# Regioselective Oxidative CDC Reactions: An Efficient Synthesis of α-Aryl Carbonyls, Biphenols and Quinones

**A Thesis**

**Submitted in Partial Fulfillment of the Requirements**

**of the Degree of**

## Doctor of Philosophy

By

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

**September-2017**

*Dedicated to*

*My parents*

*And*

*My Beloved family*

**INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH**
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## CERTIFICATE

Certified that the work described in this thesis entitled ***"Regioselective Oxidative Cross Dehydrogenative Coupling Reactions: An Efficient Synthesis of α-Aryl Carbonyls, Biphenols and Quinones"*** submitted by ***Mr. Nagnath Yadav More*** was carried out by the candidate, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other university or institution.

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# Declaration

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

Date: 12th September 2017

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Nagnath Y More

# Synopsis

The thesis entitled ***"Regioselective Oxidative CDC Reactions: An Efficient Synthesis of α-Aryl Carbonyls, Biphenols and Quinones"*** consists of four chapters followed by Experimental details, References, and Spectra.

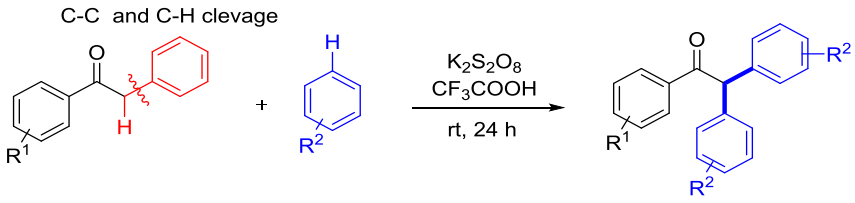
My doctoral research focuses on a transition metal-free C-H bond functionalization through cross-dehydrogenative coupling (CDC) reactions. Cross-dehydrogenative coupling (CDC) reactions from the coupling of two C-H bonds, represents a new state of the art in the field of organic chemistry for C-C or C-X bonds formation. In particular, CDC reactions do not require any pre-functionalization. Hence, these are efficient, practical, and high atom economical processes for the constructions of natural products, medically potential compounds, and other vital organic molecules. In this context, recently, coordination-directed selective C-H bond activation has been established to accomplish CDC reactions. These transformations involve a variety of transition and late transition metals such as like Pd, Rh, Ir, Ru, Co, Cu, Fe, and Mn, etc. as catalysts, which do not need pre-functionalization of at least one substrate. In recent years, due to the high cost of metal catalysts, toxicity, and necessity of ligands, the organic chemist has initiated to develop metal free C-H bond functionalization as an alternative for many reactions along with discovering new methods. The present doctoral thesis aimed to demonstrate unprecedented transition-metal-free aerobic oxidative cross-dehydrogenative coupling (CDC) methods for regioselective formation of the C-C bond by coupling of two C-H bonds and applied in the synthesis of complex organic molecules. In this context, this doctoral research describes oxidative cross-coupling of two C-H bonds via single electron transfer under mild reaction conditions for the synthesis of α-aryl carbonyl compounds, non-symmetrical biphenols, binaphthols and substituted quinones. This thesis has been divided into following four chapters:

**Chapter 1** of this thesis gives a brief introduction of C-H bond functionalization for C-C and C-X bond formation. It provides complete literature survey on transition metal-catalyzed and metal-free C-H bond functionalization and application in the synthesis of natural products, medically potential compounds and other organic molecules. Apart from literature, it describes the objective of the thesis work.

**Chapter 2** deals with a regio-selective aerobic α-arylation of benzyl ketones with un-activated arenes. We have demonstrated an unprecedented metal-free aerobic oxidative dehydrogenative α-arylation at the tertiary $Sp^3$ C-H bond of benzyl ketones with aromatics through carbon-carbon and C-H bond cleavage in the presence of $K_2S_2O_8$ in $CF_3COOH$ at room temperature. Recently, the chemistry of $K_2S_2O_8$ has gained tremendous attention in C–H bond functionalization due to its remarkable reactivity and selectivity. Chapter 2 divided into the following sections.

**Section 2A: Aerobic Dehydrogenative α-Diarylation of Benzyl Ketones with Aromatics through Carbon–Carbon Bond Cleavage**

Substituted benzyl ketones reacted with readily available aromatic hydrocarbons in the presence of $K_2S_2O_8$ in $CF_3COOH$ at room temperature, yielding α-diaryl benzyl ketones through a carbon–carbon bond cleavage. It is important to mention that, in the present reaction, two electronically mismatched coupling partners such as substituted benzyl ketones and electron-rich aromatics were coupled without any metal and pre-activation, which is even more useful in organic synthesis regarding atom economy and green chemistry. Under these modified conditions, the coupling of substituted benzyl phenyl ketones proceeds with high efficiency and regiocontrol to introduce two aryl moieties at methylene position (Scheme 2.1).

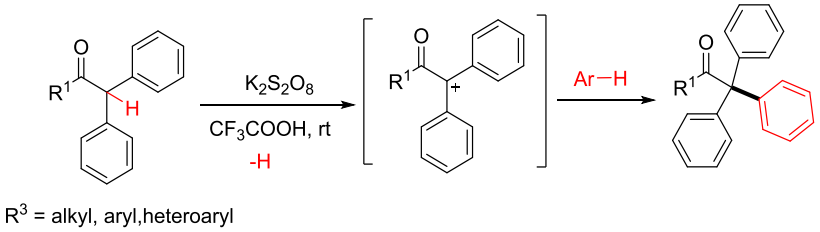



**Scheme 2.1:** α-Diarylation of benzyl ketones with aromatics through carbon–carbon bond cleavage

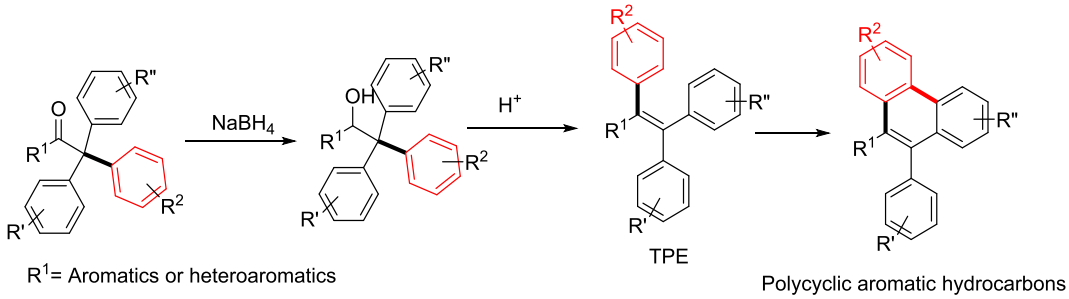
**Section 2B: A Regioselective Synthesis of Benzopinacolones via Aerobic Dehydrogenative α-Arylation at Tertiary $Sp^3$ C-H Bond of 1,1-Diphenylketones With Aromatics and Heteroaromatics**

Section 2B debates on the regioselective synthesis of symmetrical and unsymmetrical benzo-pinacolones via aerobic dehydrogenative mono-arylation at the tertiary $Sp^3$ C-H bond of substituted 1,1-diphenylketone with aromatics and heteroaromatics. The demonstrated conditions in hand, next we sought to define selective mono **α**-arylation without C-C bond cleavage. In the presence of $K_2S_2O_8$ or other oxidants, 2-phenylacetophenone suffered completely to produce selective mono arylation. Hence, we anticipated that evaluation of the oxidative coupling reaction should examine with exposure of modified ketone such as 1,1-Diphenylketones and substituted aromatics. Indeed as expected, a series of 1,1-diaryl ketones readily undergo single aryl

incorporation in the presence of $K_2S_2O_8$, to generate 1,1,1-triaryl carbonyls with excellent efficiency in a highly regioselective manner (Scheme 2.2). In the reaction, two different nucleophiles such as substituted ketones and aromatics were coupled together through coupling of two C-H bonds. Finally, the utility of mono **α**-arylation demonstrated for the synthesizing high profile tetraphenylethylene derivatives and polycyclic aromatic hydrocarbons such as 9,10-phenanthrenes (Scheme 2.3).

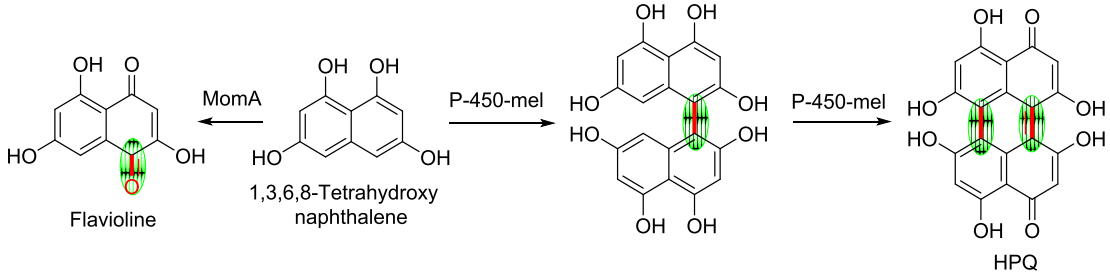



**Scheme 2.2:** Selective mono-arylation of 1,1-diphenyl ketones



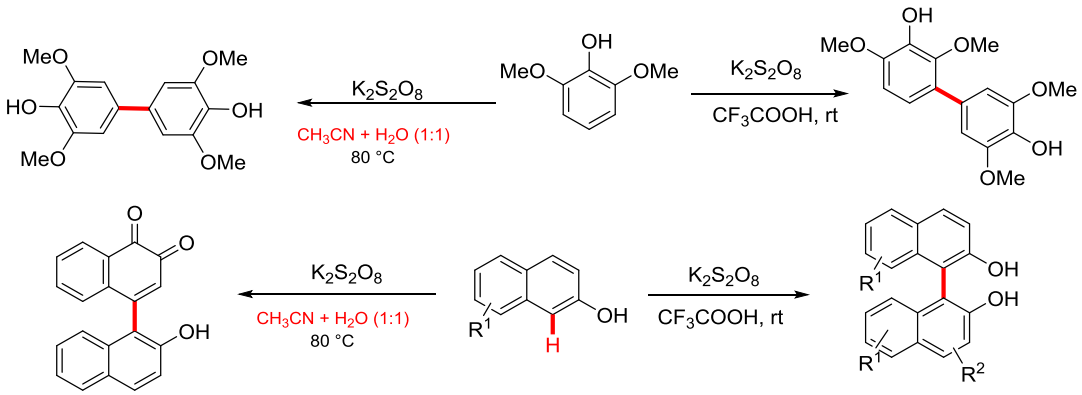

**Scheme 2.3:** Synthesis of TPE and PAH

**Chapter 3** is on the progress of solvent controlled the selective synthesis of biphenols and quinones via oxidative coupling of phenols. It is well recognized that phenols or naphthols undergo direct oxidative coupling processes in the presence of external oxidizing reagents. Nature has been synthesizing natural products and biomaterials via oxidative phenol coupling as a key step using enzymes such as laccase, peroxidase and cytochrome P450 (CYP) as catalysts. A quinone-forming enzyme, momA oxidizes selectively 1,3,6,8-Tetrhydroxynaphthalene to flavioline and P-450-mel catalyzes selectively dimerization of 1,3,6,8-Tetrhydroxynaphthalene selectively to produce homocoupling product (Scheme 2.4).



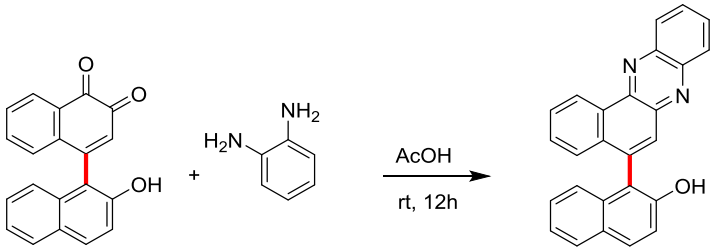

**Scheme 2.4:** Bio-catalytic selective oxidation of 1,3,6,8-tetrahydroxynaphthalene

Thus, we accepted this challenges in our laboratory and found optimization conditions to describe the completely selective formation of either quinone then Michael type of addition to provide unsymmetrical quinones or oxidative homocoupling providing biphenols (Scheme 2.5). A gram scale synthesis of biphenols, binaphthols, and quinones was demonstrated.




**Scheme 2.5:** Synthesis of biphenols and quinones

It includes the application of coupling reaction in the synthesis of phenazine derivative anti-plasmodial activity. (Scheme 3).

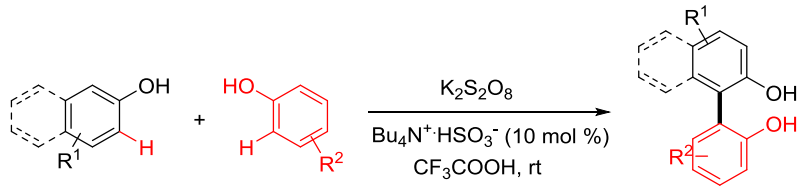



**Scheme 2.6:** Synthesis of phenazine

**Chapter 4** discusses oxidative cross-coupling of two different phenols and phenols with substituted aromatics in the presence of the easily affordable and environmentally benign $SO_4^{-\bullet}$ anion radical and a catalytic amount of $Bu_4N^{+}HSO_4^{-}$ in $CF_3COOH$ (TFA) solvent at ambient conditions providing unsymmetrical biaryls. Phenols are highly oxidized compounds in the presence of external oxidizing reagents to give competitive side products. While designing of oxidative cross-coupling reactions of phenols, controlling competitive side products and selectivity is very important. However, a defining attribute of $SO_4^{-\bullet}$ as an oxidant in the presence of counter ion such as $Bu_4N^{+}HSO_4^{-}$ is its potential to provide direct oxidative cross coupling of two different phenols and phenols with arenes with suppressed side products. This chapter contains two subdivisions as follows:

## Section 4A: Oxidative Cross-Coupling of two different Phenols: An Efficient Route to Unsymmetrical Biphenols

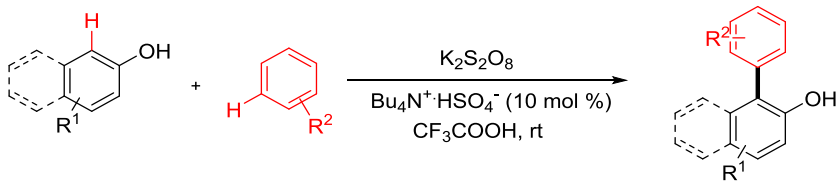
The development of highly effective, easily accessible and environmentally friendly method for synthesizing unsymmetric biphenol molecules under the mild reaction conditions in a highly atom economical manner is highly important in organic synthesis. This section demonstrates a practical route to synthesize of unsymmetrical biphenols via the oxidative cross-coupling of two different phenols in the presence of $K_2S_2O_8$ in $CF_3COOH$ at ambient temperature under air. The cross-coupling reaction was also successfully extended into 1:1 cross-coupling of substituted phenols with naphthols and 1:2 cross-coupling of naphthols with phenols.




**Scheme 2.7:** Phenol-phenol and phenol-naphthol cross-coupling

## Section 4B: Oxidative cross-coupling of substituted phenols with unactivated aromatics at ambient temperature

The synthesis of phenol-based bi-aryls is very challenging and has not been well documented. Although the oxidative coupling of phenols is known in the literature for several decades, the cross-coupling of phenols with unactivated aromatics is not well documented. The oxidative cross-coupling of phenols with aromatics is a productive method synthesizes bi-aryl molecules, without the protection of the OH group, in one pot. This section discusses unprecedented regio-selective arylation of phenols with arenes via oxidative cross-coupling reactions in the presence of $K_2S_2O_8$ and $Bu_4N^+HSO_4^-$.




**Scheme 2.8:** Regio-selective arylation of phenols with arenes

***Publications*:**

1. **More, N. Y.;** Jeganmohan, M.; "Aerobic Dehydrogenative α-Diarylation of Benzyl Ketones with Aromatics through Carbon-Carbon Bond Cleavage". *Org. Lett*. **2014,** *16*, 804.

2. **More, N. Y**.; Jeganmohan, M.; "A Regio-selective Synthesis of Benzopinacolones through Aerobic Dehydrogenative & α-arylation of a Tertiary $Sp^3$ C-H bond of 1,1-Diphenylketones with Aromatic and Heteroaromatic Compounds". *Chem. Eur. J.* **2015**, *21*, 1337.

3. **More, N. Y.;** Jeganmohan, M.; "Oxidative Cross-Coupling of Two Different Phenols: An Efficient Route to Unsymmetrical Biphenols". *Org. Lett*. **2015,** *17*, 3040.

4. **More, N. Y**.; Jeganmohan, M.; "Oxidative Cross-Coupling of Phenols with Unactivated Arenes at Room Temperature manuscript". *Eur. J. Org. Chem.* **2017**, *2017*, 4305.

5. **More, N. Y**.; Jeganmohan, M.; "Solvent-Controlled Selective Synthesis of Biphenols and Quinones via Oxidative Coupling of Phenols". *Chem. Commun.* ***2017,*** 53**,** 9616.

6. **More, N. Y.;** Kishor, P.; Jeganmohan, M.; "Ruthenium(II)-Catalyzed Regio-selective *Ortho* C-H –Benzoxylation of cyclic and *N, N* –Dialkyl Benzamides with Aromatic Acids by week coordination". *J. Org. Chem*., **2017**, *82*, 12691.

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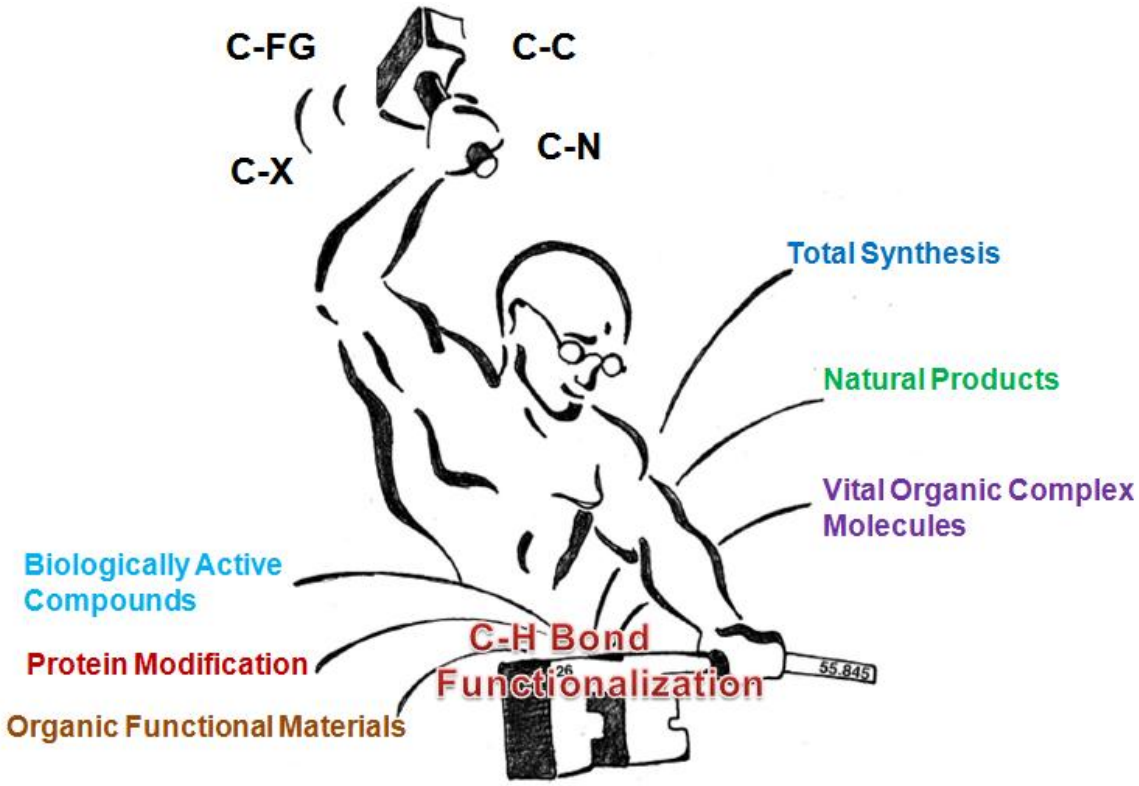
# Chapter 1

## *Introduction: C-H Bond Functionalization*



## 1.1: Significance of C–H Bond Functionalization

Synthetic chemistry represents a challenge to a chemist regarding the ability to convert carbon-hydrogen (C-H) bond into a new functional groups for achieving the molecular complexity. In the past twenty years, many diverse examples of C–H bond functionalization were examined and developed at organic chemistry laboratories, often under remarkably mild conditions and with high selectivity. Very recently, Yamaguchi and Itami achieved the synthesis of dictyodendrin A and F using a logical series of C-H bond functionalization methods (Fig.1.1).[1]

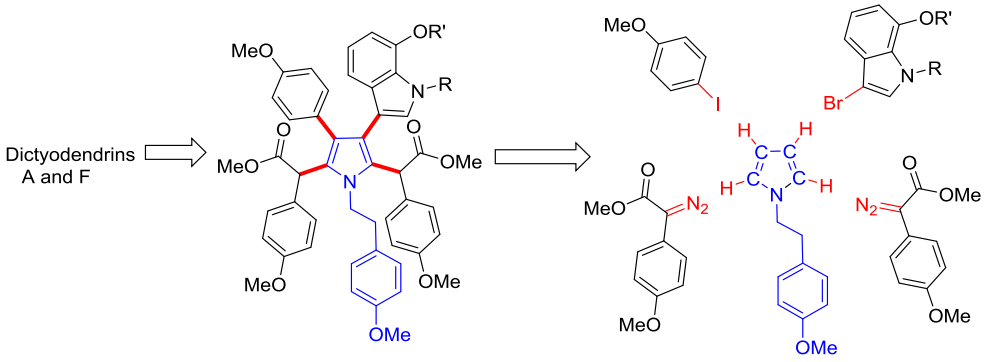
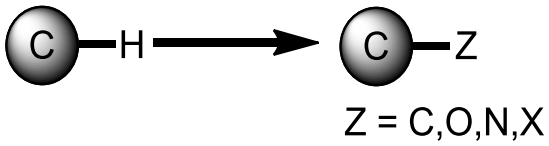



**Fig 1.1:** Sequential C-H bond functionalization to generate complexity

The activation of the strong and localized C–H bond of organic molecules has fundamentally revolutionized synthetic concepts for the construction of chemical bonds in organic synthesis.[2] By employing this method, various chemical bonds such as C-C, C-N, C-X (X = halogens), C-O and C-M are efficiently constructed in highly atom-economical and environmentally friendly manner in one pot (Scheme 1.1).




**Scheme 1.1:** C–H bond functionalization

These reactions can be widely used for the synthesis of biologically active molecules, biopolymers, pharmaceuticals, natural products, materials and polymers (Fig. 1.2).[2]

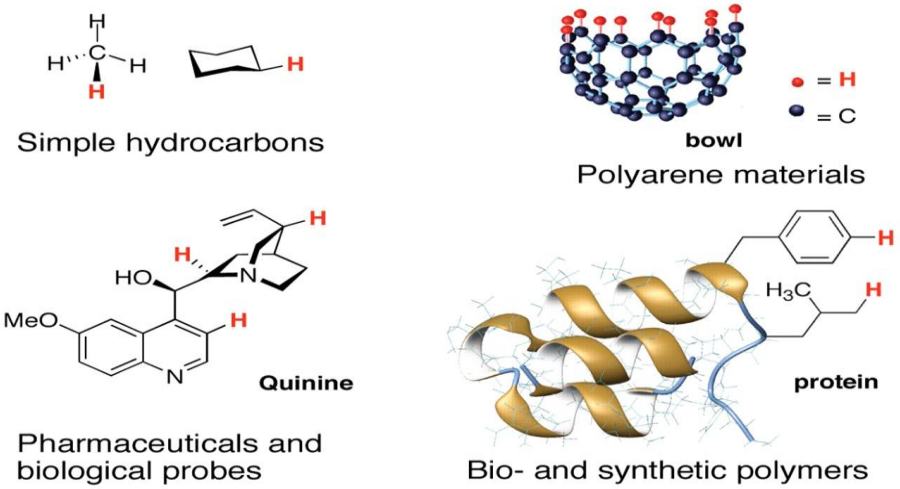
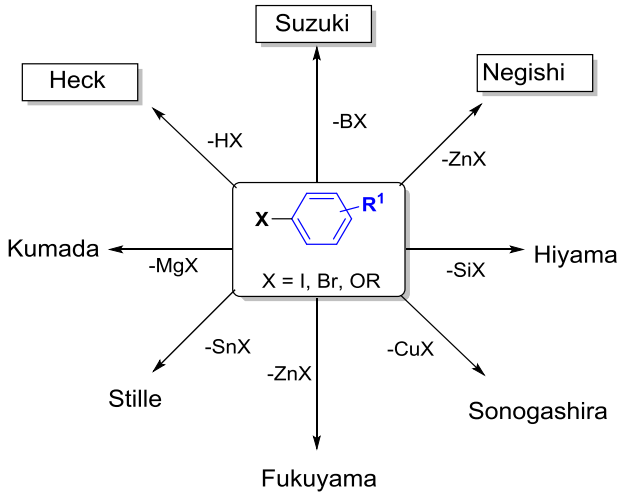



**Fig. 1.2:** C–H bonds are found in nearly all organic compounds.

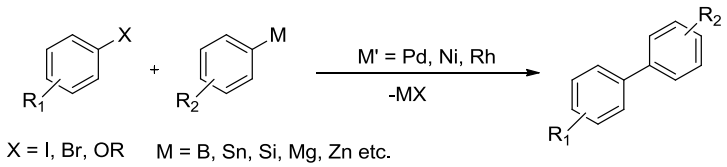
## 1.2: Cross-Coupling Reactions

Direct replacement of carbon-hydrogen bonds with new bonds (such as C–C, C–O, and C–N) represents an important and long-standing goal in chemistry. These transformations have broad potential in synthesis because C–H bonds are ubiquitous in organic substances. Transition metal catalyzed coupling processes were initiated in the 19$^{th}$ century to develop these types of reactions.[3] Transition metal catalyzed cross-coupling reactions have made significant progress and became a revolution in modern organic chemistry (Scheme 1.2).




**Scheme 1.2:** Cross-coupling reactions for C-C bond formation

This great successes and significance of transition metal-catalyzed coupling reactions were also highlighted by the Nobel Prize in chemistry in 2010.[4] Nevertheless; transition-metal-catalyzed coupling reactions are still having some drawbacks and confront challenges to some extent, owing to the instinctive drawbacks of the catalytic systems.[5-7] The first high cost of metal, and necessity of supporting ligands.[5a] Second, most of the transition metals are toxic, and removal of trace amounts of transition-metal residues from desired products is quite costly and challenging. Third, many transition-metal catalysts are usually sensitive to oxygen ($O_2$) and moisture.[6] Fourth, in many cases, special additives and cocatalysts are also critical to promote the efficiency and selectivity of transformations. Last, the large consumption of transition metals does not indeed meet the requirement of sustainable development.[7]




**Scheme 1.3:** Typical cross-coupling

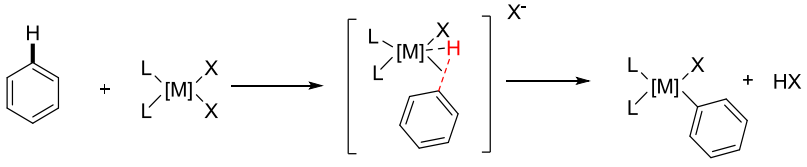
### 1.3: C-H Bond Activation

In the next leap towards the ideal chemical synthesis, methodologies were developed that do not need pre-functionalization of at least one substrate; the development of transition metal-catalyzed C-H bond activation processes has since become established. The C-H bond activation is a type of reaction in which C-H bond is cleaved and replaced with electrophiles or nucleophiles such as aryl halides, alkyl halides and organometallic reagents and forming C-C and C-X bonds (where X is N, O or halogen).

### 1.4: Transition-Metal Catalyzed C-H Bond Activation

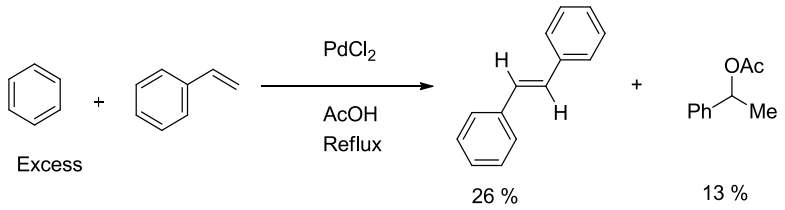
### 1.5: Fujiwara-Moritani Reaction

Recently, transition metal-catalyzed C-H bond activation has emerged as an atom-economical to construct new bonds without requiring of pre-functionalized starting materials. Transition metal activates C-H bond by lowering the activation energy for bond weakening (Scheme 1.4). If the C-H bond activation occurs without a chelating group that is called as non-chelation assisted C-H bond activation.




**Scheme 1.4:** Metal-catalyzed C-H activation

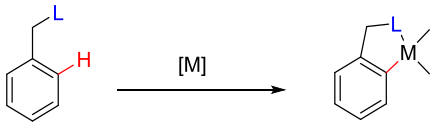
In this context, 1968, Fujiwara's group developed the non-chelation assisted C-H bond activation reaction (Scheme 1.5).[8] This method is atom economical but not selective.




**Scheme 1.5:** Fujiwara-Moritani reaction

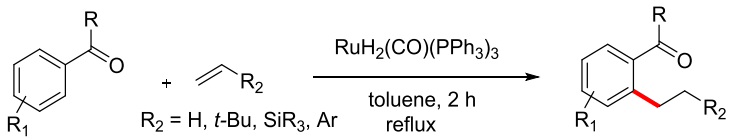
## 1.6: Functional Group Coordinated C-H Bond Activation

Ligand-directed C-H bond activation provides a system for addressing the challenge of site selectivity. In the C-H bond activation, ligand coordinates to the metal center through the formation of a dative bond (Scheme 1.6).



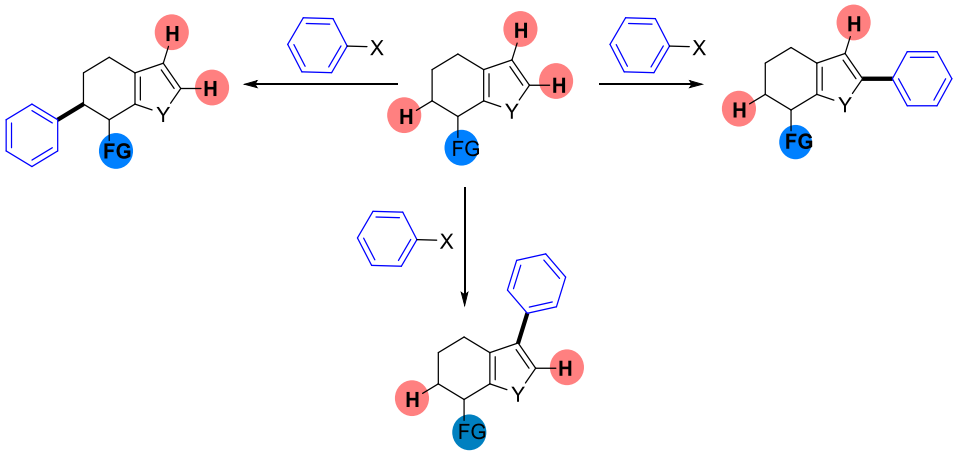

**Scheme 1.6:** Ligand directed C-H bond activation by transition metal

The concept of the functional group directed C-H bond activation was first time introduced by Murai's group using Ru (0) as the metal catalyst. In the reaction, aromatic ketones reacted with alkenes in the presence of ruthenium catalyst giving *ortho*-alkylated aromatic ketones (Scheme 1.7).[9] A remarkable feature of this transformation was the high regioselective C-H bond activation in highly atom economical manner.




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

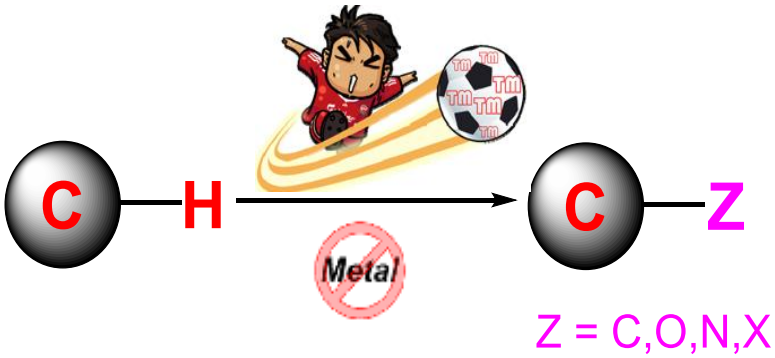
Murai's report attracted much attention and inspired for the development of many catalytic systems to bring out coordination-directed selective C–C formation at aromatic rings ($Sp^2$ C–H bonds) through activation of C-H bond proximal to a suitable functional group (Scheme 1.8). These transformations involve a variety of transition metals like Pd, Rh, Ir, Ru, Co, Cu, and Mn, etc. as a catalyst.[10]




**Scheme 1.8:** Functional group directed selective arylation

## 1.7: Metal-Free C-H Bond Activation

Transition metal-catalyzed C-H bond fictionalization is an efficient method to generate useful products for the pharmaceuticals and chemical industries. However, high cost of metal catalysts, toxicity, and necessity of ligands prompted chemists to put significant efforts in developing metal free C-H bond functionalization as an alternative for many reactions along with discovering new reactions (Scheme 1.9).[5-7]




**Scheme 1.9:** Metal-free C-H bond functionalization

Transition metal-free C-H bond activation is an alternative efficient, and environmentally benign strategy to construct C-C or C-X bonds and it is highly appealing.[11] Functionalization of C-H bond totally depends on bond dissociation energies of particular C-H bond. Among all $C(Sp)^3$-H bond functionalization is considered the most challenging due to its low reactivity. Allylic, benzylic, and $C(Sp)^3$-H bonds adjacent to a heteroatom (N, O) have mostly been used to functionalize,[11] as they are having relatively small bond-dissociation energies (Fig. 1.3).

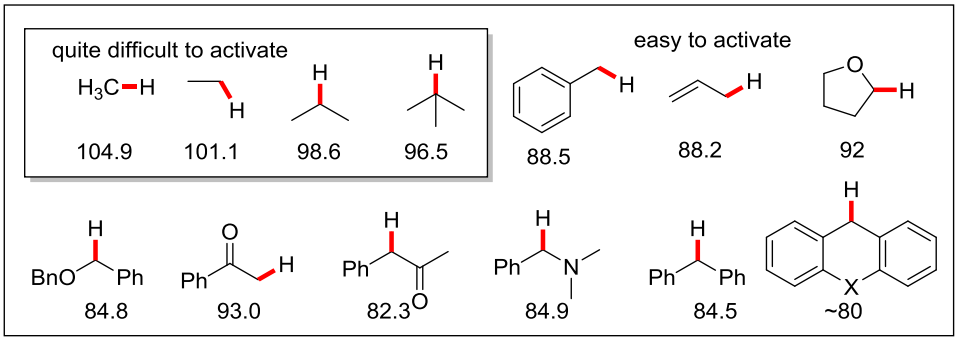
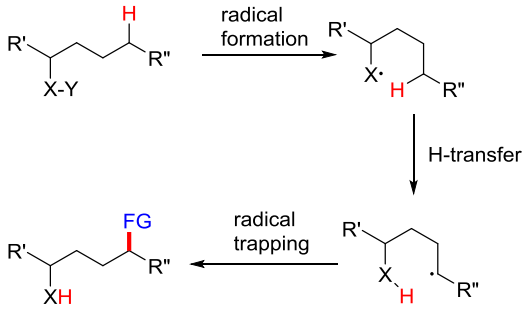
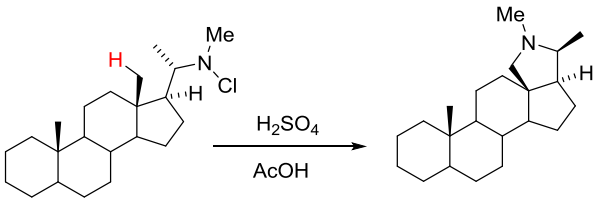



**Fig. 1.3:** Bond dissociation energies (BDE, kcal $mol^{-1}$) of C-H bonds

In 1800, Hoffmann investigated intramolecular $C(Sp)^3$-H bond functionalization through radical process (Scheme 1.10).[12] The synthetic possibilities presented by this process, known today as the Hoffmann-Löffler-Freytag reaction, were demonstrated in the synthesis of nicotine [12c] and, much later, in the synthesis of conanine steroidal alkaloids (Scheme 1.11).[12d]



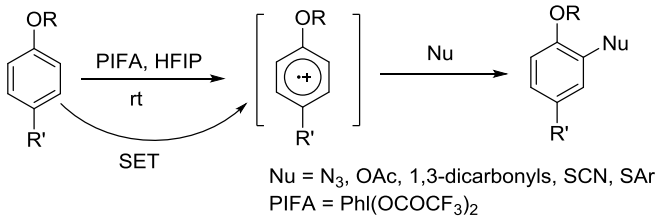

**Scheme 1.10:** Intramolecular radical reactions to functionalize




**Scheme 1.11:** Synthesis of conanine

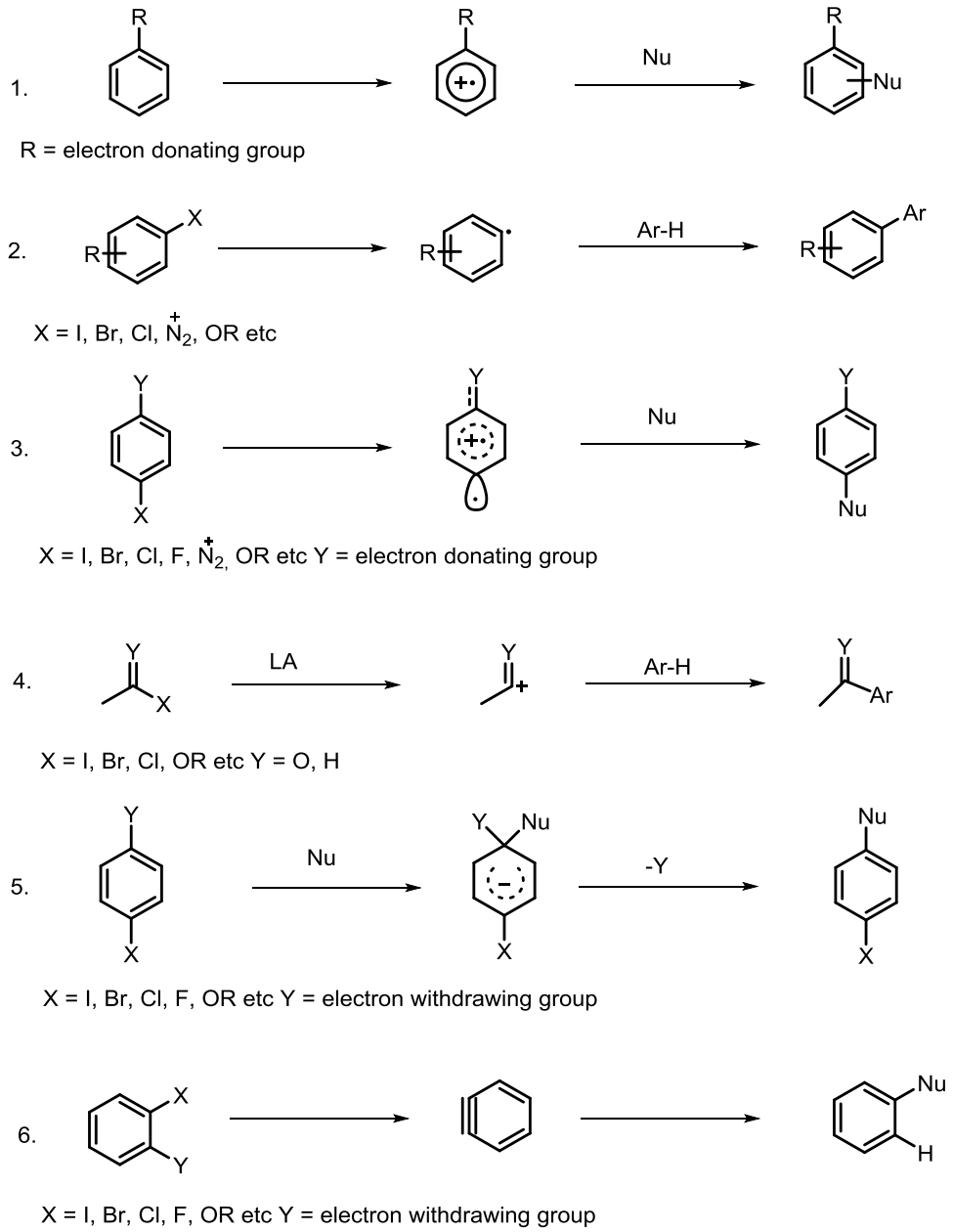
Later, the invention and development of new synthetic methodologies such as the Grignard reaction, the Claisen rearrangement, the Diels-Alder reaction, the Wittig reaction, palladium cross-coupling reaction, and olefin metathesis reactions gave a deeper understanding of the reaction mechanisms and the electronic nature of molecules and chemical bonding. Metal-free methods for activation of unactivated C-H bonds provide a new strategy for the achieving the target molecules, and their development represents an intensively developing area of research.

In 1990, the first example of metal-free oxidative activation of C-H bond was evinced by Kita and his co-workers.[13a] In the reaction, phenol ethers reacted with a variety of nucleophiles in the presence of $PhI(OCOCF_3)_2$ (PIFA) to construct C-C, C-N, and C-O bonds (Scheme 1.12).




**Scheme 1.12:** Metal-free oxidative C-H bond activation

The nucleophilic substitution of *para*-substituted phenol ethers found to proceed via cation radicals as reactive intermediates by SET from aromatics to PIFA (Scheme 1.12), and it was confirmed by UV and ESR spectroscopic studies. Later, the same group extended the chemistry of hypervalent iodine reagents to demonstrate a series of oxidative coupling reactions.[13] In the meantime, to activate selective C-H bonds with high efficiency, other approaches such as using organic and inorganic reagents, photochemical and electrochemical methods were investigated.[11] On the basis of literature survey and the concept of transition metal-free cross-coupling reactions, the mechanistic pathways can be classified as shown in Scheme 1.13: (1) radical pathway, mainly referring to homolytic aromatic substitution type reactions; (2) radical cation pathway, (3) cationic pathway, including DDQ, promoted oxidative coupling reactions and photo-induced reactions via formation of triplet aryl cations; (4) electrophilic aromatic substitution (Friedel–Crafts reaction as the typical example); (5) nucleophilic aromatic substitution; (6) aryne pathway; and (7) classical organocatalysis pathway.




**Scheme 1.13:** Mechanistic pathways

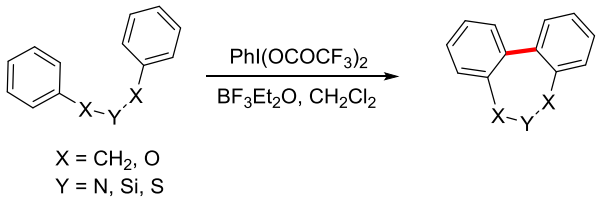
### 1.8: Metal-free C-H bond activation using organic and inorganic reagents

The selective reagents have been used to perform a functional transformation are $PhI(OAc)_2$, $PhI(OCOCF_3)_2$, $KO^tBu$, DDQ, TBAX, Peroxides, $O_2$, and Persulfates. The oxidative cross-coupling reactions of two different C−H bonds are also called "cross-dehydrogenating coupling" (CDC) reactions.[14] Various reagents such as hypervalent iodine reagents, DDQ and its derivatives, dioxygen, persulfates are demonstrated to develop CDC reactions.

### 1.9: Hypervalent-Iodine-Mediated Oxidative Coupling Reactions

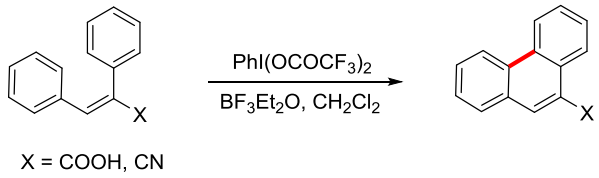
Hypervalent iodine (III) reagents recently demonstrated as efficient oxidants for a wide range of transformations. Kita and co-workers made significant contributions in the

extension of hypervalent iodine (III)-promoted reactions.[13] Kita and co-workers constructed an intramolecular C-C bond using unsaturated tethered aryl groups to generate various tricyclic systems (Scheme 1.14).[15]



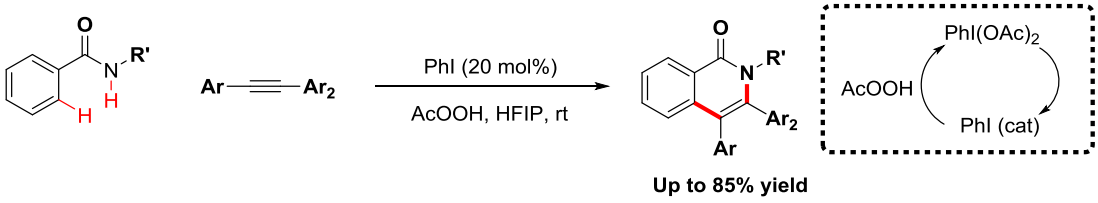

**Scheme 1.14:** Metal-free intramolecular C-C bond formation

Subsequently, Waldvogel and coworkers for the first time reported $PhI(CO_2CF_3)_2$-mediated oxidative cyclization of α-benzyl cinnamic acid derivatives having saturated tethered aryl groups to form the tricyclic compounds, which represents important structural units found in many biologically active compounds such as allocolchicine (Scheme 1.15).[16]




**Scheme 1.15:** Oxidative cyclization of α-benzyl cinnamic acid derivatives

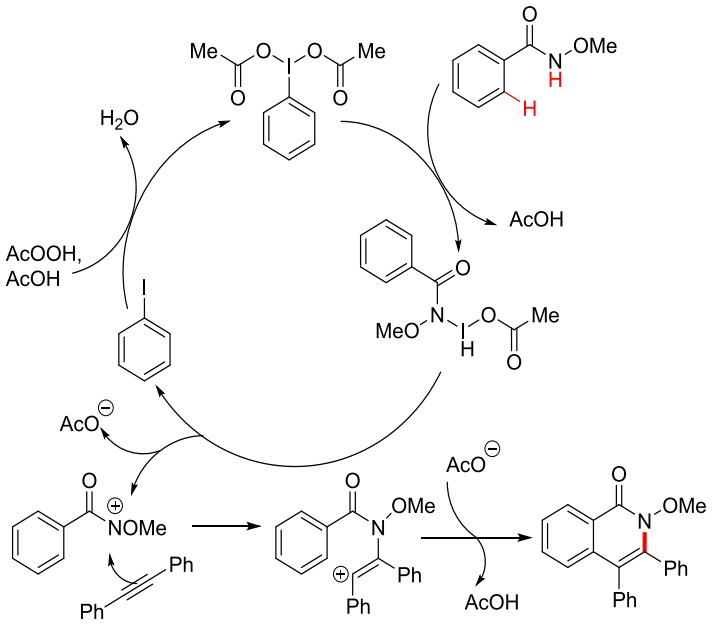
Recently, Antonchick group described a hypervalent iodine mediated an oxidative intermolecular annulation of benzamide with alkynes (Scheme 1.16).[17]




**Scheme 1.16:** Synthesis of *N*-alkoxy isoquinolones

In this reaction, *N*-alkoxy benzamide derivatives reacted with readily available alkynes to deliver *N*-alkoxy isoquinolones as final expected products. The desired products formed smoothly at ambient temperature in short times using peracetic acid as the oxidant. A notably high regioselectivity was described in annulation of unsymmetrical diaryl acetylenes demonstrating that the developed organocatalytic approach is superior to transition-metal-catalyzed reactions.

**Plausible Mechanism**

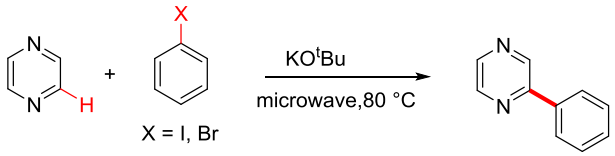



**Scheme 1.17:** Proposed mechanism of organocatalyzed annulation of benzamide

In the recent years, the organic chemist has paid full attention towards the development of 'transition metal-free' or 'metal-free' oxidative dehydrogenative C-C bond-forming reactions. In this concern, the chemistry of common reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), KO$^t$Bu, DDQ, TBAX, Peroxides, $O_2$, and Persulfates has been successfully implemented in the field of metal-free C-H bond functionalization.

### 1.10: KO$^t$Bu -Promoted Coupling Reactions

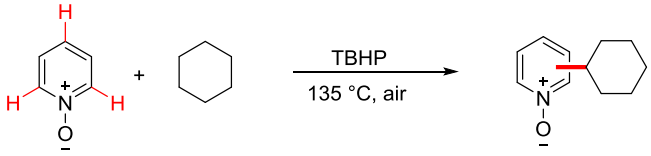
In 2008, Itami and coworkers showed that KO$^t$Bu also could be used to develop inactive C-H bond functionalization. Itami's reaction described a coupling of pyrazine and aromatic halides with the help of microwave (Scheme 1.18).[18a] Later, many discoveries and developments were discussed for the coupling reactions of aryl halides with arenes and alkenes in the presence of ligand. KO$^t$Bu-promoted Base mediated HAS reactions involve single electron transfer process.[18]




**Scheme 1.18:** Arylation of phenazine

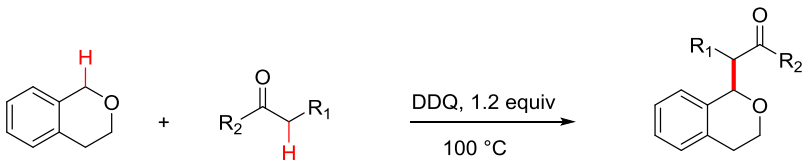
### 1.11: Peroxides, Quinones and $O_2$ for Coupling Reactions

Itami, Li, and co-workers established a synthetic methodology for alkylation of pyridine N-oxide using peroxides such as TBHP. They showed that TBHP oxidizes cyclohexane to produce cyclohexyl radical through single electron transfer (Scheme 1.19).[19]



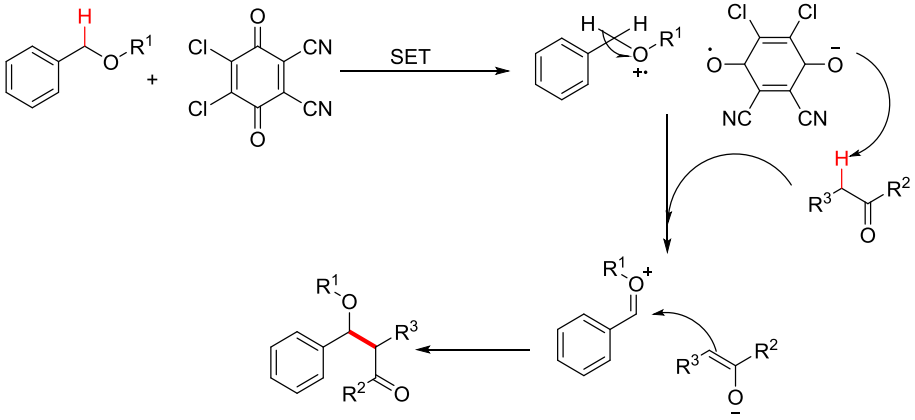

**Scheme 1.19:** Peroxide catalyzed alkylation

Li group observed first DDQ-mediated direct cross dehydrogenative coupling reaction of benzyl ethers with ketones for the selective C-C bond formation (Scheme 1.20).[20] In this experiment, C-H bond attached to the oxygen atom is activated using DDQ as a single electron acceptor through single electron transfer.



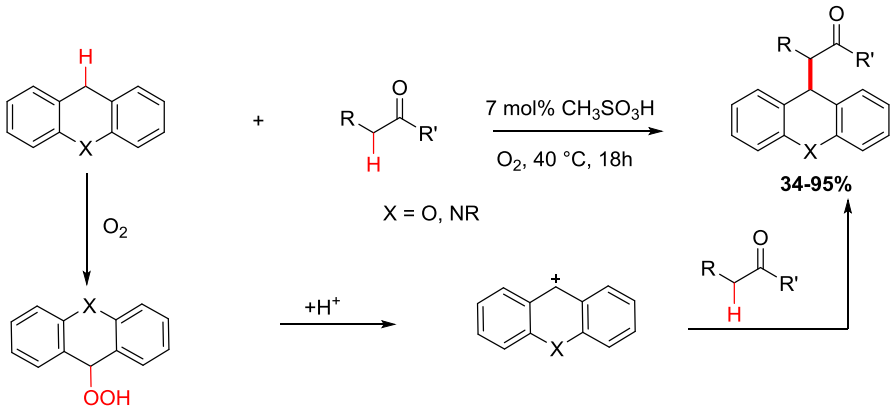

**Scheme 1.20:** DDQ-promoted oxidative coupling reaction

Drawing inspiration from Li's DDQ employed reaction, Bao and co-workers developed a series of DDQ-promoted oxidative coupling ideal transformations between allylic/propargylic $sp^3$ C–H and variety of nucleophiles, such as 1,3-dicarbonyl compounds, aliphatic alcohols and thiols, aromatic thiophenols, and even oximes.[20] All the DDQ-promoted cross-coupling reactions shared a single electron or hydrogen transfer mechanism, involving a key step as DDQ-promoted twofold oxidation (Scheme 1.21).



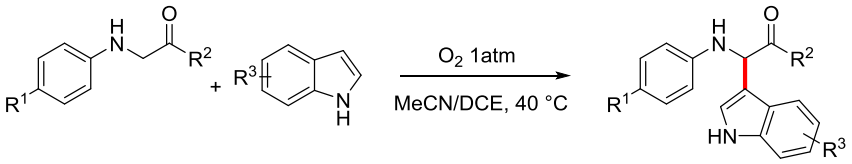

**Scheme 1.21:** Mechanism for two folds oxidation

Next, Klussmann's group investigated similar type of coupling reaction in the presence of dioxygen as a green oxidant using catalytic amount of methanesulfonic acid (Scheme 1.22).[21]



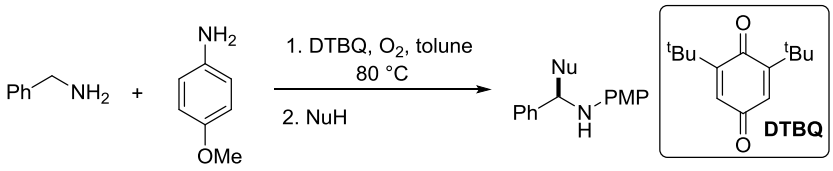

**Scheme 1.22:** Mechanism for two folds oxidation by $O_2$

Subsequently, Hua and coworkers discussed a direct α-arylation of glycine derivatives with indole derivatives using only oxygen in organic solvent (Scheme 1.23).[22]




**Scheme 1.23:** Arylation of glycine derivatives with indol by $O_2$

2,6-Di-*tert*-butyl-p-benzoquinone (DTBQ) was also employed to mediate the aerobic oxidation to form C-C bonds. Recently, the Clift group described the α-functionalization of primary amines through sequential quinone-catalyzed amine oxidation/nucleophilic addition (Scheme 1.24).[23]



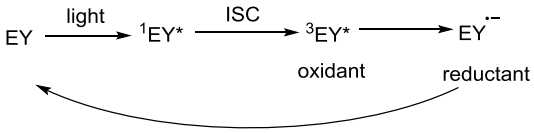

**Scheme 1.24:** Quinone-Catalyzed Oxidation/Nucleophilic Addition of Primary Amines

In this reaction, benzylamine oxidized to the corresponding N-protected imines using quinone, which then reacted with appropriate nucleophiles such as organolithium reagents or Grignard reagents to furnish α-branched amines at low temperature. In the most cases, carbon-hydrogen (C-H) bonds with relatively low energy are activated using single electron acceptors such as DDQ, $O_2$, peroxides, and persulfates.

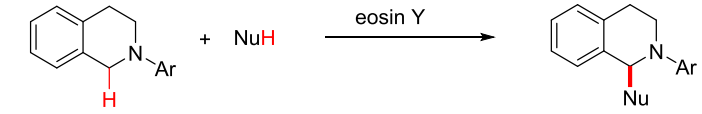
### 1.12: Photochemical reactions

The photochemical methods displayed great potential in transition-metal-free reactions for functionalization of C-H bonds on the radical base mechanism. It is an eco-friendly, versatile, and practical method for coupling of two C-H bonds. The single electron transfer process takes place between organic substrate and light-excited photo redox catalysts such as eosin Y* and rose bengal to initiate the reaction (Scheme 1.25). In 2009,

Kçnig and co-workers demonstrated the catalytic activity of eosin Y* in the organocatalytic reaction of tetrahydroisoquinoline and active methylene compounds for the oxidative C-C bond formation (Scheme 1.26).[24a] Later, the idea of using light to excite photo-redox catalyst much explored and documented to develop a variety of ideal transformations. People have developed similar kind of coupling reactions by using rose Bengal.[24b-c]

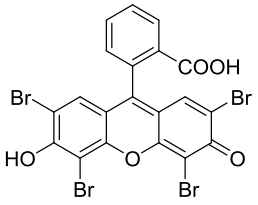



**Scheme 1.25:** Photoredox cycle of eosin Y

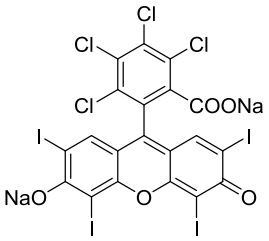



Nu = nitroalkanes, malonates, malonitriles and carbonyls

**Scheme 1.26:** Photoredox catalysts for the oxidative coupling



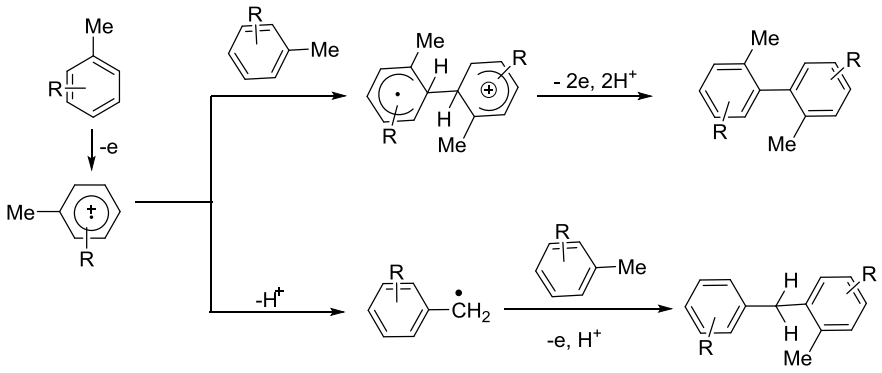

eosin Y




rose bengal

## 1.13: Electrochemical methods:

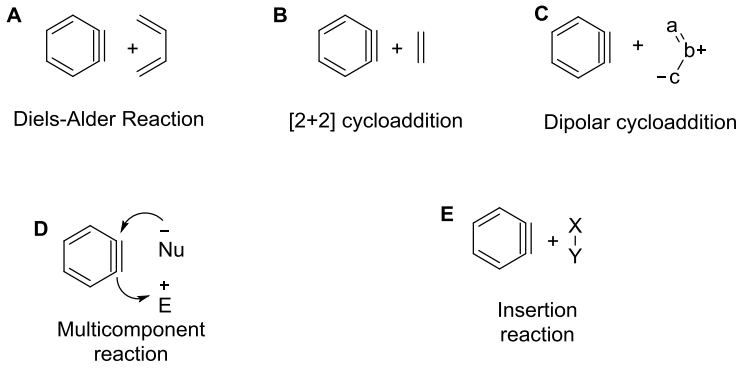
Electrolysis allows the reactivity of a substrate to be changed, or its polarity to be reversed ("*redox umpolung*"). The usage of electrons provides a metal-free alternative for addressing functional group transformations synthetic chemistry, and at the same time, a number of reaction steps in multi-stage syntheses can be reduced.[25] The tools necessary for an electrolytic process are a cell, a power source, electrodes, and an electrolyte. A series of electroanalytical methods provide information on the electrode reaction mechanisms. At the anode, arenes, phenolic ethers, and electron-rich olefins dimerize via radical cations intermediate. Electroorganic synthesis is an attractive method for the formation of organic compounds, including C-C coupling reactions, because only electrons serve as a reagent. In 1971, Nyberg showed the formation of biphenyl and diphenylmethane derivatives via cationic radical intermediate by using electrochemical method (Scheme 1.27).[26] In recent years, Waldvogel and his coworkers extended electro-organic synthesis to the oxidative cross-coupling of phenols.[27]




**Scheme 1.27:** Electrolysis of arenes

## 1.14: Transition-metal Free Reactions Employing Arynes

Arynes are highly electrophilic reactive intermediates, which have been widely used in various C−C formation and C−X bond formation reactions.[28] Recent developments in aryne chemistry have been devoted to transition-metal-free reactions. The chemistry of aryne could be classified as Diels-Alder reaction (A), [2+2] cycloaddition (B), dipolar cycloaddition (C), multicomponent reactions (D), and insertion reactions (E) (Scheme 1.28).




**Scheme 1.28:** Types of aryne reactions

**1.15: Introduction to Persulfates:**

Persulfates are comparatively less expensive, easily available, less toxic.[29] It is very important to note that byproducts of this oxidant are easily separable, and water-soluble salts. Thus, the chemistry of persulfates in developing organic reactions meet the criteria of green chemistry. Among other persulfate sources, $K_2S_2O_8$ is very selective, and reactions can be developed in water solvents.[29e] The chemistry of persulfate is not explored and studied well in the literature for the selective oxidative C-C bond formations. Hence, there is need to find out appropriate conditions in the absence of metals to activate persulfates for producing sulfate anion radical ($SO_4^{-\bullet}$), which then can be used to functionalize C-H bonds through SET (single electron transfer) processes.[29]

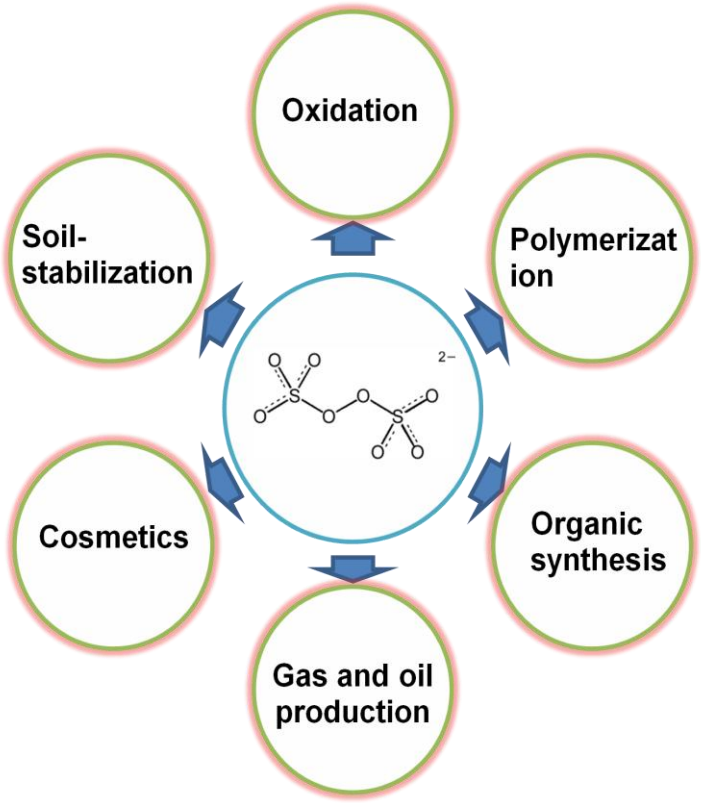



**Fig. 1.4:** Applications of Persulfate

Over the past several years, the chemistry of persulfate has been well explored in various fields including synthetic organic chemistry (Fig. 1.4). Sulfate anion radical ($SO_4^{-\bullet}$) produced from persulfates is frequently used as an oxidant for the degradation of environmental and soil carbon pollutants.[30a] Meanwhile, it has been widely used as a radical initiator in some industrial applications.[30b] Initially people activated persulfate in the presence of a metal to produce $SO_4^{-\bullet}$ anion radical for the C-H bond functionalization.[30f] Recently, it is known that sulfate anion radical can be generated by using light or at higher temperature easily from persulfate sources such as $K_2S_2O_8$,

$Na_2S_2O_8$, and $(NH_4)_2S_2O_8$ (Fig. 1.3).[30d-e] Although the oxidation potential of $SO_4^{-\bullet}$ is 2.6 eV, the reactivity between organic compounds and $SO_4^{-\bullet}$ is considered to be slow, but, very selective via a single electron transfer mechanism.[29,30d-e] Thus, sulfate anion radical can react with alcohols, ether compounds, and hydrocarbons through single electron or hydrogen (H) transfer. The oxidizing and ether compounds through single electron or hydrogen (H) transfer. The oxidizing ability of persulfate has been used in the synthesis of aldehydes, ketones, carboxylic acids, quinones, and a variety of other compounds. It is important to note that $K_2S_2O_8$ reacts with organic moieties selectively under physiological conditions (ambient temperature and pressure, neutral pH, aqueous conditions). Persulfate-based oxidants are potentially attractive alternatives to other oxidants in organic transformations. $K_2S_2O_8$ is less expensive in comparison of other oxidants,[29a] and the byproducts of this oxidant are easily separable, water-soluble salts.

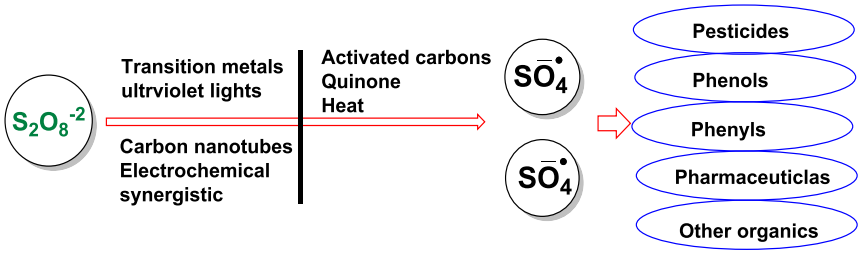
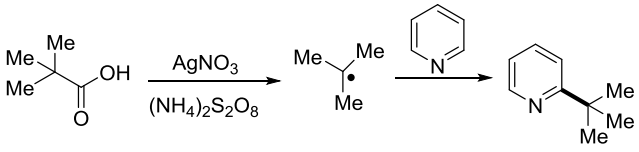



**Fig. 1.5:** Activation of persulfate anion

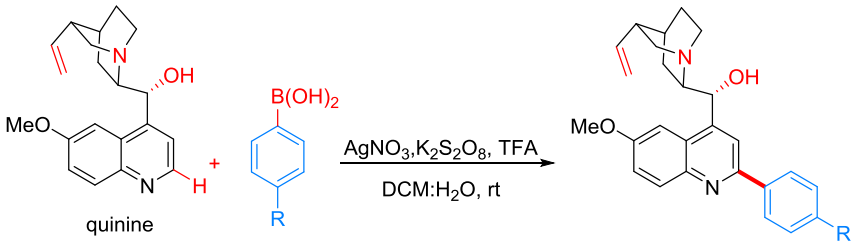
### 1.16. Recent advances by persulfates in C-H bond functionalization:

It is well known that persulfates are quite good oxidants. In transition metal-catalyzed C-H bond activation, persulfates have been used to oxidize metals to regenerate them in their original oxidation state for next catalytic cycle.[31] In 1971, F. Minisci found that Ag catalysts are crucible to activate persulfate anion ($S_2O_8^{-2}$) (Scheme 1.29).[32] In this reaction, $(NH_4)_2S_2O_8$ was used as a source for $SO_4^{-\bullet}$ to generate alkyl radical. In the next couple of years, Minisci's conditions illustrated to develop several versatile organic reactions for the synthesis small as well as highly complex organic molecules.[32b-g]

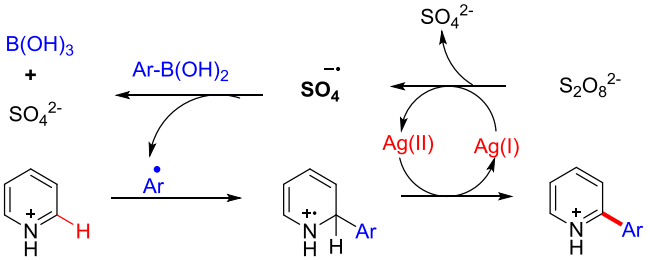



**Scheme 1.29:** Radical addition to heteroaromatics

Recently, Phil Baran studied a silver (I)-catalyzed addition of aryl boronic acids to a range of electron-deficient heterocycles (Scheme 1.30).[33] The radical mechanism was proposed for this transformation (Scheme 1.18). The complexity demonstrated by applying the synthetic methodology in the coupling of naturally occurring quinine and aryl boronic acids.

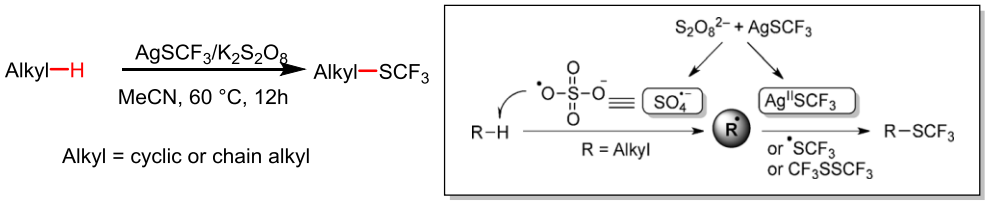



**Scheme 1.30:** Arylation of quinine with aryl boronic acids




**Scheme 1.31:** A mechanism consistent with previous studies by Minisci

Very recently, Liu and Chen presented a remarkable direct trifluoromethyl thiolation of inactivated alkyl C-H using silver catalyst and $K_2S_2O_8$. In the reaction, $K_2S_2O_8$ plays key roles in both the activation of the $Sp^3$ C-H bond and the oxidation of $AgSCF_3$ (Scheme 1.32).[34a]

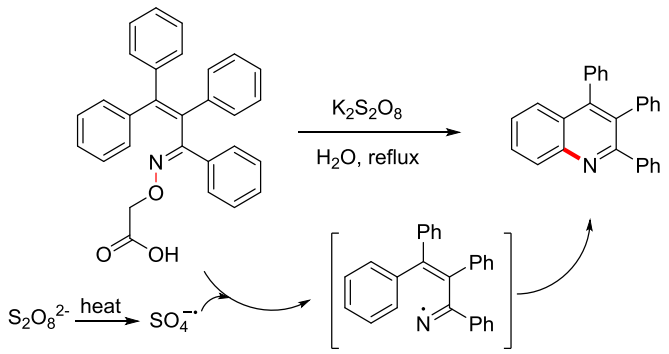



**Scheme 1.32:** A trifluoromethyl thiolation of unactivated alkyl C($sp^3$)-H

In the same time, Tang and his coworkers described another trifluoromethyl thiolation of unactivated alkyl C-H using silver catalyst and $K_2S_2O_8$.[34b] Reaction conditions are modified and then applied for selective C-H bond activation.

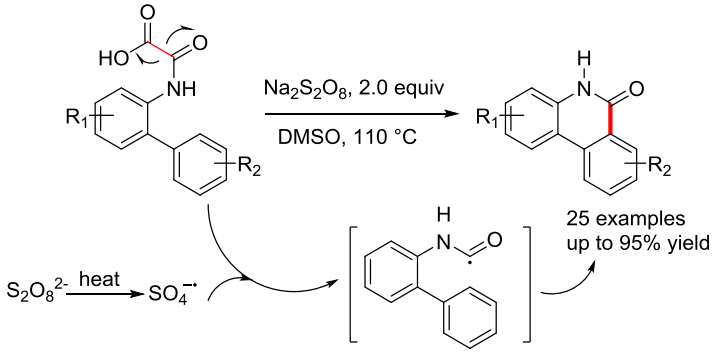
After careful evaluation and survey of the literature, it is clear that metals are used only for activation of persulfates. Thus, it would be more useful to investigate the reaction conditions to activate persulfates without using metals to construct C-C, or C-X binds via C-H bond functionalization. In this context, in 1979, Forrester observed N centered radical in the reaction of O-hydroxy carbonyl methyl oximes in the presence of $K_2S_2O_8$

and water at reflux temperature. In the synthesis of quinolines, the heat was crucial for the activation of $K_2S_2O_8$ to produce $SO_4^{-\bullet}$ (Scheme 1.33).[35]



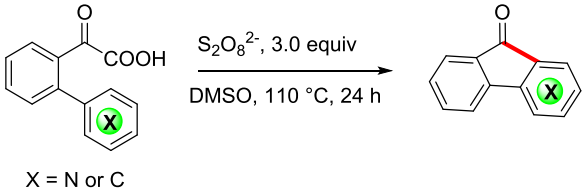

**Scheme 1.33:** Homolytic cleavage of N-O bond by persulfate

In a recent report, Zhang's group developed an intramolecular C-C bond formation for the synthesis quinolines by oxidation of biaryl-2-oxamic acid through decarboxylation process in the presence of persulfate as the oxidant. They proposed that carbamoyl radical is produced by as key intermediates through homolytic cleavage of C-C bond (Schemes 1.34).[36]



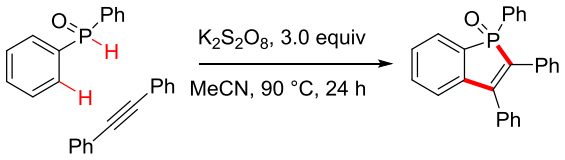

**Scheme 1.34:** Intramolecular C-C bond formation via decarboxylation

Recently, the chemistry of persulfate for C-H bond functionalization has been well studied by Laha's group.[37] In this regard, in their recent report, intramolecular C-C bond was described for the synthesis of azafluorenones and fluorenones using persulfate under neutral conditions (Scheme 1.35). [37d]



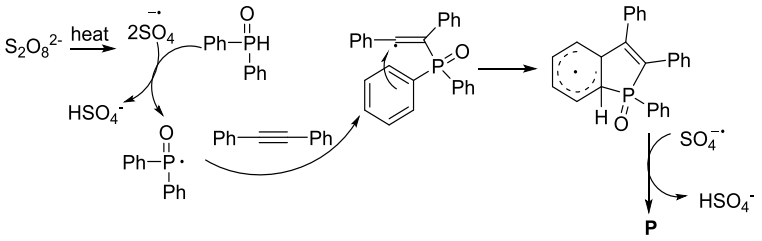

**Scheme 1.35:** Silver-free Minisci acylation

For the first time, Gao and coworkers introduced $K_2S_2O_8$-promoted intermolecular annulation of benzo-phosphole oxides with alkynes for the synthesis of benzo-phosphole (Scheme 1.36).[38]



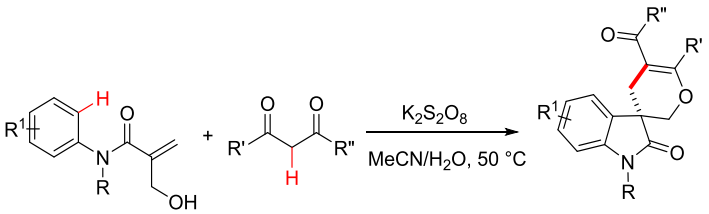

**Scheme 1.36:** Intermolecular annulation with alkynes

**Mechanism**



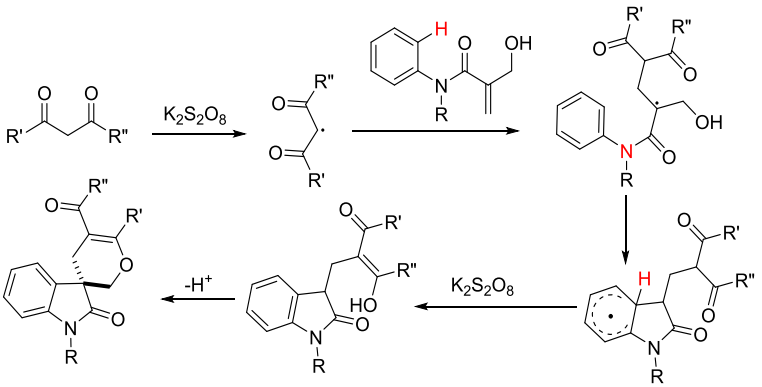

**Scheme 1.37:** Proposed mechanism

Recently, Duan and coworkers activated 1,3-dicarbonyl using $K_2S_2O_8$ through α-hydrogen atom abstraction to generate a carbon radical at reported α-position. Then, it added to the olefinic carbon of hydroxymethyl acrylamide to deliver spiro-oxindoles (Scheme 1.38).[39] It is very simple and operational method using very simple but versatile reagent.



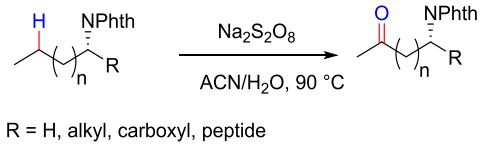

**Scheme 1.38:** Synthesis of spiro-oxindoles

**Mechanism**




**Scheme 1.39:** Proposed mechanism for C-C bond formation.

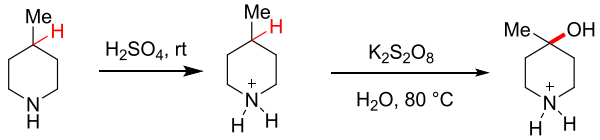
The activation of persulfate and using them in alkyl C-H bond activation now days attracting area in the organic synthesis. Shi and co-workers used $Na_2S_2O_8$ to oxidize aliphatic C-H bond to synthesis carbonyl compounds. By employing a simple, inexpensive, and transition-metal-free oxidation system, secondary C–H bonds in a series of phthaloyl protected primary amines, and amino acid derivatives were oxidized to carbonyls with good regioselectivities (scheme 1.40).[40]




R = H, alkyl, carboxyl, peptide

**Scheme 1.40:** Selective oxidation of aliphatic C-H bond

Very recently, Sanford's group described a remote C($sp^3$)-H oxygenation of protonated aliphatic amines with potassium persulfate in a highly regioselective manner (Scheme 1.41).[41] The oxygenation reaction was developed in water solvent. Hence, protonation helps to increase the solubility of amines in a solvent. This method successfully worked to activate a variety of C-H bonds of primary, secondary and tertiary amine substrates.




**Scheme 1.41:** Persulfate mediated Oxygenation of protonated amines

The chemistry of persulfate not extended and well examined for the direct conversion of C-H bonds to C-C bonds. Hence, it would be even more important to investigate methods to construct C-C bonds by coupling of two different C-H bonds using $SO_4^{-\bullet}$ that is cross-dehydrogenative coupling (CDC). These protocols are atom economical, efficient and cost-effective as it does not need pre-activated starting compounds.

### 1.17: Aim to Work:

The development of mild, sustainable and selective functionalization of $sp^3$ or $sp^2$ C-H bonds remains an essential challenge for an organic chemist. Cross-dehydrogenative coupling (CDC) reactions from the coupling of two C-H bonds, represents a new state of the art in the field of organic chemistry for C-C bond formations (Fig. 1.4). In particular, the functionalization of C-H bonds undertaking to become increasingly important as a versatile method of constructing carbon-carbon (C-C) bonds. The hydrocarbon chains are the fundamental skeleton of organic molecules. The constructions of C-C bonds embodies the core of organic the core of organic chemistry because of fundamental application in molecular diversity and complexity.

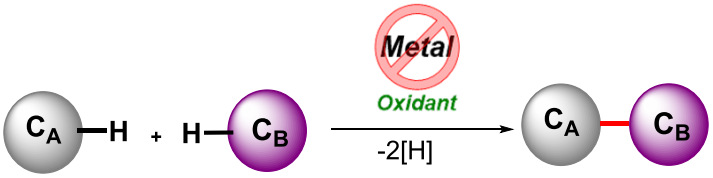



**Fig 1.4:** Oxidative dehydrogenative C-C bond formation

The present doctoral thesis aimed to demonstrate unprecedented transition metal-free aerobic oxidative dehydrogenative synthetic methods for regio-selective formation of the C-C bond by coupling of two C-H bonds and applied in the synthesis of complex organic molecules. Doctoral research describes oxidative cross-coupling of two C-H via single electron transfer under mild reaction conditions to tackle the synthesis of α-aryl carbonyl compounds, non-symmetrical biphenols, binaphthols and substituted quinones. This thesis has been divided into following four chapters.

- ***Chapter 2*** deals with the development of an efficient cross dehydrogenative synthesis of 1,1-diaryl and 1,1,1-triaryl carbonyl compounds (benzo-pinacolone) through α-arylation. The present methodology also applied in the synthesis of tetraphenyl ethylene and 9,10-substituted phenanthrene derivatives.
- ***Chapter 3*** describes our efforts to investigate a transition metal free protocol for the synthesis of symmetric biphenols and substituted 1,4-quinones. The synthesis of the antimalarial drug also described.
- ***Chapter 4*** presents a synthesis of phenol-based non-symmetric biaryls by using oxidative cross-coupling reactions. In this chapter synthesis of polyhydroxy biaryls also reported.

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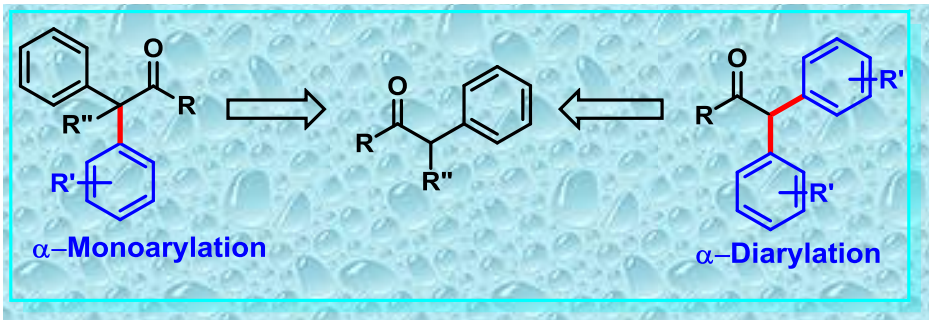
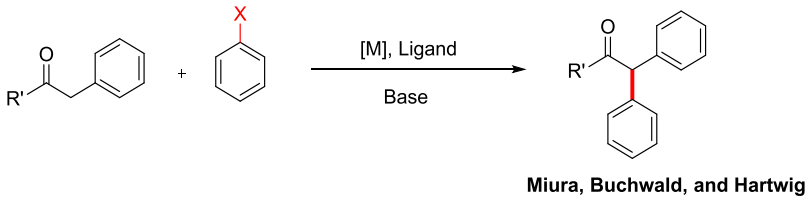
# Chapter 2

## *A regio-selective Aerobic α-Arylation of Benzyl Ketones with Un-activated Arenes*



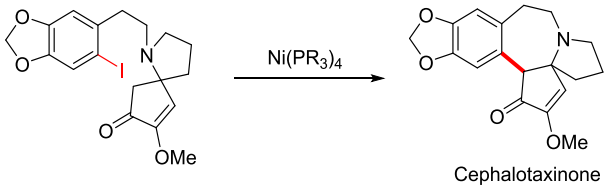
## Introduction

The α -diaryl or triaryl-substituted carbonyl compounds are synthetically useful organic derivatives, which are appeared in various natural products, clinical drugs, a dye precursor, and materials.[1] Hence, during past decade, seminal efforts have been paid toward the development of efficient methods for the synthesis of α-aryl carbonyl compounds. There are very limited synthetic methods in the literature. Among them, transition-metal catalyzed α-arylation of substituted ketones with aromatic halides or organometallic reagents is highly efficient method to construct α-aryl carbonyl compounds (Scheme 2.1).[2-4]



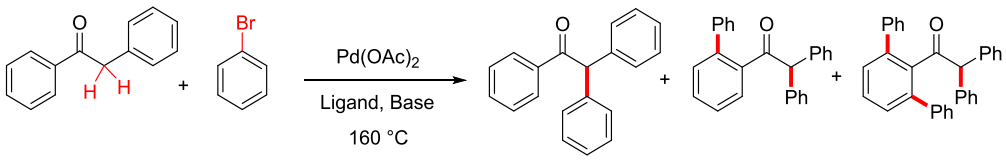

**Scheme 2.1:** Palladium-Catalyzed arylation of benzyl phenyl ketones

In this context, the first report of intramolecular direct α-arylation was demonstrated by Semmelhack's group using Ni (0) as a catalyst (Scheme 2.2).[2] Intramolecular α-arylation of the carbonyl with aromatic iodide served as a key step in the total synthesis of the cephalotaxinone drug.



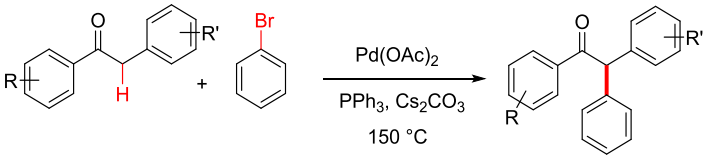

**Scheme 2.2:** Ni (0)-catalyzed intra-molecular coupling

Independent discovery of practical and efficient, palladium based catalytic systems to produce α-aryl carbonyl compounds was initiated by Miura,[3] Buchwald,[4] and Hartwig.[5] In 1999, for the first time, Miura's group discovered α–arylation of benzyl phenyl ketones with aryl halides in the presence of palladium (II) catalyst (Scheme 2.3).[3] This conversion mainly was associated with ligands and bases along with preactivated aromatic coupling partners.



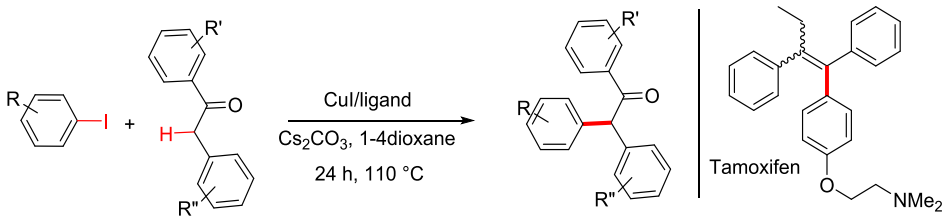

**Scheme 2.3:** Palladium-Catalyzed arylation of benzyl phenyl ketones

After that, phenomenal efforts have been paid to extend a research work for the selective mono α-arylation of carbonyl compounds.[6] In this regard, a simple and high yielding, palladium catalyzed protocol reported by Domínguez and coworkers for the preparation of 1,2,2-triarylethanones (Scheme 2.4).[7] In this catalytic reaction, substituted phenyl benzyl ketones coupled with aromatic bromides in the presence of $Pd(OAc)_2$, triphenylphosphine, and cesium carbonate at quite higher temperature.



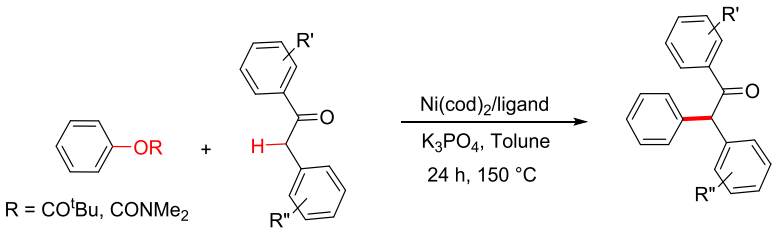

**Scheme 2.4:** Palladium-catalyzed arylation of benzyl phenyl ketones

Recently, Taillefer and his coworkers described a α-arylation of 2-phenyl acetophenone with iodoarenes using CuI as cheap and easily available catalyst (Scheme 2.5).[8] As often, the coupling reaction requires ligand and base to proceed. The potential of coupling reaction is illustrated by its application in the total synthesis of tamoxifen, a medication to prevent breast cancer in women.




**Scheme 2.5:** Copper-catalyzed arylation of deoxybenzoin

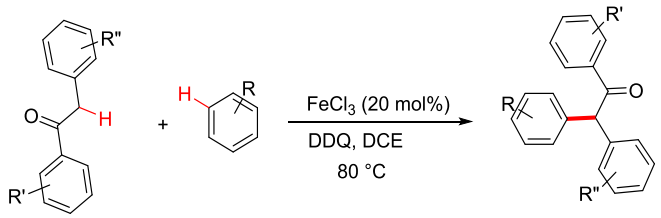
Very recently, by using Ni catalyst, Itami's group reported a α-arylation of benzyl ketones with phenol derivatives.[9] In this conversion, phenol derivatives were used as a pre-activated coupling partner in the presence base and ligand (Scheme 2.6).




**Scheme 2.6:** Ni-catalyzed α-arylation with phenol derivatives

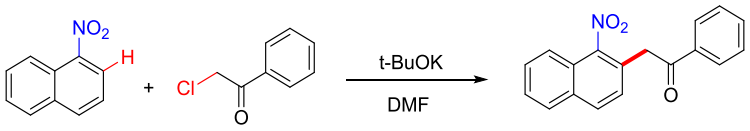
In all reported synthetic methods for direct α-arylation of benzyl phenyl ketones, either one coupling partner is used with functionalization. However, although transition metal catalyzed cross-coupling reaction of carbonyl compounds with pre-activated aromatics is a unique and highly efficient method, it suffers, particularly high cost, the toxicity of the metal, and the necessity of using well designed expensive ligands. Hence, instead of using

a pre-functionalized coupling partner such as C-X or C-M functionalized moiety, if the same reaction is developed with C-H bond of aromatics, it would be more useful and high atom economical in organic synthesis. To establish such a synthetic methodology, Zang's group applied a $FeCl_3$-catalytic system in the presence of DDQ as oxidant for the α-arylation of deoxybenzoin with arenes via oxidative dehydrogenative approach (Scheme 2.7).[10]



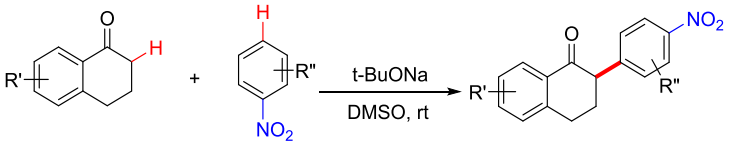

**Scheme 2.7:** $FeCl_2$-Catalyzed dehydrogenative arylation

In the meantime, several transition metal-free α-arylation processes of carbonyl compounds have also been developed. Metal-free cross-coupling of substituted ketones with aromatics has several advantages and gained much attention in organic synthesis.[11-15] In 1992, Maksoza used *t*-BuOK for the addition of α-chloroalkyl ketones to electron deficient nitroarenes (Scheme 2.8).[14]




**Scheme 2.8:** Arylation of α-chloroacetophenone

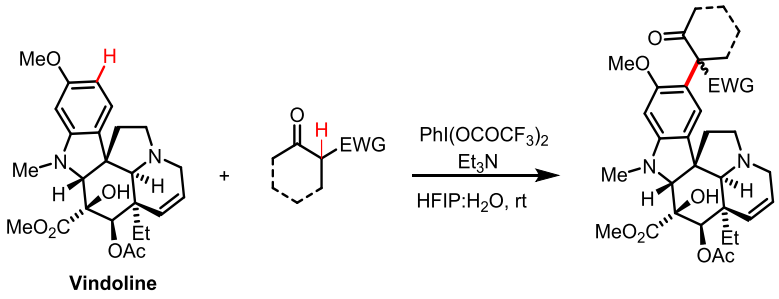
An earlier example of *t*-BuONa mediated α-arylation of alkyl aryl ketones with nitroarenes was demonstrated by Kürti and coworkers (Scheme 2.9).[11c] Under this condition, a variety of carbonyl compounds such as alkyl alkyl, alkyl aryl, cyclic, and acyclic ketones worked well to produce corresponding coupling products.




**Scheme 2.9:** Arylation of cyclic ketones with nitroarenes

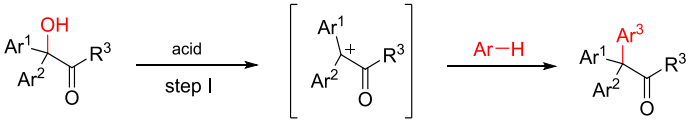
In these reported transition metal-free α-arylation reactions, only electron-deficient aromatic compounds were used as the arylating agent and, in addition, arylation is most often achieved at the methene $Sp^3$ carbon atom of substituted ketones. More recently, Boger's group described hypervalent iodine promoted α-arylation of ketones with vindoline as an unactivated aromatic coupling partner. With this simple protocol, naturally occurring vindoline derivatized with a variety of cyclic and acyclic carbonyl

compound through oxidative dehydrogenative α-arylation (Scheme 2.10).[16] However, to afford corresponding products, triethylamine as a base and highly fluorinated solvent was used.




**Scheme 2.10:** Derivatization of vindoline through α-arylation

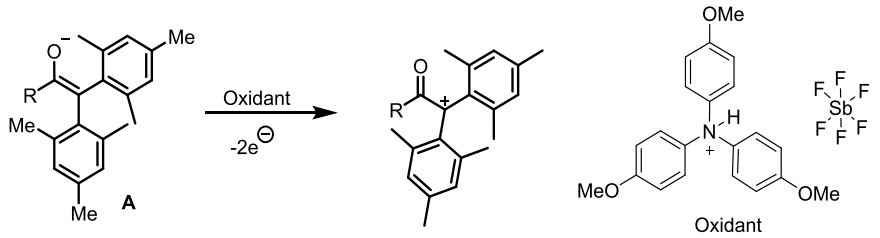
Thus, there is a need to develop a TM-free direct α-arylation of benzyl ketones with aromatic hydrocarbons that are operationally simple, green and high-atom economical. There are very limited synthetic methods are documented for the synthesis of α-diaryl or α-triaryl carbonyl compounds. In particular, 1,1,1-triphenyl carbonyl compounds are key intermediates in the synthesis of tetraphenylethylene (TPE) and polyaromatic hydrocarbons such as phenanthrene derivatives.[17] Additionally, triaryl carbonyl frameworks are highly useful in the pharmaceutical field and catalyst design.[18] Benzopinacolone derivatives or 1,1,1-triphenyl carbonyl compounds are also efficiently prepared by an acid-mediated Friedel–Crafts reaction of substituted alcohols with electron-rich aromatics.[18] Acid-catalyzed Friedel–Crafts reaction of alcohols and electron-rich aromatic compounds is a highly atom-efficient method for the preparation of aromatic compounds with diverse applications, and only water is generated as the byproduct. In the reaction, carbocation generates at α position in the presence of acid. It requires hydroxyl functionality as leaving the group at α-position of carbonyl compounds (Scheme 2.11).




**Scheme 2.11:** Acid-catalyzed Friedel-Craft alkylation

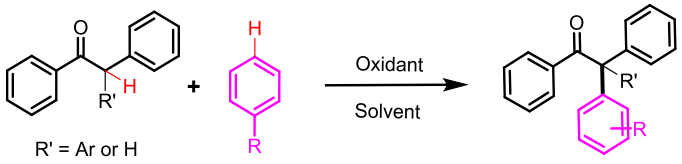
Therefore, development of highly efficient, easily accessible and environmentally friendly methods for the α-arylation of benzyl ketones and other carbonyl compounds under the mild reaction conditions in a highly atom economical manner is highly important and desirable in organic synthesis. In 1993 Michael et. al. derived α-carbonyl

cation derived by using two-fold oxidation in the presence of tris-(*p*-methoxypheny1) aminium hexafluoroantimonate. (Scheme 2.12).[19]




**Scheme 2.12:** Two fold oxidation of enolate A

After the careful observation of the existing literature on α-arylation of carbonyl compounds, we aimed to investigate a coupling reaction between two electronically mismatched coupling partners such as benzyl phenyl ketones and unactivated aromatics under transition metal-free conditions (Scheme 2.13).




**Scheme 2.13:** Cross-dehydrogenative arylation

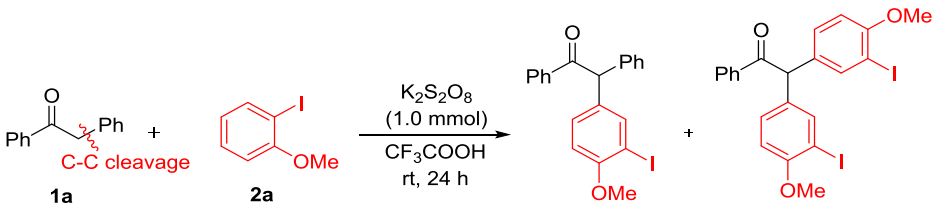
## 2A: Aerobic Dehydrogenative α-Diarylation of Benzyl Ketones with Aromatics through Carbon–Carbon Bond Cleavage

### 2A.1: Results and Discussion

With the existing background, initially, we began our evaluation of coupling reaction with the reaction between 2-phenyl acetophenone (**1a**) (1 mmol) and 2-iodoanisole (**2a**) (excess) in the presence of $K_2S_2O_8$ (2 mmol) in AcOH as a solvent under $N_2$, no desired α-aryl product was observed. Next, a series of a solvent such as MeOH, pivalic acid, toluene, benzene, THF, DMF, DCE, *tert*-BuOH, $CF_3SOOH$ and $CF_3COOH$ in the presence of $K_2S_2O_8$ were examined for α-arylation of 2-phenyl acetophenone (**1a**) with 2-iodoanisole (**2a**). Surprisingly, in $CF_3COOH$ as a solvent, two different arylation products such as α-monoarylated ketone **3a** in 29% yield and α-diarylated ketone **4a** in 41% yield were observed (Scheme 2.14, entry 1). We wondered for the formation of unexpected α-diarylated compound **4a** through C-C bond cleavage in the form of the complete phenyl ring. Notably, no undesired Buchwald-Hartwig coupling product was observed. The aromatic partner was chosen with halogen substituent. It is very important to note that, the reaction is highly regioselective, only *para* C-H bond of methoxy substituent of **2a** was added to the methene carbon of **1a**. In the reaction, two new carbon-carbon bonds were formed, and one carbon-carbon bond was cleaved. It is important to mention that, in the

present reaction two nucleophiles such as substituted ketones and electron-rich aromatics were coupled without any metal through C-C bond cleavage which is unusual in organic synthesis. This result prompted us to optimize reaction condition for the selective formation of α-diarylated compound **4a** exclusively.

**2A.2: Optimization Studies**




| | | | | |
|---|---|---|---|---|
| 1. 1.0 mmol | 1.0 mmol | under $N_2$ | **3a**, 29% | **4a**, 41% |
| 2. 1.0 mmol | 2.2 mmol | under $N_2$ | **3a**, 0% | **4a**, 77% |
| 3. 4.0 mmol | 1.0 mmol | under $N_2$ | **3a**, 25% | **4a**, 35% |
| 4. 1.0 mmol | 2.2 mmol | under air | **3a**, 0% | **4a**, 85% |

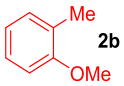
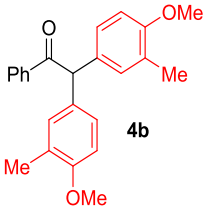
**Scheme 2.14:** *α*- arylation of 2-phenyl acetophenone

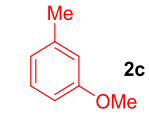
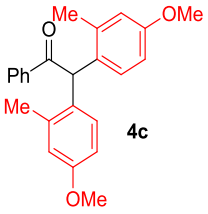
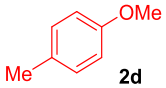
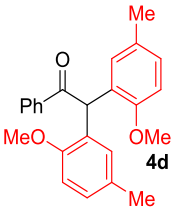
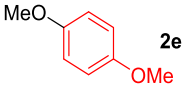
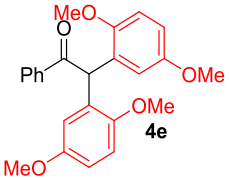
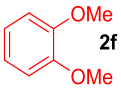
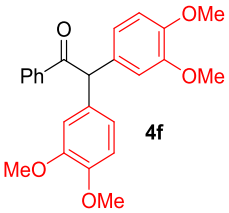
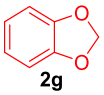
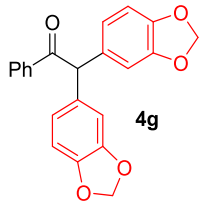
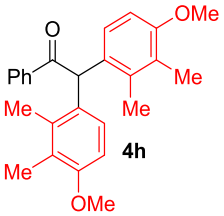
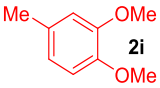
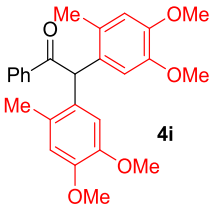
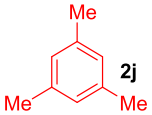
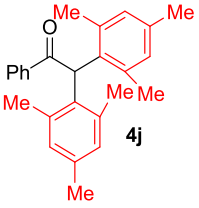
With optimized conditions in hand (Scheme 2.14), Further, the reaction was tested with other oxidants (1.0 mmol) such as DDQ, $Ag_2O$, $PhI(OAc)_2$, benzoquinone, $Cu(OAc)_2$, $(NH_4)_2S_2O_8$ and oxone instead of $K_2S_2O_8$ in $CF_3COOH$. Among them, oxidant $(NH_4)_2S_2O_8$ producing product **4a** in 70% isolated yield. Remaining oxidants were not effective. Next, when the reaction of **1a** and **2a** was tested under air. Surprisingly, the reaction worked very well, yielding product **4a** in 85% isolated yield (Scheme 2.10, entry 4). Then, the same reaction was tested without $K_2S_2O_8$ under ambient air atmosphere. In the reaction, product **4a** was observed only in 45% yield. It seems $K_2S_2O_8$ plays an important role to initiate the reaction to enhance the yield of product **4a** drastically under ambient air atmosphere. Based on these optimization studies, we have concluded that $K_2S_2O_8$ is the better oxidant and $CF_3COOH$ is the better solvent for the reaction under air for 24 h at room temperature. In addition, in the present reaction, α-diaryl ketones **3** were prepared by using easily affordable reagents $K_2S_2O_8$ and $CF_3COOH$ without any metal.

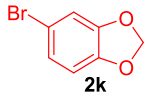
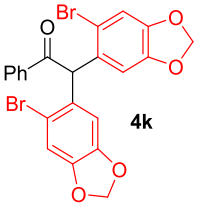
### 2A.3: Scope of substituted aromatics

Under modified optimized conditions, the scope of the α-bisarylation reaction was extended with substituted aromatics (Table 2.1). The reaction of benzyl phenyl ketone (**1a**) with 2-methylanisole (**2b**) and 3-methylanisole (**2c**) yielded α-diarylketones **4b** and **4c** in 68% and 72% yields, respectively (entries 1 and 2). In the reaction, *para* C-H of methoxy group of **2b** and **2c** were involved. Whereas, in the reaction of 4-methylanisole (**2d**) with **1a**, *ortho* C-H bond of methoxy group of **2d** was added at the methene carbon of **1a**, yielding α-diarylketone **4d** in 71% yield (entry 3). The structure of compound **4d** was confirmed by a single crystal X-ray diffraction. Similarly, 1,4-dimethoxybenzene (**2e**) afforded α-diarylketone **4e** in 68% yield in which *ortho* C-H bond of the methoxy group of **2e** participated in the reaction (entry 4). 1,2-Dimethoxybenzene (**2f**) was also efficiently involved in the reaction, affording α-bisarylketone **4f** in 72% yield in a highly regioselective manner (entry 5). Interestingly, a less electron-rich benzo[*d*][1,3]dioxole (**2g**) was nicely involved in the reaction, providing product **4g** in 75% yield (entry 6). In the reaction, C-4 carbon of **2g** was inserted at the methene carbon of **1a**. Further, the reaction was examined with various trisubstituted benzenes **2h-k** (entries 7-10). Thus, the treatment of 2,3-dimethylanisole (**2i**) or 1,2-dimethoxy-4-methylbenzene (**2j**) with **1a** gave α-diarylketones **4i** and **4j** in 77% and 85% yields, respectively (entries 7 and 8). In these reactions, *para* C-H of methoxy group of **2i-j** participated in the reaction. Surprisingly, mesitylene (**2k**) efficiently participated in the reaction, giving α-diaryl ketone **4k** in 86% yield (entry 9). In the reaction, a sterically hindered C-H bond of **2k** participated. Highly useful 5-bromobenzo[*d*][1,3]dioxole (**2l**) reacted nicely with **1a** affording α-diaryl ketone **4l** in 66% yield (entry 10). In the reaction, *ortho* C-H bond of bromo group of **2l** was involved. The arylation reaction was also performed with aromatics and heteroaromatics such as anilines, bromobenzene, fluorobenzene, nitrobenzene, indoles, and pyrroles. However, in these reactions, no arylation product was observed.

**Table 2.1 :** The Arylation of **1a** with Aromatics **2b-k**[a]

| entry | **1** | product **3** | yield (%)[b] |
|---|---|---|---|
| **1** |  **2b** |  **4b** | 68 |

| | | | |
|---|---|---|---|
| **2** |  **2c** |  **4c** | 72 |
| **3** |  **2d** |  **4d** | 71 |
| **4** |  **2e** |  **4e** | 68 |
| **5** |  **2f** |  **4f** | 72 |
| **6** |  **2g** |  **4g** | 75 |
| **7** | **2h** |  **4h** | 77 |
| **8** |  **2i** |  **4i** | 85 |
| **9** |  **2j** |  **4j** | 86 |

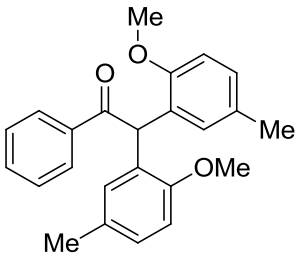
| | | | |
|---|---|---|---|
| **10** |  **2k** |  **4k** | 66 |

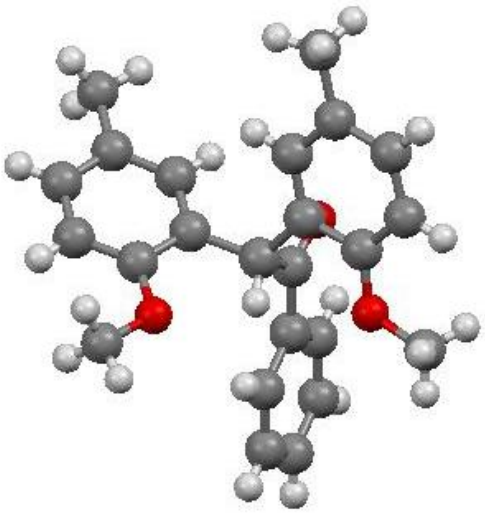
[a]All reactions were carried out using **1a** (1.0 mmol), **2b-k** (2.20 mmol) and $K_2S_2O_8$ (1.0 mmol) in $CF_3COOH$ (1.0 mL) at room temperature under air for 24 h. [b]Isolated yield.

## 2A.4: Regioselectivity Studies

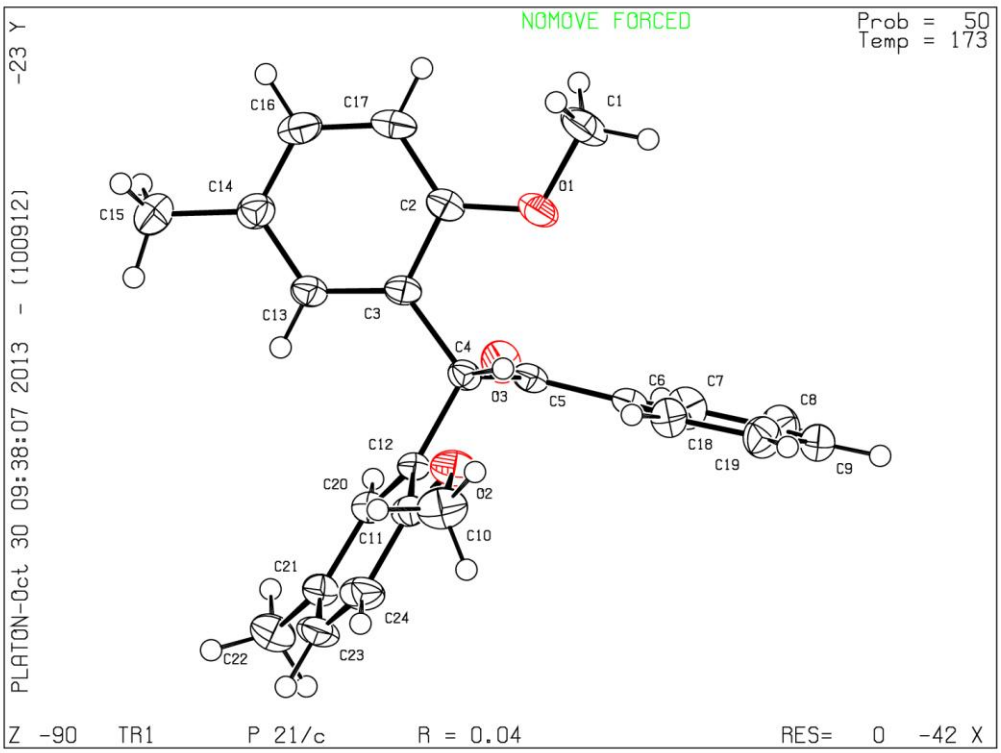
The regiochemistry of compound **4d** was established by

**X-ray analysis for compound 4d.**



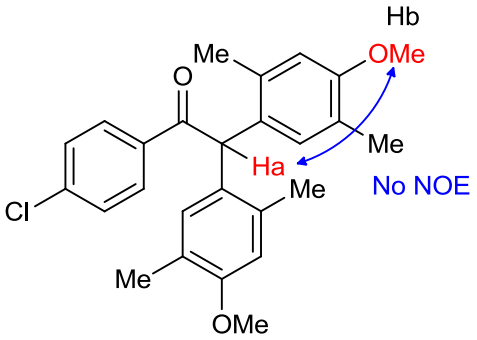



**Red Colour is Oxygen**



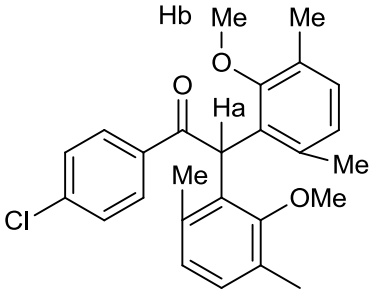

The regiochemistry of compound **3n** was established by NOESY experiments.

NOESY Spectrum of compound **4o:**



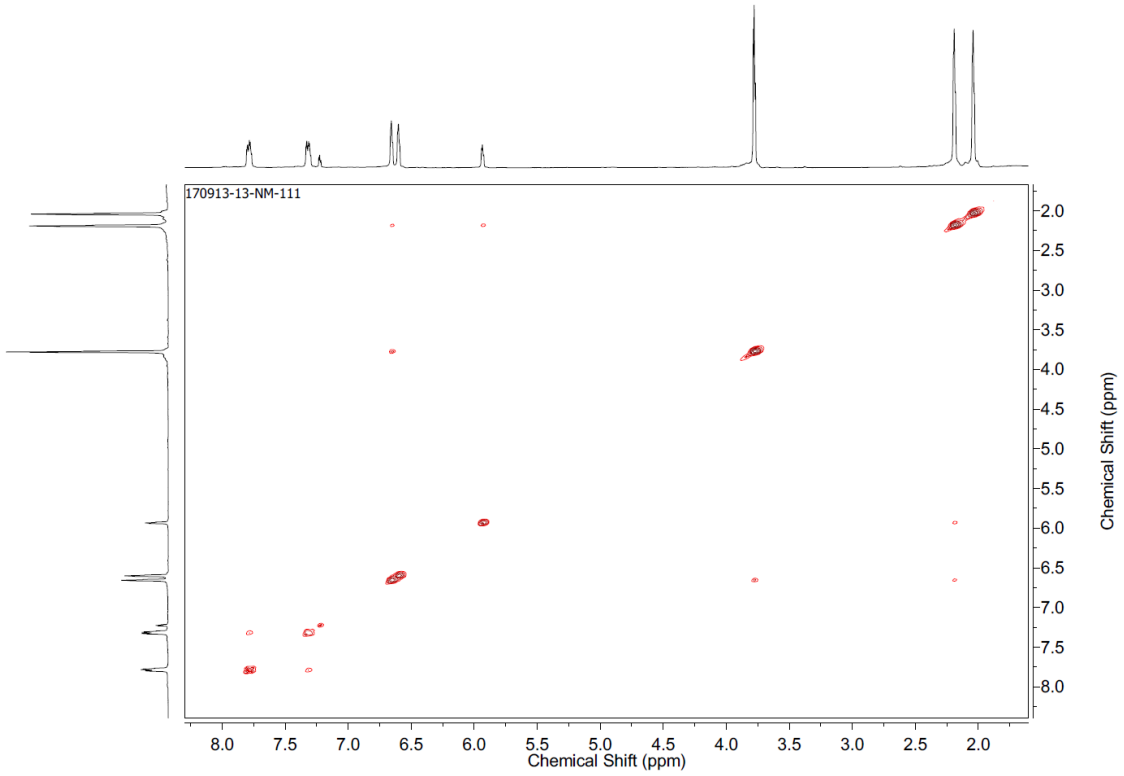

δ Ha = 5.95, Hb = 3.79

**Observed product**




**Possible regioisomer**
**Not observed**

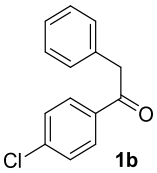
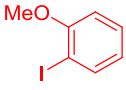
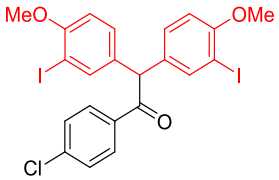
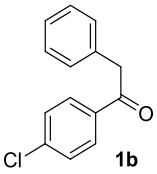
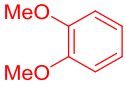
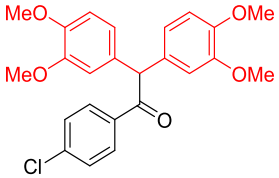
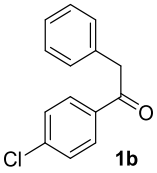
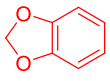
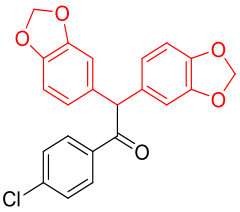
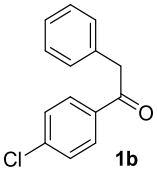
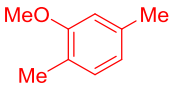
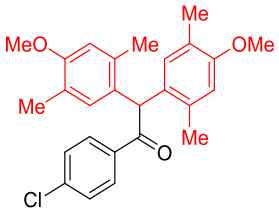
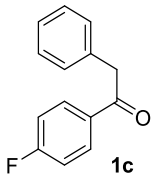
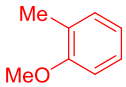
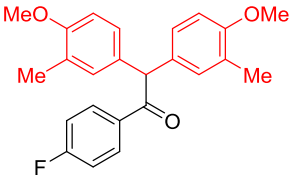
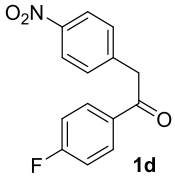
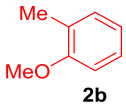
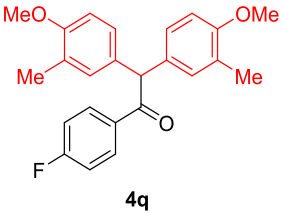
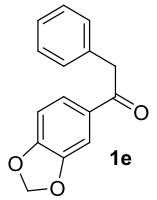
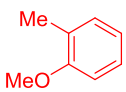
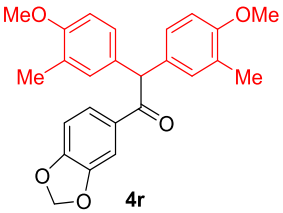
There is no NOE correlation between Ha (δ 5.95, s) and Hb (δ 3.79, s). This result revealed that the regiochemistry of compound **4o** is correct.

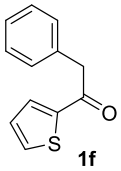
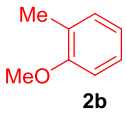
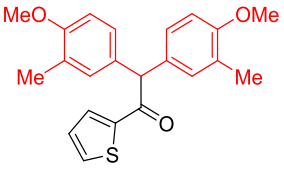



**2A.5: Scope of substituted benzyl ketones**

The present α-diarylation reaction was successfully extended to various substituted benzyl ketones **1b-e** (Table 2.2). When chloro substituted benzyl phenyl ketone **1b** was treated with 2-iodoanisole (**2a**), 1,2-dimethoxy benzene (**2f**) and benzo[*d*][1,3]dioxole (**2g**) under the optimized reaction conditions, α-diaryl ketones **4l-n** was observed in 75%, 85%, and 73% yields, respectively. Interestingly, trisubstituted aromatic, 2-methoxy-1,4-dimethylbenzene (**2l**), also efficiently participated in the reaction, yielding product **4o** in 79% yield. Similarly, 2-methyl anisole (**2b**) reacted efficiently with fluoro substituted benzyl phenyl ketone **1c** giving the corresponding α-diaryl ketone **4p** in 72% yield. But, the $NO_2$ substituent at benzyl group **1d** yielded **4q** only in 51% yields. Further, benzo[*d*][1,3]dioxole group substituted benzyl ketone **1f** reacted with **2c** providing α-diaryl ketone **4r** in 53% yield. The arylation reaction was also compatible with heteroaromatic group substituted benzyl ketone **1g**. Thus, treatment of **1g** with 2-methyl anisole (**2b**) gave α-diaryl ketone **4s** in 57% yield. Subsequently, the reaction was also tested with CN, $CO_2Me$, $NO_2$, and alkyls such as Me and *iso*-Pr instead of phenyl substituted ketones. In these reactions, no α-arylation products were observed.

**Table 2.2 :** Results of the Reaction of substituted 2-phenylacetophenone (**1a**), Acetophenone **(1b),** or 4-Methylacetophenone (**1e**) with Substituted Alkenes **2b-f**[a]

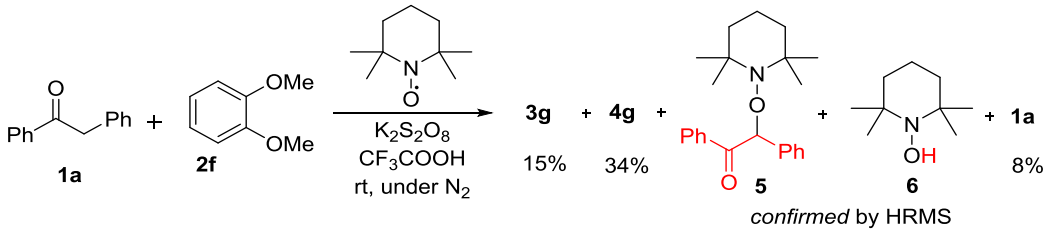
| entry | 1 | 2 | Product **3** | Yield (%)[b] |
|---|---|---|---|---|
| **1** |  **1b** |  **2a** |  **4l** | 75 |
| **2** |  **1b** |  **2f** |  **4m** | 85 |
| **3** |  **1b** |  **2h** |  **4n** | 73 |
| **4** |  **1b** |  **2b** |  **4o** | 79 |
| **5** |  **1c** |  **2b** |  **4p** | 72 |
| **6** |  **1d** |  **2b** |  **4q** | 51 |
| **7** |  **1e** |  **2b** |  **4r** | 53 |

| | | | | |
|---|---|---|---|---|
| **8** |  **1f** |  **2b** |  **4s** | 57 |

[a]All reactions were carried out using **1b-f** (1.0 mmol), **2b-l** (2.20 mmol) and $K_2S_2O_8$ (1.0 mmol) in $CF_3COOH$ (1.0 mL) at room temperature under air for 24 h. [b]Isolated yield.

## 2A.6: Mechanism

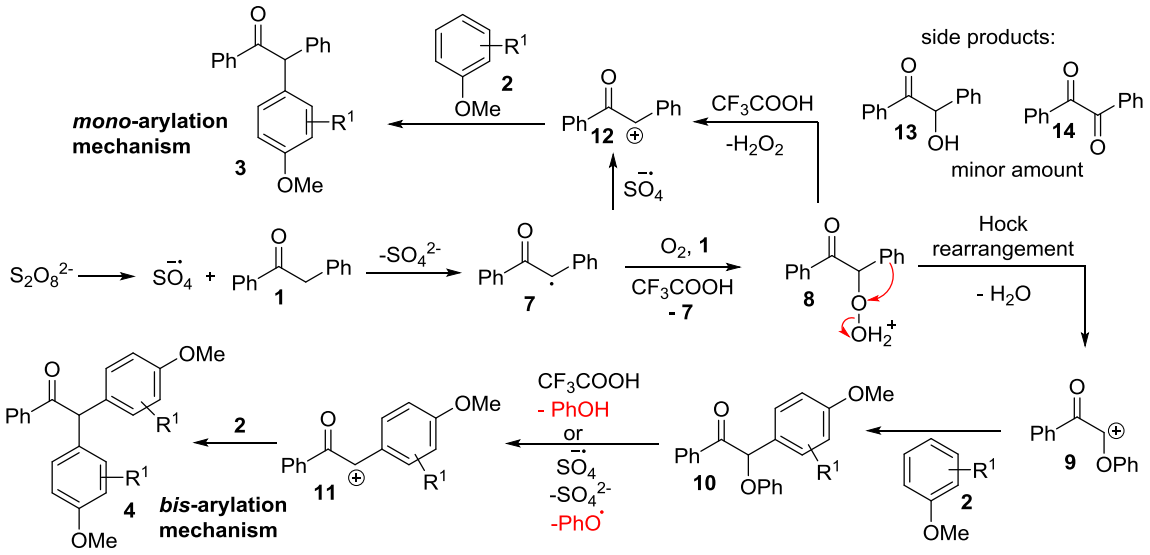
We strongly believe that the present arylation reaction proceeds via a radical mechanism. To support the mechanism, the following reaction was carried out (Scheme 2.15). The reaction of **1a** with **2g** was tested in the presence of TEMPO free radical (1.0 equiv) and $K_2S_2O_8$ in $CF_3COOH$ at rt for 24 h under $N_2$. In the reaction, α-monoaryl ketone **3g** and α-diaryl ketone **4g** were observed in 15% and 34% yields, respectively. In addition, TEMPO adducts **5** and **6** were also observed. The TEMPO adducts were confirmed by HRMS analysis. Meanwhile, 8% of starting material **1a** was recovered.




**Scheme 2.15:** Examination in the presence of TEMPO radical

A possible reaction mechanism is proposed in Scheme 2.16. It is known that $K_2S_2O_8$ generates $SO_4^{-\bullet}$ radical anion and the corresponding anionic radical can abstract hydrogen from acidic C-H bond of organic molecules.[20a] In the present reaction, $SO_4^{-\bullet}$ abstracts hydrogen from the acidic methene carbon of **1a**, generating radical **7**. Further, a radical of intermediate **7** inserts into $O_2$ followed by abstracting hydrogen from another **1** and protonation in the presence of $CF_3COOH$ producing intermediate **8**. Intermediate **8** underwent an *ipso*-substitution rearrangement (Hock type rearrangement) giving intermediate **9** and elimination of water (see Cumene process).[20b-c] Nucleophilic addition of aromatic **2** into intermediate **9** affords intermediate **10**.[20c] Subsequently, intermediate **10** eliminates a phenoxy radical providing cationic intermediate **11** in the presence of $SO_4^{-\bullet}$[18d-e] It is also possible that the carbocation intermediate **11** may also form from intermediate **10** by $CF_3COOH$-mediated ionic pathway with a loss of PhOH as like a Cumene process.[20b-c] Further, the addition of aromatic **2** into intermediate **11** affords

product **4**.[20c] *mono*-Arylated compound **3** observed via nucleophilic addition of aromatic **2** into intermediate **12**. We have tried to trap a phenoxy radical. However, we were not able to trap it. It is known that a phenoxy radical spontaneously reacts themselves or with $O_2$ giving a mixture of phenol and quinone derivatives.[20f] It is also highly possible that it could decompose spontaneously under air and very hard to trap.[20f]




**Scheme 2.16:** Proposed mechanism

In fact, we have observed a minor amount of phenol derivatives which was confirmed by GC-MS. A loss of PhOH moiety was anticipated in the ionic transformation of intermediates **10** to **11** mediated by acid. In fact, we have tried to isolate PhOH moiety. However, we were not able to isolate it. It is well known that the PhOH moiety rapidly converts into a phenoxy radical in the presence of a radical initiator under air or oxygen atmosphere.[20f] The present reaction was also performed under an air atmosphere. Thus, we strongly believe that a phenoxy radical was formed from PhOH under the reaction conditions. In some of the reactions, a minor amount of side products **13** and **14** were observed. The observation of these products supports the reaction of oxygen into intermediate **7** and the formation of $H_2O_2$ which oxidizes **1** to **13** and **14**.

## 2A.7: Conclusion

1. We have developed a mild, simplest and regioselective synthesis of α-diaryl ketones by the reaction of benzyl ketones with aromatics using very simple but versatile reagent $K_2S_2O_8$.
2. In the present reaction, two new carbon-carbon bonds formed, and one carbon-carbon bond was cleaved.

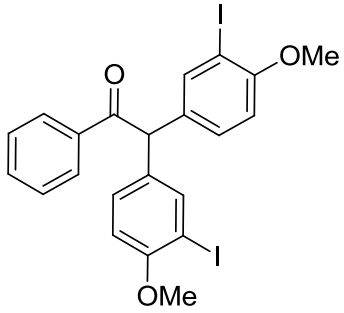
## 2A.8: Experimental Section

### General Procedure for the α-Diarylation:

In a 25-mL round bottom flask equipped with a magnetic stir bar, $K_2S_2O_8$ (1.0 equiv), benzyl ketones **1** (200 mg) and aromatics **2** (2.2 equiv) were taken. To the flask, was then added $CF_3COOH$ (1.0 mL) via syringe. Then, the reaction mixture was allowed to stir at room temperature for 24 h under an air atmosphere. After 24 h, the reaction mixture was diluted with $CH_2Cl_2$ and solvents were evaporated under vacuum. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **4**.

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

**2,2-*bis*(3-Iodo-4-methoxyphenyl)-1-phenylethanone (4a)**.



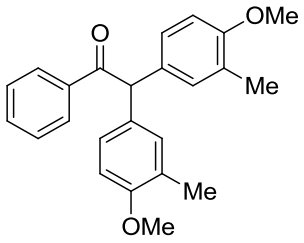

Yellow viscous oil; eluent (4% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.94 (d, *J* = 8.0 Hz, 2 H), 7.64 (s, 2 H), 7.52(t, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 8.0 Hz, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 6.75 (d, *J* = 8.0 Hz, 2 H), 5.81 (s, 1 H), 3.82 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 197.6, 157.3, 139.7, 136.3, 133.3, 132.9, 129.9, 128.9, 128.7, 110.9, 86.4, 56.4, 56.4.

**HRMS (ESI**): calc. for $[(C_{22}H_{18}I_2O_3)H]$ (M+H) 584.9424, measured 584.9422.

**2,2-*bis*(4-Methoxy-3-methylphenyl)-1-phenylethanone (4b).**



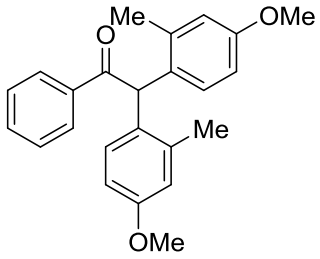

White solid; eluent (5% ethyl acetate in hexanes).

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.98 (d, *J* = 8.0 Hz, 2 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 7.02 (s, 2H),7.01 (d, *J* = 8.0 Hz, 2 H), 6.74 (d, *J* = 8.0 Hz, 2 H), 5.85 (s, 1 H), 3.77 (s, 6 H), 2.16 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 199.0, 156.7, 136.9, 132.8, 131.2, 131.0, 128.9, 128.5, 127.2, 126.8, 109.9, 57.9, 55.2, 16.3**.**

**HRMS (ESI):** calc. for [($C_{24}H_{24}O_3$)H] (M+H) 361.1804, measured 361.1820**.**

**2,2-*bis*(4-Methoxy-2-methylphenyl)-1-phenylethanone (4c).**



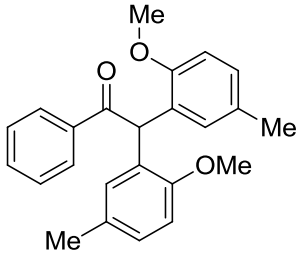

Colorless liquid; eluent (5% ethyl acetate in hexanes).

**$^{1}$H NMR ($CDCl_3$, 400 MHz)**: δ 7.79 (d, *J* = 8.0 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 7.29 (t, *J* = 8.0 Hz, 2 H), 7.16 (d, *J* = 2.0 Hz, 2 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 6.76 (s, 2 H), 5.97 (s, 1 H), 3.67 (s, 6 H), 2.14 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 199.6, 158.5, 137.3, 136.9, 132.8, 130.2, 129.3, 128.6, 128.6, 116.6, 110.9, 73.9, 52.3, 20.0.

**HRMS (ESI)**: calc. for [($C_{24}H_{24}O_3$)Na] (M+Na) 383.1623, measured 383.1617.

**2,2-*bis*(2-Methoxy-5-methylphenyl)-1-phenylethanone (4d).**



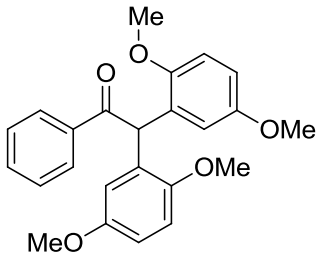

White solid; eluent (5% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 8.01 (d, *J* = 8.0 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 7.37 (t, *J* = 8.0 Hz, 2 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 6.81 (dd, *J* = 8.0, 4.0 Hz, 2 H), 6.79 (s, 2 H), 6.62 (s, 1 H), 3.73 (s, 6 H), 2.20 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 200.0, 154.7, 137.3, 132.3, 130.5, 129.7, 128.6, 128.5, 128.3, 126.7, 110.6, 55.7, 46.1, 20.8.

**HRMS (ESI)**: calc. for [($C_{24}H_{24}O_3$)H] (M+H) 361.1804, measured 361.1811.

**2,2-*bis*(2,5-Dimethoxyphenyl)-1-phenylethanone (4e).**



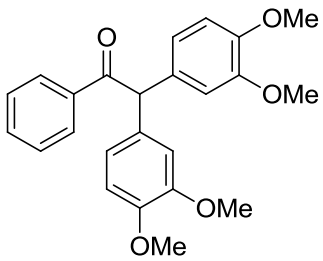

Colorless liquid; eluent (10% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 8.00 (d, *J* = 8.0 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 7.36 (t, *J* = 8.0 Hz, 2 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 6.73 (dd, *J* = 8.0, 4.0 Hz, 2 H), 6.60 (s, 2 H), 6.58 (s, 1 H), 1 3.70 (s, 6 H), 3.66 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 198.8, 153.6, 150.7, 137.4, 137.1, 130.3, 128.9, 128.8, 116.8, 112.2, 111.4, 56.1, 55.7, 53.3.

**HRMS (ESI):** calc. for [($C_{24}H_{24}O_5$)H] (M+H) 393.1702, measured 393.1704.

**2,2-*bis*(3,4-Dimethoxyphenyl)-1-phenylethanone (4f).**



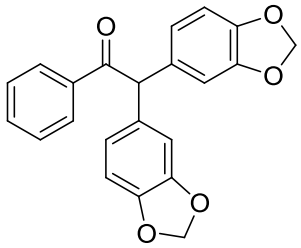

Dark yellow liquid; eluent (10% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 8.00 (d, *J* = 8.0 Hz, 2 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 8.0 Hz, 2 H), 6.80 (d, *J* = 8.0 Hz, 6 H), 5.93 (s, 1 H), 3.84 (s, 6 H), 3.82 (s, 6 H).

**$^{13}$CNMR ($CDCl_3$, 100 MHz):** δ 198.8, 149.2, 148.2, 137.0, 133.0, 131.8, 128.9, 128.6, 121.4, 112.4, 111.3, 58.4, 55.8, 55.8.

**HRMS (ESI):** calc. for [($C_{24}H_{24}O_5$)Na] (M+Na) 415.1521, measured 415.1522**.**

**2,2-*bis*(Benzo[*d*][1,3]dioxol-5-yl)-1-phenylethanone (4g).**



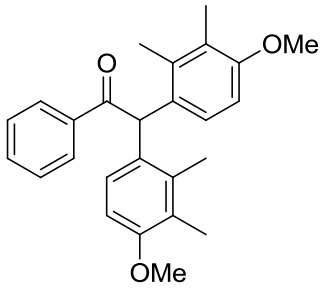
Colorless semisolid; eluent (5% ethyl acetate in hexanes).

**$^{1}$H NMR (CDCl$_3$, 400 MHz)**: δ 7.97 (d, *J* = 8.0 Hz, 2 H), 7.50 (t, *J* = 8.0 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 6.71 (dd, *J* = 8.0 Hz, 4.0 Hz, 6 H), 5.93 – 5.88 (m, 4 H), 5.83 (s, 1 H).

**$^{13}$C NMR (CDCl$_3$, 100 MHz):** δ 198.2, 148.0, 146.7, 136.6, 133.1, 132.9, 128.9, 128.6, 122.1, 109.5, 108.4, 101.1, 58.4.

**HRMS (ESI**): calc. for [($C_{22}H_{16}O_5$)H] (M+H) 361.1076, measured 361.1089**.**

**2,2-*bis*(4-Methoxy-2,3-dimethylphenyl)-1-phenylethanone (4h).**



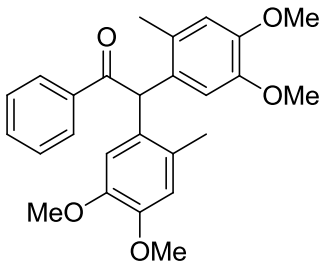
Yellow semisolid; eluent (3% ethyl acetate in hexanes)**.**

**$^{1}$H NMR (CDCl$_3$, 400 MHz):** δ 7.90 (d, *J* = 8.0 Hz, 2 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 6.69 (d, *J* = 8.0 Hz, 2 H), 6.61 (d, *J* = 8.0 Hz, 2 H), 6.20 (s, 1 H), 3.76 (s, 6 H), 2.20 (s, 6 H), 2.16 (s, 6 H).

**$^{13}$C NMR (CDCl$_3$, 100 MHz):** δ 200.0, 156.5, 137.0, 135.6, 132.7, 129.4, 128.6, 128.6, 127.3, 125.5, 107.5, 55.3, 53.8, 15.9, 12.3.

**HRMS (ESI):** calc. for [($C_{26}H_{28}O_3$)Na] (M+Na) 411.1936, measured 411.1946.

**2,2-*bis*(4,5-Dimethoxy-2-methylphenyl)-1-phenylethanone (4i).**



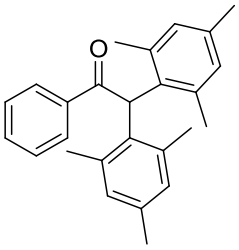
Yellow semisolid; eluent (15% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.88 (d, *J* = 8.0 Hz, 2 H), 7.50 (t, *J* =8.0 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 6.73 (s, 2 H), 6.47 (s, 2 H), 6.07 (s, 1 H), 3.85 (s, 6 H), 3.64 (s, 6 H), 2.20 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 199.8, 147.7, 146.9, 137.0, 132.9, 128.8, 128.7, 128.4, 128.2, 113.9, 112.7, 55.9, 55.7, 52.9, 19.4.

**HRMS (ESI):** calc. for [($C_{26}H_{28}O_5$)Na] (M+Na) 443.1834, measured 443.1828.

**2,2-Dimesityl-1-phenylethanone (4j).**



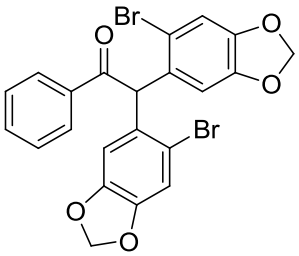
Dark yellow liquid; eluent (1% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.90 (d, *J* = 8.0 Hz, 2 H), 7.52 – 7.46 (t, *J* = 8.0 Hz, 1 H), 7.36 (t, *J* = 8.0 Hz, 2 H), 6.77 (s, 4 H), 6.16 (s, 1 H), 2.23 (s, 6 H), 2.01 (s, 12 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 201.2, 137.6, 137.4, 136.2, 134.1, 132.9, 130.4, 128.7, 127.9, 55.1, 21.4, 20.7.

**HRMS (ESI):** calc. for [($C_{26}H_{28}O$)Na] (M+Na) 379.2038, measured 379.2034.

**2,2-*bis*(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-1-phenylethanone (4k).**



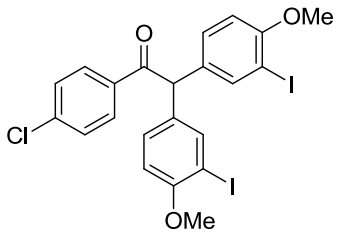
Colourless solid; eluent (20% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.97 (d, *J* = 8.0 Hz, 2 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 2 H), 7.07 (s, 2 H), 6.59 (s, 1 H), 6.50 (s, 2 H), 5.95 (d, *J* = 2.0 Hz, 2 H), 5.92 (d, *J* = 2.0 Hz, 2 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 197.7, 147.8, 147.6, 136.1, 133.4, 130.3, 130.2, 128.8, 115.7, 113.2, 110.4, 102.0, 58.4.

**HRMS (ESI):** calc. for [($C_{22}H_{14}Br_2O_5$)H] (M+H) 516.9286, measured 516.9295.

**1-(4-Chlorophenyl)-2,2-*bis*(3-iodo-4-methoxyphenyl)ethanone (4l).**



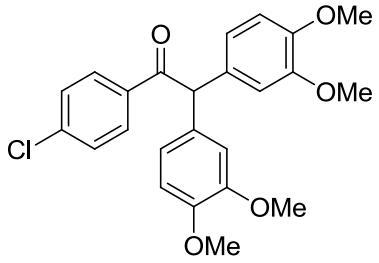

Colorless solid; eluent (5% ethyl acetate in hexanes).

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.87 (d, *J* = 8.0 Hz, 2 H), 7.61 (d, *J* = 4.0 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.13 (dd, *J* = 8.0, 4.0 Hz, 2 H), 6.74 (d, *J* = 8.0 Hz, 2 H), 5.74 (s, 1 H), 3.83 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 196.5, 157.4, 139.8, 139.6, 134.5, 132.6, 130.3, 129.9, 129.1, 110.9, 86.5, 56.5, 56.4.

**HRMS (ESI):** calc. for [($C_{22}H_{17}ClI_2O_3$)H] (M+H) 618.9034, measured 618.9025.

**1-(4-Chlorophenyl)-2,2-bis(3,4-dimethoxyphenyl)ethanone (4m).**



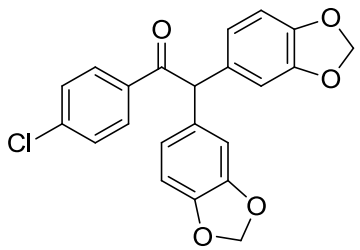

Brown liquid; eluent (50% ethyl acetate in hexanes).

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.91 (d, *J* = 8.0 Hz, 2 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 6.76 (d, *J* = 8.0 Hz, 2 H), 6.74 (s, 2 H), 5.83 (s, 1 H), 3.83 (s, 6 H), 3.79 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 197.4, 149.1, 148.3, 139.4, 135.1, 131.3, 130.3, 128.9, 121.2, 112.1, 111.2, 58.5, 55.9, 55.8.

**HRMS (ESI):** calc. for [($C_{24}H_{23}ClO_5$)Na] (M+Na) 449.1132 , measured 449.1138.

**2-Acetamido-5-methoxyphenyl 4-fluorobenzoate (4n).**



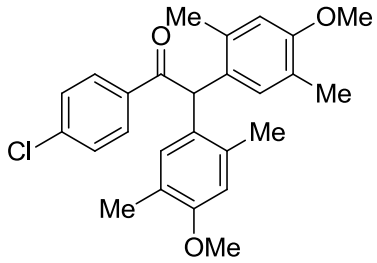

Colorless liquid; eluent (20% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.89 (d, *J* = 8.0 Hz, 2 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 6.74 (dd, *J* = 8.0 Hz, 4.0 Hz 2 H), 6.72 (s, 2 H), 6.70 (dd, *J* = 8.0 Hz, 4.0 Hz, 2 H), 5.93 – 5.88 (m, 4 H), 5.83 (s, 1 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 197.0, 148.0, 146.9, 139.5, 134.9, 132.5, 130.3, 128.9, 122.1, 109.4, 108.4, 101.1, 58.5.

**HRMS (ESI):** calc. for [($C_{22}H_{15}ClO_5$)H] (M+H) 395.0686, measured 395.0685.

**1-(4-Chlorophenyl)-2,2-*bis*(4-methoxy-2,5-dimethylphenyl)ethanone (4o).**



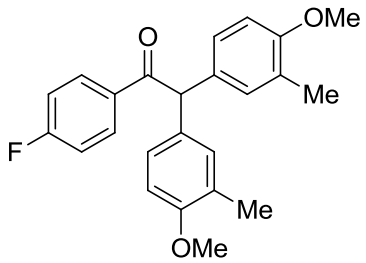

Yellow liquid; eluent (4% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.80 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 6.67 (s, 2 H), 6.61 (s, 2 H), 5.95 (s, 1 H), 3.79 (s, 6 H), 2.20 (s, 6 H), 2.05 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 198.8, 156.6, 139.1, 135.4, 134.1, 131.3, 130.0, 128.9, 128.2, 123.9, 112.5, 105.5, 55.2, 52.4, 19.9, 15.9.

**HRMS (ESI)**: calc. for [($C_{26}H_{27}ClO_3$)Na] (M+Na) 445.1546, measured 445.1546.

**1-(4- Fluorophenyl)-2,2-bis(4- methoxy-3-methylphenyl) ethanone (4p).**



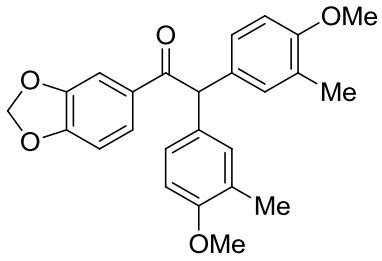

Light yellow solid; eluent (30% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 8.12 (d, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 6.86 (s, 2 H), 6.82 (d, *J* = 8.0 Hz, 2 H), 6.74 (d, *J* = 8.0 Hz, 2 H), 5.46 (s, 1 H), 3.81 (s, 6 H), 2.16 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 192.9, 156.5, 152.7, 146.3, 134.4, 131.5, 130.1, 127.3, 126.8, 123.4, 109.7, 55.3, 55.1, 16.3.

**HRMS (ESI):** calc. for [($C_{24}H_{23}FO_3$)H] (M+H) 379.1709, measured 379.1715.

**1-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-*bis*(4-methoxy-3-methylphenyl)ethanone (4r).**



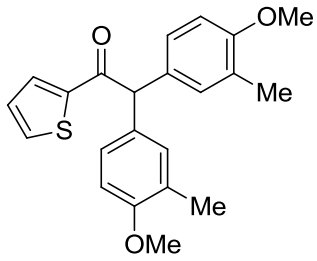

Yellow liquid; eluent (6% ethyl acetate in hexanes).

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.60 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.45 (d, *J* = 4.0 Hz, 1 H), 6.99 (m, 4 H), 6.77( d, *J* = 8.0 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 2 H), 5.98 (s, 2 H), 5.76 (s, 1 H), 3.77 (s, 6 H), 2.15 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 197.3, 173.0, 156.7, 151.5, 148.0, 131.2, 131.2, 127.1, 126.8, 125.2, 110.1, 108.8, 107.9, 101.8, 57.7, 55.5, 16.4.

**HRMS (ESI):** calc. for [($C_{25}H_{24}O_5$)Na] (M+Na) 427.1521, measured 427.1515.

**,2-*bis*(4-Methoxy-3-methylphenyl)-1-(thiophen-2-yl)ethanone (4s).**




Colourless liquid; eluent (4% ethyl acetate in hexanes).

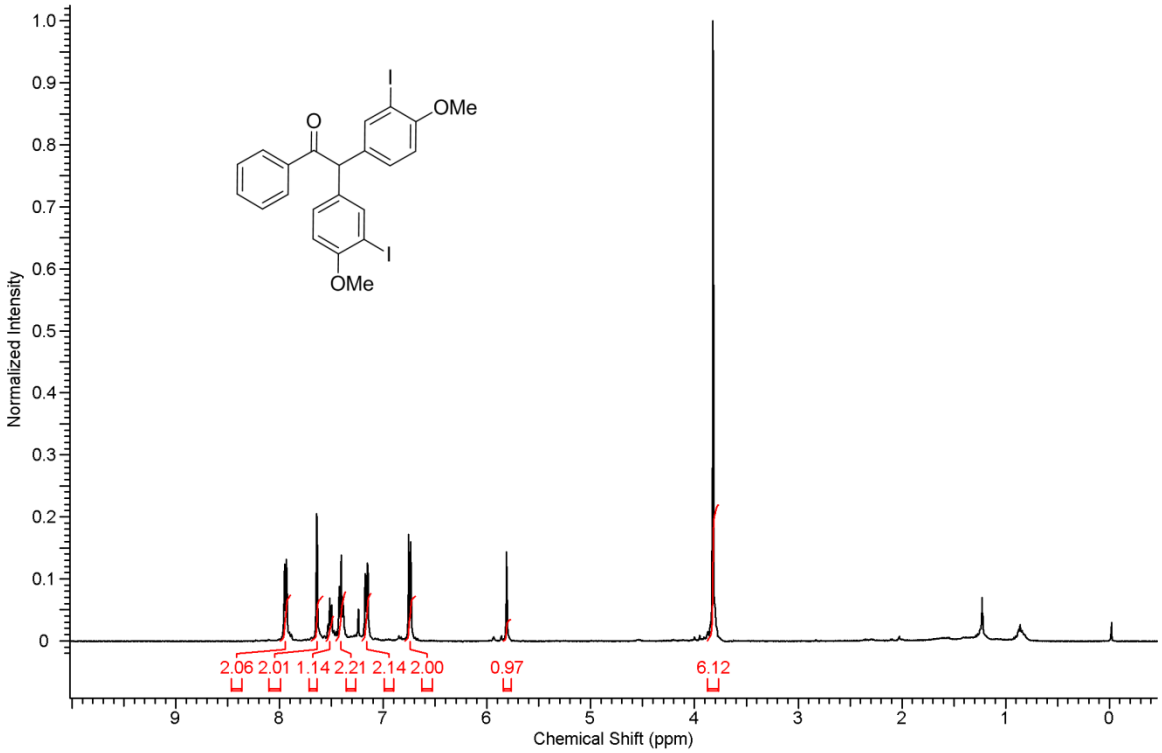
**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.73 (d, *J* = 4.0 Hz, 1 H), 7.57 (d, *J* = 4.0 Hz, 1 H), 7.11 – 7.03 (m, 5 H), 6.74 (d, *J* = 8.0 Hz, 2 H), 5.69 (s, 1 H), 3.77 (s, 6 H), 2.16 (s, 6 H).

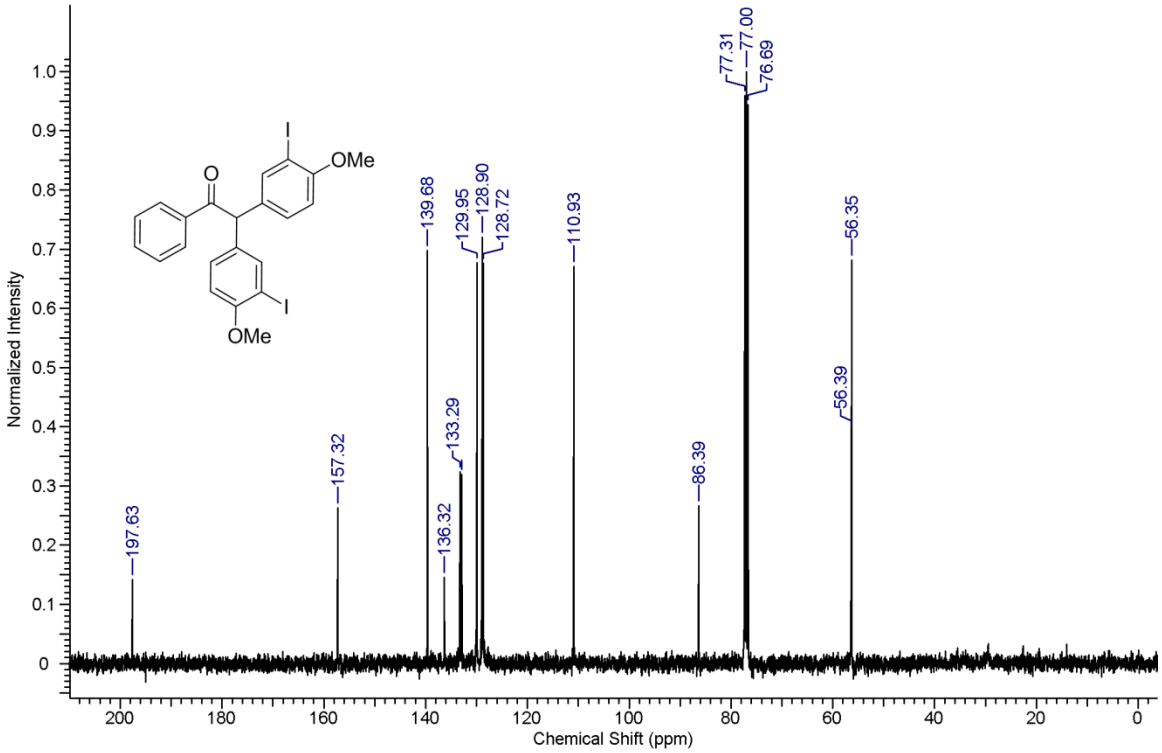
**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 192.1, 172.9, 156.8, 133.7, 132.6, 131.2, 130.8, 128.1, 127.1, 126.8, 109.9, 59.0, 55.3, 16.3.

**HRMS (ESI):** calc. for [($C_{22}H_{22}SO_3$)Na] (M+Na) 389.1187, measured 389.1186.

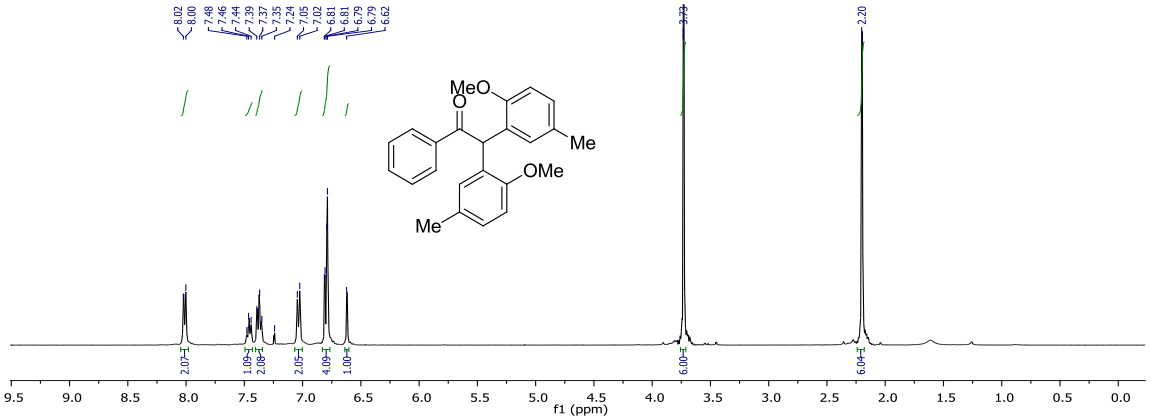
## 2A.10: Spectral Copies of Selected Compounds

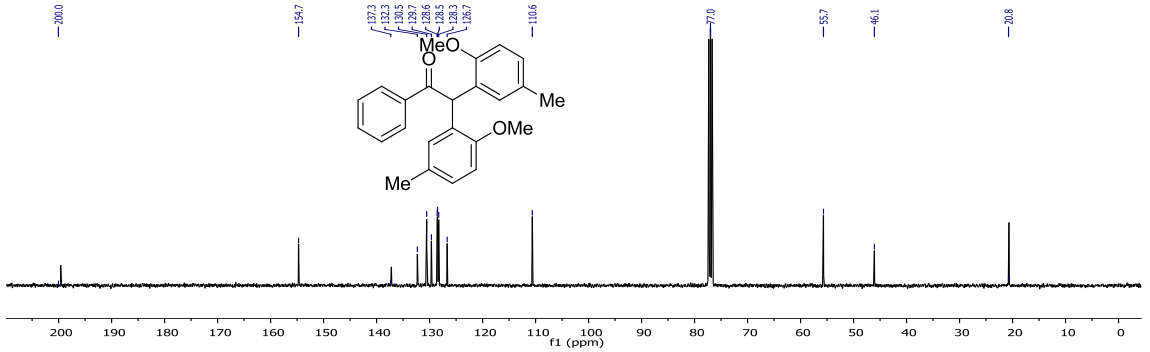
Spectral data of compound **4a**.



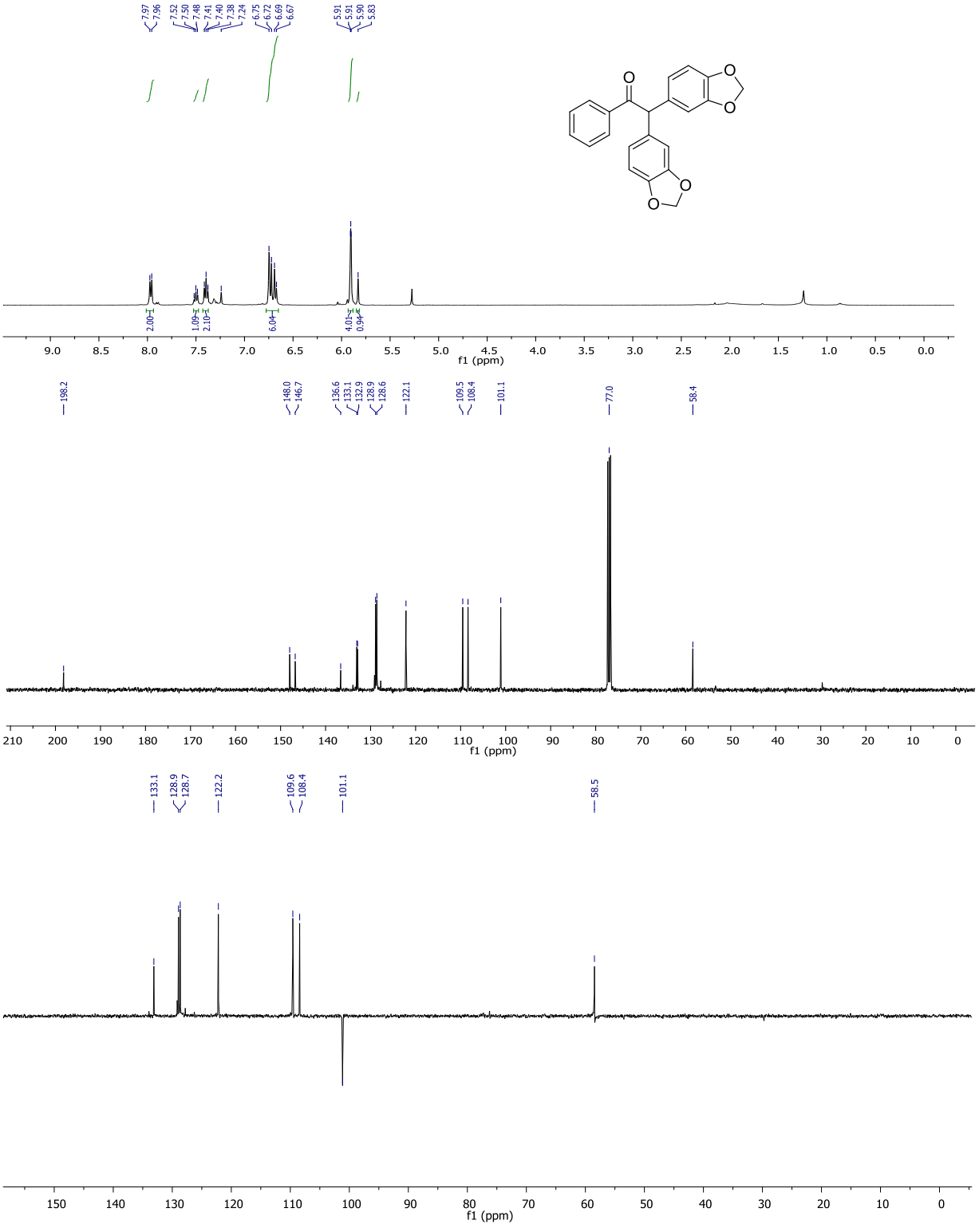



Spectral data of compound **4d**.

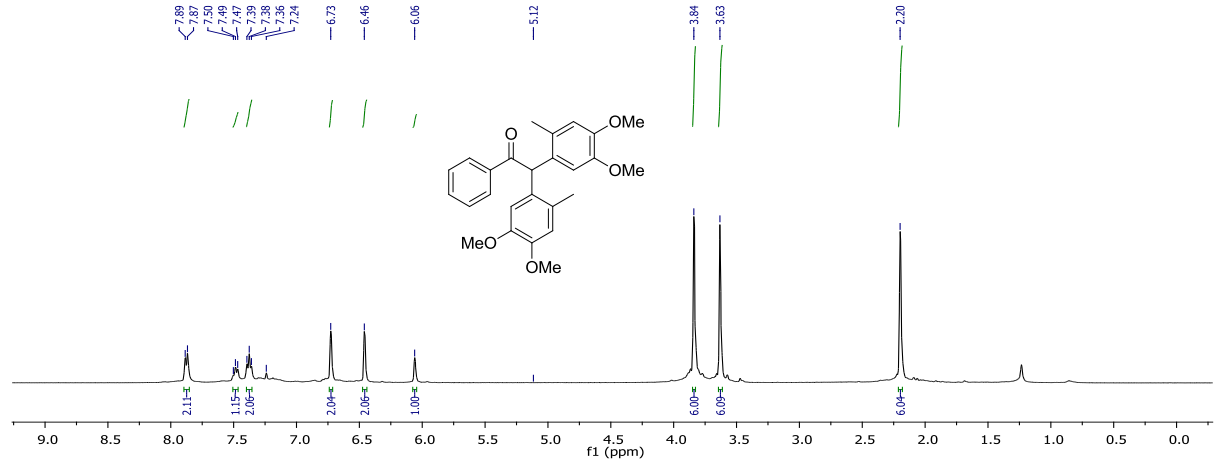


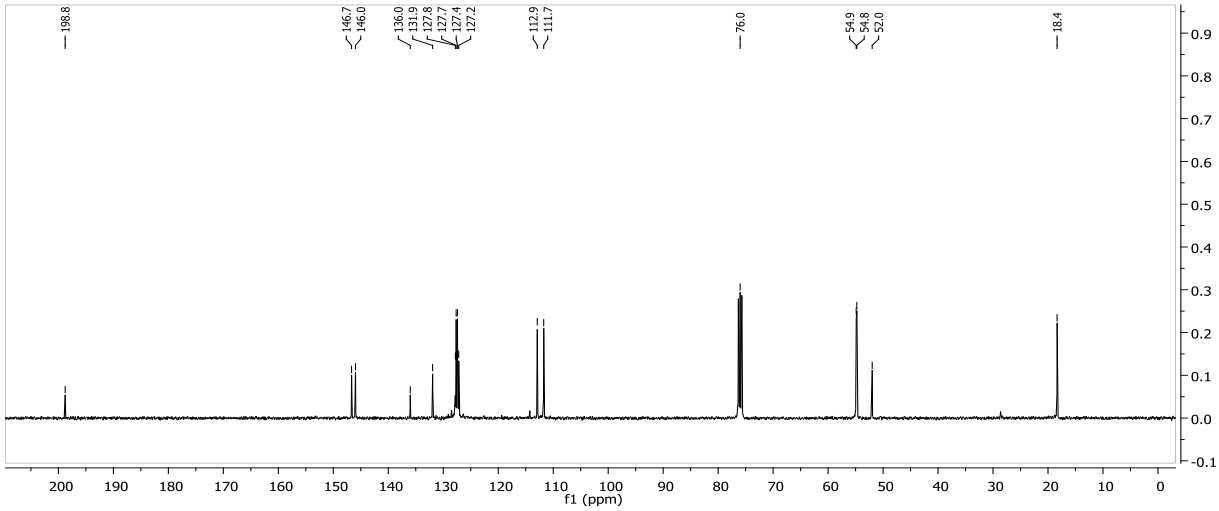



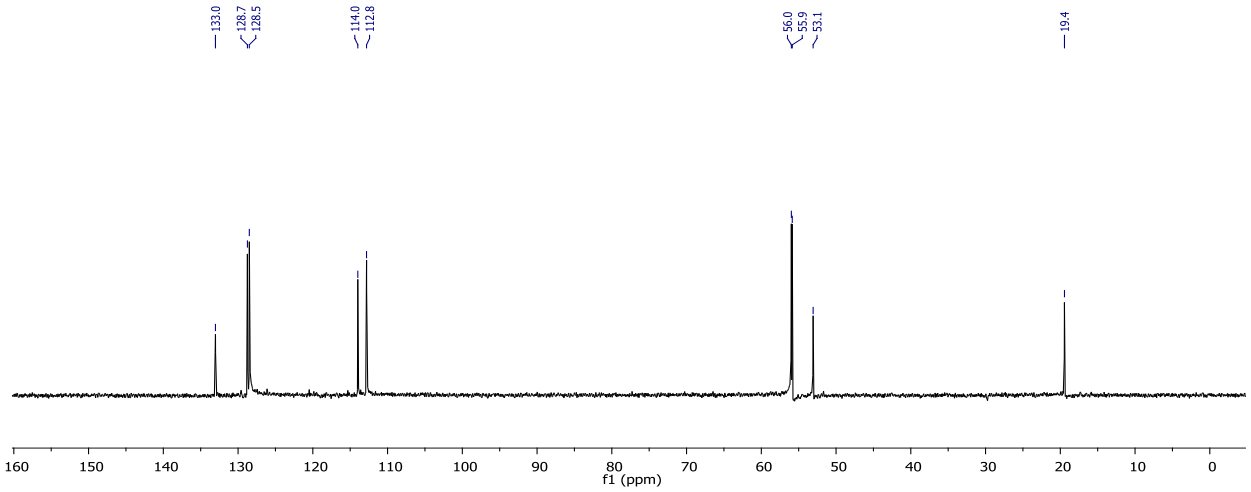
Spectral data of compound **4h**.



Spectral data of compound **4j**.



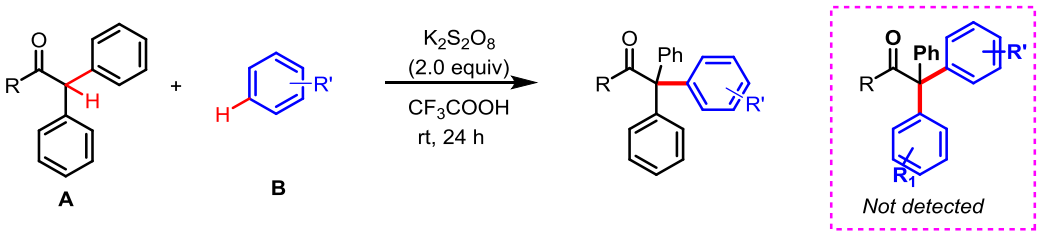



**2B: A regioselective synthesis of benzopinacolones through aerobic dehydrogenative & α-arylation of a tertiary $Sp^3$ C-H bond of 1,1-diphenylketone with aromatic and heteroaromatic compounds**

**2B.1: Results and Discussion**

In the last section, we have developed $K_2S_2O_8$ mediated cross dehydrogenative coupling reaction of substituted 2-phenyl acetophenone with electron-rich aromatics to the synthesis of α-diaryl benzyl ketones through a carbon-carbon bond cleavage at room temperature. In the reaction, two new carbon-carbon bonds were formed, and one carbon-carbon bond was cleaved. It is very interesting that two different nucleophiles such as benzyl ketones and aromatics were coupled together without metal which is unusual in organic synthesis. These results prompted us to optimize reaction conditions for selective monoarylation without carbon-carbon bond cleavage. We were failed to optimize by changing parameters or amount of $K_2S_2O_8$. Thus, we evaluated the efficiency of coupling reaction by reaction of 1,1-diphenyl propane-2-one and 1,3-dimethoxybenzene to produce only and only monoarylation. Hence, α-monoarylation of 1,1-diphenylpropan-2-one performed under ambient conditions with high efficiency and regiocontrol to introduce one molecule of 1,3-dimethoxy benzene at the methylene position (Scheme 2.17). No other competitive C-C cleaved product was observed. In this section, herein, we wish to debate on a new type of α-monoarylation of substituted 1,1-diphenylbenzyl ketones with aromatics or heteroaromatics in the presence of $K_2S_2O_8$ in $CF_3COOH$ at room temperature giving highly useful and sterically hindered benzopinacolone derivatives in good to moderate yields under the mild reaction conditions.




**Scheme 2.17:** Selective mono-arylation

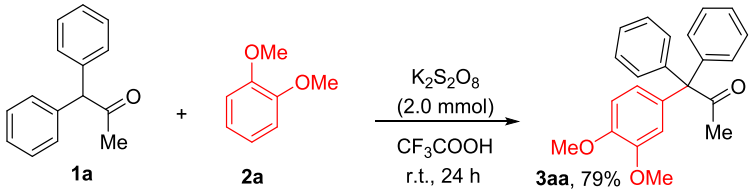
In the reaction, the electron-rich aromatic moiety is used as an arylating agent, and also arylation is done at the sterically hindered tertiary $Sp^3$ carbon of ketones. Traditionally, benzo-pinacolones are prepared from benzo pinacol via a Pinacol-Pinacolone rearrangement.[21] However, this reaction is usually limited to the preparation of symmetrical benzopinacolones. By employing the present α-arylation reaction, symmetrical as well as unsymmetrical benzo-pinacolones are prepared with diverse

substituents. Later, benzo-pinacolones were converted into tetrasubstituted alkenes and polycyclic aromatic compound.

**2B.2: Optimization Studies**

Treatment of 1,1-diphenyl propane-2-one (**1a**) (1.0 mmol) with 1,2-dimethoxybenzene (**2a**) (4.0 mmol) in $CF_3COOH$ at room temperature for 24 h under an air atmosphere gave α-arylated benzopinacolone derivative **3aa** in 55% isolated yield (Table 2.3). The reaction is highly regioselective, and only the *para* C-H bond of the OMe group of **2a** was added at the tertiary carbon of **1a** and Me group of **1a** remains intact. Further, the same reaction provided product **3aa** in 79% yield in the presence of $K_2S_2O_8$ (2.0 mmol). It is very clear that $K_2S_2O_8$ is important to increase the yield of the product. The same reaction was also tried without $K_2S2O_8$ under the nitrogen atmosphere. However, compound **3aa** was observed only in a very less 9% yield. It seems air atmosphere is also crucial for the reaction and the reaction is not moisture sensitive. It seems $K_2S_2O_8$-mediated reaction proceeds via a radical mechanism and $K_2S_2O_8$ free reaction proceeds via an ionic mechanism. Next, the reaction was tested with other solvents such as $CH_3COOH$, MeOH, pivalic acid, toluene, benzene, THF, DMF, DCE, *tert*-BuOH, and $CF_3SO_3H$ instead of $CF_3COOH$. These solvents were not effective. Further, the reaction was tested with other oxidants such as DDQ, $Ag_2O$, $PhI(OAc)_2$, Benzoquinone, $Cu(OAc)_2$, and Oxone instead of $K_2S_2O_8$. None of them worked well except $K_2S_2O_8$.

**Table 2.3:** Optimization Studies with Various Solvents, Oxidants, and Additives.[a]

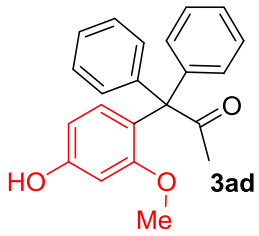



| entry | oxidant | solvent | yield of **3a** (%)[b] |
|---|---|---|---|
| 1 | $K_2S_2O_8$(2.0equiv) | AcOH | NR |
| 2 | $K_2S_2O_8$(2.0equiv) | MeOH | NR |
| 3 | $K_2S_2O_8$(2.0equiv) | Toulene | NR |
| 4 | $K_2S_2O_8$(2.0equiv) | Benzene | NR |
| 5 | $K_2S_2O_8$(2.0equiv) | THF | NR |
| 6 | $K_2S_2O_8$(2.0equiv) | DMF | NR |
| **7** | $K_2S_2O_8$(2.0equiv) | *tert*-BuOH | NR |
| 8 | $K_2S_2O_8$(2.0equiv) | $CF_3SO_3H$ | NR |
| 9 | - | TFA | 55 |
| **10** | **$K_2S_2O_8$(2.0equiv)** | **TFA** | **79** |
| 11 | DDQ | TFA | NR |
| 12 | $PhI(OAc)_2$ | TFA | ND |
| 13 | Oxone | TFA | NR |
| 14 | Benzoquinone | TFA | ND |
| 15 | Toluene | $Cu(OAc)_2.H_2O$ | NR |

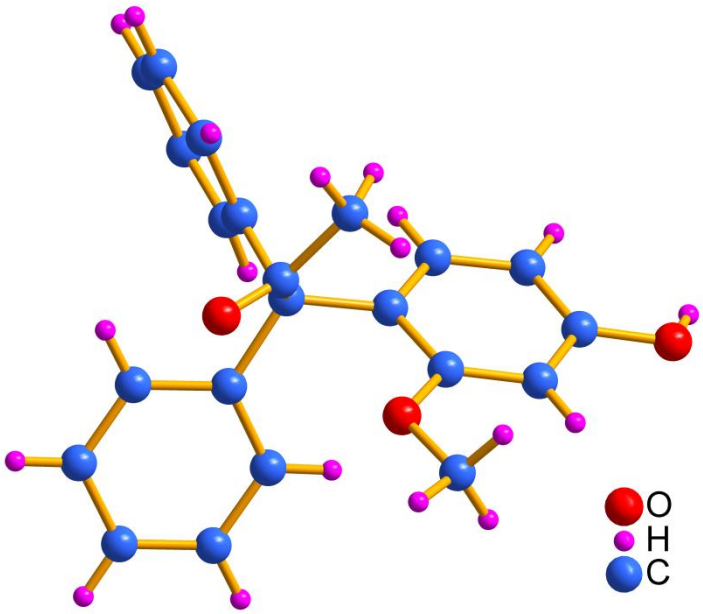
[a]All reactions were carried out using **1a**, **2b-k** (4.0 equiv) and $K_2S_2O_8$ (2.0 equiv) in $CF_3COOH$ (1.0 mL) at room temperature under air for 24 h. [b]Isolated yield.

## 2B.3: Regioselectivity Studies

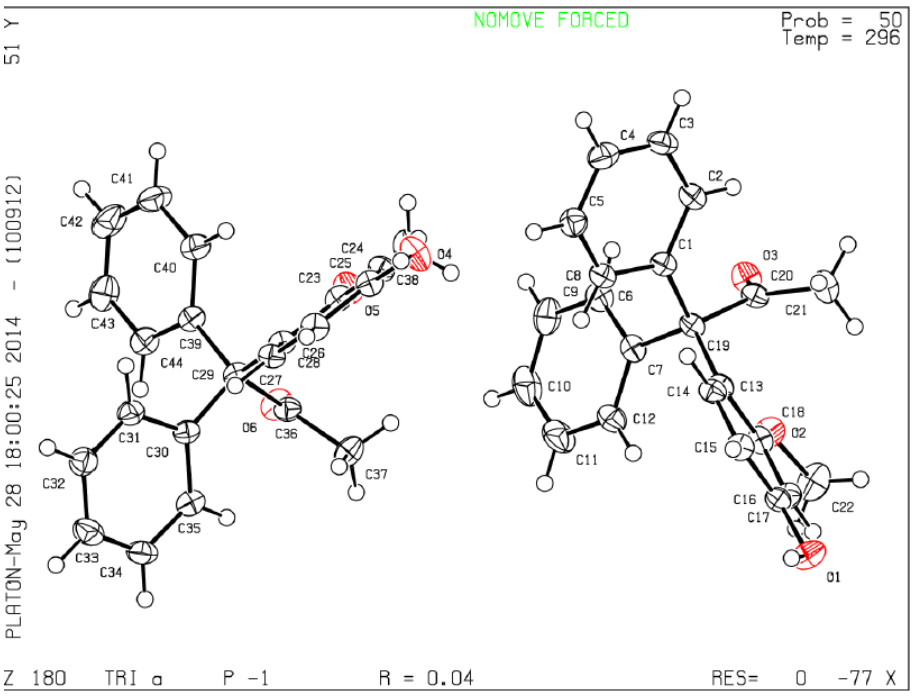
The regiochemistry of compound **3n** was established by **X-ray analysis for compound 4e.**



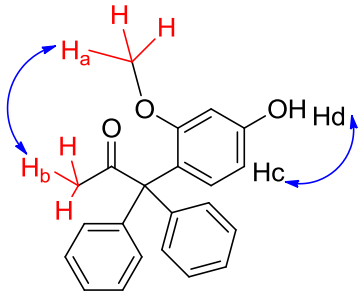

**3ad**




**Red Colour is Oxygen**

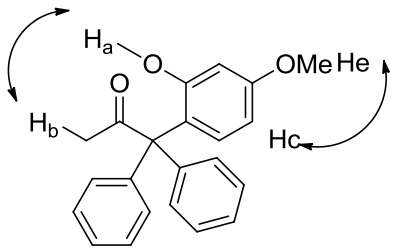


The regiochemistry of compound **3ad** was established by NOESY experiments**.**




δ Ha = 3.5, Hb = 2.1, Hc = 6.3, Hd = 5.6

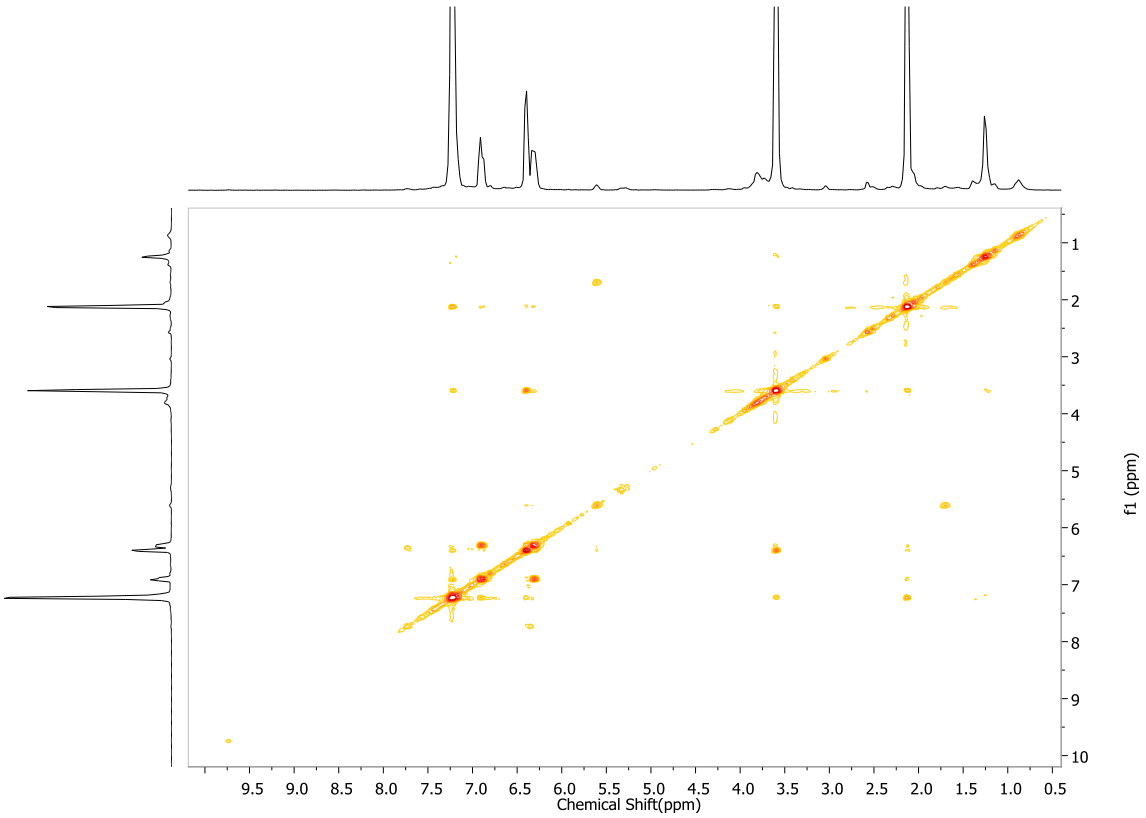
**observed product**




δ Ha = 3.5, Hb = 2.1, Hc = 6.3, He = 3.5

**other possible regioisomer not observed**

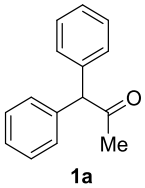
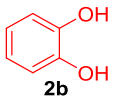
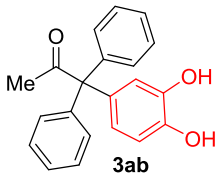
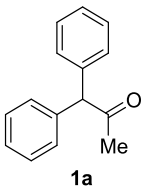
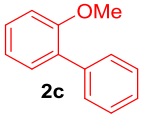
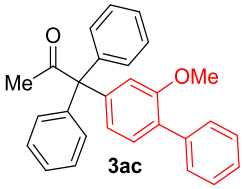
In the proton NMR, a strong NOE correlation between Ha OMe (δ 3.5, s) and Hb Me (δ 2.1, s) was observed. But, there is no NOE correlation between Hd OH (δ 5.6, bs) with Hb Me (δ 2.1, s). This result clearly revealed that the regiochemistry of compound **3ad** is correct.

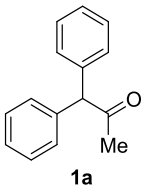
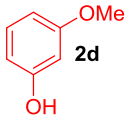
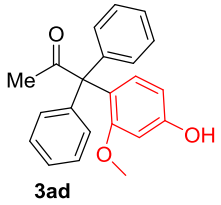
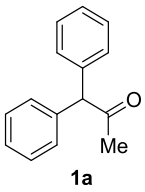
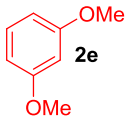
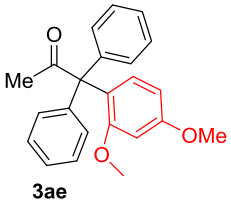
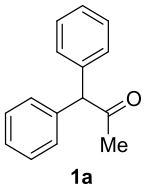
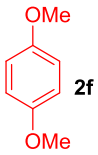
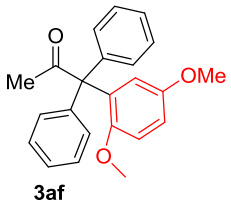
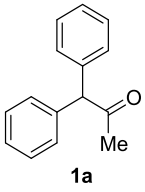
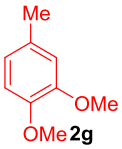
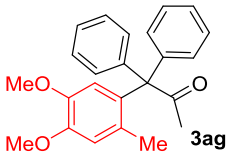
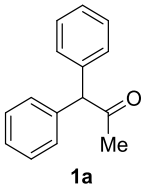
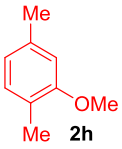
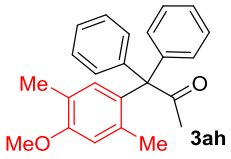
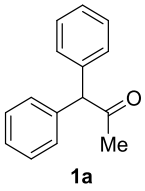
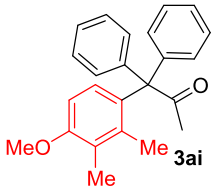
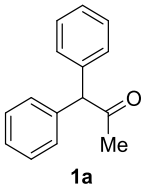
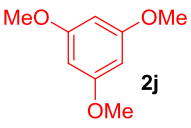
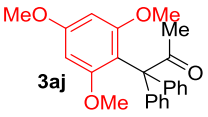
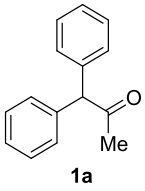
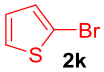
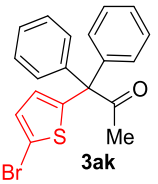


## 2B.4: Scope of Substituted Aromatics

The scope The scope of the α-arylation reaction was examined with various aromatics and heteroaromatic **2b-k** with **1a** under the optimized reaction conditions (Table 2.4). Disubstituted aromatics such as 1,2-dihydroxybenzene (**2b**), 2-phenylanisole (**2c**), 3-hydroxyanisole (**2d**) and 3-methoxy anisole (**2e**) provided benzopinacolone derivatives **3ab-ae** in 50%, 79%, 50% and 52% yields, respectively (entry 1-4). In the substrates, **2b,** and 2**d**, the *para* C-H bond of the hydroxy group of **2b** and **2d** was connected with **1a**. But, in the substrates, **2c** and 2**e**, the *para* C-H bond of the methoxy group of **2c** and **2e** participated in the arylation reaction. The structure and regioselectivity of product **3ad** were confirmed by a single-crystal X-ray diffraction (see SI). It is interesting to note that a free hydroxy group of aromatics **2b** and **2d** was not affected by the reaction conditions and it can be used for further modifications. Whereas, in 4-methoxy anisole (**2f**), the *ortho* C-H bond of the methoxy group of **2f** was involved, affording product **3af** in 59% yield (entry 5). The reaction was also tested with hindered trisubstituted aromatics **2g-j**. 3,4-Dimethoxytoluene (**2g**), 2-methoxy-4-methyl toluene (**2h**) and 2,3-dimethyl anisole (**2i**) underwent arylation with **1a,** affording benzopinacolones **3ag-ai** in 51%, 46%, and 47% yields, respectively, in which the para C-H bond of OMe group of **2g-i** was connected with **1a** (entries 6-8). In 1,3,5-trimethylbenzene (**2j**), a sterically hindered C-H bond of an aromatic moiety was involved in the reaction, providing product **3aj** in 80% yield (entry 9). Interestingly, 2-Bromo thiophene (**2k**) also efficiently participated in the reaction, yielding product **3ak** in 53% yield, in which C-H bond of C5 of **2k** was added at the tertiary carbon of **1a** (entry 10).

**Table 2.4 :** α-Arylation of Ketone **1a** with Aromatics **2b-k**[a]

| entry | **1** | **2** | product **3** | yield (%)[b] |
|---|---|---|---|---|
| **1** |  **1a** |  **2b** |  **3ab** | 50 |
| **2** |  **1a** |  **2c** |  **3ac** | 79 |

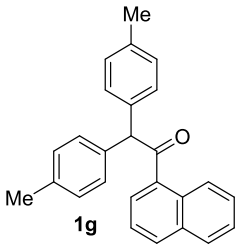
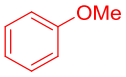
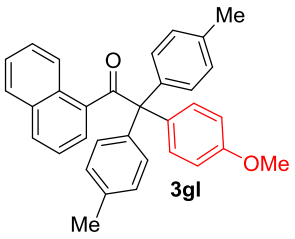
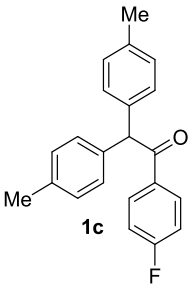
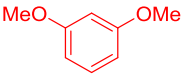
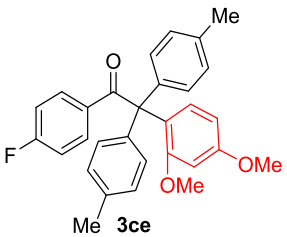
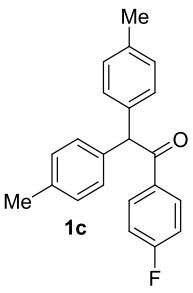
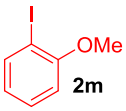
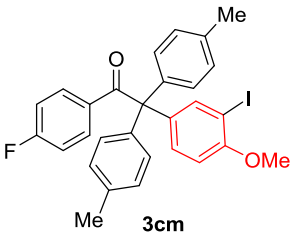
| | | | | |
|---|---|---|---|---|
| **3** |  **1a** |  **2d** |  **3ad** | 50 |
| **4** |  **1a** |  **2e** |  **3ae** | 52 |
| **5** |  **1a** |  **2f** |  **3af** | 59 |
| **6** |  **1a** |  **2g** |  **3ag** | 51 |
| **6** |  **1a** |  **2h** |  **3ah** | 46 |
| **7** |  **1a** | **2i** |  **3ai** | 47 |
| **8** |  **1a** |  **2j** |  **3aj** | 80 |
| **9** |  **1a** |  **2k** |  **3ak** | 53 |

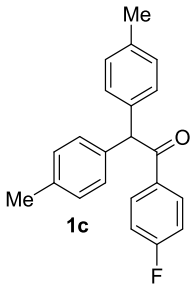
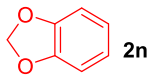
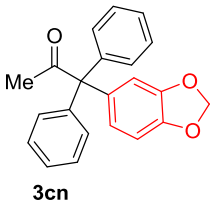
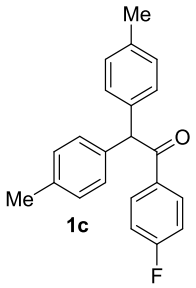
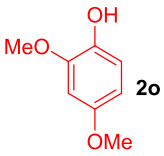
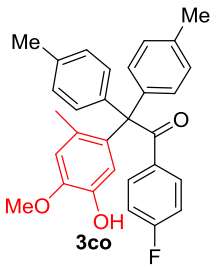
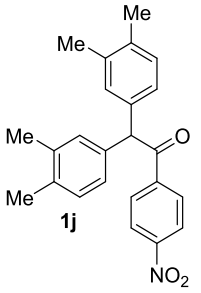
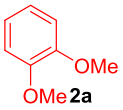
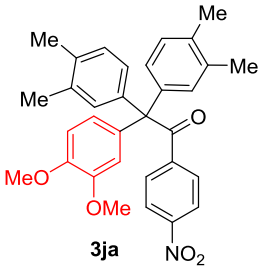
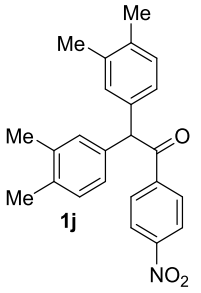
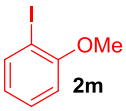
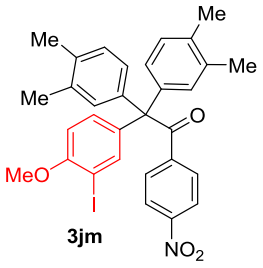
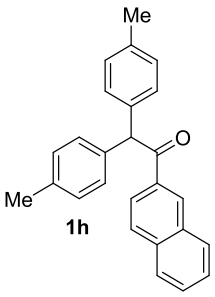
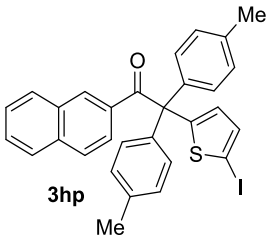
[a]All reactions were carried out using **1a**, **2b-k** (4.0 equiv) and $K_2S_2O_8$ (2.0 equiv) in $CF_3COOH$ (1.0 mL) at room temperature under air for 24 h. [b]Isolated yield.

### 2B.5: Scope of Substituted Aromatics and heteroaromatics

Apart from the aromatics **2a-k** (Table 1), other aromatics and heteroaromatic such as anisole (**2l**), 2-iodoanisole (**2m**), benzo[*d*][1,3]dioxole (**2n**), 2-methoxy-4-methyl phenol (**2o**) and 2-iodo thiophene (**2p**) were also compatible for the reaction (Table 2.5). Anisole (**2l**) reacted efficiently with **1g** yielding α-triaryl substituted ketone **3gl** in 52% yield, in which the para C-H bond of **2l** participated in the reaction (entry 1). Similarly, **2a**, **2e**, 2-iodoanisole (**2m**), benzo[*d*][1,3]dioxole (**2n**) and 2-methoxy-4-methyl phenol (**2o**) reacted with **1c** or **1j** affording α-arylated products **3ce-3jm** in 53%, 50%, 46%, 43%, 53% and 49% yields, respectively (entries 2-7). In benzo[*d*][1,3]dioxole (**2n**), C-4 carbon was connected to the $sp^3$ C-H bond of **1c** (entry 4). In 2-iodoanisole (**2m**) and 2-methoxy- 4-methyl phenol (**2o**), the *para* C-H bond of the methoxy group of aromatics was involved (entry 5). Interestingly, 2-iodothiophene (**2p**) also efficiently participated in the reaction with **1h**, giving product **3hp** in 40% yield, in which C-5 carbon of **2p** was involved (entry 8). The arylation reaction was compatible with OH, OMe, Me, 1,3-dioxol, Br and I substituted aromatics and heteroaromatic.

**Table 2.5:** α-Arylation of Ketone **1g**, **1c**, **1j** and **1h** with Aromatics and heteroaromatics [a]

| entry | **1** | **2** | product **3** | yield (%)[b] |
|---|---|---|---|---|
| **1** |  **1g** |  **2l** |  **3gl** | 50 |
| **2** |  **1c** |  **2e** |  **3ce** | 79 |
| **3** |  **1c** |  **2m** |  **3cm** | 50 |

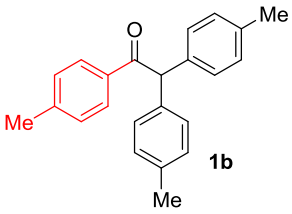
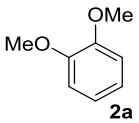
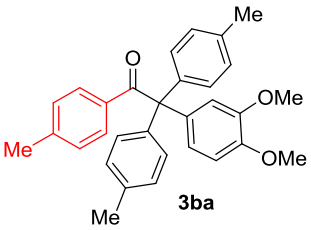
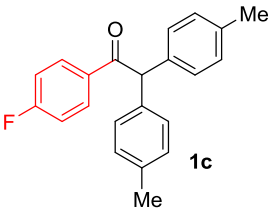
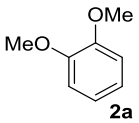
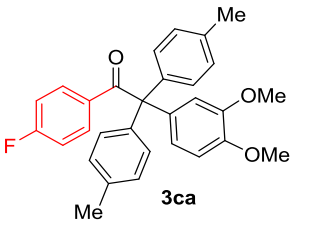
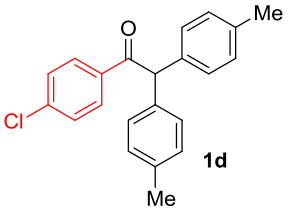
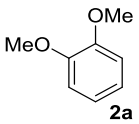
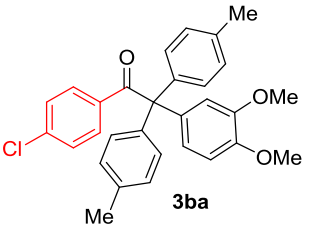
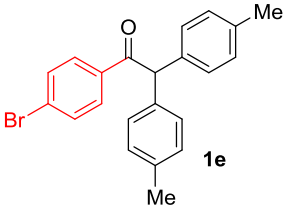
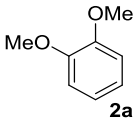
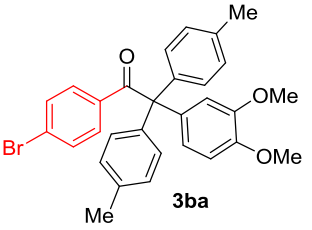
| | | | | |
|---|---|---|---|---|
| **4** |  **1c** |  **2n** |  **3cn** | 52 |
| **5** |  **1c** |  **2o** |  **3co** | 59 |
| **6** |  **1j** |  **2a** |  **3ja** | 46 |
| **7** |  **1j** |  **2m** |  **3jm** | 80 |
| **8** |  **1h** | **2p** |  **3hp** | 53 |

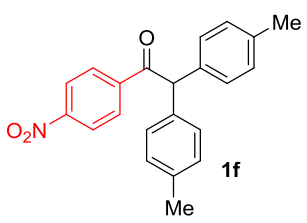
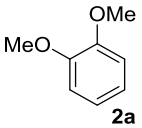
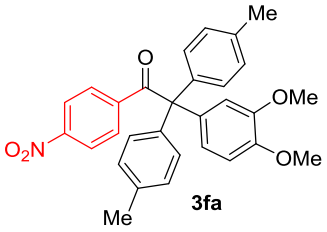
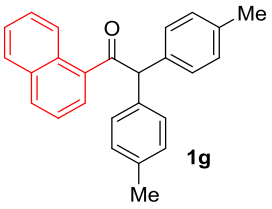
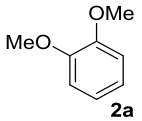
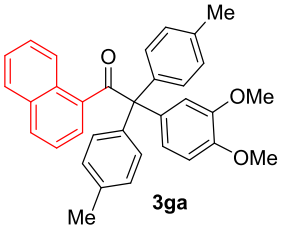
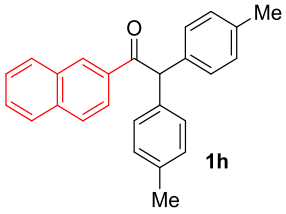
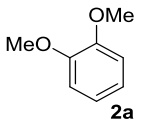
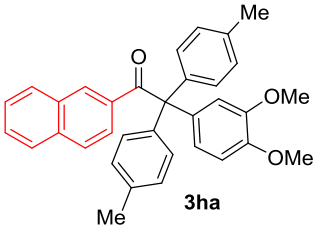
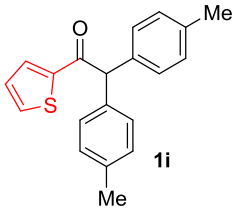
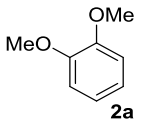
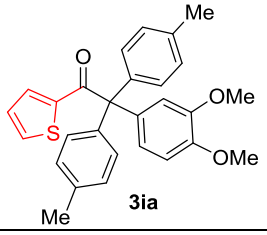
[a]All reactions were carried out using **1**, **2** (4.0 equiv) and $K_2S_2O_8$ (2.0 equiv) in $CF_3COOH$ (1.0 mL) at room temperature under air for 24 h. [b]Isolated yield.

**2B.6: Scope of 1,2,2-triphenylethanones 1b-i**

The α-arylation reaction was also tested with substituted 1,2,2-triphenylethanones **1b-i** with **2a** (Table 2.6). When electron-donating, halogen and electron-withdrawing groups such as Me, F, Cl, Br, and $NO_2$ substituted 1,2,2-triphenylethanones **1b-f** were treated with **2a** under similar reaction conditions, α-triaryl substituted ketones **3ba-fa** were observed in good to moderate yields, in a highly regioselective manner (entries 1-5). Further, the sterically hindered 1-naphthyl **1g** and 2-naphthyl **1h** substituted α-bisarylketones also efficiently participated in the reaction, yielding the corresponding α-tri arylated products **3ga** and **3ha** in 73% and 53% yields, respectively (entries 6 and 7). Likewise, 2-thienyl group substituted α-diaryl ketone **1i** was also nicely involved in the reaction, giving α-triaryl-substituted ketone **3ia** in 62% yield (entry 7).

**Table 2.6:** Results of the Reaction of 1,2,2-triphenylethanones **1** with **2a**[a]

| entry | **1** | **2** | product **3** | yield (%)[b] |
|---|---|---|---|---|
| **1** |  **1b** |  **2a** |  **3ba** | 68 |
| **2** |  **1c** |  **2a** |  **3ca** | 85 |
| **3** |  **1d** |  **2a** |  **3ba** | 55 |
| **4** |  **1e** |  **2a** |  **3ba** | 47 |

| | | | | |
|---|---|---|---|---|
| **5** |  **1f** |  **2a** |  **3fa** | 58 |
| **6** |  **1g** |  **2a** |  **3ga** | 73 |
| **7** |  **1h** |  **2a** |  **3ha** | 53 |
| **8** |  **1i** |  **2a** |  **3ia** | 62 |

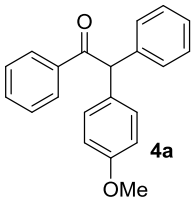
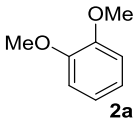
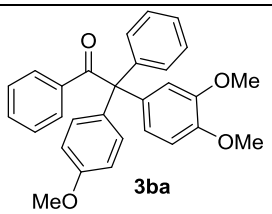
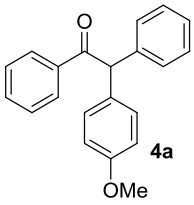
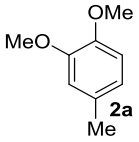
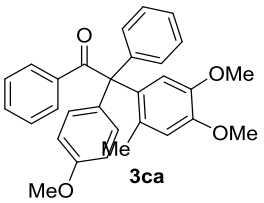
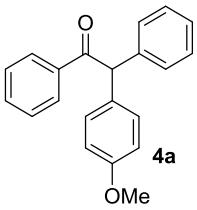
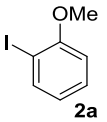
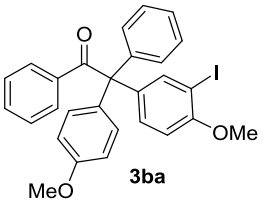
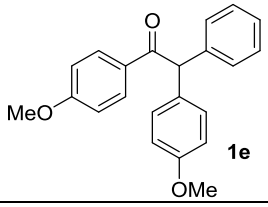
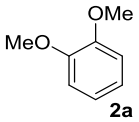
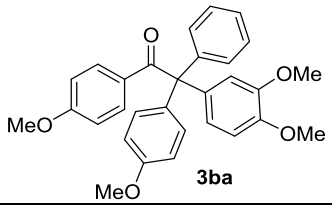
[a]All reactions were carried out using ketones **1b-i**, **2a** (4.0 equiv) and $K_2S_2O_8$ (2.0 equiv) in $CF_3COOH$ (1.0 mL) at room temperature under air for 24 h. [b]Isolated yield.

### 2B.7: Synthesis of Unsymmetrical Benzopinacolones

By employing the present protocol, we have tried to prepare unsymmetrical benzopinacolones having four different substituents at the tertiary carbon by using 1,2,2-triphenylethanones **4a-b** (Table 2.7). Treatment of α-bisarylketone **4a** with **2a** or sterically hindered **2g** or 2-iodoanisole (**2m)** under similar reaction conditions gave unsymmetrical benzopinacolones **5aa-am** in 75%, 58% and 61%, yields, respectively, in a highly regioselective manner (entries 1-3). It is important to note that unsymmetrical quaternary carbon substituted organic compounds are highly useful in organic synthesis and very difficult to prepare due to the steric hindrance. Similarly, electron-donating OMe substituted α-diarylketone **4b** reacted with **2a** yielding unsymmetrical α-triaryl-substituted ketone **5ba** in 71% yield in a highly regioselective manner (entry 4).

**Table 2.7:** Results of the Reaction of 1,2,2-triphenylethanones **1** with **2a**[a]

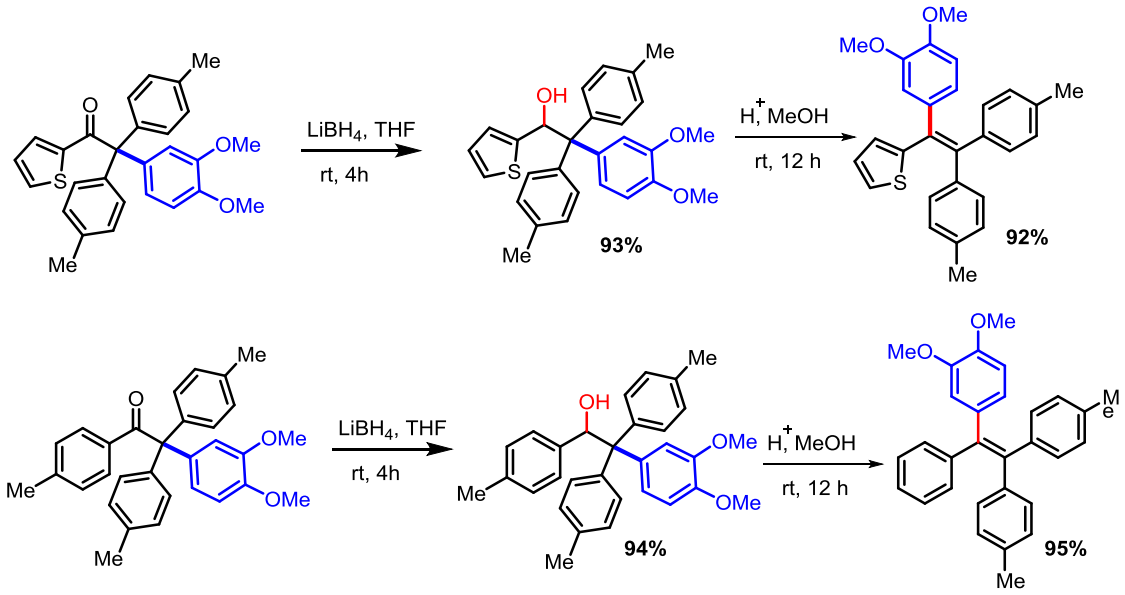
| entry | **1** | **2** | product **3** | yield |
|---|---|---|---|---|

| | | | | (%)[b] |
|---|---|---|---|---|
| **1** |  **4a** |  **2a** |  **3ba** | 75 |
| **2** |  **4a** |  **2a** |  **3ca** | 58 |
| **3** |  **4a** |  **2a** |  **3ba** | 61 |
| **4** |  **1e** |  **2a** |  **3ba** | 71 |

[a]All reactions were carried out using ketones **1b-i**, **2a** (4.0 equiv) and $K_2S_2O_8$ (2.0 equiv) in $CF_3COOH$ (1.0 mL) at room temperature under air for 24 h. [b]Isolated yield.

**2B.8: Synthetic application to synthesis of TPEs and 9,10-phenanthrene derivatives**

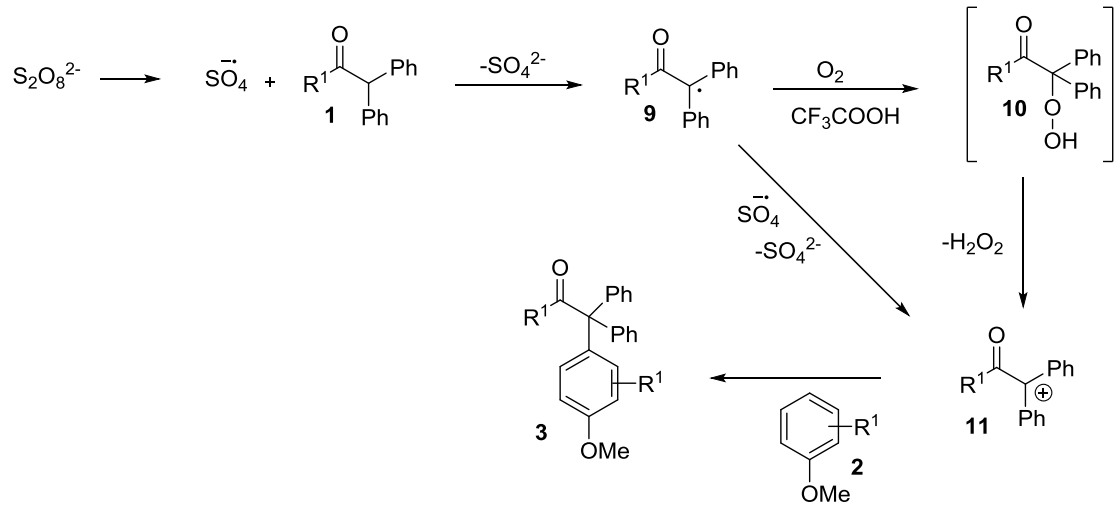
A synthetic application of product **3** in organic synthesis is shown in Scheme 2.18. The carbonyl group of **3ia** and **3ba** was reduced into secondary alcohol derivatives **6a-b** in excellent yields in the presence of $LiBH_4$ in THF at room temperature for 4 h (Scheme 2.18).[21a-c] Similarly, **3ia** underwent reduction with $LiBH_4$ followed by an acid-mediated rearrangement, providing hindered tetrasubstituted alkene derivative **7a** in 92% yield.[16d] Under similar reaction conditions, α-triaryl ketone **3ba** was also converted into alkene derivative **7b** in 95% yield in a highly regioselective manner. Further, alkene derivative **7b** reacted with DDQ in $MeSO_3H$ providing a polycyclic aromatic compound **8a** in 94% yield.[21d]




**Scheme 2.18:** Synthetic application of α-arylation

## 2B.9: Mechanism

A possible reaction mechanism is proposed to account for the present reaction in scheme 4. $K_2S_2O_8$ generates $SO_4^{-\bullet}$ radical anion which abstracts hydrogen from the acidic tertiary carbon of **1** providing a radical intermediate **9**.[20a-b] Further, a radical of intermediate **9** inserts into $O_2$ in the presence of $CF_3COOH$ producing an unstable peroxide intermediate **10**. Intermediate **10** dissociates $H_2O_2$ affords a carbocation intermediate **11.**[20f] Alternatively, intermediate **11** can also be formed by the reaction of intermediate **10** into $SO_4^-$ radical anion. A similar type of unstable carbocation intermediate **11** has been previously proposed and isolated by Kitagawa's group.[20c-d] Nucleophilic addition of aromatic moiety **2** into intermediate **11** provides α-arylated product **3**. It is important to note that the peroxide intermediate **10** allows the new C-C bond formation rather than the C-C bond cleavage.[20b] The arylation reaction also proceeds without $K_2S_2O_8$. It might proceeds via one-electron oxidation of substituted ketone **1** by molecular oxygen provides peroxide intermediate **10** directly via an ionic pathway.[20e] $CF_3COOH$ could stabilize the peroxide intermediate **10** by a hydrogen bond. It is also important to point out that in most of the $S_N1$ type reaction, only solvent acts as a nucleophile to attack the tertiary carbon. But, in the present reaction, only aromatic moiety acts as a nucleophile, and solvent $CF_3COOH$ remains intact.



**Scheme 2.19:** Proposed mechanism

## 2B.10: Conclusion

1. We have investigated a mild and regioselective transition metal-free aerobic dehydrogenative α-arylation at the tertiary carbon of substituted 1,1-diphenylketone with aromatics at room temperature. We have applied this method to the synthesis of unsymmetrical benzo-pinacolones.
2. No pre-activation results in high atom economy with minimal wastes
3. The Synthetic method has been demonstrated in the synthesis of tetraphenylethylene (TPE) and phenanthrenes derivatives.

## 2B.11: Experimental Section

### General Procedure for the α-Arylation Reaction:

In a 25-mL round bottom flask equipped with a magnetic stir bar, $K_2S_2O_8$ (2.0 equiv), 1,1-diphenylketone **1** (the exact amount was specified along with data, approx. 100 mg) and aromatics **2** (4.0 equiv) were taken. To the flask, was then added $CF_3COOH$ (1.0 mL) via syringe. Then, the reaction mixture was allowed to stir at room temperature for 24 h under an air atmosphere. After 24 h, the reaction mixture was diluted with $CH_2Cl_2$ and solvents were evaporated under vacuum. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3** or **5**.

### General Procedure for the Reduction Reaction:

In a 20-mL round bottom flask, benzo-pinacolone **3** (the exact amount was specified along with data, approx. 100 mg) was dissolved in THF (10 mL). To the flask, was then added $LiBH_4$ (1.2 equiv). Then, the reaction mixture was allowed to stir at room temperature for 3 h under an air atmosphere. After 3 h, the reaction mixture was quenched with water and the organic layer was separated and the aqueous layer was

extracted with ethyl acetate (2 x 10 mL) and combined organic layers were washed with water and brine, dried over anhydrous $Na_2SO_4$ and evaporated under vacuum to afford pure secondary alcohols **6** (further purification was not necessary).

**General Procedure for the Preparation of Alkene Derivatives 7:**

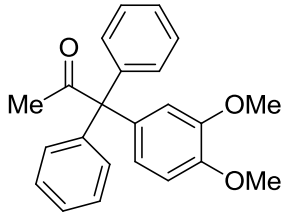
Compound secondary alcohol **6** was dissolved in methanol (15.0 mL) in a 25 mL round bottom flask attached to condenser. To the flask, a catalytic amount of $H_2SO_4$ (approx. 3 drops) was added, and then the reaction mixture was refluxed for overnight. To the reaction mixture, water was added, and the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). Combined organic layers were washed with water and brine, dried over anhydrous $Na_2SO_4$ and evaporated under vacuum to afford pure alkene derivative **7** (further purification was not necessary).

**Procedure for the Preparation of Polycyclic Aromatic Compound 8:**

Compound **7b** (33 mg) was dissolved in dry dichloromethane (9.0 mL) and cooled to 0 °C. To this solution, methanesulfonic acid (1.0 mL) and solid DDQ (20 mg, 1.0 equiv) were added, and the resulting highly colored mixture was stirred. After 30 min, the resulting reaction mixture was quenched by pouring onto saturated aqueous $NaHCO_3$ (20 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 x 10 mL). Combined organic layers were washed with water and brine, dried over anhydrous $Na_2SO_4$ and evaporated under vacuum to afford pure compound **8a** (further purification was not necessary).

**2B.12: Spectral Data of Compounds**

**1-(3,4-Dimethoxyphenyl)-1,1-diphenylpropan-2-one (3aa).**



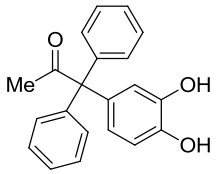

Yellow solid; eluent (7% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 136 mg 76% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.30 – 7.28 (m, 2 H), 7.27 – 7.24 (m, 6 H), 7.21 (dd, *J* = 8.0, 4.0 Hz, 2 H), 6.83 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 6.74 (d, *J* = 4.0 Hz, 1 H), 3.85 (s, 3 H), 3.70 (s, 3 H), 2.10 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 206.1, 148.3, 147.8, 142.5, 134.1, 130.1, 128.0, 126.6, 122.6, 114.1, 110.4, 72.6, 55.8, 55.7, 29.6.

**HRMS (ESI):** calc. for [($C_{23}H_{22}O_3$)Na] (M+Na) 369.1467, measured 369.1464.

**1-(3,4-Dihydroxyphenyl)-1,1-diphenylpropan-2-one (3ab)**.



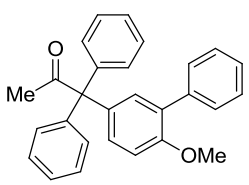

Yellow liquid; eluent (20% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 75 mg 50% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz)**: δ 7.28 – 7.24 (m, 4 H), 7.23 – 7.17 (m, 6 H), 6.75 (d, *J* = 8.0 Hz, 2 H), 6.66 (dd, *J* = 8.0, 4.0 Hz, 1 H), 2.08 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 208.2, 143.2, 142.9, 142.3, 133.9, 130.1, 128.1, 126.7, 123.0, 117.7, 114.8, 72.8, 29.7.

**HRMS (ESI):** calc. for [($C_{21}H_{18}O_3$)Na] (M+Na) 341.1154, measured 341.1154.

**1-(6-Methoxy-[1,1'-biphenyl]-3-yl)-1,1-diphenylpropan-2-one (3ac).**



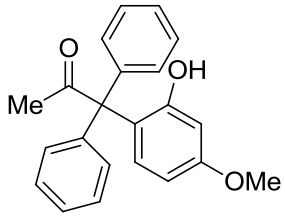

White solid; eluent (5% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 149 mg 79% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.51 (d, *J* = 8.0 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.38 – 7.30 (m, 10 H), 7.27 (dd, *J* = 8.0, 4.0 Hz, 3 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 3.82 (s, 3 H), 2.19 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 206.0, 155.0, 142.4, 138.1, 134.2, 132.9, 130.5, 130.1, 129.9, 129.5, 128.1, 127.9, 126.9, 126.7, 110.6, 72.5, 55.4, 29.5.

**HRMS (ESI):** calc. for [($C_{28}H_{24}O_2$)Na] (M+Na) 415.1674, measured 415.1673.

**1-(2-Hydroxy-4-methoxyphenyl)-1,1-diphenylpropan-2-one (3ad).**



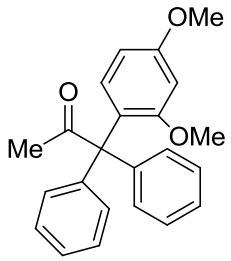

Colorless semisolid; eluent (20% ethyl acetate in hexanes). The reaction scale is 70 mg, isolated product 55 mg 50% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz):** 7.24 – 7.21 (m, 8 H), 7.21 – 7.16 (m, 2 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.39 (d, *J* = 4.0 Hz, 1 H), 6.30 (dd, *J* = 8.0, 4.0 Hz, 1 H), 5.60 (s, 1 H), 3.58 (s, 3 H), 2.12 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 207.2, 157.9, 156.4, 142.5, 131.2, 130.6, 127.5, 126.4, 124.8, 107.2, 99.7, 69.3, 54.9, 28.7.

**HRMS (ESI):** calc. for [($C_{22}H_{20}O_3$)Na] (M+Na) 355.1310, measured 355.1307.

**1-(2,4-Dimethoxyphenyl)-1,1-diphenylpropan-2-one (3ae).**



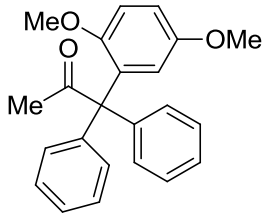

White solid; eluent (7% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 93 mg 52% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.28 – 7.24 (m, 7 H), 7.24 – 7.17 (m, 3 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 6.49 (d, *J* = 4.0 Hz, 1 H), 6.44 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.78 (s, 3 H), 3.66 (s, 3 H), 2.14 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 206.1, 160.1, 157.8, 142.5, 130.9, 130.5, 127.4, 126.3, 125.1, 104.3, 99.1, 77.0, 69.1, 55.2, 54.8, 28.6.

**HRMS (ESI):** calc. for [($C_{23}H_{22}O_3$)Na] (M+Na) 369.1467, measured 369.1465.

**1-(2,5-Dimethoxyphenyl)-1,1-diphenylpropan-2-one (3af).**



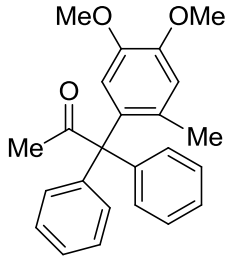

White solid; eluent (10% ethyl acetate in hexanes). The reaction scale is 70 mg, isolated product 65 mg 59% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.29 – 7.25 (m, 7 H), 7.24 – 7.17 (m, 3 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.78 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.72 (d, *J* = 4.0 Hz, 1 H), 3.66 (s, 3 H), 3.63 (s, 3 H), 2.14 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 205.6, 153.5, 151.1, 142.1, 134.0, 130.6, 127.6, 126.5, 117.6, 112.2, 112.1, 69.8, 55.5, 55.4, 28.7.

**HRMS (ESI):** calc. for [($C_{23}H_{22}O_3$)Na] (M+Na) 369.1467, measured 369.1459.

**1-(4,5-Dimethoxy-2-methylphenyl)-1,1-diphenylpropan-2-one (3ag).**



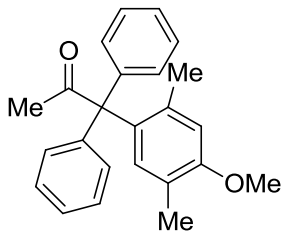

Colorless liquid; eluent (10% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 75 mg 47% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.25 (dd, *J* = 8.0, 4.0 Hz, 4H), 7.21 – 7.16 (m, 6 H), 6.71 (d, *J* = 8.0 Hz, 2 H), 3.87 (s, 3 H), 3.63 (s, 3 H), 2.12 (s, 3 H), 1.81 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 206.5, 147.9, 146.4, 142.4, 131.9, 131.1, 130.2, 127.8, 126.4, 115.2, 114.6, 71.6, 55.8, 55.7, 30.7, 21.6.

**HRMS (ESI):** calc. for [($C_{24}H_{24}O_3$)Na] (M+Na) 383.1623, measured 383.1628.

**1-(4-Methoxy-2,5-dimethylphenyl)-1,1-diphenylpropan-2-one (3ah).**



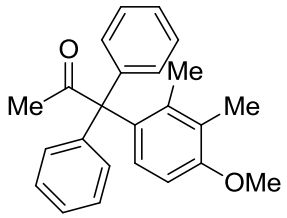
Colourless liquid; eluent (6% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 75 mg 46% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.27 (d, *J* = 8.0 Hz, 4 H), 7.22 – 7.17 (m, 6 H), 6.95 (s, 1 H), 6.65 (s, 1 H), 3.83 (s, 3 H), 2.13 (s, 3 H), 2.09 (s, 3 H), 1.82 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 206.9, 156.7, 142.3, 137.2, 132.6, 131.6, 130.4, 127.7, 126.3, 123.4, 113.9, 71.6, 55.2, 30.7, 22.2, 16.0.

**HRMS (ESI):** calc. for [($C_{24}H_{24}O_2$)Na] (M+Na) 367.1674, measured 367.1671.

**1-(4-Methoxy-2,3-dimethylphenyl)-1,1-diphenylpropan-2-one (3ai).**



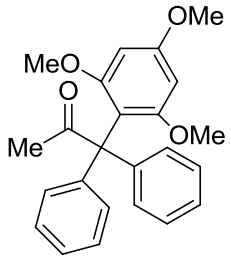

White solid; eluent (6% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 75 mg 47% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.30 – 7.24 (m, 4 H), 7.17 – 7.14 (m, 6 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 3.83 (s, 3 H), 2.15 (s, 3 H), 2.12 (s, 3 H), 1.78 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 207.9, 156.6, 143.0, 138.3, 132.7, 130.4, 128.5, 127.7, 126.8, 126.3, 107.1, 71.8, 55.3, 31.0, 19.6, 12.1.

**HRMS (ESI):** calc. for [($C_{24}H_{24}O_2$)Na] (M+Na) 367.1674, measured **367.1671.**

**1,1-Diphenyl-1-(2,4,6-trimethoxyphenyl)propan-2-one (3aj).**



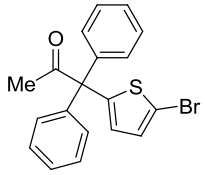

White solid; eluent (15% ethyl acetate in hexanes). The reaction scale is 70 mg, isolated product 94 mg 80% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.43 (d, *J* = 8.0 Hz, 4 H), 7.24 – 7.16 (m, 6 H), 6.12 (s, 2 H), 3.78 (s, 3 H), 3.64 (s, 6 H), 1.79 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 202.7, 160.4, 158.1, 140.8, 130.5, 126.8, 126.0, 112.9, 91.6, 68.0, 55.2, 54.8, 26.8.

**HRMS (ESI):** calc. for [($C_{24}H_{24}O_4$)Na] (M+Na) 399.1572, measured 399.1565.

**1-(5-Bromothiophen-2-yl)-1,1-diphenylpropan-2-one (3ak).**



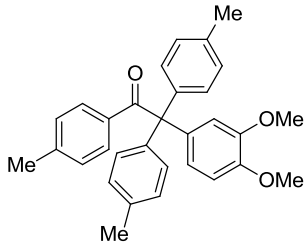

Yellow liquid; eluent (3% ethyl acetate in hexanes). The reaction scale is 70 mg, isolated product 61 mg 51% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.36 – 7.30 (m, 6 H), 7.25 – 7.22 (m, 4 H), 6.86 (d, *J* = 4.0 Hz, 1 H), 6.48 (d, *J* = 4.0 Hz, 1 H), 2.18 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 205.8, 148.0, 141.7, 129.4, 128.6, 128.4, 128.3, 127.6, 113.6, 70.2, 29.3.

**HRMS (ESI):** calc. for [($C_{19}H_{15}BrOS$)Na] (M+Na) 392.9925, measured 392.9922.

**2-(3,4-Dimethoxyphenyl)-1,2,2-tri-*p*-tolylethanone (3ba).**



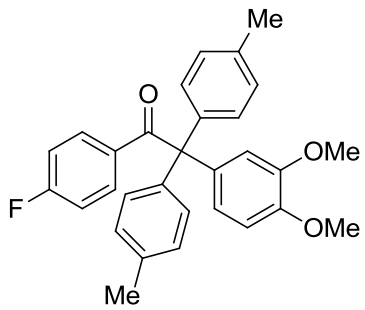

White solid; eluent (8% ethyl acetate in hexanes). The reaction scale is 130 mg, isolated product 135 mg 68% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.59 (d, *J* = 8.0 Hz, 2 H), 7.07 – 7.02 (m, 8 H), 6.94 (d, *J* = 8.0 Hz, 2 H), 6.80 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 6.69 (d, *J* = 4.0 Hz, 1 H), 3.83 (s, 3 H), 3.61 (s, 3 H), 2.28 (s, 6 H), 2.25 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 198.7, 148.0, 147.5, 142.2, 140.9, 136.0, 135.4, 134.9, 131.1, 130.6, 128.3, 128.2, 122.8, 114.8, 110.0, 69.9, 55.8, 55.6, 21.4, 20.9.

**HRMS (ESI):** calc. for [($C_{31}H_{30}O_3$)Na] (M+Na) 473.2093, measured 473.2090.

**2-(3,4-Dimethoxyphenyl)-1-(4-fluorophenyl)-2,2-di-*p*-tolylethanone (3ca).**



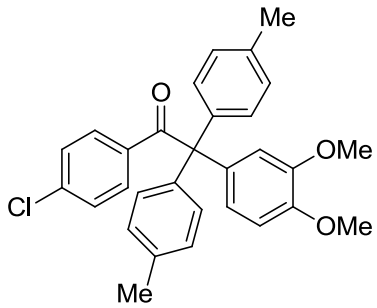
Colorless solid; eluent (12% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 78 mg 43% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.72 (dd, Fluorine coupling *J* = 8.0, 4.0 Hz, 2 H), 7.08 – 7.03 (m, 8 H), 6.83 (d, *J* = 8.0 Hz, 2 H), 6.80 – 6.78 (m, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 6.68 (d, *J* = 2.0 Hz, 1 H), 3.83 (s, 3 H), 3.62 (s, 3 H), 2.29 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 197.6, 165.5, 163.0, 148.1 and 147.6 (Fluorine coupling), 140.5, 136.2, 135.1, 133.8, 133.6, 133.5, 130.5, 128.4, 127.4, 122.8, 114.71 and 114.5(Fluorine coupling), 110.1, 69.9, 55.8, 55.6, 20.9.

**HRMS (ESI):** calc. for [($C_{30}H_{27}FO_3$)Na] (M+Na) 477.1842, measured 477.1838.

**1-(4-Chlorophenyl)-2-(3,4-dimethoxyphenyl)-2,2-di-*p*-tolylethanone (3da).**



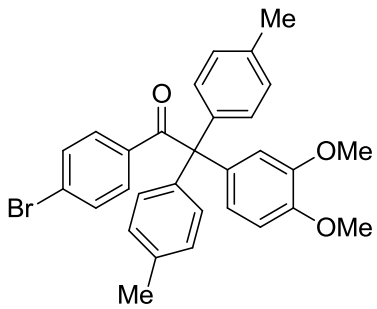

Colourless liquid; eluent (10% ethyl acetate in hexanes). The reaction scale is 75 mg, isolated product 55 mg 55% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.62 (d, *J* = 8.0 Hz, 2 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 7.08 – 7.05 (m, 8 H), 6.78 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 6.66 (d, *J* = 2.0 Hz, 1 H), 3.83 (s, 3 H), 3.61 (s, 3 H), 2.28 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 198.0, 148.1, 147.7, 140.4, 137.9, 136.3, 135.8, 135.0, 132.4, 130.5, 128.5, 127.8, 122.8, 114.7, 110.1, 77.0, 69.9, 55.8, 55.7, 20.9.

**HRMS (ESI):** calc. for [($C_{30}H_{27}ClNO_3$)Na] (M+Na) 493.1546, measured 493.1535.

**1-(4-Bromophenyl)-2-(3,4-dimethoxyphenyl)-2,2-di-*p*-tolylethanone (3ea).**



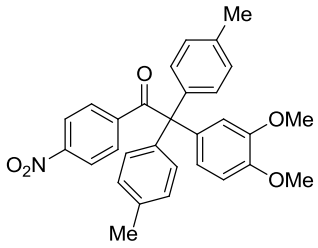

Yellow solid; eluent (10% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 64 mg 47% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.55 (d, *J* = 8.0 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.11 – 7.09 (m, 8 H), 6.78 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 6.67 (d, *J* = 2.0 Hz, 1 H), 3.83 (s, 3 H), 3.62 (s, 3 H), 2.29 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 198.2, 148.1, 147.7, 140.3, 136.3, 134.9, 132.5, 130.8, 130.4, 128.5, 126.7, 122.8, 114.7, 110.1, 77.0, 69.9, 55.8, 55.7, 20.9.

**HRMS (ESI):** calc. for [($C_{30}H_{27}BrO_3$)H] (M+H) 515.1222, measured 515.1250.

**2-(3,4-Dimethoxyphenyl)-1-(4-nitrophenyl)-2,2-di-*p*-tolylethanone (3fa).**



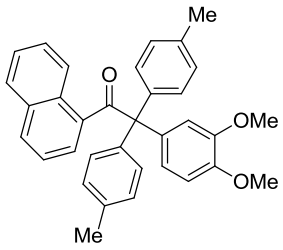

Yellow semisolid; eluent (10% ethyl acetate in hexanes). The reaction scale is 80 mg, isolated product 58 mg 52% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.98 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 7.06 – 7.04 (s, 8 H), 6.78 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 6.65 (d, *J* = 4.0 Hz, 1 H), 3.83 (s, 3 H), 3.62 (s, 3 H), 2.29 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 198.0, 148.8, 148.3, 148.0, 142.8, 139.7, 136.7, 134.3, 131.6, 130.4, 128.7, 122.8, 122.7, 114.6, 110.3, 70.2, 55.9, 55.7, 21.0.

**HRMS (ESI):** calc. for [($C_{30}H_{27}NO_5$)Na] (M+Na) 504.1787, measured 504.1786.

**2-(3,4-Dimethoxyphenyl)-1-(naphthalen-1-yl)-2,2-di-*p*-tolylethanone (3ga).**



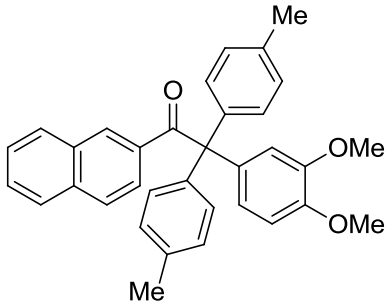

White solid; eluent (10% ethyl acetate in hexanes). The reaction scale is 150 mg, isolated product 145 mg 73% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.92 (d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.42 – 7.36 (m, 2 H), 7.12 (t, *J* = 8.0 Hz, 5 H), 7.07 (t, *J* = 8.0 Hz, 4 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 6.70 - 6.65 (m, 3 H), 3.79 (s, 3 H), 3.31 (s, 3 H), 2.31 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 206.7, 147.6, 140.5, 139.1, 136.4, 134.7, 133.4, 130.8, 129.7, 128.4, 128.2, 126.9, 125.9, 125.6, 125.3, 123.8, 123.4, 114.9, 109.8, 72.9, 55.6, 55.3, 20.9.

**HRMS (ESI):** calc. for [($C_{34}H_{30}O_3$)Na] (M+Na) 509.2093, measured 509.2085.

**2-(3,4-Dimethoxyphenyl)-1-(naphthalen-2-yl)-2,2-di-*p*-tolylethanone (3ha).**



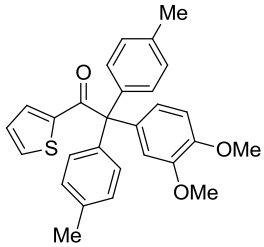

Colourless semisolid; eluent (10% ethyl acetate in hexanes). The reaction scale is 94 mg, isolated product 70 mg 53% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 8.31 (s, 1 H), 7.73 – 7.69 (m, 3 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 8.0 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 4 H), 7.05 (d, *J* = 8.0 Hz, 4 H), 6.86 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.77 (d, *J* = 4.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1 H), 3.82 (s, 3 H), 3.60 (s, 3 H), 2.29 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 199.0, 148.0, 147.6, 140.7, 136.1, 135.4, 134.9, 134.4, 132.6, 132.0, 130.6, 129.7, 128.4, 128.1, 127.3, 126.9, 126.2, 122.9, 114.8, 110.1, 70.1, 55.8, 55.6, 20.9.

**HRMS (ESI):** calc. for [($C_{34}H_{30}O_3$)Na] (M+Na) 509.2093, measured 509.2086.

**2-(3,4-Dimethoxyphenyl)-1-(thiophen-2-yl)-2,2-di-*p*-tolylethanone (3ia).**



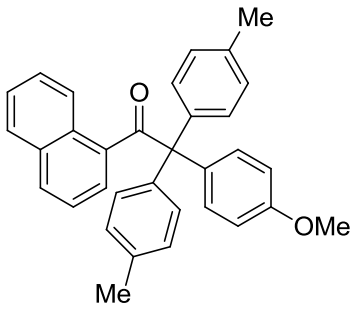

Light brick red semisolid; eluent (6% ethyl acetate in hexanes). The reaction scale is 50 mg, isolated product 45 mg 62% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.40 (d, *J* = 4.0 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 4 H), 7.04 (d, *J* = 8.0 Hz, 4 H), 7.00 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.80 (dd, *J* = 4.0, 2.0 Hz, 2 H), 6.75 (s, 1 H), 6.73 (d, *J* = 4.0 Hz, 1 H), 3.83 (s, 3 H), 3.63 (s, 3 H), 2.29 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 192.2, 148.0, 147.7, 145.0, 140.3, 136.3, 135.1, 134.5, 132.9, 130.6, 128.4, 123.1, 114.8, 110.0, 70.0, 55.8, 55.7, 21.0.

**HRMS (ESI):** calc. for [($C_{28}H_{26}O_3S$)Na] (M+Na) 465.1500, measured 465.1503.

**2-(4-Methoxyphenyl)-1-(naphthalen-1-yl)-2,2-di-*p*-tolylethanone (3gi).**



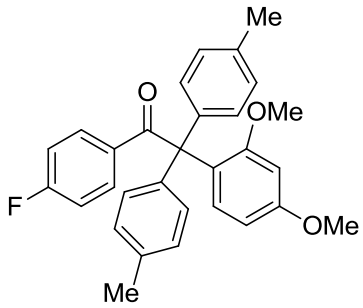

White solid; eluent (6% ethyl acetate in hexanes). The reaction scale is 80 mg, isolated product 51 mg 51% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.95 (d, *J* = 8.0 Hz, 1 H), 7.76 – 7.73 (m, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.42 – 7.36 (m, 2 H), 7.11 – 7.06 (m, 7 H), 7.01 (d, *J* = 8.0 Hz, 5 H), 6.71 (d, *J* = 8.0 Hz, 2 H), 3.74 (s, 3 H), 2.28 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 206.5, 158.1, 140.4, 138.6, 136.3, 135.1, 133.4, 132.2, 130.8, 129.9, 128.4, 128.2, 126.9, 126.3, 125.8, 125.5, 123.7, 112.9, 72.6, 55.1, 20.9.

**HRMS (ESI):** calc. for [($C_{33}H_{28}O_2$)Na] (M+Na) 479.1987, measured 479.1991.

**2-(2,4-Dimethoxyphenyl)-1-(4-fluorophenyl)-2,2-di-*p*-tolylethanone (3ce).**



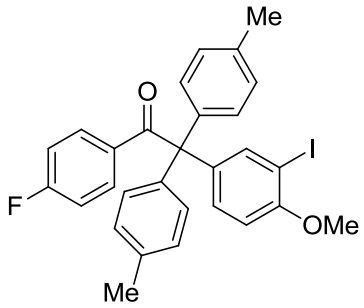

Colourless solid; eluent (10% ethyl acetate in hexanes). The reaction scale is 60 mg, isolated product 48 mg 56% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.61 – 7.53 (m, Fluorine coupling 2 H), 7.18 (d, *J* = 8.0 Hz, 1 H), 7.00 (q, *J* = 8.0 Hz, 8 H), 6.78 (m, Fluorine coupling 2 H), 6.45 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.25 (d, *J* = 4.0 Hz, 1 H), 3.77 (s, 3 H), 3.25 (s, 3 H), 2.30 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 199.6, 165.2, 162.7, 160.4, 158.1, 141.0, 135.9, 135.2, 132.1 and 132.0 (Fluorine coupling), 130.9, 130.2, 127.9, 124.7, 114.1 and 113.9 (Fluorine coupling), 104.3, 99.0, 66.6, 66.6, 55.2, 54.6, 20.9.

**HRMS (ESI):** calc. for [($C_{30}H_{27}FO_3$)Na] (M+Na) 477.1842, measured 477.1830.

**1-(4-Fluorophenyl)-2-(3-iodo-4-methoxyphenyl)-2,2-di-*p*-tolylethanone (3cm).**



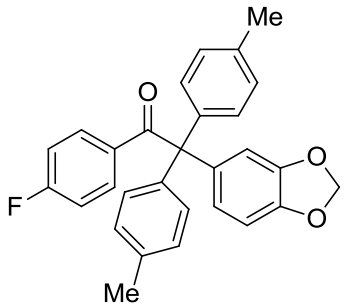

Colourless semisolid; eluent (10% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 80 mg 46% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.69 (dd, Fluorine coupling *J* = 8.0, 4.0 Hz, 2 H), 7.55 (d, *J* = 2.0 Hz, 1 H), 7.8 – 7.05 (s, 8 H), 7.04 (d, *J* = 2.0 Hz, 1 H), 6.82 (s, 2 H), 6.67 (d, *J* = 8.0 Hz, 1 H), 3.81 (s, 3 H), 2.29 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** 197.1, 165.6, 163.1, 156.4, 141.1, 139.5, 138.0, 136.5, 133.7 and 133.6 (Fluorine coupling), 132.1, 130.4, 128.7, 114.8 and 114.6 (Fluorine coupling), 109.7, 85.1, 69.2, 56.2, 20.9. 55.6, 20.9.

**HRMS (ESI):** calc. for [($C_{29}H_{24}FIO_2$)Na] (M+Na) 573.0703, measured 573.0705.

**2-(Benzo[*d*][1,3]dioxol-5-yl)-1-(4-fluorophenyl)-2,2-di-*p*-tolylethanone (3cn).**



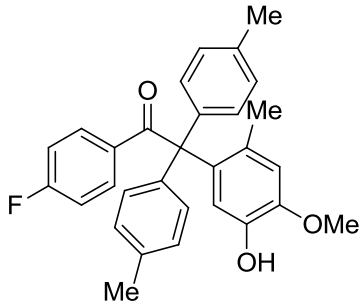

White solid; eluent (12% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 70 mg 53% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.74 – 7.68 (m, Fluorine coupling 2 H), 7.09 – 7.02 (m, 8 H), 6.86 – 6.79 (m, Fluorine coupling 2 H), 6.68 – 6.64 (m, 2 H), 6.62 (dd, *J* = 8.0, 4.0 Hz, 1 H), 5.90 (s, 2 H), 2.29 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 197.3, 165.6, 163.1, 147.2, 146.1, 140.0, 137.3, 136.4, 133.7 and 133.6 (Fluorine coupling), 130.5, 128.6, 123.8, 114.8 and 114.5 (Fluorine coupling), 111.7, 107.3, 101.1, 70.0, 20.9.

**HRMS (ESI):** calc. for [($C_{29}H_{23}FO_3$)H] (M+H) 439.1709, measured 439.1706.

**1-(4-Fluorophenyl)-2-(5-hydroxy-4-methoxy-2-methylphenyl)-2,2-di-p-tolylethanone (3co).**



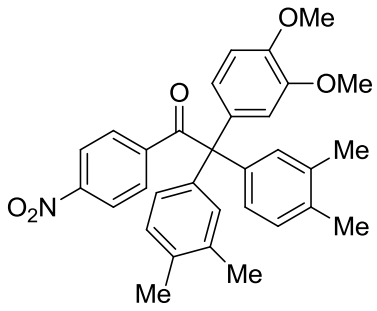

Colourless semisolid; eluent (15% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 78 mg 43% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.69 – 7.64 (m, Fluorine coupling 2 H), 7.01 – 6.09 (m, 8 H), 6.96 (s, 1 H), 6.81 (dd, Fluorine coupling *J* = 8.0, 4.0 Hz, 2 H), 6.50 (s, 1 H), 5.38 (s, 1 H), 3.82 (s, 3 H), 2.28 (s, 6 H), 1.67 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 198.9, 165.5, 163.0, 145.2, 143.1, 140.6, 136.1, 134.8, 133.9, 133.4 and 133.3 (Fluorine coupling), 130.9, 130.4, 128.2, 116.7, 114.5 and 114.3 (Fluorine coupling), 69.2, 55.7, 48.0, 21.8, 20.9.

**HRMS (ESI):** calc. for [($C_{30}H_{27}FO_3$)H] (M+H) 455.2022, measured 455.2001.

**2-(3,4-Dimethoxyphenyl)-2,2-bis(3,4-dimethylphenyl)-1-(4-nitrophenyl)ethanone (3ja).**



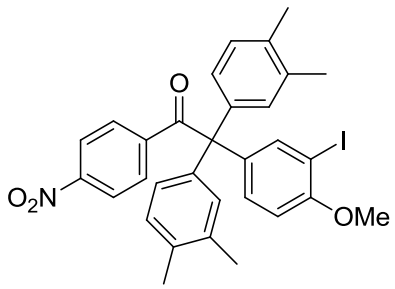

Pale yellow semisolid; eluent (6% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 60 mg 47% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.96 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 6.93 (s, 2 H), 6.89 (dd, *J* = 8.0, 2.0 Hz, 2 H), 6.78 (d, *J* = 2.0 Hz, 1 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 6.66 (d, *J* = 2.0 Hz, 1 H), 3.83 (s, 3 H), 3.62 (s, 3 H), 2.20 (s, 6 H), 2.14 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 198.2, 148.7, 148.2, 147.8, 142.9, 139.9, 136.1, 135.3, 134.5, 131.7, 131.6, 129.2, 127.9, 122.9, 122.6, 114.7, 110.2, 70.2, 55.9, 55.7, 20.1, 19.3.

**HRMS (ESI):** calc. for [($C_{32}H_{31}NO_5$)Na] (M+Na) 532.2100, measured 532.2098.

**2,2-*bis*(3,4-Dimethylphenyl)-2-(3-iodo-4-methoxyphenyl)-1-(4-nitrophenyl)ethanone (3jm).**



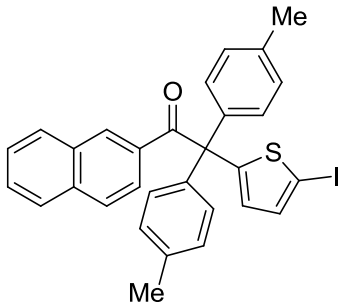

Colorless solid; eluent (5% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated product 75 mg 44% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.97 (d, *J* = 8.0 Hz, 2 H), 7.78 (d, *J* = 8.0 Hz, 2 H), 7.54 (d, *J* = 2.0 Hz, 1 H), 7.04 (dd, *J* = 8.0, 4.0 Hz, 3 H), 6.95 – 6.88 (m, 4 H), 6.67 (d, *J* = 8.0 Hz, 1 H), 3.82 (s, 3 H), 2.20 (s, 6 H), 2.15 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 197.5, 170.8, 156.6, 148.8, 142.5, 141.1, 138.8, 137.6, 136.4, 135.6, 132.0, 131.6, 129.5, 127.8, 122.7, 109.7, 85.1, 69.5, 56.2, 20.0, 19.3.

**HRMS (ESI):** calc. for [($C_{31}H_{28}NIO_4$)Na] (M+Na) 628.0961, measured 628.0974.

**2-(5-Iodothiophen-2-yl)-1-(naphthalen-2-yl)-2,2-di-*p*-tolylethanone (3hp).**



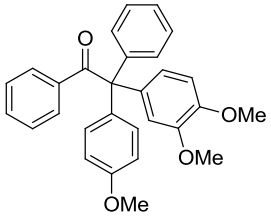

Colourless semisolid; eluent (7% ethyl acetate in hexanes). The reaction scale is 64 mg, isolated product 42 mg 42% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 8.15 (s, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.63 – 7.57 (m, 2 H), 7.52 – 7.48 (m, 1 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 4 H), 7.06 (d, *J* = 8.0 Hz, 4 H), 6.98 (d, *J* = 4.0 Hz, 1 H), 6.24 (d, *J* = 4.0 Hz, 1 H), 2.30 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 199.1, 154.9, 139.8, 137.2, 135.4, 134.6, 134.6, 132.7, 132.0, 130.4, 129.8, 129.8, 128.9, 128.4, 127.4, 127.2, 126.6, 126.4, 75.3, 68.4, 21.0.

**HRMS (ESI):** calc. for [($C_{30}H_{23}IOS$)Na] (M+Na) 581.0412, measured 581.0431.

**2-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-1,2-diphenylethanone (5aa).**



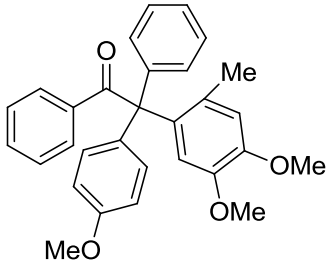

Light white semisolid; eluent (20% ethyl acetate in hexanes).

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.70 (d, *J* = 8.0 Hz, 2 H), 7.36 – 7.26 (m, 3 H), 7.25 – 7.14 (m, 7 H), 6.86 – 6.77 (m, 4 H), 6.73 (d, *J* = 2.0 Hz, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.64 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 199.1, 157.9, 148.0, 147.6, 143.9, 137.7, 135.5, 135.3, 131.8, 131.6, 130.9, 130.6, 127.6, 127.6, 126.5, 122.9, 114.8, 113.0, 110.1, 70.0, 55.7, 55.7, 55.1.

**HRMS (ESI):** calc. for [($C_{29}H_{26}O_4$)Na] (M+Na) 461.1729, measured 461.1728.

**2-(4,5-Dimethoxy-2-methylphenyl)-2-(4-methoxyphenyl)-1,2-diphenylethanone (5ag).**



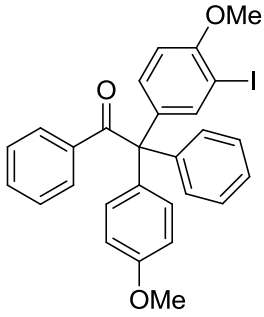

Pale yellow semisolid; eluent (20% ethyl acetate in hexanes). The reaction scale is 60 mg, isolated product 46 mg 51% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.60 (d, *J* = 8.0 Hz, 2 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 7.22 – 7.19 (m, 3 H), 7.17 – 7.11 (m, 4 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 6.87 (s, 1 H), 6.76 (d, *J* = 8.0 Hz, 2 H), 6.53 (s, 1 H), 3.81 (s, 3 H), 3.76 (s, 3 H), 3.58 (s, 3 H), 1.69 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 200.1, 157.9, 147.6, 146.3, 143.7, 138.7, 135.4, 133.2, 132.3, 131.5, 131.3, 131.1, 130.6, 127.4, 127.4, 126.5, 115.0, 114.4, 112.8, 69.5, 55.8, 55.7, 55.1, 21.8.

**HRMS (ESI):** calc. for [($C_{30}H_{28}O_4$)H] (M+H) 453.2066, measured 453.2072.

**2-(3-Iodo-4-methoxyphenyl)-2-(4-methoxyphenyl)-1,2-diphenylethanone (5am).**



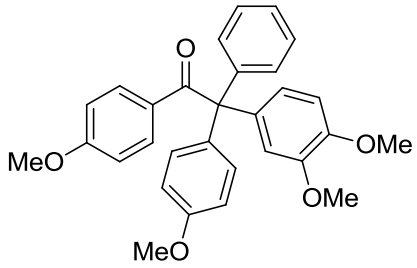

White solid; eluent (10% ethyl acetate in hexanes).

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.63 (d, *J* = 8.0 Hz, 2 H), 7.55 (d, *J* = 2.0 Hz, 1 H), 7.30 (t, *J* = 8.0 Hz, 1 H), 7.23 (s, 1 H), 7.19 – 7.17 (m, 6 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 7.07 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.78 (d, *J* = 8.9 Hz, 2 H), 6.67 (d, *J* = 8.0 Hz, 1 H), 3.82 (s, 3 H), 3.76 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 198.8, 158.1, 156.5, 143.0, 141.2, 138.1, 137.2, 134.5, 132.2, 131.8, 131.0, 130.6, 127.9, 127.7, 126.8, 113.3, 113.1, 109.7, 85.1, 69.4, 56.3, 55.2.

**HRMS (ESI):** calc. for [($C_{28}H_{23}IO_3$)Na] (M+Na) 557.0590, measured 557.0594.

**2-(3,4-Dimethoxyphenyl)-1,2-bis(4-methoxyphenyl)-2-phenylethanone (5ba).**



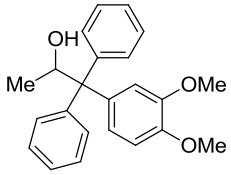

Pale yellow liquid; eluent (30% ethyl acetate in hexanes). The reaction scale is 48 mg, isolated product 50 mg 75% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.67 (d, *J* = 8.0 Hz, 2 H), 7.23 – 7.16 (m, 5 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 6.76 (dd, *J* = 8.0, 4.0 Hz, 4 H), 6.68 (s, 1 H), 6.63 (d, *J* = 8.0 Hz, 2 H), 3.83 (s, 3 H), 3.75 (d, *J* = 4.0 Hz, 6 H), 3.60 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 197.6, 162.0, 157.9, 148.0, 147.5, 144.2, 135.8, 135.6, 133.4, 131.8, 130.7, 130.2, 127.6, 126.4, 122.8, 114.8, 113.0, 112.8, 110.1, 69.8, 55.8, 55.7, 55.2, 55.1.

**HRMS (ESI):** calc. for [($C_{30}H_{28}O_5$)Na] (M+Na) 491.1834, measured 491.1827.

**1-(3,4-Dimethoxyphenyl)-1,1-diphenylpropan-2-ol (6a).**



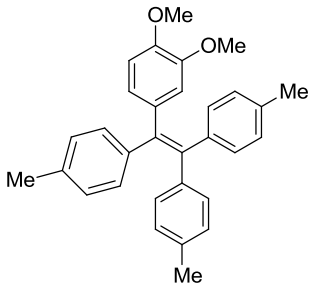

Colorless semisolid; eluent (5% ethyl acetate in hexanes).

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.34 (dd, *J* = 8.0, 4.0 Hz, 4 H), 7.27 (t, *J* = 8.0 Hz, 4 H), 7.18 (t, *J* = 8.0 Hz, 2 H), 6.86 (d, *J* = 8.0 Hz, 2 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 5.40 (q, *J* = 8.0 Hz, 1 H), 3.84 (s, 3 H), 3.70 (s, 3 H), 1.14 (d, *J* = 4.0 Hz, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 148.0, 147.3, 129.8, 127.8, 127.7, 126.1, 126.1, 122.1, 114.0, 110.2, 69.9, 62.1, 55.8, 55.7, 19.9, 14.1, 14.1.

**HRMS (ESI):** calc. for [($C_{23}H_{24}O_3$)Na] (M+Na) 371.1623, measured 371.1620.

**4,4',4''-(2-(3,4-Dimethoxyphenyl)ethene-1,1,2-triyl)tris(methylbenzene) (7b).**



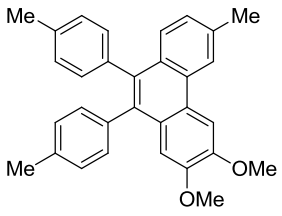

Yellow semisolid; the compound was not required to purify.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 6.90 (d, *J* = 4.0 Hz, 4 H), 6.88 (d, *J* = 4.0 Hz, 8 H), 6.60 (d, *J* = 8.0 Hz, 1 H), 6.52 – 6.49 (m, 2 H), 3.80 (s, 3 H), 3.45 (s, 3 H), 2.25 (s, 3 H), 2.23 (s, 3 H), 2.23 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 147.6, 147.3, 141.7, 141.2, 141.0, 139.6, 136.8, 135.7, 131.3, 131.2, 131.1, 128.4, 128.3, 123.8, 115.2, 110.1, 55.6, 55.5, 21.2, 21.1.

**HRMS (ESI):** calc. for [($C_{31}H_{30}O_2$)Na] (M+Na) 457.2143, measured 457.2129.

**2,3-Dimethoxy-6-methyl-9,10-di-p-tolylphenanthrene (8a).**




Yellow liquid, the compound was not required to purify.

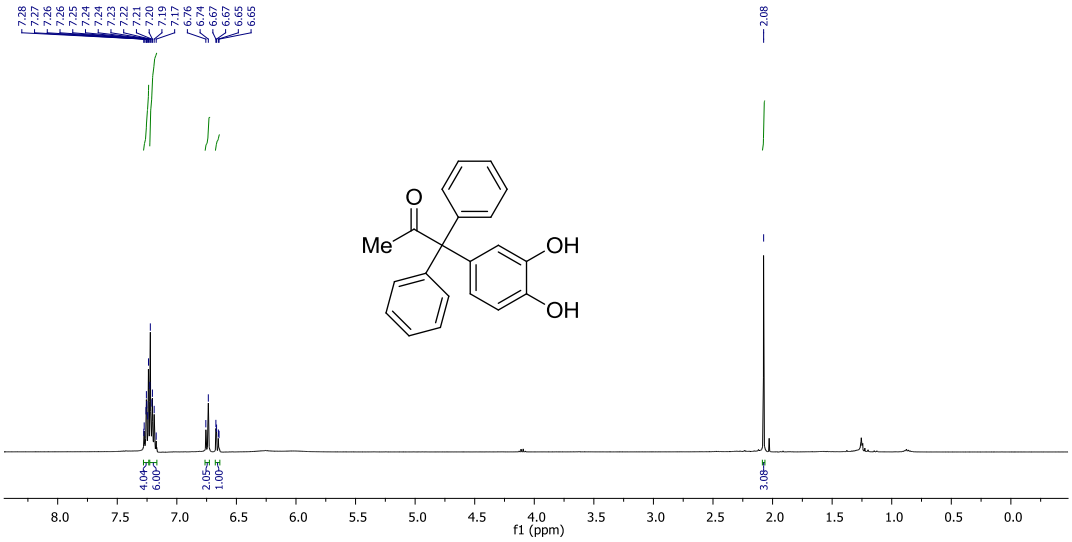
**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 8.37 (s, 1H ), 8.08 (s, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 1 H), 7.02 (d, *J* = 4.0 Hz, 8 H), 6.91 (s, 1 H), 4.15 (s, 3 H), 3.71 (s, 3 H), 2.61 (s, 3 H), 2.30 (s, 3 H), 2.30 (s, 3 H).

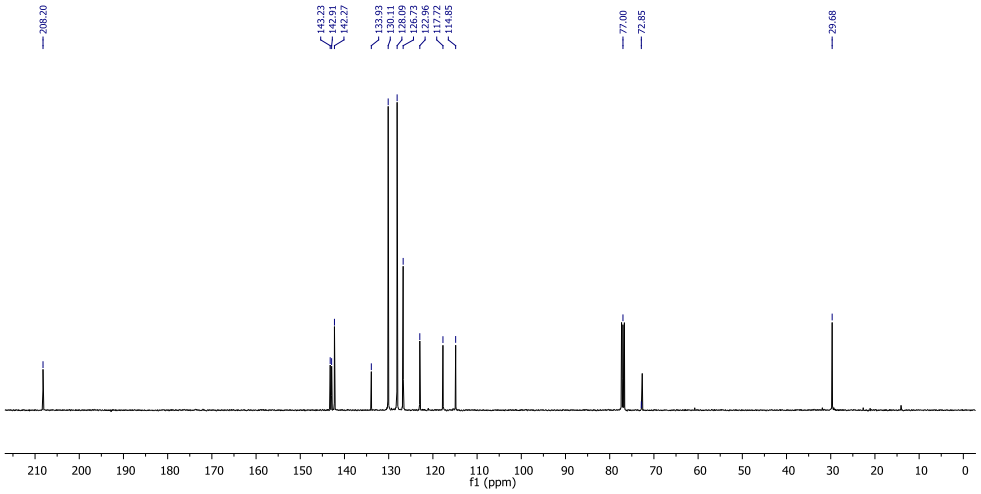
**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 148.9, 137.0, 136.9, 135.6, 135.5, 131.0, 130.80, 129.4, 129.4, 128.3, 128.2, 127.8, 127.4, 127.3, 124.3, 121.6, 108.1, 103.0, 56.1, 55.6, 22.0, 21.3, 21.2.

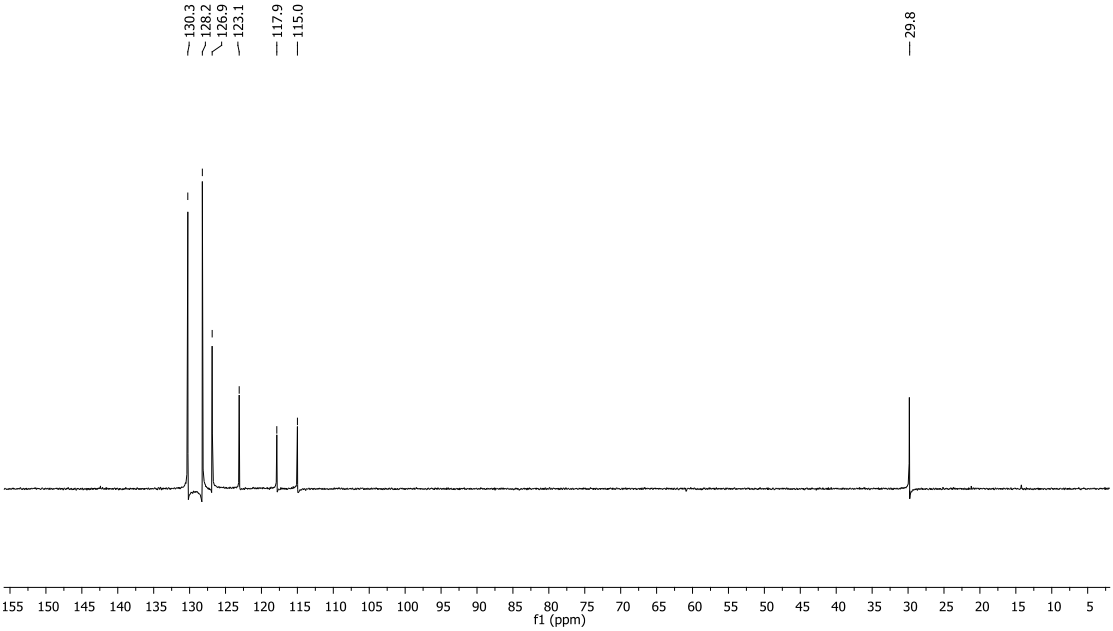
**HRMS (ESI):** calc. for [($C_{31}H_{28}O_2$)H] (M+H) 433.2168, measured 433.2164.

## 2B.13: Spectral Copies of Selected Compounds

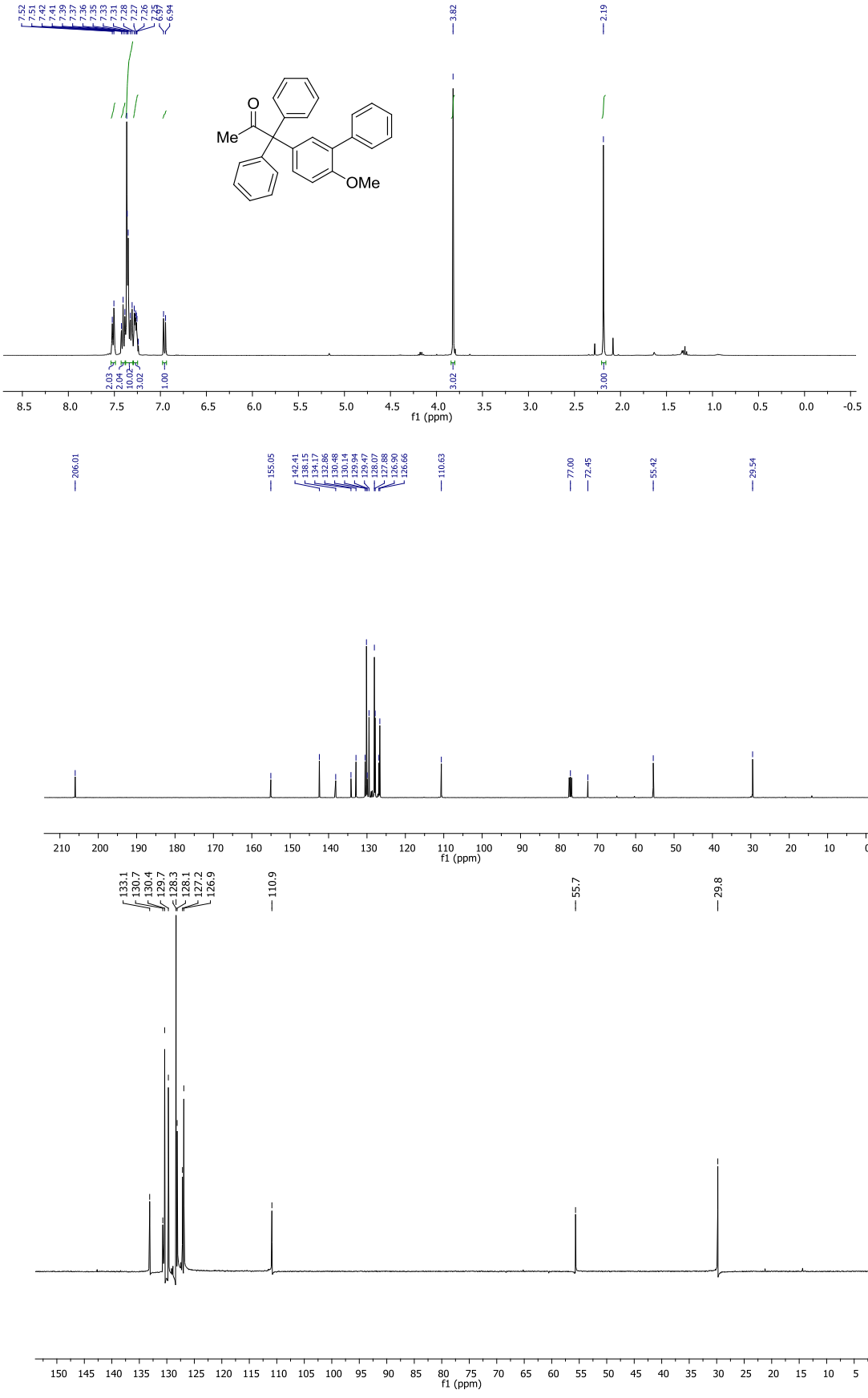
Spectral data of compound **3a**.



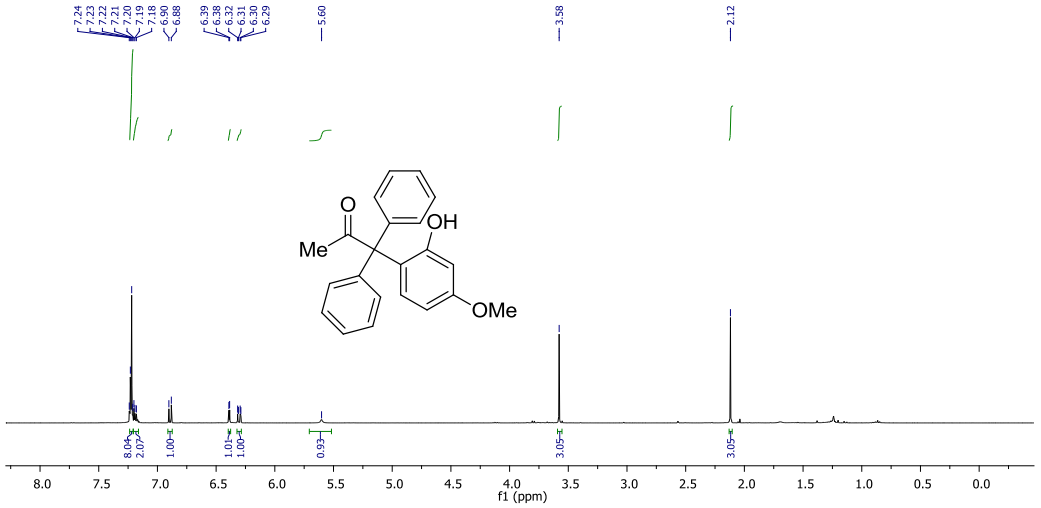



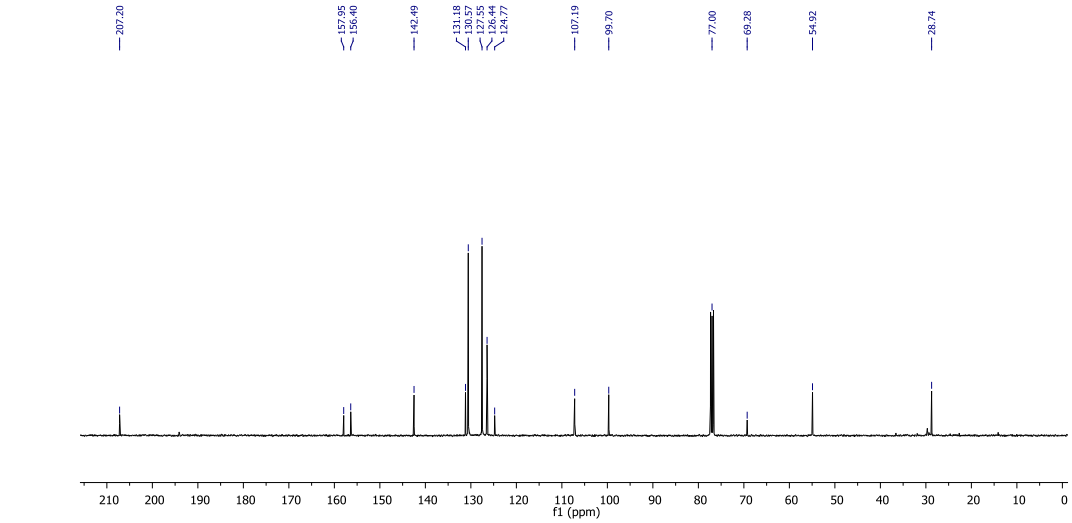



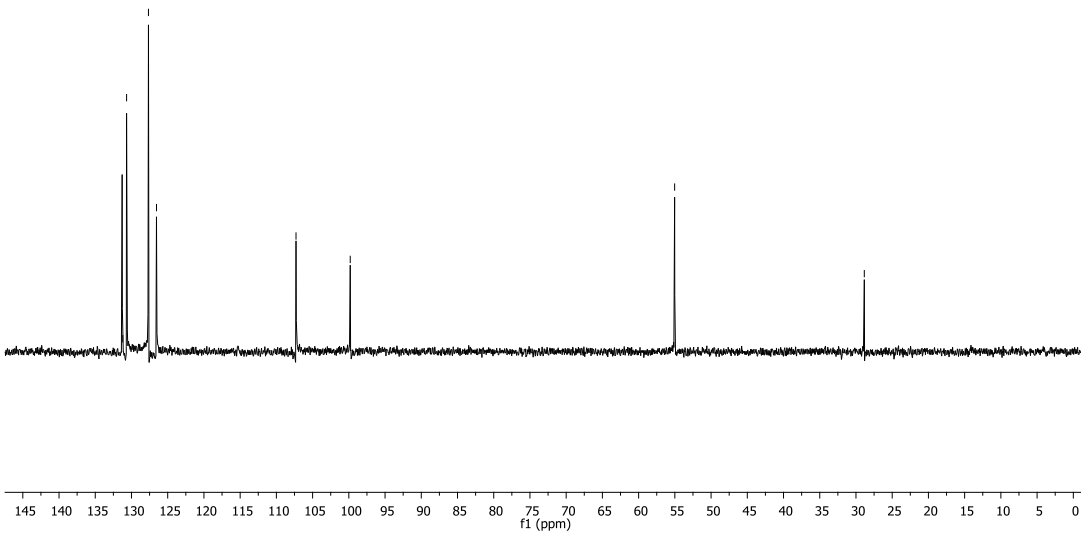
Spectral data of compound **3ac**.



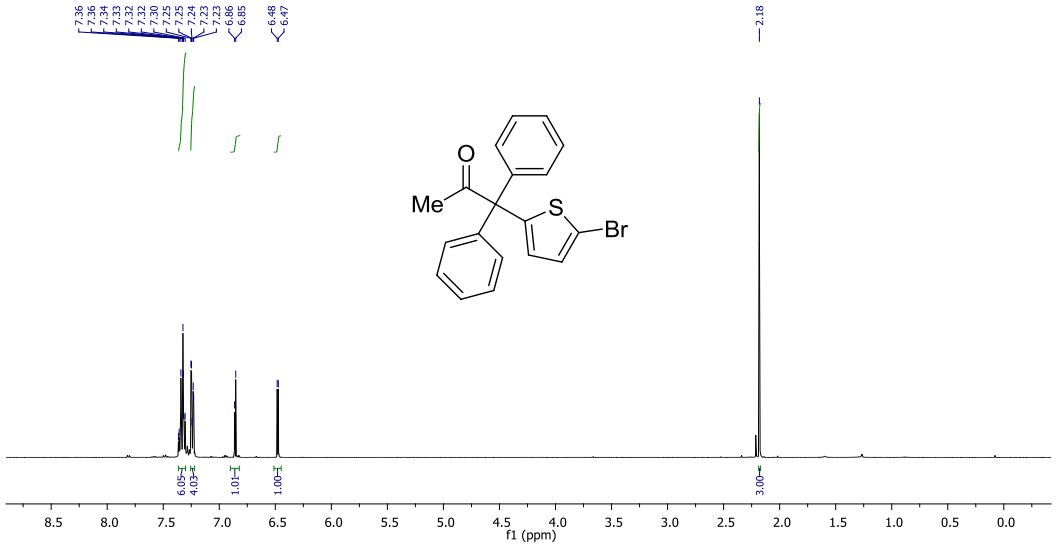
Spectral data of compound **3g**.

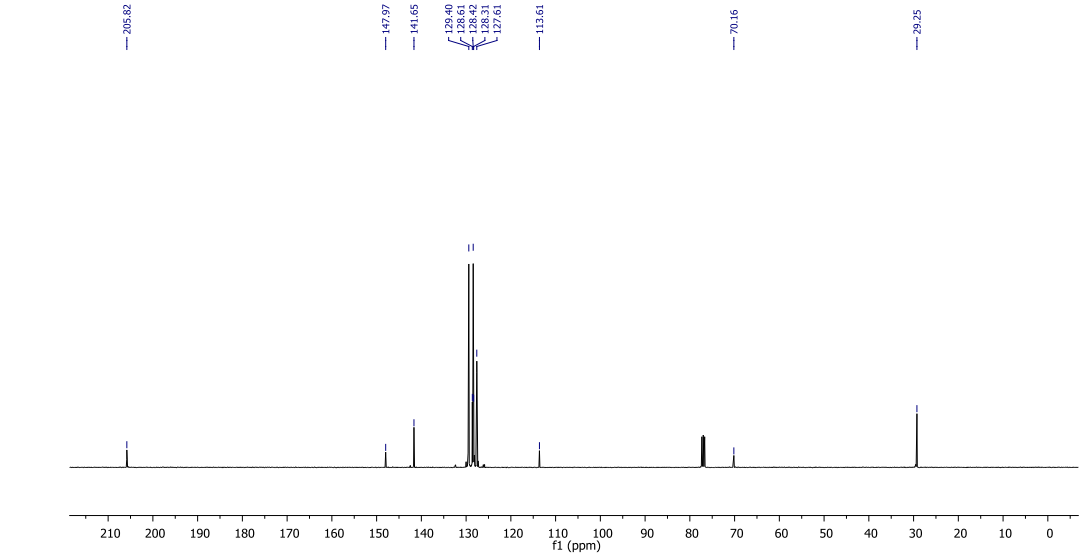


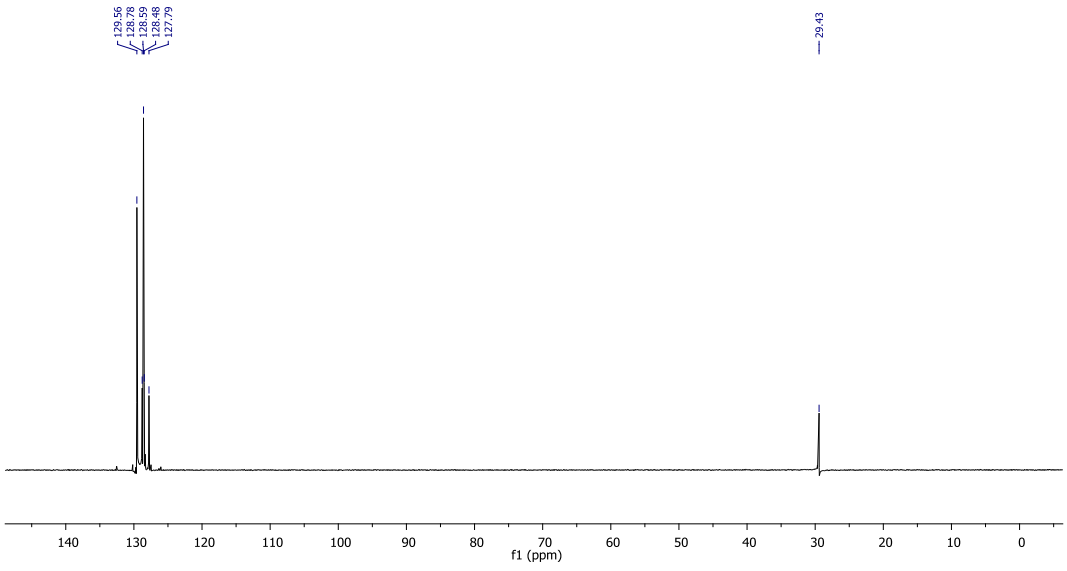



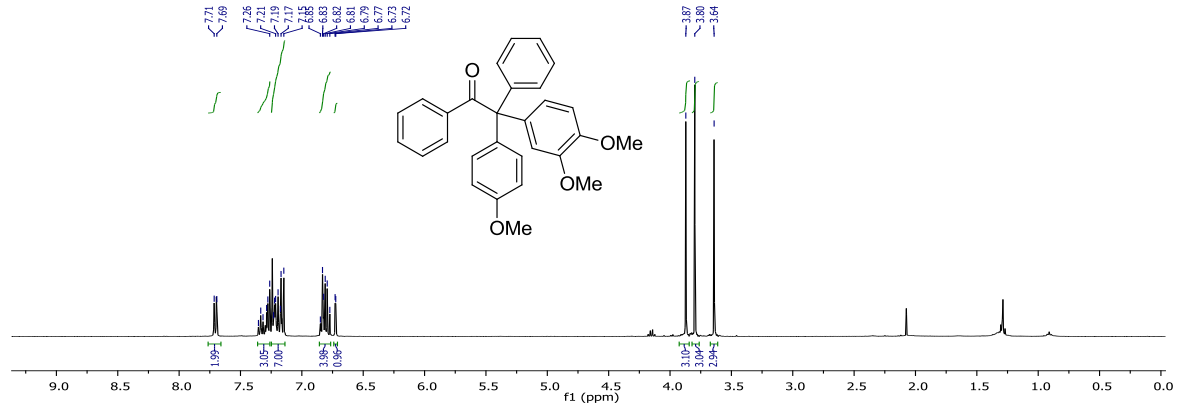
Spectral data of compound **3k**.

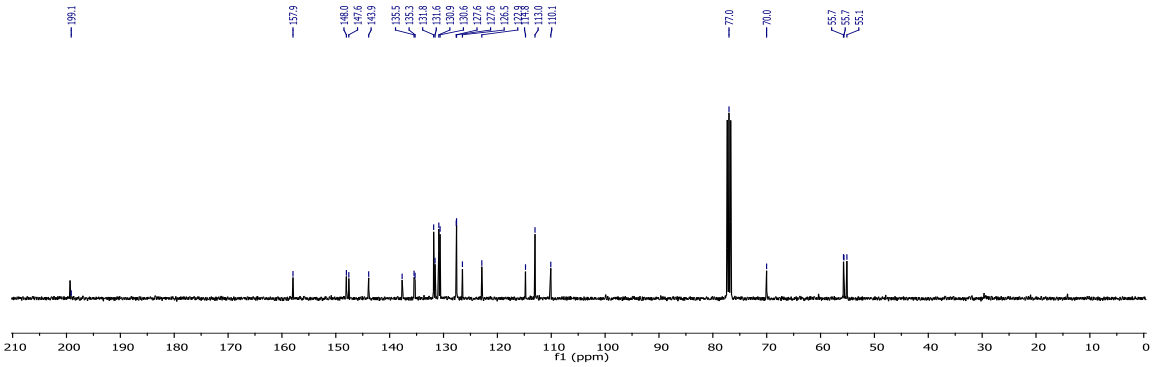


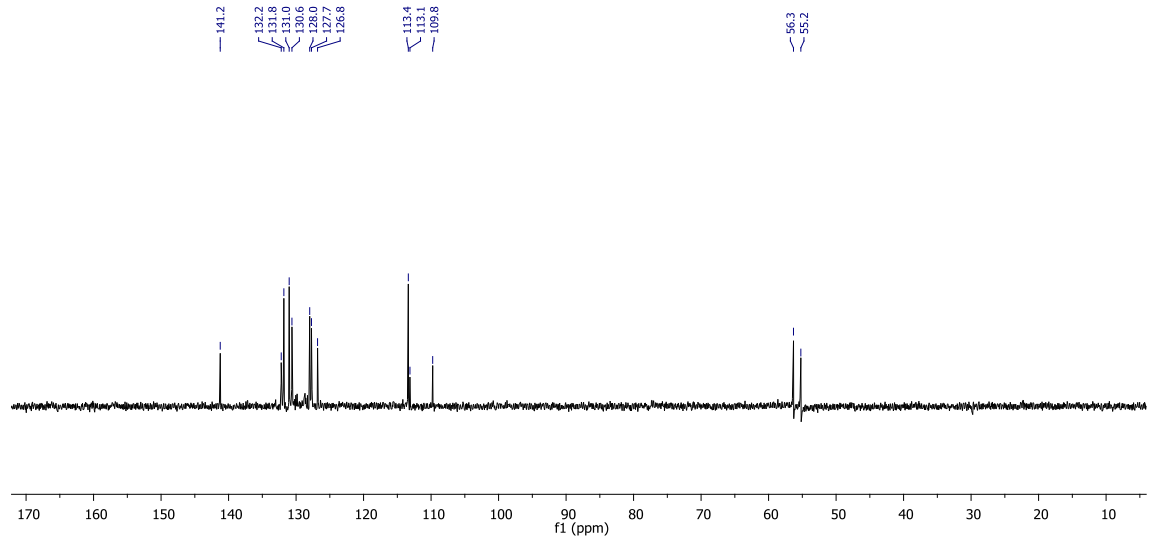



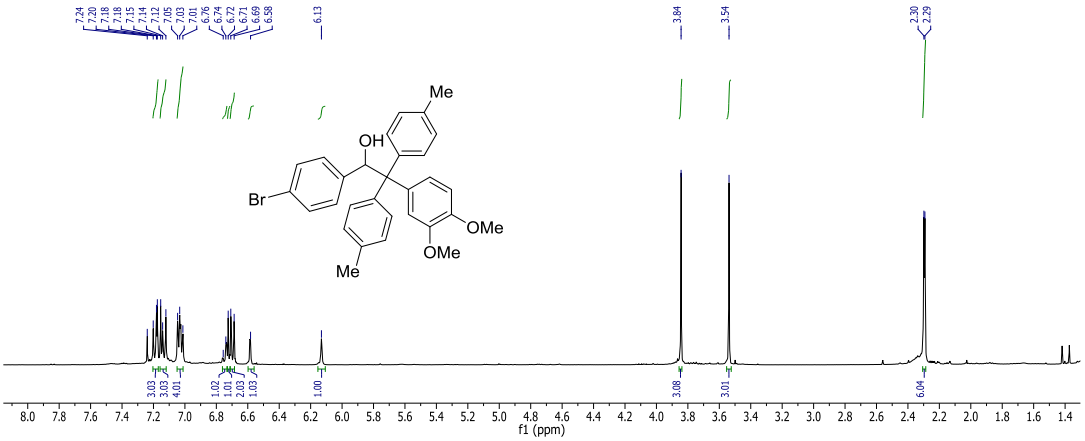
Spectral data of compound **3o**.

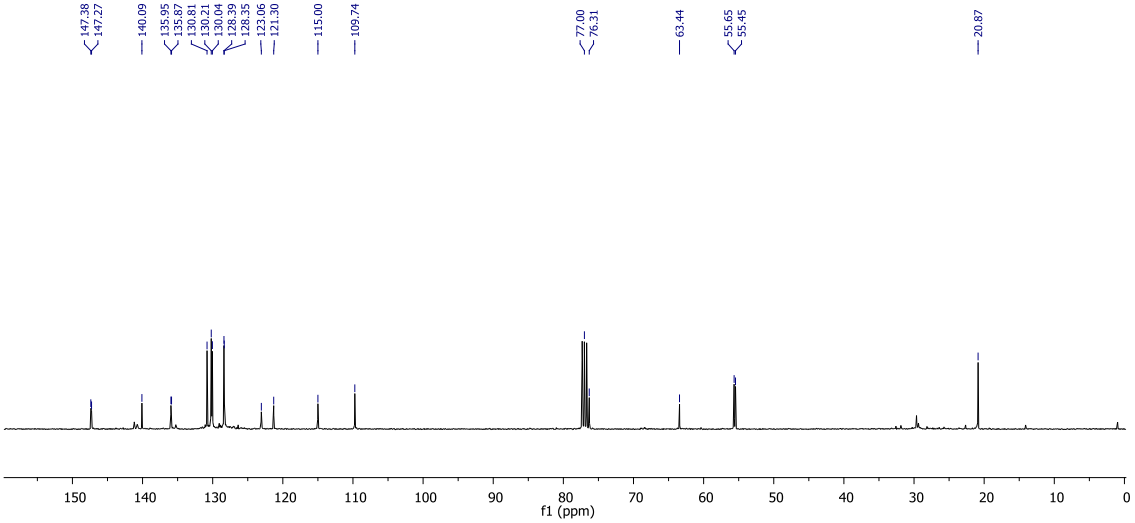


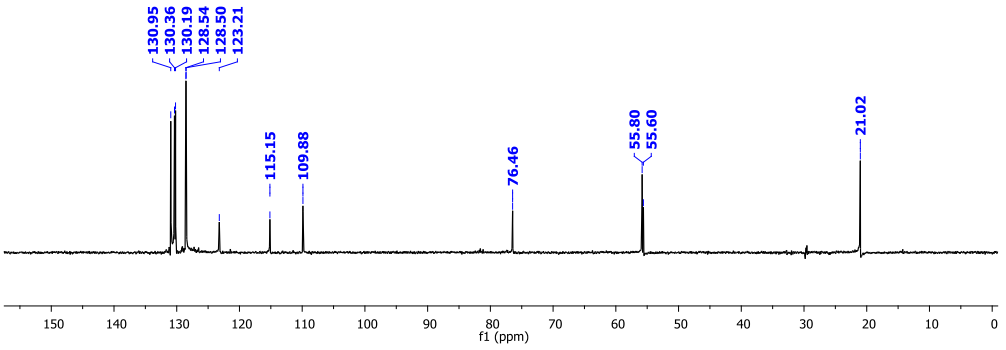



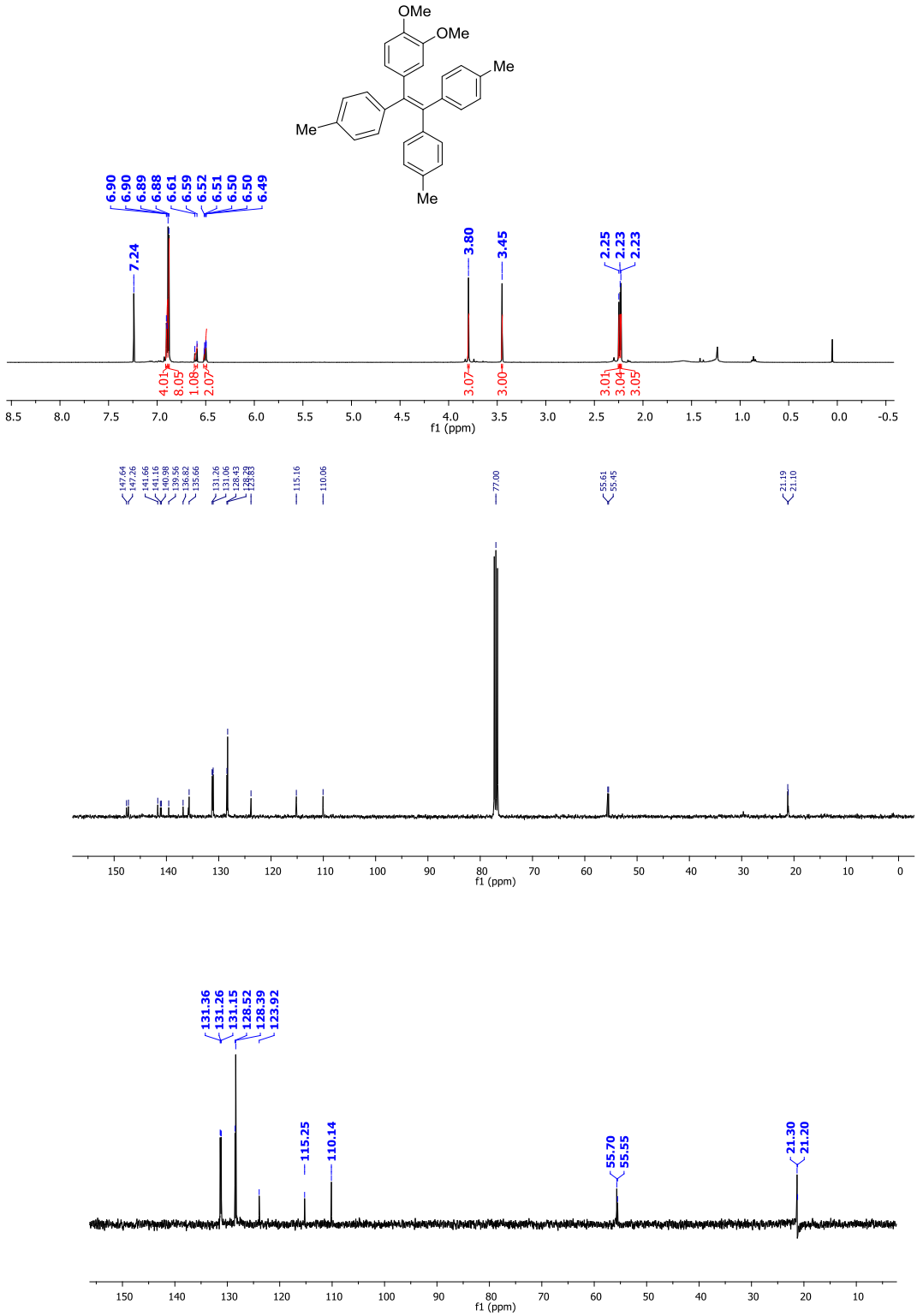
Spectral data of compound **3q**.



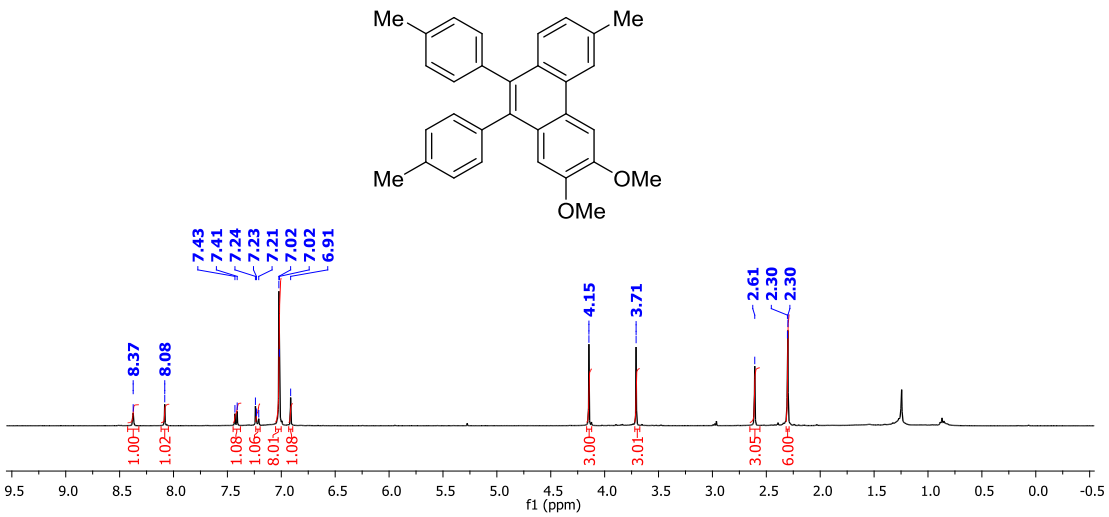



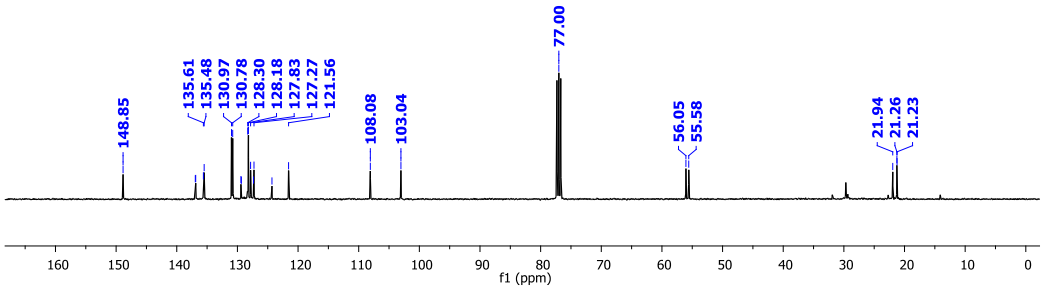



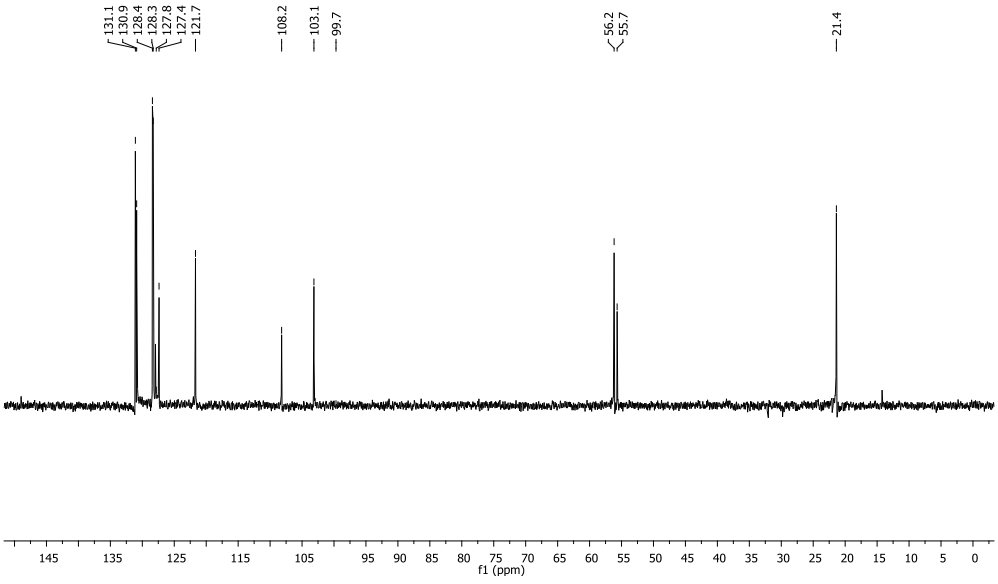
Spectral data of compound **4c**.



Spectral data of compound **4d**.



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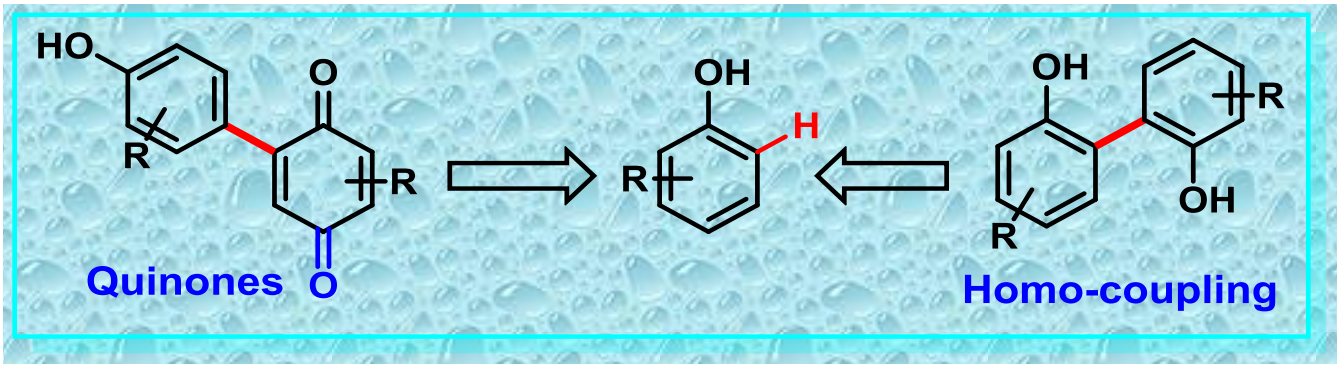
# Chapter 3

## Solvent-Controlled Selective Synthesis of Biphenols and Quinones via Oxidative Coupling of Phenols



### 3.1: Introduction

Biphenols are very common structural units in natural products, pharmaceutically active compounds, and functional materials.[1] Substituted quinones exhibit a wide range of antimicrobial efficacies.[2a-b] In addition, quinones and their derivatives play an important role in many biological processes from phosphorylation to electron transfer.[2c] Numerous natural products can be synthesized via different oxidative phenol-phenol coupling reactions, including *ortho-ortho* homo-coupling, oxidative quinone adduct formation and coupling at two different sites (Fig. 3.1). Hence, oxidative coupling reactions of phenols and naphthols to install C-C bond have been attracted considerable attention for several decades.

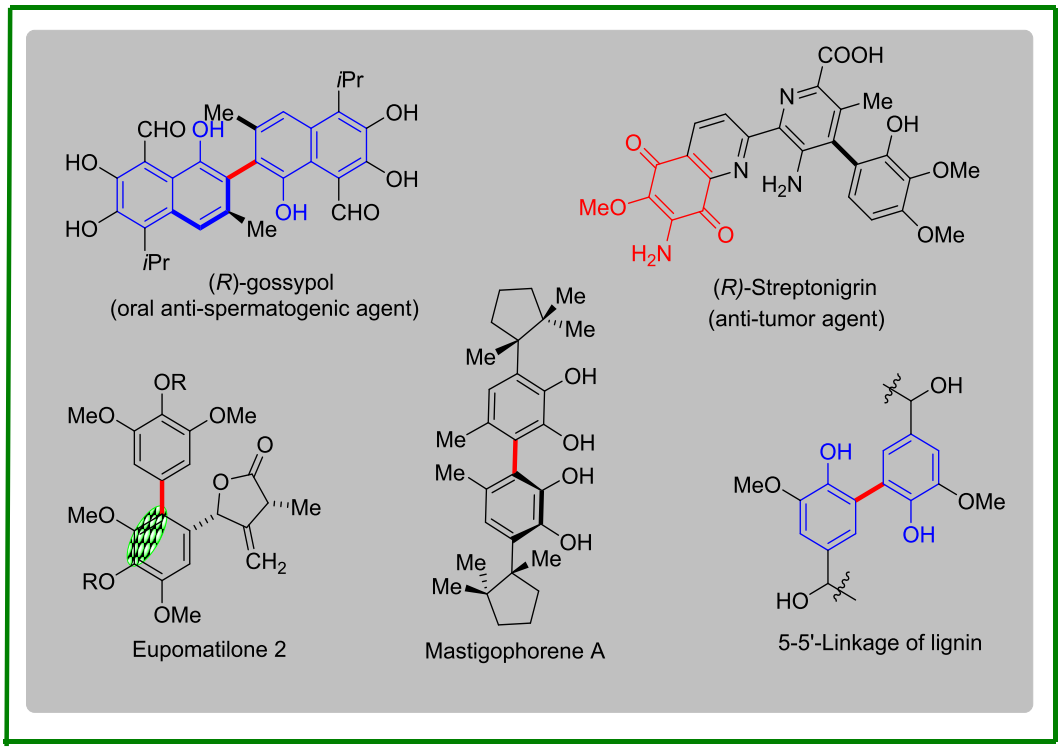
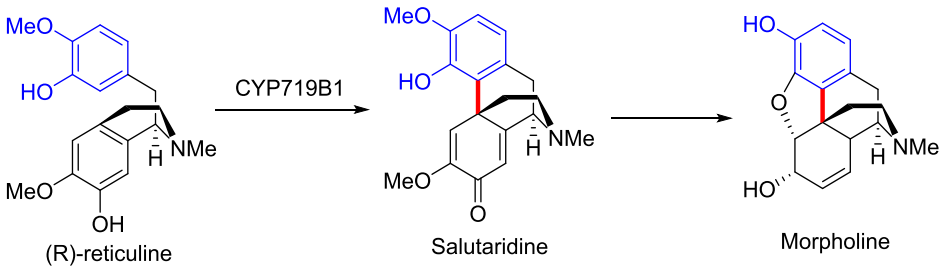



**Fig. 3.1:** Medically potential complex molecules

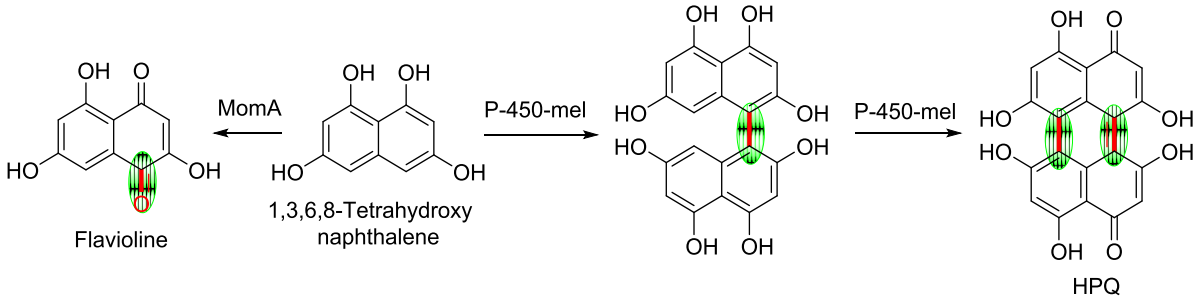
It is important to note that nature has been utilizing oxidative tailoring steps to deliver a large number of medically potential natural products and biomaterials by introducing single or multiple bi-aryl linkages.[3] Such modifications are found in many oxidative enzymes catalyzed transformations using laccase, peroxidase and cytochrome P450 (CYP) as biocatalysts.[3a] Naturally occurring alkaloids are being received much attention for its biological activity, for example, morpholine is a narcotic and analgesic drug. The oxidative phenol coupling is a key step to synthesize quinone compound in morpholine biosynthesis. The reaction is catalyzed by salutaridine synthase CYP719B1 via a single

cycle of iron oxidation in highly regio- and stereoselective manner (Scheme 3.1). In this reaction, a precursor of morpholine, salutasdine is afforded from (*R*)-reticuline.



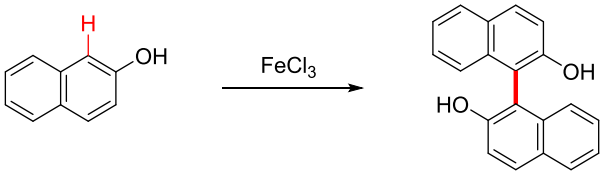

**Scheme 3.1:** Biocatalytic biosynthesis of morpholine

Here, I would like to discuss one more interesting biocatalytic oxidative transformation. A quinone-forming enzyme, momA oxidizes selectively 1,3,6,8-Tetrhydroxynaphthalene to flavioline and P-450-mel catalyzes selectively dimerization of 1,3,6,8-Tetrhydroxynaphthalene selectively to produce homocoupling product (Scheme 3.2).[3a]




**Scheme 3.2:** Biocatalytic biosynthesis of morpholine

Thus, to understand the reaction mechanism and to establish laboratory methods for the construct biphenol along with other oxidative coupling products of phenols has been a long time interest among the organic chemists.[4-14] In this regard, a first practical example of oxidative homocoupling of 2-naphthols was reported by Dianin in the presence of $FeCl_3$ in 1873 (Scheme 3.3).[4]

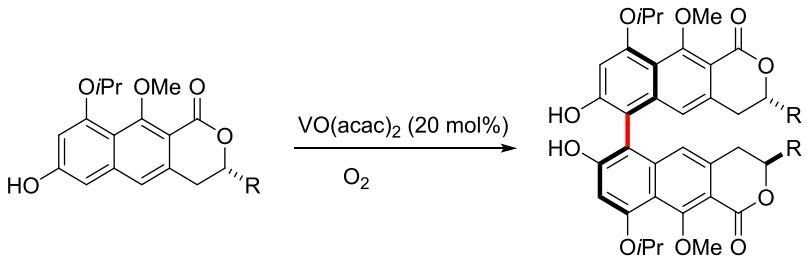



**Scheme 3.3:** Synthesis of racemic 1,10-bi-2-naphthol (Binol)

The most common route to binaphthols or biphenols is oxidation of substituted phenolic compounds via a single electron transfer, and the most frequently used metal salts are Fe, Cr, Mn, Cu, Fe, Ru, and V salts as oxidants.[5] Among these transformations, Cu, V and Fe metals salts mediated are explored much, and most of the oxidative coupling reactions are limited to 2-naphthol.[4-6]

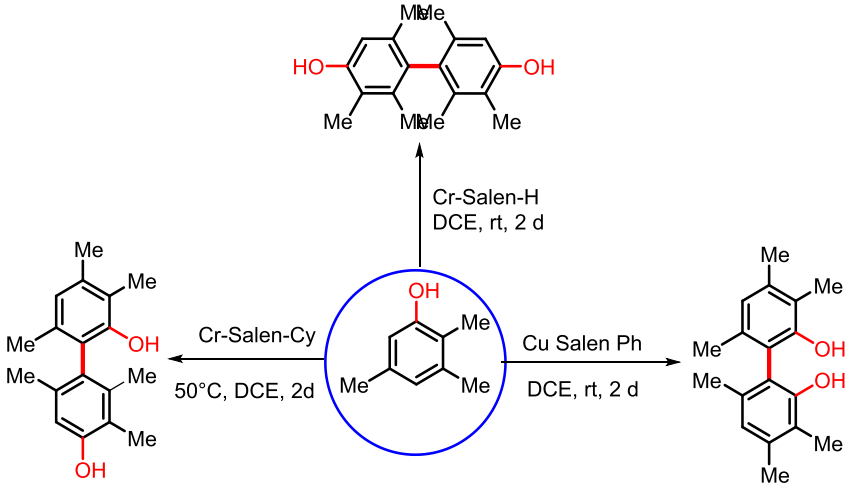
In 1968, Nakaya et al. explored oxidative homocoupling reaction of 2-naphthol and 2,6-disubstituted phenol with manganic tris(acety1acetonate) (MTA) as a metal salt.[6]

Later, oxidative coupling reaction was successfully extended with metal catalysts along with stoichiometric oxidants.[7] Recently, Shaw and coworkers showed a catalytic system for the synthesis of binaphthol from substituted naphthol in the presence of [$VO(acac)_2$] as the catalyst, which a key step in the synthesis of (-)-viriditoxin, which is an inhibitor of bacterial cell division (Scheme 3.4).[8]




**Scheme 3.4:** Vanadium-catalyzed aerobic oxidation of naphthol

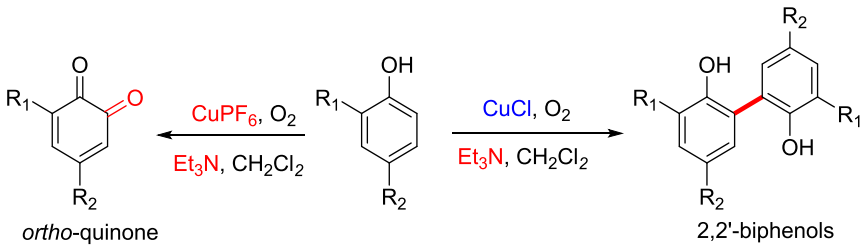
In recent years, number of interesting coppers catalyzed oxidative coupling reactions of naphthols were investigated by Kozlowski's group, and described methods had been successfully implemented in the synthesis of numerous natural binaphthyl products.[9] Meantime, same group has described site-selective oxidative phenol homo-coupling by using catalytic amount metal salen/salan complexes (Ru, Cu, V and Mn salen/salan complexes) in the presence of $O_2$ as a terminal oxidant (Scheme 3.5).[9e] In this report, chemoselectivity has been achieved by choosing a variety of ligands and optimizing parameters.




**Scheme 3.5:** Site-selective homocoupling of phenols

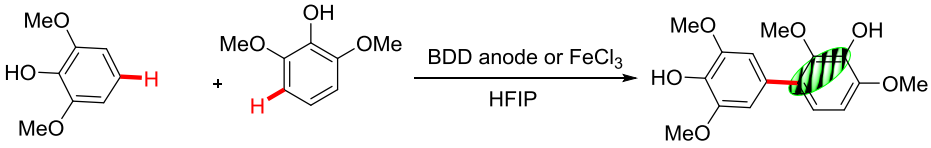
Same time, Lumb et al. disclosed copper (Cu)-catalyzed mild aerobic conditions for the *ortho*-oxygenation or homo-coupling of phenols that result in the formation of *ortho*-quinone or *ortho*-*ortho*-biphenols (Scheme 3.6).[10] The formation of the different selective

products has been accessed by the appropriate choice of Cu(I) salts, amine ligand, and other parameters.



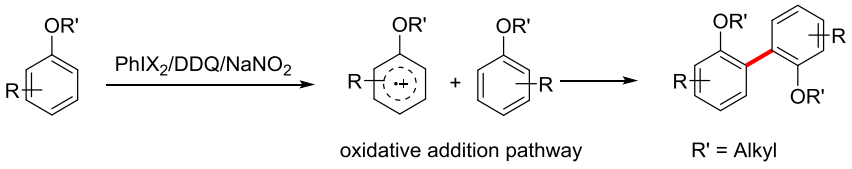

**Scheme 3.6:** Selective catalytic aerobic oxidation

Very recently, Pappo's group has utilized t-BuOOt-Bu peroxide as a terminal oxidant in iron catalytic oxidative homocoupling of an iron-catalyzed radical-anion mechanism to unsymmetrical *para-meta* biphenol of 2, 6-dimethoxy phenol (scheme 3.7).[11]

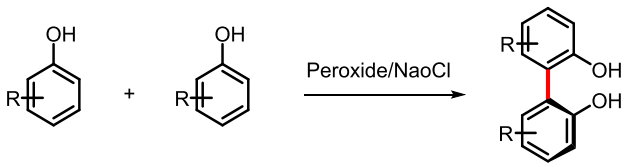



**Scheme 3.7:** Synthesis of alkenes by C-H bond activation

In the meantime, to install bi-aryl bonds in biphenols, metal-free oxidative dehydrogenative coupling reactions have received tremendous attention over the past few years.[12-15] A similar type of coupling reaction has been done in the presence of organic reagents such as hypervalent iodine (III) reagents, DDQ, and $NaNO_2$ (Scheme 3.8).[12] However, in all these oxidative homocoupling reactions, the sensitive free OH group of phenol is not tolerated, and it has to be protected. Only peroxides and NaOCl mediated homo-coupling reactions of phenols led to symmetrical biphenols (Scheme 3.9).[13]



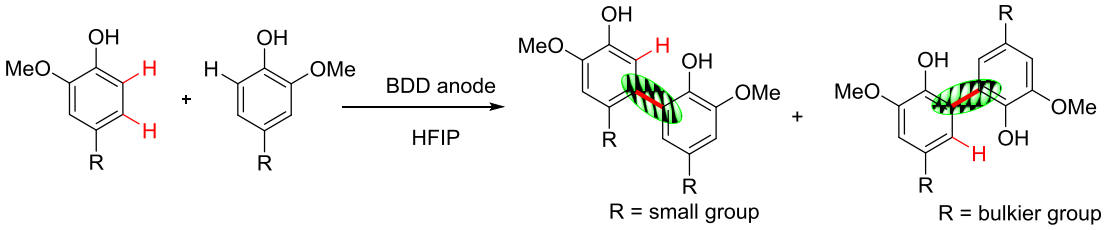

**Scheme 3.8**: Metal-free oxidative homo-coupling of protected phenols




**Scheme 3.9:** Metal-free oxidative homo-coupling of phenols

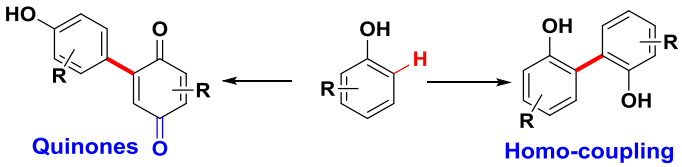
Oxidative homo-coupling phenols often resulted in the formation of symmetrical *ortho-ortho* or *para-para* biphenols in most reports. Subsequently, Waldvogel's group demonstrated that the oxidative coupling reactions of phenols could be achieved via an electrochemical oxidation pathway using boron-doped diamond electrode.[14] Same group

reported the direct anodic homo-dimerization of naturally occurring guaiacol derivatives to nonsymmetric biphenols. The formation of either symmetrical or non-symmetrical biphenols depends on the steric demand of the substituent in the position of phenols (Scheme 3.10).[14a]




**Scheme 3.10:** Synthesis of alkenes by C-H bond activation

Drawing inspiration from the recent literature on oxidative coupling reactions and our continuous interest on $SO_4^{-\bullet}$ radical anion chemistry[15] prompted us to explore the possibility of using $SO_4^{-\bullet}$ anionic radical for oxidative coupling of phenols and naphthols. Herein, we wish to study an efficient route and direct oxidative dehydrogenative coupling of phenols to unsymmetrical and symmetrical biphenols in the presence of $K_2S_2O_8$ at ambient conditions. Metalloenzymes catalyze either selective oxygenation or oxidative coupling of phenols. Thus, we accepted this challenge in our laboratory and found optimization conditions to describe completely selective formation of either quinone then Michael type of addition to provide unsymmetrical quinones or oxidative homocoupling providing biphenols (Scheme 3.11).




**Scheme 3.11:** Selective oxidation of phenols

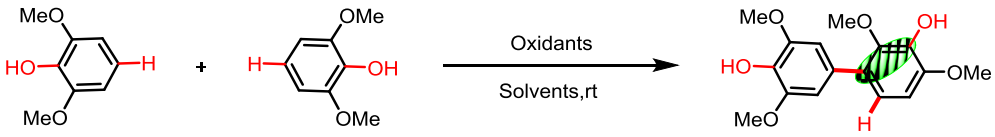
### 3.2: Results and Discussion

When initially, the oxidative homocoupling of 2, 6-dimethoxylphenol (**1a)** was carried out in the presence of $K_2S_2O_8$ in $CF_3COOH$ at room temperature for 4 h. Interestingly, in this reaction, only unsymmetrical biphenol **2a** was observed in 69% yield via the *meta*, *para* C-H coupling corresponding with the hydroxy group of phenol (Table 3.1). No other competitive symmetrical *ortho-ortho* coupled biphenol was observed in the reaction. This result intrigued us to optimize the reaction condition and elaborate the substrate scope.

### 3.3: Optimization Studies

The coupling reaction did not proceed without $K_2S_2O_8$. Apart from $K_2S_2O_8$, the reaction was also examined with $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, $PhI(OAc)_2$ and oxone. Among them, $(NH_4)_2S_2O_8$ was effective as like $K_2S_2O_8$, giving **2a** in 65% yield. $Na_2S_2O_8$ and oxone were partially effective, affording **2a** in 40% and 49% yields, respectively. $PhI(OAc)_2$ was not effective for the reaction. $CF_3COOH$ is also crucial for the reaction. AcOH and *iso*-PrOH solvents were less effective, providing product **2a** in 31% and 23% yields, respectively. Other solvents MeOH, DCE, $H_2O$, and $CF_3SO_3H$ were not effective. The coupling reaction was examined with various amount of $K_2S_2O_8$. In 1.0 equiv and 1.5 equiv of $K_2S_2O_8$, product **2a** was observed only in 55% and 66% yields, respectively. In 2.0 equiv of $K_2S_2O_8$, product **2a** was observed in 69% yield (Table 3.1).

**Table 3.1:** Optimization Studies with Various Solvent and Oxidant




| Entry | Solvent | Oxidants | Amount | Yield of **2a** (%)[b] |
|---|---|---|---|---|
| 1 | TFA | No | 2.0 equiv | NR |
| 2 | AcOH | $K_2S_2O_8$ | 2.0 equiv | 31 |
| 3 | *i*-propanol | $K_2S_2O_8$ | 2.0 equiv | 23 |
| 4 | MeOH | $K_2S_2O_8$ | 2.0 equiv | NR |
| 5 | DCE | $K_2S_2O_8$ | | |
| | | | 2.0 equiv | NR |
| 6 | $H_2O$ | $K_2S_2O_8$ | 2.0 equiv | NR |
| 7 | $CF_3SO_3H$ | $K_2S_2O_8$ | 2.0 equiv | NR |

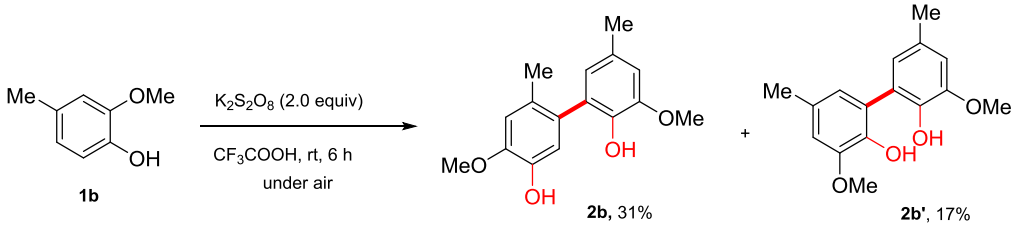
| | | | | |
|---|---|---|---|---|
| **8** | **TFA** | **$K_2S_2O_8$** | **2.0 equiv** | **69** |
| 9 | TFA | $K_2S_2O_8$ | 1.0 equiv | 55 |
| 10 | TFA | $K_2S_2O_8$ | 1.5 equiv | 66 |
| 11 | TFA | $PhI(OAc)_2$ | 2.0 equiv | 52 |
| 12 | TFA | $Na_2S_2O_8$ | 2.0 equiv | 40 |
| 13 | TFA | Oxone | 2.0 equiv | 49 |
| 14 | TFA | $(NH)_4S_2O_8$ | 2.0 equiv | 65 |

[a]All reactions were carried out under the following conditions: **1a** (100 mg), $K_2S_2O_8$ (2.0 equiv), in a solvent (0.5 mL) at rt. [b]GC yield.

### 3.4: Scope of Substituted phenols

#### 3.4.1: *ortho-meta* coupling of phenols

Next, the oxidative coupling reaction was examined with 4-methyl-2-methoxy phenol (**1b**) (Scheme 3.12). In the reaction, interestingly 49% yield of *ortho-meta* coupling unsymmetrical biphenol **2b** along with *ortho-ortho* coupling biphenol **2b'** in 13% yield were observed. Due to the substitution at the *para* position of **1b** could cause of the dropping of the yield of *ortho-meta* coupling product **2b**.



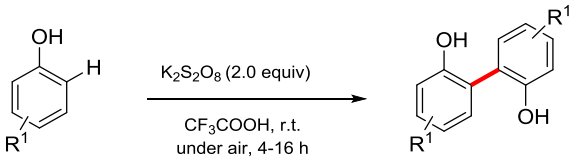

**Scheme 3.12:** Synthesis of alkenes by C-H bond activation

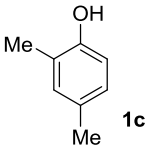
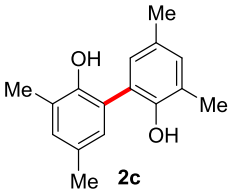
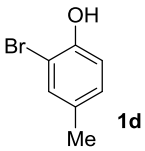
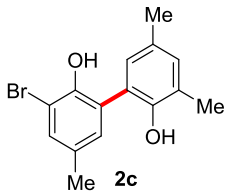
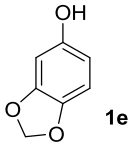
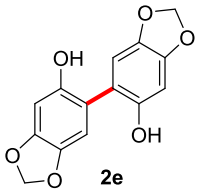
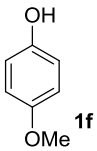
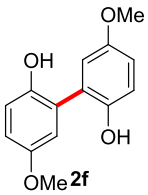
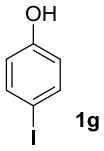
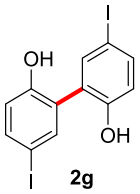
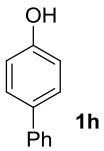
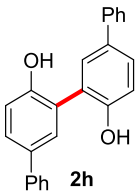
#### 3.4.2: *ortho-ortho* coupling of phenols

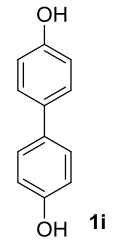
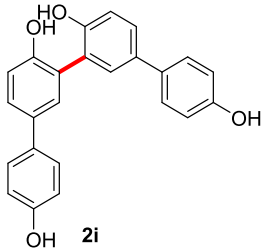
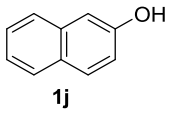
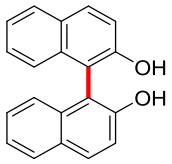
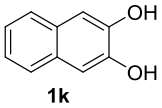
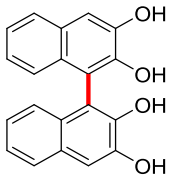
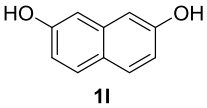
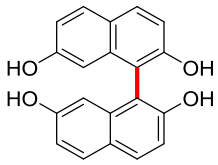
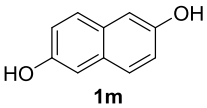
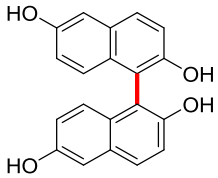
The scope of oxidative coupling reaction was examined with various substituted phenols **1d-i** (Table 3.2). The homocoupling of 2-Bromo-4-methyl phenol (**1d**) and naturally occurring sesamol (**1e**) proceeded well in the presence of $K_2S_2O_8$ giving symmetrical biphenol **2d** and **2e** in 58% and 80% yields, respectively. 4-Methoxy phenol (**1f**) and 4-iodophenol (**1g**) also efficiently participated in the reaction, providing biphenol **2f** and **2g** in 55% and 49% yields, respectively. It is important to note that the sensitive iodo and bromo groups were compatible for the reaction. Interestingly, 4-phenyl phenol (**1h**) and hydroxyl substituted 4-phenyl phenol **1i** afforded the corresponding biphenols **2h** and **2i** in 69% and 79% yields, respectively. Next, the scope of the reaction was examined with naphthols **1j-m**. 2-Naphthol (**1j**) underwent homocoupling efficiently at room temperature giving binaphthol derivative **2j** in 80% yield. A highly useful naphthalene-2,

3-diol (**1k**), naphthalene-2,7-diol (**1l**) and naphthalene-2,6-diol (**1m**) provided the corresponding binaphthols **2k-m** in 70%, 72% and 78% yields, respectively. It is important to note that in **1i** and **1l-m**, two hydroxy groups are present on the aromatic ring. Chemoselectively, only one of the hydroxy groups was involved in the coupling reaction.

**Table 3.2:** Scope of substituted phenols **1c-m**[a]




| Entry | Substituted phenols **1c-m** | Product **2c-m** | Yield (%)[b] |
|---|---|---|---|
| 1 |  **1c** |  **2c** | 73 |
| 2 |  **1d** |  **2c** | 56 |
| 3 |  **1e** |  **2e** | 80 |
| 4 |  **1f** |  **2f** | 55 |
| 5 |  **1g** |  **2g** | 49 |
| 6 |  **1h** |  **2h** | 69 |

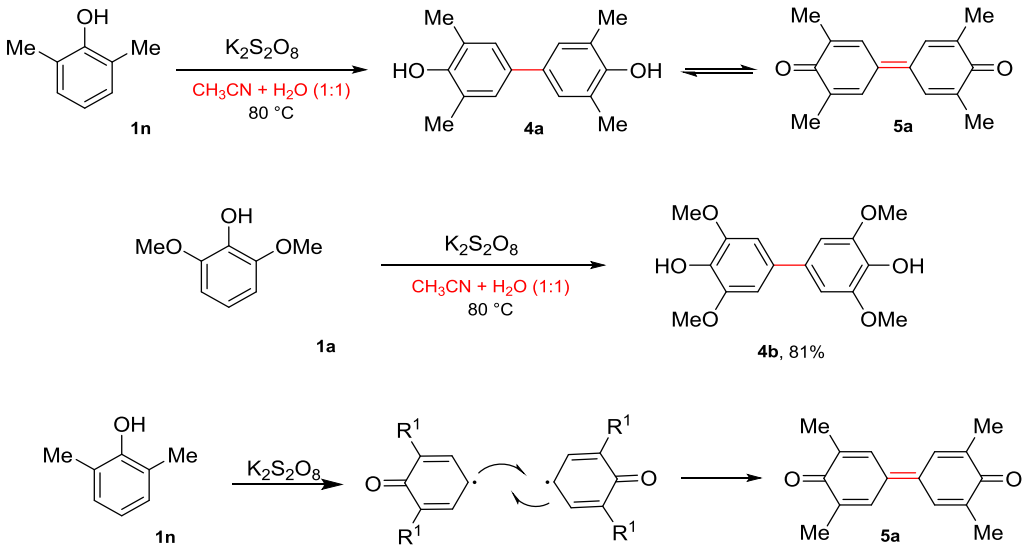
| | | | |
|---|---|---|---|
| 7 |  **1i** |  **2i** | 79 |
| 8 |  **1j** |  **3j** | 80 |
| 9 |  **1k** |  **2k** | 70 |
| 10 |  **1l** |  **2l** | 72 |
| 11 |  **1m** |  **2m** | 78 |

[a]All reactions were carried using **1a-n** (100 mg), $\mathbf{K_2S_2O_8}$ (2.0 equiv) in TFA for 4-16 h. [b]Isolated yield.

### 3.4.3: *para-para* coupling of phenols

A similar type of oxidative coupling reaction was examined with 2, 6-dimethyl phenol (**1n**) under the optimized reaction conditions. However, no coupling product was observed. Later, the solvent and temperature optimization was done. We paid our efforts to optimize appropriate reaction conditions for the successful formation *para-para* coupling biphenol of 2,6-dimethyl phenol. When the biphasic solvent system that is 1:1 ratio of $H_2O$ and $CH_3CN$ solvent mixtures was used instead of $CF_3COOH$ at 80 °C, the oxidative coupling reaction yielded symmetrical *para-para* coupling biphenol **4a** in 62% yield (Scheme 3.13). The oxidative homocoupling of 2,6-dimethoxyphenol (**1a**) yielded nonsymmetrical, para-meta biphenol in TFA solvent at room temperature (Table 3.1).

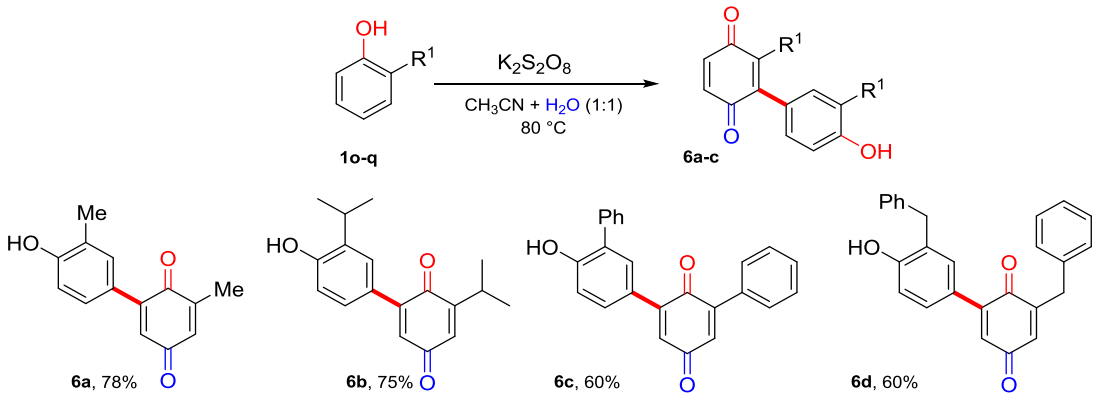
When the biphasic solvent system that is 1:1 ratio of $H_2O$ and $CH_3CN$ applied for 2,6-dimethoxyphenol at 80 °C, now it provided *para-para* coupling symmetrical biphenol **4b** (Scheme 3.13). It is interesting to note that the 2,6-methoxyphenol (**1a**) provides unsymmetrical *meta*, *para* C-H coupling product **2a** in $CF_3COOH$ solvent. Whereas, in 1:1 ratio of $H_2O$ and $CH_3CN$ solvent mixtures, the same substrate provided the symmetrical *para-para* coupling product **4b**.




**Scheme 3.13:** Regioselective *para-para* Coupling of Phenols

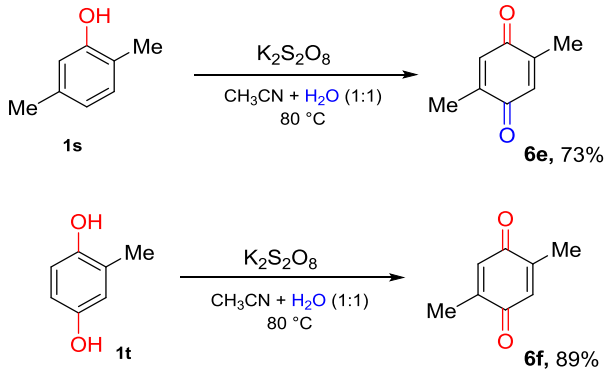
### 3.5: Synthesis of substituted quinones from phenols and naphthols

It is surprising to note the different type of reactivity and coupling product was observed in the oxidative coupling of *ortho*-substituted phenols in the presence of $K_2S_2O_8$ at 80 °C in 1:1 mixture of water and $CH_3CN$ solvents. When 2-methylphenol (**1o**) was treated with $K_2S_2O_8$ in a 1:1 mixture of water and $CH_3CN$ solvents, quinoid coupling product **6a** was observed in 78% yield.[16a] In a similar fashion, 2-*iso*propylphenol (**1p**) and 2-phenylphenol (**1q**), and 2-benzylphenol (**1r**) provided quinoid coupling products **6b, 6c,** and **6d** in 75%, 60%, and 51% yields, respectively (Scheme 3.14). The reaction was further examined with *meta*-substituted phenols such as *meta*. Me and OMe substituted phenols. These substrates were not compatible with the reaction, and no expected coupling product was observed.



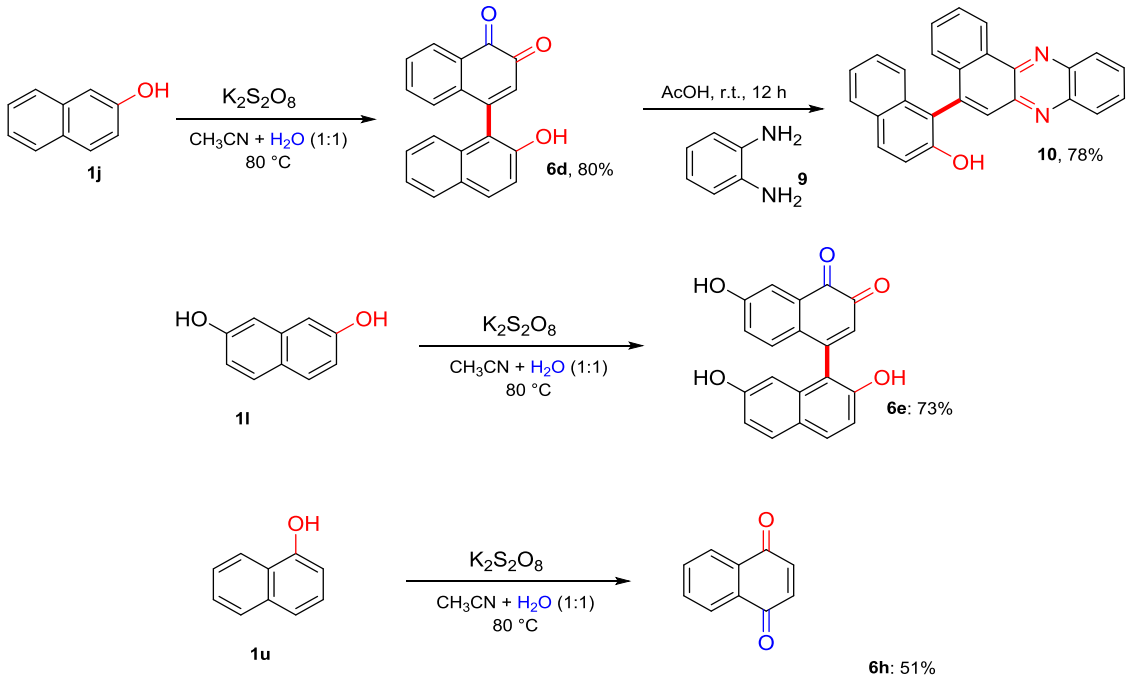

**Scheme 3.14:** Synthesis of substituted quinones

However, 2,5-dimethylphenol (**1s**) and 2-methyl-4-hydroxy phenol (**1t**) provided quinone derivatives **6e** and **6f** in good yields (Scheme 3.15).




**Scheme 3.15:** Synthesis of substituted quinones

The coupling reaction was also examined with substituted 2-naphthols. 2-Naphthol (**1j**) and 2,7-dihydroxy naphthalene (**1l**) underwent oxidative coupling reaction under similar reaction conditions providing quinoid products **6d** and **6e** in 80% and 73% yields, respectively (Scheme 3.16). Product **6d** undergoes condensation with benzene-1,2-diamine (**7**) providing biologically active phenazine derivative **8** in 69% yield.[16b]




**Scheme 3.16:** Synthesis quinones of substituted naphthols

### 3.6: A scale up reactions for the synthesis of biphenols

A gram scale synthesis of biphenols and binaphthols was demonstrated in Scheme 6. The homocoupling of 500 mg of sesamol (**1e**), 1.0 gm of 4-methoxy phenol (**1f**) and 1.0 gm of 2-naphthol (**1j**) in the presence of $K_2S_2O_8$ at ambient conditions provided the expected products **2e**, **2f** and **2j** in 70%, 55% and 60% yields, respectively (Scheme 3.17).

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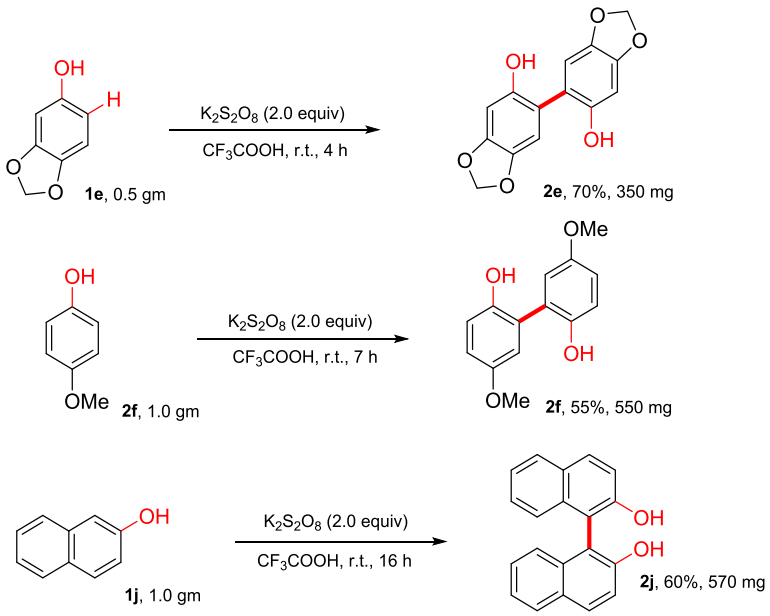
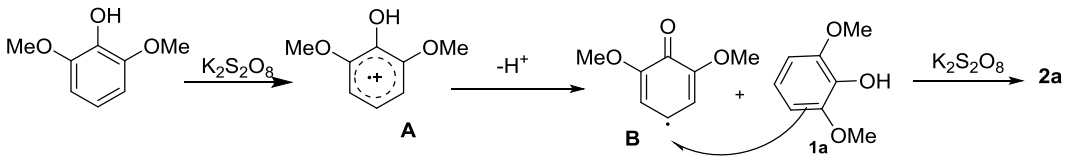



**Scheme 3.17:** A gram scale synthesis of biphenols

### 3.7: Mechanism

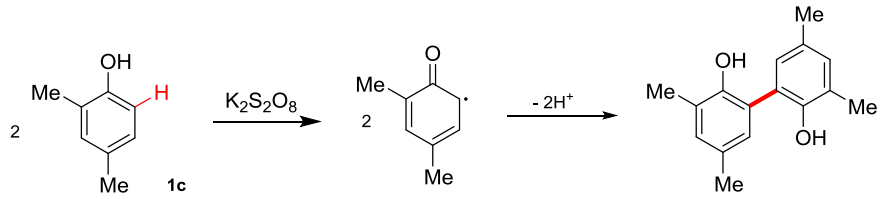
### 3.7.1: Radical-Anion coupling




**Scheme 3.18:** Proposed mechanism

The naturally occurring Syringol undergoes SET mechanism giving phenol cationic radical intermediate **A** in the presence of $K_2S_2O_8$.The stability of phenoxyl and phenol cationic radical was well demonstrated in the literature.[17] Further, intermediate **A** converts into *para*-phenoxyl radical **B** under the reaction conditions. Later, intermediate **B** undergoes radical-anion coupling with another molecule **2a** to produce exclusively unsymmetrical biphenol **2a** (Scheme 3.18).

### 3.7.2: Radical-Radical coupling




**Scheme 3.19:** Proposed mechanism

### 3.8: Conclusion

1. We have developed a new synthetic route for the efficient synthesis of symmetrical and unsymmetrical biphenols and binaphthols by using green and easily available $K_2S_2O_8$.

2. By controlling parameters, selectively the preparation of unsymmetrical *para*-quinoid of phenols and *ortho*-quinoid of naphthols coupling products is also described.

3. A gram scale synthesis of biphenols and binaphthols was also demonstrated.

### 3.9: Experimental Section

**General Procedure for the Homocoupling of Phenols and Naphthols 1:**

In a 10-mL Schlenk tube, substituted phenols or naphthols **1** (100 mg) and $K_2S_2O_8$ (2.0 equiv) were taken. To the tube, was then added $CF_3COOH$ (0.5 mL) via syringe. Then, the tube was covered with a septum and stirred at room temperature. The reaction worked very well under an air atmosphere (The whole reaction mixture is an under air atmosphere. Nitrogen purging was not done). The consumption of the substrate was monitored by TLC. The reaction mixture was diluted with $CH_2Cl_2$ and solvents were evaporated under vacuum. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **2**.

**General Procedure for Synthesis of Substituted Quinones:**

A In a 10-mL Schlenk tube, substituted phenols or naphthols **1** (100 mg) and $K_2S_2O_8$ (2.0 equiv) were taken. To the tube, was then added $CH_3CN$ and $H_2O$ (1.0 + 1.0 mL) via syringe (Normal water was used without further distillation). Then, the tube was covered with a septum and stirred at 80 °C for 3 h. The reaction worked very well under an air atmosphere (The whole reaction mixture is an under air atmosphere. Nitrogen purging was not done). After 3 h, the reaction mixture was quenched with water, and the organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 10mL), and combined organic layers were washed with water and brine, dried over anhydrous $Na_2SO_4$ and evaporated under vacuum. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **4**, **5** and **6**.

**Procedure for the Homocoupling of Sesamol (1e) for 500 mg Scale Reaction.**

In a 25-mL round bottom flask, sesamol **1e** (500 mg) and $K_2S_2O_8$ (2.0 equiv) were taken. To the flask, was then added $CF_3COOH$ (5.0 mL) via syringe and the flask was covered with a septum. Then, the reaction mixture was allowed to stir at room temperature for 4 h. The reaction worked very well under an air atmosphere (The whole reaction mixture is an air atmosphere. Nitrogen purging was not done). The reaction mixture was diluted with $CH_2Cl_2$ and solvents were evaporated under vacuum. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **2e**.

**Procedure for the Homocoupling of 4-Methoxy phenol (1f) for 1.0 Gram Scale.**

In a 25-mL round bottom flask, 4-methoxy phenol (**1f**) (1.0 gm) and $K_2S_2O_8$ (2.0 equiv) were taken. To the flask, was then added $CF_3COOH$ (5.0 mL) via syringe and the flask was covered with a septum. Then, the reaction mixture was allowed to stir at room temperature for 7 h. The reaction worked very well under an air atmosphere (The whole

reaction mixture is an air atmosphere. Nitrogen purging was not done).The reaction mixture was diluted with $CH_2Cl_2$ and solvents were evaporated under vacuum. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **2f**.

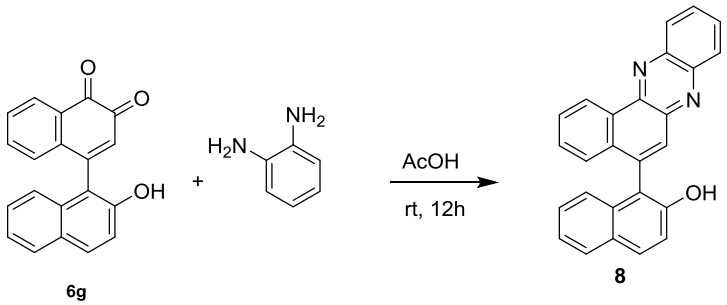
**Procedure for the Homocoupling of 2-Naphthol (1j) for 1.0 Gram Scale.**

In a 25-mL round bottom flask, 2-naphthol (**1j**) (1.0 gm) and $K_2S_2O_8$ (2.0 equiv) were taken. To the flask, was then added $CF_3COOH$ (5.0 mL) via syringe and the flask was covered with a septum. Then, the reaction mixture was allowed to stir at room temperature for 16 h. The reaction worked very well under an air atmosphere (The whole reaction mixture is an air atmosphere. Nitrogen purging was not done).The reaction mixture was diluted with $CH_2Cl_2$ and solvents were evaporated under vacuum. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **2j**.

**Procedure for the coupling of 1o for 1.0 Gram Scale.**

In a 25-mL round bottom flask, 2-methyl phenol (**1o**) (1.0 gm) and $K_2S_2O_8$ (2.0 equiv) were taken. To the tube, was then added $CH_3CN$ and $H_2O$ (8.0 + 8.0 mL) via syringe (Normal water was used without further distillation). Then, the tube was covered with a septum and stirred at 80 °C for 6 h. After 6 h, the reaction mixture was quenched by water and the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 100 mL) and combined organic layers were washed with water and brine, dried over anhydrous $Na_2SO_4$ and evaporated under vacuum. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **6a**. (550 mg, 55%).

**Procedure for the preparation of Phenazine 8.**



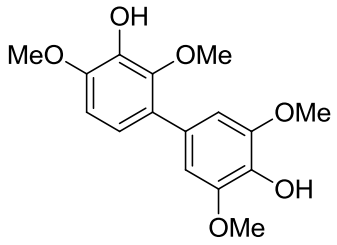

**Scheme 3.20:** preparation of phenazine derivative

In a 25-mL round bottom flask, 2'-hydroxy-[1,1'-binaphthalene]-3,4-dione **6g** (100 mg) and 1,2-diaminobenzene **7** (4.0 equiv) were taken in AcOH (10 mL). Then, the reaction

mixture was cover with a septum and allowed to stir at room temperature for 12 h. After 12 h, the reaction mixture was diluted with $CH_2Cl_2$ and solvents were evaporated under vacuum. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **8** (Scheme 3.2).

**3.10: Spectral Data of Compounds**

**2,3',4,5'-Tetramethoxy-[1,1'-biphenyl]-3,4'-diol (2a).**




The representative general procedure **A** was followed using **1a** (100 mg). The reaction time is 4 h. Product **2m** was isolated in 69 mg and yield is 69%. Dark red solid; mp.156-158 °C; eluent (12 % ethyl acetate in hexanes).

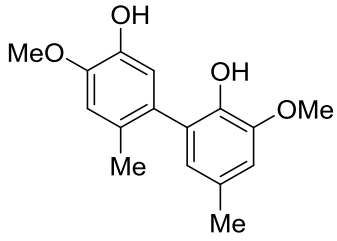
**IR (ATR) ṽ ($cm^{-1}$):** 3425, 2932, 1726, 1608, 1493, 1452, 1211, 1109, 1082, 900, 800, 733.

**$^1$H NMR ($CDCl_3$, 400 MHz):**δ 6.81 (d, *J* = 8.0 Hz, 1 H), 6.77 (s, 2 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 3.90 (d, *J* = 4.0 Hz, 9 H), 3.55 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 146.8, 144.5, 138.7, 133.8, 129.2, 127.9, 120.1, 106.9, 105.7, 60.5, 56.3, 56.2.

**HRMS (ESI):** calc. for [($C_{16}H_{18}O_6$)H] (M+H) 307.1182, measured 307.1181.

**3,4'-Dimethoxy-5,6'-dimethyl-[1,1'-biphenyl]-2,3'-diol (2b).**




The representative general procedure **A** was followed using **1b** (100 mg). The reaction time is 6 h. Product **2l**was isolated in 31 mg and yield is 31%. Brown semisolid; eluent (12 % ethyl acetate in hexanes).

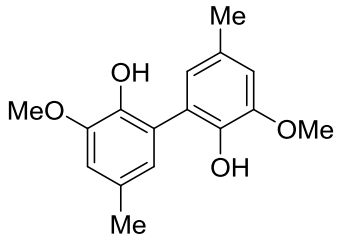
**IR (ATR) ṽ (cm-1):** 3852, 3671, 3286, 2366, 2319, 1698, 1648, 1477, 1388, 1263, 1222, 1113, 1074, 1018 814, 735.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 6.79 (s, 1H), 6.75 (s, 1H), 6.67 (d, *J* = 4.0 Hz, 1H), 6.54 (d, *J* = 4.0 Hz, 1H), 5.43 (s, 1H), 5.42 (s, 1H), 3.9 (s, 3H), 3.89 (s, 3H), 2.29 (s, 3H), 2.12 (s, 3H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 146.2, 145.8, 143.2, 140.4, 129.9, 128.7, 128.3, 127.3, 123.3, 116.1, 112.3, 110.4, 56.0, 55.9, 21.1, 19.6.

**HRMS (ESI):** calc. for [($C_{16}H_{18}O_4$)H] (M+H) 275.1283, measured 275.1280.

**3,3'-Dimethoxy-5,5'-dimethyl-[1,1'-biphenyl]-2,2'-diol (2b').**




The representative general procedure **A** was followed using **1b** (100 mg). The reaction time is 6 h. Product **2b'** was isolated in 17 mg and yield is 17%. Brown solid; mp.133-135 °C; eluent (15 % ethyl acetate in hexanes).

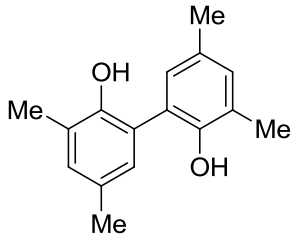
**IR (ATR) ṽ (cm$^{-1}$):** 3852, 3671, 3286, 2366, 2319, 1698, 1648, 1477, 1388, 1263, 1222, 1113, 1074, 1018 814, 735.

**$^1$H NMR ($CDCl_3$, 400 MHz):**δ 6.71 (d, *J* = 4.0 Hz, 4 H), 5.96 (s, 2 H), 3.91 (s, 6 H), 2.32 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 147.0, 140.3, 129.6, 124.3, 123.4, 111.3, 56.0, 21.2.

**HRMS (ESI):** calc. for [($C_{16}H_{18}O_4$)H] (M+H) 275.1283, measured 275.1280.

**3,3',5,5'-Tetramethyl-[1,1'-biphenyl]-2,2'-diol (2c).**




The representative general procedure **A** was followed using **1c** (100 mg). The reaction time is 16 h. Product **2a** was isolated in 73 mg and yield is 73%.White solid; mp 133-134 °C; eluent (5% ethyl acetate in hexanes).

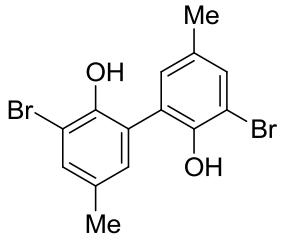
**IR (ATR) ṽ (cm$^{-1}$)**:3861, 3744, 3535, 2960, 2924, 2369, 1711, 1698, 1477, 1281, 1216, 1122, 1074, 861, 786, 743.

**$^1$H NMR ($CDCl_3$, 400 MHz):**δ6.98 (s, 2 H), 6.85 (s, 2 H), 5.07 (s, 2 H), 2.26 (s, 12 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ149.1, 132.0, 130.0, 128.5, 125.2, 122.2, 20.4, 16.2.

**HRMS (ESI):** calc. for [($C_{16}H_{18}O_2$)H] (M+H) 243.1385, measured 243.1380.

**3,3'-Dibromo-5,5'-dimethyl-[1,1'-biphenyl]-2,2'-diol (2d).**




The representative general procedure **A** was followed using **1d** (100 mg). The reaction time is 16 h. Product **2a** was isolated in 58 mg and yield is 58%. Pale yellow solid; mp.136-138 °C; eluent (12 % ethyl acetate in hexanes).

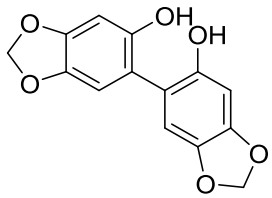
**IR (ATR) ṽ ($cm^{-1}$):** 3838, 3744, 3442, 2907, 2366, 2318, 1741, 1541, 1462, 1305, 1231, 1160, 847, 773, 671.

**$^1$H NMR ($CDCl_3$, 400 MHz):**δ 7.34 (d, *J* = 4.0 Hz, 2 H), 6.99 (d, *J* = 4.0 Hz, 2 H), 5.80 (s, 2 H), 2.29 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ147.1, 132.6, 131.6, 131.4, 125.3, 110.9, 20.2.

**HRMS (ESI):** calc. for [($C_{14}H_{12}BrO_2$)H] (M+H) 370.9282, measured 370.9279.

**[5,5'-bibenzo[*d*][1,3]dioxole]-6,6'-diol (2e).**




The representative general procedure **A** was followed using **1e** (100 mg). The reaction time is 4 h. Product **2c** was isolated in 79 mg and yield is 80%.Ash color solid; mp.202-203 °C; eluent (15 % ethyl acetate in hexanes).

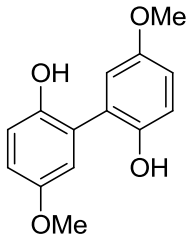
**IR (ATR) ṽ ($cm^{-1}$):**3837, 3744, 3210, 2898, 2366, 2318, 1743, 1698, 1634, 1540, 1486, 1229, 1164, 1030, 927, 763.

**$^1$H NMR (MeOH-$d_4$, 400 MHz):**δ 6.65 (s, 2 H), 6.47 (s, 2 H), 5.88 (s, 4 H).

**$^{13}$C NMR (MeOH-$d_4$, 100 MHz):**δ 149.6, 148.9, 142.8, 119.2, 111.2, 102.4, 99.4, 49.0.

**HRMS (ESI):** calc. for [($C_{14}H_{10}O_6$)H] (M+H) 275.0556, measured 275.0554.

**5,5'-Dimethoxy-[1,1'-biphenyl]-2,2'-diol (2f).**




The representative general procedure **A** was followed using **1f** (100 mg). The reaction time is 7 h. Product **2d** was isolated in 55 mg and yield is 55%. Colourless semisolid; eluent (10 % ethyl acetate in hexanes).

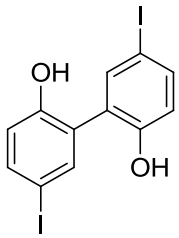
**IR (ATR) ṽ (cm$^{-1}$):** 3852, 3671, 3286, 2366, 2319, 1698, 1648, 1477, 1388, 1263, 1222, 1113, 1074, 1018 814, 735.

**$^{1}$H NMR (MeOH-$d_4$, 400 MHz):**δ 6.88 – 6.84 (m, 2 H), 6.81 (m, 4 H), 6.62 (s, 2 H), 3.76 (s, 6 H).

**$^{13}$C NMR (MeOH-$d_4$, 400 MHz):**δ 154.1, 146.4, 125.6, 117.8, 116.0, 115.3, 55.83.

**HRMS (ESI):** calc. for [($C_{14}H_{14}O_4$)H] (M+H) 247.0970, measured 247.0964.

**5,5'-Diiodo-[1,1'-biphenyl]-2,2'-diol (2g).**




The representative general procedure **A** was followed using **1g** (100 mg). The reaction time is 16 h. Product **2e** was isolated in 49 mg and yield is 49%. Pale yellow solid; mp.112-115 °C; eluent (12 % ethyl acetate in hexanes).

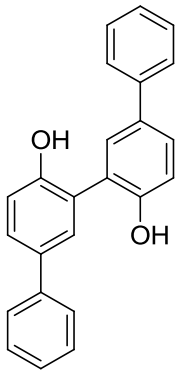
**IR (ATR) ṽ (cm$^{-1}$)**:3852, 3671, 3286, 2366, 2319, 1698, 1648, 1477, 1388, 1263, 1222, 1113, 1074, 1018 814, 735.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):**δ 7.59 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.54 (d, *J* = 4.0 Hz, 2 H), 6.78 (d, *J* = 8.0 Hz, 2 H), 5.66 (s, 2 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz)**: δ 152.7, 139.6, 138.9, 125.4, 119.1, 83.6.

**HRMS (ESI):** calc. for [($C_{12}H_8I_2O_2$)H] (M+H) 438.8692, measured 438.8689.

**Compound 2h.**




The representative general procedure **A** was followed using **1h** (100 mg). The reaction time is 16 h. Product **2f** was isolated in 69 mg and yield is 69%. Colourless semisolid; eluent (15 % ethyl acetate in hexanes).

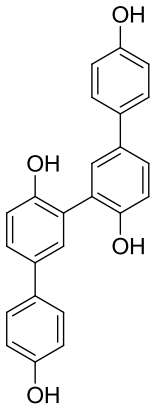
**IR (ATR) ṽ (cm$^{-1}$):** 3744, 3441, 3937, 2107, 1727, 1514, 1277, 1212, 1170, 1030, 835.

**$^{1}$H NMR (CDCl$_3$, 400 MHz):**δ 7.58 – 7.54 (m, 8 H), 7.41 (t, *J* = 8.0 Hz, 4 H), 7.31 (t, *J* = 8.0 Hz, 2 H), 7.10 (d, *J* = 8.0 Hz, 2 H).

**$^{13}$C NMR (CDCl$_3$, 100 MHz):** 152.4, 140.2, 134.9, 130.1, 128.8, 128.6, 127.0, 126.8, 124.3, 117.2.

**HRMS (ESI):** calc. for [($C_{24}H_{18}O_2$)H] (M+H) 339.1385, measured 339.1382.

**Compound 2i.**



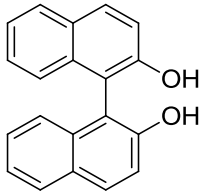

The representative general procedure **A** was followed using **1i** (100 mg). The reaction time is 16 h. Product **2g** was isolated in 79 mg and yield is 79%.Yellow semisolid; eluent (25 % ethyl acetate in hexanes).

**IR (ATR) ṽ (cm$^{-1}$):** 3744, 3671, 3441, 3937, 2107, 1727, 1514, 1277, 1212, 1170, 1030, 835.

**$^{1}$H NMR (CDCl$_3$, 400 MHz):**δ 7.46 (d, *J* = 4.0 Hz, 2 H), 7.43 – 7.40 (m, 6 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 6.83 (d, *J* = 8.0 Hz, 4 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 157.5, 154.1, 134.8, 133.8, 130.7, 128.80, 128.6, 127.8, 117.7, 116.5.**HRMS (ESI):** calc. for [($C_{24}H_{18}O_4$)H] (M+H) 371.1283, measured 371.1291.

**[1,1'-Binaphthalene]-2,2'-diol (2j).**



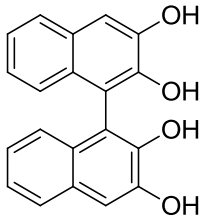

The representative general procedure **A** was followed using **1j** (100 mg). The reaction time is 16 h. Product **2h** was isolated in 80 mg and yield is 80%. Black solid; mp.213-215 °C; eluent (12 % ethyl acetate in hexanes).

**IR (ATR) ṽ (cm$^{-1}$):** 3485, 3418, 3059, 1619, 1511, 1382, 1268, 1211, 1180, 1145, 970, 818, 746.

**$^1$H NMR ($CDCl_3$, 400 MHz):**δ7.94 (d, *J* = 8.0 Hz, 2 H), 7.87 (d, *J* = 8.0 Hz, 2 H), 7.36 (dd, *J* = 8.0, 4.0 Hz, 4 H), 7.29 (t, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 5.06 (s, 2 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ152.7, 133.4, 131.4, 129.4, 128.4, 127.5, 124.2, 124.0, 117.7, 110.8.**HRMS (ESI):** calc. for [($C_{20}H_{14}O_2$)H] (M+H) 287.1072, measured 287.1071.

**[1,1'-Binaphthalene]-2,2',3,3'-tetraol (2k).**




The representative general procedure **A** was followed using **1k** (100 mg). The reaction time is 16 h. Product **2i** was isolated in 70 mg and yield is 70%. Brown solid; eluent (12 % ethyl acetate in hexanes).

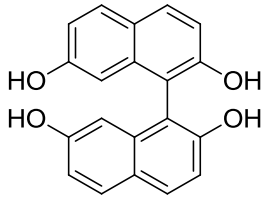
**IR (ATR) ṽ (cm-1):** 3851, 3743, 3395, 2318, 1698, 1341, 1300, 1240, 1146, 941, 725.

**$^1$H NMR (MeOH-$d_4$, 400 MHz):**δ7.64 (d, *J* = 8.0 Hz, 2 H), 7.27 (s, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 6.99 (t, *J* = 8.0 Hz, 2 H), 6.93 (d, *J* = 8.0 Hz, 2 H).

**$^{13}$C NMR (MeOH-$d_4$, 100 MHz):**δ147.4, 145.8, 131.0, 130.3, 127.1, 125.7, 124.3, 124.2, 116.8, 110.3.

**HRMS (ESI):** calc. for [($C_{20}H_{14}O_4$)H] (M+H) 319.0970, measured 319.0969.

**[1,1'-Binaphthalene]-2,2',7,7'-tetraol (2l).**




The representative general procedure **A** was followed using **1l** (100 mg). The reaction time is 16 h. Product **2j** was isolated in 72 mg and yield is 72%. Pale red solid; mp.118-120 °C; eluent (20 % ethyl acetate in hexanes).

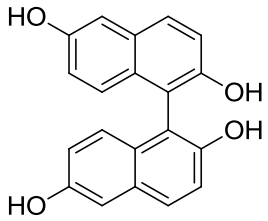
**IR (ATR) ṽ ($cm^{-1}$):** 3851, 3743, 3395, 2318, 1698, 1341, 1300, 1240, 1146, 941, 725.

**$^1$H NMR (MeOH-$d_4$, 400 MHz):** δ7.73 (d, *J* = 8.0 Hz, 2 H), 7.67 (d, *J* = 8.0 Hz, 2 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 6.82 (dd, *J* = 8.0, 4.0 Hz, 2 H), 6.40 (d, *J* = 4.0 Hz, 2 H).

**$^{13}$C NMR (MeOH-$d_4$), 100 MHz):**δ164.9, 162.7, 145.5 138.9, 137.7, 132.5, 124.8, 124.3, 123.82, 115.7.

**HRMS (ESI):** calc. for [($C_{20}H_{14}O_4$)H] (M+H) 319.0970, measured 319.0967.

**[1,1'-Binaphthalene]-2,2',6,6'-tetraol (2m).**




The representative general procedure **A** was followed using **1m** (100 mg). The reaction time is 16 h. Product **2k** was isolated in 78 mg and yield is 78%. Dark grey solid; eluent (12 % ethyl acetate in hexanes).

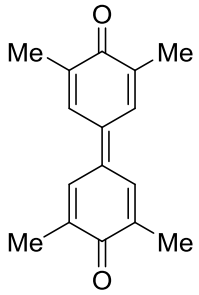
**IR (ATR) ṽ ($cm^{-1}$):** 3851, 3743, 3395, 2318, 1698, 1341, 1300, 1240, 1146, 941, 725.

**$^1$H NMR (MeOH-$d_4$, 400 MHz):** δ7.66 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.13 (d, *J* = 4.0 Hz, 2 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 6.80 (dd, *J* = 8.0, 4.0 Hz, 2 H).

**$^{13}$C NMR (MeOH-$d_4$, 100 MHz)**: δ154.1, 151.9, 131.6, 130.4, 128.8, 127.5, 119.6, 119.2, 116.5, 110.5.

**HRMS (ESI):** calc. for [($C_{20}H_{14}O_4$)H] (M+H) 319.0970, measured 319.0971.

**3,3',5,5'-Tetramethyl-[1,1'-bi(cyclohexylidene)]-2,2',5,5'-tetraene-4,4'-dione (4a).**



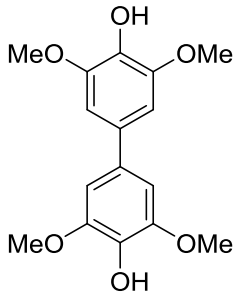

The representative general procedure **B** was followed using **1n** (100 mg). The reaction time is 3 h. Product **2a** was isolated in 62 mg and yield is 62%. Dark red solid, eluent (15% ethyl acetate in hexanes).

**$^{1}$H NMR ($CDCl_3$, 400 MHz)** δ 7.70 (s, 4 H), 2.13 (s, 12 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 187.4, 138.9, 135.6, 129.7, 17.2.

**HRMS (ESI):** calc. for [($C_{16}H_{16}O_2$)H] (M+H) 241.1229, measured 241.1233.

**3,3',5,5'-Tetramethoxy-[1,1'-biphenyl]-4,4'-diol (4b).**



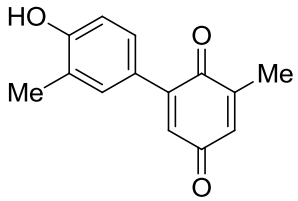

The representative general procedure **B** was followed using **1a** (100 mg). The reaction time is 3 h. Product **2a**[1]was isolated in 81 mg and yield is 81%. Brown semisolid, eluent (20% ethyl acetate in hexanes).

**$^{1}$H NMR ($CDCl_3$, 400 MHz)** δ 6.72 (s, 4 H), 5.61 (s, 2 H), 3.96 (s, 12 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 147.2, 134.2, 133.4, 104.1, 56.5.

**HRMS (ESI):** calc. for [($C_{16}H_{18}O_6$)H] (M+H) 307.1182, measured 307.1184.

**4'-Hydroxy-3',6-dimethyl-[1,1'-biphenyl]-2,5-dione (6a).**



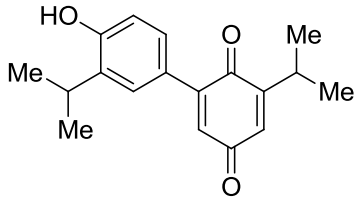

The representative general procedure **B** was followed using **1o** (100 mg). The reaction time is 3 h. Product **2a** was isolated in 82 mg and yield is 74%. Dark brown solid, eluent (20% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):**δ 7.26 (d, *J* = 4.0 Hz, 1 H), 7.21 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.72 (d, *J* = 4.0 Hz, 1 H), 6.63 (m, 1 H), 5.54 (s, 1 H), 2.26 (s, 3H), 2.10 (d, *J* = 4.0 Hz, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 187.9, 187.6, 155.9, 146.1, 145.7, 133.1, 132.1, 131.1, 128.5, 125.3, 124.2, 115.0, 16.4, 15.8.

**HRMS (ESI):** calc. for [($C_{14}H_{12}O_3$)H] (M+H) 229.0865, measured 229.0864.

**4'-Hydroxy-3',6-diisopropyl-[1,1'-biphenyl]-2,5-dione (6b).**



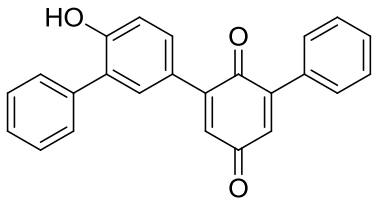

The representative general procedure **B** was followed using **1p** (100 mg). The reaction time is 3 h. Product **2a** was isolated in 79 mg and yield is 72%. Dark brown solid, eluent (20% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):**δ 7.31 (d, *J* = 4.0 Hz, 1H), 7.22 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 4.0 Hz, 1H), 6.56 (m, 1H), 5.24 (s, 1H), 3.22 (m, 1H), 3.12 (m, 1H), 1.26 (d, *J* = 8.0 Hz, 6H), 1.16 (d, *J* = 8.0 Hz, 6H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 188.4, 187.0, 155.3, 154.8, 146.3, 134.7, 130.7, 130.1, 128.3, 127.9, 125.8, 115.3, 27.1, 27.1, 22.4, 21.6.

**HRMS (ESI):** calc. for [($C_{18}H_{20}O_3$)H] (M+H) 285.1491, measured 285.1499.

**4''-Hydroxy-[1,1':2',1'':3'',1'''-quaterphenyl]-3',6'-dione (6c).**



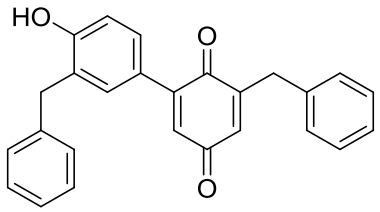

The representative general procedure **B** was followed using **1q** (100 mg). The reaction time is 3 h. Product **8c** was isolated in 63 mg and yield is 58%. Dark brown solid, eluent (25% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):**δ 7.47 (m, 12 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.89 (dd, *J* = 8.0, 4.0 Hz, 2 H), 5.63 (s, 1 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 187.6, 186.5, 154.5, 146.5, 145.7, 136.1, 133.2, 132.7, 131.8, 131.2, 130.5, 130.0, 129.4, 129.3, 129.1, 128.5, 128.5, 128.3, 125.7, 116.2.

**HRMS (ESI):** calc. for [($C_{24}H_{16}O_3$)H] (M+H) 353.1178, measured 353.1184.

**3,3'-Dibenzyl-4'-hydroxy-[1,1'-biphenyl]-2,5-dione (6d).**



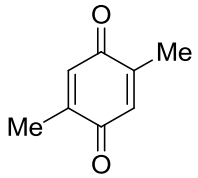

The representative general procedure **A** was followed using **1r** (100 mg). The reaction time is 3 h. Product **2a** was isolated in 49 mg and yield is 49%. Dark brown semisolid, eluent (20% ethyl acetate in hexanes).

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.34 – 7.25 (m, 7 H), 7.23 – 7.18 (m, 5 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 6.69 (d, *J* = 4.0 Hz, 1 H), 6.38 (m, 1 H), 5.23 (s, 1 H), 4.00 (s, 2H), 3.78 (d, *J* = 4.0 Hz, 2 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 187.80, 186.9, 155.8, 148.9, 145.6, 139.3, 136.7, 133.2, 132.1, 131.1, 129.4, 129.3, 128.8, 128.7, 128.7, 127.4, 127.0, 126.6, 125.6, 115.8, 36.3, 35.7.

**HRMS (ESI):** calc. for [($C_{26}H_{20}O_3$)H] (M+H) 381.1491, measured 381.1489.

**2,5-Dimethylcyclohexa-2,5-diene-1,4-dione (6e).**



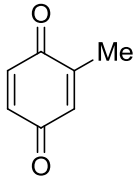

The representative general procedure **B** was followed using **1s** (100 mg). The reaction time is 3 h. Product **8d** was isolated in 41 mg and yield is 73%. Colourless solid, eluent (10% ethyl acetate in hexanes).

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 6.57 (q, *J* = 4.0 Hz, 2 H), 2.01 (d, *J* = 4.0 Hz, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 188.0, 145.8, 133.4, 15.5.

**HRMS (ESI):** calc. for [($C_8H_8O_2$)H] (M+H) 137.0603, measured 137.0600.

**2-Methylcyclohexa-2,5-diene-1,4-dione (6f).**



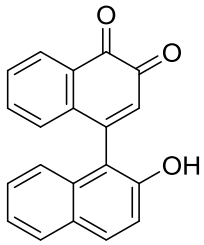

The representative general procedure **B** was followed using **1t** (100 mg). The reaction time is 3 h. Product **8e** was isolated in 44 mg and yield is 89%. Yellow solid, eluent (5% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):**δ 6.72 (d, *J* = 8.0 Hz, 1H), 6.67 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.57 (m, 1H), 2.01 (d, *J* = 4.0 Hz, 3H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 187.7, 187.5, 145.8, 136.5, 136.4, 133.3, 15.8.

**HRMS (ESI):** calc. for [($C_7H_6O_2$)H] (M+H) 123.0446, measured 123.0444.

**2'-Hydroxy-[1,1'-binaphthalene]-3,4-dione (6g).**



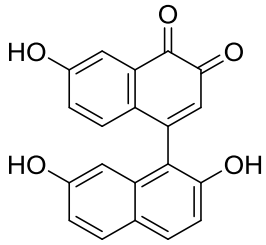

The representative general procedure **B** was followed using **1j** (100 mg). The reaction time is 3 h. Product **8g** was isolated in 84 mg and yield is 80%. Dark brown solid, eluent (25% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz)**δ 8.16 (d, *J* = 8.0 Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 7.38 – 7.29 (m, 2 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.41 (s, 1 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** 181.8, 181.0, 155.5, 152.9, 137.2, 136.5, 134.0, 133.2, 131.9, 131.7, 131.3, 130.5, 130.1, 129.8, 129.3, 128.2, 124.9, 124.5, 118.9, 117.1.

**HRMS (ESI):** calc. for [($C_{20}H_{12}O_3$)H] (M+H) 301.0865, measured 301.0871.

**2',6,7'-Trihydroxy-[1,1'-binaphthalene]-3,4-dione (6h).**



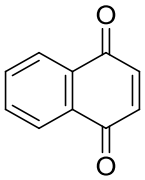

The representative general procedure **A** was followed using **1l** (100 mg). The reaction time is 3 h. Product **8h** was isolated in 76 mg and yield is 73%. Dark brown solid, eluent (25% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz)** δ 7.76 (d, *J* = 8.0 Hz, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 4.0 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 6.88 (m, 3 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 6.24 (s, 1 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 182.4, 181.4, 161.6, 157.6, 157.2, 153.0, 135.5, 134.7, 132.5, 131.5, 131.0, 128.79, 127.8, 124.7, 122.6, 117.5, 116.6, 116.2, 115.7, 106.7.

**HRMS (ESI):** calc. for [($C_{20}H_{12}O_5$)H] (M+H) 333.0763, measured 333.0759.

**Naphthalene-1,4-dione (6i).**



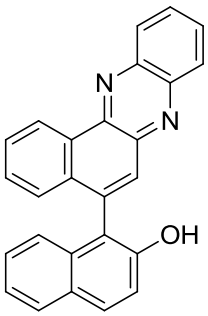
The representative general procedure **A** was followed using **1u** (100 mg). The reaction time is 3 h. Product **8i** was isolated in 38 mg and yield is 83%. Ash colour solid, eluent (5% ethyl acetate in hexanes).

**$^1$H NMR ($CDCl_3$, 400 MHz):**δ 7.92 (d, *J* = 8.0 Hz, 2H), 6.98 (s, 1H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):**δ 185.0, 138.6, 133.9, 131.8, 126.3.

**HRMS (ESI):** calc. for [($C_{10}H_6O_2$)H] (M+H) 159.0446, measured 159.0448.

**1-(Benzo[a]phenazin-5-yl)naphthalen-2-ol (8).**



The representative general procedure **C** was followed using **6g** (100 mg). The reaction time is 12 h. Product **8** was isolated in 97 mg and yield is 78%. Yellow solid, mp.229-231 °C eluent (10% ethyl acetate in hexanes).

**IR (ATR) ṽ (cm$^{-1}$):** 3412, 3050, 1707, 1434, 1363, 750, 700

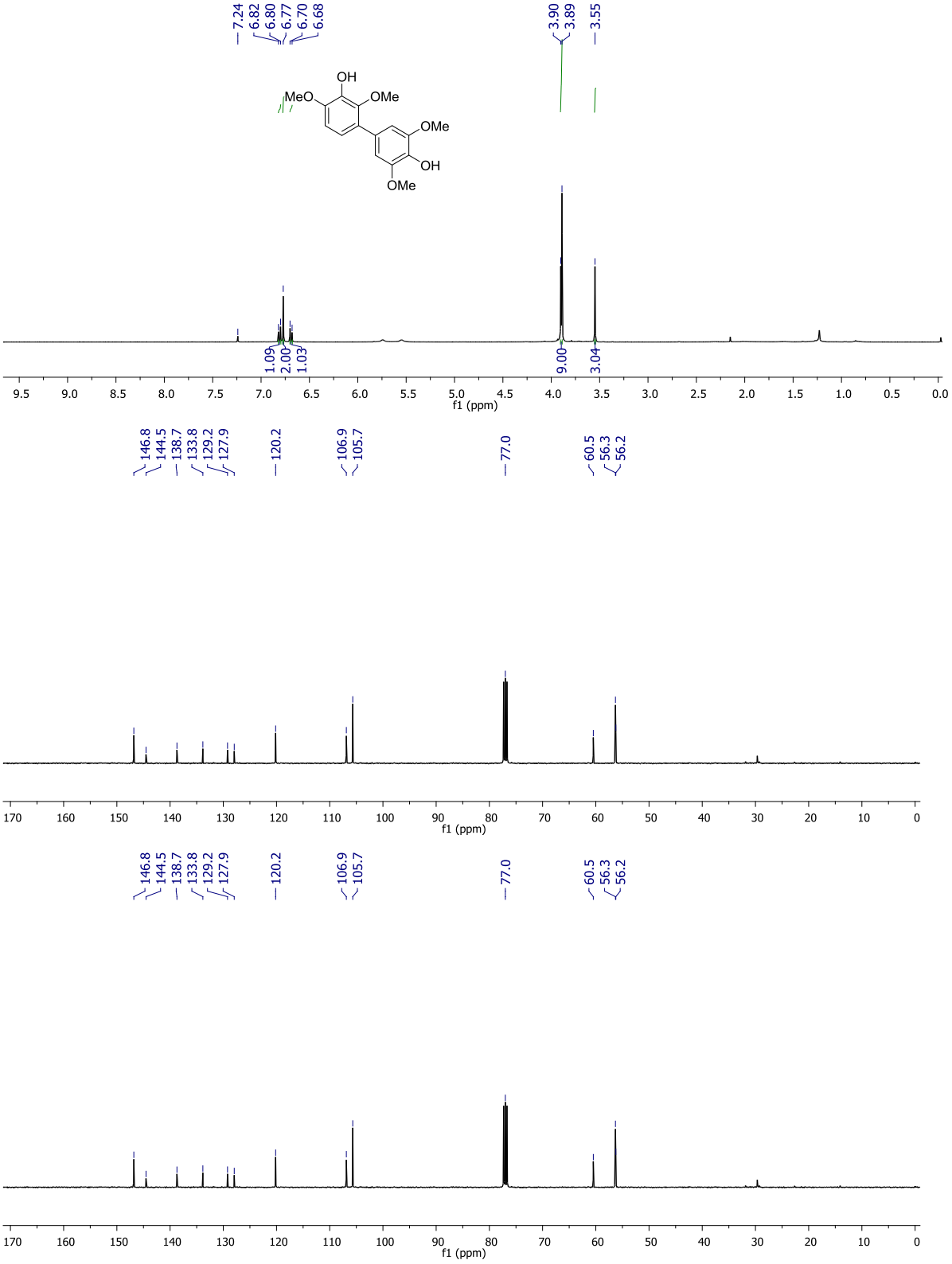
**$^1$H NMR (**DMSO-D6**, 400 MHz)**δ 9.83 (s, 1 H), 9.44 (d, *J* = 8.0 Hz, 1 H), 8.37 (dd, *J* = 8.0, 4.0 Hz, 2 H), 8.00 (m, 3 H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H).

**$^{13}$C NMR (**DMSO-D6**, 100 MHz):**δ 152.7, 143.1, 142.6, 141.9, 141.4, 140.6, 133.7, 133.4, 130.84, 130.8, 130.7, 130.3, 130.0, 129.5, 129.0, 129.0, 128.3, 128.0, 126.8, 126.8, 125.1, 124.1, 123.0, 118.5, 117.4.

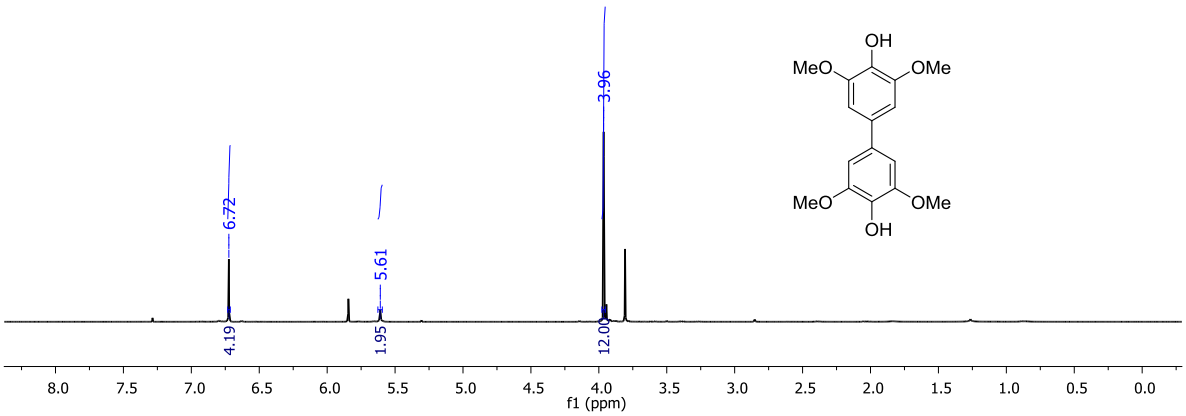
**HRMS (ESI):** calc. for [($C_{26}H_{16}O$)H] (M+H) 373.1341, measured 373.1340.

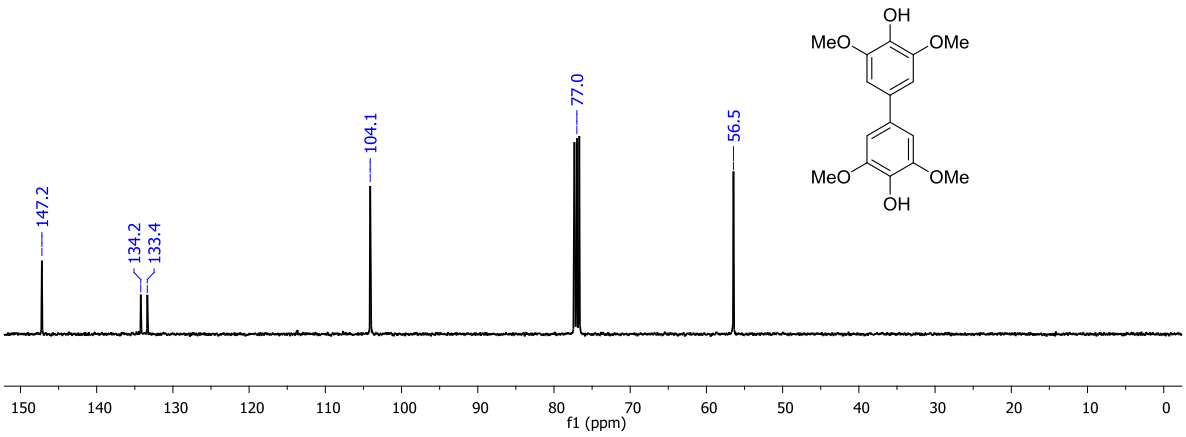
## 3.11: Spectral Copies of Selected Compounds

Spectral data of compound **2a**.

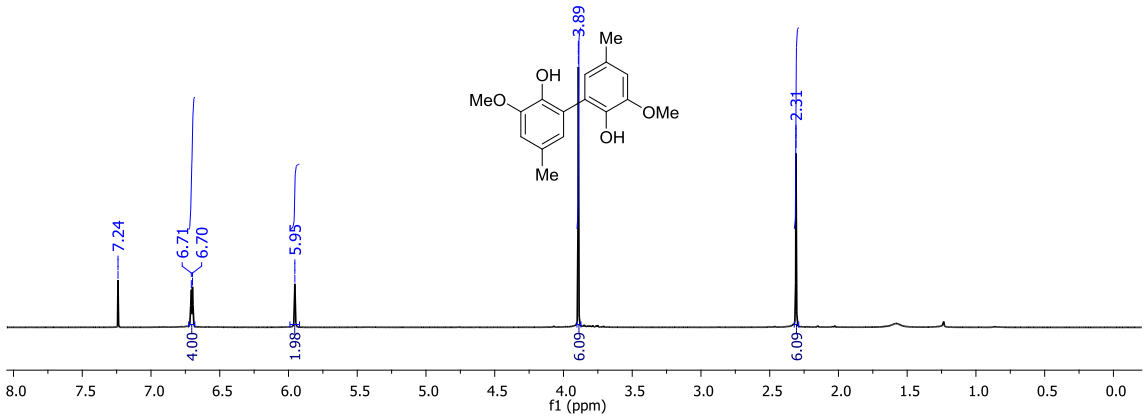


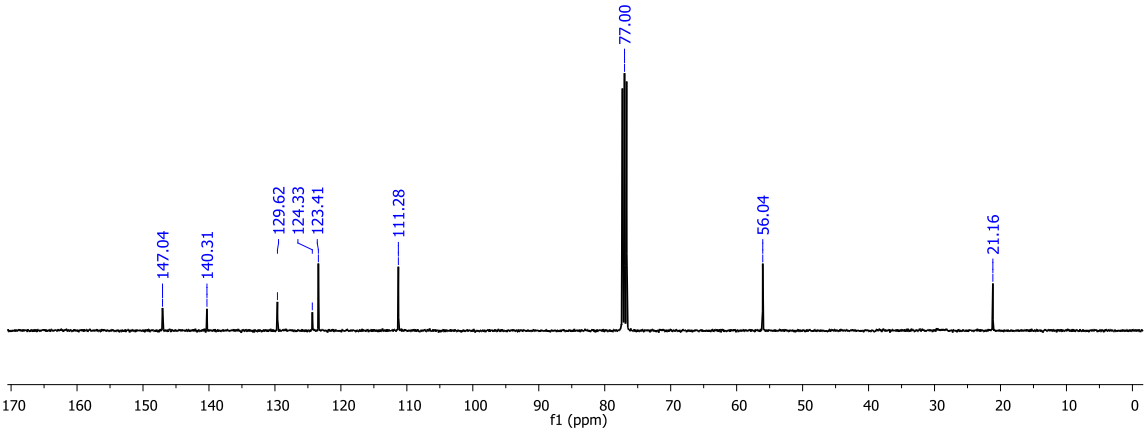
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **4b-5b** (**5b** was minor).

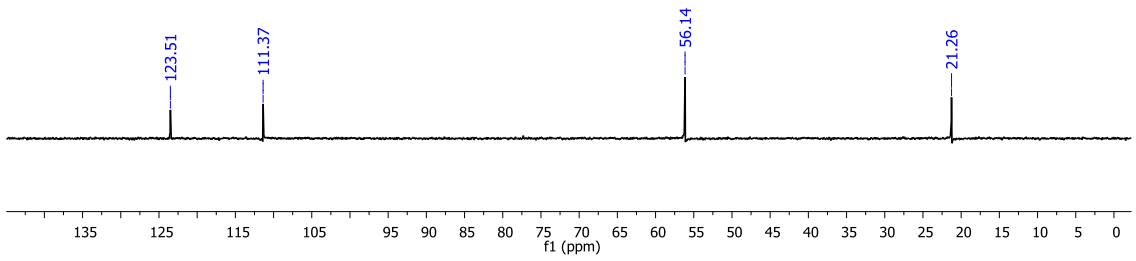


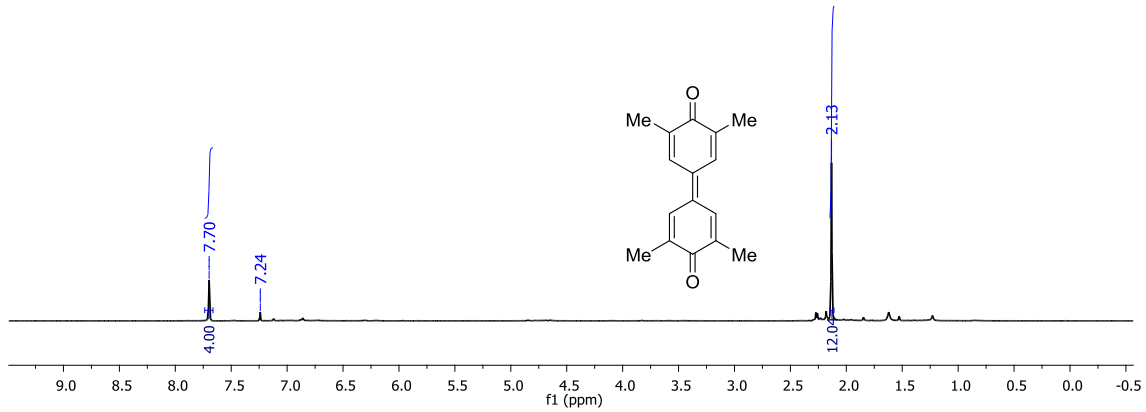
Spectral data of compound **2b'**.

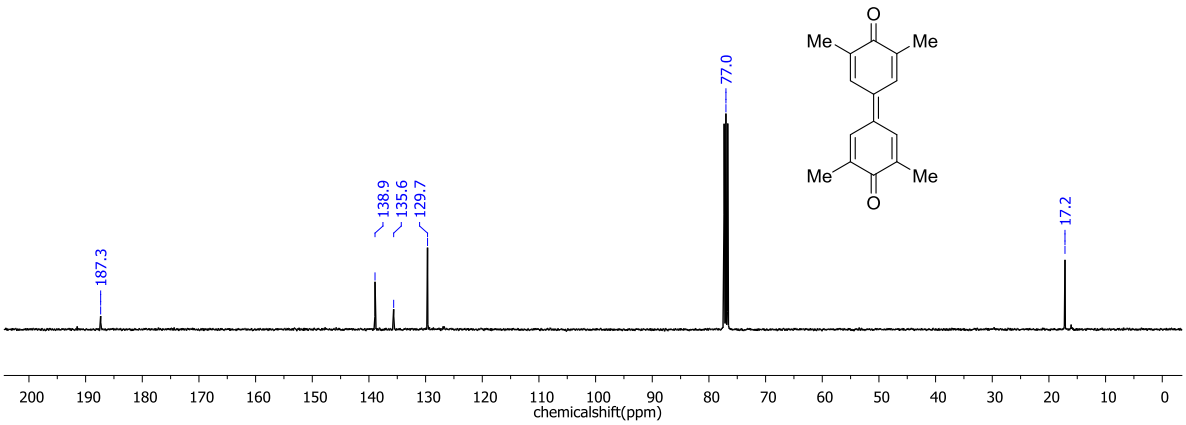


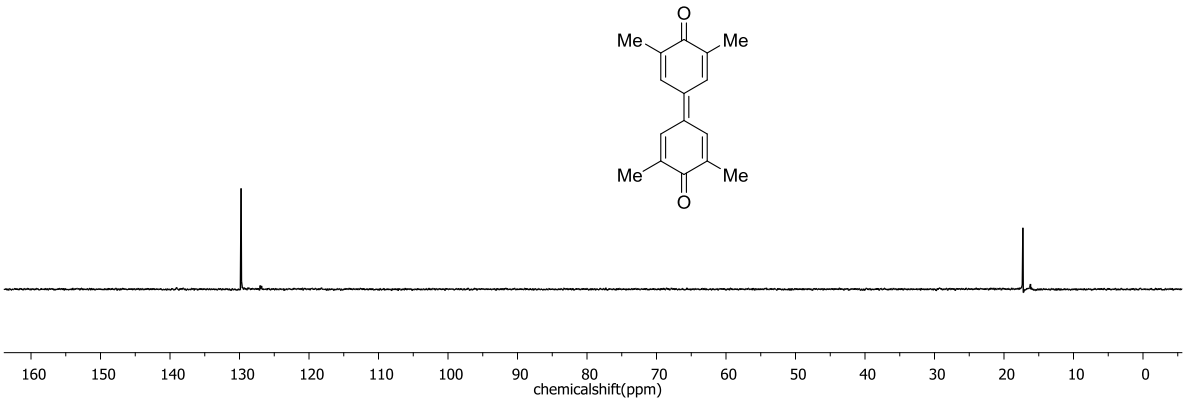



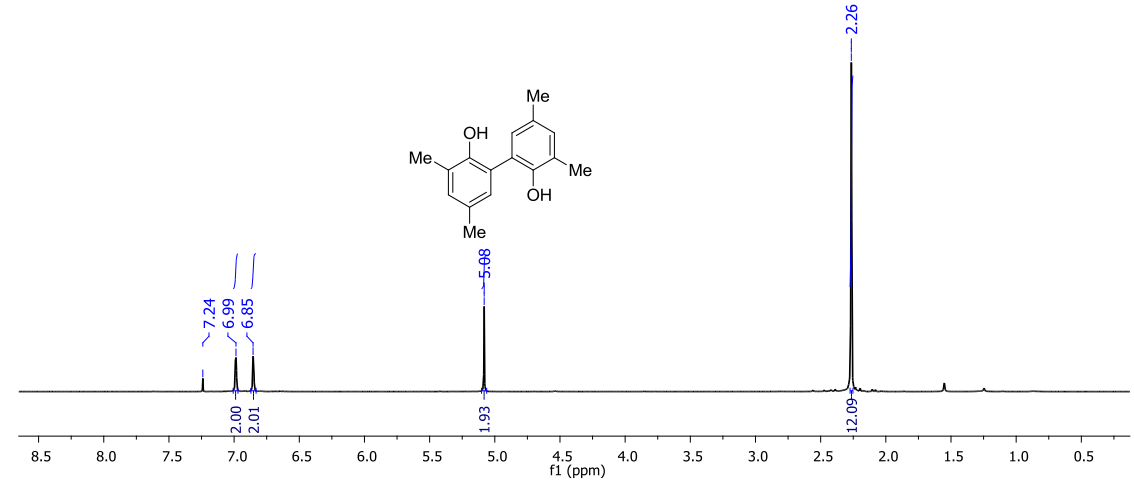
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **4a-5a** (isomer).

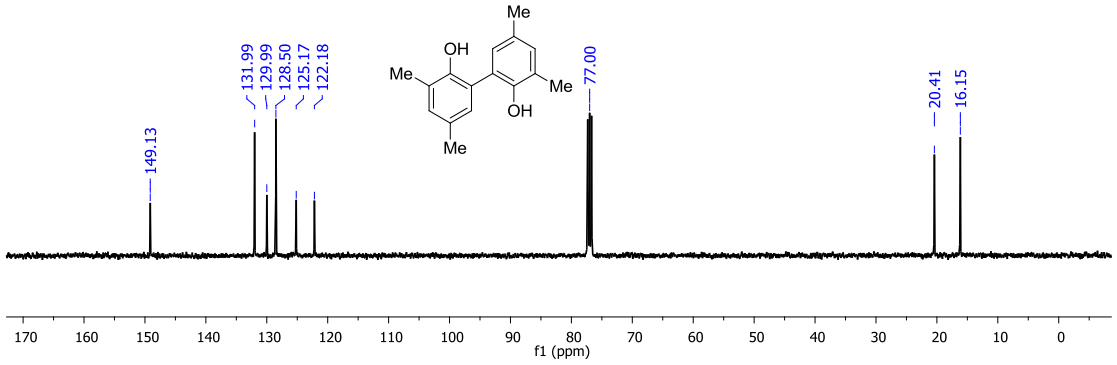


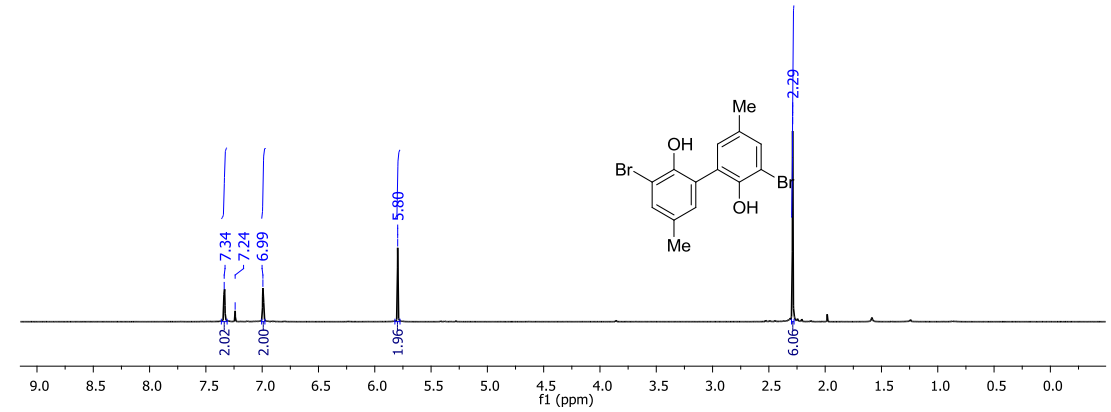



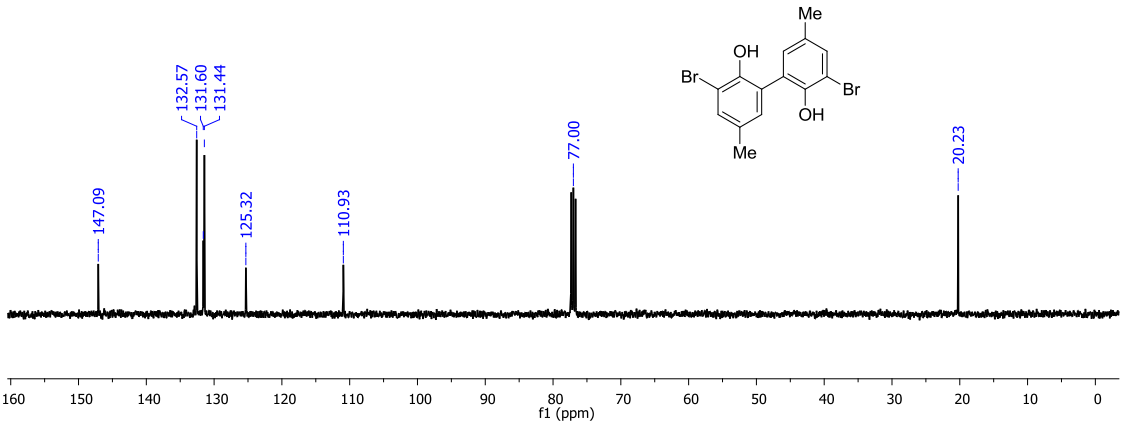
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **2c**.

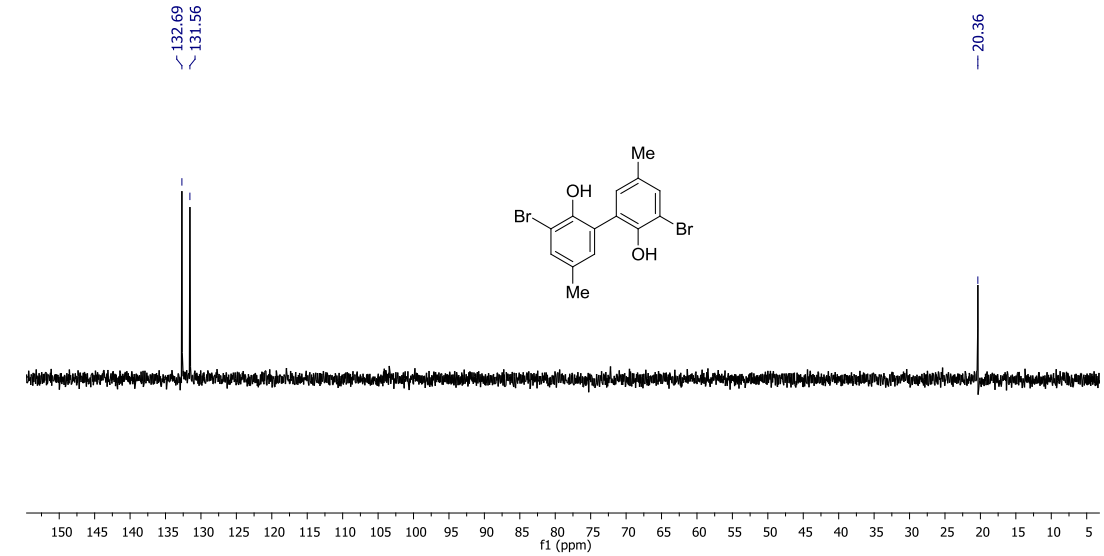


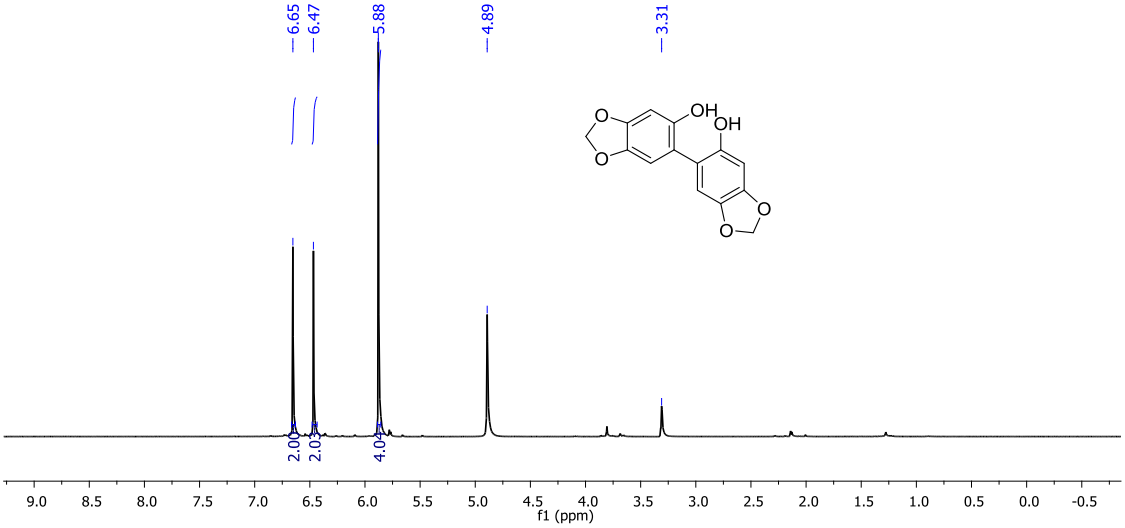
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **2d**.

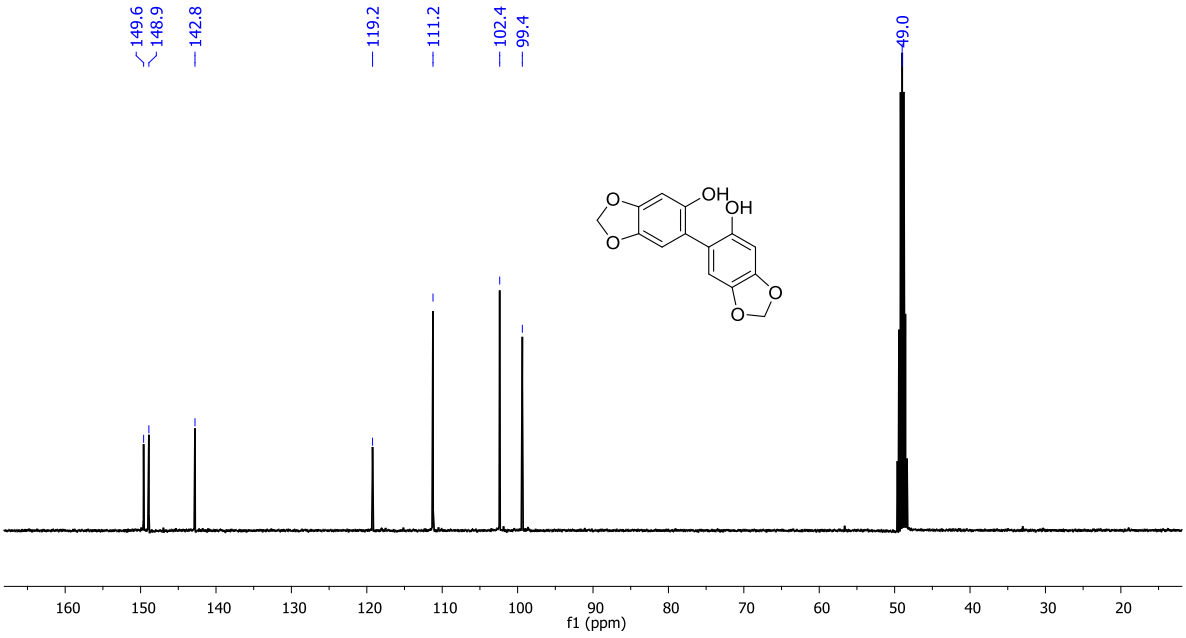


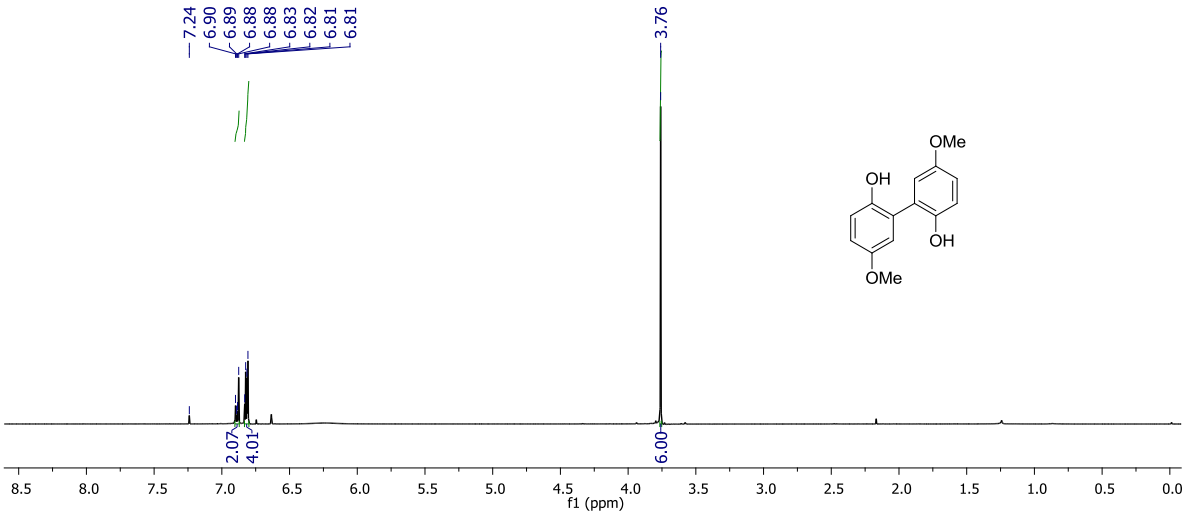



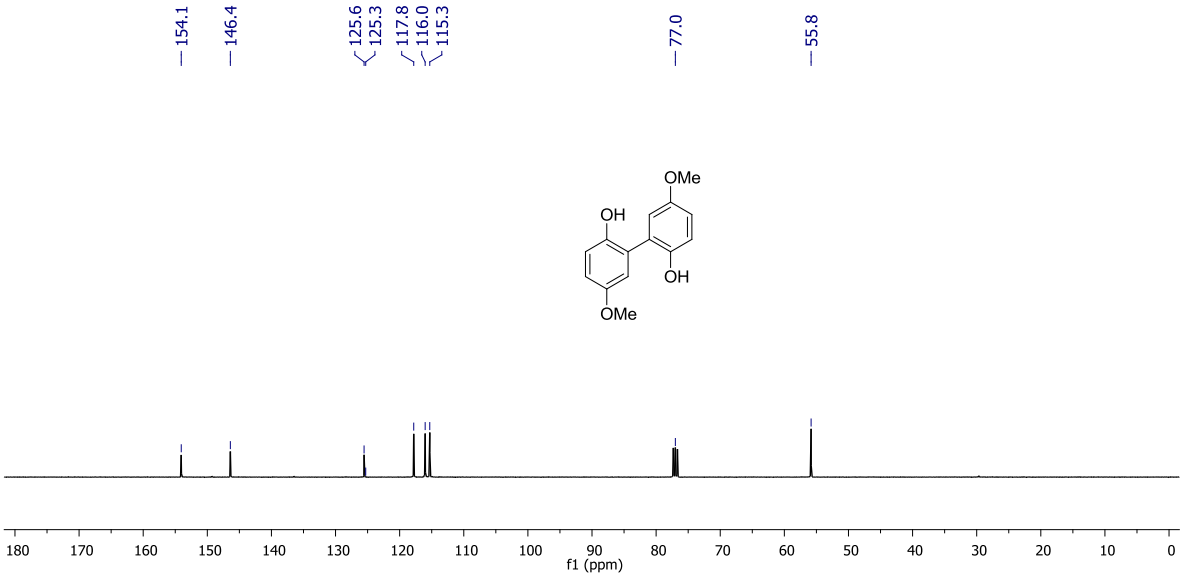
## $^{1}H$ and $^{13}C$ NMR Spectra of Compound 2e.

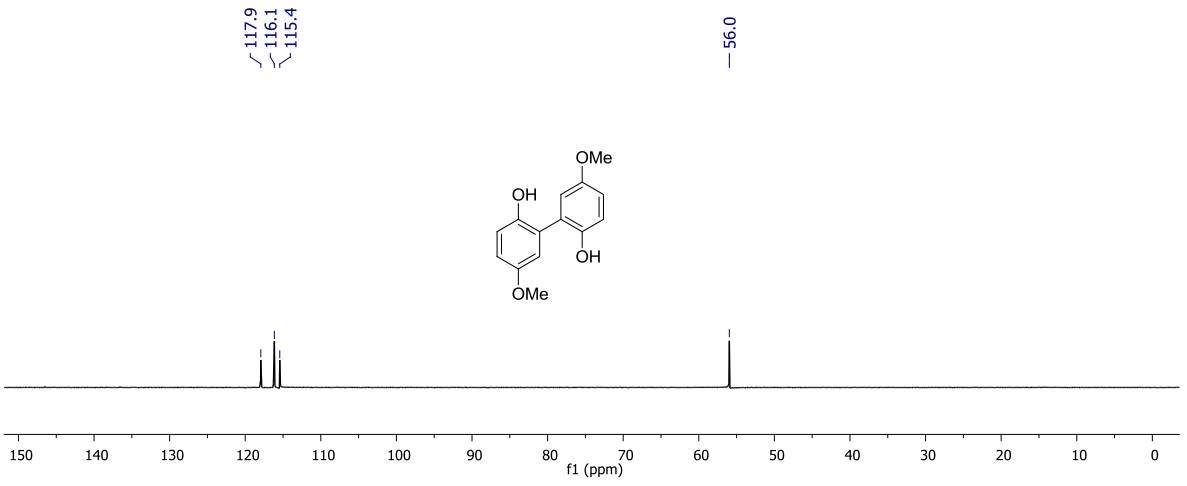


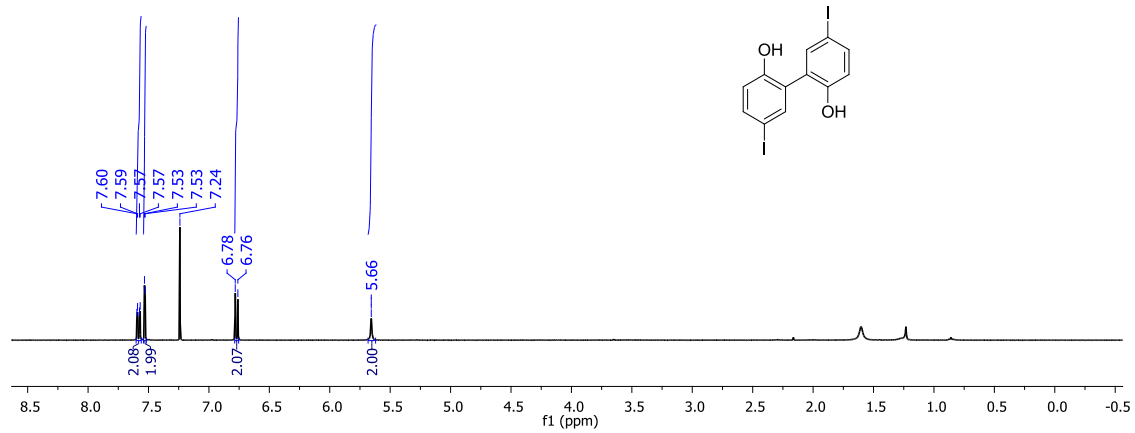
## $^{1}H$ and $^{13}C$ NMR Spectra of Compound 2f.

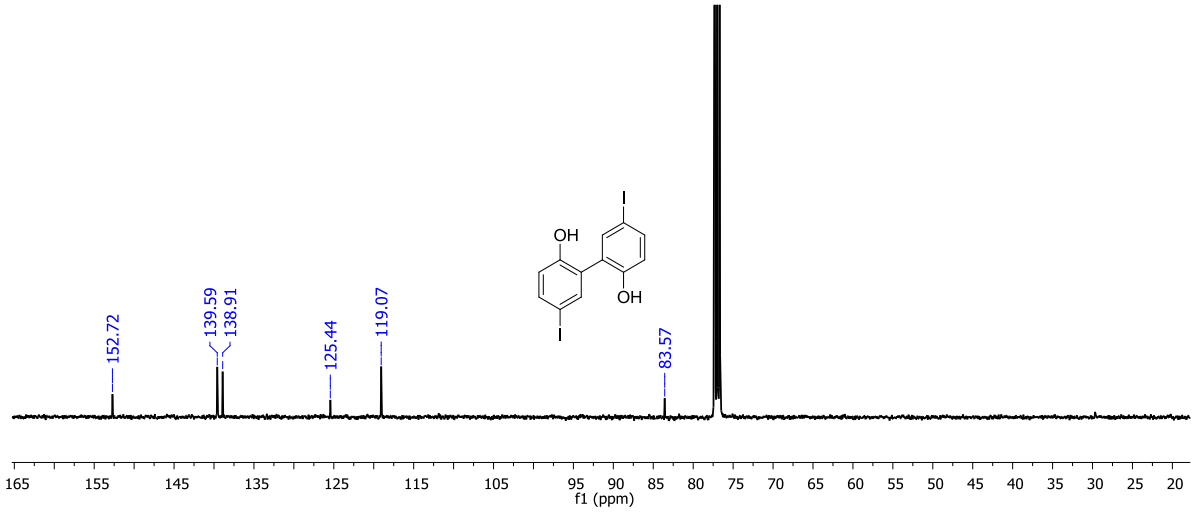


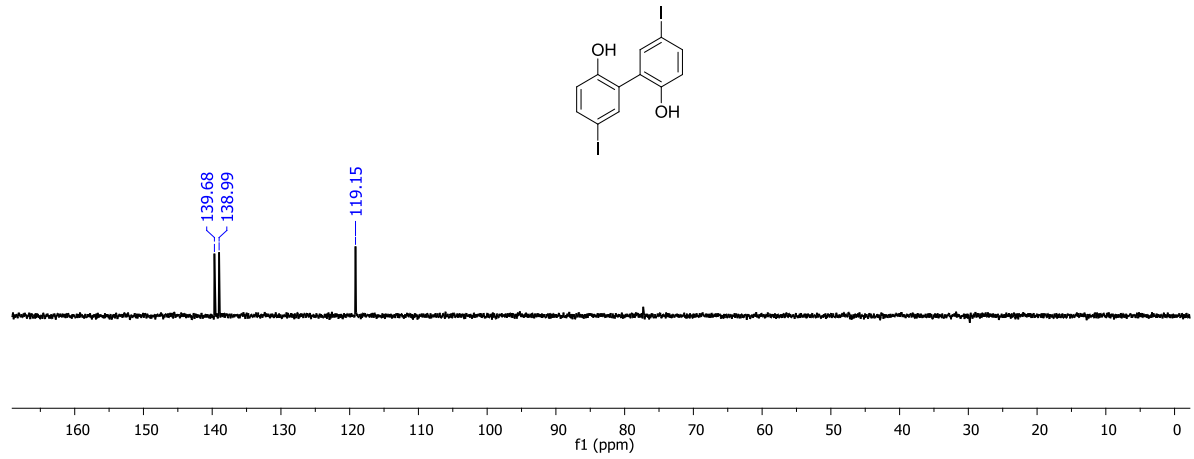



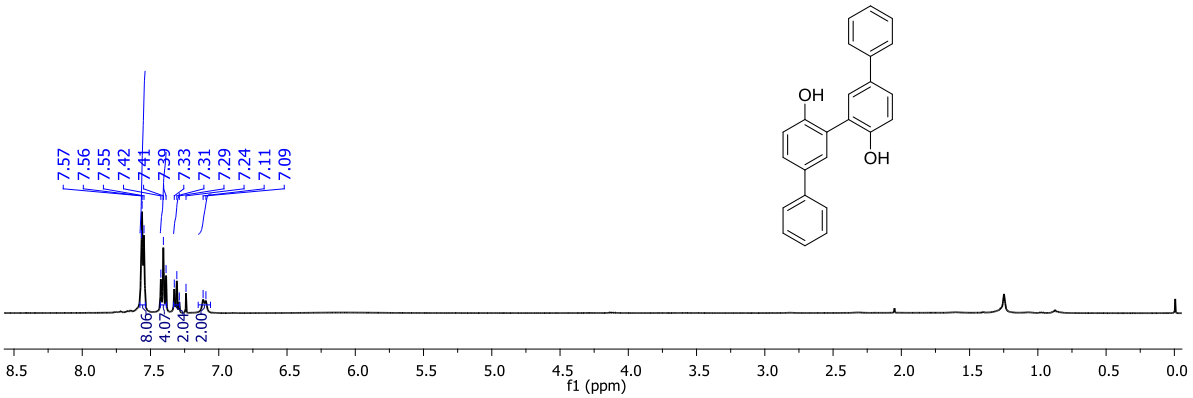
## $^{1}H$ and $^{13}C$ NMR Spectra of Compound 2g.

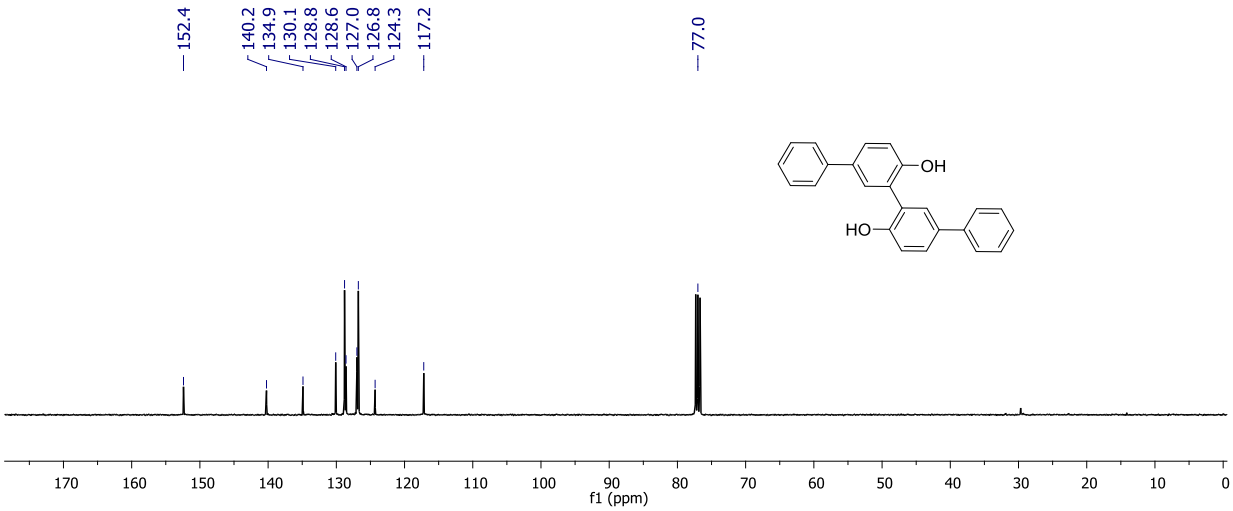


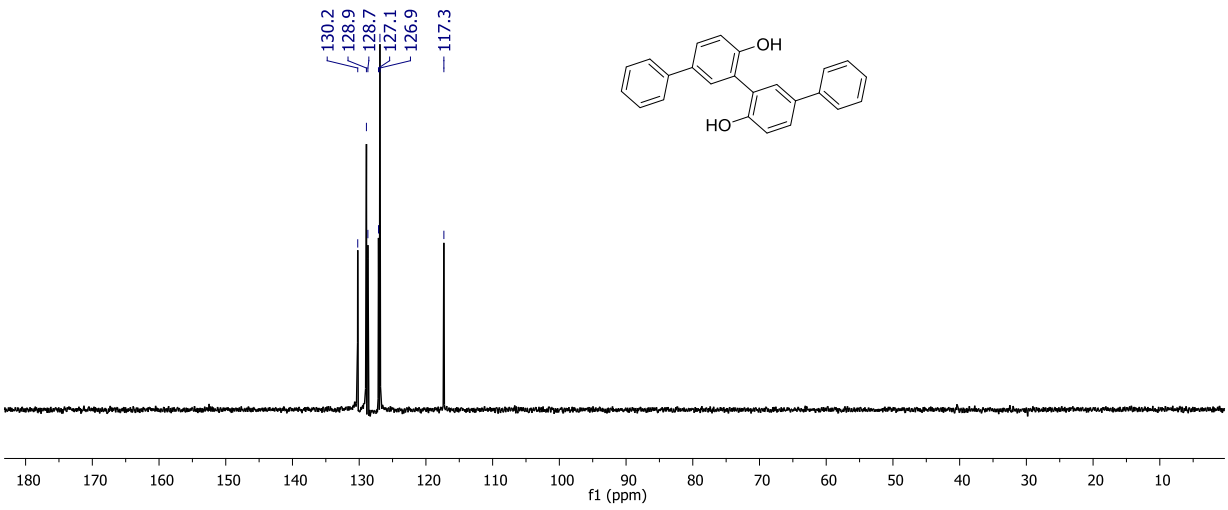



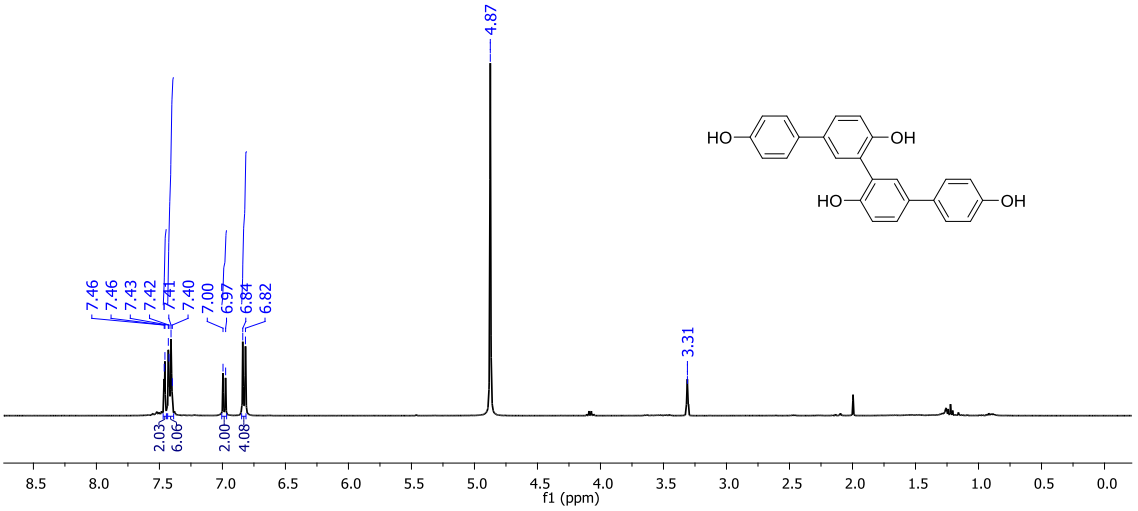
## $^{1}H$ and $^{13}C$ NMR Spectra of Compound 2h.

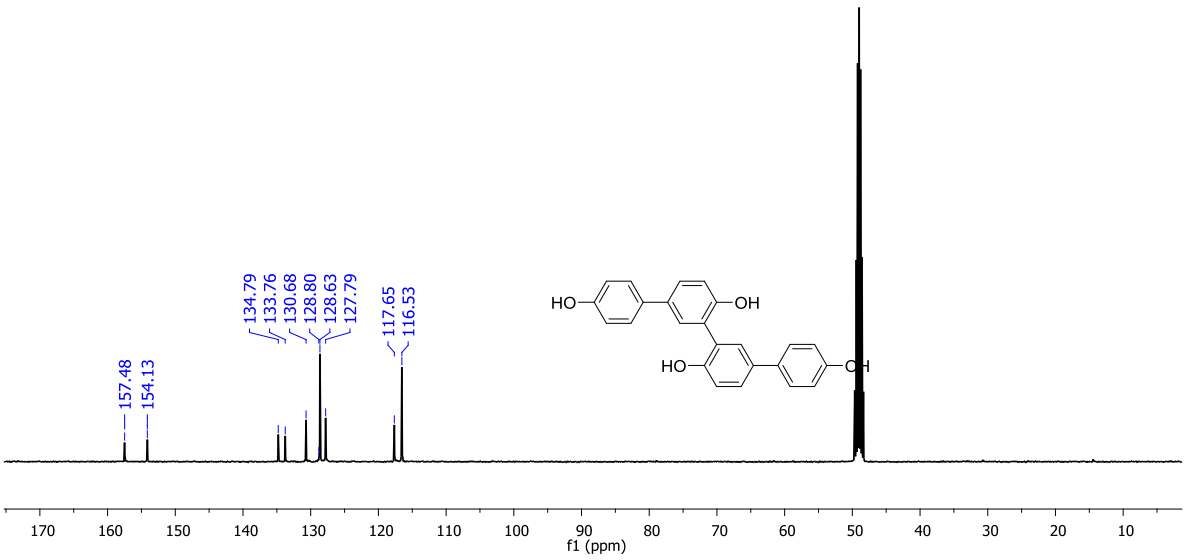


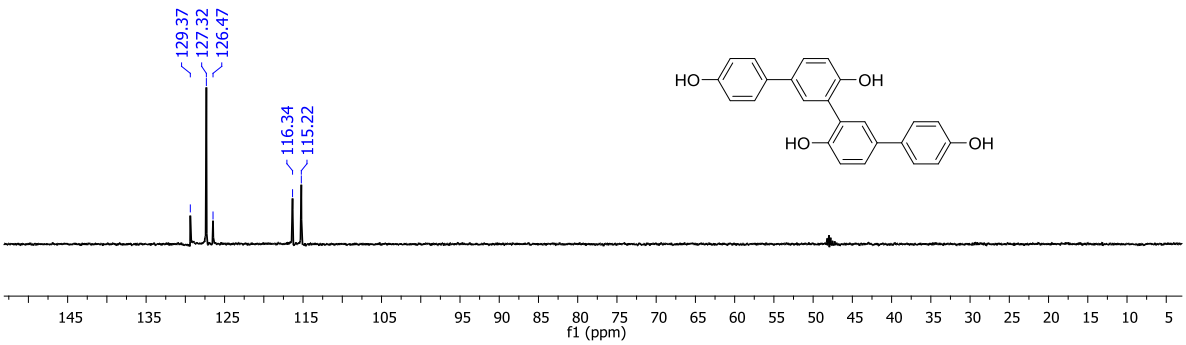



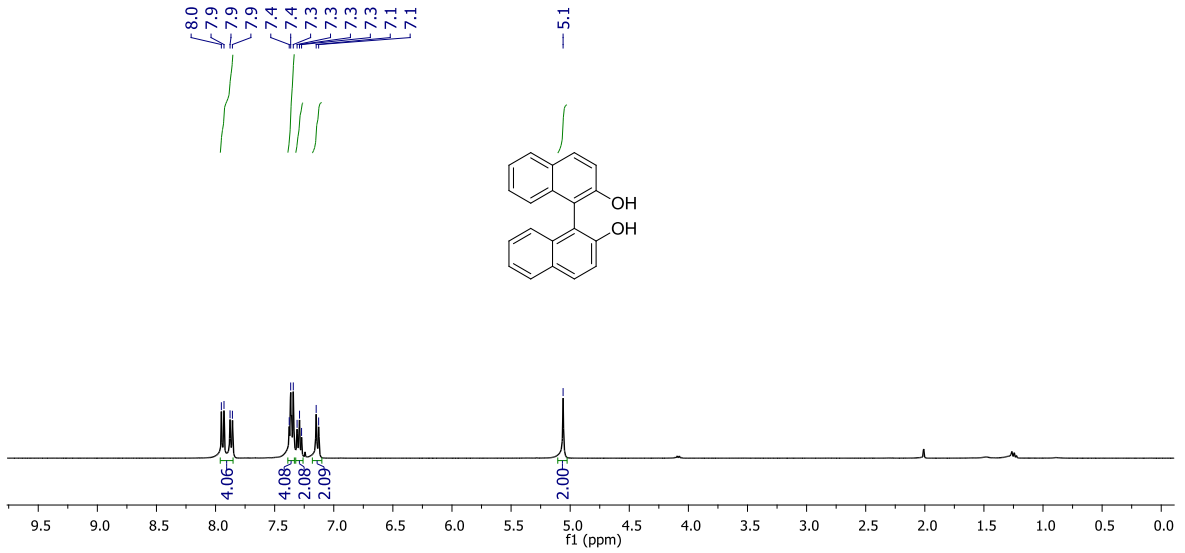
## $^{1}H$ and $^{13}C$ NMR Spectra of Compound 2i.

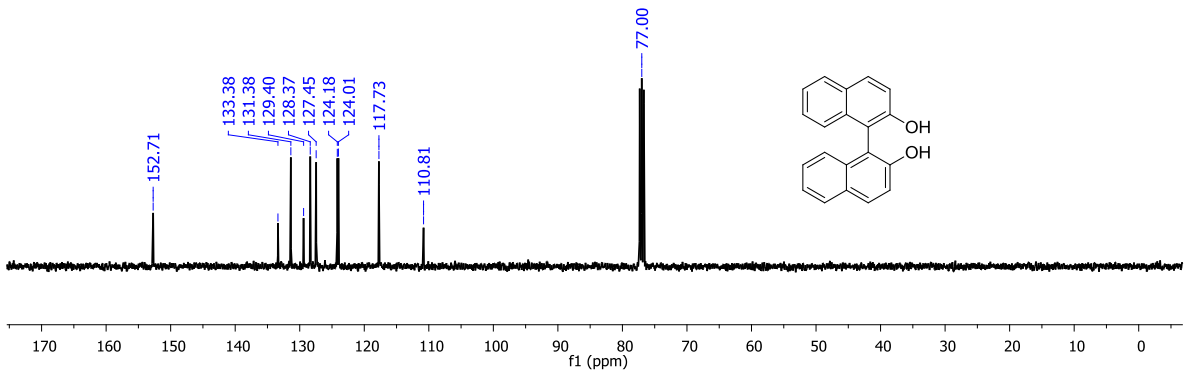


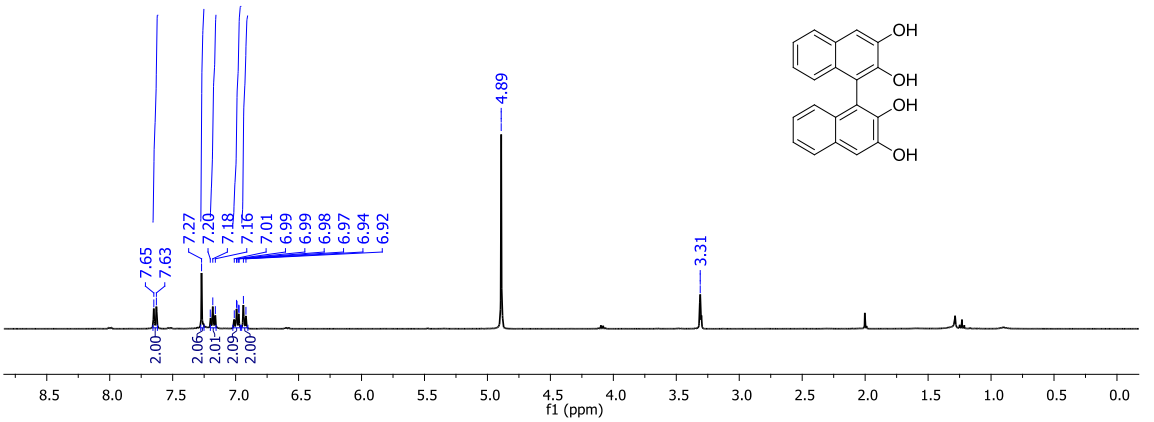



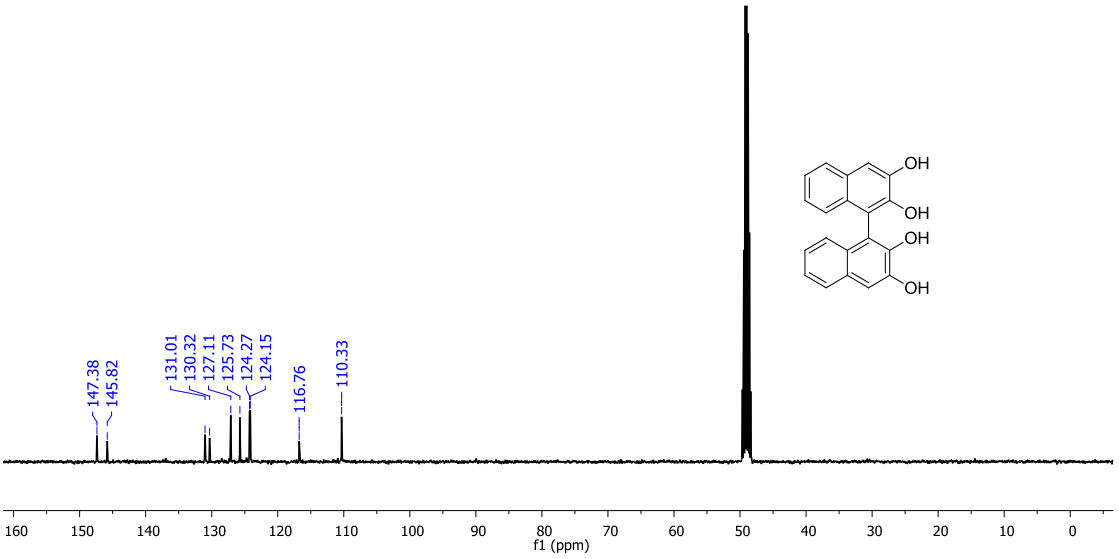
## $^{1}H$ and $^{13}C$ NMR Spectra of Compound 2j.

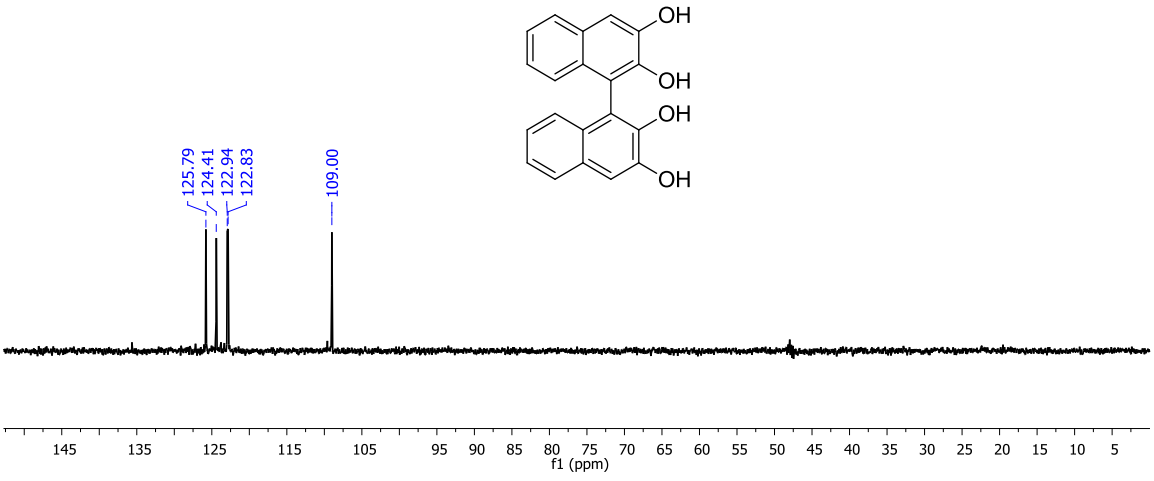


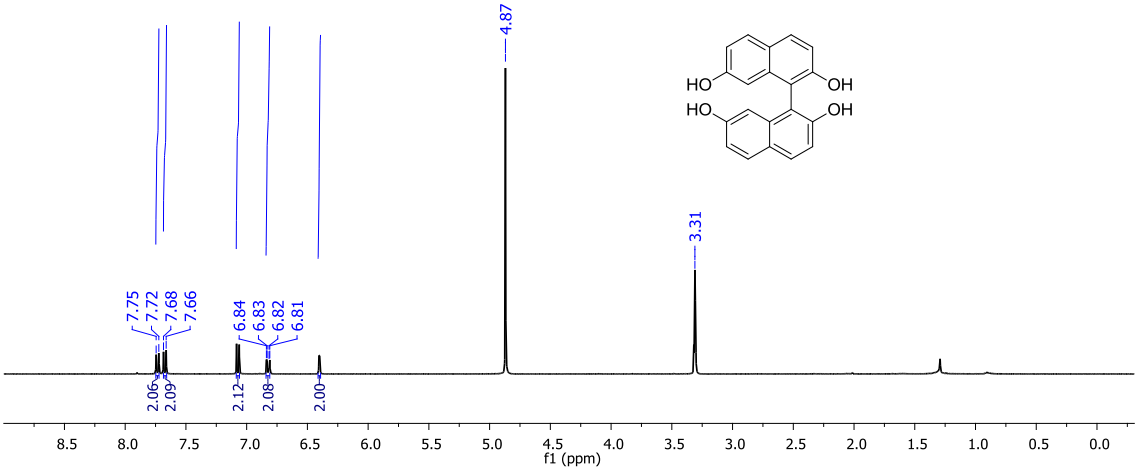
## $^{1}H$ and $^{13}C$ NMR Spectra of Compound 2k.

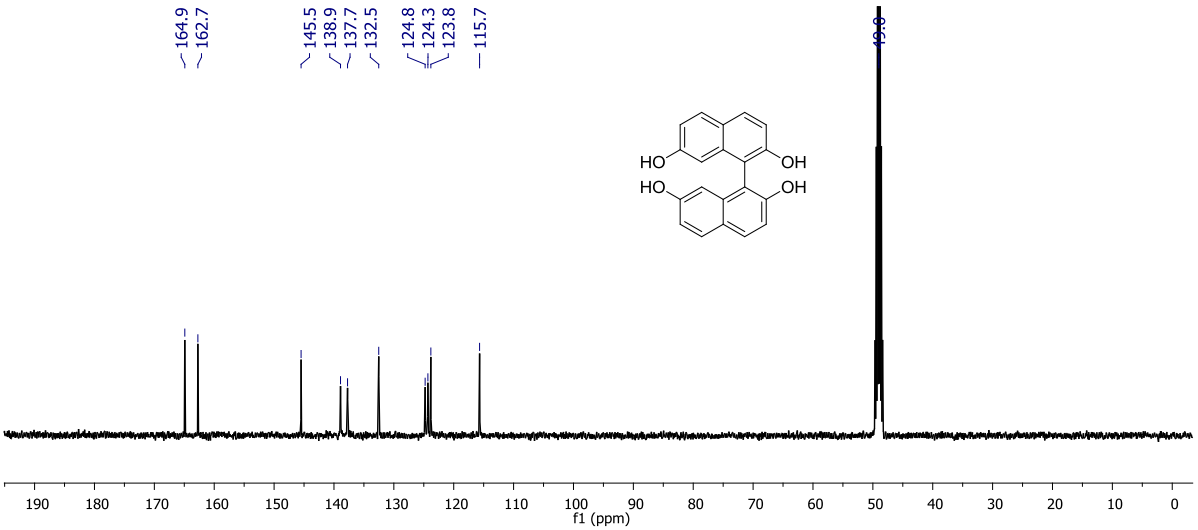


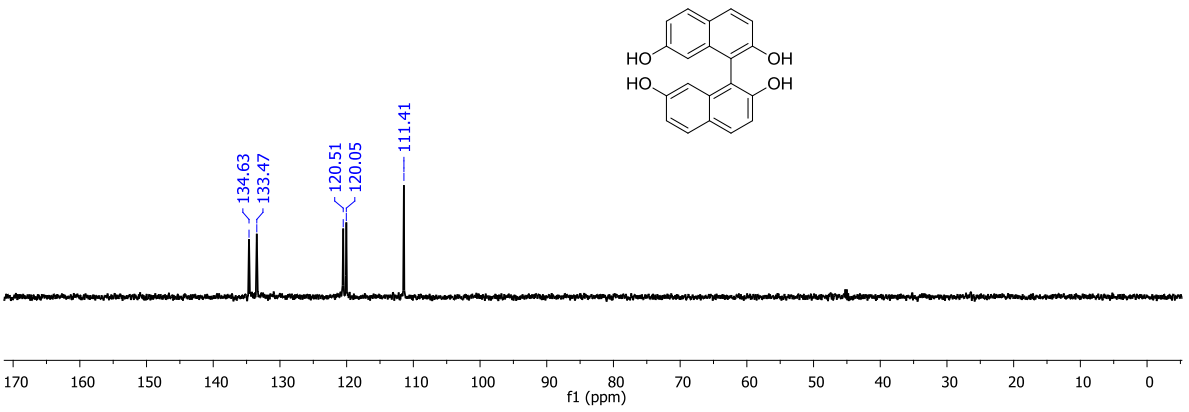



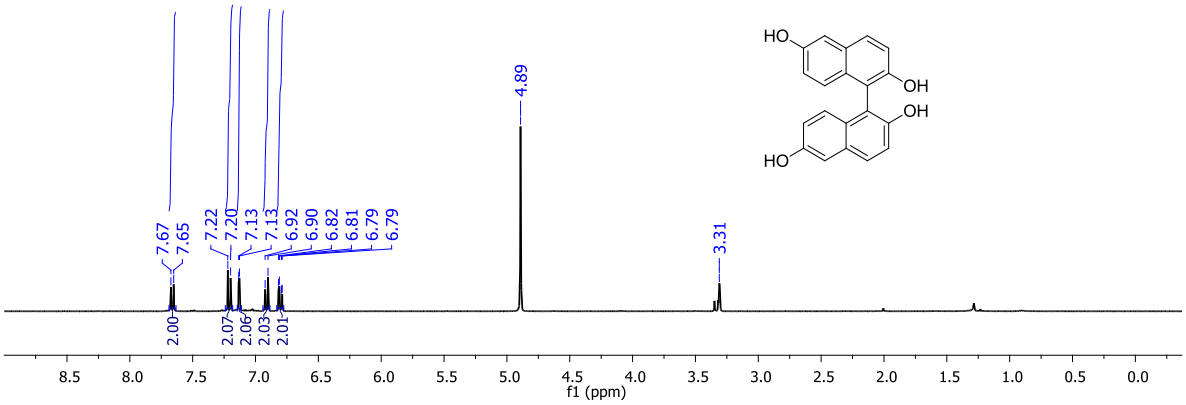
## $^{1}H$ and $^{13}C$ NMR Spectra of Compound 2l.

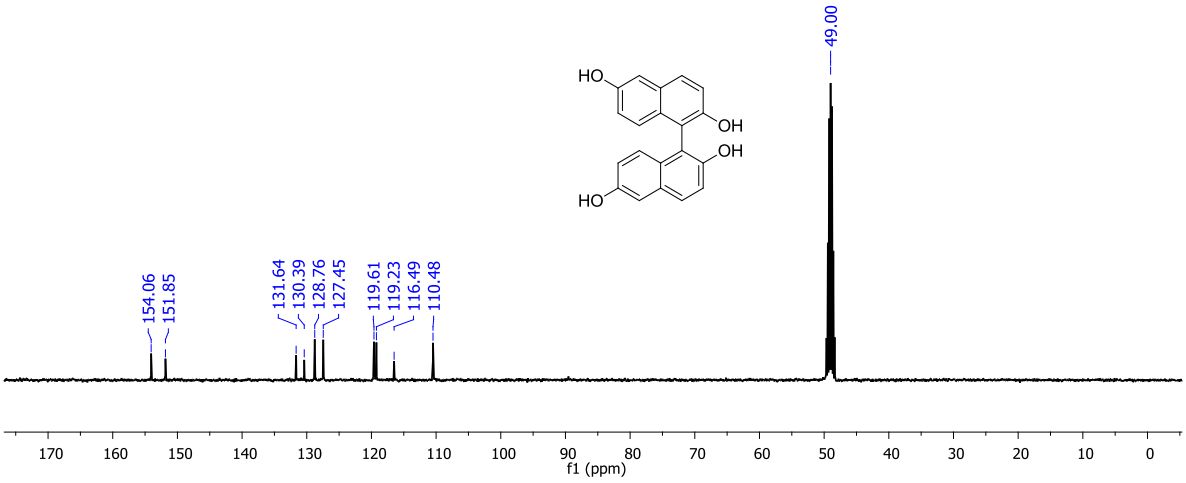


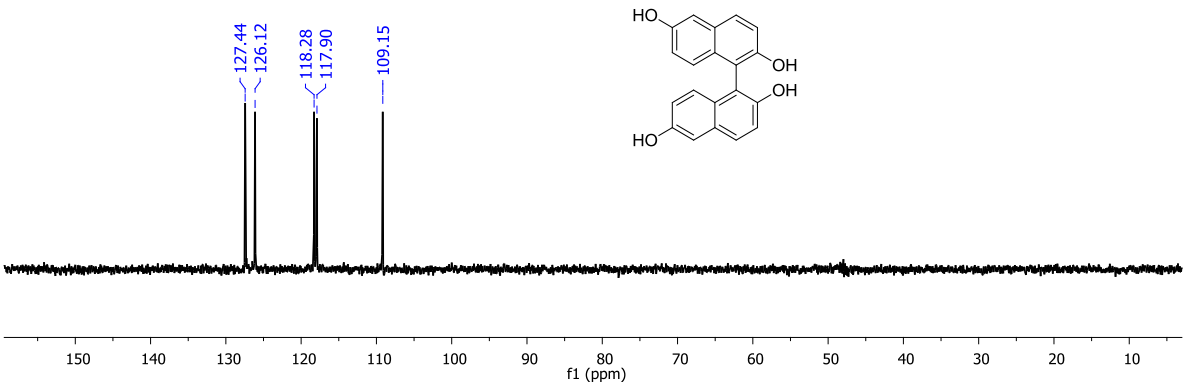



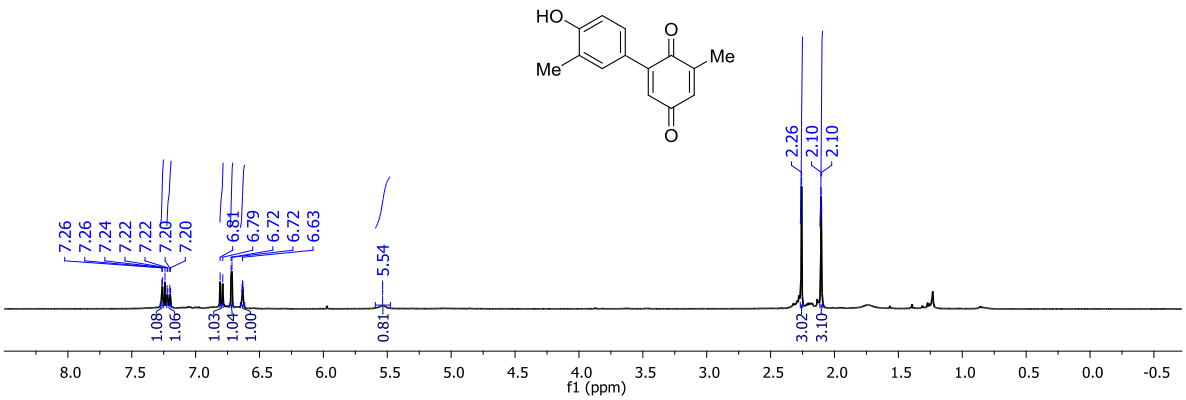
## $^{1}$H and $^{13}$C NMR Spectra of Compound 2m.

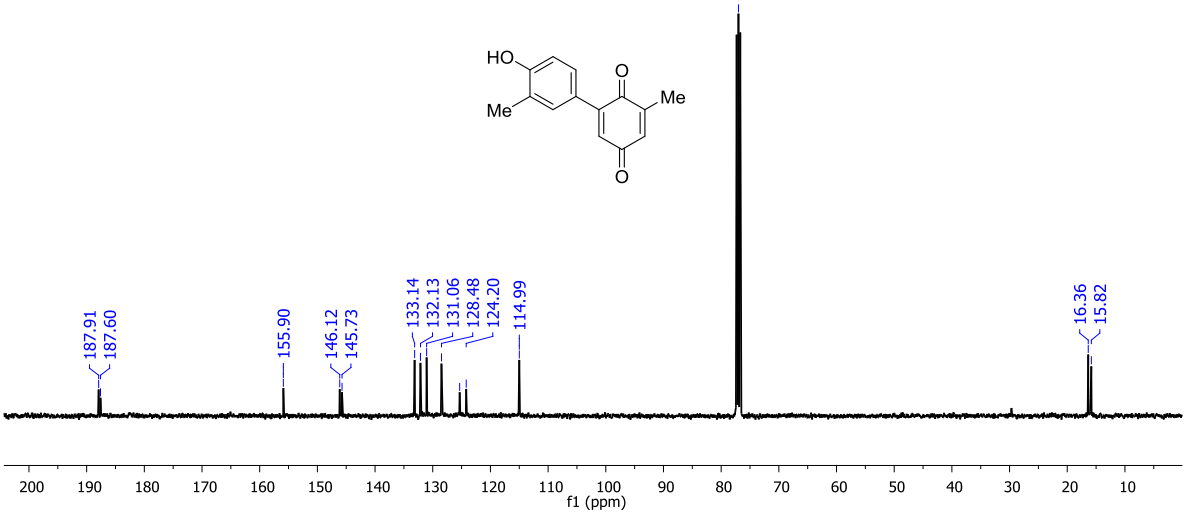


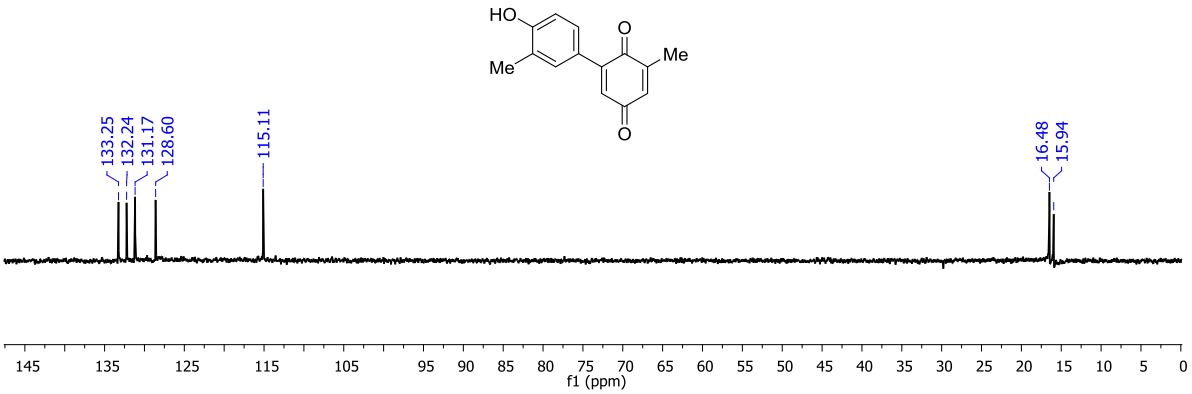



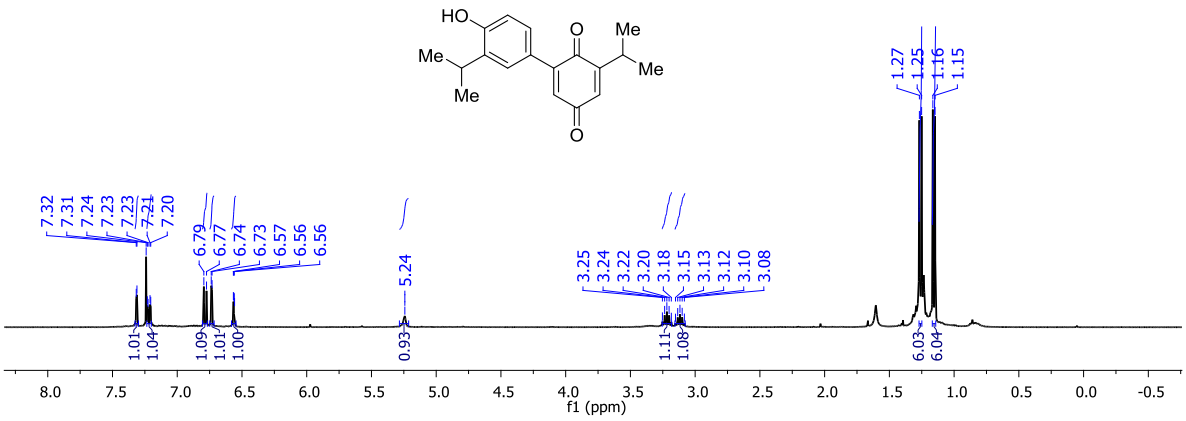
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **6a**.

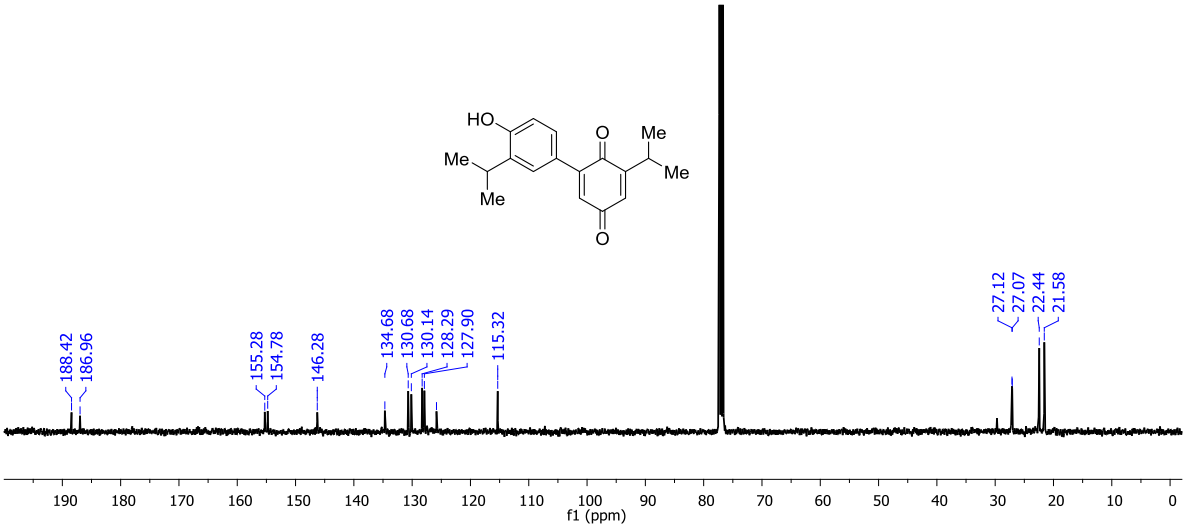


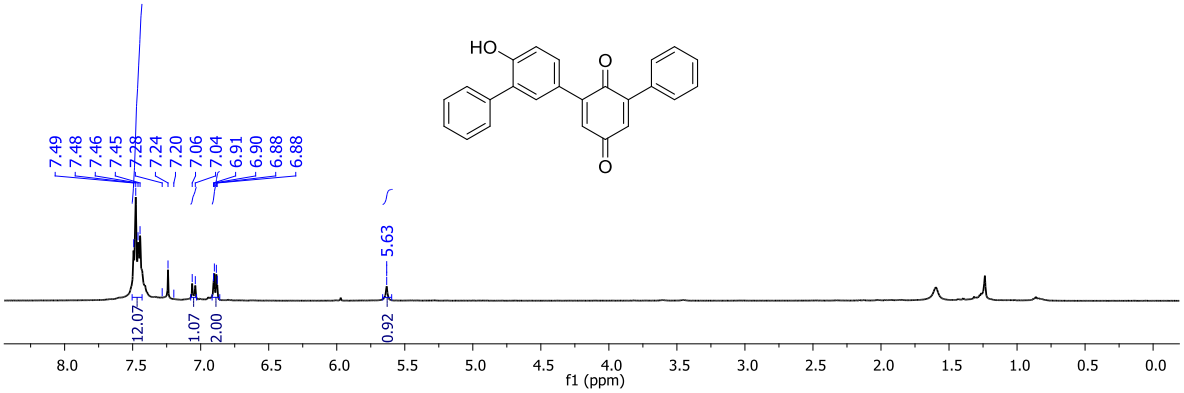



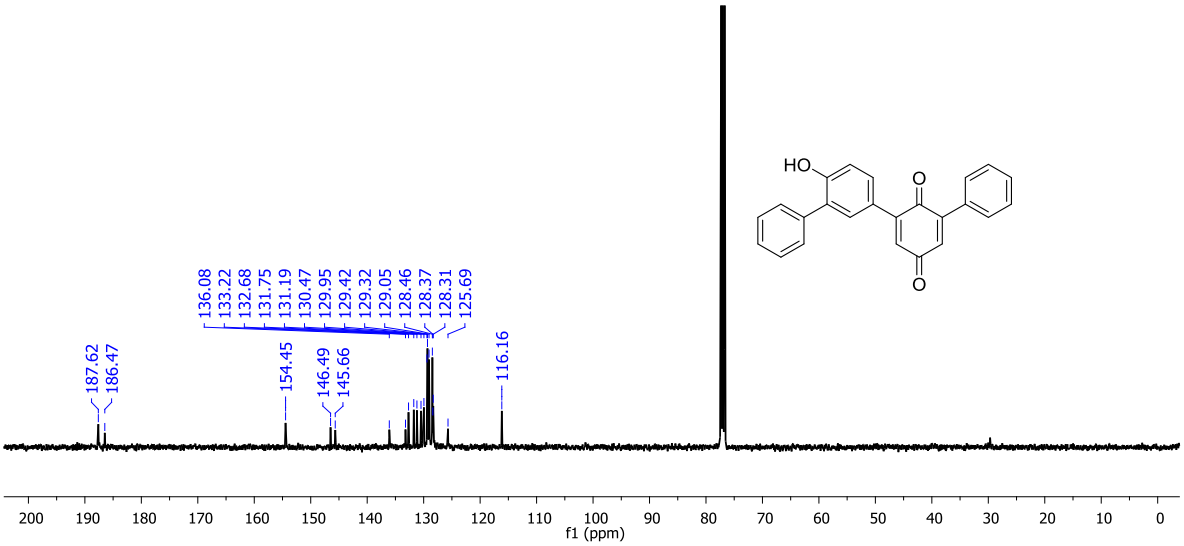
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **6b**.

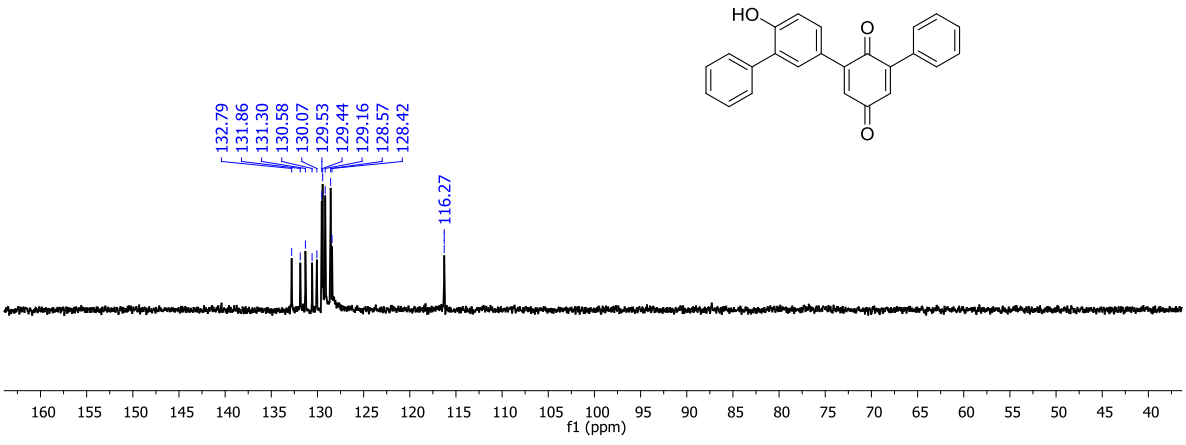


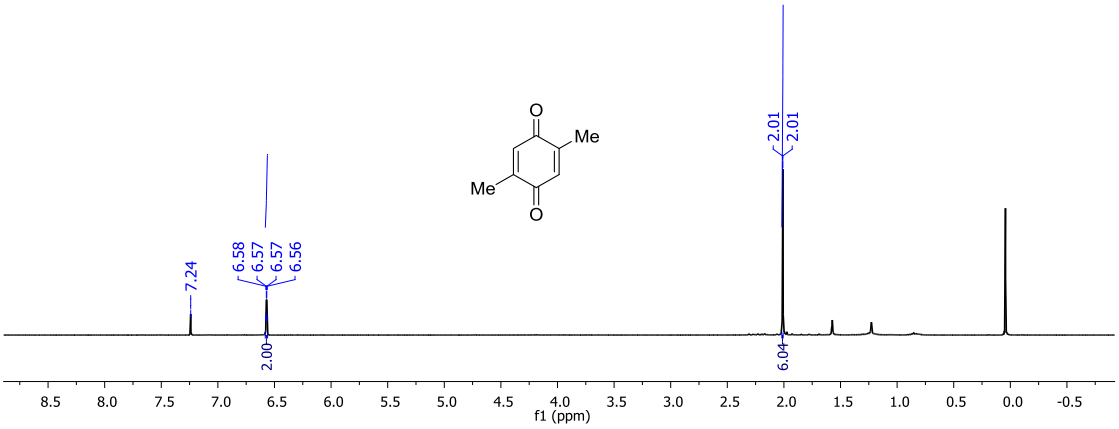
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **6c**.

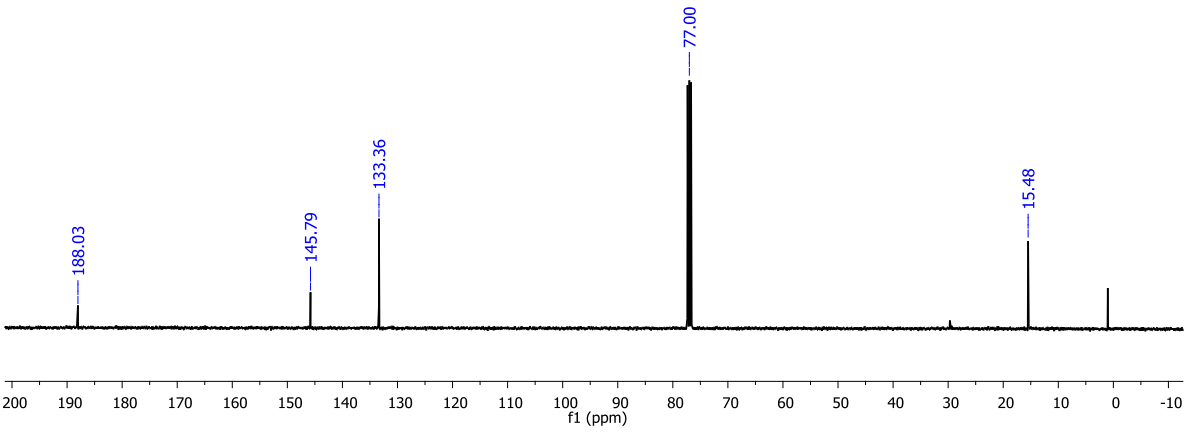


$^{1}H$ and $^{13}C$ NMR Spectra of Compound **6e**.



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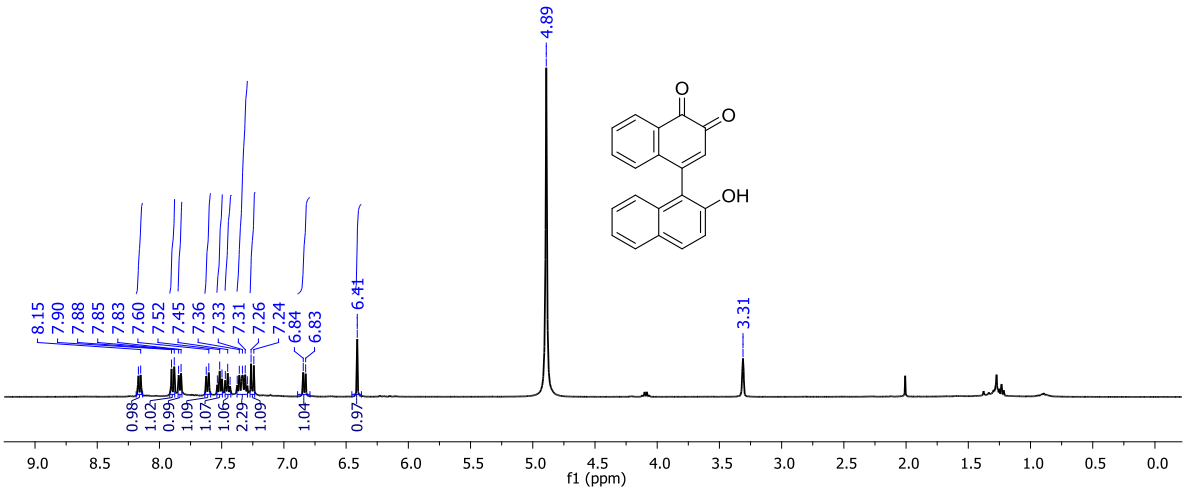
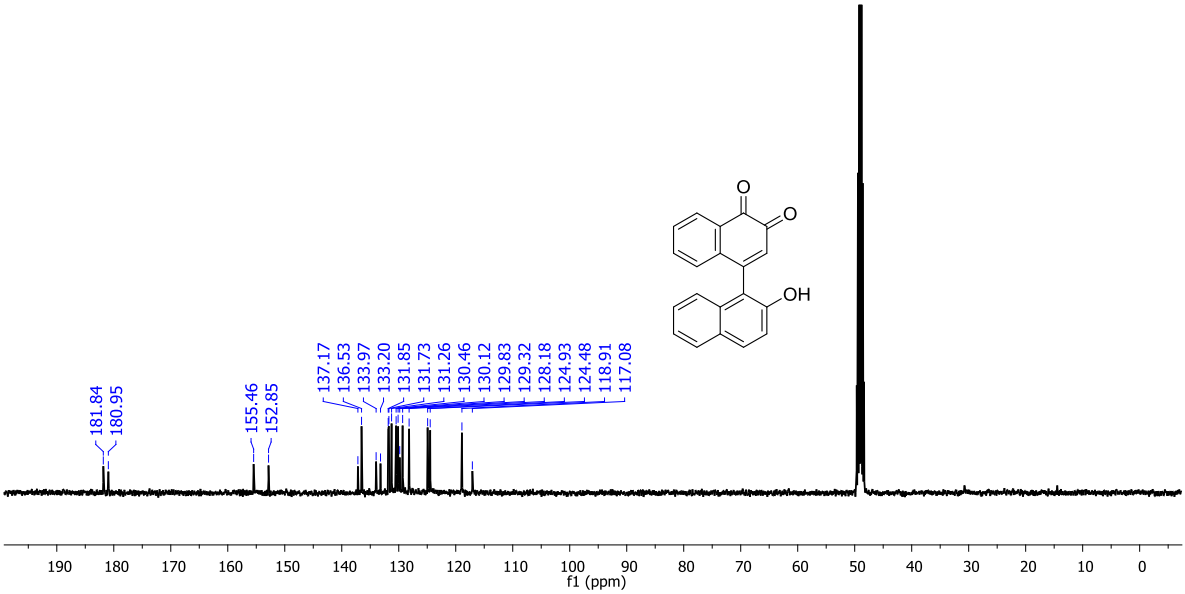
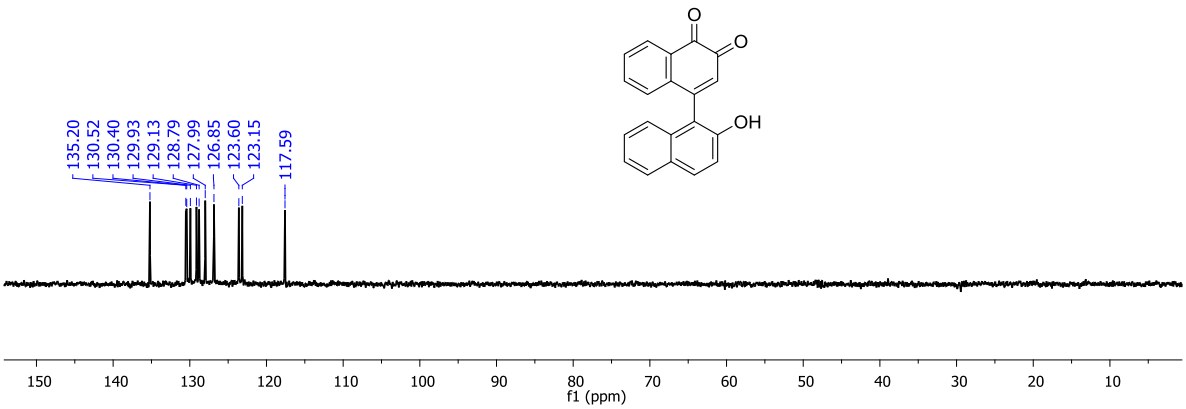
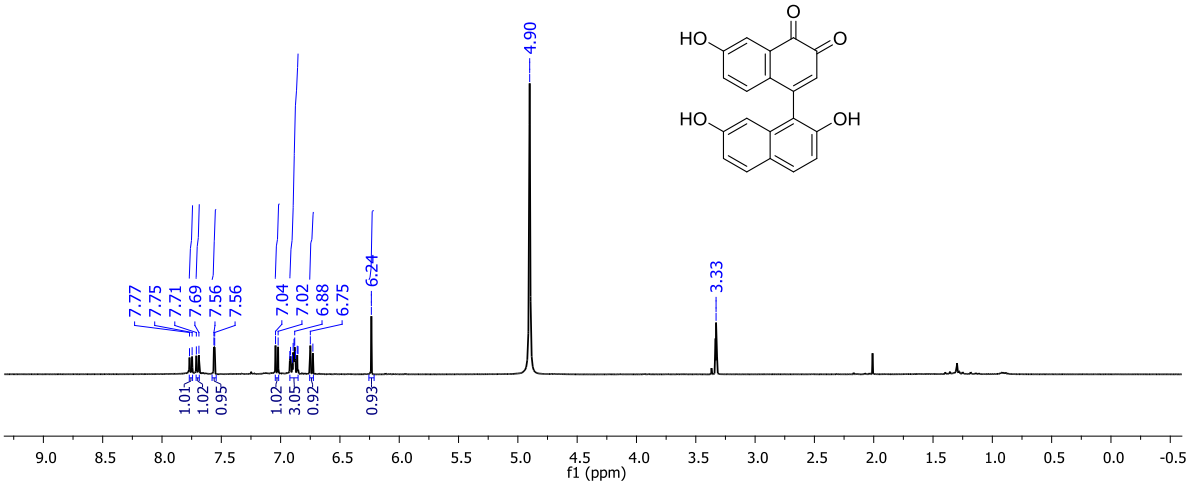
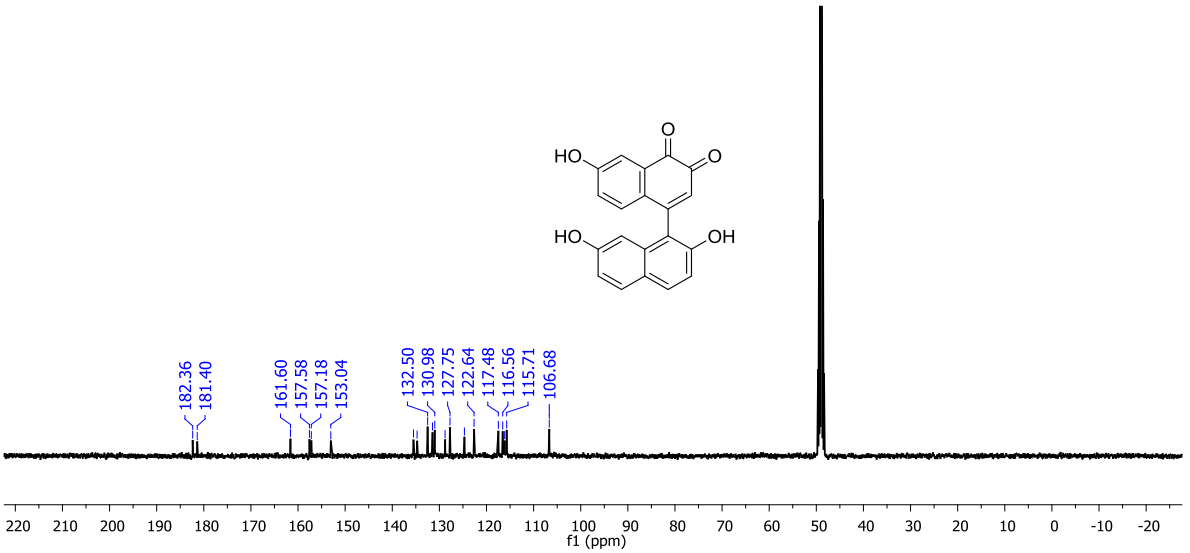


$^{1}H$ and $^{13}C$ NMR Spectra of Compound **6h**.



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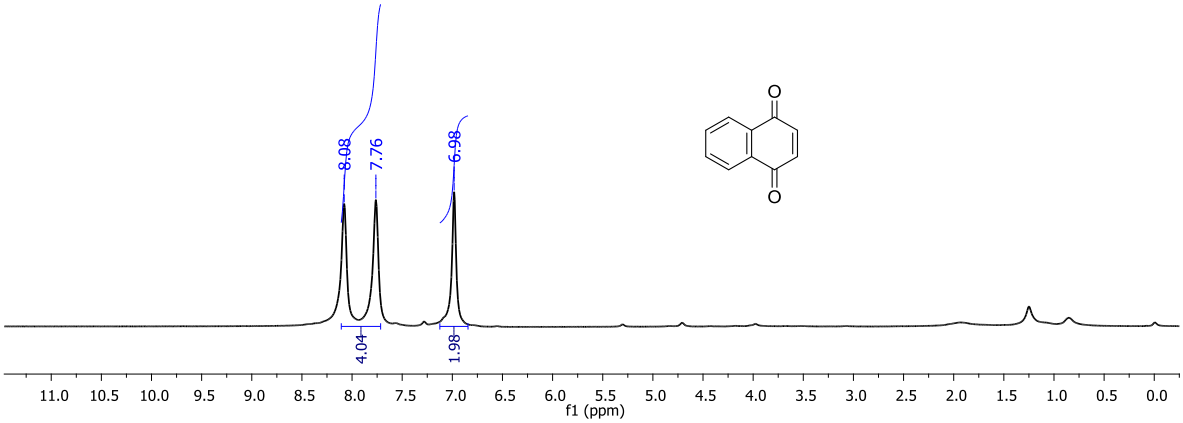


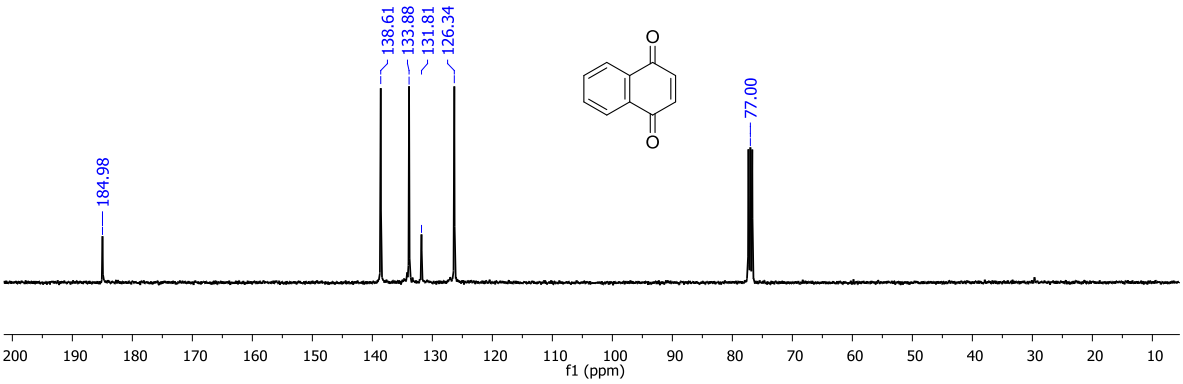


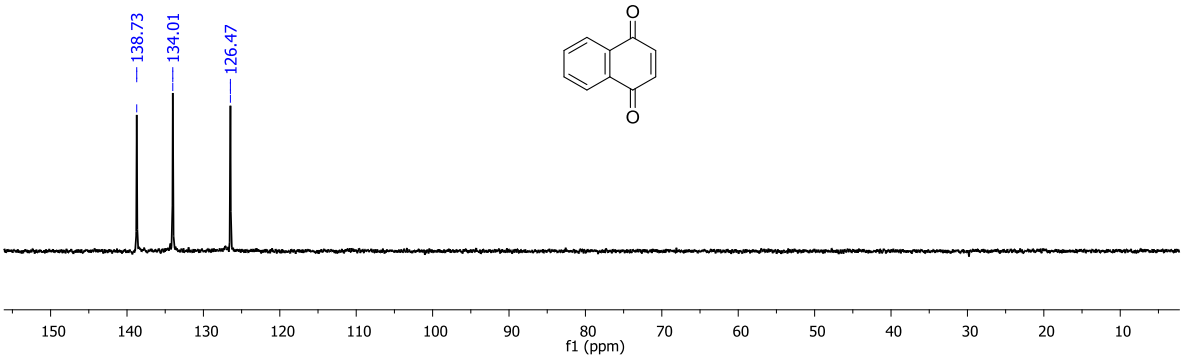

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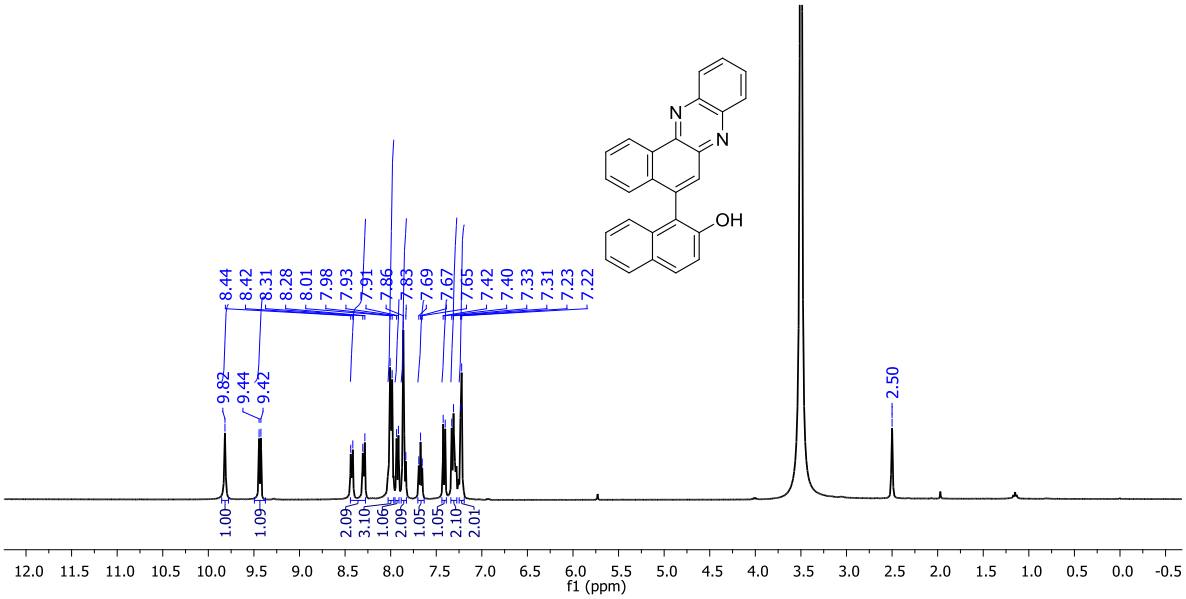


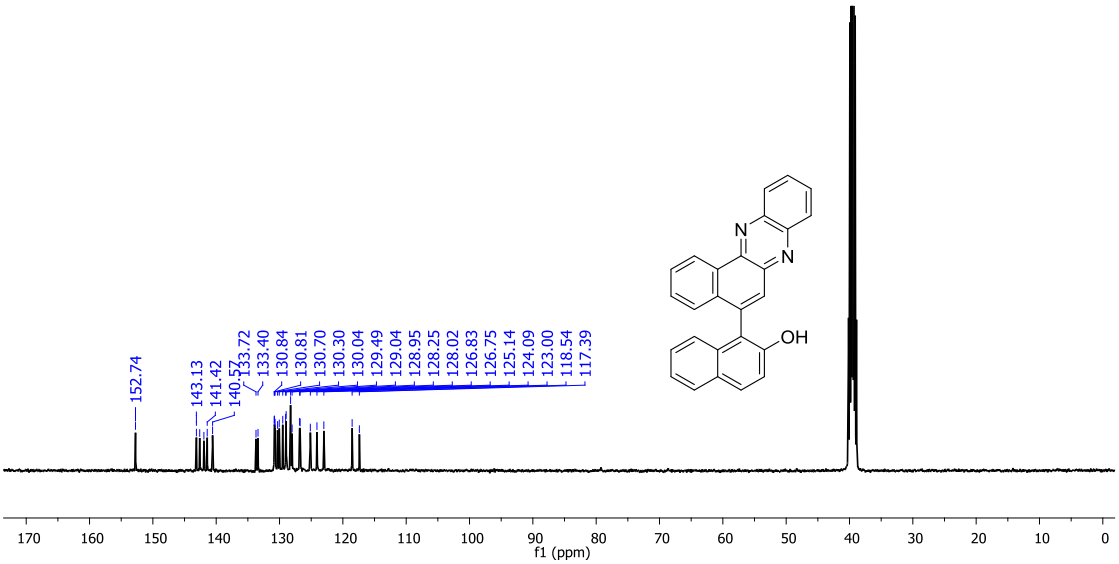


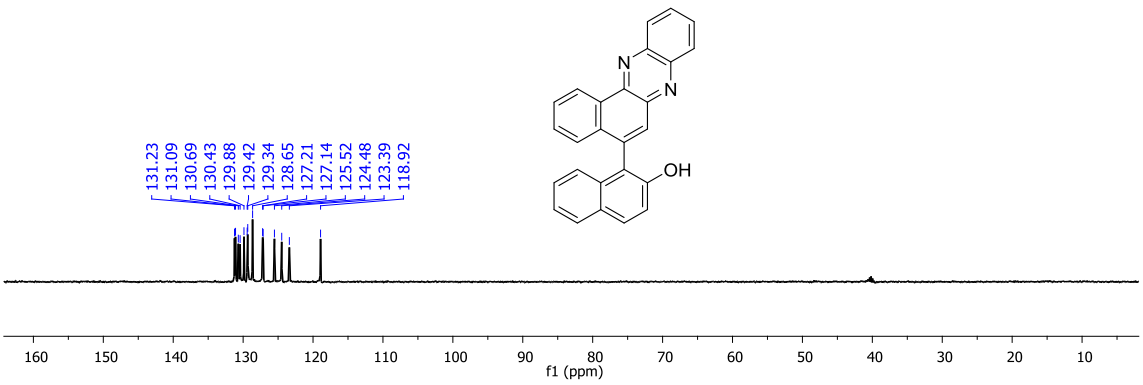

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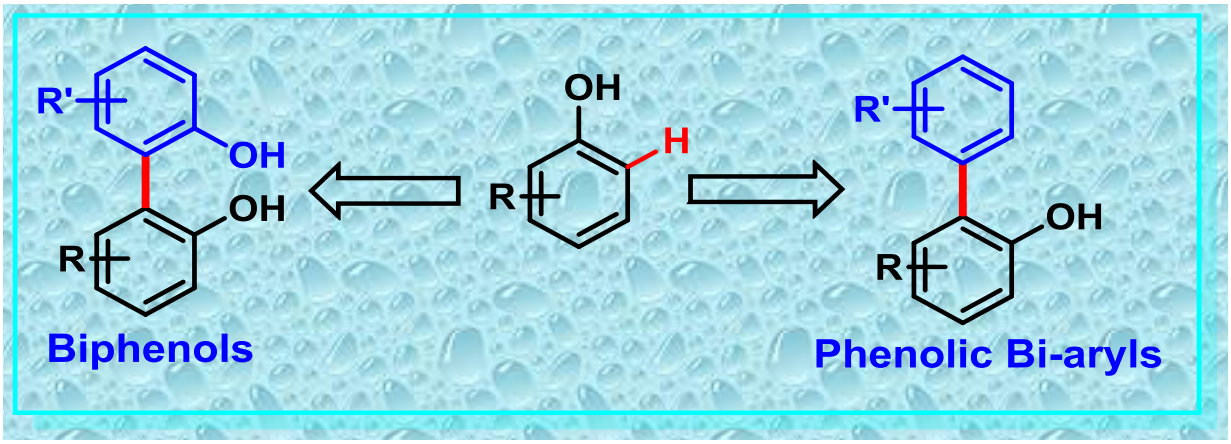
# Chapter 4

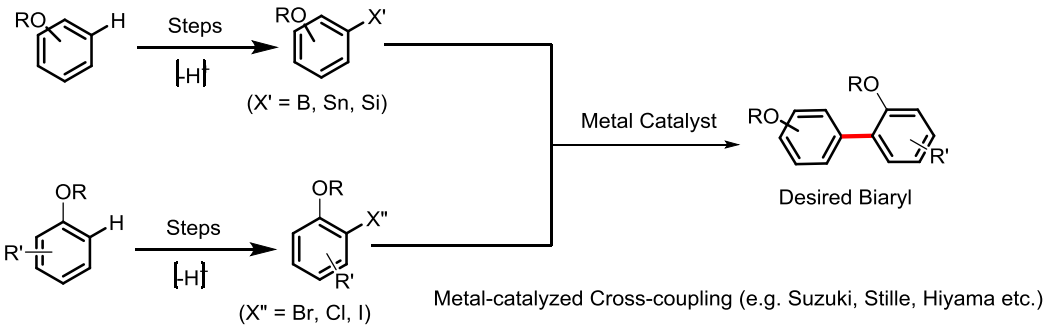
## *Direct Oxidative Cross-Coupling of Phenols with Aromatic Hydrocarbons: An Efficient Route to Unsymmetrical Biaryls*



## 4A: Oxidative Cross-Coupling of Two Different Phenols: An Efficient Route to Unsymmetrical Biphenols

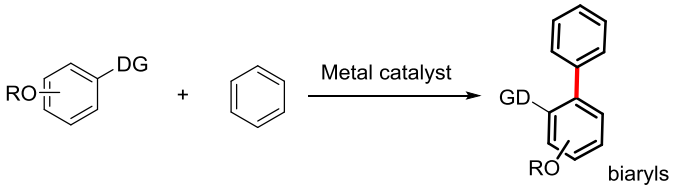
### Introduction:

Unsymmetrical biphenols are highly valuable organic molecules that have found widespread applications in various natural products, liquid crystals and as ligands in metal-catalyzed reactions.[1] The development of highly efficient, easily accessible and environmentally friendly method for synthesizing biphenol molecules in a highly atom economical manner is highly desirable in organic synthesis. Transition-metal-catalyzed cross-coupling of aryl electrophiles with aryl metallic reagents is a robust method to synthesize biaryls in a highly efficient manner.[2] However, pre-activated coupling partners such as C–X and C–M are required on the aromatic moieties for the cross-coupling reaction (Scheme 4.1). In these reactions, multiple synthetic steps are involved. And also transition metals are sensitive to a hydroxyl group. Protection of phenol is necessary for the synthesis of bi-aryls via cross-coupling reactions.



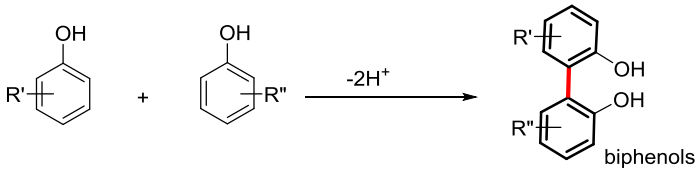

**Scheme 4.1:** Bi-aryl synthesis by metal catalyzed cross-coupling

Recently, bi-aryl molecules have been synthesized in a high atom- and step-economical manner through metal-catalyzed C–H bond-activation reactions.[3] Metal-catalyzed C-H bond activation for the synthesis of bi-aryls requires only one activated partner and has recently found significant attention (Scheme 4.2).



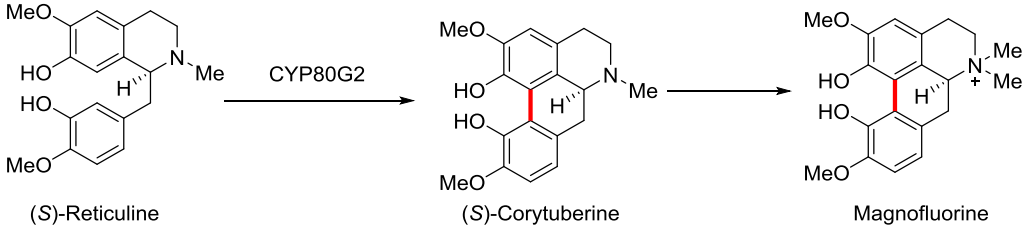

**Scheme 4.2:** Synthesis of bi-aryls by C-H bond activation

In these reactions, complex of noble metals such as rhodium, iridium, ruthenium, or palladium are required as catalysts for the efficient conversion into unsymmetrical bi-aryls. However, the synthesis of phenol-based bi-aryls is very challenging and has not been well documented.[4] Although the oxidative coupling of phenols is known in the literature for several decades, the cross-coupling of two different phenols is not well studied and very challenging due to the formation of many competitive side products.[4g] While designing this type of oxidative coupling reaction, controlling of competitive side products such as homo-coupling of phenols, Pummerer's ketones, C-O bond formation between two phenols, quinones, polymers, and dehydrotrimers is very important. Seminal efforts have recently paid toward the development of direct oxidative cross-coupling of phenols. The direct oxidative cross-coupling of phenols is a cutting-edge concept which sacrifices only hydrogen atom substituent and is consequently very attractive in terms of atom economy (Scheme 4.3).[5]



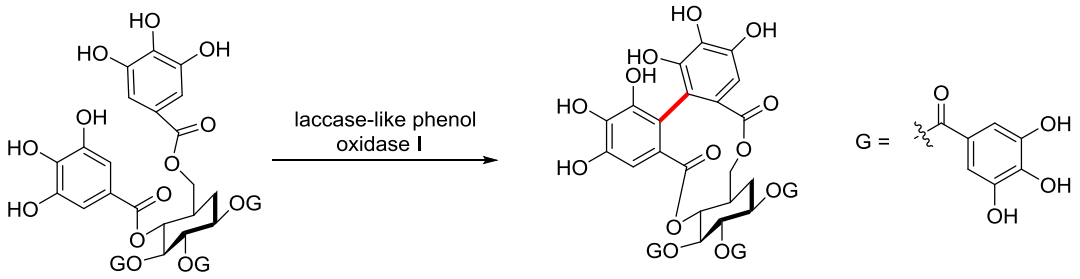

**Scheme 4.3:** Synthesis of biaryls by C-H bond activation

These studies have drawn inspiration from the enzyme catalyzed oxidative phenolic coupling in nature. Nature prefers to synthesize phenolic ligands, biomaterials, isoquinoline alkaloids and natural products via an oxidative phenol coupling in the presence of oxidative enzymes such as laccase, peroxidase and cytochrome P450 (CYP) as catalysts.[6] In the biosynthesis of magnofluorine, the intra-molecular oxidative coupling of phenols is a key step (Scheme 4.4). In this reaction, the magnofluorine precursor (*S*)-corytuberine is synthesized by stereospecific oxidation of (*S*)-reticuline catalyzed by the oxidase CYP80G2.[6j] In this enzyme catalyzed the reaction; the coupling is postulated to proceed through a biradical reaction.



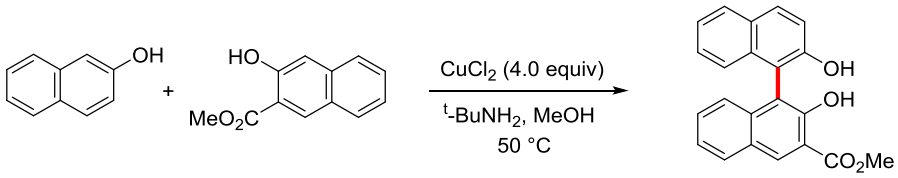
**Scheme 4.4:** Oxidative phenol coupling reaction in biosynthesis of magnofluorine

Another interesting example that laccase-like phenol oxidase-I catalyzed oxidative dimerization of 1,2,3,4,6-Penta-O-galloyl-β-glucopyranose to tellimagrandin II (Scheme 4.5).[6j] In this transformation laccase-like phenol oxidase catalyzes the oxidation of phenols by single-electron transfer and simultaneous reduction of molecular oxygen.



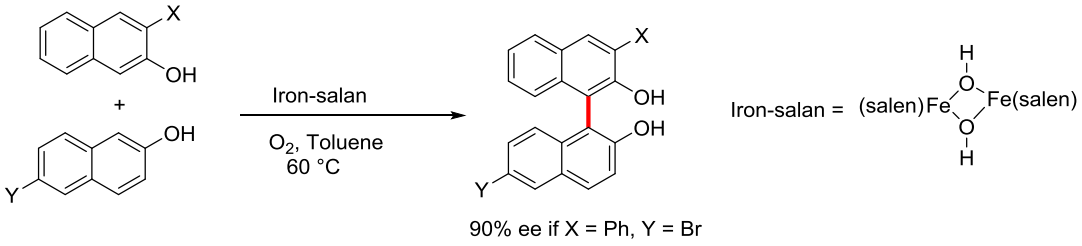

**Scheme 4.5:** Laccase-mediated oxidative cross-coupling

In 1999, Hovorka and co-workers reported the first example of oxidative cross-coupling of two different naphthols with excess $CuCl_2$ and either *t*-$BuNH_2$ or $EtNH_2$ in methanol.[7] In the reaction, binuclear Cu (II) complex containing metal centers with different redox potentials accounts for the chemo-selectivity (Scheme 4.6).



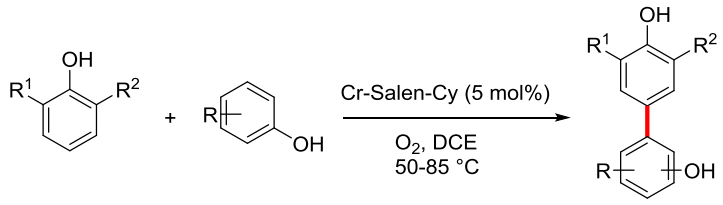

**Scheme 4.6:** Oxidative cross-coupling of different naphthols

Later, Katsuki's group demonstrated an aerobic enantioselective cross-coupling of 2-naphthols by iron(salan) complex.[8] Selective cross-coupling between 3-substituted naphthol and 6-substituted 2-naphthol partner described by radical-anion coupling (Scheme 4.7).



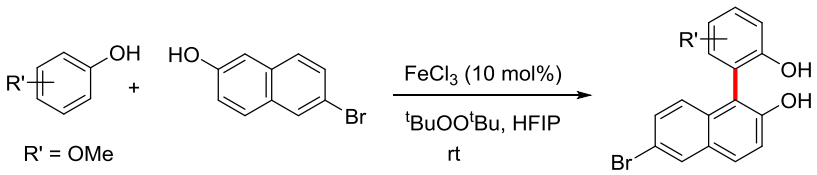

**Scheme 4.7:** Cross-coupling by Chromium salen catalyst

Various kinds of stoichiometric oxidation reagents such as Fe, Cu, Mn, V, Ru, and Ti salts have been employed for the oxidative cross-coupling of naphthol,[8, 9] they are often hazardous, expensive, stoichiometric, and difficult to remove from the reaction solution. These metal salts are not extended fully for the development of cross-coupling of two different phenols. Recently, cross-coupling of 2,6-dialkyl phenols with various substituted phenols has been successfully achieved by Kozlowski's group in the presence of chromium salen catalyst (Scheme 4.8).[10] In the reaction, metal oxy radicals are key intermediate, which abstract hydrogen atom from phenols and initiates the coupling reaction.



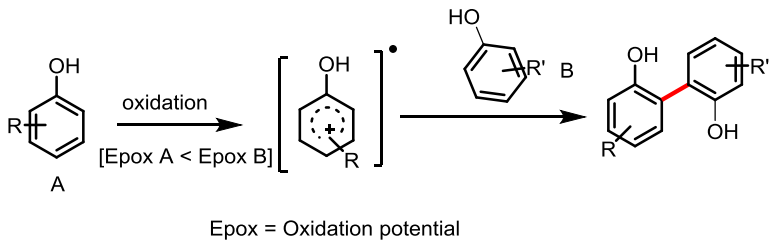

**Scheme 4.8:** Cross-coupling by Chromium salen catalyst

Very recently, Pappo's group discussed iron-catalyzed oxidative cross-coupling of two different phenols for the synthesis of unsymmetrical biphenols in the presence of a stoichiometric amount of oxidant.[11] In the presented coupling reaction, electron-rich aromatic phenols reacted with a variety of substituted phenols to afford desired cross-coupled products. In this reaction, along with di-$^{t}$butyl peroxide, the highly fluorinated solvent is crucial for the reaction. (Scheme 4.9).[11a] The cross-coupling reaction proceeds via a chelated radical-anion coupling mechanism.



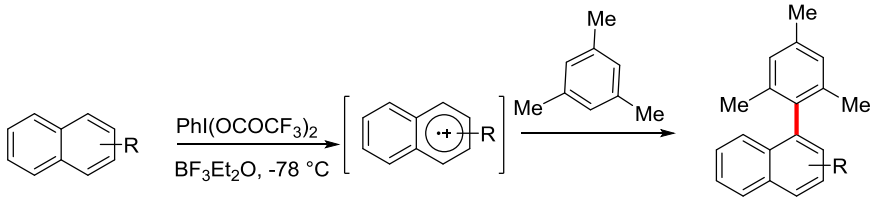

**Scheme 4.9:** Oxidative coupling of phenol with naphthol

The general strategy for oxidative cross-coupling process can be explained by oxidation potential of phenolic partners. If two phenolic coupling partners are chosen with sufficiently different oxidation potential, the electron rich or more oxidized phenol will be selectively oxidized to convert into phenolic cation radical intermediate. The resulting intermediate then undergoes C-C bond formation with a second phenolic partner to give desired nonsymmetrical biphenols (Scheme 4.10).



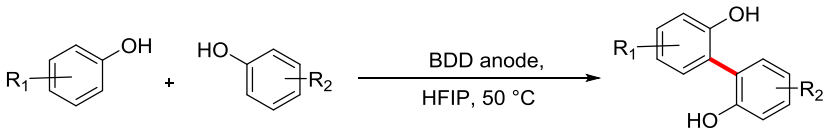

**Scheme 4.10:** general mechanism for cross-coupling of two phenols

This concept was demonstrated by Kita and co-workers for the synthesis of bi-aryls using phenyliodine (III) bis(trifluoroacetate).[12] In the reaction substituted naphthalene reacted with electron-rich arenes by single electron transfer mechanism to produce desired bi-aryl compounds (Scheme 4.11).[12a] In the reaction aromatic coupling partners are used in excess.



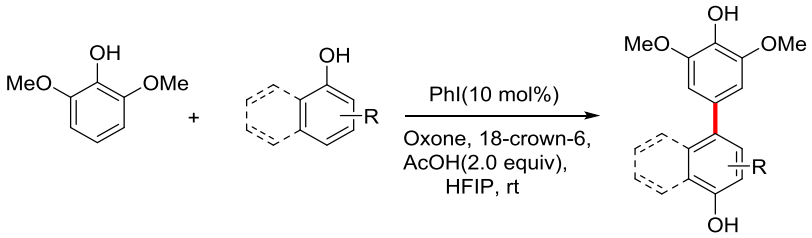

**Scheme 4.11:** Hypervalent iodine mediated cross-coupling of naphthalene and arenes

Waldvogel and coworkers reported a reagent- and metal-free approach that electrochemical oxidative pathway for the synthesis of biphenols (Scheme 4.12).[13] In the electrochemical oxidation pathway, hydroxyl or alkoxyl radicals are generated by applying electric current at BDD electrode. The highly reactive hydroxyl or alkoxy radicals initiate the coupling reaction through single electron transfer from phenols.



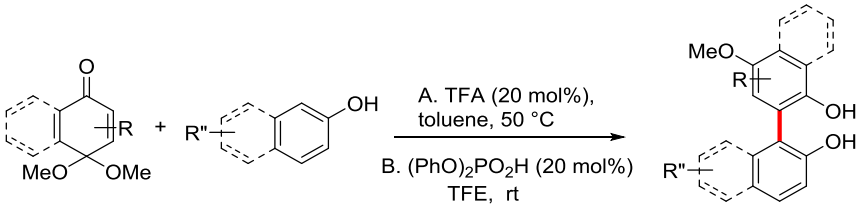

**Scheme 4.12:** Anodic coupling of phenols

Subsequently, the same group reported a selective cross-coupling of two different phenols using selenium dioxide as a oxidant.[13i] Very recently, Kita's group developed very prominent organocatalytic method uses aryl iodides with oxone as a terminal oxidant (Scheme 4.13).[12h] In the reaction hypervalent iodine reagent is generated by reaction of iodoarene, oxidant and acetic acid, which then initiates coupling reaction through single electron transfer. The catalytic amount of iodoarene was used in the reaction.




**Scheme 4.13:** Phenol-phenol cross-coupling reaction

Non-symmetrical biphenols are also synthesized using quinone monoacetals as a coupling partner with naphthols or phenols under metal-free conditions.[14] Recently, Kürti and co-workers described an organo-catalytic synthesis of functionalized atropisomeric biphenols using Bronsted acid in catalytic amount.[14b-d] In this reaction quinone, monoacetals were reacted with unprotected naphthols (Scheme 4.14).




**Scheme 4.14:** Phenol-phenol cross-coupling reaction

Among these transformations, cross-coupling of two different phenols by using transition metal free conditions is less focused in the literature. Phenols are highly oxidized compounds in the presence of external oxidizing reagents to give competitive side products. While designing of oxidative cross-coupling reactions of phenols, controlling competitive side products and selectivity is very important. A sulfate anion radical ($SO_4^{-\bullet}$) is efficiently used as a potential oxidant for the degradation of environmental pollutant.[15a] Although the oxidation potential of $SO_4^{-\bullet}$ is 2.6 eV, the reactivity between organic compounds and $SO_4^{-\bullet}$ is considered to be slow, but, very selective via a single electron transfer mechanism.[15b-c, 16] Thus, sulfate anion radical can react with alcohols, phenols, ether compounds, and hydrocarbons through single electron or hydrogen (H) transfer. $K_2S_2O_8$, $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ are commonly used sources to generate $SO_4^{-\bullet}$.

The $K_2S_2O_8$, source for $SO_4^{-\bullet}$ is non-toxic, less expensive, easily available and green oxidant. Recently, the chemistry of $K_2S_2O_8$ has gained tremendous attention in C–H bond functionalization due to its remarkable reactivity and selectivity. Our continuous interest in the $SO_4^{-\bullet}$anion radical chemistry prompted us to explore the possibility of using $SO_4^{-\bullet}$ as an oxidant for the cross-coupling of two different phenols under mild reaction

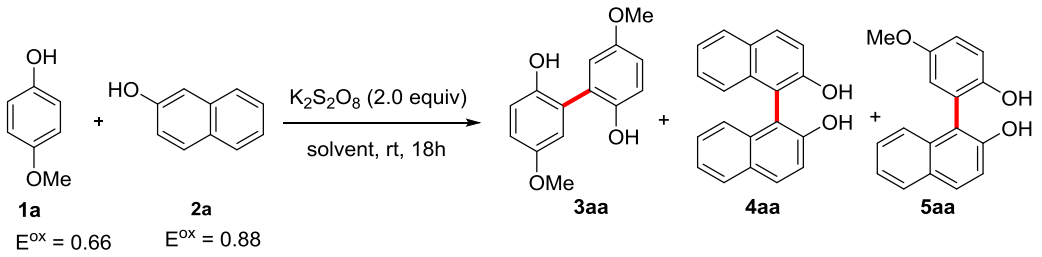
conditions.[16] In this section we are discourse unprecedented oxidative cross-coupling of two different phenols in the presence of $K_2S_2O_8$ in a highly regio-selective manner.

**4A.1: Results and Discussion**

To accomplish the cross-coupling reaction, initially, a combination of phenol and 2-naphthol substrates such as 4-methoxyphenol (**1a**) and 2-naphthol (**2a**) was selected (Scheme 1). The cross-coupling reaction of **1a** with **2a** was tested in the presence of $K_2S_2O_8$ in $CF_3COOH$ at room temperature for 16 h under air. In the reaction, the homocoupling of **1a** (product **3aa** in 23% yield), the homocoupling of **2a** (product **4aa** in 27% yield) and the expected cross-coupling product **5aa** in 21% yield were observed. In the reaction, $K_2S_2O_8$ generates $SO_4^{\cdot-}$ anion radical at ambient temperature. It is believed that $SO_4^{\cdot-}$ anion radical was stabilized by $CF_3COOH$ solvent via hydrogen bonding. Later, $SO_4^{\cdot-}$ anion radical abstracts hydrogen from **1a** or **2a** in the presence of $CF_3COOH$, providing a cationic phenol or naphthol radical intermediate **6** and non toxic $HSO_4^-$ salt. To know further about the radical formation, the oxidation potential of **1a** and **2a** was tested by using Cyclic Voltammetry (see Supporting Information). The oxidation potential of 4-methoxyphenol (**1a**) is 0.66 eV and 2-naphthol (**2a**) is 0.88 eV. It is expected that the $SO_4^{\cdot-}$ anion radical prefer to abstracts hydrogen from **1a** and forming a cationic intermediate **6a** compared to **2a** due to the lower oxidation potential value. To support the formation of a cationic intermediate **6a**, the UV-Vis spectroscopy study was done. An intense absorption band was observed in the visible region between 400 to 500 nm during the reaction of phenol **1a** with $K_2S_2O_8$ at room temperature. This study strongly supports that a cationic intermediate is formed during the reaction as previously observed by Kochi's group. Later, the nucleophilic addition of **2a** into cationic intermediate **6a** provides the cross-coupling product **5aa**.

**4A.2: Optimization Studies**

**Table 4.1:** Optimization Studies with Various solvents and Counter ions




| entry | solvent | Counter ion (mol%) | yield of **3aa** (%)[b] | yield of **4aa** (%)[b] | yield of **5aa** (%)[b] |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 1 | MeOH | - | NR | NR | NR |
| 2 | AcOH | - | NR | NR | NR |
| 3 | $ClCH_2CH_2Cl$ | - | NR | NR | NR |
| 4 | TFA | - | 23 | 27 | 21 |
| 5 | TFA | $Bu_4N^+HSO_4^-$ | 0 | 1 | 63 |
| 6 | TFA | $Bu_4N^+I^-$ | 0 | 33 | 23 |
| 7 | TFA | $Bu_4N^+F^-$ | 0 | 0 | 37 |
| 8 | *tert*-BuOH | $Bu_4N^+HSO_4^-$ | NR | NR | NR |
| 9 | $CF_3SO_3H$ | $Bu_4N^+HSO_4^-$ | ND | ND | ND |
| 10 | $H_2O$ | $Bu_4N^+HSO_4^-$ | NR | NR | NR |

[a]All reactions were carried out under the following conditions: **1a** (1.0 equiv), **2a** (1.5 equiv), $K_2S_2O_8$ (2.0 equiv), and counter ion (10 mol %) in solvent (0.5 mL) at ambient conditions for 18 h. [b]Isolated yield.

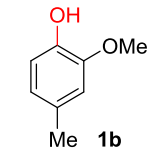
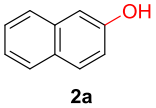
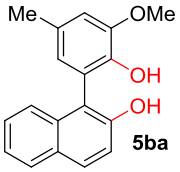
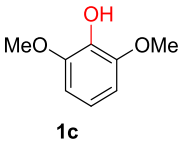
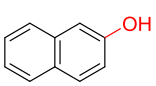
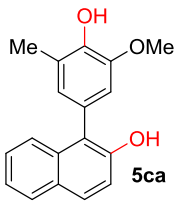
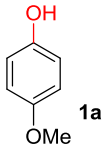
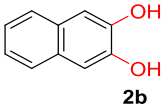
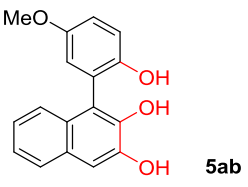
It is clear that the coupling reaction proceeds via a cationic radical intermediate. We expected that if the reaction is done in the presence of an ionic salt, a negatively charged counterion could coordinate with a cationic phenol radical intermediate **6a** and stabilize it. Thus, the possibility is there to increase the yield of cross-coupling product **5aa**. With this idea, the reaction was tested with a catalytic amount of 10 mol % of salts such as $Bu_4N^+$ $I^-$, $Bu_4N^+\cdot Br^-$, $Bu_4N^+\cdot Cl^-$, $Bu_4N^+\cdot F^-$, and $Bu_4N^+\cdot HSO_4^-$. $Bu_4N^+\cdot I^-$ provided homocoupling product **4aa** in 33% yield and cross-coupling product **5aa** in 23% yield, respectively. The other homocoupling product **3aa** was not observed (Scheme 1). Surprisingly, $Bu_4N^+\cdot HSO_4^-$ afforded cross-coupling product **5aa** in 61% yield and homocoupling product **4aa** in a very minor 1% yield (for mass balance, see Supporting Information). Other salts were not active for the reaction. The same reaction was also done under a nitrogen atmosphere. In the reaction, product **5aa** was observed in 60% yield as in the case of under air. This result reveals that the reaction is not air sensitive. $K_2S_2O_8$ is crucial for the reaction, and without that, the reaction did not proceed. Meanwhile, 2.0 equiv of $K_2S_2O_8$ are also needed to raise the yield of cross-coupling product **5aa**. The reaction was also examined with 1.0 and 1.5 equiv of $K_2S_2O_8$. In these reactions, product **5aa** was observed only in 40% and 57% yields, respectively. The cross-coupling reaction was also examined with various solvents such as AcOH, MeOH, $ClCH_2Cl$, *tert*-amyl alcohol, *tert*-BuOH, and $CF_3SO_3H$. In acetic acid solvent, product **5aa** was observed in very low 5% yield and the remaining solvents were not effective.

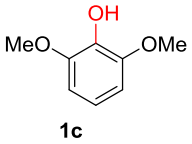
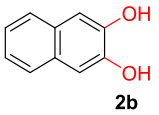
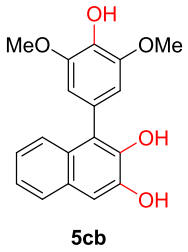
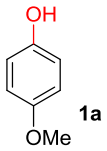
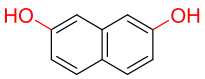
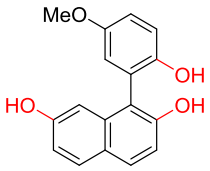
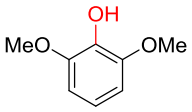
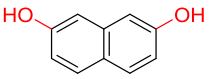
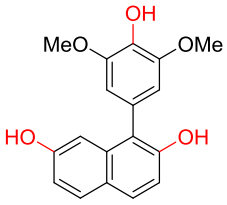
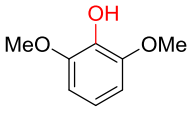
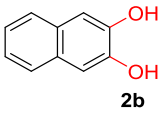
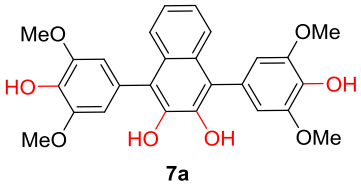
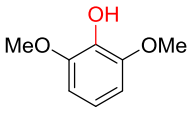
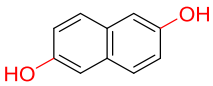
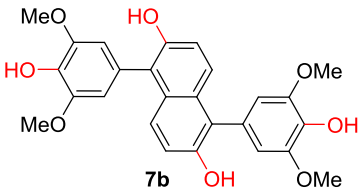
The reaction was also tried with $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$. $(NH_4)_2S_2O_8$ was also equally effective, providing product **5aa** in 60% yield. But, $Na_2S_2O_8$ provided only product **5aa** in 40% yield. It is expected that the solubility of $Na_2S_2O_8$ is less in an organic solvent. (entry 9).

### 4A.3: Cross-Coupling of Phenols and Naphthols

This *ortho* benzoxylation In the presence of $Bu_4N^{+}HSO_3^{-}$ (10 mol %), 2-naphthol (**2a**) underwent cross-coupling with 4-methyl-2-methoxy phenol (**1b**) or 2,6-dimethoxy phenol (**1c**), providing products **5ba** and **5ca** in 61% and 82% yields, respectively (Table 1, entries 1 and 2). In the reaction of **1c** with **2a**, the *para* C-H bond of **1c** was coupled with α C-H bond of 2-naphthol (**2a**). The oxidation potential of **1b** is 0.7 eV and **1c** is 0.62 eV. Thus, in these reactions, only phenols **1b-c** form the cationic radical species and **2a** acts as a nucleophile. Similarly, naphthalene-2,3-diol (**2b**) reacted with **1a** or **1c**, affording the cross-coupling products **5ab** and **5cb** in 64% and 51% yields, respectively (entries 3 and 4). Further, naphthalene-2,7-diol (**2c**) reacted with **1a** or **1c**, providing coupling products **5ac** and **5cc** in 73% and 69% yields, respectively. In the naphthols **2b** and **2d**, two OH groups are present on the aromatic moiety. We tried to incorporate two phenol moieties at the α C-H bond of the corresponding OH groups (Scheme 2). Thus, the treatment of **2b** or **2d** with an excess amount of 2,6-dimethoxyphenol (**1c**) (2.2 equiv) gave a polycyclic naphthol derivatives **7a** and **7b** in 71% and 75% yields, respectively.

**Table 4.2:** Cross-Coupling of Phenols and Naphthols[a]

| entry | 1 | 2 | 3 | yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1b** |  **2a** |  **5ba** | 61 |
| 2 |  **1c** |  **2a** |  **5ca** | 82 |
| 3 |  **1a** |  **2b** |  **5ab** | 64 |

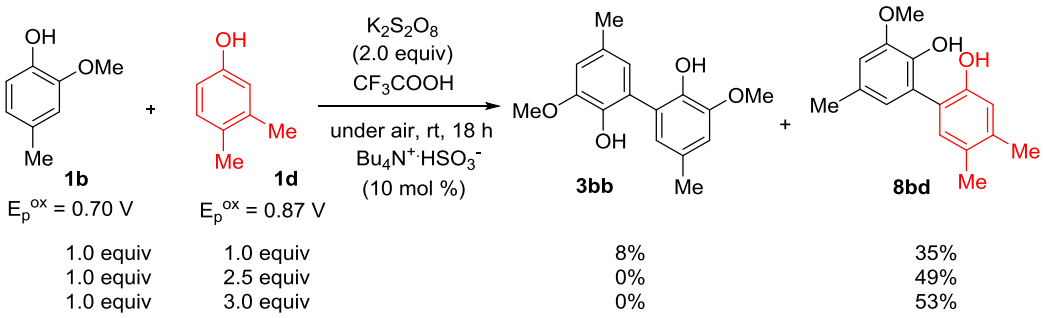
| | | | | |
|---|---|---|---|---|
| 4 |  **1c** |  **2b** |  **5cb** | 51 |
| 5 |  **1a** |  **2c** |  **5ac** | 73 |
| 6 |  **1c** |  **2c** |  **5cc** | 69 |
| 7 |  **1c** |  **2b** |  **7a** | 71[c] |
| 8 |  **1c** |  **2d** |  **7b** | 69[c] |

[a]All reactions were carried out using **1a-c** (1.0 equiv), **2a-d** (1.5 equiv), $K_2S_2O_8$ (2.0 equiv), and $Bu_4N^{+}\cdot HSO_4^{-}$ (10 mol%) in TFA at ambient conditions for 18 h. [b]Isolated yield. [c]**1c** (2.2 equiv) is used insted 1.0 equiv and **2b** and **2d** are used 1.0 equiv

### 4A.4: Cross-Coupling of Two Different Phenols

To elaborate the substrate scope of the cross-coupling reaction, the possibility of cross-coupling of two different phenols were tested (Scheme 3). The cross-coupling of two different phenols is difficult to do due to the similar oxidation potential values. Initially, 2-methoxy-4-methylphenol (**1b**) with 3,4-dimethylphenol (**1d**) were taken as model substrates for the reaction. The oxidation potential of **1b** is 0.7 V and **1d** is 0.87 V. Thus, **1b** prefers to form a cationic radical intermediate in the presence of $SO_4^{\cdot-}$. The oxidation potential difference between **1b** and **1d** is very less; thus, the homo-coupling of these phenols would be expected more compared with the cross-coupling product. Treatment of

**1b** (1.o equiv) with **1d** (1.0 equiv) in the presence of $Bu_4N^{+}\cdot HSO_3^{-}$ (10 mol %) in $CF_3COOH$ at ambient temperature gave the cross-coupling product **8bd** in 35% yield along with homo coupling product of **1b**, product **3bb**, in 8% yield. Surprisingly, the homo coupling product of **1d** was not observed, and the remaining starting material was recovered. To increase the yield of cross-coupling product, the amount of **1d** was increased up to 2.5 equiv to 3.0 equiv. Surprisingly, in 3.0 equiv, cross-coupling product **8bd** was observed in 53% yield, and no homo coupling product of **1b** was detected. In 2.5 equiv, product **8bd** was observed in 49% yield. Next, the scope of cross-coupling reaction was examined with various substituted phenols **1e-n** (Table 2). Trisubstituted phenols such as 2,3-dihydro-1*H*-inden-5-ol (**1e**) or 2,4-dimethylphenol (**1f**) or 4-*tert* butyl-2-methyl phenol (**1g**) reacted efficiently with **1b**, giving the corresponding biphenols **8be-bg** in 56%, 57% and 43% yields (entries 1-3). In the reaction of **1b** with **1f**, homo-coupling product of **1f** was observed in 7% yield.

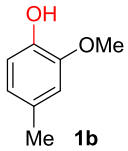
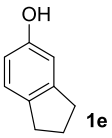
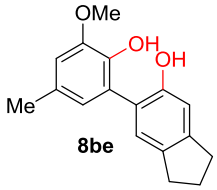
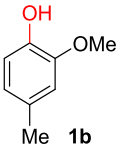
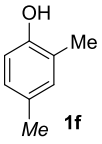
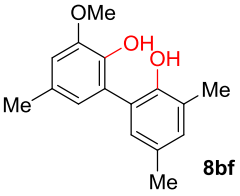
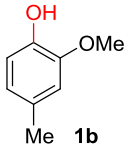
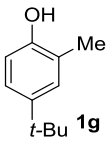
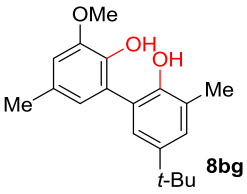
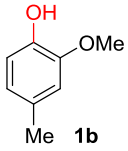
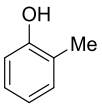
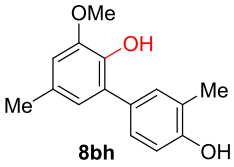
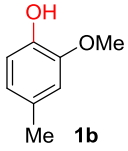
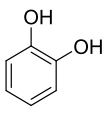
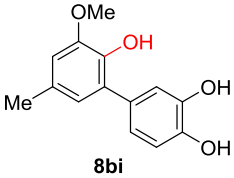
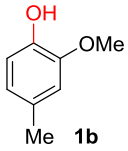
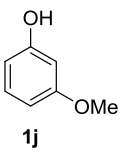
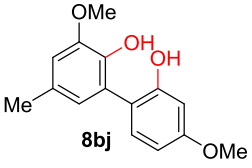



**Scheme 4.15:** Cross-Coupling of Two Different Phenols

Next, the cross-coupling reaction was examined with disubstituted phenols. Thus, treatment of 2-methyl phenol (**1h**) with **1b** gave a mixture of two regioisomeric products 2,4'-biphenol **8bf** in 46% yield and 2,2'-biphenol **8bf'** in 8% yield, respectively (entry 4). Interestingly, in the reaction of 2-hydroxy phenol (**1i**) with **1b**, only 2,4'-biphenol **8bi** was observed in 38% yield (entry 5). In the reaction of **1b** with **1i**, the *ortho* C-H bond of **1b** was coupled with the *para* C-H bond of **1i**. 1,3-Disubstituted phenols such as 3-methoxy (**1j**) or 3-methyl (**1k**) phenols reacted with **1b,** affording 2,2'-biphenols **8bj** and **8bk** in 26% and 49% yields, respectively (entries 6 and 7). In addition, the other regioisomers **8bj'** and **8bk'** were observed in 8% and 6% yields, respectively (eq 1). 1,4-Disubstituted phenols such as 4-methyl (**1l**) or 4-*tert*-butyl phenols (**1m**) were also nicely involved in the reaction, giving the corresponding cross-coupling products **8bl** and **8bm** in 42% and 38% yields, respectively (entries 8 and 9). We have tried the cross-coupling of a less reactive unsubstituted phenol (**1n**) with **1b**. In the reaction, interestingly, 2,2'-biphenol (**8an**) was observed in 33% yield and another regioisomer 2,4'-biphenol was not observed

(entry 10). In most of the phenols cross-coupling reaction, only good to moderate yields were observed. It is important to note that for the first time in the literature, this type of cross-coupling with various new phenols was demonstrated. Apart from the *ortho-ortho* cross-coupling of phenols, the *ortho-para* cross-coupling of phenols was also demonstrated (Scheme 4). Treatment of **1b** or **1d** or **1f** with 2,6-dimethoxy phenol (**1c**) under similar reaction conditions gave *ortho-para* cross-coupling products **8cb-8cf** in 48% ,59% and 56% yields, respectively.

**Table 4.3:** Cross-Coupling of Phenols and Naphthols[a]

| entry | **1** | **2** | **3** | yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1b** |  **1e** |  **8be** | 56 |
| 2 |  **1b** |  **1f** |  **8bf** | 57[c] |
| 3 |  **1b** |  **1g** |  **8bg** | 43 |
| 4 |  **1b** |  **1h** |  **8bh** | 46[d] |
| 5 |  **1b** |  **1i** |  **8bi** | 38 |
| 6 |  **1b** |  **1j** |  **8bj** | 26 |

| | | | | |
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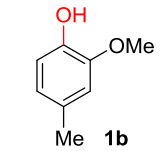
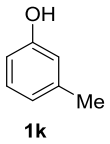
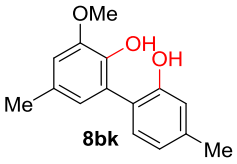
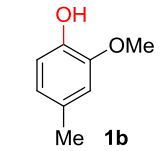
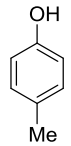
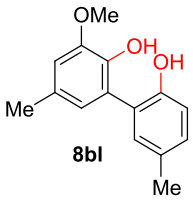
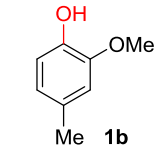
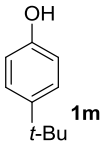
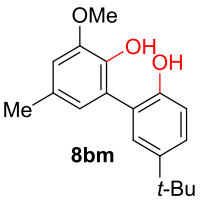
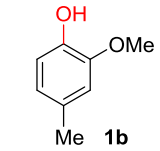
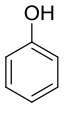
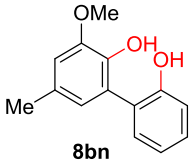
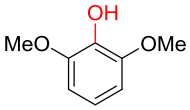
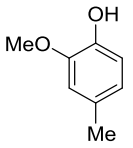
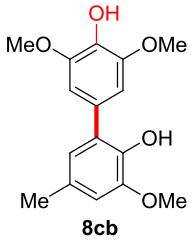
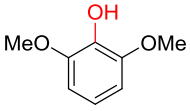
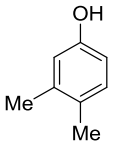
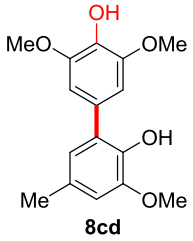
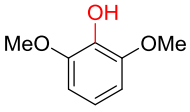
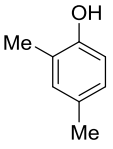
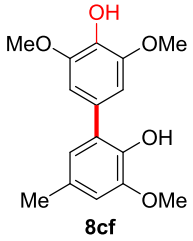
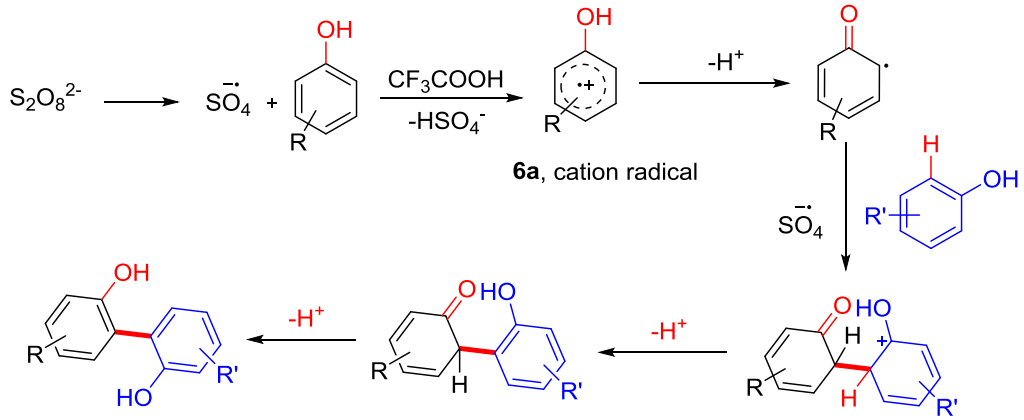
| 7 |  **1b** |  **1k** |  **8bk** | 49 |
| 8 |  **1b** |  **1l** |  **8bl** | 42 |
| 9 |  **1b** |  **1m** |  **8bm** | 38 |
| 10 |  **1b** |  **1n** |  **8bn** | 33 |
| 11 |  **1c** |  **1b** |  **8cb** | 48 |
| 12 |  **1c** |  **1d** |  **8cd** | 59 |
| 13 |  **1c** |  **1f** |  **8cf** | 56 |

[a]All reactions were carried out using **1b** (1.0 mmol), **1e-n** (2.5 mmol), $Bu_4N^+HSO_3^-$ (10 mol %) and $K_2S_2O_8$ (2.0 mmol) in $CF_3COOH$ (0.5 mL) at room temperature for 16 h. [b]Isolated yield. [c]Homocoupling of **1f** was observed in 7% yield. [d]Other regioisomeric 2,2'-biphenol **8bf'** was observed in 8% yield.

### 4A.5: Oxidation potential of Phenols

We have checked the oxidation potential value of several phenols and naphthols and compared with the present reaction. This result reveals that the oxidation potential of phenol up to 0.7 V nicely reacts with $SO_4^{\cdot-}$, providing the corresponding cationic phenolic radical intermediate. If the oxidation potential is above 0.7 V, does not oxidize and participate in the reaction. For example, 4-*tert*-butyl-2-methyl phenol (**1g**) ($E_p^{ox}$ = 0.81) or 2-naphthol (**2a**) ($E_p^{ox}$ = 0.81) did not react with 3,4-dimethylphenol (**1d**) ($E_p^{ox}$ = 0.87). In these reactions, even no homo-coupling product was observed. But, **1a** ($E_p^{ox}$ = 0.66 eV), **1b** ($E_p^{ox}$ = 0.70 V) and **1c** ($E_p^{ox}$ = 0.62 V) were nicely involved in the reaction.

### 4A.6: Mechanism




**Scheme 4.16:** Proposed mechanism

### 4A.7: Conclusion

1. We have investigated an efficient synthesis of unsymmetrical biphenols via the oxidative cross-coupling of two different phenols in the presence of $K_2S_2O_8$ under mild reaction conditions.
2. By using $Bu_4N^{+\cdot}HSO_4^-$, the homo-coupling of phenols or naphthols and also over-oxidation of the desired cross-coupling products were controlled.

## 4A.8: Experimental Section

**General Procedure for the Cross-Coupling reaction of Phenols with Naphthols:**

In a 25-mL round bottom flask, substituted Phenols **1a-c** (100 mg), $K_2S_2O_8$ (2.0 equiv), tetrabutylammonium hydrogen sulfate (10 mol %) and naphthols **2a-c** (1.5 equiv.) were dissolved in $CF_3COOH$ (0.5 mL). Then, the reaction mixture was allowed to stir at room temperature for 16 h under an air atmosphere. After 16 h, the reaction mixture was diluted with $CH_2Cl_2$ and solvents were evaporated under vacuum. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure hetero-coupling products **5aa-cc**.

**General Procedure for the Cross-Coupling reaction of two different Phenols:**

In a 25-mL round bottom flask, substituted Guaiacol **1b** (100 mg), $K_2S_2O_8$ (2.0 equiv), tetrabutylammonium hydrogen sulfate (10 mol %) and phenols **1d-n** (3.0 equiv) were dissolved in $CF_3COOH$ (0.5 mL). Then, the reaction mixture was allowed to stir at room temperature for 16 h under an air atmosphere. After 16 h, the reaction mixture was diluted with $CH_2Cl_2$ and solvents were evaporated under vacuum. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure hetero-coupling product **8bd-8bn**.

**UV-Vis Study to Detect a Phenol Cation Radical Intermediate:**

To support the formation of a phenol cationic radical intermediate, the UV-Vis spectroscopy study was done. An intense absorption band was observed in the visible region between 400 to 500 nm during the reaction of phenol **1a** with $K_2S_2O_8$ at room temperature in $CF_3COOH$. This study strongly supports that a cationic intermediate is involved in the reaction as reported by Kochi et al. and Kita et al.

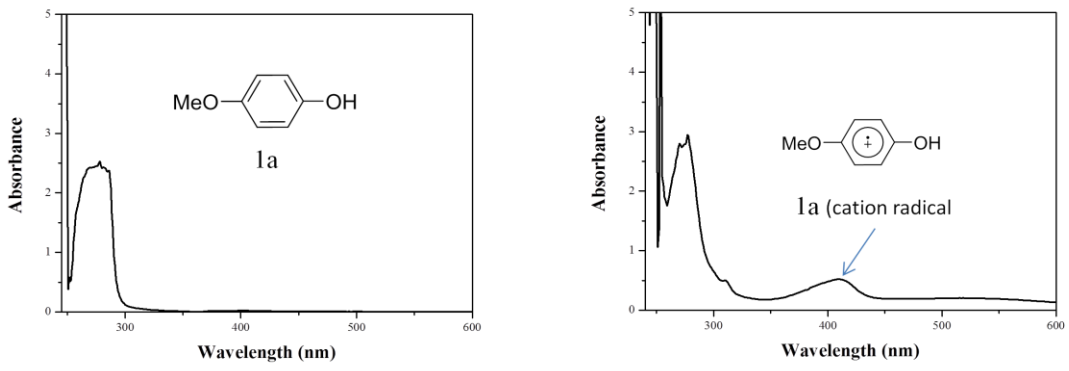
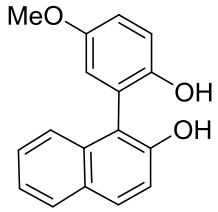



**Figure 1**: UV-Vis spectroscopy study at ambient temperature

Reference.1. Sankararaman, S.; Haney, W. A.; Kochi, J. K. *J. Am. Chem. Soc*. **1987**, *109*, 7824. (b) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujata, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc*. **1994**, *116*, 3684.

**4A.9: Spectral Data of Compounds**

**1-(2-Hydroxy-5-methoxyphenyl)naphthalene-2-ol (5aa).**



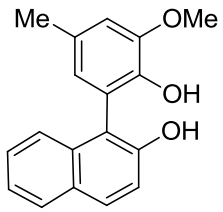

Colourless semisolid; eluent (12% ethyl acetate in hexanes). The reaction scale is 100 mg, the isolated amount is 112 mg, 61% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.85 (d, *J* = 8.0 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.37 (dd, *J* = 8.0, 4.0 Hz, 3 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.07 (d, *J* = 8.0 Hz, 1 H), 6.98 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.78 (d, *J* = 4.0 Hz, 1 H), 5.33 (s, 1 H), 4.55 (s, 1 H), 3.76 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 154.1, 151.6, 148.2, 132.9, 130.9, 129.1, 128.3, 127.3, 124.1, 123.8, 119.5, 117.7, 117.5, 116.9, 116.0, 114.05, 55.8.

**HRMS (ESI):** calc. for $[(C_{17}H_{14}O_3)H]$ (M+H) 267.1021, measured 267.1020.

**1-(2-Hydroxy-5-methoxyphenyl)naphthalen-2-ol (5ba).**



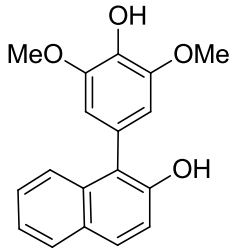

Colourless solid; eluent (12% ethyl acetate in hexanes). The reaction scale is 60 mg, isolated amount is 71 mg, 61% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.81 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.38 – 7.30 (m, 2 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 6.82 (s, 1 H), 6.72 (s, 1 H), 5.63 (s, 1 H), 5.46 (s, 1 H), 3.94 (s, 3 H), 2.35 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 150.7, 147.1, 141.6, 133.0, 130.3, 129.8, 129.1, 128.1, 126.4, 124.8, 124.3, 123.3, 119.2, 117.7, 116.5, 111.9, 56.0, 21.1

**HRMS (ESI):** calc. for $[(C_{18}H_{16}O_3)H]$ (M+H) 281.1178, measured 281.1173.

**1-(4-Hydroxy-3,5-dimethoxyphenyl)naphthalen-2-ol (5ca).**



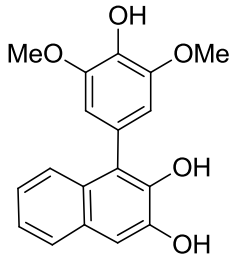

Brown semisolid; eluent (20 % ethyl acetate in hexanes). The reaction scale is 70 mg, isolated amount is 117 mg, 82% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.82 – 7.77 (m, 2 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.38 – 7.30 (m, 2 H), 7.26 (d, *J* = 8.0 Hz, 1 H), 6.62 (s, 2 H), 5.74 (s, 1 H), 5.39 (s, 1 H), 3.87 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 150.3, 147.9, 134.6, 133.4, 129.4, 128.8, 128.0, 126.5, 124.6, 123.2, 121.0, 117.2, 107.4, 56.3.

**HRMS (ESI):** calc. for $[(C_{18}H_{16}O_4)H]$ (M+H) 297.1127, measured 297.1126.

**1-(4-Hydroxy-3,5-dimethoxyphenyl)naphthalene-2,3-diol (5cb).**



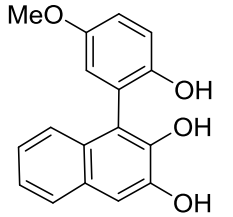

Brown solid; eluent (20 % ethyl acetate in hexanes). The reaction scale is 80 mg, isolated amount is 101 mg, 64% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz:** δ 7.68 (d, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.33 – 7.28 (m, 2 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 6.61 (s, 2 H), 5.70 (s, 3 H), 3.88 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 147.9, 144.3, 140.5, 134.7, 129.5, 128.3, 126.7, 124.6, 124.4, 124.1, 124.0, 121.8, 109.7, 107.1, 56.4.

**HRMS (ESI):** calc. for $[(C_{18}H_{16}O_5)H]$ (M+H) 313.1076, measured 313.1073.

**1-(2-Hydroxy-5-methoxyphenyl)naphthalene-2,3-diol (5ab).**



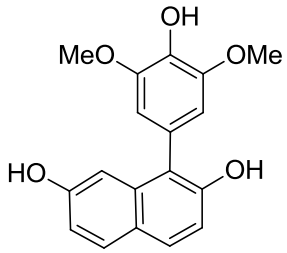
Brown semisolid; eluent (18 % ethyl acetate in hexanes). The reaction scale is 60 mg, isolated amount is 54 mg, 51% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.68 (d, *J* = 8.0 Hz, 1 H), 7.33 (td, *J* = 8.0, 4.0 Hz, 3 H), 7.26 (s, 1 H), 7.04 (d, *J* = 8.0 Hz, 1 H), 6.95 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.78 (d, *J* = 4.0 Hz, 1 H), 3.74 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 154.0, 147.8, 144.6, 141.8, 129.9, 127.6, 126.9, 124.7, 124.7, 124.2, 119.9, 117.6, 116.7, 116.07, 115.5, 110.9, 55.8.

**HRMS (ESI):** calc. for [($C_{17}H_{14}O_4$)H] (M+H) 283.0970, measured 283.0968.

**1-(4-Hydroxy-3,5-dimethoxyphenyl)naphthalene-2,7-diol.(5cc).**



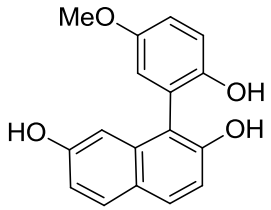

Brick red semisolid; eluent (18 % ethyl acetate in hexanes). The reaction scale is 80 mg, isolated amount is 115 mg, 74% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz:** δ 7.68 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.07 (d, *J* = 8.0 Hz, 1 H), 6.93 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.78 (d, *J* = 4.0 Hz, 1 H), 6.58 (s, 2 H), 5.71 (s, 2 H), 5.31 (s, 1 H), 3.82 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 154.4, 150.8, 147.8, 135.0, 134.4, 129.9, 129.3, 124.8, 124.1, 119.7, 114.9, 114.66, 107.3, 106.9, 56.3.

**HRMS (ESI):** calc. for [($C_{18}H_{16}O_5$)H] (M+H) 313.1076, measured 313.1071.

**1-(2-Hydroxy-5-methoxyphenyl)naphthalene-2,7-diol (5ac).**



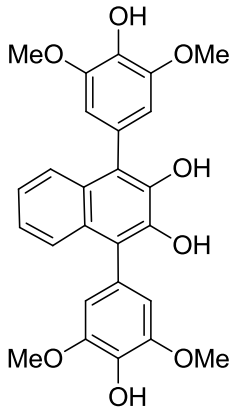

Pale yellow solid; eluent (20 % ethyl acetate in hexanes). The reaction scale is 60 mg, isolated amount is 70 mg, 69% yield.

**$^1$H NMR (MeOH-$d_4$, 400 MHz):** δ 7.69 (dd, *J* = 12.0, 8.0 Hz, 2 H), 7.06 (d, *J* = 8.0 Hz, 1 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 6.90 (t, *J* = 8.0 Hz, 2 H), 6.73 (d, *J* = 4.0 Hz, 1 H), 6.61 (s, 1 H), 5.70 (s, 1 H), 5.42 (s, 1 H), 4.80 (s, 1 H), 3.70 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 155.0, 153.9, 152.2, 148.1, 134.4, 130.7, 130.3, 124.4, 119.8, 117.4, 116.7, 116.1, 115.5, 115.1, 112.8, 106.3, 55.8.

**HRMS (ESI):** calc. for [($C_{17}H_{14}O_4$)H] (M+H) 283.0970, measured 283.0969.

**1,4-Bis(4-hydroxy-3,5-dimethoxyphenyl)naphthalene-2,3-diol (7a).**



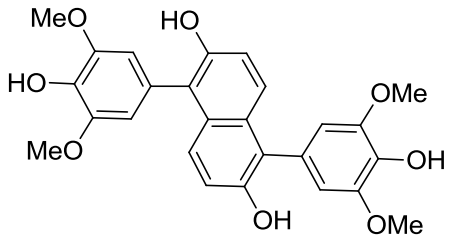

Brick red solid; eluent (35 % ethyl acetate in hexanes). The reaction scale is 40 mg, isolated amount is 82 mg, 71% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz**: δ 7.50 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.26 (dd, *J* = 4.0 Hz, 2 H), 6.66 (s, 4 H), 5.67 (s, 4 H), 3.89 (s, 12 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 147.6, 140.7, 134.6, 128.5, 125.0, 125.0, 124.2, 121.7, 107.3, 56.4.

**HRMS (ESI):** calc. for [($C_{26}H_{24}O_8$)H] (M+H) 465.1549, measured 465.1541.

**1,4-Bis(4-hydroxy-3,5-dimethoxyphenyl)naphthalene-2,6-diol (7b).**



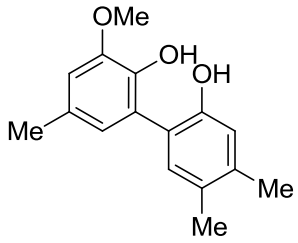

Brick red solid; eluent (40 % ethyl acetate in hexanes). The reaction scale is 60 mg, isolated amount is 125 mg, 69% yield.

**$^{1}$H NMR (MeOH-$d_4$, 400 MHz)**: δ 7.56 (d, *J* = 8.0 Hz, 1 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 7.11 (d, *J* = 8.0 Hz, 1 H), 7.06 (d, *J* = 8.0 Hz, 1 H), 6.68 – 6.58 (m, 4 H), 5.71 (s, 1 H), 5.06 (d, *J* = 4.0 Hz, 3 H), 3.90 (d, *J* = 4.0 Hz, 6 H), 3.86 (d, *J* = 8.0 Hz, 6 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 150.8, 149.2, 148.1, 135.0, 129.5, 128.5, 128.1, 125.6, 124.6, 122.0, 118.6, 118.2, 111.6, 107.5, 104.2, 56.5.

**HRMS (ESI):** calc. for [($C_{26}H_{24}O_8$)H] (M+H) 465.1549, measured 465.1543.

**3-Methoxy-4',5,5'-trimethyl-[1,1'-biphenyl]-2,2'-diol (8bd).**



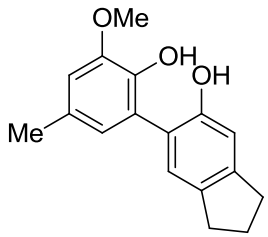

White solid; eluent (8 % ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 96 mg, 53% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz**: ) δ 7.04 (s, 1 H), 6.84 (s, 1 H), 6.73 (d, *J* = 4.0 Hz, 1 H), 6.70 (d, *J* = 4.0 Hz, 1 H), 6.16 (s, 1 H), 6.11 (s, 1 H), 3.91 (s, 3 H), 2.33 (s, 3 H), 2.25 (s, 3 H), 2.22 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 151.4, 146.3, 139.3, 137.9, 131.7, 130.4, 129.0, 123.9, 123.8, 122.5, 118.9, 110.7, 56.1, 21.2, 19.6, 18.8.

**HRMS (ESI):** calc. for [($C_{16}H_{18}O_3$)Na] (M+Na) 281.1154, measured 281.1161.

**6-(2-Hydroxy-3-methoxy-5-methylphenyl)-2,3-dihydro-1*H*-inden-5-ol (8be).**



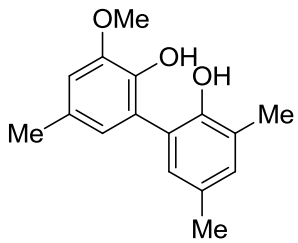

Colourless solid; eluent (8 % ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 101 mg, 56% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz**: δ 7.14 (s, 1 H), 6.93 (s, 1 H), 6.75 (s, 1 H), 6.72 (s, 1 H), 3.91 (s, 3 H), 2.94 – 2.86 (m, 4 H), 2.34 (s, 3 H), 2.10 (dd, *J* = 8.0, 4.0 Hz, 2 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 152.0, 146.3, 145.9, 139.3, 136.7, 130.4, 126.1, 124.3, 123.9, 123.1, 113.4, 110.8, 56.1, 32.9, 32.0, 25.8, 21.2.

**HRMS (ESI):** calc. for [($C_{17}H_{18}O_3$)H] (M+H) 271.1334, measured 271.1345.

**3,4'-Dimethoxy-5-methyl-[1,1'-biphenyl]-2,2'-diol (8bf).**



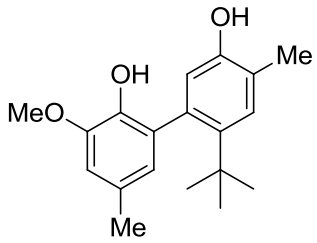
Yellow liquid; eluent (7 % ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 103 mg, 57% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz**: δ 6.99 (s, 1 H), 6.94 (s, 1 H), 6.74 (s, 1 H), 6.73 (s, 1 H), 3.91 (s, 3 H), 2.34 (s, 3 H), 2.31 (s, 3 H), 2.30 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 149.3, 146.3, 139.5, 131.3, 130.3, 129.5, 128.8, 126.1, 124.6, 124.1, 123.9, 110.92, 56.1, 21.1, 20.5, 16.4.

**HRMS (ESI):** calc. for [($C_{16}H_{18}O_3$)H] (M+H) 259.1334, measured 259.1345.

**5-(*tert*-Butyl)-3'-methoxy-3,5'-dimethyl-[1,1'-biphenyl]-2,2'-diol (8bg).**



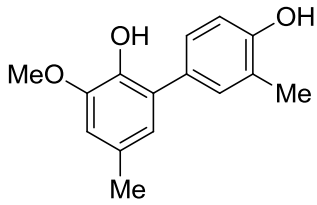

Yellow liquid; eluent (7 % ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 88 mg, 43% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz**: δ 7.18 (d, *J* = 4.0 Hz, 1 H), 7.11 (d, *J* = 4.0 Hz, 1 H), 6.73 (s, 2 H), 6.09 (s, 1 H), 6.08 (s, 1 H), 3.92 (s, 3 H), 2.34 (s, 3 H), 2.32 (s, 3 H), 1.31 (s, 9 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 149.3, 146.4, 143.0, 139.5, 130.4, 127.8, 125.5, 125.3, 124.5, 124.1, 124.0, 56.12, 34.1, 31.6, 21.2, 16.8.

**HRMS (ESI):** calc. for [($C_{19}H_{24}O_3$)Na] (M+Na) 323.1622, measured 323.1621.

**3-Methoxy-3',5-dimethyl-[1,1'-biphenyl]-2,4'-diol (8bh).**



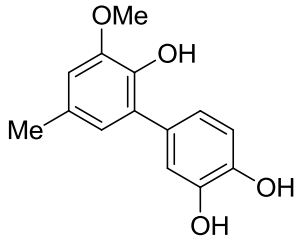

Brick red solid; eluent (6 % ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 75 mg, 43% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz**: δ 7.33 (s, 1 H), 7.30 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.71 (s, 1 H), 6.64 (s, 1 H), 5.62 (s, 1 H), 4.69 (s, 1 H), 3.89 (s, 3 H), 2.30 (s, 3 H), 2.27 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 153.0, 146.5, 140.3, 131.8, 130.3, 129.0, 127.9, 127.1, 123.5, 122.7, 114.7, 110.2, 56.1, 21.1, 15.9.

**HRMS (ESI):** calc. for [($C_{15}H_{16}O_3$)Na] (M+Na) 267.0996, measured 267.0995.

**3-Methoxy-5-methyl-[1,1'-biphenyl]-2,3',4'-triol (8bi).**



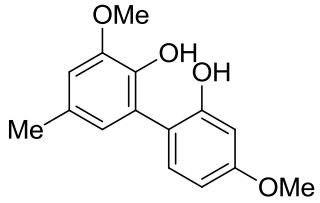

Red solid; eluent (18% ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 68 mg, 38% yield.

**$^1$H NMR (MeOH-$d_4$, 400 MHz)**: δ 6.77 (d, *J* = 8.0 Hz, 2 H), 6.69 (d, *J* = 4.0 Hz, 1 H), 6.63 (s, 1 H), 6.56 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.84 (s, 3 H), 2.16 (s, 3 H).

**$^{13}$C NMR (MeOH-$d_4$, 100 MHz):** δ 147.7, 145.7, 145.0, 144.9, 136.1, 135.2, 127.5, 121.8, 117.8, 117.6, 116.0, 114.8, 56.5, 20.1.

**HRMS (ESI):** calc. for [($C_{14}H_{14}O_4$)H] (M+H) 270.0970, measured 270.0973.

**3,4'-Dimethoxy-5-methyl-[1,1'-biphenyl]-2,2'-diol (8bj).**



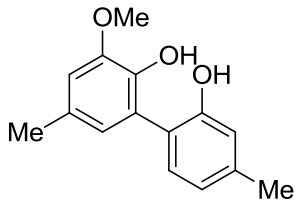

Colourless solid; eluent (12 % ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 47 mg, 26% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz**: δ 7.20 (d, *J* = 8.0 Hz, 1 H), 6.71 (s, 1 H), 6.70 (s, 1 H), 6.62 – 6.57 (m, 2 H), 6.59 (s, 1 H), 6.19 (s, 1 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 2.32 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 160.8, 154.6, 146.3, 139.2, 131.5, 130.5, 123.8, 123.7, 117.9, 110.7, 107.6, 102.8, 56.1, 55.3, 21.2.

**HRMS (ESI):** calc. for [($C_{15}H_{16}O_4$)Na] (M+Na) 283.0946, measured 283.0945.

**3-Methoxy-4',5-dimethyl-[1,1'-biphenyl]-2,2'-diol (8bk).**



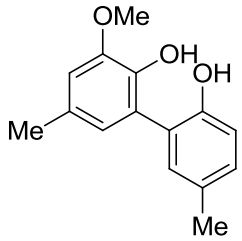

Red sold; eluent (7 % ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 83 mg, 49% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz**: δ 7.18 (d, *J* = 8.0 Hz, 1 H), 6.87 (s, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.73 (s, 1 H), 6.71 (s, 1 H), 6.36 (s, 1 H), 6.17 (s, 1 H), 3.91 (s, 3 H), 2.35 (s, 3 H), 2.33 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 153.3, 146.3, 139.5, 139.3, 130.7, 130.5, 123.8, 123.8, 122.4, 121.9, 118.2, 110.8, 56.1, 21.2, 21.1.

**HRMS (ESI):** calc. for [($C_{15}H_{16}O_3$)H] (M+H) 245.1178, measured 245.1177.

**3-Methoxy-5,5'-dimethyl-[1,1'-biphenyl]-2,2'-diol (8bl).**



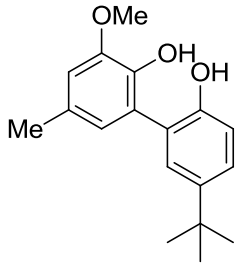

Pale red solid; eluent (7 % ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 70 mg, 42% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz**: δ 7.09 (d, *J* = 8.0 Hz, 2 H), 6.94 (d, *J* = 8.0Hz, 1 H), 6.74 (s, 1 H), 6.72 (s, 1 H), 6.26 (s, 1 H), 6.19 (s, 1 H), 3.91 (s, 3 H), 2.34 (s, 3 H), 2.32 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 151.3, 146.3, 139.3, 131.3, 130.5, 130.2, 130.0, 125.1, 124.0, 123.8, 117.5, 110.9, 56.1, 21.2, 20.5.

**HRMS (ESI):** calc. for [($C_{15}H_{16}O_3$)H] (M+H) 245.1178, measured 245.1182.

**5'-(*tert*-Butyl)-3-methoxy-5-methyl-[1,1'-biphenyl]-2,2'-diol (8bm).**



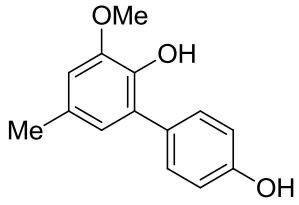

Yellow liquid; eluent (7 % ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 77 mg, 38% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz**: δ 7.31 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.28 (d, *J* = 4.0 Hz, 1 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 6.74 (s, 1 H), 6.73 (s, 1 H), 6.27 (s, 1 H), 6.19 (s, 1 H), 3.92 (s, 3 H), 2.35 (s, 3 H), 1.32 (s, 9 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 151.2, 146.3, 143.7, 139.3, 130.5, 127.8, 126.3, 124.6, 124.4, 124.0, 117.2, 110.9, 56.6, 34.2, 31.6, 21.2.

**HRMS (ESI):** calc. for [($C_{18}H_{22}O_3$)Na] (M+Na) 309.1467, measured 309.1471.

**3-Methoxy-5-methyl-[1,1'-biphenyl]-2,4'-diol (8bn).**



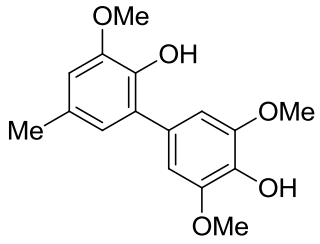

Yellow liquid; eluent (12 % ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 53 mg, 33% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz**: δ 7.28 (dd, *J* = 8.0, 4.0 Hz, 2 H), 7.02 (dd, *J* = 8.0, 4.0 Hz, 2 H), 6.74 (s, 1 H), 6.73 (s, 1 H), 6.36 (s, 1 H), 6.17 (s, 1 H), 3.92 (s, 3 H), 2.33 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 153.5, 146.3, 139.4, 130.9, 130.6, 129.3, 125.4, 123.9, 123.78, 121.0, 117.7, 111.1, 56.2, 21.2.

**HRMS (ESI):** calc. for [($C_{14}H_{14}O_3$)H] (M+H) 231.1021, measured 231.1024.

**3,3',5'-Trimethoxy-5-methyl-[1,1'-biphenyl]-2,4'-diol (8cb).**



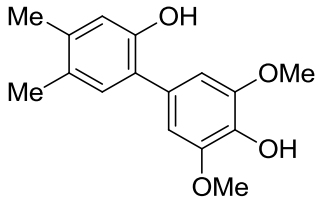

Yellow liquid; eluent (18 % ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 96 mg, 48% yield.

**$^1$H NMR ($CDCl_3$, 400 MHz**: δ 6.83 (s, 1 H), 6.73 (s, 1 H), 6.49 (s, 2 H), 5.52 (s, 2 H), 3.89 (s, 3 H), 3.86 (s, 6 H), 2.21 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 146.6, 145.5, 143.2, 134.9, 133.6, 132.8, 126.8, 115.9, 112.7, 106.3, 56.3, 56.0, 20.0.

**HRMS (ESI):** calc. for [($C_{16}H_{18}O_5$)H] (M+H) 291.1232, measured 191.1233.

**3',5'-Dimethoxy-4,5-dimethyl-[1,1'-biphenyl]-2,4'-diol (8cd).**



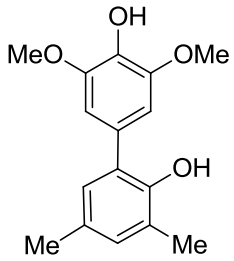

White solid; eluent (15 % ethyl acetate in hexanes). The reaction scale is 100 mg, isolated amount is 116mg, 59% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz**: δ 6.98 (s, 1 H), 6.78 (s, 1 H), 6.63 (s, 2 H), 5.58 (s, 1 H), 5.17 (s, 1 H), 3.88 (s, 6 H), 2.24 (s, 3 H), 2.21 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 150.1, 147.6, 137.5, 134.3, 130.9, 128.5, 128.1, 125.4, 116.8, 105.8, 56.4, 19.6, 18.7.

**HRMS (ESI):** calc. for $[(C_{16}H_{18}O_4)H]$ (M+H) 275.1283, measured 275.1286.

**3',5'-Dimethoxy-3,5-dimethyl-[1,1'-biphenyl]-2,4'-diol (8cf).**




Colourless semisolid; eluent (20 % ethyl acetate in hexanes). The reaction scale is 80 mg, isolated amount is 100 mg, 56% yield.

**$^{1}$H NMR ($CDCl_3$, 400 MHz:** δ 6.93 (s, 1 H), 6.85 (s, 1 H), 6.62 (s, 2 H), 5.58 (s, 1 H), 5.22 (s, 1 H), 3.89 (s, 6 H), 2.26 (d, *J* = 4.0 Hz, 6 H).

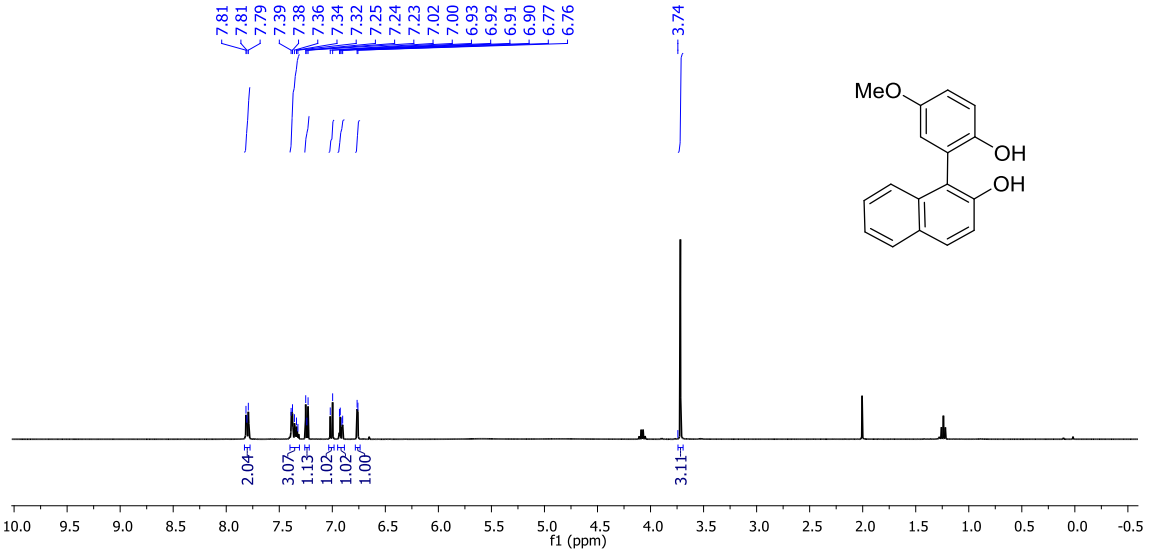
**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 148.3, 147.6, 134.3, 131.0, 129.2, 128.3, 127.8, 127.4, 124.3, 105.6, 56.4, 20.4, 16.1.

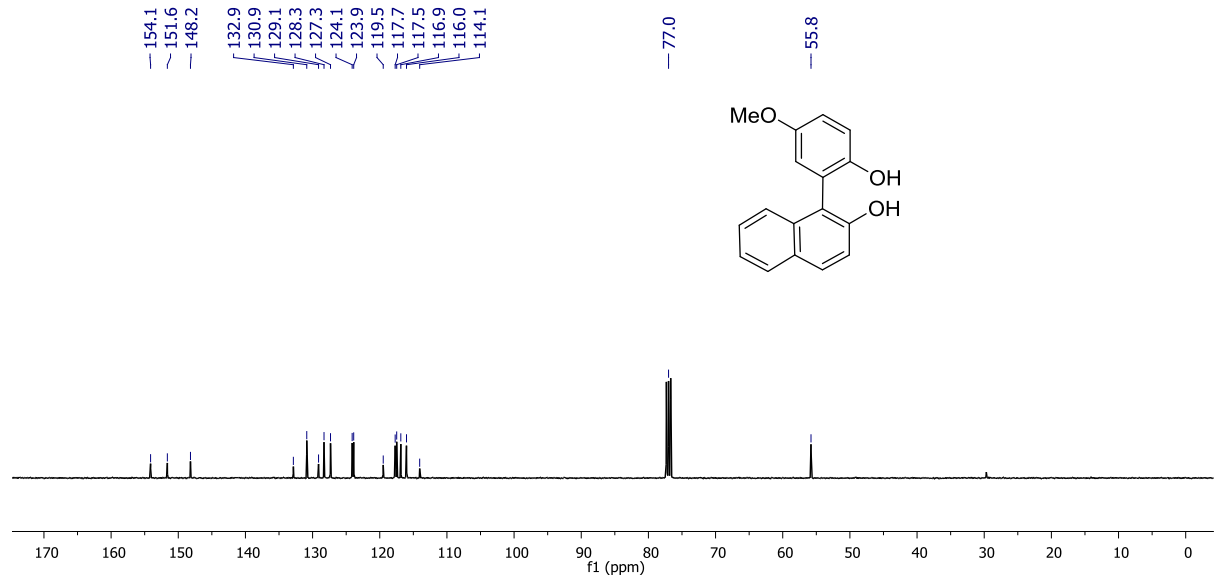
**HRMS (ESI):** calc. for $[(C_{16}H_{18}O_4)H]$ (M+H) 275.1283, measured 275.1284.

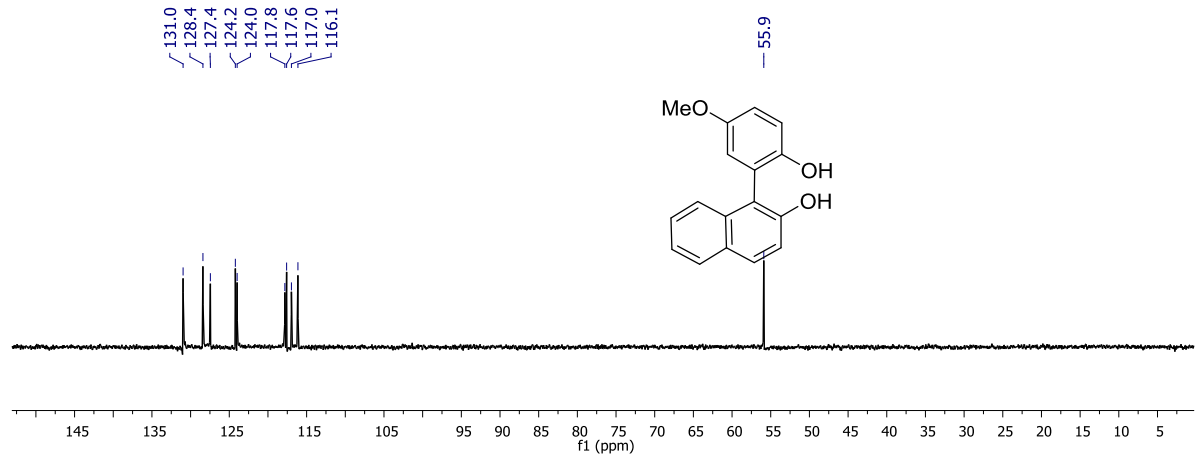
.

## 4A.10: Spectral Copies of Selected Compounds

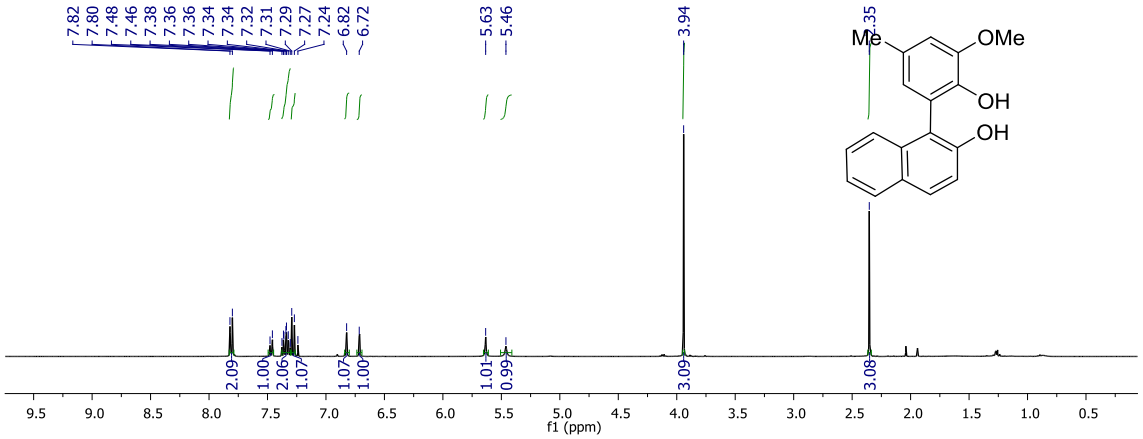
$^{1}$H and $^{13}$C NMR Spectra of Compound **5aa.**

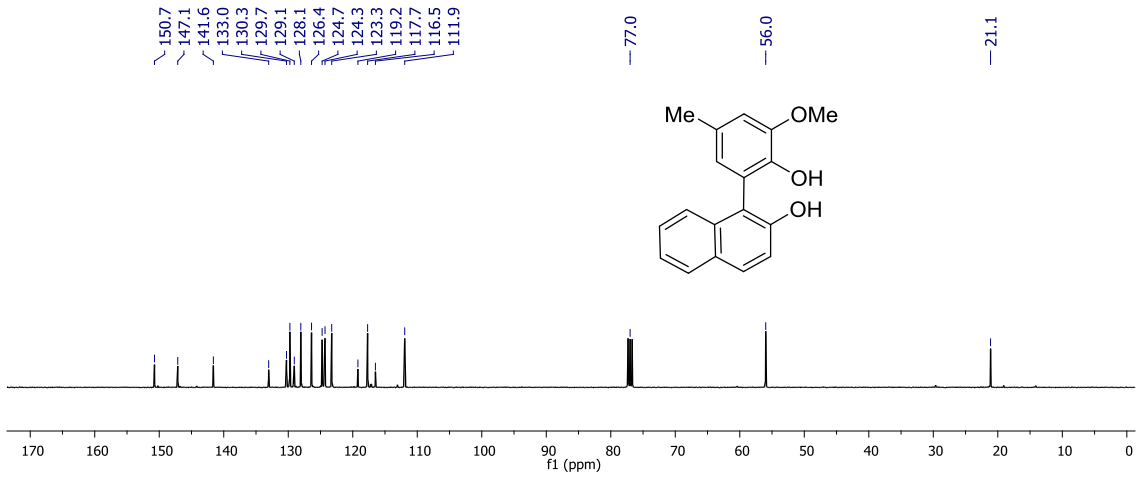


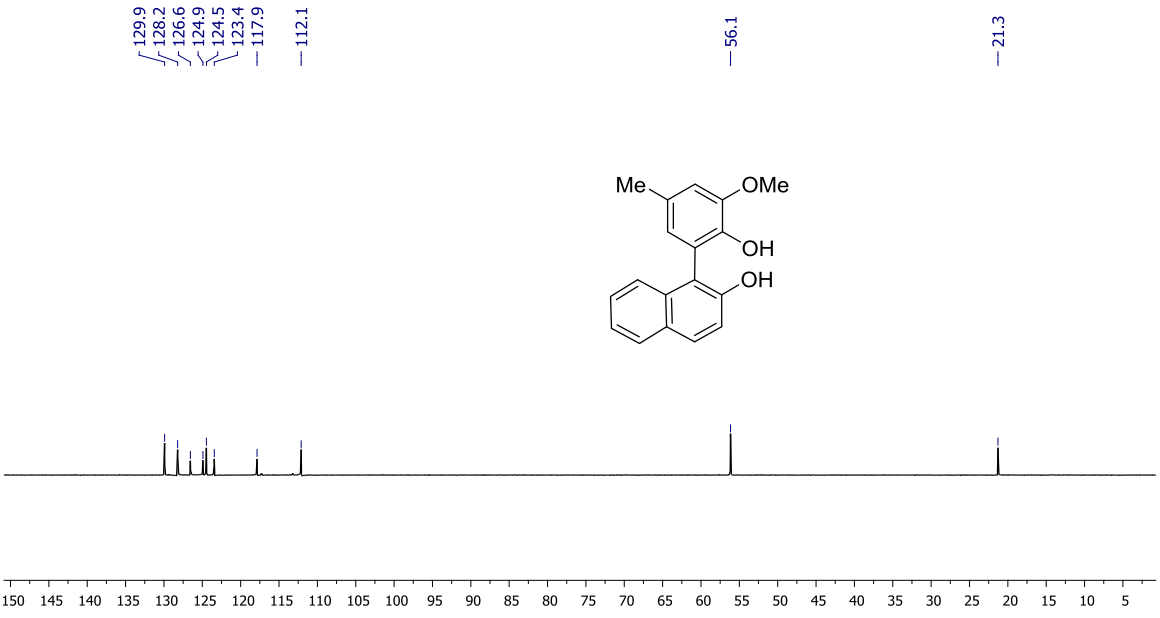



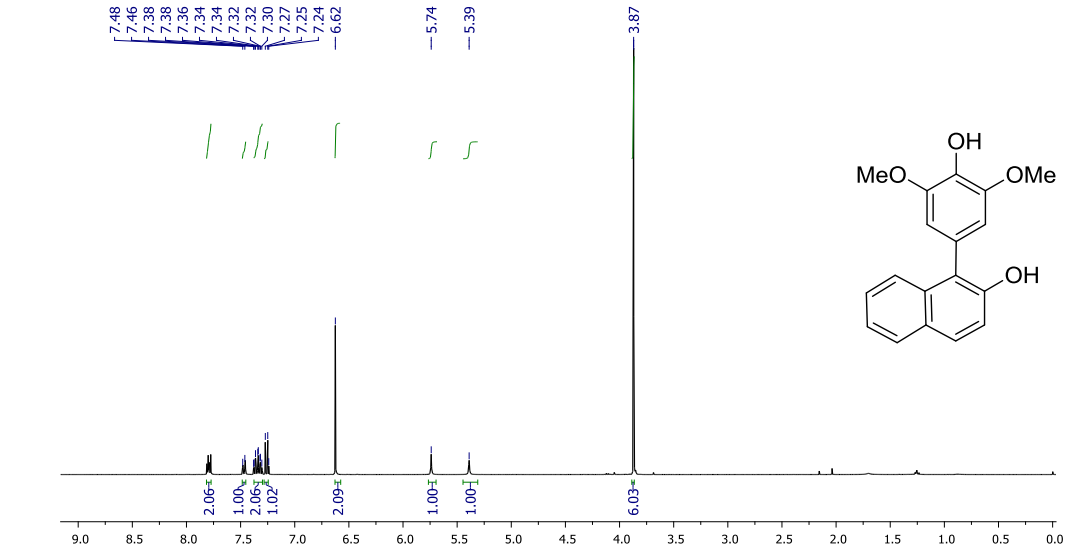
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **5ba**.

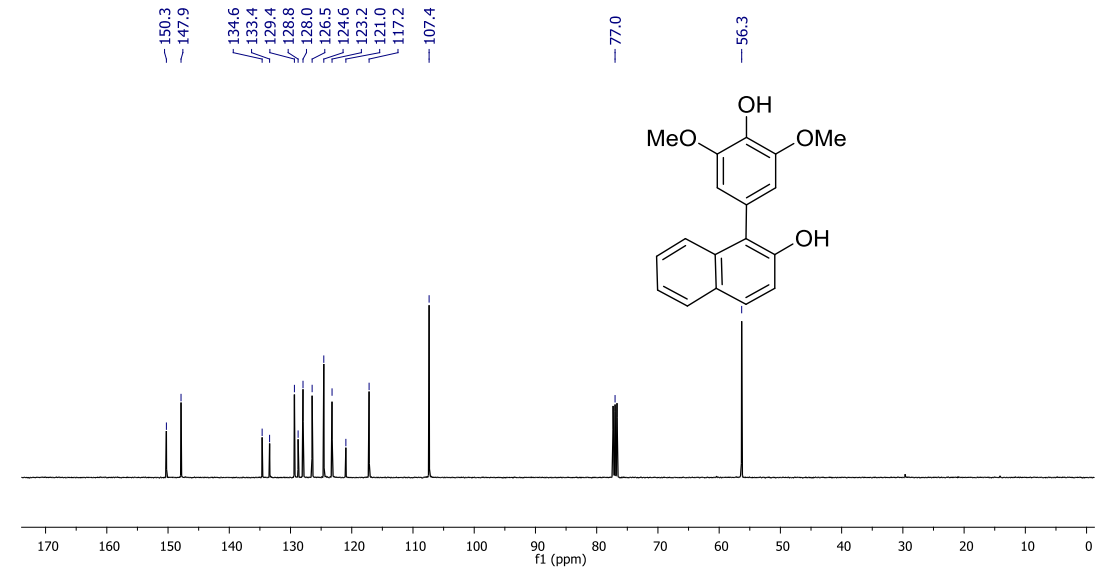


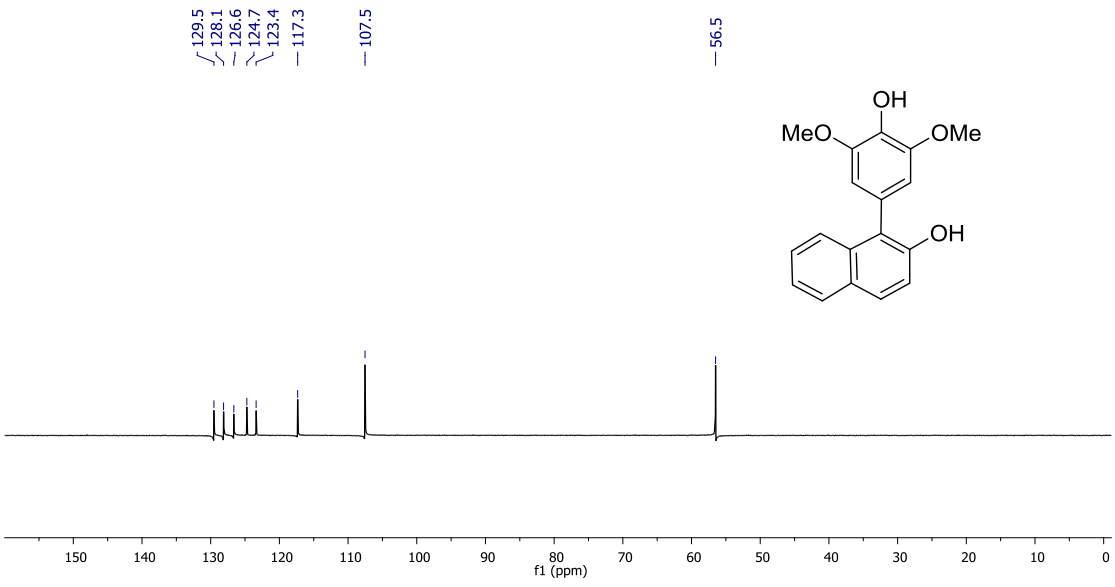



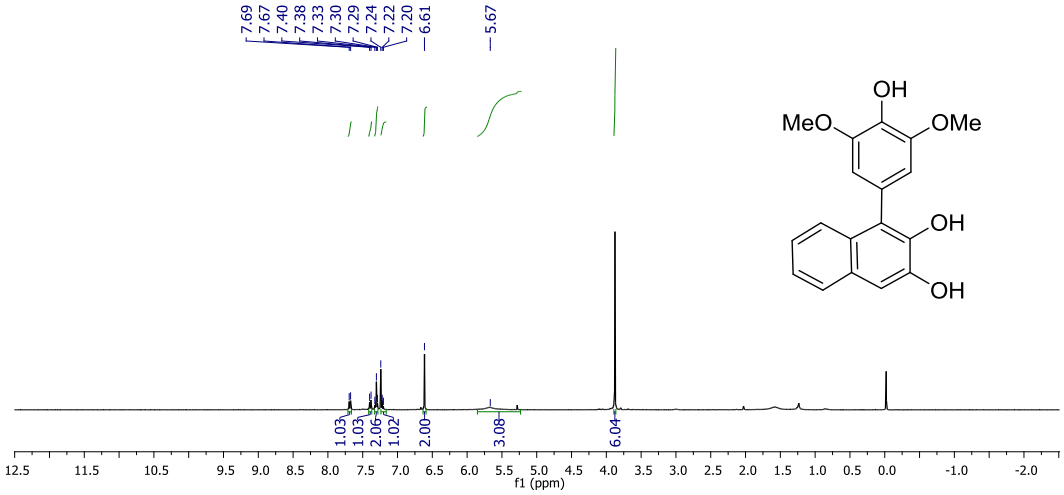
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **5ca**.

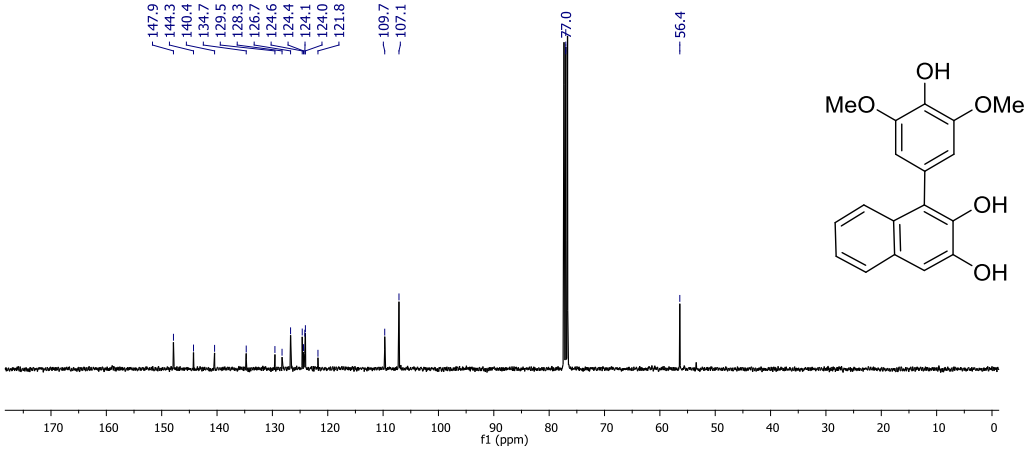


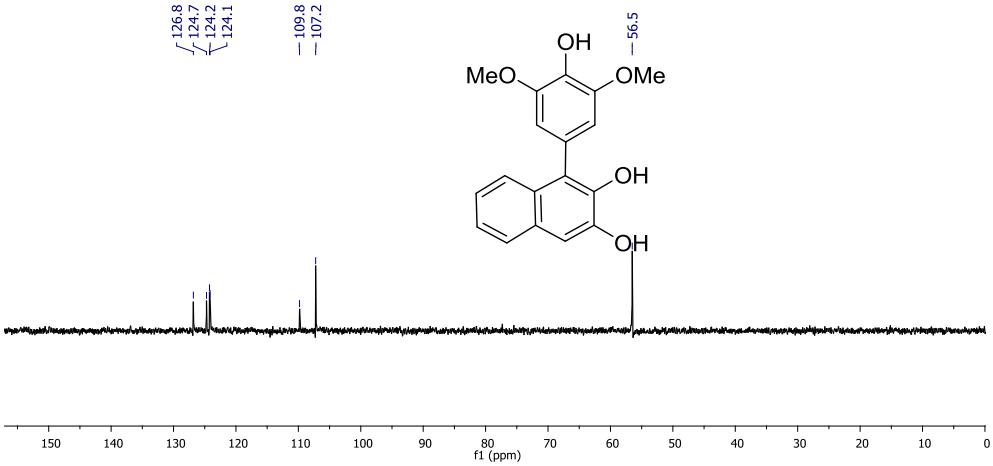



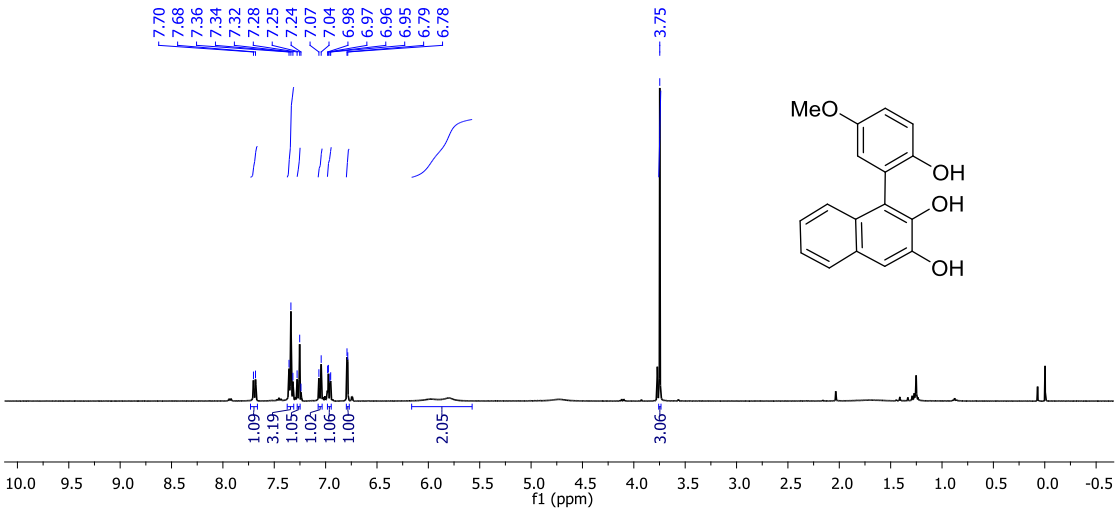
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **5cb**.

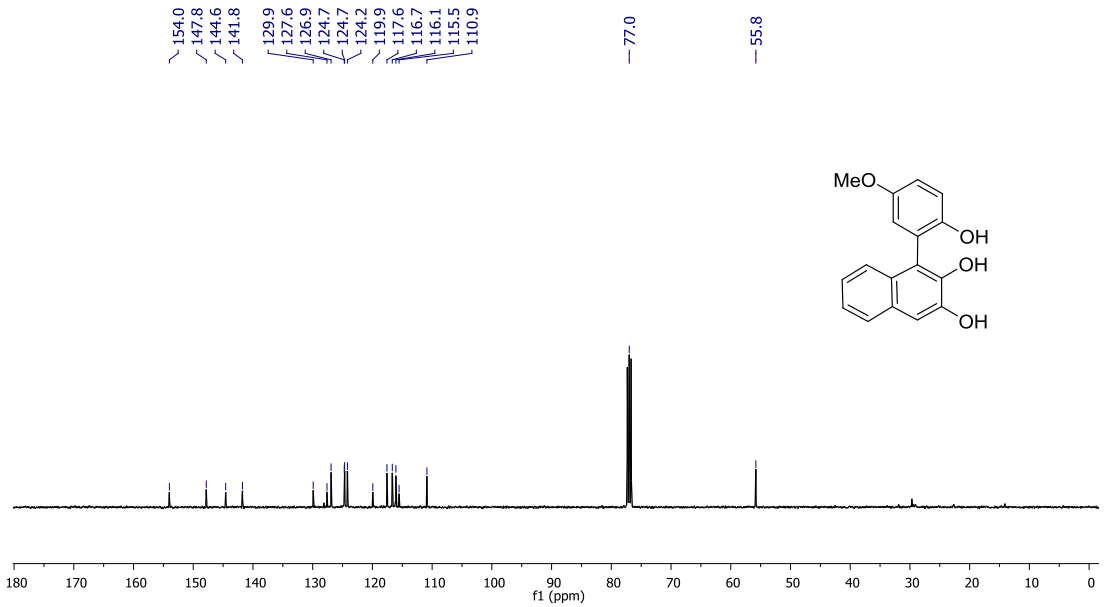


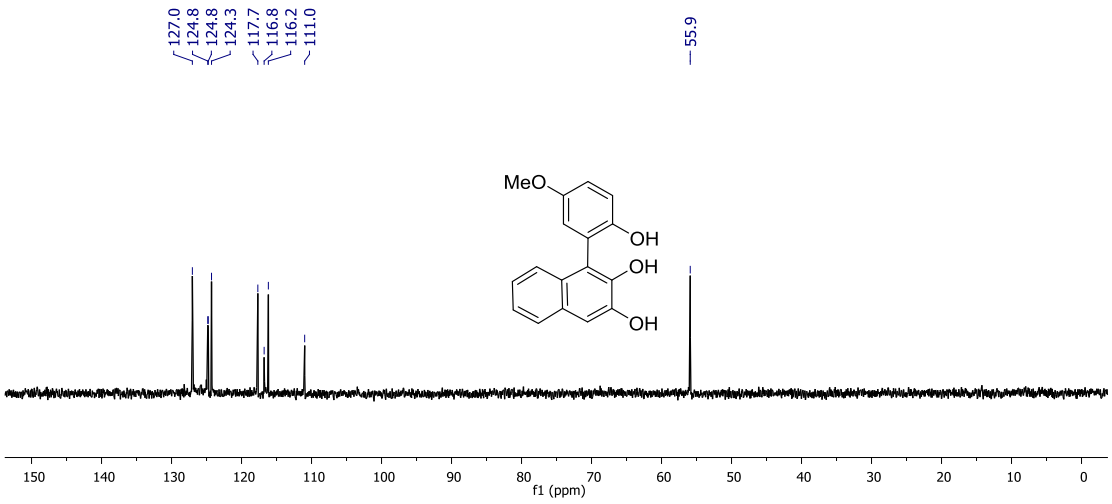



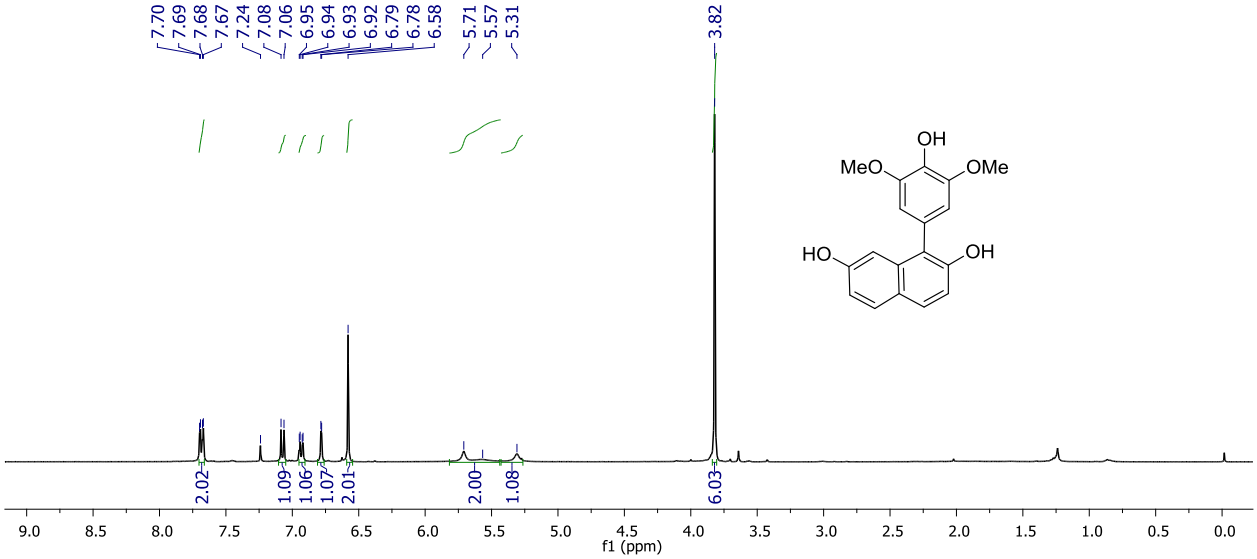
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **5ab**.

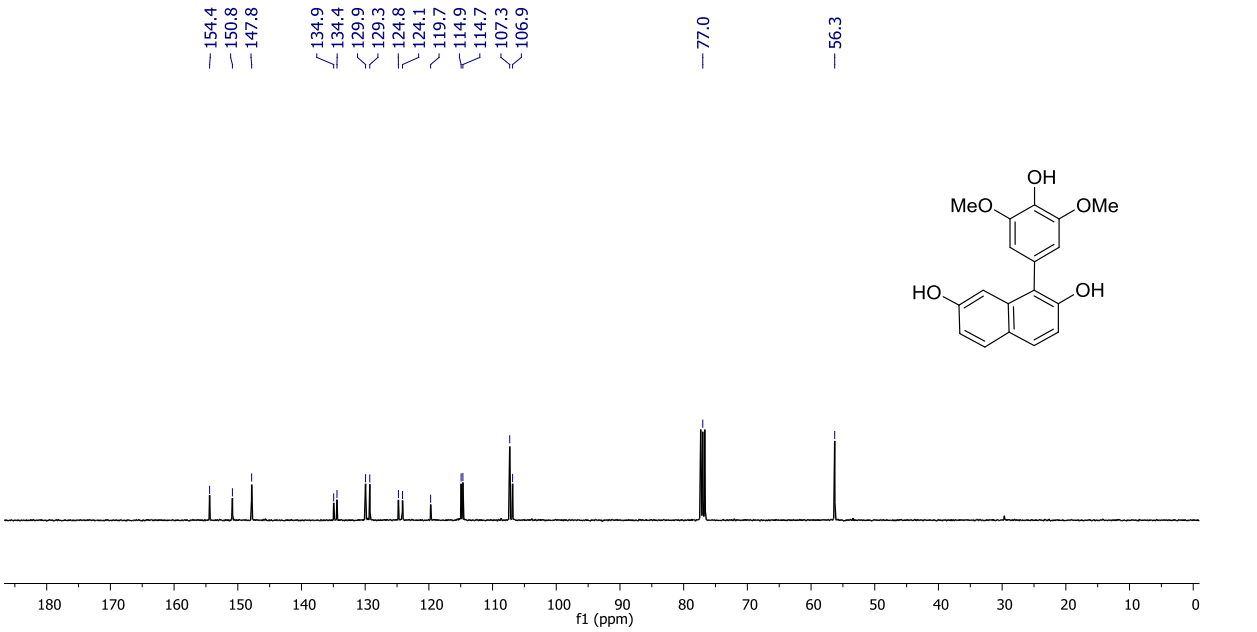


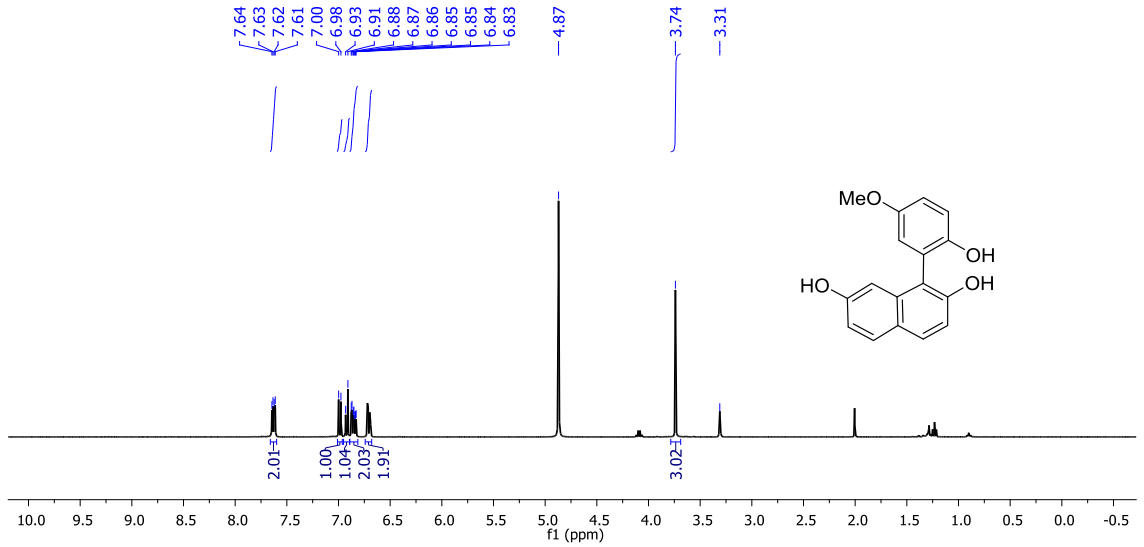



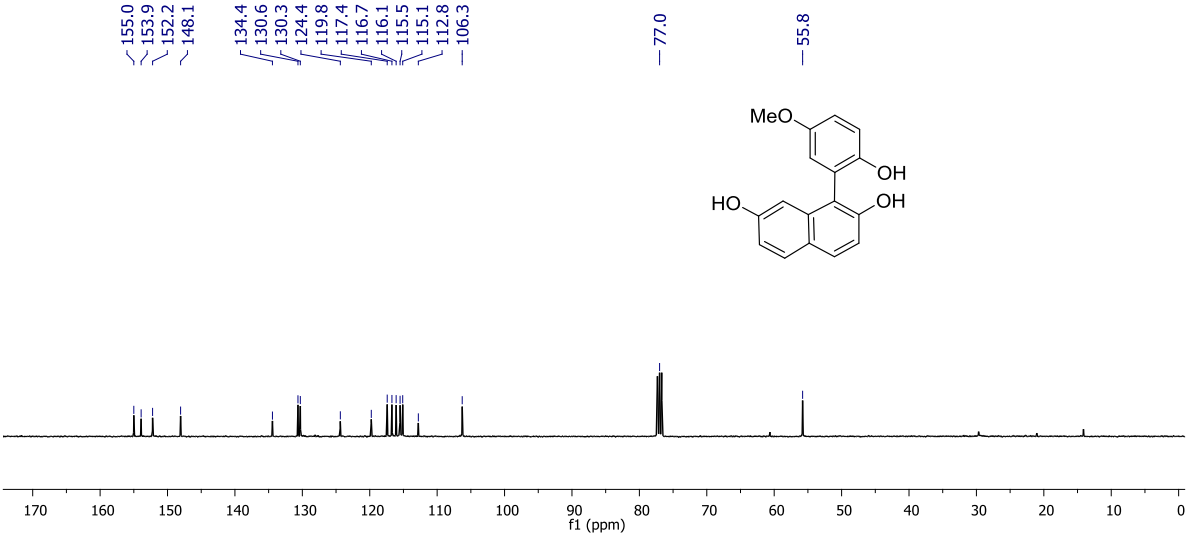
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **5cc**.

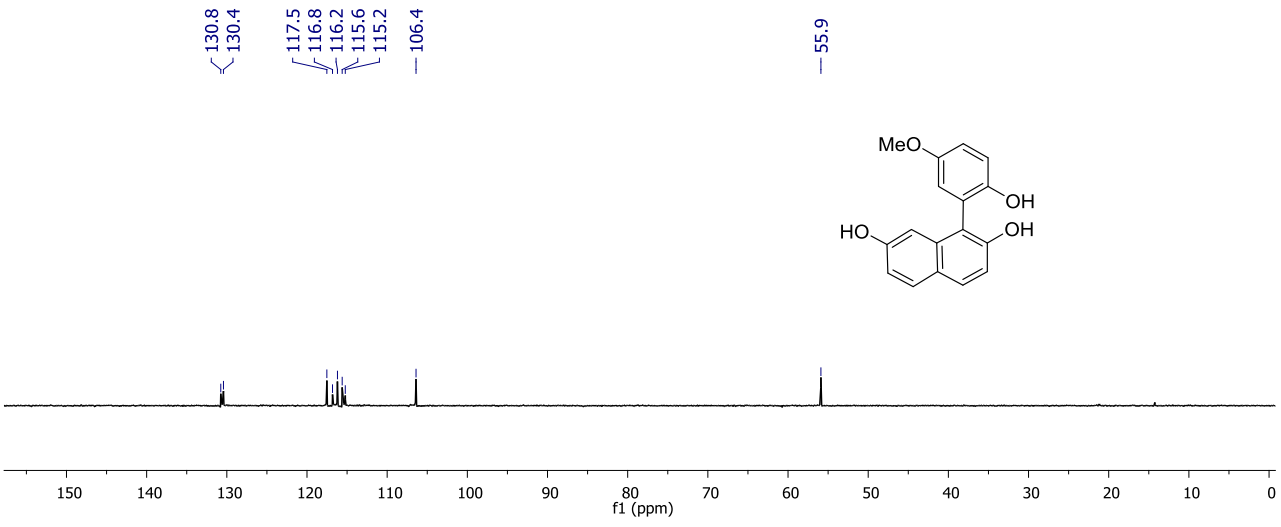


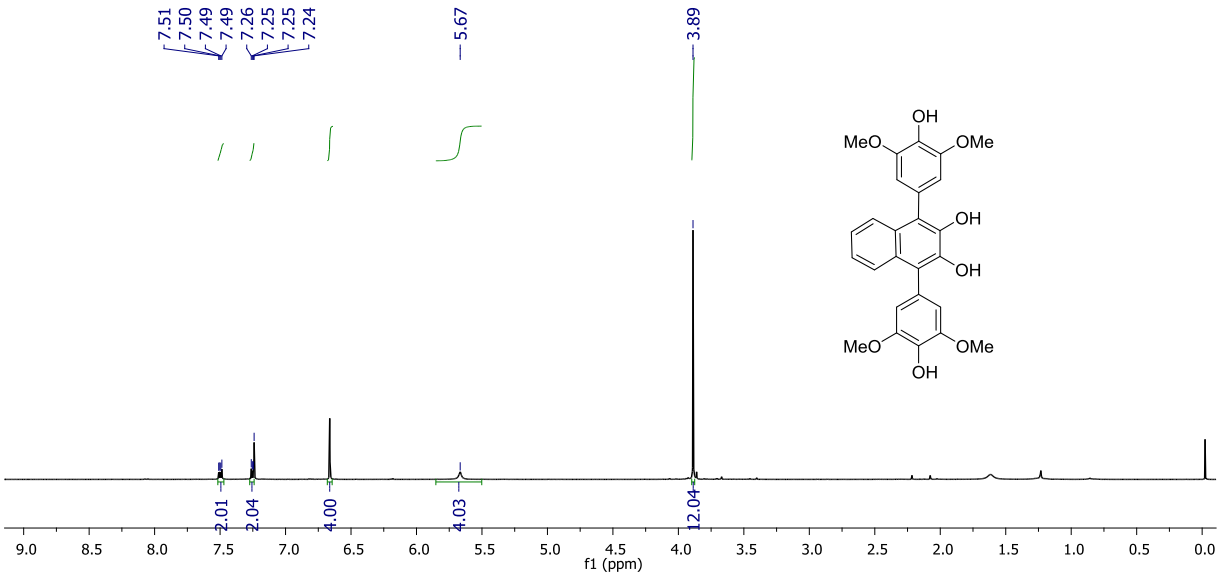
$^{1}$H and $^{13}$C NMR Spectra of Compound **5ac**.

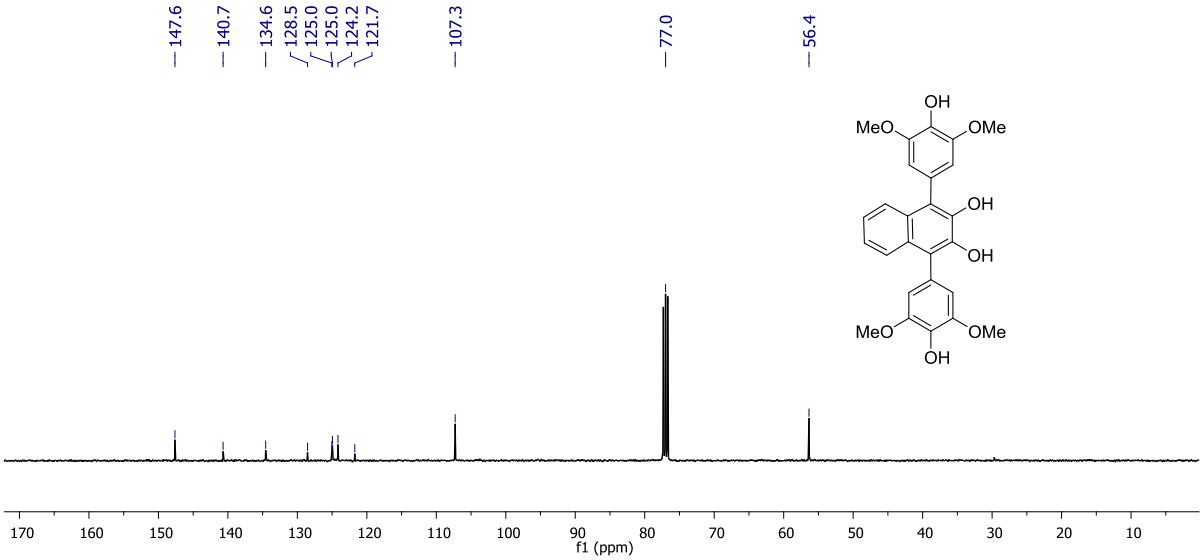


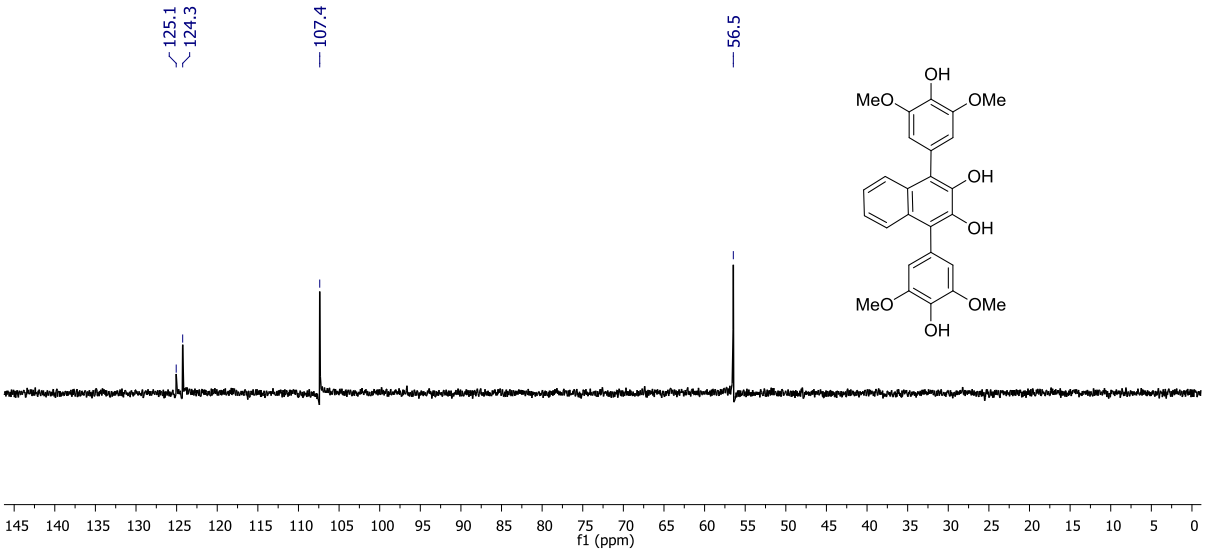



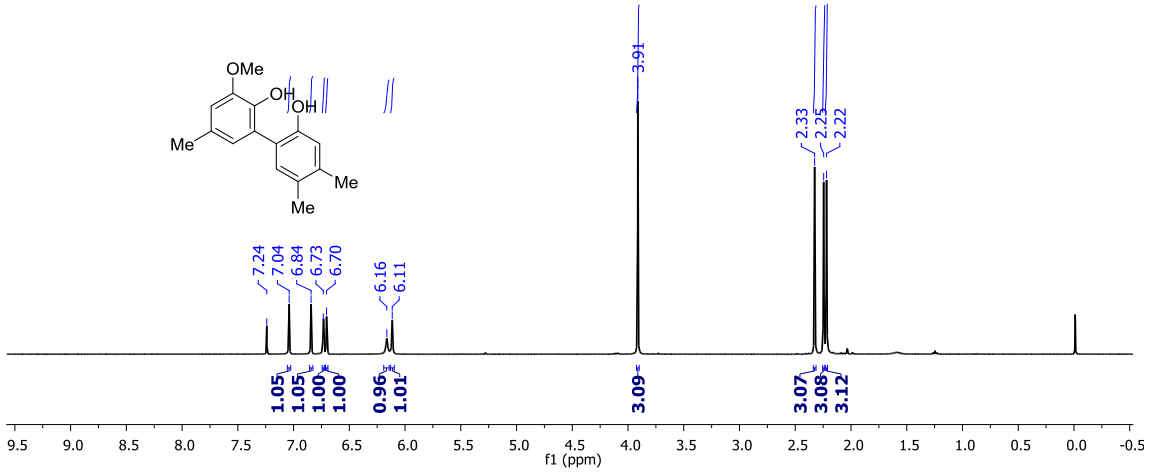
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **7a**.

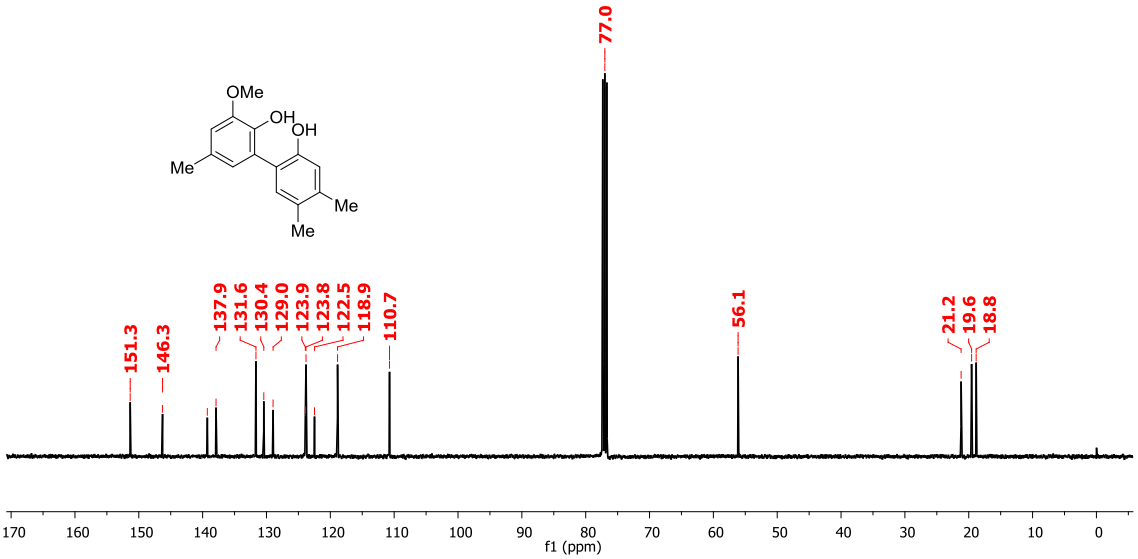


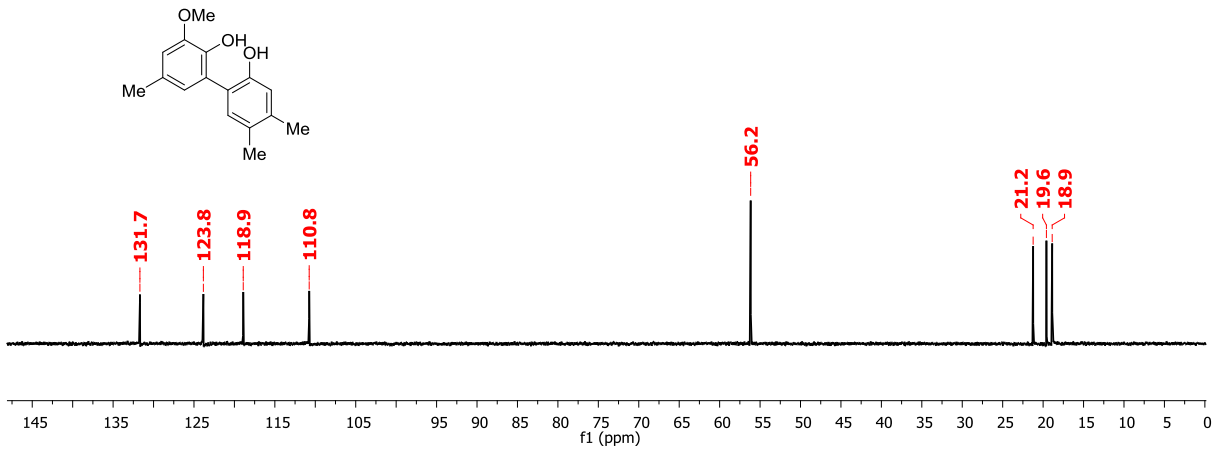



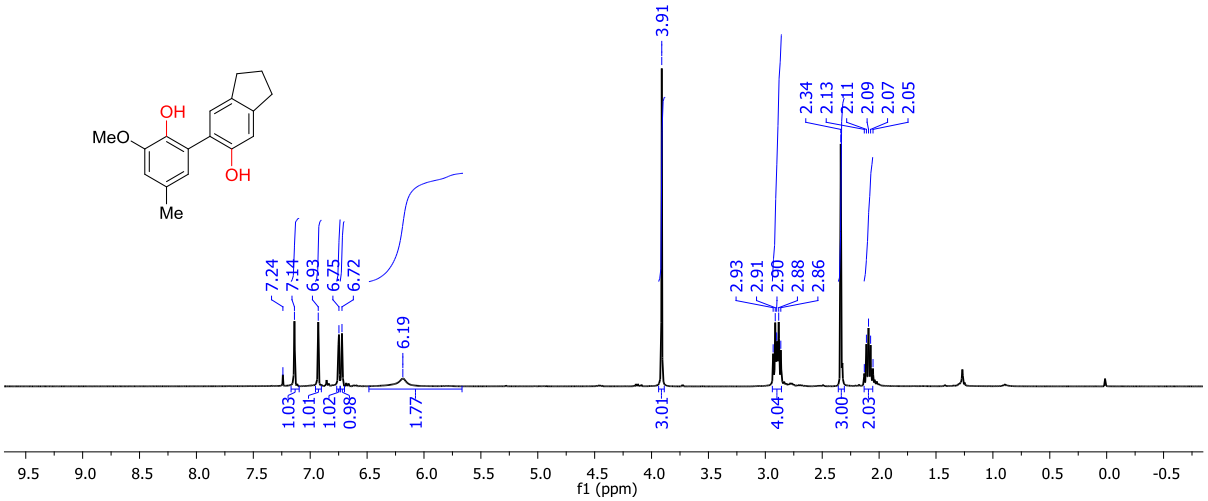
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **8bd**.

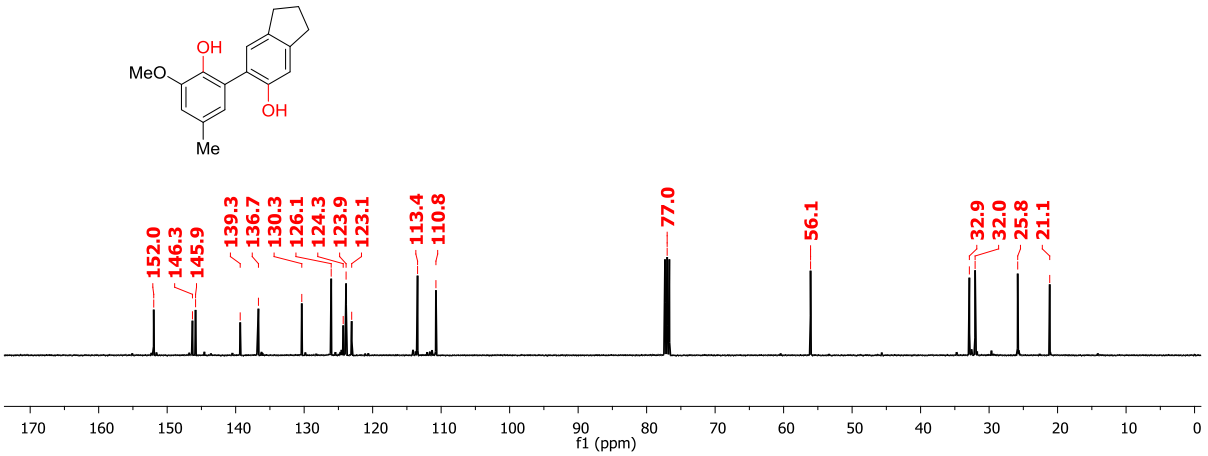


$^{1}H$ and $^{13}C$ NMR Spectra of Compound **8be**.



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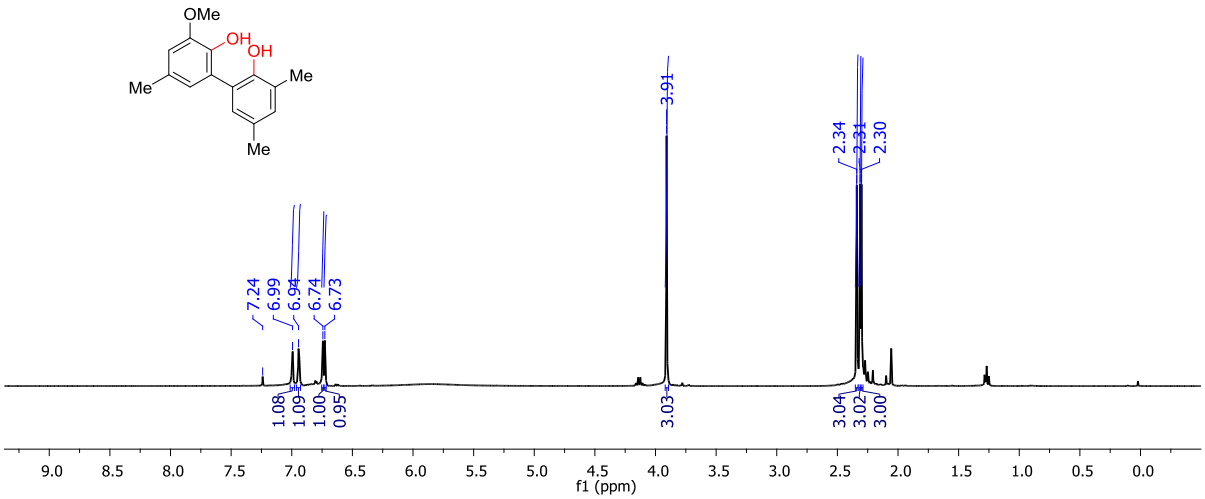
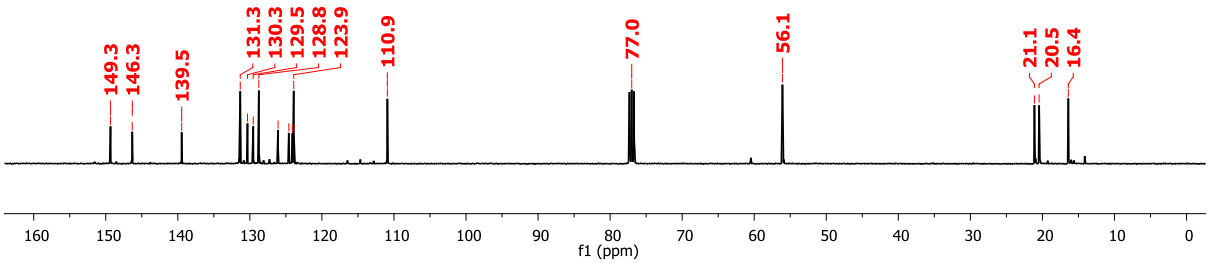
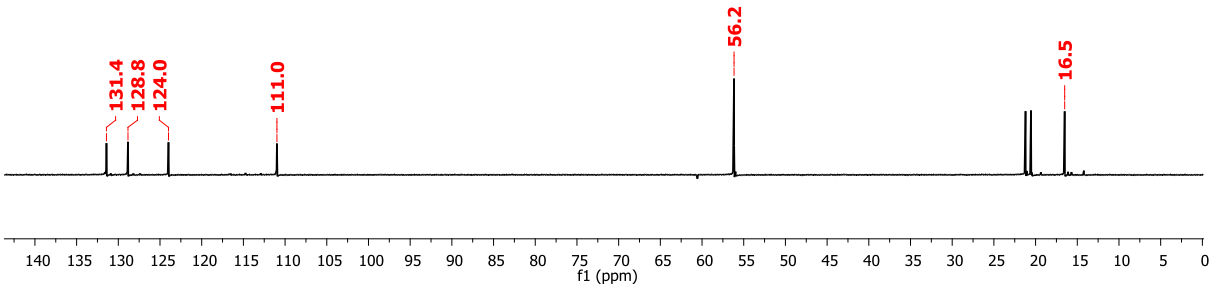
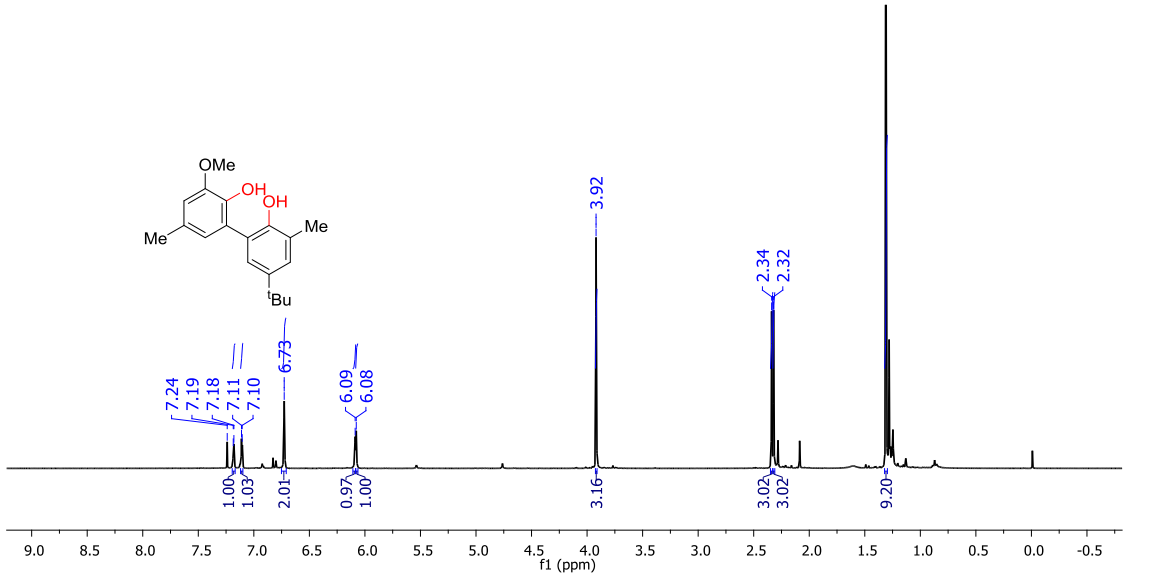
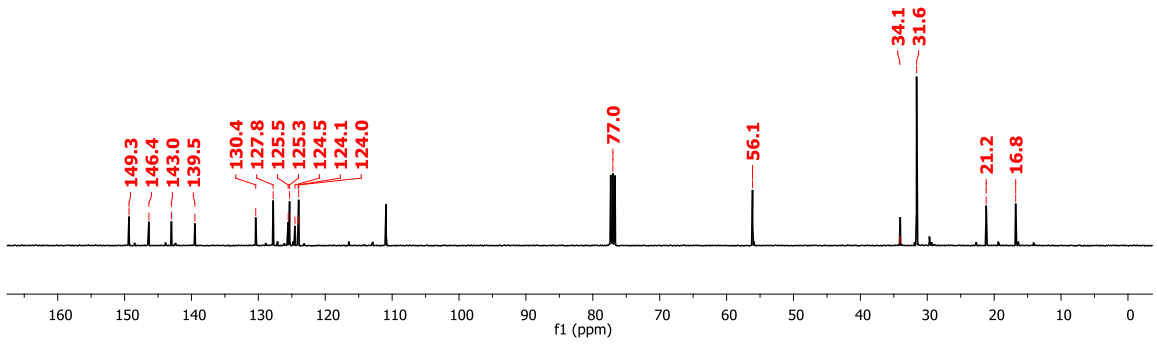


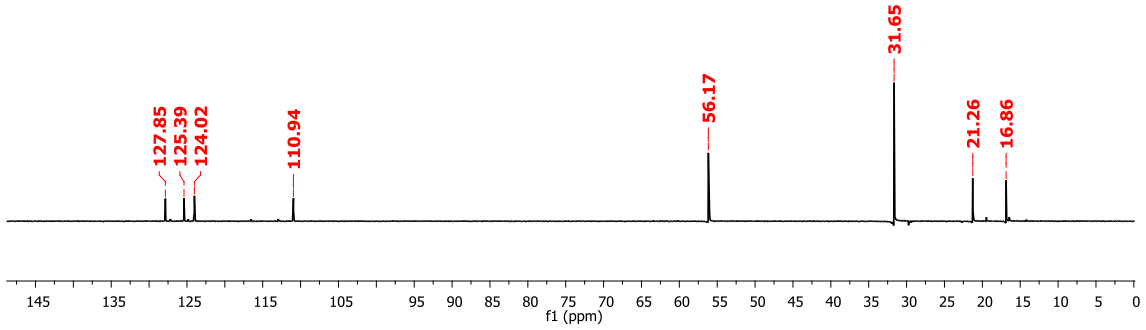



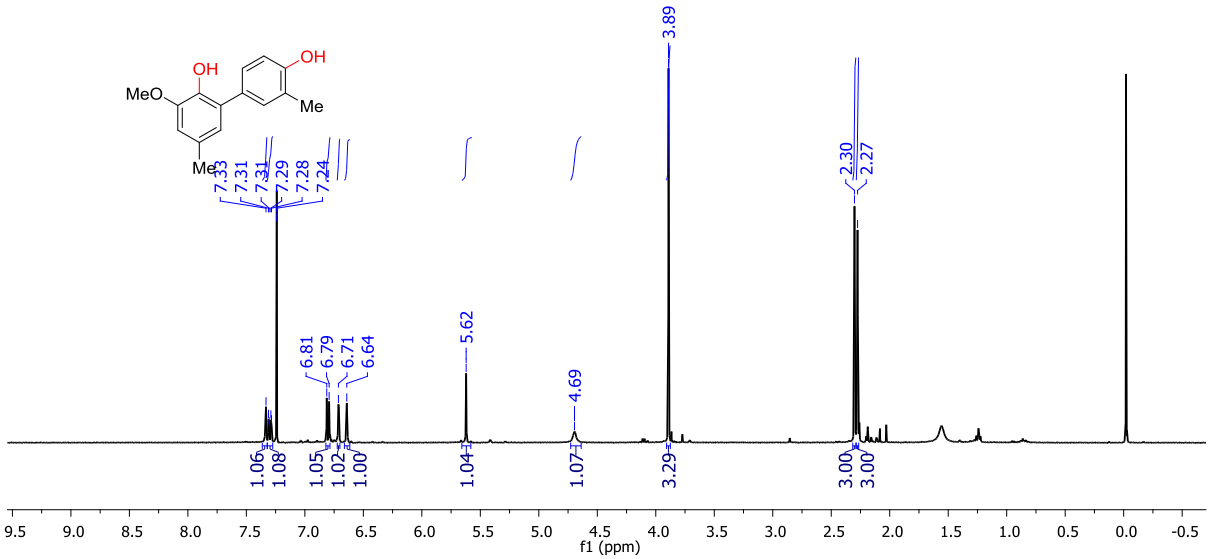
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **8bg.**

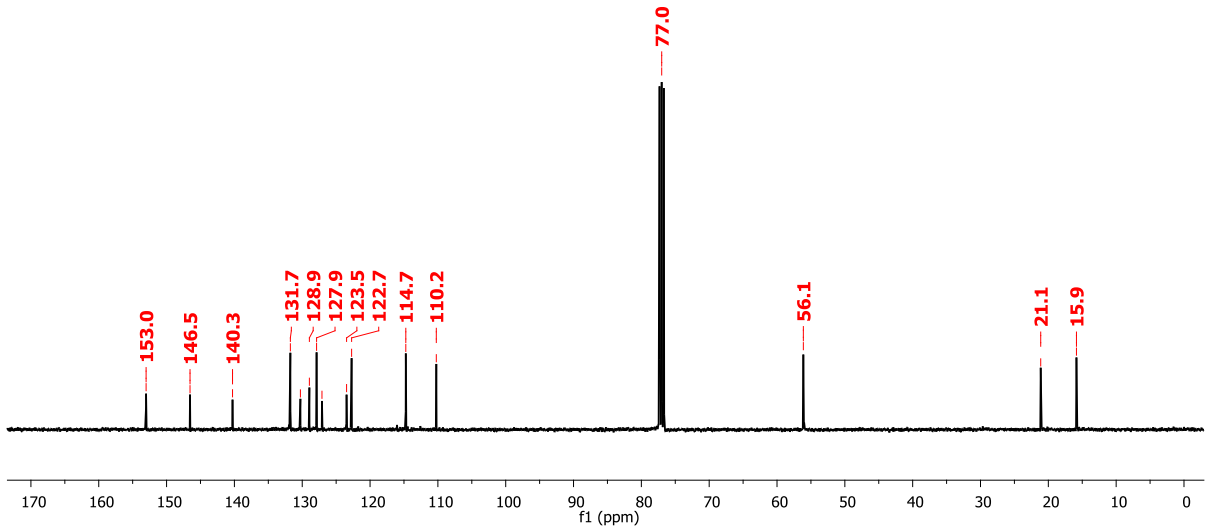


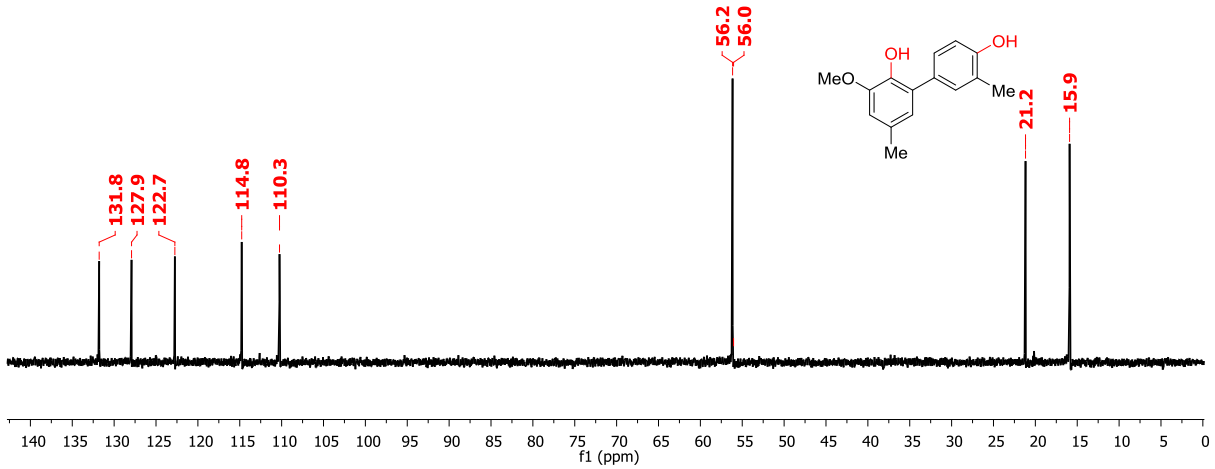



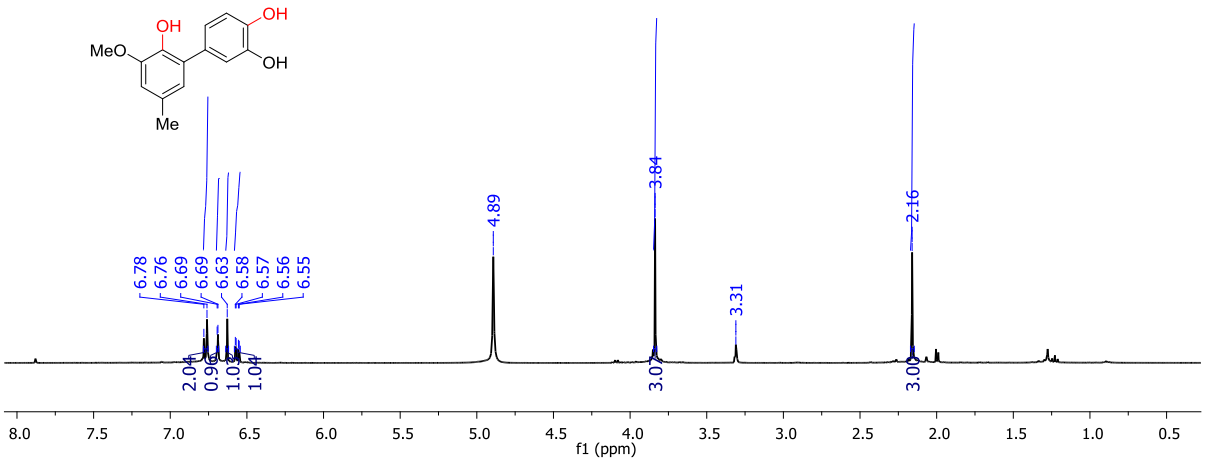
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **8bh**.

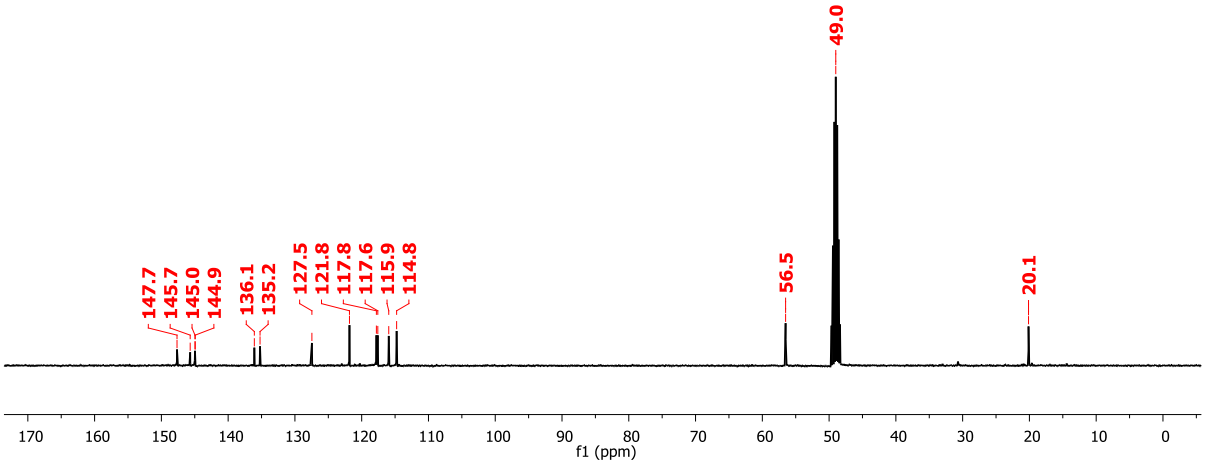


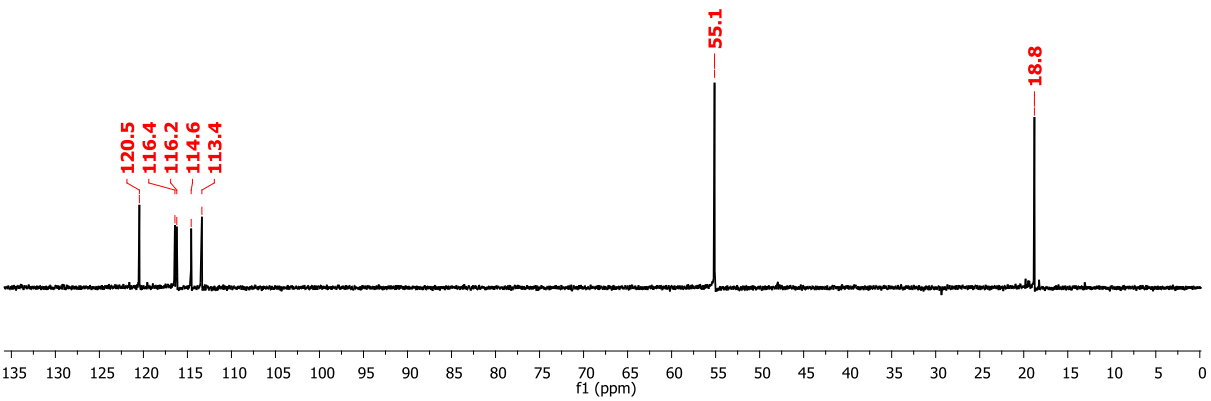



$^{1}H$ and $^{13}C$ NMR Spectra of Compound **8bi**.



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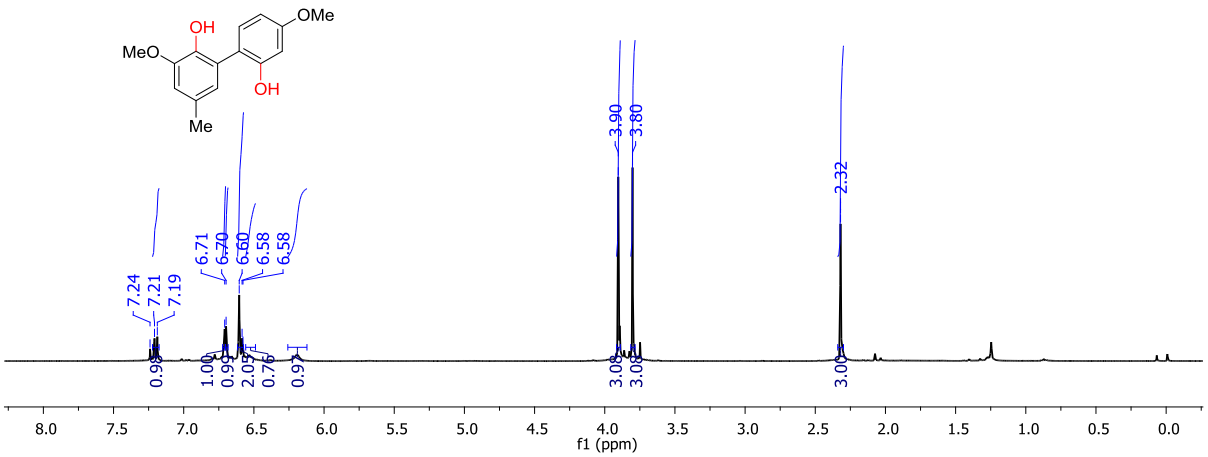


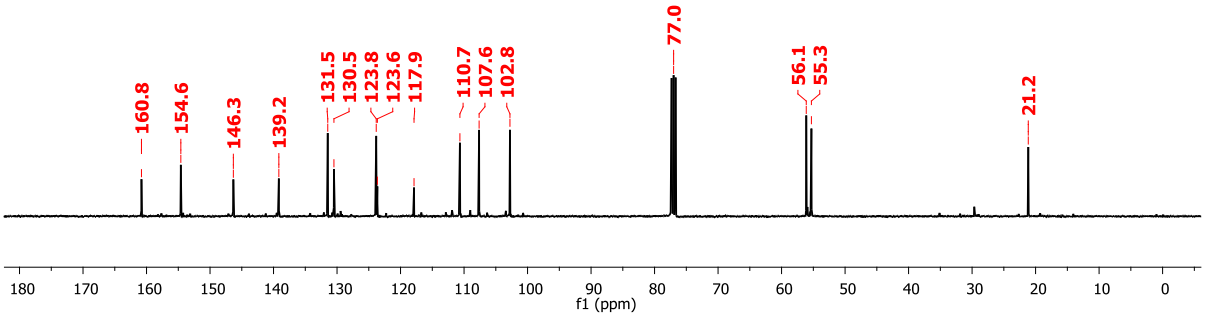


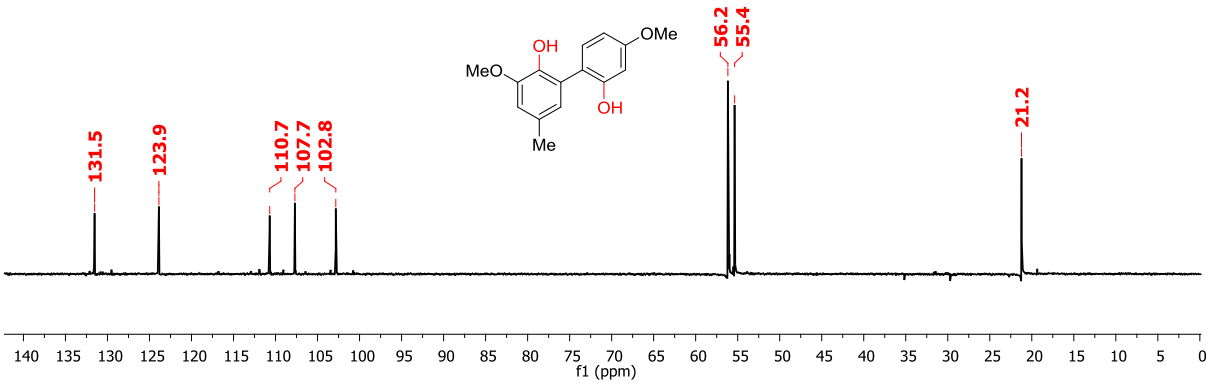

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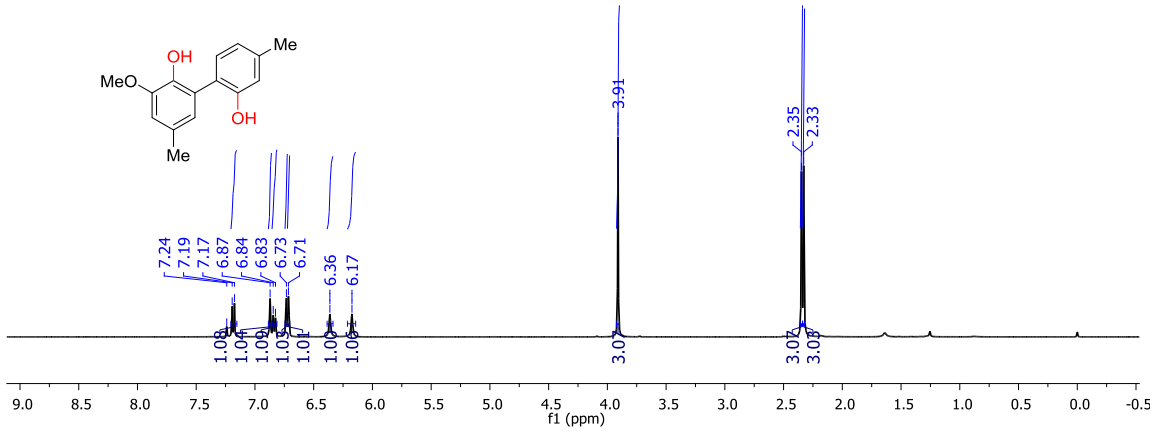


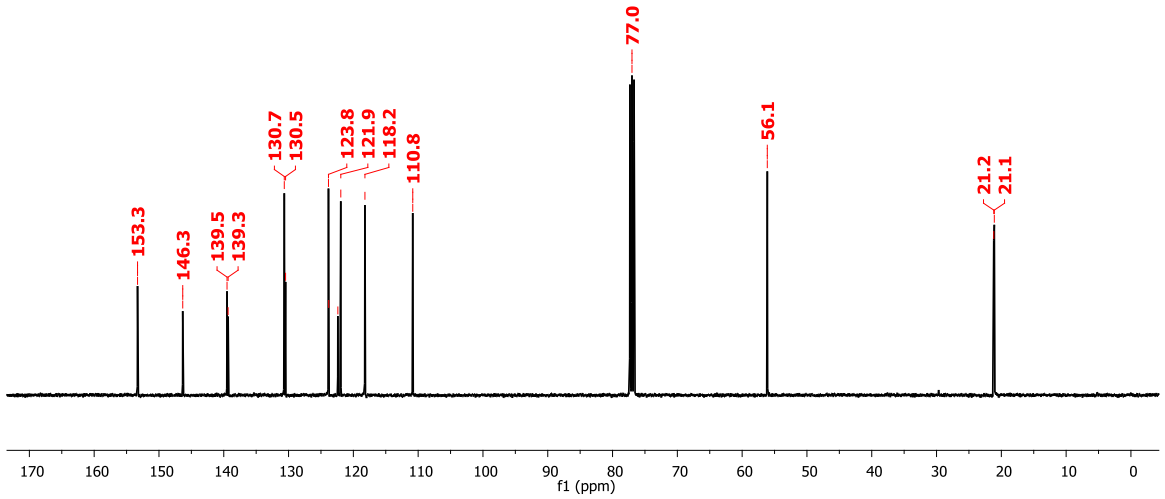


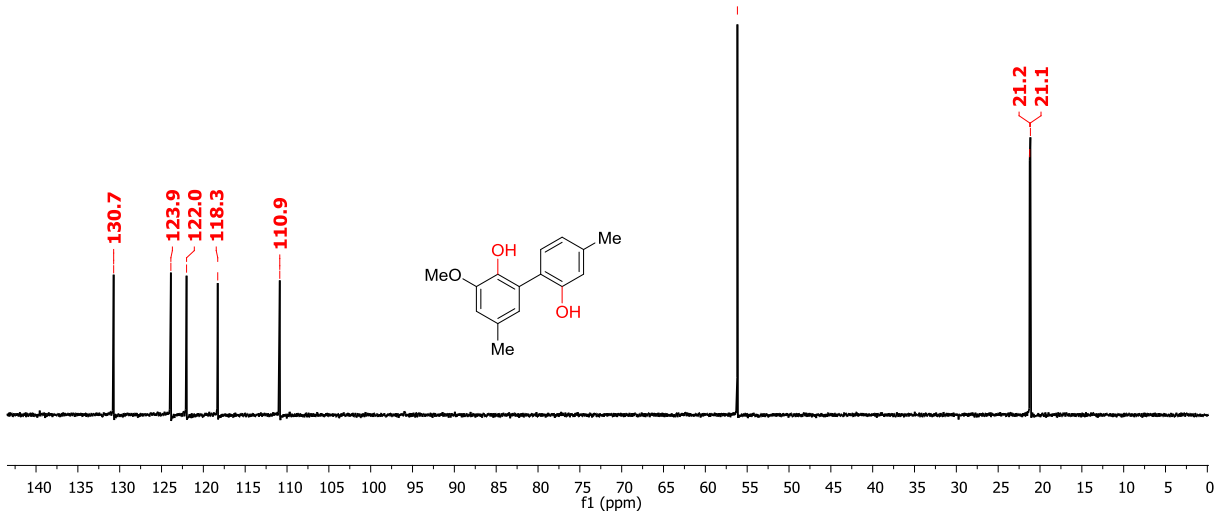

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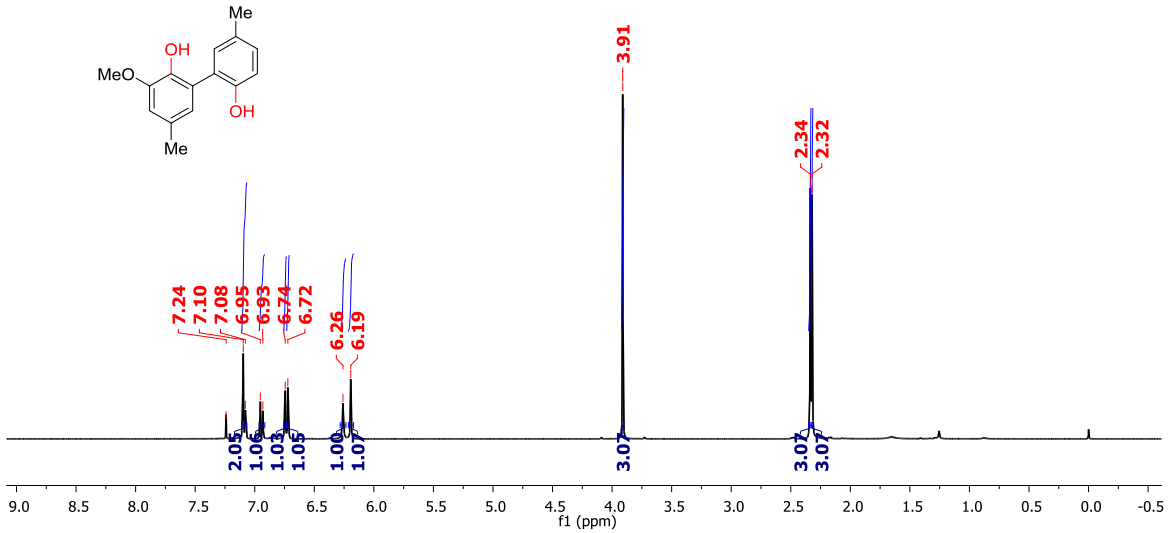


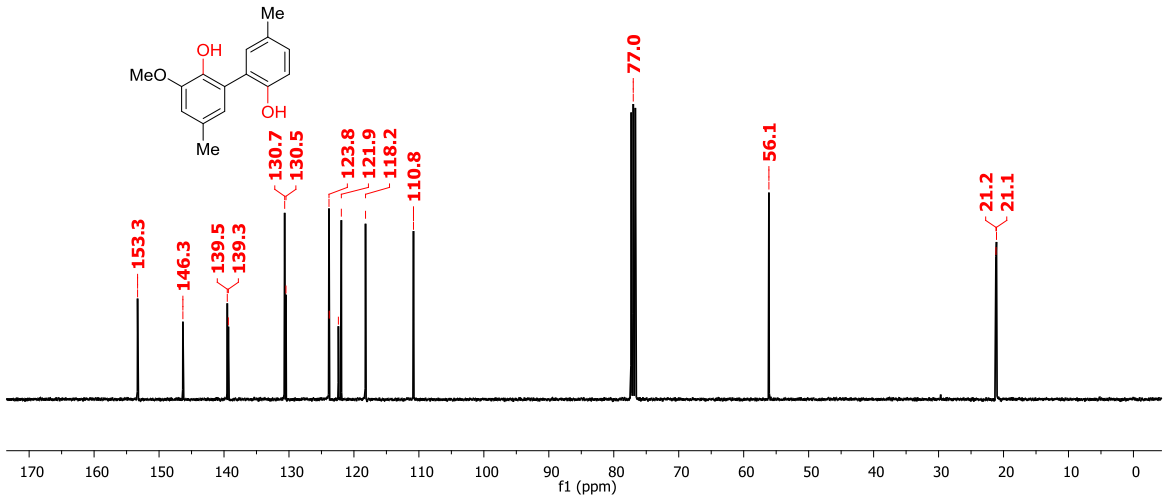


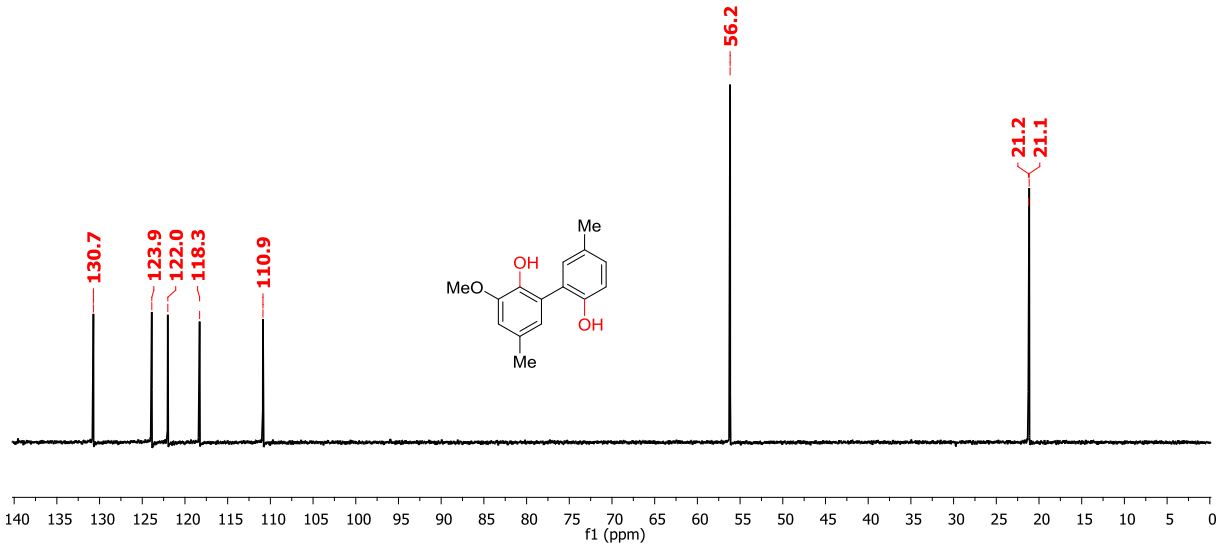

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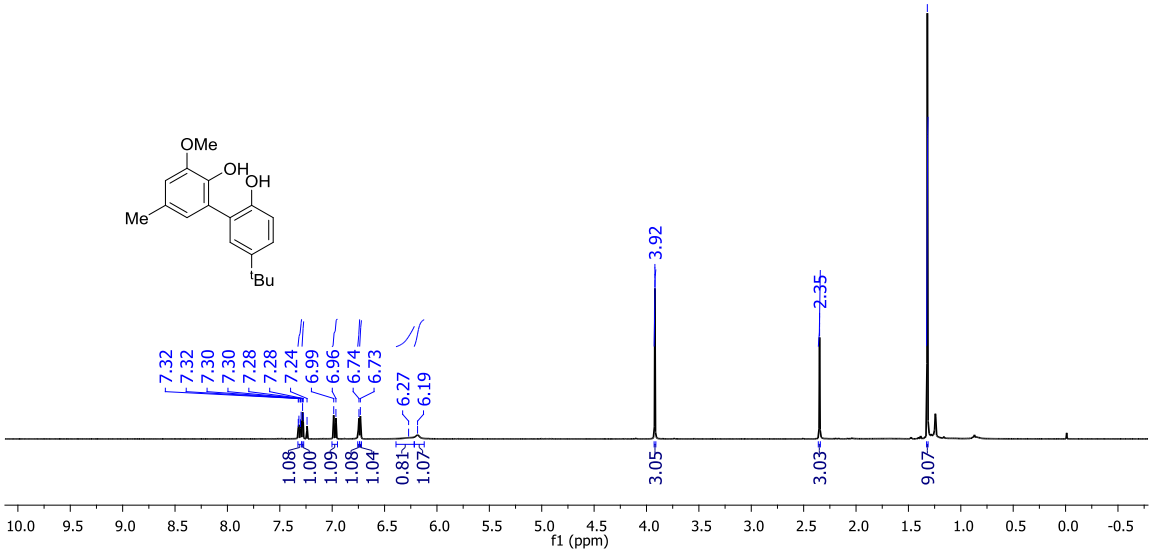


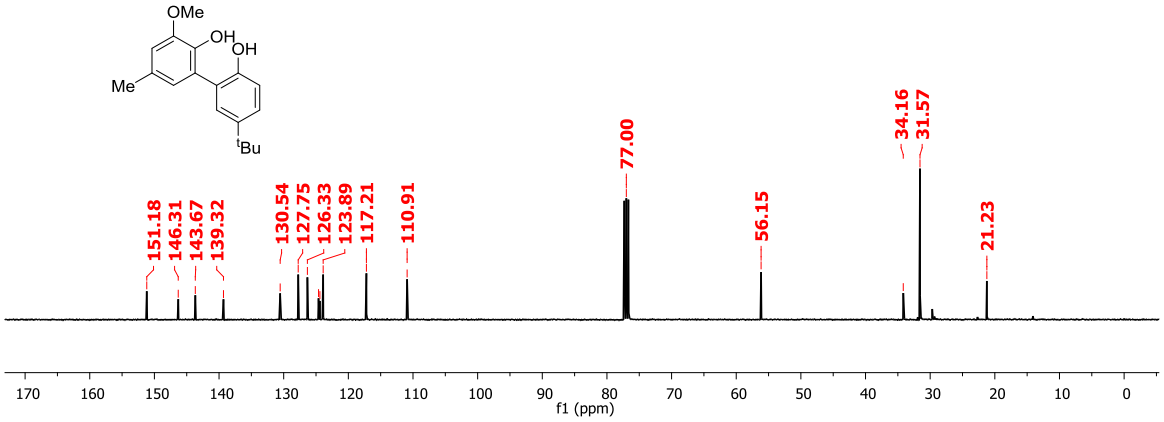

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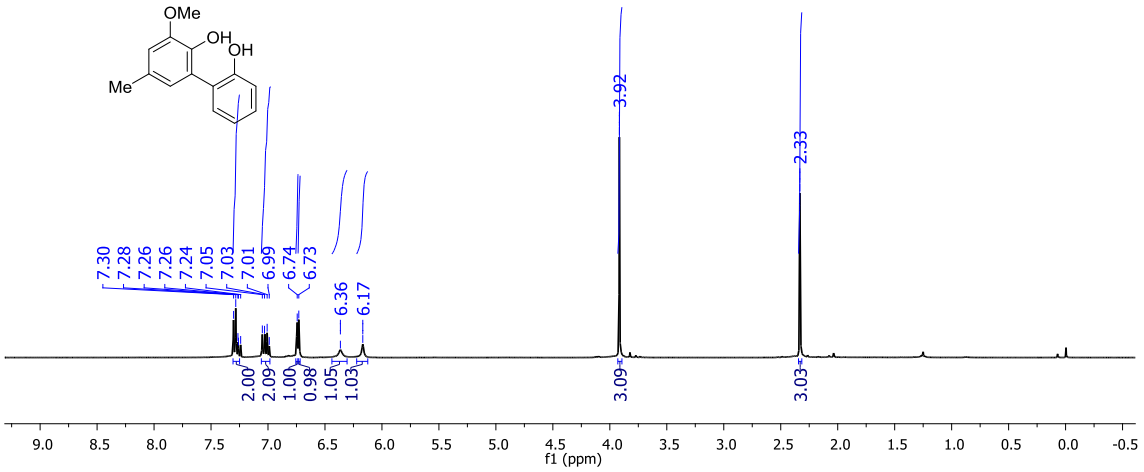
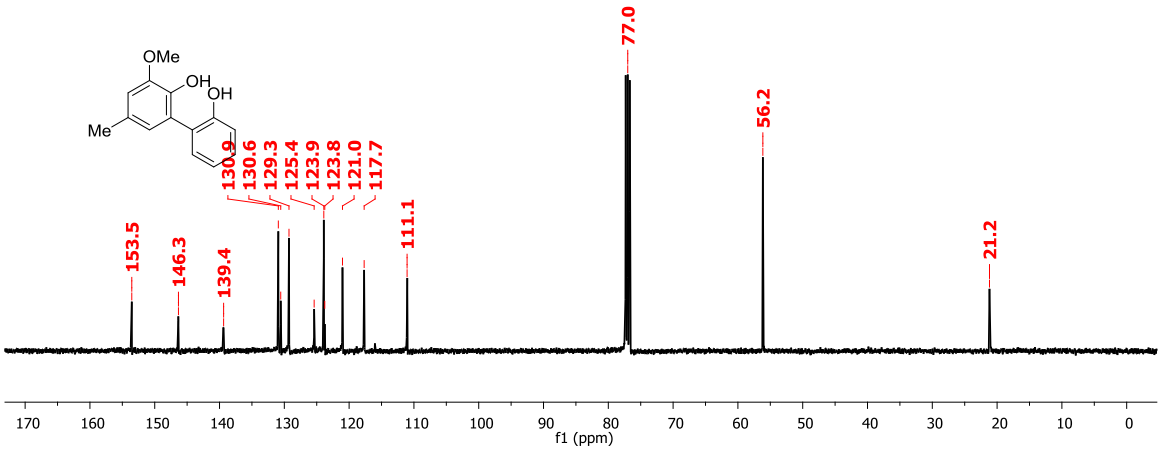
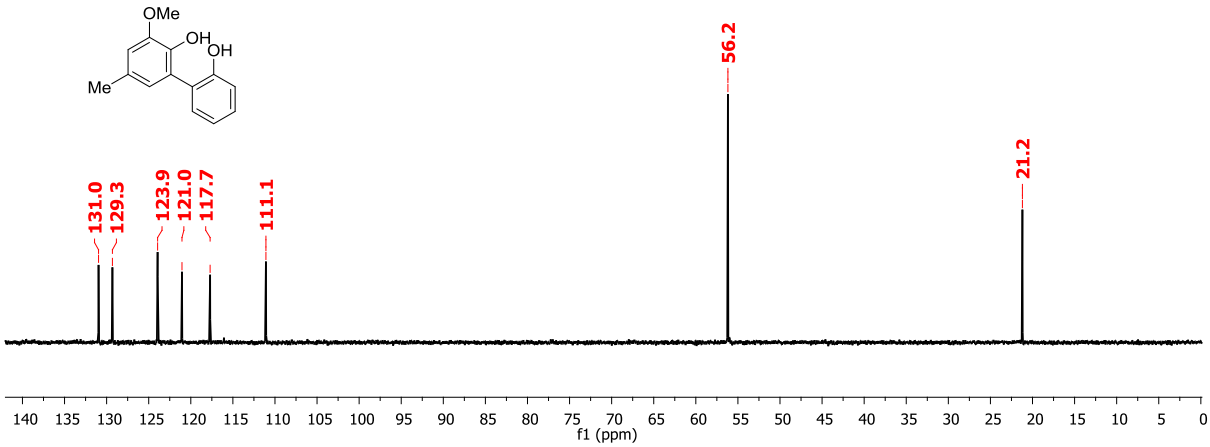
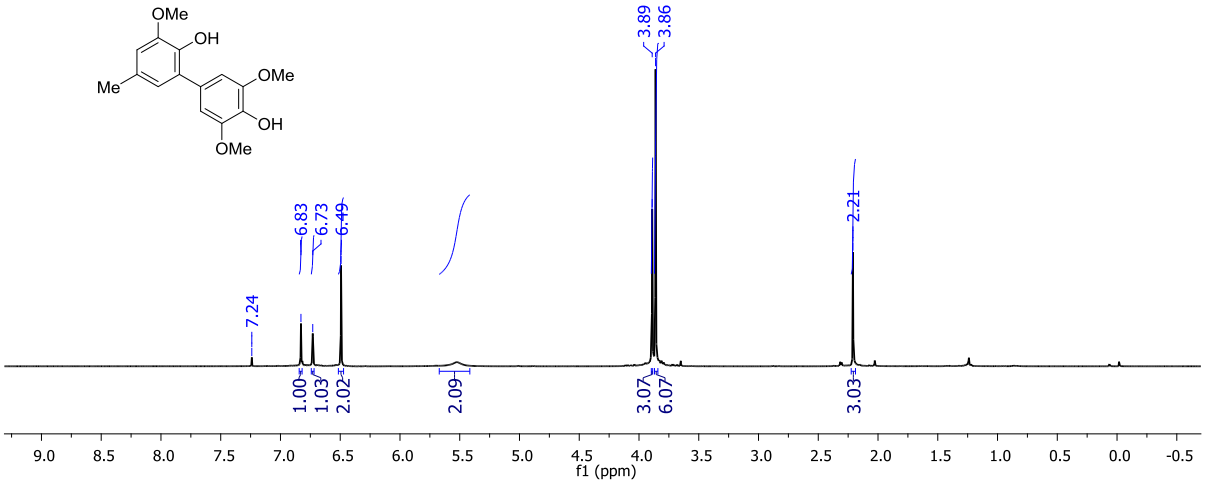
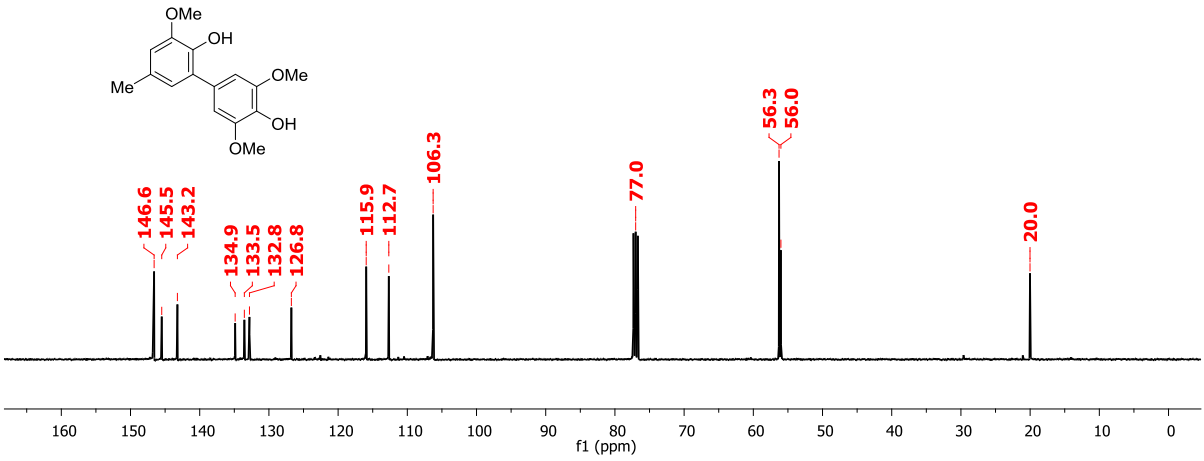


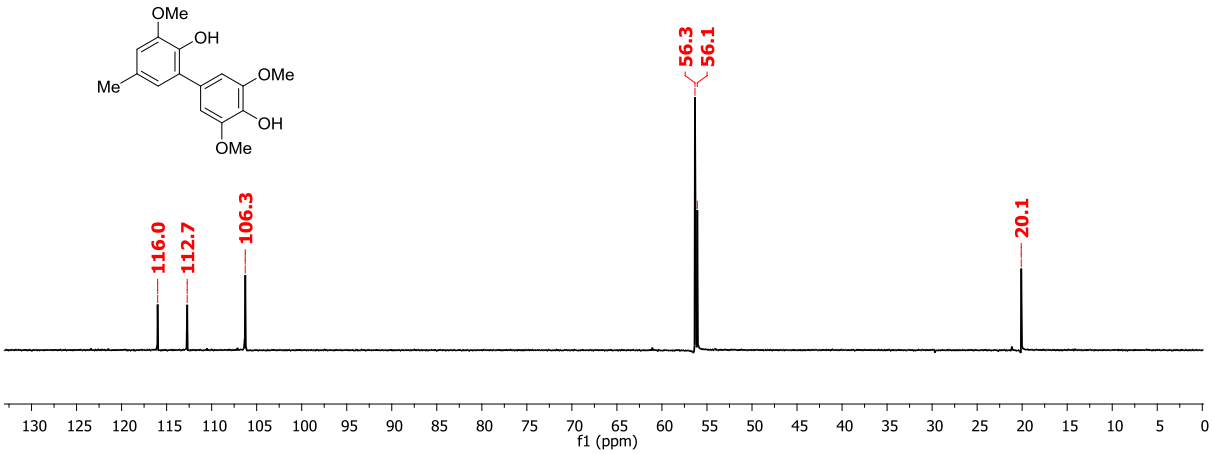



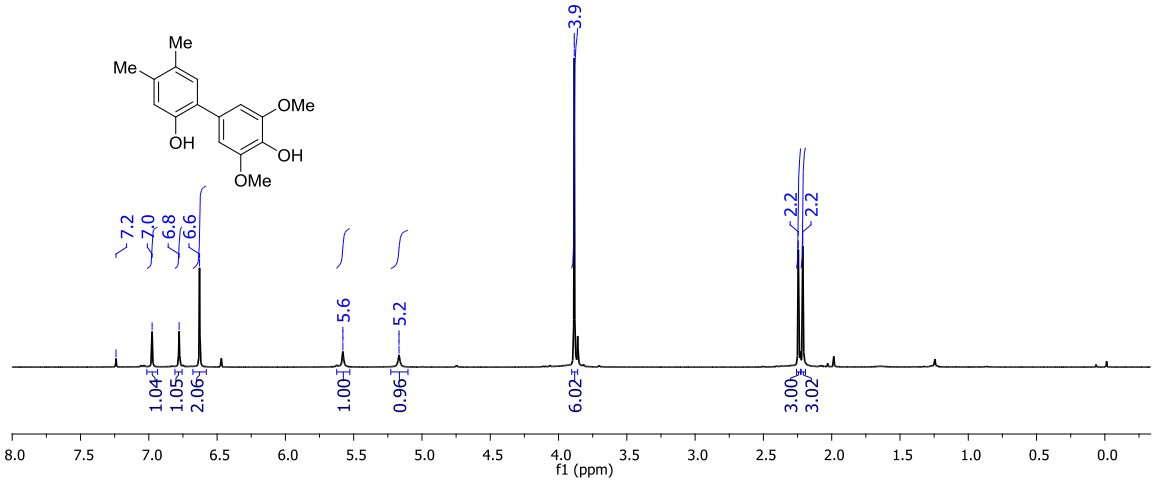
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **8cb**.

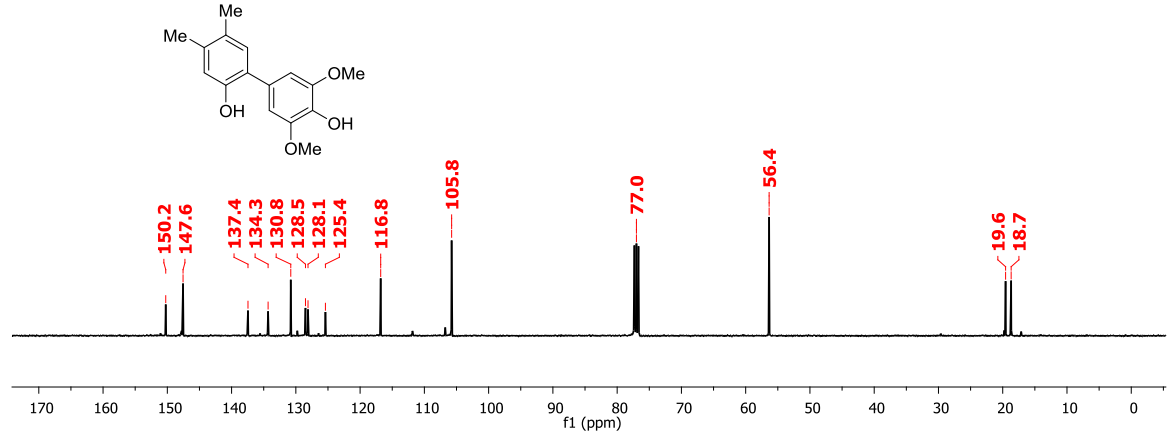


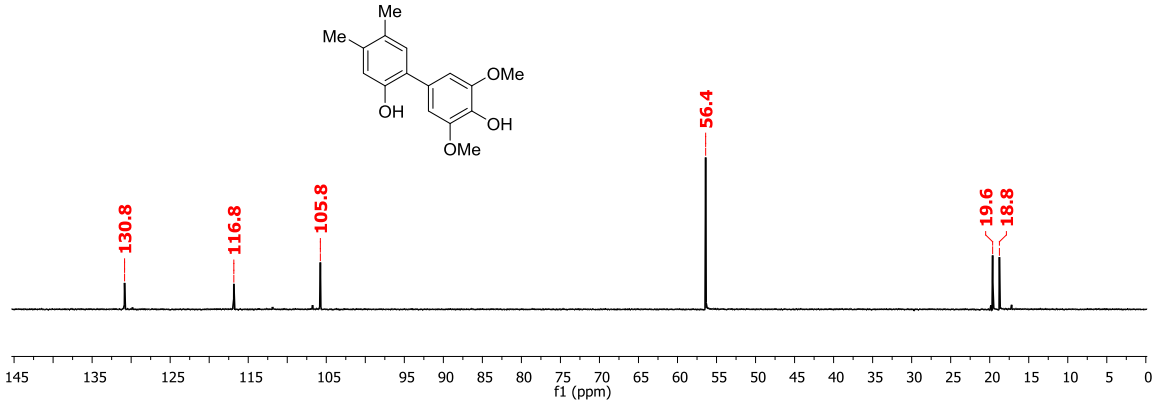



$^{1}H$ and $^{13}C$ NMR Spectra of Compound **8cd.**



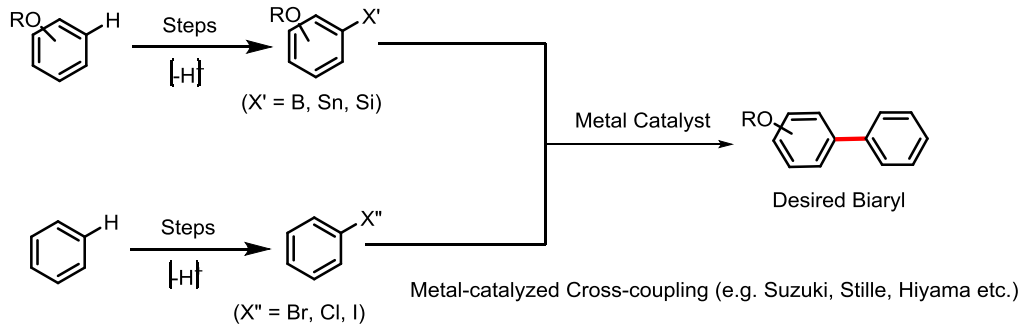



## 4B: Oxidative Cross-Coupling of Substituted Phenols with Inactivated Aromatics

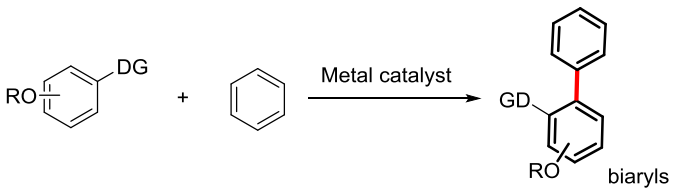
### Introduction:

Unsymmetrical phenol based bi-aryls represent potent structural unit for a wide range of functional materials such as natural products, active biological compounds, and liquid crystals.[1] Traditionally phenol base bi-aryls are prepared by transition-metal-catalyzed cross-coupling of reactions.[2] In these multi-step reactions; phenol moiety often has to be protected (Scheme 4.17).




**Scheme 4.17:** Bi-aryl synthesis by metal catalyzed cross-coupling

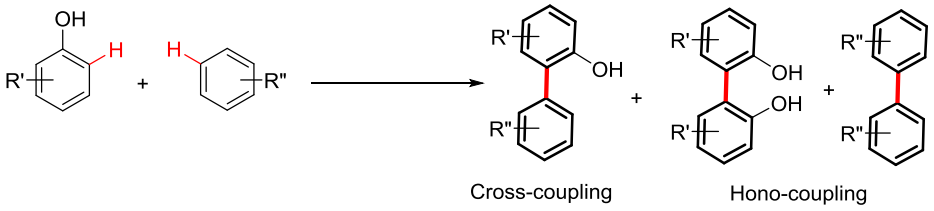
Recently, arylation of substituted aromatics has been achieved in a high atom- and step-economical manner through metal-catalyzed C–H bond-activation reactions.[3] Metal-catalyzed C-H bond activation for the synthesis of bi-aryls requires only one activated partner and has recently found significant attention (Scheme 4.18). In these reactions, a complex of Nobel metals such as rhodium, iridium, ruthenium, or palladium is required as catalysts for the efficient conversion into unsymmetrical biaryls.




**Scheme 4.18:** Synthesis of biaryls by C-H bond activation

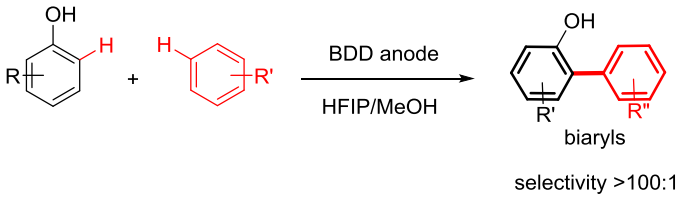
However, the synthesis of phenol-based bi-aryls is very challenging and has not been well documented. Although the oxidative coupling of phenols is known in the literature for several decades, the cross-coupling of phenols with unactivated aromatics is not well documented. The oxidative cross-coupling of phenols with aromatics is a productive method synthesizes bi-aryl molecules, without the protection of the OH group, in one pot.

Therefore, this type of oxidative coupling reaction has been a topic of great interest to synthetic chemists in recent years. Particularly, in this reaction, the suppression of homo-coupling of phenols as well as substituted aromatics is very challenging (Scheme 4.19).



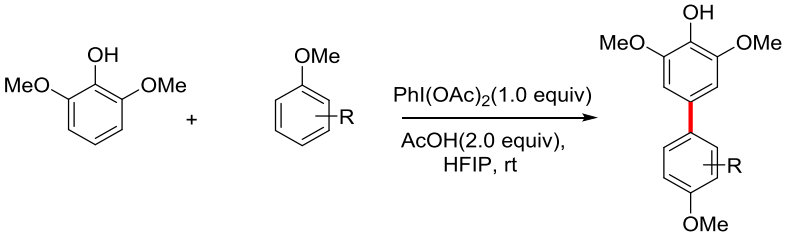

**Scheme 4.19:** Synthesis of biaryls by C-H bond activation

In this context, Waldvogel and co-workers investigated an electrochemical cross-coupling substituted phenols with aromatic hydrocarbons using boron-doped diamond electrodes (Scheme 4.20).[13] Fluorinated solvents like 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) was crucial solvent, and it stabilizes radical intermediates to minimize mineralization of the substrates. The competitive formation of homo-coupling products was prevented or either suppressed.

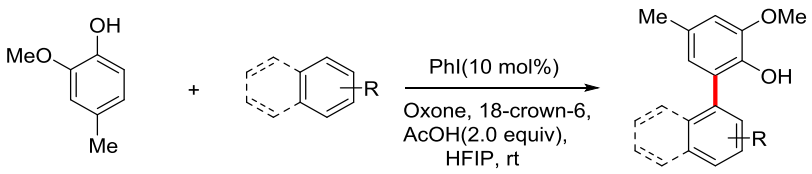



**Scheme 4.20:** Synthesis of biaryls by C-H bond activation

Kita's group described an efficient oxidative cross-coupling of phenols with arenes at the *para* position using hypervalent iodine reagents (Scheme 4.21).[12] Very recently, the same group extended hypervalent iodine chemistry to develop cross-coupling reaction of phenols with aromatics at *para*- and *ortho*- positions (Scheme 4.22).[12] In this reaction, first-time heteroaromatic coupling partner has been used for cross-coupling.

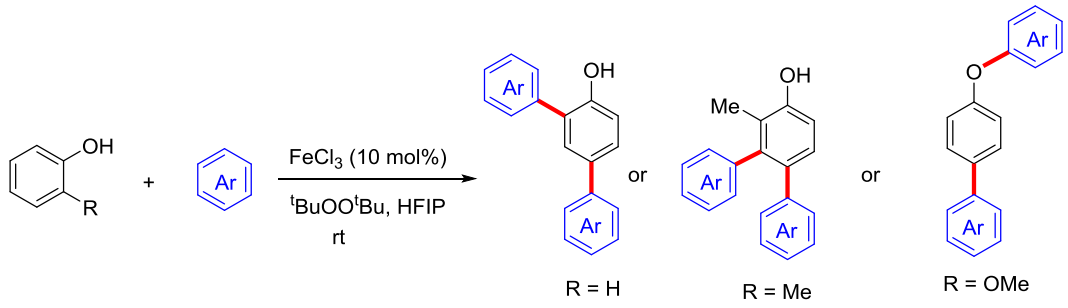



**Scheme 4.21:** The oxidative *para* cross-coupling of phenols



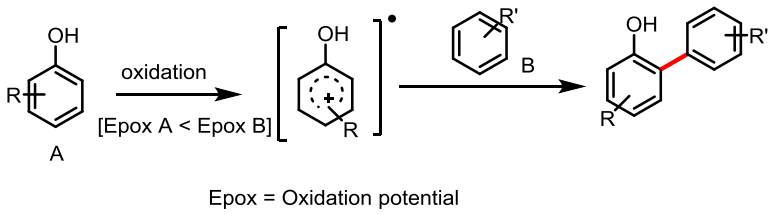

**Scheme 4.22:** Oxidative *ortho* arylation of phenols with aromatics

Pappo's group investigated a catalytic system for selective oxidative coupling of phenols in the highly region-selective manner by a catalytic amount of $FeCl_3$ in hexafluoroisopropanol (HFIP) using t-BuOOt-Bu as the external oxidant.[11] By applying these conditions, selective oxidation of phenols via single electron transfer produces phenoxyl radicals that react with nucleophilic aromatic coupling partner. In their recent report, complex poly aryl compounds are synthesized by consecutive oxidative cross-coupling reactions between a single phenolic molecule and aromatics (Scheme 4.23).




**Scheme 4.23:** Oxidative coupling of phenol with naphthol

The general strategy for oxidative cross-coupling process can be explained by oxidation potential of phenolic partners. If two phenolic coupling partners are chosen with sufficiently different oxidation potential, the electron rich or more oxidized phenol will be selectively oxidized to convert into phenolic cation radical intermediate. The resulting intermediate then undergoes C-C bond formation with a second phenolic partner to give desired nonsymmetrical biphenols (Scheme 4.24).




**Scheme 4.24:** general mechanism for cross-coupling of two phenols

Our continuous interest in the $SO_4^{-\bullet}$ anion radical chemistry prompted us to explore the possibility of using $SO_4^{-\bullet}$ as an oxidant for the oxidative cross-coupling of phenols with substituted aromatic hydrocarbons in the presence of an easily affordable and environmentally benign per sulfate source. In this section, we discuss unprecedented region-selective arylation of phenols with arenes via oxidative cross-coupling reactions in the presence of $K_2S_2O_8$.

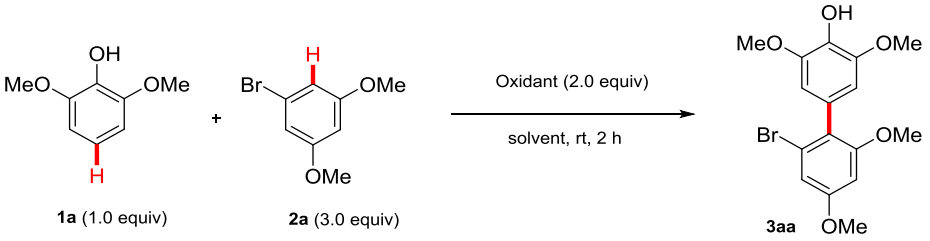
**4B.1: Results and Discussion**

When 2,6-dimethoxy phenol (**1a**) was treated with 1-bromo-3,5-dimethoxybenzene (**2a**) in the presence of $K_2S_2O_8$ (2.0 equiv) and $Bu_4N^+HSO_4^-$ (10 mol %) in $CF_3COOH$ at ambient temperature for 2 h, an unsymmetrical biaryl derivative **3aa** was observed in 92% yield (Scheme 1). It is interesting to note that the *para* C-H bond of **1a** and the *ortho* C-H bond to bromo group of **2a** were coupled together in a highly regioselective manner. The solvent $CF_3COOH$ is crucial for the success of the reaction.

**4B.2: Optimization Studies**

The reaction was examined with various solvents such as $CH_3COOH$, $(CF_3)_2CHOH$ (HFIP), *iso*-propanol, MeOH, $CF_3CH_2OH$, $ClCH_2CH_2Cl$, and *tert*-BuOH. These solvents were found to be not suitable for the reaction. The reaction was also examined with $K_2S_2O_8$, $(NH_4)_2S_2O_8$ and $PhI(OAc)_2$. $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ were equally effective, providing **3aa** in 92 and 87% yields, respectively. $PhI(OAc)_2$ was not effective for the reaction. It is believed that the cross-coupling reaction proceeds via a phenol cationic radical intermediate **4a** or phenoxy radical intermediate **4b**. Thus, to stabilize the intermediate **4**, a catalytic amount of various counter ions (10 mol %) such as $Bu_4N^{+\cdot}HSO_4^-$, $Bu_4N^{+\cdot}PF_6^-$, $Bu_4N^{+\cdot}F^-$ and $Bu_4N^{+\cdot}I^-$ were examined. $Bu_4N^{+\cdot}HSO_4^-$ and $Bu_4N^{+\cdot}PF_6^-$ were equally potent, providing product **3aa** in 92% and 88% yields, respectively. The remaining salts were not effective and resulted in complex reaction mixtures. The 2.0 equiv amount of $K_2S_2O_8$ is crucial to increase the yield of product **3aa**. With 1.5 equiv and 1.0 equiv, product **3aa** was observed in 80% and 69% yields, respectively. The coupling reaction did not proceed without $K_2S_2O_8$.

**Table 4.4:** Cross-Coupling of Phenol **1a** with aromatics **2a**[a]




| Entry | Solvent | Oxidant | Additive | Yield of **3aa** (%)[b] |
|---|---|---|---|---|
| 1 | $CF_3CH_2OH$ | $K_2S_2O_8$ | $Bu_4N^+HSO_4^-$ | NR |
| 2 | *tert*-BuOH | $K_2S_2O_8$ | $Bu_4N^+HSO_4^-$ | NR |
| 3 | *iso*-propanol | $K_2S_2O_8$ | $Bu_4N^+HSO_4^-$ | NR |
| 4 | HFIP | $K_2S_2O_8$ | $Bu_4N^+HSO_4^-$ | NR |
| 5 | MeOH | $K_2S_2O_8$ | $Bu_4N^+HSO_4^-$ | NR |
| 6 | $ClCH_2CH_2Cl$ | $K_2S_2O_8$ | $Bu_4N^+HSO_4^-$ | NR |
| 7 | TFA | $K_2S_2O_8$ | $Bu_4N^+I^-$ | NR |
| 8 | TFA | $K_2S_2O_8$ | $Bu_4N^+F^-$ | NR |
| 9 | TFA | $K_2S_2O_8$ | $Bu_4N^+PF_6^-$ | 88 |
| 10 | TFA | $PhI(OAc)_2$ | $Bu_4N^+HSO_4^-$ | ND |
| 11 | TFA | $(NH_4)_2S_2O_8$ | $Bu_4N^+HSO_4^-$ | 87 |
| 12 | TFA | $K_2S_2O_8$ | $Bu_4N^+HSO_4^-$ | 92 |
| 13 | $ClCH_2CH_2Cl$ | - | $AgSbF_6$ | trace |
| 14 | $ClCH_2CH_2Cl$ | $(NH_4)_2S_2O_8$ | - | NR |

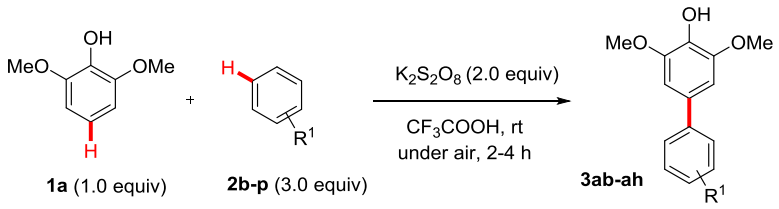
[a] All reactions were carried out under the following conditions: **1a** (1.0 equiv), **2a** (3.0 equiv), $K_2S_2O_8$ (2.0 equiv), and counter ion (10 mol %) in solvent (0.5 mL) at ambient conditions for 2 h. [b] Isolated yields.

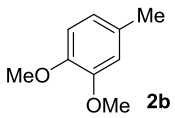
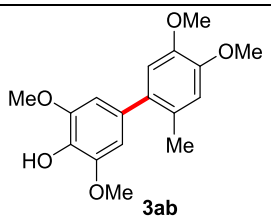
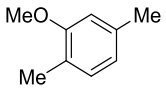
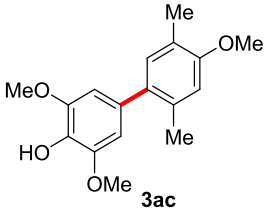
### 4B.3: Scope of Substituted Aromatics

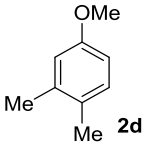
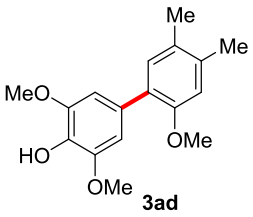
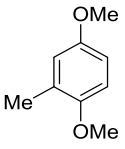
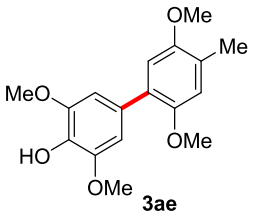
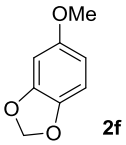
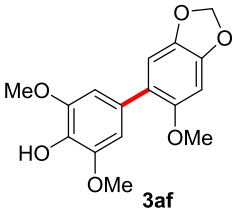
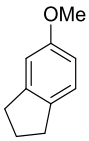
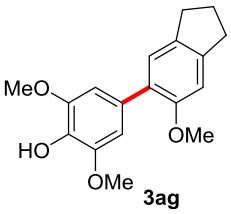
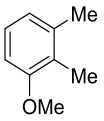
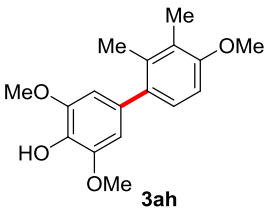
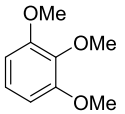
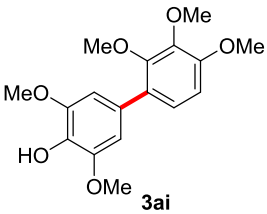
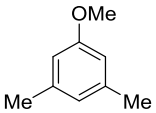
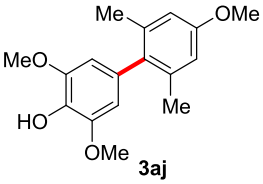
The scope of the present cross-coupling reaction was examined with various substituted aromatics **2b-p** (Scheme 2). 1,2-Dimethoxy-4-methylbenzene (**2b**) and 2-methoxy-1,4-dimethylbenzene (**2c**) reacted with **1a** providing, cross-coupling products **3ab** and **3ac** in excellent 94% and 82% yields, respectively. In these substrates, the *para* C-H bond of the OMe group of **2b-c** participated in the reaction. 4-Methoxy-1,2-dimethylbenzene (**2d**), 1,4-dimethoxy-2-methylbenzene (**2e**), 5-methoxybenzo[*d*]-[1,3]dioxole (**2f**) and 5-methoxy-2,3-dihydro-1*H*-indene (**2g**) afforded coupling products **3ad-ag** in 60-30% yields. In these substrates, the *ortho* C-H bond of OMe group which is *para* to the alkyl

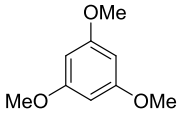
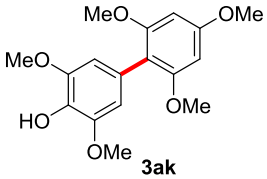
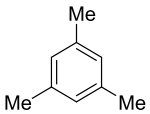
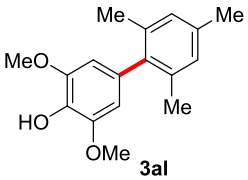
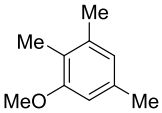
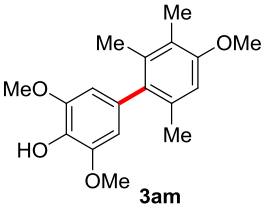
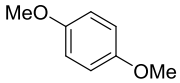
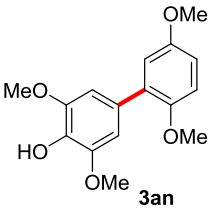
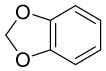
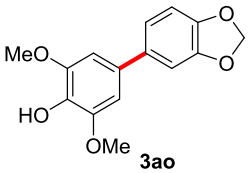
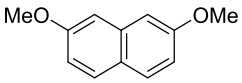
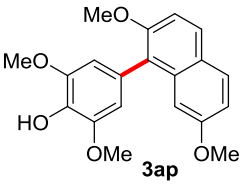
group **2d-g** were involved in the reaction. 1-Methoxy-2,3-dimethylbenzene (**2h**) and 1,2,3-trimethoxybenzene (**2i**) reacted with **1a** yielding, products **3ah** and **3ai** in 62% and 35% yields, respectively. 1-Methoxy-3,5-dimethylbenzene (**2j**) and 1,3,5-trimethoxybenzene (**2k**) provided products **3aj** and **3ak** in 42% and 40% yields, respectively. A less reactive mesitylene (**2l**) was also a suitable partner, yielding product **3al** in 45% yield. A sterically hindered *tetra*-substituted benzene derivative (**2m**) provided the expected product **3am** in 51% yield. In all these reactions, the *para* C-H bond of the OMe group which is *ortho* to Me or the OMe group of **2h-m** participated in the reaction. Disubstituted benzenes such as 1,4-dimethoxybenzene (**2n**) and benzo[*d*][1,3]dioxole (**2o**) afforded the expected cross-coupling products **3an** and **3ao** in lower yields. The remaining unreacted **2a** was converted into the homocoupling product. Interestingly, 2,7-dimethoxynaphthalene (**2p**) was also found to participate in the reaction, providing coupling product **3ap** in 61% yield. The reaction of **1a** with 1,2,4-trimethoxybenzene provided only homocoupling products of **1a** and **2a**.[27] No cross-coupling product was observed. Aromatics such as toluene, anisole, benzene, and naphthalene were not compatible for the reaction.

**Table 4.5:** The Coupling of **1a** with Substituted Aromatics[a]




| Entry | **2** | Product **3** | Yield [%][b] |
|---|---|---|---|
| 1 |  **2b** |  **3ab** | 94 |
| 2 |  **2c** |  **3ac** | 82 |

| | | | |
|---|---|---|---|
| 3 |  **2d** |  **3ad** | 60 |
| 4 |  **2e** |  **3ae** | 30 |
| 5 |  **2f** |  **3af** | 38 |
| 6 |  **2g** |  **3ag** | 36 |
| 7 |  **2h** |  **3ah** | 62 |
| 8 |  **2i** |  **3ai** | 71 |
| 9 |  **2j** |  **3aj** | 42 |

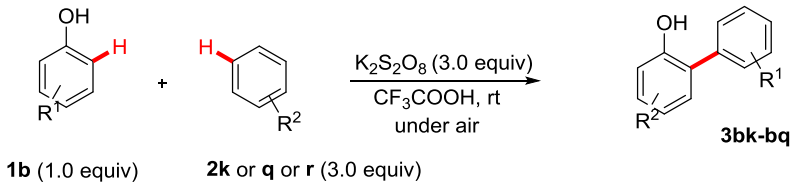
| | | | |
|---|---|---|---|
| 10 |  **2k** |  **3ak** | 40 |
| 11 |  **2l** |  **3al** | 45 |
| 12 |  **2m** |  **3am** | 51 |
| 13 |  **2n** |  **3an** | 25 |
| 14 |  **2o** |  **3ao** | 21 |
| 15 |  **2p** |  **3ap** | 61 |

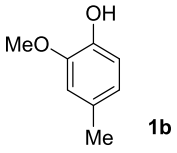
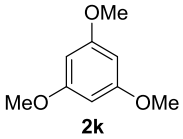
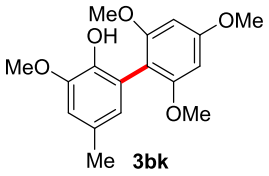
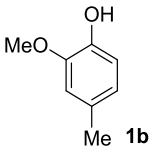
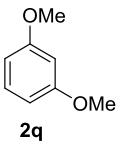
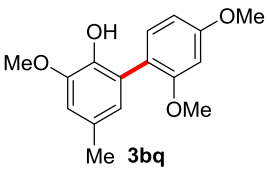
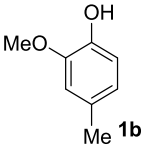
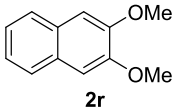
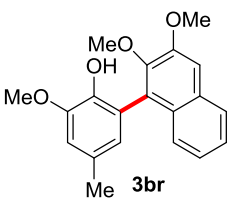
[a]All reactions were carried out using **1a** (1.0 equiv), **2b-p** (3.0 equiv), $K_2S_2O_8$ (2.0 equiv) and $Bu_4N^{+}\cdot HSO_4^{-}$ (10 mol %) in $CF_3COOH$ (0.5 mL) at an amient conditions for 2-4 h. [b] Isolated yield.

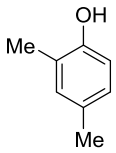
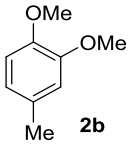
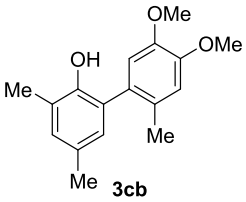
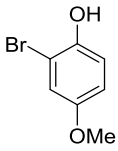
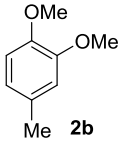
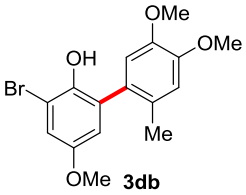
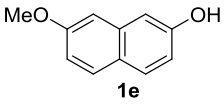
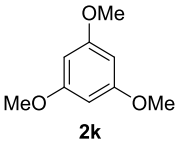
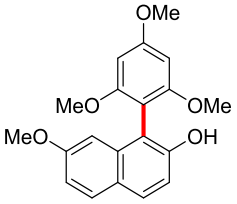
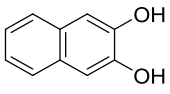
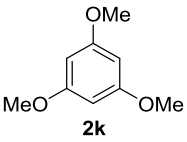
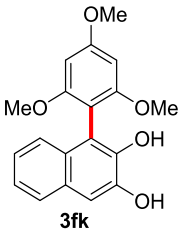
### 4B.4: Scope of phenols and naphthols

The cross-coupling reaction was further examined with substituted phenols and naphthols (Scheme 3). 2-Methoxy-4-methylphenol (**1b**) reacted efficiently with substituted aromatics **2k** or 1,3-dimethoxybenzene (**2q**) or 2,3-dimethoxynaphthalene (**2r**) under similar reaction conditions, providing the expected cross-coupling products **3bk**–**br** in 56, 55, and 60 % yields, respectively. Similarly, 2,4-dimethylphenol (**1c**) and 2-bromo-4-methylphenol (**1d**) reacted with **2b** to afford coupling products **3cb** and **3db** in 32 and 28 % yields, respectively. In all these reactions, the C–H bond *ortho* to phenols **1b**–**d** was involved in the coupling reaction. Apart from phenols, substituted naphthols were also found to be compatible with the reaction. The reaction of 7-methoxynaphthalen-2-ol (**1e**) or naphthalene-2,3-diol (**1f**) with **2k** gave the expected cross-coupling products **3ek** and **3fk** in 35 and 40 % yields, respectively. Particularly, in substrate **1f**, the arylation reaction takes place at one of the carbon atoms adjacent to the hydroxyl groups.

**Table 4.6:** The Coupling of Phenol **1b-f** with **2k, 2q,** and **2r**[a]



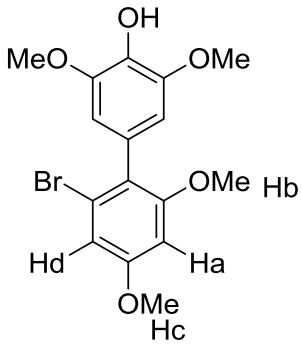

| Entry | 1 | 2 | Product 3 | Yield [%][b] |
|---|---|---|---|---|
| 1 |  |  |  | 56 |
| 2 |  |  |  | 55 |
| 3 |  |  |  | 60 |

| | | | | |
|---|---|---|---|---|
| 4 |  **1c** |  **2b** |  **3cb** | 32 |
| 5 |  **1d** |  **2b** |  **3db** | 28 |
| 6 |  **1e** |  **2k** |  **3ek** | 35 |
| 7 |  **1f** |  **2k** |  **3fk** | 35 |

[a]All reactions were carried out using **1a** (1.0 equiv), **2b-p** (3.0 equiv), $K_2S_2O_8$ (2.0 equiv) and $Bu_4N^+HSO_4^-$ (10 mol %) in $CF_3COOH$ (0.5 mL) at an amient conditions for 2-4 h. [b] Isolated yield.

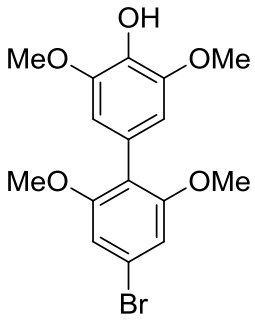
### 4B.5: Regioselective Studies

**NOESY Experiment of Compound 3aa.**



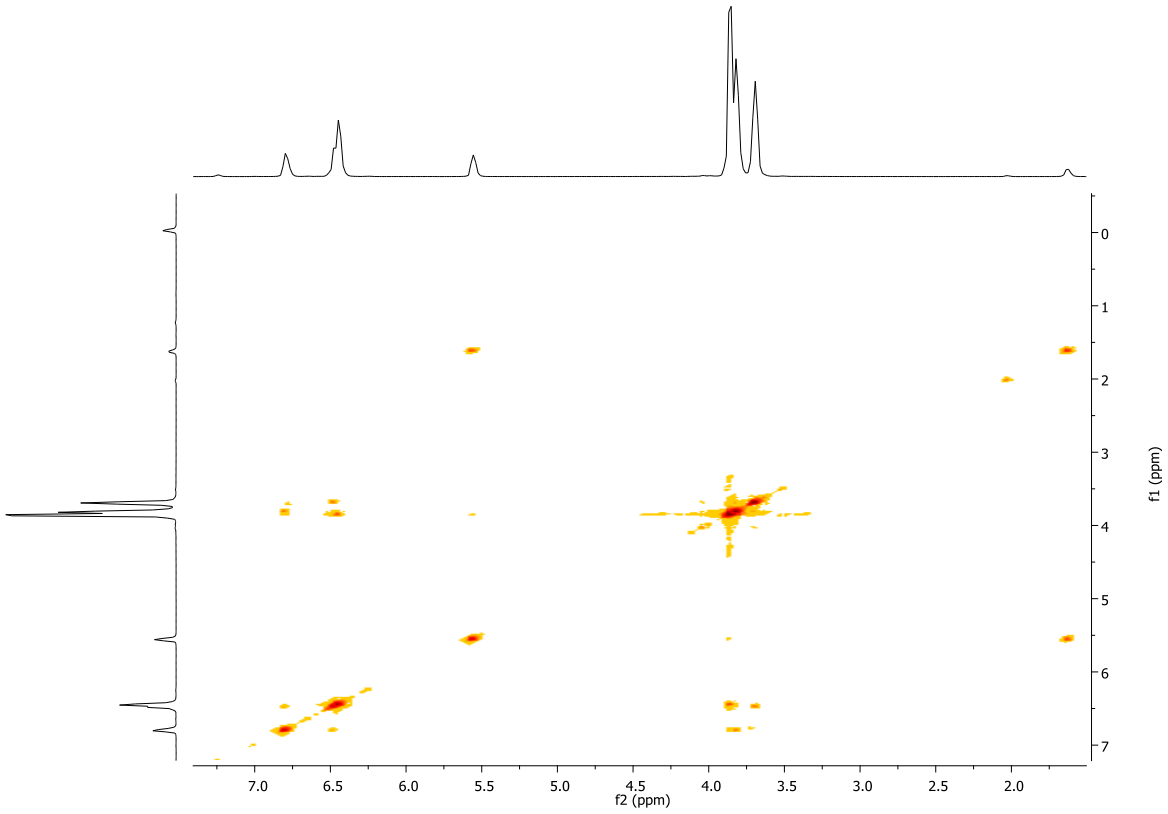

δ Ha = 6.47, Hb = 3.69, Hc = 3.81, Hd = 6.80

**Observed product**

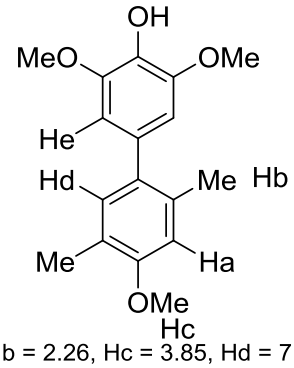



**Possible regioisomer**
**Not observed**

There is very strong NOE correlation between Ha (6.47, s) with Hb (3.69, s) and Hc (3.81, s) of OMe groups. Also, a very strong NOE correlation was found between Hc (3.81, s) of OMe group and Hd (6.80). In the other regioisomer, no signals should be observed. This result revealed that the regiochemistry of compound **3aa** is correct.

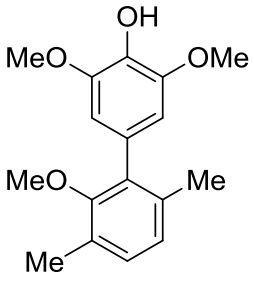


**NOESY Experiment of Compound 3ac.**



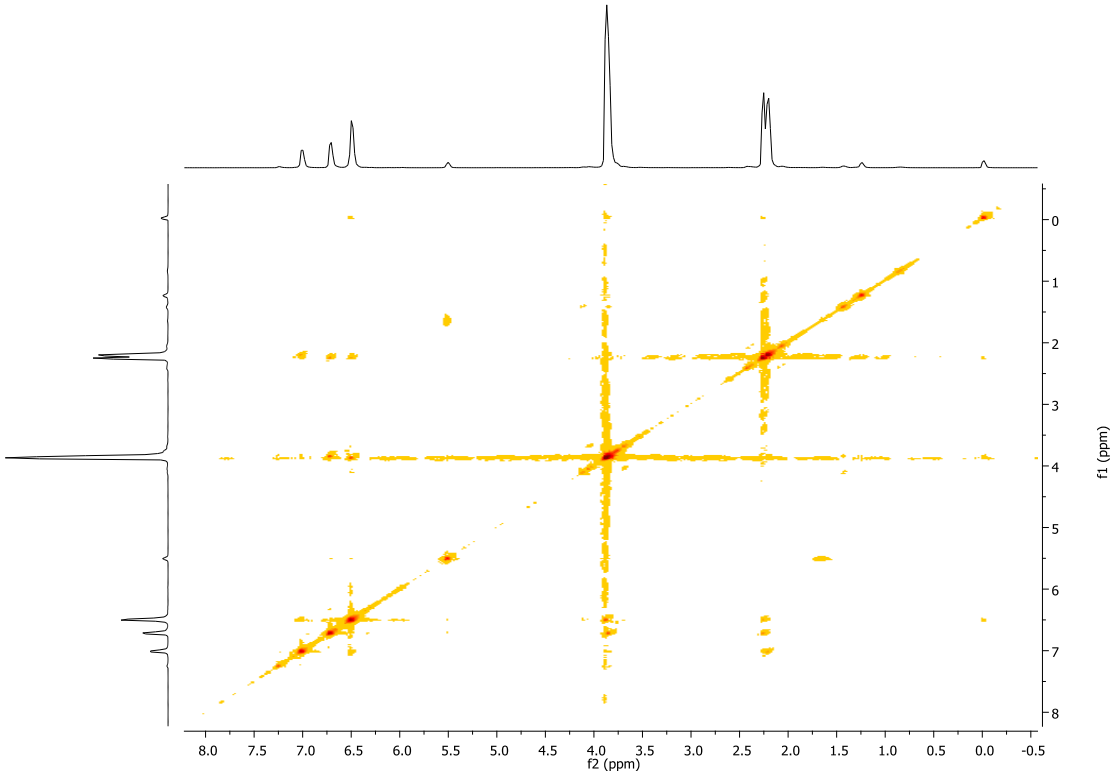

δ Ha = 6.71, Hb = 2.26, Hc = 3.85, Hd = 7.01, He = 6.50

**Observed product**




**Possible regioisomer Not observed**

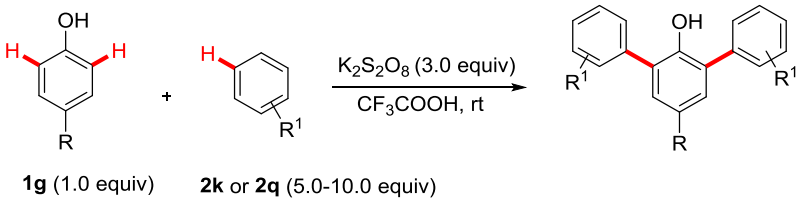
There is very strong NOE correlation of Ha (6.71, s) with Hb (2.26, s) of Me as well as with Hc (3.81, s) of OMe group. Also, a very strong NOE correlation was found between Hd (7.01, s) and Hd (6.50). In the other regioisomer, no signals should be observed. This result clearly revealed that the regiochemistry of compound **3ac** is correct.

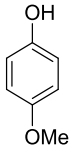
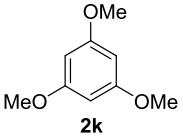
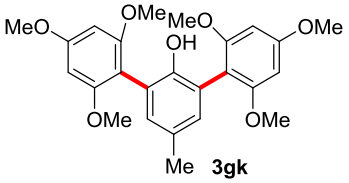
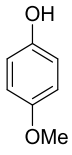
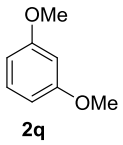
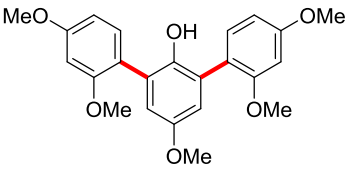
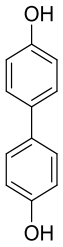
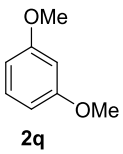
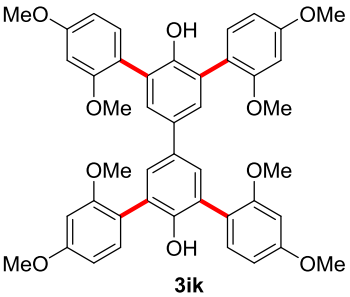


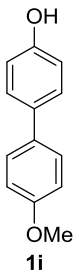
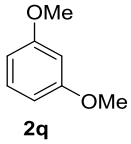
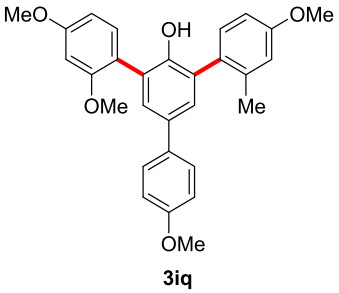
### 4B.6: *bis* Arylation of Substituted Phenols

Interestingly, it was found that the bis arylation was observed in the cross-coupling reaction of 4-substituted phenols with substituted aromatics (Scheme 4). 4-Methoxy phenol (**1g**) reacted with aromatics **2k** or **2q**, yielding cross-coupling products **3gk** and **3gq** in 42% and 53% yields, respectively. Further, [1,1'-biphenyl]-4,4'-diol (**1h**) having two hydroxyl groups reacted with **2q**, providing tetra arylated phenol **3hq** in 27% yield. In phenol **1h**, one of the OH groups was protected with methyl group **1i** and further treated with **2q**. In the reaction, bis arylated phenol **3iq** was observed in 39% yield.

**Table 4.6:** The Coupling of Phenol **1g-i** with **2k, and 2q**[a]




| Entry | 1 | 2 | Product 3 | Yield [%][b] |
|---|---|---|---|---|
| 1 |  **1g** |  **2k** |  **3gk** | 42 |
| 2 |  **1g** |  **2q** |  **3gq** | 53 |
| 3 |  **1h** |  **2q** |  **3ik** | 27 |

| | | | | |
|---|---|---|---|---|
| 4 |  **1i** |  **2q** |  **3iq** | 39 |

[a]All reactions were carried out using **1g-i** (1.0 equiv), **2k** or **2q** (5.0-10.0 equiv), $K_2S_2O_8$ (3.0 - 4.0 equiv) and $Bu_4N^{+}HSO_4^{-}$ (10 mol %) in $CF_3COOH$ (2.0 mL) at an amient conditions for 2-4 h. [b] Isolated yield.

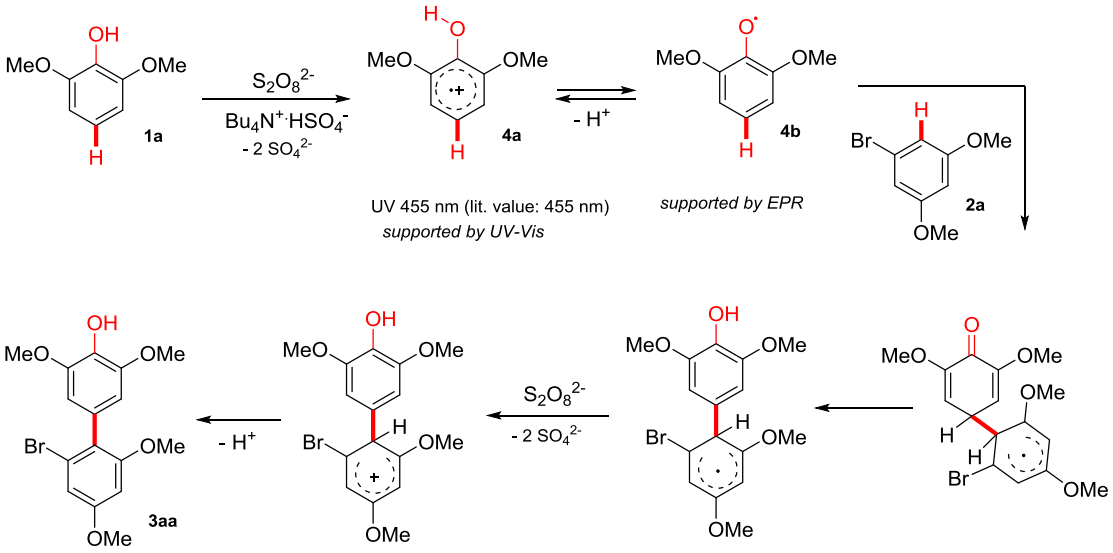
### 4B.6: C-V (Cyclic-Voltammeter) Studies

To obtain more insight into the scope of the substrates, the oxidation potentials of phenols and aromatics were measured and further compared with substituted aromatics. The results showed that phenols with oxidation potential up to 0.68 V and naphthols up to 0.88 V are favorable for the reaction. For example, 2,6-dimethoxyphenol (**1a**) ($E_p^{ox}$ = 0.62 V in ACN vs. $Ag/AgNO_3$), 4-methyl-2-methoxyphenol (**1b**) ($E_p^{ox}$ = 0.63 V in ACN vs. $Ag/AgNO_3$), 2,4-dimethylphenol (**1c**) ($E_p^{ox}$ = 0.68 V in ACN vs. $Ag/AgNO_3$), 2,3-dihydroxy naphthalene (**1f**) ($E_p^{ox}$ = 0.83 V in ACN vs. $Ag/AgNO_3$), and 4-methoxyphenol (**1g**) ($E_p^{ox}$ = 0.68 V in ACN vs. $Ag/AgNO_3$) were involved in the cross-coupling reaction. If the oxidation potential of the phenol is above 0.7 V and naphthol above 0.88 V, the corresponding substrate did not participate in the reaction. For example, 2,6-dimethylphenol ($E_p^{ox}$ = 0.76 V in ACN vs. $Ag/AgNO_3$), 4-methylphenol ($E_p^{ox}$ = 0.78 V), 3,4-dimethylphenol ($E_p^{ox}$ = 0.87 V), and 2-naphthol (**2a**) ($E_p^{ox}$ = 0.92 V) were not involved in the cross-coupling reaction.

The nucleophilicity of aromatics is also crucial for the reaction. It is observed that the aromatic C–H bond that is involved in the coupling reaction should have electron releasing groups such as OMe or Me at the *para* position as well as at the *ortho* position for better reactivity. In all substrates, **2a–n**, an electron-releasing group Me or OMe is present at the *para* as well as at the *ortho* position of aromatics. However, in substrate benzo[*d*][1,3]dioxole (**2o**), no electron-releasing group is present at the *para* or at the *ortho* positions. Thus, a low yield (21 %) of product **3ao** was observed. In the cross-coupling of **1a** with 1,4-dimethoxybenzene (**2n**), cross-coupling product **3an** was observed in 25 % yield. In **2n**, both *para* positions had electron-releasing OMe groups. Thus, the nucleophilicity of **2n** is decreased as compared with **1a**. In the reaction, apart

from **3an**, the homocoupling of **1a** was observed in a higher yield. In the reaction of **1a** with toluene or xylene, only homocoupling product of **1a** was observed due to the poor nucleophilicity of toluene or xylene.

### 4B.9: Proposed Mechanism




**Scheme 4.25**: Preparation of *ortho* hydroxy *N*-alkyl benzamides

Based on the previous reports and present observation, a possible reaction mechanism is proposed for coupling of **1a** with **2a** in Scheme 1. $K_2S_2O_8$ reacts with substituted phenol **1a** in the presence of $Bu_4N^{+\cdot}HSO_4^-$, forming a cationic phenol radical intermediate **4a**. It is also possible that the $K_2S_2O_8$ generates a $SO_4^{-\bullet}$ anion radical at ambient temperature which abstracts an electron from phenol **1a** in the presence of $Bu_4N^{+\cdot}HSO_4^-$, forming a cationic phenol radical intermediate **4a**.[11*a*] Intermediate **4a** is highly unstable, and it simply converted into phenol radical intermediate **4b** by the dissociation of $H^+$ on the OH group of phenol. Later, aromatic molecule **2a** undergoes the nucleophilic addition with intermediate **4b**, forming the cross-coupling product **3aa**. The exact role of $Bu_4N^+HSO_4^-$ is not clear to us, but it could stabilize and increases the life time of the intermediate **4a** or **4b**.

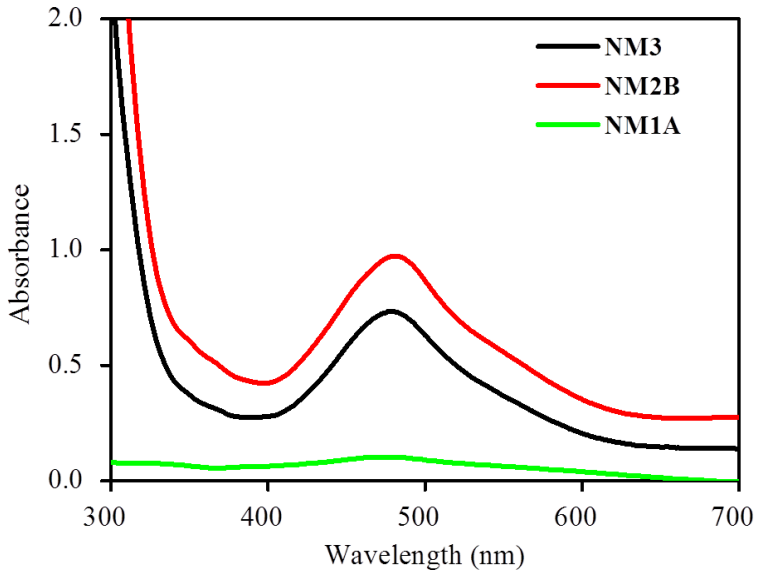



**Fig 4.1:** UV-Vis spectra for the formation of phenol cationic radical intermediate **4a**: a) NM1A: the substrate **1a** in $CF_3COOH$; b) NM2B: The reaction of **1a** with $K_2S_2O_8$ in $CF_3COOH$ at ambient temperature; and c) The reaction of **1a** with $K_2S_2O_8$ in the presence of $Bu_4N^{+\cdot}HSO_4^-$ in $CF_3COOH$ at ambient temperature.

To verify the formation of phenol cationic radical intermediate **4a**, 2,6-dimethoxy phenol (**1a**) was treated with $K_2S_2O_8$ in TFA at ambient temperature. The reaction mixture was monitored by UV/Vis spectroscopy. It is known that the phenol cationic radical intermediate **4a** shows a broad absorbance at 455 nm. In the present reaction mixture, the absorption band was observed at 455 nm (Figure 1), which indicates the formation of intermediate **4a** in the reaction mixture. Furthermore, to confirm the formation of intermediate **4b**, phenol **1a** was treated with $K_2S_2O_8$ in $CF_3COOH$ under a nitrogen atmosphere for 15 min and subjected to EPR analysis. A clear, very sharp radical signal was observed at $g$ = 1.9907 (Figure 2). Meanwhile, in the same region, a clear signal was also observed in the presence of $Bu_4N^+\cdot HSO_4^-$ under the same reaction conditions. However, no signal was observed for the reaction of **1a** with $CF_3COOH$ without $K_2S_2O_8$ and **1a** alone without solvent. Subsequently, **2a** was treated with $K_2S_2O_8$ in $CF_3COOH$ and subjected to EPR analysis. In the mixture also, no EPR signal was observed. It should be noted that a free radical signal appears at the 2.0023 region in the EPR spectrum. This result clearly reveals that the phenoxyl radical intermediate **4b** is formed from **1a** in the reaction.

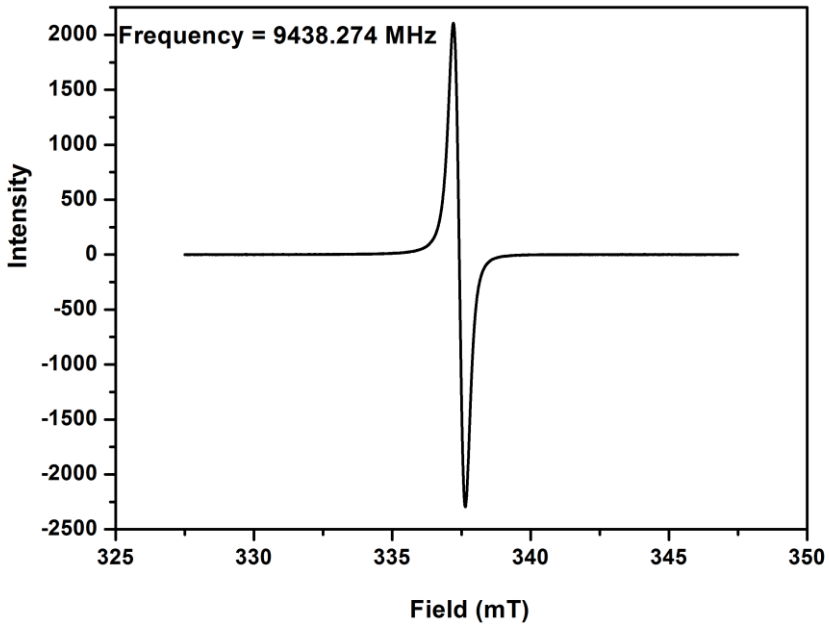



**Fig 4.2:** EPR spectrum of the reaction mixture of **1a** with $K_2S_2O_8$ in TFA.

## 4B.10: Conclusion

1. We have demonstrated a highly regioselective oxidative C-H arylation of substituted phenols with substituted aromatics in the presence of $K_2S_2O_8$ and $Bu_4N^+ \cdot HSO_4^-$ in $CF_3COOH$ at ambient temperature, providing unsymmetrical biaryls. Phenols with oxidation potentials up to 0.68 V and naphthols up to 0.88 V participated in the reaction.
2. Further, the formation of cationic phenol radical intermediate and phenoxy radical intermediate was confirmed by UV/Vis and EPR studies.acid.

## 4B.11: Experimental Section

### General Procedure for the Arylation of Phenols and Naphthols

In a 10-mL Schlenk tube, substituted phenols or naphthols **1** (100 mg), $K_2S_2O_8$ (2.0 equiv), tetrabutylammonium hydrogen sulfate (10 mol %) and substituted aromatics **2** (specific equivalent is mentioned below in the spectral data section) were taken. To the tube, was then added $CF_3COOH$ (0.5 mL) via syringe. Then, the tube was covered with a septum and stirred at room temperature (The reaction worked very well under an air atmosphere also. Nitrogen purging is not needed). The consumption of the substrate was monitored by TLC (the reaction time is mentioned below for all substrates in the spectral data section). The reaction mixture was diluted with $CH_2Cl_2$ and filtered through the celite pad. Then, the filtrate was concentrated and purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure product **3**.

### General Procedure for the Bisarylation of Phenols

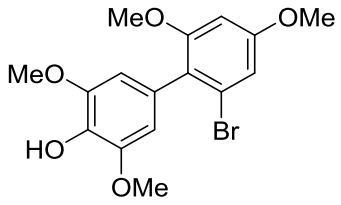
In a 10-mL Schlenk tube, substituted phenols or naphthols **1** (100 mg), $K_2S_2O_8$ (3.0 equiv), tetrabutylammonium hydrogen sulfate (20 mol %) and substituted aromatics **2** (specific equivalent is mentioned below in the spectral data section) were taken. To the tube, was then added $CF_3COOH$ (1.0 mL) via syringe. Then, the tube was covered with a septum and stirred at room temperature (The reaction worked very well under an air atmosphere also. Nitrogen purging is not needed). The consumption of the substrate was monitored by TLC (the reaction time is mentioned below for all substrates in the spectral data section). The reaction mixture was diluted with $CH_2Cl_2$ and filtered through the celite pad. Then, filtrate was concentrated and purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure *bis* arylated phenols **3gk**, **3gq,** and **3iq**.

### Procedure for the Preparation of Polyarylated Phenol 3hq

In a 10-mL Schlenk tube, substituted phenol **1h** (100 mg), $K_2S_2O_8$ (6.0 equiv), tetrabutylammonium hydrogen sulfate (40 mol %) and aromatic **2q** (10 equiv) were taken. To the tube, was then added $CF_3COOH$ (2.0 mL) via syringe. Then, the tube was covered with a septum and stirred at room temperature for 18 h (The reaction worked very well under an air atmosphere. Nitrogen purging is not needed). The reaction mixture was diluted with $CH_2Cl_2$ and filtered through the celite pad. Then filtrate was concentrated and purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure **3hq**.

**4B.12: Spectral Data of Compounds**

**2'-Bromo-3,4',5,6'-tetramethoxy-[1,1'-biphenyl]-4-ol (3aa).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2c** (3.0 equiv, 422 mg). The reaction time is 2 h. The desired product **3aa** was isolated in 193 mg and yield is 80%. Colorless solid; mp 141-144 °C; eluent (25% ethyl acetate in hexanes). Unreacted starting material **1a** was decomposed and remaining **2a** was recovered back (Minor amount of homocoupling product of **2c** was observed).

**IR (ATR) ṽ (cm$^{-1}$)**: 3510, 2970, 2836, 2377, 2314, 1739, 1598, 1557, 1484, 1454, 1249, 1212, 1106, 1023, 940, 846, 802, 647, 752.

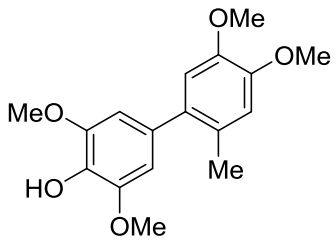
**$^{1}$H NMR (CDCl$_3$, 400 MHz):** δ 6.79 (d, *J* = 9.8 Hz, 1H), 6.49 (d, *J* = 13.6 Hz, 1H), 6.45 (s, 2H), 5.54 (s, 1H), 3.86 (s, 6H), 3.81 (s, 3H), 3.69 (s, 3H).

**$^{13}$C NMR (CDCl$_3$, 100 MHz):** δ 159.9, 158.6, 146.5, 133.9, 128.1, 125.1, 124.8, 108.7, 107.4, 98.30, 56.2, 56.0, 55.6.

**HRMS (ESI):** calc. for [($C_{16}H_{17}O_5Br$)H] (M+H) 369.0338, measured 369.0335.

The regiochemistry of compound **3aa** was confirmed by K. Morimoto, K. Sakamoto, Y. Ohnishi, T. Miyamoto, M. Ito, T. Dohi, Y. Kita, *Chem. Eur. J*. **2013**, 19, 8726.

**3,4',5,5'-Tetramethoxy-2'-methyl-[1,1'-biphenyl]-4-ol (3ab).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2a** (3.0 equiv, 296 mg). The reaction time is 2 h. The desired product was isolated in 185 mg and yield is 94%. Colorless solid; mp 114-116 °C; eluent (30% ethyl acetate in hexanes). The yield of 2% of homocoupling product of **1a** was observed and remaining starting material **1a** was decomposed. Aromatic **2a** was recovered back.

**IR (ATR) ṽ (cm$^{-1}$)**: 3496, 2930, 2839, 2378, 2316, 1734, 1609, 1503, 1450, 1251, 1211, 1113, 1062, 988, 752.

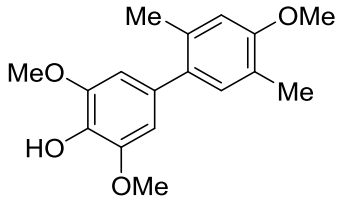
**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 6.75 (s, 2 H), 6.50 (s, 2 H), 5.53 (s, 1 H), 3.88 (s, 3 H), 3.87 (s, 6 H), 3.84 (s, 3 H), 2.20 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 147.8, 146.5, 134.1, 133.4, 133.0, 127.4, 113.2, 113.1, 106.1, 56.24, 56.0, 55.9, 19.9.

**HRMS (ESI):** calc. for [($C_{17}H_{20}O_5$)H] (M+H) 305.1389, measured 305.1379.

The regiochemistry of compound **3ab** was confirmed by K. Morimoto, K. Sakamoto, T. Ohshika, T. Dohi, Y. Kita, *Angew. Chem. Int. Ed*. **2016**, *55*, 3652 and A. Kirste, B. Elsler, G. Schnakenburg, S. R. Waldvogel, *J. Am. Chem. Soc*. **2012**, *134*, 3571.

**3,4',5-Trimethoxy-2',5'-dimethyl-[1,1'-biphenyl]-4-ol (3ac).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2b** (3.0 equiv, 265 mg). The reaction time is 2 h. The desired product was isolated in 154 mg and yield is 82%. Colorless liquid; eluent (15% ethyl acetate in hexanes. Remaining starting material **1a** was decomposed, 3% of homocoupling of **2b** was observed and remaining **2b** was recovered. Meanwhile, 6% of unidentified product was observed. We were not able to find out the correct structure.

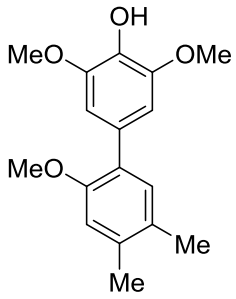
**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.01 (s, 1 H), 6.71 (s, 1 H), 6.50 (s, 2 H), 5.50 (s, 1 H), 3.87 (s, 6 H), 3.85 (s, 3 H), 2.26 (s, 3 H), 2.21 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 156.7, 146.6, 134.0, 133.7, 133.4, 133.1, 132.0, 123.7, 111.9, 106.3, 56.29, 55.4, 20.5, 15.6.

**HRMS (ESI):** calc. for [($C_{17}H_{20}O_4$)H] (M+H) 289.1440, measured 289.1434.

The regiochemistry of compound **3ac** was confirmed by B. Elsler, D. Schollmeyer, K. M. Dyballa, R. Franke, S. R. Waldvogel, *Chem. Eur. J.* **2015**, *21*, 12321.

**2',3,5-Trimethoxy-4',5'-dimethyl-[1,1'-biphenyl]-4-ol (3ad).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2d** (3.0 equiv, 265 mg). The reaction time is 2 h. The desired product was isolated in 112 mg and yield is 60%. Brown semisolid; eluent (20% ethyl acetate in hexanes). Homocoupling of **1a** was observed in 5% yield. Remaining starting material **1a** and **2d** was recovered back.

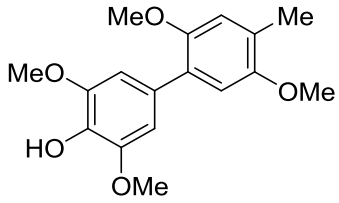
**$^{1}$H NMR ($CDCl_3$, 400 MHz):**7.08 (s, 1H), 6.79 (s, 1H), 6.75 (s, 2H), 5.56 (s, 1H), 3.90 (s, 6H), 3.79 (s, 3H), 2.31 (s, 3H), 2.25 (s, 3H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 154.3, 146.6, 136.5, 133.8, 131.7, 129.6, 128.5, 128.0, 113.2, 106.5, 56.3, 55.8, 19.8, 18.7.

**HRMS (ESI):** calc. for $[(C_{18}H_{20}O_4)H]$ (M+H) 289.1440, measured 289.1447.

The regiochemistry of compound **3ad** was confirmed by B. Elsler, D. Schollmeyer, K. M. Dyballa, R. Franke, S. R. Waldvogel, *Chem. Eur. J.* **2015**, *21*, 12321

**2',3,5,5'-Tetramethoxy-4'-methyl-[1,1'-biphenyl]-4-ol (3ae).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2e** (3.0 equiv, 296 mg). The reaction time is 2 h. The desired product was isolated in 60 mg and yield is 30%. Brown semi-solid; eluent (25% ethyl acetate in hexanes). Remaining starting material, **1a** was decomposed, and **2e** was recovered back.

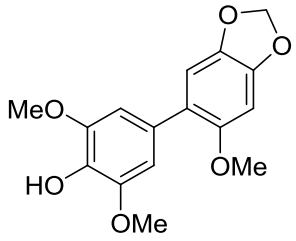
**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 6.79 (s, 2 H), 6.75 (s, 2 H), 5.54 (s, 1 H), 3.90 (s, 6 H), 3.81 (s, 3 H), 3.73 (s, 3 H), 2.26 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 151.8, 150.0, 146.6, 134.0, 129.8, 128.6, 126.4, 115.2, 113.1, 106.4, 56.52, 56.3, 56.1, 16.2.

**HRMS (ESI):** calc. for $[(C_{17}H_{20}O_5)H]$ (M+H) 305.1389, measured 305.1392.

The regiochemistry of compound **3ae** was confirmed by A. Kirste, B. Elsler, G. Schnakenburg, S. R. Waldvogel, *J. Am. Chem. Soc.* **2012**, *134*, 3571

**2,6-Dimethoxy-4-(6-methoxybenzo[*d*][1,3]dioxol-5-yl)phenol (3af).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2f** (3.0 equiv, 296 mg). The reaction time is 2 h. The desired product was isolated in 74 mg and yield is 38%. Brown solid; mp 118-120 °C eluent (25% ethyl acetate in hexanes). Remaining starting material, **1a** was decomposed and unreacted aromatic **2f** was converted into homocoupling product.

**IR (ATR) ṽ (cm$^{-1}$)**: 3503, 2922, 2837, 1726, 1609, 1514, 1484, 1400, 1338, 1215, 1162, 1112, 1030, 923, 840, 762, 681

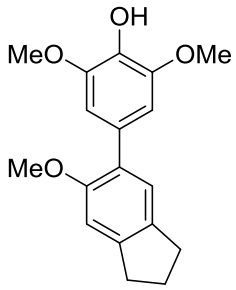
**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 6.79 (s, 1H), 6.68 (s, 2H), 6.60 (s, 1H), 5.94 (s, 2H), 3.88 (s, 6H), 3.71 (s, 3H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 151.6, 147.2, 146.6, 141.4, 133.8, 129.5, 123.3, 110.2, 106.4, 101.3, 95.5, 56.8, 56.3.

**HRMS (ESI):** calc. for [($C_{16}H_{16}O_6$)H] (M+H) 305.1025, measured 305.1031.

The regiochemistry of compound **3af** was confirmed by A. Kirste, G. Schnakenburg, F. Stecker, A. Fischer, S. R. Waldvogel, *Angew. Chem. Int. Ed*. **2010**, *49*, 971.

**2,6-Dimethoxy-4-(6-methoxy-2,3-dihydro-1*H*-inden-5-yl)phenol (3ag).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2g** (3.0 equiv, 289 mg). The reaction time is 2 h. The desired product was isolated in 69 mg and yield is 36%. Colorless semi-solid; eluent (15% ethyl acetate in hexanes). Unreacted starting material **1a** and **2g** were recovered.

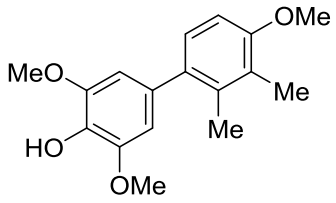
**IR (ATR) ṽ (cm$^{-1}$)**: 3501, 2936, 2839, 1739, 1609, 1514, 1484, 1400, 1338, 1212, 1106, 840, 762.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.14 (s, 1H), 6.87 (s, 1H), 6.72 (s, 2H), 3.88 (s, 6H), 3.77 (s, 3H), 2.90 (m, 4H), 2.14 – 2.06 (m, 2H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 155.3, 146.5, 144.5, 142.5, 136.1, 133.7, 130.2, 128.8, 126.3, 107.9, 106.5, 56.3, 55.9, 33.3, 32.1, 25.8.

**HRMS (ESI):** calc. for [($C_{18}H_{20}O_4$)Na] (M+Na) 323.1259, measured 323.1254.

**3,4',5-Trimethoxy-2',3'-dimethyl-[1,1'-biphenyl]-4-ol (3ah).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2a** (3.0 equiv, 265 mg). The reaction time is 2 h. The desired product was isolated in 117 mg and yield is 62%.Colourless solid; mp 143-144 °C; eluent (15% ethyl acetate in hexanes). Remaining starting material, **1a** was decomposed, and **2h** was recovered back.

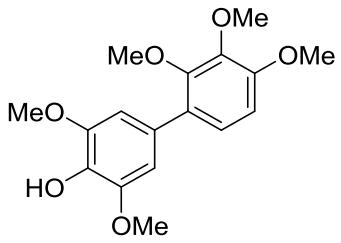
**IR (ATR) ṽ (cm$^{-1}$)**: 3442, 2935, 2836, 2381, 2312, 1732, 1597, 1518, 1482, 1250, 1205, 1111, 1027, 807, 662.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.07 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.49 (s, 2H), 5.52 (s, 1H), 3.87 (s, 6H), 3.85 (s, 3H), 2.22 (s, 3H), 2.17 (s, 3H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 156.6, 146.5, 135.4, 135.1, 133.8, 133.3, 127.4, 125.4, 107.4, 106.4, 56.25, 55.6, 17.5, 12.1.

**HRMS (ESI):** calc. for [($C_{17}H_{20}O_4$)H] (M+H) 289.1440, measured 289.1434.

**2',3,3',4',5-Pentamethoxy-[1,1'-biphenyl]-4-ol (3ai).**



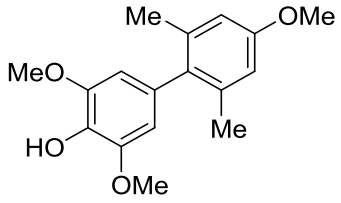

The representative general procedure **A** was followed using **1a** (100 mg) and **2i** (3.0 equiv, 327 mg). The reaction time is 3 h. The desired product was isolated in 73 mg and yield is 35%. Colorless solid; mp 134-136 °C; eluent (25% ethyl acetate in hexanes). 7% of homocoupling of **1a** was observed and remaining starting material **1a** was decomposed and **2i** was recovered back.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.01 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.53 (s, 1H), 3.91 (s, 3H), 3.89 (s, 6H), 3.87 (s, 3H), 3.65 (s, 3H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 152.9, 151.3, 146.7, 142.6, 133.8, 129.4, 128.7, 124.5, 107.4, 106.0, 61.1, 60.9, 56.3, 56.1.

**HRMS (ESI):** calc. for [($C_{17}H_{20}O_6$)H] (M+H) 321.1338, measured 321.1347.

**3,4',5-Trimethoxy-2',6'-dimethyl-[1,1'-biphenyl]-4-ol (3aj).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2j** (3.0 equiv, 265 mg). The reaction time is 4 h. The desired product was isolated in 79 mg and yield is 42%. Colorless solid; mp 96-98 °C; eluent (15% ethyl acetate in hexanes). Remaining starting material, **1a** was decomposed, and 2**a** was recovered.

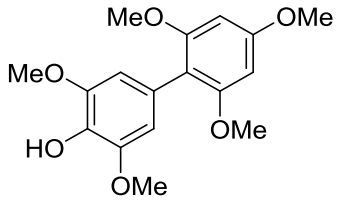
**IR (ATR) ṽ (cm$^{-1}$)**: 3492, 2930, 2836, 2381, 2316, 1717, 1605, 1520, 1453, 1245, 1201, 1105, 1091, 1025, 823, 776, 671.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 6.72 (s, 1 H), 6.63 (s, 1 H), 6.42 (s, 2 H), 5.48 (s, 1 H), 3.84 (s, 6 H), 3.70 (s, 3 H), 2.35 (s, 3 H), 2.05 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 157.0, 146.7, 137.8, 137.8, 133.4, 128.6, 128.1, 123.1, 109.3, 106.8, 56.2, 55.8, 21.5, 20.3.

**HRMS (ESI):** calc. For [($C_{17}H_{20}O_4$)H] (M+H) 289.1440, measured 289.1445.

**2',3,4',5,6'-Pentamethoxy-[1,1'-biphenyl]-4-ol (3ak).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2k** (3.0 equiv, 327 mg). The reaction time is 2 h. The desired product was isolated in 84 mg and yield is 40%. Colorless solid; mp 140-142 °C; eluent (20% ethyl acetate in hexanes). Remaining starting material **1a** was decomposed and **2k** was recovered back.

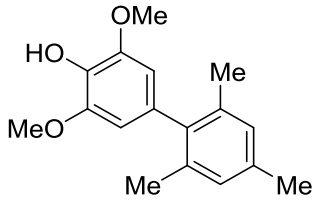
**IR (ATR) ṽ (cm$^{-1}$)**: 3398, 2922, 2841, 2378, 2317, 1584, 1496, 1451, 1284, 1220, 1107, 1062, 808, 780, 655.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 6.54 (s, 2H), 6.21 (s, 2H), 3.85 (s, 9H), 3.72 (s, 6H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 160.3, 158.4, 146.4, 133.4, 124.7, 112.4, 107.9, 90.8, 56.2, 55.9, 55.4.

**HRMS (ESI):** calc. for [($C_{17}H_{20}O_6$)H] (M+H) 321.1338, measured 321.1340.

**3,5-Dimethoxy-2',4',6'-trimethyl-[1,1'-biphenyl]-4-ol (3al).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2l** (5.0 equiv, 389 mg).The reaction time is 2 h. The desired product was isolated in 79 mg and yield is 45%.White solid; eluent (10% ethyl acetate in hexanes). Remaining starting material **1a** yielded the homocoupling product and **2l** was recovered back.

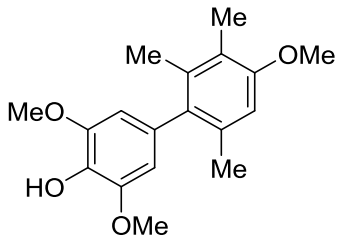
**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 6.93 (s, 2H), 6.36 (s, 2H), 3.84 (s, 6H), 2.32 (s, 3H), 2.04 (s, 6H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 147.03, 139.04, 136.61, 136.31, 133.07, 132.05, 127.94, 105.72, 56.23, 20.94, 20.56.

**HRMS (ESI):** calc. for [($C_{17}H_{20}O_3$)H] (M+H) 273.1491, measured 273.1485.

The regiochemistry of compound **3aa** was confirmed by K. Morimoto, K. Sakamoto, Y. Ohnishi, T. Miyamoto, M. Ito, T. Dohi, Y. Kita, *Chem. Eur. J*. **2013**, 19, 8726

**3,4',5-Trimethoxy-2',3',6'-trimethyl-[1,1'-biphenyl]-4-ol (3am).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2m** (3.0 equiv, 292 mg). The reaction time is 2 h. The desired product was isolated in 100 mg and yield is 51%. Colorless solid; mp 150-151 °C; eluent (12% ethyl acetate in hexanes). Remaining starting material **1a** was decomposed, 2% homocoupling of **1a** was observed. The remaining amount of **2m** was recovered. Meanwhile, 10% of unidentified product was observed. We were not able to find out the correct structure.

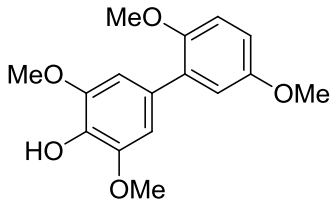
**IR (ATR) ṽ ($cm^{-1}$)**: 3443, 2970, 2836, 2378, 2311, 1738, 1601, 1517, 1481, 1452, 1205, 1111, 832, 742, 674.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 6.65 (s, 1H), 6.35 (s, 2H), 5.44 (s, 1H), 3.84 (s, 9H), 2.17 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 156.3, 147.0, 136.3, 134.6, 134.1, 133.02, 132.8, 122.3, 119.0, 109.2, 106.3, 104.9, 56.2, 55.5, 21.0, 17.6, 11.8.

**HRMS (ESI):** calc. for [($C_{18}H_{22}O_4$)H] (M+H) 303.1596, measured 303.1599.

**2',3,5,5'-tetramethoxy-[1,1'-biphenyl]-4-ol (3an).**



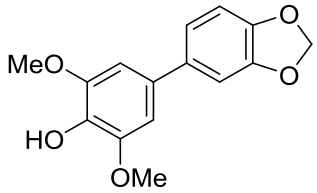

The representative general procedure **A** was followed using **1a** (100 mg) and **2n** (5.0 equiv, 448 mg) .The reaction time is 3 h. The desired product was isolated in 47 mg and yield is 25%. Colorless semi-solid; eluent (15% ethyl acetate in hexanes). Unreacted starting material **1a** yielded homo-coupling product and **2o** was recovered back.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 6.91 – 6.87 (m, 2H), 6.81 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.75 (s, 2H), 5.53 (s, 1H), 3.89 (s, 6H), 3.79 (s, 3H), 3.74 (s, 3H).

**$^{13}$C NMR ($CDCl_3$, 400 MHz):** δ 153.7, 150.7, 146.6, 134.1, 131.8, 129.4, 116.9, 112.7, 112.4, 106.4, 56.38, 56.3, 55.8.

**HRMS (ESI):** calc. for [($C_{16}H_{18}O_5$)H] (M+H) 291.1232, measured 291.1227.

**4-(Benzo[d][1,3]dioxol-5-yl)-2,6-dimethoxyphenol (3ao).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2o** (5.0 equiv, 396 mg). The reaction time is 3 h. The desired product was isolated in 36 mg and yield is 21%. Colorless liquid; eluent (15% ethyl acetate in hexanes). Remaining starting material **1a** yielded homo-coupling product and **2p** was recovered back.

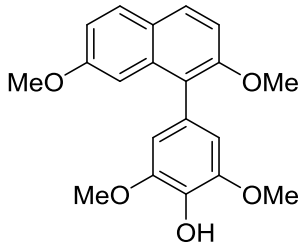
**IR (ATR) ṽ (cm$^{-1}$)**: 3590, 2921, 2836, 1726, 1609, 1512, 1481, 1405, 1338, 1212, 1162, 1109, 1030, 923, 840, 762, 681

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.01 – 6.96 (m, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.69 (s, 2H), 5.97 (s, 2H), 5.49 (s, 1H), 3.92 (s, 6H).

**$^{13}$C NMR ($CDCl_3$, 400 MHz):** δ 148.0, 147.2, 146.7, 135.9, 134.1, 132.7, 120.3, 108.5, 107.5, 103.8, 101.1, 56.3.

**HRMS (ESI):** calc. for [($C_{15}H_{14}O_5$)H] (M+H) 275.0919, measured 275.0914.

**4-(2,7-Dimethoxynaphthalen-1-yl)-2,6-dimethoxyphenol (3ap).**




The representative general procedure **A** was followed using **1a** (100 mg) and **2p** (3.0 equiv, 366 mg). The reaction time is 2 h. The desired product was isolated in 135 mg and yield is 61%. Colorless solid; mp158-159 °C; eluent (30% ethyl acetate in hexanes). Remaining starting material **1a** and **2p** were recovered back.

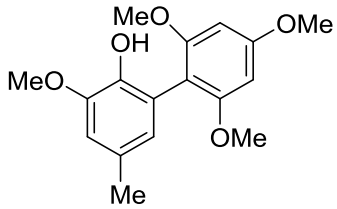
**IR (ATR) ṽ (cm$^{-1}$)**: 3490, 2930, 2835, 2378, 2311, 1740, 1613, 1507, 1456, 1418, 1371, 1304, 1211, 1144, 1110, 1041, 957, 836, 752, 696, 637.

**$^{1}$H NMR (CDCl$_3$, 400 MHz):**δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.83 (s, 1H), 6.59 (s, 2H), 5.59 (s, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 3.69 (s, 3H).

**$^{13}$C NMR (CDCl$_3$, 400 MHz):** δ 158.1, 154.4, 147.0, 135.1, 133.6, 129.40, 128.7, 127.5, 124.5, 124.3, 116.3, 111.1, 107.4, 103.6, 56.6, 56.3, 55.1.

**HRMS (ESI):** calc. for [($C_{20}H_{20}O_5$)H] (M+H) 341.1389, measured 341.1392.

**2',3,4',6'-tetramethoxy-5-methyl-[1,1'-biphenyl]-2-ol (3bk).**




The representative general procedure **A** was followed using **1b** (100 mg) and **2k** (3.0 equiv, 365 mg). The reaction time is 4 h. The desired product was isolated in 123 mg and yield is 56%. Colorless solid; mp 149-150 °C; eluent (25% ethyl acetate in hexanes). Remaining unreacted starting materials **1b** and **2k** were recovered back.

**IR (ATR) ṽ (cm$^{-1}$)**: 3476, 2951, 2839, 2378, 2311, 1738, 1584, 1508, 1489, 1452, 1220, 1117, 1030, 941, 838, 809, 746

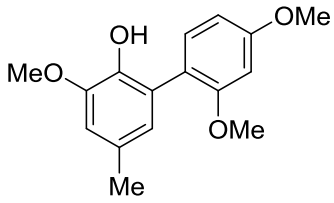
**$^{1}$H NMR (CDCl$_3$, 400 MHz):** δ 6.67 (s, 1 H), 6.59 (s, 1 H), 6.24 (s, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.73 (s, 6 H), 2.31 (s, 3 H).

**$^{13}$C NMR (CDCl$_3$, 100 MHz):** δ 161.0, 158.7, 146.6, 141.2, 128.3, 124.6, 120.4, 111.0, 107.4, 91.10, 56.1, 56.0, 55.7, 55.3, 55.1, 21.2.

**HRMS (ESI):** calc. for [($C_{17}H_{20}O_5$)H] (M+H) 305.1389, measured 305.1394.

The regiochemistry of compound **3af** was confirmed by A. Kirste, G. Schnakenburg, F. Stecker, A. Fischer, S. R. Waldvogel, *Angew. Chem. Int. Ed*. **2010**, *49*, 971.

**2',3,4'-Trimethoxy-5-methyl-[1,1'-biphenyl]-2-ol** (**3bq**).




The representative general procedure **A** was followed using **1b** (100 mg) and **2q** (3.0 equiv, 500 mg). The reaction time is 4 h. The desired product was isolated in 110 mg and yield is 55%. Colorless liquid; eluent (15% ethyl acetate in hexanes). Unreacted starting material **1b** yielded 5% of homocoupling product and remaining **1b** was decomposed. **2n** was recovered back.

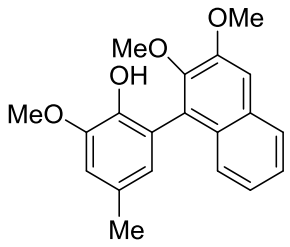
1H NMR ($CDCl_3$, 400 MHz): δ 7.21 (d, *J* = 8.0 Hz, 1 H), 6.68 (s, 1 H), 6.65 (s, 1H), 6.60 – 6.56 (m, 2 H), 3.89 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 2.31 (s, 3 H).

13C NMR (CDCl3, 100 MHz): δ 160.5, 157.2, 147.1, 140.9, 132.1, 129.0, 125.0, 123.7, 119.5, 111.0, 105.0, 98.9, 55.9, 55.9, 55.4, 21.1.

HRMS (ESI): calc. for [($C_{16}H_{18}O_4$)H] (M+H) 275.1283, measured 275.1278.

The regiochemistry of compound **3aa** was confirmed by K. Morimoto, K. Sakamoto, Y. Ohnishi, T. Miyamoto, M. Ito, T. Dohi, Y. Kita, *Chem. Eur. J*. **2013**, 19, 8726

**2-(2,3-Dimethoxynaphthalen-1-yl)-6-methoxy-4-methylphenol (3bh).**




The representative general procedure **A** was followed using **1b** (100 mg) and **2h** (3.0 equiv, 408 mg). The reaction time is 2 h. The desired product was isolated in 137 mg and yield is 60%. Red solid; mp 116-117 °C eluent (20% ethyl acetate in hexanes). Unreacted starting material **1b** was decomposed and **2q** was recovered back.

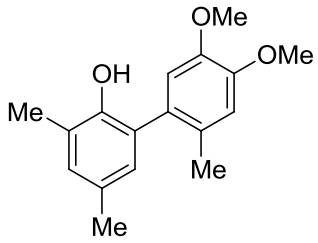
**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.77 (d, *J* = 8.0 Hz, 1 H), 7.41 (m, 2 H), 7.27 (m, 2 H), 6.82 (s, 1 H), 6.69 (s, 1 H), 5.48 (s, 1 H), 4.05 (s, 3 H), 3.98 (s, 3 H), 3.76 (s, 3 H), 2.38 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 152.2, 147.0, 146.6, 141.2, 131.3, 128.9, 128.4, 127.4, 126.6, 125.6, 125.2, 124.1, 123.9, 121.9, 111.2, 107.1, 61.0, 55.9, 55.6, 21.2.

**HRMS (ESI):** calc. for [($C_{20}H_{20}O_4$)H] (M+H) 325,1440, measured 325.1436.

The regiochemistry of compound **3ae** was confirmed by A. Kirste, B. Elsler, G. Schnakenburg, S. R. Waldvogel, *J. Am. Chem. Soc*. **2012**, *134*, 3571

**4',5'-Dimethoxy-2',3,5-trimethyl-[1,1'-biphenyl]-2-ol (3cb).**




The representative general procedure **A** was followed using **1c** (100 mg) and **2b** (3.0 equiv, 373 mg). The reaction time is 3 h. The desired product was isolated in 72 mg and yield is 32%. White solid; mp 210-212 °C; eluent (40% ethyl acetate in hexanes). Remaining starting material **1c** yielded homo coupling product and **2b** was recovered back.

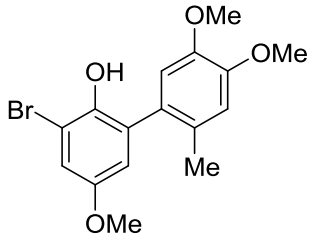
**IR (ATR) ṽ ($cm^{-1}$)**: 3461, 2924, 2822, 1716, 1644, 1605, 1511, 1446, 1321, 1251, 1209, 1172, 1070, 1001, 860, 769, 750, 669.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 6.93 (s, 1 H), 6.80 (s, 1 H), 6.74 (s, 1 H), 6.71 (s, 1 H), 4.70 (s, 1 H), 3.90 (s, 3 H), 3.82 (s, 3 H), 2.26 (s, 3 H), 2.25 (s, 3 H), 2.09 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 148.7, 148.6, 147.3, 130.9, 129.4, 128.8, 128.1, 127.6, 126.8, 123.8, 113.5, 113.4, 56.0, 55.9, 20.5, 19.2, 16.1.

**HRMS (ESI):** calc. for [($C_{17}H_{20}O_3$)H] (M+H) 273.1491, measured 273.1485.

**3-Bromo-4',5,5'-trimethoxy-2'-methyl-[1,1'-biphenyl]-2-ol (3db).**




The representative general procedure **A** was followed using **1d** (100 mg) and **2b** (3.0 equiv, 225 mg). The reaction time is 3 h. The desired product was isolated 64 mg and yield is 35%. Colorless solid; mp 144-145 °C; eluent (20% ethyl acetate in hexanes). Remaining starting material **1d** and **2b** were recovered back.

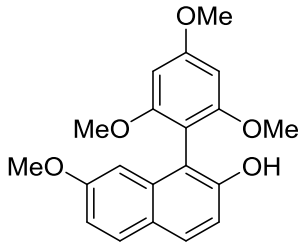
**IR (ATR) ṽ (cm$^{-1}$)**: 3403, 2924, 2377, 2318, 2837, 1709, 1607, 1508, 1452, 1312, 1223, 1152, 1106, 1036, 980, 850, 817, 778, 746, 697.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.04 (d, *J* = 4.0 Hz, 1 H), 6.78 (s, 1 H), 6.69 (s, 1 H), 6.66 (d, *J* = 4.0 Hz, 1 H), 5.06 (s, 1 H), 3.89 (s, 3 H), 3.82 (s, 3 H), 3.75 (s, 3 H), 2.11 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 153.1, 148.8, 147.0, 143.9, 129.4, 129.1, 127.7, 116.7, 116.3, 113.3, 112.9, 109.7, 56.0, 55.9, 55.8, 19.3.

**HRMS (ESI):** calc. for [($C_{16}H_{17}O_4Br$)H] (M+H) 353.0388, measured 353.0383.

**7-Methoxy-1-(2,4,6-trimethoxyphenyl)naphthalen-2-ol (3ek).**




The representative general procedure **A** was followed using **1e** (100 mg) and **2k** (3.0 equiv, 289 mg). The reaction time is 3 h. The desired product was isolated in 71 mg along with homocoupling product of **2k**. Both products were not able to separate and overall yield is 35%. Colorless solid; eluent (20% ethyl acetate in hexanes). Unreacted starting material **1e** was recovered back, a part of **2k** was yielded homo-coupling product and remaining **2k** was recovered back.

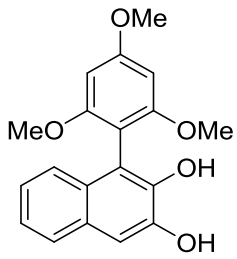
**Note**: Only product **3ek** peaks were mentioned and homocoupling product of **2k** was excluded.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):**δ 7.69 (m, 2 H), 7.11 (d, *J* = 8.0 Hz, 1 H), 6.95 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.57 (d, *J* = 4.0 Hz, 1 H), 6.32 (s, 2 H), 5.28 – 4.94 (m, 1 H), 3.92 (s, 3 H), 3.70 (s, 3 H), 3.66 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 400 MHz):** δ 160.5, 159.8, 159.1, 157.9, 135.1, 129.55, 129.0, 124.4, 114.8, 114.7, 104.8, 103.9, 102.3, 91.3, 56.1, 55.9, 55.4.

**HRMS (ESI):** calc. for [($C_{20}H_{20}O_5$)H] (M+H) 341.1389, measured 341.1384.

**1-(2,4,6-Trimethoxyphenyl)naphthalene-2,3-diol (3fk).**



The representative general procedure **A** was followed using **1f** (100 mg) and **2k** (3.0 equiv, 315 mg). The reaction time is 16 h. The desired product was isolated in 81 mg and yield is 40%. Dark red solid; mp 210-212 °C; eluent (40% ethyl acetate in hexanes). Unreacted starting material **1k** and **2k** were recovered back.

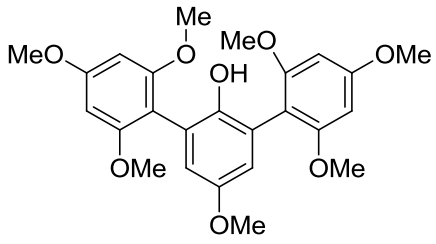
**IR (ATR) ṽ ($cm^{-1}$)**: 3727, 3447, 3394, 2379, 2314, 1734, 1585, 1510, 1451, 1123, 1199, 1151, 1119, 1052, 948, 923, 840, 762, 681

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.69 (d, *J* = 8.0 Hz, 1 H), 7.30 (m, 2 H), 7.25 – 7.16 (m, 2 H), 6.36 (s, 2 H), 5.90 (s, 1 H), 5.47 (s, 1 H), 3.94 (s, 3 H), 3.68 (s, 6 H).

**$^{13}$C NMR ($CDCl_3$, 400 MHz):** δ 162.2, 159.6, 144.8, 141.3, 129.8, 128.5, 126.7, 124.8, 123.7, 123.4, 115.0, 109.5, 102.6, 91.4, 56.0, 55.5.

**HRMS (ESI):** calc. for [($C_{19}H_{18}O_5$)Na] (M+Na) 349.1052, measured 349.1046.

**2,2'',4,4'',5',6,6''-Heptamethoxy-[1,1':3',1''-terphenyl]-2'-ol (3gk).**



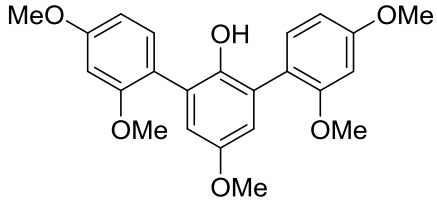

The representative general procedure **A** was followed using **1g** (100 mg) and **2k** (5.0 equiv, 677 mg). The reaction time is 3 h. The desired product was isolated 152 mg and yield is 42%. Dark red solid; mp 204-206 °C; eluent (30% ethyl acetate in hexanes). Remaining starting material **1g** was decomposed and **2k** was recovered back.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 6.76 (s, 2 H), 6.25 (s, 4 H), 3.84 (s, 6 H), 3.76 (s, 3 H), 3.74 (s, 12 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 160.9, 158.6, 152.0, 145.9, 122.2, 116.9, 108.4, 91.2, 56.0, 55.3, 55.3.

**HRMS (ESI):** calc. for [($C_{25}H_{28}O_8$)H] (M+H) 457.1862, measured 457.1857.

**2,2'',4,4'',5'-Pentamethoxy-[1,1':3',1''-terphenyl]-2'-ol (3gq).**




The representative general procedure **A** was followed using **1g** (100 mg) and **2n** (5.0 equiv, 556 mg). The reaction time is 4 h. The desired product was isolated 170 mg and

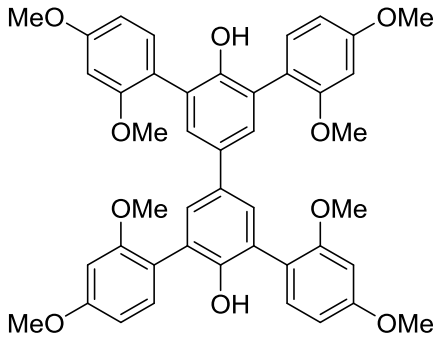
yield is 53%. Red solid; eluent (30% ethyl acetate in hexanes). Remaining starting material **1g** was decomposed and **2q** was recovered back.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.29 (d, *J* = 8.0 Hz, 2H), 6.80 (s, 2H), 6.60 (d, *J* = 8.0 Hz, 2H), 6.57 (s, 2H), 5.92 (s, 1H), 3.84 (s, 6H), 3.81 (s, 6H), 3.78 (s, 3H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 160.6, 157.2, 152.9, 145.3, 132.4, 127.5, 116.0, 105.2, 100.0, 55.9, 55.7, 55.4.

**HRMS (ESI):** calc. for [($C_{23}H_{24}O_6$)H] (M+H) 397.1651, measured 397.1654.

**Compound (3hq).**



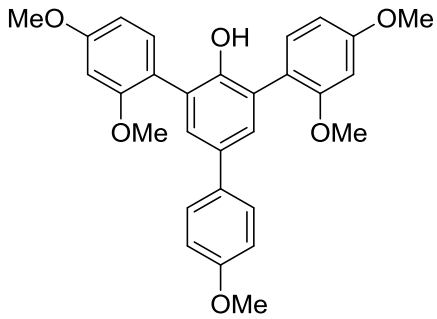

The representative general procedure **A** was followed using **1h** (100 mg) and **2q** (10.0 equiv, 741 mg). The reaction time is 18 h. The desired product was isolated in 108 mg and yield is 27%. Red solid; mp 198-200 °C; eluent (50% ethyl acetate in hexanes). Remaining starting material **1h** and **2n** were recovered back.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 7.48 (s, 4 H), 7.33 (d, *J* = 8.0 Hz, 4 H), 6.63 – 6.57 (m, 8 H), 6.29 (s, 2 H), 3.84 (s, 12 H), 3.82 (s, 12 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 160.5, 157.2, 150.3, 133.3, 132.6, 129.3, 126.8, 120.4, 105.2, 98.9, 55.9, 55.4.

**HRMS (ESI):** calc. for [($C_{44}H_{42}O_{10}$)H] (M+H) 731.2856, measured 731.2853.

**2,2'',4,4''-Tetramethoxy-5'-(4-methoxyphenyl)-[1,1':3',1''-terphenyl]-2'-ol (3iq).**




The representative general procedure **A** was followed using **1i** (100 mg) and **2q** (6.0 equiv, 414 mg). The reaction time is 8 h. The desired product was isolated 93 mg and

yield is 39%. Colorless semisolid; eluent (30% ethyl acetate in hexanes). Remaining starting material **1i** and **2q** were recovered back.

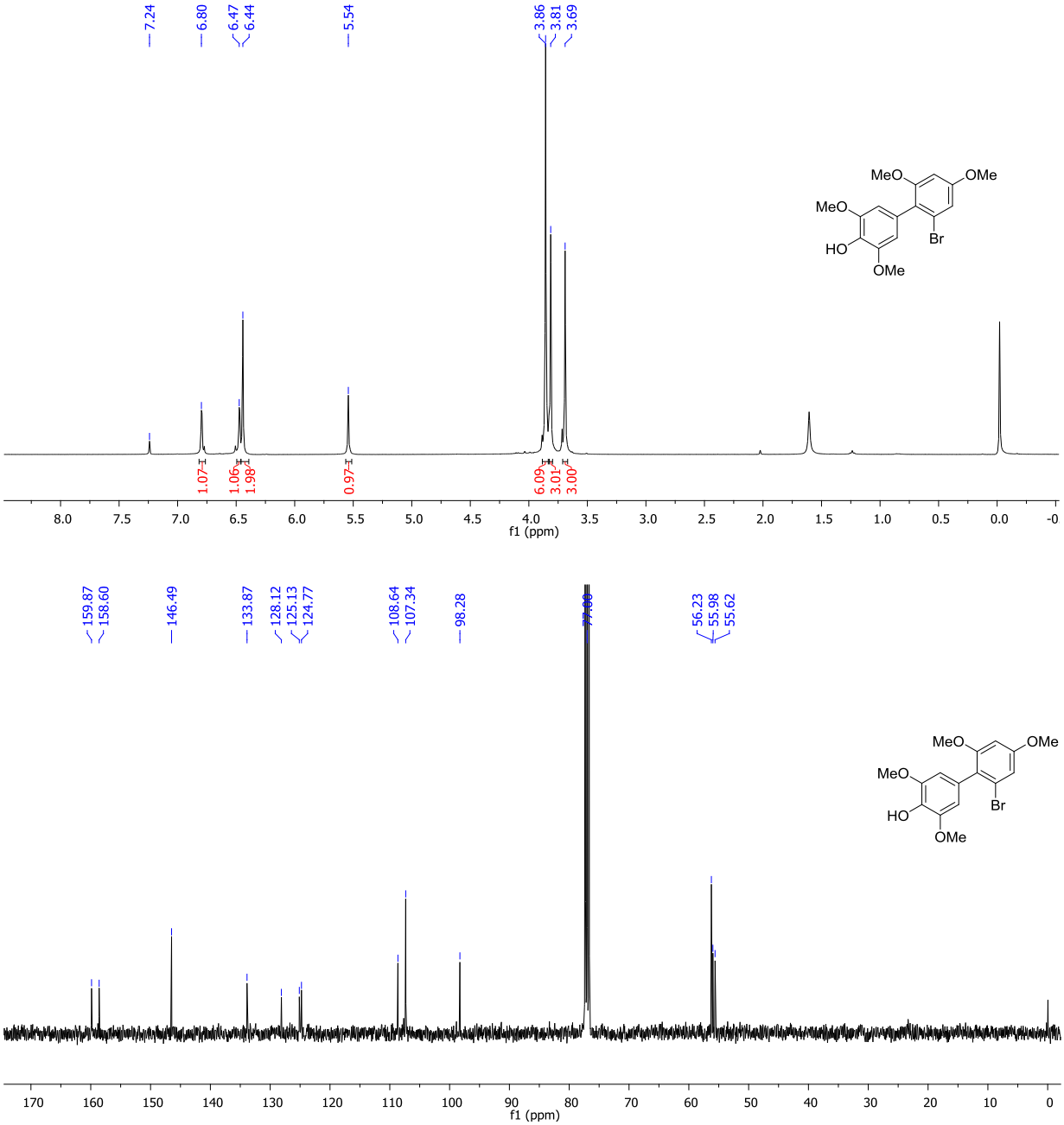
**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 7.52 (d, *J* = 8.0 Hz, 2 H), 7.43 (s, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 6.93 (d, *J* = 8.0 Hz, 2 H), 6.63 (dd, *J* = 8.0, 4.0 Hz, 2 H), 6.60 (d, *J* = 4.0 Hz, 2 H), 6.23 (s, 1 H), 3.85 (s, 6 H), 3.83 (s, 6 H), 3.82 (s, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 160.6, 158.5, 157.3, 150.4, 133.6, 133.1, 132.6, 129.1, 127.7, 126.9, 120.2, 114.0, 105.1, 98.9, 55.9, 55.4, 55.3.

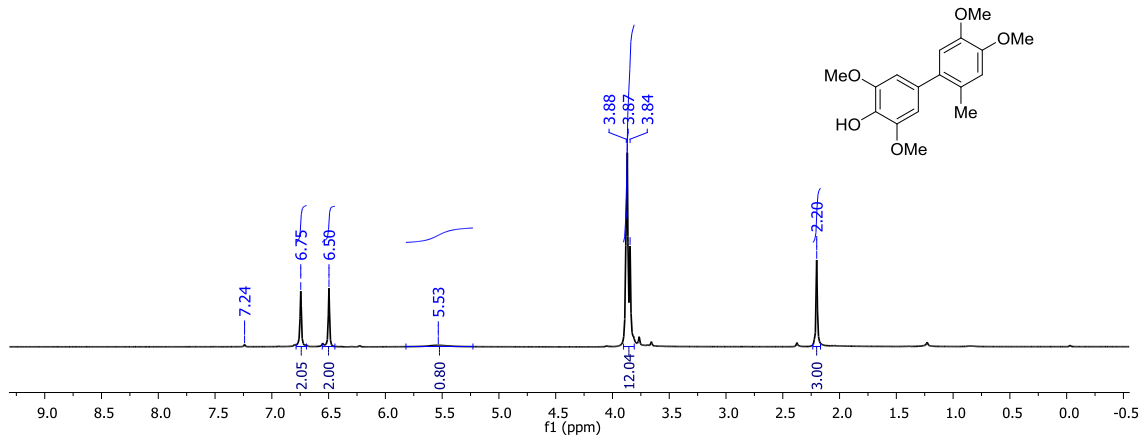
**HRMS (ESI):** calc. for [($C_{29}H_{28}O_6$)H] (M+H) 473.1964, measured 473.1959.

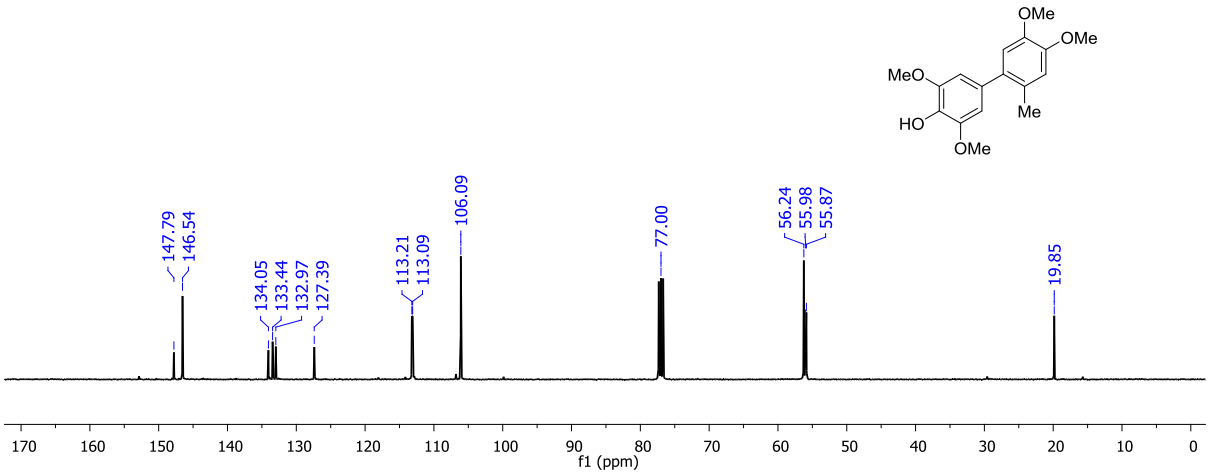
## 4B.13: Spectral Copies of Selected Compounds

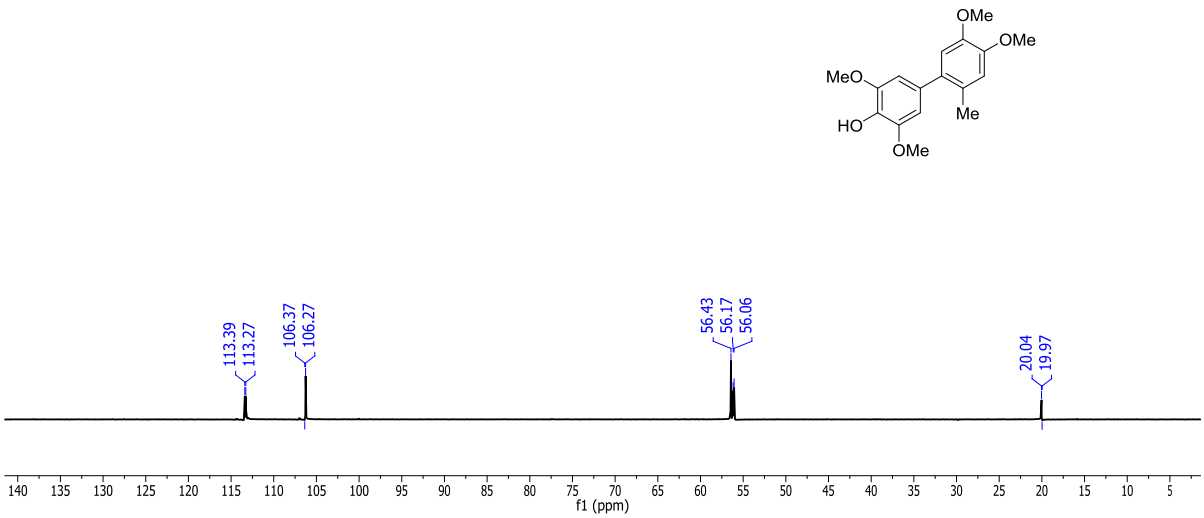
$^{1}$H and $^{13}$C NMR Spectra of Compound **3aa**.



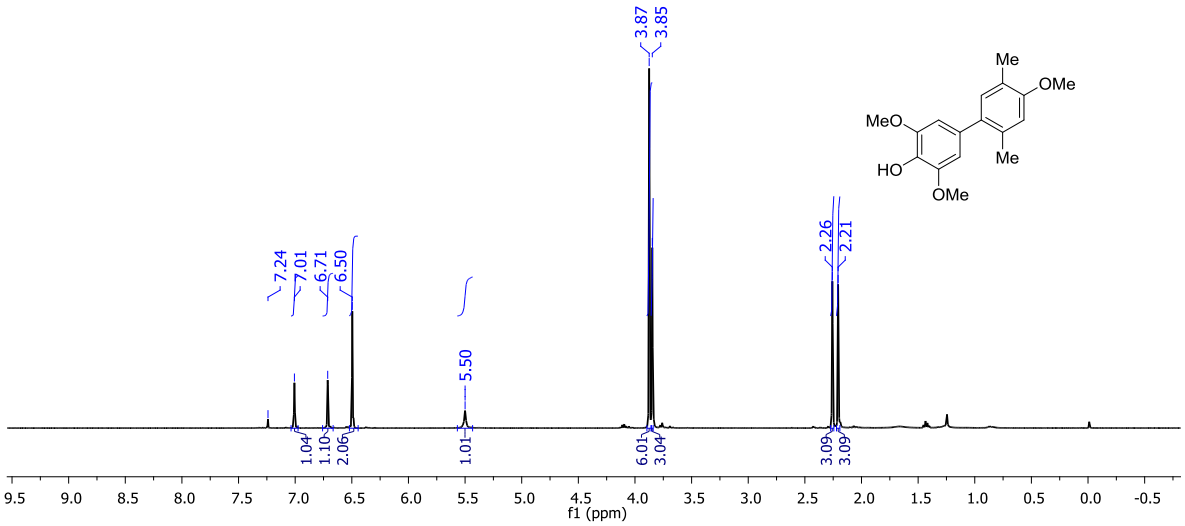
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **3ab**.

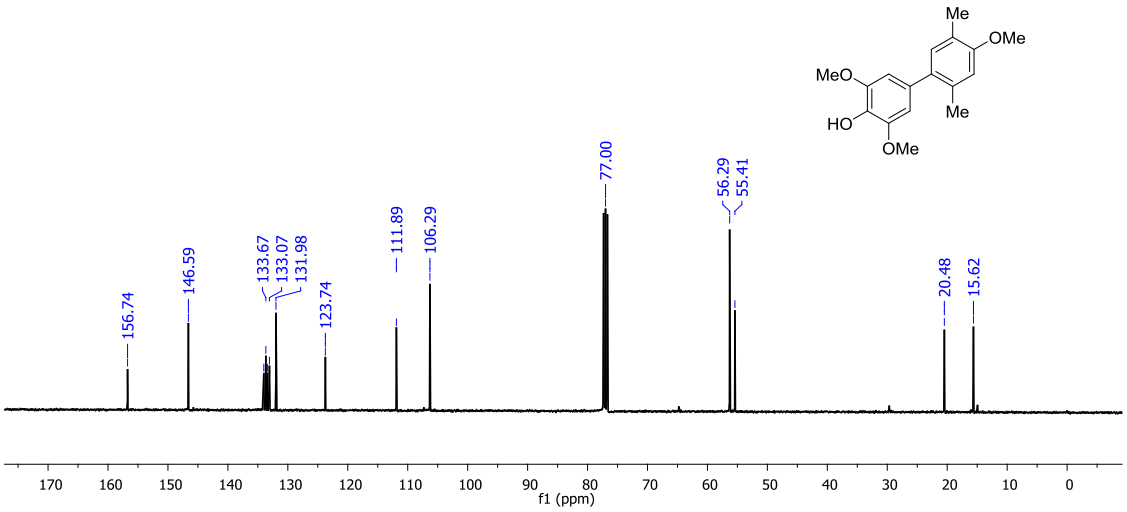


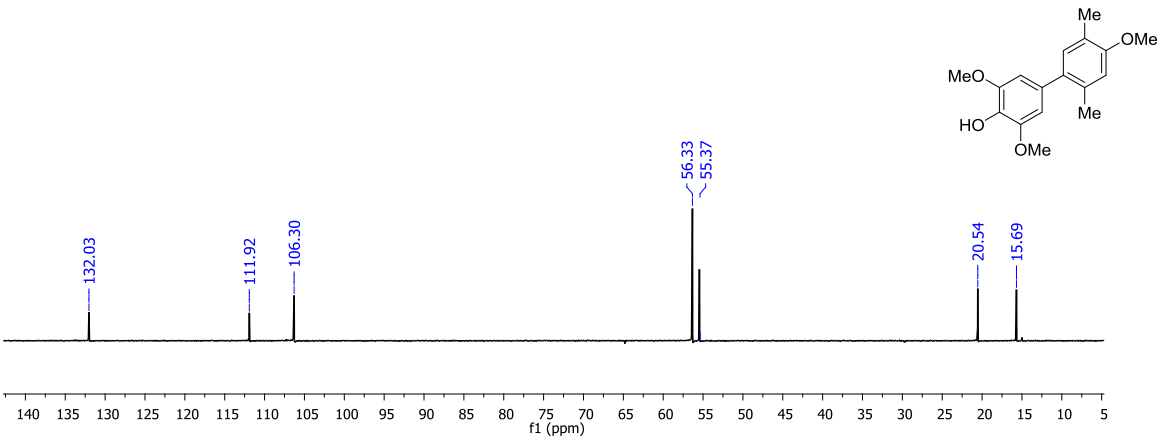



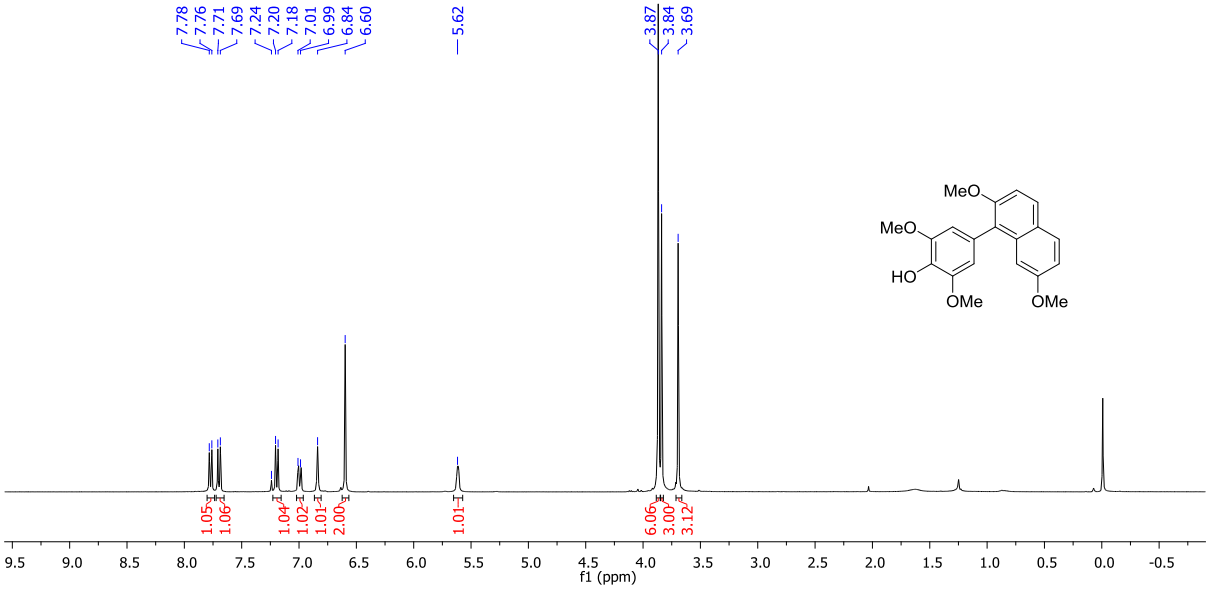
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **3ac**.

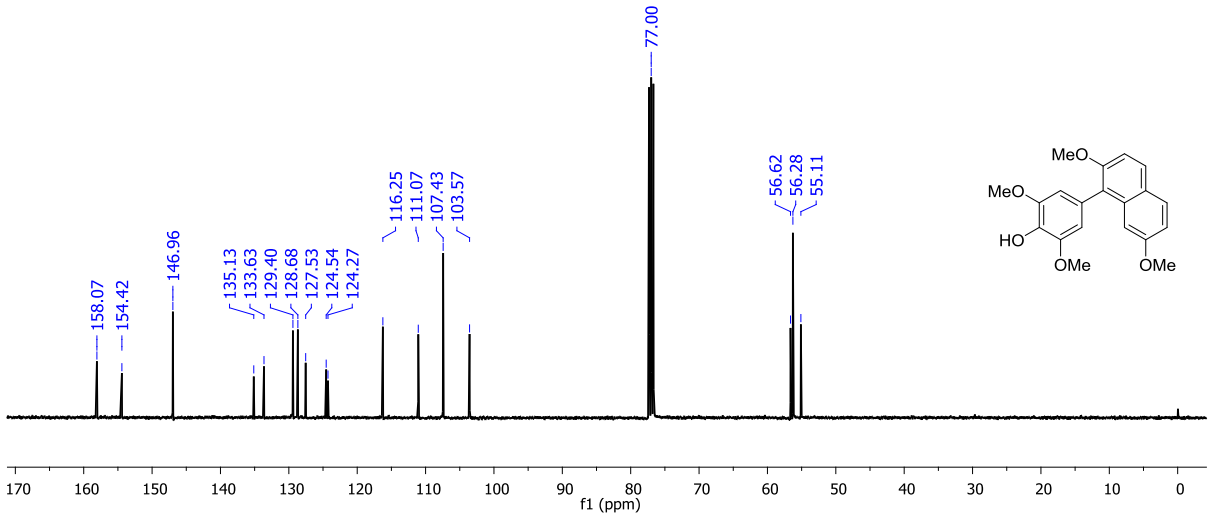


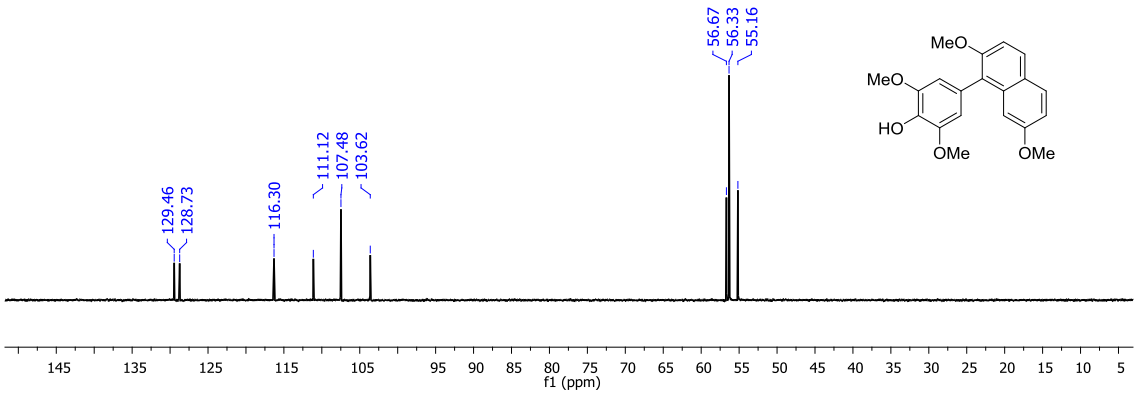



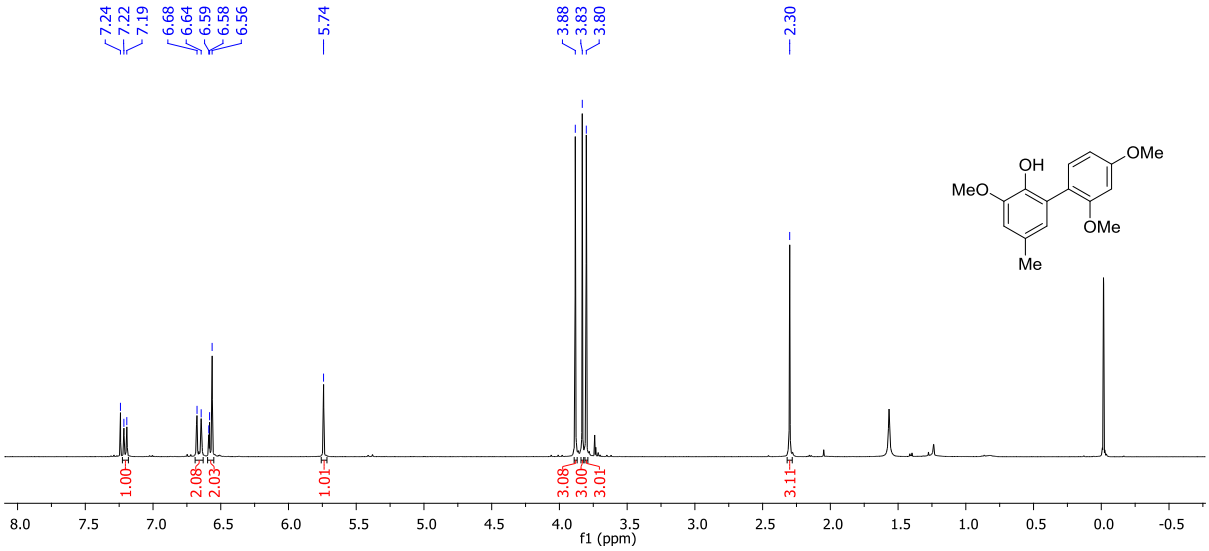
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **3ap**.

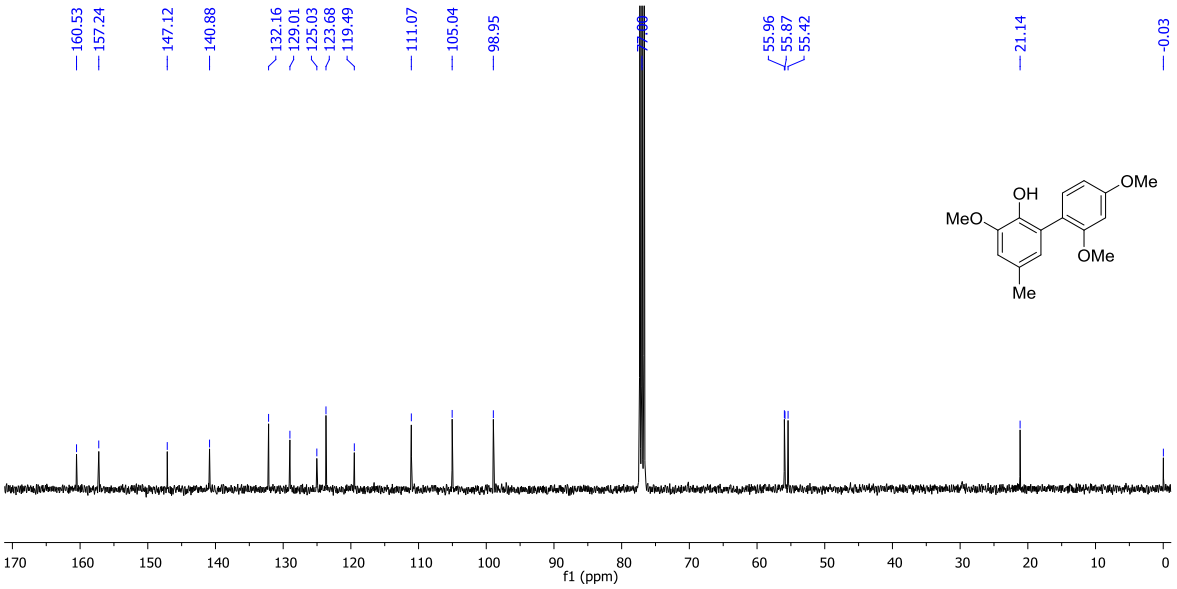


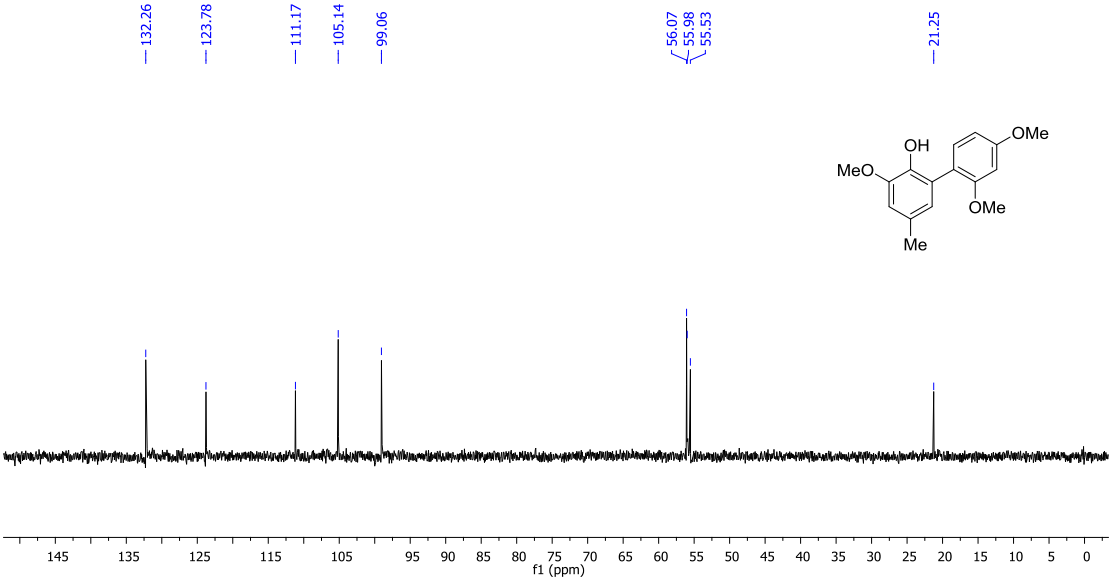



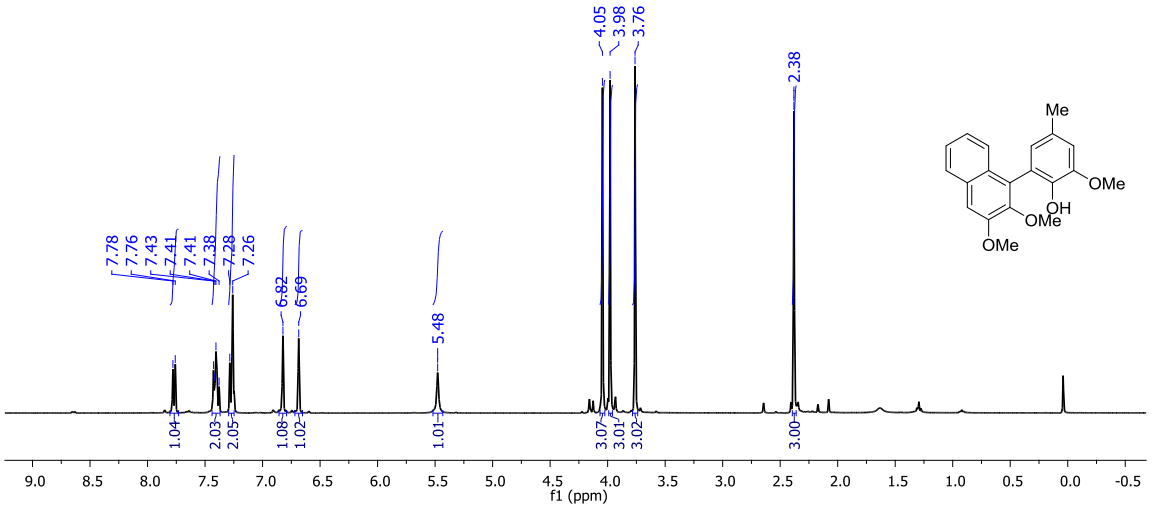
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **3bq**.

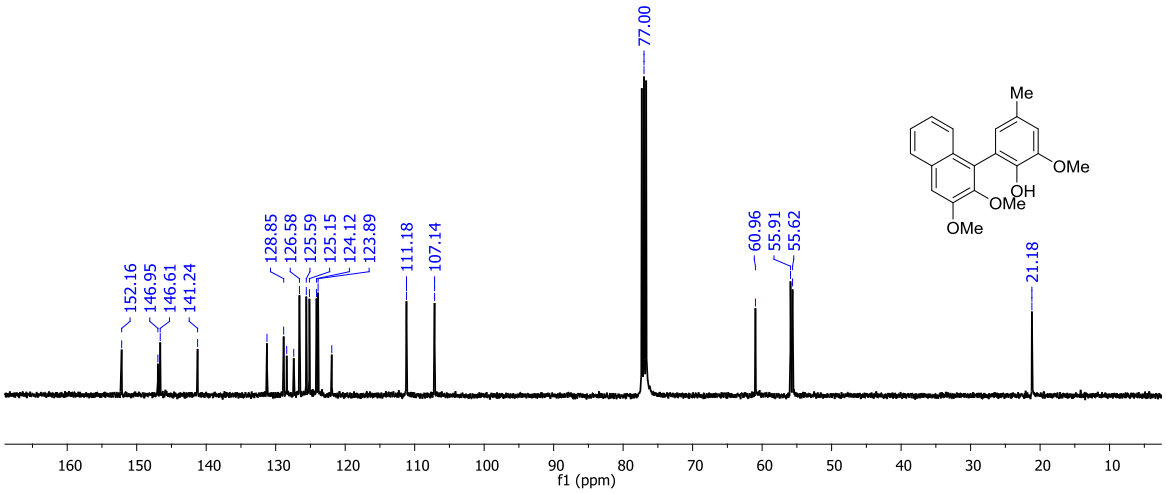


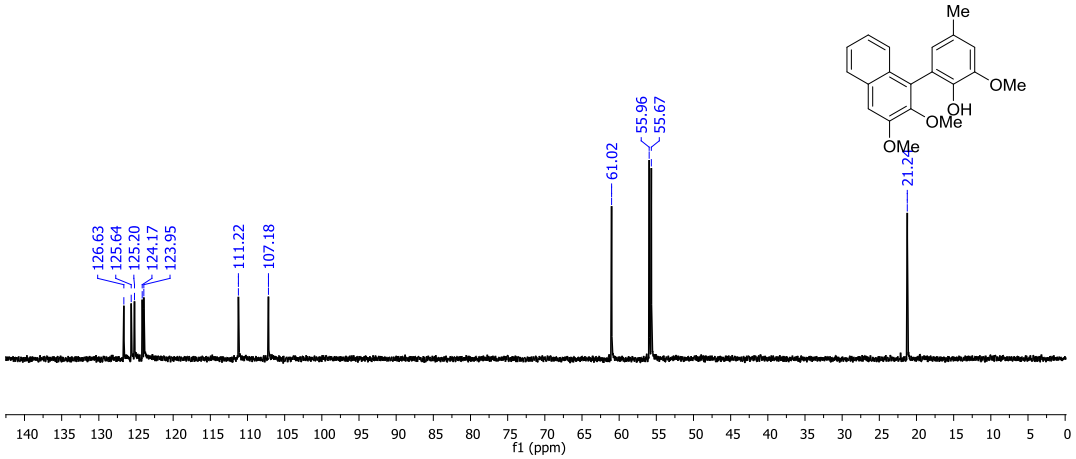



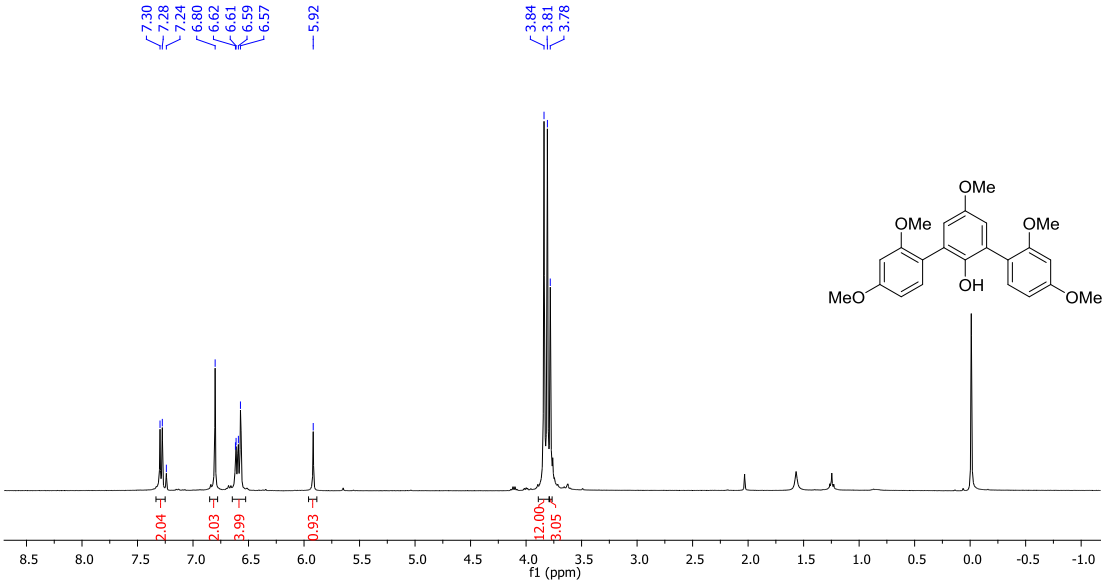
$^{1}H$ and $^{13}C$ NMR Spectra of Compound **3bp**.

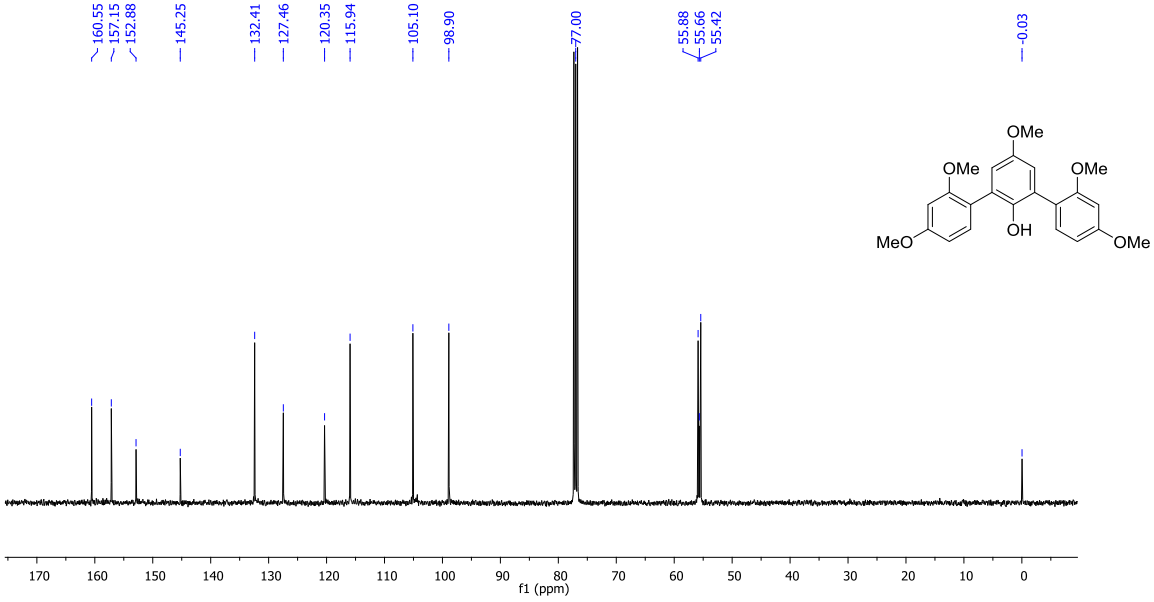


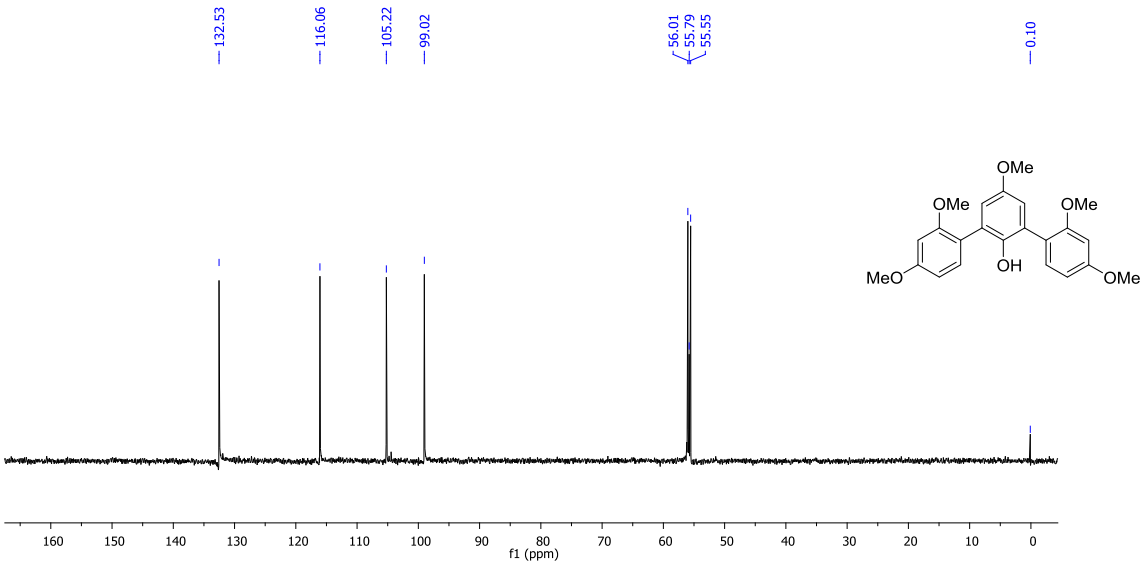



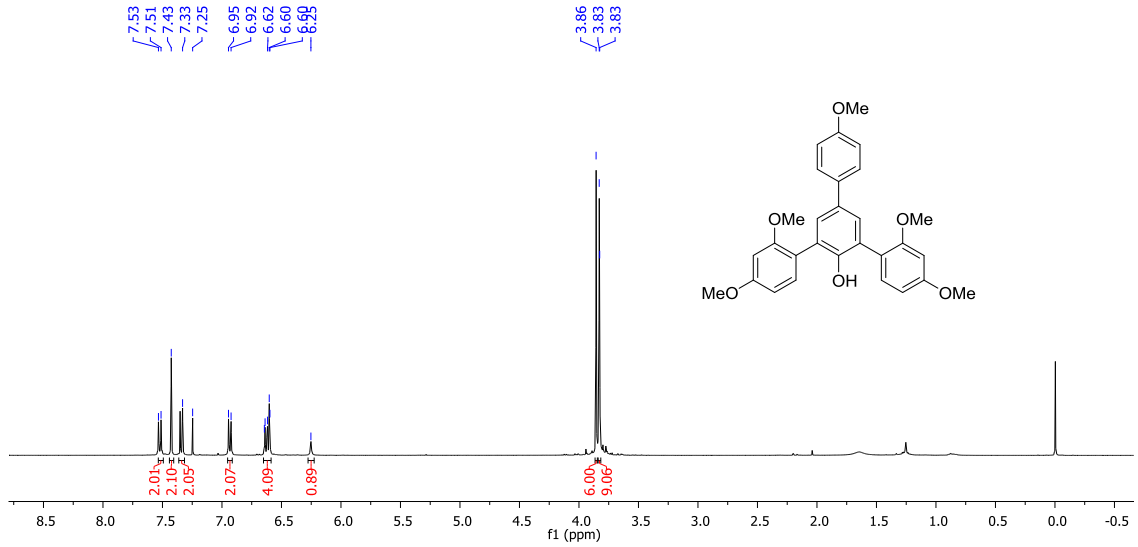
$^{1}$H and $^{13}$C NMR Spectra of Compound **3gq**.

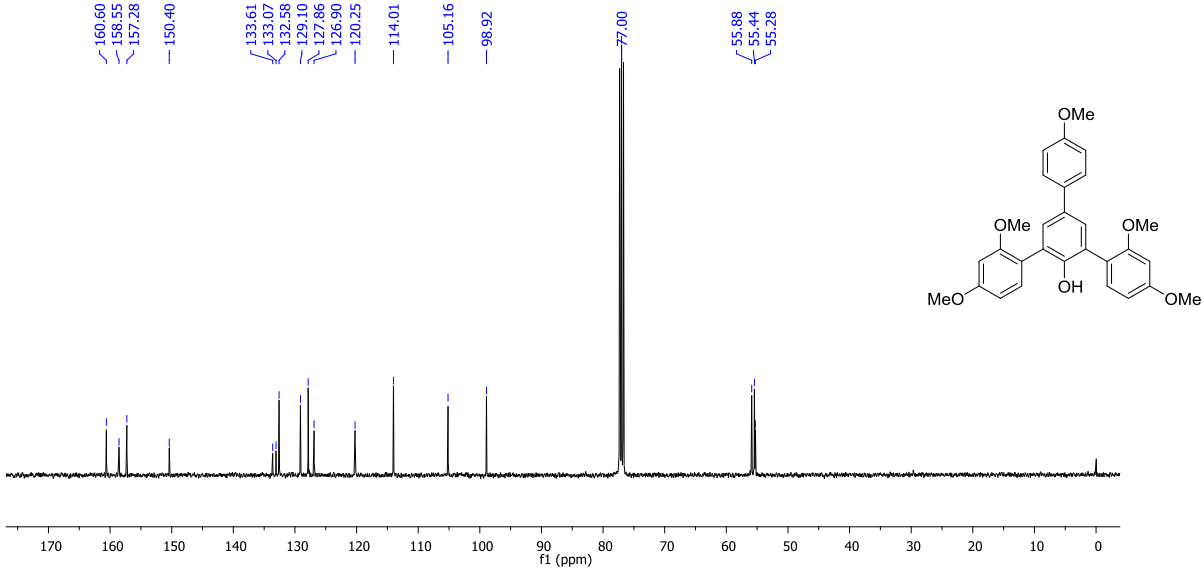


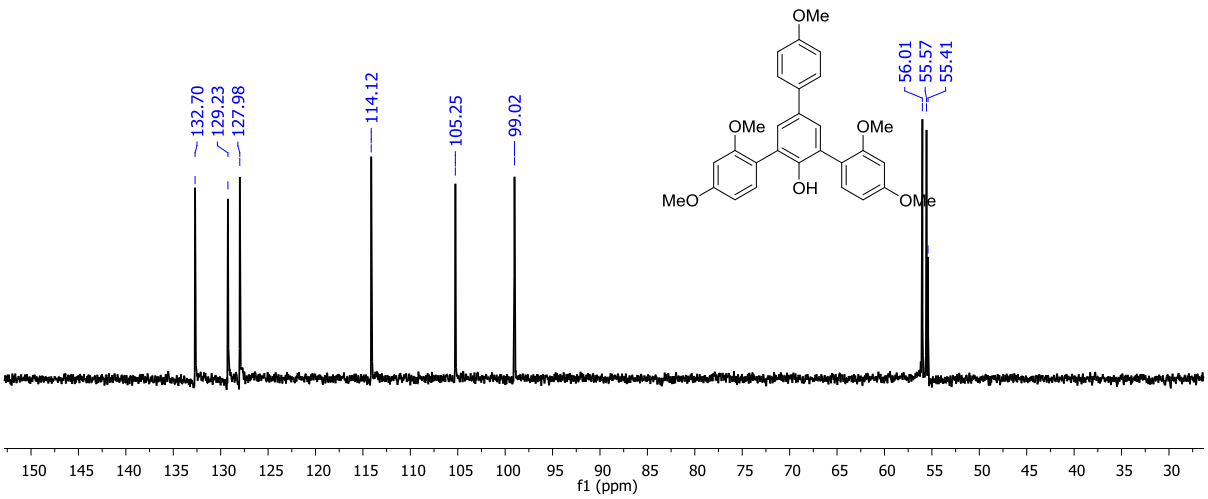



$^{1}H$ and $^{13}C$ NMR Spectra of Compound **3iq**.



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