spectra of Compound **4d**



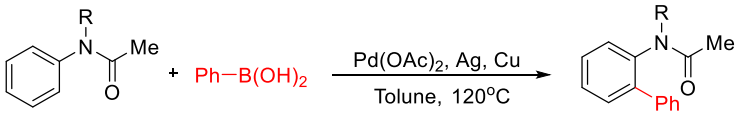


Section 4B: Ruthenium-Catalyzed *ortho*-Arylation of Acetanilides with Aromatic Boronic acids: An Easy Route to Phenanthridines and Carbazoles

4B.1 Introduction

ortho-Arylation of heteroatom substituted aromatics with aromatic electrophiles or organometallic reagents catalyzed by metal complexes via chelation-assisted C-H bond activation is one of the efficient method to synthesize biaryl derivatives.[1] Various chelating groups such as ketone, oxime, amide, acetamino (NH-COR), 2-pyridyl, cyano, ester, carboxylic acid and amine are efficiently used for the arylation reaction. Among them, acetamino (NH-COR) directed *ortho*-arylation of aromatics has gained much attention in organic synthesis.[2-3] Since, the derived *ortho*-arylated *N*-substituted anilines are key synthetic intermediates for various organic transformations and synthesizing heterocyclic moieties. Metal-catalyzed *ortho*-arylation of acetamino directed aromatics with aromatic electrophiles has been extensively studied in the literature.[2] However, in the reaction of symmetrical acetanilides with aromatic electrophiles, a mixture of *mono*- and *di*-arylated acetanilides were observed. The diarylated compounds cannot be suppressed in the reaction, but, it can be suppressed by doing arylation using aromatic organometallic reagents.[2-3] Aromatic boranes, aromatic stannenes and aromatic silanes are commonly used arylating agents in the coupling reaction. Among them, organoborane reagents display multifarious advantages and the observed boron-derived byproducts are not harmful unlike other organometallic reagents.[3]

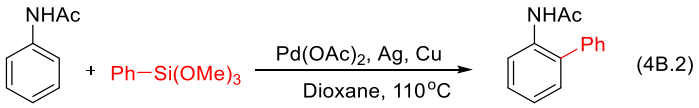
In 2007, Shi's group demonstrated *ortho*-arylation of acetanilides with aromatic boronic acids in the presence of palladium complex. In the reaction, *N*-substituted anilides (Ph-N*R*COR) showed good reactivity and selectivity. But, N-H free anilides (Ph-N*H*COR) showed poor reactivity and selectivity with the formation of *N*-arylated anilide as a major by-product (eq. 4B.1).[4a]



(4B.1)

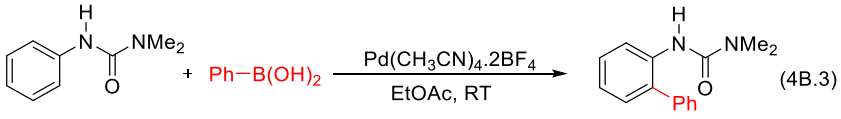
Subsequently, the same group has reported *ortho*-arylation of N-H free anilides (Ph-N*H*COR) with trialkoxy phenylsilanes in the presence of palladium complex. However, an excess amount

of oxidants such as AgF (2.0 equiv) and $Cu(OTf)_2$ (2.0 equiv) were used and the availability of trialkoxy phenylsilanes is also limited (eq. 4B.2).[4b]



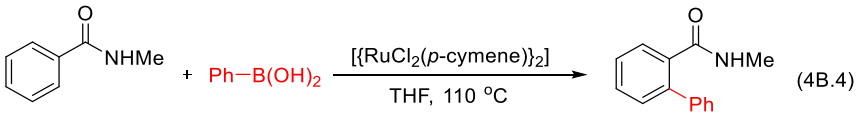
(4B.2)

Recently, Lipshutz's group reported *ortho*-arylation of aryl ureas (Ph-NH-$CONR_2$) with phenylboronic acids in the presence of a cationic palladium complex. However, in the reaction of symmetrical aryl ureas with aromatic boronic acids, a minor amount of *di*-arylated compounds were observed (eq. 4B.3).[4c]



(4B.3)

Owing to the extraordinary reactivity and selectivity, [{$RuCl_2$(*p*-cymene)}$_2$] complex has been efficiently used as a catalyst for various C-H bond functionalization reactions. Ru(II)-catalyzed arylation of 2-pyridyl, oxazoline, azole, amide and oxime substituted aromatics with aromatic electrophiles has been elaborately studied in the literature.[5] Very recently, we have reported a ruthenium-catalyzed *ortho*-arylation of benzamides with boronic acids (eq. 4B.4).[6a]



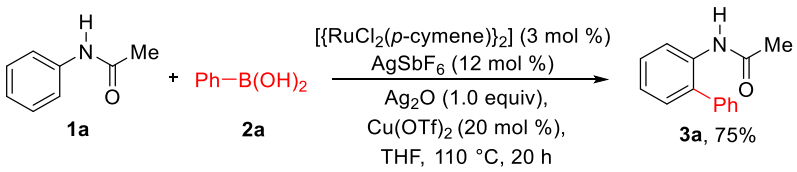
(4B.4)

In the reported ruthenium-catalyzed arylation reactions, directing groups having a better coordinating nitrogen atom such as 2-pyridyl, oxime, oxazoline, azole and amide are explored. But, directing groups having a less coordinating oxygen atom are not explored. Herein, we wish to statement a less coordination oxygen atom directed *ortho*-arylation of acetanilides with aromatic boronic acids in the presence of Ru(II) catalyst.

4B.2 Results and Discussion

The highly regioselective *ortho*-arylation of acetanilides with aromatic boronic acids in the presence of a Ru(II) complex (3 mol%), $AgSbF_6$ (12 mol%), $Cu(OTf)_2$ (20 mol%) and Ag_2O (1.0

equiv) is described. The catalytic reaction was compatible with various functional groups such as electron-rich, electron-deficient and halogen substituted aromatic anilides and aromatic boronic acids. In the reaction, no diarylated products or *N*-arylated acetanilides were observed. Further, *ortho*-arylated anilides were converted into useful heteroaromatics such as phenanthridine and carbazole derivatives by using Ph_3PO and Tf_2O or palladium catalyst.[7]



Treatment of acetanilide (1a) with phenylboronic acid (2a) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (12 mol %), Ag_2O (1.0 mmol) and $Cu(OTf)_2$ (20 mol %) in tetrahydrofuran (THF) at 110 °C for 20 h gave *ortho*-arylated anilide 3a in 75% isolated yield (eq. 4B.5). The catalytic reaction is highly selective, only *mono*-arylation product was observed.

4B.2.1 Optimization Studies

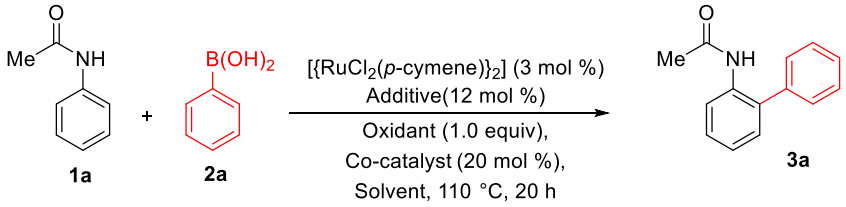


Table 4B.1 Ruthenium-catalyzed *ortho*-arylation of acetanilide (**1a**) with phenylboronic acid (**2a**).[a]

Entry	Solvent	Oxidant	Additive	co-catalyst	Yield[b]
1	THF	Ag_2O	$AgSbF_6$	--	71
2	MeOH	Ag_2O	$AgSbF_6$	--	nr
3	AcOH	Ag_2O	$AgSbF_6$	--	nr
4	Toluene	Ag_2O	$AgSbF_6$	--	nr
5	DCE	Ag_2O	$AgSbF_6$	--	nr
6	DME	Ag_2O	$AgSbF_6$	--	nr
7	DMF	Ag_2O	$AgSbF_6$	--	20

8	THF	AgOTf	$AgSbF_6$	--	15
9	THF	AgOAc	$AgSbF_6$	--	10
10	THF	AgF	$AgSbF_6$	--	5
11	THF	$K_2S_2O_8$	$AgSbF_6$	--	nr
12	THF	$(NH_4)_2S_2O_8$	$AgSbF_6$	--	nr
13	THF	Oxone	$AgSbF_6$	--	nr
14	THF	$Cu(OAc)_2$	$AgSbF_6$	--	nr
15	THF	Ag_2O	$AgBF_4$	--	60
16	THF	Ag_2O	AgOTf	--	55
17	THF	Ag_2O	KPF_6	--	nr
18	THF	Ag_2O	$AgSbF_6$	$Cu(OTf)_2$	82[c]
19	THF	Ag_2O	$AgSbF_6$	$Cu(OTf)_2$	83
20	THF	Ag_2O	--	$Cu(OTf)_2$	68

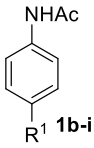
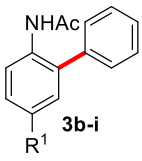
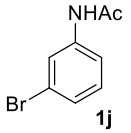
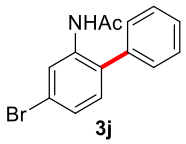
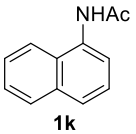
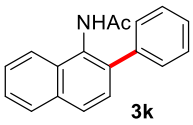
[a]All reactions were carried out with acetanilide (**1a)** (1.00 mmol), phenylboronic acid (**2a**) (1.50 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), oxidant (1.2 equiv), additive (12 mol %), co-catalyst (20 mol %) and solvent (3.0 mL) at 110 °C for 16 h. [b]Isolated yields. [c]$Cu(OTf)_2$ (1.0 equiv)

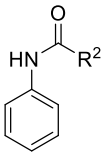
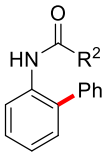
To optimize the arylation reaction, various additives, solvents and oxidants were examined in the reaction of **1a** with **2a** in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %) at 110 °C for 20 h. First, the catalytic reaction was tested with various solvents such as THF, MeOH, AcOH, Tolune, DCE, DME, and DMF in the presence of catalyst, $AgSbF_6$ (12 mol %) and Ag_2O (1.0 equiv) (Table 1). Among them, THF solvent was the best, providing coupling product **3a** in 71% GC yield (Table 4B.1, entry 1). DMF is less effective, providing couplind product **3a** in 20% yield (entry 7). The remaining solvents were totally ineffective (entry 2-6). Next, the catalytic reaction was tested with various oxidants such as Ag_2O, AgOTf, AgOAc, AgF, $K_2S_2O_8$, $(NH_4)_2S_2O_8$, Oxone and $Cu(OAc)_2$ (entry 8-14). Among them, Ag_2O was very effective, giving **3a** in 71% GC yield (entry 1). AgOTf, AgOAc and AgF were less effective, giving **3a** in 15, 10, and 5% GC yields, respectively (entry 8-10). Remaining oxidants were totally ineffective (entry

11-14). The catalytic reaction was studied with variety of additives such as $AgSbF_6$, $AgBF_4$, AgOTf and KPF_6 were also tested (entry 15-17). Among them, $AgSbF_6$ was very effective, giving **3a** in 71% GC yield (entry 1). $AgBF_4$ and AgOTf were moderately effective, giving **3a** in 60% and 55% GC yields, respectively (entry 15 and 16). But, KPF_6 was totally ineffective (entry 17). Further, the reaction was tested with 1.0 equiv and 20 mol % of $Cu(OTf)_2$. In the reaction, **3a** was observed 82 and 83% GC yields, respectively (entry 18 and 19). It is believed that $Cu(OTf)_2$ increases the rate of C-H bond activation and stabilizes the active catalyst. The catalytic reaction was also tested without $AgSbF_6$, only with Ag_2O (1.0 equiv) and $Cu(OTf)_2$ (20 mol %). In the reaction, 3a was observed in 68% GC yield (entry 20).

4B.2.2 *ortho*-Arylation of Acetanilides

Table 4B.2 *ortho*-Arylation of substituted acetanilides **1b**–**n** with phenylboronic acid (**2a**).[a]

Entry	Acetanilide (1b-n)	Compound (3b-n)	Yeild[b]
			
1	**1b**: R^1 = OMe	**3b**: R^1 = OMe	71%
2	**1c**: R^1 = Me	**3c**: R^1 = Me	73%
3	**1d**: R^1 = Br	**3d**: R^1 = Br	75%
4	**1e**: R^1 = Cl	**3e**: R^1 = Cl	76%
5	**1f**: R^1 = F	**3f**: R^1 = F	73%
6	**1g**: R^1 = CN	**3g**: R^1 = CN	68%
7	**1h**: R^1 = NO_2	**3h**: R^1 = NO_2	65%
8	**1i**: R^1 = CO_2Me	**3i**: R^1 = CO_2Me	70%
9			72%
10			76%

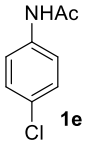
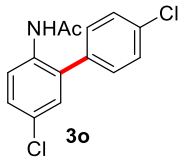
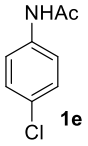
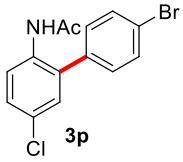
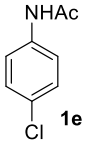
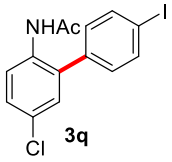
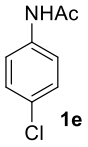
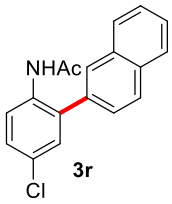
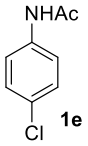
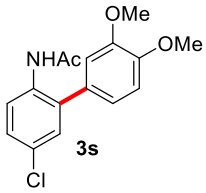
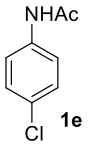
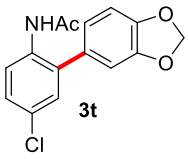
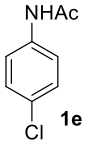
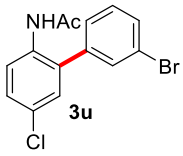
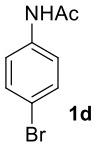
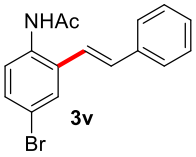
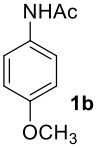
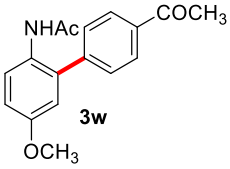
	 1l-n	 3l-n	
11	**1l**: R^2 = Et	**3l**: R^2 = Et	59
12	**1m**: R^2 = *tert*-Bu	**3m**: R^2 = *tert*-Bu	5
13	**1n**: R^2 = CF_3	**3n**: R^2 = CF_3	0

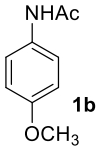
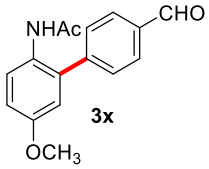
[a]All reactions were carried out with substituted acetanilides **1** (1.00 mmol), phenylboronic acids (**2**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3.0 mol %), $AgSbF_6$ (12 mol %), Ag_2O (1.0 equiv), and THF (3.0 mL) at 110 °C for 16 h. [b]Isolated yields.

To explore the scope of the arylation reaction, various substituted aromatic acetanilides **1b-n** were examined (Table 4B.2). Thus, electron-donating and halo groups such as 4-methoxy, 4-methyl, 4-bromo, 4-chloro and 4-fluoro substituted acetanilides **1b-f** reacted efficiently with phenylboronic acid (**2a**) providing *ortho*-arylated acetanilides **3b-f** in excellent to moderate 71%, 73%, 75%, 76% and 73% yields, respectively (entries 1-5). Interestingly, a less reactive electron-withdrawing groups such as 4-cyano, 4-nitro and 4-methylester substituted acetanilides **1g-i** also efficiently participated in the coupling reaction, giving arylated products **3g-i** in 68%, 65% and 70% yields, respectively (entries 6-8). It seems the catalytic reaction is insensitive to the electronic effect of acetanilides. Next, the reaction was tested with unsymmetrical acetanilides such as 3-bromoacetanilide (**1j**) and 2-napthylacetanilide (**1k**) with **2a**. In the reaction, coupling products **3j** and **3k** were observed in 72% and 76% yields, respectively (entries 9 and 10). In the reaction, there are two *ortho* C-H bonds for arylation. Regioselectively, arylation takes place at a sterically less hindered side. Meanwhile, the effect of changing substituent on the *N*-group of anilides such as Et, *tert*-Bu and CF_3 instead of methyl was studied (entries 11-13). Ethyl **1l** and *tert*-Bu **1m** substituted anilides reacted with **2a** giving products **3l** and **3m** in 59% and 5% yields, respectively. CF_3 substituted anilide **1n** was not effective for the reaction.

Table 4B.3 *ortho*-Arylation of substituted acetanilides **1** with substituted phenylboronic acids (**2**).[a]

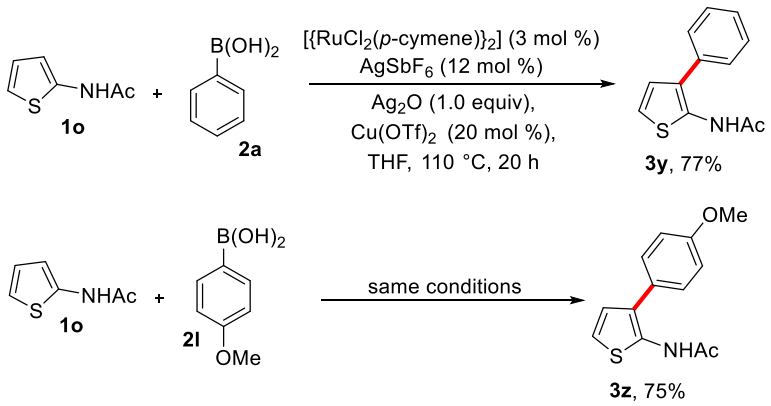
Entry	Acetanilide (**1**)	Compound (**3o-x**)	Yeild[b]

1	 **1e**	 **3o**	71%
2	 **1e**	 **3p**	73%
3	 **1e**	 **3q**	75%
4	 **1e**	 **3r**	74%
5	 **1e**	 **3s**	78%
6	 **1e**	 **3t**	72%
7	 **1e**	 **3u**	71%
8	 **1d**	 **3v**	73%
9	 **1b**	 **3w**	69%

10	 **1b**	 **3x**	62%

[a]All reactions were carried out with substituted acetanilides **1** (1.00 mmol), substituted phenylboronic acids (**2**) (1.20 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3.0 mol %), $AgSbF_6$ (12 mol %), Ag_2O (1.0 equiv), and THF (3.0 mL) at 110 °C for 16 h. [b]Isolated yields.

The present arylation reaction was successfully extended with substituted aromatic boronic acids **2b-l** (Table 4B.3). Halogen groups such as 4-chloro, 4-bromo and 4-iodo substituted phenylboronic acids **2b-d** underwent coupling with **1e** giving coupling products **3o-q** in 71%, 73%, 75% yields, respectively (entry 1-3). Nicely, sterically hindered 2-napthylboronic acid (**2e**), 3,4-dimethoxyphenylboronic acid (**2f**) and 3,4-(methylenedioxy)phenylboronic acid (**2g**) yielded products **3r-t** in excellent 74%, 78%, 72% yields, respectively (entry 4-6). 3-Bromophenylboronic acid (**2h**) was also nicely participated in the reaction, yielding product **3u** in 71% yields (entry 7). Further, the coupling of 4-vinylphenylboronic acid (**2i**) with **1d** was tested. However, in the reaction, a Heck-type alkenylation product **3v** in 73% yield with the cleavage of boronic acid was observed. Interestingly (enrty 8), electron-deficient 4-acetylphenylboronic acid (**2j**) and 4-formylphenylboronic acid (**2k**) also reacted efficiently with 4-methoxyacetanilide (**1b**) affording coupling products **3w** and **3x** in 69% and 62% yields, respectively (enrty 9 and 10). It is important to note that a very sensitive functional groups such as I, Br, Cl, OR, COMe and CHO substituted phenylboronic acids were compatible for the reaction.



Scheme 4B.1 Studies of the hetero aromatic anilides

The catalytic reaction was also tested with acetamino substituted heteroaromatic (Scheme 4B.1). Thus, thiophen-2-acetamine **1q** underwent coupling with **2a** or 4-methoxyphenylboronic acid (**2l)** yielding arylation products **3y** and **3z** in excellent 77% and 75% yields, respectively (Scheme 4B.1).

4B.2.3 Synthesis of Phananthridines and Carbazoles

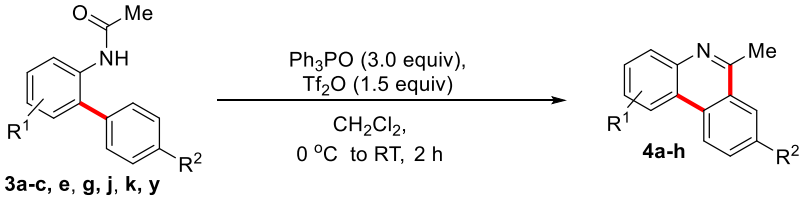
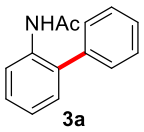
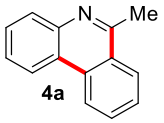
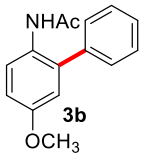
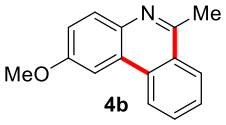
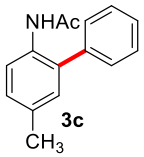
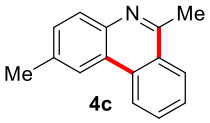
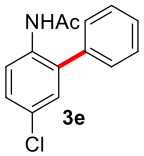
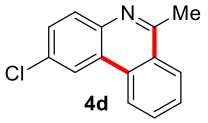
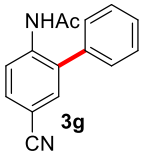
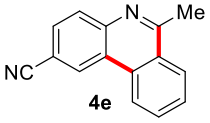
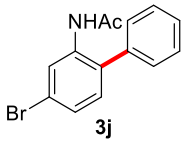
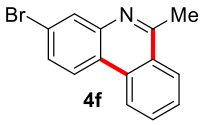
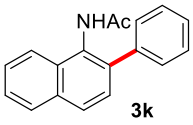
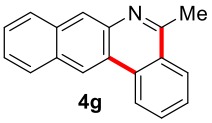
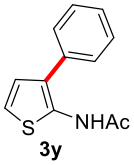
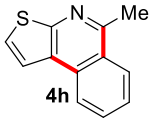
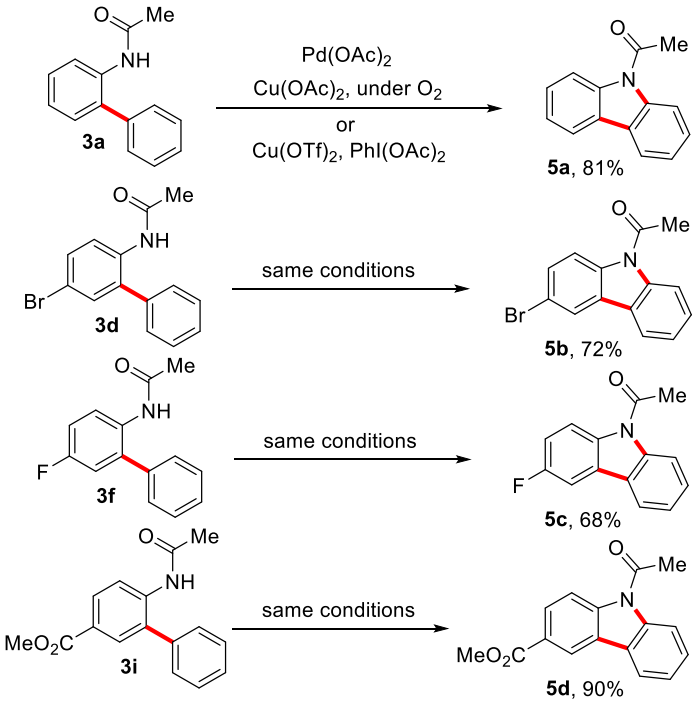


Table 4B.4 Synthesis of phenanthridines (**4**).[a]

Entry	Compound (**3**)	Compound (**4a-h**)	Yeild[b]
1			94%
2			96%
3			93%
4			92%
5			89%

6			97%
7			91%
8			89%

[a]All reactions were carried out with substituted *ortho*-arylated acetanilides **3** (1.00 mmol) triphenylphosphine oxide (3.0 equiv), Tf_2O (1.5 equiv) and Dichloromethane (3.0 mL) at 0 °C to RT for 2 h. [b]Isolated yields.



Scheme 4B.2 Synthesis of carbazoles

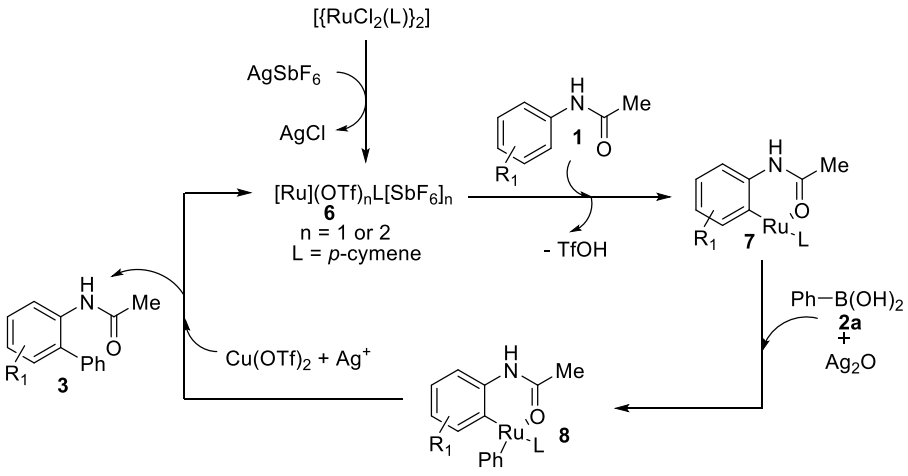
To show the synthetic utility of *ortho*-arylated acetanilides **3** in synthetic organic chemistry, we have tried intramolecular cyclization of *ortho*-arylated acetanilides **3** in the presence of Ph_3PO and Tf_2O (Table 4B.4).[7a] The intramolecular cyclization of **3a, 3b, 3c** and **3e** proceeded smoothly in the presence of Ph_3PO and Tf_2O in CH_2Cl_2 at 0 °C to r.t for 2 h, yielding phenanthridine derivatives **4a-d** in 94%, 96%, 93% and 92% yields, respectively (entry 1-4).

Similarly, **3g, 3j** and **3k** underwent intramolecular cyclization under similar reaction conditions, giving **4e-g** in 89%, 97% and 91% yields, respectively (entry 5-7). Nicely, *ortho* arylated thiophen-2-acetamine **3y** was also nicely participated in the reaction, giving product **4h** in excellent 89% yield (enty 8).

Meanwhile, *ortho*-arylated acetanilides **3a**, **3d**, **3f** and **3i** were converted into carbazole derivatives **5a-d** in 81%, 72%, 68% and 90% yields, respectively (Scheme 4B.2), in the presence $Pd(OAc)_2$ (5 mol %) and $Cu(OAc)_2$ (1.0 equiv) under O_2 or $Cu(OTf)_2$ (5 mol %) and $PhI(OAc)_2$ (1.5 equiv).[7b-c] It is important to note that phenanthridine and carbazole scaffolds present in natural products and biologically active molecules.[7a-c]

4B.2.4 Mechanism

On the basis of known metal-catalyzed C-H bond activation reactins, a plausible reaction mechanism is proposed in Scheme 4B.3. The first step likely involves the removal of Cl ligand from Ru catalyst by $AgSbF_6$ providing a cationic ruthenium complex **6**. Coordination of the carbonyl oxygen of acetanilide **1** to the cationic ruthenium complex followed by *ortho*-metalation gives a ruthenacycle intermediate **7**. Transmetallation of phenylboronic acid (**2a**) into intermediate **7** in the presence of base AgO^- provides intermediate **8**. Reductive elimination of intermediate **8** in the presence of $Cu(OTf)_2$ and Ag^+ affords product **3** and regenerates the active ruthenium species. In the reaction, Ag_2O acts as a oxidant to oxidize the catalyst from Ru(0) to Ru(II) and base to cleave boronic acid moiety of **2**. It is believed that $Cu(OTf)_2$ plays an important role to regenerate the active catalyst in the presence of oxidant Ag^+.



Scheme 4B.3 Proposed mechanism

4B.3 Conclusions

In conclusion, we have described The highly regioselective *ortho*-arylation of acetanilides with aromatic boronic acids in the presence of Ru(II) complex (3 mol %), $AgSbF_6$ (12 mol %), $Cu(OTf)_2$ (20 mol %) and Ag_2O (1.0 eq) is described. Later, *ortho*-arylated acetanilides were converted into phenanthridine and carbazole derivatives by using Ph_3PO and Tf_2O or palladium or $Cu(OTf)_2$ catalyst.

4B.4 References

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4B.5 Experimental Section

4B.5.1 General Procedure for the Coupling of Acetanilides 1 with Aromaticboronic acids 2 Catalyzed by Ruthenium Complex

A 15-mL pressure tube equipped with a magnetic stirrer and septum containing acetanilide (**1**) (100 mg, if it is solid), [{$RuCl_2$(*p*-cymene)}$_2$] (0.03 equiv), Ag_2O (1.0 equiv), $Cu(OTf)_2$ (0.20 equiv) and aromaticboronic acid **2** (1.5 equiv) was evacuated and purged with nitrogen gas three times. To the tube was added $AgSbF_6$ (0.12 mmol inside the glove box. Then, dry THF (3.0 mL) was added in the tube via syringe (If the acetanilide (**1**) is liquid, 100 mg of acetanilide (**1**) was dissolved in the dry THF (3.0 mL) and added to the tube via syringe). Then, the pressure tube

was covered with a screw cap and the reaction mixture was allowed to stir at 110 °C for 20 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3**.

Note: The reaction is moisture sensitive. Dry THF should be used in order to get good conversation.

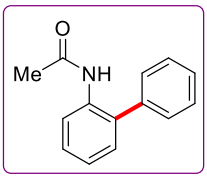
4B.5.2 General Procedure for the Preparation of Phenanthridines

Note: For Phenanthridines synthesis, crude product **3** was taken directly without column purification. In the reaction, pure as well as crude product **3** worked equally.

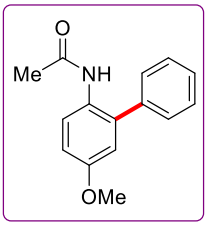
To a solution of Ph_3PO (3.0 equiv) in dry CH_2Cl_2 (5.0 mL), was added Tf_2O (1.5 equiv) under the nitrogen atmosphere at 0 ^oC. After 15 min, the above crude arylated anilides **3** (1.00 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and added to the solution via syringe. The reaction was then warmed to r.t. and stirred until the complete completion (approx. 3 h). After completion, the reaction mixture was quenched by addition of sat. aq. $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were washed with brine, dried anhydrous Na_2SO_4 and concentrated it under the reduced pressure. The crude product was purified by column chromatography on silica gel using a mixture of hexanes and EtOAc as eluent to afford phenanthridine derivatives **4**.

4B.5.3 Spectral Data of Compounds 3a-z, 4a-h and 5a-d

***N*-([1,1'-biphenyl]-2-yl)acetamide (3a):** Colorless solid; m.p. 184-186 °C, Rf value: 0.3 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.26 (d, *J* = 8.0 Hz, 1 H), 7.49 (t, *J* = 8.0 Hz, 2 H), 7.44 – 7.35 (m, 4 H), 7.25 (d, *J* = 8.0, Hz, 1 H), 7.18 (t, *J* = 8.0, Hz, 1 H), 7.14 (bs, 1 H), 2.02 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):**δ 168.2, 138.1, 134.6, 132.1, 130.0, 129.2, 129.1, 128.4, 127.9, 124.3, 121.6, 24.6. **HRMS (ESI):** calc. for [($C_{14}H_{13}NO$)H] (M+H) 212.1075, measured 212.1073.

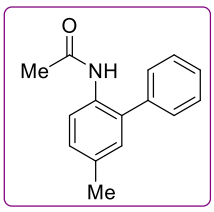


***N*-(5-Methoxy-[1,1'-biphenyl]-2-yl)acetamide** (**3b**): Colorless solid; m.p. 164-166 °C, Rf value: 0.33 in 50% ethyl acetate in hexanes; eluent (50% ethyl acetate in hexanes). **^{1}H NMR**

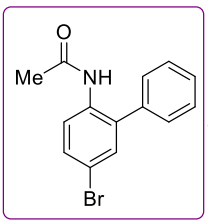


($CDCl_3$, 400 MHz): δ 8.00 (d, *J* = 8.0 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0, Hz, 2 H), 6.98 (bs, 1 H), 6.91 (dd, *J* = 8.0, 4.0, Hz, 1 H), 6.81 (s, 1 H), 3.81 (s, 3 H), 2.00 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):**δ 168.4, 156.4, 138.2, 134.7, 129.0, 128.9, 127.9, 127.6, 124.3, 115.4, 113.4, 55.5, 24.2. **HRMS (ESI):** calc. for [($C_{15}H_{15}NO_2$)H] (M+H) 242.1181, measured 242.1184.

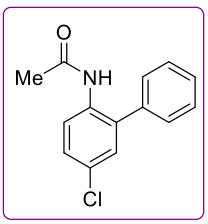
***N*-(5-Methyl-[1,1'-biphenyl]-2-yl)acetamide (3c):** Colorless solid; m.p. 230-232 °C, Rf value: 0.33 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.09 (d, *J* = 8.0 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0, Hz, 2 H), 7.18 (d, *J* = 8.0, Hz, 1 H), 7.07 (s, 2 H), 2.36 (s, 3 H), 2.02 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):**δ 168.3, 138.3, 134.1, 132.5, 132.0, 130.6, 129.1, 128.9, 128.9, 127.8, 122.0, 24.4, 20.8. **HRMS (ESI):** calc. for [($C_{15}H_{15}NO$)H] (M+H) 226.1232, measured 226.1235.



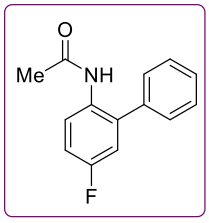
***N*-(5-Bromo-[1,1'-biphenyl]-2-yl)acetamide** (**3d**): Colorless solid; m.p. 155-157 °C, Rf value: 0.34 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.16 (d, *J* = 8.0 Hz, 1 H).7.48 – 7.40 (m, 4 H), 7.34 – 7.30 (m, 3 H), 7.08 (bs, 1 H), 1.97 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 168.2, 136.6, 133.8, 132.6, 131.2, 129.2, 129.0, 128.5, 122.9, 116.9, 24.6. **HRMS (ESI):** calc. for [($C_{14}H_{12}BrNO$)H] (M+H) 290.0181, measured 290.0182.



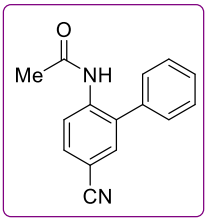
***N*-(5-Chloro-[1,1'-biphenyl]-2-yl)acetamide** (**3e**): Colorless solid; m.p. 191-193 °C, Rf value: 0.33 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.25 (d, *J* = 8.0 Hz, 1 H), 7.53 – 7.45 (m, 3 H), 7.37 – 7.32 (m, 3 H), 7.24 (s, 1 H), 7.11 (bs, 1 H), 2.02 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 168.2, 136.8, 133.6, 133.3, 129.8, 129.3, 129.0, 128.5, 128.2, 127.6, 122.7, 24.6. **HRMS (ESI):** calc. for [($C_{14}H_{12}ClNO$)H] (M+H) 246.0686, measured 246.0681.



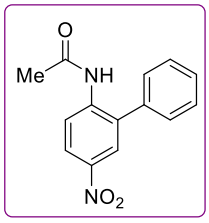
***N*-(5-Fluoro-[1,1'-biphenyl]-2-yl)acetamide** (**3f**): Colorless solid; m.p. 225-227 °C, Rf value: 0.29 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$,**



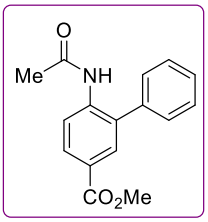
400 MHz): δ 8.14 (s, 1 H), 7.52 – 7.42 (m, 3 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.06 (t, *J* = 8.0 Hz, 2 H), 7.36 (dd, *J* = 8.0, 4.0 Hz, 1 H), 2.02 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 160.4, 158.0, 137.1, 130.7, 129.1, 129.0, 128.3, 124.1, 124.0 (due to F-coupling), 116.7 and 116.5 (due to F-coupling), 114.9 and 114.7 (due to F-coupling), 24.4. **HRMS (ESI):** calc. for [($C_{14}H_{12}FNO$)H] (M+H) 230.0981, measured 230.0980.

***N*-(5-Cyano-[1,1'-biphenyl]-2-yl)acetamide** (**3g**): Colorless solid; Rf value: 0.25 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). 

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.57 (d, *J* = 8.0 Hz 1 H), 7.65 (d, *J* = 8.0 Hz 1 H), 7.57 – 7.50 (m, 4 H), 8.35 (d, *J* = 8.0 Hz 3 H), 2.06 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 168.4, 138.9, 135.6, 133.7, 132.5, 131.9, 129.6, 129.0, 128.9, 120.7, 118.7, 107.0, 24.7. HRMS (ESI): calc. for [($C_{15}H_{12}N_2O$)H] (M+H) 237.1028, measured 237.1025.

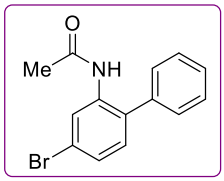
***N*-(5-Nitro-[1,1'-biphenyl]-2-yl)acetamide** (**3h**): Colorless solid; Rf value: 0.3 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). 

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.65 (d, *J* = 8.0 Hz 1 H). 8.24 (dd, *J* = 8.0, 4.0 Hz, 1 H), 8.14 (s, 1 H), 7.59 – 7.52 (m, 3 H), 7.46 (bs, 1 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 2.08. (s, 3 H), **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 168.4, 148.6, 141.3, 141.0, 137.9, 130.2, 129.1, 129.0, 128.5, 125.1, 122.4, 26.8. **HRMS (ESI):** calc. for [($C_{14}H_{12}N_2O_3$)H] (M+H) 257.0926, measured 257.0924.

Methyl 6-acetamido-[1,1'-biphenyl]-3-carboxylate. (3i): Colorless solid; Rf value: 0.2 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). 

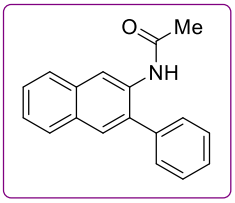
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (d, *J* = 8.0 Hz 1 H), 8.03 (dd, *J* = 8.0, 4.0 Hz 1 H), 7.92 (s, 1 H), 7.54 (t, *J* = 8.0 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz 1 H), 8.49 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.36 (bs, 1 H), 3.90 (s, 3 H), 2.05 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 168.3, 166.5, 138.9, 137.0, 131.5, 131.1, 130.0, 129.6, 129.2, 128.5, 135.3, 120.0, 52.0, 24.8. **HRMS (ESI):** calc. for [($C_{16}H_{15}NO_3$)H] (M+H) 270.1130, measured 270.1133.

***N*-(4-Bromo-[1,1'-biphenyl]-2-yl)acetamide** (**3j**): Colorless solid; Rf value: 0.33 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.53

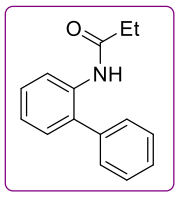


(s, 1 H), 7.50 (t, *J* = 8.0 Hz, 2 H), 7.44 (t, *J* = 8.0 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0, Hz, 1 H), 7.17 (s, 1 H), 7.10 (d, *J* = 8.0, Hz, 1 H), 2.02 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 168.2, 137.0, 135.8, 131.1, 130.6, 129.2, 129.0, 128.3, 127.2, 124.0, 122.0, 24.6. **HRMS (ESI):** calc. for [($C_{14}H_{12}BrNO$)H] (M+H) 290.0181, measured 290.0182.

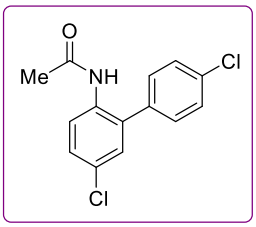
***N*-(3-Phenylnaphthalen-2-yl)acetamide** (**3k**): Colorless solid; Rf value: 0.34 in 25% ethyl acetate in hexanes; eluent (25% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.84 (s, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.72 (s, 1 H), 7.56 – 7.41 (m, 7 H), 7.30 (bs, 1 H), 2.07 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 168.3, 137.9, 133.6, 132.5, 132.0, 130.2, 129.4, 129.1, 128.2, 127.7, 127.4, 126.5, 125.4, 118.0, 24.8. **HRMS (ESI):** calc. for [($C_{18}H_{15}NO$)H] (M+H) 262.1232, measured 262.1230.



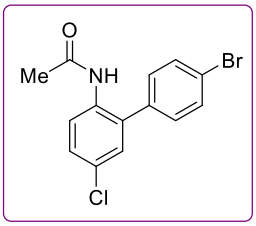
***N*-([1,1'-biphenyl]-2-yl)propionamide** (**3l**): Colorless solid; Rf value: 0.3 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.32 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 8.0, 4.0 Hz, 2 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.39-7.35 (m, 3 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 7.20-7.16 (m, 2 H), 2.24 (q, *J* = 8.0 Hz, 2 H), 1.12 (t, *J* = 8.0 Hz, 3 H) **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 171.8, 138.1, 134.7, 132.0, 129.9, 129.2, 129.0, 128.4, 127.9, 124.1, 121.4, 30.8, 9.5. **HRMS (ESI):** calc. for [($C_{15}H_{15}NO$)H] (M+H) 226.1232, measured 226.1233.



***N*-(4',5-Dichloro-[1,1'-biphenyl]-2-yl)acetamide** (**3o**): Colorless solid; Rf value: 0.33 in 30% ethyl acetate in hexanes; (30% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.19 (d, *J* = 8.0 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.21 (s, 1 H), 6.98 (bs, 1 H), 2.01 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 168.3, 135.3, 134.7, 133.2, 132.7, 130.4, 129.7, 129.5, 128.6, 123.4, 24.5. **HRMS (ESI):** calc. for [($C_{14}H_{11}Cl_2NO$)H] (M+H) 280.0296, measured 280.0293.

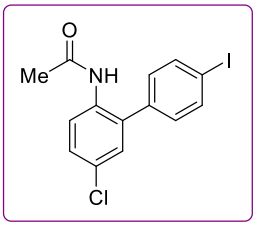


***N*-(4'-Bromo-5-chloro-[1,1'-biphenyl]-2-yl)acetamide** (**3p**): Colorless solid; Rf value: 0.34 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.14 (d, *J* = 8.0 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.33 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.23

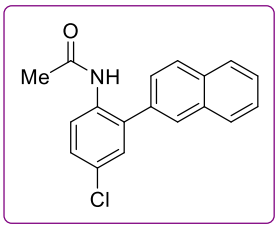


(d, *J* = 8.0 Hz, 2 H), 7.20 (s, 1 H), 7.03 (bs, 1 H), 2.03 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 168.3, 135.7, 133.1, 132.8, 132.4, 130.6, 129.6, 128.6, 123.5, 122.8, 24.4. **HRMS (ESI):** calc. for [($C_{14}H_{11}ClBrNO$)H] (M+H) 323.9791, measured 323.9794.

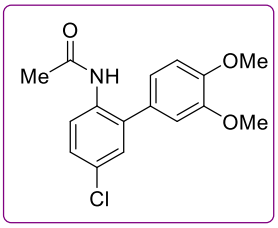
***N*-(5-Chloro-4'-iodo-[1,1'-biphenyl]-2-yl)acetamide** (**3q**): Colorless solid; Rf value: 0.35 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 8.15 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 2 H), 7.33 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.20 (s, 1 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 7.01 (bs, 1 H), 2.04 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 168.3, 138.6, 136.3, 133.1, 132.8, 130.8, 129.6, 129.5, 128.6, 123.5, 94.5, 24.5. **HRMS (ESI):** calc. for [($C_{14}H_{11}ClINO$)H] (M+H) 371.9652, measured 371.9651.

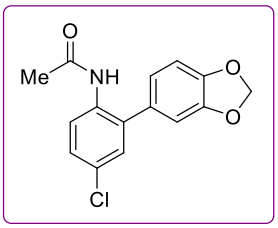


***N*-(4-Chloro-2-(naphthalen-2-yl)phenyl)acetamide** (**3r**): Colorless solid; Rf value: 0.39 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 8.27 (d, *J* = 8.0 Hz, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 7.94 – 7.88 (m, 2 H), 7.84 (s, 1 H), 7.60 – 7.57 (m, 2 H),7.45 (d, *J* = 8.0, Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.34 (s, 1 H), 7.18 (bs, 1 H), 1.98 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 168.3, 134.2, 133.6, 133.5, 133.4, 132.1, 129.9, 129.3, 129.0, 128.34, 128.32, 128.0, 127.8, 126.9, 126.8, 126.5, 122.9, 24.5. **HRMS (ESI):** calc. for [($C_{18}H_{14}ClNO$)H] (M+H) 296.0842, measured 296.0842.

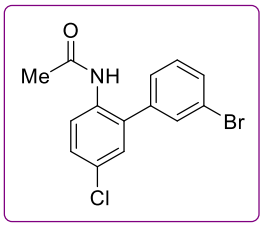


***N*-(5-Chloro-3',4'-dimethoxy-[1,1'-biphenyl]-2-yl)acetamide.(3s**): Colorless solid; Rf value: 0.35 in 50% ethyl acetate in hexanes; eluent (50% ethyl acetate in hexanes). **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 8.34 (d, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.21 (s, 2 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.83 (s, 1 H), 3.94 (s, 3 H), 3.89 (s, 3 H), 2.03 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 173.2, 168.1, 149.4, 149.0, 133.5, 129.7, 129.1, 129.0, 127.9, 122.5, 121.2, 112.0, 111.5, 55.97, 55.91, 24.6. **HRMS (ESI):** calc. for [($C_{16}H_{16}ClNO_3$)H] (M+H) 306.0897, measured 306.0894.

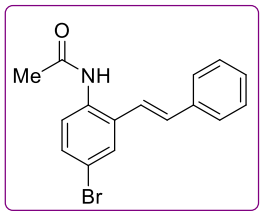


***N*-(2-(Benzo[*d*][1,3]dioxol-5-yl)-4-chlorophenyl)acetamide** (**3t**): Colorless solid; Rf value: 0.37 in 50% ethyl acetate in hexanes; eluent (50% ethyl acetate in hexanes). 

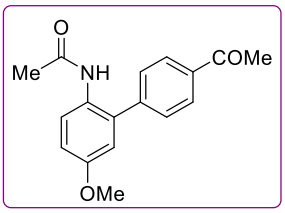
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, *J* = 8.0 Hz, 1 H), 7.26 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.16 (s, 2 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.77 (s, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.01 (s, 2 H), 2.01 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 168.2, 148.3, 147.7, 133.4, 130.3, 129.8, 129.1, 128.0, 122.7, 122.5, 120.9, 109.4, 108.9, 101.4, 24.5. **HRMS (ESI):** calc. for [($C_{15}H_{12}ClNO_3$)H] (M+H) 290.0584, measured 290.0583.

***N*-(3'-Bromo-5-chloro-[1,1'-biphenyl]-2-yl)acetamide** (**3u**): Colorless solid; Rf value: 0.34 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). 

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, *J* = 8.0 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.52 (s, 1 H), 7.39 – 7.28 (m, 3 H), 7.22 (s, 1 H), 7.05 (bs, 1 H), 2.04 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 168.3, 138.9, 133.1, 132.5, 132.1, 131.5, 130.6, 129.6, 128.7, 127.5, 123.6, 123.3, 24.4. **HRMS (ESI):** calc. for [($C_{14}H_{11}BrClNO$)H] (M+H) 323.9791, measured 323.9790.

(*E*)-*N*-(4-bromo-2-styrylphenyl)acetamide (**3v**): Colorless solid; Rf value: 0.35 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). 

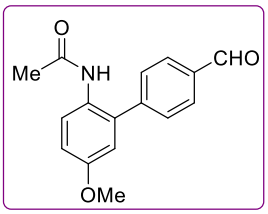
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, *J* = 8.0 Hz, 1 H), 7.64 (s, 1 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 7.41 – 7.31 (m, 5 H), 7.33 (dd, *J* = 16.0, 8.0 Hz, 2 H), 2.19 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 168.7, 136.4, 133.6, 132.2, 130.9, 129.4, 128.8, 128.5, 126.8, 125.8, 121.9, 118.7, 24.2. **HRMS (ESI):** calc. for [($C_{16}H_{14}BrNO$)H] (M+H) 316.0337, measured 316.0338.

***N*-(4'-acetyl-5-methoxy-[1,1'-biphenyl]-2-yl)acetamide**(**3w**): Colorless solid; Rf value: 0.29 in 50% ethyl acetate in hexanes; eluent (50% ethyl acetate in hexanes). 

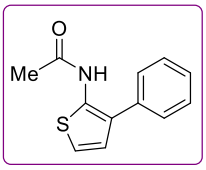
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, *J* = 8.0 Hz, 2 H), 7.88 (d, *J* = 8.0, Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 2 H), 6.95 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.94 (bs, 1 H), 6.81 (s, 1 H), 3.82 (s, 3 H), 2.65 (s, 3 H), 2.02 (s, 3 H). **^{13}C**

NMR (DMSO-d_6, 100 MHz): δ 197.7, 168.9, 157.4, 143.9, 137.7, 135.5, 129.5, 128.9, 128.2, 127.7, 114.8, 113.9, 55.4, 26.8, 22.8. **HRMS (ESI):** calc. for [($C_{17}H_{17}NO_3$)H] (M+H) 284.1287, measured 284.1287.

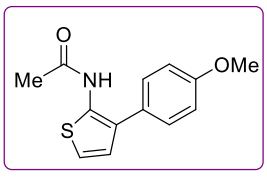
***N*-(4'-formyl-5-methoxy-[1,1'-biphenyl]-2-yl)acetamide** (**3x**): Colorless semisolid; Rf value: 0.28 in 50% ethyl acetate in hexanes; eluent (50% ethyl acetate in hexanes). **^{1}H NMR (DMSO-d_6, 400 MHz):** δ 10.05 (s, 1 H), 9.30 (s, 1 H), 7.96 (d, *J* = 8.0 Hz, 2 H), 7.61 (d, *J* = 8.0, Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 6.98 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.93 (s, 1 H), 3.79 (s, 3 H), 1.84 (s, 3 H). **^{13}C NMR (DMSO-d_6, 100 MHz):** δ 192.9, 168.9, 157.4, 145.4, 137.6, 134.9, 129.5, 129.4, 127.8, 120.6, 114.8, 114.2, 55.4, 22.8. **HRMS (ESI):** calc. for [($C_{16}H_{15}NO_3$)H] (M+H) 270.1130, measured 270.1132.



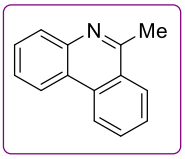
***N*-(3-Phenylthiophen-2-yl)acetamide** (**3y**): Colorless solid; Rf value: 0.32 in 25% ethyl acetate in hexanes; eluent (25% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.96 (bs, 1 H), 7.49 (t, *J* = 8.0, Hz, 2 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.38 (t, *J* = 8.0, Hz, 1 H), 6.96 – 6.92 (m, 2 H), 2.16 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 166.5, 135.2, 133.4, 129.4, 128.3, 127.4, 126.0, 125.7, 117.8, 23.3. **HRMS (ESI):** calc. for [($C_{12}H_{11}NOS$)H] (M+H) 218.0640, measured 218.0634.



***N*-(3-(4-methoxyphenyl)thiophen-2-yl)acetamide** (**3z**): Colorless solid; Rf value: 0.35 in 30% ethyl acetate in hexanes; eluent (30% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.85 (bs, 1 H), 7.73 (d, *J* = 8.0, Hz, 2 H), 7.02 (d, *J* = 8.0, Hz, 2 H), 6.94 (d, *J* = 8.0, Hz, 1 H), 6.89 (d, *J* = 8.0, Hz, 1 H), 3.87 (s, 3 H), 2.16 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 166.5, 158.9, 132.9, 129.5, 127.5, 125.8, 125.8, 117.6, 114.8, 55.4, 23.4. **HRMS (ESI):** calc. for [($C_{13}H_{13}NO_2S$)H] (M+H) 248.0745, measured 248.0744.

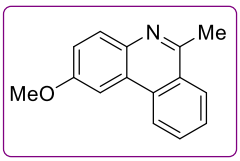


6-Methylphenanthridine (**4a**): Colorless solid; m.p. 185-187 °C, Rf value: 0.4 in 10% ethyl acetate in hexanes; eluent (10% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz): δ):** 8.62 (d, *J* = 8.0 Hz, 1 H), 8.54 (d, *J* = 8.0 Hz, 1 H), 8.22 (d, *J* = 8.0 Hz, 1 H), 8.13 (d, *J* = 8.0 Hz, 1 H), 7.85 (t, *J* = 8.0 Hz, 1 H), 7.74 – 7.68 (m, 2 H), 7.63 (t, *J* = 8.0 Hz, 1 H), 3.06 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 158.9, 143.4,



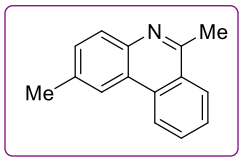
132.5, 130.6, 129.1, 128.7, 127.3, 126.6, 126.4, 125.8, 123.7, 122.3, 121.9, 23.2. **HRMS (ESI):** calc. for [($C_{14}H_{11}N$)H] (M+H) 194.0970, measured 194.0972.

2-Methoxy-6-methylphenanthridine (**4b**): Colorless solid; m.p. 205-207 °C, Rf value: 0.36 in



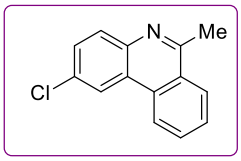
15% ethyl acetate in hexanes; eluent (15% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.56 (d, *J* = 8.0 Hz, 1 H), 8.22 (d, *J* = 8.0 Hz, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.87 (s, 1 H), 7.85 (t, *J* = 8.0 Hz, 1 H), 7.71 (t, *J* = 8.0 Hz, 1 H), 7.35 (dd, *J* = 8.0, 4.0 Hz, 1 H), 4.02 (s, 3 H), 3.06 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz)**: δ 158.1, 156.2, 137.9, 132.2, 130.6, 130.1, 127.6, 126.7, 125.8, 124.8, 122.4, 118.5, 103.1, 55.6, 22.6. **HRMS (ESI):** calc. for [($C_{15}H_{13}NO$)H] (M+H) 224.1075, measured 224.1081.

2,6-Dimethylphenanthridine (**4c**): Colorless solid; Rf value: 0.4 in 10% ethyl acetate in



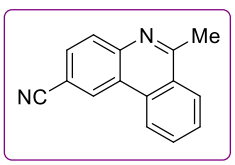
hexanes; eluent (10% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.60 (d, *J* = 8.0 Hz, 1 H), 8.30 (s, 1 H), 8.19 (d, *J* = 8.0 Hz, 1 H), 8.00 (d, *J* = 8.0 Hz, 1 H), 7.81 (t, *J* = 8.0 Hz, 1 H), 7.67 (t, *J* = 8.0 Hz, 1 H), 7.53 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.03 (s, 3 H), 2.61 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 157.7, 141.8, 136.0, 132.25, 130.24, 130.2, 128.9, 127.0, 126.4, 125.7, 123.5, 122.2, 121.5, 23.2, 21.8. **HRMS (ESI):** calc. for [($C_{15}H_{13}N$)H] (M+H) 208.1126, measured 208.1128.

2-Chloro-6-methylphenanthridine(**4d**): Colorless solid; Rf value: 0.39 in 10% ethyl acetate in



hexanes; eluent (10% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.53 (d, *J* = 8.0 Hz, 1 H), 8.47 (s, 1 H), 8.23 (d, *J* = 8.0 Hz, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 7.87 (t, *J* = 8.0 Hz, 1 H), 7.74 (t, *J* = 8.0 Hz, 1 H), 7.64 (dd, *J* = 8.0, 4.0, Hz, 1 H), 3.04 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 159.2, 141.8, 132.2, 131.5, 130.8, 130.6, 129.1, 128.0, 126.6, 125.9, 124.8, 122.3, 121.6, 23.23. **HRMS (ESI)**: calc. for [($C_{14}H_{10}ClN$)H] (M+H) 228.0580, measured 228.0584.

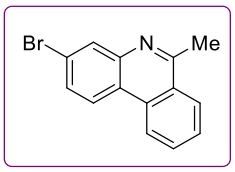
6-methylphenanthridine-2-carbonitrile (**4e**): Colorless solid; Rf value: 0.34 in 10% ethyl



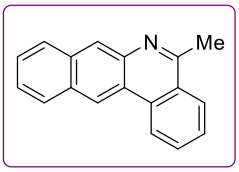
acetate in hexanes; eluent (10% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.87 (s, 1 H), 8.59 (d, *J* = 8.0 Hz, 1 H), 8.29 (d, *J* = 8.0 Hz, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 7.94 (t, *J* = 8.0 Hz, 1 H), 7.90 (dd, *J* = 8.0, 4.0 Hz, 1

H), 7.81 (t, *J* = 8.0 Hz, 1 H), 3.09 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):**δ 162.5, 145.4, 131.5, 131.4, 130.6, 130.3, 128.7, 127.7, 126.9, 126.2, 123.9, 122.3, 119.2, 109.7, 23.6. **HRMS (ESI):** calc. for [($C_{15}H_{10}N_2$)H] (M+H) 219.0922, measured 219.0923.

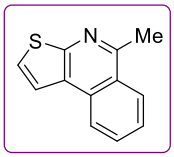
3-Bromo-6-methylphenanthridine (**4f**): Colorless solid; Rf value: 0.4 in 10% ethyl acetate in hexanes; eluent (10% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.57 (d, *J* = 8.0 Hz, 1 H), 8.37 (dd, *J* = 8.0, 4.0 Hz, 1 H), 8.29 (s, 1 H), 8.23 (d, *J* = 8.0 Hz, 1 H), 7.87 (t, *J* = 8.0 Hz, 1 H), 7.76 - 7.69 (m, 2 H), 3.05 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):**δ 160.3, 144.3, 132.2, 131.6, 131.0, 129.6, 127.8, 126.7, 125.8, 123.4, 122.6, 122.3, 122.2, 23.2. **HRMS (ESI):** calc. for [($C_{14}H_{10}BrN$)H] (M+H) 272.0075, measured 272.0078.



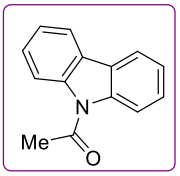
5-Methylbenzo[b]phenanthridine (**4g**): Colorless solid; Rf value: 0.42 in 10% ethyl acetate in hexanes; eluent (10% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.99 (s, 1 H), 8.75 (d, *J* = 8.0 Hz, 1 H), 8.58 (s, 1 H), 8.18 (d, *J* = 8.0 Hz, 1 H), 8.11 – 8.08 (m, 2 H), 7.86 (t, *J* = 8.0 Hz, 1 H), 7.70 (t, *J* = 8.0 Hz, 1 H), 7.58 – 7.56 (m, 2 H), 3.04 (s, 3 H) **^{13}C NMR ($CDCl_3$, 100 MHz):**δ 159.7, 141.2, 133.3, 132.5, 131.5, 130.7, 128.2, 128.1, 127.7, 127.0, 126.7, 126.0, 125.9, 123.0, 122.5, 121.0, 23.7. **HRMS (ESI):** calc. for [($C_{18}H_{13}N$)H] (M+H) 244.1126, measured 244.1125.

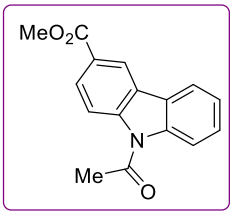


5-Methylthieno[2,3-c]isoquinoline (**4h**): Colorless solid; m.p. 145-147 °C, Rf value: 0.43 in 10% ethyl acetate in hexanes; eluent (10% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.27 (d, *J* = 8.0 Hz, 1 H), 8.23 (d, *J* = 8.0 Hz, 1 H), 7.82 - 7.78 (m, 2 H), 7.64 (t, *J* = 8.0 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 3.05 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):**δ 156.1, 131.9, 130.3, 126.6, 126.0, 124.7, 124.4, 123.3, 119.7, 22.8. **HRMS (ESI):** calc. for [($C_{12}H_9NS$)H] (M+H) 200.0534, measured 200.0530.

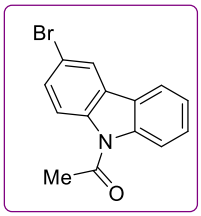


1-(9*H*-Carbazol-9-yl)ethanone (**5a**):[1] Colorless solid; m.p. 184-186 °C, Rf value: 0.43 in 5% ethyl acetate in hexanes; eluent (5% ethyl acetate in hexanes). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.22 (d, *J* = 8.0 Hz, 2 H), 8.00 (d, *J* = 8.0 Hz, 2 H), 7.49 (t, *J* = 8.0 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 2.89 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):**δ 170.1, 138.6, 127.3, 126.4, 123.7, 119.8, 116.2, 27.7. **HRMS (ESI):** calc. for [($C_{14}H_{11}NO$)H] (M+H) 210.0919, measured 210.0920.

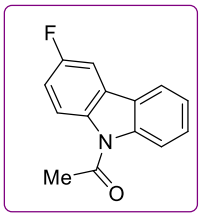


Methyl 9-acetyl-9*H*-carbazole-3-carboxylate (**5b**):[2] Colorless solid; Rf value: 0.4 in 5% ethyl acetate in hexanes; eluent (5% ethyl acetate in hexanes). 

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.65 (s, 1 H), 8.28 (d, *J* = 8.0 Hz, 1 H), 8.15 (d, *J* = 8.0 Hz, 2 H), 8.04 (d, *J* = 4.0 Hz, 1 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.43 (t, *J* = 8.0 Hz, 1 H), 4.00 (s, 3 H) 2.09 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):**δ 170.1, 116.9, 141.3, 138.9, 128.7, 127.9, 126.2, 125.8, 125.4, 124.0, 121.6, 120.2, 116.0, 115.9, 52.2, 27.7. **HRMS (ESI):** calc. for [($C_{16}H_{13}NO_3$)H] (M+H) 268.0974, measured 268.0973.

1-(3-Bromo-9*H*-carbazol-9-yl)ethanone (**5c**):[2] Colorless solid; Rf value: 0.44 in 5% ethyl acetate in hexanes; eluent (5% ethyl acetate in hexanes). 

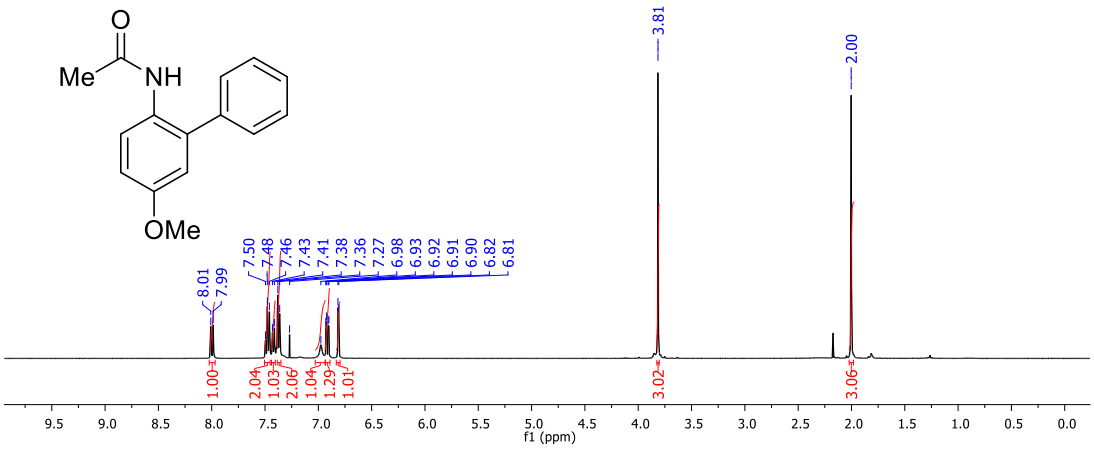
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, *J* = 8.0 Hz, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 8.04 (s, 1 H), 7.91 (t, *J* = 8.0 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 8.0 Hz, 1 H), 7.39 (t, *J* = 8.0 Hz, 1 H), 2.85 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):**δ 170.0, 138.6, 137.4, 130.1, 128.0, 125.2, 123.6, 122.6, 122.4, 120.0, 117.8, 116.8, 115.7, 27.8. **HRMS (ESI):** calc. for [($C_{14}H_{10}BrNO$)H] (M+H) 288.0024, measured 288.0021.

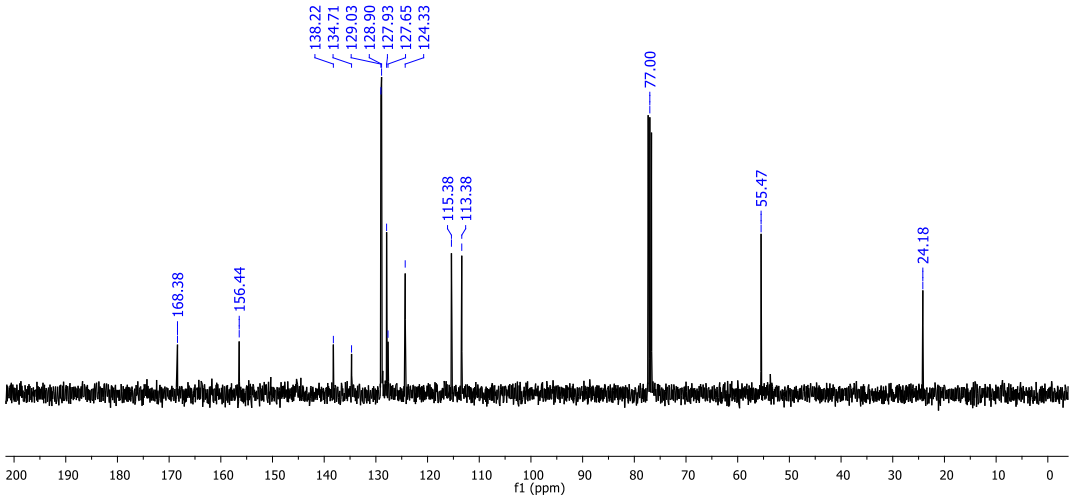
1-(3-Fluoro-9*H*-carbazol-9-yl)ethanone (**5d**):[2] Colorless solid; Rf value: 0.41 in 5% ethyl acetate in hexanes; eluent (5% ethyl acetate in hexanes). 

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31 (m, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 7.64 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 8.0 Hz, 1 H), 7.21 (t, *J* = 8.0 Hz, 1 H), 2.89 (s, 3 H). **HRMS (ESI):** calc. for [($C_{14}H_{10}FNO$)H] (M+H) 228.0825, measured 228.0823.

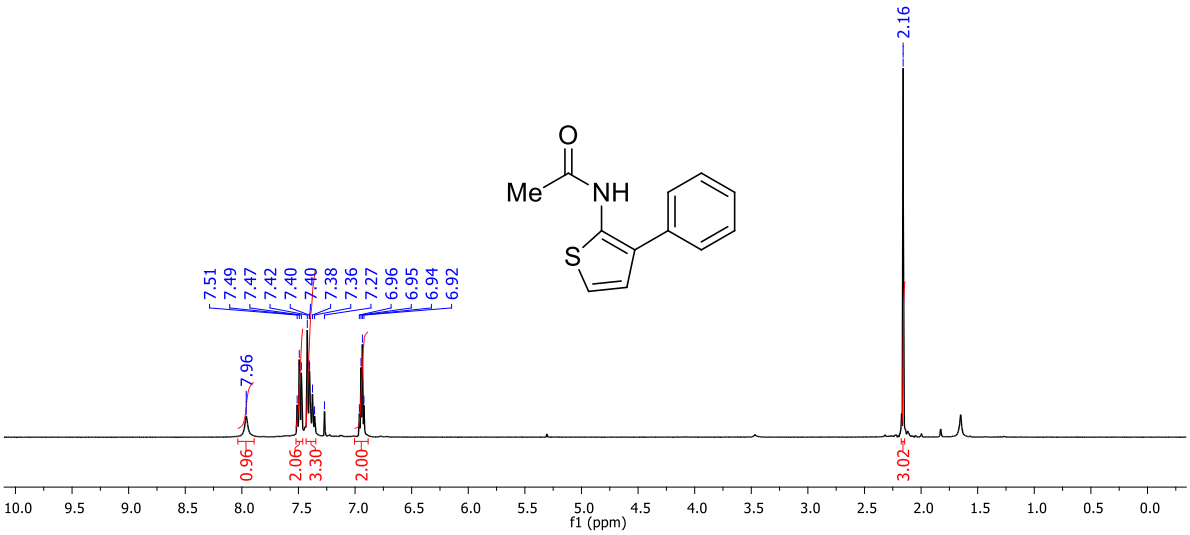
4B.5.4. Spectral Copies of Selected Compounds

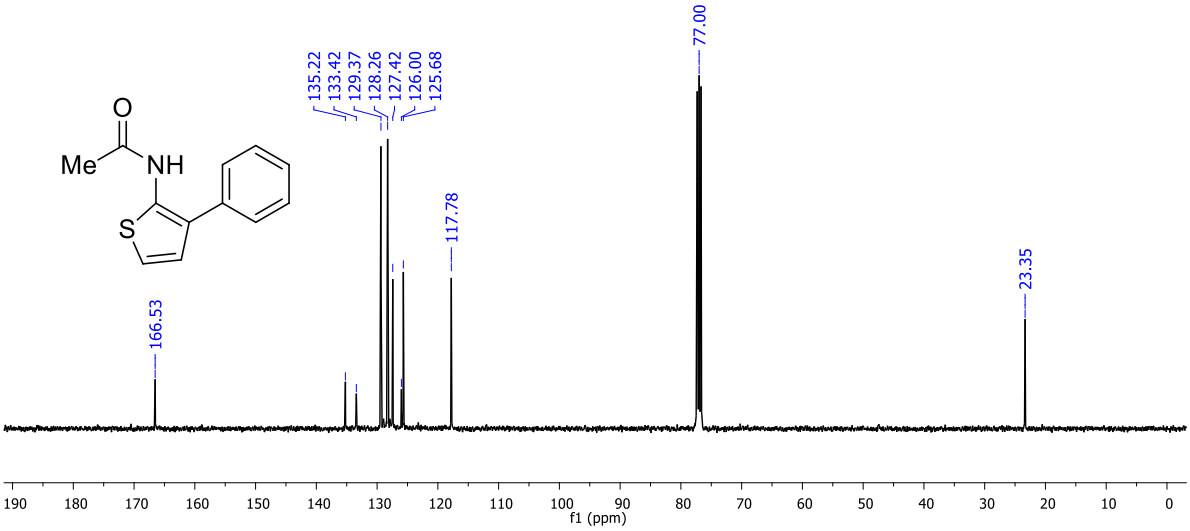
^{1}H, ^{13}C and DEPT NMR Spectra of Compound **3b**



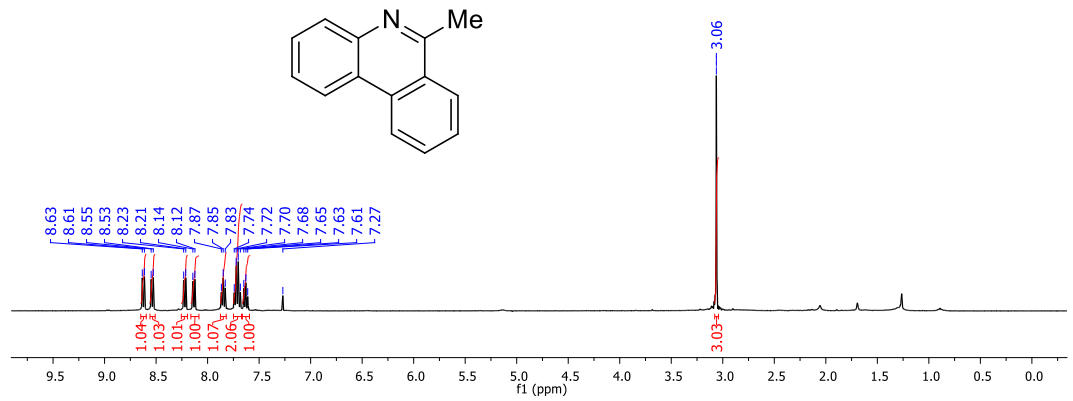


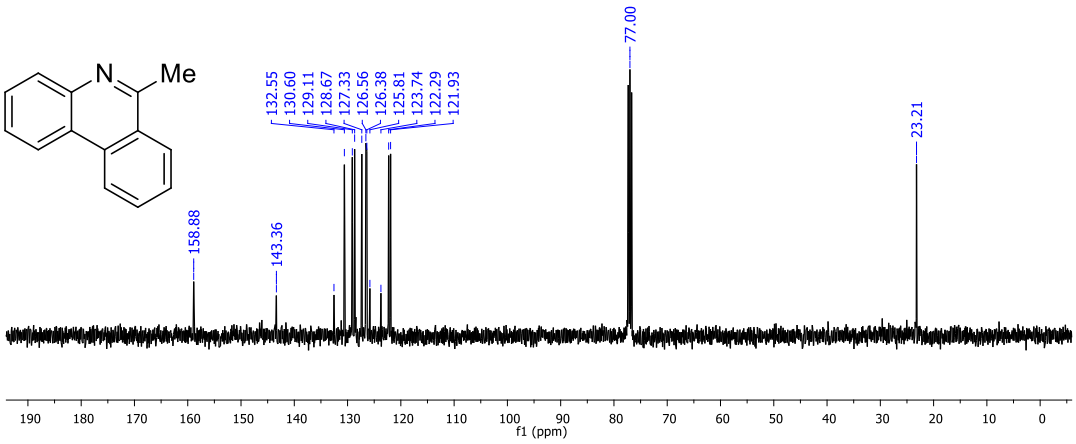
^{1}H, ^{13}C and DEPT NMR Spectra of Compound **3y**

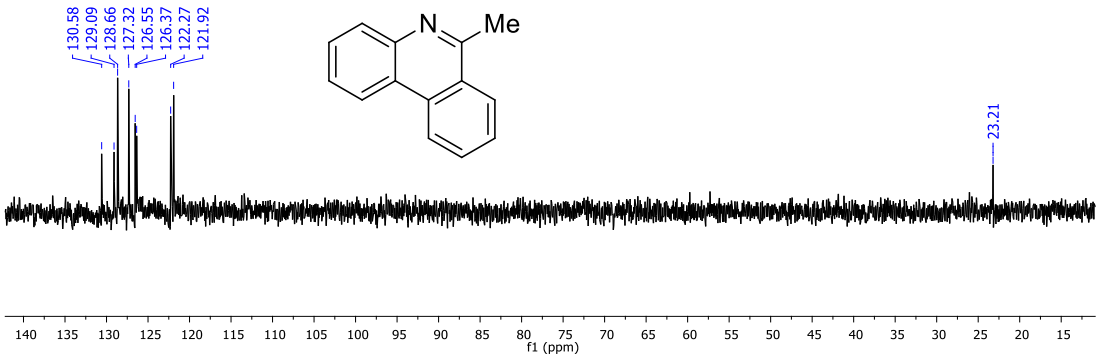




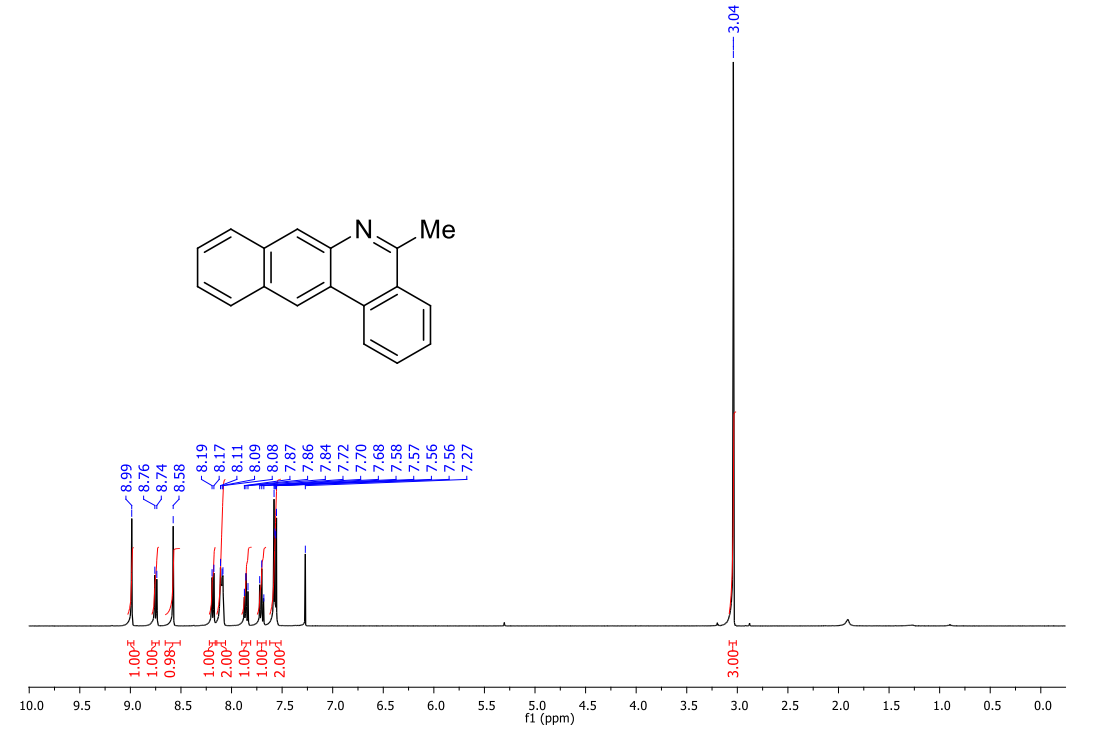
^{1}H, ^{13}C and DEPT NMR Spectra of Compound **4a**

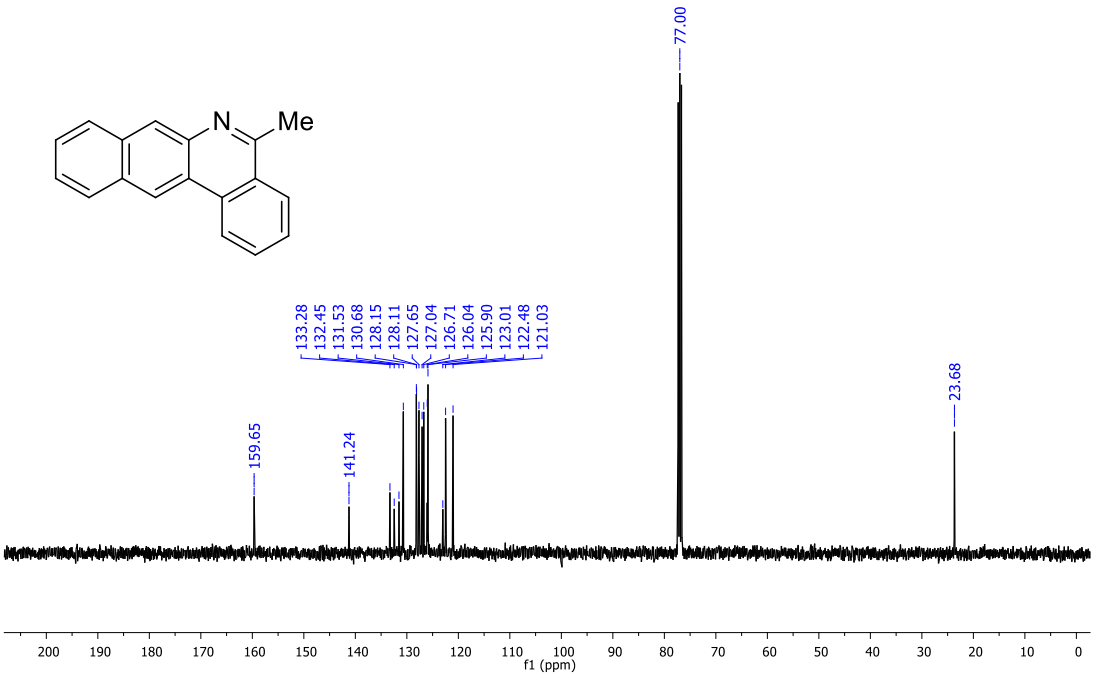




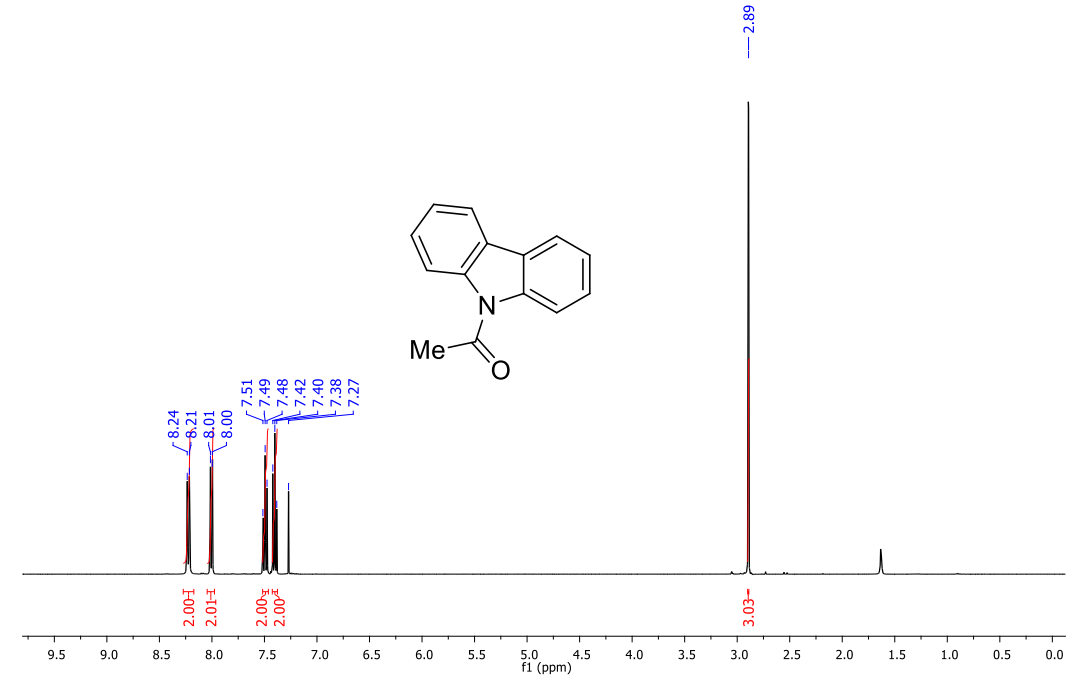


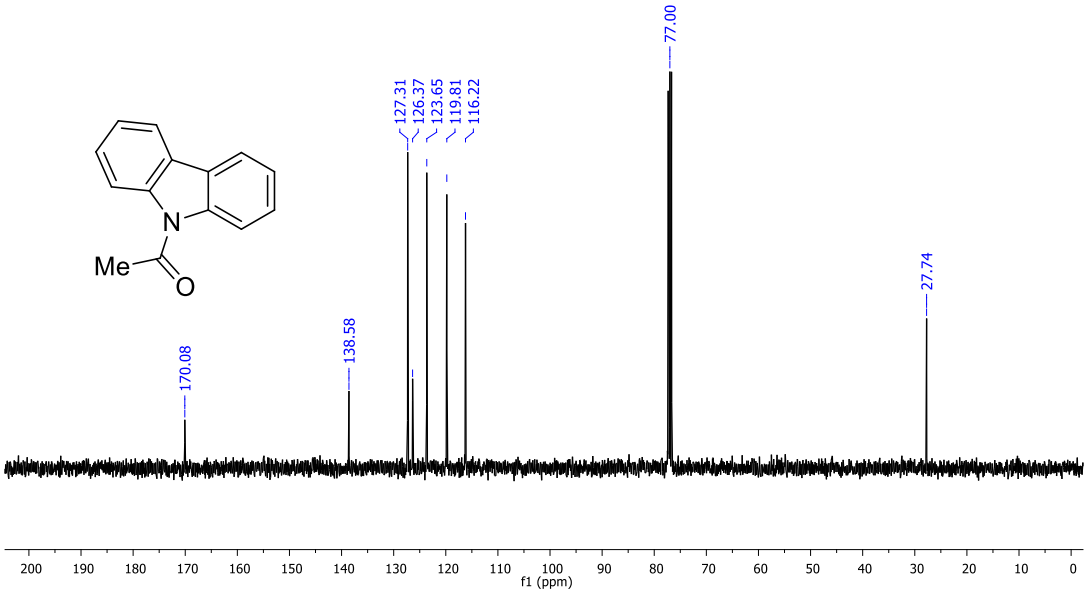
^{1}H and ^{13}C NMR Spectra of Compound **4g**





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

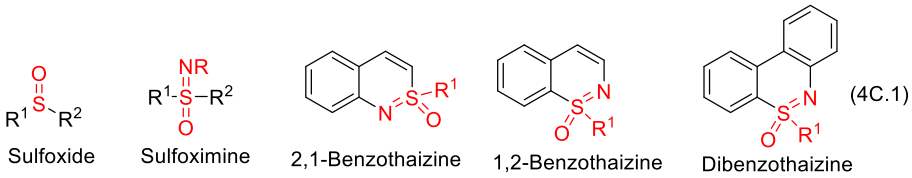




Section 4C: Ruthenium- and Palladium-Catalyzed Consecutive Coupling and Cyclization of Aromatic Sulfoximines with Phenylboronic acids: An Efficient Route to Dibenzothiazines

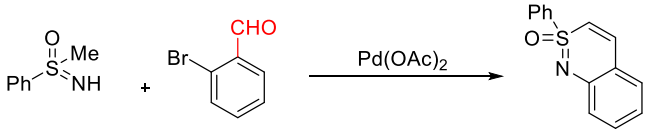
4C.1 Introduction

The sulfoximine is a pivotal structural motif which presents in various biologically active molecules, pharmaceuticals and agrochemicals (eq. 4C.1).[1] The sulfoximine derivatives are also successfully used as chiral auxiliaries and ligands in asymmetric synthesis of various chiral organic molecules.[2] Several methods are available in the literature to synthesize linear sulfoximine derivatives.[3] But, the synthesis of cyclic sulfoximines is limited in the literature.[4] Recently, the synthesis of cyclic sulfoximines has gained much attention in organic synthesis despite their usefulness as scaffolds in drug development and acts as chiral ligands in enantioselective reactions.[5] Meanwhile, the sulfoximine derivatives are also served as key synthetic intermediates in various organic transformations.



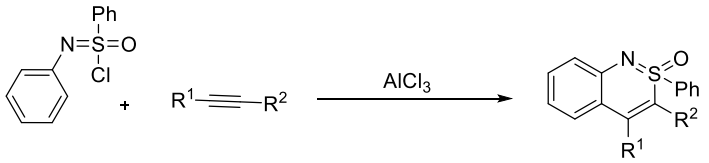
(4C.1)

Harmata's group reported the synthesis of bicyclic sulfoximine derivatives such as 1,2-benzothiazine and 2,1-benzothiazine by a palladium-catalyzed cyclization of 2-bromo benzaldehydes with sulfoximines (eq. 4C.2).[6a]



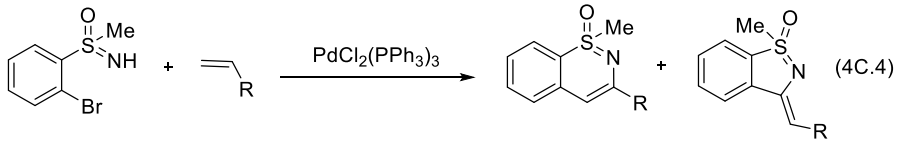
(4C.2)

Later, the same group described $AlCl_3$-mediated cyclization of sulfonimidoyl chlorides with alkynes to synthesis benzothiazine derivatives (eq. 4C.3).[6c-d]

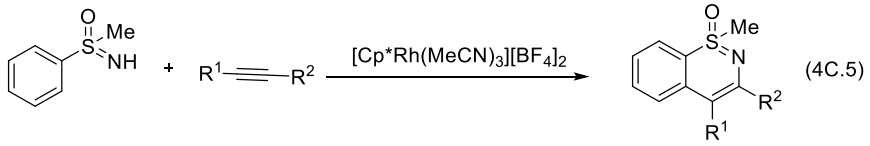


(4C.3)

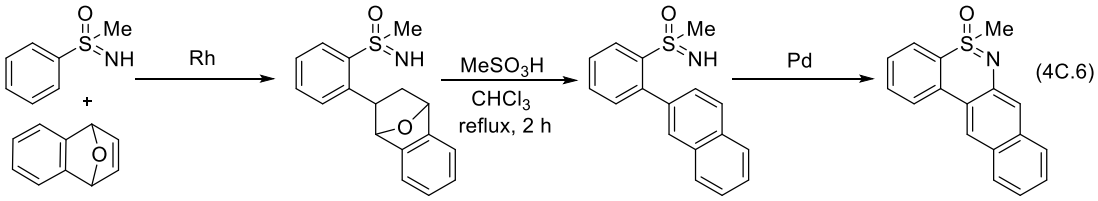
In 2005, Harmata's group stated that the electrophilic cyclization of 2-bromophenyl substituted sulfoximines with terminal alkynes in the presence of palladium and copper catalysts (eq. 4C.4).[6e]



Very recently, Bolm's group reported the synthesis of bicyclic 1,2-benzothiazine derivatives via a rhodium-catalyzed oxidative cyclizationof phenyl sulfoximines with alkynes via chelation-assisted C-H bond activation reaction (eq. 4C.5). [7a]

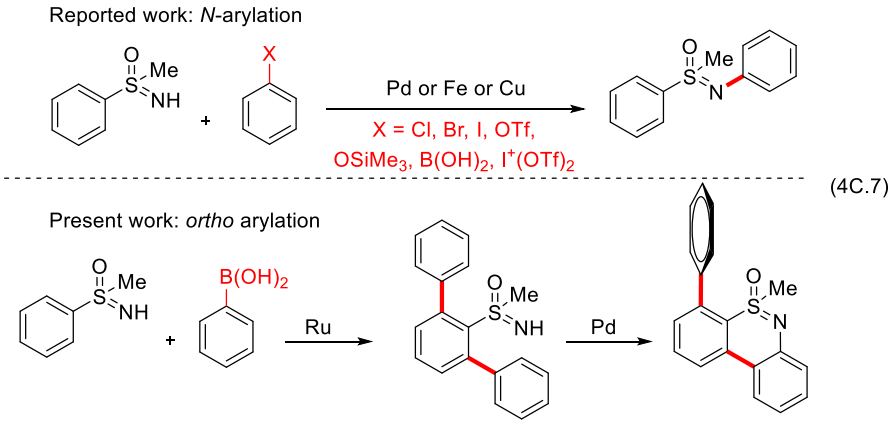


Subsequently, the same group described sulfoximine directed *ortho* alkenylation of phenyl sulfoximines with heterobicyclic alkenes in the presence of a rhodium catalyst followed dehydration occurred in presence of methyl sulfonic acid in chloroform to provide the corresponding *ortho*-naphthylated products. Later, *ortho*-naphthylated products were converted in to aryl-fused thiazines derivatives in presence of palladium catalyst (eq. 4C.6).[7b-e] In all these reports, sulfoximine containing bicyclic benzothiazine derivatives were synthesized efficiently.[6-7]



Herein, we wish to account the synthesis of tricyclic dibenzothiazines by a ruthenium-catalyzed *ortho* arylation of phenyl sulfoximines with aromatic boronic acids followed by intramolecular cyclization in the presence of palladium catalyst in the consecutive two steps (eq. 4C.7). *N*-Arylation of sulfoximines with aryl halides or pseudo halides reported by several research groups in presence of palladium, iron, rhodium and copper catalysts.[8] In contrast, ruthenium catalyzed reaction of aromatic sulfoximines with phenylboronic acids. In the reaction *ortho*-arylation of sulfoximines darivatives was observed in good to excellent yield. Recently, less expensive

ruthenium catalyst gained much attention in this type of *ortho* arylation of aromatics with organo halides or organomattalic reagents.[9-11]



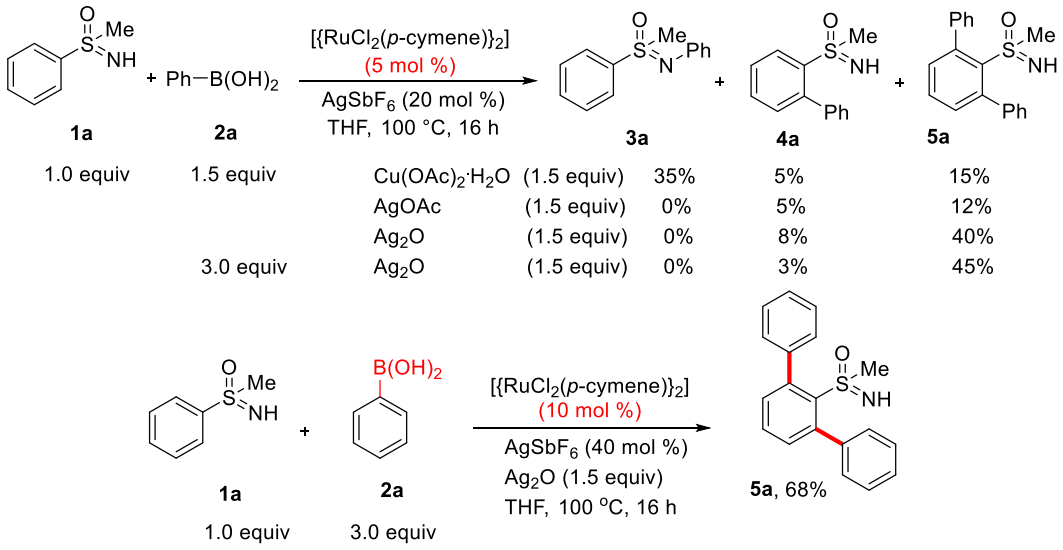
4C.2 Results and Discussion

A ruthenium-catalyzed *ortho* arylation of aromatic sulfoximines with aromatic boronic acids followed by intramolecular cyclization in the presence of palladium catalyst, providing dibenzothiazine derivatives in two consecutive steps is described. The present reaction was compatible with various sensitive and useful functional group substituted phenyl sulfoximines and aromatic boronic acids. An enantioselective version of *ortho* arylation of phenyl sulfoximines with phenylboronic acids followed by cyclization, and this transformation leads to chiral dibenzothiazines in excellent 99% ee ratio was also disclosed.

4C.2.1 Optimization Studies

Initially, the *ortho* arylation of phenyl sulfoximine (**1a**) with phenylboronic acid (**2a**) (1.5 equiv) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv) in THF at 100 °C for 16 h was examined (Scheme 1). In the reaction, *N*-arylated phenyl sulfoximine **3a** in 35% yield, mono *ortho* arylated phenyl sulfoximine **4a** in 5% yield and *bis ortho* arylated phenyl sulfoximine **5a** in 15% yield were observed, respectively (Scheme 4C.1). It is known that the free N-H group of **1a** is acidic in nature and smoothly undergoes *N*-arylation with aromatic electrophiles or organometallic reagents providing *N*-arylated sulfoximines **3** in the presence of metal catalysts (eq. 4C.7).[11] To success the *ortho* arylation reaction, the suppression of product **3** is highly important. Next, the reaction was examined with other oxidant and acetate sources such as AgOAc, NaOAc, K_2CO_3, CsOAc and Ag_2O. Among them, silver

salts such AgOAc and Ag_2O were active for the reaction and no *N*-arylated product **3a** was observed. In AgOAc, product **4a** in 5% and **5a** in 12% yields were observed, respectively. In Ag_2O, product **4a** in 8% and **5a** in 40% yields were observed, respectively. Other acetate sources were not active for the reaction. Next, the coupling reaction was examined with an excess amount of phenylboronic acid **2a** (3.0 equiv). In the reaction also, a mixture of products **4a** and **5a** were observed in 3% and 45% yields, respectively. To increase the yield of **5a**, the coupling reaction was done in the presence of 10 mol % of catalyst and 40 mol % of $AgSbF_6$. Interestingly, in the reaction, only *bis ortho* arylated product **5a** was observed in 68% isolated yield and no *mono* arylated product **4a** was observed.



Scheme 4C.1 Optimization studies

Table 4C.1 *otho*-Arylation of phenyl sulfoximine (**1a**) with phenylboronic acid (**2a**).[a]

Entry	Solvent	Additive	3a (%)	4a (%)	5a (%)[b]
1	THF	$AgBF_4$	0	5	55
2	THF	AgOTf	0	8	40
3	THF	KPF_6	0	0	0
4	THF	$AgSbF_6$	0	0	68
5	THF	--	43	8	0

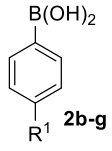
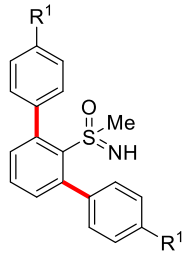
6	MeOH	$AgSbF_6$	24	0	12
7	1,4-Dioxane	$AgSbF_6$	33	6	42
8	DMF	$AgSbF_6$	24	5	7
9	Toluene	$AgSbF_6$	10	5	0

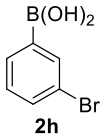
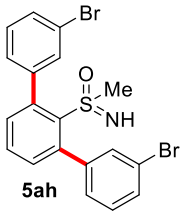
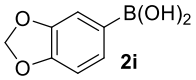
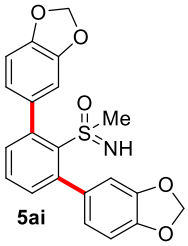
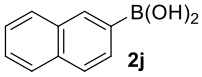
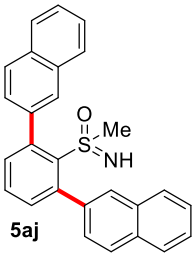
[a]All reactions were carried out with substituted phenyl sulfoximine (**1)** (1.00 mmol), phenylboronic acid (**2a**) (3.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (10 mol %), oxidant (1.5 equiv), additive (40 mol %) and solvent (3.0 mL) at 100 °C for 16 h. [b]Isolated yields.

Further, the coupling reaction was examined with other additives such as AgOTf, $AgBF_4$ and KPF_6 apart from $AgSbF_6$. $AgBF_4$ and AgOTf was partially active, providing product **5a** in 55% and 40% yields, respectively (Table 4C.1, entry 1 and 2). KPF_6 was not active for the reaction (entry 3). Next, the reaction was tested with solvents such as MeOH, 1,4-dioxane, DMF and toluene apart from THF (entry 6-9). However, in all these solvents, a mixture of **3a**, **4a** and **5a** were observed in moderate yields (entry 6-9). THF solvent was effective solvent for the reaction giving 68% yield (entry 4). The optimization studies clearly revealed that [{$RuCl_2$(*p*-cymene)}$_2$] (10 mol %), $AgSbF_6$ (40 mol %) and Ag_2O (1.5 equiv) in THF at 100 °C for 16 h is the best conditions for the reaction. It is important to note that the C-H bond activation of both *ortho* carbons of phenyl sulfoximines were very facile and cannot be controlled. Due to the facile *bis* arylation, an excess amount of catalyst is required.

4C.2.2 *ortho*-Arylation of Phenyl Sulfoximines

Table 4C.2 *ortho*-Arylation of substituted phenylboronic acids **2b-j** with phenyl sulfoximine (**1a**).[a]

Entry	Boronic acid (**2b-j**)	Compound (**5b-n**)	Yields[b]
	 **2b-g**		

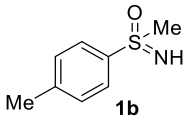
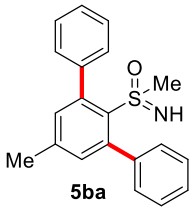
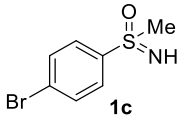
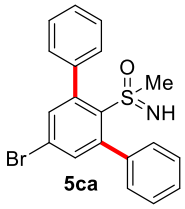
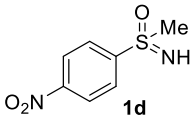
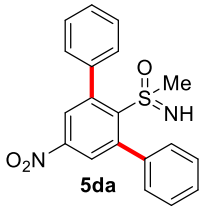
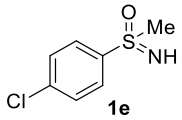
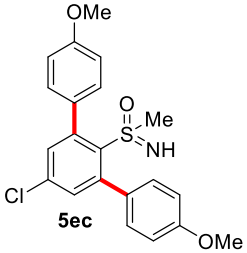
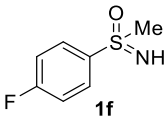
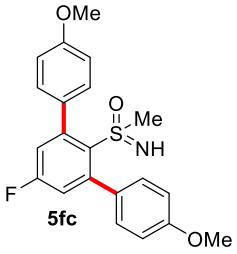
1	**2b**: R^1 = Ph	**5ab**: R^1 = Ph	72%
2	**2c**: R^1 = OMe	**5ac**: R^1 = OMe	66%
3	**2d**: R^1 = I	**5ad**: R^1 = I	65%
4	**2e**: R^1 = Br	**5ae**: R^1 = Br	62%
5	**2f**: R^1 = Cl	**5af**: R^1 = Cl	64%
6	**2g**: R^1 = F	**5ag**: R^1 = F	60%
7	 **2h**	 **5ah**	19%
8	 **2i**	 **5ai**	61%
9	 **2j**	 **5aj**	64%

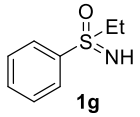
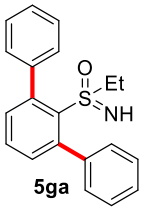
[a]All reactions were carried out with phenyl sulfoximine **1** (1.00 mmol), phenylboronic acids (**2**) (3.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (10 mol %), $AgSbF_6$ (12 mol %), Ag_2O (1.5 equiv), and THF (3.0 mL) at 110 °C for 16 h. [b]Isolated yields.

In addition to phenylboronic acid (**2a**), a wide range of aromatic boronic acids **2b-j** also readily participates in the reaction with **1a**. Table 4C.2 summarizes the results of these reactions. Treatment of 4-phenyl substituted phenylboronic acid (**2b**) with **1a** provided *ortho bis* arylated product **5ab** in 72% yield (entry 1). Electron rich 4-methoxyphenyl boronic acid (**2c**) reacts smoothly with **1a**, yielding the corresponding product **5ac** in 66% yield (entry 2). Aromatic boronic acids having halogen groups I, Br, Cl and F **2d-g** also undergo *ortho* arylation reaction with **1a** efficiently, giving products **5ad-ag** in 65%, 62%, 64% and 60% yields, respectively (entries 3-6). However, 3-bromo phenylboronic acid (**2h**) yielded product **5ah** only in 19% yield (entry 7). Benzo[*d*][1,3]dioxol-5-ylboronic acid (**2i**) and 2-naphthylboronic acid (**2j**) also

efficiently participated in the reaction, affording coupling products **5ai** and **5aj** in 61% and 64% yields, respectively (entries 8 and 9).

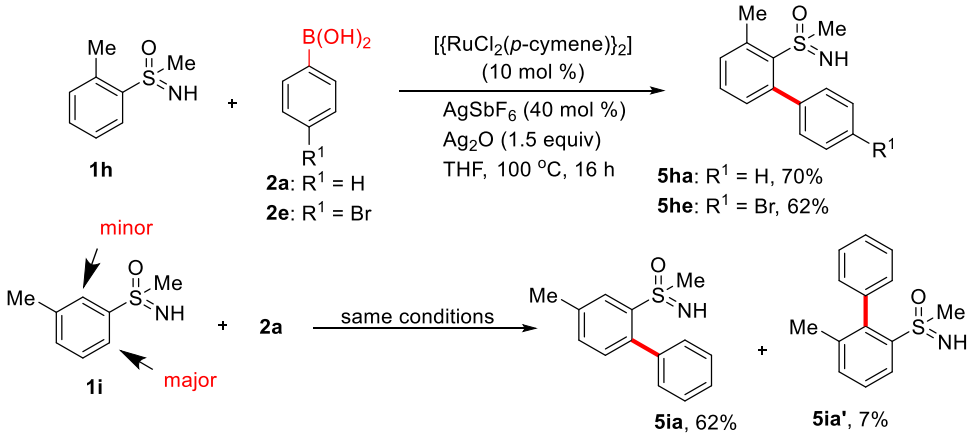
Table 4C.3 *ortho*-Arylation of substituted phenyl sulfoximines **1** with phenylboronic acid (**2a**).[a]

Entry	Phenyl sulfoximine (**1**)	Compound (**5**)	Yeild[b]
1	 **1b**	 **5ba**	65%
2	 **1c**	 **5ca**	63%
3	 **1d**	 **5da**	54%
4	 **1e**	 **5ec**	60%
5	 **1f**	 **5fc**	63%

6	 1g	 5ga	71%

[a]All reactions were carried out with phenyl sulfoximine **1** (1.00 mmol), phenylboronic acids (**2**) (3.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (10 mol %), $AgSbF_6$ (12 mol %), Ag_2O (1.5 equiv), and THF (3.0 mL) at 110 °C for 16 h. [b]Isolated yields. [c]GC yield.

The arylation reaction was examined with substituted aromatic sulfoximines **1b-g** (Table 4C.3). Electron-rich, halogen and electron-deficient group substituted sulfoximines were compatible for the reaction. Methyl, Br and NO_2 substituted sulfoximines **1b-d** reacted with **2a,** yielding products **5ba-da** in 65%, 63% and 54% yields, respectively (entry 1-3). Similarly, Cl and F substituted aromatic sulfoximines **1e-f** reacted with **2c**, providing products **5ec-fc** in 60% and 63% yields, respectively (entry 4 and 5). Likewise, (ethylsulfonimidoyl)benzene (**1g**) yielded **5ga** in 71% yield (entry 6).

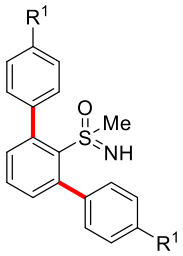
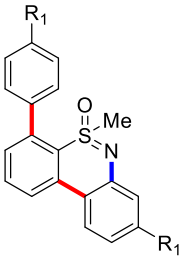
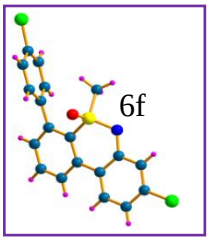
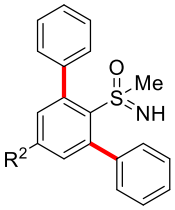
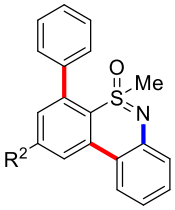
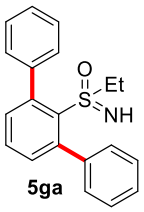
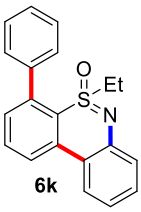
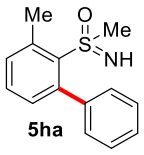
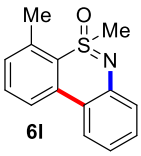


Scheme 4C.2 Mono arylation of aromatic sulfoximines **1h-i**

Apart from the *bis* arylation, *mono* arylation of phenyl sulfoximines was also disclosed (Scheme 4C.2). Treatment of 2-methyl phenylsulfoximine (**1h**) with **2a** or **2f** gave *mono* arylated sulfoximine derivatives **5ha** and **5he** in 70% and 62% yields, respectively. However, 3-methyl phenylsulfoximine (**1i**) afforded regioisomeric *mono* arylated products **5ia** and **5ia'** in 62% and 7% yields, respectively (Scheme 4C.2).

4C.2.3 Synthesis of Dibenzothiazines

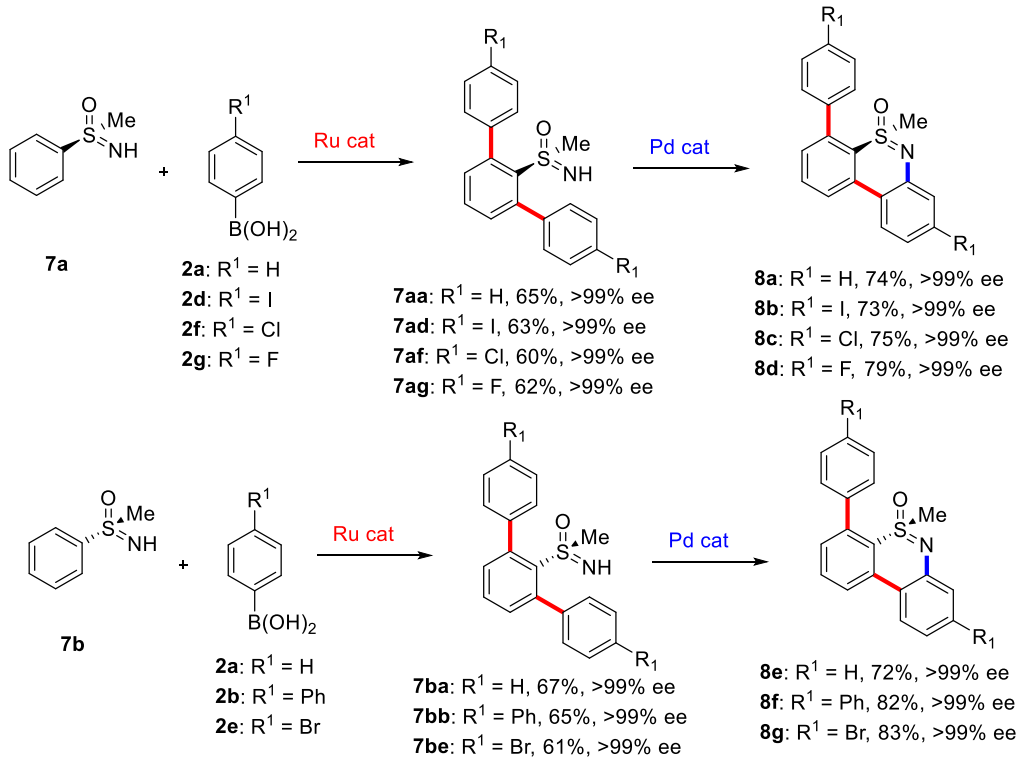
Table 4C.4. Synthesis of dibenzothiazines (**6**).[a]

Entry	Compound (**5**)	Compound (**6**)	Yeild[b]
			 6f
1	**5aa**: R^1 = H	**6a**: R^1 = H	76%
2	**5ab**: R^1 = Ph	**6b**: R^1 = Ph	85%
3	**5ac**: R^1 = OMe	**6c**: R^1 = OMe	65%
4	**5ad**: R^1 = I	**6d**: R^1 = I	77%
5	**5ae**: R^1 = Br	**6e**: R^1 = Br	85%
6	**5af**: R^1 = Cl	**6f**: R^1 = Cl	79%
7	**5ag**: R^1 = F	**6g**: R^1 = F	81%
			
8	**5ba**: R^2 = Me	**6h**: R^2 = Me	80%
9	**5ca**: R^2 = Br	**6i**: R^2 = Br	84%
10	**5da**: R^2 = NO_2	**6j**: R^2 = NO_2	79%
11	 5ga	 6k	83%
12	 5ha	 6l	41%

[a]All reactions were carried out with compound **5** (100 mg), $Pd(OAc)_2$ (10 mol %) and $PhI(OAc)_2$ (2.0 equiv) in toluene (3.0 mL) at 120 °C for 10 h. [b]Isolated yields.

Next, we have tried to couple the N-H bond of sulfoximine with one of the C-H bond of phenyl groups of compound **5** via chelation-assisted remote C-H activation in order to prepare tricyclic dibenzothiazine derivatives. $Pd(OAc)_2$ catalyst along with an oxidant is the suitable conditions for this type of cyclization.[12] The intramolecular cyclization of compound **5aa** proceeded smoothly in the presence of $Pd(OAc)_2$ (10 mol %) and $PhI(OAc)_2$ (2.0 equiv) in toluene at 120 °C for 10 h giving a tricyclic dibenzothiazine derivative **6a** in 76% yield (Table 4C.4, entry 1). The cyclization reaction also proceeded in the presence of $PhI(OAc)_2$ without palladium catalyst. However, product **6a** was observed in a less amount of 25% yield. Under similar reaction conditions, products **5ab**, **5ac**, **5ad**, **5ae**, **5af** and **5ag** also efficiently participated in the reaction, providing cyclization products **6b-g** in good to excellent yields (entries 2-7). Similarly, products **5ba**, **5ca**, **5da**, **5ga** and **5ha** afforded dibenzothiazines **6h-l** in 80%, 84%, 79%, 83% and 41% yields, respectively (entries 8-12). The structure of compound **6f** was further confirmed by a single crystal X-ray analysis.

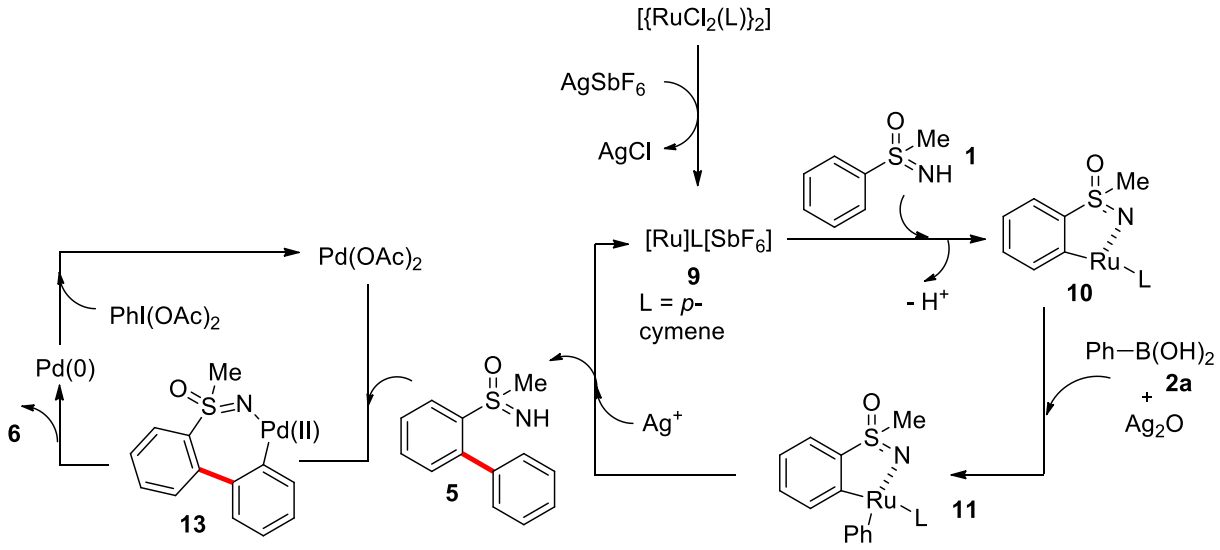
4C.2.4 Synthesis of Chiral Dibenzothiazines



Scheme 4C.3 Synthesis of chiral dibenzothiazines

This result prompted us to explore the possibility of synthesis of chiral tricyclic dibenzothiazines by using chiral phenyl sulfoximines **7a-b** (Scheme 4C.3). Treatment of chiral (*R*)-(-)-*S*-methyl-*S*-phenylsulfoximine (**7a**) with substituted phenyl boronic acids **2a**, **2d**, **2f** and **2g** in the presence of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and Ag_2O in THF at 100 °C for 16 h gave chiral *ortho* arylated phenyl sulfoximines **7aa-ag** in 65%, 63%, 60% and 62% yields, respectively (Scheme 3). Interestingly, the enantiomeric excess (ee) of products **7aa-ag** were not dropped and in all cases >99% ee ratios were observed. Later, compounds **7aa-ag** were cyclized into chiral dibenzothiazines **8a-d** in excellent 74%, 73%, 75% and 79% yields, respectively, in the presence of palladium catalyst. In all these reactions, >99% ee ratios were observed. Further, (*S*)-(-)- *S*-methyl-*S*-phenylsulfoximine (**7b**) underwent *ortho* arylation with aromatic boronic acids **2a**, **2b** and **2e** in the presence of ruthenium catalyst, providing chiral *ortho* arylated phenyl sulfoximines **7ba-be** in 67%, 65% and 61% yields, respectively, with >99% ee ratios. Further, **7ba-be** were converted into chiral dibenzothiazines **8e-g** in the presence of $Pd(OAc)_2$ in 72%, 82% and 83% yields, respectively (Scheme 4C.3).

4C.2.5. Mechanism



Scheme 4C.4 Proposed mechanism

A possible reaction mechanism is proposed to account for the present reaction in Scheme 4C.4. Two different catalytic reactions were involved in the reaction. In the first catalytic cycle,

$AgSbF_6$ likely removes all Cl^- ligands from the ruthenium complex providing a cationic ruthenium complex **9**. Coordination of the nitrogen atom of sulfoximine **1** into catalyst **9** followed by *ortho*-metalation provides a ruthenacycle intermediate **10**. Transmetallation of phenyl boronic acid **2** into intermediate **10** in the presence of Ag_2O affords intermediate **11**. Subsequent reductive elimination of intermediate **11** in the presence of Ag^+ source provides product **5** and regenerates the active ruthenium species **9** for the next catalytic cycle. Another *ortho* arylation is also taken place in a similar fashion. In the second catalytic cycle, compound **5** reacts with $Pd(OAc)_2$ giving palladacycle **12**. Reductive elimination of intermediate **12** in the presence of $PhI(OAc)_2$ provides cyclic product **6** and regenerates the active $Pd(OAc)_2$ catalyst for the next catalytic cycle. The exact role of Ag_2O is not clear to us, it could be possible that the AgO^- anion acts as a base to accelerate the transmetallation of boronic acid **2** into intermediate **12** and the Ag^+ ion acts as an oxidant to oxidize Ru(0) to Ru(II).

4C.3 Conclusions

In conclusion, we have developed a two-step synthesis of dibenzothiazines via a ruthenium-catalyzed *ortho* arylation of phenyl sulfoximines with phenyl boronic acids followed by intramolecular cyclization in the presence of $Pd(OAc)_2$. Chiral dibenzothiazines were prepared efficiently by using chiral phenyl sulfoximine in a similar protocol. A possible reaction mechanism was proposed to account for the present arylation followed by cyclization reaction.

4C.4 References

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4C.5 Experimental Section

4C.5.1 General Procedure for the Coupling of Sulfoximine 1 with Aromaticboronic acids 2 Catalyzed by Ruthenium Complex

A 15-mL pressure tube equipped with a magnetic stirrer and septum containing sulfoximine (**1**) (100 mg, if it is solid), [{$RuCl_2$(*p*-cymene)}$_2$] (10 mol %), Ag_2O (1.5 equiv) and boronic acid (**2a)** (3.0 equiv) was evacuated and purged with nitrogen gas three times. Then, to the tube was then added $AgSbF_6$ (40 mol %) inside the glove box ($AgSbF_6$ was moisture sensitive, thus, it was added inside the glove box). Later, sulfoximine (**1a**) (100 mg, if it is liquid along with solvent via syringes) and dry THF (3.0 mL) were added via syringes. Then, the pressure tube was covered with a screw cap and the reaction mixture was allowed to stir at 100 °C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through Celite and

silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **5**.

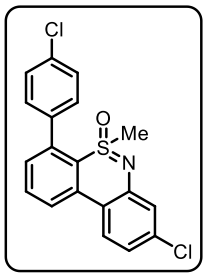
Note: Dry THF solvent is crucial for the reaction. If the solvent is not dry, the yield of product is decreased. This reaction requires inert condition (N_2 gas).

4C.5.2 General Procedure for the Synthesis of Dibenzothiazines Catalyzed by Palladium Catalyst

A Schlenk tube (25 mL) equipped with a stir bar was loaded with *ortho*-aryl sulfoximine **(5)** (100 mg), $Pd(OAc)_2$ (10 mol %) and $PhI(OAc)_2$ (2.0 equiv). Then, dry toluene (2.0 mL) was added, and the mixture was allowed to stir at 120 °C for 10 h. After cooling to room temperature, the mixture was filtered through a short celite pad and washed with dichloromethane (3 × 20 mL). The filtrate was concentrated, and the product was purified by column chromatography using silica gel as stationary phase and a mixture of hexane and ethyl acetate as eluent to give pure **6**.

4C.4.3 X-Ray Analysis

8-Chloro-4-(4-Chlorophenyl)-5-methyldibenzo[c,e][1,2]thiazine 5-oxide (6f).



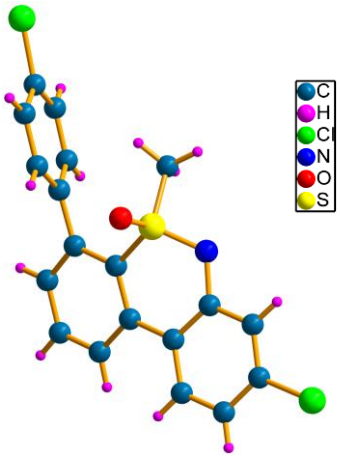


Table 4C.5 Crystal data and structure refinement for (6f).

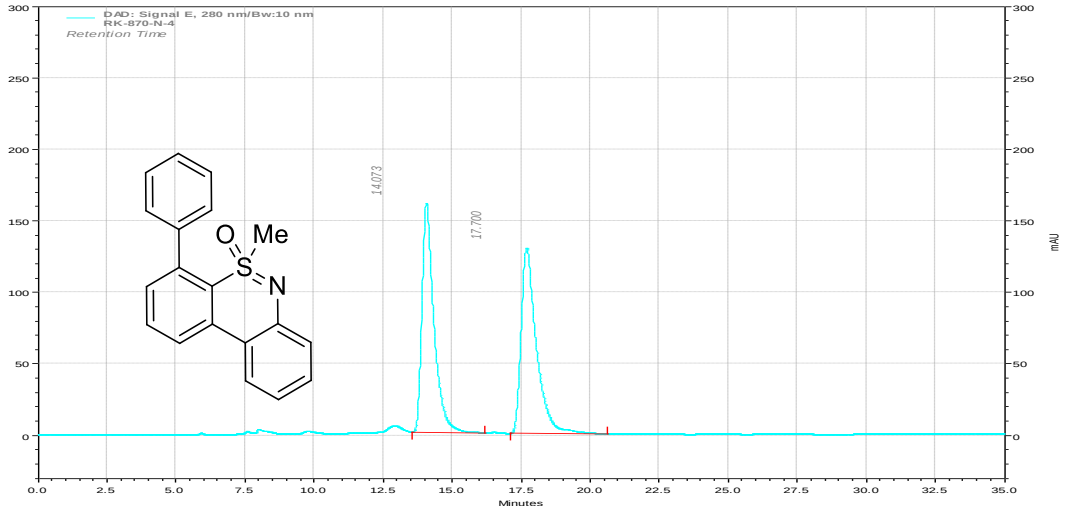
Identification code	RK-855
Empirical formula	C19 H13 Cl2 N O S
Formula weight	374.26
Temperature	298(2) K
Wavelength	0.71073 Å

Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.960(2) Å	α = 89.003(6)°.
	b = 9.715(3) Å	β = 75.173(7)°.
	c = 11.230(3) Å	ϒ = 82.452(6)°.
Volume	832.1(4) $Å^3$	
Z	2	
Density (calculated)	1.494 Mg/m^3	
Absorption coefficient	0.521 mm^{-1}	
F(000)	384	
Crystal size	0.400 x 0.350 x 0.250 mm^3	
Theta range for data collection	1.876 to 28.575°.	
Index ranges	-10<=h<=8, -12<=k<=13, -13<=l<=15	
Reflections collected	14798	
Independent reflections	4149 [R(int) = 0.0426]	
Completeness to theta = 25.242°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.878 and 0.812	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4149 / 0 / 218	
Goodness-of-fit on F^2	0.898	
Final R indices [I>2sigma(I)]	R_1 = 0.0460, wR_2 = 0.1373	
R indices (all data)	R_1 = 0.0512, wR_2 = 0.1493	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.633 and -0.600 $e.A^{-3}$	

4C.5.4 HPLC Data of Selected Compounds

5-Methyl-4-phenyldibenzo[c,e][1,2]thiazine 5-oxide (6a)

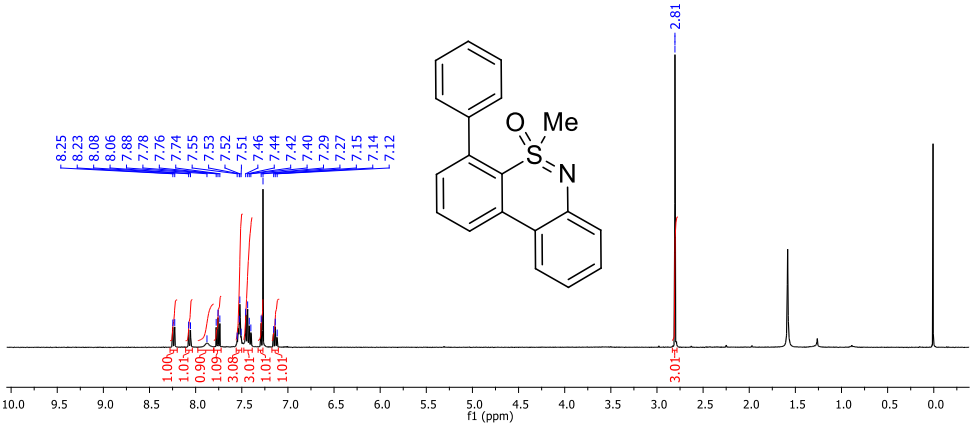
HPLC analysis of **6a**: Chiralpak IA 7:3 *n*-Hexane : Ethyl acetate, 0.5 mL/min; t_R = 14.07 min (*S*), t_R = 17.70 min (*R*).



DAD: Signal E, 280 nm/Bw:10 nm Results

Retention Time	Area	Area %	Height	Height %
14.073	10116408	49.22	335880	55.26
17.700	10436761	50.78	271969	44.74

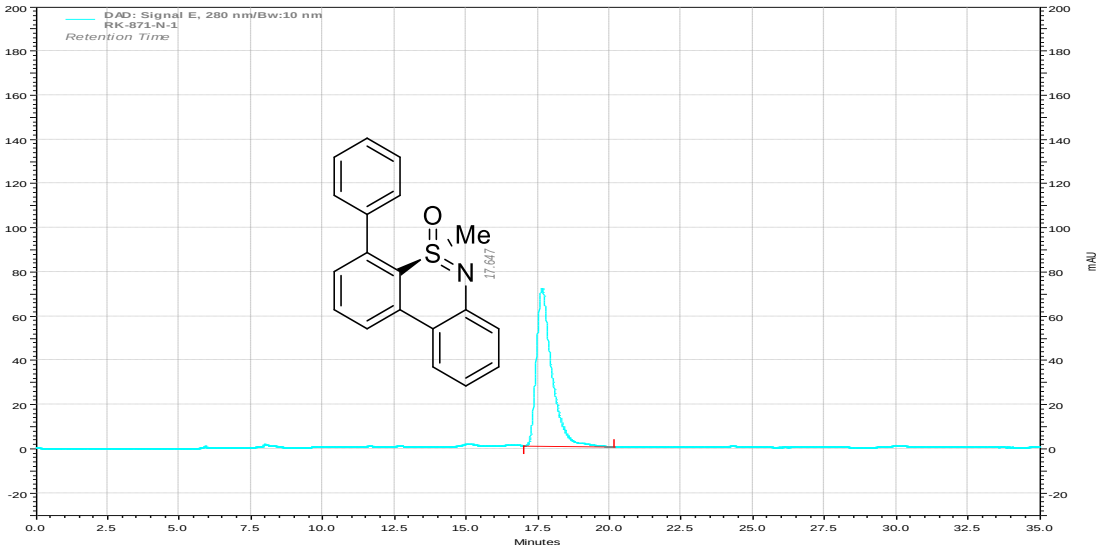
Totals	20553169	100.00	607849	100.00



(*R*)-(-)-5-Methyl-4-phenyldibenzo[c,e][1,2]thiazine 5-oxide (8a)

100 mg of **7aa** was taken and 74.4 mg of product **8a** was isolated (yield 74%).

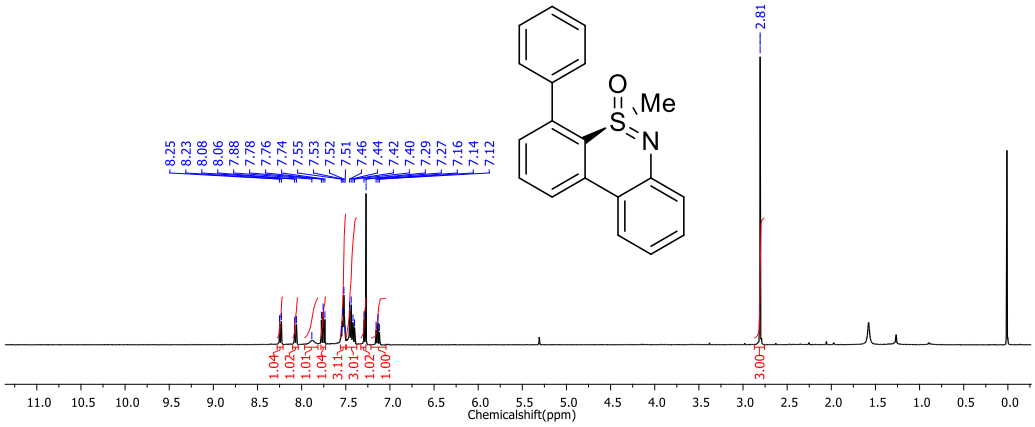
HPLC analysis of **8a**: Chiralpak IA 7:3 *n*-Hexane : Ethyl acetate, 0.5 mL/min; t_R = 17.64 min (*R*).



DAD: Signal E, 280 nm/Bw:10 nm Results

Retention Time	Area	Area %	Height	Height %
17.647	5610162	100.00	149265	100.00

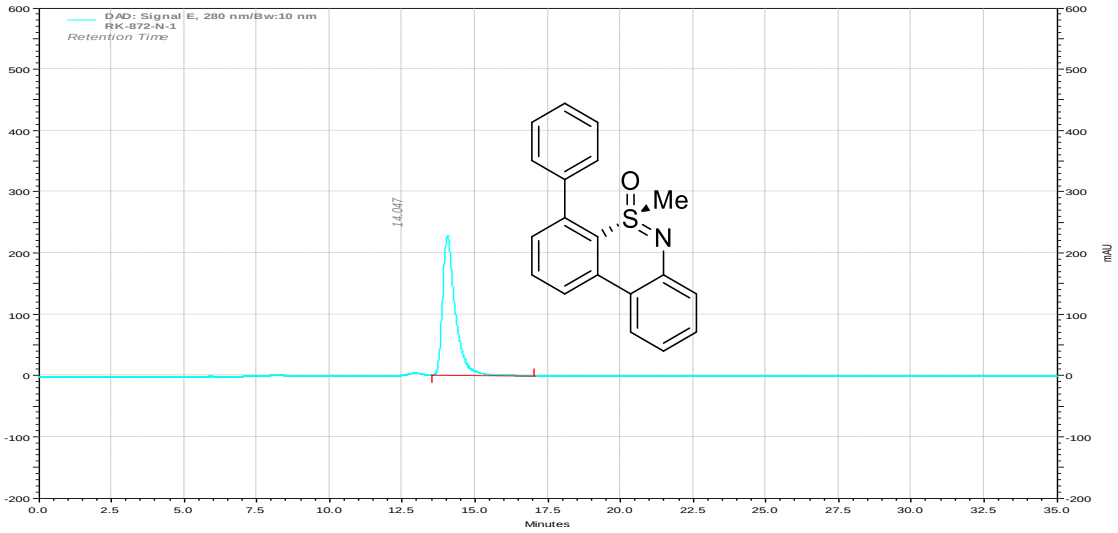
Totals	5610162	100.00	149265	100.00



(*S*)-(+)-5-Methyl-4-phenyldibenzo[c,e][1,2]thiazine 5-oxide (8e).

100 mg of **7ba** was taken and 72.4 mg of product **8e** was isolated (yield 72%).

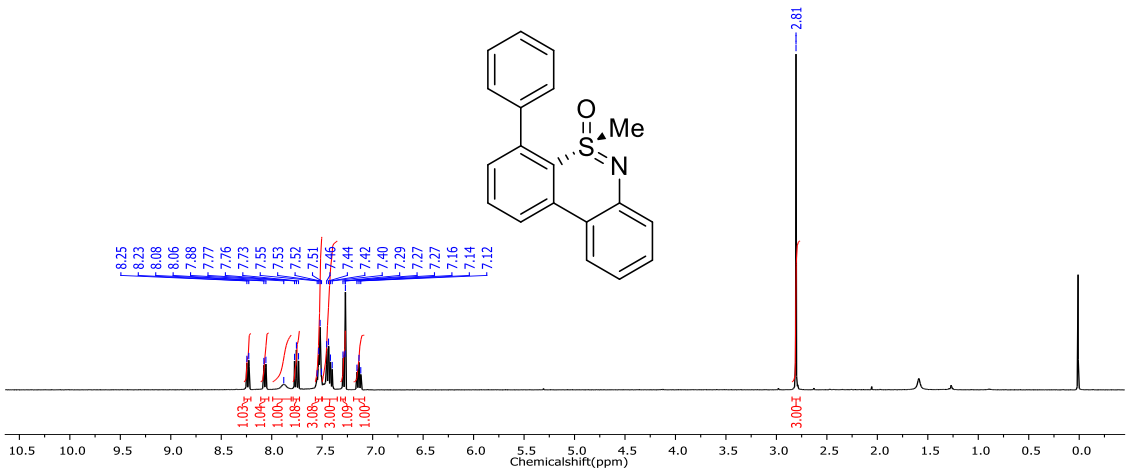
HPLC analysis of **8e**: Chiralpak IA 7:3 *n*-Hexane : Ethyl acetate, 0.5 mL/min; t_R = 14.04 min (*S*)**.**



DAD: Signal E, 280 nm/Bw:10 nm Results

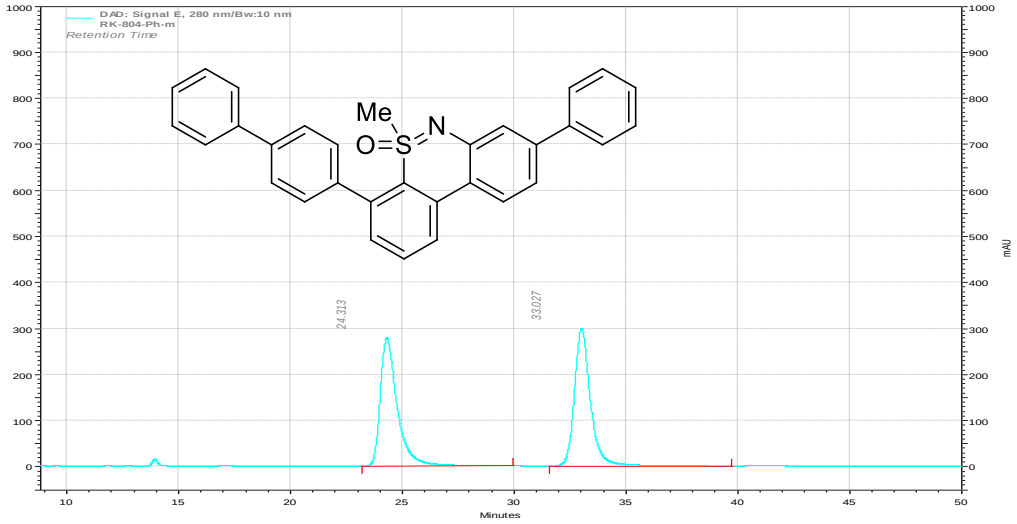
Retention Time	Area	Area %	Height	Height %
14.047	14447782	100.00	477825	100.00

Totals	14447782	100.00	477825	100.00



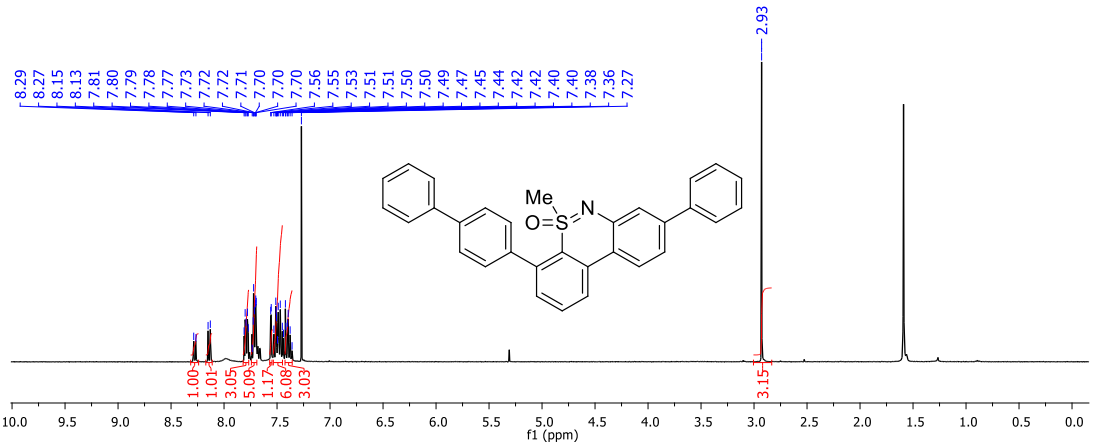
4-([1,1'-Biphenyl]-4-yl)-5-methyl-8 phenyldibenzo[c,e][1,2]thiazine 5-oxide (6b).

HPLC analysis of **6b**: Chiralpak IA 7:3 *n*-Hexane : Ethyl acetate, 0.5 mL/min; t_R = 24.31 min (*S*), t_R = 33.02 min (*R*).



DAD: Signal E, 280 nm/Bw:10 nm Results

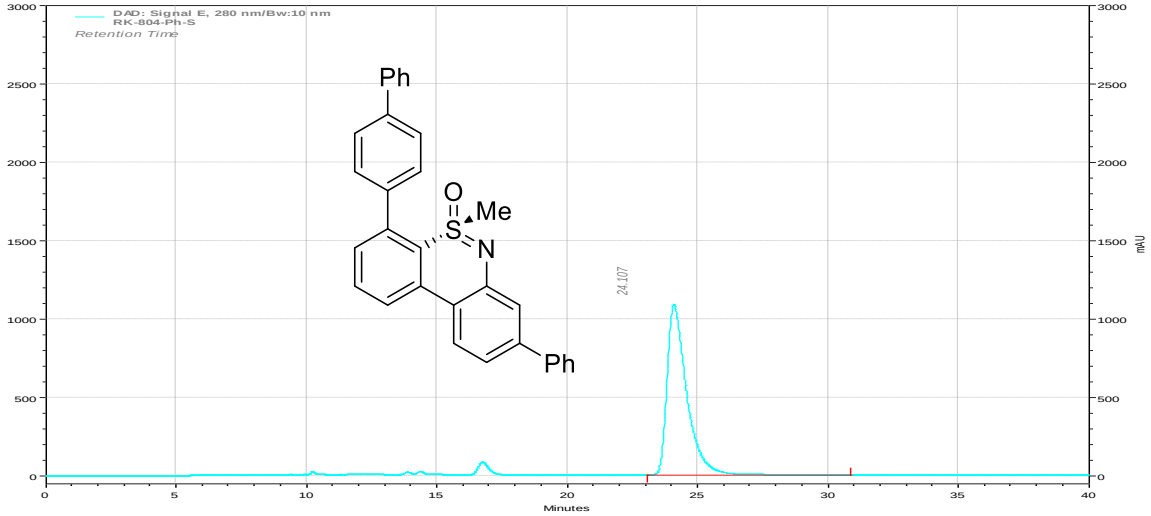
Retention Time	Area	Area %	Height	Height %
24.313	31140080	49.79	584240	48.29
33.027	31402759	50.21	625676	51.71
Totals	62542839	100.00	1209916	100.00



(*S*)-(+)-4-([1,1'-Biphenyl]-4-yl)-5-methyl-8-phenyldibenzo[c,e][1,2]thiazine 5-oxide (8f).

100 mg of **7bb** was taken and 81.6 mg of product **8f** was isolated (yield 82%).

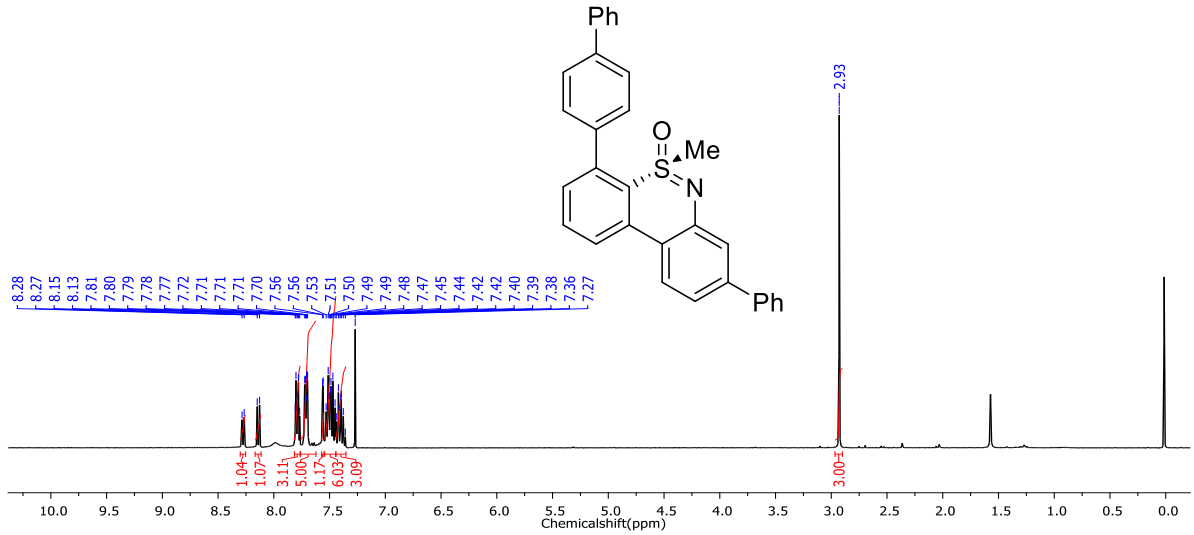
HPLC analysis of **8f**: Chiralpak IA 7:3 *n*-Hexane : Ethyl acetate, 0.5 mL/min; t_R = 24.31 min (*S*).



DAD: Signal E, 280 nm/Bw:10 nm Results

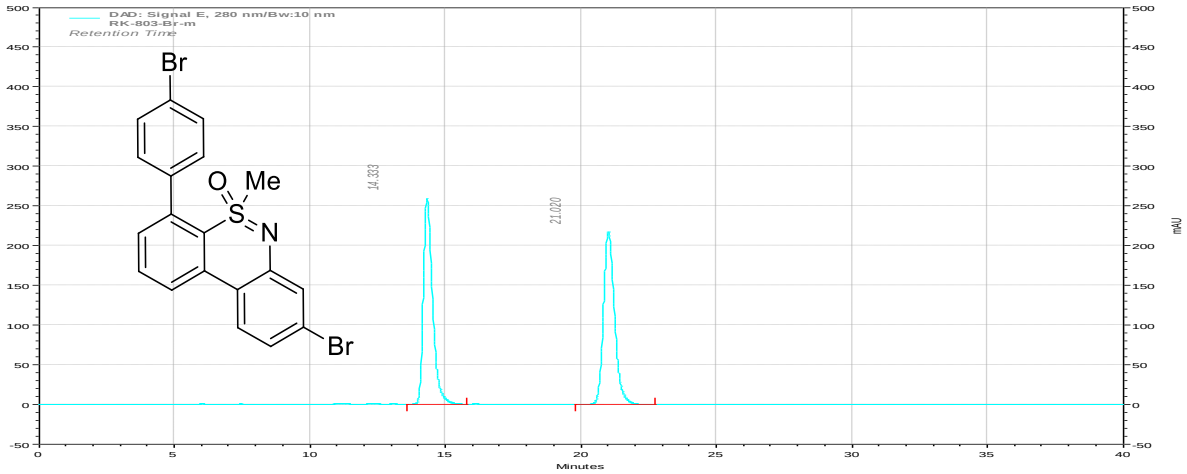
Retention Time	Area	Area %	Height	Height %
24.107	120311701	100.00	2286249	100.00

Totals				
	120311701	100.00	2286249	100.00



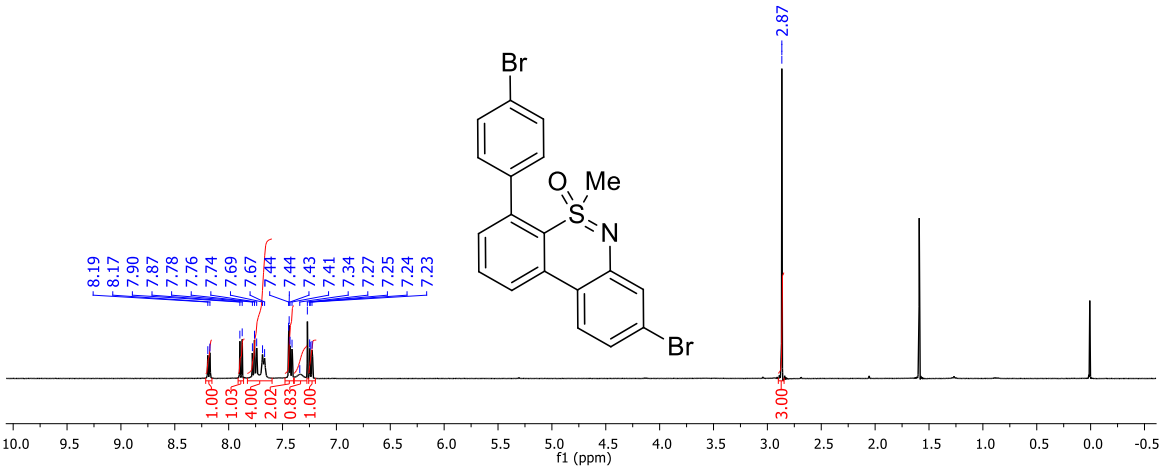
8-Bromo-4-(4-bromophenyl)-5-methyldibenzo[c,e][1,2]thiazine 5-oxide (6e).

HPLC analysis of **6e**: Chiralpak IA 7:3 *n*-Hexane : Ethyl acetate, 0.5 mL/min; t_R = 14.33 min (*S*), t_R = 21.02 min (*R*).



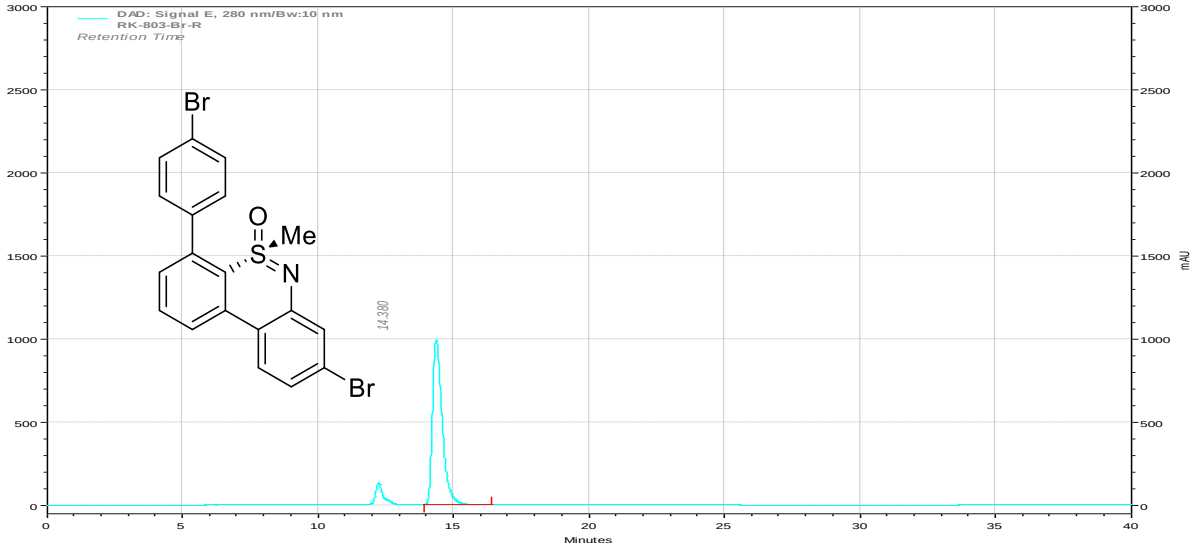
DAD: Signal E, 280 nm/Bw:10 nm Results

Retention Time	Area	Area %	Height	Height %
14.333	12784527	49.62	542993	54.34
21.020	12981589	50.38	456238	45.66
Totals	25766116	100.00	999231	100.00



(*S*)-(+)-8-Bromo-4-(4-bromophenyl)-5-methyldibenzo[c,e][1,2]thiazine 5-oxide (8g).

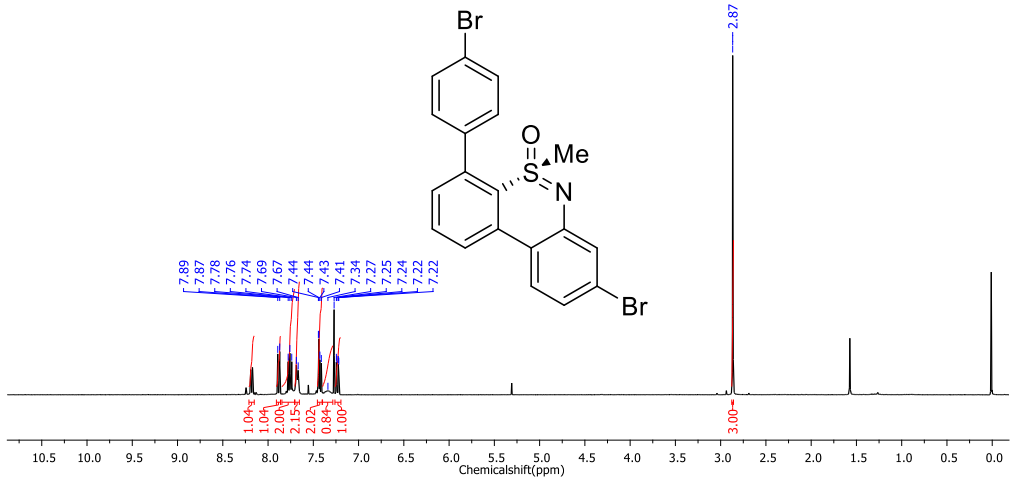
100 mg of **7be** was taken and 82.0 mg of product **8g** was isolated (yield 83%). HPLC analysis of **8g**: Chiralpak IA 7:3 *n*-Hexane : Ethyl acetate, 0.5 mL/min; t_R = 14.38 min (*S*).



DAD: Signal E, 280 nm/Bw:10 nm Results

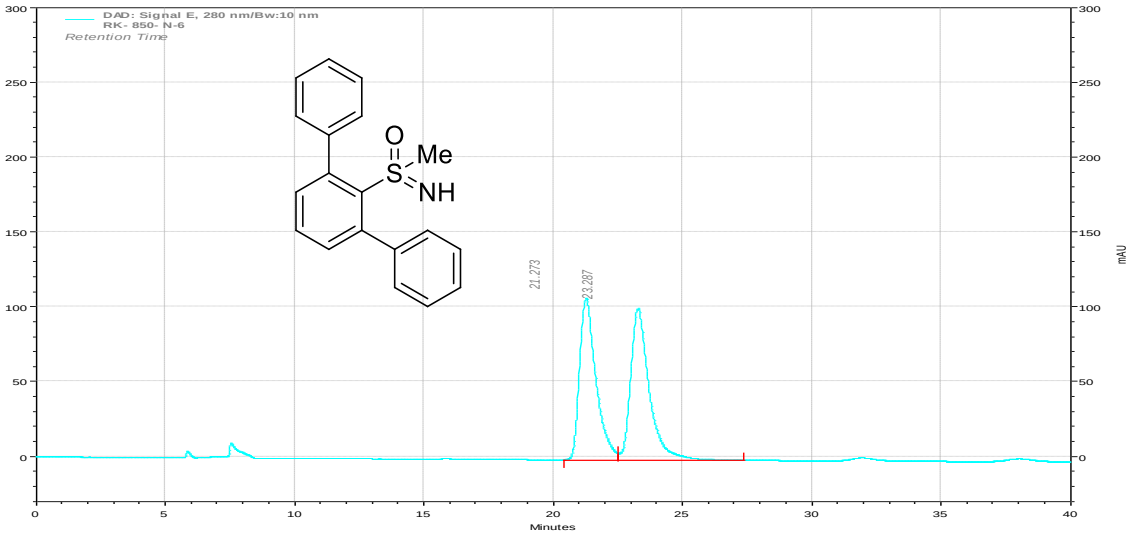
Retention Time	Area	Area %	Height	Height %
14.380	51349286	100.00	2076540	100.00

Totals				
	51349286	100.00	2076540	100.00



2'-(*S*-Methylsulfonimidoyl)-1,1':3',1''-terphenyl (5a).

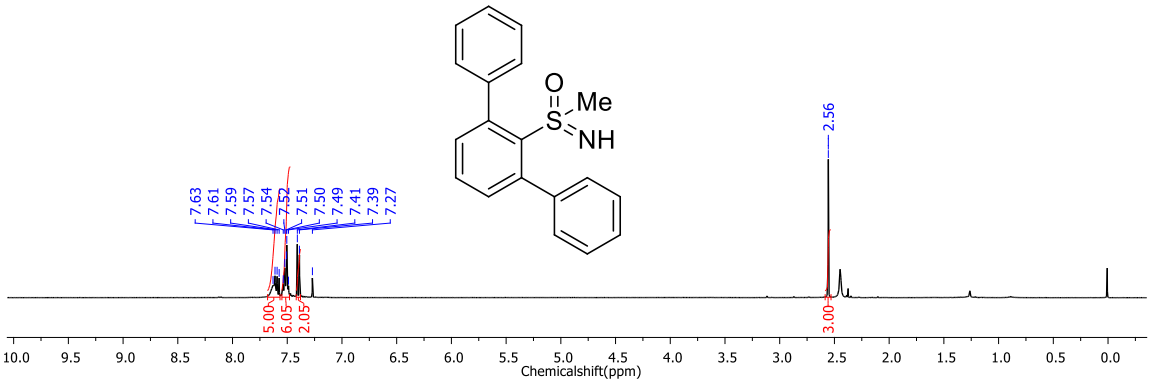
HPLC analysis of 5a: Chiralpak IA 6:4 *n*-Hexane : Ethyl acetate, 0.5 mL/min; t_R = 21.27 min (*S*), t_R = 23.28 min (*R*).



DAD: Signal E, 280 nm/Bw:10 nm Results

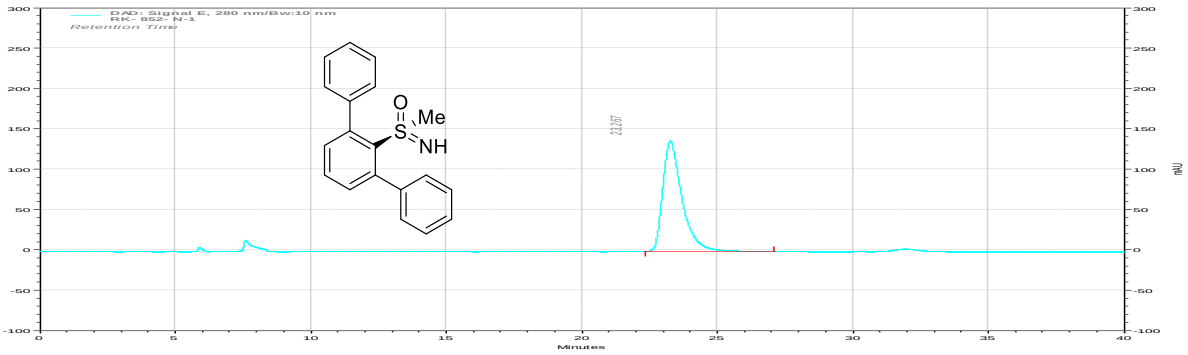
Retention Time	Area	Area %	Height	Height %
21.273	10002524	48.58	226528	51.63
23.287	10588614	51.42	212195	48.37

Totals	20591138	100.00	438723	100.00



(*R*)-(-)-[1,1':3',1''-Terphenyl]-2'-yl(imino)(methyl)sulfanone (7aa).

100 mg of **7a** was taken and 128.7 mg of product **7aa** was isolated (yield 65%). 3.0 equiv of boronic acid (**2a**) was taken. HPLC analysis of **7aa**: Chiralpak IA 6:4 *n*-Hexane : Ethyl acetate, 0.5 mL/min; t_R = 23.26 min (*R*).



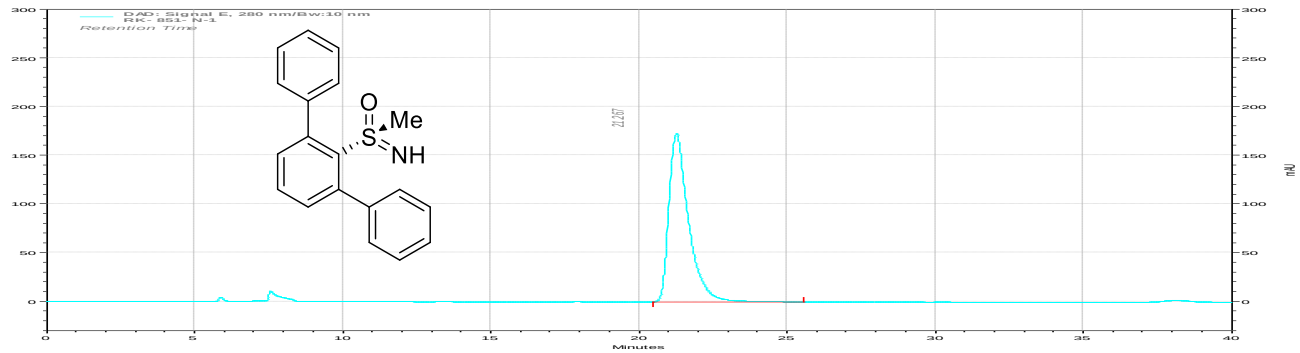
DAD: Signal E, 280 nm/Bw:10 nm Results

Retention Time	Area	Area %	Height	Height %
23.267	14140439	100.00	287085	100.00

Totals	14140439	100.00	287085	100.00

(*S*)-(+)-[1,1':3',1''-Terphenyl]-2'-yl(imino)(methyl)sulfanone (7ba).

100 mg of **7b** was taken and 133.0 mg of product **7ba** was isolated (yield 67%). 3.0 equiv of boronic acid (**2a**) was taken. HPLC analysis of **7ba**: Chiralpak IA 6:4 *n*-Hexane : Ethyl acetate, 0.5 mL/min; t_R = 21.26 min (*S*).



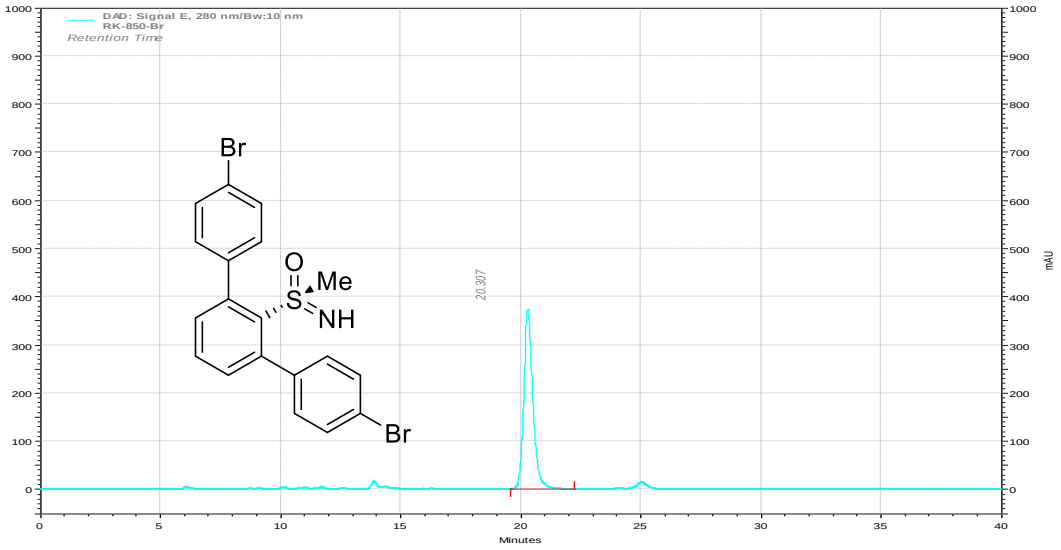
DAD: Signal E, 280 nm/Bw:10 nm Results

Retention Time	Area	Area %	Height	Height %
21.267	16713945	100.00	362213	100.00

Totals				
	16713945	100.00	362213	100.00

(*S*)-(+)-(4,4''-Dibromo-[1,1':3',1''-terphenyl]-2'-yl)(imino)(methyl)sulfanone (7be).

100 mg of **7b** was taken and 181.7 mg of product **7be** was isolated (yield 61%). 3.0 equiv of boronic acid (**2c**) was taken. HPLC analysis of **7be**: Chiralpak IA 6:4 *n*-Hexane : Ethyl acetate, 0.5 mL/min; t_R = 23.30 min (*S*).



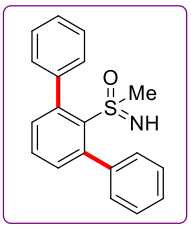
DAD: Signal E, 280 nm/Bw:10 nm Results

Retention Time	Area	Area %	Height	Height %
20.307	20584097	100.00	781762	100.00

Totals				
	20584097	100.00	781762	100.00

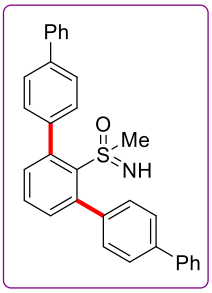
4C.5.5 Spectral Data of all Compounds

2'-(*S*-Methylsulfonimidoyl)-1,1':3',1''-terphenyl (5aa): The representative general procedure



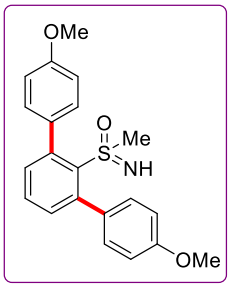
A was followed using **1a** (100 mg) and phenylboronic acid (**2a**) (3.0 equiv). Product **5aa** was isolated in 135.0 mg and yield is 68%. Colorless solid; mp 130-133 °C; eluent (40% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3564, 3524, 3065, 2876, 2354, 2367, 1743, 1698, 1648, 1540, 1518, 1424, 1218, 1017. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 7.63 (bs, 4 H), 7.59 (t, *J* = 8.0, Hz, 2 H), 7.52 – 7.49 (m, 6 H), 7.40 (d, *J* = 8.0, Hz, 2 H), 2.56 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):**δ 141.9, 141.4, 140.2, 132.3, 130.6, 129.8, 129.1, 128.8, 46.3. **Elemental Analysis:** C (72.7%), H (6.0%), N (4.2%), S (9.3%). **HRMS (ESI):** calc. for [(C$_{19}$H$_{17}$NOS)H] (M+H) 308.1109, measured 308.1106. **MALDI-TOF-MS:** calc. for [(C$_{19}$H$_{17}$NOS)K] (M+K) 346.06, measured 346.02.

2''-(*S*-Methylsulfonimidoyl)-1,1':4',1'':3'',1''':4''',1''''-quinquephenyl (5ab): The



representative general procedure **A** was followed using **1a** (100 mg) and boronic acid **2b** (3.0 equiv). Product **5ab** was isolated in 213 mg and yield is 72%.Colorless solid; mp 213-216 °C; (35% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3563, 3524, 3095, 2962, 2362, 2317, 1743, 1699, 1649, 1540, 1517, 1459, 1424, 1221, 1018. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 7.76 (bm, 8 H), 7.69 (d, *J* = 8.0 Hz, 4 H), 7.58 (t, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 8.0 Hz, 4 H), 7.43 (s, 1 H), 7.42 – 7.38 (m, 3 H), 2.59 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 143.5, 141.3, 140.7, 140.1, 139.5, 132.1, 130.2, 130.0, 128.9, 127.7, 127.3, 127.1, 46.7. **Elemental Analysis:** C (83.5%), H (6.3%), N (3.4%), S (7.1%). **HRMS (ESI):** calc. for [(C$_{31}$H$_{25}$NOS)H] (M+H) 460.1735, measured 460.1731. **MALDI-TOF-MS:** calc. for [(C$_{31}$H$_{25}$NOS)K] (M+K) 498.12, measured 498.08.

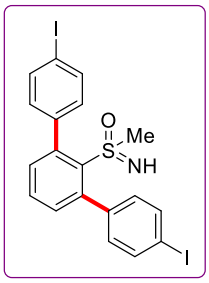
4,4''-Dimethoxy-2'-(*S*-methylsulfonimidoyl)-1,1':3',1''-terphenyl (**5ac**): The representative



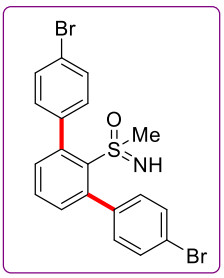
general procedure **A** was followed using **1a** (100 mg) and boronic acid **2c** (3.0 equiv). Product **5ac** was isolated in 156 mg and yield is 66%. Colorless solid; mp 120-123 °C; eluent (50% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3562, 3525, 3000, 2936, 2360, 2317, 1743, 1699, 1648, 1540, 1513, 1457, 1248, 1029. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 7.55 (t, *J* = 8.0 Hz 1 H), 7.54 (bs,

4 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.04 (d, *J* = 8.0 Hz, 4 H), 3.88 (s, 6 H), 2.60 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 160.2, 141.2, 132.0, 131.1, 130.9, 129.4, 123.5, 114.4, 55.4, 46.0. **Elemental Analysis:** C (70.2%), H (7.1%), N (3.6%), S (7.2%). **HRMS (ESI):** calc. for [($C_{21}H_{21}NO_3S$)H] (M+H) 368.1320, measured 368.1314. **MALDI-TOF-MS:** calc. for [($C_{21}H_{21}NO_3S$)K] (M+K) 406.08, measured 406.12.

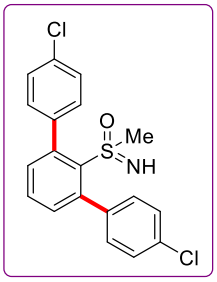
4,4''-Iodo-2'-(*S*-methylsulfonimidoyl)-1,1':3',1''-terphenyl (**5ad**): The representative general procedure **A** was followed using **1a** (100 mg) and boronic acid **2d** (3.0 equiv). Product **5ad** was isolated in 234 mg and yield is 65%. Colorless solid; mp 225-227 °C; eluent (35% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3565, 3523, 3054, 2927, 2367, 2314, 1741, 1693, 1646, 1540, 1515, 1484, 1424, 1264, 1217, 1004. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.83 (d, *J* = 8.0 Hz, 4 H), 7.53 (t, *J* = 8.0 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 4 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 2.55 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 142.8, 140.3, 140.0, 137.7, 132.2, 131.5, 130.3, 94.6, 46.9. **Elemental Analysis:** C (40.8%), H (2.5%), N (2.5%), S (5.8%). **HRMS (ESI):** calc. for [($C_{19}H_{15}I_2NOS$)H] (M+H) 559.9042, measured 559.9059. **MALDI-TOF-MS:** calc. for [($C_{19}H_{15}I_2NOS$)K] (M+K) 597.86, measured 597.82.



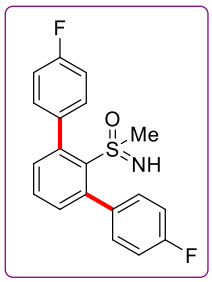
4,4''-Bromo-2'-(*S*-methylsulfonimidoyl)-1,1':3',1''-terphenyl (**5ae**): The representative general procedure **A** was followed using **1a** (100 mg) and boronic acid **2e** (3.0 equiv). Product **5ae** was isolated in 185 mg and yield is 62%. Colorless solid; mp 145-148 °C; eluent (40% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3564, 3525, 3056, 2925, 2367, 2315, 1741, 1700, 1648, 1540, 1518, 1418, 1220, 1009. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.63 (d, *J* = 8.0 Hz, 4 H), 7.54 (t, *J* = 8.0 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 4 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 2.55 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 143.0, 140.2, 139.4, 132.3, 131.8, 131.3, 130.3, 122.9, 46.7. **Elemental Analysis:** C (47.2%), H (3.4%), N (3.1%), S (6.3%). **HRMS (ESI):** calc. for [($C_{19}H_{15}Br_2NOS$)H] (M+H) 463.9319, measured 463.9321. **MALDI-TOF-MS:** calc. for [($C_{19}H_{15}Br_2NOS$)K] (M+K) 501.88, measured 501.85.



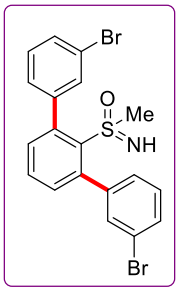
4,4''-Dichloro-2'-(*S*-methylsulfonimidoyl)-1,1':3',1''-terphenyl (**5af**): The representative general procedure **A** was followed using **1a** (100 mg) and boronic acid **2f** (3.0 equiv). Product **5af** was isolated in 154 mg and yield is 64%. Colorless solid; mp 125-128 °C; eluent (40% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3565, 2962, 2962, 2367, 1723, 1647, 1493, 1452, 1279, 1125, 1077, 1013. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 7.55 (d, *J* = 8.0 Hz, 4 H), 7.54 (t, *J* = 8.0 Hz, 1 H), 7.47 (d, *J* = 8.0 Hz, 4 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 2.55 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 143.1, 140.1, 138.9, 134.8, 132.4, 131.0, 130.3, 128.8, 46.8. **HRMS (ESI):** calc. for [($C_{19}H_{15}Cl_2NOS$)H] (M+H) 376.0330, measured 376.0331. **MALDI-TOF-MS:** calc. for [($C_{19}H_{15}Cl_2NOS$)K] (M+K) 413.98, measured 413.94.



4,4''-Difluoro-2'-(*S*-methylsulfonimidoyl)-1,1':3',1''-terphenyl (**5ag**): The representative general procedure **A** was followed using **1a** (100 mg) and boronic acid **2g** (3.0 equiv). Product **5ag** was isolated in 132 mg and yield is 60%. Colorless solid; mp 150-153 °C; eluent (40% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3565, 3523, 3059, 2927, 2365, 1740, 1693, 1647, 1510, 1451, 1416, 1221, 1044. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 7.59 (bs, 4 H), 7.53 (t, *J* = 8.0, Hz 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.20 (t, *J* = 8.0 Hz, 4 H), 2.52 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 164.1, 161.6 (F-coupling), 143.3, 140.1, 136.45 and 136.42 (F-coupling), 132.4, 131.5 and 131.4 (F-coupling), 130.1, 115.8 and 115.6 (F-coupling), 46.7. **HRMS (ESI):** calc. for [($C_{19}H_{15}F_2NOS$)H] (M+H) 344.0921, measured 344.0927. **MALDI-TOF-MS:** calc. for [($C_{19}H_{15}F_2NOS$)K] (M+K) 382.04, measured 382.01.



3,3''-Dibromo-2'-(S-methylsulfonimidoyl)-1,1':3',1''-terphenyl (**5ah**): The representative general procedure **A** was followed using **1a** (100 mg) and boronic acid **2h** (3.0 equiv). Product **5ah** was isolated in 56 mg and yield is 19%. Colorless solid; mp 146-149 °C; eluent (40% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3563, 3525, 3060, 2922, 2361, 2317, 1741, 1699, 1648, 1553, 1518, 1456, 1218, 1042. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 7.73 (bs, 1 H), 7.61 – 7.53 (m, 6 H), 7.38 – 7.33 (m, 4 H), 2.59 (s, 3 H). **HRMS (ESI):** calc. for [($C_{19}H_{15}Br_2NOS$)H] (M+H) 463.9319, measured 463.9321. **MALDI-TOF-MS:** calc. for [($C_{19}H_{15}Br_2NOS$)K] (M+K) 501.88, measured 501.84



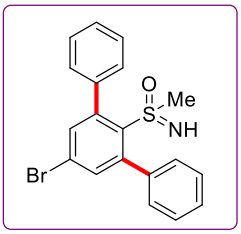
5,5'-(2-(*S*-Methylsulfonimidoyl)-1,3-phenylene)bis(benzo[*d*][1,3]dioxole) (**5ai**): The representative general procedure **A** was followed using **1a** (100 mg) and boronic acid **2i** (3.0 equiv). Product **5ai** was isolated in 155 mg and yield is 61%. Colorless solid; mp 165-168 °C; eluent (50% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3564, 3524, 3059, 2923, 2363, 2321, 1742, 1700, 1649, 1540, 1516, 1459, 1264, 1037. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 7.59 (t, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0, 4.0 Hz, 2 H), 7.08 (bs, 4 H), 6.95 (d, *J* = 8.0 Hz, 2 H), 6.09 (s, 4 H), 2.68 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 148.6, 148.2, 145.3, 141.4, 132.9, 132.3, 131.1, 129.4, 123.5, 108.7, 101.7, 43.8. **HRMS (ESI):** calc. for [($C_{21}H_{17}NO_5S$)H] (M+H) 396.0906, measured 396.0903. **MALDI-TOF-MS:** calc. for [($C_{21}H_{17}NO_5S$)K] (M+K) 434.04, measured 434.06.

2,2'-(2-(*S*-Methylsulfonimidoyl)-1,3-phenylene)dinaphthalene (**5aj**): The representative general procedure **A** was followed using **1a** (100 mg) and boronic acid **2j** (3.0 equiv). Product **5aj** was isolated in 168 mg and yield is 64%. Colorless solid; mp 85-88 °C; eluent (30% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3563, 3527, 3060, 2925, 2358, 2321, 1742, 1699, 1648, 1540, 1516, 1459, 1216, 1043. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 8.13 (bs, 2 H), 8.01 – 7.91 (m, 6 H), 7.79 (bs, 2 H), 7.61 – 7.55 (m, 5 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 2.48 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 143.6, 141.2, 138.1, 137.8, 132.9, 132.9, 132.5, 129.8, 128.98, 128.9, 128.3, 127.8, 127.6, 126.8, 46.7. **Elemental Analysis:** C (80.2%), H (5.8%), N (3.2%), S (6.5%). **HRMS (ESI):** calc. for [($C_{27}H_{21}NOS$)H] (M+H) 408.1422, measured 408.1419. **MALDI-TOF-MS:** calc. for [($C_{27}H_{21}NOS$)K] (M+K) 446.09, measured 446.06.

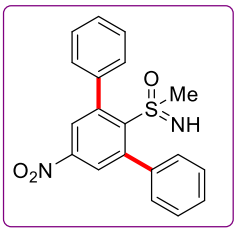
5'-Methyl-2'-(*S*-methylsulfonimidoyl)-1,1':3',1''-terphenyl (**5ba**): The representative general procedure **A** was followed using **1b** (100 mg) and phenyl boronic acid (**2a**) (3.0 equiv). Product **5ba** was isolated in 135 mg and yield is 65%. Colorless solid; mp 156-159 °C; eluent (40% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3564, 3523, 3062, 2923, 2364, 1741, 1706, 1646, 1547, 1516, 1462, 1221, 1049. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 7.61 (bs, 4 H), 7.51 – 7.43 (m, 6 H), 7.16 (s, 2 H), 2.46 (s, 3 H), 2.43 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 141.0, 140.7,

140.3, 132.7, 129.7, 128.7, 128.5, 128.3, 46.6, 20.9. **HRMS (ESI):** calc. for [($C_{20}H_{19}NOS$)H] (M+H) 322.1266, measured 322.1269. **MALDI-TOF-MS:** calc. for [($C_{20}H_{19}NOS$)K] (M+K) 360.08, measured 360.05.

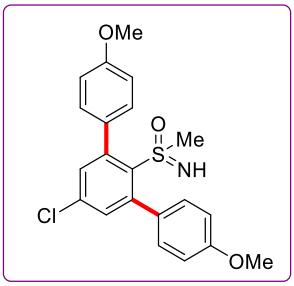
5'-Bromo-2'-(*S*-methylsulfonimidoyl)-1,1':3',1''-terphenyl (**5ca**): The representative general procedure **A** was followed using **1c** (100 mg) and phenyl boronic acid (**2a)** (3.0 equiv). Product **5ca** was isolated in 104 mg and yield is 63%. Colorless solid; mp 162-165 °C; eluent (40% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3564, 3526, 3056, 2928, 2356, 2325, 1741, 1701, 1647, 1542, 1515, 1455, 1218, 1045. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.61 (bs, 4 H), 7.53 – 7.48 (m, 8 H), 2.45 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 142.8, 142.6, 139.3, 134.5, 129.7, 129.0, 128.8, 124.0, 46.5. **HRMS (ESI):** calc. for [($C_{19}H_{16}BrNOS$)H] (M+H) 386.0214, measured 386.0218. **MALDI-TOF-MS:** calc. for [($C_{19}H_{16}BrNOS$)K] (M+K) 423.97, measured 423.95.



2'-(*S*-Methylsulfonimidoyl)-5'-nitro-1,1':3',1''-terphenyl (**5da**): The representative general procedure **A** was followed using **1d** (100 mg) and phenyl boronic acid (**2a)** (3.0 equiv). Product **5da** was isolated in 95 mg and yield is 54%. Yellow solid; mp 173-176 °C; eluent (40% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3565, 3525, 3065, 2924, 2356, 2320, 1744, 1697, 1647, 1543, 1515, 1459, 1217, 1040. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.20 (s, 2 H), 7.66 (bs, 4 H), 7.58 – 7.55 (m, 6 H), 2.48 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 148.9, 146.9, 142.9, 138.7, 129.7, 129.6, 129.1, 126.2, 46.3. **HRMS (ESI):** calc. for [($C_{19}H_{16}N_2O_3S$)H] (M+H) 353.0960, measured 353.0974. **MALDI-TOF-MS:** calc. for [($C_{19}H_{16}N_2O_3S$)K] (M+K) 391.05, measured 391.03.

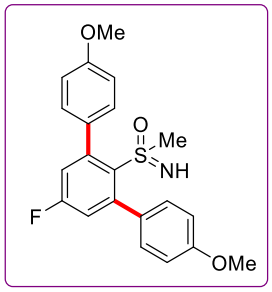


5'-Chloro-4,4''-dimethoxy-2'-(S-methylsulfonimidoyl)-1,1':3',1''-terphenyl (**5ec**): The representative general procedure **A** was followed using **1e** (100 mg) and boronic acid **2c** (3.0 equiv). Product **5ec** was isolated in 127 mg and yield is 60%. Colorless solid; 153-156 °C; eluent (50% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3565, 3523, 3055, 2938, 2364, 1741, 1706, 1646, 1548, 1512, 1462, 1217, 1030. **^{1}H NMR ($CDCl_3$, 400**

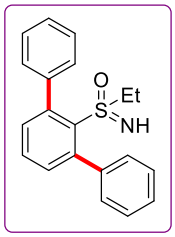


MHz): δ 7.54 (bs, 4 H), 7.31 (s, 2 H), 7.03 (d, *J* = 8.0 Hz, 4 H), 3.88 (s, 6 H), 2.48 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):**δ 160.2, 142.5, 142.3, 135.5, 131.6, 131.3, 130.9, 114.3, 55.4, 46.5. **HRMS (ESI):** calc. for [($C_{21}H_{20}ClNO_3S$)H] (M+H) 402.0931, measured 402.0930. **MALDI-TOF-MS:** calc. for [($C_{21}H_{20}ClNO_3S$)K] (M+K) 440.04, measured 440.01.

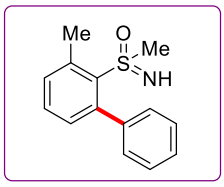
5'-Fluoro-4,4''-dimethoxy-2'-(*S*-methylsulfonimidoyl)-1,1':3',1''-terphenyl (**5fc**): The representative general procedure **A** was followed using **1f** (100 mg) and boronic acid **2c** (3.0 equiv). Product **5fc** was isolated in 140 mg and yield is 63%. Colorless solid; 133-136 °C; eluent (50% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3564, 3525, 3062, 2939, 2360, 2321, 1743, 1699, 1648, 1540, 1513, 1460, 1215, 1078. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.55 (bd, *J* = 8.0 Hz, 4 H), 7.04 (d, *J* = 8.0 Hz, 4 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 7.88 (s, 6 H), 2.51 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):**δ 163.0, 160.5 and 160.3 (C-F coupling), 144.0, 143.9 (C-F coupling), 139.6, 131.7, 130.8, 118.5 and 118.2 (C-F coupling), 114.3, 55.4, 46.6. **Elemental Analysis:** C (66.3%), H (5.5%), N (3.2%), S (7.7%). **HRMS (ESI):** calc. for [($C_{21}H_{20}FNO_3S$)H] (M+H) 386.1226, measured 386.1227. **MALDI-TOF-MS:** calc. for [($C_{21}H_{20}FNO_3S$)K] (M+K) 424.07, measured 424.02.



2'-(Ethylsulfonimidoyl)-1,1':3',1''-terphenyl (**5ga**): The representative general procedure **A** was followed using **1g** (100 mg) and phenyl boronic acid (**2a)** (3.0 equiv). Product **5ga** was isolated in 135 mg and yield is 71%. Colorless solid; 152-155 °C; (40% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3565, 3523, 3057, 2925, 2362, 2322, 1740, 1693, 1646, 1546, 1516, 1452, 1208, 1052. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.61 (bs, 4 H), 7.55 – 7.43 (m, 7 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 2.55 – 2.48 (m, 1 H), 2.45 – 2.38 (m, 1 H), 0.93 (d, *J* = 8.0 Hz, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 141.9, 140.6, 132.3, 130.0, 129.7, 129.6, 128.4, 128.3, 50.5, 8.5. **HRMS (ESI):** calc. for [($C_{20}H_{19}NOS$)H] (M+H) 322.1266, measured 322.1269. **MALDI-TOF-MS:** calc. for [($C_{20}H_{19}NOS$)K] (M+K) 360.08, measured 360.03.

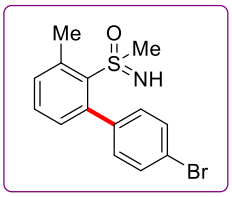


3-Methyl-2-(S-methylsulfonimidoyl)-1,1'-biphenyl (**5ha**): The representative general procedure **A** was followed using **1h** (100 mg) and phenyl boronic acid (**2a)** (3.0 equiv). Product **5ha** was isolated in 133 mg and yield is 70%. Colorless solid; 91-94 °C; (50% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3565, 3524, 3056, 2932, 2363, 2323, 1741, 1706, 1646, 1546,

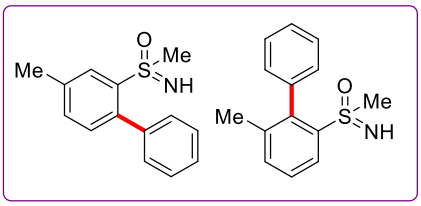


1515, 1453, 1217, 1047. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.42 – 7.38 (m, 5 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.13 (d, *J* = 8.0 Hz, 1 H), 2.94 (s, 3 H), 2.87 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 141.8, 141.1, 138.2, 132.8, 131.0, 130.6, 129.1, 128.6, 128.2, 127.7, 46.7, 22.9. **HRMS (ESI):** calc. for [($C_{14}H_{15}NOS$)H] (M+H) 246.0952, measured 246.0950. **MALDI-TOF-MS:** calc. for [($C_{14}H_{15}NOS$)K] (M+K) 284.05, measured 284.02.

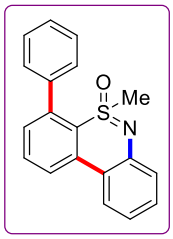
4'-Chloro-3-methyl-2-(*S*-methylsulfonimidoyl)-1,1'-biphenyl (**5he**): The representative general procedure **A** was followed using **1h** (100 mg) and boronic acid **2e** (3.0 equiv). Product **5he** was isolated in 138 mg and yield is 62%. Colorless solid; 122-125 °C; (50% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3567, 3523, 3054, 2931, 2363, 2323, 1743, 1709, 1649, 1548, 1517, 1455, 1219, 1046. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.54 (t, *J* = 8.0 Hz, 2 H), 7.43 (t, *J* = 8.0 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.24 – 7.19 (m, 2 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 3.03 (s, 3 H), 2.86 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 141.6, 139.1, 138.3, 134.0, 133.6, 131.9, 131.4, 130.2, 128.5, 128.2, 46.4, 22.9. **HRMS (ESI):** calc. for [($C_{14}H_{14}BrNOS$)H] (M+H) 324.0058, measured 324.0061. **MALDI-TOF-MS:** calc. for [($C_{14}H_{14}BrNOS$)K] (M+K) 361.96, measured 361.92.



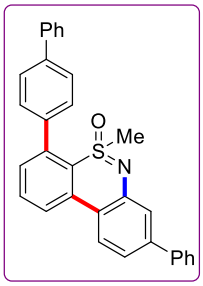
4-Methyl-2-(S-methylsulfonimidoyl)-1,1'-biphenyl and 2-Methyl-6-(S -methylsulfonimidoyl)-1,1'-biphenyl (7.3 : 2.7) (**5ia** and **5ia).** The representative general procedure **A** was followed using **1i** (100 mg) and phenyl boronic acid (**2a)** (3.0 equiv). Product **5ia** and **5ia'** were isolated.in 118 mg and 13 mg yield is 62% and yield is 7%. Colorless semisolid; (45% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3563, 3524, 3016, 2922, 2360, 1742, 1699, 1647, 1541, 1517, 1475, 1256, 1018. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.07 (d, *J* = 8.0 Hz, 0.76 H), 7.59 (d, *J* = 8.0 Hz, 0.76 H), 7.46 – 7.31 (m, 8 H), 7.46 – 7.31 (m, 1.14 H), 7.20 (d, *J* = 8.0 Hz, 0.38 H), 3.20 (s, 1.21 H), 2.72 (s, 3 H), 2.51 (s, 1.16 H), 2.44 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 144.8, 139.9, 139.7, 139.5, 136.7, 136.2, 133.6, 132.6, 132.1, 130.2, 130.2, 129.8, 129.5, 129.2, 129.1, 128.4, 128.0, 127.8, 123.8, 120.6, 43.6, 43.1, 21.4, 21.0. **HRMS (ESI):** calc. for [($C_{14}H_{15}NOS$)H] (M+H) 246.0952, measured 246.0951. **MALDI-TOF-MS:** calc. for [($C_{14}H_{15}NOS$)K] (M+K) 284.05, measured 284.02.



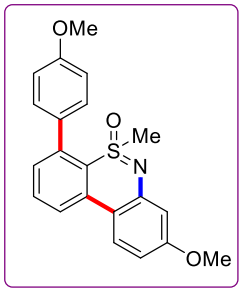
5-Methyl-4-phenyldibenzo[c,e][1,2]thiazine 5-oxide (6a): The representative general procedure **B** was followed using **5aa** (100 mg). Product **6a** was isolated in 76 mg and yield is 76%. Colorless solid; 170-173 °C; eluent (20% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3058, 2926, 1706, 1647, 1578, 1456, 1313, 1269, 1204, 1010. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 8.24 (d, *J* = 8.0 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H), 7.88 (bs, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.55 – 7.51 (m, 3 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.29 (s, 1 H), 7.14 (t, *J* = 8.0 Hz, 1 H), 2.81 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 141.9, 139.0, 138.7, 134.3, 131.5, 131.2, 130.6, 129.4, 129.3, 129.0, 128.9, 128.5, 126.6, 124.6, 124.2, 124.1, 121.1, 118.7, 45.3. **Elemental Analysis:** C (72.5%), H (5.1%), N (4.1%), S (9.2%). **HRMS (ESI):** calc. for [(C$_{19}$H$_{15}$NOS)H] (M+H) 306.0953, measured 306.0951. **MALDI-TOF-MS:** calc. for [(C$_{19}$H$_{15}$NOS)K] (M+K) 344.05, measured 344.00.



4-([1,1'-Biphenyl]-4-yl)-5-methyl-8 phenyldibenzo[c,e][1,2]thiazine 5-oxide (6b): The representative general procedure **B** was followed using **5ab** (100 mg). Product **6b** was isolated in 84 mg and yield is 85%. Colorless solid; 172-175 °C; (20% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3034, 2922, 1707, 1647, 1570, 1452, 1324, 1226, 1195, 1013. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 8.28 (d, *J* = 8.0 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 7.81 - 7.77 (m, 3 H), 7.73 - 7.70 (m, 5 H), 7.56 (s, 1 H), 7.53 – 7.45 (m, 6 H), 7.42 – 7.36 (m, 3 H), 2.93 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 143.2, 142.3, 141.6, 140.4, 139.9, 138.5, 137.9, 134.2, 131.7, 130.6, 129.8, 128.9, 128.8, 127.9, 127.6, 127.5, 127.4, 127.1, 126.4, 124.7, 124.1, 122.7, 120.1, 117.7, 45.6. **Elemental Analysis:** C (80.3%), H (5.0%), N (3.4%), S (6.2%). **HRMS (ESI):** calc. for [(C$_{31}$H$_{23}$NOS)H] (M+H) 458.1579, measured 458.1583. **MALDI-TOF-MS:** calc. for [(C$_{31}$H$_{23}$NOS)K] (M+K) 496.11, measured 496.06.

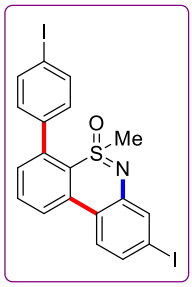


8-Methoxy-4-(4-methoxyphenyl)-5-methyldibenzo[c,e][1,2]thiazine 5-oxide (6c): The representative general procedure **B** was followed using **5ac** (100 mg). Product **6c** was isolated in 64 mg and yield is 65%. Colorless solid; 273-176 °C; eluent (40% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3002, 2927, 1741, 1707, 1646, 1578, 1453, 1338, 1251, 1220, 1029. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 8.10 (d, *J* = 8.0 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H),

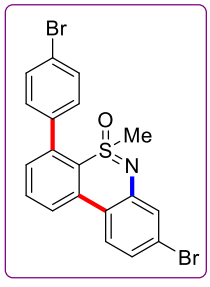


7.80 (bs, 1 H), 7.69 (t, *J* = 8.0 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 6.77 (s, 1 H), 6.73 (d, *J* = 8.0 Hz 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 2.84 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 161.6, 159.9, 143.7, 138.7, 138.6, 134.5, 132.3, 131.6, 131.2, 129.7, 125.5, 125.2, 123.2, 114.8, 112.0, 110.2, 106.7, 55.6, 45.5. **HRMS (ESI):** calc. for [($C_{21}H_{19}NO_3S$)H] (M+H) 366.1164, measured 366.1162. **MALDI-TOF-MS:** calc. for [($C_{21}H_{19}NO_3S$)K] (M+K) 404.07, measured 404.02.

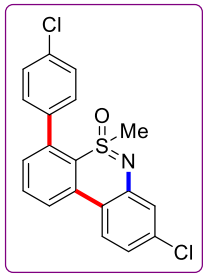
8-Iodo-4-(4-iodophenyl)-5-methyldibenzo[c,e][1,2]thiazine 5-oxide (6d): The representative general procedure **B** was followed using **5ad** (100 mg). Product **6d** was isolated in 76 mg and yield is 77%. Colorless solid; 262-265 °C; eluent (20% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3057, 2920, 2375, 1741, 1706, 1647, 1579, 1451, 1312, 1264, 1193, 1017. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.19 (d, *J* = 8.0 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 2 H), 7.78 – 7.74 (m, 2 H), 7.72 (s, 1 H), 7.66 (bs, 1 H), 7.43 (t, *J* = 8.0 Hz, 2 H), 7.20 (s, 1 H), 2.87 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 143.0, 138.3, 137.8, 134.0, 133.4, 132.9, 131.9, 131.1, 130.9, 130.1, 130.0, 126.1, 125.5, 125.4, 124.2, 118.0, 96.3, 95.2, 45.7. **Elemental Analysis:** C (42.3%), H (2.1%), N (3.3%), S (6.1%). **HRMS (ESI):** calc. for [($C_{19}H_{13}I_2NOS$)H] (M+H) 557.8885, measured 557.8879. **MALDI-TOF-MS:** calc. for [($C_{19}H_{13}I_2NOS$)K] (M+K) 595.84, measured 595.80.



8-Bromo-4-(4-bromophenyl)-5-methyldibenzo[c,e][1,2]thiazine 5-oxide (6e): The representative general procedure **B** was followed using **5ae** (100 mg). Product **6e** was isolated in 84 mg and yield is 85%. Colorless solid; 239-242 °C; eluent (20% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3061, 2952, 2375, 1741, 1706, 1646, 1562, 1462, 1316, 1268, 1205, 1017. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.18 (d, *J* = 8.0 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.78 – 7.76 (m, *J* = 8.0 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 2 H), 7.44 (s, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.34 (bs, 1 H), 7.24 (d, *J* = 8.0 Hz, 1 H), 2.87 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 143.2, 137.7, 137.6, 133.9, 132.9, 132.8, 132.1, 132.3, 131.9, 130.8, 127.2, 126.0, 125.5, 124.34, 124.3, 124.2, 123.5, 117.4, 45.7. **Elemental Analysis:** C (48.5%), H (2.8%), N (3.1%), S (7.4%). **HRMS (ESI):** calc. for [($C_{19}H_{13}Br_2NOS$)H] (M+H) 461.9163, measured 461.9160. **MALDI-TOF-MS:** calc. for [($C_{19}H_{13}Br_2NOS$)K] (M+K) 499.87, measured 499.82.

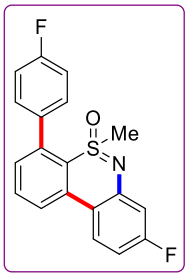


8-Chloro-4-(4-chlorophenyl)-5-methyldibenzo[c,e][1,2]thiazine 5-oxide (6f): The



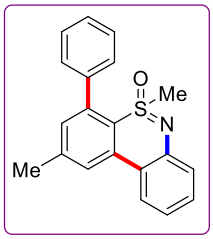
representative general procedure **B** was followed using **5af** (100 mg). Product **6f** was isolated in 78 mg and yield is 79%. Colorless solid; 252-255 °C; eluent (20% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3062, 2949, 2375, 1742, 1699, 1649, 1541, 1457, 1315, 1272, 1206, 1021. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 8.17 (d, *J* = 8.0 Hz, 1 H), 7.81 (bs, 1 H), 7.76 (t, *J* = 8.0 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.27 (s, 1 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 2.86 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 143.1, 137.7, 137.2, 136.1, 135.3, 133.9, 132.6, 131.9, 130.8, 130.6, 129.3, 128.8, 126.0, 125.3, 124.3, 124.2, 121.5, 117.0, 45.6. **Elemental Analysis:** C (59.5%), H (3.5%), N (3.6%), S (8.6%). **HRMS (ESI):** calc. for [($C_{19}H_{13}Cl_2NOS$)H] (M+H) 374.0173, measured 374.0168. **MALDI-TOF-MS:** calc. for [($C_{19}H_{13}Cl_2NOS$)K] (M+K) 411.97, measured 411.92.

8-Fluoro-4-(4-fluorophenyl)-5-methyldibenzo[c,e][1,2]thiazine 5-oxide (6g): The



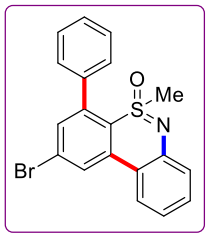
representative general procedure **B** was followed using **5ag** (100 mg). Product **6g** was isolated in 80 mg and yield is 81%. Colorless solid; 115-118 °C; eluent (20% ethyl acetate in hexanes) **IR (ATR) ṽ (cm^{-1}):** 3070, 2370, 1743, 1699, 1648, 1513, 1458, 1338, 1223, 1161, 1020. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 8.15 (d, *J* = 8.0 Hz 1 H), 8.01 (dd, *J* = 8.0, 4.0 Hz 1 H), 7.84 (bs, 1 H), 7.75 (t, *J* = 8.0 Hz 1 H), 7.44 (d, *J* = 8.0 Hz 1 H), 7.40 (d, *J* = 8.0 Hz 1 H), 7.23 (d, *J* = 8.0 Hz 2 H), 6.95 (d, *J* = 8.0 Hz 1 H), 6.85 (d, *J* = 8.0 Hz 1 H), 2.86 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 165.4, 164.3, 162.9, 161.8, 144.0 and 143.9 (C-F coupling), 137.9, 134.8 and 134.1 (C-F coupling), 133.1, 131.8, 131.1, 130.6, 126.0 and 125.9 (C-F coupling), 125.8, 124.0, 115.7, 115.1, 110.5 and 110.3 (C-F coupling), 109.3 and 109.0 (C-F coupling), 45.5. **Elemental Analysis:** C (67.4%), H (4.5%), N (4.3%), S (10.6%). **HRMS (ESI):** calc. for [($C_{19}H_{13}F_2NOS$)H] (M+H) 342.0764, measured 342.0765. **MALDI-TOF-MS:** calc. for [($C_{19}H_{13}F_2NOS$)K] (M+K) 380.03, measured 380.00.

2,5-Dimethyl-4-phenyldibenzo[c,e][1,2]thiazine 5-oxide (6h): The representative general procedure **B** was followed using **5ba** (100 mg) Product **6h** was isolated in 79 mg and yield is 80%. Colorless solid; 185-188 °C; eluent (20% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3061, 2926, 2372, 1742, 1700, 1649, 1542, 1460, 1317, 1277, 1161, 1057. **^{1}H NMR (CDCl$_3$,**



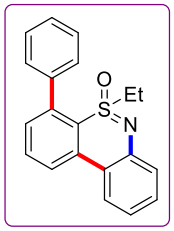
400 MHz): δ 8.06 (d, *J* = 8.0 Hz 1 H), 8.03 (s, 1 H), 7.86 (bs, 1 H), 7.54 – 7.49 (m, 3 H), 7.43 – 7.38 (m, 2 H), 7.28 – 7.25 (m, 2 H), 7.12 (t, *J* = 8.0 Hz 1 H), 2.79 (s, 3 H), 2.56 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 142.1, 142.0, 139.1, 138.7, 134.4, 131.9, 131.6, 131.2, 130.4, 129.3, 128.7, 128.4, 128.1, 124.5, 124.2, 124.1, 120.9, 118.7, 45.4, 21.8. **HRMS (ESI):** calc. for [($C_{20}H_{17}NOS$)H] (M+H) 320.1109, measured 320.1108. **MALDI-TOF-MS:** calc. for [($C_{20}H_{17}NOS$)K] (M+K) 358.06, measured 358.02.

2-Bromo-5-methyl-4-phenyldibenzo[c,e][1,2]thiazine 5-oxide (6i): The representative general procedure **B** was followed using **5ca** (100 mg). Product **6i** was isolated in 83 mg and yield is 84%. Colorless solid; 166-169 °C; eluent (20% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3060, 2926, 2373, 1742, 1700, 1648, 1555, 1459, 1316, 1268, 1208, 1008. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.36 (s, 1 H), 8.00 (d, *J* = 8.0 Hz 1 H), 7.85 (bs, 1 H), 7.59 (s, 1 H), 7.54 – 7.53 (m, 3 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 2.78 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 142.2, 140.2, 137.7, 136.1, 133.1, 131.2, 131.1, 129.3, 129.1, 128.6, 126.9, 126.3, 125.3, 124.7, 124.3, 121.3, 117.7, 45.3. **Elemental Analysis:** C (58.6%), H (4.3%), N (3.7%), S (8.0%). **HRMS (ESI):** calc. for [($C_{19}H_{14}BrNOS$)H] (M+H) 384.0058, measured 384.0060. **MALDI-TOF-MS:** calc. for [($C_{19}H_{14}BrNOS$)K] (M+K) 421.96, measured 421.90.



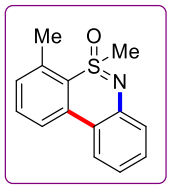
5-Methyl-2-nitro-4-phenyldibenzo[c,e][1,2]thiazine 5-oxide (6j): The representative general procedure **B** was followed using **5da** (100 mg). Product **6j** was isolated in 78 mg and yield is 79%. Yellow color solid; 156-159 °C; eluent (20% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3068, 2925, 2315, 1742, 1700, 1648, 1529, 1459, 1317, 1269, 1211, 1014. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 9.07 (s, 1 H), 8.25 (s, 1 H), 8.14 (d, *J* = 8.0 Hz 1 H), 7.87 (bs, 1 H), 7.59 (s, 3 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.23 (d, *J* = 8.0 Hz, 1 H), 2.83 (s, 3 H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 148.5, 142.1, 140.8, 137.2, 136.2, 131.97, 130.9, 130.0, 129.8, 129.5, 129.1, 128.9, 124.9, 124.5, 124.0, 121.9, 119.2, 118.0, 45.1. **HRMS (ESI):** calc. for [($C_{19}H_{14}N_2O_3S$)H] (M+H) 351.0803, measured 351.0804. **MALDI-TOF-MS:** calc. for [($C_{19}H_{14}N_2O_3S$)K] (M+K) 389.03, measured 389.01.

5-Ethyl-4-phenyldibenzo[c,e][1,2]thiazine 5-oxide (**6k**): The representative general procedure



B was followed using **5ga** (100 mg). Product **6k** was isolated in 82 mg and yield is 83%. Colorless solid; 183-186 °C; eluent (20% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3059, 2927, 2312, 1742, 1700, 1648, 1573, 1458, 1319, 1274, 1195, 1015. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 8.27 (d, *J* = 8.0 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H), 7.90 (bs, 1 H), 7.76 (t, *J* = 8.0 Hz, 1 H), 7.53 – 7.50 (m, 1 H), 7.45 – 7.40 (m, 3 H), 7.29 (d, *J* = 8.0 Hz 3 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 7.15 – 7.06 (m, 1 H), 7.49 – 7.40 (m, 1 H), 7.12 (t, *J* = 8.0 Hz, 3 H), **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 142.6, 139.2, 138.8, 135.6, 131.7, 131.5, 130.7, 130.5, 128.8, 128.7, 128.2, 124.6, 124.1, 122.3, 120.7, 117.9, 49.7, 9.9. **Elemental Analysis:** C (73.0%), H (5.2%), N (4.0%), S (9.4%). **HRMS (ESI):** calc. for [($C_{20}H_{17}NOS$)H] (M+H) 320.1109, measured 320.1107. **MALDI-TOF-MS:** calc. for [($C_{20}H_{17}NOS$)K] (M+K) 358.06, measured 358.01.

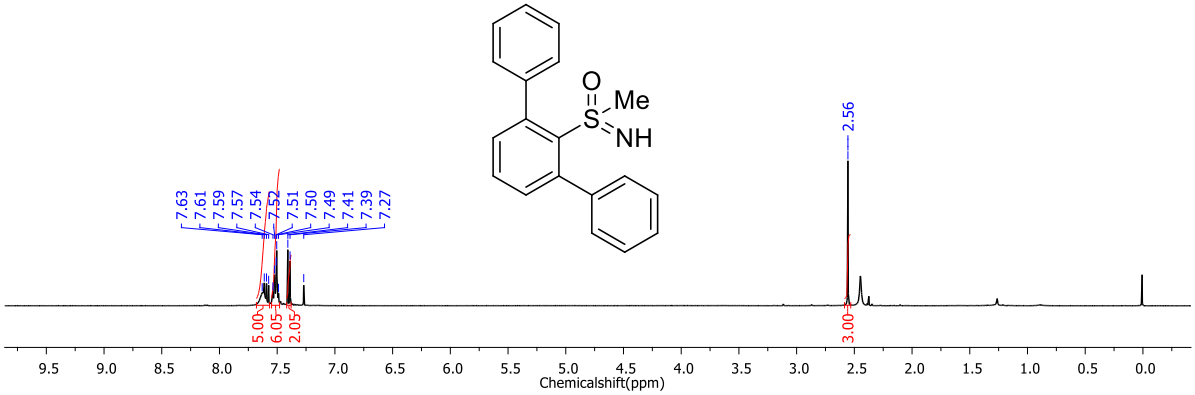
4,5-Dimethyldibenzo[c,e][1,2]thiazine 5-oxide (6l): The representative general procedure **B**

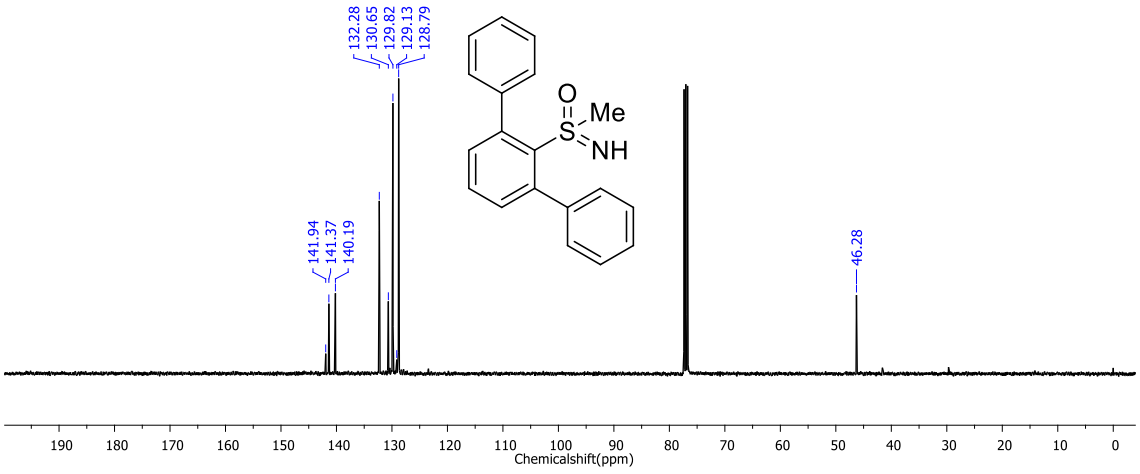


was followed using **5ha** (100 mg). Product **6l** was isolated in 40 mg and yield is 41%. Colorless solid; 174-177 °C; eluent (35% ethyl acetate in hexanes). **IR (ATR) ṽ (cm^{-1}):** 3064, 2927, 2366, 1742, 1699, 1648, 1541, 1460, 1321, 1261, 1202, 1015. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ 8.08 (d, *J* = 8.0 Hz, 1 H), 7.96 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.63 (t, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.37 (t, *J* = 8.0 Hz, 1 H), 7.23 (d, *J* = 8.0 Hz, 1 H), 7.06 (t, *J* = 8.0 Hz, 1 H), 3.51 (s, 3 H), 2.85 (s, 3 H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 142.2, 135.5, 135.2, 132.6, 131.2, 130.5, 124.6, 124.2, 123.9, 121.9, 120.6, 117.5, 47.8, 21.0. **HRMS (ESI):** calc. for [($C_{14}H_{13}NOS$)H] (M+H) 244.0796, measured 244.0799. **MALDI-TOF-MS:** calc. for [($C_{14}H_{13}NOS$)K] (M+K) 282.03, measured 282.01.

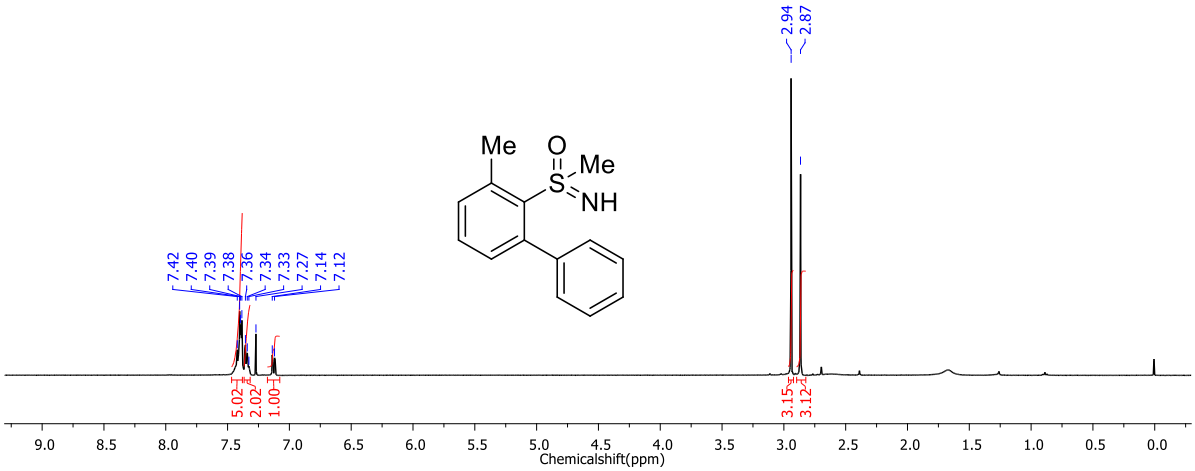
4C.5.6 Spectral Copies of Selected Compounds

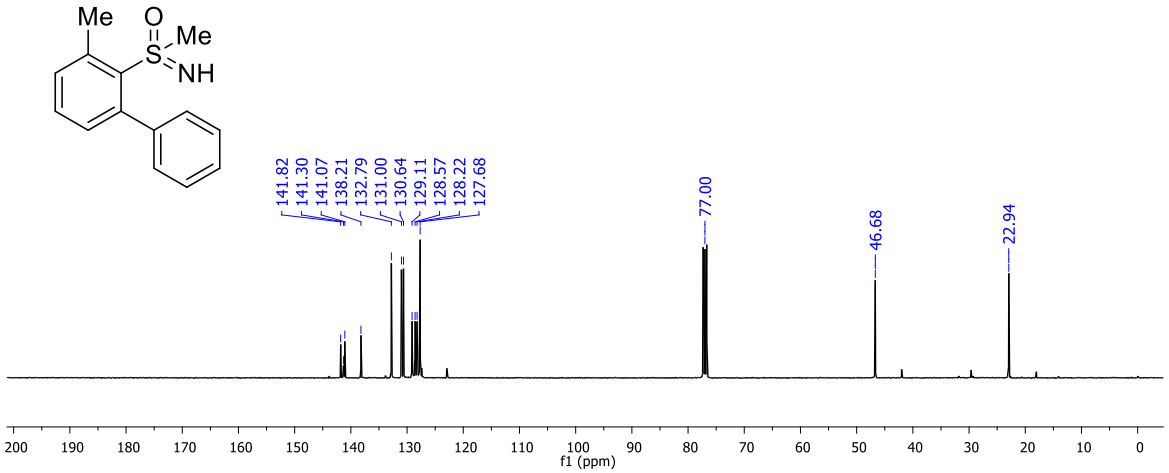
2'-(*S*-Methylsulfonimidoyl)-1,1':3',1''-terphenyl (5aa).



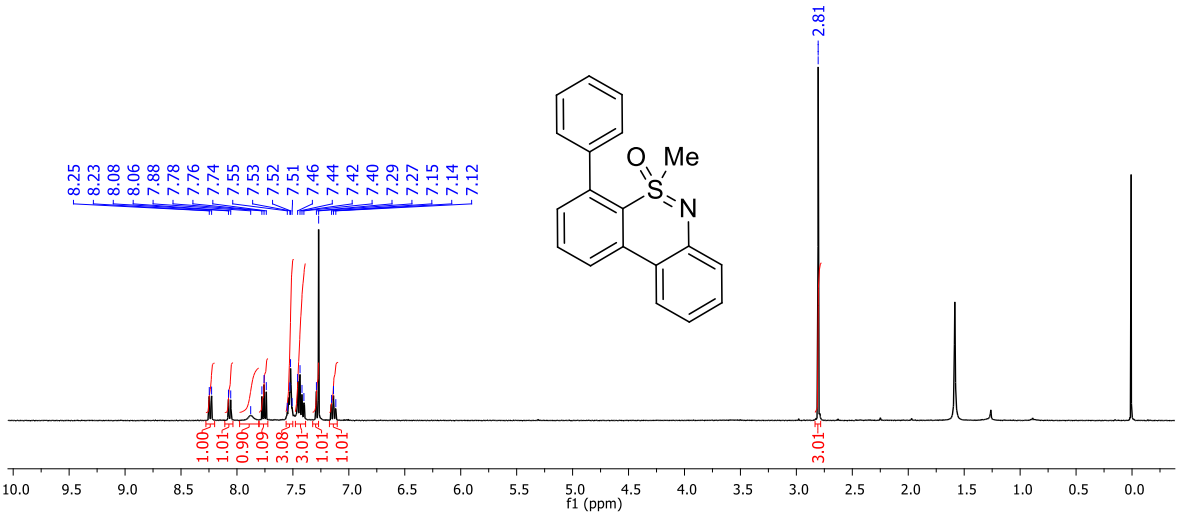


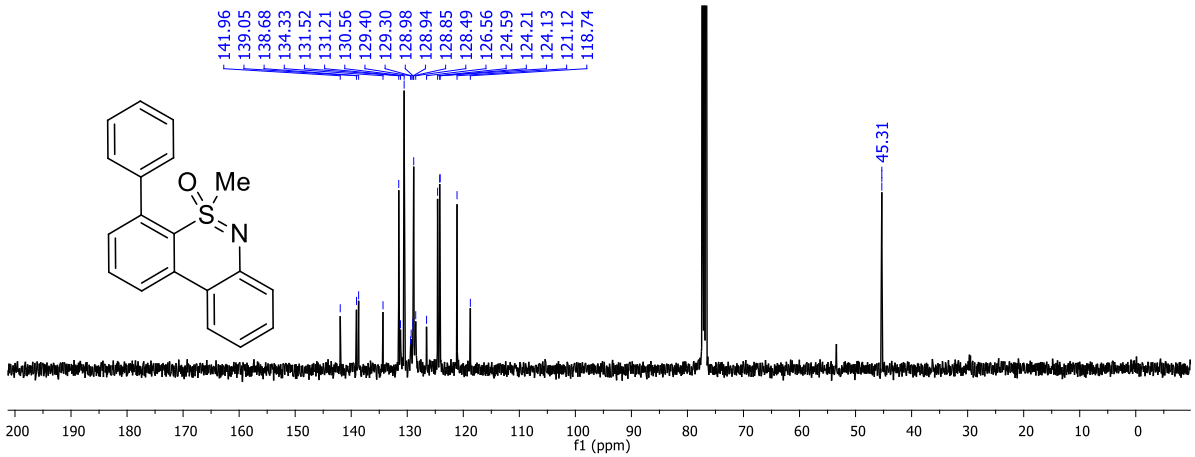
3-Methyl-2-(S-methylsulfonimidoyl)-1,1'-biphenyl (5ha).

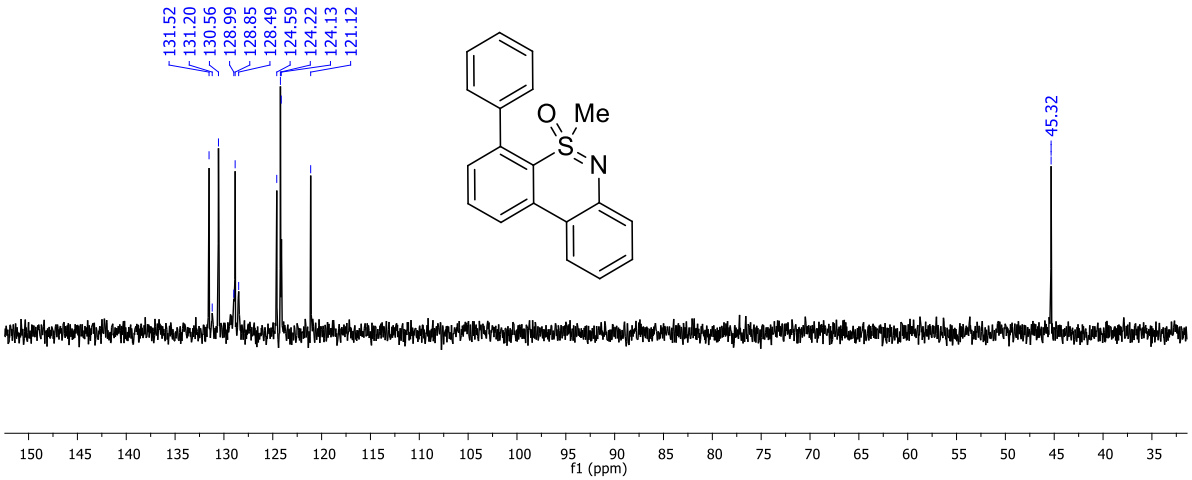




5-Methyl-4-phenyldibenzo[c,e][1,2]thiazine 5-oxide (6a).







4,5-Dimethyldibenzo[c,e][1,2]thiazine 5-oxide (6l).