Development of new metal-catalyzed reactions for the synthesis of spirobi[indene]-diones, aryl esters, *β*-keto esters and pyrrolidinones

by

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Registration No: **10CC16A38006**

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Under the supervision of

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Ghaziabad, U.P.-201002, INDIA

2022

CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled *"Development of new metal-catalyzed reactions for the synthesis of spirobi[indene]-diones, aryl esters, β-keto esters and pyrrolidinones"* submitted by *Ms. Bidisha Rani Bora* to the Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of *Doctor of Philosophy*, embodies original research work carried out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) has been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) etc., used in the thesis from other source(s), have also been duly cited and acknowledged.

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DEDICATED

TO

MY PARENTS

(Mr. Baneswar Bora)

(Mrs. Dipali Bora)

CONTENT

Acknowledgement

At the outset, I would like to offer my sincere gratitude to my supervisor Dr. Sanjib Gogoi, Principal Scientist, Chemical Science & Technology Division, NEIST, Jorhat, for his relentless and continuous support during the course of my research work leading to Ph.D. degree. He had been a pivotal and illuminating source of inspiration for me during the entire period of my study and his guidance was highly influential in achieving this task.

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Finally, I would like to thank the almighty for making me spiritually strong every time I fall apart.

Date: 22.03.2022

Place: Jorhat

Bidisha Rani Bora

Experimental Remarks

1. Solvents and all commercially available chemicals were used as received without purification unless otherwise specified and whenever needed, were purified by standard protocols prior to use. Anhydrous solvents were prepared with standard methods.
2. Reaction progress and product purity were monitored by ascending TLC using TLC Silica gel 60F254 plates. Visualization of spots on TLC plates was achieved *via* the development with iodine chamber, UV chamber or in *p*-anisaldehyde.
3. Reaction products were purified by either gravity column chromatography over Silica Gel (60-120 mesh and 100-200 mesh), neutral alumina or basic alumina and flash chromatography.
4. All moisture sensitive reactions were performed under argon atmosphere.
5. Elemental analyses were performed on Perkin Elmer-2400 spectrometer.
6. Melting points were determined in open capillary (pyrex) tubes with a Buchi-540 micro melting point apparatus and are uncorrected.
7. IR spectra were recorded on a Perkin-Elmer system 2000 FT-IR spectrometer.
8. HRMS data were recorded by Electrospray ionization with a Q-TOF mass analyzer.
9. ^{1}H, ^{13}C NMR spectra were recorded on 500/400 MHz and 125/100 MHz NMR spectrometers respectively in $CDCl_3$/DMSO-d_6. Chemical shifts (δ) are quoted in ppm and coupling constants (J) are measured in Hertz (Hz).

Abbreviations/symbols used

Ar : Aryl group

EtOAc : Ethylacetate

Et : Ethyl

DMF : Dimethyl formamide

Cacld. : Calculated

DMF : Dimethyl formamide

Et : Ethyl

^{o}C : Degree centigrade

h : Hour

MCR : Multi-component reactions

M.p. : Melting point

mL : Milliliter

EDG : Electrondonating group

TLC : Thin layer chromatography

^{1}H : Proton

s : Singlet (NMR)

dd : Double doublet (NMR)

q : Quartet (NMR)

bs : Broad singlet (NMR)

δ : Chemical Shift (NMR)

HRMS : High Resolution Mass Spectrometry

EtOH : Ethanol

DCM : Dichloromethane

Ph : Phenyl

mmol : Millimole

conc. : Concentrated

$CDCl_3$: Deuterated chloroform

ESI : Electron spray ionization

Hz : Hertz

rt : Room temperature

Me : Methyl

eq : Equation

EWG : Electronwithdrawing group

R_f : Retention factor

equiv : Equivalent

^{13}C : Carbon-13

d : Doublet (NMR)

t : Triplet (NMR)

m : Multiplet (NMR)

J : Coupling constant

ppm : Parts per million

SUMMARY OF THE THESIS

The main focus of the research work reported in this thesis is on development of new synthetic strategies for the construction of some important organic scaffolds and their analogues, which have not been attempted to synthesize before or which could not be synthesized by already reported C-H bond activation reactions by using readily available starting materials. In this regards, we have successfully synthesized some of the important organic molecules like spirobi[indene]-diones, aryl esters, *β*-keto esters and pyrrolidinones by using ruthenium-catalyzed C-H activation as well as alkyne annulations, decarbonylative/decarboxylative type of strategies.

General introduction

The general introduction part of the thesis contains a brief discussion on transition-metal-catalyzed C-H activation, which highlights the properties and reactivity of C-H bonds, mechanistic studies, historical overview and different types of additives and their roles in C-H activation reaction. Also, it contains a brief literature review on Ru-catalyzed C-H activation reactions.

Chapter 1

This chapter describes a new methodology towards the synthesis of spirobi[indene]-dione from phenyl indandione and alkyne. It is suggested that keto-enol tautomerization of the dione unit transiently provides an -OH directing group to facilitate directed *ortho*-C-H metalation and subsequent annulations with alkyne provides the spirobi[indene]-dione compounds. This spirobi[indene] scaffold is the key motif of the antitumor antibiotic fredericamycin A as well as some other pharmaceutically important compounds. The structure of the spiro compounds was determined by analyzing the NMR spectra and confirmed by the single X-ray crystallography studies.

Chapter 2

In this chapter, a novel Ru(II)-catalyzed coupling reaction of isatoic anhydride and salicylaldehyde is reported. This reaction proceeds through decarboxylation and decarbonylation to afford good yields of important aryl 2-aminobenzoates. Further, we have performed a gram-scale esterification reaction which indicates the practical applicability of this reaction.

Chapter 3

This chapter describes a Ru-catalyzed reaction of cinnamic acids with alcohol for the synthesis of *β*-ketoesters. This unprecedented Ru(II)-catalyzed reaction proceeds through activation of the olefinic double bond and subsequent esterfication of the acid to afford the important class of molecule *β*-ketoesters in good yield. Seeing the importance of 1,3-dicarbonyl compounds in general, along with the simple and mild nature of this reaction, we belief that it will accumulate with extensive application in synthetic chemistry.

Chapter 4

This chapter describes an efficient strategy for the synthesis of 3-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-phenylpyrrolidine-2,5-dione from 1-Hydroxybenzotriazole and *N*-phenyl maleimide *via* Ru(II)-catalyzed C-H activation in a single reaction vessel. This methodology provides good to moderate yield of substituted pyrrolidinone and tolerates variety of functional groups.

General Introduction

The general introduction part contains a brief overview on transition-metal-catalyzed C-H activation which includes mechanistic studies and some pioneer reactions. Also it contains a brief literature review on Ru-catalyzed C-H activation/functionalization reaction.

INTRODUCTION

1.1 C-H activation/functionalization

"C-H activation is at the center of organic chemistry"

- Albert Eschenmoser, 2010

A few decades ago, the use of non-activated C-H bonds in coupling reactions as reaction sites looked like an unrealistic dream. It has difficulty with both challenges and opportunities for nearly every branch of chemistry. However, the field of C-H activation has emerged as one of the most rapidly evolving field of homogeneous catalysis in the last 20 years,[1] refurbishing the scenario of both organometallic catalysis and synthetic chemistry.[2]

Majority of our chemical feedstock consists of hydrocarbons (molecules containing only carbon and hydrogen atom). However, most compounds require nitrogen, oxygen, phosphorus, sulphur, halogen and other elements in the molecule for getting the desired properties. As a result, to get the molecule we want, we must break the C-H bonds in order to get new ones. Again, an organic synthetic chemist's primary task is to modify molecules in the direction of increasing functionalization. That is, conversion of C-H bond to C-C or C-heteroatom bonds. Because of the apolar nature and relatively high energy of C-H bonds, the formation of C-C and C-heteroatom bonds by the breaking of C-H bonds have been believed to be difficult which reflects their lack of reactivity. Keeping their ubiquitous nature in mind, if C-H bonds can be selectively functionalized, it could potentially prove to be a powerful class of transformations in organic synthesis.

In traditional method, people generally used the activated bond like C-Br, C-triflate bond and then they perform some cross-coupling reactions to deliver the desired C-C or C-heteroatom bond. But, this strategy is having some problem, because, it requires breaking the activated compound, which takes a series of steps and then side product is also another problem. After few decades, researchers found that, transition metal offers an intriguing alternative as reagents or catalysts to overcome this problem. Because, transition metals have the capacity to form the C-M bond directly from the C-H bond and this transaction is recognized as C-H activation. This C-M bond is very active and reacts with different nucleophile/C or heteroatom nucleophile and it will give the desired C-C/C-heteroatom bond. Transition metal acts as Lewis σ-acids and π-bases at the same time since d-orbital lie at relatively high energy level, resulting in interactions that are peculiar to this group of elements. This approach has the advantage that the active bond does not need to be synthesized, so it is step economic and at the same time exterminate the side product, therefore, environmentally friendly process.

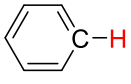
During the last decades, transition-metal-catalyzed C-H bond activation occupy a huge area of research, resulting in a slew of new methods for converting C-H bonds into other bonds that are both cheap and simple. Developing a new approach of this kind normally involves two challenges. Firstly, C-H bond has low thermodynamic and kinetic reactivity. This problem is typically fixed by using high energy reagents and catalysts which can form active species like halogen or oxygen radicals to resolve reaction barriers and eventually form new bonds of equal strength (e.g. O-H bond) to reimburse the energy cost by breaking a C-H bond. Secondly, large organic molecules

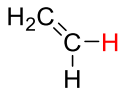
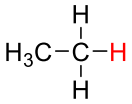
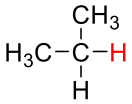
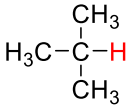
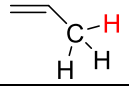
usually have multiple C-H bonds, all of which can have identical properties, and only a few of them can be broken to get a specific target molecule. This can be resolved by beginning with a substance with specific C-H bonds that are more likely to be substituted due to specific electronic predispositions and also using substrate that contain coordinating ligand (directing group). They bind to the metal core and selectively deliver the catalyst to adjacent C-H bond.

1.1.1 Reactivity/properties of C-H bond

Breaking C-H bond is a common problem in organic synthesis. This makes difficult for this bond to deal with many interactions. It is one of the strongest single bond. C-H bonds are traditionally considered as unreactive and can be broken by coordination. It has a bond length of about 1.09 Å (1.09×10^{-10} m) and about 413 kJ/mol of bond energy. Table 1.1 shows the bond dissociation energies (BDEs) and acidities of C-H bonds in seven different hydrocarbons. The BDE decreases from C(sp)-H → C(sp^2)-H → C(sp^3)-H, and from 1°→ 2°→ 3°→ allylic C(sp^3)-H bond, in accordance with the idea that this value is inversely proportional to the stability of the radicals gained from homolytic dissociation of the bond. Differently, acidity is proportional to the stability of the deprotonated species, the pK_a trend goes approximately in the opposite direction, with the apparent exception of the allyl C-H bond.[3]

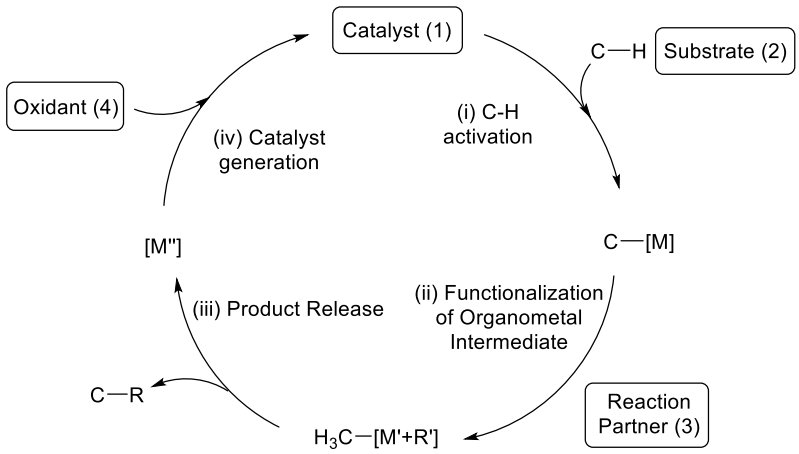
Table 1.1: BDEs and pK_a values of selected C-H bonds:

Type of C-H bond	Structure	BDE (kJ/mol)	BDE (kcal/mol)	pK_a
C(sp)		552.2	132	~25
$C(sp^2)_{arom}$		473.0	113	43

$C(sp^2)_{vinyl}$		460.2	110	44
$C(sp^3)_1{}^o$		410.8	98.2	~50
$C(sp^3)_2{}^o$		397.9	95	~50
$C(sp^3)_3{}^o$		389.9	93.2	~50
$C(sp^3)_{allylic}$		361.1	86.3	43

1.1.2 Mechanism of C-H activation by a metal catalyst

In several ways, the improvement made has been due to a better understanding of the mechanisms of C-H activation. A standard transition between a C-H activation substrate (referred to as the "substrate") and an appropriate reactant (referred to as the "reaction partner") can be divided into four general steps: (i) C-H activation step (ii) functionalization of resulting organometallic species (iii) product molecule release and (iv) if necessary, active catalyst regeneration (Scheme 1.1).



Scheme 1.1: Generalized mechanistic scheme for C-H activation catalysis

Over the last few decades, many efforts on catalytic investigations on late-transition metals (e.g. Ru, Pd, Pt, Rh, Ir) have led to some generalities on how a C-H bond is triggered. Which C-H activation mechanism can be used in any given reaction is largely determined by the identity and oxidation state of the metal.[4] Mechanistically, the C-H activation/functionalization processes can be classified into two main classes: (A) Outer sphere and (B) Inner sphere. Outer sphere mechanism comprise with the initial insertion of a C-H bond into the ligand of a transition metal complex, while the inner sphere mechanism involves coordination of the non-activated C-H bond to the metal vacant site to create an organometallic complex wherein the hydrocarbyl species remain associated in the inner-sphere during the cleavage of C-H bond. In present scenario, consensus is growing among chemist to limit the C-H activation to inner-sphere mechanisms.

Depending on the different properties of metal M and ligand set L_n in active L_nM species, different situations are confronted.[5] There are some well-established mechanisms, such as oxidative addition (OA), σ-bond metathesis (σ-BM), 1,2-addition, electrophilic aromatic substitution (S_EAr) and single electron transfer (SET), whereas others, such as concerted metalation deprotonation (CMD) and base-assisted intramolecular electrophilic-type substitution (BIES) are relatively new to this field. Herein, we present a brief overview of each of them:

(i) Oxidative addition (OA):

It is most commonly caused by an electron-rich metal centre (low oxidation state) interacting synergistically with the C-H bond through a σ-C-H bond coordination to the metal and a $d\pi$-backdonation to the σ^*-C-H orbital, lowering its bond order,

resulting in homolytic bond cleavage and oxidizing the metal centre in two units (Figure 1.1a). This will result in the formation of a reactive organometallic species bearing hydride and alkyl/aryl ligands at the oxidized metal center. This mechanism is common for electron-rich, low-valent late transition metal complexes, e.g. the higher oxidation state of the metal and the required change in geometry upon formation of the two new bonds are energetically favourable for Re, Pt, Fe, Ir, Ru and Os.

(ii) σ-bond metathesis:

This mechanism is preferred for electron deficient metal centres (i.e. high oxidation state), since the bond breaking and bond forming actions occurs in a concerted way by forming a four-centered metalacycle transition state without affecting the metal centre's oxidation state. Transition metals having d^0 electronic configuration (group 3 and 4, lanthanides and actinides) cannot undergo oxidative addition and thus preferred mechanism involves usually an alkyl or a hydride complex which proceeds through a four-centered transition state in which formation of M-R^2 and R^1-H bonds and breaking of M-R^1 and R^2-H bonds take place in a single step without change of the metal oxidation state (Figure 1.1b). This is usually common for late or post-transition metals *viz.* Pd^{2+}, Pt^{2+}/Pt^{4+}, Hg^{2+}.

(iii) 1,2-addition:

In this pathway, the C-H bond directly adds across an unsaturated M-X bond in a 1,2-addition manner. This mechanism is quite similar to that of σ-bond metathesis, although, this newly formed X-H does not detach from the metal complex as M-X σ-bond is still present in the product (Figure 1.1c). Amido, alkylidene, alkoxy and

alkylidyne complexes of early to middle transition metals have been known to follow this activation mode.

(iv) Electrophilic aromatic substitution (S_EAr):

Since the metallic centres can serve as Lewis acids, this activation reaction is based on an electronic interaction in between the substrate's π-electronic cloud and the electrophilic metal centre, resulting a new C(aryl)-M bond without changing the metal oxidation state (Figure 1.1d). This greatly increases the acidity on the vicinal C(aryl)-H bond, which may otherwise be lost as a proton due to re-aromatization or base action. The same mechanism is also known as a base assisted intramolecular electrophillic substitution (BIES), when the base is inside the coordination sphere of the metal centre (Figure 1.1g).

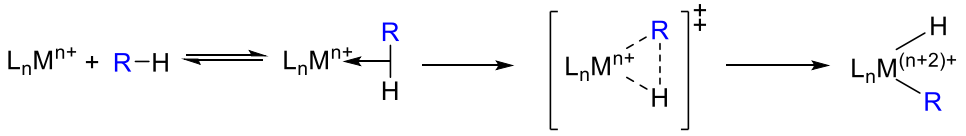
(v) Single electron transfer (SET):

It is a two-electron process with two basic stages, each involving one electron each. The C-H bond is first homolytically cleaved, resulting in the metal-hydride species and carbon-centered radical (Figure 1.1e). Then, the alkyl/aryl-hydride metal oxidized species is generated by a recombination reaction between the radical and the metal core.

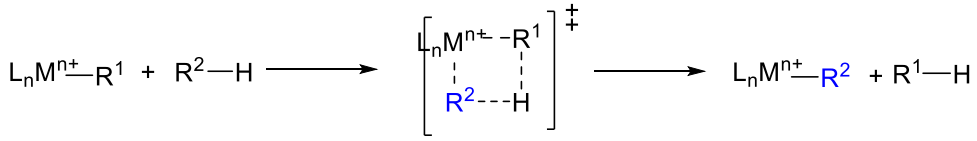
(vi) Concerted metalation deprotonation (CMD):

This C-H activation pathway depends on the near proximity of the C-H bond to the metal centre, which is normally aided by a directing donor group. During the formation of the C-M bond, the metal centre has a coordinated base that facilitates the deprotonation of the C-H bond in a concerted manner (Figure 1.1f).

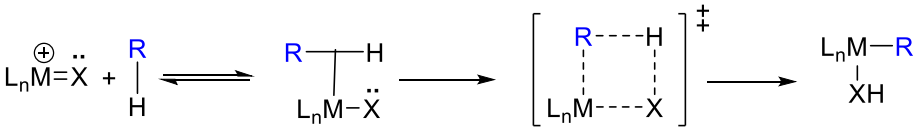
(a) *Oxidative addition (OA)*



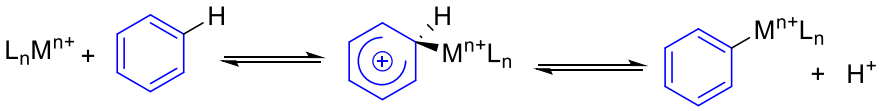
(b) *σ -bond metathesis*



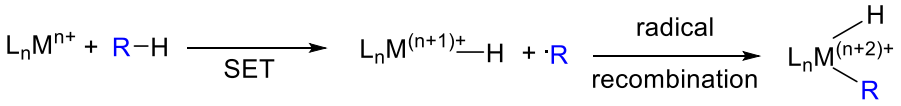
(c) *1,2-addition*



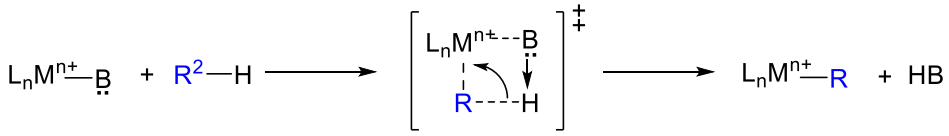
(d) *Electrophilic aromatic substitution (S_EAr)*



(e) *Single electron transfer (SET)*



(f) *Concerted metalation deprotonation (CMD)*



(g) *Base-assisted intramolecular electrophilic substitution (BIES)*

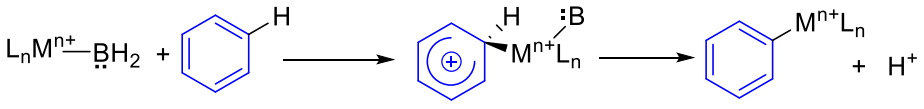


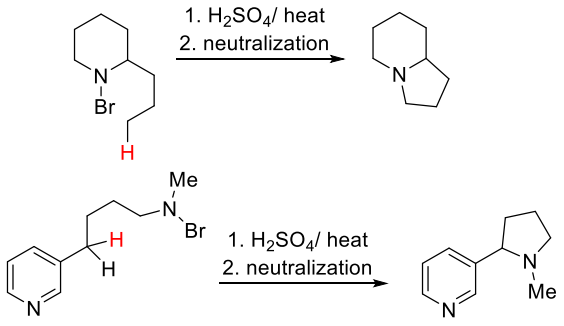
Figure 1.1: Mechanisms of C-H activation.

1.1.3 Historical overview

The application of transition-metal-catalyzed cross coupling reactions in organic synthesis has been hailed as one of the most significant breakthroughs of the new

millennium. Heck, Noyori and Suzuki established a new frontier between homogeneous catalysis and synthetic organic chemistry with their seminal works based on Pd-catalysts in the 1970s.[6-10] Late transition metals, especially precious metals, are the most versatile catalytic systems for a wide range of functionalization reactions, demonstrating their durability in a number of organic synthesis applications.[11-17]

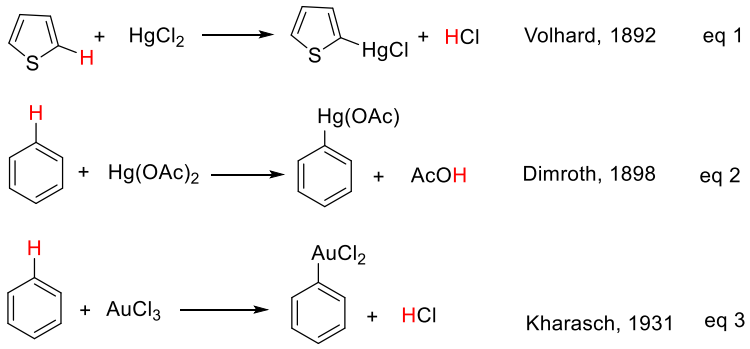
In 1883, Hoffman published the first example of isolated alkyl C-H bond functionalization. Under strongly acidic conditions, C-H reactivity was dependent on the formation of highly reactive oxygen and nitrogen-based radicals. Because of the indiscriminate reactivity of these radicals, selectivity could only be achieved by using structural proximity between the high energy radical produced and the C-H group to be functionalized.[18] Löffler and Freytag later extended this approach to secondary amines, which they expertly applied to the synthesis of nitrogen-heterocyclic derivatives (Scheme 1.2).[19]



Scheme 1.2

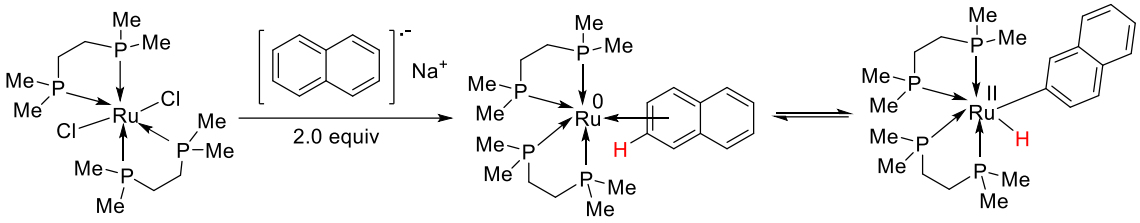
In 1892, Jacob Volhard reported the first example of metal promoted C-H activation in which thiophene was treated with mercury(II) chloride to afford chloromercurythiophene (Scheme 1.3, eq 1).[20a] Few years later, in 1902, Otto Dimroth

treated various aromatic hydrocarbons with $Hg(OAc)_2$ to synthesize a number of arylmercury acetates (Scheme 1.3, eq 2).[20b-20d] Subsequently, Kharasch and Isbell were able to perform the reaction of $AuCl_3$ with benzene, to form phenyl auric dichloride ($PhAuCl_2$) with evolution of HCl gas. Further, $PhAuCl_2$ reacts with excess of benzene to form unstable diphenyl auric chloride intermediate, which underwent decomposition in the presence of HCl to form PhCl and AuCl (Scheme 1.3, eq 3).[20e] But, later these reactions did not qualify to be classified under true C-H activation. Another, pioneering work in the field of C-H activation was reported by Murahashi in 1955 using cobalt catalysis during the synthesis of *N*-phenyl isoindolinone using carbon monoxide (CO) as a carbonyl source.[21]



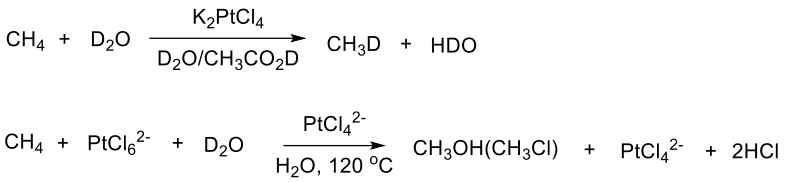
Scheme 1.3

Nonetheless, Chatt is likely to be credited with inventing the metal-promoted C-H activation reaction, who in 1965 reported the insertion of ruthenium(0) complex, $RuCl_2(dmpe)_2$ into the C-H bond of naphthalene (Scheme 1.4).



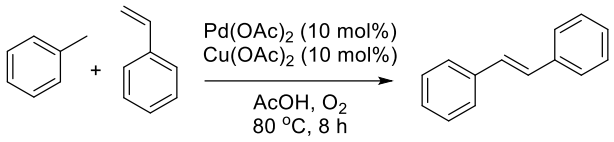
Scheme 1.4

In 1969, A. E. Shilov reported Pt(II) induced H/D exchange between methane and heavy water involving binding of Pt(II) to methane (Scheme 1.5).[23] In 1972, Shilov group was able to produce the selectively oxidized species methanol and methyl chloride by the addition of catalytic amount of potassium hexachloroplatinate to aqueous reaction of stoichiometric amount of potassium tetrachloroplatinate with methane.[24] Till date, Shilov mechanism is one of the only genuine catalytic mechanism capable of selective alkane functionalization under mild conditions. It was the first example of such a transition, establishing Shilov chemistry as a pioneer in the field of C-H activation.



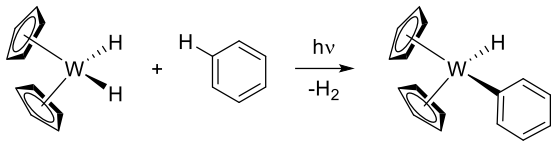
Scheme 1.5

In 1967, Fujiwara and Moritani disclosed an excellent work showing the Pd(II)-promoted vinylation of arenes. Soon after, the same researchers developed a catalytic aerobic version of this dehydrogenative coupling, which used a $Cu(OAc)_2/O_2$ system as oxidizing system (Scheme 1.6).[25]



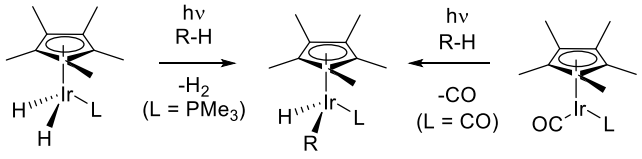
Scheme 1.6

In 1970, M. L. H. Green reported a photochemical addition of benzene to bis-*n*-cyclopentadienyltantalum hydride Cp_2WH_2, which involves the activation of C-H bond to form Cp_2WHPh with the liberation of H_2 (Scheme 1.7).[26]

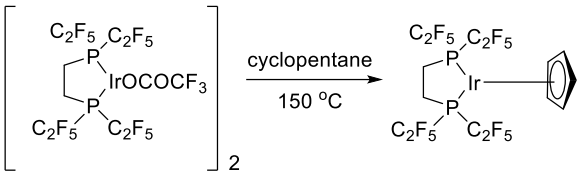


Scheme 1.7

Following the reports of M. L. H. Green in 1982, R. G. Bergman[27a] and W. A. G. Graham[27b] reported the first examples of oxidative addition of unactivated and completely saturated hydrocarbons to coordinatively unsaturated Cp*(PMe_3)Ir species, resulting in the formation of hydrido alkyl products (Scheme 1.8). These results were considered as the pioneering work that revealed oxidative addition breakthrough which must constitute a major milestone. Again, in 1996, Roddick reported an oxidative aromatisation of a saturated carbocycle (Scheme 1.9).[28]

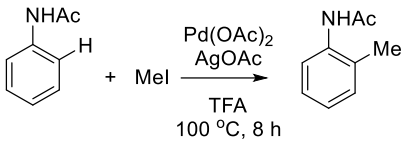


Scheme 1.8



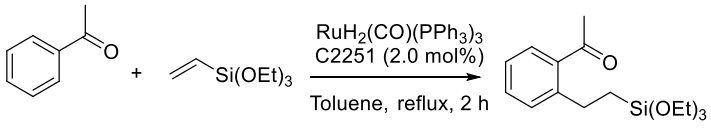
Scheme 1.9

Later, in 1984 Tremont et al. reported an *ortho*-alkylation of acetanilides with $Pd(OAc)_2$ and alkyl iodides (Scheme 1.10). This transformation eliminates the need for Pd^0 to Pd^{II} recycle and may involve a Pd^{IV} intermediate.[29]



Scheme 1.10

In 1993, Murai et al. reported the first chelation assisted catalytic addition of C-H bonds of aromatic ketones to olefins using carbonyl(dihydrido)tris(triphenylphosphine)ruthenium(II) catalyst (Scheme 1.11).[30] Since then, a plethora of directing group assisted C-H bond activation reactions have been reported.[31] In recent years, the use of a directing group supported strategy to functionalize inert C-H bonds in simple and complex molecules has proven to be an effective tool.



Scheme 1.11

1.1.4 Different types of additives and their roles in C-H functionalization reaction

In case of C-H functionalization, the situation is far more complicated due to the greater diversity of coupling partners, which often react through distinct reaction mechanisms, and the wide variety of specific additives that these reactions necessitate (complex mixtures of reagents and additives are frequently needed for each transformation). To expedite the understanding and to choose a preferred procedure, the various types of additives and their functions in C-H functionalization reactions are discussed below. It is important to note that, while the key groups of additives and their functions are fairly obvious, several compounds can play multiple roles in the reaction, making their selection and combination difficult.

(1) Oxidants: Cu salts (commonly $Cu(OAc)_2$) and Ag salts (AgOAc, AgOTf, AgOPiv), sometimes Mn salts has commonly used in oxidative reactions in stoichiometric or superstoichiometric quantities. Other oxidants that can be used alone or in addition with Cu or Ag are benzoquinones, peroxides, O_2/air, $K_2S_2O_8$ or hypervalent iodine compounds.

(2) Catalytic Ag salts: Catalytic amount of Ag salts are generally used jointly with metal halide dimers from group 8 or 9 which are widely used as catalysts (e.g. $[RhCp^*Cl_2]_2$). In these cases, Ag serves as a halide scavenger, while the counteranion (typically OTf, NTf_2, or SbF_6) aids the in situ formation of cationic metal catalysts in solution.

(3) Carboxylates (acetates, benzoates, pivalates, adamantanecarboxylates, trifluoroacetates etc): Many C-H functionalization procedures use these additives. Their primary function is to deprotonate the desired C-H bond, which is mostly

accomplished *via* the concerted metallation-deprotonation (CMD) pathway (also known as ambiphilic metal ligand activation (AMLA). These additives have usually added as acids either in stoichiometric or catalytic quantities, mostly in combination with bases, or as Cu, Ag, Zn or Na salts.

(4) Ligands: The structure and reactivity of a metal catalyst are affected by ligand coordination, which also affects the activation energy of elementary steps in a catalytic phase. The kinetic reactivity of the reaction changes as a result of this change, which can expand the effective substrate scope of the reaction. Furthermore, ligands can affect selectivity (enantioselectivity, diastereoselectivity, regioselectivity, and chemoselectivity) in transformations that produce multiple products, suppress metal catalyst degradation pathways and increase metal catalyst solubility in organic solvents. While in most C-H functionalization reactions, no external ligands are needed as DG itself acts as an "internal ligand", in some cases an external auxiliary (catalytic amounts) is required to speed up the reaction. Examples of such ligands are phosphines, carbenes, mono protected amino acids (MPAA) or other bidentate ligands etc. It's worth noting that the ligand chosen will be heavily influenced by the mechanism of C-H activation.

(5) Bases: Capturing HX from the catalytic cycle, accelerating the transmetallation process, and promoting the formation of nucleophilic reagents are all important functions of the bases. Base participation in ligand exchange, as well as its effects on activity and selectivity, is also a well-known phenomenon. Mostly, carbonates like Ag_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3, alkali metal hydroxide or alkoxide etc are used.

1.2 Ruthenium catalyst: An overview of Ru-catalyzed C-H activation

Metal-catalyzed reactions have made a significant contribution to the recent development of organic synthesis with the published of a number of synthetic methods, mostly using group 8 transition metal complexes. In particular, Ru-complexes have been used as excellent and appealing catalysts because of the following properties: (i) high versatility, a broad range of reactions are available with variety of conditions, often in C-C bond coupling reactions, (ii) good selectivity, because of special directing properties, *ortho*-ruthenation, as well as *para/meta*-functionalization is possible in many situations, (iii) greater reactivity and mild reaction conditions for different transformation, (iv) availability of different valence state such as Ru(0)/(II), Ru(II)/(IV) and Ru(II)/(0) catalytic cycles, results in high versatility, (v) relatively cheaper when compared to other Pd, Rh, Ir and Pt catalyst, (vi) it's complexes are more compatible with organic ligands in both air and moisture. As a result, Ru has become a common choice for C-H functionalization in organic synthesis and it has contributed tremendously to the development of less expensive and more effective catalytic systems for use in milder reaction conditions.

Since, electronic configuration of ruthenium is $4d^7 5s^1$, it has largest range of oxidation states and different coordination geometries for each electron configuration, in comparison to palladium which has limited scope of oxidation states and basic square planer structure. Ruthenium complexes, for example, prefer trigonal-bipyramidal and octahedral structures in the lower oxidation states of 0, II and III, respectively. With such a diverse range of ruthenium complexes, new catalytic

reactions and synthetic methods have a lot of promises. Some of the commonly used Ru(II) and Ru(III) catalyst are presented in figure 1.2.

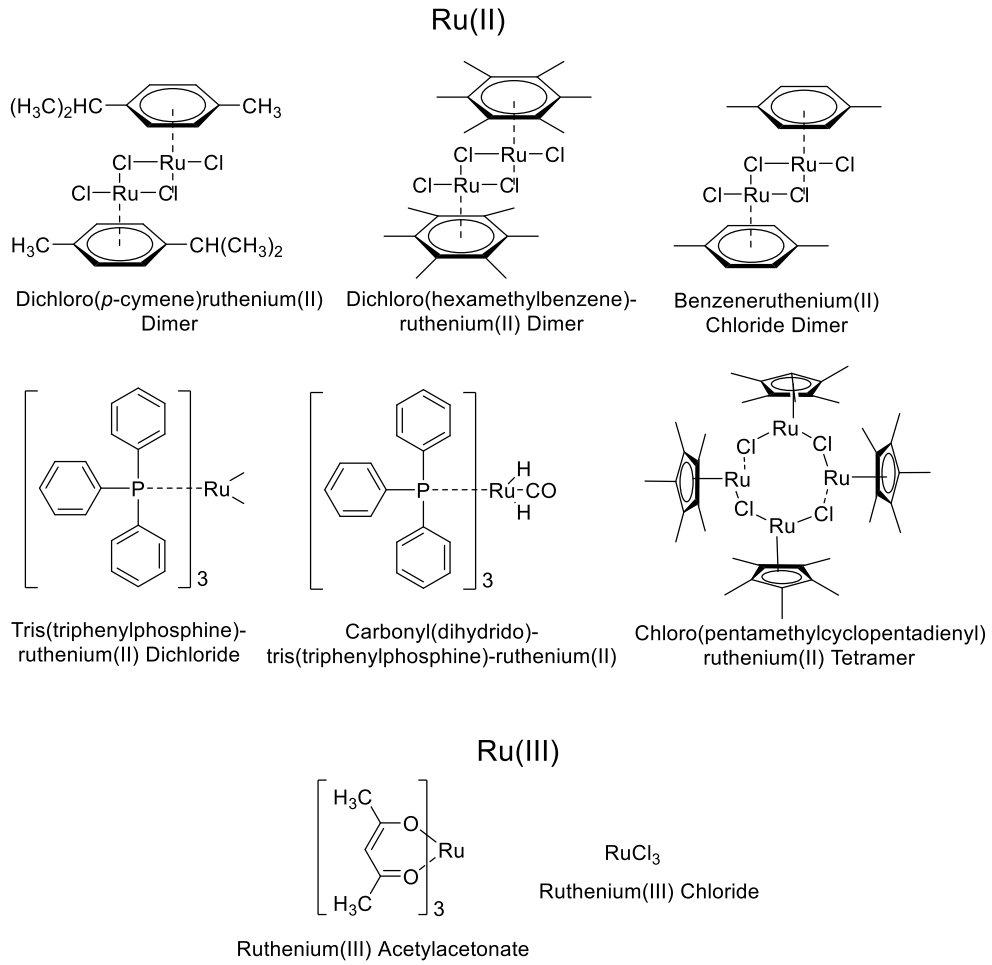


Figure 1.2

The mechanism of Ru-catalyzed C-H bond cleavage has been well established by DFT (Density Functional Theory). The mechanistic pathways in ruthenium-catalyzed C-H activation are discussed below:

1. Concerted metallation deprotonation (CMD): In this mechanism C-H bond can be cleaved by deprotonation with the help of a base and generating C-metal bond at the same time. Although weakly-coordinated directing group ease the CMD process, some

C-H bonds can be cleaved without the presence of a directing group. However, it is important to mention that presence of directing group can partly counter-balance the intermolecular entropy loss during C-H cleavage due to high activation free energy. In ruthenium-catalyzed C-H activation reaction, the presence of ligand *p*-cymene or any one of its derivatives makes Ru-centre coordinatively saturated when two acetate counter ions are attached to the centre. Therefore, the attachment of arenes containing a directing group to the catalyst led to the dissociation of one acetate ion which is endothermic and hence unfavorable for the cleavage of the C-H bond. Use of acidic directing group is helpful to avoid charge separation in Ru-catalyzed C-H activation and several reports are available in support of this fact.[32]

2. Base-assisted internal electrophilic type substitution (BIES): BIES mechanism is almost similar to CMD mechanism both in terms of reaction condition and transition state geometrical structure. When a carboxylate has been used in the presence of a cationic Ru^{II}-complex, base-assisted C-H bond cleavage occurs through a six-membered cyclic transition state. Electron-rich arenes, on the other hand, respond preferentially, which contradicts the CMD mechanism. Only difference in BIES mechanism is that C-H bond gets activated by a Brønsted base unlike by an electrophilic metal in case of CMD. C-H bond is activated by Brønsted base by producing positively charged hydrogen, that can be considered as internal substitution step. In the BIES step, carbon having more negative centre is found beneficial. This is consistent with higher reactivity of electron rich arenes.

3. σ-Complex assisted metathesis (σ-CAM): In the presence of an σ-bond between ruthenium and the bonding base, Ru-catalyzed C-H bond activation can occur through

the σ-CAM pathway, in which the C-H and Ru-base σ-bonds are cleaved and the C-Ru and H-base σ-bonds are formed at the same time.

4. Oxidative addition: Oxidative addition pathway proceeds through a three-membered cyclic transition state where at first there is cleavage of C-H bond and both the two atoms get added to ruthenium thereby increasing the ruthenium oxidation state by two.

As already discussed, the first ruthenium mediated C-H bond cleavage was published by Chatt and Davidson in 1965, the breakthrough discovery in the field of ruthenium catalyzed C-H bond functionalization was disclosed by Murai et al. in 1993, which has been considered as the first synthetically useful catalytic C-H activation for the formation of C-C bond.[30] Here, aromatic ketones have been alkylated with olefins in the presence of a stable precursor of Ru(0) catalyst, $RuH_2(CO)(PPh_3)_3$. As a result of this, new atom-efficient reactions based on initial Ru(0) injection into the C-H bond have been discovered, which led to the generation of *ortho*-ruthenated C-Ru-H intermediates, followed by insertion of unsaturated substrate. Later, this method proved to be a strong base for the functionalization of C-H bonds on a wide variety of substrates. The pioneering works of Lewis and Murai opened the gateway to a new era for ruthenium catalyzed C-H functionalization. Subsequently, various groups such as Oi-Inoue,[33] Ackermann,[34] Bruneau and Dixnueuf[35] established an array of ruthenium(II) catalyzed C-H functionalization reactions. Their key contributions in this field of ruthenium(II) catalyzed C-H functionalization are notably significant. The achievements of Ru(II)-catalyst is also

due to a distinct C-H bond activation mechanism compared to Ru(0) catalysts, which allows for the deprotonation of C-H bonds prior to any oxidative addition.

While significant progress has been made in Ru-catalyzed C-H functionalization reactions, some of these conversions have a low turnover number, which may be due to the high activation energy of the rate-determining stage, making these transformations difficult to complete and thus lowering the catalyst's catalytic efficiency. Sometimes, Ru-catalyst can become inactive due to the valence changes. As a result, new ideas must be developed to improve the performance of reactions (i) using a suitable ligand to stabilize the catalyst, (ii) altering the electronic or steric effects of the substrate, (iii) designing new Ru-catalysts or (iv) using a suitable directing group.

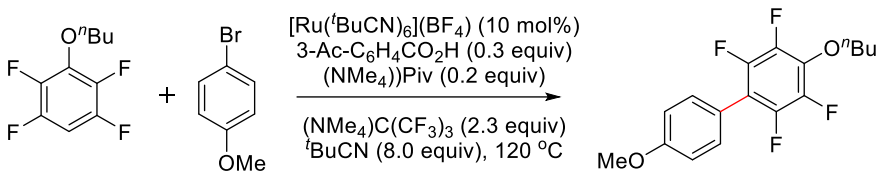
A number of reactions involving Ru-catalyzed C-H functionalization have been documented, including arylation, allylation, alkylation, alkenylation, acylation and annulation. Some new reactions that have been studied in recent years are direct C-H bond amidation, amination, halogenation, cyanation, selenylation and oxygenation. In the past years, various types of directing groups such as ketones, amides, esters, carboxylic acids and *N*-heteroaryl groups have been investigated in Ru-catalyzed C-H activation and functionalization reactions. As my research work is specifically based on Ru(II)-catalyzed C-H activation, some interesting reports on Ru(II)-catalyzed C-H activation reactions are mentioned below.

1.2.1 Ruthenium-catalyzed C-C bond formation

The formation of carbon-carbon bonds and functional group transformations are the most fundamental reactions in the construction of a molecular structure, and therefore

these are at the forefront of organic chemistry research. In these years, ruthenium-catalyzed characteristic C-C bond forming reactions have received a lot of attention. In particular, new ruthenium-catalyzed C-H arylation reactions have yielded appealing and highly efficient synthetic approaches to functionalize biaryls. New mechanistic manifolds have appeared, paving the way for the advancement of a diverse range of novel reactions.

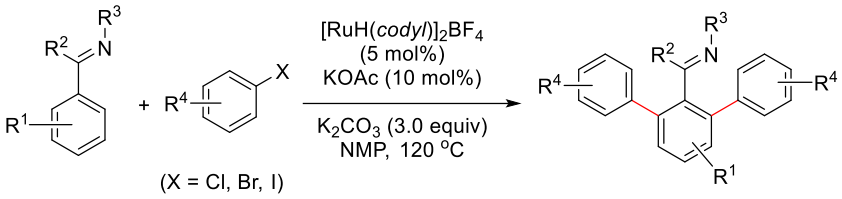
In 2016, Larrosa and co-workers reported C-H bond arylation of fluoroarenes with aryl halides in the presence of a base and without the use of a directing group using various ruthenium(II) complexes as the catalyst (Scheme 1.12).[36] They performed the reaction with arene-free cationic ruthenium complex $[Ru(^tBuCN)_6](BF_4)_2$ to avoid the arene ligand dissociation, which could affect the reaction yield, and obtained a good yield of the desired arylated product.



Scheme 1.12

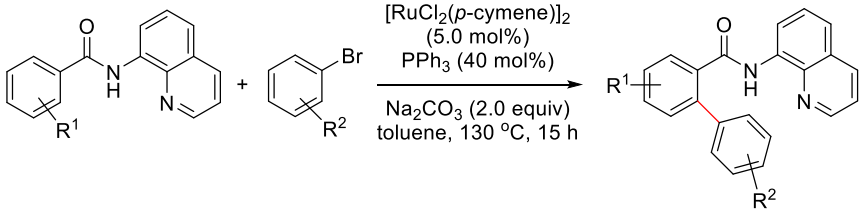
Arylation of C-H bond by using *N*-heterocycles as directing group serves as a prime factor in the production of *N*-heterocyclic biaryl products because of the formation of specific ruthenacycles. The Dixneuf group developed a number of high-activity ruthenium(II) catalyst systems for direct C-H arylation of 2-aryl *N*-heterocycles.[37] In 2011, they developed diarylation of *N*-heterocycles with aryl chloride, which was carried out with $[RuH(codyl)_2]BF_4$ (codyl = η^5-cyclooctadienyl) and coordinating additives like KOAc, KOPiv or potassium phthalimide in the

presence of 3.0 equiv of K_2CO_3 acting as a base and halide trap (Scheme 1.13).[38] Other heterocycles, such as 2-aryloxazolines and pyrazoles, have also been combined with aryl chlorides to produce the desired terphenyl products.



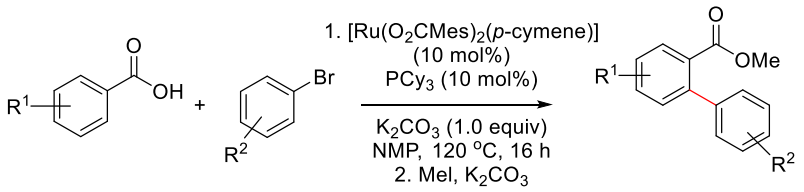
Scheme 1.13

The Chatani group was the first to use ruthenium catalysis to C-H arylate aromatic amides with bidentate directing groups in 2013 (Scheme 1.14).[39] They used 8-aminoquinoline as directing group to allow direct C-H coupling with a variety of aryl bromides in the presence of $[RuCl_2(p\text{-cymene})]_2$, PPh_3 and Na_2CO_3 in toluene.



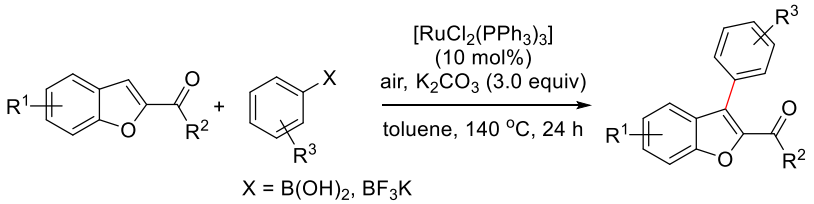
Scheme 1.14

Direct C-H arylation of aromatic carboxylic acids is an appealing method for the synthesis of functionalized biaryls, because of the utility of 2-arylcarboxylic acid derivatives in pharmaceuticals and agrochemicals. In this regard, Ackermann and co-workers reported a new Ru(II)-catalyzed direct C-H arylation of aromatic carboxylic acids with aryl iodides and bromides by utilizing a well-defined [Ru(*p*-cymene)$(MesCO_2)_2$] as catalyst (Scheme 1.15).[40]



Scheme 1.15

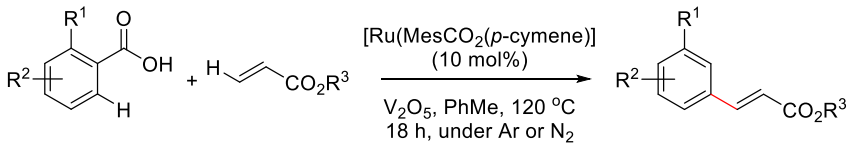
C-H arylation directed by ketone shows a significant synthetic challenge due to low lewis basicity of ketone. The Ramana group announced arylation of electron-rich 2-aroylbenzofurans with aryl boronic acids by poor co-ordination *via* Ru(II)-catalyzed direct C-H arylation (Scheme 1.16).[41]



Scheme 1.16

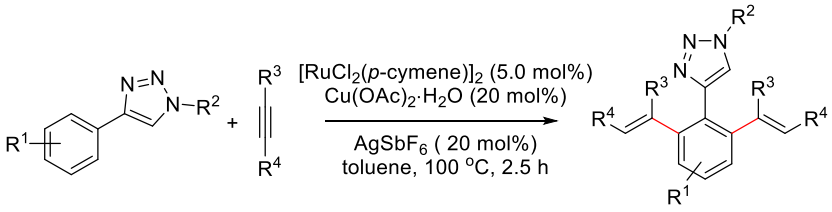
In organic synthesis, direct alkenylation of the sp^2 or sp^3 C-H bond is a powerful tool for C-C cross-coupling reactions. Transition-metal-catalysts could easily alkenylate several aromatic and heteroaromatic C-H bonds, resulting in a variety of alkenylated products. In the alkenylation process, Heck coupling is the most efficient one. However, it necessitates the pre-functionalization of starting materials, which reduce the scope of reaction. From 2011 onwards, the oxidative alkenylation of the C-H bond has been performed successfully using stable ruthenium(II)-catalysts.

Ackermann et al. demonstrated ruthenium-catalyzed decarboxylative oxidative C-H functionalization *via* *meta*-selective C-H alkenylation of aromatic carboxylic acid which produce *meta*-substituted arenes (Scheme 1.17).[42]



Scheme 1.17

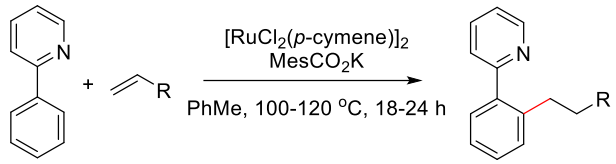
Catalytic hydroarylation of alkynes may also be used to produce alkenylarenes. Li et al. reported catalytic alkenylation of alkynes to other arene compounds through hydroarylation. They used $[RuCl_2(p\text{-cymene})]_2$ in the presence of an additive to alkenylate 2-phenyltriazole derivatives with alkynes, resulting in dialkenylated products (Scheme 1.18).[43]



Scheme 1.18

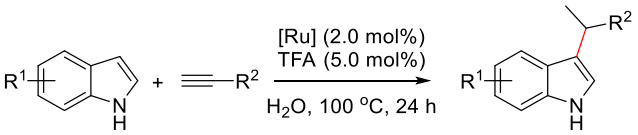
The hydroarylation of alkene or the alkylation with unreactive alkyl halides are the most popular methods for transition-metal-catalyzed C-H bond alkylation. In 1986, Lewis and Smith published their ground breaking work on regioselective *ortho*-alkylation through hydroarylation of an alkene. Later, Ackermann et al. reported the hydroarylation of 2-phenylpyridine with acrylates using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst in the presence of an additive (Scheme 1.19).[44] When $MesCO_2K$ and $AdCO_2K$ were used as additives, the reaction had the highest efficacy. Again, when the reaction was carried out by using additives like PPh_3, AgOTf or AgOAc, there was little or no

benefit. However, no reaction took place in the absence of an additive or when KPF_6 or $NaPF_6$ was used as the additive.



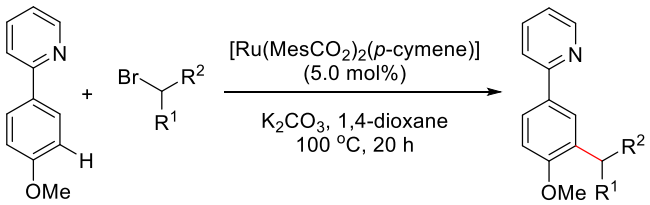
Scheme 1.19

Cadierno et al. published a paper in 2010 describing the C-3 alkylation of indole with a terminal alkyne using ruthenium catalysts.[45] The reaction was carried out by using 2 mol% ruthenium catalyst in the presence of TFA. They screened the reaction with a variety of ruthenium catalysts, and found that $[RuCl_2(p\text{-cymene})]_2$ and $[RuCl_2(\eta^6\text{-}C_{10}H_{16})]_2$ produced the best results (Scheme 1.20).



Scheme 1.20

Another typical method for obtaining alkylated products is direct alkylation of arenes with alkyl halides. Ackermann et al. reported a *meta*-selective C-H bond alkylation of aromatic C-H bond of ketimine with secondary alkyl halide catalyzed by $[Ru(MesCO_2)_2(p\text{-cymene})]$ in the presence of a base (Scheme 1.21).[46]



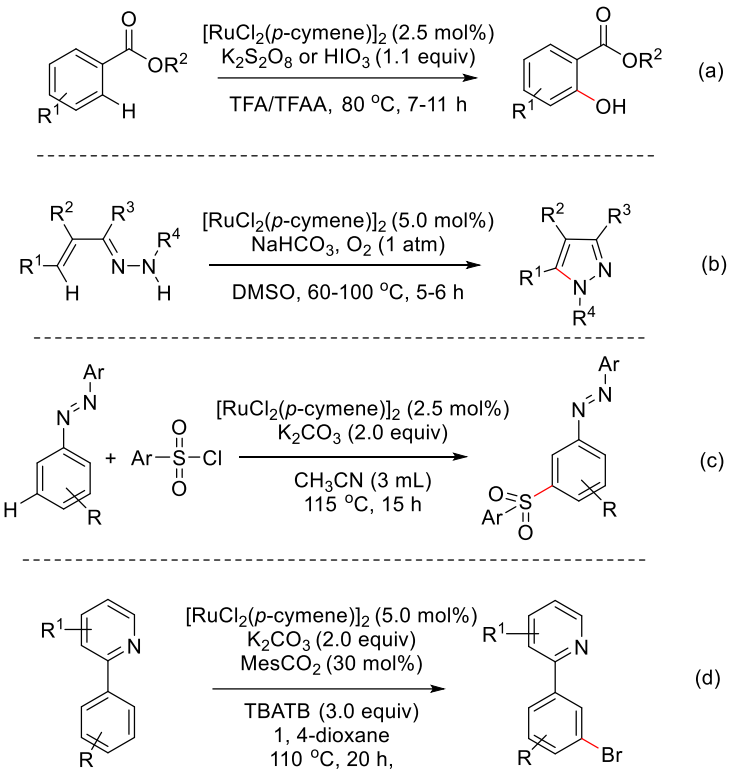
Scheme 1.21

1.2.2 Ruthenium-Catalyzed C-Heteroatom Bond Formation

In recent decades, in addition to transition-metal-catalyzed C-C bond formation reactions, C-heteroatom bond formation reactions also significantly contributed to the manufacture of fine chemicals, pharmaceuticals, natural products and synthetic building blocks. The base of many organic compounds is made up of C-C bonds, but the active site of these molecules is often made up of heteroatoms like nitrogen, oxygen, and sulphur, which are retained in these molecules by C-heteroatom bonds. Ruthenium-catalyzed C-H activation reactions have been successfully investigated for the construction of C-N, C-O, C-halogen, C-S and other bonds along with other transition metals.

In this regard, Rao and co-worker demonstrated a method for the synthesis of hydroxylated arenes *via* Ru(II)-catalyzed *ortho*-hydroxylation of ethyl benzoates by utilizing ester as an efficient directing group (Scheme 1.22a).[47] They developed a highly efficient catalyst system for this particular C-O bond formation reaction by combining $[RuCl_2(p\text{-cymene})]_2$, terminal oxidants like potassium persulfate, selectfluor or iodic acid, and a TFA/TFAA solvent system. Same group developed another method for the quick and easy synthesis of a wide range of tri- and tetrasubstituted pyrazoles from readily available starting materials *via* Ru(II)-catalyzed oxidative C-N coupling (Scheme 1.22b).[48] Ruthenium-catalyzed *meta*-selective C-H sulfonation of azoarenes with arylsulfonyl chloride was reported by Wang and his group (Scheme 1.22c).[49] Catalytic system consist of $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol%), Cs_2CO_3 (2.0 equiv) and acetonitrile as solvent was refluxed under N_2 atmosphere.

Greaney and his group disclosed an one pot route of Ru(II)-mediated *meta*-selective C-H bromination reaction of 2-phenylpyridine by using tetrabutylammonium tribromide as brominating agent (Scheme 1.22d).[50] Despite using an excessive amount of brominating agent, the reaction was surprisingly selective for the monobrominated rather than the dibrominated product.



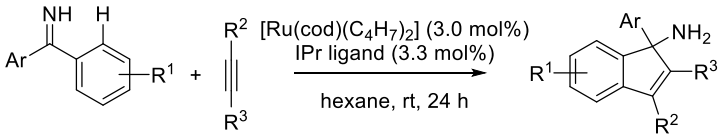
Scheme 1.22

1.2.3 Ruthenium-catalyzed annulation reactions of arenes with alkynes

One of the most versatile methods for the synthesis of different heterocyclic compounds is annulation or cyclization. The transition-metal-catalyzed annulation reaction is a fascinating reaction because it enables the formation of two bonds and a ring in a single step. The reaction is carried out by the formation of a cyclometal

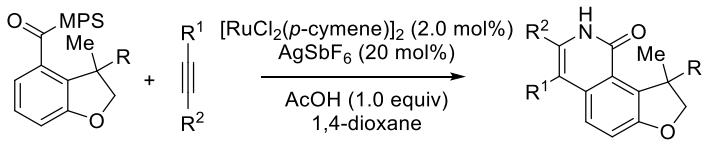
complex, the migratory addition of the unsaturated partner, and the reductive elimination of the metal. In most annulation reactions, one heteroatom is required to direct the metal complex to the reacting C-H bond, and the heteroatom is most often incorporated into the final ring. In recent years, Ru(II)-catalysts have been used extensively in the discovery of novel C-H activation and annulation reactions. Among others, Ru-catalyzed alkyne annulation reactions have received considerable interest from organic chemists.[51] Our group has been exploring this field extensively from the last few years and has successfully published some good papers and reviews.

Zhao and co-worker established a Ru(II)-catalyzed [3+2] annulation method involving the reaction between N-H ketimines with alkynes to generate indenamines using mild reaction condition (Scheme 1.23).[52]



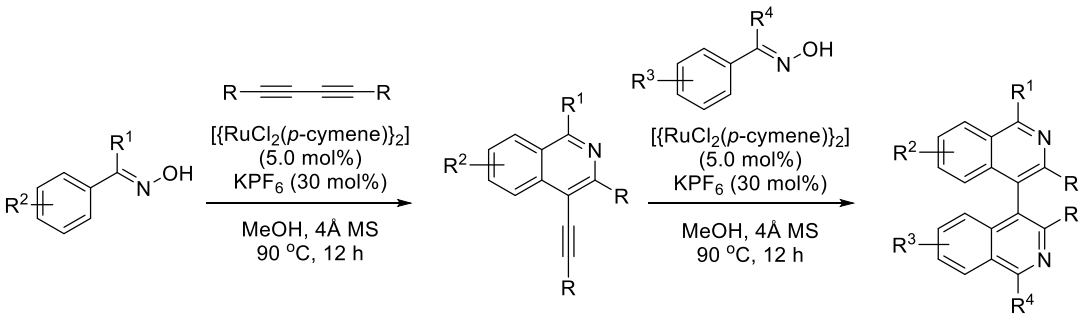
Scheme 1.23

Sahoo et al. reported the synthesis of dihydrobenzofuran derivatives containing isoquinolone moiety *via* Ru(II)-catalyzed C-H activation and alkyne annulation of dihydrobenzofurans where methyl phenyl sulfoximines (MPS) act as a directing group (Scheme 1.24).[53]



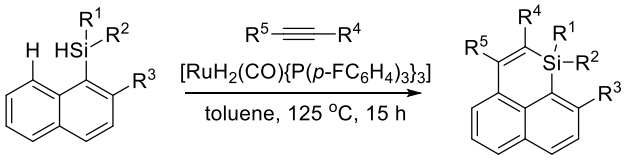
Scheme 1.24

Volla and his group reported an efficient selective Ru(II)-catalyzed C-H activation of *N*-hydroxyoximes with 1,3-diynes to generate 4-alkynylated isoquinolines. Further, under identical reaction conditions, reaction of 4-alkynylated isoquinolines with *N*-hydroxyoximes afforded 4,4-biisoquinolines in good yields (Scheme 1.25).[54]



Scheme 1.25

Fukuzawa and co-worker developed a Ru-catalyzed annulation of 1-naphthylsilanes with alkynes *via* cleavage of the 8-position C-H bond of naphthalene to afford silaphenalenes. 1-Naphthyldiphenylsilanes containing phenyl groups on Si-atom underwent C-H annulation smoothly and generated silaphenalenes in a better yield as compared to silanes with alkyl groups on Si-atom (Scheme 1.26).[55]



Scheme 1.26

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CHAPTER 1

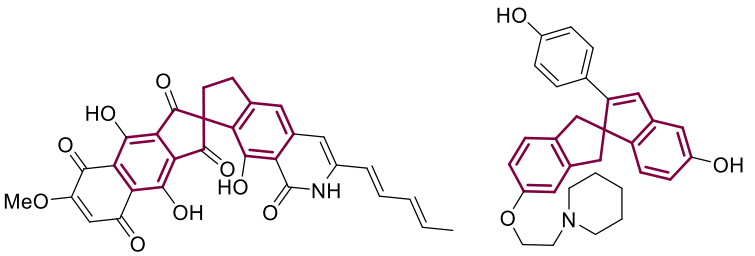
Synthesis of spirobi[indene]-diones *via* Ru(II)-catalyzed C-H activation and alkyne annulation reaction of phenyl indanedione

ABSTRACT:

A ruthenium-catalyzed reaction has been established for the synthesis of spirobi[indene]-dione from 2-phenyl-indanedione and internal alkyne. This reaction proceeds via in-situ formed hydroxy group directed C(sp^2)-H bond activation, keto-enol tautomerization and alkyne annulation. This methodology affords good yields of spirobi[indene] and tolerates variety of functional groups. This strategy provides a potent route for the construction of important spirocyclic scaffold of fredericamycin A.

2.1 INTRODUCTION

Carbocyclic spiro motifs and their derivatives display imperative pharmacological activities, and are found in several natural products of biological relevance. In this context, the spirobi[indene] is a privileged organic scaffold which is present in different biologically important natural products and synthetic compounds (Figure 2.1).[1] For example, tetrahydro-1,2'-spirobi[indene] is the key scaffold of fredericamycin A (Figure 2.1), which is an antitumor antibiotic isolated from Streptomyces griseus in 1981.[1a,1e] This compound demonstrates very potent *in-vitro* cytotoxic activity and promising antitumor activity against various tumor models such as CD8F mammary, B16 melanoma and P388 leukemia. Again, this spirobi[indene] is a structural motif present in Acutumine, which is an alkaloid demonstrates selective T-cell cytotoxicity and antiamnesic properties,[2] originally isolated from the Asian vine *Menispermum dauricum*. Besides, for the development of chiral ligands like Spinol based ligands, these rigid structures proof as an ideal platform, which have been applied for various reactions.[3]

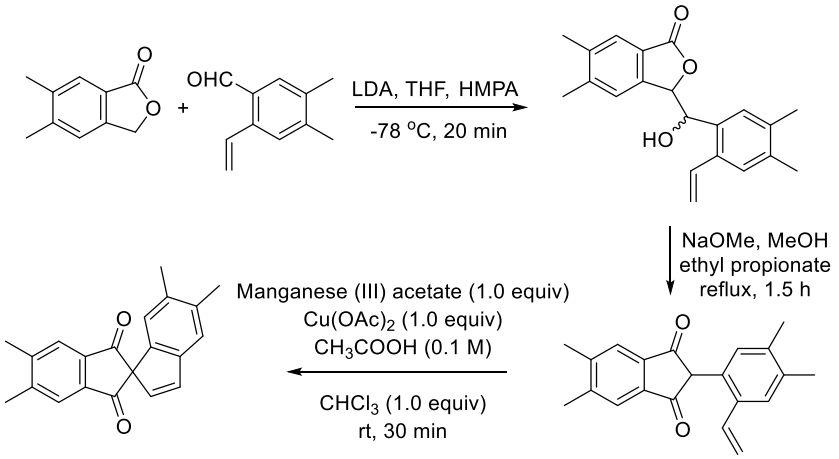


Fredericamycin A[1a] Estrogen receptor ligand[1b]

Figure 2.1

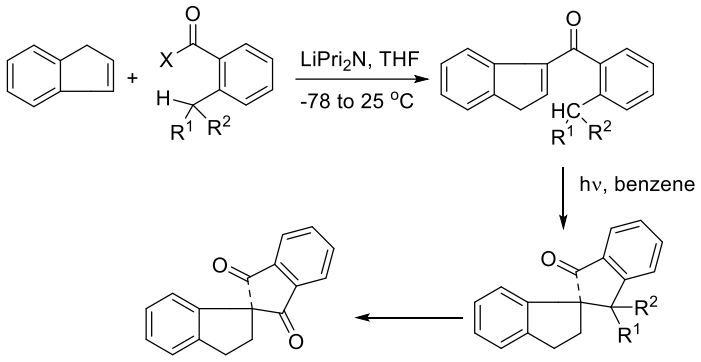
Because of the promising bioactivity and challenging structure of this compound, various routes have been developed for the synthesis of this key scaffold tetrahydro-1,2'-spirobi[indene].

Rama Rao and co-workers developed a Mn(III)-mediated oxidative free-radical cyclization reaction nearly three decades ago to construct this scaffold (Scheme 2.1).[4]



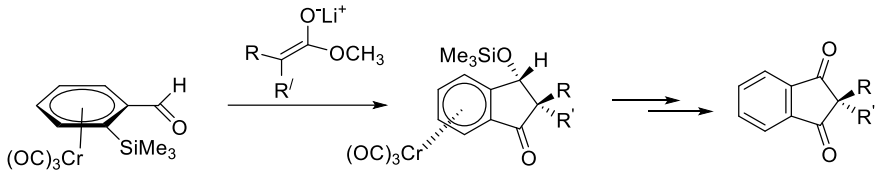
Scheme 2.1

In 1990, Pandey and co-workers developed a photochemical synthesis of this spirocycle *via* the intramolecular hydrogen abstraction and cyclization reaction of an enone (Scheme 2.2).[5]



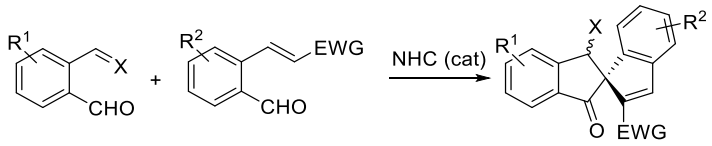
Scheme 2.2

Recently, Moser and co-workers developed one-pot aldol addition/Brook rearrangement/cyclization type of annulation reaction of arene chromium tricarbonyl for the construction of this trahydro-1,2'-spirobi[indene] scaffold (Scheme 2.3).[6]



Scheme 2.3

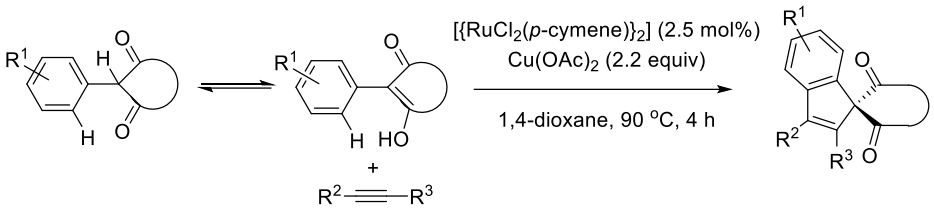
Furthermore, very recently, M. Gravel et al. developed one NHC-catalyzed domino Stetter-aldol-Michael (SAM) and Stetter-aldol-aldol (SAA) spiro-cyclization reaction to synthesize this spirocyclic scaffold (Scheme 2.4).[7]



Scheme 2.4

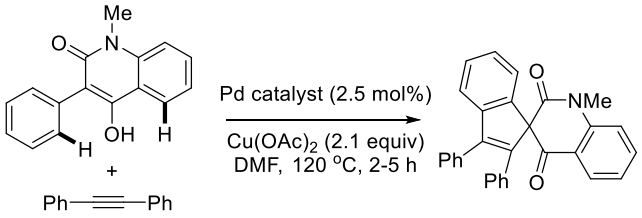
Again, metal-catalyzed reactions dealing with the C-H bond activation and alkyne annulation have emerged recently as an efficient tool for the efficient synthesis of various heterocyclic and carbocyclic scaffolds.[8] In this regard, enolate-directed metal catalyzed reaction plays an important role for the synthesis of many spiro compounds.[9-14]

Lam and co-workers developed a ruthenium-catalyzed oxidative annulation reaction of alkyne with 2-aryl cyclic 1,3-dicarbonyls to afford spiroindenes in comperatively good yield (Scheme 2.5).[9]



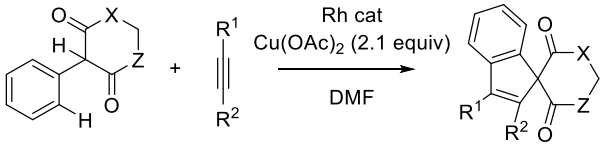
Scheme 2.5

Replacing these substrates with unsymmetrical variants, again the same group developed the divergent C-H functionalization of 2-aryl cyclic 1,3-dicarbonyl compounds. By using Pd-catalyst, these substrates undergo oxidative annulation reaction with alkynes to afford spiroindenes (Scheme 2.6).[10]



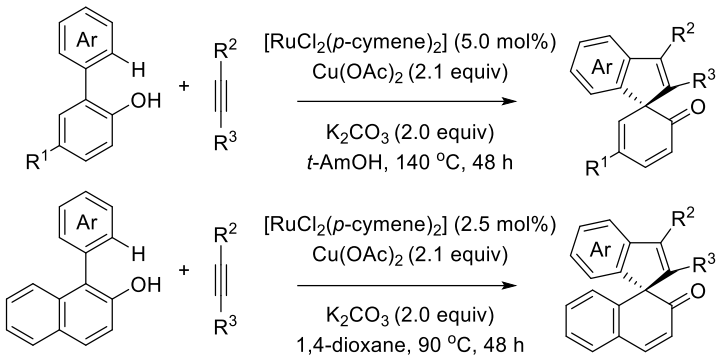
Scheme 2.6

Again, they demonstrated another methodology for the synthesis of spiroindenes *via* Rh(III)-catalyzed C-H functionalization and oxidative alkyne annulation reaction (Scheme 2.7).[11]



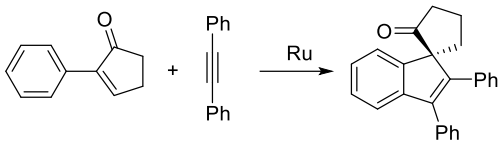
Scheme 2.7

Luan and his group disclosed a dearomatisation strategy of 2-Aryl phenol and naphthols *via* C(sp^2)-H bond activation to construct various spirocyclic indenes (Scheme 2.8).[12]



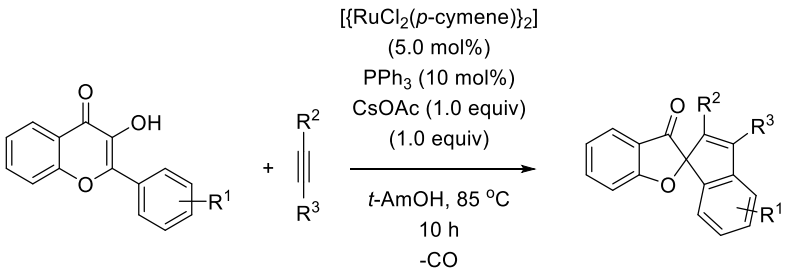
Scheme 2.8

Another synthesis of spiro carbocyclic indenes bearing a quaternary carbon was reported by Gao et al. using 2-arylcyclo-2-enones and alkynes *via* Ru-complex catalyzed C(sp^2)-H/alkene functionalization (Scheme 2.9).[13]



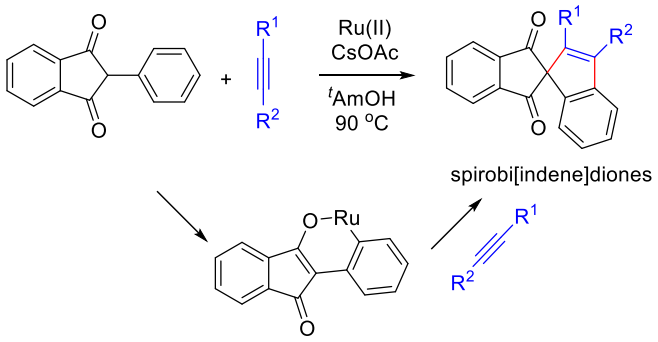
Scheme 2.9

Very recently, our group reported the hydroxy group directed C(sp^2)-H bond activation, keto-enol tautomerization and alkyne annulation reaction of 3-hydroxy-2-phenylchromones for the synthesis of spiro-benzofuranones (Scheme 2.10).[14]



Scheme 2.10

Similarly, the spiro-annulation reaction of phenyl 1,3-indandiones with alkynes would be an effective reaction to construct the important spirobi[indene] scaffold, which is yet not explored. In the present work, we demonstrates an *in-situ* formed hydroxy group directed C(sp^2)-H bond activation, keto-enol tautomerization and alkyne annulation reaction of 2-phenyl-indandiones (Scheme 2.11). This Ru(II)-catalyzed reaction provides a potent route for the construction of important spirocyclic scaffold of fredericamycin A.



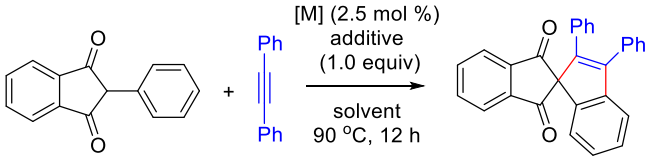
Scheme 2.11

2.2 RESULTS AND DISCUSSION

Initially, the optimized reaction conditions were determined using 2-phenyl-indandione **1a** and alkyne **2a** as the starting materials to synthesize spiro compound

3aa (Table 2.1). Initial screening of various commonly used metal catalysts revealed [{$RuCl_2$(*p*-cymene)}$_2$] as the best catalyst which afforded 54% yield of **3aa** (entry 2). To further improve the yield of the product **3aa** some of the additives and solvents

Table 2.1. Optimization of the reaction conditions for **3aa**[a]



1a **2a** **3aa**

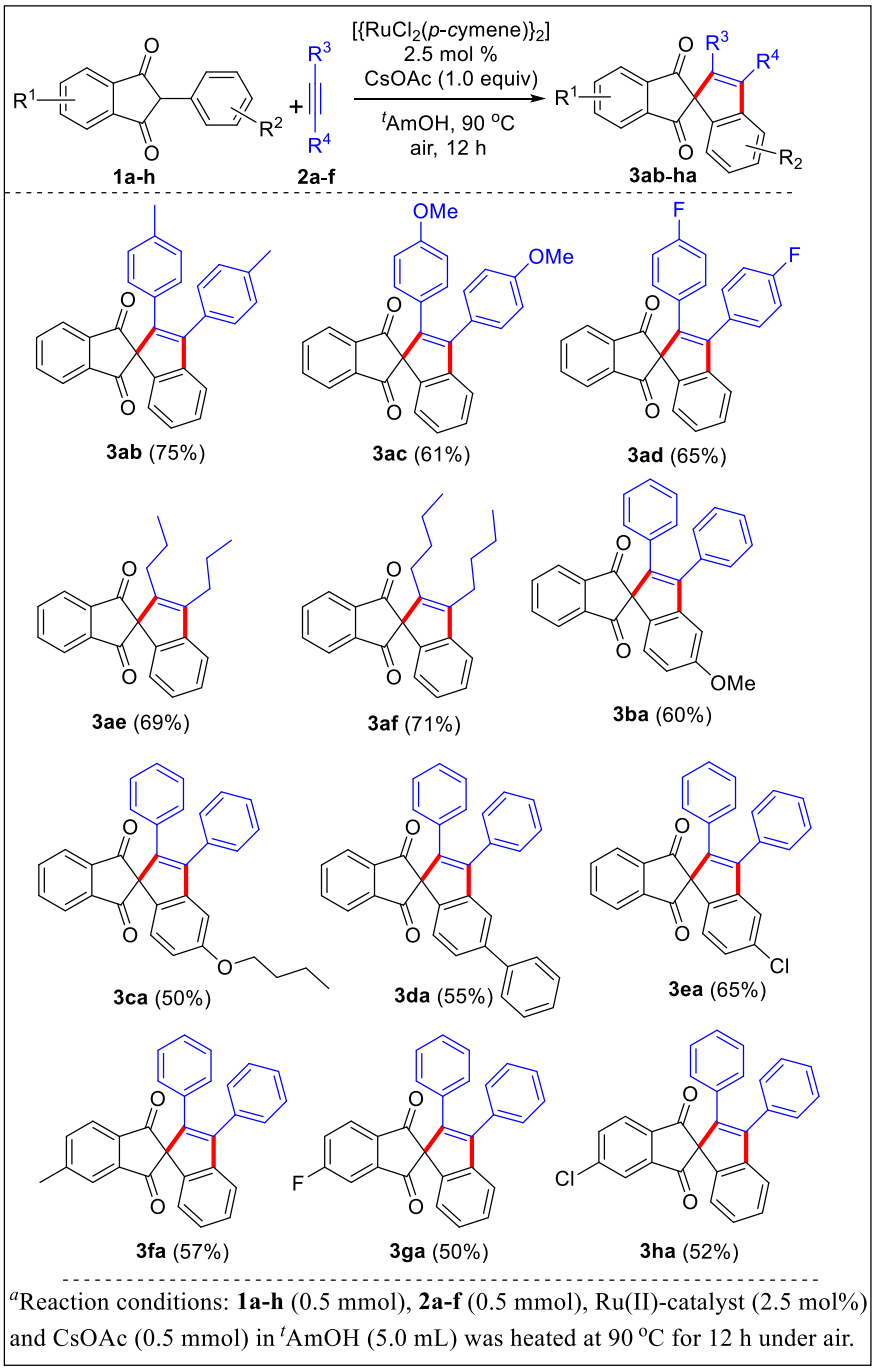
Entry	Catalyst	Additive	Solvent	**3aa** (%)[b]
1	$[RuCl_2(PPh_3)_3]$	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	0
2	[{$RuCl_2$(*p*-cymene)}$_2$]	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	54
3	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	17
4	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	0
5	$PdCl_2$	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	0
6	**[{$RuCl_2$(*p*-cymene)}$_2$]**	**CsOAc**	**^{t}AmOH**	**78**
7	[{$RuCl_2$(*p*-cymene)}$_2$]	NaOAc	^{t}AmOH	19
8	[{$RuCl_2$(*p*-cymene)}$_2$]	AgOAc	^{t}AmOH	31
9	[{$RuCl_2$(*p*-cymene)}$_2$]	Ag_2O	^{t}AmOH	22
10	[{$RuCl_2$(*p*-cymene)}$_2$]	CsOAc	MeCN	52
11	[{$RuCl_2$(*p*-cymene)}$_2$]	CsOAc	1,4-dioxane	48
12	[{$RuCl_2$(*p*-cymene)}$_2$]	CsOAc	DMF	0
13	[{$RuCl_2$(*p*-cymene)}$_2$]	CsOAc	toluene	33
14	[{$RuCl_2$(*p*-cymene)}$_2$]	CsOAc	CH_3OH	58

[a]Reaction conditions: **1a** (0.5 mol), **2a** (0.5 mmol), catalyst (2.5 mol%), additive (0.5 mmol) and solvent (5.0 mL) at 90 °C under air for 12 h. [b]Isolated yields.

were also screened (entries 6-14), which revealed CsOAc and ^{t}AmOH as the best additive and solvent to perform this cyclization reaction which provided 78% yield of **3aa** (entry 6). Further, loading the catalyst mol% to 5 mol% showed that the reaction provided the maximum yield with 2.5 mol% of the catalyst.

Then, the highest yielding reaction conditions were used to study the substrate scope of this annulation reaction with phenyl indandiones **1a-h** and various symmetrical alkynes **2a-f** which is shown in Scheme 2.12. Initially, the symmetric 1,2-diarylethylenes **2b-d** possessing electron-donating groups such as 4-Me, 4-OMe and electron-withdrawing group (4-F) were tested with phenyl indandione **1a** to provide 61-75% yields of the spirobi[indene]-diones **3ab-ad**. Similarly, the dialkyl substituted alkynes such as oct-4-yne (**2e**) and dec-5-yne (**2f)** were also tested and these alkynes were also found to be good annulation partner to perform this reaction which provided 69-71% yields of **3ae-af**. Next, the possibility of this annulation reaction was tested with some representative indandiones **1b-h** with alkyne **2a.** The 2-phenyl-indandiones **1b-e** bearing substituents such as -OMe, -O^{n}Bu, Ph and Cl at *para*-position of the substituted phenyl ring of indandione were studied to provide the corresponding spiro compounds **3ba-ea** in 50-65% yields, respectively. Then, some of the 2-phenyl-indandiones, substituted with electron-releasing methyl substituent **1f** and electron-withdrawing fluoro, chloro substituents **1g-h** on the fused aromatic ring of 2-phenyl-indandione, were studied with alkyne **2a** to afford 50-57% yields of the spiro compounds **3fa-ha**.

Scheme 2.12. Scope of phenyl indandiones **1a-h** with symmetrical alkynes **2a-f**[a]

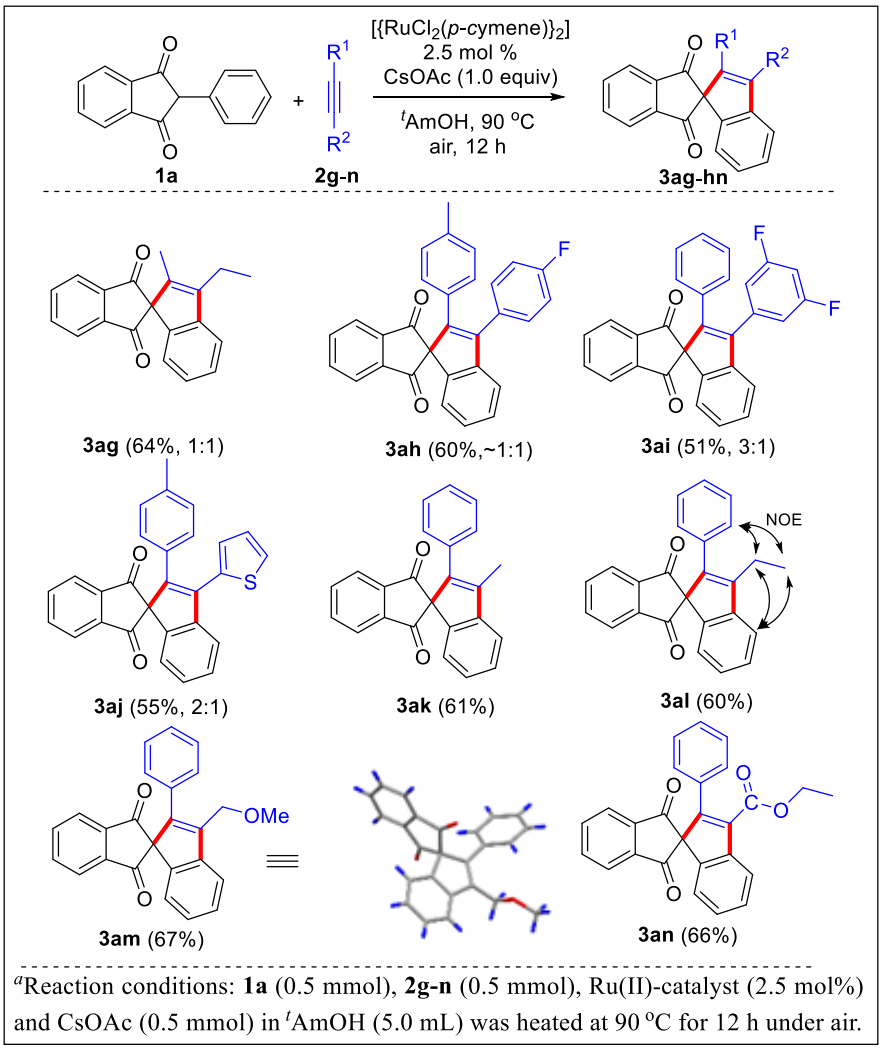


[a]Reaction conditions: **1a-h** (0.5 mmol), **2a-f** (0.5 mmol), Ru(II)-catalyst (2.5 mol%) and CsOAc (0.5 mmol) in ^{t}AmOH (5.0 mL) was heated at 90 °C for 12 h under air.

Further, generalization of the reaction was explored with unsymmetrically substituted alkynes **2g-n** (Scheme 2.13). The unsymmetrically substituted alkyne *i.e.* pent-2-yne (**2g)** and 1-fluoro-4-(p-tolylethynyl)benzene (**2h**) afforded a mixture of two

regioisomers **3ag** and **3ah** in 1:1 ratio with **1a**. Similarly, reaction of **1a** with alkynes such 1,3-difluoro-5-(phenylethynyl)benzene (**2i**) or heteroaryl substituent 2-(*p*-tolylethynyl)thiophene (**2j**) provided mixture of regioisomers **3ai-aj** in 3:1 and 2:1 with 51-60% yields with unkown major isomers**.** In contrast, the unsymmetrically substituted arylalkylacetylenes such as prop-1-yn-1-ylbenzene (**2k**), and but-1-yn-1-ylbenzene (**2l**) provided the regioselective product **3ak-al** in 60-62% yields. Finally, the alkynes (3-methoxyprop-1-yn-1-yl)benzene (**2m**) and ethyl 3-phenylpropiolate (**2n**) was examined with **1a** to afford the spiro-compound **3am-an** in 66-70% yields. The annulation pattern of these unsymmetrical alkynes **2k-n** is similar to the reported metal-catalyzed spiro-cyclization reactions, where the sterically hindered phenyl substituent occupies the 2-position of the 1,2'-spirobi[indene]-1',3'-dione scaffold.[9-11] The regioselectivity of the spiro compounds **3ak-am** were proved by NOE interaction of ethyl protons of compound **3al** with the neighbouring aromatic protons (Scheme 2.13). The structure of the spiro compounds was determined by analyzing the NMR spectra and confirmed by the single X-ray crystallography studies of compound **3am**.[15] The reaction of **1a** with phenylacetylene and 1-phenyl-2-trimethylsilylacetylene were unsuccessful under the reaction conditions.

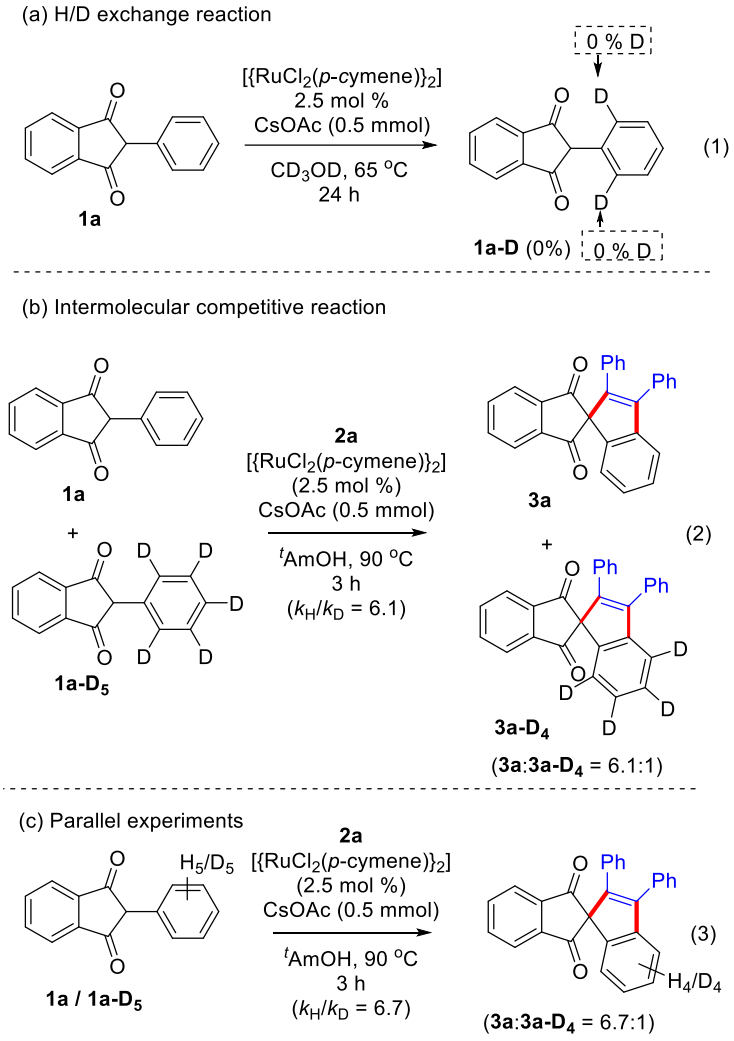
Scheme 2.13. Scope of phenyl indandiones **1a** with unsymmetrical alkynes **2g-n**[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2g-n** (0.5 mmol), Ru(II)-catalyst (2.5 mol%) and CsOAc (0.5 mmol) in ^{t}AmOH (5.0 mL) was heated at 90 °C for 12 h under air.

To gain an insight into mechanism, we have done a series of isotopically labelling experiment as shown in Scheme 2.14. The H/D exchanged reaction of **1a** could not provide the H/D exchanged compound **1a-D** (Scheme 2.14, eq 1), which indicates the non-reversible C-Ru bond formation, however, Lam et al. reported a reversible cycloruthenation.[9] The intermolecular competitive reaction between **1a** and **1a-D$_5$** with alkyne **2a** provided k_H/k_D= 6.1 (Scheme 2.14, eq 2). Again, the competitive parallel reactions of **1a** and **1a-D$_5$** with alkyne **2a** afforded k_H/k_D= 6.7 (Scheme 2.14,

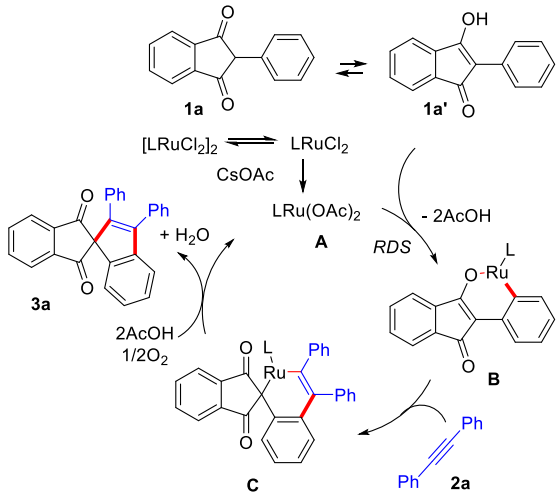
eq 3). A KIE of this magnitude suggests that the C-H bond cleavage could be involved in the rate determining step.[16]



Scheme 2.14

Based on the literature reports,[9,11,14] the probable mechanism for the formation of spiro compound **3aa** is proposed (Scheme 2.15). The hydroxy group directed Ru(II)-catalyzed activation of C-H bond of *in-situ* formed compound **1a′** affords Ru(II) complex **B**, which on subsequent metal alkyne coordination and alkyne insertion in Ru-C bond affords Ru(II) complex **C**. Reductive elimination of the metal finally

affords compound **3** and Ru(0) is reoxidized to active metal complex **A** by the help of molecular oxygen and AcOH.[17]



Scheme 2.15

2.3 CONCLUSION

In conclusion, an unprecedented Ru(II)-catalyzed alkyne annulation reaction of 2-phenyl-indandione is developed. This reaction has opened up a new efficient route for the construction of the spirobi[indene] scaffold which is the key motif of the antitumor antibiotic fredericamycin A as well as some other pharmaceutically important compounds.

2.4 EXPERIMENTAL SECTION

General Information:

Melting points were measured by using a Buchi B-540 melting point apparatus and are uncorrected. NMR spectra has recorded on Bruker Avance III 500 MHz FTNMR and 400 MHz FTNMR spectrometer using tetramethylsilane (TMS) as an internal standard. All other solvents and reagents were purified according to standard

procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-backed silica gel plates (0.2 mm thickness); the chromatograms were visualized first with ultraviolet light (254 nm) and then by immersion in solutions of *p*-anisaldehyde followed by heating. Column chromatography was performed with silica gel (100-200 mesh, Merck). HRMS data were recorded by electronspray ionization with a Q-TOF mass analyzer. The starting 2-phenylindandiones were synthesized using acetic anhydride, phenylacetic acid and phthalic anhydride by following a known procedure.[18]

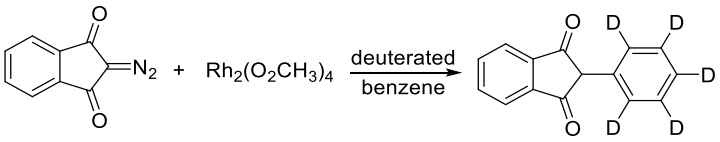
General procedure for the synthesis of spirobi[indene] scaffold by using phenylindanedione and alkyne:

A mixture of 2-phenylindandione (**1**, 0.5 mmol), alkyne (**2**, 0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), CsOAc (1.0 equiv) in ^{t}AmOH (5.0 mL) was stirred at 90 ^{o}C under open air for 12 hours. The solvent was removed under vacuo. Water (10 mL) was added to the reaction mixture and the organic layer was extracted with ethyl acetate (25 mL x 2). The combined organic phases were washed with brine and dried over sodium sulfate. The solvent was removed under vacuo and the residue was purified by column chromatography on silica gel (100-200 mesh) using hexanes/ethyl acetate as an eluent to afford **3**.

***Synthesis of deuterated 2-phenylindandione 1a-d_5[19]*:**

A mixture of 2-diazo-1,3-indandione (344 mg, 2.0 mmol) and rhodium acetate (44 mg, 5 mol %) in deuterated benzene (2 mL) was refluxed for 10 hours. The reaction mixture was cooled to room temperature and the solvent was removed under vacuo.

The crude product thus obtained was purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane (1:9) as the eluant to afford **1a-d$_5$** (345 mg, 76%).

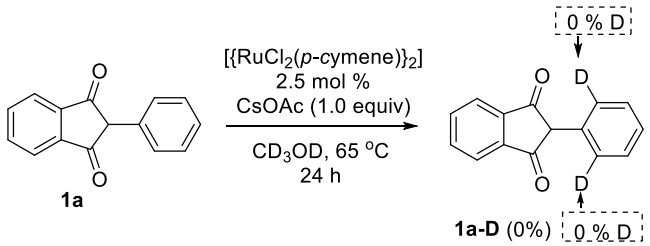


Scheme 2.16: Synthesis of 1a-d$_5$

Mechanistic Experiments:

Isotopically labelling experiments

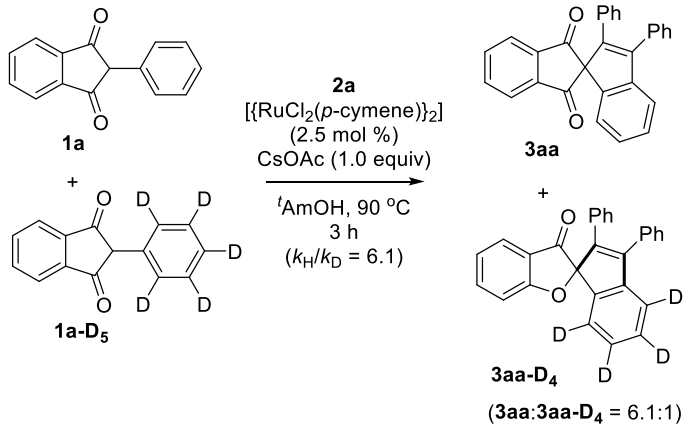
(a) ***H/D exchange reaction:*** A solution of 2-phenylindandione **1a** (111 mg, 0.5 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (8 mg, 2.5 mol %), and CsOAc (96 mg, 0.5 mmol) in CD$_3$OD (5.0 mL) was stirred at 65 ^{o}C for 24 hours. The solvent was evaporated and the crude product obtained was purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane (1:9) as the eluant. The H/D exchange was found to be 0% at the protons attached to C-2′ and C-6′ of the phenyl ring of recovered **1a**.



Scheme 2.17: H/D exchange reaction

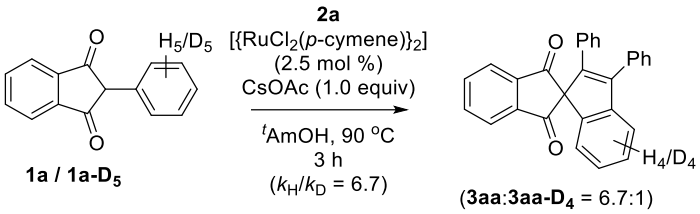
*(b)**Intermolecular competition experiment**:* A mixture of 2-phenylindandione **1a** (111 mg, 0.5 mmol), **1a-D$_5$** (114 mg, 0.5 mmol), alkyne **2a** (107 mg, 0.6 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (2.5 mol %) and CsOAc (96 mg, 0.5 mmol) in ^{t}AmOH (5.0 mL) was stirred

at 90 °C for 3 hours. The solvent was removed under vacuo and the crude reaction mixture was purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane (1:9) as the eluant to provide a mixture of **3aa** and **3aa-D$_4$**. The ratio of **3aa** and **3aa-D$_4$** was determined to be 6.1:1 by ^{1}H NMR integration method (k_H/k_D = 6.1)



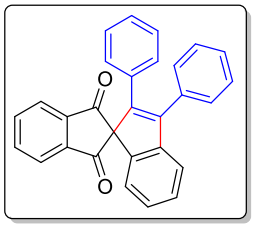
Scheme 2.18: Intermolecular competition reaction

(c) ***Parallel competition experiments****:* A mixture of **1a** (111 mg, 0.5 mmol), alkyne **2a** (89 mg, 0.5 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (8 mg, 2.5 mol %) and CsOAc (96 mg, 0.50 mmol) in ^{t}AmOH (5.0 mL) was stirred at 90 °C for 3 hours. At the same time, a solution of **1a-D$_5$** (114 mg, 0.5 mmol), alkyne **2a** (89 mg, 0.5 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (8 mg, 2.5 mol %) and CsOAc (96 mg, 0.50 mmol) in ^{t}AmOH (5.0 mL) was stirred at 90 °C in another round bottom flask for 3 hours. The reaction mixtures were combined, solvent was removed and the residue was purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane (1:9) as the eluant to afford a mixture of **3aa** and **3aa-D$_4$** (**3aa**:**3aa-D$_4$** = 6.7:1, k_H/k_D = 6.7).

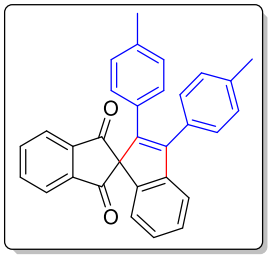


Scheme 2.19: Parallel competition reaction

2.5 SPECTRAL AND ANALYTICAL DATA



2,3-Diphenyl-1,2'-spirobi[indene]-1',3'-dione (3aa). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3aa** ((155 mg, 78%). M.p.: 160 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11-8.09 (m, 2H), 7.94-7.92 (m, 2H), 7.46-744 (m, 2H), 7.38-7.31 (m, 5H), 7.12 (t, J = 7.0 Hz, 1H), 7.05-6.99 (m, 5H), 6.81 (d, J = 7.0 Hz, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 146.5, 145.9, 143.4, 143.3, 141.0, 136.0, 134.4, 134.0, 129.5, 128.8, 128.4, 128.3, 128.1, 127.8, 127.4, 126.2, 124.2, 121.7, 121.2, 75.6. IR (KBr) 2913, 1721, 1557, 1443, 1215, 1130, 1035, 713 cm^{-1}. HRMS (+ESI) Calcd for $C_{29}H_{19}O_2$ [M+H]+: 399.1380; found: 399.1385.



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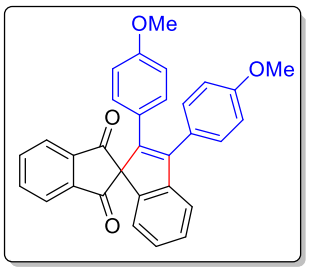
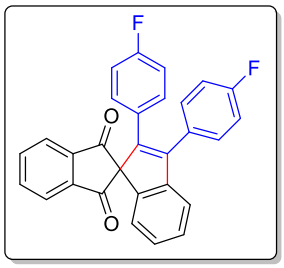
2,3-di-p-Tolyl-1,2'-spirobi[indene]-1',3'-dione (3ab). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2b** (103 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ab** (160 mg, 75%). M.p.: 210 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10-8.07 (m, 2H), 7.91 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.37-7.33 (m, 3H), 7.28 (t, *J* = 8.0 Hz 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 7.5 Hz, 1H), 2.37 (s, 3H), 2.15 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 146.3, 145.9, 143.5, 143.3, 140.6, 137.4, 137.1, 136.0, 131.6, 131.1, 129.4, 129.2, 129.0, 128.6, 128.3, 126.0, 124.2, 121.6, 121.1, 75.6, 21.3, 21.0. IR (KBr) 2919, 1716, 1567, 1460, 1226, 1155, 1100, 717 cm^{-1}. HRMS (+ESI) Calcd for $C_{31}H_{23}O_2$ $[M+H]^+$: 427.1704; found: 427.1698.

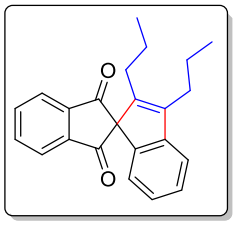


2,3-bis(4-Methoxyphenyl)-1,2'-spirobi[indene]-1',3'-dione (3ac). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2c** (119 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford yellow solid of **3ac** (140 mg, 61%). M.p.:100 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11-8.09 (m, 2H), 7.93-7.92 (m, 2H), 7.40-7.37 (m, 3H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.92 (t, *J* = 9.0 Hz, 3H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 8.5 Hz, 2H), 3.83 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 159.0, 158.6, 146.3, 145.1, 143.4, 143.2, 140.0, 136.0, 130.7, 130.0, 128.3, 126.9, 126.3, 125.9,

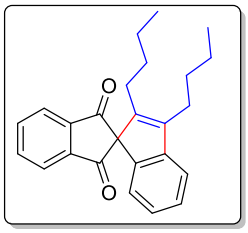
124.2, 121.4, 121.1, 113.8, 113.6, 75.6, 55.1, 54.9. IR (KBr) 2919, 1723, 1581, 1430, 1259, 769 cm^{-1}. Anal. calcd of $C_{31}H_{22}O_4$ for C, 81.21; H, 4.84; found: C, 81.52; H, 4.92.



2,3-bis(4-Fluorophenyl)-1,2'-spirobi[indene]-1',3'-dione (3ad). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2d** (107 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford yellow solid of **3ad** (141 mg, 65%). M.p.: 150 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 8.11-8.09 (m, 2H), 7.95-7.93 (m, 2H), 7.42-7.38 (m, 2H), 7.37-7.30 (m, 2H), 7.13 (t, J = 7.5 Hz, 1H), 7.10-7.04 (m, 2H), 7.01- 6.97 (m, 2H), 6.81 (d, J = 7.5 Hz, 1H), 6.76 (t, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 162.2 (d, J = 246.3 Hz), 161.9 (d, J = 247.5 Hz), 145.7, 145.4, 143.4, 143.1, 140, 136.2, 131.2 (d, J = 7.5 Hz), 130.7 (d, J = 8.8 Hz), 129.5 (d, J = 2.5 Hz), 130.7 (d, J = 8.8 Hz), 129.5, 128.5, 126.5, 124.3, 121.4 (d, J = 23.8 Hz), 121.3, 115.6 (d, J = 21.3 Hz), 115.4 (d, J = 21.3 Hz), 75.7. IR (KBr) 3140, 2918, 1743, 1713, 1587, 1437, 1225, 710 cm^{-1}. HRMS (+ESI) Calcd for $C_{29}H_{17}F_2O_2[M+H]+$: 435.1196; found: 435.1197.

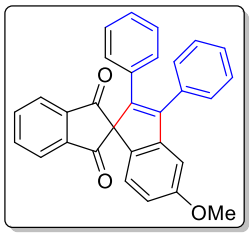


2,3-Dipropyl-1,2'-spirobi[indene]-1',3'-dione (3ae). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2e** (55 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ae** (114 mg, 69%). M.p.: 100 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12-8.11 (m, 2H), 7.96-7.94 (m, 2H), 7.31-7.25 (m, 2H), 6.99 (t, *J* = 7.0 Hz, 1H), 6.67 (d, *J* = 7.5 Hz, 1H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.26 (t, *J* = 8.0 Hz, 2H), 1.71 (q, *J* = 7.5 Hz, 2H), 1.28-1.21 (m, 2H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 146.6, 144.8, 143.3, 143.2, 141.3, 135.9, 128.0, 125.1, 123.9, 120.8, 119.7, 74.5, 29.3, 27.6, 22.4, 21.8, 14.2, 14.0. IR (KBr) 1740, 1711, 1584, 1430 cm^{-1}. HRMS (+ESI) Calcd for $C_{23}H_{23}O_2$ $[M+H]^+$: 331.1695; found: 331.1698.

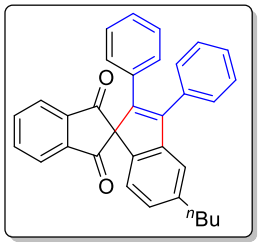


2,3-Dibutyl-1,2'-spirobi[indene]-1',3'-dione (3af). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2e** (55 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3af** (127 mg, 71%). M.p.: 120 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05-8.04 (m, 2H), 7.89-7.87 (m, 2H), 7.23-7.18 (m, 2H), 6.92 (t, *J* = 7.0 Hz, 1H), 6.62 (d, *J* = 7.5 Hz, 1H), 2.54 (t, *J* = 7.5 Hz, 2H), 2.19 (t, *J* = 6.5 Hz, 2H), 1.59-1.54 (m, 4H), 1.40 (q, *J* = 7.5 Hz, 2H), 1.18-1.13 (m, 2H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.68 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 146.7, 144.8, 143.3, 143.2, 141.2, 135.9, 128.0, 125.0, 123.9, 120.9, 119.6, 74.5, 31.2, 30.8, 27.1, 25.4, 22.8, 22.7, 13.9, 13.6. IR

(KBr) 2915, 2855, 1743, 1716, 1586, 1480, 1431, 1241 cm^{-1}. HRMS (+ESI) Calcd for $C_{25}H_{27}O_2$ $[M+H]^+$: 359.2006; found: 359.2011.

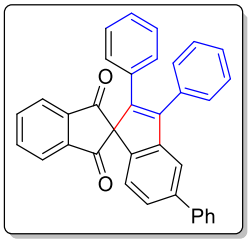


5-Methoxy-2,3-diphenyl-1,2'-spirobi[indene]-1',3'-dione (3ba). Synthesized using general procedure from **1b** (126 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:4) to afford white solid of **3ba** (128 mg, 60%). M.p.: 182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.08 (m, 2H), 7.93-7.90 (m, 2H), 7.45-7.43 (m, 2H), 7.38-7.33 (m, 3H), 7.05-6.98 (m, 5H), 6.93 (s, 1H), 6.70 (d, J = 8.5 Hz, 1H), 6.66-6.63 (m, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 160.3, 147.6, 146.4, 143.4, 142.3, 136.1, 135.8, 134.4, 133.9, 129.5, 128.9, 128.6, 128.2, 127.9, 127.5, 124.2, 121.9, 111.9, 107.7, 74.9, 55.5. IR (KBr) 2922, 1715, 1584 cm^{-1}. HRMS (+ESI) Calcd for $C_{30}H_{21}O_3$ $[M+H]^+$: 429.1496; found: 429.1491.

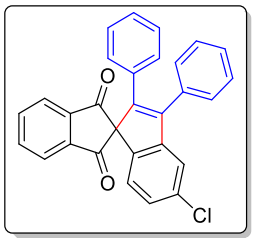


5-Butoxy-2,3-diphenyl-1,2'-spirobi[indene]-1',3'-dione (3ca). Synthesized using general procedure from **1c** (147 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford thick gum of **3ca** (117 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.08 (m, 2H), 7.93-

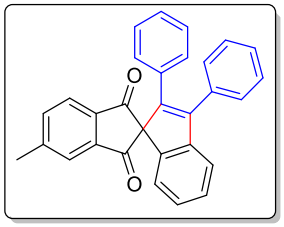
7.91 (m, 2H), 7.45-7.43 (m, 2H), 7.39-7.33 (m, 3H), 7.05-6.97 (m, 5H), 6.91 (m, 1H), 6.70-6.62 (m, 2H), 3.90 (t, *J* = 6.4 Hz, 2H), 1.75-1.68 (m, 2H), 1.47-1.42 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 159.9, 147.5, 146.4, 143.4, 142.1, 136.0, 135.1, 134.4, 134.0, 129.5, 128.8, 128.7, 128.5, 128.1, 127.8, 127.8, 127.4, 124.2, 121.8, 112.3, 108.4, 74.9, 67.9, 31.2, 19.1, 13.8. IR ($CHCl_3$) 2911, 2859, 1744, 1710, 1585 cm^{-1}. HRMS (+ESI) Calcd for $C_{33}H_{27}O_3$ $[M+H]^+$: 471.1955; found: 471.1960.



2,3,5-Triphenyl-1,2'-spirobi[indene]-1',3'-dione (3da). Synthesized using general procedure from **1d** (149 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3da** (130 mg, 55%). M.p.: 180 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-811 (m, 2H), 7.94-7.92 (m, 2H), 7.57 (s, 1H), 7.52-7.47 (m, 4H), 7.41-7.31 (m, 8H), 7.05-7.02 (m, 4H), 6.88 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 146.7, 146.5, 143.5, 142.4, 142.0, 141.7, 141.2, 136.2, 134.4, 133.9, 129.6, 128.9, 128.7, 128.6, 128.3, 127.6, 127.5, 127.4, 125.5, 124.3, 121.5, 120.7, 75.5. IR (KBr) 2917, 1716, 1587, 1439, 1099 cm^{-1}. Anal. calcd for $C_{35}H_{22}O_2$: C, 88.58; H, 4.67; found: 88.87; H, 4.87.

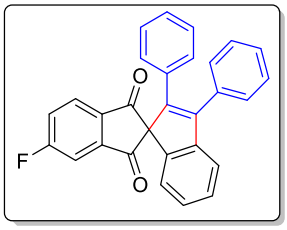


5-Chloro-2,3-diphenyl-1,2'-spirobi[indene]-1',3'-dione (3ea). Synthesized using general procedure from **1e** (128 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ea** (140 mg, 65%). M.p.: 172 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10-8.08 (m, 2H), 7.92-7.90 (m, 2H), 7.42-7.33 (m, 6H), 7.09-6.98 (m, 6H), 6.74 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 147.9, 145.5, 143.3, 142.7, 141.4, 136.2, 134.6, 133.9, 133.2, 129.3, 128.8, 128.6, 128.2, 128.1, 127.7, 126.1, 124.3, 122.2, 121.9, 75.2. IR (KBr) 1714, 1588, 1442, 1233, 729 cm^{-1}. Anal. calcd for $C_{29}H_{17}ClO_2$: C, 80.46; H, 3.96; found: C, 80.78; H, 4.01.

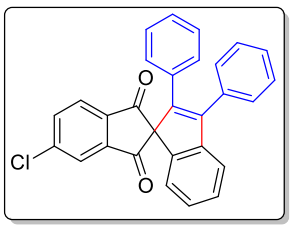


5'-Methyl-2,3-diphenyl-1,2'-spirobi[indene]-1',3'-dione (3fa). Synthesized using general procedure from **1f** (118 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3fa** (117 mg, 57%). M.p.: 182 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.0 Hz, 2H), 7.39-7.28 (m, 5H), 7.09 (t, J = 7.5 Hz, 1H), 7.04-7.02 (m, 5H), 6.81 (d, J = 7.5 Hz, 1H), 2.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 197.9, 148.0, 146.5, 146.1, 144.0, 143.6,

141.5, 141.1, 137.4, 134.6, 134.1, 129.6, 128.9, 128.5, 128.4, 128.3, 127.9, 127.5, 126.3, 124.3, 124.2, 121.7, 121.3, 76.1, 22.3. IR (KBr) 2920, 1702, 1591, 1461, 1252, 1041 cm^{-1}. HRMS (+ESI) Calcd for $C_{30}H_{21}O_2$ $[M+H]^+$: 413.1539; found: 413.1542.

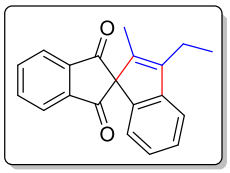


5'-Fluoro-2,3-diphenyl-1,2'-spirobi[indene]-1',3'-dione (3ga). Synthesized using general procedure from **1g** (128 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ga** (100 mg, 48%). M.p.: 166 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.14-8.10 (m, 1H), 7.71 (dd, J = 7.0, 2.5 Hz, 1H), 7.60 (t, J = 8.5 Hz, 1H), 7.45-7.42 (m, 2H), 7.40-7.31 (m, 5H), 7.15-7.11 (m, 1H), 7.07 -7.03 (m, 3H), 7.00-6.98 (m, 2H), 6.83 (d, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 196.5, 168.7 (d, J = 260.9 Hz), 146.7, 146.1 (d, J = 9.0 Hz), 146.0, 143.1, 140.6, 139.8, 134.3, 133.7, 129.5, 128.9, 128.7, 128.6, 128.2, 127.9, 127.5, 126.9 (d, J = 10.0 Hz), 126.5, 124.3 (d, J = 23.8 Hz), 121.9, 121.3, 110.7 (d, J = 22.7 Hz), 76.0. IR (KBr) 2922, 1705, 1546, 1461, 1256 cm^{-1}. HRMS (+ESI) Calcd for $C_{29}H_{18}FO_2$ $[M+H]^+$: 417.1288; found: 417.1291.

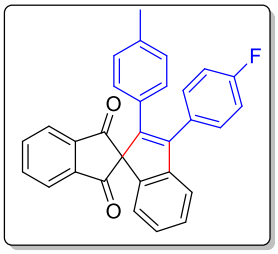


5'-Chloro-2,3-diphenyl-1,2'-spirobi[indene]-1',3'-dione (3ha). Synthesized using general procedure from **1h** (128 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol) which was

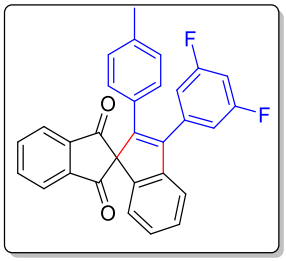
then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ia** (112 mg, 52%). M.p.: 168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-8.03 (m, 2H), 7.88-7.86 (m, 1H), 7.45-7.30 (m, 8H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.07-7.05 (m, 2H), 7.00-6.97 (m, 2H), 6.82 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 197.0, 146.8, 146.0, 144.7, 143.3, 143.1, 141.6, 140.7, 136.4, 134.3, 133.8, 129.5, 128.9, 128.6, 128.5, 128.3, 127.9, 127.6, 126.4, 125.5, 124.3, 121.9, 121.3, 75.8. IR (KBr) 1714, 1586, 1455, 1342, 1267 cm^{-1}. Anal. calcd for$C_{29}H_{17}ClO_2$: C, 80.46; H, 3.96; found: C, 80.88; H, 4.18.



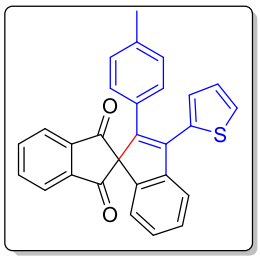
3-Ethyl-2-methyl-1,2'-spirobi[indene]-1',3'-dione and 2-ethyl-3-methyl-1,2'-spirobi[indene]-1',3'-dione (3ag, 1:1 mixture of isomers). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2g** (34 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ag** (92 mg, 64%). M.p.: 135 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.10 (m, 2H), 7.95-7.93 (m, 2H), 7.31-7.26 (m, 2H), 7.02-6.99 (m, 1H), 6.78-6.66 (m, 1H), 2.62 (q, *J* = 7.5 Hz, 1H), 2.33 (q, *J* = 7.7 Hz, 1H), 2.18 (s, 1.5H), 1.80 (s, 1.5H), 1.24 (t, *J* = 7.6 Hz, 1.5H), 0.92 (t, *J* = 7.7 Hz, 1.5H).^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 199.3, 147.4, 146.6, 145.7, 143.5, 143.3, 142.8, 142.7, 142.4, 139.9, 136.1, 136.0, 135.9, 128.2, 128.1, 125.2, 124.9, 124.0, 123.9, 121.1, 120.6, 119.4, 75.0, 20.4, 18.6, 13.4, 13.2, 11.3, 10.6. IR (KBr) 2976, 2925, 2853, 1702, 1590, 1455, 1338, 1253 cm^{-1}. HRMS (+ESI) Calcd for $C_{20}H_{17}O_2$ $[M+H]^+$: 289.1227; found: 289.1229.



3-(4-Fluorophenyl)-2-(p-tolyl)-1,2'-spirobi[indene]-1',3'-dione and 2-(4-fluorophenyl)-3-(p-tolyl)-1,2'-spirobi[indene]-1',3'-dione (3ah, 1:1). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2h** (105 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford yellow solid of **3ah** (129 mg, 60%). M.p.:142 ^{o}C.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12-8.09 (m, 2H), 7.94-7.92 (m, 2H), 7.44-7.39 (m, 1.5H), 7.35-7.29 (m, 2.5H), 7.18 (d, J = 8.2 Hz, 1H), 7.12-7.05 (m, 2H), 7.01-6.98 (m, 1H), 6.86 (q, J = 8.5 Hz, 2H), 6.79 (d, J = 7.5 Hz, 1H), 6.74 (t, J = 8.5 Hz, 1H), 2.37 (s, 1.5H), 2.17 (s, 1.5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 198.2, 162.2 (d, J = 245.0 Hz), 147.2, 147.0, 145.8, 145.0, 144.6, 143.4, 143.1, 141.6, 141.0, 139.7, 137.7, 137.4, 136.1, 136.0, 131.2 (d, J = 8.8 Hz), 130.6 (d, J = 8.8 Hz), 130.1, 130.0, 129.9, 129.3, 129.2, 129.0, 128.5, 128.3, 126.2 ,124.2 (d, J = 2.5 Hz), 121.8, 121.3, 121.2, 115.5 (d, J = 21.3 Hz), 115.2 (d, J = 21.3 Hz), 75.7, 75.6, 21.0, 20.6. IR (KBr) 2937, 1743, 1701, 1586, 1461, 1342, 1251 cm^{-1}. Anal. calcd for $C_{30}H_{19}FO_2$: C, 83.70; H, 4.45; found: C, 83.78; H, 4.56.

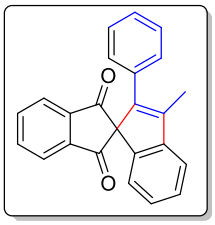


3-(3,5-Difluorophenyl)-2-(p-tolyl)-1,2'-spirobi[indene]-1',3'-dione and 2-(3,5-difluorophenyl)-3-(p-tolyl)-1,2'-spirobi[indene]-1',3'-dione (3ai, 3:1). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2i** (119 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid compound of **3ai** (114 mg, 51%). M.p.: 160 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16-8.12 (m, 1.5H), 8.12-8.08 (m, 0.5H), 7.99-7.96 (m, 1.5H), 7.95-7.92 (m, 0.5H), 7.42-6.95 (m, 7H), 6.88 (s, 1H), 6.82-6.75 (m, 1H), 6.56-6.48 (m, 2H), 2.40 (s, 2.25H), 2.19(s, 0.75H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 197.6, 162.5 (d, J = 247.5 Hz), 162.4 (d, J = 247.5Hz), 148.6, 145.3, 143.5, 143.3, 143.1, 138.2, 136.3, 136.1, 130.0, 129.5, 129.4, 129.2, 129.1, 128.7, 128.5, 128.4, 126.8, 124.4, 124.3, 122.1, 111.8 (d, J = 19.4 Hz), 111.7 (d, J = 18.8 Hz), 103.1, 102.9, 102.7, 21.3, 21.0. IR (KBr) 2937, 1717, 1590, 1460, 1252 cm^{-1}. Anal. calcd for $C_{29}H_{16}F_2O_2$: C, 80.18; H, 3.71; found: C, 80.23; H, 3.89.

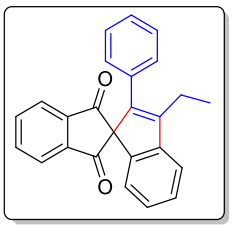


3-(Thiophen-2-yl)-2-(p-tolyl)-1,2'-spirobi[indene]-1',3'-dione and 2-(thiophen-2-yl)-3-(p-tolyl)-1,2'-spirobi[indene]-1',3'-dione (3aj, 2:1). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2j** (99 mg, 0.5 mmol) which was then purified by using EtOAc/Hexane (1:4) to afford brown solid of compound **3aj** (115 mg, 55%). M.p.: 160 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22-7.68 (m, 4H), 7.47-7.30 (m, 4H), 7.23-6.42 (m, 7H), 2.49 (s, 2H), 2.21 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

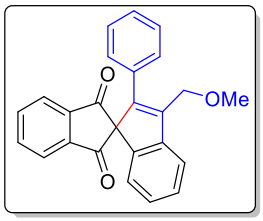
198.2, 197.6, 146.6, 145.9, 145.4, 143.6, 143.4, 142.6, 138.4, 137.8, 136.8, 136.3, 136.2, 134.9, 134.2, 130.9, 129.8, 129.6, 129.2, 129.1, 128.7, 128.6, 128.0, 127.0, 126.4, 126.3, 126.1, 124.6, 124.3, 121.9, 121.6, 121.5, 120.9, 76.0, 21.6, 21.3. IR (KBr) 2918, 2850, 1711, 1589, 1459, 1257, 1099, 882 cm^{-1}. HRMS (+ESI) Calcd for $C_{28}H_{19}O_2S$ $[M+H]^+$: 419.1102; found: 419.1106.



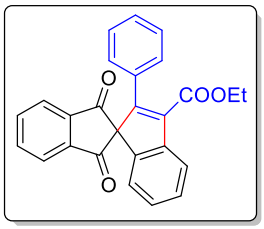
3-Methyl-2-phenyl-1,2'-spirobi[indene]-1',3'-dione (3ak). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2k** (58 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ak** (102 mg, 61%). M.p.: 140 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.05-8.03 (m, 2H), 7.88-7.85 (m, 2H), 7.40 (d, J = 7.0 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.24-7.15 (m, 5H), 7.08 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 146.9, 143.4, 143.1, 142.4, 140.0, 135.9, 134.7, 128.6, 128.4, 128.3, 127.4, 126.1, 124.0, 120.9, 120.4, 75.5, 11.9. IR (KBr) 2957, 1727, 1593, 1415, 1253, 1071 cm^{-1}. Anal. calcd for $C_{24}H_{16}O_2$: C, 85.69; H, 4.79; found: C, 85.41; H, 4.62.



3-Ethyl-2-phenyl-1,2'-spirobi[indene]-1',3'-dione (3al). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2l** (65 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of compound **3al** (105 mg, 60%). M.p.: 139 ^{o}C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.01 (m, 2H), 7.86-7.83 (m, 2H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.22-7.17 (m, 5H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 2.64 (q, *J* = 8.0 Hz, 2H), 1.30 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 148.3, 146.1, 143.6, 143.5, 139.8, 135.9, 134.9, 128.7, 128.3, 128.2, 127.5, 125.9, 123.9, 121.2, 120.6, 75.7, 19.5, 13.8. IR (KBr) 2967, 2931, 1707, 1596, 1465, 1442, 1257, 1074, 1023, 768 cm^{-1}. Anal. calcd for $C_{25}H_{18}O_2$: C, 85.69; H, 5.18; found: C, 85.72; H, 5.05.

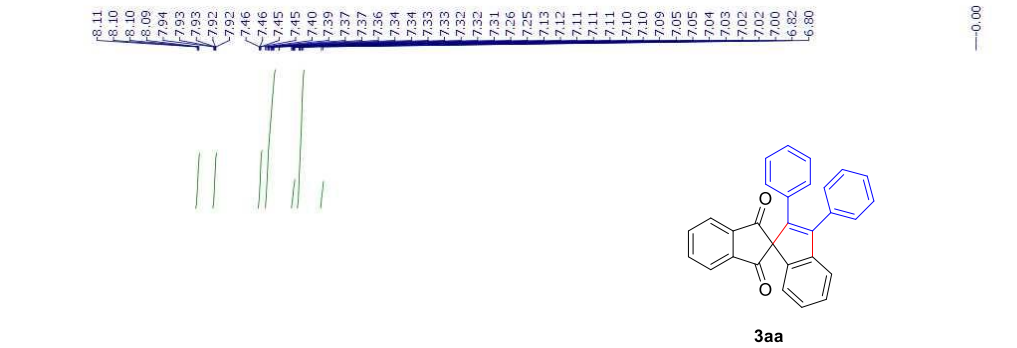


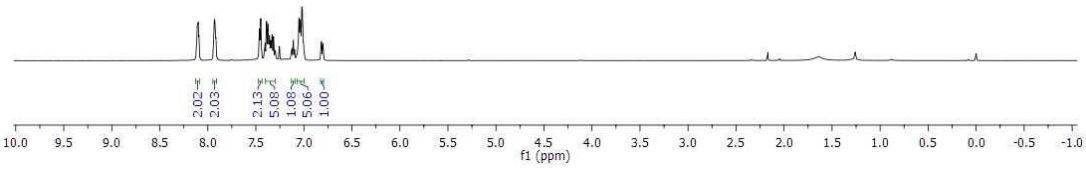
3-Methoxy-2-phenyl-1,2'-spirobi[indene]-1',3'-dione (3am). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2m** (73 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3am** (122 mg, 67%). M.p.: 115 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-804 (m, 2H), 7.91-7.88 (m, 2H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.24-7.21 (m, 3H), 7.19-7.16 (m, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.51 (s, 2H), 3.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 145.1, 144.1, 143.5, 143.1, 142.5, 136.0, 135.6, 133.9, 130.4, 128.7, 128.4, 128.0, 127.5, 126.2, 124.1, 123.7, 121.8, 121.0, 76.0, 66.2, 57.8. IR (KBr) 2962, 1709, 1592, 1461, 1252, 763 cm^{-1}. Anal. calcd for $C_{25}H_{18}O_3$: C, 81.95; H, 4.95; found: C, 82.01; H, 4.97.

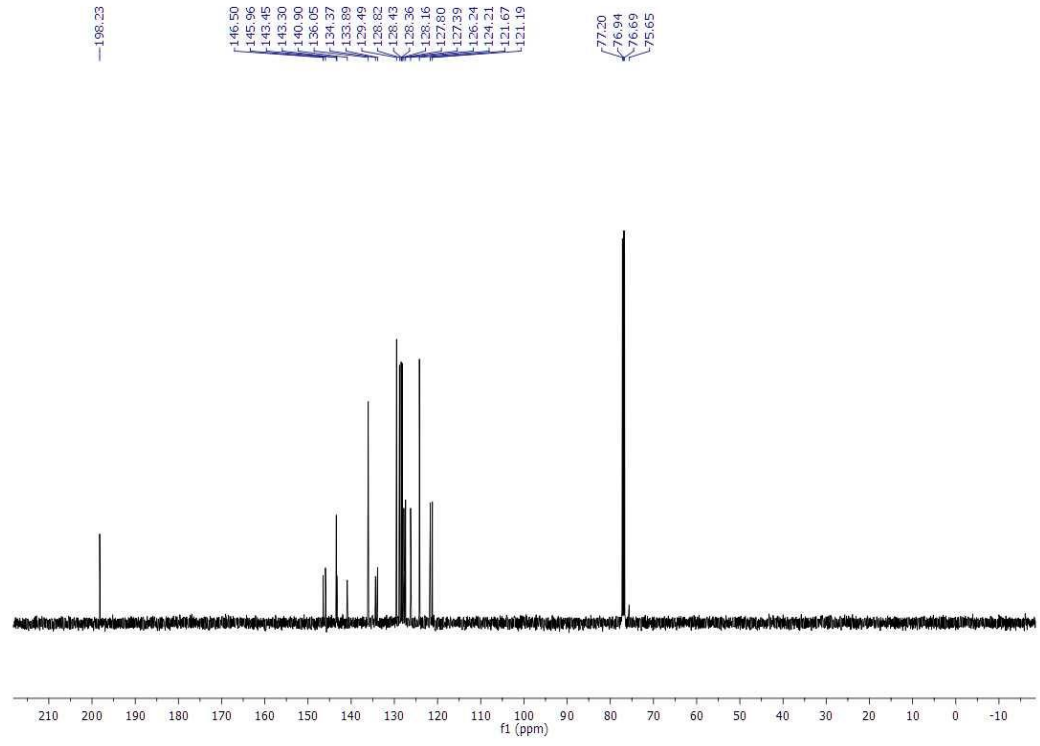


Ethyl 1',3'-dioxo-2-phenyl-1',3'-dihydro-1,2'-spirobi[indene]-3 carboxylate (3an). Synthesized using general procedure from **1a** (111 mg, 0.5 mmol) and **2n** (87 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford yellow solid of **3an** (130 mg, 66%). M.p.: 125 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90-7.88 (m, 2H), 7.75-7.73 (m, 2H), 7.65-7.63 (m, 2H), 7.39-7.33 (m, 3H), 7.14-7.12 (m, 2H), 7.04-7.02 (m, 2H), 3.88 (q, J = 7.0 Hz, 2H), 0.95 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 165.0, 155.2, 141.6, 137.2, 135.9, 133.4, 128.9, 128.5, 128.4, 127.6, 127.5, 126.4, 123.7, 70.9, 60.0, 29.6, 13.7. IR (KBr) 2932, 1717, 1592, 1462, 1255 cm^{-1}. Anal. calcd for $C_{26}H_{18}O_4$: C, 79.17; H, 4.60; found: C, 79.25; H, 4.68.

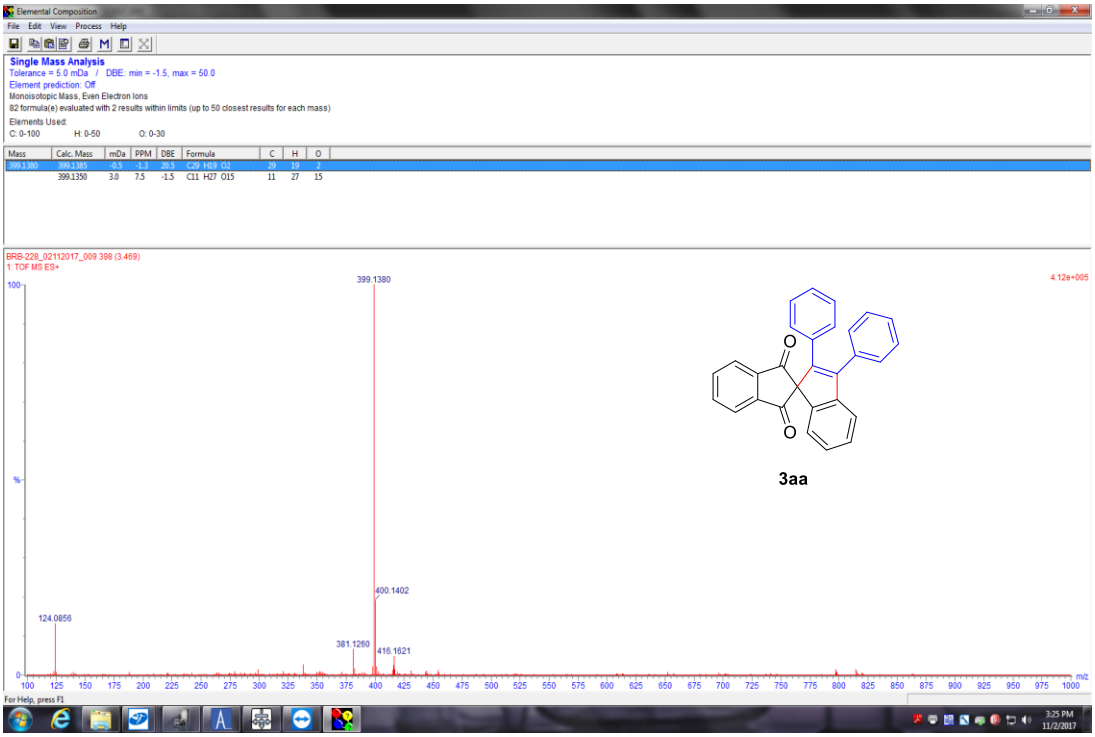
^{1}H & ^{13}C NMR Spectra of compound **3aa**



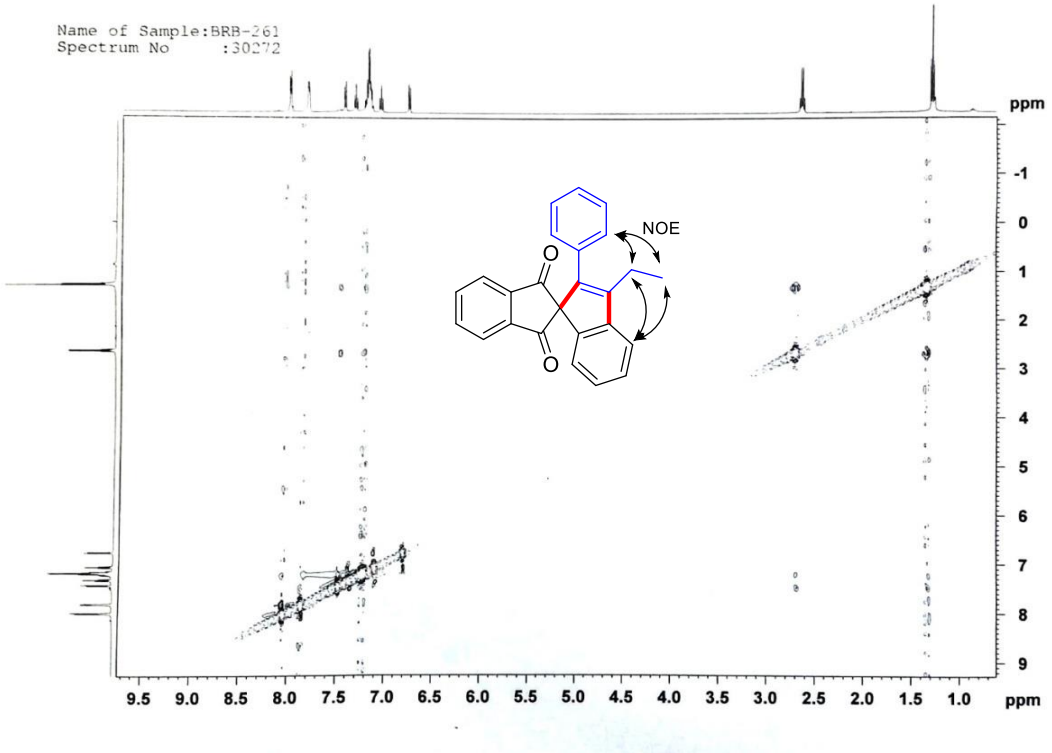




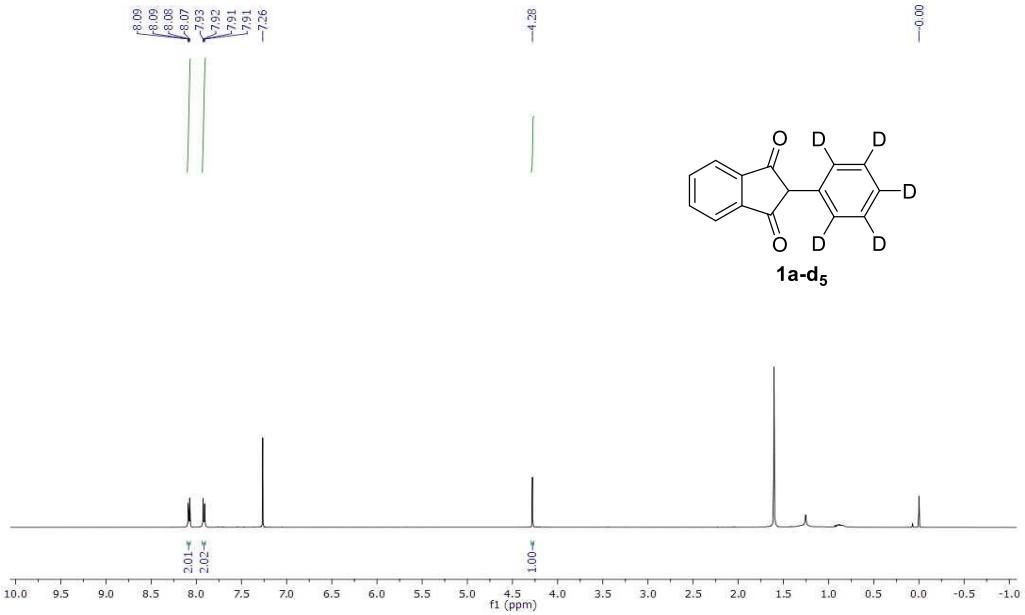
HRMS spectra of compound **3aa**



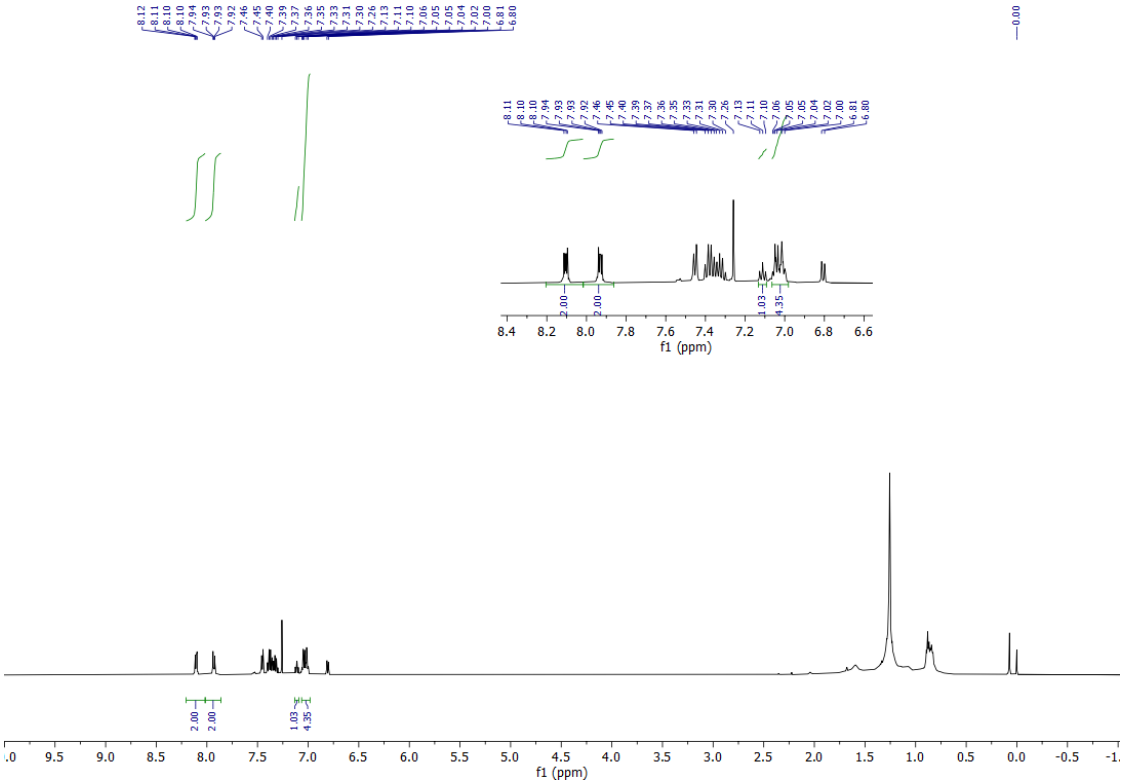
NOE spectra of compound **3al**



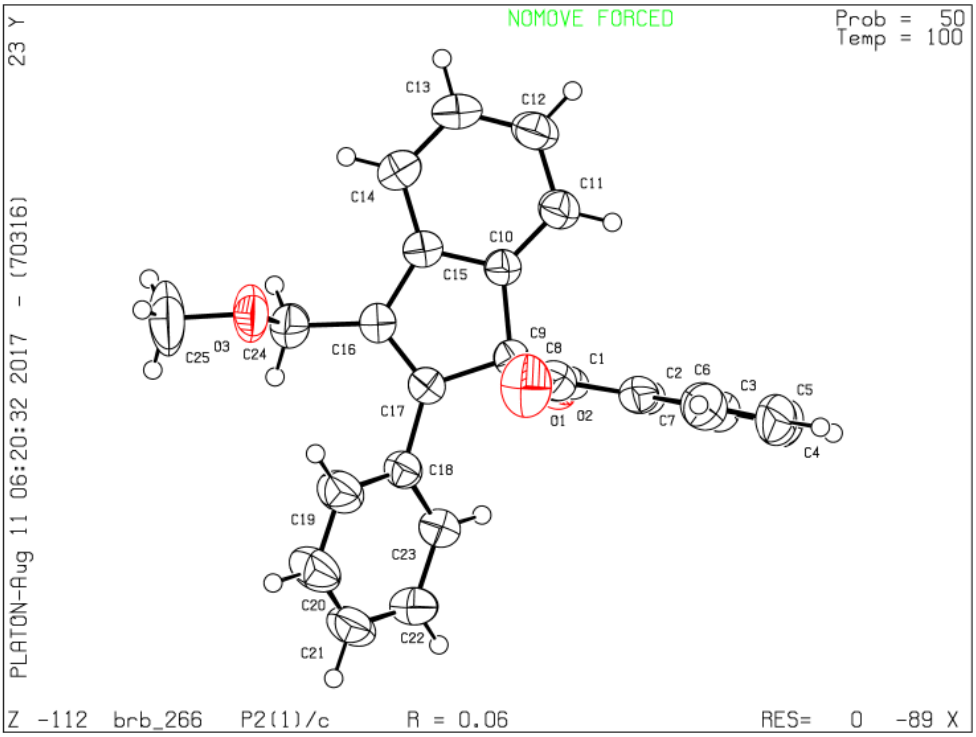
^{1}H NMR spectra of compound **1a-d$_5$**



Intermolecular competitive reaction



X-ray crystallographic structure of **3am** with CCDC number: 2045360



X-ray crystallographic CIF report of **3am**

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: brb_266

Bond precision: C-C = 0.0032 A Wavelength=0.71073

Cell: a=9.0550(7) b=10.0800(8) c=21.3514(17)
alpha=90 beta=98.681(5) gamma=90
Temperature: 100 K

	Calculated	Reported
Volume	1926.5(3)	1926.5(3)
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Hall group	-P 2ybc	?
Moiety formula	C25 H18 O3	?
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F000'	768.37	
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Nref	5047	4992
Tmin,Tmax	0.980,0.986	0.977,0.986
Tmin'	0.977	

Correction method= # Reported T Limits: Tmin=0.977 Tmax=0.986
AbsCorr = MULTI-SCAN

Data completeness= 0.989 Theta(max)= 28.860

R(reflections)= 0.0592(2431) wR2(reflections)= 0.1770(4992)

S = 1.007 Npar= 254

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Click on the hyperlinks for more details of the test.

2.6 REFERENCES

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15. CCDC 2045360 contains the crystallographic data of the compound **3am**.

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CHAPTER 2

Synthesis of aryl 2-aminobenzoates *via* Ru(II)-catalyzed decarbonylative and decarboxylative coupling of isatoic anhydrides with salicylaldehydes

ABSTRACT:

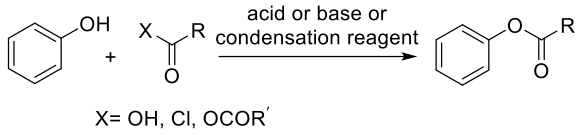
A novel ruthenium-catalyzed synthesis of aryl 2-aminobenzoates from salicylaldehydes and isatoic anhydrides is developed. This reaction proceeds via Ru(II)-catalyzed decarboxylation and decarbonylation to afford good yields of important aryl 2-aminobenzoates.

3.1 INTRODUCTION:

Aryl esters of benzoic acids are very important synthons for the synthesis of various pharmaceutically active compounds, natural products, agrochemicals and polymers.[1] In recent years, aryl esters have also engrossed much significance as green and low-cost arylating agents *via* C-O activation in transition-metal-catalyzed coupling reactions.[2] In photochemistry, aryl benzoates are used as chemiluminescent indicators.[3] Among the aryl benzoates, particularly, the aryl 2-aminobenzoates have received significant attention because of their utility in the synthesis of bioactive nitrogen containing heterocycles.[4] Some of these 2-aminobenzoates have application in fragrance and flavor industries owing to their pleasant scent.[5] Furthermore, some of the aminobenzoate derivatives exhibit anti-bacterial, anti-fungal and anti-inflammatory activities.[6] The drug glafenine is a nonsteroidal anti-inflammatory drug that possesses 2-aminobenzoate as the key skeleton.

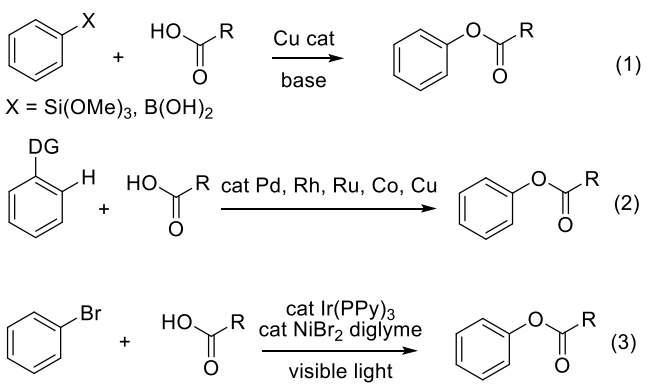
These aryl benzoates are traditionally synthesized by esterification, transesterification and Baeyer-Villiger oxidation reactions.[7] However, the highly acidic and basic conditions used in esterification and transesterification reactions might not be suitable for some compounds possessing sensitive functional groups in the molecule. In Baeyer-Villiger oxidation reaction the regiospecificity depends on the relative migratory capacity of the substituents attached to the carbonyl group, and if the substituent groups have similar migratory rates, then mixture will be obtained with low regioselectivity. Again, acid-catalyzed esterification of anthranilic acid to get the ester is a tough reaction owing to the presence of *ortho* amino group. This amino group consumes large amount of the acid before esterification with the alcohol.

Amid a range of synthetic routes for aryl esters, one of most conventional and traditional transformations is condensation of phenols and carboxylic acids or their derivatives, i.e., the C_{acyl}-O_{aryl} bond formations (Scheme 3.1).[8]



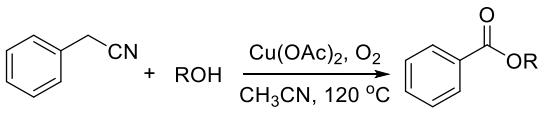
Scheme 3.1

In contrast, less attention was paid for the synthesis of aryl esters by using carboxylic acids as an *O*-nucleophile in transition-metal-catalyzed C_{aryl}-O_{acyl} bond formation such as copper-catalyzed Chan-Lam-Evans coupling reaction (Scheme 3.2, eq 1),[9] directing group assisted C-H activation reaction of aryl halide and carboxylic acid (Scheme 3.2, eq 2)[10] and energy transfer coupling (Scheme 3.2, eq 3).[11]



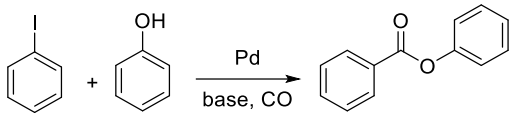
Scheme 3.2

Again, Dong and co-workers reported an easy and direct aerobic oxidative esterification reaction of arylacetonitriles with alcohols/phenols in the presence of a copper salt and molecular oxygen (Scheme 3.3).[12]



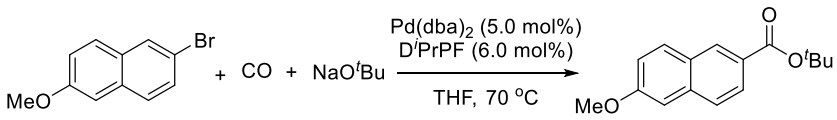
Scheme 3.3

Recently, Mika and co-workers reported a Pd-catalyzed aryloxy and alkoxycarbonylation reaction of iodoaromatic compounds using γ-valerolactone as a renewable, environmentally benign reaction medium (Scheme 3.4).[13]



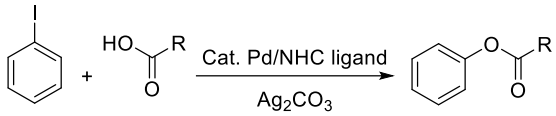
Scheme 3.4

Skrydstrup et al. reported an efficient synthesis of tertiary esters by palladium-catalyzed alkoxycarbonylation of aryl bromides (Scheme 3.5).[14]



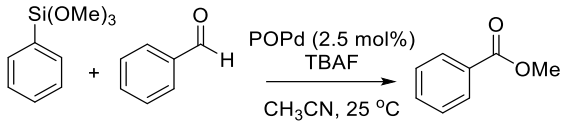
Scheme 3.5

Again, Itami and co-workers reported a palladium-catalyzed esterification of aryl iodides with carboxylic acids (Scheme 3.6).[15]



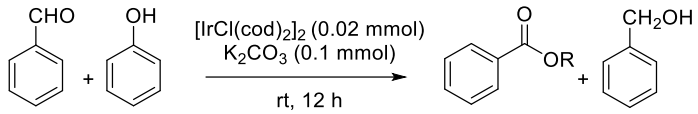
Scheme 3.6

In last few years, immense development has been made in the synthesis of aryl benzoate derivatives by using aldehydes.[16] Recently, Wolf et al. developed an efficient palladium phosphinous acid-catalyzed oxidative conversion of aldehydes towards the synthesis of aryl esters (Scheme 3.7).[17]



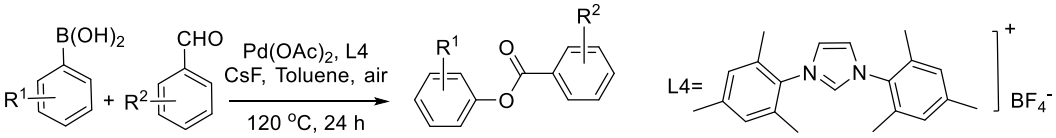
Scheme 3.7

More recently, Kiyooka and co-workers reported Ir-catalyzed direct oxidative esterification of aldehydes with solvent alcohols (Scheme 3.8).[18]



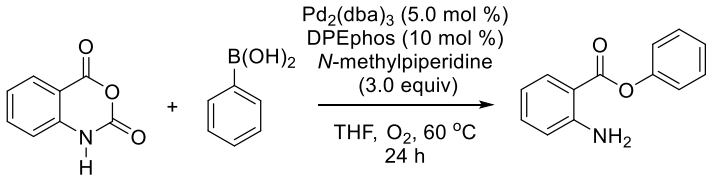
Scheme 3.8

Wu and co-workers reported a palladium-catalyzed esterification reaction of aldehydes with arylboronic acids under an air atmosphere (Scheme 3.9).[19]



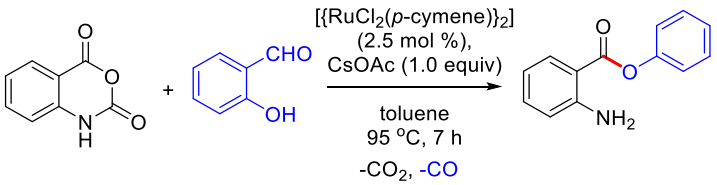
Scheme 3.9

Although there are many routes available for the synthesis of aryl esters, metal-catalyzed reactions for the synthesis of aryl 2-aminobenzoates are rare. Wu and co-workers reported a $Pd_2(dba)_3$-catalyzed reaction of isatoic anhydrides with arylboronic acids in the presence of the ligand DPEphos for the synthesis of aryl *o*-aminobenzoates (Scheme 3.10).[20]



Scheme 3.10

Herein, we have disclosed an unprecedented decarbonylative and decarboxylative coupling reaction of isatoic anhydrides and salicylaldehydes for the synthesis of aryl 2-aminobenzoates (Scheme 3.11).



Scheme 3.11: Ru-catalyzed synthesis of aryl 2-aminobenzoates

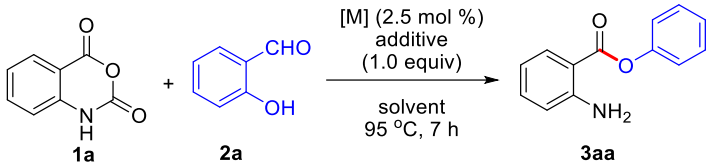
3.2 RESULTS AND DISCUSSION

Initially, the Ru(II)-catalyzed coupling reaction between isatoic anhydride (**1a**) and salicyldehyde (**2a**) was selected as a model reaction to find out the optimized reaction conditions for the synthesis of the ester **3aa**. As shown in Table 3.1, among all the metal complexes studied for this esterification reaction, only the [{$RuCl_2$(*p*-cymene)}$_2$] catalyst provided the ester **3aa** in 43% yield using $Cu(OAc)_2$ and ^{t}AmOH as the additive and solvent, respectively. To improve the yield of **3aa**, some other commonly used additives such as CsOAc, AgOAc and KOAc were tested which revealed CsOAc to be the best additive which afforded 58% yield of **3aa** (entry 5). Then, further screening of some common solvents proved the aprotic solvent toluene to be the best solvent for the synthesis of the ester **3aa** (81%, entry 10).

Initially the optimized reaction conditions were applied to study the substrate scope of the isatoic anhydrides (**1a-g**). As shown in Scheme 3.12, isatoic anhydrides substituted with mono-methyl and di-methyl substituents **1b-c** provided 70-78% yields of the products **3ba-ca**. Similarly, isatoic anhydrides substituted with electron-

withdrawing substituents such as fluoro, chloro and bromo **1d-g**, provided good yields (56-68%) of the products **3da-ga**, irrespective of the position of the substituents on the aromatic ring. Next, the scope of the salicylaldehydes **2b-p** were studied with **1a** for

Table 3.1. Reaction conditions optimization for **3aa**[a]

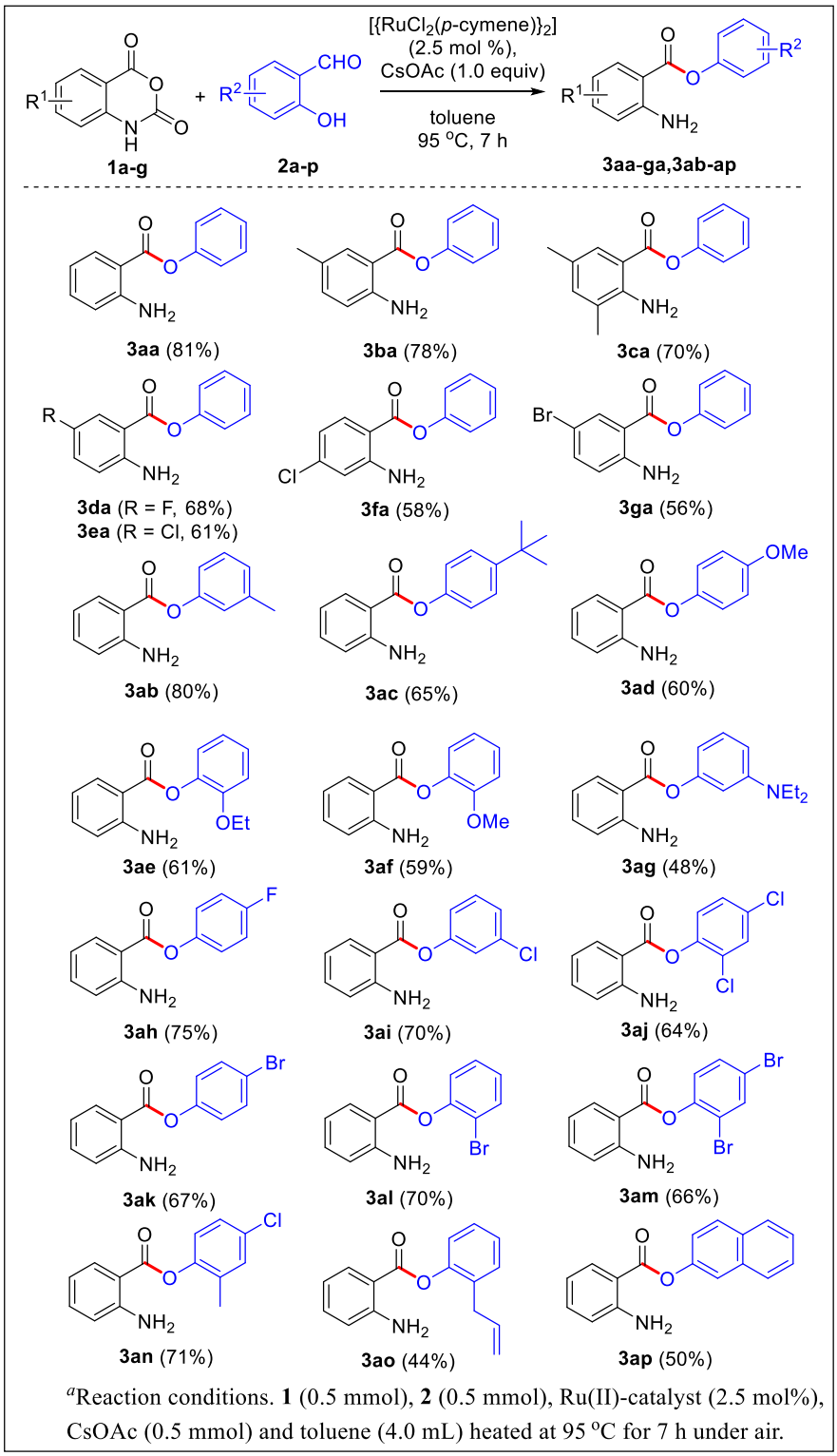


Entry	Catalyst	Additive	Solvent	**3aa** (%)[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$	^{t}AmOH	0
2	$RuCl_3 \cdot xH_2O$	$Cu(OAc)_2 \cdot H_2O$	^{t}AmOH	0
3	$RuCl_2(PPh_3)_3$	$Cu(OAc)_2 \cdot H_2O$	^{t}AmOH	0
4	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2 \cdot H_2O$	^{t}AmOH	43
5	$[\{RuCl_2(p\text{-cymene})\}_2]$	CsOAc	^{t}AmOH	58
6	$[\{RuCl_2(p\text{-cymene})\}_2]$	AgOAc	^{t}AmOH	27
7	$[\{RuCl_2(p\text{-cymene})\}_2]$	KOAc	^{t}AmOH	38
8	$[\{RuCl_2(p\text{-cymene})\}_2]$	CsOAc	MeCN	25
9	$[\{RuCl_2(p\text{-cymene})\}_2]$	CsOAc	DCE	42
10	**$[\{RuCl_2(p\text{-cymene})\}_2]$**	**CsOAc**	**toluene**	**81**
11	$[\{RuCl_2(p\text{-cymene})\}_2]$	CsOAc	dioxane	54

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (2.5 mol%), additive (0.5 mmol) and solvent (4.0 mL) heated at 95 °C for 7 h under air. [b]Isolated yields.

this esterification reaction. As shown in Scheme 2.12, various salicylaldehydes possessing electron-rich substituents such as methyl, *tert*-butyl, methoxy, ethoxy and diethylamino on the phenyl ring of salicylaldehyde **2b-g** provided 48-80% yields of the esters **3ab-ag**. Similarly, some of the salicylaldehydes substituted with one or two

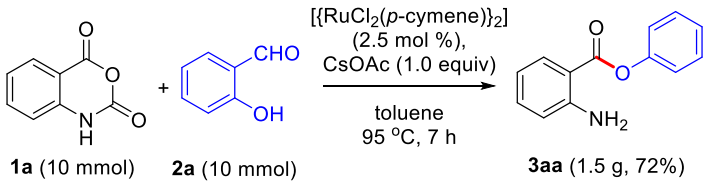
Scheme 3.12. Scope with isatoic anhydrides and salicylaldehydes[a]



[a]Reaction conditions. **1** (0.5 mmol), **2** (0.5 mmol), Ru(II)-catalyst (2.5 mol%), CsOAc (0.5 mmol) and toluene (4.0 mL) heated at 95 °C for 7 h under air.

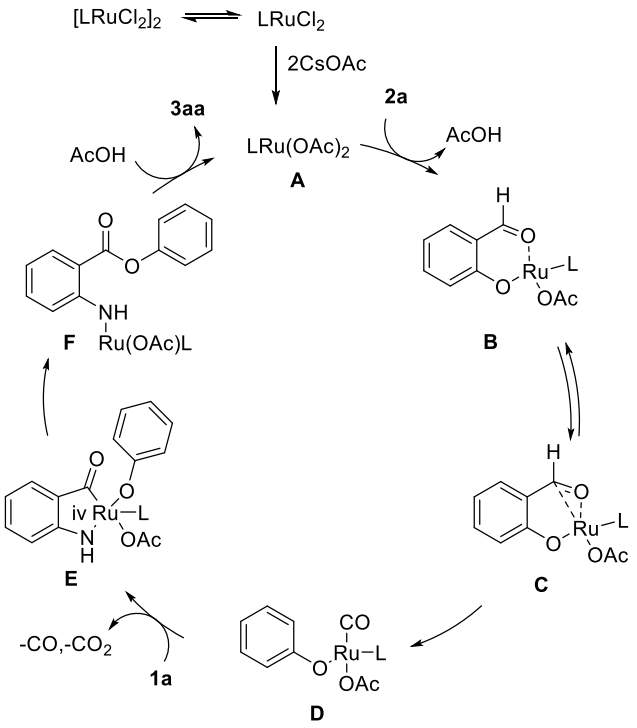
electron-withdrawing substituents such as fluoro, chloro and bromo on the phenyl ring of salicylaldehyde **2h-m** provided 64-75% yields of the products **3ah-am**. For the products **3ag** and **3ai**, 4-(diethylamino)-2-hydroxybenzaldehyde (**2g**) and 4-chloro-2-hydroxybenzaldehyde (**2i**) were used. The methyl and chloro group substituted salicylaldehyde **1n** also turned out to be a good substrate for this reaction which provided 71% yield of product **3an**. The sensitive allyl group containing salicylaldehyde **2o** provided 44% yield of **3ao**. Finally, 2-hydroxy-1-naphthaldehyde **2p** was tested to afford 50% yield of ester **3ap**. A gram-scale esterification reaction between **1a** and **2a** provided 72% yield of **3aa**, which suggest the practical applicability of this reaction (Scheme 3.13). The phosphomolybdic acid test and lime water test indicated the evaluation of carbon monoxide and carbon dioxide, respectively, from the reaction mixture.[21]

Scheme 3.13. Gram-scale synthesis of ester **3aa**



A plausible mechanism for the formation of **3aa** is proposed in Scheme 3.14, based on literature reports.[22] First, the active catalyst **A** forms Ru(II)-complex **B** by elimination of one molecule of acetic acid. This complex **B** might exist as tautomer with π-bonded Ru-complex **C**, which on decarbonylation generates a Ru-CO complex **D**.[22a] Then, oxidative addition of this Ru complex in the C-O bond of **1a** followed by decarboxylation and decarbonylation affords Ru-complex **E**. Reductive elimination of

the metal initially generates Ru complex **F**, which in the presence of acetic acid affords the active catalyst **A** and the ester **3aa**.



Scheme 3.14. Possible mechanism

3.3 CONCLUSION

In conclusion, a novel Ru(II)-catalyzed coupling reaction of isatoic anhydride and salicylaldehyde was developed. The use of salicylaldehyde as phenolic compound source is unique and versatile. This reaction proceeds through decarboxylation and decarbonylation to afford good yields of important aryl 2-aminobenzoates.

3.4 EXPERIMENTAL SECTION

General information

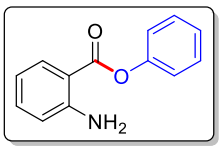
Melting points were measured with a Buchi B-540 melting point apparatus. The NMR spectra were recorded on Bruker Avance III 500 MHz FTNMR and 400 MHz FTNMR spectrometer using tetramethylsilane (TMS) as an internal standard. All other solvents

and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-backed silica gel plates (0.2 mm thickness); the chromatograms were visualized first with ultraviolet light (254 nm) and then by immersion in solutions of *p*-anisaldehyde followed by heating. Column chromatography was performed with silica gel (100-200 mesh, Merck). The starting isatoic anhydrides were synthesized using isatins by following a known procedure.[23]

General procedure for the synthesis of aryl 2-aminobenzoates:

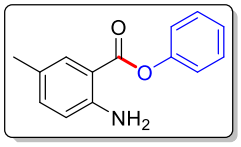
A mixture of isatoic anhydride (**1**, 0.5 mmol), salicyaldehyde (**2**, 0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), CsOAc (0.5 mmol) in toluene (4.0 mL) was stirred at 95 ^oC under open air for 7 hours. The solvent was removed under vacuo and the crude reaction mixture was poured into water and extracted with dichloromethane (25 mL x 2). The dichloromethane layer was then washed with brine. Finally, it was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuo. The crude product thus obtained was purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane as the eluant to afford **3**.

3.5 SPECTRAL AND ANALYTICAL DATA

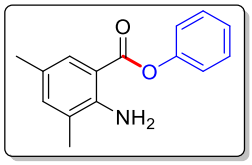


Phenyl 2-aminobenzoate (3aa).[20] Synthesized using GPA from **1a** (81 mg,0.5 mmol) and **2a** (61 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3aa** (86 mg, 81%). M.p.: 70-72 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 7.9 Hz, 1H), 7.43 (t, J =

7.5 Hz, 2H), 7.36-7.33 (m, 1H), 7.29-7.26 (m, 1H), 7.20-7.18 (m, 2H), 6.74-6.70 (m, 2H), 5.78 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 151.1, 150.7, 134.8, 131.5, 129.4, 125.7, 122.6, 121.9, 116.7, 116.3, 114.4, 109.5. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.68; H, 5.01; N, 6.81.

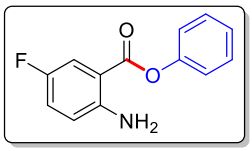


Phenyl 2-amino-5-methylbenzoate (3ba).[20] Synthesized using GPA from **1b** (88 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid (88 mg, 78%). M.p.: 60-62 ^{o}C. ^{1}H NMR (500 MHz, CDCl3) δ 7.89 (s, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.29-7.25 (m, 1H), 7.15-7.20 (m, 3H), 6.64 (d, J = 8.4 Hz, 1H), 5.62 (bs, 2H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 150.7, 149.1, 136.0, 131.0, 129.4, 125.7, 125.4, 121.9, 116.8, 109.3, 20.2. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.20; H, 5.83; N, 5.93.

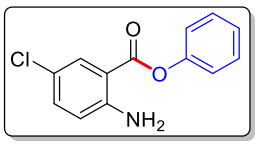


Phenyl 2-amino-3,5-dimethylbenzoate(3ca). Synthesized using GPA from **1c** (95 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid (84 mg, 70%). M.p.: 101-103^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.29-7.25 (m, 1H), 7.18 (d, J = 8.3 Hz, 2H), 7.12 (s, 1H), 5.73 (bs, 2H), 2.27 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 150.8, 147.6, 136.9, 129.4, 128.8,

125.6, 124.7, 123.2, 122.0, 108.9, 20.2, 17.3. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.51; H, 6.45; N, 6.09.

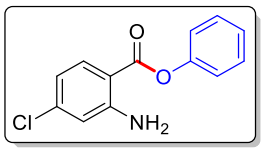


Phenyl 2-amino-5-fluorobenzoate (3da).[20] Synthesized using GPA from **1d** (90 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford yellow solid of **3da** (78 mg, 68%). M.p.: 110-112 ^oC.^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, J = 9.6, 3.0 Hz, 1H), 7.47-7.42 (m, 2H), 7.31-7.25 (m, 1H), 7.20-7.16 (m, 2H), 7.09-7.14 (m, 1H), 6.68 (dd, J = 9.1, 4.5 Hz, 1H), 5.65 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 153.7 (d, J = 234 Hz), 150.4, 147.7, 129.4, 125.9, 122.9 (d, J= 23.8 Hz), 121.8, 117.9 (d, J = 7.5 Hz), 116.2 (d, J= 23.8 Hz), 116.14, 109.3 (d, J= 7.5 Hz). Anal. Calcd for $C_{13}H_{10}FNO_2$: C, 67.53; H, 4.36; N, 6.06. Found: C, 67.79; H, 4.30; N, 5.87.

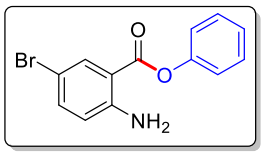


Phenyl 2-amino-5-chlorobenzoate (3ea).[20] Synthesized using GPA from **1e** (98 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford yellow solid of **3ea** (75 mg) with 61% yield. M.p.: 100-102 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.44 (t, J = 8.1 Hz, 2H), 7.30-7.26 (m, 2H), 7.18 (d, J = 7.6 Hz, 2H), 6.66 (d, J = 8.8 Hz, 1H), 5.79 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 150.4, 149.6, 134.8, 130.6, 129.4,

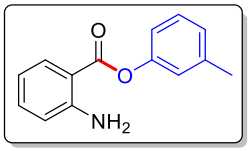
125.9, 121.7, 120.7, 118.1, 110.3. Anal. Calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.27; H, 4.30; N, 5.82.



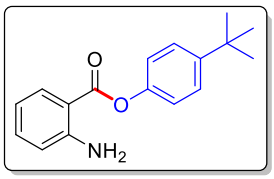
Phenyl 2-amino-4-chlorobenzoate (3fa).[24] Synthesized using GPA from **1f** (98 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3fa** (71 mg, 58%). M.p.: 95-97°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 8.6 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.29-7.25 (m, 1H), 7.19-7.16 (m, 2H), 6.73-6.66 (m, 2H), 5.86 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 151.8, 150.5, 140.8, 132.9, 129.4, 125.8, 121.8, 116.8, 116.0, 108.1. Anal. Calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 62.86; H, 4.08; N, 5.93.



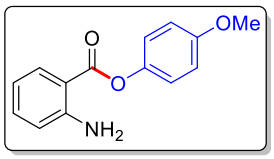
Phenyl 2-amino-5-bromobenzoate (3ga). Synthesizedusing GPA from **1g** (121 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ga** (82 mg, 56%). M.p.: 111-113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.45-7.37 (m, 3H), 7.29-7.24 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.59 (d, J = 8.8 Hz, 1H), 5.80 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 150.4, 150.0, 137.4, 133.6, 129.4, 125.9, 121.8, 118.4, 110.8, 107.3. Anal. Calcd for $C_{13}H_{10}BrNO_2$: C, 53.45; H, 3.45; N, 4.79. Found: C, 53.46; H, 3.32; N, 4.97.



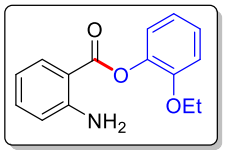
m-Tolyl 2-aminobenzoate (3ab).[20] Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2b** (68 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colorless oily product of **3ab** (91 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 7.7 Hz, 1H), 7.36-7.30 (m, 2H), 7.09 (d, J = 7.6 Hz, 1H), 7.00-6.98 (m, 2H), 6.73-6.70 (m, 2H), 5.78 (bs, 2H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 151.1, 150.6, 139.6, 134.7, 131.5, 129.1, 126.5, 122.5, 118.8, 116.6, 116.3, 109.6, 21.3. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.37; H, 5.91; N, 6.39.



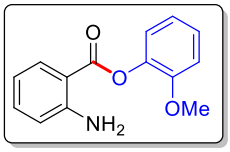
4-(Tert-butyl)phenyl 2-aminobenzoate (3ac). Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2c** (89 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford yellow solid of **3ac** (87 mg, 65%). M.p.: 119-121 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 7.1 Hz, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.36-7.32 (m, 1H), 7.11 (d, J = 8.6 Hz, 2H), 6.73- 6.70 (m, 2H), 5.78 (bs, 2H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 151.1, 148.5, 148.2, 134.7, 131.5, 126.3, 121.2, 116.6, 116.3, 109.6, 34.5, 31.6. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.89; H, 7.34; N, 5.52.



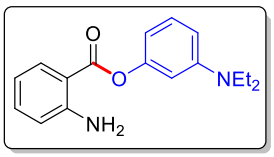
4-Methoxyphenyl 2-aminobenzoate (3ad).[20] Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2d** (76 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ad** (72 mg, 60%). M.p.: 102-105 ^{o}C.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.6 Hz, 1H), 7.34 (t, J =7.3 Hz, 1H), 7.10 (d, J = 8.9 Hz, 2H), 6.94 (d, J= 8.9 Hz, 2H), 6.71 (t, J = 8.1 Hz, 2H), 5.77 (bs, 2H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 157.1, 151.1, 144.1, 134.7, 131.5, 122.6, 116.6, 116.3, 114.4, 109.6, 55.5. Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.80; H, 5.27; N, 5.30.



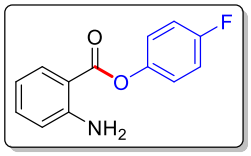
2-Ethoxyphenyl 2-aminobenzoate (3ae). Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2e** (83 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ae** (78 mg, 61%). M.p.: 67-70 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.35-7.32 (m, 1H), 7.23-7.19 (m, 1H), 7.15 (dd, J = 7.8, 1.6 Hz, 1H), 7.02-6.97 (m, 2H), 6.74-6.70 (m, 2H), 5.73 (bs, 2H), 4.07 (q, J = 6.9 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 150.9, 150.7, 140.2, 134.5, 131.8, 126.6, 123.1, 120.7, 116.5, 116.3, 113.7, 109.8, 64.4, 14.7. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.31; H, 5.94; N, 5.37.



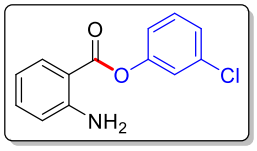
2-Methoxyphenyl 2-aminobenzoate (3af).[20] Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2f** (76 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3af** (71 mg, 59%). M.p.: 111-112 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 1H), 7.37-7.29 (m, 2H), 6.84-6.77 (m, 2H), 6.75-6.69 (m, 3H), 5.77 (bs, 2H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 160.5, 151.7, 151.1, 134.8, 131.5, 129.7, 116.7, 116.3, 114.1, 111.6, 109.5, 107.8, 55.3. Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.26; H, 5.10; N, 5.83.



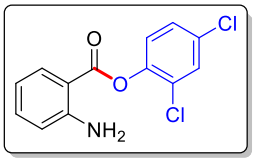
3-(Diethylamino)phenyl 2-aminobenzoate (3ag). Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2g** (96 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford yellow solid of **3ag** (68 mg, 48%). M.p.: 43-45 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10-8.07 (d, J = 8.0 Hz, 1H), 7.35-7.31 (m, 1H), 7.22 (t, J = 8.1 Hz, 1H), 6.73-6.70 (m, 2H), 6.57-6.55 (m, 1H), 6.45-6.42 (m, 2H), 5.78 (bs, 2H), 3.34 (q, J = 7.0 Hz, 4H), 1.16 (t, J = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 152.0, 151.0, 134.5, 131.5, 129.7, 116.6, 116.2, 109.9, 109.0, 108.3, 104.8, 44.3, 12.4. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.59; H, 6.90; N, 9.52.



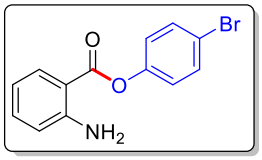
4-Fluorophenyl 2-aminobenzoate (3ah).[20] Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2h** (70 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ah** (86 mg, 75%). M.p.: 91-93 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 7.3 Hz, 1H), 7.36-7.33 (m, 1H), 7.16-7.09 (m, 4H), 6.73-6.70 (m, 2H), 5.76 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 160.1 (d, J = 242.5 Hz), 151.2, 146.5 (d, J = 2.5 Hz), 134.9, 131.4, 123.3 (d, J = 8.8 Hz), 116.7, 116.3, 116.1 (d, J = 22.5 Hz), 115.9, 109.2. Anal. Calcd for $C_{13}H_{10}FNO_2$: C, 67.53; H, 4.36; N, 6.06. Found: C, 67.69; H, 4.67; N, 5.85.



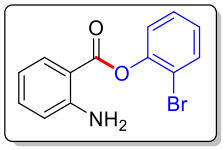
3-Chlorophenyl 2-aminobenzoate (3ai). Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2i** (78 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ai** (86 mg, 70%). M.p.: 85-87 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.8, 1.6 Hz, 1H), 7.41-7.32 (m, 3H), 7.13 (d, J = 8.8 Hz, 2H), 6.74-6.70 (m, 2H), 5.76 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 151.3, 149.2, 135.0, 131.5, 131.1, 129.4, 123.3, 116.7, 116.4, 109.1. Anal. Calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.31; H, 3.88; N, 5.28.



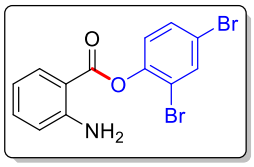
2,4-Dichlorophenyl 2-aminobenzoate (3aj). Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2j** (95 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3aj** (89 mg, 64%).M.p.: 90-93 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.9 Hz, 1H), 7.43 (s, 1H), 7.29 (t, J = 8.1 Hz, 1H), 7.23-7.18 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 6.65 (t, J = 8.9 Hz, 2H), 5.67 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 151.4, 145.8, 135.3, 131.7, 131.6, 130.0, 128.2, 127.8, 124.9, 116.7, 116.5, 108.6. Anal. Calcd for $C_{13}H_9Cl_2NO_2$: C, 55.35; H, 3.22; N, 4.96. Found: C, 55.01; H, 3.07; N, 5.30.



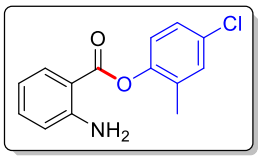
4-Bromophenyl 2-aminobenzoate (3ak).[20] Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2k** (100 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ak** (97 mg, 67%). M.p.: 77-79 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.4 Hz, 1H), 7.56-7.52 (m, 2H), 7.37-7.32 (m, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.73-6.69 (m, 2H), 5.77 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 151.3, 149.7, 135.0, 132.4, 131.4, 130.8, 123.8, 118.8, 116.7, 116.4, 109.1. Anal. Calcd for $C_{13}H_{10}BrNO_2$: C, 53.45; H, 3.45; N, 4.79. Found: C, 53.81; H, 3.62; N, 4.70.



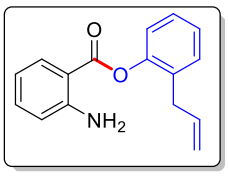
2-Bromophenyl 2-aminobenzoate (3al).[20] Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2l** (100 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colorless oily product of **3al** (101 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, J = 8.0, 1.6 Hz, 1H), 7.70 (dd, J = 8.0, 1.6 Hz, 1H), 7.43-7.36 (m, 2H), 7.32-7.29 (m, 1H), 7.20-7.16 (m, 1H), 6.71 (d, J = 8.4 Hz, 2H), 5.83 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 151.2, 148.0, 134.9, 133.0, 131.5, 128.2, 127.0, 123.9, 116.5, 116.3, 116.1, 108.5. Anal. Calcd for $C_{13}H_{10}BrNO_2$: C, 53.45; H, 3.45; N, 4.79. Found: C, 53.75; H, 3.36; N, 4.98.



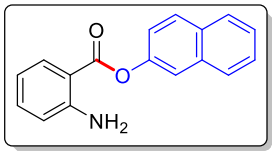
2,4-Dibromophenyl 2-aminobenzoate (3am). Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2m** (139 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3am** (122 mg, 66%).M.p.: 99-101 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.11 (m, 1H), 7.81-7.79 (m, 1H), 7.50-7.48 (m, 1H), 7.37-7.34 (m, 1H), 7.13 (d, J = 8.6 Hz, 1H), 6.74-6.70 (m, 2H), 5.74 (bs, 2H).^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 151.4, 147.6, 135.6, 135.2, 131.7, 131.4, 125.3, 119.3, 117.5, 116.7, 116.5, 108.6. Anal. Calcd for $C_{13}H_9Br_2NO_2$: C, 42.08; H, 2.45; N, 3.78. Found: C, 42.30; H, 2.60; N, 4.06.



4-Chloro-2-methylphenyl 2-aminobenzoate (3an). Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2n** (85 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3an** (92 mg, 71%). M.p.: 61–64 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10-8.07 (m, 1H), 7.37-7.33 (m, 1H), 7.27-7.25 (m, 1H), 7.23-7.20 (m, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.72 (m, 2H), 5.76 (bs, 2H), 2.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 151.2, 147.8, 135.0, 132.4, 131.4, 131.0, 130.8, 126.8, 123.5, 116.7, 116.4, 109.1, 16.1. Anal. Calcd for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; N, 5.35. Found: C, 64.13; H, 4.60; N, 5.09.

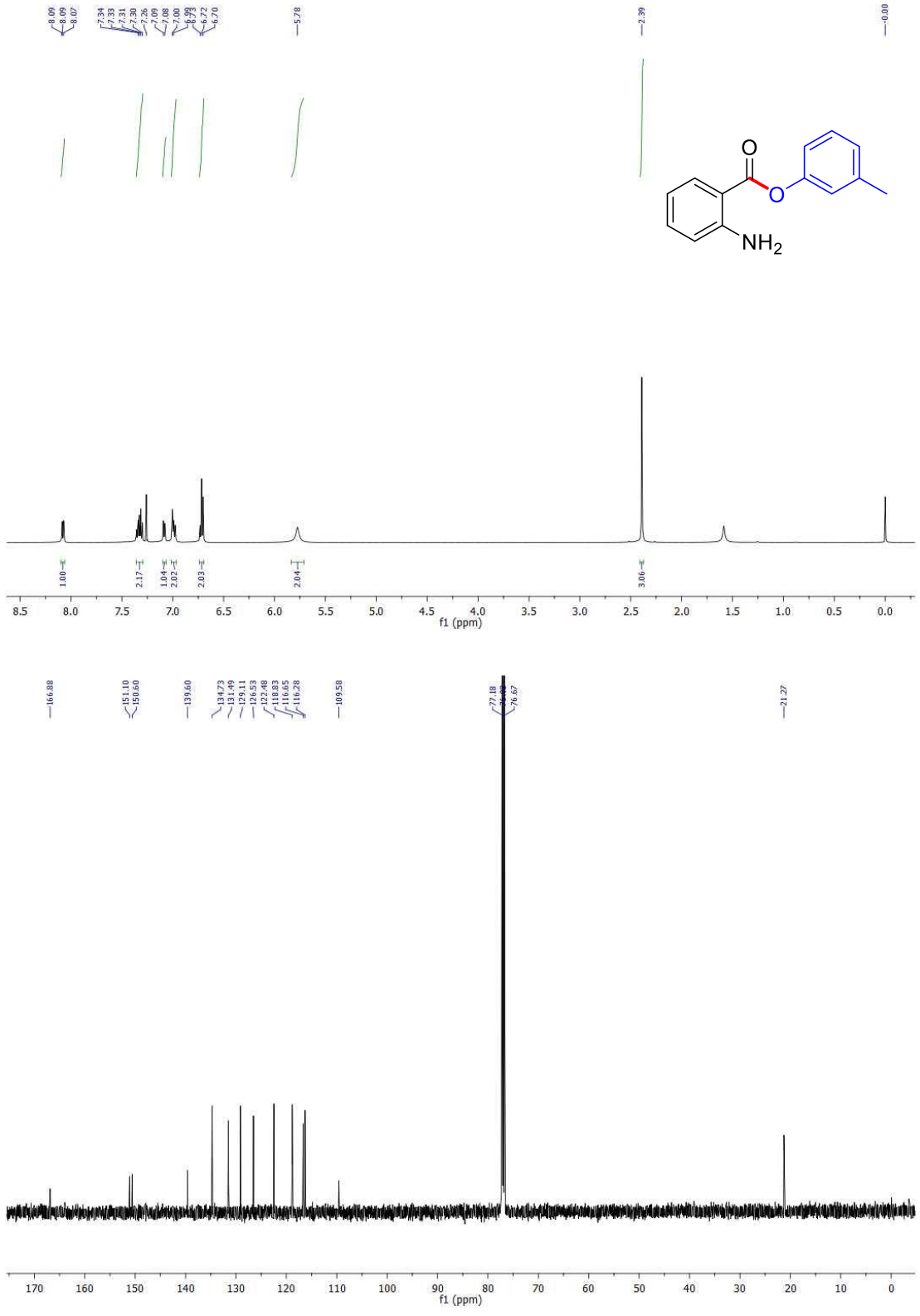


2-Allylphenyl 2-aminobenzoate (3ao). Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2o** (81 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3ao** (55 mg, 44%). M.p.: 45–48 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 1H), 7.37-7.21 (m, 4H), 7.15 (d, J = 8.1 Hz, 1H), 6.75-6.71 (m, 2H), 5.98-5.88 (m, 1H), 5.78 (bs, 2H), 5.06-5.01 (m, 2H), 3.36 (d, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 151.2, 148.9, 135.8, 134.8, 132.3, 131.5, 130.3, 127.4, 126.1, 122.6, 116.7, 116.4, 116.3, 109.9, 34.6. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.60; H, 6.05; N, 5.77.



Naphthalen-2-yl 2-aminobenzoate (3ap).[20] Synthesized using general procedure from **1a** (81 mg, 0.5 mmol) and **2p** (86 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford yellow solid of **3ap** (65 mg, 50%). M.p.: 121-122 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz, 1H), 7.93-7.82 (m, 3H), 7.65 (s, 1H), 7.54-7.47 (m, 2H), 7.39-7.32 (m, 2H), 6.77-6.71 (m, 2H), 5.80 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 151.2, 148.3, 134.8, 133.7, 131.5, 131.4, 129.3, 127.7, 127.6, 126.4, 125.6, 121.5, 118.8, 116.7, 116.3,109.5. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.84; H, 5.22; N, 5.49.

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



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CHAPTER 3

Synthesis of *β*-keto ester *via* Ru(II)-catalyzed oxidation of cinnamic acid

ABSTRACT:

A novel ruthenium-catalyzed synthesis of β-keto ester from cinnamic acid is developed. This reaction proceeds via Ru(II)-catalyzed olefinic oxidation followed by esterification of the acid to afford the important class of molecule β-keto esters in good yield.

4.1 INTRODUCTION

The importance of *β*-keto esters and 1,3-diketones in organic synthesis is difficult to overestimate. These are multicoupling reagents with both electrophilic and nucleophilic sites. Their accessibility, stability and often unique properties make them valuable for use in different fields of organic synthesis. Since the discovery of Claisen condensation, synthetic organic chemists have believed in the inimitable properties of *β*-ketoesters for the synthesis of highly complex organic molecules. Specially, 1,3-diketones and *β*-keto esters exihibit different kinds of biological activities and demonstrate a wide range of ionophoric properties[1-3] and therefore, it becomes an area of intense research among researchers working in various fields of medicinal chemistry and chemistry of metallocomplexes. Various drugs containing the heterocyclic moieties are synthesized by using 1,3-diketone as a key building block and also these are used as an important chelating ligand for various lanthanide and transition metals in material chemistry. Again, fluorine-containing 1,3-dicarbonyl compounds are extensively employed as valuable skeletons for the synthesis of biologically active molecules.[4]

Many naturally occurring 1,3-diketones exhibit different types of biological activities including antioxidant, antitumor, antimicrobial, antiviral and antifungal activity. Dibenzoylmethane (DBM) and *n*-tritriacontane-16,18-dione (TTAD) (Figure 4.1) and their closet structural derivatives found in many plants, for example, in *Eucalyptus* leaf [5] and *Licorice*[6] are natural antioxidants and acquire marked anticancer properties with low toxicity.[5-8] Other examples of naturally occurring 1,3-diketones are Curcumin and Cassumunin A (Figure 4.1) which exhibit different antioxidant,[9]

antitumor[6,10] and detoxification[11-12] properties. The spirocyclic antibiotic Gloiosiphone A (Figure 4.1), found in the red marine alga, *Gloiosiphonia verticillaris*, possess potent activity against several pathogenic microorganisms.[13]

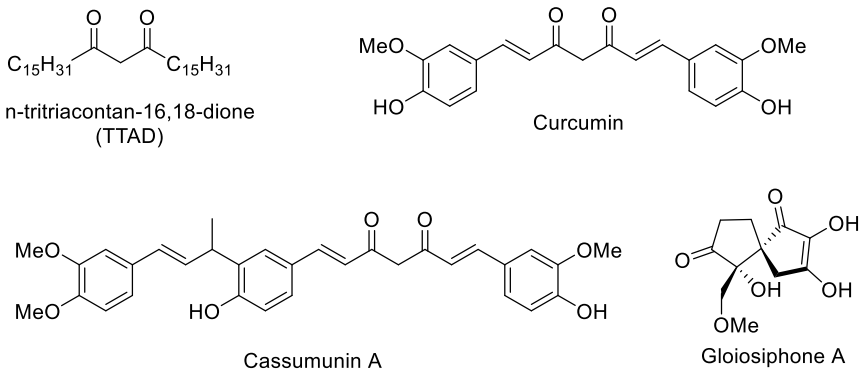
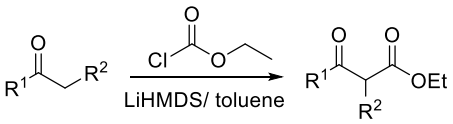


Figure 4.1: Biologically active 1,3-diketone

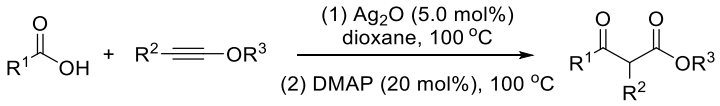
Regarding the synthesis of 1,3-diketones and *β*-ketoesters, significant research has been conducted over the years with the goal of achieving even better methods. The most common and general approaches for the synthesis of 1,3-diketone and *β*-ketoesters based on acylation, hydrolysis, oxidation, rearrangement and cycloaddition reactions that were developed during the past decade. One most traditional and conventional method for the synthesis of this *β*-diketone is typical Claisen condensation, where a hard enolate is generated by the deprotonation of the *α*-hydrogen atom on the ketone using a strong base which required a harsh reaction conditions and hence limited substrate scope.

Vijayakumar and co-workers reported a method for the synthesis of *β*-ketoesters by using ketones and chloroformate in the presence of base (Scheme 4.1).[14]



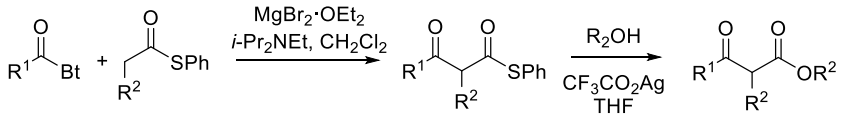
Scheme 4.1

Cui et al. developed a one pot reaction for the synthesis of *β*-ketoesters from carboxylic acids and ynol ethers.[15] First, in the presence of Ag_2O, various carboxylic acids and ynol ethers transformed to *α*-acyloxy enol esters, which then went a DMAP-catalyzed rearrangement to give *β*-keto esters (Scheme 4.2).



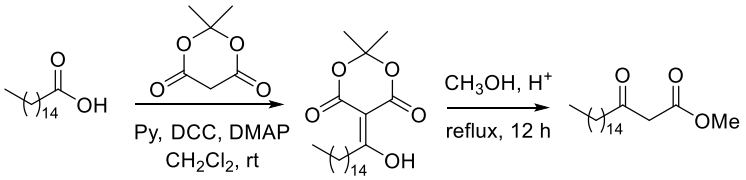
Scheme 4.2

Coltart and co-workers reported a direct crossed-Claisen reaction between thioesters and *N*-acylbenzotriazoles to give *β*-keto thioesters.[16] The reaction was conducted in the presence of $MgBr_2 \cdot OEt_2$ and *i*-Pr_2Net in CH_2Cl_2 under air. The resulting *β*-keto thioesters act as a stable synthetic equivalents of *β*-keto acids and can be directly converted to *β*-keto esters (Scheme 4.3).



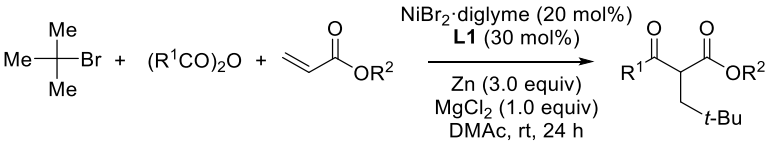
Scheme 4.3

D'Oca and co-workers reported a method for the synthesis of *β*-keto esters from Meldrum's acids and fatty acids by using *N*,*N*-dicyclohexylcarbodiimide and dimethylaminopyridine (Scheme 4.4).[17]



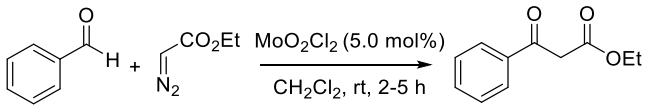
Scheme 4.4

Recently, a nickel-catalyzed three component reaction for the synthesis of *β*-keto ester was proposed by Wang and his group.[18] The reaction proceeds *via* 1,2-carboacylation of alkenes with tertiary alkyl bromides and acid anhydrides (Scheme 4.5).



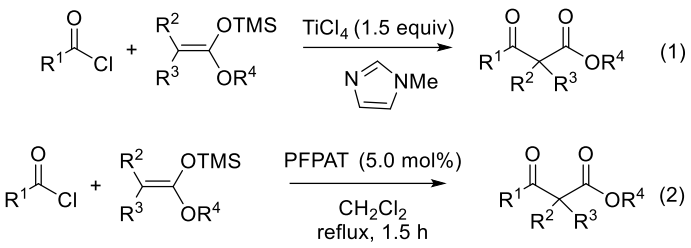
Scheme 4.5

Chand and co-workers developed a molybdenum(VI) dichloride dioxide catalyzed reaction between ethyl diazoacetate and aldehydes for the synthesis of *β*-keto ester (Scheme 4.6).[19]



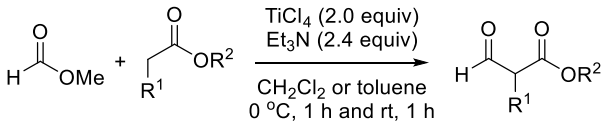
Scheme 4.6

Tanabe and his group developed a Ti-crossed-Claisen condensation reaction for the synthesis of *β*-keto esters by using ketene silyl acetals with acid chlorides in the presence of *N*-methylimidazoles (Scheme 4.7, eq 1).[20] They developed another crossed-Claisen type condensation reaction of ketene silyl acetals (KSAs) with acid chlorides *via* pentafluorophenylammonium triflate (PFPAT)-catalyzed C-acylation for the synthesis of *β*-keto ester (Scheme 4.7, eq 2).[21]



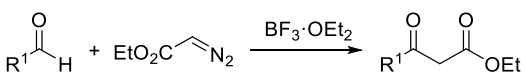
Scheme 4.7

Again, same group developed another $TiCl_4$-promoted *α*-formylation of esters to give *α*-formyl esters (Scheme 4.8).[22]



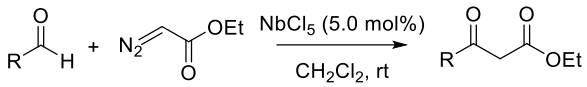
Scheme 4.8

Hayes and co-workers proposed a $BF_3{\cdot}OEt_2$-catalyzed synthesis of *β*-keto ester from ethyl diazoacetate and aldehyde (Scheme 4.9).[23]



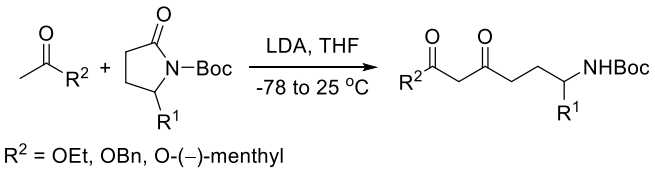
Scheme 4.9

Yadav and co-workers reported a method for the synthesis of *β*-keto ester from aldehyde and ethyl diazoacetate by using $NbCl_5$ as catalyst in dichloromethane (Scheme 4.10).[24]



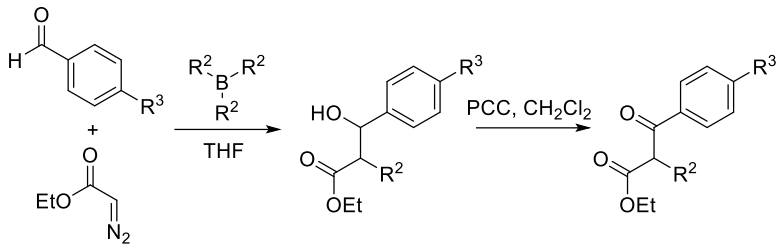
Scheme 4.10

Elliot and co-workers used substituted lactams as acylating agent for the synthesis of 1,3-diketones and *β*-ketoester. The reaction of *N*-*tert*-butoxycarbonylpyrrolidin-2-ones with ketone and ester enolates in tetrahydrofuran in the presence of lithium diisopropylamide (LDA), provided a range of 1,3-diketones and *β*-ketoester (Scheme 4.2).[25]



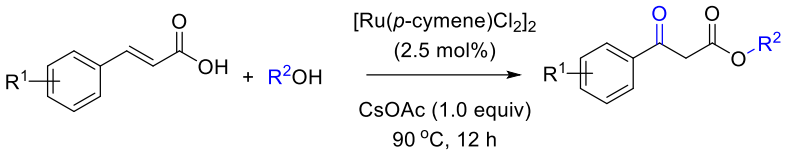
Scheme 4.2

Miranda and co-workers reported that 1,3-diketones and *β*-ketoesters could be efficiently synthesized in a three component reaction, starting from *α*-diazocarbonyl compounds, trialkylboranes and aromatic aldehydes under a base free condition (Scheme 4.11).[26]



Scheme 4.11

Because of the tremendous biological activity and unusual chemical properties of these *β*-keto esters as well as the need for a diligent synthetic route for these compounds, encouraged us for the development of a new synthetic method. Herein, we have developed an efficient one-pot reaction for the synthesis of *β*-ketoesters by using readily available starting material cinnamic acids and alcohols as coupling partner *via* Ru(II)-catalyzed olefinic oxidation and concomitant esterification of the acid (Scheme 4.12).



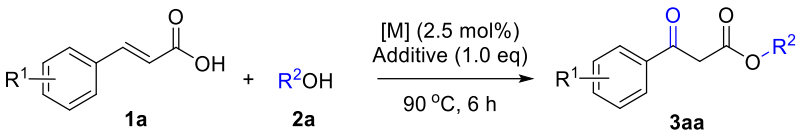
Scheme 4.12

4.2 RESULTS AND DISCUSSION

Our investigation started with the evaluation of catalyst and the reaction conditions for the reaction between cinnamic acid and *tert*-Amyl alcohol. Initial screening of various metal catalysts notified that only $\{RuCl_2(p\text{-cymene})\}_2$ favor the formation of our desired *β*-ketoester in 40% yield (Table 4.1, entry 5) in presence of $Cu(OAc)_2 \cdot H_2O$ as an additive. To increase the yield of the reaction, we next surveyed some other

commonly used additives like CsOAc, AgOAc, NaOAc, KOAc and Ag_2O (entries 6-10). Fortunately, the additive CsOAc provided 78% yield of product **3aa** (entry 6).

Table 4.1. Reaction conditions optimization for **3aa**[a]



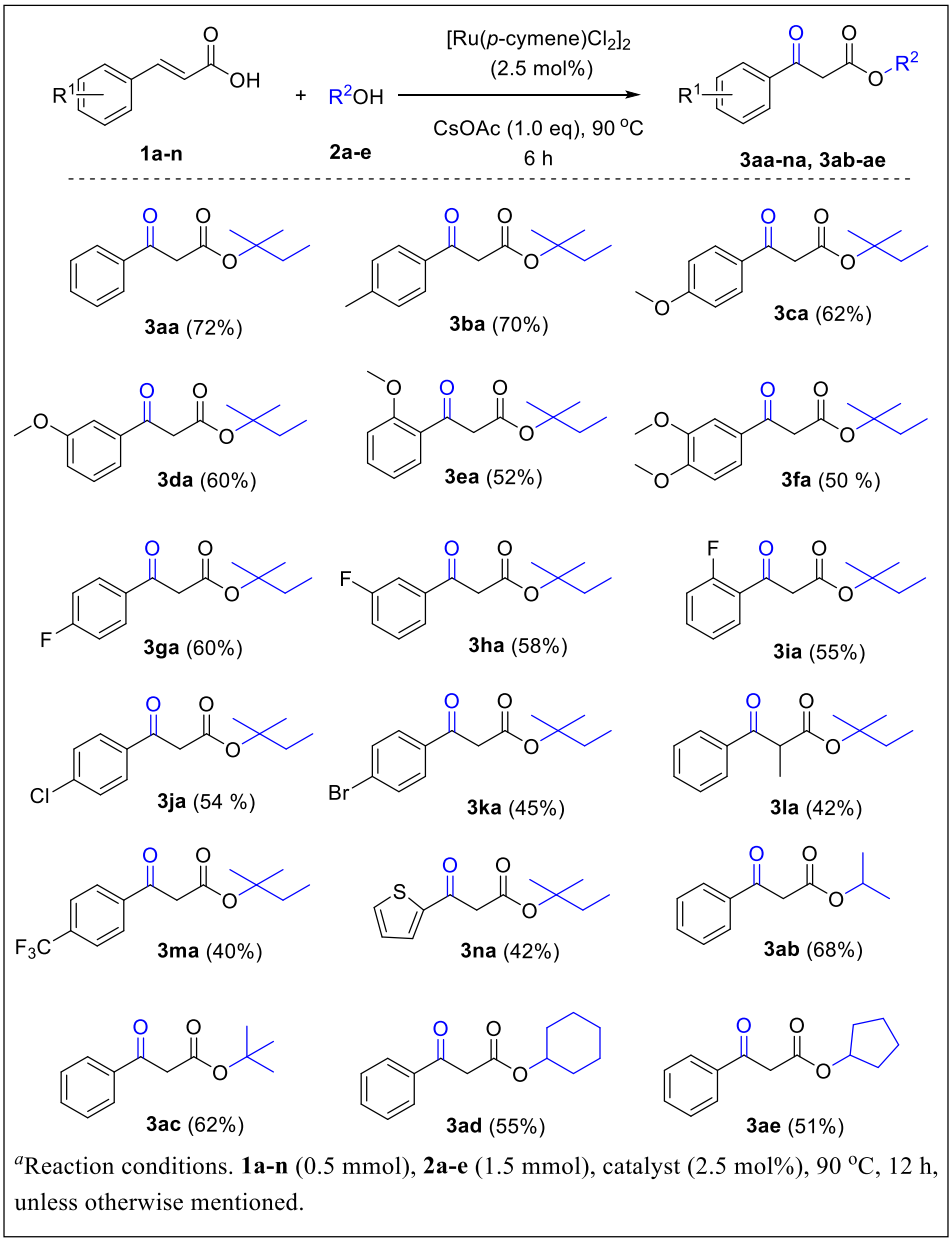
entry	catalyst	additive	**3aa** (%)[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2·H_2O$	0
2	$PdCl_2$	$Cu(OAc)_2·H_2O$	0
3	$RuCl_3·xH_2O$	$Cu(OAc)_2·H_2O$	0
4	$[RuCl_2(PPh_3)_3]$	$Cu(OAc)_2·H_2O$	0
5	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2·H_2O$	40
6	**$[\{RuCl_2(p\text{-cymene})\}_2]$**	**CsOAc**	**78**
7	$[\{RuCl_2(p\text{-cymene})\}_2]$	AgOAc	27
8	$[\{RuCl_2(p\text{-cymene})\}_2]$	NaOAc	20
9	$[\{RuCl_2(p\text{-cymene})\}_2]$	KOAc	25
10	$[\{RuCl_2(p\text{-cymene})\}_2]$	Ag_2O	10
11	$[\{RuCl_2(p\text{-cymene})\}_2]$	-	0
12	-	CsOAc	0

[a]Reaction conditions. **1a** (0.5 mmol), **2a** (1.5 mmol), catalyst (2.5 mol%), additive (0.5 mmol) heated at 90 °C for 6 h under air. [b]Isolated yields.

With this optimized reaction conditions in hand, we next studied the substrate scope for this reaction. As shown in Scheme 4.15, various cinnamic acids substituted with one or two electron donating substituents like Me, -OMe (**1a-f)** provided 50-60% yields of *β*-ketoesters **3aa-3fa.** Similarly, cinnamic acids substituted with electron withdrawing substituents such as F, Cl, Br **(1g-k)** were well tolerated, irrespective of

the position of the substituent on the phenyl ring of cinnamic acid, provided 64-75% of desired products **3ga-3ka**. Cinnamic acid having substituent at the α-position **1i**

Scheme 4.15: Scope of cinnamic acids and alcohols[a]



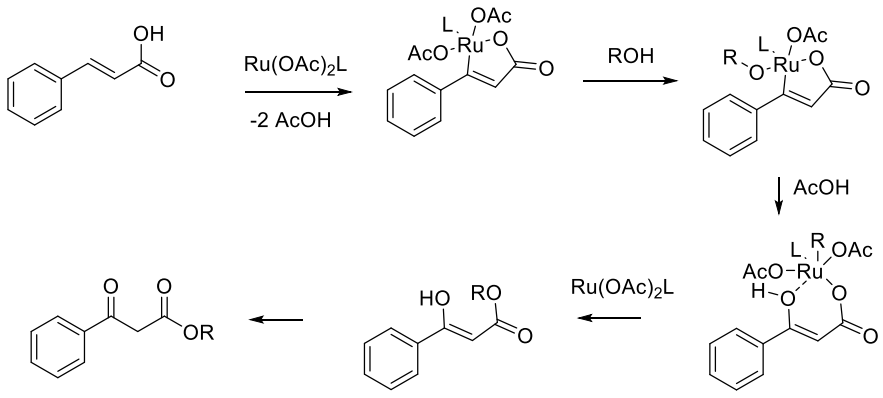
[a]Reaction conditions. **1a-n** (0.5 mmol), **2a-e** (1.5 mmol), catalyst (2.5 mol%), 90 °C, 12 h, unless otherwise mentioned.

also proved as a good substrate for this reaction and desired product **3ia** was obtained in 45% yield. Furthermore, CF_3 group bearing cinnamic acid (**1m**) provides 40% yield

of the product **3ma**. Similarly, scope of heterocycle containing cinnamic acid **1n** was also tested, which provided 42% yield of *β*-ketoester **3na**.

Next, evaluation was performed by taking a set of different types of alcohols (Scheme 4.15). The reaction of cinnamic acid **1a** with isopropyl alcohol (**2b)** and *tert*-butyl alcohol (**2c)** provided 62-68% yields of **3ab-ac**. Also, we have tested cyclic alcohols **2d-e** and these alcohols tolerated the reaction conditions to give corresponding *β*-ketoesters **3ad-3ae** in 51-55% yields.

One probable mechanism for the formation of this *β*-keto ester is shown in Scheme 4.16, which proceeds *via* activation of the olefinic double bond, followed by coordination and insertion of one -OH group at the olefinic position. Subsequent, formation of O-R bond and reductive elimination and tautomerization affords the product.



Scheme 4.16

3.3 CONCLUSION

In conclusion, we have described the first Ru-catalyzed reaction of cinnamic acids with alcohol for the synthesis of *β*-ketoesters. This unprecedented Ru(II)-catalyzed

reaction proceeds through activation of the olefinic double bond and subsequent esterfication of the acid to afford the important class of molecule *β*-keto esters in good yield. Seeing the importance of 1,3-dicarbonyl compounds in general, along with the simple and mild nature of this reaction, we belief that it will accumulate extensive application in synthetic chemistry.

3.4 EXPERIMENTAL SECTION

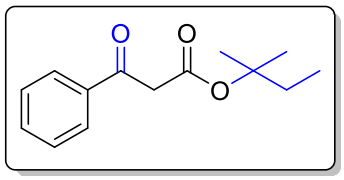
General information

Melting points were measured with a Buchi B-540 melting point apparatus. The NMR spectra were recorded on Bruker Avance III 500 MHz FTNMR spectrometer using tetramethylsilane (TMS) as an internal standard. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-backed silica gel plates (0.2 mm thickness); the chromatograms were visualized first with ultraviolet light (254 nm) and then by immersion in solutions of *p*-anisaldehyde followed by heating. Column chromatography was performed with silica gel (100-200 mesh, Merck).

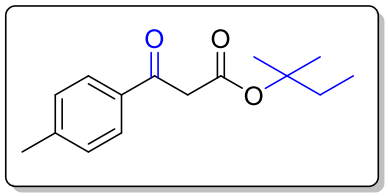
General procedure for the synthesis of *β*-ketoester. A mixture of cinnamic acid (**1**, 0.5 mmol), alcohol (**2**, 1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %) and CsOAc (0.5 mmol) was stirred at 90 ^oC under open air for 6 hours. Then, the solvent was removed under vacuo. Water (10 mL) was added to the reaction mixture and the organic layer was extracted with ethyl acetate (25 mL x 2). The combined organic phases were washed with brine and dried over sodium sulphate. The solvent was removed under

vacuo and the residue was purified by column chromatography on silica gel (100-200 mesh) using hexanes/ethyl acetate as an eluent to afford **3**.

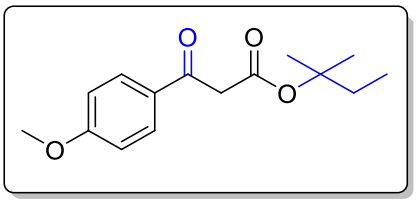
4.5 SPECTRAL AND ANALYTICAL DATA



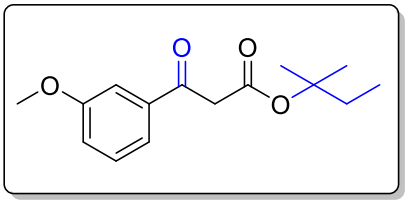
tert-pentyl 3-oxo-3-phenylpropanoate (3aa). Synthesized using general procedure from **1a** (74 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3aa** (84 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 7.4 Hz, 2H), 7.58-7.56 (m, 1H), 7.47 (t, J = 7.7 Hz, 2H), 3.90 (s, 2H), 1.73 (q, J = 7.5 Hz, 2H), 1.40 (s, 6H), 0.81 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 166.6, 136.1, 133.5, 128.6, 128.4, 125.8, 84.5, 47.2, 33.3, 25.2, 7.9.



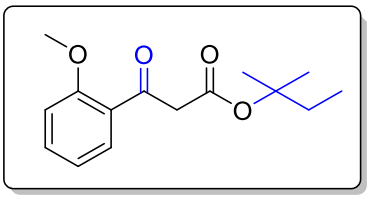
tert-pentyl 3-oxo-3-(p-tolyl)propanoate (3ba). Synthesized using general procedure from **1b** (81 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ba** (87 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 2H), 7.28-7.25 (m, 2H), 3.88 (s, 2H), 2.41 (s, 3H), 1.74 (q, J = 7.5 Hz, 2H), 1.40 (s, 6H), 0.82 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 166.7, 144.4, 133.7, 129.3, 128.5, 84.6, 47.2, 33.3, 25.2, 21.8, 7.9.



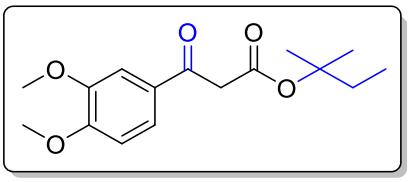
tert-pentyl 3-(4-methoxyphenyl)-3-oxopropanoate (3ca). Synthesized using general procedure from **1c** (89 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ca** (82 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.9 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 2H), 1.74 (q, J = 7.5 Hz, 2H), 1.41 (s, 6H), 0.82 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 166.8, 163.7, 130.8, 130.5, 129.2, 113.7, 84.4, 55.4, 47.1, 33.3, 25.2, 7.9.



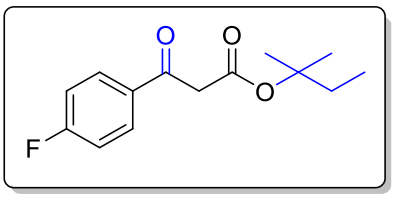
tert-pentyl 3-(3-methoxyphenyl)-3-oxopropanoate (3da). Synthesized using general procedure from **1d** (89 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3da** (79 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.39-7.36 (m, 1H), 7.14-7.12 (m, 1H), 3.89 (s, 2H), 3.86 (s, 3H), 1.76-1.71 (m, 2H), 1.41 (s, 6H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 166.5, 159.8, 137.5, 129.6, 121.1, 120.2, 112.2, 84.5, 55.3, 47.3, 33.3, 25.2, 7.9.



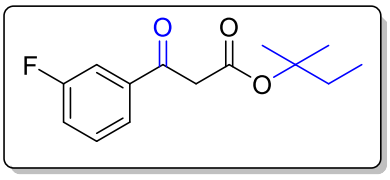
tert-pentyl 3-(2-methoxyphenyl)-3-oxopropanoate (3ea). Synthesized using general procedure from **1e** (89 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ea** (68 mg, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, J = 7.8, 1.8 Hz, 1H), 7.52-7.47 (m, 1H), 7.03-7.00 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 2H), 1.67 (q, J = 7.5 Hz, 2H), 1.37 (s, 6H), 0.77 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 167.1, 158.9, 134.3, 130.9, 126.4, 120.6, 111.2, 83.6, 55.2, 51.8, 33.5, 25.1, 7.9.



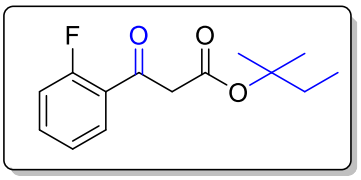
tert-pentyl 3-(3,4-dimethoxyphenyl)-3-oxopropanoate (3fa). Synthesized using general procedure from **1f** (104 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3fa** (73 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60-7.56 (m, 1H), 7.53 (s, 1H), 6.89 (d, J = 8.0 Hz, 1H), 3.98-3.93 (m, 6H), 2.58 (s, 2H), 1.75 (q, J = 7.4 Hz, 2H), 1.41 (s, 6H), 0.83 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.8, 168.1, 153.1, 148.8, 130.3, 123.2, 109.9, 109.7, 84.4, 56.0, 55.9, 47.0, 33.3, 26.1, 8.0.



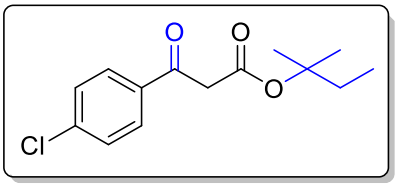
tert-pentyl 3-(4-fluorophenyl)-3-oxopropanoate (3ga). Synthesized using general procedure from **1g** (83 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ga** (75 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01-7.96 (m, 2H), 7.18-7.12 (m, 2H), 3.88 (s, 2H), 1.73 (q, J = 7.5 Hz, 2H), 1.40 (s, 6H), 0.81 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 166.3, 162.4, 132.6, 131.1, 124.6, 120.8, 115.8, 115.7, 84.7, 47.2, 33.3, 25.2, 7.9.



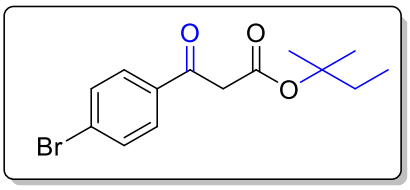
tert-pentyl 3-(3-fluorophenyl)-3-oxopropanoate (3ha). Synthesized using general procedure from **1h** (83 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ha** (73 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 7.7 Hz, 1H), 7.65-7.63 (m, 1H), 7.50-7.44 (m, 1H), 7.32-7.26 (m, 1H), 3.89 (s, 2H), 1.73 (q, J = 7.4 Hz, 2H), 1.41 (s, 6H), 0.82 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6, 166.1, 163.7, 138.1, 130.3, 124.2, 120.6, 117.8, 113.0, 84.8, 47.3, 33.3, 25.2, 7.9.



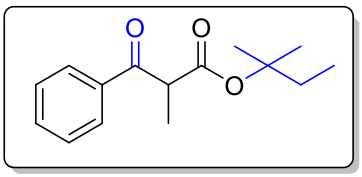
tert-pentyl 3-(2-fluorophenyl)-3-oxopropanoate (3ia). Synthesized using general procedure from **1i** (83 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ia** (69 mg, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (td, J = 7.7, 1.8 Hz, 1H), 7.57-7.52 (m, 1H), 7.27-7.22 (m, 1H), 7.17-7.11 (m, 1H), 3.91 (s, 2H), 1.72 (q, J = 7.5 Hz, 2H), 1.41 (s, 6H), 0.82 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 166.4, 163.0, 135.2, 131.9, 130.7, 129.0, 124.6, 116.6, 84.4, 50.9, 33.3, 25.1, 7.9.



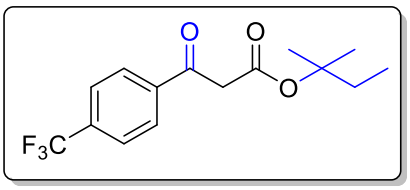
tert-pentyl 3-(4-chlorophenyl)-3-oxopropanoate (3ja). Synthesized using general procedure from **1j** (91 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ja** (72 mg, 54%). ^{1}H NMR (500 MHz, $CDCl_3$)) δ 7.89 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 3.88 (s, 2H), 1.73 (q, J = 7.5 Hz, 2H), 1.40 (s, 6H), 0.81 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6, 166.2, 140.0, 134.4, 129.8, 128.9, 127.1, 84.8, 47.2, 33.3, 25.2, 7.9.



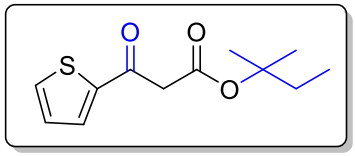
tert-pentyl 3-(4-bromophenyl)-3-oxopropanoate (3ka). Synthesized using general procedure from **1k** (113 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ka** (70 mg, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.6 Hz, 2H), 3.88 (s, 2H), 1.73 (q, J = 7.5 Hz, 2H), 1.40 (s, 6H), 0.81 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, CDCl3) δ 191.9, 166.2, 134.8, 131.9, 131.6, 129.9, 128.8, 127.3, 84.8, 47.2, 33.3, 25.2, 8.0.



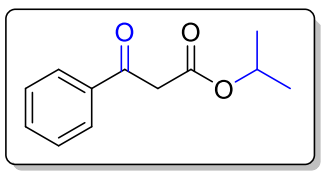
tert-pentyl 2-methyl-3-oxo-3-phenylpropanoate (3la). Synthesized using general procedure from **1l** (81 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3la** (52 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.1 Hz, 2H), 7.60-7.55 (m, 1H), 7.49-7.44 (m, 2H), 4.27 (q, J = 7.0 Hz, 1H), 1.69-1.62 (m, 2H), 1.46 (d, J = 7.0 Hz, 3H), 1.31 (s, 6H), 0.72 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 169.9, 136.2, 133.1, 128.5, 128.4, 84.1, 49.4, 33.3, 25.0, 13.4, 7.8.



tert-pentyl 3-oxo-3-(4-(trifluoromethyl)phenyl)propanoate (3ma). Synthesized using general procedure from **1m** (108 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ma** (60 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 3.94 (s, 2H), 1.73 (q, J = 7.6 Hz, 2H), 1.40 (s, 6H), 0.81 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 166.0, 128.7, 138.7, 128.7, 126.1, 125.7, 125.6, 125.3, 85.0, 47.3, 33.3, 25.2, 7.9.

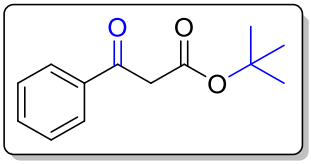


tert-pentyl 3-oxo-3-(thiophen-2-yl)propanoate (3na). Synthesized using general procedure from **1n** (77 mg, 0.5 mmol) and **2a** (132 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3na** (48 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75-7.73 (m, 1H), 7.70-7.68 (m, 1H), 7.16-7.14 (m, 1H), 3.84 (s, 2H), 1.75 (q, J = 7.5 Hz, 2H), 1.42 (s, 6H), 0.82 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.4, 166.0, 143.4, 134.5, 133.0, 128.1, 84.7, 47.8, 33.3, 25.2, 7.9.

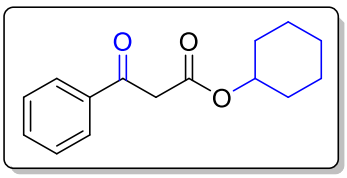


isopropyl 3-oxo-3-phenylpropanoate (3ab). Synthesized using general procedure from **1a** (74 mg, 0.5 mmol) and **2b** (90 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ab** (70 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96-7.92 (m, 2H), 7.61-7.56 (m, 1H),

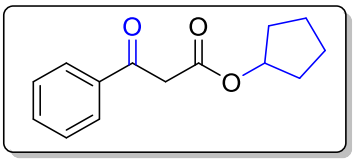
7.50-7.45 (m, 2H), 5.11-5.04 (m, 1H), 3.96 (s, 2H), 1.23 (d, J = 6.3 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 167.0, 135.9, 133.6, 131.1, 128.6, 128.3, 125.9, 87.7, 69.0, 46.2, 21.5.



tert-butyl 3-oxo-3-phenylpropanoate (3ac). Synthesized using general procedure from **1a** (74 mg, 0.5 mmol) and **2c** (111 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ac** (68 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96-7.92 (m, 2H), 7.61-7.56 (m, 1H), 7.50-7.45 (m, 2H), 3.90 (s, 2H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 166.6, 138.7, 136.1, 133.4, 128.6, 128.3, 125.8, 81.9, 47.3, 27.8.

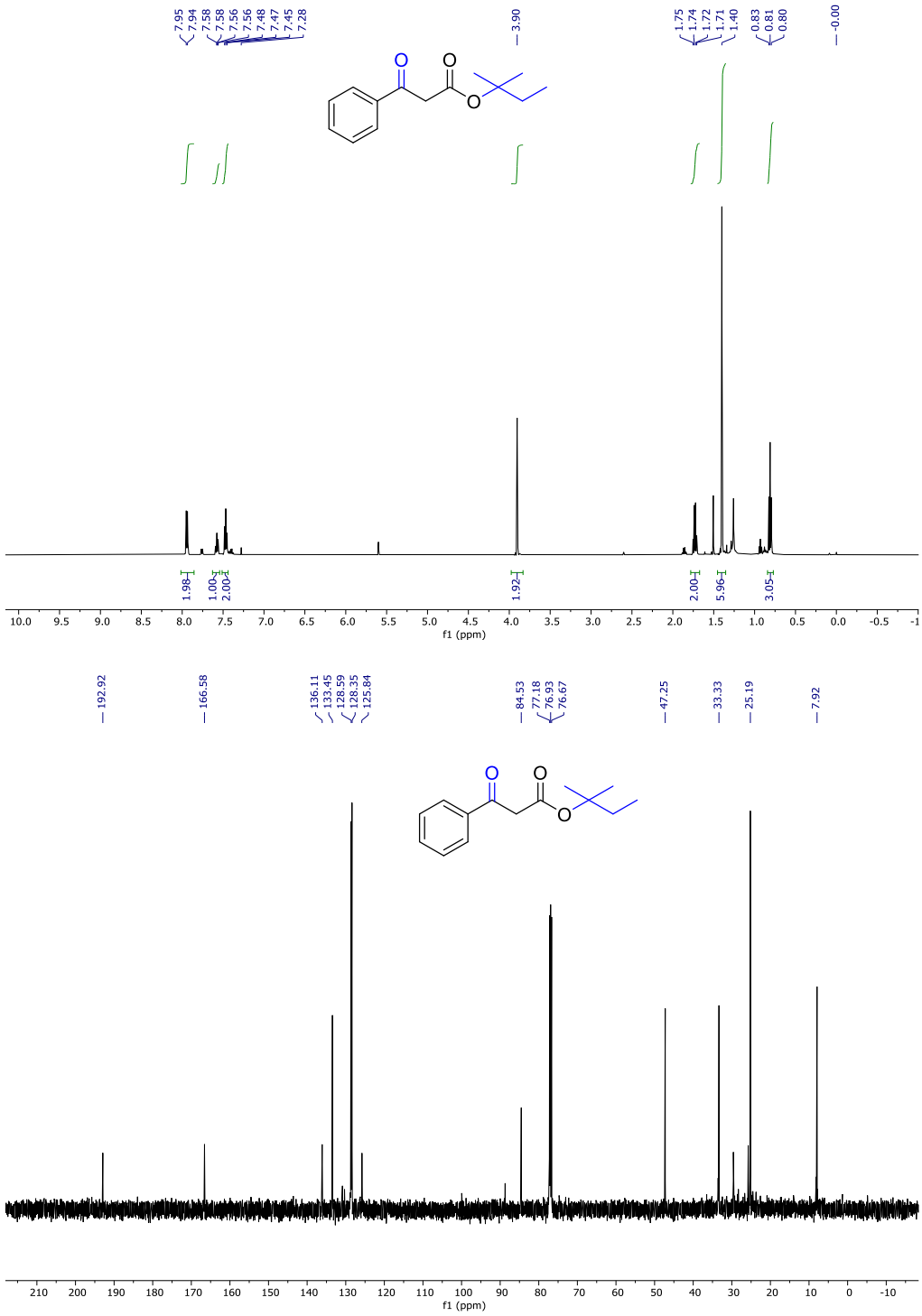


cyclohexyl 3-oxo-3-phenylpropanoate (3ad). Synthesized using general procedure from **1a** (74 mg, 0.5 mmol) and **2d** (150 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ad** (67 mg, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2H), 7.62-7.57 (m, 1H), 7.51-7.46 (m, 2H), 4.88-4.81 (m, 1H), 3.98 (s, 2H), 1.85-1.20 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 166.9, 135.9, 133.6, 131.1, 128.6, 128.4, 125.9, 87.8, 73.8, 46.3, 31.2, 25.1, 23.4.



cyclopentyl 3-oxo-3-phenylpropanoate (3ae). Synthesized using general procedure from **1a** (74 mg, 0.5 mmol) and **2e** (129 mg, 1.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1:9) to afford colourless oily product of **3ae** (59 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96-7.93 (m, 2H), 7.61-7.58 (m, 1H), 7.51-7.46 (m, 2H), 5.25-5.21 (m, 1H), 3.95 (s, 2H), 1.85-1.53 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 167.2, 136.0, 133.5, 128.6, 128.3, 125.9, 78.3, 46.2, 32.4, 23.5.

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



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CHAPTER 4

Synthesis of pyrrolidinone *via* Ru(II)-catalyzed C-H activation

ABSTRACT:

A ruthenium-catalyzed reaction has been established for the synthesis of pyrrolidinone by using 1-Hydroxybenzotriazole and N-phenyl maleimide. This reaction proceeds via Ru(II)-catalyzed C-H activation in a single reaction vessel. This methodology affords good yields of 3-(1H-benzo[d][1,2,3]triazol-1-yl)-1-phenylpyrrolidine-2,5-dione and is tolerant of a variety of functional groups.

5.1 INTRODUCTION

Organic compounds with cyclic amide group exhibit many pharmacological properties.[1] Specially, pyrrolidine-2,5-dione derivatives are an important class of heterocyclic compounds with various applications in organic synthesis as well as in medicinal chemistry.[2-3] Due to the presence of amide group, these compounds show excellent *in-vivo* activity as it can cross the biological membrane easily.[4] Pyrrolidine derivatives are also served as an intermediates for the synthesis of various polycyclic compounds[5] and peptide substances[6] and also serve as key precursors in the synthesis of natural products[7] and pharmaceuticals[8] (Figure 5.1). Pyrrolidine-2,5-diones derivatives, such as 1-bromopyrrolidine-2,5-dione (NBS), are used as a halogenation reagents. Nitidumpeptins A, a novel cyclic hexapeptides, isolated from the herb *Zanthoxylum nitidum* var. *tomentosum*, is the first occurance moiety in a naturally occurring cyclohexapeptide with a pyrrolidine-2,5-dione unit.[9] The drug KA-11 is a promising candidate for a new broad-spectrum anticonvulsant that possesses pyrrolidine-2,5-dione as the key skeleton.[10]

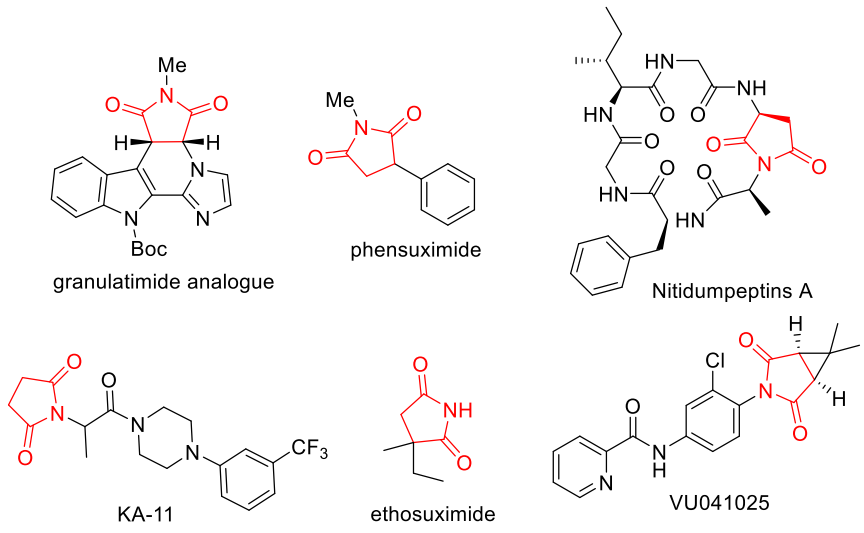
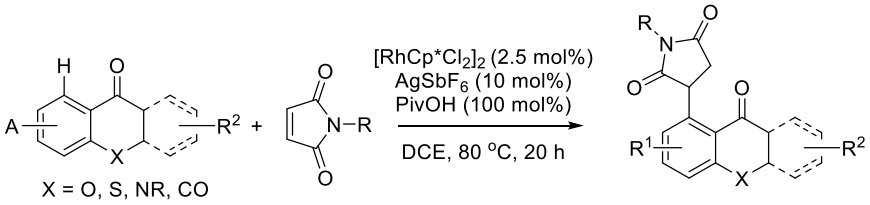


Figure 5.1

Meanwhile, this motif is a core pharmacophore of phensuximide, ethosuximide, piracetam, oxiracetam, aniracetam molecules. 2-Pyrrolidinone derivatives substituted in position-4 are able to reduce extracellular glutamate level, and therefore effective for the prophylaxis and treatment of stroke.[11]

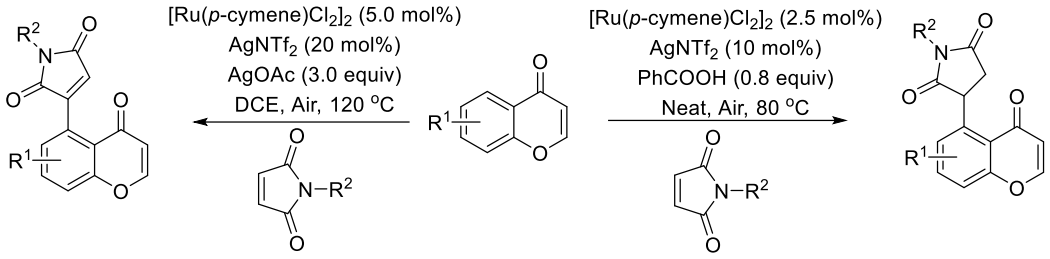
Because of the promising bioactivity and challenging structure of this compound, varieties of synthetic protocols have been developed for the synthesis of substituted pyrrolidinone. In this regards, maleimides have been extensively used in the straight functionalization of C(sp^2)-H and C(sp^3)-H bonds *via* transition-metal catalysis to provide the corresponding succinimides.[12]

Kim et al. reported a Rh(III)-catalyzed ketone group directed C-H alkylation of chromones, 1,4-naphthoquinones, and xanthones with various maleimides to afford various succinimide derivatives (Scheme 5.1).[13]



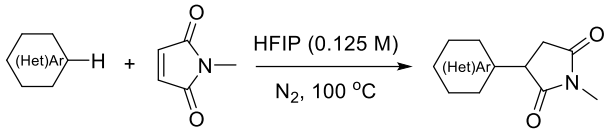
Scheme 5.1

Another, weak keto-group directed reaction was developed by Song and his group.[14] The reaction proceeds *via* Ru(II)-catalyzed coupling of chromones at the C5-position with maleimides (Scheme 5.2). The reaction gives two different products simply by changing additive. Silver acetate leads to the formation of Heck-type products, and benzoic acid furnishes 1,4-addition products under solvent-free conditions.



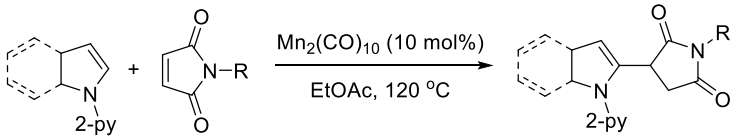
Scheme 5.2

Ye et al. reported a HFIP promoted Michael reaction approach between *N*,*N*-disubstituted anilines and maleimides to afford 3-arylsuccinimides (Scheme 5.3).[15]



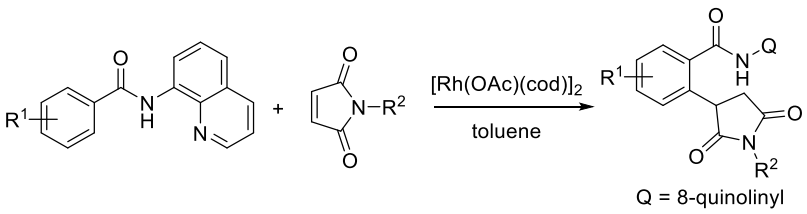
Scheme 5.3

A pyridine group directed approach to 3-(Indol-2-yl)succinimide derivatives was demonstrated by Song and co-workers *via* manganese-catalyzed C-H activation of indoles and maleimides under additive free condition (Scheme 5.4).[16]



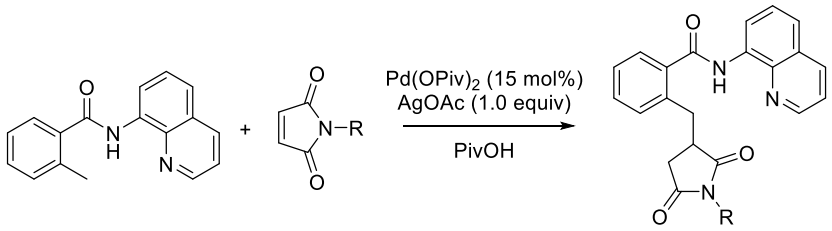
Scheme 5.4

Chatani and co-workers proposed a Rh(I)-catalyzed C-H alkylation of aromatic amide containing 8-aminoquinoline as the directing group with maleimides (Scheme 5.5).[17]



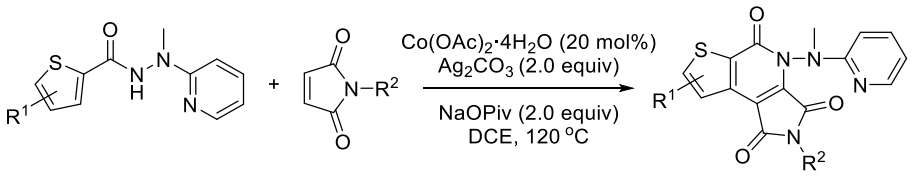
Scheme 5.5

Later, they proposed another site-selective C-H alkylation method. In the presence of Pd(II)-catalyst, followed by C-H alkylation, occurs preferentially at the *ortho*-methyl C-H bond over *ortho*-C-H bond of aromatic amide with maleimide. The reaction successfully afford pyrrolidine-2,5-dione derivative as a product (Scheme 5.6).[18]



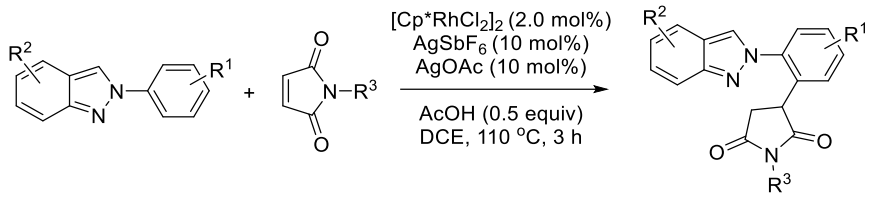
Scheme 5.6

Recently, Zhai and co-workers developed a cobalt-catalyzed C-H/N-H functionalization of thienyl hydrazides with maleimides by employing 2-(1-methylhydrazinyl)pyridine (MHP) as an easily removable bidentate directing group (Scheme 5.7).[19]



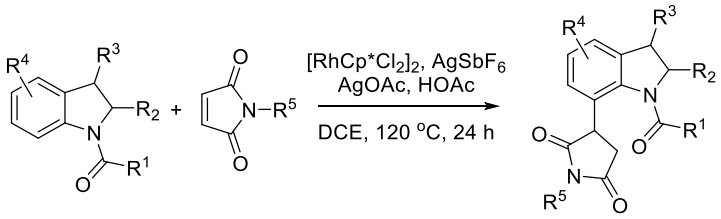
Scheme 5.7

Hajra et al. reported a Rh(III)-catalyzed hydroarylation of maleimide with 2-arylindazole *via* C-H activation (Scheme 5.8) to afford a series of 3-(2-(2*H*-indazol-2-yl)phenyl)succinimides.[20]



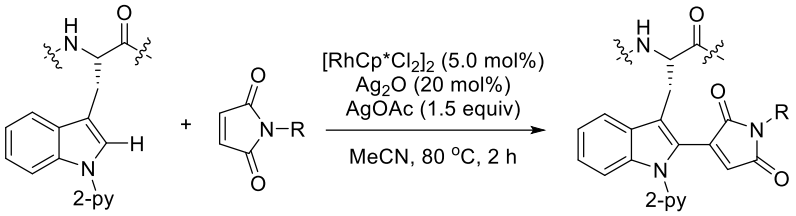
Scheme 5.8

A rhodium(III)-catalyzed C-H activation reaction of indoline with maleimide was developed by Yu and co-workers to afford C7 modified indoline derivatives including maleimide analogues (Scheme 5.9).[21]



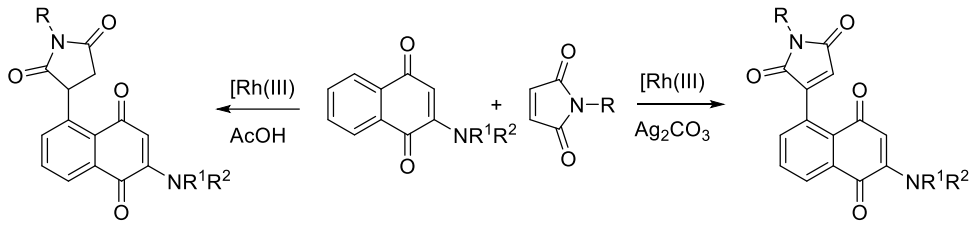
Scheme 5.9

Recently, Liu et al. disclosed a Rh(III)-catalyzed C-H alkenylation of tryptophan and tryptophan containing peptides with maleimide, towards the synthesis of maleimide-decorated peptides (Scheme 5.10).[22]



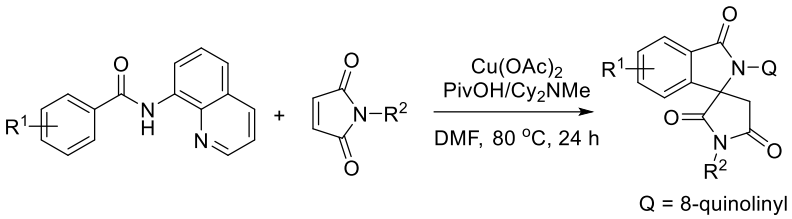
Scheme 5.10

Another, Rh(III)-catalyzed regioselective C-H alkylation and alkenylation at the C5 position of 1,4-naphthoquinone with maleimide under acidic and basic conditions respectively was reported by Sharma and his group (Scheme 5.11).[23]



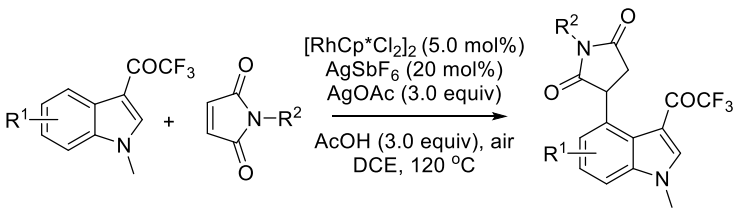
Scheme 5.11

Miura and co-workers proposed an 8-aminoquinoline-directed intramolecular aza-Michael-type addition reaction towards the synthesis of spirosuccinimides.[24] The reaction proceeds *via* Cu-mediated oxidative direct coupling of benzamide with maleimide (Scheme 5.12).



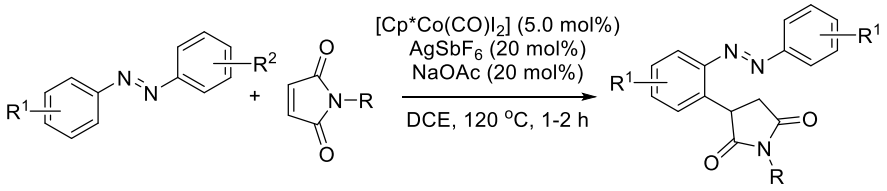
Scheme 5.12

Prabhu and co-workers reported various methods on conjugate addition of maleimide with oxygen-based directing groups like amide, ketone, and carboxylic acid.[25] They developed another Heck-type reactions of maleimides by using weakly co-ordinating $COCF_3$ as directing group.[26] This reaction proceeds *via* Rh(III)-catalyzed C-H activation of indole at the C4-position followed by functionalization with maleimide (Scheme 5.13).



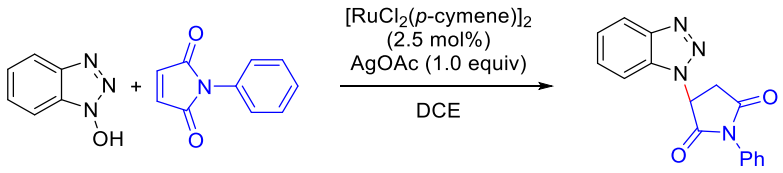
Scheme 5.13

Again, the same group disclosed another azo directed selective 1,4-addition of *ortho* C-H bond to maleimide for the construction of 3-arylated succinimide (Scheme 5.14).[27]



Scheme 5.14

Considering the increasing interest in ruthenium catalyzed reactions and to achieve the synthesis of highly important pyrrolidinone derivatives, herein, we demonstrate a new method to access 3-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-phenylpyrrolidine-2,5-dione by using 1-Hydroxybenzotriazole and *N*-phenyl maleimide *via* Ru(II)-catalyzed C-H activation in a single reaction vessel (Scheme 5.15).



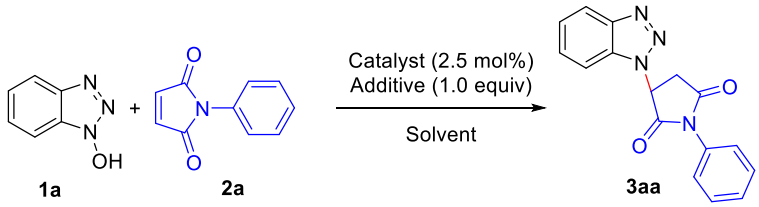
Scheme 5.15

5.2 RESULTS AND DISCUSSION

We commenced our investigation by probing the reaction condition for the synthesis of **3aa** using 1-Hydroxybenzotriazole **1a** and *N*-phenyl maleimide **2a** as the starting compounds. Preliminary studies of various metal catalysts revealed that only [{$RuCl_2$(*p*-cymene)}$_2$] catalyst together with $Cu(OAc)_2$ and *t*-AmOH as additive and solvent respectively, furnished pyrrolidinone **3aa** in 40% yield (Table 5.1, entry 4).

Encouraged by these results, we then studies some of the commonly used additives such as CsOAc, KOAc, AgOAc to improve the yield of **3aa** and we found that the reaction conducted with AgOAc led to high yield of **3aa** (56%) (Table 5.1, entry 6). Next investigations were performed by using variety of solvents and increased the yield of **3aa** to 75% by using DCE as solvent (entry 11).

Table 5.1: Reaction conditions optimization for **3aa**[a]

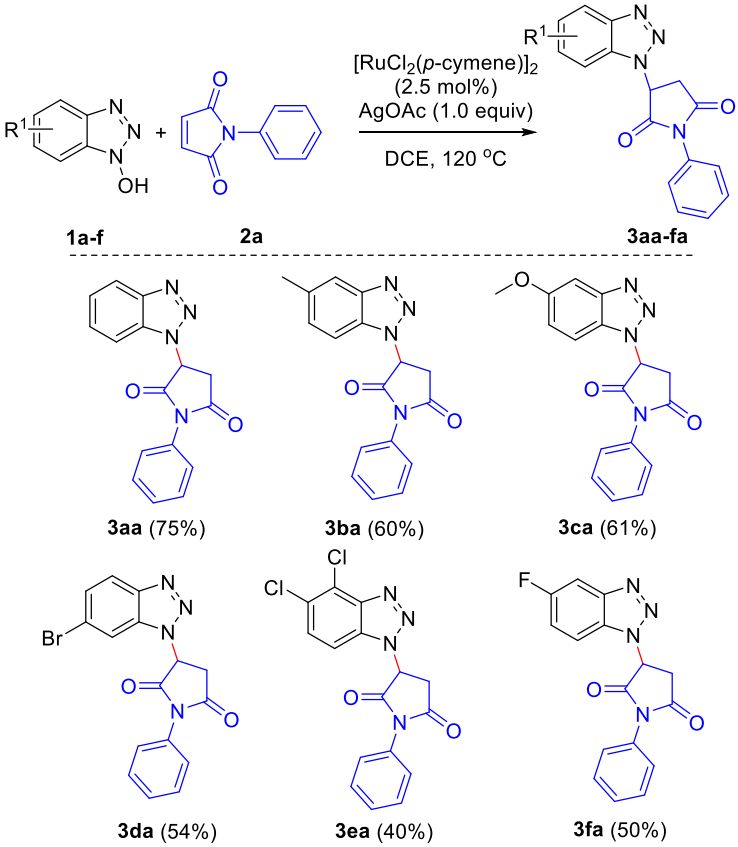


Entry	Catalyst	Additive	Solvent	**3aa** (%)[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$	*t*-AmOH	0
2	$RuCl_3 \cdot xH_2O$	$Cu(OAc)_2 \cdot H_2O$	*t*-AmOH	0
3	$[RuCl_2(PPh_3)_3]$	$Cu(OAc)_2 \cdot H_2O$	*t*-AmOH	0
4	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2 \cdot H_2O$	*t*-AmOH	40
5	$[\{RuCl_2(p\text{-cymene})\}_2]$	CsOAc	*t*-AmOH	12
6	$[\{RuCl_2(p\text{-cymene})\}_2]$	AgOAc	*t*-AmOH	56
7	$[\{RuCl_2(p\text{-cymene})\}_2]$	KOAc	*t*-AmOH	11
8	$[\{RuCl_2(p\text{-cymene})\}_2]$	AgOAc	dioxane	16
9	$[\{RuCl_2(p\text{-cymene})\}_2]$	AgOAc	Toluene	10
10	$[\{RuCl_2(p\text{-cymene})\}_2]$	AgOAc	CH_3CN	15
11	**$[\{RuCl_2(p\text{-cymene})\}_2]$**	**AgOAc**	**DCE**	**75**

[a]Reaction conditions. **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (2.5 mol%), additive (1.0 mmol) and solvent (5.0 mL) heated at 120 °C in sealed tube for 7 h. [b]Isolated yields.

Having this optimized reaction condition in hand, we next explored its versatility in the C-H functionalization with some representative set of 1-Hydroxybenzotriazoles **1a-f** which is shown in Scheme 5.16. 1-Hydroxybenzotriazoles bearing electron-donating group (**1b-c**) provided 60-61% yields of the products **3ba-ca**. Similarly, 1-Hydroxybenzotriazoles substituted with one or two electron-withdrawing groups (**1d-f**) were tested, which provided 40-54% yield of **3da-fa**. Next, we explored the reaction with some decorated *N*-substituted maleimides (Scheme 5.17). First, we examined a series of *N*-substituted maleimides

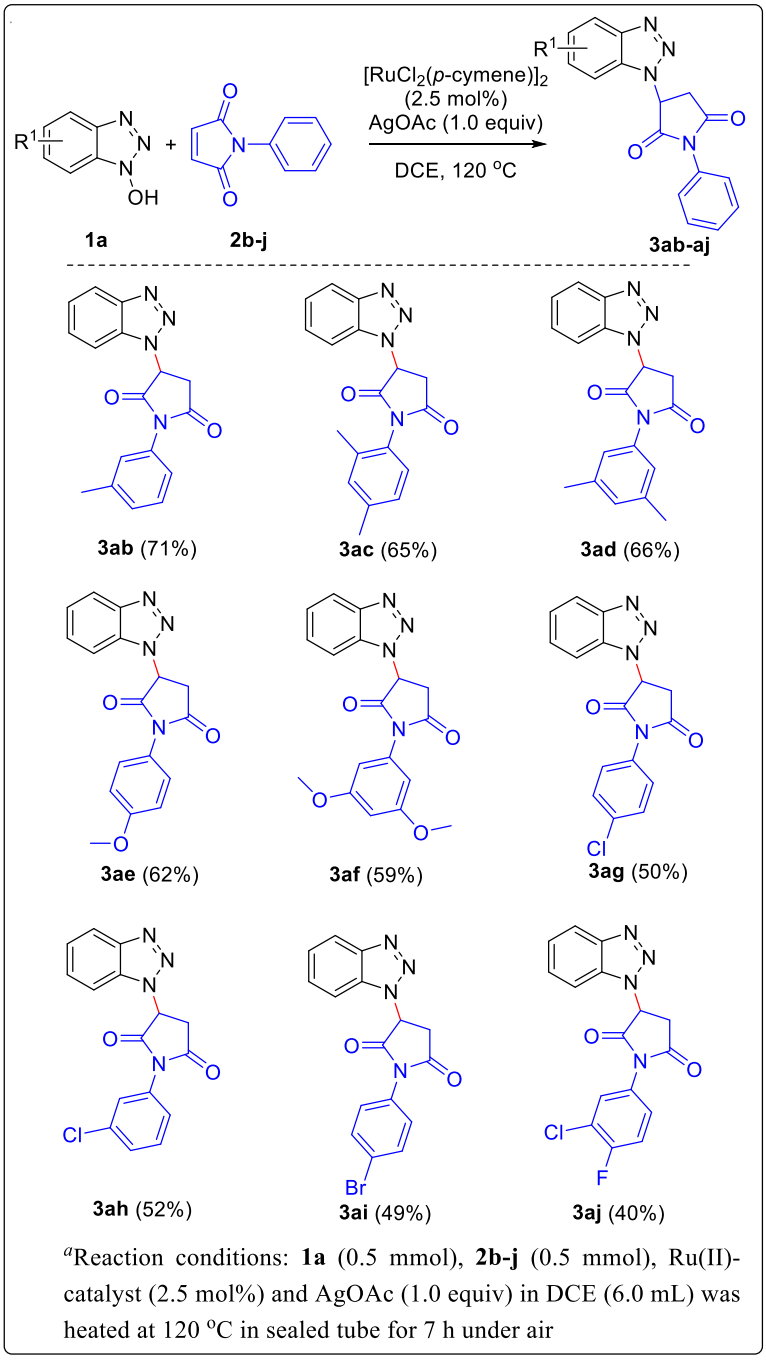
Scheme 5.16: Scope of 1-hydroxybenzotriazoles **1a-f** with *N*-phenyl maleimide **2a**[a]



[a]Reaction conditions: **1a-f** (0.5 mmol), **2a** (0.5 mmol), Ru(II)-catalyst (2.5 mol%) and AgOAc (1.0 equiv) in DCE (6.0 mL) was heated at 120 °C in sealed tube for 7 h under air

possessing mono and di-substituted electron donating group **2b-f**, which provided the pyrolidinones **3ab-af** in 59-71% yields. Similarly, the reactions of 1-hydroxybenzotriazole **1a** with *N*-phenyl maleimides substituted with electron

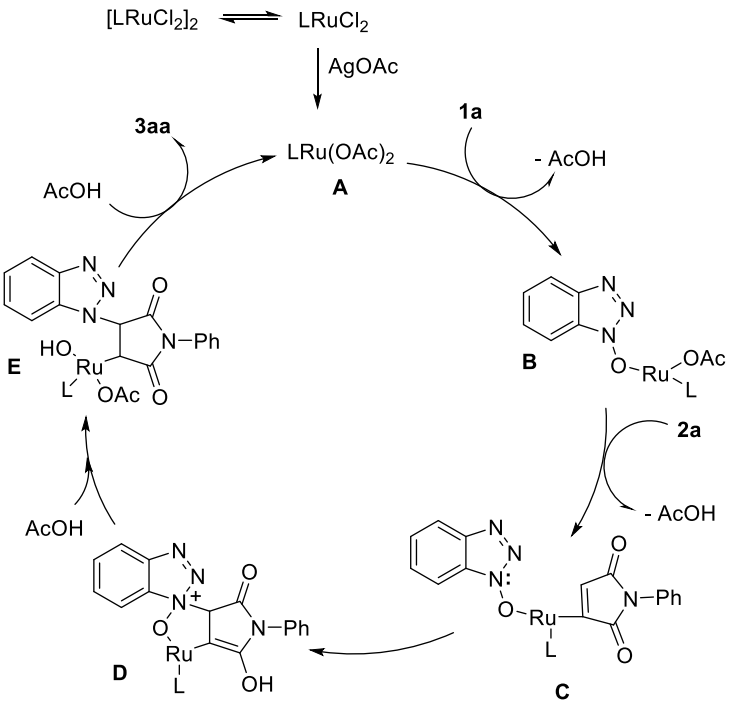
Scheme 5.17: Scope of 1-hydroxybenzotriazole **1a** with *N*-phenyl maleimides **2b-j**[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2b-j** (0.5 mmol), Ru(II)-catalyst (2.5 mol%) and AgOAc (1.0 equiv) in DCE (6.0 mL) was heated at 120 °C in sealed tube for 7 h under air

withdrawing group such as fluoro, chloro and bromo on the phenyl ring of maleimide were found compatible with the reaction conditions leading to the formation of corresponding pyrrolidinones **3ag-aj** in 40-50% yields (Scheme 5.17).

Based on the previous literature reports, a plausible mechanism for the formation of **3aa** is proposed in Scheme 5.18. First, the active catalyst **A** forms Ru(II)-complex **B** by elimination of one molecule of acetic acid. Then, co-ordination of the olefin **2a** with the metal, followed by C-H activation gives Ru(II) complex **C**. Next, intermolecular Michael type of addition of the amine with the α,β-unsaturated ketone gives Ru complex **D**. Then, in the presence of AcOH, complex **D** gives another Ru complex **E**, which on protonation and reductive elimination of the metal finally gives product **3aa** and regenerates the active catalyst.



Scheme 5.18

5.3 CONCLUSION

In conclusion, we have developed a new method for the synthesis of 3-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-phenylpyrrolidine-2,5-dione from 1-Hydroxybenzotriazole and *N*-phenyl maleimide *via* Ru(II)-catalyzed C-H activation in a single reaction vessel. This methodology provides good to moderate yield of substituted pyrrolidinones and tolerates variety of functional groups.

5.4 EXPERIMENTAL SECTION

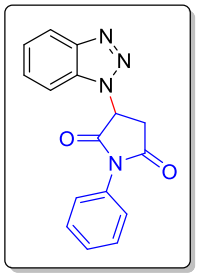
General information

Melting points were measured with a Buchi B-540 melting point apparatus. The NMR spectra were recorded on Bruker Avance III 500 MHz FTNMR and 400 MHz FTNMR spectrometer using tetramethylsilane (TMS) as an internal standard. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-backed silica gel plates (0.2 mm thickness); the chromatograms were visualized first with ultraviolet light (254 nm) and then by immersion in solutions of *p*-anisaldehyde followed by heating. Column chromatography was performed with silica gel (100-200 mesh, Merck). The starting material 1-Hydroxybenzotriazoles were synthesized using *o*-halonitrobenzene according to a known procedure.[28] Again, starting material *N*-phenyl maleimides were synthesized by the reaction of corresponding aniline with maleic anhydride by following an earlier reported method.[29]

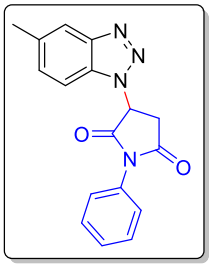
General procedure for the synthesis of 3-(1H-benzo[d][1,2,3]triazol-1-yl)-1-phenylpyrrolidine-2,5-dione:

A mixture of 1-hydroxy benztrizole (**1**, 0.5 mmol), *N*-phenyl maleimide (**2**, 0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), AgOAc (1.0 equiv) in dichloroethane (4.0 mL) was stirred at 120 ^oC in sealed tube for 7 hours. The solvent was removed under vacuo and the crude reaction mixture was poured into water and extracted with dichloromethane (25 mL x 2). The dichloromethane layer was then washed with brine. Finally, it was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuo. The crude product thus obtained was purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane as the eluant to afford **3**.

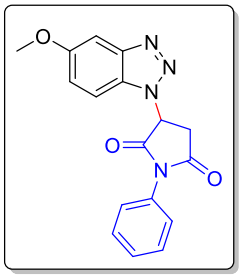
5.5 SPECTRAL AND ANALYTICAL DATA



3-(1H-benzo[d][1,2,3]triazol-1-yl)-1-phenylpyrrolidine-2,5-dione (3aa). Synthesized using general procedure from **1a** (67 mg, 0.5 mmol) and **2a** (86 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford brown solid of **3aa** (109 mg, 75%). M.p.: 148-150 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 1H), 7.61-7.55 (m, 2H), 7.51-7.42 (m, 4H), 7.37-7.35 (m, 2H), 6.00-5.97 (m, 1H), 3.85-3.79 (m, 1H), 3.65-3.59 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 170.9, 146.2, 133.3, 131.2, 129.5, 129.3, 128.7, 126.4, 126.2, 124.9, 120.6, 109.1, 55.7, 34.9.

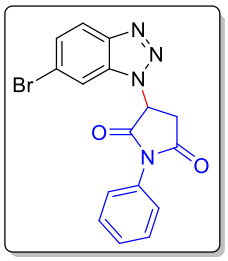


3-(5-methyl-1H-benzo[d][1,2,3]triazol-1-yl)-1-phenylpyrrolidine-2,5-dione (3ba). Synthesized using general procedure from **1b** (74 mg, 0.5 mmol) and **2a** (86 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford red solid of **3ba** (91 mg, 60%). M.p.: 182-184 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.83 (m, 1H), 7.49-7.41 (m, 3H), 7.35-7.31 (m, 3H), 7.26-7.23 (m, 1H), 5.96-5.91 (m, 1H), 3.79-3.73 (m, 1H), 3.60-3.52 (m, 1H), 2.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 171.1, 146.8, 144.9, 139.5, 135.0, 133.7, 130.8, 129.5, 126.4, 120.0, 119.4, 108.3, 55.6, 35.0, 22.2.

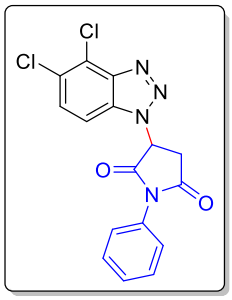


3-(5-methoxy-1H-benzo[d][1,2,3]triazol-1-yl)-1-phenylpyrrolidine-2,5-dione (3ca). Synthesized using general procedure from **1c** (82 mg, 0.5 mmol) and **2a** (86 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford red solid of **3ca** (98 mg, 61%). M.p.: 124-126 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 1H), 7.52-7.47 (m, 3H), 7.38-7.33 (m, 3H), 7.26-7.23 (m, 1H), 5.96-5.91 (m, 1H), 3.86 (s, 3H), 3.79-3.73 (m, 1H), 3.60-3.52

(m, 1H), 2.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 171.6, 147.1, 145.2, 139.8, 135.6, 133.9, 132.2, 130.8, 126.8, 120.9, 119.6, 108.7, 55.8, 55.5, 36.2.

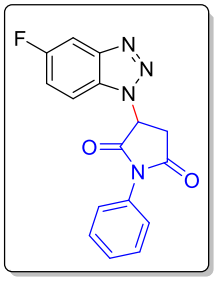


3-(6-bromo-1H-benzo[d][1,2,3]triazol-1-yl)-1-phenylpyrrolidine-2,5-dione (3da). Synthesized using general procedure from **1d** (107 mg, 0.5 mmol) and **2a** (86 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford brown solid of **3da** (100 mg, 54%). M.p.: 135-137 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.12 (m, 1H), 7.66-7.63 (m, 1H), 7.52-7.39 (m, 4H), 7.35-7.32 (m, 2H), 5.94-5.90 (m, 1H), 3.92-3.86 (m, 1H), 3.66-3.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 170.7, 147.4, 132.4, 132.0, 131.1, 129.5, 129.4, 126.3, 123.2, 118.1, 110.6, 55.9, 34.7.



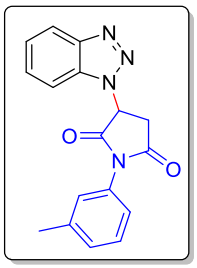
3-(4,5-dichloro-1H-benzo[d][1,2,3]triazol-1-yl)-1-phenylpyrrolidine-2,5-dione (3ea). Synthesized using general procedure from **1e** (102 mg, 0.5 mmol) and **2a** (86 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford brown solid of **3aa** (72 mg, 40%). M.p.: 170-172 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1H), 7.66-7.63 (m, 3H), 7.52-7.39 (m,

3H), 5.93-5.88 (m, 1H), 3.93-3.87 (m, 1H), 3.68-3.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 170.7, 148.4, 133.4, 132.8, 131.4, 129.6, 129.1, 126.7, 123.5, 118.3, 110.8, 55.6, 34.6.



3-(5-fluoro-1H-benzo[d][1,2,3]triazol-1-yl)-1-phenylpyrrolidine-2,5-dione (3fa).

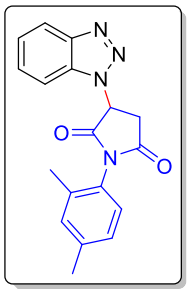
Synthesized using general procedure from **1f** (76 mg, 0.5 mmol) and **2a** (86 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford brown solid of **3fa** (77 mg, 50%). M.p.: 175-177 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.15 (m, 1H), 7.68-7.65 (m, 1H), 7.55-7.40 (m, 4H), 7.37-7.34 (m, 2H), 5.96-5.92 (m, 1H), 3.94-3.88 (m, 1H), 3.68-3.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 170.9, 147.6, 132.6, 132.2, 131.3, 129.7, 129.6, 126.5, 123.4, 118.3, 110.8, 55.5, 34.5.



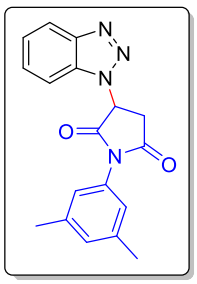
3-(1H-benzo[d][1,2,3]triazol-1-yl)-1-(m-tolyl)pyrrolidine-2,5-dione (3ab).

Synthesized using general procedure from **1a** (67 mg, 0.5 mmol) and **2b** (93 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford brown solid of **3ab** (108 mg, 71%). M.p.: 180-182 ^{o}C.

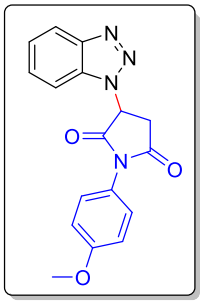
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 1H), 7.58-7.52 (m, 2H), 7.45-7.40 (m, 1H), 7.34 (t, J = 7.7 Hz, 1H), 7.23-7.21 (m, 1H), 7.13-7.09 (m, 2H), 5.99-5.96 (m, 1H), 3.78-3.72 (m, 1H), 3.60-3.53 (m, 1H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 170.9, 146.0, 139.5, 133.1, 130.9, 130.0, 129.1, 128.4, 126.8, 124.7, 123.3, 120.3, 108.9, 55.5, 34.8, 21.2.



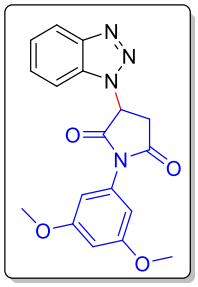
3-(1H-benzo[d][1,2,3]triazol-1-yl)-1-(2,4-dimethylphenyl)pyrrolidine-2,5-dione (3ac). Synthesized using general procedure from **1a** (67 mg, 0.5 mmol) and **2c** (100 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford brown solid of **3ac** (104 mg, 65%). M.p.: 200-205 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12-8.09 (m, 1H), 7.61-7.55 (m, 2H), 7.44-7.41 (m, 1H), 7.14-7.06 (m, 3H), 6.03-5.95 (m, 1H), 3.77-3.73 (m, 1H), 3.66-3.57 (m, 1H), 2.34 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 171.2, 146.0, 140.3, 135.8, 134.9, 132.3, 128.6, 127.8, 127.6, 127.4, 124.8, 120.5, 109.2, 55.7, 35.5, 21.3, 17.7.



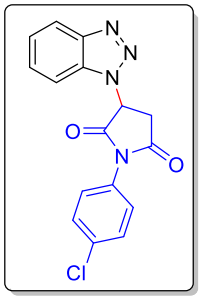
3-(1H-benzo[d][1,2,3]triazol-1-yl)-1-(3,5-dimethylphenyl)pyrrolidine-2,5-dione (3ad). Synthesized using general procedure from **1a** (67 mg, 0.5 mmol) and **2c** (100 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford brown solid of **3ad** (105 mg, 66%). M.p.: 185-188 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 1H), 7.57-7.52 (m, 2H), 7.42-7.39 (m, 1H), 7.03 (s, 1H), 6.90 (s, 2H), 6.00-5.97 (m, 1H), 3.72-3.66 (m, 1H), 3.58-3.51 (m, 1H), 2.30 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 171.3, 146.1, 139.4, 139.2, 133.3, 131.2, 131.0, 128.6, 124.8, 124.2, 124.0, 120.5, 109.3, 55.8, 35.0, 21.3.



3-(1H-benzo[d][1,2,3]triazol-1-yl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3ae). Synthesized using general procedure from **1a** (67 mg, 0.5 mmol) and **2e** (101 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford brown solid of **3ae** (99 mg, 62%). M.p.: 170-172 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 1H), 7.60-7.58 (m, 2H), 7.47-7.44 (m, 1H), 7.29-7.27 (m, 3H), 7.00 (d, J = 9.0 Hz, 1H), 6.00-5.96 (m, 1H), 3.86-3.80 (m, 4H), 3.65-3.59 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 171.1, 160.0, 146.3, 133.3, 128.7, 127.7, 124.8, 123.6, 120.7, 114.7, 109.1, 55.6, 34.9, 29.8.

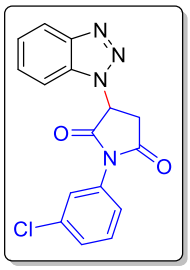


3-(1H-benzo[d][1,2,3]triazol-1-yl)-1-(3,5-dimethoxyphenyl)pyrrolidine-2,5-dione (3af). Synthesized using general procedure from **1a** (67 mg, 0.5 mmol) and **2f** (116 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford red solid of **3af** (103 mg, 59%). M.p.: 150-153 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4, Hz, 1H), 7.57-7.52 (m, 2H), 7.43-7.39 (m, 1H), 6.50-6.47 (m, 3H), 5.98-5.95 (m, 1H), 3.78-3.76 (m, 1H), 3.73 (s, 6H), 3.62-3.55 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 171.0, 161.2, 146.1, 133.4, 132.7, 128.6, 124.9, 120.4, 109.3, 104.9, 101.5, 55.7, 35.0, 29.8.

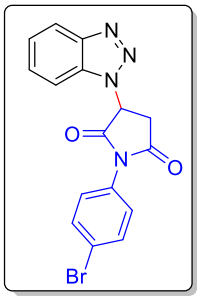


3-(1H-benzo[d][1,2,3]triazol-1-yl)-1-(4-chlorophenyl)pyrrolidine-2,5-dione (3ag). Synthesized using general procedure from **1a** (67 mg, 0.5 mmol) and **2g** (103 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford red solid of **3ag** (81 mg, 50%). M.p.: 135-137 ^{o}C. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 1H), 7.55-7.50 (m, 2H), 7.43-7.37 (m, 3H), 7.24 (d, J = 8.5 Hz, 2H), 5.99-5.96 (m, 1H), 3.76-3.70 (m, 1H), 3.60-3.53 (m,

1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 170.9, 146.1, 135.1, 133.3, 129.6, 128.8, 127.7, 125.0, 120.5, 109.1, 55.7, 35.0.

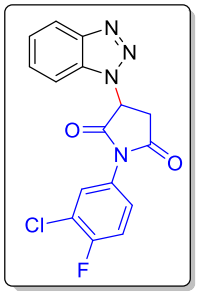


3-(1H-benzo[d][1,2,3]triazol-1-yl)-1-(3-chlorophenyl)pyrrolidine-2,5-dione (3ah). Synthesized using general procedure from **1a** (67 mg, 0.5 mmol) and **2h** (103 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford red solid of **3ag** (84 mg, 52%). M.p.: 190-192 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.08 (m, 1H), 7.57-7.55 (m, 2H), 7.45-7.41 (m, 1H), 7.39-7.37 (m, 3H), 7.26-7.23 (m, 1H), 6.00-5.97 (m, 1H), 3.84-3.78 (m, 1H), 3.65-3.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.7, 146.2, 135.0, 133.3, 132.1, 130.4, 129.6, 128.8, 126.7, 125.0, 124.6, 120.6, 109.1, 55.6, 35.0.



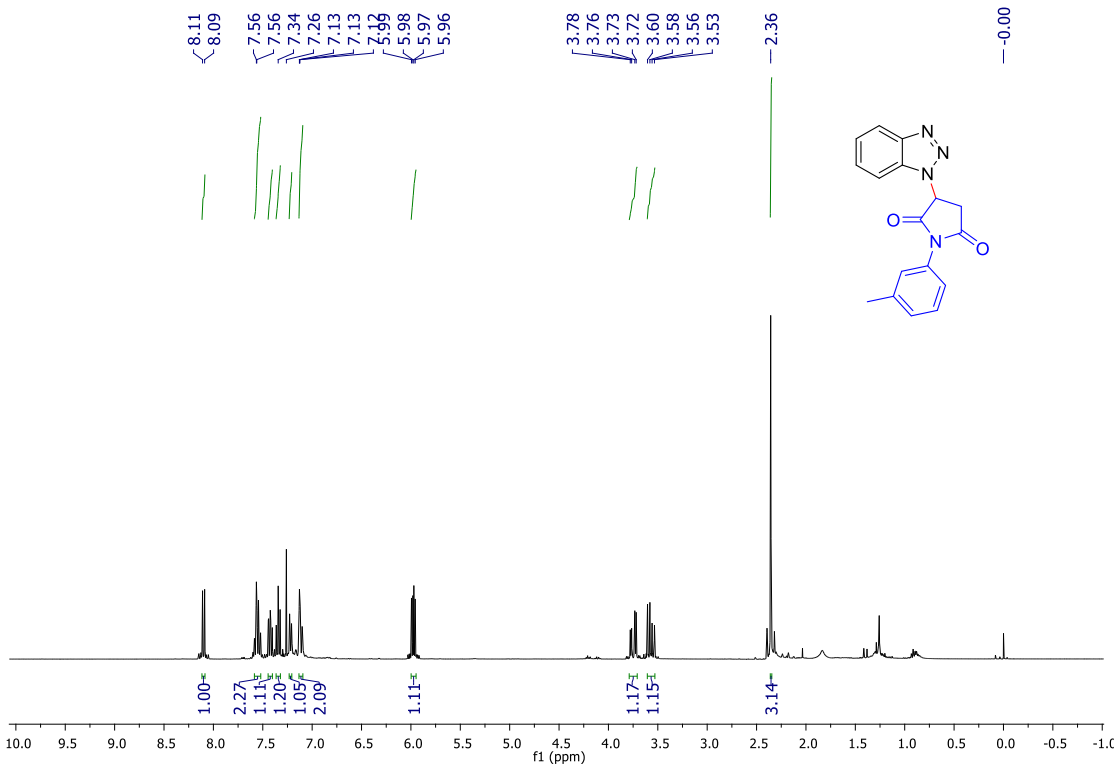
3-(1H-benzo[d][1,2,3]triazol-1-yl)-1-(4-bromophenyl)pyrrolidine-2,5-dione (3ai). Synthesized using general procedure from **1a** (67 mg, 0.5 mmol) and **2i** (126 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford brown solid of **3ai** (90 mg, 49%). M.p.: 140-142 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.4 Hz, 1H), 7.65-7.60 (m, 4H), 7.50-7.46 (m,

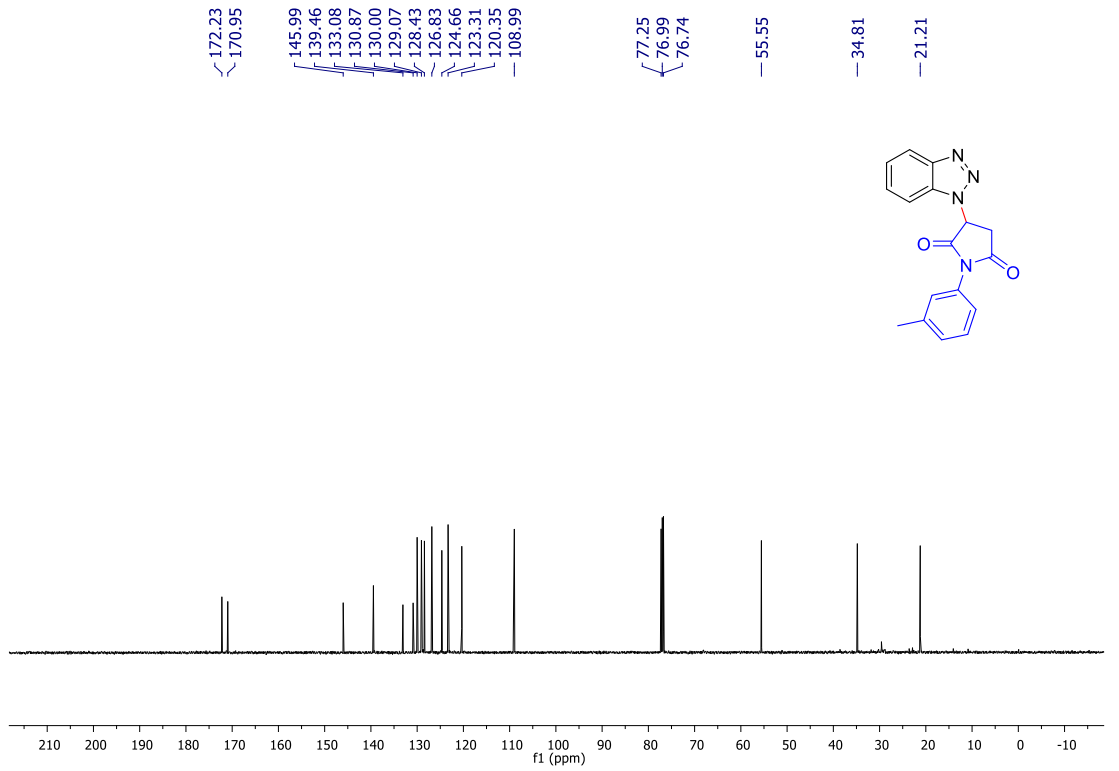
1H), 7.29-7.27 (m, 2H), 5.98-5.95 (m, 1H), 3.91-3.86 (m, 1H), 3.68-3.63 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 170.3, 133.1, 132.5, 129.9, 128.6, 127.7, 127.3, 124.8, 123.1, 120.5, 108.8, 55.4, 34.7.



3-(1H-benzo[d][1,2,3]triazol-1-yl)-1-(3-chloro-4-fluorophenyl)pyrrolidine-2,5-dione (3aj). Synthesized using general procedure from **1a** (67 mg, 0.5 mmol) and **2j** (112 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford brown solid of **3aj** (68 mg, 40%). M.p.: 210-212 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 1H), 7.60-7.57 (m, 2H), 7.46-7.43 (m, 2H), 7.26-7.18 (m, 2H), 6.03-5.99 (m, 1H), 3.82-3.77 (m, 1H), 3.66-3.61 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 170.5, 158.9, 156.9, 145.9, 133.2, 128.6, 128.3, 127.3, 127.2, 126.3, 126.2, 124.8, 121.9, 121.8, 120.3, 117.2, 117.0, 108.8, 55.3, 34.8.

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





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ABSTRACT

Name of the Student: Bidisha Rani Bora **Registration No. :** 10CC16A38006

Faculty of Study: Chemical Science **Year of Submission:** 2021

AcSIR academic centre/CSIR Lab: CSIR-NEIST **Name of the Supervisor:** Dr Sanjib Gogoi

Title of the thesis: Development of new metal-catalyzed reactions for the synthesis of spirobi[indene]-diones, aryl esters, *β*-keto esters and pyrrolidinones.

The use of transition metal catalysis for C-H bond activation has witnessed great development which has lead to many pioneering discoveries. Inspired by the literature on transition-metal-catalyzed C-H activation reaction, which consists of a rich array of versatile approaches, my thesis work is particularly focused on development of new methodologies for the synthesis of some biologically valuable heterocyclic or carbocyclic moieties like spirobi[indene]-diones, aryl esters, *β*-keto esters and pyrrolidinones by using Ru(II)-catalyzed C-H functionalization. The molecular structure of spirobi[indene]-diones are important skeleton for organic synthesis as well as found in various natural products and synthetic bioactives. On this aspect, we have developed a novel Ru(II)-catalyzed annulation reaction towards the synthesis of spiroindenes. A broad substrate scope has been demonstrated for both 2-phenyl indandiones as well as internal alkynes. On the other hand, aryl esters and 1,3-diketones are important synthons for the synthesis of various pharmaceutically active compounds as well as natural products. In this context, we have developed two novel routes for the synthesis of aryl 2-aminobenzoates and *β*-ketoesters *via* Ru(II)-catalyzed C-H activation reaction by using readily available starting materials. Again, we have developed a new methodology for the synthesis of pyrrolidinones from 1-Hydroxybenzotriazoles and *N*-phenyl maleimides *via* Ru(II)-catalyzed C-H activation. The structures of our synthesized compounds were elucidated using various spectroscopic techniques including ^{1}H NMR, ^{13}C NMR and HRMS analysis.

Appendix I

List of Publications

and

seminars/symposium attended

List of research publications:

1. Prakash, R.; **Bora, B. R**.; Boruah, R. C.; Gogoi, S.* "Ru(II)-Catalyzed C-H activation and annulations reaction *via* Carbon-Carbon triple bond cleavage." *Org Lett*. **2018**, *20*, 2297.
2. Gogoi, K.; **Bora**, **B. R**.; Borah, G.; Sarma, B.; Gogoi, S.* "Synthesis of quaternary carbon-centered indolo[1,2-a]quinazolinones and indazolo-[1,2-a]indazolones *via* C-H functionalization." *Chem. Commun*. **2021**, *57*, 1388.
3. **Bora, B. R**.; Prakash, R.; Sultana, S.; Gogoi, S.* "Ruthenium(II)-catalyzed decarbonylative and decarboxylative coupling of isatoic anhydrides with salicylaldehydes: access to aryl 2-aminobenzoates." *Org. Biomol. Chem.* **2021**, *19*, 2725.
4. **Bora, B. R**.; Sultana, S.; Sarma, B.; Gogoi, S.* "Ru(II)-Catalyzed C-H Activation and Alkyne Annulation Reaction of Phenyl Indandiones: Synthesis of Spirobi[indene]diones." *Synthesis.* **2021** (under revision).

Seminars/symposium attended:

1. International conference on Emerging Trends in Chemical Sciences, (ETCS) held on 26-28 February, 2018, organized by Dibrugarh University.
2. MRSI-North-East conference-2018: National conference on "Frontiers in Chemical Biology", organized by CSIR-NEIST, Jorhat.

Appendix II

Copies of

SCI publications

emanating from the thesis

Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
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Cite this: *Org. Biomol. Chem.*, 2021, **19**, 2725

Ruthenium(II)-catalyzed decarbonylative and decarboxylative coupling of isatoic anhydrides with salicylaldehydes: access to aryl 2-aminobenzoates†

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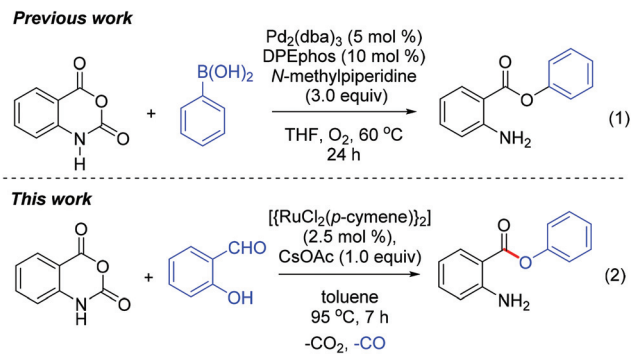
A ruthenium(II)-catalyzed coupling reaction of isatoic anhydrides and salicylaldehydes has been developed for the synthesis of 2-aminobenzoates. This reaction proceeds through metal-catalyzed decarbonylation and decarboxylation to afford good yields of aryl 2-aminobenzoates.

The aryl esters of benzoic acids are very important synthons for the synthesis of various pharmaceutically active compounds as well as natural products.[1] In photochemistry, aryl benzoates are used as chemiluminescent indicators.[2] Among the aryl benzoates, particularly, the aryl 2-aminobenzoates have received significant attention because of their utility in the synthesis of bioactive nitrogen containing heterocycles.[3] Some of these 2-aminobenzoates have application in fragrance and flavor industries owing to their pleasant scent.[4] Furthermore, some of the aminobenzoate derivatives exhibit anti-bacterial, anti-fungal and anti-inflammatory activities.[5] The drug glafenine is a nonsteroidal anti-inflammatory drug that possesses 2-aminobenzoate as the key skeleton.

These aryl benzoates are traditionally synthesized by esterification, transesterification and Baeyer–Villiger oxidation reactions.[6] However, the highly acidic and basic conditions used in esterification and transesterification reactions might not be suitable for some compounds possessing sensitive functional groups in the molecule. Again, acid-catalyzed esterification of anthranilic acid to get the ester is a tough reaction owing to the presence of *ortho* amino group. This amino group consumes large amount of the acid before esterification with the alcohol. To overcome these problems, designing of new method for the synthesis of these esters are very essential. In recent years, various metal-catalyzed coupling reactions have been developed for the synthesis of benzoic esters.[7] However, metal-catalyzed reactions for the synthesis of aryl 2-aminobenzoates are rare. Wu and co-workers reported a $Pd_2(dba)_3$-catalyzed reaction of isatoic anhydrides with arylboronic acids in the presence of the ligand DPEphos for the synthesis of aryl *o*-aminobenzoates (Scheme 1, eqn (1)).[8] In continuation of our work on metal-catalyzed C–H, C–C functionalization reactions,[9] herein, we disclose an unprecedented decarbonylative and decarboxylative coupling reaction of isatoic anhydrides and salicylaldehydes for the synthesis of aryl 2-aminobenzoates (Scheme 1, eqn (2)).

Initially, the Ru(II)-catalyzed coupling reaction between isatoic anhydride (**1a**) and salicyldehyde (**2a**) was selected as a model reaction to find out the optimized reaction conditions for the synthesis of the ester **3aa**. As shown in Table 1, among all the metal complexes studied for this esterification reaction, only the $[\{RuCl_2(p\text{-cymene})\}_2]$ catalyst provided the ester **3aa** in 43% yield using $Cu(OAc)_2$ and ^{t}AmOH as the additive and solvent, respectively. To improve the yield of **3aa**, some other commonly used additives such as CsOAc, AgOAc and KOAc were tested which revealed CsOAc to be the best additive which afforded 58% yield of **3aa** (entry 5). Then, further screening of some common solvents proved the aprotic solvent



Scheme 1 Metal-catalyzed synthesis of aryl 2-aminobenzoates.

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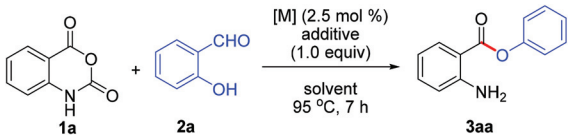
†Electronic supplementary information (ESI) available: Copies of ^{1}H NMR, ^{13}C NMR spectra of the synthesized compounds. See DOI: 10.1039/d1ob00027f

Table 1 Reaction conditions optimization for **3aa**[a]

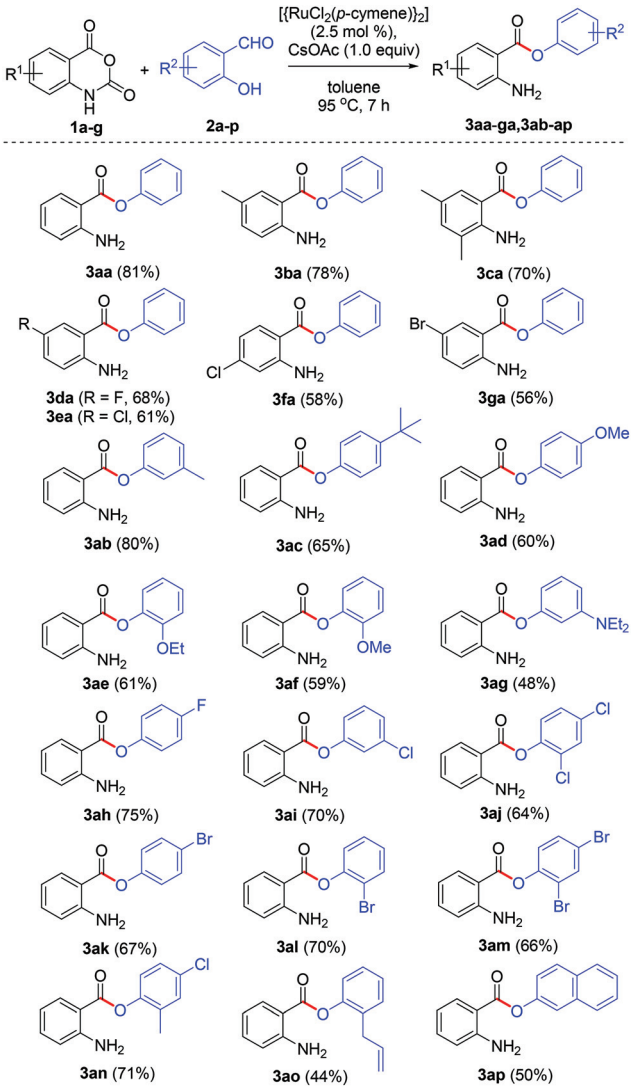


Entry	Catalyst	Additive	Solvent	**3aa**[b] (%)
1	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	0
2	$RuCl_3{\cdot}xH_2O$	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	0
3	$[RuCl_2(PPh_3)_3]$	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	0
4	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	43
5	$[\{RuCl_2(p\text{-cymene})\}_2]$	CsOAc	^{t}AmOH	58
6	$[\{RuCl_2(p\text{-cymene})\}_2]$	AgOAc	^{t}AmOH	27
7	$[\{RuCl_2(p\text{-cymene})\}_2]$	KOAc	^{t}AmOH	38
8	$[\{RuCl_2(p\text{-cymene})\}_2]$	CsOAc	MeCN	25
9	$[\{RuCl_2(p\text{-cymene})\}_2]$	CsOAc	DCE	42
10	$[\{RuCl_2(p\text{-cymene})\}_2]$	CsOAc	Toluene	81
11	$[\{RuCl_2(p\text{-cymene})\}_2]$	CsOAc	Dioxane	54

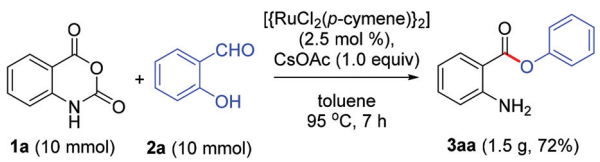
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (2.5 mol%), additive (0.5 mmol) and solvent (4.0 mL) heated at 95 °C for 7 h under air. [b] Isolated yields.

toluene to be the best solvent for the synthesis of the ester **3aa** (81%, entry 10).

Initially the optimized reaction conditions were applied to study the substrate scope of the isatoic anhydrides (**1a–g**). As shown in Scheme 2, isatoic anhydrides substituted with mono-methyl and di-methyl substituents **1b–c** provided 70–78% yields of the products **3ba–ca**. Similarly, isatoic anhydrides substituted with electron-withdrawing substituents such as fluoro, chloro and bromo **1d–g**, provided good yields (56–68%) of the products **3da–ga**, irrespective of the position of the substituents on the aromatic ring. Next, the scope of the salicylaldehydes **2b–p** were studied with **1a** for this esterification reaction. As shown in Scheme 2, various salicylaldehydes possessing electron-rich substituents such as methyl, *tert*-butyl, methoxy, ethoxy and diethylamino on the phenyl ring of salicylaldehyde **2b–g** provided 48–80% yields of the esters **3ab–ag**. Similarly, some of the salicylaldehydes substituted with one or two electron-withdrawing substituents such as fluoro, chloro and bromo on the phenyl ring of salicylaldehyde **2h–m** provided 64–75% yields of the products **3ah–am**. For the products **3ag** and **3ai**, 4-(diethylamino)-2-hydroxybenzaldehyde (**2g**) and 4-chloro-2-hydroxybenzaldehyde (**2i**) were used. The methyl and chloro group substituted salicylaldehyde **1n** also turned out to be a good substrate for this reaction which provided 71% yield of product **3an**. The sensitive allyl group containing salicylaldehyde **2o** provided 44% yield of **3ao**. Finally, 2-hydroxy-1-naphthaldehyde **2p** was tested to afford 50% yield of ester **3ap**. The reaction of **1a** and 3-hydroxy-2-naphthaldehyde also provided the same ester **3ap** in 53% yield under the standard reaction conditions. A gram-scale esterification reaction between **1a** and **2a** provided 72% yield of **3aa**, which suggest the practical applicability of this reaction (Scheme 3). The phosphomolybdic acid test and lime water test indicated



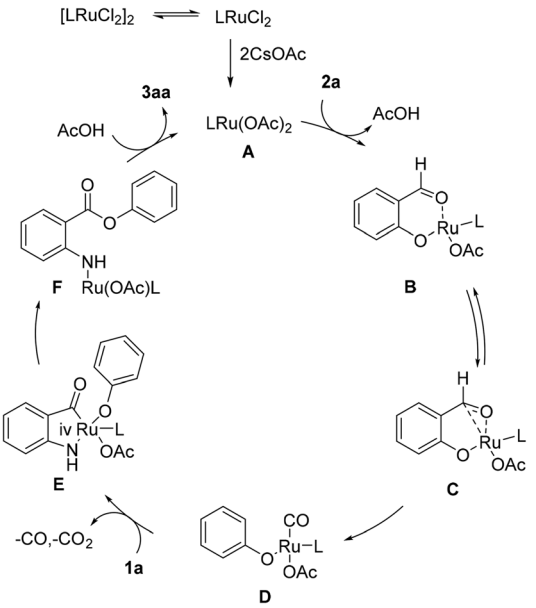
Scheme 2 Scope with isatoic anhydrides and salicylaldehydes. Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), Ru(II) catalyst (2.5 mol%), CsOAc (0.5 mmol) and toluene (4.0 mL) heated at 95 °C for 7 h under air.



Scheme 3 Gram-scale synthesis of ester **3aa**.

the evaluation of carbon monoxide and carbon dioxide, respectively, from the reaction mixture.[9b]

A plausible mechanism for the formation of **3aa** is proposed in Scheme 4, based on literature reports.[10] As the reaction of **1a**, **2a** and $[\{RuCl_2(p\text{-cymene})\}_2]$ in the absence of the additive CsOAc could not provide **3aa** in toluene at 95 °C, probably $[Ru(OAc)_2(p\text{-cymene})]$ (**A**) might be the active catalyst.[10e]



Scheme 4 Possible mechanism.

First, the active catalyst **A** forms Ru(II)-complex **B** by elimination of one molecule of acetic acid. This complex **B** might exist as tautomer with π-bonded Ru-complex **C**, which on decarbonylation generates a Ru–CO complex **D**.[10a] Then, oxidative addition of this Ru complex in the C–O bond of **1a** followed by decarboxylation and decarbonylation affords Ru-complex **E**. Reductive elimination of the metal initially generates Ru complex **F**, which in the presence of acetic acid affords the active catalyst **A** and the ester **3aa**.

In conclusion, a novel Ru(II)-catalyzed coupling reaction of isatoic anhydride and salicylaldehyde was developed. This reaction proceeds through decarboxylation and decarbonylation to afford good yields of important aryl 2-aminobenzoates.

Experimentalsections

General information

Melting points were measured with a Buchi B-540 melting point apparatus. The NMR spectra were recorded on Bruker Avance III 500 MHz FTNMR spectrometer using tetramethylsilane (TMS) as an internal standard. All the commercially available regents were used as received. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on Merck TLC Silica gel 60 F254 precoated plates. Column chromatography was performed on silica gel (100–200 mesh, Merck). The starting isatoic anhydrides were synthesized using isatins by following a known procedure.[11]

General procedure A (GPA)

A mixture of isatoic anhydride (**1**, 0.5 mmol), salicyaldehyde (**2**, 0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), CsOAc (0.5 mmol) in toluene (4.0 mL) was stirred at 95 °C under open air for 7 hours. The solvent was removed under vacuum and the crude reaction mixture was poured into water and extracted with dichloromethane (25 mL × 2). The dichloromethane layer was then washed with brine. Finally, it was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The crude product thus obtained was purified by silica gel (100–200 mesh) column chromatography using EtOAc/Hexane as the eluant to afford **3**.

Compound characterizations

Phenyl 2-aminobenzoate (3aa).[8] Synthesized using GPA from **1a** (81 mg,0.5 mmol) and **2a** (61 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3aa** (86 mg, 81%). M.p.: 70–72 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 7.9 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.36–7.33 (m, 1H), 7.29–7.26 (m, 1H), 7.20–7.18 (m, 2H), 6.74–6.70 (m, 2H), 5.78 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 151.1, 150.7, 134.8, 131.5, 129.4, 125.7, 122.6, 121.9, 116.7, 116.3, 114.4, 109.5. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.68; H, 5.01; N, 6.81.

Phenyl 2-amino-5-methylbenzoate (3ba).[8] Synthesized using GPA from **1b** (88 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid (88 mg, 78%). M.p.: 60–62 °C. ^{1}H NMR (500 MHz, CDCl3) δ 7.89 (s, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.29–7.25 (m, 1H), 7.15–7.20 (m, 3H), 6.64 (d, J = 8.4 Hz, 1H), 5.62 (bs, 2H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 150.7, 149.1, 136.0, 131.0, 129.4, 125.7, 125.4, 121.9, 116.8, 109.3, 20.2. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.20; H, 5.83; N, 5.93.

Phenyl 2-amino-3,5-dimethylbenzoate(3ca). Synthesized using GPA from **1c** (95 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid (84 mg, 70%). M.p.: 101–103 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.29–7.25 (m, 1H), 7.18 (d, J = 8.3 Hz, 2H), 7.12 (s, 1H), 5.73 (bs, 2H), 2.27 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 150.8, 147.6, 136.9, 129.4, 128.8, 125.6, 124.7, 123.2, 122.0, 108.9, 20.2, 17.3. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.51; H, 6.45; N, 6.09.

Phenyl 2-amino-5-fluorobenzoate(3da).[8] Synthesized using GPA from **1d** (90 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford yellow solid of **3da** (78 mg, 68%). M.p.: 110–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, J = 9.6, 3.0 Hz, 1H), 7.47–7.42 (m, 2H), 7.31–7.25 (m, 1H), 7.20–7.16 (m, 2H), 7.09–7.14 (m, 1H), 6.68 (dd, J = 9.1, 4.5 Hz, 1H), 5.65 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 153.7 (d, J = 234 Hz), 150.4, 147.7, 129.4, 125.9, 122.9 (d, J = 23.8 Hz), 121.8, 117.9 (d, J = 7.5 Hz), 116.2 (d, J = 23.8 Hz), 116.14, 109.3 (d, J = 7.5 Hz). Anal. Calcd for $C_{13}H_{10}FNO_2$: C, 67.53; H, 4.36; N, 6.06. Found: C, 67.79; H, 4.30; N, 5.87.

Phenyl 2-amino-5-chlorobenzoate (3ea).[8] Synthesized using GPA from **1e** (98 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol)

which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford yellow solid of **3ea** (75 mg) with 61% yield. M.p.: 100–102 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.44 (t, J = 8.1 Hz, 2H), 7.30–7.26 (m, 2H), 7.18 (d, J = 7.6 Hz, 2H), 6.66 (d, J = 8.8 Hz, 1H), 5.79 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 150.4, 149.6, 134.8, 130.6, 129.4, 125.9, 121.7, 120.7, 118.1, 110.3. Anal. Calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.27; H, 4.30; N, 5.82.

Phenyl 2-amino-4-chlorobenzoate (3fa).[12] Synthesized using GPA from **1f** (98 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3fa** (71 mg, 58%). M.p.: 95–97 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 8.6 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.29–7.25 (m, 1H), 7.19–7.16 (m, 2H), 6.73–6.66 (m, 2H), 5.86 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 151.8, 150.5, 140.8, 132.9, 129.4, 125.8, 121.8, 116.8, 116.0, 108.1. Anal. Calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 62.86; H, 4.08; N, 5.93.

Phenyl 2-amino-5-bromobenzoate (3ga). Synthesizedusing GPA from **1g** (121 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3ga** (82 mg, 56%). M.p.: 111–113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.45–7.37 (m, 3H), 7.29–7.24 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.59 (d, J = 8.8 Hz, 1H), 5.80 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 150.4, 150.0, 137.4, 133.6, 129.4, 125.9, 121.8, 118.4, 110.8, 107.3. Anal. Calcd for $C_{13}H_{10}BrNO_2$: C, 53.45; H, 3.45; N, 4.79. Found: C, 53.46; H, 3.32; N, 4.97.

***m*-Tolyl 2-aminobenzoate (3ab).**[8] Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2b** (68 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford colorless oily product of **3ab** (91 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 7.7 Hz, 1H), 7.36–7.30 (m, 2H), 7.09 (d, J = 7.6 Hz, 1H), 7.00–6.98 (m, 2H), 6.73–6.70 (m, 2H), 5.78 (bs, 2H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 151.1, 150.6, 139.6, 134.7, 131.5, 129.1, 126.5, 122.5, 118.8, 116.6, 116.3, 109.6, 21.3. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.37; H, 5.91; N, 6.39.

4-(*tert*-Butyl)phenyl 2-aminobenzoate (3ac). Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2c** (89 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford yellow solid of **3ac** (87 mg, 65%). M.p.: 119–121 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 7.1 Hz, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.36–7.32 (m, 1H), 7.11 (d, J = 8.6 Hz, 2H), 6.73–6.70 (m, 2H), 5.78 (bs, 2H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 151.1, 148.5, 148.2, 134.7, 131.5, 126.3, 121.2, 116.6, 116.3, 109.6, 34.5, 31.6. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.89; H, 7.34; N, 5.52.

4-Methoxyphenyl 2-aminobenzoate (3ad).[8] Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2d** (76 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3ad** (72 mg, 60%). M.p.: 102–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.6 Hz, 1H), 7.34 (t, J = 7.3 Hz, 1H), 7.10 (d, J = 8.9 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 6.71 (t, J = 8.1 Hz, 2H), 5.77 (bs, 2H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 157.1, 151.1, 144.1, 134.7, 131.5, 122.6, 116.6, 116.3, 114.4, 109.6, 55.5. Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.80; H, 5.27; N, 5.30.

2-Ethoxyphenyl 2-aminobenzoate (3ae). Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2e** (83 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3ae** (78 mg, 61%). M.p.: 67–70 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.35–7.32 (m, 1H), 7.23–7.19 (m, 1H), 7.15 (dd, J = 7.8, 1.6 Hz, 1H), 7.02–6.97 (m, 2H), 6.74–6.70 (m, 2H), 5.73 (bs, 2H), 4.07 (q, J = 6.9 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 150.9, 150.7, 140.2, 134.5, 131.8, 126.6, 123.1, 120.7, 116.5, 116.3, 113.7, 109.8, 64.4, 14.7. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.31; H, 5.94; N, 5.37.

2-Methoxyphenyl 2-aminobenzoate (3af).[8] Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2f** (76 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3af** (71 mg, 59%). M.p.: 111–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 1H), 7.37–7.29 (m, 2H), 6.84–6.77 (m, 2H), 6.75–6.69 (m, 3H), 5.77 (bs, 2H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 160.5, 151.7, 151.1, 134.8, 131.5, 129.7, 116.7, 116.3, 114.1, 111.6, 109.5, 107.8, 55.3. Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.26; H, 5.10; N, 5.83.

3-(Diethylamino)phenyl 2-aminobenzoate (3ag). Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2g** (96 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford yellow solid of **3ag** (68 mg, 48%). M.p.: 43–45 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10–8.07 (d, J = 8.0 Hz, 1H), 7.35–7.31 (m, 1H), 7.22 (t, J = 8.1 Hz, 1H), 6.73–6.70 (m, 2H), 6.57–6.55 (m, 1H), 6.45–6.42 (m, 2H), 5.78 (bs, 2H), 3.34 (q, J = 7.0 Hz, 4H), 1.16 (t, J = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 152.0, 151.0, 134.5, 131.5, 129.7, 116.6, 116.2, 109.9, 109.0, 108.3, 104.8, 44.3, 12.4. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.59; H, 6.90; N, 9.52.

4-Fluorophenyl 2-aminobenzoate (3ah).[8] Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2h** (70 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3ah** (86 mg, 75%). M.p.: 91–93 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 7.3 Hz, 1H), 7.36–7.33 (m, 1H), 7.16–7.09 (m, 4H), 6.73–6.70 (m, 2H), 5.76 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 160.1 (d, J = 242.5 Hz), 151.2, 146.5 (d, J = 2.5 Hz), 134.9, 131.4, 123.3 (d, J = 8.8 Hz), 116.7, 116.3, 116.1 (d, J = 22.5 Hz), 115.9, 109.2. Anal. Calcd for $C_{13}H_{10}FNO_2$: C, 67.53; H, 4.36; N, 6.06. Found: C, 67.69; H, 4.67; N, 5.85.

3-Chlorophenyl 2-aminobenzoate (3ai). Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2i** (78 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3ai** (86 mg, 70%). M.p.: 85–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.8, 1.6 Hz, 1H), 7.41–7.32 (m, 3H), 7.13 (d, J = 8.8 Hz, 2H),

6.74–6.70 (m, 2H), 5.76 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 151.3, 149.2, 135.0, 131.5, 131.1, 129.4, 123.3, 116.7, 116.4, 109.1. Anal. Calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.31; H, 3.88; N, 5.28.

2,4-Dichlorophenyl 2-aminobenzoate (3aj). Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2j** (95 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3aj** (89 mg, 64%). M.p.: 90–93 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.9 Hz, 1H), 7.43 (s, 1H), 7.29 (t, J = 8.1 Hz, 1H), 7.23–7.18 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 6.65 (t, J = 8.9 Hz, 2H), 5.67 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 151.4, 145.8, 135.3, 131.7, 131.6, 130.0, 128.2, 127.8, 124.9, 116.7, 116.5, 108.6. Anal. Calcd for $C_{13}H_9Cl_2NO_2$: C, 55.35; H, 3.22; N, 4.96. Found: C, 55.01; H, 3.07; N, 5.30.

4-Bromophenyl 2-aminobenzoate (3ak).[8] Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2k** (100 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3ak** (97 mg, 67%). M.p.: 77–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.4 Hz, 1H), 7.56–7.52 (m, 2H), 7.37–7.32 (m, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.73–6.69 (m, 2H), 5.77 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 151.3, 149.7, 135.0, 132.4, 131.4, 130.8, 123.8, 118.8, 116.7, 116.4, 109.1. Anal. Calcd for $C_{13}H_{10}BrNO_2$: C, 53.45; H, 3.45; N, 4.79. Found: C, 53.81; H, 3.62; N, 4.70.

2-Bromophenyl 2-aminobenzoate (3al).[8] Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2l** (100 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford colorless oily product of **3al** (101 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, J = 8.0, 1.6 Hz, 1H), 7.70 (dd, J = 8.0, 1.6 Hz, 1H), 7.43–7.36 (m, 2H), 7.32–7.29 (m, 1H), 7.20–7.16 (m, 1H), 6.71 (d, J = 8.4 Hz, 2H), 5.83 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 151.2, 148.0, 134.9, 133.0, 131.5, 128.2, 127.0, 123.9, 116.5, 116.3, 116.1, 108.5. Anal. Calcd for $C_{13}H_{10}BrNO_2$: C, 53.45; H, 3.45; N, 4.79. Found: C, 53.75; H, 3.36; N, 4.98.

2,4-Dibromophenyl 2-aminobenzoate (3am). Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2m** (139 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3am** (122 mg, 66%). M.p.: 99–101 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13–8.11 (m, 1H), 7.81–7.79 (m, 1H), 7.50–7.48 (m, 1H), 7.37–7.34 (m, 1H), 7.13 (d, J = 8.6 Hz, 1H), 6.74–6.70 (m, 2H), 5.74 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 151.4, 147.6, 135.6, 135.2, 131.7, 131.4, 125.3, 119.3, 117.5, 116.7, 116.5, 108.6. Anal. Calcd for $C_{13}H_9Br_2NO_2$: C, 42.08; H, 2.45; N, 3.78. Found: C, 42.30; H, 2.60; N, 4.06.

4-Chloro-2-methylphenyl 2-aminobenzoate (3an). Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2n** (85 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3an** (92 mg, 71%). M.p.: 61–64 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10–8.07 (m, 1H), 7.37–7.33 (m, 1H), 7.27–7.25 (m, 1H), 7.23–7.20 (m, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.72 (m, 2H), 5.76 (bs, 2H), 2.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 151.2, 147.8, 135.0, 132.4, 131.4, 131.0, 130.8, 126.8, 123.5, 116.7, 116.4, 109.1, 16.1. Anal. Calcd for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; N, 5.35. Found: C, 64.13; H, 4.60; N, 5.09.

2-Allylphenyl 2-aminobenzoate (3ao). Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2o** (81 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford white solid of **3ao** (55 mg, 44%). M.p.: 45–48 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 1H), 7.37–7.21 (m, 4H), 7.15 (d, J = 8.1 Hz, 1H), 6.75–6.71 (m, 2H), 5.98–5.88 (m, 1H), 5.78 (bs, 2H), 5.06–5.01 (m, 2H), 3.36 (d, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 151.2, 148.9, 135.8, 134.8, 132.3, 131.5, 130.3, 127.4, 126.1, 122.6, 116.7, 116.4, 116.3, 109.9, 34.6. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.60; H, 6.05; N, 5.77.

Naphthalen-2-yl 2-aminobenzoate (3ap).[8] Synthesized using GPA from **1a** (81 mg, 0.5 mmol) and **2p** (86 mg, 0.5 mmol) which was then purified by column chromatography using EtOAc/Hexane (1 : 9) to afford yellow solid of **3ap** (65 mg, 50%). M.p.: 121–122 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz, 1H), 7.93–7.82 (m, 3H), 7.65 (s, 1H), 7.54–7.47 (m, 2H), 7.39–7.32 (m, 2H), 6.77–6.71 (m, 2H), 5.80 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 151.2, 148.3, 134.8, 133.7, 131.5, 131.4, 129.3, 127.7, 127.6, 126.4, 125.6, 121.5, 118.8, 116.7, 116.3, 109.5. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.84; H, 5.22; N, 5.49.

Conflicts of interest

There are no conflicts to declare.

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CORRECTION

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Correction: Ruthenium(II)-catalyzed decarbonylative and decarboxylative coupling of isatoic anhydrides with salicylaldehydes: access to aryl 2-aminobenzoates

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The authors regret that there was an error in the affiliations provided. The correct addresses are '[a]Applied Organic Chemistry, Chemical Science & Technology Division, CSIR-North East Institute of Science and Technology, Jorhat-785006, India; E-mail: skgogoi1@gmail.com, sanjibgogoi@neist.res.in and [b]Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India', and the affiliations are as included in this correction.

The Royal Society of Chemistry apologises for these errors and any consequent inconvenience to authors and readers.

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Synthesis

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Abstract:
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Ru(II)-Catalyzed C−H Activation and Alkyne Annulation Reaction of Phenyl Indandiones: Synthesis of Spirobi[indene]diones

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Abstract

A Ru(II)-catalyzed synthesis of spirobi[indene]dione is reported from phenyl indandione and alkyne. This metal-catalyzed cyclization reaction proceeds *via* the hydroxy group directed C(sp^2)-H bond activation, keto-enol tautomerization and alkyne annulation pathways.

Introduction

The spirobi[indene] is a privileged organic scaffold which is found in various biologically important natural products and synthetic compounds (Figure 1).[1] For example, tetrahydro-1,2'-spirobi[indene] is the key scaffold of fredericamycin A (Figure 1),which is an antitumor antibiotic isolated from Streptomyces griseus in 1981.[1a,1e] This compound demonstrates very potent in-vitro cytotoxic activity and promising antitumor activity against various tumor models such as CD8F mammary, B16 melanoma and P388 leukemia. Because of the promising bioactivity and challenging structure of this compound, various routes have been developed for the synthesis of the key scaffold tetrahydro-1,2'-spirobi[indene]. A. V. Rama Rao and co-workers developed a Mn(III)-mediated oxidative free radicalcyclization reaction to construct this scaffold.[2] In 1990, B. Pandey and co-workers developed a photochemical synthesis of this spirocycle *via* the intramolecular hydrogen abstraction and cyclization reaction of an enone.[3] Recently, W. H. Moser and co-workers developed one-pot aldol addition/Brook rearrangement/cyclization type of annulation reaction of arene chromium tricarbonyl for the construction of this trahydro-1,2'-spirobi[indene] scaffold.[4] Furthermore, recently, M. Gravel *et al.* developed one NHC-catalyzed domino Stetter-aldol-Michael (SAM) and Stetter-aldol-aldol (SAA) spiro-cyclization reaction to synthesize this spirocyclic scaffold.[5]

The metal-catalyzed reactions dealing with the C-H bond activation and alkyne annulation have emerged recently as an efficient tool for the efficient synthesis of various heterocyclic and carbocyclic scaffolds.[6] In this regard, keto and enolate-directed metal-catalyzed reaction

plays an important role for the synthesis of many spiro compounds. Lam group described Ru-, Rh- and Pd-catalyzed hydroxyl group assisted spiro-annulation reactions of 2-aryl-1,3-diketones, 4-hydroxy-6-methyl-3-phenyl-2*H*-pyran-2-ones and 4-hydroxy-3-phenylquinolin-2-ones with alkynes (Schemes 1a-c).[6c-e] Gao *et al.* reported a Ru-catalyzed [3+2] spiro-

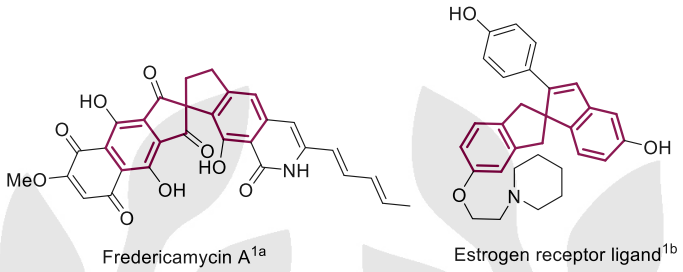
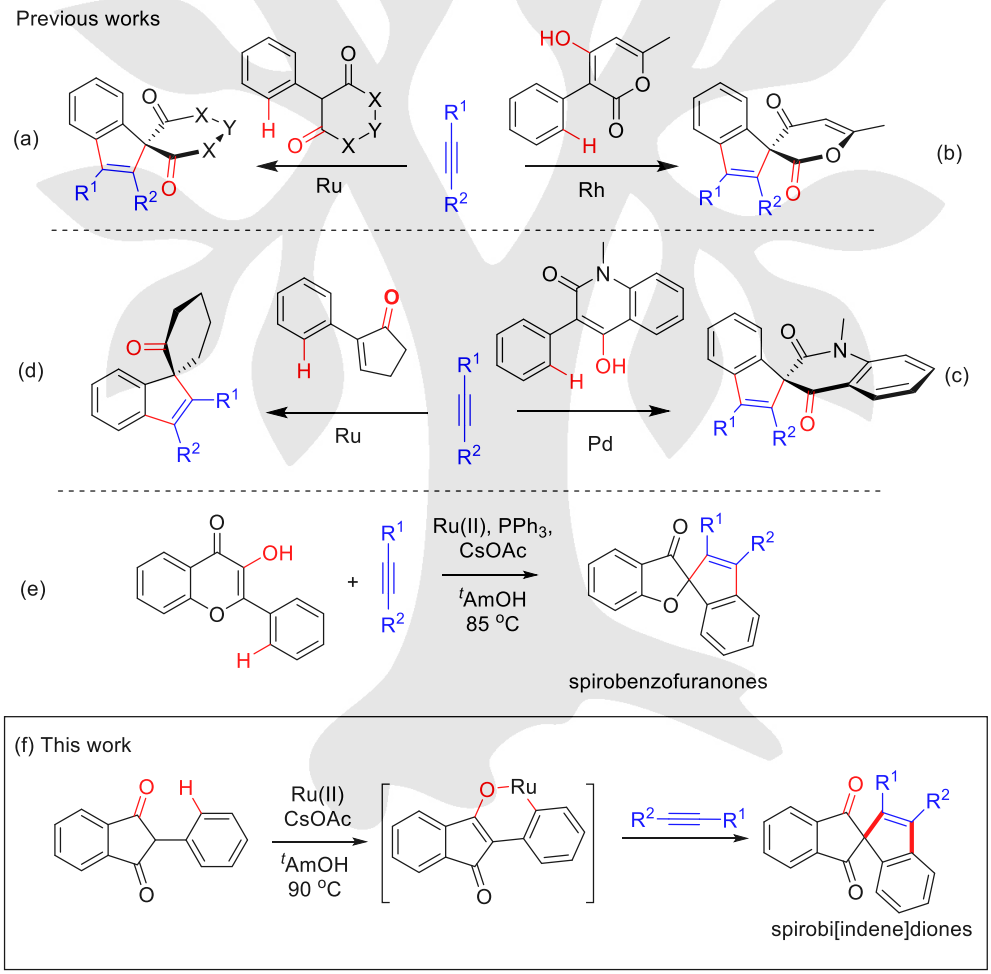


Figure 1. Representative examples of spirobi[indene] containing compounds

annulation reaction of 2-arylcyclo-2-enones with alkynes (Scheme 1d).[6f] Very recently, we have utilized the hydroxy group directed C(sp^2)-H bond activation, keto-enol tautomerization and alkyne annulation reaction of 3-hydroxy-2-phenylchromones for the synthesis of spiro-



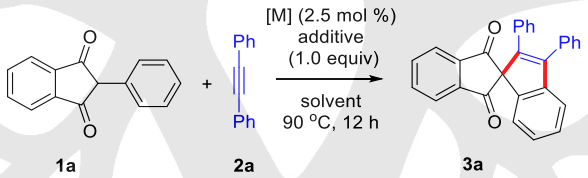
Scheme 1. Hydroxy or keto group directed synthesis of spiro-cycles

benzofuranones (Scheme 1e).[7a] Similarly, the spiro-annulation reaction of phenyl 1,3-indandiones with alkynes would be an effective reaction to construct the important spirobi[indene] scaffold, which is yet not explored. Therefore, in continuation of our effort to develop novel metal-catalyzed reactions,[7] herein we report an *in-situ* formed hydroxy group directed C(sp^2)-H bond activation, keto-enol tautomerization and alkyne annulation reaction of 2-phenyl-indandiones for the synthesis of spirobi[indene] scaffold (Scheme 1f).

Results and discussion

The optimized reaction conditions were determined using 2-phenyl-indandione (**1a**) and alkyne **2a** as the starting materials to synthesize spiro compound **3a** (Table 1). Initial screening of various commonly used metal catalysts revealed [{$RuCl_2$(*p*-cymene)}$_2$] as the best catalyst which afforded 54% yield of **3a** (entry 2). To further improve the yield of the product **3a** some of the additives and solvents were also screened (entries 6-14), which revealed CsOAc and ^{t}AmOH as the best additive and solvent to perform this cyclization

Table 1. Optimization of the reaction conditions for **3a**[a]



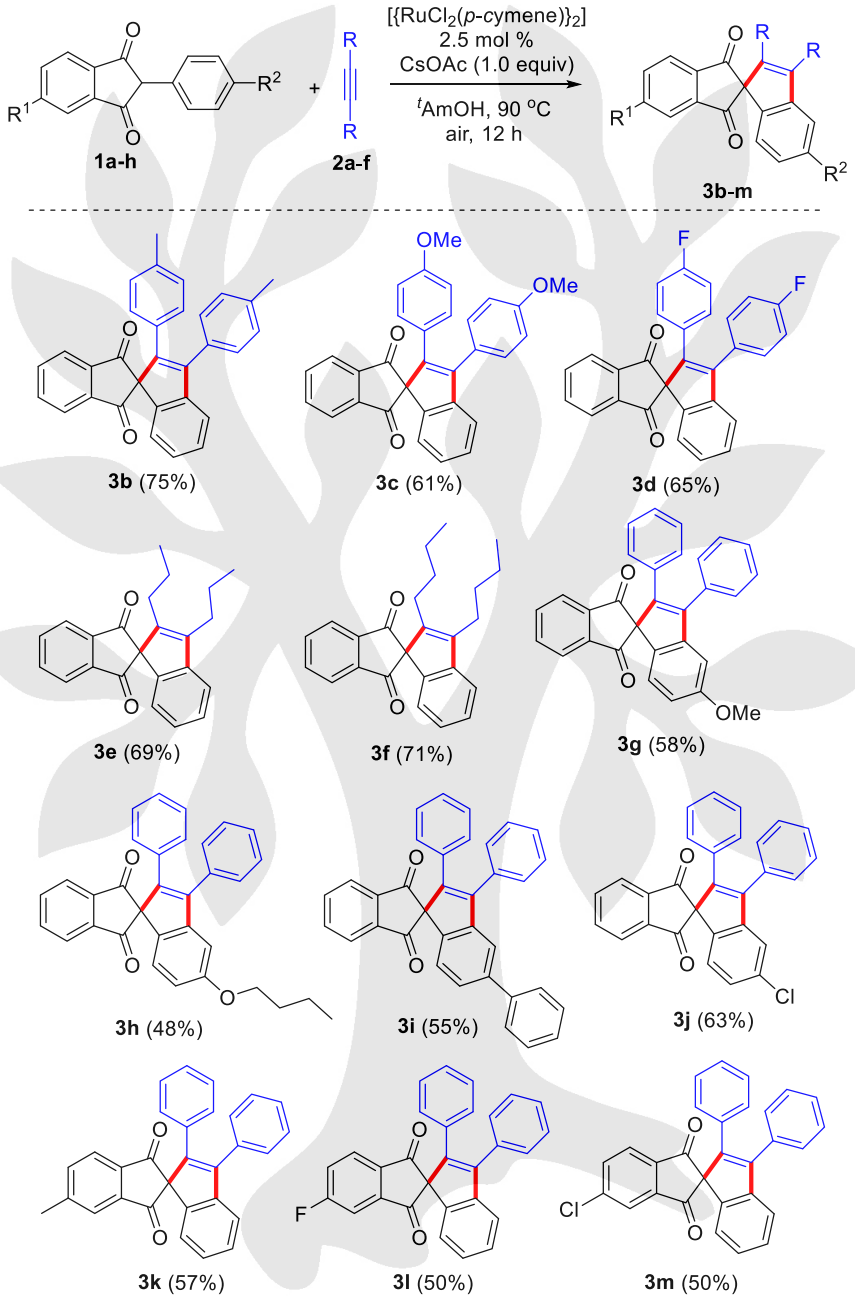
1a **2a** **3a**

entry	catalyst	additive	solvent	**3a** (%)[b]
1	[$RuCl_2(PPh_3)_3$]	$Cu(OAc)_2·H_2O$	^{t}AmOH	0
2	[{$RuCl_2$(*p*-cymene)}$_2$]	$Cu(OAc)_2·H_2O$	^{t}AmOH	54
3	[RhCp*Cl_2]$_2$	$Cu(OAc)_2·H_2O$	^{t}AmOH	17
4	$Pd(OAc)_2$	$Cu(OAc)_2·H_2O$	^{t}AmOH	0
5	$PdCl_2$	$Cu(OAc)_2·H_2O$	^{t}AmOH	0
6	[{$RuCl_2$(*p*-cymene)}$_2$]	CsOAc	^{t}AmOH	78
7	[{$RuCl_2$(*p*-cymene)}$_2$]	NaOAc	^{t}AmOH	19
8	[{$RuCl_2$(*p*-cymene)}$_2$]	AgOAc	^{t}AmOH	31
9	[{$RuCl_2$(*p*-cymene)}$_2$]	Ag_2O	^{t}AmOH	22
10	[{$RuCl_2$(*p*-cymene)}$_2$]	CsOAc	MeCN	52
11	[{$RuCl_2$(*p*-cymene)}$_2$]	CsOAc	1,4-dioxane	48
12	[{$RuCl_2$(*p*-cymene)}$_2$]	CsOAc	DMF	0
13	[{$RuCl_2$(p-cymene)}$_2$]	CsOAc	Toluene	33
14	[{$RuCl_2$(p-cymene)}$_2$]	CsOAc	CH_3OH	58
15[c]	[{$RuCl_2$(*p*-cymene)}$_2$]	CsOAc	^{t}AmOH	77
16[d]	[{$RuCl_2$(*p*-cymene)}$_2$]	CsOAc	^{t}AmOH	42

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (2.5 mol %), additive (0.5 mmol) and solvent (5.0 mL) at 90 °C under air for 12 h. [b]Isolated yields. [c]Catalyst loading (5 mol%). [d]Catalyst loading (1 mol%)

reaction which provided 78% yield of **3a** (entry 6). Furthermore, 5 mol % loading of the catalyst provided 77% yield of **3a** (entry 15), whereas 1 mol % loading of the catalyst provided 42% yield of **3a** (entry 16).

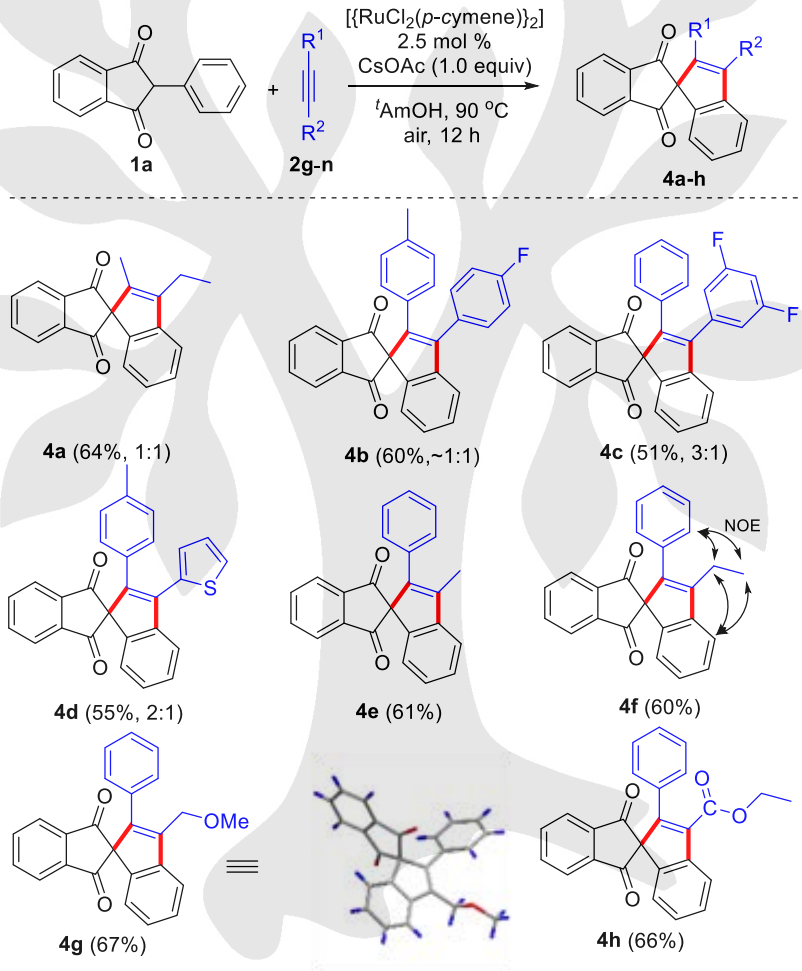
Scheme 2. Scope of phenyl indandiones **1a-h** and with symmetrical alkynes **2a-f**[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), Ru(II) catalyst (2.5 mol %) and CsOAc (0.5 mmol) in ^{t}AmOH (5.0 mL) was heated at 90 °C for 12 h under air.

Then, the highest yielding reaction conditions were used to study the substrate scope of this annulation reaction with phenyl indandiones **1a-h** and various symmetrical alkynes **2a-f** which is shown in Scheme 2. Initially, the symmetric 1,2-diarylethylenes **2b-d** possessing electron-donating groups such as 4-Me, 4-OMe and electron-withdrawing group 4-F were tested with phenyl indandione **1a** to provide 61-75% yields of the spirobi[indene]diones **3b-d**. Similarly, the dialkyl substituted alkynes such as oct-4-yne (**2e**) and dec-5-yne (**2f**) were also tested and these alkynes were also found to be good annulation partner to perform this reaction which provided 69-71% yields of **3e-f**. Next, the possibility of this annulation reaction was tested with some representative indandiones **1b-h** with alkyne **2a.** The 2-phenyl-indandiones **1b-e** bearing substituents such as -OMe, -O^{n}Bu, Ph and Cl at *para*-position of

Scheme 3. Scope of phenyl indandiones **1a** with unsymmetrical alkynes **2g-n**[a]

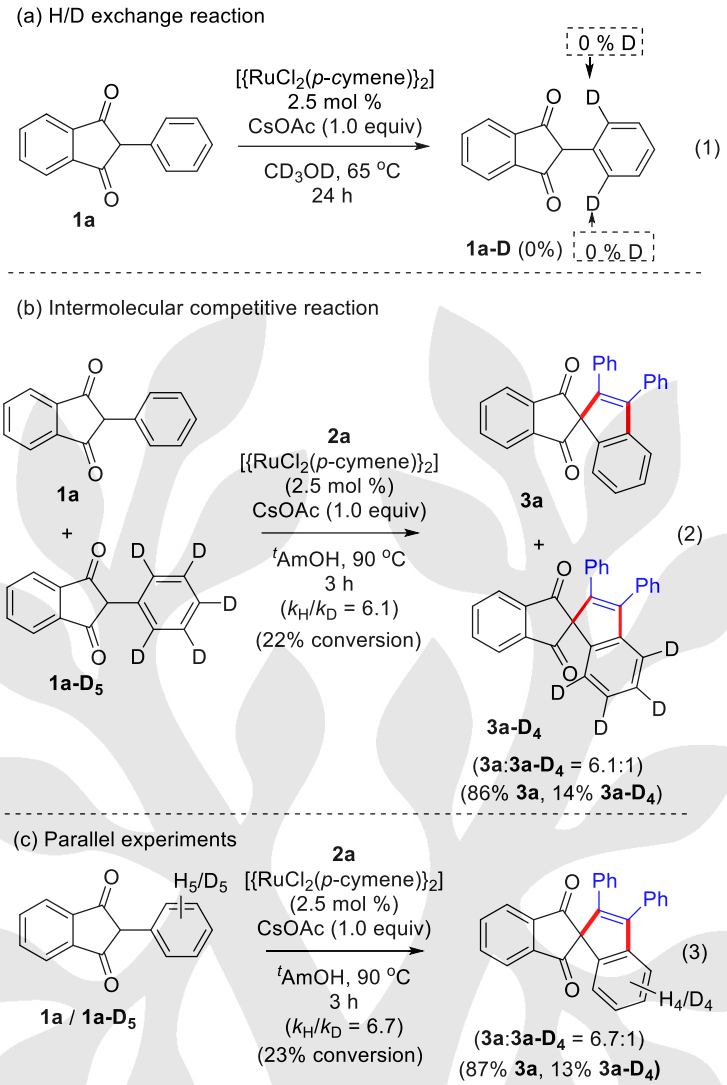


[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), Ru(II) catalyst (2.5 mol %) and CsOAc (0.5 mmol) in ^{t}AmOH (5.0 mL) was heated at 90 °C for 12 h under air.

the substituted phenyl ring of indandione were studied to provide the corresponding spiro compounds **3g-j** in 48-63% yields, respectively. Then, some of the 2-phenyl-indandiones, substituted with electron-releasing methyl substituent **1f** and electron-withdrawing fluoro, chloro substituents **1g-h** on the fused aromatic ring of 2-phenyl-indandione, were studied with alkyne **2a** to afford 50-57% yields of the spiro compounds **3k-m**.

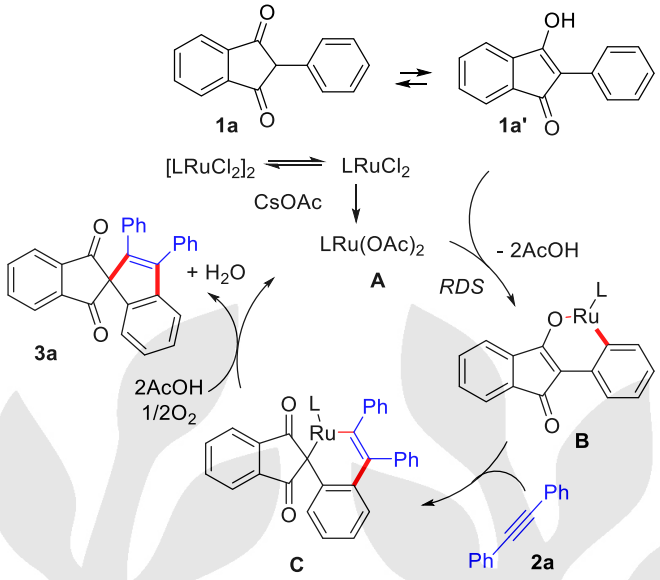
Further, generalization of the reaction was explored with unsymmetrically substituted alkynes **2g-n** (Scheme 3). The unsymmetrically substituted alkynes *i.e.* pent-2-yne (**2g)** and 1-fluoro-4-(*p*-tolylethynyl)benzene (**2h**) afforded a mixture of two regioisomers **4a** and **4b** in ~1:1 ratio with **1a**. Similarly, reaction of **1a** with alkynes such as 1,3-difluoro-5-(phenylethynyl)benzene (**2i**) or heteroaryl substituent 2-(*p*-tolylethynyl)thiophene (**2j**) provided mixture of regioisomers **4c** (3:1) and **4d** (2:1) with 51-60% yields (identity of major isomers is not known). In contrast, the unsymmetrically substituted arylalkylacetylenes such as prop-1-yn-1-ylbenzene (**2k**) and but-1-yn-1-ylbenzene (**2l**) provided the regioselective products **4e-4f** in 60-62% yields. Finally, the alkynes (3-methoxyprop-1-yn-1-yl)benzene (**2m**) and ethyl 3-phenylpropiolate (**2n)** was examined with **1a** to afford the spiro-compound **4g-h**[6g] in 66-70% yields. The annulation pattern of these unsymmetrical alkynes **2k-n** is similar to the reported metal-catalyzed spiro-cyclization reactions, where the sterically hindered phenyl substituent occupies the 2-position of the 1,2'-spirobi[indene]-1',3'-dione scaffold.[6c-g] The regioselectivity of the spiro compounds **4e-g** were proved by NOE interaction of ethyl protons of compound **4f** with the neighboring aromatic protons (Scheme 3). The structure of the spiro compounds was determined by analyzing the NMR spectra and confirmed by the single X-ray crystallography studies of compound **4g**.[8] The reaction of **1a** with phenylacetylene and 1-phenyl-2-trimethylsilylacetylene were unsuccessful under the reaction conditions. This hydroxyl directed Ru-catalyzed C-H activation and alkyne reaction provided only the *ortho*-C-H activation product because of the formation of stable six membered Ru-complex and *para*-C-H activation product was not observed.

To gain an insight into mechanism, we have done a series of isotopically labelling experiments as shown in Scheme 4. The H/D exchanged reaction of **1a** could not provide the H/D exchanged compound **1a-D** (Scheme 4, eq 1), which indicates the non-reversible C-Ru bond formation, however, Lam *et al.* reported a reversible cycloruthenation on similar substrate.[6c] The intermolecular competitive reaction between **1a** and **1a-D$_5$** with alkyne **2a** provided k_H/k_D= 6.1 (Scheme 4, eq 2).[9] Again, the competitive parallel reactions of **1a** and **1a-D$_5$** with alkyne **2a** afforded k_H/k_D= 6.7 (Scheme 4, eq 3).[9] A KIE of this magnitude suggests that the C-H bond cleavage could be involved in the rate determining step.[9]



Scheme 4. Isotopically labelling experiments

Based on the literature reports,[6c-d,7a] the probable mechanism for the formation of spiro compound **3a** is proposed (Scheme 5). The hydroxy group directed Ru(II)-catalyzed activation of C-H bond of in-situ formed compound **1a′** affords a six-membered Ru(II) complex **B**, which on subsequent metal alkyne coordination and alkyne insertion in Ru-C bond affords Ru(II) complex **C**. Reductive elimination of the metal finally affords compound **3** and Ru(0) is reoxidized to active metal complex **A** with the help of molecular oxygen and AcOH.[10]



Scheme 5. Possible mechanism

In conclusion, an unprecedented Ru(II)-catalyzed alkyne annulation reaction of 2-phenyl-indandione is developed. This reaction has opened up a new efficient route for the construction of the spirobi[indene] scaffold which is the key motif of the antitumor antibiotic fredericamycin A as well as some other pharmaceutically important compounds.

EXPERIMENTAL SECTIONS

General Information. Melting points were measured with a Buchi B-540 melting point apparatus and are uncorrected. NMR spectra were recorded on Bruker Avance III 500 MHz FTNMR spectrometer using tetramethylsilane (TMS) as an internal standard. All the commercially available regents were used as received. All experiments were monitored by thin layer chromatography. TLC was performed on Merck TLC Silica gel 60 F254 precoated plates. Column chromatography was performed on silica gel (100-200 mesh, Merck). The starting 2-phenylindandiones were synthesized using acetic anhydride, phenylacetic acid and phthalic anhydride by following a known procedure.[11]

General procedure A (GPA). A mixture of 2-phenylindandione (**1**, 0.5 mmol), alkyne (**2**, 0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), CsOAc (0.5 mmol) in ^{t}AmOH (5.0 mL) was stirred at 90 ^{o}C under open air for 12 hours. The solvent was removed under vacuo and the crude reaction mixture was poured into water and extracted with dichloromethane (20 mL x 2). The dichloromethane layer was then washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under vacuo. The crude product thus obtained was

purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane as the eluent to afford **3**.

Synthesis of deuterated 2-phenylindandione 1a-d$_5$.[12] A mixture of 2-diazo-1,3-indandione (344 mg, 2.0 mmol) and rhodium acetate (44 mg, 5 mol %) in deuterated benzene (2 mL) was refluxed for 10 hours. The reaction mixture was cooled to room temperature and the solvent was removed under vacuo. The crude product thus obtained was purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane (1:9) as the eluent to afford **1a-d$_5$** (345 mg, 76%).

Isotopically labelling experiments

(a) **H/D Exchange reaction:** A solution of 2-phenylindandione **1a** (111 mg, 0.5 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (8 mg, 2.5 mol %), and CsOAc (96 mg, 0.5 mmol) in CD_3OD (5.0 mL) was stirred at 65 ºC for 24 hours. The solvent was evaporated and the crude product obtained was purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane (1:9) as the eluent. The H/D exchange was found to be 0% at the protons attached to C-2′ and C-6′ of the phenyl ring of recovered **1a**.

(b) **Intermolecular competition experiment**: A mixture of 2-phenylindandione **1a** (111 mg, 0.5 mmol), **1a-D$_5$** (114 mg, 0.5 mmol), alkyne **2a** (107 mg, 0.6 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (2.5 mol %) and CsOAc (96 mg, 0.5 mmol) in ^{t}AmOH (5.0 mL) was stirred at 90 ºC for 3 hours. The solvent was removed under vacuo and the crude reaction mixture was purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane (1:9) as the eluent to provide a mixture of **3a** and **3a**-D$_4$. The ratio of **3a** and **3a-d$_4$** was determined to be 6.1:1 by ^{1}H NMR integration method (k_H/k_D = 6.1).

(c) **Parallel competition experiments**: A mixture of **1a** (111 mg, 0.5 mmol), alkyne **2a** (89 mg, 0.5 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (8 mg, 2.5 mol %) and CsOAc (96 mg, 0.50 mmol) in ^{t}AmOH (5.0 mL) was stirred at 90 ºC for 3 hours. At the same time, a solution of **1a-D$_5$** (114 mg, 0.5 mmol), alkyne **2a** (89 mg, 0.5 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (8 mg, 2.5 mol %) and CsOAc (96 mg, 0.50 mmol) in ^{t}AmOH (5.0 mL) was stirred at 90 ºC in another round bottom flask for 3 hours. The reaction mixtures were combined, solvent was removed and the residue was purified by silica gel (100-200 mesh) column

chromatography using EtOAc/Hexane (1:9) as the eluent to afford a mixture of **3a** and **3a-D$_4$** (**3a**:**3a-D$_4$** = 6.7:1, k_H/k_D = 6.7).

Compound Characterizations.

2,3-Diphenyl-1,2'-spirobi[indene]-1',3'-dione (3a). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3a** (155 mg, 78%). M.p.: 160 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11-8.09 (m, 2H), 7.94-7.92 (m, 2H), 7.46-744 (m, 2H), 7.38-7.31 (m, 5H), 7.12 (t, J = 7.0 Hz, 1H), 7.05-6.99 (m, 5H), 6.81 (d, J = 7.0 Hz, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 146.5, 145.9, 143.4, 143.3, 141.0, 136.0, 134.4, 134.0, 129.5, 128.8, 128.4, 128.3, 128.1, 127.8, 127.4, 126.2, 124.2, 121.7, 121.2, 75.6. IR (KBr) 2913, 1721, 1557, 1443, 1215, 1130, 1035, 713 cm^{-1}. HRMS (+ESI) Calcd for $C_{29}H_{19}O_2$ $[M+H]^+$: 399.1380; found: 399.1385.

2,3-di-*p*-Tolyl-1,2'-spirobi[indene]-1',3'-dione (3b). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2b** (103 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3b** (160 mg,75%). M.p.: 210 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10-8.07 (m, 2H), 7.91 (dd, J = 5.5, 3.0 Hz, 2H), 7.37-7.33 (m, 3H), 7.28 (t, J = 8.0 Hz 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.07 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 7.5 Hz, 1H), 2.37 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 146.3, 145.9, 143.5, 143.3, 140.6, 137.4, 137.1, 136.0, 131.6, 131.1, 129.4, 129.2, 129.0, 128.6, 128.3, 126.0, 124.2, 121.6, 121.1, 75.6, 21.3, 21.0. IR (KBr) 2919, 1716, 1567, 1460, 1226, 1155, 1100, 717 cm^{-1}. HRMS (+ESI) Calcd for $C_{31}H_{23}O_2$ $[M+H]^+$: 427.1704; found: 427.1698.

2,3-bis(4-Methoxyphenyl)-1,2'-spirobi[indene]-1',3'-dione (3c). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2c** (119 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:5) to afford yellow solid of **3c** (140 mg, 61%). M.p.: 100 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11-8.09 (m, 2H), 7.93-7.92 (m, 2H), 7.40-7.37 (m, 3H), 7.29 (t, J = 7.5 Hz, 2H), 7.08 (t, J = 7.5 Hz, 1H), 6.92 (t, J = 9.0 Hz, 3H), 6.77 (d, J = 7.5 Hz, 1H), 6.57 (d, J = 8.5 Hz, 2H), 3.83 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 159.0, 158.6, 146.3, 145.1, 143.4, 143.2, 140.0, 136.0, 130.7, 130.0, 128.3, 126.9, 126.3, 125.9, 124.2, 121.4, 121.1, 113.8, 113.6, 75.6, 55.1, 54.9. IR (KBr)

2919, 1723, 1581, 1430, 1259, 769 cm^{-1}. Anal. calcd of $C_{31}H_{22}O_4$ for C, 81.21; H, 4.84; found: C, 81.52; H, 4.92.

2,3-bis(4-Fluorophenyl)-1,2'-spirobi[indene]-1',3'-dione (3d). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2d** (107 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford yellow solid of **3d** (141 mg, 65%). M.p.: 150 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11-8.09 (m, 2H), 7.95-7.93 (m, 2H), 7.42-7.38 (m, 2H), 7.37-7.30 (m, 2H), 7.13 (t, J = 7.5 Hz, 1H), 7.10-7.04 (m, 2H), 7.01- 6.97 (m, 2H), 6.81 (d, J = 7.5 Hz, 1H), 6.76 (t, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 162.2 (d, ^1J = 246.3 Hz), 161.9 (d, ^1J = 247.5 Hz), 145.7, 145.4, 143.4, 143.1, 140.1, 136.2, 131.2 (d, ^3J = 7.5 Hz), 129.5 (d, ^4J = 2.5 Hz), 130.3 (d, ^4J = 3.5 Hz), 130.7 (d, ^3J = 8.8 Hz), 129.5, 128.5, 126.5, 124.3, 121.4 (d, ^2J = 23.8 Hz), 121.3, 115.6 (d, ^2J = 21.3 Hz), 115.4, 75.7. IR (KBr) 3140, 2918, 1743, 1713, 1587, 1437, 1225, 710 cm^{-1}. HRMS (+ESI) Calcd for $C_{29}H_{17}F_2O_2[M+H]^+$: 435.1196; found: 435.1197.

2,3-Dipropyl-1,2'-spirobi[indene]-1',3'-dione (3e). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2e** (55 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3e** (114 mg, 69%). M.p.: 100 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12-8.11 (m, 2H), 7.96-7.94 (m, 2H), 7.31-7.25 (m, 2H), 6.99 (t, J = 7.0 Hz, 1H), 6.67 (d, J = 7.5 Hz, 1H), 2.61 (t, J = 7.5 Hz, 2H), 2.26 (t, J = 8.0 Hz, 2H), 1.71 (q, J = 7.5 Hz, 2H), 1.27-1.22 (m, 2H), 1.03 (t, J = 7.5 Hz, 3H), 0.81 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 146.7, 144.8, 143.3, 143.2, 141.3, 136.0, 128.0, 125.1, 123.9, 120.8, 119.7, 74.5, 29.6, 27.6, 22.5, 21.9, 14.2, 14.1. IR (KBr) 1740, 1711, 1584, 1430 cm^{-1}. HRMS (+ESI) Calcd for $C_{23}H_{23}O_2$ $[M+H]^+$: 331.1695; found: 331.1698.

2,3-Dibutyl-1,2'-spirobi[indene]-1',3'-dione (3f). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2f** (55 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3f** (127 mg, 71%). M.p.: 120 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05-8.04 (m, 2H), 7.89-7.87 (m, 2H), 7.23-7.18 (m, 2H), 6.92 (t, J = 7.0 Hz, 1H), 6.62 (d, J = 7.5 Hz, 1H), 2.54 (t, J = 7.5 Hz, 2H), 2.19 (t, J = 6.5 Hz, 2H), 1.59-1.54 (m, 4H), 1.40 (q, J = 7.5 Hz, 2H), 1.18-1.13 (m, 2H), 0.90 (t, J = 7.0 Hz, 3H), 0.68 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 146.7, 144.8, 143.3, 143.2, 141.2, 135.9, 128.0, 125.0, 123.9, 120.9, 119.6, 74.5, 31.2, 30.8, 27.1, 25.4, 22.8, 22.7,

13.9, 13.6. IR (KBr) 2915, 2855, 1743, 1716, 1586, 1480, 1431, 1241 cm^{-1}. HRMS (+ESI) Calcd for $C_{25}H_{27}O_2$ $[M+H]^+$: 359.2006; found: 359.2011.

5-Methoxy-2,3-diphenyl-1,2'-spirobi[indene]-1',3'-dione (3g). Synthesized using GPA from **1b** (126 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:4) to afford white solid of **3g** (124 mg, 58%). M.p.: 182 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10-8.08 (m, 2H), 7.93-7.91 (m, 2H), 7.45-7.43 (m, 2H), 7.39-7.33 (m, 3H), 7.05-6.97 (m, 5H), 6.93 (s, 1H), 6.71 (d, J = 8.5 Hz, 1H), 6.66-6.63 (m, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 160.3, 147.6, 146.4, 143.4, 142.3, 136.1, 135.8, 134.4, 133.9, 129.5, 128.9, 128.6, 128.2, 127.9, 127.5, 124.2, 121.9, 111.9, 107.7, 75.0, 55.6. IR (KBr) 2922, 1715, 1584 cm^{-1}. HRMS (+ESI) Calcd for $C_{30}H_{21}O_3$ $[M+H]^+$: 429.1496; found: 429.1491.

5-Butoxy-2,3-diphenyl-1,2'-spirobi[indene]-1',3'-dione (3h). Synthesized using GPA from **1c** (147 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford thick gum of **3ca** (113 mg, 48%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.10-8.08 (m, 2H), 7.93-7.91 (m, 2H), 7.45-7.43 (m, 2H), 7.39-7.33 (m, 3H), 7.05-6.97 (m, 5H), 6.92-6.91 (m, 1H), 6.70-6.68 (m, 1H), 6.64-6.62 (m, 1H), 3.90 (t, J = 6.4 Hz, 2H), 1.74-1.69 (m, 2H), 1.47-1.42 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 159.9, 147.5, 146.4, 143.4, 142.1, 136.0, 135.6, 134.5, 134.0, 129.5, 128.8, 128.7, 128.5, 128.2, 127.8, 127.4, 124.2, 121.8, 112.3, 108.4, 74.9, 67.9, 31.2, 19.2, 13.8. IR ($CHCl_3$) 2911, 2859, 1744, 1710, 1585 cm^{-1}. HRMS (+ESI) Calcd for $C_{33}H_{27}O_3$ $[M+H]^+$: 471.1955; found: 471.1960.

2,3,5-Triphenyl-1,2'-spirobi[indene]-1',3'-dione (3i). Synthesized using GPA from **1d** (149 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3i** (130 mg, 55%). M.p.: 180 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13-811 (m, 2H), 7.94-7.92 (m, 2H), 7.57 (s, 1H), 7.52-7.47 (m, 4H), 7.41-7.31 (m, 8H), 7.05-7.02 (m, 4H), 6.88 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 146.7, 146.5, 143.5, 142.4, 142.0, 141.7, 141.2, 136.2, 134.4, 133.9, 129.6, 128.9, 128.7, 128.6, 128.3, 127.6, 127.5, 127.4, 125.5, 124.3, 121.5, 120.7, 75.5. IR (KBr) 2917, 1716, 1587, 1439, 1099 cm^{-1}. Anal. calcd for $C_{35}H_{22}O_2$: C, 88.58; H, 4.67; found: 88.87; H, 4.87.

5-Chloro-2,3-diphenyl-1,2'-spirobi[indene]-1',3'-dione (3j). Synthesized using GPA from **1e** (128 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3j** (136 mg, 63%). M.p.: 172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.09 (m, 2H), 7.95-7.92 (m, 2H), 7.44-7.34 (m, 6H), 7.11-6.97 (m, 6H), 6.75 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 147.9, 145.6, 143.3, 142.7, 141.5, 136.3, 134.7, 133.9, 133.3, 129.4, 129.0, 128.8, 128.7, 128.3, 128.1, 127.8, 126.2, 124.4, 122.2, 121.9, 75.2. IR (KBr) 1714, 1588, 1442, 1233, 729 cm^{-1}. Anal.calcd for $C_{29}H_{17}ClO_2$: C, 80.46; H, 3.96; found: C, 80.78; H, 4.01.

5'-Methyl-2,3-diphenyl-1,2'-spirobi[indene]-1',3'-dione (3k). Synthesized using GPA from **1f** (118 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3k** (117 mg, 57%). M.p.: 182 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.0 Hz, 2H), 7.39-7.28 (m, 5H), 7.09 (t, J = 7.5 Hz, 1H), 7.04-7.02 (m, 5H), 6.81 (d, J = 7.5 Hz, 1H), 2.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 197.9, 148.0, 146.5, 146.1, 144.0, 143.6, 141.5, 141.1, 137.4, 134.6, 134.1, 129.6, 128.9, 128.5, 128.4, 128.3, 127.9, 127.5, 126.3, 124.3, 124.2, 121.7, 121.3, 76.1, 22.3. IR (KBr) 2920, 1702, 1591, 1461, 1252, 1041 cm^{-1}. HRMS (+ESI) Calcd for $C_{30}H_{21}O_2$ $[M+H]^+$: 413.1539; found: 413.1542.

5'-Fluoro-2,3-diphenyl-1,2'-spirobi[indene]-1',3'-dione (3l). Synthesized using GPA from **1g** (128 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3l** (100 mg, 48%). M.p.: 166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.10 (m, 1H), 7.71 (dd, J = 7.0, 2.5 Hz, 1H), 7.60 (t, J = 8.5 Hz, 1H), 7.45-7.42 (m, 2H), 7.40-7.31 (m, 5H), 7.15-7.11 (m, 1H), 7.07 -7.03 (m, 3H), 7.00-6.98 (m, 2H), 6.83 (d, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 196.5, 168.7 (d, ^{1}J = 260.9 Hz), 146.7, 146.1 (d, $^{3'}J$ = 9.0 Hz), 146.0, 143.1, 140.6, 139.8, 134.3, 133.7, 129.5, 128.9, 128.7, 128.6, 128.2, 127.9, 127.5, 126.9 (d, ^{3}J = 10.0 Hz), 126.5, 124.3 (d, $^{2'}J$ = 23.8 Hz), 121.9, 121.3, 110.7 (d, ^{2}J = 22.7 Hz), 76.0. IR (KBr) 2922, 1705, 1546, 1461, 1256 cm^{-1}. HRMS (+ESI) Calcd for $C_{29}H_{18}FO_2$ $[M+H]^+$: 417.1288; found: 417.1291.

5'-Chloro-2,3-diphenyl-1,2'-spirobi[indene]-1',3'-dione (3m). Synthesized using GPA from **1h** (128 mg, 0.5 mmol) and **2a** (89 mg, 0.5 mmol). The crude product was purified by

column chromatography using EtOAc/Hexane (1:9) to afford white solid of **3m** (108 mg, 50%). M.p.: 168 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-8.03 (m, 2H), 7.88-7.86 (m, 1H), 7.45-7.30 (m, 8H), 7.12 (t, J = 7.5 Hz, 1H), 7.07-7.05 (m, 2H), 7.00-6.97 (m, 2H), 6.82 (d, J = 7.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 197.0, 146.8, 146.0, 144.7, 143.3, 143.1, 141.6, 140.7, 136.4, 134.3, 133.8, 129.5, 128.8, 128.6, 128.5, 128.3, 127.9, 127.6, 126.4, 125.5, 124.2, 121.9, 121.3, 75.8. IR (KBr) 1714, 1586, 1455, 1342, 1267 cm^{-1}. Anal.calcd for $C_{29}H_{17}ClO_2$: C, 80.46; H, 3.96; found: C, 80.88; H, 4.18.

3-Ethyl-2-methyl-1,2'-spirobi[indene]-1',3'-dione and 2-ethyl-3-methyl-1,2'-spirobi[indene]-1',3'-dione (4a, 1:1 mixture of isomers). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2g** (34 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **4a** (92 mg, 64%). M.p.: 135 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.10 (m, 2H), 7.95-7.93 (m, 2H), 7.31-7.26 (m, 2H), 7.02-6.99 (m, 1H), 6.78-6.66 (m, 1H), 2.62 (q, J = 7.5 Hz, 1H), 2.33 (q, J = 7.7 Hz, 1H), 2.18 (s, 1.5H), 1.80 (s, 1.5H), 1.24 (t, J = 7.6 Hz, 1.5H), 0.92 (t, J = 7.7 Hz, 1.5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 199.3, 147.4, 146.6, 145.7, 143.5, 143.3, 142.8, 142.7, 142.4, 139.9, 136.1, 136.0, 135.9, 128.2, 128.1, 125.2, 124.9, 124.0, 123.9, 121.1, 120.6, 119.4, 75.0, 20.4, 18.6, 13.4, 13.2, 11.3, 10.6. IR (KBr) 2976, 2925, 2853, 1702, 1590, 1455, 1338, 1253 cm^{-1}. HRMS (+ESI) Calcd for $C_{20}H_{17}O_2$ $[M+H]^+$: 289.1227; found: 289.1229.

3-(4-Fluorophenyl)-2-(*p*-tolyl)-1,2'-spirobi[indene]-1',3'-dione and 2-(4-fluorophenyl)-3-(*p*-tolyl)-1,2'-spirobi[indene]-1',3'-dione (4b, 1:1). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2i** (105 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford yellow solid of **4b** (125 mg, 58%). M.p.:142 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.09 (m, 2H), 7.95-7.93 (m, 2H), 7.45-7.39 (m, 1.5H), 7.34-7.29 (m, 2.5H), 7.18 (d, J = 8.2 Hz, 1H), 7.13-7.05 (m, 2H), 7.02-6.98 (m, 1H), 6.89-6.84 (m, 2H), 6.81-6.73 (m, 2H), 2.38 (s, 1.5H), 2.17 (s, 1.5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 162.2 (d, ^1J = 245.0 Hz), 146.8, 145.9, 145.0, 144.6, 143.5, 143.3, 141.2, 139.4, 137.7, 137.4, 136.1, 136.0, 131.2 (d, ^3J = 8.8 Hz), 130.6 (d, ^3J = 8.8 Hz), 130.1, 130.0, 129.9, 129.3, 129.2, 129.0, 128.5, 128.3, 126.2, 124.2 (d, ^4J = 2.5 Hz), 121.8, 121.4, 121.2, 115.5 (d, ^2J = 21.3 Hz), 115.2 (d, ^2J = 21.3 Hz), 75.8, 75.6, 21.3, 21.1. IR (KBr) 2937, 1743, 1701, 1586, 1461, 1342, 1251 cm^{-1}. Anal. calcd for $C_{30}H_{19}FO_2$: C, 83.70; H, 4.45; found: C, 83.78; H, 4.56.

3-(3,5-Difluorophenyl)-2-(*p*-tolyl)-1,2'-spirobi[indene]-1',3'-dione and 2-(3,5-difluorophenyl)-3-(*p*-tolyl)-1,2'-spirobi[indene]-1',3'-dione (4c, 3:1). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2i** (119 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid compound of **4c** (114 mg, 51%). M.p.: 160 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16-8.12 (m, 1.5H), 8.12-8.08 (m, 0.5H), 7.99-7.96 (m, 1.5H), 7.95-7.92 (m, 0.5H), 7.42-6.95 (m, 7H), 6.88 (s, 1H), 6.82-6.75 (m, 1H), 6.56-6.48 (m, 2H), 2.40 (s, 2.25H), 2.19(s, 0.75H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 197.6, 162.5 (d, ^{1}J = 247.5 Hz), 162.4 (d, ^{1}J = 247.5Hz), 148.6, 145.3, 143.5, 143.3, 143.1, 138.2, 136.3, 136.1, 130.0, 129.5, 129.4, 129.2, 129.1, 128.7, 128.5, 128.4, 126.8, 124.4, 124.3, 122.1, 111.8 (d, ^{2}J = 19.4 Hz), 111.7 (d, ^{2}J = 18.8 Hz), 103.1, 102.9, 102.7, 21.3, 21.0. IR (KBr) 2937, 1717, 1590, 1460, 1252 cm^{-1}. Anal. calcd for $C_{29}H_{16}F_2O_2$: C, 80.18; H, 3.71; found: C, 80.23; H, 3.89.

3-(Thiophen-2-yl)-2-(*p*-tolyl)-1,2'-spirobi[indene]-1',3'-dione and 2-(thiophen-2-yl)-3-(*p*-tolyl)-1,2'-spirobi[indene]-1',3'-dione (4d, 2:1). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2j** (99 mg, 0.5 mmol).The crude product was purified by using EtOAc/Hexane (1:4) to afford brown solid of compound **4d** (115 mg, 55%). M.p.: 160 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22-7.68 (m, 4H), 7.47-7.30 (m, 4H), 7.23-6.42 (m, 7H), 2.49 (s, 2H), 2.21 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 197.6, 146.6, 145.9, 145.4, 143.6, 143.4, 142.6, 138.4, 137.8, 136.8, 136.3, 136.2, 134.9, 134.2, 130.9, 129.8, 129.6, 129.2, 129.1, 128.7, 128.6, 128.0, 127.0, 126.4, 126.3, 126.1, 124.6, 124.3, 121.9, 121.6, 121.5, 120.9, 76.0, 21.6, 21.3. IR (KBr) 2918, 2850, 1711, 1589, 1459, 1257, 1099, 882 cm^{-1}. HRMS (+ESI) Calcd for $C_{28}H_{19}O_2S$ $[M+H]^+$: 419.1102; found: 419.1106.

3-Methyl-2-phenyl-1,2′-spirobi[indene]-1′,3′-dione (4e). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2k** (58 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **4e** (102 mg, 61%). M.p.: 140 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05-8.03 (m, 2H), 7.88-7.85 (m, 2H), 7.40 (d, J = 7.0 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.24-7.15 (m, 5H), 7.08 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 146.9, 143.4, 143.1, 142.4, 140.0, 135.9, 134.7, 128.6, 128.4, 128.3, 127.4, 126.1, 124.0, 120.9, 120.4, 75.5, 11.9. IR (KBr) 2957, 1727, 1593, 1415, 1253, 1071 cm^{-1}. Anal. calcd for $C_{24}H_{16}O_2$: C, 85.69; H, 4.79; found: C, 85.41; H, 4.62.

3-Ethyl-2-phenyl-1,2'-spirobi[indene]-1',3'-dione (4f). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2l** (65 mg, 0.5 mmol).The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of compound **4f** (105 mg, 60%). M.p.: 139 ºC.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.01 (m, 2H), 7.86-7.83 (m, 2H), 7.45 (d, J = 7.5 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.22-7.17 (m, 5H), 7.08 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 2.64 (q, J = 8.0 Hz, 2H), 1.30 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 148.3, 146.1, 143.6, 143.5, 139.8, 135.9, 134.9, 128.7, 128.3, 128.2, 127.5, 125.9, 123.9, 121.2, 120.6, 75.7, 19.5, 13.8. IR (KBr) 2967, 2931, 1707, 1596, 1465, 1442, 1257, 1074, 1023, 768 cm^{-1}. Anal. calcd for $C_{25}H_{18}O_2$: C, 85.69; H, 5.18; found: C, 85.72; H, 5.05.

3-Methoxy-2-phenyl-1,2'-spirobi[indene]-1',3'-dione (4g). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2m** (73 mg, 0.5 mmol).The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford white solid of **4g** (122 mg, 67%). M.p.: 115 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-804 (m, 2H), 7.91-7.88 (m, 2H), 7.66 (d, J = 7.5 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.24-7.21 (m, 3H), 7.19-7.16 (m, 2H), 7.10 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 4.51 (s, 2H), 3.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 145.1, 144.1, 143.5, 143.1, 142.5, 136.0, 135.6, 133.9, 130.4, 128.7, 128.4, 128.0, 127.5, 126.2, 124.1, 123.7, 121.8, 121.0, 76.0, 66.2, 57.8. IR (KBr) 2962, 1709, 1592, 1461, 1252, 763 cm^{-1}. Anal. calcd for $C_{25}H_{18}O_3$: C, 81.95; H, 4.95; found: C, 82.01; H, 4.97.

Ethyl-1',3'-dioxo-2-phenyl-1',3'-dihydro-1,2'-spirobi[indene]-3-carboxylate (4h). Synthesized using GPA from **1a** (111 mg, 0.5 mmol) and **2n** (87 mg, 0.5 mmol). The crude product was purified by column chromatography using EtOAc/Hexane (1:9) to afford yellow solid of **3an** (126 mg, 64%). M.p.: 125 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.88 (m, 2H), 7.75-7.73 (m, 2H), 7.65-7.63 (m, 2H), 7.40-7.33 (m, 3H), 7.15-7.11 (m, 2H), 7.04-7.01 (m, 2H), 3.88 (q, J = 7.0 Hz, 2H), 0.95 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 165.1, 155.2, 141.6, 137.3, 136.0, 133.5, 129.0, 128.6, 128.5, 127.6, 127.5, 126.5, 123.8, 71.0, 60.1, 13.7. IR (KBr) 2932, 1717, 1592, 1462, 1255 cm^{-1}. Anal. calcd for $C_{26}H_{18}O_4$: C, 79.17; H, 4.60; found: C, 79.25; H, 4.68.

ASSOCIATED CONTENT

Electronic supplementary information (ESI) available: Copies of ^{1}H NMR, ^{13}C NMR, NOE and HRMS spectrum of the synthesized compounds. See DOI:

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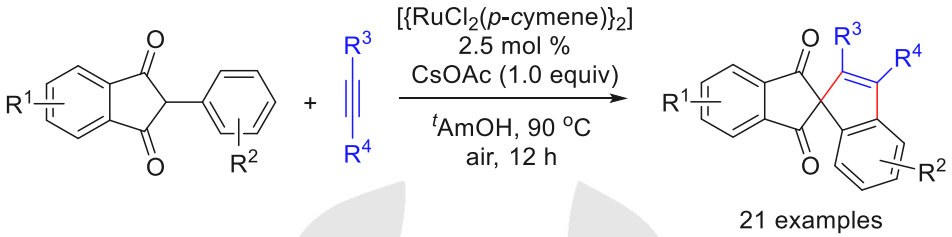

Ru(II)-Catalyzed C-H Activation and Alkyne Annulation Reaction of Phenyl Indandiones: Synthesis of Spirobi[indene]diones

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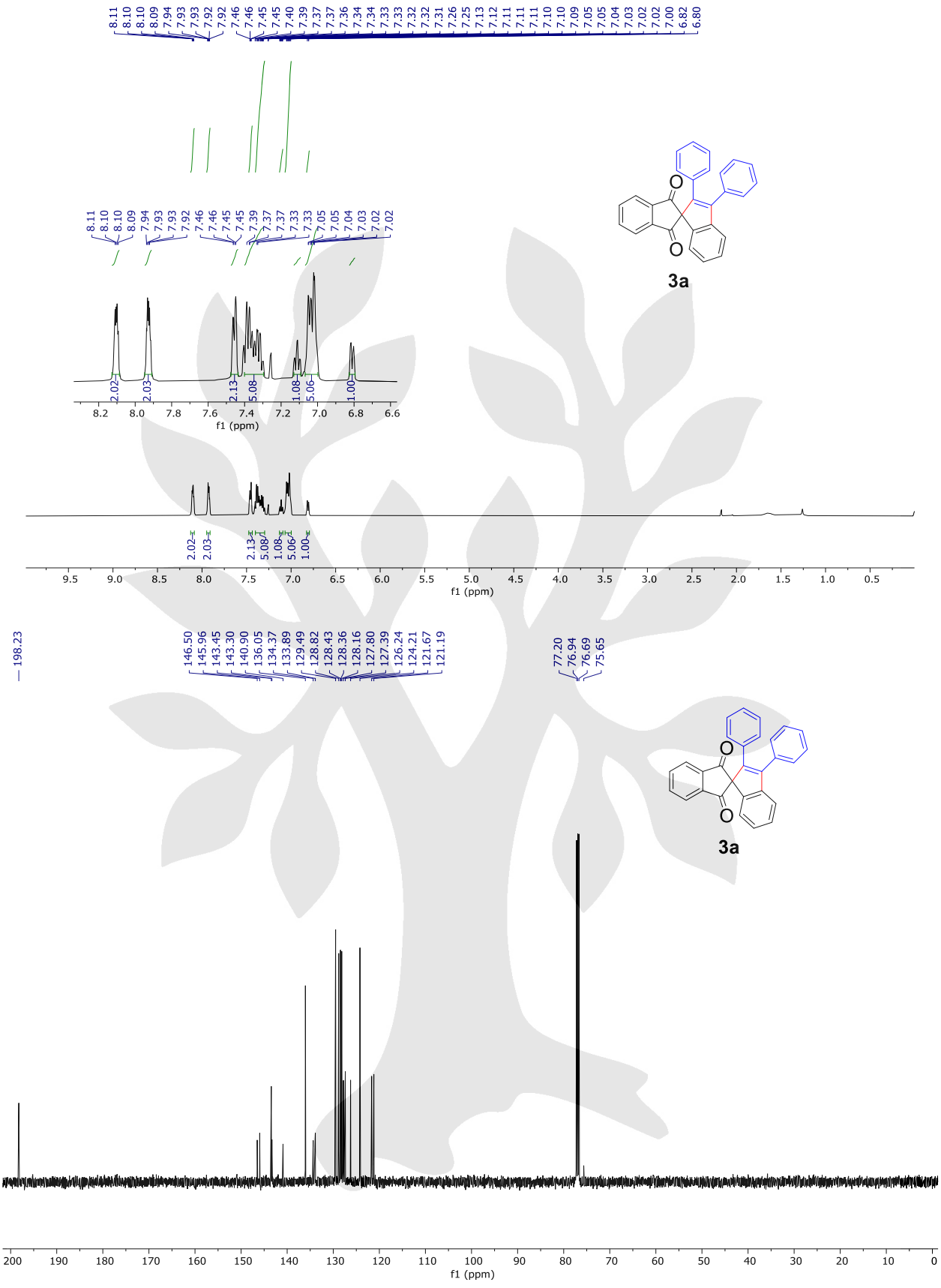
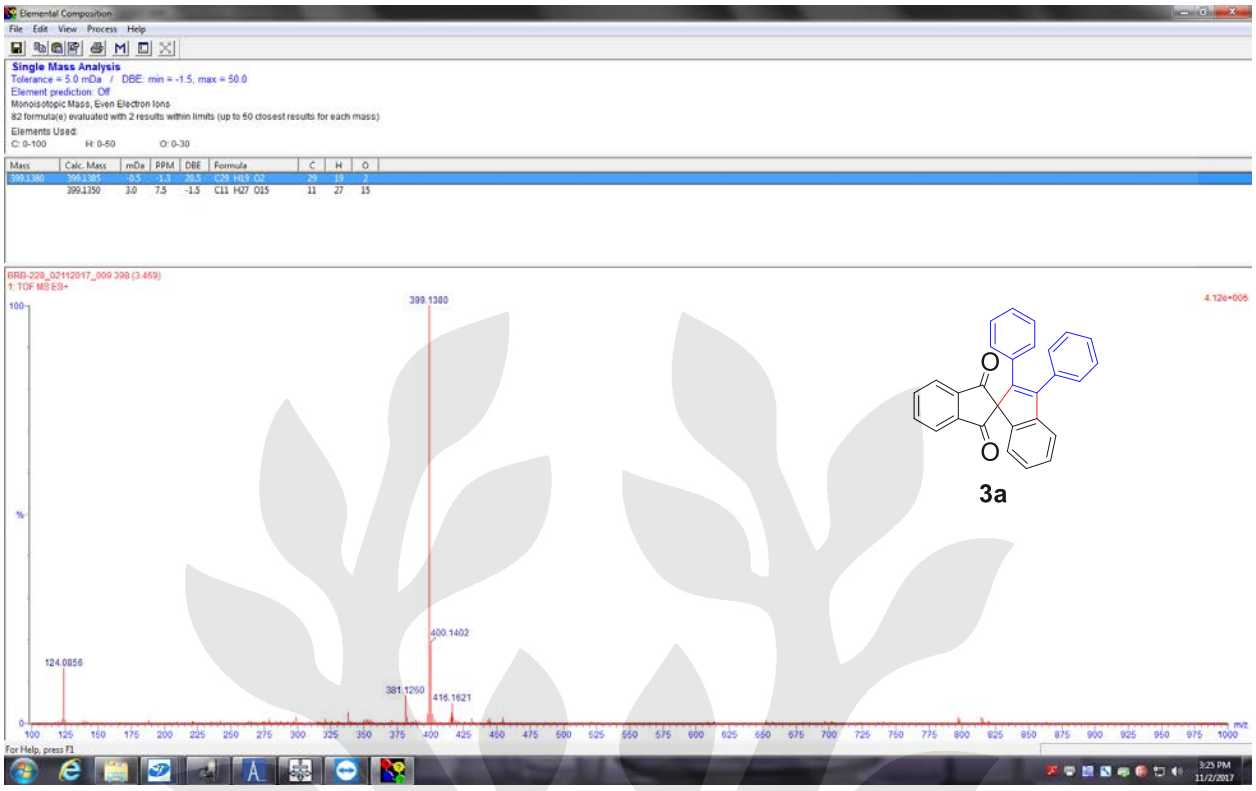
Supporting Information





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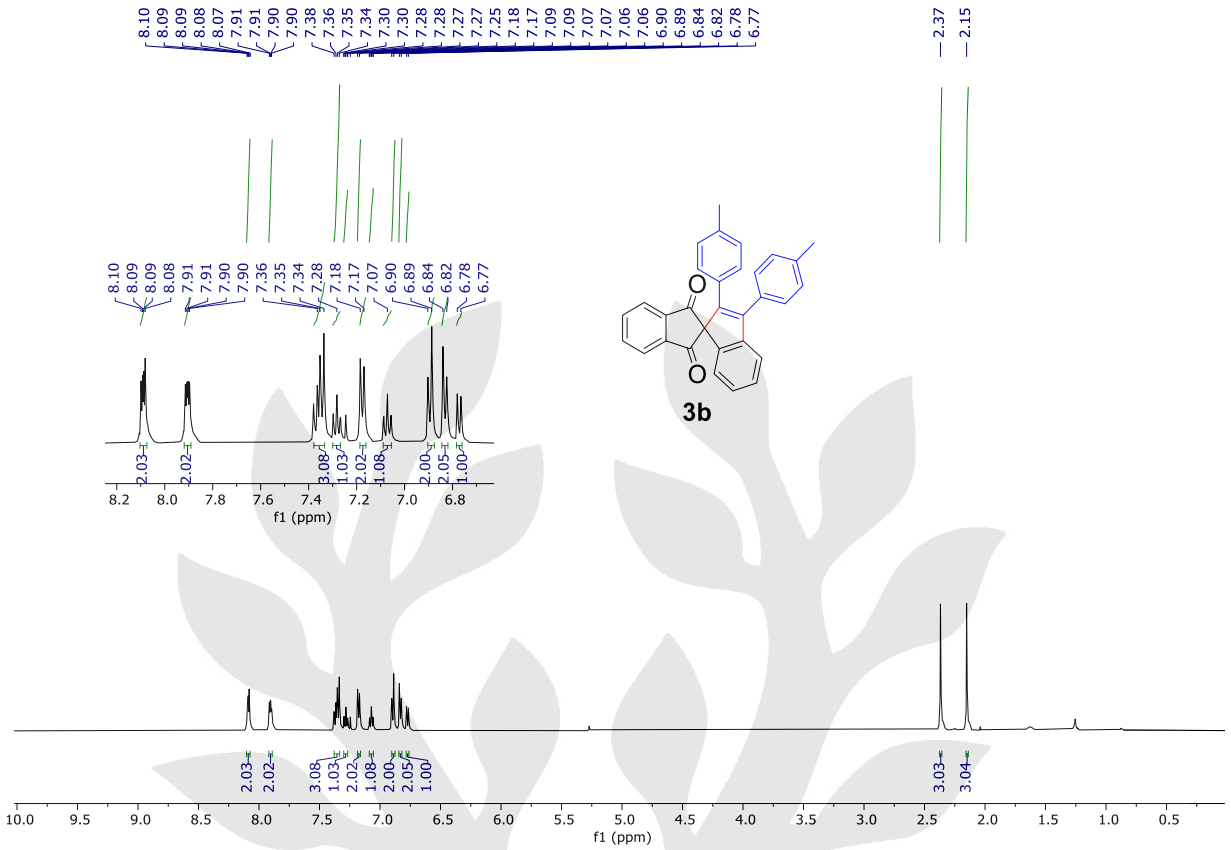

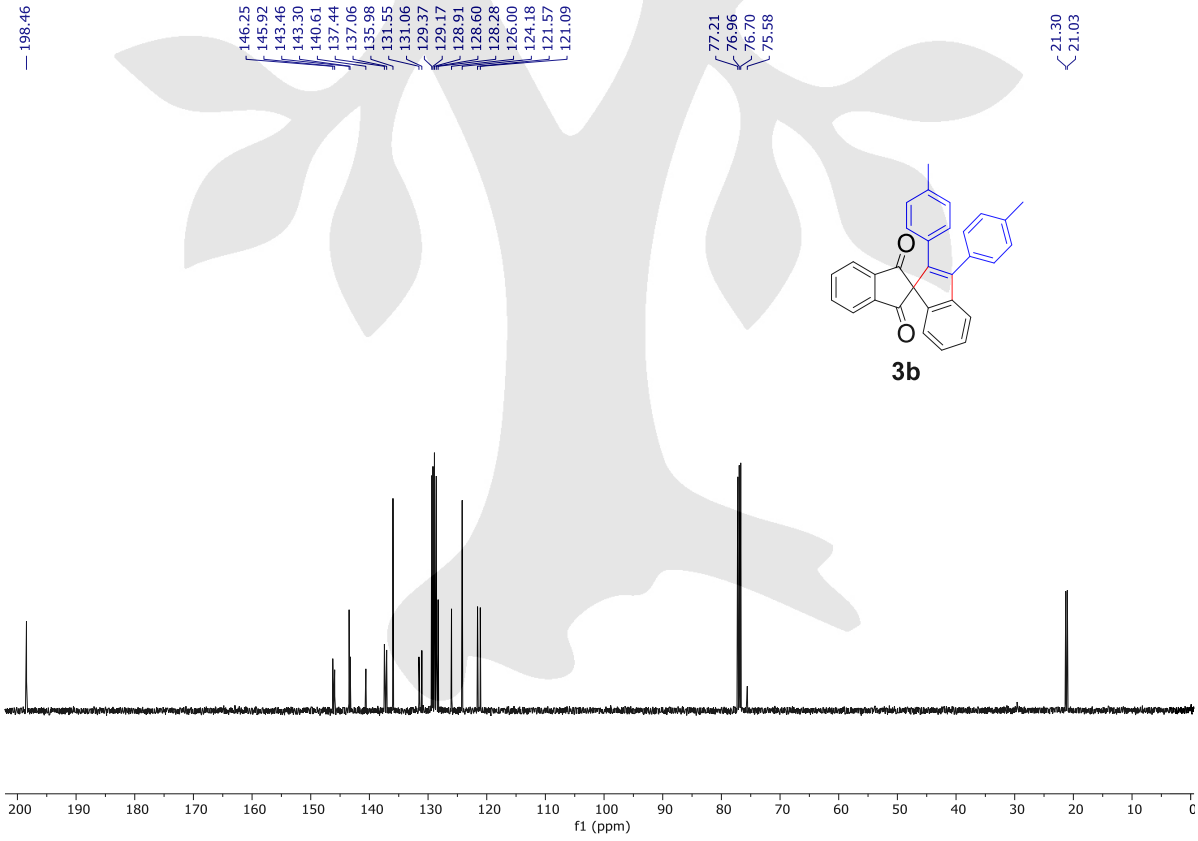

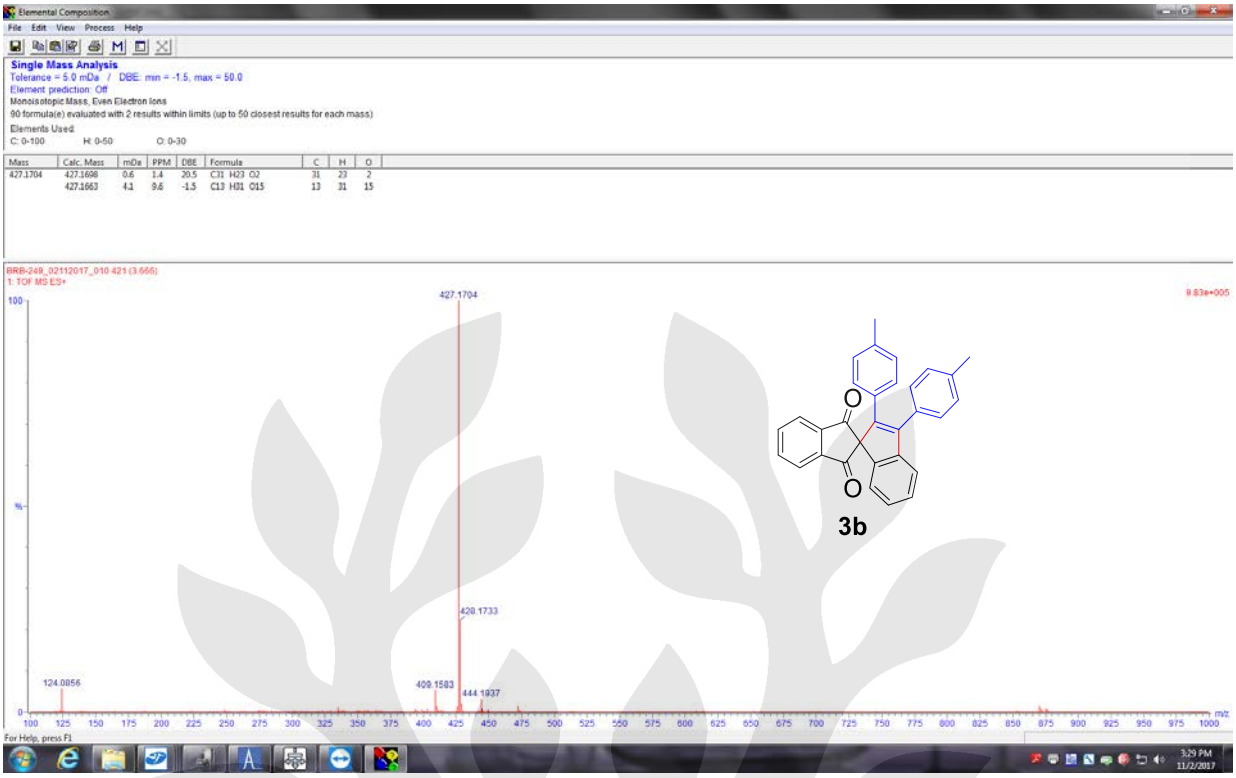

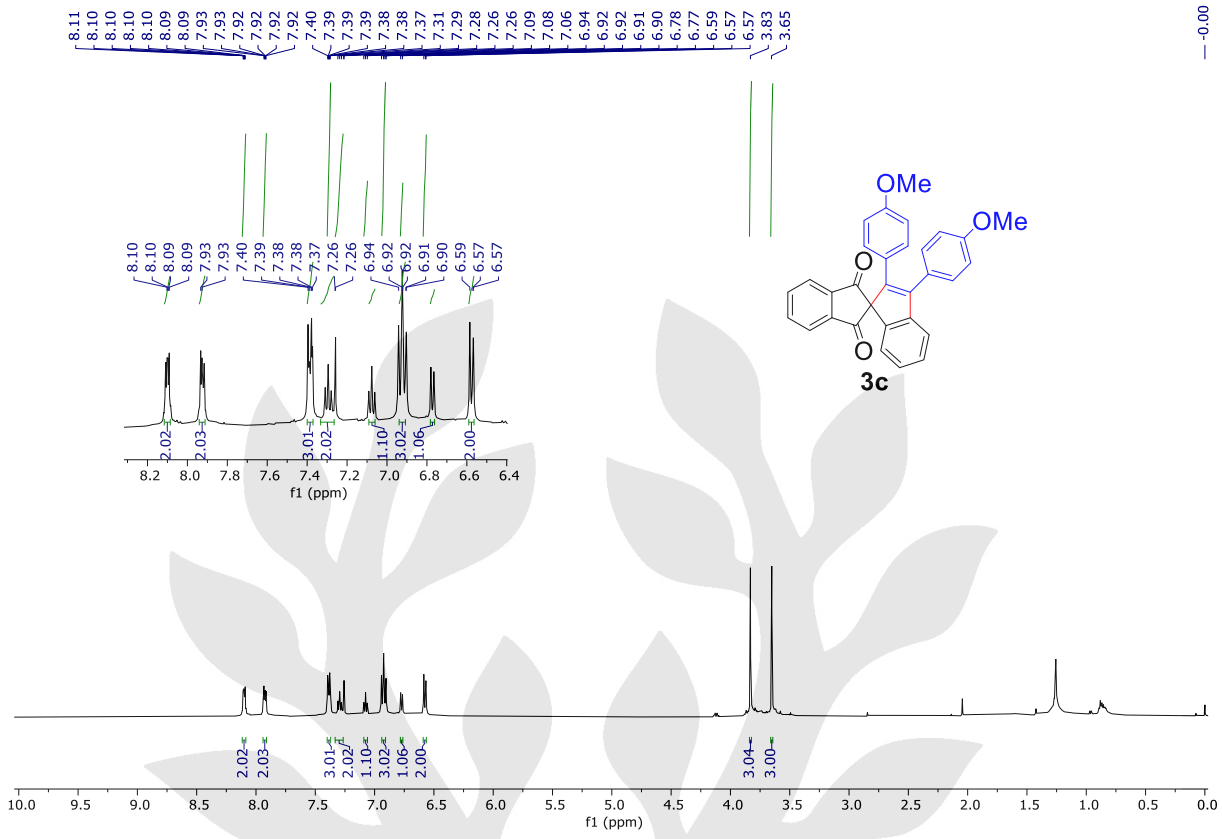

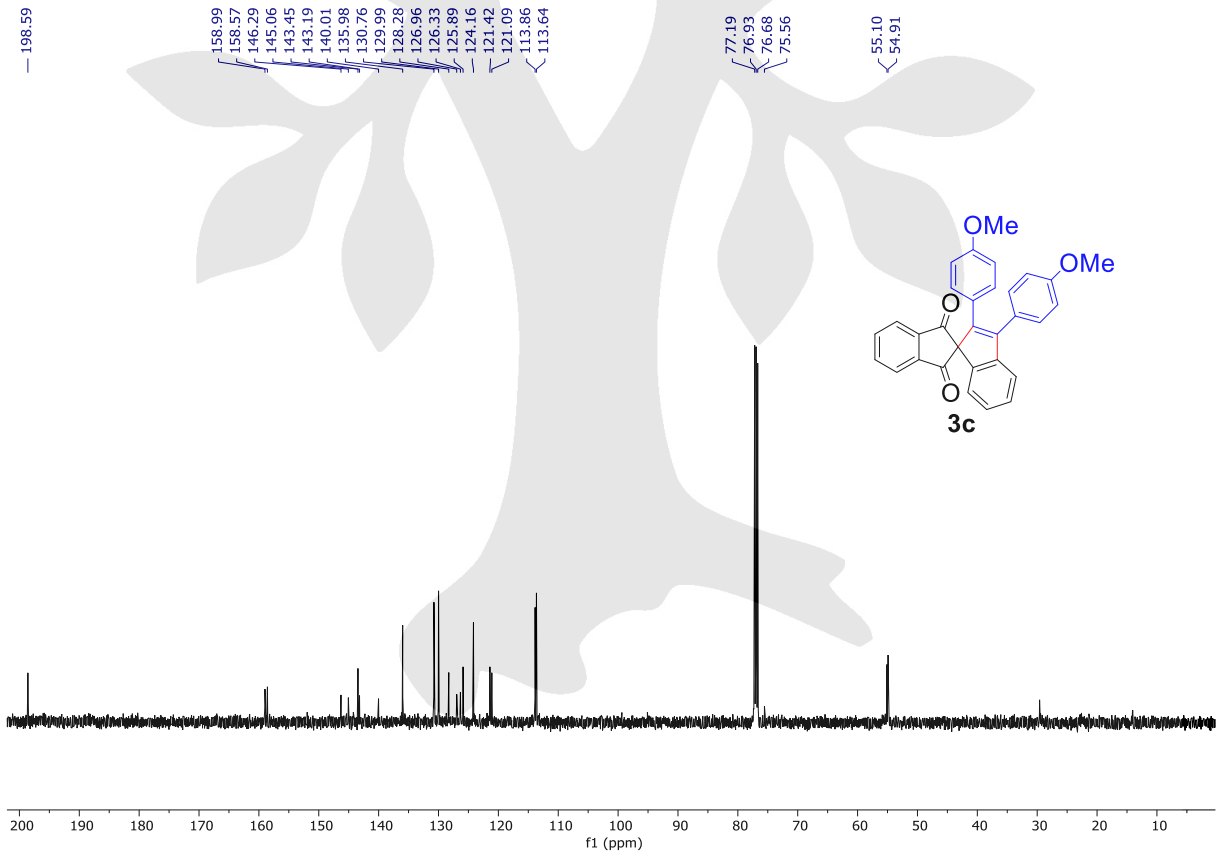

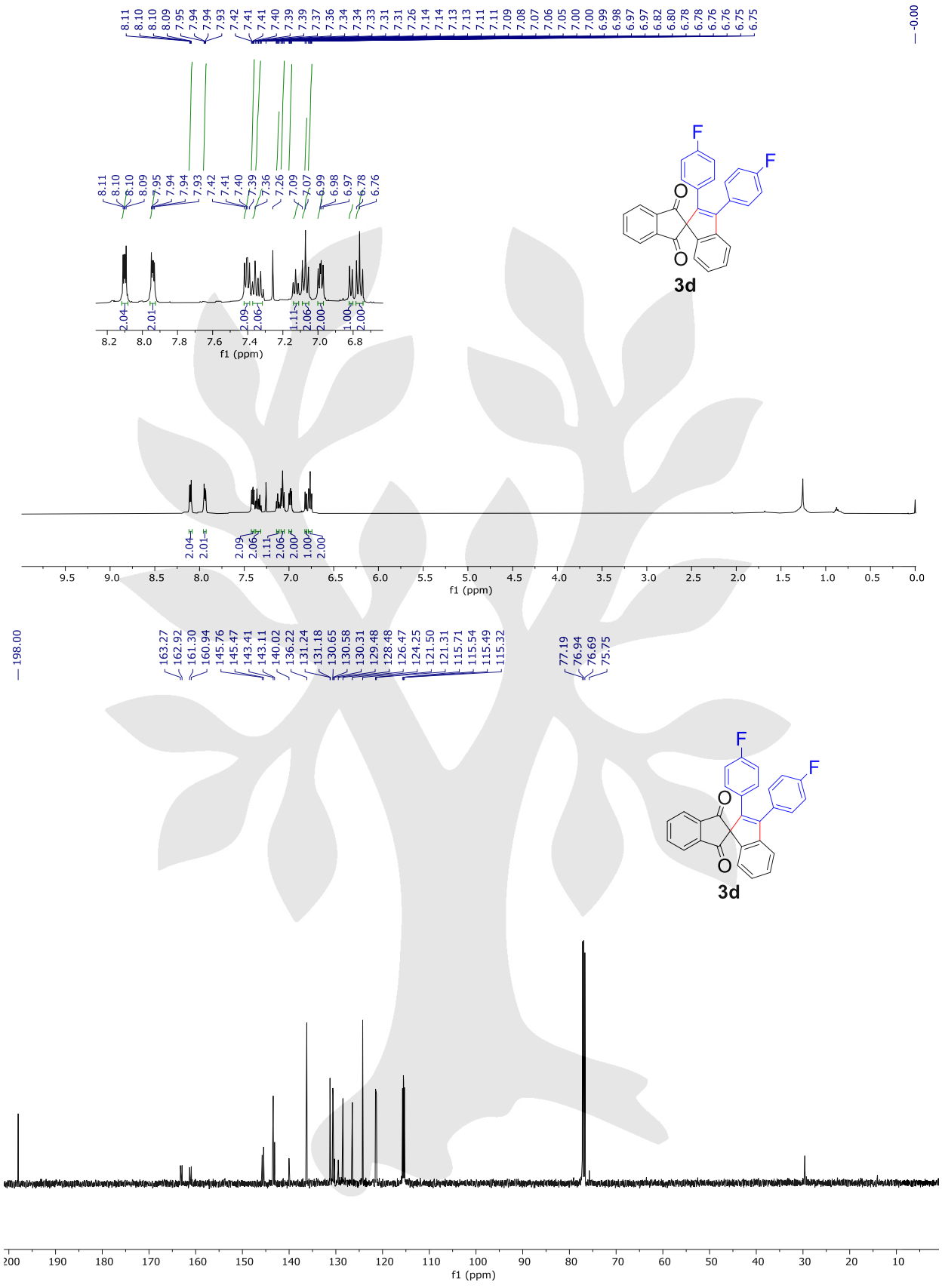

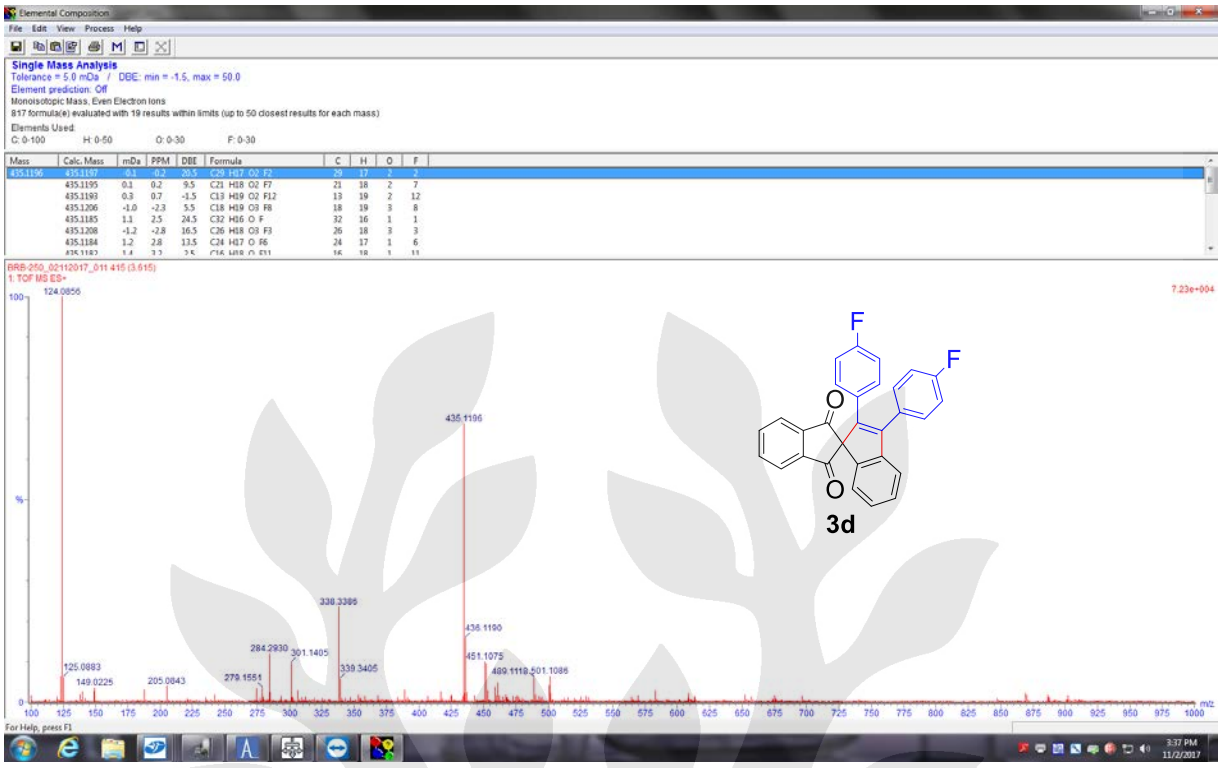

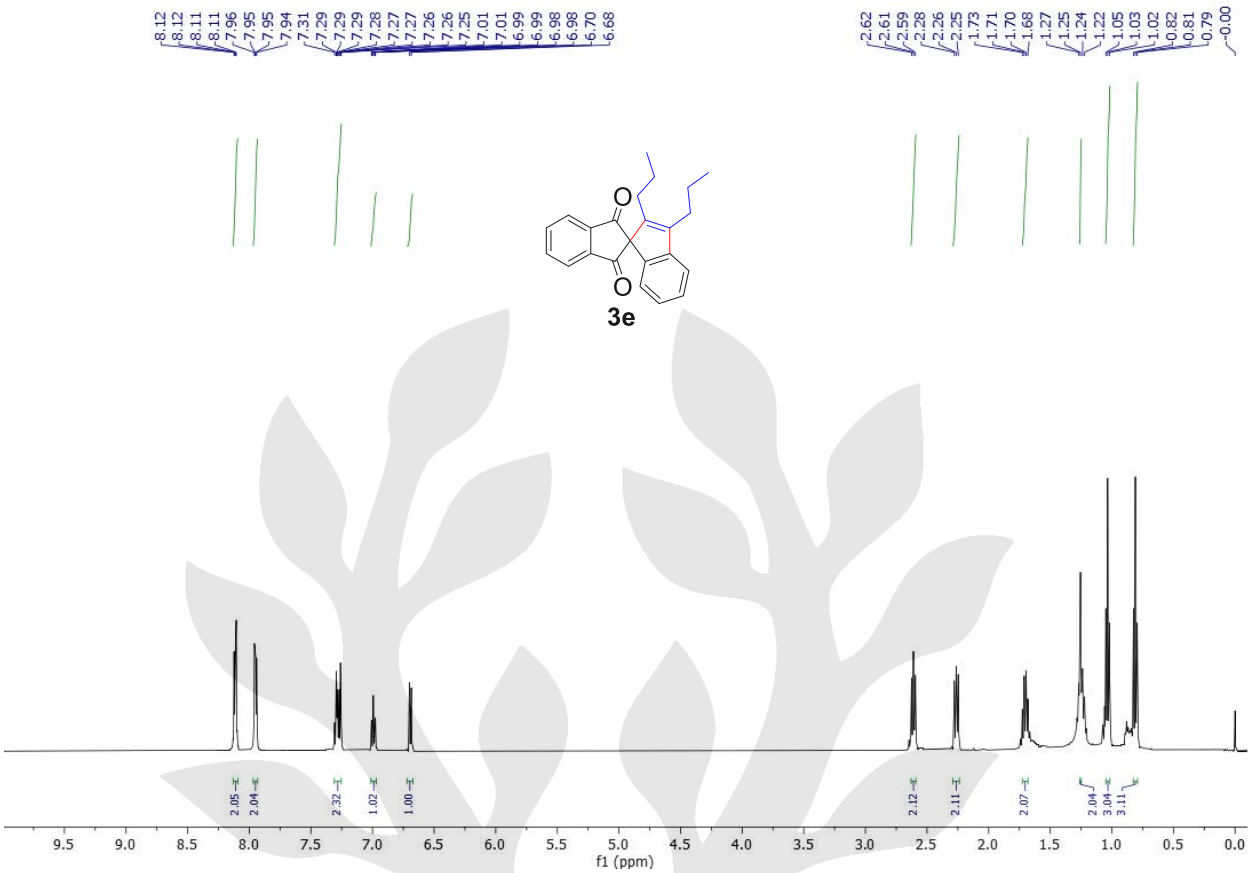

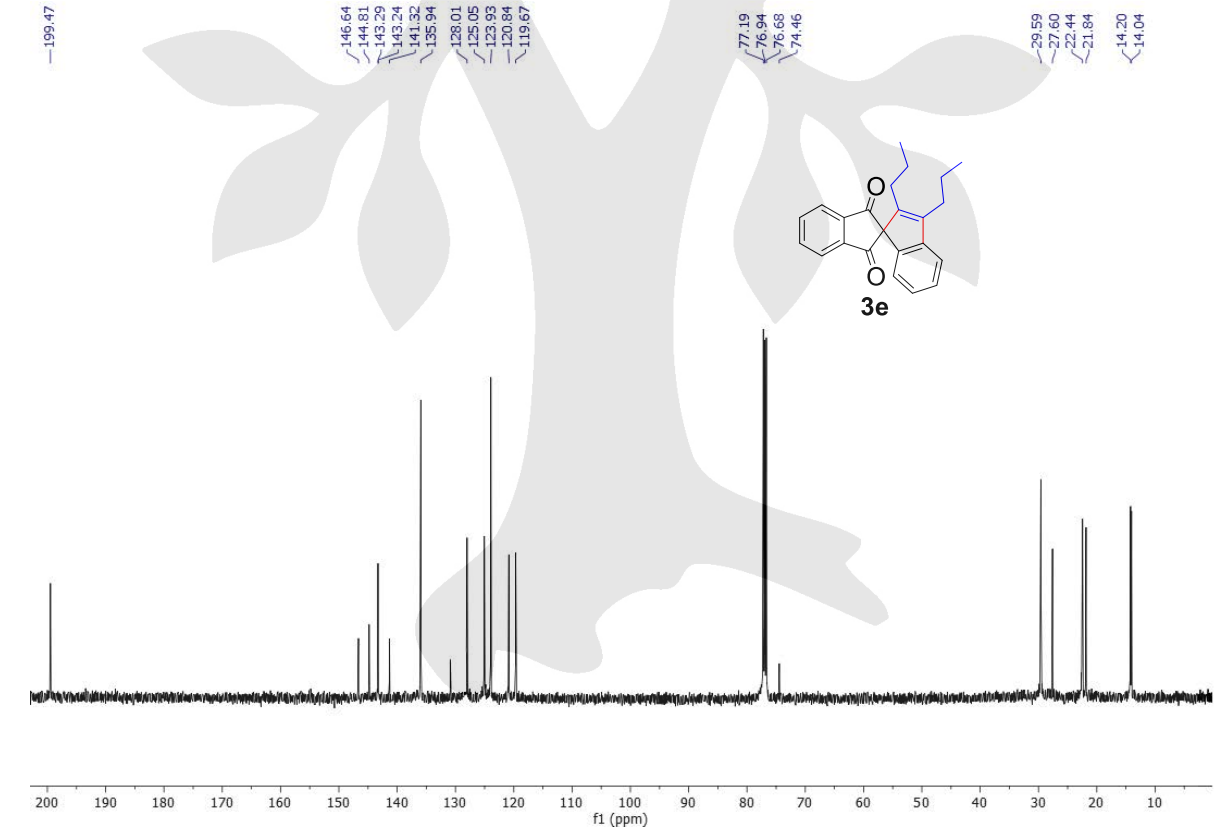

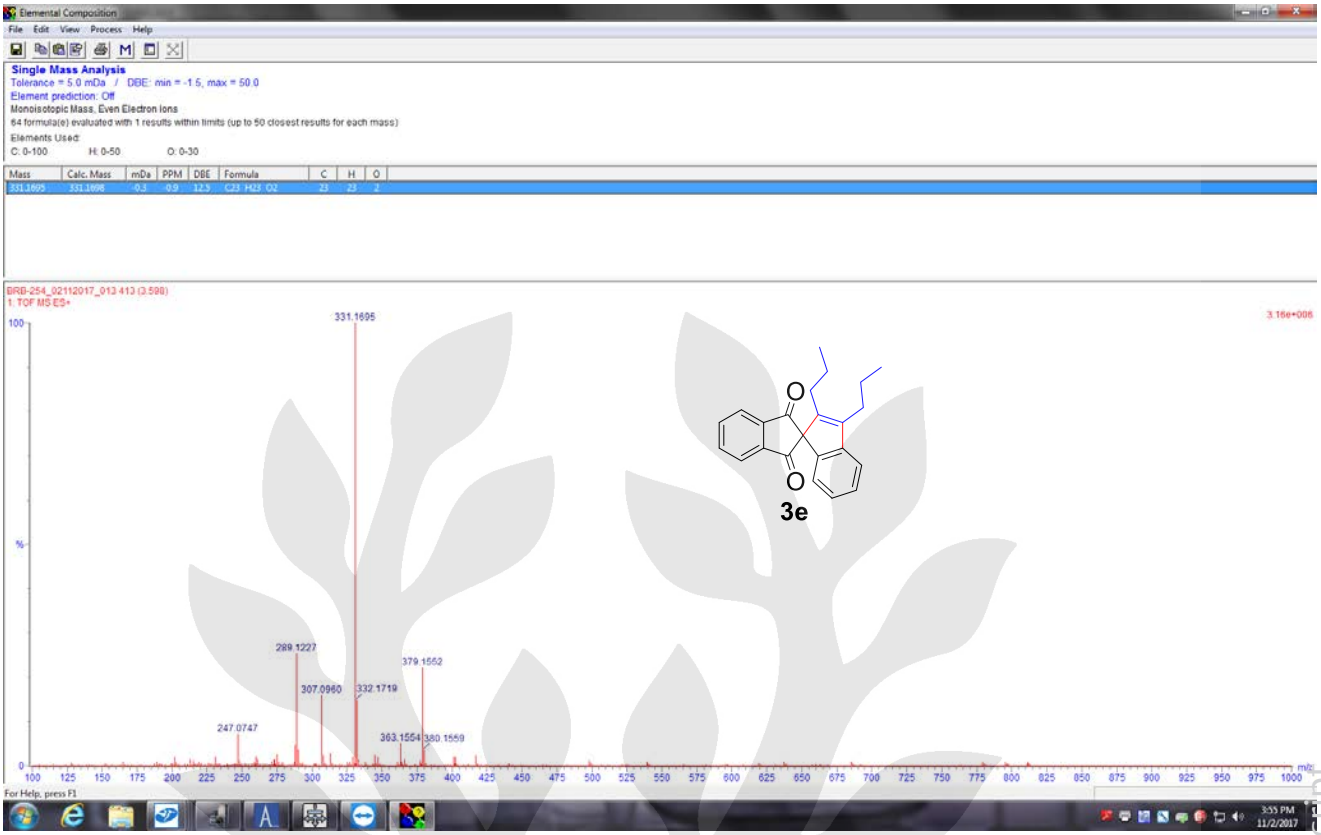

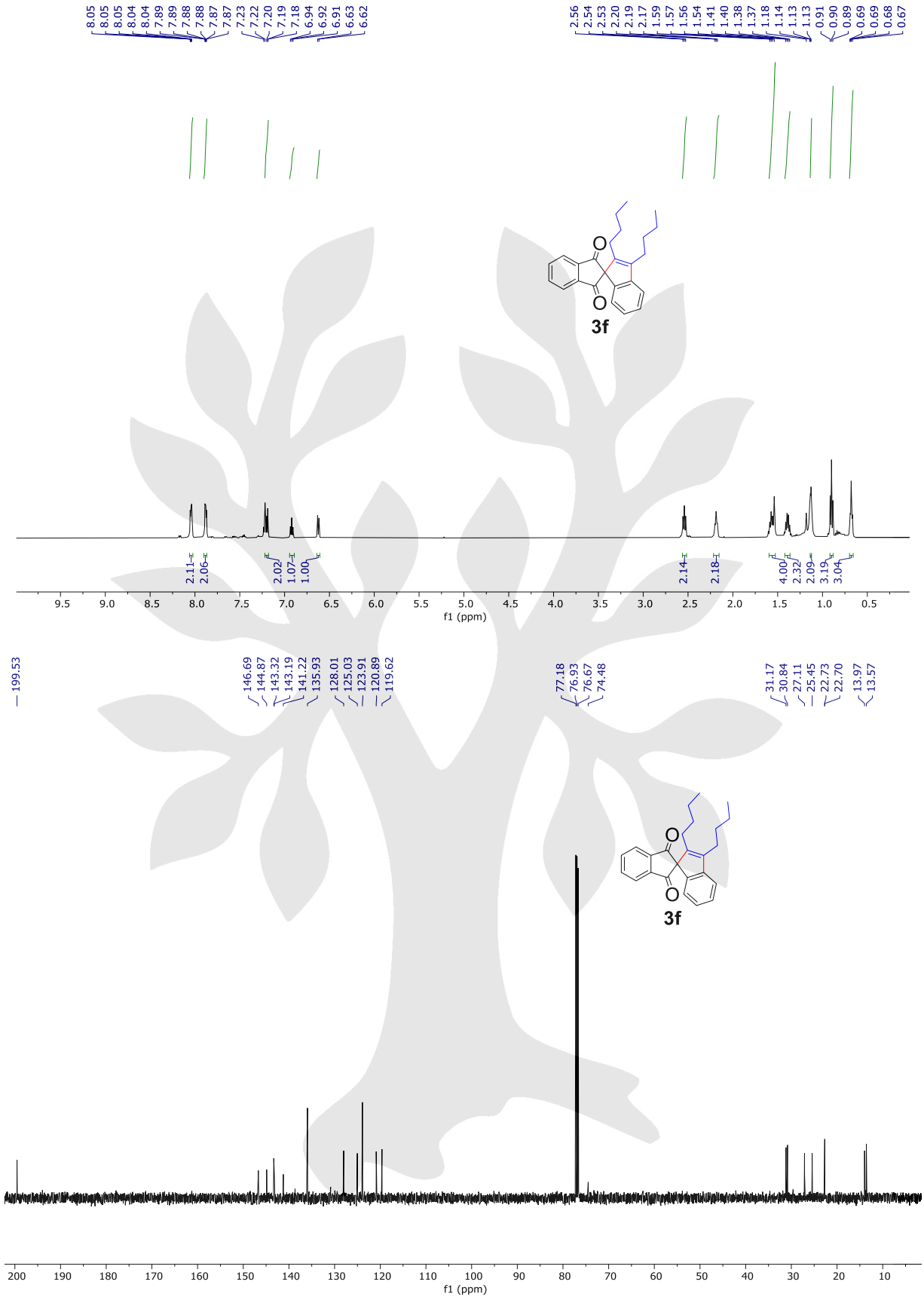

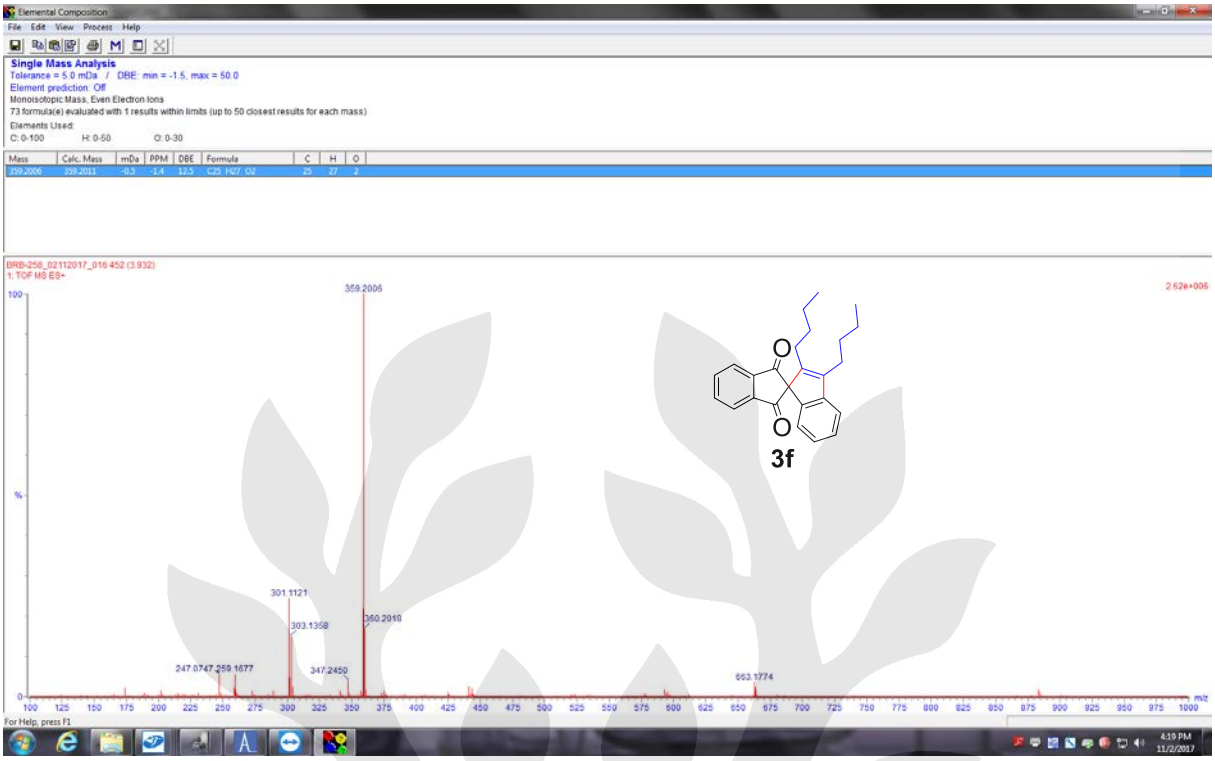

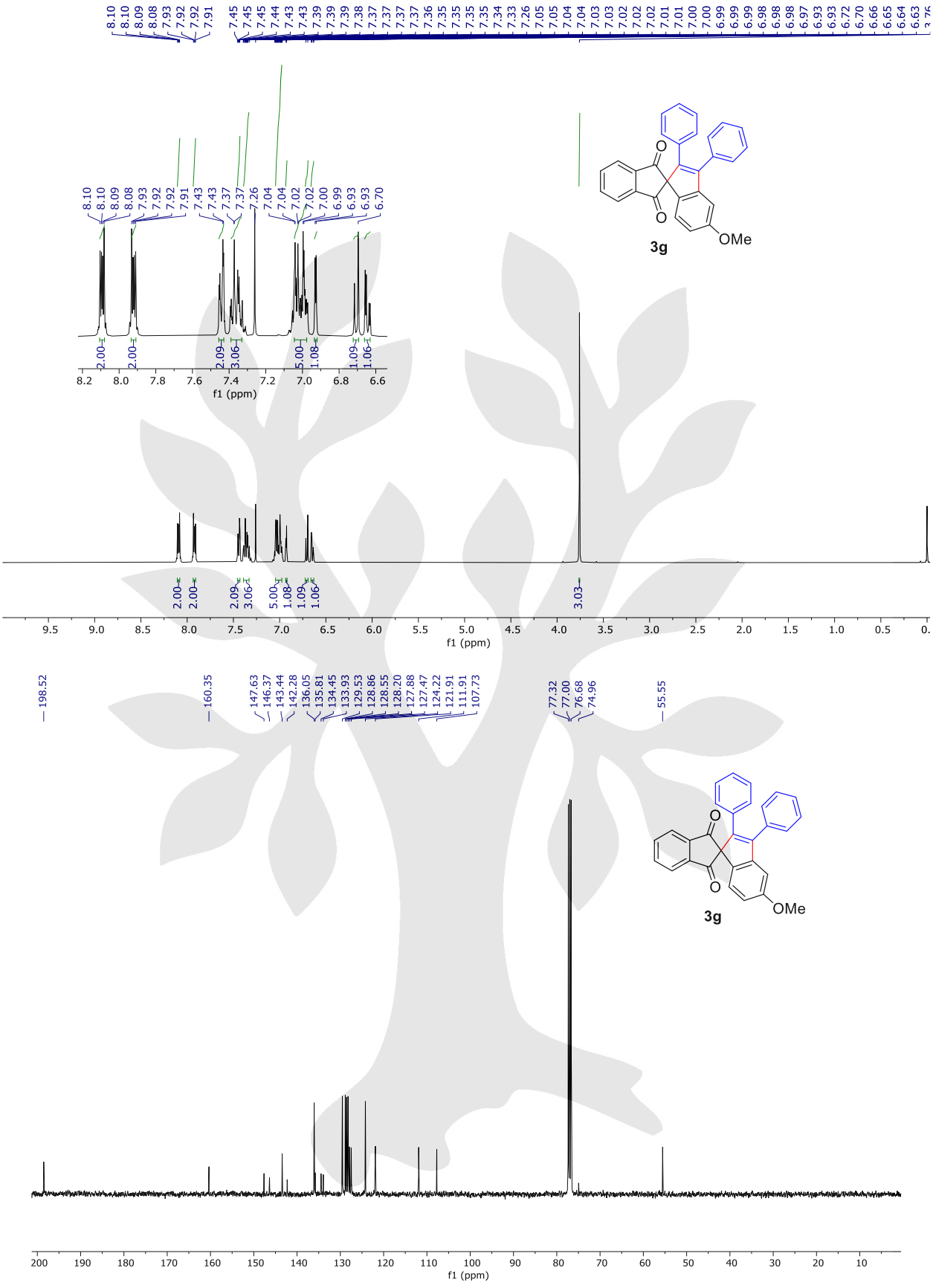

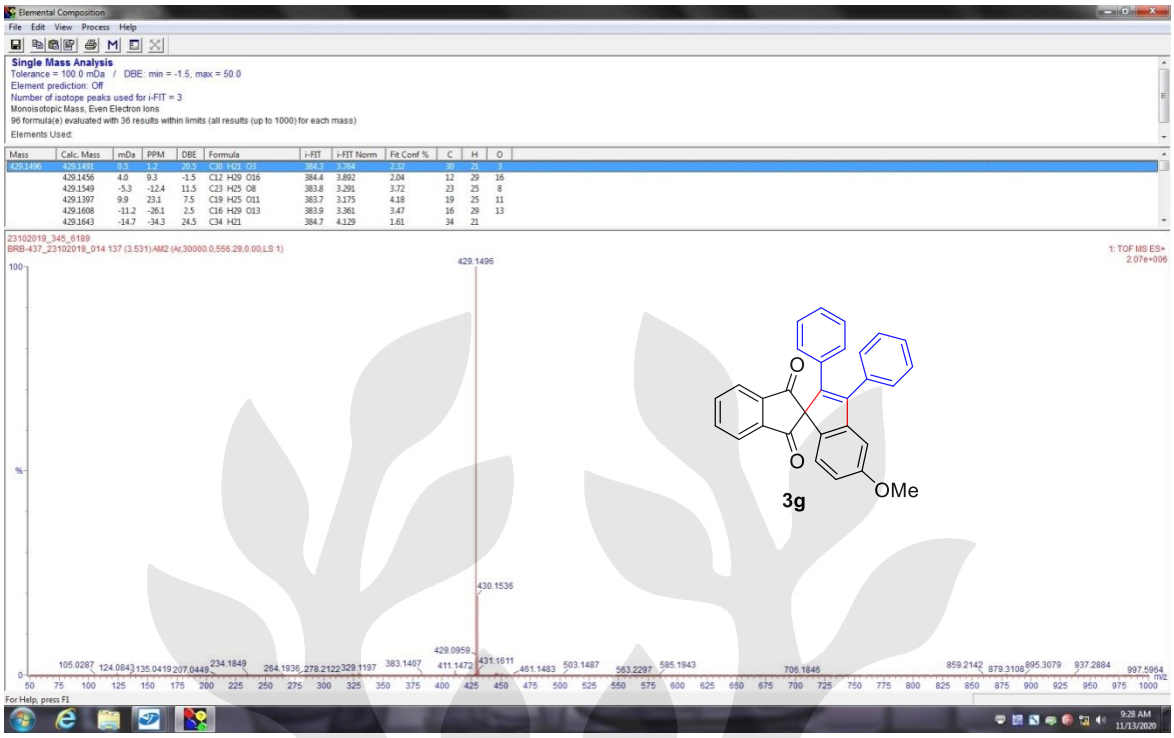

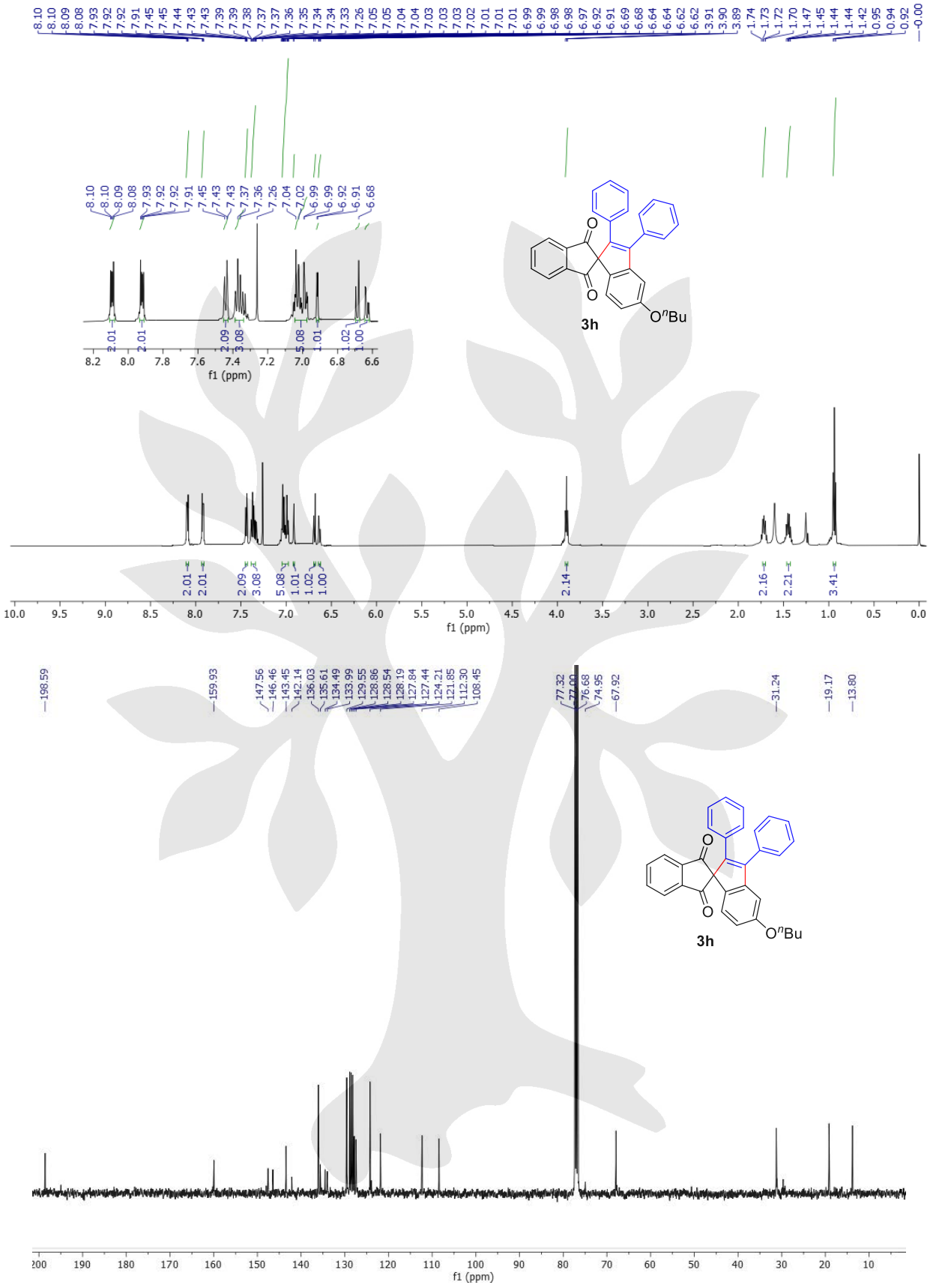

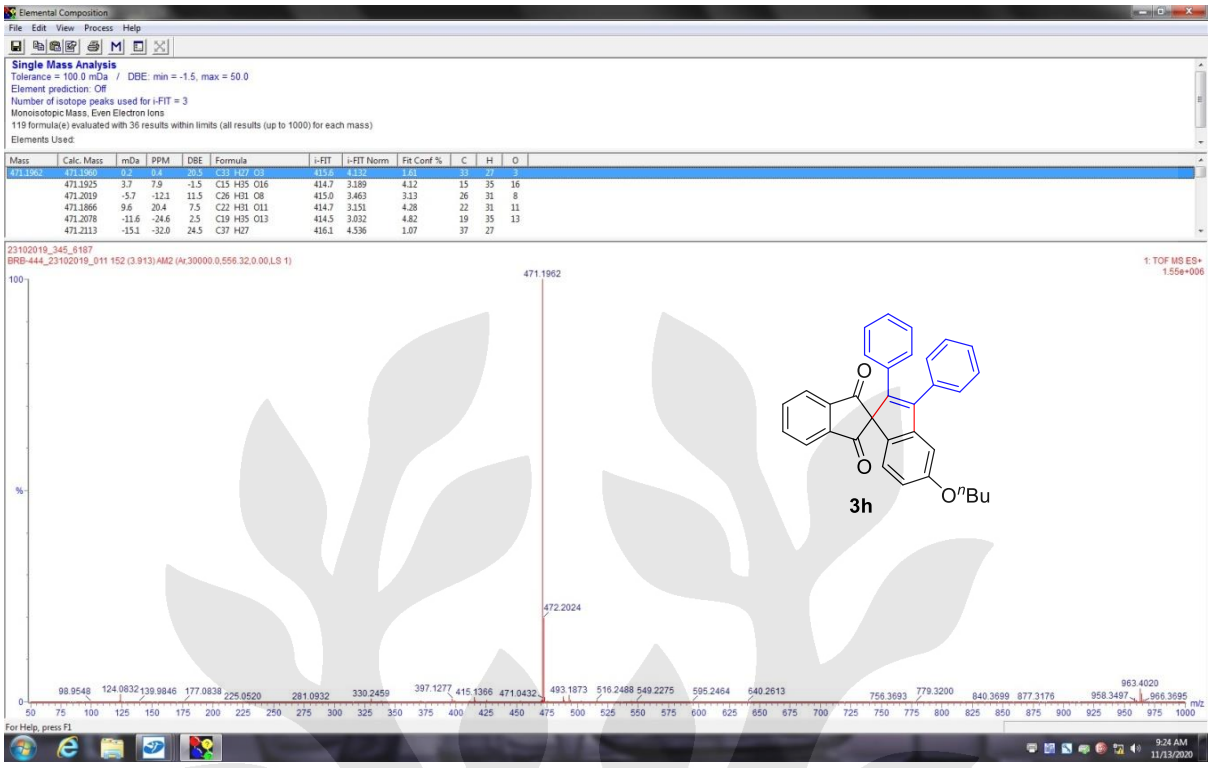

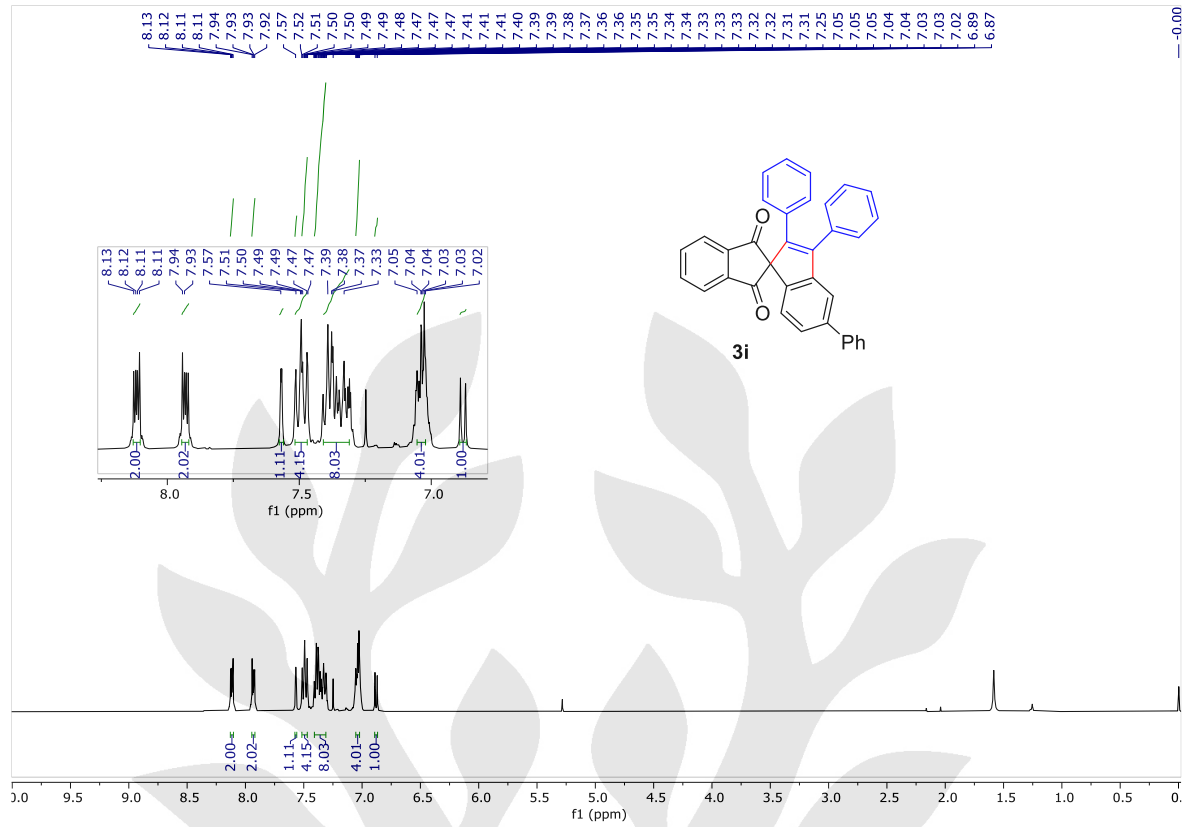

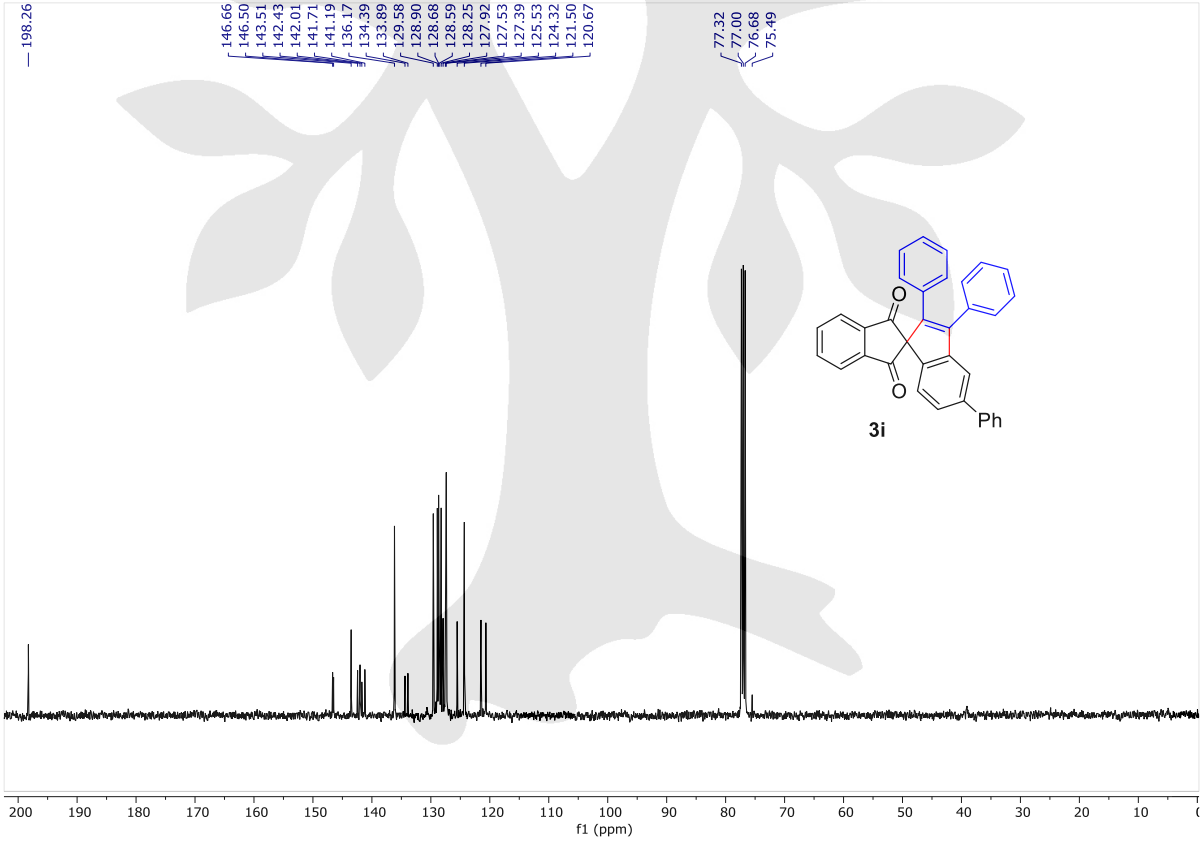

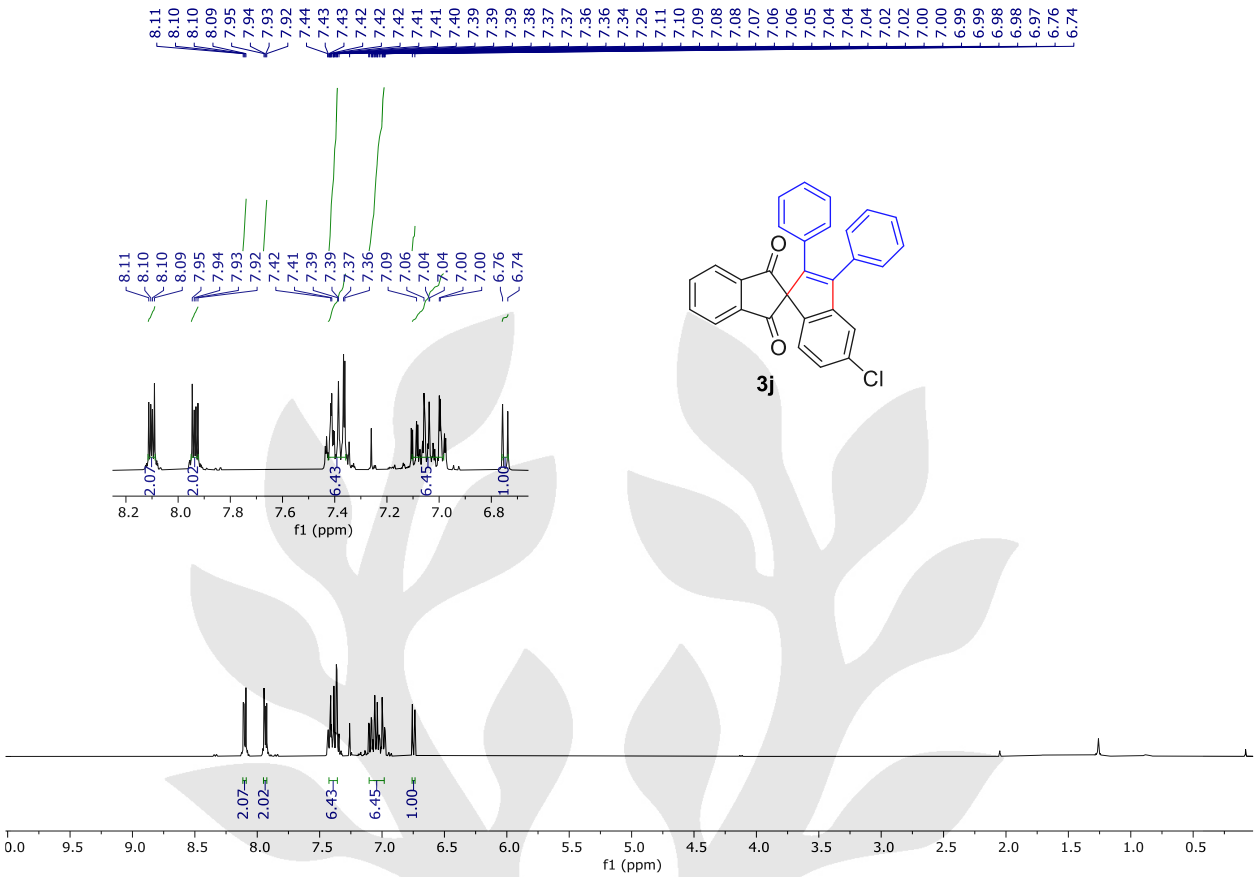

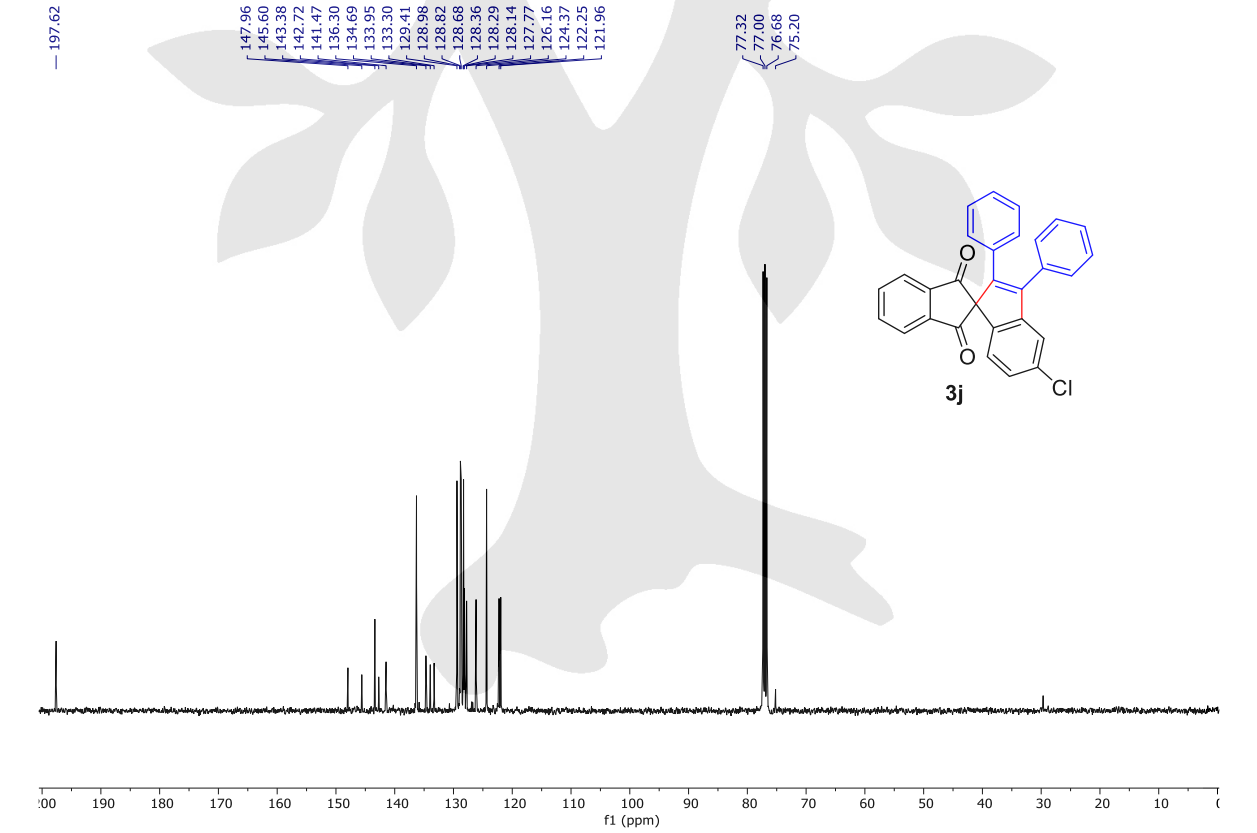

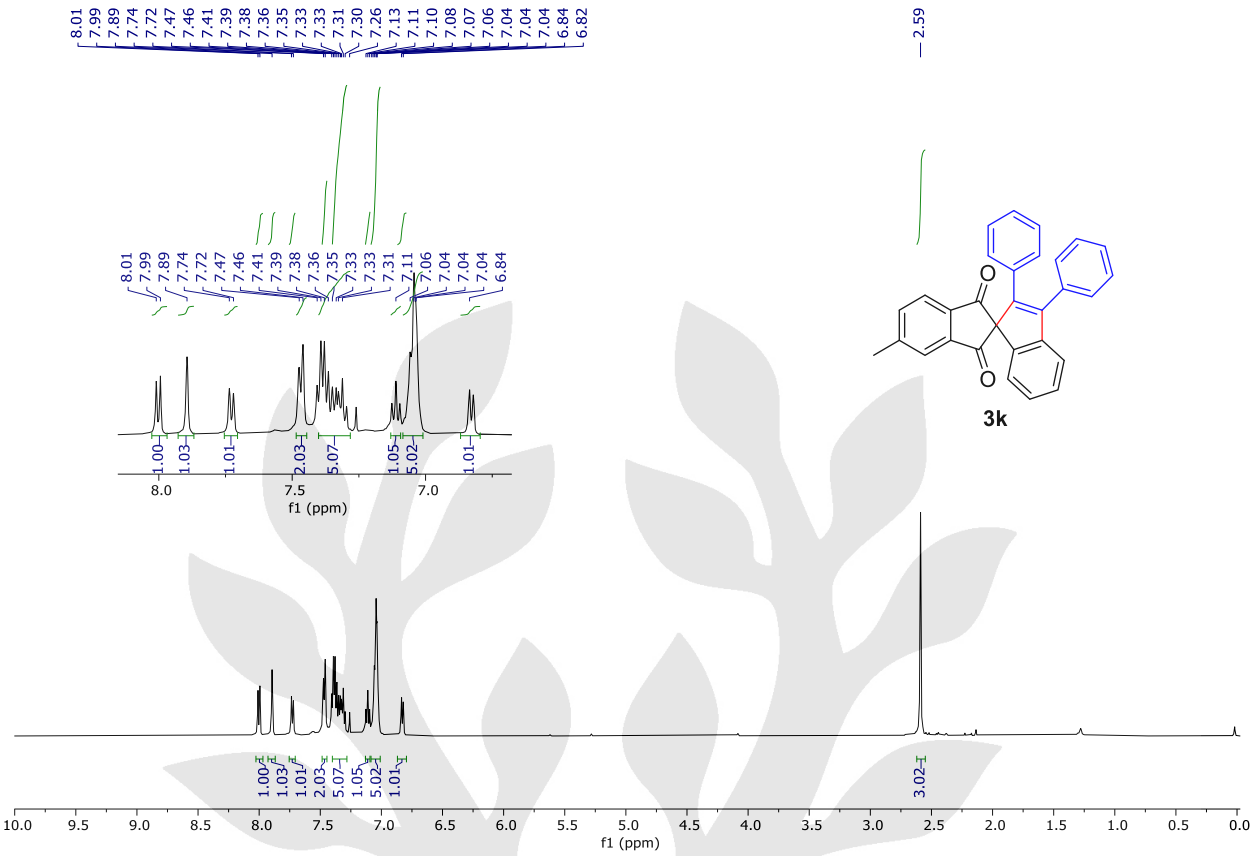

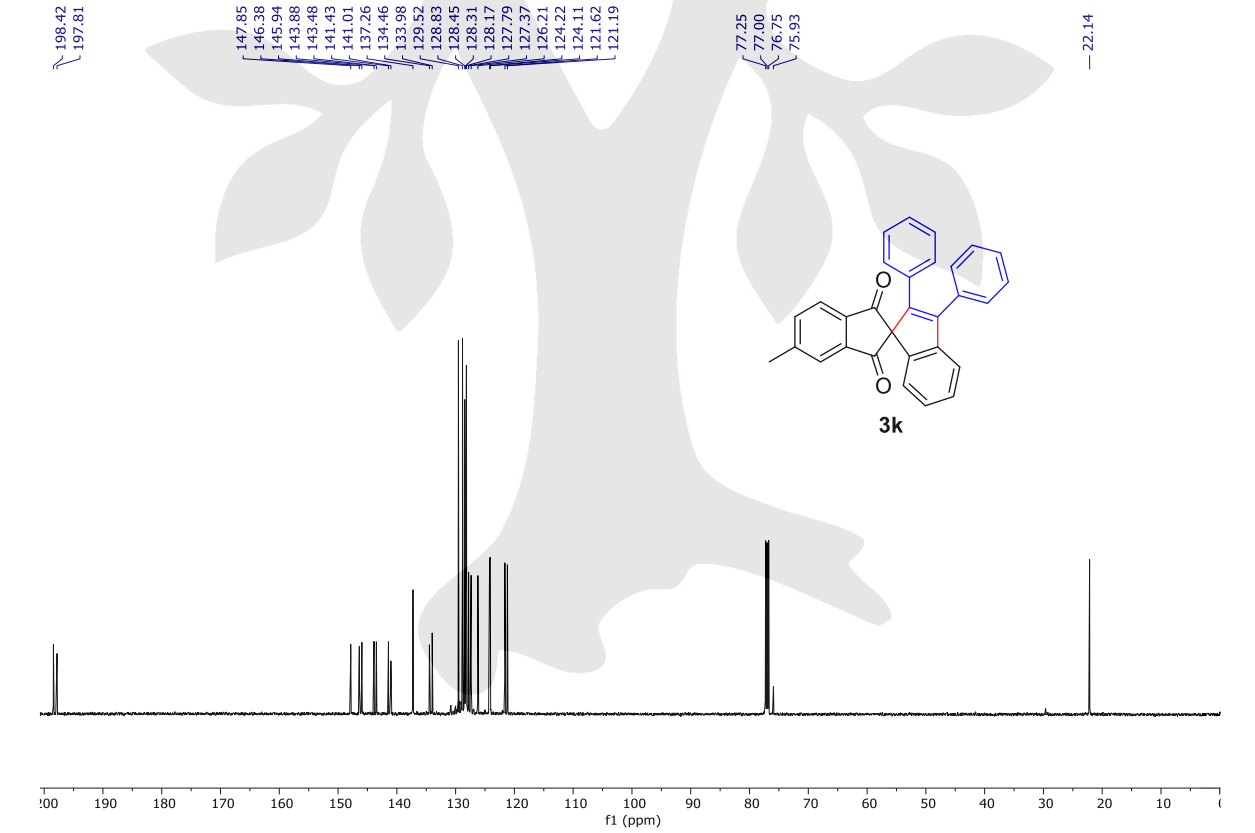

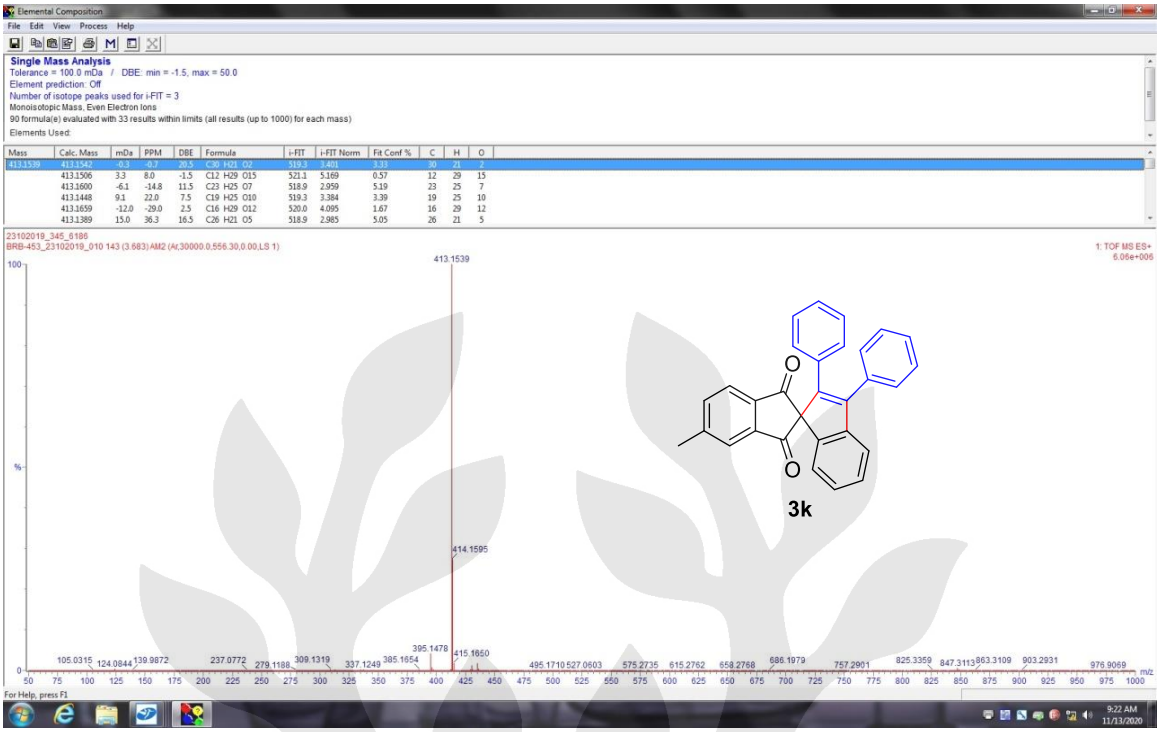

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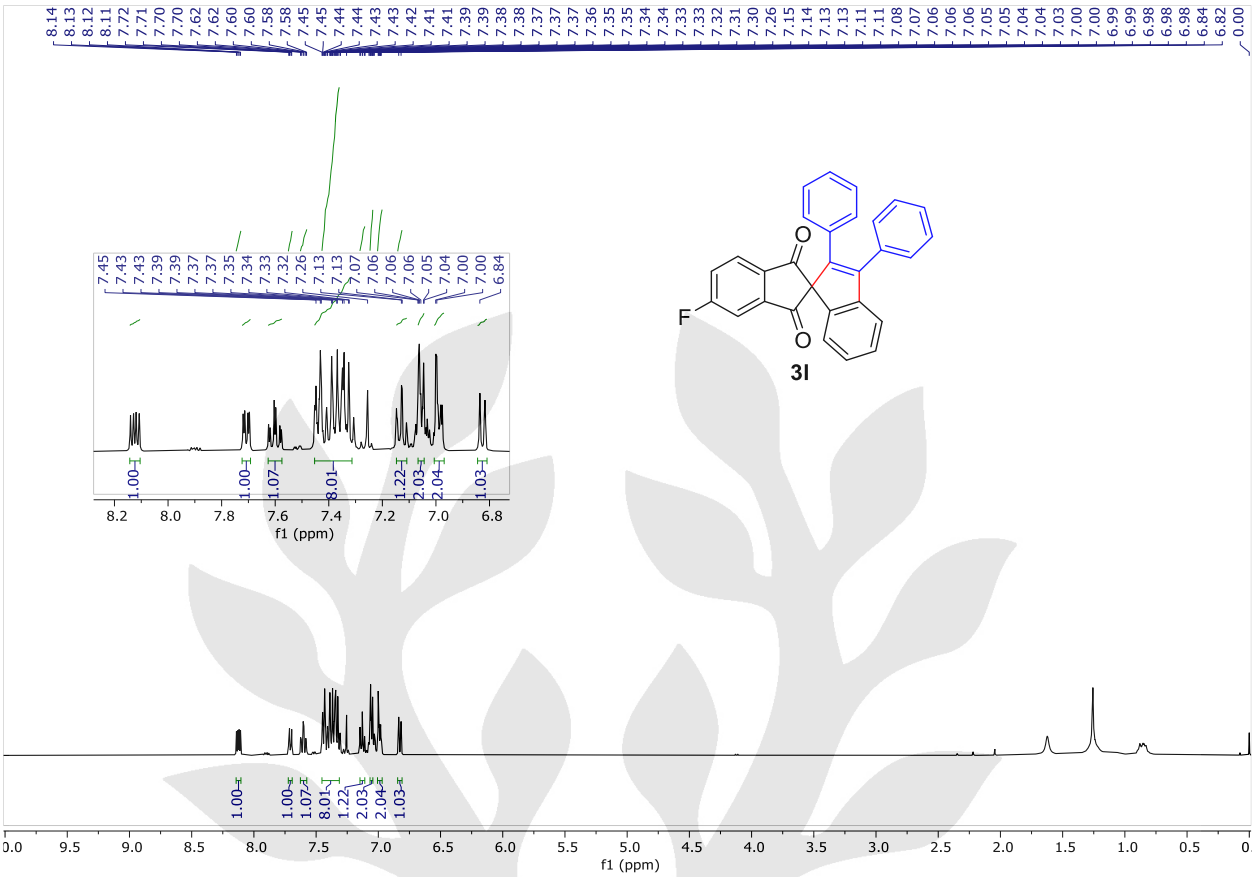
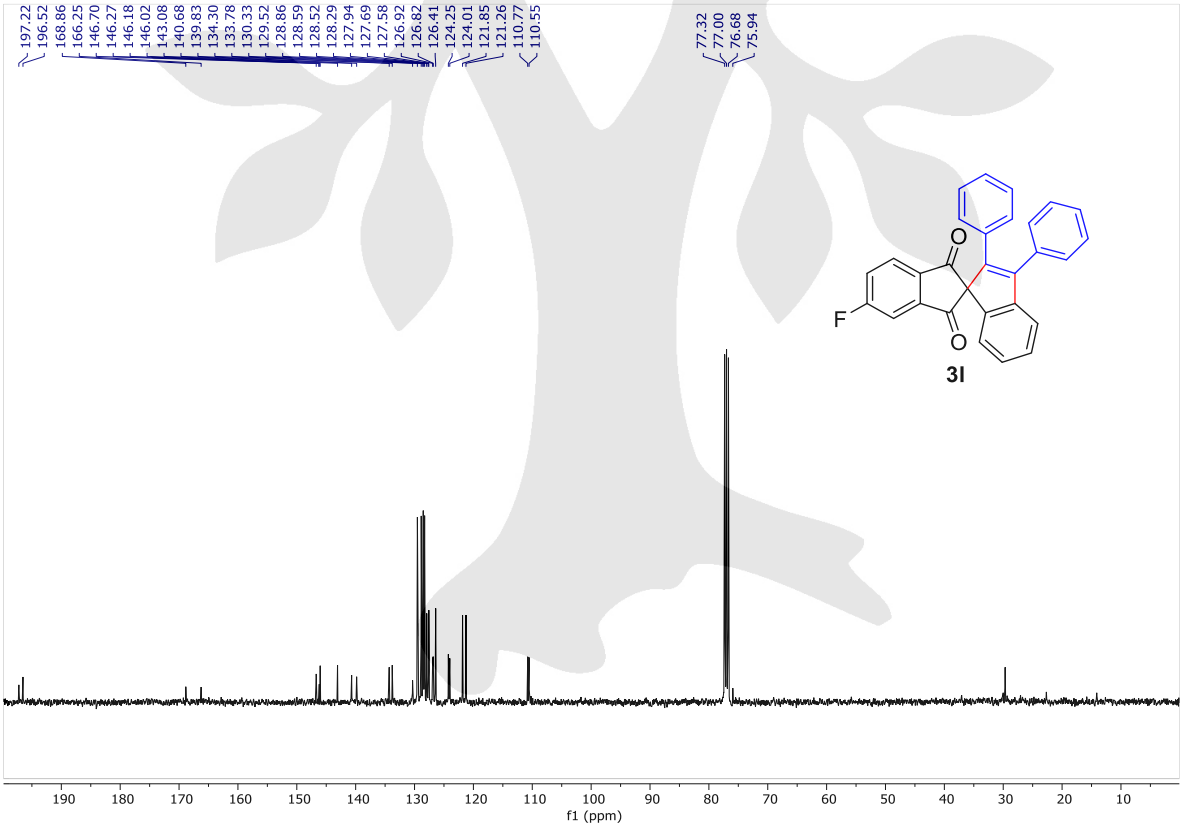
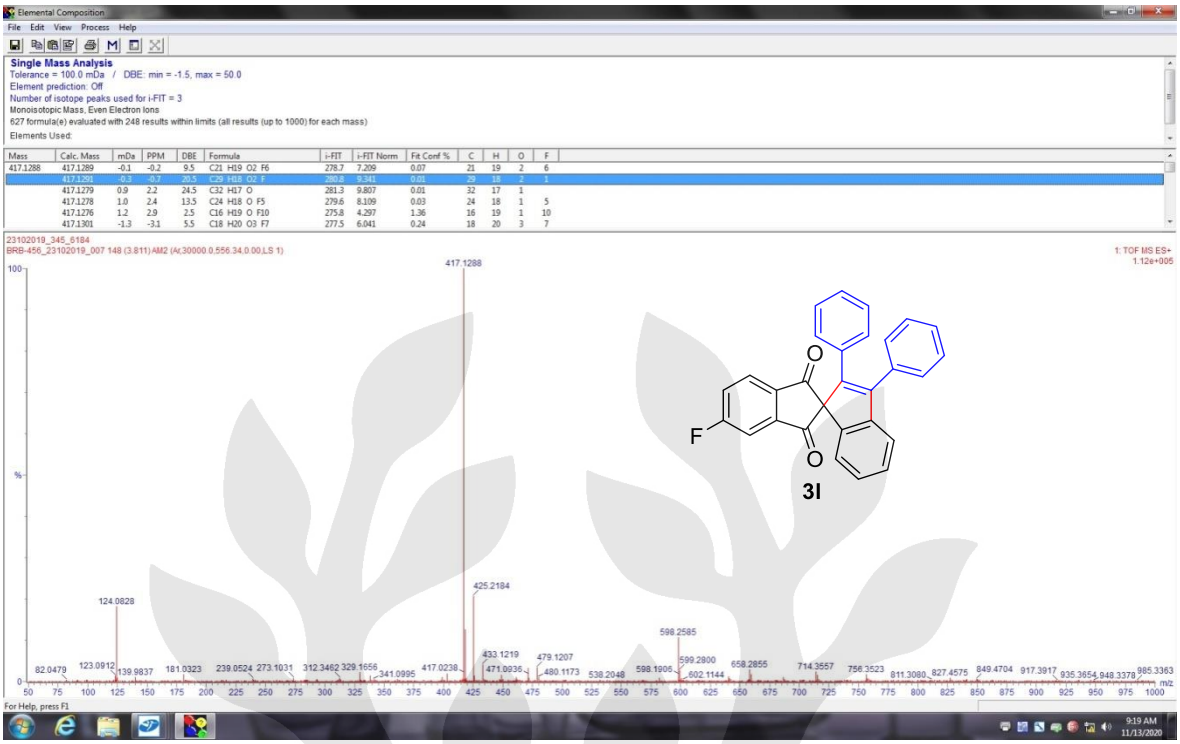
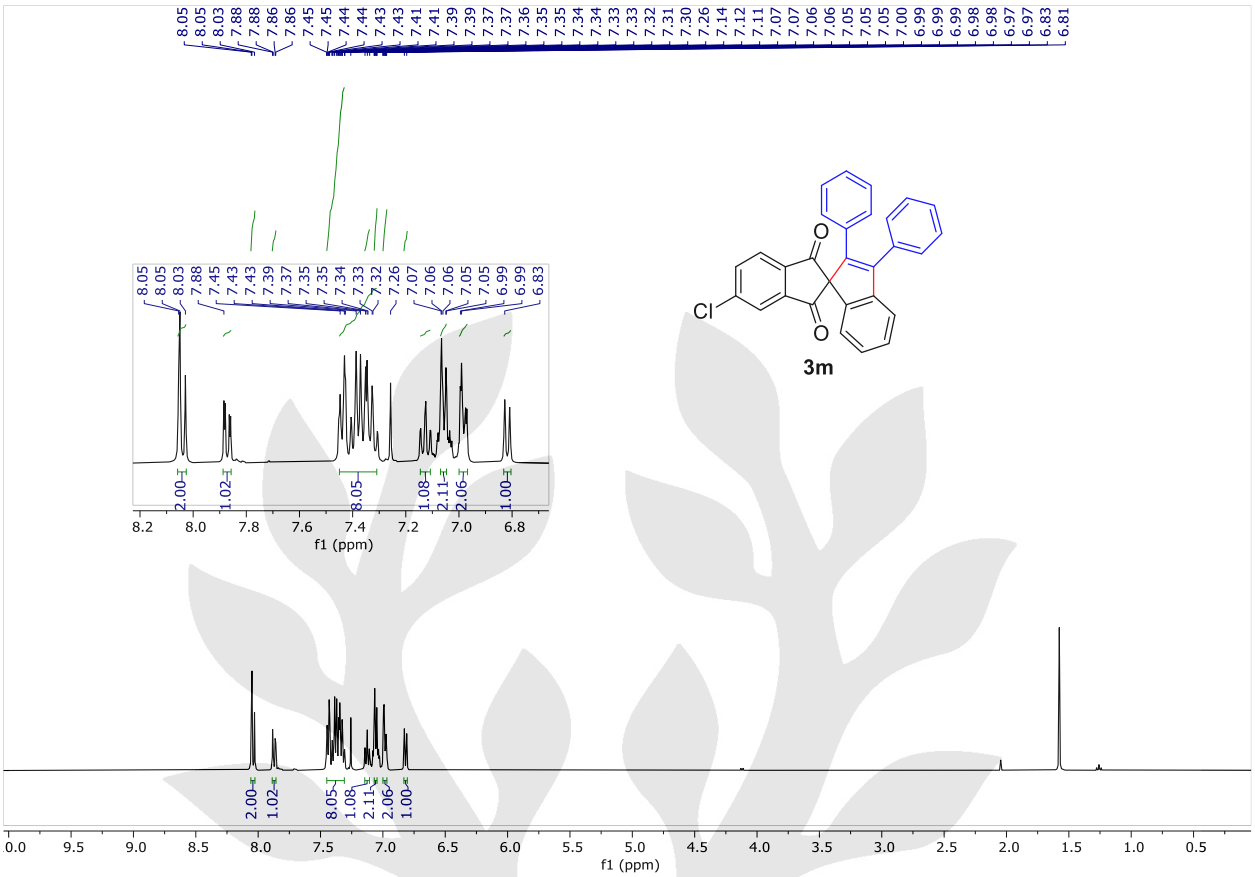
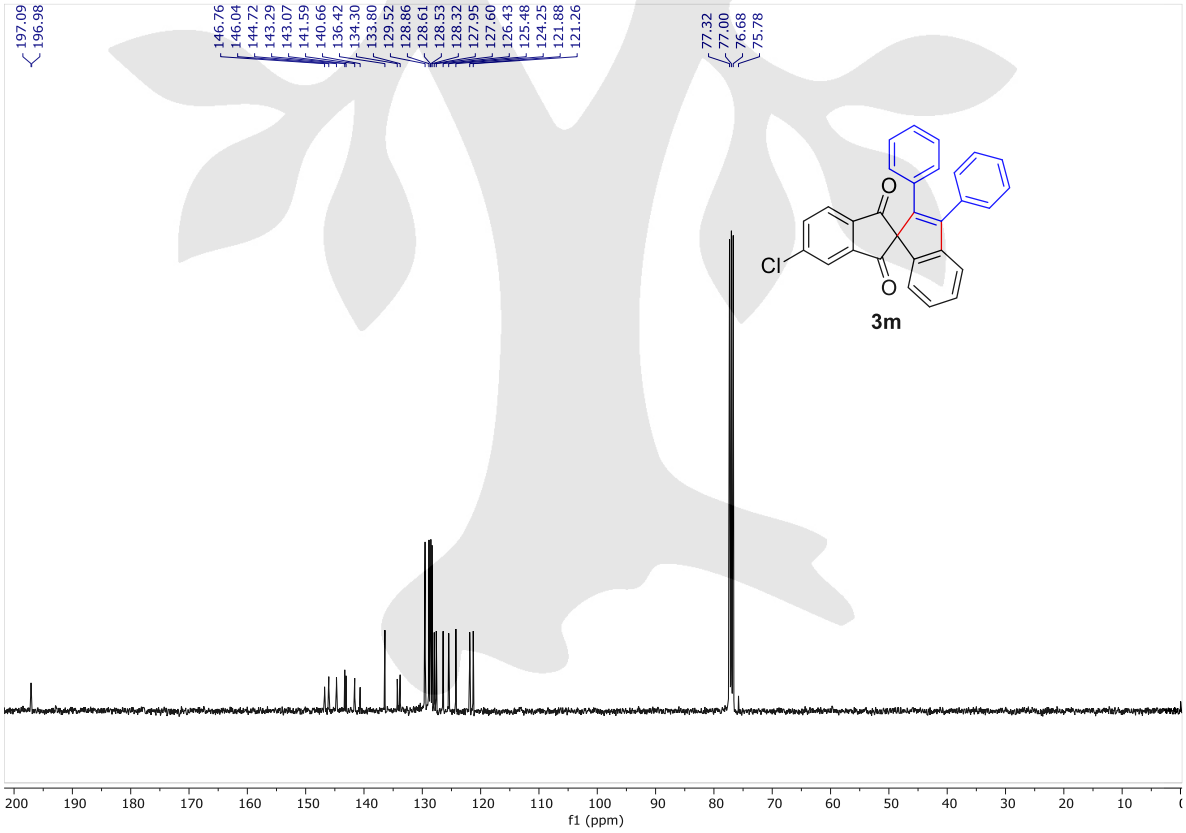
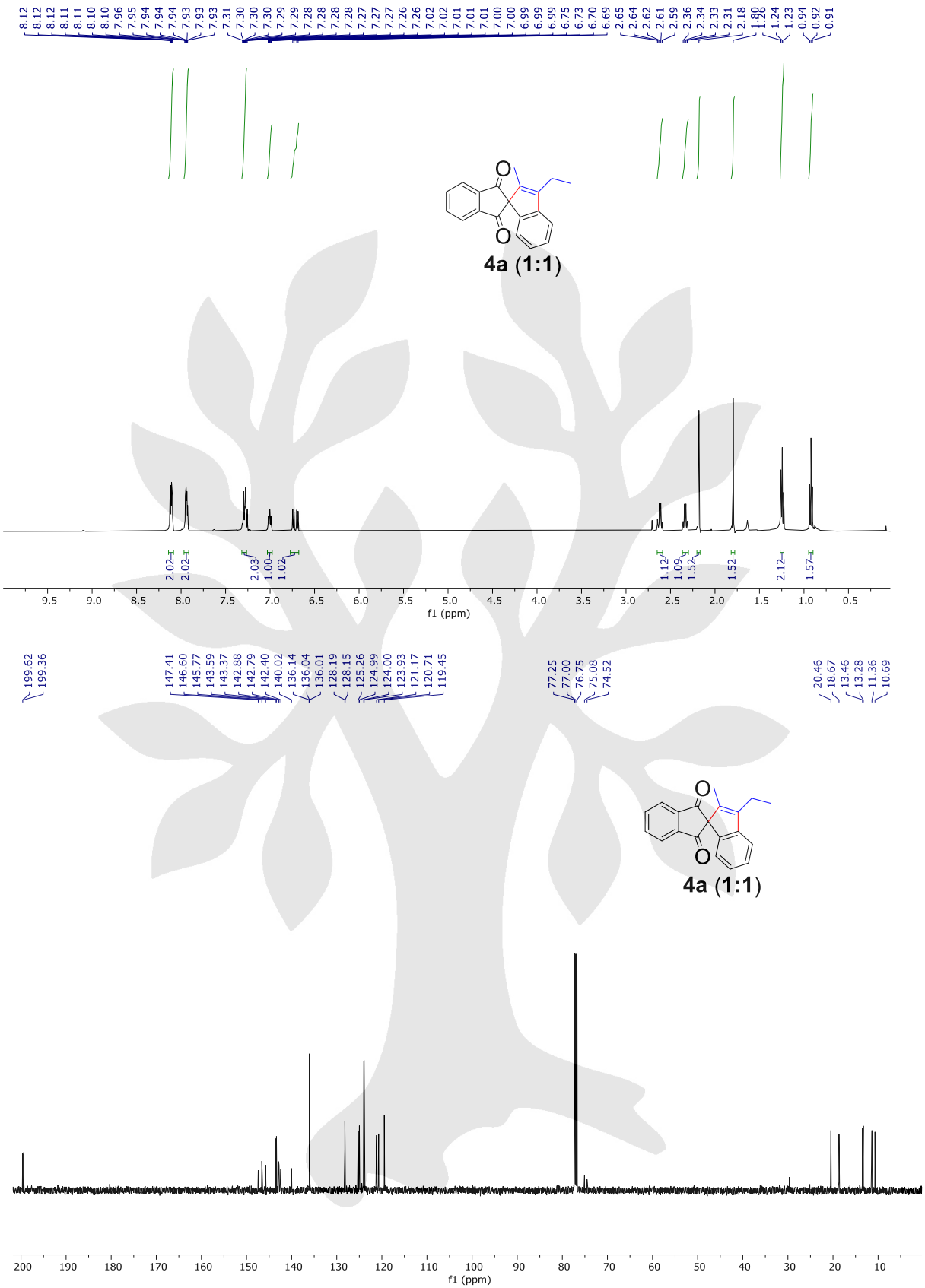


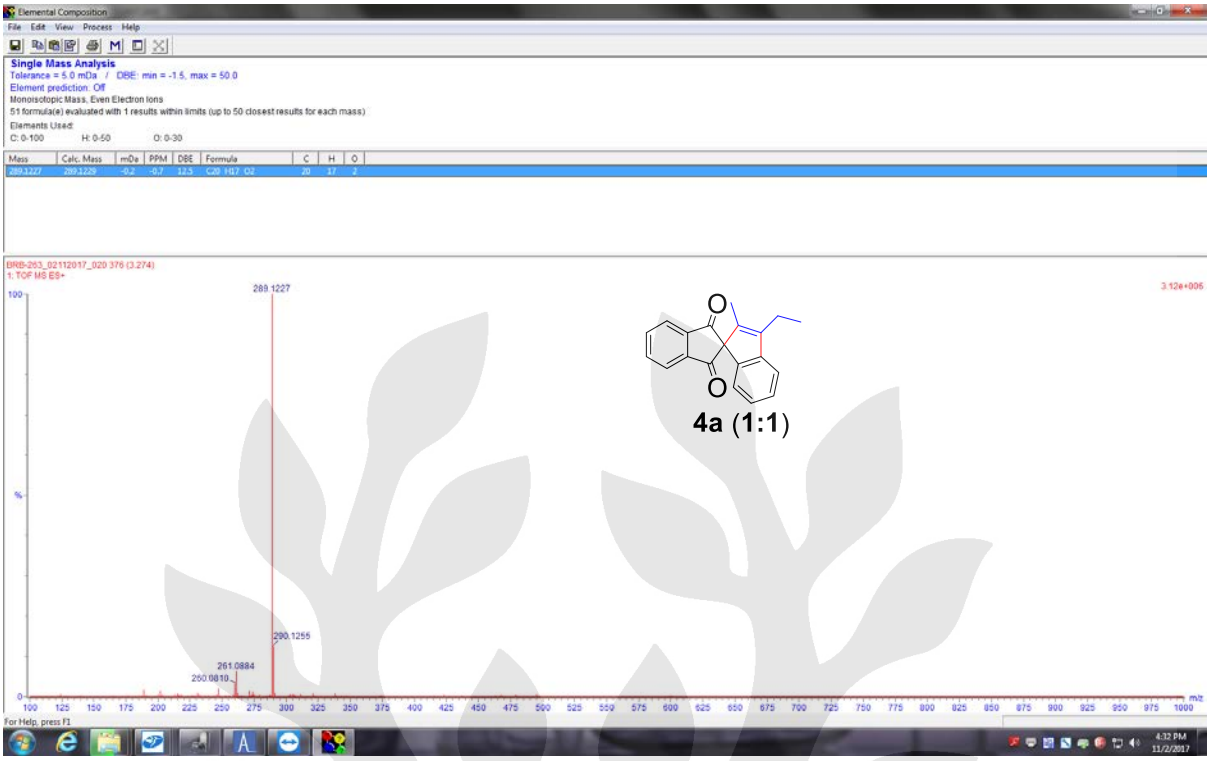




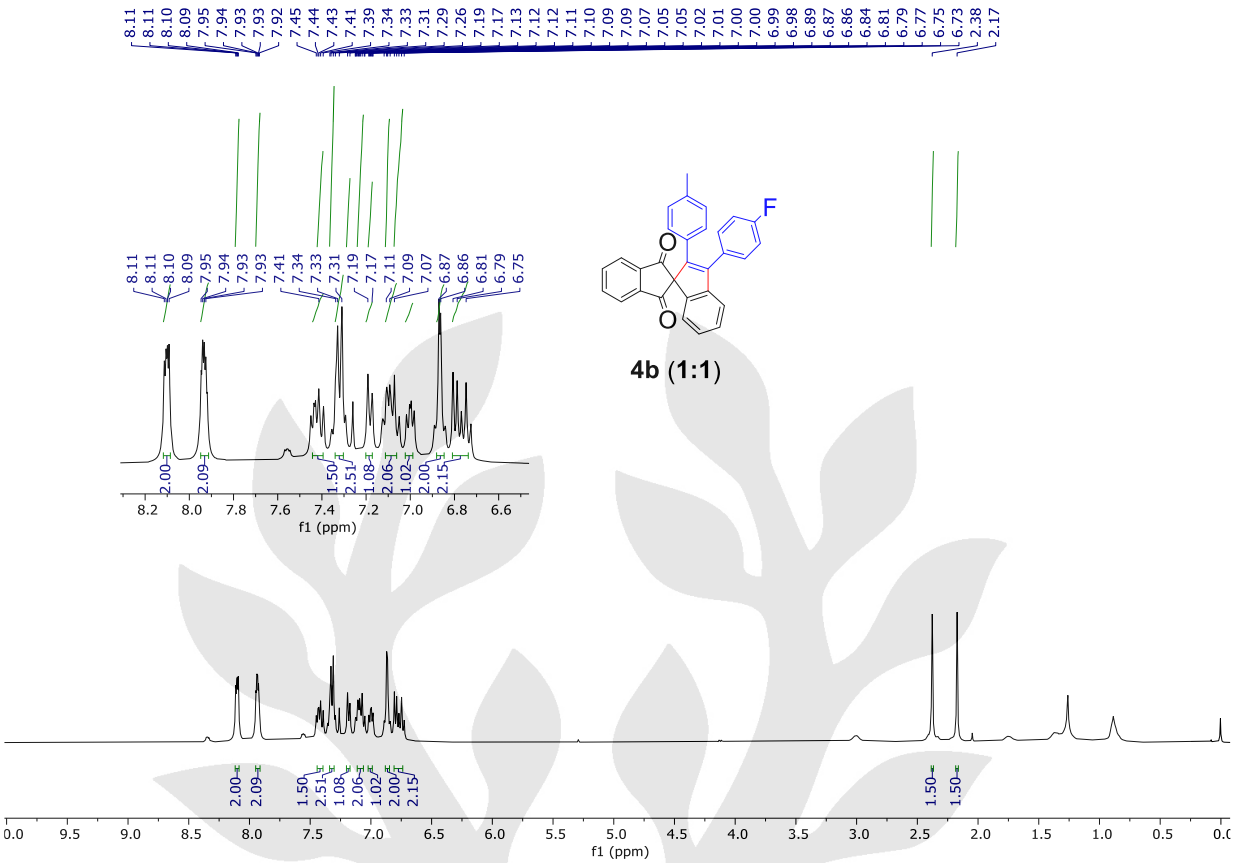


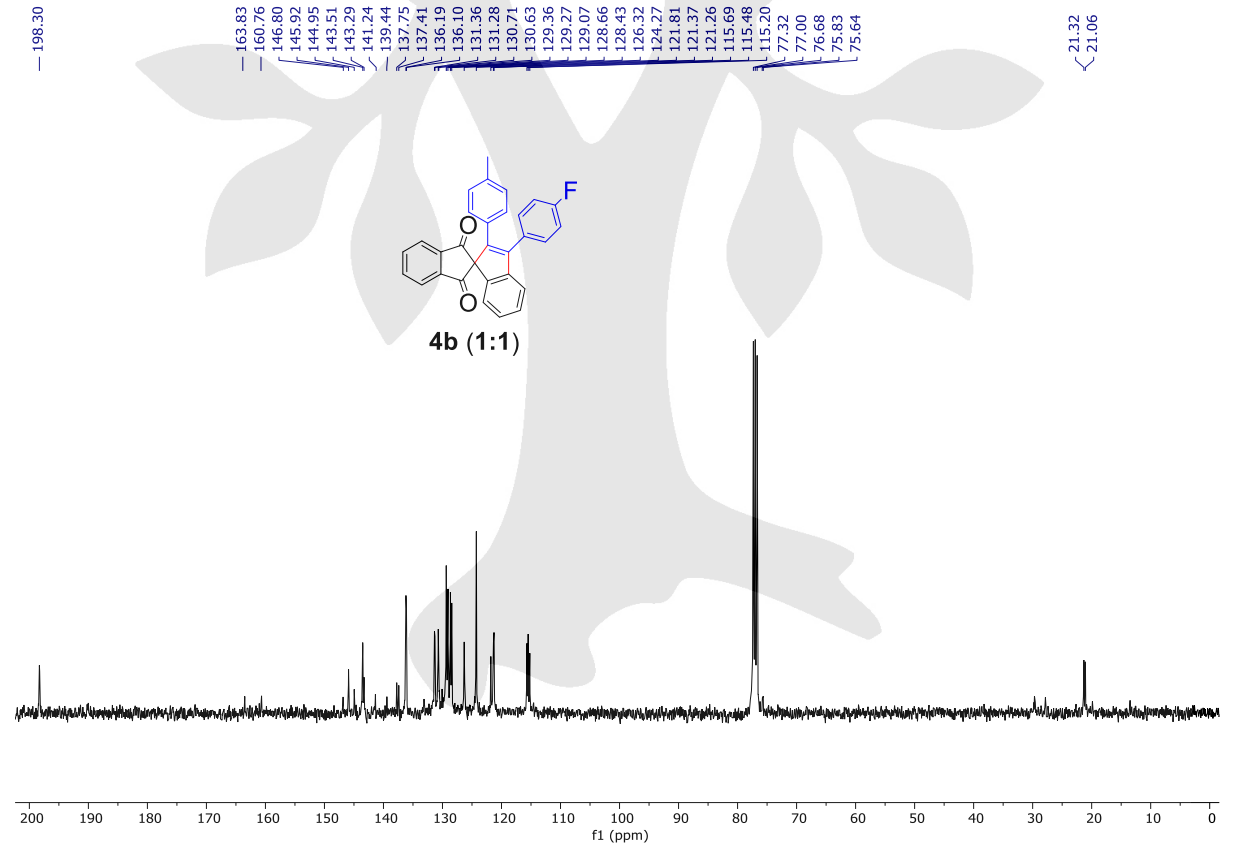


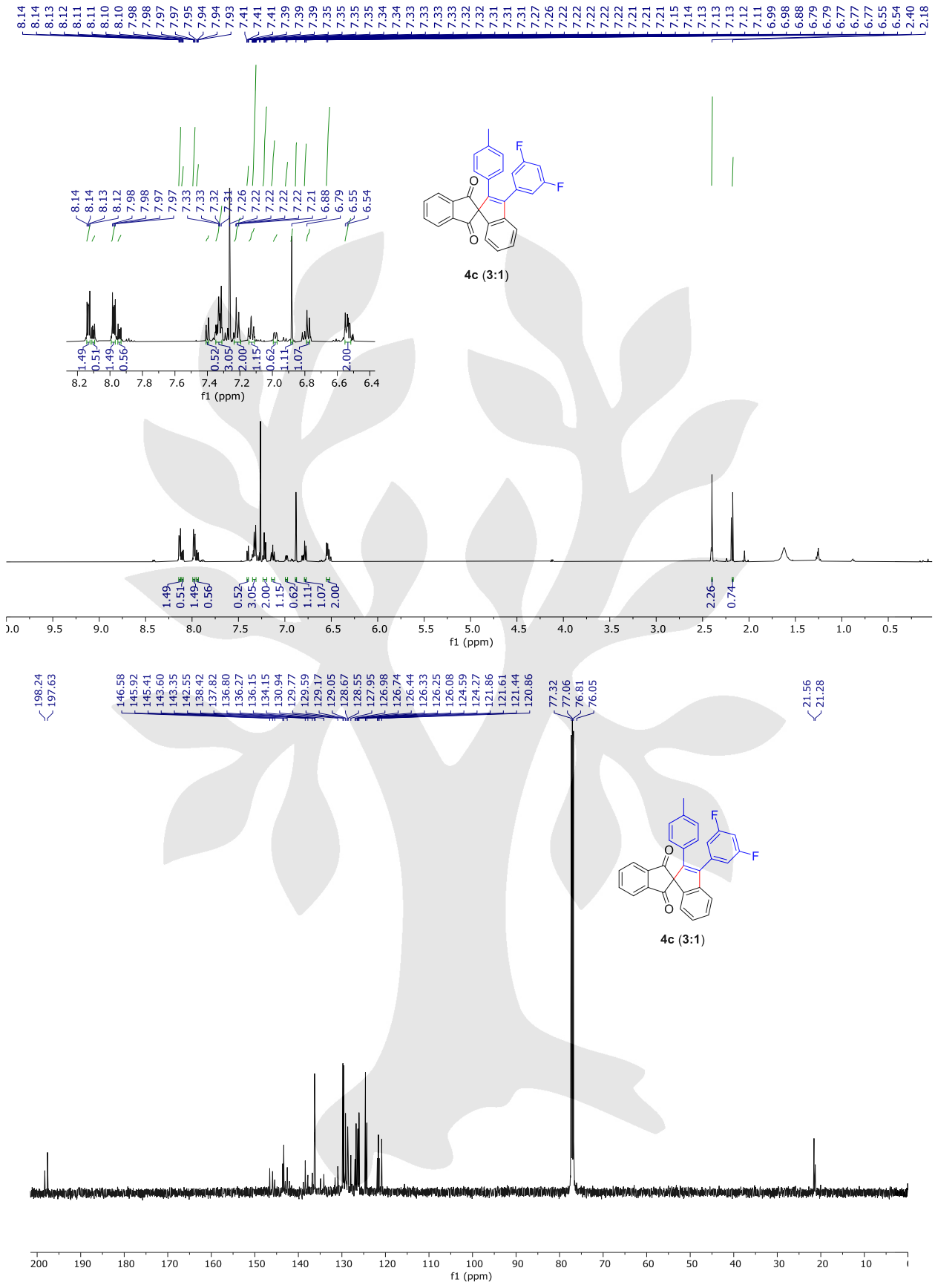


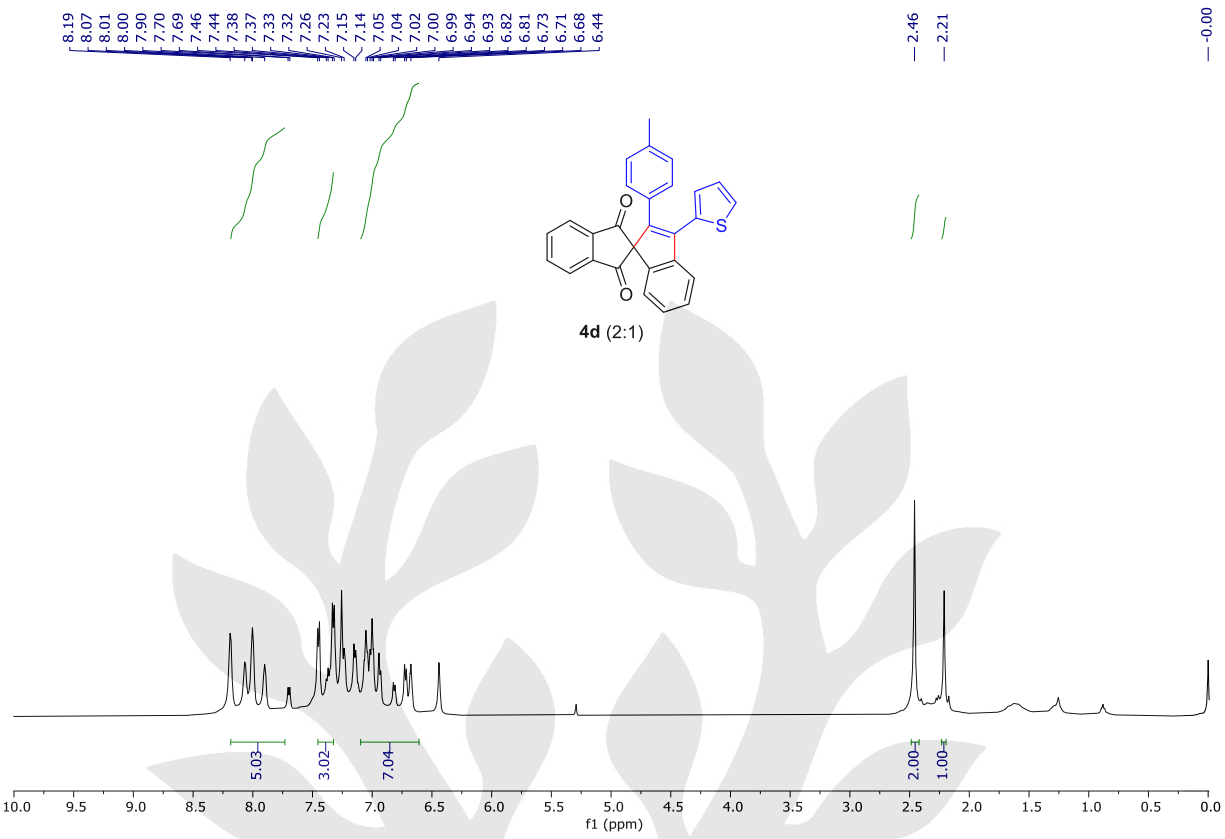


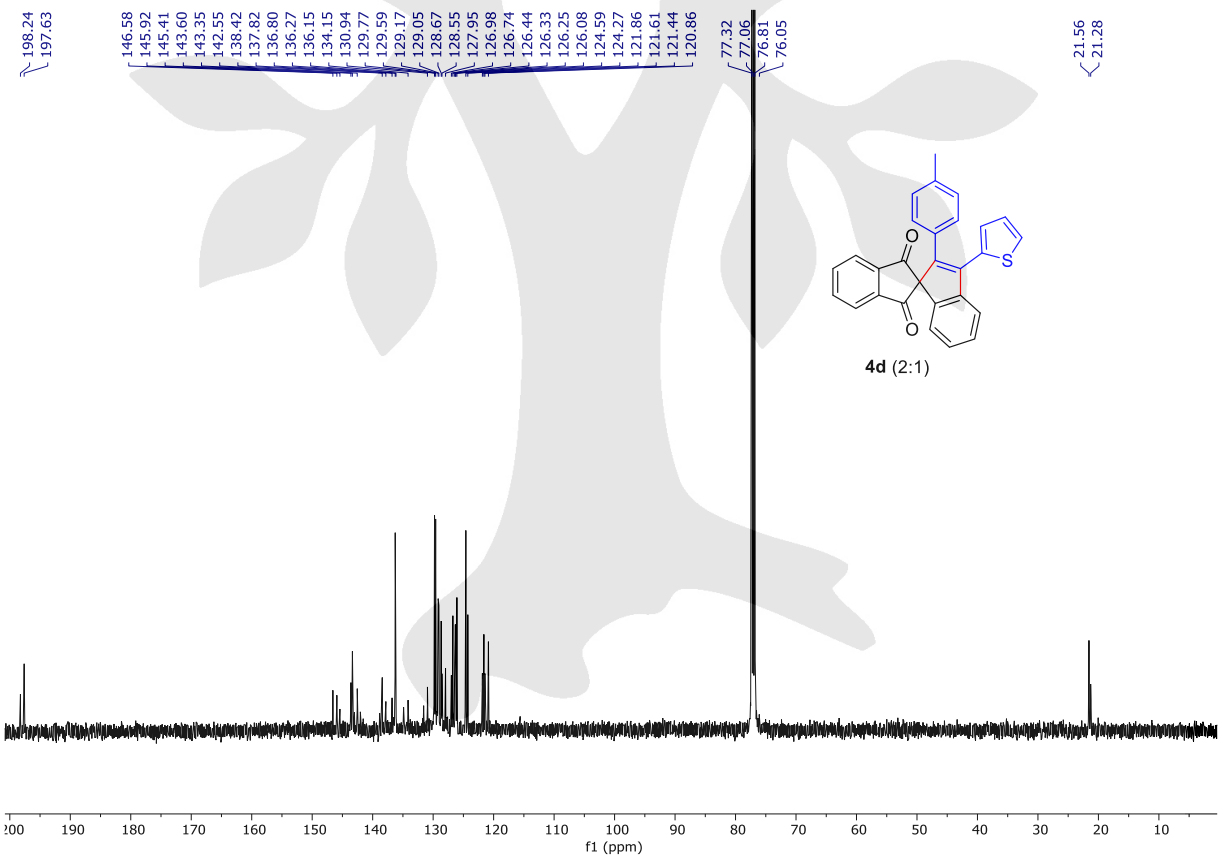
4a (1:1)

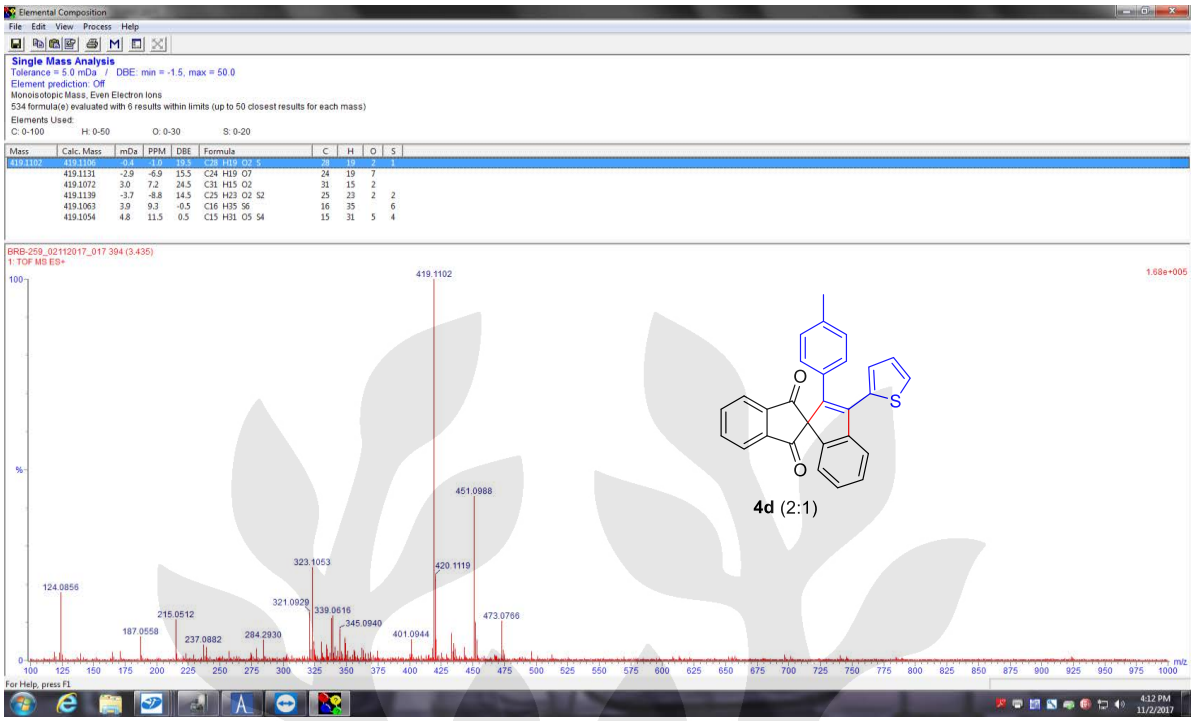




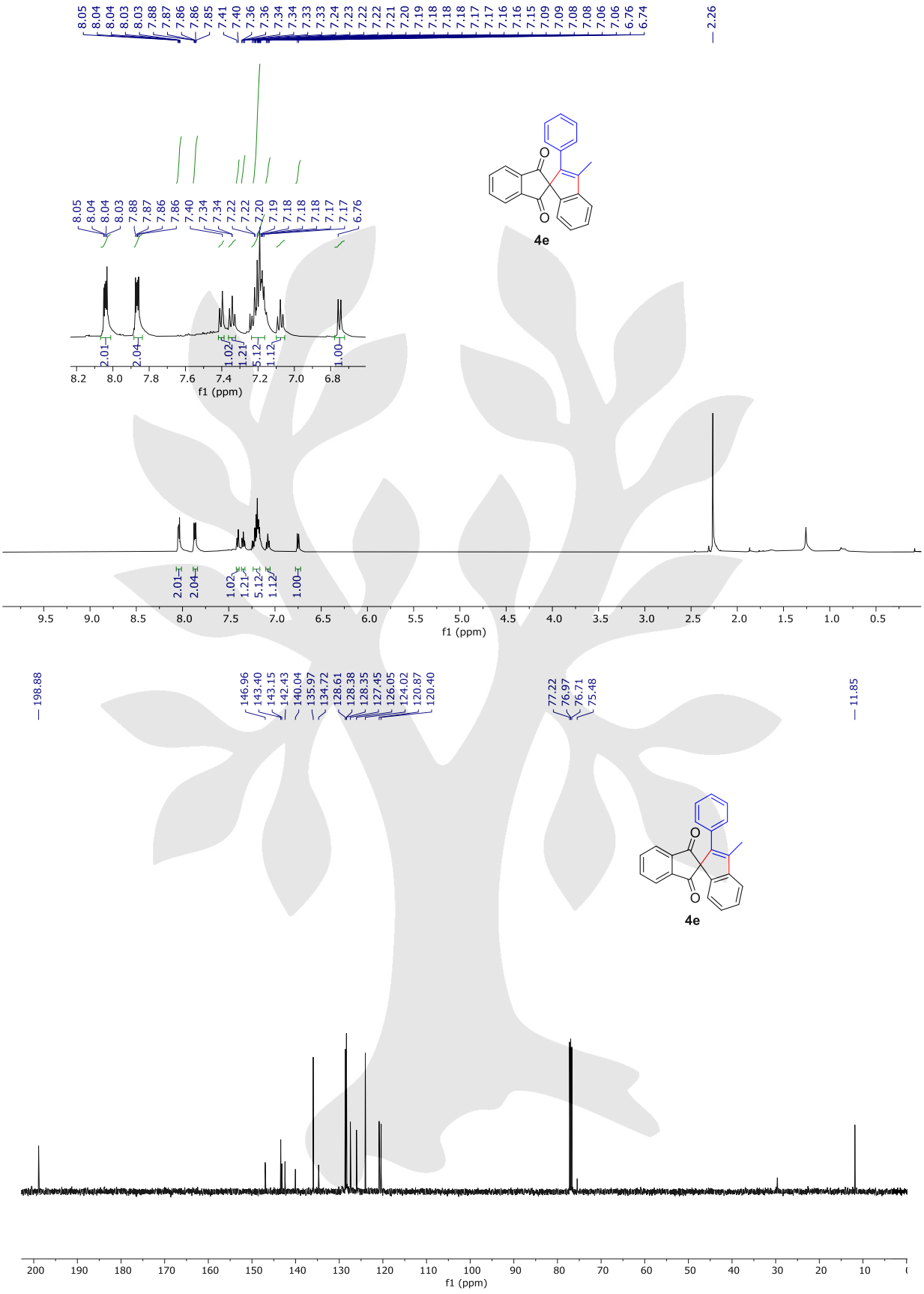


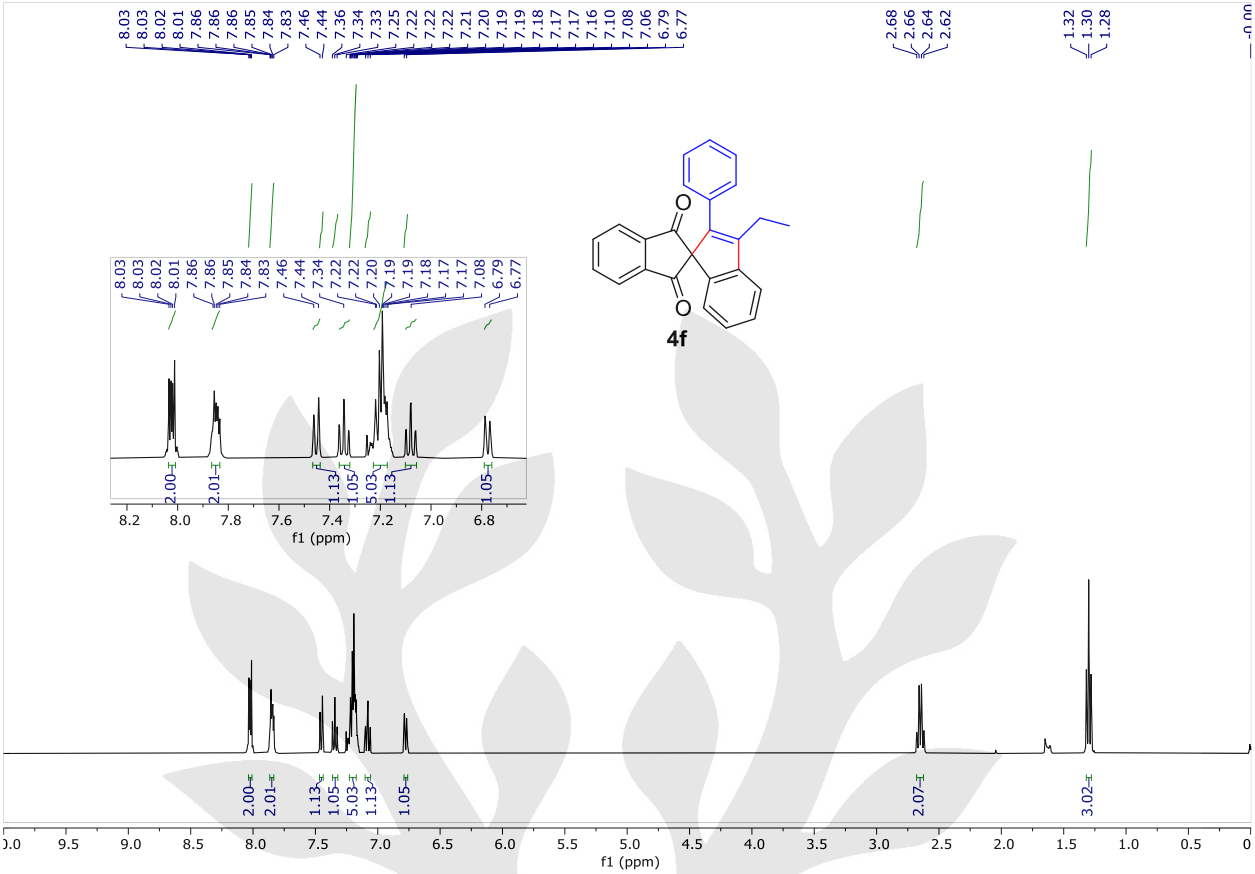


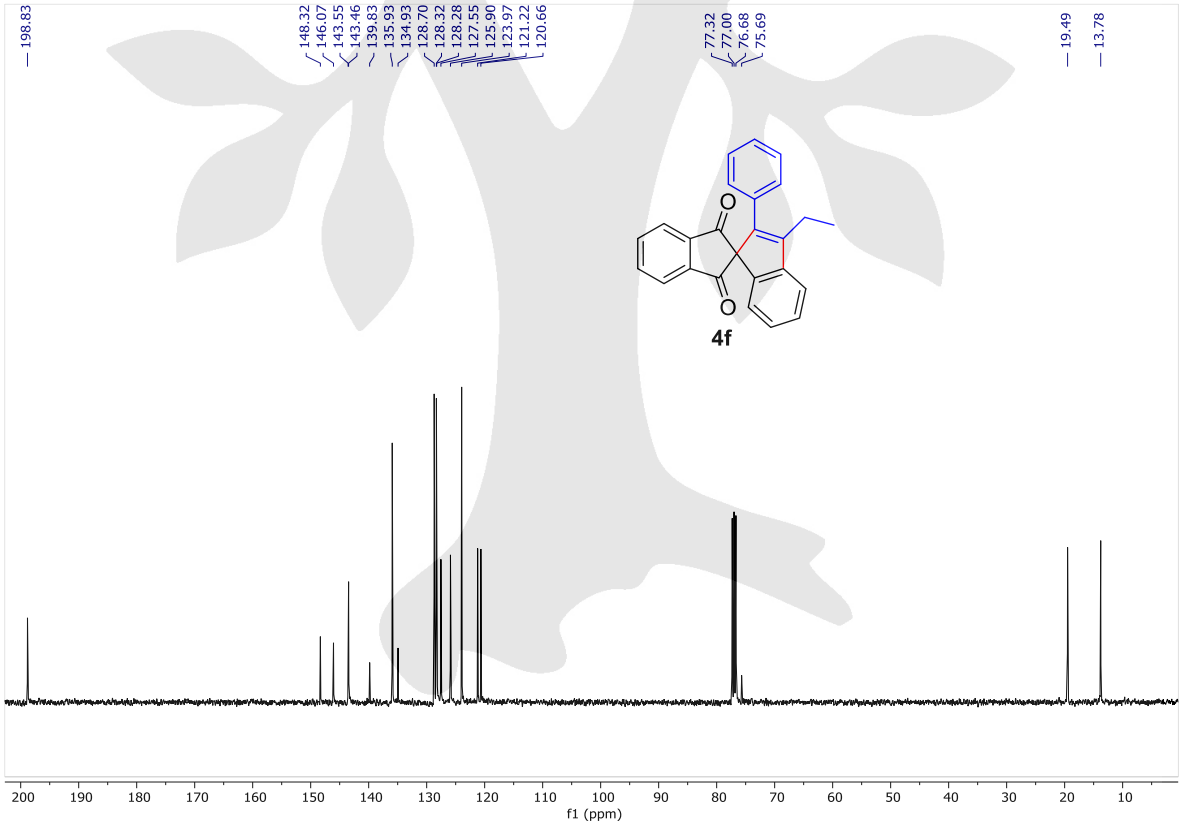


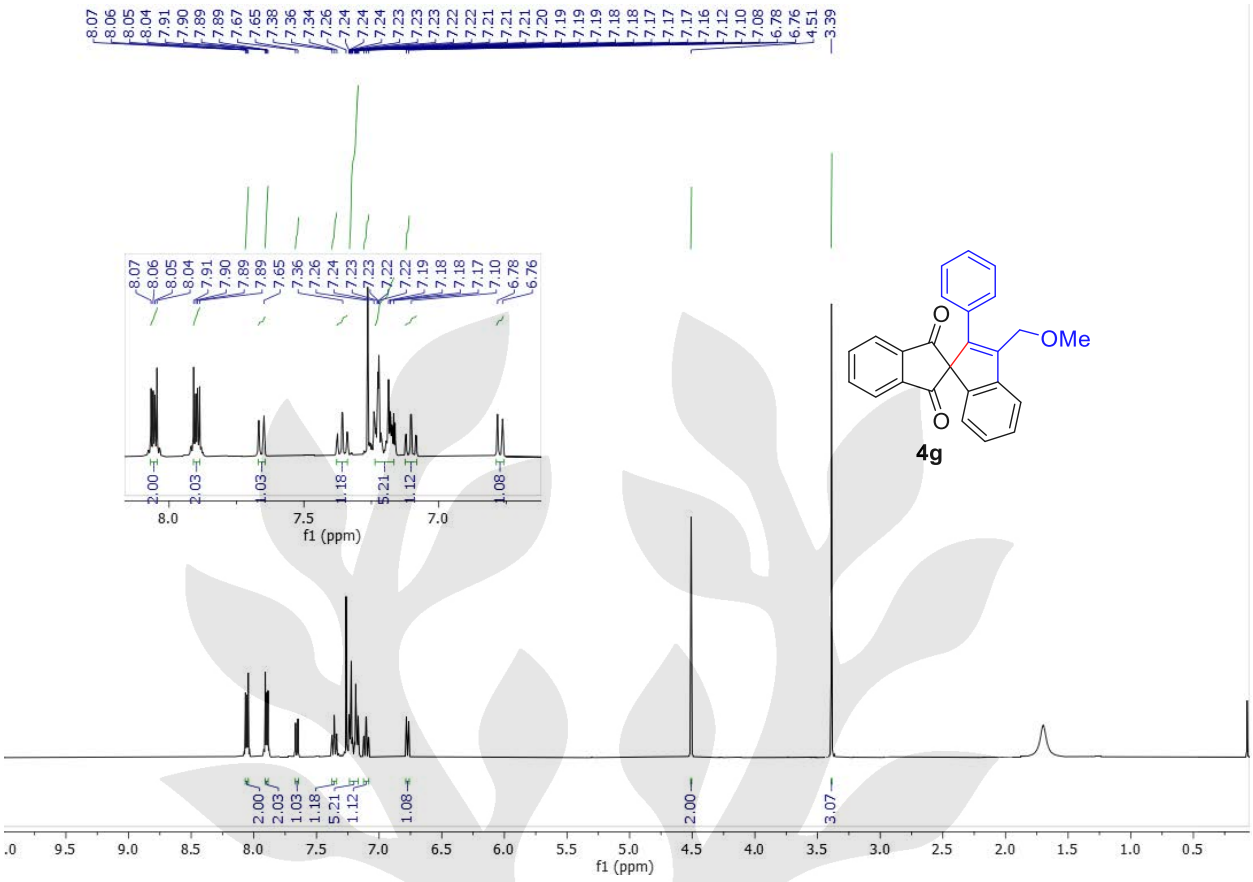


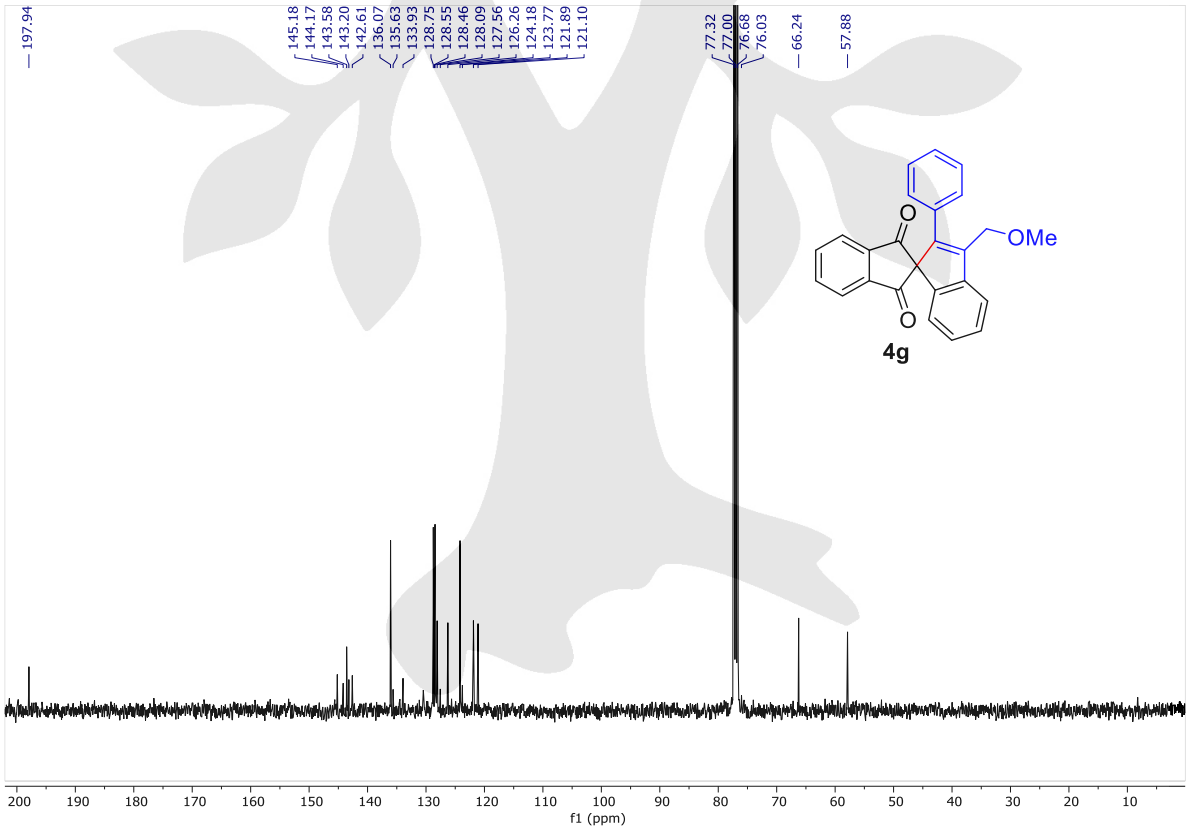
4d (2:1)

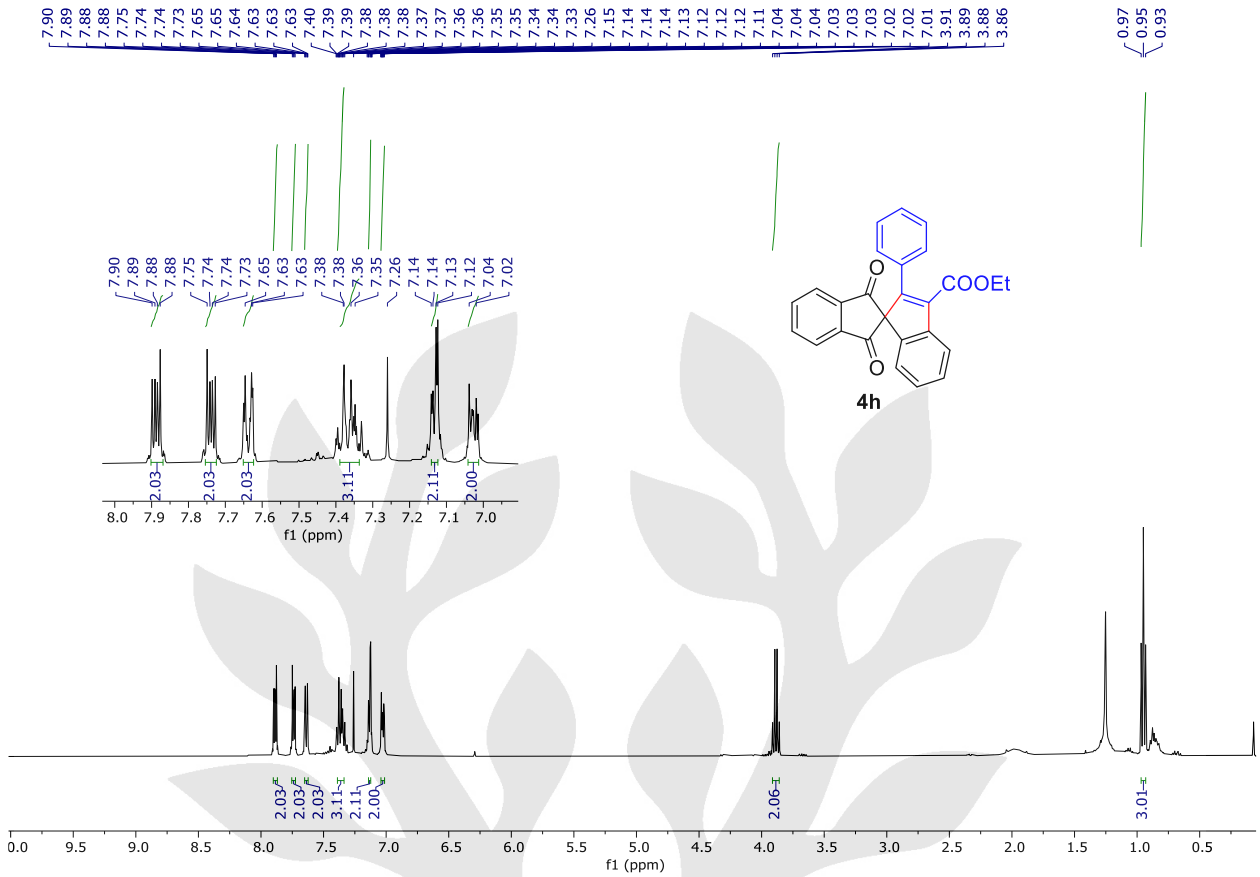


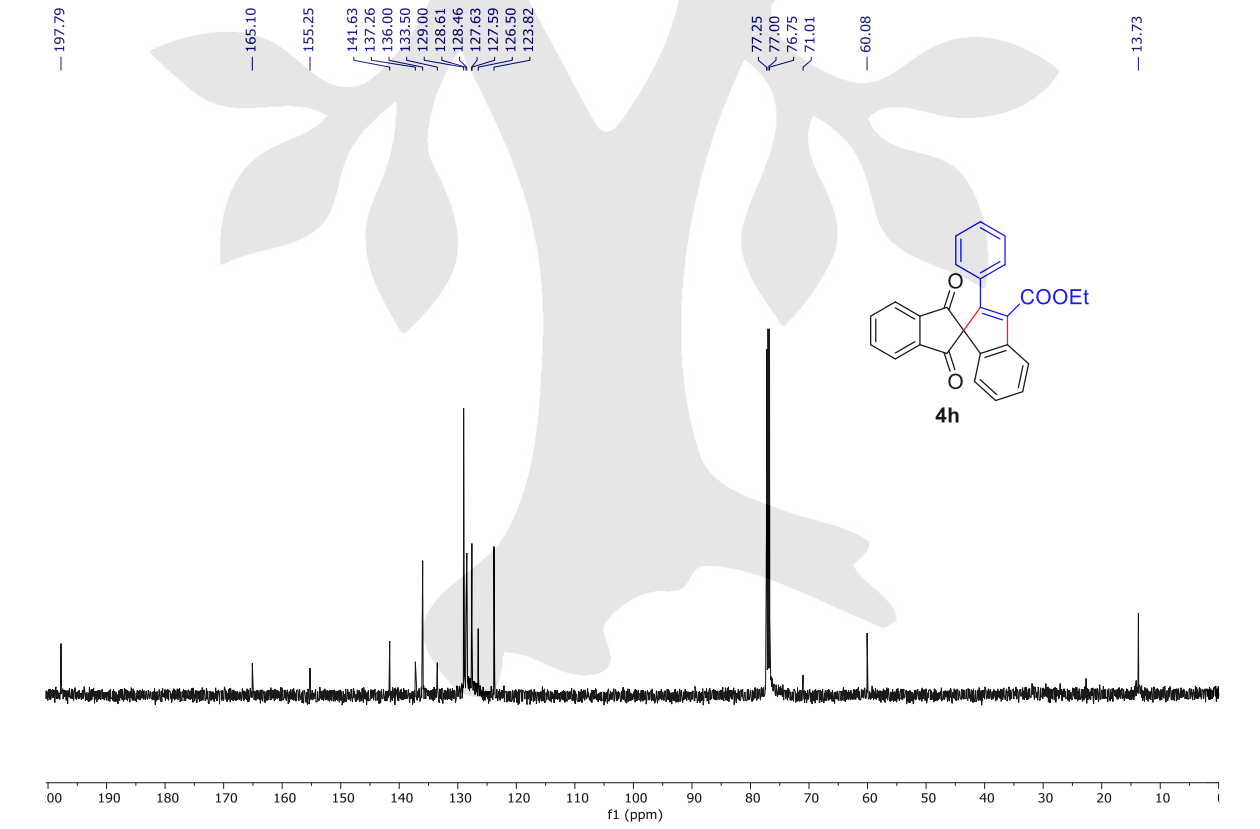


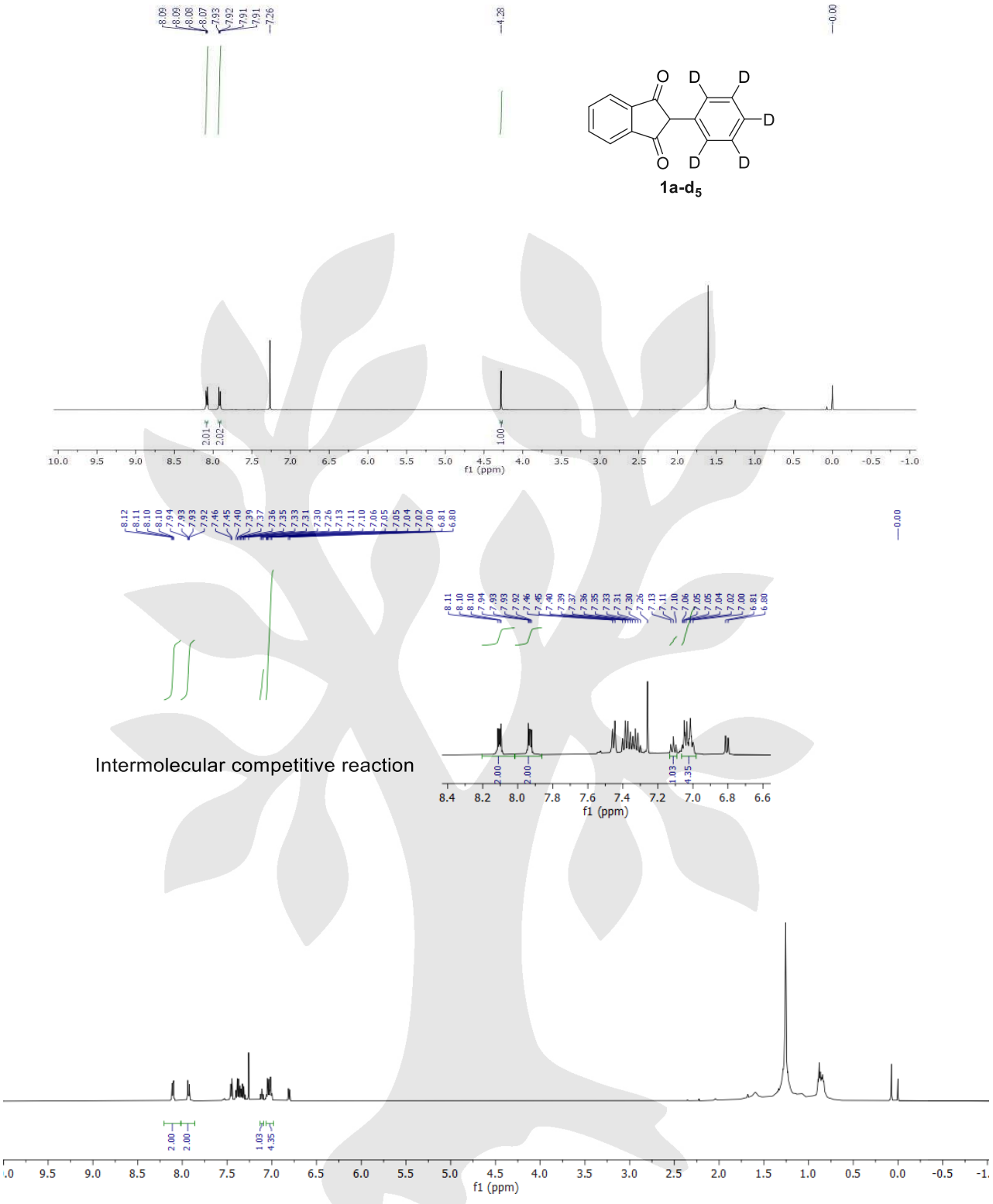




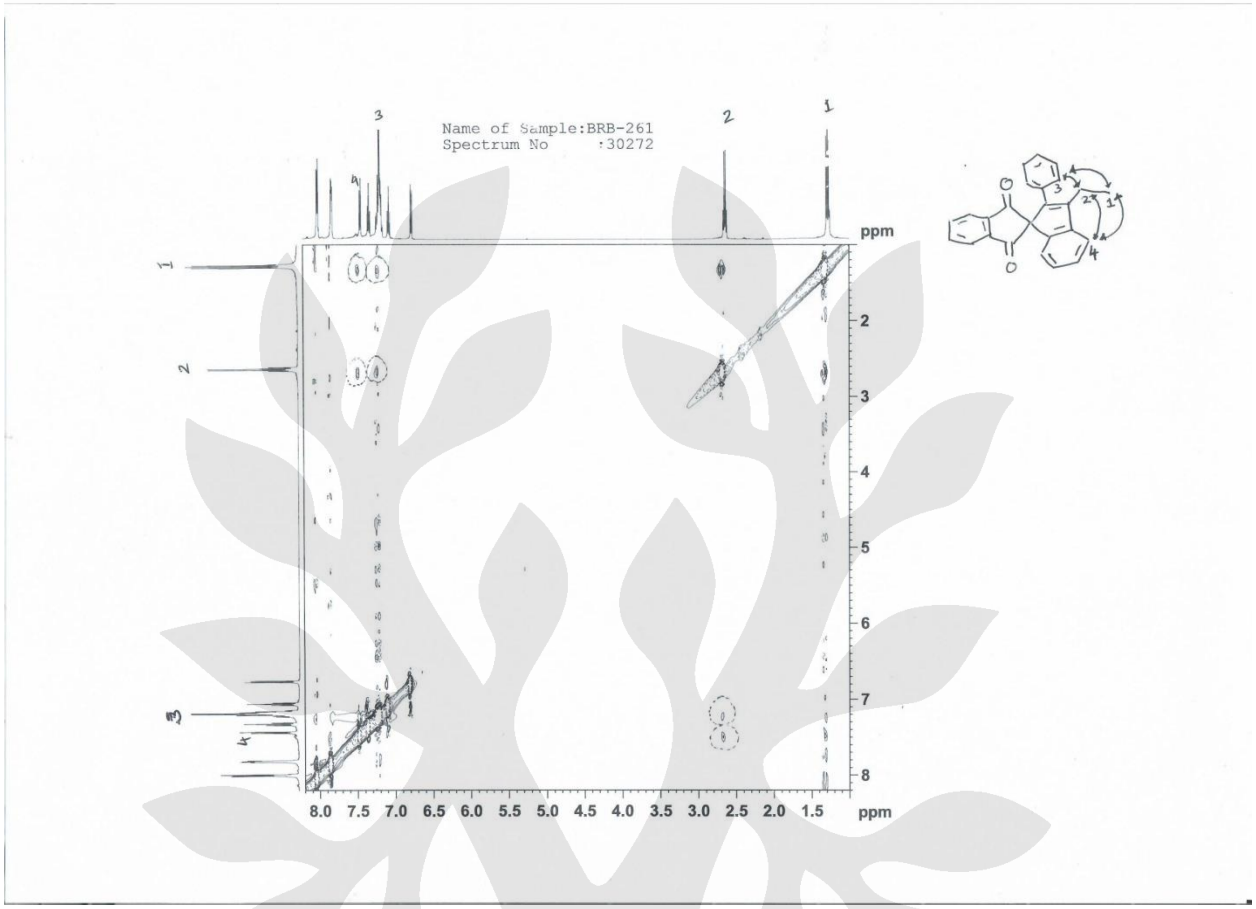








NOE Spectrum of 4f



The NOE experiment of the compound **4f** showed interaction of methyl and methylene protons with the aromatic protons of different δ values which suggest the structure **4f**, not **4f′**.